Dossier zur Nutzenbewertung gemäß § 35a SGB V

Durvalumab (Imfinzi®)

AstraZeneca GmbH

Anhang 4-G

Durvalumab in Kombination mit Gemcitabin und Cisplatin bei Erwachsenen zur Erstlinienbehandlung nicht resezierbarer oder metastasierter biliärer Tumore

Analysen für das Nutzendossier

Stand: 30.03.2023

Inhaltsverzeichnis

Table 1.1 TOPAZ: Summary of observation period (months) for efficacy endpoints
Full Analysis Set

		Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Overall Survival (OS) [a]	n	405	405
	Median	12.45	10.68
	Min	0.1	0.2
	Max	33.2	32.5
Progression-free survival (PFS) by investigator [b]	n	405	405
	Median	6.60	5.45
	Min	0.0	0.0
	Max	24.0	20.4
Duration of Response (DoR) [b]	n	99	69
	Median	9.20	9.03
	Min	3.6	4.0
	Max	24.0	18.5

[a] DCO 25FEB2022 and 14OCT2022 for China Patients
[b] DCO 11AUG2021 and 14OCT2022 for China Patients
Observation period for OS and PFS is defined as the time from randomisation to the earliest of the DCO and the last date endpoint data are collected for the respective endpoint. Observation period for DoR is defined as the time from date of first response to the earliest of the DCO and last date endpoint data are collected.

Table 1.1.1.1 TOPAZ: Summary of Overall Survival
Full Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
Overall survival (OS)	405	290 (71.6)	12.6 (11.1,13.6)	405	327 (80.7)	10.9 (9.7,11.7)	0.77	0.66, 0.90	0.0008*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model stratified for disease status and primary tumor location. Stratification factors are from IXRS. Efron method for handling ties. 95% CI from profile likelihood estimation.
[c] Determined using log-rank test stratified for disease status and primary tumor location. Hazard ratio <1 favours durvalumab. * p<0.05.

Table 1.1.1.2 TOPAZ: Summary of Kaplan-Meier estimates for Overall Survival at 12 months (OS12), 18 months (OS18) and 24 months (OS24)
Full Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Survival rate at 12 months (%)	52.2	44.2
95% CI for survival rate at 12 months	47.2, 57.0	39.2, 49.0
Survival rate at 18 months (%)	33.8	22.6
95% CI for survival rate at 18 months	29.0, 38.6	18.4, 27.0
Survival rate at 24 months (%)	23.3	10.7
95% CI for survival rate at 24 months	18.6, 28.3	7.1, 15.0

Calculated using the Kaplan-Meier technique. CI for survival rate derived based on Brookmeyer-Crowley method.
CI = Confidence interval. NC = Non-calculable.

Table 1.1.1.3 TOPAZ: Summary of Progression Free Survival (PFS) by investigator
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
Progression-free survival (PFS) by investigator	405	325 (80.2)	7.2 (6.4, 7.4)	405	344 (84.9)	5.7 (5.4, 5.9)	0.76	0.65, 0.88	0.0005*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model stratified for disease status and primary tumor location.
Stratification factors are from IXRS. Efron method for handling ties. 95% CI from profile likelihood estimation.
[c] Determined using log-rank test stratified for disease status and primary tumor location.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 1.1.1.4 TOPAZ: Summary of Kaplan-Meier estimates for PFS by investigator at 12 months, 18 months and 24 months
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Survival rate at 12 months (%)	15.0	6.6
95% CI for survival rate at 12 months	11.4, 19.2	4.2, 9.8
Survival rate at 18 months (%)	10.5	3.7
95% CI for survival rate at 18 months	7.3, 14.4	1.7, 7.0
Survival rate at 24 months (%)	NC	NC
95% CI for survival rate at 24 months	NC, NC	NC, NC

Calculated using the Kaplan-Meier technique. CI for survival rate derived based on Brookmeyer-Crowley method.
CI = Confidence interval. NC = Non-calculable.

Table 1.1.1.5 TOPAZ: Summary of Duration of Response
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
Duration of Response (DoR)	99	66 (66.7)	6.3 (5.9, 8.1)	69	53 (76.8)	6.2 (4.6, 7.3)	0.77	0.53, 1.11	0.1729

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model stratified for disease status and primary tumor location.
Stratification factors are from IXRS. Efron method for handling ties. 95% CI from profile likelihood estimation.
[c] Determined using log-rank test stratified for disease status and primary tumor location.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 1.1.1.6 TOPAZ: Summary of analysis of Objective Response Rate (ORR)
(odds ratio, relative risk and risk difference)
Full Analysis Set, subjects with measurable disease at baseline, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)		Placebo + Gem + Cis (N=404)		Treatment effect					
					Odds Ratio		Relative Risk		Risk Difference	
	n	Number (%) of patients with events	n	Number (%) of patients with events	Estimate (95% CI)	2-sided p-value	Estimate (95% CI)	2-sided p-value	Estimate (95% CI)	2-sided p-value
Objective Response Rate (ORR) [a][d][g]	405	99(24.4)	404	69(17.1)	1.59(1.12, 2.26)	0.0090 *	1.40(1.07, 1.84)	0.0141 *	0.07(0.02, 0.13)	0.0068 *

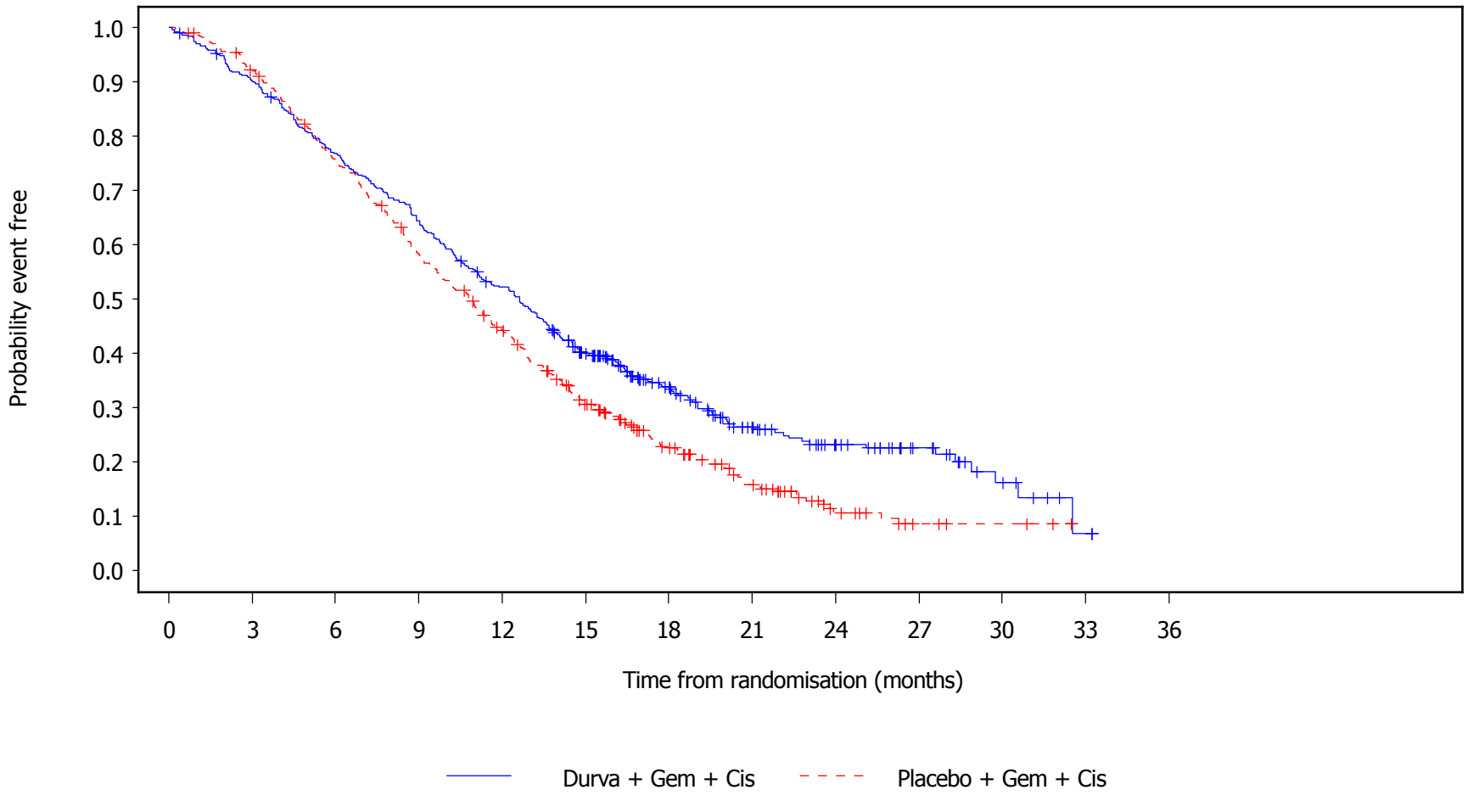
Responses include confirmed complete or partial response based on investigator assessment according to RECIST 1.1.
Does not include subjects who discontinue randomized treatment without progression, receive a subsequent anti-cancer therapy and then respond.
Model stratified with factors for disease status and tumor location. Stratification factors are from IXRS.
CI=Confidence interval. PL=Profile likelihood. LR=Likelihood ratio test.
[a] Odds ratio (OR), 95% PL CI, LR p-value via logistic regression.
[d] Relative risk (RR), 95% PL CI, LR p-value via log-binomial regression.
[g] Risk difference (RD), 95% PL CI, LR p-value via binomial regression.
Odds ratio and relative risk <1, and risk difference <0 favours durvalumab. * p<0.05.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/orrrardeff.sas eorrrardeffaa 02FEB2023:08:54 khcs324

Table 1.1.1.7 TOPAZ: Disease Control Rate based on investigator assessments according to RECIST 1.1
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Number (%) of subjects	
Disease control rate	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
24 weeks [a]	222 (54.8)	181 (44.7)
32 weeks [b]	164 (40.5)	135 (33.3)

[a] Disease control rate at 24 weeks is defined as the percentage of subjects who have best objective response of CR or PR (by week 24 + 7 days) or who have SD at least 24 weeks (- 7 days), following start of treatment.
[b] Disease control rate at 32 weeks is defined as the percentage of subjects who have best objective response of CR or PR (by week 32 + 7 days) or who have SD at least 32 weeks (- 7 days), following start of treatment.
RECIST = Response Evaluation Criteria in Solid Tumors. CR = Complete response. PR = Partial response. SD = Stable disease.

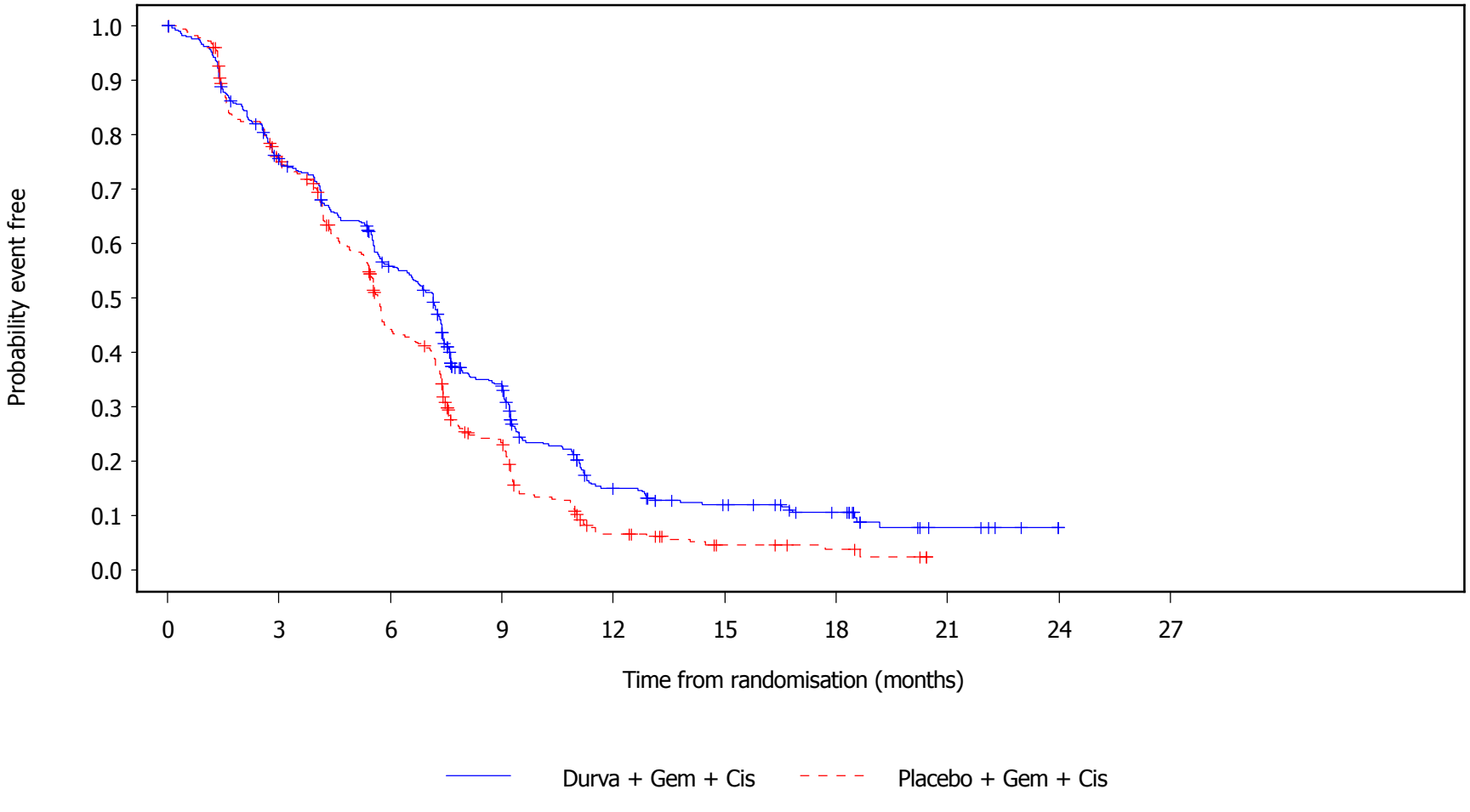
Figure 1.1.2.1 TOPAZ: Kaplan-Meier plot of time to Overall Survival
Full Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

405	364	309	259	207	147	92	54	36	21	8	1	0	Durva + Gem + Cis
405	370	300	231	171	111	67	38	14	5	3	0	0	Placebo + Gem + Cis

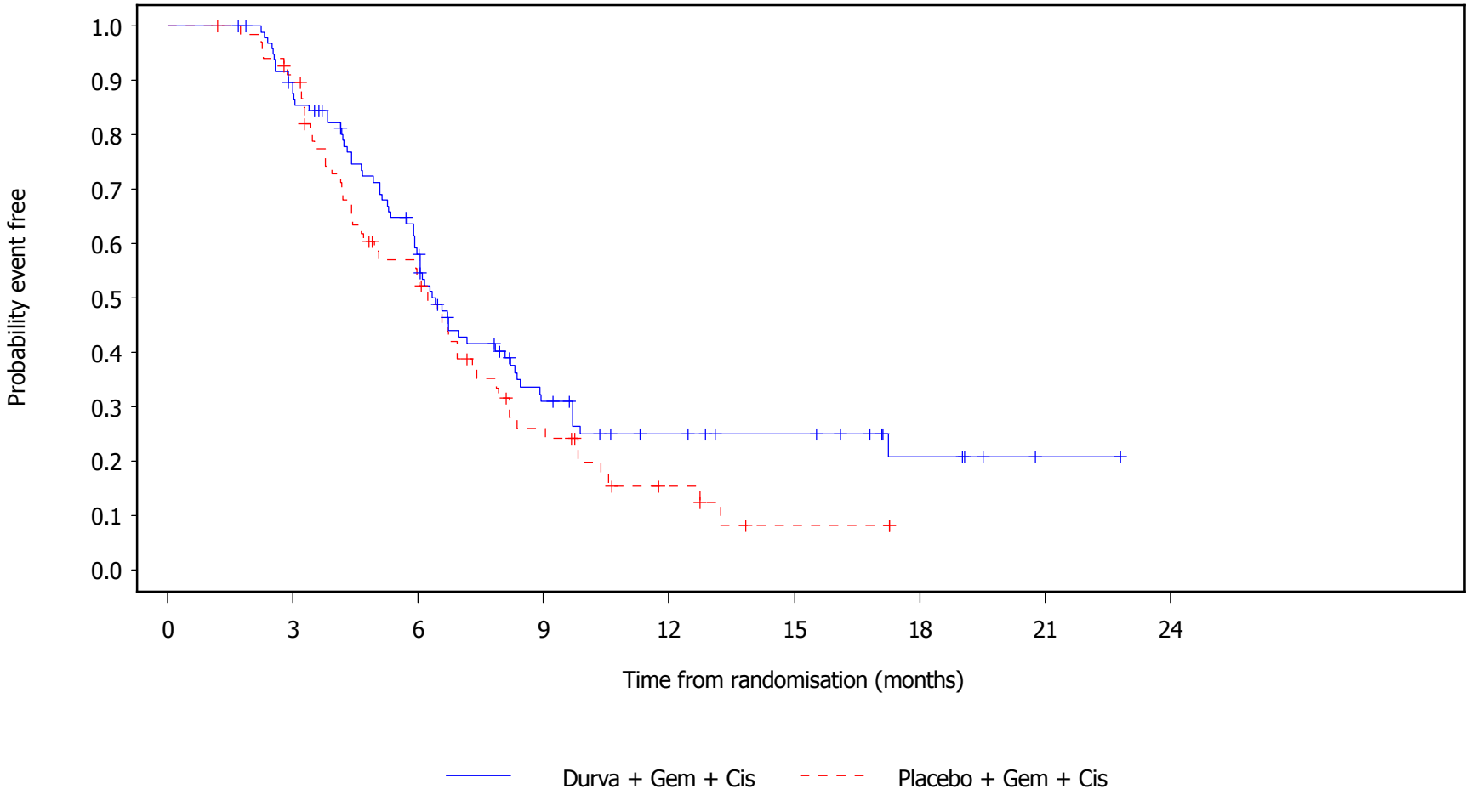
Figure 1.1.2.2 TOPAZ: Kaplan-Meier plot of time to Progression Free Survival (PFS) by investigator
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

405	296	211	114	42	28	18	5	0	0	Durva + Gem + Cis
405	291	162	77	18	7	4	0	0	0	Placebo + Gem + Cis

Figure 1.1.2.3 TOPAZ: Kaplan-Meier plot of Duration of Response
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

99	84	52	23	14	11	5	1	0	Durva + Gem + Cis
69	60	33	14	5	1	0	0	0	Placebo + Gem + Cis

Table 1.2.1.1.1 TOPAZ: Summary of subgroup analysis of time to first Overall survival (OS)
Full Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	246 (74.8)	11.1 (9.9,12.7)	334	285 (85.3)	9.8 (8.9,11.0)	0.77	0.65, 0.91	0.0024*
Recurrent	76	44 (57.9)	19.5 (16.6,27.6)	70	42 (60.0)	16.2 (12.8,20.7)	0.82	0.54, 1.25	0.3587
Interaction p-value									0.7772
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	48 (65.8)	14.7 (10.0,19.0)	72	61 (84.7)	10.9 (7.8,14.2)	0.61	0.42, 0.89	0.0101*
Intrahepatic CCA	236	168 (71.2)	12.7 (10.9,14.0)	235	185 (78.7)	11.0 (9.7,12.1)	0.79	0.64, 0.98	0.0284*
Gallbladder cancer	96	74 (77.1)	10.9 (8.9,13.6)	98	81 (82.7)	10.3 (8.4,12.1)	0.87	0.63, 1.19	0.3699
Interaction p-value									0.3565
Age Group									
<65	220	151 (68.6)	12.5 (10.3,14.0)	230	185 (80.4)	10.8 (9.7,12.1)	0.74	0.60, 0.92	0.0064*
>=65	185	139 (75.1)	12.6 (10.7,14.1)	175	142 (81.1)	11.0 (8.9,12.7)	0.80	0.64, 1.02	0.0688
Interaction p-value									0.6162
Region									
Asia	242	172 (71.1)	12.9 (11.1,14.1)	257	218 (84.8)	10.8 (9.7,11.6)	0.70	0.57, 0.86	0.0005*
Rest of World	163	118 (72.4)	11.9 (10.3,13.7)	148	109 (73.6)	11.0 (8.7,14.0)	0.91	0.70, 1.18	0.4567
Interaction p-value									0.1269
PD-L1 Status									
High (>=1%)	241	176 (73.0)	12.9 (10.7,14.5)	251	208 (82.9)	10.7 (9.2,11.6)	0.74	0.60, 0.90	0.0033*
Low (<1%)	119	80 (67.2)	11.6 (9.7,14.1)	117	92 (78.6)	10.3 (8.9,12.7)	0.77	0.57, 1.03	0.0807
Interaction p-value									0.8516
Sex									
Male	199	148 (74.4)	11.3 (9.6,13.2)	208	171 (82.2)	10.8 (9.0,11.6)	0.78	0.63, 0.97	0.0275*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 1.2.1.1.1 TOPAZ: Summary of subgroup analysis of time to first Overall survival (OS)
Full Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)						
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]		2-sided p-value [b]
Female	206	142 (68.9)	13.6 (11.6,15.8)	197	156 (79.2)	11.0 (9.6,12.6)	0.76	0.61,	0.96	0.0202*
Interaction p-value										0.8939
Race										
Asian	249	176 (70.7)	12.8 (11.1,14.1)	262	222 (84.7)	10.9 (9.7,11.7)	0.70	0.57,	0.85	0.0004*
Non-Asian	156	114 (73.1)	12.1 (10.3,13.7)	143	105 (73.4)	10.7 (8.5,13.6)	0.92	0.70,	1.20	0.5265
Interaction p-value										0.1074
WHO ECOG Status at Screening										
0	189	136 (72.0)	13.7 (11.9,15.8)	185	142 (76.8)	12.6 (10.9,14.4)	0.85	0.67,	1.08	0.1903
1	216	154 (71.3)	11.3 (9.3,12.8)	220	185 (84.1)	9.7 (8.6,11.0)	0.70	0.57,	0.87	0.0012*
Interaction p-value										0.2241
Disease Extent										
Locally Advanced	55	30 (54.5)	15.9 (13.6, NE)	73	56 (76.7)	12.8 (9.2,13.6)	0.56	0.35,	0.86	0.0082*
Metastatic	350	260 (74.3)	11.6 (10.3,13.0)	331	271 (81.9)	10.3 (9.2,11.5)	0.80	0.67,	0.95	0.0102*
Interaction p-value										0.1309
MSI Status										
MSI High	3	1 (33.3)	NE (NE, NE)	2	2 (100)	16.3 (13.7, NE)	NC	NC		NC
MSI Stable	167	119 (71.3)	13.7 (10.9,16.1)	178	144 (80.9)	12.1 (10.8,13.3)	0.76	0.60,	0.98	0.0313*
Interaction p-value										NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 1.2.1.2.1 TOPAZ: Summary of subgroup analysis of time to first Progression-free survival (PFS) by investigator
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	271 (82.4)	6.6 (5.6, 7.2)	334	290 (86.8)	5.6 (5.2, 5.8)	0.79	0.67, 0.93	0.0054*
Recurrent	76	54 (71.1)	9.0 (7.4,11.0)	70	54 (77.1)	7.3 (5.6, 9.1)	0.65	0.45, 0.95	0.0277*
Interaction p-value									0.3656
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	56 (76.7)	7.6 (6.8, 9.1)	72	62 (86.1)	5.7 (4.6, 7.0)	0.50	0.35, 0.72	0.0002*
Intrahepatic CCA	236	189 (80.1)	7.2 (5.8, 7.4)	235	198 (84.3)	5.7 (5.3, 6.7)	0.79	0.65, 0.97	0.0233*
Gallbladder cancer	96	80 (83.3)	6.1 (5.5, 7.2)	98	84 (85.7)	5.7 (4.5, 6.7)	0.92	0.67, 1.25	0.5818
Interaction p-value									0.0340*
Age Group									
<65	220	175 (79.5)	7.2 (6.2, 7.5)	230	195 (84.8)	5.6 (5.3, 5.8)	0.70	0.57, 0.86	0.0006*
>=65	185	150 (81.1)	6.8 (5.6, 7.4)	175	149 (85.1)	5.7 (5.3, 7.2)	0.83	0.66, 1.04	0.1074
Interaction p-value									0.2640
Region									
Asia	242	191 (78.9)	7.2 (6.2, 7.6)	257	221 (86.0)	5.6 (5.3, 5.7)	0.69	0.57, 0.84	0.0002*
Rest of World	163	134 (82.2)	6.9 (5.6, 7.4)	148	123 (83.1)	6.1 (5.5, 7.3)	0.87	0.68, 1.11	0.2638
Interaction p-value									0.1459
PD-L1 Status									
High (>=1%)	239	193 (80.8)	6.6 (5.6, 7.3)	251	218 (86.9)	5.6 (4.9, 5.7)	0.70	0.57, 0.85	0.0003*
Low (<1%)	119	93 (78.2)	7.4 (6.7, 7.6)	117	95 (81.2)	5.8 (5.3, 7.4)	0.84	0.63, 1.12	0.2339
Interaction p-value									0.2962
Sex									
Male	199	160 (80.4)	6.6 (5.5, 7.4)	208	175 (84.1)	5.6 (5.3, 5.8)	0.76	0.61, 0.95	0.0135*

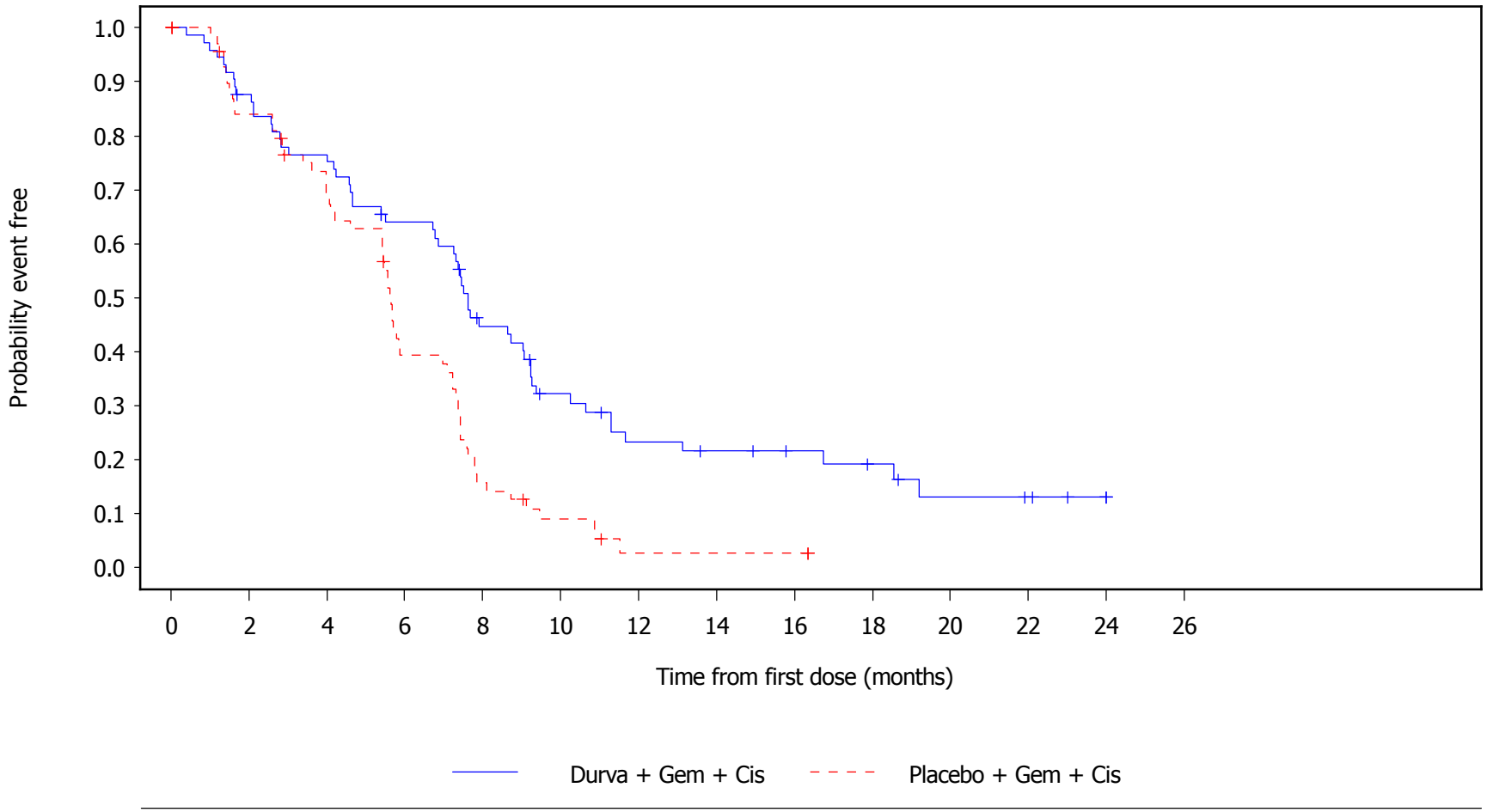
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 1.2.1.2.1 TOPAZ: Summary of subgroup analysis of time to first Progression-free survival (PFS) by investigator
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	165 (80.1)	7.2 (6.7, 7.6)	197	169 (85.8)	5.8 (5.4, 7.0)	0.75	0.60, 0.93	0.0084*
Interaction p-value									0.9017
Race									
Asian	249	196 (78.7)	7.2 (6.2, 7.6)	262	226 (86.3)	5.6 (5.3, 5.7)	0.69	0.57, 0.84	0.0001*
Non-Asian	156	129 (82.7)	6.7 (5.6, 7.4)	143	118 (82.5)	6.1 (5.5, 7.3)	0.88	0.68, 1.13	0.3127
Interaction p-value									0.1287
WHO ECOG Status at Screening									
0	189	153 (81.0)	7.4 (6.9, 7.7)	185	159 (85.9)	5.7 (5.4, 7.1)	0.75	0.60, 0.93	0.0107*
1	216	172 (79.6)	6.2 (5.4, 7.2)	220	185 (84.1)	5.6 (5.2, 5.8)	0.76	0.62, 0.94	0.0105*
Interaction p-value									0.9147
Disease Extent									
Locally Advanced	55	37 (67.3)	9.1 (7.6,11.0)	73	61 (83.6)	6.0 (5.6, 7.2)	0.51	0.34, 0.76	0.0010*
Metastatic	350	288 (82.3)	6.6 (5.7, 7.2)	331	283 (85.5)	5.6 (5.3, 5.8)	0.80	0.68, 0.94	0.0083*
Interaction p-value									0.0427*
MSI Status									
MSI High	3	1 (33.3)	NE (NE, NE)	2	2 (100)	10.7 (7.3, NE)	NC	NC	NC
MSI Stable	160	135 (84.4)	7.2 (5.8, 7.6)	168	145 (86.3)	5.8 (5.5, 7.2)	0.78	0.62, 0.99	0.0422*
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

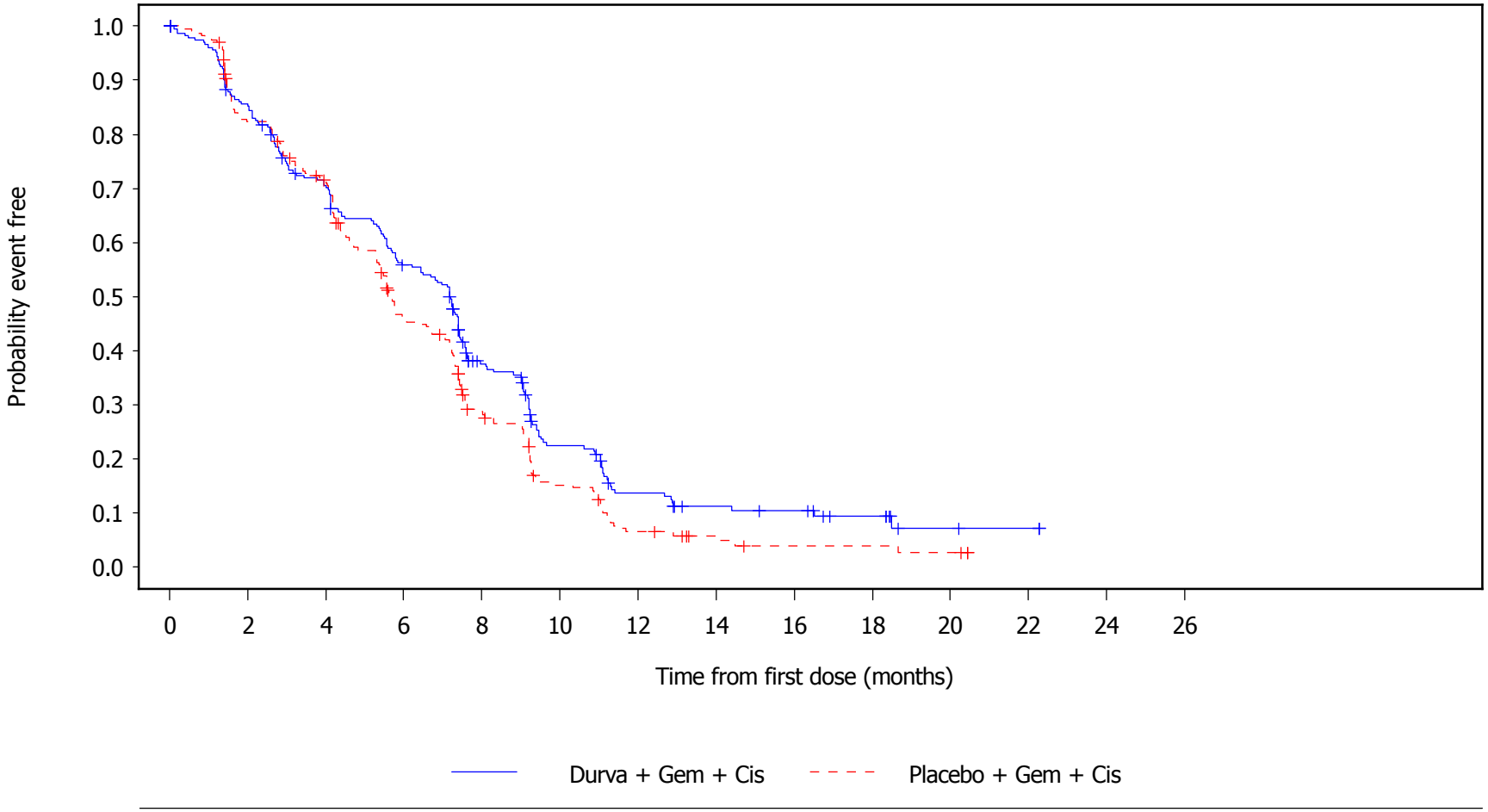
Figure 1.2.2.2.1 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of Progression-free survival (PFS) by investigator for Primary Tumor Location [eCRF]=Extrahepatic CCA
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

73	63	55	44	29	19	13	11	9	7	4	3	0	0	Durva + Gem + Cis
72	57	45	25	10	5	1	1	1	0	0	0	0	0	Placebo + Gem + Cis

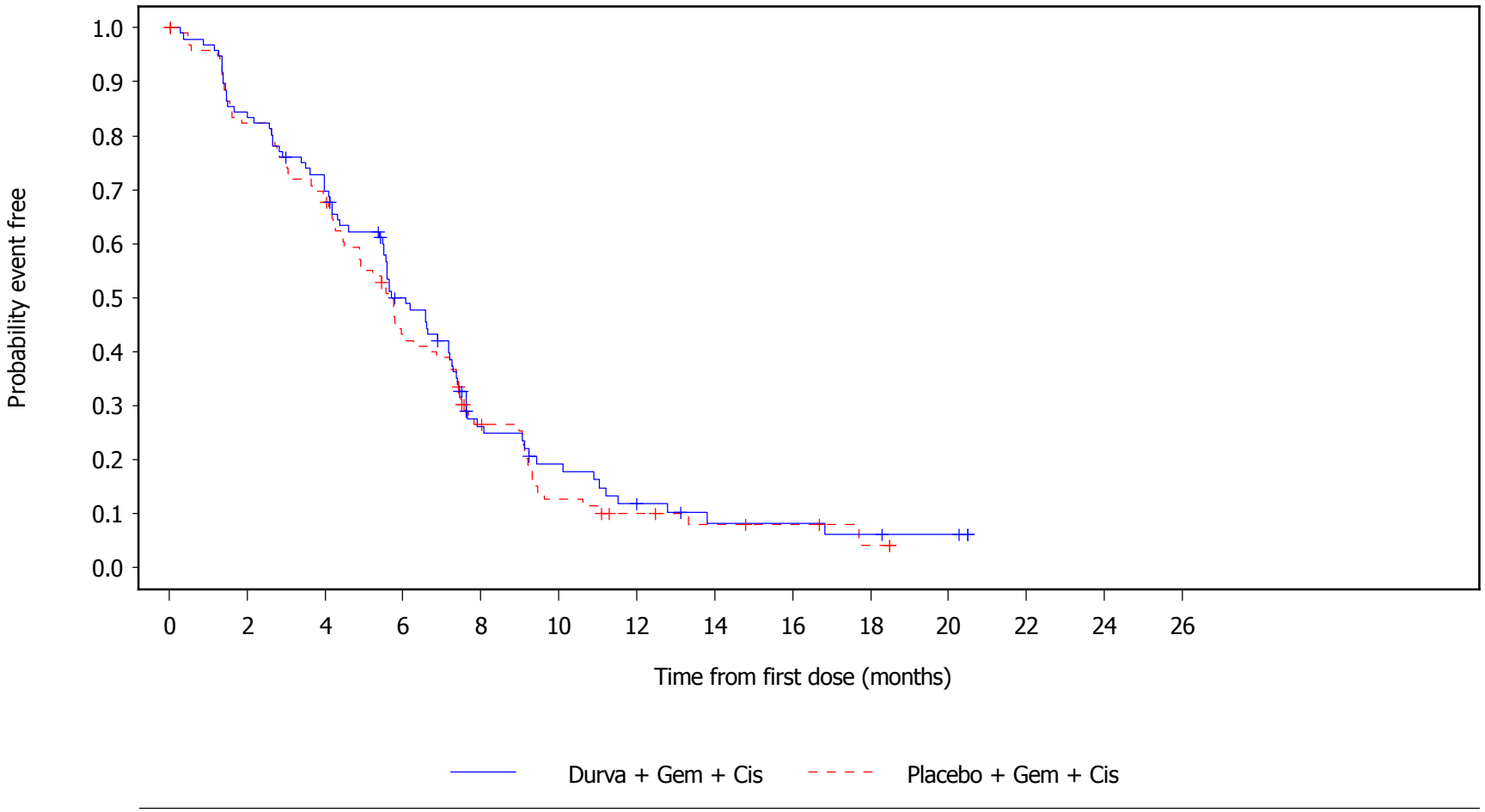
Figure 1.2.2.2.2 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of Progression-free survival (PFS) by investigator for Primary Tumor Location [eCRF]=Intrahepatic CCA
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

236	196	158	123	73	40	22	15	13	8	2	1	0	0	Durva + Gem + Cis
235	184	156	97	55	27	11	6	3	3	2	0	0	0	Placebo + Gem + Cis

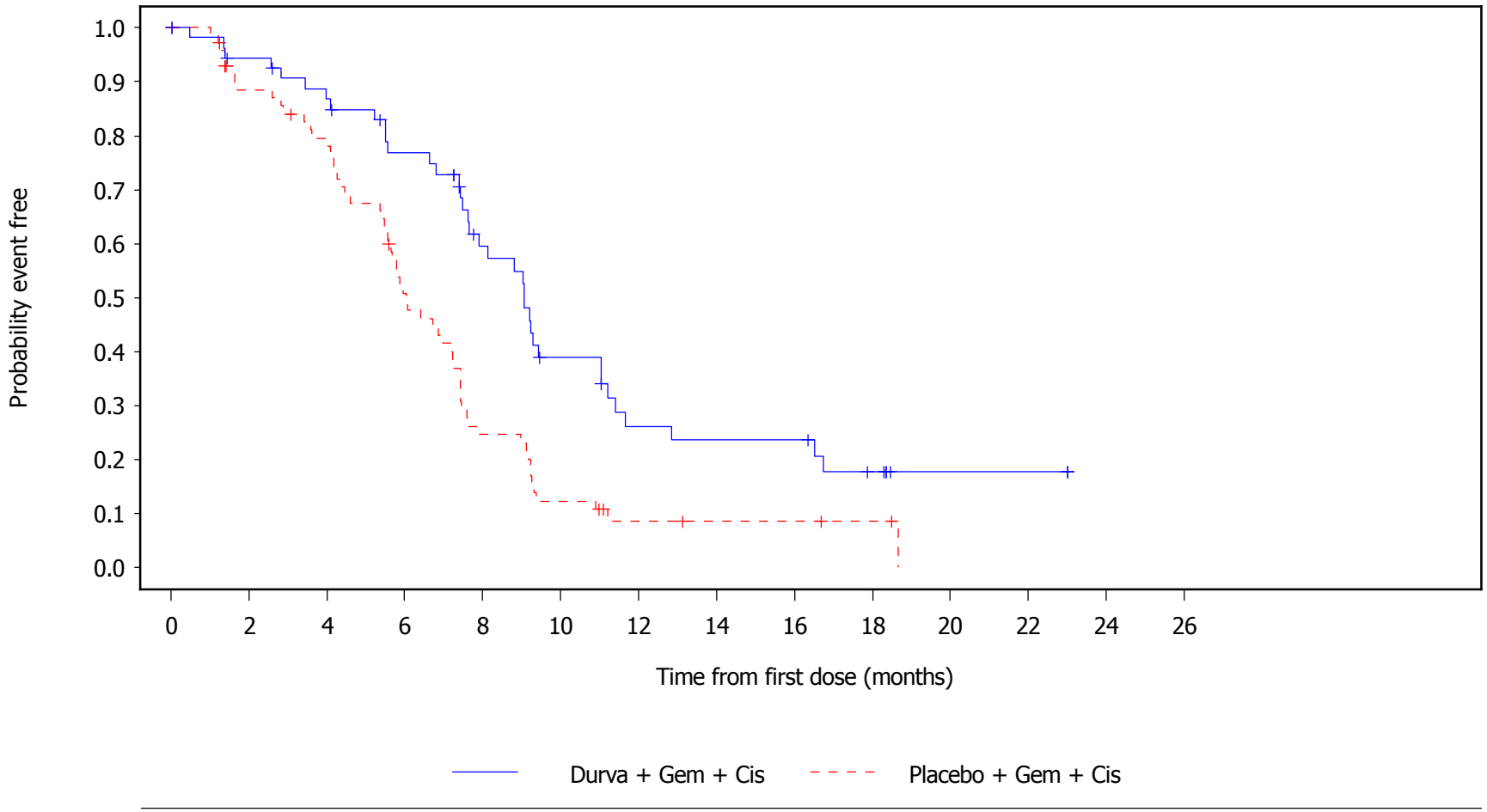
Figure 1.2.2.2.3 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of Progression-free survival (PFS) by investigator for Primary Tumor Location [eCRF]=Gallbladder cancer
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

96	81	66	44	19	13	7	4	4	3	2	0	0	0	Durva + Gem + Cis
98	79	66	40	22	10	6	4	3	1	0	0	0	0	Placebo + Gem + Cis

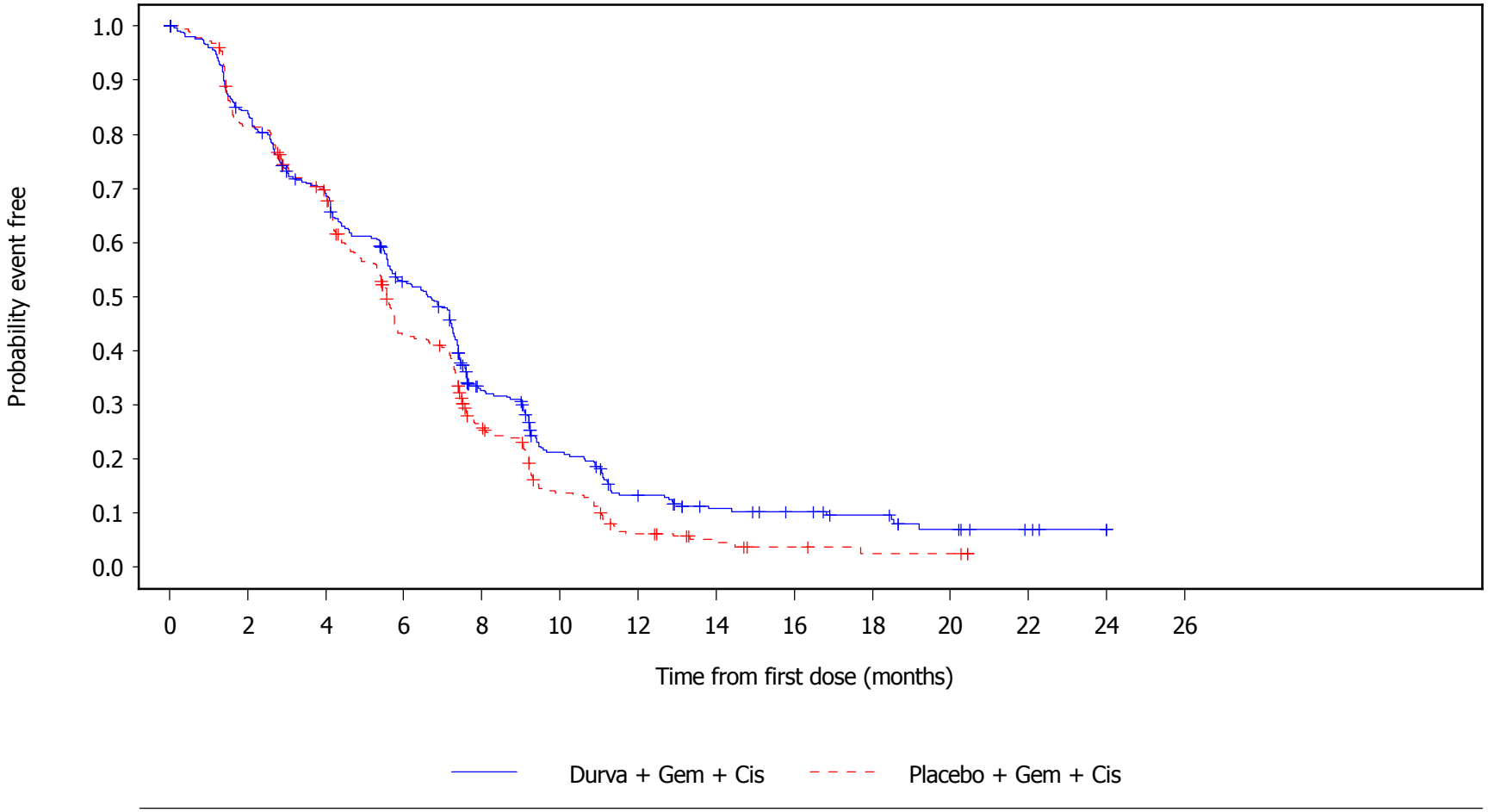
Figure 1.2.2.2.4 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of Progression-free survival (PFS) by investigator for Disease Extent=Locally Advanced
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

55	50	45	38	26	16	10	9	9	5	1	1	0	0	Durva + Gem + Cis
73	60	52	33	16	8	4	3	3	2	0	0	0	0	Placebo + Gem + Cis

Figure 1.2.2.2.5 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of Progression-free survival (PFS) by investigator for Disease Extent=Metastatic
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

350	290	234	173	95	56	32	21	17	13	7	3	0	0	Durva + Gem + Cis
331	260	215	129	71	34	14	8	4	2	2	0	0	0	Placebo + Gem + Cis

Table 2.1 TOPAZ: Summary of observation period for PRO endpoints
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

		Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
EORTC QLQ-C30	n	405	405
	Median	5.16	4.73
	Min	0.0	0.0
	Max	23.2	21.3
EORTC QLQ-BIL21	n	405	405
	Median	4.96	4.63
	Min	0.0	0.0
	Max	23.2	21.3
EQ-5D VAS	n	405	405
	Median	5.16	4.73
	Min	0.0	0.0
	Max	23.2	21.3
PGIS	n	405	405
	Median	5.16	4.73
	Min	0.0	0.0
	Max	23.2	21.3

Observation period for PROs is defined as the time from randomisation to the earliest of the DCO and last assessment for each questionnaire.

Table 2.2.1 TOPAZ: Summary of status at time to deterioration in EORTC QLQ-C30 global QoL/health status, functional, symptom and single item scales
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

		Reason	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
EORTC QLQ-C30 Global QoL/health status	Deterioration	Total	145 (35.8)	145 (35.8)
	Censored	Total	260 (64.2)	260 (64.2)
		No evaluable assessments or no baseline data	109 (26.9)	96 (23.7)
		Alive and no deterioration	68 (16.8)	97 (24.0)
		Death	16 (4.0)	17 (4.2)
		Two or more missed visits before deterioration or death	67 (16.5)	50 (12.3)
EORTC QLQ-C30 Functional scale: Physical	Deterioration	Total	141 (34.8)	138 (34.1)
	Censored	Total	264 (65.2)	267 (65.9)
		No evaluable assessments or no baseline data	109 (26.9)	96 (23.7)
		Alive and no deterioration	79 (19.5)	105 (25.9)
		Death	18 (4.4)	13 (3.2)
		Two or more missed visits before deterioration or death	58 (14.3)	53 (13.1)
EORTC QLQ-C30 Functional scale: Role	Deterioration	Total	166 (41.0)	171 (42.2)
	Censored	Total	239 (59.0)	234 (57.8)
		No evaluable assessments or no baseline data	109 (26.9)	96 (23.7)
		Alive and no deterioration	68 (16.8)	79 (19.5)
		Death	15 (3.7)	10 (2.5)
		Two or more missed visits before deterioration or death	47 (11.6)	49 (12.1)
EORTC QLQ-C30 Functional scale: Cognitive	Deterioration	Total	158 (39.0)	142 (35.1)
	Censored	Total	247 (61.0)	263 (64.9)
		No evaluable assessments or no baseline data	109 (26.9)	96 (23.7)

Table 2.2.1 TOPAZ: Summary of status at time to deterioration in EORTC QLQ-C30 global QoL/health status, functional, symptom and single item scales
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

		Reason	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
		Alive and no deterioration	60 (14.8)	99 (24.4)
		Death	15 (3.7)	12 (3.0)
		Two or more missed visits before deterioration or death	63 (15.6)	56 (13.8)
EORTC QLQ-C30 Functional scale: Emotional	Deterioration	Total	100 (24.7)	111 (27.4)
	Censored	Total	305 (75.3)	294 (72.6)
		No evaluable assessments or no baseline data	109 (26.9)	96 (23.7)
		Alive and no deterioration	101 (24.9)	119 (29.4)
		Death	23 (5.7)	15 (3.7)
		Two or more missed visits before deterioration or death	72 (17.8)	64 (15.8)
EORTC QLQ-C30 Functional scale: Social	Deterioration	Total	152 (37.5)	142 (35.1)
	Censored	Total	253 (62.5)	263 (64.9)
		No evaluable assessments or no baseline data	109 (26.9)	96 (23.7)
		Alive and no deterioration	69 (17.0)	99 (24.4)
		Death	14 (3.5)	14 (3.5)
		Two or more missed visits before deterioration or death	61 (15.1)	54 (13.3)
EORTC QLQ-C30 Single item symptom scale: Loss of appetite	Deterioration	Total	142 (35.1)	145 (35.8)
	Censored	Total	263 (64.9)	260 (64.2)
		No evaluable assessments or no baseline data	109 (26.9)	96 (23.7)
		Alive and no deterioration	68 (16.8)	92 (22.7)
		Death	22 (5.4)	13 (3.2)
		Two or more missed visits before deterioration or death	64 (15.8)	59 (14.6)

Table 2.2.1 TOPAZ: Summary of status at time to deterioration in EORTC QLQ-C30 global QoL/health status, functional, symptom and single item scales
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

		Reason	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
EORTC QLQ-C30 Single item symptom scale: Constipation	Deterioration	Total	135 (33.3)	139 (34.3)
	Censored	Total	270 (66.7)	266 (65.7)
		No evaluable assessments or no baseline data	109 (26.9)	96 (23.7)
		Alive and no deterioration	80 (19.8)	100 (24.7)
		Death	22 (5.4)	17 (4.2)
		Two or more missed visits before deterioration or death	59 (14.6)	53 (13.1)
EORTC QLQ-C30 Single item symptom scale: Diarrhoea	Deterioration	Total	81 (20.0)	84 (20.7)
	Censored	Total	324 (80.0)	321 (79.3)
		No evaluable assessments or no baseline data	109 (26.9)	96 (23.7)
		Alive and no deterioration	106 (26.2)	139 (34.3)
		Death	26 (6.4)	20 (4.9)
		Two or more missed visits before deterioration or death	83 (20.5)	66 (16.3)
EORTC QLQ-C30 Single item symptom scale: Dyspnoea	Deterioration	Total	123 (30.4)	121 (29.9)
	Censored	Total	282 (69.6)	284 (70.1)
		No evaluable assessments or no baseline data	109 (26.9)	96 (23.7)
		Alive and no deterioration	89 (22.0)	114 (28.1)
		Death	13 (3.2)	18 (4.4)
		Two or more missed visits before deterioration or death	71 (17.5)	56 (13.8)
EORTC QLQ-C30 Symptom scale: Fatigue	Deterioration	Total	183 (45.2)	188 (46.4)
	Censored	Total	222 (54.8)	217 (53.6)
		No evaluable assessments or no baseline data	109 (26.9)	96 (23.7)
		Alive and no deterioration	54 (13.3)	72 (17.8)
		Death	14 (3.5)	10 (2.5)

Table 2.2.1 TOPAZ: Summary of status at time to deterioration in EORTC QLQ-C30 global QoL/health status, functional, symptom and single item scales
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

		Reason	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
		Two or more missed visits before deterioration or death	45 (11.1)	39 (9.6)
EORTC QLQ-C30 Single item scale: Financial difficulties	Deterioration	Total	89 (22.0)	93 (23.0)
	Censored	Total	316 (78.0)	312 (77.0)
		No evaluable assessments or no baseline data	109 (26.9)	96 (23.7)
		Alive and no deterioration	108 (26.7)	130 (32.1)
		Death	21 (5.2)	21 (5.2)
		Two or more missed visits before deterioration or death	78 (19.3)	65 (16.0)
EORTC QLQ-C30 Symptom scale: Nausea and vomiting	Deterioration	Total	168 (41.5)	164 (40.5)
	Censored	Total	237 (58.5)	241 (59.5)
		No evaluable assessments or no baseline data	109 (26.9)	96 (23.7)
		Alive and no deterioration	60 (14.8)	84 (20.7)
		Death	14 (3.5)	13 (3.2)
		Two or more missed visits before deterioration or death	54 (13.3)	48 (11.9)
EORTC QLQ-C30 Symptom scale: Pain	Deterioration	Total	147 (36.3)	144 (35.6)
	Censored	Total	258 (63.7)	261 (64.4)
		No evaluable assessments or no baseline data	109 (26.9)	96 (23.7)
		Alive and no deterioration	69 (17.0)	99 (24.4)
		Death	15 (3.7)	15 (3.7)
		Two or more missed visits before deterioration or death	65 (16.0)	51 (12.6)
EORTC QLQ-C30 Single item symptom scale: Insomnia	Deterioration	Total	124 (30.6)	121 (29.9)

Table 2.2.1 TOPAZ: Summary of status at time to deterioration in EORTC QLQ-C30 global QoL/health status, functional, symptom and single item scales
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Reason	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Censored	Total	281 (69.4)	284 (70.1)
	No evaluable assessments or no baseline data	109 (26.9)	96 (23.7)
	Alive and no deterioration	84 (20.7)	115 (28.4)
	Death	26 (6.4)	17 (4.2)
	Two or more missed visits before deterioration or death	62 (15.3)	56 (13.8)

Table 2.2.2 TOPAZ: Summary of analysis of time to deterioration in EORTC QLQ-C30 global QoL/health status, functional, symptom and single item scales
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)						
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]		2-sided p-value [c]
EORTC QLQ-C30 Time to Deterioration - Global QoL/health status	405	145 (35.8)	4.3 (2.8, 6.3)	405	145 (35.8)	4.2 (2.4, 6.7)	0.96	0.76,	1.21	0.7458
EORTC QLQ-C30 Time to Deterioration - Functional scale: Physical	405	141 (34.8)	3.5 (2.8, 6.5)	405	138 (34.1)	4.2 (3.2, 6.5)	1.02	0.80,	1.29	0.8388
EORTC QLQ-C30 Time to Deterioration - Functional scale: Role	405	166 (41.0)	2.2 (2.1, 2.9)	405	171 (42.2)	2.6 (2.1, 3.5)	1.03	0.83,	1.28	0.7395
EORTC QLQ-C30 Time to Deterioration - Functional scale: Cognitive	405	158 (39.0)	3.0 (2.8, 3.6)	405	142 (35.1)	3.8 (2.8, 5.4)	1.12	0.89,	1.41	0.2833
EORTC QLQ-C30 Time to Deterioration - Functional scale: Emotional	405	100 (24.7)	12.2 (5.8, NE)	405	111 (27.4)	6.8 (4.3, NE)	0.85	0.65,	1.11	0.2284
EORTC QLQ-C30 Time to Deterioration - Functional scale: Social	405	152 (37.5)	3.1 (2.1, 4.5)	405	142 (35.1)	3.7 (2.7, 5.6)	1.08	0.86,	1.35	0.4496

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards. [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] Estimated from Cox proportional hazards model adjusted for disease status and primary tumor location. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test stratified by disease status and primary tumor location. Hazard ratio <1 favours durva *p<0.05.
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Table 2.2.2 TOPAZ: Summary of analysis of time to deterioration in EORTC QLQ-C30 global QoL/health status, functional, symptom and single item scales
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)						
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]		2-sided p-value [c]
EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Loss of appetite	405	142 (35.1)	3.9 (2.9, 5.1)	405	145 (35.8)	3.5 (2.4, 5.6)	0.97	0.77,	1.22	0.7591
EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Constipation	405	135 (33.3)	4.2 (2.2, 9.2)	405	139 (34.3)	3.5 (2.5, 9.2)	0.97	0.76,	1.23	0.7112
EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Diarrhoea	405	81 (20.0)	NE (NE, NE)	405	84 (20.7)	11.0 (9.2, NE)	0.95	0.70,	1.29	0.8988
EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Dyspnoea	405	123 (30.4)	4.4 (3.5, 8.7)	405	121 (29.9)	5.5 (3.5, 9.8)	1.04	0.81,	1.34	0.8154
EORTC QLQ-C30 Time to Deterioration - Symptom scale: Fatigue	405	183 (45.2)	1.5 (1.4, 2.1)	405	188 (46.4)	1.8 (1.4, 2.2)	1.02	0.83,	1.26	0.8243
EORTC QLQ-C30 Time to Deterioration - Single item scale: Financial difficulties	405	89 (22.0)	NE (NE, NE)	405	93 (23.0)	NE (NE, NE)	0.97	0.73,	1.30	0.8611

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards. [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] Estimated from Cox proportional hazards model adjusted for disease status and primary tumor location. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test stratified by disease status and primary tumor location. Hazard ratio <1 favours durva *p<0.05.
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Table 2.2.2 TOPAZ: Summary of analysis of time to deterioration in EORTC QLQ-C30 global QoL/health status, functional, symptom and single item scales
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)						
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]		2-sided p-value [c]
EORTC QLQ-C30 Time to Deterioration - Symptom scale: Nausea and vomiting	405	168 (41.5)	2.2 (1.6, 2.8)	405	164 (40.5)	2.8 (2.1, 3.6)	1.07	0.86,	1.32	0.6409
EORTC QLQ-C30 Time to Deterioration - Symptom scale: Pain	405	147 (36.3)	3.6 (2.9, 4.9)	405	144 (35.6)	4.9 (3.5, 6.2)	1.11	0.88,	1.39	0.3780
EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Insomnia	405	124 (30.6)	5.0 (4.2, 6.7)	405	121 (29.9)	5.8 (3.7, 9.4)	1.00	0.78,	1.29	0.8531

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards. [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] Estimated from Cox proportional hazards model adjusted for disease status and primary tumor location. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test stratified by disease status and primary tumor location. Hazard ratio <1 favours durva *p<0.05.
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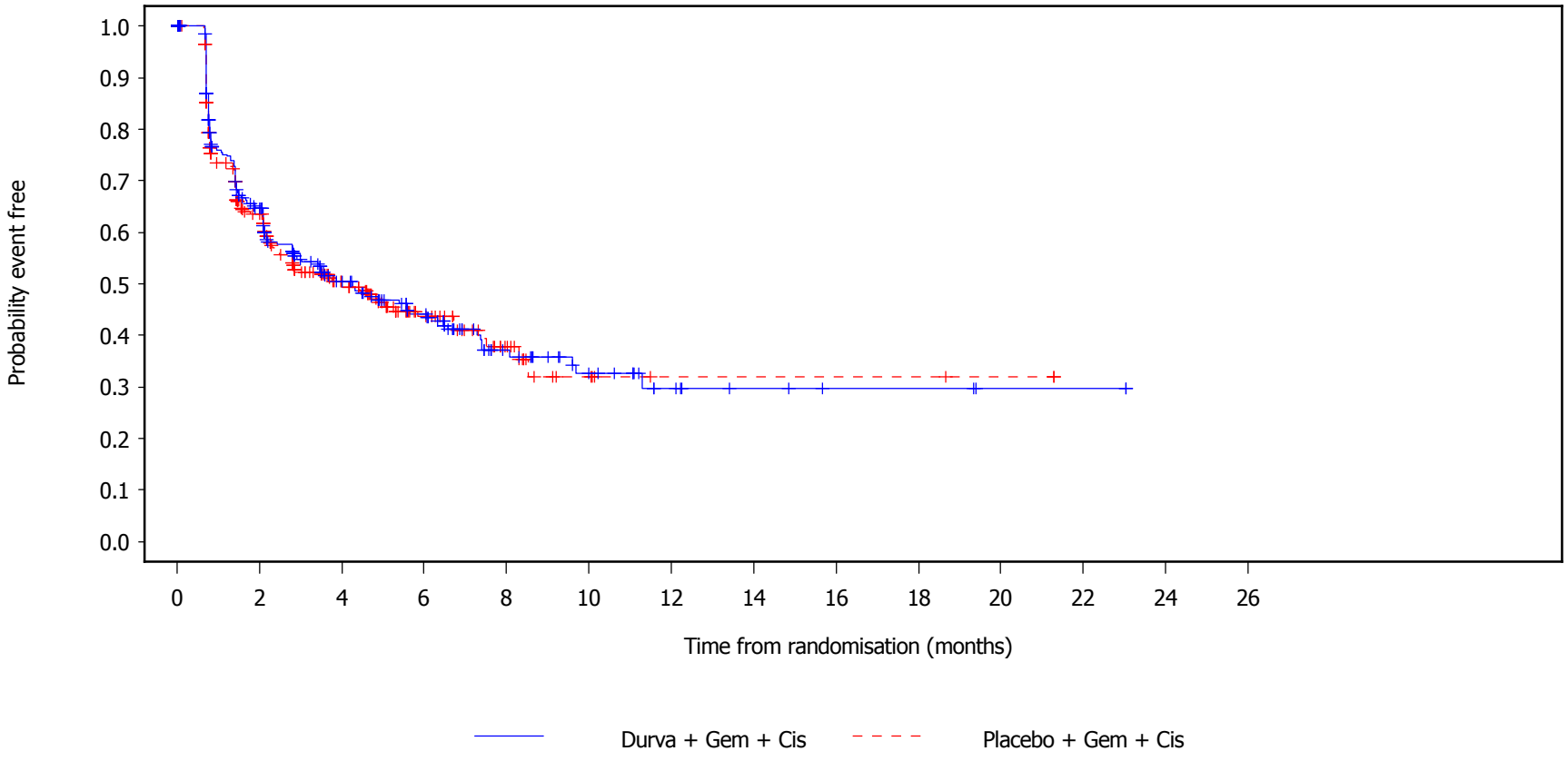
Figure 2.2.3.1 TOPAZ: Kaplan-Meier plot of EORTC QLQ-C30 Time to Deterioration - Global QoL/health status
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

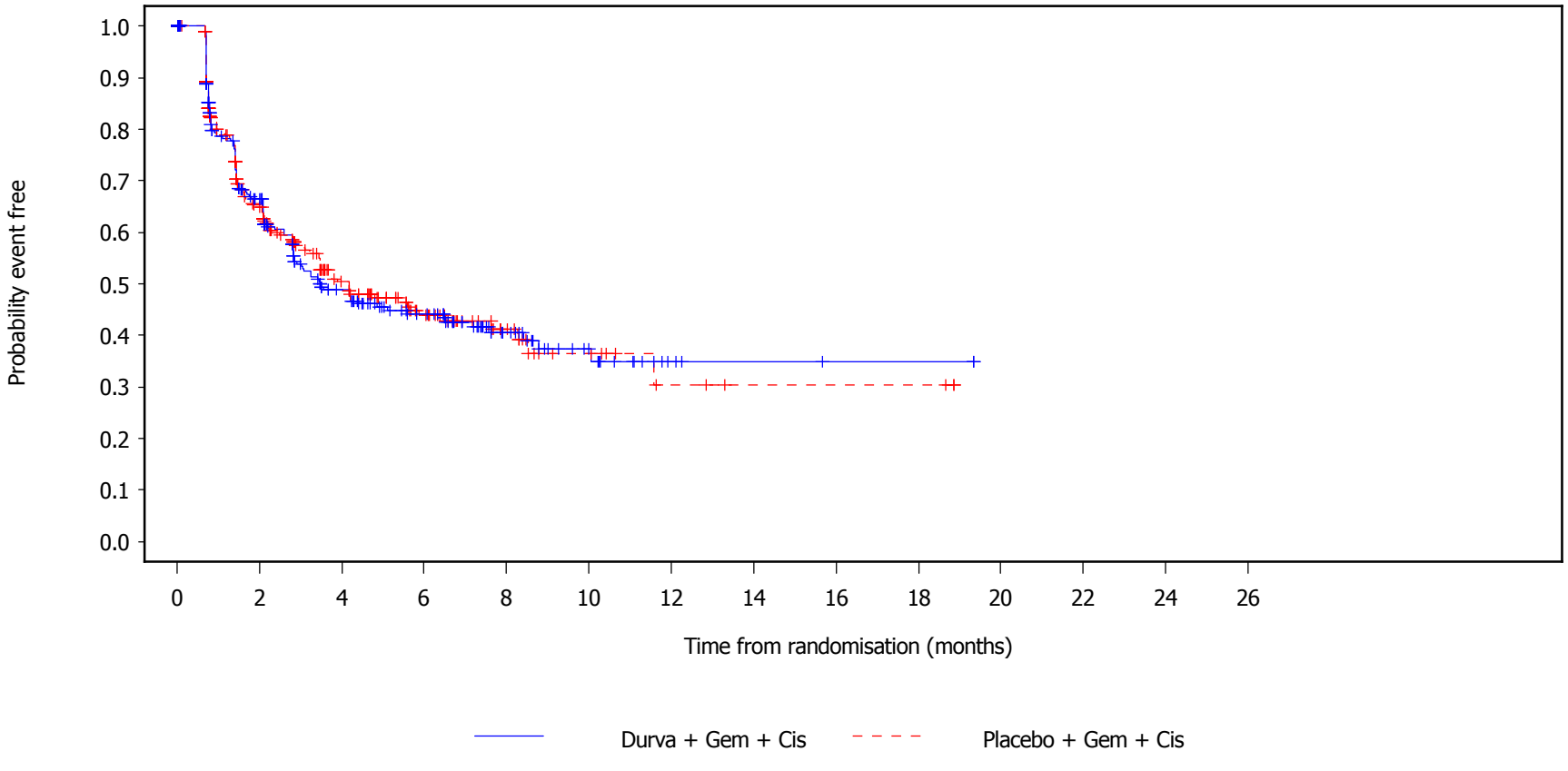


Number of patients at risk:

405	155	88	63	30	18	9	5	3	3	1	1	0	0	Durva + Gem + Cis
404	153	81	40	19	6	2	2	2	2	1	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.2.3.2 TOPAZ: Kaplan-Meier plot of EORTC QLQ-C30 Time to Deterioration - Functional scale: Physical
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

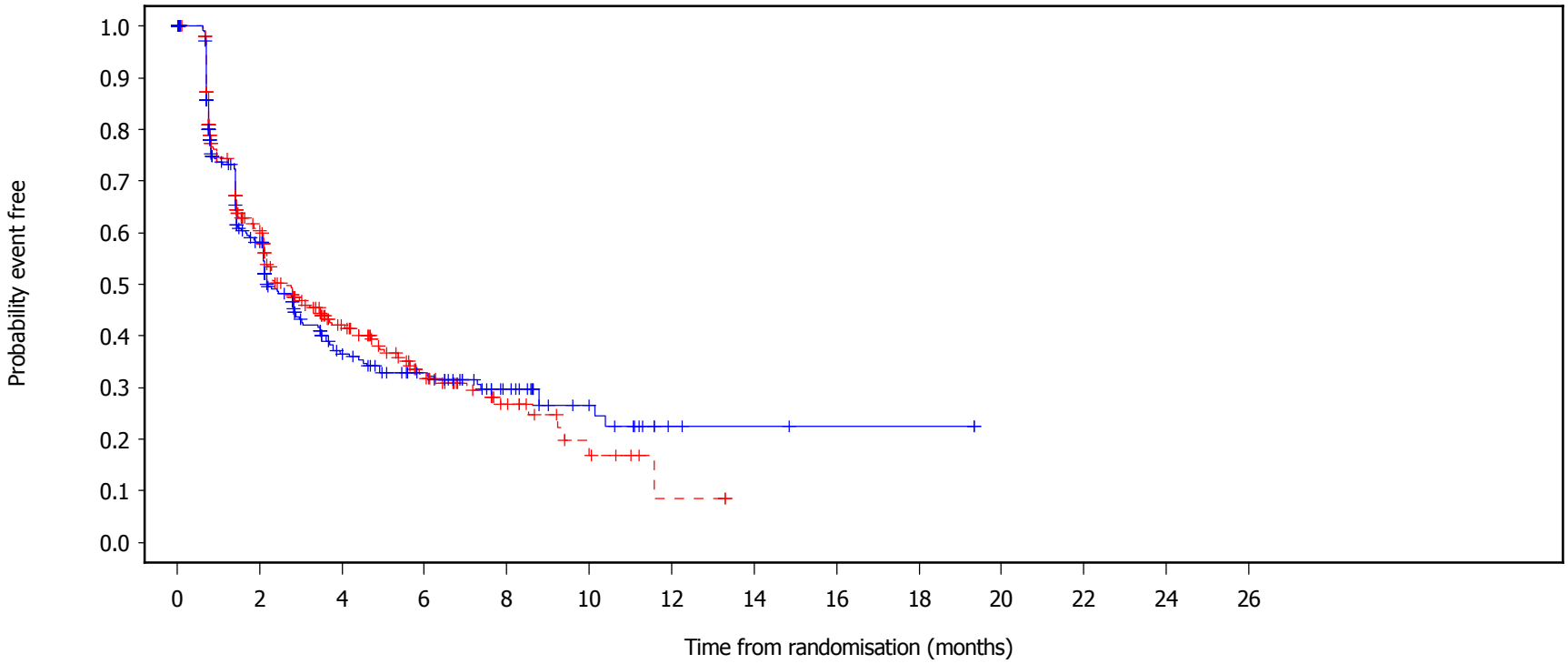


Number of patients at risk:

405	160	89	63	31	15	4	2	1	1	0	0	0	0	Durva + Gem + Cis
404	154	83	48	22	10	4	2	2	2	0	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.2.3.3 TOPAZ: Kaplan-Meier plot of EORTC QLQ-C30 Time to Deterioration - Functional scale: Role
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

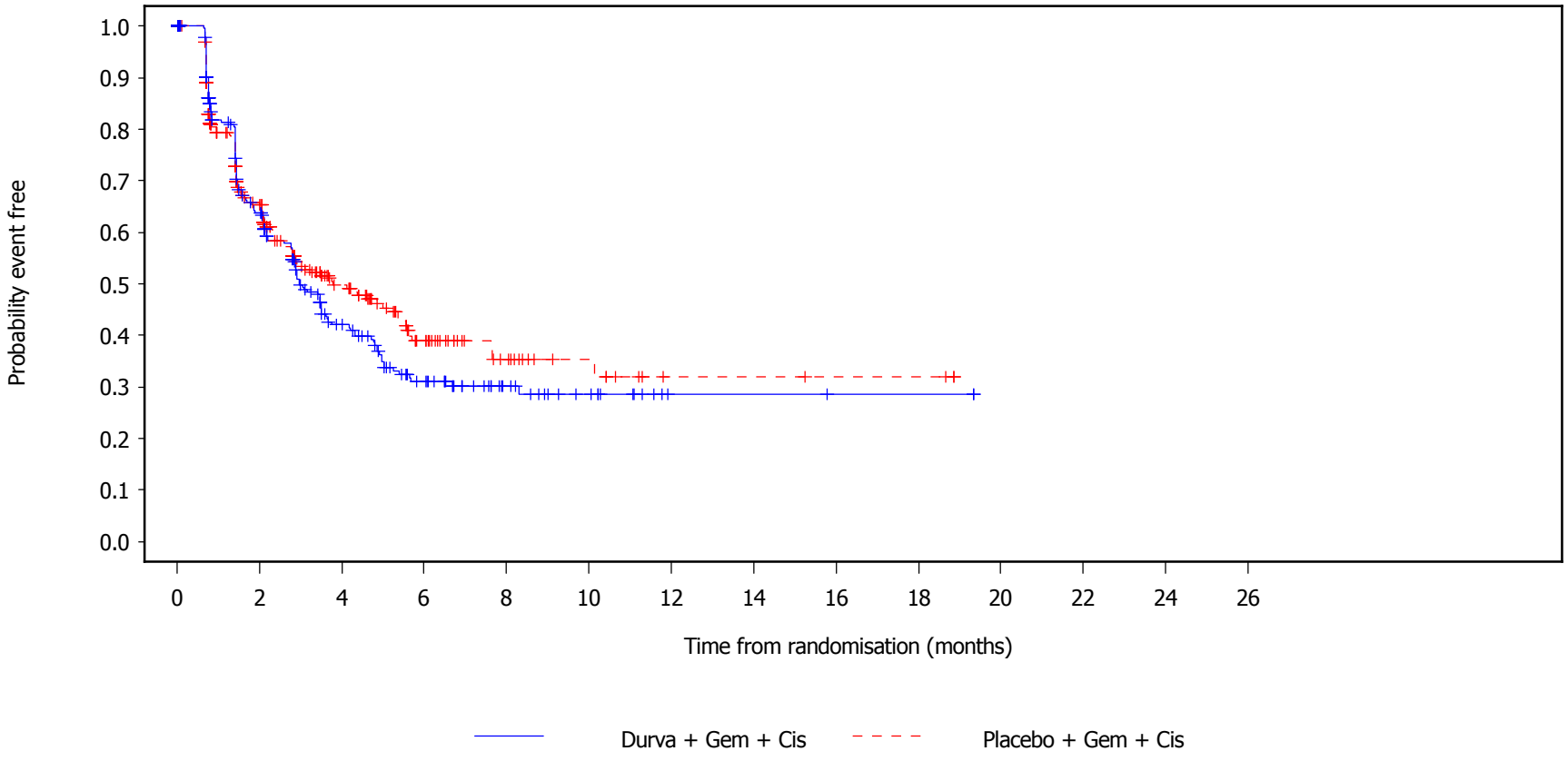


Number of patients at risk:

405	134	63	46	26	13	3	2	1	1	0	0	0	0	Durva + Gem + Cis
404	145	69	37	17	6	1	0	0	0	0	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.2.3.4 TOPAZ: Kaplan-Meier plot of EORTC QLQ-C30 Time to Deterioration - Functional scale: Cognitive
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

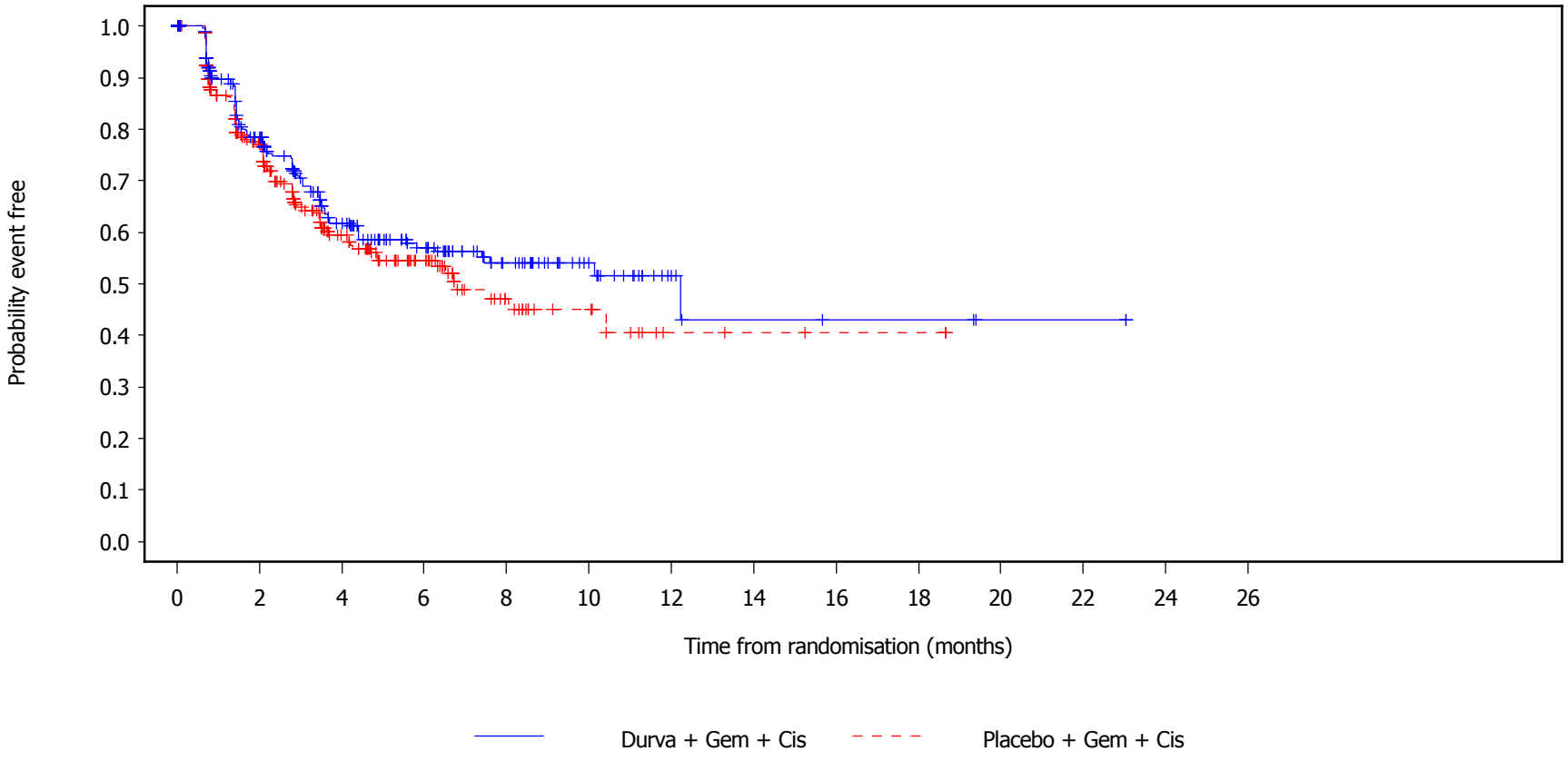


Number of patients at risk:

405	152	76	43	21	12	2	2	1	1	0	0	0	0	Durva + Gem + Cis
404	156	77	37	18	10	3	3	2	2	0	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.2.3.5 TOPAZ: Kaplan-Meier plot of EORTC QLQ-C30 Time to Deterioration - Functional scale: Emotional
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

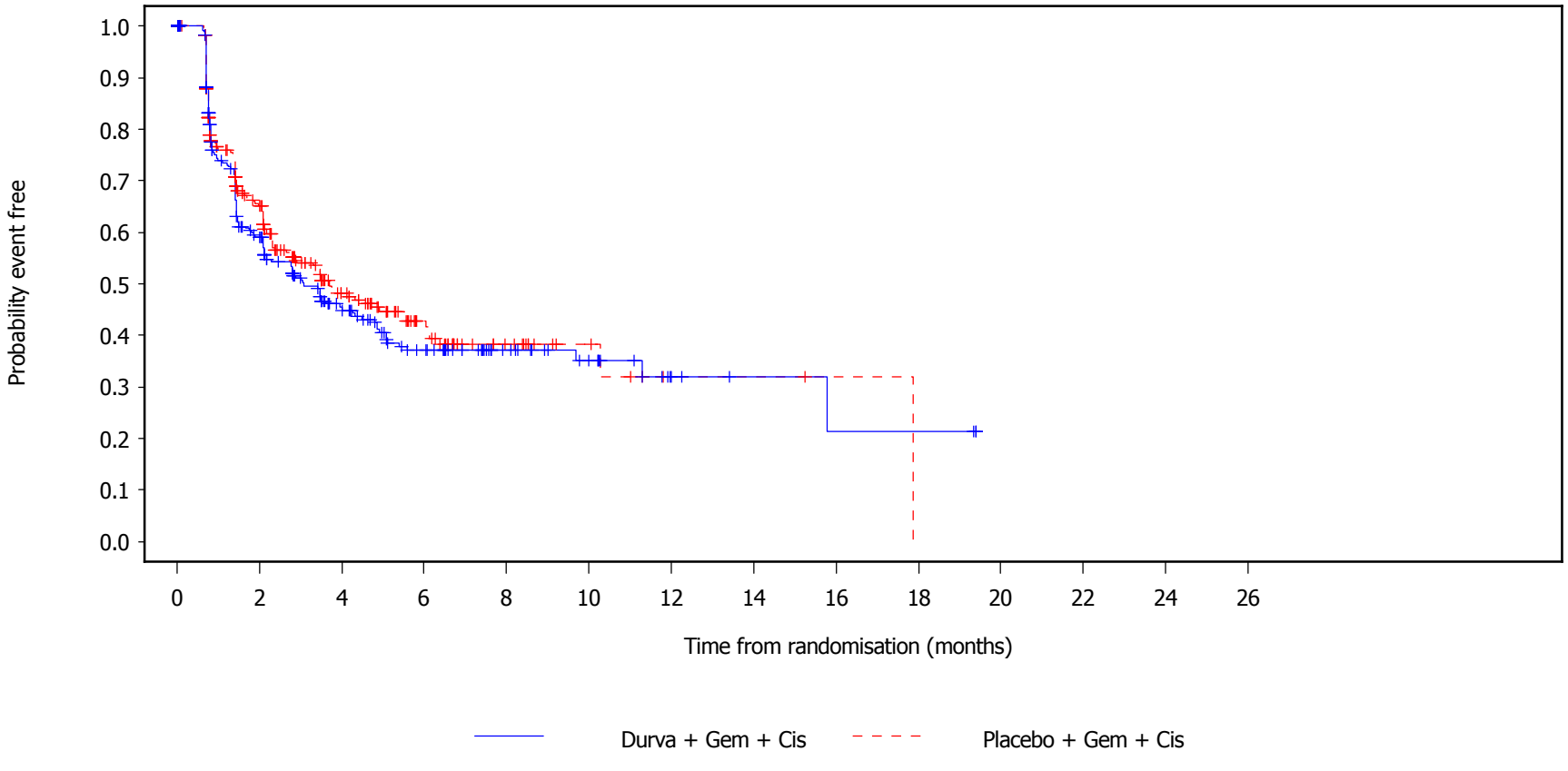


Number of patients at risk:

405	184	107	71	41	23	7	4	3	3	1	1	0	0	Durva + Gem + Cis
404	180	90	53	22	12	3	2	1	1	0	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.2.3.6 TOPAZ: Kaplan-Meier plot of EORTC QLQ-C30 Time to Deterioration - Functional scale: Social
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

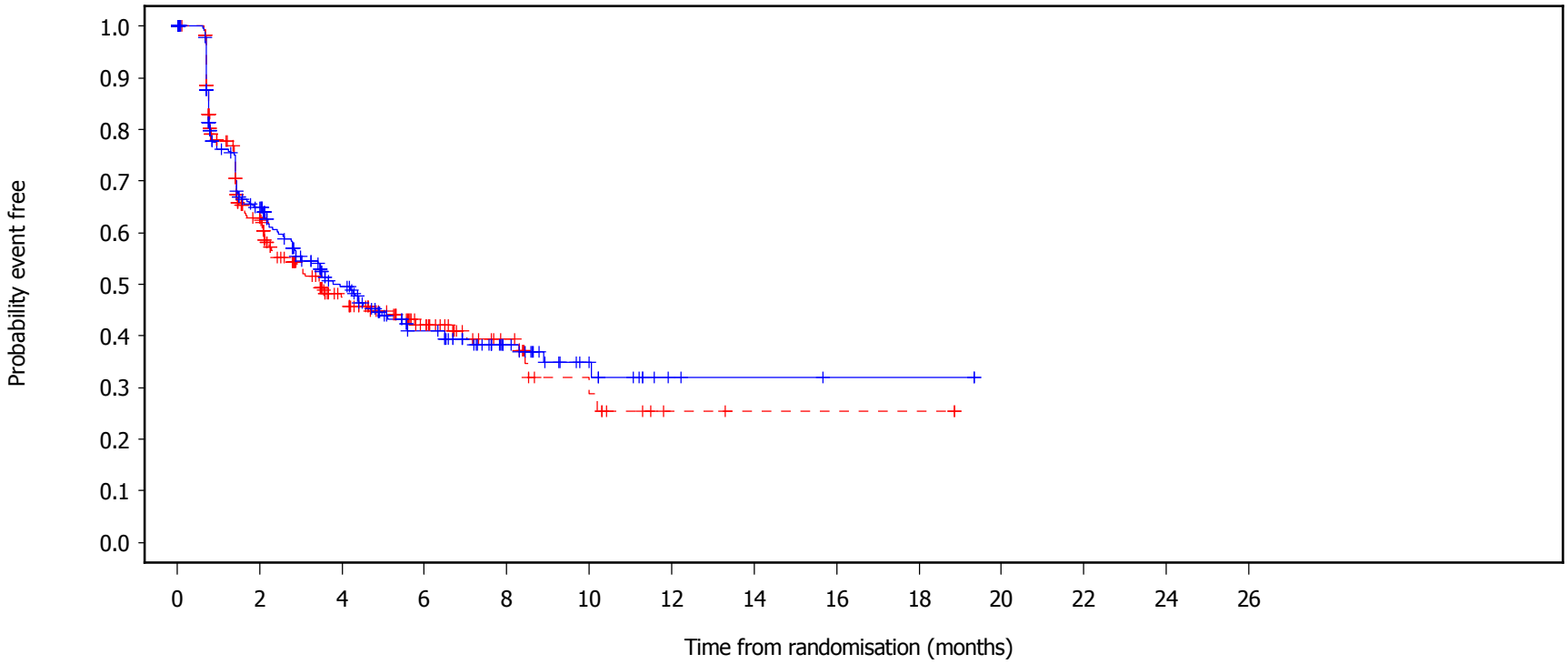


Number of patients at risk:

405	143	80	51	26	16	5	3	2	2	0	0	0	0	Durva + Gem + Cis
404	153	74	39	16	7	2	2	1	0	0	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.2.3.7 TOPAZ: Kaplan-Meier plot of EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Loss of appetite
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

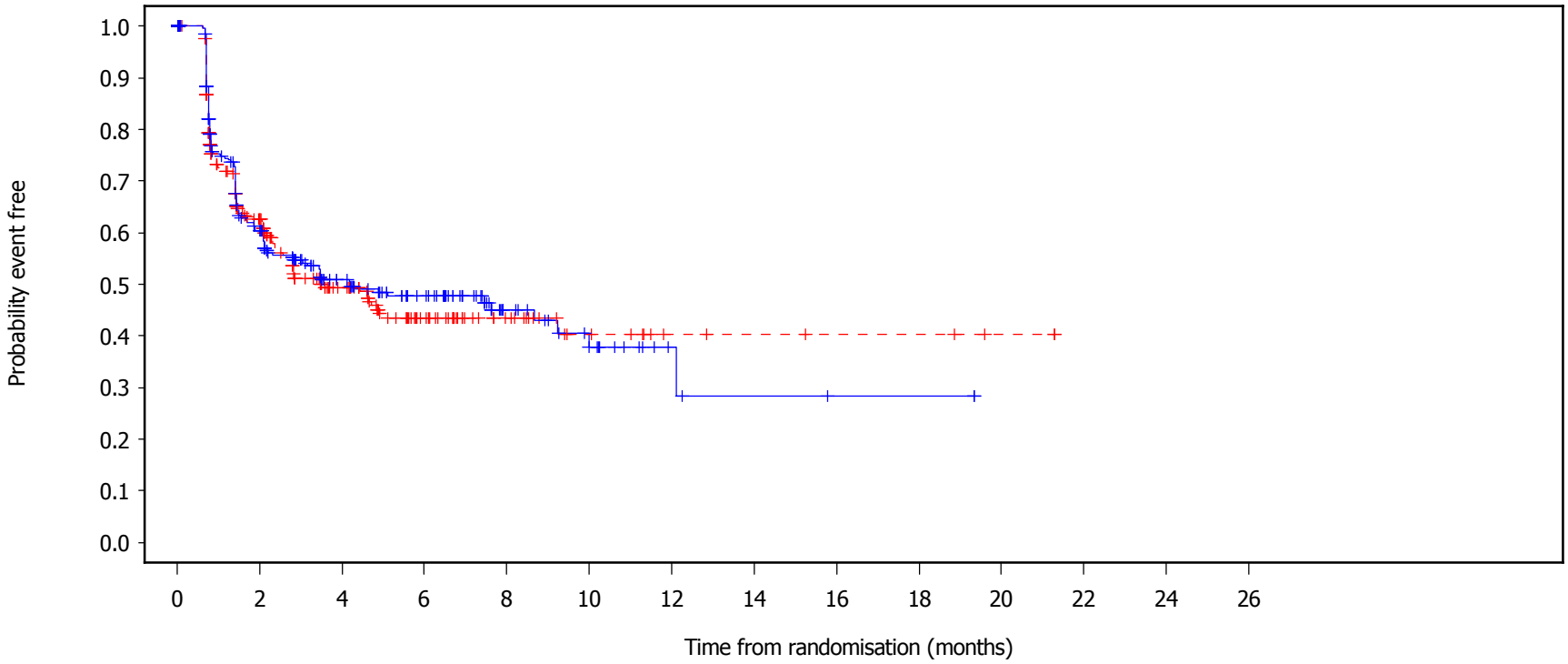


Number of patients at risk:

405	154	85	53	27	12	3	2	1	1	0	0	0	0	Durva + Gem + Cis
404	149	74	40	20	9	2	1	1	1	0	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.2.3.8 TOPAZ: Kaplan-Meier plot of EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Constipation
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

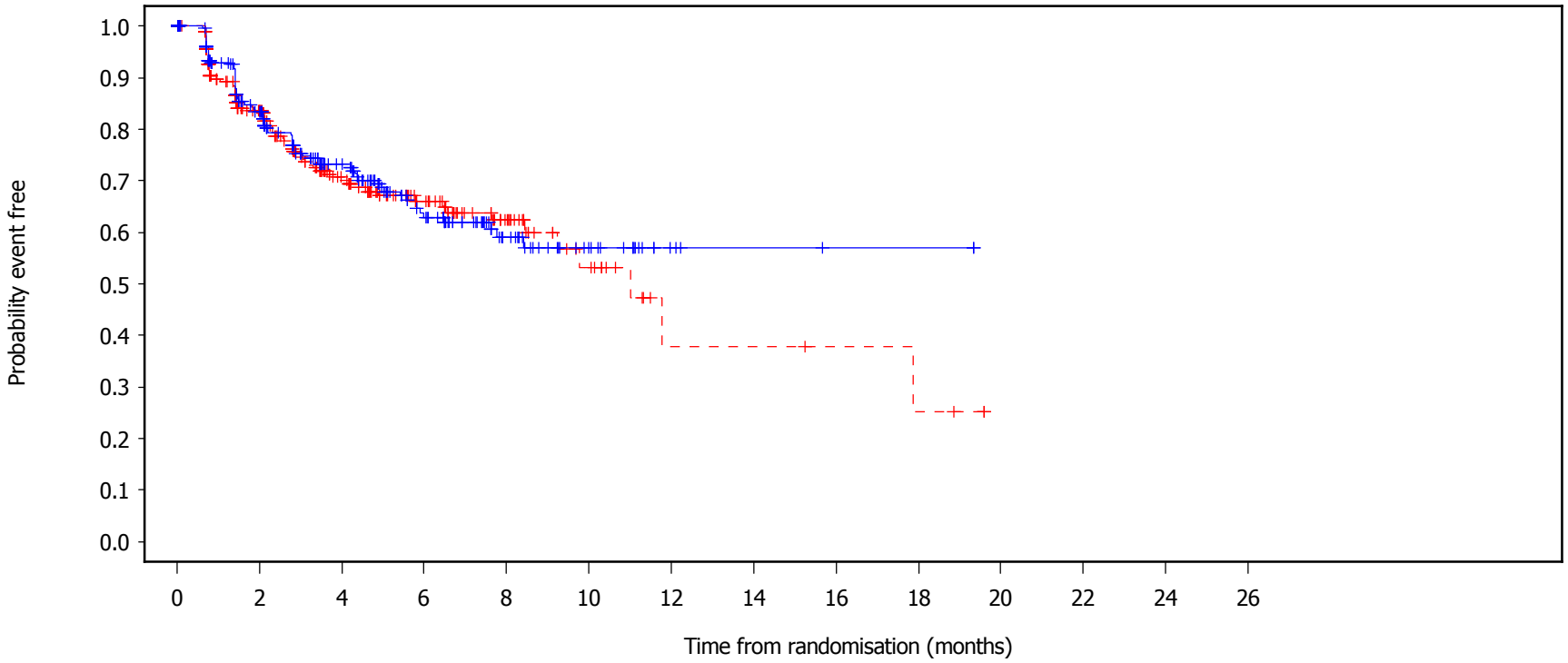


Number of patients at risk:

405	146	84	62	24	13	4	2	1	1	0	0	0	0	Durva + Gem + Cis
404	145	82	43	22	11	5	4	3	3	1	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.2.3.9 TOPAZ: Kaplan-Meier plot of EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Diarrhoea
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

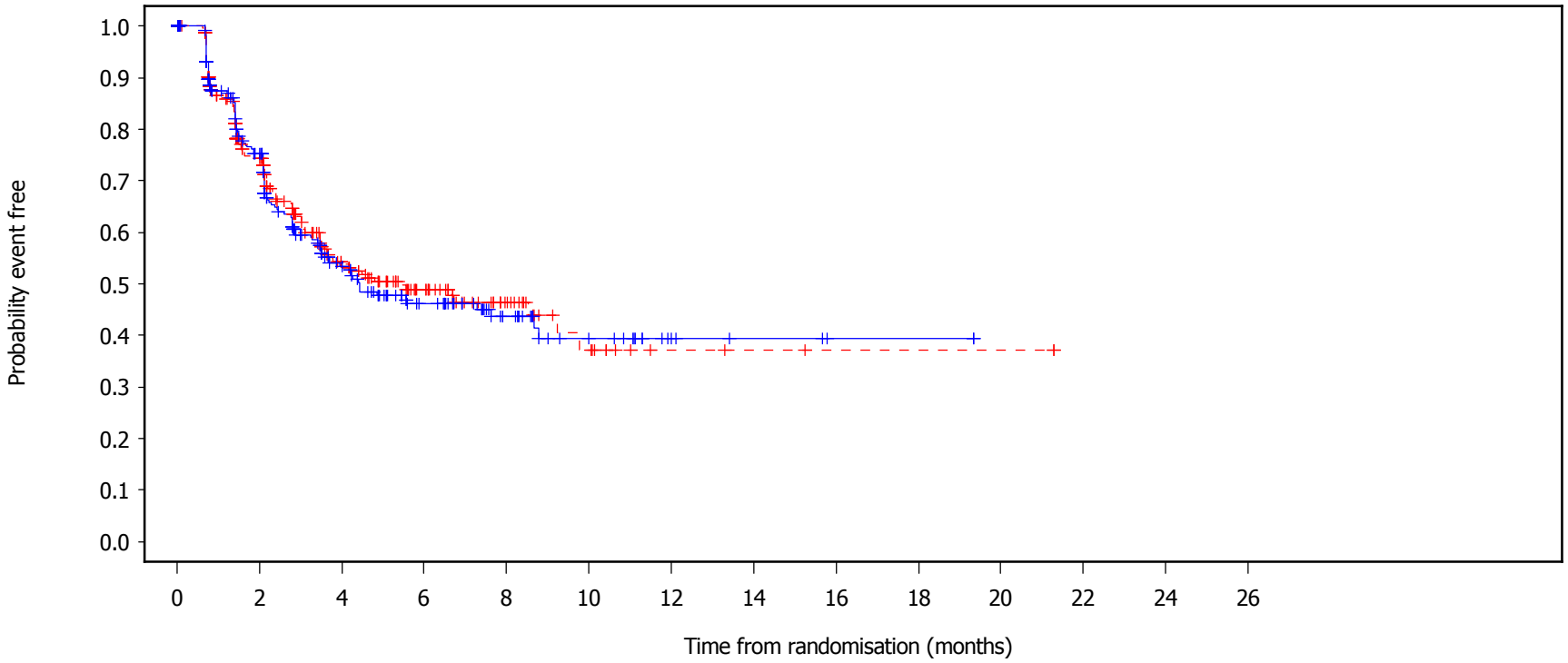


Number of patients at risk:

405	194	121	75	35	17	4	2	1	1	0	0	0	0	Durva + Gem + Cis
404	187	108	66	35	15	4	4	3	2	0	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.2.3.10 TOPAZ: Kaplan-Meier plot of EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Dyspnoea
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

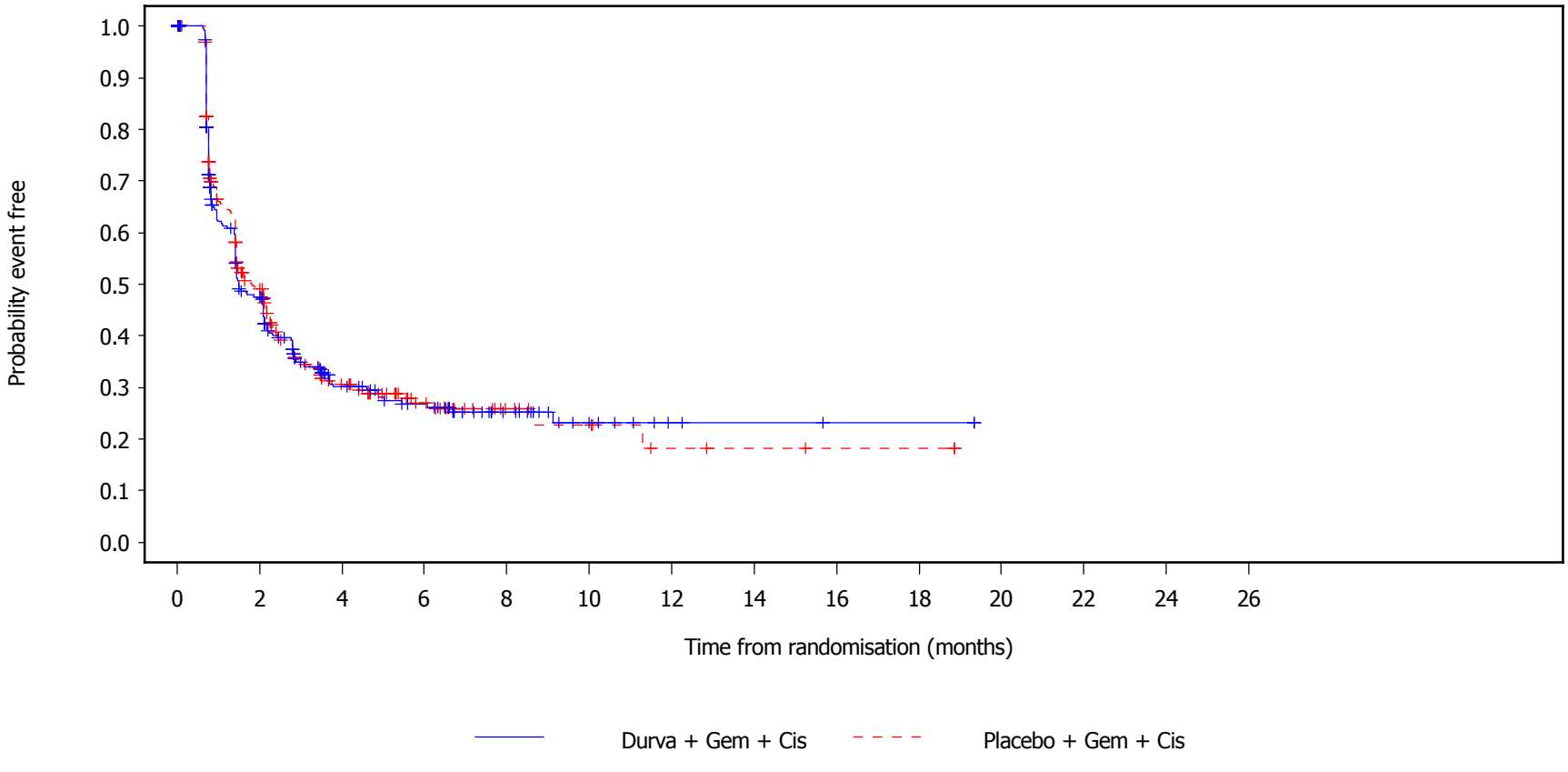


Number of patients at risk:

405	175	88	54	29	15	5	3	1	1	0	0	0	0	Durva + Gem + Cis
404	172	90	52	25	11	3	2	1	1	1	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.2.3.11 TOPAZ: Kaplan-Meier plot of EORTC QLQ-C30 Time to Deterioration - Symptom scale: Fatigue
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

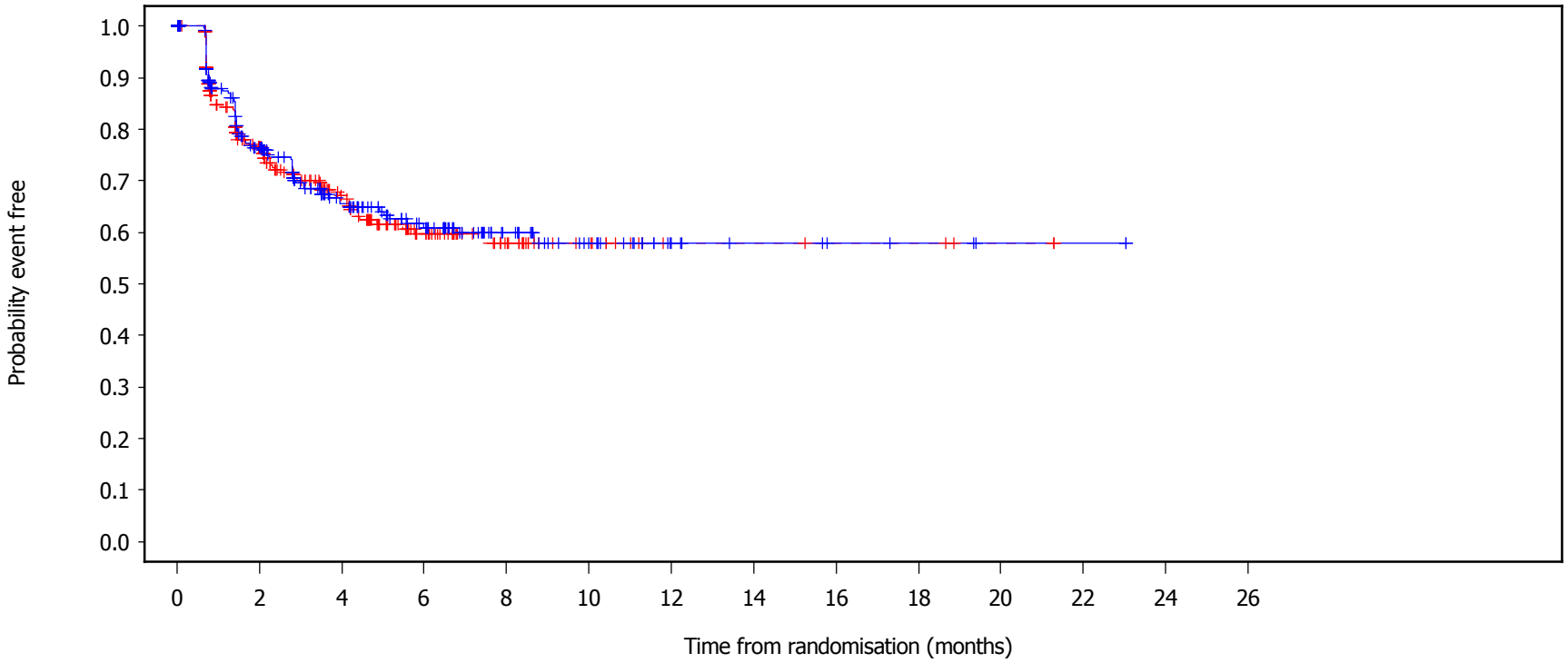


Number of patients at risk:

405	115	51	38	19	8	3	2	1	1	0	0	0	0	Durva + Gem + Cis
404	119	53	27	11	7	3	2	1	1	0	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.2.3.12 TOPAZ: Kaplan-Meier plot of EORTC QLQ-C30 Time to Deterioration - Single item scale: Financial difficulties
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

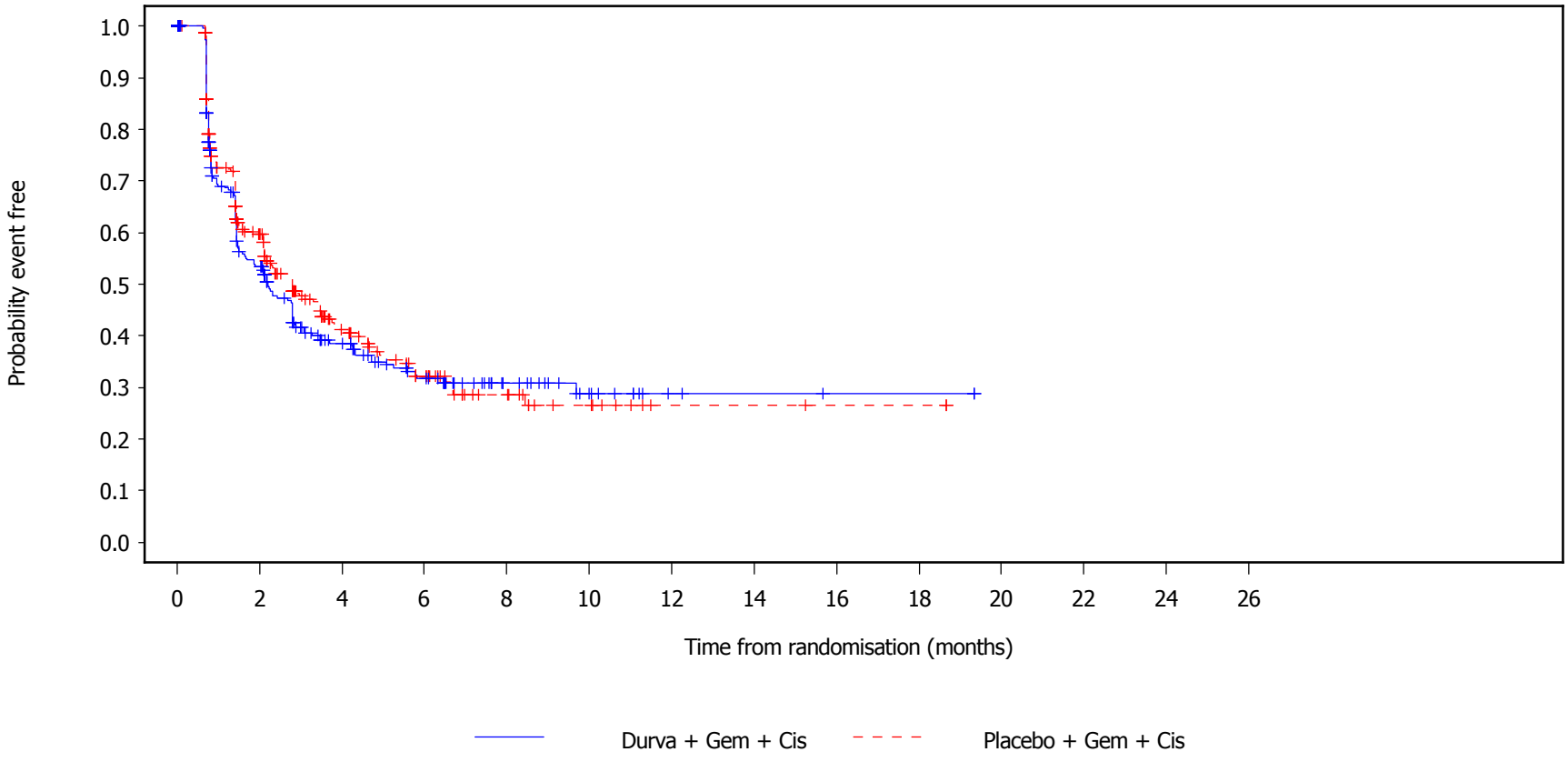


Number of patients at risk:

405	175	103	73	38	23	9	6	4	3	1	1	0	0	Durva + Gem + Cis
404	178	103	57	29	14	4	4	3	3	1	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.2.3.13 TOPAZ: Kaplan-Meier plot of EORTC QLQ-C30 Time to Deterioration - Symptom scale: Nausea and vomiting
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

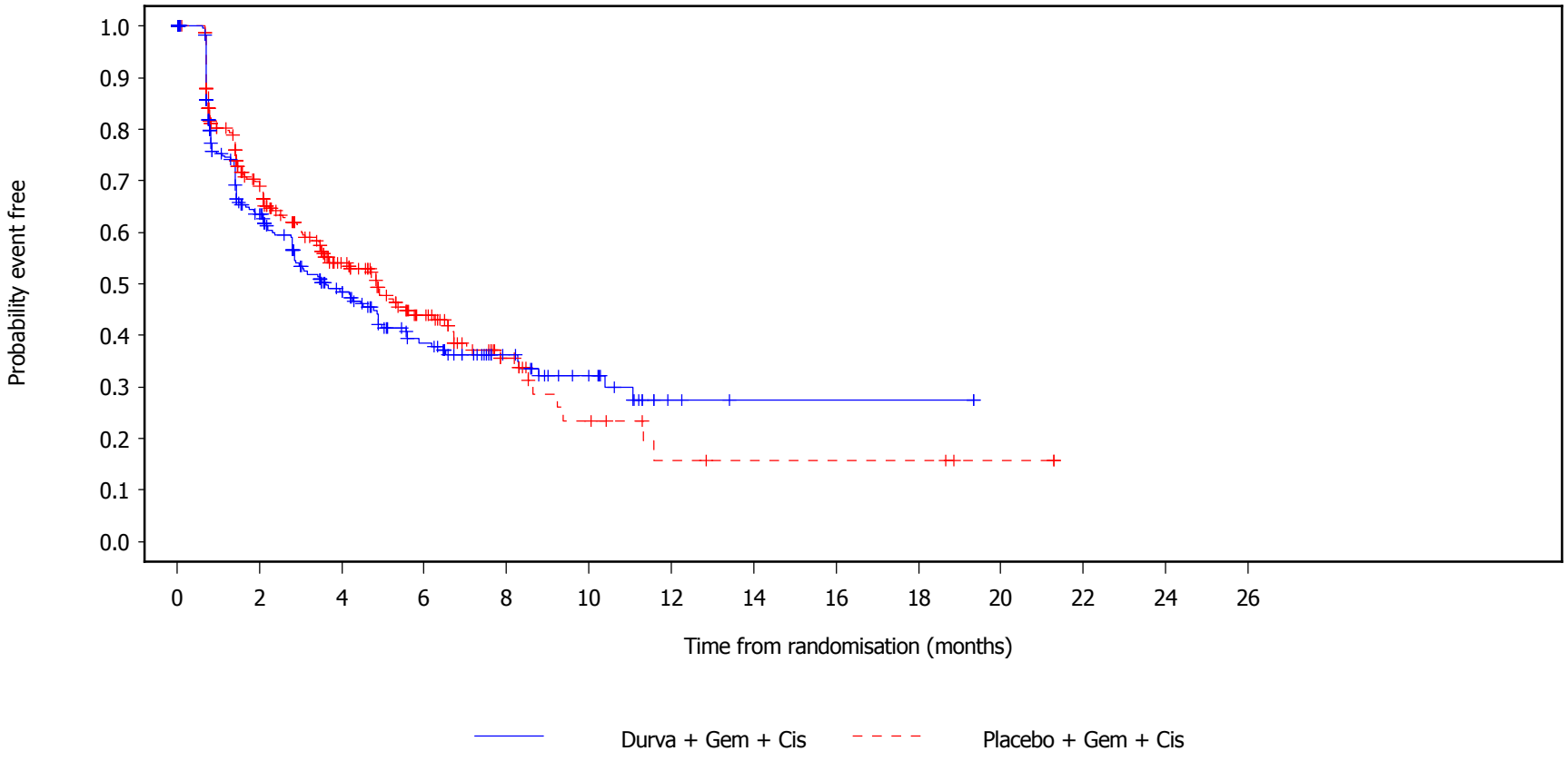


Number of patients at risk:

405	132	70	46	22	11	3	2	1	1	0	0	0	0	Durva + Gem + Cis
404	140	64	36	18	9	2	2	1	1	0	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.2.3.14 TOPAZ: Kaplan-Meier plot of EORTC QLQ-C30 Time to Deterioration - Symptom scale: Pain
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

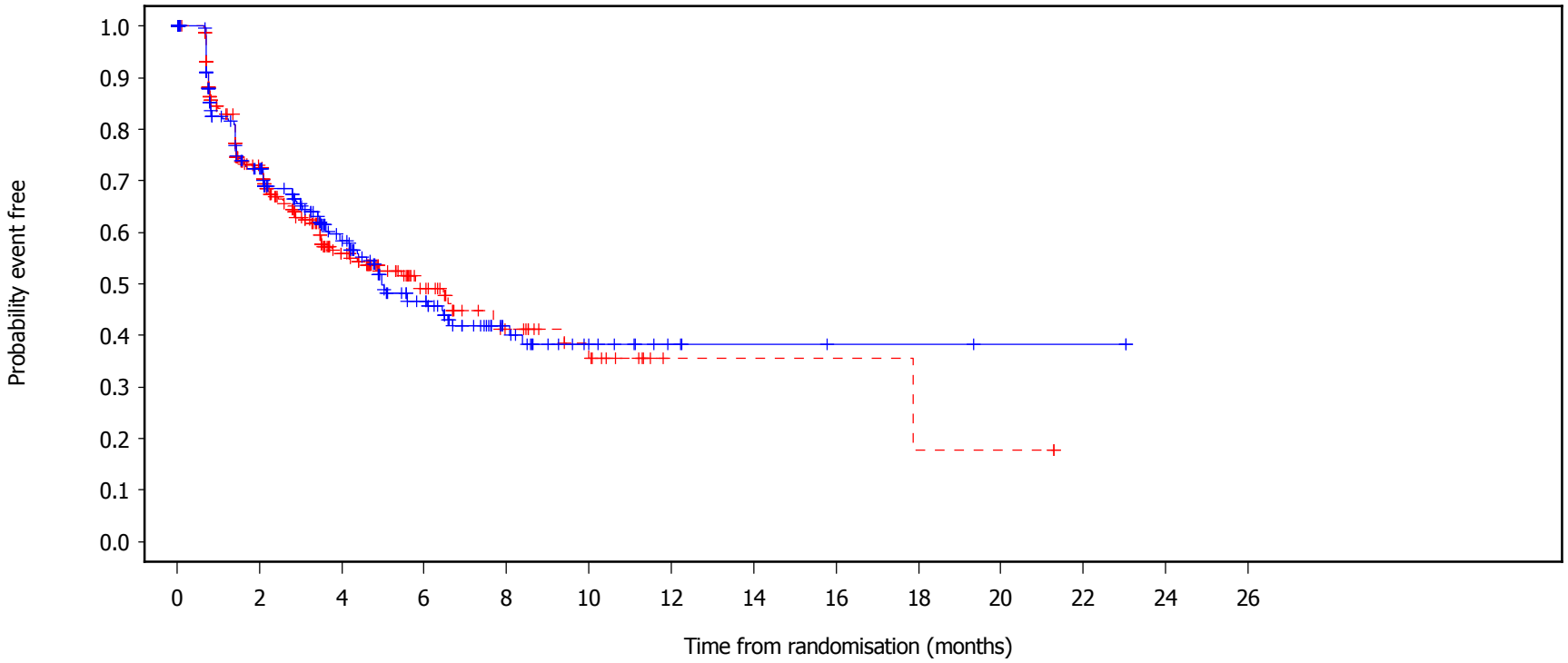


Number of patients at risk:

405	146	83	52	29	17	3	1	1	1	0	0	0	0	Durva + Gem + Cis
404	165	89	48	20	9	4	3	3	3	1	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.2.3.15 TOPAZ: Kaplan-Meier plot of EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Insomnia
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

405	173	97	57	24	11	5	3	2	2	1	1	0	0	Durva + Gem + Cis
404	167	79	40	21	12	2	2	2	1	1	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Table 2.2.4.1 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Global QoL/health status
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	105 (31.9)	5.6 (2.9, 7.4)	334	107 (32.0)	4.9 (2.4, 8.5)	0.96	0.74, 1.26	0.7897
Recurrent	76	40 (52.6)	2.2 (1.5, 4.9)	70	38 (54.3)	2.8 (1.4, 4.8)	0.99	0.63, 1.54	0.9520
Interaction p-value									0.9306
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	27 (37.0)	3.5 (2.1, 8.1)	72	22 (30.6)	5.1 (2.3, NE)	1.35	0.77, 2.39	0.2952
Intrahepatic CCA	236	85 (36.0)	4.7 (2.2, 7.4)	235	93 (39.6)	2.9 (2.1, 6.7)	0.84	0.62, 1.12	0.2317
Gallbladder cancer	96	33 (34.4)	3.9 (1.5, 7.4)	98	30 (30.6)	4.2 (2.1, NE)	1.13	0.69, 1.87	0.6196
Interaction p-value									0.2588
Age Group									
<65	220	76 (34.5)	4.3 (2.9, 7.4)	230	85 (37.0)	4.2 (2.3, 6.7)	0.89	0.65, 1.22	0.4781
>=65	185	69 (37.3)	3.4 (2.1, 5.6)	175	60 (34.3)	3.7 (2.1, NE)	1.08	0.76, 1.52	0.6798
Interaction p-value									0.4344
Region									
Asia	242	108 (44.6)	3.7 (2.2, 5.7)	257	99 (38.5)	4.8 (2.7, 7.4)	1.07	0.81, 1.40	0.6390
Rest of World	163	37 (22.7)	5.6 (2.2, NE)	148	46 (31.1)	3.5 (2.1, 5.8)	0.77	0.50, 1.18	0.2324
Interaction p-value									0.2072
PD-L1 Status									
High (>=1%)	239	90 (37.7)	4.3 (2.2, 6.5)	251	93 (37.1)	3.7 (2.2, 5.8)	0.95	0.71, 1.28	0.7557
Low (<1%)	119	46 (38.7)	3.7 (2.1, 7.3)	117	39 (33.3)	6.7 (2.1, NE)	1.11	0.72, 1.70	0.6426
Interaction p-value									0.5760
Sex									
Male	199	73 (36.7)	3.7 (2.8, 8.1)	208	71 (34.1)	4.9 (2.9, NE)	1.06	0.77, 1.48	0.7102

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.1 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Global QoL/health status
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	72 (35.0)	4.3 (2.1, 6.5)	197	74 (37.6)	2.5 (1.6, 6.7)	0.88	0.63, 1.22	0.4359
Interaction p-value									0.4156
Race									
Asian	249	108 (43.4)	3.7 (2.2, 6.3)	262	100 (38.2)	4.8 (2.7, 7.4)	1.05	0.80, 1.39	0.7005
Non-Asian	156	37 (23.7)	5.6 (2.2, NE)	143	45 (31.5)	3.7 (2.1, 8.3)	0.79	0.51, 1.22	0.2844
Interaction p-value									0.2660
WHO ECOG Status at Screening									
0	189	71 (37.6)	4.3 (2.1, 7.4)	185	69 (37.3)	3.7 (2.3, 6.7)	1.01	0.73, 1.41	0.9354
1	216	74 (34.3)	3.9 (2.2, 6.3)	220	76 (34.5)	4.8 (2.2, 7.5)	0.93	0.68, 1.29	0.6752
Interaction p-value									0.7265
Disease Extent									
Locally Advanced	55	23 (41.8)	3.4 (1.4, 7.4)	73	26 (35.6)	4.6 (2.1, NE)	1.17	0.66, 2.06	0.5806
Metastatic	350	122 (34.9)	4.3 (2.8, 6.5)	331	119 (36.0)	4.2 (2.3, 6.7)	0.94	0.73, 1.21	0.6204
Interaction p-value									0.4791
MSI Status									
MSI High	3	1 (33.3)	5.6 (NE, NE)	2	1 (50.0)	5.3 (NE, NE)	NC	NC	NC
MSI Stable	160	59 (36.9)	5.6 (2.9, 9.6)	168	68 (40.5)	2.7 (1.5, 6.7)	0.78	0.55, 1.10	0.1581
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.2 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Functional scale: Physical
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	105 (31.9)	3.5 (2.8, 7.6)	334	105 (31.4)	4.2 (3.4, 6.5)	1.02	0.78, 1.34	0.8643
Recurrent	76	36 (47.4)	3.4 (2.6, 8.4)	70	33 (47.1)	3.4 (2.1,11.6)	1.01	0.63, 1.63	0.9681
Interaction p-value									0.9599
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	27 (37.0)	4.2 (2.1, 8.4)	72	19 (26.4)	NE (NE, NE)	1.48	0.83, 2.71	0.1849
Intrahepatic CCA	236	84 (35.6)	3.1 (2.6, 8.8)	235	85 (36.2)	3.9 (2.2, 7.7)	0.98	0.73, 1.33	0.9050
Gallbladder cancer	96	30 (31.3)	4.2 (2.8, NE)	98	34 (34.7)	3.7 (1.4, 8.3)	0.87	0.53, 1.41	0.5627
Interaction p-value									0.3534
Age Group									
<65	220	69 (31.4)	6.5 (3.1, NE)	230	76 (33.0)	3.7 (2.8, NE)	0.90	0.65, 1.24	0.5129
>=65	185	72 (38.9)	2.8 (2.1, 4.2)	175	62 (35.4)	4.2 (2.5, 8.3)	1.18	0.84, 1.66	0.3424
Interaction p-value									0.2555
Region									
Asia	242	103 (42.6)	3.4 (2.8, 6.5)	257	99 (38.5)	4.2 (2.8, 7.7)	1.02	0.77, 1.34	0.8918
Rest of World	163	38 (23.3)	5.1 (2.6, NE)	148	39 (26.4)	4.2 (2.2, NE)	1.02	0.65, 1.60	0.9161
Interaction p-value									0.9855
PD-L1 Status									
High (>=1%)	239	90 (37.7)	3.4 (2.8, 6.5)	251	82 (32.7)	5.7 (3.4, 8.5)	1.17	0.86, 1.58	0.3139
Low (<1%)	119	42 (35.3)	3.5 (2.8, NE)	117	45 (38.5)	3.5 (1.5, 5.5)	0.82	0.53, 1.24	0.3435
Interaction p-value									0.1752
Sex									
Male	199	67 (33.7)	4.4 (2.9, 8.8)	208	66 (31.7)	5.6 (3.5, NE)	1.09	0.78, 1.53	0.6194

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.2 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Functional scale: Physical
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	74 (35.9)	2.9 (2.1, 7.6)	197	72 (36.5)	3.4 (1.9, 5.9)	0.95	0.68, 1.31	0.7392
Interaction p-value									0.5556
Race									
Asian	249	103 (41.4)	3.4 (2.8, 6.5)	262	99 (37.8)	4.2 (2.9, 7.7)	1.02	0.77, 1.34	0.8955
Non-Asian	156	38 (24.4)	4.9 (2.1, NE)	143	39 (27.3)	4.2 (2.2, NE)	1.03	0.66, 1.61	0.9057
Interaction p-value									0.9747
WHO ECOG Status at Screening									
0	189	61 (32.3)	5.1 (2.6, NE)	185	56 (30.3)	7.7 (3.7, NE)	1.21	0.84, 1.74	0.3068
1	216	80 (37.0)	3.1 (2.8, 5.6)	220	82 (37.3)	2.9 (1.7, 4.2)	0.88	0.64, 1.19	0.4055
Interaction p-value									0.1875
Disease Extent									
Locally Advanced	55	20 (36.4)	4.2 (1.5, NE)	73	22 (30.1)	11.6 (3.2, NE)	1.27	0.69, 2.34	0.4376
Metastatic	350	121 (34.6)	3.4 (2.8, 6.5)	331	116 (35.0)	3.7 (2.7, 5.9)	0.97	0.75, 1.25	0.7924
Interaction p-value									0.4134
MSI Status									
MSI High	3	1 (33.3)	1.0 (NE, NE)	2	2 (100)	0.8 (0.7, NE)	NC	NC	NC
MSI Stable	160	56 (35.0)	4.2 (3.0, NE)	168	59 (35.1)	5.5 (3.0,11.6)	1.00	0.69, 1.45	0.9841
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.3 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Functional scale: Role
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	122 (37.1)	2.3 (2.1, 3.5)	334	129 (38.6)	2.8 (2.2, 3.7)	1.02	0.80, 1.31	0.8777
Recurrent	76	44 (57.9)	2.1 (1.4, 3.1)	70	42 (60.0)	2.1 (1.4, 4.9)	1.02	0.67, 1.56	0.9333
Interaction p-value									0.9955
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	36 (49.3)	2.1 (1.4, 2.8)	72	32 (44.4)	2.2 (1.4, 4.7)	1.28	0.80, 2.08	0.3068
Intrahepatic CCA	236	90 (38.1)	3.0 (2.1, 4.2)	235	103 (43.8)	2.6 (2.2, 3.6)	0.85	0.64, 1.12	0.2472
Gallbladder cancer	96	40 (41.7)	1.4 (0.8, 3.6)	98	36 (36.7)	2.8 (1.7, 5.9)	1.42	0.90, 2.23	0.1300
Interaction p-value									0.1007
Age Group									
<65	220	90 (40.9)	2.8 (2.1, 4.2)	230	98 (42.6)	2.3 (2.1, 3.5)	0.92	0.69, 1.23	0.5831
>=65	185	76 (41.1)	2.1 (1.7, 2.9)	175	73 (41.7)	3.1 (2.1, 4.9)	1.17	0.85, 1.61	0.3483
Interaction p-value									0.2871
Region									
Asia	242	114 (47.1)	2.8 (2.1, 3.5)	257	127 (49.4)	2.3 (2.1, 3.5)	0.90	0.69, 1.15	0.3926
Rest of World	163	52 (31.9)	2.1 (1.4, 2.8)	148	44 (29.7)	3.5 (2.0, 8.5)	1.43	0.96, 2.14	0.0825
Interaction p-value									0.0542
PD-L1 Status									
High (>=1%)	239	101 (42.3)	2.5 (2.1, 3.1)	251	110 (43.8)	2.3 (2.1, 3.7)	0.98	0.74, 1.28	0.8632
Low (<1%)	119	53 (44.5)	2.1 (1.4, 3.6)	117	49 (41.9)	2.4 (1.4, 4.9)	1.09	0.74, 1.62	0.6495
Interaction p-value									0.6370
Sex									
Male	199	77 (38.7)	2.9 (2.1, 4.2)	208	87 (41.8)	3.0 (2.1, 4.9)	0.91	0.67, 1.23	0.5319

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.3 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Functional scale: Role
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	89 (43.2)	1.9 (1.4, 2.8)	197	84 (42.6)	2.3 (1.9, 3.5)	1.15	0.85, 1.55	0.3558
Interaction p-value									0.2744
Race									
Asian	249	114 (45.8)	2.8 (2.1, 3.6)	262	127 (48.5)	2.3 (2.1, 3.6)	0.89	0.69, 1.15	0.3844
Non-Asian	156	52 (33.3)	2.1 (1.4, 2.8)	143	44 (30.8)	2.8 (2.0, 8.5)	1.44	0.96, 2.16	0.0750
Interaction p-value									0.0489*
WHO ECOG Status at Screening									
0	189	82 (43.4)	2.1 (1.4, 2.9)	185	79 (42.7)	3.5 (2.2, 5.0)	1.28	0.94, 1.74	0.1212
1	216	84 (38.9)	2.8 (2.1, 3.8)	220	92 (41.8)	2.3 (1.5, 3.1)	0.83	0.62, 1.12	0.2272
Interaction p-value									0.0504
Disease Extent									
Locally Advanced	55	25 (45.5)	2.2 (1.4, 4.6)	73	31 (42.5)	2.8 (2.1,10.0)	1.15	0.67, 1.94	0.6158
Metastatic	350	141 (40.3)	2.5 (2.1, 3.0)	331	140 (42.3)	2.3 (2.1, 3.7)	0.99	0.78, 1.25	0.9459
Interaction p-value									0.6262
MSI Status									
MSI High	3	1 (33.3)	1.0 (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	160	72 (45.0)	2.2 (1.9, 3.9)	168	72 (42.9)	3.1 (2.2, 5.0)	1.11	0.80, 1.54	0.5468
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.4 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Functional scale: Cognitive
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	121 (36.8)	2.9 (2.2, 3.7)	334	109 (32.6)	3.8 (2.8, 5.6)	1.15	0.89, 1.49	0.2878
Recurrent	76	37 (48.7)	3.1 (2.1, 5.4)	70	33 (47.1)	4.2 (1.4, 7.7)	1.03	0.64, 1.65	0.9058
Interaction p-value									0.6826
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	29 (39.7)	2.8 (1.5, 3.7)	72	28 (38.9)	2.8 (1.4, 5.6)	1.06	0.63, 1.78	0.8400
Intrahepatic CCA	236	93 (39.4)	3.5 (2.6, 4.9)	235	87 (37.0)	3.7 (2.4, 5.7)	1.04	0.77, 1.39	0.8153
Gallbladder cancer	96	36 (37.5)	2.9 (1.5, 4.7)	98	27 (27.6)	5.2 (2.3, NE)	1.50	0.91, 2.49	0.1118
Interaction p-value									0.4431
Age Group									
<65	220	91 (41.4)	3.5 (2.8, 4.3)	230	80 (34.8)	4.6 (2.8, 7.6)	1.17	0.87, 1.58	0.3046
>=65	185	67 (36.2)	2.9 (2.1, 4.2)	175	62 (35.4)	3.5 (2.3, 5.6)	1.06	0.75, 1.50	0.7345
Interaction p-value									0.6766
Region									
Asia	242	114 (47.1)	2.9 (2.2, 3.6)	257	101 (39.3)	3.8 (2.8, 5.6)	1.15	0.88, 1.51	0.3011
Rest of World	163	44 (27.0)	3.5 (2.6, 4.9)	148	41 (27.7)	4.2 (2.0, NE)	1.05	0.69, 1.61	0.8145
Interaction p-value									0.7249
PD-L1 Status									
High (>=1%)	239	97 (40.6)	2.9 (2.2, 3.5)	251	86 (34.3)	4.4 (2.8, 5.7)	1.22	0.91, 1.63	0.1844
Low (<1%)	119	48 (40.3)	3.6 (2.2, 4.9)	117	43 (36.8)	3.7 (2.1,10.2)	1.08	0.71, 1.63	0.7204
Interaction p-value									0.6371
Sex									
Male	199	80 (40.2)	2.9 (2.2, 4.2)	208	72 (34.6)	4.2 (2.4, 7.6)	1.16	0.84, 1.59	0.3744

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.4 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Functional scale: Cognitive
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	78 (37.9)	3.4 (2.2, 4.7)	197	70 (35.5)	3.7 (2.4, 5.6)	1.09	0.79, 1.51	0.6076
Interaction p-value									0.7962
Race									
Asian	249	114 (45.8)	2.9 (2.2, 4.2)	262	102 (38.9)	3.8 (2.8, 5.6)	1.13	0.87, 1.48	0.3555
Non-Asian	156	44 (28.2)	3.5 (2.6, 4.7)	143	40 (28.0)	4.2 (2.0, NE)	1.09	0.71, 1.68	0.6850
Interaction p-value									0.8849
WHO ECOG Status at Screening									
0	189	71 (37.6)	3.0 (2.1, 4.7)	185	54 (29.2)	7.6 (4.1, NE)	1.56	1.10, 2.23	0.0131*
1	216	87 (40.3)	3.0 (2.8, 3.7)	220	88 (40.0)	2.6 (1.6, 3.7)	0.85	0.63, 1.14	0.2732
Interaction p-value									0.0093*
Disease Extent									
Locally Advanced	55	20 (36.4)	3.7 (2.9, NE)	73	24 (32.9)	5.4 (2.3, NE)	1.13	0.62, 2.04	0.6917
Metastatic	350	138 (39.4)	2.9 (2.2, 3.5)	331	118 (35.6)	3.3 (2.4, 5.4)	1.11	0.87, 1.42	0.4168
Interaction p-value									0.9548
MSI Status									
MSI High	3	1 (33.3)	1.9 (NE, NE)	2	2 (100)	0.8 (0.7, NE)	NC	NC	NC
MSI Stable	160	71 (44.4)	2.8 (2.1, 3.5)	168	59 (35.1)	5.6 (2.9,10.2)	1.46	1.03, 2.07	0.0329*
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.5 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Functional scale: Emotional
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	75 (22.8)	12.2 (6.3, NE)	334	86 (25.7)	6.5 (4.2, NE)	0.82	0.60, 1.12	0.2151
Recurrent	76	25 (32.9)	NE (NE, NE)	70	25 (35.7)	8.0 (3.5, NE)	0.93	0.53, 1.62	0.7851
Interaction p-value									0.7135
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	21 (28.8)	4.4 (3.1, NE)	72	18 (25.0)	NE (NE, NE)	1.14	0.61, 2.16	0.6819
Intrahepatic CCA	236	64 (27.1)	10.2 (4.4, NE)	235	70 (29.8)	6.7 (3.6,10.4)	0.88	0.62, 1.23	0.4420
Gallbladder cancer	96	15 (15.6)	NE (NE, NE)	98	23 (23.5)	NE (NE, NE)	0.56	0.29, 1.07	0.0783
Interaction p-value									0.2919
Age Group									
<65	220	52 (23.6)	NE (NE, NE)	230	59 (25.7)	10.4 (6.3, NE)	0.84	0.58, 1.22	0.3656
>=65	185	48 (25.9)	7.4 (3.7, NE)	175	52 (29.7)	4.3 (3.5, NE)	0.85	0.57, 1.25	0.4036
Interaction p-value									0.9857
Region									
Asia	242	74 (30.6)	12.2 (4.4, NE)	257	79 (30.7)	7.5 (4.2, NE)	0.89	0.64, 1.22	0.4602
Rest of World	163	26 (16.0)	NE (NE, NE)	148	32 (21.6)	6.8 (3.5, NE)	0.75	0.44, 1.25	0.2667
Interaction p-value									0.5764
PD-L1 Status									
High (>=1%)	239	63 (26.4)	12.2 (3.7, NE)	251	69 (27.5)	6.8 (4.2, NE)	0.88	0.63, 1.24	0.4697
Low (<1%)	119	30 (25.2)	10.2 (4.4, NE)	117	31 (26.5)	7.5 (4.2, NE)	0.89	0.53, 1.47	0.6380
Interaction p-value									0.9864
Sex									
Male	199	44 (22.1)	12.2 (7.4, NE)	208	58 (27.9)	6.7 (3.6, NE)	0.71	0.48, 1.05	0.0894

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.5 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Functional scale: Emotional
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	56 (27.2)	6.3 (3.5, NE)	197	53 (26.9)	8.0 (4.2, NE)	0.99	0.68, 1.44	0.9589
Interaction p-value									0.2351
Race									
Asian	249	74 (29.7)	12.2 (4.4, NE)	262	80 (30.5)	7.5 (4.2, NE)	0.87	0.64, 1.20	0.4073
Non-Asian	156	26 (16.7)	NE (NE, NE)	143	31 (21.7)	6.8 (3.5, NE)	0.77	0.46, 1.30	0.3322
Interaction p-value									0.6909
WHO ECOG Status at Screening									
0	189	40 (21.2)	NE (NE, NE)	185	44 (23.8)	8.0 (6.3, NE)	0.88	0.57, 1.35	0.5460
1	216	60 (27.8)	10.2 (3.5, NE)	220	67 (30.5)	4.2 (2.8, NE)	0.81	0.57, 1.15	0.2494
Interaction p-value									0.7958
Disease Extent									
Locally Advanced	55	13 (23.6)	NE (NE, NE)	73	20 (27.4)	NE (NE, NE)	0.77	0.37, 1.53	0.4553
Metastatic	350	87 (24.9)	10.2 (5.6, NE)	331	91 (27.5)	6.7 (4.2, NE)	0.85	0.63, 1.14	0.2879
Interaction p-value									0.7862
MSI Status									
MSI High	3	1 (33.3)	1.0 (NE, NE)	2	2 (100)	0.8 (0.7, NE)	NC	NC	NC
MSI Stable	160	39 (24.4)	12.2 (6.3, NE)	168	48 (28.6)	7.5 (4.9, NE)	0.75	0.49, 1.15	0.1876
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.6 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Functional scale: Social
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	117 (35.6)	3.0 (2.1, 4.5)	334	104 (31.1)	3.8 (2.9, NE)	1.23	0.94, 1.60	0.1254
Recurrent	76	35 (46.1)	3.9 (1.5,15.8)	70	38 (54.3)	2.1 (1.4, 4.3)	0.73	0.46, 1.15	0.1730
Interaction p-value									0.0518
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	24 (32.9)	5.1 (2.8, NE)	72	22 (30.6)	17.9 (2.0, NE)	1.04	0.58, 1.87	0.8862
Intrahepatic CCA	236	94 (39.8)	2.9 (2.1, 4.8)	235	90 (38.3)	3.5 (2.3, 4.8)	1.06	0.79, 1.41	0.6996
Gallbladder cancer	96	34 (35.4)	2.1 (1.4, NE)	98	30 (30.6)	4.6 (2.1, NE)	1.21	0.74, 2.00	0.4409
Interaction p-value									0.8851
Age Group									
<65	220	80 (36.4)	3.4 (2.1, 4.9)	230	81 (35.2)	3.7 (2.2, NE)	1.06	0.78, 1.44	0.7141
>=65	185	72 (38.9)	2.8 (1.7, 5.1)	175	61 (34.9)	3.7 (2.3, 6.1)	1.12	0.79, 1.58	0.5235
Interaction p-value									0.8205
Region									
Asia	242	108 (44.6)	2.8 (2.1, 4.8)	257	95 (37.0)	4.8 (2.8, NE)	1.22	0.93, 1.61	0.1537
Rest of World	163	44 (27.0)	3.5 (2.1, 5.4)	148	47 (31.8)	2.9 (1.6, 3.7)	0.82	0.54, 1.24	0.3448
Interaction p-value									0.1142
PD-L1 Status									
High (>=1%)	239	90 (37.7)	3.5 (2.1, 5.1)	251	80 (31.9)	6.0 (2.4, NE)	1.20	0.89, 1.63	0.2304
Low (<1%)	119	47 (39.5)	3.1 (2.1, 5.1)	117	46 (39.3)	3.5 (2.1, 5.5)	0.96	0.64, 1.44	0.8334
Interaction p-value									0.3771
Sex									
Male	199	75 (37.7)	3.9 (2.1, 5.1)	208	67 (32.2)	6.1 (3.3, NE)	1.21	0.87, 1.69	0.2567

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.6 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Functional scale: Social
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)						
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]		2-sided p-value [b]
Female	206	77 (37.4)	3.0 (1.7, 4.3)	197	75 (38.1)	2.9 (2.1, 4.2)	0.97	0.71,	1.34	0.8562
Interaction p-value										0.3471
Race										
Asian	249	108 (43.4)	2.8 (2.1, 4.9)	262	96 (36.6)	4.6 (2.8, NE)	1.21	0.92,	1.59	0.1823
Non-Asian	156	44 (28.2)	3.5 (1.9, 5.1)	143	46 (32.2)	2.9 (1.5, 3.7)	0.84	0.56,	1.27	0.4118
Interaction p-value										0.1549
WHO ECOG Status at Screening										
0	189	70 (37.0)	3.0 (1.9, 4.5)	185	67 (36.2)	3.7 (2.3,10.3)	1.20	0.86,	1.68	0.2838
1	216	82 (38.0)	3.5 (2.1, 5.1)	220	75 (34.1)	3.8 (2.1, 6.0)	0.99	0.72,	1.35	0.9308
Interaction p-value										0.3998
Disease Extent										
Locally Advanced	55	18 (32.7)	3.5 (1.4, NE)	73	30 (41.1)	3.5 (2.2, 6.1)	0.77	0.42,	1.37	0.3823
Metastatic	350	134 (38.3)	2.9 (2.1, 4.3)	331	112 (33.8)	3.7 (2.3, 6.3)	1.15	0.90,	1.48	0.2671
Interaction p-value										0.2130
MSI Status										
MSI High	3	1 (33.3)	1.9 (NE, NE)	2	2 (100)	1.2 (0.7, NE)	NC	NC		NC
MSI Stable	160	63 (39.4)	3.6 (2.8, 5.1)	168	65 (38.7)	3.7 (2.1, 6.3)	0.96	0.67,	1.35	0.7967
Interaction p-value										NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.7 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Loss of appetite
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	100 (30.4)	5.0 (3.5, 8.3)	334	110 (32.9)	4.2 (2.4, 6.6)	0.88	0.67, 1.15	0.3413
Recurrent	76	42 (55.3)	2.8 (1.4, 3.6)	70	35 (50.0)	3.0 (1.6, 7.0)	1.25	0.80, 1.97	0.3253
Interaction p-value									0.1825
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	30 (41.1)	3.0 (1.4, 4.4)	72	32 (44.4)	2.2 (1.4, 3.1)	0.94	0.57, 1.54	0.7938
Intrahepatic CCA	236	77 (32.6)	5.0 (2.9, NE)	235	80 (34.0)	5.3 (3.1, 8.5)	0.91	0.67, 1.25	0.5771
Gallbladder cancer	96	35 (36.5)	4.3 (1.8, 5.6)	98	33 (33.7)	3.4 (2.0,10.0)	1.12	0.69, 1.80	0.6475
Interaction p-value									0.7821
Age Group									
<65	220	78 (35.5)	4.3 (3.0, 5.6)	230	89 (38.7)	3.1 (2.1, 4.2)	0.84	0.62, 1.13	0.2501
>=65	185	64 (34.6)	3.5 (1.8, 8.3)	175	56 (32.0)	6.6 (2.1, 8.5)	1.16	0.81, 1.67	0.4118
Interaction p-value									0.1711
Region									
Asia	242	108 (44.6)	3.6 (2.6, 4.6)	257	112 (43.6)	2.8 (2.1, 4.2)	0.91	0.70, 1.19	0.4985
Rest of World	163	34 (20.9)	5.1 (2.8, NE)	148	33 (22.3)	6.6 (3.5, NE)	1.09	0.68, 1.77	0.7092
Interaction p-value									0.5132
PD-L1 Status									
High (>=1%)	239	91 (38.1)	3.5 (2.5, 4.5)	251	90 (35.9)	2.9 (2.1, 8.5)	0.99	0.74, 1.32	0.9312
Low (<1%)	119	39 (32.8)	4.9 (2.6, NE)	117	45 (38.5)	4.0 (2.1, 5.8)	0.84	0.55, 1.30	0.4375
Interaction p-value									0.5532
Sex									
Male	199	73 (36.7)	3.5 (2.4, 5.6)	208	79 (38.0)	3.0 (2.1, 7.0)	0.93	0.68, 1.28	0.6556

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.7 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Loss of appetite
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	69 (33.5)	4.5 (2.9, 6.5)	197	66 (33.5)	3.6 (2.8, 8.3)	1.00	0.71, 1.40	0.9912
Interaction p-value									0.7656
Race									
Asian	249	108 (43.4)	3.6 (2.6, 4.6)	262	113 (43.1)	2.4 (2.1, 4.0)	0.90	0.69, 1.17	0.4396
Non-Asian	156	34 (21.8)	5.1 (2.3, NE)	143	32 (22.4)	6.6 (3.5, NE)	1.14	0.70, 1.86	0.5906
Interaction p-value									0.3992
WHO ECOG Status at Screening									
0	189	61 (32.3)	4.9 (3.0, NE)	185	63 (34.1)	4.2 (3.1, 8.5)	1.01	0.71, 1.43	0.9694
1	216	81 (37.5)	3.5 (2.2, 4.6)	220	82 (37.3)	2.4 (1.6, 4.7)	0.91	0.67, 1.24	0.5536
Interaction p-value									0.6757
Disease Extent									
Locally Advanced	55	20 (36.4)	3.0 (1.4, NE)	73	31 (42.5)	3.1 (1.7, 8.4)	0.85	0.48, 1.48	0.5620
Metastatic	350	122 (34.9)	4.3 (2.9, 5.6)	331	114 (34.4)	3.6 (2.4, 6.6)	0.99	0.77, 1.28	0.9367
Interaction p-value									0.6211
MSI Status									
MSI High	3	1 (33.3)	1.0 (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	160	54 (33.8)	4.5 (3.5, NE)	168	65 (38.7)	3.1 (1.7, 7.0)	0.81	0.56, 1.16	0.2484
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.8 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Constipation
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	110 (33.4)	3.5 (2.1, 8.7)	334	109 (32.6)	4.4 (2.5, NE)	1.05	0.81, 1.37	0.7051
Recurrent	76	25 (32.9)	NE (NE, NE)	70	30 (42.9)	3.5 (1.4, NE)	0.71	0.42, 1.21	0.2096
Interaction p-value									0.1966
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	26 (35.6)	4.2 (1.9,10.0)	72	22 (30.6)	4.7 (2.1, NE)	1.13	0.64, 2.02	0.6627
Intrahepatic CCA	236	79 (33.5)	4.3 (2.2, NE)	235	91 (38.7)	2.6 (1.6, 5.1)	0.81	0.60, 1.09	0.1699
Gallbladder cancer	96	30 (31.3)	2.3 (1.4, NE)	98	26 (26.5)	4.9 (2.9, NE)	1.40	0.83, 2.38	0.2092
Interaction p-value									0.1703
Age Group									
<65	220	64 (29.1)	9.2 (4.2, NE)	230	79 (34.3)	4.4 (2.3, NE)	0.80	0.57, 1.11	0.1888
>=65	185	71 (38.4)	2.2 (1.7, 4.2)	175	60 (34.3)	2.8 (1.7, NE)	1.19	0.84, 1.68	0.3259
Interaction p-value									0.1059
Region									
Asia	242	86 (35.5)	8.7 (3.2, NE)	257	98 (38.1)	3.5 (2.4, 9.2)	0.88	0.66, 1.18	0.3946
Rest of World	163	49 (30.1)	2.2 (1.4, 7.5)	148	41 (27.7)	3.5 (1.4, NE)	1.17	0.77, 1.77	0.4701
Interaction p-value									0.2803
PD-L1 Status									
High (>=1%)	239	82 (34.3)	3.5 (2.1, NE)	251	84 (33.5)	4.7 (2.5, NE)	0.98	0.72, 1.33	0.9032
Low (<1%)	119	40 (33.6)	7.6 (2.1, NE)	117	45 (38.5)	2.9 (1.8, 9.2)	0.86	0.56, 1.31	0.4782
Interaction p-value									0.6127
Sex									
Male	199	61 (30.7)	8.7 (3.2, NE)	208	73 (35.1)	4.4 (2.4, NE)	0.84	0.60, 1.18	0.3235

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.8 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Constipation
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	74 (35.9)	2.3 (1.5, 7.5)	197	66 (33.5)	3.5 (2.1, NE)	1.10	0.79, 1.54	0.5671
Interaction p-value									0.2687
Race									
Asian	249	87 (34.9)	8.7 (3.2, NE)	262	99 (37.8)	3.5 (2.4, 9.2)	0.88	0.66, 1.18	0.3952
Non-Asian	156	48 (30.8)	2.3 (1.4, 7.5)	143	40 (28.0)	4.4 (1.4, NE)	1.17	0.77, 1.79	0.4597
Interaction p-value									0.2753
WHO ECOG Status at Screening									
0	189	68 (36.0)	3.5 (1.5, 7.6)	185	68 (36.8)	2.8 (2.1, NE)	1.06	0.76, 1.48	0.7434
1	216	67 (31.0)	8.7 (2.2, NE)	220	71 (32.3)	4.6 (2.8, NE)	0.89	0.64, 1.25	0.5071
Interaction p-value									0.4841
Disease Extent									
Locally Advanced	55	17 (30.9)	9.2 (1.5, NE)	73	18 (24.7)	NE (NE, NE)	1.28	0.66, 2.50	0.4598
Metastatic	350	118 (33.7)	4.2 (2.1, 8.7)	331	121 (36.6)	2.8 (2.2, 4.6)	0.91	0.70, 1.17	0.4427
Interaction p-value									0.3352
MSI Status									
MSI High	3	1 (33.3)	1.9 (NE, NE)	2	2 (100)	0.8 (0.7, NE)	NC	NC	NC
MSI Stable	160	66 (41.3)	2.2 (1.5, 4.2)	168	70 (41.7)	2.5 (1.6, 4.4)	0.98	0.70, 1.37	0.9129
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.9 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Diarrhoea
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	58 (17.6)	NE (NE, NE)	334	65 (19.5)	9.8 (8.4, NE)	0.87	0.61, 1.23	0.4272
Recurrent	76	23 (30.3)	NE (NE, NE)	70	19 (27.1)	11.8 (7.7, NE)	1.22	0.66, 2.26	0.5263
Interaction p-value									0.3436
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	15 (20.5)	NE (NE, NE)	72	15 (20.8)	17.9 (NE, NE)	0.89	0.43, 1.84	0.7585
Intrahepatic CCA	236	45 (19.1)	NE (NE, NE)	235	49 (20.9)	11.0 (8.4, NE)	0.88	0.58, 1.31	0.5196
Gallbladder cancer	96	21 (21.9)	6.5 (4.4, NE)	98	20 (20.4)	9.8 (6.5, NE)	1.19	0.64, 2.21	0.5822
Interaction p-value									0.7073
Age Group									
<65	220	47 (21.4)	NE (NE, NE)	230	48 (20.9)	9.8 (9.2, NE)	0.99	0.66, 1.48	0.9611
>=65	185	34 (18.4)	NE (NE, NE)	175	36 (20.6)	11.8 (8.4, NE)	0.89	0.55, 1.42	0.6129
Interaction p-value									0.7248
Region									
Asia	242	60 (24.8)	NE (NE, NE)	257	59 (23.0)	11.0 (8.4,17.9)	1.03	0.72, 1.47	0.8847
Rest of World	163	21 (12.9)	NE (NE, NE)	148	25 (16.9)	NE (NE, NE)	0.76	0.42, 1.35	0.3473
Interaction p-value									0.3814
PD-L1 Status									
High (>=1%)	239	47 (19.7)	NE (NE, NE)	251	48 (19.1)	11.8 (9.8, NE)	0.98	0.65, 1.47	0.9256
Low (<1%)	119	24 (20.2)	NE (NE, NE)	117	27 (23.1)	11.0 (5.8, NE)	0.83	0.48, 1.45	0.5164
Interaction p-value									0.6395
Sex									
Male	199	34 (17.1)	NE (NE, NE)	208	42 (20.2)	11.8 (8.4, NE)	0.82	0.52, 1.28	0.3815

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.9 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Diarrhoea
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	47 (22.8)	8.4 (5.6, NE)	197	42 (21.3)	9.8 (6.6, NE)	1.06	0.70, 1.61	0.7927
Interaction p-value									0.4115
Race									
Asian	249	60 (24.1)	NE (NE, NE)	262	59 (22.5)	11.0 (8.4,17.9)	1.02	0.71, 1.47	0.8932
Non-Asian	156	21 (13.5)	NE (NE, NE)	143	25 (17.5)	NE (NE, NE)	0.76	0.42, 1.36	0.3530
Interaction p-value									0.3897
WHO ECOG Status at Screening									
0	189	37 (19.6)	NE (NE, NE)	185	45 (24.3)	9.2 (7.7, NE)	0.83	0.54, 1.29	0.4136
1	216	44 (20.4)	NE (NE, NE)	220	39 (17.7)	11.0 (9.8, NE)	1.07	0.69, 1.65	0.7611
Interaction p-value									0.4269
Disease Extent									
Locally Advanced	55	12 (21.8)	NE (NE, NE)	73	13 (17.8)	9.8 (7.7, NE)	1.31	0.59, 2.89	0.5015
Metastatic	350	69 (19.7)	NE (NE, NE)	331	71 (21.5)	11.0 (9.2, NE)	0.87	0.63, 1.22	0.4249
Interaction p-value									0.3533
MSI Status									
MSI High	3	1 (33.3)	5.6 (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	160	32 (20.0)	NE (NE, NE)	168	37 (22.0)	17.9 (7.7, NE)	0.92	0.57, 1.48	0.7331
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.10 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Dyspnoea
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	90 (27.4)	5.6 (3.5, NE)	334	94 (28.1)	5.6 (3.6, 9.8)	1.00	0.75, 1.34	0.9971
Recurrent	76	33 (43.4)	3.9 (2.8, 7.3)	70	27 (38.6)	3.5 (2.4, NE)	1.15	0.69, 1.93	0.5845
Interaction p-value									0.6362
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	31 (42.5)	2.8 (2.1, 4.4)	72	23 (31.9)	3.5 (2.4, NE)	1.46	0.86, 2.53	0.1648
Intrahepatic CCA	236	64 (27.1)	8.7 (4.2, NE)	235	75 (31.9)	4.6 (3.1, 9.2)	0.81	0.58, 1.13	0.2167
Gallbladder cancer	96	28 (29.2)	4.4 (2.5, NE)	98	23 (23.5)	9.8 (4.5, NE)	1.44	0.83, 2.52	0.1933
Interaction p-value									0.0801
Age Group									
<65	220	65 (29.5)	5.6 (3.5, NE)	230	74 (32.2)	4.6 (3.5, 9.8)	0.89	0.64, 1.24	0.4883
>=65	185	58 (31.4)	3.7 (2.4, NE)	175	47 (26.9)	8.5 (3.1, NE)	1.27	0.87, 1.88	0.2161
Interaction p-value									0.1653
Region									
Asia	242	91 (37.6)	4.2 (2.8, 8.8)	257	89 (34.6)	4.8 (3.5, 9.8)	1.06	0.79, 1.42	0.6822
Rest of World	163	32 (19.6)	4.9 (3.5, NE)	148	32 (21.6)	8.5 (3.0, NE)	0.98	0.60, 1.60	0.9239
Interaction p-value									0.7706
PD-L1 Status									
High (>=1%)	239	83 (34.7)	3.5 (2.8, 5.6)	251	71 (28.3)	6.7 (3.6, NE)	1.29	0.94, 1.78	0.1113
Low (<1%)	119	32 (26.9)	8.7 (3.7, NE)	117	36 (30.8)	9.2 (3.0, NE)	0.82	0.51, 1.33	0.4275
Interaction p-value									0.1230
Sex									
Male	199	60 (30.2)	7.3 (3.6, NE)	208	62 (29.8)	5.5 (3.5, NE)	1.06	0.74, 1.52	0.7416

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.10 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Dyspnoea
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	63 (30.6)	4.2 (2.8, 7.6)	197	59 (29.9)	5.6 (3.5, NE)	1.01	0.71, 1.44	0.9692
Interaction p-value									0.8369
Race									
Asian	249	91 (36.5)	4.2 (2.8, 8.8)	262	90 (34.4)	4.8 (3.5, 9.8)	1.05	0.78, 1.40	0.7547
Non-Asian	156	32 (20.5)	4.4 (3.5, NE)	143	31 (21.7)	8.5 (3.5, NE)	1.02	0.62, 1.67	0.9519
Interaction p-value									0.9150
WHO ECOG Status at Screening									
0	189	56 (29.6)	4.9 (3.3, NE)	185	59 (31.9)	4.5 (3.5, NE)	1.00	0.69, 1.44	0.9980
1	216	67 (31.0)	4.2 (2.9, NE)	220	62 (28.2)	5.5 (3.5, NE)	1.07	0.76, 1.51	0.7011
Interaction p-value									0.7907
Disease Extent									
Locally Advanced	55	17 (30.9)	4.9 (2.2, NE)	73	24 (32.9)	4.2 (2.8, NE)	0.88	0.47, 1.63	0.6902
Metastatic	350	106 (30.3)	4.4 (3.5, 8.7)	331	97 (29.3)	6.7 (3.5, NE)	1.07	0.81, 1.41	0.6251
Interaction p-value									0.5734
MSI Status									
MSI High	3	1 (33.3)	5.6 (NE, NE)	2	2 (100)	2.7 (0.7, NE)	NC	NC	NC
MSI Stable	160	53 (33.1)	4.2 (3.3, 8.8)	168	53 (31.5)	6.7 (3.1, NE)	1.03	0.70, 1.50	0.8957
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.11 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Symptom scale: Fatigue
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	136 (41.3)	1.5 (1.4, 2.1)	334	145 (43.4)	2.1 (1.4, 2.4)	1.05	0.83, 1.33	0.6722
Recurrent	76	47 (61.8)	2.1 (1.4, 2.8)	70	43 (61.4)	1.4 (0.8, 2.2)	0.96	0.63, 1.45	0.8348
Interaction p-value									0.6968
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	33 (45.2)	2.1 (1.4, 2.2)	72	34 (47.2)	2.2 (1.3, 3.1)	1.15	0.71, 1.85	0.5770
Intrahepatic CCA	236	105 (44.5)	1.7 (1.4, 2.8)	235	117 (49.8)	1.6 (1.4, 2.2)	0.89	0.68, 1.16	0.3775
Gallbladder cancer	96	45 (46.9)	1.4 (0.8, 2.3)	98	37 (37.8)	2.1 (1.4, 5.6)	1.44	0.93, 2.24	0.0983
Interaction p-value									0.1562
Age Group									
<65	220	98 (44.5)	2.1 (1.4, 2.9)	230	110 (47.8)	1.6 (1.4, 2.2)	0.91	0.69, 1.19	0.4838
>=65	185	85 (45.9)	1.4 (1.1, 2.1)	175	78 (44.6)	2.1 (1.4, 2.8)	1.23	0.90, 1.67	0.1881
Interaction p-value									0.1480
Region									
Asia	242	127 (52.5)	1.5 (1.4, 2.1)	257	133 (51.8)	2.1 (1.4, 2.3)	1.02	0.80, 1.29	0.9044
Rest of World	163	56 (34.4)	1.5 (0.9, 2.2)	148	55 (37.2)	1.6 (1.4, 2.2)	1.09	0.75, 1.58	0.6635
Interaction p-value									0.7655
PD-L1 Status									
High (>=1%)	239	112 (46.9)	1.4 (1.4, 2.1)	251	116 (46.2)	2.1 (1.4, 2.2)	1.08	0.84, 1.41	0.5402
Low (<1%)	119	58 (48.7)	1.5 (1.1, 2.2)	117	59 (50.4)	1.4 (1.0, 2.2)	0.97	0.67, 1.39	0.8525
Interaction p-value									0.6113
Sex									
Male	199	88 (44.2)	1.7 (1.4, 2.1)	208	100 (48.1)	2.1 (1.4, 2.8)	1.02	0.77, 1.36	0.8718

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.11 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Symptom scale: Fatigue
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	95 (46.1)	1.4 (1.0, 2.5)	197	88 (44.7)	1.6 (1.4, 2.2)	1.04	0.78, 1.39	0.7852
Interaction p-value									0.9357
Race									
Asian	249	127 (51.0)	1.5 (1.4, 2.2)	262	133 (50.8)	2.1 (1.4, 2.3)	1.01	0.79, 1.29	0.9159
Non-Asian	156	56 (35.9)	1.5 (0.9, 2.2)	143	55 (38.5)	1.5 (1.4, 2.2)	1.09	0.75, 1.58	0.6469
Interaction p-value									0.7448
WHO ECOG Status at Screening									
0	189	87 (46.0)	1.4 (1.4, 2.1)	185	84 (45.4)	2.2 (1.5, 2.8)	1.23	0.91, 1.66	0.1804
1	216	96 (44.4)	2.1 (1.4, 2.8)	220	104 (47.3)	1.4 (1.4, 2.2)	0.89	0.67, 1.17	0.3978
Interaction p-value									0.1193
Disease Extent									
Locally Advanced	55	24 (43.6)	1.5 (0.8, 6.1)	73	35 (47.9)	2.3 (1.5, 3.1)	1.14	0.67, 1.91	0.6154
Metastatic	350	159 (45.4)	1.5 (1.4, 2.1)	331	153 (46.2)	1.5 (1.4, 2.2)	1.00	0.80, 1.25	0.9768
Interaction p-value									0.6517
MSI Status									
MSI High	3	1 (33.3)	1.0 (NE, NE)	2	2 (100)	0.8 (0.7, NE)	NC	NC	NC
MSI Stable	160	80 (50.0)	1.9 (1.4, 2.5)	168	92 (54.8)	1.4 (1.3, 2.2)	0.88	0.65, 1.18	0.3904
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.12 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Single item scale: Financial difficulties
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	70 (21.3)	NE (NE, NE)	334	70 (21.0)	NE (NE, NE)	1.06	0.76, 1.48	0.7220
Recurrent	76	19 (25.0)	NE (NE, NE)	70	23 (32.9)	NE (NE, NE)	0.71	0.38, 1.31	0.2751
Interaction p-value									0.2592
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	14 (19.2)	NE (NE, NE)	72	16 (22.2)	NE (NE, NE)	0.84	0.41, 1.73	0.6368
Intrahepatic CCA	236	51 (21.6)	NE (NE, NE)	235	56 (23.8)	NE (NE, NE)	0.90	0.62, 1.32	0.6050
Gallbladder cancer	96	24 (25.0)	NE (NE, NE)	98	21 (21.4)	NE (NE, NE)	1.27	0.71, 2.31	0.4177
Interaction p-value									0.5734
Age Group									
<65	220	51 (23.2)	NE (NE, NE)	230	53 (23.0)	NE (NE, NE)	1.01	0.68, 1.48	0.9712
>=65	185	38 (20.5)	NE (NE, NE)	175	40 (22.9)	NE (NE, NE)	0.92	0.59, 1.44	0.7136
Interaction p-value									0.7634
Region									
Asia	242	63 (26.0)	NE (NE, NE)	257	68 (26.5)	NE (NE, NE)	0.95	0.67, 1.34	0.7567
Rest of World	163	26 (16.0)	NE (NE, NE)	148	25 (16.9)	NE (NE, NE)	1.02	0.59, 1.78	0.9312
Interaction p-value									0.8124
PD-L1 Status									
High (>=1%)	239	50 (20.9)	NE (NE, NE)	251	54 (21.5)	NE (NE, NE)	0.98	0.66, 1.44	0.9131
Low (<1%)	119	30 (25.2)	8.7 (5.2, NE)	117	28 (23.9)	NE (NE, NE)	1.01	0.60, 1.69	0.9837
Interaction p-value									0.9348
Sex									
Male	199	39 (19.6)	NE (NE, NE)	208	48 (23.1)	NE (NE, NE)	0.85	0.56, 1.30	0.4549

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.12 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Single item scale: Financial difficulties
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	50 (24.3)	NE (NE, NE)	197	45 (22.8)	NE (NE, NE)	1.08	0.72, 1.62	0.7038
Interaction p-value									0.4219
Race									
Asian	249	63 (25.3)	NE (NE, NE)	262	69 (26.3)	NE (NE, NE)	0.93	0.66, 1.31	0.6842
Non-Asian	156	26 (16.7)	NE (NE, NE)	143	24 (16.8)	NE (NE, NE)	1.07	0.61, 1.88	0.8057
Interaction p-value									0.6725
WHO ECOG Status at Screening									
0	189	40 (21.2)	NE (NE, NE)	185	36 (19.5)	NE (NE, NE)	1.18	0.76, 1.87	0.4600
1	216	49 (22.7)	NE (NE, NE)	220	57 (25.9)	7.3 (4.2, NE)	0.83	0.56, 1.21	0.3253
Interaction p-value									0.2302
Disease Extent									
Locally Advanced	55	10 (18.2)	NE (NE, NE)	73	16 (21.9)	NE (NE, NE)	0.80	0.35, 1.75	0.5831
Metastatic	350	79 (22.6)	NE (NE, NE)	331	77 (23.3)	NE (NE, NE)	0.99	0.72, 1.35	0.9302
Interaction p-value									0.6336
MSI Status									
MSI High	3	0	NE (NE, NE)	2	2 (100)	2.3 (0.7, NE)	NC	NC	NC
MSI Stable	160	41 (25.6)	NE (NE, NE)	168	38 (22.6)	NE (NE, NE)	1.17	0.75, 1.82	0.4953
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.13 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Symptom scale: Nausea and vomiting
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	127 (38.6)	2.3 (1.7, 3.3)	334	125 (37.4)	3.1 (2.2, 4.6)	1.09	0.85, 1.39	0.5112
Recurrent	76	41 (53.9)	1.5 (1.4, 2.8)	70	39 (55.7)	2.1 (1.4, 3.5)	1.02	0.66, 1.59	0.9244
Interaction p-value									0.8103
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	30 (41.1)	1.5 (1.4, 5.1)	72	26 (36.1)	4.2 (1.4, NE)	1.34	0.79, 2.28	0.2763
Intrahepatic CCA	236	99 (41.9)	2.3 (1.7, 3.3)	235	99 (42.1)	2.9 (2.2, 3.9)	1.03	0.78, 1.37	0.8204
Gallbladder cancer	96	39 (40.6)	2.2 (1.0, 2.9)	98	39 (39.8)	2.1 (1.4, 2.8)	1.00	0.64, 1.56	0.9883
Interaction p-value									0.6510
Age Group									
<65	220	93 (42.3)	2.3 (1.9, 2.9)	230	97 (42.2)	2.7 (1.9, 3.7)	1.00	0.75, 1.33	0.9995
>=65	185	75 (40.5)	1.7 (1.4, 3.1)	175	67 (38.3)	3.3 (2.1, 5.0)	1.18	0.85, 1.64	0.3248
Interaction p-value									0.4565
Region									
Asia	242	122 (50.4)	2.2 (1.5, 2.8)	257	125 (48.6)	2.4 (1.9, 3.0)	1.01	0.79, 1.30	0.9284
Rest of World	163	46 (28.2)	2.3 (1.4, 3.5)	148	39 (26.4)	3.7 (2.1, NE)	1.27	0.83, 1.95	0.2760
Interaction p-value									0.3713
PD-L1 Status									
High (>=1%)	239	102 (42.7)	2.2 (1.4, 2.9)	251	116 (46.2)	2.1 (1.5, 2.8)	0.90	0.69, 1.17	0.4158
Low (<1%)	119	49 (41.2)	2.4 (1.4, 4.3)	117	34 (29.1)	6.6 (3.5, NE)	1.65	1.07, 2.57	0.0240*
Interaction p-value									0.0189*
Sex									
Male	199	78 (39.2)	2.8 (1.9, 4.7)	208	77 (37.0)	3.6 (2.8, 5.6)	1.16	0.85, 1.59	0.3574

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.13 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Symptom scale: Nausea and vomiting
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	90 (43.7)	1.7 (1.4, 2.8)	197	87 (44.2)	1.9 (1.4, 2.9)	0.97	0.72, 1.30	0.8251
Interaction p-value									0.4103
Race									
Asian	249	122 (49.0)	2.2 (1.5, 2.8)	262	126 (48.1)	2.3 (1.9, 3.0)	1.00	0.78, 1.28	0.9911
Non-Asian	156	46 (29.5)	2.2 (1.4, 3.5)	143	38 (26.6)	4.4 (2.1, NE)	1.32	0.86, 2.03	0.2088
Interaction p-value									0.2749
WHO ECOG Status at Screening									
0	189	74 (39.2)	2.8 (1.9, 4.2)	185	71 (38.4)	3.8 (2.1, 6.7)	1.17	0.84, 1.62	0.3524
1	216	94 (43.5)	1.6 (1.4, 2.8)	220	93 (42.3)	2.7 (1.5, 3.5)	0.99	0.74, 1.32	0.9483
Interaction p-value									0.4591
Disease Extent									
Locally Advanced	55	25 (45.5)	1.9 (1.4, 5.1)	73	32 (43.8)	3.0 (1.9, 4.6)	1.12	0.66, 1.88	0.6791
Metastatic	350	143 (40.9)	2.2 (1.5, 2.8)	331	132 (39.9)	2.8 (2.1, 3.8)	1.07	0.84, 1.35	0.5912
Interaction p-value									0.8755
MSI Status									
MSI High	3	1 (33.3)	1.0 (NE, NE)	2	2 (100)	2.7 (0.7, NE)	NC	NC	NC
MSI Stable	160	66 (41.3)	2.8 (1.5, 5.6)	168	70 (41.7)	2.8 (1.9, 4.4)	0.97	0.69, 1.36	0.8561
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.14 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Symptom scale: Pain
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	117 (35.6)	2.9 (2.2, 4.9)	334	112 (33.5)	4.9 (3.1, 6.7)	1.15	0.89, 1.49	0.2925
Recurrent	76	30 (39.5)	4.9 (3.5, 8.8)	70	32 (45.7)	4.9 (3.4, 7.0)	0.93	0.57, 1.54	0.7880
Interaction p-value									0.4683
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	26 (35.6)	4.5 (2.8, 6.5)	72	23 (31.9)	4.9 (4.7, 7.0)	1.28	0.73, 2.26	0.3924
Intrahepatic CCA	236	85 (36.0)	3.7 (2.9, 5.9)	235	86 (36.6)	4.9 (3.0, 8.3)	1.00	0.74, 1.36	0.9785
Gallbladder cancer	96	36 (37.5)	2.3 (1.4, 5.6)	98	35 (35.7)	3.4 (1.5, 6.6)	1.25	0.78, 2.00	0.3488
Interaction p-value									0.6327
Age Group									
<65	220	81 (36.8)	4.3 (2.9, 5.6)	230	79 (34.3)	4.9 (3.5, 6.7)	1.04	0.76, 1.43	0.7848
>=65	185	66 (35.7)	3.0 (2.1, 5.9)	175	65 (37.1)	4.9 (2.9, 7.0)	1.17	0.83, 1.65	0.3653
Interaction p-value									0.6274
Region									
Asia	242	108 (44.6)	3.5 (2.8, 4.9)	257	99 (38.5)	4.9 (3.5, 6.7)	1.20	0.91, 1.58	0.1873
Rest of World	163	39 (23.9)	3.6 (2.3,11.1)	148	45 (30.4)	4.8 (2.4, 6.7)	0.88	0.57, 1.35	0.5452
Interaction p-value									0.2226
PD-L1 Status									
High (>=1%)	239	92 (38.5)	4.2 (2.8, 5.0)	251	88 (35.1)	4.9 (3.4, 6.7)	1.16	0.87, 1.56	0.3130
Low (<1%)	119	42 (35.3)	3.6 (2.2, 8.3)	117	43 (36.8)	4.8 (2.1, 6.2)	0.93	0.61, 1.43	0.7482
Interaction p-value									0.4028
Sex									
Male	199	62 (31.2)	6.5 (4.2,11.1)	208	69 (33.2)	6.2 (4.7, 7.9)	0.91	0.65, 1.29	0.6126

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.14 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Symptom scale: Pain
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)						
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]		2-sided p-value [b]
Female	206	85 (41.3)	2.2 (1.4, 3.0)	197	75 (38.1)	3.5 (2.5, 4.9)	1.30	0.95,	1.77	0.1001
Interaction p-value										0.1394
Race										
Asian	249	108 (43.4)	3.5 (2.8, 4.9)	262	100 (38.2)	4.9 (3.5, 6.7)	1.19	0.90,	1.56	0.2210
Non-Asian	156	39 (25.0)	3.6 (2.3,11.1)	143	44 (30.8)	4.8 (2.4, 6.7)	0.90	0.58,	1.39	0.6408
Interaction p-value										0.2942
WHO ECOG Status at Screening										
0	189	70 (37.0)	3.5 (1.9, 4.9)	185	67 (36.2)	5.1 (3.6, 7.0)	1.24	0.89,	1.74	0.2027
1	216	77 (35.6)	3.6 (2.8, 6.2)	220	77 (35.0)	4.2 (2.2, 5.7)	0.98	0.71,	1.34	0.8757
Interaction p-value										0.3007
Disease Extent										
Locally Advanced	55	22 (40.0)	4.2 (1.5, 8.3)	73	25 (34.2)	5.3 (3.6,11.6)	1.28	0.72,	2.28	0.3965
Metastatic	350	125 (35.7)	3.5 (2.8, 4.9)	331	119 (36.0)	4.9 (3.1, 6.6)	1.05	0.82,	1.36	0.6804
Interaction p-value										0.5395
MSI Status										
MSI High	3	1 (33.3)	1.0 (NE, NE)	2	2 (100)	0.8 (0.7, NE)	NC	NC		NC
MSI Stable	160	62 (38.8)	3.9 (2.1, 6.5)	168	62 (36.9)	4.8 (3.0, 7.0)	1.16	0.82,	1.66	0.4025
Interaction p-value										NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.15 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Insomnia
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	92 (28.0)	5.6 (4.6, 8.4)	334	90 (26.9)	6.7 (3.7, NE)	1.00	0.75, 1.34	0.9985
Recurrent	76	32 (42.1)	3.9 (2.8, NE)	70	31 (44.3)	4.2 (3.5,10.0)	0.98	0.60, 1.62	0.9474
Interaction p-value									0.9554
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	20 (27.4)	6.4 (3.9, NE)	72	21 (29.2)	5.8 (3.8, NE)	0.82	0.44, 1.51	0.5138
Intrahepatic CCA	236	78 (33.1)	4.9 (3.5, 6.6)	235	73 (31.1)	5.8 (3.3, NE)	1.07	0.78, 1.48	0.6575
Gallbladder cancer	96	26 (27.1)	6.1 (3.0, NE)	98	27 (27.6)	5.5 (3.5,10.0)	0.96	0.56, 1.65	0.8754
Interaction p-value									0.7233
Age Group									
<65	220	73 (33.2)	4.9 (3.5, 8.4)	230	71 (30.9)	5.8 (3.5, 7.9)	1.03	0.74, 1.43	0.8602
>=65	185	51 (27.6)	6.4 (4.2, NE)	175	50 (28.6)	6.7 (3.8, NE)	0.95	0.65, 1.41	0.8151
Interaction p-value									0.7701
Region									
Asia	242	87 (36.0)	5.1 (4.2, 8.1)	257	77 (30.0)	7.9 (4.2, NE)	1.12	0.82, 1.52	0.4788
Rest of World	163	37 (22.7)	4.9 (3.1, 8.4)	148	44 (29.7)	3.7 (1.5, 5.8)	0.78	0.50, 1.20	0.2613
Interaction p-value									0.1849
PD-L1 Status									
High (>=1%)	239	75 (31.4)	5.6 (3.6, NE)	251	77 (30.7)	5.8 (3.5, 7.7)	0.95	0.69, 1.31	0.7717
Low (<1%)	119	39 (32.8)	4.9 (3.9, 6.6)	117	31 (26.5)	7.9 (3.7, NE)	1.29	0.80, 2.08	0.2944
Interaction p-value									0.3032
Sex									
Male	199	62 (31.2)	5.0 (4.2, NE)	208	66 (31.7)	4.9 (3.5, NE)	0.97	0.68, 1.37	0.8648

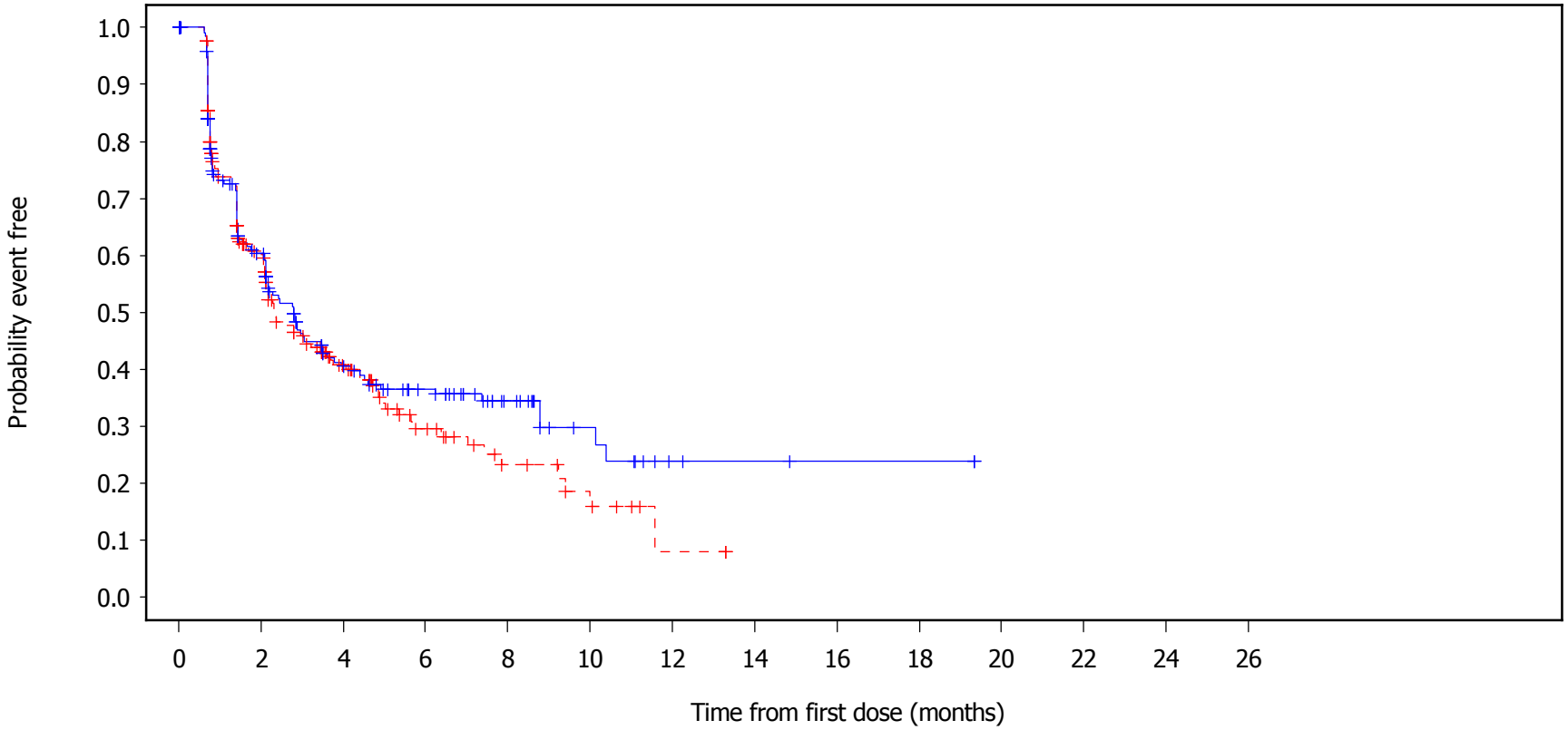
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.2.4.15 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-C30 Time to Deterioration - Single item symptom scale: Insomnia
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	62 (30.1)	4.9 (3.6, 8.4)	197	55 (27.9)	6.5 (3.5, 7.9)	1.03	0.72, 1.48	0.8767
Interaction p-value									0.8181
Race									
Asian	249	88 (35.3)	5.0 (4.2, 8.1)	262	78 (29.8)	7.7 (4.2, NE)	1.12	0.83, 1.52	0.4651
Non-Asian	156	36 (23.1)	4.9 (3.1, 8.4)	143	43 (30.1)	3.7 (1.5, 5.8)	0.77	0.49, 1.19	0.2368
Interaction p-value									0.1651
WHO ECOG Status at Screening									
0	189	59 (31.2)	4.9 (3.4, NE)	185	52 (28.1)	7.9 (3.8, NE)	1.24	0.85, 1.80	0.2611
1	216	65 (30.1)	5.6 (4.4, 8.1)	220	69 (31.4)	4.4 (2.9, 6.6)	0.82	0.58, 1.15	0.2468
Interaction p-value									0.1072
Disease Extent									
Locally Advanced	55	22 (40.0)	4.9 (2.8, 6.5)	73	25 (34.2)	6.7 (1.4, NE)	0.95	0.53, 1.68	0.8515
Metastatic	350	102 (29.1)	5.6 (3.9, NE)	331	96 (29.0)	5.8 (3.7, 9.4)	1.01	0.77, 1.34	0.9300
Interaction p-value									0.8361
MSI Status									
MSI High	3	1 (33.3)	5.6 (NE, NE)	2	2 (100)	2.3 (1.4, NE)	NC	NC	NC
MSI Stable	160	49 (30.6)	6.4 (3.9, NE)	168	54 (32.1)	5.8 (3.5, NE)	0.92	0.62, 1.35	0.6713
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

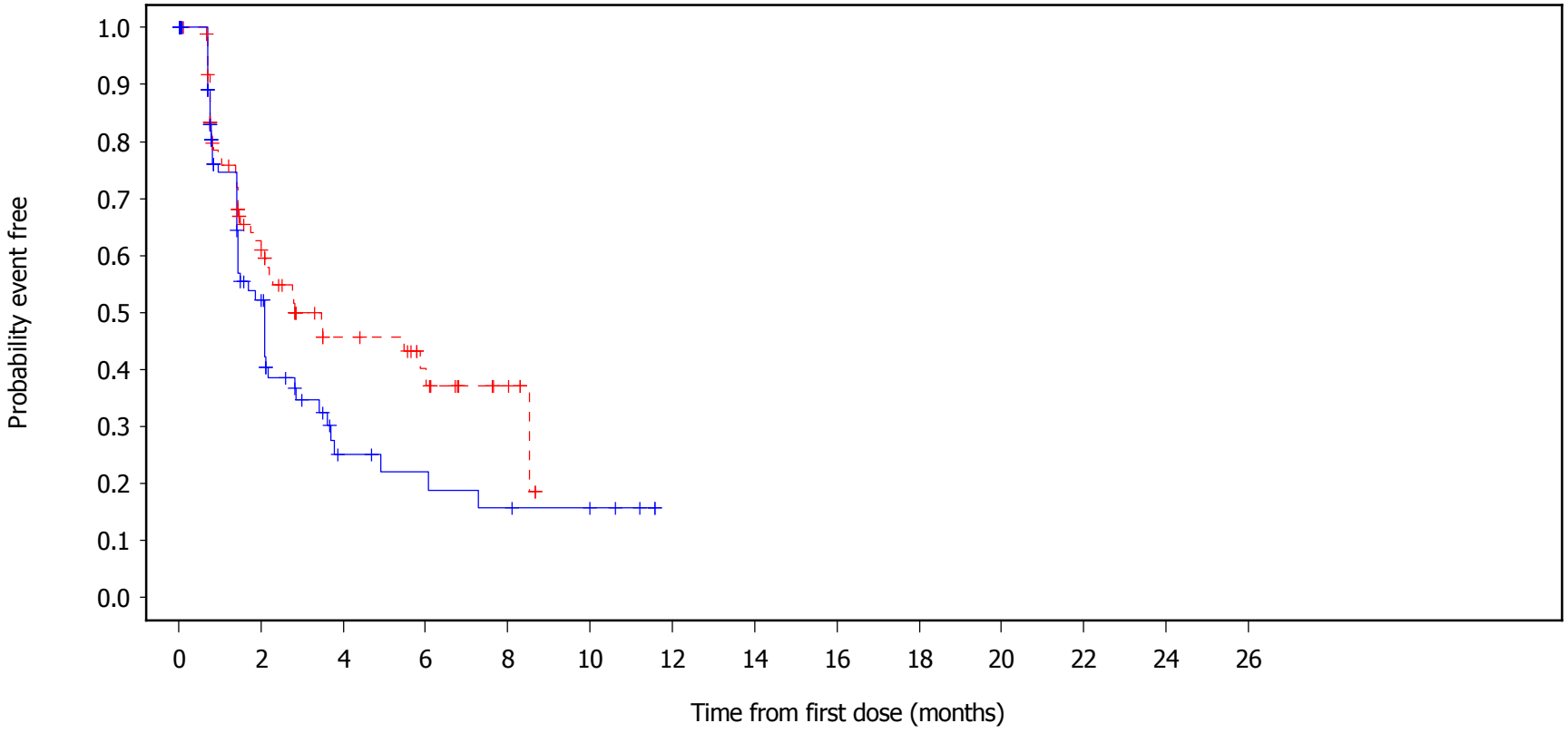
Figure 2.2.5.1 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of EORTC QLQ-C30 Time to Deterioration - Functional scale: Role for Race=Asian
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

249	101	54	39	21	10	3	2	1	1	0	0	0	0	Durva + Gem + Cis
262	102	49	24	12	6	1	0	0	0	0	0	0	0	Placebo + Gem + Cis

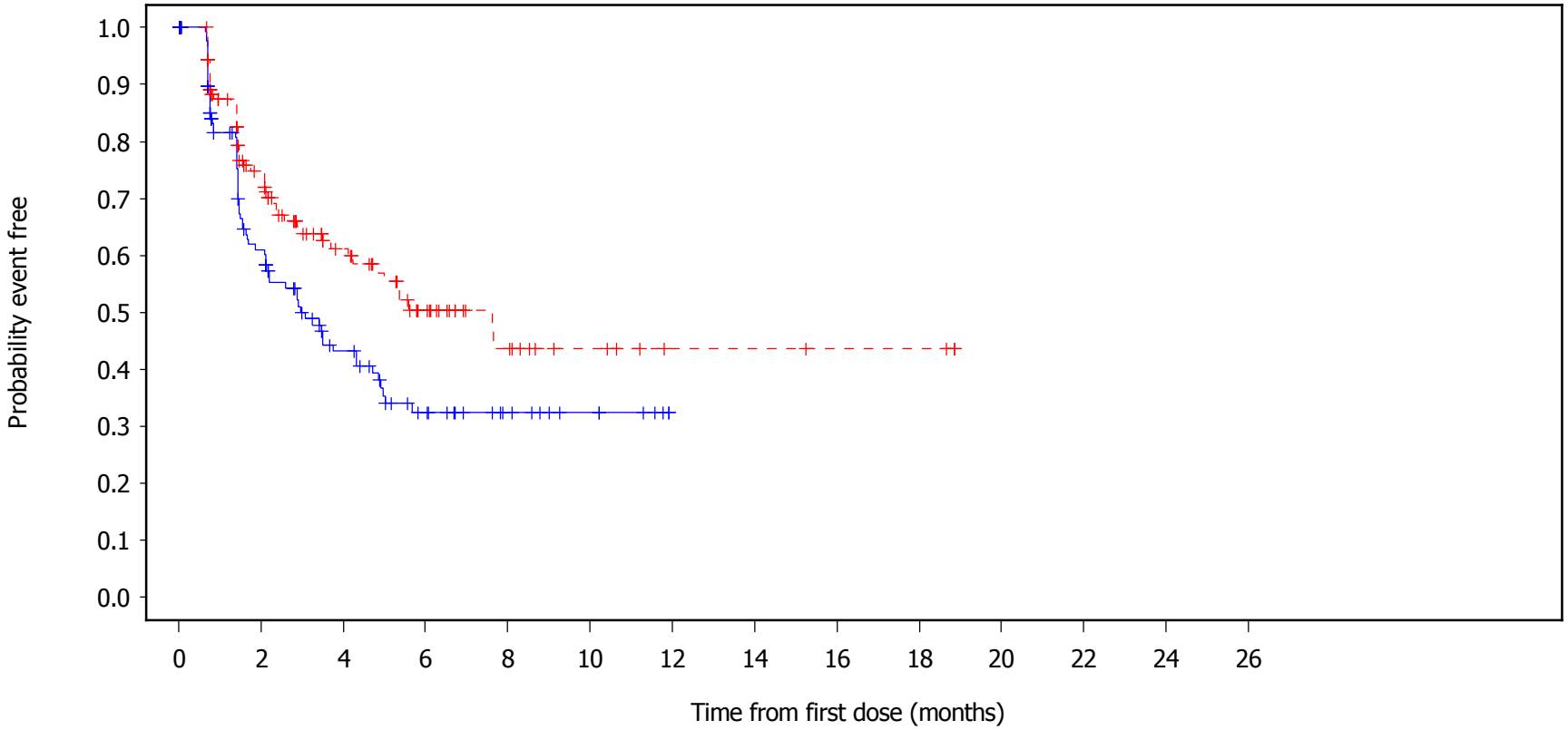
Figure 2.2.5.2 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of EORTC QLQ-C30 Time to Deterioration - Functional scale: Role for Race=Non-Asian
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

156	33	9	7	5	3	0	0	0	0	0	0	0	0	Durva + Gem + Cis
142	43	20	13	5	0	0	0	0	0	0	0	0	0	Placebo + Gem + Cis

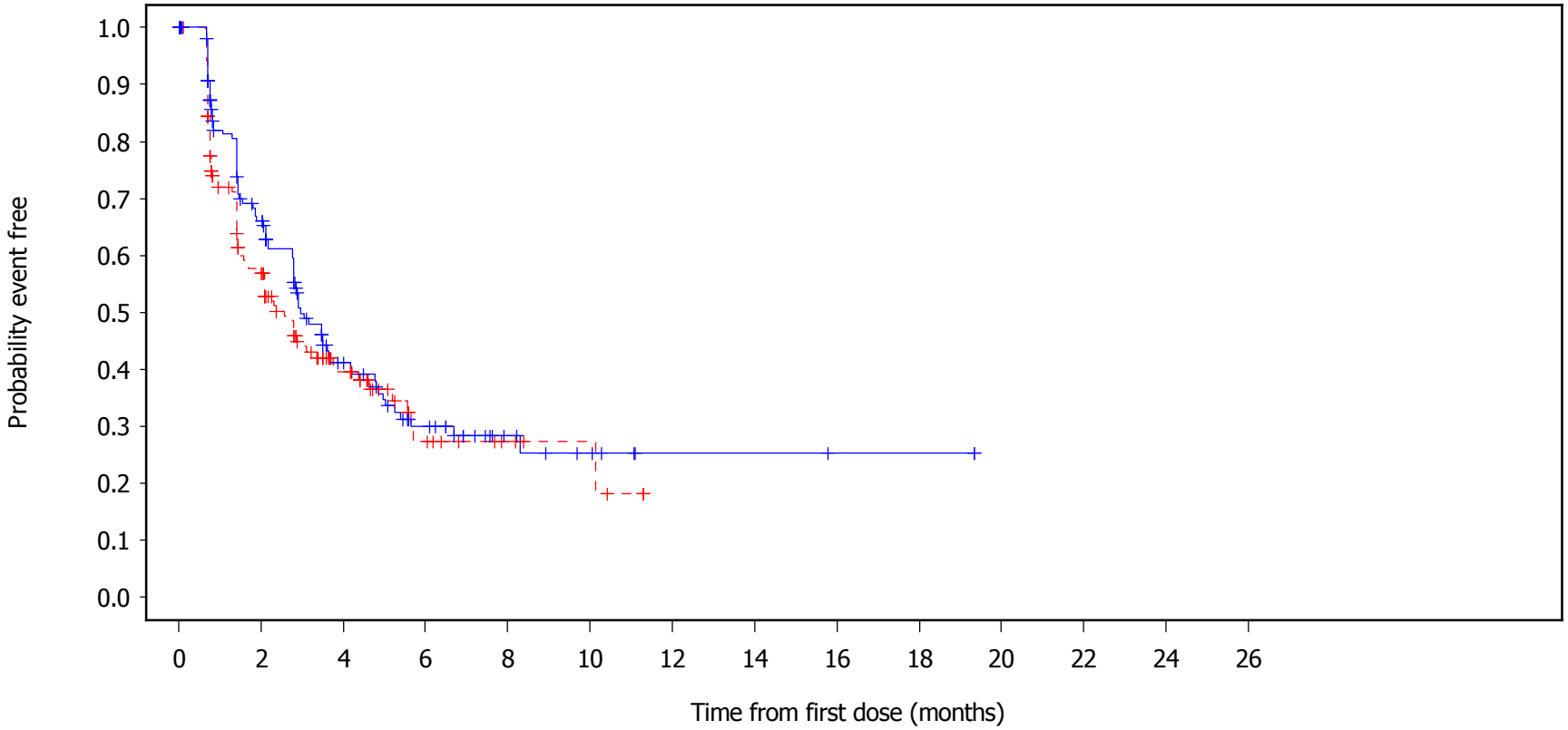
Figure 2.2.5.3 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of EORTC QLQ-C30 Time to Deterioration - Functional scale: Cognitive for WHO ECOG Status at Screening=0
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

189	67	36	20	11	6	0	0	0	0	0	0	0	0	Durva + Gem + Cis
185	81	45	26	13	7	3	3	2	2	0	0	0	0	Placebo + Gem + Cis

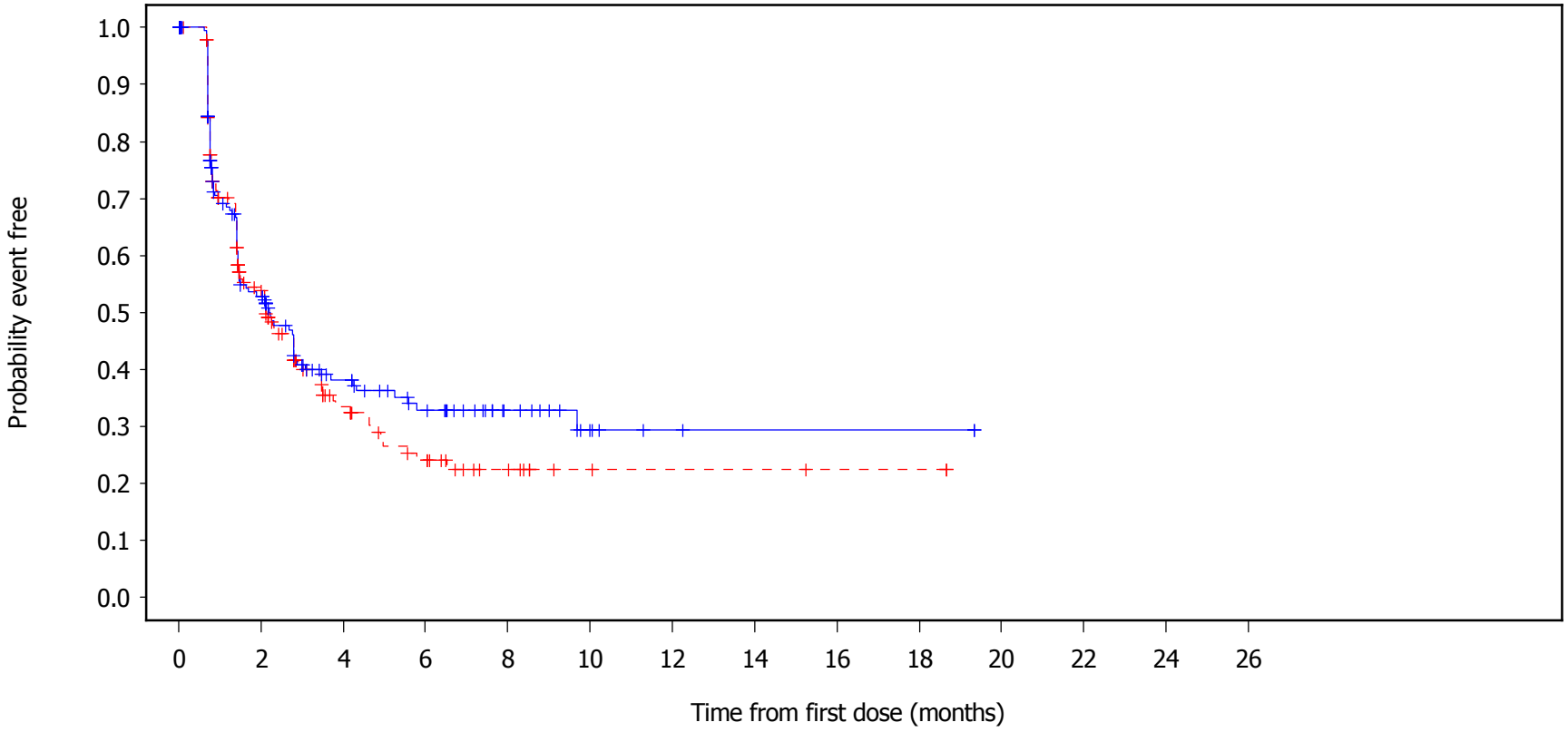
Figure 2.2.5.4 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of EORTC QLQ-C30 Time to Deterioration - Functional scale: Cognitive for WHO ECOG Status at Screening=1
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

216	85	40	23	10	6	2	2	1	1	0	0	0	0	Durva + Gem + Cis
219	75	32	11	5	3	0	0	0	0	0	0	0	0	Placebo + Gem + Cis

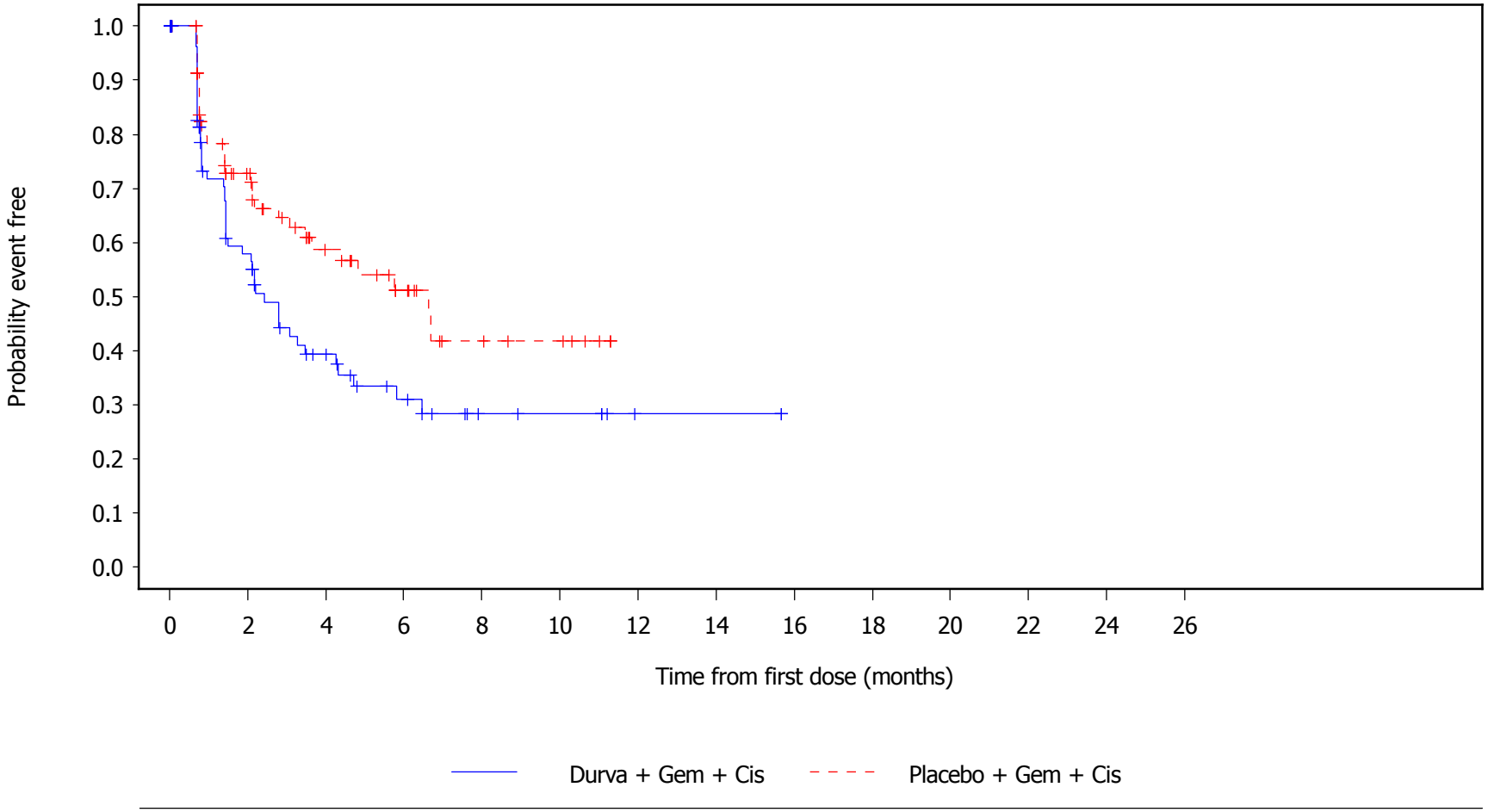
Figure 2.2.5.5 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of EORTC QLQ-C30 Time to Deterioration - Symptom scale: Nausea and vomiting for PD-L1 Status=High (>=1%)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

239	80	42	29	14	5	2	1	1	1	0	0	0	0	Durva + Gem + Cis
251	81	33	19	9	3	2	2	1	1	0	0	0	0	Placebo + Gem + Cis

Figure 2.2.5.6 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of EORTC QLQ-C30 Time to Deterioration - Symptom scale: Nausea and vomiting for PD-L1 Status=Low (<1%)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

119	41	22	13	6	5	1	1	0	0	0	0	0	0	Durva + Gem + Cis
116	47	27	15	7	5	0	0	0	0	0	0	0	0	Placebo + Gem + Cis

Table 2.3.1 TOPAZ: Summary of status at time to deterioration in EORTC QLQ-BIL21 symptom and single item scales
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

		Reason	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
EORTC QLQ-BIL21 Symptom scale: Pain	Deterioration	Total	86 (21.2)	92 (22.7)
	Censored	Total	319 (78.8)	313 (77.3)
		No evaluable assessments or no baseline data	129 (31.9)	115 (28.4)
		Alive and no deterioration	94 (23.2)	117 (28.9)
		Death	21 (5.2)	19 (4.7)
		Two or more missed visits before deterioration or death	75 (18.5)	62 (15.3)
EORTC QLQ-BIL21 Symptom scale: Tiredness	Deterioration	Total	165 (40.7)	166 (41.0)
	Censored	Total	240 (59.3)	239 (59.0)
		No evaluable assessments or no baseline data	129 (31.9)	115 (28.4)
		Alive and no deterioration	55 (13.6)	68 (16.8)
		Death	10 (2.5)	11 (2.7)
		Two or more missed visits before deterioration or death	46 (11.4)	45 (11.1)
EORTC QLQ-BIL21 Symptom scale: Jaundice	Deterioration	Total	119 (29.4)	123 (30.4)
	Censored	Total	286 (70.6)	282 (69.6)
		No evaluable assessments or no baseline data	129 (31.9)	115 (28.4)
		Alive and no deterioration	76 (18.8)	98 (24.2)
		Death	15 (3.7)	15 (3.7)
		Two or more missed visits before deterioration or death	66 (16.3)	54 (13.3)
EORTC QLQ-BIL21 Symptom scale: Anxiety	Deterioration	Total	91 (22.5)	92 (22.7)
	Censored	Total	314 (77.5)	313 (77.3)
		No evaluable assessments or no baseline data	129 (31.9)	115 (28.4)

Table 2.3.1 TOPAZ: Summary of status at time to deterioration in EORTC QLQ-BIL21 symptom and single item scales
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

		Reason	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
		Alive and no deterioration	94 (23.2)	122 (30.1)
		Death	20 (4.9)	14 (3.5)
		Two or more missed visits before deterioration or death	71 (17.5)	62 (15.3)
EORTC QLQ-BIL21 Symptom scale: Eating	Deterioration	Total	133 (32.8)	116 (28.6)
	Censored	Total	272 (67.2)	289 (71.4)
		No evaluable assessments or no baseline data	129 (31.9)	115 (28.4)
		Alive and no deterioration	67 (16.5)	102 (25.2)
		Death	21 (5.2)	12 (3.0)
		Two or more missed visits before deterioration or death	55 (13.6)	60 (14.8)
EORTC QLQ-BIL21 Function: Treatment side effects	Deterioration	Total	173 (42.7)	172 (42.5)
	Censored	Total	232 (57.3)	233 (57.5)
		No evaluable assessments or no baseline data	129 (31.9)	115 (28.4)
		Alive and no deterioration	49 (12.1)	66 (16.3)
		Death	12 (3.0)	12 (3.0)
		Two or more missed visits before deterioration or death	42 (10.4)	40 (9.9)
EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes	Deterioration	Total	49 (12.1)	31 (7.7)
	Censored	Total	356 (87.9)	374 (92.3)
		No evaluable assessments or no baseline data	129 (31.9)	115 (28.4)
		Alive and no deterioration	117 (28.9)	161 (39.8)
		Death	21 (5.2)	25 (6.2)
		Two or more missed visits before deterioration or death	89 (22.0)	73 (18.0)

Table 2.3.1 TOPAZ: Summary of status at time to deterioration in EORTC QLQ-BIL21 symptom and single item scales
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

		Reason	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
EORTC QLQ-BIL21 Function: Concerns regarding weight loss	Deterioration	Total	97 (24.0)	85 (21.0)
	Censored	Total	308 (76.0)	320 (79.0)
		No evaluable assessments or no baseline data	129 (31.9)	115 (28.4)
		Alive and no deterioration	87 (21.5)	127 (31.4)
		Death	22 (5.4)	18 (4.4)
		Two or more missed visits before deterioration or death	70 (17.3)	60 (14.8)

Table 2.3.2 TOPAZ: Summary of analysis of time to clinically meaningful deterioration in EORTC QLQ-BIL21, symptom and single item scales
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Pain	405	86 (21.2)	NE (NE, NE)	405	92 (22.7)	8.5 (6.6, NE)	0.98	0.73, 1.32	0.8847
EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Tiredness	405	165 (40.7)	1.5 (1.4, 2.1)	405	166 (41.0)	2.2 (1.5, 2.9)	1.16	0.93, 1.44	0.1883
EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Jaundice	405	119 (29.4)	5.6 (3.6, 7.5)	405	123 (30.4)	4.8 (3.9, 7.5)	0.98	0.76, 1.26	0.9133
EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Anxiety	405	91 (22.5)	11.1 (6.7, NE)	405	92 (22.7)	NE (NE, NE)	0.96	0.71, 1.28	0.6696
EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Eating	405	133 (32.8)	3.9 (2.8, 4.9)	405	116 (28.6)	5.7 (3.9, 9.2)	1.22	0.95, 1.57	0.1239
EORTC QLQ-BIL21 Time to Deterioration - Function: Treatment side effects	405	173 (42.7)	1.5 (1.4, 2.1)	405	172 (42.5)	2.3 (1.6, 2.9)	1.16	0.93, 1.43	0.2360
EORTC QLQ-BIL21 Time to Deterioration - Function: Difficulties with drainage bags/tubes	405	49 (12.1)	NE (NE, NE)	405	31 (7.7)	NE (NE, NE)	1.67	1.07, 2.65	0.0243*

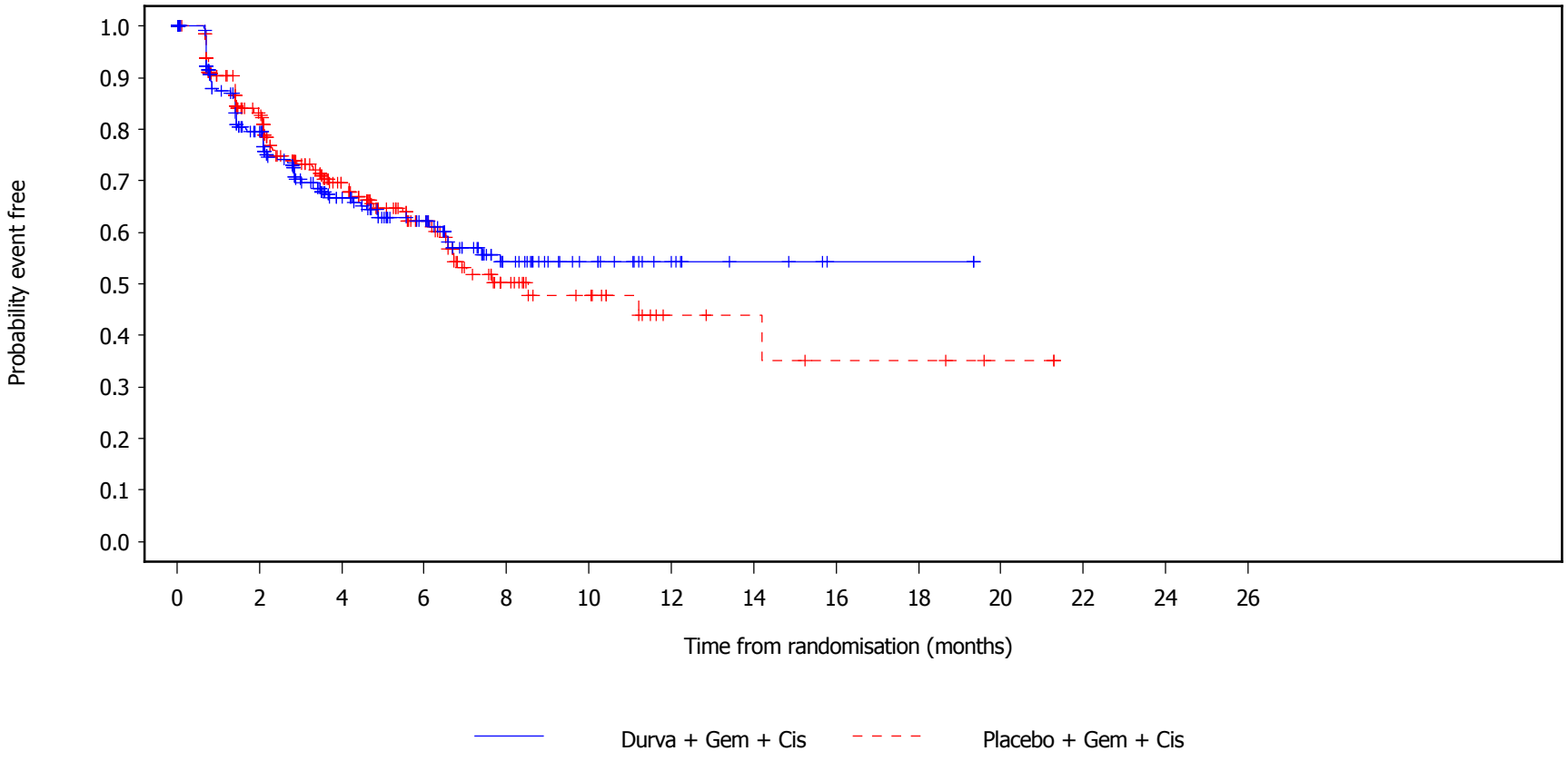
Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards. [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] Estimated from Cox proportional hazards model adjusted for disease status and primary tumor location. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test stratified by disease status and primary tumor location. Hazard ratio <1 favours durva *p<0.05.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttemainpr.sas ettemainprab 19JAN2023:19:39 kjpc654

Table 2.3.2 TOPAZ: Summary of analysis of time to clinically meaningful deterioration in EORTC QLQ-BIL21, symptom and single item scales
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
EORTC QLQ-BIL21 Time to Deterioration - Function: Concerns regarding weight loss	405	97 (24.0)	9.3 (6.3, NE)	405	85 (21.0)	17.5 (9.2, NE)	1.22	0.91, 1.64	0.1845

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards. [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] Estimated from Cox proportional hazards model adjusted for disease status and primary tumor location. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test stratified by disease status and primary tumor location. Hazard ratio <1 favours durva *p<0.05.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttemainpr.sas ettemainprab 19JAN2023:19:39 kjpc654

Figure 2.3.3.1 TOPAZ: Kaplan-Meier plot of EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Pain
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

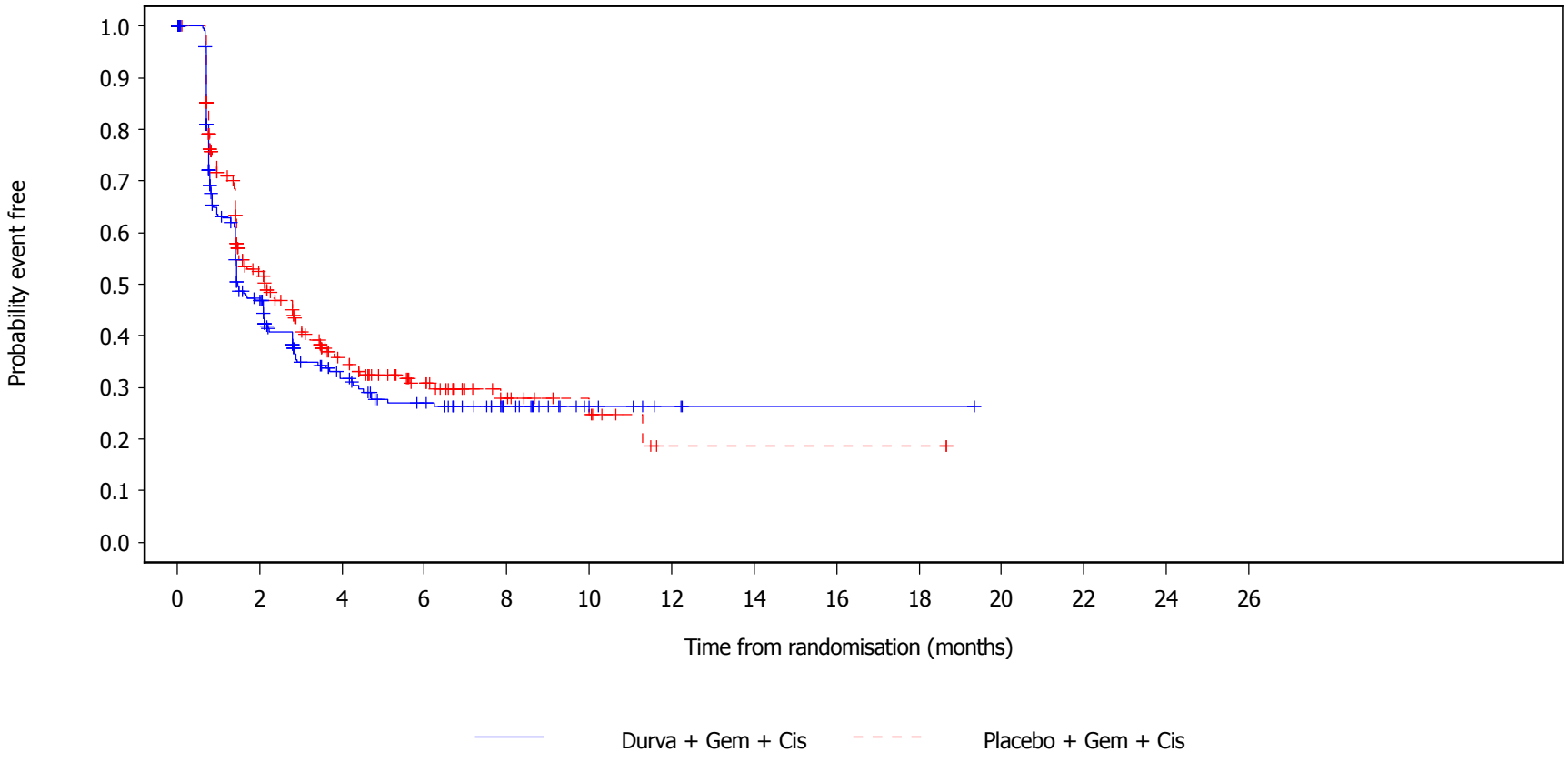


Number of patients at risk:

405	169	98	71	32	18	8	4	1	1	0	0	0	0	Durva + Gem + Cis
404	180	105	65	27	17	6	5	3	3	1	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.3.3.2 TOPAZ: Kaplan-Meier plot of EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Tiredness
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

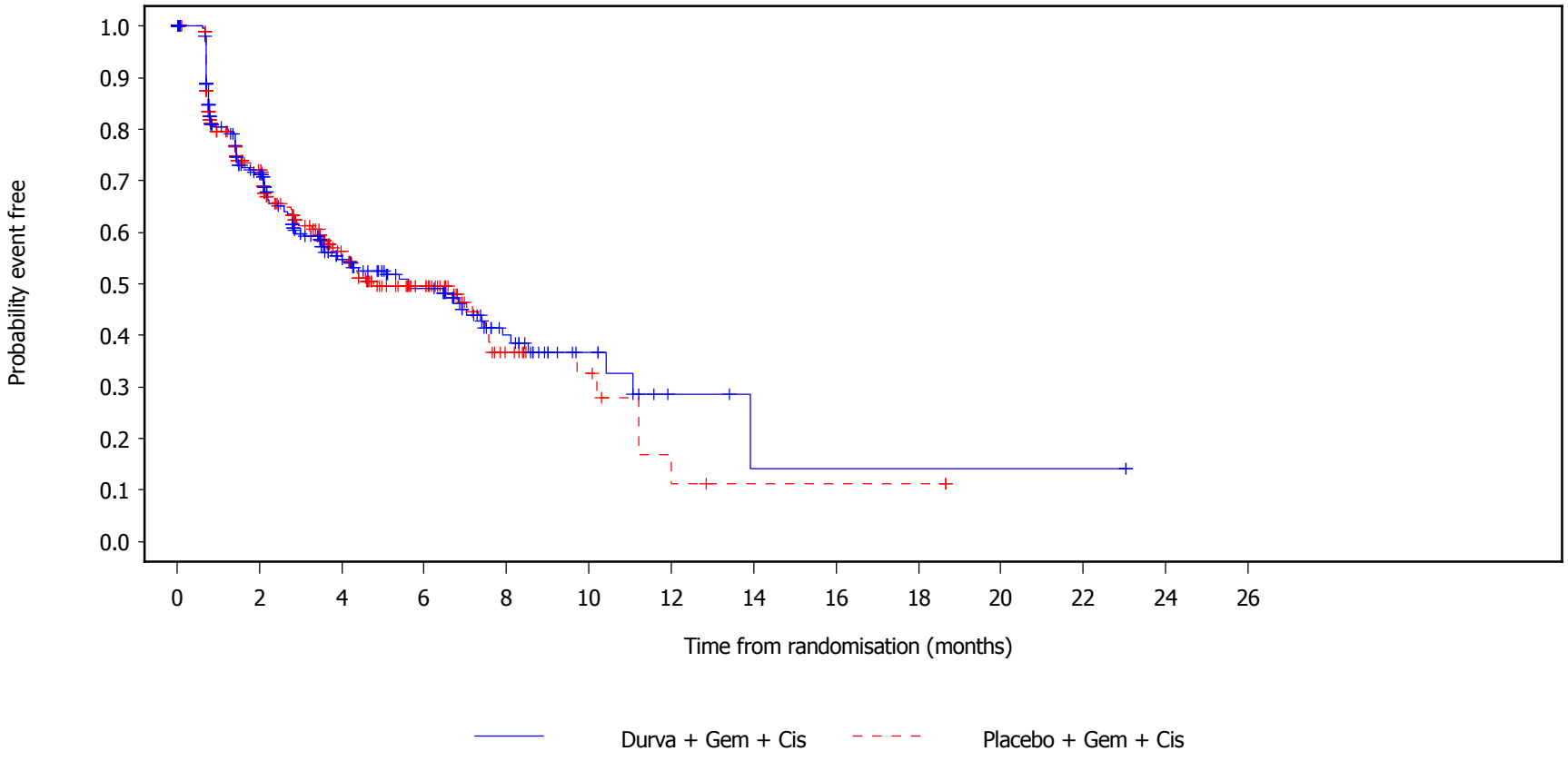


Number of patients at risk:

405	101	50	36	19	7	3	1	1	1	0	0	0	0	Durva + Gem + Cis
404	115	56	33	14	8	1	1	1	1	0	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.3.3.3 TOPAZ: Kaplan-Meier plot of EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Jaundice
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

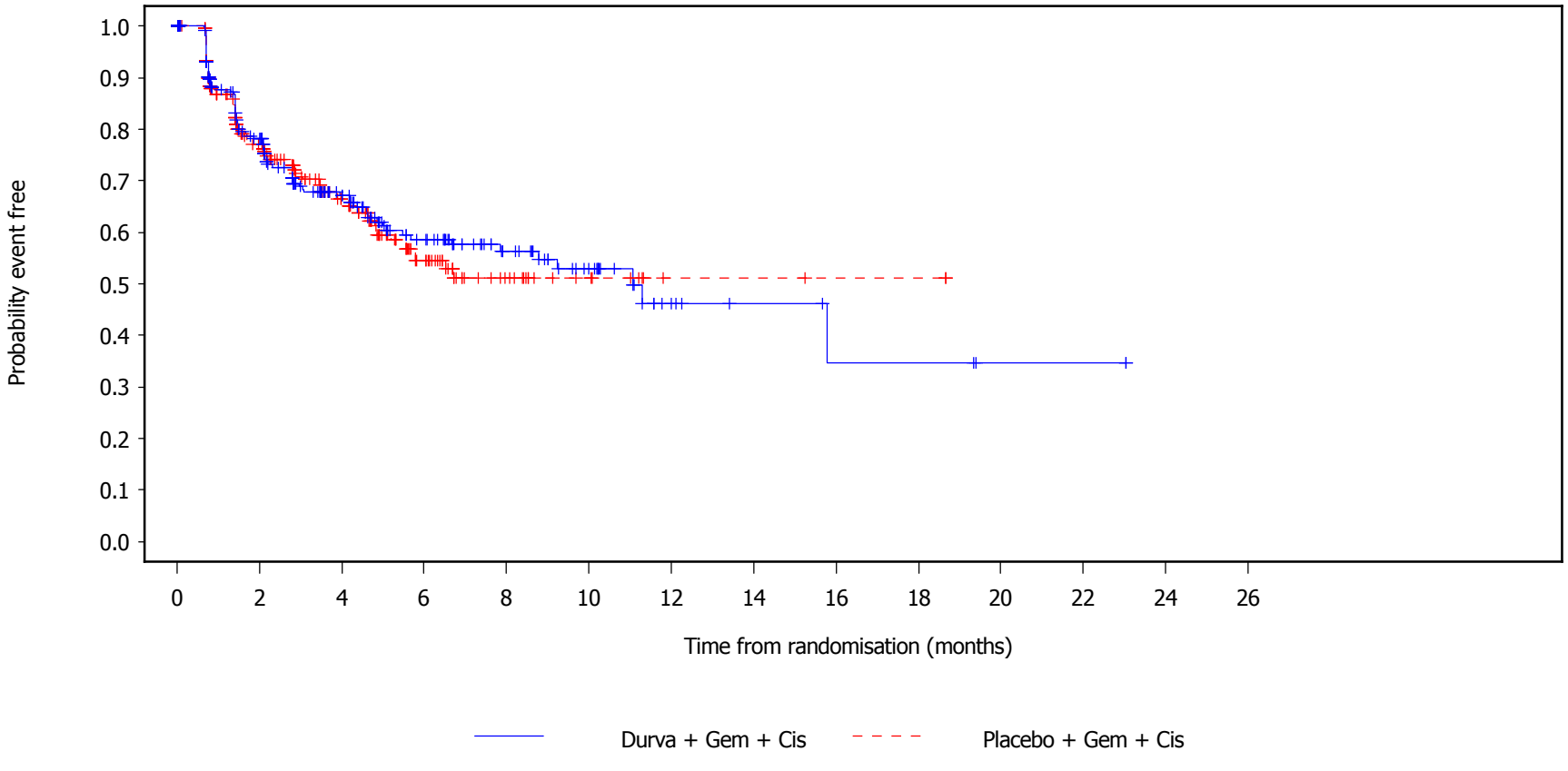


Number of patients at risk:

405	150	80	57	26	11	3	1	1	1	1	1	0	0	Durva + Gem + Cis
404	157	81	44	15	8	2	1	1	1	0	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.3.3.4 TOPAZ: Kaplan-Meier plot of EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Anxiety
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

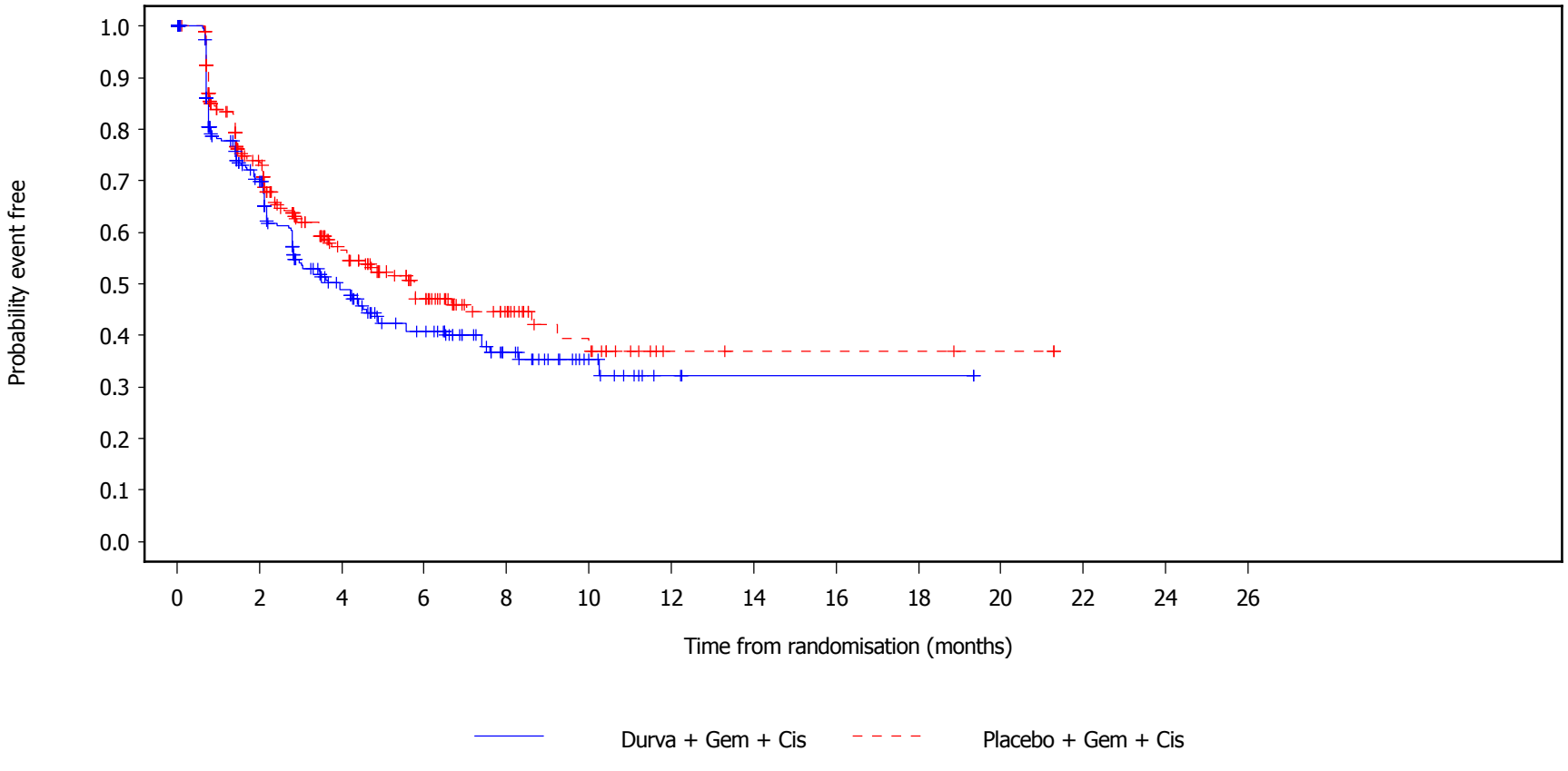


Number of patients at risk:

405	168	101	66	40	24	8	5	3	3	1	1	0	0	Durva + Gem + Cis
404	162	96	47	19	9	2	2	1	1	0	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.3.3.5 TOPAZ: Kaplan-Meier plot of EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Eating
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

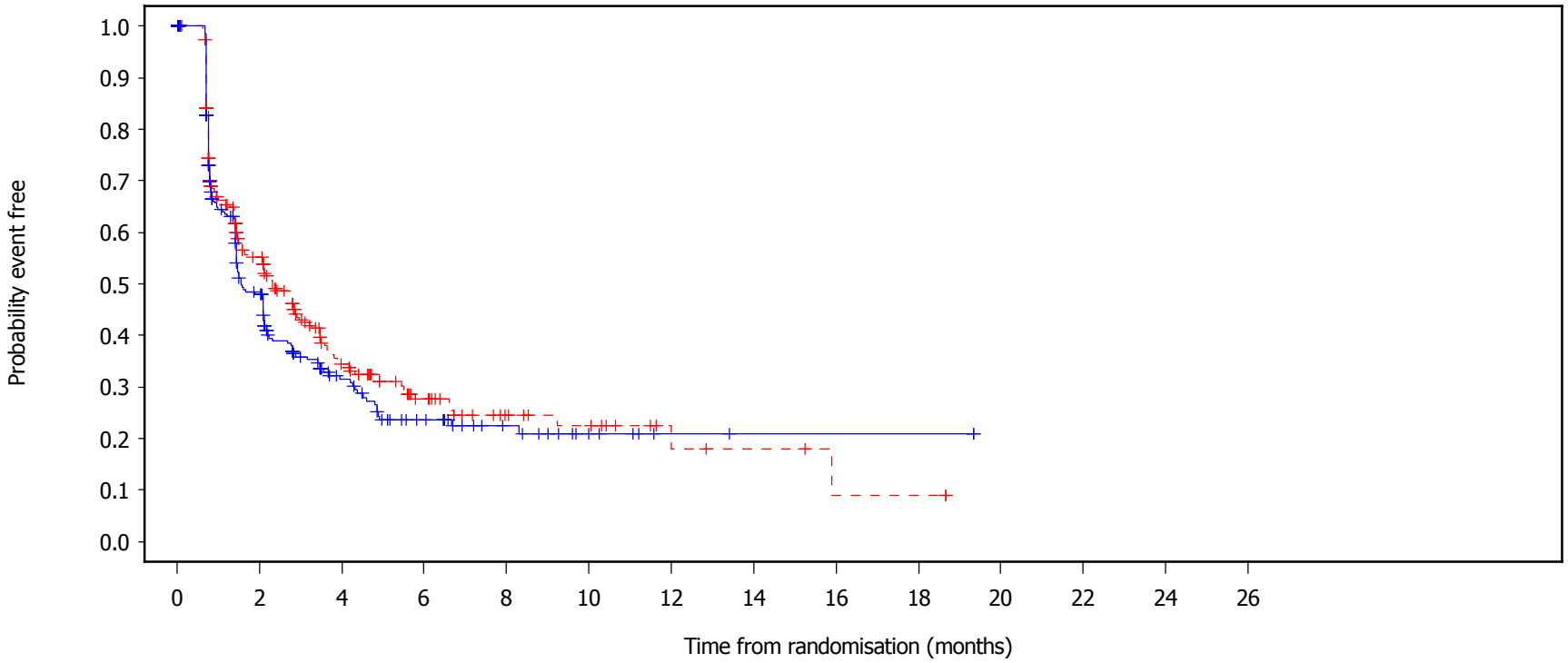


Number of patients at risk:

405	154	81	54	28	12	3	1	1	1	0	0	0	0	Durva + Gem + Cis
404	159	86	52	27	14	3	2	2	2	1	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.3.3.6 TOPAZ: Kaplan-Meier plot of EORTC QLQ-BIL21 Time to Deterioration - Function: Treatment side effects
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

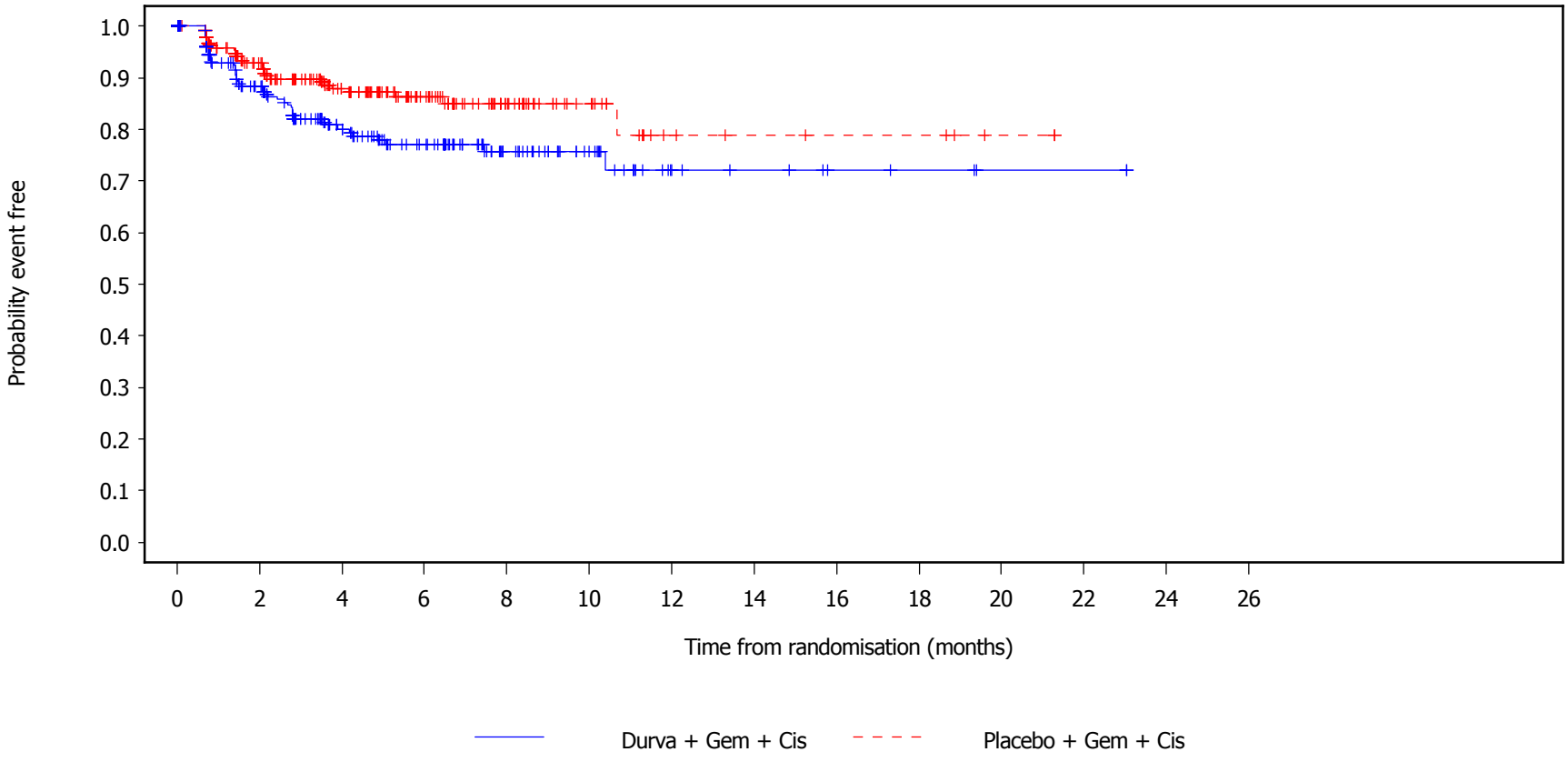


Number of patients at risk:

405	108	46	26	14	6	2	1	1	1	0	0	0	0	Durva + Gem + Cis
404	124	57	30	15	11	4	3	1	1	0	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.3.3.7 TOPAZ: Kaplan-Meier plot of EORTC QLQ-BIL21 Time to Deterioration - Function: Difficulties with drainage bags/tubes
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

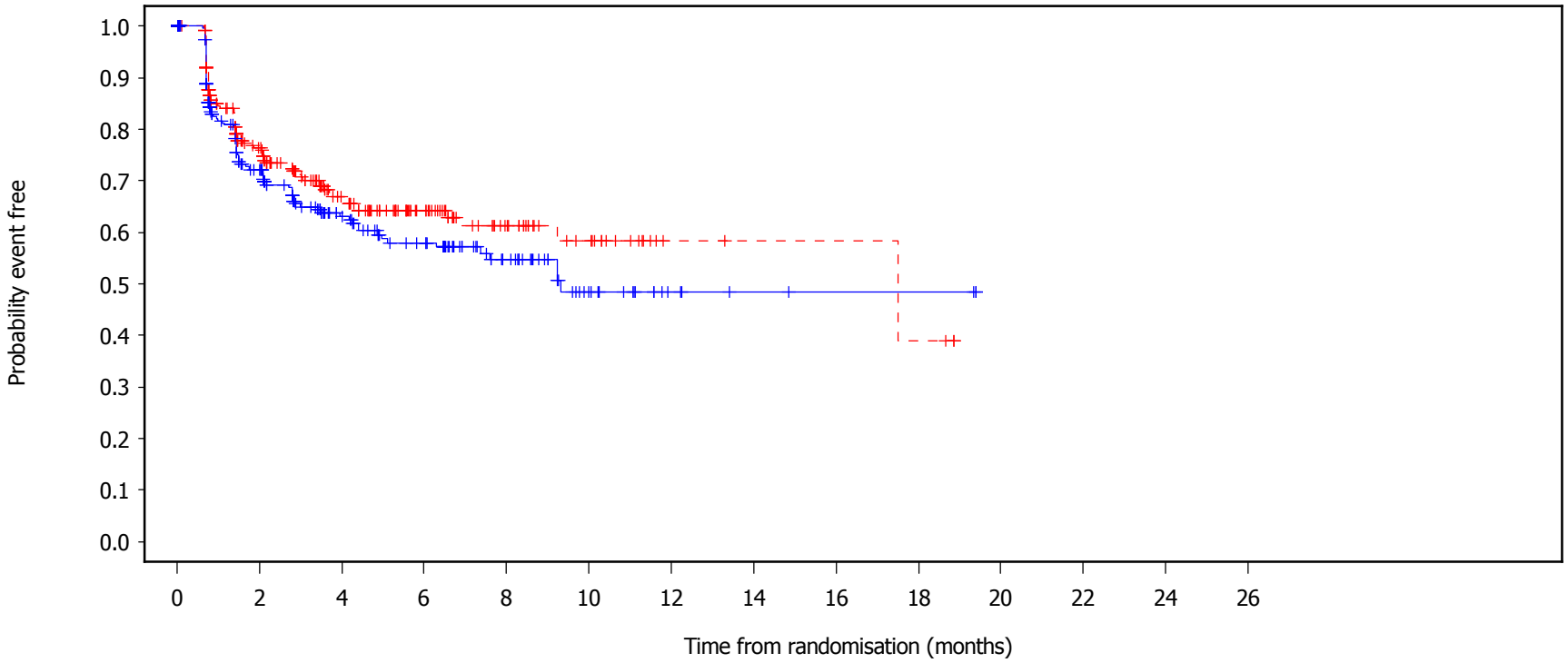


Number of patients at risk:

405	188	116	87	45	26	9	7	4	3	1	1	0	0	Durva + Gem + Cis
404	196	126	78	41	20	7	5	4	4	1	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Figure 2.3.3.8 TOPAZ: Kaplan-Meier plot of EORTC QLQ-BIL21 Time to Deterioration - Function: Concerns regarding weight loss
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

405	153	94	72	40	17	6	3	2	2	0	0	0	0	Durva + Gem + Cis
404	162	98	60	33	18	4	3	3	2	0	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Table 2.3.4.1 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Pain
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	68 (20.7)	NE (NE, NE)	334	64 (19.2)	8.5 (6.6, NE)	1.20	0.86, 1.70	0.2848
Recurrent	76	18 (23.7)	NE (NE, NE)	70	28 (40.0)	4.7 (2.3, NE)	0.54	0.29, 0.96	0.0371*
Interaction p-value									0.0194*
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	17 (23.3)	NE (NE, NE)	72	17 (23.6)	7.0 (4.2, NE)	1.07	0.54, 2.11	0.8489
Intrahepatic CCA	236	49 (20.8)	NE (NE, NE)	235	58 (24.7)	8.5 (6.5, NE)	0.82	0.56, 1.20	0.3048
Gallbladder cancer	96	20 (20.8)	5.6 (3.0, NE)	98	17 (17.3)	NE (NE, NE)	1.55	0.81, 2.99	0.1850
Interaction p-value									0.2425
Age Group									
<65	220	51 (23.2)	NE (NE, NE)	230	50 (21.7)	7.7 (6.6, NE)	1.10	0.74, 1.63	0.6381
>=65	185	35 (18.9)	NE (NE, NE)	175	42 (24.0)	8.5 (4.8, NE)	0.85	0.54, 1.33	0.4858
Interaction p-value									0.4044
Region									
Asia	242	64 (26.4)	NE (NE, NE)	257	63 (24.5)	11.2 (6.6, NE)	1.06	0.75, 1.51	0.7285
Rest of World	163	22 (13.5)	NE (NE, NE)	148	29 (19.6)	7.7 (5.5, NE)	0.81	0.46, 1.40	0.4491
Interaction p-value									0.4095
PD-L1 Status									
High (>=1%)	239	56 (23.4)	NE (NE, NE)	251	54 (21.5)	7.0 (6.5, NE)	1.12	0.77, 1.63	0.5576
Low (<1%)	119	27 (22.7)	NE (NE, NE)	117	27 (23.1)	11.2 (6.1, NE)	1.05	0.61, 1.79	0.8626
Interaction p-value									0.8455
Sex									
Male	199	40 (20.1)	NE (NE, NE)	208	49 (23.6)	7.7 (6.2, NE)	0.90	0.59, 1.37	0.6350

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.3.4.1 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Pain
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	46 (22.3)	7.4 (4.9, NE)	197	43 (21.8)	8.5 (6.1, NE)	1.06	0.70, 1.61	0.7860
Interaction p-value									0.5976
Race									
Asian	249	64 (25.7)	NE (NE, NE)	262	64 (24.4)	11.2 (6.6, NE)	1.04	0.74, 1.48	0.8067
Non-Asian	156	22 (14.1)	NE (NE, NE)	143	28 (19.6)	7.7 (5.5, NE)	0.84	0.48, 1.47	0.5474
Interaction p-value									0.5224
WHO ECOG Status at Screening									
0	189	41 (21.7)	NE (NE, NE)	185	46 (24.9)	7.7 (6.1, NE)	0.99	0.65, 1.51	0.9569
1	216	45 (20.8)	NE (NE, NE)	220	46 (20.9)	NE (NE, NE)	0.98	0.65, 1.48	0.9212
Interaction p-value									0.9758
Disease Extent									
Locally Advanced	55	10 (18.2)	NE (NE, NE)	73	14 (19.2)	14.2 (5.6, NE)	0.93	0.40, 2.08	0.8612
Metastatic	350	76 (21.7)	NE (NE, NE)	331	78 (23.6)	7.7 (6.6, NE)	0.98	0.71, 1.34	0.8782
Interaction p-value									0.9147
MSI Status									
MSI High	3	1 (33.3)	1.0 (NE, NE)	2	1 (50.0)	6.9 (NE, NE)	NC	NC	NC
MSI Stable	160	39 (24.4)	NE (NE, NE)	168	42 (25.0)	7.0 (6.1, NE)	0.98	0.63, 1.51	0.9184
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.3.4.2 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Tiredness
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	118 (35.9)	1.6 (1.4, 2.8)	334	123 (36.8)	2.8 (1.6, 3.2)	1.19	0.92, 1.53	0.1755
Recurrent	76	47 (61.8)	1.4 (1.0, 2.1)	70	43 (61.4)	1.4 (0.9, 2.2)	1.02	0.68, 1.55	0.9150
Interaction p-value									0.5383
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	36 (49.3)	1.4 (0.8, 1.5)	72	31 (43.1)	2.8 (1.4, 4.2)	1.77	1.09, 2.87	0.0205*
Intrahepatic CCA	236	89 (37.7)	2.1 (1.4, 2.9)	235	100 (42.6)	2.2 (1.4, 2.9)	0.93	0.70, 1.24	0.6431
Gallbladder cancer	96	40 (41.7)	1.4 (0.8, 2.1)	98	35 (35.7)	2.1 (1.4, 4.3)	1.48	0.94, 2.35	0.0880
Interaction p-value									0.0440*
Age Group									
<65	220	93 (42.3)	1.4 (1.4, 2.8)	230	92 (40.0)	2.2 (1.4, 3.2)	1.24	0.93, 1.65	0.1480
>=65	185	72 (38.9)	1.5 (1.4, 2.2)	175	74 (42.3)	2.1 (1.4, 2.9)	1.07	0.77, 1.48	0.6727
Interaction p-value									0.5184
Region									
Asia	242	119 (49.2)	1.5 (1.4, 2.2)	257	118 (45.9)	2.3 (1.6, 3.2)	1.25	0.97, 1.61	0.0860
Rest of World	163	46 (28.2)	1.5 (1.0, 3.4)	148	48 (32.4)	1.5 (1.4, 2.9)	0.96	0.64, 1.44	0.8484
Interaction p-value									0.2813
PD-L1 Status									
High (>=1%)	239	98 (41.0)	1.5 (1.4, 2.8)	251	104 (41.4)	2.1 (1.5, 3.1)	1.12	0.85, 1.47	0.4271
Low (<1%)	119	51 (42.9)	1.4 (1.1, 2.2)	117	46 (39.3)	2.2 (1.4, 3.5)	1.27	0.85, 1.90	0.2393
Interaction p-value									0.6073
Sex									
Male	199	79 (39.7)	1.9 (1.4, 2.9)	208	85 (40.9)	2.3 (1.5, 4.2)	1.18	0.87, 1.60	0.2937

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.3.4.2 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Tiredness
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	86 (41.7)	1.4 (1.4, 2.1)	197	81 (41.1)	1.9 (1.4, 2.9)	1.13	0.83, 1.53	0.4372
Interaction p-value									0.8413
Race									
Asian	249	119 (47.8)	1.5 (1.4, 2.2)	262	119 (45.4)	2.3 (1.6, 3.2)	1.23	0.95, 1.59	0.1102
Non-Asian	156	46 (29.5)	1.4 (0.9, 2.2)	143	47 (32.9)	1.5 (1.4, 2.9)	1.00	0.66, 1.50	0.9894
Interaction p-value									0.3905
WHO ECOG Status at Screening									
0	189	74 (39.2)	1.7 (1.4, 2.9)	185	74 (40.0)	2.8 (2.1, 3.5)	1.21	0.88, 1.67	0.2442
1	216	91 (42.1)	1.4 (1.4, 2.2)	220	92 (41.8)	1.5 (1.4, 2.8)	1.12	0.83, 1.49	0.4611
Interaction p-value									0.7086
Disease Extent									
Locally Advanced	55	24 (43.6)	1.4 (0.8, 2.1)	73	30 (41.1)	2.8 (1.4, 4.4)	1.40	0.81, 2.39	0.2239
Metastatic	350	141 (40.3)	1.5 (1.4, 2.2)	331	136 (41.1)	2.1 (1.5, 2.9)	1.12	0.88, 1.42	0.3457
Interaction p-value									0.4582
MSI Status									
MSI High	3	1 (33.3)	1.0 (NE, NE)	2	2 (100)	0.8 (0.7, NE)	NC	NC	NC
MSI Stable	160	69 (43.1)	2.1 (1.4, 3.9)	168	76 (45.2)	2.1 (1.5, 2.9)	0.96	0.69, 1.34	0.8261
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.3.4.3 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Jaundice
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	91 (27.7)	4.4 (2.9, 6.9)	334	95 (28.4)	6.9 (3.7, 7.5)	1.03	0.77, 1.37	0.8482
Recurrent	76	28 (36.8)	7.9 (3.5,13.9)	70	28 (40.0)	4.4 (2.8,10.2)	0.82	0.48, 1.39	0.4585
Interaction p-value									0.4578
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	24 (32.9)	5.4 (2.7,13.9)	72	15 (20.8)	NE (NE, NE)	1.52	0.80, 2.97	0.1990
Intrahepatic CCA	236	72 (30.5)	6.5 (2.9, 8.5)	235	77 (32.8)	4.3 (3.5, 7.5)	0.90	0.65, 1.24	0.5296
Gallbladder cancer	96	23 (24.0)	6.9 (2.1, NE)	98	31 (31.6)	3.5 (2.1, 7.6)	0.87	0.50, 1.49	0.6139
Interaction p-value									0.3238
Age Group									
<65	220	67 (30.5)	4.4 (2.9, 7.4)	230	74 (32.2)	4.4 (3.5, 7.3)	0.96	0.69, 1.34	0.8251
>=65	185	52 (28.1)	7.0 (3.6,10.4)	175	49 (28.0)	7.0 (3.6,11.2)	0.98	0.66, 1.46	0.9345
Interaction p-value									0.9361
Region									
Asia	242	90 (37.2)	4.4 (2.8, 6.9)	257	91 (35.4)	6.7 (3.5, 7.6)	1.05	0.79, 1.41	0.7232
Rest of World	163	29 (17.8)	7.4 (3.7, NE)	148	32 (21.6)	4.6 (2.8, NE)	0.78	0.47, 1.28	0.3214
Interaction p-value									0.3001
PD-L1 Status									
High (>=1%)	239	68 (28.5)	7.4 (4.3,10.4)	251	76 (30.3)	6.9 (3.5, 7.6)	0.84	0.60, 1.17	0.2984
Low (<1%)	119	37 (31.1)	3.9 (2.2,11.1)	117	34 (29.1)	4.8 (3.6, NE)	1.22	0.77, 1.96	0.3992
Interaction p-value									0.1971
Sex									
Male	199	57 (28.6)	5.6 (3.6,11.1)	208	60 (28.8)	7.6 (4.3,11.2)	1.04	0.72, 1.49	0.8505

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.3.4.3 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Jaundice
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)						
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]		2-sided p-value [b]
Female	206	62 (30.1)	5.6 (2.2, 7.4)	197	63 (32.0)	3.7 (2.8, 6.9)	0.88	0.62,	1.26	0.4875
Interaction p-value										0.5356
Race										
Asian	249	90 (36.1)	4.4 (2.8, 6.9)	262	92 (35.1)	4.8 (3.5, 7.6)	1.04	0.77,	1.39	0.8142
Non-Asian	156	29 (18.6)	7.4 (3.7,11.1)	143	31 (21.7)	4.6 (2.8, NE)	0.81	0.49,	1.35	0.4207
Interaction p-value										0.4145
WHO ECOG Status at Screening										
0	189	55 (29.1)	5.4 (3.5, 7.9)	185	59 (31.9)	4.8 (3.3, 9.7)	0.94	0.65,	1.37	0.7606
1	216	64 (29.6)	6.7 (2.8, 8.5)	220	64 (29.1)	6.9 (3.5, 7.6)	0.99	0.70,	1.40	0.9425
Interaction p-value										0.8638
Disease Extent										
Locally Advanced	55	17 (30.9)	6.9 (3.7,11.1)	73	21 (28.8)	7.6 (4.3,11.2)	1.10	0.57,	2.08	0.7786
Metastatic	350	102 (29.1)	5.4 (3.1, 7.5)	331	102 (30.8)	4.4 (3.5, 7.5)	0.93	0.71,	1.23	0.6303
Interaction p-value										0.6541
MSI Status										
MSI High	3	1 (33.3)	8.1 (NE, NE)	2	2 (100)	1.2 (0.7, NE)	NC	NC		NC
MSI Stable	160	54 (33.8)	4.4 (2.8, 8.5)	168	48 (28.6)	7.3 (6.7, 9.7)	1.15	0.78,	1.70	0.4920
Interaction p-value										NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.3.4.4 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Anxiety
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	67 (20.4)	11.1 (5.5, NE)	334	66 (19.8)	NE (NE, NE)	1.04	0.74, 1.47	0.8062
Recurrent	76	24 (31.6)	15.8 (3.9, NE)	70	26 (37.1)	5.2 (4.1, NE)	0.76	0.43, 1.33	0.3324
Interaction p-value									0.3390
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	17 (23.3)	15.8 (2.2, NE)	72	19 (26.4)	5.8 (4.7, NE)	0.84	0.43, 1.62	0.5969
Intrahepatic CCA	236	57 (24.2)	9.2 (5.5, NE)	235	53 (22.6)	NE (NE, NE)	1.04	0.71, 1.51	0.8462
Gallbladder cancer	96	17 (17.7)	NE (NE, NE)	98	20 (20.4)	NE (NE, NE)	0.88	0.45, 1.68	0.6881
Interaction p-value									0.8150
Age Group									
<65	220	49 (22.3)	11.1 (5.7, NE)	230	47 (20.4)	NE (NE, NE)	1.11	0.74, 1.66	0.6197
>=65	185	42 (22.7)	15.8 (5.1, NE)	175	45 (25.7)	5.8 (3.5, NE)	0.81	0.53, 1.23	0.3181
Interaction p-value									0.2859
Region									
Asia	242	69 (28.5)	11.1 (5.5, NE)	257	64 (24.9)	NE (NE, NE)	1.07	0.76, 1.50	0.7143
Rest of World	163	22 (13.5)	NE (NE, NE)	148	28 (18.9)	6.7 (3.5, NE)	0.73	0.41, 1.28	0.2728
Interaction p-value									0.2597
PD-L1 Status									
High (>=1%)	239	55 (23.0)	11.3 (8.8, NE)	251	53 (21.1)	NE (NE, NE)	1.07	0.73, 1.57	0.7162
Low (<1%)	119	28 (23.5)	11.1 (4.6, NE)	117	27 (23.1)	NE (NE, NE)	0.91	0.53, 1.54	0.7130
Interaction p-value									0.6089
Sex									
Male	199	46 (23.1)	11.1 (5.7, NE)	208	50 (24.0)	6.7 (5.2, NE)	0.88	0.59, 1.32	0.5347

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.3.4.4 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Anxiety
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	45 (21.8)	NE (NE, NE)	197	42 (21.3)	NE (NE, NE)	1.06	0.70, 1.62	0.7812
Interaction p-value									0.5285
Race									
Asian	249	69 (27.7)	11.1 (6.7, NE)	262	65 (24.8)	NE (NE, NE)	1.05	0.74, 1.47	0.7928
Non-Asian	156	22 (14.1)	NE (NE, NE)	143	27 (18.9)	6.7 (3.5, NE)	0.76	0.43, 1.34	0.3478
Interaction p-value									0.3472
WHO ECOG Status at Screening									
0	189	36 (19.0)	NE (NE, NE)	185	38 (20.5)	NE (NE, NE)	0.96	0.61, 1.52	0.8714
1	216	55 (25.5)	6.7 (4.4,15.8)	220	54 (24.5)	5.8 (4.1, NE)	0.94	0.65, 1.38	0.7667
Interaction p-value									0.9486
Disease Extent									
Locally Advanced	55	12 (21.8)	NE (NE, NE)	73	16 (21.9)	NE (NE, NE)	0.95	0.44, 1.99	0.8826
Metastatic	350	79 (22.6)	11.1 (6.7, NE)	331	76 (23.0)	NE (NE, NE)	0.95	0.69, 1.31	0.7666
Interaction p-value									0.9835
MSI Status									
MSI High	3	1 (33.3)	1.9 (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	160	36 (22.5)	15.8 (8.8, NE)	168	36 (21.4)	NE (NE, NE)	0.89	0.55, 1.41	0.6101
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.3.4.5 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Eating
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	94 (28.6)	3.9 (2.8, 7.4)	334	83 (24.9)	6.7 (3.7, NE)	1.28	0.95, 1.72	0.1060
Recurrent	76	39 (51.3)	3.6 (2.2, 4.9)	70	33 (47.1)	4.7 (2.1, 7.0)	1.10	0.69, 1.76	0.6759
Interaction p-value									0.6071
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	29 (39.7)	3.0 (2.0, 5.6)	72	18 (25.0)	7.0 (4.2, NE)	1.89	1.06, 3.46	0.0313*
Intrahepatic CCA	236	79 (33.5)	3.7 (2.8, 7.4)	235	69 (29.4)	5.7 (3.5, NE)	1.19	0.86, 1.65	0.2883
Gallbladder cancer	96	25 (26.0)	4.5 (2.1, NE)	98	29 (29.6)	3.9 (2.1,10.0)	0.95	0.55, 1.63	0.8585
Interaction p-value									0.2220
Age Group									
<65	220	71 (32.3)	4.2 (2.9, 7.4)	230	64 (27.8)	5.8 (4.1, 9.2)	1.23	0.87, 1.72	0.2387
>=65	185	62 (33.5)	3.1 (2.4, 6.5)	175	52 (29.7)	5.1 (2.9, NE)	1.24	0.86, 1.80	0.2508
Interaction p-value									0.9612
Region									
Asia	242	97 (40.1)	3.5 (2.8, 5.6)	257	87 (33.9)	4.7 (3.5, 9.2)	1.18	0.88, 1.57	0.2743
Rest of World	163	36 (22.1)	4.2 (2.2, NE)	148	29 (19.6)	8.6 (4.4, NE)	1.40	0.86, 2.31	0.1712
Interaction p-value									0.5371
PD-L1 Status									
High (>=1%)	239	79 (33.1)	3.9 (2.8,10.3)	251	74 (29.5)	5.8 (3.5,10.0)	1.15	0.84, 1.58	0.3916
Low (<1%)	119	41 (34.5)	3.9 (2.4, 5.6)	117	33 (28.2)	5.8 (3.5, NE)	1.36	0.86, 2.17	0.1822
Interaction p-value									0.5444
Sex									
Male	199	65 (32.7)	4.3 (2.9, 8.3)	208	62 (29.8)	6.7 (3.5,10.0)	1.07	0.75, 1.52	0.7108

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.3.4.5 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Eating
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	68 (33.0)	3.0 (2.2, 4.9)	197	54 (27.4)	4.9 (3.5, NE)	1.44	1.01, 2.07	0.0433*
Interaction p-value									0.2368
Race									
Asian	249	97 (39.0)	3.9 (2.8, 6.5)	262	88 (33.6)	4.7 (3.5, 9.2)	1.15	0.86, 1.54	0.3303
Non-Asian	156	36 (23.1)	3.7 (2.2, 4.9)	143	28 (19.6)	8.6 (4.4, NE)	1.48	0.91, 2.45	0.1176
Interaction p-value									0.3926
WHO ECOG Status at Screening									
0	189	62 (32.8)	4.3 (2.8, 5.6)	185	46 (24.9)	9.2 (5.1, NE)	1.59	1.09, 2.34	0.0168*
1	216	71 (32.9)	3.5 (2.4, 8.3)	220	70 (31.8)	3.7 (2.4, 5.7)	1.00	0.71, 1.39	0.9785
Interaction p-value									0.0694
Disease Extent									
Locally Advanced	55	21 (38.2)	2.9 (2.1, 4.6)	73	17 (23.3)	10.0 (3.6, NE)	2.06	1.09, 3.95	0.0267*
Metastatic	350	112 (32.0)	4.2 (2.8, 5.6)	331	99 (29.9)	4.9 (3.5, 7.0)	1.11	0.85, 1.46	0.4414
Interaction p-value									0.0815
MSI Status									
MSI High	3	1 (33.3)	1.0 (NE, NE)	2	2 (100)	0.8 (0.7, NE)	NC	NC	NC
MSI Stable	160	56 (35.0)	4.9 (2.8,10.3)	168	50 (29.8)	5.8 (4.1, NE)	1.18	0.81, 1.74	0.3870
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.3.4.6 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-BIL21 Time to Deterioration - Function: Treatment side effects
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	126 (38.3)	1.5 (1.4, 2.1)	334	134 (40.1)	2.3 (1.6, 3.1)	1.10	0.87, 1.41	0.4219
Recurrent	76	47 (61.8)	1.5 (1.4, 2.7)	70	38 (54.3)	2.1 (1.4, 3.5)	1.25	0.82, 1.93	0.3007
Interaction p-value									0.6163
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	38 (52.1)	1.4 (0.8, 2.1)	72	36 (50.0)	1.5 (0.9, 3.5)	1.42	0.90, 2.25	0.1329
Intrahepatic CCA	236	99 (41.9)	2.1 (1.5, 2.8)	235	100 (42.6)	2.7 (1.5, 3.2)	1.01	0.77, 1.34	0.9380
Gallbladder cancer	96	36 (37.5)	1.4 (0.9, 3.9)	98	36 (36.7)	2.8 (1.5, 5.5)	1.34	0.84, 2.13	0.2146
Interaction p-value									0.3560
Age Group									
<65	220	91 (41.4)	2.1 (1.5, 2.8)	230	100 (43.5)	2.1 (1.4, 2.8)	0.98	0.74, 1.30	0.8940
>=65	185	82 (44.3)	1.4 (1.1, 1.9)	175	72 (41.1)	2.9 (2.1, 4.2)	1.38	1.01, 1.90	0.0451*
Interaction p-value									0.1138
Region									
Asia	242	123 (50.8)	1.6 (1.4, 2.2)	257	116 (45.1)	2.9 (2.1, 3.6)	1.27	0.98, 1.63	0.0685
Rest of World	163	50 (30.7)	1.5 (0.9, 2.1)	148	56 (37.8)	1.4 (0.8, 2.1)	0.88	0.60, 1.28	0.4955
Interaction p-value									0.1146
PD-L1 Status									
High (>=1%)	239	106 (44.4)	1.5 (1.4, 2.1)	251	108 (43.0)	2.3 (1.5, 2.9)	1.13	0.87, 1.48	0.3631
Low (<1%)	119	50 (42.0)	2.1 (1.4, 2.8)	117	47 (40.2)	2.3 (1.4, 4.3)	1.20	0.80, 1.79	0.3748
Interaction p-value									0.8193
Sex									
Male	199	85 (42.7)	2.1 (1.5, 2.9)	208	85 (40.9)	2.8 (2.1, 3.9)	1.21	0.89, 1.63	0.2182

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.3.4.6 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-BIL21 Time to Deterioration - Function: Treatment side effects
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	88 (42.7)	1.4 (1.4, 2.1)	197	87 (44.2)	1.5 (1.2, 2.7)	1.06	0.79, 1.43	0.6935
Interaction p-value									0.5480
Race									
Asian	249	123 (49.4)	1.7 (1.4, 2.2)	262	117 (44.7)	2.9 (2.2, 3.6)	1.25	0.97, 1.61	0.0842
Non-Asian	156	50 (32.1)	1.5 (0.9, 2.1)	143	55 (38.5)	1.4 (0.8, 2.1)	0.90	0.61, 1.32	0.5847
Interaction p-value									0.1589
WHO ECOG Status at Screening									
0	189	86 (45.5)	1.4 (0.9, 1.6)	185	88 (47.6)	2.1 (1.4, 2.9)	1.27	0.94, 1.72	0.1127
1	216	87 (40.3)	2.1 (1.5, 3.2)	220	84 (38.2)	2.8 (1.6, 3.5)	1.05	0.78, 1.42	0.7413
Interaction p-value									0.3762
Disease Extent									
Locally Advanced	55	27 (49.1)	1.0 (0.8, 1.5)	73	37 (50.7)	2.2 (0.8, 3.3)	1.40	0.84, 2.29	0.1889
Metastatic	350	146 (41.7)	2.1 (1.4, 2.2)	331	135 (40.8)	2.3 (1.5, 3.5)	1.12	0.88, 1.41	0.3591
Interaction p-value									0.4197
MSI Status									
MSI High	3	1 (33.3)	1.0 (NE, NE)	2	1 (50.0)	3.9 (NE, NE)	NC	NC	NC
MSI Stable	160	80 (50.0)	1.4 (1.1, 2.1)	168	74 (44.0)	2.8 (1.6, 3.6)	1.31	0.96, 1.81	0.0926
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.3.4.7 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-BIL21 Time to Deterioration - Function: Difficulties with drainage bags/tubes
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	38 (11.6)	NE (NE, NE)	334	27 (8.1)	NE (NE, NE)	1.53	0.94, 2.53	0.0886
Recurrent	76	11 (14.5)	NE (NE, NE)	70	4 (5.7)	NE (NE, NE)	2.65	0.91, 9.56	0.0763
Interaction p-value									0.3751
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	8 (11.0)	NE (NE, NE)	72	4 (5.6)	NE (NE, NE)	2.03	0.64, 7.60	0.2349
Intrahepatic CCA	236	31 (13.1)	NE (NE, NE)	235	22 (9.4)	NE (NE, NE)	1.45	0.85, 2.54	0.1765
Gallbladder cancer	96	10 (10.4)	NE (NE, NE)	98	5 (5.1)	NE (NE, NE)	2.32	0.83, 7.46	0.1114
Interaction p-value									0.6961
Age Group									
<65	220	26 (11.8)	NE (NE, NE)	230	21 (9.1)	NE (NE, NE)	1.33	0.75, 2.39	0.3279
>=65	185	23 (12.4)	NE (NE, NE)	175	10 (5.7)	NE (NE, NE)	2.37	1.16, 5.20	0.0176*
Interaction p-value									0.2250
Region									
Asia	242	38 (15.7)	NE (NE, NE)	257	26 (10.1)	NE (NE, NE)	1.55	0.95, 2.59	0.0800
Rest of World	163	11 (6.7)	NE (NE, NE)	148	5 (3.4)	NE (NE, NE)	2.27	0.83, 7.21	0.1138
Interaction p-value									0.5195
PD-L1 Status									
High (>=1%)	239	35 (14.6)	NE (NE, NE)	251	20 (8.0)	NE (NE, NE)	1.87	1.09, 3.30	0.0224*
Low (<1%)	119	11 (9.2)	NE (NE, NE)	117	9 (7.7)	NE (NE, NE)	1.21	0.50, 3.00	0.6716
Interaction p-value									0.4111
Sex									
Male	199	25 (12.6)	NE (NE, NE)	208	18 (8.7)	NE (NE, NE)	1.51	0.83, 2.80	0.1821

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.3.4.7 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-BIL21 Time to Deterioration - Function: Difficulties with drainage bags/tubes
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	24 (11.7)	NE (NE, NE)	197	13 (6.6)	NE (NE, NE)	1.89	0.98, 3.82	0.0588
Interaction p-value									0.6236
Race									
Asian	249	38 (15.3)	NE (NE, NE)	262	26 (9.9)	NE (NE, NE)	1.55	0.95, 2.58	0.0810
Non-Asian	156	11 (7.1)	NE (NE, NE)	143	5 (3.5)	NE (NE, NE)	2.28	0.83, 7.23	0.1125
Interaction p-value									0.5148
WHO ECOG Status at Screening									
0	189	20 (10.6)	NE (NE, NE)	185	11 (5.9)	NE (NE, NE)	2.00	0.98, 4.32	0.0585
1	216	29 (13.4)	NE (NE, NE)	220	20 (9.1)	NE (NE, NE)	1.47	0.84, 2.64	0.1825
Interaction p-value									0.5143
Disease Extent									
Locally Advanced	55	5 (9.1)	NE (NE, NE)	73	6 (8.2)	NE (NE, NE)	1.05	0.30, 3.47	0.9406
Metastatic	350	44 (12.6)	NE (NE, NE)	331	25 (7.6)	NE (NE, NE)	1.79	1.10, 2.96	0.0181*
Interaction p-value									0.4128
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	5.3 (NE, NE)	NC	NC	NC
MSI Stable	160	25 (15.6)	NE (NE, NE)	168	10 (6.0)	NE (NE, NE)	2.62	1.29, 5.72	0.0068*
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.3.4.8 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-BIL21 Time to Deterioration - Function: Concerns regarding weight loss
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	72 (21.9)	NE (NE, NE)	334	66 (19.8)	17.5 (9.2, NE)	1.23	0.88, 1.72	0.2199
Recurrent	76	25 (32.9)	9.3 (3.9, NE)	70	19 (27.1)	NE (NE, NE)	1.19	0.66, 2.19	0.5615
Interaction p-value									0.9247
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	21 (28.8)	6.3 (2.7, NE)	72	14 (19.4)	NE (NE, NE)	1.57	0.81, 3.16	0.1863
Intrahepatic CCA	236	58 (24.6)	9.2 (5.0, NE)	235	55 (23.4)	17.5 (6.9, NE)	1.11	0.77, 1.61	0.5749
Gallbladder cancer	96	18 (18.8)	NE (NE, NE)	98	16 (16.3)	NE (NE, NE)	1.28	0.65, 2.54	0.4760
Interaction p-value									0.6680
Age Group									
<65	220	54 (24.5)	9.2 (5.0, NE)	230	43 (18.7)	NE (NE, NE)	1.42	0.96, 2.14	0.0830
>=65	185	43 (23.2)	9.3 (4.4, NE)	175	42 (24.0)	17.5 (3.7, NE)	1.02	0.66, 1.56	0.9421
Interaction p-value									0.2576
Region									
Asia	242	75 (31.0)	9.2 (4.4, NE)	257	65 (25.3)	17.5 (6.9, NE)	1.24	0.89, 1.73	0.2111
Rest of World	163	22 (13.5)	NE (NE, NE)	148	20 (13.5)	NE (NE, NE)	1.17	0.64, 2.16	0.6130
Interaction p-value									0.8747
PD-L1 Status									
High (>=1%)	239	59 (24.7)	NE (NE, NE)	251	52 (20.7)	NE (NE, NE)	1.18	0.81, 1.72	0.3780
Low (<1%)	119	28 (23.5)	9.2 (4.9, NE)	117	27 (23.1)	17.5 (4.4, NE)	1.15	0.67, 1.95	0.6135
Interaction p-value									0.9247
Sex									
Male	199	49 (24.6)	9.3 (5.1, NE)	208	52 (25.0)	9.2 (4.4, NE)	0.98	0.66, 1.45	0.9346

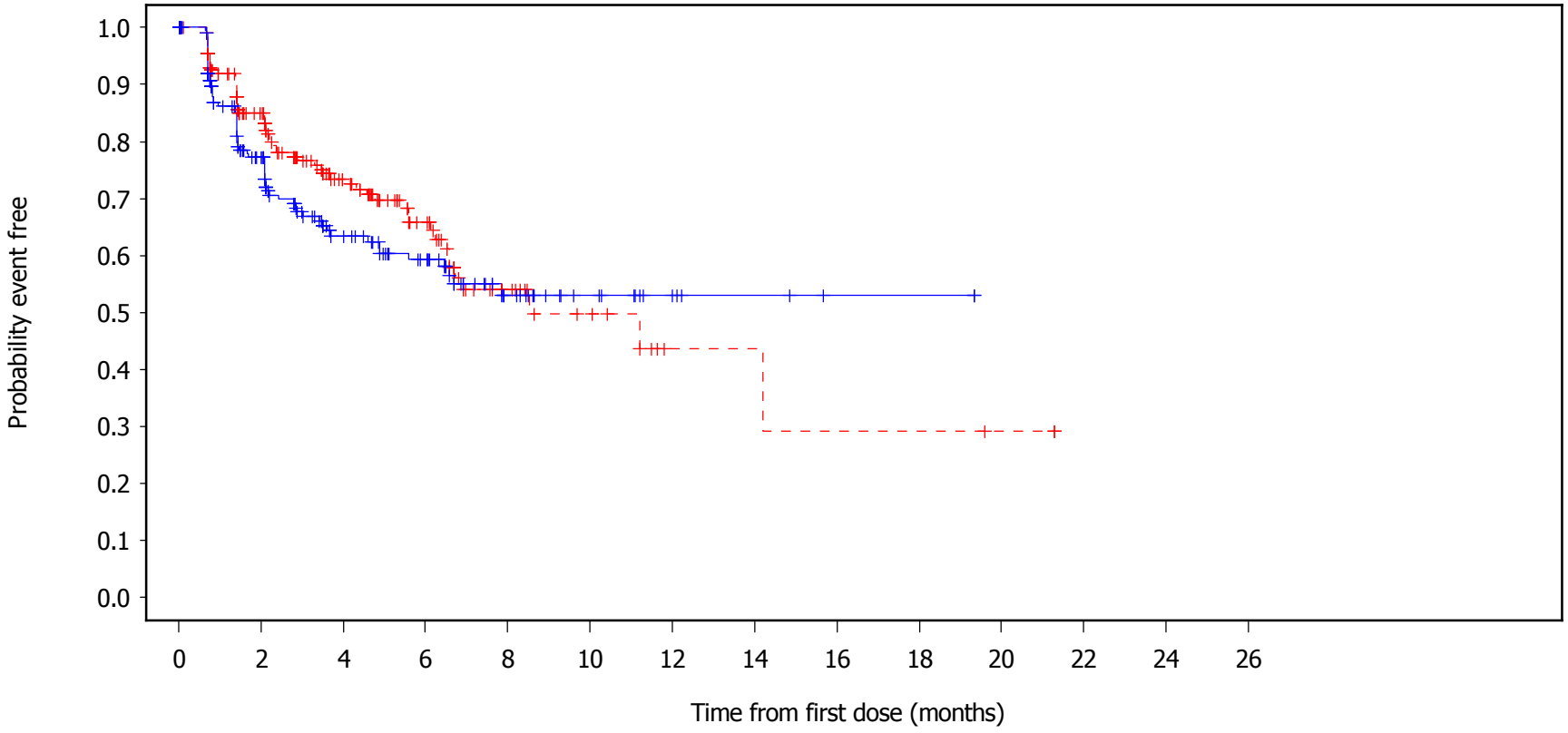
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.3.4.8 TOPAZ: Summary of subgroup analysis of time to first EORTC QLQ-BIL21 Time to Deterioration - Function: Concerns regarding weight loss
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	48 (23.3)	7.6 (4.3, NE)	197	33 (16.8)	17.5 (17.5, NE)	1.59	1.03, 2.50	0.0376*
Interaction p-value									0.1087
Race									
Asian	249	75 (30.1)	9.2 (4.4, NE)	262	66 (25.2)	17.5 (6.9, NE)	1.21	0.87, 1.69	0.2519
Non-Asian	156	22 (14.1)	NE (NE, NE)	143	19 (13.3)	NE (NE, NE)	1.24	0.67, 2.31	0.4915
Interaction p-value									0.9512
WHO ECOG Status at Screening									
0	189	41 (21.7)	NE (NE, NE)	185	39 (21.1)	NE (NE, NE)	1.15	0.74, 1.79	0.5208
1	216	56 (25.9)	9.2 (4.2, NE)	220	46 (20.9)	17.5 (6.6, NE)	1.27	0.86, 1.88	0.2315
Interaction p-value									0.7538
Disease Extent									
Locally Advanced	55	11 (20.0)	NE (NE, NE)	73	16 (21.9)	NE (NE, NE)	0.83	0.38, 1.78	0.6382
Metastatic	350	86 (24.6)	9.2 (5.0, NE)	331	69 (20.8)	17.5 (9.2, NE)	1.30	0.95, 1.79	0.1057
Interaction p-value									0.2911
MSI Status									
MSI High	3	1 (33.3)	1.0 (NE, NE)	2	2 (100)	3.8 (0.7, NE)	NC	NC	NC
MSI Stable	160	44 (27.5)	9.3 (4.4, NE)	168	32 (19.0)	17.5 (17.5, NE)	1.42	0.90, 2.26	0.1283
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

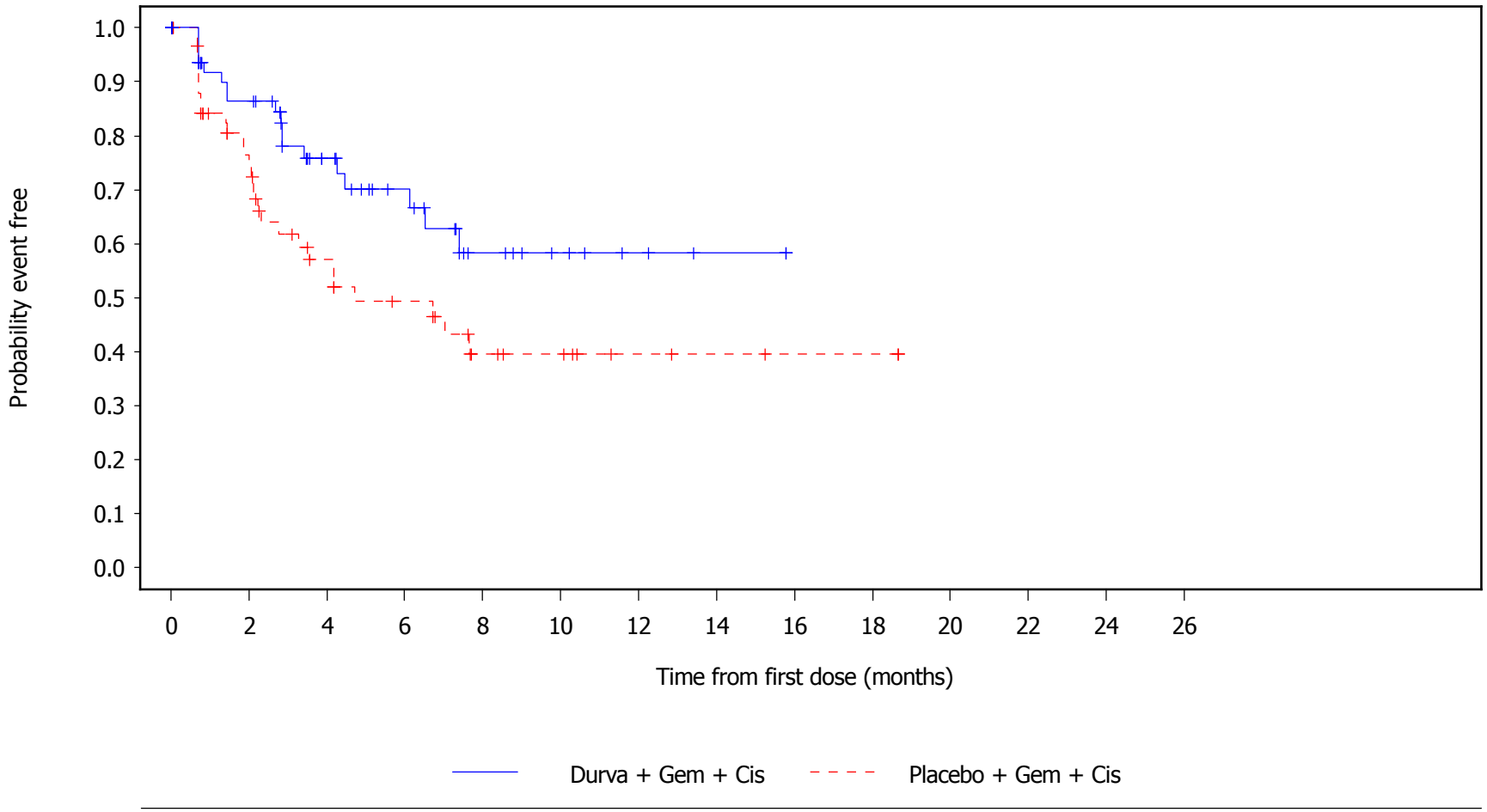
Figure 2.3.5.1 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Pain for Disease Status [eCRF]=Initially unresectable
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

329	121	69	51	22	12	5	3	1	1	0	0	0	0	Durva + Gem + Cis
333	142	82	48	18	10	3	3	2	2	1	0	0	0	Placebo + Gem + Cis

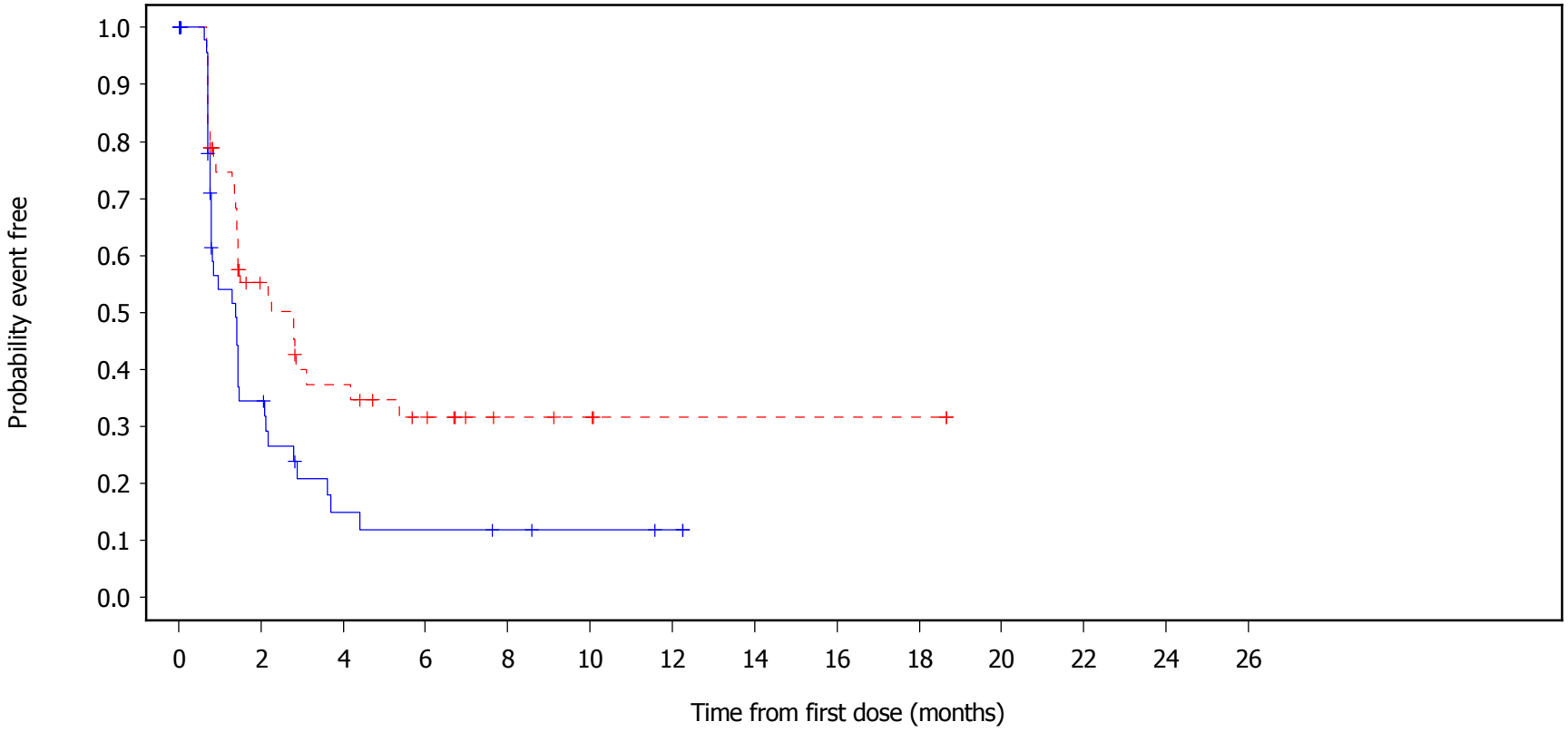
Figure 2.3.5.2 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Pain for Disease Status [eCRF]=Recurrent
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

76	48	29	20	10	6	3	1	0	0	0	0	0	0	Durva + Gem + Cis
70	38	23	17	9	7	3	2	1	1	0	0	0	0	Placebo + Gem + Cis

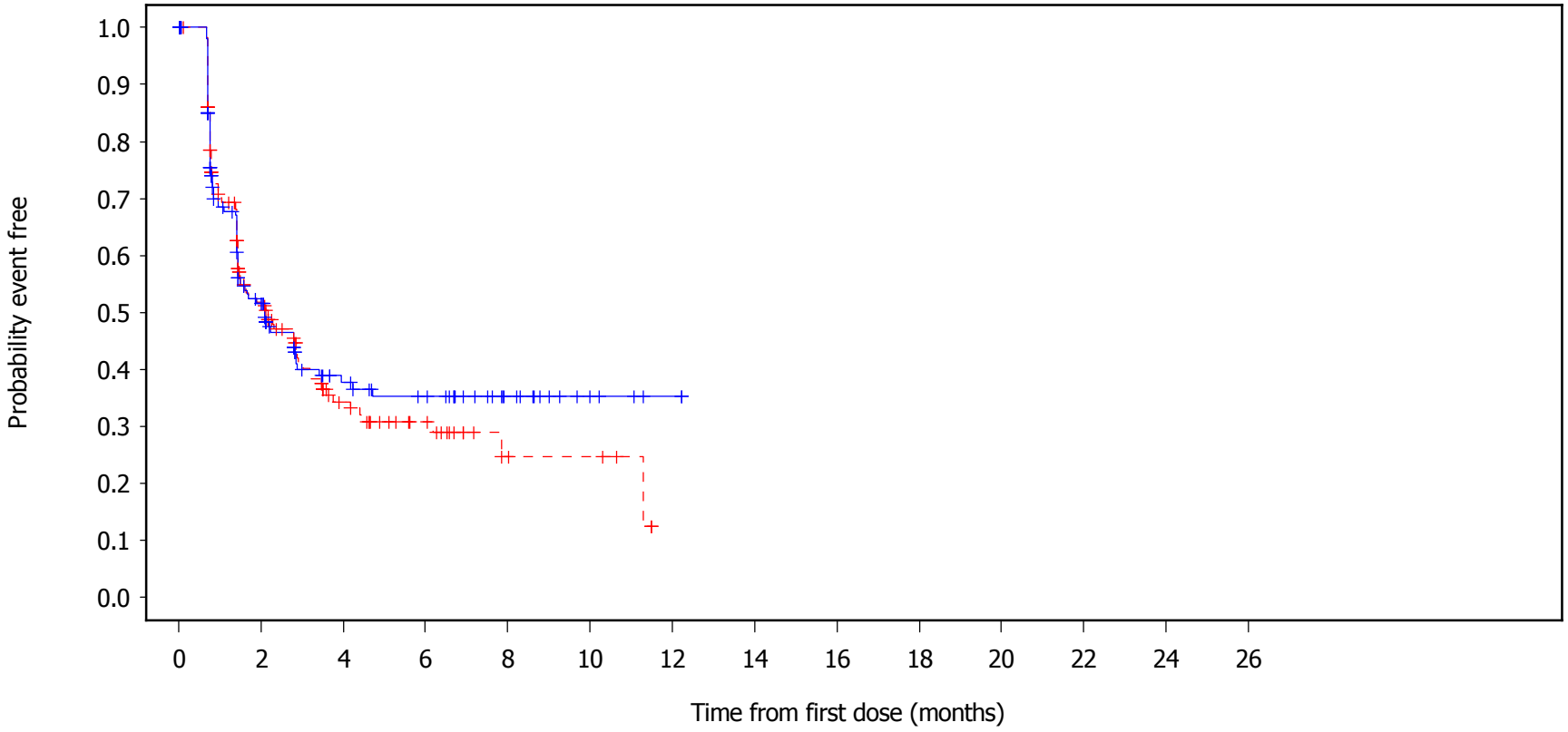
Figure 2.3.5.3 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Tiredness for Primary Tumor Location [eCRF]=Extrahepatic CCA
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

73	14	5	4	3	2	1	0	0	0	0	0	0	0	Durva + Gem + Cis
71	22	14	9	4	3	1	1	1	1	0	0	0	0	Placebo + Gem + Cis

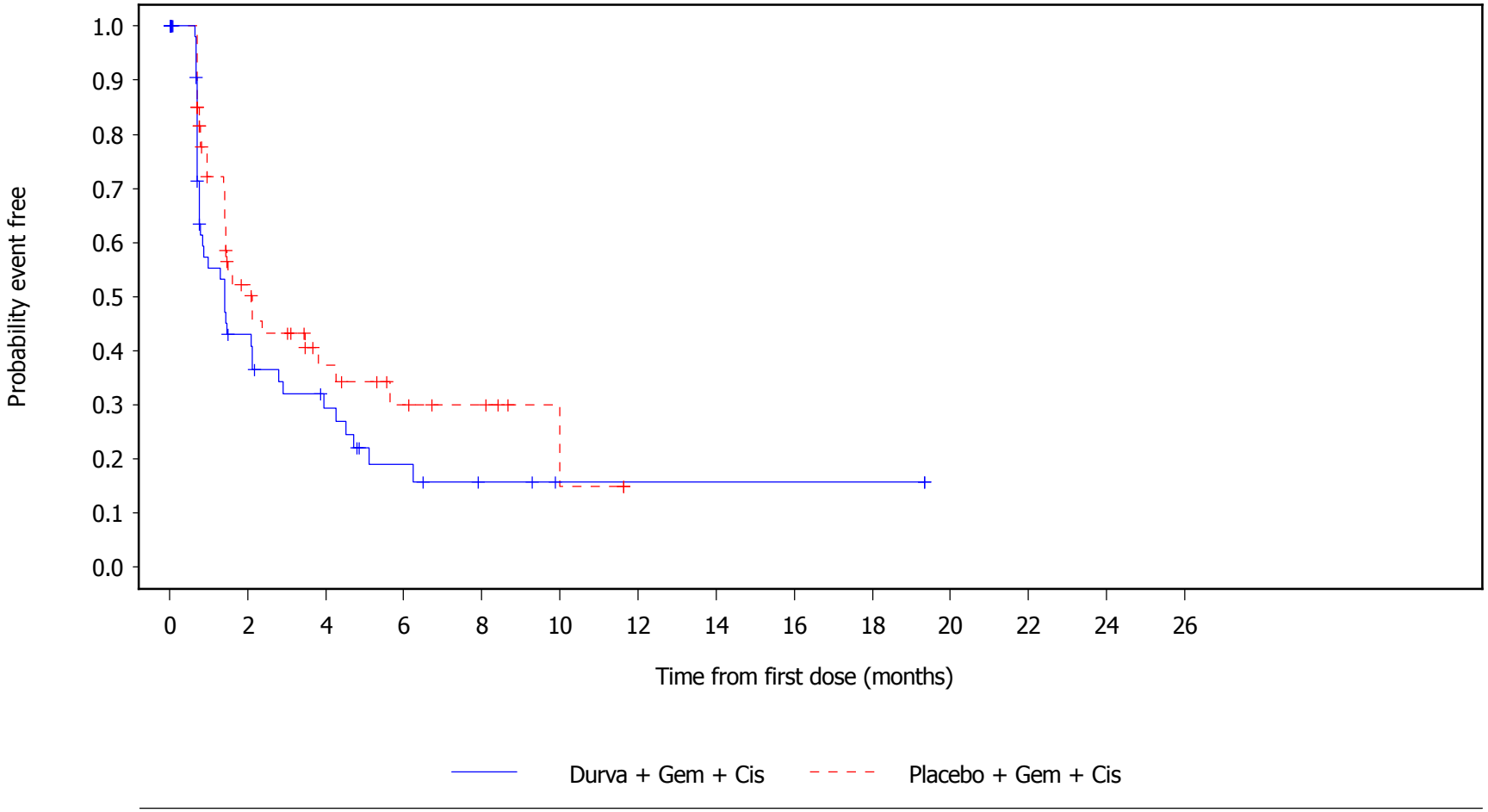
Figure 2.3.5.4 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Tiredness for Primary Tumor Location [eCRF]=Intrahepatic CCA
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

236	67	33	26	13	4	1	0	0	0	0	0	0	0	Durva + Gem + Cis
235	69	30	17	5	4	0	0	0	0	0	0	0	0	Placebo + Gem + Cis

Figure 2.3.5.5 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of EORTC QLQ-BIL21 Time to Deterioration - Symptom scale: Tiredness for Primary Tumor Location [eCRF]=Gallbladder cancer
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

96	20	12	6	3	1	1	1	1	1	0	0	0	0	Durva + Gem + Cis
98	24	12	7	5	1	0	0	0	0	0	0	0	0	Placebo + Gem + Cis

Table 2.4.1 TOPAZ: Summary of status at time to deterioration in EQ-5D VAS
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

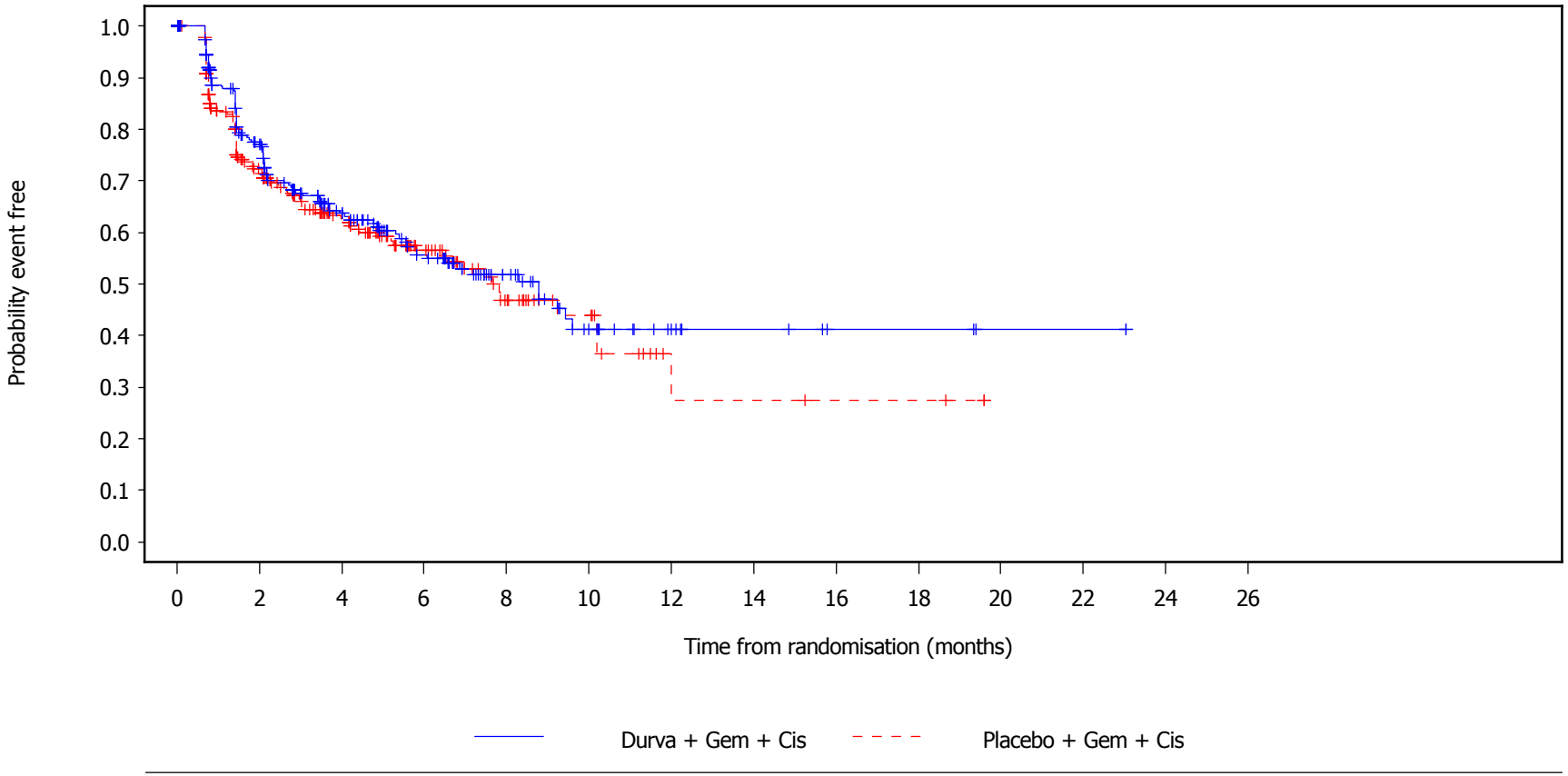
		Reason	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
EQ-5D VAS	Deterioration	Total	104 (25.7)	109 (26.9)
	Censored	Total	301 (74.3)	296 (73.1)
		No evaluable assessments or no baseline data	122 (30.1)	114 (28.1)
		Alive and no deterioration	91 (22.5)	112 (27.7)
		Death	17 (4.2)	14 (3.5)
		Two or more missed visits before deterioration or death	71 (17.5)	56 (13.8)

Table 2.4.2 TOPAZ: Summary of analysis of time to deterioration in EQ-5D VAS
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
EQ-5D VAS Time to Deterioration	405	104 (25.7)	8.8 (5.6, NE)	405	109 (26.9)	7.7 (5.8,10.2)	0.90	0.69, 1.18	0.4211

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards. [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] Estimated from Cox proportional hazards model adjusted for disease status and primary tumor location. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test stratified by disease status and primary tumor location. Hazard ratio <1 favours durva *p<0.05.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttemainpr.sas ettemainprac 19JAN2023:19:39 kjpc654

Figure 2.4.3.1 TOPAZ: Kaplan-Meier plot of EQ-5D VAS Time to Deterioration
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

405	174	104	69	37	18	9	6	3	3	1	1	0	0	Durva + Gem + Cis
404	161	99	56	28	15	3	3	2	2	0	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Table 2.4.4.1 TOPAZ: Summary of subgroup analysis of time to first EQ-5D VAS Time to Deterioration
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	329	79 (24.0)	8.3 (5.6, NE)	334	79 (23.7)	7.9 (6.5,12.0)	0.97	0.71, 1.33	0.8545
Recurrent	76	25 (32.9)	8.8 (3.9, NE)	70	30 (42.9)	4.9 (2.7, NE)	0.72	0.42, 1.22	0.2207
Interaction p-value									0.3360
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	19 (26.0)	7.2 (3.1, NE)	72	21 (29.2)	4.4 (2.5, NE)	0.82	0.44, 1.54	0.5405
Intrahepatic CCA	236	63 (26.7)	8.3 (5.6, 9.4)	235	63 (26.8)	9.2 (6.5, NE)	0.92	0.65, 1.30	0.6288
Gallbladder cancer	96	22 (22.9)	NE (NE, NE)	98	25 (25.5)	7.0 (4.9, NE)	0.92	0.51, 1.63	0.7723
Interaction p-value									0.9536
Age Group									
<65	220	59 (26.8)	8.8 (5.3, NE)	230	60 (26.1)	9.2 (5.8,10.2)	1.01	0.70, 1.44	0.9705
>=65	185	45 (24.3)	8.3 (5.4, NE)	175	49 (28.0)	7.5 (3.1, NE)	0.78	0.52, 1.16	0.2201
Interaction p-value									0.3468
Region									
Asia	242	80 (33.1)	8.3 (5.6, 9.6)	257	77 (30.0)	9.2 (5.2,12.0)	0.97	0.71, 1.33	0.8486
Rest of World	163	24 (14.7)	NE (NE, NE)	148	32 (21.6)	7.7 (4.4, NE)	0.73	0.42, 1.23	0.2381
Interaction p-value									0.3599
PD-L1 Status									
High (>=1%)	239	61 (25.5)	8.8 (5.6, NE)	251	67 (26.7)	7.0 (4.9, NE)	0.85	0.60, 1.21	0.3762
Low (<1%)	119	32 (26.9)	8.3 (4.9, NE)	117	33 (28.2)	7.8 (4.4, NE)	0.88	0.54, 1.43	0.5943
Interaction p-value									0.9358
Sex									
Male	199	50 (25.1)	8.8 (6.1, NE)	208	54 (26.0)	7.9 (6.5, NE)	0.92	0.62, 1.35	0.6600

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.4.4.1 TOPAZ: Summary of subgroup analysis of time to first EQ-5D VAS Time to Deterioration
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Female	206	54 (26.2)	5.8 (3.7, NE)	197	55 (27.9)	6.6 (4.0, NE)	0.88	0.60, 1.28	0.4897
Interaction p-value									0.8665
Race									
Asian	249	80 (32.1)	8.3 (5.8, 9.6)	262	78 (29.8)	7.5 (5.2,12.0)	0.95	0.70, 1.30	0.7646
Non-Asian	156	24 (15.4)	NE (NE, NE)	143	31 (21.7)	7.7 (4.4, NE)	0.76	0.44, 1.29	0.3139
Interaction p-value									0.4742
WHO ECOG Status at Screening									
0	189	49 (25.9)	8.3 (4.9, NE)	185	45 (24.3)	9.2 (5.8, NE)	1.15	0.76, 1.72	0.5104
1	216	55 (25.5)	9.4 (5.4, NE)	220	64 (29.1)	7.0 (4.2,10.2)	0.73	0.51, 1.05	0.0904
Interaction p-value									0.1057
Disease Extent									
Locally Advanced	55	9 (16.4)	NE (NE, NE)	73	19 (26.0)	NE (NE, NE)	0.48	0.20, 1.03	0.0581
Metastatic	350	95 (27.1)	6.9 (4.9, 9.4)	331	90 (27.2)	7.7 (5.8,10.2)	0.98	0.73, 1.31	0.8818
Interaction p-value									0.0859
MSI Status									
MSI High	3	1 (33.3)	5.6 (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	160	44 (27.5)	8.8 (5.6, NE)	168	54 (32.1)	5.8 (3.1,12.0)	0.72	0.48, 1.07	0.0996
Interaction p-value									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Global QoL/health status	Durva + Gem + Cis (N=405)	Baseline [a]	324	64.12	20.023	8.3	66.67	100.0
		Cycle 02 Day 01	303	66.14	18.987	0.0	66.67	100.0
		Cycle 03 Day 01	255	67.78	17.912	16.7	66.67	100.0
		Cycle 04 Day 01	248	68.38	18.494	16.7	66.67	100.0
		Cycle 05 Day 01	226	68.14	17.924	8.3	66.67	100.0
		Cycle 06 Day 01	205	68.33	18.550	8.3	66.67	100.0
		Cycle 07 Day 01	172	69.96	17.113	16.7	66.67	100.0
		Cycle 08 Day 01	172	68.27	19.524	0.0	66.67	100.0
		Cycle 09 Day 01	147	68.42	18.843	8.3	66.67	100.0
		Cycle 10 Day 01	147	70.58	18.693	16.7	75.00	100.0
		Cycle 11 Day 01	97	73.63	15.482	33.3	75.00	100.0
		Cycle 12 Day 01	80	70.94	16.239	33.3	66.67	100.0
		Cycle 13 Day 01	51	71.90	15.896	33.3	75.00	100.0
		Cycle 14 Day 01	45	76.11	14.499	33.3	83.33	100.0
		Cycle 15 Day 01	30	72.50	14.038	41.7	70.83	100.0
		Cycle 16 Day 01	36	70.60	15.747	33.3	70.83	91.7
		Cycle 18 Day 01	24	73.96	15.602	41.7	70.83	100.0
		Cycle 20 Day 01	21	71.83	17.771	41.7	66.67	100.0
		Cycle 22 Day 01	18	70.37	15.713	41.7	66.67	100.0
		Cycle 24 Day 01	11	74.24	18.429	33.3	83.33	100.0
		Cycle 26 Day 01	5	80.00	21.731	50.0	83.33	100.0
		Cycle 28 Day 01	3	88.89	9.623	83.3	83.33	100.0
		Follow-up Day 30	99	57.15	26.753	0.0	66.67	100.0
		Follow-up Month 2	41	61.38	23.699	0.0	66.67	100.0
		Follow-up Month 3	24	58.68	15.635	33.3	66.67	83.3
	Placebo + Gem + Cis (N=405)	Baseline [a]	333	66.44	20.630	0.0	66.67	100.0
		Cycle 02 Day 01	321	66.41	19.058	16.7	66.67	100.0
		Cycle 03 Day 01	252	66.73	18.950	8.3	66.67	100.0
		Cycle 04 Day 01	246	66.67	20.509	0.0	66.67	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	200	67.75	17.330	0.0	66.67	100.0
		Cycle 06 Day 01	200	68.21	18.171	0.0	66.67	100.0
		Cycle 07 Day 01	166	67.12	17.654	16.7	66.67	100.0
		Cycle 08 Day 01	150	65.28	17.866	8.3	66.67	100.0
		Cycle 09 Day 01	122	70.56	15.753	33.3	66.67	100.0
		Cycle 10 Day 01	110	69.09	17.095	16.7	66.67	100.0
		Cycle 11 Day 01	67	68.91	16.577	33.3	66.67	100.0
		Cycle 12 Day 01	59	69.07	16.742	33.3	66.67	100.0
		Cycle 13 Day 01	29	72.41	21.023	25.0	83.33	100.0
		Cycle 14 Day 01	29	70.11	20.596	25.0	83.33	100.0
		Cycle 15 Day 01	16	71.35	17.994	25.0	83.33	83.3
		Cycle 16 Day 01	13	69.23	20.801	33.3	75.00	100.0
		Cycle 18 Day 01	10	70.83	20.507	33.3	66.67	100.0
		Cycle 20 Day 01	6	68.06	25.504	33.3	75.00	91.7
		Cycle 22 Day 01	4	62.50	30.807	25.0	66.67	91.7
		Cycle 24 Day 01	2	62.50	29.463	41.7	62.50	83.3
		Cycle 26 Day 01	2	66.67	23.570	50.0	66.67	83.3
		Follow-up Day 30	113	56.93	23.541	0.0	58.33	100.0
		Follow-up Month 2	37	59.91	19.527	16.7	66.67	100.0
		Follow-up Month 3	25	66.33	19.317	25.0	66.67	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Functional scale: Physical	Durva + Gem + Cis (N=405)	Baseline [a]	324	80.21	18.957	13.3	86.67	100.0
		Cycle 02 Day 01	303	81.74	17.573	6.7	86.67	100.0
		Cycle 03 Day 01	255	82.25	16.228	13.3	86.67	100.0
		Cycle 04 Day 01	248	82.58	16.662	13.3	86.67	100.0
		Cycle 05 Day 01	226	82.48	16.443	6.7	86.67	100.0
		Cycle 06 Day 01	205	83.58	16.363	13.3	86.67	100.0
		Cycle 07 Day 01	172	85.04	15.018	33.3	86.67	100.0
		Cycle 08 Day 01	172	83.80	15.715	0.0	86.67	100.0
		Cycle 09 Day 01	147	84.31	15.563	33.3	86.67	100.0
		Cycle 10 Day 01	147	84.63	16.582	0.0	86.67	100.0
		Cycle 11 Day 01	97	86.60	13.454	40.0	86.67	100.0
		Cycle 12 Day 01	80	84.50	16.494	26.7	86.67	100.0
		Cycle 13 Day 01	51	85.36	15.378	40.0	86.67	100.0
		Cycle 14 Day 01	45	89.33	13.058	40.0	93.33	100.0
		Cycle 15 Day 01	30	87.11	12.371	53.3	90.00	100.0
		Cycle 16 Day 01	36	86.30	13.039	53.3	86.67	100.0
		Cycle 18 Day 01	24	90.56	9.813	73.3	93.33	100.0
		Cycle 20 Day 01	21	87.30	17.115	26.7	93.33	100.0
		Cycle 22 Day 01	18	81.48	25.826	0.0	86.67	100.0
		Cycle 24 Day 01	11	91.52	10.787	66.7	93.33	100.0
		Cycle 26 Day 01	5	88.00	8.692	80.0	86.67	100.0
		Cycle 28 Day 01	3	82.22	16.777	66.7	80.00	100.0
		Follow-up Day 30	99	69.43	27.962	0.0	80.00	100.0
		Follow-up Month 2	41	70.41	24.452	20.0	73.33	100.0
		Follow-up Month 3	24	72.22	26.497	13.3	80.00	100.0
	Placebo + Gem + Cis (N=405)	Baseline [a]	333	83.86	17.869	6.7	86.67	100.0
		Cycle 02 Day 01	321	83.16	17.151	6.7	86.67	100.0
		Cycle 03 Day 01	252	83.99	17.342	0.0	86.67	100.0
		Cycle 04 Day 01	246	83.39	18.267	6.7	86.67	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	200	83.63	17.993	6.7	86.67	100.0
		Cycle 06 Day 01	200	83.67	18.325	0.0	86.67	100.0
		Cycle 07 Day 01	166	82.61	18.666	0.0	86.67	100.0
		Cycle 08 Day 01	150	82.84	17.737	20.0	86.67	100.0
		Cycle 09 Day 01	122	85.52	15.010	33.3	86.67	100.0
		Cycle 10 Day 01	110	84.67	15.551	33.3	86.67	100.0
		Cycle 11 Day 01	67	85.67	14.414	46.7	86.67	100.0
		Cycle 12 Day 01	59	86.55	16.306	20.0	93.33	100.0
		Cycle 13 Day 01	29	85.75	13.654	53.3	86.67	100.0
		Cycle 14 Day 01	29	85.06	16.776	40.0	86.67	100.0
		Cycle 15 Day 01	16	87.50	18.196	46.7	93.33	100.0
		Cycle 16 Day 01	13	84.10	17.751	46.7	93.33	100.0
		Cycle 18 Day 01	10	82.00	19.889	40.0	86.67	100.0
		Cycle 20 Day 01	6	78.89	25.791	33.3	86.67	100.0
		Cycle 22 Day 01	4	65.00	31.914	26.7	66.67	100.0
		Cycle 24 Day 01	2	73.33	37.712	46.7	73.33	100.0
		Cycle 26 Day 01	2	86.67	18.856	73.3	86.67	100.0
		Follow-up Day 30	113	73.16	24.551	0.0	80.00	100.0
		Follow-up Month 2	37	73.33	21.943	20.0	80.00	100.0
		Follow-up Month 3	25	76.53	22.699	13.3	80.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Functional scale: Role	Durva + Gem + Cis (N=405)	Baseline [a]	324	81.12	24.418	0.0	91.67	100.0
		Cycle 02 Day 01	303	81.57	21.714	0.0	83.33	100.0
		Cycle 03 Day 01	255	80.00	23.957	0.0	83.33	100.0
		Cycle 04 Day 01	248	78.56	22.563	0.0	83.33	100.0
		Cycle 05 Day 01	226	80.97	22.263	0.0	83.33	100.0
		Cycle 06 Day 01	205	81.14	23.438	0.0	83.33	100.0
		Cycle 07 Day 01	172	83.62	19.866	0.0	100.00	100.0
		Cycle 08 Day 01	172	81.49	21.813	0.0	83.33	100.0
		Cycle 09 Day 01	147	82.20	20.520	0.0	100.00	100.0
		Cycle 10 Day 01	147	82.43	19.776	0.0	83.33	100.0
		Cycle 11 Day 01	97	84.88	18.175	33.3	100.00	100.0
		Cycle 12 Day 01	80	86.04	17.679	33.3	100.00	100.0
		Cycle 13 Day 01	51	85.62	19.442	33.3	100.00	100.0
		Cycle 14 Day 01	45	87.78	16.049	33.3	100.00	100.0
		Cycle 15 Day 01	30	88.89	14.735	66.7	100.00	100.0
		Cycle 16 Day 01	36	82.87	21.634	16.7	100.00	100.0
		Cycle 18 Day 01	24	88.19	15.910	66.7	100.00	100.0
		Cycle 20 Day 01	21	85.71	19.920	33.3	100.00	100.0
		Cycle 22 Day 01	18	75.93	25.063	0.0	66.67	100.0
		Cycle 24 Day 01	11	87.88	15.076	66.7	100.00	100.0
		Cycle 26 Day 01	5	86.67	18.257	66.7	100.00	100.0
		Cycle 28 Day 01	3	77.78	19.245	66.7	66.67	100.0
		Follow-up Day 30	99	66.50	33.290	0.0	66.67	100.0
		Follow-up Month 2	41	66.67	30.505	0.0	66.67	100.0
		Follow-up Month 3	24	69.44	28.090	0.0	66.67	100.0
	Placebo + Gem + Cis (N=405)	Baseline [a]	333	82.93	22.477	0.0	100.00	100.0
		Cycle 02 Day 01	321	81.88	21.400	0.0	83.33	100.0
		Cycle 03 Day 01	252	83.66	21.325	0.0	100.00	100.0
		Cycle 04 Day 01	246	81.64	23.725	0.0	100.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	200	82.00	22.748	0.0	100.00	100.0
		Cycle 06 Day 01	200	82.42	21.669	0.0	100.00	100.0
		Cycle 07 Day 01	166	80.22	23.254	0.0	83.33	100.0
		Cycle 08 Day 01	150	79.67	23.718	0.0	83.33	100.0
		Cycle 09 Day 01	122	82.79	20.657	0.0	83.33	100.0
		Cycle 10 Day 01	110	85.30	19.386	33.3	100.00	100.0
		Cycle 11 Day 01	67	85.32	18.007	33.3	100.00	100.0
		Cycle 12 Day 01	59	85.59	18.429	33.3	100.00	100.0
		Cycle 13 Day 01	29	83.91	20.646	33.3	100.00	100.0
		Cycle 14 Day 01	29	85.63	18.753	33.3	100.00	100.0
		Cycle 15 Day 01	16	87.50	20.638	33.3	100.00	100.0
		Cycle 16 Day 01	13	85.90	19.059	50.0	100.00	100.0
		Cycle 18 Day 01	10	80.00	32.203	0.0	100.00	100.0
		Cycle 20 Day 01	6	88.89	17.213	66.7	100.00	100.0
		Cycle 22 Day 01	4	66.67	30.429	33.3	66.67	100.0
		Cycle 24 Day 01	2	66.67	47.140	33.3	66.67	100.0
		Cycle 26 Day 01	2	83.33	23.570	66.7	83.33	100.0
		Follow-up Day 30	113	72.57	26.626	0.0	66.67	100.0
		Follow-up Month 2	37	70.72	29.241	0.0	66.67	100.0
		Follow-up Month 3	25	69.33	25.766	0.0	66.67	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Functional scale: Cognitive	Durva + Gem + Cis (N=405)	Baseline [a]	324	87.60	17.043	16.7	100.00	100.0
		Cycle 02 Day 01	303	87.90	16.674	16.7	100.00	100.0
		Cycle 03 Day 01	255	87.71	16.515	16.7	100.00	100.0
		Cycle 04 Day 01	248	87.84	15.904	33.3	100.00	100.0
		Cycle 05 Day 01	226	88.27	15.442	0.0	100.00	100.0
		Cycle 06 Day 01	205	87.48	16.598	16.7	100.00	100.0
		Cycle 07 Day 01	172	88.95	14.888	50.0	100.00	100.0
		Cycle 08 Day 01	172	85.66	16.747	0.0	83.33	100.0
		Cycle 09 Day 01	147	87.41	15.677	16.7	100.00	100.0
		Cycle 10 Day 01	147	87.19	14.992	50.0	100.00	100.0
		Cycle 11 Day 01	97	89.18	15.031	33.3	100.00	100.0
		Cycle 12 Day 01	80	87.92	15.228	50.0	100.00	100.0
		Cycle 13 Day 01	51	89.22	14.073	50.0	100.00	100.0
		Cycle 14 Day 01	45	91.48	11.581	66.7	100.00	100.0
		Cycle 15 Day 01	30	86.67	12.685	66.7	83.33	100.0
		Cycle 16 Day 01	36	86.57	13.105	66.7	83.33	100.0
		Cycle 18 Day 01	24	86.81	14.727	66.7	91.67	100.0
		Cycle 20 Day 01	21	87.30	15.728	66.7	100.00	100.0
		Cycle 22 Day 01	18	90.74	13.064	66.7	100.00	100.0
		Cycle 24 Day 01	11	87.88	16.817	50.0	100.00	100.0
		Cycle 26 Day 01	5	93.33	9.129	83.3	100.00	100.0
		Cycle 28 Day 01	3	94.44	9.623	83.3	100.00	100.0
		Follow-up Day 30	99	79.29	22.724	16.7	83.33	100.0
		Follow-up Month 2	41	82.11	19.145	16.7	83.33	100.0
		Follow-up Month 3	24	79.17	19.193	33.3	83.33	100.0
	Placebo + Gem + Cis (N=405)	Baseline [a]	333	89.24	14.980	33.3	100.00	100.0
		Cycle 02 Day 01	321	89.62	14.713	16.7	100.00	100.0
		Cycle 03 Day 01	252	87.90	16.165	16.7	100.00	100.0
		Cycle 04 Day 01	246	88.55	16.663	0.0	100.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	200	87.75	17.877	0.0	100.00	100.0
		Cycle 06 Day 01	200	86.92	18.064	0.0	100.00	100.0
		Cycle 07 Day 01	166	86.95	17.417	0.0	100.00	100.0
		Cycle 08 Day 01	150	85.11	19.032	0.0	83.33	100.0
		Cycle 09 Day 01	122	88.80	15.517	16.7	100.00	100.0
		Cycle 10 Day 01	110	86.52	17.267	33.3	100.00	100.0
		Cycle 11 Day 01	67	86.57	17.465	33.3	100.00	100.0
		Cycle 12 Day 01	59	87.29	17.326	33.3	100.00	100.0
		Cycle 13 Day 01	29	82.18	17.779	50.0	83.33	100.0
		Cycle 14 Day 01	29	81.61	20.579	33.3	83.33	100.0
		Cycle 15 Day 01	16	84.38	17.710	50.0	91.67	100.0
		Cycle 16 Day 01	13	83.33	15.215	66.7	83.33	100.0
		Cycle 18 Day 01	10	76.67	19.563	50.0	75.00	100.0
		Cycle 20 Day 01	6	83.33	10.541	66.7	83.33	100.0
		Cycle 22 Day 01	4	79.17	20.972	50.0	83.33	100.0
		Cycle 24 Day 01	2	83.33	0.000	83.3	83.33	83.3
		Cycle 26 Day 01	2	66.67	23.570	50.0	66.67	83.3
		Follow-up Day 30	113	82.45	19.901	16.7	83.33	100.0
		Follow-up Month 2	37	86.04	17.792	33.3	83.33	100.0
		Follow-up Month 3	25	85.33	18.207	33.3	83.33	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Functional scale: Emotional	Durva + Gem + Cis (N=405)	Baseline [a]	324	76.70	19.042	0.0	83.33	100.0
		Cycle 02 Day 01	303	82.81	16.147	16.7	83.33	100.0
		Cycle 03 Day 01	255	81.83	17.683	8.3	83.33	100.0
		Cycle 04 Day 01	248	82.53	17.790	8.3	83.33	100.0
		Cycle 05 Day 01	226	82.12	17.935	16.7	83.33	100.0
		Cycle 06 Day 01	205	81.67	18.421	8.3	83.33	100.0
		Cycle 07 Day 01	172	83.87	16.100	16.7	83.33	100.0
		Cycle 08 Day 01	172	81.88	20.240	0.0	91.67	100.0
		Cycle 09 Day 01	147	83.45	18.221	8.3	91.67	100.0
		Cycle 10 Day 01	147	84.01	17.187	25.0	91.67	100.0
		Cycle 11 Day 01	97	83.33	17.264	8.3	83.33	100.0
		Cycle 12 Day 01	80	85.21	15.687	50.0	91.67	100.0
		Cycle 13 Day 01	51	83.66	15.720	50.0	91.67	100.0
		Cycle 14 Day 01	45	86.30	15.807	33.3	91.67	100.0
		Cycle 15 Day 01	30	83.61	15.854	50.0	87.50	100.0
		Cycle 16 Day 01	36	83.80	15.032	58.3	83.33	100.0
		Cycle 18 Day 01	24	84.03	14.099	58.3	83.33	100.0
		Cycle 20 Day 01	21	85.71	13.474	66.7	83.33	100.0
		Cycle 22 Day 01	18	81.02	19.345	41.7	79.17	100.0
		Cycle 24 Day 01	11	94.70	10.050	75.0	100.00	100.0
		Cycle 26 Day 01	5	85.00	17.078	66.7	91.67	100.0
		Cycle 28 Day 01	3	83.33	16.667	66.7	83.33	100.0
		Follow-up Day 30	99	74.41	26.386	0.0	83.33	100.0
		Follow-up Month 2	41	75.00	24.580	8.3	83.33	100.0
		Follow-up Month 3	24	76.74	18.386	41.7	79.17	100.0
	Placebo + Gem + Cis (N=405)	Baseline [a]	333	80.33	17.154	8.3	83.33	100.0
		Cycle 02 Day 01	321	83.28	17.280	8.3	83.33	100.0
		Cycle 03 Day 01	252	82.84	18.039	0.0	87.50	100.0
		Cycle 04 Day 01	246	82.52	19.134	0.0	91.67	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	200	82.33	18.371	0.0	83.33	100.0
		Cycle 06 Day 01	200	82.04	18.229	0.0	83.33	100.0
		Cycle 07 Day 01	166	81.58	18.068	8.3	83.33	100.0
		Cycle 08 Day 01	150	81.78	18.506	0.0	83.33	100.0
		Cycle 09 Day 01	122	85.04	14.170	33.3	83.33	100.0
		Cycle 10 Day 01	110	83.26	17.212	25.0	91.67	100.0
		Cycle 11 Day 01	67	82.71	16.749	41.7	83.33	100.0
		Cycle 12 Day 01	59	83.33	18.179	25.0	83.33	100.0
		Cycle 13 Day 01	29	81.90	19.297	33.3	91.67	100.0
		Cycle 14 Day 01	29	83.33	19.416	25.0	91.67	100.0
		Cycle 15 Day 01	16	83.85	10.745	66.7	83.33	100.0
		Cycle 16 Day 01	13	82.05	21.743	25.0	91.67	100.0
		Cycle 18 Day 01	10	76.67	28.814	8.3	91.67	100.0
		Cycle 20 Day 01	6	81.94	14.353	66.7	75.00	100.0
		Cycle 22 Day 01	4	81.25	14.232	66.7	79.17	100.0
		Cycle 24 Day 01	2	79.17	17.678	66.7	79.17	91.7
		Cycle 26 Day 01	2	79.17	5.893	75.0	79.17	83.3
		Follow-up Day 30	113	75.15	21.128	0.0	75.00	100.0
		Follow-up Month 2	37	81.98	17.181	41.7	83.33	100.0
		Follow-up Month 3	25	79.67	20.138	25.0	83.33	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

					Absolute Values			
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Functional scale: Social	Durva + Gem + Cis (N=405)	Baseline [a]	324	80.04	21.417	16.7	83.33	100.0
		Cycle 02 Day 01	303	81.30	20.356	16.7	83.33	100.0
		Cycle 03 Day 01	255	80.52	21.930	0.0	83.33	100.0
		Cycle 04 Day 01	248	80.65	22.081	0.0	83.33	100.0
		Cycle 05 Day 01	226	80.31	21.186	0.0	83.33	100.0
		Cycle 06 Day 01	205	80.98	21.796	0.0	83.33	100.0
		Cycle 07 Day 01	172	82.27	19.675	0.0	83.33	100.0
		Cycle 08 Day 01	172	81.01	19.772	0.0	83.33	100.0
		Cycle 09 Day 01	147	82.77	20.217	0.0	83.33	100.0
		Cycle 10 Day 01	147	83.11	18.401	16.7	83.33	100.0
		Cycle 11 Day 01	97	85.40	18.043	33.3	100.00	100.0
		Cycle 12 Day 01	80	85.42	19.192	16.7	100.00	100.0
		Cycle 13 Day 01	51	83.33	18.559	33.3	83.33	100.0
		Cycle 14 Day 01	45	85.19	18.540	16.7	83.33	100.0
		Cycle 15 Day 01	30	86.11	15.832	66.7	100.00	100.0
		Cycle 16 Day 01	36	88.89	19.107	33.3	100.00	100.0
		Cycle 18 Day 01	24	83.33	18.389	33.3	83.33	100.0
		Cycle 20 Day 01	21	84.92	17.404	50.0	100.00	100.0
		Cycle 22 Day 01	18	80.56	26.352	0.0	91.67	100.0
		Cycle 24 Day 01	11	87.88	15.076	66.7	100.00	100.0
		Cycle 26 Day 01	5	80.00	13.944	66.7	83.33	100.0
		Cycle 28 Day 01	3	88.89	19.245	66.7	100.00	100.0
		Follow-up Day 30	99	71.89	28.734	0.0	66.67	100.0
		Follow-up Month 2	41	77.64	26.249	0.0	83.33	100.0
		Follow-up Month 3	24	72.92	29.819	0.0	83.33	100.0
	Placebo + Gem + Cis (N=405)	Baseline [a]	333	82.58	20.704	0.0	83.33	100.0
		Cycle 02 Day 01	321	83.02	21.608	0.0	100.00	100.0
		Cycle 03 Day 01	252	83.27	20.855	0.0	100.00	100.0
		Cycle 04 Day 01	246	82.45	22.445	0.0	100.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	200	84.00	21.517	0.0	100.00	100.0
		Cycle 06 Day 01	200	80.83	23.197	0.0	83.33	100.0
		Cycle 07 Day 01	166	79.42	23.919	0.0	83.33	100.0
		Cycle 08 Day 01	150	81.78	22.381	0.0	100.00	100.0
		Cycle 09 Day 01	122	84.97	18.974	0.0	100.00	100.0
		Cycle 10 Day 01	110	83.94	18.191	16.7	83.33	100.0
		Cycle 11 Day 01	67	84.33	18.999	33.3	100.00	100.0
		Cycle 12 Day 01	59	81.64	22.252	0.0	83.33	100.0
		Cycle 13 Day 01	29	84.48	20.379	33.3	100.00	100.0
		Cycle 14 Day 01	29	85.06	16.272	50.0	83.33	100.0
		Cycle 15 Day 01	16	88.54	13.220	66.7	91.67	100.0
		Cycle 16 Day 01	13	87.18	16.879	50.0	100.00	100.0
		Cycle 18 Day 01	10	76.67	32.584	0.0	91.67	100.0
		Cycle 20 Day 01	6	83.33	18.257	66.7	83.33	100.0
		Cycle 22 Day 01	4	91.67	16.667	66.7	100.00	100.0
		Cycle 24 Day 01	2	83.33	23.570	66.7	83.33	100.0
		Cycle 26 Day 01	2	75.00	11.785	66.7	75.00	83.3
		Follow-up Day 30	113	74.34	26.822	0.0	83.33	100.0
		Follow-up Month 2	37	72.97	27.597	0.0	66.67	100.0
		Follow-up Month 3	25	72.67	27.588	16.7	83.33	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Single item symptom scale: Loss of appetite	Durva + Gem + Cis (N=405)	Baseline [a]	324	25.72	28.679	0.0	33.33	100.0
		Cycle 02 Day 01	303	24.53	26.500	0.0	33.33	100.0
		Cycle 03 Day 01	255	23.79	26.132	0.0	33.33	100.0
		Cycle 04 Day 01	248	23.92	24.937	0.0	33.33	100.0
		Cycle 05 Day 01	226	20.80	24.040	0.0	33.33	100.0
		Cycle 06 Day 01	205	20.49	22.453	0.0	33.33	100.0
		Cycle 07 Day 01	172	18.99	23.661	0.0	0.00	100.0
		Cycle 08 Day 01	172	22.29	27.230	0.0	0.00	100.0
		Cycle 09 Day 01	147	16.55	19.652	0.0	0.00	66.7
		Cycle 10 Day 01	147	14.06	20.982	0.0	0.00	100.0
		Cycle 11 Day 01	97	13.40	20.219	0.0	0.00	66.7
		Cycle 12 Day 01	80	9.17	16.751	0.0	0.00	66.7
		Cycle 13 Day 01	51	10.46	15.621	0.0	0.00	33.3
		Cycle 14 Day 01	45	5.19	14.134	0.0	0.00	66.7
		Cycle 15 Day 01	30	10.00	17.833	0.0	0.00	66.7
		Cycle 16 Day 01	36	9.26	17.110	0.0	0.00	66.7
		Cycle 18 Day 01	24	5.56	12.690	0.0	0.00	33.3
		Cycle 20 Day 01	21	11.11	19.245	0.0	0.00	66.7
		Cycle 22 Day 01	18	11.11	25.565	0.0	0.00	100.0
		Cycle 24 Day 01	11	3.03	10.050	0.0	0.00	33.3
		Cycle 26 Day 01	5	0.00	0.000	0.0	0.00	0.0
		Cycle 28 Day 01	3	0.00	0.000	0.0	0.00	0.0
		Follow-up Day 30	99	33.67	34.171	0.0	33.33	100.0
		Follow-up Month 2	41	26.02	32.070	0.0	0.00	100.0
		Follow-up Month 3	24	22.22	23.399	0.0	33.33	66.7
	Placebo + Gem + Cis (N=405)	Baseline [a]	333	21.52	27.146	0.0	0.00	100.0
		Cycle 02 Day 01	321	20.77	24.108	0.0	0.00	100.0
		Cycle 03 Day 01	252	22.75	25.475	0.0	33.33	100.0
		Cycle 04 Day 01	246	20.87	24.614	0.0	0.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	200	18.17	23.581	0.0	0.00	100.0
		Cycle 06 Day 01	200	18.33	24.270	0.0	0.00	100.0
		Cycle 07 Day 01	166	18.88	24.173	0.0	0.00	100.0
		Cycle 08 Day 01	150	18.22	24.298	0.0	0.00	100.0
		Cycle 09 Day 01	122	14.75	20.123	0.0	0.00	66.7
		Cycle 10 Day 01	110	15.45	21.971	0.0	0.00	100.0
		Cycle 11 Day 01	67	8.96	15.978	0.0	0.00	66.7
		Cycle 12 Day 01	59	13.56	19.690	0.0	0.00	66.7
		Cycle 13 Day 01	29	10.34	20.125	0.0	0.00	66.7
		Cycle 14 Day 01	29	14.94	24.537	0.0	0.00	100.0
		Cycle 15 Day 01	16	12.50	23.960	0.0	0.00	66.7
		Cycle 16 Day 01	13	15.38	25.875	0.0	0.00	66.7
		Cycle 18 Day 01	10	26.67	37.843	0.0	0.00	100.0
		Cycle 20 Day 01	6	11.11	17.213	0.0	0.00	33.3
		Cycle 22 Day 01	4	8.33	16.667	0.0	0.00	33.3
		Cycle 24 Day 01	2	16.67	23.570	0.0	16.67	33.3
		Cycle 26 Day 01	2	16.67	23.570	0.0	16.67	33.3
		Follow-up Day 30	113	29.20	32.162	0.0	33.33	100.0
		Follow-up Month 2	37	31.53	31.374	0.0	33.33	100.0
		Follow-up Month 3	25	24.00	34.048	0.0	0.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Single item symptom scale: Constipation	Durva + Gem + Cis (N=405)	Baseline [a]	324	17.59	25.481	0.0	0.00	100.0
		Cycle 02 Day 01	303	20.79	26.238	0.0	0.00	100.0
		Cycle 03 Day 01	255	23.01	28.411	0.0	0.00	100.0
		Cycle 04 Day 01	248	20.03	25.582	0.0	0.00	100.0
		Cycle 05 Day 01	226	17.26	23.978	0.0	0.00	100.0
		Cycle 06 Day 01	205	17.40	24.382	0.0	0.00	100.0
		Cycle 07 Day 01	172	16.09	21.771	0.0	0.00	100.0
		Cycle 08 Day 01	172	16.47	22.941	0.0	0.00	100.0
		Cycle 09 Day 01	147	14.97	21.786	0.0	0.00	100.0
		Cycle 10 Day 01	147	16.78	23.204	0.0	0.00	100.0
		Cycle 11 Day 01	97	10.65	18.350	0.0	0.00	100.0
		Cycle 12 Day 01	80	10.42	18.059	0.0	0.00	66.7
		Cycle 13 Day 01	51	12.42	18.810	0.0	0.00	66.7
		Cycle 14 Day 01	45	7.41	15.713	0.0	0.00	66.7
		Cycle 15 Day 01	30	5.56	12.635	0.0	0.00	33.3
		Cycle 16 Day 01	36	10.19	15.573	0.0	0.00	33.3
		Cycle 18 Day 01	24	5.56	12.690	0.0	0.00	33.3
		Cycle 20 Day 01	21	7.94	14.548	0.0	0.00	33.3
		Cycle 22 Day 01	18	11.11	25.565	0.0	0.00	100.0
		Cycle 24 Day 01	11	12.12	16.817	0.0	0.00	33.3
		Cycle 26 Day 01	5	13.33	18.257	0.0	0.00	33.3
		Cycle 28 Day 01	3	11.11	19.245	0.0	0.00	33.3
		Follow-up Day 30	99	17.85	23.958	0.0	0.00	100.0
		Follow-up Month 2	41	17.89	23.685	0.0	0.00	66.7
		Follow-up Month 3	24	23.61	25.020	0.0	33.33	66.7
	Placebo + Gem + Cis (N=405)	Baseline [a]	333	15.42	25.268	0.0	0.00	100.0
		Cycle 02 Day 01	321	19.73	26.057	0.0	0.00	100.0
		Cycle 03 Day 01	252	18.25	24.394	0.0	0.00	100.0
		Cycle 04 Day 01	246	18.56	24.347	0.0	0.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	200	16.33	24.326	0.0	0.00	100.0
		Cycle 06 Day 01	200	14.67	21.564	0.0	0.00	100.0
		Cycle 07 Day 01	166	15.66	23.691	0.0	0.00	100.0
		Cycle 08 Day 01	150	16.00	22.756	0.0	0.00	100.0
		Cycle 09 Day 01	122	15.57	21.506	0.0	0.00	66.7
		Cycle 10 Day 01	110	13.64	18.778	0.0	0.00	66.7
		Cycle 11 Day 01	67	11.44	18.849	0.0	0.00	66.7
		Cycle 12 Day 01	59	10.17	20.765	0.0	0.00	100.0
		Cycle 13 Day 01	29	17.24	26.157	0.0	0.00	66.7
		Cycle 14 Day 01	29	18.39	28.986	0.0	0.00	100.0
		Cycle 15 Day 01	16	20.83	20.638	0.0	33.33	66.7
		Cycle 16 Day 01	13	28.21	32.903	0.0	33.33	100.0
		Cycle 18 Day 01	10	30.00	33.148	0.0	33.33	100.0
		Cycle 20 Day 01	6	27.78	25.092	0.0	33.33	66.7
		Cycle 22 Day 01	4	33.33	27.217	0.0	33.33	66.7
		Cycle 24 Day 01	2	16.67	23.570	0.0	16.67	33.3
		Cycle 26 Day 01	2	16.67	23.570	0.0	16.67	33.3
		Follow-up Day 30	113	19.47	26.624	0.0	0.00	100.0
		Follow-up Month 2	37	14.41	22.961	0.0	0.00	66.7
		Follow-up Month 3	25	14.67	23.727	0.0	0.00	66.7

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Single item symptom scale: Diarrhoea	Durva + Gem + Cis (N=405)	Baseline [a]	324	6.38	15.083	0.0	0.00	100.0
		Cycle 02 Day 01	303	5.17	14.571	0.0	0.00	100.0
		Cycle 03 Day 01	255	6.14	14.839	0.0	0.00	66.7
		Cycle 04 Day 01	248	5.78	13.671	0.0	0.00	66.7
		Cycle 05 Day 01	226	6.34	14.877	0.0	0.00	100.0
		Cycle 06 Day 01	205	4.07	11.422	0.0	0.00	66.7
		Cycle 07 Day 01	172	4.46	12.468	0.0	0.00	66.7
		Cycle 08 Day 01	172	5.04	14.435	0.0	0.00	100.0
		Cycle 09 Day 01	147	4.99	12.554	0.0	0.00	66.7
		Cycle 10 Day 01	147	3.85	11.386	0.0	0.00	66.7
		Cycle 11 Day 01	97	5.15	14.704	0.0	0.00	100.0
		Cycle 12 Day 01	80	3.33	11.375	0.0	0.00	66.7
		Cycle 13 Day 01	51	3.92	10.847	0.0	0.00	33.3
		Cycle 14 Day 01	45	0.74	4.969	0.0	0.00	33.3
		Cycle 15 Day 01	30	2.22	8.457	0.0	0.00	33.3
		Cycle 16 Day 01	36	0.93	5.556	0.0	0.00	33.3
		Cycle 18 Day 01	24	2.78	9.411	0.0	0.00	33.3
		Cycle 20 Day 01	21	1.59	7.274	0.0	0.00	33.3
		Cycle 22 Day 01	18	5.56	17.150	0.0	0.00	66.7
		Cycle 24 Day 01	11	3.03	10.050	0.0	0.00	33.3
		Cycle 26 Day 01	5	0.00	0.000	0.0	0.00	0.0
		Cycle 28 Day 01	3	0.00	0.000	0.0	0.00	0.0
		Follow-up Day 30	99	9.09	21.199	0.0	0.00	100.0
		Follow-up Month 2	41	9.76	20.061	0.0	0.00	66.7
		Follow-up Month 3	24	6.94	13.828	0.0	0.00	33.3
	Placebo + Gem + Cis (N=405)	Baseline [a]	333	5.91	13.998	0.0	0.00	66.7
		Cycle 02 Day 01	321	6.65	15.280	0.0	0.00	100.0
		Cycle 03 Day 01	252	5.42	13.026	0.0	0.00	66.7
		Cycle 04 Day 01	246	4.47	12.154	0.0	0.00	66.7

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	200	4.17	12.020	0.0	0.00	66.7
		Cycle 06 Day 01	200	5.83	13.954	0.0	0.00	66.7
		Cycle 07 Day 01	166	5.82	14.198	0.0	0.00	66.7
		Cycle 08 Day 01	150	3.78	11.284	0.0	0.00	66.7
		Cycle 09 Day 01	122	3.01	9.587	0.0	0.00	33.3
		Cycle 10 Day 01	110	4.24	12.039	0.0	0.00	66.7
		Cycle 11 Day 01	67	3.98	10.890	0.0	0.00	33.3
		Cycle 12 Day 01	59	5.08	14.925	0.0	0.00	66.7
		Cycle 13 Day 01	29	8.05	14.516	0.0	0.00	33.3
		Cycle 14 Day 01	29	8.05	14.516	0.0	0.00	33.3
		Cycle 15 Day 01	16	8.33	14.907	0.0	0.00	33.3
		Cycle 16 Day 01	13	7.69	14.618	0.0	0.00	33.3
		Cycle 18 Day 01	10	6.67	14.055	0.0	0.00	33.3
		Cycle 20 Day 01	6	0.00	0.000	0.0	0.00	0.0
		Cycle 22 Day 01	4	8.33	16.667	0.0	0.00	33.3
		Cycle 24 Day 01	2	0.00	0.000	0.0	0.00	0.0
		Cycle 26 Day 01	2	16.67	23.570	0.0	16.67	33.3
		Follow-up Day 30	113	7.67	15.436	0.0	0.00	66.7
		Follow-up Month 2	37	11.71	21.106	0.0	0.00	100.0
		Follow-up Month 3	25	6.67	16.667	0.0	0.00	66.7

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Single item symptom scale: Dyspnoea	Durva + Gem + Cis (N=405)	Baseline [a]	324	15.64	22.616	0.0	0.00	100.0
		Cycle 02 Day 01	303	12.43	20.196	0.0	0.00	100.0
		Cycle 03 Day 01	255	14.12	21.962	0.0	0.00	100.0
		Cycle 04 Day 01	248	15.32	21.167	0.0	0.00	100.0
		Cycle 05 Day 01	226	14.45	20.062	0.0	0.00	100.0
		Cycle 06 Day 01	205	14.96	20.705	0.0	0.00	100.0
		Cycle 07 Day 01	172	16.86	22.367	0.0	0.00	100.0
		Cycle 08 Day 01	172	17.83	23.747	0.0	0.00	100.0
		Cycle 09 Day 01	147	14.29	20.272	0.0	0.00	66.7
		Cycle 10 Day 01	147	16.33	22.536	0.0	0.00	100.0
		Cycle 11 Day 01	97	11.68	17.375	0.0	0.00	66.7
		Cycle 12 Day 01	80	12.92	19.483	0.0	0.00	66.7
		Cycle 13 Day 01	51	7.84	15.760	0.0	0.00	66.7
		Cycle 14 Day 01	45	4.44	11.459	0.0	0.00	33.3
		Cycle 15 Day 01	30	6.67	13.561	0.0	0.00	33.3
		Cycle 16 Day 01	36	9.26	15.142	0.0	0.00	33.3
		Cycle 18 Day 01	24	9.72	15.477	0.0	0.00	33.3
		Cycle 20 Day 01	21	9.52	15.430	0.0	0.00	33.3
		Cycle 22 Day 01	18	18.52	26.127	0.0	0.00	66.7
		Cycle 24 Day 01	11	9.09	15.570	0.0	0.00	33.3
		Cycle 26 Day 01	5	6.67	14.907	0.0	0.00	33.3
		Cycle 28 Day 01	3	11.11	19.245	0.0	0.00	33.3
		Follow-up Day 30	99	24.92	29.100	0.0	0.00	100.0
		Follow-up Month 2	41	24.39	30.754	0.0	0.00	100.0
		Follow-up Month 3	24	16.67	19.659	0.0	0.00	66.7
	Placebo + Gem + Cis (N=405)	Baseline [a]	333	14.11	21.746	0.0	0.00	100.0
		Cycle 02 Day 01	321	14.33	20.470	0.0	0.00	100.0
		Cycle 03 Day 01	252	13.62	21.956	0.0	0.00	100.0
		Cycle 04 Day 01	246	14.77	21.371	0.0	0.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	200	15.17	22.366	0.0	0.00	100.0
		Cycle 06 Day 01	200	15.83	22.151	0.0	0.00	100.0
		Cycle 07 Day 01	166	14.26	20.537	0.0	0.00	100.0
		Cycle 08 Day 01	150	13.11	21.811	0.0	0.00	100.0
		Cycle 09 Day 01	122	13.39	19.479	0.0	0.00	66.7
		Cycle 10 Day 01	110	13.64	19.834	0.0	0.00	66.7
		Cycle 11 Day 01	67	10.95	19.582	0.0	0.00	100.0
		Cycle 12 Day 01	59	11.86	20.307	0.0	0.00	100.0
		Cycle 13 Day 01	29	13.79	20.925	0.0	0.00	66.7
		Cycle 14 Day 01	29	13.79	18.934	0.0	0.00	66.7
		Cycle 15 Day 01	16	10.42	20.069	0.0	0.00	66.7
		Cycle 16 Day 01	13	17.95	25.875	0.0	0.00	66.7
		Cycle 18 Day 01	10	13.33	23.307	0.0	0.00	66.7
		Cycle 20 Day 01	6	5.56	13.608	0.0	0.00	33.3
		Cycle 22 Day 01	4	25.00	31.914	0.0	16.67	66.7
		Cycle 24 Day 01	2	16.67	23.570	0.0	16.67	33.3
		Cycle 26 Day 01	2	16.67	23.570	0.0	16.67	33.3
		Follow-up Day 30	113	23.60	25.072	0.0	33.33	100.0
		Follow-up Month 2	37	14.41	20.093	0.0	0.00	66.7
		Follow-up Month 3	25	25.33	25.963	0.0	33.33	66.7

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Symptom scale: Fatigue	Durva + Gem + Cis (N=405)	Baseline [a]	324	31.04	23.632	0.0	33.33	100.0
		Cycle 02 Day 01	303	30.14	20.875	0.0	33.33	100.0
		Cycle 03 Day 01	255	29.28	20.147	0.0	33.33	100.0
		Cycle 04 Day 01	248	29.30	19.737	0.0	33.33	100.0
		Cycle 05 Day 01	226	29.40	18.558	0.0	33.33	100.0
		Cycle 06 Day 01	205	29.11	20.410	0.0	33.33	100.0
		Cycle 07 Day 01	172	26.87	19.111	0.0	33.33	100.0
		Cycle 08 Day 01	172	28.36	19.534	0.0	33.33	100.0
		Cycle 09 Day 01	147	24.79	19.027	0.0	22.22	77.8
		Cycle 10 Day 01	147	24.04	19.203	0.0	22.22	77.8
		Cycle 11 Day 01	97	22.68	18.209	0.0	22.22	77.8
		Cycle 12 Day 01	80	21.67	17.934	0.0	22.22	77.8
		Cycle 13 Day 01	51	20.26	16.436	0.0	22.22	66.7
		Cycle 14 Day 01	45	17.04	15.094	0.0	22.22	55.6
		Cycle 15 Day 01	30	18.15	14.438	0.0	22.22	33.3
		Cycle 16 Day 01	36	19.75	15.738	0.0	22.22	55.6
		Cycle 18 Day 01	24	15.74	12.223	0.0	22.22	33.3
		Cycle 20 Day 01	21	19.05	17.618	0.0	22.22	66.7
		Cycle 22 Day 01	18	22.84	22.698	0.0	22.22	77.8
		Cycle 24 Day 01	11	12.12	13.567	0.0	11.11	33.3
		Cycle 26 Day 01	5	15.56	16.851	0.0	11.11	33.3
		Cycle 28 Day 01	3	18.52	16.973	0.0	22.22	33.3
		Follow-up Day 30	99	39.17	27.646	0.0	33.33	100.0
		Follow-up Month 2	41	41.46	29.083	0.0	33.33	100.0
		Follow-up Month 3	24	39.35	25.163	0.0	33.33	100.0
	Placebo + Gem + Cis (N=405)	Baseline [a]	333	27.93	21.432	0.0	22.22	100.0
		Cycle 02 Day 01	321	29.11	20.765	0.0	33.33	100.0
		Cycle 03 Day 01	252	28.88	20.549	0.0	33.33	100.0
		Cycle 04 Day 01	246	28.86	21.521	0.0	33.33	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	200	27.06	20.827	0.0	33.33	100.0
		Cycle 06 Day 01	200	27.94	20.173	0.0	33.33	100.0
		Cycle 07 Day 01	166	29.65	21.964	0.0	33.33	100.0
		Cycle 08 Day 01	150	29.56	21.573	0.0	33.33	100.0
		Cycle 09 Day 01	122	25.14	18.994	0.0	33.33	88.9
		Cycle 10 Day 01	110	24.95	19.635	0.0	27.78	77.8
		Cycle 11 Day 01	67	21.89	17.934	0.0	22.22	66.7
		Cycle 12 Day 01	59	21.09	15.119	0.0	22.22	66.7
		Cycle 13 Day 01	29	21.07	16.626	0.0	22.22	66.7
		Cycle 14 Day 01	29	21.46	16.515	0.0	22.22	66.7
		Cycle 15 Day 01	16	22.92	15.433	0.0	22.22	44.4
		Cycle 16 Day 01	13	27.35	16.111	0.0	22.22	55.6
		Cycle 18 Day 01	10	33.33	26.189	0.0	27.78	88.9
		Cycle 20 Day 01	6	22.22	17.213	0.0	22.22	44.4
		Cycle 22 Day 01	4	36.11	13.981	22.2	33.33	55.6
		Cycle 24 Day 01	2	16.67	7.857	11.1	16.67	22.2
		Cycle 26 Day 01	2	33.33	31.427	11.1	33.33	55.6
		Follow-up Day 30	113	37.66	25.434	0.0	33.33	100.0
		Follow-up Month 2	37	36.04	26.111	0.0	33.33	100.0
		Follow-up Month 3	25	32.44	27.577	0.0	33.33	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Single item scale: Financial difficulties	Durva + Gem + Cis (N=405)	Baseline [a]	324	18.62	25.423	0.0	0.00	100.0
		Cycle 02 Day 01	303	14.85	23.402	0.0	0.00	100.0
		Cycle 03 Day 01	255	15.56	22.475	0.0	0.00	100.0
		Cycle 04 Day 01	248	14.78	23.351	0.0	0.00	100.0
		Cycle 05 Day 01	226	15.49	23.541	0.0	0.00	100.0
		Cycle 06 Day 01	205	15.28	24.129	0.0	0.00	100.0
		Cycle 07 Day 01	172	13.37	21.223	0.0	0.00	100.0
		Cycle 08 Day 01	172	13.95	22.493	0.0	0.00	100.0
		Cycle 09 Day 01	147	13.83	21.667	0.0	0.00	100.0
		Cycle 10 Day 01	147	12.24	20.303	0.0	0.00	100.0
		Cycle 11 Day 01	97	13.75	24.885	0.0	0.00	100.0
		Cycle 12 Day 01	80	12.08	21.376	0.0	0.00	100.0
		Cycle 13 Day 01	51	13.07	22.190	0.0	0.00	100.0
		Cycle 14 Day 01	45	9.63	22.045	0.0	0.00	100.0
		Cycle 15 Day 01	30	5.56	15.371	0.0	0.00	66.7
		Cycle 16 Day 01	36	5.56	14.907	0.0	0.00	66.7
		Cycle 18 Day 01	24	8.33	17.720	0.0	0.00	66.7
		Cycle 20 Day 01	21	7.94	14.548	0.0	0.00	33.3
		Cycle 22 Day 01	18	16.67	26.197	0.0	0.00	100.0
		Cycle 24 Day 01	11	12.12	16.817	0.0	0.00	33.3
		Cycle 26 Day 01	5	6.67	14.907	0.0	0.00	33.3
		Cycle 28 Day 01	3	0.00	0.000	0.0	0.00	0.0
		Follow-up Day 30	99	24.92	31.710	0.0	0.00	100.0
		Follow-up Month 2	41	17.89	23.685	0.0	0.00	100.0
		Follow-up Month 3	24	25.00	31.470	0.0	0.00	100.0
	Placebo + Gem + Cis (N=405)	Baseline [a]	333	17.22	25.027	0.0	0.00	100.0
		Cycle 02 Day 01	321	15.58	23.710	0.0	0.00	100.0
		Cycle 03 Day 01	252	14.15	23.006	0.0	0.00	100.0
		Cycle 04 Day 01	246	14.23	23.922	0.0	0.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	200	14.17	24.428	0.0	0.00	100.0
		Cycle 06 Day 01	200	14.83	24.714	0.0	0.00	100.0
		Cycle 07 Day 01	166	13.45	23.493	0.0	0.00	100.0
		Cycle 08 Day 01	150	14.67	24.265	0.0	0.00	100.0
		Cycle 09 Day 01	122	12.84	21.189	0.0	0.00	100.0
		Cycle 10 Day 01	110	13.33	20.790	0.0	0.00	100.0
		Cycle 11 Day 01	67	13.43	20.970	0.0	0.00	100.0
		Cycle 12 Day 01	59	12.43	23.076	0.0	0.00	100.0
		Cycle 13 Day 01	29	13.79	22.743	0.0	0.00	100.0
		Cycle 14 Day 01	29	17.24	22.923	0.0	0.00	100.0
		Cycle 15 Day 01	16	6.25	13.437	0.0	0.00	33.3
		Cycle 16 Day 01	13	17.95	29.235	0.0	0.00	100.0
		Cycle 18 Day 01	10	20.00	32.203	0.0	0.00	100.0
		Cycle 20 Day 01	6	11.11	17.213	0.0	0.00	33.3
		Cycle 22 Day 01	4	8.33	16.667	0.0	0.00	33.3
		Cycle 24 Day 01	2	0.00	0.000	0.0	0.00	0.0
		Cycle 26 Day 01	2	16.67	23.570	0.0	16.67	33.3
		Follow-up Day 30	114	18.42	27.008	0.0	0.00	100.0
		Follow-up Month 2	37	20.72	27.612	0.0	0.00	100.0
		Follow-up Month 3	25	26.67	28.868	0.0	33.33	66.7

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Symptom scale: Nausea and vomiting	Durva + Gem + Cis (N=405)	Baseline [a]	324	7.87	14.567	0.0	0.00	66.7
		Cycle 02 Day 01	303	11.44	15.560	0.0	0.00	100.0
		Cycle 03 Day 01	255	10.65	14.893	0.0	0.00	83.3
		Cycle 04 Day 01	248	10.82	16.239	0.0	0.00	100.0
		Cycle 05 Day 01	226	10.55	15.336	0.0	0.00	83.3
		Cycle 06 Day 01	205	10.81	17.257	0.0	0.00	100.0
		Cycle 07 Day 01	172	9.40	13.979	0.0	0.00	66.7
		Cycle 08 Day 01	172	11.43	16.074	0.0	0.00	100.0
		Cycle 09 Day 01	147	8.96	14.762	0.0	0.00	83.3
		Cycle 10 Day 01	147	7.60	13.687	0.0	0.00	66.7
		Cycle 11 Day 01	97	3.61	8.412	0.0	0.00	33.3
		Cycle 12 Day 01	80	3.54	9.448	0.0	0.00	50.0
		Cycle 13 Day 01	51	3.59	9.611	0.0	0.00	50.0
		Cycle 14 Day 01	45	1.48	4.797	0.0	0.00	16.7
		Cycle 15 Day 01	30	2.78	12.444	0.0	0.00	66.7
		Cycle 16 Day 01	36	3.70	10.624	0.0	0.00	50.0
		Cycle 18 Day 01	24	4.17	7.372	0.0	0.00	16.7
		Cycle 20 Day 01	21	3.97	8.983	0.0	0.00	33.3
		Cycle 22 Day 01	18	0.93	3.928	0.0	0.00	16.7
		Cycle 24 Day 01	11	1.52	5.025	0.0	0.00	16.7
		Cycle 26 Day 01	5	0.00	0.000	0.0	0.00	0.0
		Cycle 28 Day 01	3	5.56	9.623	0.0	0.00	16.7
		Follow-up Day 30	99	18.69	23.362	0.0	16.67	100.0
		Follow-up Month 2	41	12.60	20.676	0.0	0.00	100.0
		Follow-up Month 3	24	16.67	19.035	0.0	16.67	66.7
	Placebo + Gem + Cis (N=405)	Baseline [a]	333	6.76	15.422	0.0	0.00	100.0
		Cycle 02 Day 01	321	10.64	16.512	0.0	0.00	100.0
		Cycle 03 Day 01	252	11.04	15.111	0.0	0.00	100.0
		Cycle 04 Day 01	246	10.98	16.813	0.0	0.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	200	9.08	13.656	0.0	0.00	83.3
		Cycle 06 Day 01	200	9.83	14.196	0.0	0.00	100.0
		Cycle 07 Day 01	166	10.74	16.819	0.0	0.00	100.0
		Cycle 08 Day 01	150	11.44	16.400	0.0	0.00	83.3
		Cycle 09 Day 01	122	8.47	12.900	0.0	0.00	66.7
		Cycle 10 Day 01	110	6.06	13.111	0.0	0.00	83.3
		Cycle 11 Day 01	67	5.22	9.713	0.0	0.00	33.3
		Cycle 12 Day 01	59	4.80	12.007	0.0	0.00	66.7
		Cycle 13 Day 01	29	3.45	8.188	0.0	0.00	33.3
		Cycle 14 Day 01	29	2.30	5.849	0.0	0.00	16.7
		Cycle 15 Day 01	16	2.08	5.693	0.0	0.00	16.7
		Cycle 16 Day 01	13	6.41	10.841	0.0	0.00	33.3
		Cycle 18 Day 01	10	15.00	28.814	0.0	0.00	83.3
		Cycle 20 Day 01	6	2.78	6.804	0.0	0.00	16.7
		Cycle 22 Day 01	4	0.00	0.000	0.0	0.00	0.0
		Cycle 24 Day 01	2	0.00	0.000	0.0	0.00	0.0
		Cycle 26 Day 01	2	0.00	0.000	0.0	0.00	0.0
		Follow-up Day 30	113	15.78	21.917	0.0	0.00	100.0
		Follow-up Month 2	37	9.01	16.940	0.0	0.00	83.3
		Follow-up Month 3	25	11.33	18.459	0.0	0.00	66.7

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Symptom scale: Pain	Durva + Gem + Cis (N=405)	Baseline [a]	324	25.93	23.716	0.0	16.67	100.0
		Cycle 02 Day 01	303	22.55	23.398	0.0	16.67	100.0
		Cycle 03 Day 01	255	17.58	20.790	0.0	16.67	100.0
		Cycle 04 Day 01	248	15.19	18.185	0.0	16.67	100.0
		Cycle 05 Day 01	226	16.00	18.144	0.0	16.67	83.3
		Cycle 06 Day 01	205	16.18	19.866	0.0	16.67	100.0
		Cycle 07 Day 01	172	12.98	16.696	0.0	0.00	66.7
		Cycle 08 Day 01	172	16.38	19.536	0.0	16.67	100.0
		Cycle 09 Day 01	147	15.08	16.475	0.0	16.67	66.7
		Cycle 10 Day 01	147	14.29	18.195	0.0	0.00	66.7
		Cycle 11 Day 01	97	12.89	16.048	0.0	0.00	66.7
		Cycle 12 Day 01	80	15.83	19.649	0.0	16.67	100.0
		Cycle 13 Day 01	51	13.40	17.003	0.0	0.00	66.7
		Cycle 14 Day 01	45	11.48	13.211	0.0	0.00	33.3
		Cycle 15 Day 01	30	8.89	14.993	0.0	0.00	66.7
		Cycle 16 Day 01	36	8.33	10.911	0.0	0.00	33.3
		Cycle 18 Day 01	24	10.42	11.849	0.0	8.33	33.3
		Cycle 20 Day 01	21	11.90	15.936	0.0	16.67	66.7
		Cycle 22 Day 01	18	15.74	27.696	0.0	0.00	100.0
		Cycle 24 Day 01	11	7.58	13.670	0.0	0.00	33.3
		Cycle 26 Day 01	5	10.00	14.907	0.0	0.00	33.3
		Cycle 28 Day 01	3	16.67	16.667	0.0	16.67	33.3
		Follow-up Day 30	99	34.68	28.440	0.0	33.33	100.0
		Follow-up Month 2	41	35.77	29.945	0.0	33.33	100.0
		Follow-up Month 3	24	32.64	26.684	0.0	33.33	100.0
	Placebo + Gem + Cis (N=405)	Baseline [a]	333	22.02	23.260	0.0	16.67	100.0
		Cycle 02 Day 01	321	18.59	20.555	0.0	16.67	100.0
		Cycle 03 Day 01	252	15.94	19.583	0.0	16.67	100.0
		Cycle 04 Day 01	246	17.14	20.281	0.0	16.67	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	200	15.92	18.402	0.0	16.67	100.0
		Cycle 06 Day 01	200	16.00	19.112	0.0	16.67	100.0
		Cycle 07 Day 01	166	15.76	18.373	0.0	16.67	100.0
		Cycle 08 Day 01	150	18.00	21.547	0.0	16.67	100.0
		Cycle 09 Day 01	122	13.39	17.360	0.0	0.00	83.3
		Cycle 10 Day 01	110	17.58	20.045	0.0	16.67	83.3
		Cycle 11 Day 01	67	17.16	23.386	0.0	16.67	100.0
		Cycle 12 Day 01	59	14.12	16.899	0.0	16.67	66.7
		Cycle 13 Day 01	29	13.79	21.394	0.0	0.00	66.7
		Cycle 14 Day 01	29	14.94	19.591	0.0	0.00	66.7
		Cycle 15 Day 01	16	10.42	14.751	0.0	0.00	33.3
		Cycle 16 Day 01	13	12.82	18.199	0.0	0.00	50.0
		Cycle 18 Day 01	10	18.33	27.722	0.0	0.00	66.7
		Cycle 20 Day 01	6	5.56	13.608	0.0	0.00	33.3
		Cycle 22 Day 01	4	8.33	16.667	0.0	0.00	33.3
		Cycle 24 Day 01	2	0.00	0.000	0.0	0.00	0.0
		Cycle 26 Day 01	2	0.00	0.000	0.0	0.00	0.0
		Follow-up Day 30	113	27.29	26.452	0.0	33.33	100.0
		Follow-up Month 2	37	20.27	23.285	0.0	16.67	83.3
		Follow-up Month 3	25	22.67	23.998	0.0	16.67	83.3

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Single item symptom scale: Insomnia	Durva + Gem + Cis (N=405)	Baseline [a]	324	24.59	27.802	0.0	33.33	100.0
		Cycle 02 Day 01	303	20.46	24.551	0.0	0.00	100.0
		Cycle 03 Day 01	255	18.56	23.189	0.0	0.00	100.0
		Cycle 04 Day 01	248	18.15	23.761	0.0	0.00	100.0
		Cycle 05 Day 01	226	16.67	23.360	0.0	0.00	100.0
		Cycle 06 Day 01	205	18.37	24.109	0.0	0.00	100.0
		Cycle 07 Day 01	172	17.05	22.653	0.0	0.00	100.0
		Cycle 08 Day 01	172	19.38	25.473	0.0	0.00	100.0
		Cycle 09 Day 01	147	15.87	21.487	0.0	0.00	66.7
		Cycle 10 Day 01	147	17.91	22.504	0.0	0.00	66.7
		Cycle 11 Day 01	97	14.78	22.551	0.0	0.00	100.0
		Cycle 12 Day 01	80	17.08	24.301	0.0	0.00	100.0
		Cycle 13 Day 01	51	17.65	24.361	0.0	0.00	66.7
		Cycle 14 Day 01	45	16.30	20.868	0.0	0.00	66.7
		Cycle 15 Day 01	30	12.22	20.498	0.0	0.00	66.7
		Cycle 16 Day 01	36	12.04	18.088	0.0	0.00	66.7
		Cycle 18 Day 01	24	16.67	24.077	0.0	0.00	66.7
		Cycle 20 Day 01	21	14.29	24.881	0.0	0.00	66.7
		Cycle 22 Day 01	18	20.37	28.328	0.0	0.00	100.0
		Cycle 24 Day 01	11	6.06	13.484	0.0	0.00	33.3
		Cycle 26 Day 01	5	13.33	18.257	0.0	0.00	33.3
		Cycle 28 Day 01	3	0.00	0.000	0.0	0.00	0.0
		Follow-up Day 30	99	28.28	30.994	0.0	33.33	100.0
		Follow-up Month 2	41	20.33	25.688	0.0	0.00	100.0
		Follow-up Month 3	24	22.22	21.234	0.0	33.33	66.7
	Placebo + Gem + Cis (N=405)	Baseline [a]	333	22.12	26.278	0.0	0.00	100.0
		Cycle 02 Day 01	321	17.96	24.279	0.0	0.00	100.0
		Cycle 03 Day 01	252	17.59	24.609	0.0	0.00	100.0
		Cycle 04 Day 01	246	17.62	23.647	0.0	0.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.1 TOPAZ: Summary of EORTC QLQ-C30 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	200	18.33	23.570	0.0	0.00	100.0
		Cycle 06 Day 01	200	17.83	22.880	0.0	0.00	100.0
		Cycle 07 Day 01	166	17.47	24.261	0.0	0.00	100.0
		Cycle 08 Day 01	150	18.22	22.381	0.0	0.00	66.7
		Cycle 09 Day 01	122	17.49	21.519	0.0	0.00	100.0
		Cycle 10 Day 01	110	17.88	24.598	0.0	0.00	100.0
		Cycle 11 Day 01	67	18.41	24.811	0.0	0.00	100.0
		Cycle 12 Day 01	59	13.56	22.419	0.0	0.00	100.0
		Cycle 13 Day 01	29	16.09	22.923	0.0	0.00	66.7
		Cycle 14 Day 01	29	14.94	24.537	0.0	0.00	100.0
		Cycle 15 Day 01	16	12.50	20.638	0.0	0.00	66.7
		Cycle 16 Day 01	13	17.95	29.235	0.0	0.00	66.7
		Cycle 18 Day 01	10	20.00	35.832	0.0	0.00	100.0
		Cycle 20 Day 01	6	16.67	18.257	0.0	16.67	33.3
		Cycle 22 Day 01	4	25.00	16.667	0.0	33.33	33.3
		Cycle 24 Day 01	2	16.67	23.570	0.0	16.67	33.3
		Cycle 26 Day 01	2	0.00	0.000	0.0	0.00	0.0
		Follow-up Day 30	113	25.07	26.551	0.0	33.33	100.0
		Follow-up Month 2	37	19.82	24.164	0.0	0.00	100.0
		Follow-up Month 3	25	24.00	28.087	0.0	33.33	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.5.2.1 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Global QoL/health status (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	264	64.84 (19.494)	0.01 (1.067)	275	66.70 (20.381)	-0.44 (1.047)	0.45 (-2.481, 3.388)	0.7616
Cycle 03 Day 01	222	66.07 (18.683)	0.04 (1.097)	223	67.45 (21.009)	-1.15 (1.088)	1.19 (-1.845, 4.227)	0.4412
Cycle 04 Day 01	214	66.67 (18.834)	-0.25 (1.192)	222	67.91 (20.181)	-1.71 (1.173)	1.46 (-1.828, 4.746)	0.3836
Cycle 05 Day 01	194	67.18 (18.048)	-0.41 (1.129)	179	68.76 (19.450)	-1.00 (1.151)	0.59 (-2.578, 3.756)	0.7147
Cycle 06 Day 01	175	68.14 (17.365)	-0.84 (1.143)	180	68.19 (19.667)	0.39 (1.131)	-1.23 (-4.391, 1.926)	0.4437
Cycle 07 Day 01	147	69.05 (16.865)	0.79 (1.218)	148	68.92 (18.863)	0.35 (1.215)	0.44 (-2.940, 3.813)	0.7995
Cycle 08 Day 01	148	67.40 (18.157)	-0.93 (1.299)	133	67.67 (19.436)	-2.32 (1.346)	1.39 (-2.283, 5.070)	0.4566
Cycle 09 Day 01	128	66.67 (18.353)	-0.63 (1.262)	111	69.07 (19.987)	1.48 (1.332)	-2.11 (-5.719, 1.503)	0.2517
Cycle 10 Day 01	128	66.99 (17.790)	1.23 (1.234)	99	69.36 (19.914)	0.16 (1.360)	1.07 (-2.543, 4.682)	0.5607
Cycle 11 Day 01	85	66.76 (16.592)	4.49 (1.398)	63	68.12 (19.199)	0.34 (1.582)	4.15 (-0.011, 8.315)	0.0506
Cycle 12 Day 01	68	64.58 (17.180)	2.16 (1.521)	57	67.25 (19.407)	0.54 (1.651)	1.62 (-2.811, 6.048)	0.4718
Cycle 13 Day 01	42	62.10 (17.958)	4.81 (1.850)	28	67.56 (20.952)	5.11 (2.178)	-0.30 (-5.975, 5.371)	0.9162
Cycle 14 Day 01	39	63.68 (18.286)	6.52 (2.010)	28	67.86 (21.362)	1.39 (2.324)	5.13 (-0.978, 11.235)	0.0988
Cycle 15 Day 01	23	60.87 (18.538)	4.38 (2.385)	15	73.33 (13.437)	3.68 (2.918)	0.71 (-7.043, 8.455)	0.8559
Cycle 16 Day 01	29	60.34 (16.911)	2.05 (2.631)	13	68.59 (19.291)	1.00 (3.627)	1.05 (-7.964, 10.065)	0.8167
Cycle 18 Day 01	18	58.80 (15.517)	4.54 (3.001)	10	65.00 (19.954)	4.85 (3.776)	-0.31 (-9.935, 9.323)	0.9492

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.1 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Global QoL/health status (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	60.53 (16.396)	1.06 (3.689)	6	66.67 (9.129)	1.96 (5.864)	-0.90 (-14.983, 13.183)	0.8972
Average over all visits	293	65.05 (19.249)	1.71 (0.926)	301	67.14 (20.196)	0.86 (1.057)	0.85 (-1.920, 3.614)	0.5476
Hedges' g SMD							0.05 (-0.112, 0.210)	0.5480

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.2 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Functional scale: Physical (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	264	81.79 (17.871)	-1.73 (0.890)	275	85.02 (16.484)	-1.56 (0.868)	-0.18 (-2.618, 2.268)	0.8882
Cycle 03 Day 01	222	81.68 (17.836)	-1.41 (0.965)	223	85.17 (17.403)	-1.57 (0.949)	0.16 (-2.505, 2.818)	0.9080
Cycle 04 Day 01	214	82.62 (16.963)	-1.79 (0.960)	222	85.47 (17.010)	-1.99 (0.940)	0.20 (-2.442, 2.840)	0.8822
Cycle 05 Day 01	194	83.88 (15.691)	-2.30 (0.988)	179	86.18 (16.407)	-2.15 (0.998)	-0.15 (-2.916, 2.606)	0.9123
Cycle 06 Day 01	175	85.18 (15.332)	-3.24 (1.029)	180	86.11 (16.479)	-2.34 (1.017)	-0.90 (-3.741, 1.945)	0.5352
Cycle 07 Day 01	147	86.67 (14.535)	-2.96 (1.042)	148	86.04 (15.867)	-1.95 (1.036)	-1.02 (-3.902, 1.869)	0.4890
Cycle 08 Day 01	148	85.23 (15.129)	-3.24 (1.028)	133	86.17 (14.463)	-2.65 (1.059)	-0.59 (-3.486, 2.315)	0.6916
Cycle 09 Day 01	128	85.26 (16.128)	-2.58 (1.023)	111	85.41 (16.392)	-1.53 (1.072)	-1.05 (-3.969, 1.862)	0.4780
Cycle 10 Day 01	128	85.31 (14.691)	-1.70 (1.053)	99	86.06 (15.996)	-2.91 (1.148)	1.21 (-1.856, 4.269)	0.4390
Cycle 11 Day 01	85	86.75 (11.751)	-0.54 (1.188)	63	86.03 (15.917)	-3.54 (1.328)	3.00 (-0.506, 6.500)	0.0932
Cycle 12 Day 01	68	87.16 (11.820)	-4.07 (1.540)	57	85.61 (17.219)	-2.29 (1.669)	-1.78 (-6.253, 2.696)	0.4340
Cycle 13 Day 01	42	85.87 (11.425)	-1.52 (1.580)	28	85.95 (15.109)	-2.31 (1.872)	0.80 (-4.050, 5.640)	0.7458
Cycle 14 Day 01	39	84.79 (10.917)	-0.26 (1.595)	28	84.52 (14.408)	-2.14 (1.855)	1.87 (-2.969, 6.717)	0.4451
Cycle 15 Day 01	23	86.38 (10.537)	0.46 (1.743)	15	89.78 (8.680)	0.83 (2.211)	-0.37 (-5.915, 5.172)	0.8940
Cycle 16 Day 01	29	87.13 (11.117)	-1.85 (2.004)	13	85.64 (13.009)	-6.08 (2.812)	4.23 (-2.641, 11.101)	0.2235
Cycle 18 Day 01	18	91.48 (7.857)	-1.25 (2.399)	10	86.00 (14.891)	-5.40 (2.951)	4.15 (-3.425, 11.726)	0.2761

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.2 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Functional scale: Physical (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	89.47 (10.730)	-1.63 (2.869)	6	88.89 (12.413)	-6.84 (4.564)	5.22 (-5.537, 15.967)	0.3304
Average over all visits	293	81.46 (18.182)	-1.86 (0.816)	301	85.09 (16.503)	-2.73 (0.918)	0.87 (-1.539, 3.279)	0.4781
Hedges' g SMD							0.06 (-0.103, 0.219)	0.4802

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.3 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Functional scale: Role (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	264	83.46 (22.422)	-2.73 (1.240)	275	84.42 (20.655)	-2.44 (1.217)	-0.29 (-3.692, 3.122)	0.8695
Cycle 03 Day 01	222	83.03 (23.083)	-4.61 (1.361)	223	85.05 (21.242)	-2.59 (1.348)	-2.02 (-5.778, 1.740)	0.2918
Cycle 04 Day 01	214	84.35 (22.442)	-6.94 (1.337)	222	85.59 (20.973)	-3.94 (1.314)	-3.00 (-6.680, 0.680)	0.1099
Cycle 05 Day 01	194	85.40 (20.537)	-5.47 (1.373)	179	85.85 (21.742)	-4.73 (1.397)	-0.74 (-4.586, 3.109)	0.7062
Cycle 06 Day 01	175	85.81 (20.535)	-7.30 (1.446)	180	86.11 (21.177)	-3.80 (1.431)	-3.50 (-7.501, 0.491)	0.0855
Cycle 07 Day 01	147	87.64 (18.821)	-5.87 (1.428)	148	85.47 (21.053)	-3.97 (1.423)	-1.90 (-5.864, 2.060)	0.3459
Cycle 08 Day 01	148	86.37 (19.637)	-6.49 (1.488)	133	86.47 (20.221)	-5.55 (1.541)	-0.94 (-5.149, 3.272)	0.6613
Cycle 09 Day 01	128	87.37 (20.142)	-7.15 (1.494)	111	85.44 (21.802)	-4.50 (1.575)	-2.65 (-6.918, 1.624)	0.2236
Cycle 10 Day 01	128	87.37 (19.367)	-5.58 (1.462)	99	86.36 (21.211)	-3.14 (1.608)	-2.43 (-6.707, 1.840)	0.2634
Cycle 11 Day 01	85	89.22 (16.408)	-3.76 (1.689)	63	84.66 (21.854)	-3.01 (1.896)	-0.76 (-5.770, 4.257)	0.7664
Cycle 12 Day 01	68	89.46 (16.518)	-4.19 (1.915)	57	85.09 (22.644)	-2.59 (2.077)	-1.60 (-7.186, 3.979)	0.5715
Cycle 13 Day 01	42	86.11 (18.740)	-3.23 (2.652)	28	87.50 (16.744)	-5.69 (3.173)	2.46 (-5.741, 10.658)	0.5534
Cycle 14 Day 01	39	86.32 (19.069)	-3.80 (2.369)	28	87.50 (16.744)	-2.60 (2.771)	-1.20 (-8.430, 6.034)	0.7430
Cycle 15 Day 01	23	86.96 (16.634)	0.33 (2.653)	15	97.78 (5.864)	-3.71 (3.672)	4.03 (-4.937, 13.004)	0.3708
Cycle 16 Day 01	29	86.78 (15.672)	-8.37 (3.783)	13	93.59 (14.495)	-10.10 (5.602)	1.73 (-11.740, 15.194)	0.7980
Cycle 18 Day 01	18	87.96 (13.774)	-7.45 (4.497)	10	91.67 (16.197)	-13.55 (6.171)	6.10 (-9.182, 21.375)	0.4238

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.3 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Functional scale: Role (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	85.96 (15.970)	-4.47 (3.698)	6	97.22 (6.804)	-1.99 (6.668)	-2.47 (-17.957, 13.011)	0.7469
Average over all visits	293	82.76 (22.867)	-5.12 (1.154)	301	84.22 (21.238)	-4.58 (1.384)	-0.54 (-4.077, 2.996)	0.7640
Hedges' g SMD							-0.02 (-0.185, 0.136)	0.7653

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.4 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Functional scale: Cognitive (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	264	88.64 (15.493)	-0.92 (0.839)	275	89.58 (14.254)	-0.02 (0.824)	-0.90 (-3.213, 1.408)	0.4433
Cycle 03 Day 01	222	89.49 (15.196)	-2.67 (0.961)	223	89.69 (14.438)	-1.37 (0.954)	-1.30 (-3.963, 1.361)	0.3374
Cycle 04 Day 01	214	89.41 (15.472)	-2.93 (0.985)	222	89.34 (14.753)	-1.35 (0.969)	-1.57 (-4.289, 1.140)	0.2550
Cycle 05 Day 01	194	90.46 (14.169)	-2.71 (1.066)	179	89.48 (15.283)	-2.59 (1.085)	-0.12 (-3.110, 2.866)	0.9361
Cycle 06 Day 01	175	90.10 (15.485)	-3.33 (1.031)	180	89.54 (14.952)	-2.93 (1.020)	-0.40 (-3.245, 2.452)	0.7847
Cycle 07 Day 01	147	90.93 (15.013)	-2.50 (1.028)	148	90.77 (14.714)	-2.37 (1.026)	-0.13 (-2.982, 2.722)	0.9285
Cycle 08 Day 01	148	89.30 (15.675)	-5.24 (1.145)	133	90.10 (15.081)	-4.12 (1.187)	-1.12 (-4.364, 2.121)	0.4969
Cycle 09 Day 01	128	90.49 (15.036)	-4.36 (1.075)	111	89.79 (15.598)	-2.56 (1.135)	-1.80 (-4.870, 1.278)	0.2513
Cycle 10 Day 01	128	89.84 (15.403)	-3.68 (1.151)	99	89.90 (15.940)	-3.35 (1.267)	-0.33 (-3.693, 3.042)	0.8492
Cycle 11 Day 01	85	91.57 (14.689)	-2.47 (1.303)	63	87.57 (16.111)	-3.78 (1.472)	1.31 (-2.574, 5.194)	0.5071
Cycle 12 Day 01	68	89.71 (16.040)	-3.64 (1.509)	57	86.55 (16.499)	-2.17 (1.660)	-1.46 (-5.892, 2.964)	0.5150
Cycle 13 Day 01	42	91.27 (14.833)	-1.54 (1.826)	28	83.33 (15.713)	-4.12 (2.236)	2.57 (-3.200, 8.345)	0.3789
Cycle 14 Day 01	39	91.88 (14.745)	-0.79 (1.827)	28	85.12 (15.934)	-4.69 (2.162)	3.90 (-1.773, 9.575)	0.1755
Cycle 15 Day 01	23	89.13 (17.122)	-0.98 (1.974)	15	87.78 (14.729)	-4.20 (2.468)	3.22 (-3.126, 9.562)	0.3137
Cycle 16 Day 01	29	88.51 (16.728)	-3.02 (2.313)	13	85.90 (14.979)	-5.23 (3.340)	2.21 (-5.925, 10.347)	0.5879
Cycle 18 Day 01	18	90.74 (17.360)	-3.33 (3.251)	10	83.33 (15.713)	-9.25 (4.473)	5.92 (-5.350, 17.193)	0.2940

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.4 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Functional scale: Cognitive (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	91.23 (17.004)	-3.57 (3.274)	6	88.89 (17.213)	-7.55 (5.531)	3.99 (-9.158, 17.133)	0.5404
Average over all visits	293	88.34 (15.835)	-2.80 (0.845)	301	89.70 (14.111)	-3.63 (1.006)	0.82 (-1.769, 3.415)	0.5326
Hedges' g SMD							0.05 (-0.110, 0.212)	0.5327

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.5 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Functional scale: Emotional (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	264	77.68 (18.019)	4.70 (0.886)	275	80.88 (16.461)	3.32 (0.871)	1.38 (-1.065, 3.827)	0.2679
Cycle 03 Day 01	222	77.33 (18.308)	2.73 (1.021)	223	80.98 (16.678)	2.37 (1.012)	0.35 (-2.476, 3.185)	0.8060
Cycle 04 Day 01	214	77.92 (18.260)	3.02 (1.073)	222	80.93 (17.382)	1.52 (1.056)	1.50 (-1.459, 4.468)	0.3191
Cycle 05 Day 01	194	79.38 (16.541)	2.36 (1.132)	179	80.59 (17.417)	1.09 (1.149)	1.28 (-1.897, 4.448)	0.4300
Cycle 06 Day 01	175	78.90 (16.298)	1.69 (1.139)	180	80.42 (17.473)	1.43 (1.127)	0.26 (-2.886, 3.416)	0.8689
Cycle 07 Day 01	147	79.08 (17.044)	3.54 (1.128)	148	80.69 (17.253)	1.68 (1.127)	1.86 (-1.276, 4.998)	0.2442
Cycle 08 Day 01	148	78.83 (17.614)	2.20 (1.221)	133	81.39 (17.161)	1.84 (1.262)	0.36 (-3.097, 3.814)	0.8386
Cycle 09 Day 01	128	79.17 (17.685)	2.01 (1.132)	111	81.38 (17.622)	2.19 (1.192)	-0.18 (-3.416, 3.056)	0.9131
Cycle 10 Day 01	128	79.23 (17.809)	4.15 (1.235)	99	82.15 (16.017)	0.45 (1.355)	3.69 (0.085, 7.303)	0.0449*
Cycle 11 Day 01	85	78.73 (17.035)	2.68 (1.453)	63	79.63 (16.652)	0.33 (1.631)	2.35 (-1.954, 6.656)	0.2830
Cycle 12 Day 01	68	78.31 (18.558)	4.56 (1.614)	57	78.95 (16.749)	1.60 (1.757)	2.96 (-1.749, 7.667)	0.2165
Cycle 13 Day 01	42	74.21 (20.562)	3.74 (1.948)	28	79.46 (17.045)	2.42 (2.278)	1.32 (-4.619, 7.258)	0.6606
Cycle 14 Day 01	39	75.43 (19.113)	3.99 (1.968)	28	78.87 (17.196)	4.49 (2.265)	-0.50 (-6.440, 5.445)	0.8684
Cycle 15 Day 01	23	76.45 (17.705)	4.63 (2.068)	15	78.89 (14.388)	1.75 (2.542)	2.89 (-3.676, 9.447)	0.3819
Cycle 16 Day 01	29	76.44 (16.528)	3.53 (2.464)	13	80.77 (13.344)	1.85 (3.467)	1.68 (-6.840, 10.203)	0.6946
Cycle 18 Day 01	18	73.61 (17.209)	5.21 (3.035)	10	80.83 (13.059)	-2.64 (3.920)	7.84 (-2.215, 17.901)	0.1232

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.5 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Functional scale: Emotional (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	75.00 (17.347)	4.54 (3.147)	6	86.11 (11.386)	-0.81 (5.224)	5.34 (-7.340, 18.028)	0.3959
Average over all visits	293	77.42 (18.314)	3.49 (0.926)	301	81.01 (16.573)	1.46 (1.057)	2.02 (-0.744, 4.791)	0.1514
Hedges' g SMD							0.12 (-0.043, 0.279)	0.1517

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.6 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Functional scale: Social (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	264	80.74 (21.027)	-0.10 (1.151)	275	83.03 (20.360)	0.29 (1.130)	-0.40 (-3.567, 2.774)	0.8061
Cycle 03 Day 01	222	79.95 (21.386)	-1.54 (1.298)	223	83.71 (19.850)	-0.63 (1.285)	-0.92 (-4.508, 2.678)	0.6169
Cycle 04 Day 01	214	81.39 (20.810)	-2.65 (1.341)	222	84.46 (19.483)	-1.44 (1.321)	-1.22 (-4.920, 2.485)	0.5186
Cycle 05 Day 01	194	82.13 (19.822)	-2.92 (1.315)	179	84.64 (18.483)	-0.60 (1.339)	-2.32 (-6.009, 1.373)	0.2179
Cycle 06 Day 01	175	82.29 (20.385)	-2.95 (1.398)	180	85.56 (18.594)	-2.71 (1.388)	-0.24 (-4.118, 3.632)	0.9019
Cycle 07 Day 01	147	83.22 (20.036)	-2.91 (1.445)	148	85.59 (18.611)	-3.12 (1.447)	0.21 (-3.809, 4.229)	0.9183
Cycle 08 Day 01	148	81.76 (19.858)	-3.19 (1.377)	133	84.84 (18.742)	-0.70 (1.426)	-2.49 (-6.392, 1.412)	0.2104
Cycle 09 Day 01	128	83.33 (19.842)	-2.82 (1.438)	111	85.44 (18.548)	1.33 (1.519)	-4.15 (-8.266, -0.040)	0.0478*
Cycle 10 Day 01	128	82.29 (19.592)	-1.37 (1.359)	99	86.87 (17.861)	-0.27 (1.501)	-1.10 (-5.092, 2.885)	0.5866
Cycle 11 Day 01	85	81.37 (19.144)	1.31 (1.619)	63	84.13 (19.727)	0.32 (1.824)	0.99 (-3.823, 5.802)	0.6858
Cycle 12 Day 01	68	79.90 (19.858)	0.50 (1.916)	57	83.33 (20.654)	-2.51 (2.078)	3.01 (-2.569, 8.595)	0.2883
Cycle 13 Day 01	42	76.98 (21.131)	0.63 (2.213)	28	83.33 (18.703)	0.85 (2.586)	-0.22 (-6.973, 6.540)	0.9495
Cycle 14 Day 01	39	75.21 (21.586)	-0.24 (2.293)	28	82.14 (18.104)	3.21 (2.584)	-3.45 (-10.300, 3.395)	0.3196
Cycle 15 Day 01	23	77.54 (17.844)	2.16 (2.754)	15	91.11 (12.387)	3.41 (3.445)	-1.26 (-10.388, 7.874)	0.7834
Cycle 16 Day 01	29	77.01 (18.046)	6.09 (2.850)	13	87.18 (19.429)	-0.64 (3.967)	6.72 (-3.194, 16.643)	0.1800
Cycle 18 Day 01	18	75.93 (19.150)	-0.43 (4.693)	10	85.00 (21.445)	-11.28 (6.086)	10.85 (-4.893, 26.593)	0.1708

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.6 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Functional scale: Social (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	76.32 (18.688)	-0.64 (3.756)	6	88.89 (13.608)	-2.83 (6.091)	2.19 (-12.701, 17.072)	0.7668
Average over all visits	293	80.94 (20.781)	-0.65 (1.120)	301	83.55 (19.859)	-1.02 (1.279)	0.37 (-3.001, 3.731)	0.8311
Hedges' g SMD							0.02 (-0.143, 0.178)	0.8305

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.7 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Single item symptom scale: Loss of appetite (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	264	22.98 (27.309)	3.58 (1.338)	275	19.76 (25.183)	1.27 (1.307)	2.31 (-1.359, 5.980)	0.2168
Cycle 03 Day 01	222	22.37 (26.625)	4.54 (1.555)	223	18.98 (26.534)	3.82 (1.537)	0.71 (-3.581, 5.007)	0.7444
Cycle 04 Day 01	214	21.03 (26.025)	5.34 (1.523)	222	18.17 (25.274)	2.55 (1.494)	2.79 (-1.404, 6.977)	0.1920
Cycle 05 Day 01	194	19.59 (25.280)	3.73 (1.531)	179	18.44 (26.233)	0.05 (1.561)	3.67 (-0.623, 7.968)	0.0936
Cycle 06 Day 01	175	20.38 (26.210)	3.95 (1.575)	180	17.41 (25.519)	0.89 (1.557)	3.06 (-1.298, 7.411)	0.1684
Cycle 07 Day 01	147	17.46 (24.468)	4.36 (1.790)	148	17.34 (24.734)	0.84 (1.787)	3.52 (-1.450, 8.492)	0.1645
Cycle 08 Day 01	148	20.72 (26.770)	6.13 (1.883)	133	16.79 (24.143)	-1.22 (1.956)	7.35 (2.009, 12.699)	0.0071*
Cycle 09 Day 01	128	18.49 (25.721)	1.64 (1.628)	111	17.12 (23.726)	-1.75 (1.726)	3.39 (-1.277, 8.059)	0.1539
Cycle 10 Day 01	128	18.23 (26.409)	-2.14 (1.717)	99	16.16 (23.982)	-1.40 (1.904)	-0.74 (-5.783, 4.304)	0.7731
Cycle 11 Day 01	85	17.65 (24.445)	-2.86 (1.881)	63	13.76 (24.418)	-4.71 (2.155)	1.85 (-3.779, 7.481)	0.5175
Cycle 12 Day 01	68	15.69 (21.908)	-5.81 (2.020)	57	13.45 (25.087)	-1.94 (2.227)	-3.87 (-9.772, 2.029)	0.1970
Cycle 13 Day 01	42	19.05 (24.575)	-5.05 (2.405)	28	15.48 (27.936)	-4.76 (2.898)	-0.29 (-7.765, 7.183)	0.9386
Cycle 14 Day 01	39	17.95 (23.996)	-10.09 (2.670)	28	16.67 (27.962)	0.40 (3.135)	-10.49 (-18.661, -2.320)	0.0124*
Cycle 15 Day 01	23	13.04 (19.434)	-5.51 (3.687)	15	11.11 (27.217)	-0.04 (4.617)	-5.48 (-17.105, 6.154)	0.3492
Cycle 16 Day 01	29	14.94 (21.056)	-8.68 (2.952)	13	15.38 (29.235)	-2.67 (4.253)	-6.01 (-16.330, 4.311)	0.2481
Cycle 18 Day 01	18	14.81 (20.523)	-9.35 (4.549)	10	16.67 (32.394)	5.63 (6.082)	-14.97 (-30.296, 0.350)	0.0552

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.7 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Single item symptom scale: Loss of appetite (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	12.28 (19.909)	-7.28 (4.216)	6	5.56 (13.608)	-8.61 (7.289)	1.34 (-15.201, 17.876)	0.8698
Average over all visits	293	23.78 (27.856)	-1.38 (1.169)	301	19.49 (25.319)	-0.69 (1.374)	-0.70 (-4.224, 2.829)	0.6975
Hedges' g SMD							-0.03 (-0.192, 0.129)	0.7001

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.8 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Single item symptom scale: Constipation (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	264	15.53 (23.766)	5.30 (1.497)	275	13.58 (23.689)	4.31 (1.472)	0.99 (-3.134, 5.116)	0.6373
Cycle 03 Day 01	222	17.57 (26.657)	8.49 (1.654)	223	15.40 (25.055)	3.48 (1.642)	5.00 (0.423, 9.584)	0.0323*
Cycle 04 Day 01	214	16.98 (25.585)	4.01 (1.501)	222	13.81 (23.927)	3.78 (1.477)	0.22 (-3.917, 4.366)	0.9152
Cycle 05 Day 01	194	14.60 (24.441)	1.89 (1.506)	179	13.59 (24.636)	1.66 (1.538)	0.23 (-3.999, 4.459)	0.9150
Cycle 06 Day 01	175	14.86 (24.660)	2.11 (1.490)	180	13.89 (25.377)	-0.04 (1.476)	2.15 (-1.973, 6.270)	0.3061
Cycle 07 Day 01	147	15.42 (23.818)	1.06 (1.626)	148	13.96 (24.285)	-0.27 (1.626)	1.34 (-3.184, 5.859)	0.5612
Cycle 08 Day 01	148	17.12 (26.223)	1.59 (1.626)	133	15.04 (25.448)	1.35 (1.688)	0.24 (-4.374, 4.845)	0.9200
Cycle 09 Day 01	128	15.10 (23.237)	0.62 (1.571)	111	15.02 (24.920)	0.26 (1.663)	0.36 (-4.140, 4.862)	0.8747
Cycle 10 Day 01	128	17.19 (25.439)	1.25 (1.624)	99	14.48 (24.818)	-1.72 (1.794)	2.98 (-1.788, 7.741)	0.2198
Cycle 11 Day 01	85	11.76 (17.598)	-3.31 (1.832)	63	17.46 (28.623)	-3.31 (2.071)	0.01 (-5.466, 5.477)	0.9984
Cycle 12 Day 01	68	11.76 (17.050)	-3.79 (2.058)	57	18.71 (29.559)	-4.48 (2.244)	0.69 (-5.351, 6.727)	0.8223
Cycle 13 Day 01	42	12.70 (17.962)	-1.00 (2.670)	28	22.62 (34.010)	-2.16 (3.226)	1.17 (-7.192, 9.527)	0.7823
Cycle 14 Day 01	39	11.97 (17.913)	-5.22 (2.927)	28	22.62 (34.010)	0.92 (3.455)	-6.14 (-15.199, 2.928)	0.1821
Cycle 15 Day 01	23	8.70 (14.966)	-8.59 (2.333)	15	28.89 (37.515)	1.52 (2.991)	-10.11 (-17.923, -2.299)	0.0122*
Cycle 16 Day 01	29	10.34 (15.694)	-5.27 (2.683)	13	35.90 (37.172)	-0.18 (4.197)	-5.09 (-15.348, 5.172)	0.3255
Cycle 18 Day 01	18	12.96 (16.721)	-6.56 (3.698)	10	43.33 (38.650)	1.67 (5.811)	-8.23 (-22.384, 5.917)	0.2474

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.8 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Single item symptom scale: Constipation (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	10.53 (15.919)	-0.61 (3.326)	6	44.44 (45.542)	3.36 (6.119)	-3.96 (-18.639, 10.711)	0.5853
Average over all visits	293	17.41 (25.665)	-0.47 (1.113)	301	14.40 (24.026)	0.60 (1.314)	-1.07 (-4.483, 2.346)	0.5389
Hedges' g SMD							-0.05 (-0.212, 0.110)	0.5366

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.9 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Single item symptom scale: Diarrhoea (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	264	5.43 (13.940)	-0.17 (0.795)	275	5.21 (12.780)	0.77 (0.780)	-0.94 (-3.129, 1.245)	0.3979
Cycle 03 Day 01	222	6.01 (15.007)	1.43 (0.890)	223	4.78 (12.538)	0.31 (0.886)	1.11 (-1.355, 3.583)	0.3757
Cycle 04 Day 01	214	5.30 (13.040)	0.79 (0.866)	222	4.95 (12.703)	-0.82 (0.851)	1.62 (-0.769, 4.002)	0.1836
Cycle 05 Day 01	194	5.33 (13.152)	2.03 (1.001)	179	4.84 (12.794)	-0.55 (1.034)	2.58 (-0.253, 5.407)	0.0742
Cycle 06 Day 01	175	5.14 (12.593)	-0.56 (0.909)	180	5.19 (13.100)	0.58 (0.899)	-1.14 (-3.649, 1.376)	0.3745
Cycle 07 Day 01	147	3.63 (11.124)	0.36 (1.031)	148	5.41 (13.499)	0.00 (1.026)	0.36 (-2.502, 3.223)	0.8046
Cycle 08 Day 01	148	4.73 (12.301)	-0.22 (0.922)	133	5.26 (13.510)	-1.88 (0.967)	1.67 (-0.963, 4.295)	0.2133
Cycle 09 Day 01	128	4.17 (11.831)	0.55 (1.031)	111	4.20 (11.991)	-1.59 (1.102)	2.14 (-0.831, 5.105)	0.1575
Cycle 10 Day 01	128	5.21 (12.851)	-0.85 (1.016)	99	4.71 (12.608)	-0.32 (1.144)	-0.53 (-3.548, 2.479)	0.7272
Cycle 11 Day 01	85	6.27 (14.080)	0.42 (1.257)	63	4.23 (11.188)	-1.57 (1.446)	1.99 (-1.799, 5.772)	0.3019
Cycle 12 Day 01	68	4.41 (12.754)	-0.54 (1.412)	57	4.09 (11.038)	-0.45 (1.547)	-0.09 (-4.229, 4.039)	0.9639
Cycle 13 Day 01	42	7.14 (15.679)	0.28 (1.856)	28	3.57 (10.499)	2.58 (2.246)	-2.30 (-8.119, 3.524)	0.4345
Cycle 14 Day 01	39	8.55 (16.610)	-4.20 (1.525)	28	4.76 (11.878)	2.21 (1.772)	-6.41 (-11.080, -1.745)	0.0078*
Cycle 15 Day 01	23	8.70 (14.966)	-2.08 (2.405)	15	2.22 (8.607)	4.37 (2.949)	-6.45 (-14.253, 1.359)	0.1029
Cycle 16 Day 01	29	12.64 (18.716)	-3.80 (1.959)	13	2.56 (9.245)	2.50 (2.716)	-6.30 (-13.163, 0.563)	0.0710
Cycle 18 Day 01	18	11.11 (19.803)	-0.59 (2.599)	10	3.33 (10.541)	-1.55 (3.375)	0.97 (-7.847, 9.781)	0.8237

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.9 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Single item symptom scale: Diarrhoea (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	10.53 (19.413)	-2.67 (2.042)	6	0.00 (0.000)	-4.42 (3.512)	1.75 (-6.871, 10.368)	0.6768
Average over all visits	293	5.69 (14.264)	-0.58 (0.583)	301	5.09 (12.615)	0.01 (0.685)	-0.59 (-2.368, 1.192)	0.5164
Hedges' g SMD							-0.05 (-0.214, 0.107)	0.5150

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.10 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Single item symptom scale: Dyspnoea (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	264	14.02 (20.792)	-0.65 (1.080)	275	13.09 (19.481)	1.17 (1.060)	-1.82 (-4.788, 1.147)	0.2287
Cycle 03 Day 01	222	13.96 (21.277)	0.99 (1.309)	223	12.26 (19.991)	1.31 (1.297)	-0.32 (-3.940, 3.296)	0.8614
Cycle 04 Day 01	214	13.08 (20.045)	3.25 (1.264)	222	11.26 (18.715)	2.66 (1.242)	0.59 (-2.889, 4.073)	0.7383
Cycle 05 Day 01	194	12.20 (19.047)	2.99 (1.373)	179	11.17 (19.655)	3.05 (1.405)	-0.06 (-3.921, 3.802)	0.9759
Cycle 06 Day 01	175	12.19 (18.326)	3.02 (1.393)	180	10.00 (18.611)	4.43 (1.380)	-1.41 (-5.267, 2.444)	0.4722
Cycle 07 Day 01	147	12.24 (19.539)	4.67 (1.406)	148	9.01 (17.211)	1.67 (1.410)	3.01 (-0.912, 6.923)	0.1323
Cycle 08 Day 01	148	13.51 (20.879)	4.10 (1.395)	133	10.53 (18.057)	1.80 (1.453)	2.30 (-1.661, 6.270)	0.2538
Cycle 09 Day 01	128	11.98 (19.047)	2.98 (1.503)	111	9.61 (18.195)	4.22 (1.600)	-1.23 (-5.553, 3.089)	0.5753
Cycle 10 Day 01	128	13.02 (21.013)	4.18 (1.500)	99	9.43 (18.468)	3.45 (1.671)	0.73 (-3.699, 5.151)	0.7471
Cycle 11 Day 01	85	11.37 (18.935)	0.59 (1.763)	63	8.47 (16.900)	1.76 (2.023)	-1.17 (-6.454, 4.121)	0.6639
Cycle 12 Day 01	68	9.80 (18.265)	-0.56 (1.836)	57	8.77 (17.282)	2.85 (2.017)	-3.41 (-8.780, 1.951)	0.2108
Cycle 13 Day 01	42	11.11 (19.009)	-5.65 (2.085)	28	11.90 (20.716)	5.63 (2.510)	-11.28 (-17.755, -4.805)	0.0008*
Cycle 14 Day 01	39	10.26 (18.970)	-4.52 (2.039)	28	13.10 (20.963)	3.60 (2.391)	-8.12 (-14.370, -1.870)	0.0115*
Cycle 15 Day 01	23	13.04 (21.879)	-3.07 (2.767)	15	4.44 (11.729)	2.03 (3.531)	-5.09 (-14.139, 3.955)	0.2639
Cycle 16 Day 01	29	12.64 (20.728)	-2.23 (3.137)	13	7.69 (14.618)	9.10 (4.583)	-11.32 (-22.486, -0.161)	0.0469*
Cycle 18 Day 01	18	9.26 (15.363)	0.52 (3.891)	10	6.67 (14.055)	2.22 (5.277)	-1.70 (-14.897, 11.503)	0.7952

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.10 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Single item symptom scale: Dyspnoea (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	10.53 (19.413)	-1.25 (3.430)	6	5.56 (13.608)	-5.30 (5.986)	4.05 (-10.037, 18.134)	0.5605
Average over all visits	293	14.45 (21.542)	0.55 (0.968)	301	12.62 (19.515)	2.68 (1.150)	-2.13 (-5.089, 0.823)	0.1567
Hedges' g SMD							-0.12 (-0.277, 0.045)	0.1579

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.11 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Symptom scale: Fatigue (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	264	29.21 (23.351)	1.92 (1.076)	275	26.83 (21.128)	2.58 (1.052)	-0.66 (-3.610, 2.288)	0.6600
Cycle 03 Day 01	222	28.88 (23.077)	2.27 (1.172)	223	26.31 (20.825)	3.05 (1.157)	-0.79 (-4.017, 2.442)	0.6322
Cycle 04 Day 01	214	27.21 (21.193)	3.05 (1.232)	222	25.73 (20.248)	3.72 (1.209)	-0.67 (-4.062, 2.715)	0.6964
Cycle 05 Day 01	194	25.72 (20.231)	3.80 (1.240)	179	25.20 (20.317)	2.63 (1.260)	1.16 (-2.308, 4.634)	0.5106
Cycle 06 Day 01	175	25.52 (19.511)	4.56 (1.274)	180	24.88 (20.557)	2.92 (1.260)	1.64 (-1.881, 5.158)	0.3607
Cycle 07 Day 01	147	23.05 (18.714)	2.95 (1.397)	148	24.77 (19.956)	2.83 (1.391)	0.12 (-3.751, 3.991)	0.9514
Cycle 08 Day 01	148	25.15 (19.151)	4.12 (1.303)	133	24.56 (20.242)	3.99 (1.349)	0.13 (-3.556, 3.813)	0.9455
Cycle 09 Day 01	128	23.87 (17.861)	1.59 (1.319)	111	25.13 (21.593)	1.84 (1.389)	-0.26 (-4.022, 3.509)	0.8934
Cycle 10 Day 01	128	24.74 (18.718)	0.06 (1.364)	99	24.13 (21.180)	1.19 (1.501)	-1.13 (-5.120, 2.851)	0.5760
Cycle 11 Day 01	85	23.40 (14.651)	-0.33 (1.632)	63	22.75 (19.899)	0.23 (1.847)	-0.56 (-5.400, 4.275)	0.8190
Cycle 12 Day 01	68	22.39 (15.054)	-1.76 (1.657)	57	23.20 (19.952)	-1.73 (1.805)	-0.03 (-4.838, 4.779)	0.9904
Cycle 13 Day 01	42	25.66 (13.771)	-2.39 (2.219)	28	22.62 (19.941)	-0.63 (2.665)	-1.76 (-8.638, 5.120)	0.6131
Cycle 14 Day 01	39	25.93 (14.039)	-2.93 (2.033)	28	23.02 (20.043)	-1.17 (2.388)	-1.76 (-7.991, 4.468)	0.5758
Cycle 15 Day 01	23	22.22 (12.535)	-4.12 (2.578)	15	15.56 (13.801)	1.20 (3.454)	-5.32 (-13.696, 3.049)	0.2073
Cycle 16 Day 01	29	24.14 (11.904)	-3.59 (2.457)	13	19.66 (15.814)	3.09 (3.630)	-6.67 (-15.356, 2.006)	0.1292
Cycle 18 Day 01	18	23.46 (11.985)	-2.37 (3.797)	10	21.11 (16.102)	7.11 (5.196)	-9.48 (-22.423, 3.459)	0.1456

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.11 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Symptom scale: Fatigue (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	22.81 (11.986)	-2.40 (4.057)	6	18.52 (15.181)	2.48 (6.978)	-4.88 (-21.032, 11.280)	0.5423
Average over all visits	293	29.81 (23.204)	0.26 (1.024)	301	26.61 (21.023)	2.08 (1.217)	-1.82 (-4.927, 1.288)	0.2503
Hedges' g SMD							-0.09 (-0.254, 0.067)	0.2546

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.12 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Single item scale: Financial difficulties (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	264	18.18 (25.295)	-2.07 (1.233)	275	16.48 (23.026)	-0.24 (1.211)	-1.83 (-5.225, 1.556)	0.2883
Cycle 03 Day 01	222	18.77 (25.626)	-0.64 (1.362)	223	15.99 (23.427)	-0.84 (1.348)	0.20 (-3.561, 3.965)	0.9161
Cycle 04 Day 01	214	17.91 (25.556)	-1.63 (1.386)	222	14.71 (22.948)	-0.93 (1.363)	-0.70 (-4.521, 3.116)	0.7181
Cycle 05 Day 01	194	17.35 (25.213)	-0.66 (1.434)	179	13.22 (20.729)	-0.25 (1.455)	-0.41 (-4.424, 3.609)	0.8422
Cycle 06 Day 01	175	18.67 (25.411)	-0.30 (1.521)	180	11.85 (19.177)	0.43 (1.504)	-0.72 (-4.937, 3.491)	0.7362
Cycle 07 Day 01	147	14.97 (22.810)	-0.29 (1.501)	148	13.29 (20.478)	0.02 (1.497)	-0.31 (-4.479, 3.853)	0.8828
Cycle 08 Day 01	148	15.77 (21.803)	-0.18 (1.548)	133	13.03 (20.855)	-0.04 (1.596)	-0.14 (-4.513, 4.231)	0.9495
Cycle 09 Day 01	128	13.54 (19.814)	0.41 (1.538)	111	13.21 (20.241)	0.54 (1.612)	-0.13 (-4.509, 4.243)	0.9524
Cycle 10 Day 01	128	14.84 (21.251)	-1.32 (1.464)	99	11.11 (20.203)	-0.18 (1.603)	-1.14 (-5.408, 3.123)	0.5988
Cycle 11 Day 01	85	17.25 (22.190)	-0.32 (1.890)	63	12.17 (20.998)	0.37 (2.122)	-0.69 (-6.302, 4.918)	0.8083
Cycle 12 Day 01	68	15.69 (21.137)	-2.21 (1.845)	57	12.28 (20.540)	-0.62 (2.010)	-1.59 (-6.969, 3.793)	0.5614
Cycle 13 Day 01	42	17.46 (22.377)	-0.08 (2.218)	28	13.10 (18.898)	1.47 (2.633)	-1.55 (-8.372, 5.271)	0.6540
Cycle 14 Day 01	39	18.80 (22.679)	-2.78 (2.310)	28	15.48 (19.207)	3.21 (2.668)	-5.99 (-12.979, 0.991)	0.0919
Cycle 15 Day 01	23	13.04 (19.434)	-2.34 (2.752)	15	6.67 (13.801)	-3.11 (3.512)	0.76 (-8.090, 9.617)	0.8632
Cycle 16 Day 01	29	16.09 (21.121)	-4.74 (2.614)	13	12.82 (21.681)	2.61 (3.721)	-7.34 (-16.417, 1.729)	0.1110
Cycle 18 Day 01	18	18.52 (23.493)	-3.69 (3.407)	10	13.33 (23.307)	4.32 (4.524)	-8.01 (-19.424, 3.401)	0.1647

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.
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Table 2.5.2.12 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Single item scale: Financial difficulties (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	19.30 (23.083)	-4.82 (3.062)	6	5.56 (13.608)	2.67 (5.201)	-7.49 (-19.955, 4.966)	0.2293
Average over all visits	293	18.09 (25.187)	-1.63 (1.145)	301	16.28 (23.821)	0.56 (1.275)	-2.18 (-5.553, 1.188)	0.2038
Hedges' g SMD							-0.10 (-0.265, 0.057)	0.2044

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.13 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Symptom scale: Nausea and vomiting (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	264	7.13 (13.581)	4.91 (0.904)	275	6.36 (15.432)	3.46 (0.887)	1.45 (-1.038, 3.935)	0.2529
Cycle 03 Day 01	222	6.91 (13.633)	5.06 (0.969)	223	6.35 (15.684)	4.01 (0.962)	1.05 (-1.634, 3.729)	0.4432
Cycle 04 Day 01	214	6.31 (12.318)	4.89 (1.033)	222	5.78 (15.384)	4.98 (1.017)	-0.09 (-2.941, 2.756)	0.9493
Cycle 05 Day 01	194	6.01 (12.395)	4.68 (0.949)	179	6.15 (15.180)	3.77 (0.970)	0.91 (-1.757, 3.576)	0.5030
Cycle 06 Day 01	175	6.38 (12.208)	5.65 (1.107)	180	5.56 (13.417)	3.80 (1.097)	1.85 (-1.219, 4.909)	0.2372
Cycle 07 Day 01	147	5.67 (11.785)	4.33 (1.071)	148	4.62 (10.254)	3.66 (1.074)	0.67 (-2.307, 3.655)	0.6569
Cycle 08 Day 01	148	8.11 (14.740)	5.93 (1.154)	133	5.01 (11.045)	4.80 (1.198)	1.13 (-2.152, 4.405)	0.4996
Cycle 09 Day 01	128	6.12 (11.621)	4.42 (1.083)	111	4.95 (10.916)	2.39 (1.151)	2.03 (-1.084, 5.139)	0.2009
Cycle 10 Day 01	128	7.03 (13.163)	2.32 (1.064)	99	4.71 (10.389)	0.72 (1.183)	1.60 (-1.536, 4.740)	0.3158
Cycle 11 Day 01	85	5.88 (11.982)	-1.45 (0.944)	63	3.70 (10.127)	0.28 (1.083)	-1.73 (-4.564, 1.105)	0.2302
Cycle 12 Day 01	68	5.39 (10.557)	-1.66 (1.163)	57	3.51 (9.828)	-0.68 (1.288)	-0.98 (-4.401, 2.438)	0.5716
Cycle 13 Day 01	42	5.95 (11.536)	-2.54 (1.073)	28	1.79 (6.938)	-2.17 (1.327)	-0.38 (-3.768, 3.014)	0.8256
Cycle 14 Day 01	39	6.84 (11.920)	-3.51 (0.820)	28	2.98 (9.133)	-3.51 (0.975)	0.00 (-2.542, 2.550)	0.9973
Cycle 15 Day 01	23	6.52 (10.940)	-5.37 (0.869)	15	3.33 (12.910)	-3.18 (1.096)	-2.19 (-5.035, 0.654)	0.1270
Cycle 16 Day 01	29	7.47 (12.269)	-2.94 (1.596)	13	3.85 (13.868)	-0.70 (2.316)	-2.24 (-7.917, 3.439)	0.4318
Cycle 18 Day 01	18	7.41 (13.064)	-0.92 (3.454)	10	5.00 (15.811)	4.65 (4.667)	-5.57 (-17.404, 6.270)	0.3457

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.13 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Symptom scale: Nausea and vomiting (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	7.02 (12.809)	-1.12 (2.441)	6	0.00 (0.000)	0.30 (4.280)	-1.42 (-11.733, 8.895)	0.7779
Average over all visits	293	7.11 (13.988)	1.33 (0.648)	301	6.15 (14.971)	1.56 (0.769)	-0.23 (-2.213, 1.753)	0.8195
Hedges' g SMD							-0.02 (-0.180, 0.142)	0.8196

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.14 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Symptom scale: Pain (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	264	23.86 (22.628)	-0.15 (1.156)	275	20.85 (21.775)	-2.81 (1.129)	2.65 (-0.514, 5.821)	0.1005
Cycle 03 Day 01	222	23.20 (22.166)	-3.33 (1.207)	223	20.18 (22.065)	-5.06 (1.192)	1.73 (-1.604, 5.055)	0.3091
Cycle 04 Day 01	214	22.04 (21.750)	-4.41 (1.222)	222	20.05 (21.794)	-2.96 (1.199)	-1.45 (-4.813, 1.909)	0.3965
Cycle 05 Day 01	194	20.96 (20.609)	-3.37 (1.183)	179	20.67 (21.517)	-2.89 (1.205)	-0.47 (-3.789, 2.845)	0.7797
Cycle 06 Day 01	175	20.19 (20.262)	-1.97 (1.294)	180	19.44 (21.756)	-3.61 (1.279)	1.64 (-1.933, 5.214)	0.3673
Cycle 07 Day 01	147	18.25 (19.344)	-4.13 (1.213)	148	18.47 (20.402)	-4.85 (1.209)	0.72 (-2.647, 4.080)	0.6755
Cycle 08 Day 01	148	20.50 (20.305)	-1.32 (1.454)	133	19.55 (21.073)	-2.55 (1.506)	1.22 (-2.892, 5.340)	0.5591
Cycle 09 Day 01	128	19.14 (19.852)	-1.94 (1.320)	111	18.17 (21.968)	-4.36 (1.395)	2.42 (-1.359, 6.191)	0.2089
Cycle 10 Day 01	128	19.01 (20.032)	-2.90 (1.484)	99	17.68 (21.798)	-0.25 (1.639)	-2.65 (-6.992, 1.701)	0.2320
Cycle 11 Day 01	85	17.65 (18.249)	-2.01 (1.888)	63	16.40 (22.894)	2.84 (2.145)	-4.86 (-10.470, 0.756)	0.0895
Cycle 12 Day 01	68	18.38 (18.244)	0.40 (2.177)	57	16.96 (22.601)	-1.61 (2.383)	2.01 (-4.347, 8.367)	0.5332
Cycle 13 Day 01	42	21.83 (20.656)	-3.25 (2.407)	28	14.29 (23.002)	-1.38 (2.918)	-1.88 (-9.415, 5.662)	0.6225
Cycle 14 Day 01	39	23.08 (20.808)	-5.30 (2.138)	28	14.29 (23.002)	0.46 (2.523)	-5.76 (-12.382, 0.860)	0.0873
Cycle 15 Day 01	23	17.39 (17.751)	-5.87 (2.540)	15	7.78 (17.668)	-0.10 (3.404)	-5.77 (-14.159, 2.611)	0.1724
Cycle 16 Day 01	29	20.69 (16.460)	-9.19 (2.266)	13	10.26 (18.682)	0.82 (3.437)	-10.01 (-18.312, -1.714)	0.0191*
Cycle 18 Day 01	18	21.30 (16.964)	-6.23 (3.527)	10	11.67 (20.861)	7.65 (4.883)	-13.88 (-26.180, -1.578)	0.0281*

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.14 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Symptom scale: Pain (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	22.81 (17.752)	-7.50 (3.060)	6	2.78 (6.804)	1.25 (5.840)	-8.75 (-22.597, 5.107)	0.2068
Average over all visits	293	24.46 (23.100)	-3.67 (0.981)	301	20.99 (22.603)	-1.14 (1.143)	-2.53 (-5.502, 0.433)	0.0939
Hedges' g SMD							-0.14 (-0.299, 0.023)	0.0939

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.15 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Single item symptom scale: Insomnia (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	264	23.11 (26.968)	-1.90 (1.343)	275	20.48 (24.920)	-2.87 (1.315)	0.97 (-2.720, 4.660)	0.6059
Cycle 03 Day 01	222	23.57 (26.716)	-2.11 (1.435)	223	21.08 (25.296)	-3.46 (1.421)	1.35 (-2.613, 5.315)	0.5033
Cycle 04 Day 01	214	22.27 (25.784)	-1.28 (1.443)	222	19.82 (25.120)	-3.41 (1.416)	2.13 (-1.843, 6.100)	0.2928
Cycle 05 Day 01	194	21.82 (24.216)	-3.38 (1.511)	179	20.48 (25.283)	-2.59 (1.545)	-0.79 (-5.035, 3.456)	0.7149
Cycle 06 Day 01	175	19.81 (23.461)	-0.97 (1.566)	180	21.11 (25.383)	-2.95 (1.548)	1.99 (-2.342, 6.313)	0.3676
Cycle 07 Day 01	147	18.82 (24.385)	-1.69 (1.645)	148	19.14 (23.358)	-3.88 (1.641)	2.20 (-2.370, 6.763)	0.3449
Cycle 08 Day 01	148	21.40 (25.794)	-0.15 (1.655)	133	19.55 (23.616)	-3.57 (1.723)	3.42 (-1.280, 8.118)	0.1534
Cycle 09 Day 01	128	18.49 (22.838)	-2.33 (1.637)	111	15.92 (21.949)	-0.35 (1.746)	-1.98 (-6.674, 2.723)	0.4086
Cycle 10 Day 01	128	19.79 (24.548)	-1.19 (1.812)	99	16.16 (22.010)	0.63 (2.025)	-1.82 (-7.162, 3.528)	0.5039
Cycle 11 Day 01	85	16.86 (22.197)	-4.20 (1.858)	63	20.11 (24.348)	0.86 (2.110)	-5.06 (-10.602, 0.482)	0.0733
Cycle 12 Day 01	68	18.14 (22.625)	-0.83 (2.219)	57	19.88 (24.283)	-3.97 (2.423)	3.14 (-3.347, 9.619)	0.3410
Cycle 13 Day 01	42	18.25 (19.758)	-1.28 (2.844)	28	21.43 (24.367)	-2.90 (3.422)	1.63 (-7.212, 10.468)	0.7156
Cycle 14 Day 01	39	14.53 (18.409)	1.03 (2.887)	28	21.43 (24.367)	-3.22 (3.336)	4.25 (-4.541, 13.047)	0.3392
Cycle 15 Day 01	23	15.94 (17.025)	-3.00 (2.812)	15	13.33 (30.342)	-0.24 (3.560)	-2.76 (-11.769, 6.246)	0.5404
Cycle 16 Day 01	29	16.09 (16.952)	-3.91 (3.222)	13	12.82 (28.991)	0.22 (4.698)	-4.13 (-15.404, 7.143)	0.4657
Cycle 18 Day 01	18	14.81 (17.044)	6.11 (4.940)	10	16.67 (32.394)	-4.78 (6.541)	10.88 (-5.640, 27.406)	0.1895

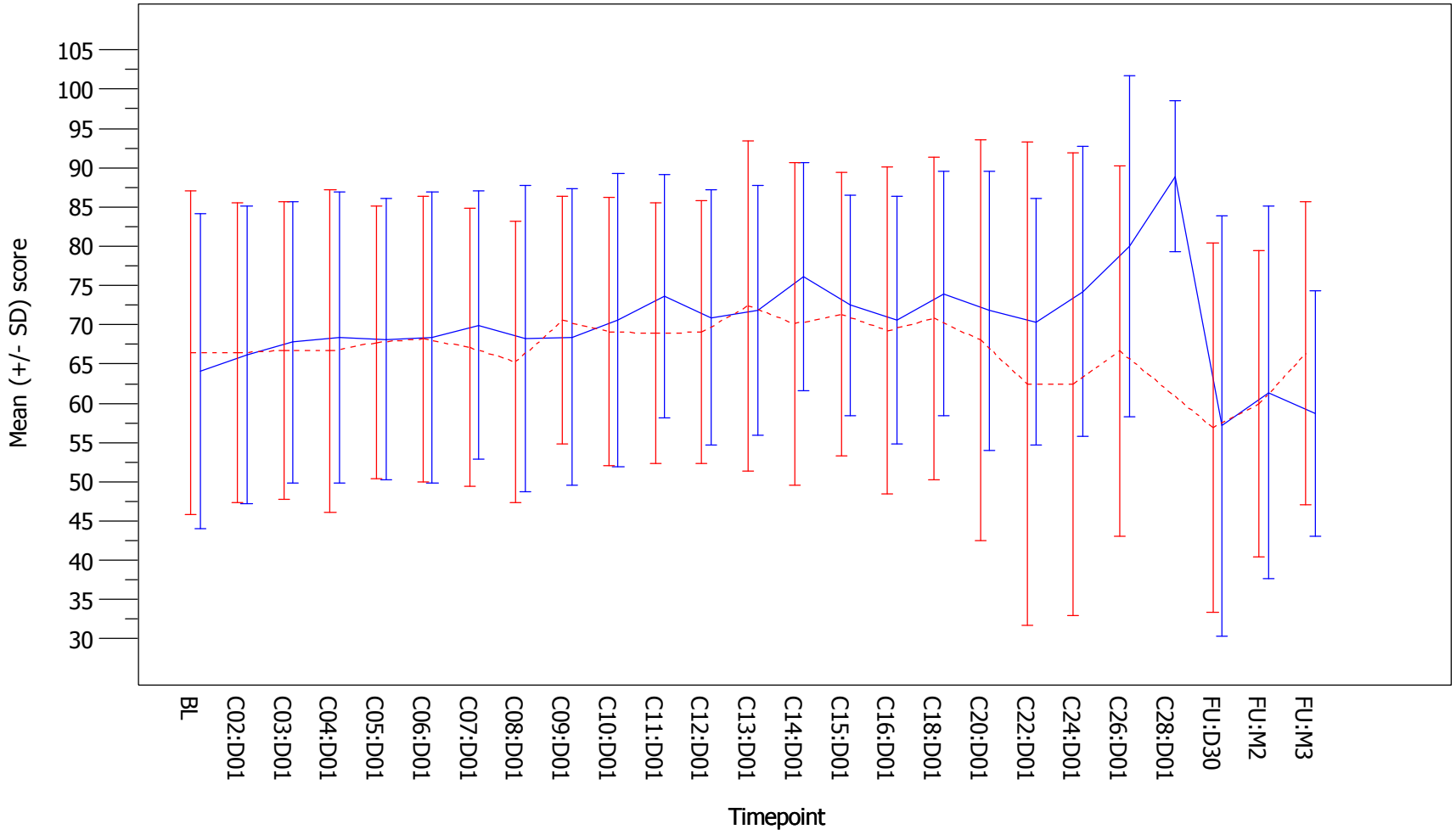
[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.5.2.15 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-C30 Single item symptom scale: Insomnia (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	15.79 (17.100)	-0.25 (5.141)	6	5.56 (13.608)	3.46 (9.303)	-3.71 (-24.612, 17.201)	0.7195
Average over all visits	293	24.35 (27.841)	-1.25 (1.175)	301	20.71 (25.153)	-1.94 (1.418)	0.69 (-2.912, 4.289)	0.7069
Hedges' g SMD							0.03 (-0.130, 0.191)	0.7095

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

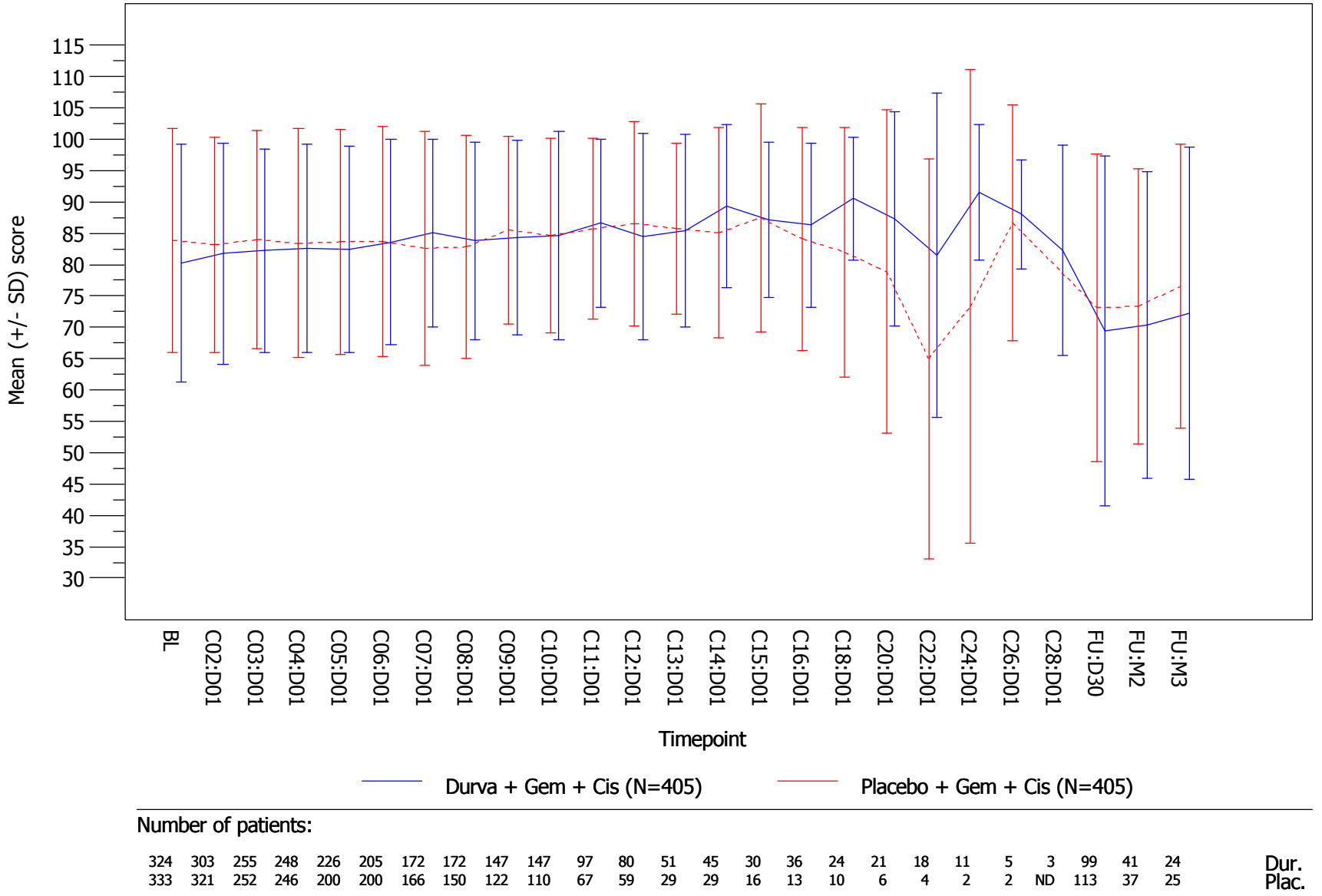
Figure 2.5.3.1 TOPAZ: Mean (+/- SD) EORTC QLQ-C30 Global QoL/health status across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

324	303	255	248	226	205	172	172	147	147	97	80	51	45	30	36	24	21	18	11	5	3	99	41	24	Dur.
333	321	252	246	200	200	166	150	122	110	67	59	29	29	16	13	10	6	4	2	2	ND	113	37	25	Plac.

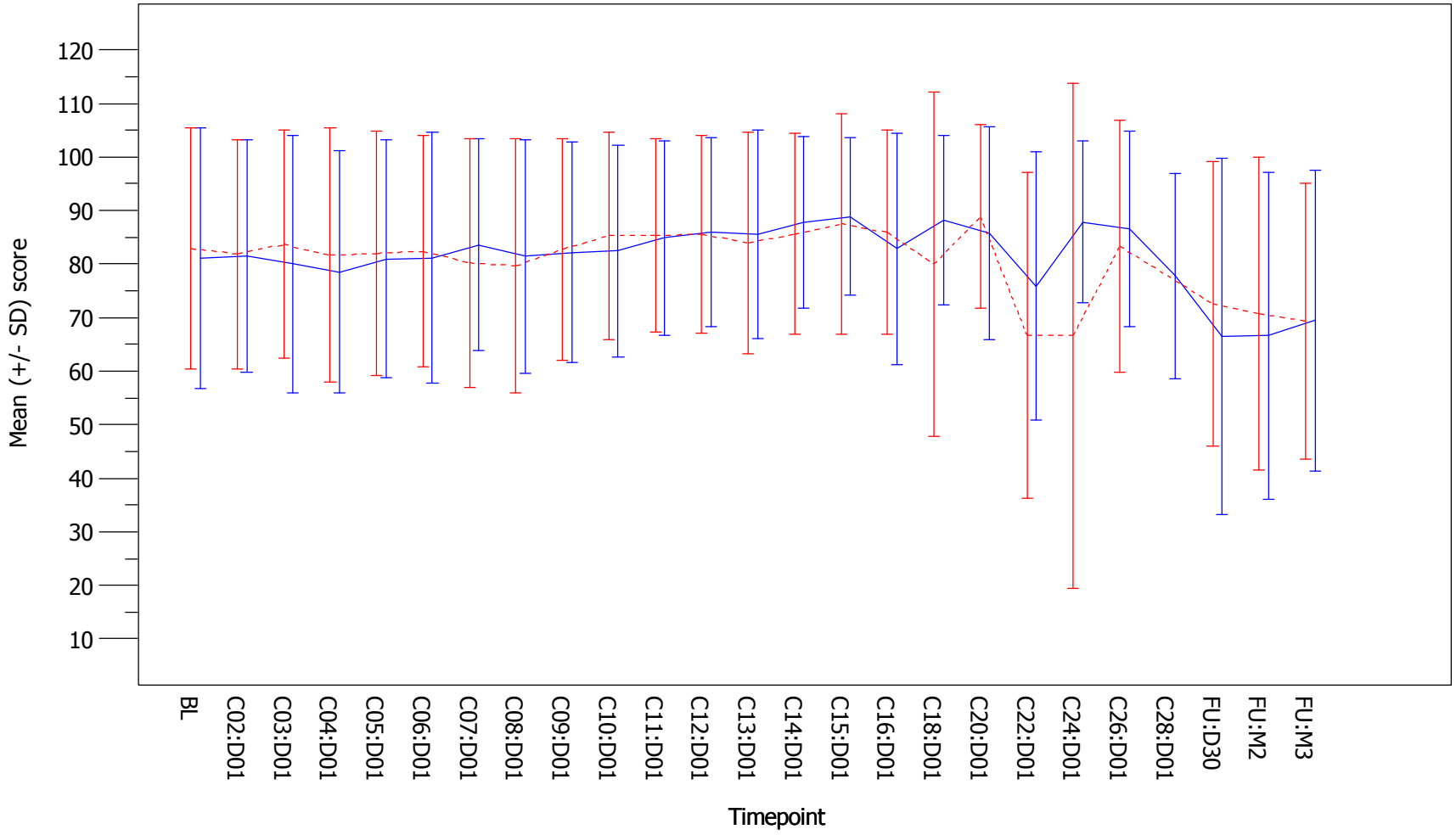
Figure 2.5.3.2 TOPAZ: Mean (+/- SD) EORTC QLQ-C30 Functional scale: Physical across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

324	303	255	248	226	205	172	172	147	147	97	80	51	45	30	36	24	21	18	11	5	3	99	41	24	Dur.
333	321	252	246	200	200	166	150	122	110	67	59	29	29	16	13	10	6	4	2	2	ND	113	37	25	Plac.

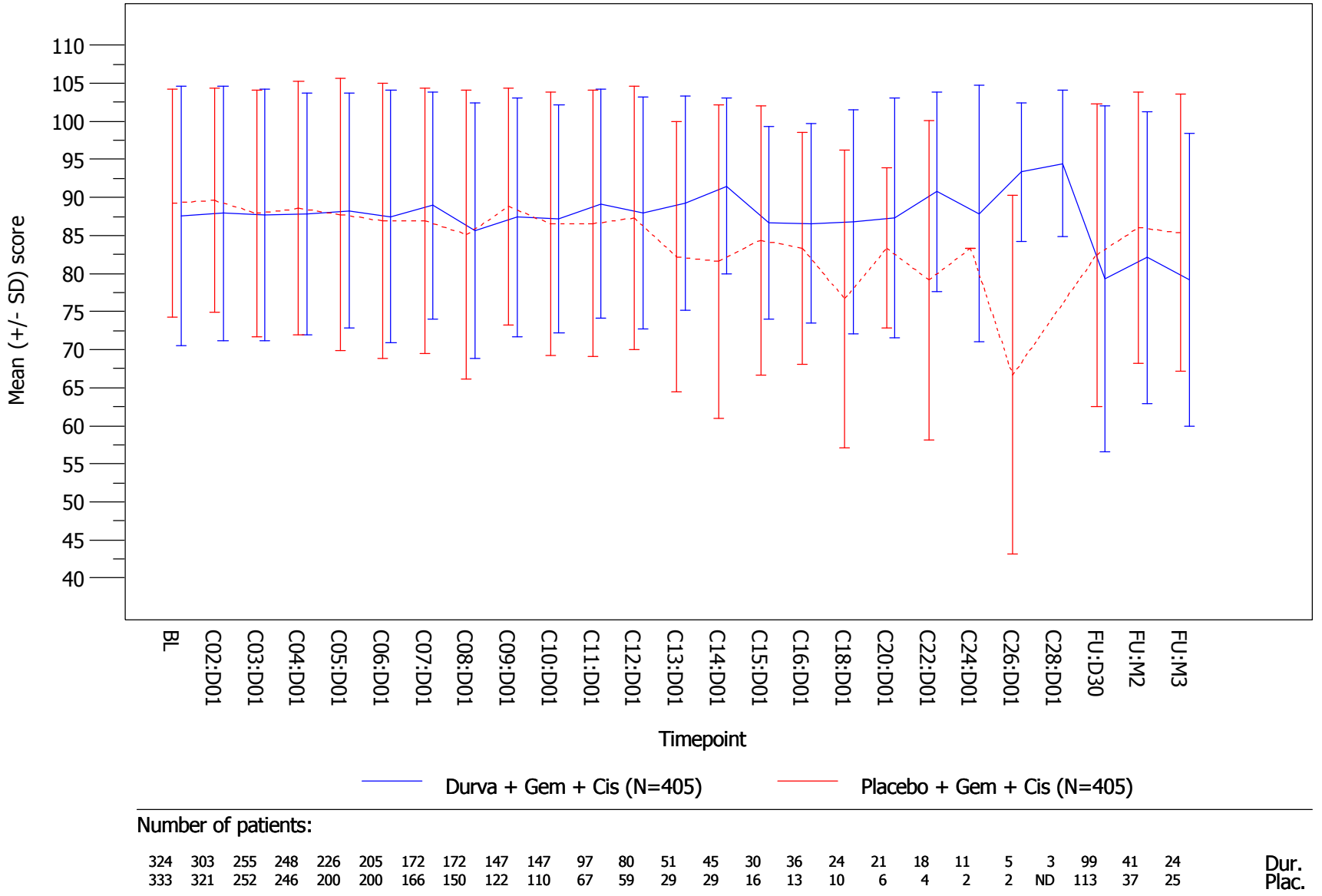
Figure 2.5.3.3 TOPAZ: Mean (+/- SD) EORTC QLQ-C30 Functional scale: Role across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

324	303	255	248	226	205	172	172	147	147	97	80	51	45	30	36	24	21	18	11	5	3	99	41	24	Dur.
333	321	252	246	200	200	166	150	122	110	67	59	29	29	16	13	10	6	4	2	2	ND	113	37	25	Plac.

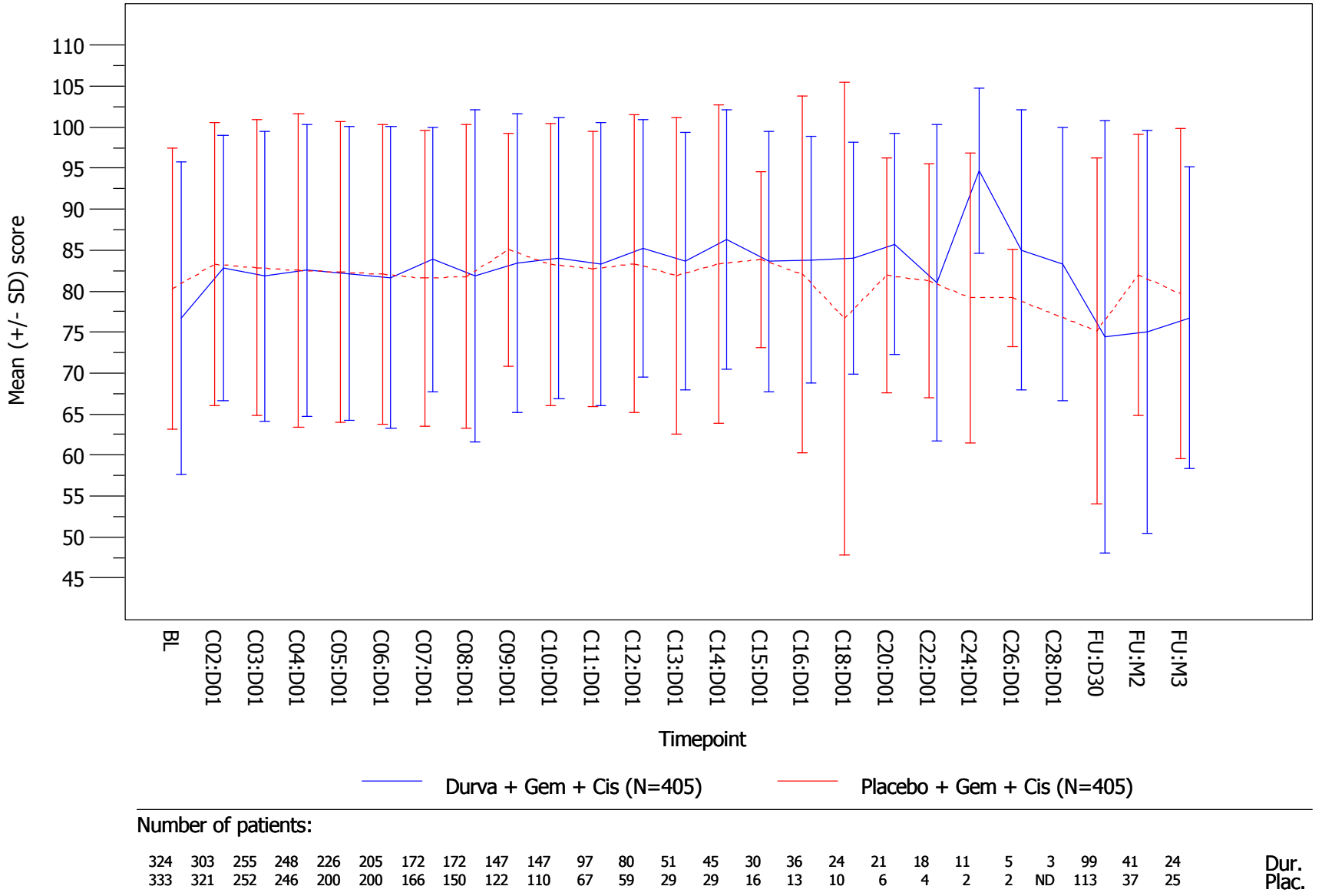
Figure 2.5.3.4 TOPAZ: Mean (+/- SD) EORTC QLQ-C30 Functional scale: Cognitive across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

324	303	255	248	226	205	172	172	147	147	97	80	51	45	30	36	24	21	18	11	5	3	99	41	24	Dur.
333	321	252	246	200	200	166	150	122	110	67	59	29	29	16	13	10	6	4	2	2	ND	113	37	25	Plac.

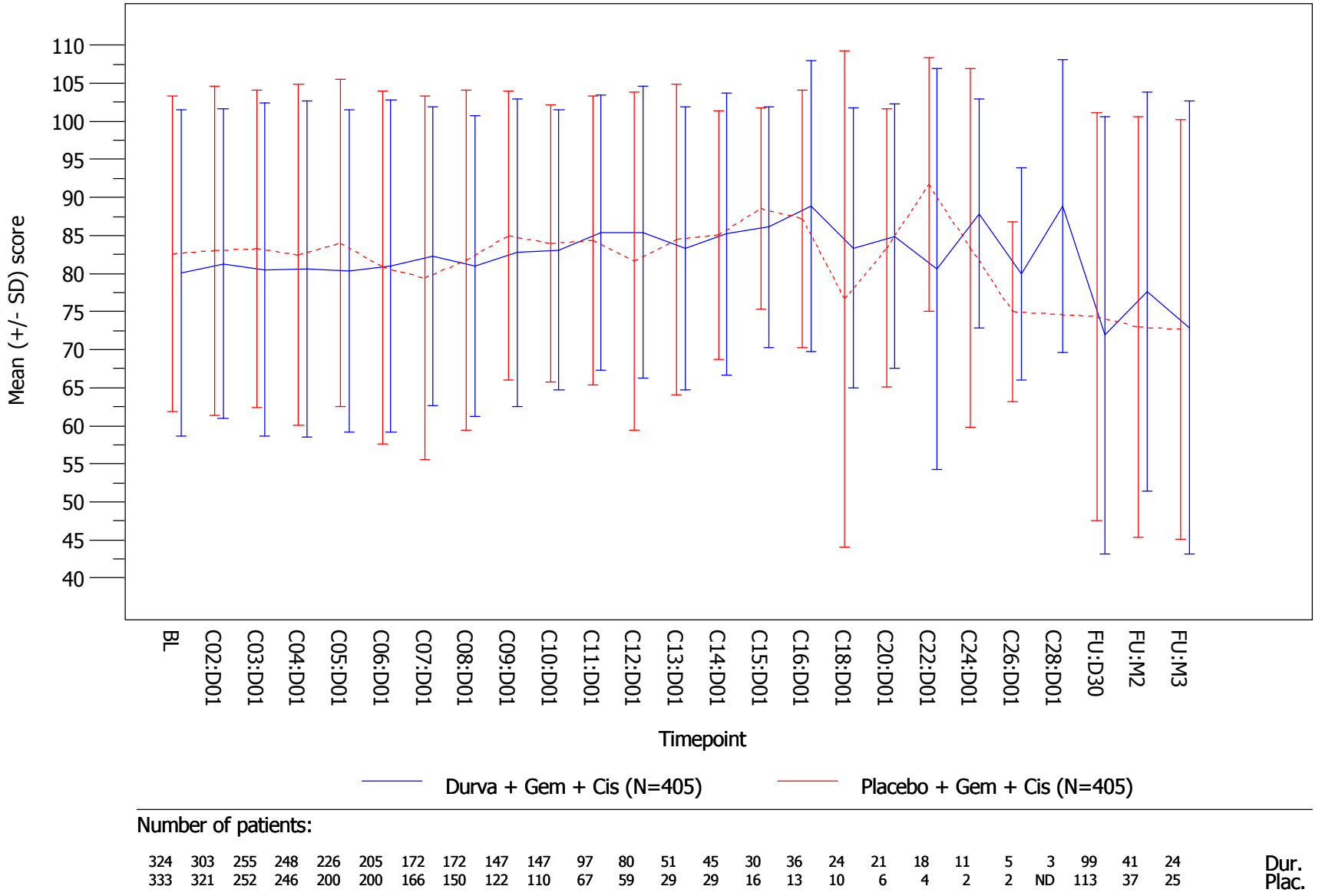
Figure 2.5.3.5 TOPAZ: Mean (+/- SD) EORTC QLQ-C30 Functional scale: Emotional across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

324	303	255	248	226	205	172	172	147	147	97	80	51	45	30	36	24	21	18	11	5	3	99	41	24	Dur.
333	321	252	246	200	200	166	150	122	110	67	59	29	29	16	13	10	6	4	2	2	ND	113	37	25	Plac.

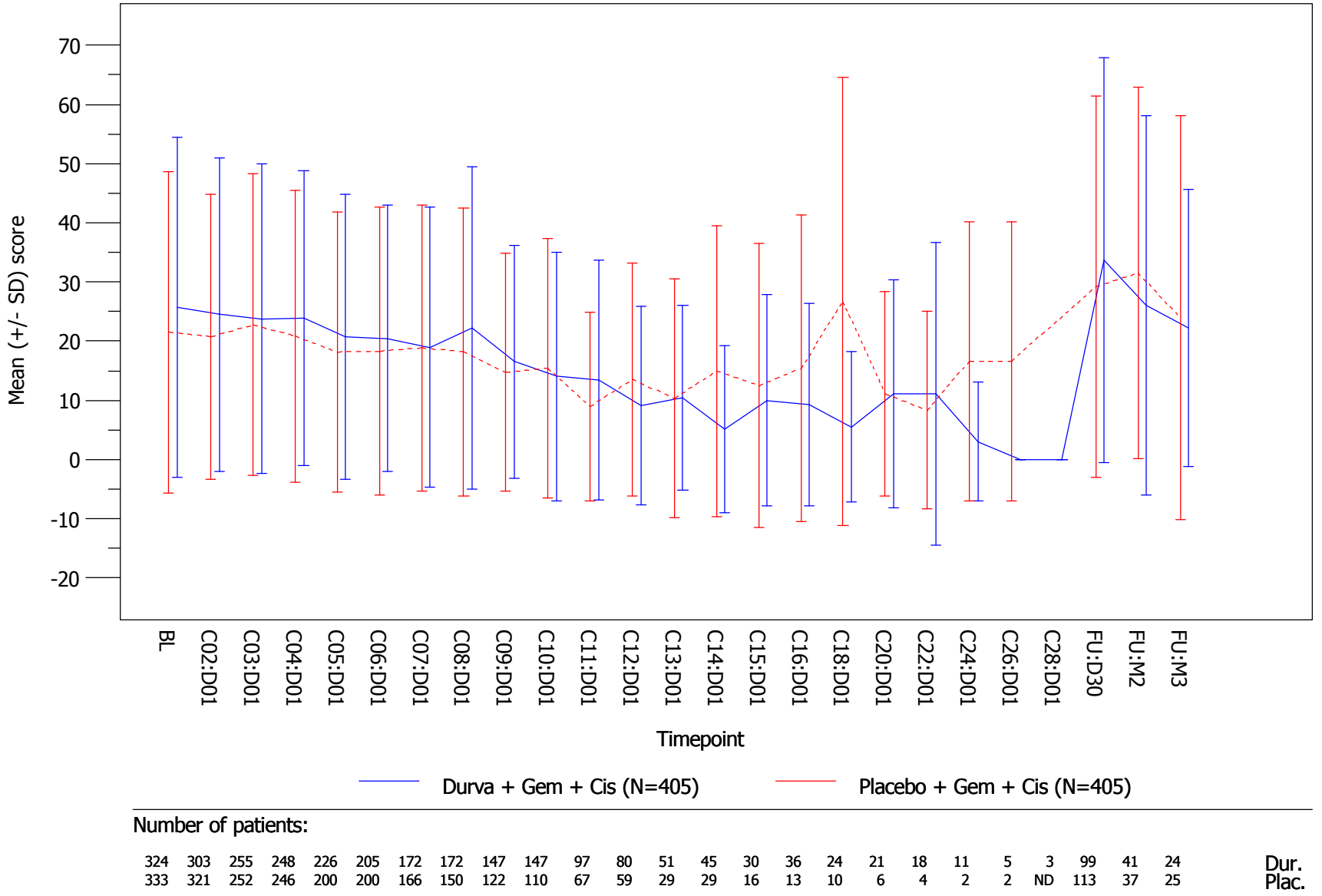
Figure 2.5.3.6 TOPAZ: Mean (+/- SD) EORTC QLQ-C30 Functional scale: Social across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

324	303	255	248	226	205	172	172	147	147	97	80	51	45	30	36	24	21	18	11	5	3	99	41	24	Dur.
333	321	252	246	200	200	166	150	122	110	67	59	29	29	16	13	10	6	4	2	2	ND	113	37	25	Plac.

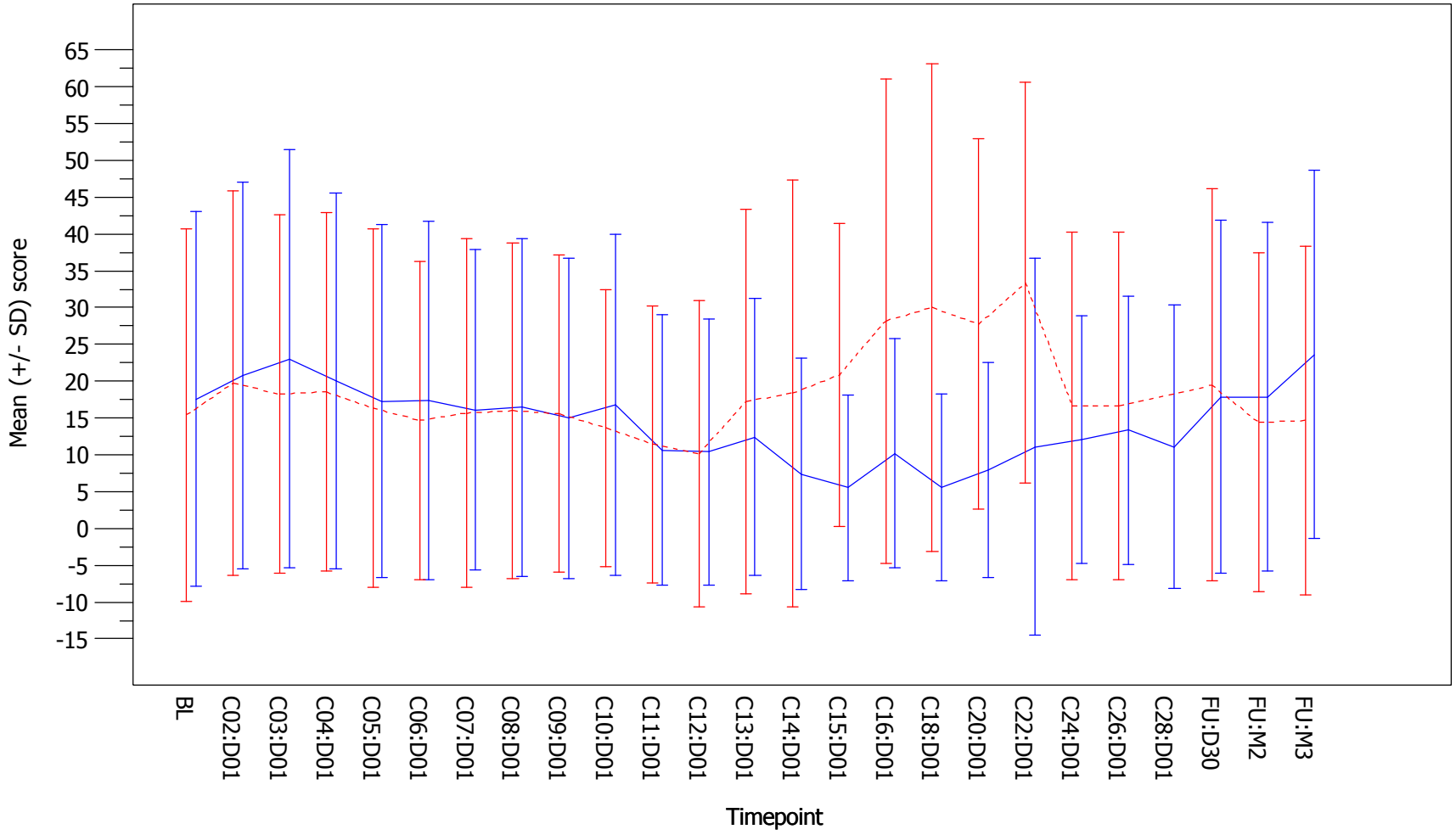
Figure 2.5.3.7 TOPAZ: Mean (+/- SD) EORTC QLQ-C30 Single item symptom scale: Loss of appetite across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

Dur.	324	303	255	248	226	205	172	172	147	147	97	80	51	45	30	36	24	21	18	11	5	3	99	41	24
Plac.	333	321	252	246	200	200	166	150	122	110	67	59	29	29	16	13	10	6	4	2	2	ND	113	37	25

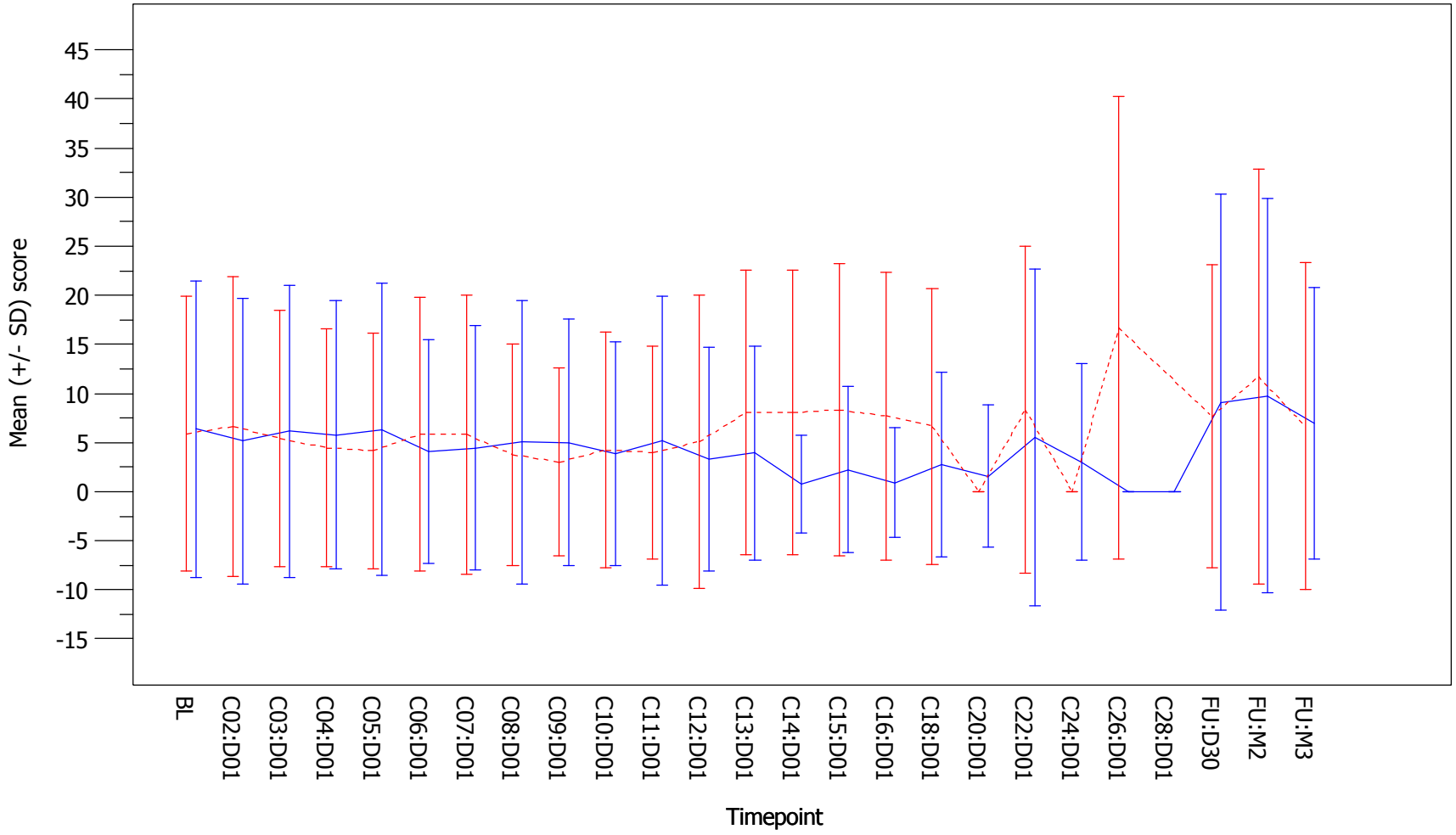
Figure 2.5.3.8 TOPAZ: Mean (+/- SD) EORTC QLQ-C30 Single item symptom scale: Constipation across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

324	303	255	248	226	205	172	172	147	147	97	80	51	45	30	36	24	21	18	11	5	3	99	41	24	Dur.
333	321	252	246	200	200	166	150	122	110	67	59	29	29	16	13	10	6	4	2	2	ND	113	37	25	Plac.

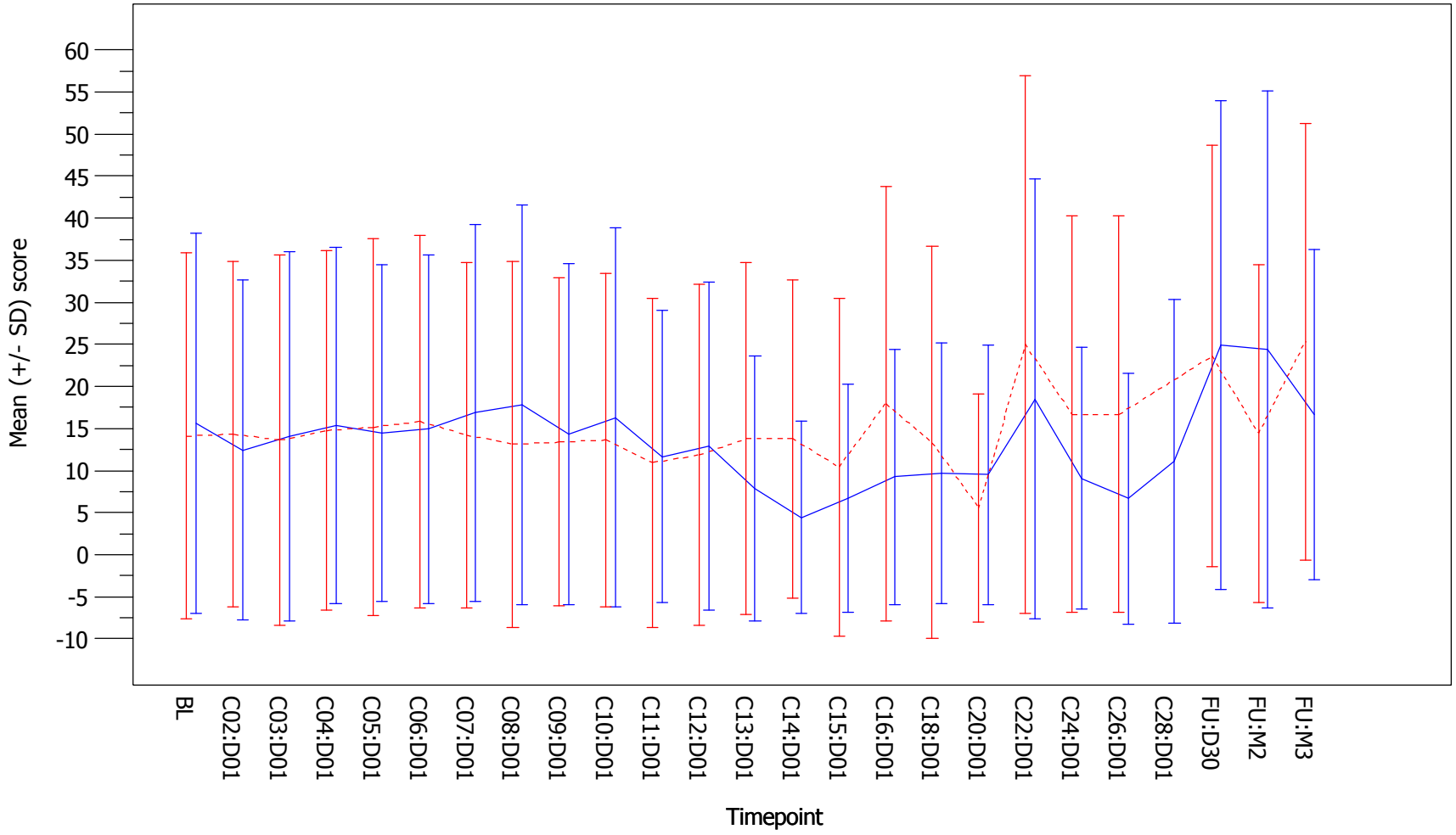
Figure 2.5.3.9 TOPAZ: Mean (+/- SD) EORTC QLQ-C30 Single item symptom scale: Diarrhoea across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

324	303	255	248	226	205	172	172	147	147	97	80	51	45	30	36	24	21	18	11	5	3	99	41	24	Dur.
333	321	252	246	200	200	166	150	122	110	67	59	29	29	16	13	10	6	4	2	2	ND	113	37	25	Plac.

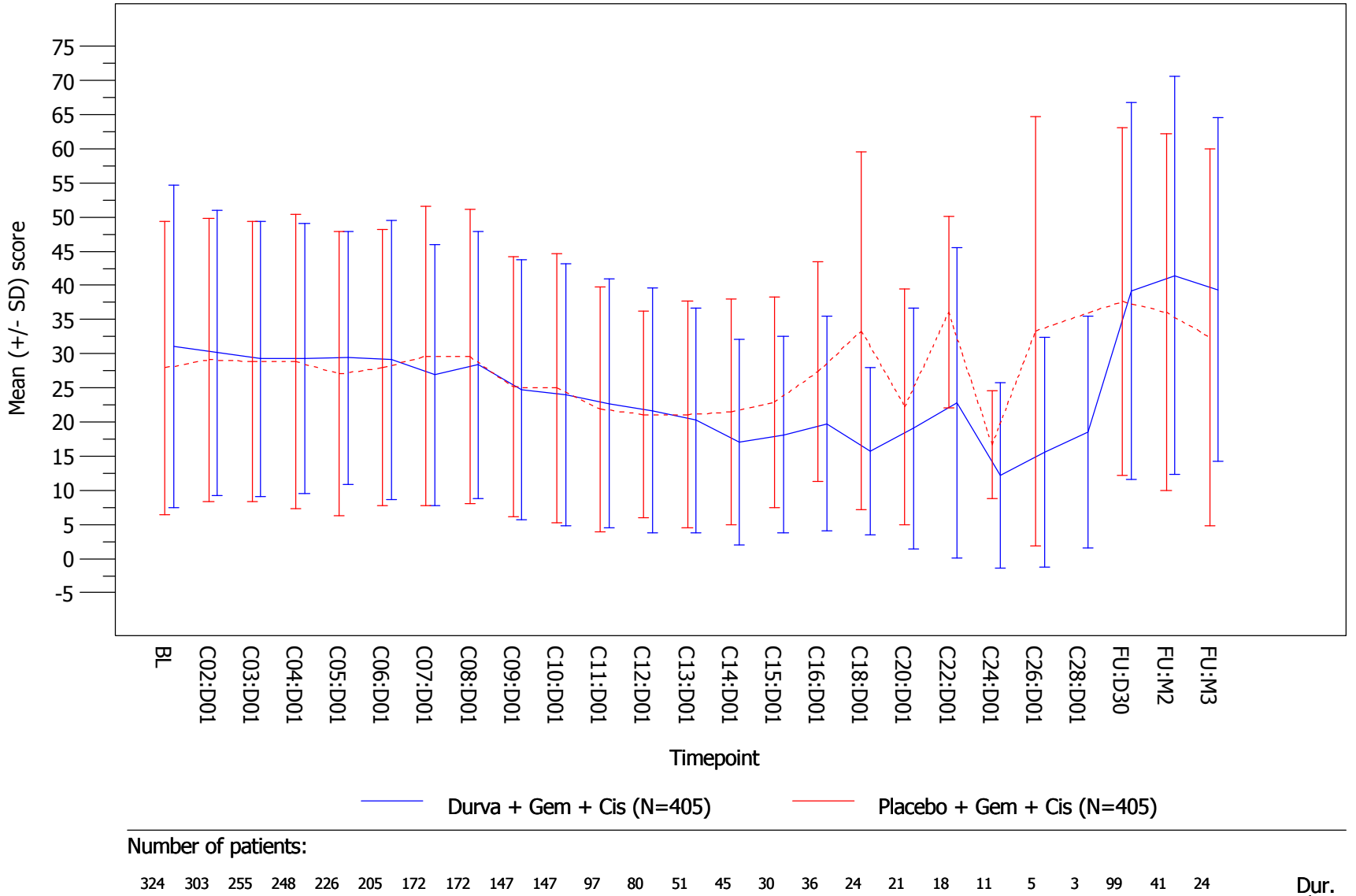
Figure 2.5.3.10 TOPAZ: Mean (+/- SD) EORTC QLQ-C30 Single item symptom scale: Dyspnoeal across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

324	303	255	248	226	205	172	172	147	147	97	80	51	45	30	36	24	21	18	11	5	3	99	41	24	Dur.
333	321	252	246	200	200	166	150	122	110	67	59	29	29	16	13	10	6	4	2	2	ND	113	37	25	Plac.

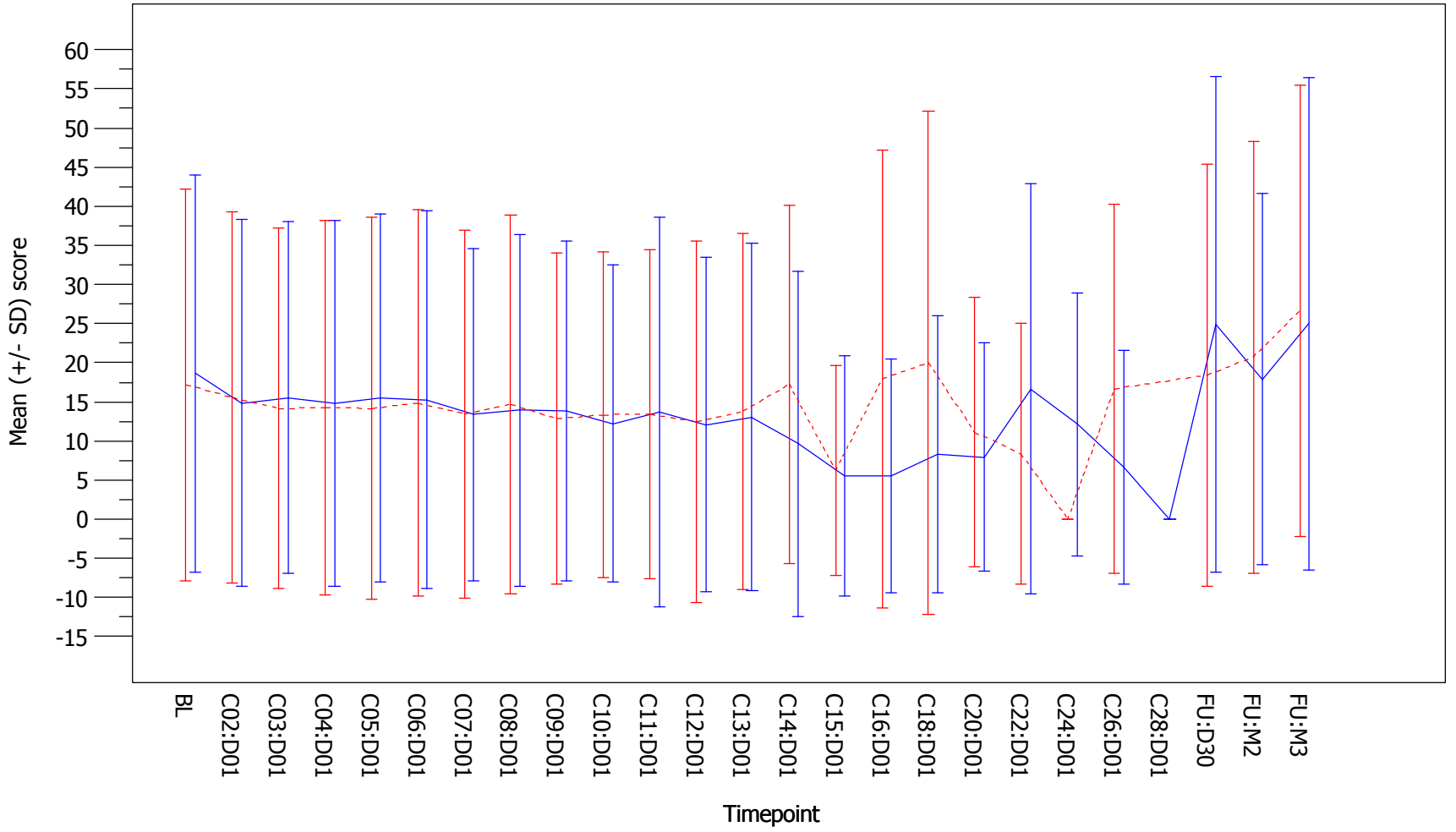
Figure 2.5.3.11 TOPAZ: Mean (+/- SD) EORTC QLQ-C30 Symptom scale: Fatigue across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

324	303	255	248	226	205	172	172	147	147	97	80	51	45	30	36	24	21	18	11	5	3	99	41	24	Dur.
333	321	252	246	200	200	166	150	122	110	67	59	29	29	16	13	10	6	4	2	2	ND	113	37	25	Plac.

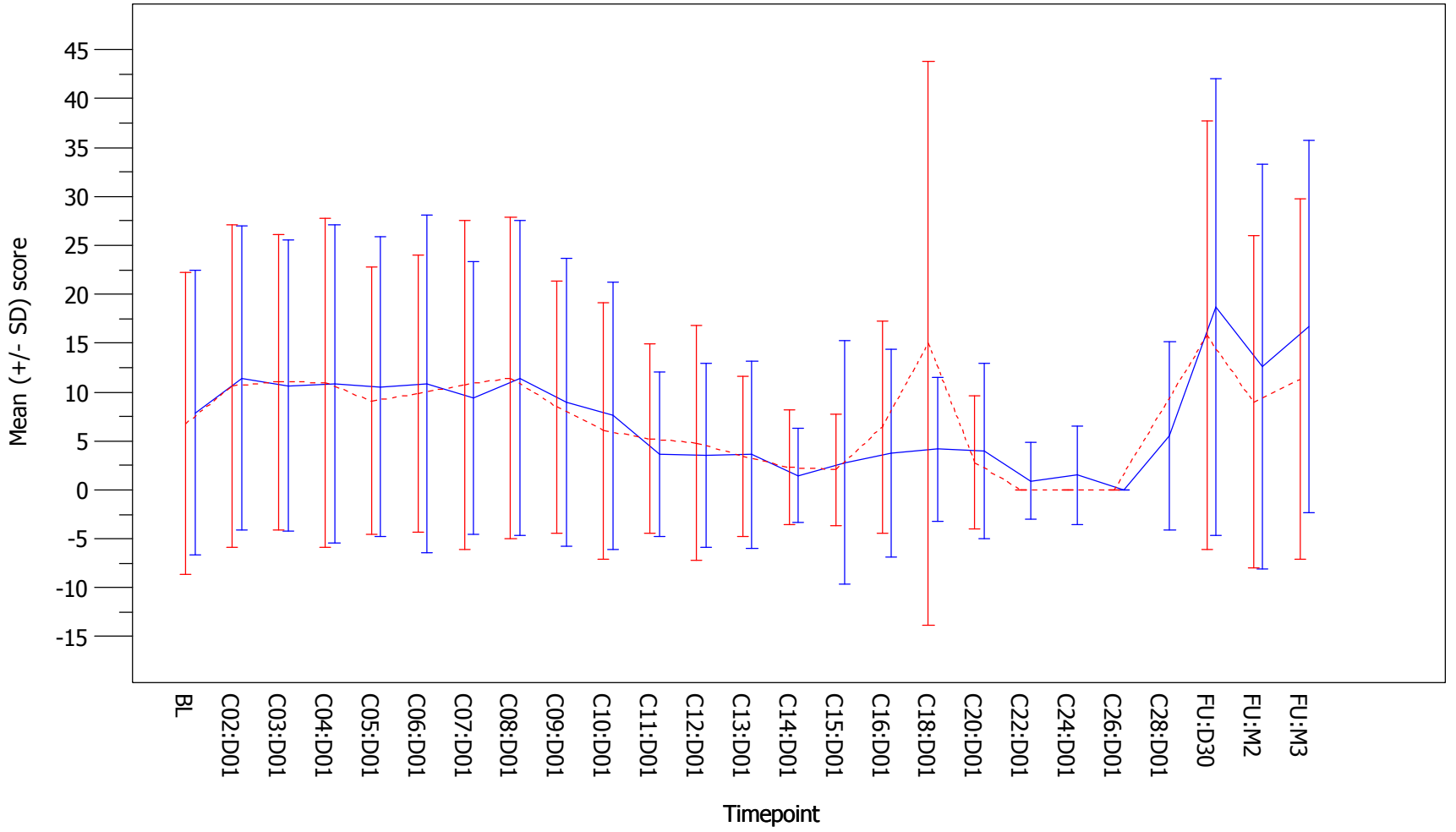
Figure 2.5.3.12 TOPAZ: Mean (+/- SD) EORTC QLQ-C30 Single item scale: Financial difficulties across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

324	303	255	248	226	205	172	172	147	147	97	80	51	45	30	36	24	21	18	11	5	3	99	41	24	Dur.
333	321	252	246	200	200	166	150	122	110	67	59	29	29	16	13	10	6	4	2	2	ND	114	37	25	Plac.

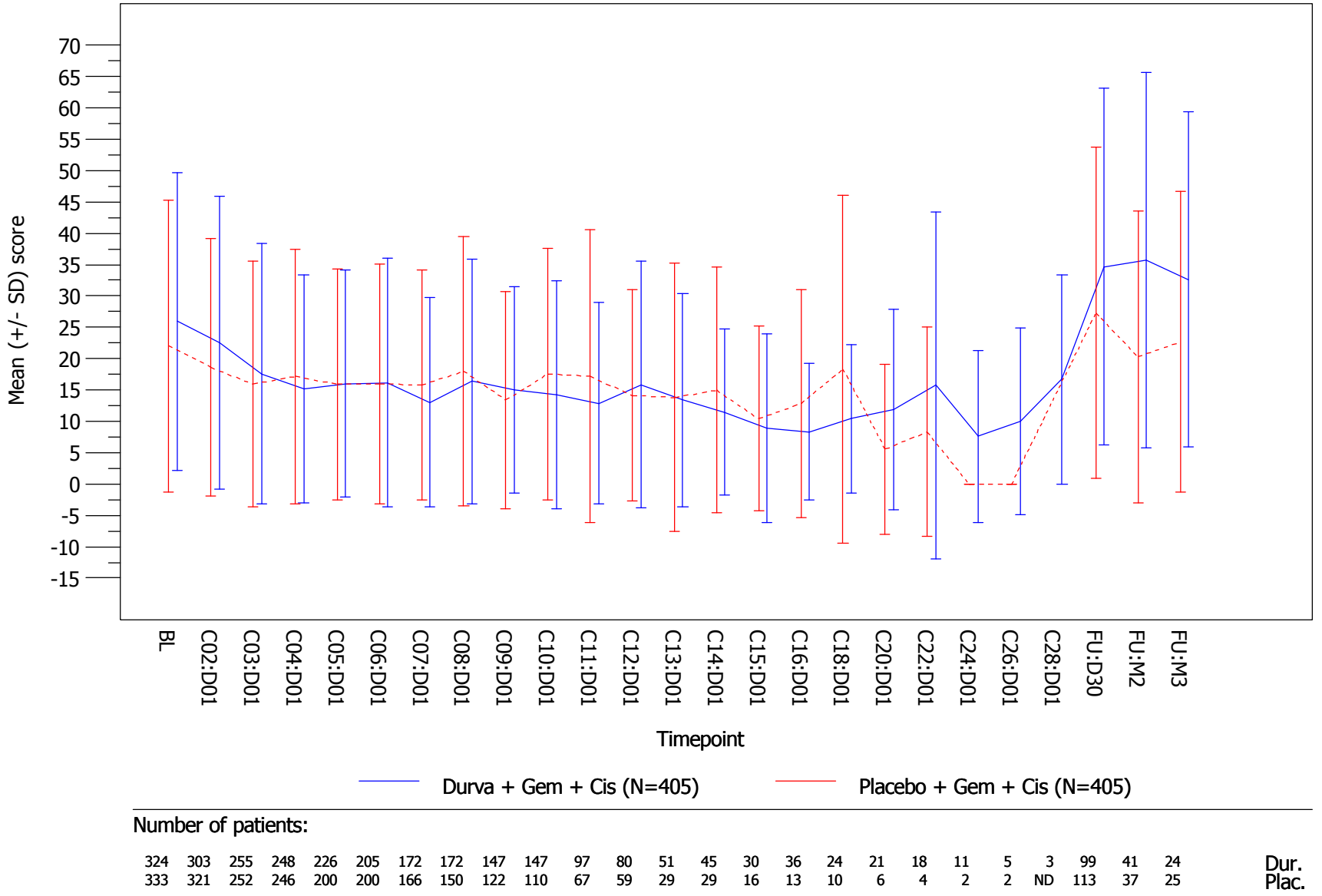
Figure 2.5.3.13 TOPAZ: Mean (+/- SD) EORTC QLQ-C30 Symptom scale: Nausea and vomiting across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

324	303	255	248	226	205	172	172	147	147	97	80	51	45	30	36	24	21	18	11	5	3	99	41	24	Dur.
333	321	252	246	200	200	166	150	122	110	67	59	29	29	16	13	10	6	4	2	2	ND	113	37	25	Plac.

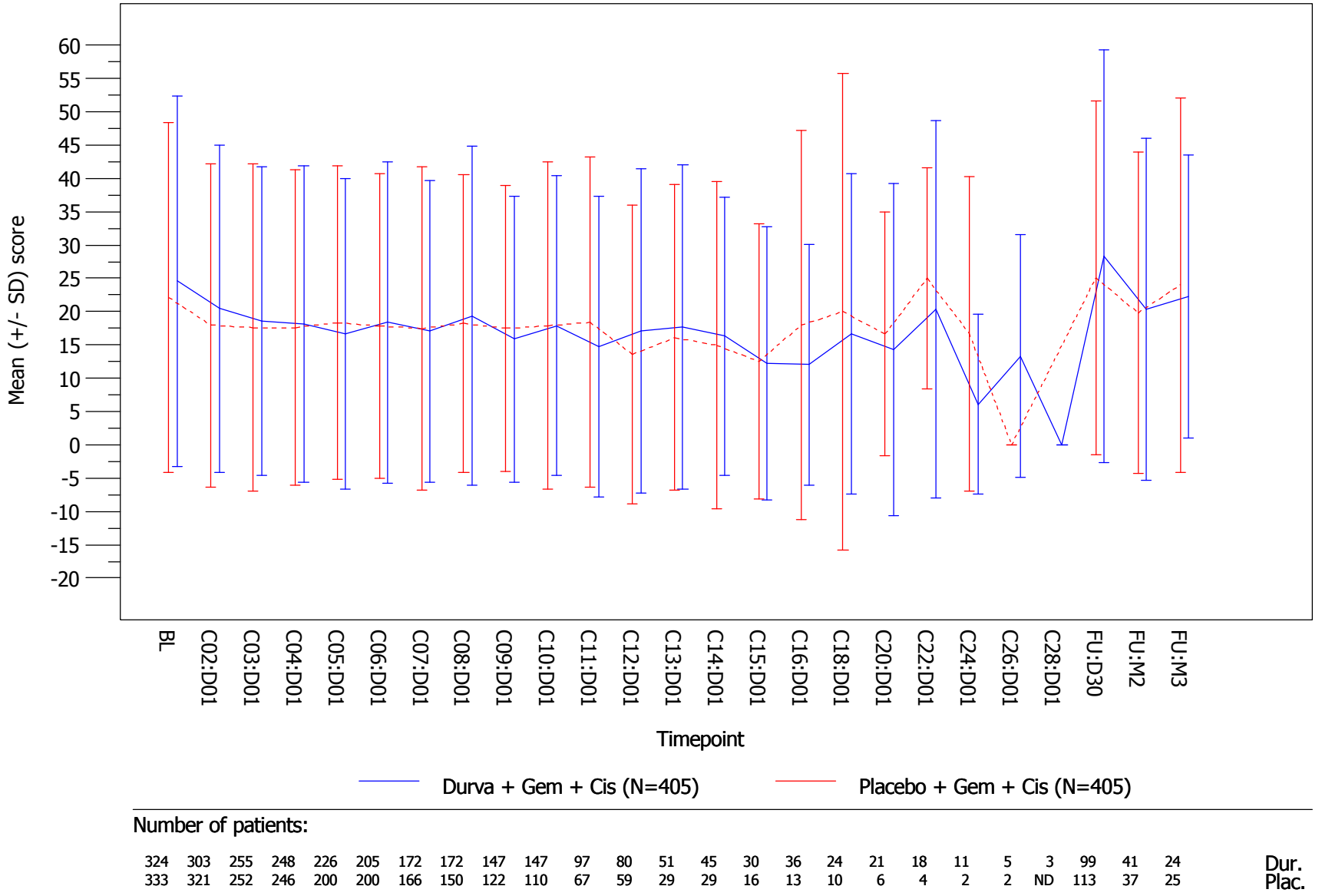
Figure 2.5.3.14 TOPAZ: Mean (+/- SD) EORTC QLQ-C30 Symptom scale: Pain across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

Dur.	324	303	255	248	226	205	172	172	147	147	97	80	51	45	30	36	24	21	18	11	5	3	99	41	24
Plac.	333	321	252	246	200	200	166	150	122	110	67	59	29	29	16	13	10	6	4	2	2	ND	113	37	25

Figure 2.5.3.15 TOPAZ: Mean (+/- SD) EORTC QLQ-C30 Single item symptom scale: Insomnia across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

Dur.	324	303	255	248	226	205	172	172	147	147	97	80	51	45	30	36	24	21	18	11	5	3	99	41	24
Plac.	333	321	252	246	200	200	166	150	122	110	67	59	29	29	16	13	10	6	4	2	2	ND	113	37	25

Table 2.6.1 TOPAZ: Summary of EORTC QLQ-BIL21 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Symptom scale: Pain	Durva + Gem + Cis (N=405)	Baseline [a]	303	21.59	21.473	0.0	16.67	100.0
		Cycle 02 Day 01	294	17.66	17.720	0.0	16.67	100.0
		Cycle 03 Day 01	244	14.75	16.242	0.0	8.33	83.3
		Cycle 04 Day 01	236	13.49	14.338	0.0	8.33	66.7
		Cycle 05 Day 01	218	14.64	14.644	0.0	8.33	66.7
		Cycle 06 Day 01	197	14.64	15.684	0.0	8.33	91.7
		Cycle 07 Day 01	164	11.64	14.408	0.0	8.33	75.0
		Cycle 08 Day 01	168	15.23	17.207	0.0	8.33	100.0
		Cycle 09 Day 01	141	11.88	13.846	0.0	8.33	58.3
		Cycle 10 Day 01	140	12.44	14.742	0.0	8.33	58.3
		Cycle 11 Day 01	93	11.20	14.407	0.0	8.33	58.3
		Cycle 12 Day 01	79	12.13	14.727	0.0	8.33	66.7
		Cycle 13 Day 01	51	11.60	13.752	0.0	8.33	58.3
		Cycle 14 Day 01	45	9.63	10.353	0.0	8.33	41.7
		Cycle 15 Day 01	30	8.89	8.736	0.0	8.33	25.0
		Cycle 16 Day 01	36	8.80	10.530	0.0	8.33	33.3
		Cycle 18 Day 01	23	11.59	12.747	0.0	8.33	33.3
		Cycle 20 Day 01	21	9.13	11.458	0.0	0.00	33.3
		Cycle 22 Day 01	18	13.89	21.198	0.0	4.17	83.3
		Cycle 24 Day 01	11	9.85	13.853	0.0	0.00	33.3
		Cycle 26 Day 01	5	16.67	16.667	0.0	16.67	33.3
		Cycle 28 Day 01	3	19.44	12.729	8.3	16.67	33.3
		Follow-up Day 30	93	27.33	23.486	0.0	25.00	100.0
		Follow-up Month 2	38	24.56	18.477	0.0	20.83	66.7
		Follow-up Month 3	24	22.57	19.424	0.0	20.83	66.7
	Placebo + Gem + Cis (N=405)	Baseline [a]	312	20.70	20.586	0.0	16.67	100.0
		Cycle 02 Day 01	318	16.48	16.881	0.0	16.67	83.3
		Cycle 03 Day 01	246	14.91	16.052	0.0	8.33	91.7
		Cycle 04 Day 01	240	14.72	17.156	0.0	8.33	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.6.1 TOPAZ: Summary of EORTC QLQ-BIL21 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	196	13.10	14.715	0.0	8.33	100.0
		Cycle 06 Day 01	195	14.02	16.035	0.0	8.33	100.0
		Cycle 07 Day 01	161	14.29	15.378	0.0	8.33	75.0
		Cycle 08 Day 01	146	13.53	16.234	0.0	8.33	91.7
		Cycle 09 Day 01	118	11.37	13.374	0.0	8.33	91.7
		Cycle 10 Day 01	107	15.19	15.477	0.0	16.67	75.0
		Cycle 11 Day 01	67	13.31	15.425	0.0	8.33	66.7
		Cycle 12 Day 01	59	11.16	13.980	0.0	0.00	41.7
		Cycle 13 Day 01	29	12.64	17.197	0.0	0.00	66.7
		Cycle 14 Day 01	29	12.07	17.336	0.0	0.00	66.7
		Cycle 15 Day 01	16	10.42	12.360	0.0	4.17	33.3
		Cycle 16 Day 01	13	14.74	18.051	0.0	8.33	50.0
		Cycle 18 Day 01	10	21.67	26.701	0.0	12.50	75.0
		Cycle 20 Day 01	6	11.11	12.546	0.0	8.33	33.3
		Cycle 22 Day 01	4	16.67	22.567	0.0	8.33	50.0
		Cycle 24 Day 01	2	0.00	0.000	0.0	0.00	0.0
		Cycle 26 Day 01	2	12.50	5.893	8.3	12.50	16.7
		Follow-up Day 30	110	23.41	20.860	0.0	16.67	100.0
		Follow-up Month 2	37	15.54	14.455	0.0	16.67	50.0
		Follow-up Month 3	25	17.33	20.259	0.0	8.33	75.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.6.1 TOPAZ: Summary of EORTC QLQ-BIL21 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Symptom scale: Tiredness	Durva + Gem + Cis (N=405)	Baseline [a]	303	28.16	25.167	0.0	22.22	100.0
		Cycle 02 Day 01	294	27.82	22.982	0.0	33.33	100.0
		Cycle 03 Day 01	244	28.37	24.612	0.0	33.33	100.0
		Cycle 04 Day 01	236	27.50	22.232	0.0	33.33	100.0
		Cycle 05 Day 01	218	26.61	20.156	0.0	33.33	100.0
		Cycle 06 Day 01	197	28.31	22.958	0.0	33.33	100.0
		Cycle 07 Day 01	164	26.42	21.504	0.0	33.33	100.0
		Cycle 08 Day 01	168	27.84	21.374	0.0	33.33	100.0
		Cycle 09 Day 01	141	24.35	20.093	0.0	22.22	66.7
		Cycle 10 Day 01	140	23.41	20.243	0.0	22.22	88.9
		Cycle 11 Day 01	93	22.94	18.375	0.0	22.22	66.7
		Cycle 12 Day 01	79	20.39	21.603	0.0	22.22	100.0
		Cycle 13 Day 01	51	20.26	19.078	0.0	22.22	66.7
		Cycle 14 Day 01	45	14.57	16.036	0.0	11.11	66.7
		Cycle 15 Day 01	30	15.93	13.587	0.0	16.67	33.3
		Cycle 16 Day 01	36	16.67	16.047	0.0	11.11	55.6
		Cycle 18 Day 01	23	18.84	15.510	0.0	22.22	44.4
		Cycle 20 Day 01	21	16.93	19.757	0.0	0.00	55.6
		Cycle 22 Day 01	18	25.31	27.955	0.0	27.78	100.0
		Cycle 24 Day 01	11	8.08	13.232	0.0	0.00	33.3
		Cycle 26 Day 01	5	15.56	16.851	0.0	11.11	33.3
		Cycle 28 Day 01	3	22.22	19.245	0.0	33.33	33.3
		Follow-up Day 30	93	36.08	30.458	0.0	33.33	100.0
		Follow-up Month 2	38	42.11	30.800	0.0	33.33	100.0
		Follow-up Month 3	24	44.91	28.840	0.0	33.33	100.0
	Placebo + Gem + Cis (N=405)	Baseline [a]	312	26.07	24.569	0.0	22.22	100.0
		Cycle 02 Day 01	318	25.51	22.119	0.0	22.22	100.0
		Cycle 03 Day 01	246	24.75	22.304	0.0	22.22	100.0
		Cycle 04 Day 01	240	25.93	23.304	0.0	22.22	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.6.1 TOPAZ: Summary of EORTC QLQ-BIL21 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	196	26.25	22.098	0.0	22.22	100.0
		Cycle 06 Day 01	195	26.27	23.273	0.0	33.33	100.0
		Cycle 07 Day 01	161	27.74	24.537	0.0	33.33	100.0
		Cycle 08 Day 01	146	25.42	23.811	0.0	22.22	100.0
		Cycle 09 Day 01	118	24.01	20.798	0.0	22.22	100.0
		Cycle 10 Day 01	107	22.74	20.668	0.0	22.22	88.9
		Cycle 11 Day 01	67	21.56	18.939	0.0	22.22	66.7
		Cycle 12 Day 01	59	17.89	17.141	0.0	22.22	77.8
		Cycle 13 Day 01	29	21.84	19.355	0.0	22.22	55.6
		Cycle 14 Day 01	29	22.99	15.122	0.0	22.22	55.6
		Cycle 15 Day 01	16	13.89	14.344	0.0	11.11	44.4
		Cycle 16 Day 01	13	26.50	22.470	0.0	22.22	66.7
		Cycle 18 Day 01	10	31.11	28.593	0.0	33.33	88.9
		Cycle 20 Day 01	6	22.22	18.592	0.0	27.78	44.4
		Cycle 22 Day 01	4	36.11	21.033	22.2	27.78	66.7
		Cycle 24 Day 01	2	16.67	23.570	0.0	16.67	33.3
		Cycle 26 Day 01	2	38.89	39.284	11.1	38.89	66.7
		Follow-up Day 30	110	37.17	28.890	0.0	33.33	100.0
		Follow-up Month 2	37	37.54	26.104	0.0	33.33	100.0
		Follow-up Month 3	25	32.89	30.000	0.0	33.33	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.6.1 TOPAZ: Summary of EORTC QLQ-BIL21 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Symptom scale: Jaundice	Durva + Gem + Cis (N=405)	Baseline [a]	303	8.98	15.699	0.0	0.00	100.0
		Cycle 02 Day 01	294	6.39	10.011	0.0	0.00	44.4
		Cycle 03 Day 01	244	5.37	10.204	0.0	0.00	66.7
		Cycle 04 Day 01	236	5.79	11.109	0.0	0.00	66.7
		Cycle 05 Day 01	218	4.54	8.946	0.0	0.00	44.4
		Cycle 06 Day 01	197	4.40	9.088	0.0	0.00	44.4
		Cycle 07 Day 01	164	4.40	9.096	0.0	0.00	44.4
		Cycle 08 Day 01	168	5.82	12.866	0.0	0.00	100.0
		Cycle 09 Day 01	141	5.44	10.168	0.0	0.00	55.6
		Cycle 10 Day 01	140	5.56	10.367	0.0	0.00	66.7
		Cycle 11 Day 01	93	5.73	9.356	0.0	0.00	44.4
		Cycle 12 Day 01	79	5.34	9.391	0.0	0.00	44.4
		Cycle 13 Day 01	51	6.32	8.679	0.0	0.00	33.3
		Cycle 14 Day 01	45	4.94	6.929	0.0	0.00	22.2
		Cycle 15 Day 01	30	5.93	8.623	0.0	0.00	22.2
		Cycle 16 Day 01	36	7.10	8.870	0.0	0.00	33.3
		Cycle 18 Day 01	23	7.73	8.498	0.0	11.11	22.2
		Cycle 20 Day 01	21	5.82	8.329	0.0	0.00	33.3
		Cycle 22 Day 01	18	11.11	23.800	0.0	0.00	100.0
		Cycle 24 Day 01	11	4.04	5.606	0.0	0.00	11.1
		Cycle 26 Day 01	5	4.44	6.086	0.0	0.00	11.1
		Cycle 28 Day 01	3	7.41	12.830	0.0	0.00	22.2
		Follow-up Day 30	93	8.84	14.334	0.0	0.00	88.9
		Follow-up Month 2	38	9.94	13.618	0.0	0.00	55.6
		Follow-up Month 3	24	6.02	11.804	0.0	0.00	44.4
	Placebo + Gem + Cis (N=405)	Baseline [a]	312	6.41	11.413	0.0	0.00	66.7
		Cycle 02 Day 01	318	5.80	10.905	0.0	0.00	77.8
		Cycle 03 Day 01	246	5.47	9.925	0.0	0.00	55.6
		Cycle 04 Day 01	240	5.56	10.757	0.0	0.00	66.7

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.6.1 TOPAZ: Summary of EORTC QLQ-BIL21 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	196	5.22	11.770	0.0	0.00	100.0
		Cycle 06 Day 01	195	5.07	10.103	0.0	0.00	55.6
		Cycle 07 Day 01	161	6.69	13.104	0.0	0.00	55.6
		Cycle 08 Day 01	146	4.64	9.478	0.0	0.00	44.4
		Cycle 09 Day 01	118	2.73	5.614	0.0	0.00	22.2
		Cycle 10 Day 01	107	5.50	10.939	0.0	0.00	55.6
		Cycle 11 Day 01	67	4.15	7.450	0.0	0.00	44.4
		Cycle 12 Day 01	59	3.95	7.371	0.0	0.00	33.3
		Cycle 13 Day 01	29	6.90	11.274	0.0	0.00	55.6
		Cycle 14 Day 01	29	5.36	6.383	0.0	0.00	22.2
		Cycle 15 Day 01	16	6.94	12.087	0.0	0.00	44.4
		Cycle 16 Day 01	13	5.13	5.765	0.0	0.00	11.1
		Cycle 18 Day 01	10	7.78	10.541	0.0	5.56	33.3
		Cycle 20 Day 01	6	11.11	12.172	0.0	11.11	33.3
		Cycle 22 Day 01	4	11.11	15.713	0.0	5.56	33.3
		Cycle 24 Day 01	2	5.56	7.857	0.0	5.56	11.1
		Cycle 26 Day 01	2	16.67	23.570	0.0	16.67	33.3
		Follow-up Day 30	110	10.00	16.756	0.0	0.00	100.0
		Follow-up Month 2	37	8.71	18.728	0.0	0.00	100.0
		Follow-up Month 3	25	5.78	14.387	0.0	0.00	66.7

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.6.1 TOPAZ: Summary of EORTC QLQ-BIL21 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Symptom scale: Anxiety	Durva + Gem + Cis (N=405)	Baseline [a]	303	34.68	23.895	0.0	33.33	100.0
		Cycle 02 Day 01	294	29.90	20.338	0.0	33.33	100.0
		Cycle 03 Day 01	244	27.90	20.920	0.0	25.00	100.0
		Cycle 04 Day 01	236	27.58	20.502	0.0	25.00	100.0
		Cycle 05 Day 01	218	28.75	20.443	0.0	25.00	100.0
		Cycle 06 Day 01	197	27.24	21.828	0.0	25.00	100.0
		Cycle 07 Day 01	164	25.81	19.673	0.0	25.00	91.7
		Cycle 08 Day 01	168	28.62	22.126	0.0	25.00	100.0
		Cycle 09 Day 01	141	25.77	19.943	0.0	25.00	91.7
		Cycle 10 Day 01	140	25.71	20.884	0.0	25.00	100.0
		Cycle 11 Day 01	93	25.09	19.094	0.0	25.00	83.3
		Cycle 12 Day 01	79	23.10	16.503	0.0	25.00	66.7
		Cycle 13 Day 01	51	25.16	17.833	0.0	25.00	58.3
		Cycle 14 Day 01	45	20.56	15.851	0.0	25.00	58.3
		Cycle 15 Day 01	30	22.22	17.824	0.0	25.00	50.0
		Cycle 16 Day 01	36	20.83	17.194	0.0	16.67	66.7
		Cycle 18 Day 01	23	26.45	18.404	0.0	33.33	58.3
		Cycle 20 Day 01	21	24.21	20.901	0.0	25.00	58.3
		Cycle 22 Day 01	18	24.54	25.481	0.0	25.00	91.7
		Cycle 24 Day 01	11	13.64	16.361	0.0	0.00	41.7
		Cycle 26 Day 01	5	23.33	24.580	0.0	25.00	58.3
		Cycle 28 Day 01	3	16.67	28.868	0.0	0.00	50.0
		Follow-up Day 30	93	33.69	25.975	0.0	33.33	100.0
		Follow-up Month 2	38	36.84	21.888	0.0	33.33	83.3
		Follow-up Month 3	24	39.93	22.385	0.0	37.50	83.3
	Placebo + Gem + Cis (N=405)	Baseline [a]	312	32.26	22.118	0.0	33.33	100.0
		Cycle 02 Day 01	318	27.20	20.678	0.0	25.00	91.7
		Cycle 03 Day 01	246	28.15	23.132	0.0	25.00	100.0
		Cycle 04 Day 01	240	26.08	22.140	0.0	25.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.6.1 TOPAZ: Summary of EORTC QLQ-BIL21 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	196	25.55	20.062	0.0	25.00	91.7
		Cycle 06 Day 01	195	26.45	21.373	0.0	25.00	100.0
		Cycle 07 Day 01	161	27.80	21.909	0.0	25.00	100.0
		Cycle 08 Day 01	146	26.54	20.623	0.0	25.00	100.0
		Cycle 09 Day 01	118	24.86	19.520	0.0	25.00	75.0
		Cycle 10 Day 01	107	24.14	19.424	0.0	25.00	66.7
		Cycle 11 Day 01	67	23.51	17.939	0.0	25.00	66.7
		Cycle 12 Day 01	59	22.60	19.144	0.0	16.67	83.3
		Cycle 13 Day 01	29	25.57	23.773	0.0	16.67	100.0
		Cycle 14 Day 01	29	25.86	22.750	0.0	25.00	83.3
		Cycle 15 Day 01	16	20.31	13.934	0.0	20.83	41.7
		Cycle 16 Day 01	13	29.49	25.142	0.0	25.00	91.7
		Cycle 18 Day 01	10	31.67	31.623	0.0	29.17	100.0
		Cycle 20 Day 01	6	31.94	22.618	0.0	33.33	66.7
		Cycle 22 Day 01	4	29.17	17.347	8.3	29.17	50.0
		Cycle 24 Day 01	2	16.67	23.570	0.0	16.67	33.3
		Cycle 26 Day 01	2	29.17	5.893	25.0	29.17	33.3
		Follow-up Day 30	110	35.61	26.277	0.0	33.33	100.0
		Follow-up Month 2	37	36.49	24.244	0.0	33.33	100.0
		Follow-up Month 3	25	29.67	26.471	0.0	25.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.6.1 TOPAZ: Summary of EORTC QLQ-BIL21 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

			Absolute Values					
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Symptom scale: Eating	Durva + Gem + Cis (N=405)	Baseline [a]	303	17.44	19.226	0.0	8.33	83.3
		Cycle 02 Day 01	294	18.17	18.003	0.0	16.67	83.3
		Cycle 03 Day 01	244	16.77	17.576	0.0	8.33	83.3
		Cycle 04 Day 01	236	17.87	16.940	0.0	16.67	75.0
		Cycle 05 Day 01	218	15.94	16.756	0.0	8.33	75.0
		Cycle 06 Day 01	197	15.69	16.413	0.0	8.33	91.7
		Cycle 07 Day 01	164	15.09	17.135	0.0	8.33	91.7
		Cycle 08 Day 01	168	16.27	18.005	0.0	8.33	100.0
		Cycle 09 Day 01	141	14.54	15.949	0.0	8.33	66.7
		Cycle 10 Day 01	140	13.33	14.786	0.0	8.33	66.7
		Cycle 11 Day 01	93	11.38	12.697	0.0	8.33	50.0
		Cycle 12 Day 01	79	8.33	10.923	0.0	8.33	41.7
		Cycle 13 Day 01	51	9.97	10.003	0.0	8.33	33.3
		Cycle 14 Day 01	45	8.52	11.165	0.0	8.33	41.7
		Cycle 15 Day 01	30	8.06	9.151	0.0	8.33	25.0
		Cycle 16 Day 01	36	8.56	9.446	0.0	8.33	33.3
		Cycle 18 Day 01	23	8.33	10.660	0.0	0.00	33.3
		Cycle 20 Day 01	21	8.73	10.026	0.0	8.33	41.7
		Cycle 22 Day 01	18	13.89	20.412	0.0	8.33	83.3
		Cycle 24 Day 01	11	8.33	11.785	0.0	0.00	33.3
		Cycle 26 Day 01	5	10.00	10.865	0.0	8.33	25.0
		Cycle 28 Day 01	3	8.33	8.333	0.0	8.33	16.7
		Follow-up Day 30	93	23.92	24.396	0.0	16.67	91.7
		Follow-up Month 2	38	24.78	27.158	0.0	16.67	100.0
		Follow-up Month 3	24	24.31	20.839	0.0	20.83	66.7
	Placebo + Gem + Cis (N=405)	Baseline [a]	312	14.56	17.573	0.0	8.33	100.0
		Cycle 02 Day 01	318	15.64	16.589	0.0	8.33	100.0
		Cycle 03 Day 01	246	15.92	16.987	0.0	8.33	100.0
		Cycle 04 Day 01	240	15.10	16.032	0.0	8.33	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.6.1 TOPAZ: Summary of EORTC QLQ-BIL21 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	196	14.97	16.166	0.0	8.33	100.0
		Cycle 06 Day 01	195	14.96	16.729	0.0	8.33	91.7
		Cycle 07 Day 01	161	14.91	15.768	0.0	8.33	66.7
		Cycle 08 Day 01	146	13.87	15.910	0.0	8.33	83.3
		Cycle 09 Day 01	118	13.21	15.459	0.0	8.33	75.0
		Cycle 10 Day 01	107	13.71	15.789	0.0	8.33	75.0
		Cycle 11 Day 01	67	8.46	11.189	0.0	0.00	33.3
		Cycle 12 Day 01	59	10.59	14.667	0.0	8.33	58.3
		Cycle 13 Day 01	29	10.06	12.276	0.0	8.33	41.7
		Cycle 14 Day 01	29	10.34	13.484	0.0	8.33	41.7
		Cycle 15 Day 01	16	8.33	11.386	0.0	4.17	33.3
		Cycle 16 Day 01	13	14.74	21.014	0.0	8.33	58.3
		Cycle 18 Day 01	10	14.17	17.146	0.0	8.33	50.0
		Cycle 20 Day 01	6	11.11	12.546	0.0	8.33	33.3
		Cycle 22 Day 01	4	12.50	14.434	0.0	8.33	33.3
		Cycle 24 Day 01	2	4.17	5.893	0.0	4.17	8.3
		Cycle 26 Day 01	2	12.50	17.678	0.0	12.50	25.0
		Follow-up Day 30	110	23.18	22.189	0.0	16.67	83.3
		Follow-up Month 2	37	24.55	24.371	0.0	16.67	91.7
		Follow-up Month 3	25	18.67	23.605	0.0	8.33	91.7

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.6.1 TOPAZ: Summary of EORTC QLQ-BIL21 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Function: Treatment side effects	Durva + Gem + Cis (N=405)	Baseline [a]	303	12.21	21.898	0.0	0.00	100.0
		Cycle 02 Day 01	294	20.63	22.486	0.0	33.33	100.0
		Cycle 03 Day 01	244	23.77	23.995	0.0	33.33	100.0
		Cycle 04 Day 01	236	22.18	22.020	0.0	33.33	100.0
		Cycle 05 Day 01	218	22.02	23.174	0.0	33.33	100.0
		Cycle 06 Day 01	197	22.50	24.188	0.0	33.33	100.0
		Cycle 07 Day 01	164	21.34	22.727	0.0	33.33	100.0
		Cycle 08 Day 01	168	21.83	23.637	0.0	33.33	100.0
		Cycle 09 Day 01	141	18.68	21.591	0.0	0.00	100.0
		Cycle 10 Day 01	140	16.90	21.716	0.0	0.00	100.0
		Cycle 11 Day 01	93	13.62	20.988	0.0	0.00	66.7
		Cycle 12 Day 01	79	12.24	17.028	0.0	0.00	66.7
		Cycle 13 Day 01	51	11.11	15.870	0.0	0.00	33.3
		Cycle 14 Day 01	45	9.63	15.279	0.0	0.00	33.3
		Cycle 15 Day 01	30	6.67	13.561	0.0	0.00	33.3
		Cycle 16 Day 01	36	7.41	14.055	0.0	0.00	33.3
		Cycle 18 Day 01	23	8.70	18.027	0.0	0.00	66.7
		Cycle 20 Day 01	21	7.94	14.548	0.0	0.00	33.3
		Cycle 22 Day 01	18	16.67	30.785	0.0	0.00	100.0
		Cycle 24 Day 01	11	6.06	13.484	0.0	0.00	33.3
		Cycle 26 Day 01	5	6.67	14.907	0.0	0.00	33.3
		Cycle 28 Day 01	3	0.00	0.000	0.0	0.00	0.0
		Follow-up Day 30	93	28.67	30.924	0.0	33.33	100.0
		Follow-up Month 2	38	26.32	28.112	0.0	33.33	100.0
		Follow-up Month 3	24	40.28	29.454	0.0	33.33	100.0
	Placebo + Gem + Cis (N=405)	Baseline [a]	312	10.68	20.353	0.0	0.00	100.0
		Cycle 02 Day 01	318	18.76	21.366	0.0	0.00	100.0
		Cycle 03 Day 01	246	20.46	21.958	0.0	33.33	100.0
		Cycle 04 Day 01	240	21.11	23.395	0.0	33.33	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.6.1 TOPAZ: Summary of EORTC QLQ-BIL21 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	196	20.24	21.714	0.0	33.33	66.7
		Cycle 06 Day 01	195	20.68	23.438	0.0	0.00	100.0
		Cycle 07 Day 01	161	22.57	24.038	0.0	33.33	100.0
		Cycle 08 Day 01	146	20.55	23.246	0.0	33.33	100.0
		Cycle 09 Day 01	118	19.77	22.323	0.0	0.00	66.7
		Cycle 10 Day 01	107	18.07	21.122	0.0	0.00	66.7
		Cycle 11 Day 01	67	13.43	18.404	0.0	0.00	66.7
		Cycle 12 Day 01	59	10.17	15.480	0.0	0.00	33.3
		Cycle 13 Day 01	29	13.79	16.708	0.0	0.00	33.3
		Cycle 14 Day 01	29	12.64	16.460	0.0	0.00	33.3
		Cycle 15 Day 01	16	10.42	15.957	0.0	0.00	33.3
		Cycle 16 Day 01	13	15.38	22.008	0.0	0.00	66.7
		Cycle 18 Day 01	10	16.67	23.570	0.0	0.00	66.7
		Cycle 20 Day 01	6	22.22	27.217	0.0	16.67	66.7
		Cycle 22 Day 01	4	16.67	33.333	0.0	0.00	66.7
		Cycle 24 Day 01	2	0.00	0.000	0.0	0.00	0.0
		Cycle 26 Day 01	2	16.67	23.570	0.0	16.67	33.3
		Follow-up Day 30	111	29.43	26.870	0.0	33.33	100.0
		Follow-up Month 2	37	31.53	30.374	0.0	33.33	100.0
		Follow-up Month 3	25	24.00	26.387	0.0	33.33	66.7

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.6.1 TOPAZ: Summary of EORTC QLQ-BIL21 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

			Absolute Values					
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Function: Difficulties with drainage bags/tubes	Durva + Gem + Cis (N=405)	Baseline [a]	303	4.95	14.897	0.0	0.00	100.0
		Cycle 02 Day 01	294	4.76	14.310	0.0	0.00	100.0
		Cycle 03 Day 01	244	4.51	13.614	0.0	0.00	66.7
		Cycle 04 Day 01	236	3.67	12.133	0.0	0.00	66.7
		Cycle 05 Day 01	218	2.91	11.392	0.0	0.00	100.0
		Cycle 06 Day 01	197	4.06	14.498	0.0	0.00	100.0
		Cycle 07 Day 01	164	4.47	15.457	0.0	0.00	100.0
		Cycle 08 Day 01	168	3.37	13.957	0.0	0.00	100.0
		Cycle 09 Day 01	141	2.36	9.466	0.0	0.00	66.7
		Cycle 10 Day 01	140	1.43	7.867	0.0	0.00	66.7
		Cycle 11 Day 01	93	3.58	12.494	0.0	0.00	66.7
		Cycle 12 Day 01	79	2.53	10.367	0.0	0.00	66.7
		Cycle 13 Day 01	51	1.96	14.003	0.0	0.00	100.0
		Cycle 14 Day 01	45	2.22	11.010	0.0	0.00	66.7
		Cycle 15 Day 01	30	1.11	6.086	0.0	0.00	33.3
		Cycle 16 Day 01	36	0.00	0.000	0.0	0.00	0.0
		Cycle 18 Day 01	23	1.45	6.950	0.0	0.00	33.3
		Cycle 20 Day 01	21	0.00	0.000	0.0	0.00	0.0
		Cycle 22 Day 01	18	5.56	23.570	0.0	0.00	100.0
		Cycle 24 Day 01	11	0.00	0.000	0.0	0.00	0.0
		Cycle 26 Day 01	5	0.00	0.000	0.0	0.00	0.0
		Cycle 28 Day 01	3	0.00	0.000	0.0	0.00	0.0
		Follow-up Day 30	93	5.02	16.260	0.0	0.00	100.0
		Follow-up Month 2	38	3.51	12.944	0.0	0.00	66.7
		Follow-up Month 3	24	4.17	14.948	0.0	0.00	66.7
	Placebo + Gem + Cis (N=405)	Baseline [a]	312	5.56	15.964	0.0	0.00	100.0
		Cycle 02 Day 01	318	3.35	13.076	0.0	0.00	100.0
		Cycle 03 Day 01	246	4.47	15.441	0.0	0.00	100.0
		Cycle 04 Day 01	240	4.44	15.508	0.0	0.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.6.1 TOPAZ: Summary of EORTC QLQ-BIL21 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	196	3.06	13.150	0.0	0.00	100.0
		Cycle 06 Day 01	195	2.39	11.476	0.0	0.00	100.0
		Cycle 07 Day 01	161	2.90	10.796	0.0	0.00	66.7
		Cycle 08 Day 01	146	1.60	8.148	0.0	0.00	66.7
		Cycle 09 Day 01	118	1.98	9.029	0.0	0.00	66.7
		Cycle 10 Day 01	107	4.67	14.800	0.0	0.00	100.0
		Cycle 11 Day 01	67	1.00	5.715	0.0	0.00	33.3
		Cycle 12 Day 01	59	1.13	6.084	0.0	0.00	33.3
		Cycle 13 Day 01	29	1.15	6.190	0.0	0.00	33.3
		Cycle 14 Day 01	29	0.00	0.000	0.0	0.00	0.0
		Cycle 15 Day 01	16	0.00	0.000	0.0	0.00	0.0
		Cycle 16 Day 01	13	0.00	0.000	0.0	0.00	0.0
		Cycle 18 Day 01	10	6.67	14.055	0.0	0.00	33.3
		Cycle 20 Day 01	6	0.00	0.000	0.0	0.00	0.0
		Cycle 22 Day 01	4	0.00	0.000	0.0	0.00	0.0
		Cycle 24 Day 01	2	0.00	0.000	0.0	0.00	0.0
		Cycle 26 Day 01	2	0.00	0.000	0.0	0.00	0.0
		Follow-up Day 30	111	5.11	17.522	0.0	0.00	100.0
		Follow-up Month 2	37	7.21	20.987	0.0	0.00	100.0
		Follow-up Month 3	25	1.33	6.667	0.0	0.00	33.3

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.6.1 TOPAZ: Summary of EORTC QLQ-BIL21 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

			Absolute Values					
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
Function: Concerns regarding weight loss	Durva + Gem + Cis (N=405)	Baseline [a]	303	20.02	25.640	0.0	0.00	100.0
		Cycle 02 Day 01	294	19.27	25.665	0.0	0.00	100.0
		Cycle 03 Day 01	244	17.90	25.180	0.0	0.00	100.0
		Cycle 04 Day 01	236	14.83	21.557	0.0	0.00	100.0
		Cycle 05 Day 01	218	13.61	20.821	0.0	0.00	100.0
		Cycle 06 Day 01	197	11.51	20.277	0.0	0.00	100.0
		Cycle 07 Day 01	164	9.96	18.892	0.0	0.00	100.0
		Cycle 08 Day 01	168	11.31	20.255	0.0	0.00	100.0
		Cycle 09 Day 01	141	9.93	17.703	0.0	0.00	66.7
		Cycle 10 Day 01	140	9.29	16.519	0.0	0.00	66.7
		Cycle 11 Day 01	93	10.04	18.898	0.0	0.00	100.0
		Cycle 12 Day 01	79	7.59	17.662	0.0	0.00	100.0
		Cycle 13 Day 01	51	6.54	14.936	0.0	0.00	66.7
		Cycle 14 Day 01	45	5.93	14.718	0.0	0.00	66.7
		Cycle 15 Day 01	30	10.00	17.833	0.0	0.00	66.7
		Cycle 16 Day 01	36	2.78	9.344	0.0	0.00	33.3
		Cycle 18 Day 01	23	5.80	16.368	0.0	0.00	66.7
		Cycle 20 Day 01	21	4.76	11.952	0.0	0.00	33.3
		Cycle 22 Day 01	18	7.41	14.260	0.0	0.00	33.3
		Cycle 24 Day 01	11	6.06	13.484	0.0	0.00	33.3
		Cycle 26 Day 01	5	6.67	14.907	0.0	0.00	33.3
		Cycle 28 Day 01	3	0.00	0.000	0.0	0.00	0.0
		Follow-up Day 30	93	17.20	24.383	0.0	0.00	100.0
		Follow-up Month 2	38	16.67	25.410	0.0	0.00	100.0
		Follow-up Month 3	24	16.67	19.659	0.0	0.00	66.7
	Placebo + Gem + Cis (N=405)	Baseline [a]	312	19.98	26.659	0.0	0.00	100.0
		Cycle 02 Day 01	318	16.98	23.642	0.0	0.00	100.0
		Cycle 03 Day 01	246	16.80	23.473	0.0	0.00	100.0
		Cycle 04 Day 01	240	14.72	21.902	0.0	0.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.6.1 TOPAZ: Summary of EORTC QLQ-BIL21 results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	196	13.10	21.714	0.0	0.00	100.0
		Cycle 06 Day 01	195	11.11	20.494	0.0	0.00	100.0
		Cycle 07 Day 01	161	12.63	21.063	0.0	0.00	66.7
		Cycle 08 Day 01	146	12.10	20.297	0.0	0.00	100.0
		Cycle 09 Day 01	118	8.19	16.270	0.0	0.00	66.7
		Cycle 10 Day 01	107	9.35	19.314	0.0	0.00	100.0
		Cycle 11 Day 01	67	4.98	11.968	0.0	0.00	33.3
		Cycle 12 Day 01	59	5.65	14.050	0.0	0.00	66.7
		Cycle 13 Day 01	29	10.34	15.694	0.0	0.00	33.3
		Cycle 14 Day 01	29	5.75	12.814	0.0	0.00	33.3
		Cycle 15 Day 01	16	10.42	20.069	0.0	0.00	66.7
		Cycle 16 Day 01	13	25.64	33.758	0.0	0.00	100.0
		Cycle 18 Day 01	10	20.00	35.832	0.0	0.00	100.0
		Cycle 20 Day 01	6	11.11	27.217	0.0	0.00	66.7
		Cycle 22 Day 01	4	25.00	31.914	0.0	16.67	66.7
		Cycle 24 Day 01	2	16.67	23.570	0.0	16.67	33.3
		Cycle 26 Day 01	2	50.00	23.570	33.3	50.00	66.7
		Follow-up Day 30	110	21.52	27.311	0.0	0.00	100.0
		Follow-up Month 2	37	27.93	33.805	0.0	33.33	100.0
		Follow-up Month 3	25	21.33	31.740	0.0	0.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.6.2.1 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-BIL21 Symptom scale: Pain (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	248	20.30 (20.378)	-2.27 (0.893)	259	19.11 (19.018)	-3.34 (0.875)	1.07 (-1.382, 3.522)	0.3917
Cycle 03 Day 01	206	19.82 (20.014)	-3.81 (0.971)	210	19.80 (19.728)	-4.15 (0.959)	0.34 (-2.336, 3.015)	0.8031
Cycle 04 Day 01	198	18.48 (17.448)	-3.46 (1.029)	208	19.23 (19.713)	-3.91 (1.009)	0.45 (-2.378, 3.278)	0.7547
Cycle 05 Day 01	179	18.34 (17.431)	-2.63 (0.962)	169	17.90 (18.403)	-4.10 (0.971)	1.47 (-1.212, 4.157)	0.2817
Cycle 06 Day 01	160	17.60 (16.614)	-2.60 (1.073)	171	17.74 (18.603)	-3.22 (1.050)	0.62 (-2.328, 3.568)	0.6796
Cycle 07 Day 01	138	16.49 (15.614)	-4.30 (1.085)	140	16.79 (17.543)	-2.73 (1.079)	-1.57 (-4.573, 1.438)	0.3057
Cycle 08 Day 01	140	18.99 (16.788)	-1.66 (1.118)	126	18.12 (19.382)	-4.52 (1.154)	2.86 (-0.299, 6.019)	0.0758
Cycle 09 Day 01	120	17.22 (16.970)	-3.99 (0.994)	104	16.67 (19.187)	-5.20 (1.048)	1.21 (-1.634, 4.046)	0.4041
Cycle 10 Day 01	119	17.09 (16.412)	-3.99 (1.127)	93	16.94 (20.019)	-1.22 (1.230)	-2.78 (-6.055, 0.505)	0.0969
Cycle 11 Day 01	80	16.04 (15.105)	-3.91 (1.308)	60	17.64 (21.265)	-2.69 (1.458)	-1.22 (-5.072, 2.640)	0.5347
Cycle 12 Day 01	65	15.00 (15.110)	-3.22 (1.521)	57	16.81 (20.803)	-3.88 (1.622)	0.65 (-3.722, 5.029)	0.7685
Cycle 13 Day 01	41	16.67 (16.351)	-4.33 (1.789)	28	18.15 (23.467)	-1.49 (2.087)	-2.84 (-8.280, 2.602)	0.3035
Cycle 14 Day 01	37	17.12 (16.544)	-4.47 (1.590)	28	18.15 (23.467)	-2.58 (1.807)	-1.88 (-6.656, 2.886)	0.4351
Cycle 15 Day 01	21	15.08 (13.596)	-6.33 (1.717)	15	13.33 (14.365)	-3.47 (2.070)	-2.86 (-8.165, 2.447)	0.2852
Cycle 16 Day 01	28	15.48 (12.972)	-4.46 (2.122)	13	17.95 (17.296)	0.69 (2.932)	-5.15 (-12.382, 2.077)	0.1591
Cycle 18 Day 01	17	15.20 (14.202)	-1.30 (3.250)	10	17.50 (18.194)	5.71 (4.200)	-7.01 (-17.708, 3.688)	0.1931

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.6.2.1 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-BIL21 Symptom scale: Pain (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	15.35 (13.683)	-4.95 (2.447)	6	9.72 (6.273)	2.44 (4.149)	-7.39 (-16.990, 2.214)	0.1268
Average over all visits	274	20.68 (20.328)	-3.63 (0.825)	282	19.56 (19.381)	-2.21 (0.933)	-1.41 (-3.855, 1.029)	0.2560
Hedges' g SMD							-0.10 (-0.262, 0.070)	0.2585

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.6.2.2 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-BIL21 Symptom scale: Tiredness (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	248	26.79 (24.694)	1.15 (1.215)	259	24.20 (23.252)	0.64 (1.189)	0.51 (-2.830, 3.841)	0.7660
Cycle 03 Day 01	206	26.54 (24.576)	3.53 (1.391)	210	24.71 (23.943)	-0.05 (1.370)	3.58 (-0.249, 7.412)	0.0668
Cycle 04 Day 01	198	24.69 (23.110)	4.18 (1.314)	208	23.56 (22.961)	1.38 (1.285)	2.80 (-0.811, 6.406)	0.1283
Cycle 05 Day 01	179	23.40 (22.300)	2.81 (1.316)	169	24.19 (22.981)	3.12 (1.327)	-0.31 (-3.983, 3.359)	0.8674
Cycle 06 Day 01	160	22.71 (21.811)	5.78 (1.461)	171	22.68 (22.494)	2.44 (1.427)	3.33 (-0.677, 7.346)	0.1031
Cycle 07 Day 01	138	20.85 (21.541)	4.75 (1.597)	140	22.54 (22.340)	2.84 (1.585)	1.91 (-2.505, 6.331)	0.3952
Cycle 08 Day 01	140	24.68 (23.164)	5.61 (1.412)	126	21.96 (22.464)	0.81 (1.456)	4.80 (0.808, 8.783)	0.0185*
Cycle 09 Day 01	120	23.80 (24.159)	3.11 (1.409)	104	21.69 (22.564)	2.12 (1.483)	0.99 (-3.029, 5.018)	0.6271
Cycle 10 Day 01	119	23.44 (24.196)	1.10 (1.466)	93	21.98 (23.051)	1.24 (1.600)	-0.14 (-4.409, 4.128)	0.9485
Cycle 11 Day 01	80	22.78 (22.840)	0.77 (1.713)	60	21.11 (22.382)	1.07 (1.920)	-0.30 (-5.372, 4.770)	0.9070
Cycle 12 Day 01	65	23.08 (23.839)	-0.99 (1.972)	57	20.47 (21.392)	-1.32 (2.118)	0.33 (-5.380, 6.038)	0.9096
Cycle 13 Day 01	41	25.20 (22.226)	0.91 (2.369)	28	19.84 (22.903)	1.94 (2.792)	-1.03 (-8.306, 6.240)	0.7788
Cycle 14 Day 01	37	24.32 (20.259)	-3.22 (2.115)	28	20.63 (22.572)	1.54 (2.416)	-4.76 (-11.148, 1.620)	0.1417
Cycle 15 Day 01	21	21.69 (14.689)	-4.83 (2.442)	15	9.63 (13.191)	-3.23 (3.365)	-1.60 (-9.736, 6.527)	0.6940
Cycle 16 Day 01	28	19.44 (15.006)	-1.98 (2.933)	13	12.82 (14.939)	7.99 (4.341)	-9.97 (-20.085, 0.144)	0.0532
Cycle 18 Day 01	17	16.99 (16.721)	-0.65 (3.684)	10	12.22 (15.226)	8.43 (5.023)	-9.07 (-20.968, 2.824)	0.1311

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.6.2.2 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-BIL21 Symptom scale: Tiredness (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	16.96 (15.873)	-0.69 (4.316)	6	7.41 (13.456)	1.62 (7.657)	-2.31 (-19.031, 14.413)	0.7803
Average over all visits	274	27.13 (24.887)	1.26 (1.122)	282	24.35 (23.356)	1.92 (1.316)	-0.66 (-4.007, 2.682)	0.6972
Hedges' g SMD							-0.03 (-0.199, 0.134)	0.7030

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.6.2.3 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-BIL21 Symptom scale: Jaundice (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	248	8.87 (14.929)	-1.29 (0.632)	259	5.83 (10.274)	-0.29 (0.618)	-1.00 (-2.736, 0.744)	0.2612
Cycle 03 Day 01	206	8.25 (14.211)	-1.79 (0.649)	210	6.51 (10.452)	-1.32 (0.640)	-0.47 (-2.264, 1.322)	0.6061
Cycle 04 Day 01	198	8.14 (14.001)	-0.61 (0.742)	208	5.93 (9.943)	-0.79 (0.725)	0.18 (-1.860, 2.223)	0.8611
Cycle 05 Day 01	179	7.82 (13.307)	-2.22 (0.725)	169	4.93 (8.814)	-0.30 (0.736)	-1.92 (-3.955, 0.119)	0.0649
Cycle 06 Day 01	160	7.78 (13.977)	-2.35 (0.698)	171	5.13 (9.355)	-0.66 (0.682)	-1.70 (-3.621, 0.224)	0.0832
Cycle 07 Day 01	138	7.41 (13.778)	-1.41 (0.915)	140	5.08 (9.645)	1.68 (0.911)	-3.10 (-5.640, -0.552)	0.0172*
Cycle 08 Day 01	140	8.41 (14.592)	-0.71 (0.911)	126	4.67 (8.817)	-1.03 (0.944)	0.32 (-2.271, 2.913)	0.8076
Cycle 09 Day 01	120	8.43 (15.038)	-0.82 (0.753)	104	4.49 (8.829)	-2.14 (0.794)	1.32 (-0.849, 3.481)	0.2326
Cycle 10 Day 01	119	8.50 (15.012)	-1.59 (0.881)	93	4.30 (7.862)	0.27 (0.965)	-1.86 (-4.447, 0.728)	0.1583
Cycle 11 Day 01	80	9.03 (15.723)	-0.56 (0.933)	60	3.70 (7.281)	-0.94 (1.048)	0.38 (-2.419, 3.170)	0.7911
Cycle 12 Day 01	65	6.67 (13.147)	-0.86 (0.983)	57	4.48 (7.817)	-1.82 (1.054)	0.95 (-1.896, 3.803)	0.5096
Cycle 13 Day 01	41	6.50 (12.417)	-0.36 (1.485)	28	4.76 (8.242)	1.04 (1.768)	-1.40 (-5.996, 3.189)	0.5449
Cycle 14 Day 01	37	6.61 (11.553)	-1.49 (1.021)	28	4.76 (8.242)	-1.15 (1.170)	-0.34 (-3.430, 2.753)	0.8279
Cycle 15 Day 01	21	7.41 (13.302)	0.25 (2.041)	15	4.44 (5.634)	2.74 (2.445)	-2.48 (-8.925, 3.958)	0.4413
Cycle 16 Day 01	28	9.13 (13.876)	0.47 (1.334)	13	4.27 (5.626)	-2.27 (1.875)	2.74 (-1.918, 7.407)	0.2426
Cycle 18 Day 01	17	7.19 (13.575)	3.98 (2.306)	10	3.33 (5.367)	-0.52 (3.025)	4.50 (-3.306, 12.300)	0.2481

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.6.2.3 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-BIL21 Symptom scale: Jaundice (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	7.02 (12.942)	0.81 (2.008)	6	3.70 (5.738)	5.84 (3.439)	-5.03 (-13.195, 3.134)	0.2175
Average over all visits	274	8.52 (14.719)	-0.62 (0.605)	282	5.95 (10.441)	-0.10 (0.683)	-0.52 (-2.326, 1.278)	0.5677
Hedges' g SMD							-0.05 (-0.215, 0.118)	0.5672

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.6.2.4 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-BIL21 Symptom scale: Anxiety (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	248	34.04 (22.961)	-4.45 (1.039)	259	31.44 (21.489)	-4.62 (1.019)	0.16 (-2.697, 3.023)	0.9110
Cycle 03 Day 01	206	34.55 (23.278)	-5.21 (1.270)	210	31.11 (22.243)	-3.12 (1.253)	-2.09 (-5.594, 1.423)	0.2434
Cycle 04 Day 01	198	32.58 (21.802)	-4.36 (1.239)	208	30.57 (21.314)	-5.76 (1.214)	1.40 (-2.014, 4.806)	0.4216
Cycle 05 Day 01	179	32.73 (21.438)	-3.33 (1.185)	169	30.67 (21.350)	-4.91 (1.195)	1.58 (-1.727, 4.892)	0.3479
Cycle 06 Day 01	160	32.66 (21.658)	-4.05 (1.267)	171	30.80 (21.506)	-4.22 (1.240)	0.17 (-3.319, 3.652)	0.9253
Cycle 07 Day 01	138	32.91 (22.746)	-6.19 (1.325)	140	30.06 (21.315)	-4.05 (1.320)	-2.14 (-5.816, 1.543)	0.2543
Cycle 08 Day 01	140	33.75 (23.788)	-2.68 (1.402)	126	29.50 (21.335)	-4.85 (1.447)	2.17 (-1.802, 6.132)	0.2839
Cycle 09 Day 01	120	33.06 (22.711)	-3.69 (1.358)	104	28.53 (21.339)	-4.01 (1.432)	0.32 (-3.572, 4.205)	0.8729
Cycle 10 Day 01	119	33.68 (23.076)	-5.92 (1.417)	93	28.14 (21.735)	-5.96 (1.550)	0.04 (-4.099, 4.182)	0.9844
Cycle 11 Day 01	80	35.21 (23.117)	-6.42 (1.682)	60	30.69 (21.562)	-7.24 (1.873)	0.83 (-4.147, 5.800)	0.7435
Cycle 12 Day 01	65	34.74 (23.780)	-8.02 (1.707)	57	29.09 (21.311)	-6.86 (1.826)	-1.15 (-6.104, 3.796)	0.6460
Cycle 13 Day 01	41	36.79 (24.079)	-7.31 (2.222)	28	30.95 (23.555)	-5.04 (2.578)	-2.27 (-9.033, 4.489)	0.5069
Cycle 14 Day 01	37	35.81 (23.722)	-9.44 (1.914)	28	30.36 (22.818)	-5.60 (2.164)	-3.84 (-9.588, 1.905)	0.1878
Cycle 15 Day 01	21	32.54 (20.566)	-11.45 (2.674)	15	22.78 (13.164)	-7.65 (3.330)	-3.80 (-12.375, 4.775)	0.3784
Cycle 16 Day 01	28	30.65 (21.040)	-7.90 (2.682)	13	26.92 (20.171)	0.19 (3.774)	-8.09 (-17.306, 1.136)	0.0846
Cycle 18 Day 01	17	36.27 (23.743)	-5.16 (3.588)	10	28.33 (22.635)	-0.85 (4.686)	-4.31 (-16.258, 7.636)	0.4710

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.6.2.4 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-BIL21 Symptom scale: Anxiety (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	33.33 (24.056)	-4.17 (4.383)	6	18.06 (16.173)	8.08 (7.604)	-12.24 (-30.218, 5.730)	0.1748
Average over all visits	274	34.25 (23.204)	-5.87 (1.080)	282	31.26 (21.616)	-3.91 (1.253)	-1.96 (-5.214, 1.300)	0.2380
Hedges' g SMD							-0.10 (-0.266, 0.066)	0.2388

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.6.2.5 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-BIL21 Symptom scale: Eating (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	248	16.33 (19.159)	2.47 (0.927)	259	13.29 (15.978)	1.64 (0.905)	0.82 (-1.723, 3.370)	0.5255
Cycle 03 Day 01	206	16.42 (18.912)	2.31 (1.035)	210	13.33 (16.226)	1.64 (1.017)	0.67 (-2.182, 3.524)	0.6444
Cycle 04 Day 01	198	14.35 (16.300)	4.28 (0.989)	208	12.74 (15.647)	1.91 (0.968)	2.37 (-0.353, 5.088)	0.0879
Cycle 05 Day 01	179	13.97 (16.727)	3.48 (1.031)	169	12.82 (15.827)	2.04 (1.040)	1.44 (-1.436, 4.320)	0.3254
Cycle 06 Day 01	160	14.01 (16.519)	3.01 (1.039)	171	11.60 (14.101)	1.71 (1.018)	1.30 (-1.556, 4.165)	0.3706
Cycle 07 Day 01	138	13.22 (15.524)	2.95 (1.167)	140	12.02 (15.365)	1.25 (1.163)	1.70 (-1.543, 4.937)	0.3037
Cycle 08 Day 01	140	15.12 (17.616)	4.14 (1.186)	126	12.04 (14.891)	0.33 (1.228)	3.81 (0.446, 7.168)	0.0265*
Cycle 09 Day 01	120	14.24 (17.961)	3.20 (1.183)	104	11.78 (14.439)	1.27 (1.251)	1.93 (-1.461, 5.319)	0.2638
Cycle 10 Day 01	119	14.43 (17.075)	1.25 (1.174)	93	11.56 (14.591)	1.67 (1.292)	-0.42 (-3.858, 3.021)	0.8110
Cycle 11 Day 01	80	13.65 (15.925)	-0.36 (1.251)	60	11.25 (14.541)	-2.24 (1.412)	1.89 (-1.838, 5.608)	0.3192
Cycle 12 Day 01	65	12.69 (16.077)	-2.27 (1.514)	57	11.26 (14.561)	-0.27 (1.634)	-2.00 (-6.398, 2.390)	0.3691
Cycle 13 Day 01	41	15.85 (18.143)	-1.55 (1.373)	28	11.31 (16.072)	-1.13 (1.614)	-0.42 (-4.635, 3.789)	0.8427
Cycle 14 Day 01	37	15.54 (17.695)	-2.73 (1.682)	28	12.20 (16.115)	-0.76 (1.918)	-1.97 (-7.049, 3.102)	0.4419
Cycle 15 Day 01	21	10.71 (10.255)	-5.51 (1.783)	15	6.11 (11.980)	-2.46 (2.261)	-3.05 (-8.641, 2.538)	0.2783
Cycle 16 Day 01	28	11.90 (12.715)	-4.66 (2.108)	13	9.62 (15.901)	2.73 (2.987)	-7.39 (-14.660, -0.122)	0.0464*
Cycle 18 Day 01	17	13.24 (13.838)	-0.67 (2.566)	10	10.00 (17.033)	-0.84 (3.421)	0.17 (-8.433, 8.766)	0.9690

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.6.2.5 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-BIL21 Symptom scale: Eating (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	12.28 (13.428)	-4.56 (2.235)	6	2.78 (4.303)	-2.13 (3.893)	-2.44 (-11.469, 6.593)	0.5861
Average over all visits	274	16.55 (19.059)	0.28 (0.774)	282	13.30 (15.876)	0.38 (0.884)	-0.09 (-2.399, 2.210)	0.9358
Hedges' g SMD							-0.01 (-0.173, 0.159)	0.9361

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.6.2.6 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-BIL21 Function: Treatment side effects (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	248	11.42 (21.195)	9.35 (1.329)	259	9.52 (19.341)	9.24 (1.303)	0.11 (-3.552, 3.764)	0.9545
Cycle 03 Day 01	206	11.00 (20.502)	13.32 (1.516)	210	9.84 (19.249)	9.77 (1.498)	3.55 (-0.642, 7.737)	0.0968
Cycle 04 Day 01	198	10.10 (19.267)	12.57 (1.466)	208	9.29 (17.311)	10.22 (1.436)	2.36 (-1.675, 6.389)	0.2513
Cycle 05 Day 01	179	10.80 (20.175)	10.75 (1.541)	169	8.28 (16.176)	10.55 (1.563)	0.20 (-4.114, 4.519)	0.9266
Cycle 06 Day 01	160	10.00 (19.354)	11.81 (1.686)	171	8.58 (16.702)	10.53 (1.646)	1.28 (-3.348, 5.917)	0.5861
Cycle 07 Day 01	138	9.18 (18.791)	11.85 (1.777)	140	9.29 (18.353)	11.75 (1.769)	0.10 (-4.826, 5.032)	0.9672
Cycle 08 Day 01	140	10.48 (19.211)	12.00 (1.731)	126	8.47 (16.295)	8.98 (1.799)	3.02 (-1.890, 7.936)	0.2270
Cycle 09 Day 01	120	11.39 (20.496)	9.56 (1.808)	104	8.33 (15.229)	11.74 (1.915)	-2.18 (-7.372, 3.005)	0.4083
Cycle 10 Day 01	119	10.08 (19.190)	8.58 (1.808)	93	8.60 (15.466)	10.85 (1.998)	-2.26 (-7.568, 3.042)	0.4017
Cycle 11 Day 01	80	10.42 (20.261)	4.76 (2.043)	60	8.33 (14.556)	3.99 (2.311)	0.77 (-5.319, 6.860)	0.8031
Cycle 12 Day 01	65	9.74 (19.296)	4.95 (1.909)	57	9.94 (16.625)	1.74 (2.048)	3.21 (-2.319, 8.744)	0.2530
Cycle 13 Day 01	41	12.20 (20.758)	4.56 (2.259)	28	9.52 (15.335)	5.59 (2.667)	-1.03 (-7.975, 5.917)	0.7692
Cycle 14 Day 01	37	10.81 (19.332)	3.73 (2.436)	28	9.52 (15.335)	3.08 (2.783)	0.66 (-6.702, 8.018)	0.8593
Cycle 15 Day 01	21	9.52 (21.455)	0.99 (2.908)	15	11.11 (16.265)	3.92 (3.484)	-2.93 (-12.076, 6.212)	0.5216
Cycle 16 Day 01	28	9.52 (19.994)	1.20 (2.995)	13	12.82 (16.879)	10.92 (4.257)	-9.72 (-20.168, 0.736)	0.0678
Cycle 18 Day 01	17	13.73 (23.743)	2.25 (4.469)	10	13.33 (17.213)	7.62 (5.835)	-5.37 (-20.224, 9.475)	0.4672

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.6.2.6 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-BIL21 Function: Treatment side effects (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	12.28 (22.800)	0.29 (4.209)	6	11.11 (17.213)	22.91 (7.102)	-22.62 (-39.542, -5.694)	0.0107*
Average over all visits	274	11.92 (21.441)	7.21 (1.132)	282	9.93 (19.783)	9.02 (1.314)	-1.81 (-5.226, 1.596)	0.2960
Hedges' g SMD							-0.09 (-0.255, 0.078)	0.2975

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.6.2.7 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	248	5.24 (15.710)	-0.71 (0.810)	259	4.76 (14.924)	-0.83 (0.796)	0.13 (-2.107, 2.358)	0.9122
Cycle 03 Day 01	206	5.02 (15.502)	-0.75 (0.830)	210	5.40 (16.057)	-1.07 (0.822)	0.32 (-1.979, 2.611)	0.7868
Cycle 04 Day 01	198	4.88 (15.887)	-0.21 (0.871)	208	5.77 (16.670)	-0.45 (0.856)	0.24 (-2.159, 2.639)	0.8440
Cycle 05 Day 01	179	5.59 (16.755)	-1.29 (0.863)	169	3.75 (13.329)	-1.31 (0.875)	0.02 (-2.399, 2.439)	0.9870
Cycle 06 Day 01	160	4.79 (14.882)	0.15 (0.989)	171	4.48 (13.981)	-1.26 (0.967)	1.41 (-1.312, 4.131)	0.3091
Cycle 07 Day 01	138	5.80 (17.972)	1.33 (0.997)	140	3.81 (13.313)	-1.24 (0.991)	2.57 (-0.195, 5.336)	0.0684
Cycle 08 Day 01	140	3.81 (12.052)	0.59 (0.904)	126	3.44 (13.219)	-2.32 (0.934)	2.91 (0.357, 5.466)	0.0256*
Cycle 09 Day 01	120	4.44 (15.541)	-1.28 (0.794)	104	4.17 (14.457)	-1.27 (0.838)	-0.01 (-2.282, 2.263)	0.9936
Cycle 10 Day 01	119	3.08 (12.268)	-2.23 (0.932)	93	3.94 (13.770)	0.77 (1.013)	-3.00 (-5.705, -0.293)	0.0300*
Cycle 11 Day 01	80	4.17 (14.403)	0.18 (1.009)	60	5.00 (17.168)	-1.33 (1.130)	1.51 (-1.479, 4.502)	0.3199
Cycle 12 Day 01	65	4.62 (15.453)	-1.25 (0.778)	57	4.09 (12.709)	-2.91 (0.827)	1.66 (-0.581, 3.904)	0.1454
Cycle 13 Day 01	41	3.25 (10.014)	-0.33 (1.129)	28	5.95 (15.853)	-1.94 (1.319)	1.61 (-1.861, 5.077)	0.3587
Cycle 14 Day 01	37	4.50 (11.553)	-0.70 (1.052)	28	3.57 (13.876)	-2.87 (1.192)	2.17 (-0.983, 5.333)	0.1745
Average over all visits	274	4.99 (15.213)	-0.50 (0.571)	282	5.32 (15.635)	-1.39 (0.580)	0.89 (-0.712, 2.487)	0.2761
Hedges' g SMD							0.09 (-0.074, 0.259)	0.2766

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.6.2.8 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-BIL21 Function: Concerns regarding weight loss (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	248	20.03 (26.276)	-0.93 (1.374)	259	18.40 (25.924)	-1.31 (1.348)	0.37 (-3.407, 4.156)	0.8458
Cycle 03 Day 01	206	20.87 (27.172)	-1.62 (1.448)	210	18.57 (25.863)	-2.18 (1.430)	0.56 (-3.438, 4.557)	0.7834
Cycle 04 Day 01	198	18.01 (25.041)	-3.25 (1.312)	208	18.59 (25.935)	-4.08 (1.285)	0.83 (-2.784, 4.434)	0.6534
Cycle 05 Day 01	179	17.32 (23.528)	-4.22 (1.370)	169	17.36 (25.740)	-5.45 (1.388)	1.23 (-2.599, 5.063)	0.5276
Cycle 06 Day 01	160	18.75 (24.426)	-5.94 (1.421)	171	17.15 (24.881)	-6.12 (1.388)	0.17 (-3.729, 4.079)	0.9299
Cycle 07 Day 01	138	16.43 (23.569)	-7.13 (1.461)	140	16.90 (25.128)	-5.94 (1.455)	-1.19 (-5.243, 2.859)	0.5631
Cycle 08 Day 01	140	18.57 (24.081)	-6.52 (1.510)	126	17.46 (25.198)	-5.93 (1.569)	-0.59 (-4.869, 3.697)	0.7881
Cycle 09 Day 01	120	18.33 (24.768)	-7.18 (1.401)	104	18.27 (25.811)	-7.51 (1.485)	0.33 (-3.689, 4.348)	0.8719
Cycle 10 Day 01	119	16.81 (24.113)	-7.90 (1.441)	93	18.28 (26.245)	-6.87 (1.589)	-1.03 (-5.253, 3.190)	0.6310
Cycle 11 Day 01	80	18.75 (24.788)	-7.25 (1.569)	60	19.44 (25.520)	-10.51 (1.771)	3.26 (-1.408, 7.929)	0.1699
Cycle 12 Day 01	65	20.00 (26.220)	-10.51 (1.678)	57	18.13 (24.455)	-10.50 (1.798)	-0.01 (-4.877, 4.850)	0.9956
Cycle 13 Day 01	41	18.70 (25.872)	-10.57 (1.976)	28	22.62 (27.297)	-5.57 (2.345)	-5.00 (-11.092, 1.083)	0.1059
Cycle 14 Day 01	37	20.72 (26.471)	-10.82 (2.007)	28	19.05 (24.727)	-10.02 (2.292)	-0.80 (-6.866, 5.262)	0.7930
Cycle 15 Day 01	21	22.22 (21.943)	-8.70 (3.783)	15	13.33 (24.560)	-0.56 (4.539)	-8.14 (-20.181, 3.896)	0.1790
Cycle 16 Day 01	28	22.62 (24.094)	-14.01 (3.450)	13	20.51 (28.991)	5.37 (4.855)	-19.38 (-31.338, -7.422)	0.0021*
Cycle 18 Day 01	17	23.53 (25.725)	-15.20 (4.099)	10	23.33 (31.623)	-3.99 (5.356)	-11.21 (-24.905, 2.492)	0.1051

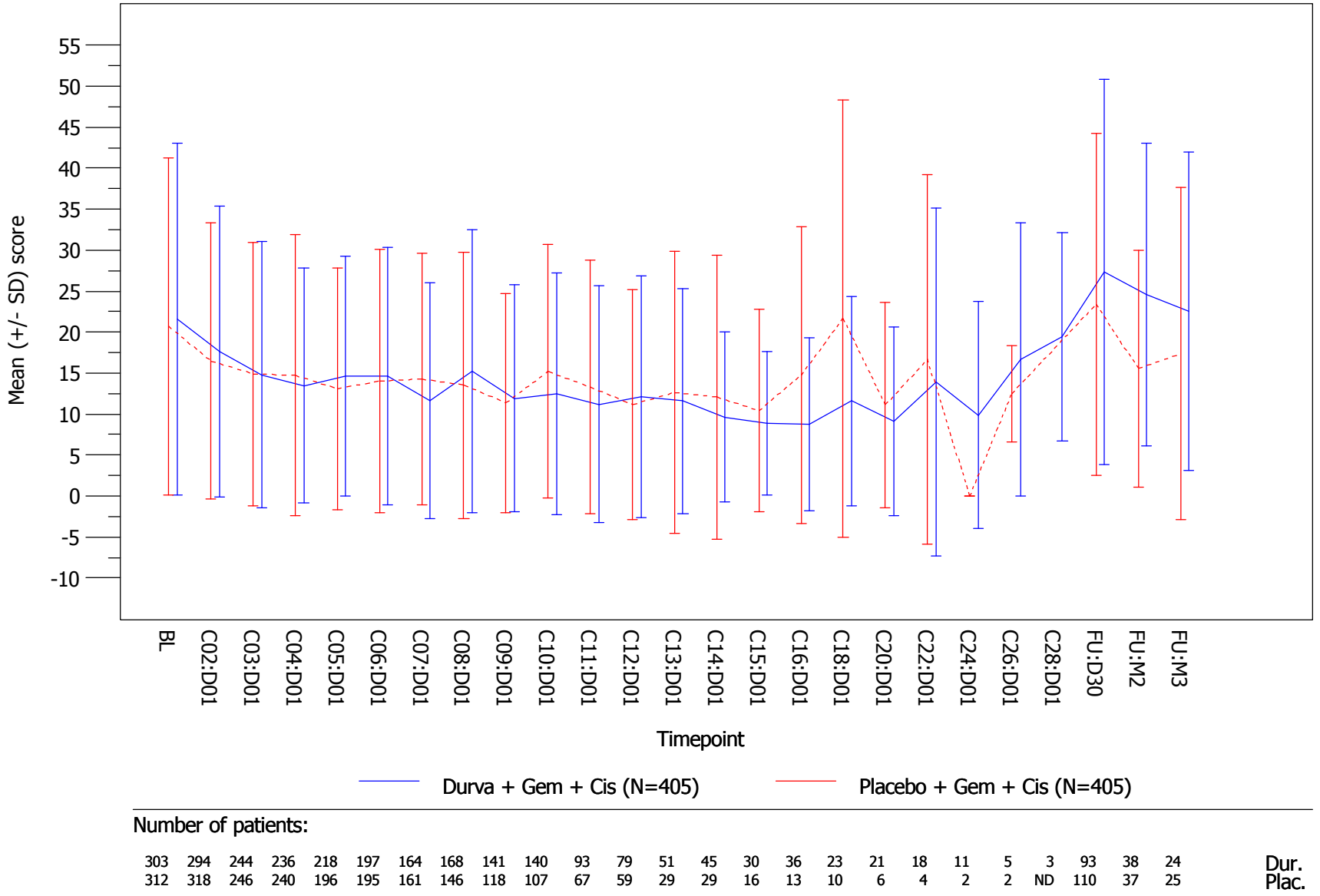
[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.6.2.8 TOPAZ: Summary of analysis of change from baseline in EORTC QLQ-BIL21 Function: Concerns regarding weight loss (mixed model for repeated measures)
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	21.05 (25.363)	-12.14 (4.290)	6	11.11 (27.217)	-3.99 (7.355)	-8.15 (-25.708, 9.409)	0.3493
Average over all visits	274	19.59 (26.024)	-7.88 (1.078)	282	18.44 (25.751)	-5.01 (1.275)	-2.87 (-6.154, 0.418)	0.0869
Hedges' g SMD							-0.15 (-0.312, 0.021)	0.0876

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

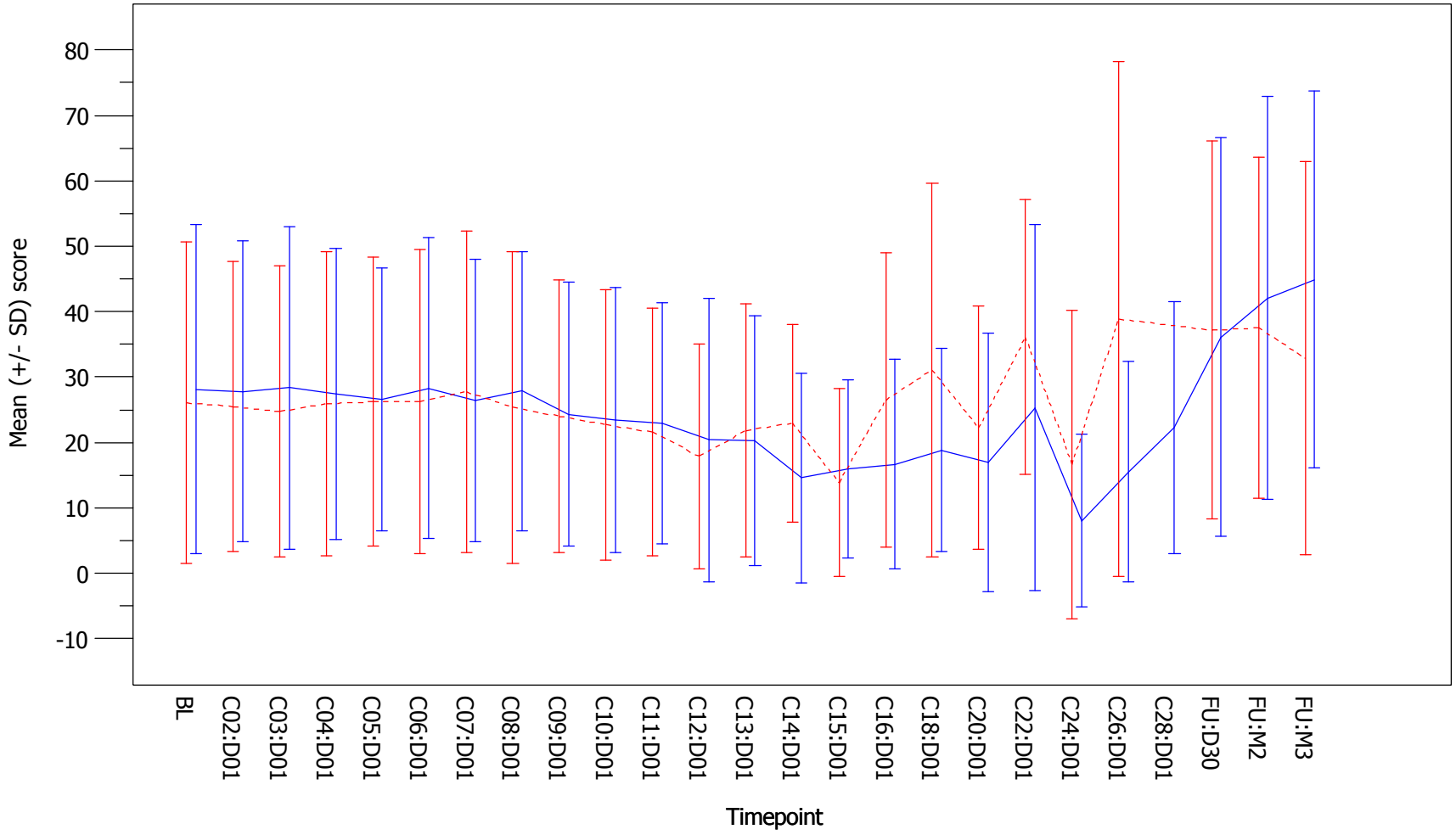
Figure 2.6.3.1 TOPAZ: Mean (+/- SD) EORTC QLQ-BIL21 Symptom scale: Pain across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

Dur.	303	294	244	236	218	197	164	168	141	140	93	79	51	45	30	36	23	21	18	11	5	3	93	38	24
Plac.	312	318	246	240	196	195	161	146	118	107	67	59	29	29	16	13	10	6	4	2	2	ND	110	37	25

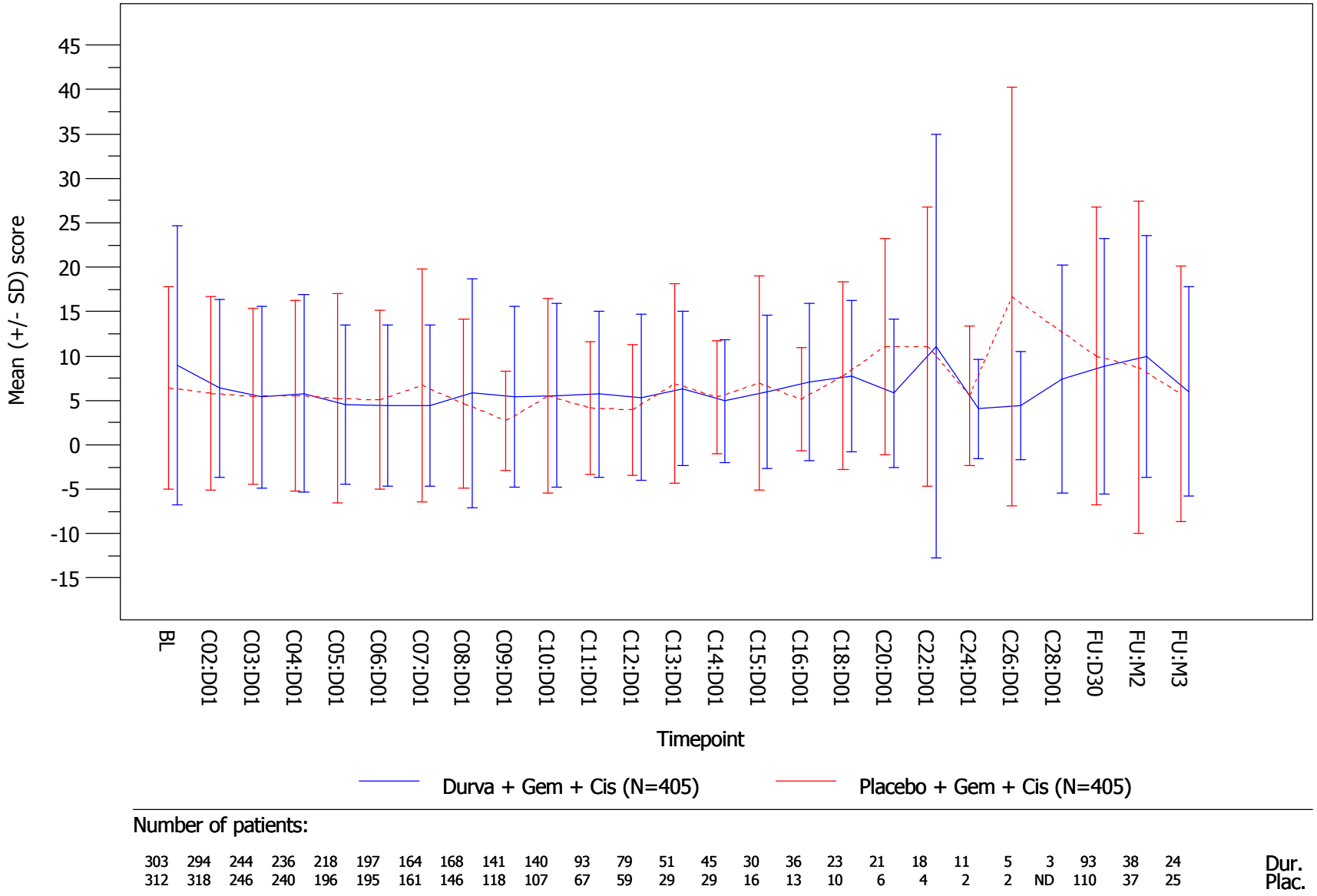
Figure 2.6.3.2 TOPAZ: Mean (+/- SD) EORTC QLQ-BIL21 Symptom scale: Tiredness across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

303	294	244	236	218	197	164	168	141	140	93	79	51	45	30	36	23	21	18	11	5	3	93	38	24	Dur.
312	318	246	240	196	195	161	146	118	107	67	59	29	29	16	13	10	6	4	2	2	ND	110	37	25	Plac.

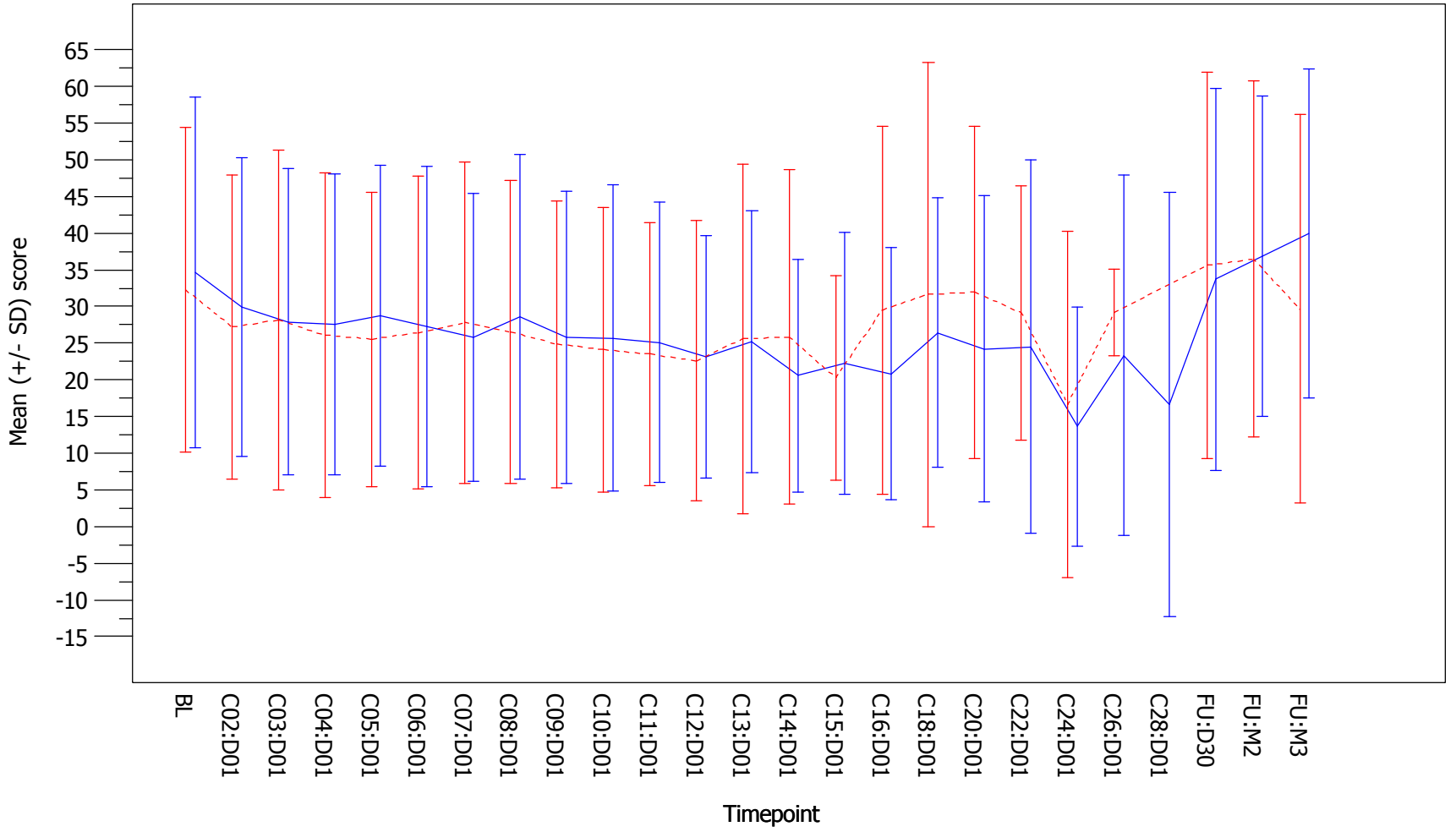
Figure 2.6.3.3 TOPAZ: Mean (+/- SD) EORTC QLQ-BIL21 Symptom scale: Jaundice across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

Dur.	303	294	244	236	218	197	164	168	141	140	93	79	51	45	30	36	23	21	18	11	5	3	93	38	24
Plac.	312	318	246	240	196	195	161	146	118	107	67	59	29	29	16	13	10	6	4	2	2	ND	110	37	25

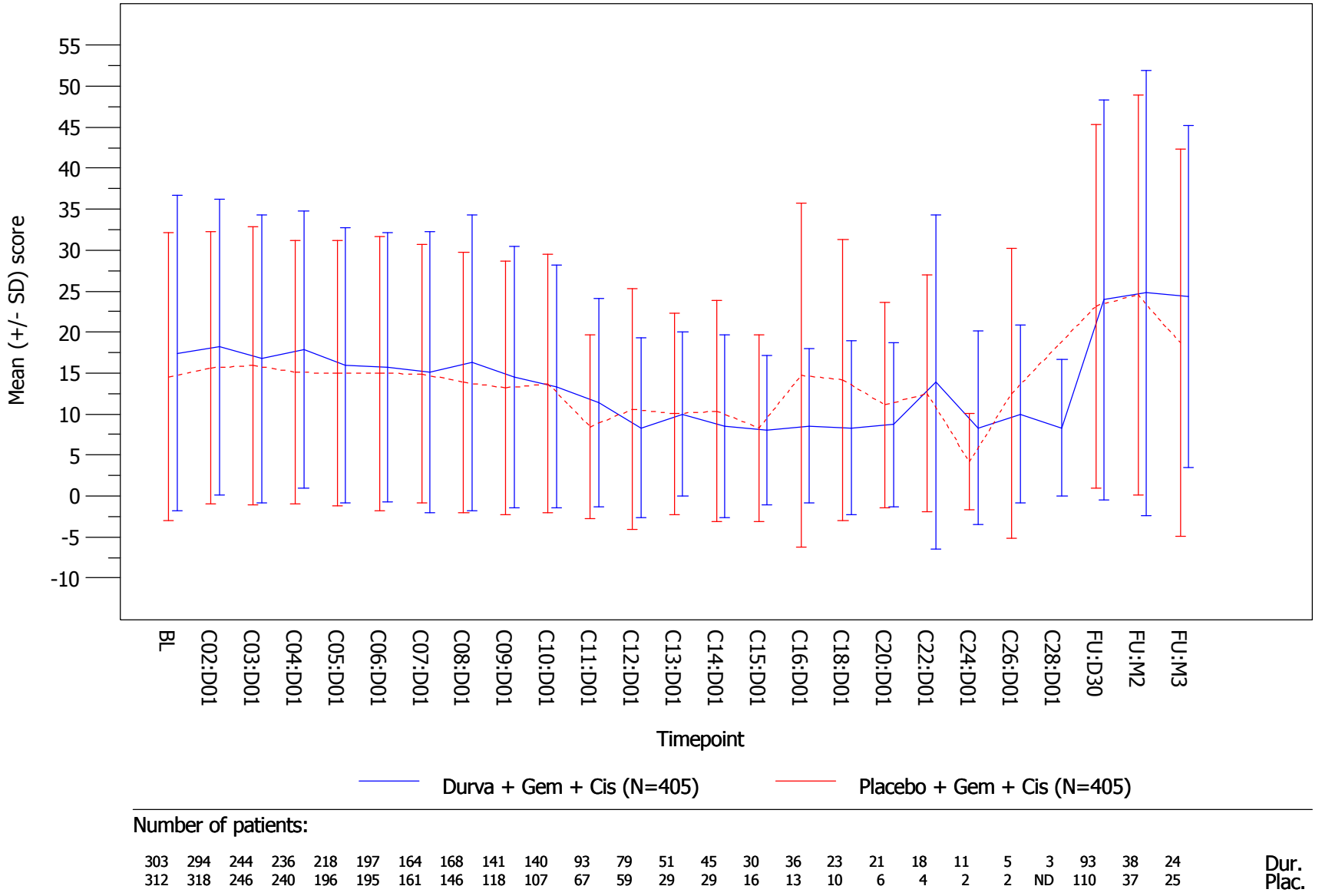
Figure 2.6.3.4 TOPAZ: Mean (+/- SD) EORTC QLQ-BIL21 Symptom scale: Anxiety across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

Dur.	303	294	244	236	218	197	164	168	141	140	93	79	51	45	30	36	23	21	18	11	5	3	93	38	24
Plac.	312	318	246	240	196	195	161	146	118	107	67	59	29	29	16	13	10	6	4	2	2	ND	110	37	25

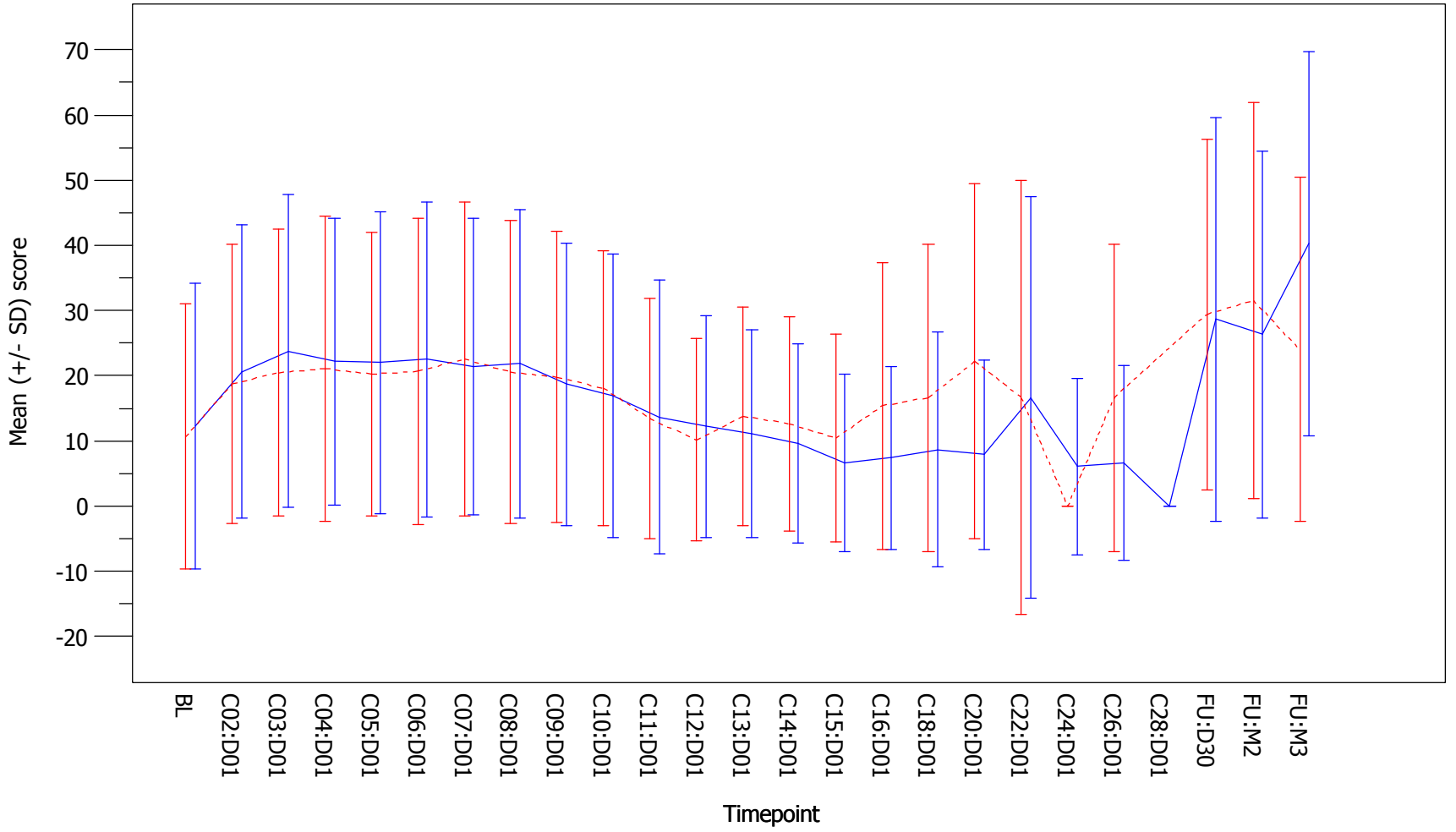
Figure 2.6.3.5 TOPAZ: Mean (+/- SD) EORTC QLQ-BIL21 Symptom scale: Eating across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

303	294	244	236	218	197	164	168	141	140	93	79	51	45	30	36	23	21	18	11	5	3	93	38	24	Dur.
312	318	246	240	196	195	161	146	118	107	67	59	29	29	16	13	10	6	4	2	2	ND	110	37	25	Plac.

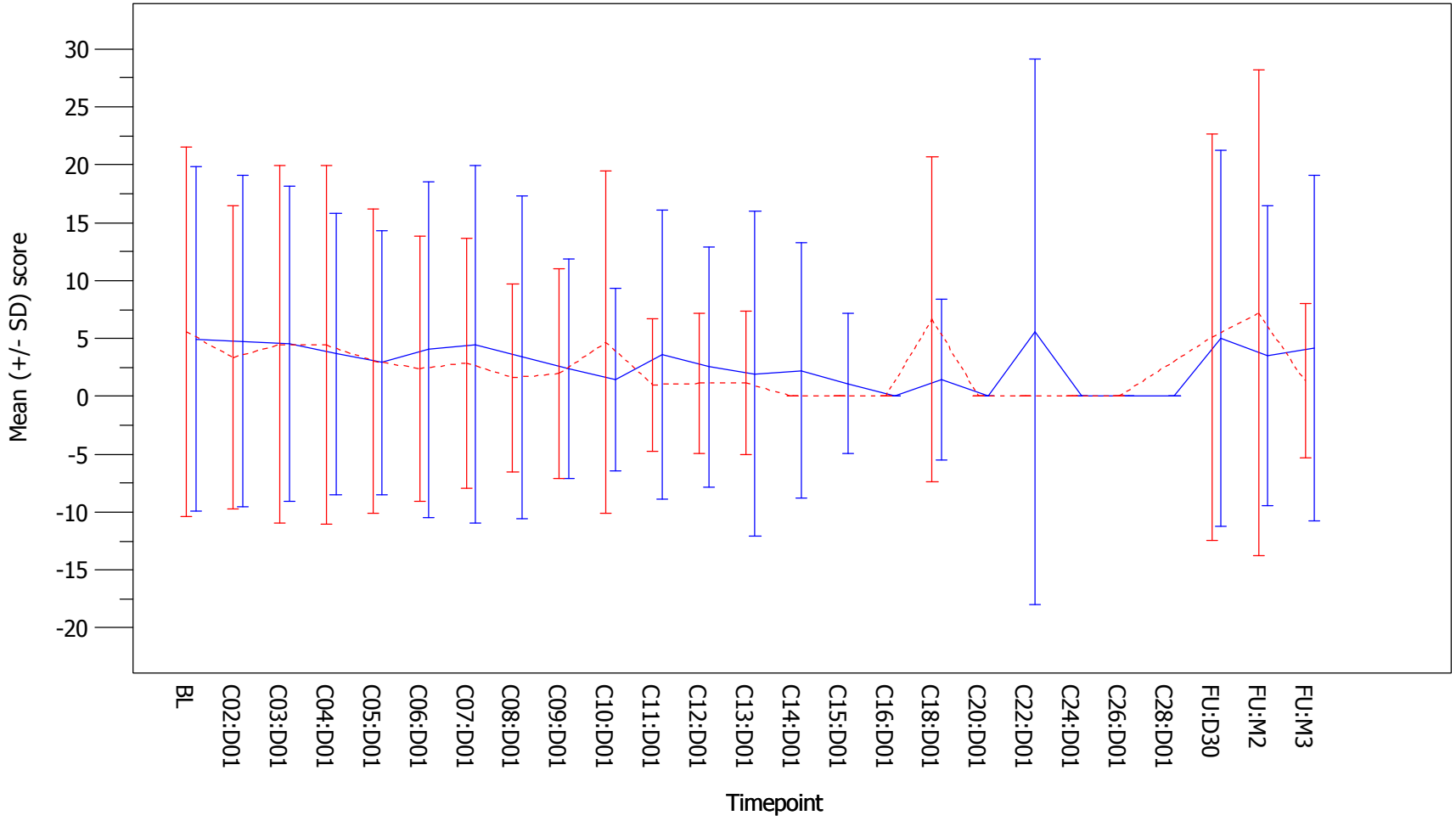
Figure 2.6.3.6 TOPAZ: Mean (+/- SD) EORTC QLQ-BIL21 Function: Treatment side effects across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

303	294	244	236	218	197	164	168	141	140	93	79	51	45	30	36	23	21	18	11	5	3	93	38	24	Dur.
312	318	246	240	196	195	161	146	118	107	67	59	29	29	16	13	10	6	4	2	2	ND	111	37	25	Plac.

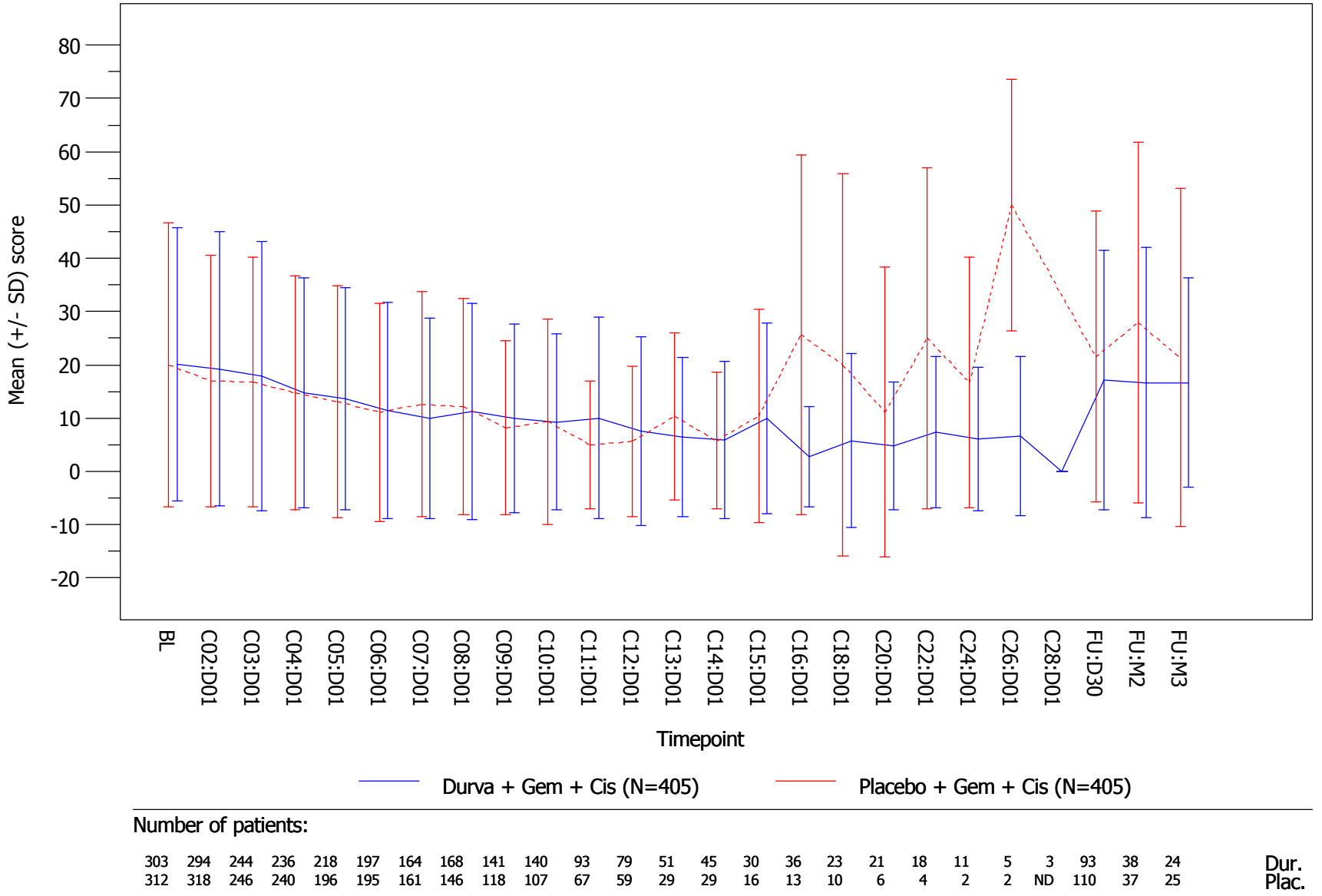
Figure 2.6.3.7 TOPAZ: Mean (+/- SD) EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

303	294	244	236	218	197	164	168	141	140	93	79	51	45	30	36	23	21	18	11	5	3	93	38	24	Dur.
312	318	246	240	196	195	161	146	118	107	67	59	29	29	16	13	10	6	4	2	2	ND	111	37	25	Plac.

Figure 2.6.3.8 TOPAZ: Mean (+/- SD) EORTC QLQ-BIL21 Function: Concerns regarding weight loss across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

Dur.	303	294	244	236	218	197	164	168	141	140	93	79	51	45	30	36	23	21	18	11	5	3	93	38	24
Plac.	312	318	246	240	196	195	161	146	118	107	67	59	29	29	16	13	10	6	4	2	2	ND	110	37	25

Table 2.7.1 TOPAZ: Summary of EQ-5D VAS results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
EQ-5D VAS	Durva + Gem + Cis (N=405)	Baseline [a]	309	70.54	19.028	0.0	75.00	100.0
		Cycle 02 Day 01	306	71.19	16.950	0.0	72.00	100.0
		Cycle 03 Day 01	253	72.84	16.254	20.0	76.00	100.0
		Cycle 04 Day 01	246	72.78	16.785	7.0	75.00	100.0
		Cycle 05 Day 01	224	74.00	14.823	19.0	75.50	100.0
		Cycle 06 Day 01	204	72.96	15.626	10.0	75.00	100.0
		Cycle 07 Day 01	171	74.36	15.057	26.0	75.00	100.0
		Cycle 08 Day 01	172	72.67	16.908	0.0	74.50	100.0
		Cycle 09 Day 01	146	73.53	15.087	20.0	75.00	100.0
		Cycle 10 Day 01	146	74.49	16.210	13.0	79.00	100.0
		Cycle 11 Day 01	97	76.70	14.509	30.0	80.00	100.0
		Cycle 12 Day 01	79	76.00	13.936	40.0	79.00	100.0
		Cycle 13 Day 01	51	77.08	12.745	45.0	80.00	100.0
		Cycle 14 Day 01	45	78.78	12.147	35.0	80.00	100.0
		Cycle 15 Day 01	30	76.80	9.185	51.0	77.00	95.0
		Cycle 16 Day 01	36	76.31	10.011	50.0	76.50	95.0
		Cycle 18 Day 01	23	78.74	14.667	40.0	81.00	100.0
		Cycle 20 Day 01	21	79.19	13.851	40.0	81.00	100.0
		Cycle 22 Day 01	18	79.00	12.252	60.0	80.00	100.0
		Cycle 24 Day 01	11	83.45	9.903	70.0	88.00	100.0
		Cycle 26 Day 01	5	79.80	13.971	60.0	89.00	90.0
		Cycle 28 Day 01	3	88.33	10.408	80.0	85.00	100.0
		Follow-up Day 30	99	62.09	21.765	5.0	68.00	100.0
		Follow-up Month 2	41	62.22	20.466	16.0	62.00	100.0
		Follow-up Month 3	24	59.33	16.426	30.0	66.50	81.0
	Placebo + Gem + Cis (N=405)	Baseline [a]	312	72.81	17.133	12.0	76.00	100.0
		Cycle 02 Day 01	320	71.04	17.766	0.0	72.50	100.0
		Cycle 03 Day 01	250	72.92	17.060	11.0	79.00	100.0
		Cycle 04 Day 01	243	72.16	17.802	0.0	75.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.7.1 TOPAZ: Summary of EQ-5D VAS results across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

				Absolute Values				
Parameter	Group	Time Point	n	Mean	SD	Min	Median	Max
		Cycle 05 Day 01	201	72.66	15.684	11.0	75.00	100.0
		Cycle 06 Day 01	199	71.75	17.118	2.0	75.00	100.0
		Cycle 07 Day 01	165	71.53	16.203	21.0	73.00	100.0
		Cycle 08 Day 01	148	72.91	15.625	29.0	75.00	100.0
		Cycle 09 Day 01	120	74.71	13.911	31.0	78.00	100.0
		Cycle 10 Day 01	110	74.49	15.319	30.0	77.00	100.0
		Cycle 11 Day 01	67	75.39	16.117	25.0	80.00	100.0
		Cycle 12 Day 01	59	77.51	15.470	26.0	80.00	100.0
		Cycle 13 Day 01	29	77.17	16.998	28.0	81.00	100.0
		Cycle 14 Day 01	29	76.41	17.342	27.0	83.00	100.0
		Cycle 15 Day 01	16	75.69	17.312	31.0	80.00	95.0
		Cycle 16 Day 01	13	66.77	25.843	0.0	70.00	93.0
		Cycle 18 Day 01	10	74.90	16.052	50.0	76.00	98.0
		Cycle 20 Day 01	6	70.83	19.416	41.0	72.50	91.0
		Cycle 22 Day 01	4	76.75	8.995	70.0	74.00	89.0
		Cycle 24 Day 01	2	79.50	13.435	70.0	79.50	89.0
		Cycle 26 Day 01	2	74.00	21.213	59.0	74.00	89.0
		Follow-up Day 30	114	63.08	19.365	4.0	65.00	99.0
		Follow-up Month 2	37	65.22	20.449	14.0	70.00	100.0
		Follow-up Month 3	25	68.76	19.507	28.0	70.00	100.0

[a] Baseline is defined as last evaluable assessment prior to dosing with study drug.
SD = standard deviation; Min = minimum ; Max = maximum; NC = not calculated.

Table 2.7.2 TOPAZ: Summary of analysis of change from baseline in EQ-5D VAS
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 02 Day 01	256	70.73 (18.974)	-0.59 (1.009)	259	73.63 (16.237)	-2.04 (1.001)	1.45 (-1.349, 4.240)	0.3101
Cycle 03 Day 01	212	71.36 (19.365)	0.18 (1.042)	210	74.15 (16.163)	-0.78 (1.041)	0.96 (-1.941, 3.853)	0.5169
Cycle 04 Day 01	203	71.90 (19.034)	-1.09 (1.006)	209	73.89 (16.155)	-1.78 (0.995)	0.68 (-2.098, 3.464)	0.6296
Cycle 05 Day 01	183	71.75 (19.251)	0.13 (0.960)	171	74.60 (15.212)	-1.31 (0.975)	1.43 (-1.258, 4.126)	0.2958
Cycle 06 Day 01	165	72.90 (17.821)	-1.46 (0.989)	172	73.63 (15.031)	-1.71 (0.978)	0.24 (-2.490, 2.978)	0.8606
Cycle 07 Day 01	140	74.19 (17.558)	0.14 (1.060)	142	73.95 (15.150)	-1.47 (1.058)	1.61 (-1.332, 4.552)	0.2827
Cycle 08 Day 01	142	73.30 (18.712)	-1.84 (1.042)	126	74.36 (15.884)	-2.00 (1.083)	0.15 (-2.801, 3.107)	0.9191
Cycle 09 Day 01	124	72.36 (18.767)	-0.61 (1.034)	104	74.24 (14.739)	-1.23 (1.100)	0.62 (-2.354, 3.589)	0.6831
Cycle 10 Day 01	120	73.02 (18.317)	-1.04 (1.158)	94	74.18 (15.495)	-0.98 (1.265)	-0.06 (-3.437, 3.313)	0.9712
Cycle 11 Day 01	81	73.30 (17.228)	2.04 (1.291)	59	71.42 (16.484)	-1.31 (1.462)	3.35 (-0.498, 7.194)	0.0876
Cycle 12 Day 01	62	71.95 (17.481)	1.16 (1.328)	56	72.09 (15.595)	1.66 (1.407)	-0.50 (-4.321, 3.311)	0.7944
Cycle 13 Day 01	38	70.87 (19.309)	2.17 (1.578)	27	72.04 (17.875)	1.65 (1.821)	0.52 (-4.249, 5.292)	0.8289
Cycle 14 Day 01	34	71.53 (18.802)	1.79 (1.845)	28	71.46 (17.523)	0.43 (2.028)	1.36 (-4.071, 6.795)	0.6201
Cycle 15 Day 01	21	72.76 (13.667)	1.34 (2.403)	15	77.93 (14.543)	-2.42 (2.909)	3.76 (-3.849, 11.369)	0.3250
Cycle 16 Day 01	28	73.64 (12.209)	0.15 (3.287)	13	73.08 (17.849)	-13.04 (4.601)	13.19 (1.816, 24.564)	0.0240*
Cycle 18 Day 01	17	74.82 (10.513)	1.64 (3.123)	10	70.70 (18.367)	-1.26 (4.111)	2.90 (-7.665, 13.463)	0.5800

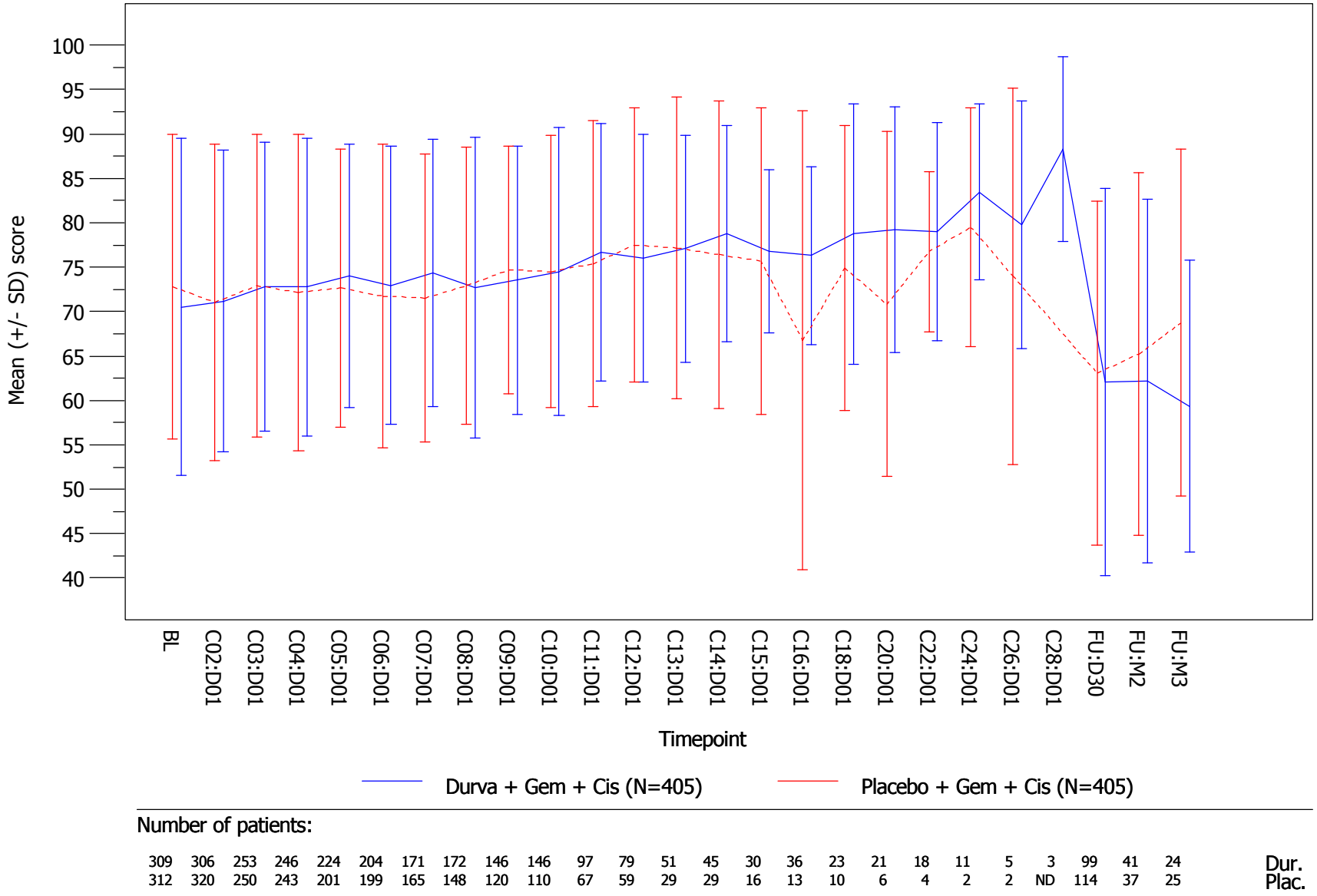
[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Table 2.7.2 TOPAZ: Summary of analysis of change from baseline in EQ-5D VAS
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)			Difference between groups	
Timepoint	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	n [a]	Mean (SD) at Baseline [b]	Mean (SE) Change from baseline	Estimated difference (95% CI)	p-value
Cycle 20 Day 01	19	73.89 (13.457)	4.70 (3.043)	6	76.67 (15.410)	-0.92 (5.068)	5.63 (-6.392, 17.647)	0.3471
Average over all visits	280	70.84 (19.106)	0.52 (0.916)	283	73.40 (16.180)	-1.68 (1.059)	2.19 (-0.565, 4.951)	0.1186
Hedges' g SMD							0.13 (-0.034, 0.297)	0.1185

[a] = number of patients with change from baseline at each timepoint in the MMRM analysis.
[b] = mean baseline for patients with change from baseline at each timepoint in the MMRM analysis.
Calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline score included as a covariate along with the baseline score by visit interaction. The analysis includes all planned visit data, except the study discontinuation visit and the safety follow-up visit which are excluded. Treatment, visit and treatment by visit interaction are fixed effects in the model, using Toeplitz with heterogeneity covariance matrix. Only includes visits with >=1% of patients in each arm, except for EORTC QLQ-BIL21 Function: Difficulties with drainage bags/tubes, where visits with >=5% of patients in each arm are included.
SMD = standardised mean difference. * p<0.05.

Figure 2.7.3 TOPAZ: Mean (+/- SD) EQ-5D VAS across timepoints, by treatment group
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients:

309	306	253	246	224	204	171	172	146	146	97	79	51	45	30	36	23	21	18	11	5	3	99	41	24
312	320	250	243	201	199	165	148	120	110	67	59	29	29	16	13	10	6	4	2	2	ND	114	37	25

Dur.
Plac.

Table 2.8.1 TOPAZ: Summary of status at time to deterioration in PGIS
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

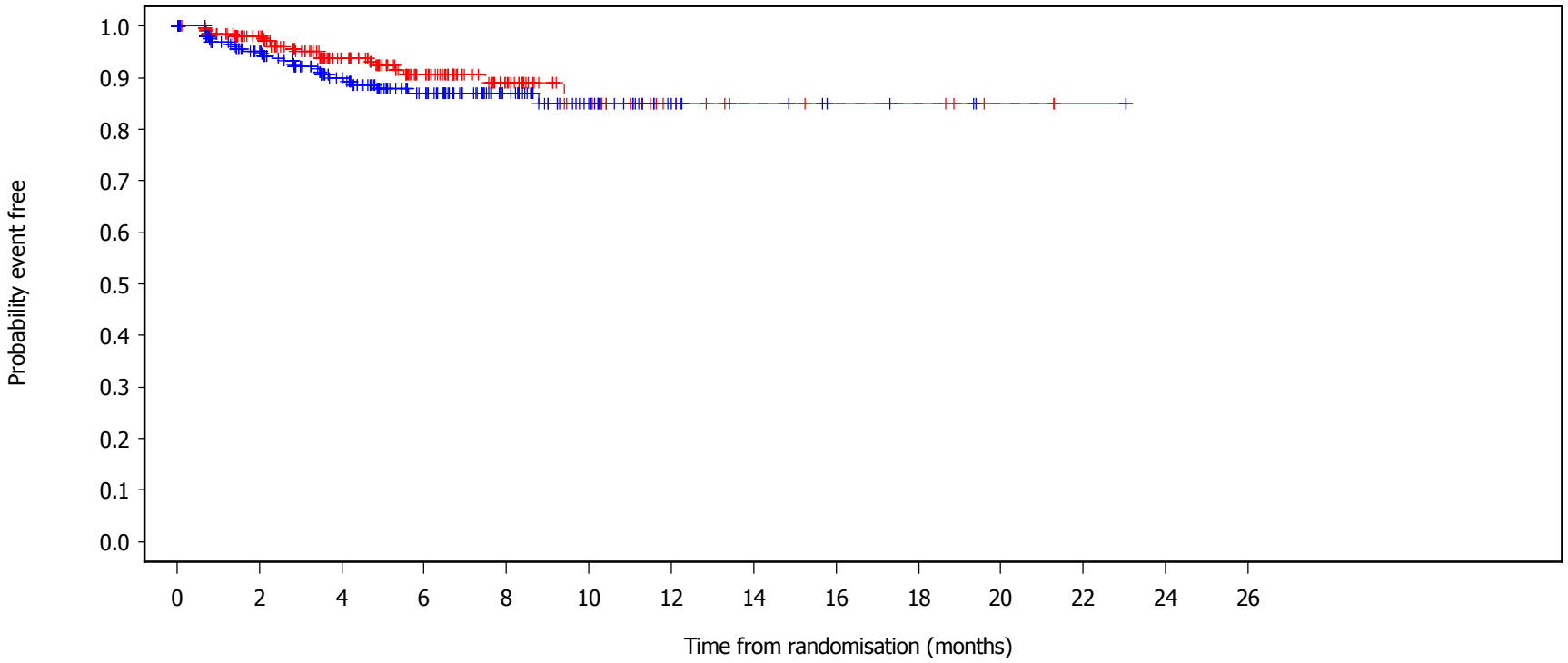
		Reason	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
PGIS	Deterioration	Total	27 (6.7)	19 (4.7)
	Censored	Total	378 (93.3)	386 (95.3)
		No evaluable assessments or no baseline data	120 (29.6)	114 (28.1)
		Alive and no deterioration	139 (34.3)	169 (41.7)
		Death	30 (7.4)	28 (6.9)
		Two or more missed visits before deterioration or death	89 (22.0)	75 (18.5)

Table 2.8.2 TOPAZ: Summary of analysis of time to deterioration in PGIS
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=405)			Placebo + Gem + Cis (N=405)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
PGIS Time to Deterioration	405	27 (6.7)	NE (NE, NE)	405	19 (4.7)	NE (NE, NE)	1.38	0.77, 2.51	0.3162

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards. [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] Estimated from Cox proportional hazards model adjusted for disease status and primary tumor location. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test stratified by disease status and primary tumor location. Hazard ratio <1 favours durva *p<0.05.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttemainpr.sas ettemainprad 19JAN2023:19:39 kjpc654

Figure 2.8.3.1 TOPAZ: Kaplan-Meier plot of PGIS Time to Deterioration
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients



Number of patients at risk:

405	212	143	100	54	29	11	7	4	3	1	1	0	0	Durva + Gem + Cis
404	209	140	89	43	20	8	5	4	4	1	0	0	0	Placebo + Gem + Cis

Time to deterioration is defined as time from randomisation date until the earliest date of deterioration in the respective score. Patients with no evaluable assessments or no baseline data are censored at day 1. Patients alive or who died more than 2 visits after last assessment, with no deterioration are censored at last evaluable assessment. Patients with available baseline values who did not experience a deterioration up to the timepoint of analyses who died within 2 visits of last assessment are censored at their death date. Patients with 2 or more missed PRO assessment visits are censored at the time of last evaluable PRO assessment prior to the 2 missed visits regardless of any deterioration or death occurring afterwards.

Table 2.9.1 TOPAZ: Summary of compliance with EORTC QLQ-C30 by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Baseline	Expected forms [a]	372	383
	Received forms [b]	324	333
	Evaluable forms [c]	324	333
	Compliance rate (%) [d]	87.1	86.9
	Evaluability rate (%) [e]	100	100
Cycle 02 Day 01	Expected forms [a]	345	353
	Received forms [b]	303	321
	Evaluable forms [c]	303	321
	Compliance rate (%) [d]	87.8	90.9
	Evaluability rate (%) [e]	100	100
Cycle 03 Day 01	Expected forms [a]	304	304
	Received forms [b]	255	252
	Evaluable forms [c]	255	252
	Compliance rate (%) [d]	83.9	82.9
	Evaluability rate (%) [e]	100	100
Cycle 04 Day 01	Expected forms [a]	287	289
	Received forms [b]	248	246
	Evaluable forms [c]	248	246
	Compliance rate (%) [d]	86.4	85.1
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.1 TOPAZ: Summary of compliance with EORTC QLQ-C30 by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 05 Day 01	Expected forms [a]	265	255
	Received forms [b]	226	200
	Evaluable forms [c]	226	200
	Compliance rate (%) [d]	85.3	78.4
	Evaluability rate (%) [e]	100	100
Cycle 06 Day 01	Expected forms [a]	247	242
	Received forms [b]	205	200
	Evaluable forms [c]	205	200
	Compliance rate (%) [d]	83.0	82.6
	Evaluability rate (%) [e]	100	100
Cycle 07 Day 01	Expected forms [a]	226	209
	Received forms [b]	172	166
	Evaluable forms [c]	172	166
	Compliance rate (%) [d]	76.1	79.4
	Evaluability rate (%) [e]	100	100
Cycle 08 Day 01	Expected forms [a]	215	193
	Received forms [b]	172	150
	Evaluable forms [c]	172	150
	Compliance rate (%) [d]	80.0	77.7
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.1 TOPAZ: Summary of compliance with EORTC QLQ-C30 by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 09 Day 01	Expected forms [a]	189	151
	Received forms [b]	147	122
	Evaluable forms [c]	147	122
	Compliance rate (%) [d]	77.8	80.8
	Evaluability rate (%) [e]	100	100
Cycle 10 Day 01	Expected forms [a]	166	126
	Received forms [b]	147	110
	Evaluable forms [c]	147	110
	Compliance rate (%) [d]	88.6	87.3
	Evaluability rate (%) [e]	100	100
Cycle 11 Day 01	Expected forms [a]	117	82
	Received forms [b]	97	67
	Evaluable forms [c]	97	67
	Compliance rate (%) [d]	82.9	81.7
	Evaluability rate (%) [e]	100	100
Cycle 12 Day 01	Expected forms [a]	97	66
	Received forms [b]	80	59
	Evaluable forms [c]	80	59
	Compliance rate (%) [d]	82.5	89.4
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.1 TOPAZ: Summary of compliance with EORTC QLQ-C30 by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 13 Day 01	Expected forms [a]	63	35
	Received forms [b]	51	29
	Evaluable forms [c]	51	29
	Compliance rate (%) [d]	81.0	82.9
	Evaluability rate (%) [e]	100	100
Cycle 14 Day 01	Expected forms [a]	56	32
	Received forms [b]	45	29
	Evaluable forms [c]	45	29
	Compliance rate (%) [d]	80.4	90.6
	Evaluability rate (%) [e]	100	100
Cycle 15 Day 01	Expected forms [a]	42	18
	Received forms [b]	30	16
	Evaluable forms [c]	30	16
	Compliance rate (%) [d]	71.4	88.9
	Evaluability rate (%) [e]	100	100
Cycle 16 Day 01	Expected forms [a]	41	14
	Received forms [b]	36	13
	Evaluable forms [c]	36	13
	Compliance rate (%) [d]	87.8	92.9
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.1 TOPAZ: Summary of compliance with EORTC QLQ-C30 by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 18 Day 01	Expected forms [a]	31	12
	Received forms [b]	24	10
	Evaluable forms [c]	24	10
	Compliance rate (%) [d]	77.4	83.3
	Evaluability rate (%) [e]	100	100
Cycle 20 Day 01	Expected forms [a]	25	6
	Received forms [b]	21	6
	Evaluable forms [c]	21	6
	Compliance rate (%) [d]	84.0	100
	Evaluability rate (%) [e]	100	100
Cycle 22 Day 01	Expected forms [a]	20	4
	Received forms [b]	18	4
	Evaluable forms [c]	18	4
	Compliance rate (%) [d]	90.0	100
	Evaluability rate (%) [e]	100	100
Cycle 24 Day 01	Expected forms [a]	12	3
	Received forms [b]	11	2
	Evaluable forms [c]	11	2
	Compliance rate (%) [d]	91.7	66.7
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.1 TOPAZ: Summary of compliance with EORTC QLQ-C30 by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 26 Day 01	Expected forms [a]	6	2
	Received forms [b]	5	2
	Evaluable forms [c]	5	2
	Compliance rate (%) [d]	83.3	100
	Evaluability rate (%) [e]	100	100
Cycle 28 Day 01	Expected forms [a]	4	NC
	Received forms [b]	3	NC
	Evaluable forms [c]	3	NC
	Compliance rate (%) [d]	75.0	NC
	Evaluability rate (%) [e]	100	NC
Follow-up Day 30	Expected forms [a]	267	312
	Received forms [b]	99	114
	Evaluable forms [c]	99	114
	Compliance rate (%) [d]	37.1	36.5
	Evaluability rate (%) [e]	100	100
Follow-up Month 2	Expected forms [a]	214	242
	Received forms [b]	41	37
	Evaluable forms [c]	41	37
	Compliance rate (%) [d]	19.2	15.3
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.1 TOPAZ: Summary of compliance with EORTC QLQ-C30 by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Follow-up Month 3	Expected forms [a]	174	205
	Received forms [b]	24	25
	Evaluable forms [c]	24	25
	Compliance rate (%) [d]	13.8	12.2
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.2 TOPAZ: Summary of compliance with EORTC QLQ-BIL21 by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Baseline	Expected forms [a]	359	377
	Received forms [b]	303	312
	Evaluable forms [c]	303	312
	Compliance rate (%) [d]	84.4	82.8
	Evaluability rate (%) [e]	100	100
Cycle 02 Day 01	Expected forms [a]	334	349
	Received forms [b]	294	318
	Evaluable forms [c]	294	318
	Compliance rate (%) [d]	88.0	91.1
	Evaluability rate (%) [e]	100	100
Cycle 03 Day 01	Expected forms [a]	294	299
	Received forms [b]	244	246
	Evaluable forms [c]	244	246
	Compliance rate (%) [d]	83.0	82.3
	Evaluability rate (%) [e]	100	100
Cycle 04 Day 01	Expected forms [a]	276	284
	Received forms [b]	236	240
	Evaluable forms [c]	236	240
	Compliance rate (%) [d]	85.5	84.5
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.2 TOPAZ: Summary of compliance with EORTC QLQ-BIL21 by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 05 Day 01	Expected forms [a]	257	250
	Received forms [b]	218	196
	Evaluable forms [c]	218	196
	Compliance rate (%) [d]	84.8	78.4
	Evaluability rate (%) [e]	100	100
Cycle 06 Day 01	Expected forms [a]	240	237
	Received forms [b]	197	195
	Evaluable forms [c]	197	195
	Compliance rate (%) [d]	82.1	82.3
	Evaluability rate (%) [e]	100	100
Cycle 07 Day 01	Expected forms [a]	219	204
	Received forms [b]	164	161
	Evaluable forms [c]	164	161
	Compliance rate (%) [d]	74.9	78.9
	Evaluability rate (%) [e]	100	100
Cycle 08 Day 01	Expected forms [a]	208	189
	Received forms [b]	168	146
	Evaluable forms [c]	168	146
	Compliance rate (%) [d]	80.8	77.2
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.2 TOPAZ: Summary of compliance with EORTC QLQ-BIL21 by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 09 Day 01	Expected forms [a]	182	148
	Received forms [b]	141	118
	Evaluable forms [c]	141	118
	Compliance rate (%) [d]	77.5	79.7
	Evaluability rate (%) [e]	100	100
Cycle 10 Day 01	Expected forms [a]	159	123
	Received forms [b]	140	107
	Evaluable forms [c]	140	107
	Compliance rate (%) [d]	88.1	87.0
	Evaluability rate (%) [e]	100	100
Cycle 11 Day 01	Expected forms [a]	113	81
	Received forms [b]	93	67
	Evaluable forms [c]	93	67
	Compliance rate (%) [d]	82.3	82.7
	Evaluability rate (%) [e]	100	100
Cycle 12 Day 01	Expected forms [a]	93	66
	Received forms [b]	79	59
	Evaluable forms [c]	79	59
	Compliance rate (%) [d]	84.9	89.4
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.2 TOPAZ: Summary of compliance with EORTC QLQ-BIL21 by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 13 Day 01	Expected forms [a]	63	35
	Received forms [b]	51	29
	Evaluable forms [c]	51	29
	Compliance rate (%) [d]	81.0	82.9
	Evaluability rate (%) [e]	100	100
Cycle 14 Day 01	Expected forms [a]	56	32
	Received forms [b]	45	29
	Evaluable forms [c]	45	29
	Compliance rate (%) [d]	80.4	90.6
	Evaluability rate (%) [e]	100	100
Cycle 15 Day 01	Expected forms [a]	42	18
	Received forms [b]	30	16
	Evaluable forms [c]	30	16
	Compliance rate (%) [d]	71.4	88.9
	Evaluability rate (%) [e]	100	100
Cycle 16 Day 01	Expected forms [a]	41	14
	Received forms [b]	36	13
	Evaluable forms [c]	36	13
	Compliance rate (%) [d]	87.8	92.9
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.2 TOPAZ: Summary of compliance with EORTC QLQ-BIL21 by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 18 Day 01	Expected forms [a]	30	12
	Received forms [b]	23	10
	Evaluable forms [c]	23	10
	Compliance rate (%) [d]	76.7	83.3
	Evaluability rate (%) [e]	100	100
Cycle 20 Day 01	Expected forms [a]	25	6
	Received forms [b]	21	6
	Evaluable forms [c]	21	6
	Compliance rate (%) [d]	84.0	100
	Evaluability rate (%) [e]	100	100
Cycle 22 Day 01	Expected forms [a]	20	4
	Received forms [b]	18	4
	Evaluable forms [c]	18	4
	Compliance rate (%) [d]	90.0	100
	Evaluability rate (%) [e]	100	100
Cycle 24 Day 01	Expected forms [a]	12	3
	Received forms [b]	11	2
	Evaluable forms [c]	11	2
	Compliance rate (%) [d]	91.7	66.7
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.2 TOPAZ: Summary of compliance with EORTC QLQ-BIL21 by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 26 Day 01	Expected forms [a]	6	2
	Received forms [b]	5	2
	Evaluable forms [c]	5	2
	Compliance rate (%) [d]	83.3	100
	Evaluability rate (%) [e]	100	100
Cycle 28 Day 01	Expected forms [a]	4	NC
	Received forms [b]	3	NC
	Evaluable forms [c]	3	NC
	Compliance rate (%) [d]	75.0	NC
	Evaluability rate (%) [e]	100	NC
Follow-up Day 30	Expected forms [a]	260	307
	Received forms [b]	93	111
	Evaluable forms [c]	93	111
	Compliance rate (%) [d]	35.8	36.2
	Evaluability rate (%) [e]	100	100
Follow-up Month 2	Expected forms [a]	210	240
	Received forms [b]	38	37
	Evaluable forms [c]	38	37
	Compliance rate (%) [d]	18.1	15.4
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.2 TOPAZ: Summary of compliance with EORTC QLQ-BIL21 by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Follow-up Month 3	Expected forms [a]	173	204
	Received forms [b]	24	25
	Evaluable forms [c]	24	25
	Compliance rate (%) [d]	13.9	12.3
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.3 TOPAZ: Summary of compliance with EQ-5D by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Baseline	Expected forms [a]	371	383
	Received forms [b]	309	312
	Evaluable forms [c]	309	312
	Compliance rate (%) [d]	83.3	81.5
	Evaluability rate (%) [e]	100	100
Cycle 02 Day 01	Expected forms [a]	345	354
	Received forms [b]	306	320
	Evaluable forms [c]	306	320
	Compliance rate (%) [d]	88.7	90.4
	Evaluability rate (%) [e]	100	100
Cycle 03 Day 01	Expected forms [a]	304	304
	Received forms [b]	253	250
	Evaluable forms [c]	253	250
	Compliance rate (%) [d]	83.2	82.2
	Evaluability rate (%) [e]	100	100
Cycle 04 Day 01	Expected forms [a]	286	289
	Received forms [b]	246	243
	Evaluable forms [c]	246	243
	Compliance rate (%) [d]	86.0	84.1
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.3 TOPAZ: Summary of compliance with EQ-5D by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 05 Day 01	Expected forms [a]	265	255
	Received forms [b]	224	201
	Evaluable forms [c]	224	201
	Compliance rate (%) [d]	84.5	78.8
	Evaluability rate (%) [e]	100	100
Cycle 06 Day 01	Expected forms [a]	247	242
	Received forms [b]	204	199
	Evaluable forms [c]	204	199
	Compliance rate (%) [d]	82.6	82.2
	Evaluability rate (%) [e]	100	100
Cycle 07 Day 01	Expected forms [a]	226	209
	Received forms [b]	171	165
	Evaluable forms [c]	171	165
	Compliance rate (%) [d]	75.7	78.9
	Evaluability rate (%) [e]	100	100
Cycle 08 Day 01	Expected forms [a]	215	192
	Received forms [b]	172	148
	Evaluable forms [c]	172	148
	Compliance rate (%) [d]	80.0	77.1
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.3 TOPAZ: Summary of compliance with EQ-5D by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 09 Day 01	Expected forms [a]	189	151
	Received forms [b]	146	120
	Evaluable forms [c]	146	120
	Compliance rate (%) [d]	77.2	79.5
	Evaluability rate (%) [e]	100	100
Cycle 10 Day 01	Expected forms [a]	165	126
	Received forms [b]	146	110
	Evaluable forms [c]	146	110
	Compliance rate (%) [d]	88.5	87.3
	Evaluability rate (%) [e]	100	100
Cycle 11 Day 01	Expected forms [a]	117	82
	Received forms [b]	97	67
	Evaluable forms [c]	97	67
	Compliance rate (%) [d]	82.9	81.7
	Evaluability rate (%) [e]	100	100
Cycle 12 Day 01	Expected forms [a]	96	66
	Received forms [b]	79	59
	Evaluable forms [c]	79	59
	Compliance rate (%) [d]	82.3	89.4
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.3 TOPAZ: Summary of compliance with EQ-5D by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 13 Day 01	Expected forms [a]	63	35
	Received forms [b]	51	29
	Evaluable forms [c]	51	29
	Compliance rate (%) [d]	81.0	82.9
	Evaluability rate (%) [e]	100	100
Cycle 14 Day 01	Expected forms [a]	56	32
	Received forms [b]	45	29
	Evaluable forms [c]	45	29
	Compliance rate (%) [d]	80.4	90.6
	Evaluability rate (%) [e]	100	100
Cycle 15 Day 01	Expected forms [a]	42	18
	Received forms [b]	30	16
	Evaluable forms [c]	30	16
	Compliance rate (%) [d]	71.4	88.9
	Evaluability rate (%) [e]	100	100
Cycle 16 Day 01	Expected forms [a]	41	14
	Received forms [b]	36	13
	Evaluable forms [c]	36	13
	Compliance rate (%) [d]	87.8	92.9
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.3 TOPAZ: Summary of compliance with EQ-5D by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 18 Day 01	Expected forms [a]	30	12
	Received forms [b]	23	10
	Evaluable forms [c]	23	10
	Compliance rate (%) [d]	76.7	83.3
	Evaluability rate (%) [e]	100	100
Cycle 20 Day 01	Expected forms [a]	25	6
	Received forms [b]	21	6
	Evaluable forms [c]	21	6
	Compliance rate (%) [d]	84.0	100
	Evaluability rate (%) [e]	100	100
Cycle 22 Day 01	Expected forms [a]	20	4
	Received forms [b]	18	4
	Evaluable forms [c]	18	4
	Compliance rate (%) [d]	90.0	100
	Evaluability rate (%) [e]	100	100
Cycle 24 Day 01	Expected forms [a]	12	3
	Received forms [b]	11	2
	Evaluable forms [c]	11	2
	Compliance rate (%) [d]	91.7	66.7
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.3 TOPAZ: Summary of compliance with EQ-5D by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 26 Day 01	Expected forms [a]	6	2
	Received forms [b]	5	2
	Evaluable forms [c]	5	2
	Compliance rate (%) [d]	83.3	100
	Evaluability rate (%) [e]	100	100
Cycle 28 Day 01	Expected forms [a]	4	NC
	Received forms [b]	3	NC
	Evaluable forms [c]	3	NC
	Compliance rate (%) [d]	75.0	NC
	Evaluability rate (%) [e]	100	NC
Follow-up Day 30	Expected forms [a]	267	312
	Received forms [b]	99	114
	Evaluable forms [c]	99	114
	Compliance rate (%) [d]	37.1	36.5
	Evaluability rate (%) [e]	100	100
Follow-up Month 2	Expected forms [a]	214	242
	Received forms [b]	41	37
	Evaluable forms [c]	41	37
	Compliance rate (%) [d]	19.2	15.3
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.3 TOPAZ: Summary of compliance with EQ-5D by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Follow-up Month 3	Expected forms [a]	174	205
	Received forms [b]	24	25
	Evaluable forms [c]	24	25
	Compliance rate (%) [d]	13.8	12.2
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.4 TOPAZ: Summary of compliance with PGIS by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Baseline	Expected forms [a]	371	383
	Received forms [b]	311	312
	Evaluable forms [c]	311	312
	Compliance rate (%) [d]	83.8	81.5
	Evaluability rate (%) [e]	100	100
Cycle 02 Day 01	Expected forms [a]	345	354
	Received forms [b]	306	320
	Evaluable forms [c]	306	320
	Compliance rate (%) [d]	88.7	90.4
	Evaluability rate (%) [e]	100	100
Cycle 03 Day 01	Expected forms [a]	304	304
	Received forms [b]	253	250
	Evaluable forms [c]	253	250
	Compliance rate (%) [d]	83.2	82.2
	Evaluability rate (%) [e]	100	100
Cycle 04 Day 01	Expected forms [a]	286	289
	Received forms [b]	246	243
	Evaluable forms [c]	246	243
	Compliance rate (%) [d]	86.0	84.1
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.4 TOPAZ: Summary of compliance with PGIS by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 05 Day 01	Expected forms [a]	265	255
	Received forms [b]	225	201
	Evaluable forms [c]	225	201
	Compliance rate (%) [d]	84.9	78.8
	Evaluability rate (%) [e]	100	100
Cycle 06 Day 01	Expected forms [a]	247	242
	Received forms [b]	204	199
	Evaluable forms [c]	204	199
	Compliance rate (%) [d]	82.6	82.2
	Evaluability rate (%) [e]	100	100
Cycle 07 Day 01	Expected forms [a]	226	209
	Received forms [b]	171	165
	Evaluable forms [c]	171	165
	Compliance rate (%) [d]	75.7	78.9
	Evaluability rate (%) [e]	100	100
Cycle 08 Day 01	Expected forms [a]	215	193
	Received forms [b]	172	149
	Evaluable forms [c]	172	149
	Compliance rate (%) [d]	80.0	77.2
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.4 TOPAZ: Summary of compliance with PGIS by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 09 Day 01	Expected forms [a]	189	151
	Received forms [b]	146	120
	Evaluable forms [c]	146	120
	Compliance rate (%) [d]	77.2	79.5
	Evaluability rate (%) [e]	100	100
Cycle 10 Day 01	Expected forms [a]	165	126
	Received forms [b]	146	110
	Evaluable forms [c]	146	110
	Compliance rate (%) [d]	88.5	87.3
	Evaluability rate (%) [e]	100	100
Cycle 11 Day 01	Expected forms [a]	117	82
	Received forms [b]	97	67
	Evaluable forms [c]	97	67
	Compliance rate (%) [d]	82.9	81.7
	Evaluability rate (%) [e]	100	100
Cycle 12 Day 01	Expected forms [a]	96	66
	Received forms [b]	79	59
	Evaluable forms [c]	79	59
	Compliance rate (%) [d]	82.3	89.4
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.4 TOPAZ: Summary of compliance with PGIS by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 13 Day 01	Expected forms [a]	63	35
	Received forms [b]	51	29
	Evaluable forms [c]	51	29
	Compliance rate (%) [d]	81.0	82.9
	Evaluability rate (%) [e]	100	100
Cycle 14 Day 01	Expected forms [a]	56	32
	Received forms [b]	45	29
	Evaluable forms [c]	45	29
	Compliance rate (%) [d]	80.4	90.6
	Evaluability rate (%) [e]	100	100
Cycle 15 Day 01	Expected forms [a]	42	18
	Received forms [b]	30	16
	Evaluable forms [c]	30	16
	Compliance rate (%) [d]	71.4	88.9
	Evaluability rate (%) [e]	100	100
Cycle 16 Day 01	Expected forms [a]	41	14
	Received forms [b]	36	13
	Evaluable forms [c]	36	13
	Compliance rate (%) [d]	87.8	92.9
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.4 TOPAZ: Summary of compliance with PGIS by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 18 Day 01	Expected forms [a]	30	12
	Received forms [b]	23	10
	Evaluable forms [c]	23	10
	Compliance rate (%) [d]	76.7	83.3
	Evaluability rate (%) [e]	100	100
Cycle 20 Day 01	Expected forms [a]	25	6
	Received forms [b]	21	6
	Evaluable forms [c]	21	6
	Compliance rate (%) [d]	84.0	100
	Evaluability rate (%) [e]	100	100
Cycle 22 Day 01	Expected forms [a]	20	4
	Received forms [b]	18	4
	Evaluable forms [c]	18	4
	Compliance rate (%) [d]	90.0	100
	Evaluability rate (%) [e]	100	100
Cycle 24 Day 01	Expected forms [a]	12	3
	Received forms [b]	11	2
	Evaluable forms [c]	11	2
	Compliance rate (%) [d]	91.7	66.7
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.4 TOPAZ: Summary of compliance with PGIS by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Cycle 26 Day 01	Expected forms [a]	6	2
	Received forms [b]	5	2
	Evaluable forms [c]	5	2
	Compliance rate (%) [d]	83.3	100
	Evaluability rate (%) [e]	100	100
Cycle 28 Day 01	Expected forms [a]	4	NC
	Received forms [b]	3	NC
	Evaluable forms [c]	3	NC
	Compliance rate (%) [d]	75.0	NC
	Evaluability rate (%) [e]	100	NC
Follow-up Day 30	Expected forms [a]	267	312
	Received forms [b]	99	114
	Evaluable forms [c]	99	114
	Compliance rate (%) [d]	37.1	36.5
	Evaluability rate (%) [e]	100	100
Follow-up Month 2	Expected forms [a]	214	242
	Received forms [b]	41	37
	Evaluable forms [c]	41	37
	Compliance rate (%) [d]	19.2	15.3
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 2.9.4 TOPAZ: Summary of compliance with PGIS by visit
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)
Follow-up Month 3	Expected forms [a]	174	205
	Received forms [b]	24	25
	Evaluable forms [c]	24	25
	Compliance rate (%) [d]	13.8	12.2
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 3.1 TOPAZ: Summary of observation period for adverse events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

		Durva + Gem + Cis (N=402)	Placebo + Gem + Cis (N=403)
All AE endpoints	n	402	403
	Median	7.92	6.97
	Min	0.1	0.2
	Max	31.1	26.8

Observation period for AEs is defined as the time from first dose to the earliest of the DCO, study treatment discontinuation +90 days, administration of subsequent treatment or death.

Table 3.2.1 TOPAZ: Summary of analysis of time to first occurrence of adverse events
(total, and by SOC and PT occurring in >=10 patients and with frequency >=1% in either treatment group)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AE	402	399 (99.3)	0.2 (0.1, 0.2)	403	399 (99.0)	0.2 (0.2, 0.2)	0.98	0.85, 1.12	0.7681
SOC: General disorders and administration site conditions	402	234 (58.2)	3.4 (2.2, 4.7)	403	221 (54.8)	4.2 (3.0, 6.5)	1.07	0.89, 1.29	0.4649
PT: Asthenia	402	52 (12.9)	NE (NE, NE)	403	51 (12.7)	NE (NE, NE)	1.00	0.68, 1.48	0.9931
PT: Fatigue	402	96 (23.9)	NE (NE, NE)	403	100 (24.8)	NE (NE, NE)	0.93	0.70, 1.23	0.6056
PT: Pyrexia	402	89 (22.1)	NE (NE, NE)	403	62 (15.4)	NE (NE, NE)	1.41	1.02, 1.97	0.0362*
PT: Oedema	402	11 (2.7)	NE (NE, NE)	403	6 (1.5)	NE (NE, NE)	1.80	0.69, 5.23	0.2395
PT: Oedema peripheral	402	28 (7.0)	NE (NE, NE)	403	19 (4.7)	NE (NE, NE)	1.43	0.80, 2.60	0.2308
PT: Chills	402	14 (3.5)	NE (NE, NE)	403	8 (2.0)	NE (NE, NE)	1.73	0.74, 4.34	0.2084
PT: Malaise	402	18 (4.5)	NE (NE, NE)	403	16 (4.0)	NE (NE, NE)	1.12	0.57, 2.21	0.7491
SOC: Eye disorders	402	15 (3.7)	NE (NE, NE)	403	14 (3.5)	NE (NE, NE)	1.03	0.49, 2.18	0.9277
SOC: Endocrine disorders	402	37 (9.2)	NE (NE, NE)	403	20 (5.0)	NE (NE, NE)	1.71	0.999, 3.00	0.0526
PT: Hypothyroidism	402	27 (6.7)	NE (NE, NE)	403	14 (3.5)	NE (NE, NE)	1.78	0.94, 3.49	0.0779

The time to event endpoint is the time to first AE or the time to censoring if the AE has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AEs with an onset date on or after the date of first dose and AEs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.1 TOPAZ: Summary of analysis of time to first occurrence of adverse events
(total, and by SOC and PT occurring in >=10 patients and with frequency >=1% in either treatment group)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
SOC: Respiratory, thoracic and mediastinal disorders	402	102 (25.4)	NE (NE, NE)	403	79 (19.6)	NE (NE, NE)	1.30	0.97, 1.75	0.0772
PT: Dyspnoea	402	22 (5.5)	NE (NE, NE)	403	20 (5.0)	NE (NE, NE)	1.02	0.56, 1.90	0.9364
PT: Cough	402	27 (6.7)	NE (NE, NE)	403	22 (5.5)	NE (NE, NE)	1.21	0.69, 2.14	0.5155
PT: Pulmonary embolism	402	16 (4.0)	NE (NE, NE)	403	14 (3.5)	NE (NE, NE)	1.11	0.54, 2.30	0.7812
PT: Hiccups	402	13 (3.2)	NE (NE, NE)	403	6 (1.5)	NE (NE, NE)	2.19	0.87, 6.25	0.1030
SOC: Reproductive system and breast disorders	402	5 (1.2)	NE (NE, NE)	403	12 (3.0)	NE (NE, NE)	0.38	0.12, 1.02	0.0578
SOC: Skin and subcutaneous tissue disorders	402	158 (39.3)	13.4 (10.1,20.6)	403	102 (25.3)	NE (NE, NE)	1.57	1.22, 2.02	0.0004*
PT: Alopecia	402	32 (8.0)	NE (NE, NE)	403	17 (4.2)	NE (NE, NE)	1.92	1.08, 3.53	0.0271*
PT: Rash	402	47 (11.7)	NE (NE, NE)	403	34 (8.4)	NE (NE, NE)	1.34	0.86, 2.10	0.1927
PT: Rash maculo-papular	402	20 (5.0)	NE (NE, NE)	403	9 (2.2)	NE (NE, NE)	2.10	0.98, 4.87	0.0596
PT: Pruritus	402	44 (10.9)	NE (NE, NE)	403	29 (7.2)	NE (NE, NE)	1.30	0.81, 2.11	0.2735
PT: Dry skin	402	8 (2.0)	NE (NE, NE)	403	14 (3.5)	NE (NE, NE)	0.51	0.20, 1.20	0.1260

The time to event endpoint is the time to first AE or the time to censoring if the AE has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AEs with an onset date on or after the date of first dose and AEs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.1 TOPAZ: Summary of analysis of time to first occurrence of adverse events
(total, and by SOC and PT occurring in >=10 patients and with frequency >=1% in either treatment group)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
SOC: Renal and urinary disorders	402	49 (12.2)	NE (NE, NE)	403	44 (10.9)	NE (NE, NE)	1.03	0.69, 1.56	0.8727
PT: Acute kidney injury	402	14 (3.5)	NE (NE, NE)	403	8 (2.0)	NE (NE, NE)	1.64	0.70, 4.11	0.2616
SOC: Blood and lymphatic system disorders	402	269 (66.9)	2.3 (2.0, 2.8)	403	259 (64.3)	2.4 (2.1, 2.9)	1.04	0.87, 1.23	0.6774
PT: Anaemia	402	212 (52.7)	4.4 (3.4, 5.8)	403	196 (48.6)	5.2 (3.5, NE)	1.09	0.90, 1.33	0.3811
PT: Leukopenia	402	26 (6.5)	NE (NE, NE)	403	21 (5.2)	NE (NE, NE)	1.24	0.70, 2.23	0.4587
PT: Neutropenia	402	111 (27.6)	NE (NE, NE)	403	104 (25.8)	NE (NE, NE)	1.07	0.82, 1.39	0.6356
PT: Thrombocytopenia	402	45 (11.2)	NE (NE, NE)	403	49 (12.2)	NE (NE, NE)	0.89	0.59, 1.33	0.5566
SOC: Gastrointestinal disorders	402	309 (76.9)	0.9 (0.7, 1.3)	403	277 (68.7)	1.2 (0.9, 1.6)	1.21	1.03, 1.42	0.0255*
PT: Abdominal pain	402	56 (13.9)	NE (NE, NE)	403	61 (15.1)	NE (NE, NE)	0.84	0.59, 1.22	0.3645
PT: Ascites	402	17 (4.2)	NE (NE, NE)	403	14 (3.5)	NE (NE, NE)	1.15	0.56, 2.37	0.7039
PT: Abdominal distension	402	19 (4.7)	NE (NE, NE)	403	15 (3.7)	NE (NE, NE)	1.17	0.59, 2.35	0.6486
PT: Diarrhoea	402	64 (15.9)	NE (NE, NE)	403	57 (14.1)	NE (NE, NE)	1.09	0.76, 1.56	0.6444
PT: Dyspepsia	402	23 (5.7)	NE (NE, NE)	403	26 (6.5)	NE (NE, NE)	0.82	0.46, 1.44	0.4850

The time to event endpoint is the time to first AE or the time to censoring if the AE has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AEs with an onset date on or after the date of first dose and AEs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties.
95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.1 TOPAZ: Summary of analysis of time to first occurrence of adverse events
(total, and by SOC and PT occurring in >=10 patients and with frequency >=1% in either treatment group)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)				
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
PT: Vomiting	402	84 (20.9)	NE (NE, NE)	403	72 (17.9)	NE (NE, NE)	1.12	0.82, 1.54	0.4750
PT: Gastrooesophageal reflux disease	402	11 (2.7)	NE (NE, NE)	403	9 (2.2)	NE (NE, NE)	1.18	0.49, 2.94	0.7153
PT: Dry mouth	402	10 (2.5)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.0017*
PT: Constipation	402	125 (31.1)	NE (NE, NE)	403	115 (28.5)	NE (NE, NE)	1.11	0.86, 1.44	0.4082
PT: Abdominal pain upper	402	44 (10.9)	NE (NE, NE)	403	31 (7.7)	NE (NE, NE)	1.32	0.84, 2.12	0.2339
PT: Stomatitis	402	23 (5.7)	NE (NE, NE)	403	22 (5.5)	NE (NE, NE)	1.02	0.57, 1.85	0.9362
PT: Nausea	402	159 (39.6)	23.8 (11.8, NE)	403	137 (34.0)	NE (NE, NE)	1.18	0.94, 1.49	0.1545
SOC: Nervous system disorders	402	101 (25.1)	NE (NE, NE)	403	82 (20.3)	NE (NE, NE)	1.22	0.91, 1.63	0.1863
PT: Dysgeusia	402	20 (5.0)	NE (NE, NE)	403	16 (4.0)	NE (NE, NE)	1.27	0.66, 2.48	0.4796
PT: Headache	402	26 (6.5)	NE (NE, NE)	403	16 (4.0)	NE (NE, NE)	1.58	0.85, 3.01	0.1486
PT: Paraesthesia	402	8 (2.0)	NE (NE, NE)	403	10 (2.5)	NE (NE, NE)	0.74	0.28, 1.88	0.5221
PT: Neuropathy peripheral	402	13 (3.2)	NE (NE, NE)	403	10 (2.5)	NE (NE, NE)	1.14	0.50, 2.69	0.7588
PT: Peripheral sensory neuropathy	402	11 (2.7)	NE (NE, NE)	403	10 (2.5)	NE (NE, NE)	1.04	0.44, 2.50	0.9261

The time to event endpoint is the time to first AE or the time to censoring if the AE has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AEs with an onset date on or after the date of first dose and AEs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.1 TOPAZ: Summary of analysis of time to first occurrence of adverse events
(total, and by SOC and PT occurring in >=10 patients and with frequency >=1% in either treatment group)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
PT: Dizziness	402	22 (5.5)	NE (NE, NE)	403	17 (4.2)	NE (NE, NE)	1.26	0.67, 2.40	0.4809
SOC: Ear and labyrinth disorders	402	18 (4.5)	NE (NE, NE)	403	12 (3.0)	NE (NE, NE)	1.35	0.65, 2.90	0.4215
PT: Tinnitus	402	10 (2.5)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	2.24	0.74, 8.23	0.1644
SOC: Vascular disorders	402	55 (13.7)	NE (NE, NE)	403	48 (11.9)	NE (NE, NE)	1.11	0.75, 1.64	0.6065
PT: Hypertension	402	20 (5.0)	NE (NE, NE)	403	21 (5.2)	NE (NE, NE)	0.87	0.46, 1.61	0.6537
SOC: Cardiac disorders	402	13 (3.2)	NE (NE, NE)	403	12 (3.0)	NE (NE, NE)	0.95	0.43, 2.13	0.8990
SOC: Infections and infestations	402	144 (35.8)	16.7 (14.9, NE)	403	134 (33.3)	11.5 (10.6,20.9)	0.97	0.77, 1.24	0.8266
PT: COVID-19	402	9 (2.2)	NE (NE, NE)	403	11 (2.7)	NE (NE, NE)	0.69	0.27, 1.70	0.4178
PT: Biliary tract infection	402	19 (4.7)	NE (NE, NE)	403	10 (2.5)	NE (NE, NE)	1.70	0.80, 3.84	0.1747
PT: Urinary tract infection	402	31 (7.7)	NE (NE, NE)	403	21 (5.2)	NE (NE, NE)	1.38	0.80, 2.44	0.2555
PT: Upper respiratory tract infection	402	13 (3.2)	NE (NE, NE)	403	11 (2.7)	NE (NE, NE)	1.15	0.51, 2.63	0.7307
PT: Nasopharyngitis	402	9 (2.2)	NE (NE, NE)	403	12 (3.0)	NE (NE, NE)	0.59	0.24, 1.42	0.2363

The time to event endpoint is the time to first AE or the time to censoring if the AE has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AEs with an onset date on or after the date of first dose and AEs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties.
95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.1 TOPAZ: Summary of analysis of time to first occurrence of adverse events
(total, and by SOC and PT occurring in >=10 patients and with frequency >=1% in either treatment group)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
PT: Pneumonia	402	16 (4.0)	NE (NE, NE)	403	13 (3.2)	NE (NE, NE)	1.03	0.49, 2.20	0.9376
PT: Sepsis	402	15 (3.7)	NE (NE, NE)	403	9 (2.2)	NE (NE, NE)	1.61	0.72, 3.84	0.2543
SOC: Hepatobiliary disorders	402	75 (18.7)	NE (NE, NE)	403	64 (15.9)	NE (NE, NE)	1.10	0.79, 1.54	0.5872
PT: Biliary obstruction	402	12 (3.0)	NE (NE, NE)	403	10 (2.5)	NE (NE, NE)	0.96	0.41, 2.30	0.9241
PT: Cholangitis	402	30 (7.5)	NE (NE, NE)	403	19 (4.7)	NE (NE, NE)	1.45	0.82, 2.63	0.2046
SOC: Psychiatric disorders	402	61 (15.2)	NE (NE, NE)	403	54 (13.4)	NE (NE, NE)	1.12	0.77, 1.62	0.5535
PT: Insomnia	402	35 (8.7)	NE (NE, NE)	403	41 (10.2)	NE (NE, NE)	0.84	0.53, 1.31	0.4377
SOC: Musculoskeletal and connective tissue disorders	402	101 (25.1)	NE (NE, NE)	403	84 (20.8)	NE (NE, NE)	1.15	0.86, 1.54	0.3413
PT: Arthralgia	402	22 (5.5)	NE (NE, NE)	403	14 (3.5)	NE (NE, NE)	1.50	0.77, 3.00	0.2362
PT: Bone pain	402	10 (2.5)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	3.30	1.01, 14.73	0.0545
PT: Myalgia	402	15 (3.7)	NE (NE, NE)	403	20 (5.0)	NE (NE, NE)	0.68	0.34, 1.33	0.2582
PT: Back pain	402	34 (8.5)	NE (NE, NE)	403	23 (5.7)	NE (NE, NE)	1.38	0.82, 2.38	0.2281
PT: Pain in extremity	402	15 (3.7)	NE (NE, NE)	403	7 (1.7)	NE (NE, NE)	1.96	0.82, 5.15	0.1368

The time to event endpoint is the time to first AE or the time to censoring if the AE has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AEs with an onset date on or after the date of first dose and AEs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties.
95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.1 TOPAZ: Summary of analysis of time to first occurrence of adverse events
(total, and by SOC and PT occurring in >=10 patients and with frequency >=1% in either treatment group)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
SOC: Metabolism and nutrition disorders	402	201 (50.0)	7.1 (4.4,13.3)	403	185 (45.9)	9.5 (5.8, NE)	1.07	0.88, 1.31	0.5110
PT: Decreased appetite	402	105 (26.1)	NE (NE, NE)	403	96 (23.8)	NE (NE, NE)	1.07	0.81, 1.42	0.6235
PT: Hypoalbuminaemia	402	29 (7.2)	NE (NE, NE)	403	25 (6.2)	NE (NE, NE)	1.11	0.65, 1.91	0.7026
PT: Hyperglycaemia	402	9 (2.2)	NE (NE, NE)	403	15 (3.7)	NE (NE, NE)	0.53	0.22, 1.21	0.1329
PT: Hyperkalaemia	402	20 (5.0)	NE (NE, NE)	403	18 (4.5)	NE (NE, NE)	1.10	0.58, 2.09	0.7794
PT: Hypokalaemia	402	38 (9.5)	NE (NE, NE)	403	22 (5.5)	NE (NE, NE)	1.61	0.96, 2.77	0.0746
PT: Hypocalcaemia	402	9 (2.2)	NE (NE, NE)	403	12 (3.0)	NE (NE, NE)	0.73	0.30, 1.72	0.4686
PT: Hypomagnesaemia	402	36 (9.0)	NE (NE, NE)	403	33 (8.2)	NE (NE, NE)	1.07	0.66, 1.72	0.7864
PT: Hyponatraemia	402	30 (7.5)	NE (NE, NE)	403	26 (6.5)	NE (NE, NE)	1.13	0.67, 1.92	0.6548
SOC: Investigations	402	243 (60.4)	3.5 (2.5, 4.1)	403	265 (65.8)	2.3 (1.7, 3.1)	0.83	0.70, 0.99	0.0388*
PT: Alanine aminotransferase increased	402	48 (11.9)	NE (NE, NE)	403	50 (12.4)	NE (NE, NE)	0.90	0.60, 1.34	0.5955
PT: Blood alkaline phosphatase increased	402	20 (5.0)	NE (NE, NE)	403	23 (5.7)	NE (NE, NE)	0.79	0.43, 1.45	0.4444

The time to event endpoint is the time to first AE or the time to censoring if the AE has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AEs with an onset date on or after the date of first dose and AEs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.1 TOPAZ: Summary of analysis of time to first occurrence of adverse events
(total, and by SOC and PT occurring in >=10 patients and with frequency >=1% in either treatment group)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
PT: Amylase increased	402	15 (3.7)	NE (NE, NE)	403	15 (3.7)	NE (NE, NE)	0.89	0.43, 1.85	0.7604
PT: Aspartate aminotransferase increased	402	42 (10.4)	NE (NE, NE)	403	47 (11.7)	NE (NE, NE)	0.83	0.54, 1.26	0.3787
PT: Blood bilirubin increased	402	18 (4.5)	NE (NE, NE)	403	33 (8.2)	NE (NE, NE)	0.49	0.27, 0.85	0.0123*
PT: Gamma-glutamyltransferase increased	402	20 (5.0)	NE (NE, NE)	403	23 (5.7)	NE (NE, NE)	0.78	0.42, 1.42	0.4135
PT: Weight decreased	402	30 (7.5)	NE (NE, NE)	403	26 (6.5)	NE (NE, NE)	1.11	0.65, 1.88	0.7088
PT: Blood creatinine increased	402	13 (3.2)	NE (NE, NE)	403	38 (9.4)	NE (NE, NE)	0.32	0.16, 0.58	0.0002*
PT: White blood cell count decreased	402	69 (17.2)	NE (NE, NE)	403	81 (20.1)	NE (NE, NE)	0.83	0.60, 1.15	0.2641
PT: Lipase increased	402	16 (4.0)	NE (NE, NE)	403	15 (3.7)	NE (NE, NE)	0.95	0.46, 1.94	0.8798
PT: Lymphocyte count decreased	402	10 (2.5)	NE (NE, NE)	403	14 (3.5)	NE (NE, NE)	0.68	0.29, 1.53	0.3583
PT: Neutrophil count decreased	402	119 (29.6)	NE (NE, NE)	403	143 (35.5)	NE (NE, NE)	0.80	0.63, 1.02	0.0764

The time to event endpoint is the time to first AE or the time to censoring if the AE has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AEs with an onset date on or after the date of first dose and AEs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.1 TOPAZ: Summary of analysis of time to first occurrence of adverse events
(total, and by SOC and PT occurring in >=10 patients and with frequency >=1% in either treatment group)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
PT: Platelet count decreased	402	99 (24.6)	NE (NE, NE)	403	111 (27.5)	NE (NE, NE)	0.84	0.64, 1.10	0.1956
SOC: Injury, poisoning and procedural complications	402	27 (6.7)	NE (NE, NE)	403	29 (7.2)	NE (NE, NE)	0.84	0.49, 1.42	0.5111

The time to event endpoint is the time to first AE or the time to censoring if the AE has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AEs with an onset date on or after the date of first dose and AEs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties.
95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.2 TOPAZ: Summary of analysis of time to first occurrence of serious adverse events
(total, and by SOC and PT occurring in >=10 patients and with frequency >=1% in either treatment group)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
SAE	402	190 (47.3)	9.5 (7.0,16.2)	403	171 (42.4)	11.2 (8.3,17.5)	1.07	0.87, 1.32	0.5291
SAE SOC: General disorders and administration site conditions	402	30 (7.5)	NE (NE, NE)	403	19 (4.7)	NE (NE, NE)	1.46	0.83, 2.65	0.1967
SAE PT: Pyrexia	402	18 (4.5)	NE (NE, NE)	403	8 (2.0)	NE (NE, NE)	2.02	0.90, 4.95	0.0923
SAE SOC: Respiratory, thoracic and mediastinal disorders	402	15 (3.7)	NE (NE, NE)	403	12 (3.0)	NE (NE, NE)	1.17	0.55, 2.56	0.6839
SAE SOC: Renal and urinary disorders	402	12 (3.0)	NE (NE, NE)	403	9 (2.2)	NE (NE, NE)	1.19	0.50, 2.93	0.6883
SAE SOC: Blood and lymphatic system disorders	402	25 (6.2)	NE (NE, NE)	403	21 (5.2)	NE (NE, NE)	1.20	0.67, 2.17	0.5343
SAE PT: Anaemia	402	14 (3.5)	NE (NE, NE)	403	5 (1.2)	NE (NE, NE)	2.85	1.09, 8.82	0.0355*
SAE SOC: Gastrointestinal disorders	402	39 (9.7)	NE (NE, NE)	403	37 (9.2)	NE (NE, NE)	0.97	0.62, 1.53	0.8980
SAE SOC: Nervous system disorders	402	11 (2.7)	NE (NE, NE)	403	5 (1.2)	NE (NE, NE)	2.13	0.77, 6.76	0.1521

The time to event endpoint is the time to first SAE or the time to censoring if the SAE has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes SAEs with an onset date on or after the date of first dose and SAEs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties.
95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.2 TOPAZ: Summary of analysis of time to first occurrence of serious adverse events
(total, and by SOC and PT occurring in >=10 patients and with frequency >=1% in either treatment group)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
SAE SOC: Vascular disorders	402	8 (2.0)	NE (NE, NE)	403	10 (2.5)	NE (NE, NE)	0.79	0.30, 2.01	0.6222
SAE SOC: Infections and infestations	402	53 (13.2)	NE (NE, NE)	403	51 (12.7)	NE (NE, NE)	0.94	0.64, 1.38	0.7371
SAE PT: Biliary tract infection	402	8 (2.0)	NE (NE, NE)	403	10 (2.5)	NE (NE, NE)	0.74	0.28, 1.88	0.5234
SAE PT: Sepsis	402	11 (2.7)	NE (NE, NE)	403	9 (2.2)	NE (NE, NE)	1.19	0.49, 2.96	0.6946
SAE SOC: Hepatobiliary disorders	402	51 (12.7)	NE (NE, NE)	403	45 (11.2)	NE (NE, NE)	1.02	0.68, 1.54	0.9161
SAE PT: Cholangitis	402	26 (6.5)	NE (NE, NE)	403	17 (4.2)	NE (NE, NE)	1.41	0.77, 2.65	0.2691
SAE SOC: Metabolism and nutrition disorders	402	11 (2.7)	NE (NE, NE)	403	10 (2.5)	NE (NE, NE)	1.05	0.44, 2.53	0.9087
SAE SOC: Investigations	402	11 (2.7)	NE (NE, NE)	403	13 (3.2)	NE (NE, NE)	0.81	0.35, 1.81	0.6011
SAE SOC: Injury, poisoning and procedural complications	402	5 (1.2)	NE (NE, NE)	403	10 (2.5)	NE (NE, NE)	0.44	0.13, 1.24	0.1233

The time to event endpoint is the time to first SAE or the time to censoring if the SAE has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes SAEs with an onset date on or after the date of first dose and SAEs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties.
95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.3 TOPAZ: Summary of analysis of time to first occurrence of adverse events leading to discontinuation of >=1 component of treatment
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AE leading to discontinuation of treatment	402	56 (13.9)	NE (NE, NE)	403	57 (14.1)	NE (NE, NE)	0.94	0.65, 1.36	0.7384

The time to event endpoint is the time to first AE or the time to censoring if the AE has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AEs with an onset date on or after the date of first dose and AEs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.4 TOPAZ: Summary of analysis of time to first occurrence of adverse events with max. CTCAE grade >=3
(total, and by SOC and PT occurring in >=10 patients and with frequency >=1% in either treatment group)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AE max CTCAE grade >=3	402	313 (77.9)	2.1 (1.6, 2.4)	403	315 (78.2)	1.6 (1.3, 2.1)	0.89	0.76, 1.04	0.1483
G>=3 SOC: General disorders and administration site conditions	402	32 (8.0)	NE (NE, NE)	403	24 (6.0)	NE (NE, NE)	1.24	0.73, 2.14	0.4203
G>=3 PT: Asthenia	402	10 (2.5)	NE (NE, NE)	403	8 (2.0)	NE (NE, NE)	1.23	0.48, 3.22	0.6657
G>=3 PT: Fatigue	402	11 (2.7)	NE (NE, NE)	403	12 (3.0)	NE (NE, NE)	0.91	0.40, 2.08	0.8280
G>=3 SOC: Respiratory, thoracic and mediastinal disorders	402	16 (4.0)	NE (NE, NE)	403	13 (3.2)	NE (NE, NE)	1.15	0.55, 2.44	0.7046
G>=3 SOC: Renal and urinary disorders	402	16 (4.0)	NE (NE, NE)	403	9 (2.2)	NE (NE, NE)	1.61	0.72, 3.80	0.2519
G>=3 PT: Acute kidney injury	402	12 (3.0)	NE (NE, NE)	403	6 (1.5)	NE (NE, NE)	1.84	0.71, 5.29	0.2160
G>=3 SOC: Blood and lymphatic system disorders	402	173 (43.0)	19.9 (5.3, NE)	403	164 (40.7)	23.6 (10.3, NE)	1.02	0.82, 1.26	0.8597
G>=3 PT: Anaemia	402	104 (25.9)	NE (NE, NE)	403	97 (24.1)	23.6 (23.6, NE)	1.04	0.78, 1.37	0.8061
G>=3 PT: Neutropenia	402	69 (17.2)	NE (NE, NE)	403	73 (18.1)	NE (NE, NE)	0.93	0.67, 1.29	0.6616

The time to event endpoint is the time to first AE or the time to censoring if the AE has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AEs with an onset date on or after the date of first dose and AEs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties.
95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.4 TOPAZ: Summary of analysis of time to first occurrence of adverse events with max. CTCAE grade >=3 (total, and by SOC and PT occurring in >=10 patients and with frequency >=1% in either treatment group)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
G>=3 PT: Thrombocytopenia	402	16 (4.0)	NE (NE, NE)	403	19 (4.7)	NE (NE, NE)	0.81	0.41, 1.58	0.5412
G>=3 SOC: Gastrointestinal disorders	402	39 (9.7)	NE (NE, NE)	403	50 (12.4)	NE (NE, NE)	0.72	0.47, 1.10	0.1272
G>=3 SOC: Nervous system disorders	402	11 (2.7)	NE (NE, NE)	403	6 (1.5)	NE (NE, NE)	1.76	0.67, 5.12	0.2594
G>=3 SOC: Vascular disorders	402	14 (3.5)	NE (NE, NE)	403	18 (4.5)	NE (NE, NE)	0.72	0.35, 1.45	0.3649
G>=3 SOC: Infections and infestations	402	59 (14.7)	NE (NE, NE)	403	55 (13.6)	NE (NE, NE)	0.98	0.68, 1.42	0.9049
G>=3 PT: Biliary tract infection	402	15 (3.7)	NE (NE, NE)	403	9 (2.2)	NE (NE, NE)	1.45	0.64, 3.50	0.3811
G>=3 PT: Sepsis	402	14 (3.5)	NE (NE, NE)	403	9 (2.2)	NE (NE, NE)	1.53	0.67, 3.66	0.3196
G>=3 SOC: Hepatobiliary disorders	402	52 (12.9)	NE (NE, NE)	403	43 (10.7)	NE (NE, NE)	1.09	0.72, 1.64	0.6861
G>=3 PT: Cholangitis	402	23 (5.7)	NE (NE, NE)	403	11 (2.7)	NE (NE, NE)	1.95	0.97, 4.16	0.0651
G>=3 SOC: Metabolism and nutrition disorders	402	44 (10.9)	NE (NE, NE)	403	33 (8.2)	NE (NE, NE)	1.26	0.80, 2.00	0.3134
G>=3 PT: Hypokalaemia	402	12 (3.0)	NE (NE, NE)	403	7 (1.7)	NE (NE, NE)	1.55	0.62, 4.19	0.3543

The time to event endpoint is the time to first AE or the time to censoring if the AE has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AEs with an onset date on or after the date of first dose and AEs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.4 TOPAZ: Summary of analysis of time to first occurrence of adverse events with max. CTCAE grade >=3 (total, and by SOC and PT occurring in >=10 patients and with frequency >=1% in either treatment group)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
G>=3 SOC: Investigations	402	143 (35.6)	NE (NE, NE)	403	153 (38.0)	16.4 (16.4, NE)	0.89	0.71, 1.11	0.3060
G>=3 PT: Blood bilirubin increased	402	6 (1.5)	NE (NE, NE)	403	12 (3.0)	NE (NE, NE)	0.43	0.15, 1.12	0.0877
G>=3 PT: White blood cell count decreased	402	28 (7.0)	NE (NE, NE)	403	29 (7.2)	NE (NE, NE)	0.96	0.57, 1.62	0.8881
G>=3 PT: Neutrophil count decreased	402	91 (22.6)	NE (NE, NE)	403	108 (26.8)	NE (NE, NE)	0.82	0.62, 1.08	0.1553
G>=3 PT: Platelet count decreased	402	44 (10.9)	NE (NE, NE)	403	43 (10.7)	NE (NE, NE)	1.01	0.66, 1.54	0.9727

The time to event endpoint is the time to first AE or the time to censoring if the AE has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AEs with an onset date on or after the date of first dose and AEs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.5 TOPAZ: Summary of analysis of time to first occurrence of adverse events of special interest (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI	402	361 (89.8)	0.8 (0.7, 0.9)	403	362 (89.8)	0.8 (0.7, 1.0)	0.96	0.83, 1.12	0.6491
AESI GT: Pneumonitis	402	6 (1.5)	NE (NE, NE)	403	6 (1.5)	NE (NE, NE)	0.85	0.26, 2.76	0.7863
AESI PT: Immune-mediated lung disease	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3155
AESI PT: Interstitial lung disease	402	2 (0.5)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	1.64	0.16, 35.46	0.6828
AESI PT: Pneumonitis	402	3 (0.7)	NE (NE, NE)	403	5 (1.2)	NE (NE, NE)	0.51	0.10, 2.10	0.3505
AESI GT: Hepatic events	402	5 (1.2)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	1.14	0.30, 4.67	0.8431
AESI PT: Drug-induced liver injury	402	0	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	NC	NC	0.1611
AESI PT: Autoimmune hepatitis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.0961
AESI PT: Hepatitis	402	3 (0.7)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	3.00	0.38, 60.71	0.3166
AESI PT: Immune-mediated hepatitis	402	2 (0.5)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.1550
AESI GT: Diarrhoea/Colitis	402	65 (16.2)	NE (NE, NE)	403	57 (14.1)	NE (NE, NE)	1.11	0.78, 1.58	0.5777

The time to event endpoint is the time to first AESI or the time to censoring if the AESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AESIs with an onset date on or after the date of first dose and AESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.5 TOPAZ: Summary of analysis of time to first occurrence of adverse events of special interest (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI PT: Diarrhoea	402	64 (15.9)	NE (NE, NE)	403	57 (14.1)	NE (NE, NE)	1.09	0.76, 1.56	0.6444
AESI PT: Enterocolitis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3072
AESI PT: Immune-mediated enterocolitis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3160
AESI PT: Colitis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3117
AESI GT: Adrenal insufficiency	402	4 (1.0)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	3.22	0.47, 63.53	0.2726
AESI PT: Adrenal insufficiency	402	4 (1.0)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	3.22	0.47, 63.53	0.2726
AESI GT: Type 1 diabetes mellitus	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3476
AESI PT: Type 1 diabetes mellitus	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3476
AESI GT: Hyperthyroid events	402	9 (2.2)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	2.86	0.85, 12.90	0.0997
AESI PT: Hyperthyroidism	402	8 (2.0)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	2.56	0.74, 11.72	0.1499
AESI PT: Immune-mediated hyperthyroidism	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3579

The time to event endpoint is the time to first AESI or the time to censoring if the AESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AESIs with an onset date on or after the date of first dose and AESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.5 TOPAZ: Summary of analysis of time to first occurrence of adverse events of special interest (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI GT: Hypophysitis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.4232
AESI PT: Hypothalamic pituitary adrenal axis suppression	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.4232
AESI GT: Hypothyroid events	402	29 (7.2)	NE (NE, NE)	403	14 (3.5)	NE (NE, NE)	1.91	1.03, 3.74	0.0433*
AESI PT: Hypothyroidism	402	27 (6.7)	NE (NE, NE)	403	14 (3.5)	NE (NE, NE)	1.78	0.94, 3.49	0.0779
AESI PT: Immune-mediated hypothyroidism	402	2 (0.5)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.1858
AESI GT: Thyroiditis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3173
AESI PT: Autoimmune thyroiditis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3173
AESI GT: Renal events	402	0	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	NC	NC	0.0284*
AESI PT: Nephritis	402	0	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	NC	NC	0.0284*
AESI GT: Dermatitis/Rash	402	81 (20.1)	NE (NE, NE)	403	51 (12.7)	NE (NE, NE)	1.56	1.10, 2.23	0.0121*
AESI PT: Rash	402	47 (11.7)	NE (NE, NE)	403	34 (8.4)	NE (NE, NE)	1.34	0.86, 2.10	0.1927
AESI PT: Rash maculo-papular	402	20 (5.0)	NE (NE, NE)	403	9 (2.2)	NE (NE, NE)	2.10	0.98, 4.87	0.0596

The time to event endpoint is the time to first AESI or the time to censoring if the AESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AESIs with an onset date on or after the date of first dose and AESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.5 TOPAZ: Summary of analysis of time to first occurrence of adverse events of special interest (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI PT: Rash pruritic	402	2 (0.5)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	0.59	0.08, 3.56	0.5569
AESI PT: Rash morbilliform	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3405
AESI PT: Rash papular	402	2 (0.5)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	2.03	0.19, 43.65	0.5551
AESI PT: Rash pustular	402	3 (0.7)	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	1.49	0.25, 11.33	0.6588
AESI PT: Dermatitis	402	7 (1.7)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	6.52	1.16,121.92	0.0432*
AESI PT: Dermatitis bullous	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3155
AESI PT: Eczema	402	6 (1.5)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	4.18	0.69, 79.79	0.1560
AESI PT: Rash erythematous	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.2804
AESI PT: Rash macular	402	2 (0.5)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	2.02	0.19, 43.50	0.5570
AESI PT: Dermatitis psoriasiform	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3769
AESI PT: Psoriasis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.2864
AESI PT: Urticarial dermatitis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.5271

The time to event endpoint is the time to first AESI or the time to censoring if the AESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AESIs with an onset date on or after the date of first dose and AESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.5 TOPAZ: Summary of analysis of time to first occurrence of adverse events of special interest (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI GT: Pancreatic events	402	5 (1.2)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	1.17	0.28, 5.84	0.8351
AESI PT: Pancreatitis	402	4 (1.0)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	1.00	0.21, 5.22	0.9975
AESI PT: Pancreatitis acute	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.5380
AESI GT: Myositis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3147
AESI PT: Polymyositis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3147
AESI GT: Infusion/hypersensitivity reactions	402	15 (3.7)	NE (NE, NE)	403	10 (2.5)	NE (NE, NE)	1.39	0.63, 3.20	0.4233
AESI PT: Anaphylactic shock	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3023
AESI PT: Drug hypersensitivity	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3622
AESI PT: Drug eruption	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3185
AESI PT: Infusion related reaction	402	5 (1.2)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	1.65	0.40, 8.04	0.4890
AESI PT: Type I hypersensitivity	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3197

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[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.5 TOPAZ: Summary of analysis of time to first occurrence of adverse events of special interest (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI PT: Urticaria	402	9 (2.2)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	1.98	0.64, 7.37	0.2487
AESI GT: Other rare/miscellaneous	402	2 (0.5)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.1771
AESI PT: Immune-mediated arthritis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3167
AESI PT: Vitiligo	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3642
AESI GT: Hepatic SMQ AEs	402	138 (34.3)	NE (NE, NE)	403	130 (32.3)	NE (NE, NE)	1.01	0.79, 1.28	0.9548
AESI PT: Alanine aminotransferase increased	402	48 (11.9)	NE (NE, NE)	403	50 (12.4)	NE (NE, NE)	0.90	0.60, 1.34	0.5955
AESI PT: Blood alkaline phosphatase increased	402	20 (5.0)	NE (NE, NE)	403	23 (5.7)	NE (NE, NE)	0.79	0.43, 1.45	0.4444
AESI PT: Drug-induced liver injury	402	0	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	NC	NC	0.1611
AESI PT: Aspartate aminotransferase increased	402	42 (10.4)	NE (NE, NE)	403	47 (11.7)	NE (NE, NE)	0.83	0.54, 1.26	0.3787
AESI PT: Ascites	402	17 (4.2)	NE (NE, NE)	403	14 (3.5)	NE (NE, NE)	1.15	0.56, 2.37	0.7039

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	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI PT: Autoimmune hepatitis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.0961
AESI PT: Blood bilirubin increased	402	18 (4.5)	NE (NE, NE)	403	33 (8.2)	NE (NE, NE)	0.49	0.27, 0.85	0.0123*
AESI PT: Blood bilirubin unconjugated increased	402	1 (0.2)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	0.91	0.04, 23.13	0.9494
AESI PT: Bilirubin conjugated increased	402	2 (0.5)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	0.50	0.07, 2.58	0.4189
AESI PT: Cholestasis	402	1 (0.2)	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	0.30	0.01, 3.40	0.3234
AESI PT: Blood cholinesterase decreased	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3160
AESI PT: Total bile acids increased	402	3 (0.7)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	3.03	0.39, 61.31	0.3118
AESI PT: Gamma-glutamyltransferase increased	402	20 (5.0)	NE (NE, NE)	403	23 (5.7)	NE (NE, NE)	0.78	0.42, 1.42	0.4135
AESI PT: Jaundice cholestatic	402	8 (2.0)	NE (NE, NE)	403	6 (1.5)	NE (NE, NE)	1.23	0.43, 3.75	0.7003
AESI PT: Hepatic encephalopathy	402	2 (0.5)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	1.82	0.17, 39.23	0.6216

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Table 3.2.5 TOPAZ: Summary of analysis of time to first occurrence of adverse events of special interest (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI PT: Hepatic cytolysis	402	4 (1.0)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.0597
AESI PT: Hepatitis	402	3 (0.7)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	3.00	0.38, 60.71	0.3166
AESI PT: Hepatitis B	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3219
AESI PT: Hepatitis E	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3167
AESI PT: Hepatorenal failure	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3180
AESI PT: Hypoalbuminaemia	402	29 (7.2)	NE (NE, NE)	403	25 (6.2)	NE (NE, NE)	1.11	0.65, 1.91	0.7026
AESI PT: Hyperbilirubinaemia	402	3 (0.7)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	0.73	0.14, 3.31	0.6770
AESI PT: Hypertransaminasaemia	402	2 (0.5)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.1659
AESI PT: Jaundice	402	2 (0.5)	NE (NE, NE)	403	6 (1.5)	NE (NE, NE)	0.26	0.04, 1.14	0.0780
AESI PT: Immune-mediated hepatitis	402	2 (0.5)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.1550
AESI PT: International normalised ratio increased	402	1 (0.2)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	1.00	0.04, 25.19	0.9983

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Hazard ratio <1 favours durvalumab. * p<0.05.

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Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI PT: Liver abscess	402	2 (0.5)	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	0.76	0.09, 6.57	0.7910
AESI PT: Hepatic enzyme increased	402	2 (0.5)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.1578
AESI PT: Hepatic function abnormal	402	7 (1.7)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	1.39	0.41, 5.39	0.5995
AESI PT: Liver function test abnormal	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3167
AESI PT: Liver function test increased	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.4671
AESI PT: Hepatotoxicity	402	1 (0.2)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	0.98	0.04, 24.87	0.9912
AESI PT: Liver injury	402	2 (0.5)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	0.65	0.09, 3.95	0.6394
AESI PT: Hepatic failure	402	3 (0.7)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	2.61	0.33, 52.97	0.3895
AESI PT: Oesophageal varices haemorrhage	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3111
AESI PT: Prothrombin level decreased	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3161
AESI PT: Prothrombin time prolonged	402	2 (0.5)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.2447

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	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI PT: Prothrombin time ratio increased	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3161
AESI PT: Hepatitis B reactivation	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3093
AESI PT: Transaminases increased	402	5 (1.2)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	1.26	0.33, 5.09	0.7288
AESI GT: Biliary SMQ AEs	402	106 (26.4)	NE (NE, NE)	403	101 (25.1)	NE (NE, NE)	0.96	0.73, 1.27	0.7780
AESI PT: Cholangitis acute	402	4 (1.0)	NE (NE, NE)	403	6 (1.5)	NE (NE, NE)	0.58	0.14, 2.05	0.3956
AESI PT: Cholecystitis acute	402	1 (0.2)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	1.01	0.04, 25.58	0.9930
AESI PT: Blood alkaline phosphatase increased	402	20 (5.0)	NE (NE, NE)	403	23 (5.7)	NE (NE, NE)	0.79	0.43, 1.45	0.4444
AESI PT: Biliary obstruction	402	12 (3.0)	NE (NE, NE)	403	10 (2.5)	NE (NE, NE)	0.96	0.41, 2.30	0.9241
AESI PT: Biliary abscess	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.2943
AESI PT: Biliary sepsis	402	5 (1.2)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	1.00	0.26, 4.10	0.9985
AESI PT: Blood bilirubin increased	402	18 (4.5)	NE (NE, NE)	403	33 (8.2)	NE (NE, NE)	0.49	0.27, 0.85	0.0123*

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AESI PT: Blood bilirubin unconjugated increased	402	1 (0.2)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	0.91	0.04, 23.13	0.9494
AESI PT: Bilirubin conjugated increased	402	2 (0.5)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	0.50	0.07, 2.58	0.4189
AESI PT: Cholangitis	402	30 (7.5)	NE (NE, NE)	403	19 (4.7)	NE (NE, NE)	1.45	0.82, 2.63	0.2046
AESI PT: Cholangitis infective	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.2207
AESI PT: Cholelithiasis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3155
AESI PT: Cholestasis	402	1 (0.2)	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	0.30	0.01, 3.40	0.3234
AESI PT: Cholecystitis	402	7 (1.7)	NE (NE, NE)	403	5 (1.2)	NE (NE, NE)	1.36	0.43, 4.60	0.5966
AESI PT: Gallbladder empyema	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.2597
AESI PT: Gallbladder obstruction	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3186
AESI PT: Biliary tract infection	402	19 (4.7)	NE (NE, NE)	403	10 (2.5)	NE (NE, NE)	1.70	0.80, 3.84	0.1747
AESI PT: Post procedural bile leak	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.5271

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	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI PT: Jaundice cholestatic	402	8 (2.0)	NE (NE, NE)	403	6 (1.5)	NE (NE, NE)	1.23	0.43, 3.75	0.7003
AESI PT: Hyperbilirubinaemia	402	3 (0.7)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	0.73	0.14, 3.31	0.6770
AESI PT: Jaundice	402	2 (0.5)	NE (NE, NE)	403	6 (1.5)	NE (NE, NE)	0.26	0.04, 1.14	0.0780
AESI PT: Gallbladder rupture	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3147
AESI PT: Biloma rupture	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3043
AESI GT: Haematopoietic cytopenias SMQ AEs	402	324 (80.6)	1.3 (1.0, 1.6)	403	323 (80.1)	1.0 (1.0, 1.6)	0.96	0.83, 1.12	0.6584
AESI PT: Anaemia	402	212 (52.7)	4.4 (3.4, 5.8)	403	196 (48.6)	5.2 (3.5, NE)	1.09	0.90, 1.33	0.3811
AESI PT: Bicytopenia	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3186
AESI PT: Red blood cell count decreased	402	2 (0.5)	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	1.01	0.12, 8.38	0.9949
AESI PT: Febrile neutropenia	402	4 (1.0)	NE (NE, NE)	403	6 (1.5)	NE (NE, NE)	0.67	0.17, 2.33	0.5276
AESI PT: Granulocyte count decreased	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3323

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AESI PT: Haematocrit decreased	402	2 (0.5)	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	1.01	0.12, 8.44	0.9900
AESI PT: Haemoglobin decreased	402	3 (0.7)	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	1.51	0.25, 11.43	0.6516
AESI PT: Leukopenia	402	26 (6.5)	NE (NE, NE)	403	21 (5.2)	NE (NE, NE)	1.24	0.70, 2.23	0.4587
AESI PT: White blood cell count decreased	402	69 (17.2)	NE (NE, NE)	403	81 (20.1)	NE (NE, NE)	0.83	0.60, 1.15	0.2641
AESI PT: Lymphopenia	402	5 (1.2)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	1.69	0.41, 8.22	0.4694
AESI PT: Lymphocyte percentage decreased	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3198
AESI PT: Lymphocyte count decreased	402	10 (2.5)	NE (NE, NE)	403	14 (3.5)	NE (NE, NE)	0.68	0.29, 1.53	0.3583
AESI PT: Monocyte count decreased	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3179
AESI PT: Myelosuppression	402	8 (2.0)	NE (NE, NE)	403	8 (2.0)	NE (NE, NE)	0.99	0.37, 2.70	0.9884
AESI PT: Neutropenia	402	111 (27.6)	NE (NE, NE)	403	104 (25.8)	NE (NE, NE)	1.07	0.82, 1.39	0.6356
AESI PT: Neutropenic sepsis	402	2 (0.5)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.1644

The time to event endpoint is the time to first AESI or the time to censoring if the AESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AESIs with an onset date on or after the date of first dose and AESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.5 TOPAZ: Summary of analysis of time to first occurrence of adverse events of special interest (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI PT: Neutrophil count decreased	402	119 (29.6)	NE (NE, NE)	403	143 (35.5)	NE (NE, NE)	0.80	0.63, 1.02	0.0764
AESI PT: Pancytopenia	402	2 (0.5)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	2.02	0.19, 43.39	0.5585
AESI PT: Platelet count decreased	402	99 (24.6)	NE (NE, NE)	403	111 (27.5)	NE (NE, NE)	0.84	0.64, 1.10	0.1956
AESI PT: Thrombocytopenia	402	45 (11.2)	NE (NE, NE)	403	49 (12.2)	NE (NE, NE)	0.89	0.59, 1.33	0.5566

The time to event endpoint is the time to first AESI or the time to censoring if the AESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AESIs with an onset date on or after the date of first dose and AESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.6 TOPAZ: Summary of analysis of time to first occurrence of adverse events of special interest with max. CTCAE grade >=3 (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI max CTCAE grade >=3	402	265 (65.9)	2.8 (2.4, 3.5)	403	264 (65.5)	2.5 (2.3, 3.1)	0.94	0.80, 1.12	0.5349
AESI G>=3 GT: Pneumonitis	402	1 (0.2)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	1.01	0.04, 25.39	0.9972
AESI G>=3 PT: Pneumonitis	402	1 (0.2)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	1.01	0.04, 25.39	0.9972
AESI G>=3 GT: Hepatic events	402	2 (0.5)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	0.55	0.07, 3.40	0.5106
AESI G>=3 PT: Drug-induced liver injury	402	0	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	NC	NC	0.1611
AESI G>=3 PT: Autoimmune hepatitis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.0961
AESI G>=3 PT: Hepatitis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3167
AESI G>=3 PT: Immune-mediated hepatitis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3149
AESI G>=3 GT: Diarrhoea/Colitis	402	5 (1.2)	NE (NE, NE)	403	7 (1.7)	NE (NE, NE)	0.70	0.21, 2.20	0.5459
AESI G>=3 PT: Diarrhoea	402	4 (1.0)	NE (NE, NE)	403	6 (1.5)	NE (NE, NE)	0.65	0.17, 2.29	0.5078
AESI G>=3 PT: Immune-mediated enterocolitis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3160

The time to event endpoint is the time to first AESI or the time to censoring if the AESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AESIs with an onset date on or after the date of first dose and AESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.6 TOPAZ: Summary of analysis of time to first occurrence of adverse events of special interest with max. CTCAE grade >=3 (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI G>=3 PT: Colitis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3117
AESI G>=3 GT: Dermatitis/Rash	402	3 (0.7)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	3.03	0.39, 61.16	0.3131
AESI G>=3 PT: Rash	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3197
AESI G>=3 PT: Rash maculo-papular	402	3 (0.7)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.0821
AESI G>=3 GT: Pancreatic events	402	2 (0.5)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.1567
AESI G>=3 PT: Pancreatitis	402	2 (0.5)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.1567
AESI G>=3 GT: Myositis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3147
AESI G>=3 PT: Polymyositis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3147
AESI G>=3 GT: Infusion/hypersensitivity reactions	402	2 (0.5)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	1.87	0.18, 40.18	0.6049
AESI G>=3 PT: Anaphylactic shock	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3023

The time to event endpoint is the time to first AESI or the time to censoring if the AESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AESIs with an onset date on or after the date of first dose and AESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.6 TOPAZ: Summary of analysis of time to first occurrence of adverse events of special interest with max. CTCAE grade >=3 (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI G>=3 PT: Drug hypersensitivity	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3622
AESI G>=3 PT: Urticaria	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3103
AESI G>=3 GT: Other rare/miscellaneous	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3167
AESI G>=3 PT: Immune-mediated arthritis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3167
AESI G>=3 GT: Hepatic SMQ AEs	402	48 (11.9)	NE (NE, NE)	403	51 (12.7)	NE (NE, NE)	0.83	0.56, 1.24	0.3634
AESI G>=3 PT: Alanine aminotransferase increased	402	8 (2.0)	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	3.34	0.82, 22.33	0.1093
AESI G>=3 PT: Blood alkaline phosphatase increased	402	2 (0.5)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	0.62	0.08, 3.74	0.5941
AESI G>=3 PT: Drug-induced liver injury	402	0	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	NC	NC	0.1611
AESI G>=3 PT: Aspartate aminotransferase increased	402	5 (1.2)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	1.40	0.33, 6.97	0.6509
AESI G>=3 PT: Ascites	402	7 (1.7)	NE (NE, NE)	403	9 (2.2)	NE (NE, NE)	0.74	0.26, 1.99	0.5532

The time to event endpoint is the time to first AESI or the time to censoring if the AESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AESIs with an onset date on or after the date of first dose and AESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.6 TOPAZ: Summary of analysis of time to first occurrence of adverse events of special interest with max. CTCAE grade >=3 (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI G>=3 PT: Autoimmune hepatitis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.0961
AESI G>=3 PT: Blood bilirubin increased	402	6 (1.5)	NE (NE, NE)	403	12 (3.0)	NE (NE, NE)	0.43	0.15, 1.12	0.0877
AESI G>=3 PT: Bilirubin conjugated increased	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3185
AESI G>=3 PT: Cholestasis	402	1 (0.2)	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	0.30	0.01, 3.40	0.3234
AESI G>=3 PT: Gamma-glutamyltransferase increased	402	4 (1.0)	NE (NE, NE)	403	8 (2.0)	NE (NE, NE)	0.48	0.13, 1.51	0.2149
AESI G>=3 PT: Jaundice cholestatic	402	7 (1.7)	NE (NE, NE)	403	5 (1.2)	NE (NE, NE)	1.27	0.40, 4.30	0.6819
AESI G>=3 PT: Hepatic encephalopathy	402	1 (0.2)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	0.86	0.03, 21.86	0.9147
AESI G>=3 PT: Hepatic cytolysis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.4652
AESI G>=3 PT: Hepatitis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3167
AESI G>=3 PT: Hypoalbuminaemia	402	0	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	NC	NC	0.1586

The time to event endpoint is the time to first AESI or the time to censoring if the AESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AESIs with an onset date on or after the date of first dose and AESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.6 TOPAZ: Summary of analysis of time to first occurrence of adverse events of special interest with max. CTCAE grade >=3 (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI G>=3 PT: Hyperbilirubinaemia	402	2 (0.5)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	0.60	0.08, 3.66	0.5782
AESI G>=3 PT: Jaundice	402	2 (0.5)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	0.36	0.05, 1.86	0.2201
AESI G>=3 PT: Immune-mediated hepatitis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3149
AESI G>=3 PT: Liver abscess	402	2 (0.5)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	1.47	0.13, 32.60	0.7568
AESI G>=3 PT: Hepatic enzyme increased	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3161
AESI G>=3 PT: Hepatic function abnormal	402	2 (0.5)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.2429
AESI G>=3 PT: Liver function test increased	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.4671
AESI G>=3 PT: Liver injury	402	2 (0.5)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	1.94	0.19, 41.66	0.5827
AESI G>=3 PT: Hepatic failure	402	3 (0.7)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	2.62	0.33, 53.08	0.3884
AESI G>=3 PT: Oesophageal varices haemorrhage	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3111

The time to event endpoint is the time to first AESI or the time to censoring if the AESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AESIs with an onset date on or after the date of first dose and AESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.6 TOPAZ: Summary of analysis of time to first occurrence of adverse events of special interest with max. CTCAE grade >=3 (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI G>=3 PT: Transaminases increased	402	2 (0.5)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	2.02	0.19, 43.40	0.5584
AESI G>=3 GT: Biliary SMQ AEs	402	61 (15.2)	NE (NE, NE)	403	59 (14.6)	NE (NE, NE)	0.93	0.65, 1.34	0.7139
AESI G>=3 PT: Cholangitis acute	402	4 (1.0)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	0.96	0.23, 4.08	0.9587
AESI G>=3 PT: Cholecystitis acute	402	1 (0.2)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	1.01	0.04, 25.58	0.9930
AESI G>=3 PT: Blood alkaline phosphatase increased	402	2 (0.5)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	0.62	0.08, 3.74	0.5941
AESI G>=3 PT: Biliary obstruction	402	7 (1.7)	NE (NE, NE)	403	8 (2.0)	NE (NE, NE)	0.67	0.23, 1.91	0.4523
AESI G>=3 PT: Biliary abscess	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.2943
AESI G>=3 PT: Biliary sepsis	402	5 (1.2)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	1.00	0.26, 4.10	0.9985
AESI G>=3 PT: Blood bilirubin increased	402	6 (1.5)	NE (NE, NE)	403	12 (3.0)	NE (NE, NE)	0.43	0.15, 1.12	0.0877
AESI G>=3 PT: Bilirubin conjugated increased	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3185

The time to event endpoint is the time to first AESI or the time to censoring if the AESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AESIs with an onset date on or after the date of first dose and AESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.6 TOPAZ: Summary of analysis of time to first occurrence of adverse events of special interest with max. CTCAE grade >=3 (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI G>=3 PT: Cholangitis	402	23 (5.7)	NE (NE, NE)	403	11 (2.7)	NE (NE, NE)	1.95	0.97, 4.16	0.0651
AESI G>=3 PT: Cholangitis infective	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.2207
AESI G>=3 PT: Cholestasis	402	1 (0.2)	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	0.30	0.01, 3.40	0.3234
AESI G>=3 PT: Cholecystitis	402	3 (0.7)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	0.71	0.14, 3.22	0.6521
AESI G>=3 PT: Gallbladder empyema	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.2597
AESI G>=3 PT: Gallbladder obstruction	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3186
AESI G>=3 PT: Biliary tract infection	402	15 (3.7)	NE (NE, NE)	403	9 (2.2)	NE (NE, NE)	1.45	0.64, 3.50	0.3811
AESI G>=3 PT: Jaundice cholestatic	402	7 (1.7)	NE (NE, NE)	403	5 (1.2)	NE (NE, NE)	1.27	0.40, 4.30	0.6819
AESI G>=3 PT: Hyperbilirubinaemia	402	2 (0.5)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	0.60	0.08, 3.66	0.5782
AESI G>=3 PT: Jaundice	402	2 (0.5)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	0.36	0.05, 1.86	0.2201
AESI G>=3 PT: Gallbladder rupture	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3147

The time to event endpoint is the time to first AESI or the time to censoring if the AESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AESIs with an onset date on or after the date of first dose and AESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.6 TOPAZ: Summary of analysis of time to first occurrence of adverse events of special interest with max. CTCAE grade >=3 (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI G>=3 PT: Biloma rupture	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3043
AESI G>=3 GT: Haematopoietic cytopenias SMQ AEs	402	236 (58.7)	3.5 (2.8, 4.3)	403	238 (59.1)	3.1 (2.5, 3.9)	0.93	0.78, 1.12	0.4527
AESI G>=3 PT: Anaemia	402	104 (25.9)	NE (NE, NE)	403	97 (24.1)	23.6 (23.6, NE)	1.04	0.78, 1.37	0.8061
AESI G>=3 PT: Bicytopenia	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3186
AESI G>=3 PT: Febrile neutropenia	402	4 (1.0)	NE (NE, NE)	403	6 (1.5)	NE (NE, NE)	0.67	0.17, 2.33	0.5276
AESI G>=3 PT: Haemoglobin decreased	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3149
AESI G>=3 PT: Leukopenia	402	9 (2.2)	NE (NE, NE)	403	5 (1.2)	NE (NE, NE)	1.81	0.63, 5.90	0.2784
AESI G>=3 PT: White blood cell count decreased	402	28 (7.0)	NE (NE, NE)	403	29 (7.2)	NE (NE, NE)	0.96	0.57, 1.62	0.8881
AESI G>=3 PT: Lymphopenia	402	2 (0.5)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	2.01	0.19, 43.19	0.5612
AESI G>=3 PT: Lymphocyte count decreased	402	2 (0.5)	NE (NE, NE)	403	5 (1.2)	NE (NE, NE)	0.40	0.06, 1.85	0.2552
AESI G>=3 PT: Myelosuppression	402	6 (1.5)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	1.48	0.42, 5.78	0.5439

The time to event endpoint is the time to first AESI or the time to censoring if the AESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AESIs with an onset date on or after the date of first dose and AESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.6 TOPAZ: Summary of analysis of time to first occurrence of adverse events of special interest with max. CTCAE grade >=3 (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
AESI G>=3 PT: Neutropenia	402	69 (17.2)	NE (NE, NE)	403	73 (18.1)	NE (NE, NE)	0.93	0.67, 1.29	0.6616
AESI G>=3 PT: Neutropenic sepsis	402	2 (0.5)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.1644
AESI G>=3 PT: Neutrophil count decreased	402	91 (22.6)	NE (NE, NE)	403	108 (26.8)	NE (NE, NE)	0.82	0.62, 1.08	0.1553
AESI G>=3 PT: Pancytopenia	402	2 (0.5)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	2.02	0.19, 43.39	0.5585
AESI G>=3 PT: Platelet count decreased	402	44 (10.9)	NE (NE, NE)	403	43 (10.7)	NE (NE, NE)	1.01	0.66, 1.54	0.9727
AESI G>=3 PT: Thrombocytopenia	402	16 (4.0)	NE (NE, NE)	403	19 (4.7)	NE (NE, NE)	0.81	0.41, 1.58	0.5412

The time to event endpoint is the time to first AESI or the time to censoring if the AESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes AESIs with an onset date on or after the date of first dose and AESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.7 TOPAZ: Summary of analysis of time to first occurrence of serious adverse events of special interest (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
SAESI	402	103 (25.6)	NE (NE, NE)	403	94 (23.3)	NE (NE, NE)	1.05	0.79, 1.39	0.7463
SAESI GT: Pneumonitis	402	4 (1.0)	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	1.91	0.37, 13.81	0.4471
SAESI PT: Immune-mediated lung disease	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3155
SAESI PT: Interstitial lung disease	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3974
SAESI PT: Pneumonitis	402	2 (0.5)	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	1.01	0.12, 8.39	0.9940
SAESI GT: Hepatic events	402	1 (0.2)	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	0.35	0.02, 3.82	0.3802
SAESI PT: Drug-induced liver injury	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3192
SAESI PT: Autoimmune hepatitis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.0961
SAESI PT: Hepatitis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3167
SAESI GT: Diarrhoea/Colitis	402	4 (1.0)	NE (NE, NE)	403	6 (1.5)	NE (NE, NE)	0.64	0.16, 2.25	0.4877
SAESI PT: Diarrhoea	402	4 (1.0)	NE (NE, NE)	403	5 (1.2)	NE (NE, NE)	0.77	0.19, 2.90	0.6927

The time to event endpoint is the time to first SAESI or the time to censoring if the SAESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes SAESIs with an onset date on or after the date of first dose and SAESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.7 TOPAZ: Summary of analysis of time to first occurrence of serious adverse events of special interest (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
SAESI PT: Immune-mediated enterocolitis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3160
SAESI GT: Adrenal insufficiency	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.4106
SAESI PT: Adrenal insufficiency	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.4106
SAESI GT: Dermatitis/Rash	402	1 (0.2)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	1.01	0.04, 25.46	0.9957
SAESI PT: Rash	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3197
SAESI PT: Rash maculo-papular	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3155
SAESI GT: Pancreatic events	402	3 (0.7)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.1269
SAESI PT: Pancreatitis	402	2 (0.5)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.1567
SAESI PT: Pancreatitis acute	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.5380
SAESI GT: Myositis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3147
SAESI PT: Polymyositis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3147

The time to event endpoint is the time to first SAESI or the time to censoring if the SAESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes SAESIs with an onset date on or after the date of first dose and SAESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.7 TOPAZ: Summary of analysis of time to first occurrence of serious adverse events of special interest (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
SAESI GT: Infusion/hypersensitivity reactions	402	1 (0.2)	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	0.49	0.02, 5.12	0.5525
SAESI PT: Anaphylactic shock	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3023
SAESI PT: Infusion related reaction	402	1 (0.2)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	1.00	0.04, 25.33	0.9986
SAESI GT: Other rare/miscellaneous	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3167
SAESI PT: Immune-mediated arthritis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3167
SAESI GT: Hepatic SMQ AEs	402	26 (6.5)	NE (NE, NE)	403	28 (6.9)	NE (NE, NE)	0.81	0.47, 1.39	0.4438
SAESI PT: Alanine aminotransferase increased	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3185
SAESI PT: Drug-induced liver injury	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3192
SAESI PT: Ascites	402	4 (1.0)	NE (NE, NE)	403	7 (1.7)	NE (NE, NE)	0.55	0.14, 1.82	0.3329
SAESI PT: Autoimmune hepatitis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.0961

The time to event endpoint is the time to first SAESI or the time to censoring if the SAESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes SAESIs with an onset date on or after the date of first dose and SAESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.7 TOPAZ: Summary of analysis of time to first occurrence of serious adverse events of special interest (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
SAESI PT: Blood bilirubin increased	402	1 (0.2)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	0.23	0.01, 1.53	0.1453
SAESI PT: Cholestasis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.0679
SAESI PT: Jaundice cholestatic	402	7 (1.7)	NE (NE, NE)	403	5 (1.2)	NE (NE, NE)	1.30	0.41, 4.39	0.6558
SAESI PT: Hepatic encephalopathy	402	1 (0.2)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	0.85	0.03, 21.56	0.9075
SAESI PT: Hepatic cytolysis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.4652
SAESI PT: Hepatitis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3167
SAESI PT: Hypoalbuminaemia	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3160
SAESI PT: Hyperbilirubinaemia	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3161
SAESI PT: Jaundice	402	2 (0.5)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	0.47	0.06, 2.94	0.4111
SAESI PT: Liver abscess	402	2 (0.5)	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	0.76	0.09, 6.57	0.7910
SAESI PT: Hepatic function abnormal	402	3 (0.7)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	2.50	0.32, 50.76	0.4132

The time to event endpoint is the time to first SAESI or the time to censoring if the SAESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes SAESIs with an onset date on or after the date of first dose and SAESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.7 TOPAZ: Summary of analysis of time to first occurrence of serious adverse events of special interest (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
SAESI PT: Liver function test increased	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.4671
SAESI PT: Liver injury	402	1 (0.2)	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	0.50	0.02, 5.23	0.5653
SAESI PT: Hepatic failure	402	3 (0.7)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	2.62	0.33, 53.08	0.3884
SAESI PT: Oesophageal varices haemorrhage	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3111
SAESI GT: Biliary SMQ AEs	402	55 (13.7)	NE (NE, NE)	403	54 (13.4)	NE (NE, NE)	0.93	0.64, 1.36	0.7154
SAESI PT: Cholangitis acute	402	4 (1.0)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	0.96	0.23, 4.08	0.9587
SAESI PT: Cholecystitis acute	402	1 (0.2)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	1.01	0.04, 25.58	0.9930
SAESI PT: Biliary obstruction	402	7 (1.7)	NE (NE, NE)	403	7 (1.7)	NE (NE, NE)	0.82	0.28, 2.44	0.7171
SAESI PT: Biliary abscess	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.2943
SAESI PT: Biliary sepsis	402	4 (1.0)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	1.00	0.22, 5.17	0.9981
SAESI PT: Blood bilirubin increased	402	1 (0.2)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	0.23	0.01, 1.53	0.1453
SAESI PT: Cholangitis	402	26 (6.5)	NE (NE, NE)	403	17 (4.2)	NE (NE, NE)	1.41	0.77, 2.65	0.2691

The time to event endpoint is the time to first SAESI or the time to censoring if the SAESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes SAESIs with an onset date on or after the date of first dose and SAESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.7 TOPAZ: Summary of analysis of time to first occurrence of serious adverse events of special interest (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
SAESI PT: Cholangitis infective	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.2207
SAESI PT: Cholestasis	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.0679
SAESI PT: Cholecystitis	402	2 (0.5)	NE (NE, NE)	403	5 (1.2)	NE (NE, NE)	0.38	0.05, 1.74	0.2231
SAESI PT: Gallbladder empyema	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.2597
SAESI PT: Gallbladder obstruction	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3186
SAESI PT: Biliary tract infection	402	8 (2.0)	NE (NE, NE)	403	10 (2.5)	NE (NE, NE)	0.74	0.28, 1.88	0.5234
SAESI PT: Jaundice cholestatic	402	7 (1.7)	NE (NE, NE)	403	5 (1.2)	NE (NE, NE)	1.30	0.41, 4.39	0.6558
SAESI PT: Hyperbilirubinaemia	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3161
SAESI PT: Jaundice	402	2 (0.5)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	0.47	0.06, 2.94	0.4111
SAESI PT: Gallbladder rupture	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3147
SAESI PT: Biloma rupture	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3043

The time to event endpoint is the time to first SAESI or the time to censoring if the SAESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes SAESIs with an onset date on or after the date of first dose and SAESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.7 TOPAZ: Summary of analysis of time to first occurrence of serious adverse events of special interest (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
SAESI GT: Haematopoietic cytopenias SMQ AEs	402	34 (8.5)	NE (NE, NE)	403	26 (6.5)	NE (NE, NE)	1.33	0.80, 2.23	0.2749
SAESI PT: Anaemia	402	14 (3.5)	NE (NE, NE)	403	5 (1.2)	NE (NE, NE)	2.85	1.09, 8.82	0.0355*
SAESI PT: Bicytopenia	402	0	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	NC	NC	0.3186
SAESI PT: Febrile neutropenia	402	4 (1.0)	NE (NE, NE)	403	5 (1.2)	NE (NE, NE)	0.80	0.20, 3.03	0.7409
SAESI PT: White blood cell count decreased	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3117
SAESI PT: Myelosuppression	402	4 (1.0)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	1.29	0.28, 6.56	0.7369
SAESI PT: Neutropenia	402	2 (0.5)	NE (NE, NE)	403	3 (0.7)	NE (NE, NE)	0.65	0.09, 3.90	0.6297
SAESI PT: Neutropenic sepsis	402	1 (0.2)	NE (NE, NE)	403	0	NE (NE, NE)	NC	NC	0.3161
SAESI PT: Neutrophil count decreased	402	3 (0.7)	NE (NE, NE)	403	2 (0.5)	NE (NE, NE)	1.52	0.25, 11.57	0.6418
SAESI PT: Pancytopenia	402	2 (0.5)	NE (NE, NE)	403	1 (0.2)	NE (NE, NE)	2.02	0.19, 43.39	0.5585
SAESI PT: Platelet count decreased	402	5 (1.2)	NE (NE, NE)	403	6 (1.5)	NE (NE, NE)	0.83	0.24, 2.75	0.7555

The time to event endpoint is the time to first SAESI or the time to censoring if the SAESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes SAESIs with an onset date on or after the date of first dose and SAESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.

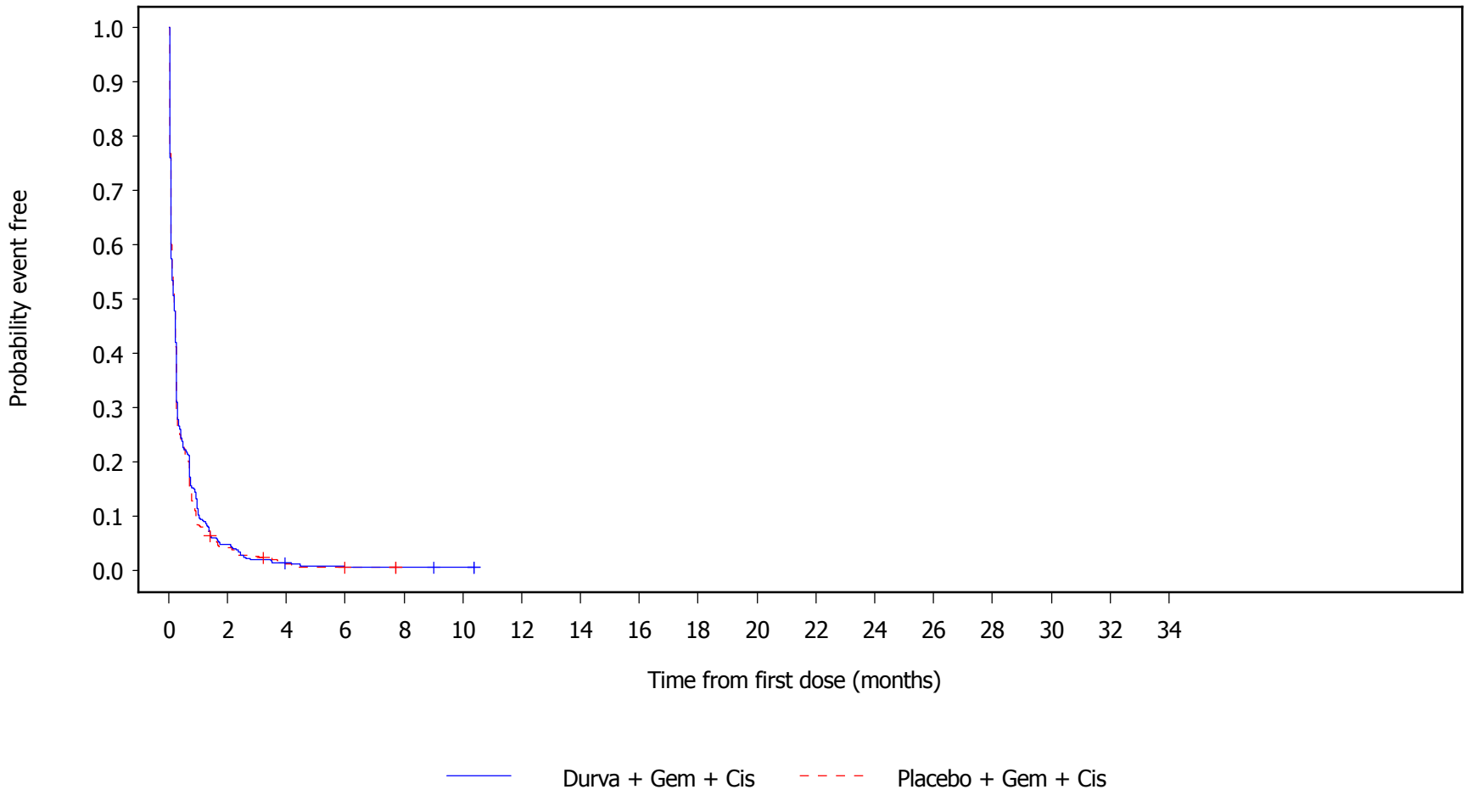
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

Table 3.2.7 TOPAZ: Summary of analysis of time to first occurrence of serious adverse events of special interest (total, and by grouped or preferred terms)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [c]
SAESI PT: Thrombocytopenia	402	3 (0.7)	NE (NE, NE)	403	4 (1.0)	NE (NE, NE)	0.77	0.15, 3.47	0.7258

The time to event endpoint is the time to first SAESI or the time to censoring if the SAESI has not occurred by 90 days following the date of last dose of durvalumab/placebo. Includes SAESIs with an onset date on or after the date of first dose and SAESIs with onset date prior to dosing which worsen after dosing, up to and including 90 days following the date of last dose or up to first subsequent therapy (whichever comes first). MedDRA version 24.0.
[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. [c] Determined using log-rank test.
Hazard ratio <1 favours durvalumab. * p<0.05.

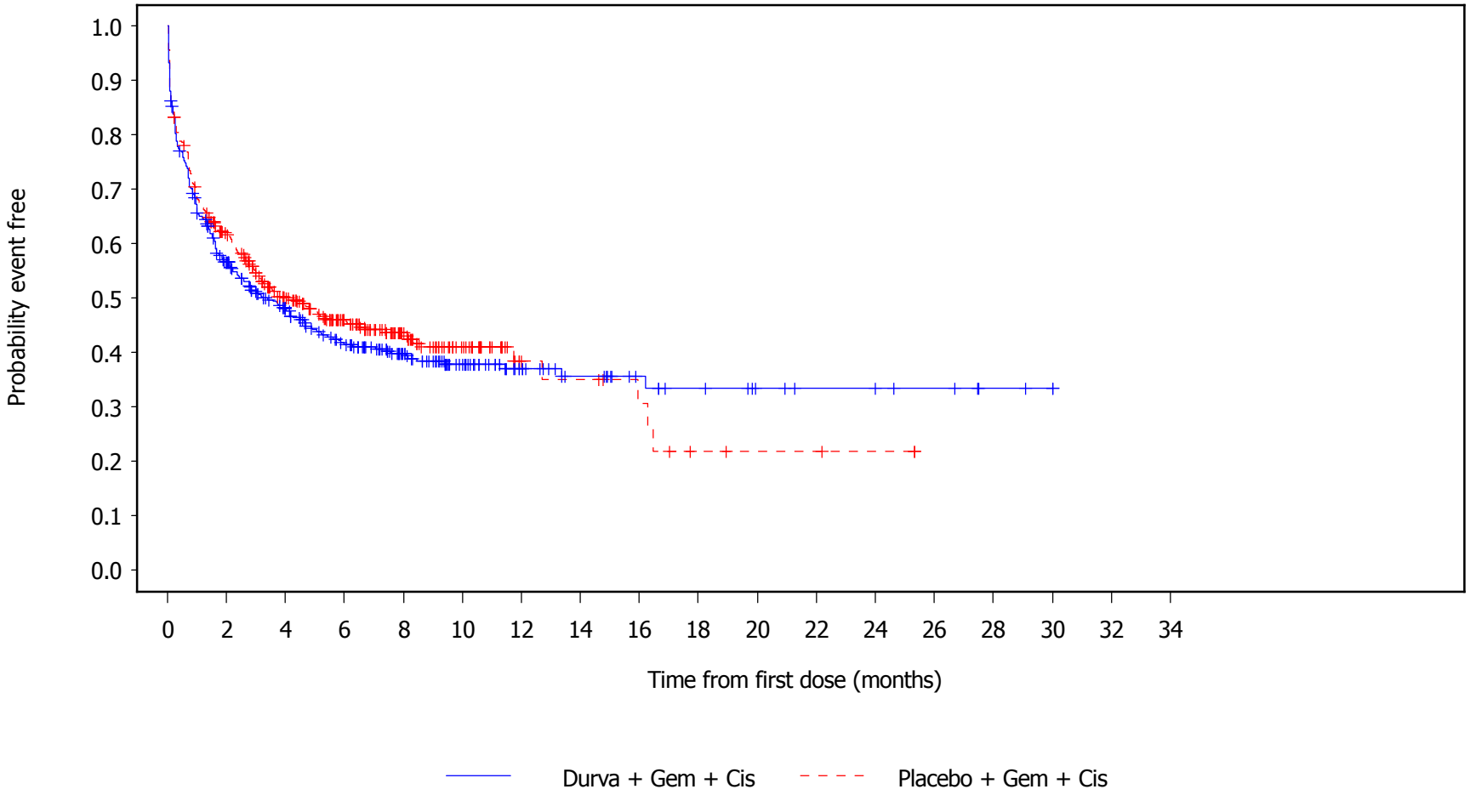
Figure 3.3.1 TOPAZ: Kaplan-Meier plot of time to first occurrence of AE
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	19	5	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	Durva + Gem + Cis
403	16	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Placebo + Gem + Cis

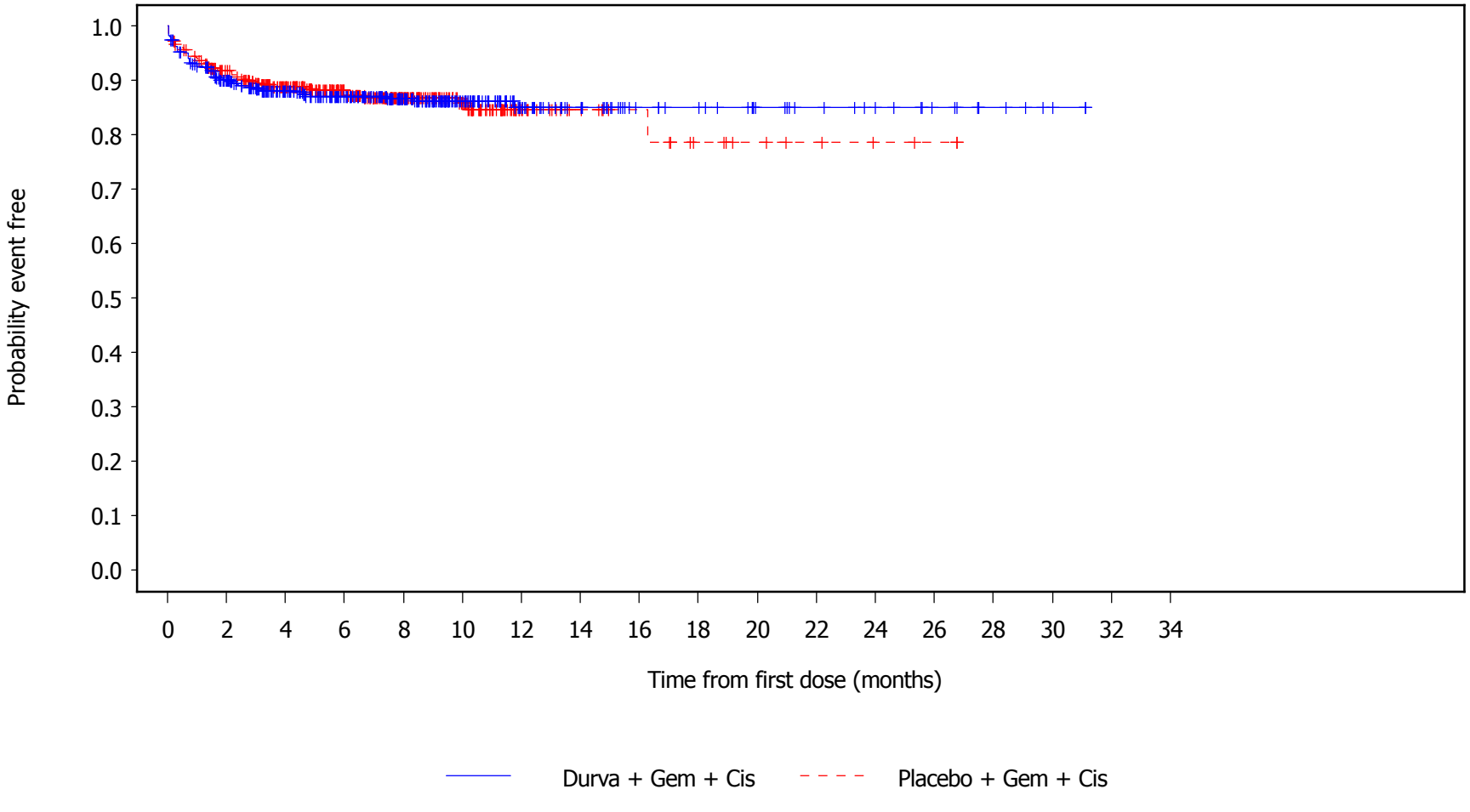
Figure 3.3.2 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: General disorders and administration site conditions
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	215	158	121	85	57	34	24	17	13	9	7	7	5	2	1	0	0	Durva + Gem + Cis
403	233	163	111	69	38	11	10	7	3	2	2	1	0	0	0	0	0	Placebo + Gem + Cis

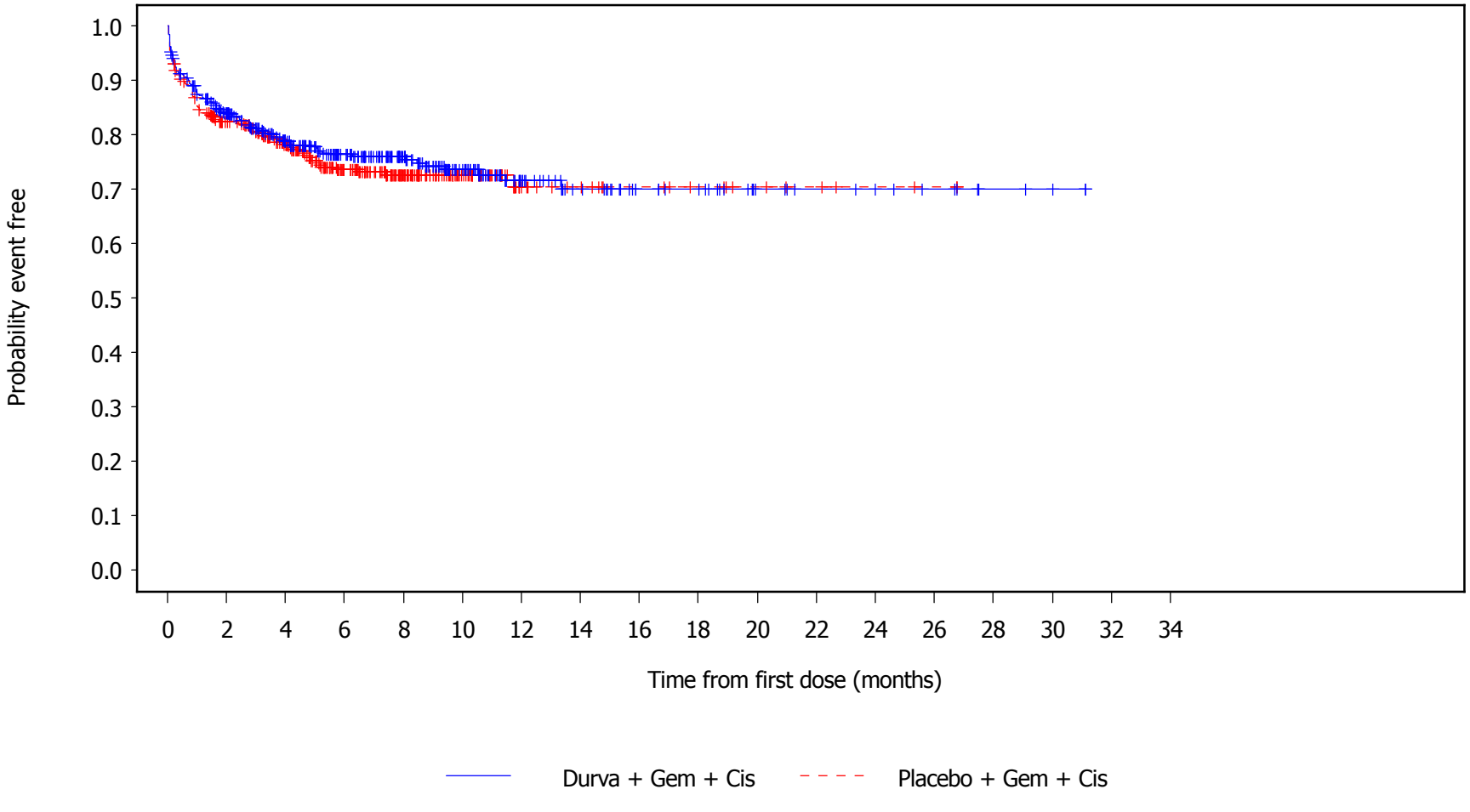
Figure 3.3.3 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Asthenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	337	277	235	173	114	67	47	32	29	21	17	14	9	5	2	0	0	Durva + Gem + Cis
403	343	280	207	138	81	31	19	14	9	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

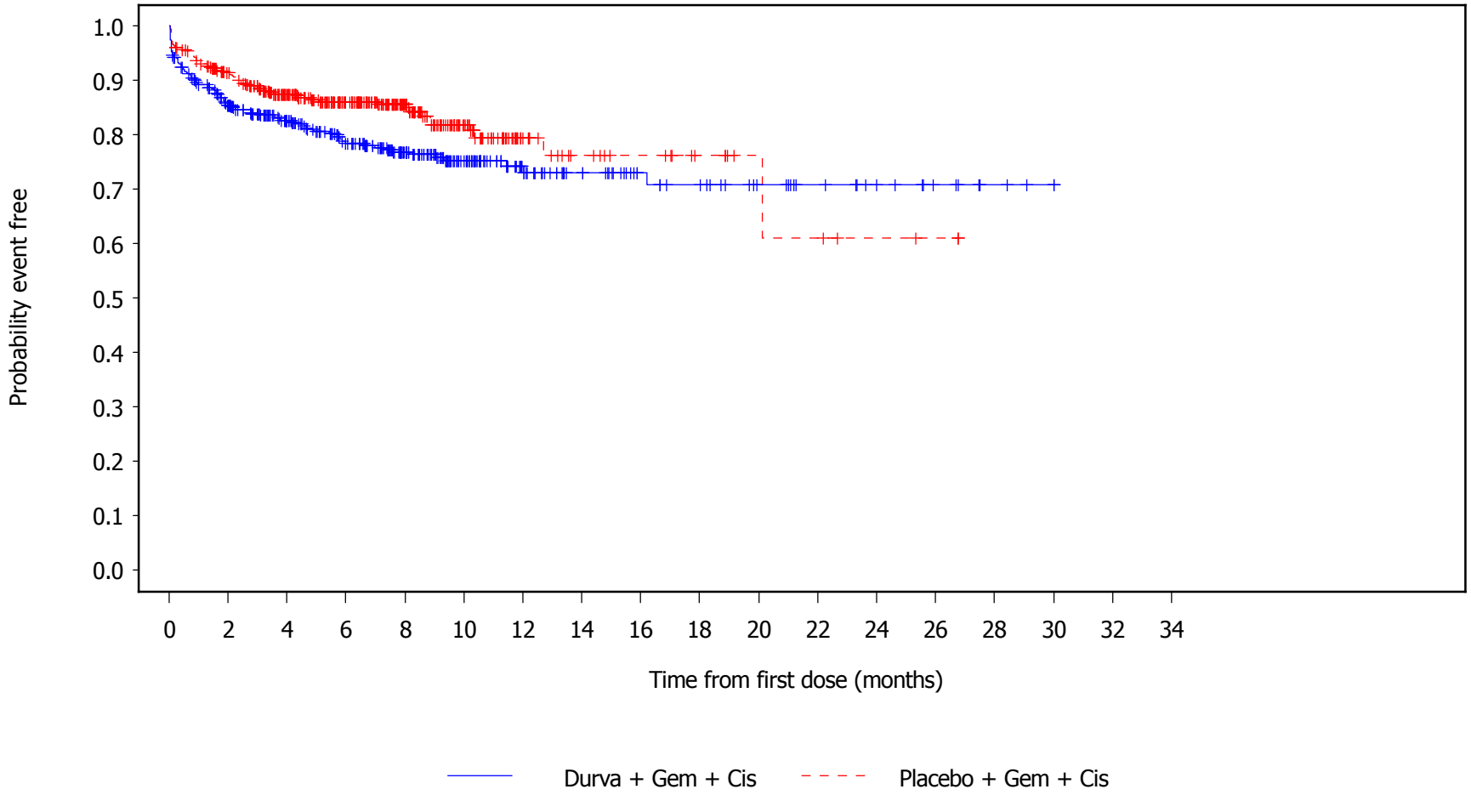
Figure 3.3.4 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Fatigue
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	314	250	199	144	94	55	39	27	24	14	11	10	7	3	2	0	0	Durva + Gem + Cis
403	304	246	169	113	62	22	17	12	9	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

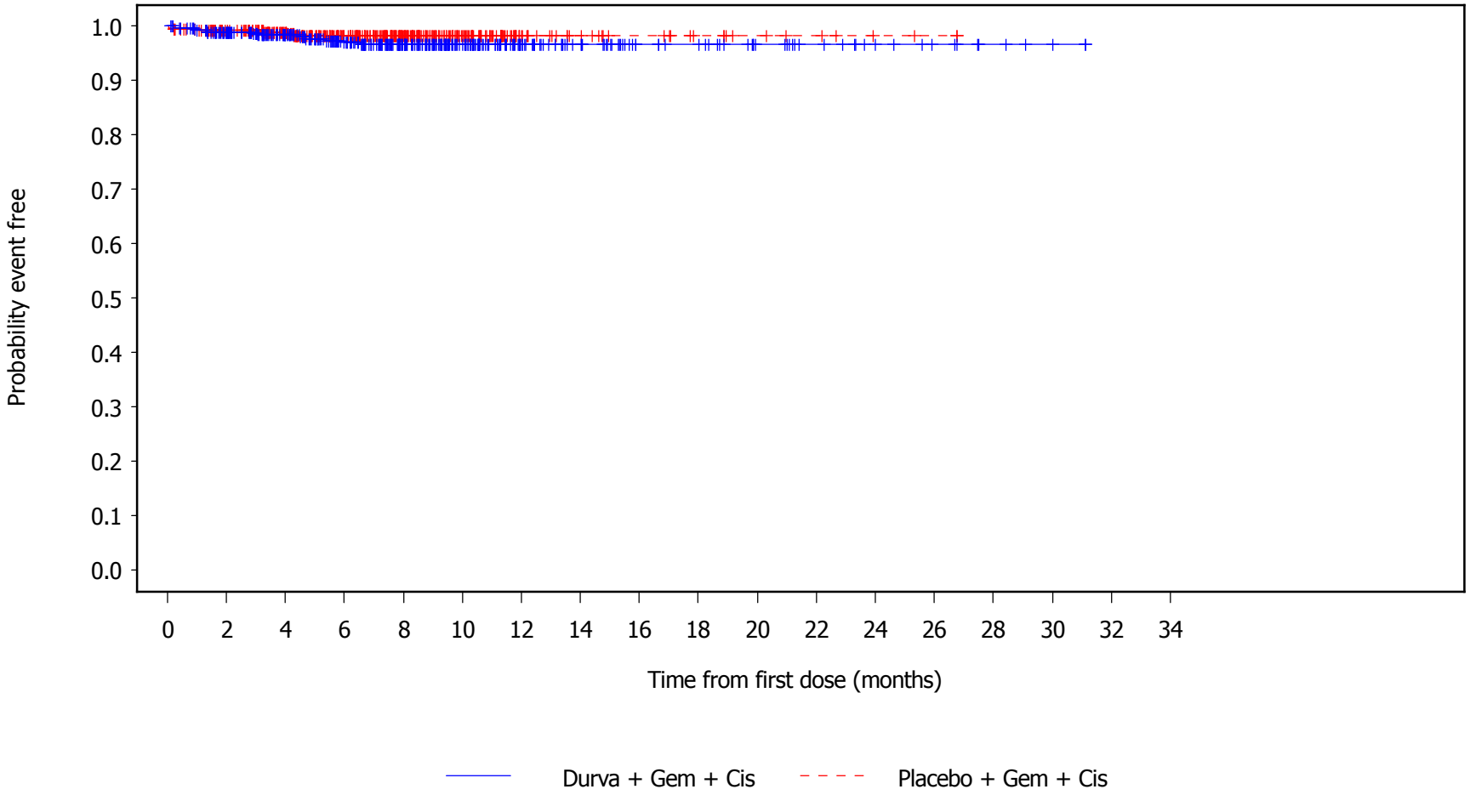
Figure 3.3.5 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Pyrexia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	323	262	216	160	109	66	47	33	29	21	16	12	7	3	1	0	0	Durva + Gem + Cis
403	340	274	202	135	75	28	18	14	9	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

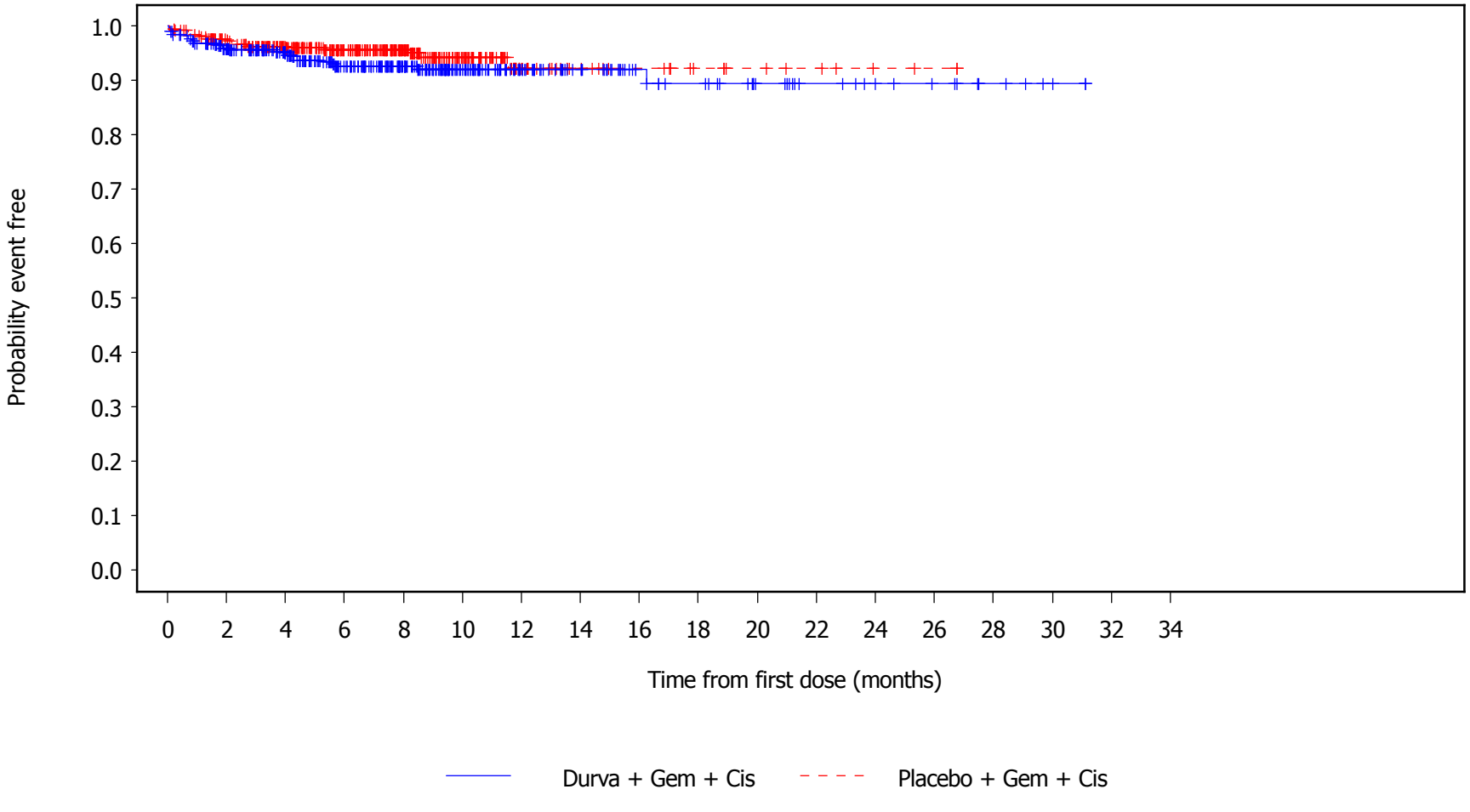
Figure 3.3.6 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Oedema
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	310	256	191	127	76	55	37	34	23	17	12	8	4	2	0	0	Durva + Gem + Cis
403	368	309	227	155	87	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

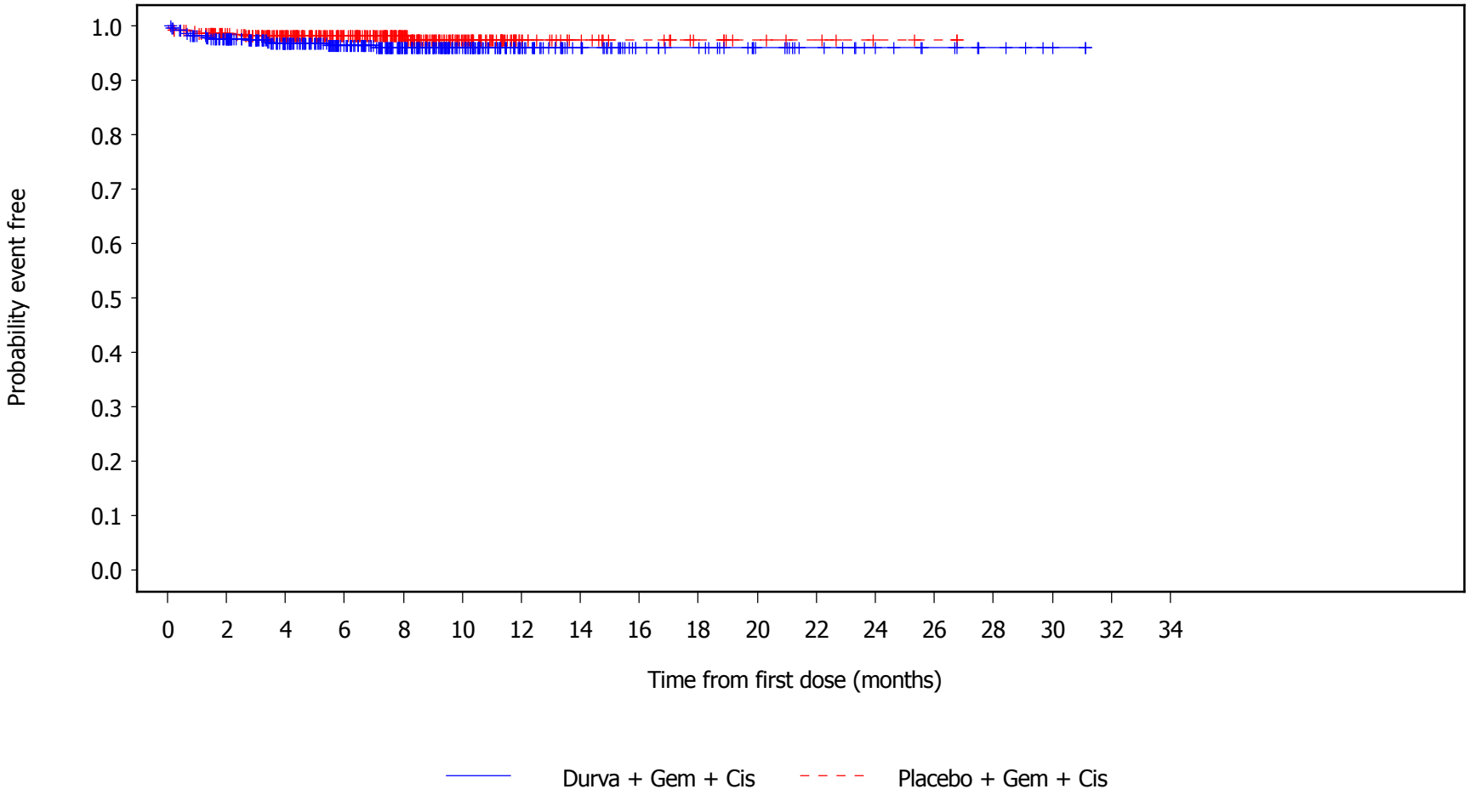
Figure 3.3.7 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Oedema peripheral
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	359	303	247	185	119	75	53	35	30	21	15	12	9	5	2	0	0	Durva + Gem + Cis
403	364	306	228	156	87	32	20	15	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

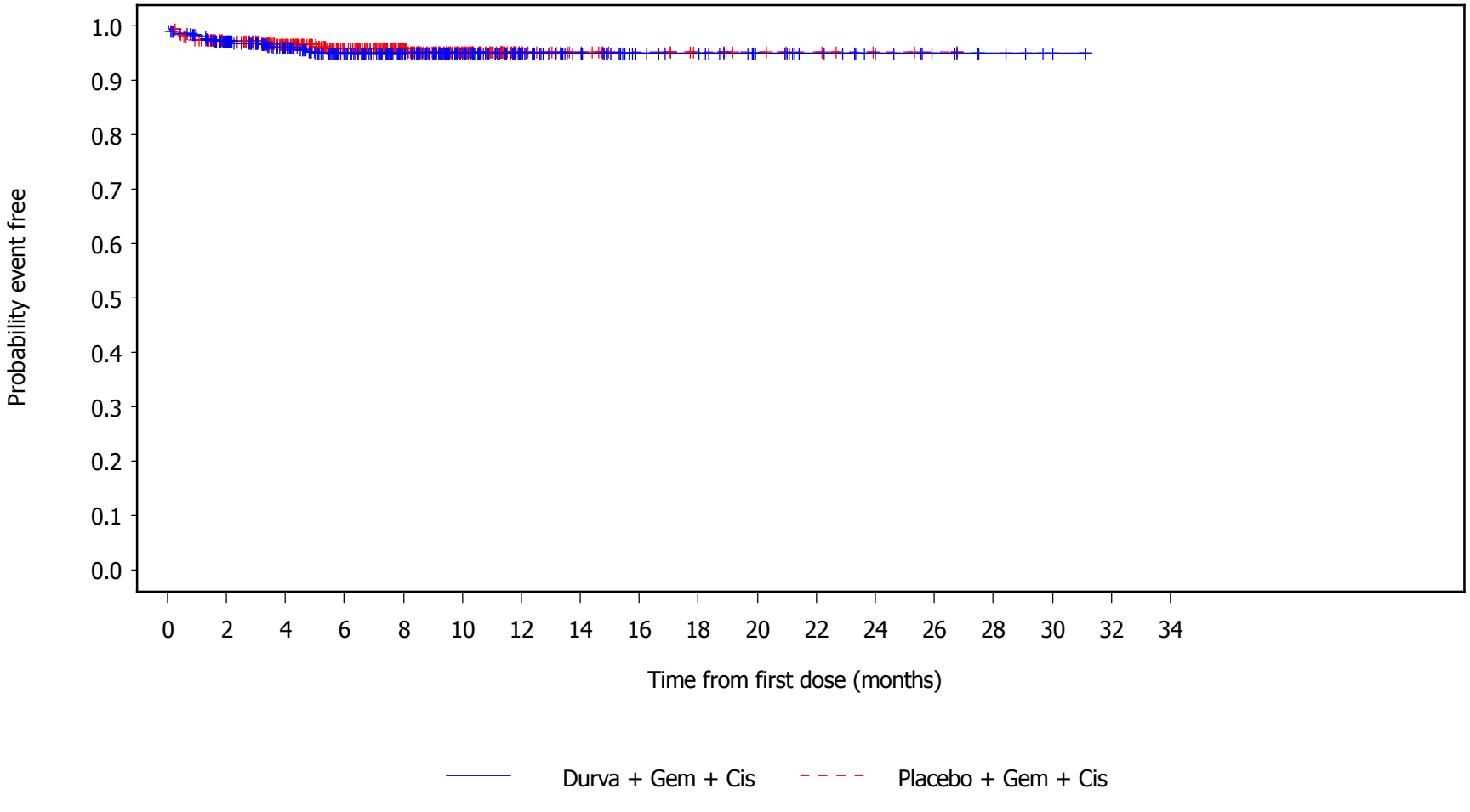
Figure 3.3.8 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Chills
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	366	307	258	192	128	79	57	39	35	24	18	13	9	5	2	0	0	Durva + Gem + Cis
403	367	307	228	155	87	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

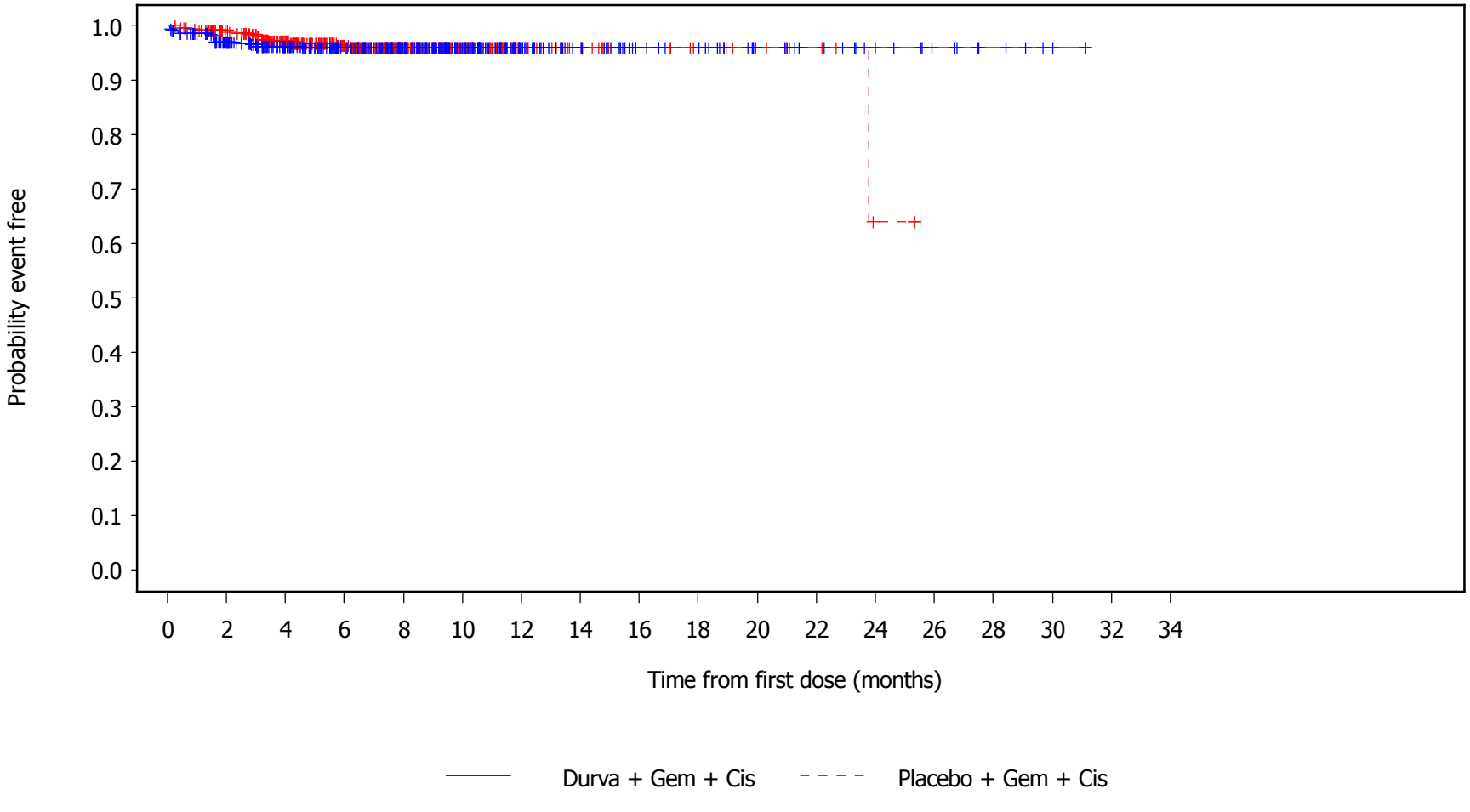
Figure 3.3.9 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Malaise
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	364	304	253	190	126	79	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	362	303	225	152	87	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

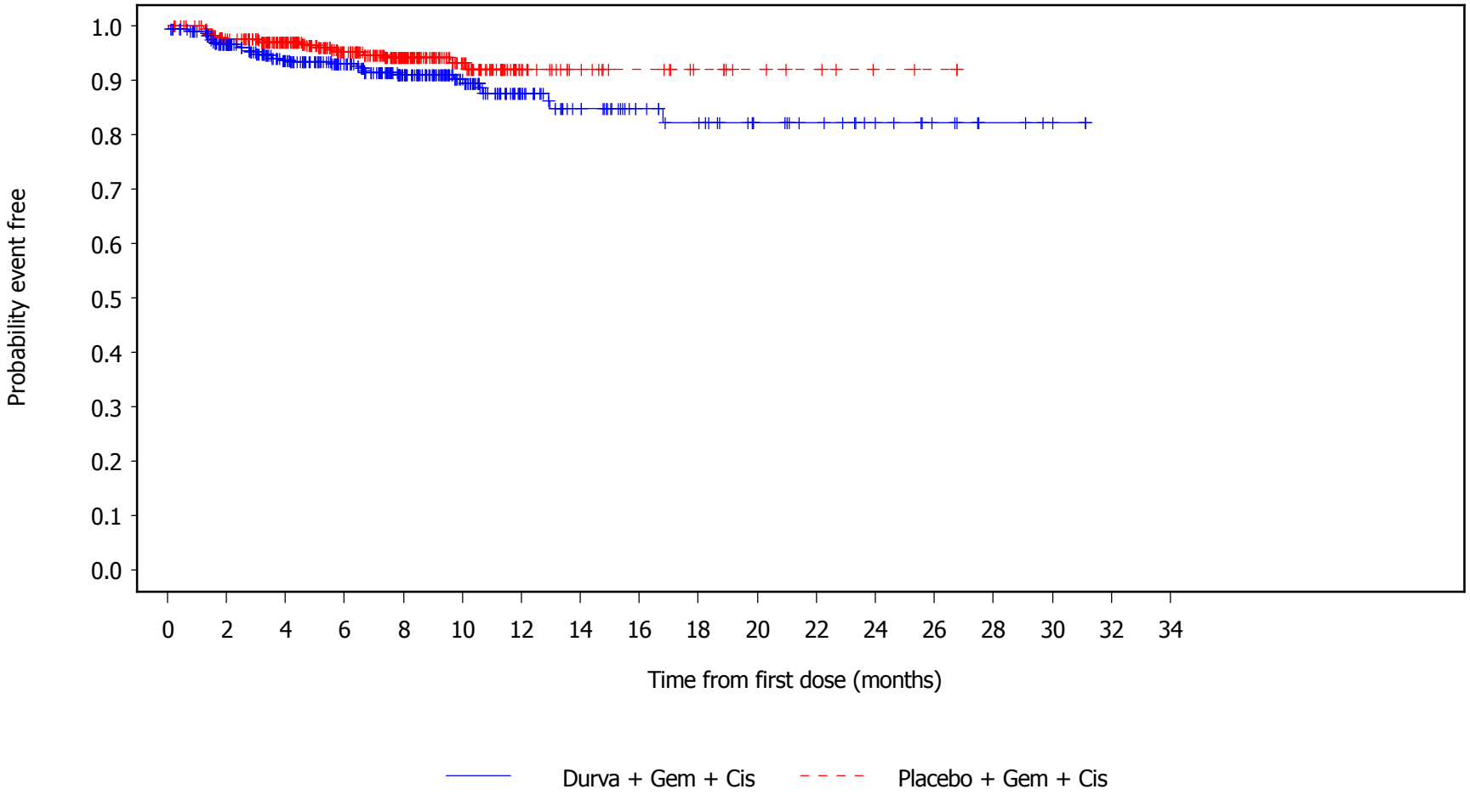
Figure 3.3.10 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Eye disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	362	303	253	189	125	78	56	39	35	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	303	222	150	84	33	21	15	11	7	5	1	0	0	0	0	0	Placebo + Gem + Cis

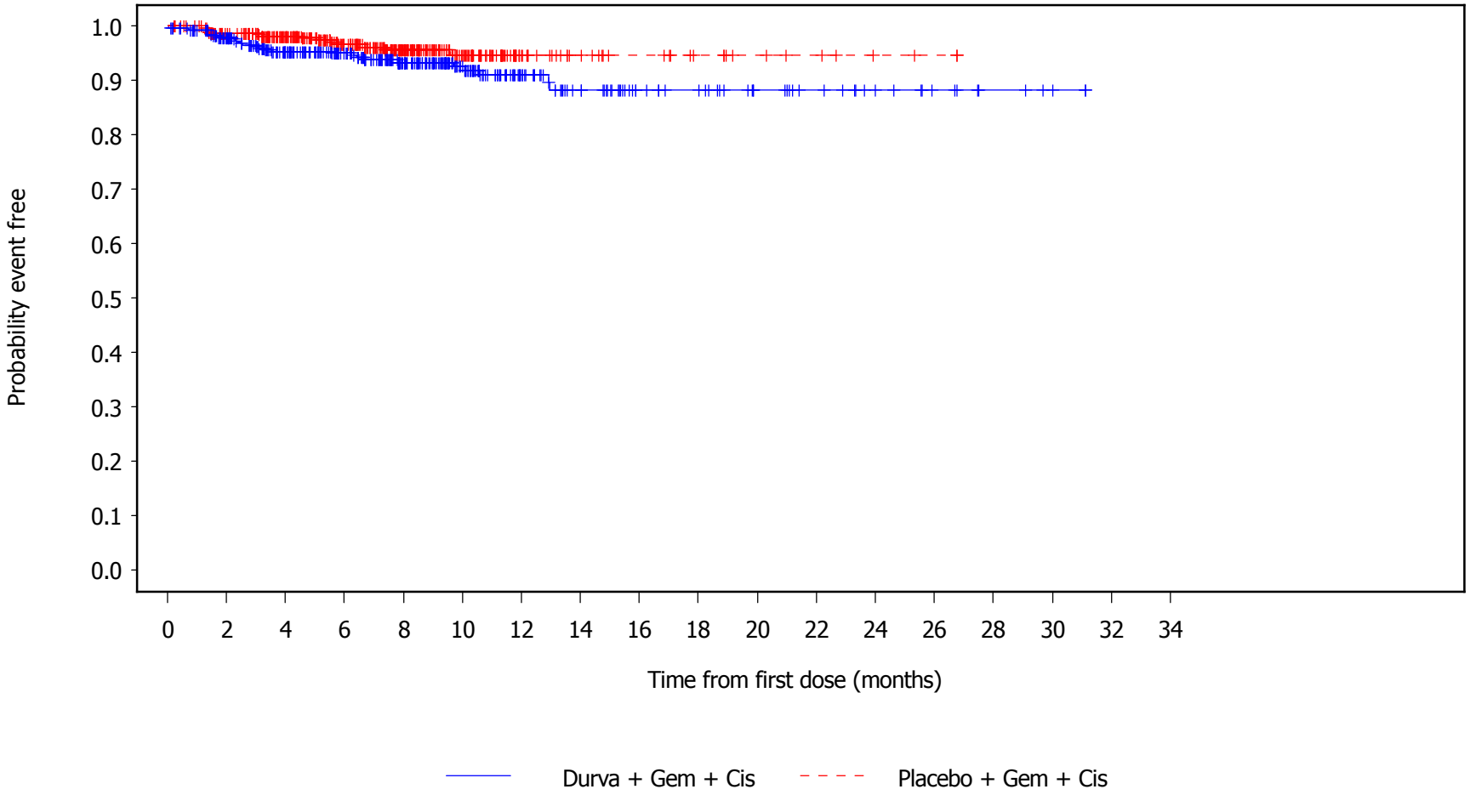
Figure 3.3.11 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Endocrine disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	360	297	248	182	121	72	51	36	31	22	18	13	8	4	2	0	0	Durva + Gem + Cis
403	362	302	219	150	86	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

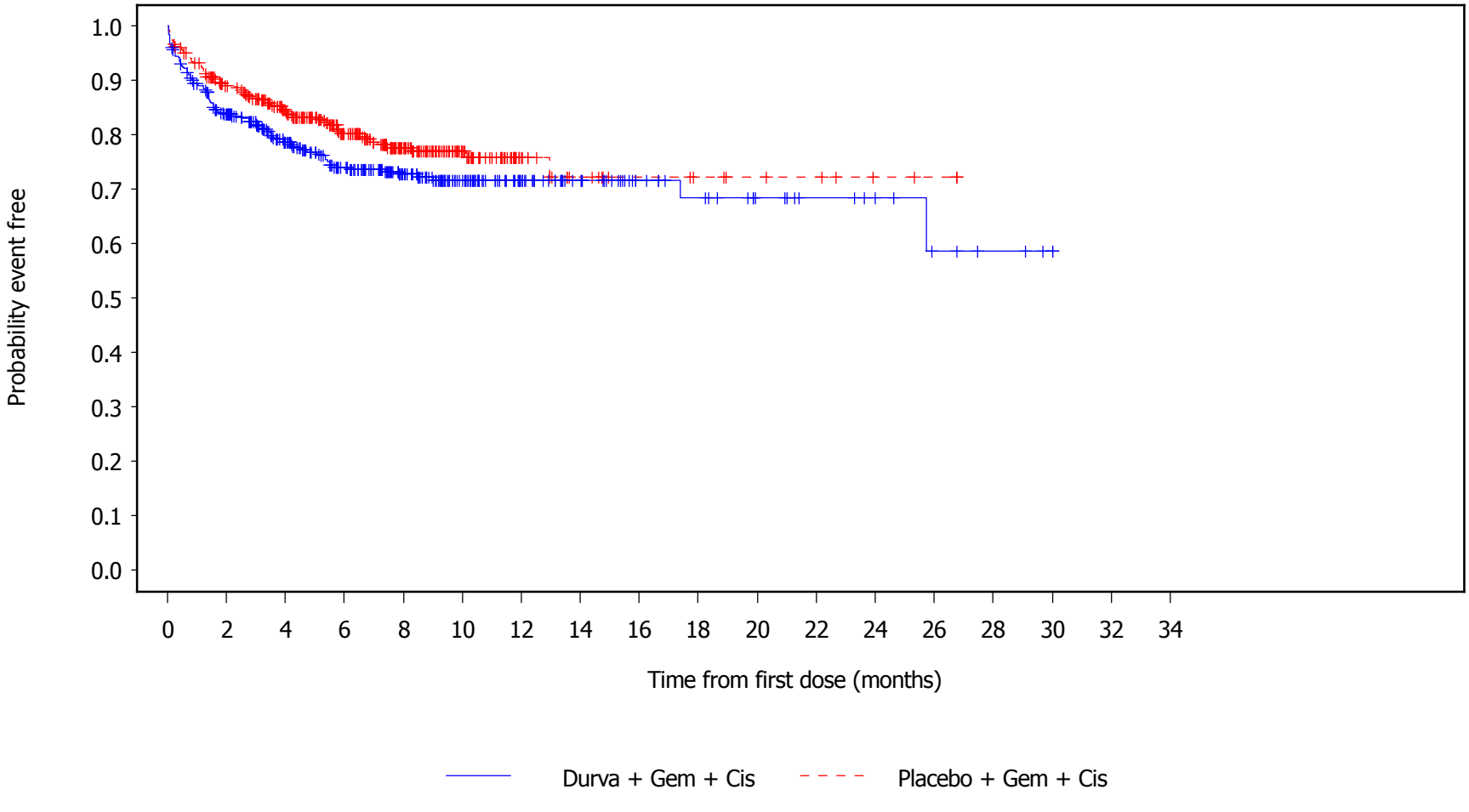
Figure 3.3.12 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Hypothyroidism
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	365	302	254	187	125	76	54	37	33	23	18	13	8	4	2	0	0	Durva + Gem + Cis
403	366	306	224	153	87	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

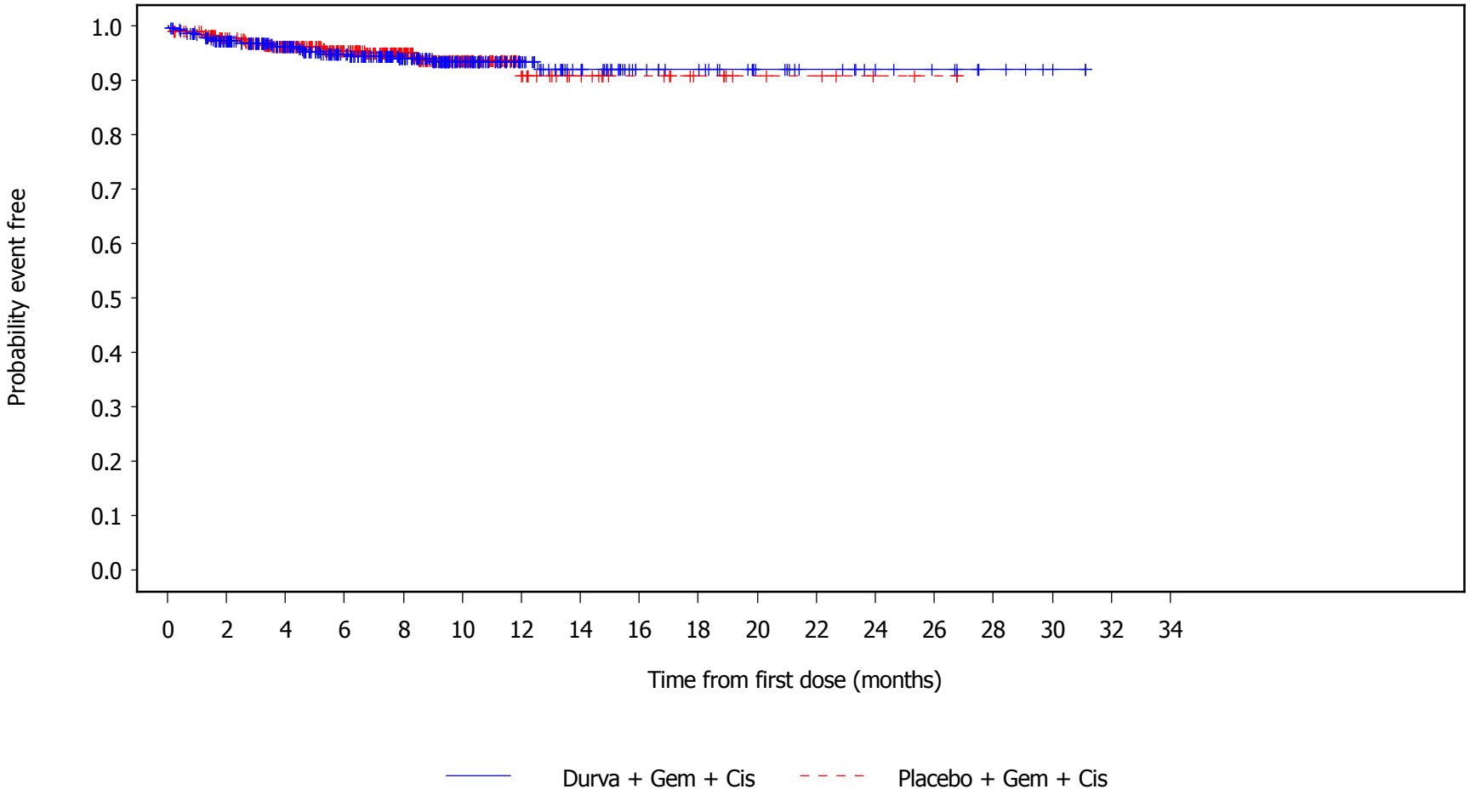
Figure 3.3.13 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Respiratory, thoracic and mediastinal disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	318	250	200	144	99	60	42	27	22	15	11	9	5	3	1	0	0	Durva + Gem + Cis
403	332	268	188	120	67	25	15	10	8	6	5	2	1	0	0	0	0	Placebo + Gem + Cis

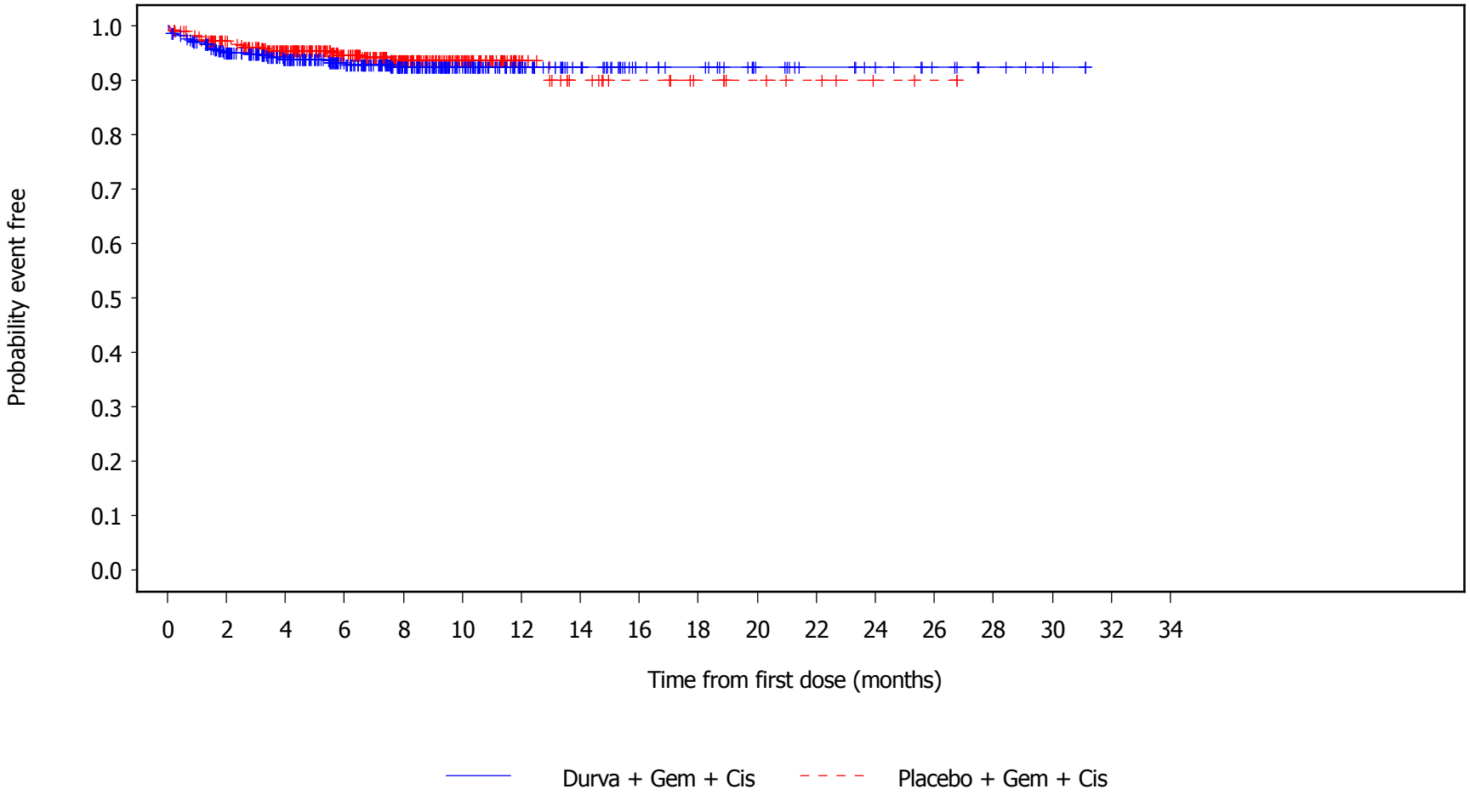
Figure 3.3.14 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Dyspnoea
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	364	305	254	188	124	75	53	35	31	21	16	12	9	5	2	0	0	Durva + Gem + Cis
403	363	301	223	153	85	32	21	15	10	6	5	2	1	0	0	0	0	Placebo + Gem + Cis

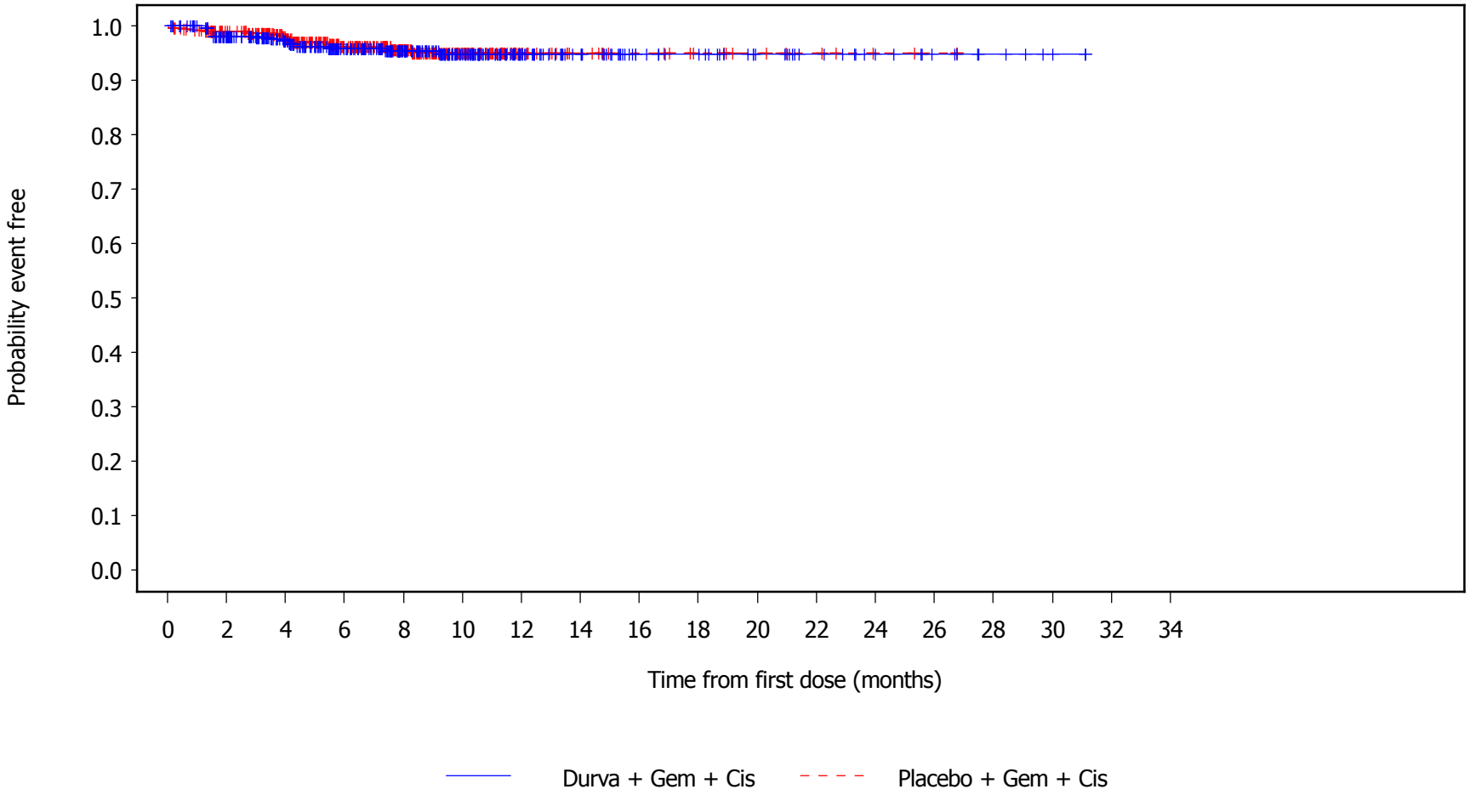
Figure 3.3.15 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Cough
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	356	296	246	181	121	74	54	36	32	22	17	14	9	5	2	0	0	Durva + Gem + Cis
403	361	302	221	149	83	30	19	14	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

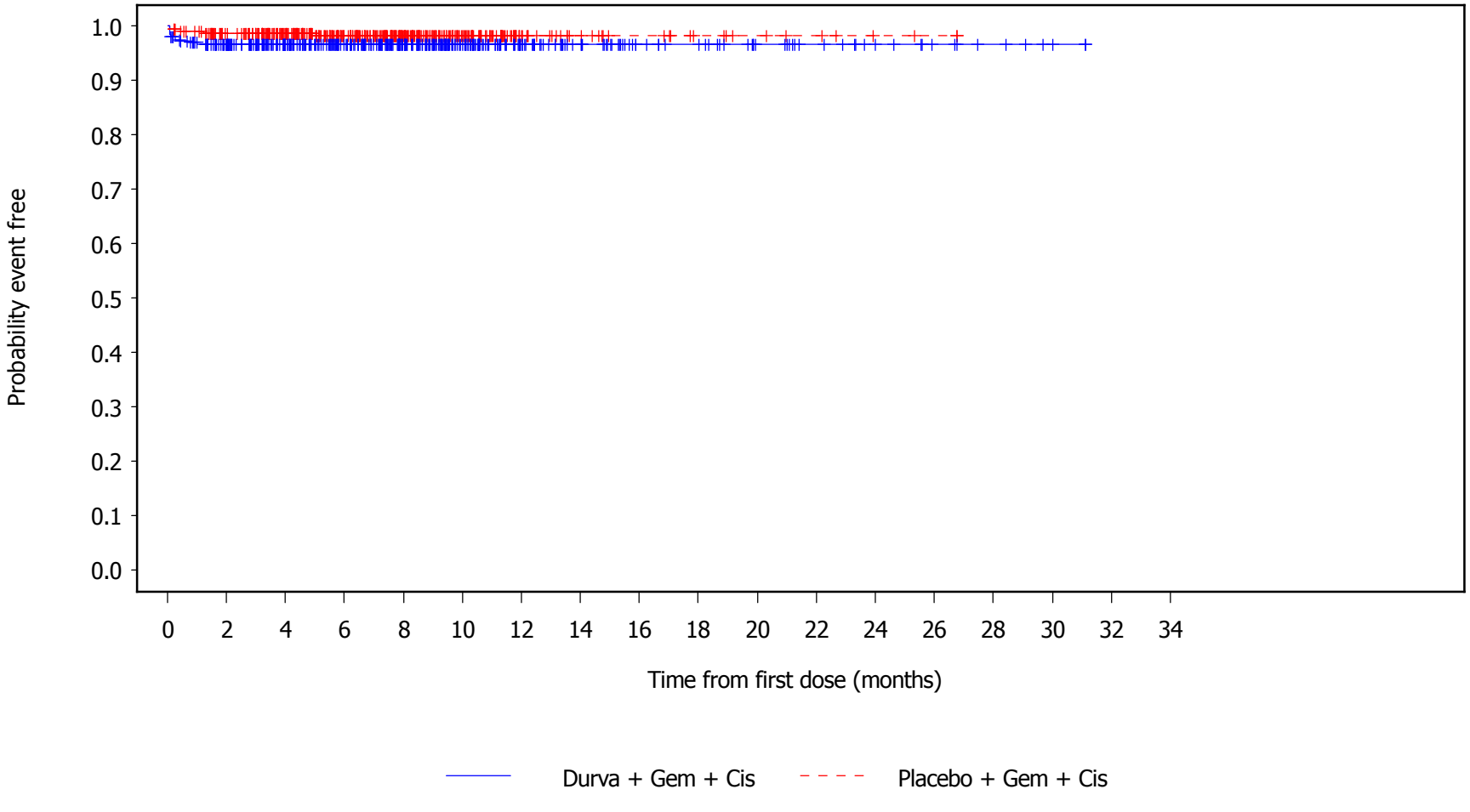
Figure 3.3.16 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Pulmonary embolism
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	306	253	187	128	77	56	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	367	308	224	154	85	31	20	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

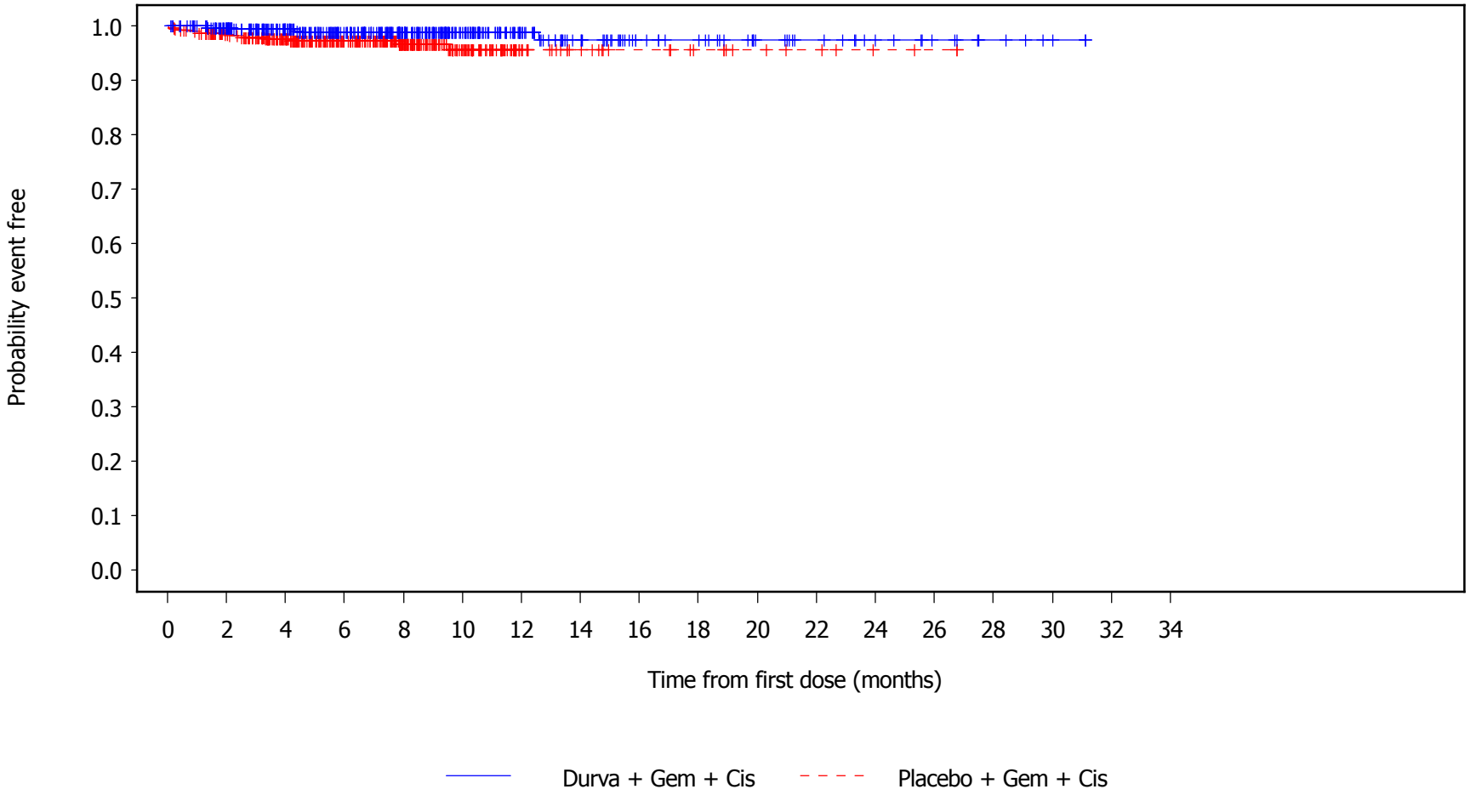
Figure 3.3.17 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Hiccups
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	361	304	255	192	127	79	57	39	35	24	18	13	8	5	2	0	0	Durva + Gem + Cis
403	366	309	229	156	88	33	21	15	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

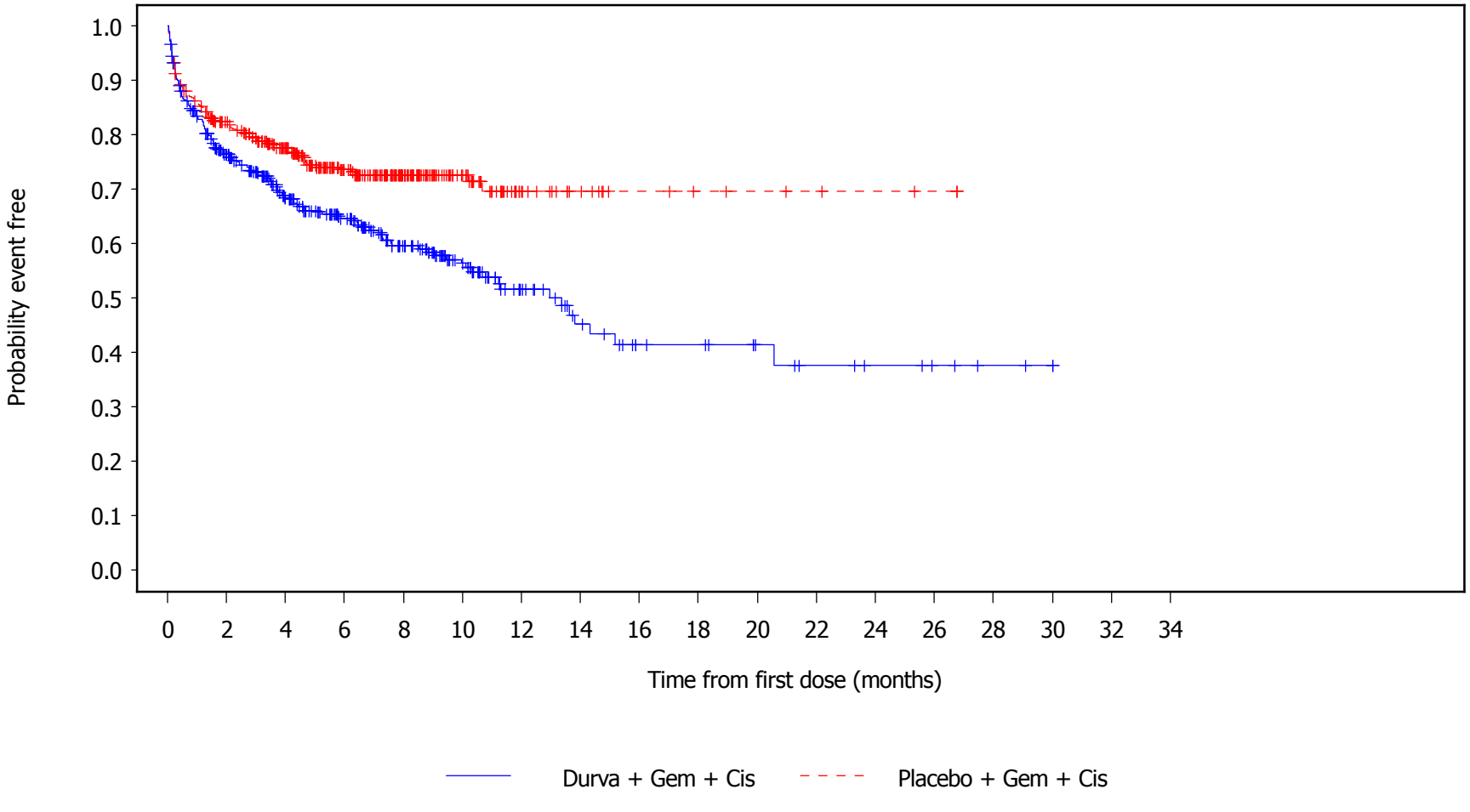
Figure 3.3.18 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Reproductive system and breast disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	313	261	196	131	80	57	39	35	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	365	305	226	154	86	32	21	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

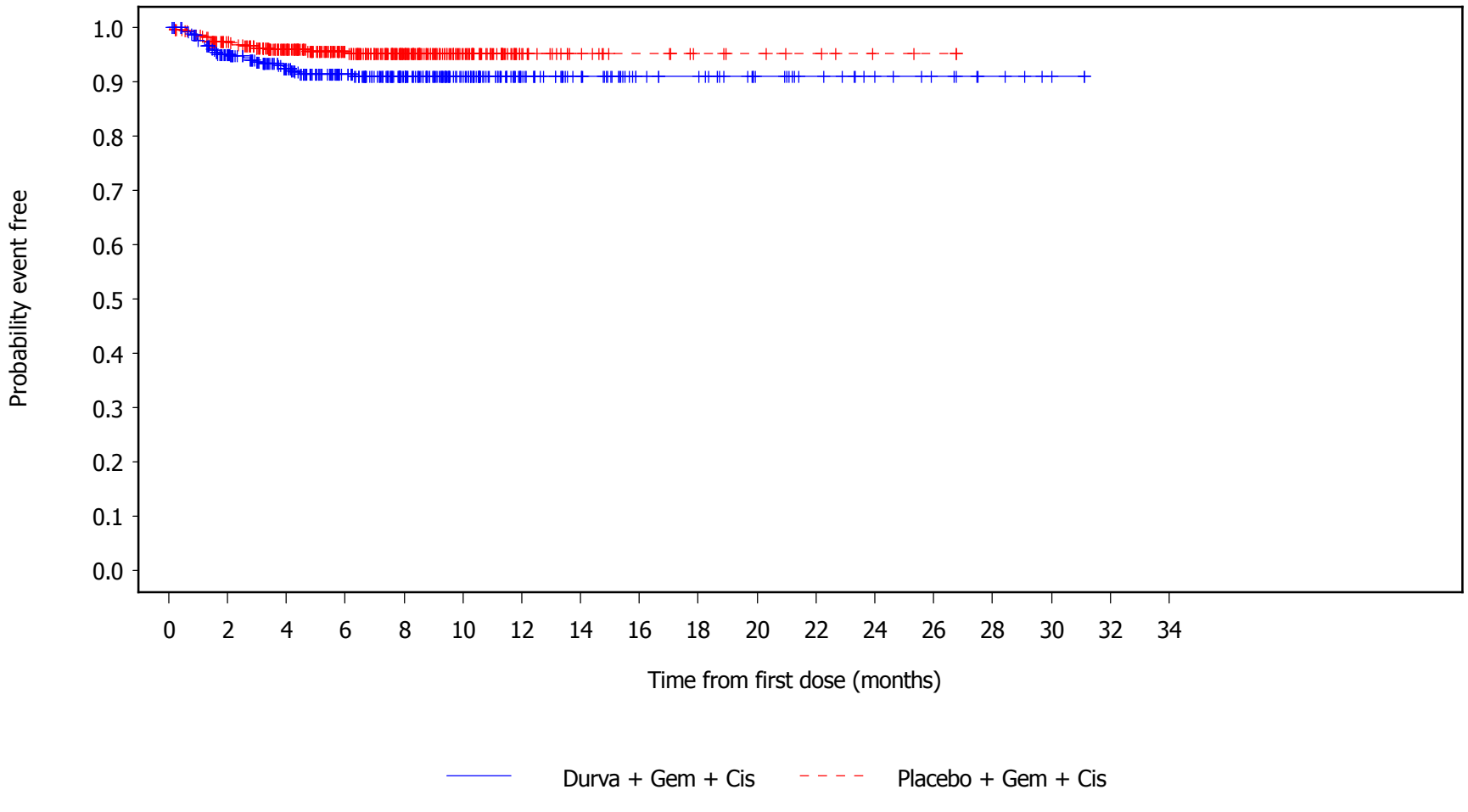
Figure 3.3.19 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Skin and subcutaneous tissue disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	282	208	163	112	74	40	26	17	16	11	8	6	4	2	1	0	0	Durva + Gem + Cis
403	305	240	164	104	57	22	13	7	5	4	3	2	1	0	0	0	0	Placebo + Gem + Cis

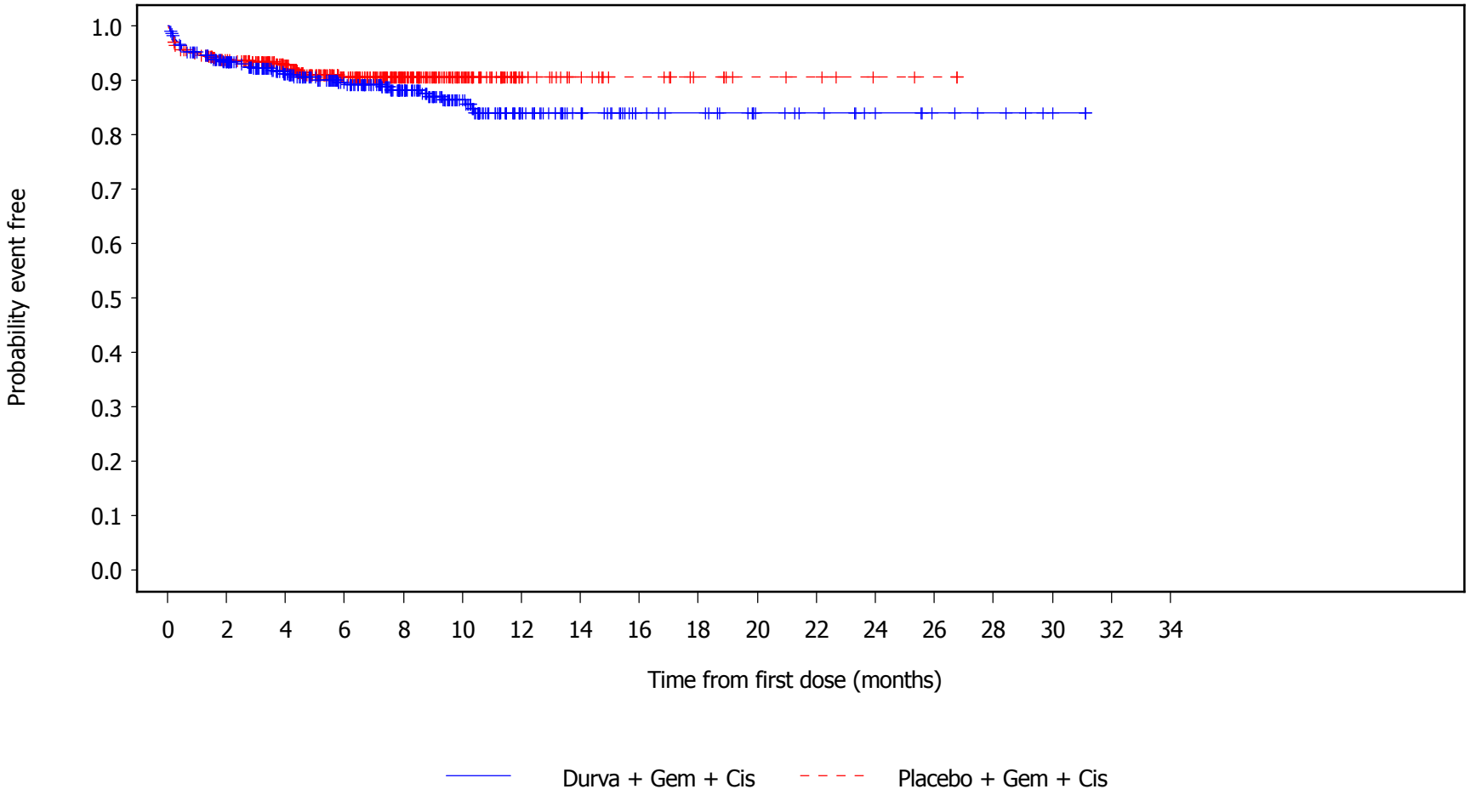
Figure 3.3.20 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Alopecia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	354	290	239	179	122	74	56	38	35	24	18	13	9	5	2	0	0	Durva + Gem + Cis
403	361	299	220	150	83	31	19	13	9	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

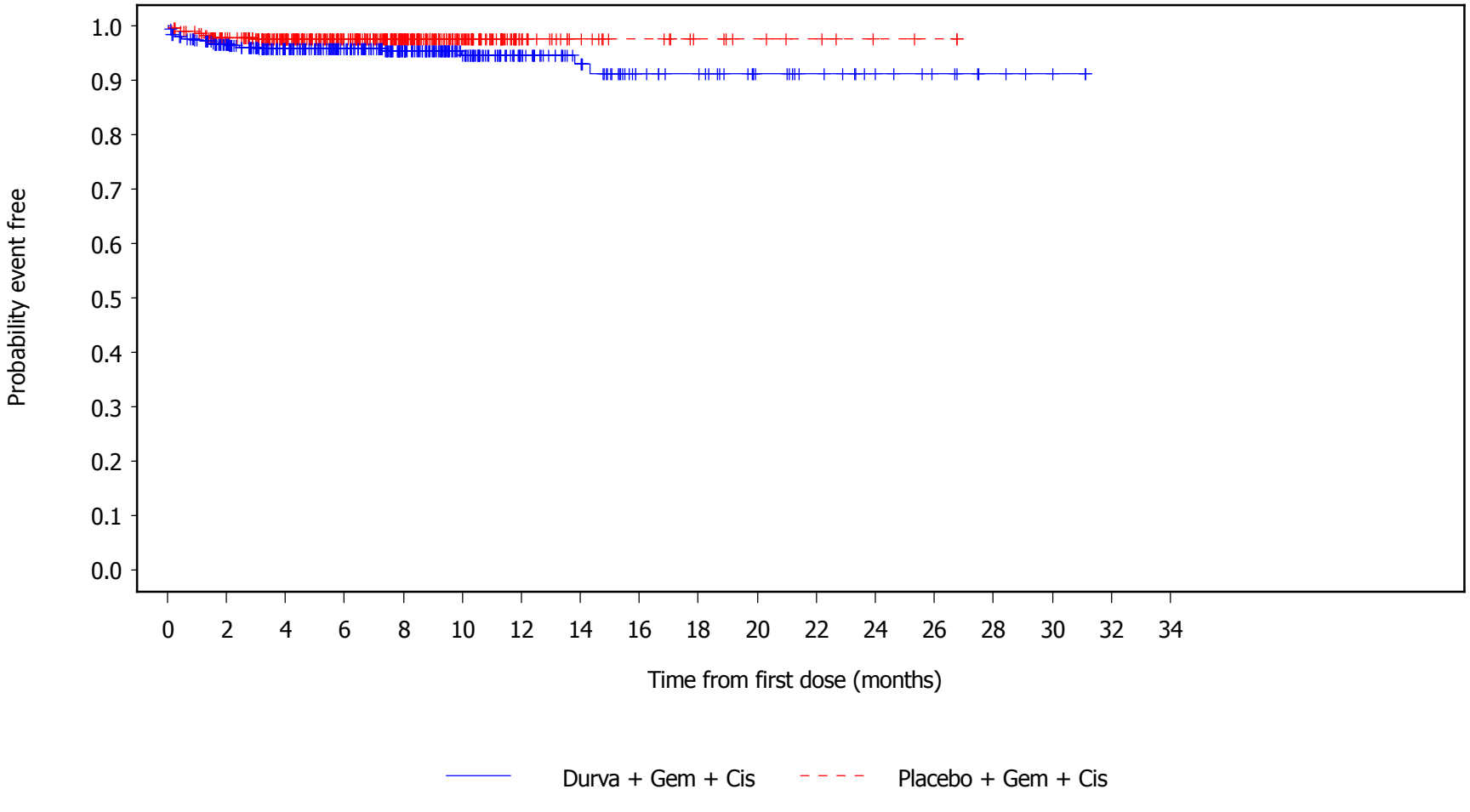
Figure 3.3.21 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	348	287	236	172	114	65	45	30	27	18	15	11	7	5	2	0	0	Durva + Gem + Cis
403	350	291	208	141	78	32	21	15	10	6	5	2	1	0	0	0	0	Placebo + Gem + Cis

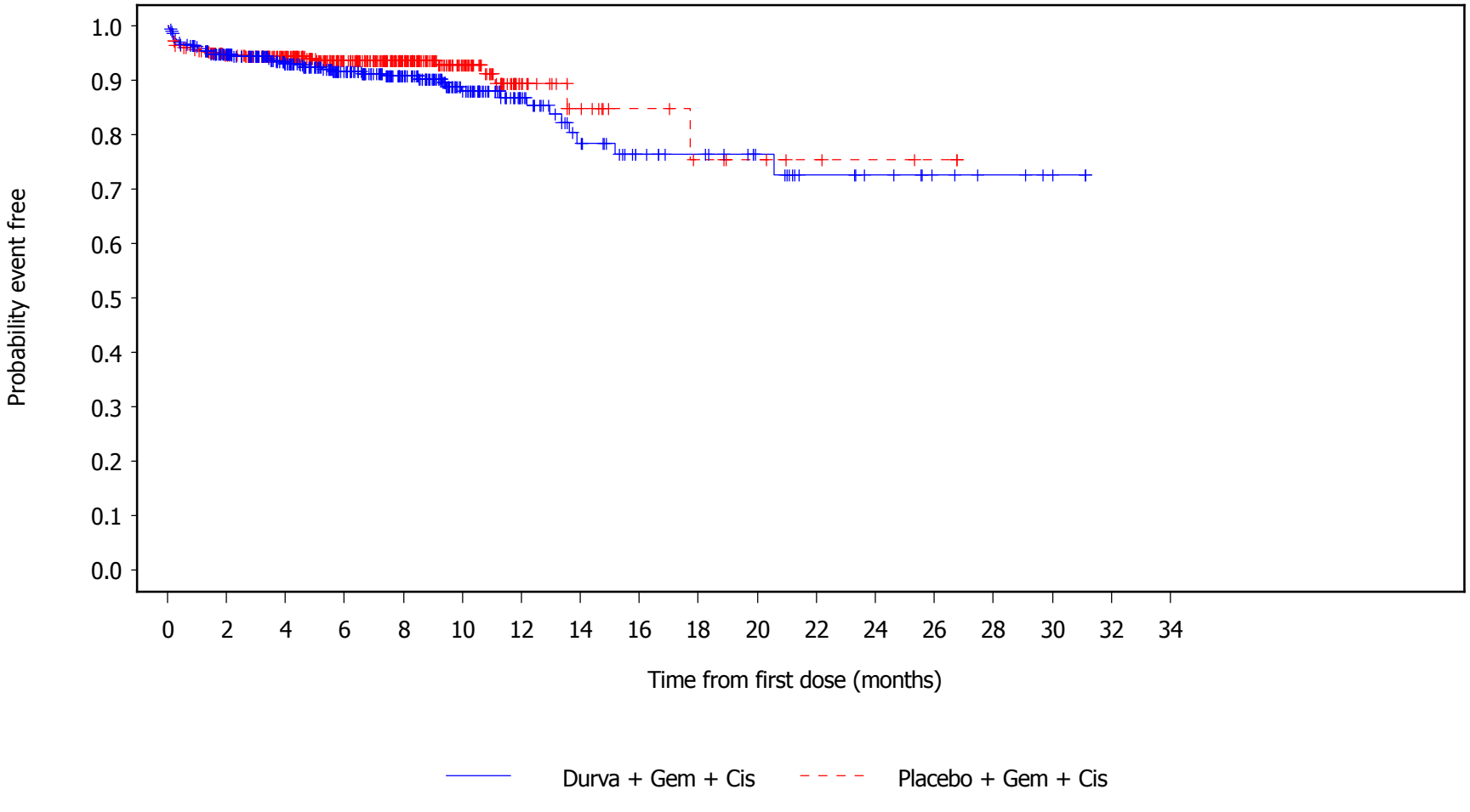
Figure 3.3.22 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Rash maculo-papular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	361	301	254	189	126	77	56	37	33	22	17	12	8	4	2	0	0	Durva + Gem + Cis
403	363	305	226	154	86	33	21	15	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

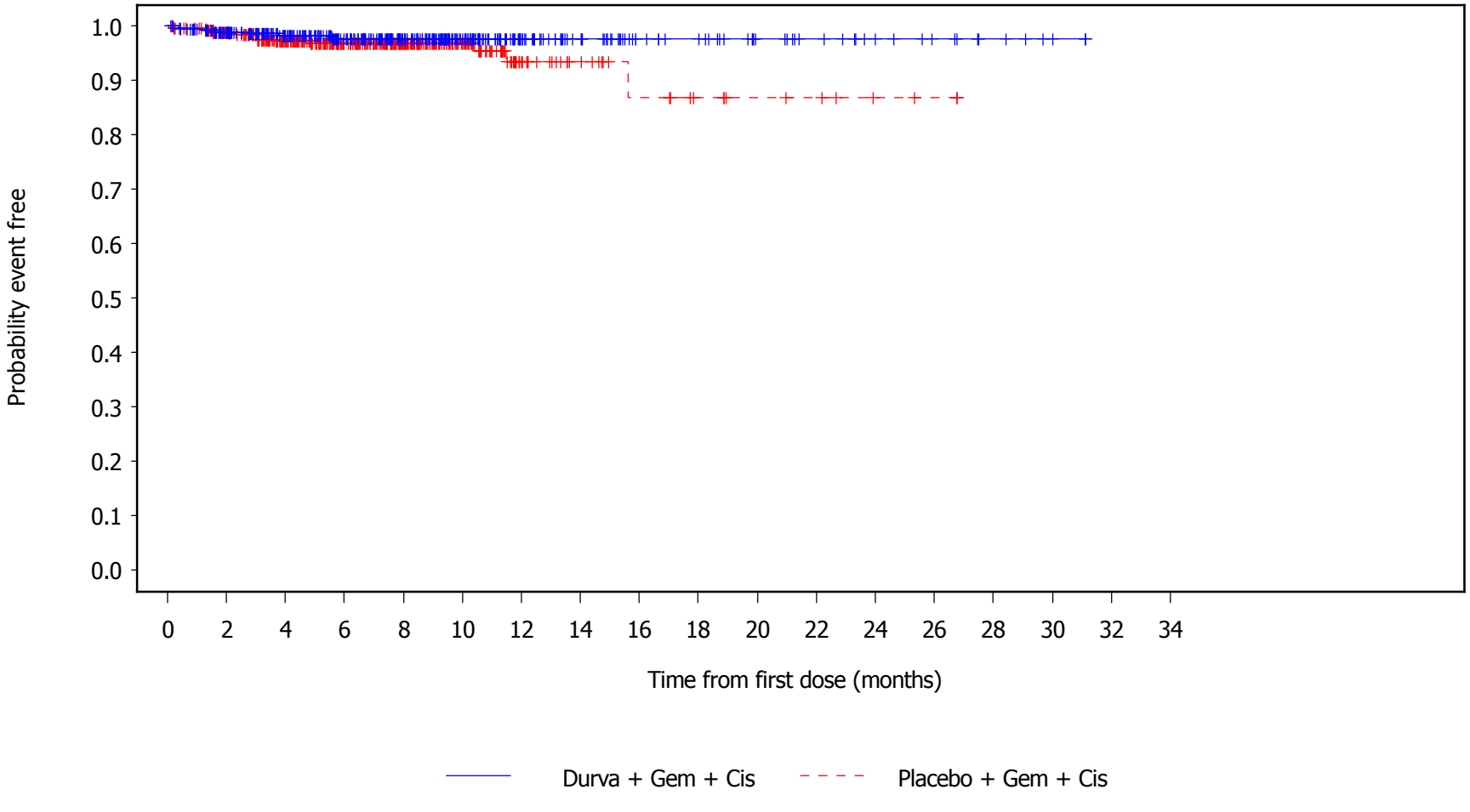
Figure 3.3.23 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Pruritus
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	353	289	235	174	109	63	43	31	27	20	13	10	6	4	2	0	0	Durva + Gem + Cis
403	350	293	216	145	80	28	16	10	7	5	3	2	1	0	0	0	0	Placebo + Gem + Cis

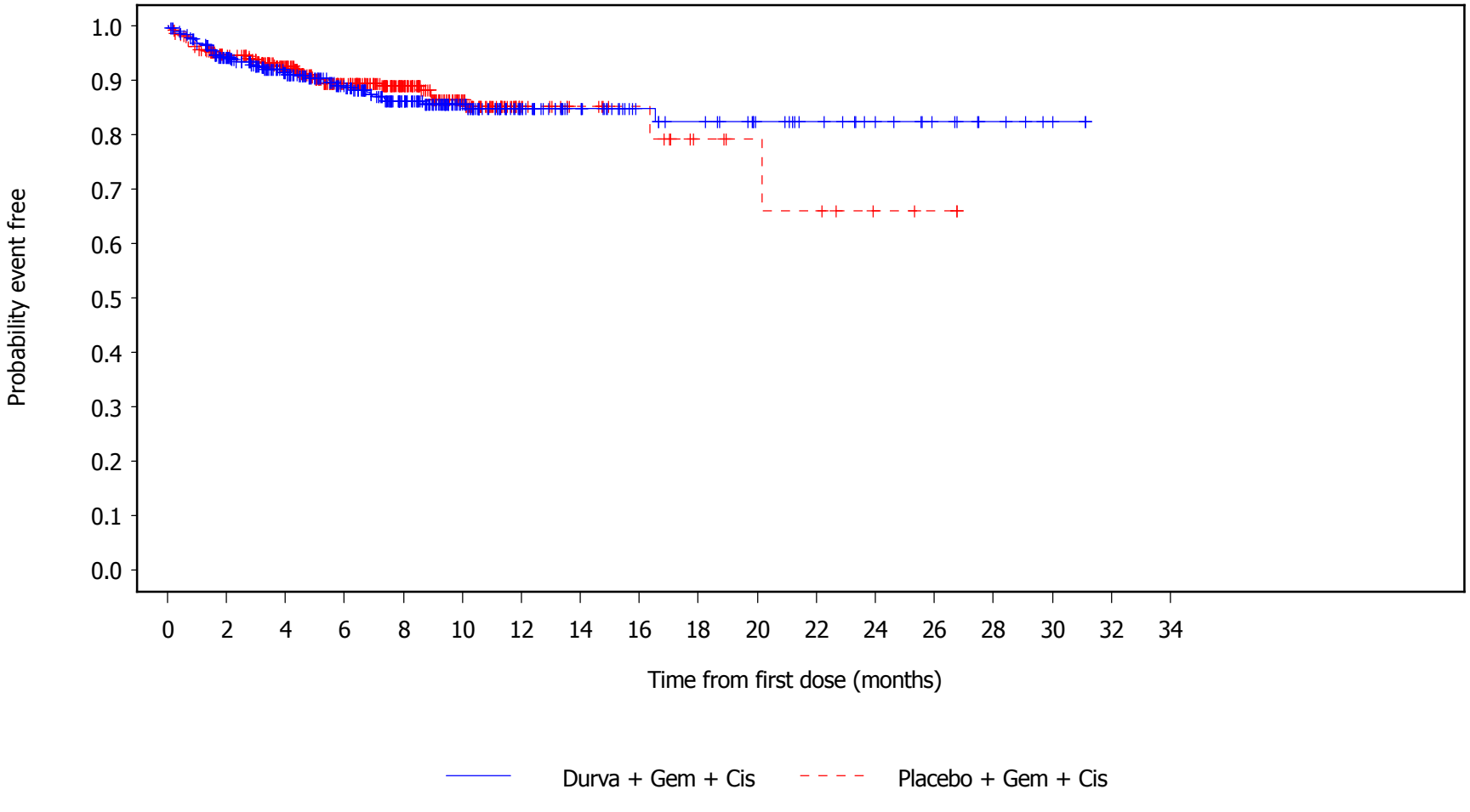
Figure 3.3.24 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Dry skin
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	309	256	190	127	78	56	38	34	23	18	13	9	5	2	0	0	Durva + Gem + Cis
403	367	304	224	154	87	32	20	13	9	6	5	2	1	0	0	0	0	Placebo + Gem + Cis

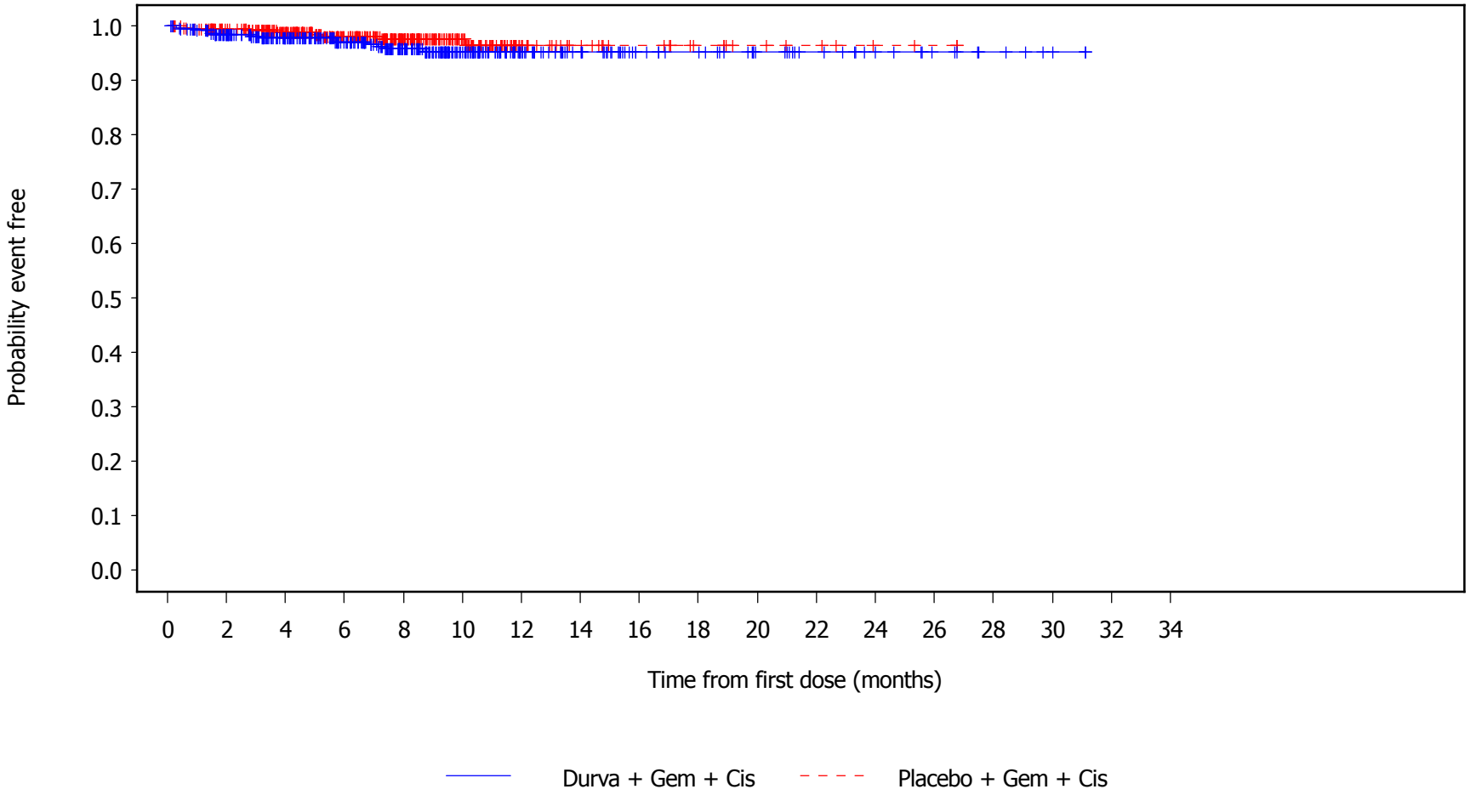
Figure 3.3.25 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Renal and urinary disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	352	288	240	177	115	70	51	36	32	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	352	291	210	140	73	26	18	14	8	6	5	2	1	0	0	0	0	Placebo + Gem + Cis

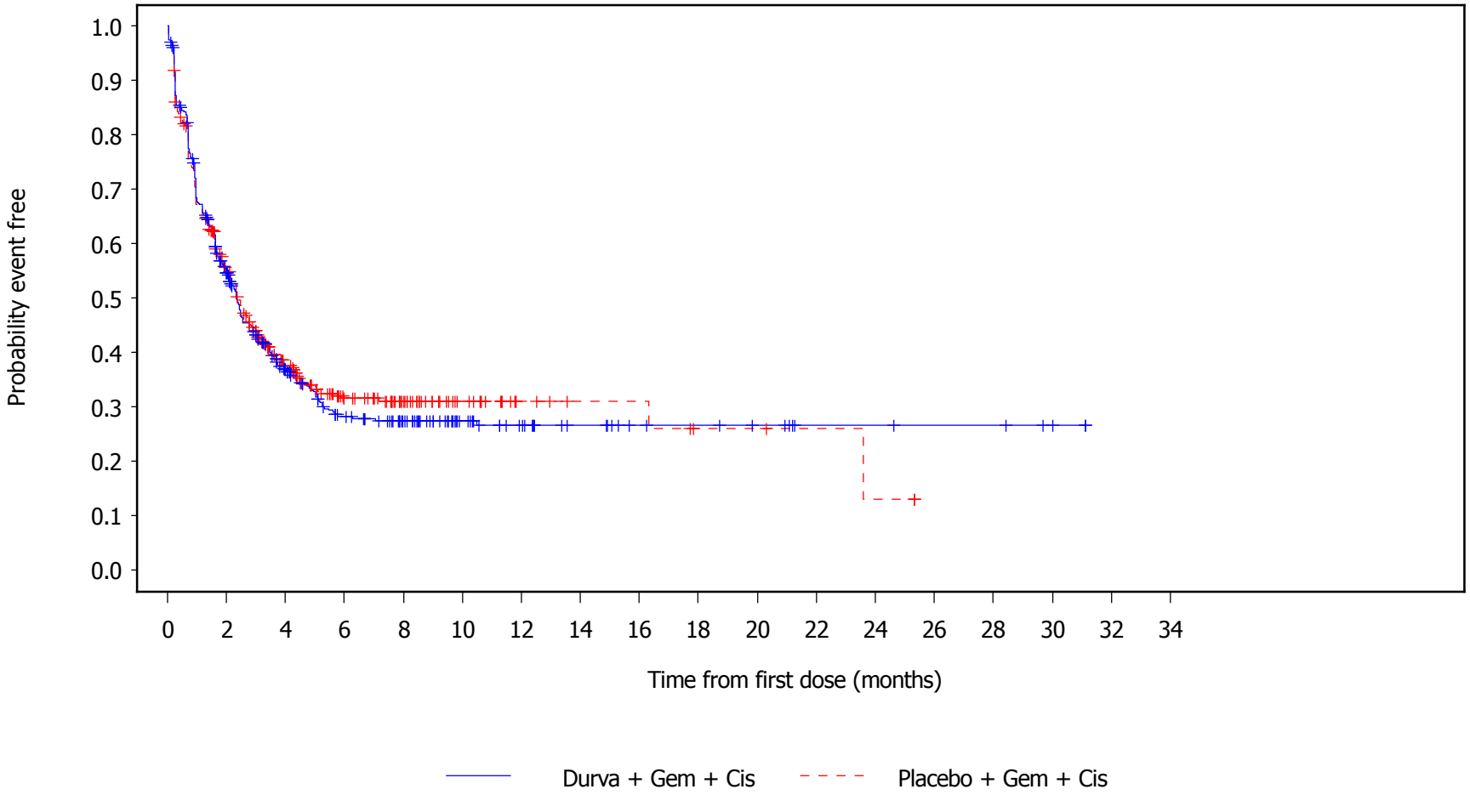
Figure 3.3.26 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Acute kidney injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	311	260	194	128	78	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	310	229	157	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

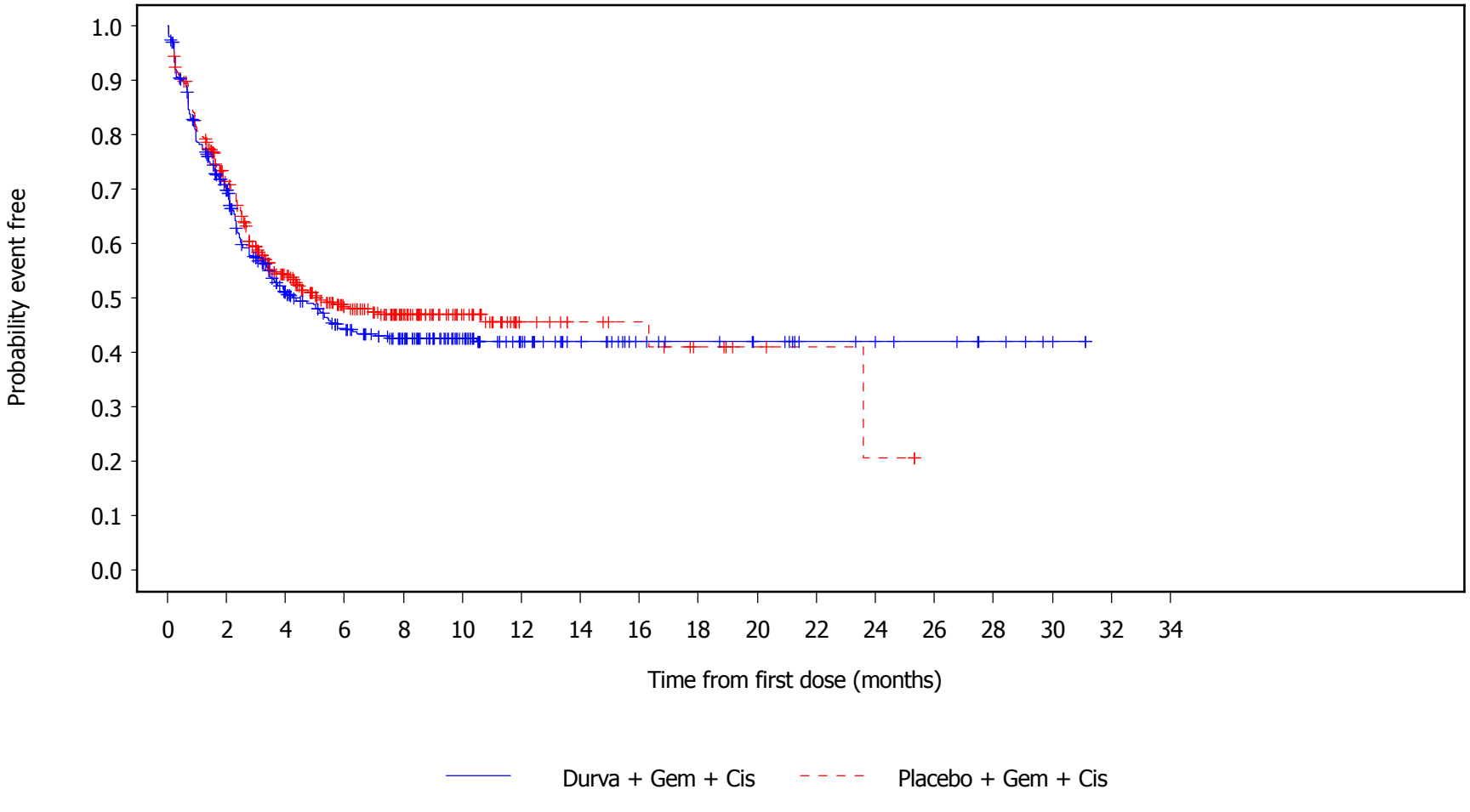
Figure 3.3.27 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Blood and lymphatic system disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	208	118	78	59	35	25	17	12	11	9	5	5	4	4	2	0	0	Durva + Gem + Cis
403	209	113	67	46	23	9	6	6	3	3	2	1	0	0	0	0	0	Placebo + Gem + Cis

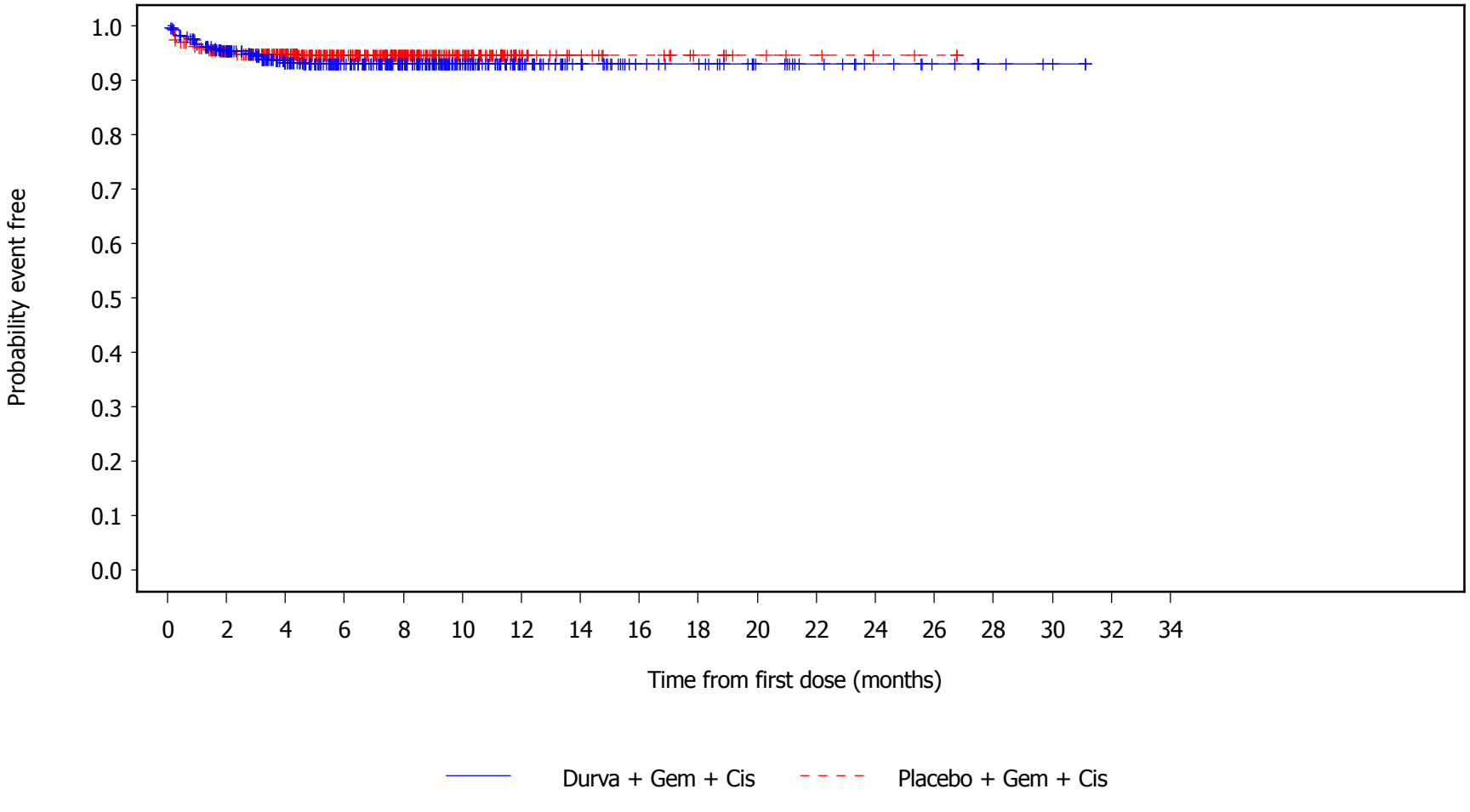
Figure 3.3.28 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Anaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	266	169	132	102	70	44	32	22	19	16	11	10	8	5	2	0	0	Durva + Gem + Cis
403	265	167	112	78	45	17	12	10	6	3	2	1	0	0	0	0	0	Placebo + Gem + Cis

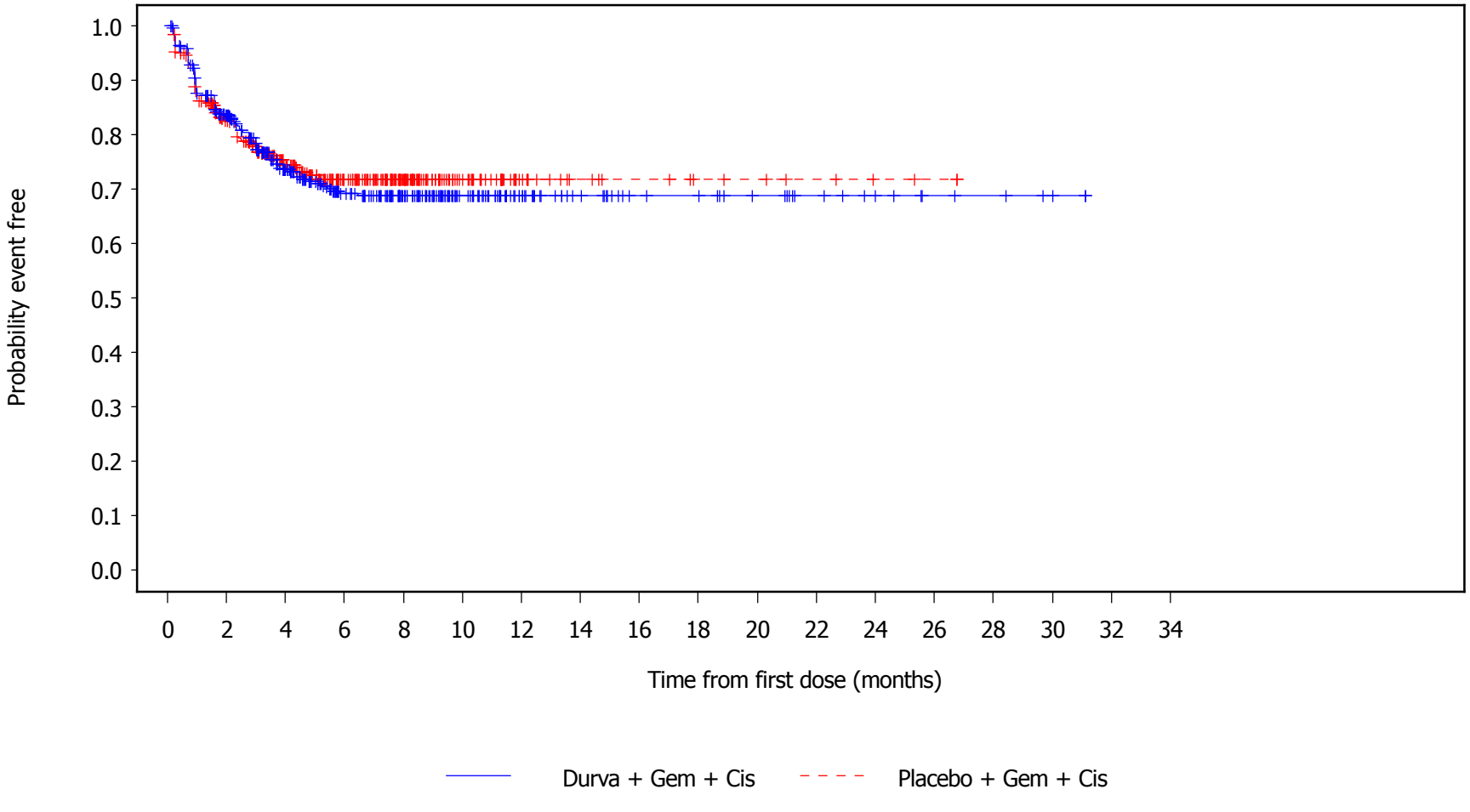
Figure 3.3.29 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Leukopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	356	293	243	182	119	74	52	36	33	22	16	11	7	4	2	0	0	Durva + Gem + Cis
403	355	298	216	148	83	30	20	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

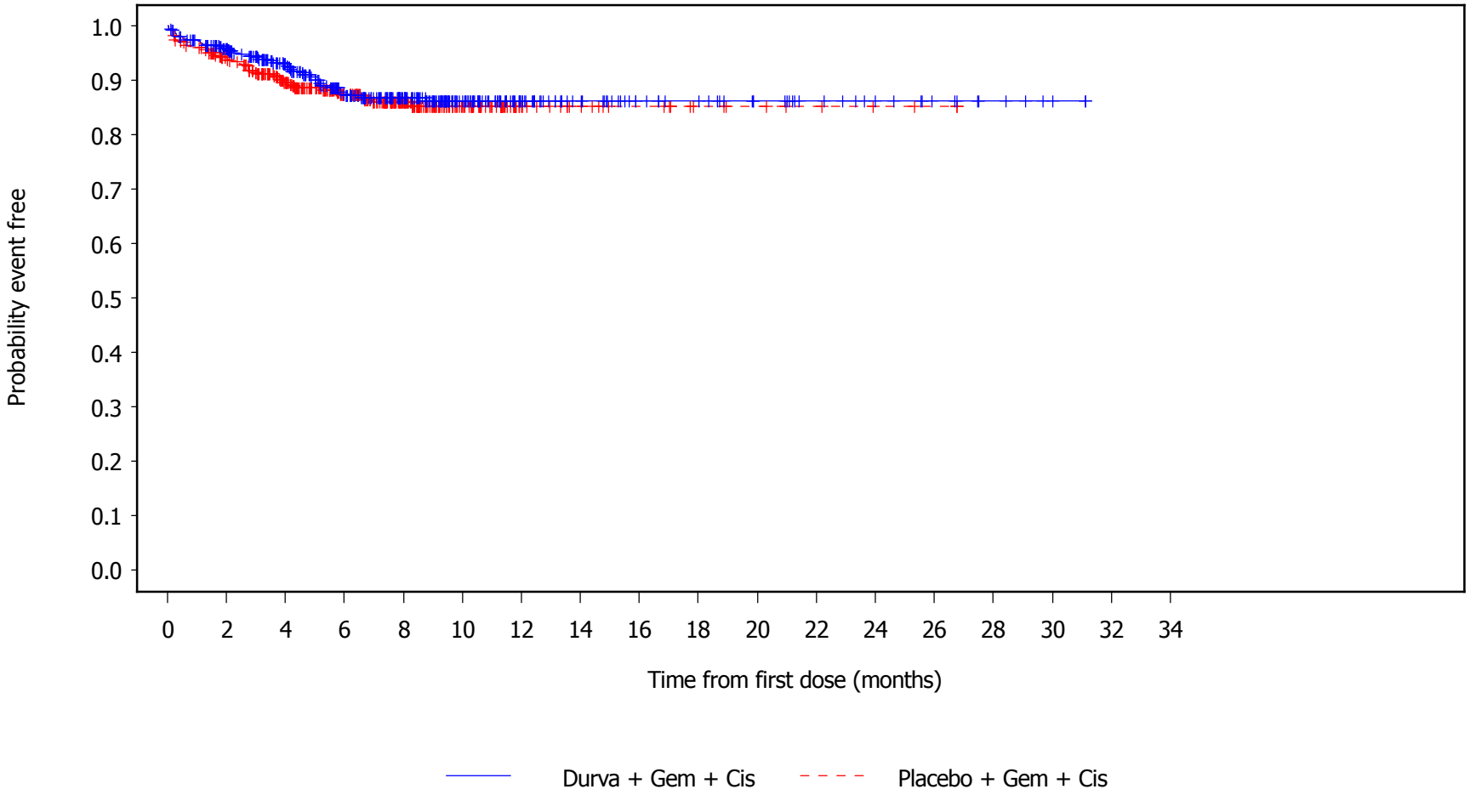
Figure 3.3.30 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	311	223	167	120	75	47	32	23	22	17	12	9	5	4	2	0	0	Durva + Gem + Cis
403	305	226	155	101	51	22	13	10	7	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

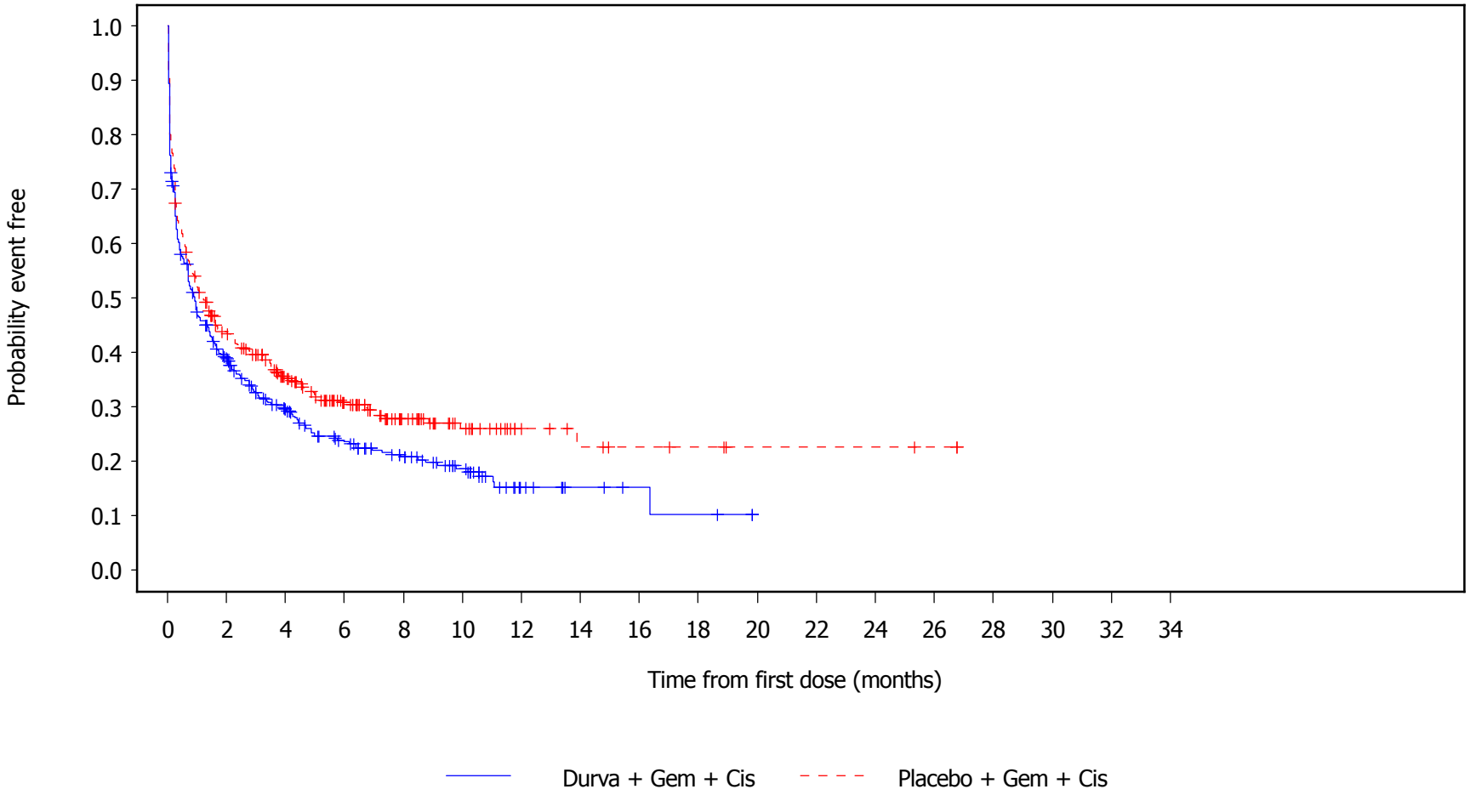
Figure 3.3.31 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Thrombocytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	359	295	233	174	112	69	49	36	32	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	355	284	200	135	71	26	18	13	8	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

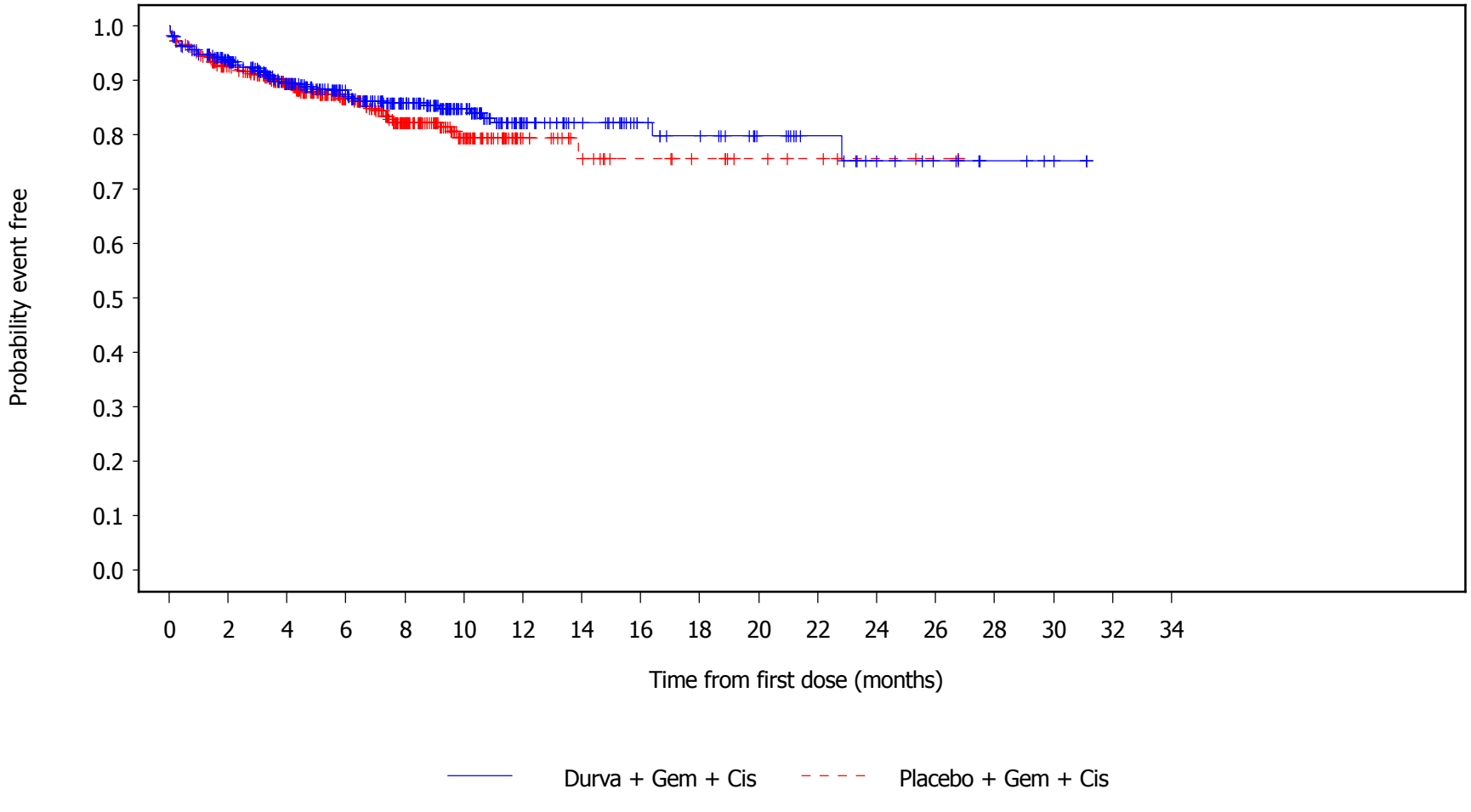
Figure 3.3.32 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Gastrointestinal disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	146	93	65	47	31	10	5	3	2	0	0	0	0	0	0	0	0	Durva + Gem + Cis
403	164	112	75	42	24	10	7	5	4	2	2	2	1	0	0	0	0	Placebo + Gem + Cis

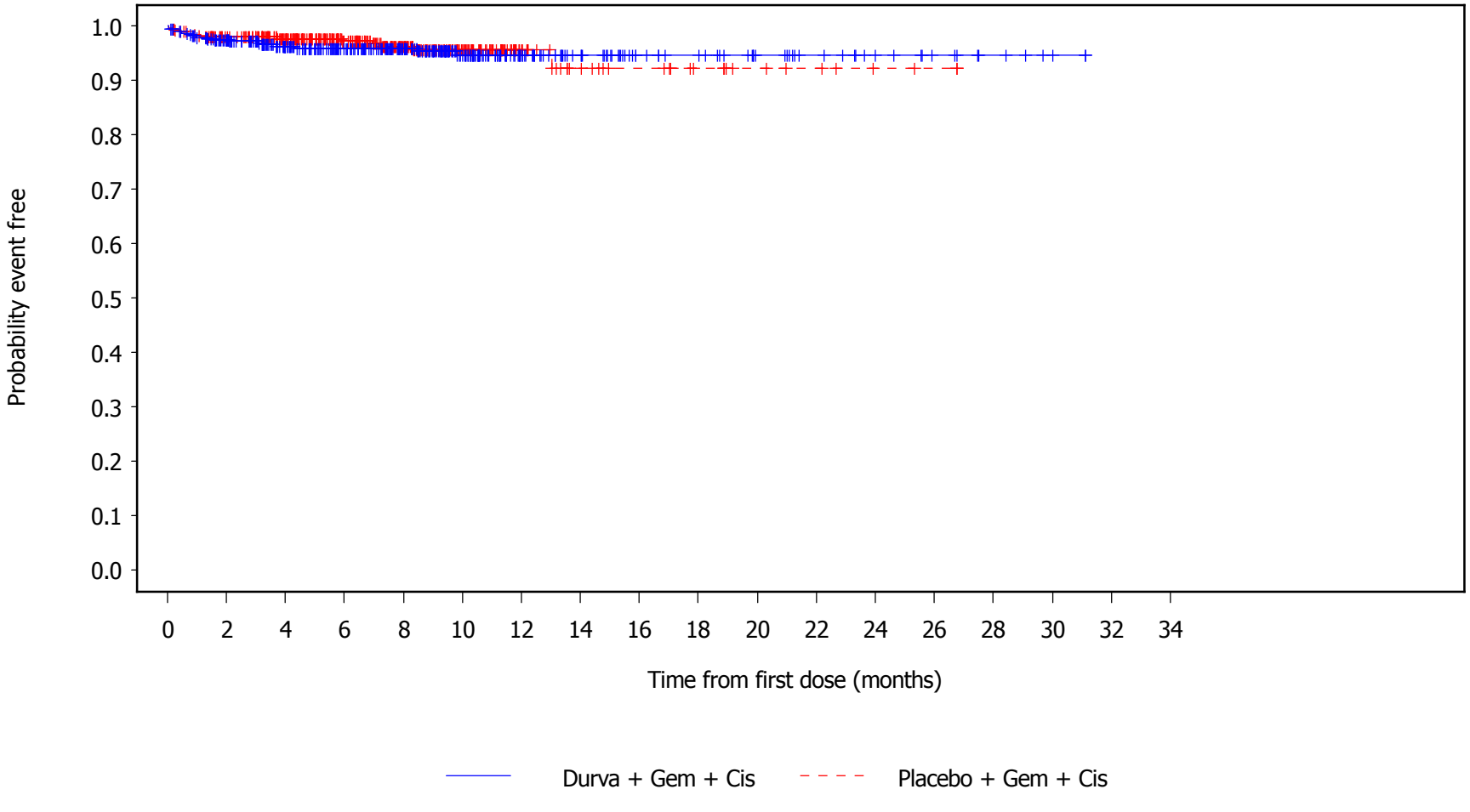
Figure 3.3.33 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Abdominal pain
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	350	285	238	179	116	67	50	36	31	23	17	12	8	4	2	0	0	Durva + Gem + Cis
403	345	283	203	135	74	29	19	13	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

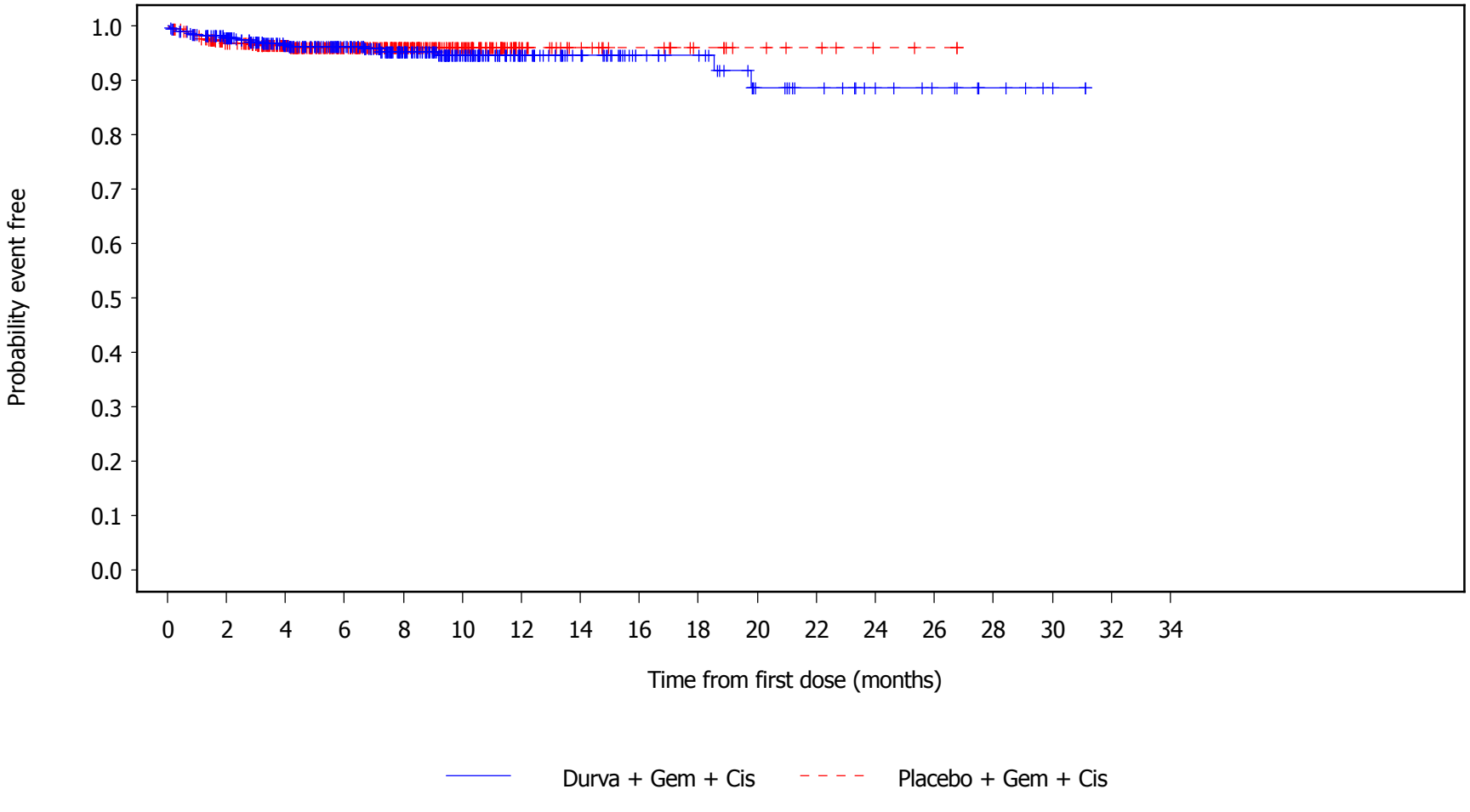
Figure 3.3.34 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Ascites
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	364	305	258	195	127	79	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	366	309	230	158	89	34	21	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

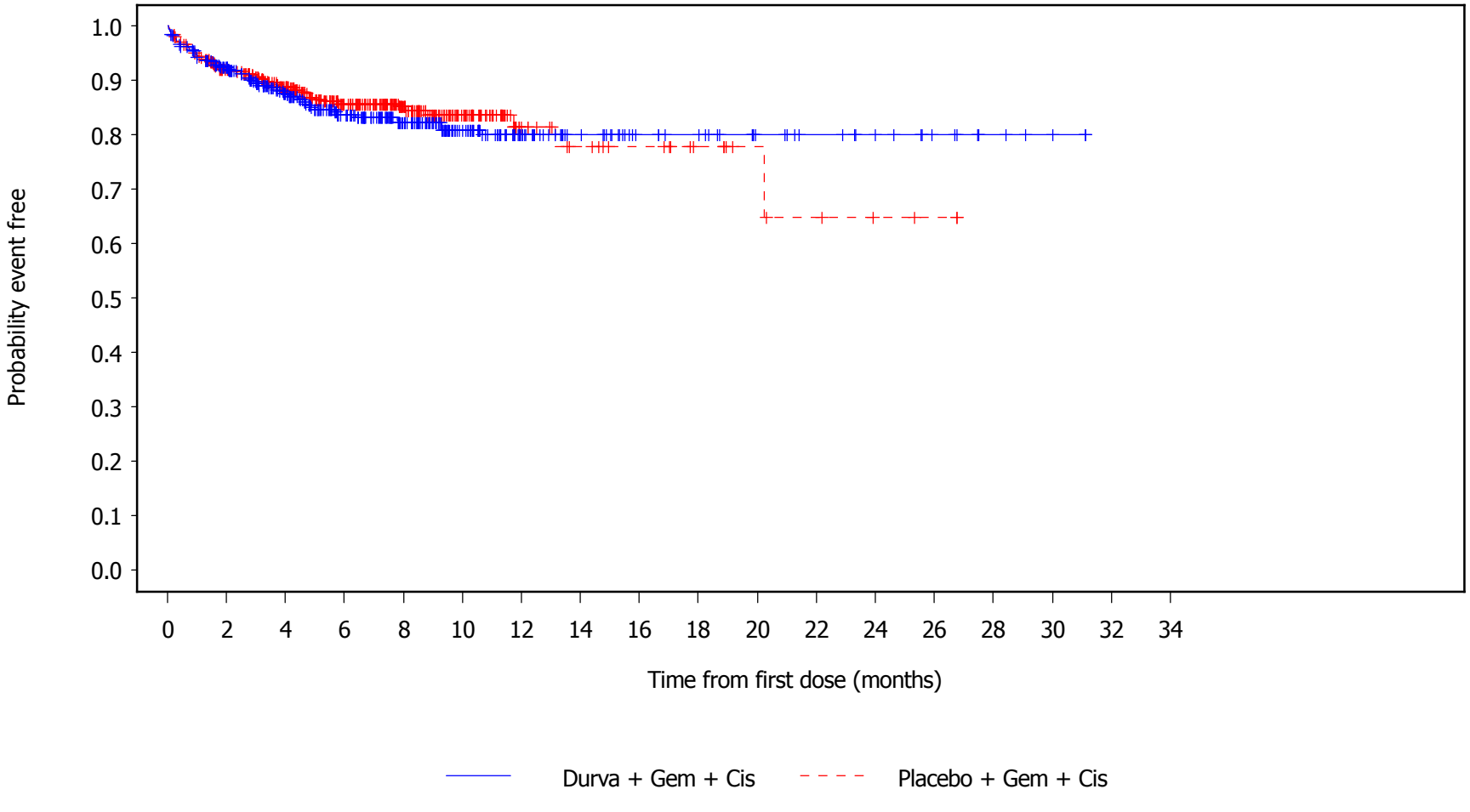
Figure 3.3.35 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Abdominal distension
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	366	303	255	191	127	79	58	40	36	23	18	13	9	5	2	0	0	Durva + Gem + Cis
403	360	303	225	154	87	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

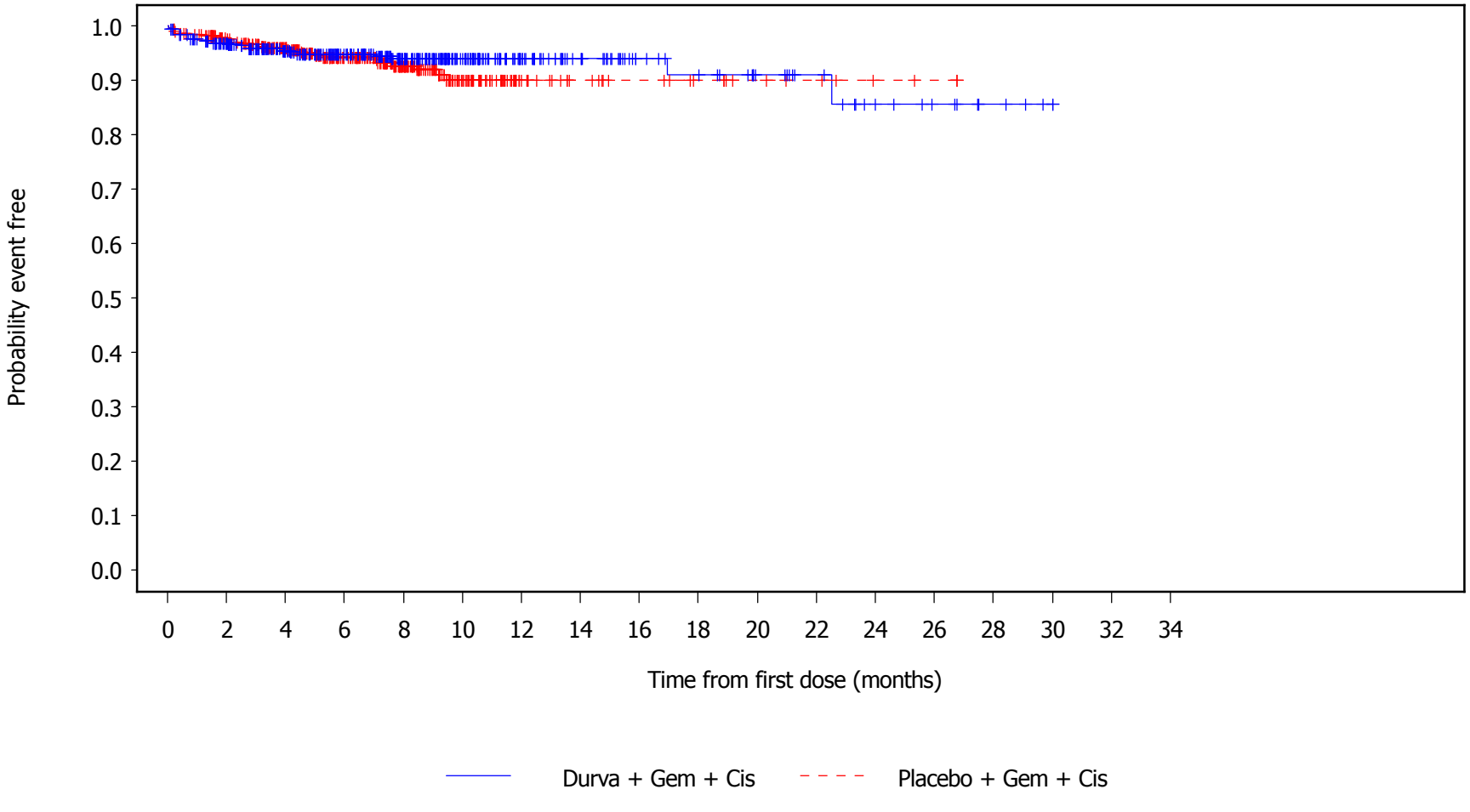
Figure 3.3.36 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Diarrhoea
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	345	274	219	159	104	64	45	32	29	20	16	13	8	4	2	0	0	Durva + Gem + Cis
403	340	279	201	136	77	27	19	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

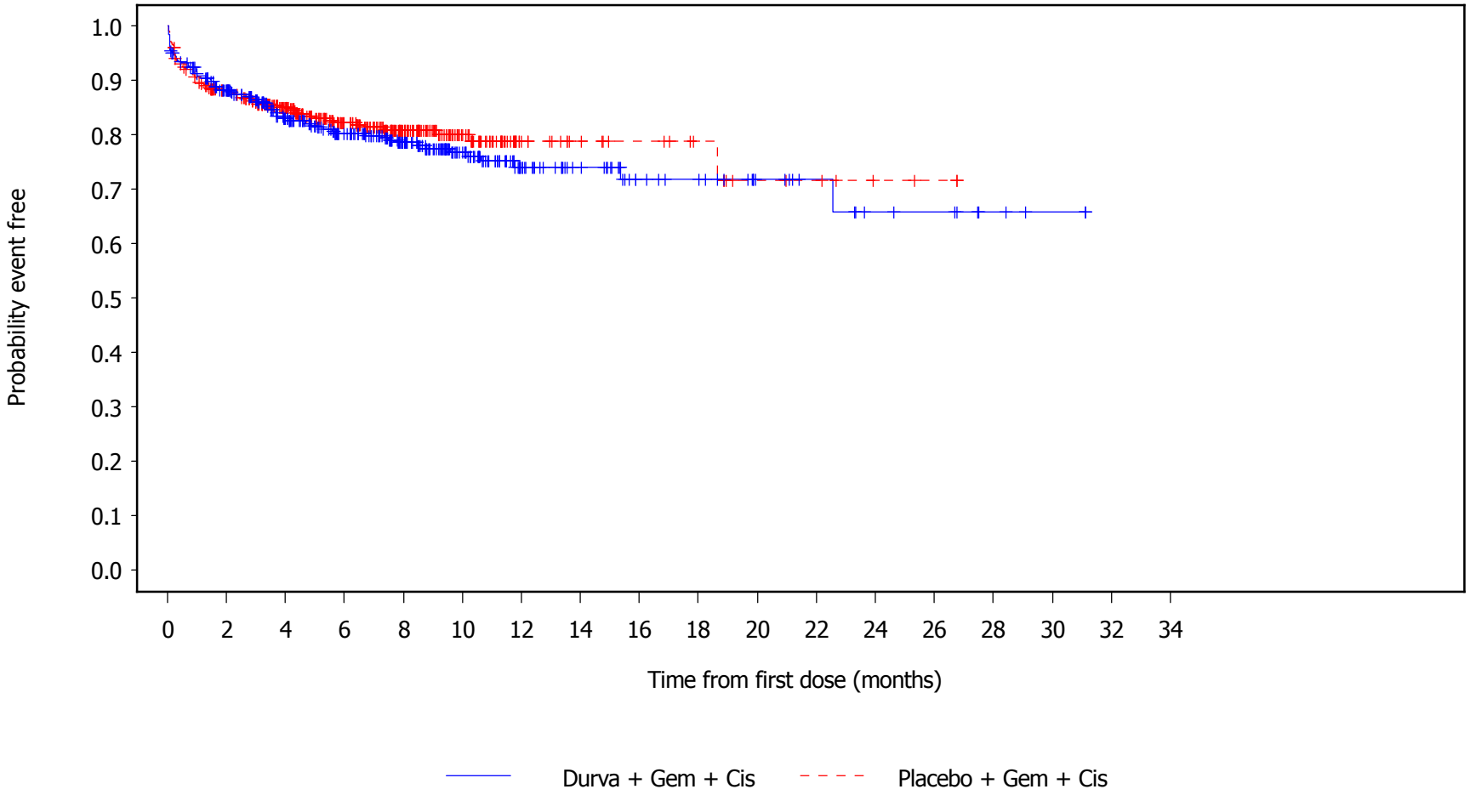
Figure 3.3.37 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Dyspepsia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	363	301	251	186	123	75	53	35	31	23	18	12	8	4	1	0	0	Durva + Gem + Cis
403	363	301	220	148	78	30	20	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

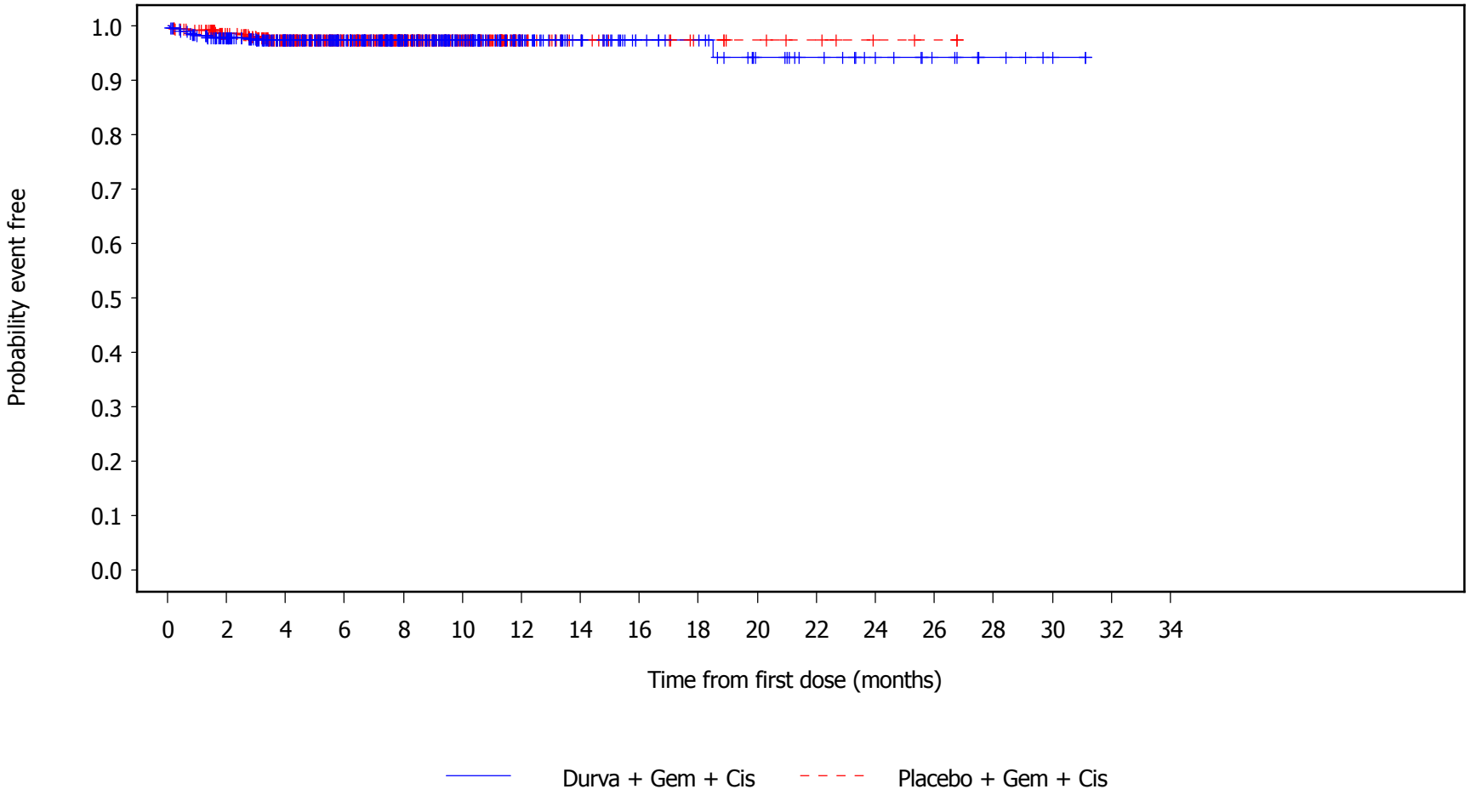
Figure 3.3.38 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Vomiting
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	331	261	216	161	106	59	43	28	25	16	12	8	7	3	1	0	0	Durva + Gem + Cis
403	329	269	193	127	72	27	19	15	11	6	5	2	1	0	0	0	0	Placebo + Gem + Cis

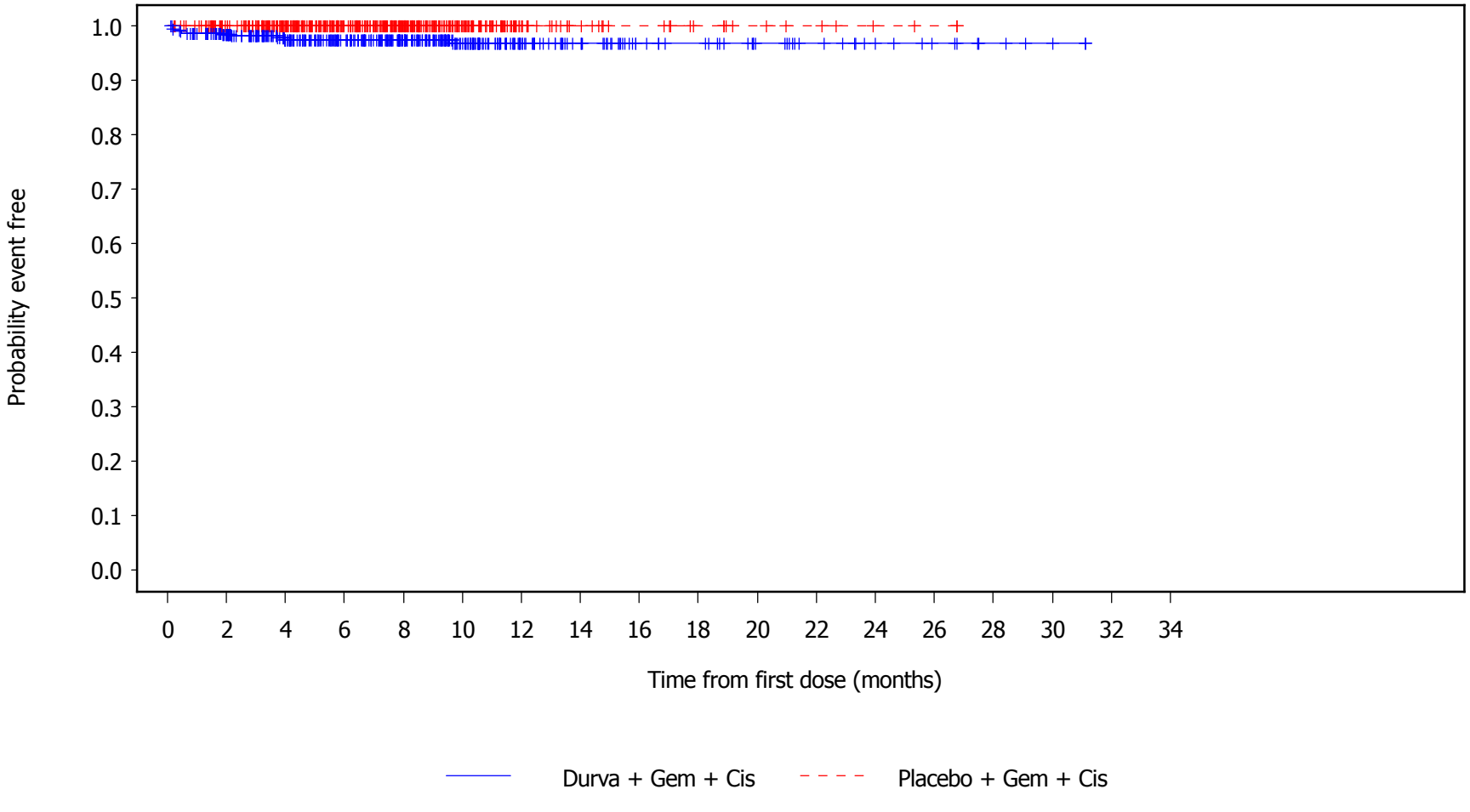
Figure 3.3.39 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Gastrooesophageal reflux disease
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	365	306	255	190	128	77	55	38	34	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	366	304	225	155	86	31	19	14	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

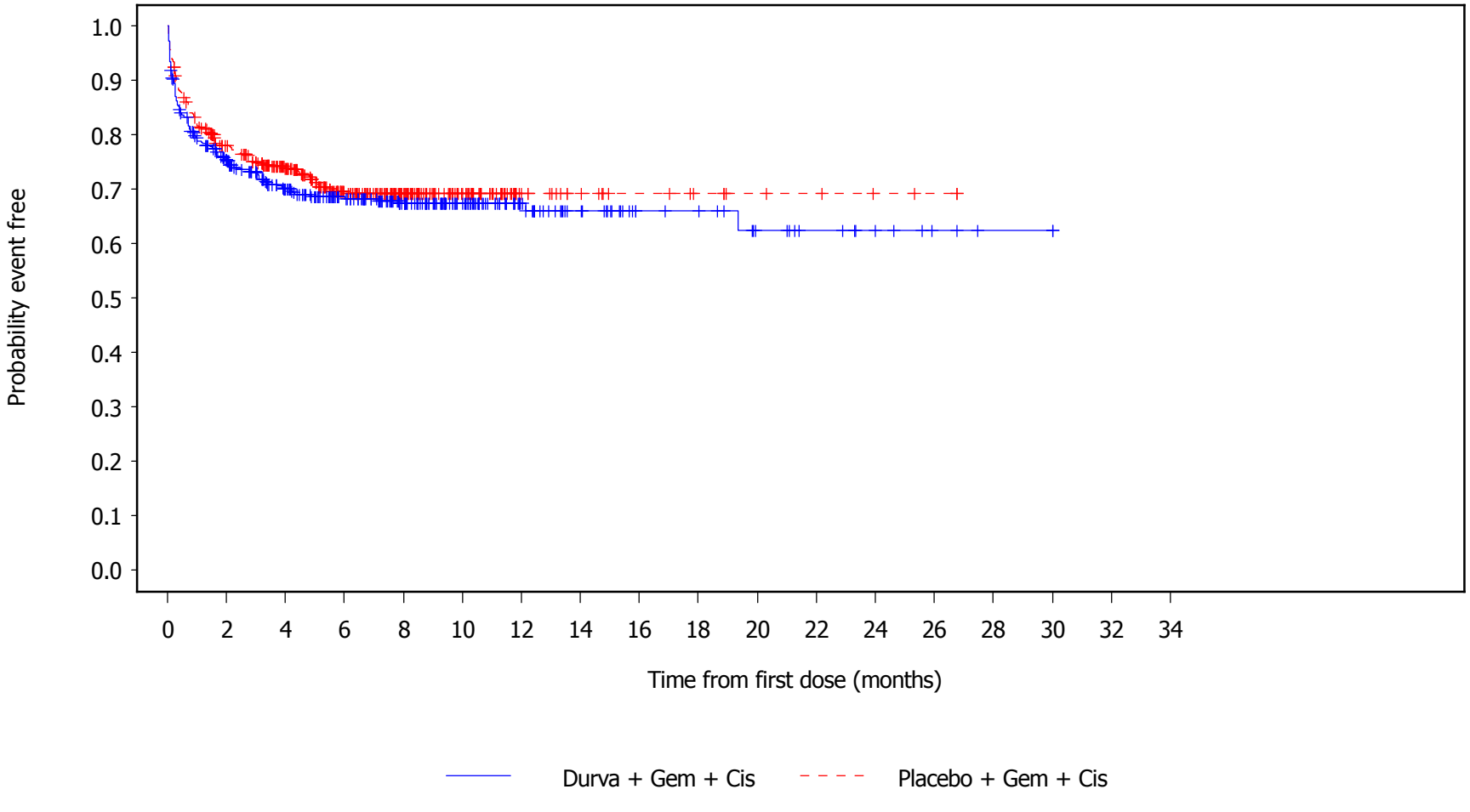
Figure 3.3.40 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Dry mouth
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	368	307	257	192	127	76	55	37	33	23	17	12	8	4	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

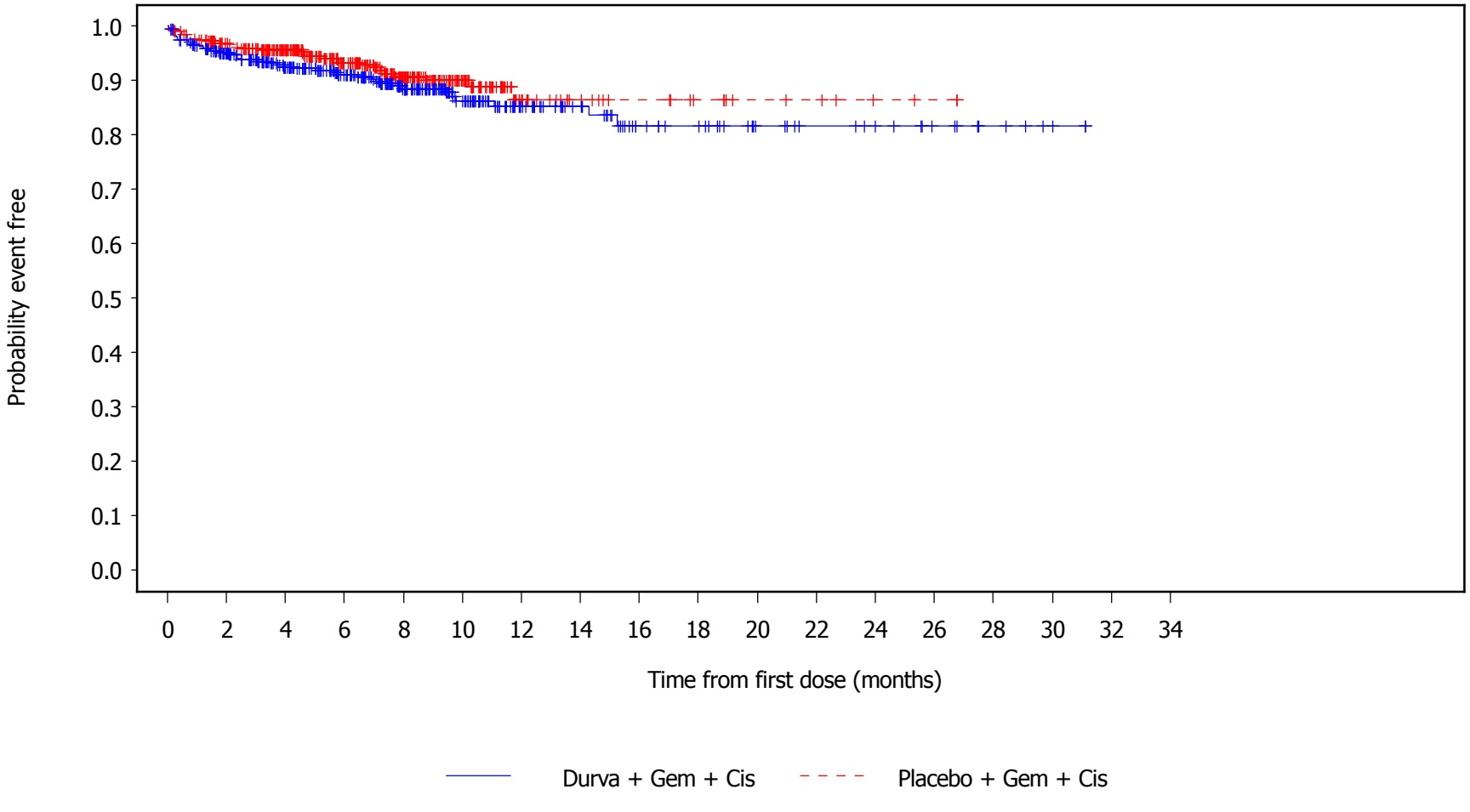
Figure 3.3.41 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Constipation
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	282	222	180	138	93	53	36	22	21	14	10	7	3	1	1	0	0	Durva + Gem + Cis
403	290	231	163	110	64	24	16	11	8	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

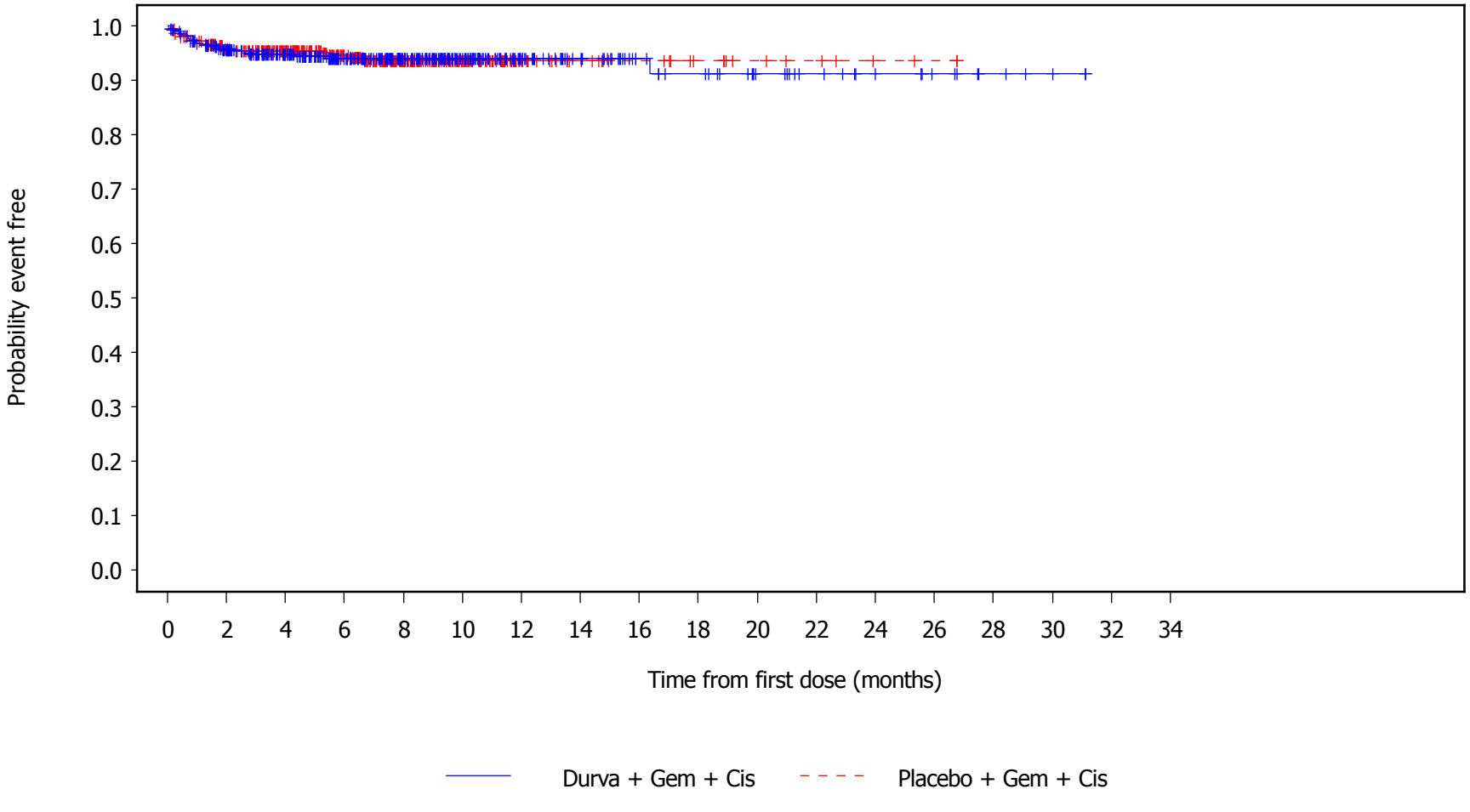
Figure 3.3.42 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Abdominal pain upper
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	354	291	244	174	113	69	51	34	30	20	16	14	9	5	2	0	0	Durva + Gem + Cis
403	360	299	218	145	82	30	19	14	10	6	5	2	1	0	0	0	0	Placebo + Gem + Cis

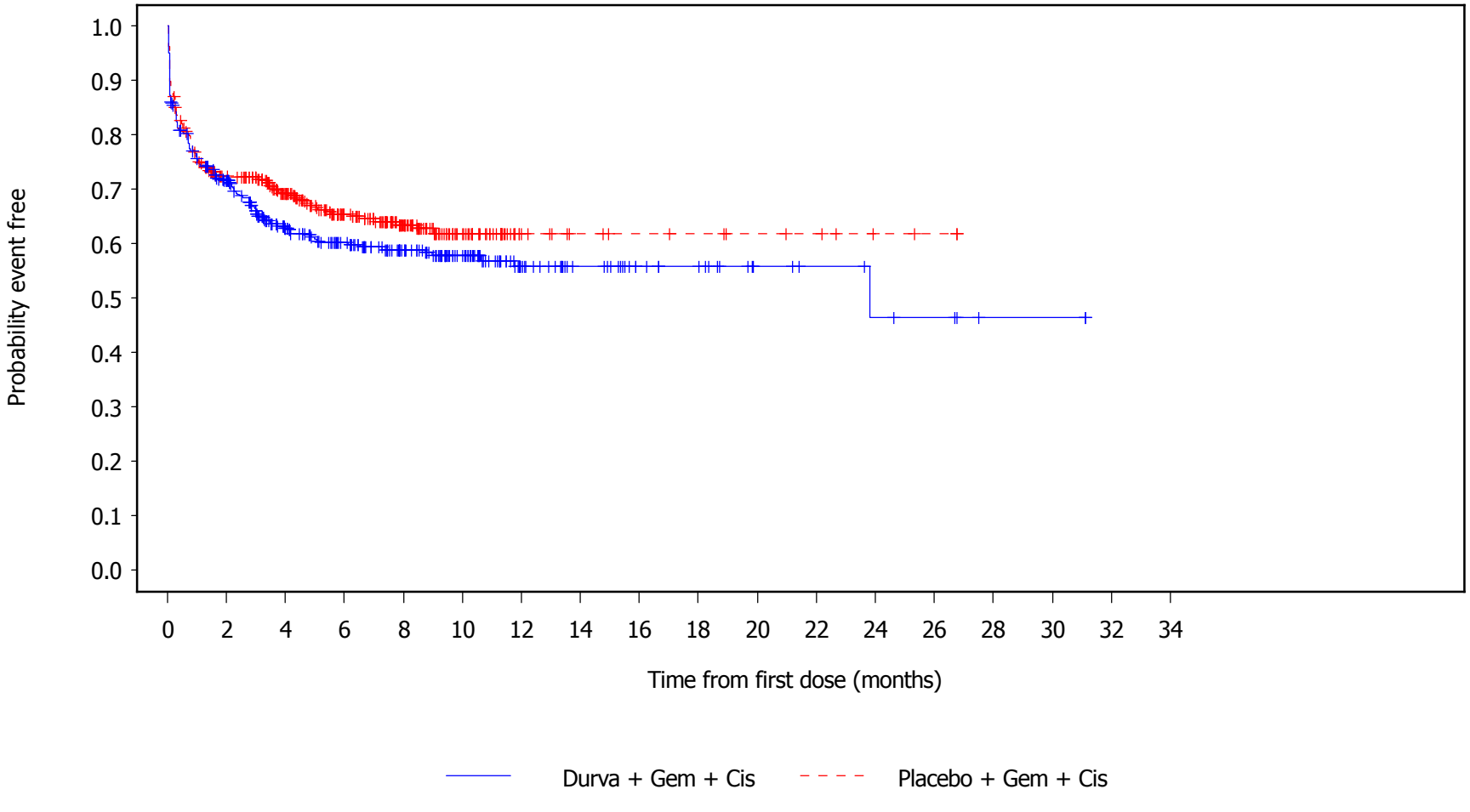
Figure 3.3.43 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Stomatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	358	299	247	184	122	72	52	35	30	21	16	12	8	4	2	0	0	Durva + Gem + Cis
403	357	299	219	148	84	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

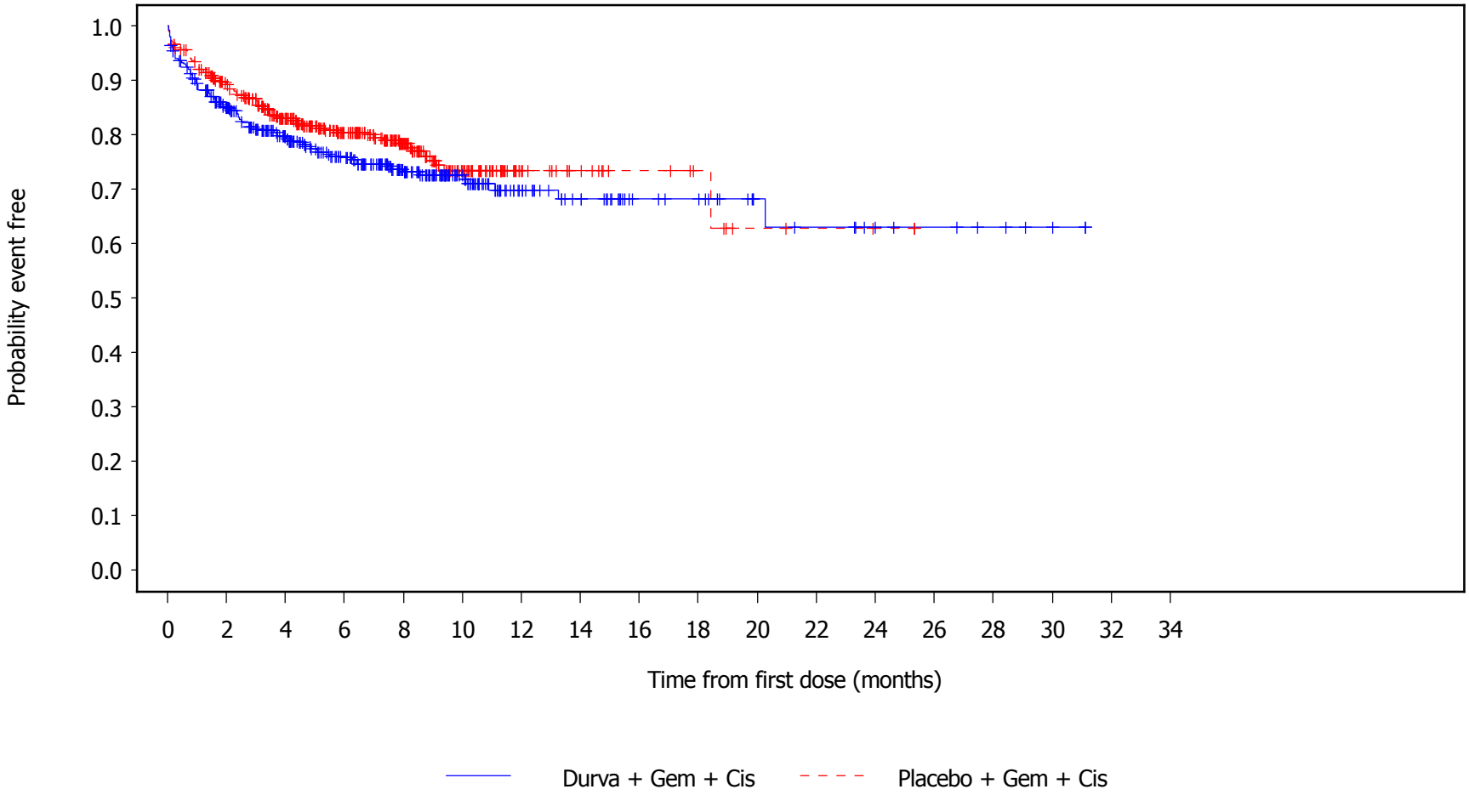
Figure 3.3.44 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Nausea
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	267	192	158	118	83	44	30	20	17	9	7	5	4	1	1	0	0	Durva + Gem + Cis
403	271	215	150	98	51	16	11	9	8	6	5	2	1	0	0	0	0	Placebo + Gem + Cis

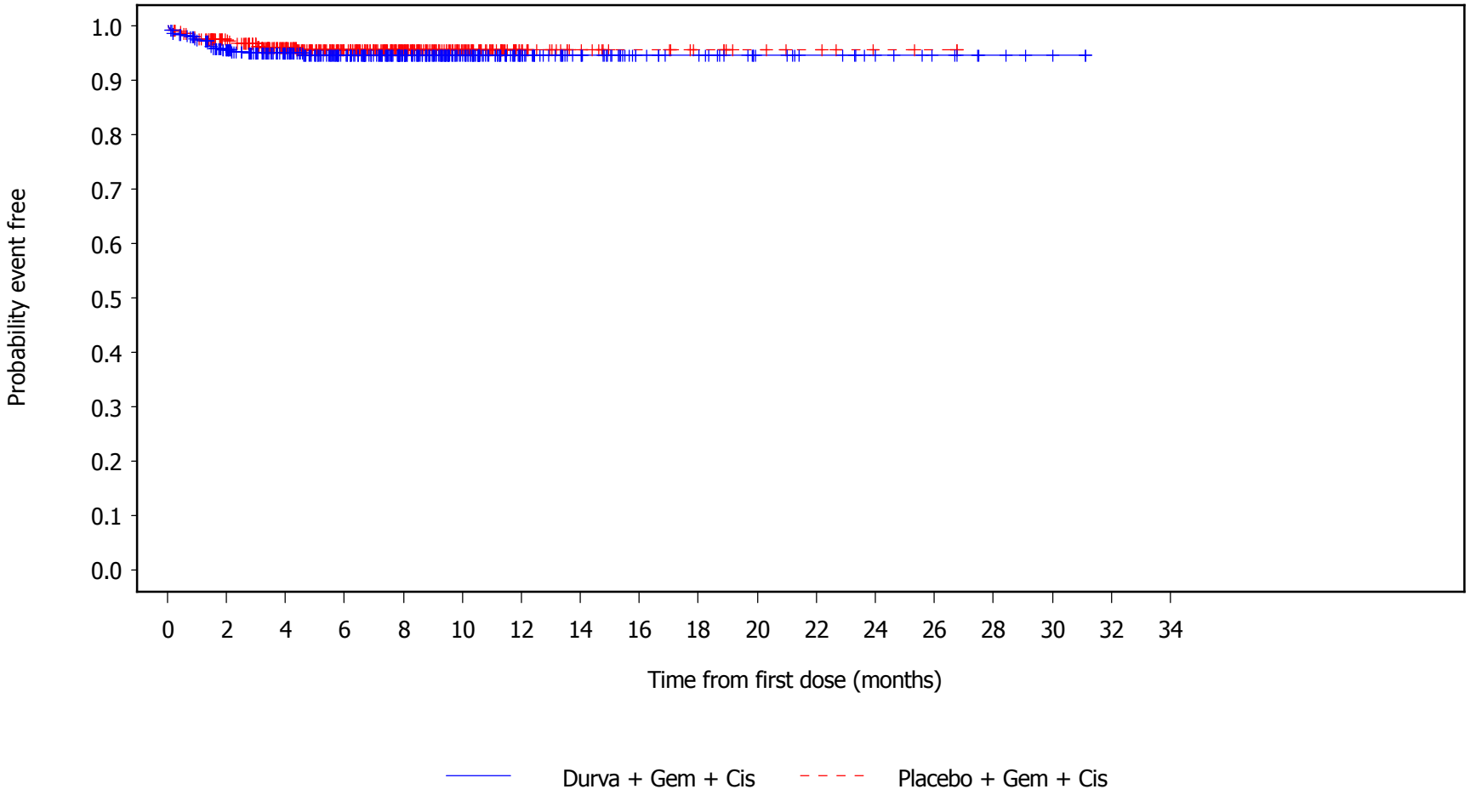
Figure 3.3.45 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Nervous system disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	319	251	204	145	91	51	38	24	22	13	11	8	6	4	2	0	0	Durva + Gem + Cis
403	332	258	184	120	64	24	16	10	7	3	2	1	0	0	0	0	0	Placebo + Gem + Cis

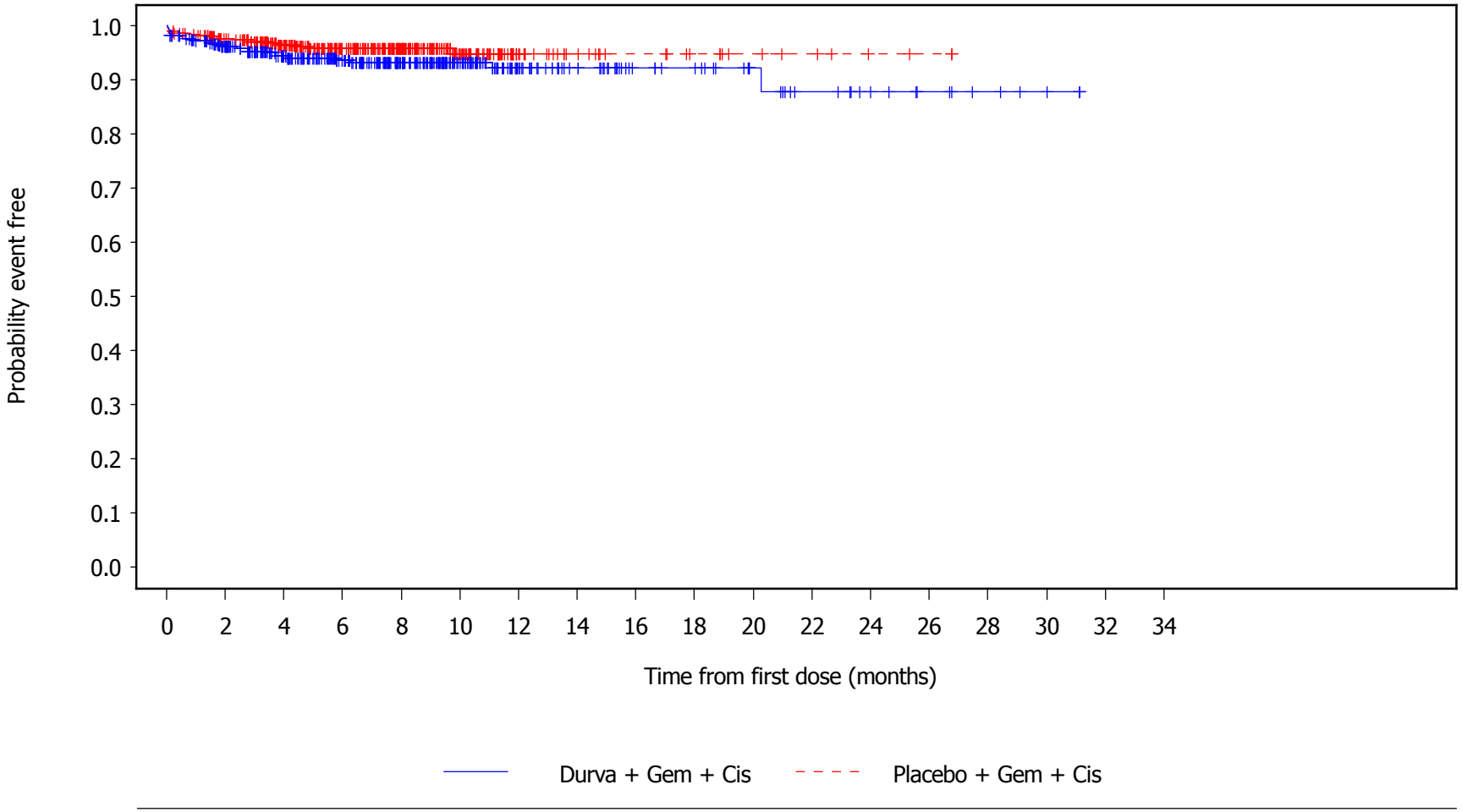
Figure 3.3.46 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Dysgeusia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	358	301	250	187	123	73	53	35	31	20	16	12	8	4	2	0	0	Durva + Gem + Cis
403	362	299	221	151	85	33	21	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

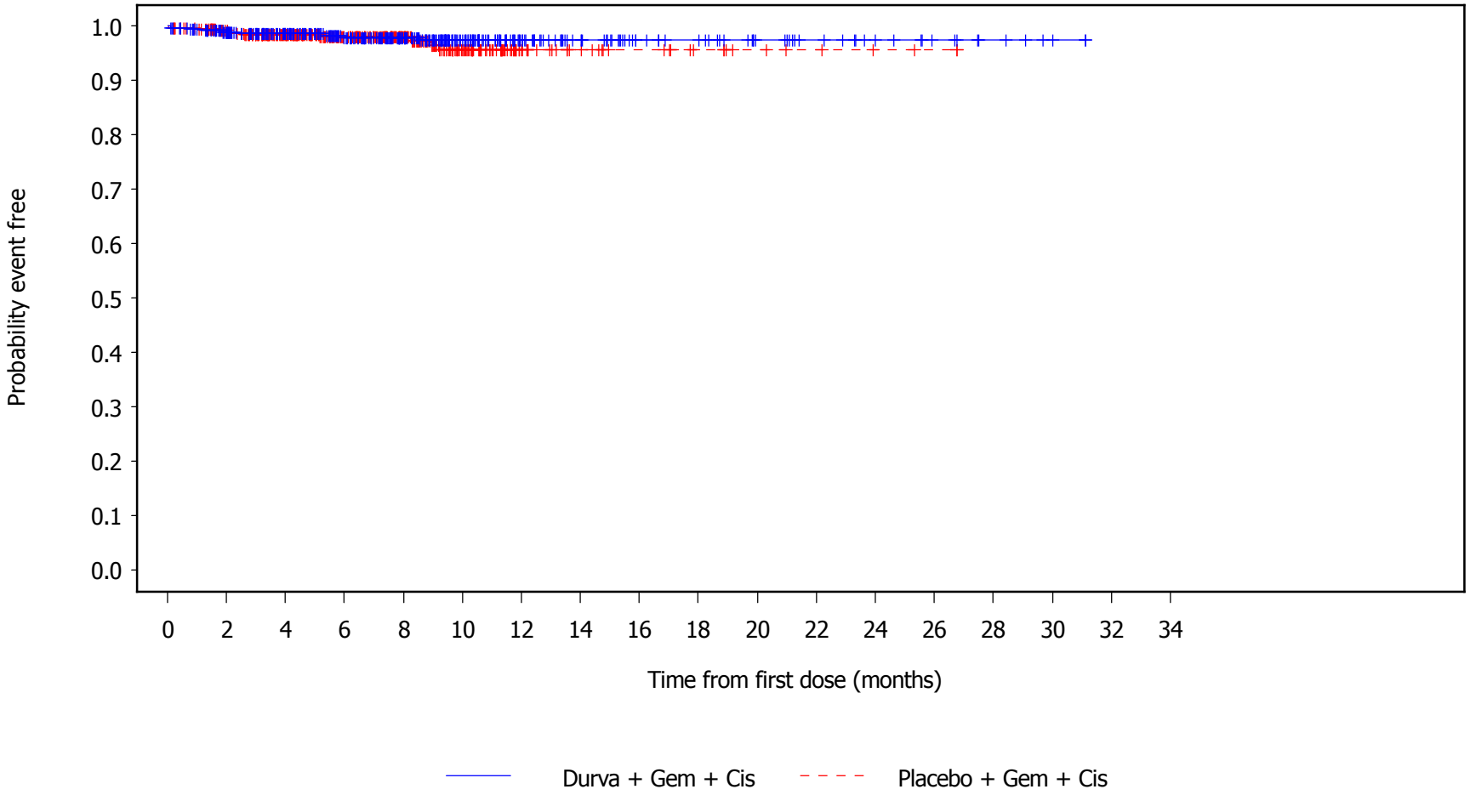
Figure 3.3.47 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Headache
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	359	298	246	180	117	67	49	33	30	21	15	11	7	4	2	0	0	Durva + Gem + Cis
403	363	302	222	154	85	33	21	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

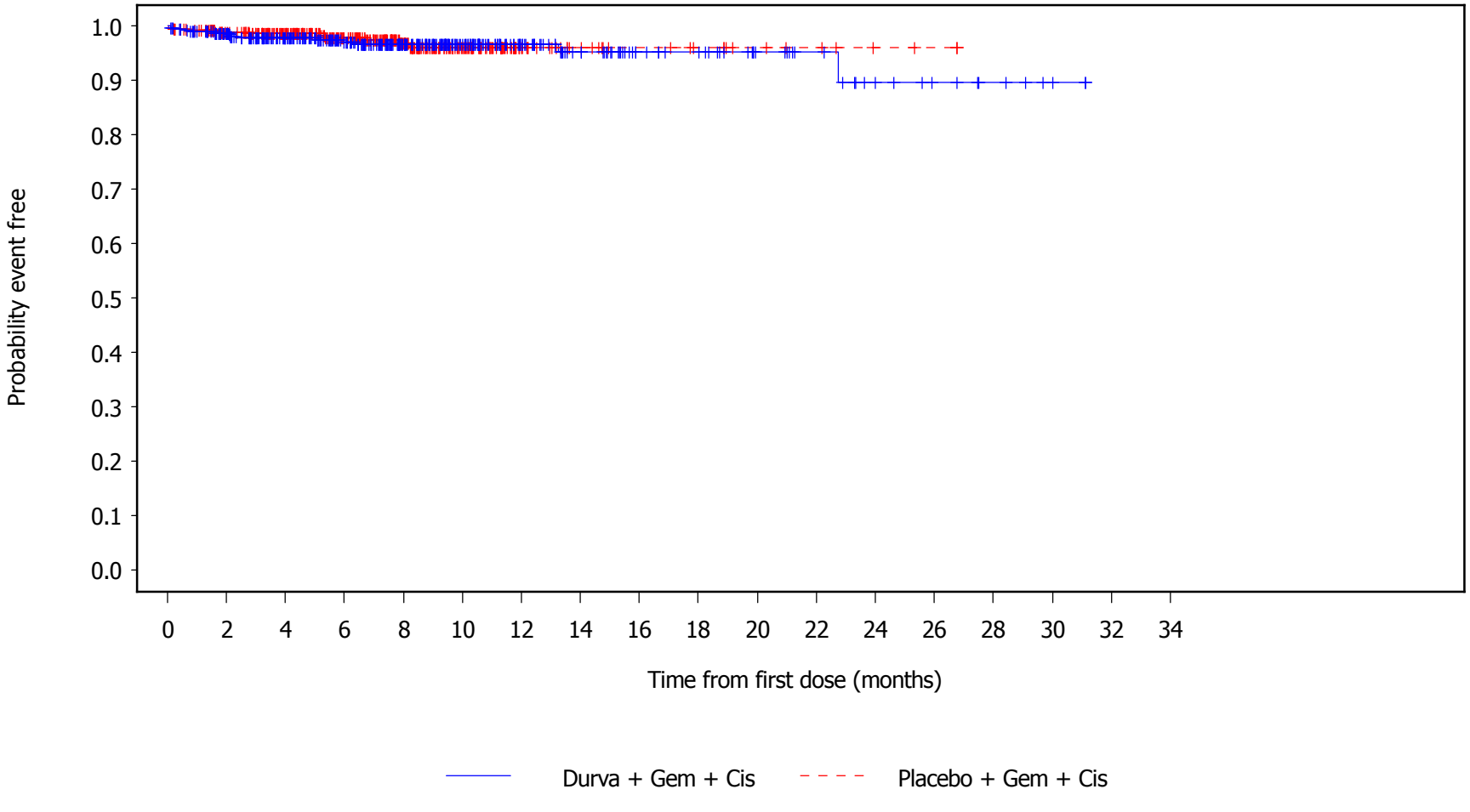
Figure 3.3.48 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Paraesthesia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	310	259	194	127	78	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	307	227	155	84	32	21	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

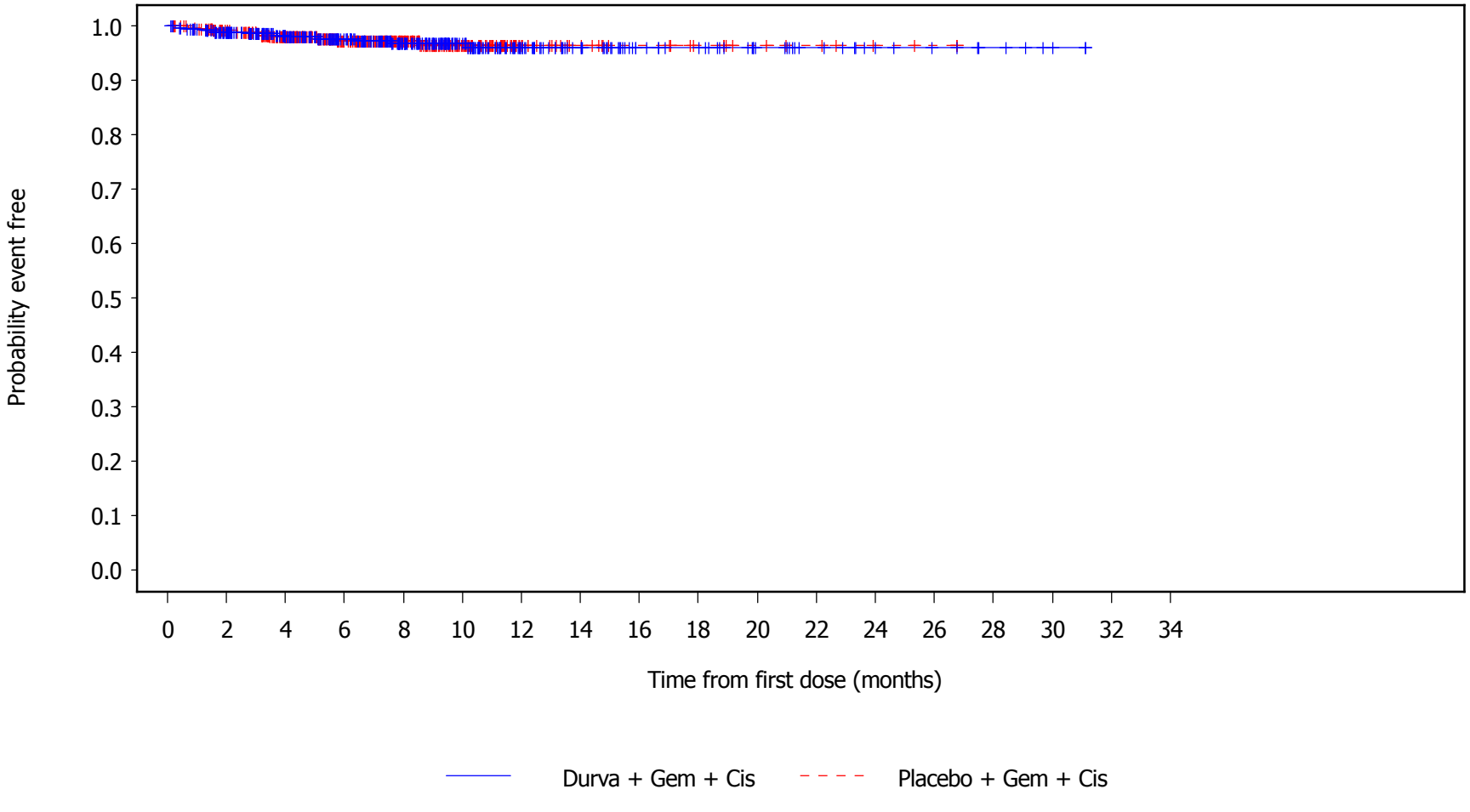
Figure 3.3.49 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Neuropathy peripheral
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	368	307	256	190	126	78	55	38	34	23	18	12	8	5	2	0	0	Durva + Gem + Cis
403	367	310	227	152	85	32	20	14	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

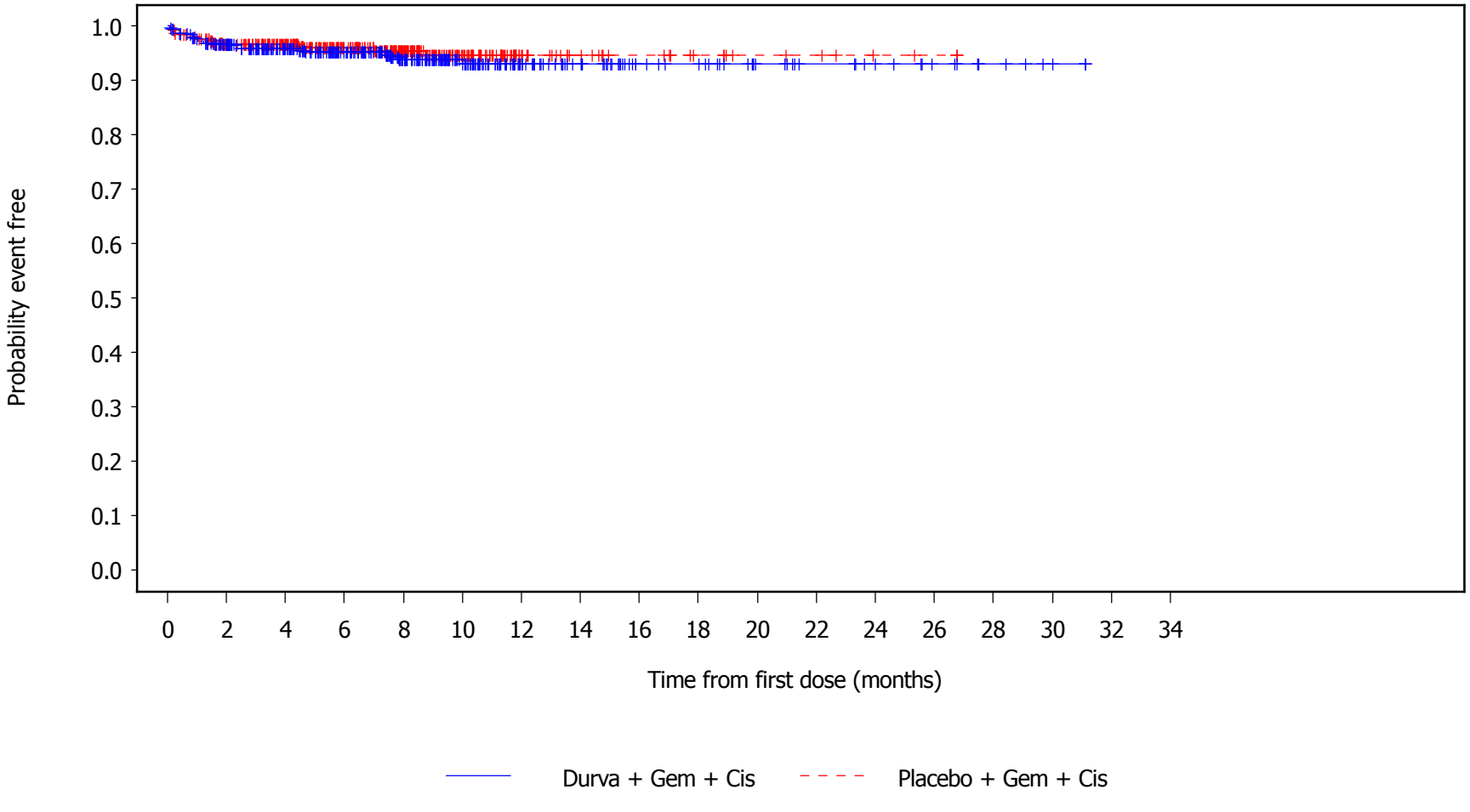
Figure 3.3.50 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Peripheral sensory neuropathy
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	309	257	192	126	76	55	37	33	22	16	11	8	5	2	0	0	Durva + Gem + Cis
403	368	306	224	153	85	32	21	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

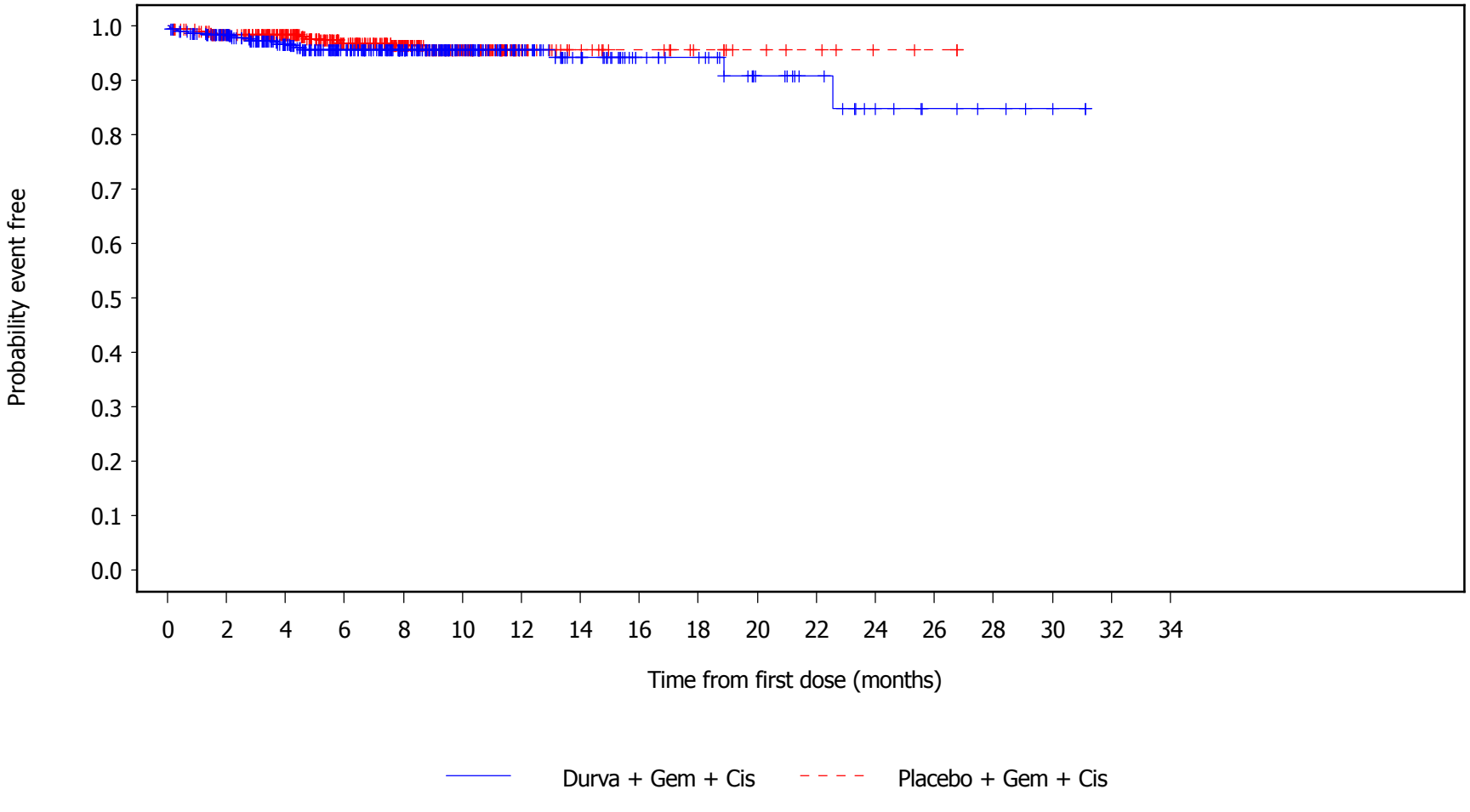
Figure 3.3.51 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Dizziness
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	360	301	252	183	122	74	54	36	33	22	17	14	9	5	2	0	0	Durva + Gem + Cis
403	358	303	221	152	83	32	21	15	10	6	5	2	1	0	0	0	0	Placebo + Gem + Cis

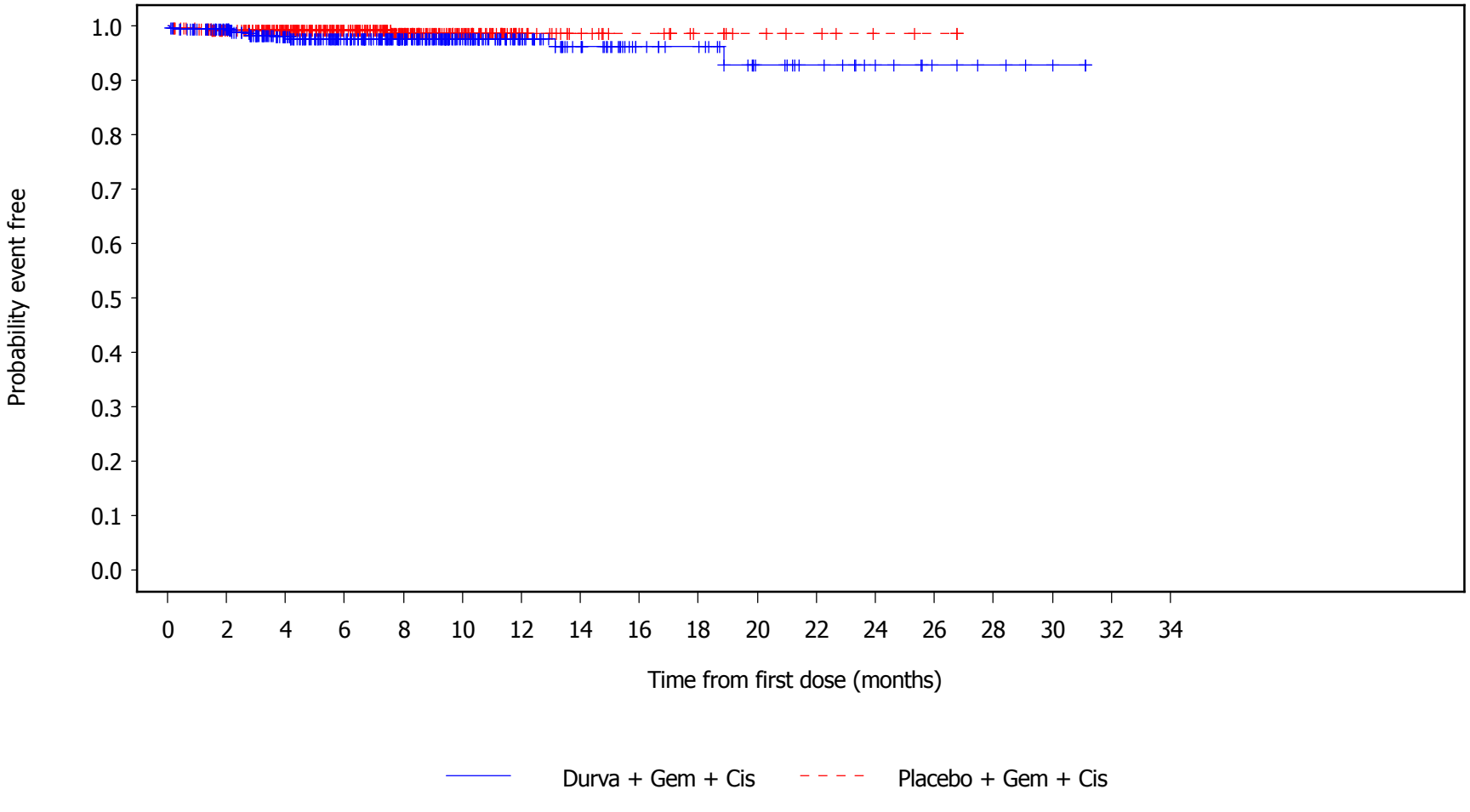
Figure 3.3.52 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Ear and labyrinth disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	304	255	191	126	78	55	37	33	21	16	10	6	4	2	0	0	Durva + Gem + Cis
403	365	307	223	153	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

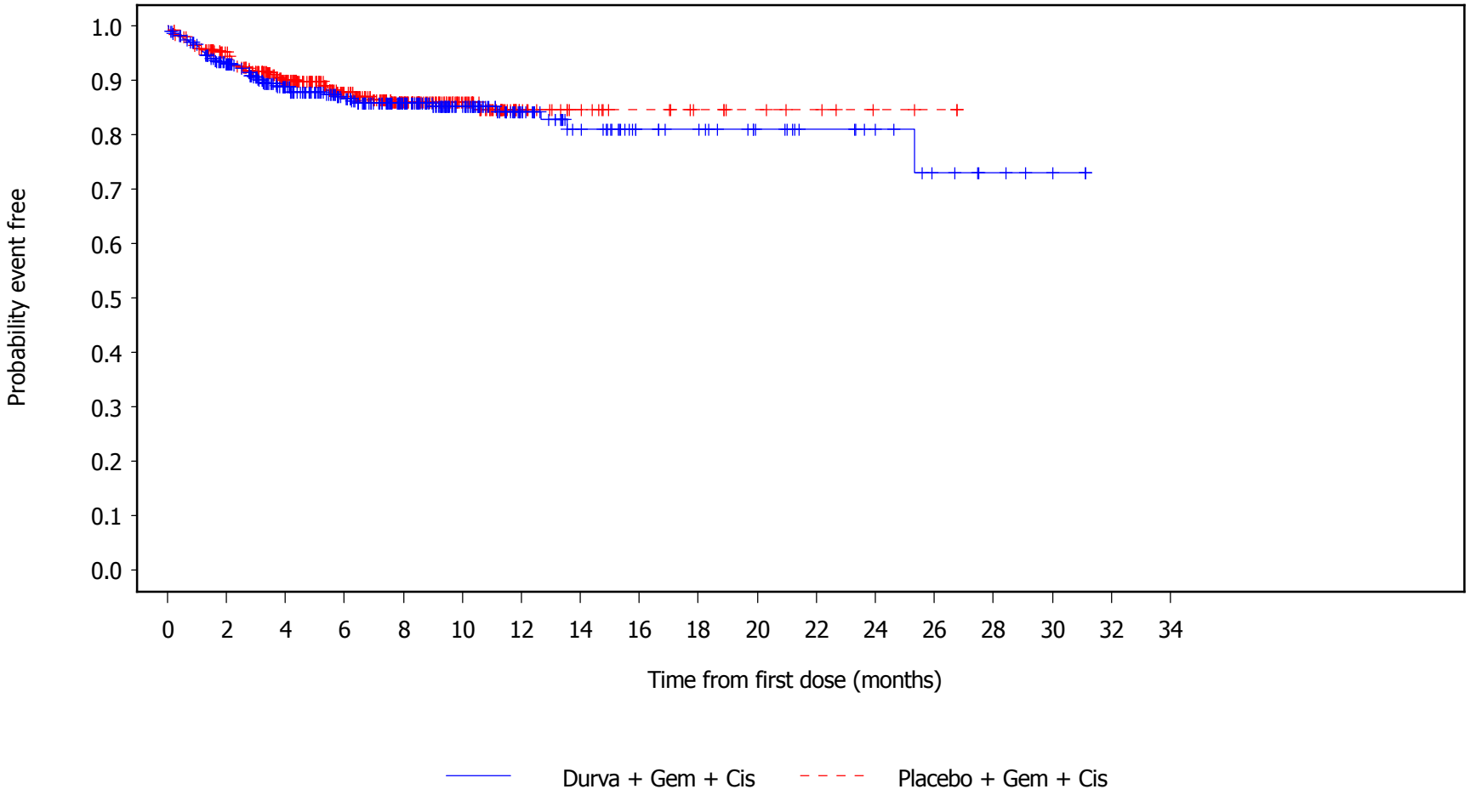
Figure 3.3.53 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Tinnitus
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	308	258	193	127	78	55	37	33	21	16	11	6	4	2	0	0	Durva + Gem + Cis
403	368	310	229	156	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

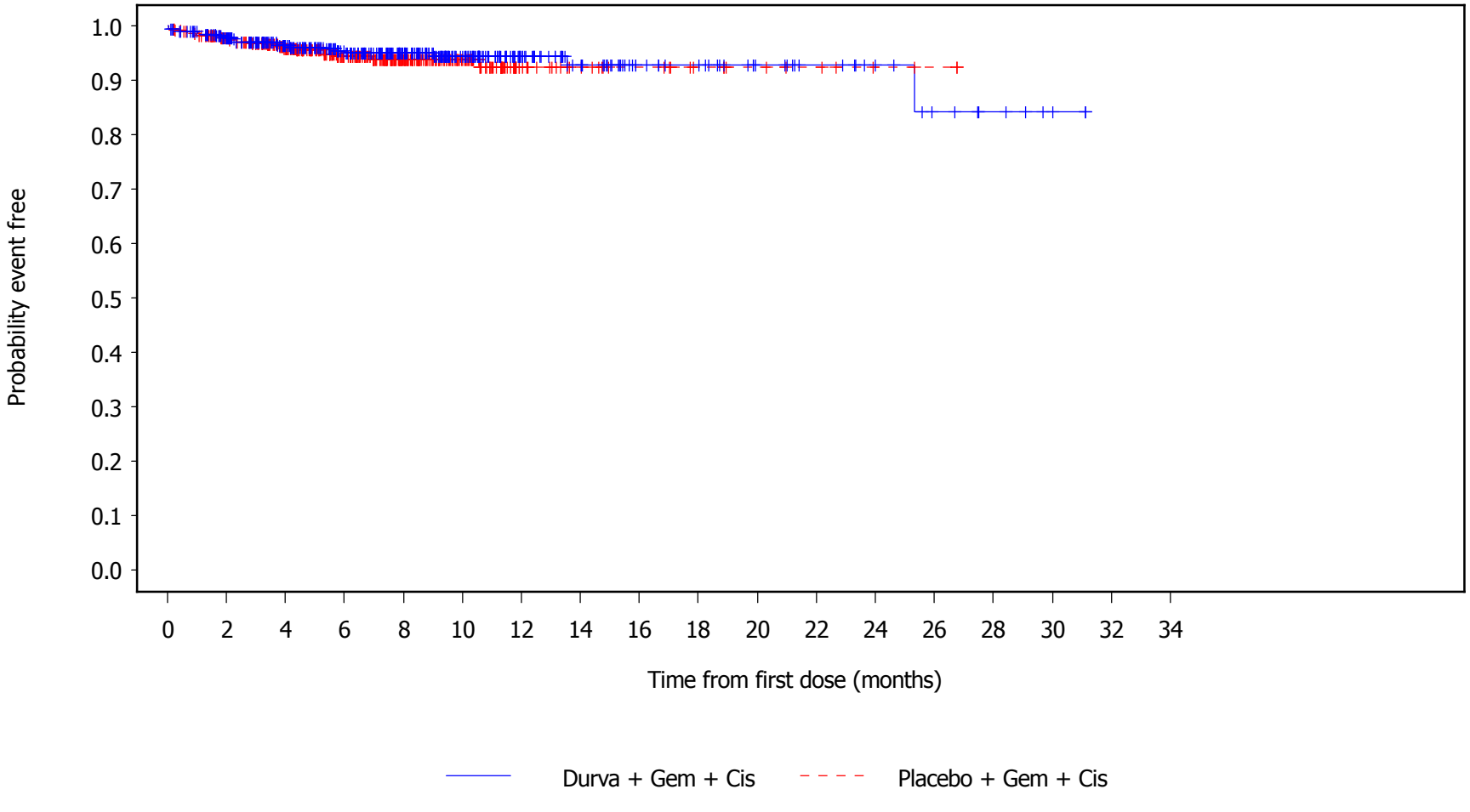
Figure 3.3.54 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Vascular disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	349	278	231	172	115	66	45	31	28	20	15	12	7	4	2	0	0	Durva + Gem + Cis
403	355	284	207	140	77	30	20	14	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

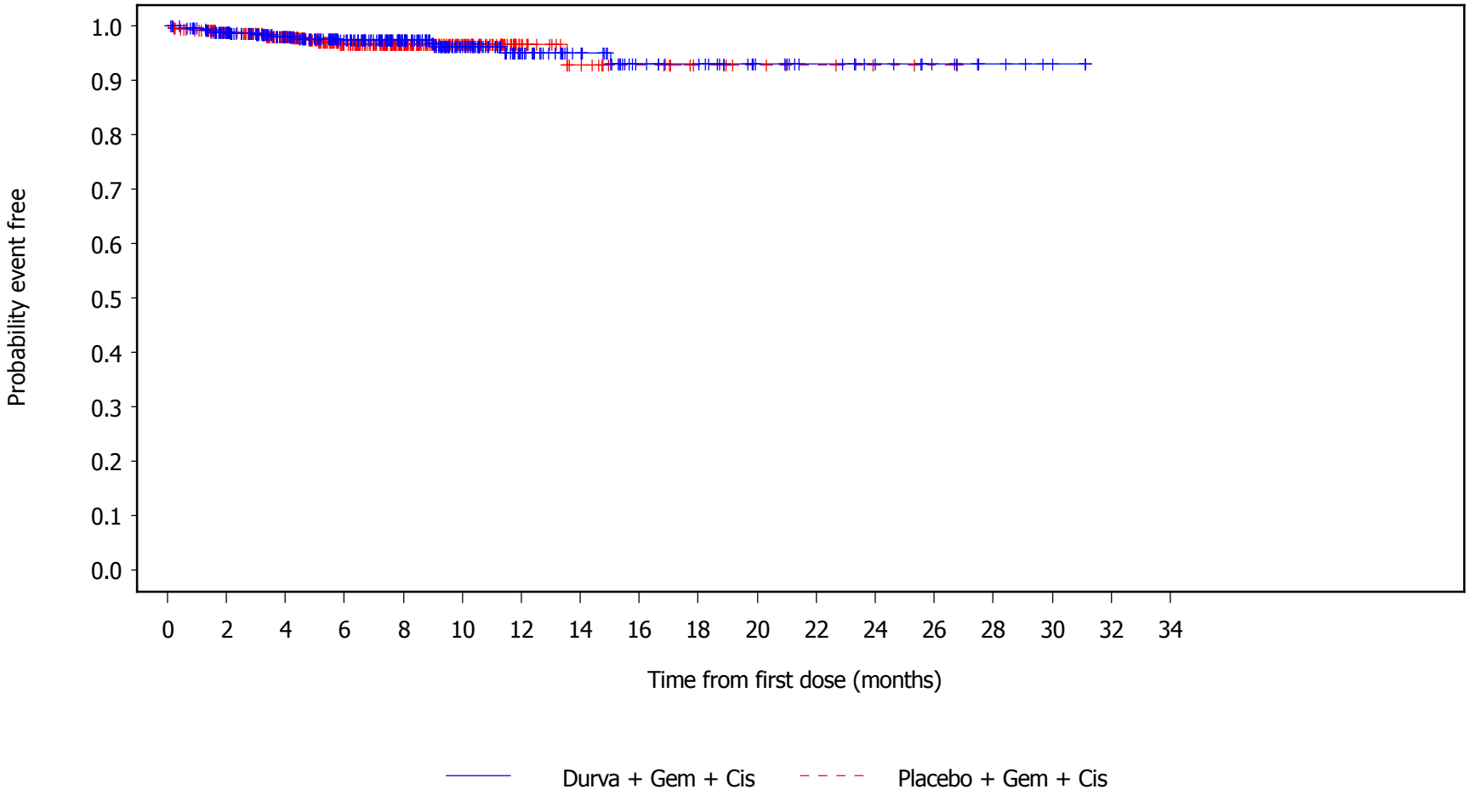
Figure 3.3.55 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Hypertension
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	366	303	253	188	126	76	54	36	32	22	17	13	8	5	2	0	0	Durva + Gem + Cis
403	363	300	218	148	82	32	21	15	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

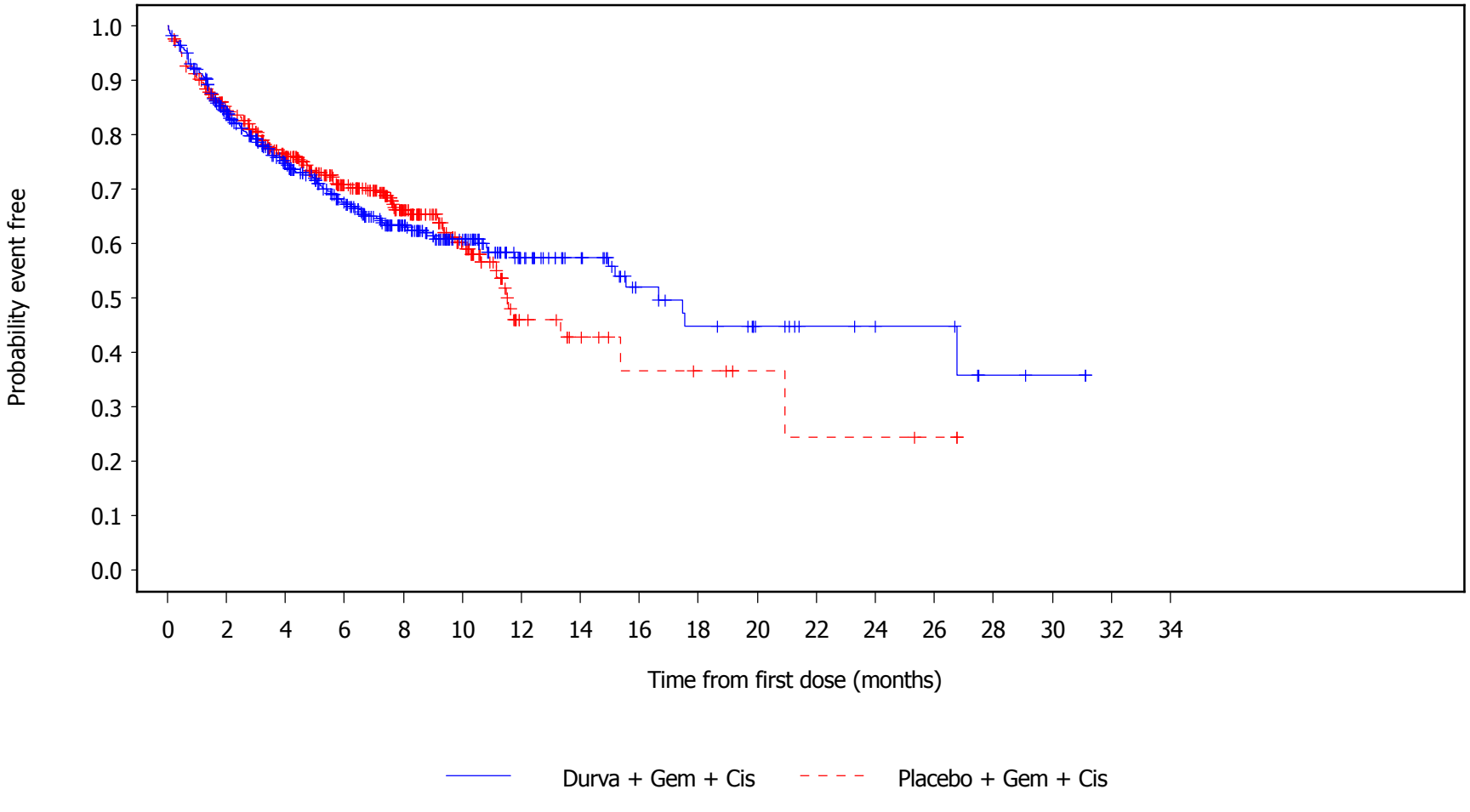
Figure 3.3.56 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Cardiac disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	370	311	260	194	126	77	55	37	33	23	18	14	9	5	2	0	0	Durva + Gem + Cis
403	369	309	226	157	88	34	21	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

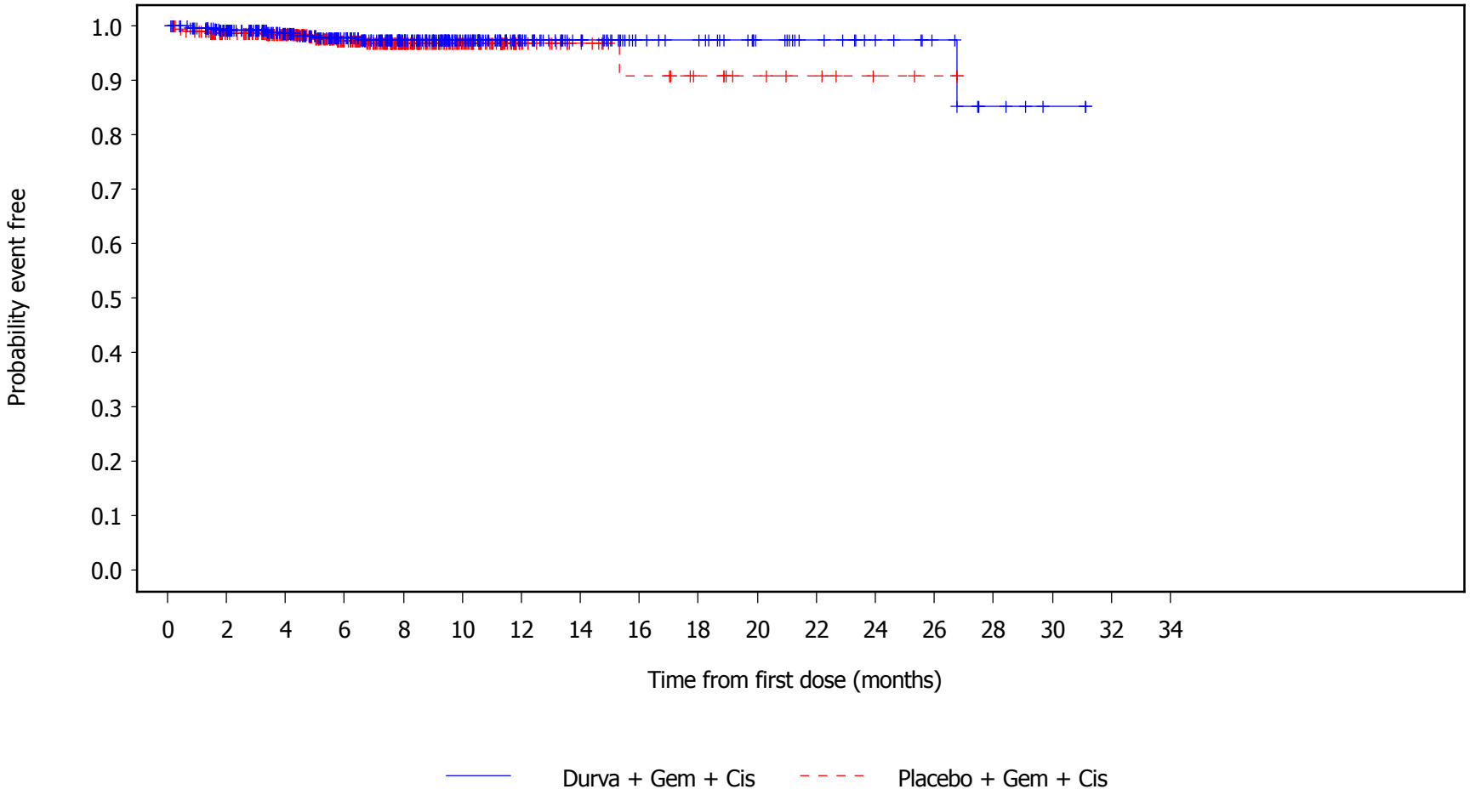
Figure 3.3.57 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Infections and infestations
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	316	245	193	138	94	53	39	23	18	12	8	7	6	2	1	0	0	Durva + Gem + Cis
403	319	249	171	108	56	16	10	6	5	3	2	2	1	0	0	0	0	Placebo + Gem + Cis

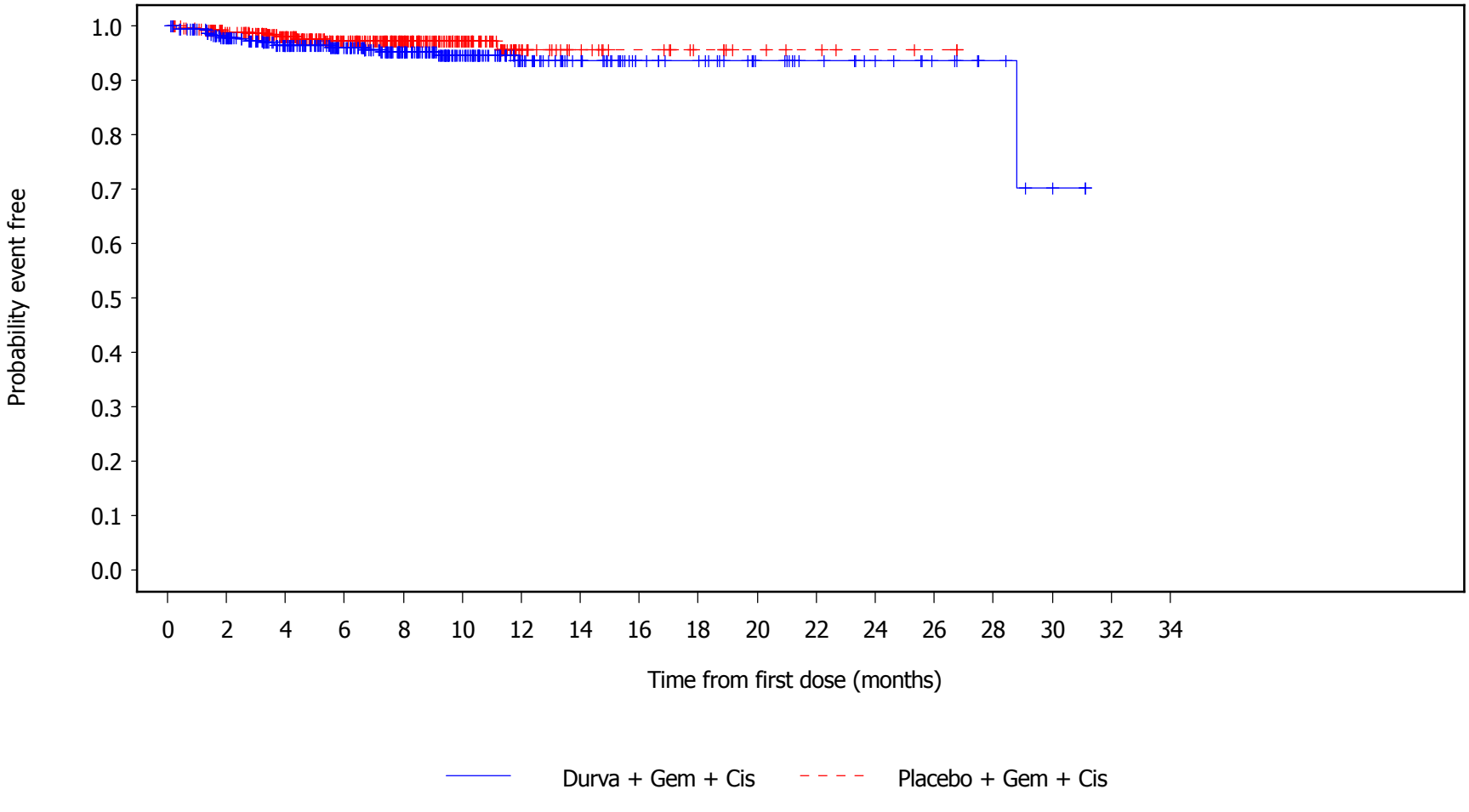
Figure 3.3.58 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: COVID-19
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	370	312	260	194	129	79	57	39	36	25	19	14	9	4	1	0	0	Durva + Gem + Cis
403	367	310	227	154	85	33	22	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

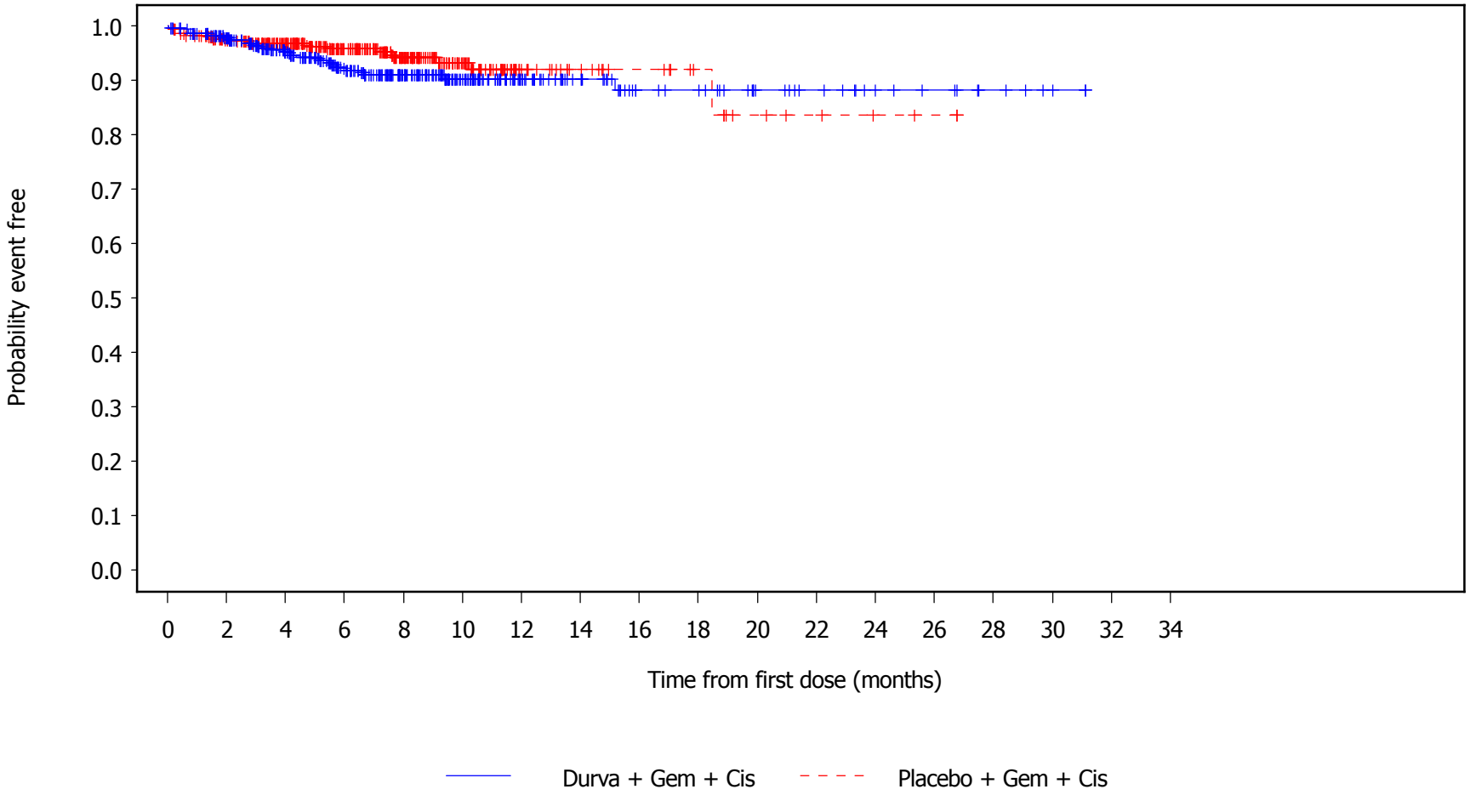
Figure 3.3.59 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Biliary tract infection
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	365	308	258	195	129	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	367	309	229	157	89	33	21	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

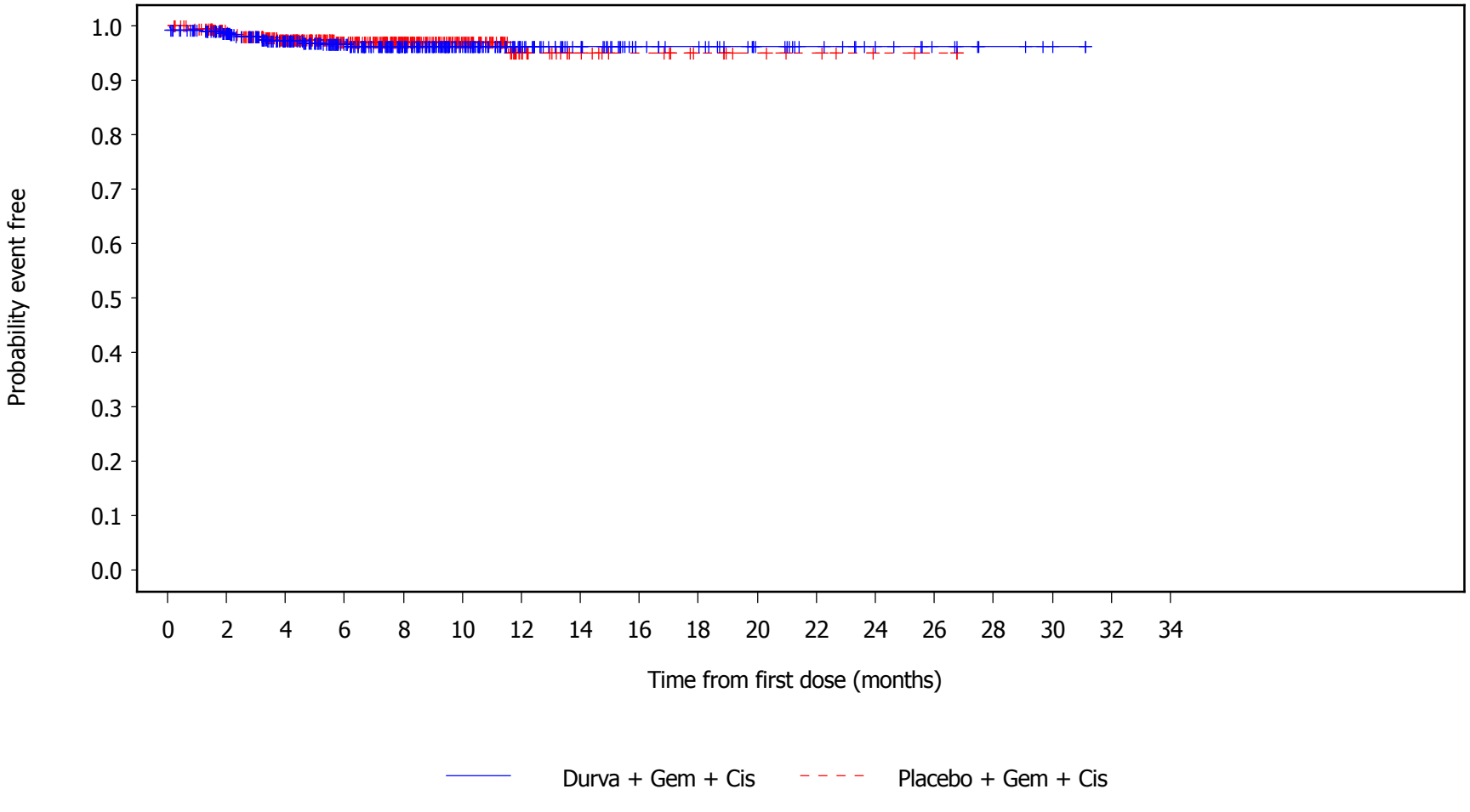
Figure 3.3.60 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Urinary tract infection
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	365	300	244	181	120	72	50	33	31	21	17	12	9	5	2	0	0	Durva + Gem + Cis
403	362	305	223	151	85	33	22	16	11	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

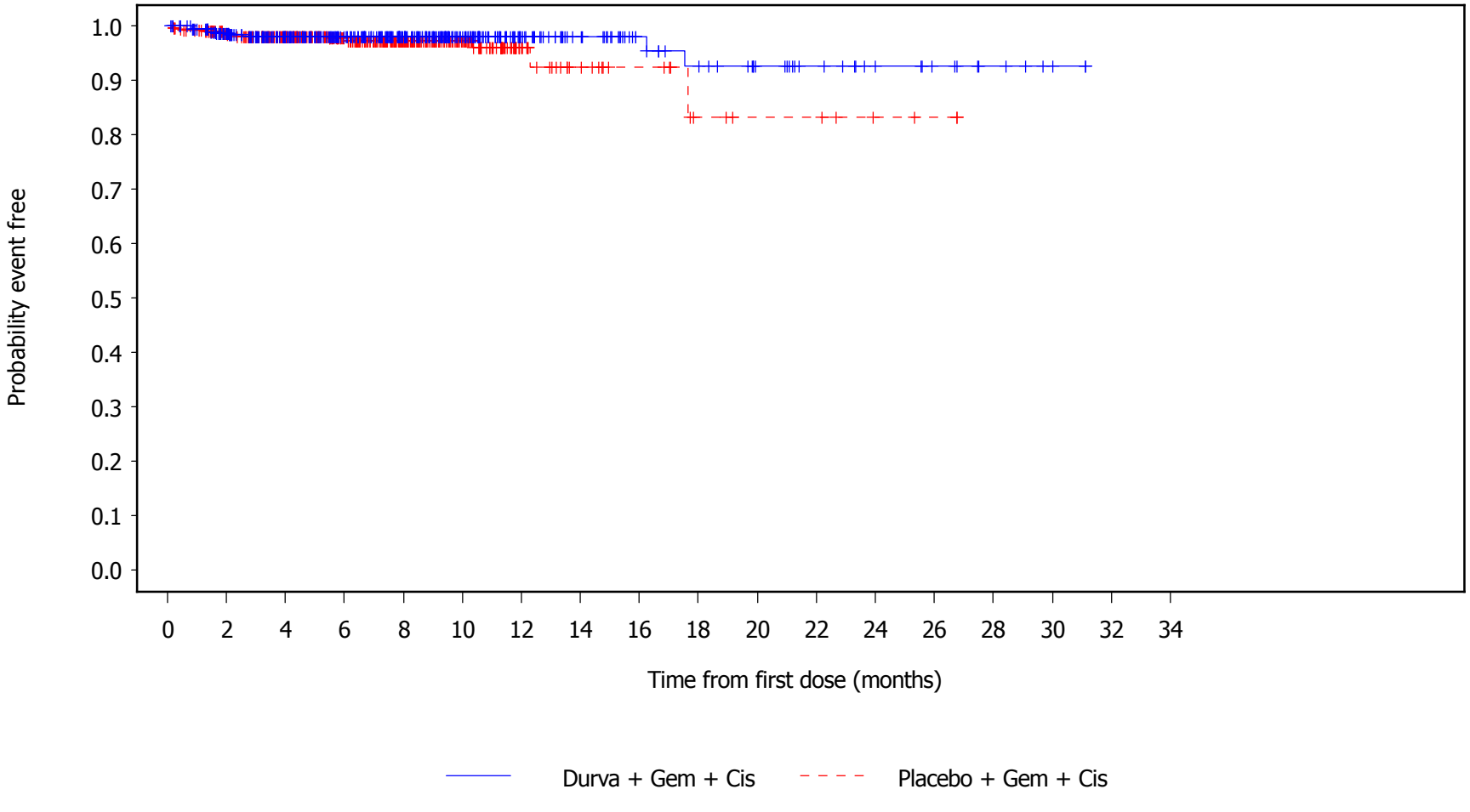
Figure 3.3.61 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Upper respiratory tract infection
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	368	306	254	189	125	77	57	39	35	24	18	13	8	4	2	0	0	Durva + Gem + Cis
403	368	305	224	153	87	32	21	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

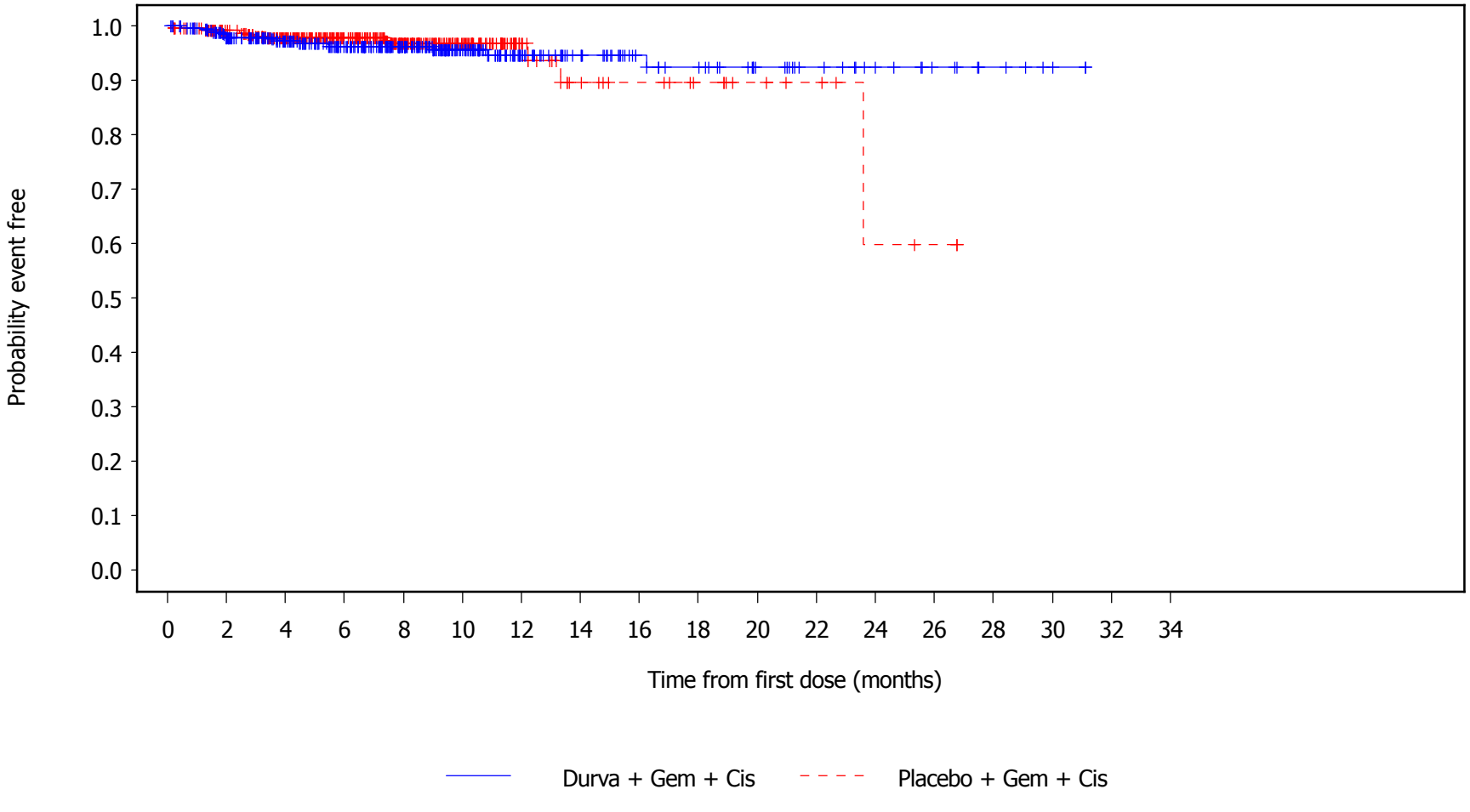
Figure 3.3.62 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Nasopharyngitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	368	308	257	193	127	76	55	38	32	24	18	13	9	5	2	0	0	Durva + Gem + Cis
403	366	308	227	153	85	32	19	13	7	5	5	2	1	0	0	0	0	Placebo + Gem + Cis

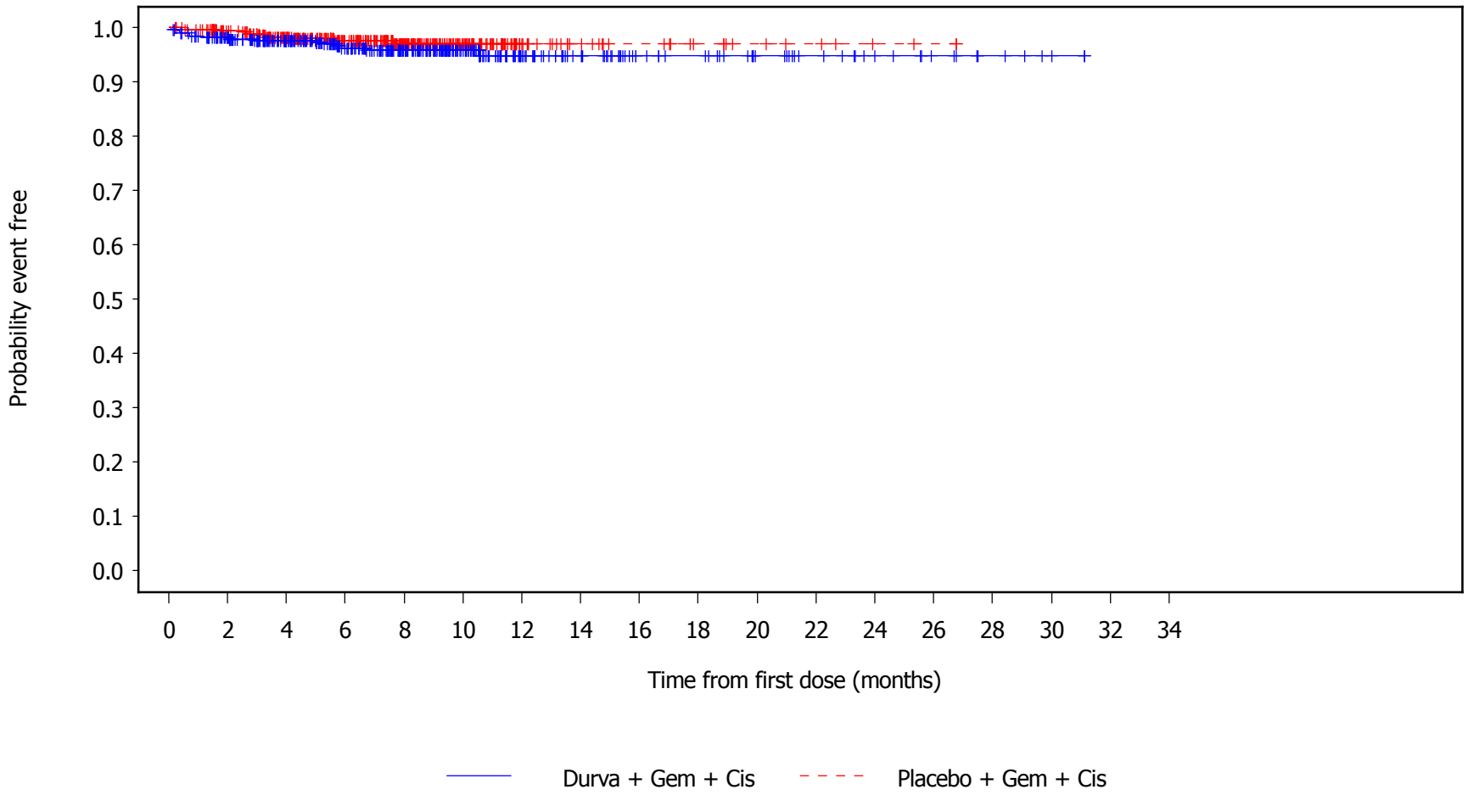
Figure 3.3.63 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Pneumonia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	366	308	262	198	131	79	58	40	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	308	229	155	86	33	19	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

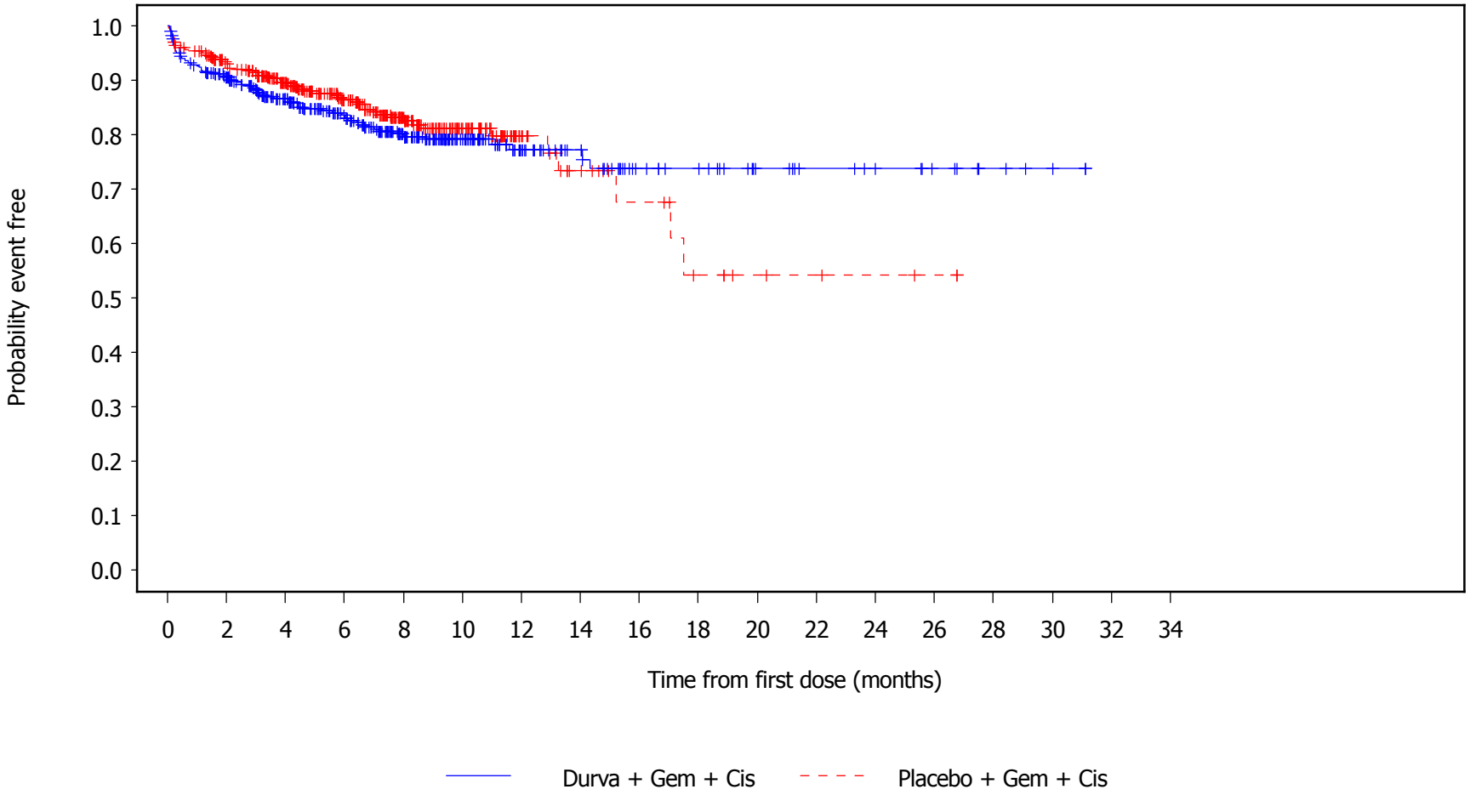
Figure 3.3.64 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	310	257	194	128	77	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	309	229	156	87	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

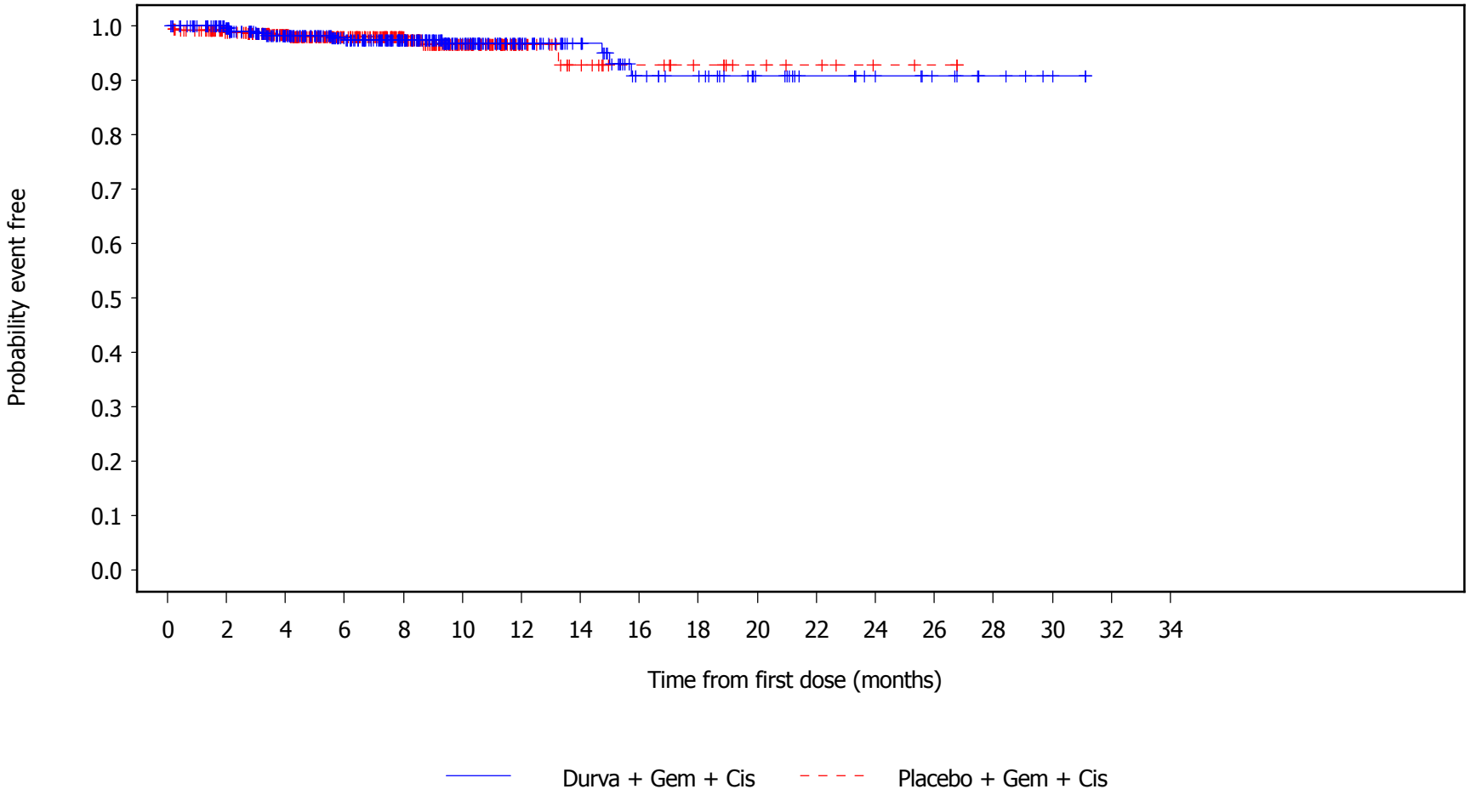
Figure 3.3.65 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Hepatobiliary disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	344	281	230	166	110	65	48	31	27	18	14	12	8	4	2	0	0	Durva + Gem + Cis
403	347	285	206	138	78	29	18	12	7	4	3	2	1	0	0	0	0	Placebo + Gem + Cis

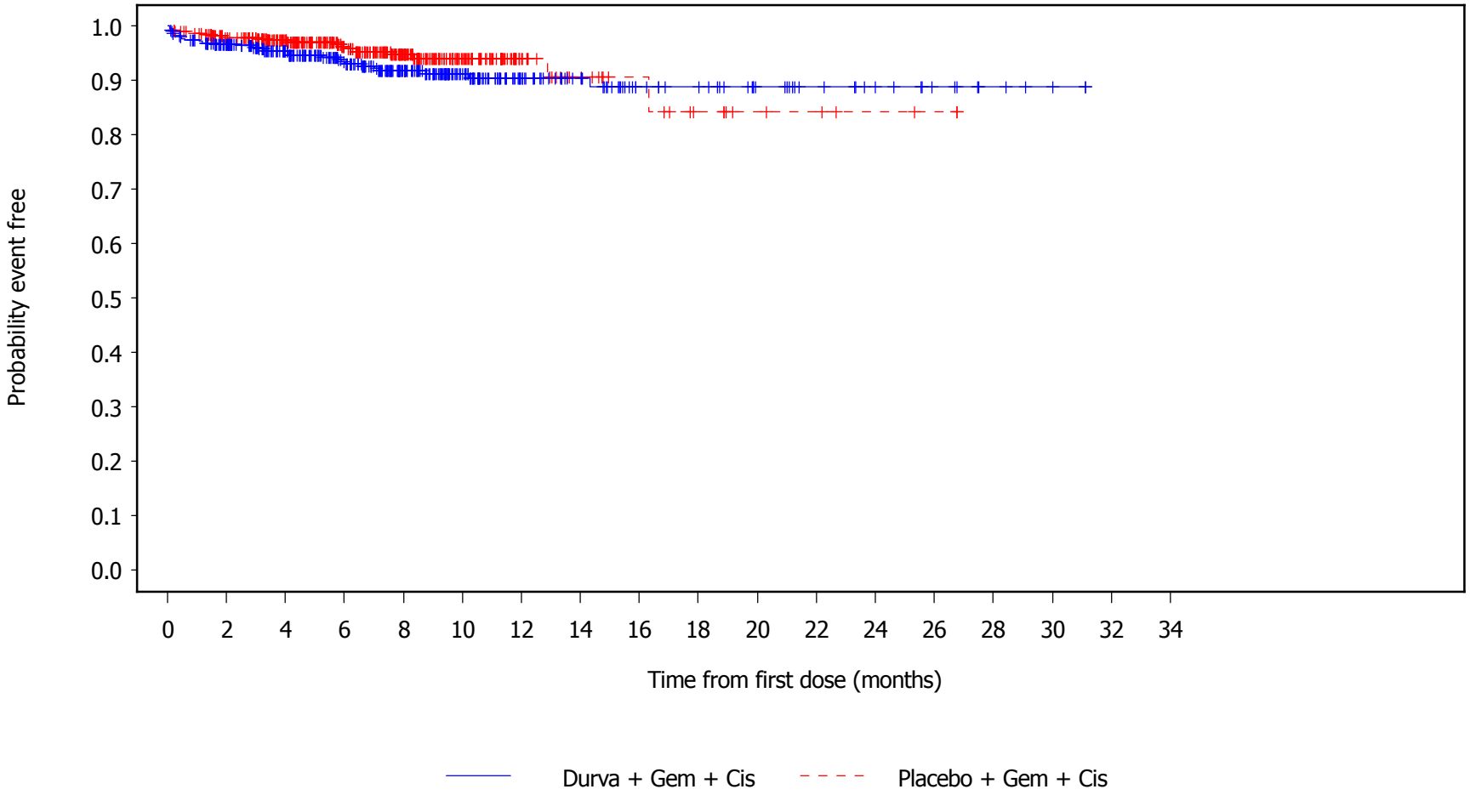
Figure 3.3.66 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Biliary obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	310	260	196	129	78	56	36	32	22	16	13	9	5	2	0	0	Durva + Gem + Cis
403	368	309	228	156	86	33	21	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

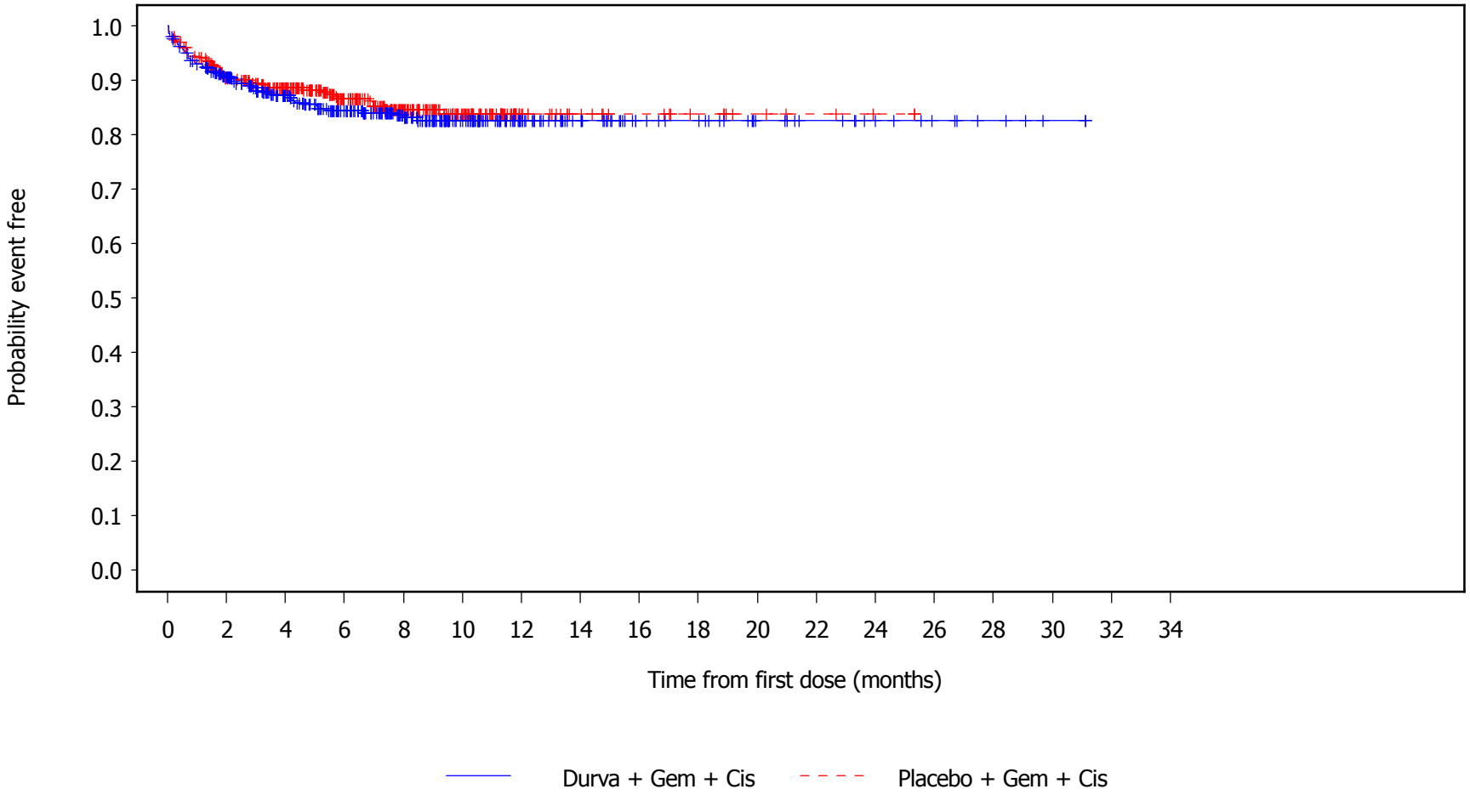
Figure 3.3.67 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Cholangitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	363	304	250	183	122	73	55	37	33	23	17	13	8	4	2	0	0	Durva + Gem + Cis
403	363	305	223	152	85	33	20	14	9	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

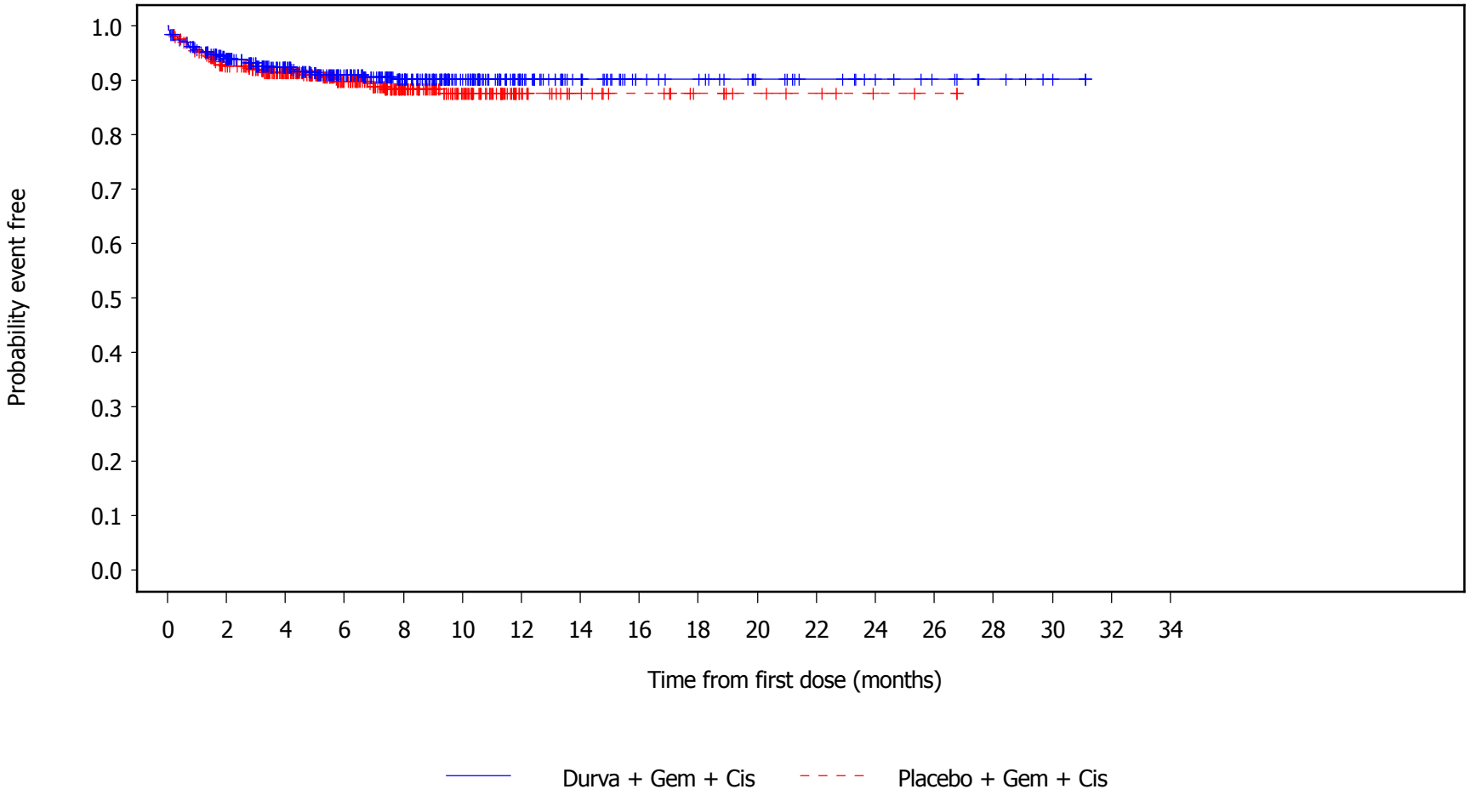
Figure 3.3.68 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Psychiatric disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	341	276	228	169	113	69	48	32	29	19	15	11	7	4	1	0	0	Durva + Gem + Cis
403	336	278	199	134	80	28	18	13	9	5	3	1	0	0	0	0	0	Placebo + Gem + Cis

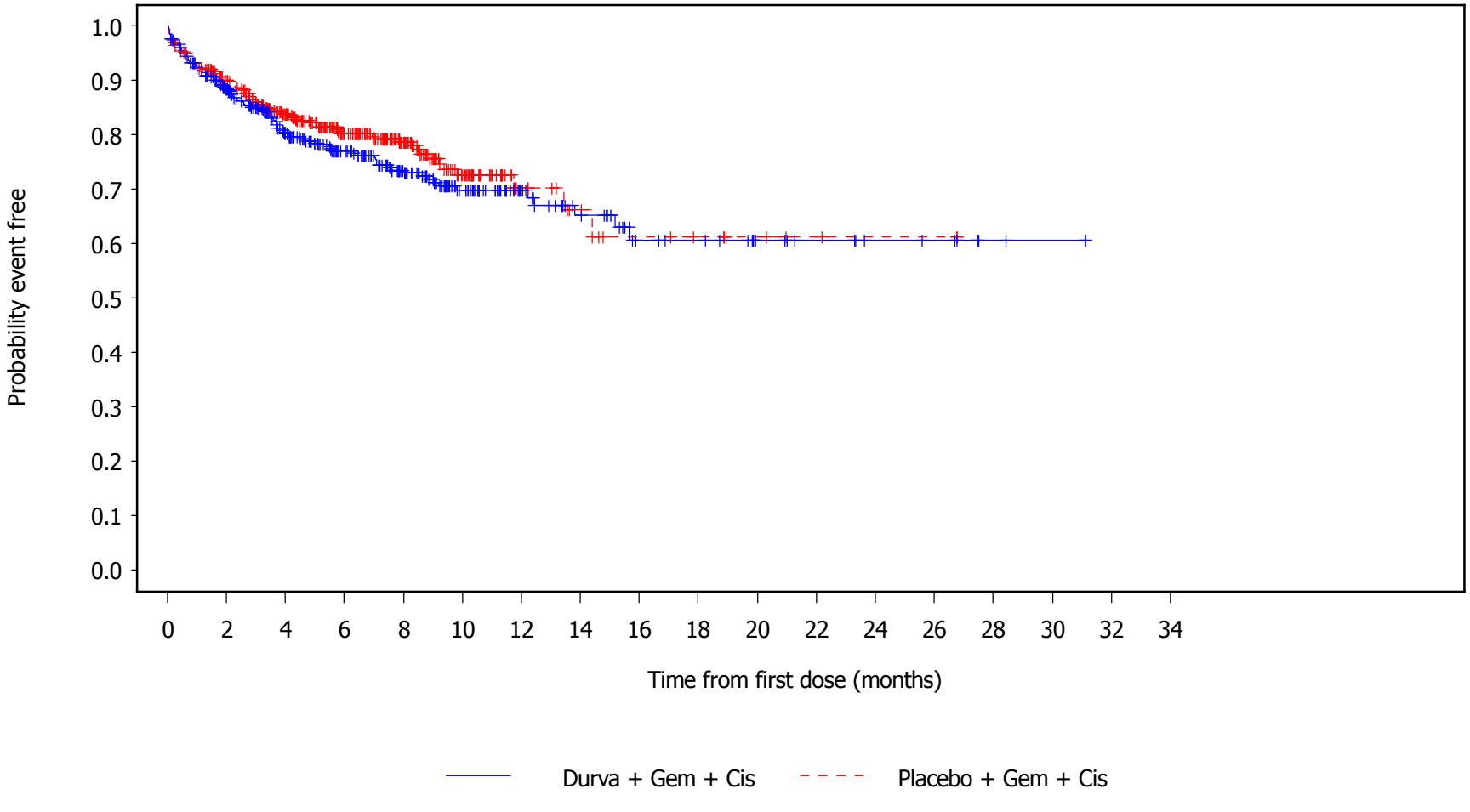
Figure 3.3.69 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Insomnia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	351	288	239	178	121	73	51	35	32	22	17	13	9	5	2	0	0	Durva + Gem + Cis
403	343	286	206	140	84	32	21	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

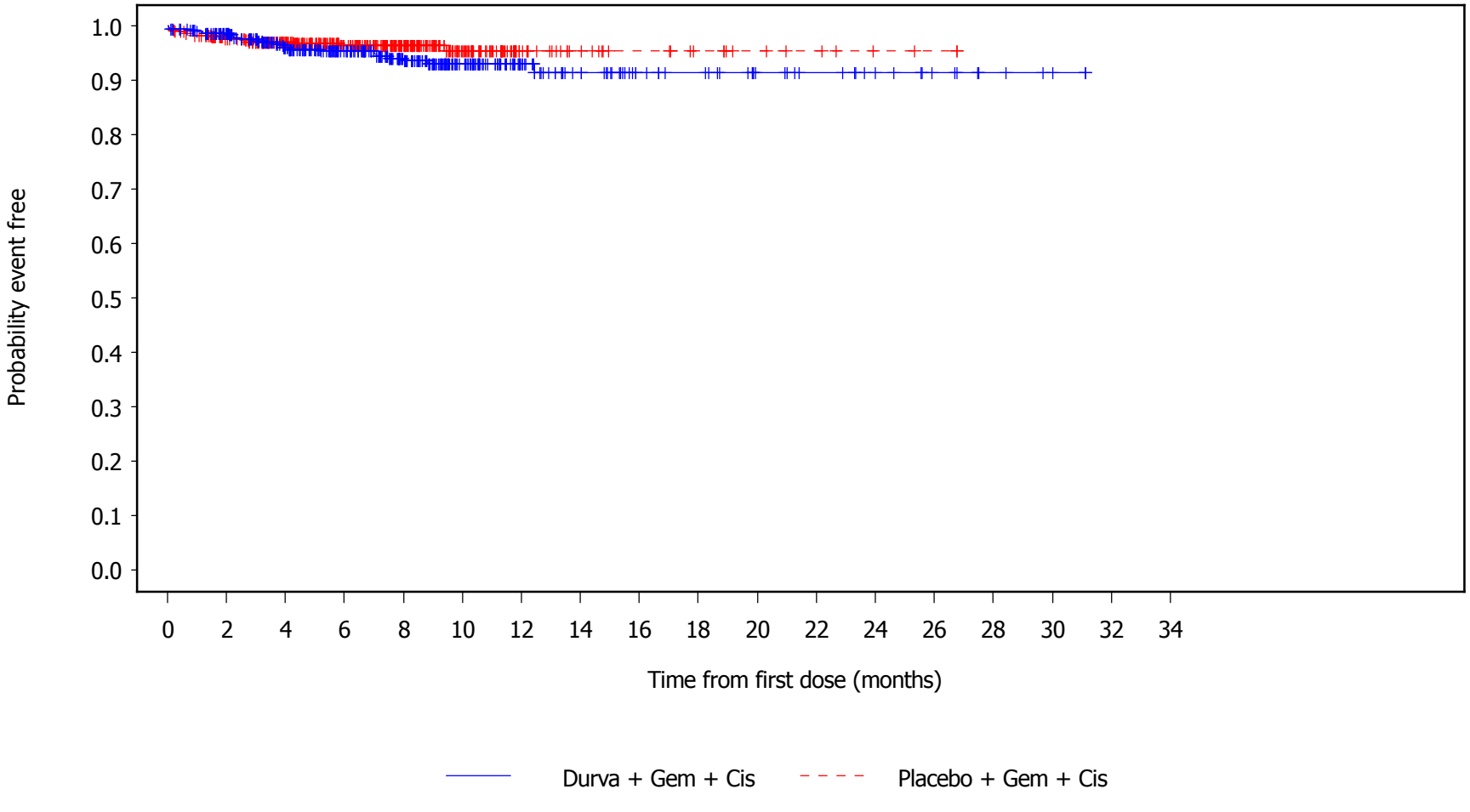
Figure 3.3.70 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Musculoskeletal and connective tissue disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	330	250	197	142	90	53	37	23	20	13	10	7	6	2	1	0	0	Durva + Gem + Cis
403	334	263	186	124	64	22	14	9	7	4	2	1	1	0	0	0	0	Placebo + Gem + Cis

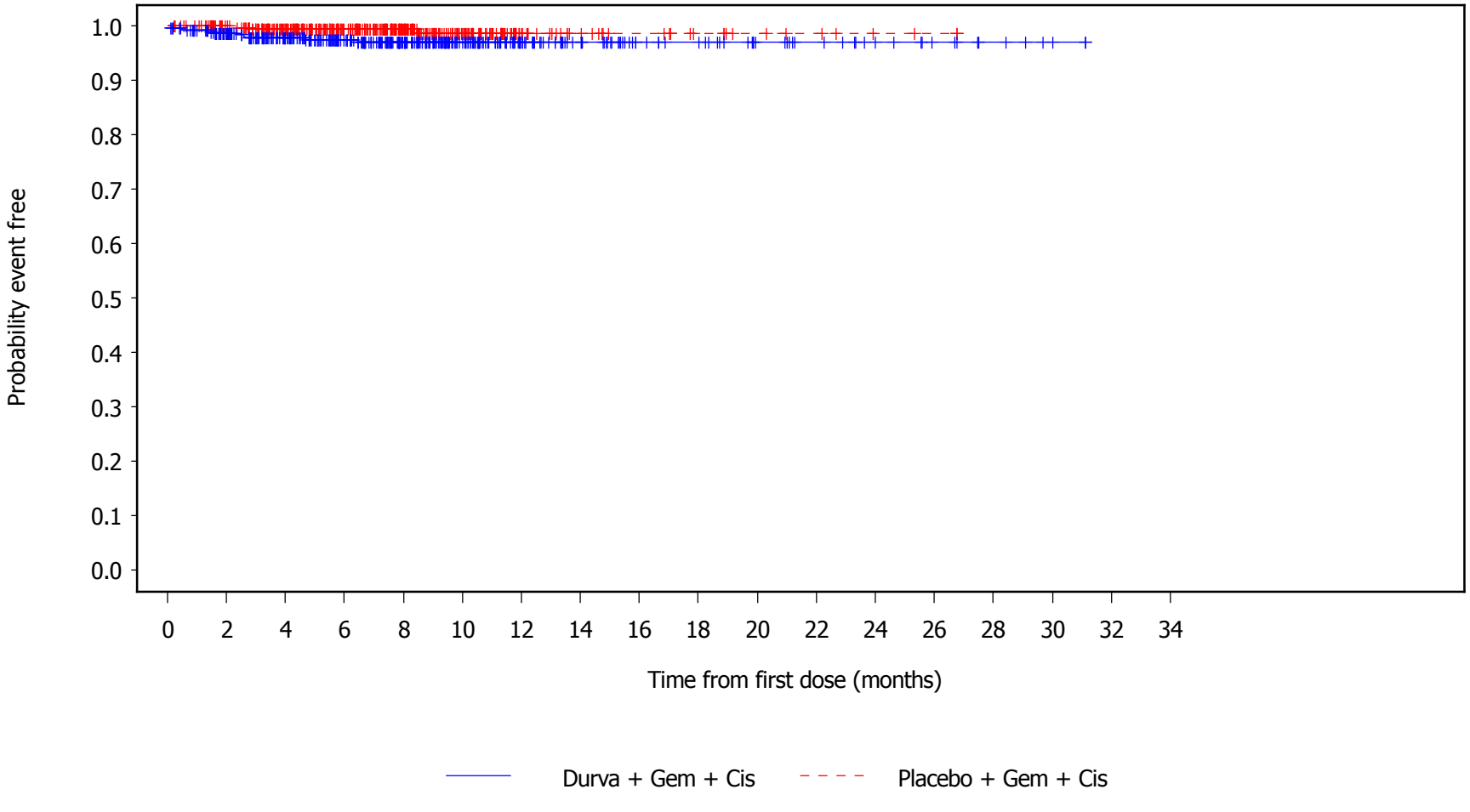
Figure 3.3.71 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Arthralgia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	368	301	249	184	118	70	49	34	30	21	17	13	8	4	2	0	0	Durva + Gem + Cis
403	362	304	225	154	85	33	21	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

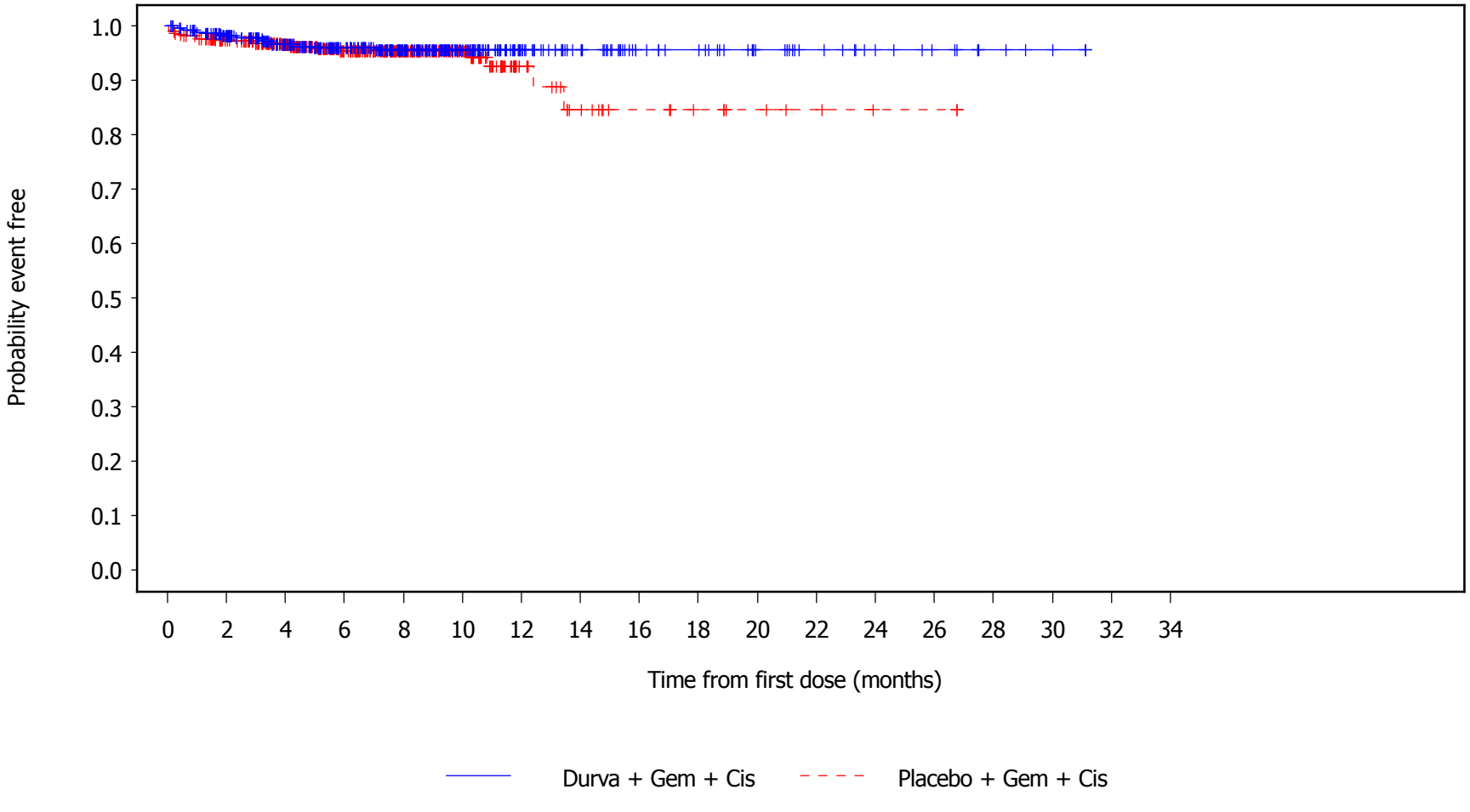
Figure 3.3.72 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Bone pain
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	368	308	257	191	127	79	57	39	35	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	311	230	157	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

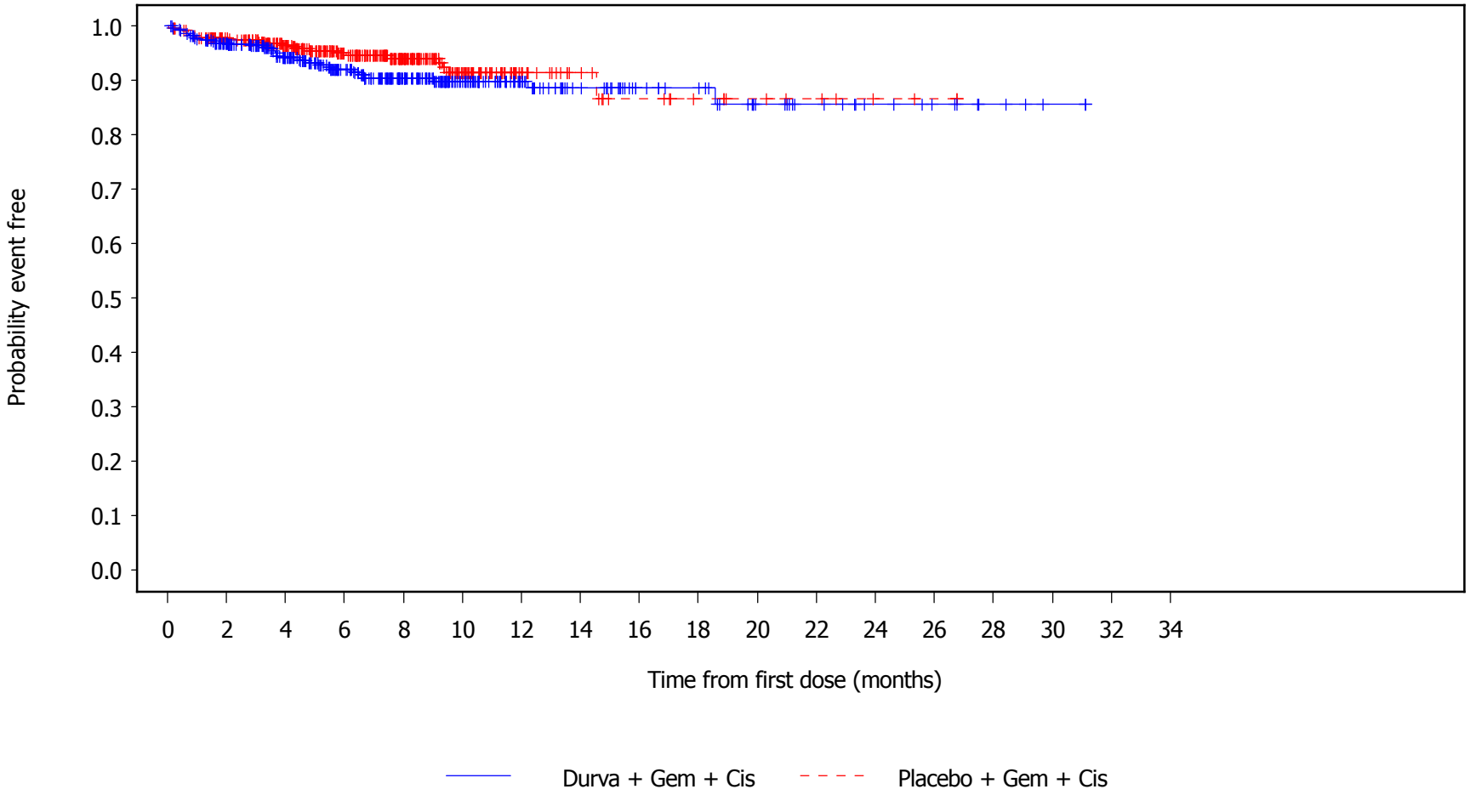
Figure 3.3.73 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Myalgia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	366	303	253	188	124	75	56	38	34	23	17	12	8	4	2	0	0	Durva + Gem + Cis
403	361	303	220	149	82	28	17	11	8	5	3	1	1	0	0	0	0	Placebo + Gem + Cis

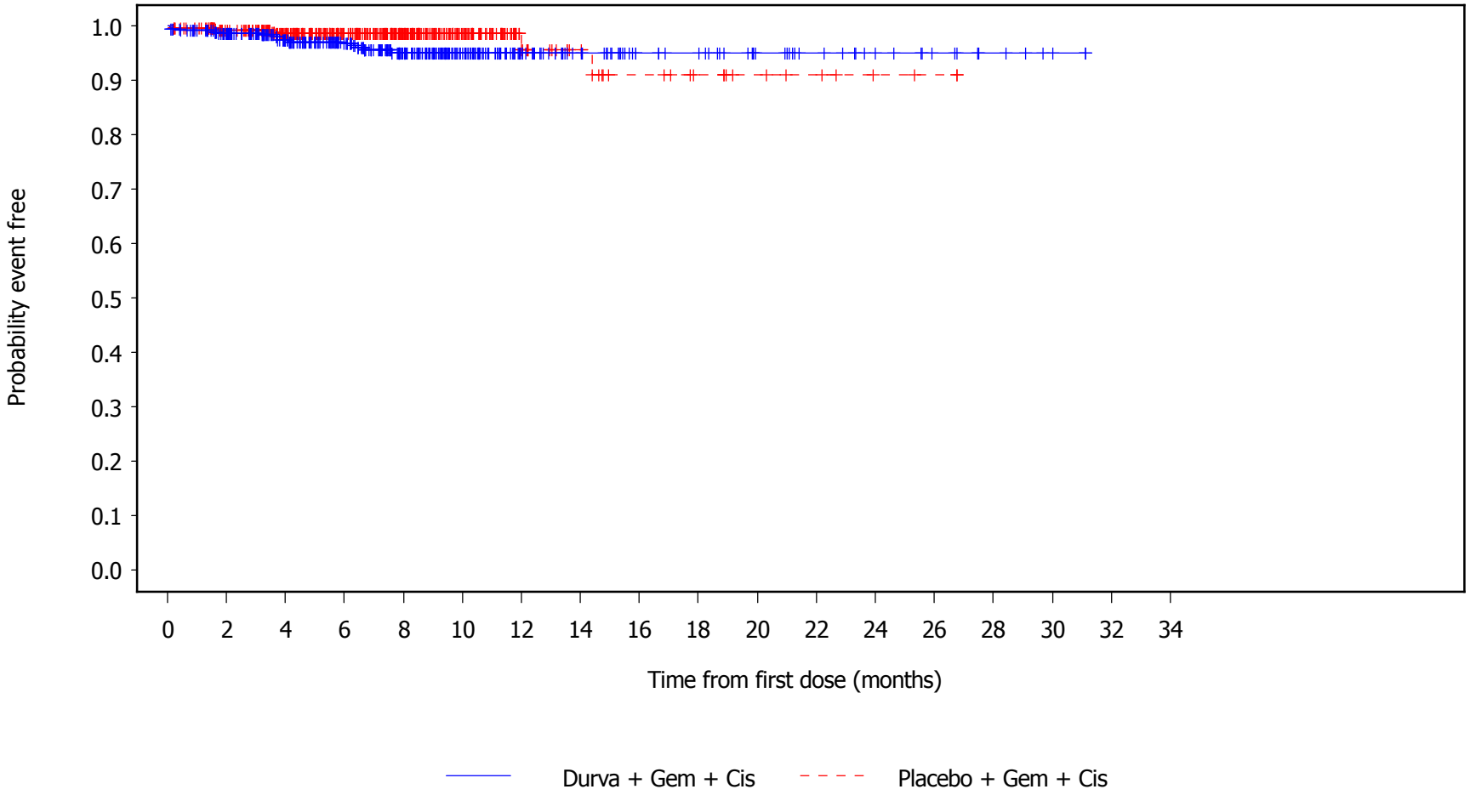
Figure 3.3.74 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Back pain
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	362	297	241	176	116	73	51	36	32	21	16	11	8	4	1	0	0	Durva + Gem + Cis
403	365	303	223	154	83	33	21	14	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

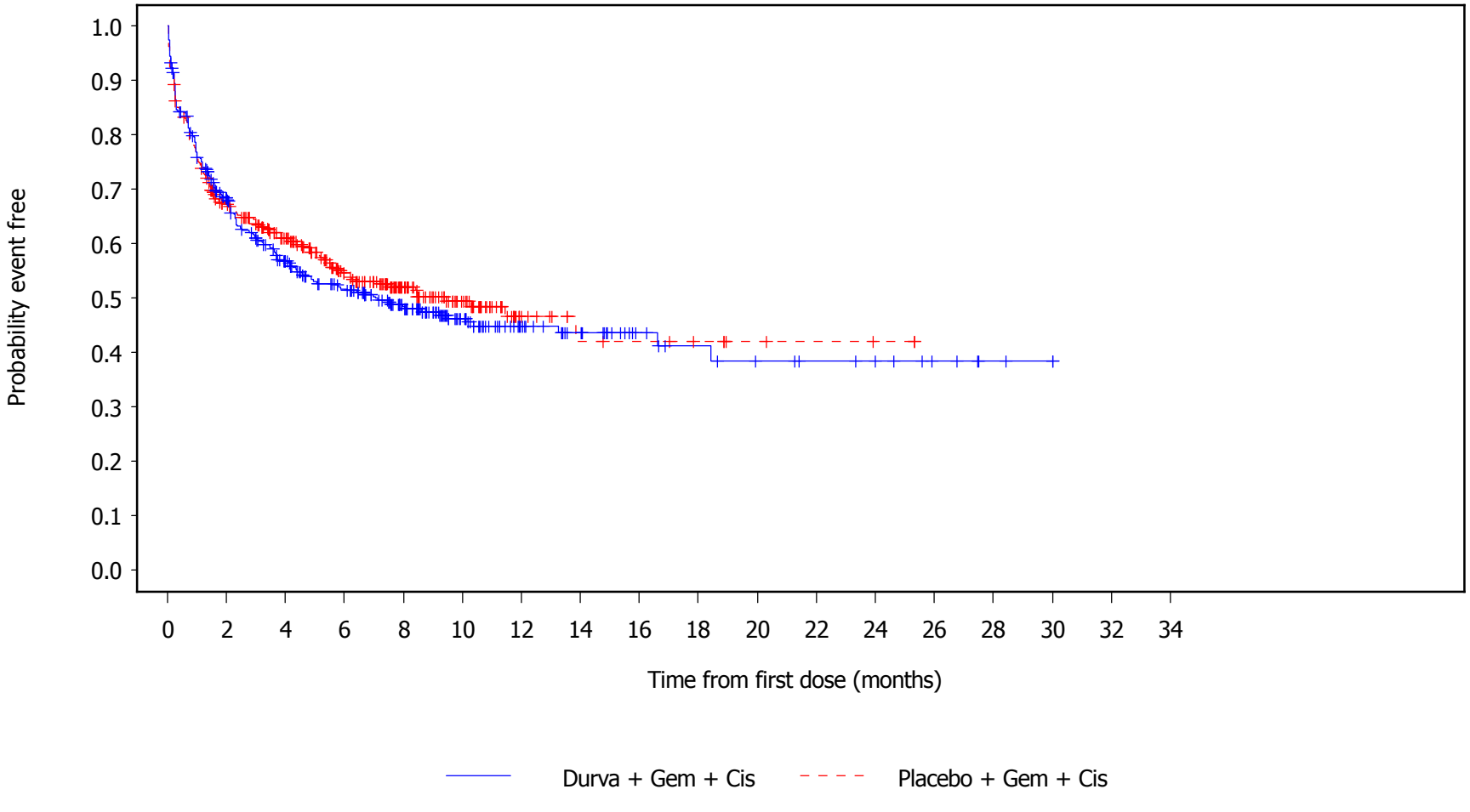
Figure 3.3.75 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Pain in extremity
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	308	256	189	125	75	55	39	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	309	230	158	88	32	22	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

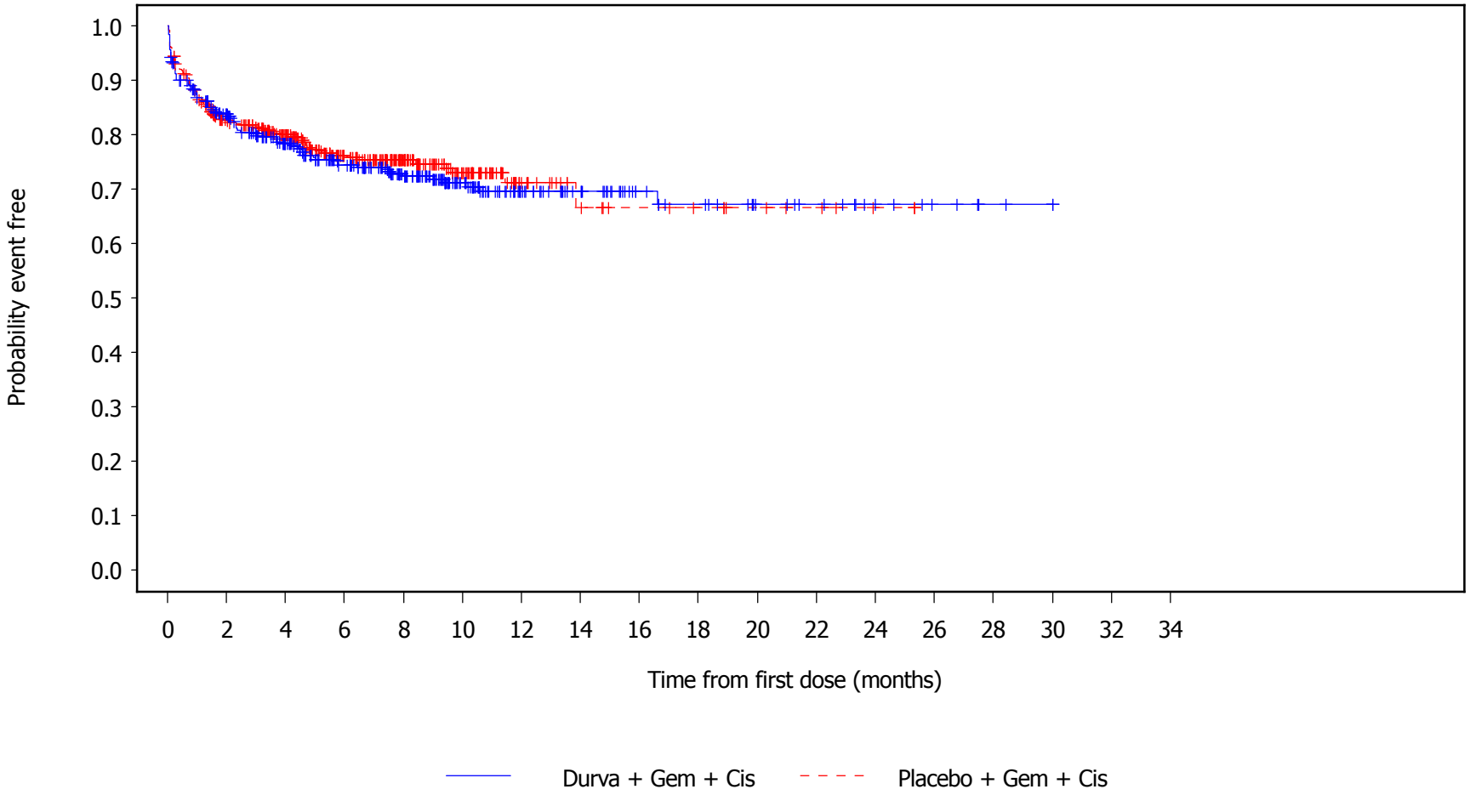
Figure 3.3.76 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Metabolism and nutrition disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	258	192	156	112	69	43	32	19	15	12	10	9	5	2	1	0	0	Durva + Gem + Cis
403	255	201	140	92	53	16	9	8	6	3	2	1	0	0	0	0	0	Placebo + Gem + Cis

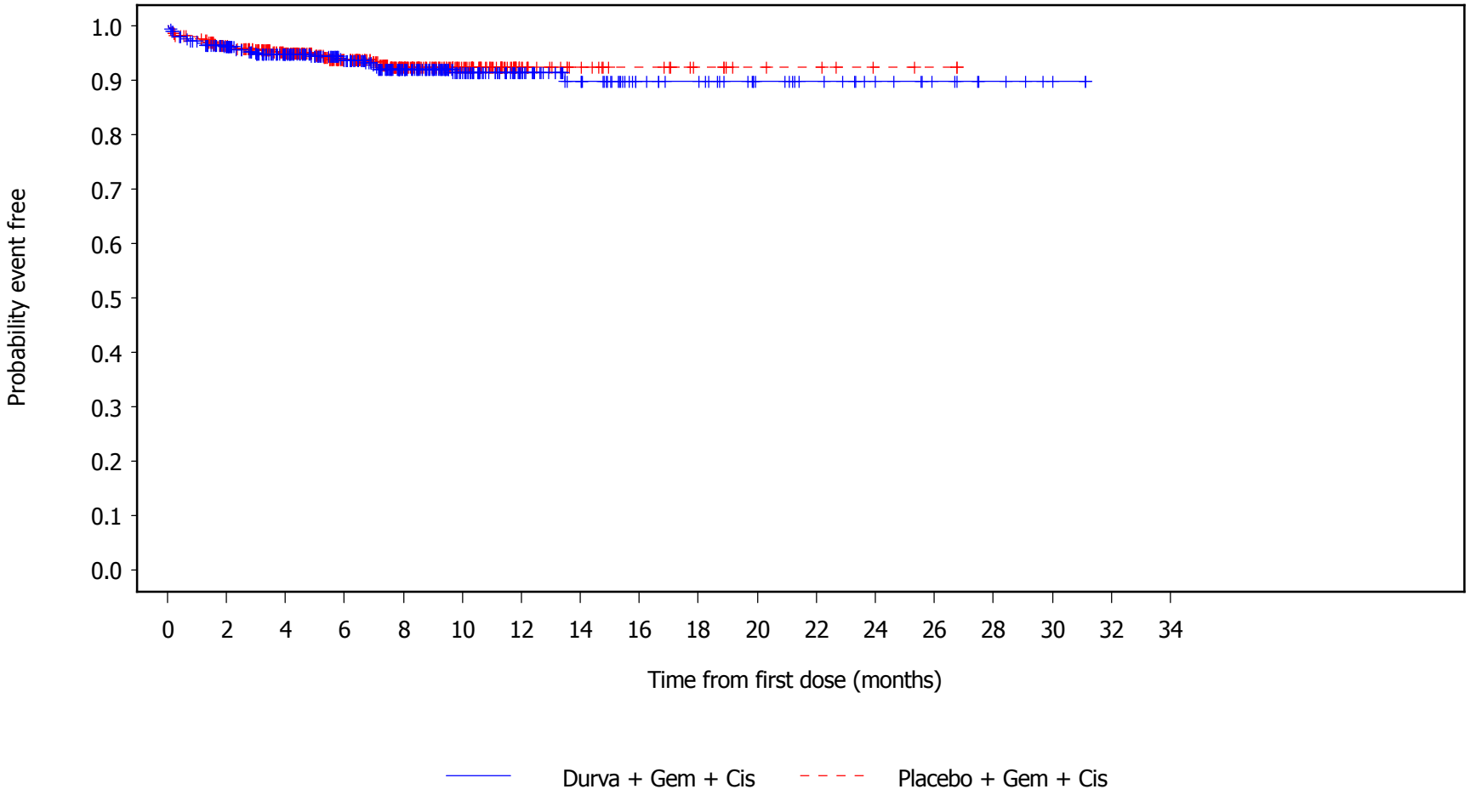
Figure 3.3.77 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Decreased appetite
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	313	255	208	155	102	62	46	29	24	17	14	9	5	2	1	0	0	Durva + Gem + Cis
403	307	255	184	128	74	26	15	11	9	6	4	1	0	0	0	0	0	Placebo + Gem + Cis

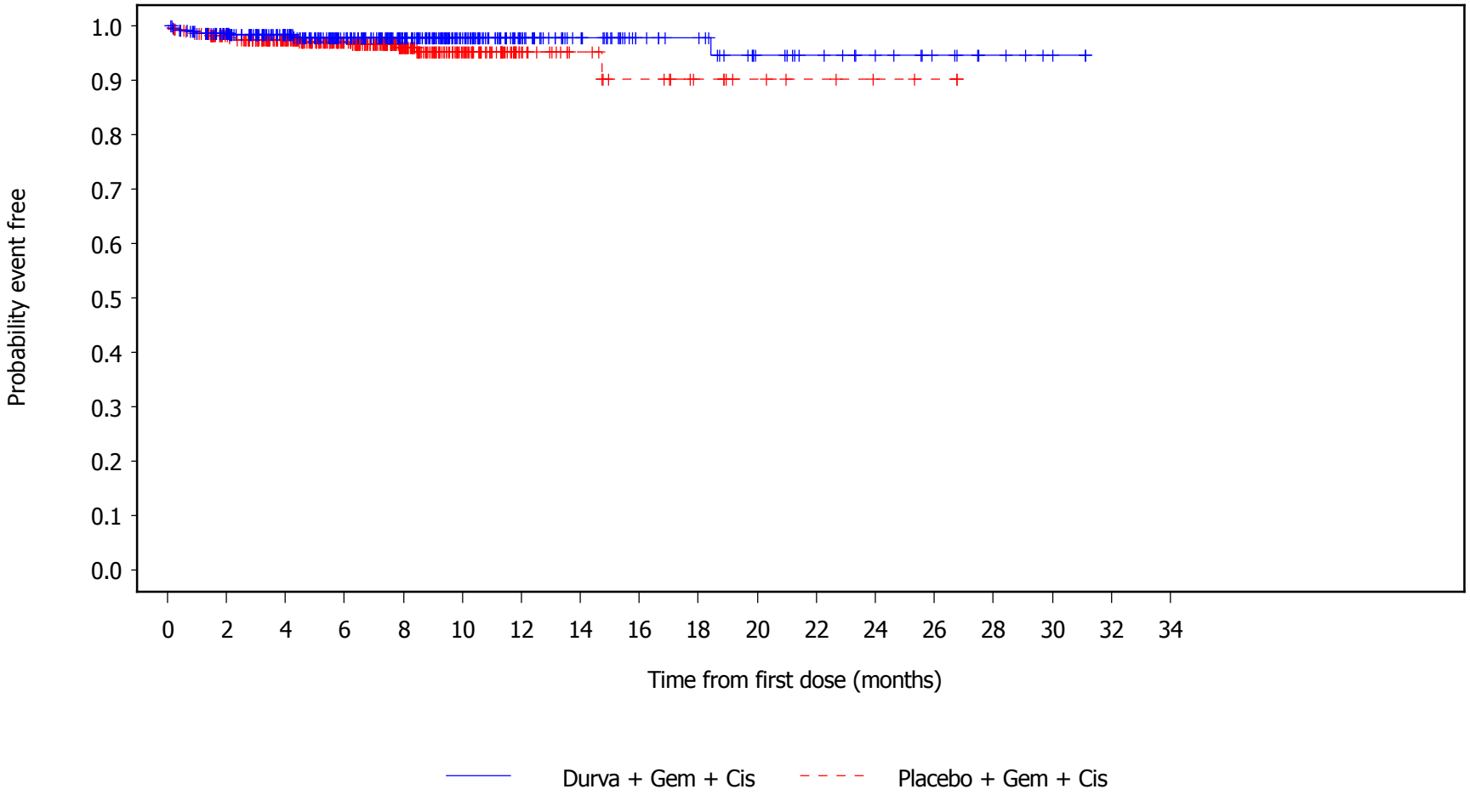
Figure 3.3.78 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Hypoalbuminaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	363	306	256	190	125	79	57	39	35	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	360	302	224	152	84	32	21	15	10	6	5	2	1	0	0	0	0	Placebo + Gem + Cis

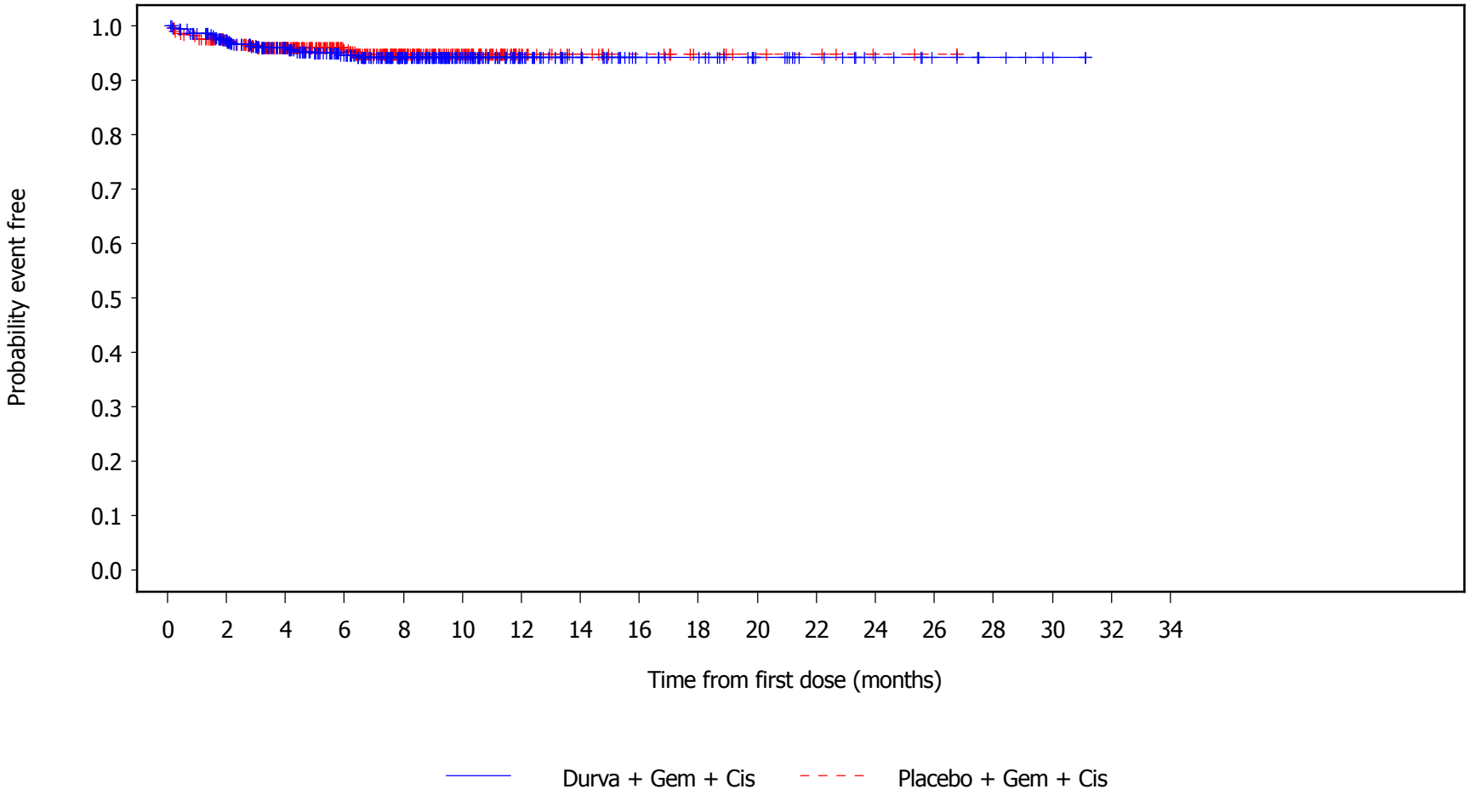
Figure 3.3.79 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Hyperglycaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	311	258	194	128	78	57	39	35	23	18	14	9	5	2	0	0	Durva + Gem + Cis
403	365	307	227	153	84	32	21	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

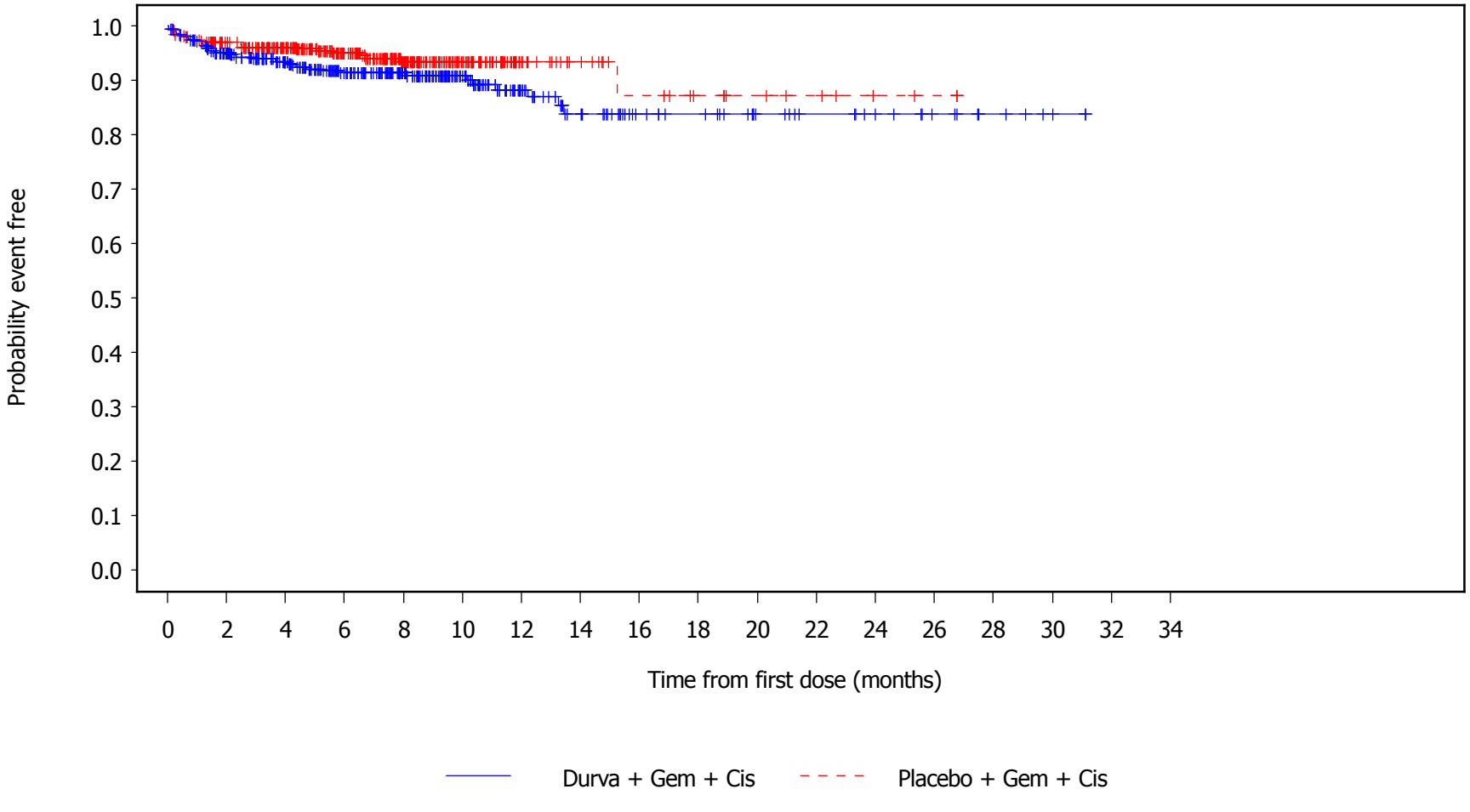
Figure 3.3.80 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Hyperkalaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	364	305	256	191	126	77	55	39	35	24	18	13	8	5	2	0	0	Durva + Gem + Cis
403	363	301	222	150	86	32	21	15	10	6	5	2	1	0	0	0	0	Placebo + Gem + Cis

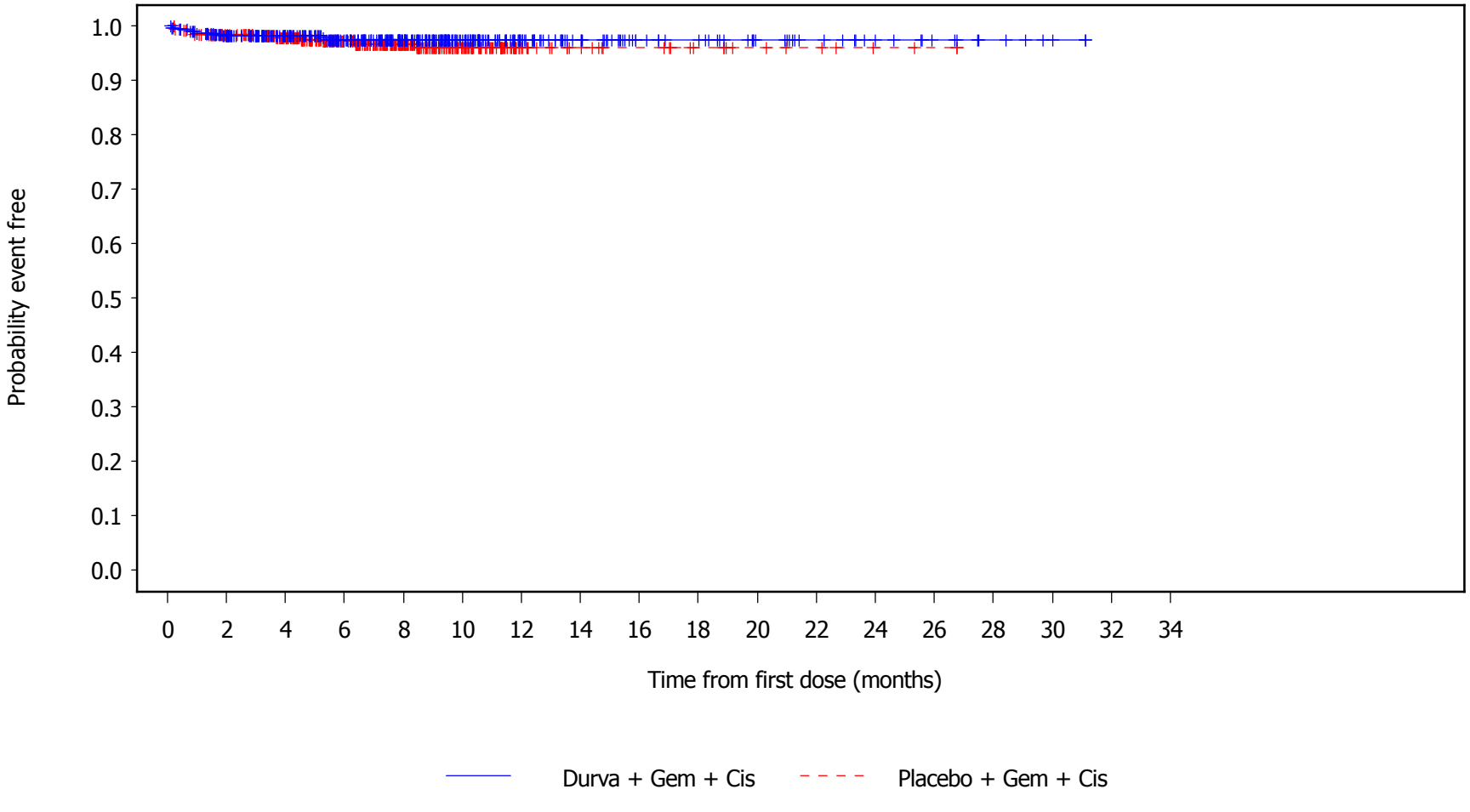
Figure 3.3.81 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Hypokalaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	356	300	246	185	122	71	50	34	30	21	17	14	9	5	2	0	0	Durva + Gem + Cis
403	362	305	224	149	84	32	21	14	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

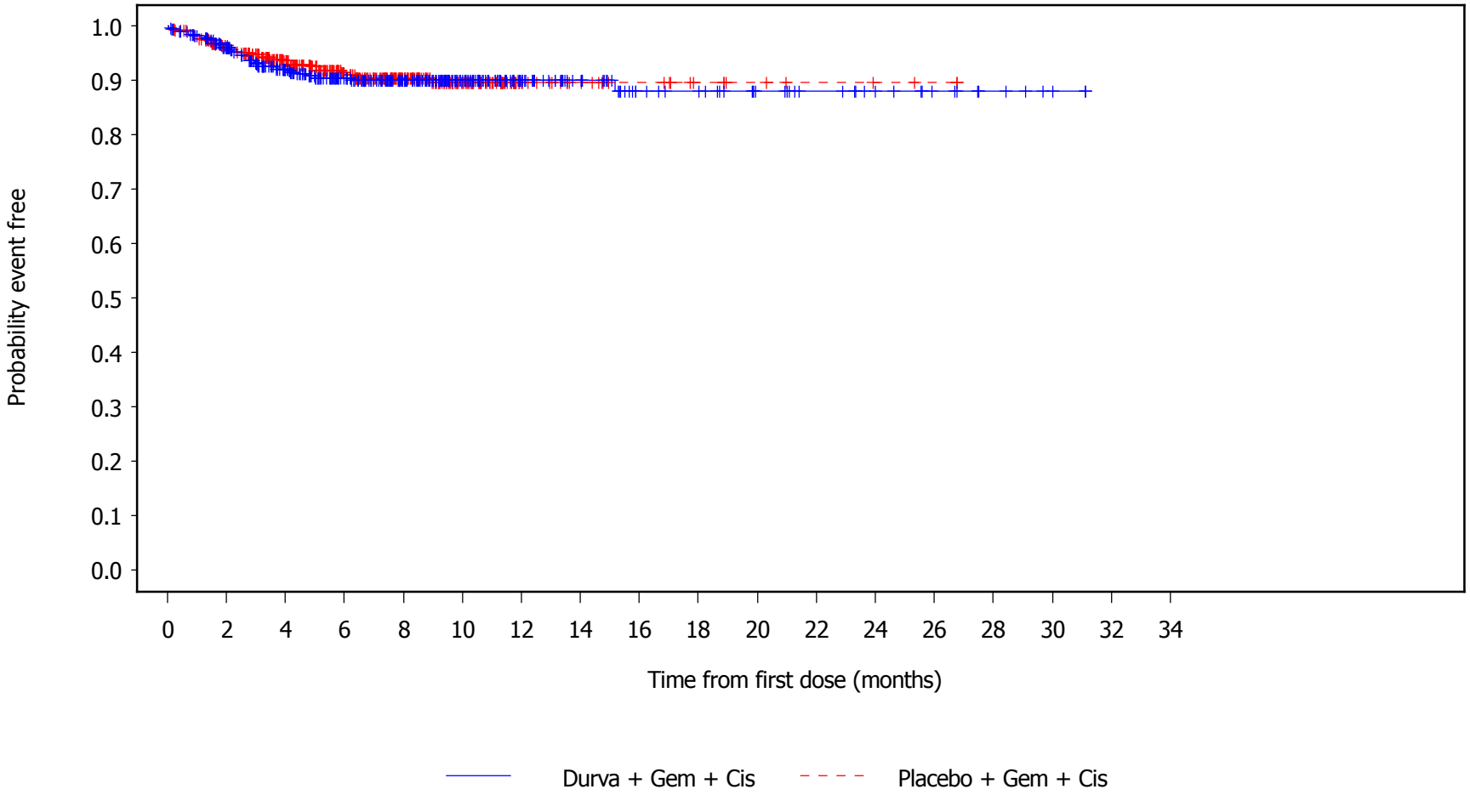
Figure 3.3.82 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Hypocalcaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	313	260	195	129	79	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	310	227	153	84	31	21	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

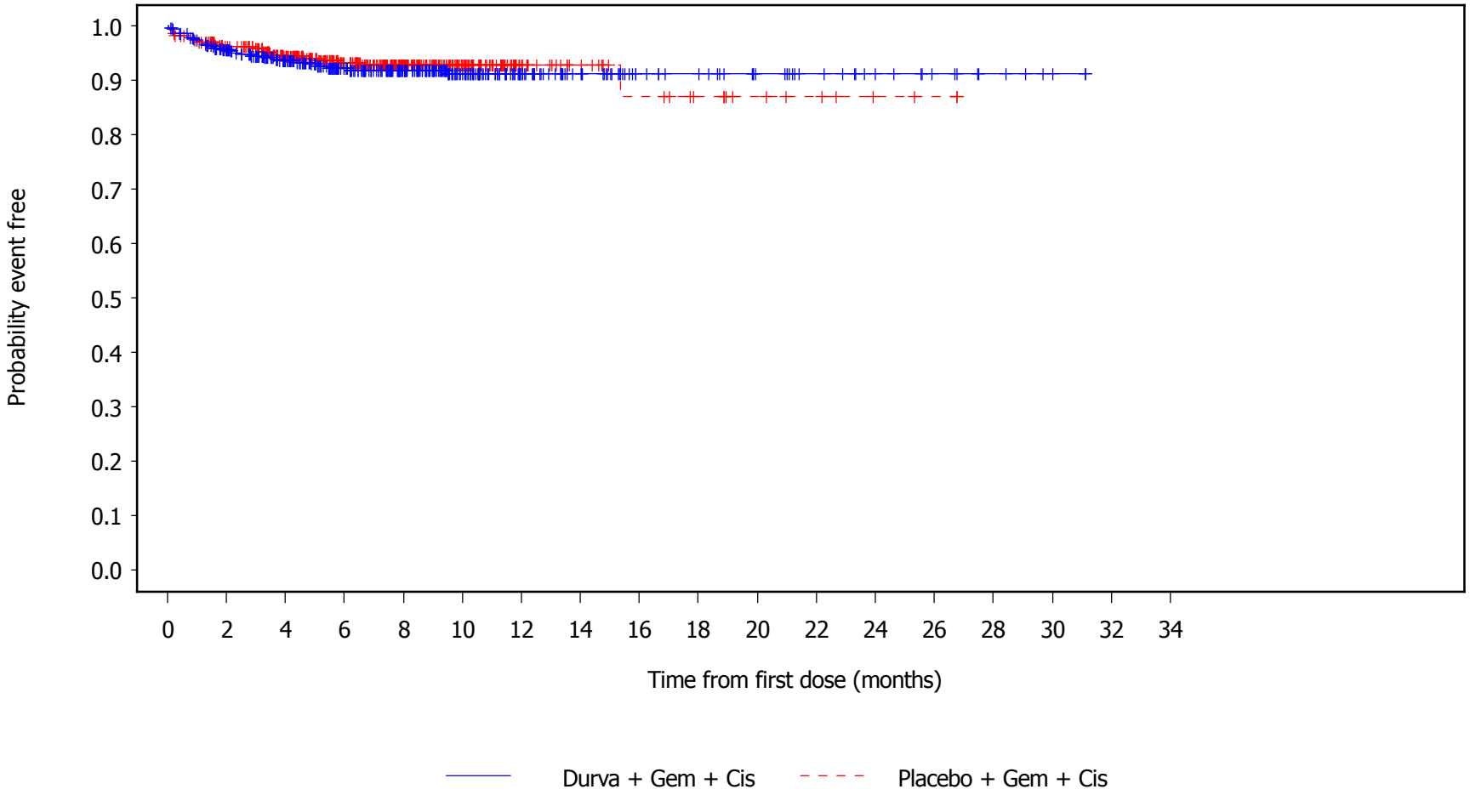
Figure 3.3.83 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Hypomagnesaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	359	293	240	180	117	72	52	35	32	23	18	14	9	5	2	0	0	Durva + Gem + Cis
403	357	293	212	141	78	28	19	13	8	5	3	2	1	0	0	0	0	Placebo + Gem + Cis

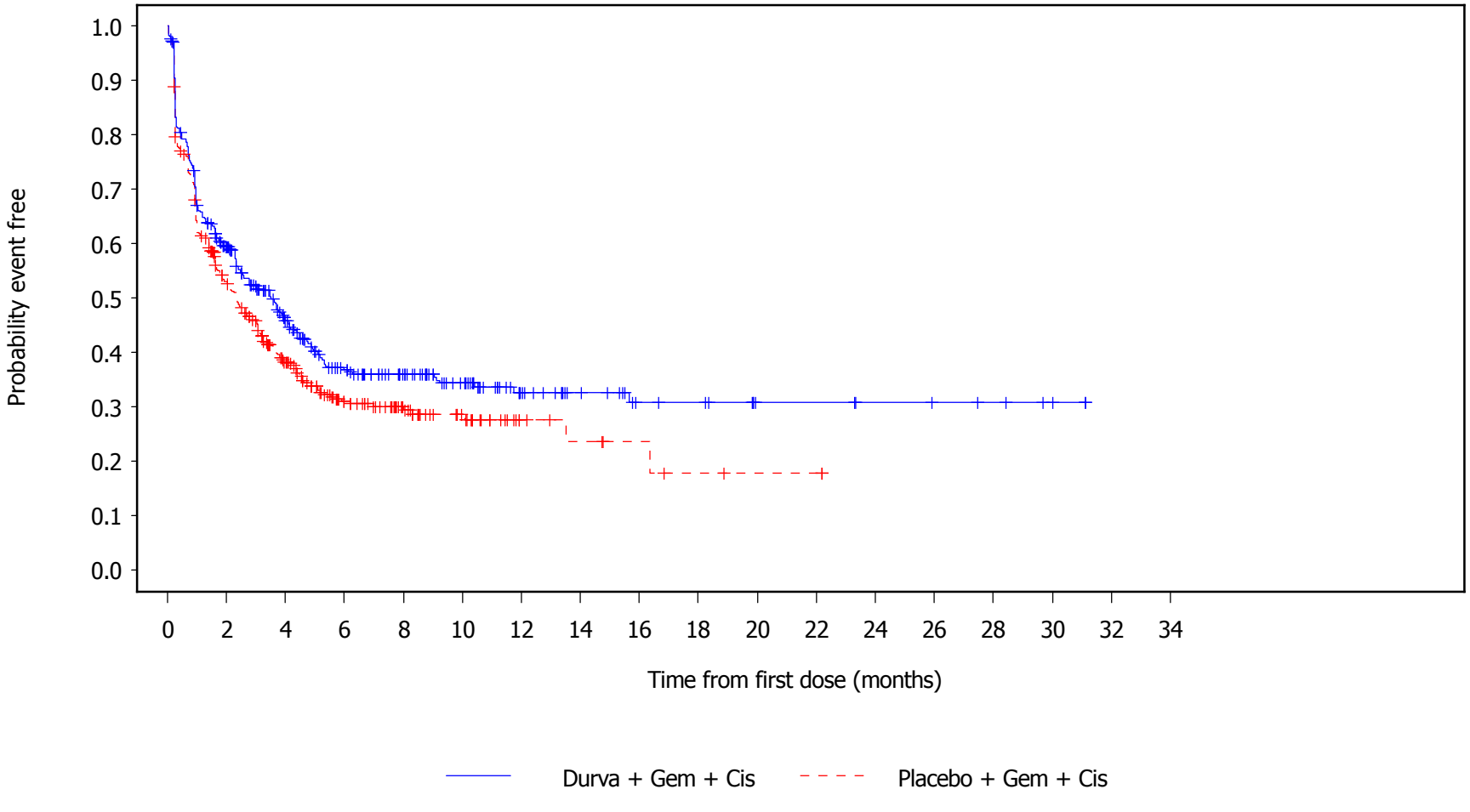
Figure 3.3.84 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Hyponatraemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	359	302	247	185	122	77	56	38	34	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	359	302	223	153	88	34	22	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

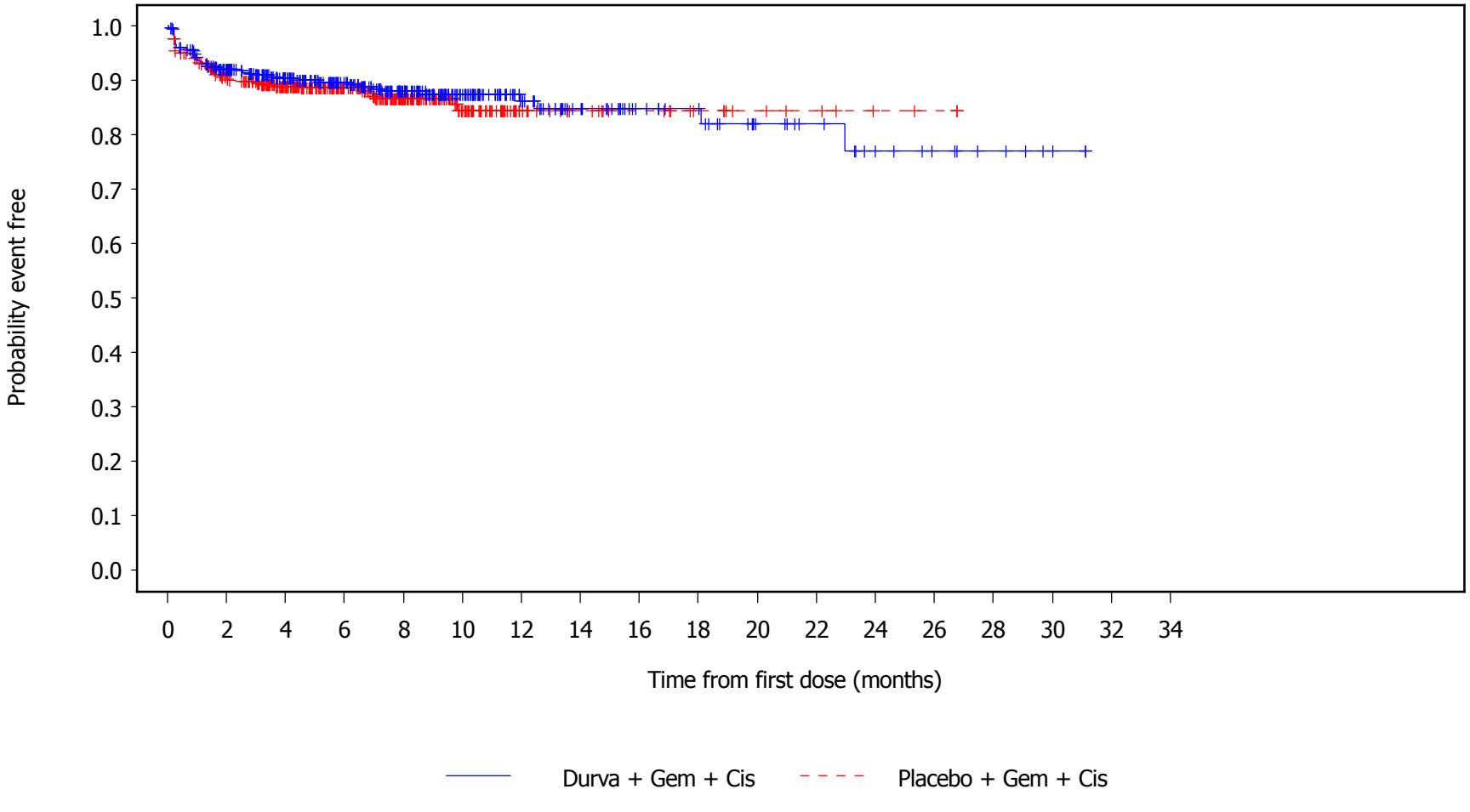
Figure 3.3.85 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Investigations
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	225	148	100	77	55	33	23	15	14	8	8	6	5	4	2	0	0	Durva + Gem + Cis
403	197	118	69	45	27	9	6	4	2	1	1	0	0	0	0	0	0	Placebo + Gem + Cis

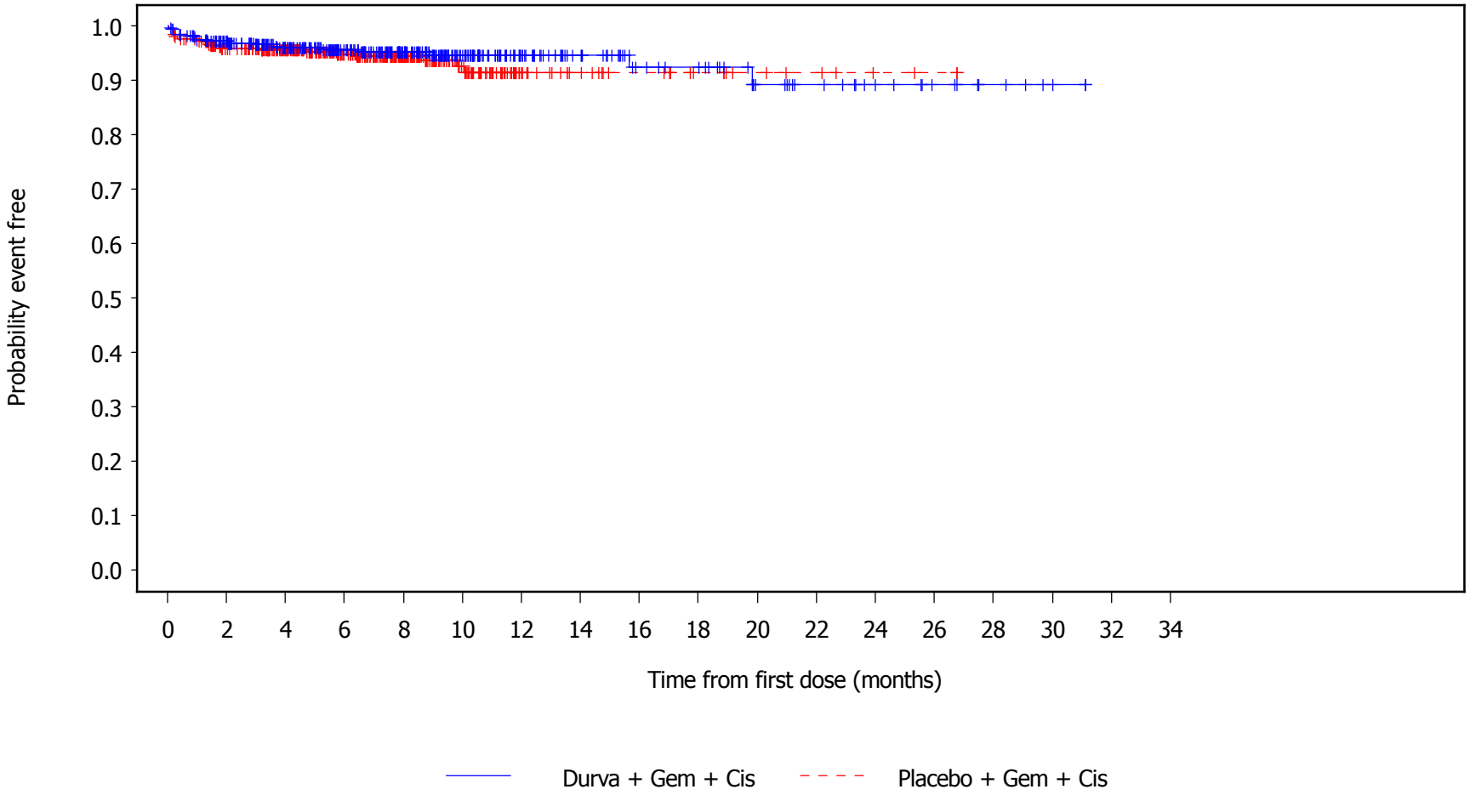
Figure 3.3.86 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Alanine aminotransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	343	281	235	174	114	70	50	36	32	21	17	12	8	5	2	0	0	Durva + Gem + Cis
403	335	274	202	140	76	31	21	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

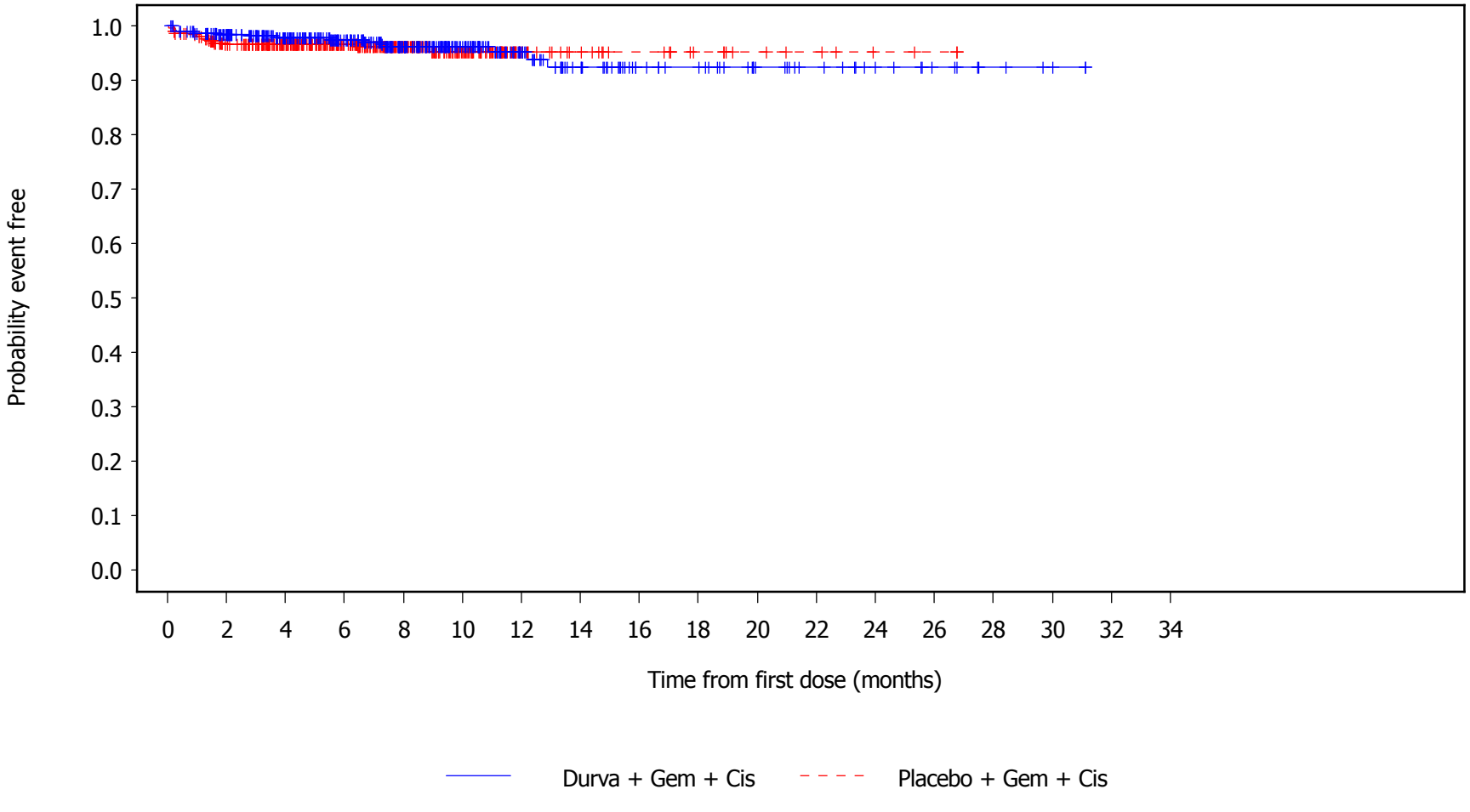
Figure 3.3.87 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Blood alkaline phosphatase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	363	304	252	188	124	77	55	39	36	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	356	298	221	151	84	32	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

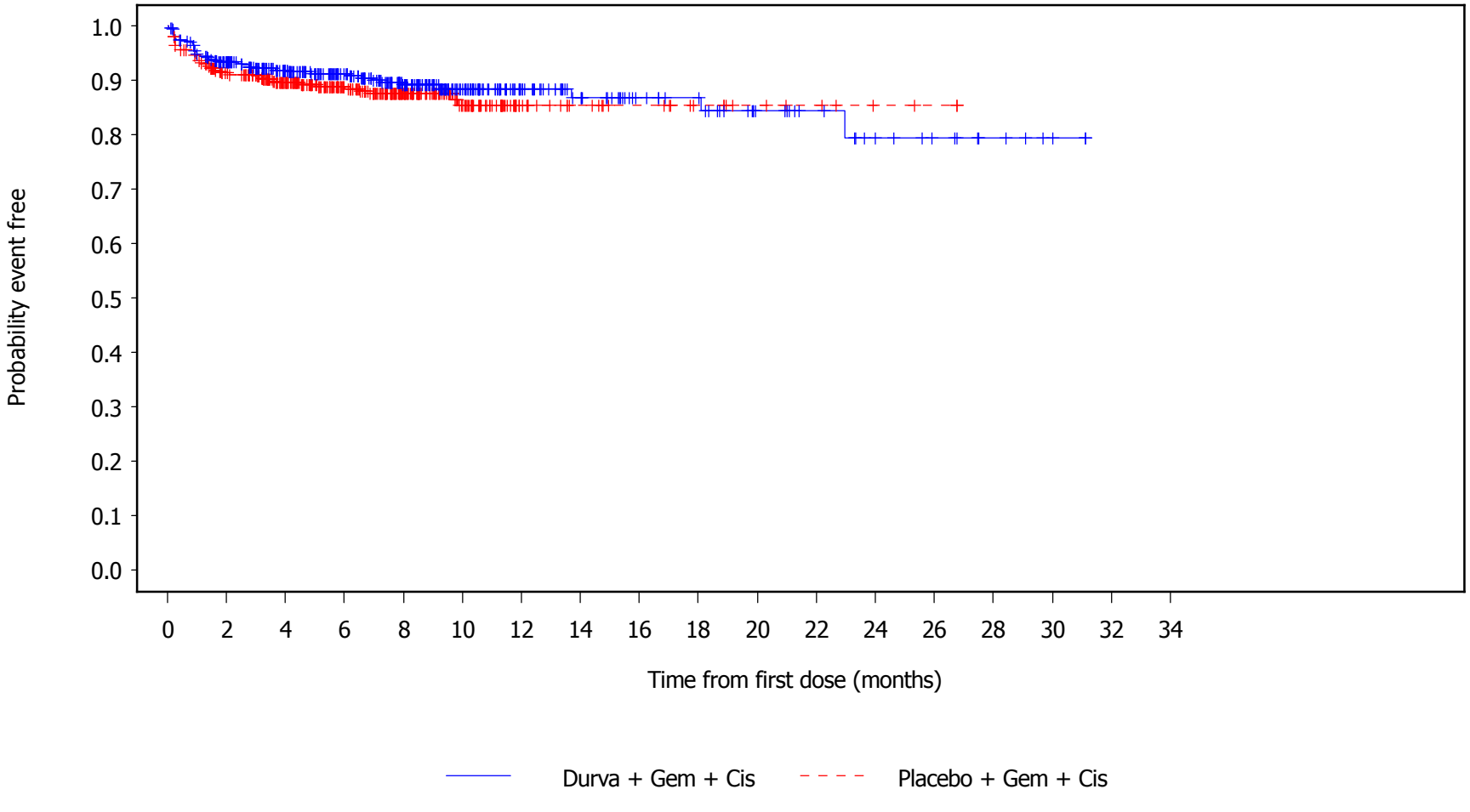
Figure 3.3.88 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Amylase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	308	257	189	126	77	55	38	34	23	18	13	8	4	2	0	0	Durva + Gem + Cis
403	358	301	222	150	83	32	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

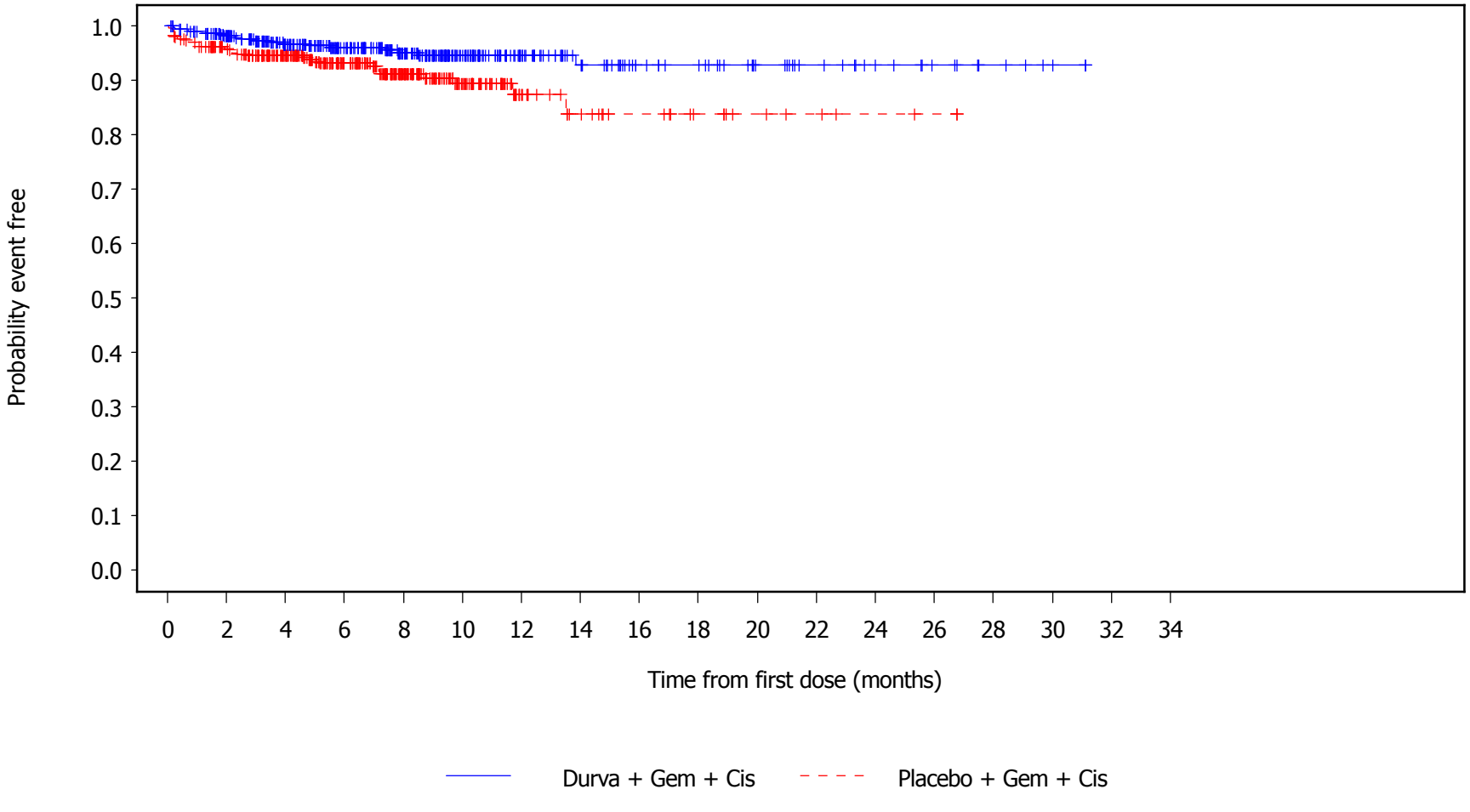
Figure 3.3.89 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Aspartate aminotransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	350	290	242	180	119	74	53	39	35	23	18	13	9	5	2	0	0	Durva + Gem + Cis
403	340	278	206	142	77	31	21	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

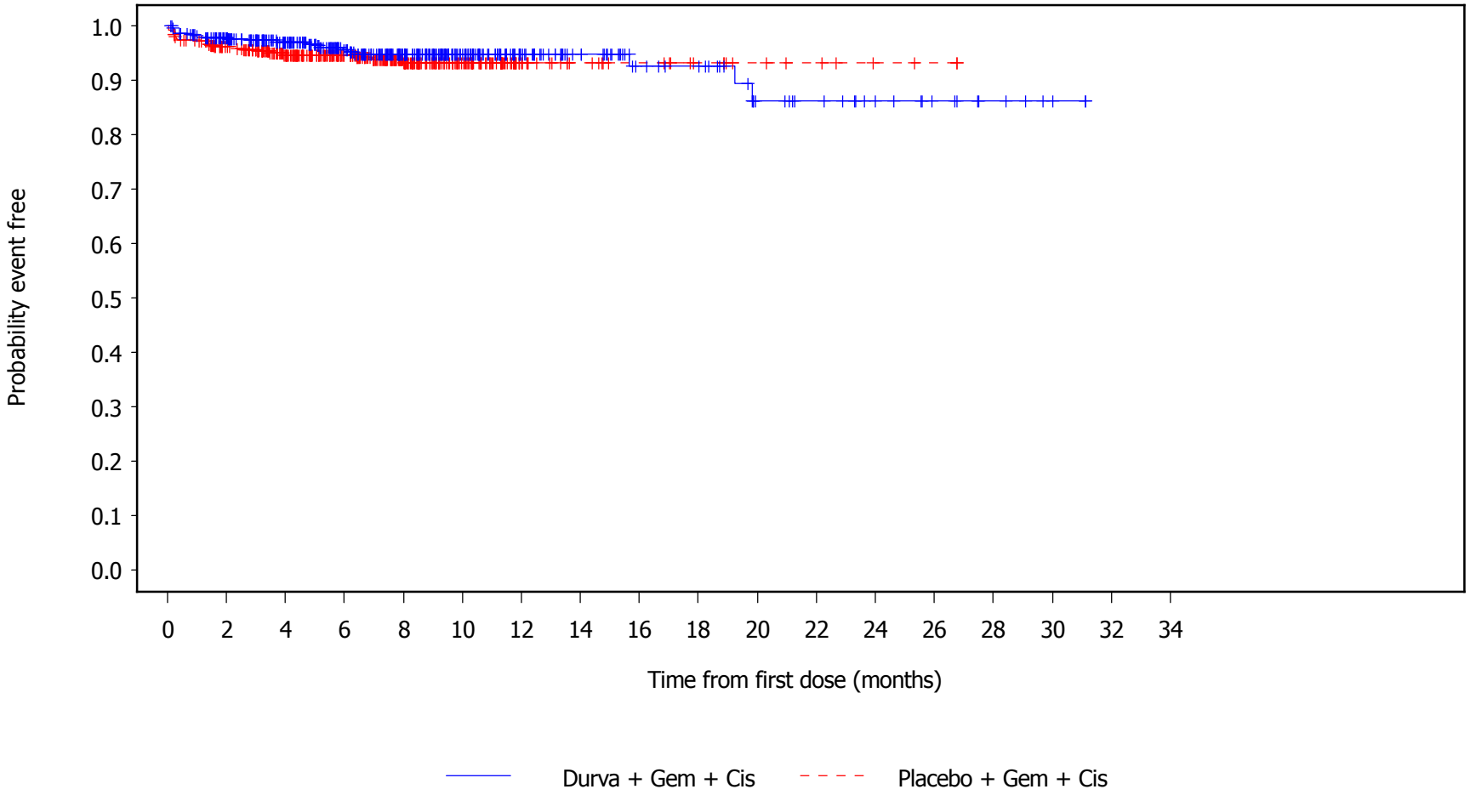
Figure 3.3.90 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	368	307	258	193	125	79	56	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	358	300	221	150	83	32	21	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

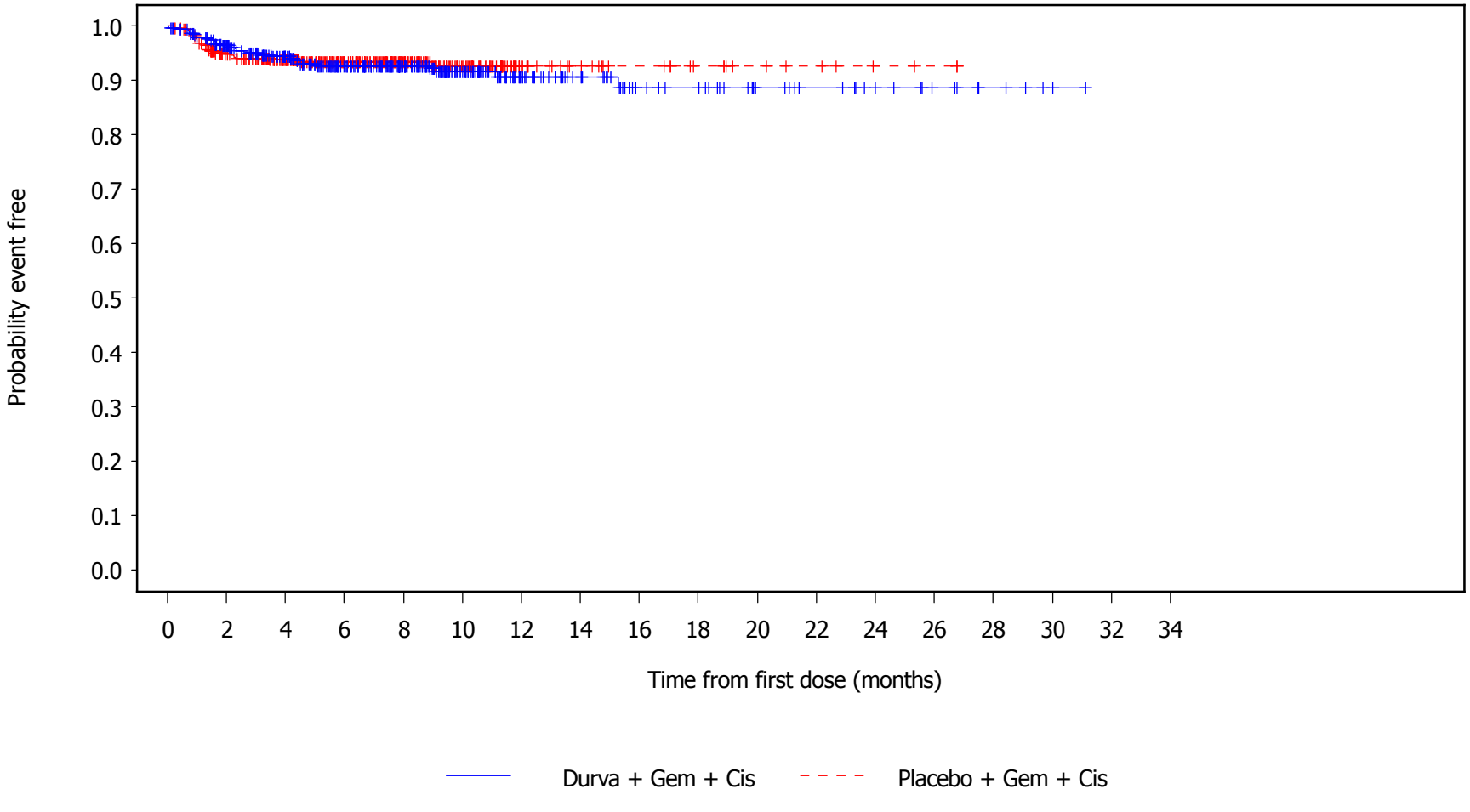
Figure 3.3.91 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Gamma-glutamyltransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	365	307	252	186	123	77	56	39	36	23	19	14	9	5	2	0	0	Durva + Gem + Cis
403	357	294	219	150	85	32	21	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

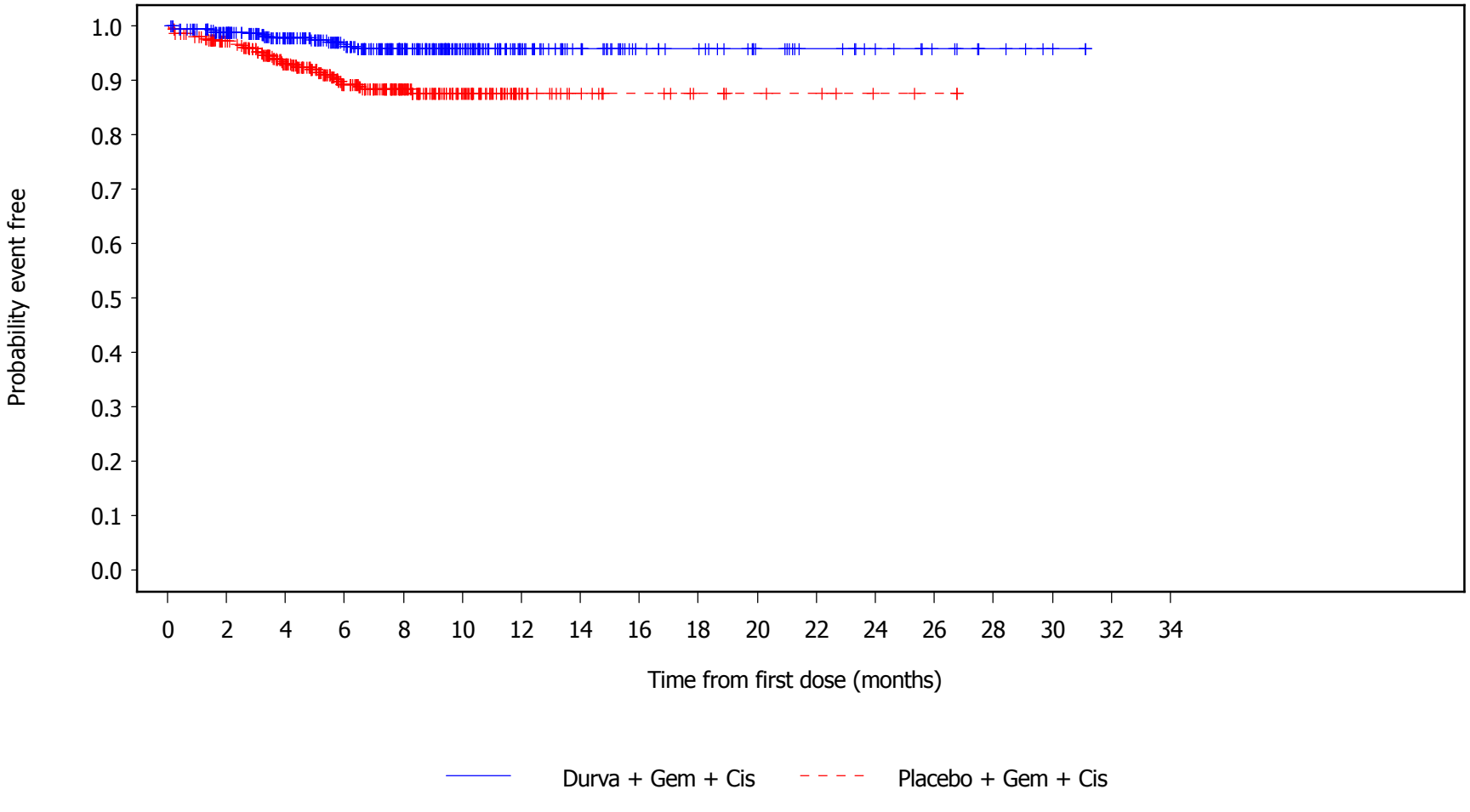
Figure 3.3.92 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Weight decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	360	300	250	188	123	76	55	37	33	22	18	14	9	5	2	0	0	Durva + Gem + Cis
403	351	297	224	154	87	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

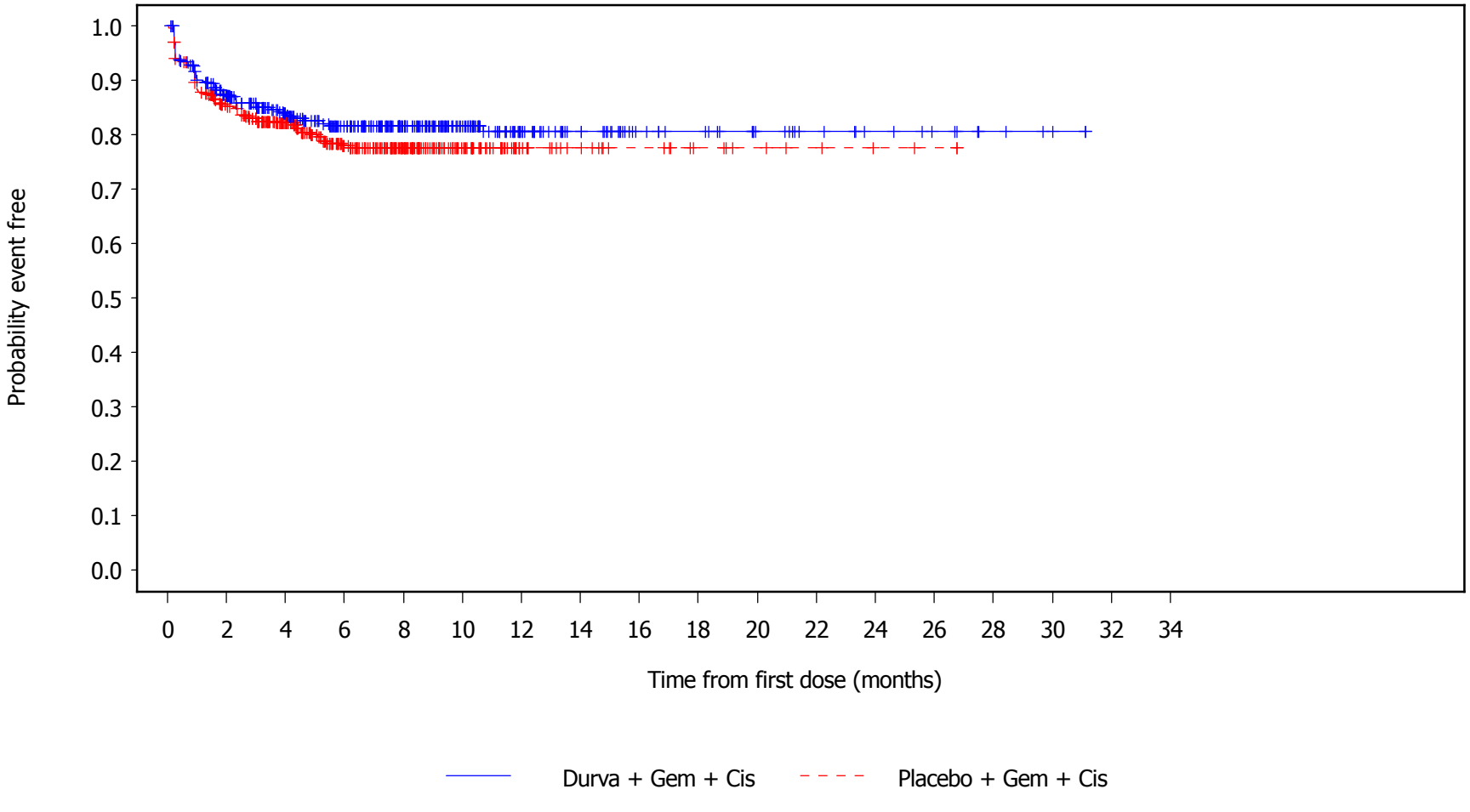
Figure 3.3.93 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Blood creatinine increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	309	257	191	127	78	56	38	34	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	360	291	204	137	80	28	18	13	9	6	5	2	1	0	0	0	0	Placebo + Gem + Cis

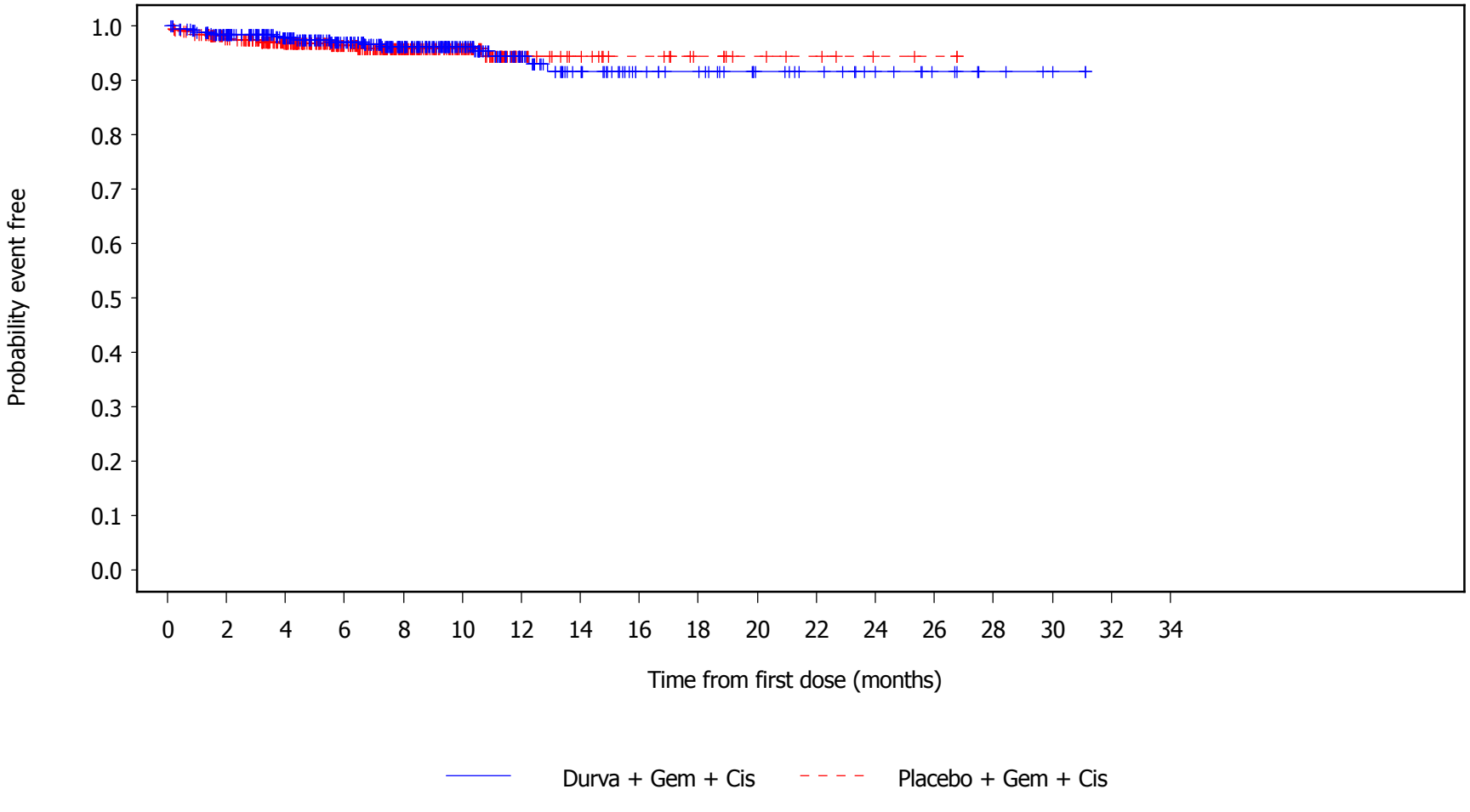
Figure 3.3.94 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: White blood cell count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	325	264	217	160	109	67	48	32	28	20	15	11	8	4	2	0	0	Durva + Gem + Cis
403	315	249	174	122	67	29	20	14	9	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

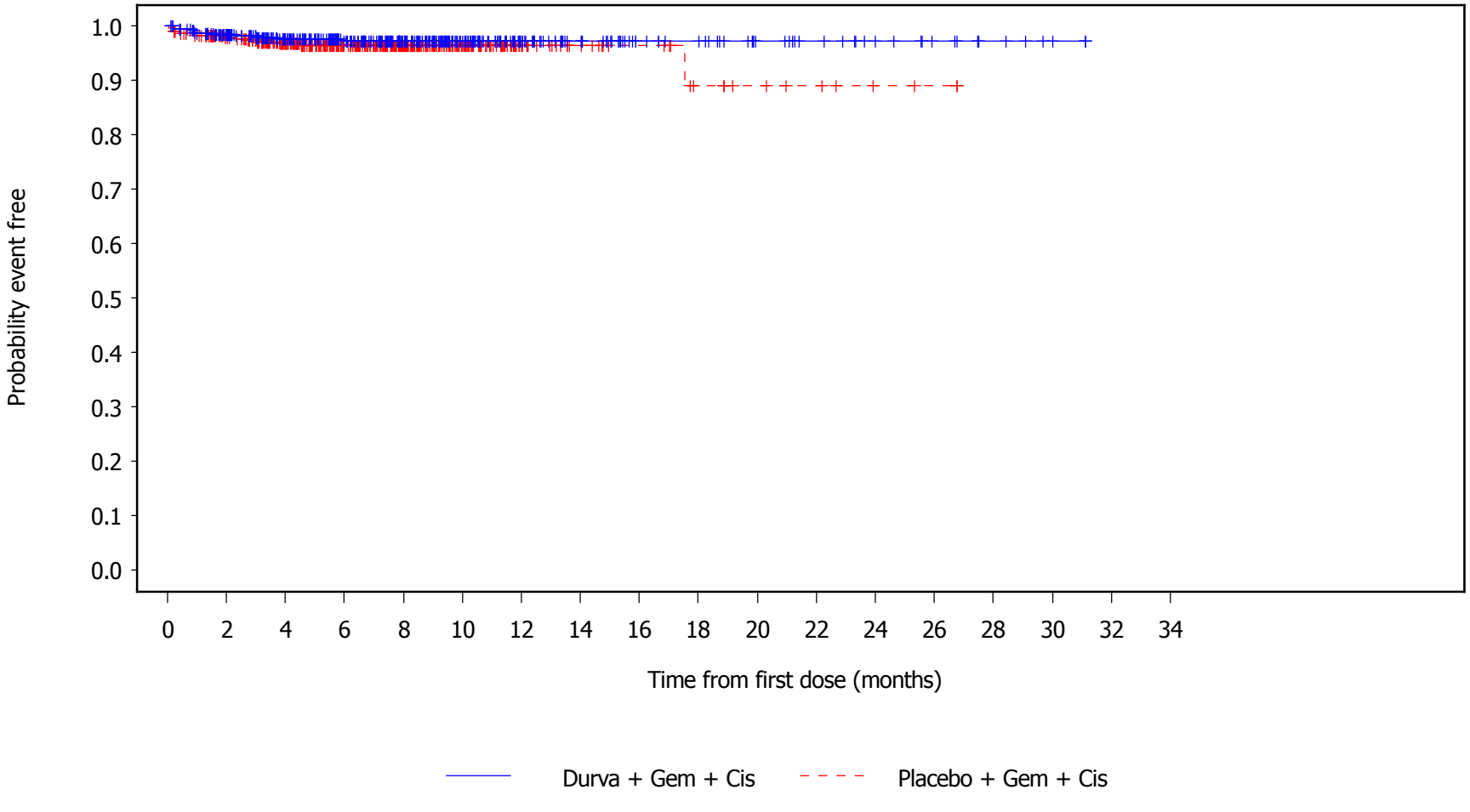
Figure 3.3.95 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Lipase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	308	258	190	126	75	52	36	32	22	18	13	8	4	2	0	0	Durva + Gem + Cis
403	362	303	222	151	86	32	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

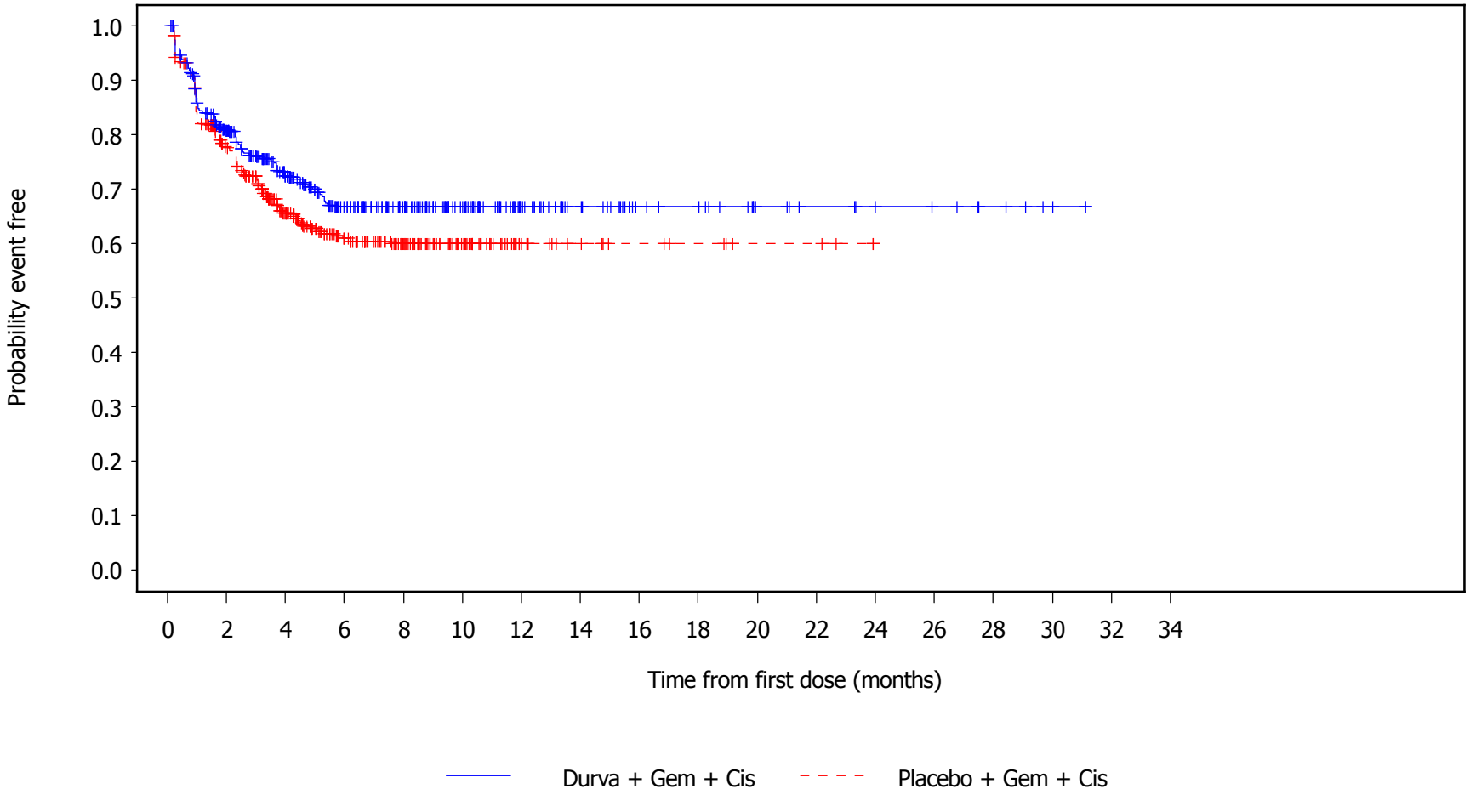
Figure 3.3.96 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Lymphocyte count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	307	257	191	126	77	56	39	35	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	364	304	225	156	88	34	22	16	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

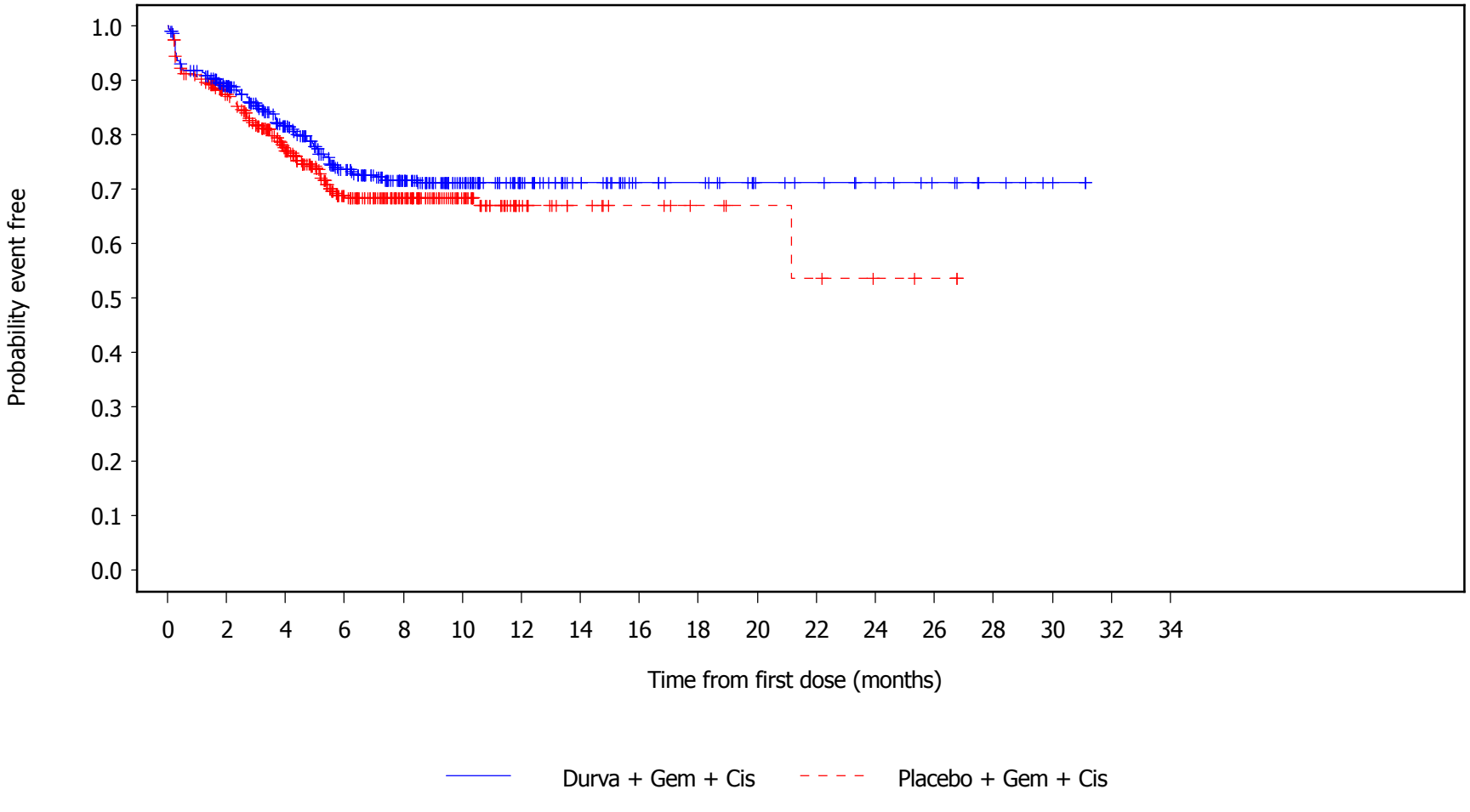
Figure 3.3.97 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Neutrophil count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	300	223	167	130	92	56	40	27	24	15	12	10	8	5	2	0	0	Durva + Gem + Cis
403	287	194	129	90	53	20	12	8	6	3	3	0	0	0	0	0	0	Placebo + Gem + Cis

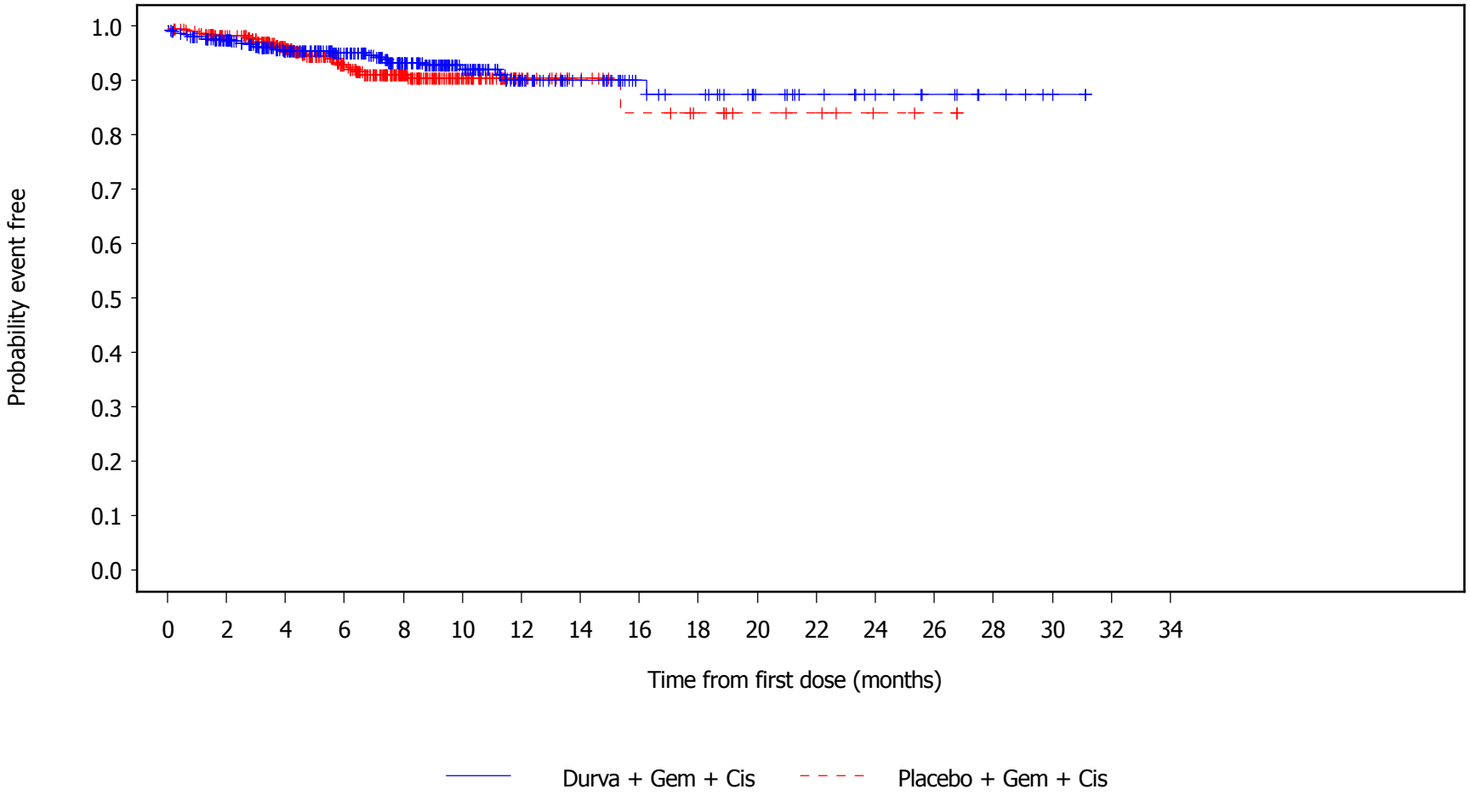
Figure 3.3.98 TOPAZ: Kaplan-Meier plot of time to first occurrence of PT: Platelet count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	336	265	205	149	99	62	44	30	27	18	16	13	9	5	2	0	0	Durva + Gem + Cis
403	326	241	157	107	59	23	14	10	7	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

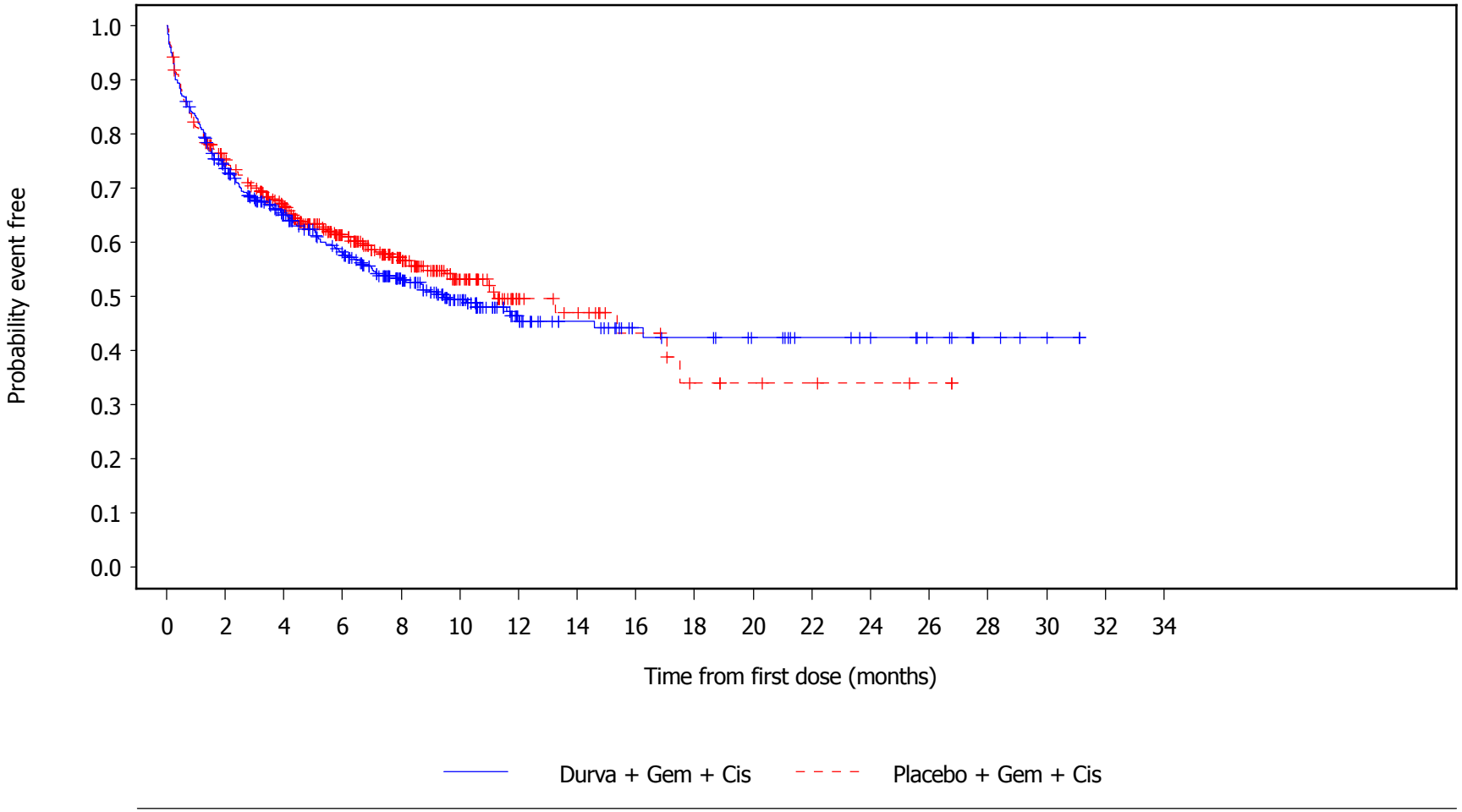
Figure 3.3.99 TOPAZ: Kaplan-Meier plot of time to first occurrence of SOC: Injury, poisoning and procedural complications
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	364	302	253	187	122	74	53	36	32	22	17	13	9	5	2	0	0	Durva + Gem + Cis
403	366	303	218	145	80	30	19	13	10	6	5	2	1	0	0	0	0	Placebo + Gem + Cis

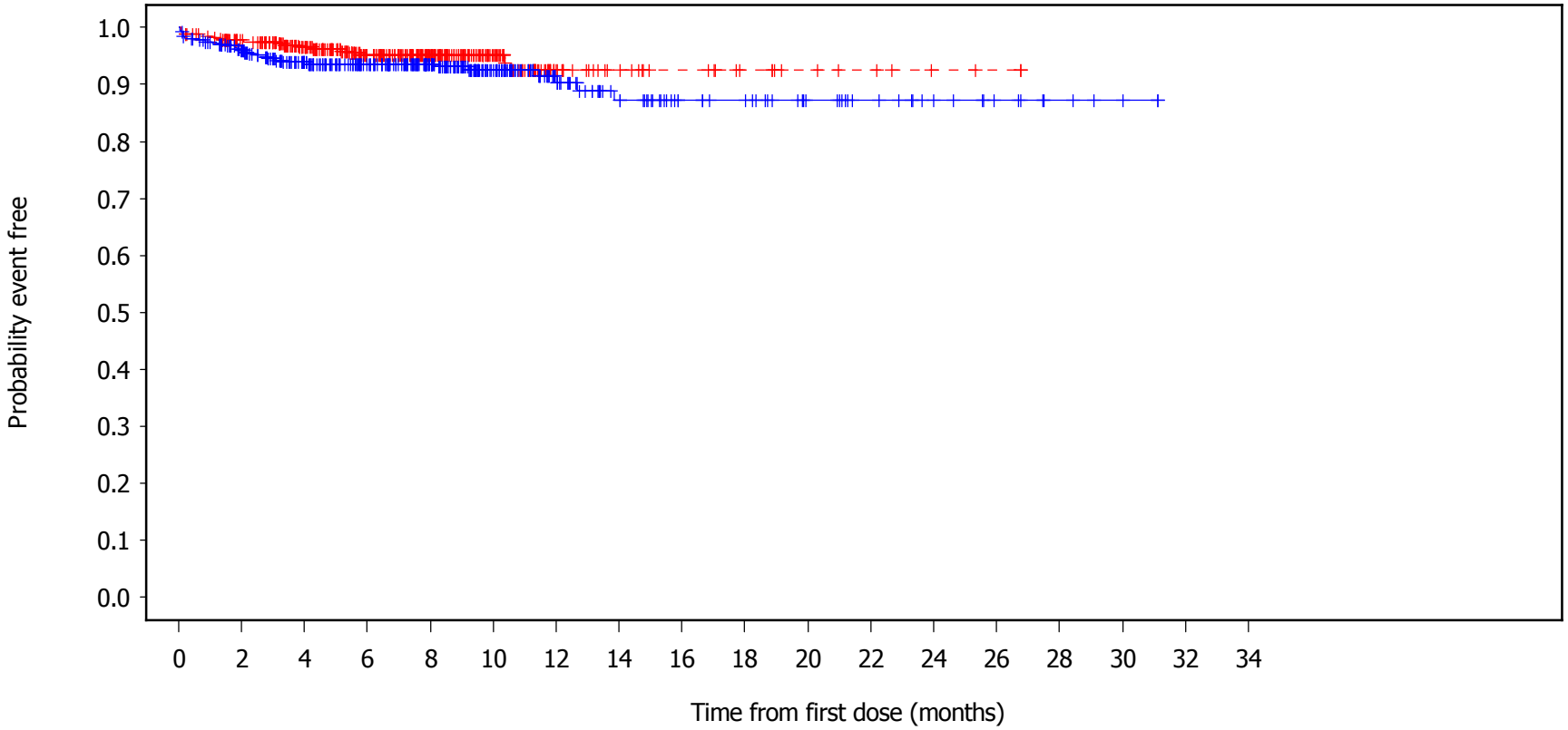
Figure 3.3.100 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	287	227	186	133	88	49	36	25	23	19	14	12	8	4	2	0	0	Durva + Gem + Cis
403	291	235	164	107	59	23	18	11	6	4	3	2	1	0	0	0	0	Placebo + Gem + Cis

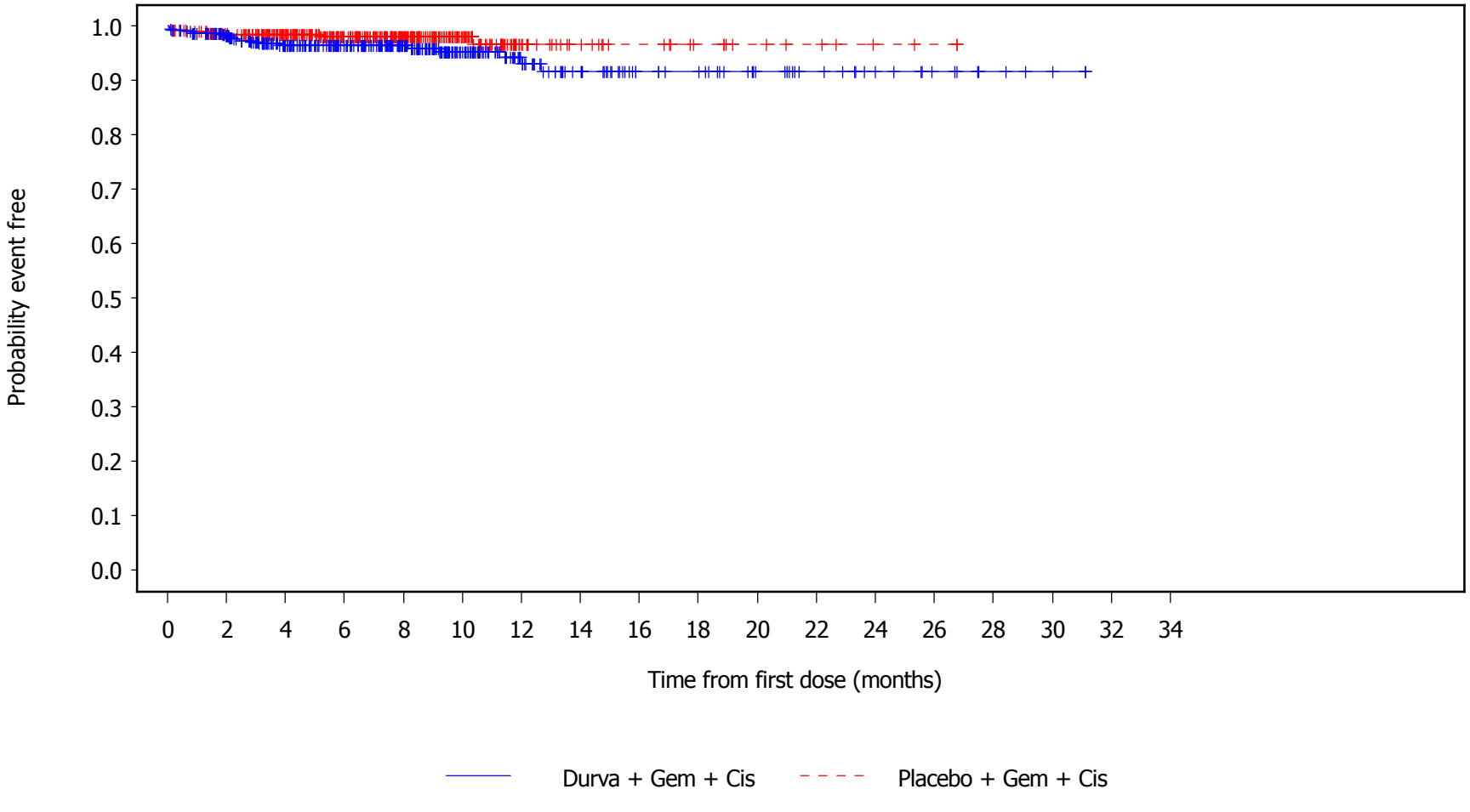
Figure 3.3.101 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE SOC: General disorders and administration site conditions
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	363	301	256	195	127	76	53	37	34	24	18	13	8	4	2	0	0	Durva + Gem + Cis
403	364	305	224	154	86	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

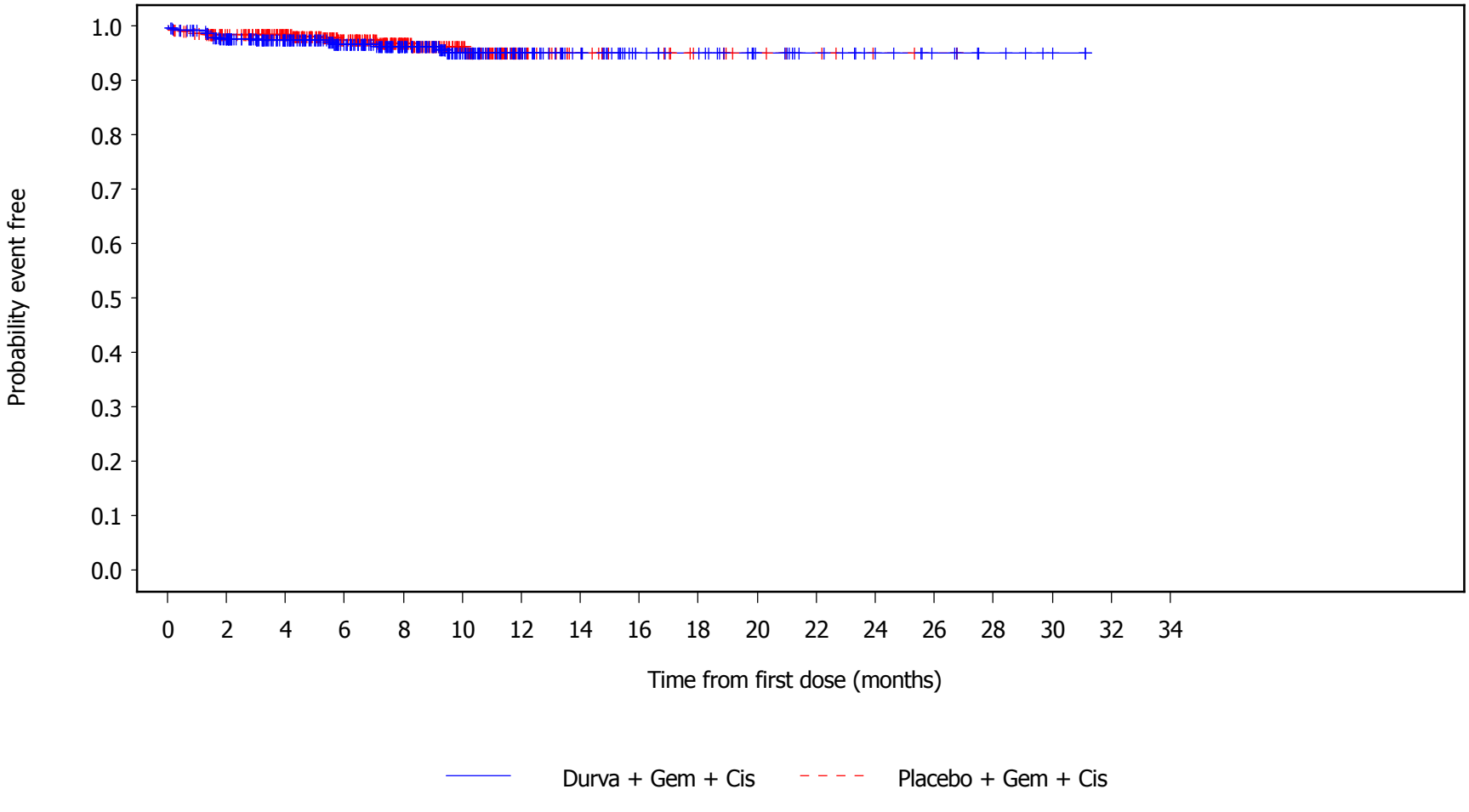
Figure 3.3.102 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE PT: Pyrexia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	304	258	195	127	76	54	37	34	24	18	13	8	4	2	0	0	Durva + Gem + Cis
403	366	308	228	156	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

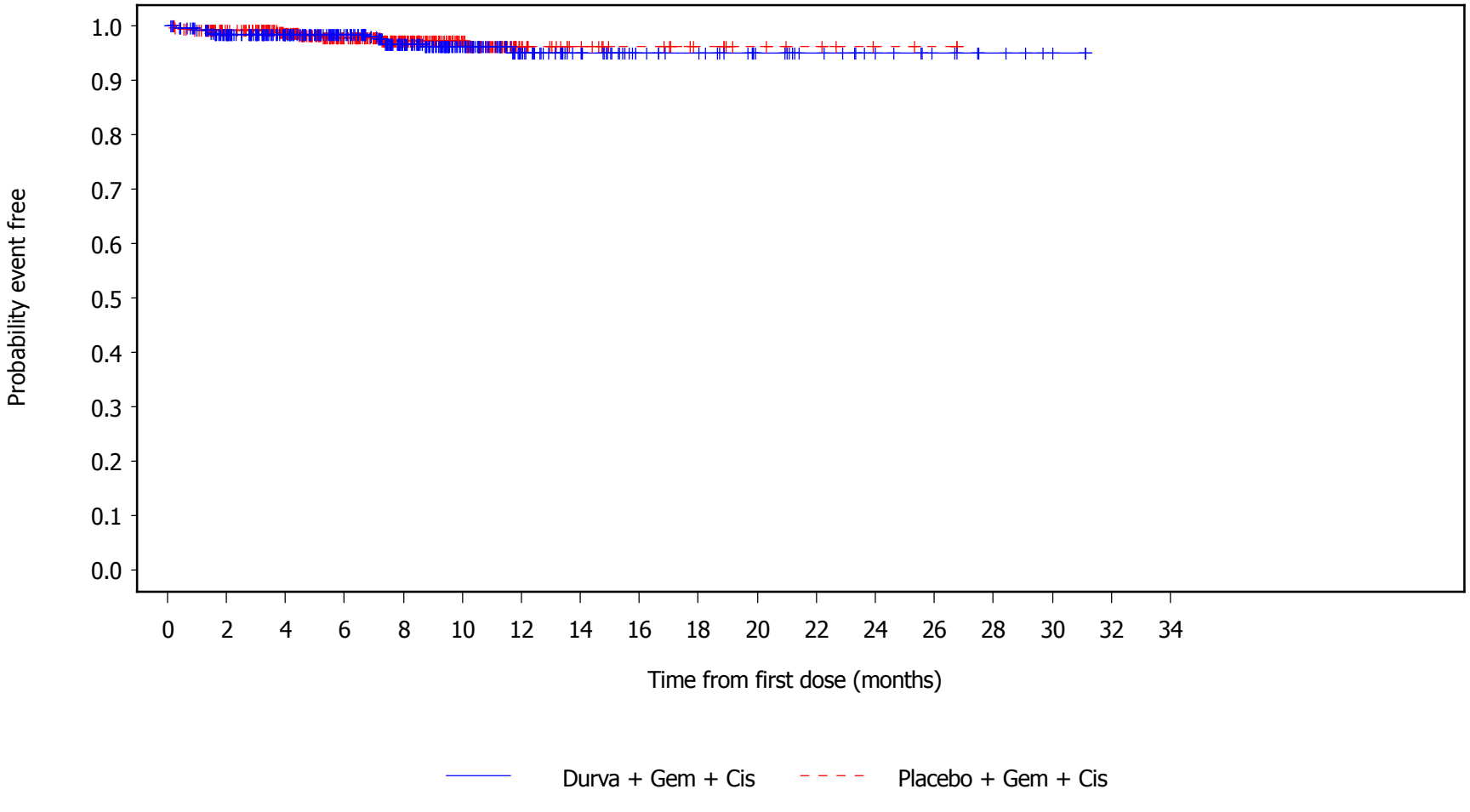
Figure 3.3.103 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE SOC: Respiratory, thoracic and mediastinal disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	368	310	258	192	128	78	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	312	228	156	87	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

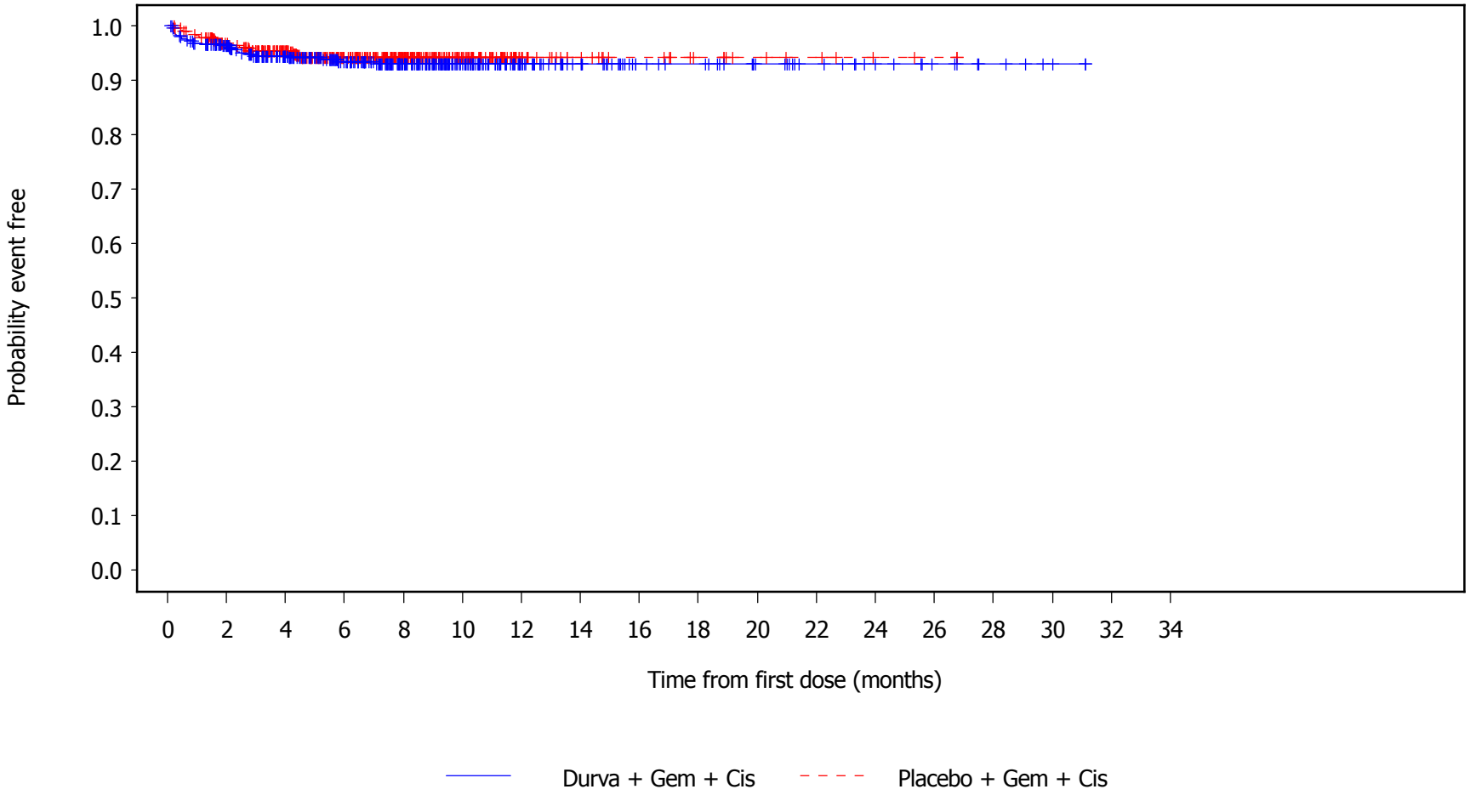
Figure 3.3.104 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE SOC: Renal and urinary disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	312	262	194	128	78	56	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	309	227	155	87	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

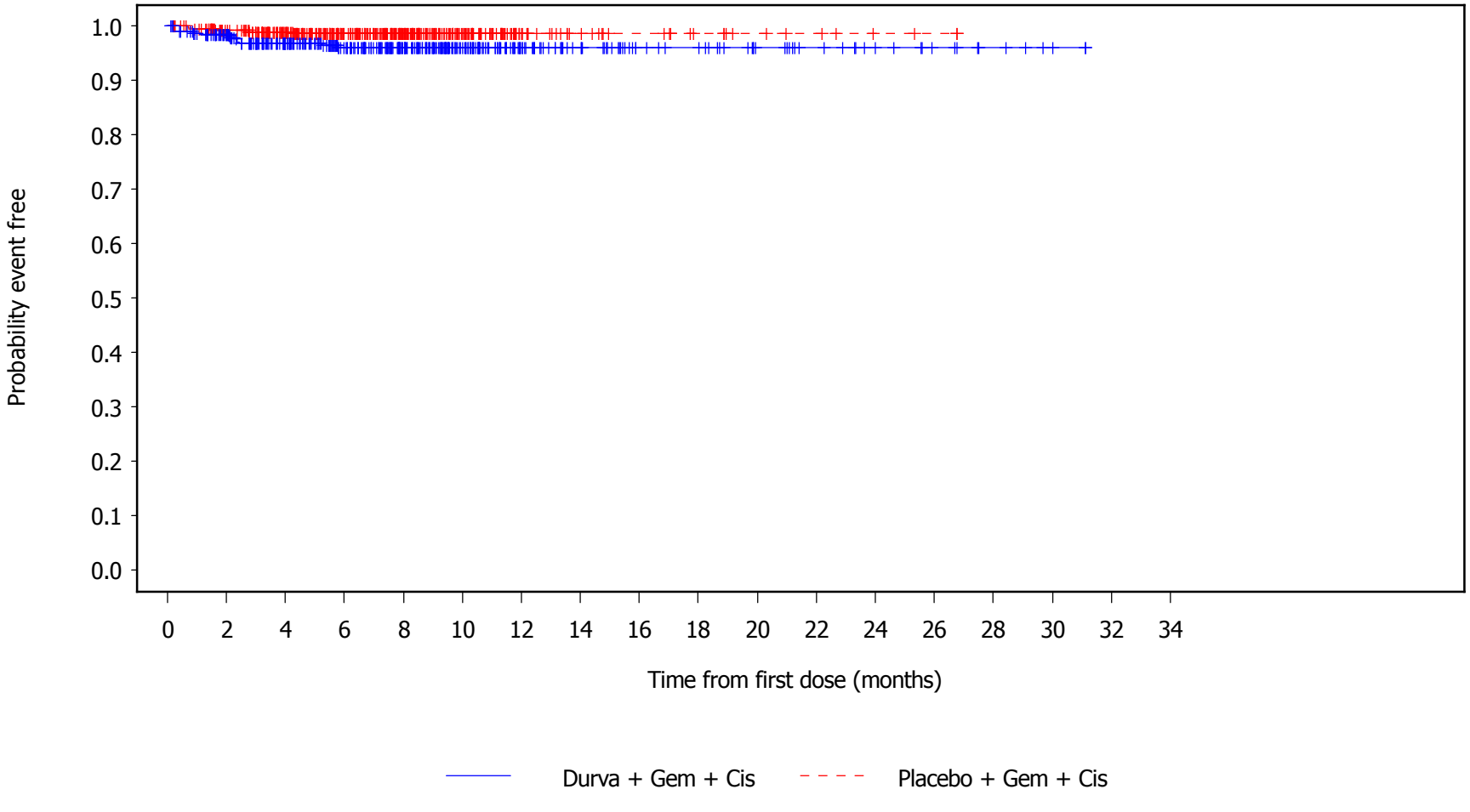
Figure 3.3.105 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE SOC: Blood and lymphatic system disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	361	301	251	188	124	75	54	37	34	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	361	301	221	153	86	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

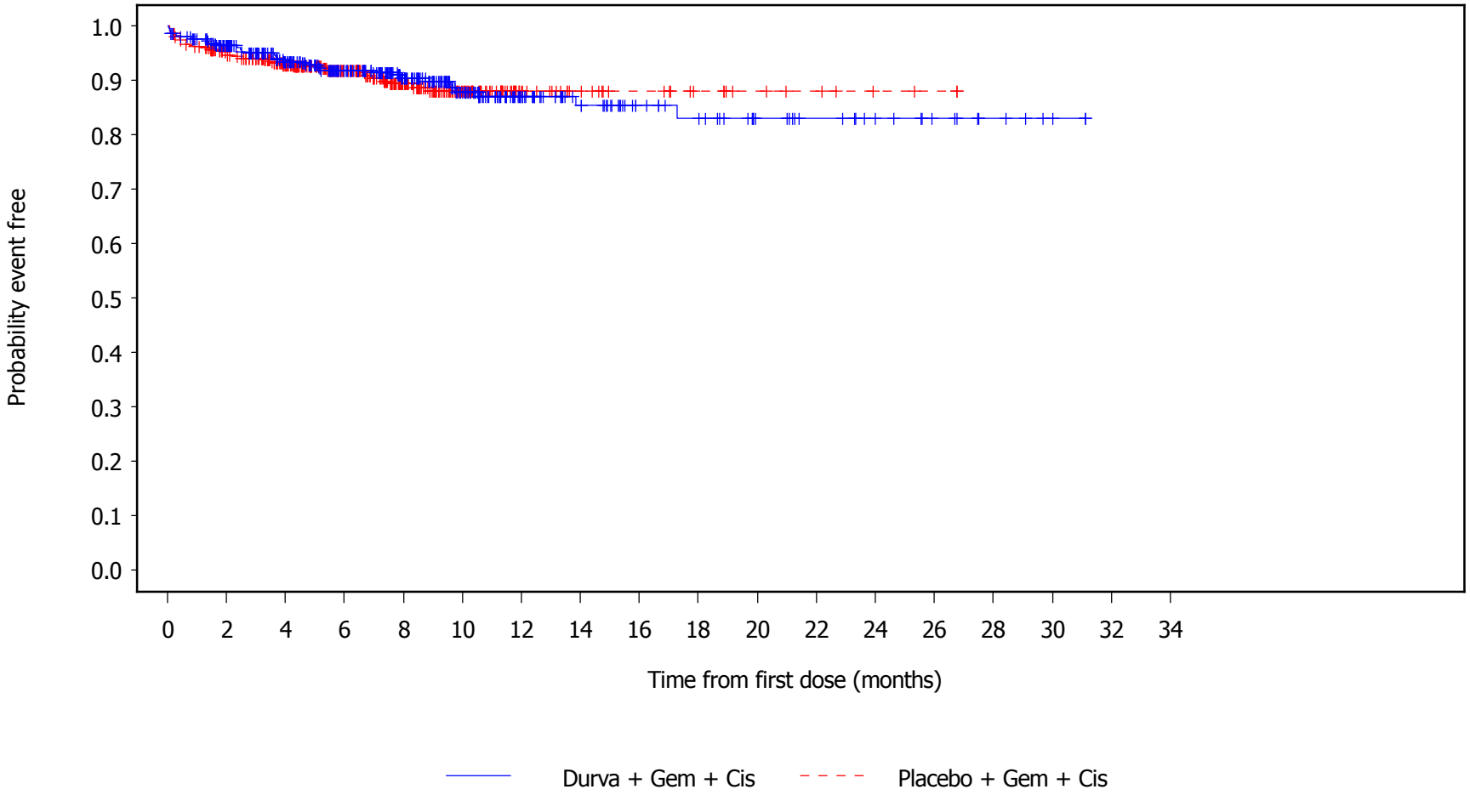
Figure 3.3.106 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE PT: Anaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	305	255	192	127	77	56	39	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	310	230	158	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

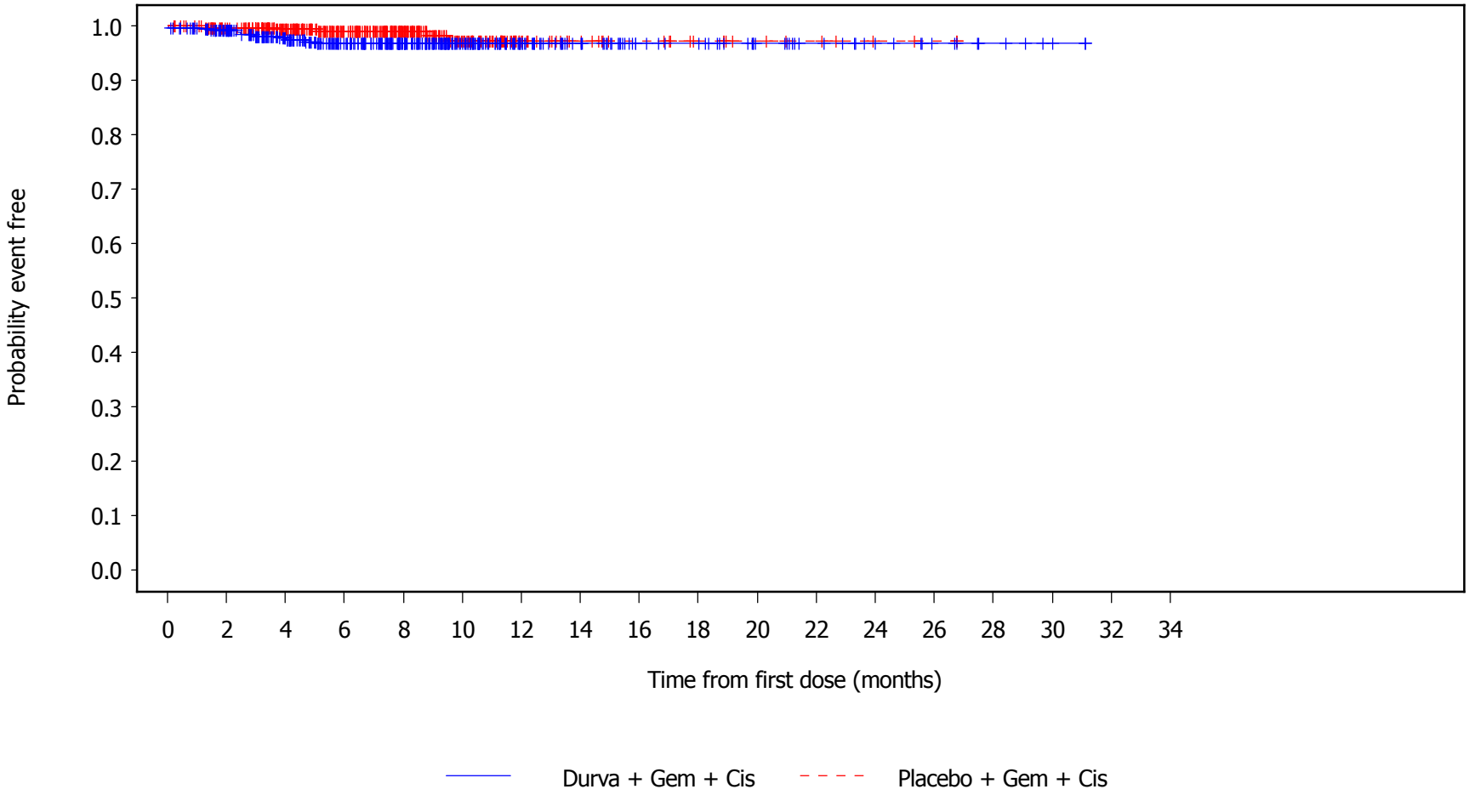
Figure 3.3.107 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE SOC: Gastrointestinal disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	361	299	249	187	123	75	54	38	33	23	18	14	9	5	2	0	0	Durva + Gem + Cis
403	356	298	219	146	82	32	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

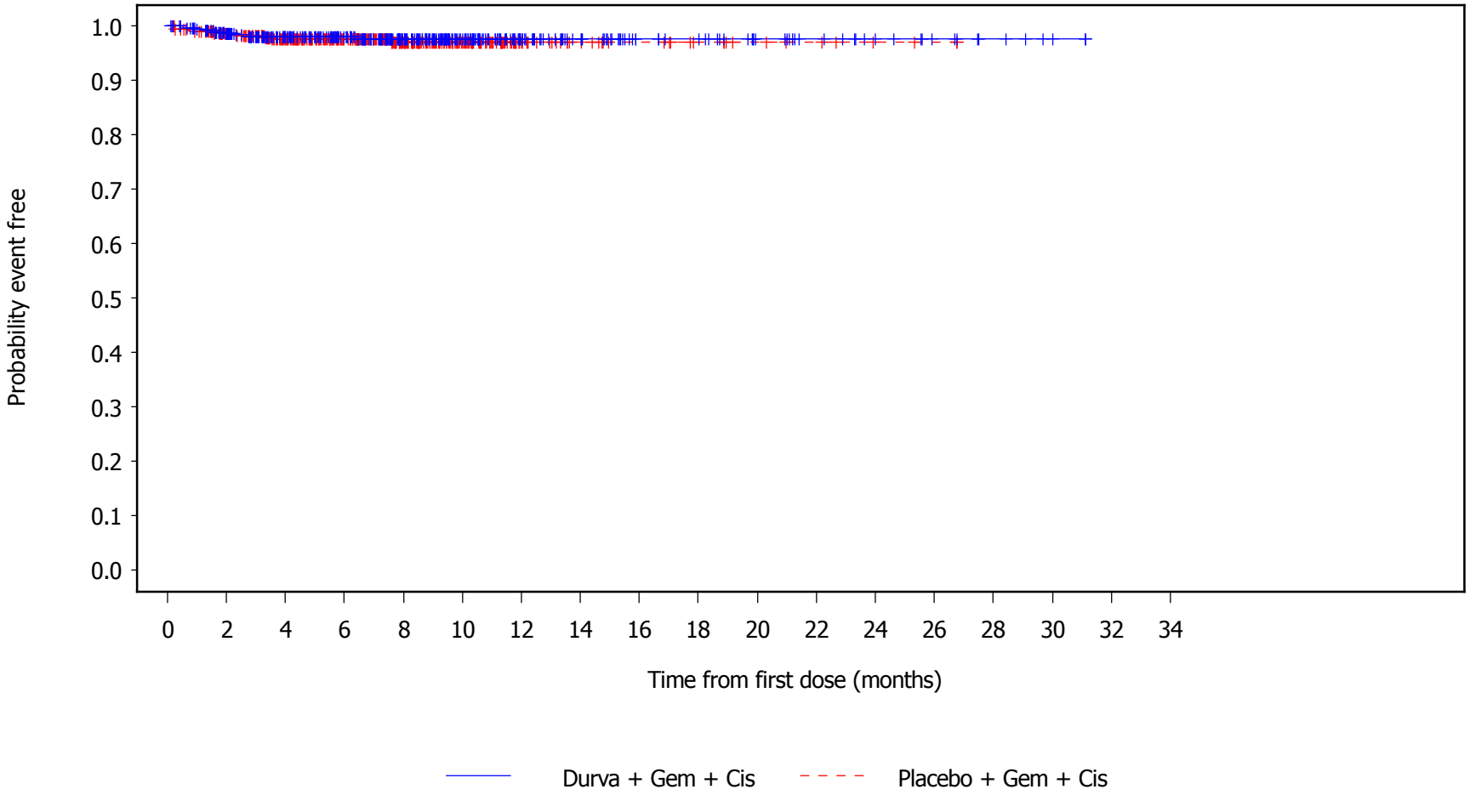
Figure 3.3.108 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE SOC: Nervous system disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	311	261	197	130	79	57	39	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	231	158	87	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

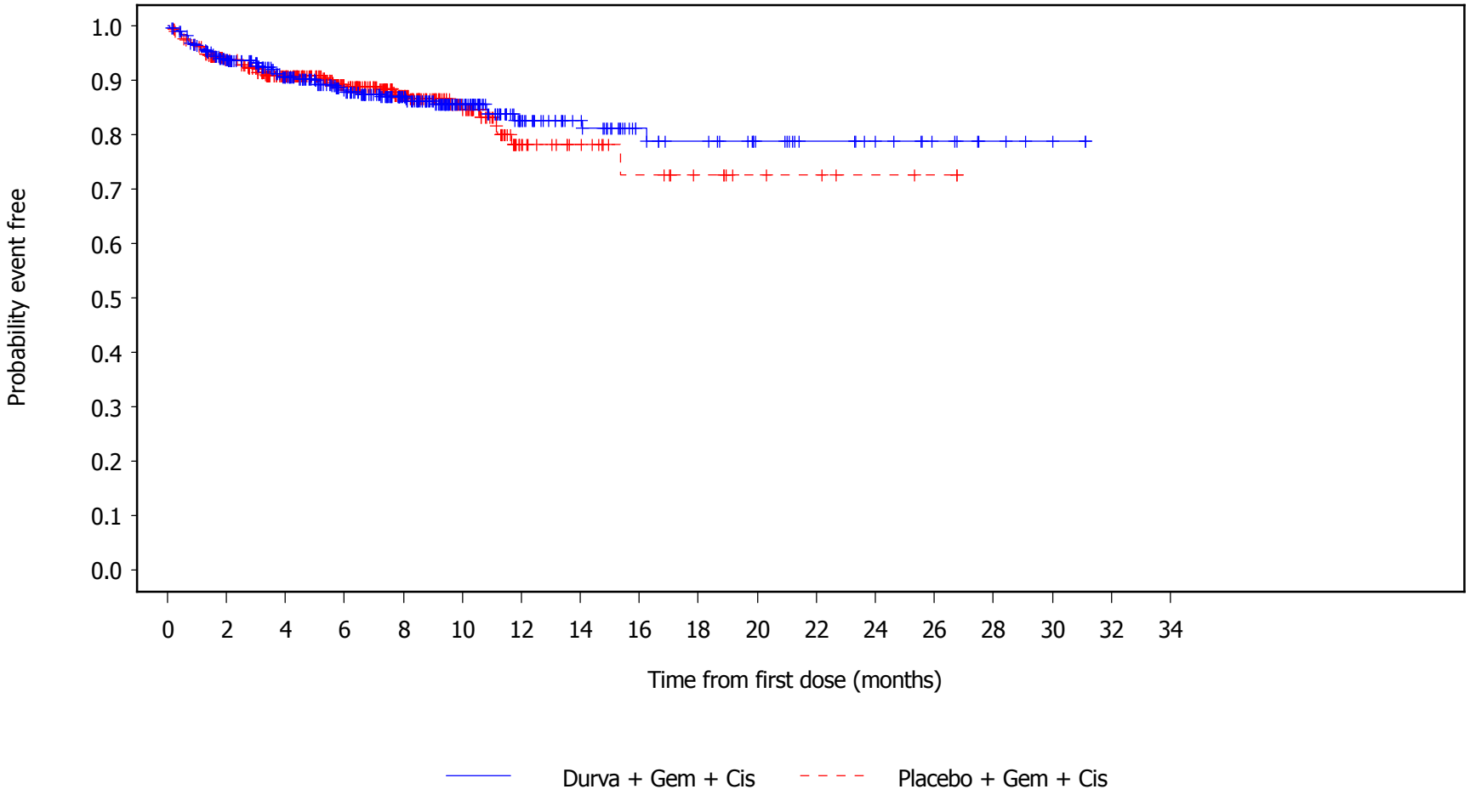
Figure 3.3.109 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE SOC: Vascular disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	368	309	262	196	130	79	57	39	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	308	229	157	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

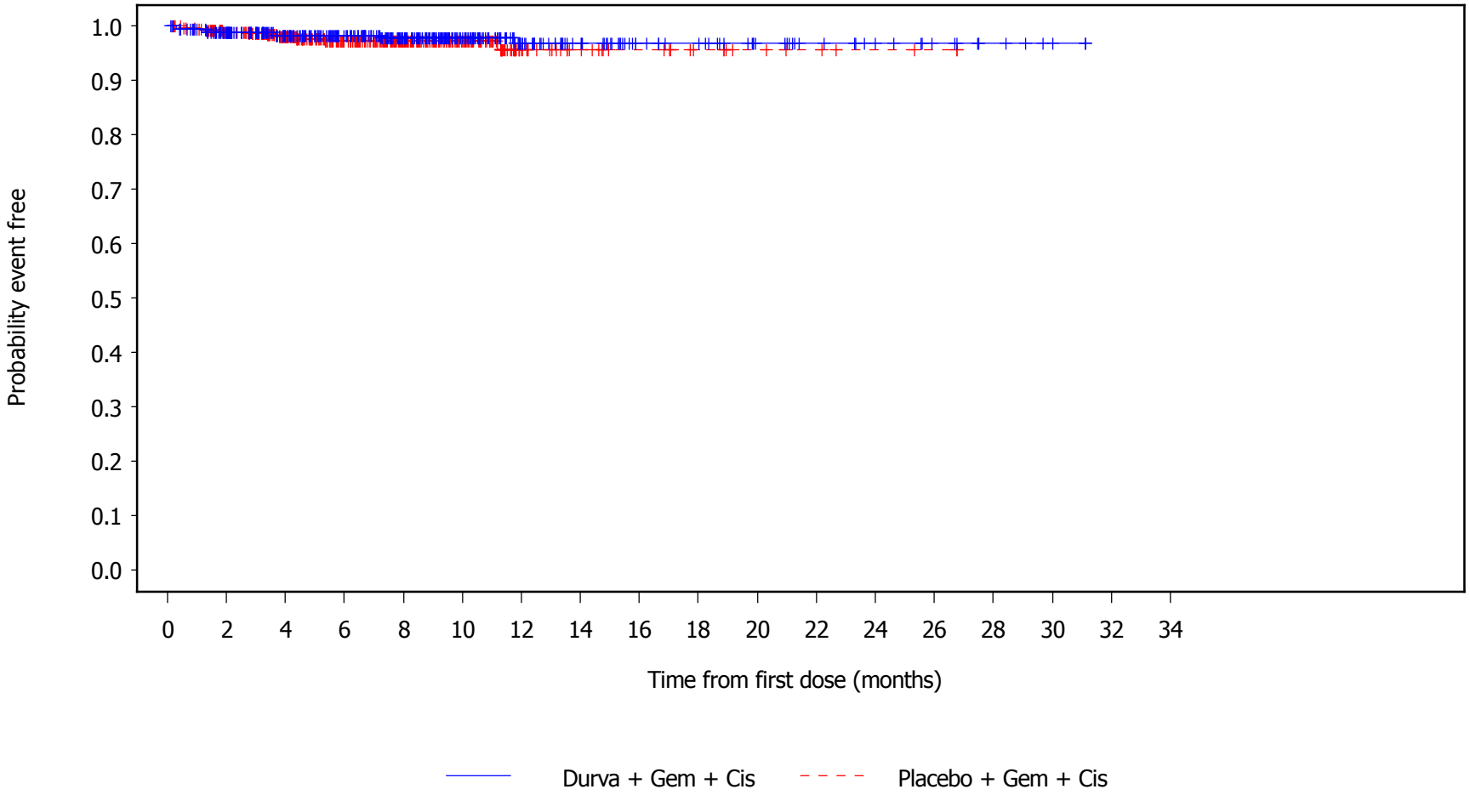
Figure 3.3.110 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE SOC: Infections and infestations
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	352	295	247	186	122	71	53	35	30	22	16	13	8	4	2	0	0	Durva + Gem + Cis
403	350	292	214	142	78	29	20	13	9	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

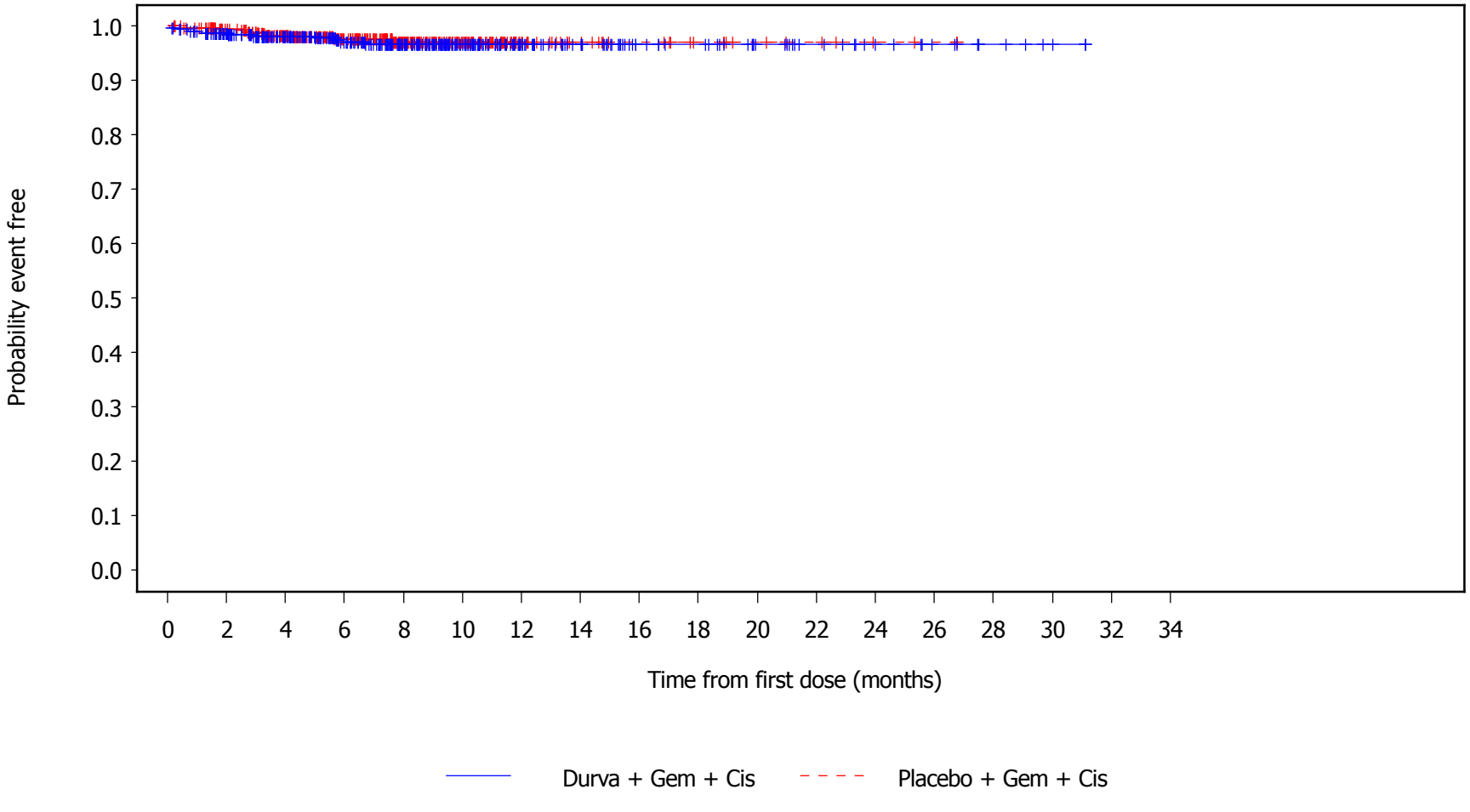
Figure 3.3.111 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE PT: Biliary tract infection
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	311	261	197	131	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	367	309	229	157	89	33	21	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

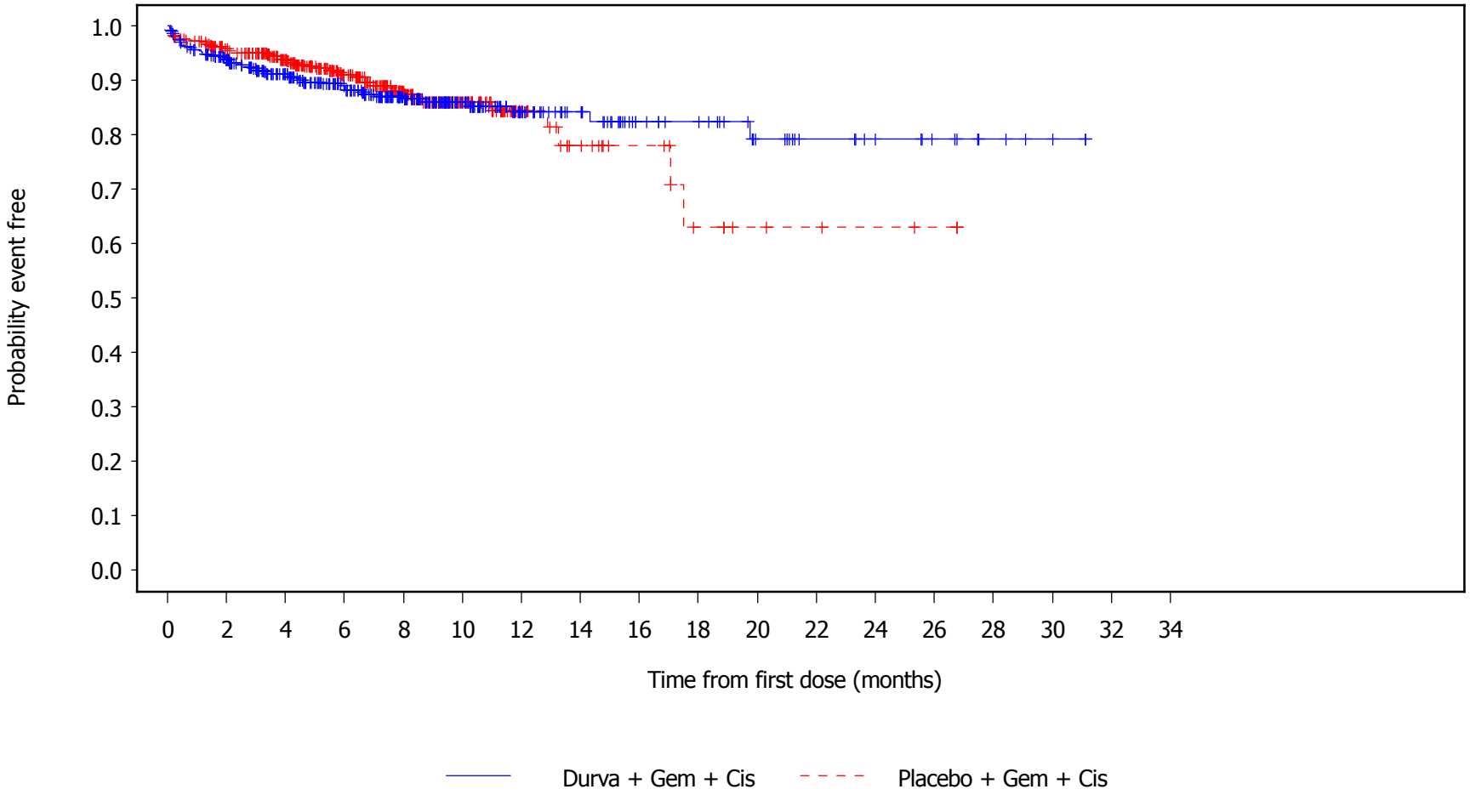
Figure 3.3.112 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE PT: Sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	370	311	258	195	128	77	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	309	229	156	87	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

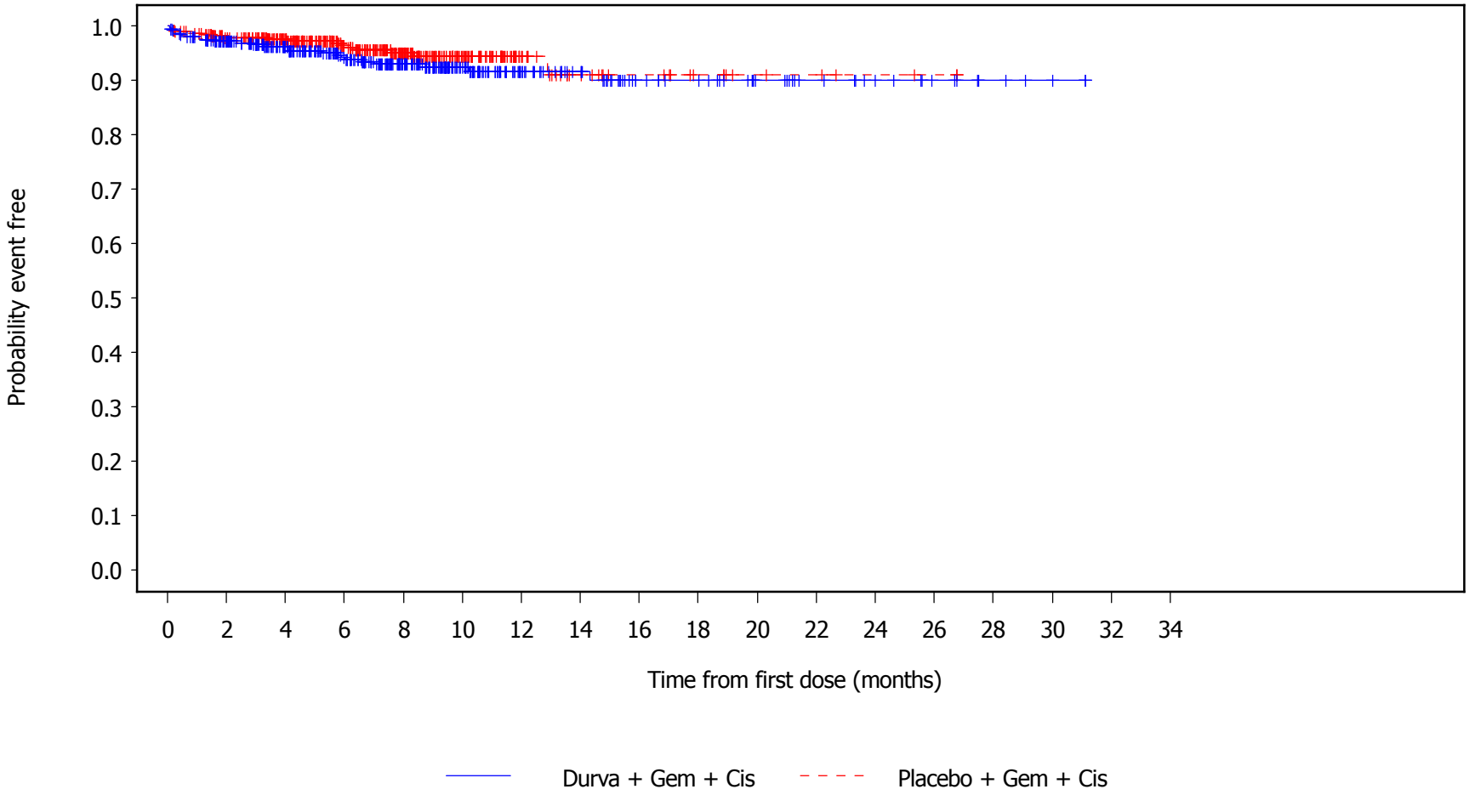
Figure 3.3.113 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE SOC: Hepatobiliary disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	353	294	243	178	118	70	53	35	31	21	15	12	8	4	2	0	0	Durva + Gem + Cis
403	356	296	212	143	80	30	19	13	7	4	3	2	1	0	0	0	0	Placebo + Gem + Cis

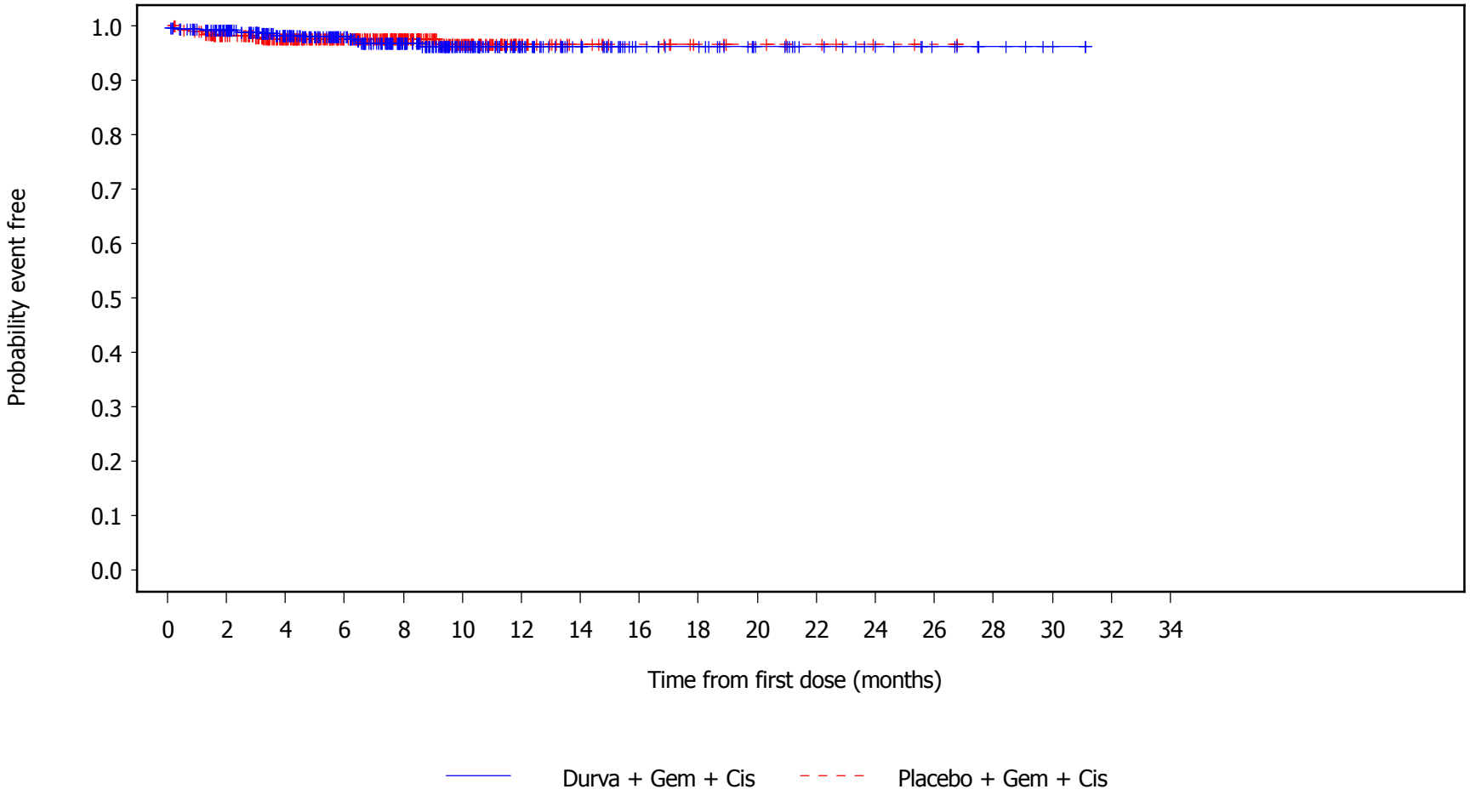
Figure 3.3.114 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE PT: Cholangitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	363	305	251	185	123	74	56	37	33	23	17	13	8	4	2	0	0	Durva + Gem + Cis
403	363	306	223	152	85	33	20	14	9	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

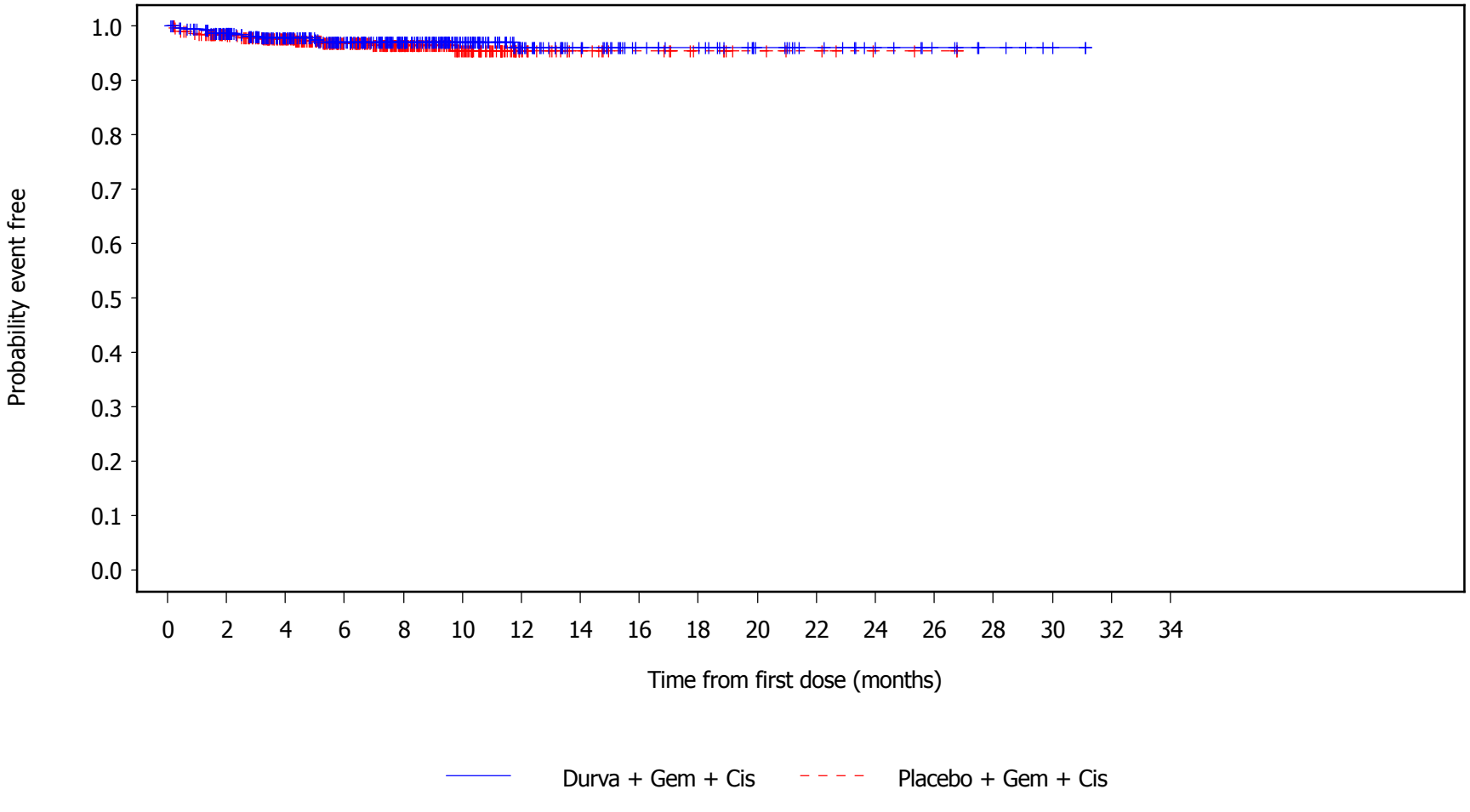
Figure 3.3.115 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE SOC: Metabolism and nutrition disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	370	309	258	191	128	78	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	366	309	228	155	87	33	21	15	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

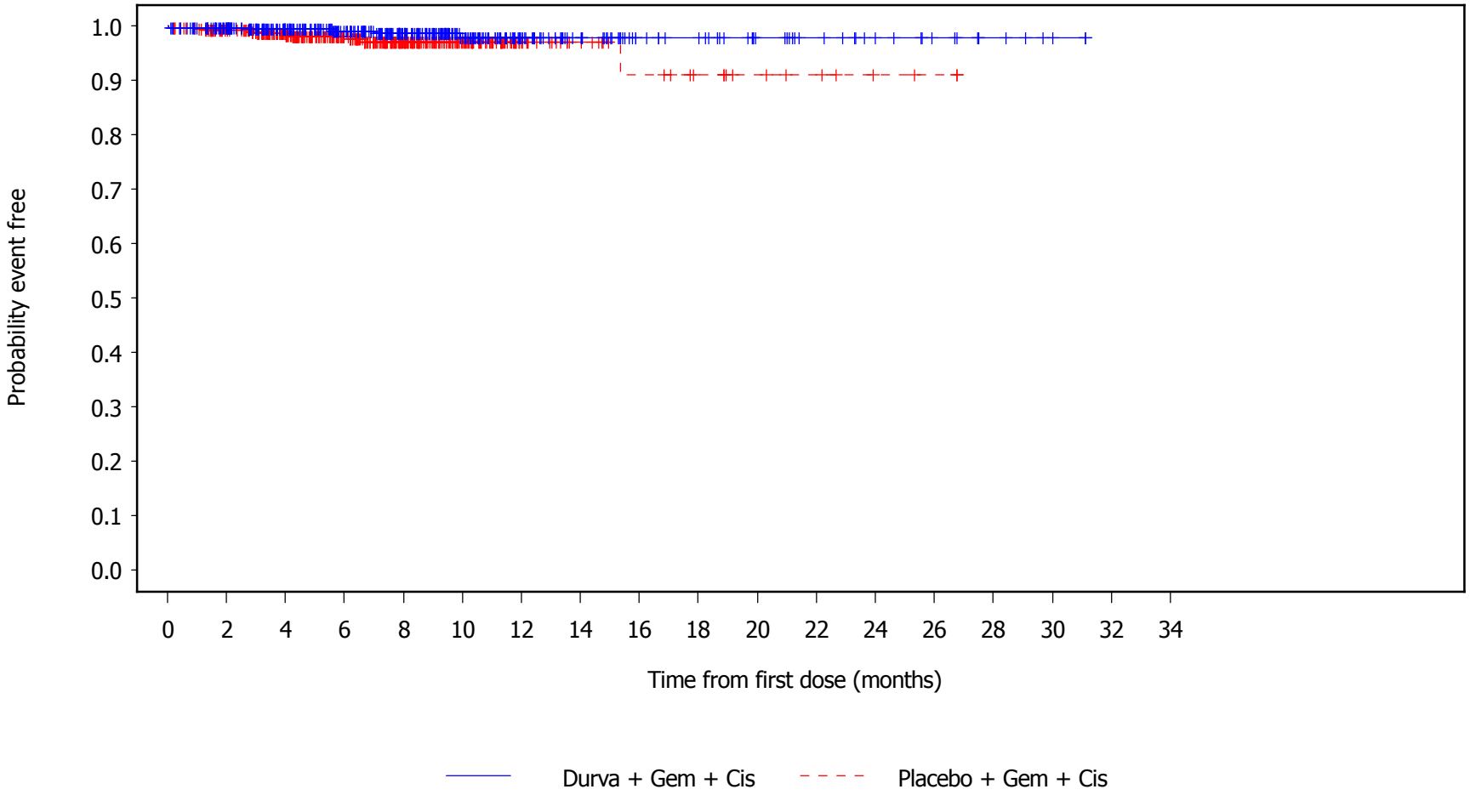
Figure 3.3.116 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE SOC: Investigations
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	310	259	194	129	78	56	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	310	228	158	87	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

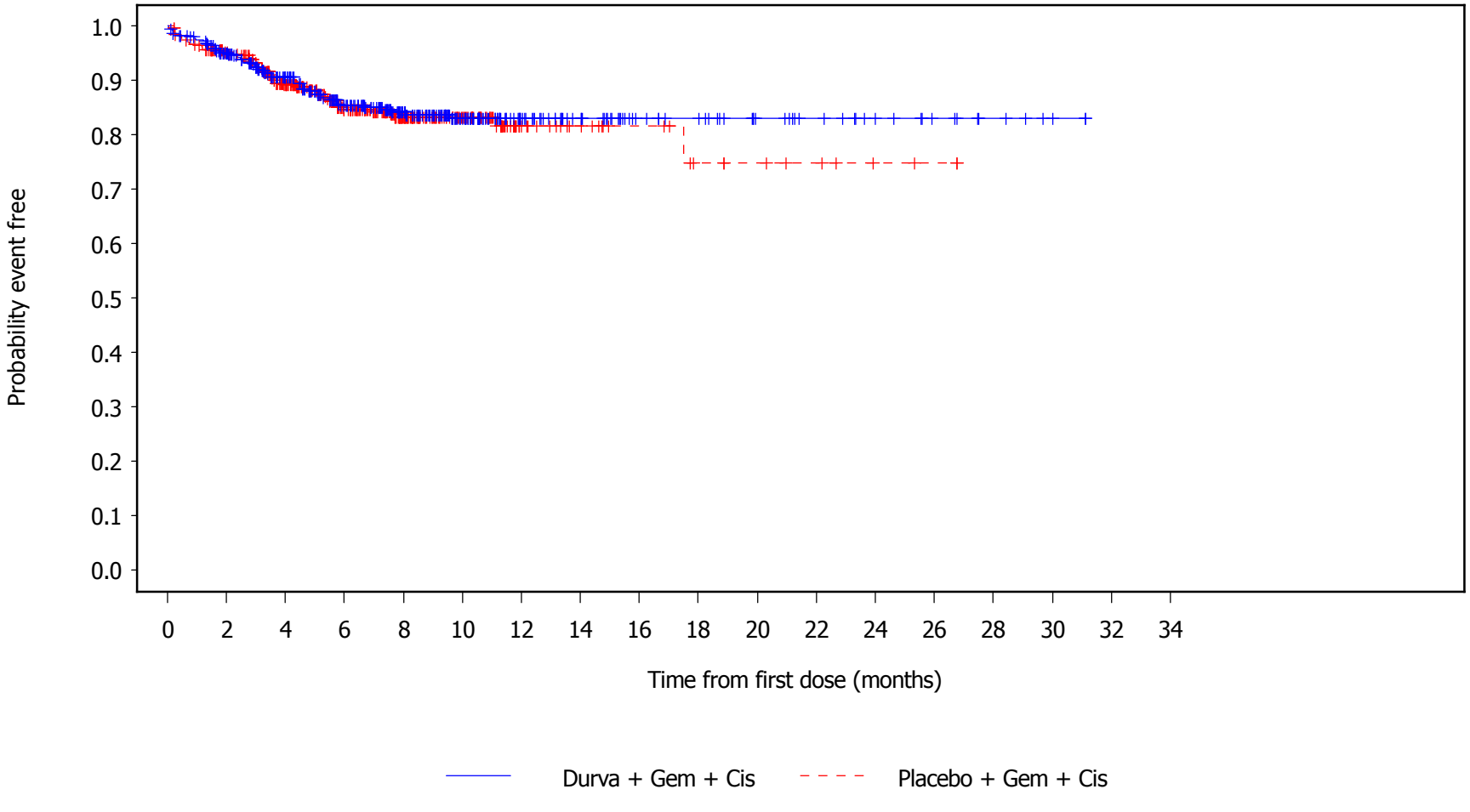
Figure 3.3.117 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAE SOC: Injury, poisoning and procedural complications
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	313	263	196	129	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	310	231	156	89	34	22	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

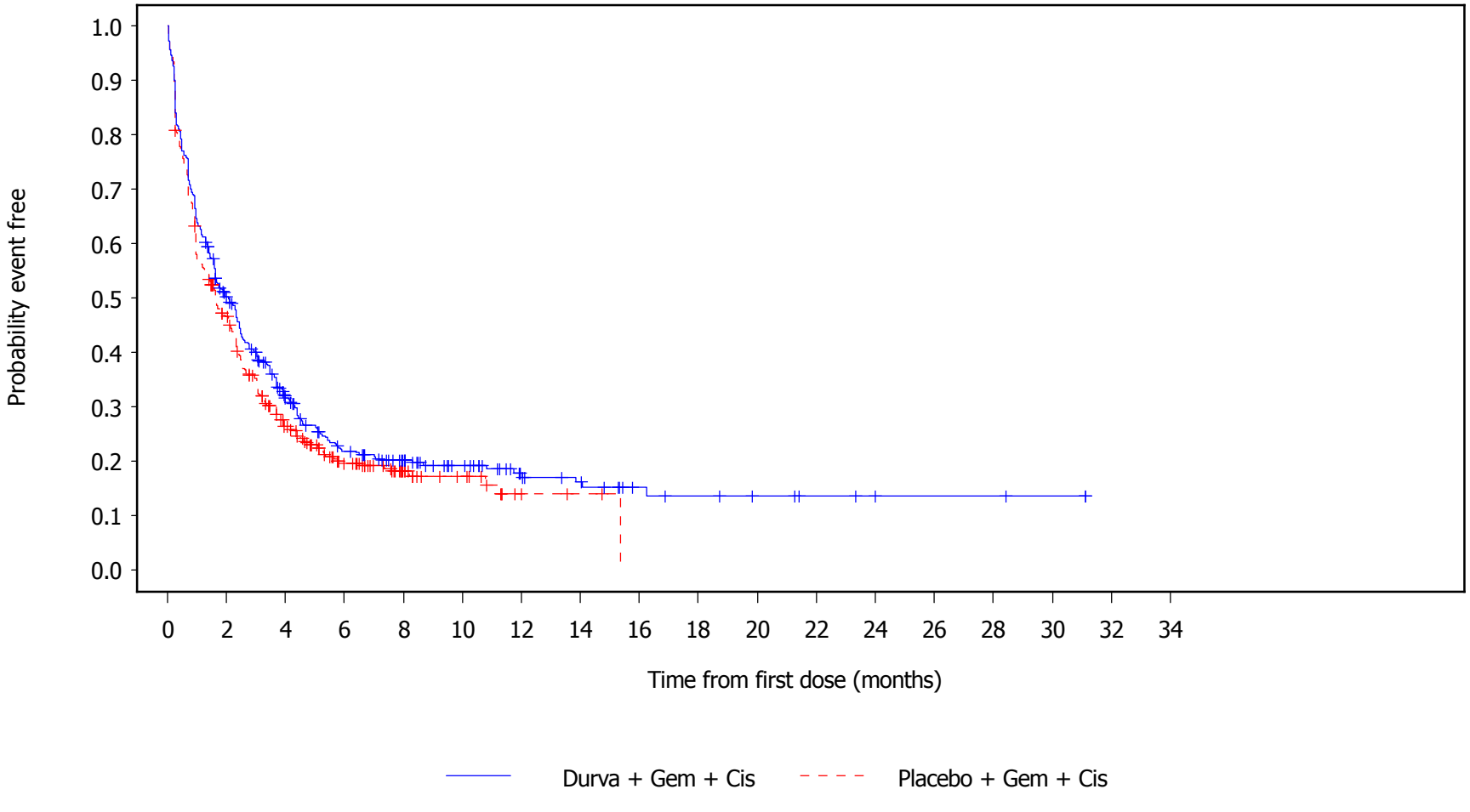
Figure 3.3.118 TOPAZ: Kaplan-Meier plot of time to first occurrence of AE leading to discontinuation of treatment
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	361	297	240	175	117	73	55	38	34	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	359	286	204	140	81	28	20	14	9	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

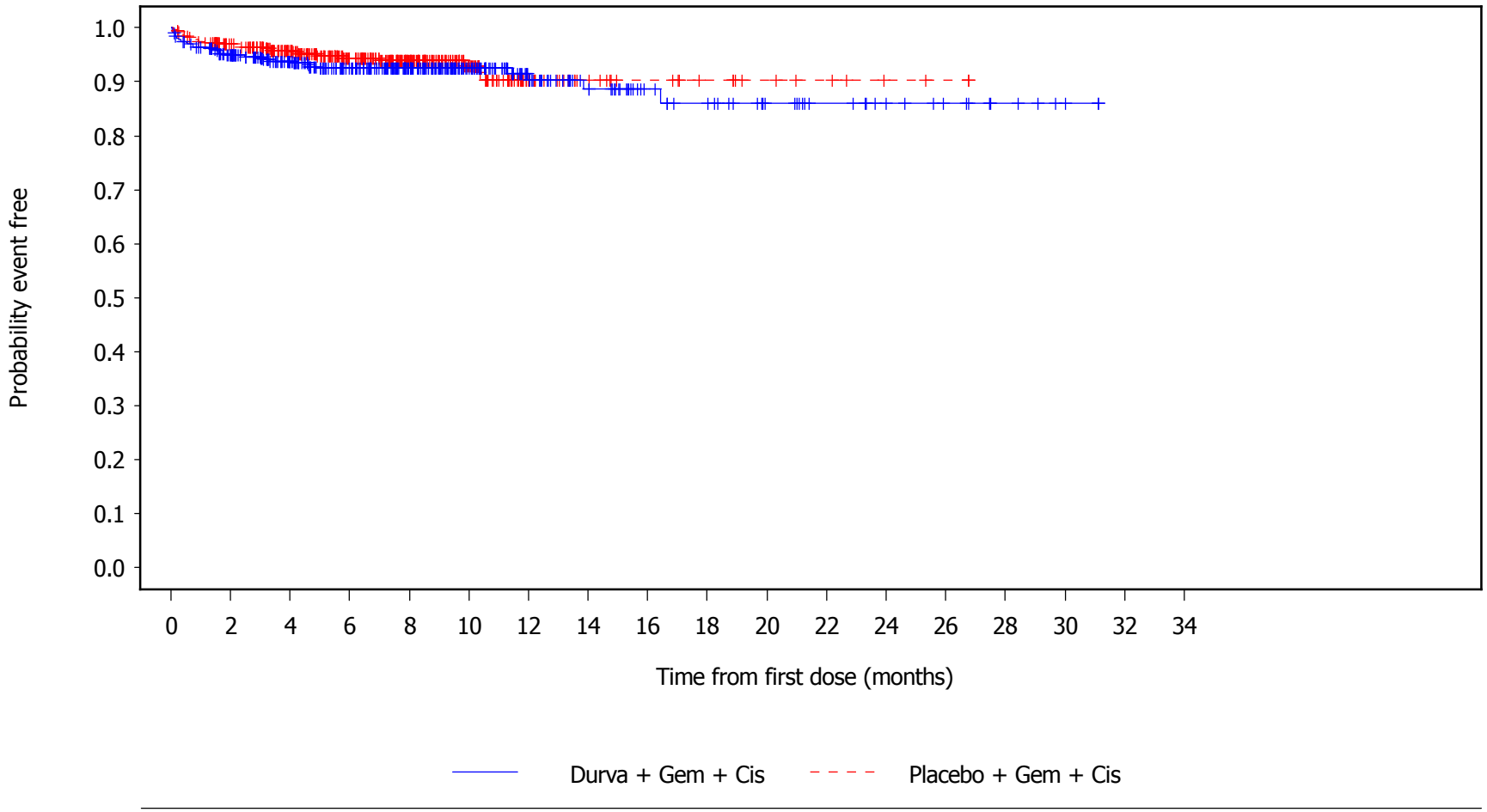
Figure 3.3.119 TOPAZ: Kaplan-Meier plot of time to first occurrence of AE max CTCAE grade >=3
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	194	110	68	51	36	22	17	10	8	6	4	3	2	2	1	0	0	Durva + Gem + Cis
403	179	88	47	24	14	3	2	0	0	0	0	0	0	0	0	0	0	Placebo + Gem + Cis

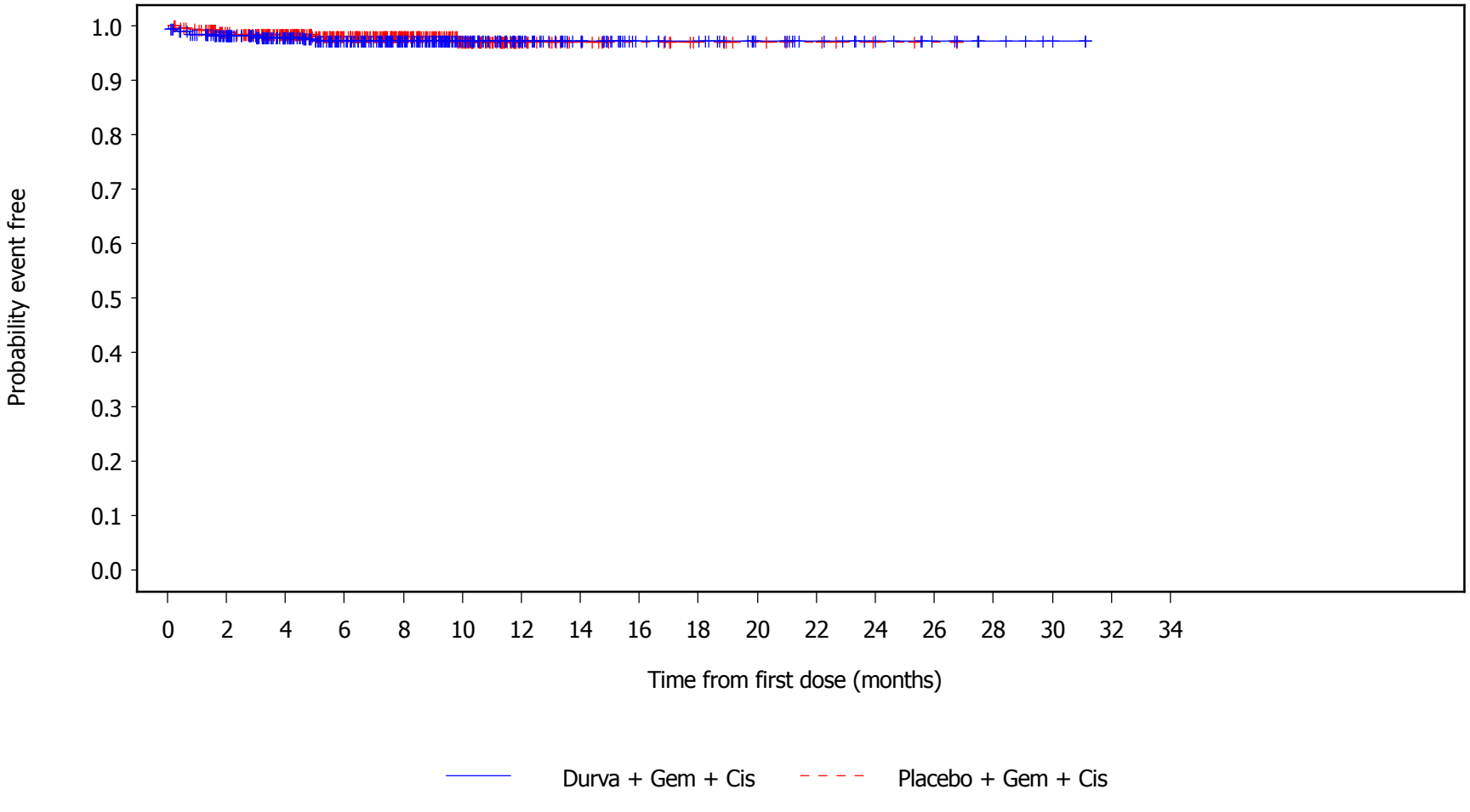
Figure 3.3.120 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: General disorders and administration site conditions
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	359	301	254	191	125	75	53	37	32	23	17	13	9	5	2	0	0	Durva + Gem + Cis
403	361	302	224	154	85	33	21	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

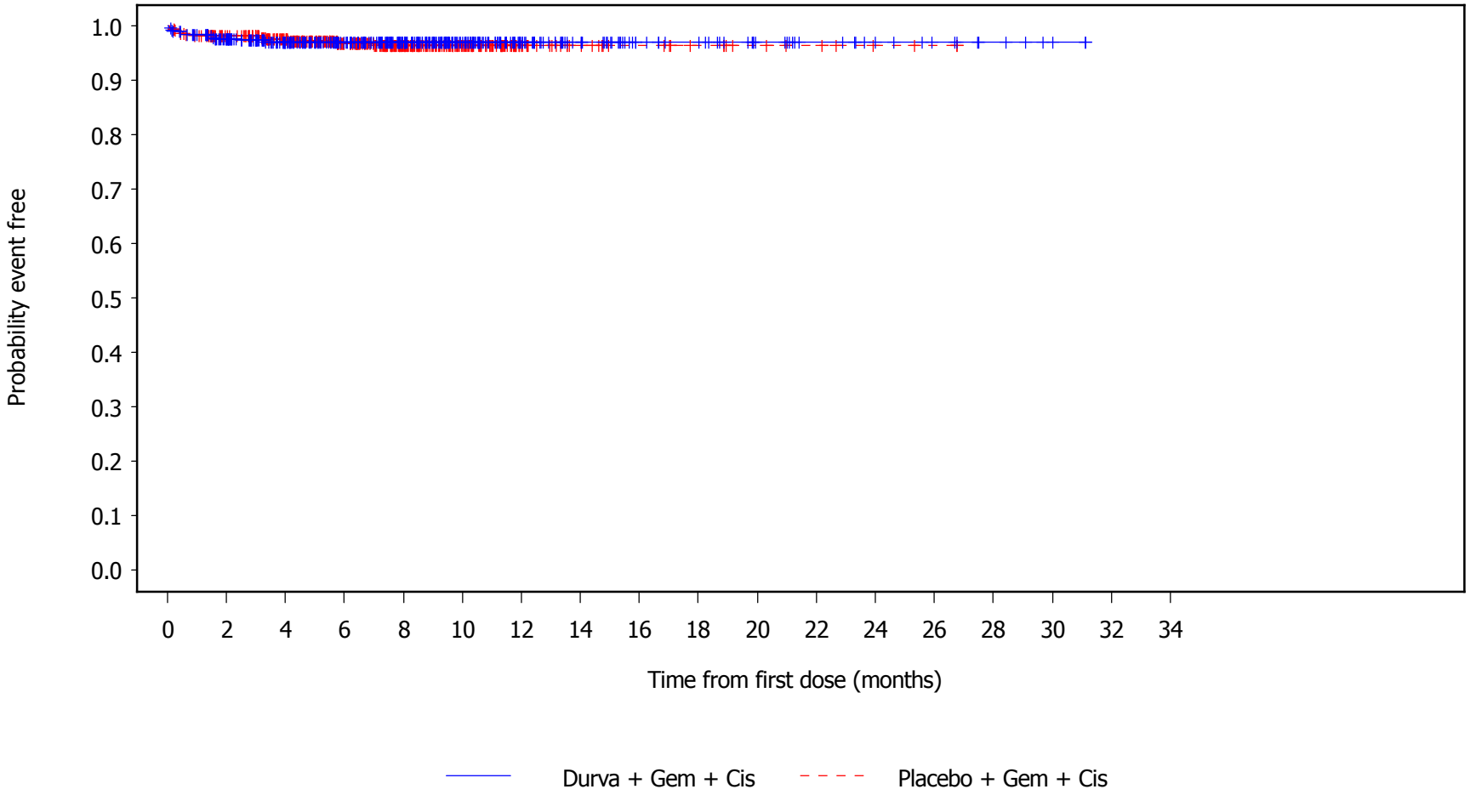
Figure 3.3.121 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Asthenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	310	261	195	128	79	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	367	309	230	157	87	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

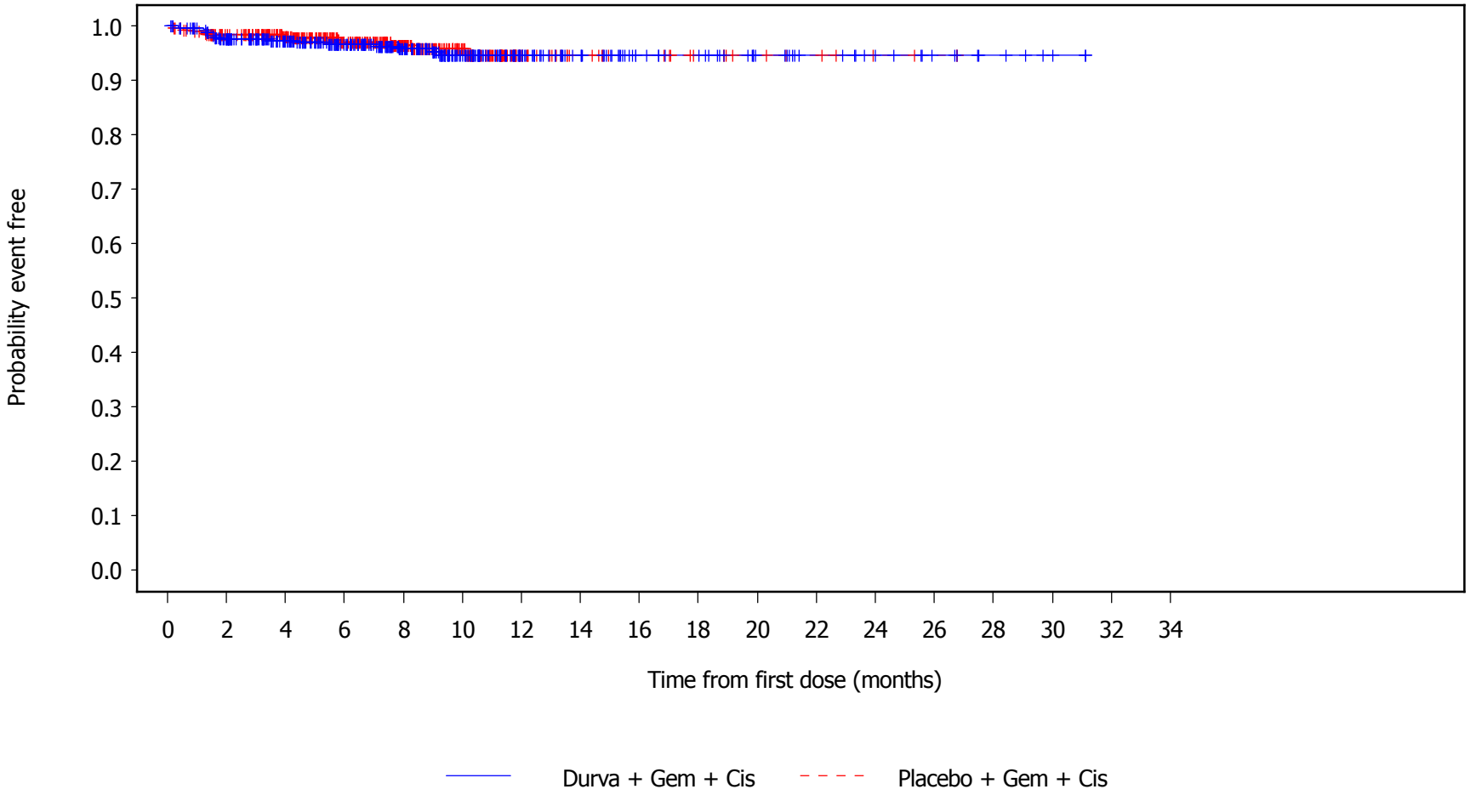
Figure 3.3.122 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Fatigue
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	309	260	195	129	78	56	38	34	23	17	13	9	5	2	0	0	Durva + Gem + Cis
403	365	307	226	156	87	33	21	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

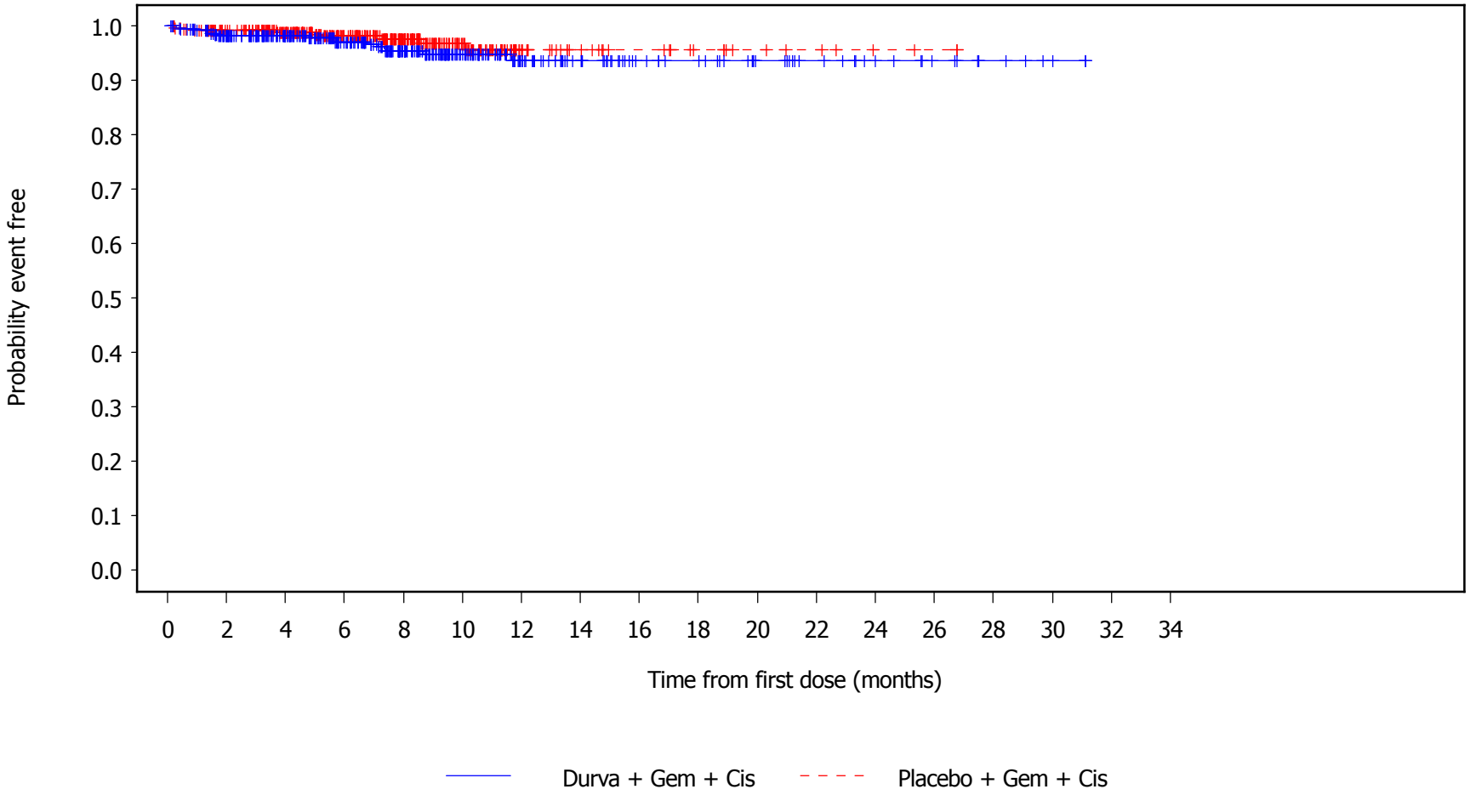
Figure 3.3.123 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Respiratory, thoracic and mediastinal disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	308	258	190	127	76	56	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	368	311	228	156	87	33	21	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

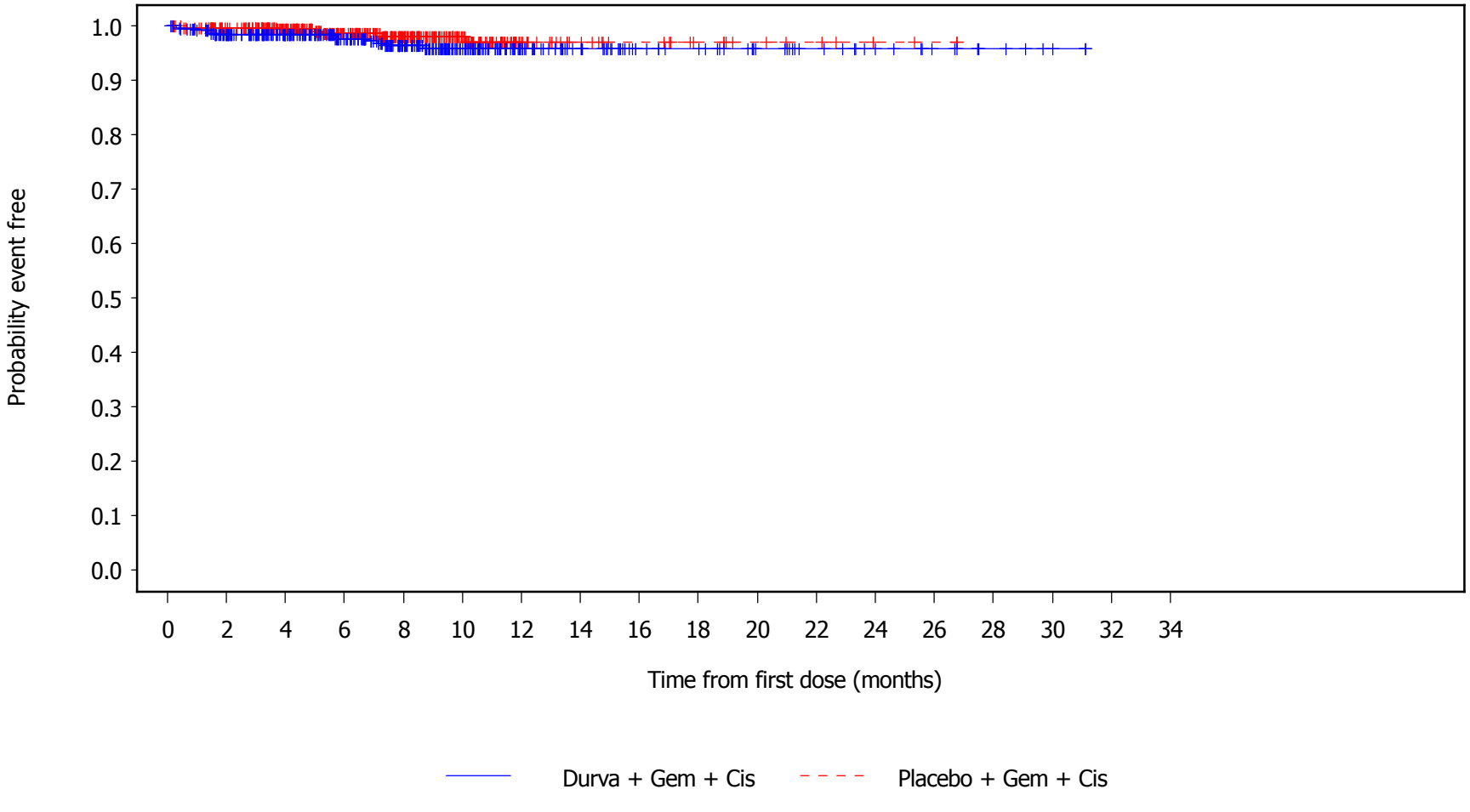
Figure 3.3.124 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Renal and urinary disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	366	311	258	191	125	76	55	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	310	229	157	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

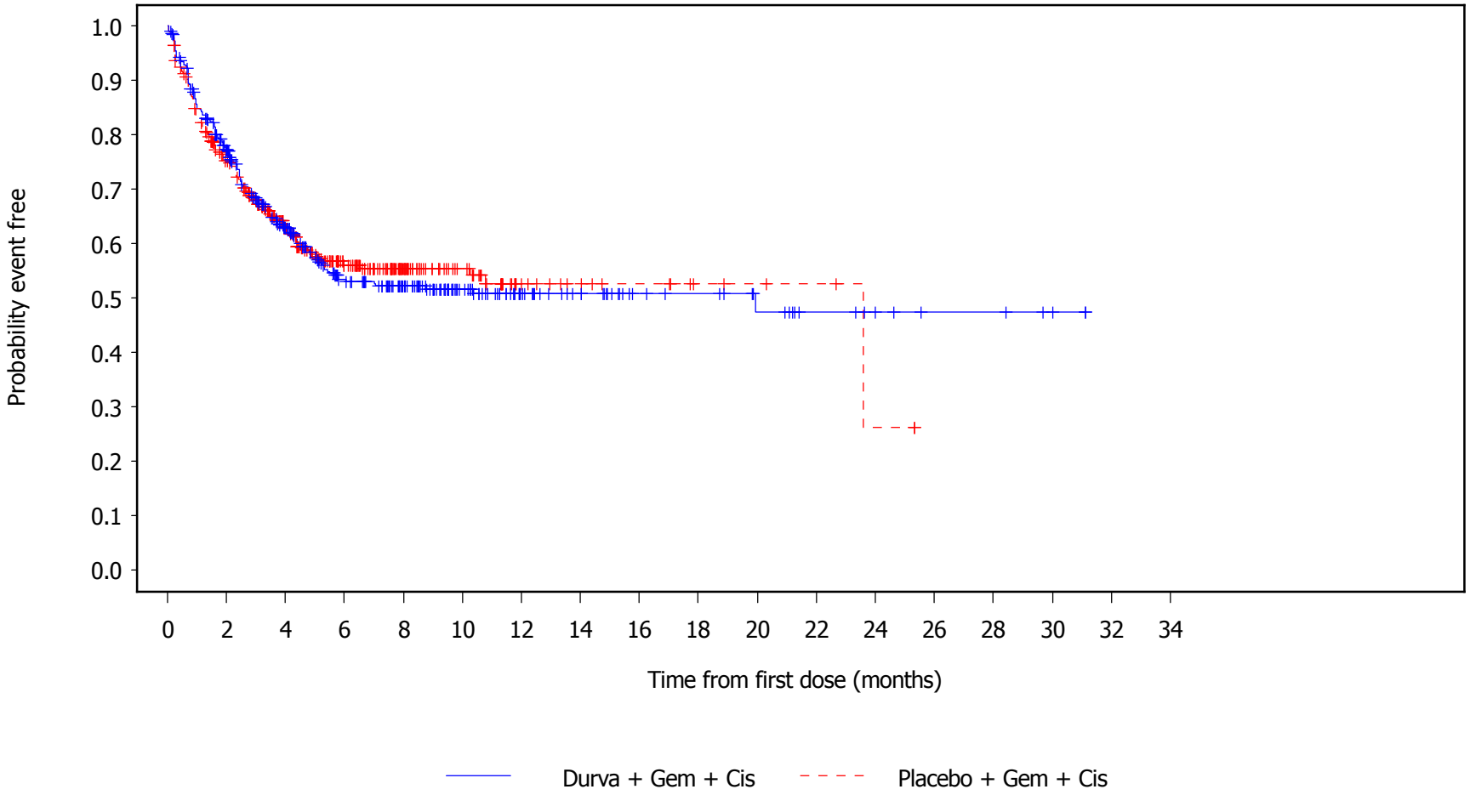
Figure 3.3.125 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Acute kidney injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	312	260	194	128	78	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	311	230	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

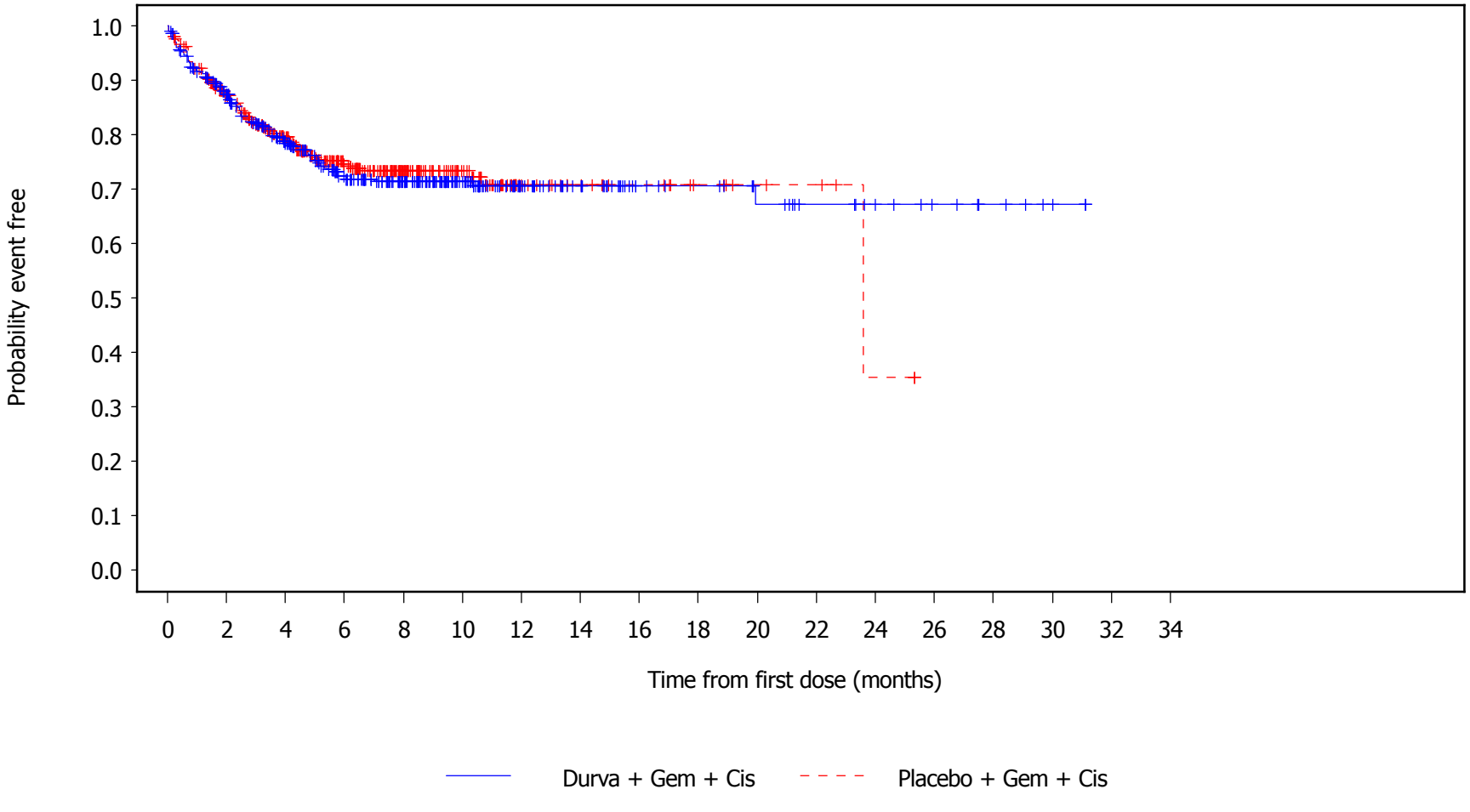
Figure 3.3.126 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Blood and lymphatic system disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	291	202	142	109	69	44	33	21	19	14	9	7	4	4	2	0	0	Durva + Gem + Cis
403	280	194	124	74	43	17	12	9	5	4	3	1	0	0	0	0	0	Placebo + Gem + Cis

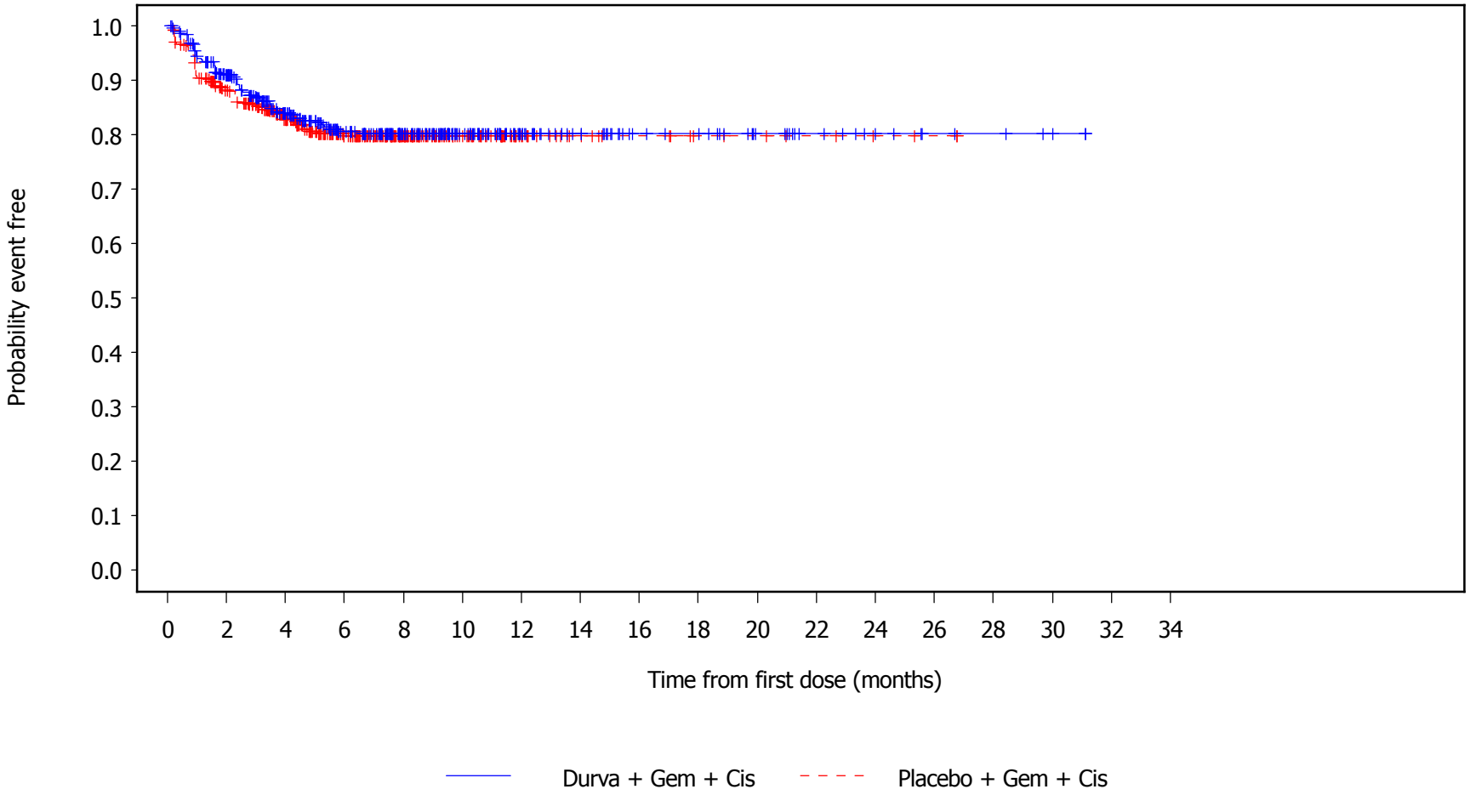
Figure 3.3.127 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Anaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	330	259	204	156	104	62	46	29	26	20	15	12	8	5	2	0	0	Durva + Gem + Cis
403	323	249	174	113	66	26	19	14	9	5	4	1	0	0	0	0	0	Placebo + Gem + Cis

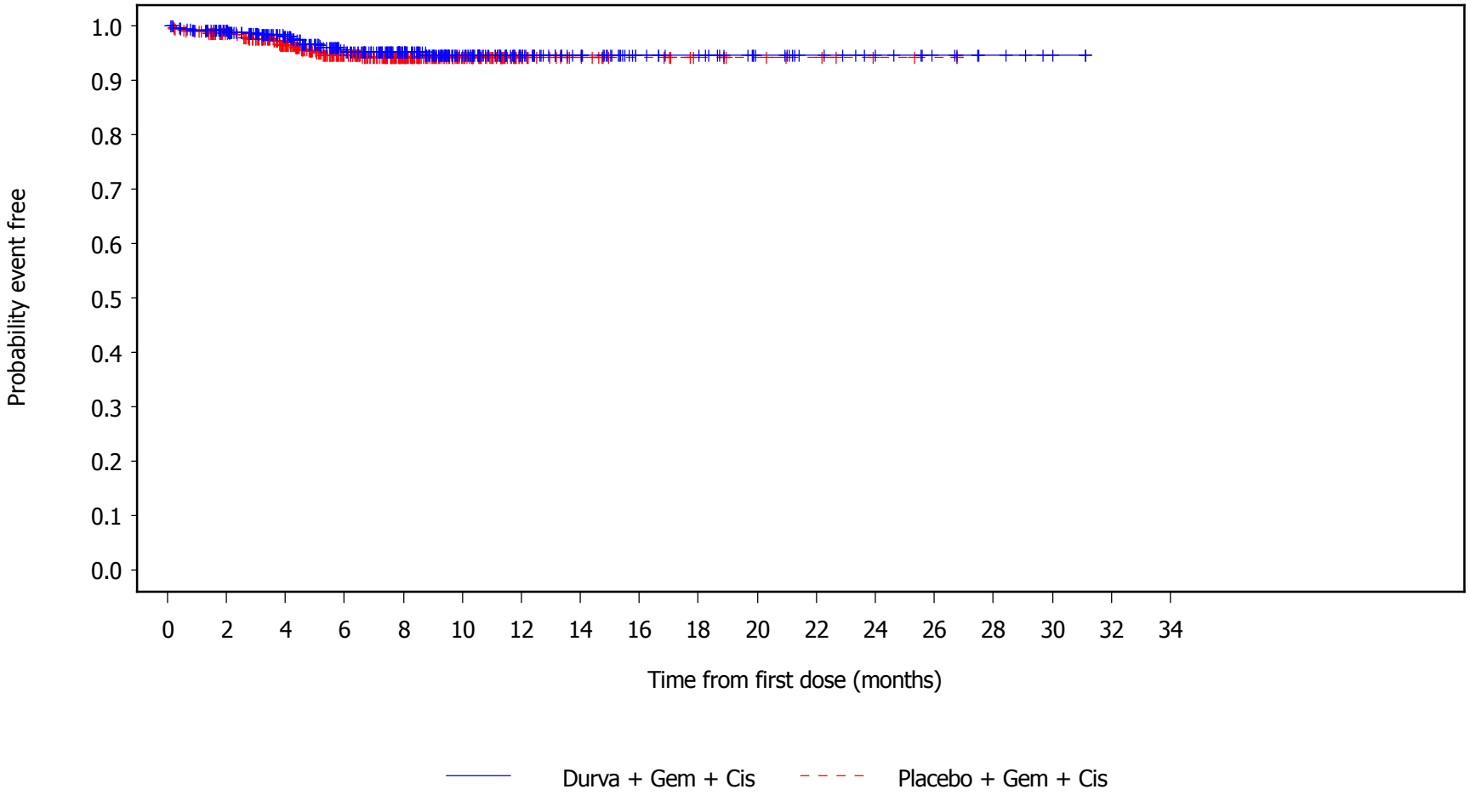
Figure 3.3.128 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	339	258	201	148	97	59	43	30	28	19	13	9	5	4	2	0	0	Durva + Gem + Cis
403	327	254	179	115	60	25	15	11	7	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

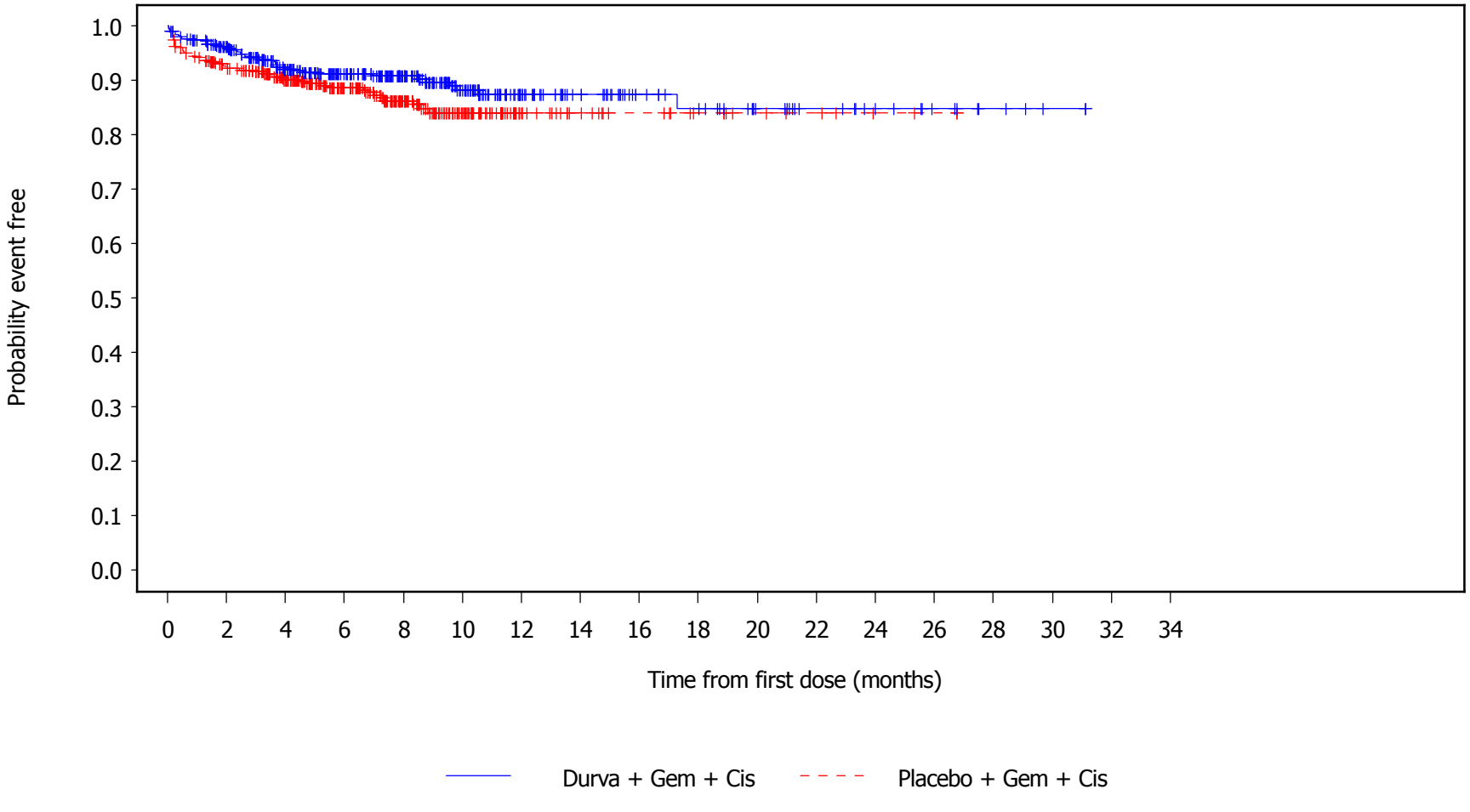
Figure 3.3.129 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Thrombocytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	310	253	190	125	77	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	368	305	220	150	84	32	21	15	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

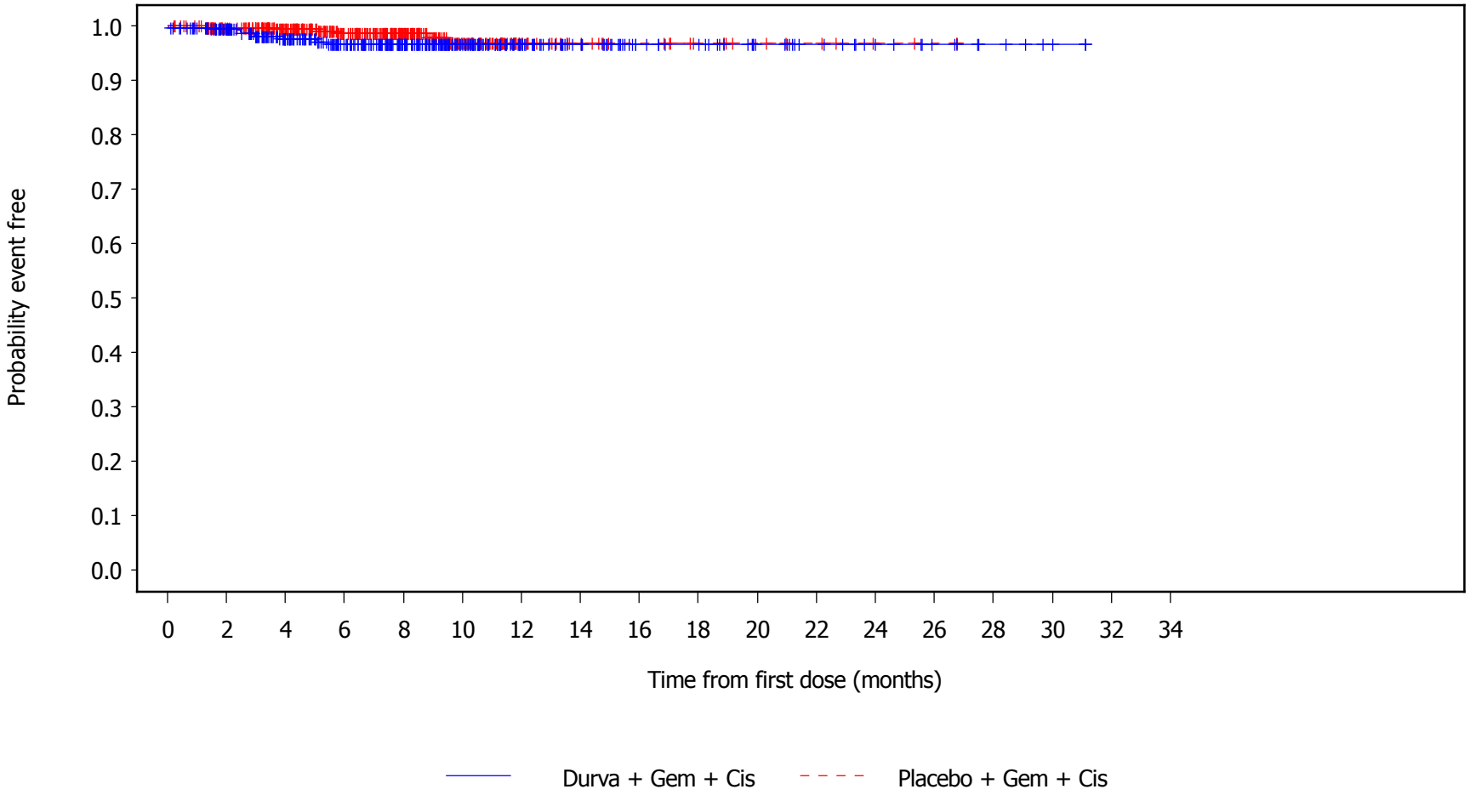
Figure 3.3.130 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Gastrointestinal disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	361	296	249	188	125	76	55	38	33	23	17	13	8	4	1	0	0	Durva + Gem + Cis
403	348	289	212	142	81	32	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

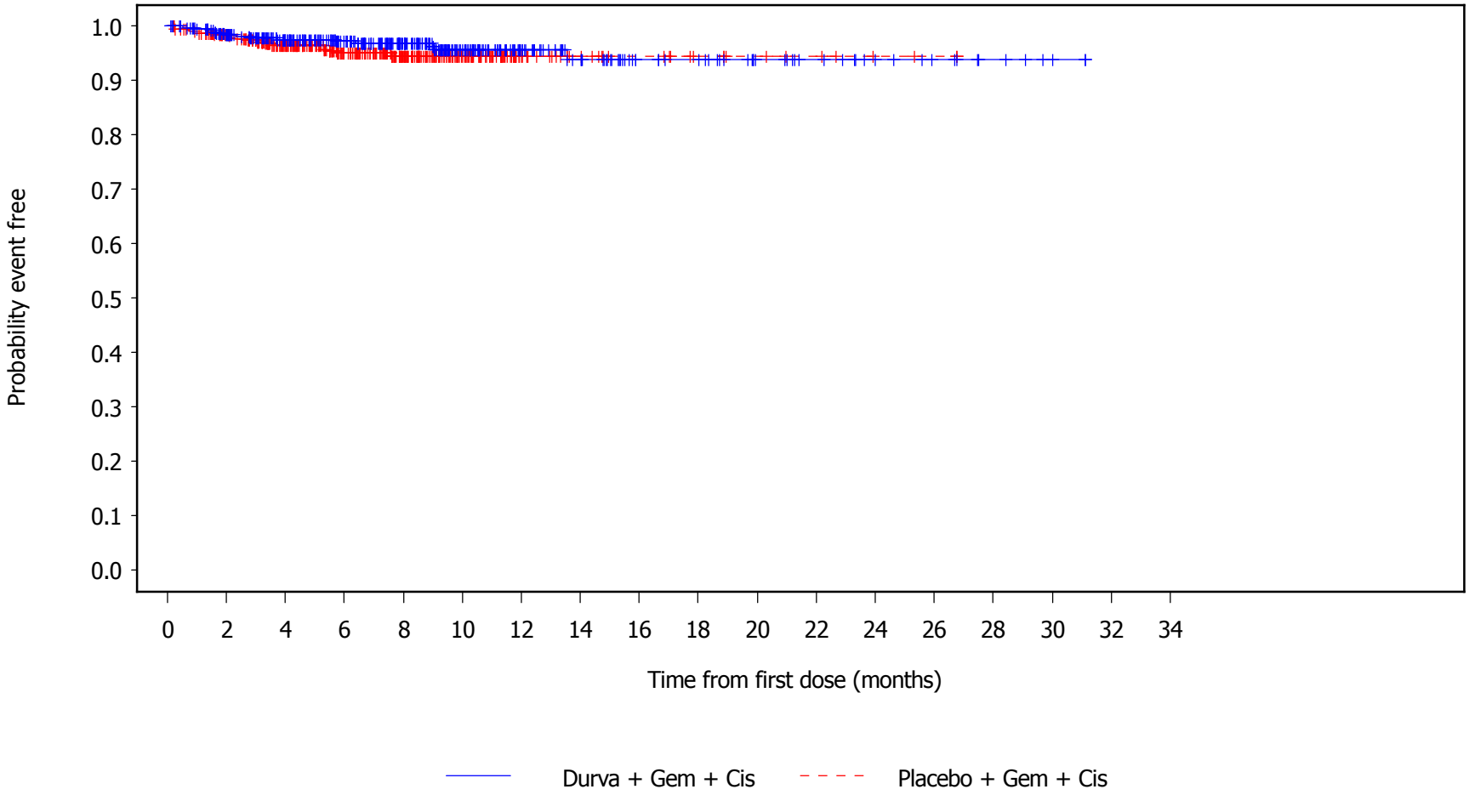
Figure 3.3.131 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Nervous system disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	310	262	197	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	230	157	87	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

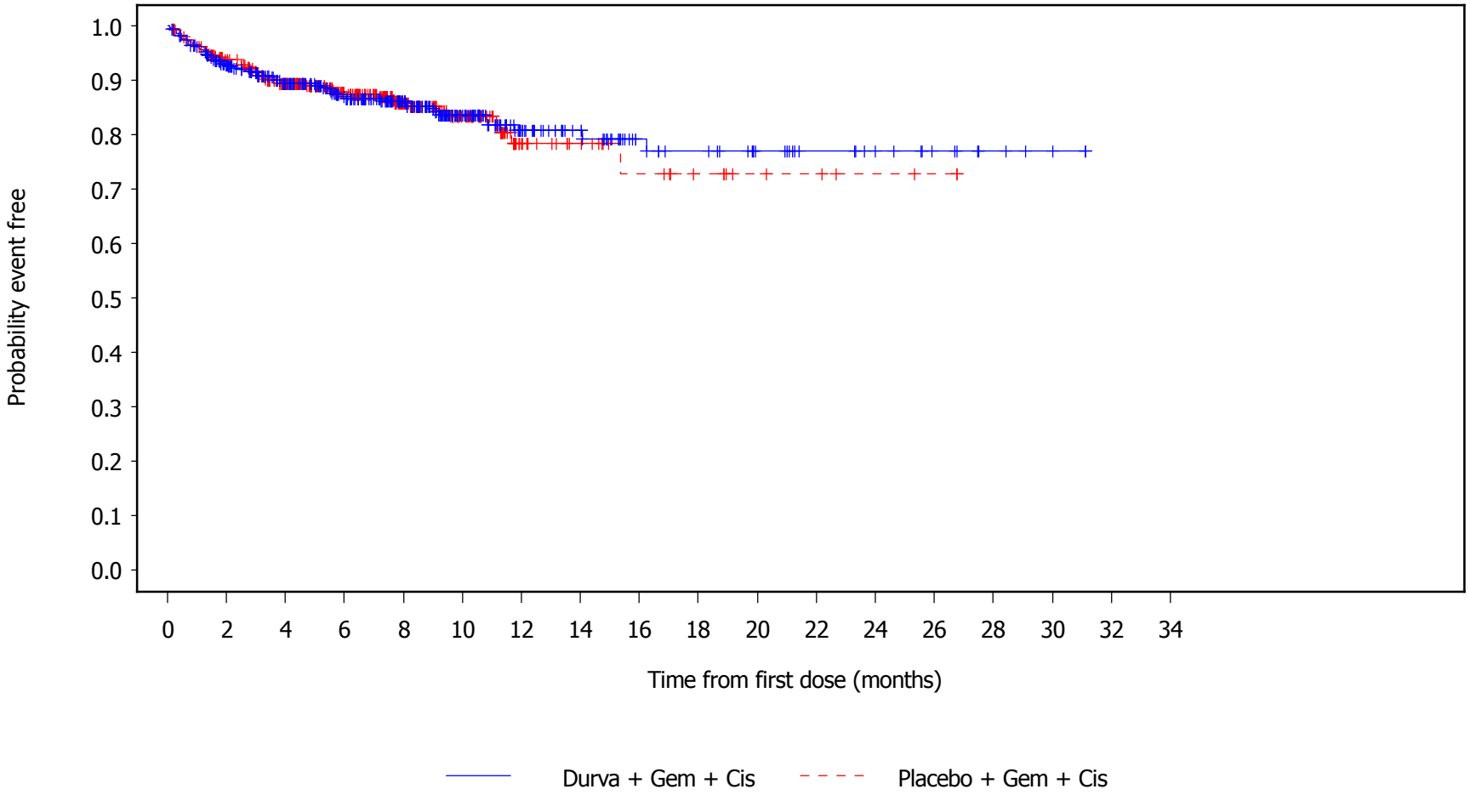
Figure 3.3.132 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Vascular disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	308	259	194	127	78	55	37	34	23	18	13	9	5	2	0	0	Durva + Gem + Cis
403	367	304	223	153	85	32	21	15	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

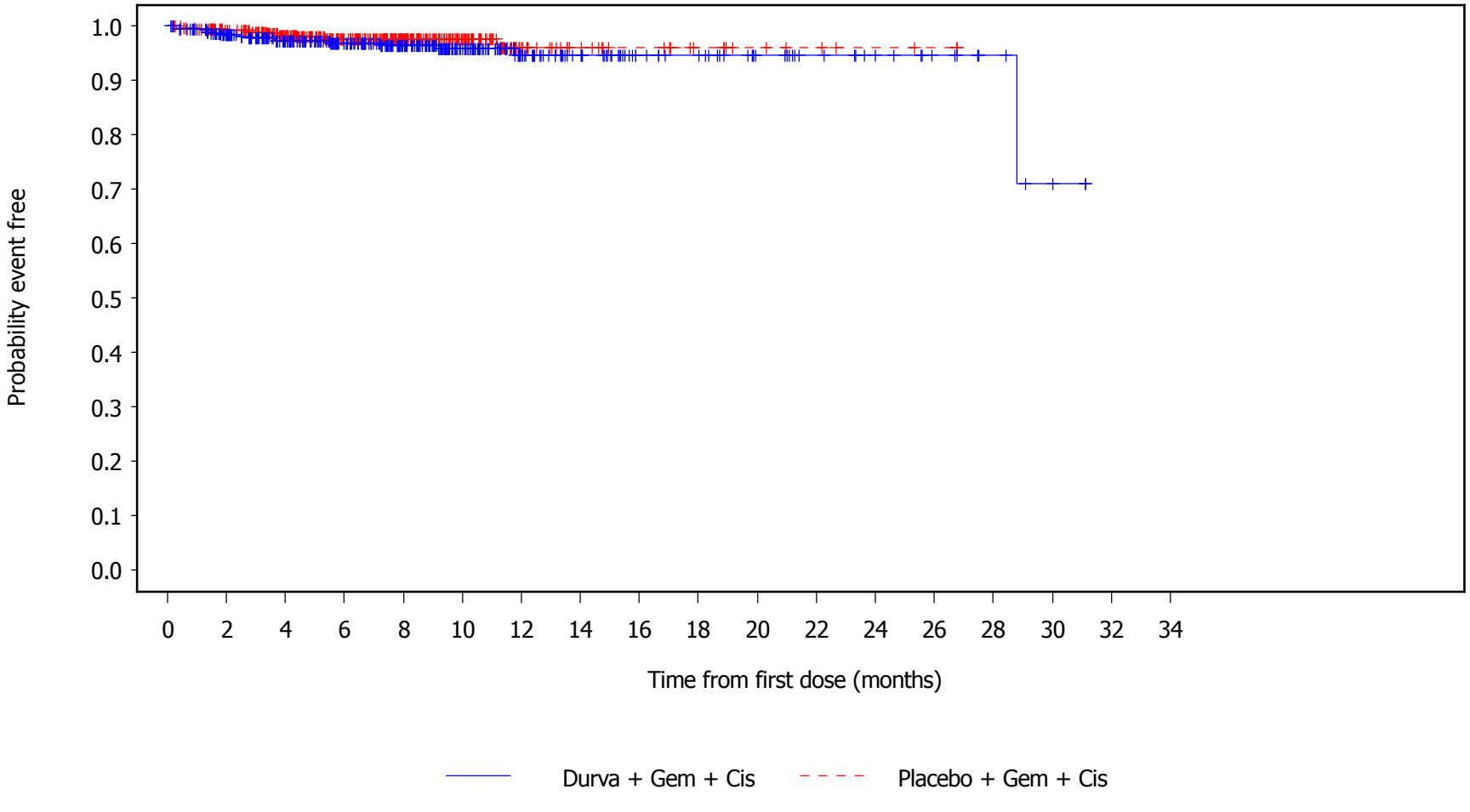
Figure 3.3.133 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Infections and infestations
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	349	293	247	186	121	72	54	35	30	22	16	13	8	4	2	0	0	Durva + Gem + Cis
403	351	288	211	139	77	29	20	13	9	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

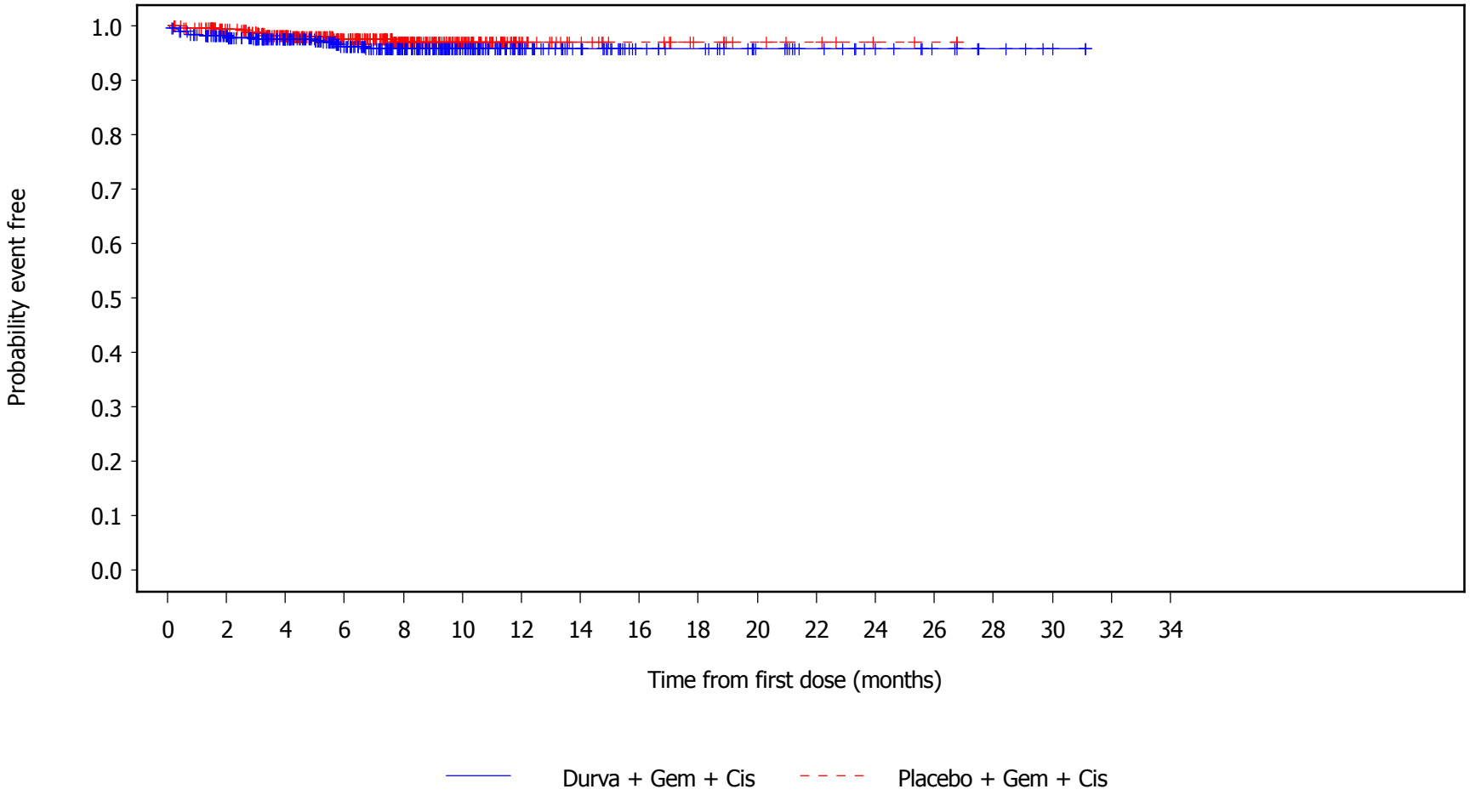
Figure 3.3.134 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Biliary tract infection
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	309	259	196	129	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	368	309	229	157	89	33	21	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

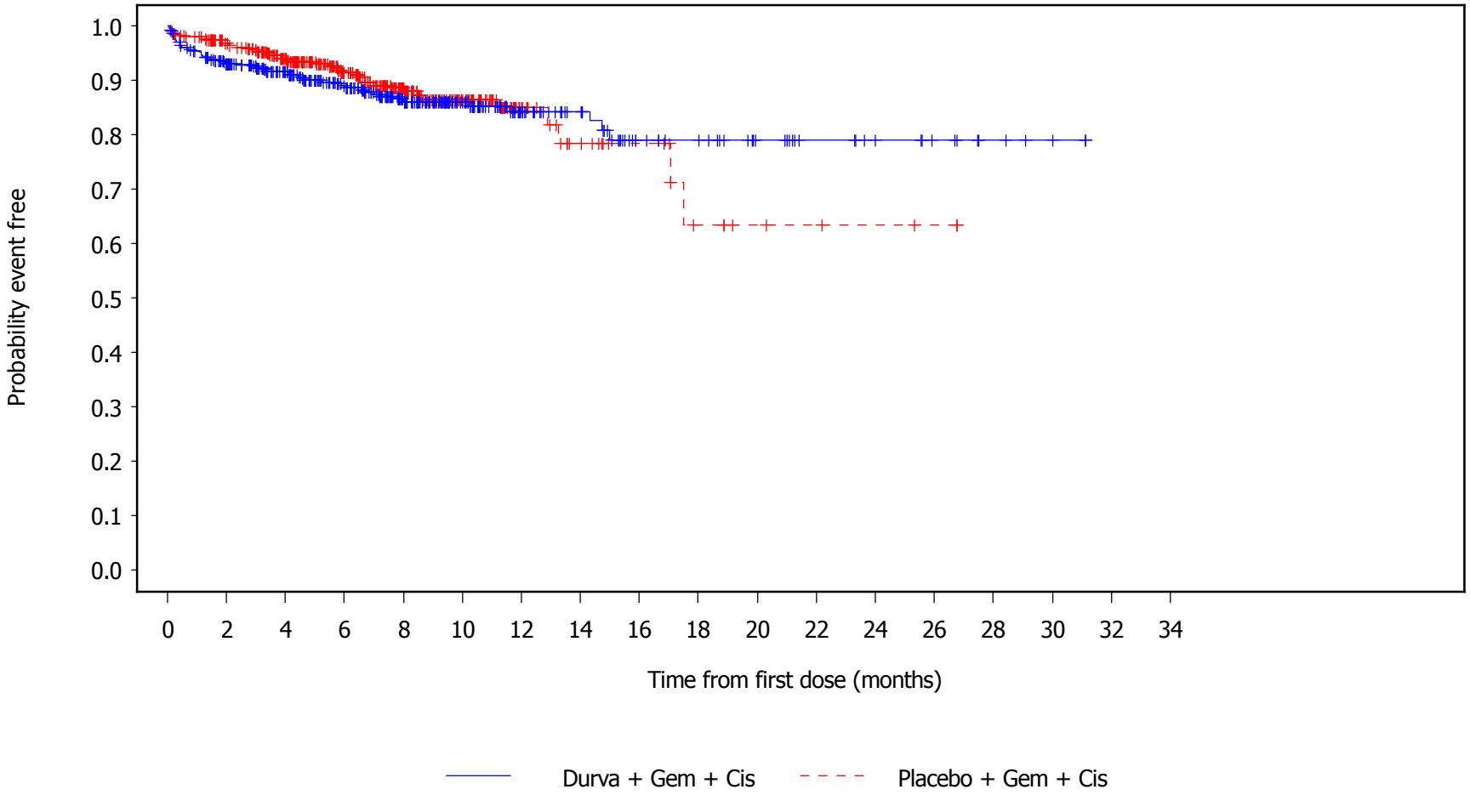
Figure 3.3.135 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	310	257	194	128	77	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	309	229	156	87	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

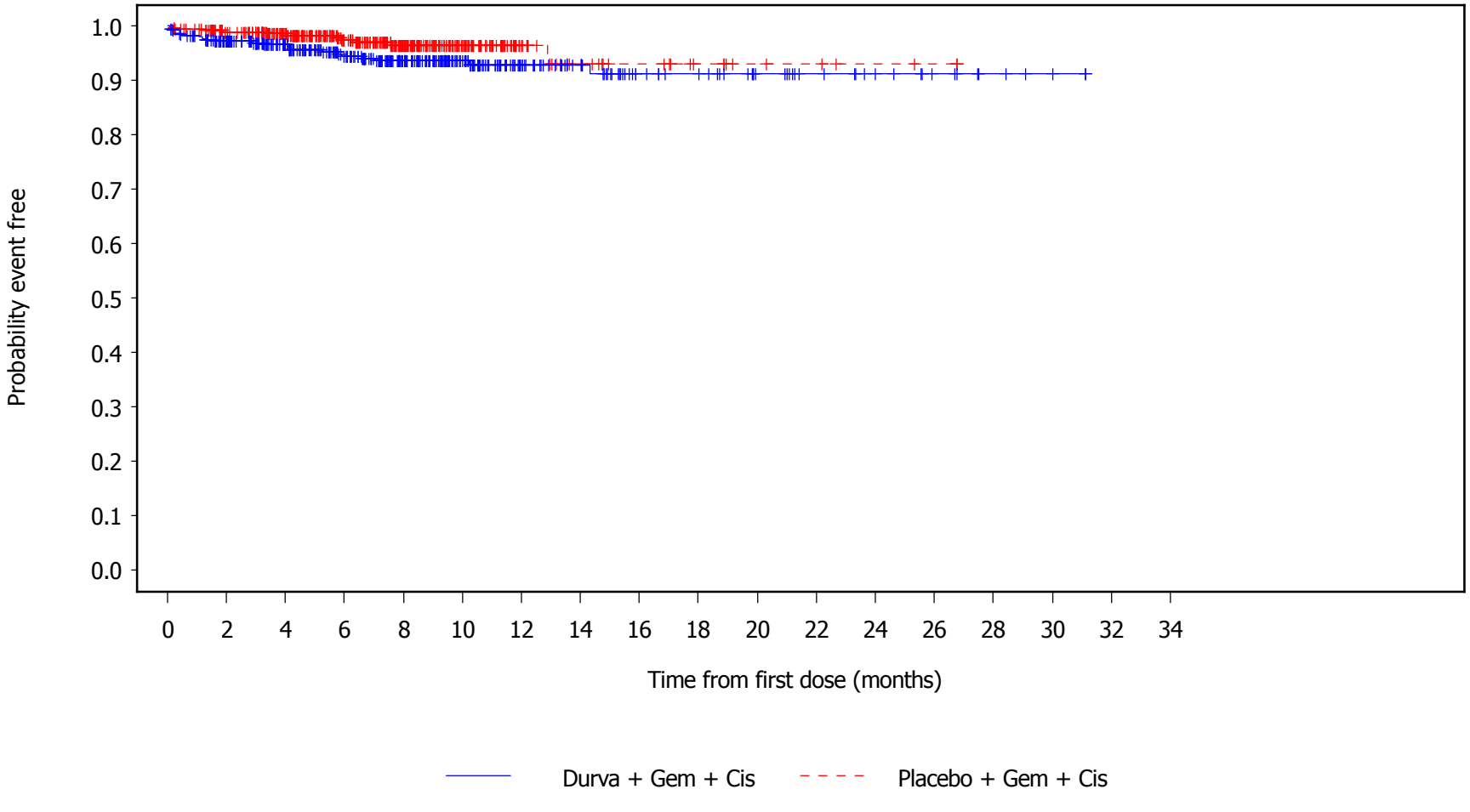
Figure 3.3.136 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Hepatobiliary disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	350	296	243	178	119	70	53	34	30	21	15	12	8	4	2	0	0	Durva + Gem + Cis
403	359	298	214	145	81	31	19	13	7	4	3	2	1	0	0	0	0	Placebo + Gem + Cis

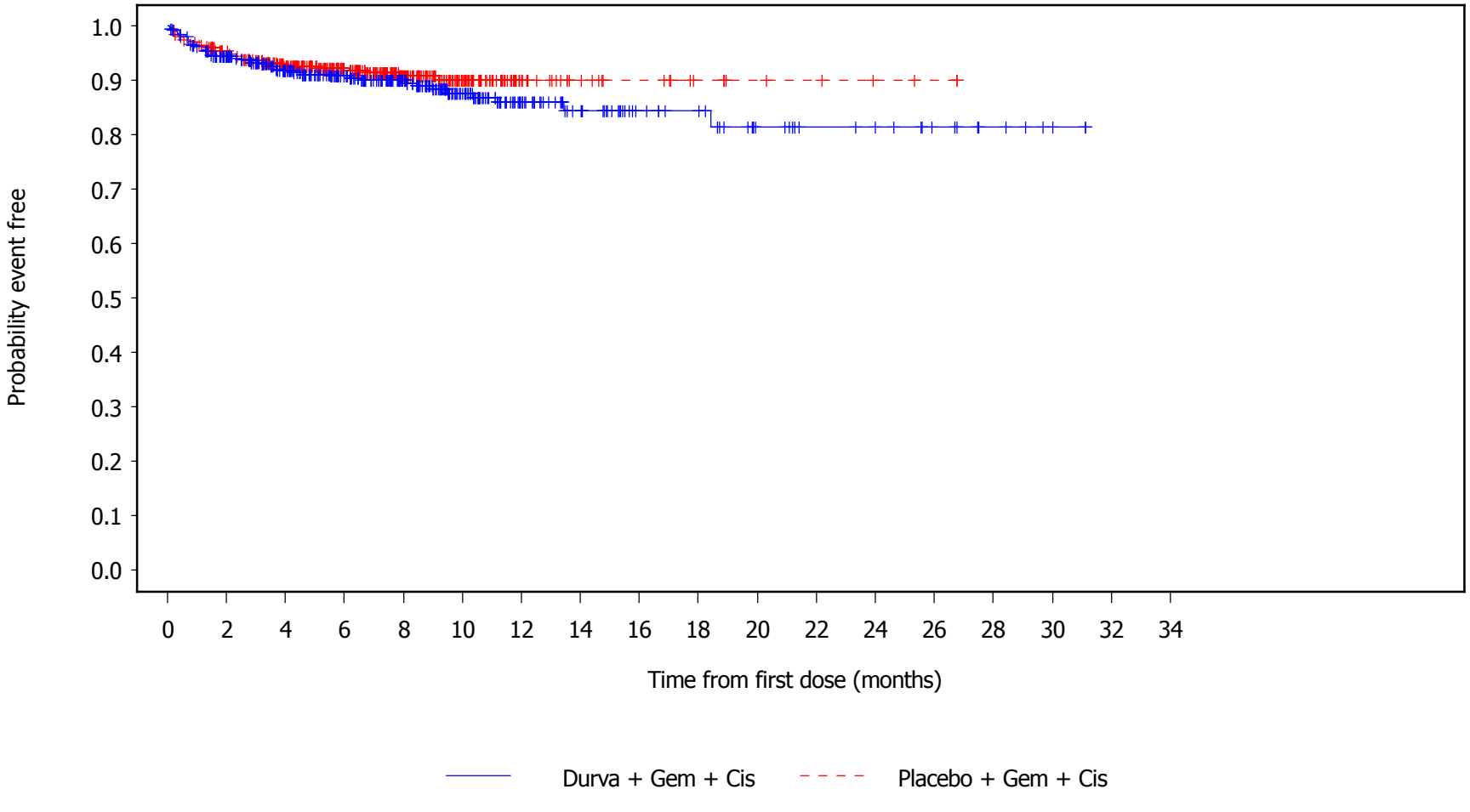
Figure 3.3.137 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Cholangitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	363	306	252	186	124	74	56	37	33	23	17	13	8	4	2	0	0	Durva + Gem + Cis
403	367	310	226	156	86	33	20	14	9	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

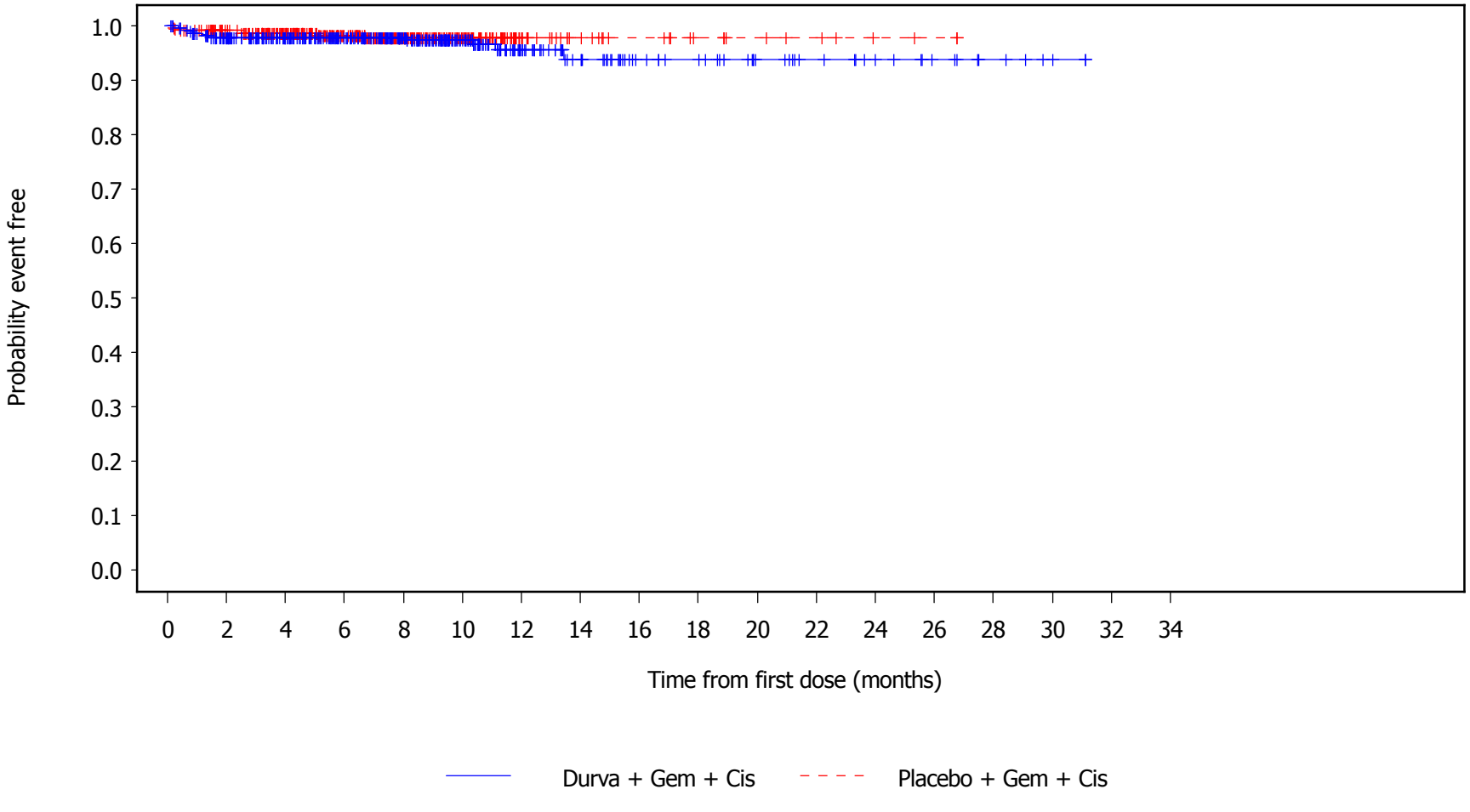
Figure 3.3.138 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Metabolism and nutrition disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	354	296	246	182	119	72	51	35	31	20	15	14	9	5	2	0	0	Durva + Gem + Cis
403	359	299	220	145	80	29	18	13	8	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

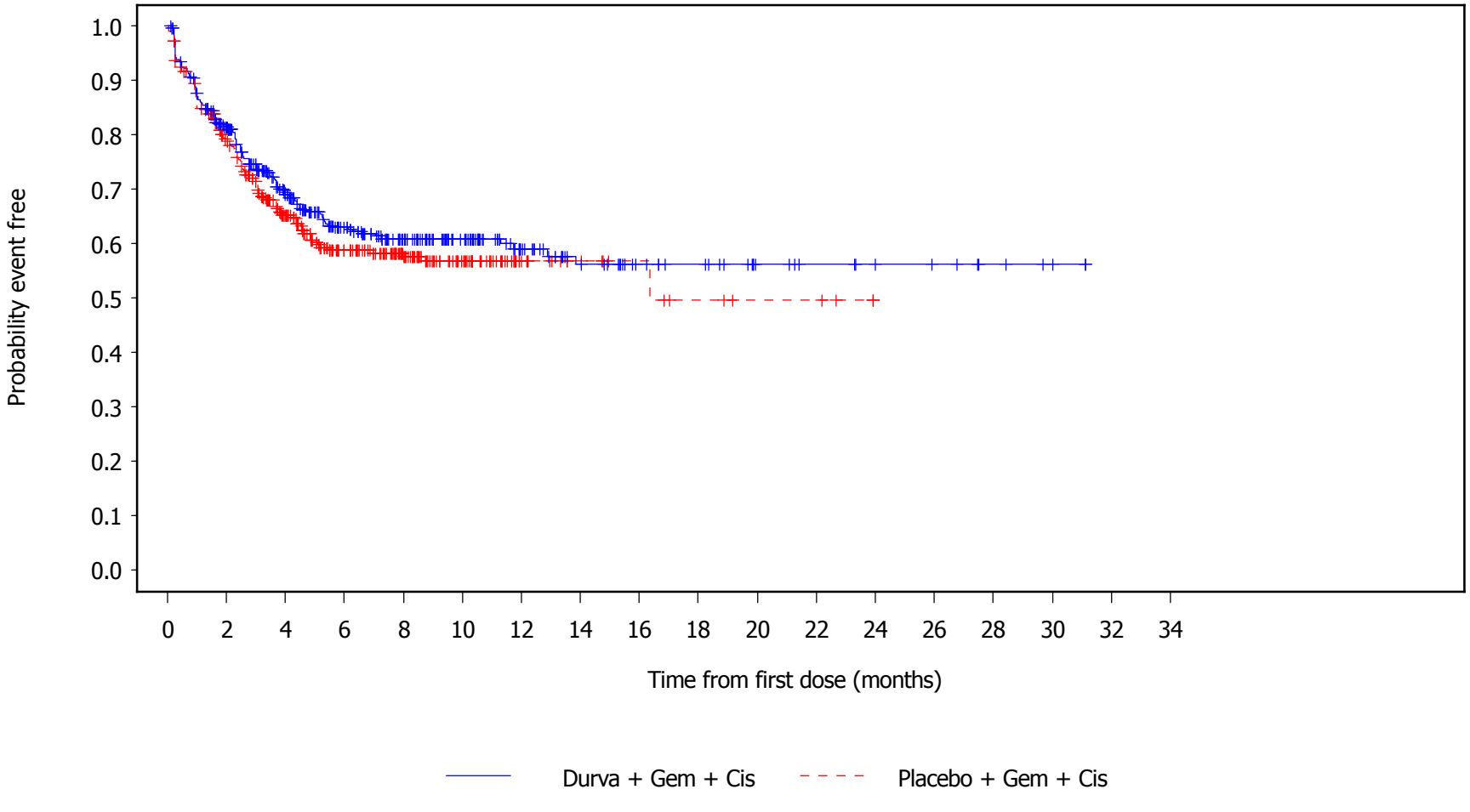
Figure 3.3.139 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Hypokalaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	312	261	195	128	76	54	37	33	23	18	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	230	156	87	33	21	15	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

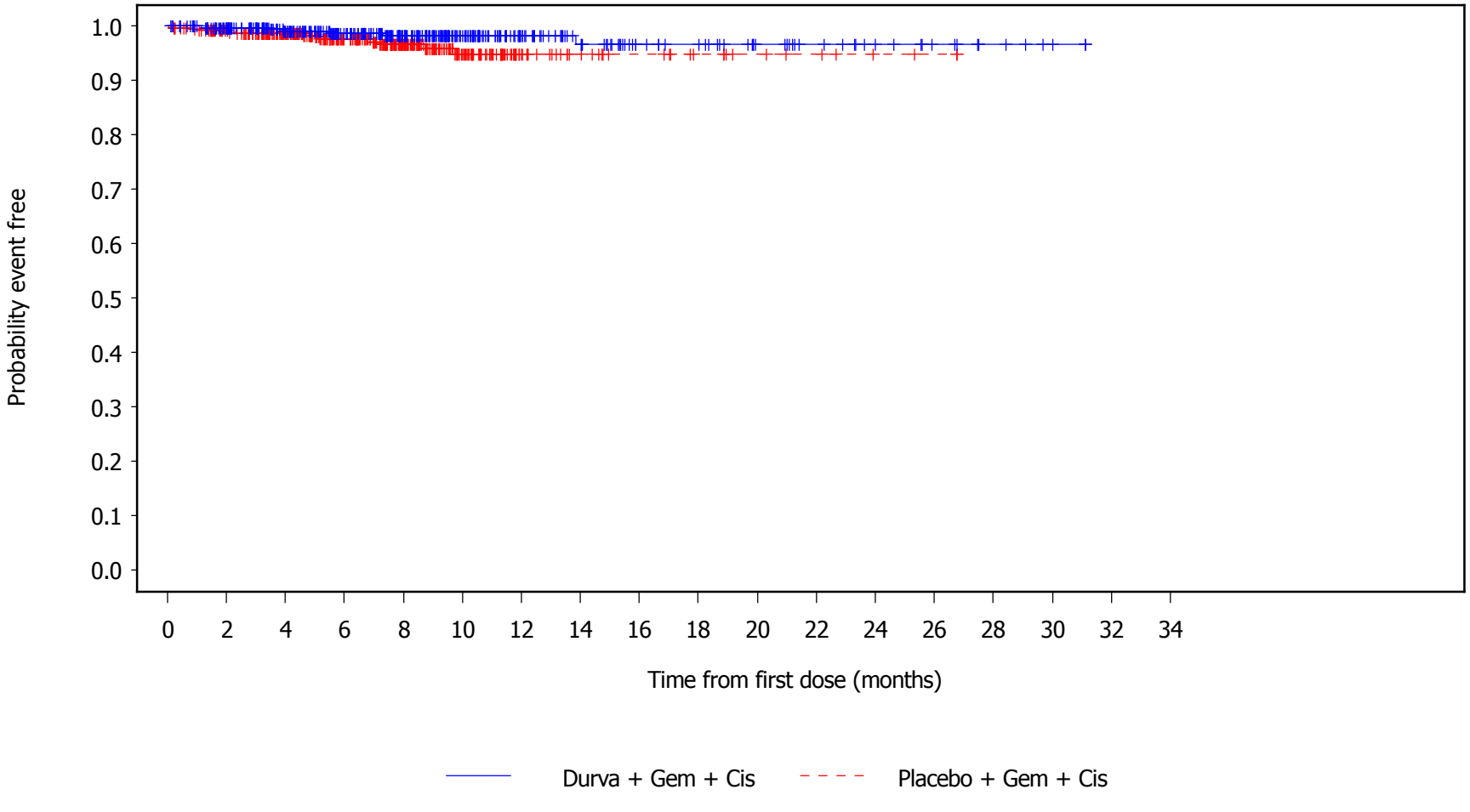
Figure 3.3.140 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Investigations
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	307	220	164	124	90	54	37	27	23	14	11	9	7	4	2	0	0	Durva + Gem + Cis
403	294	201	132	92	54	20	12	8	5	3	3	0	0	0	0	0	0	Placebo + Gem + Cis

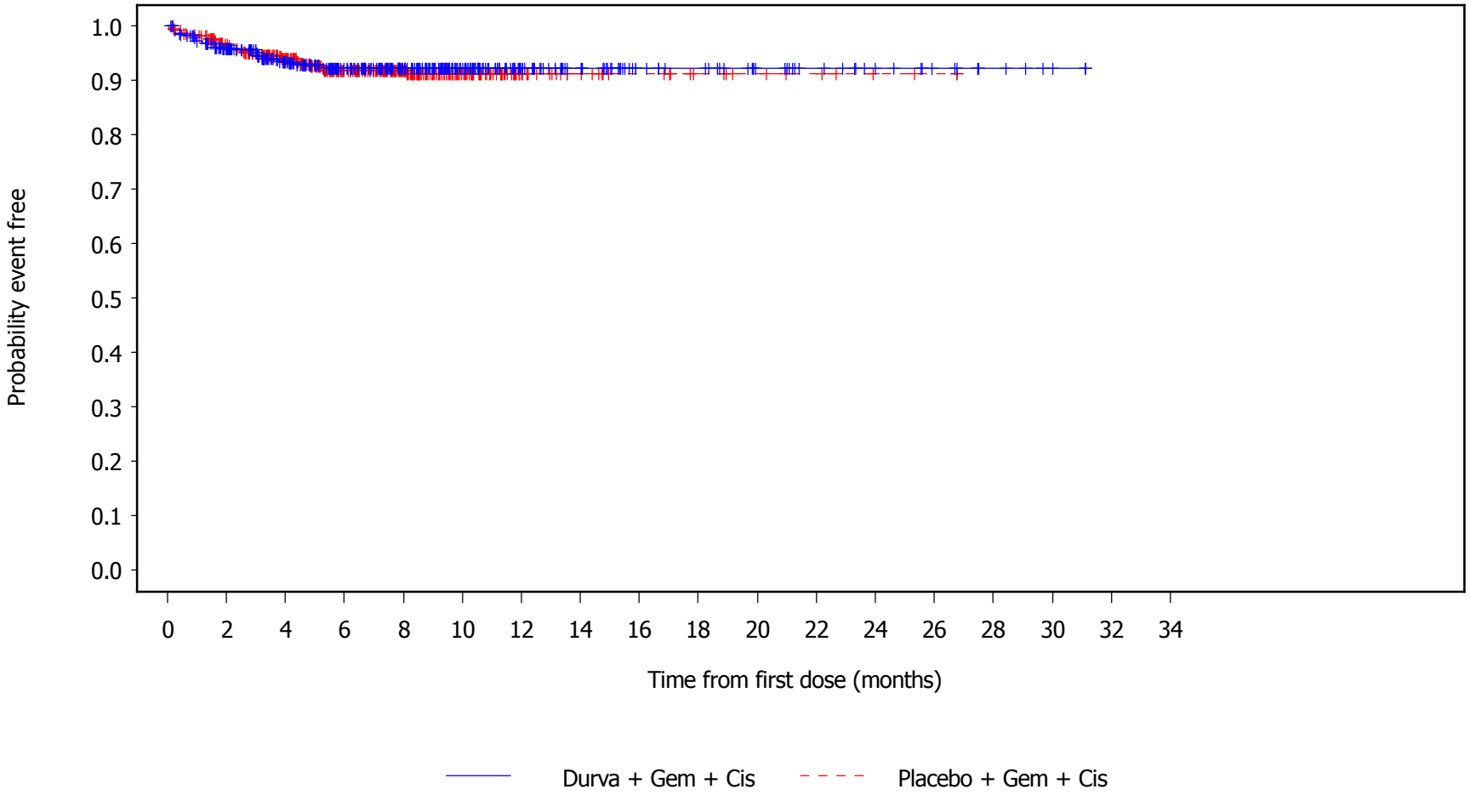
Figure 3.3.141 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	313	262	196	129	80	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	310	228	158	87	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

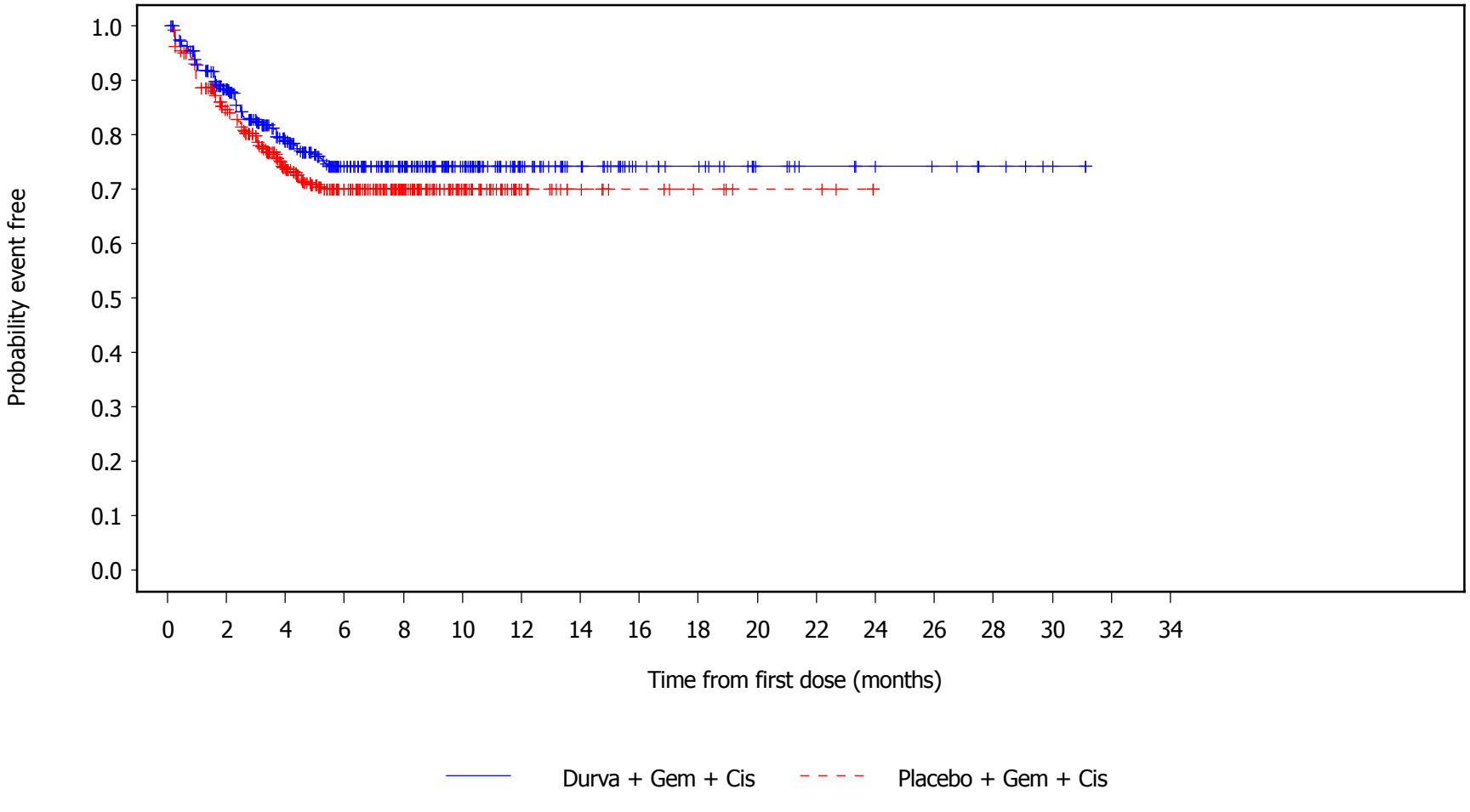
Figure 3.3.142 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 PT: White blood cell count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	357	294	245	185	124	77	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	358	291	208	145	80	32	21	15	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

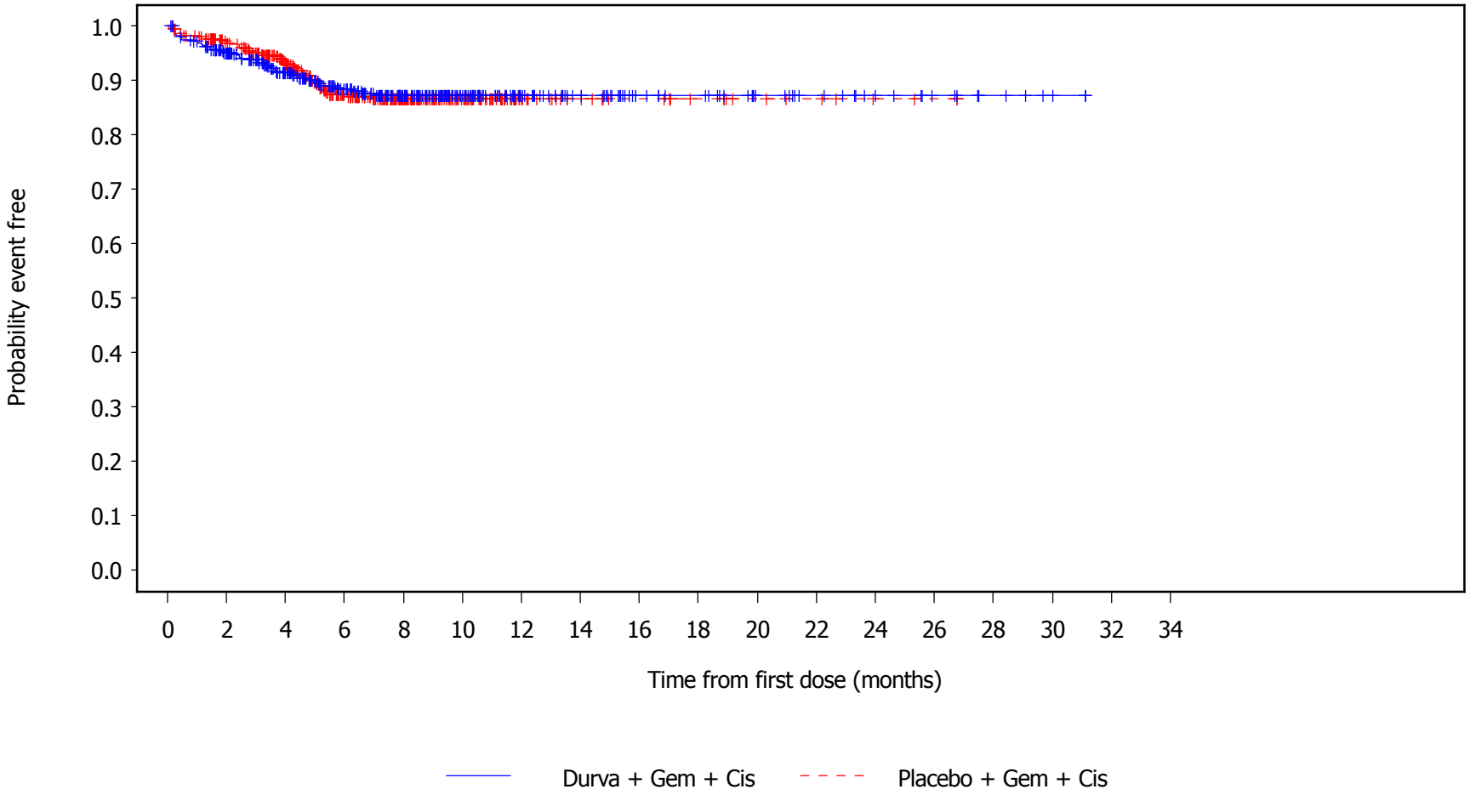
Figure 3.3.143 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Neutrophil count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	328	245	187	145	102	61	44	30	26	16	12	10	8	5	2	0	0	Durva + Gem + Cis
403	314	223	152	103	60	22	13	9	6	3	3	0	0	0	0	0	0	Placebo + Gem + Cis

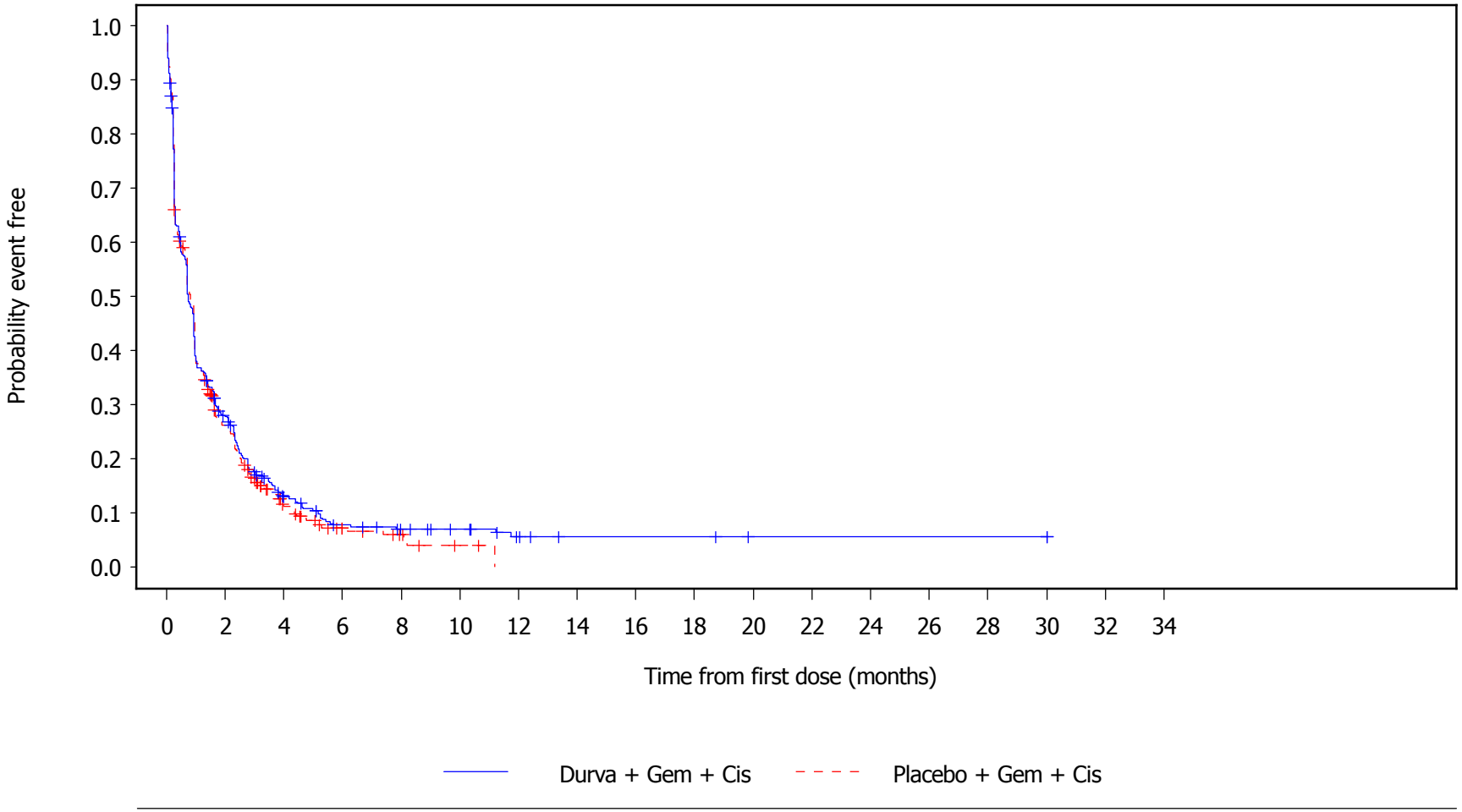
Figure 3.3.144 TOPAZ: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Platelet count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	359	295	241	182	120	73	55	38	34	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	362	295	206	142	80	31	20	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

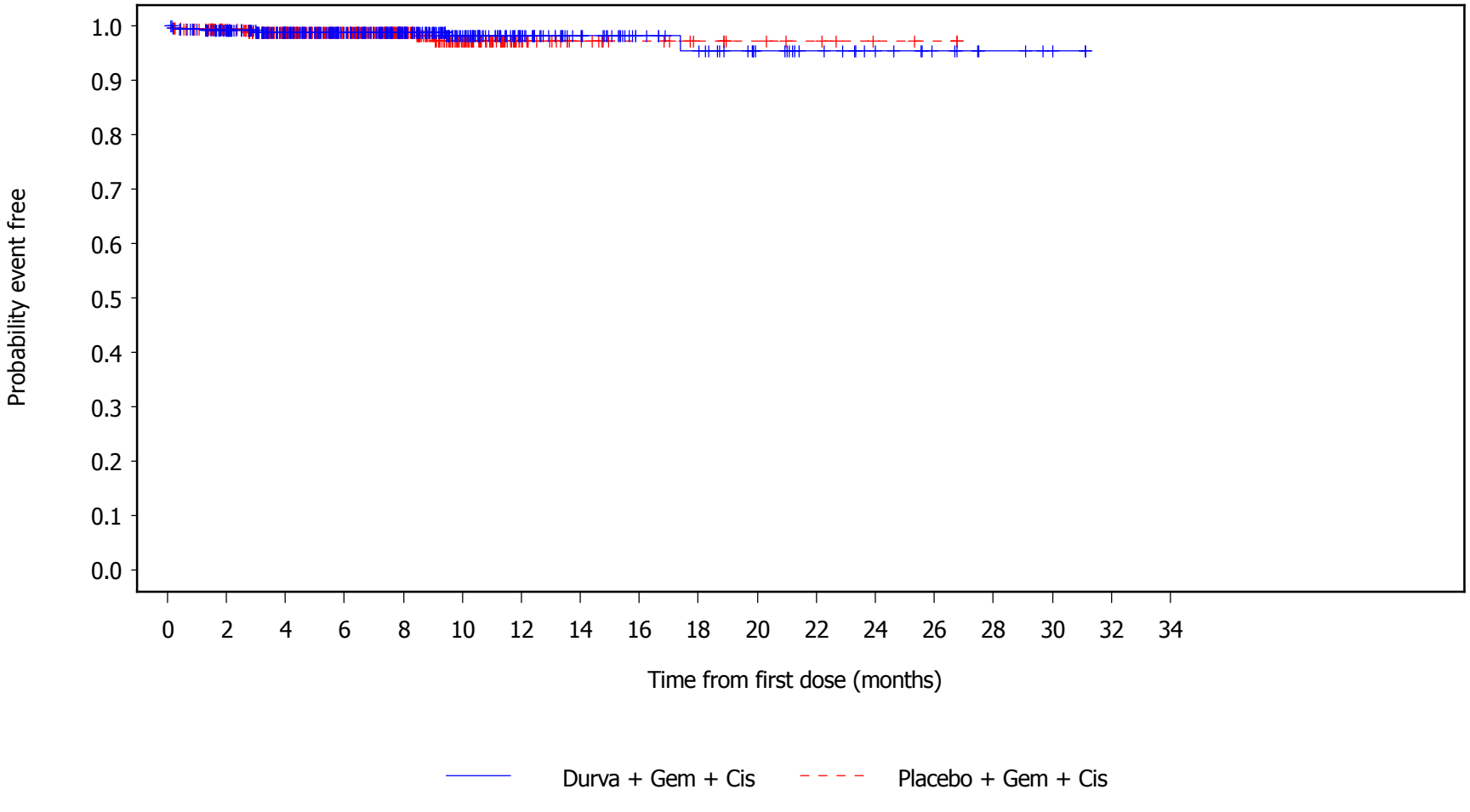
Figure 3.3.145 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	106	43	22	16	12	6	3	3	3	1	1	1	1	1	1	0	0	Durva + Gem + Cis
403	99	31	12	7	2	0	0	0	0	0	0	0	0	0	0	0	0	Placebo + Gem + Cis

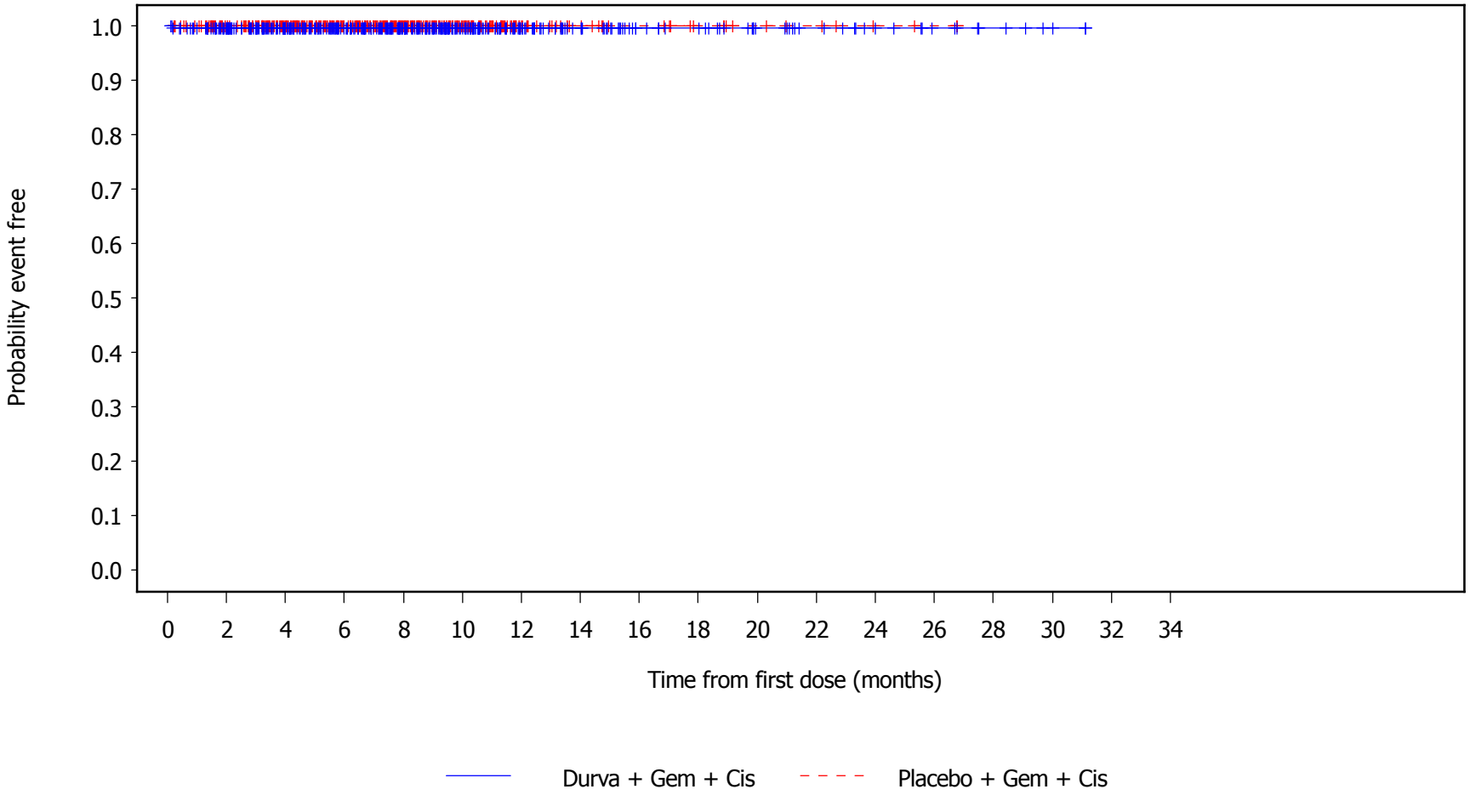
Figure 3.3.146 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	313	262	196	128	79	57	40	35	24	18	13	8	4	2	0	0	Durva + Gem + Cis
403	371	312	231	158	86	32	20	14	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

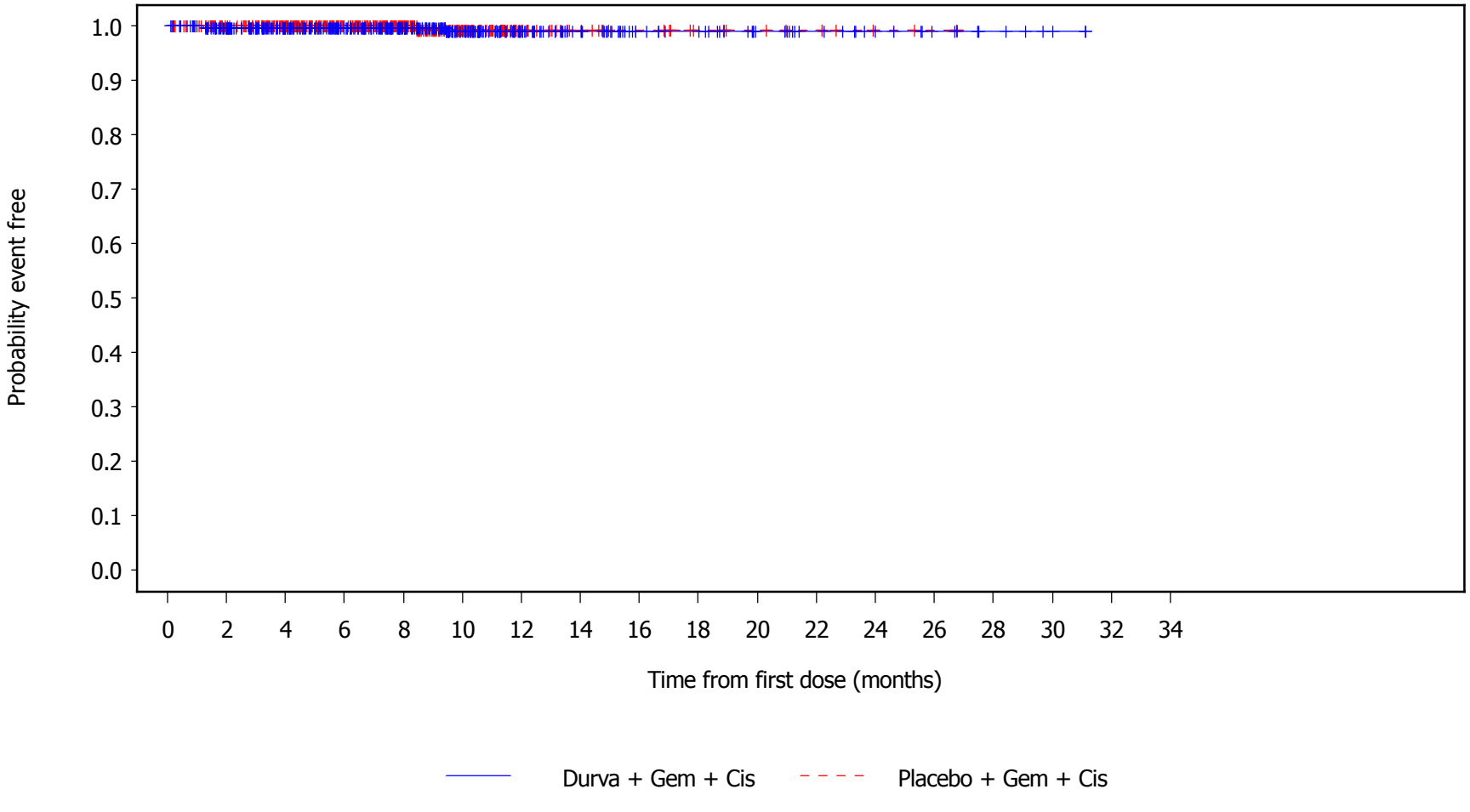
Figure 3.3.147 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Immune-mediated lung disease
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

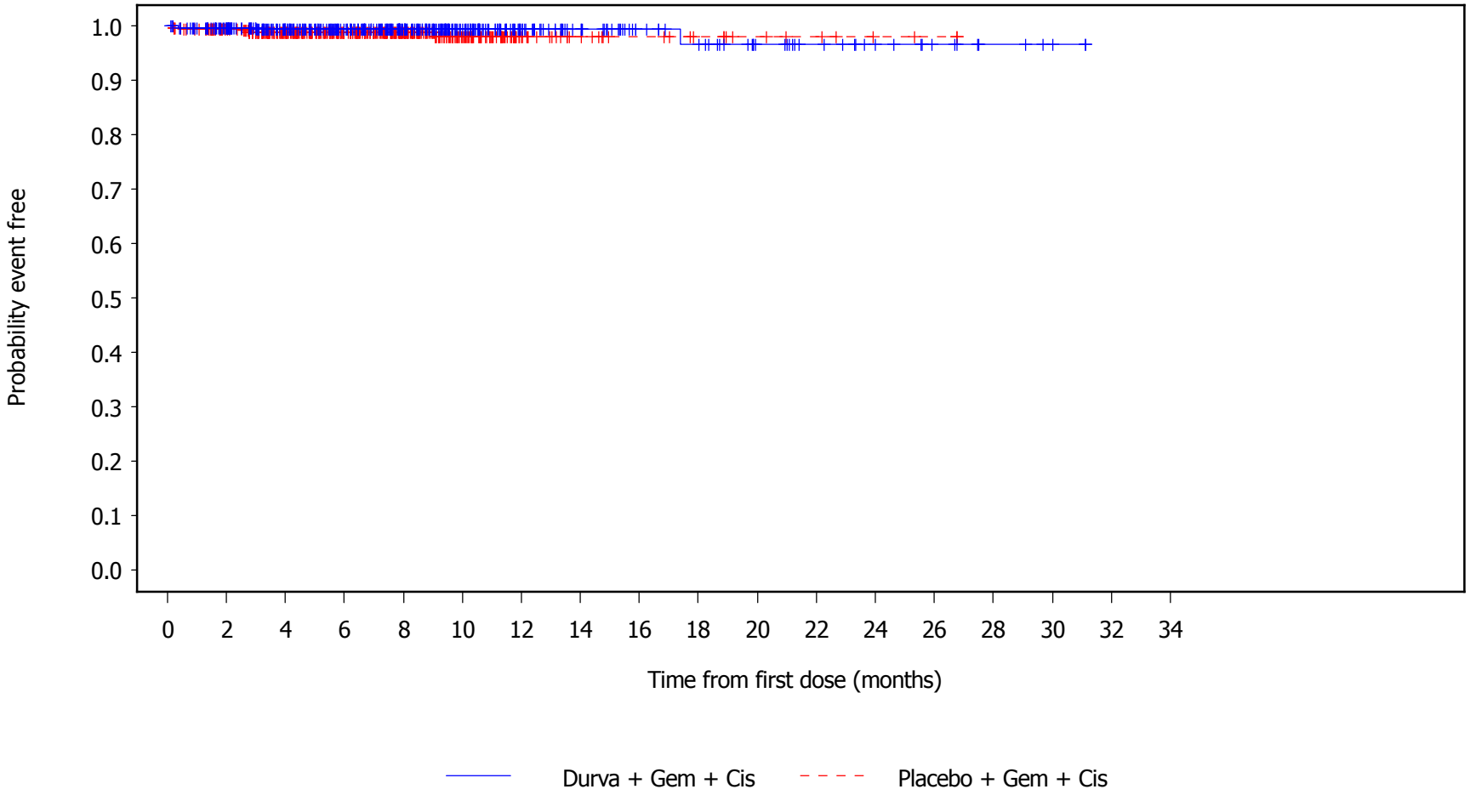
Figure 3.3.148 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Interstitial lung disease
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	263	197	129	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	88	33	21	15	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

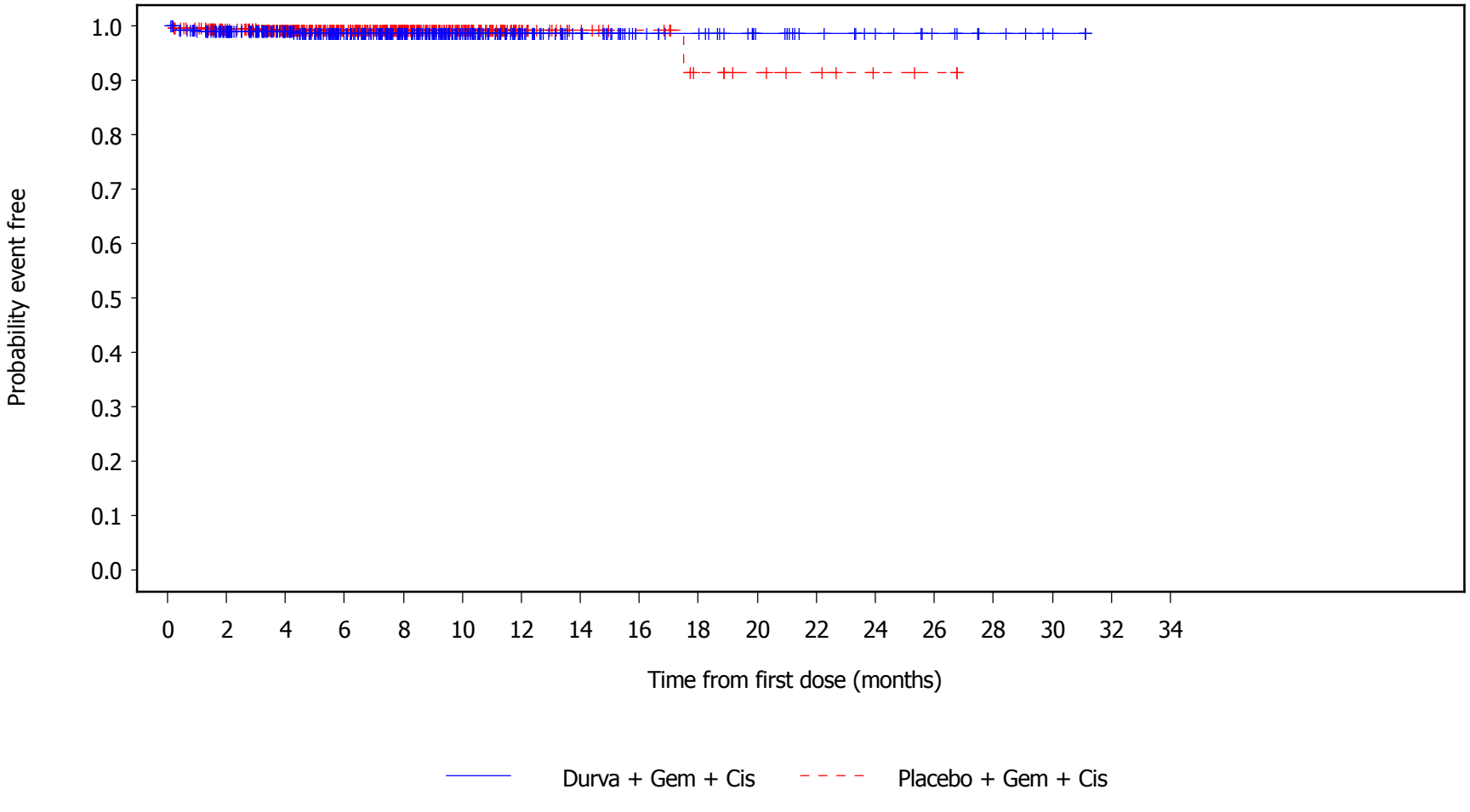
Figure 3.3.149 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	197	130	79	57	40	35	24	18	13	8	4	2	0	0	Durva + Gem + Cis
403	371	312	231	158	87	33	21	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

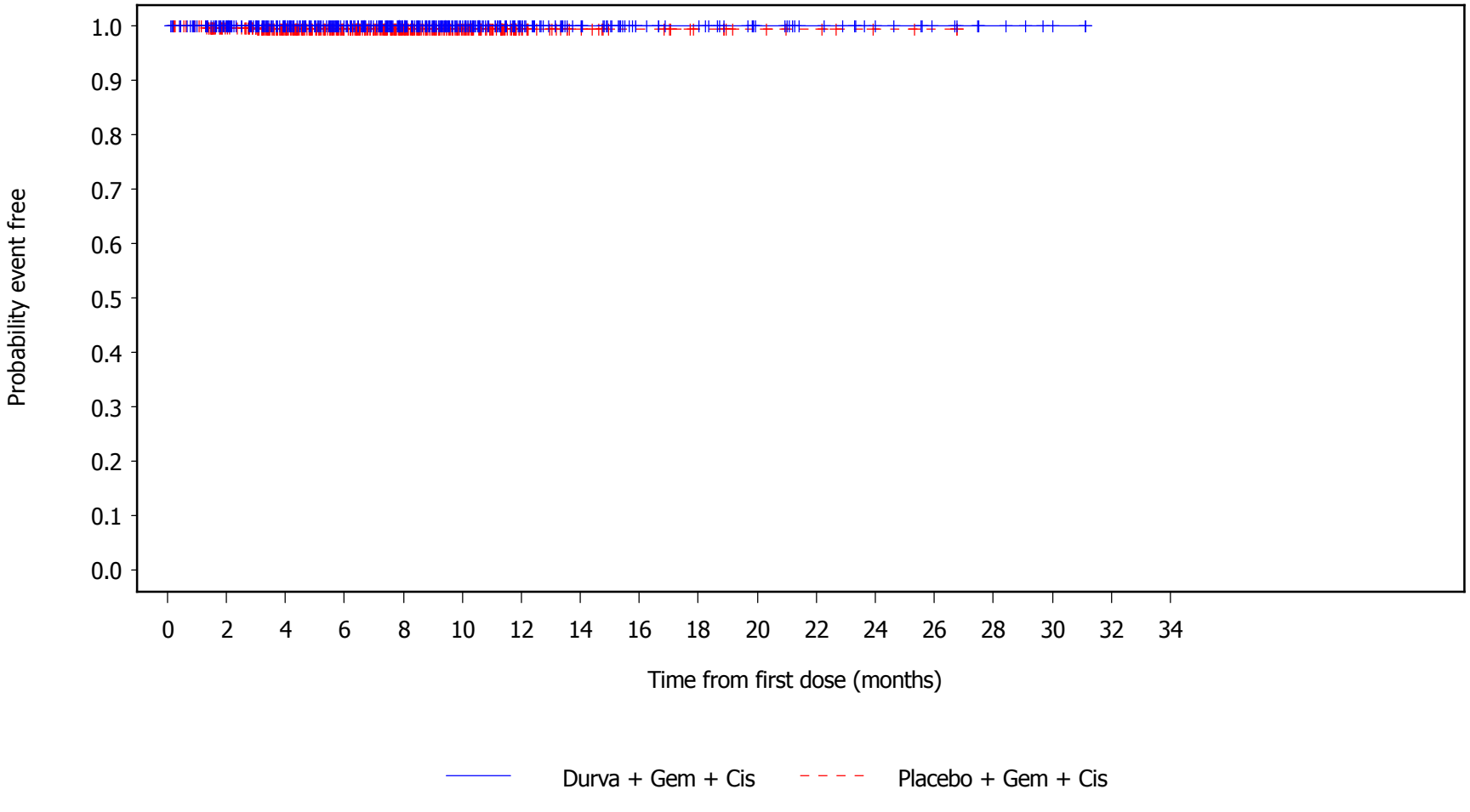
Figure 3.3.150 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Hepatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	312	260	194	129	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	369	311	231	158	88	33	21	16	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

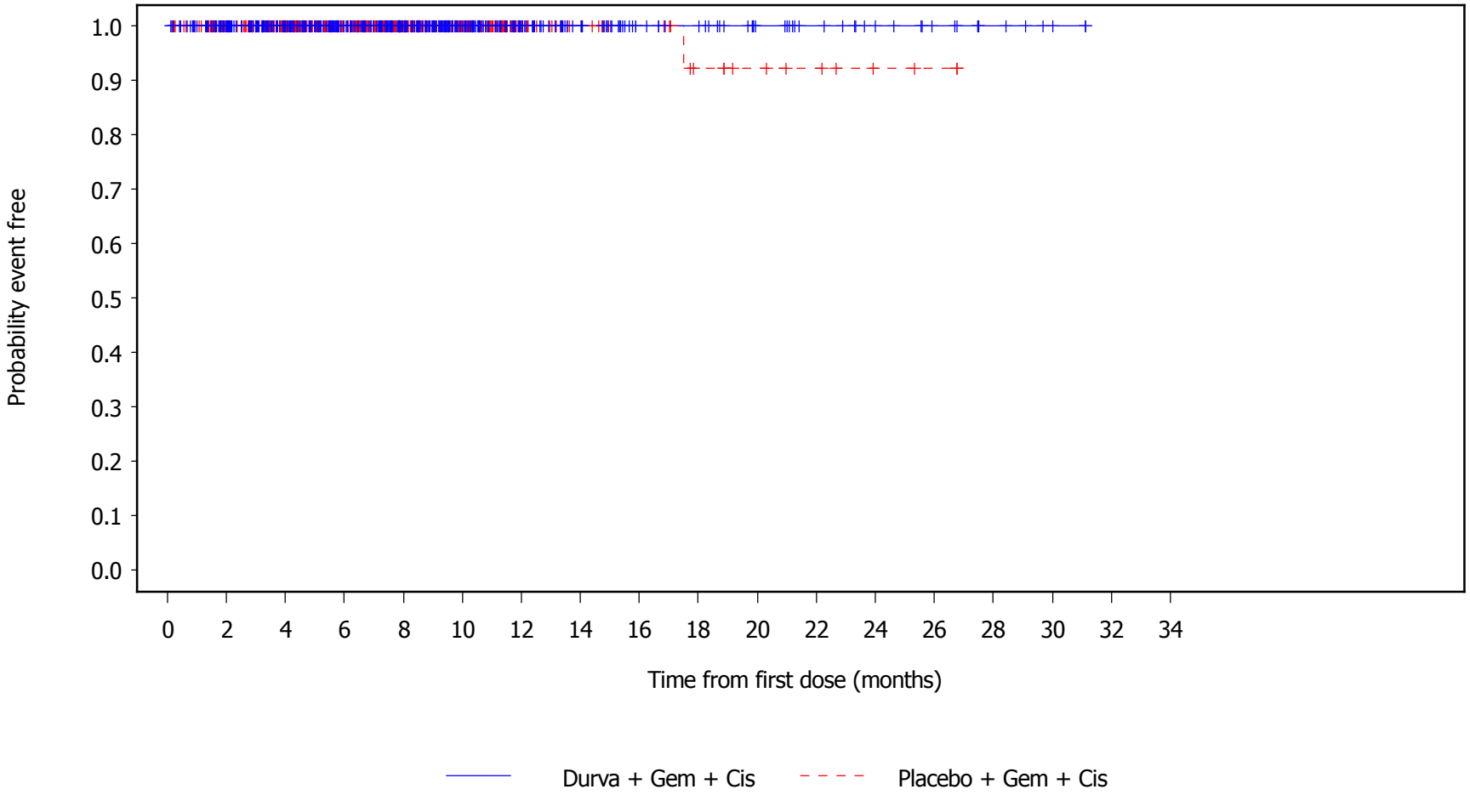
Figure 3.3.151 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

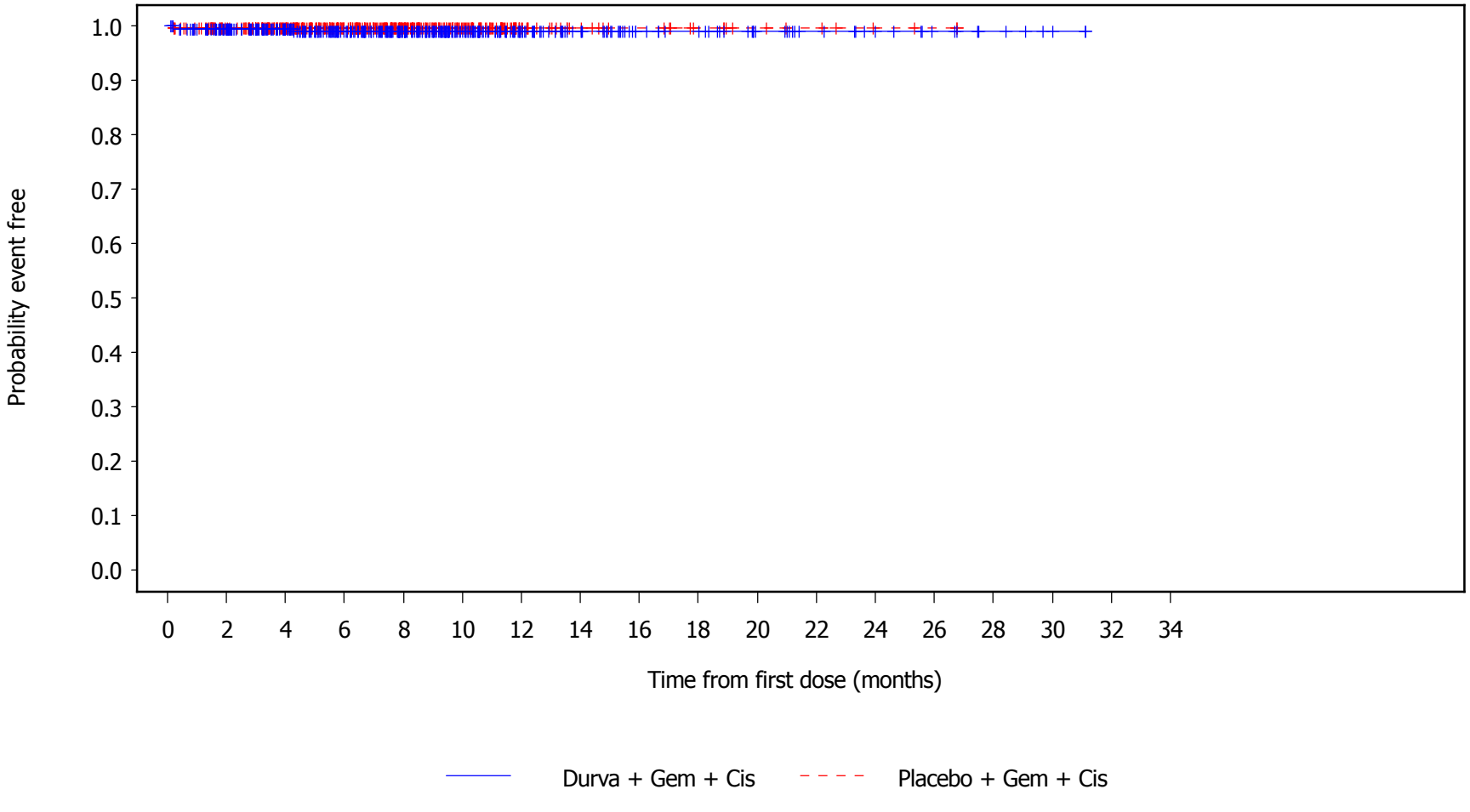
Figure 3.3.152 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

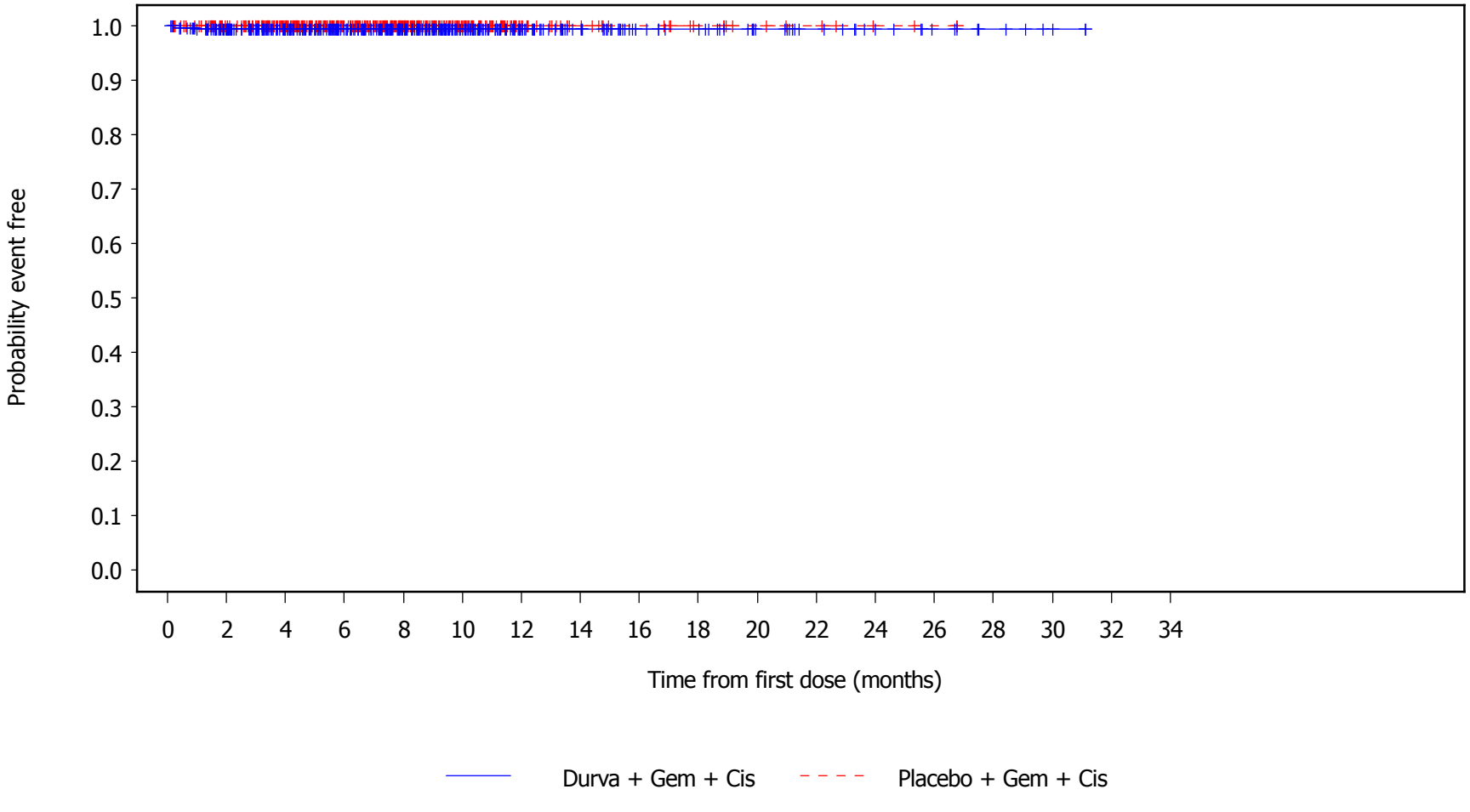
Figure 3.3.153 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	314	262	196	129	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	88	33	21	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

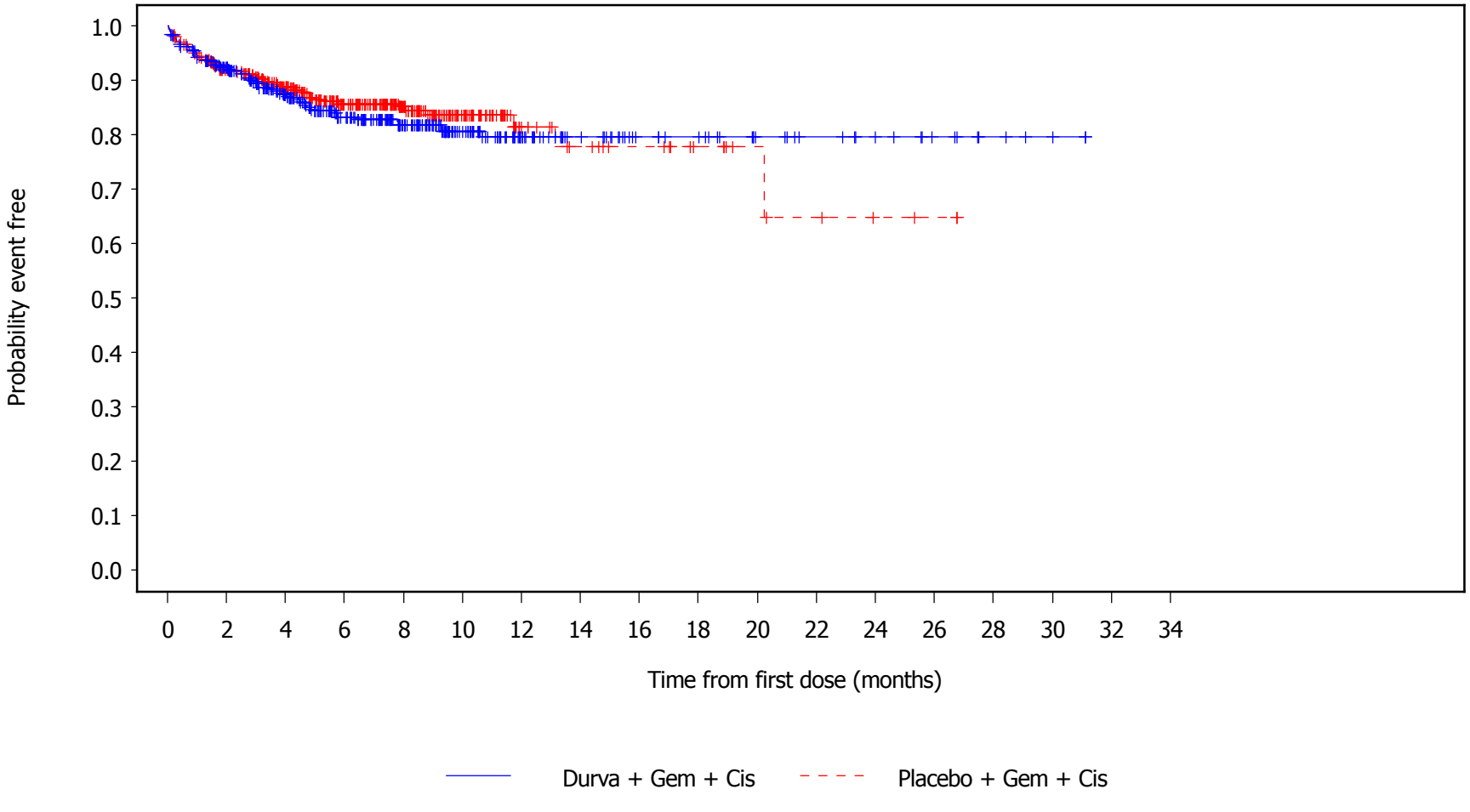
Figure 3.3.154 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Immune-mediated hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	313	262	196	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

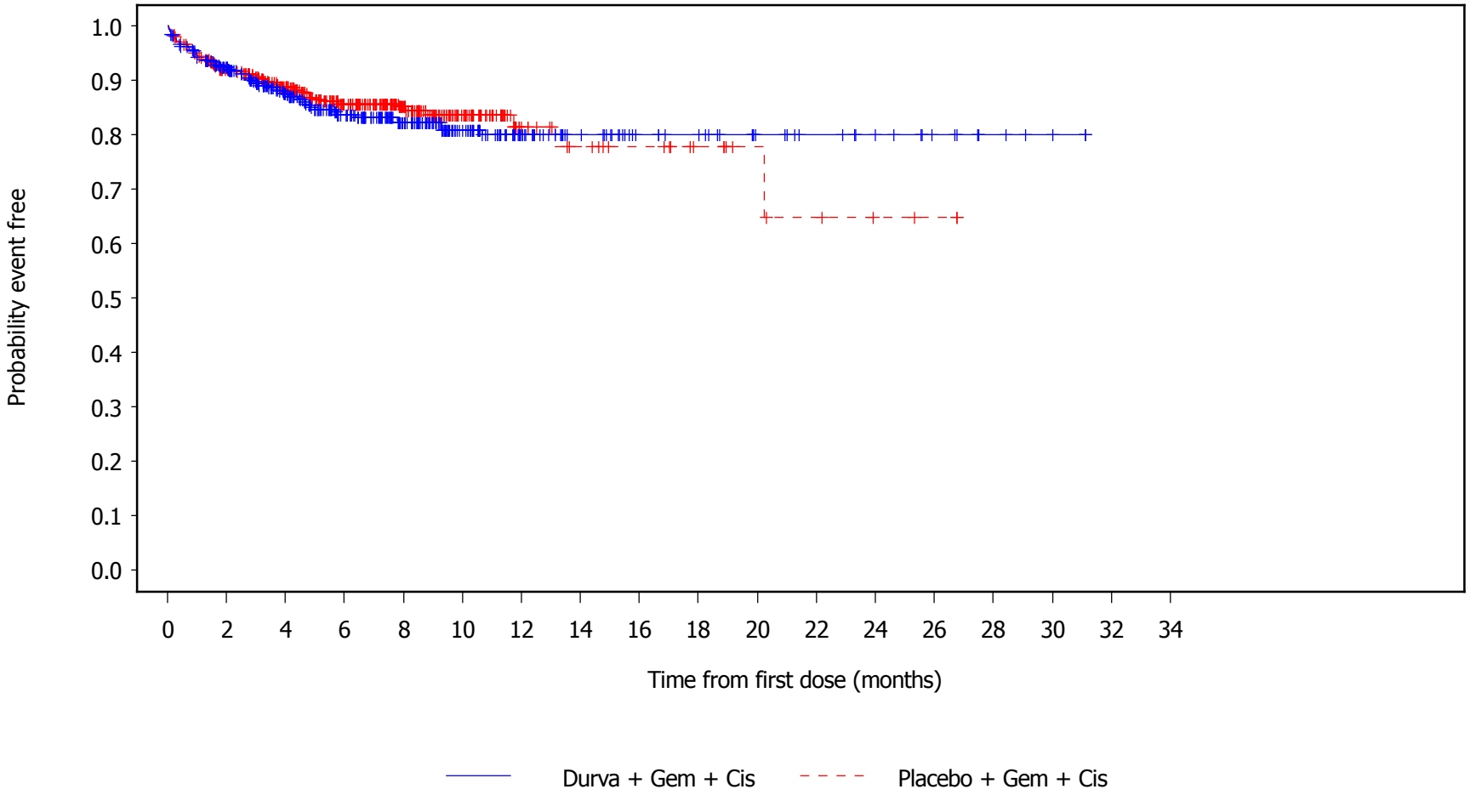
Figure 3.3.155 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Diarrhoea/Colitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	345	273	219	159	104	64	45	32	29	20	16	13	8	4	2	0	0	Durva + Gem + Cis
403	340	279	201	136	77	27	19	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

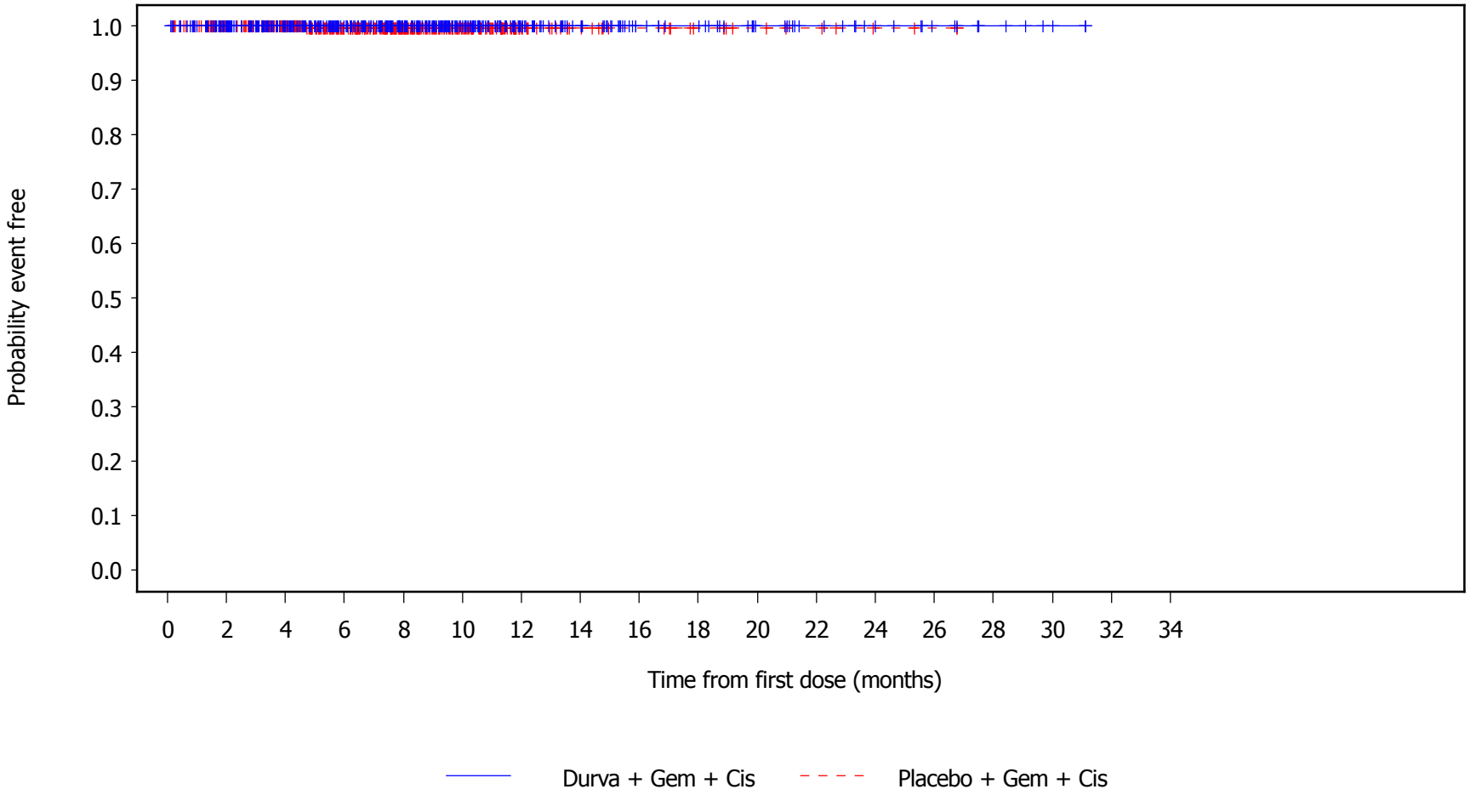
Figure 3.3.156 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Diarrhoea
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	345	274	219	159	104	64	45	32	29	20	16	13	8	4	2	0	0	Durva + Gem + Cis
403	340	279	201	136	77	27	19	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

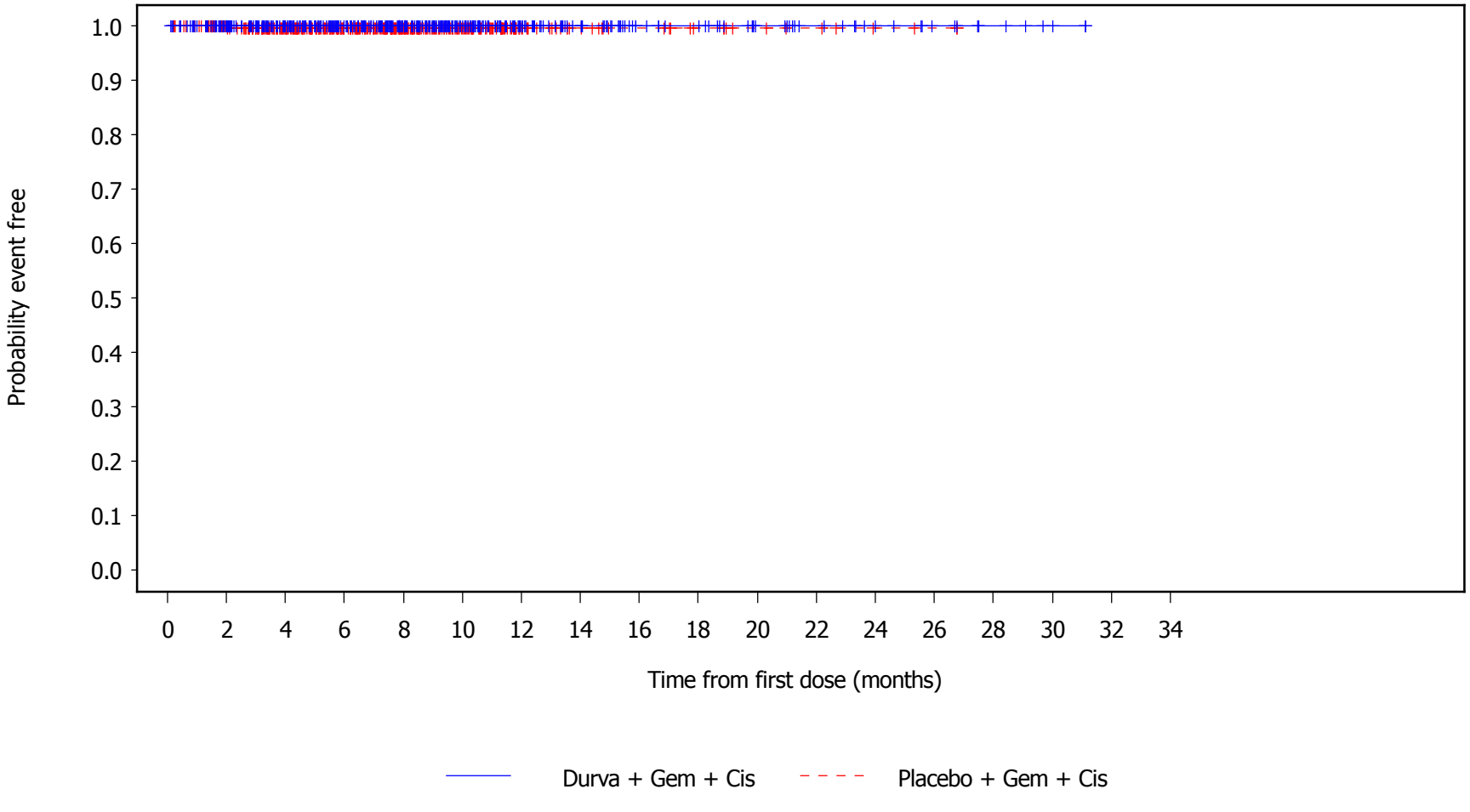
Figure 3.3.157 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Enterocolitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	231	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

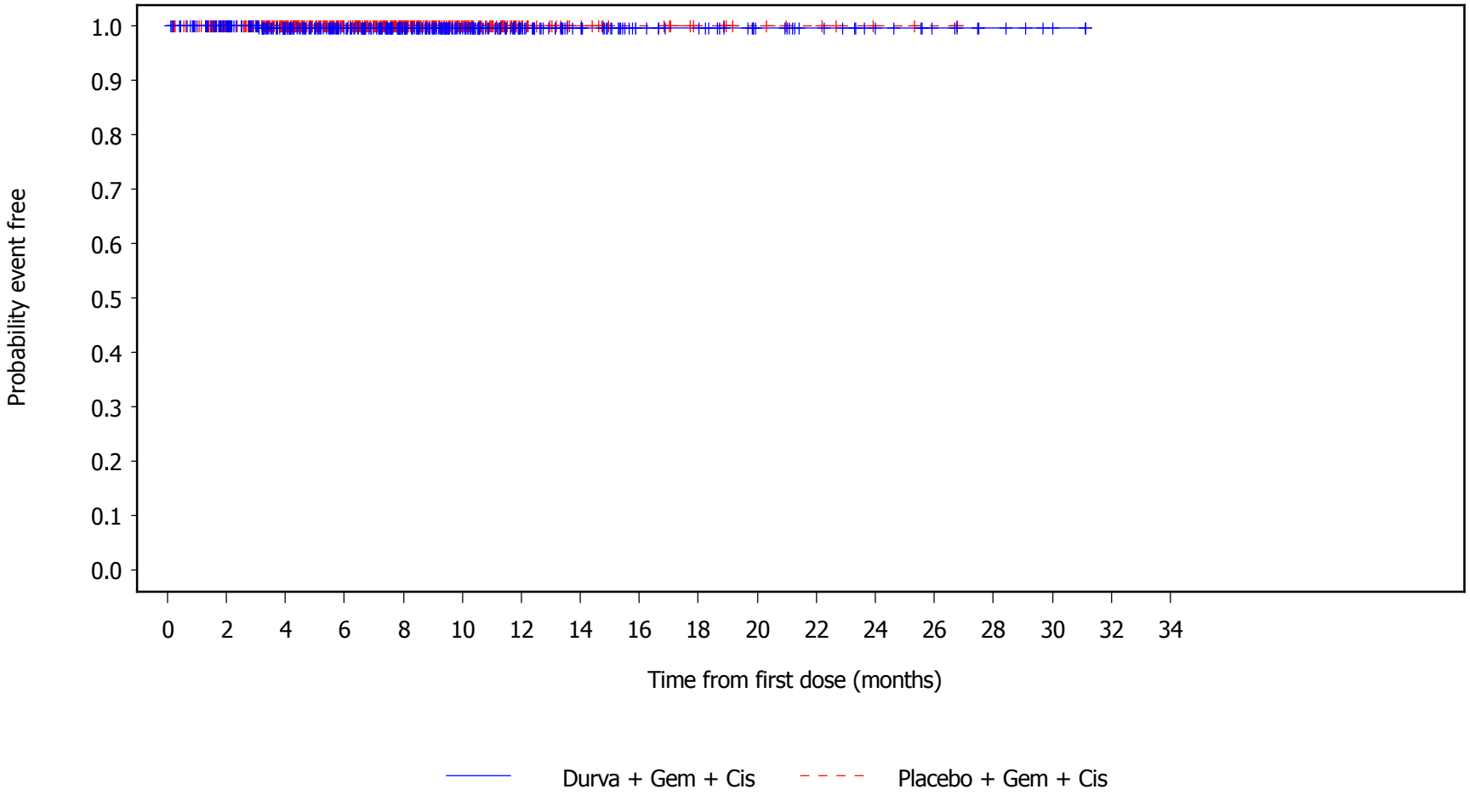
Figure 3.3.158 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Immune-mediated enterocolitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

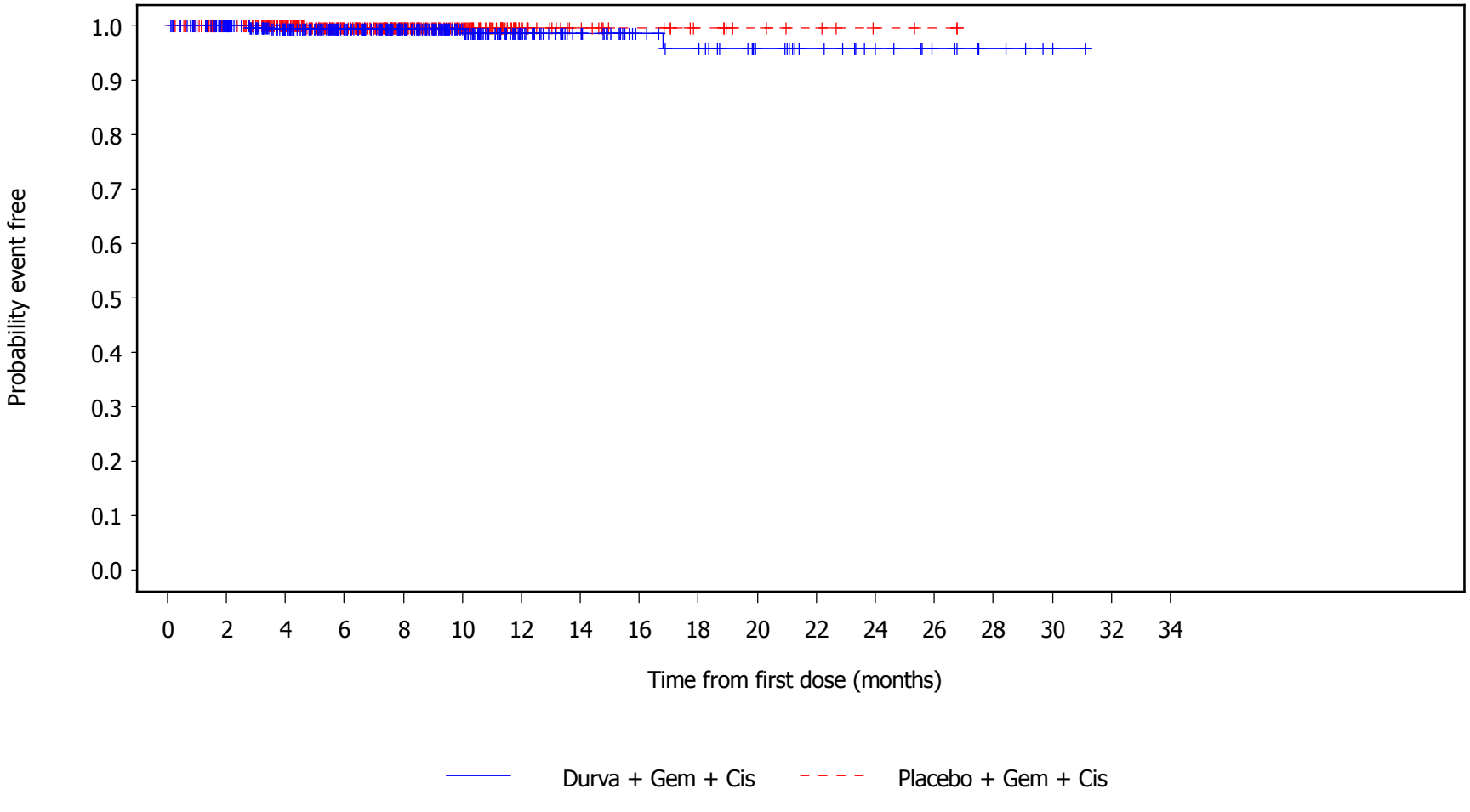
Figure 3.3.159 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Colitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

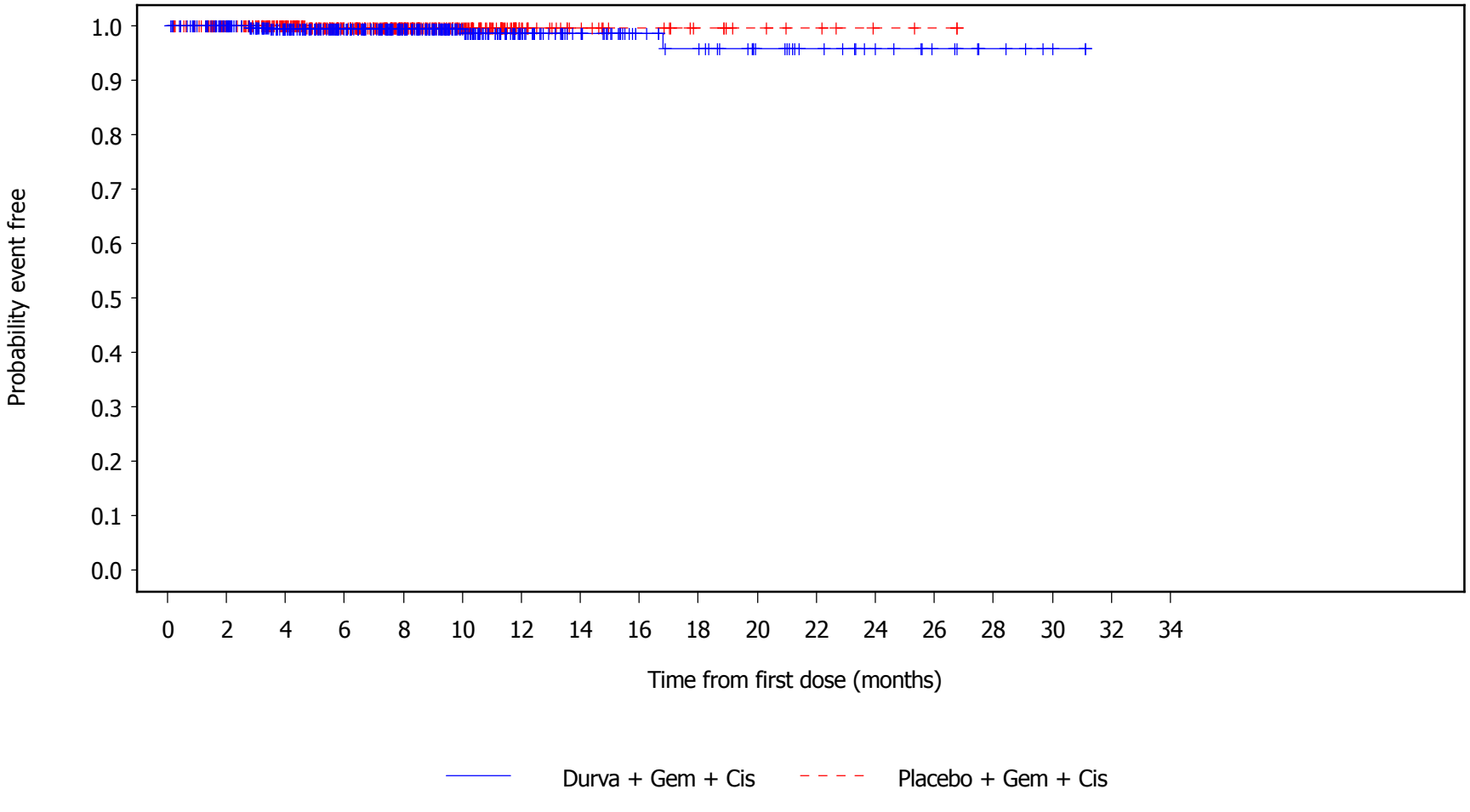
Figure 3.3.160 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Adrenal insufficiency
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	313	262	198	131	80	58	40	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	231	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

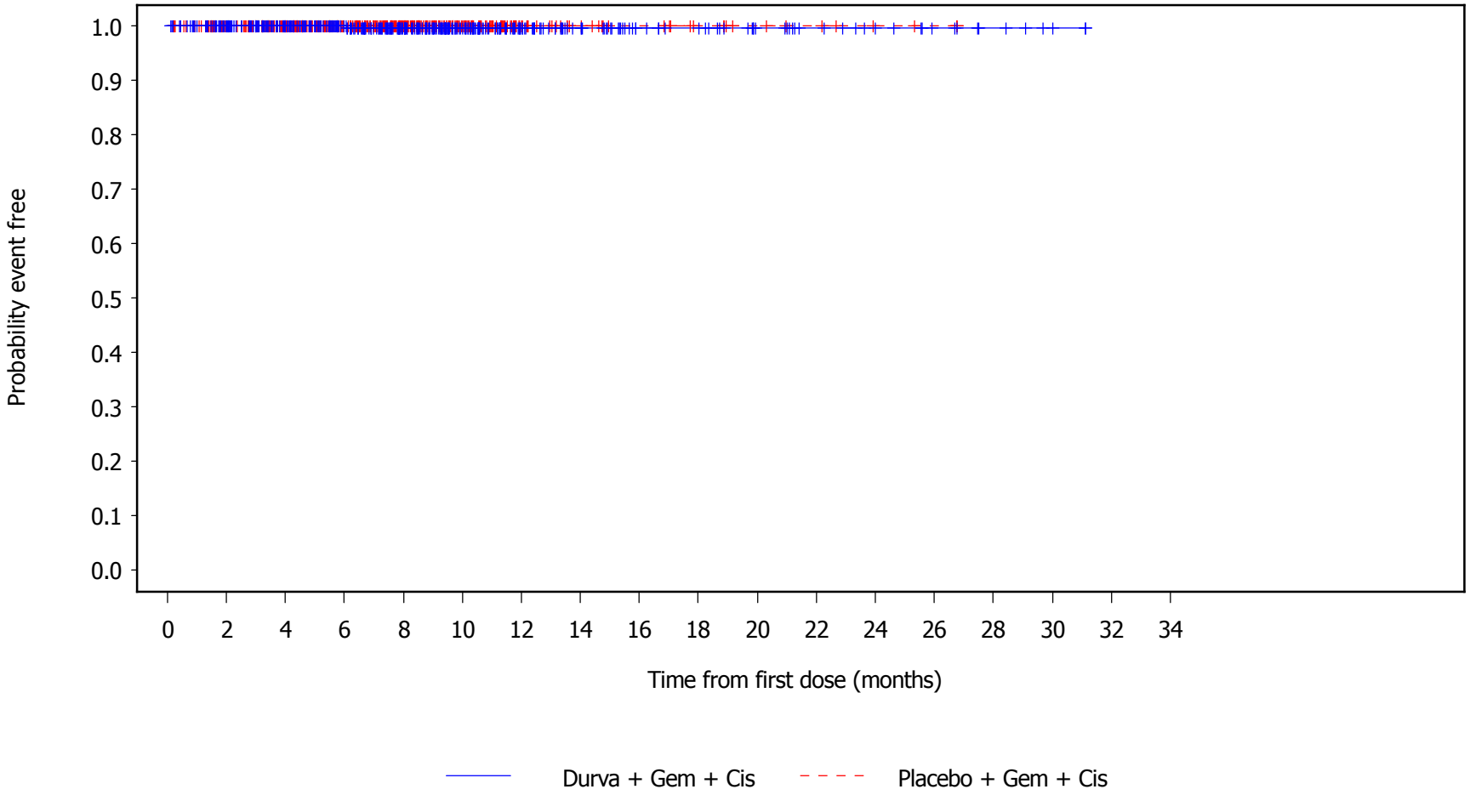
Figure 3.3.161 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Adrenal insufficiency
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	313	262	198	131	80	58	40	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	231	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

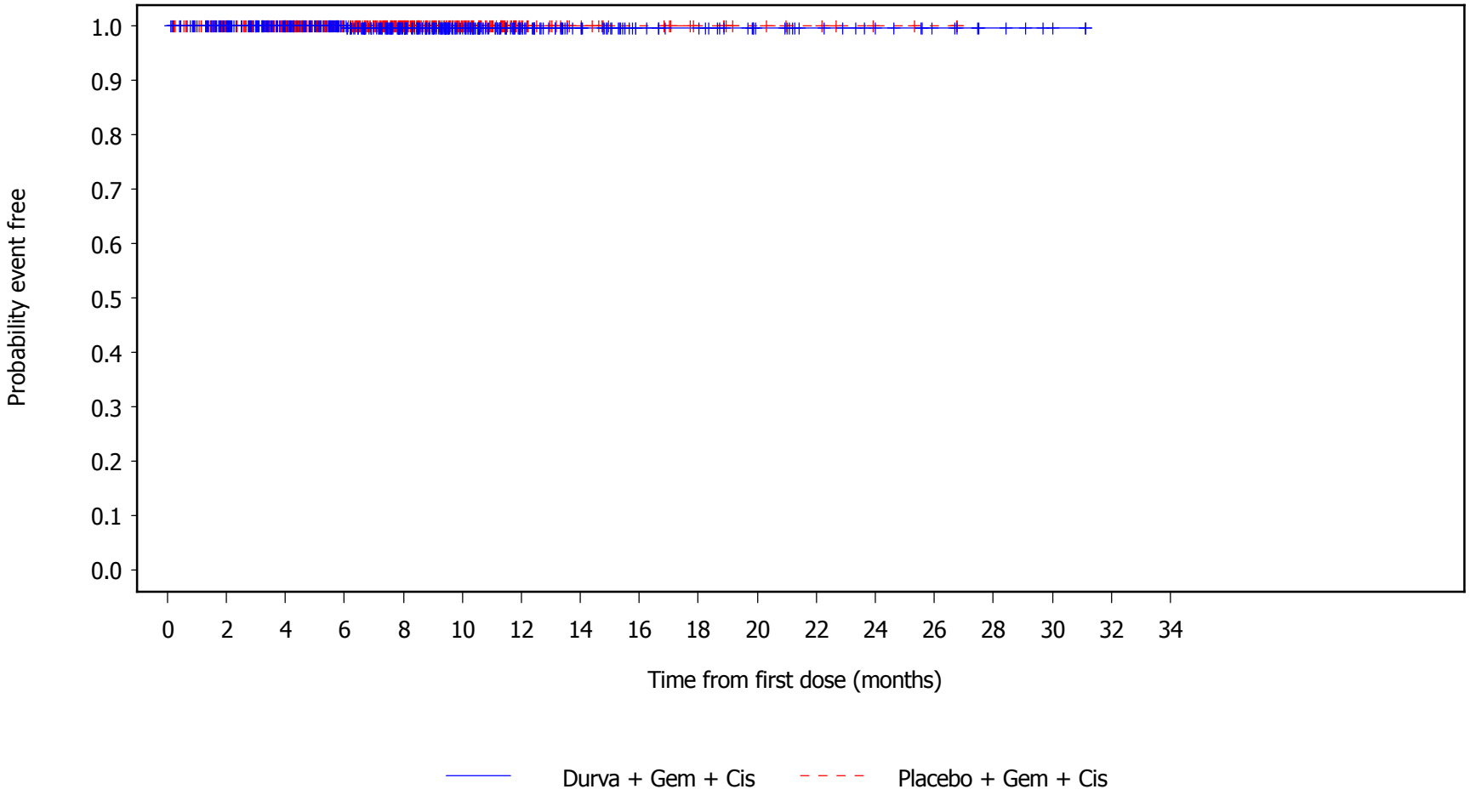
Figure 3.3.162 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Type 1 diabetes mellitus
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	197	130	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

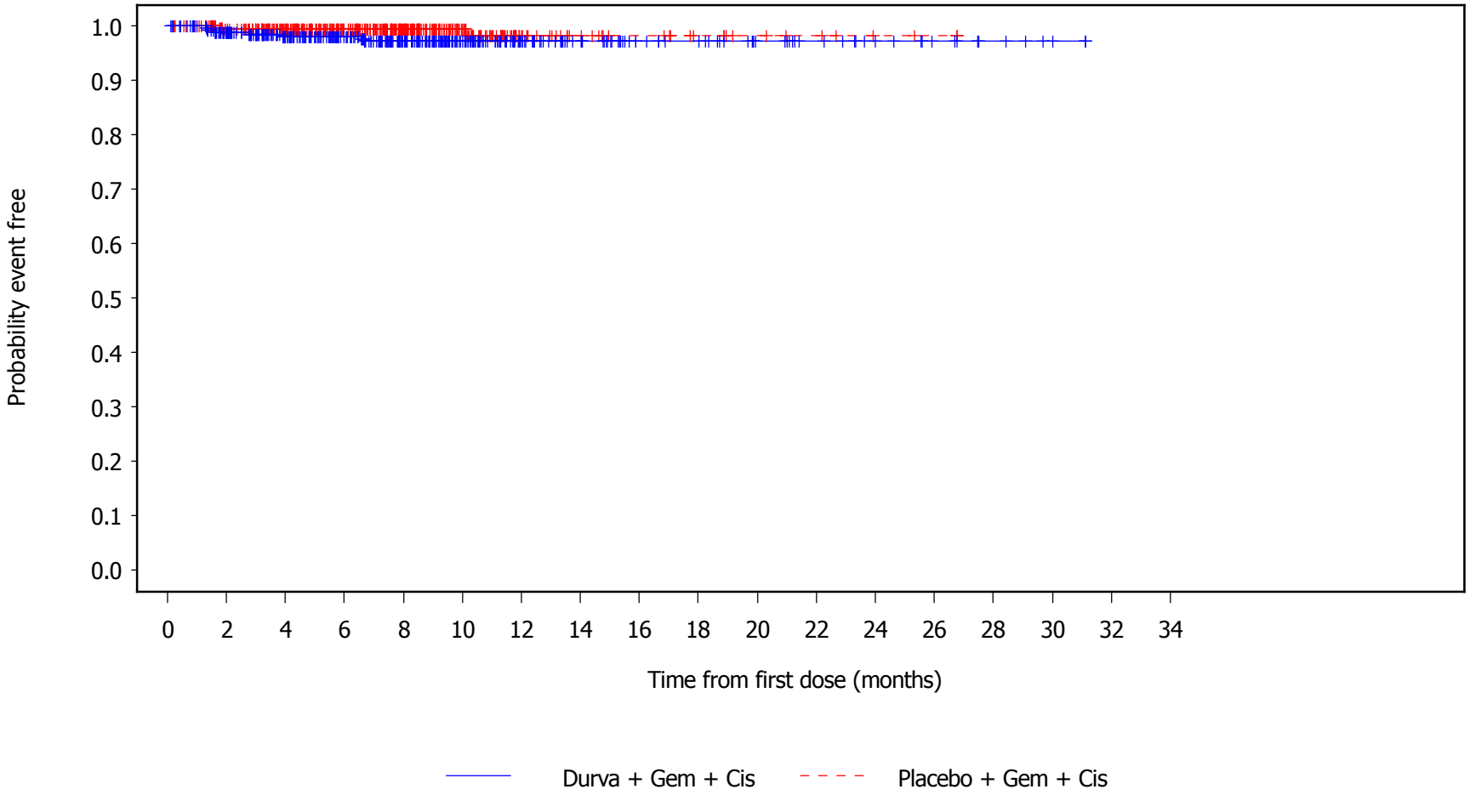
Figure 3.3.163 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Type 1 diabetes mellitus
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	197	130	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

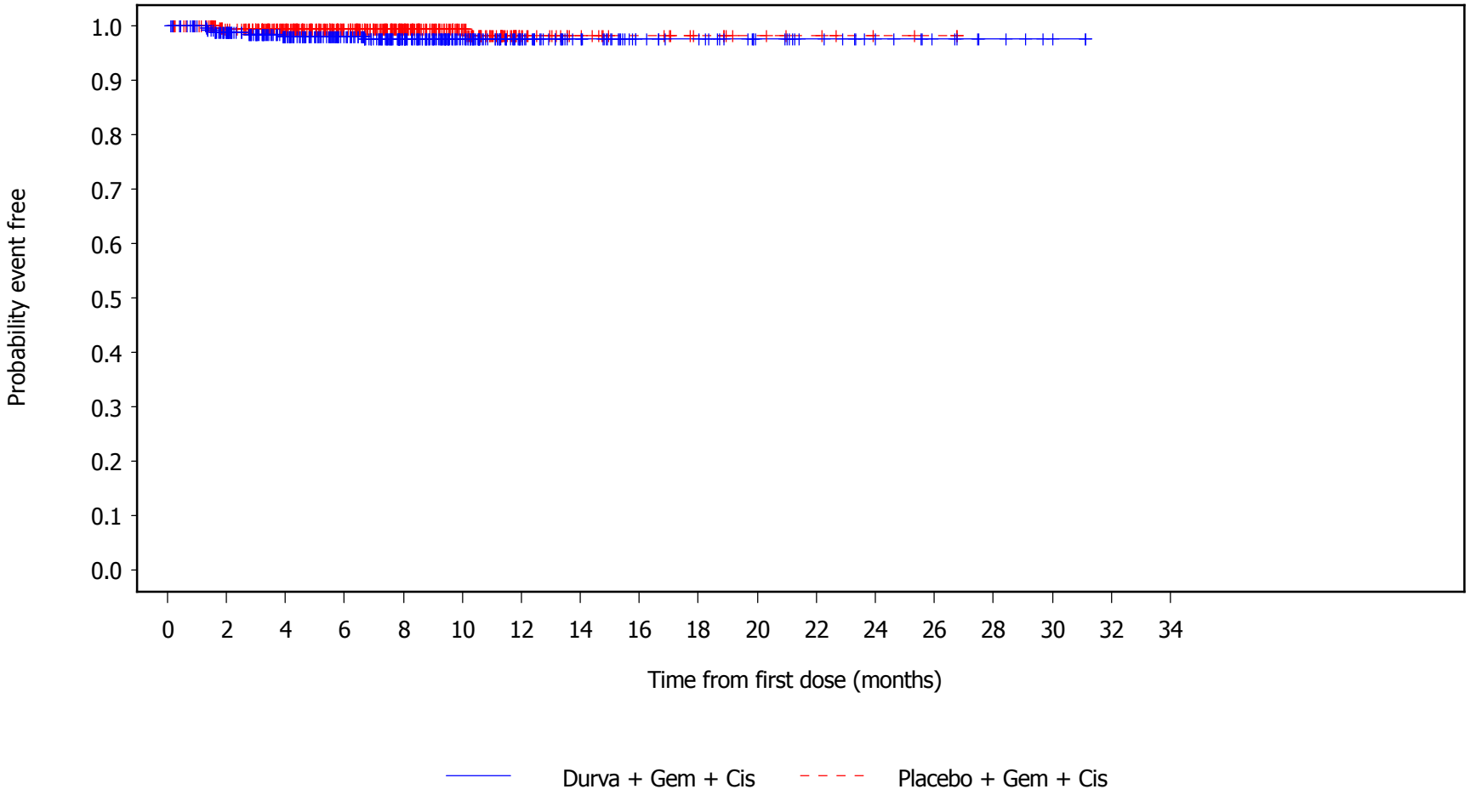
Figure 3.3.164 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Hyperthyroid events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	309	258	193	128	79	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	311	230	157	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

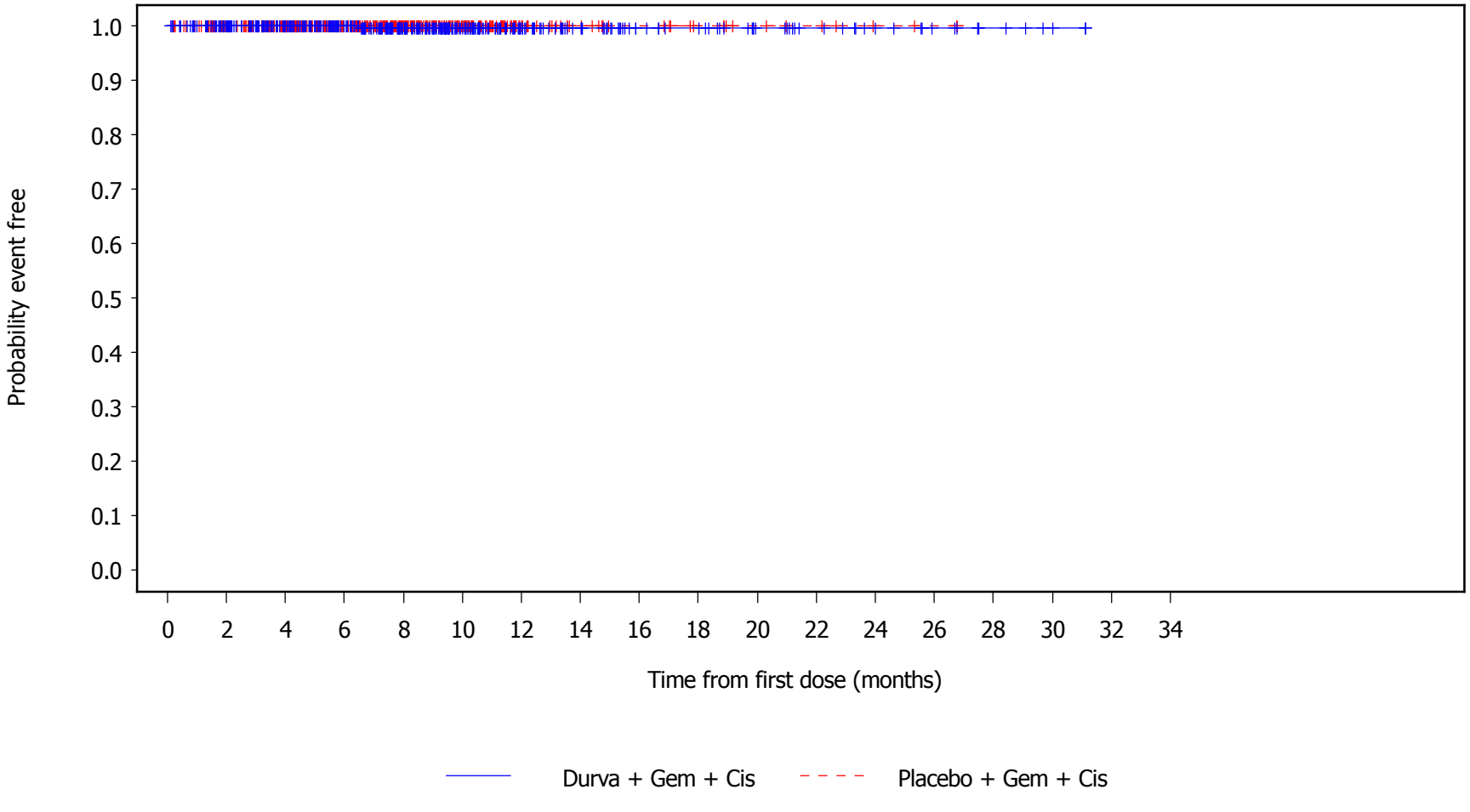
Figure 3.3.165 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hyperthyroidism
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	309	258	194	129	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	311	230	157	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

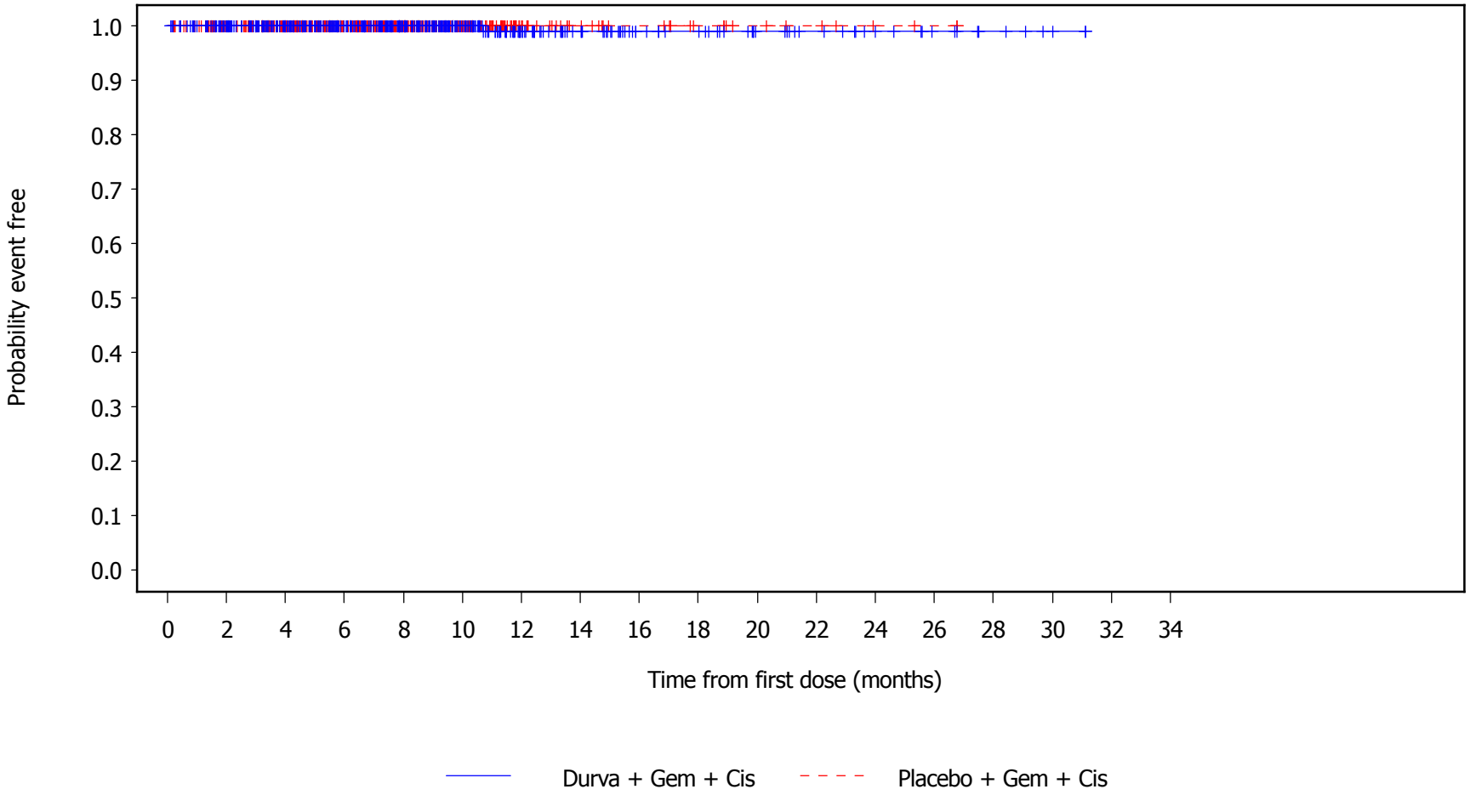
Figure 3.3.166 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Immune-mediated hyperthyroidism
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	197	130	79	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

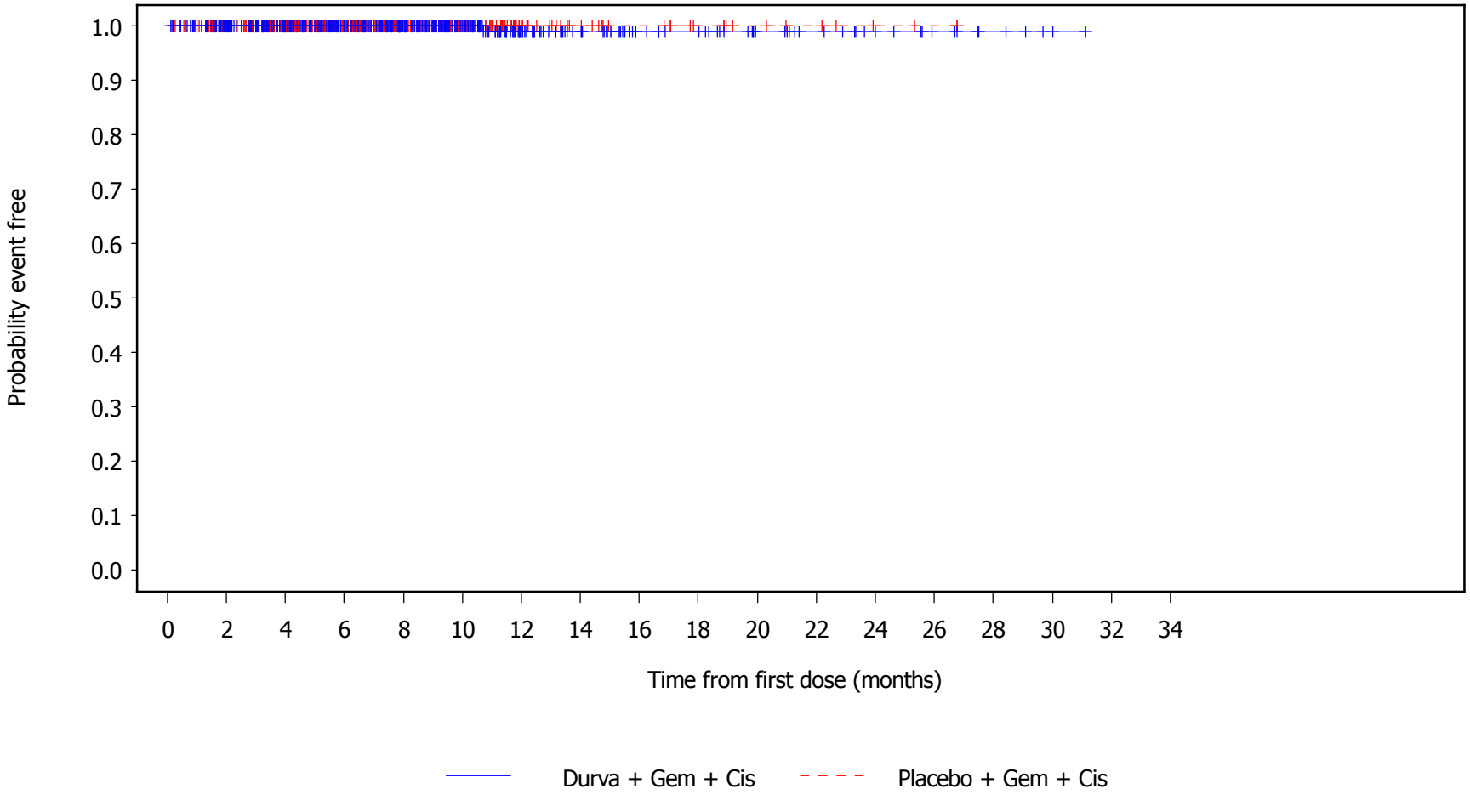
Figure 3.3.167 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Hypophysitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	79	57	39	35	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

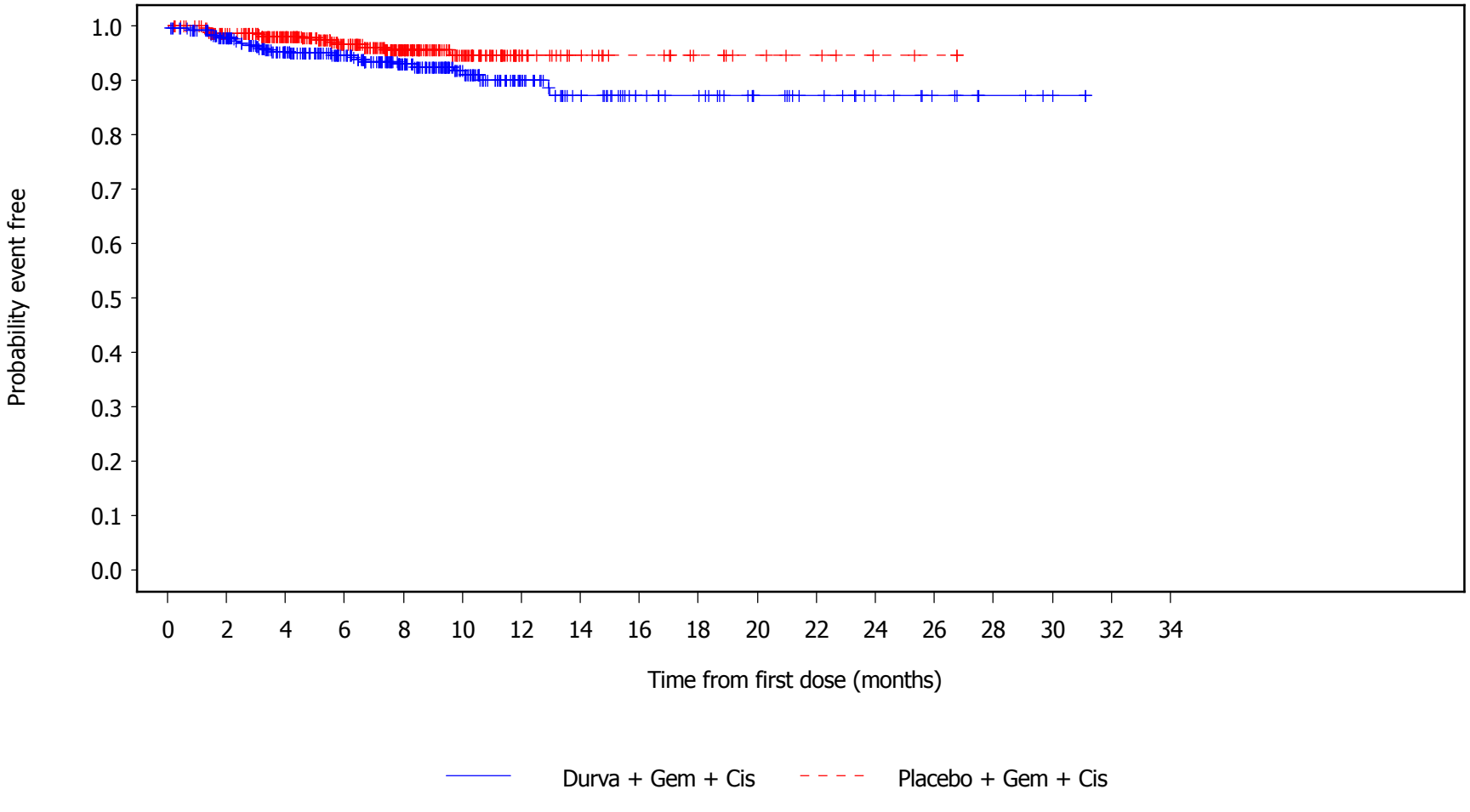
Figure 3.3.168 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hypothalamic pituitary adrenal axis suppression
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	79	57	39	35	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

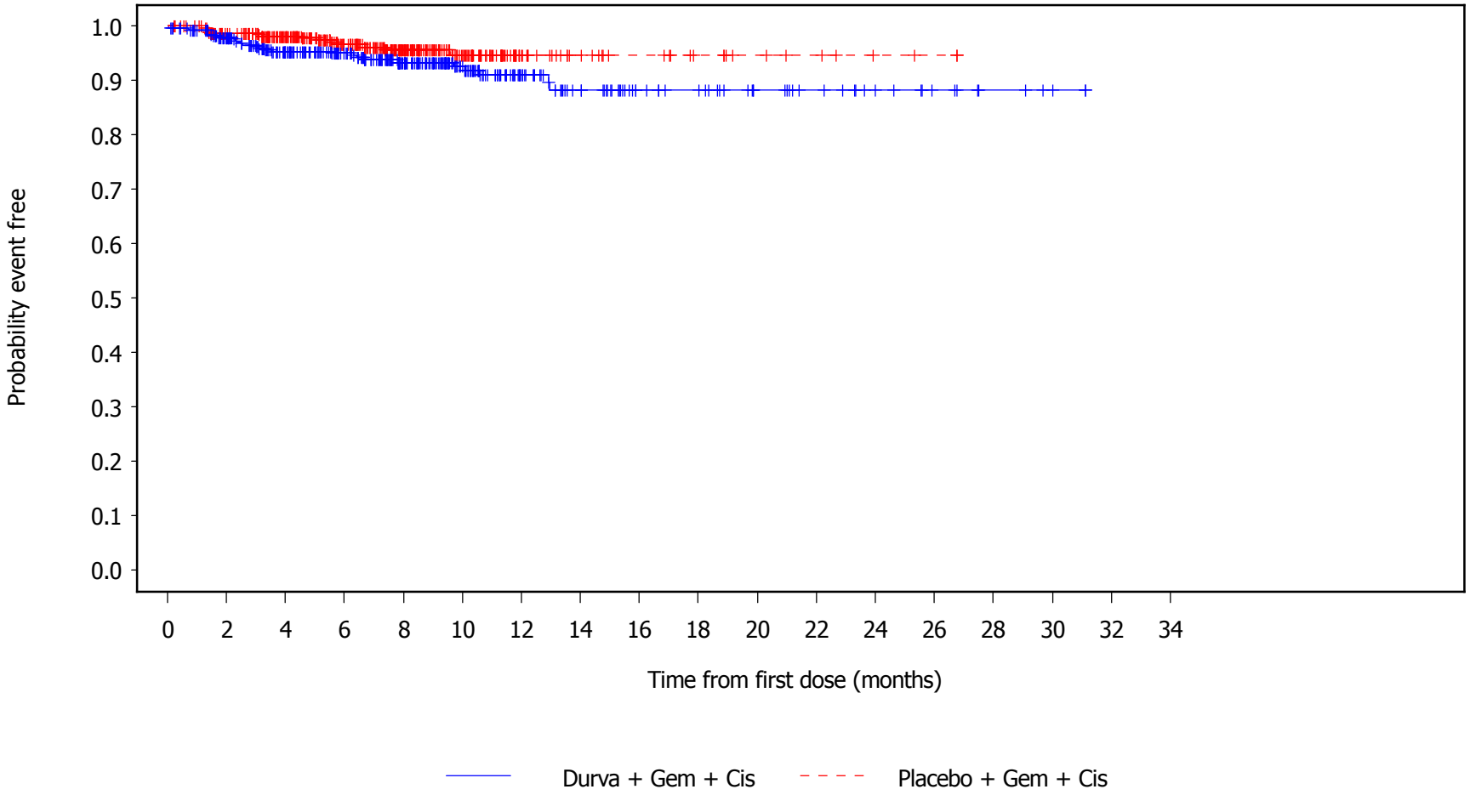
Figure 3.3.169 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Hypothyroid events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	365	302	253	186	123	74	52	37	33	23	18	13	8	4	2	0	0	Durva + Gem + Cis
403	366	306	224	153	87	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

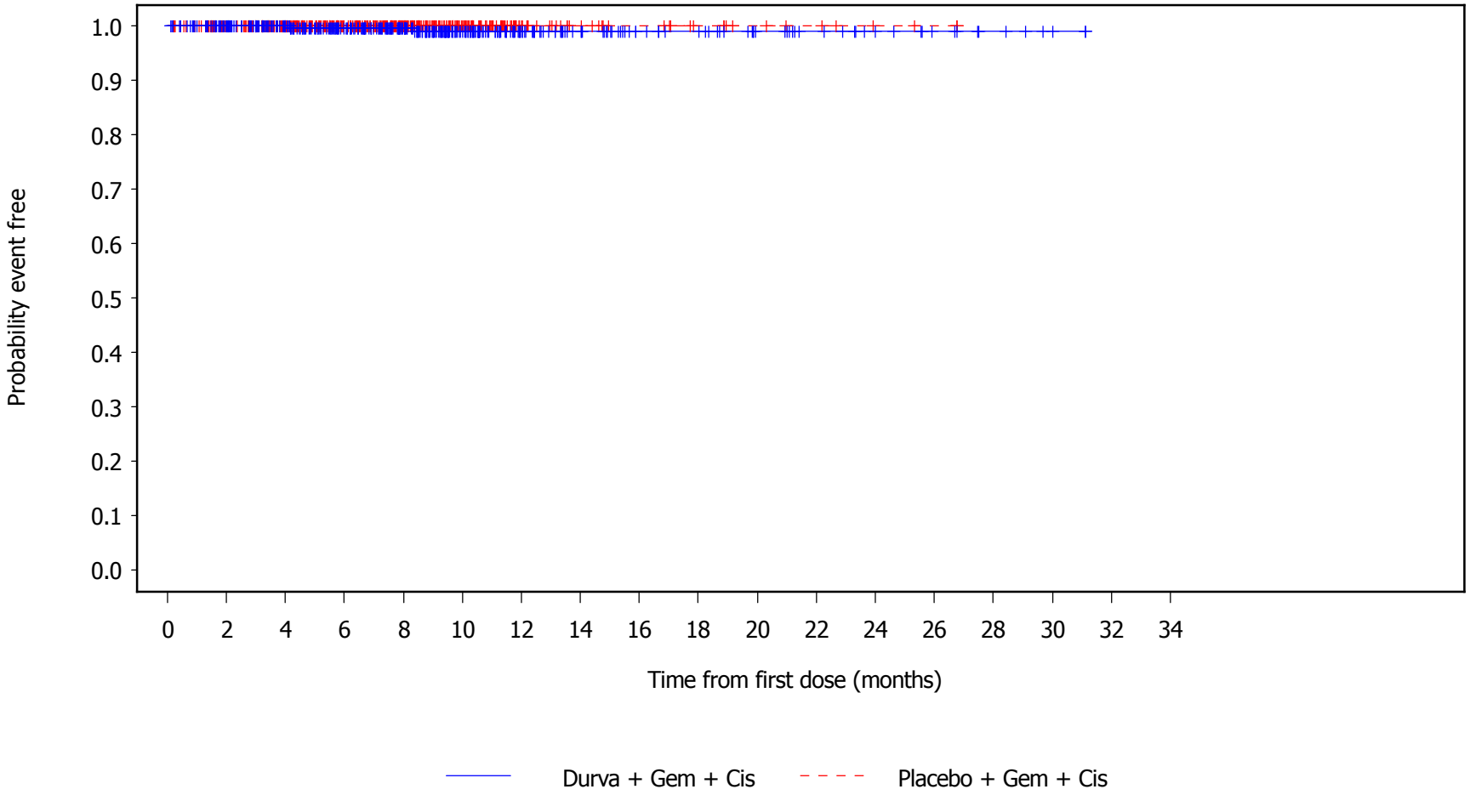
Figure 3.3.170 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hypothyroidism
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	365	302	254	187	125	76	54	37	33	23	18	13	8	4	2	0	0	Durva + Gem + Cis
403	366	306	224	153	87	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

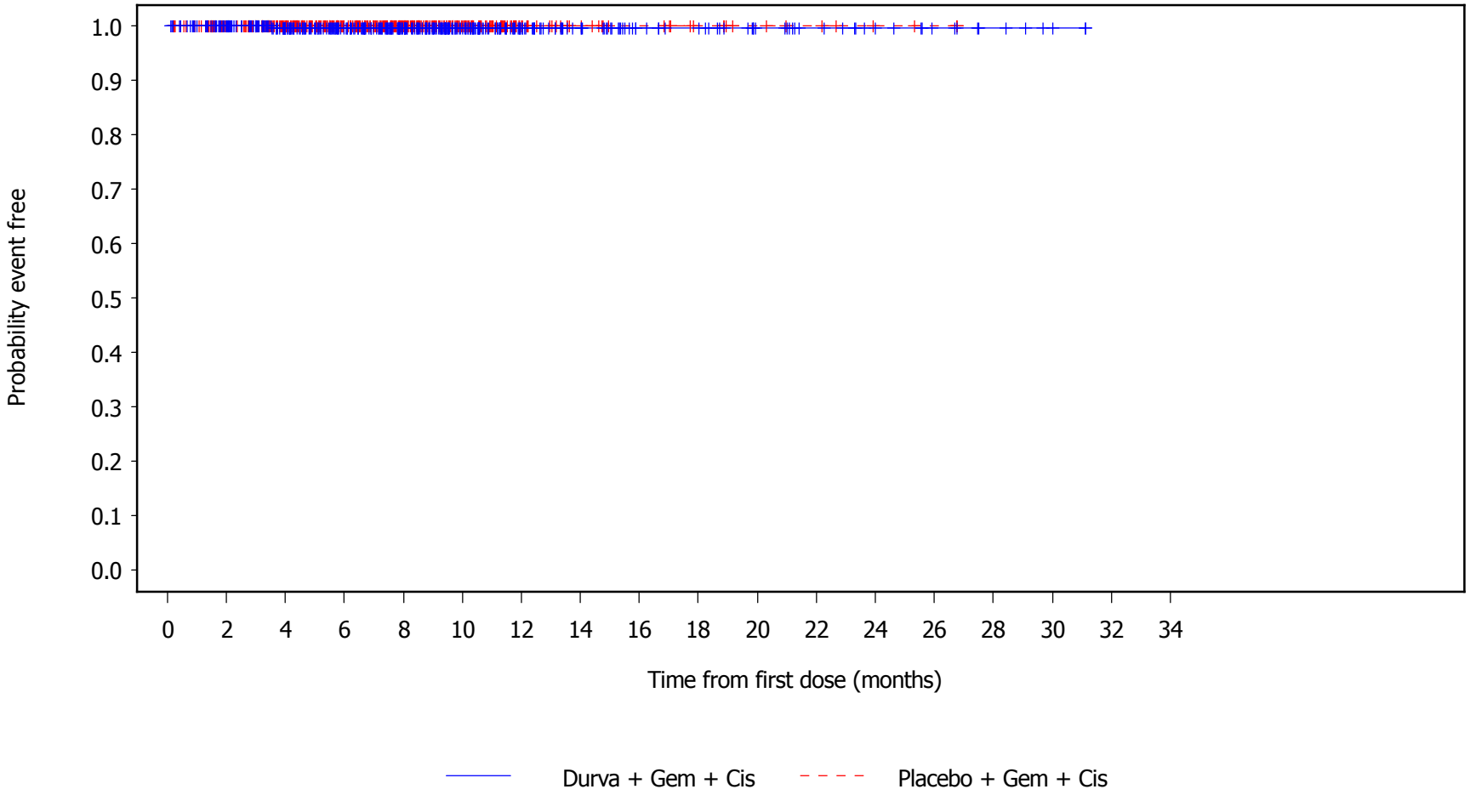
Figure 3.3.171 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Immune-mediated hypothyroidism
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	263	197	129	78	56	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

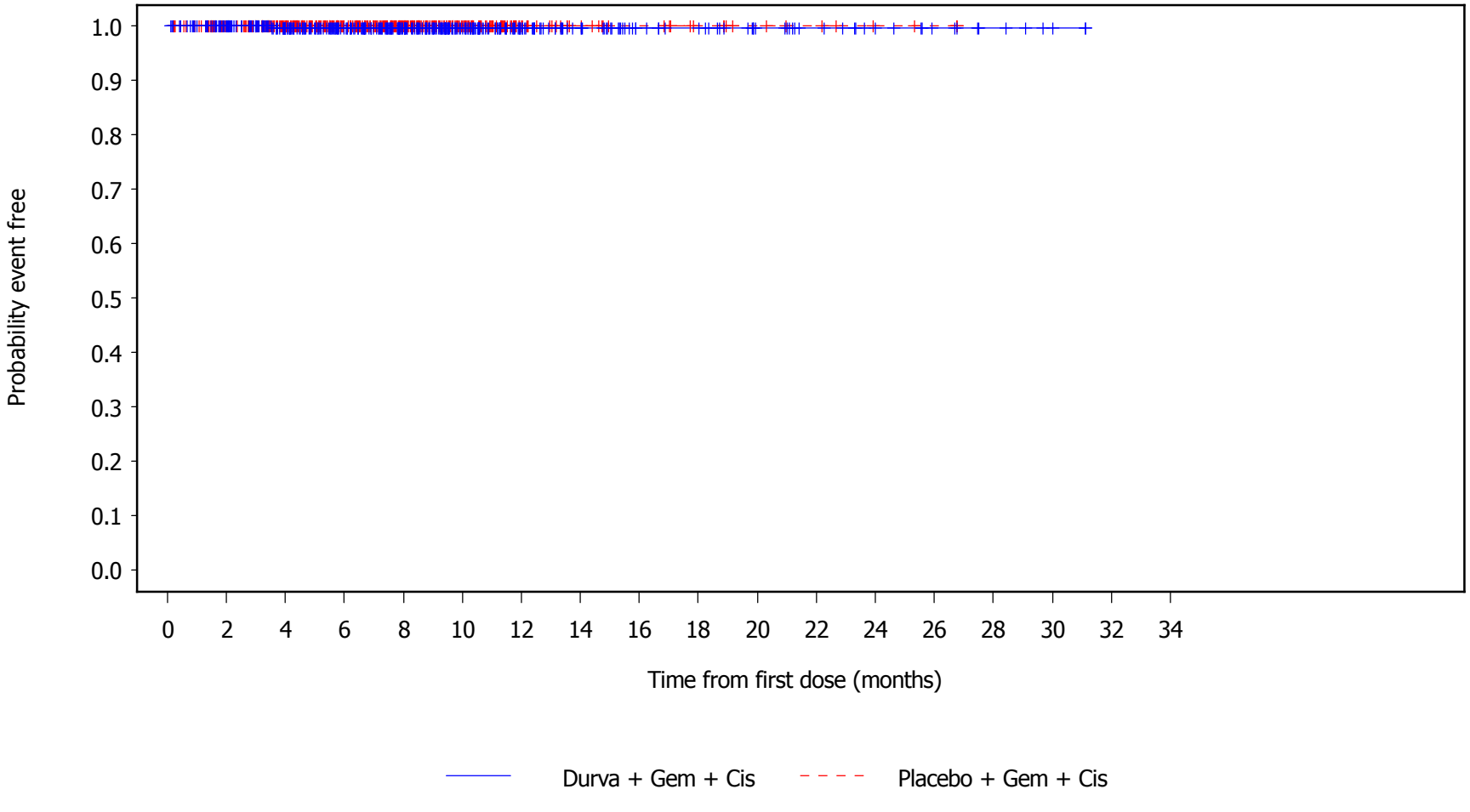
Figure 3.3.172 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Thyroiditis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	197	130	79	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

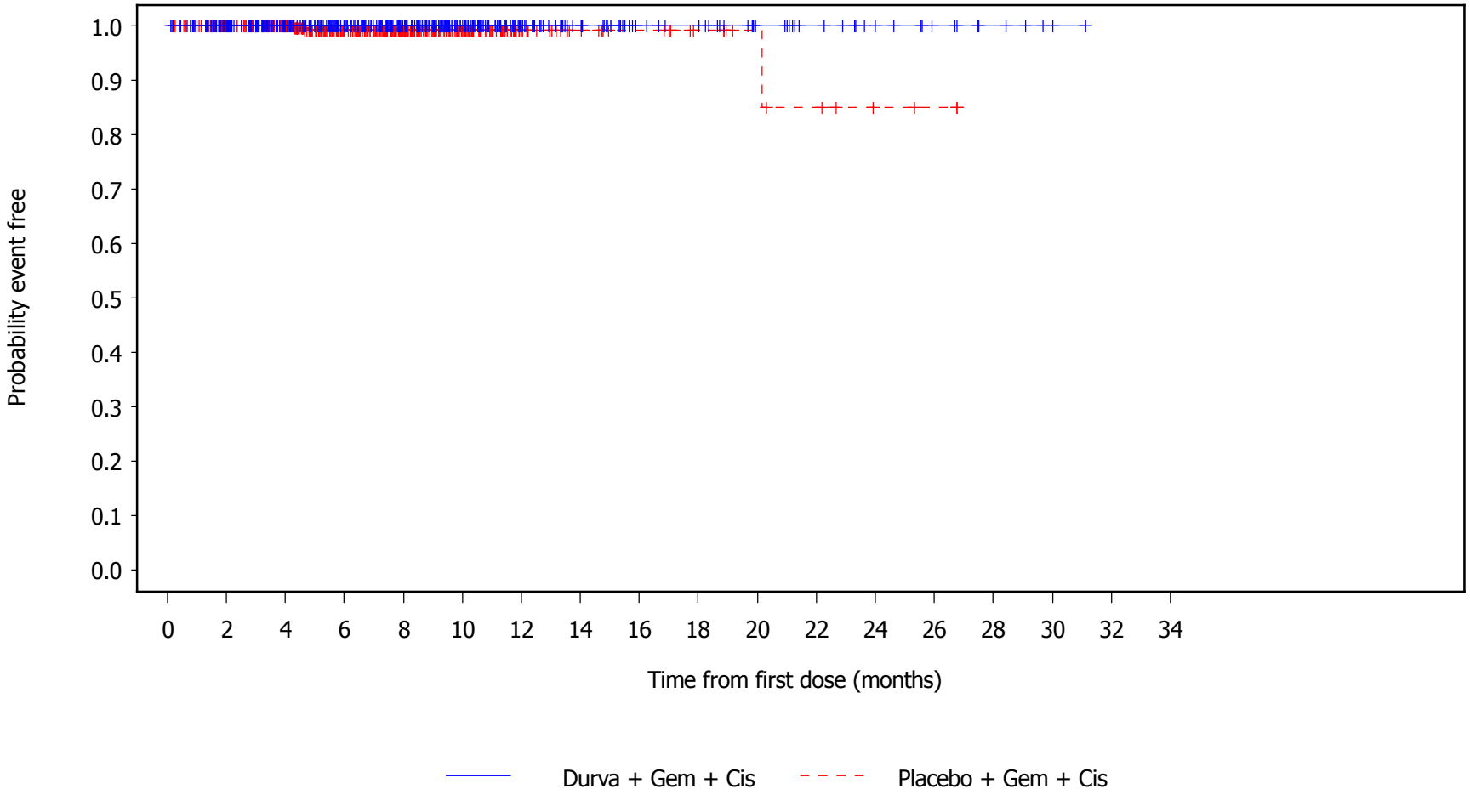
Figure 3.3.173 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Autoimmune thyroiditis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	197	130	79	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

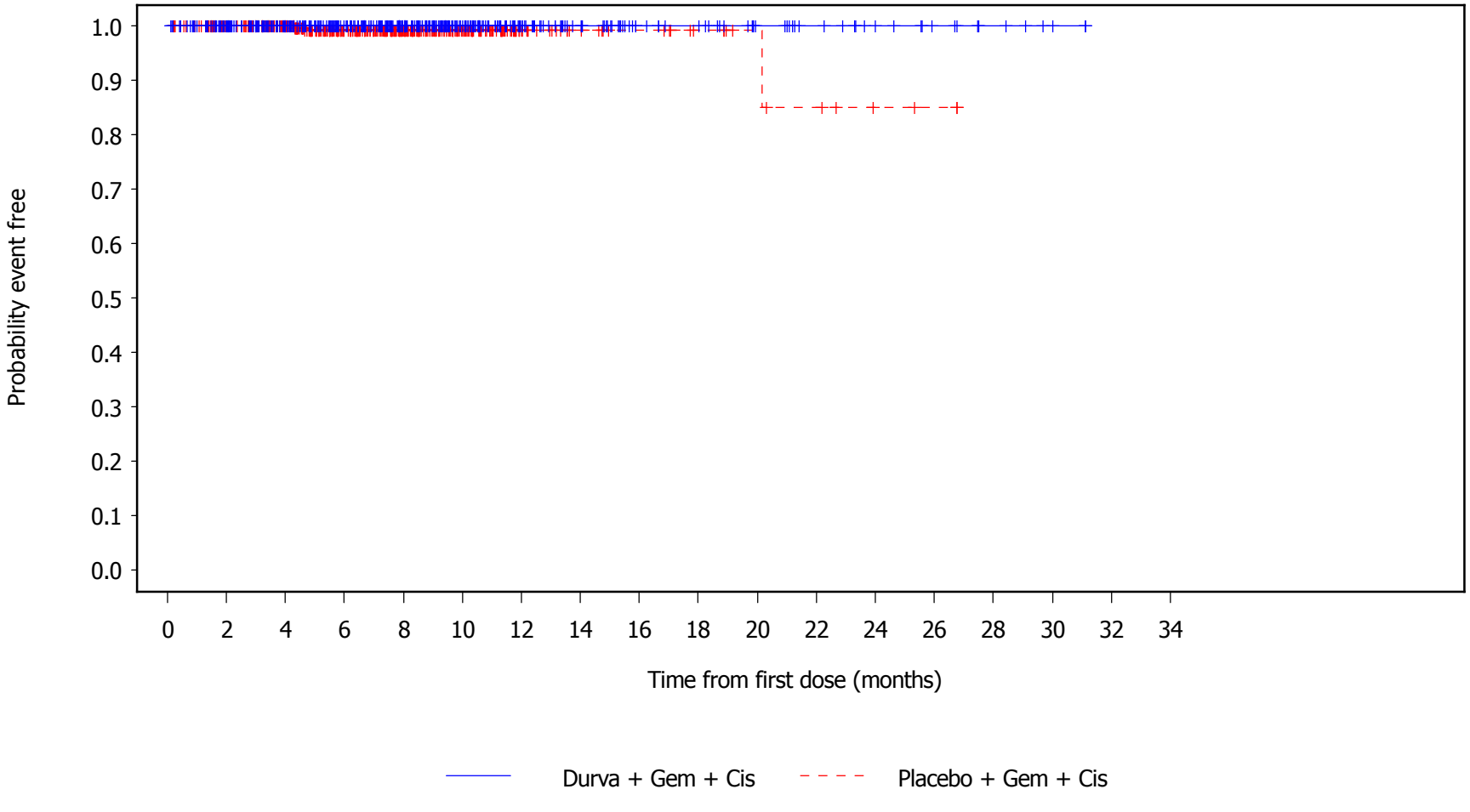
Figure 3.3.174 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Renal events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	230	157	88	33	21	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

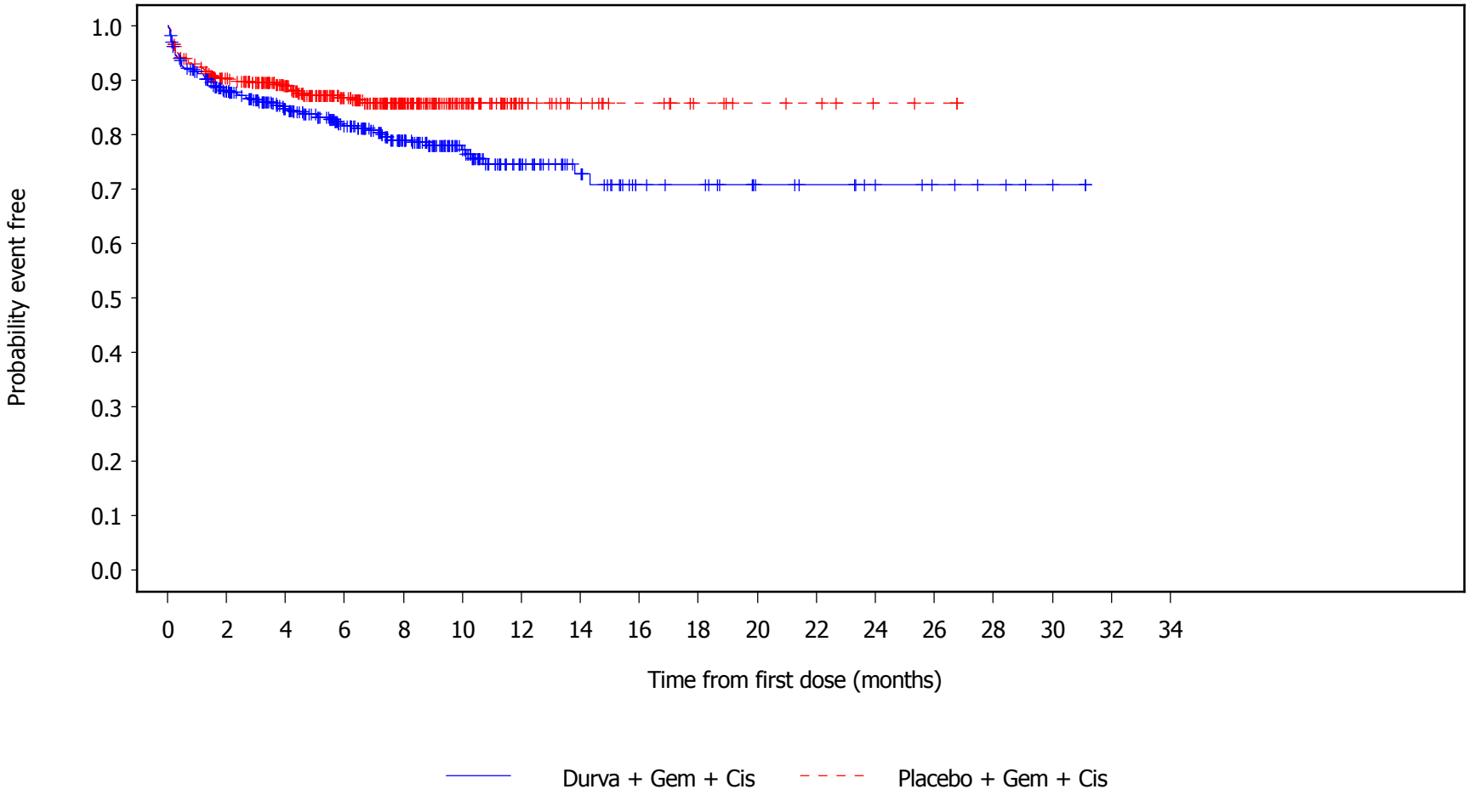
Figure 3.3.175 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Nephritis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	230	157	88	33	21	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

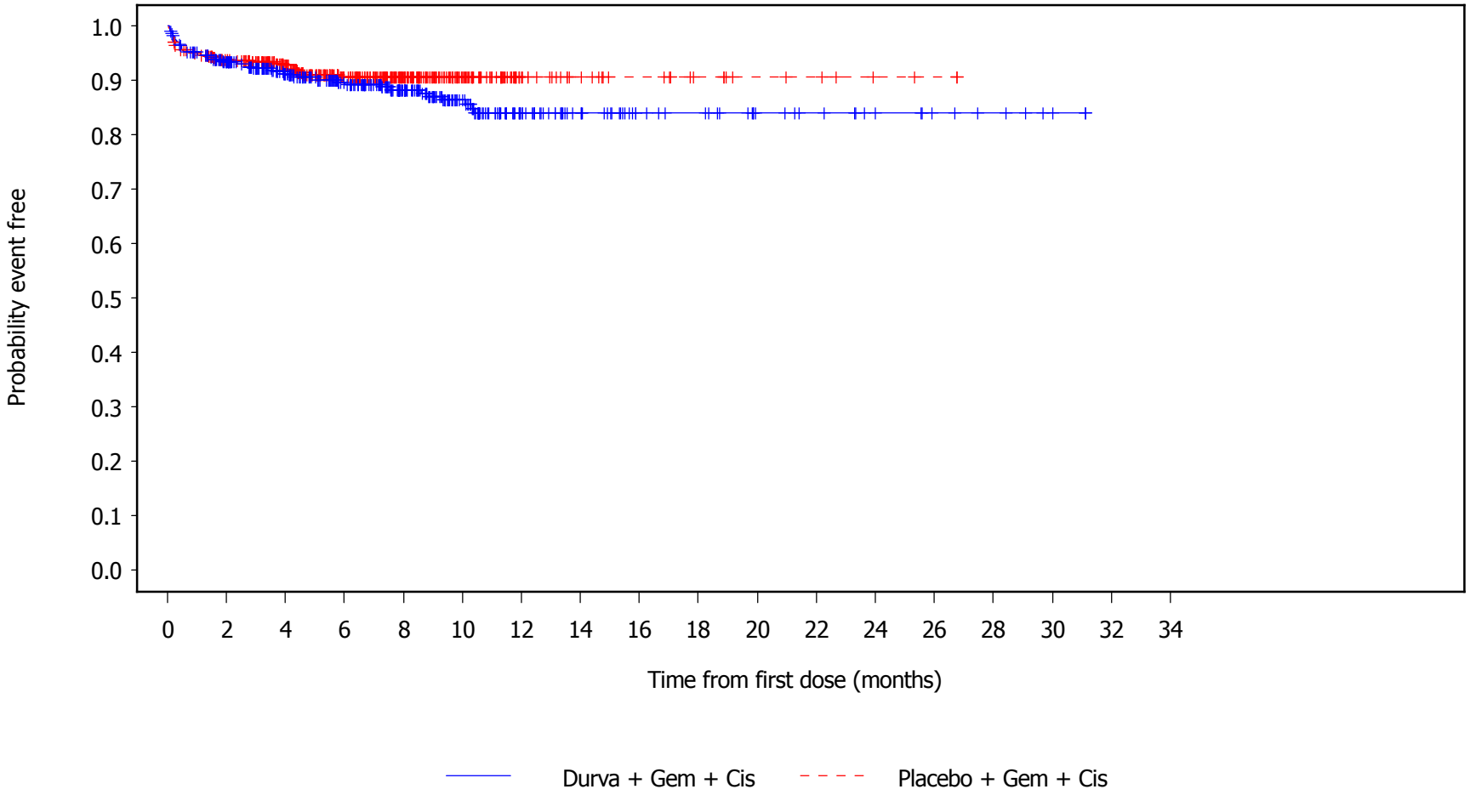
Figure 3.3.176 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Dermatitis/Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	328	265	217	156	103	59	39	24	22	14	12	9	6	4	2	0	0	Durva + Gem + Cis
403	336	277	198	130	72	31	20	14	9	6	5	2	1	0	0	0	0	Placebo + Gem + Cis

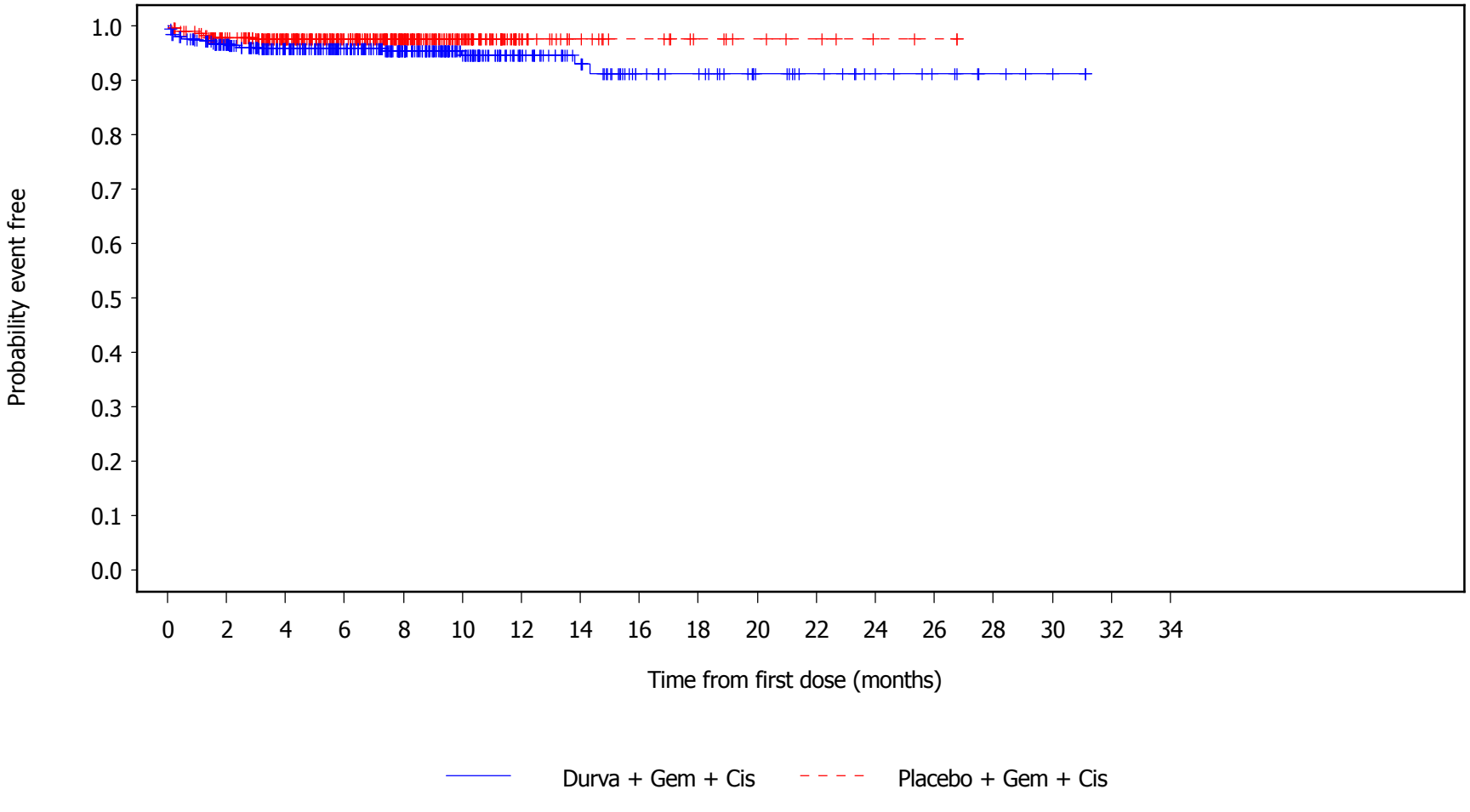
Figure 3.3.177 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	348	287	236	172	114	65	45	30	27	18	15	11	7	5	2	0	0	Durva + Gem + Cis
403	350	291	208	141	78	32	21	15	10	6	5	2	1	0	0	0	0	Placebo + Gem + Cis

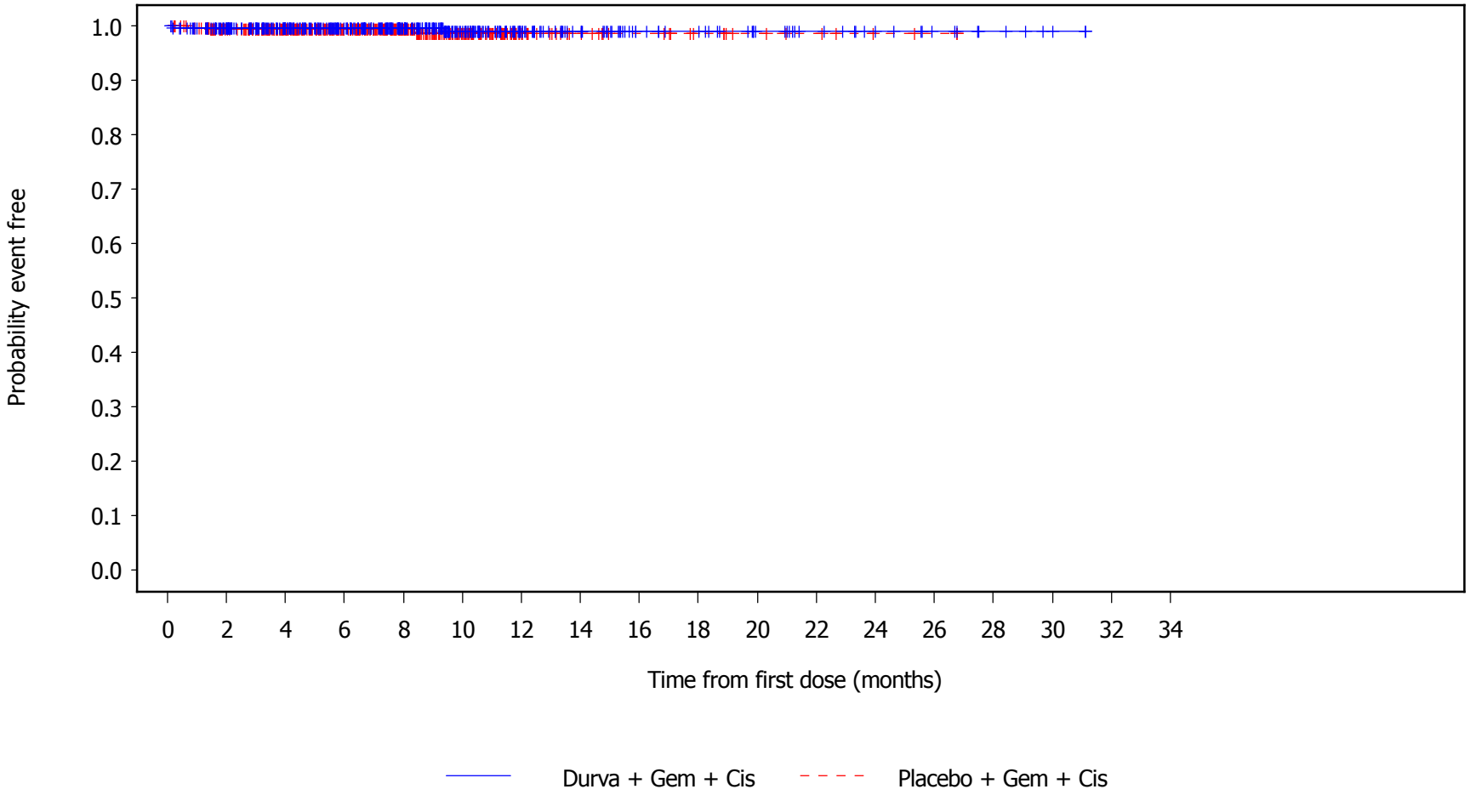
Figure 3.3.178 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Rash maculo-papular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	361	301	254	189	126	77	56	37	33	22	17	12	8	4	2	0	0	Durva + Gem + Cis
403	363	305	226	154	86	33	21	15	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

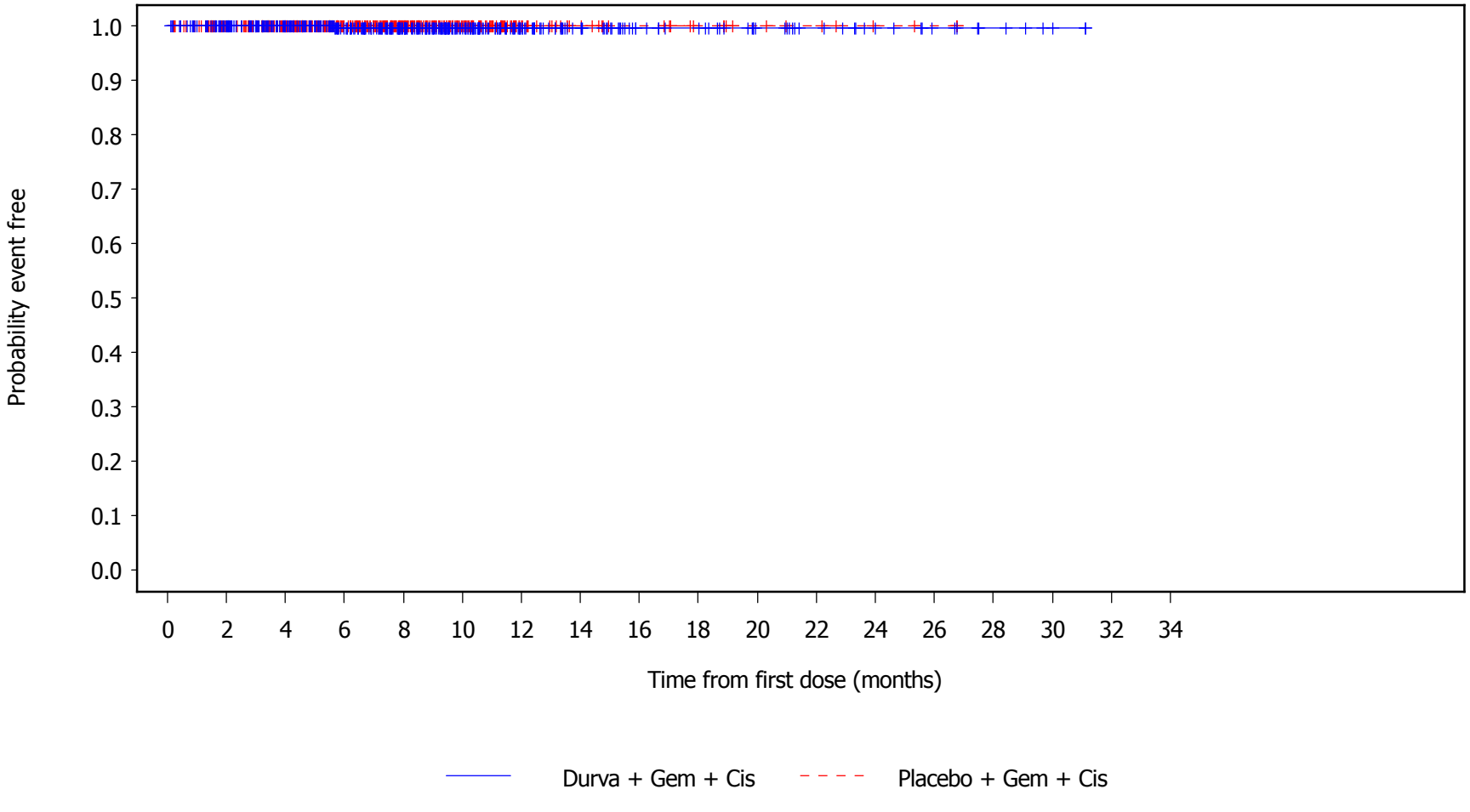
Figure 3.3.179 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Rash pruritic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	263	198	130	79	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	311	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

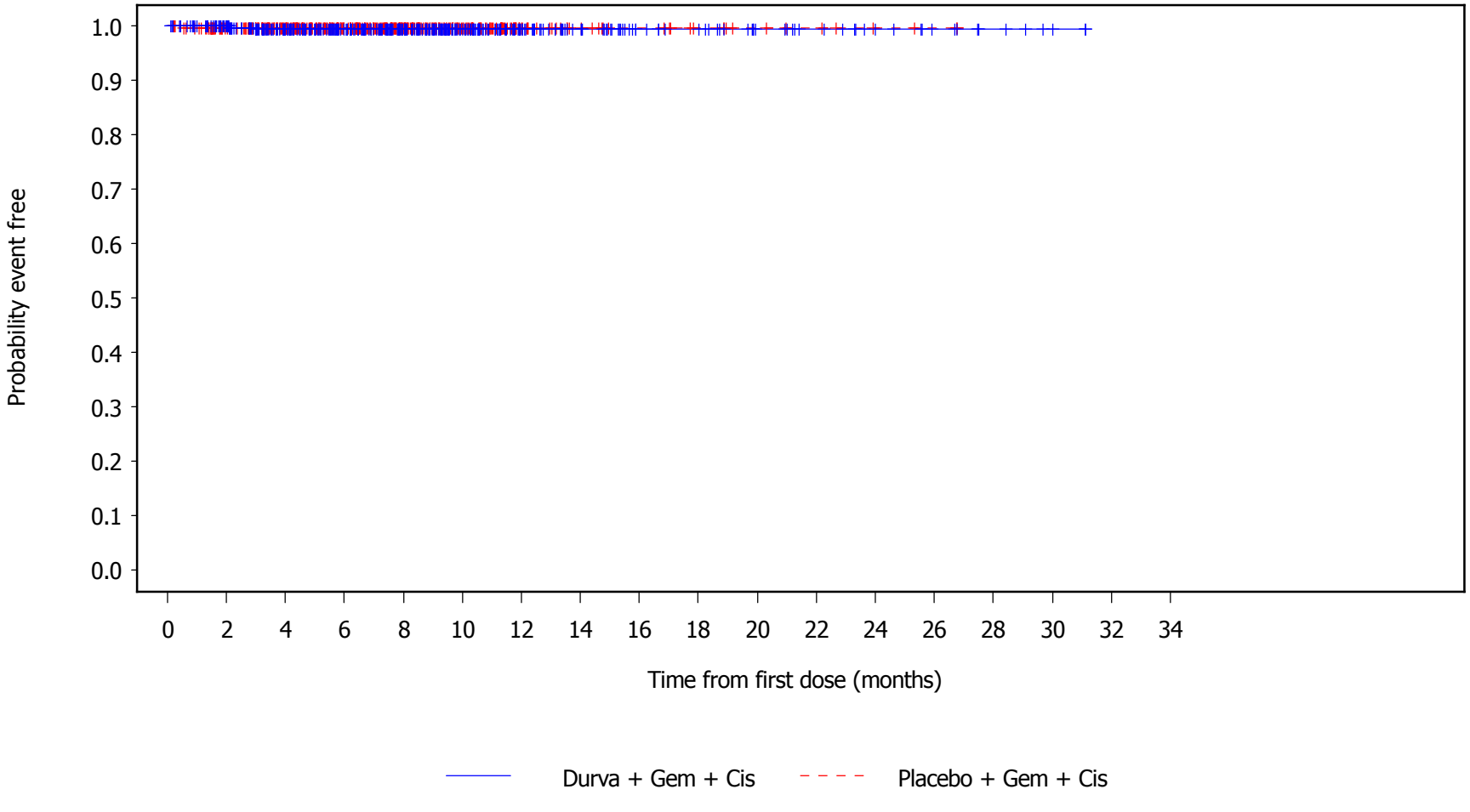
Figure 3.3.180 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Rash morbilliform
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	263	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

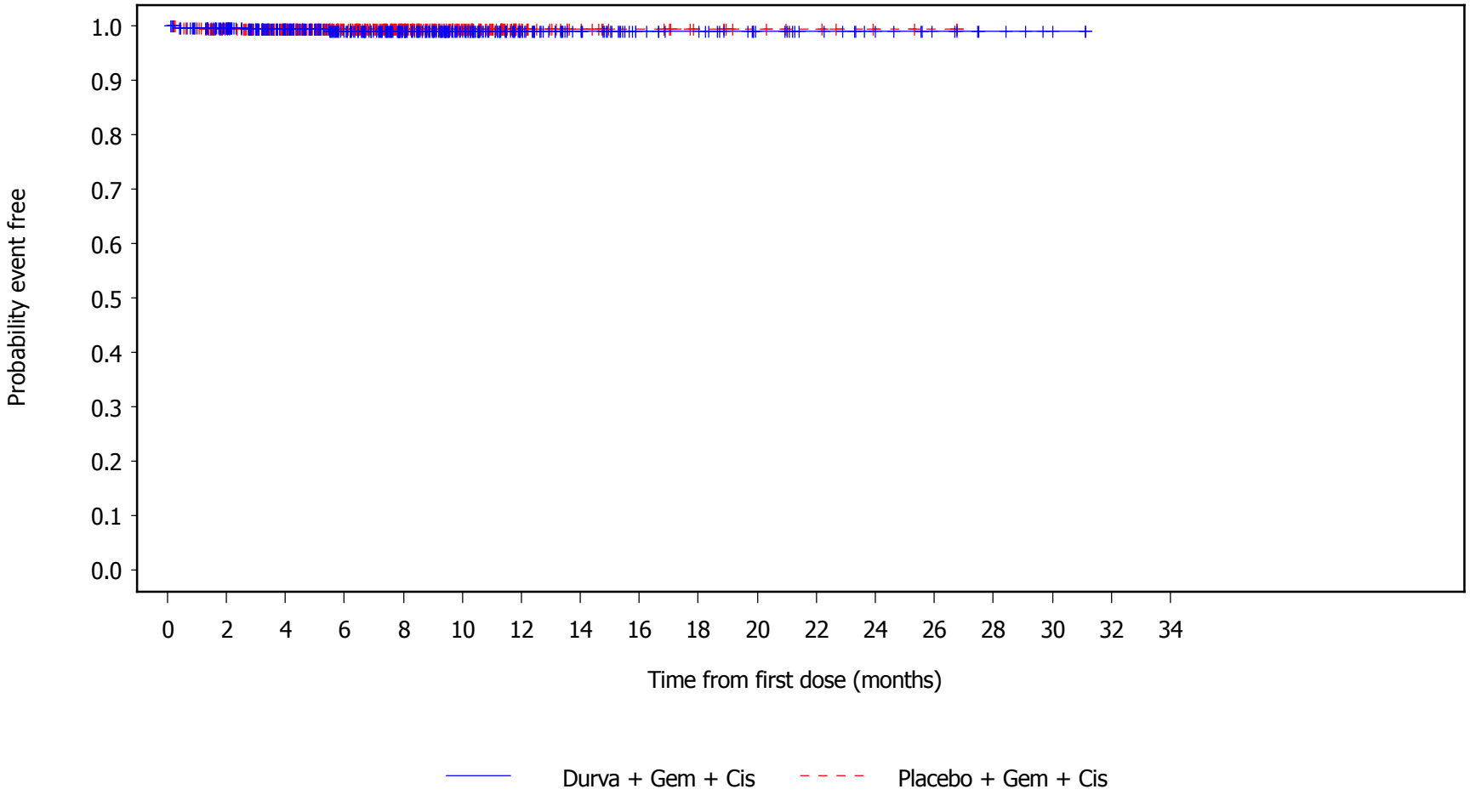
Figure 3.3.181 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Rash papular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	313	262	196	129	79	57	39	35	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

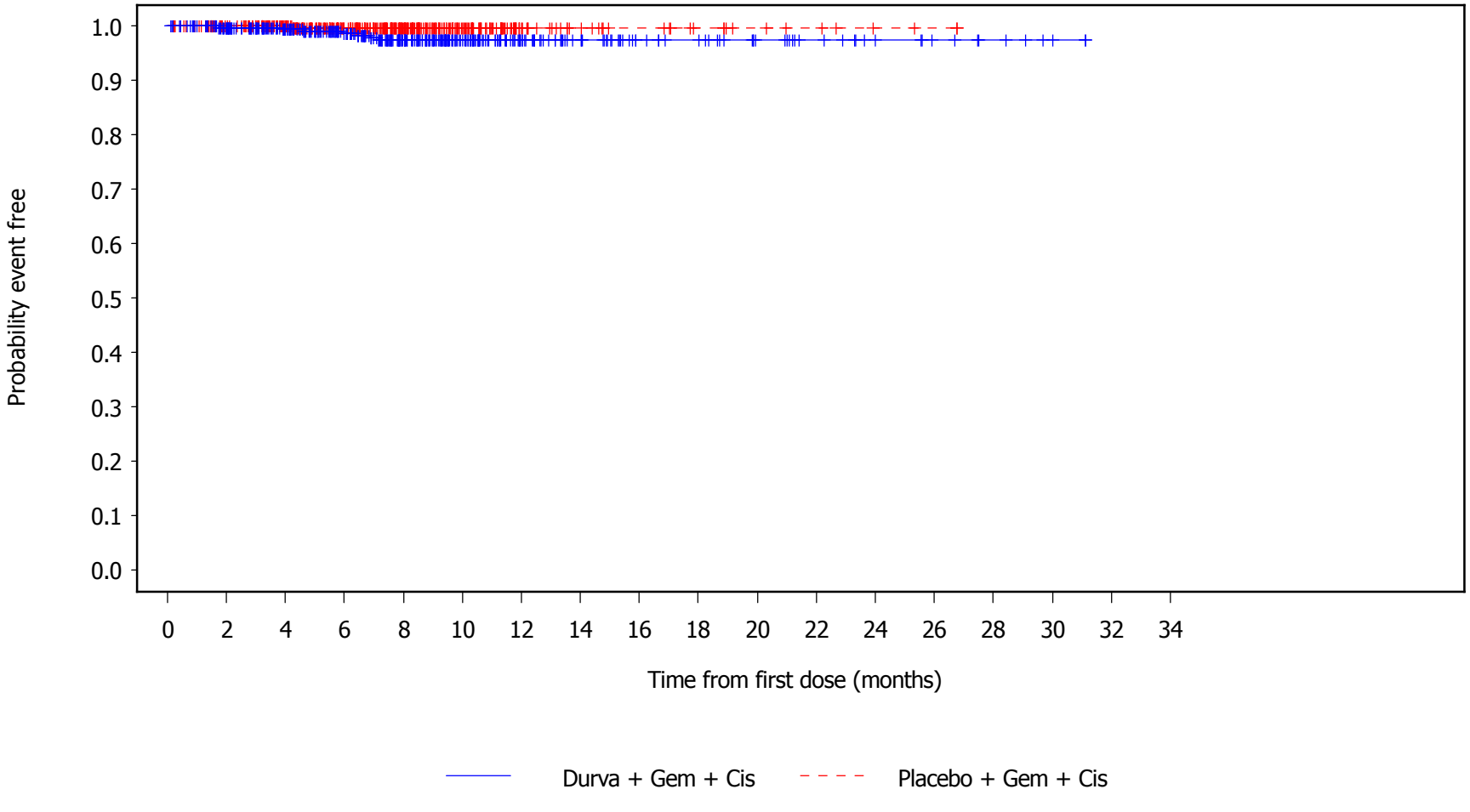
Figure 3.3.182 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Rash pustular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	313	262	196	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	311	231	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

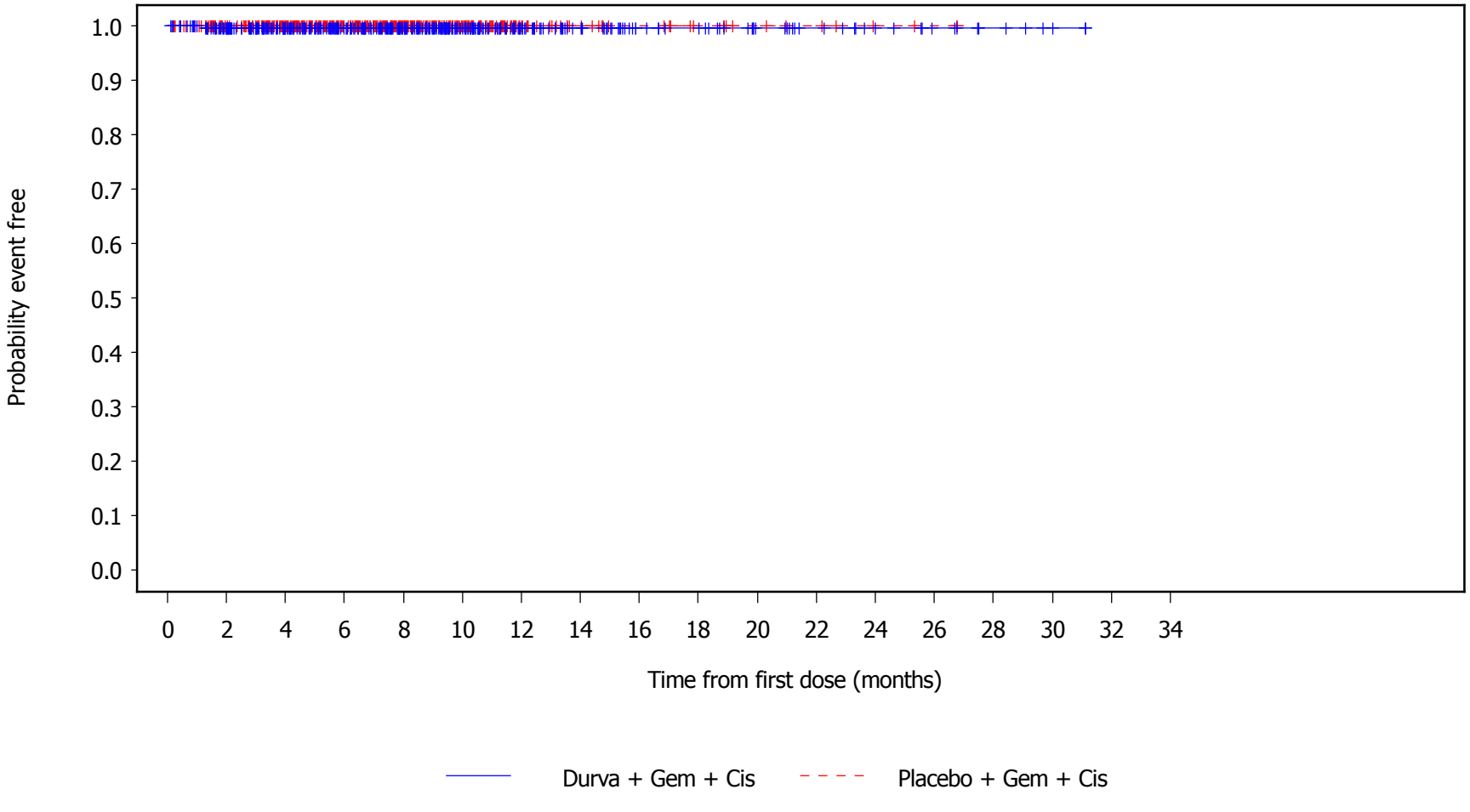
Figure 3.3.183 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Dermatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	313	260	192	125	76	54	37	33	23	17	12	8	5	2	0	0	Durva + Gem + Cis
403	371	313	231	158	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

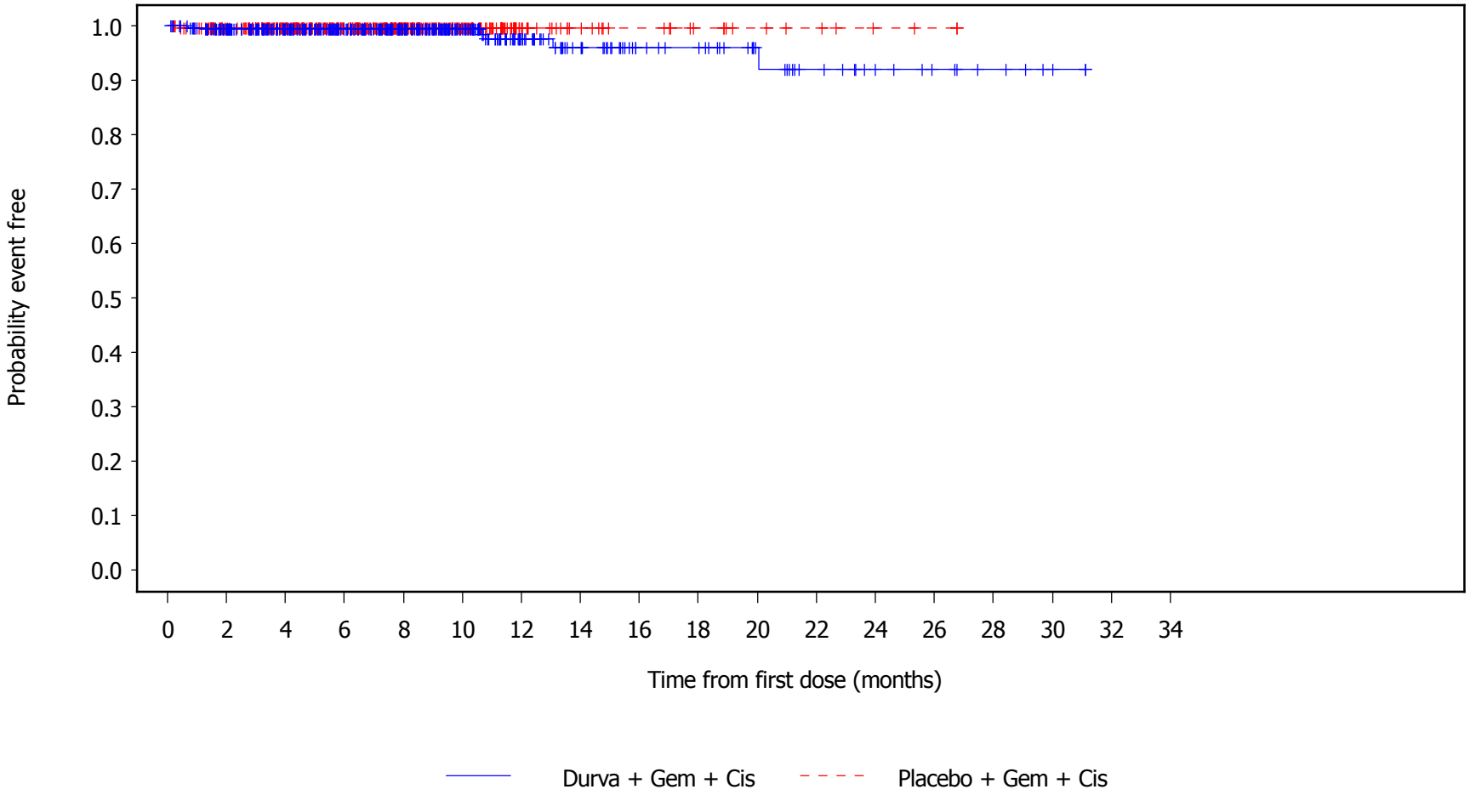
Figure 3.3.184 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Dermatitis bullous
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

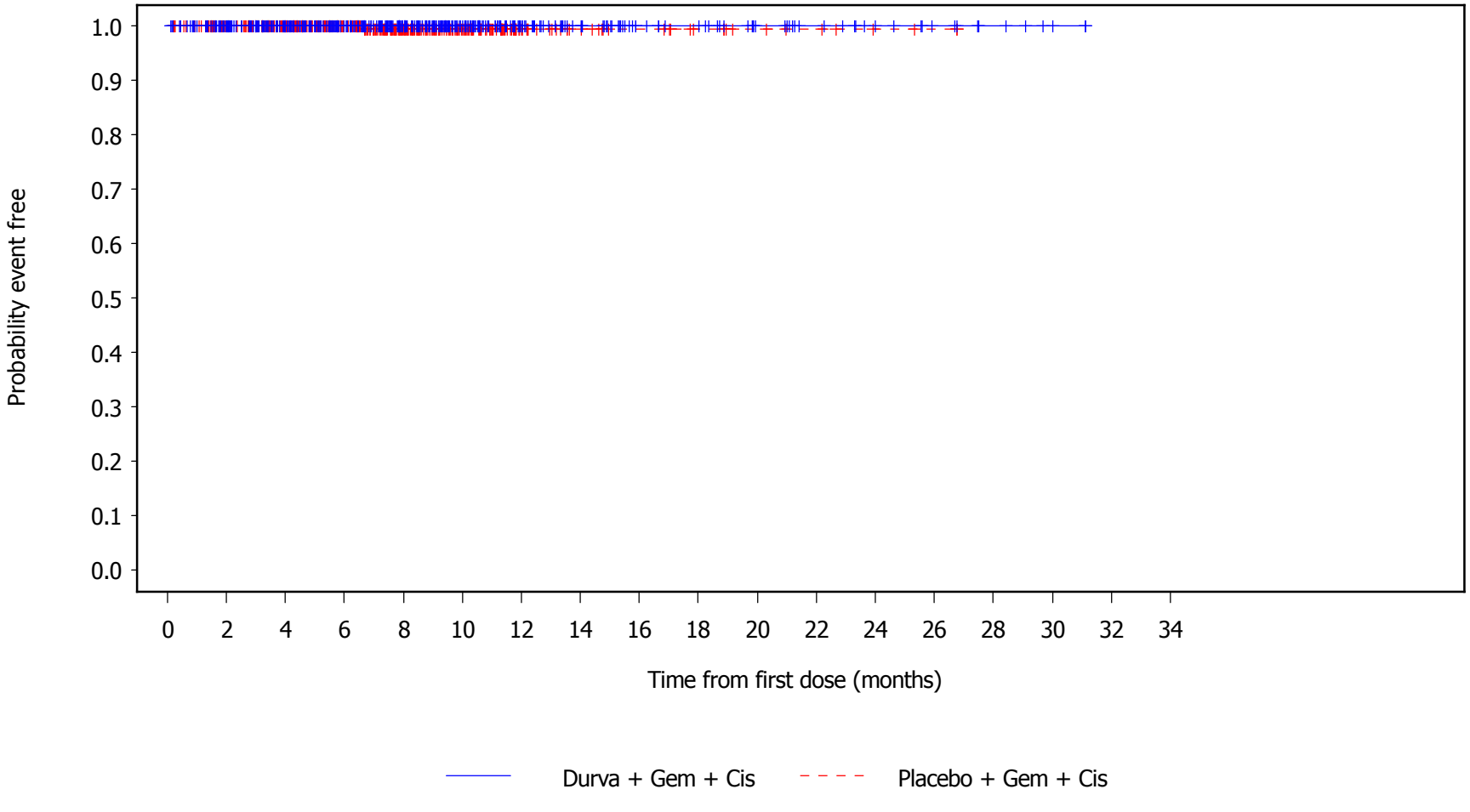
Figure 3.3.185 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Eczema
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	314	263	198	131	78	55	38	35	24	17	12	8	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

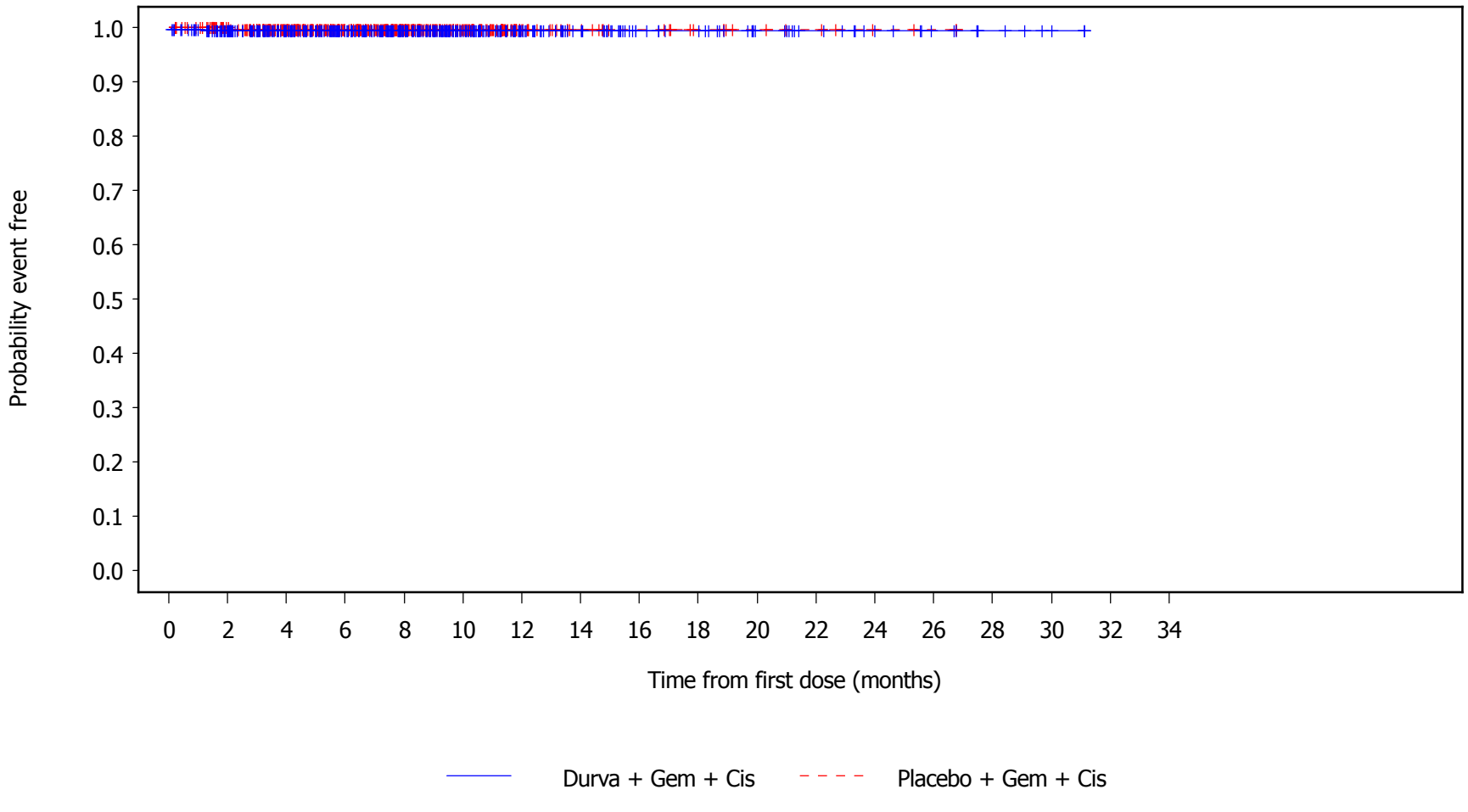
Figure 3.3.186 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Rash erythematous
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

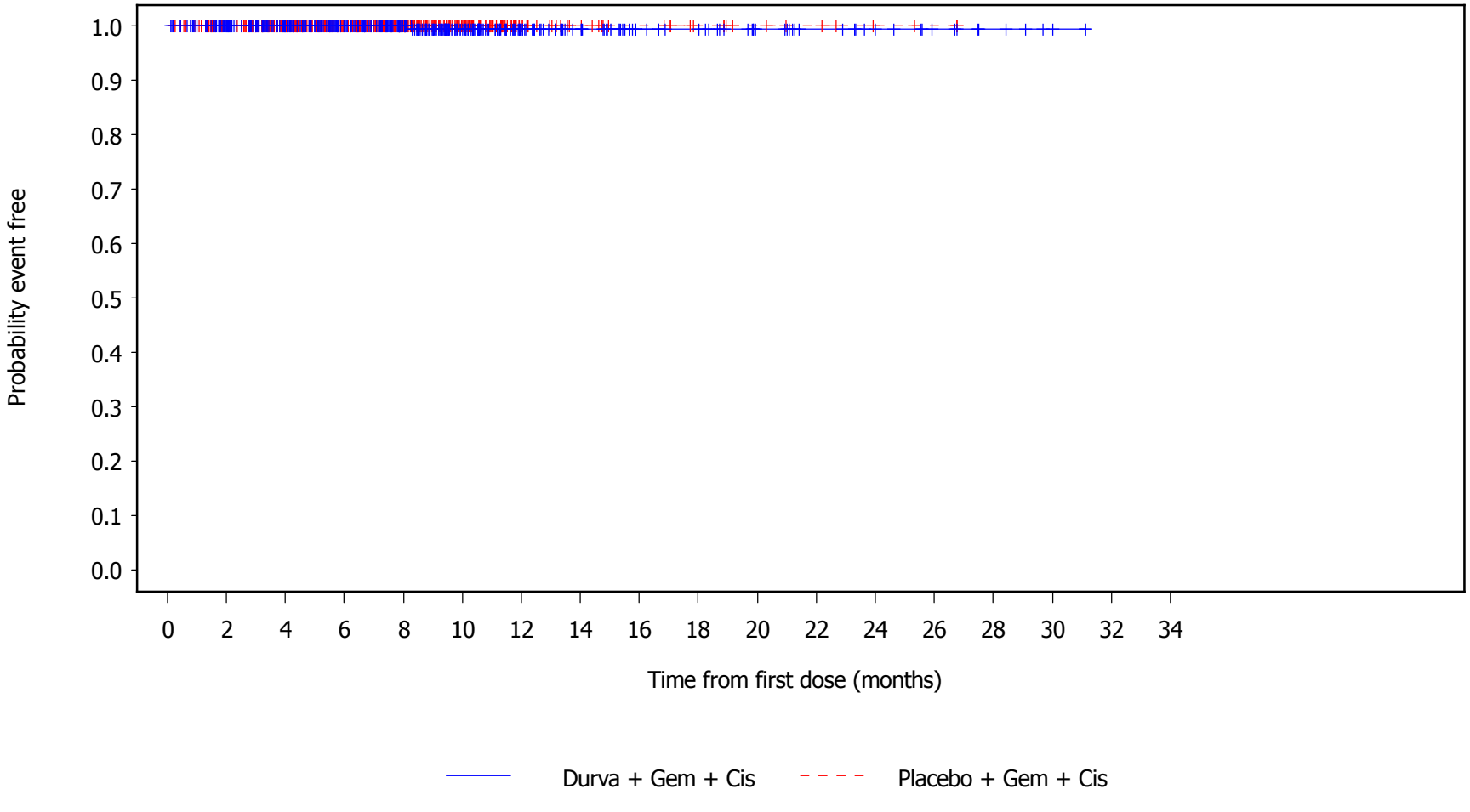
Figure 3.3.187 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Rash macular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	313	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	231	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

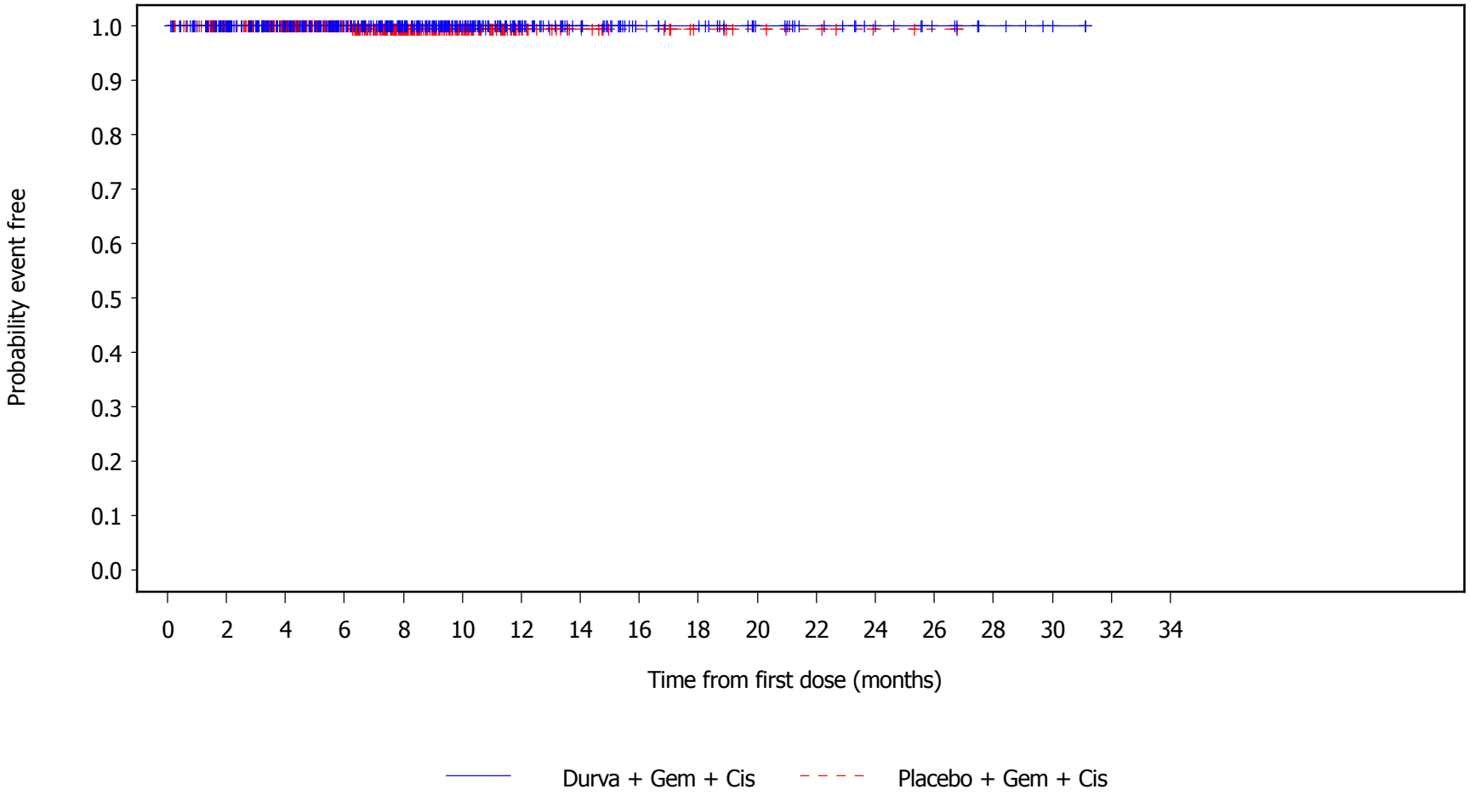
Figure 3.3.188 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Dermatitis psoriasiform
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	130	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

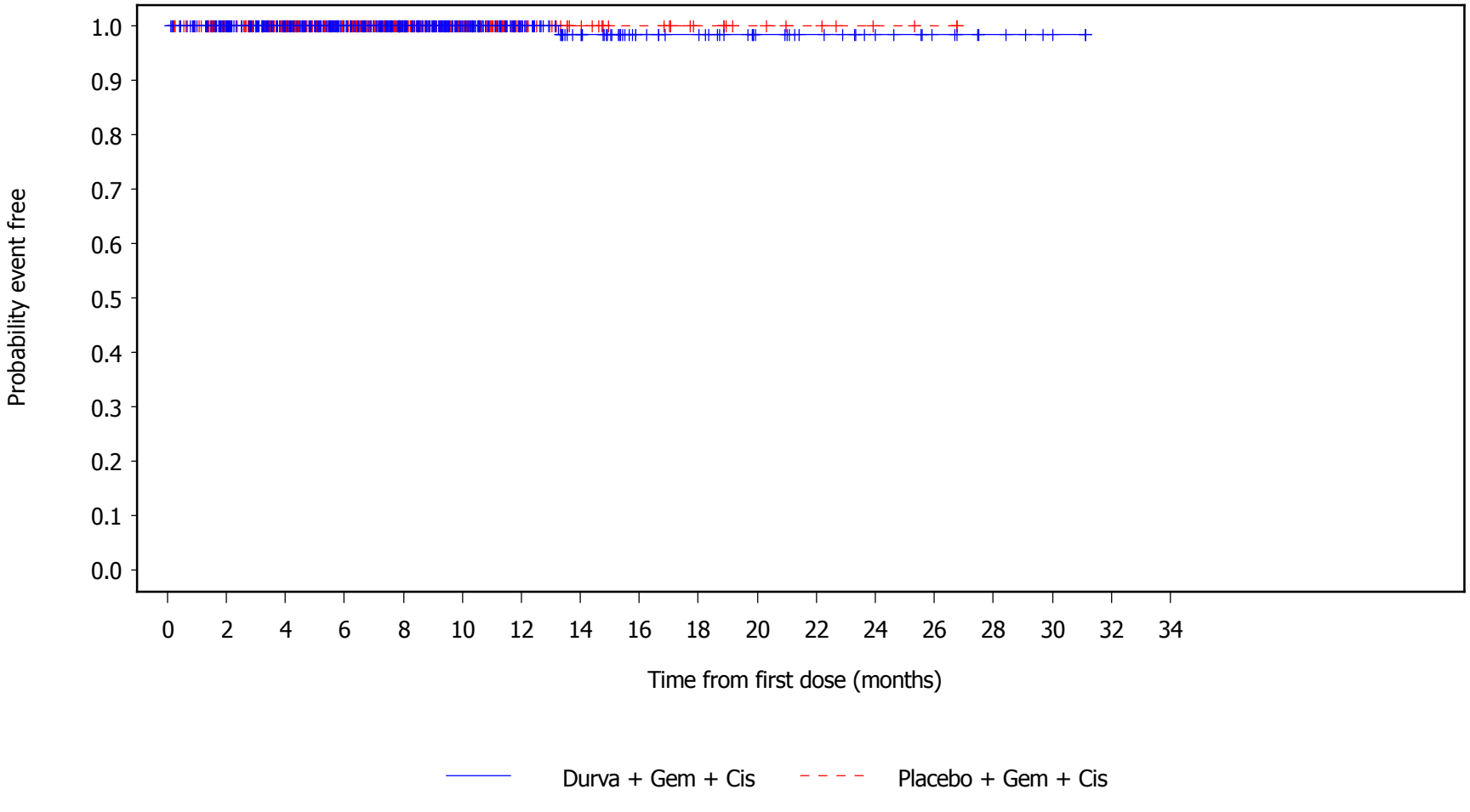
Figure 3.3.189 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Psoriasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	158	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

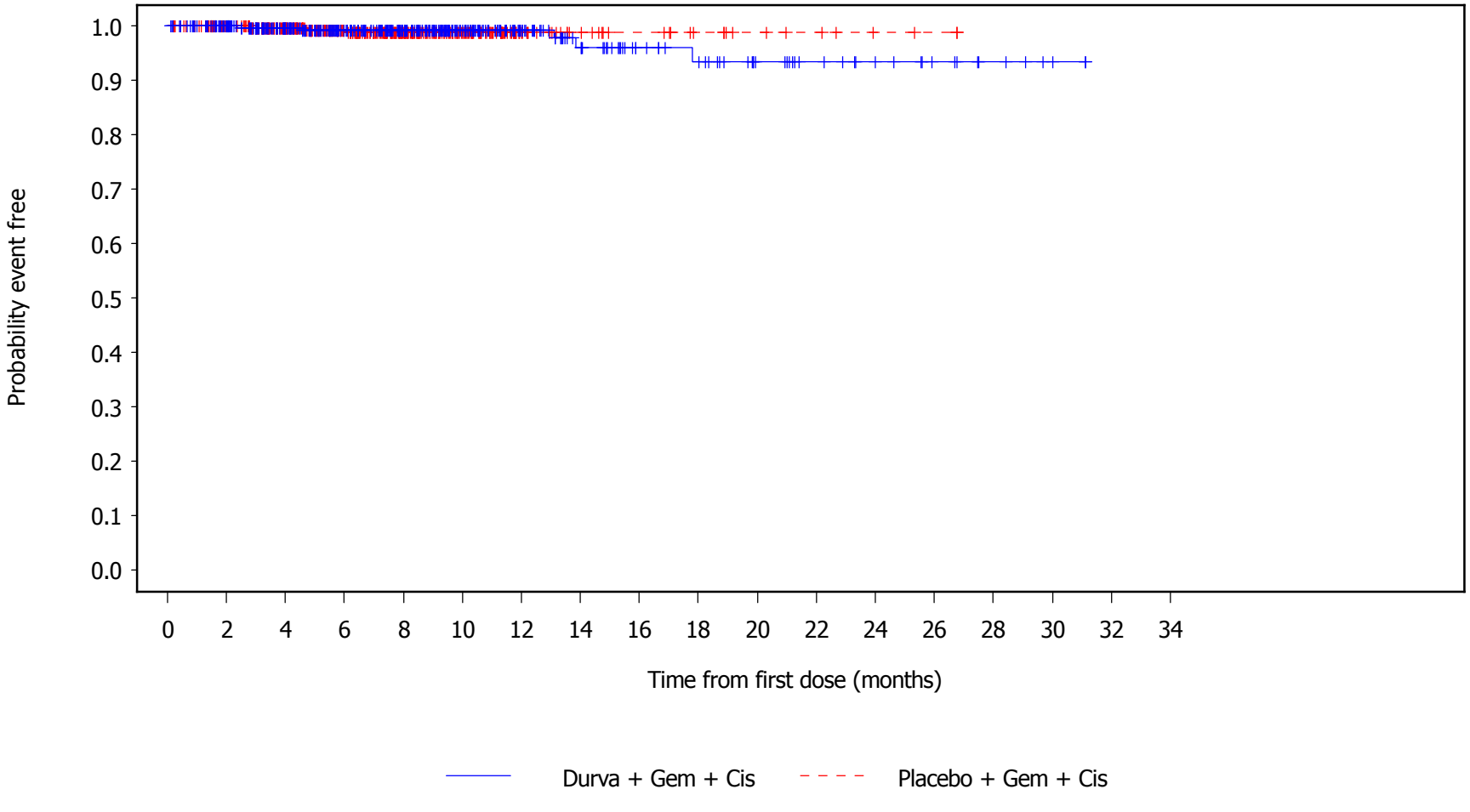
Figure 3.3.190 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Urticarial dermatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	57	39	35	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

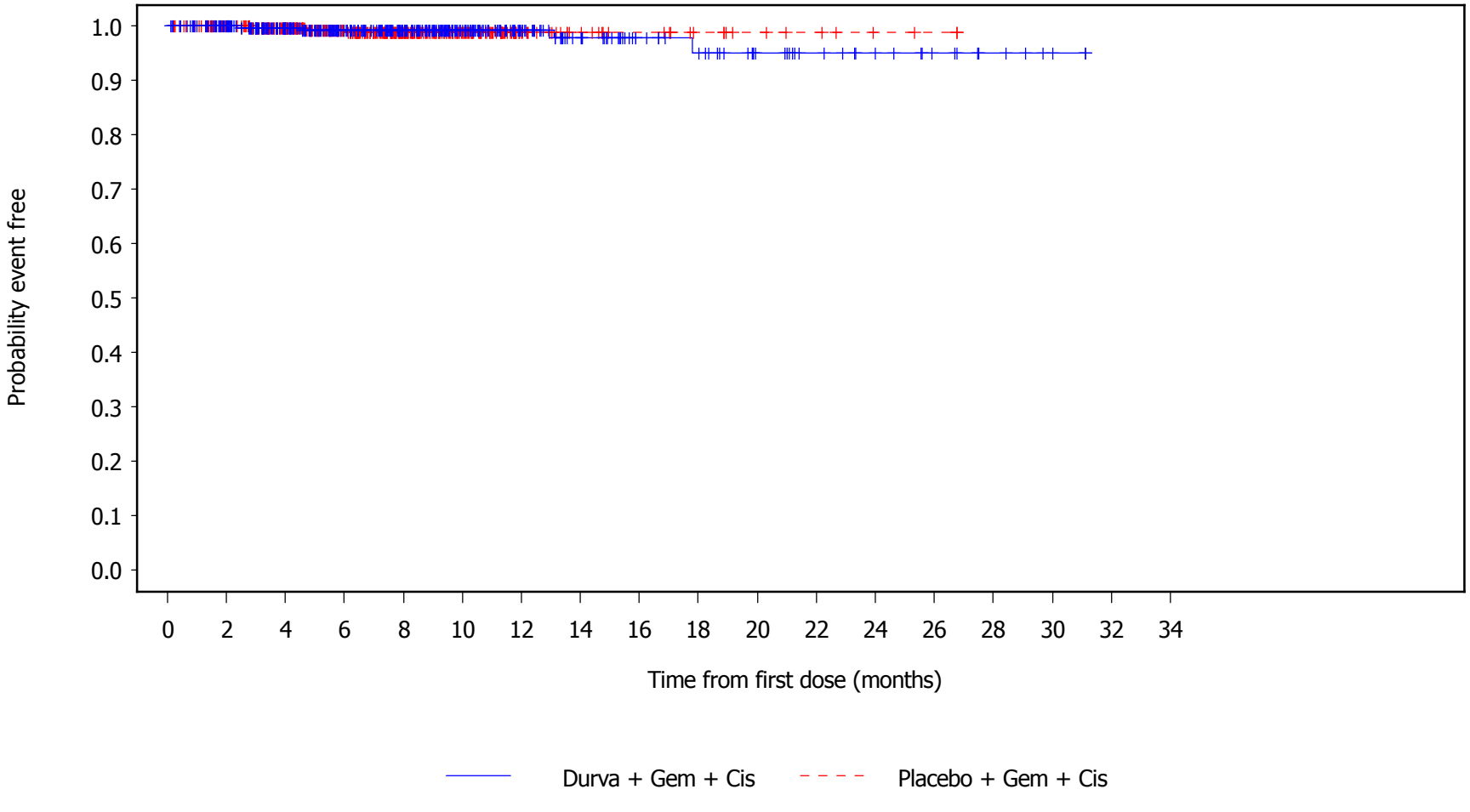
Figure 3.3.191 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Pancreatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	262	198	131	80	56	40	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	231	157	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

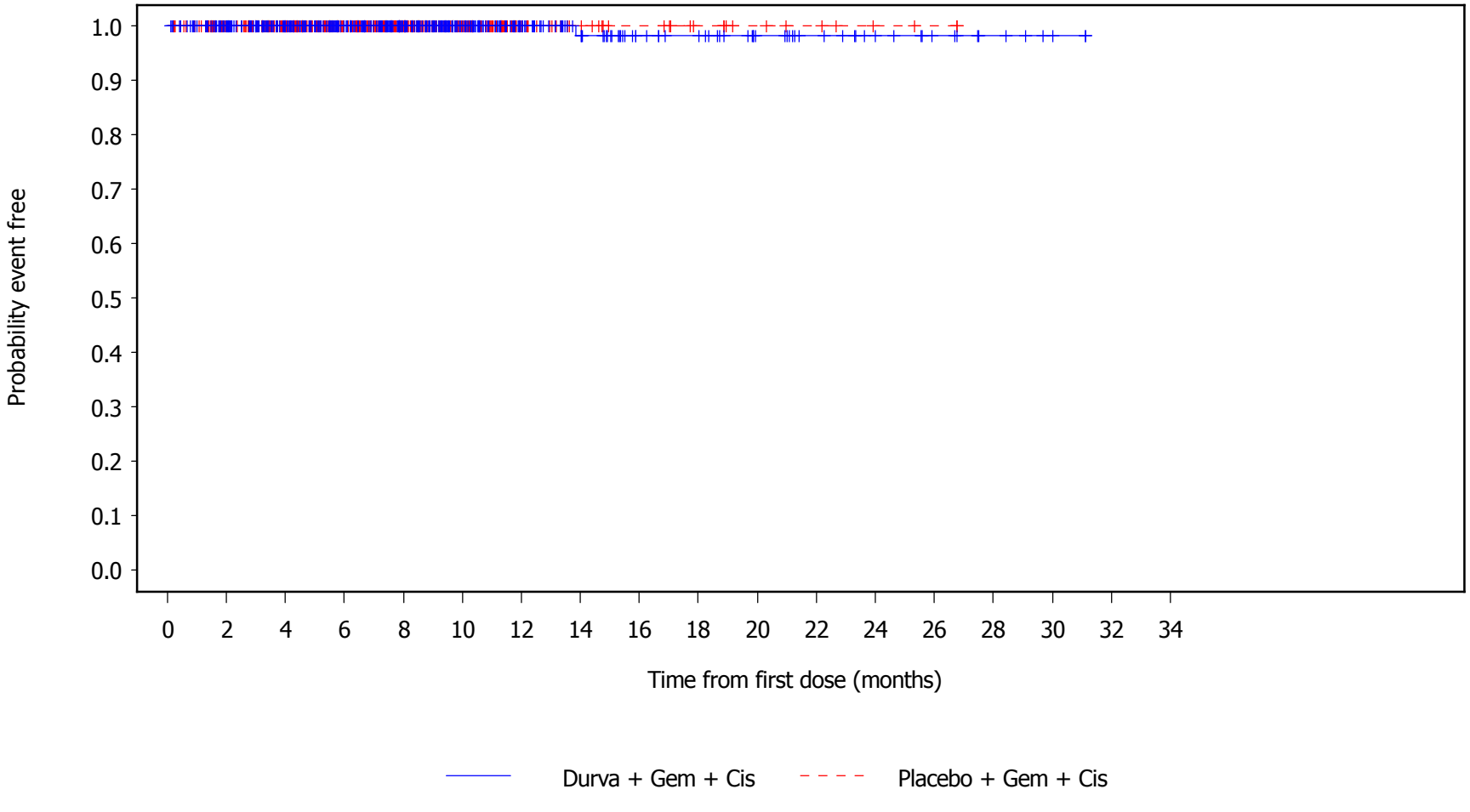
Figure 3.3.192 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Pancreatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	262	198	131	80	57	40	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	231	157	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

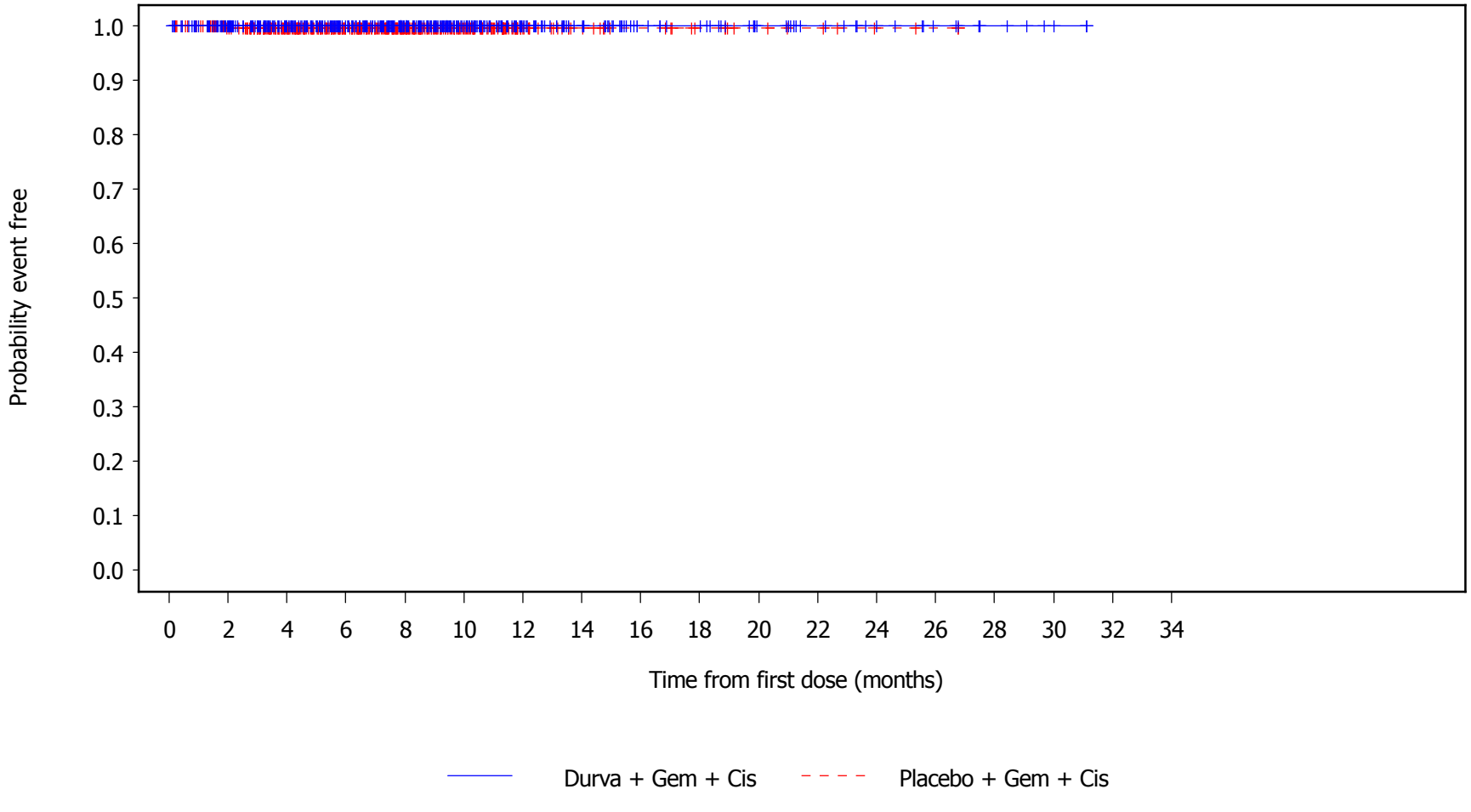
Figure 3.3.193 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Pancreatitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

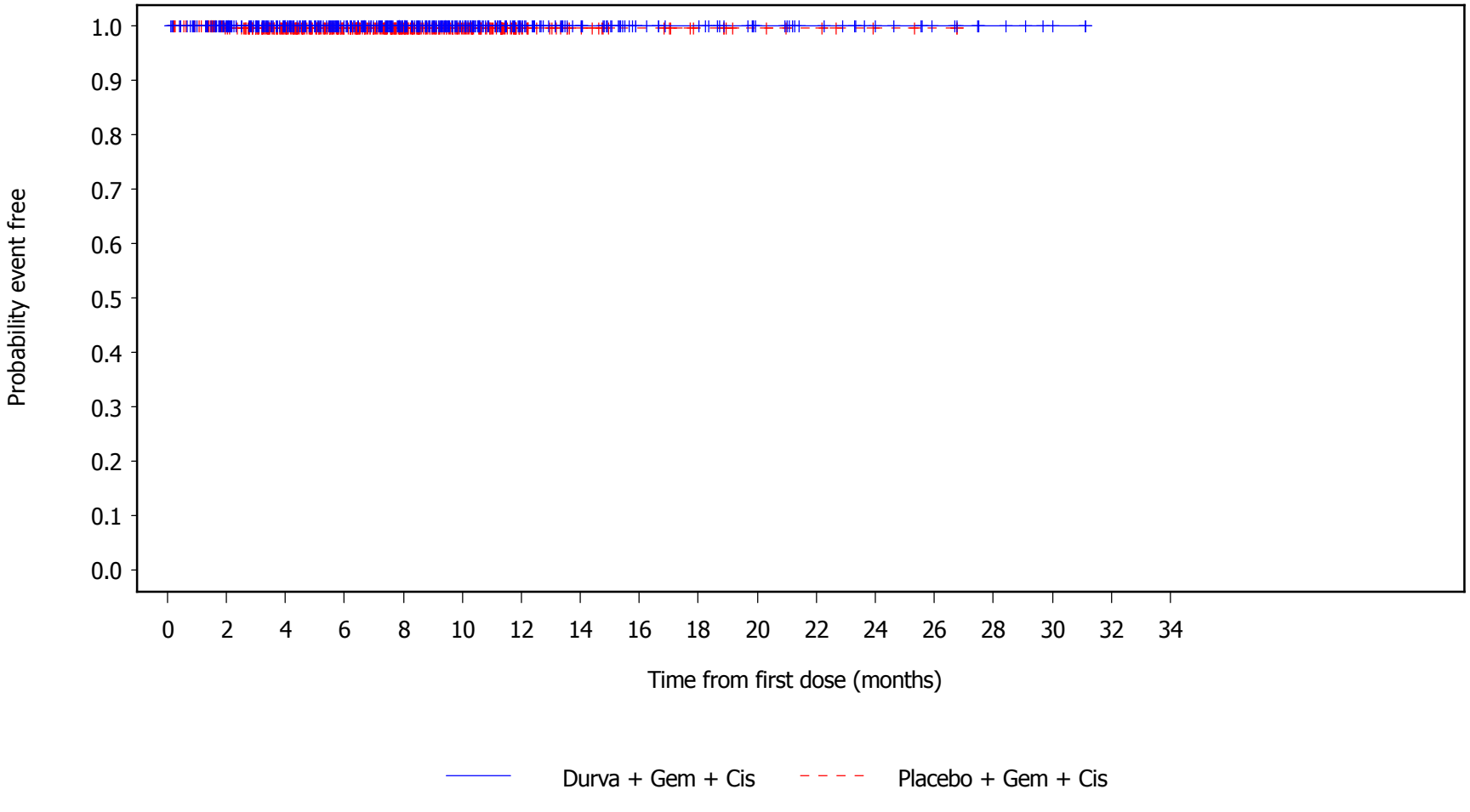
Figure 3.3.194 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Myositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

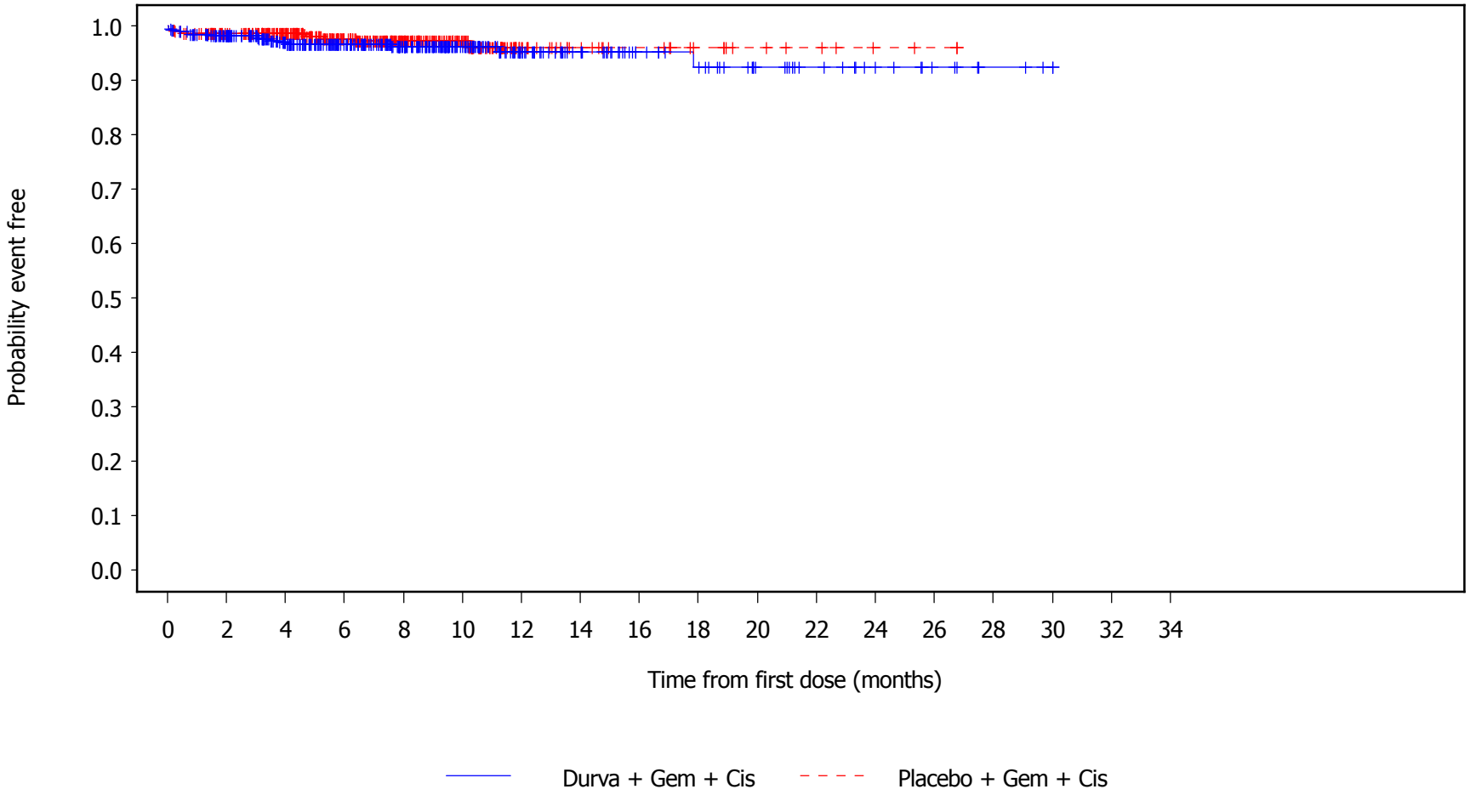
Figure 3.3.195 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Polymyositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

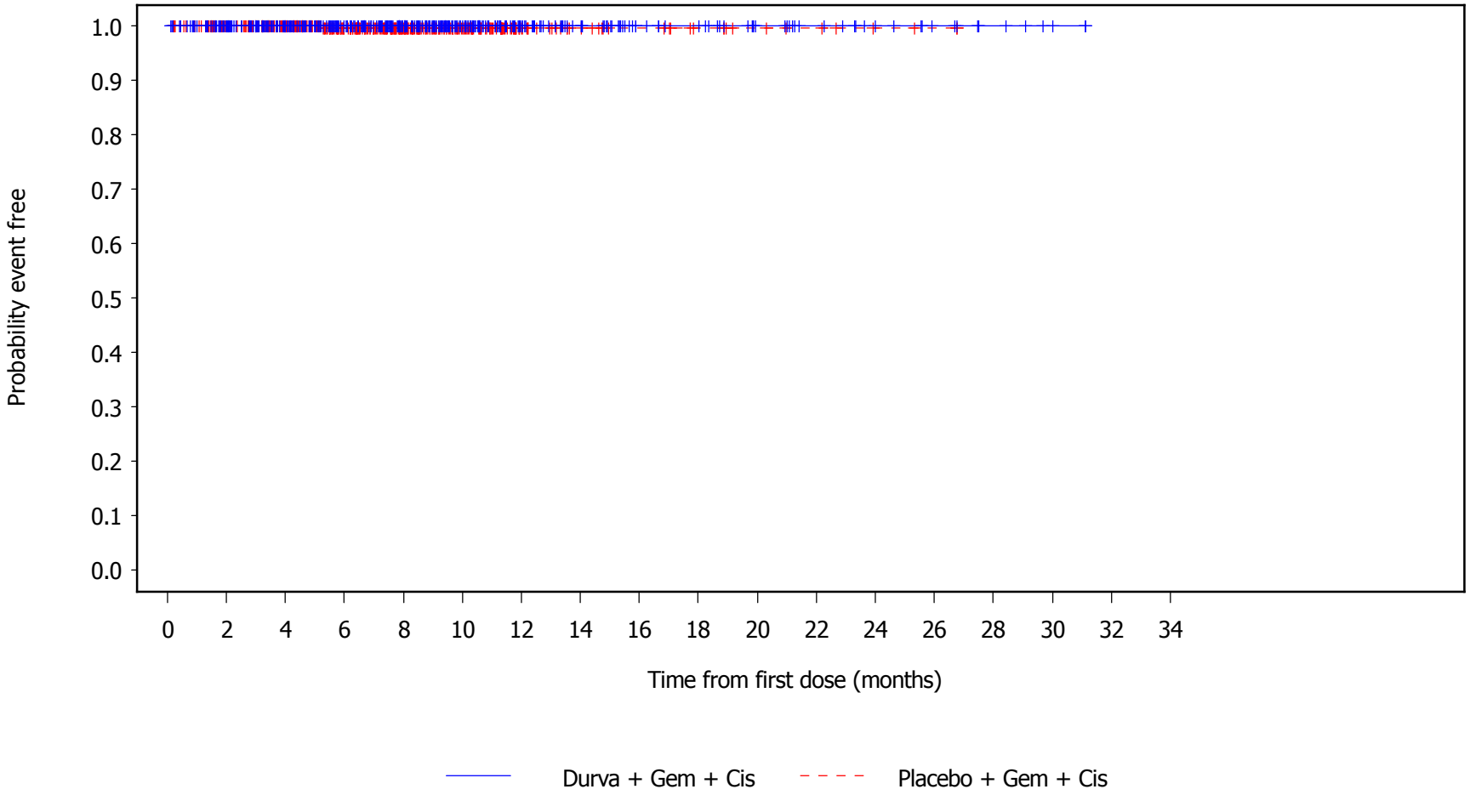
Figure 3.3.196 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Infusion/hypersensitivity reactions
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	366	306	254	191	126	78	56	39	34	23	17	12	7	3	1	0	0	Durva + Gem + Cis
403	367	310	226	154	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

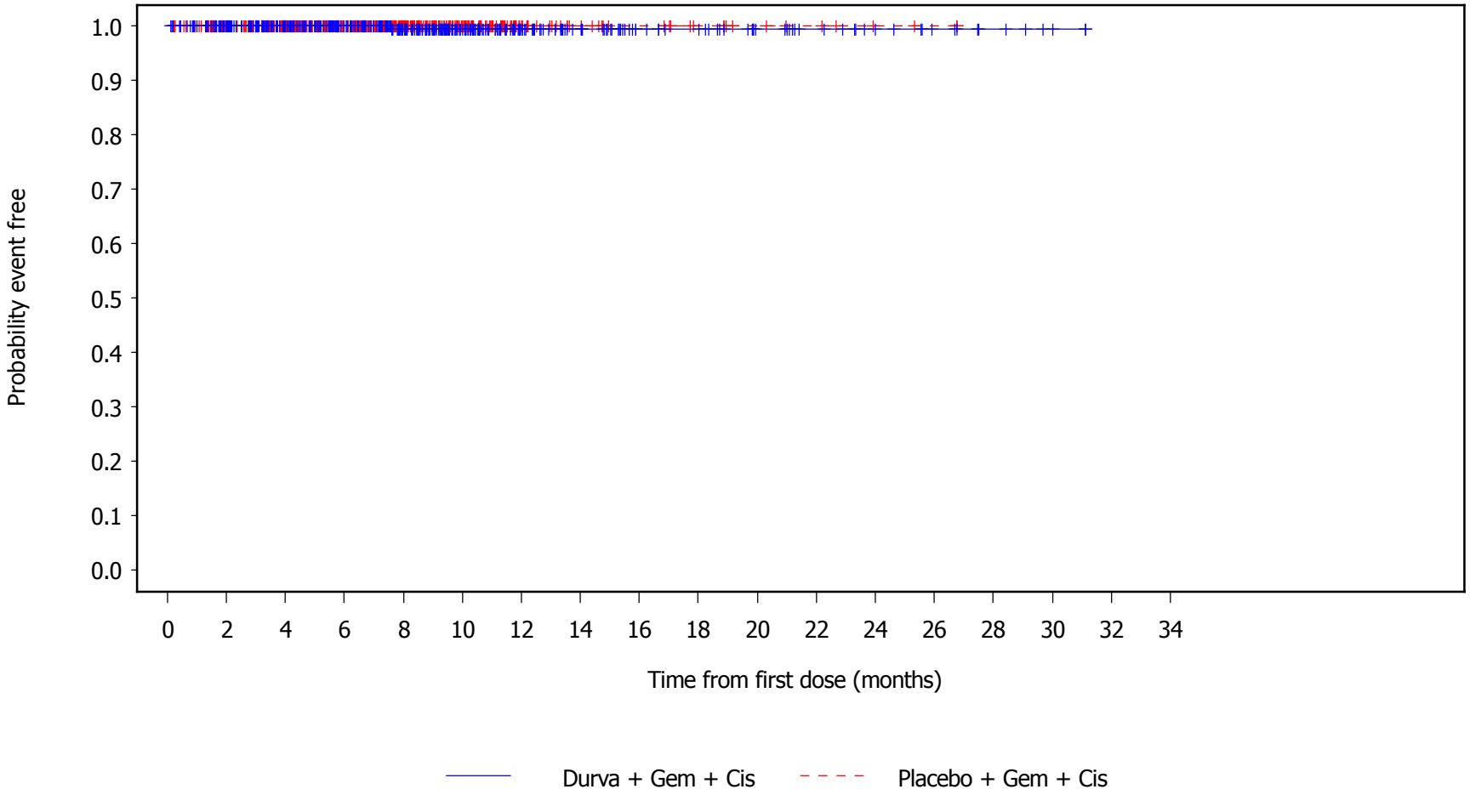
Figure 3.3.197 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Anaphylactic shock
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	231	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

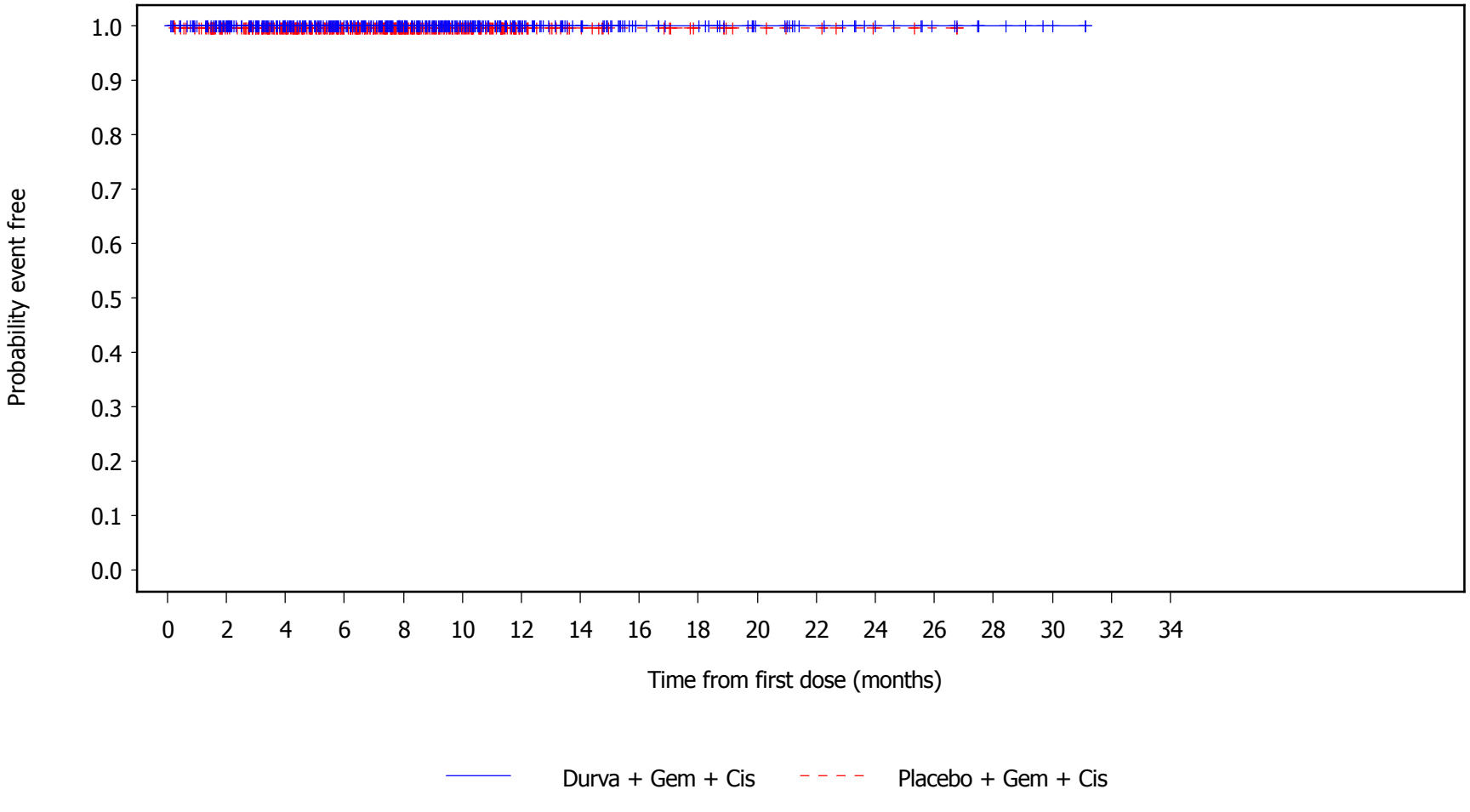
Figure 3.3.198 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Drug hypersensitivity
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	197	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

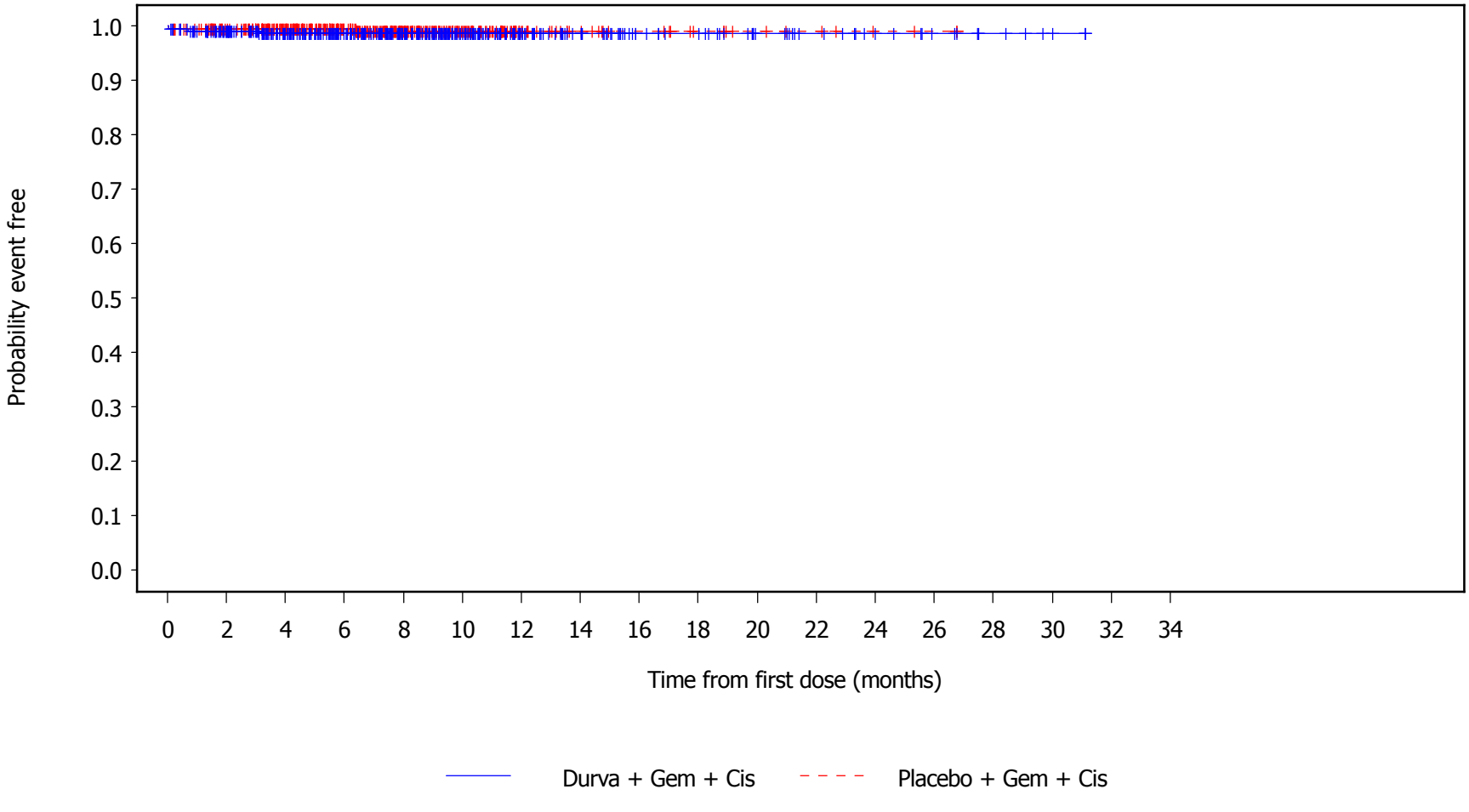
Figure 3.3.199 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Drug eruption
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

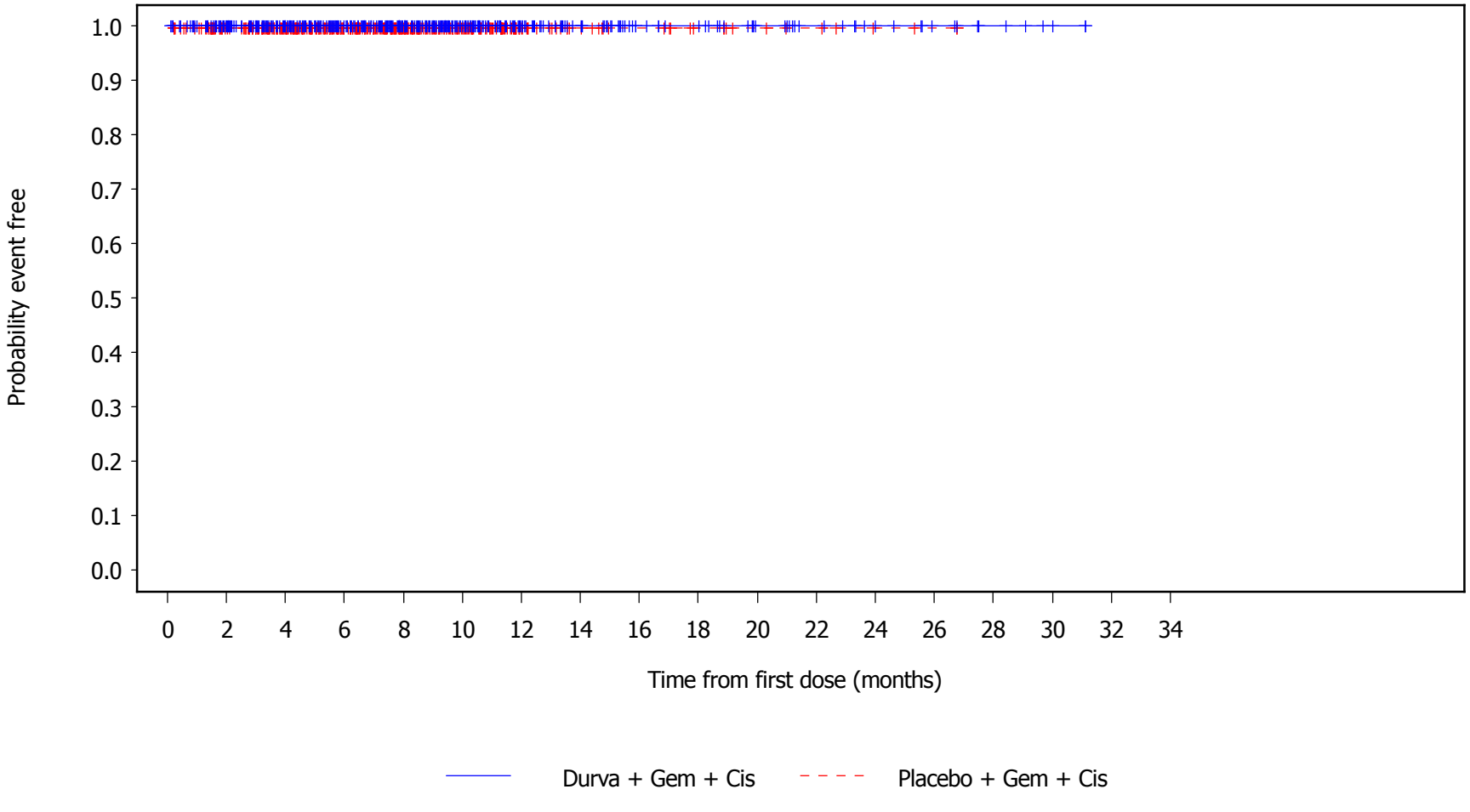
Figure 3.3.200 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Infusion related reaction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	312	261	196	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	311	230	156	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

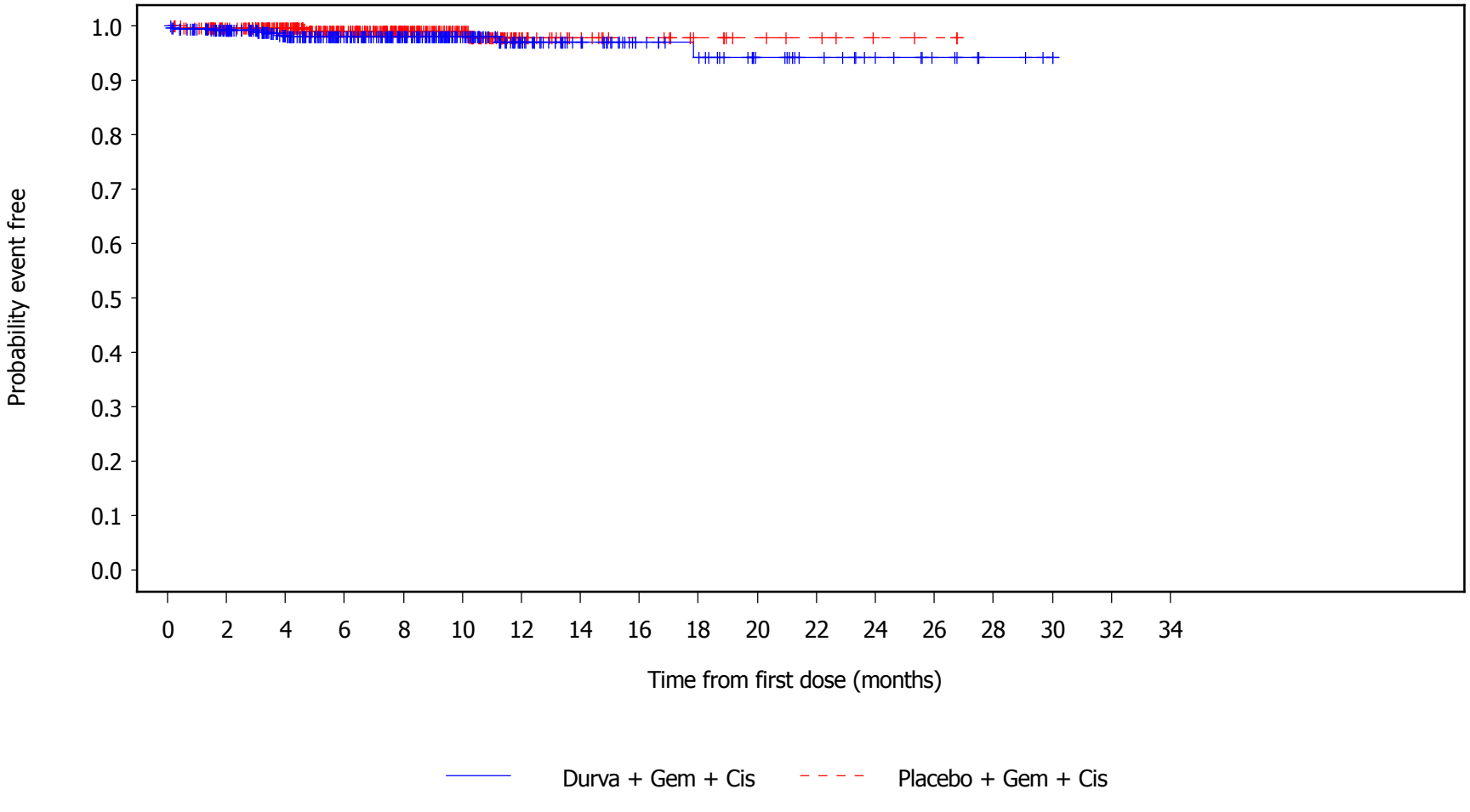
Figure 3.3.201 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Type I hypersensitivity
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

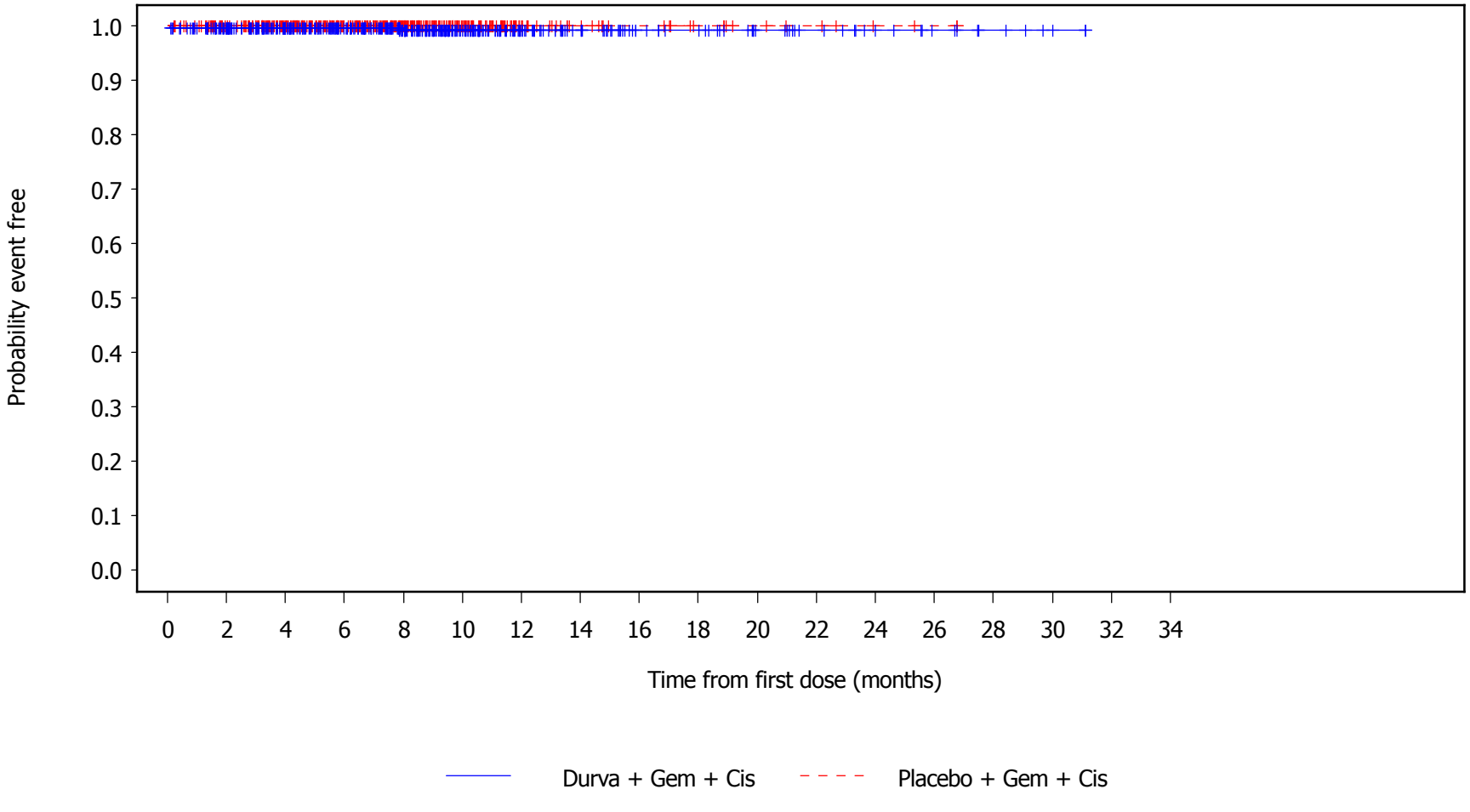
Figure 3.3.202 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Urticaria
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	370	309	257	194	128	78	56	39	34	23	17	12	7	3	1	0	0	Durva + Gem + Cis
403	370	312	229	157	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

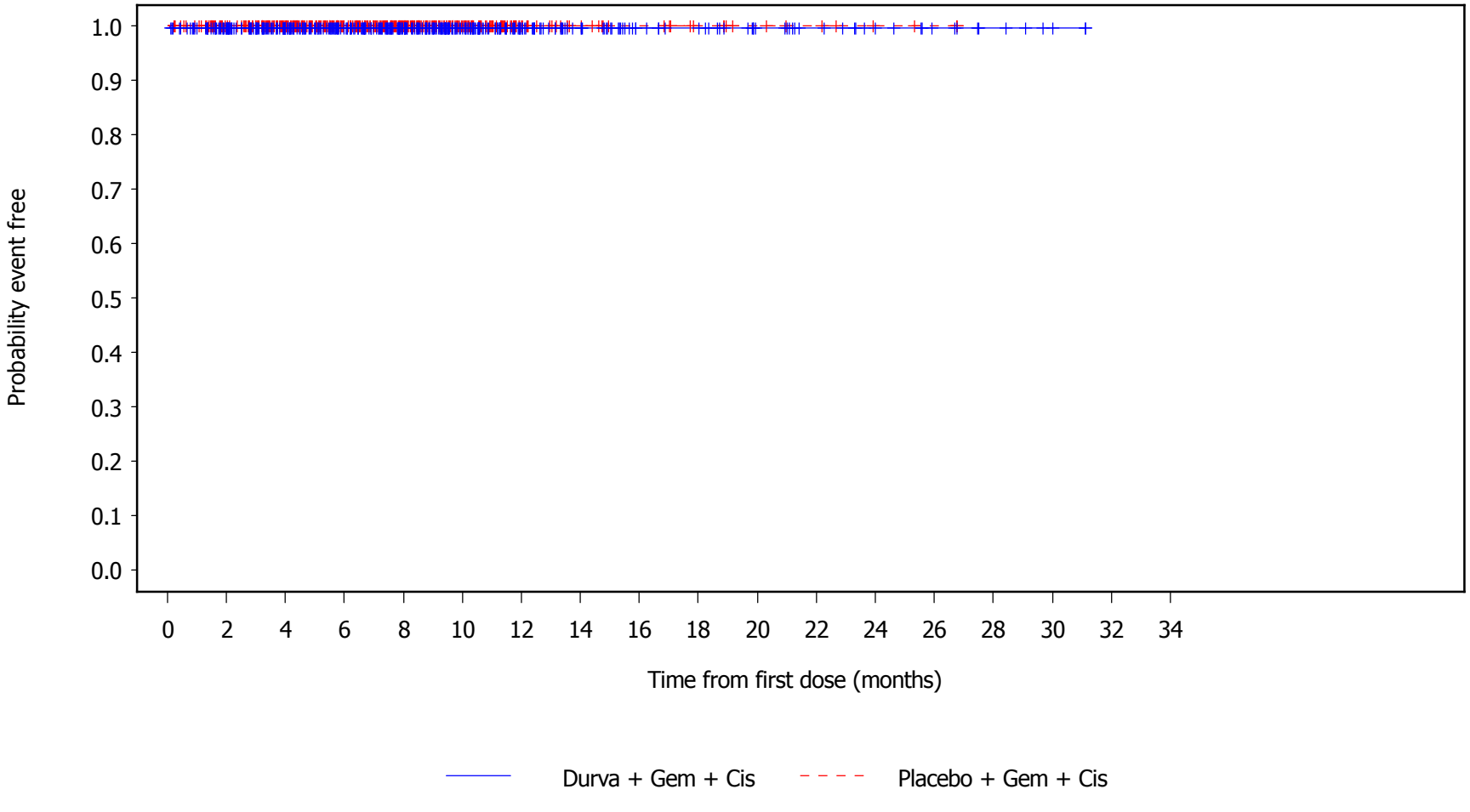
Figure 3.3.203 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Other rare/miscellaneous
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

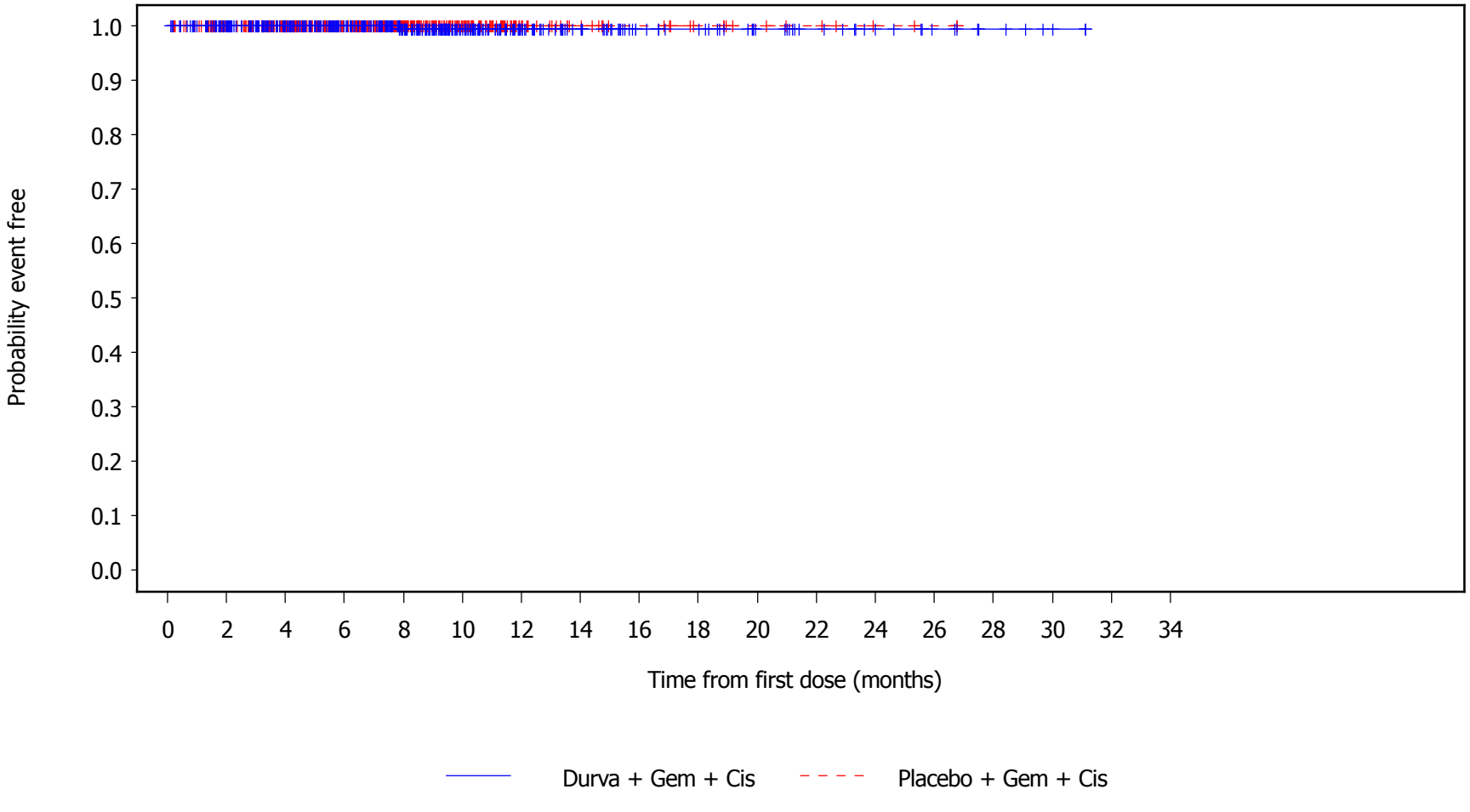
Figure 3.3.204 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Immune-mediated arthritis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

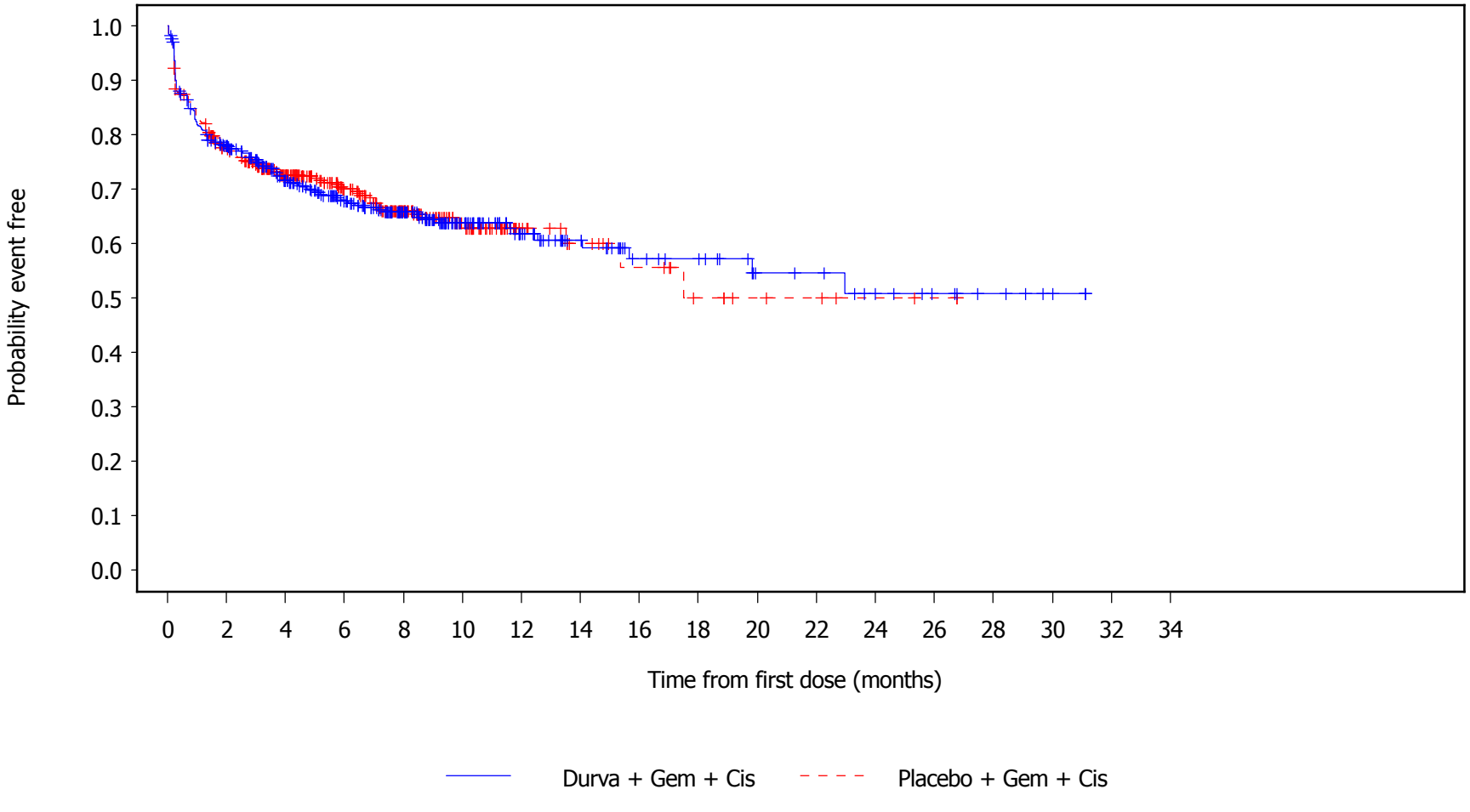
Figure 3.3.205 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Vitiligo
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

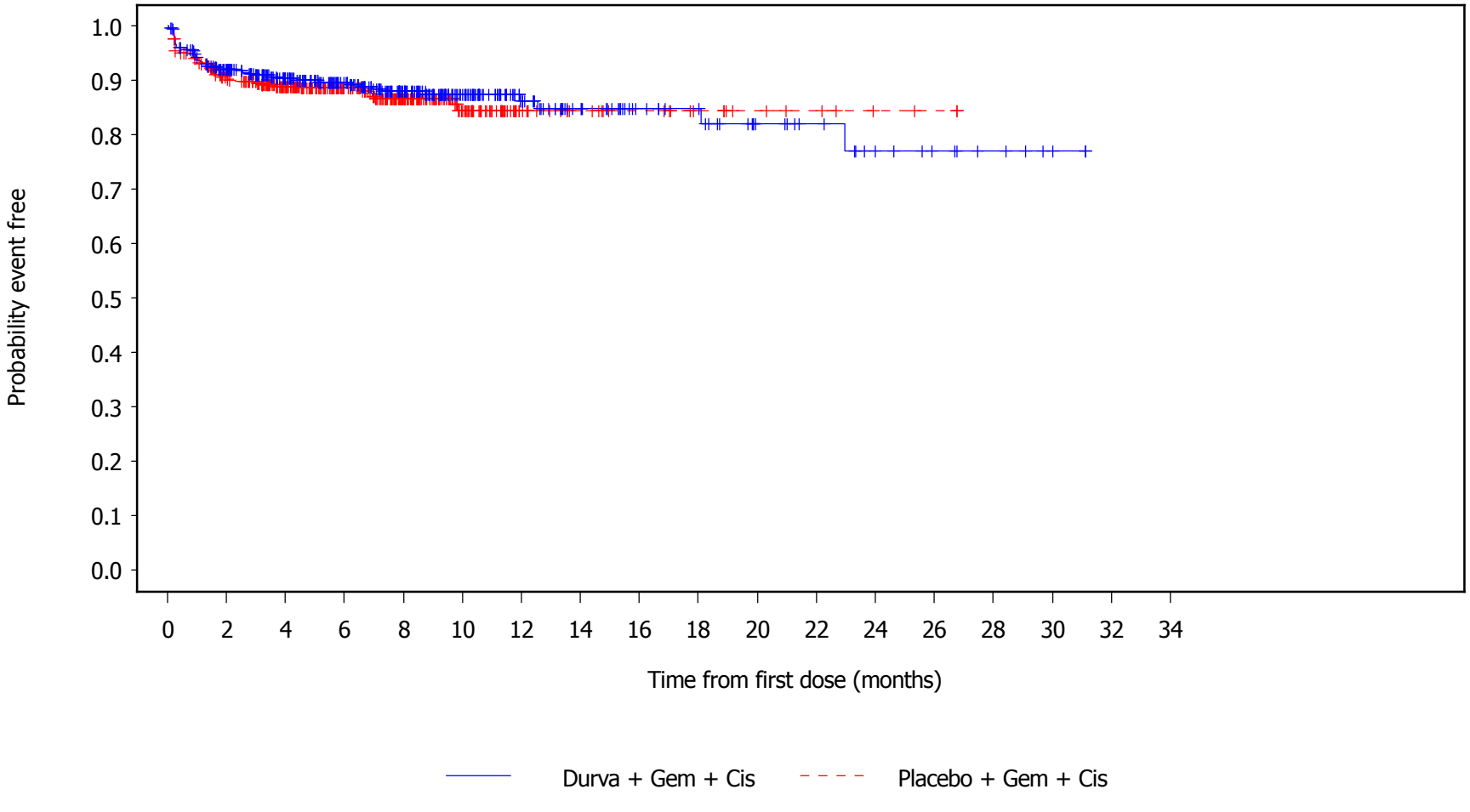
Figure 3.3.206 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Hepatic SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	298	240	196	146	92	59	42	29	26	17	16	12	8	5	2	0	0	Durva + Gem + Cis
403	293	233	172	115	64	27	18	13	8	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

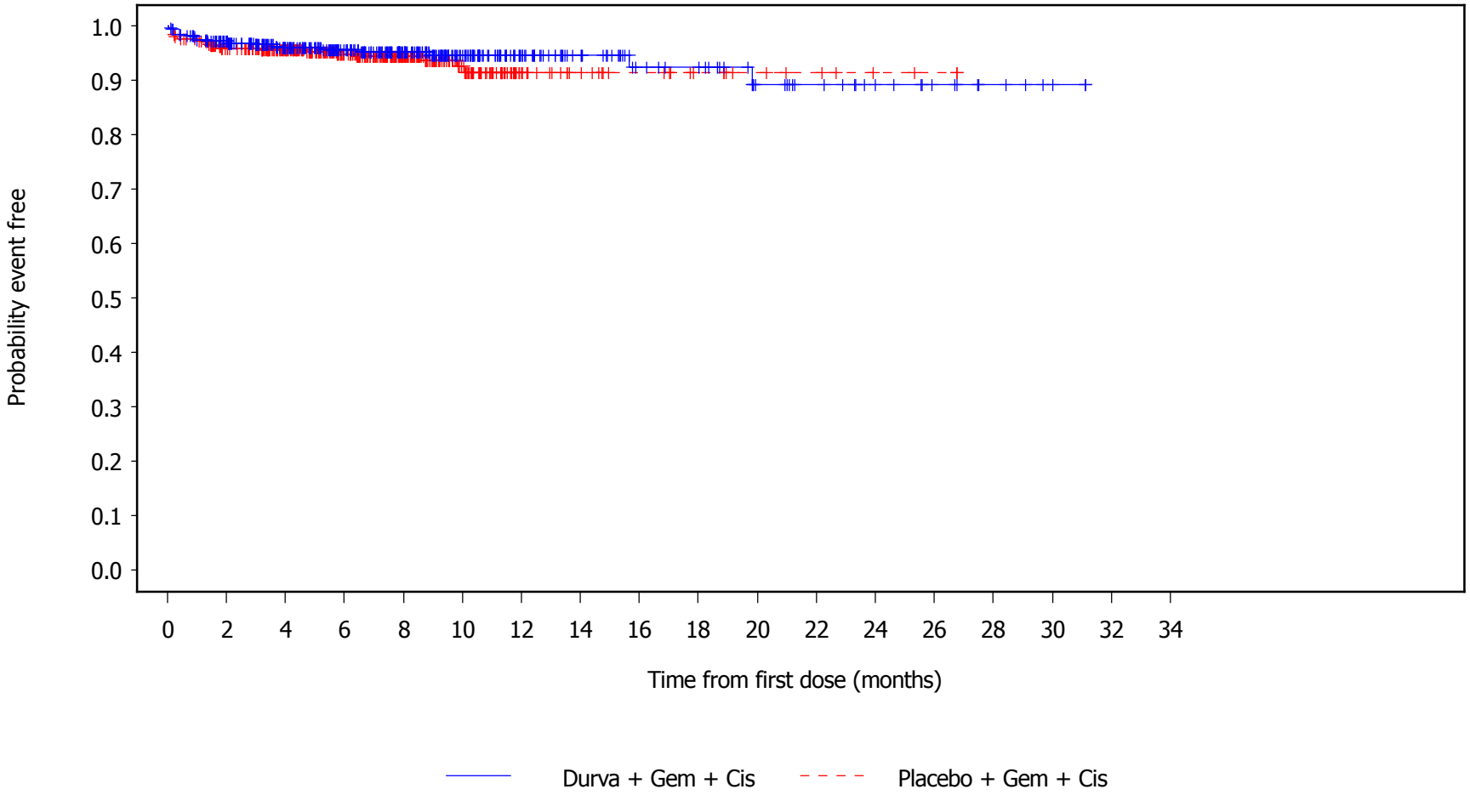
Figure 3.3.207 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Alanine aminotransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	343	281	235	174	114	70	50	36	32	21	17	12	8	5	2	0	0	Durva + Gem + Cis
403	335	274	202	140	76	31	21	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

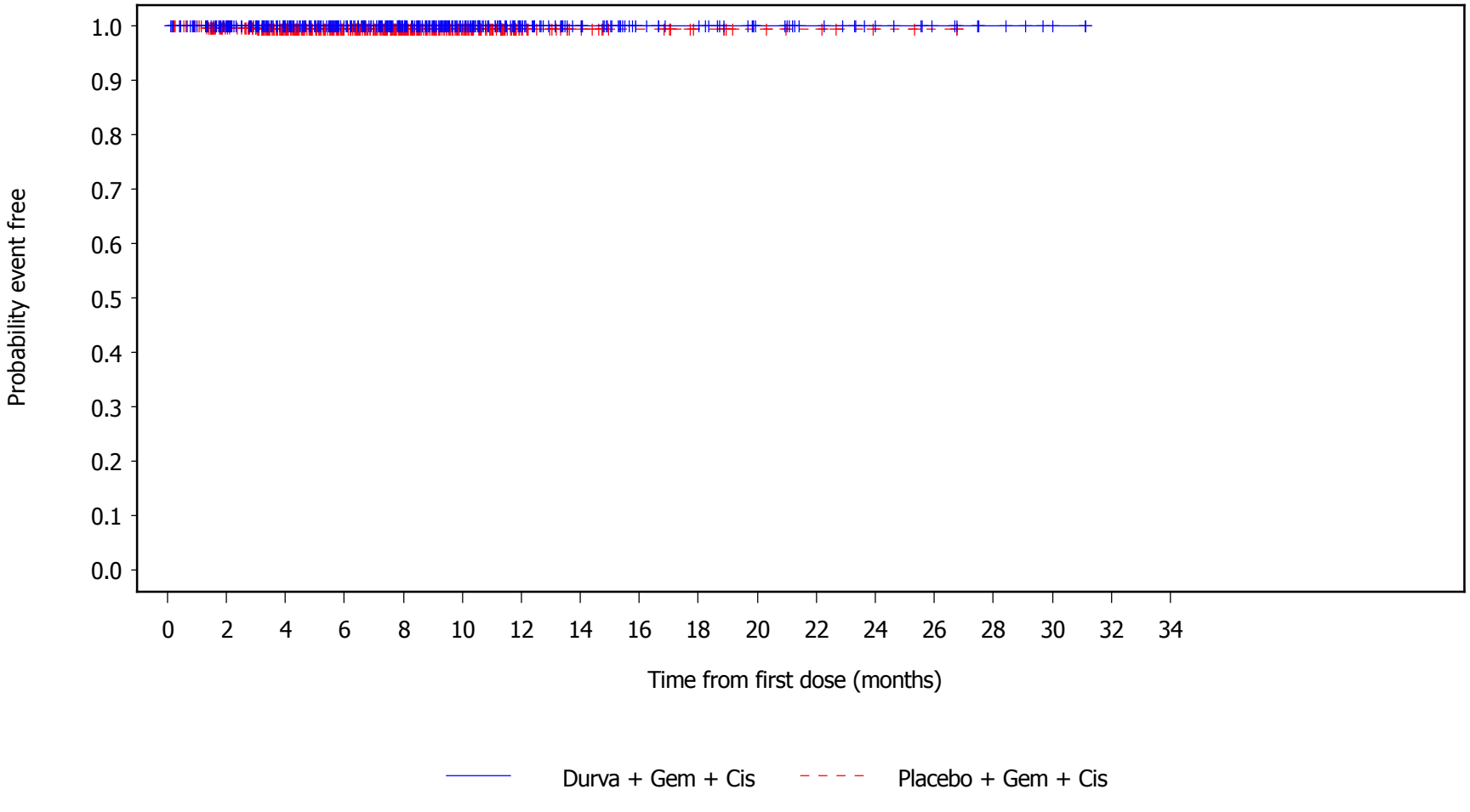
Figure 3.3.208 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Blood alkaline phosphatase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	363	304	252	188	124	77	55	39	36	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	356	298	221	151	84	32	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

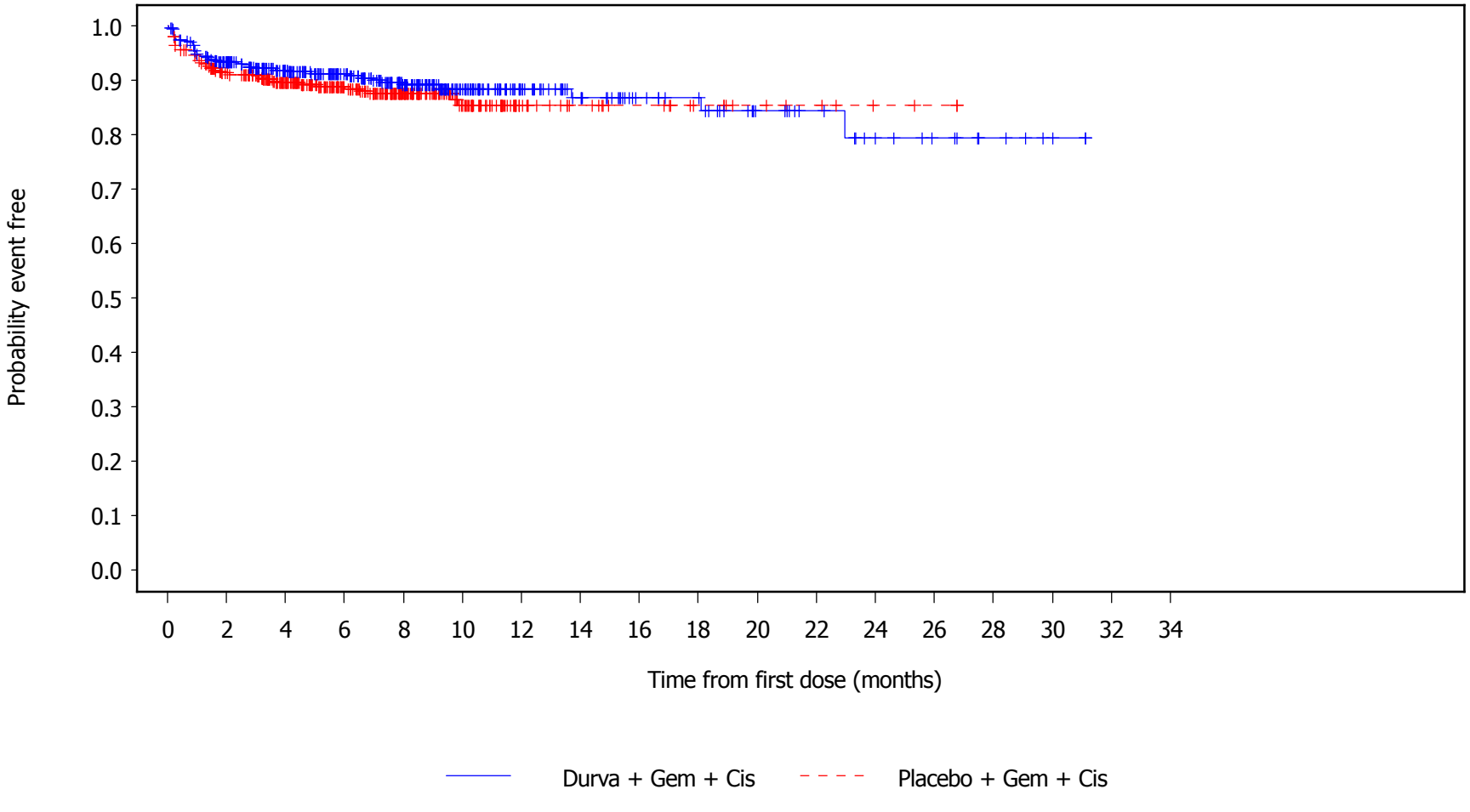
Figure 3.3.209 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

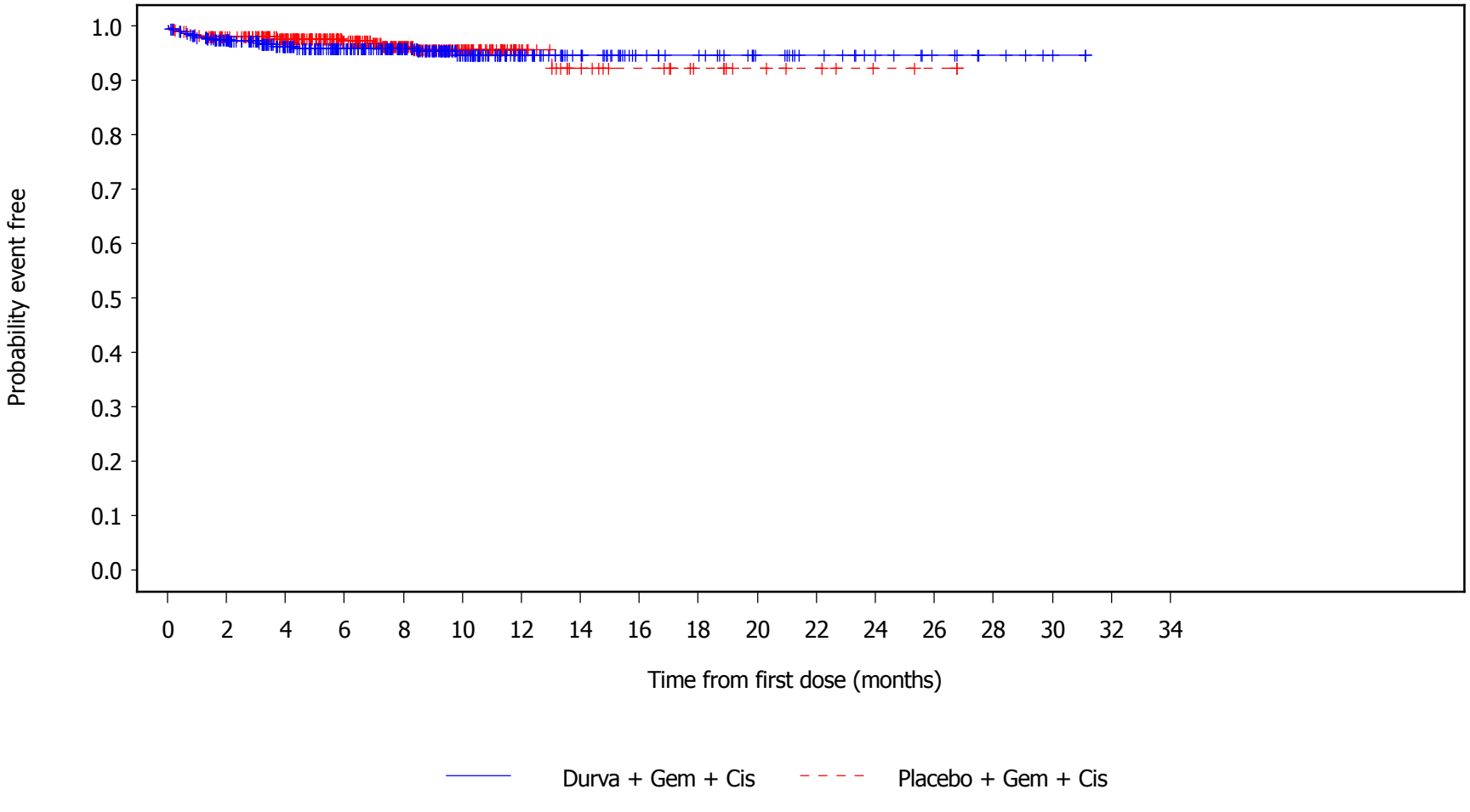
Figure 3.3.210 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Aspartate aminotransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	350	290	242	180	119	74	53	39	35	23	18	13	9	5	2	0	0	Durva + Gem + Cis
403	340	278	206	142	77	31	21	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

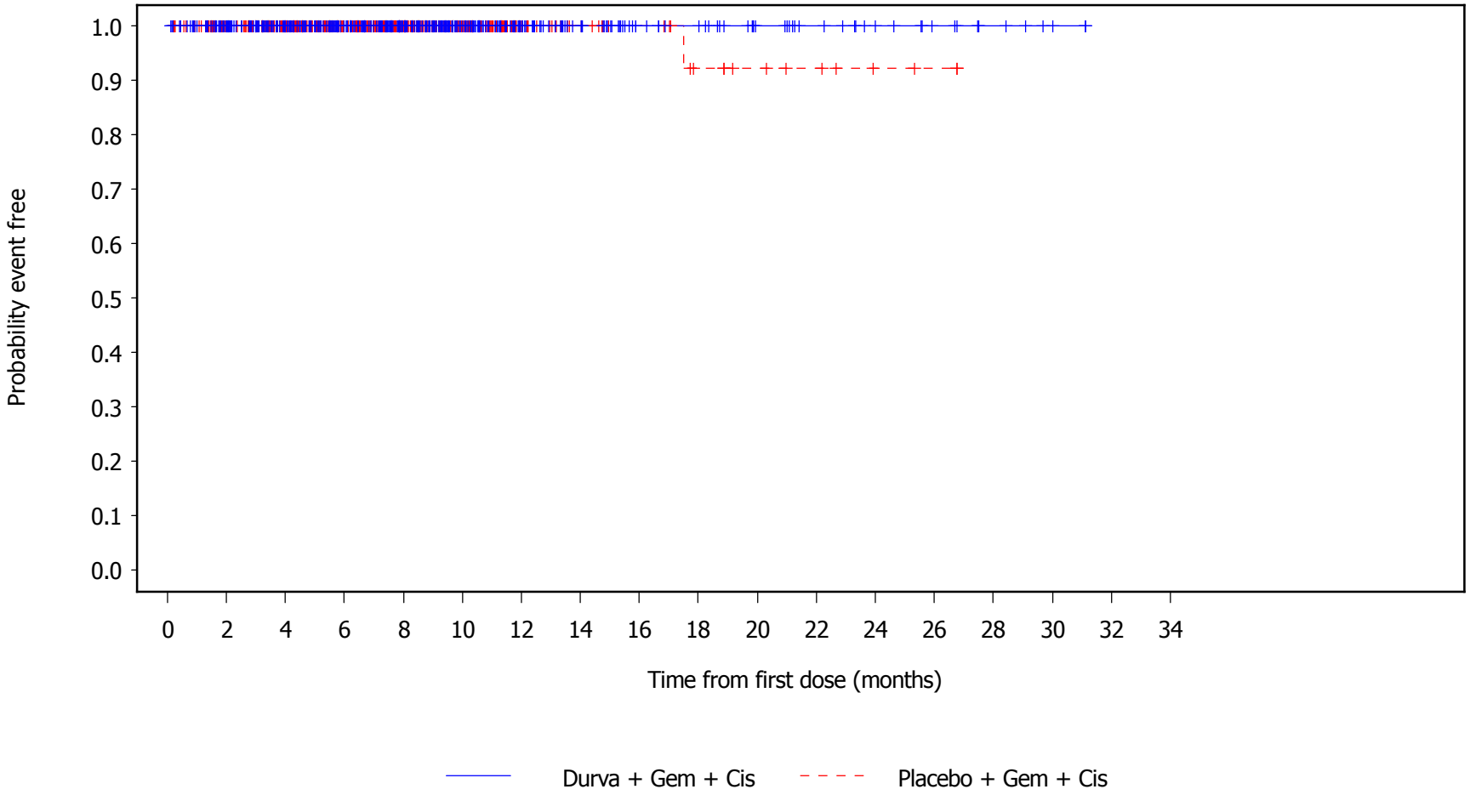
Figure 3.3.211 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Ascites
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	364	305	258	195	127	79	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	366	309	230	158	89	34	21	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

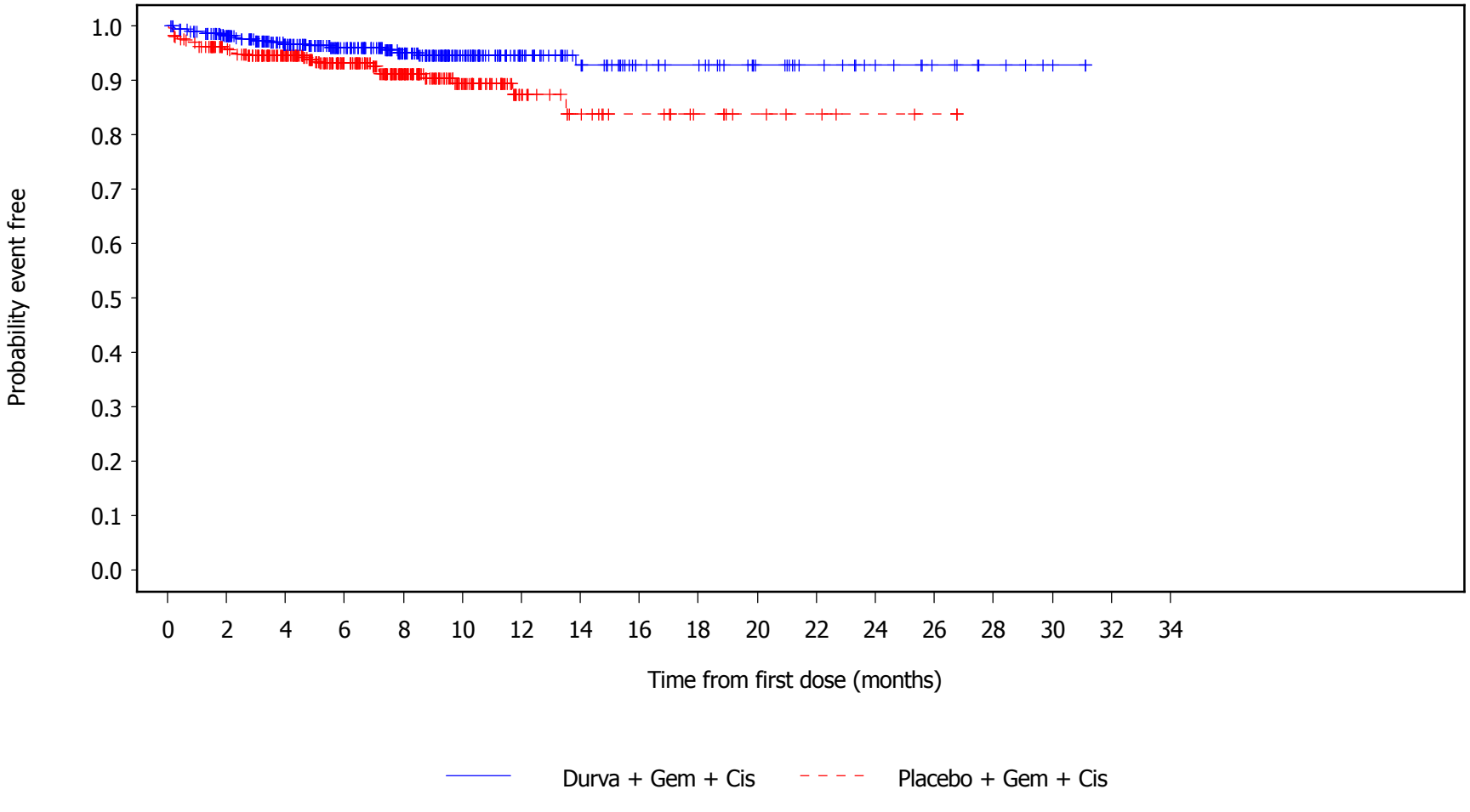
Figure 3.3.212 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

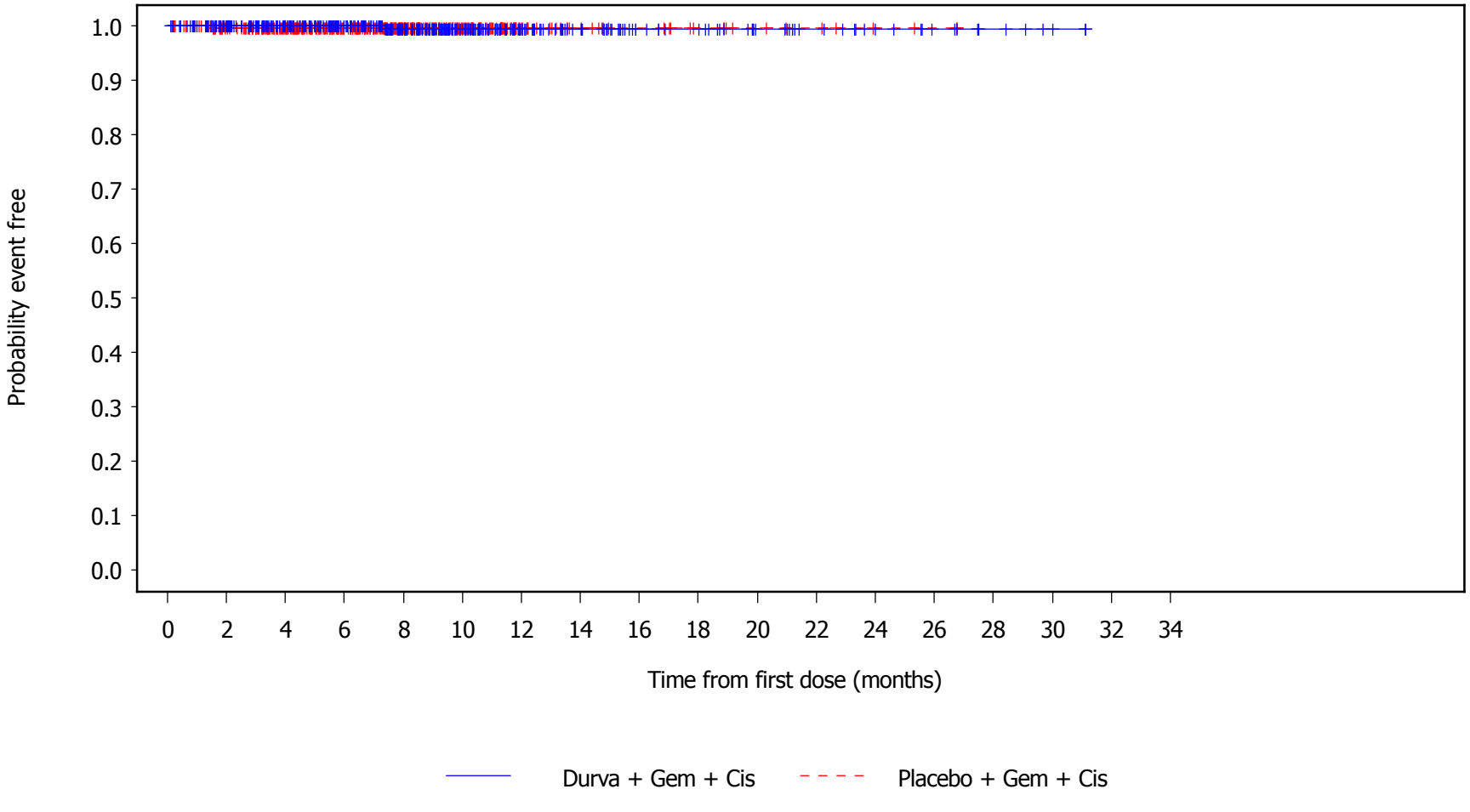
Figure 3.3.213 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	368	307	258	193	125	79	56	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	358	300	221	150	83	32	21	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

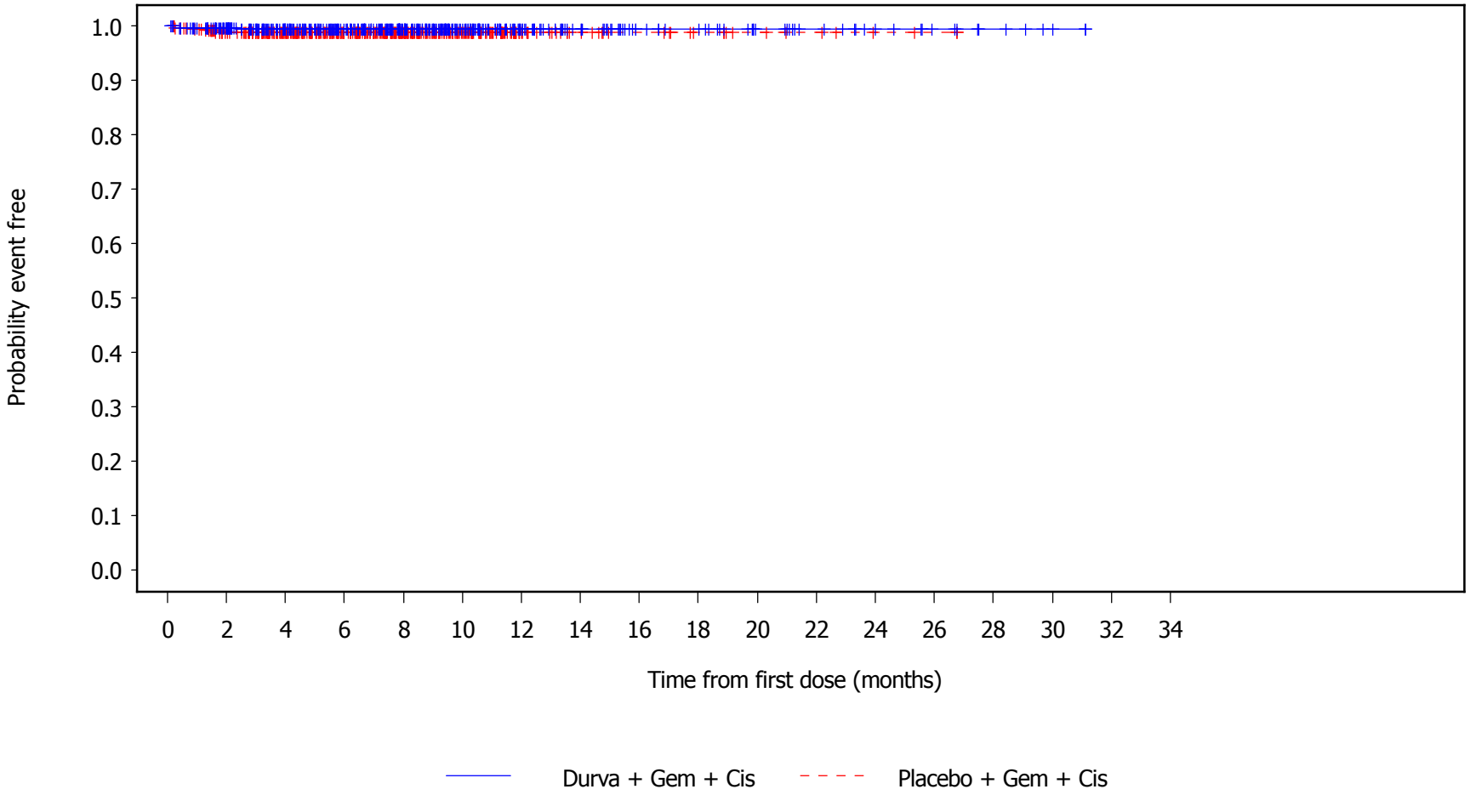
Figure 3.3.214 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Blood bilirubin unconjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	197	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

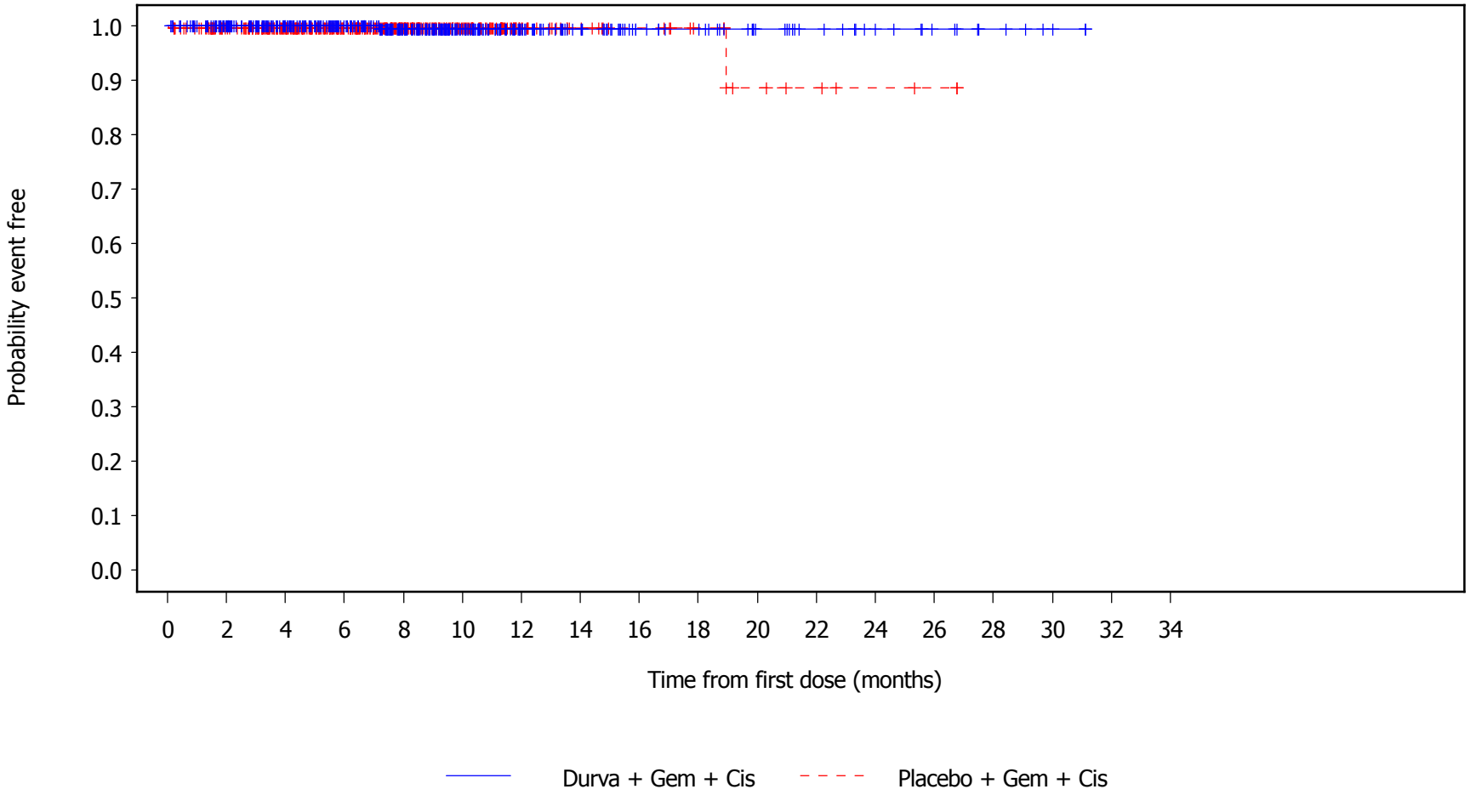
Figure 3.3.215 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Bilirubin conjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	311	231	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

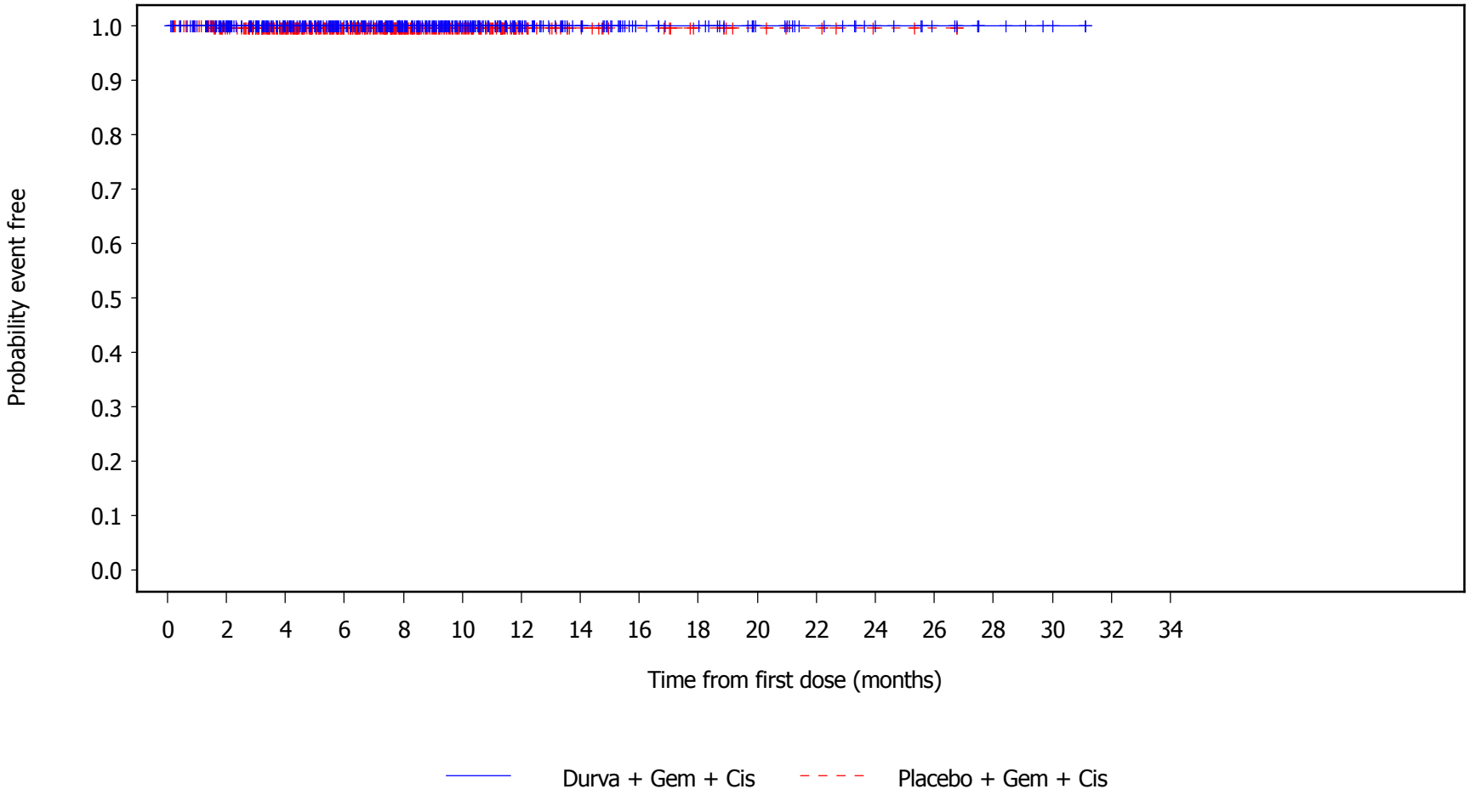
Figure 3.3.216 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	197	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	88	34	22	16	11	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

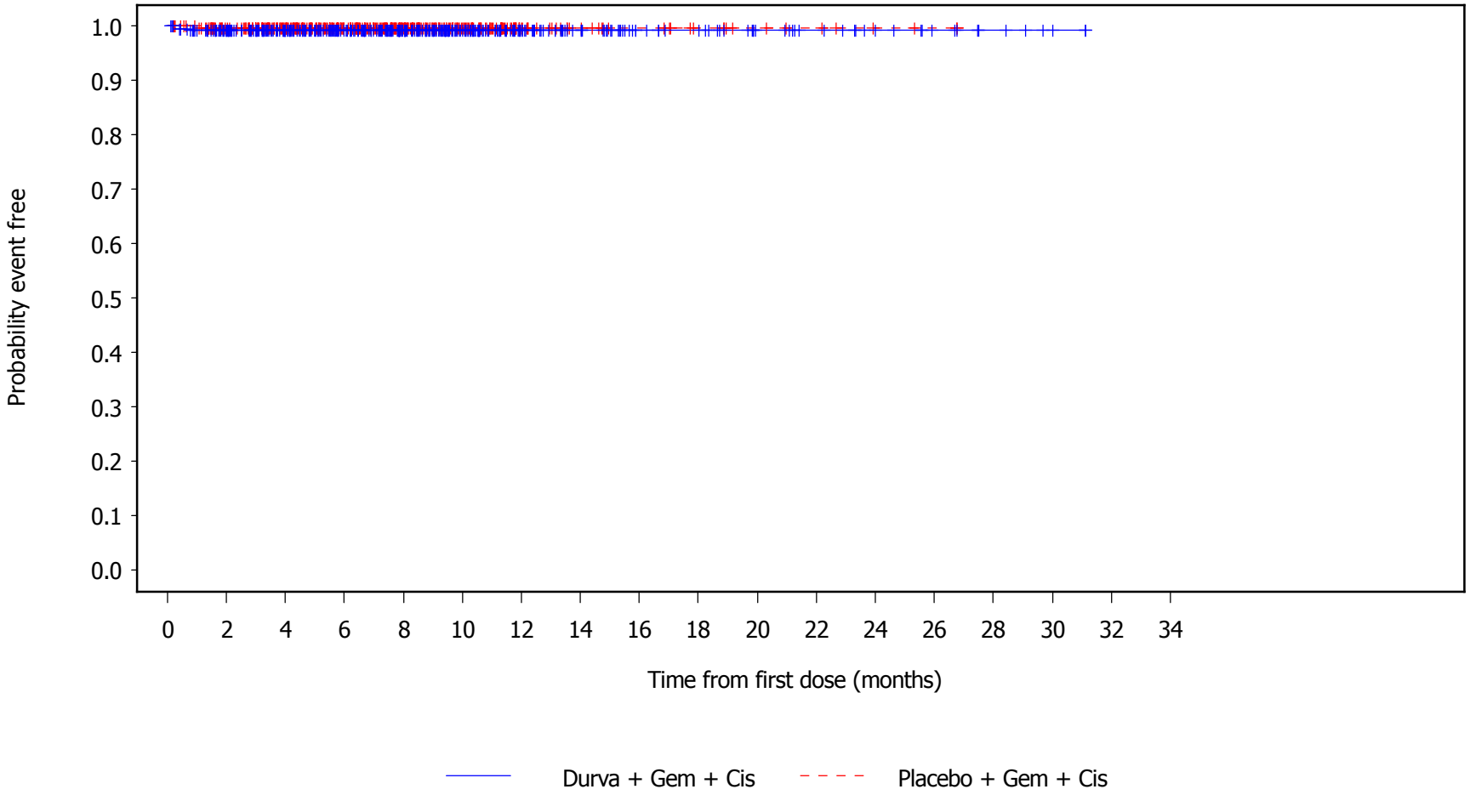
Figure 3.3.217 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Blood cholinesterase decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

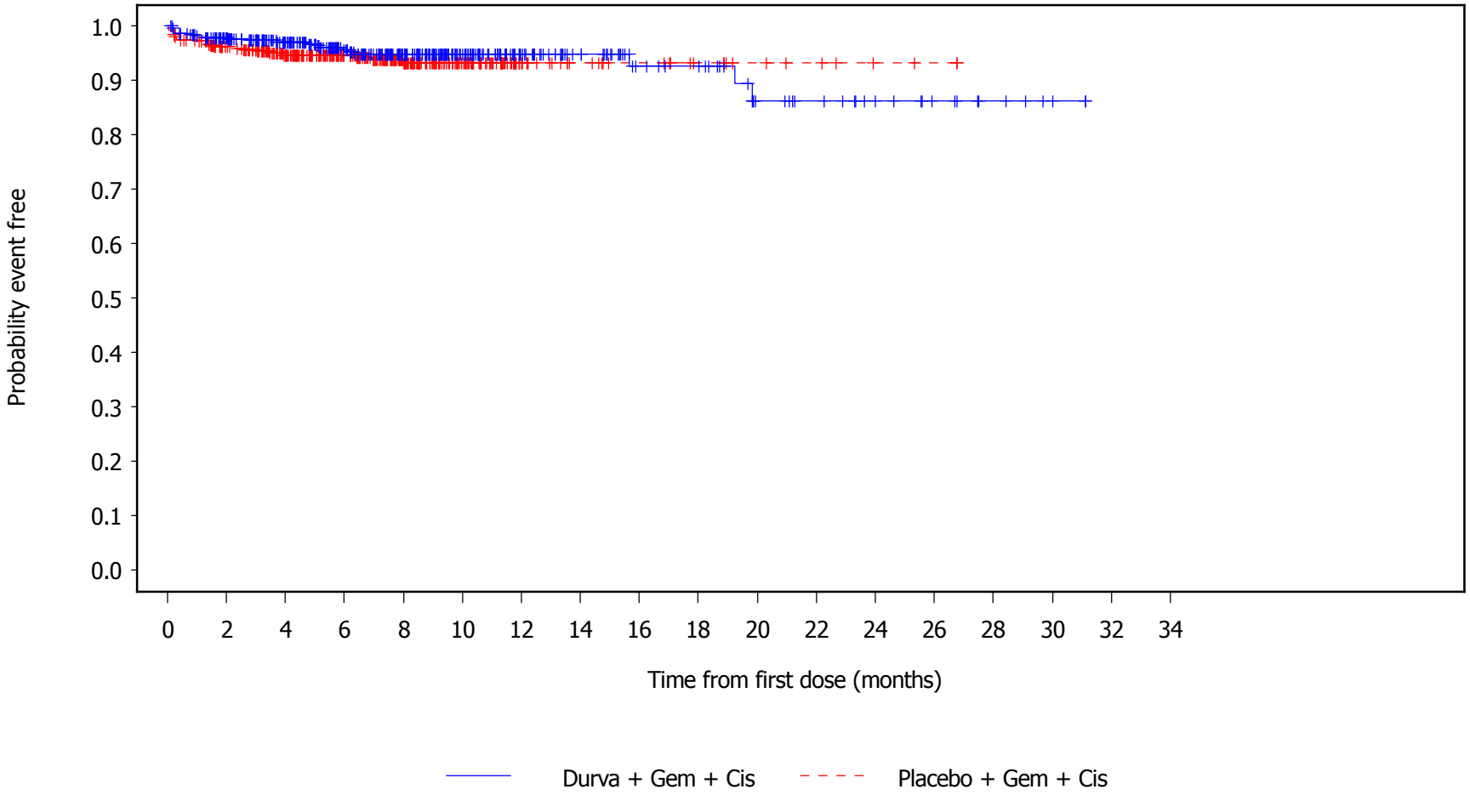
Figure 3.3.218 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Total bile acids increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	313	262	196	130	79	57	39	35	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

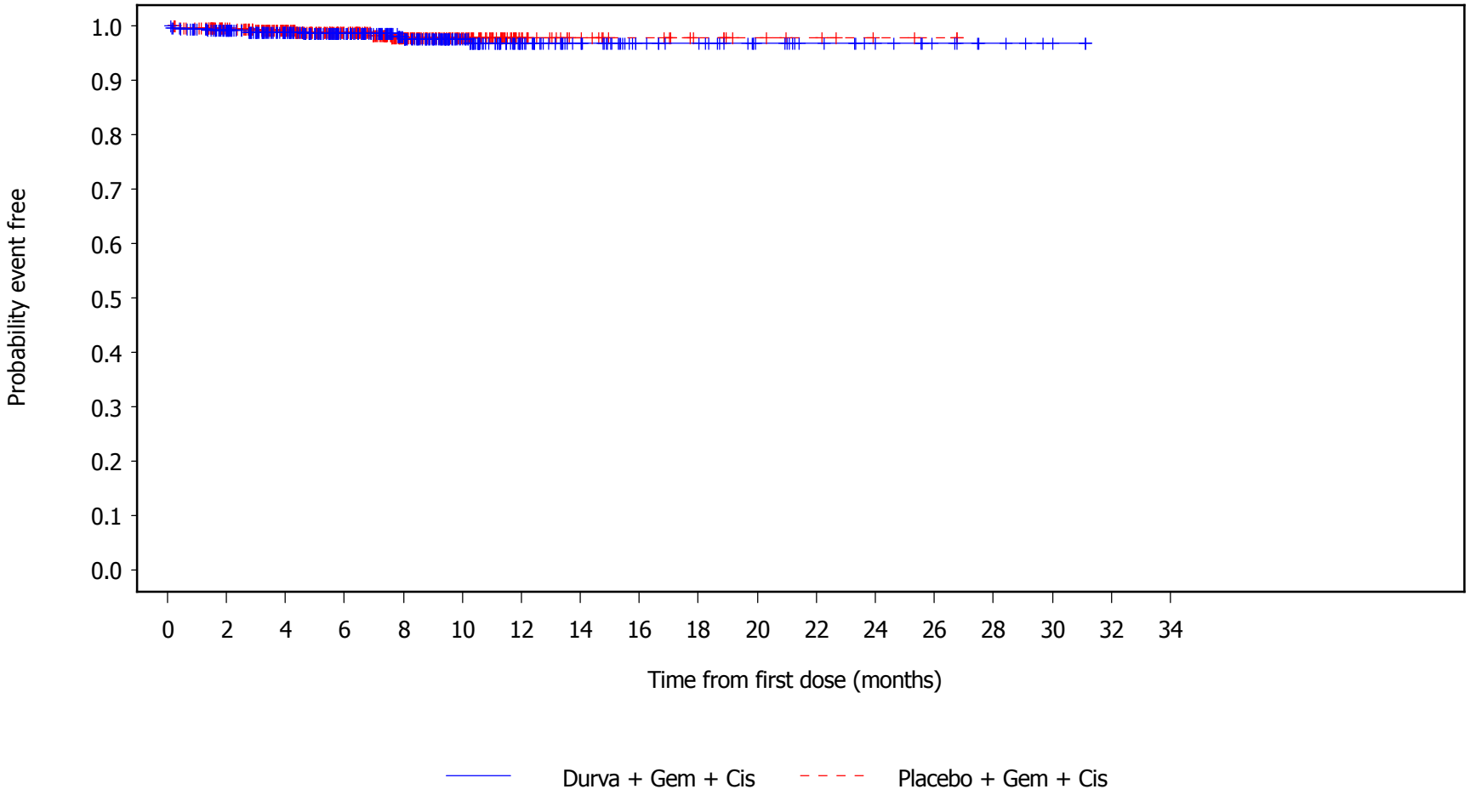
Figure 3.3.219 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Gamma-glutamyltransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	365	307	252	186	123	77	56	39	36	23	19	14	9	5	2	0	0	Durva + Gem + Cis
403	357	294	219	150	85	32	21	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

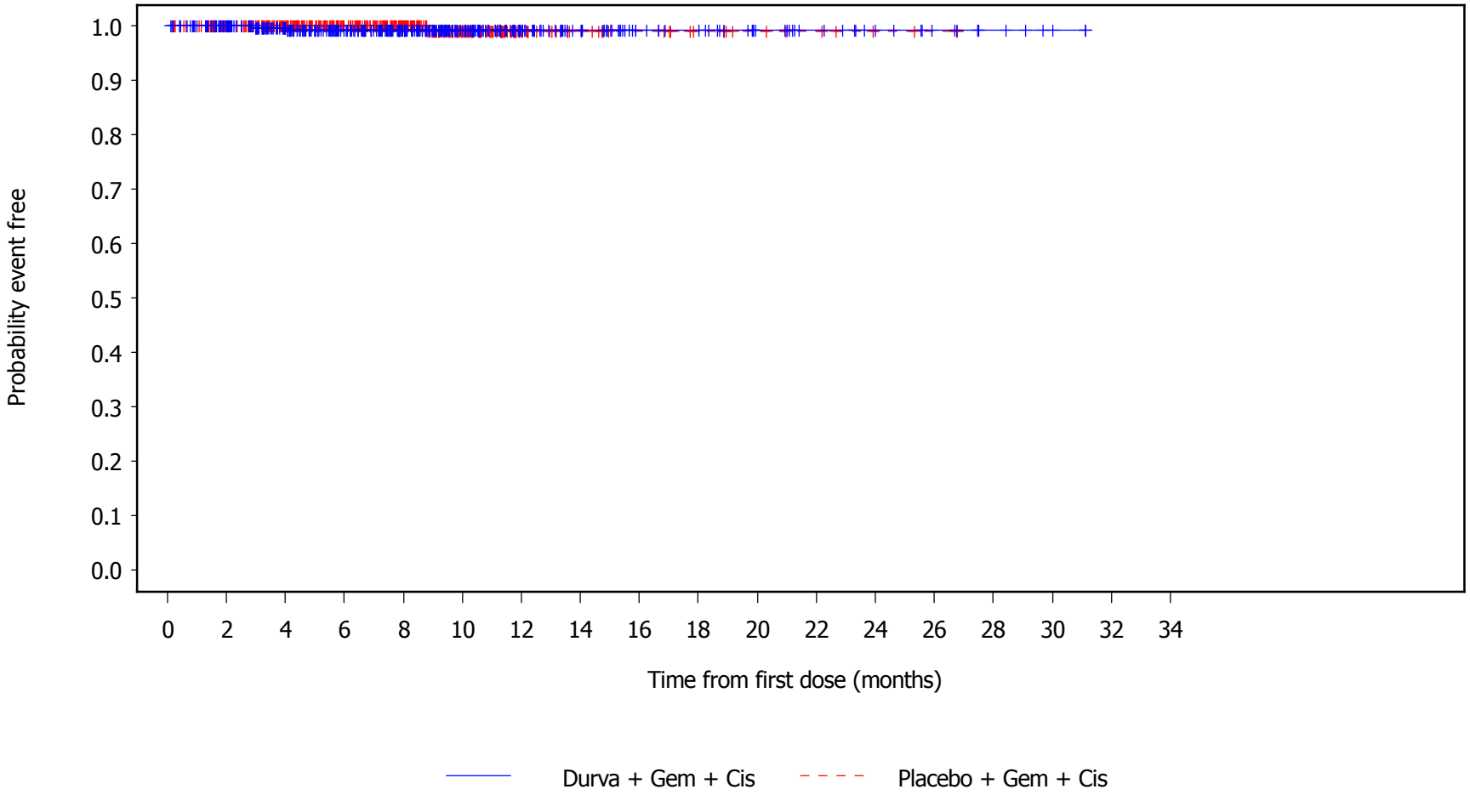
Figure 3.3.220 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	314	262	197	129	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	370	313	232	157	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

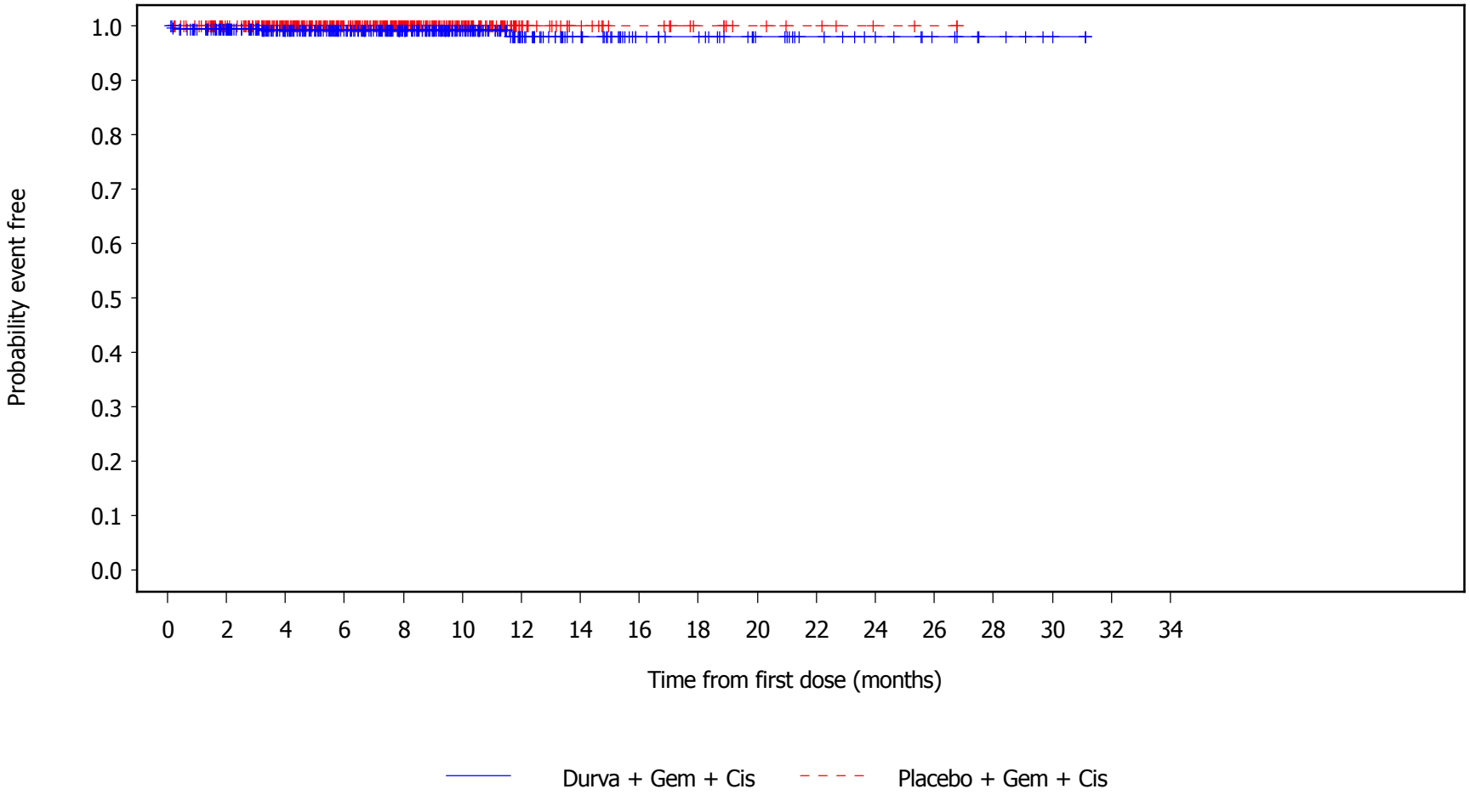
Figure 3.3.221 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hepatic encephalopathy
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

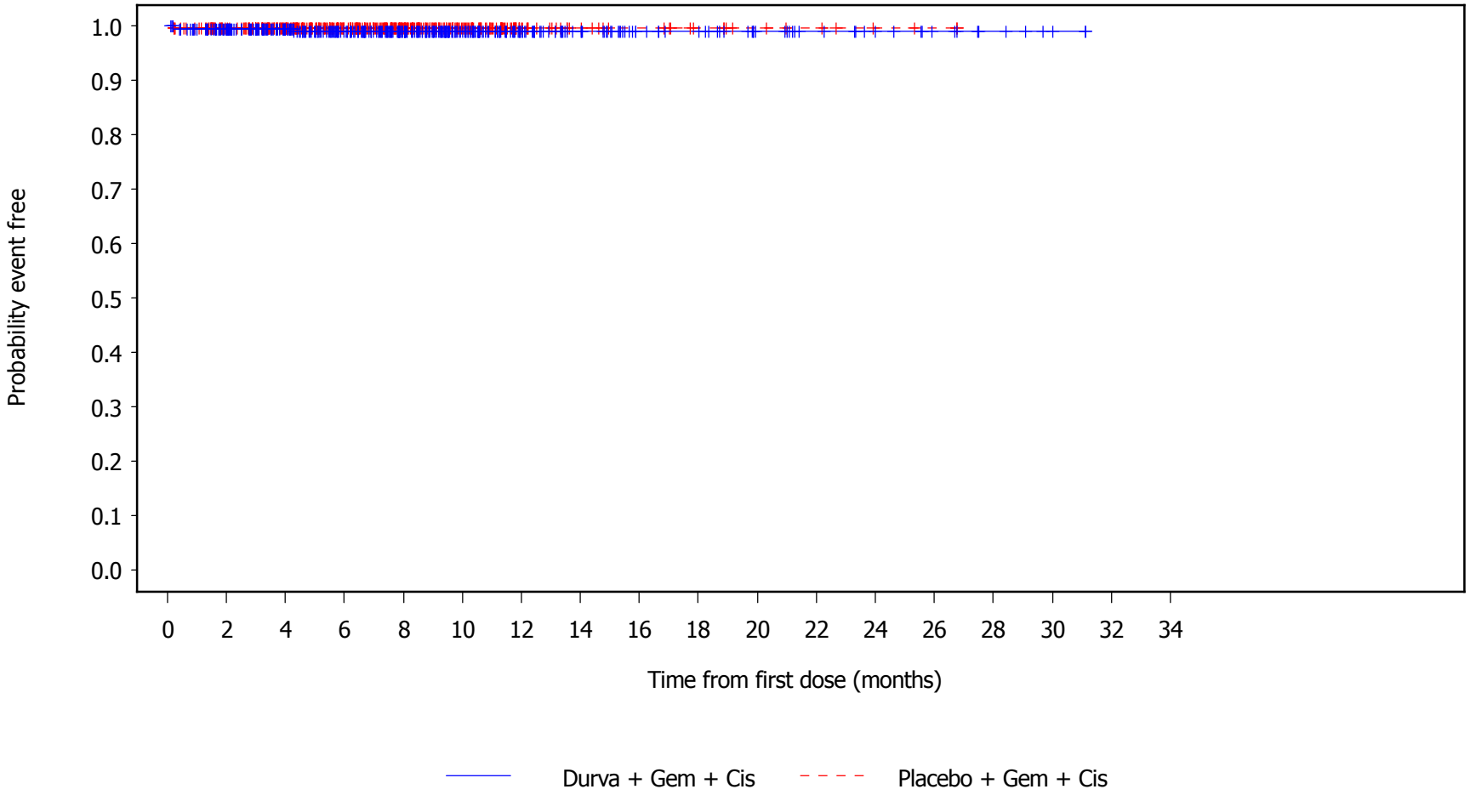
Figure 3.3.222 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hepatic cytolysis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	313	262	196	130	78	56	38	34	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

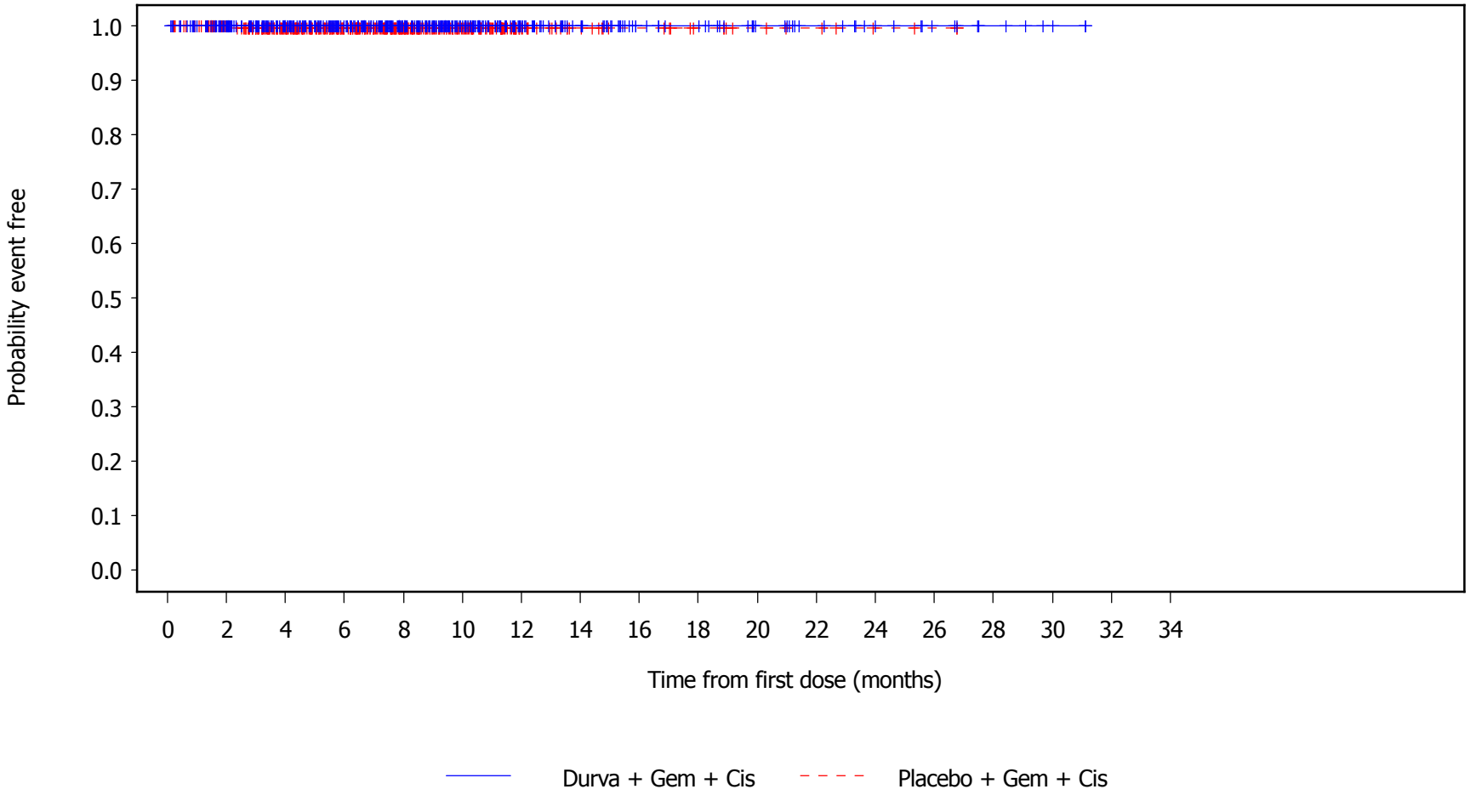
Figure 3.3.223 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	314	262	196	129	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	88	33	21	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

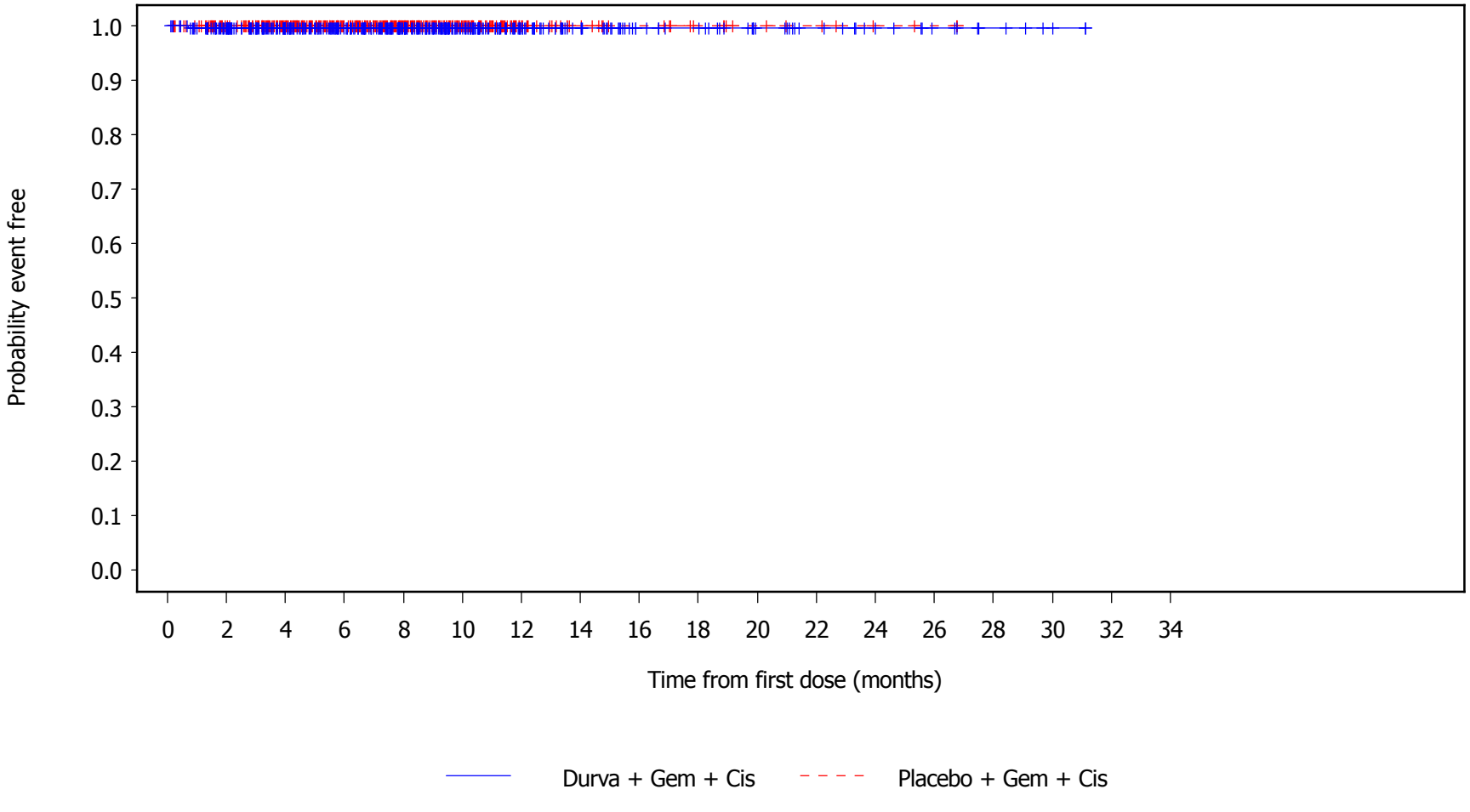
Figure 3.3.224 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hepatitis B
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	231	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

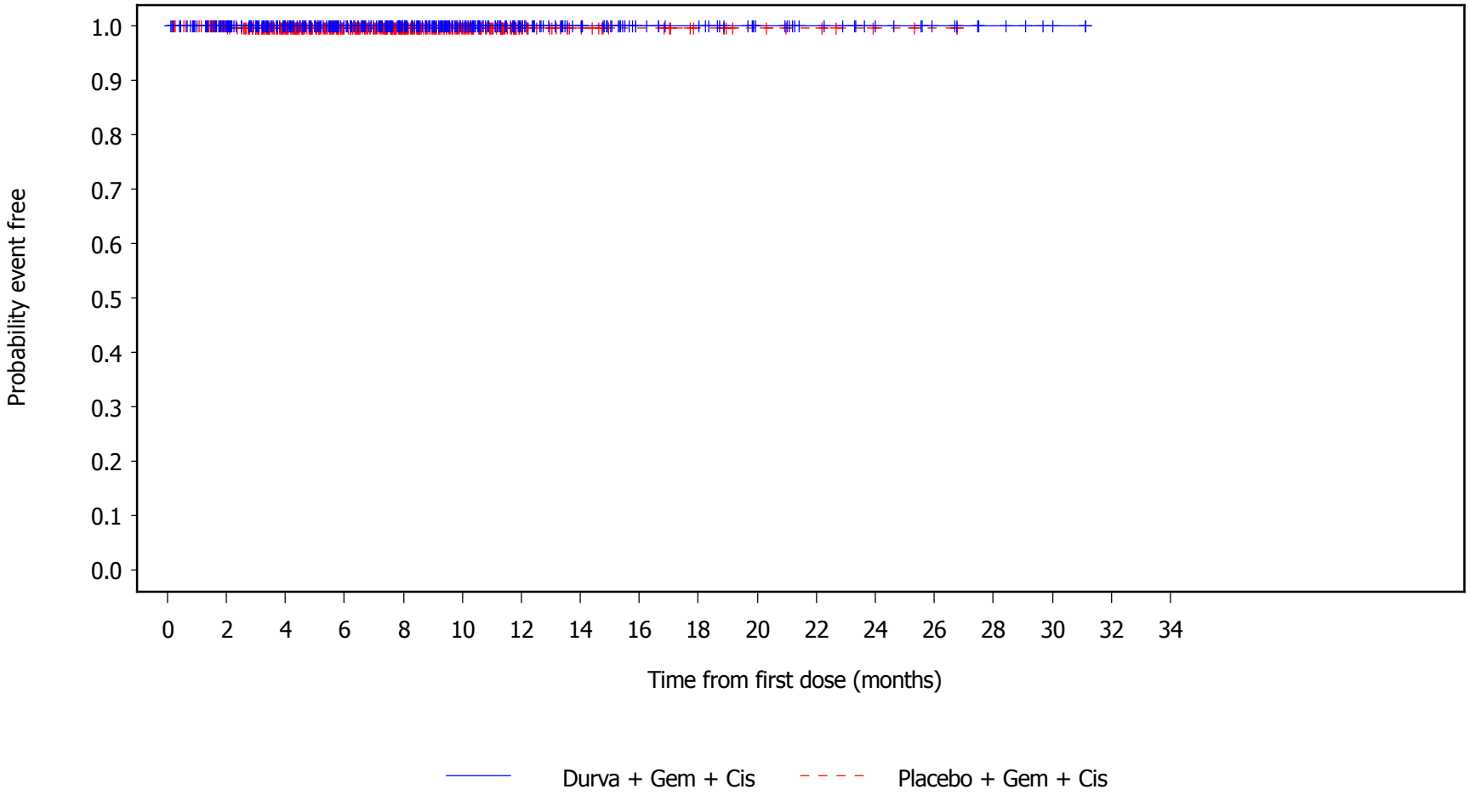
Figure 3.3.225 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hepatitis E
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

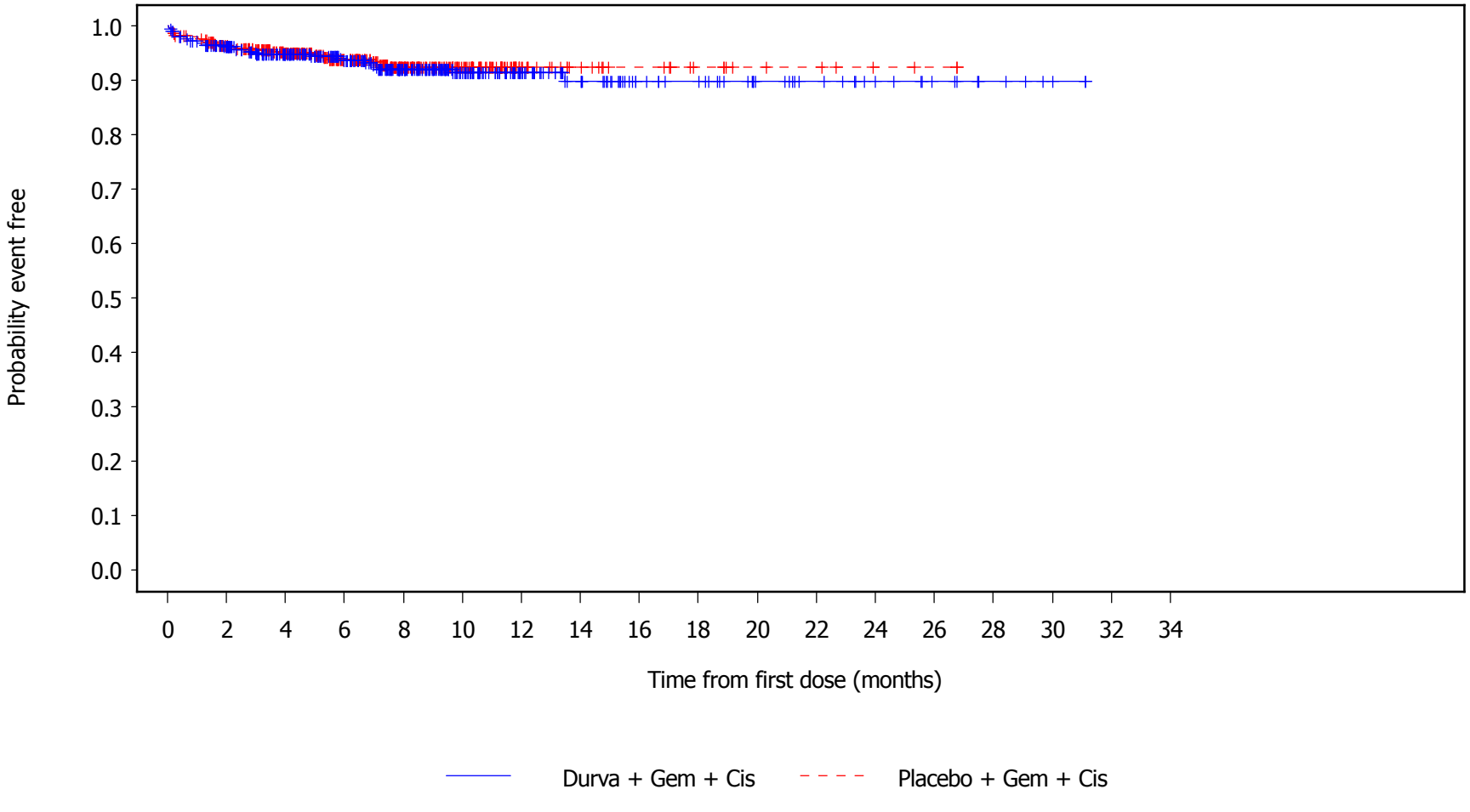
Figure 3.3.226 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hepatorenal failure
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	231	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

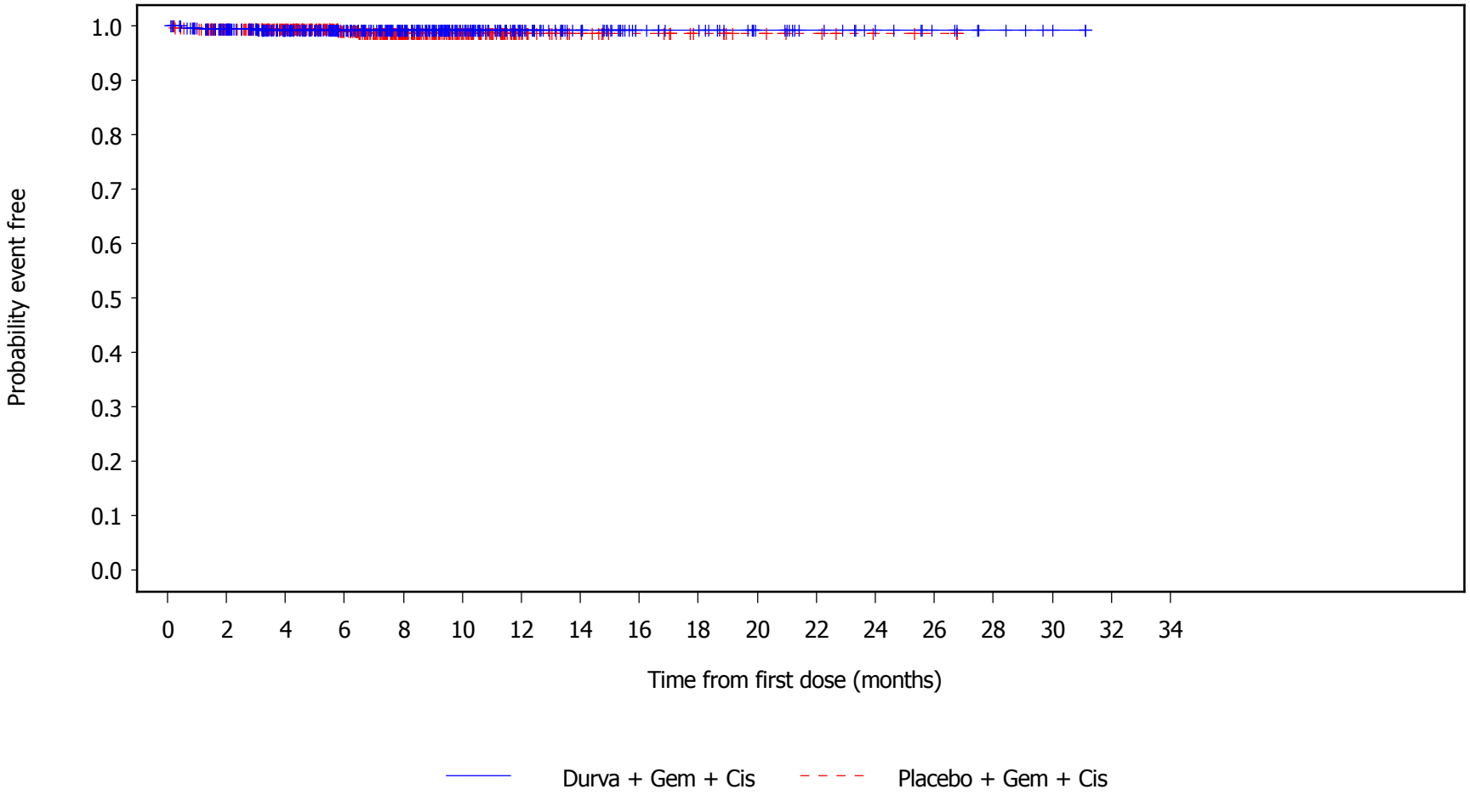
Figure 3.3.227 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hypoalbuminaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	363	306	256	190	125	79	57	39	35	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	360	302	224	152	84	32	21	15	10	6	5	2	1	0	0	0	0	Placebo + Gem + Cis

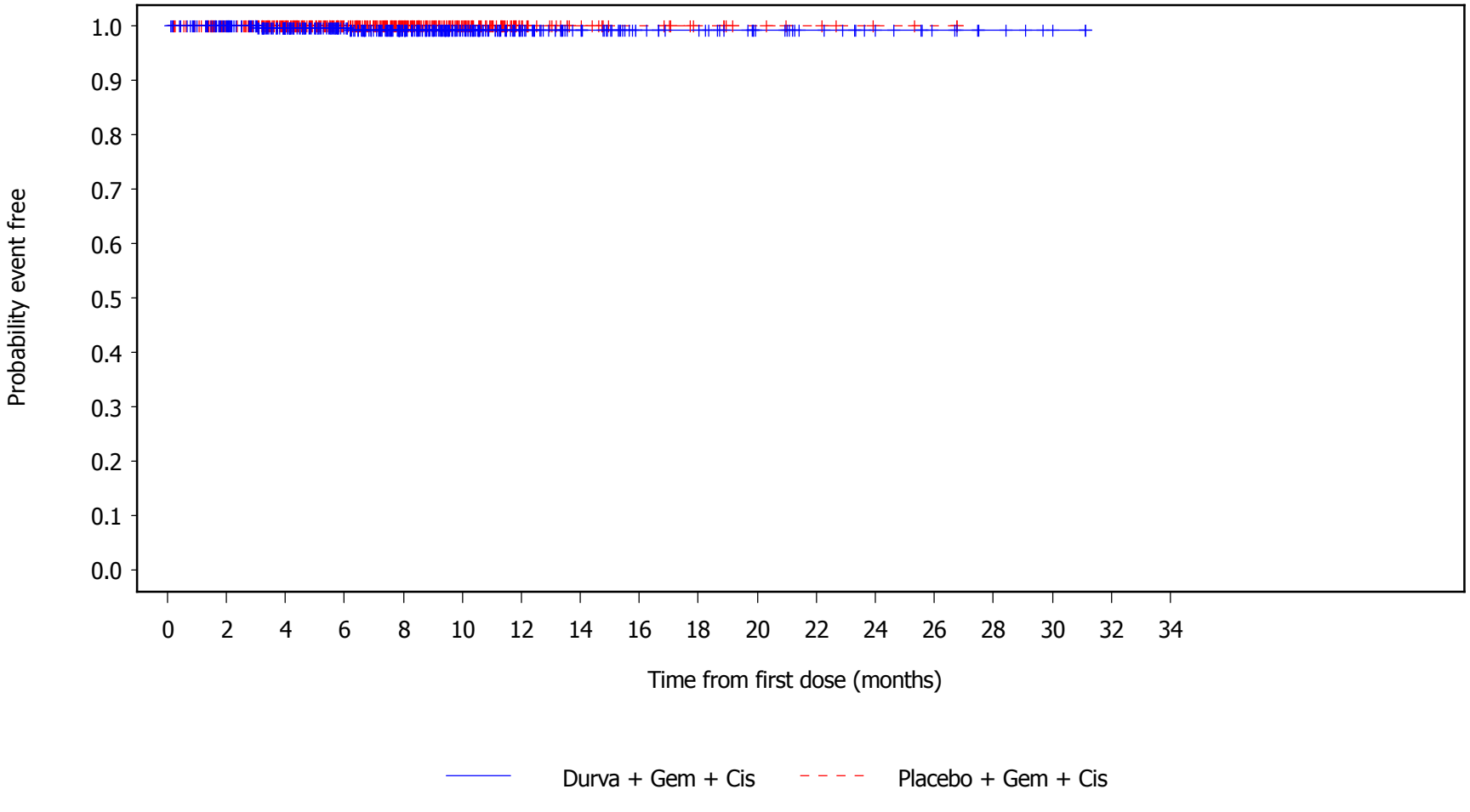
Figure 3.3.228 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	263	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	230	156	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

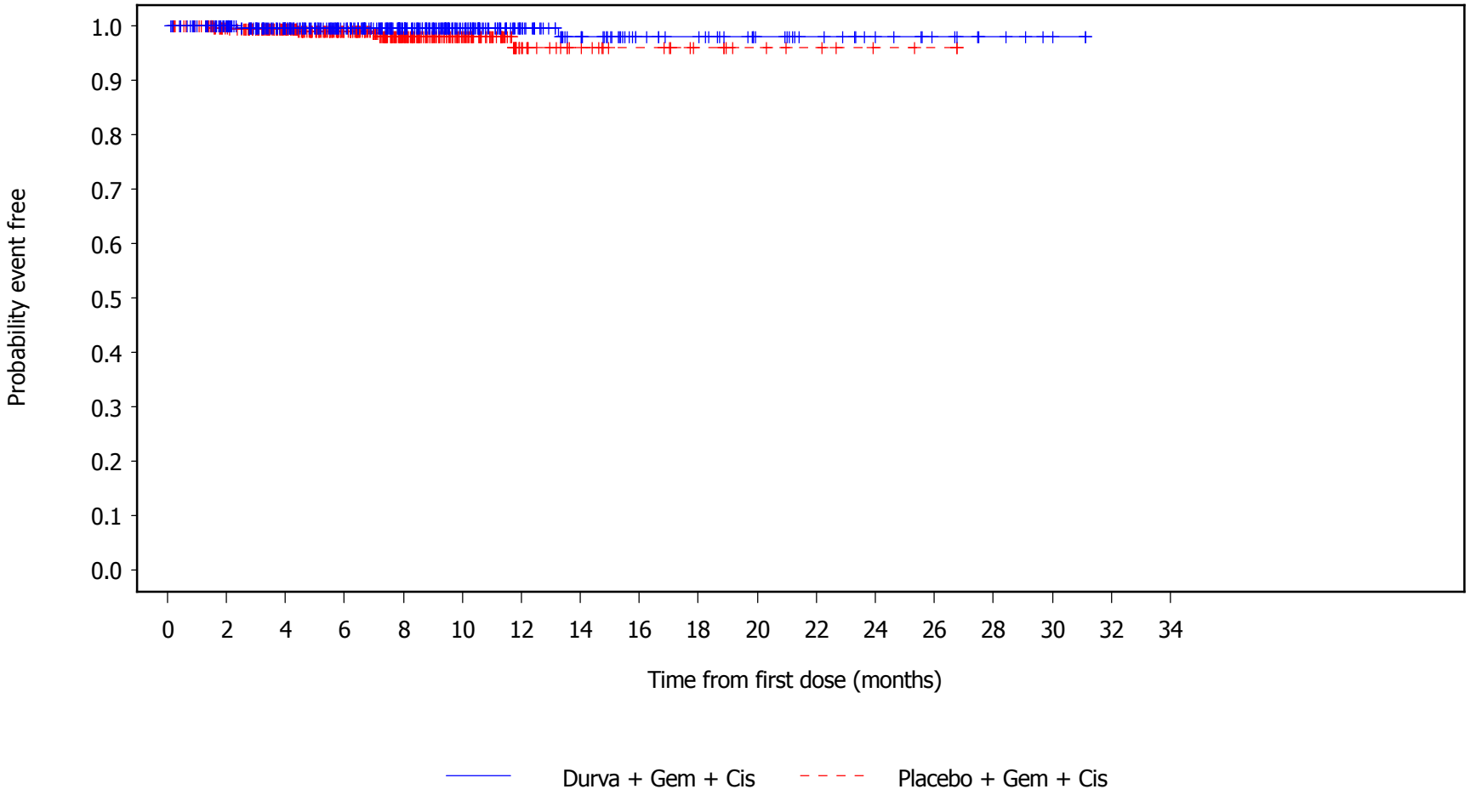
Figure 3.3.229 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hypertransaminasaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	197	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

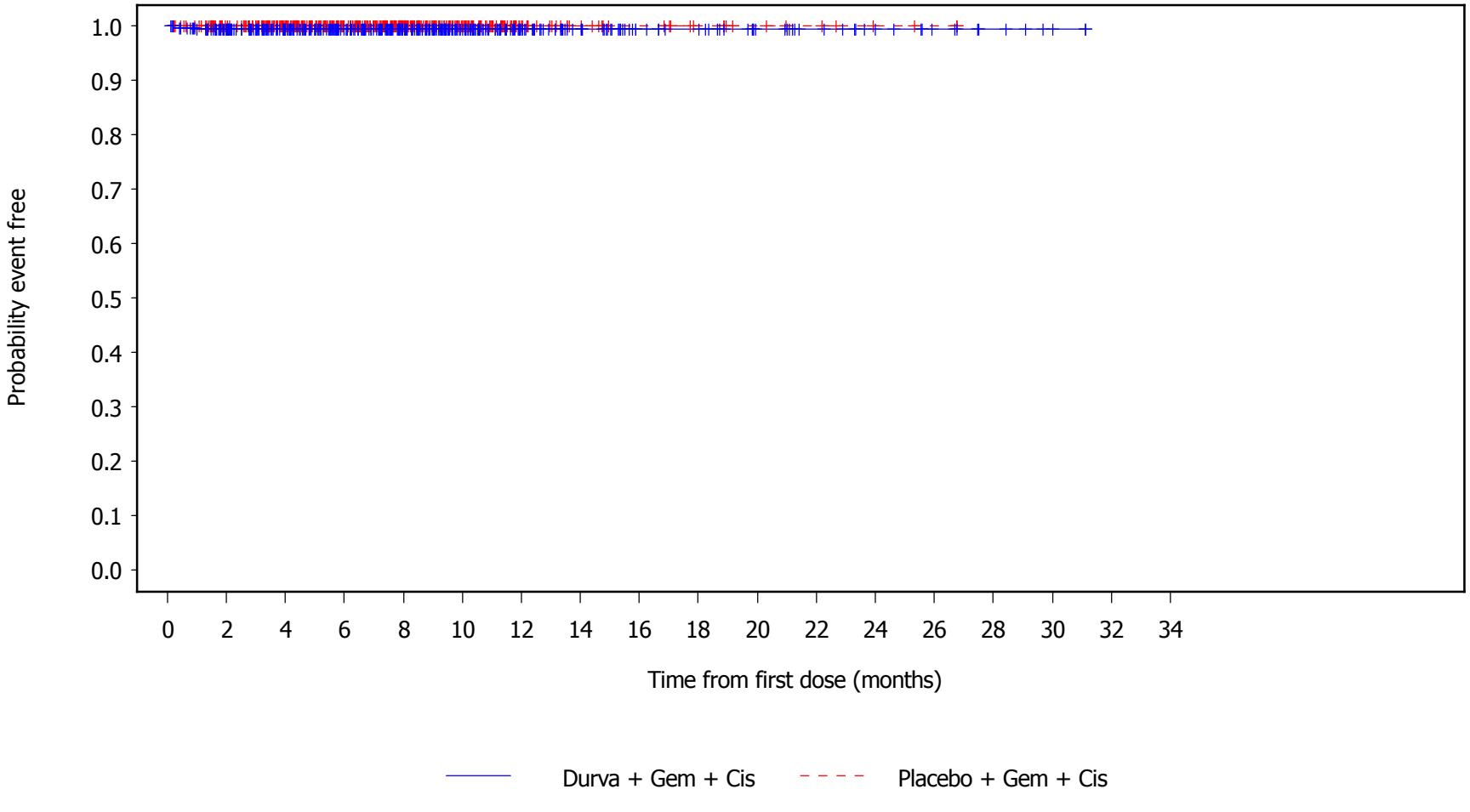
Figure 3.3.230 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	156	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

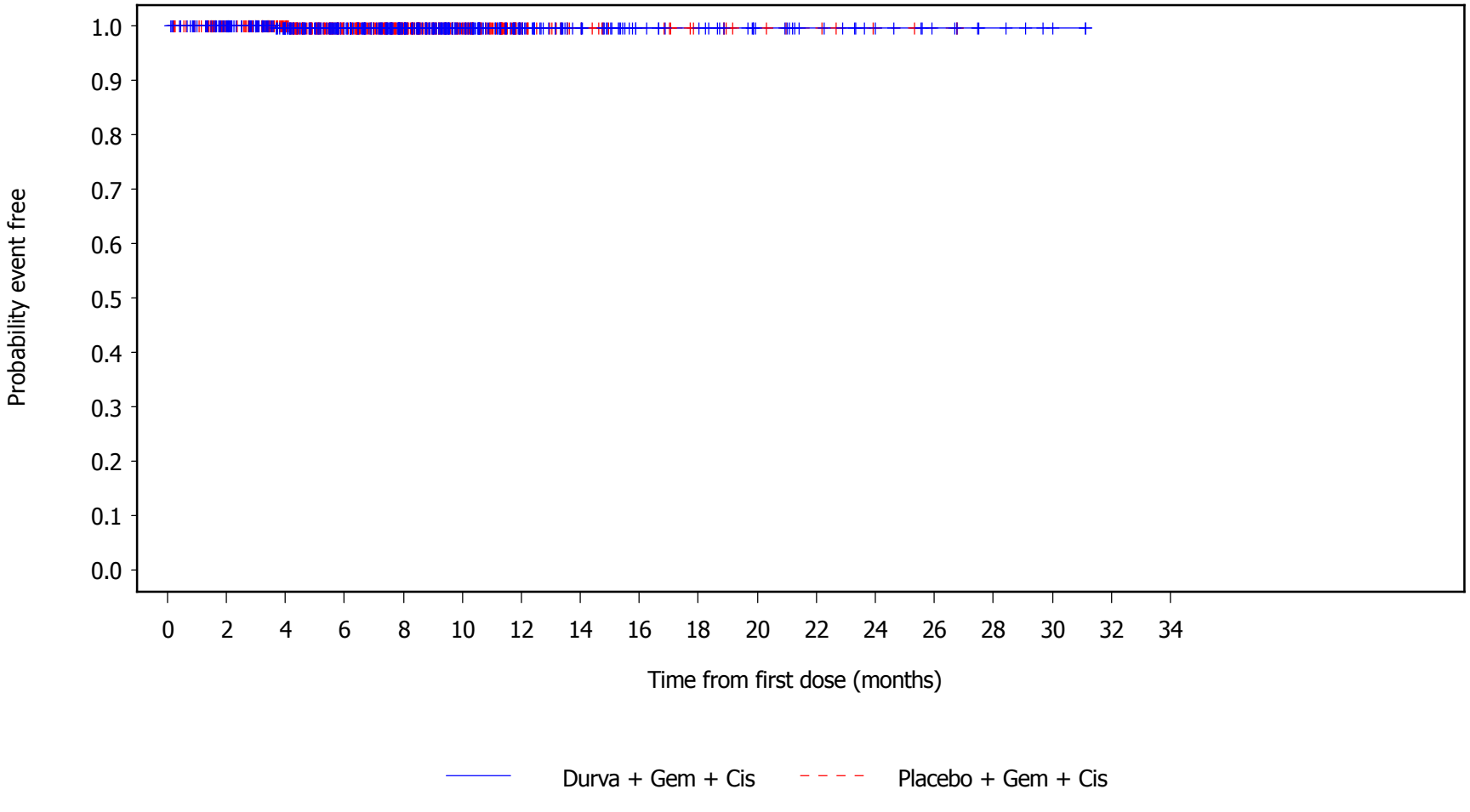
Figure 3.3.231 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Immune-mediated hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	313	262	196	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

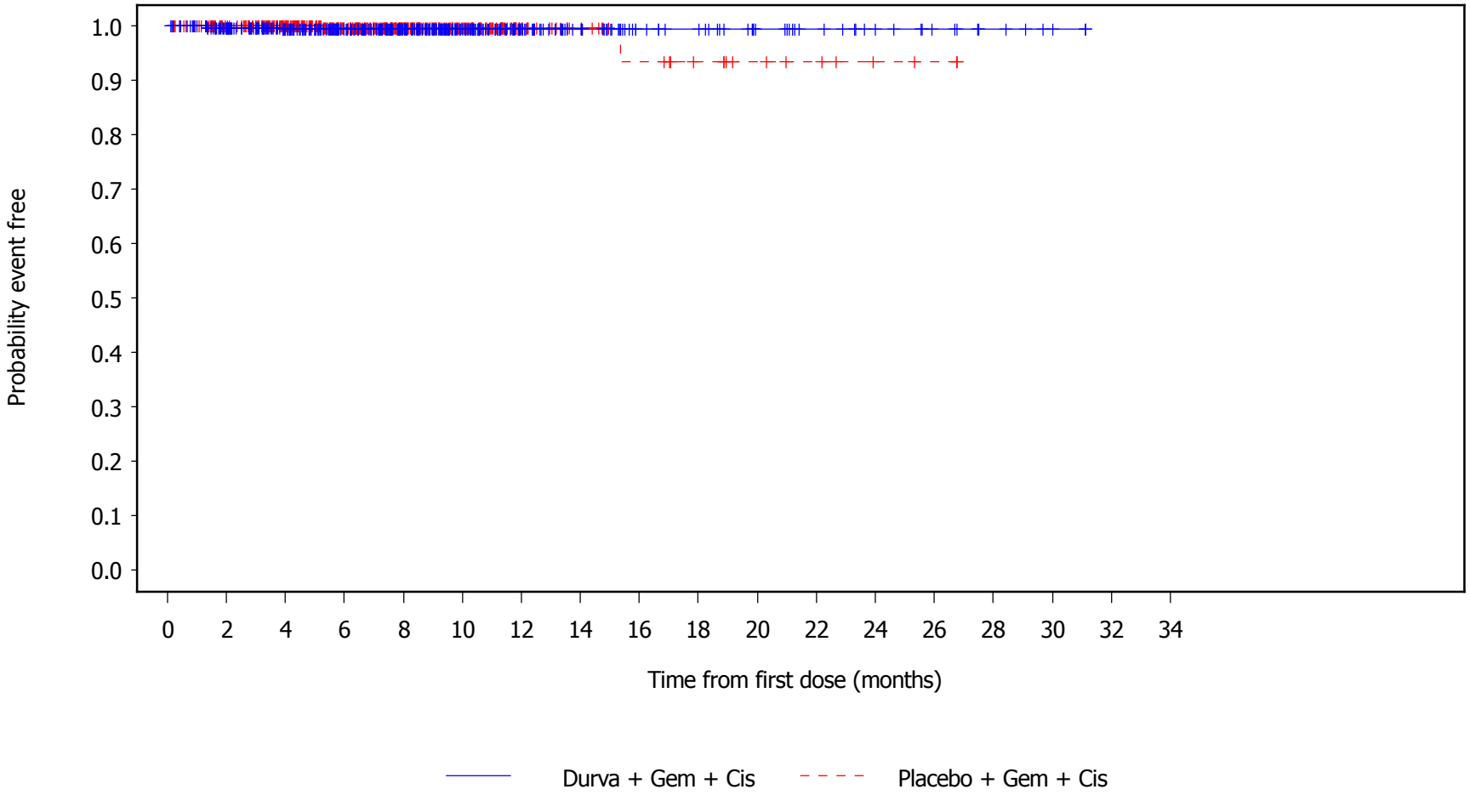
Figure 3.3.232 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: International normalised ratio increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	231	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

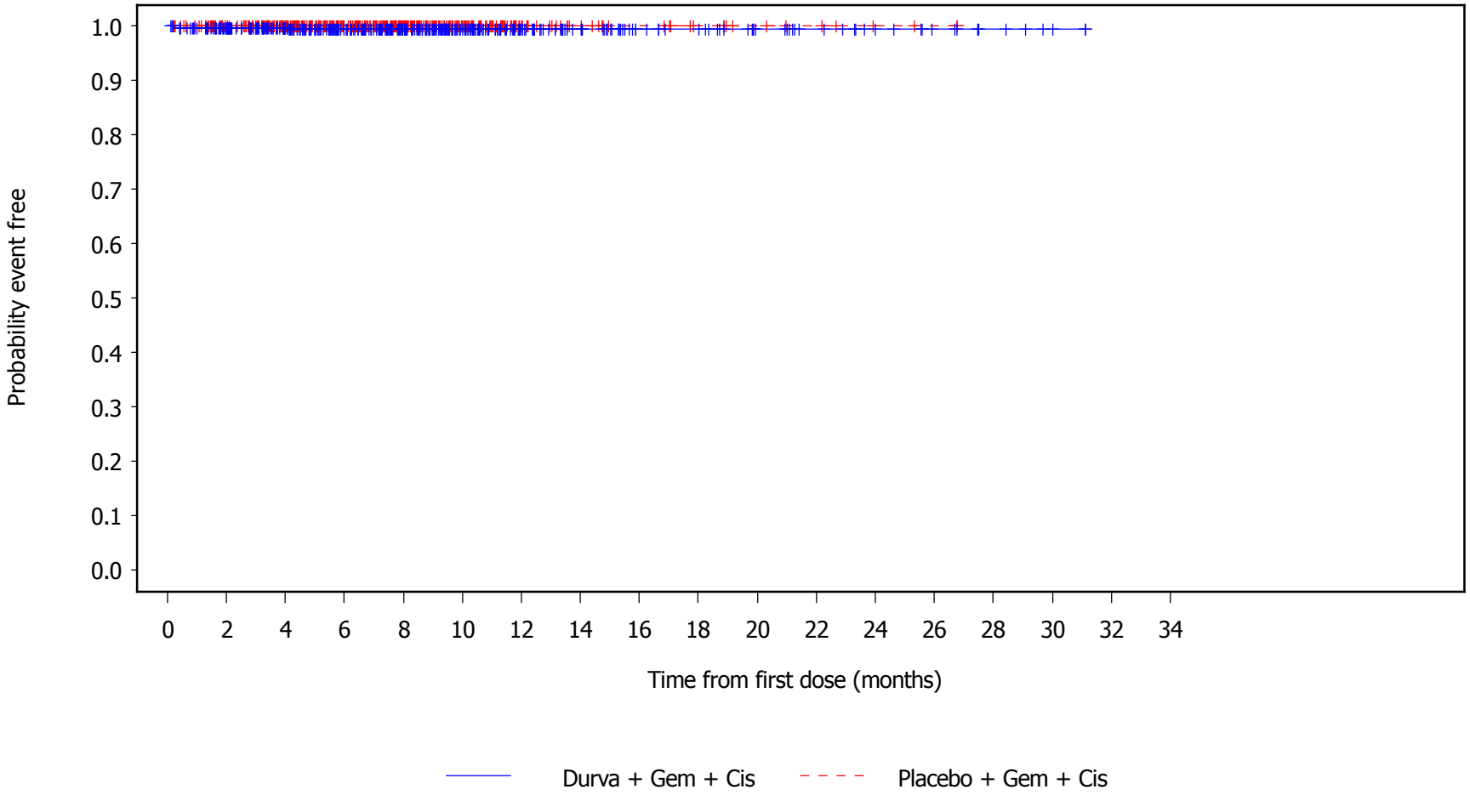
Figure 3.3.233 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Liver abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	313	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	231	159	89	34	22	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

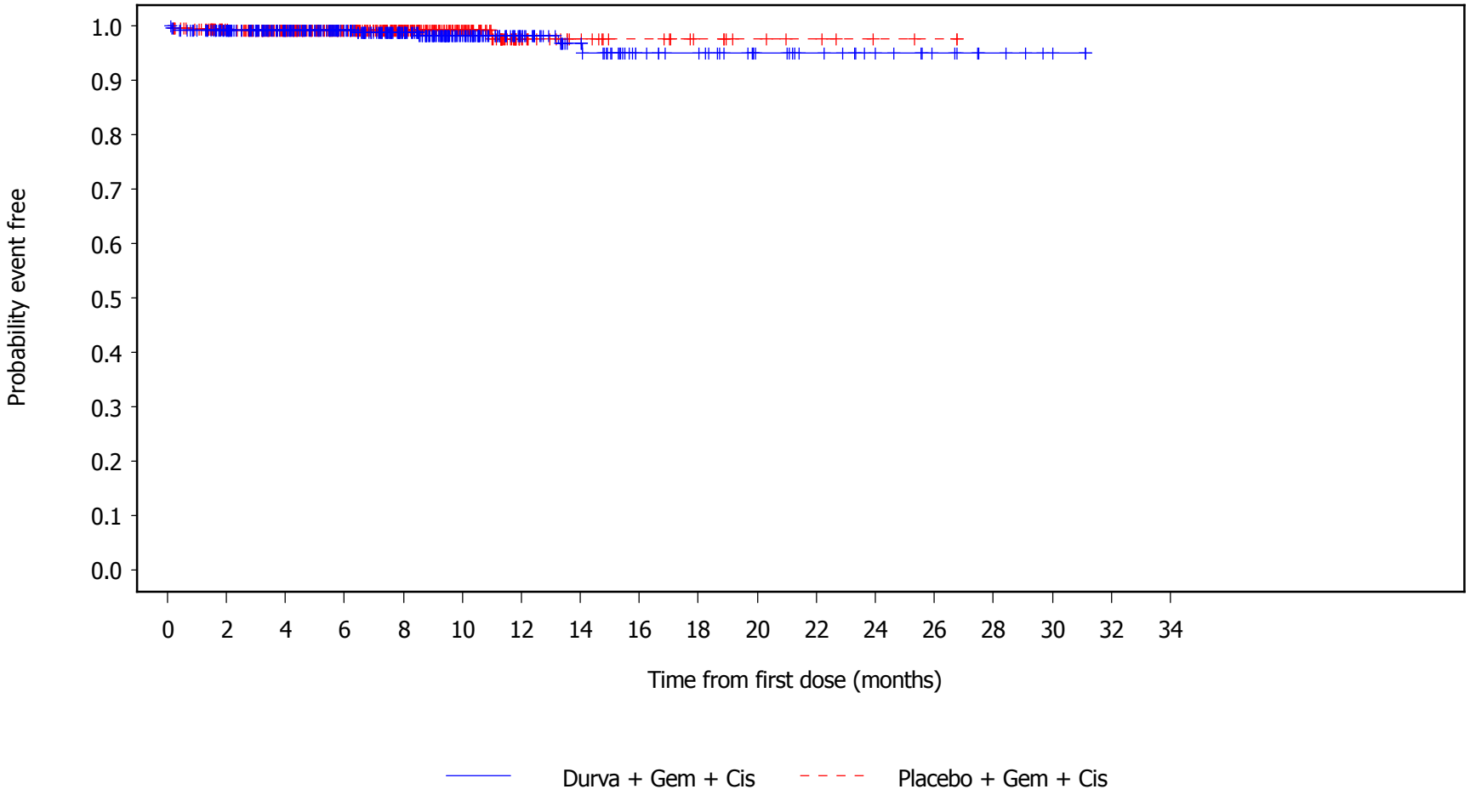
Figure 3.3.234 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hepatic enzyme increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

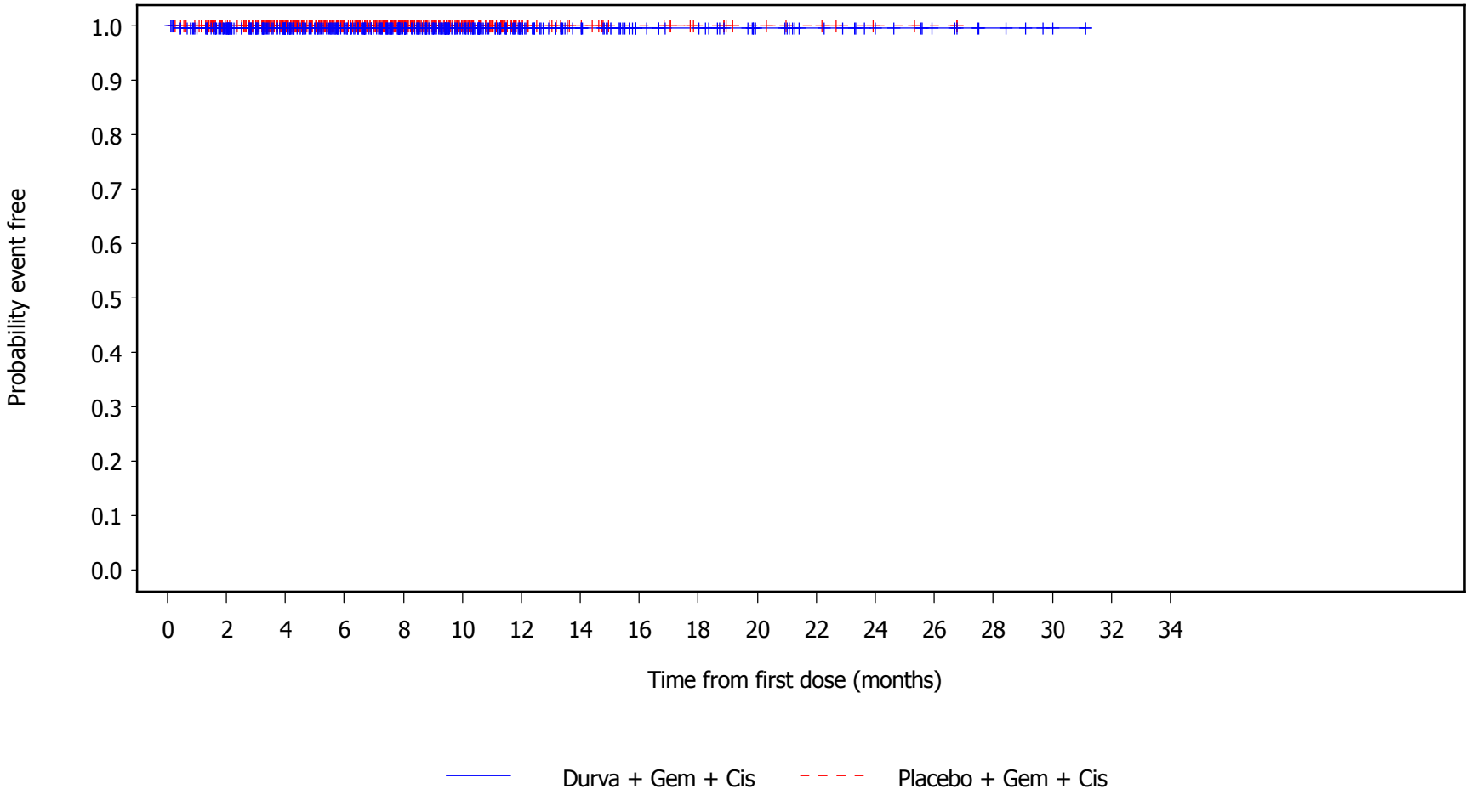
Figure 3.3.235 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hepatic function abnormal
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	264	197	129	79	58	39	35	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	310	231	159	89	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

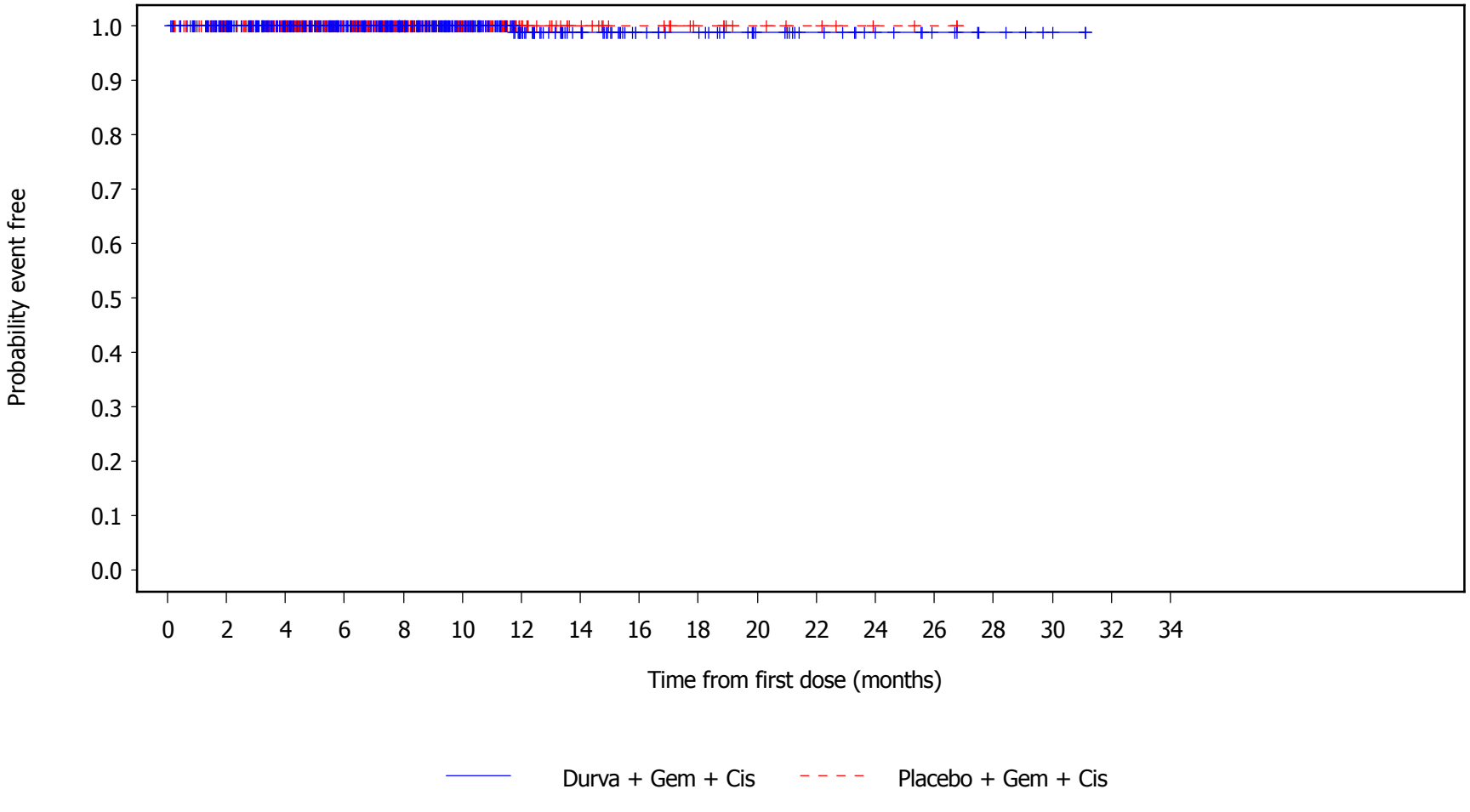
Figure 3.3.236 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Liver function test abnormal
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

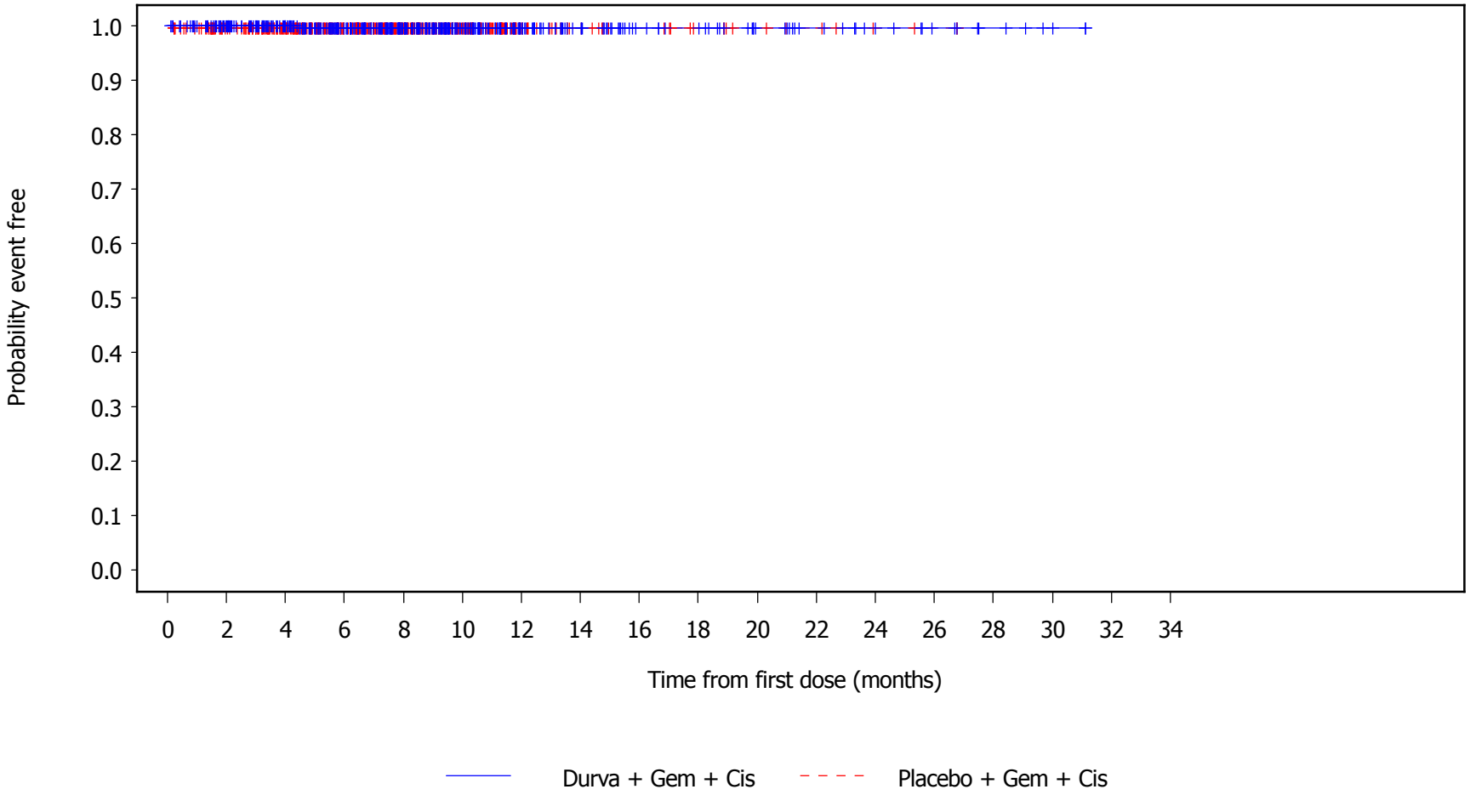
Figure 3.3.237 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Liver function test increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	79	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

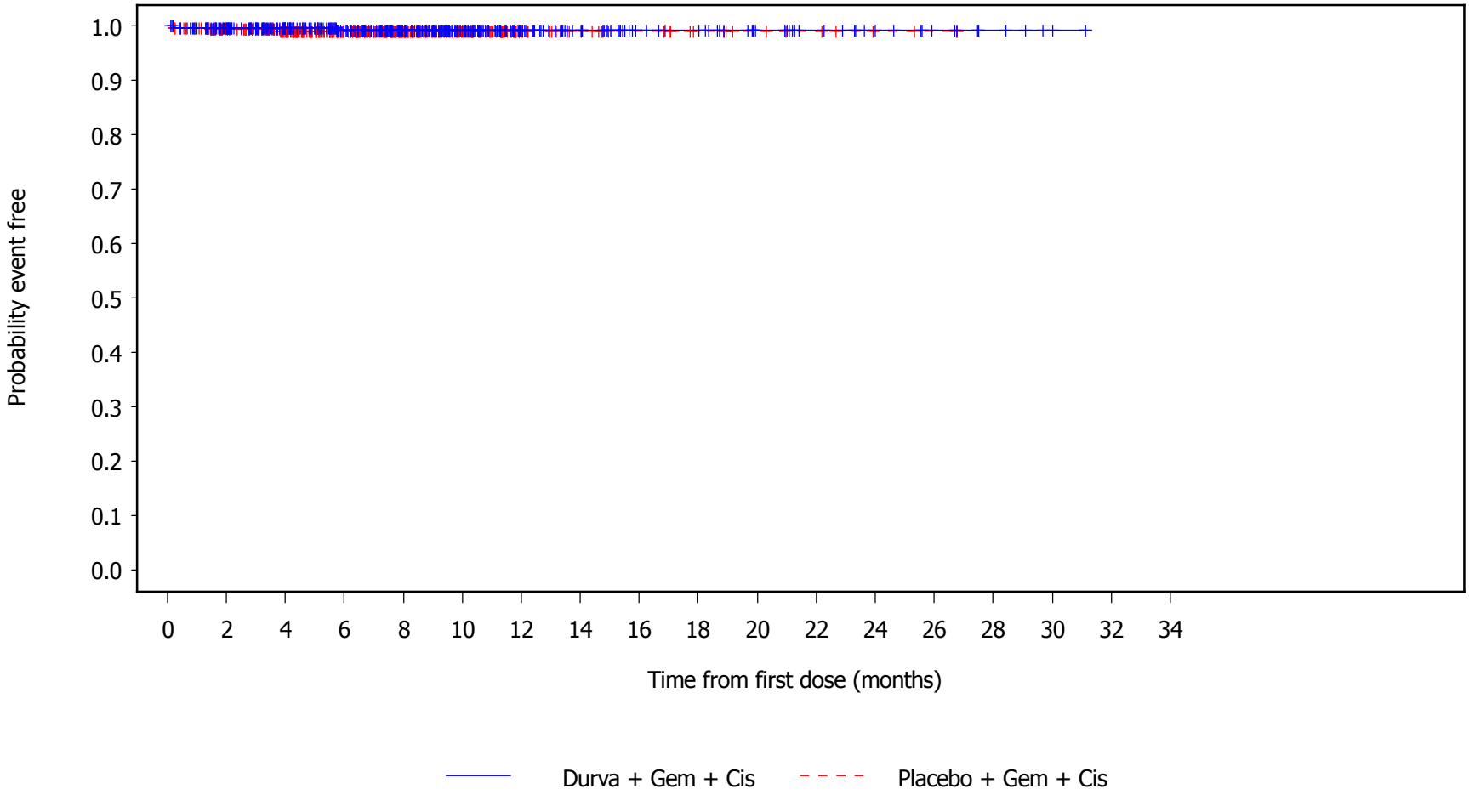
Figure 3.3.238 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hepatotoxicity
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	263	197	130	79	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

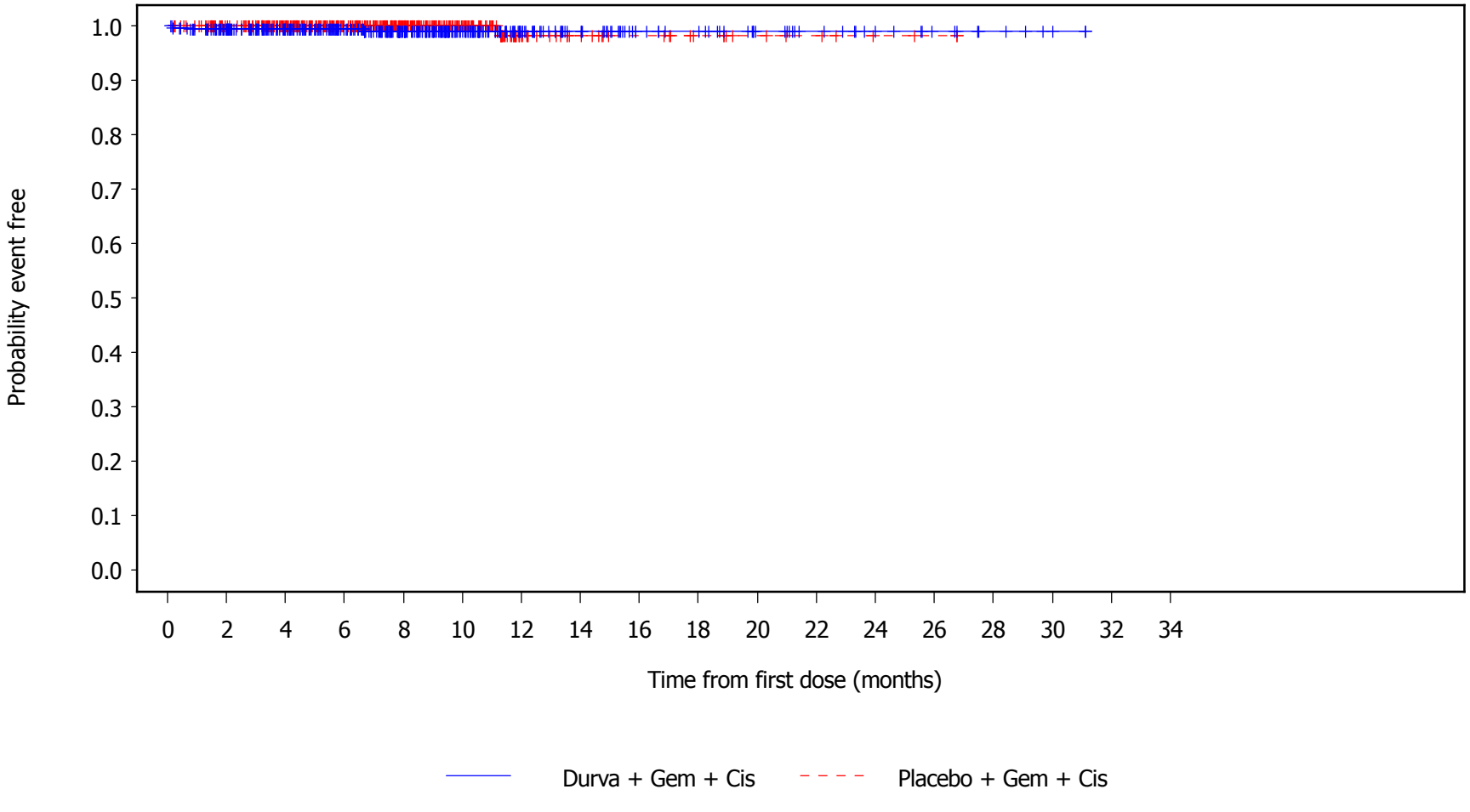
Figure 3.3.239 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	263	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	310	230	157	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

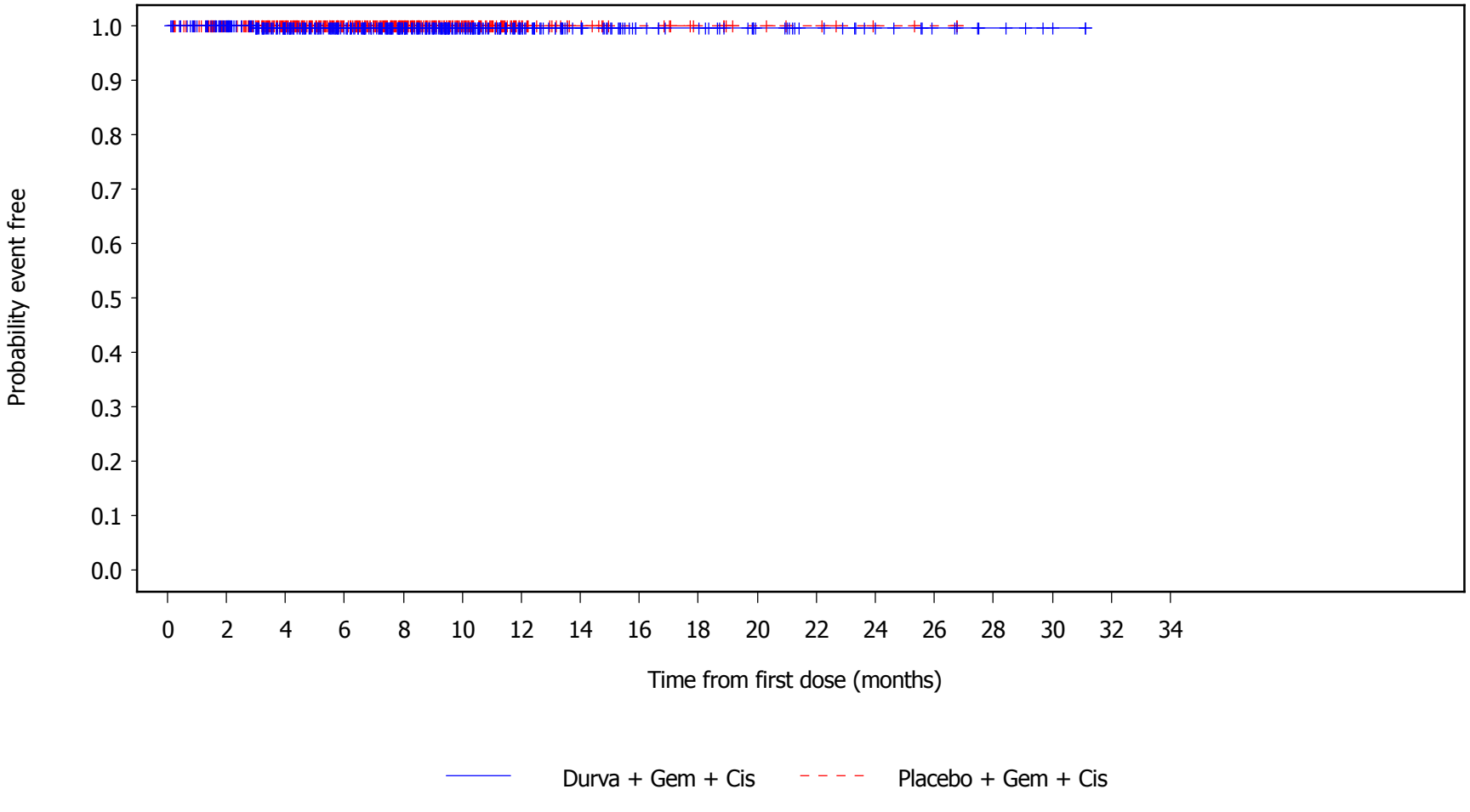
Figure 3.3.240 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hepatic failure
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	197	130	79	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

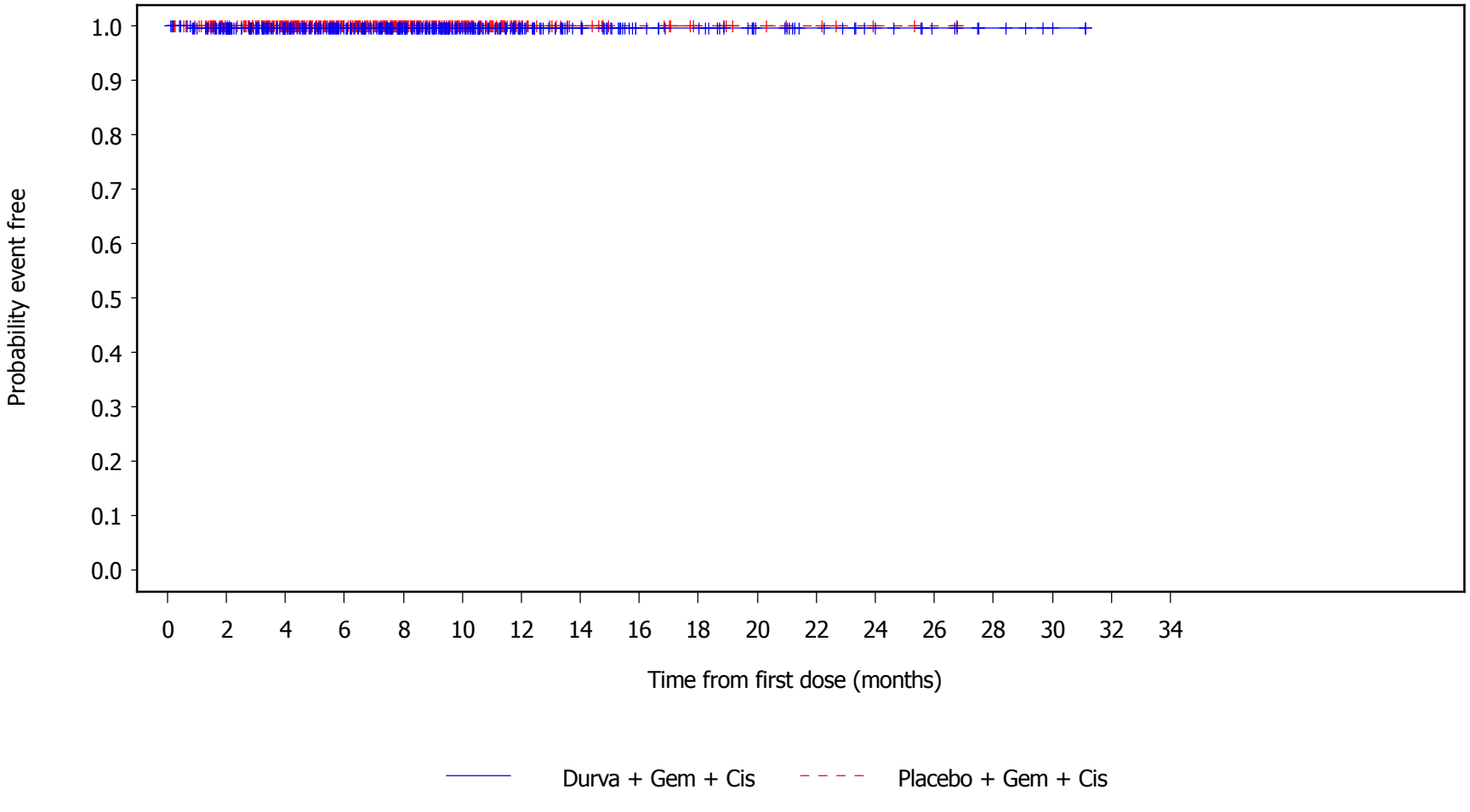
Figure 3.3.241 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Oesophageal varices haemorrhage
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

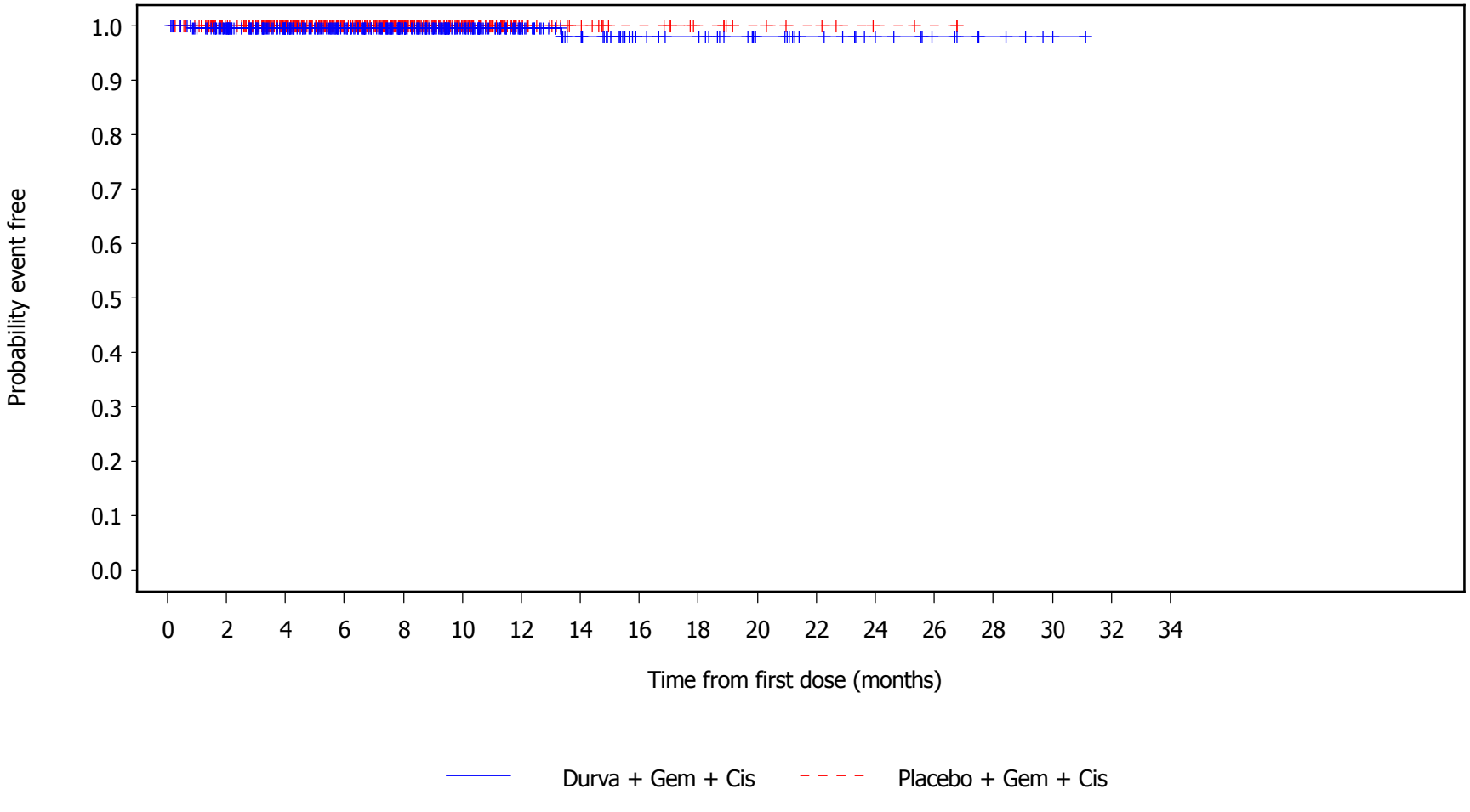
Figure 3.3.242 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Prothrombin level decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

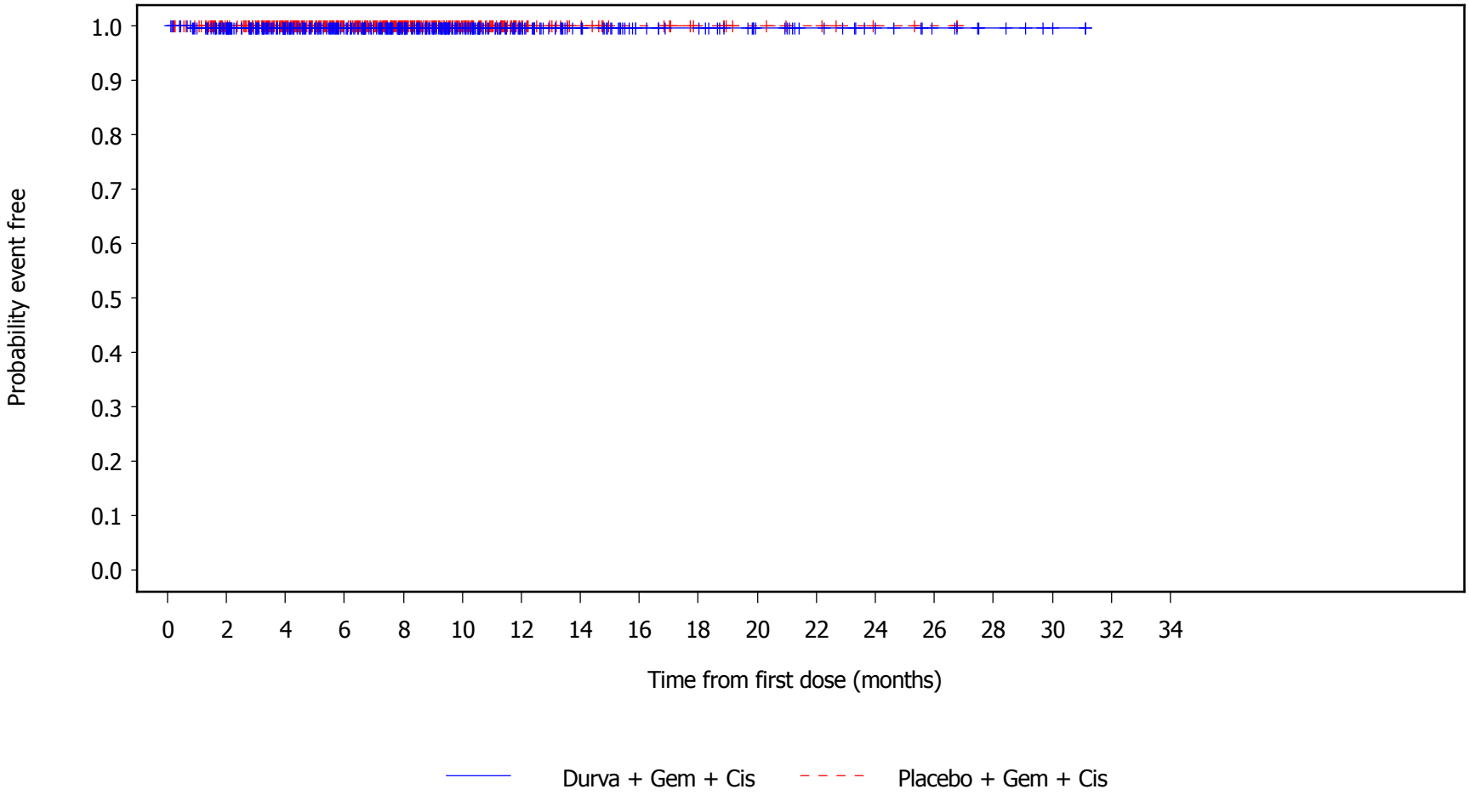
Figure 3.3.243 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Prothrombin time prolonged
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

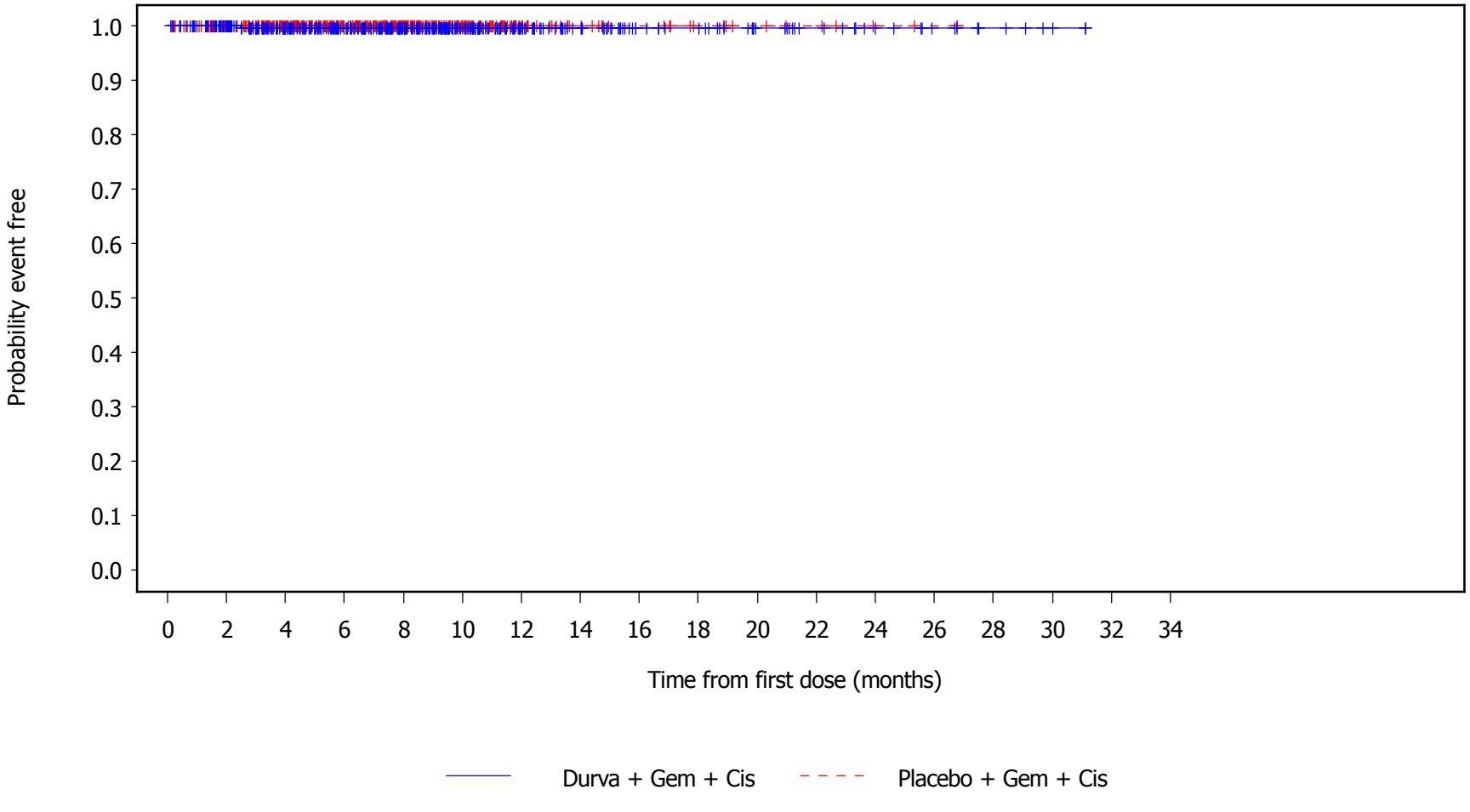
Figure 3.3.244 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Prothrombin time ratio increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

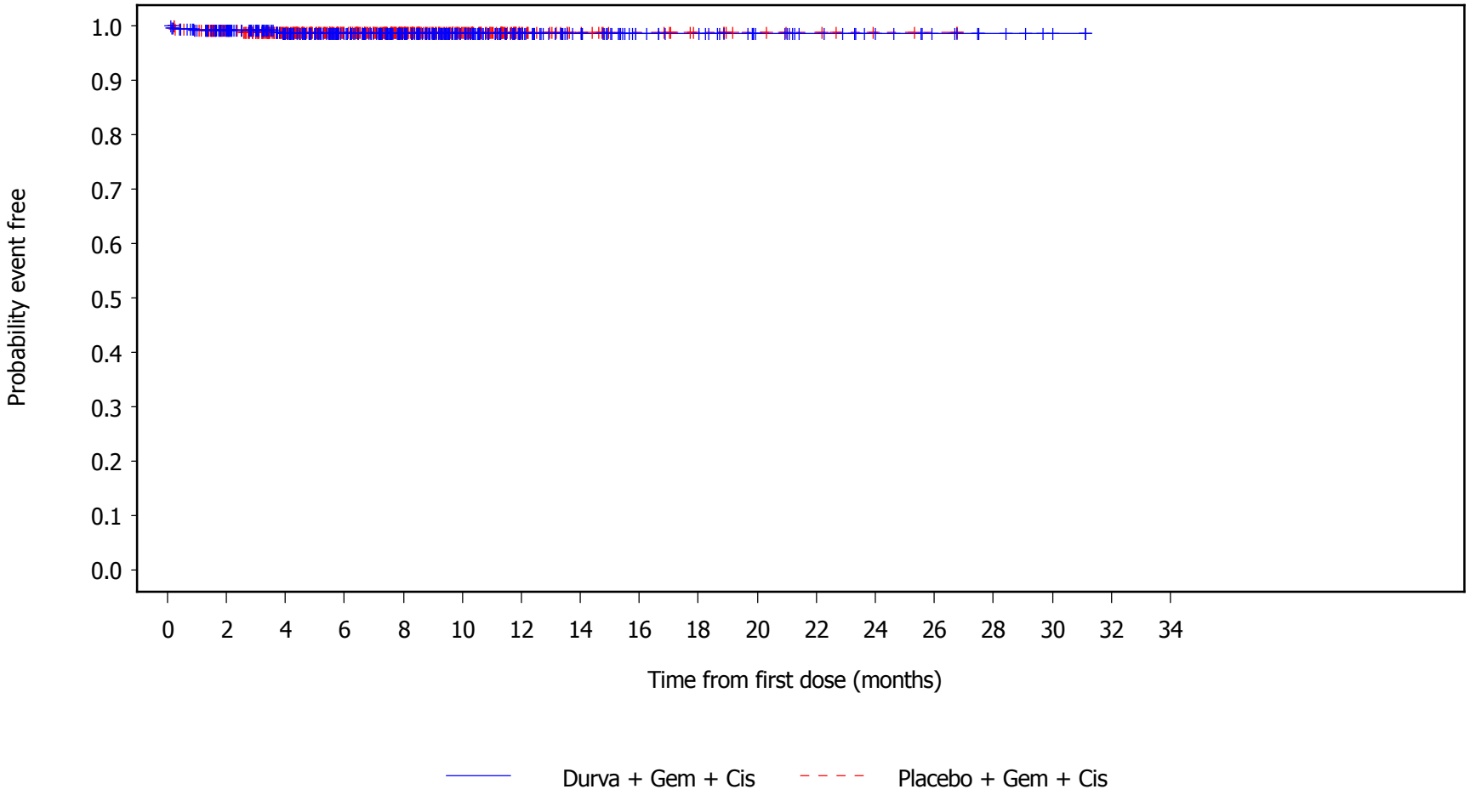
Figure 3.3.245 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hepatitis B reactivation
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

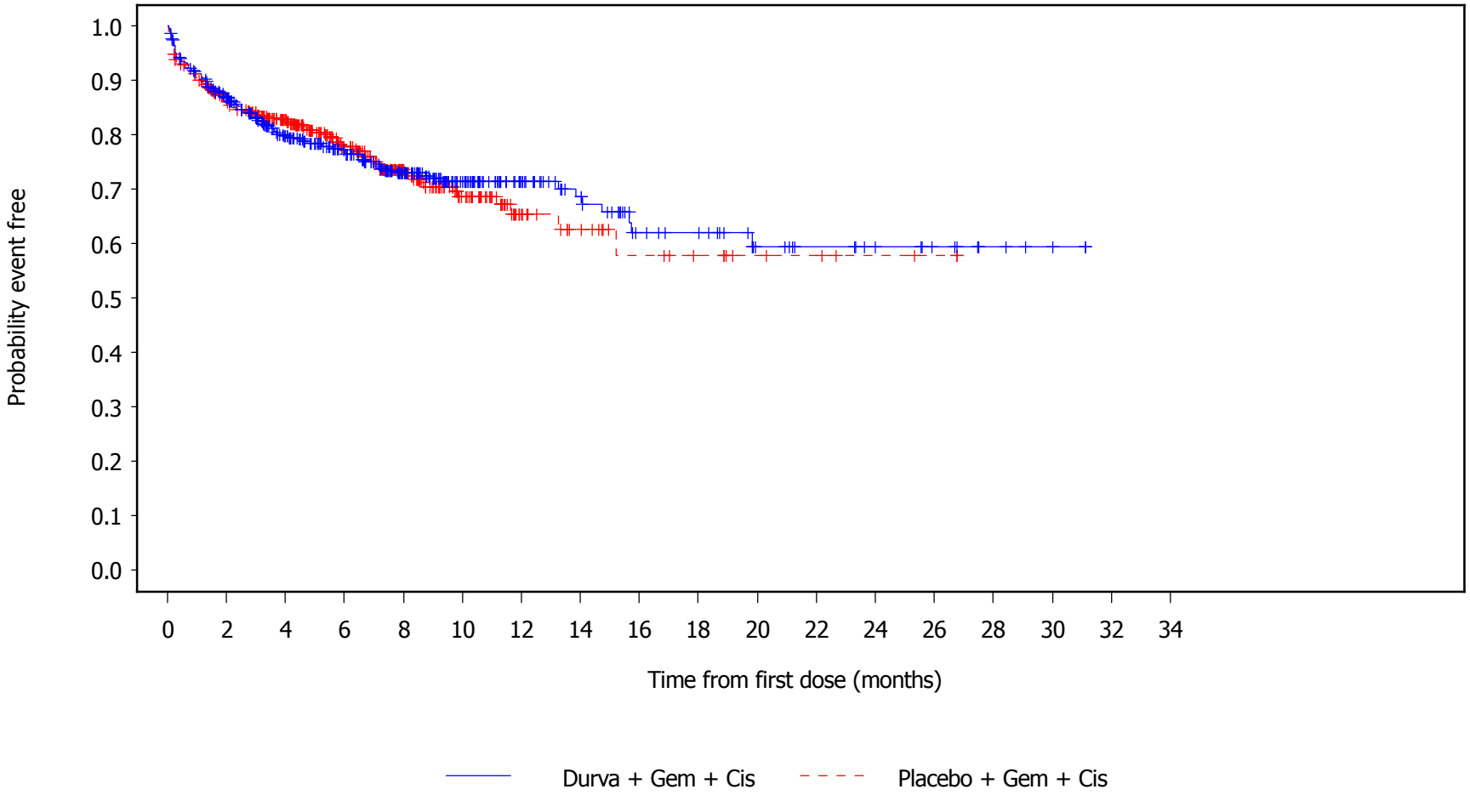
Figure 3.3.246 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Transaminases increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	311	260	195	128	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	311	230	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

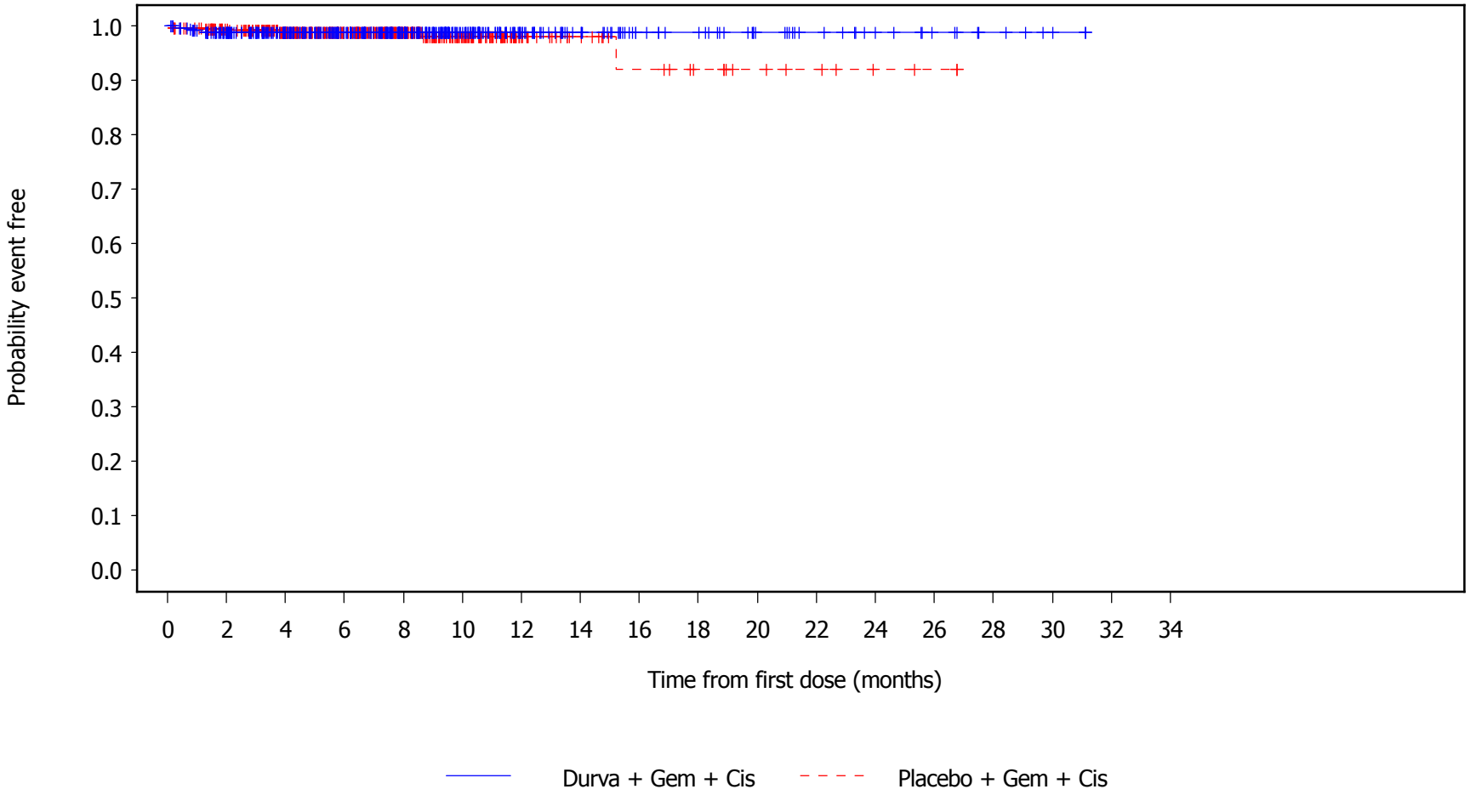
Figure 3.3.247 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Biliary SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	330	265	220	161	107	67	49	32	29	19	15	12	8	4	2	0	0	Durva + Gem + Cis
403	322	267	191	127	70	28	19	12	9	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

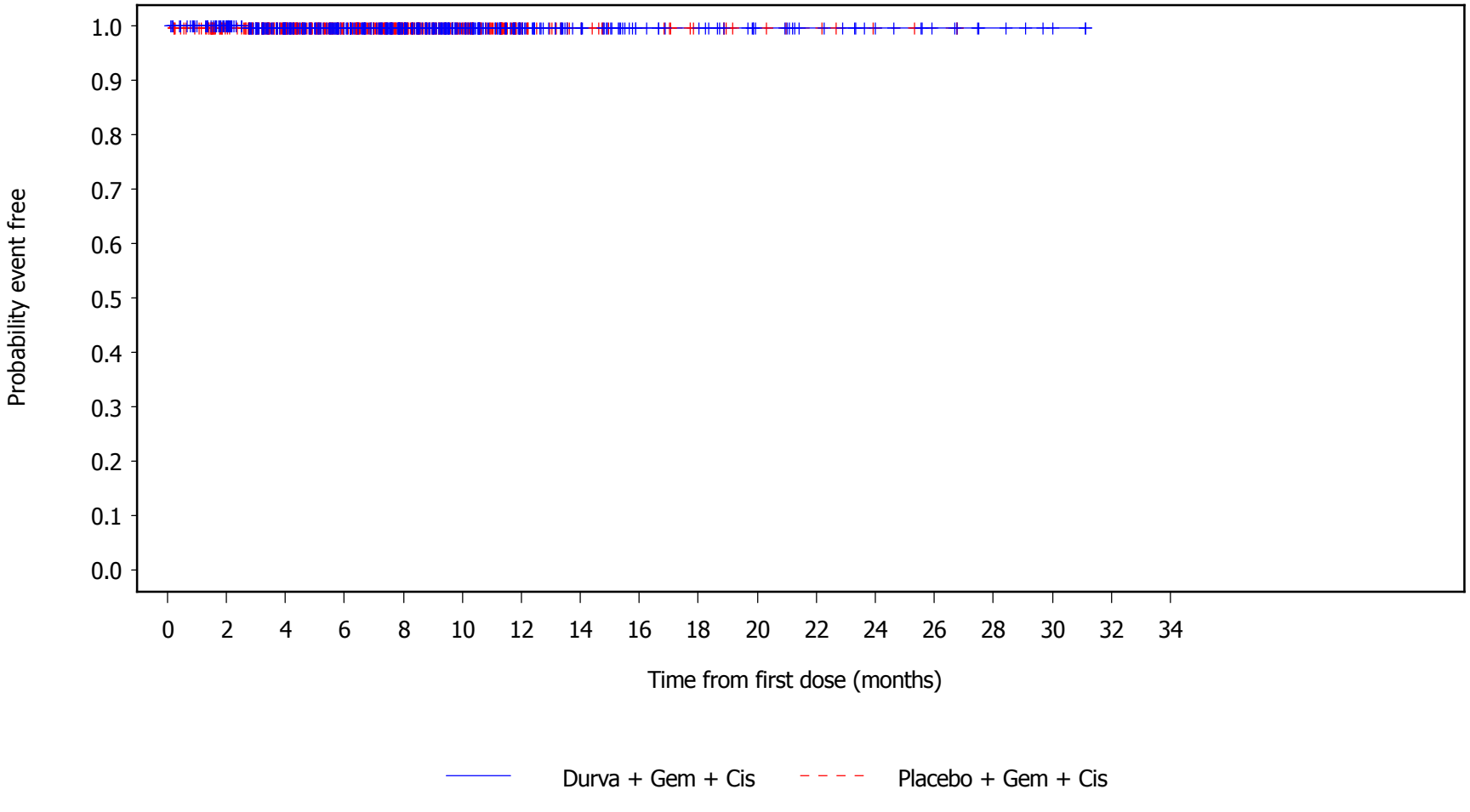
Figure 3.3.248 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Cholangitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	311	261	197	130	79	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	310	229	157	88	34	22	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

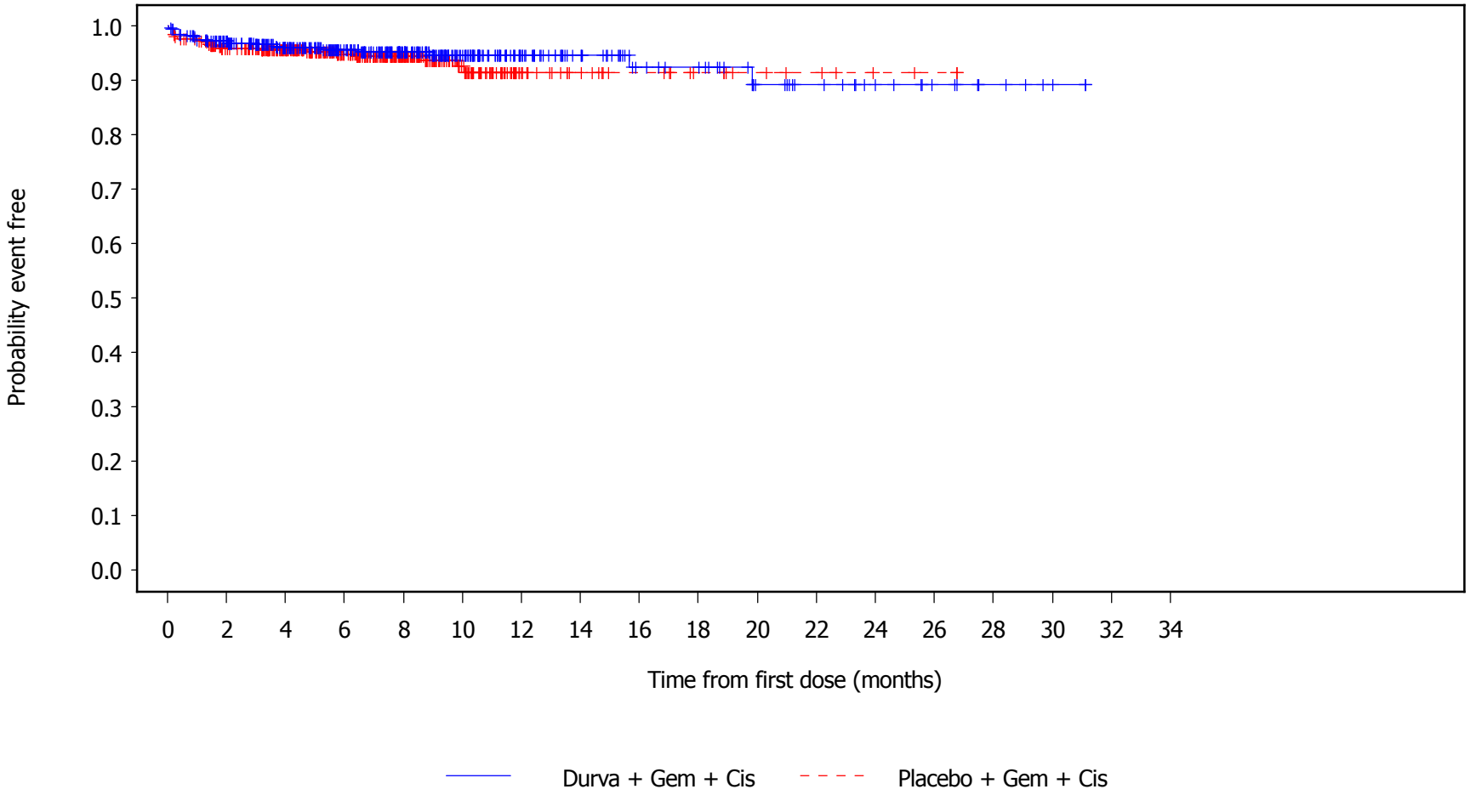
Figure 3.3.249 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Cholecystitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

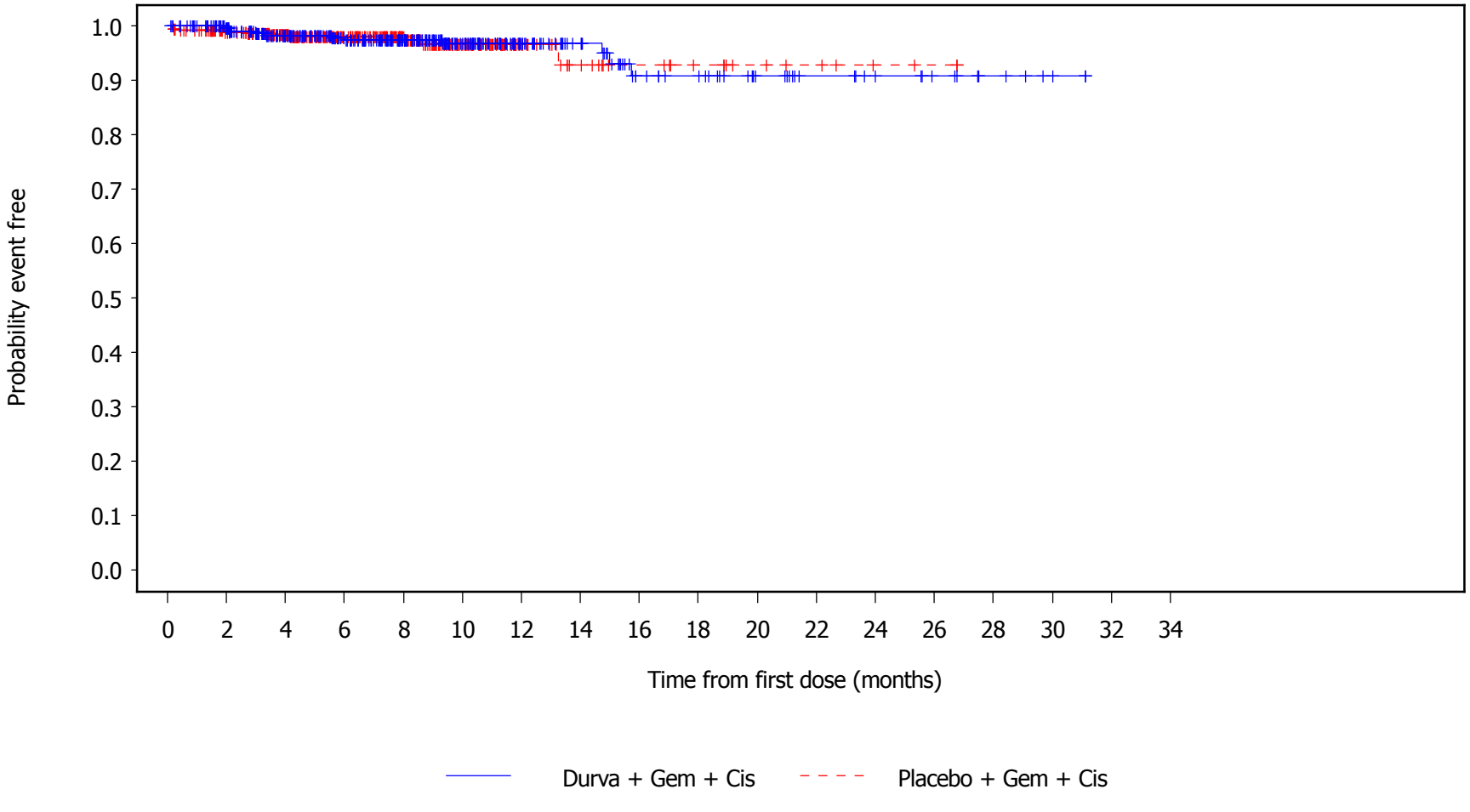
Figure 3.3.250 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Blood alkaline phosphatase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	363	304	252	188	124	77	55	39	36	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	356	298	221	151	84	32	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

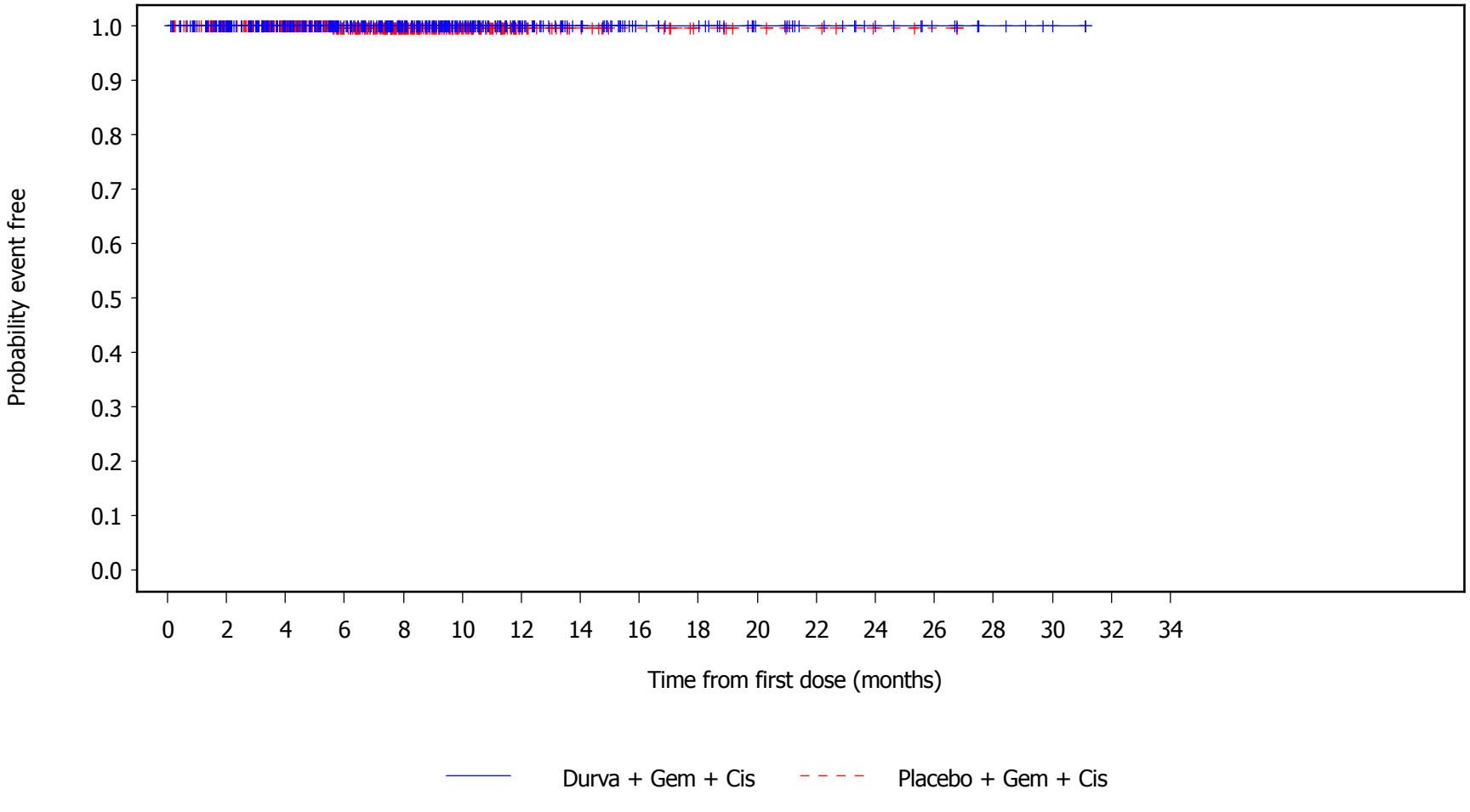
Figure 3.3.251 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Biliary obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	310	260	196	129	78	56	36	32	22	16	13	9	5	2	0	0	Durva + Gem + Cis
403	368	309	228	156	86	33	21	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

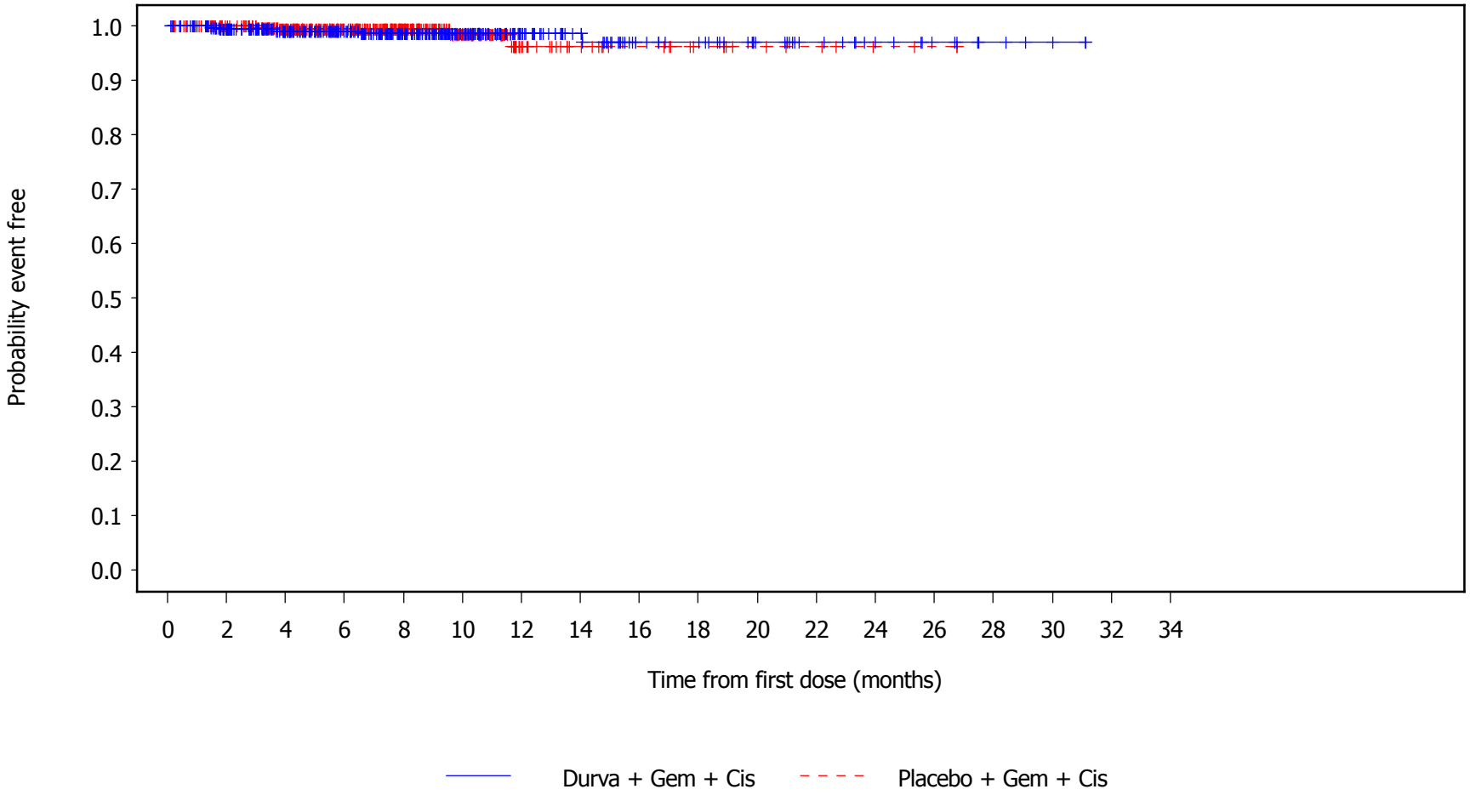
Figure 3.3.252 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Biliary abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	231	158	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

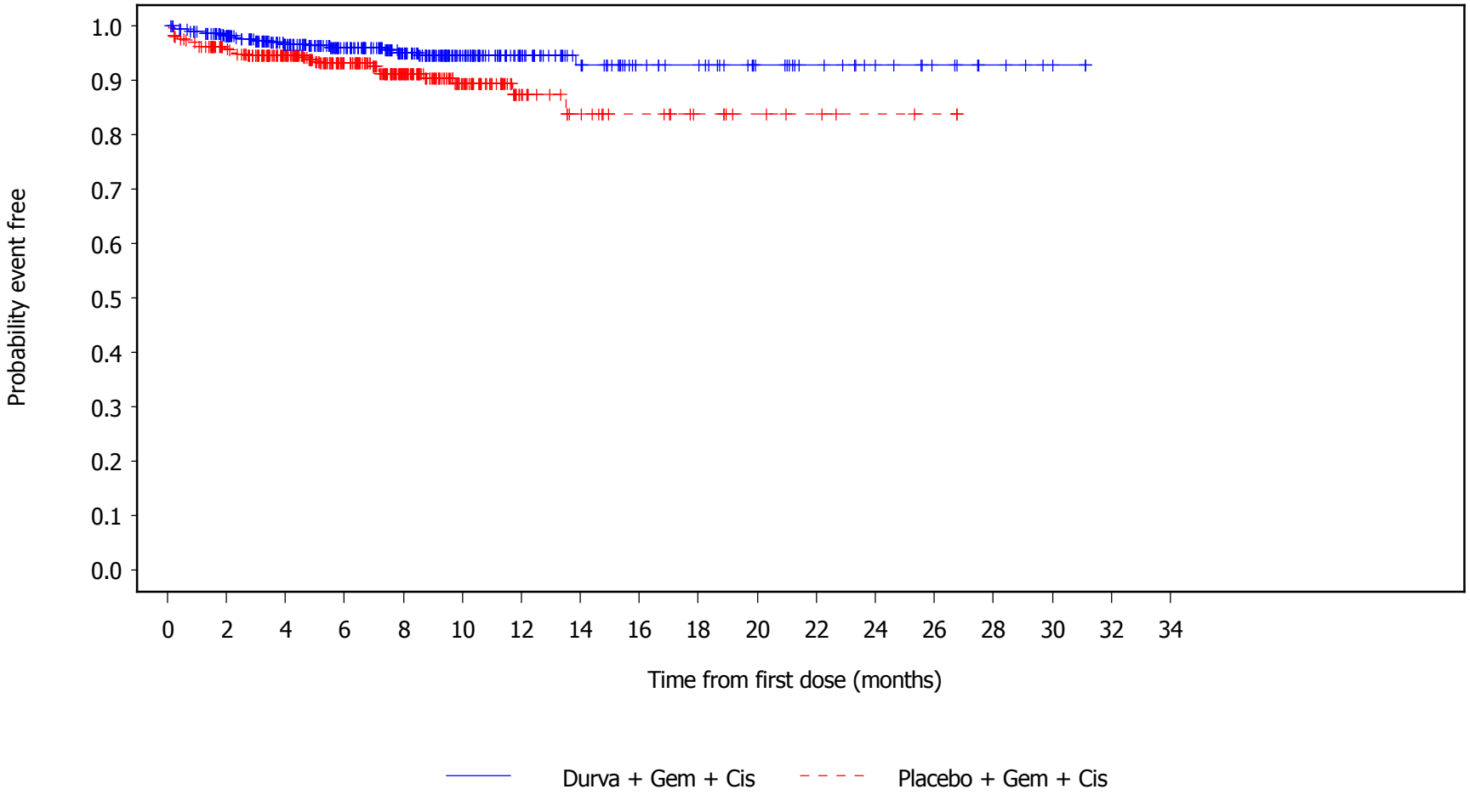
Figure 3.3.253 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Biliary sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	264	197	130	79	58	39	35	24	18	13	8	4	2	0	0	Durva + Gem + Cis
403	371	311	231	158	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

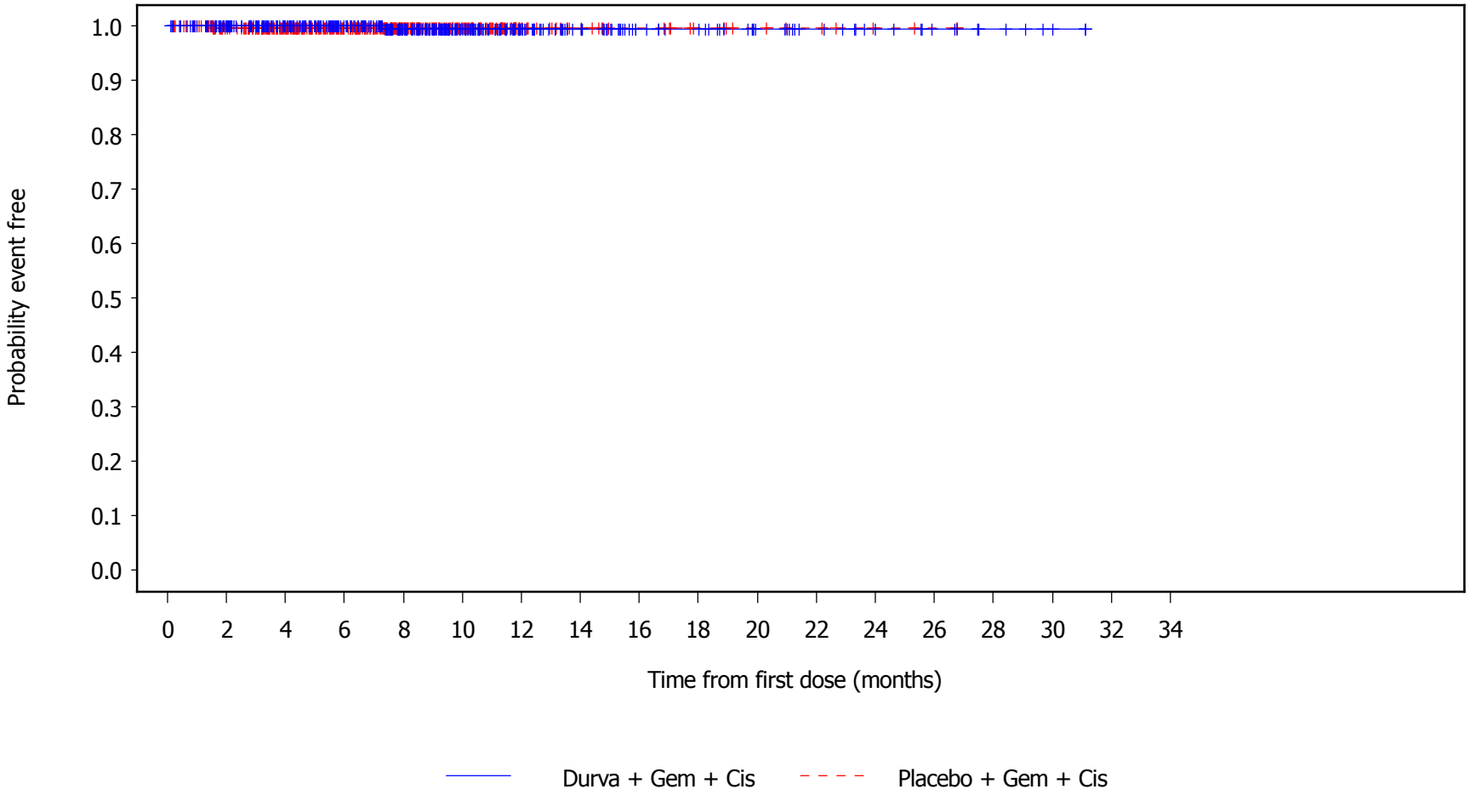
Figure 3.3.254 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	368	307	258	193	125	79	56	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	358	300	221	150	83	32	21	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

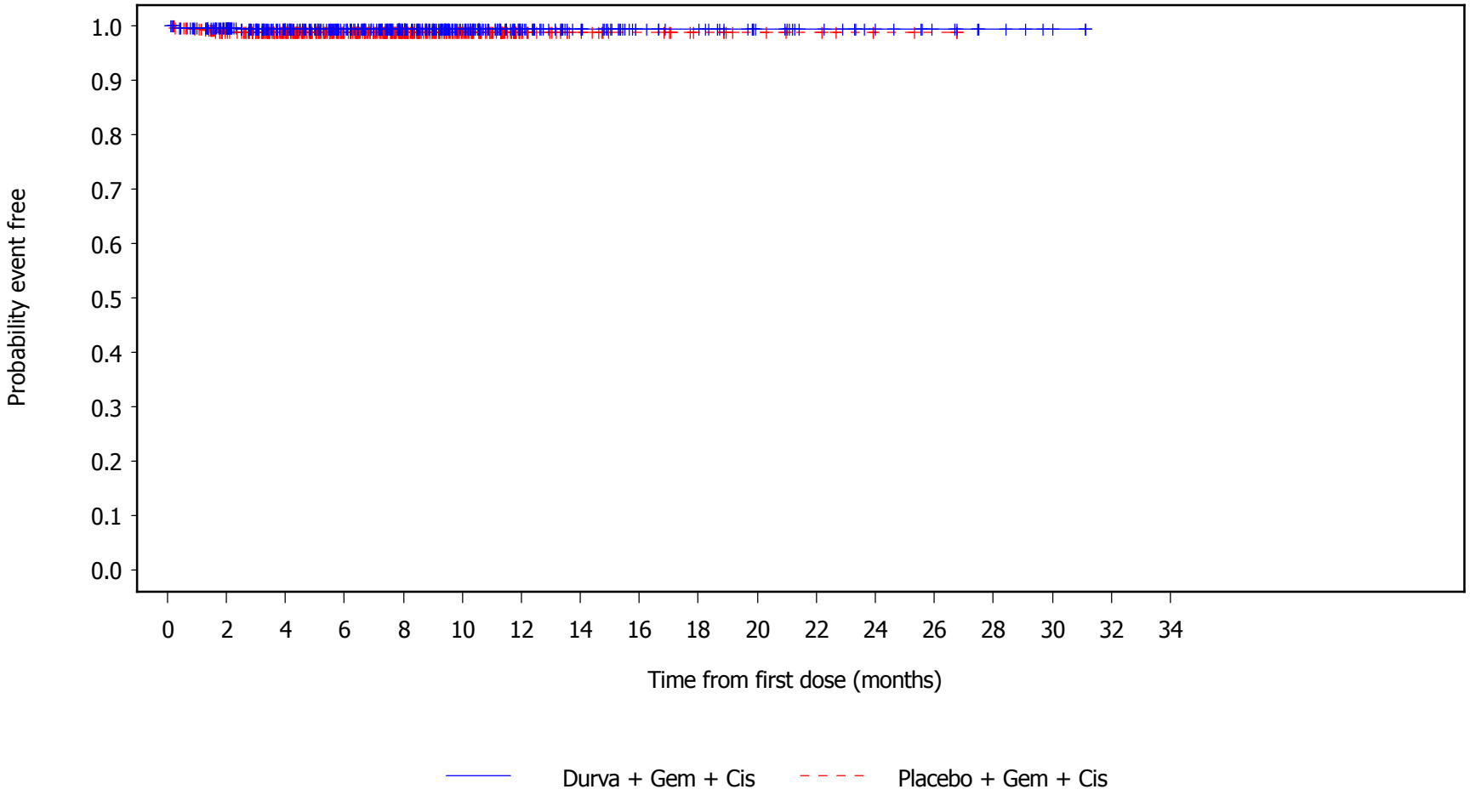
Figure 3.3.255 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Blood bilirubin unconjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	197	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

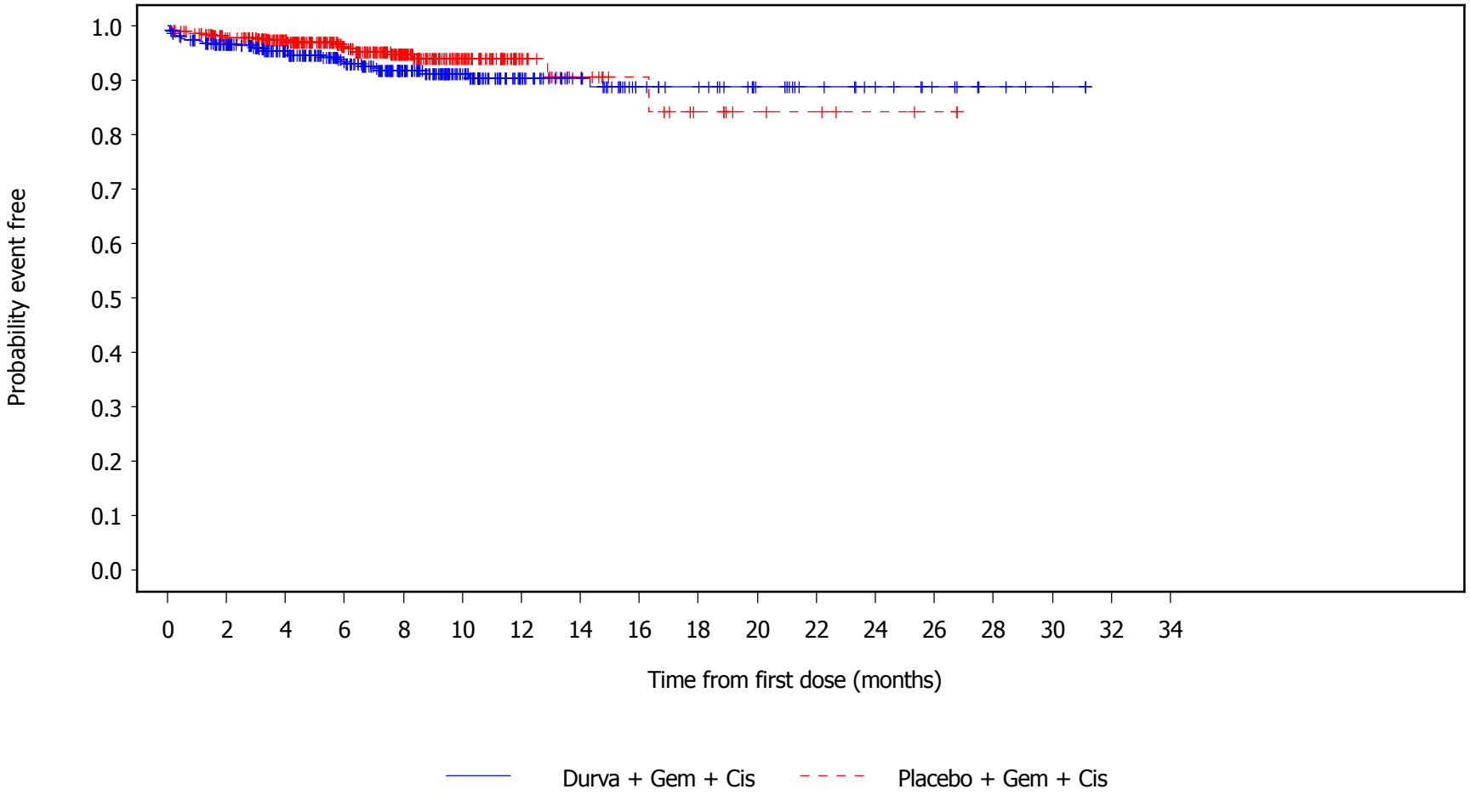
Figure 3.3.256 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Bilirubin conjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	311	231	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

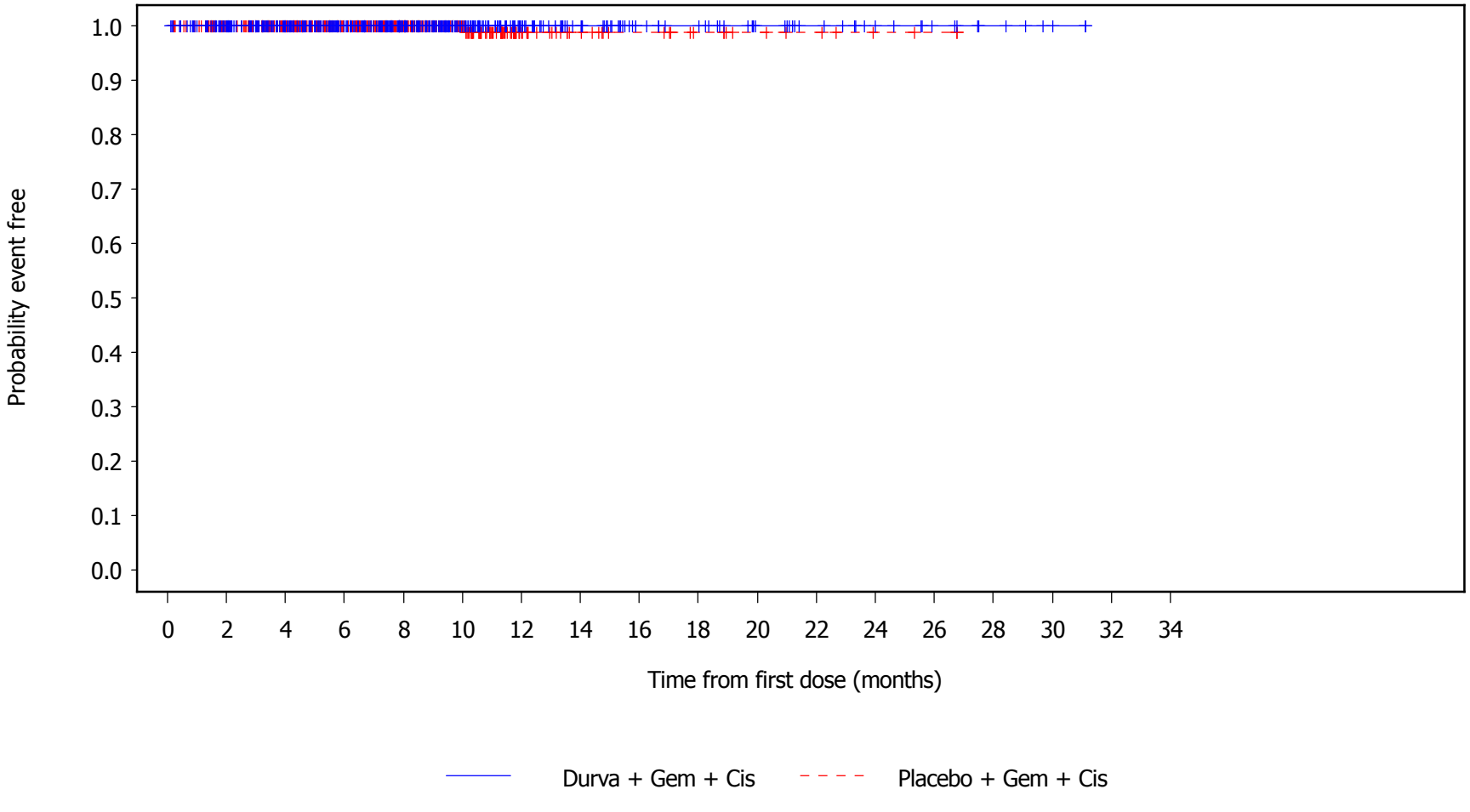
Figure 3.3.257 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Cholangitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	363	304	250	183	122	73	55	37	33	23	17	13	8	4	2	0	0	Durva + Gem + Cis
403	363	305	223	152	85	33	20	14	9	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

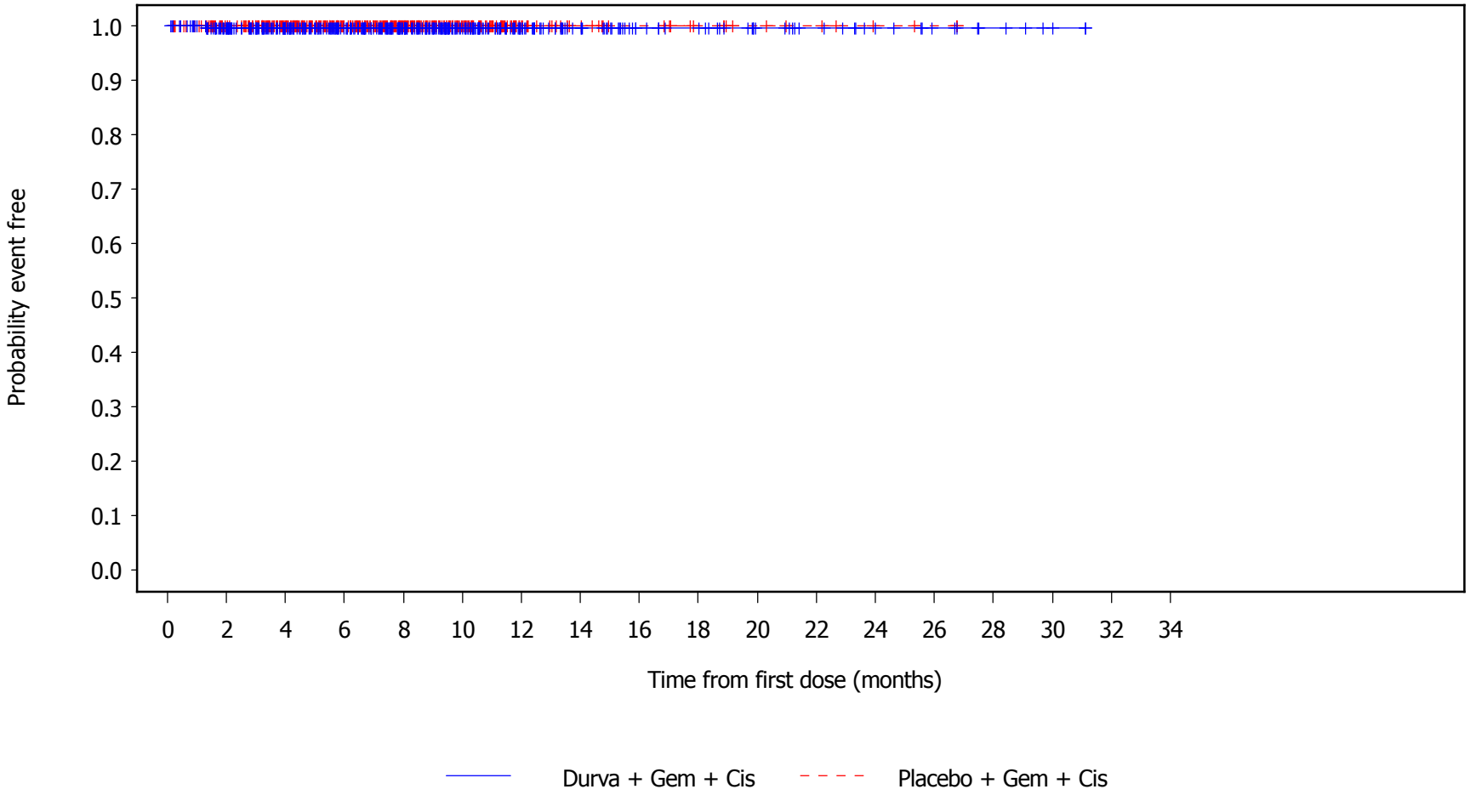
Figure 3.3.258 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Cholangitis infective
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

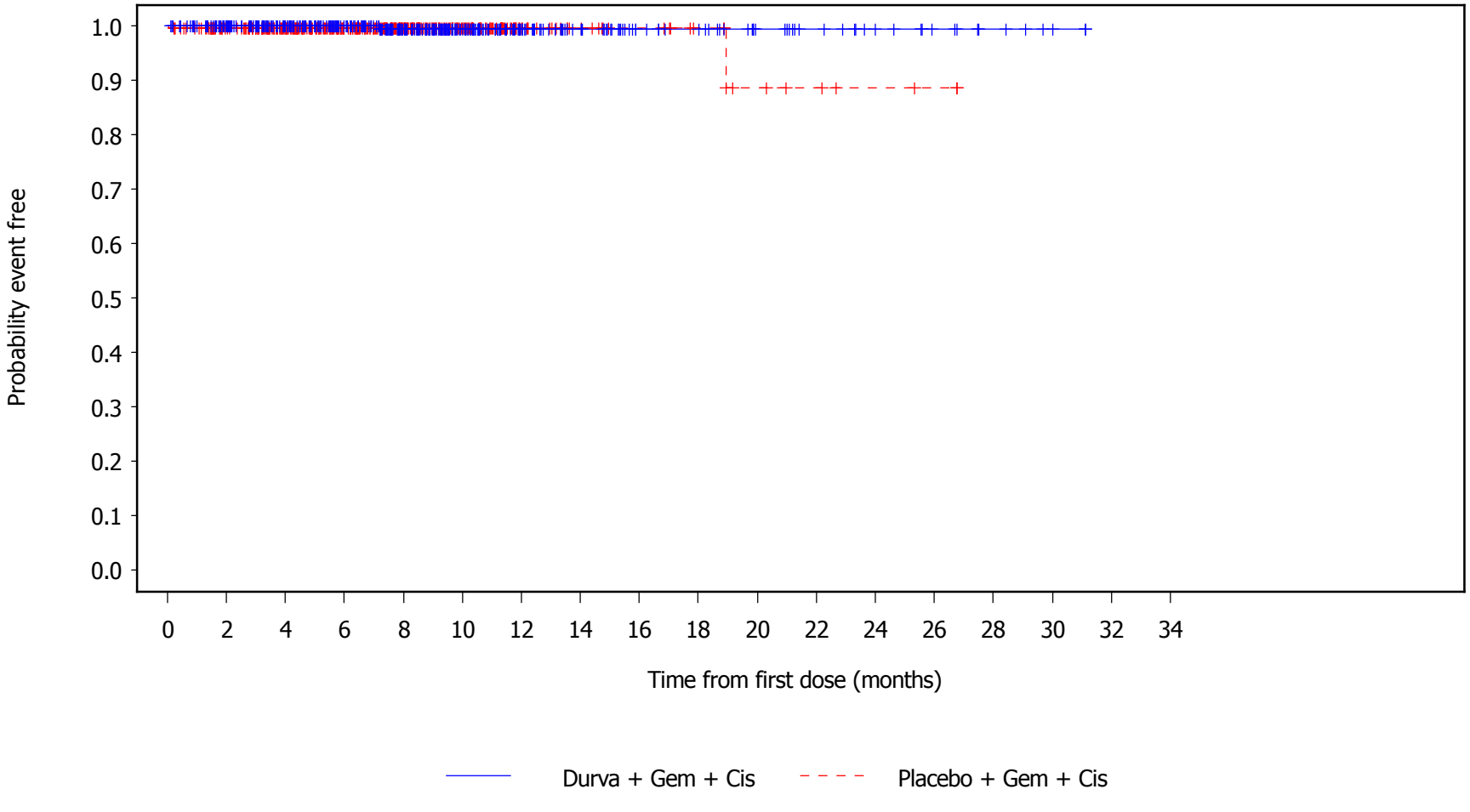
Figure 3.3.259 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Cholelithiasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	263	197	130	79	57	39	35	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

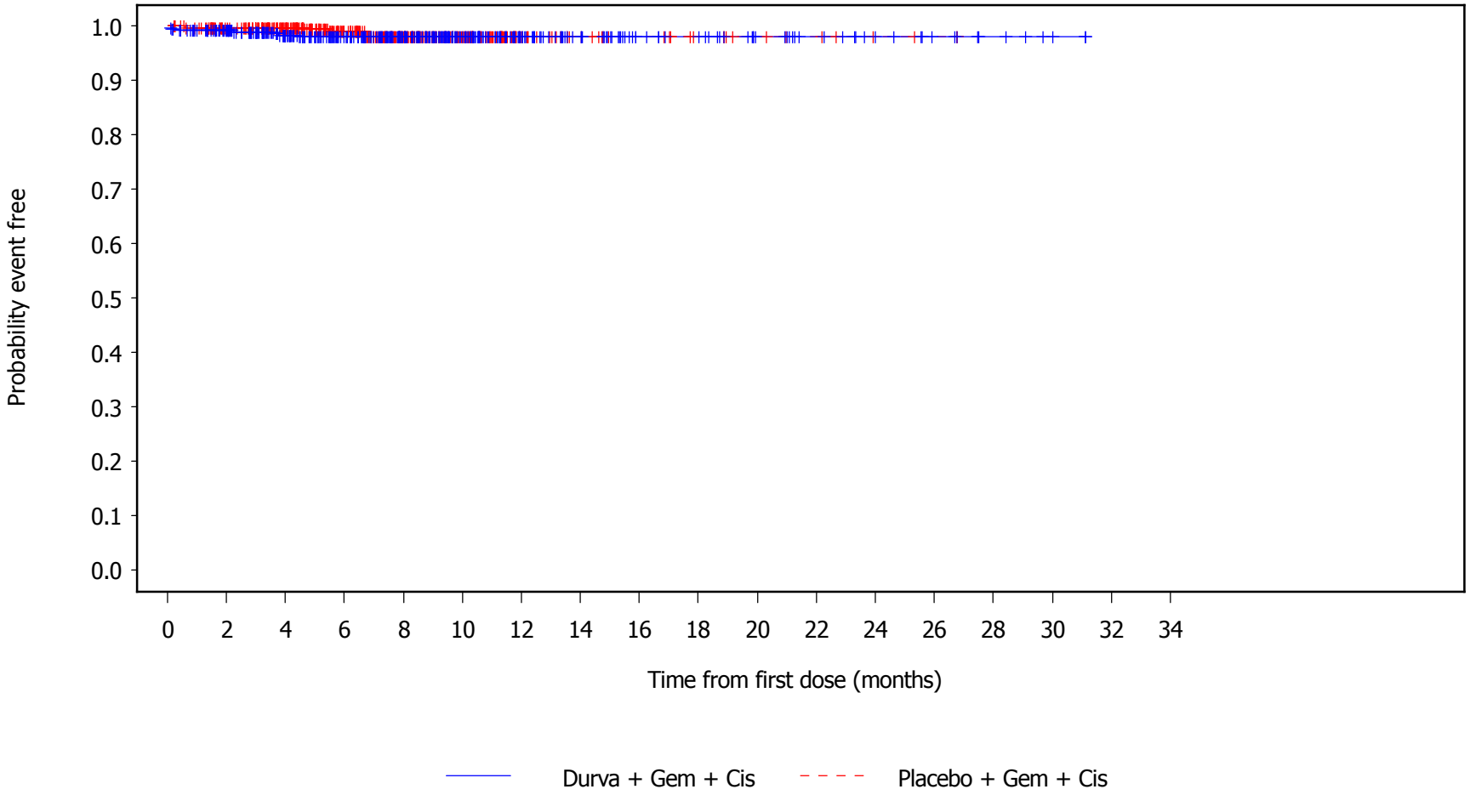
Figure 3.3.260 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	197	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	88	34	22	16	11	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

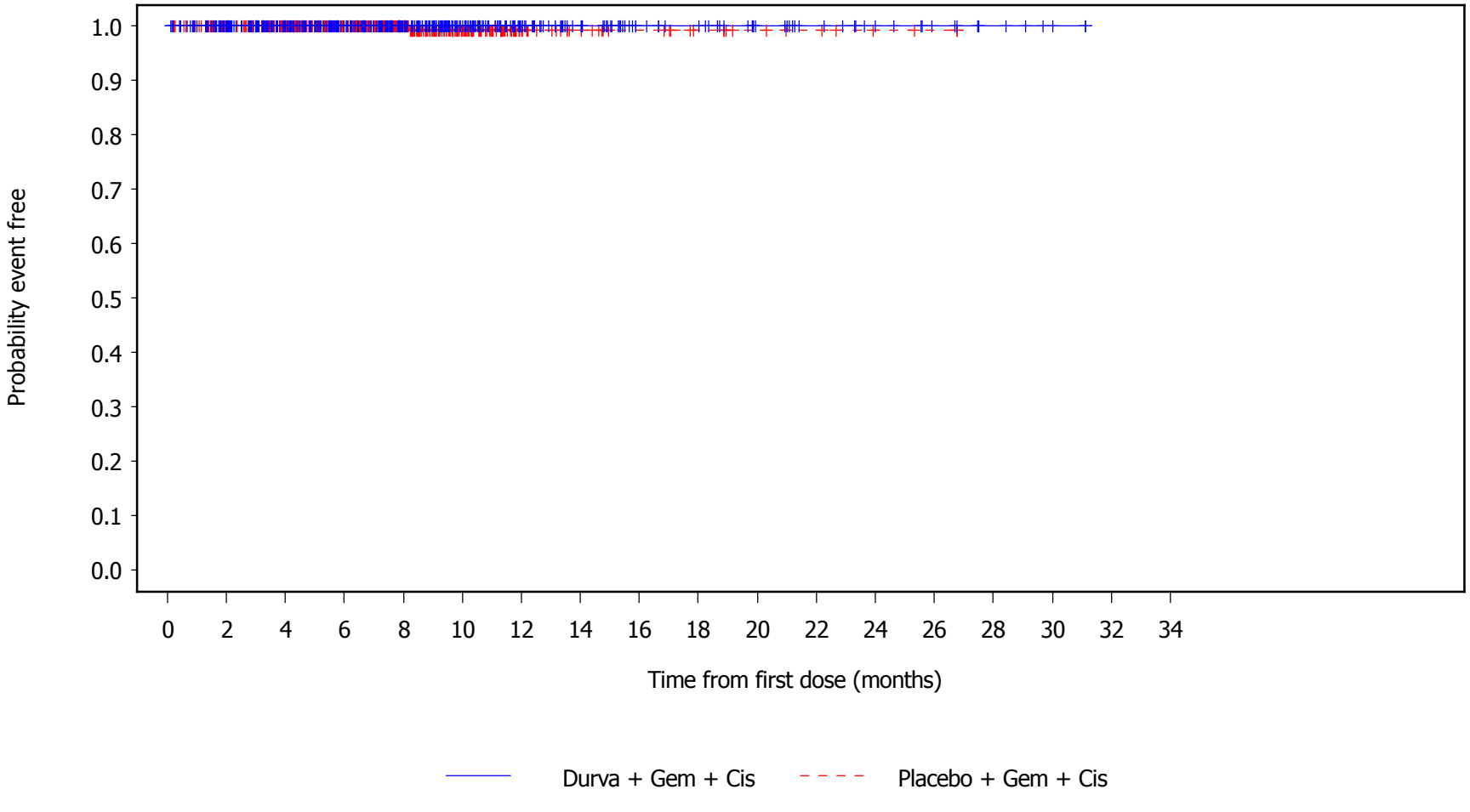
Figure 3.3.261 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Cholecystitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	310	261	196	130	79	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	230	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

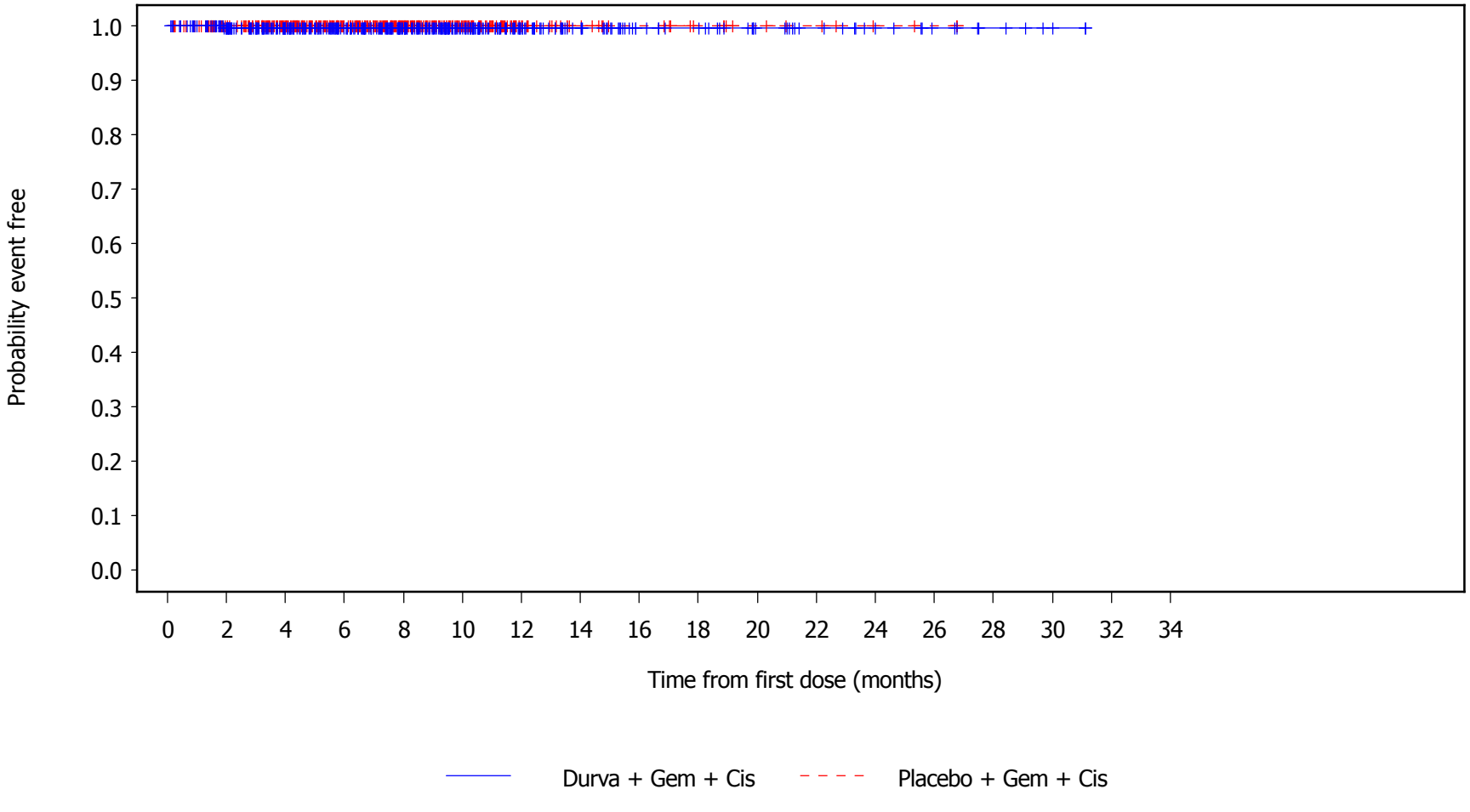
Figure 3.3.262 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Gallbladder empyema
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

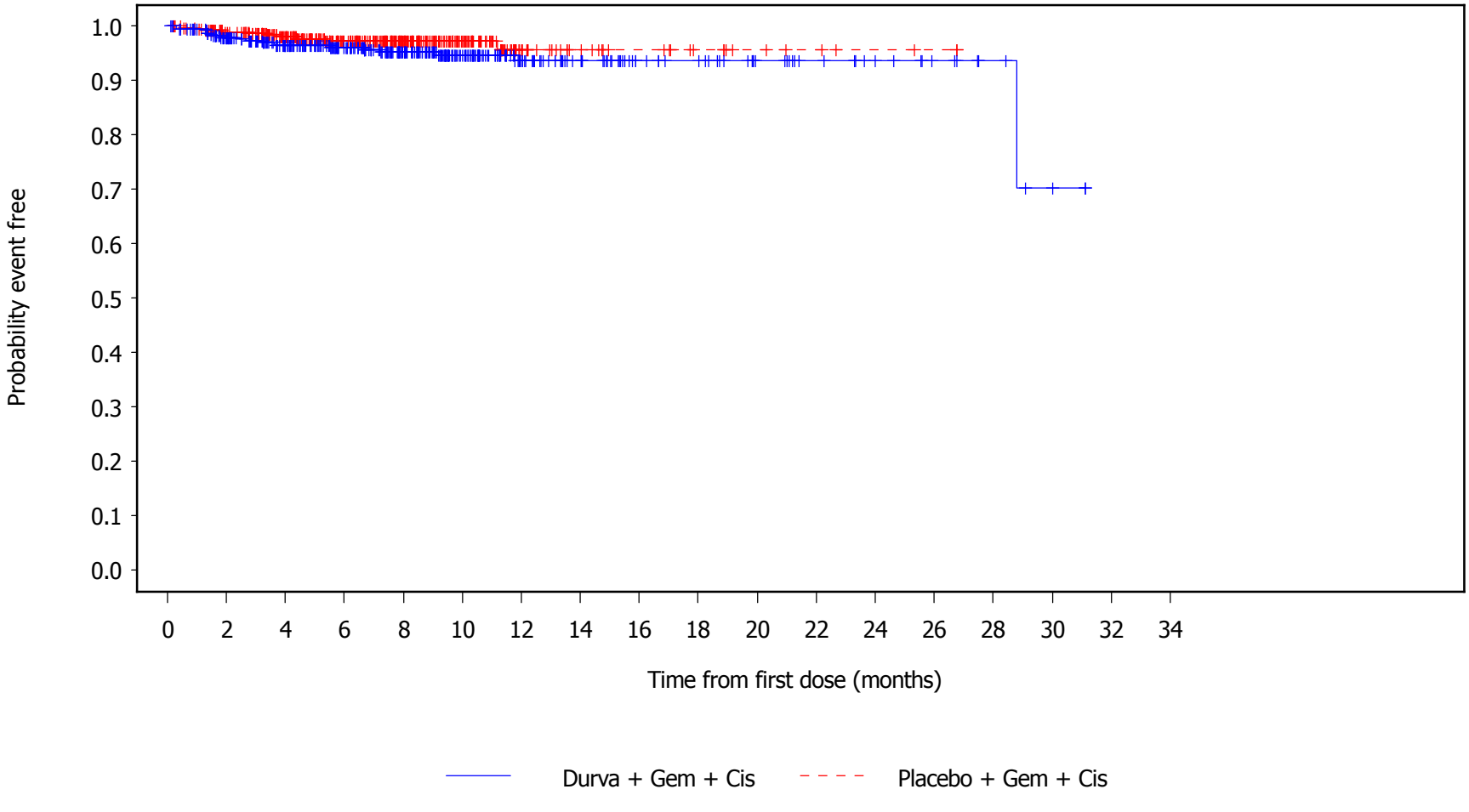
Figure 3.3.263 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Gallbladder obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

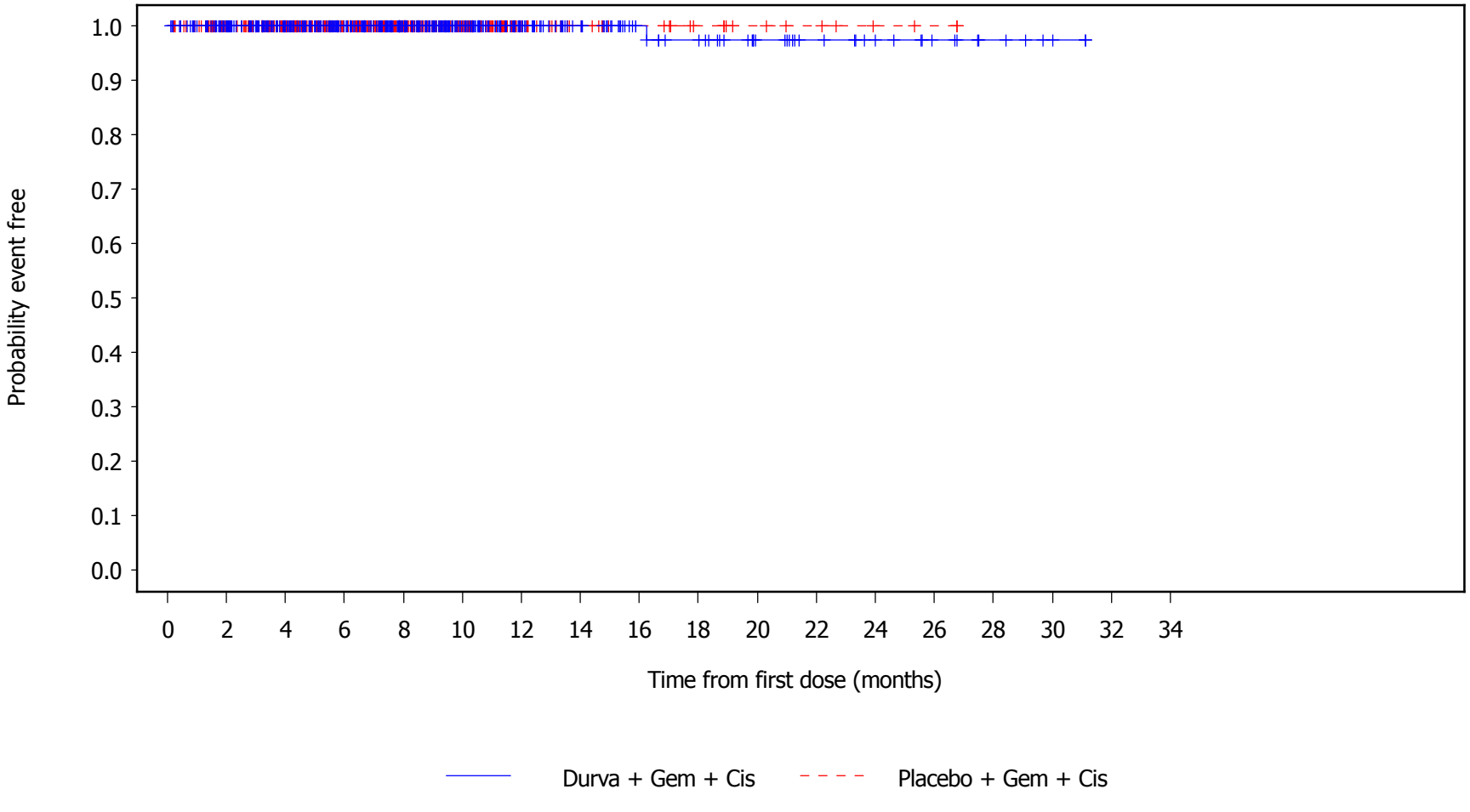
Figure 3.3.264 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Biliary tract infection
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	365	308	258	195	129	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	367	309	229	157	89	33	21	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

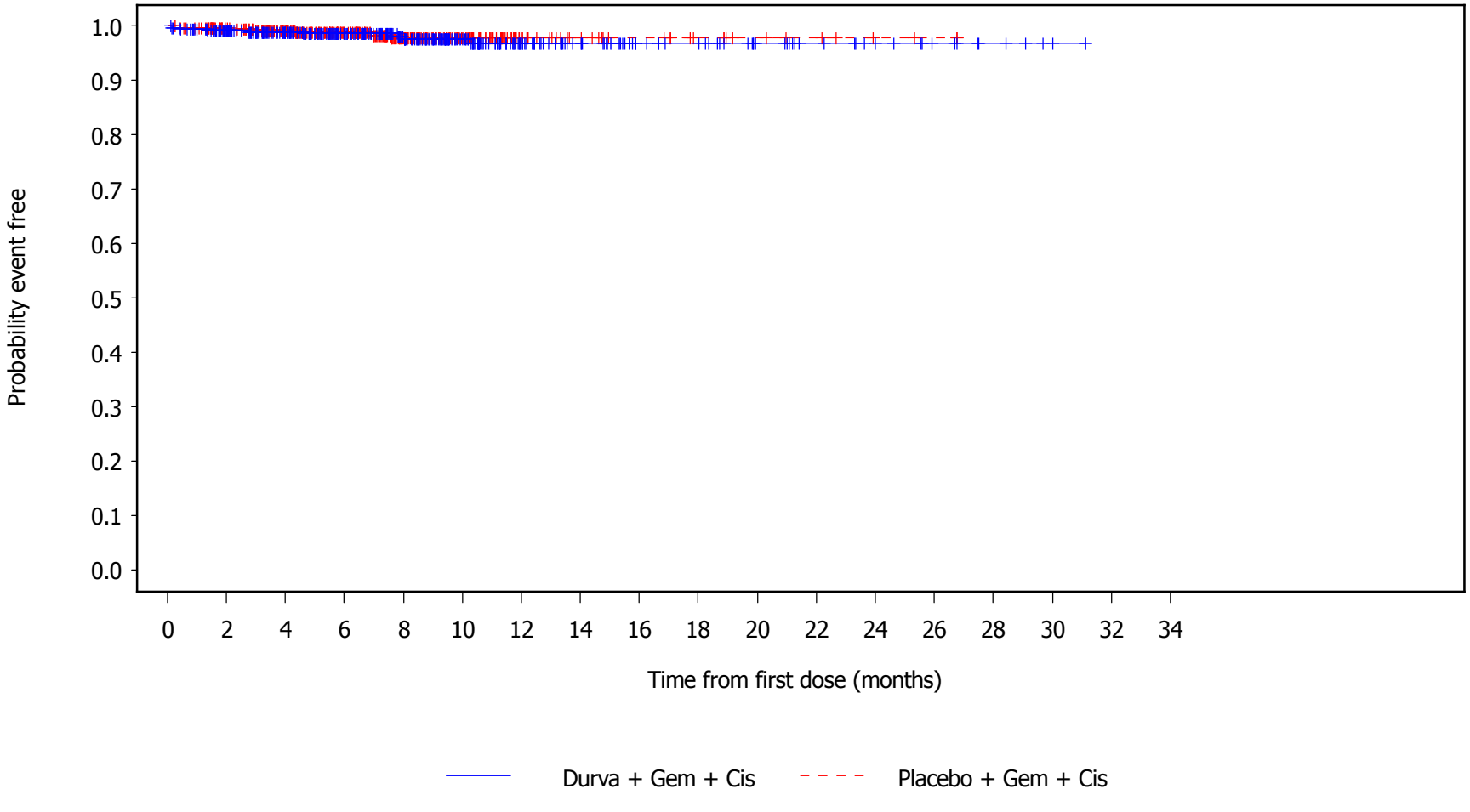
Figure 3.3.265 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Post procedural bile leak
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

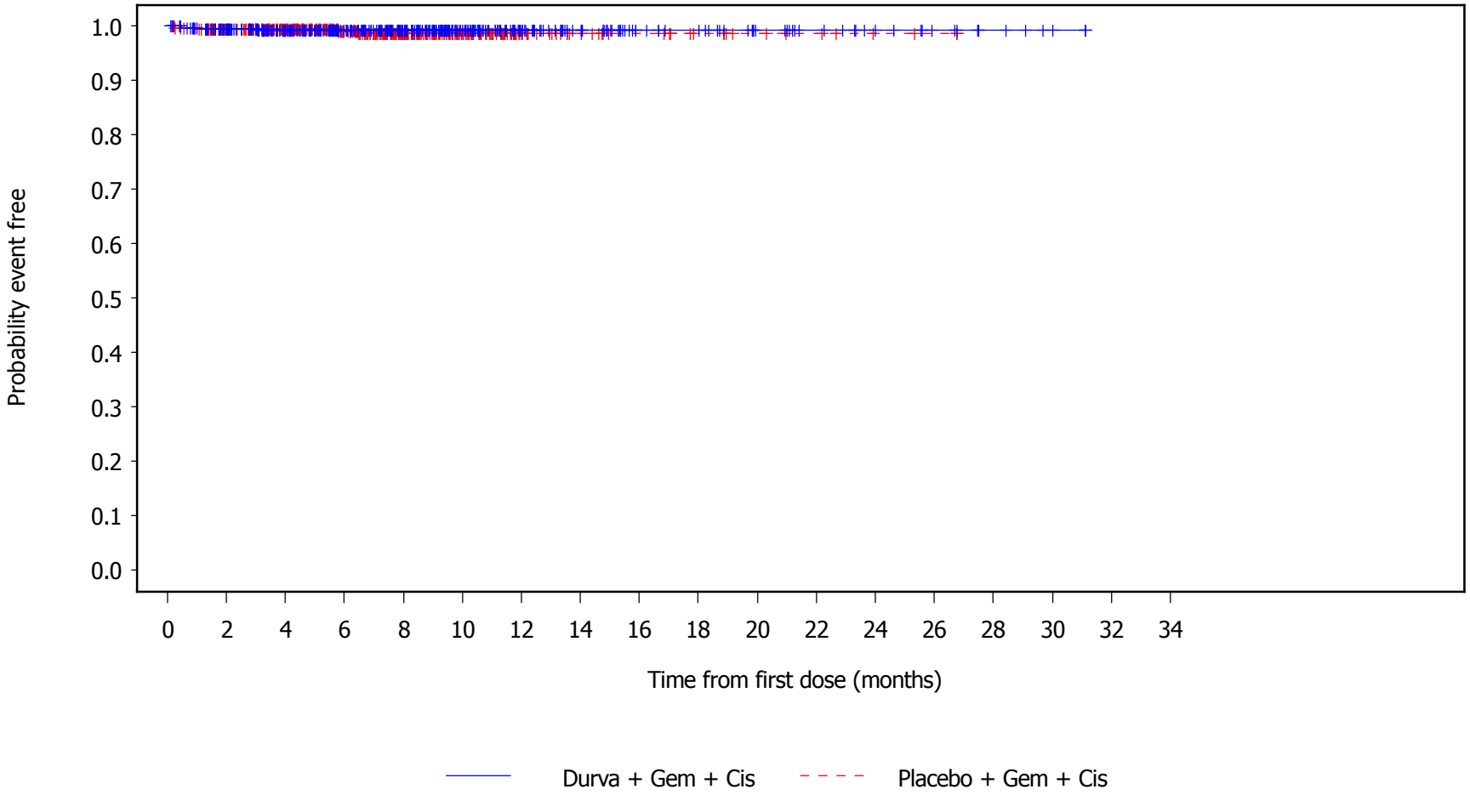
Figure 3.3.266 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	314	262	197	129	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	370	313	232	157	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

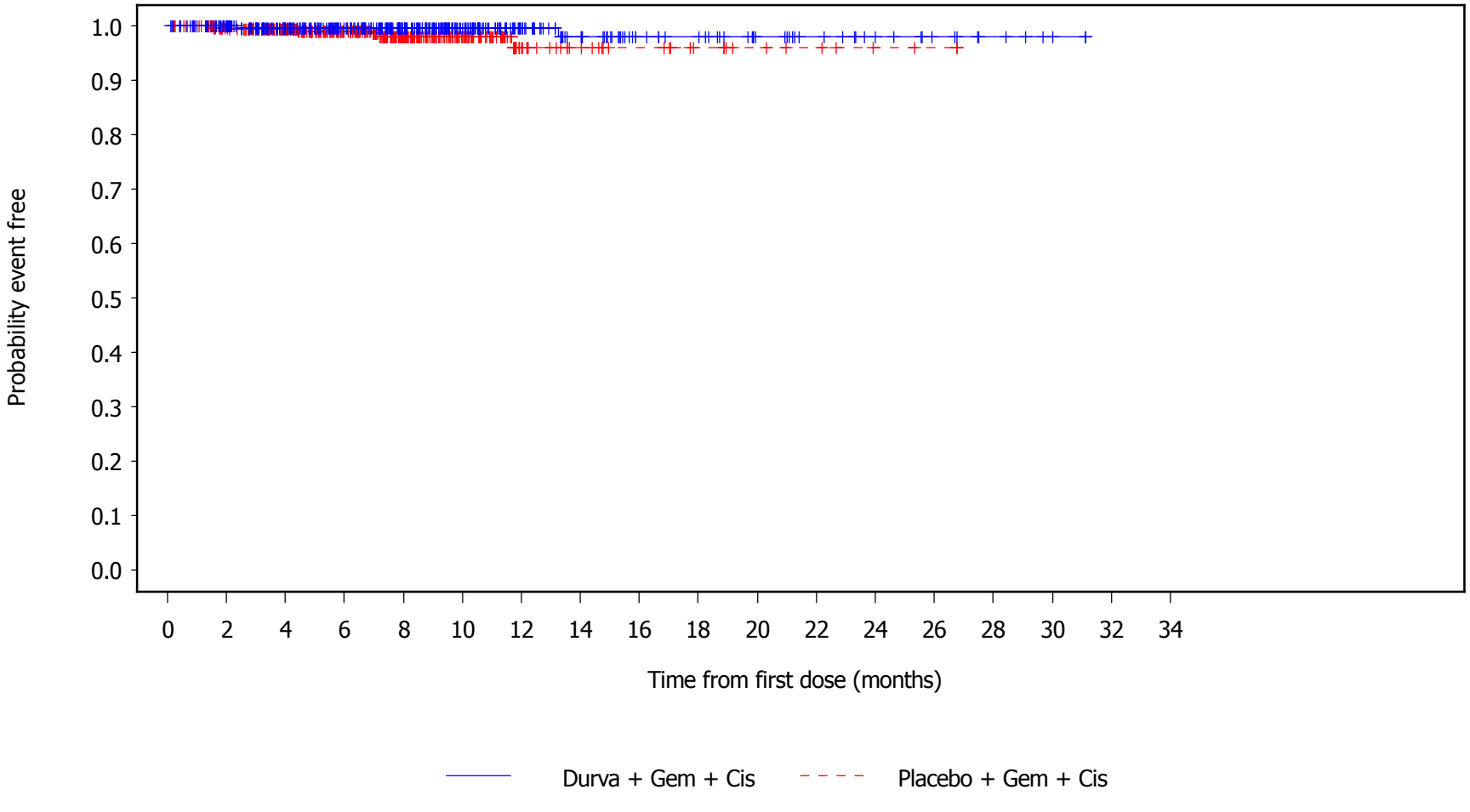
Figure 3.3.267 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	263	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	230	156	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

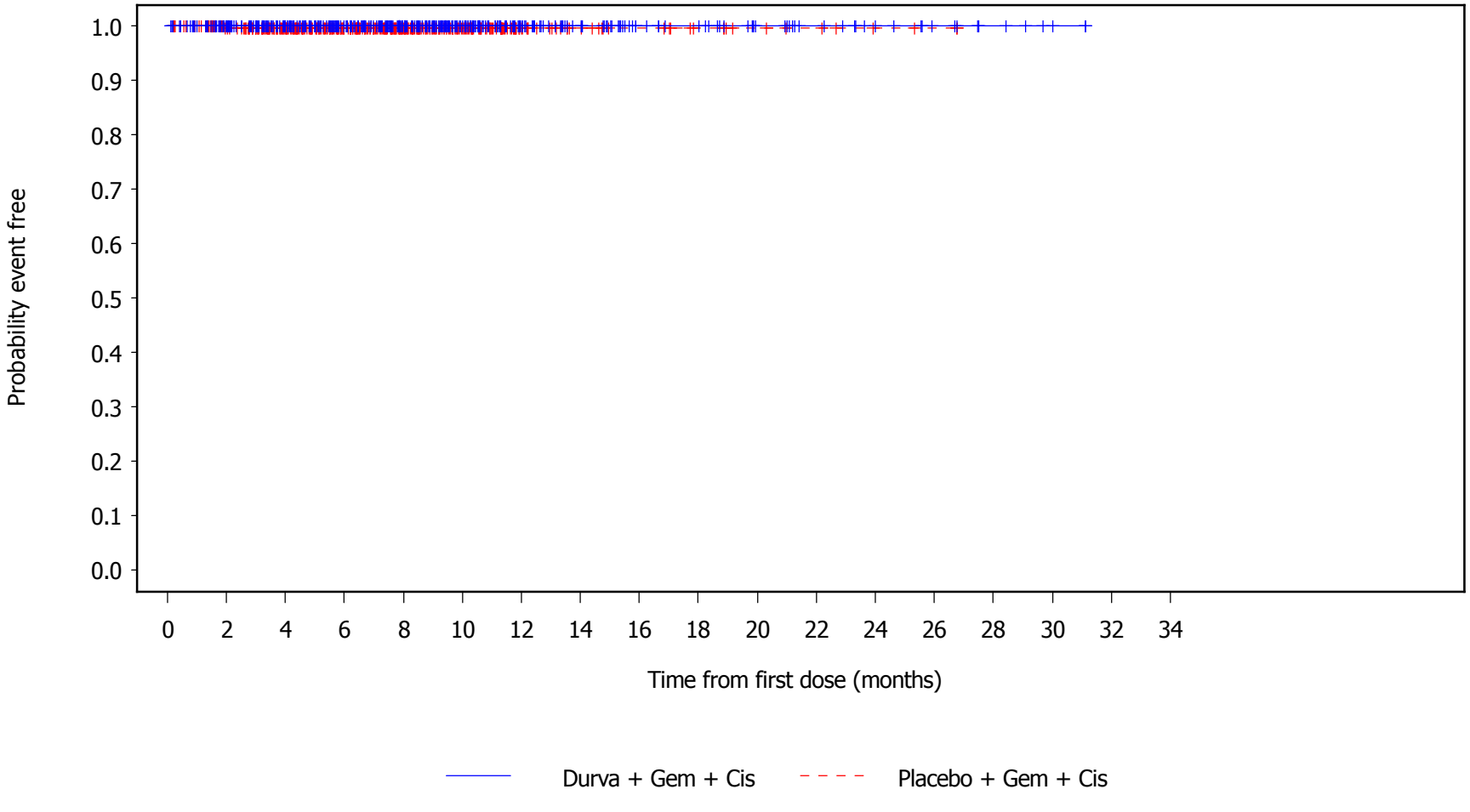
Figure 3.3.268 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	156	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

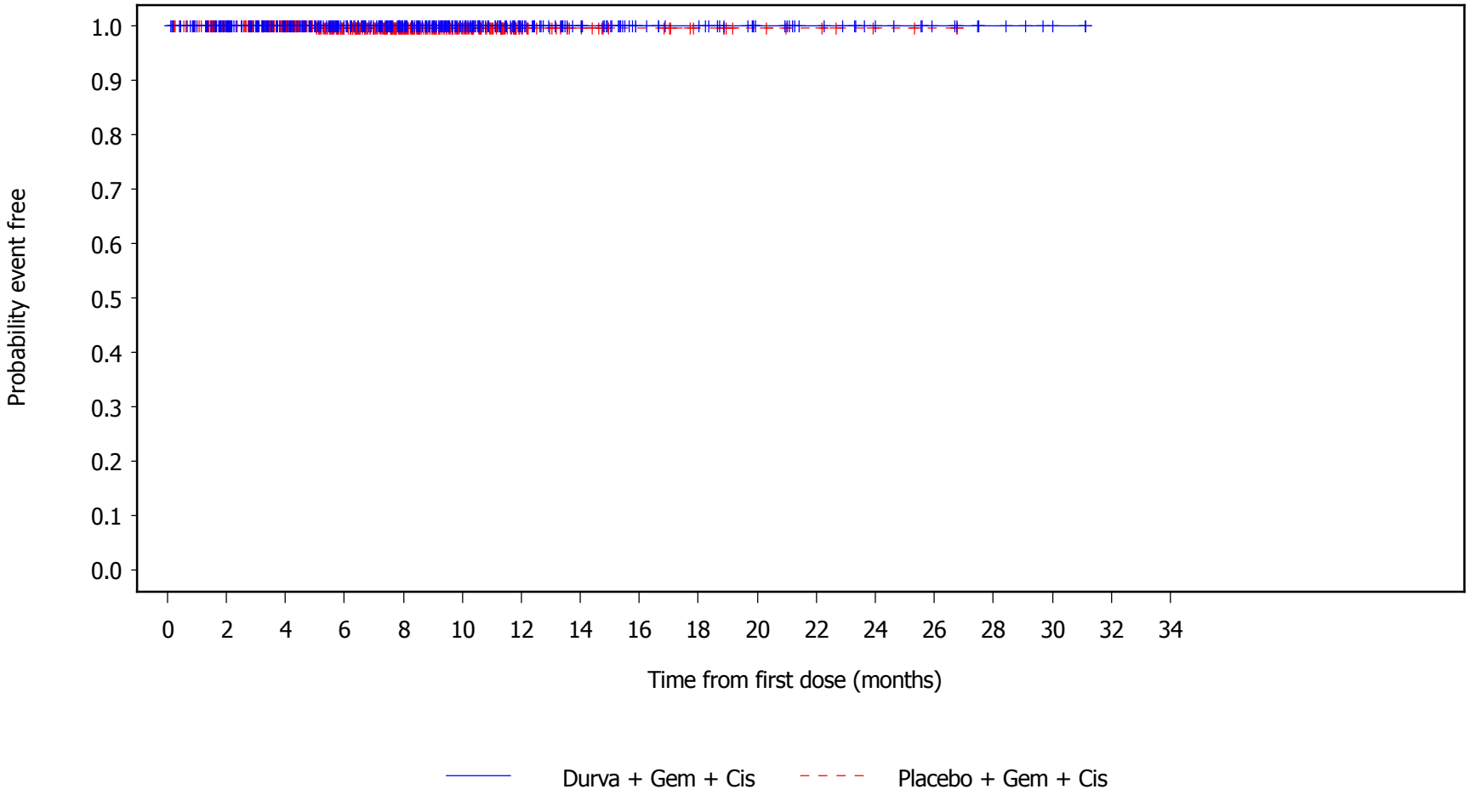
Figure 3.3.269 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Gallbladder rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

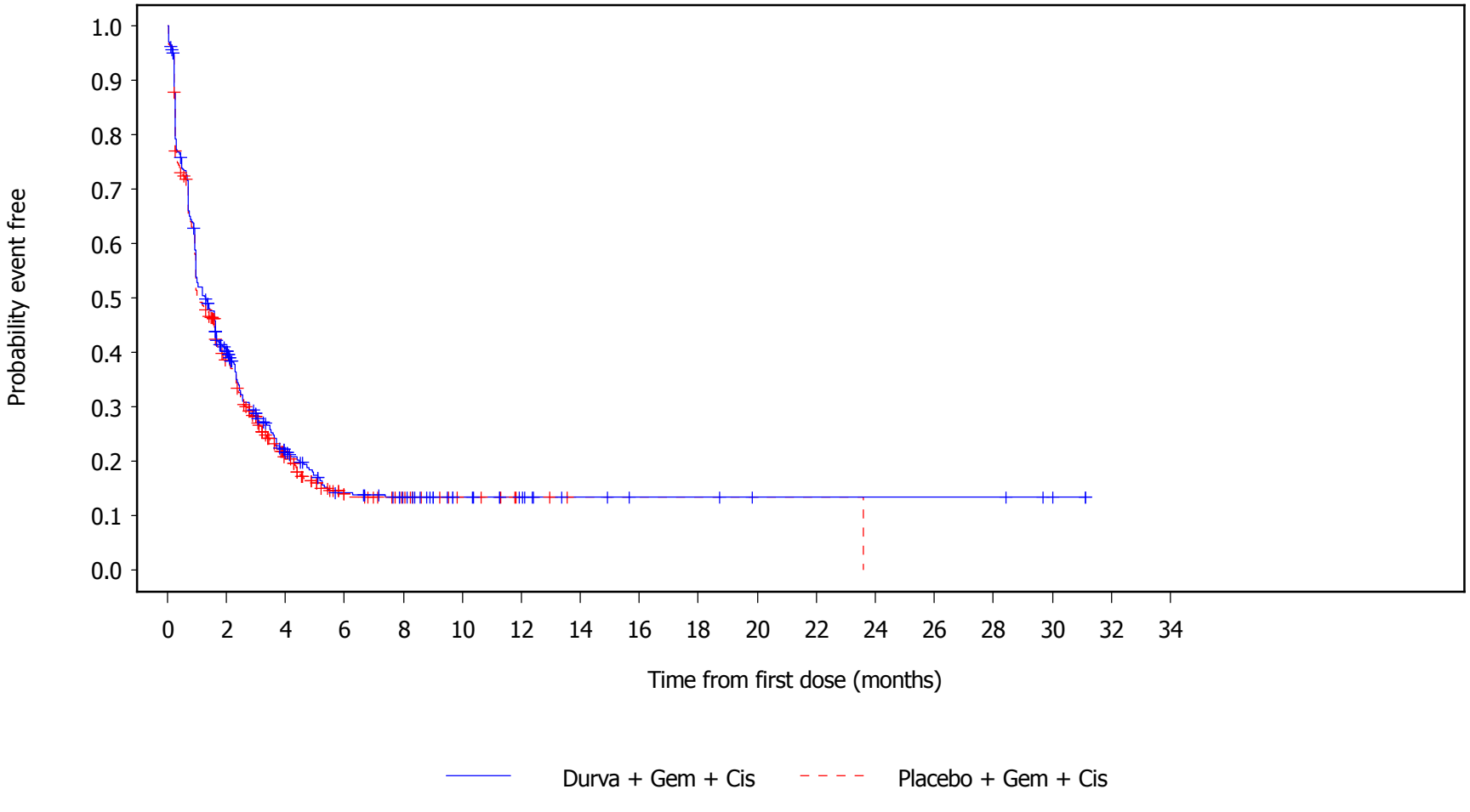
Figure 3.3.270 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Biloma rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

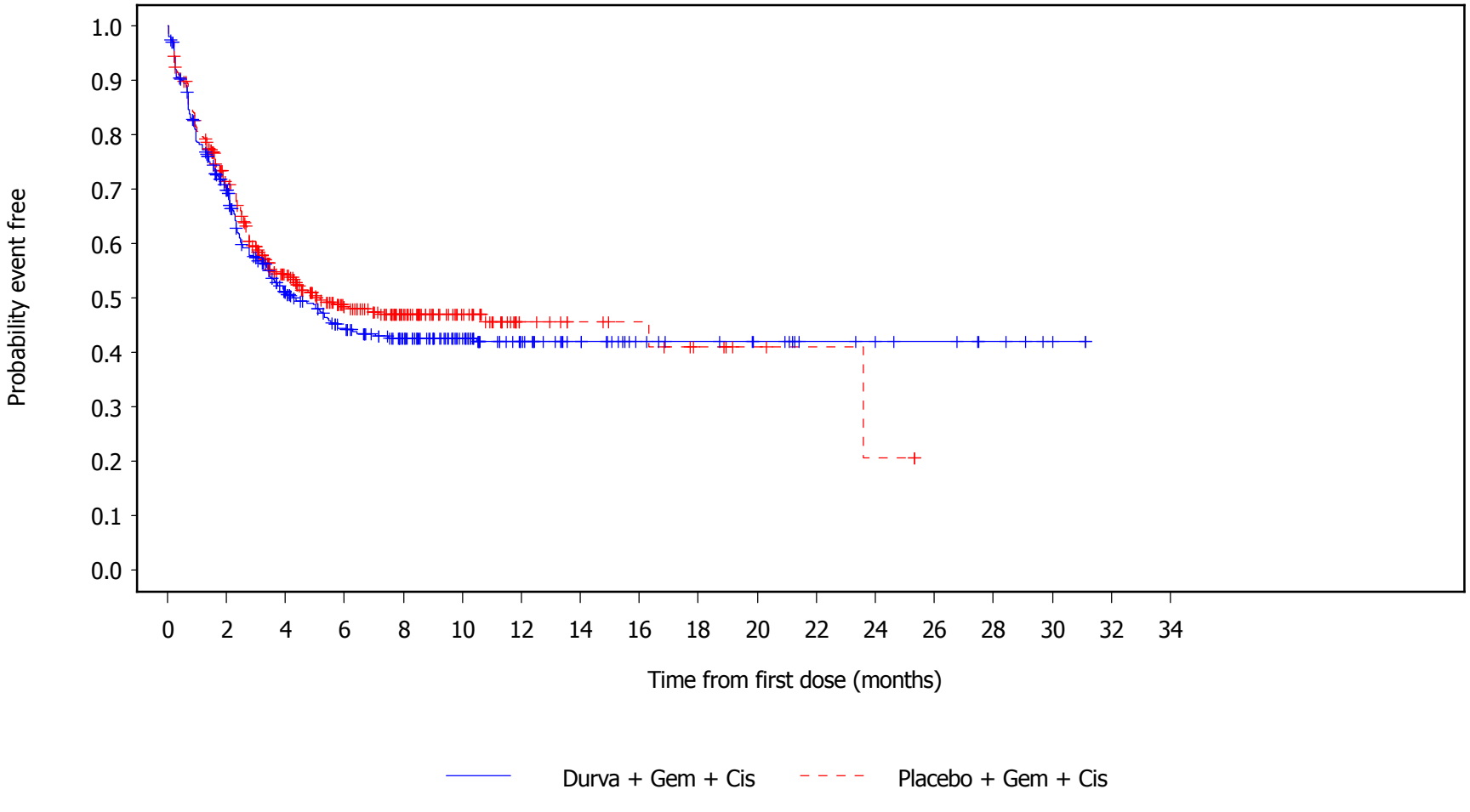
Figure 3.3.271 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI GT: Haematopoietic cytopenias SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	152	69	38	29	18	13	8	6	6	4	4	4	4	4	2	0	0	Durva + Gem + Cis
403	144	56	22	14	7	3	1	1	1	1	1	0	0	0	0	0	0	Placebo + Gem + Cis

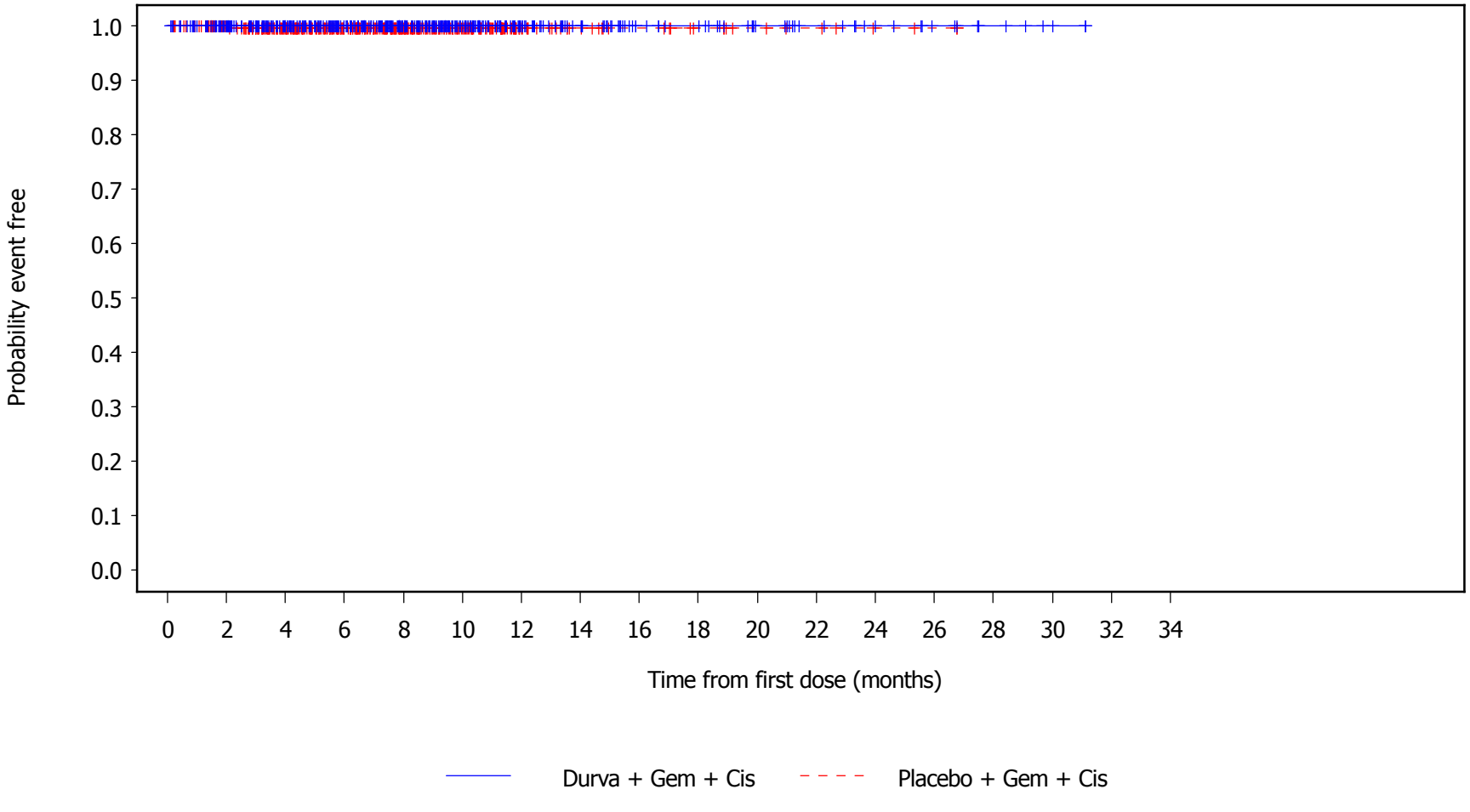
Figure 3.3.272 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Anaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	266	169	132	102	70	44	32	22	19	16	11	10	8	5	2	0	0	Durva + Gem + Cis
403	265	167	112	78	45	17	12	10	6	3	2	1	0	0	0	0	0	Placebo + Gem + Cis

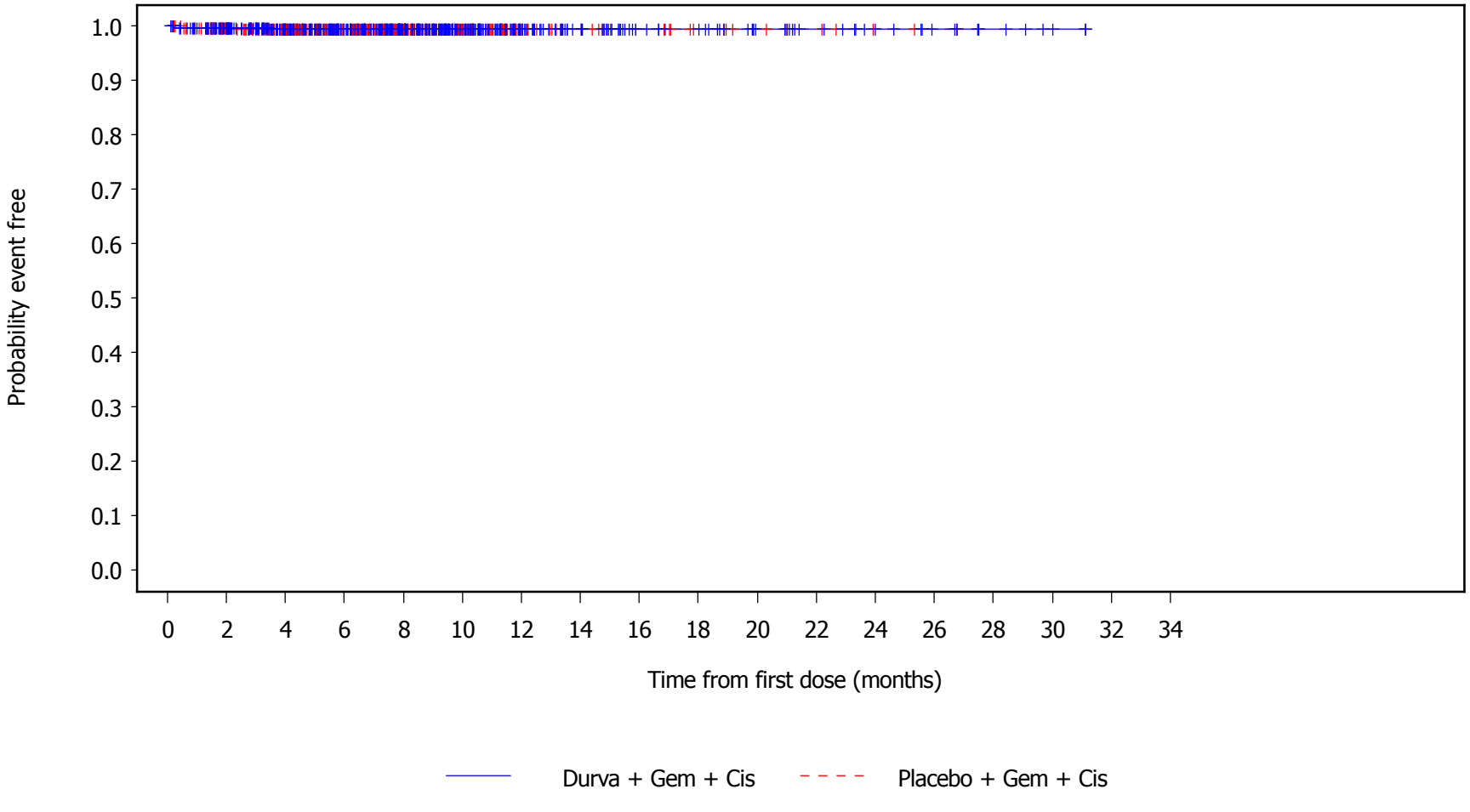
Figure 3.3.273 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Bicytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	231	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

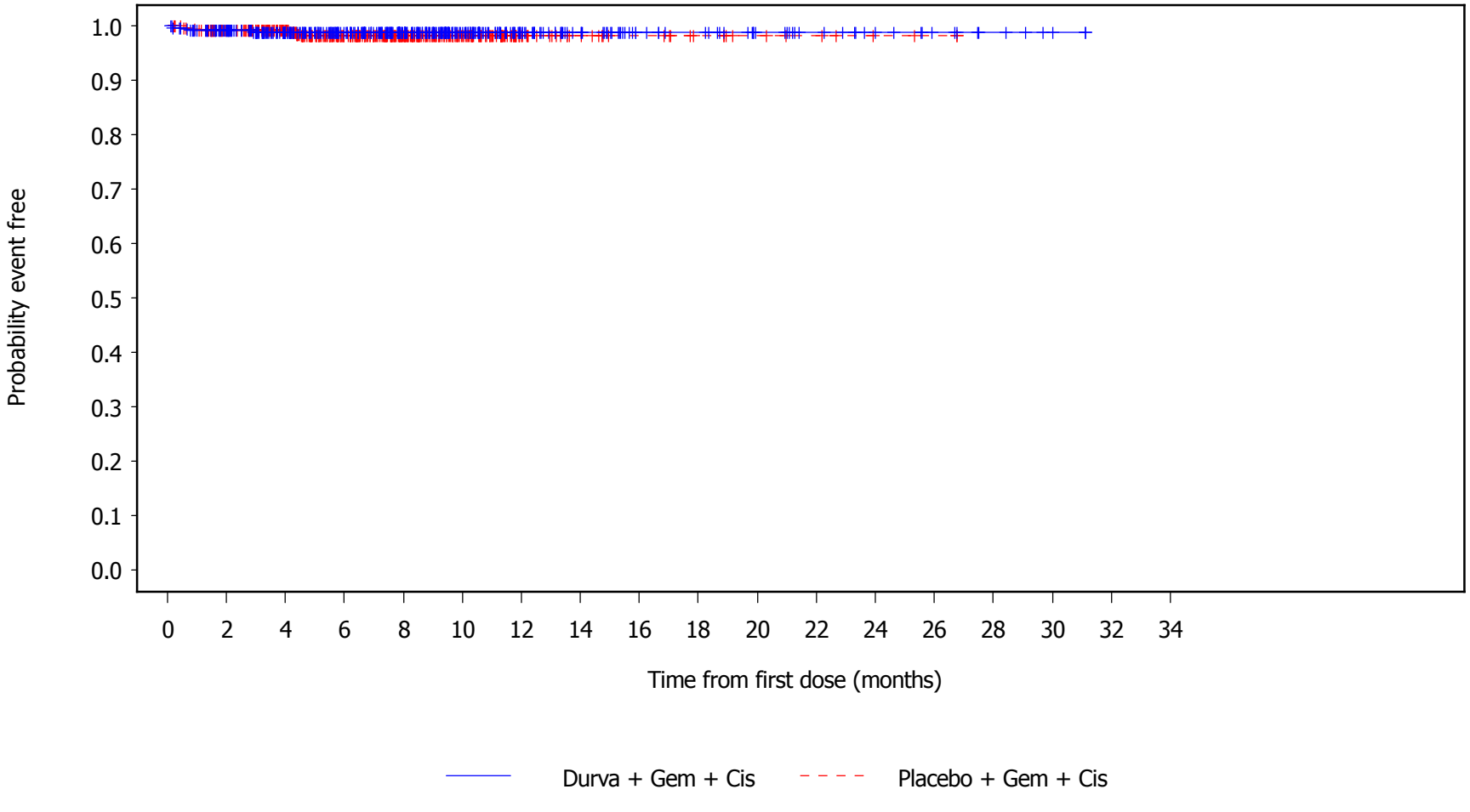
Figure 3.3.274 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Red blood cell count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	313	262	197	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	311	231	158	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

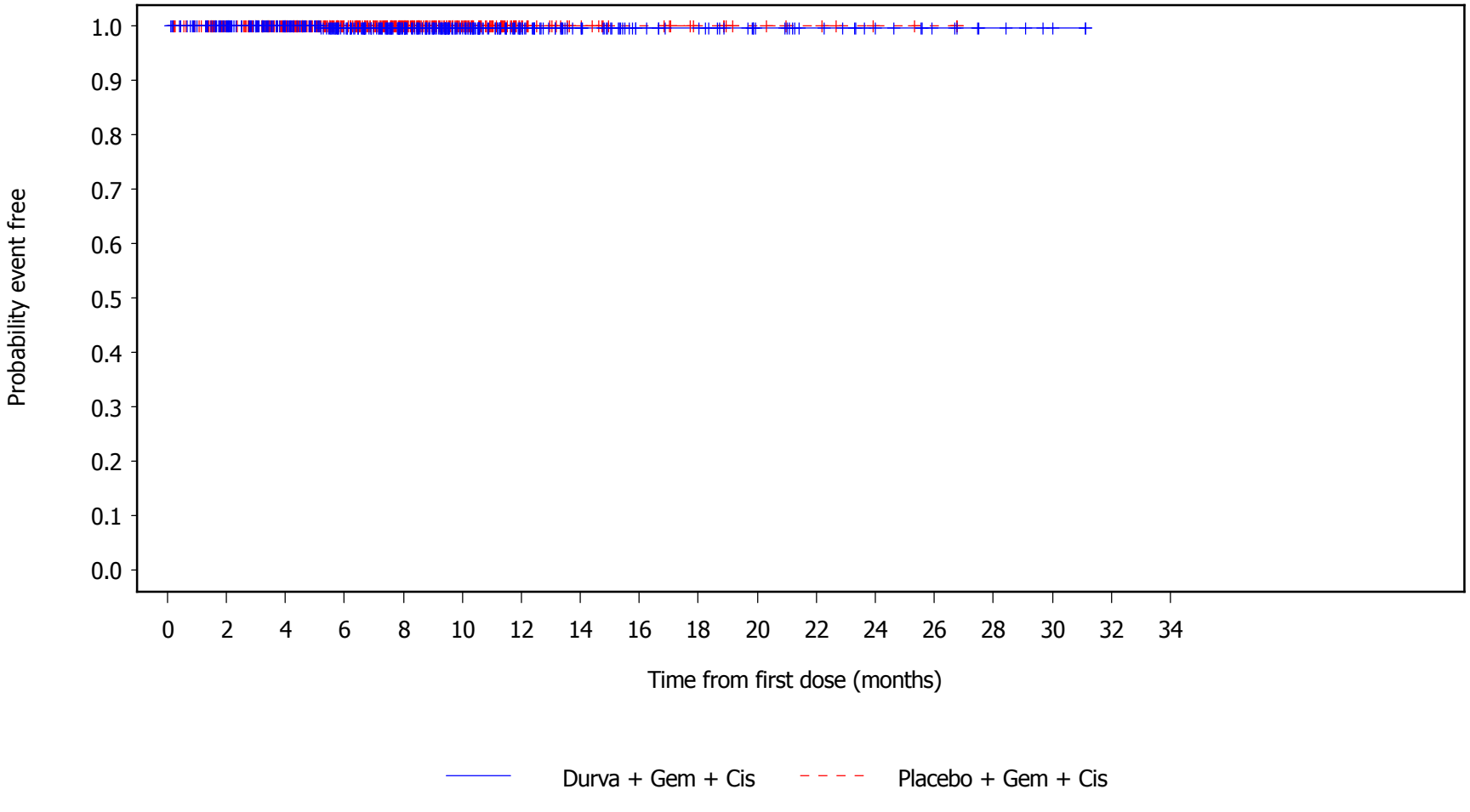
Figure 3.3.275 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Febrile neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	312	261	196	129	79	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	311	228	157	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

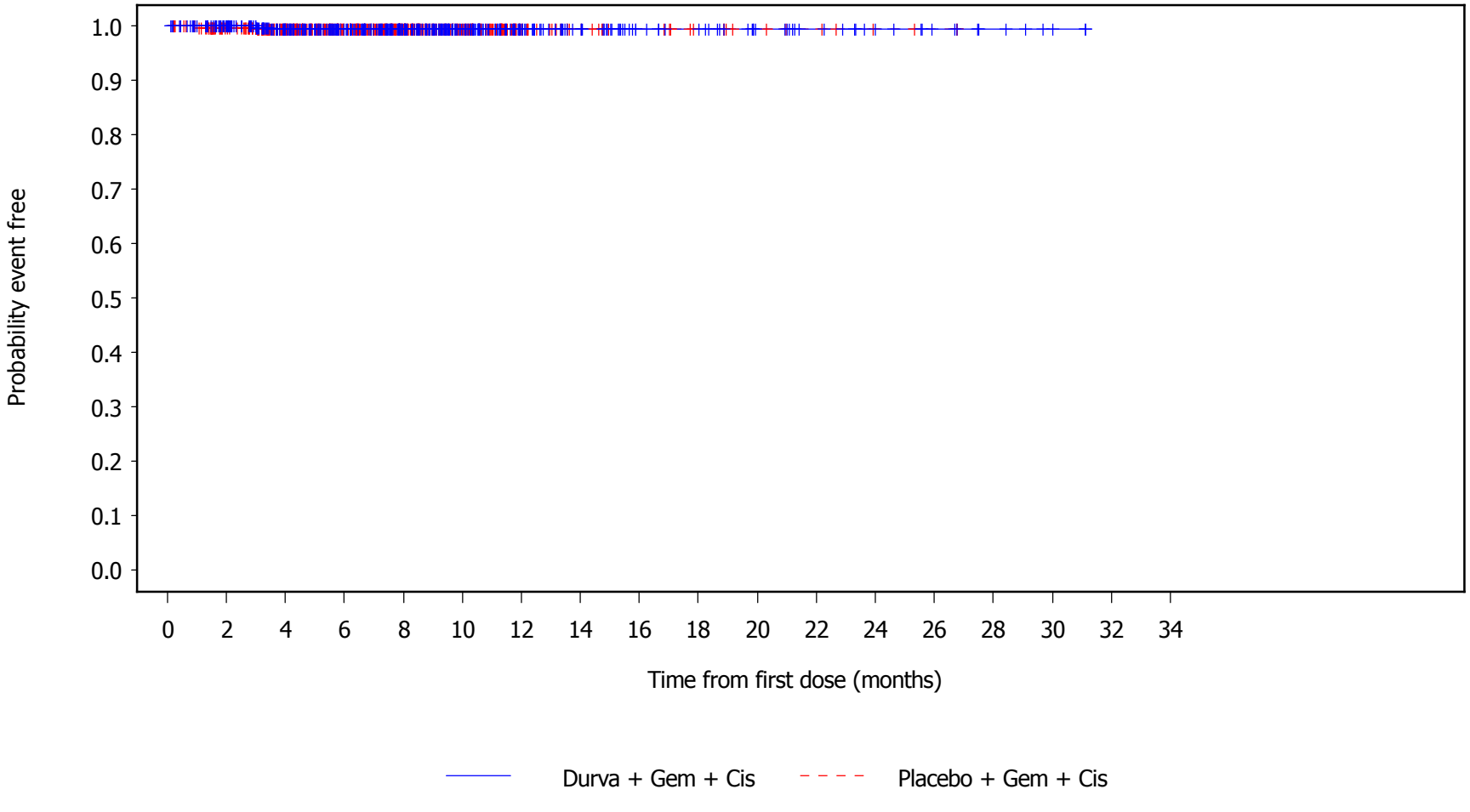
Figure 3.3.276 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Granulocyte count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	263	197	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

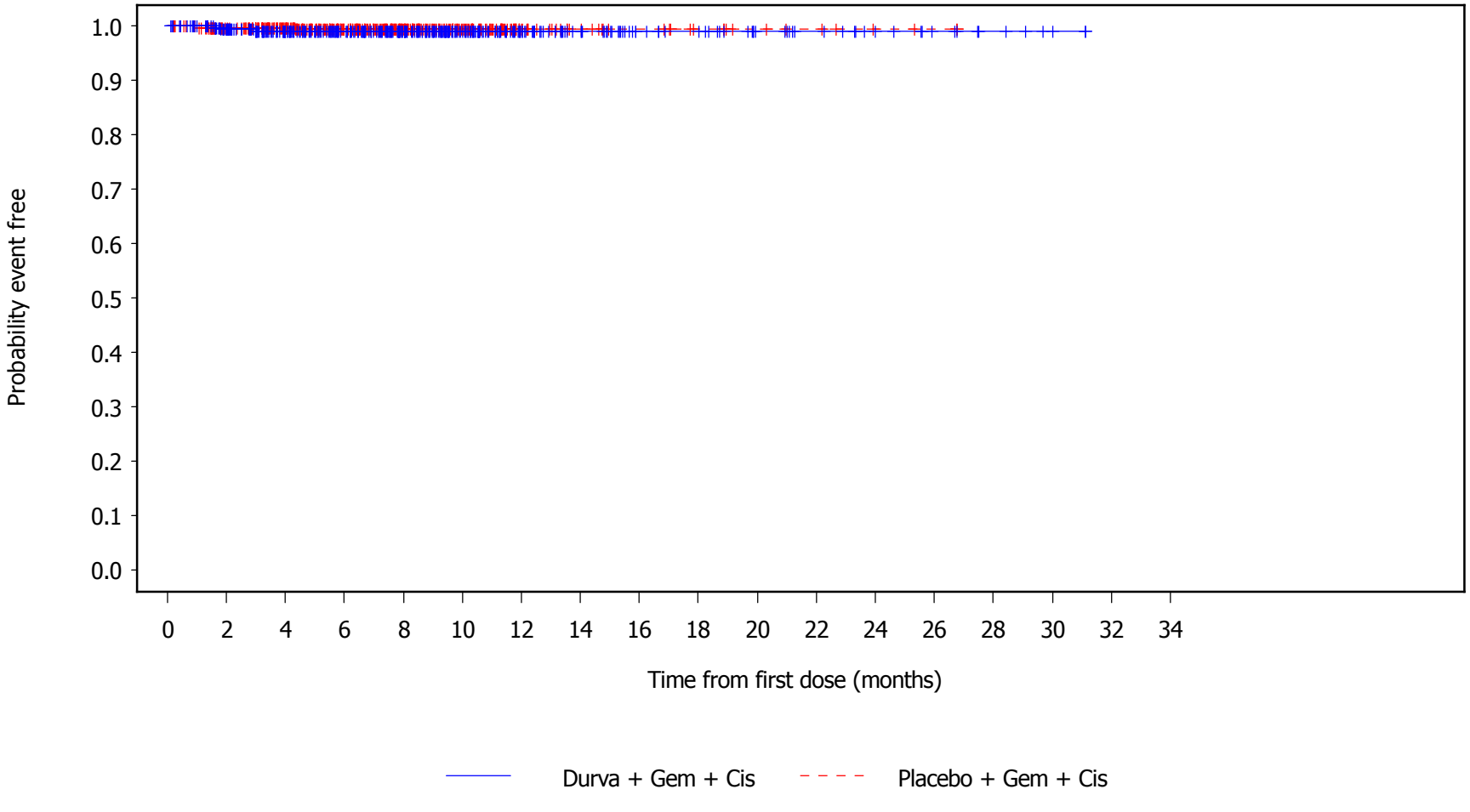
Figure 3.3.277 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Haematocrit decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	313	262	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	311	230	157	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

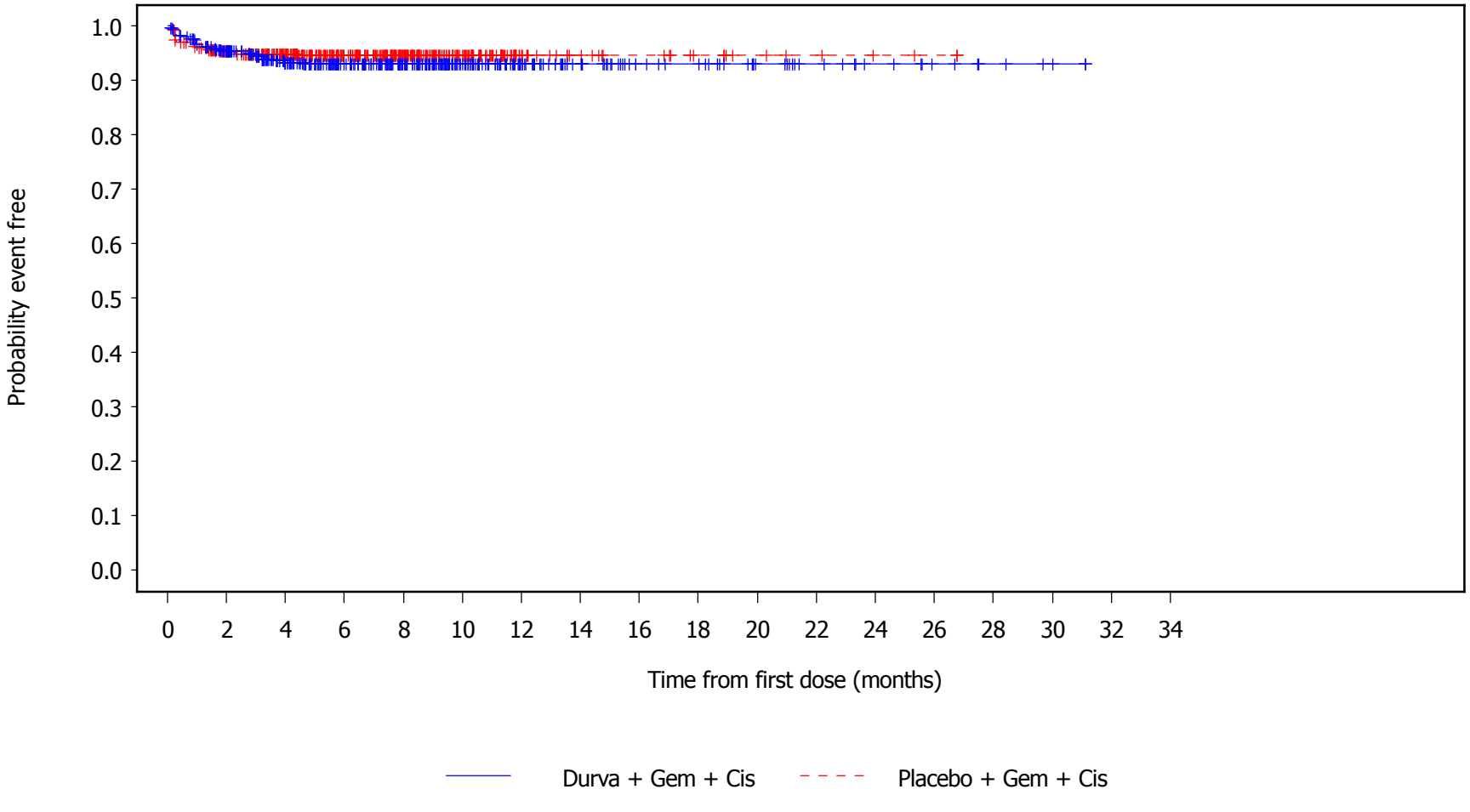
Figure 3.3.278 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Haemoglobin decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	312	262	197	130	79	57	39	35	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	230	157	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

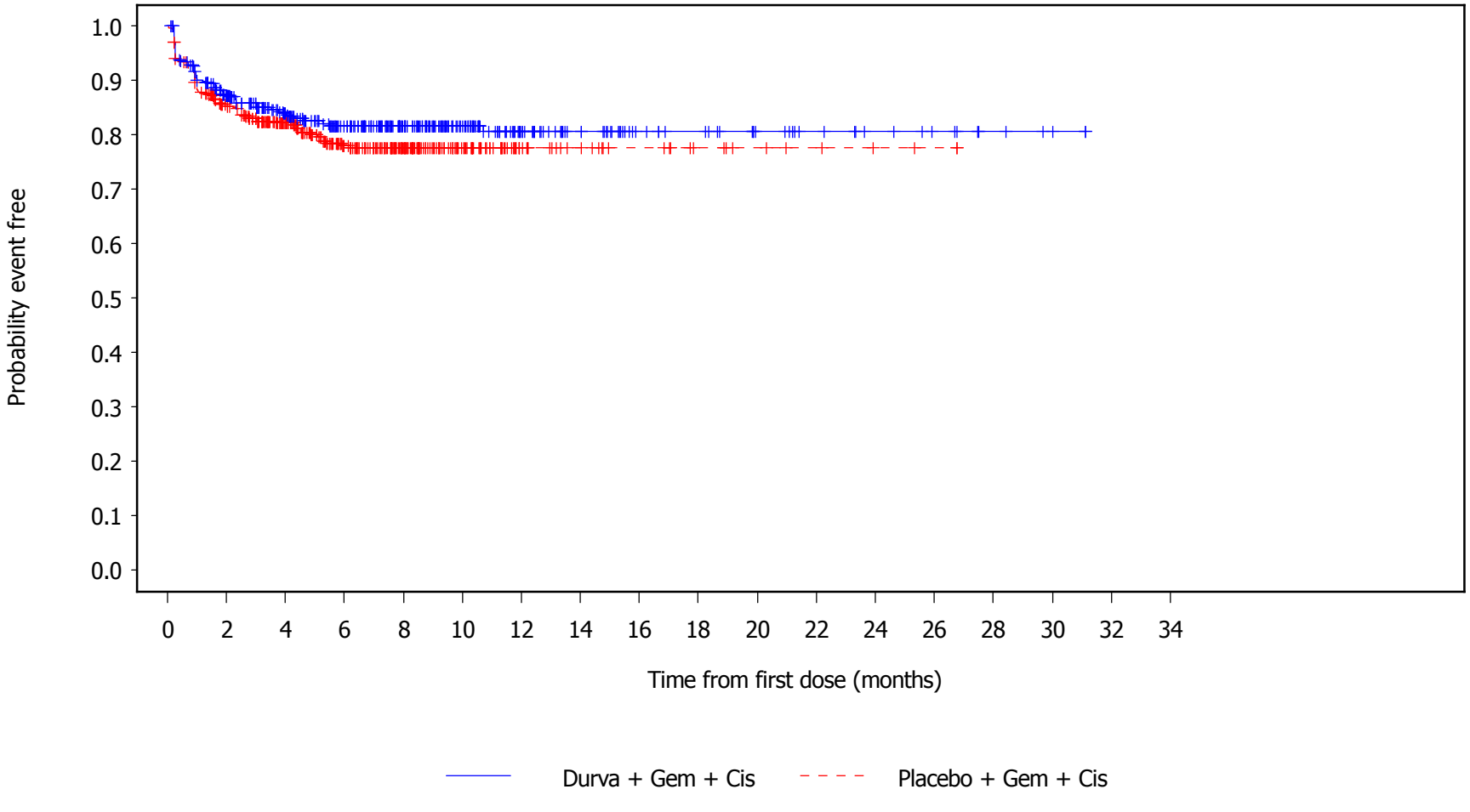
Figure 3.3.279 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Leukopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	356	293	243	182	119	74	52	36	33	22	16	11	7	4	2	0	0	Durva + Gem + Cis
403	355	298	216	148	83	30	20	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

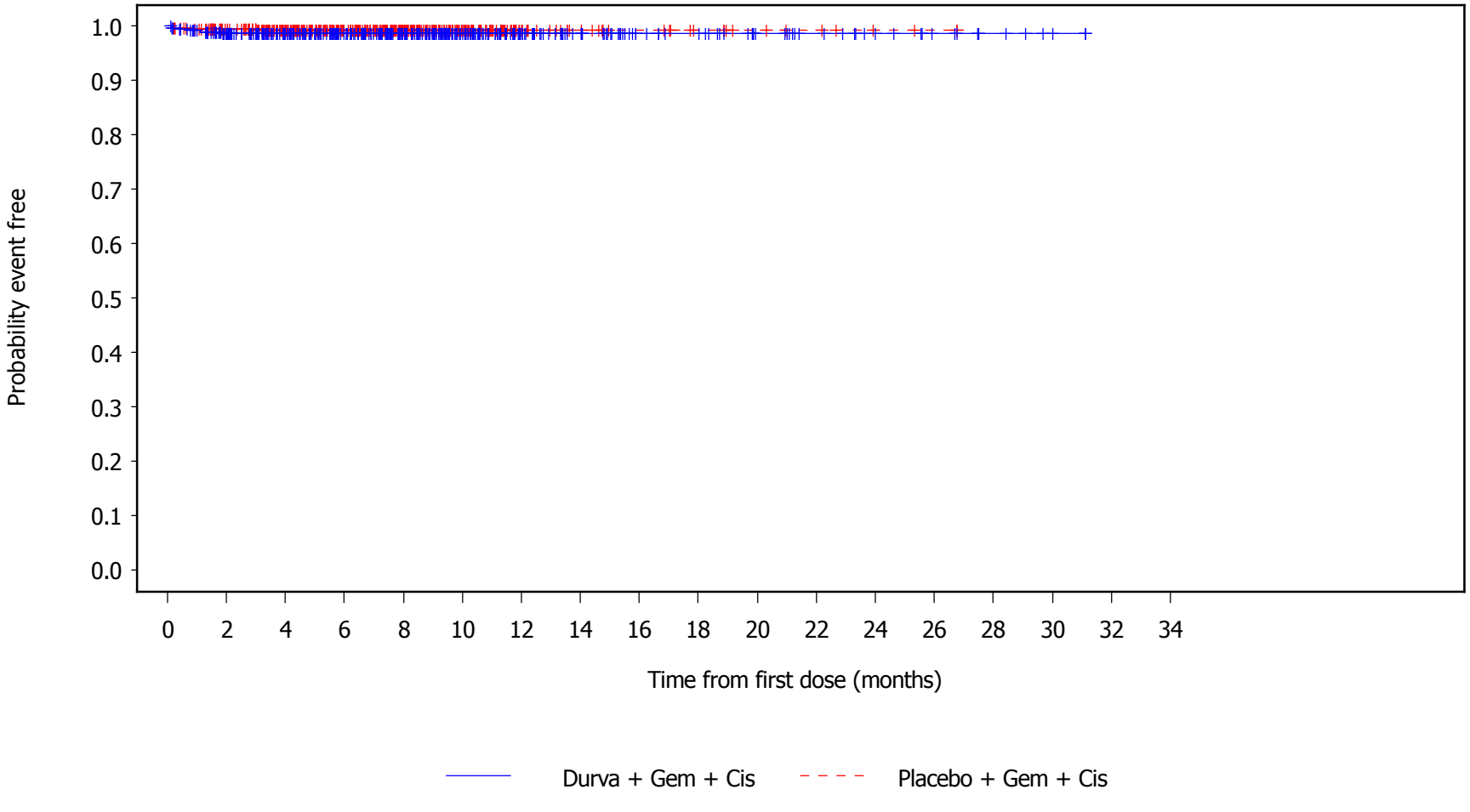
Figure 3.3.280 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: White blood cell count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	325	264	217	160	109	67	48	32	28	20	15	11	8	4	2	0	0	Durva + Gem + Cis
403	315	249	174	122	67	29	20	14	9	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

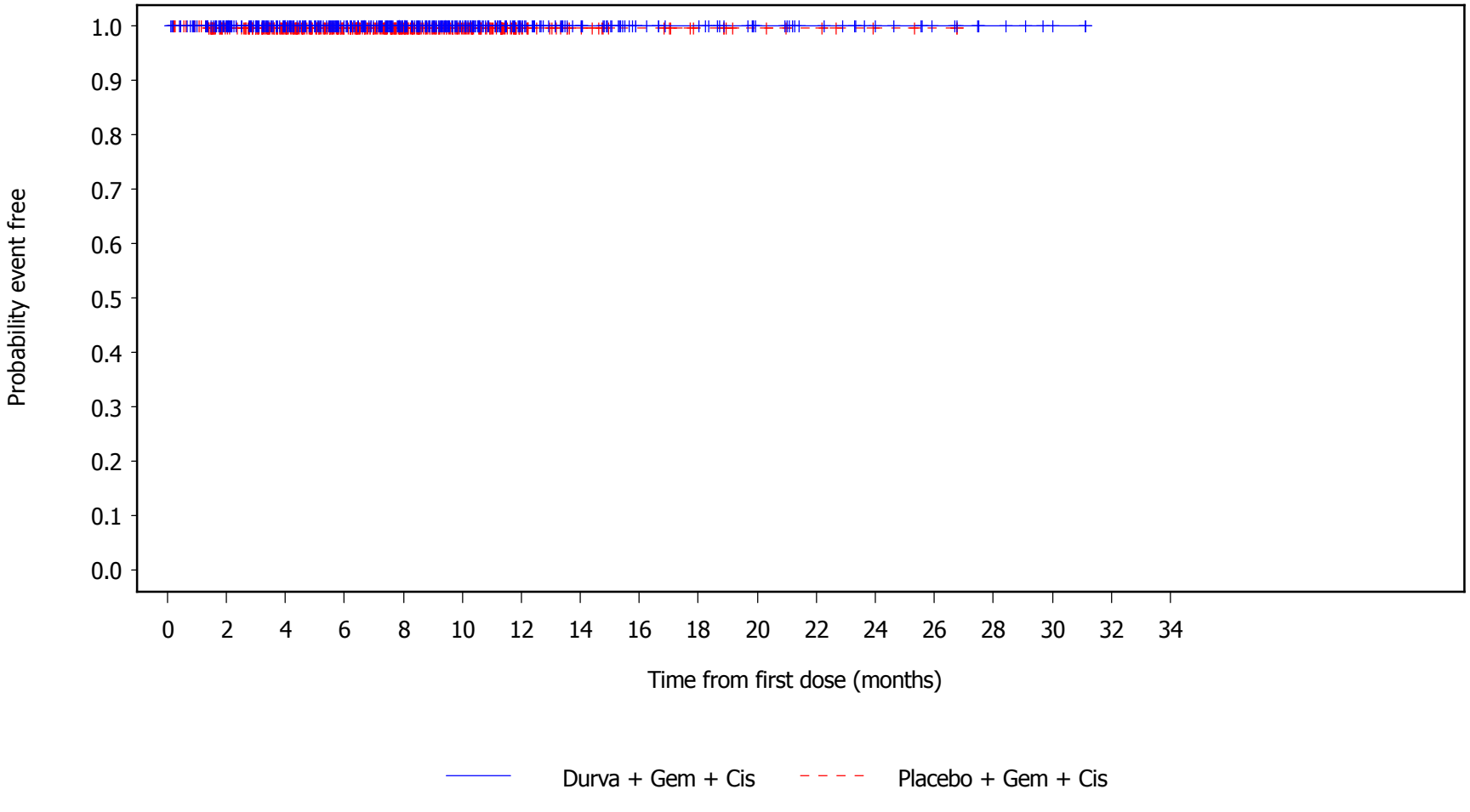
Figure 3.3.281 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Lymphopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	368	311	262	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	310	230	158	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

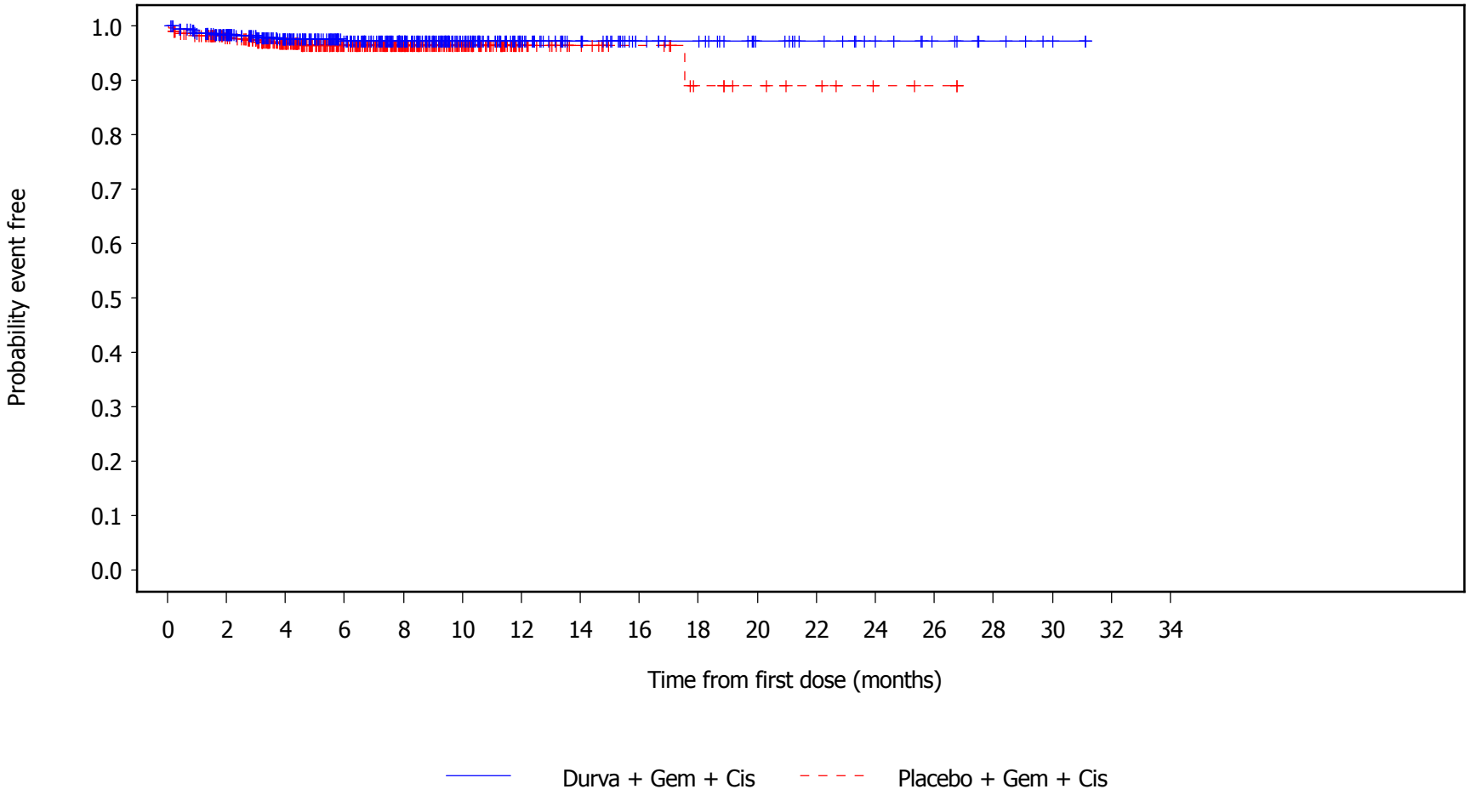
Figure 3.3.282 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Lymphocyte percentage decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

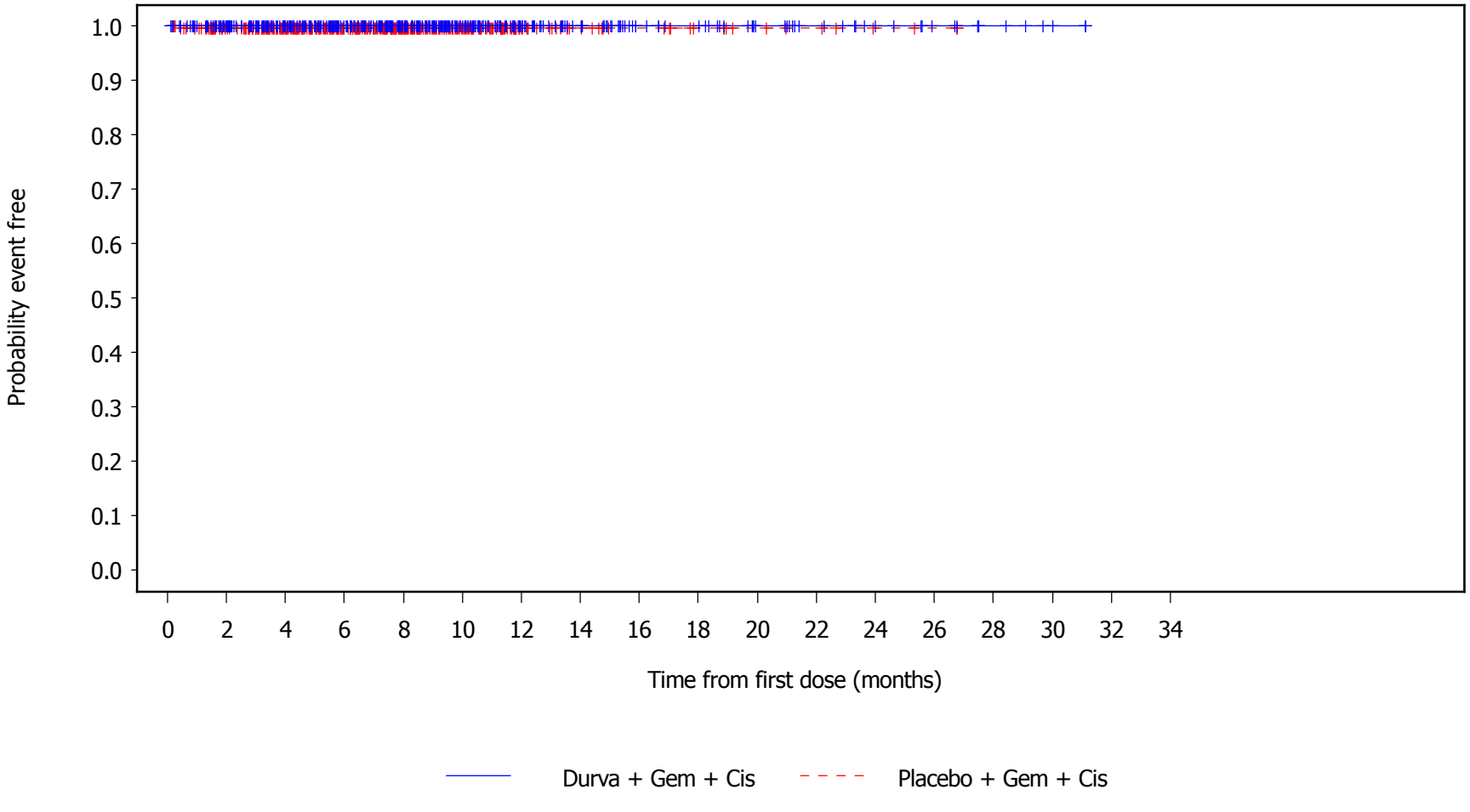
Figure 3.3.283 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Lymphocyte count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	307	257	191	126	77	56	39	35	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	364	304	225	156	88	34	22	16	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

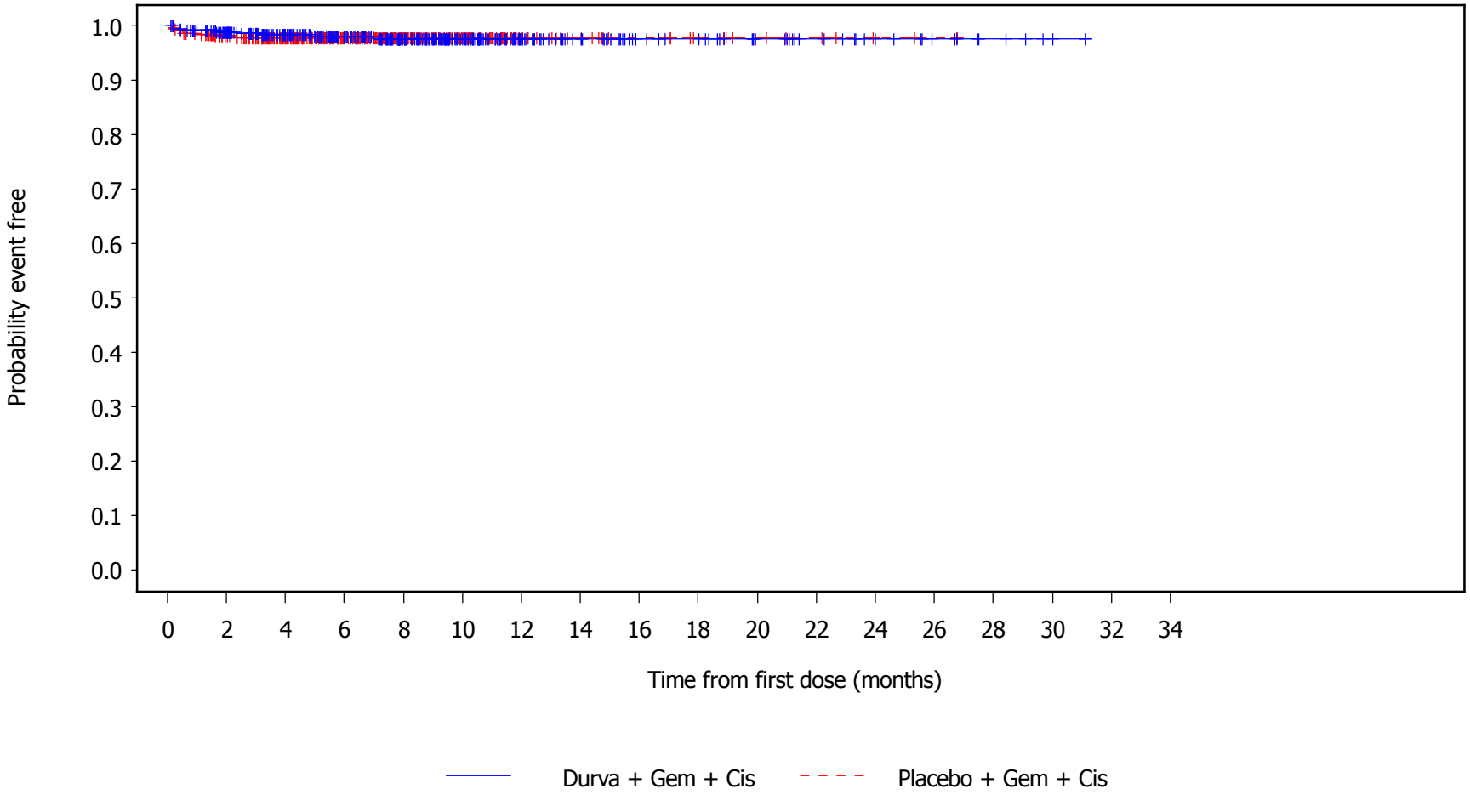
Figure 3.3.284 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Monocyte count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

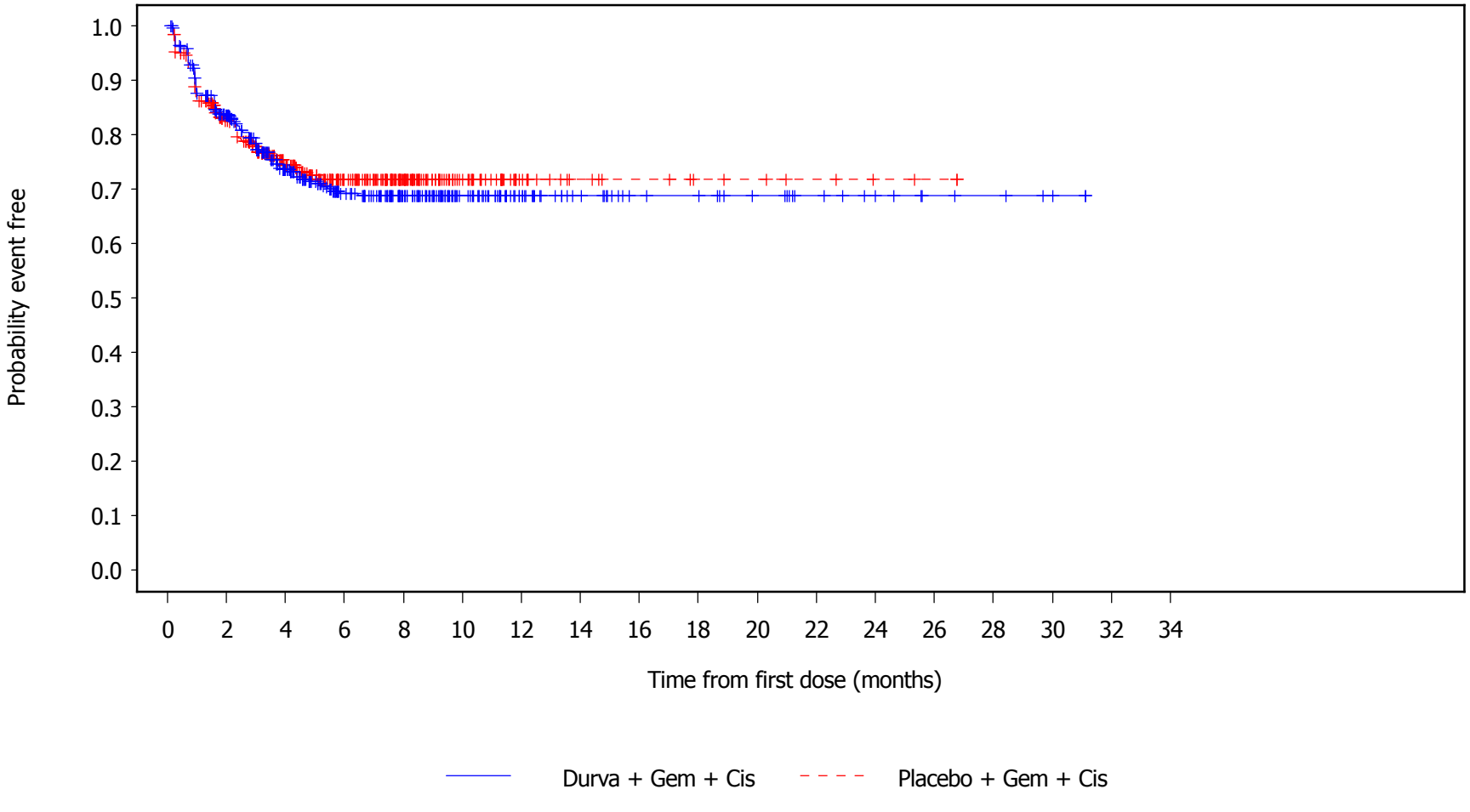
Figure 3.3.285 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Myelosuppression
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	310	260	195	129	79	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	366	307	227	157	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

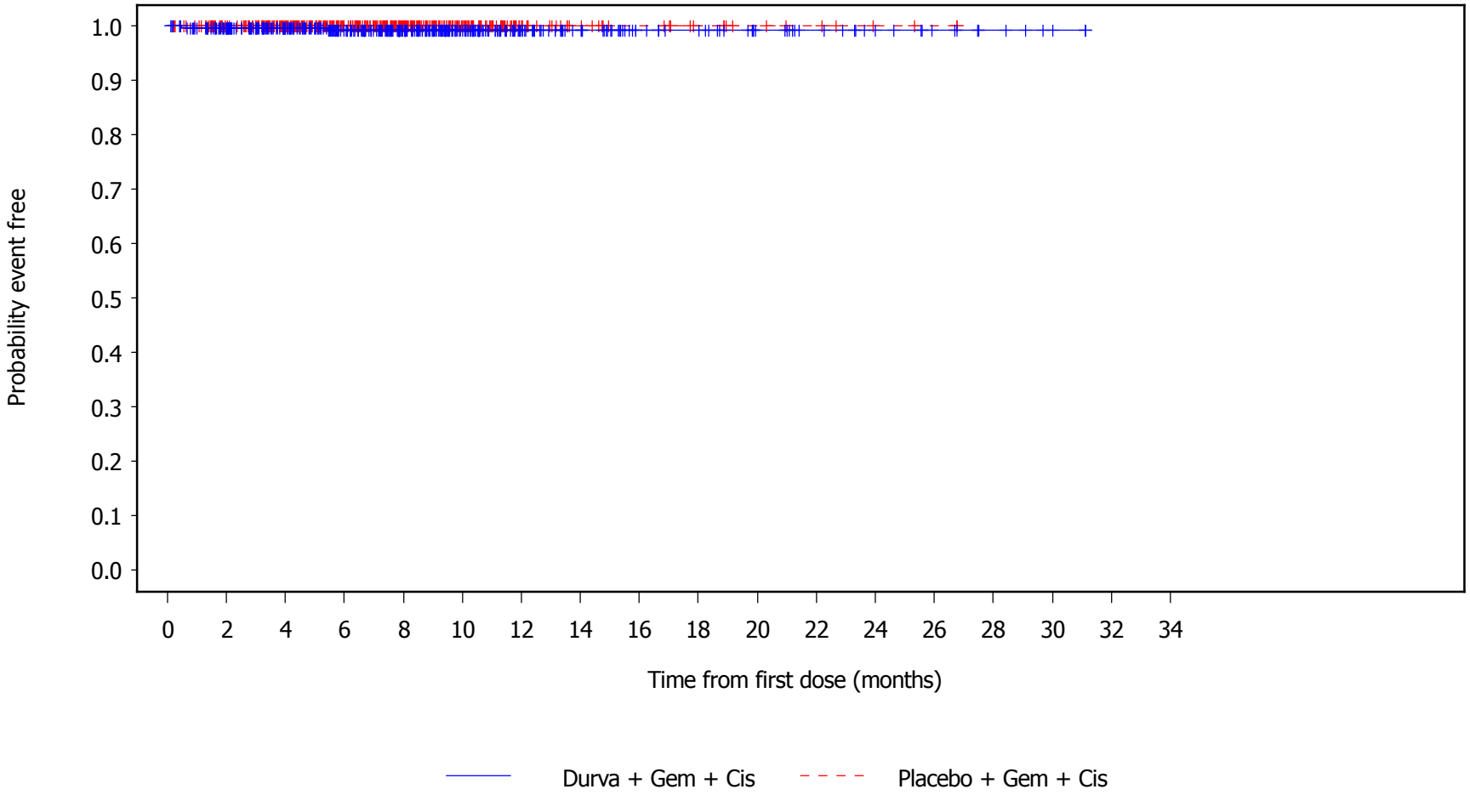
Figure 3.3.286 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	311	223	167	120	75	47	32	23	22	17	12	9	5	4	2	0	0	Durva + Gem + Cis
403	305	226	155	101	51	22	13	10	7	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

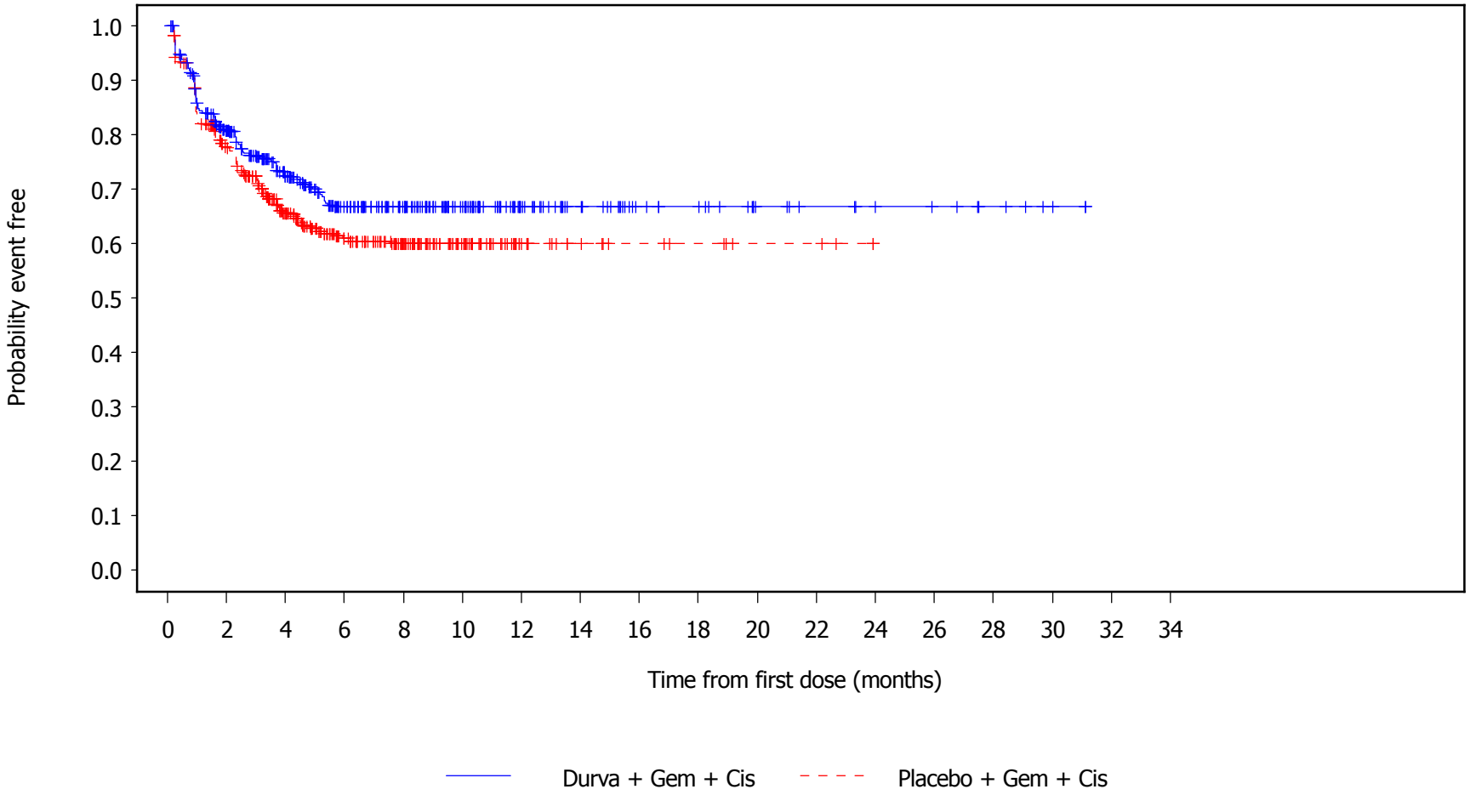
Figure 3.3.287 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Neutropenic sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	263	197	130	79	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

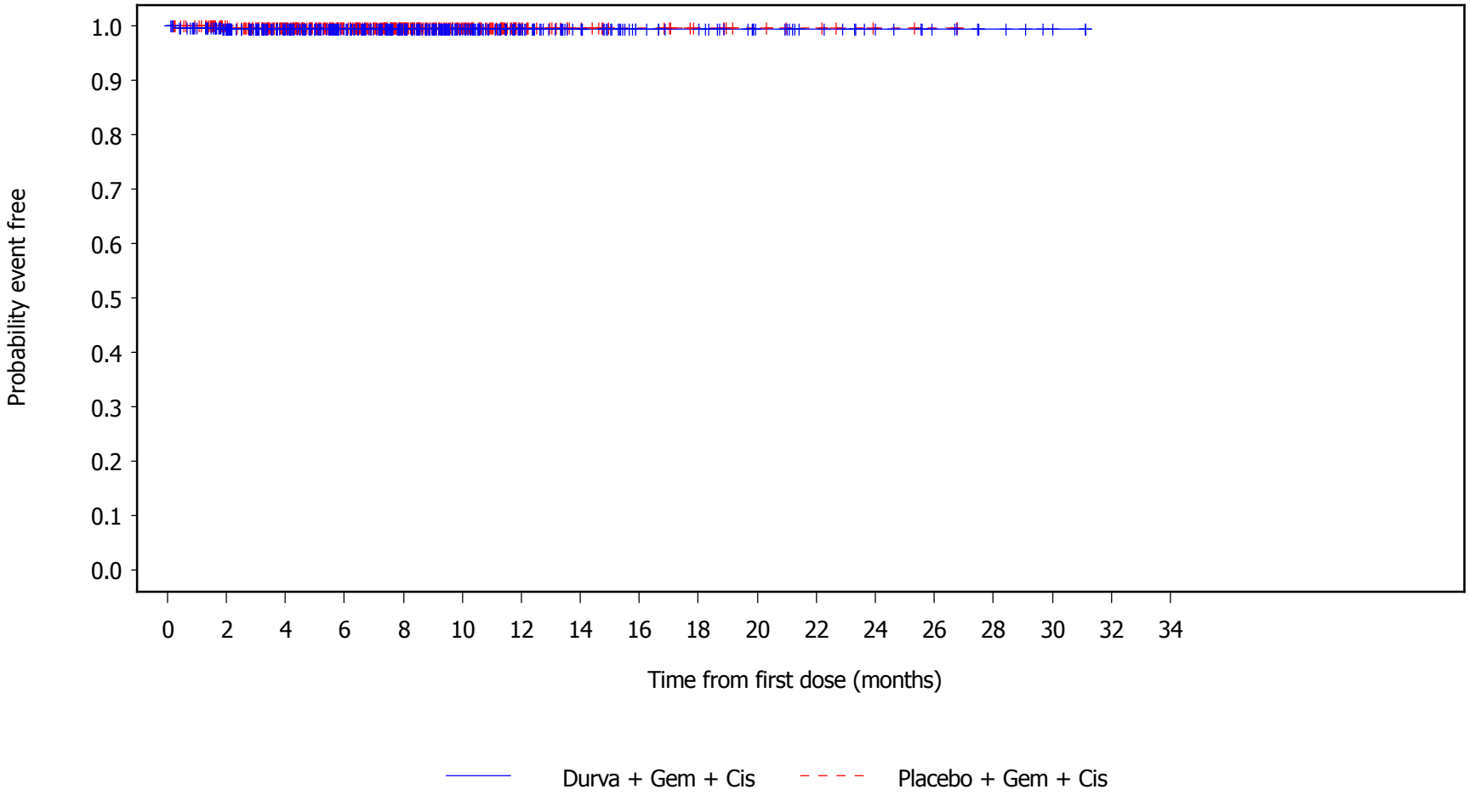
Figure 3.3.288 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Neutrophil count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	300	223	167	130	92	56	40	27	24	15	12	10	8	5	2	0	0	Durva + Gem + Cis
403	287	194	129	90	53	20	12	8	6	3	3	0	0	0	0	0	0	Placebo + Gem + Cis

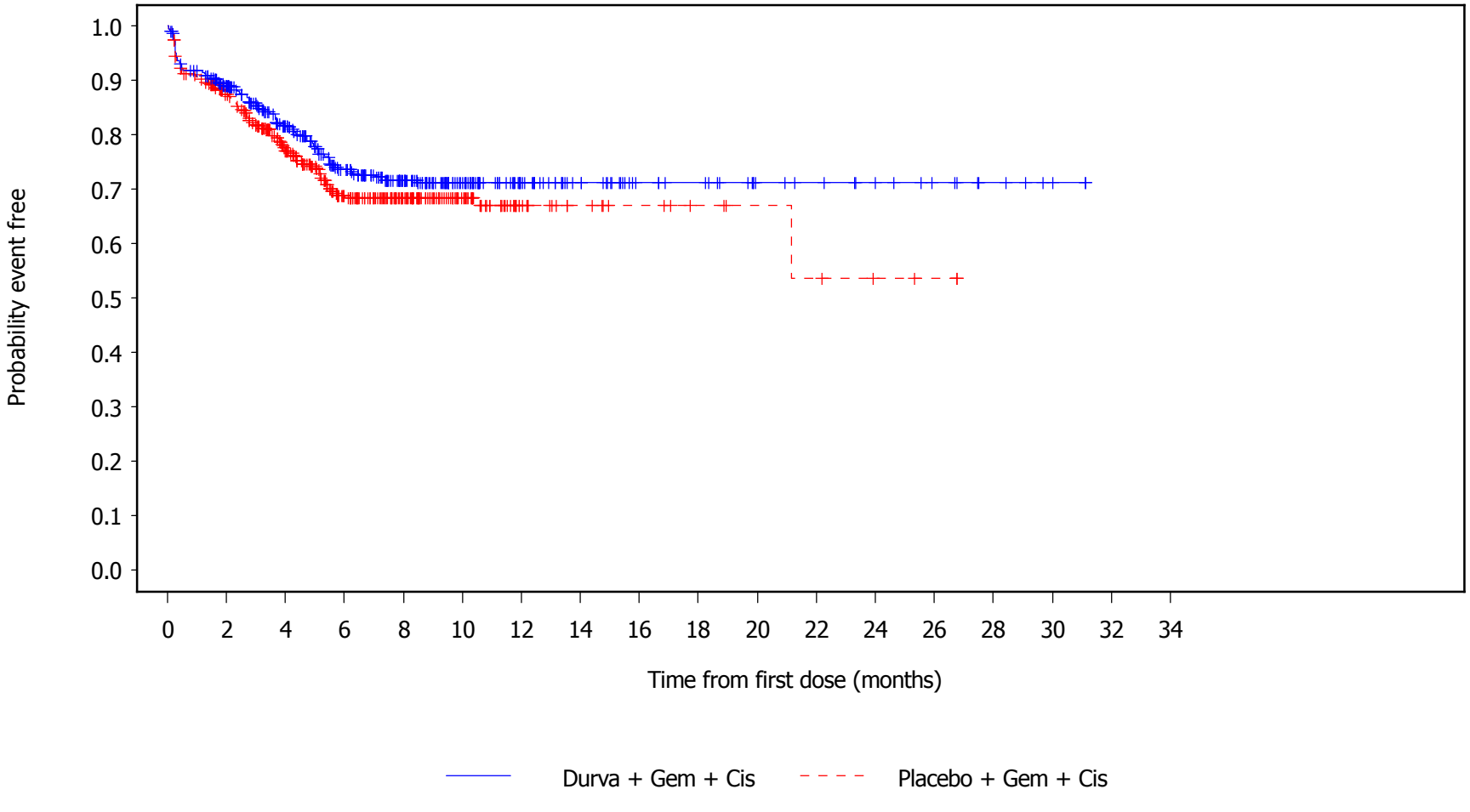
Figure 3.3.289 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Pancytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

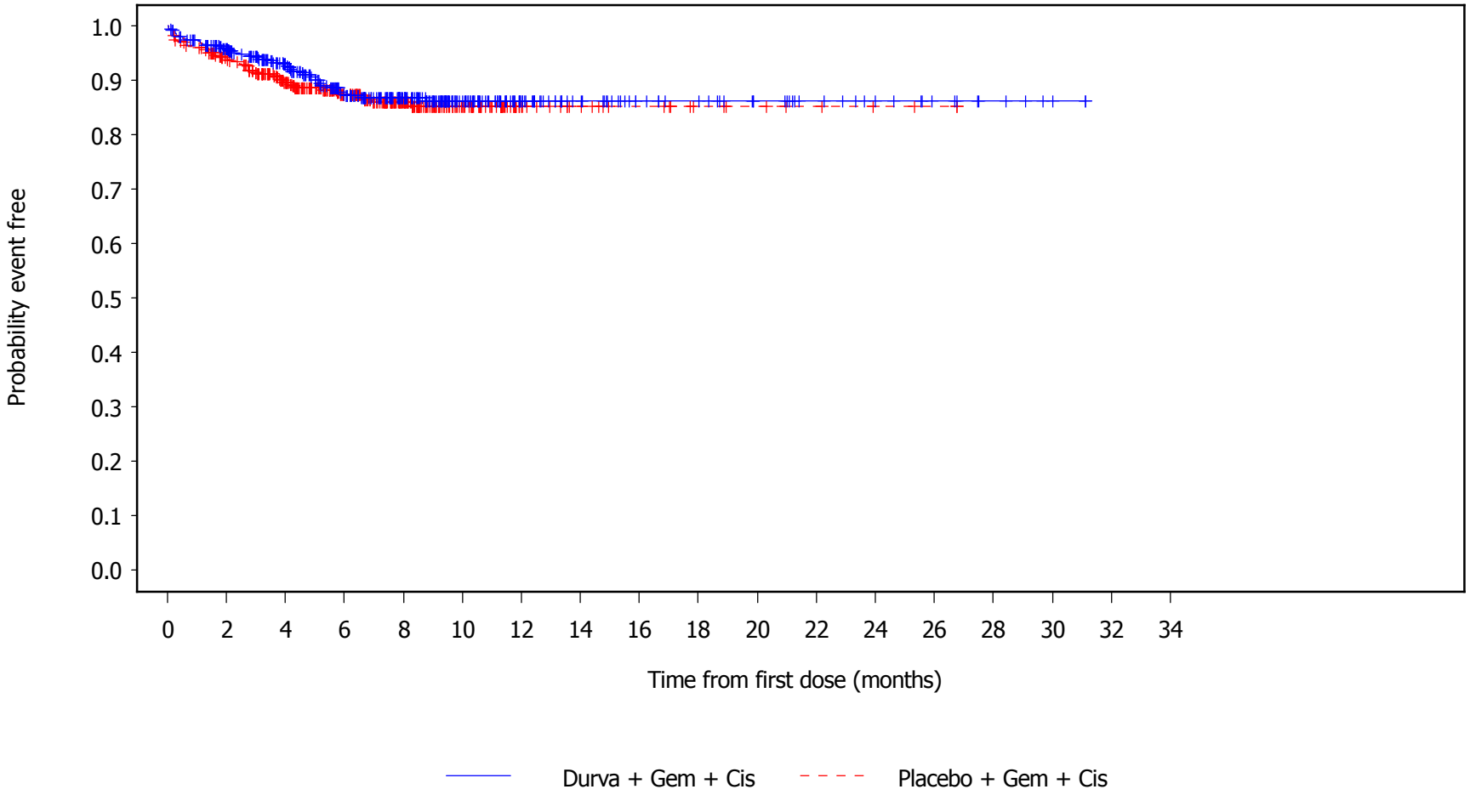
Figure 3.3.290 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Platelet count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	336	265	205	149	99	62	44	30	27	18	16	13	9	5	2	0	0	Durva + Gem + Cis
403	326	241	157	107	59	23	14	10	7	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

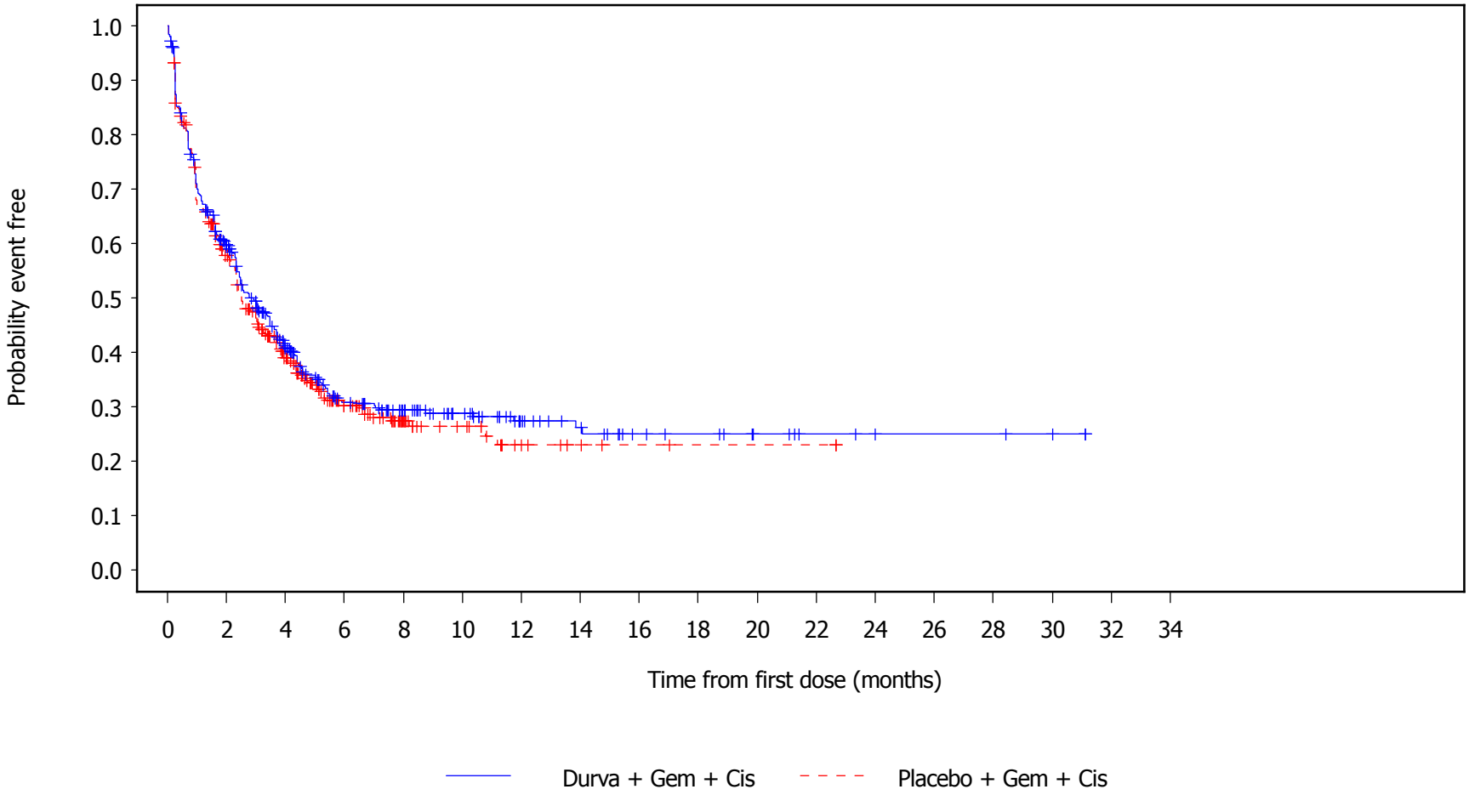
Figure 3.3.291 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI PT: Thrombocytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	359	295	233	174	112	69	49	36	32	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	355	284	200	135	71	26	18	13	8	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

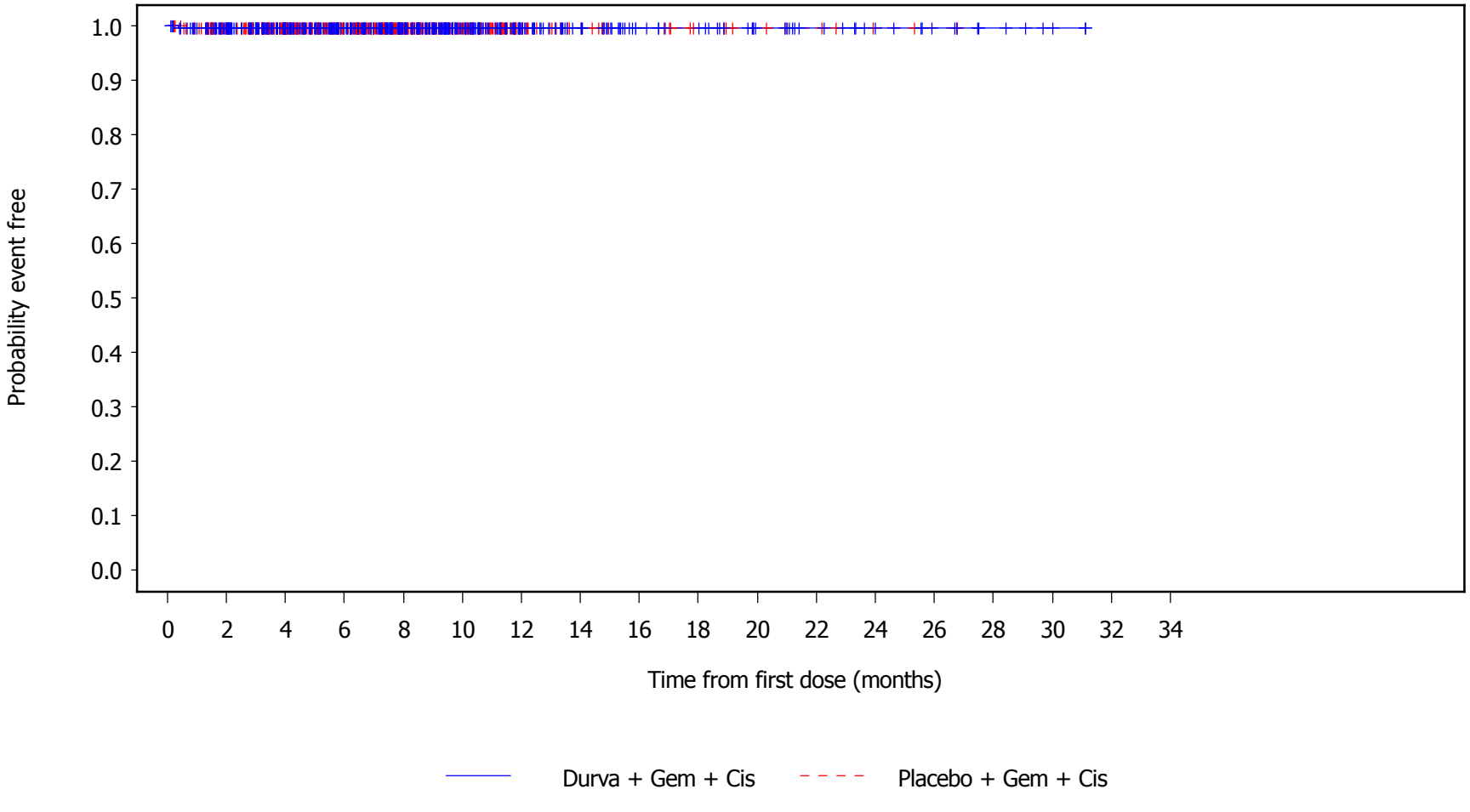
Figure 3.3.292 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI max CTCAE grade >=3
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	226	135	85	65	47	29	22	14	12	8	5	4	3	3	2	0	0	Durva + Gem + Cis
403	215	120	61	32	20	7	4	2	1	1	1	0	0	0	0	0	0	Placebo + Gem + Cis

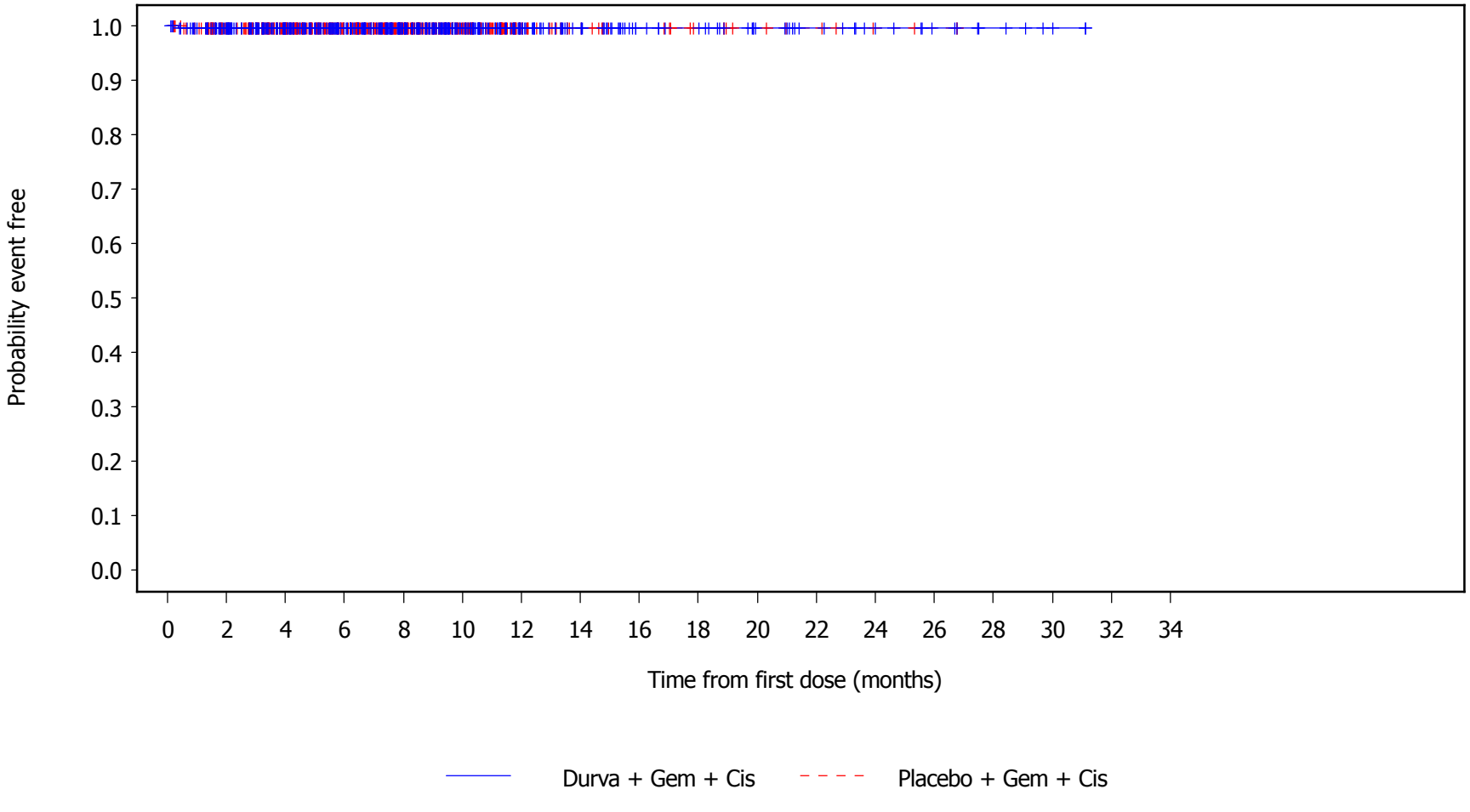
Figure 3.3.293 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

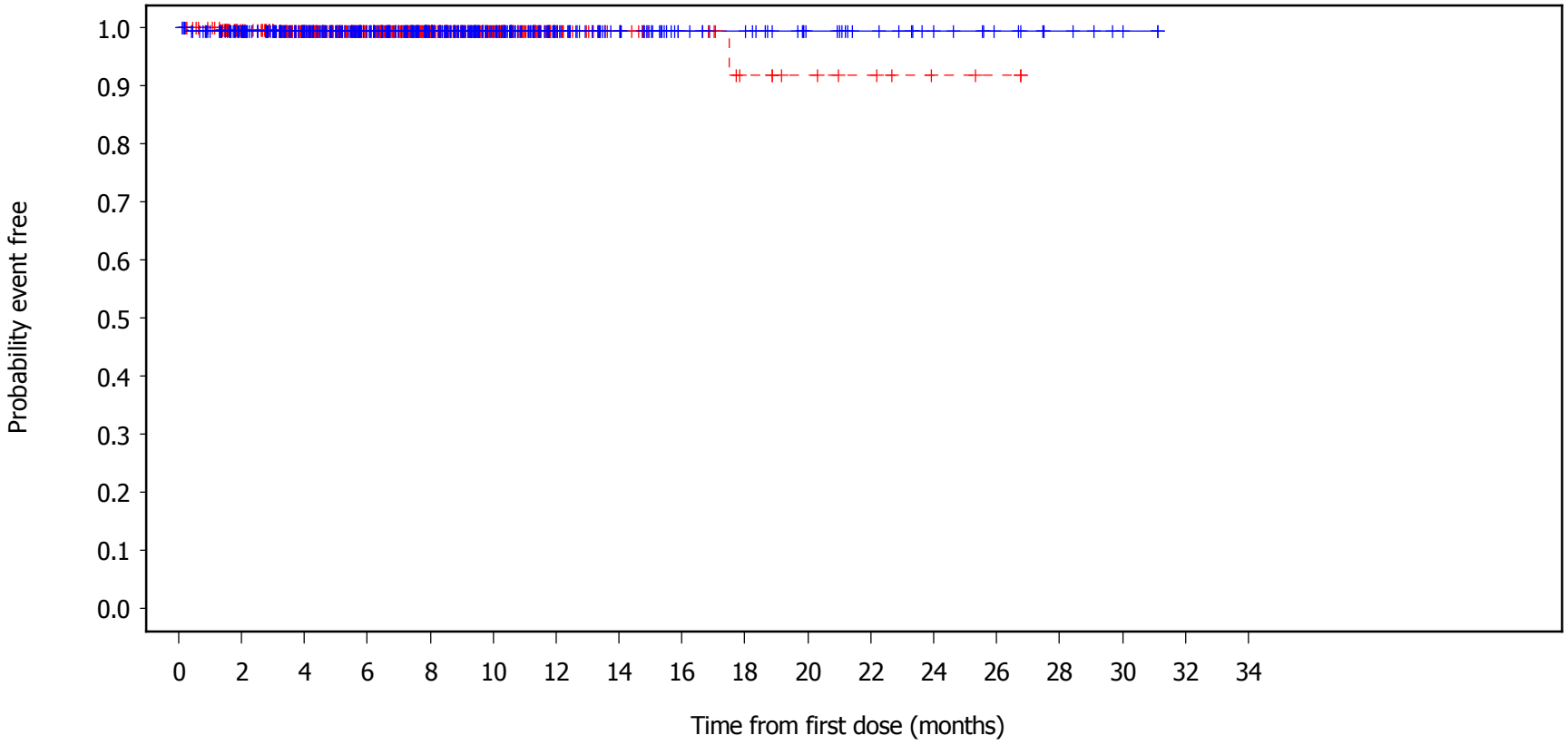
Figure 3.3.294 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

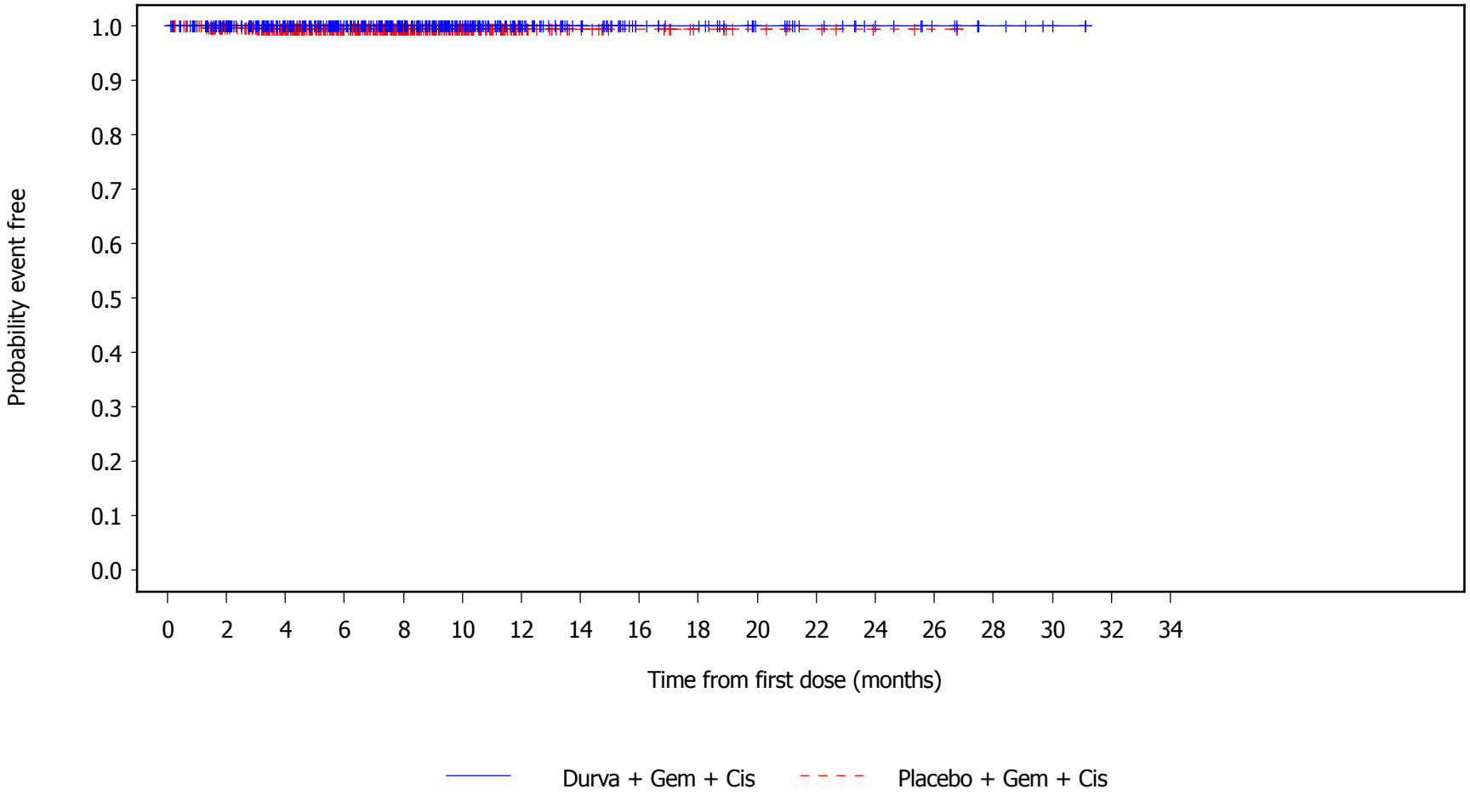
Figure 3.3.295 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Hepatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	314	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

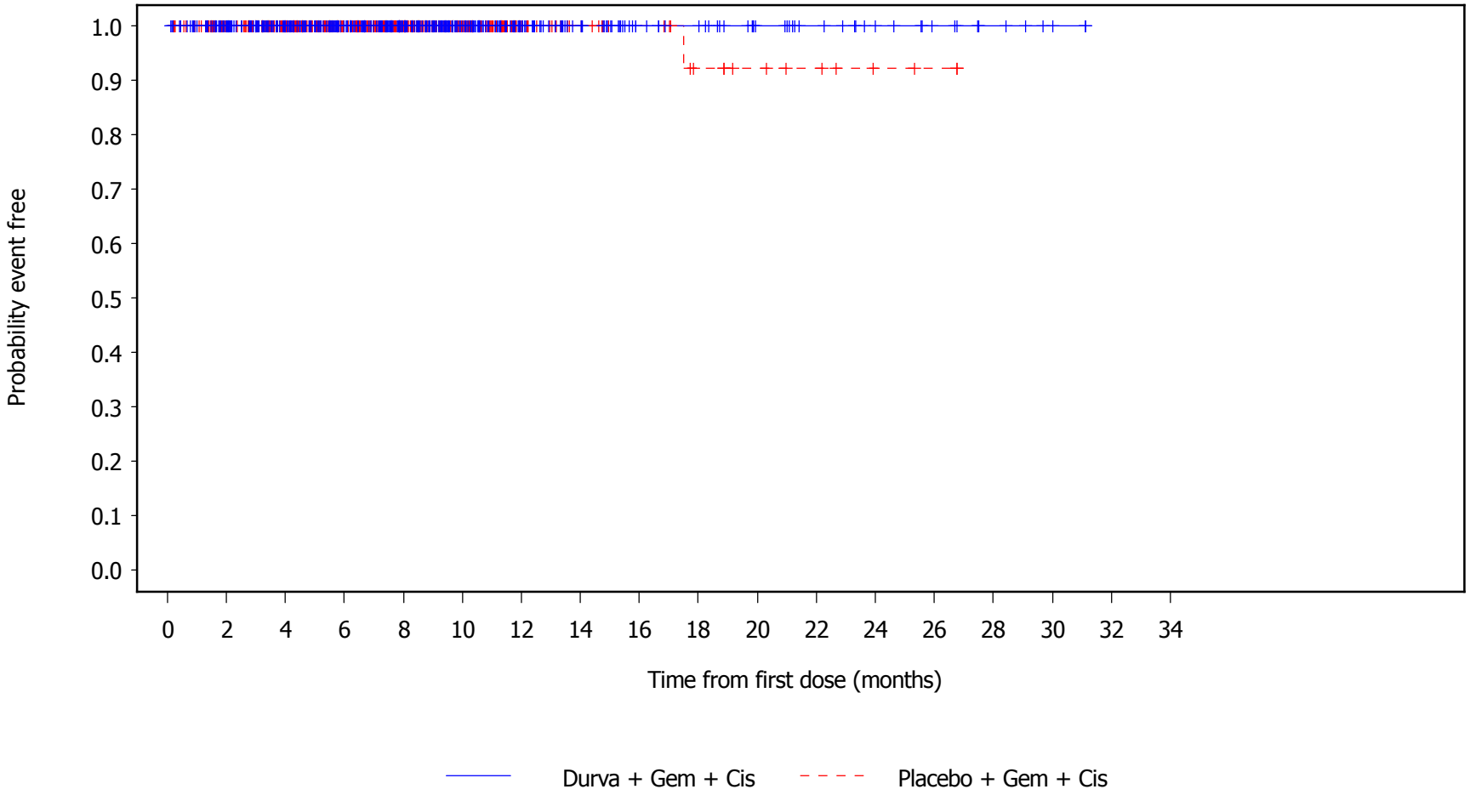
Figure 3.3.296 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

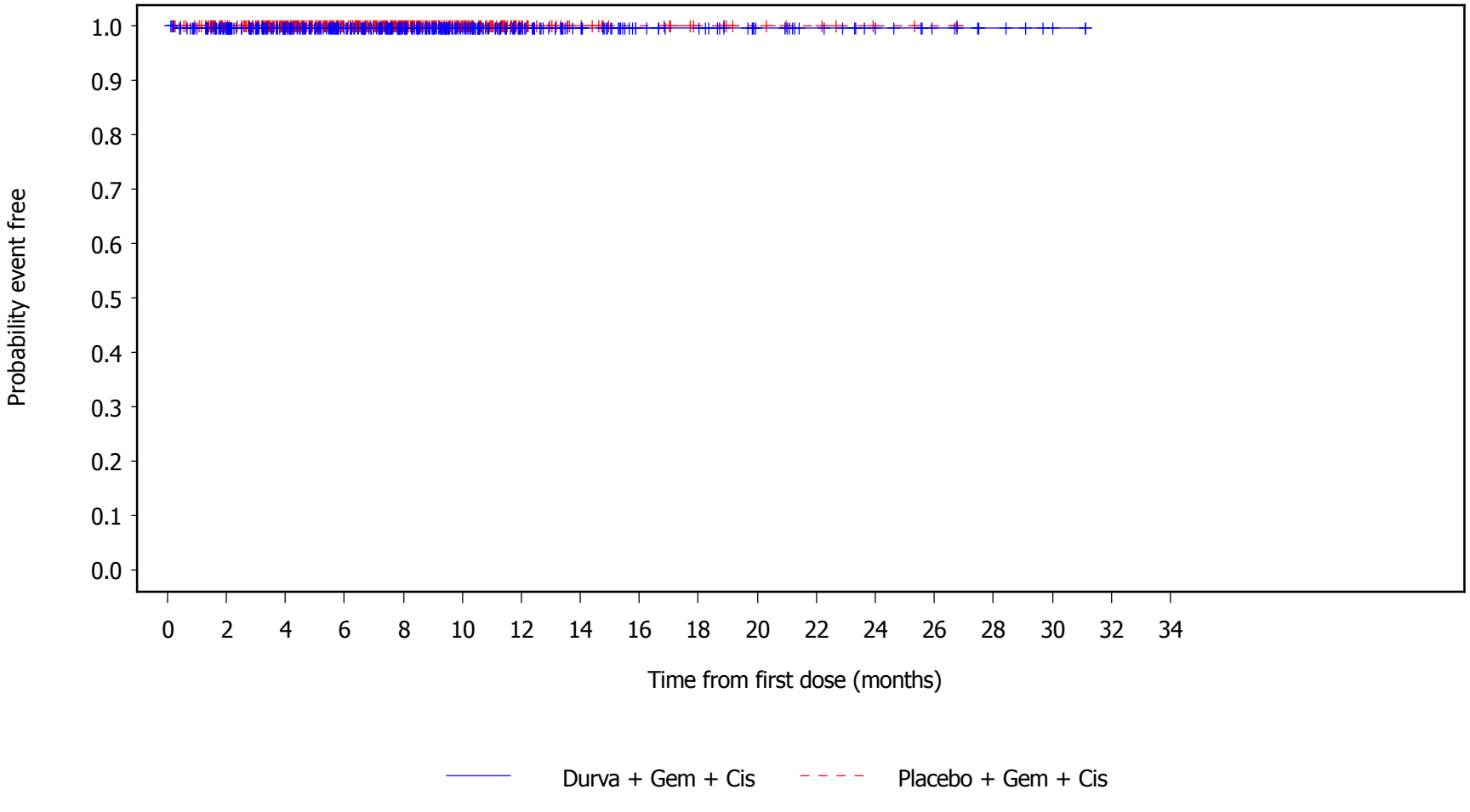
Figure 3.3.297 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

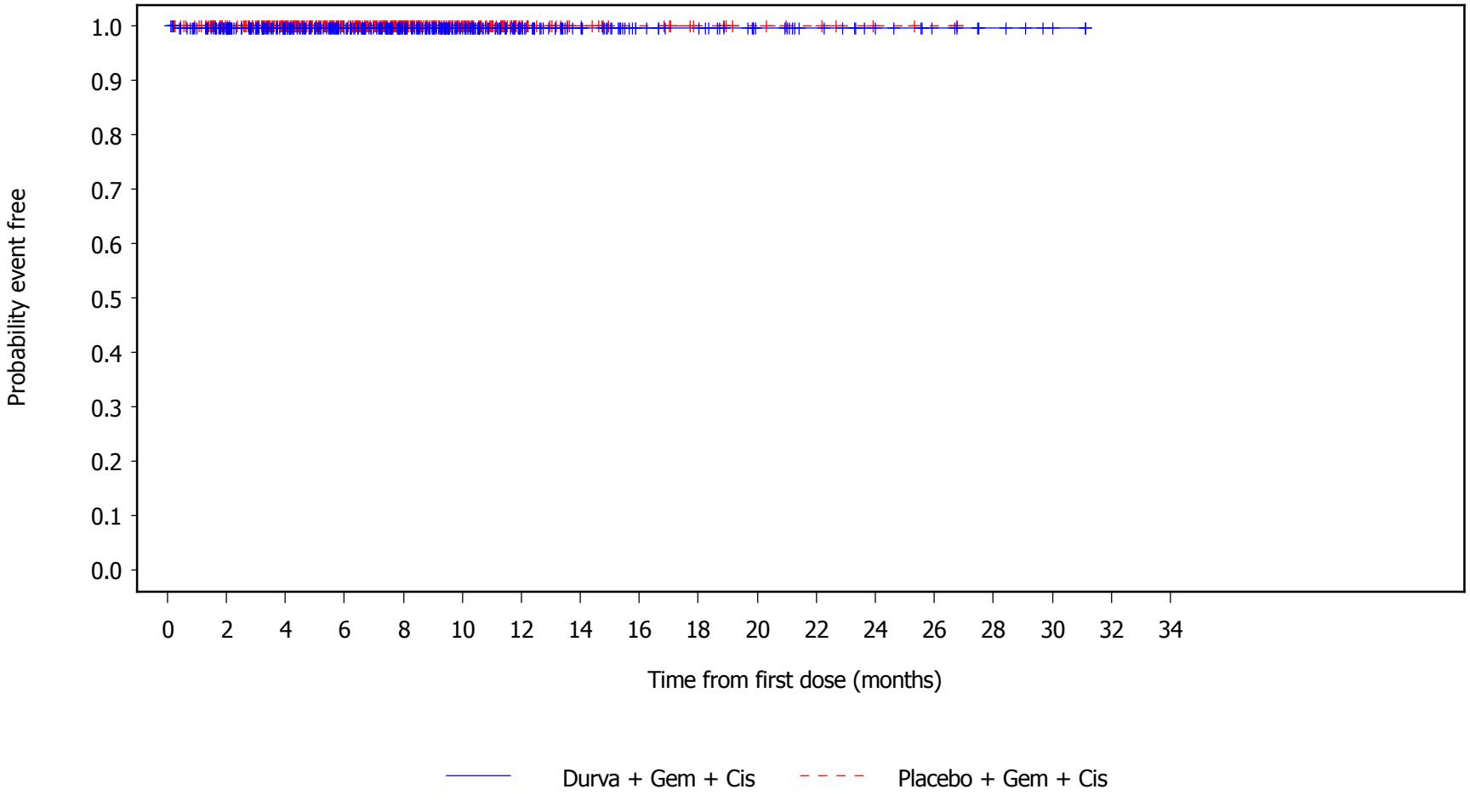
Figure 3.3.298 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

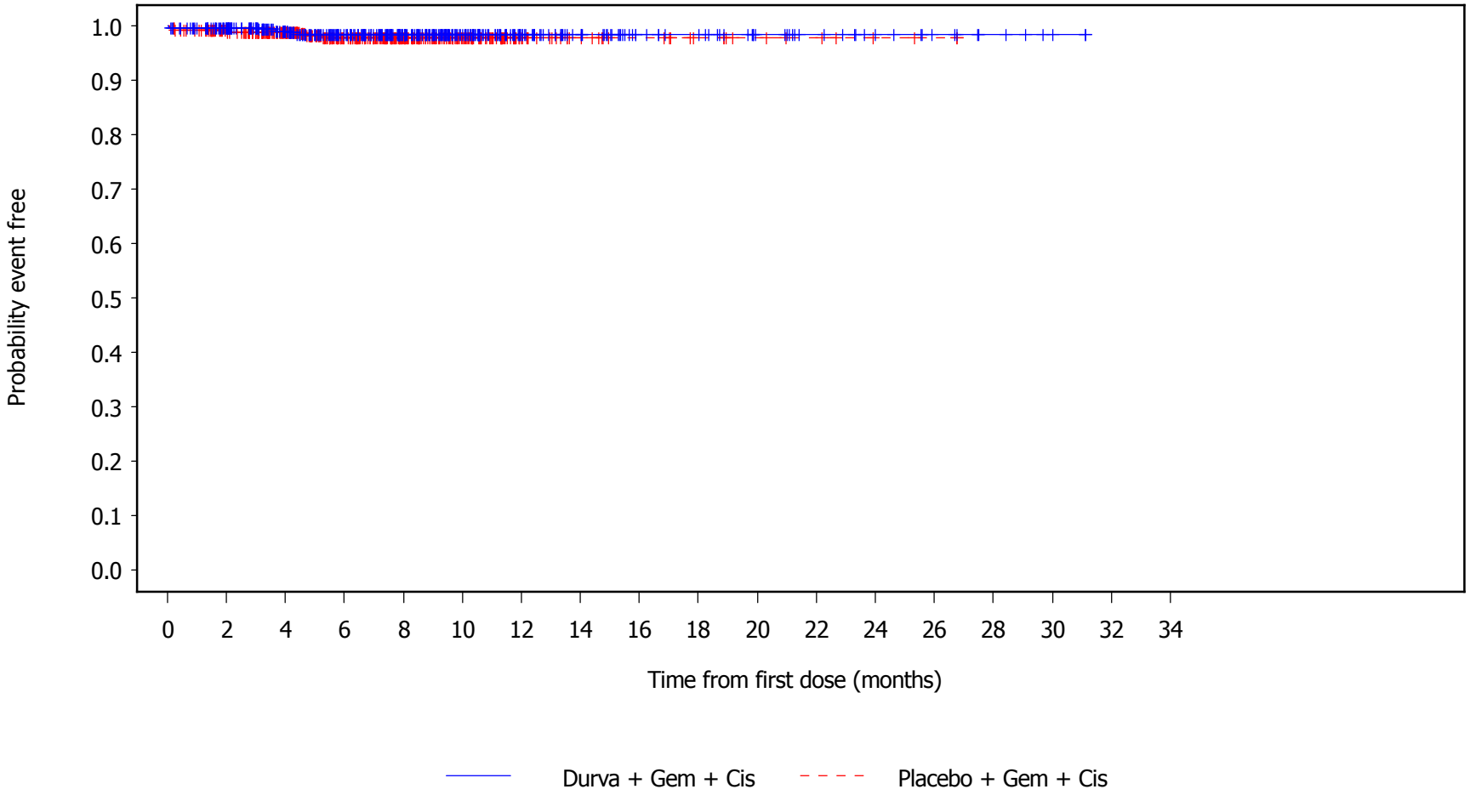
Figure 3.3.299 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Immune-mediated hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

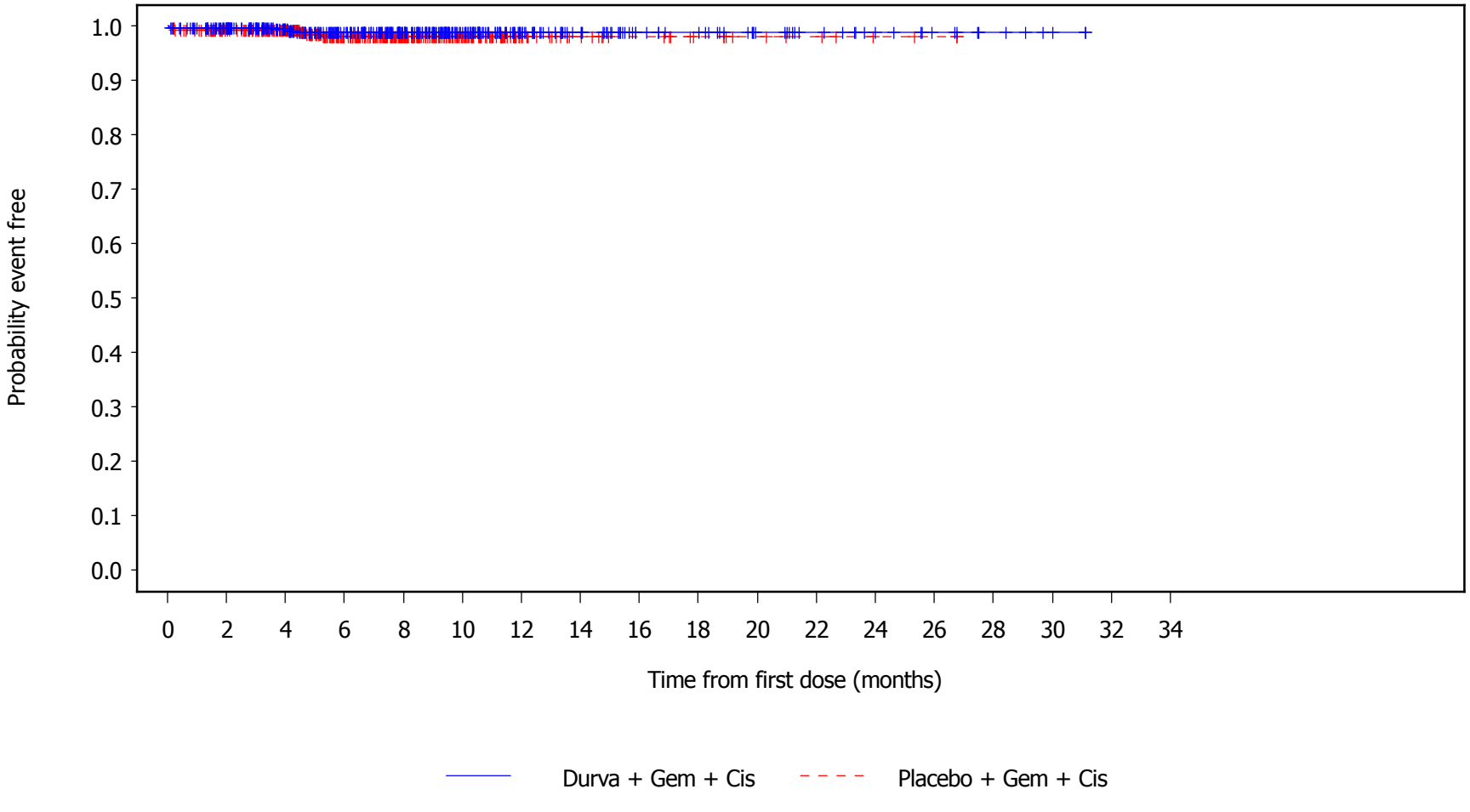
Figure 3.3.300 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Diarrhoea/Colitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	313	262	196	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	309	226	154	87	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

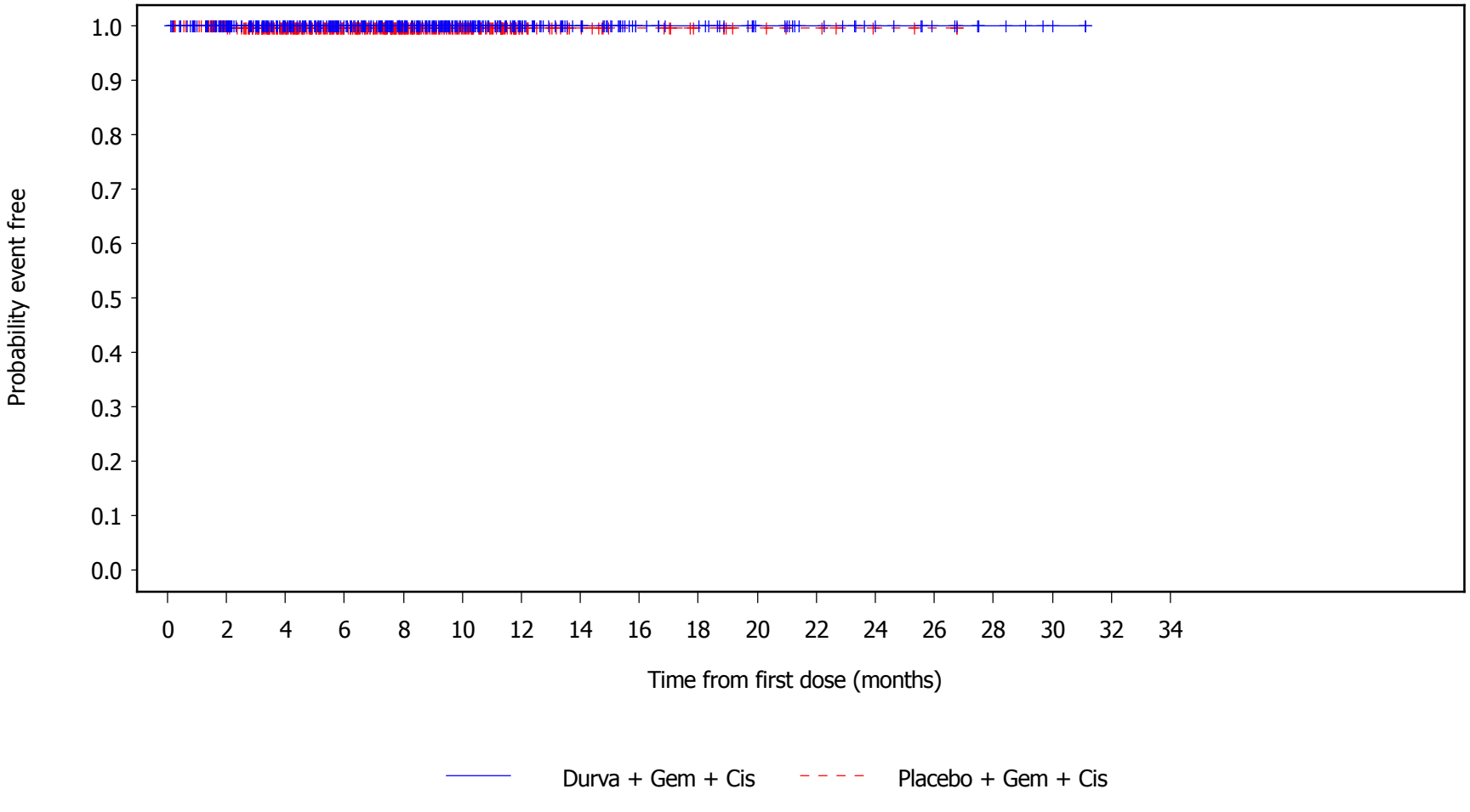
Figure 3.3.301 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Diarrhoea
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	262	196	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	310	226	154	87	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

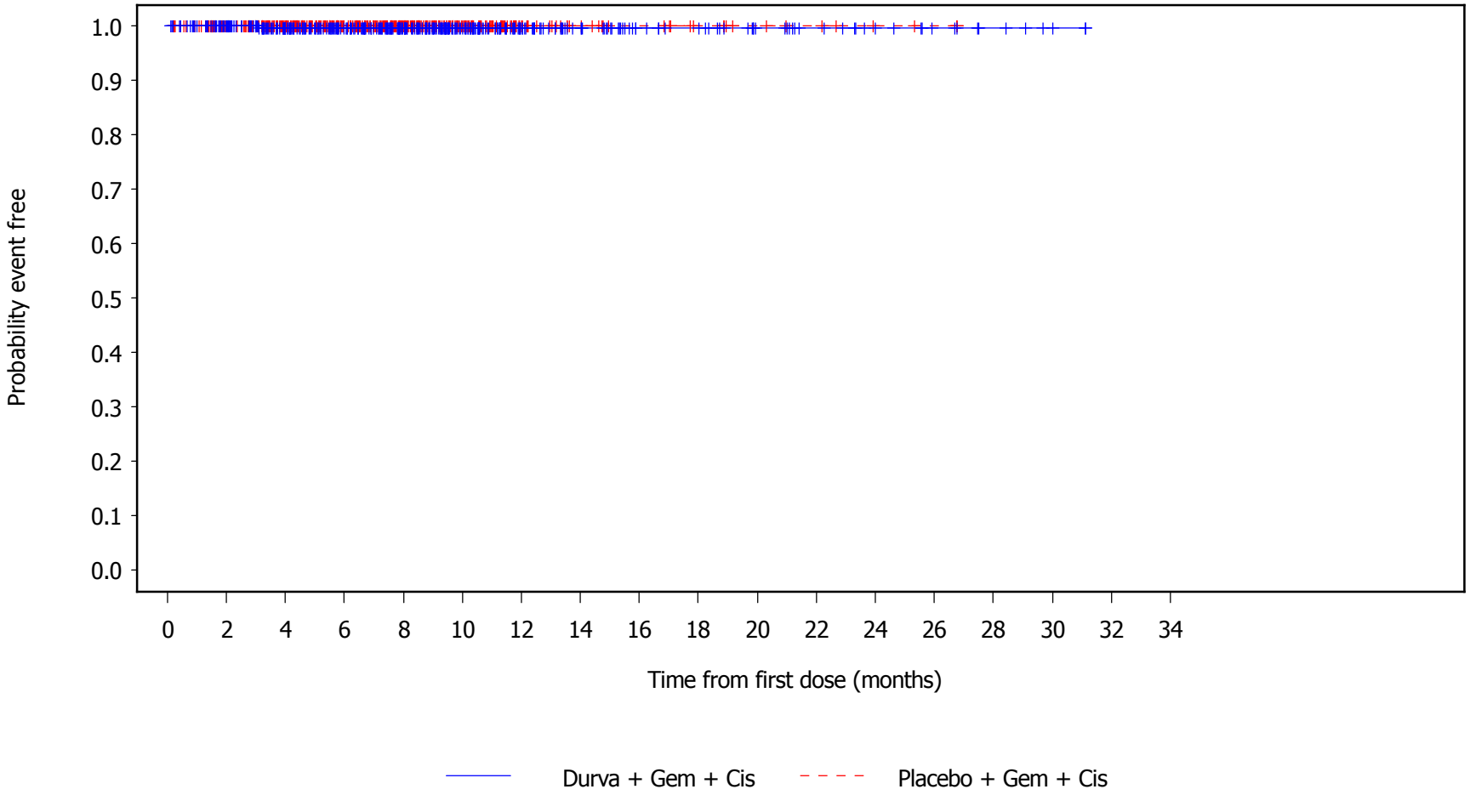
Figure 3.3.302 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Immune-mediated enterocolitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

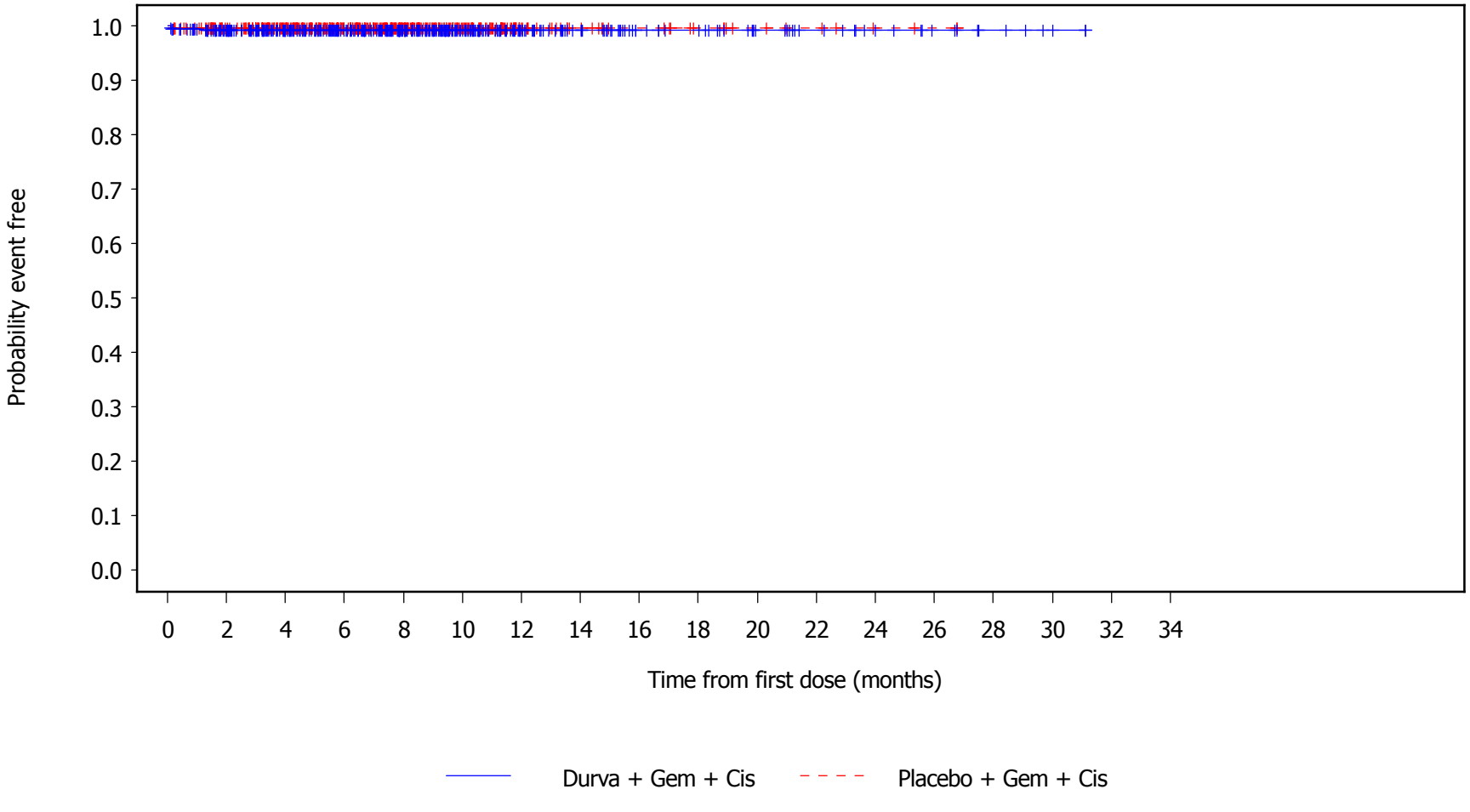
Figure 3.3.303 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Colitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

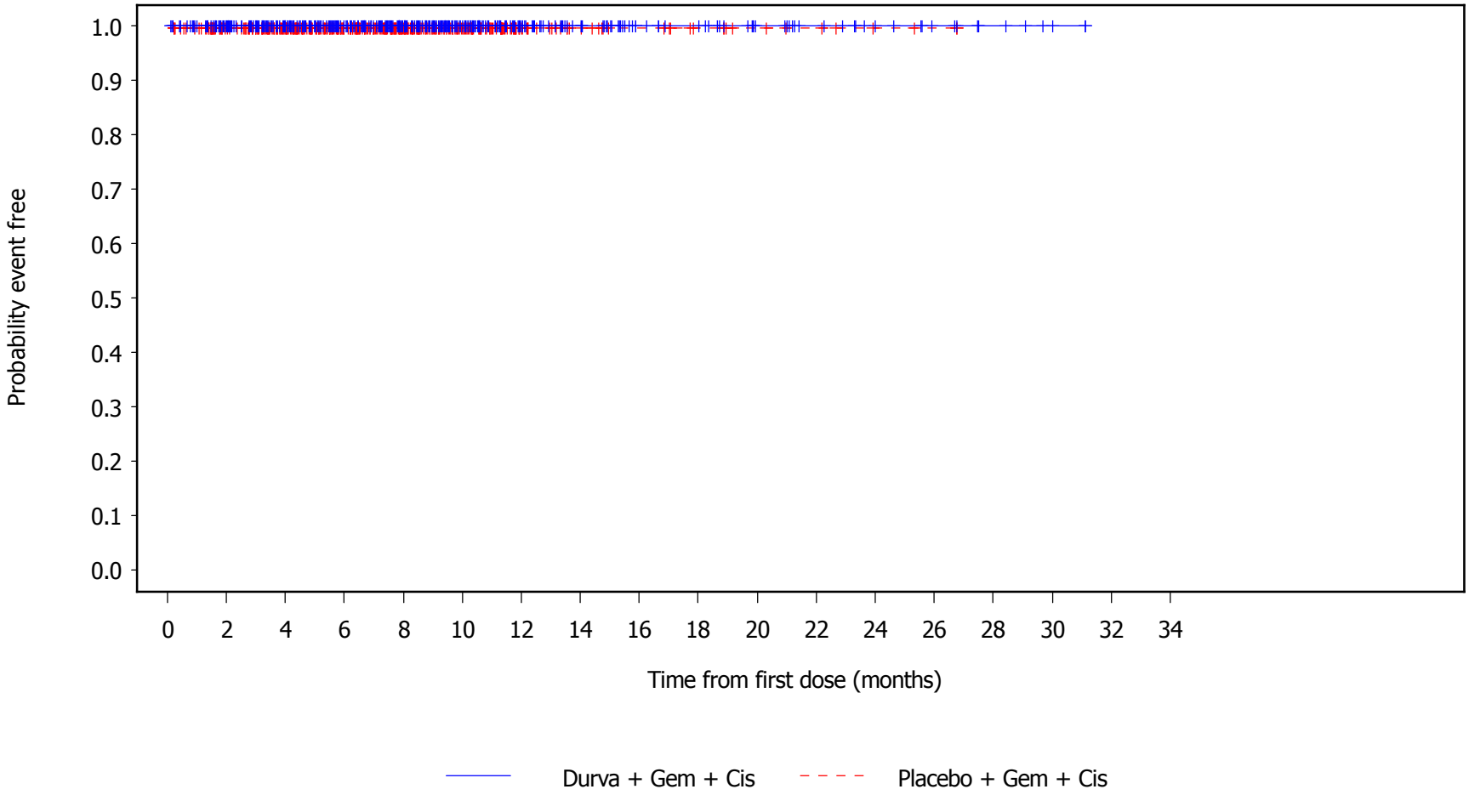
Figure 3.3.304 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Dermatitis/Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	313	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

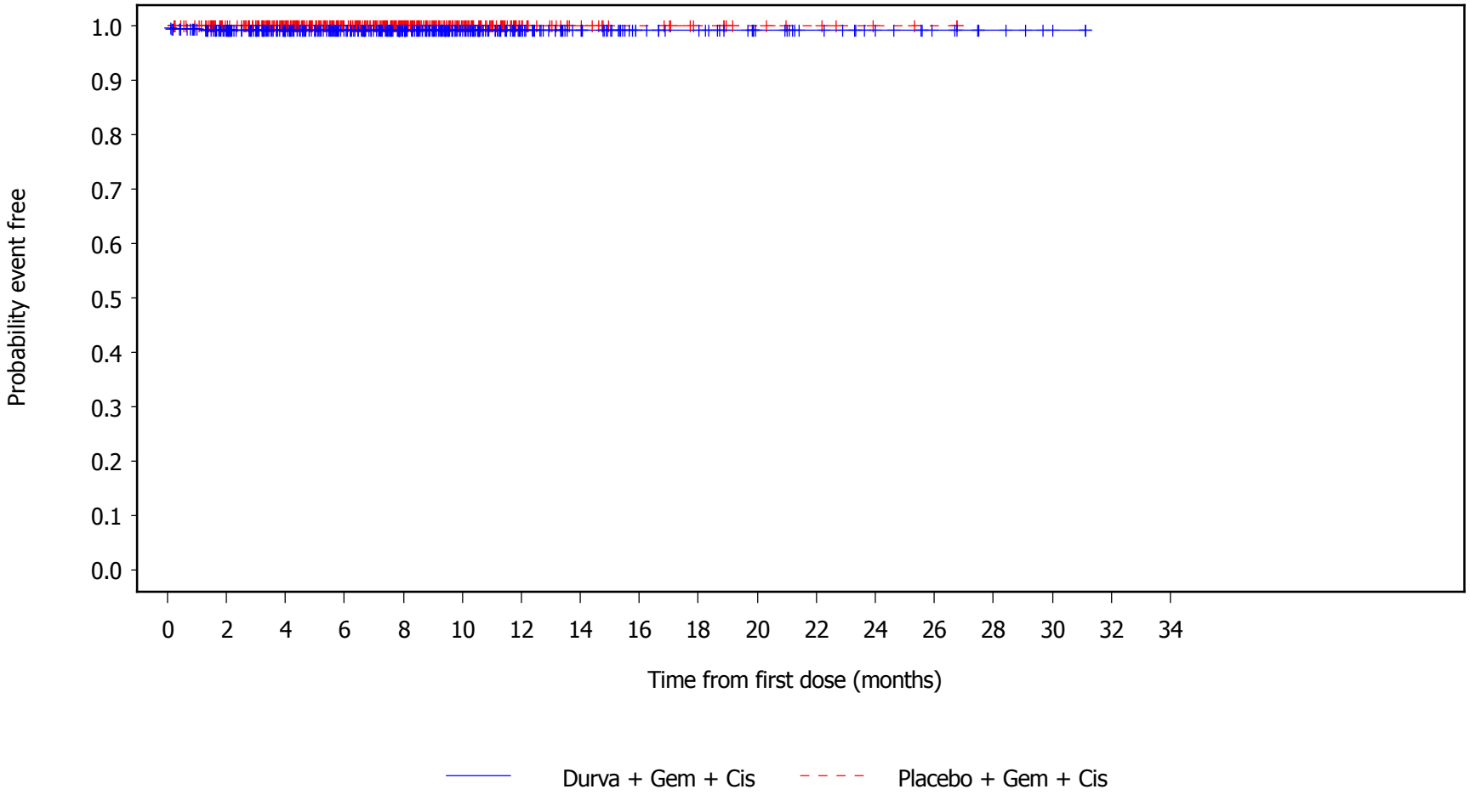
Figure 3.3.305 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

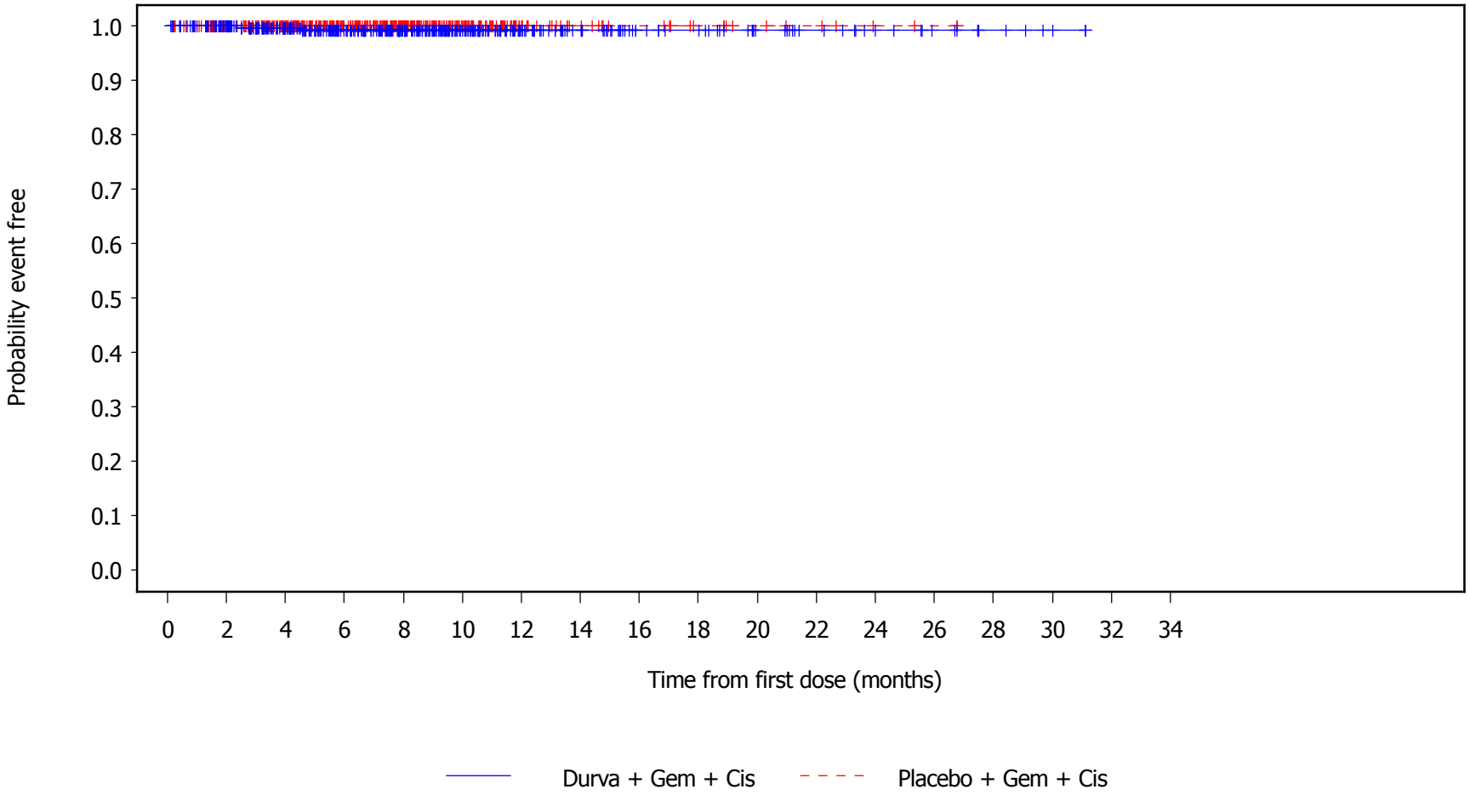
Figure 3.3.306 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Rash maculo-papular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	313	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

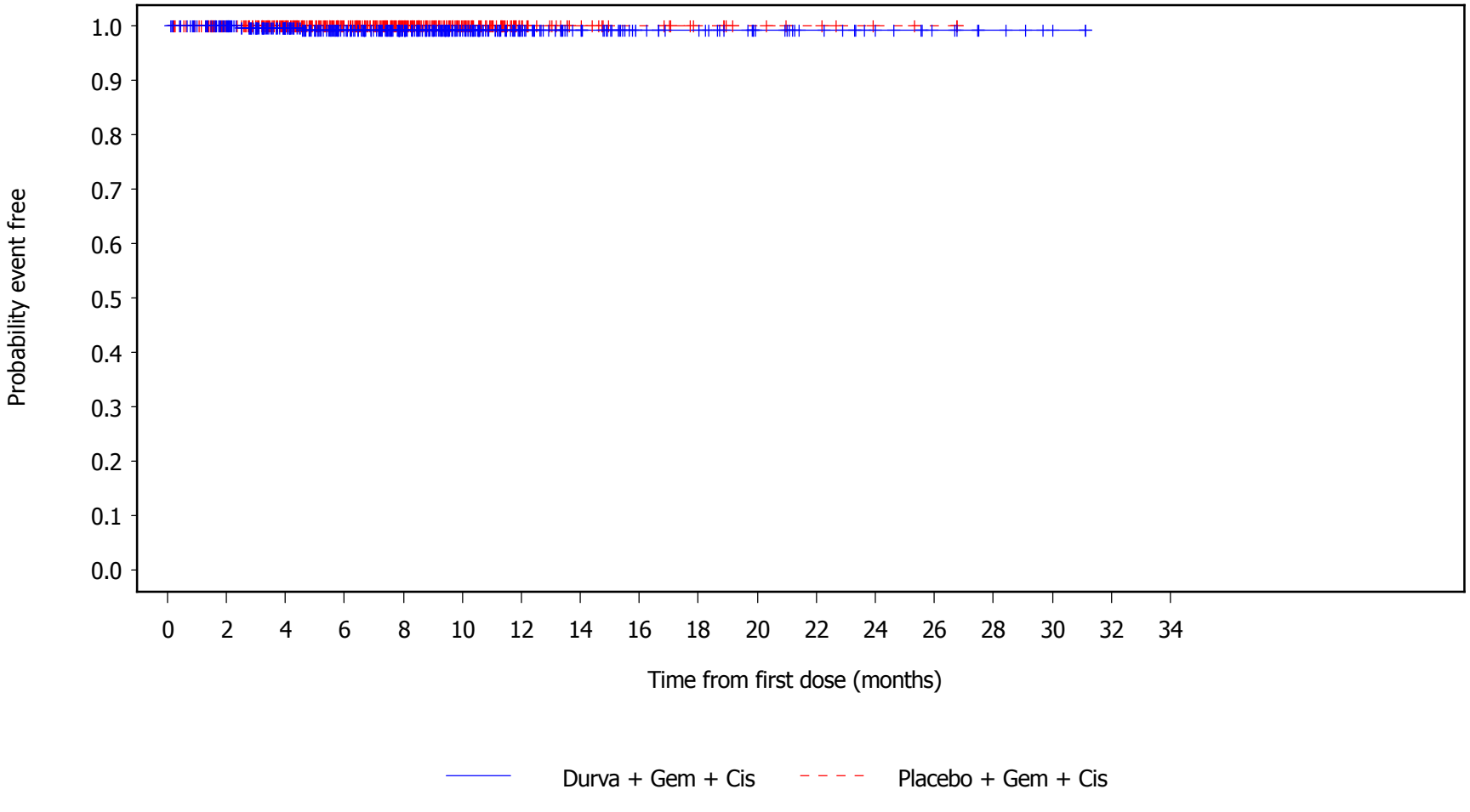
Figure 3.3.307 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Pancreatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	262	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

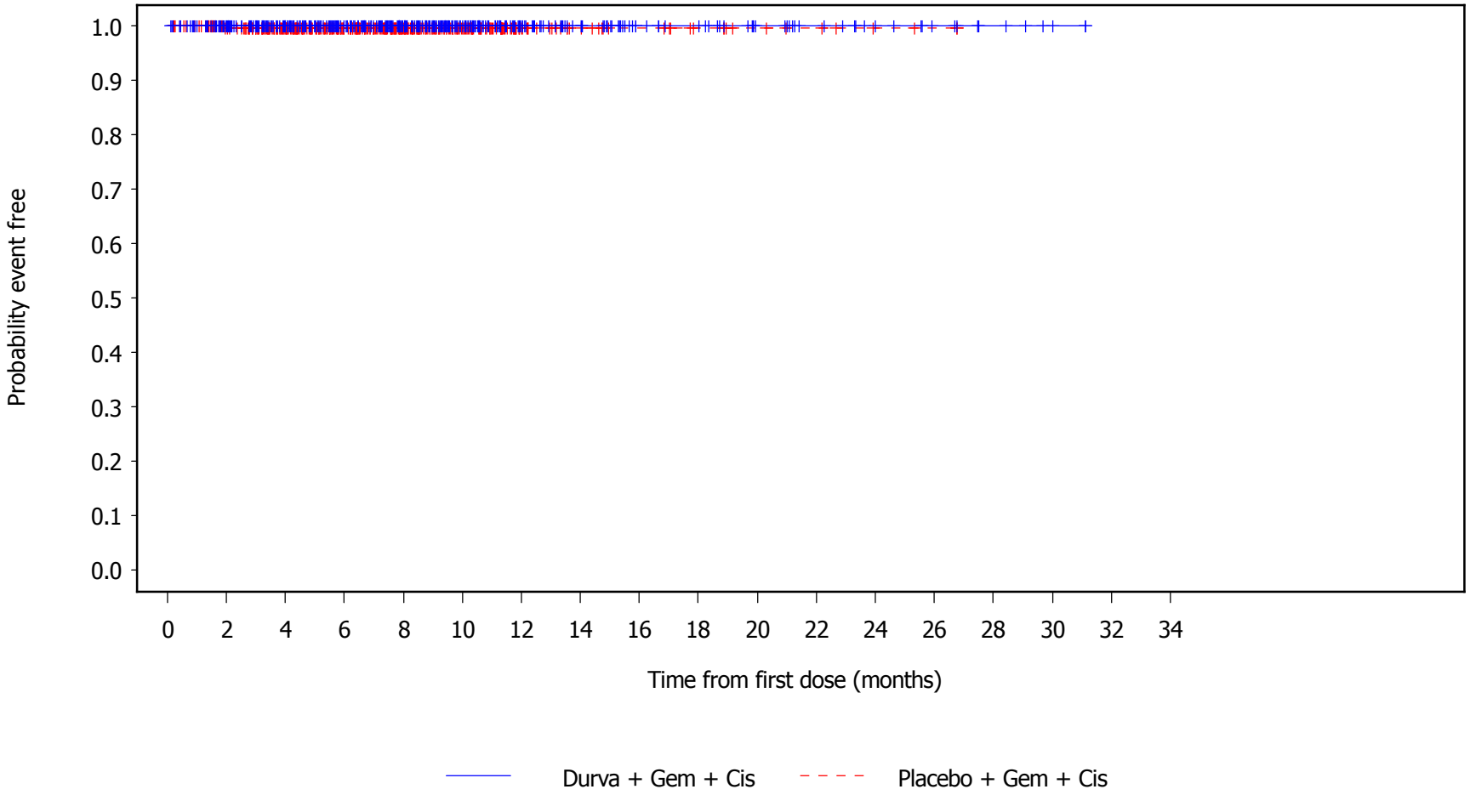
Figure 3.3.308 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Pancreatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	262	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

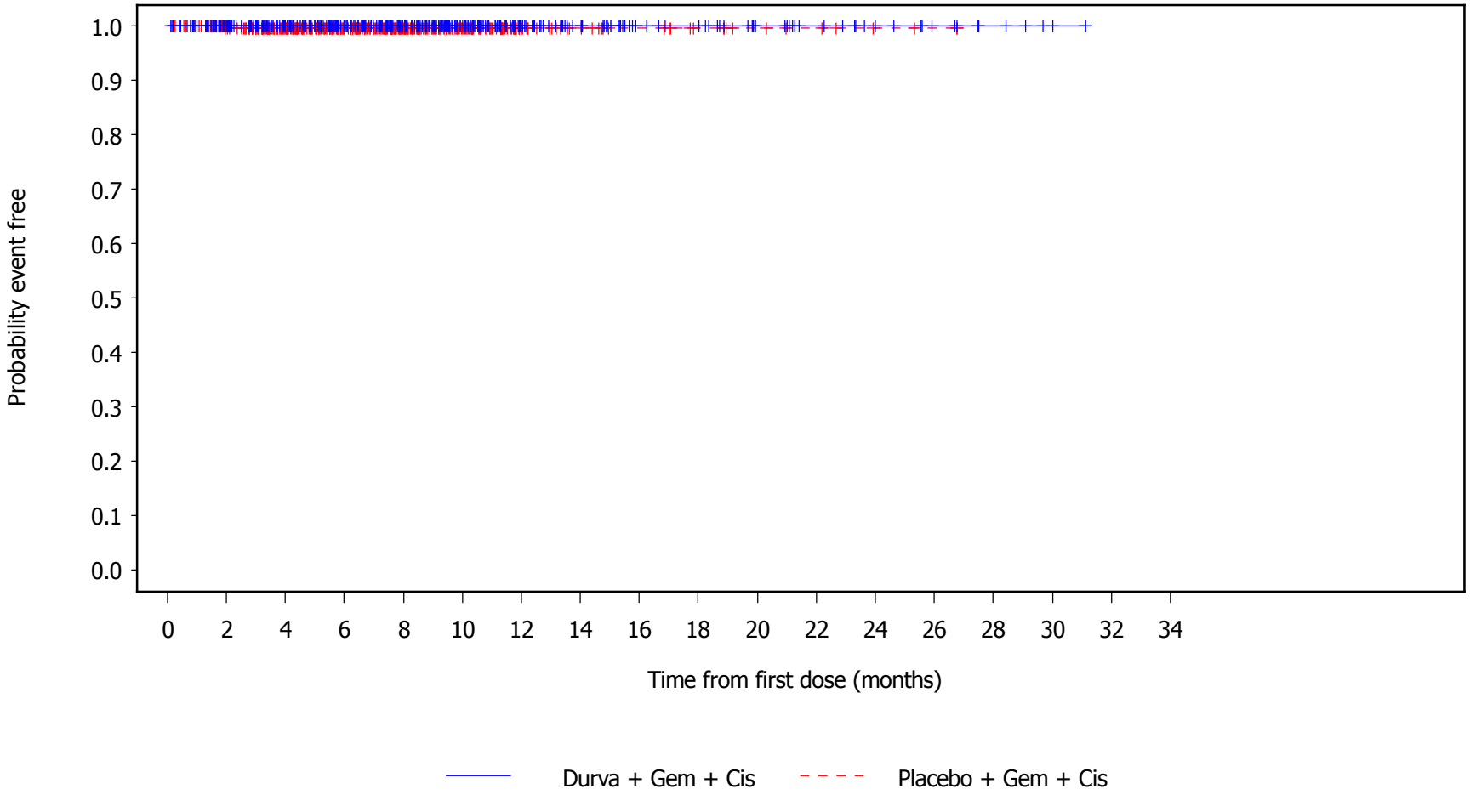
Figure 3.3.309 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Myositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

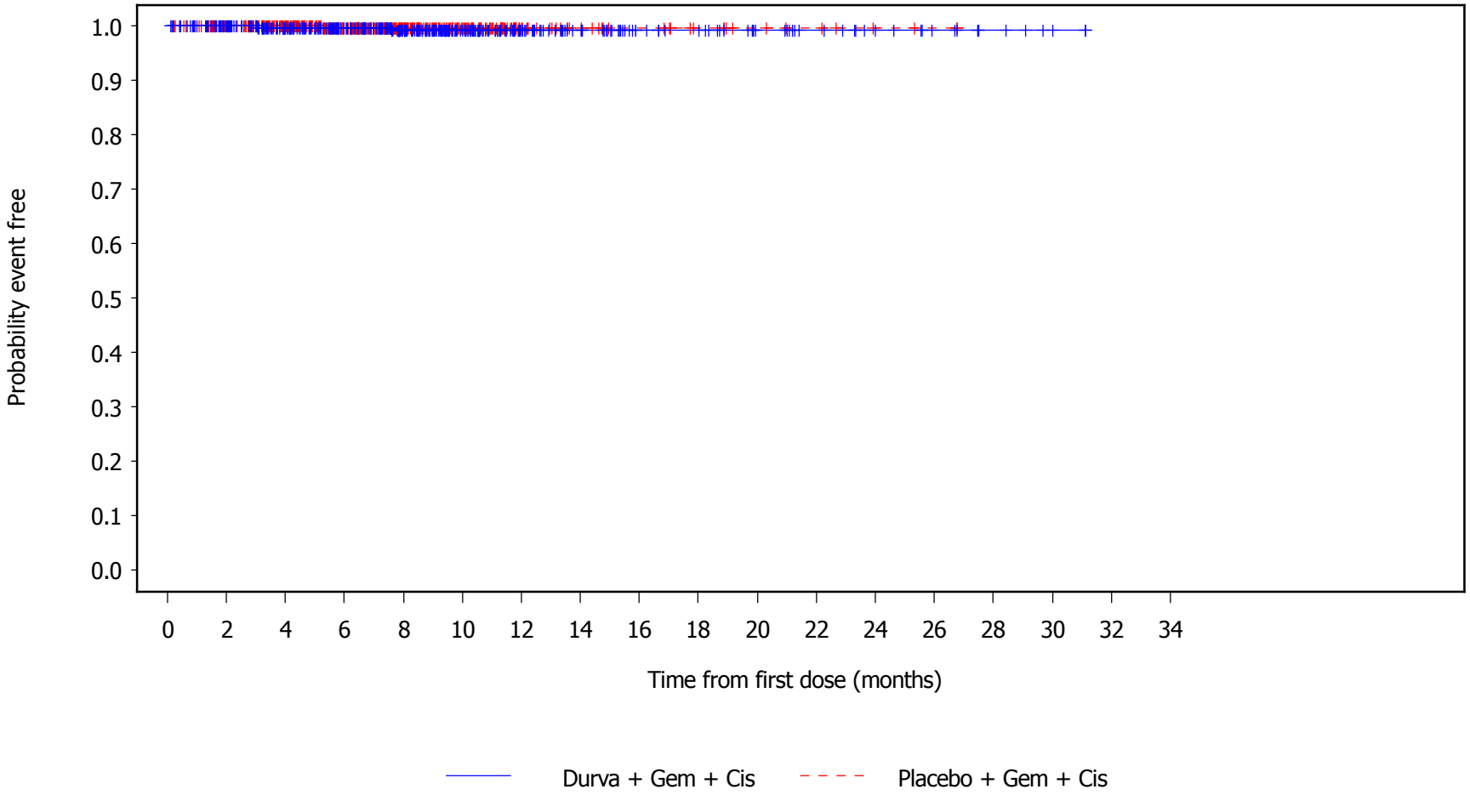
Figure 3.3.310 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Polymyositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

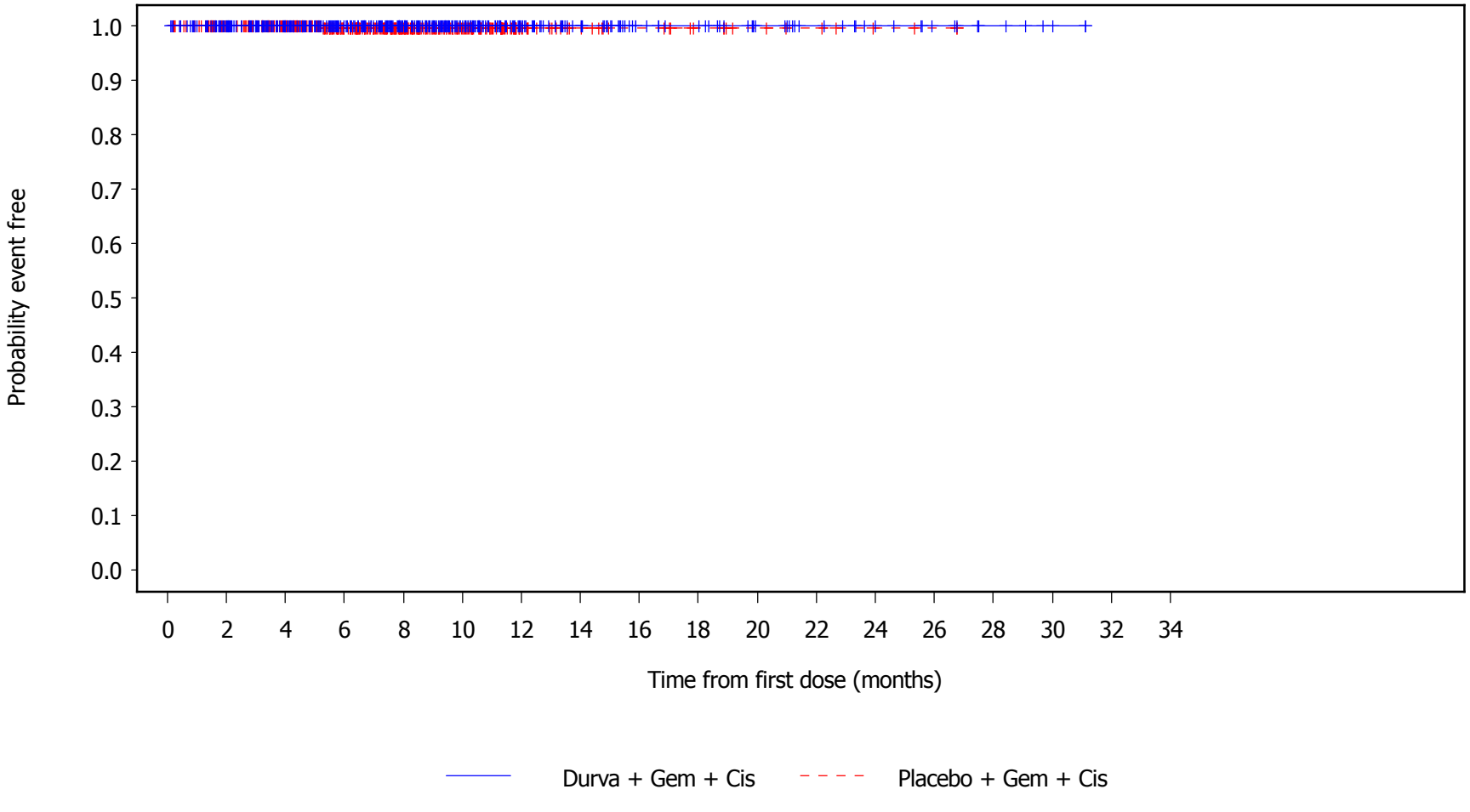
Figure 3.3.311 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Infusion/hypersensitivity reactions
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	196	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	231	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

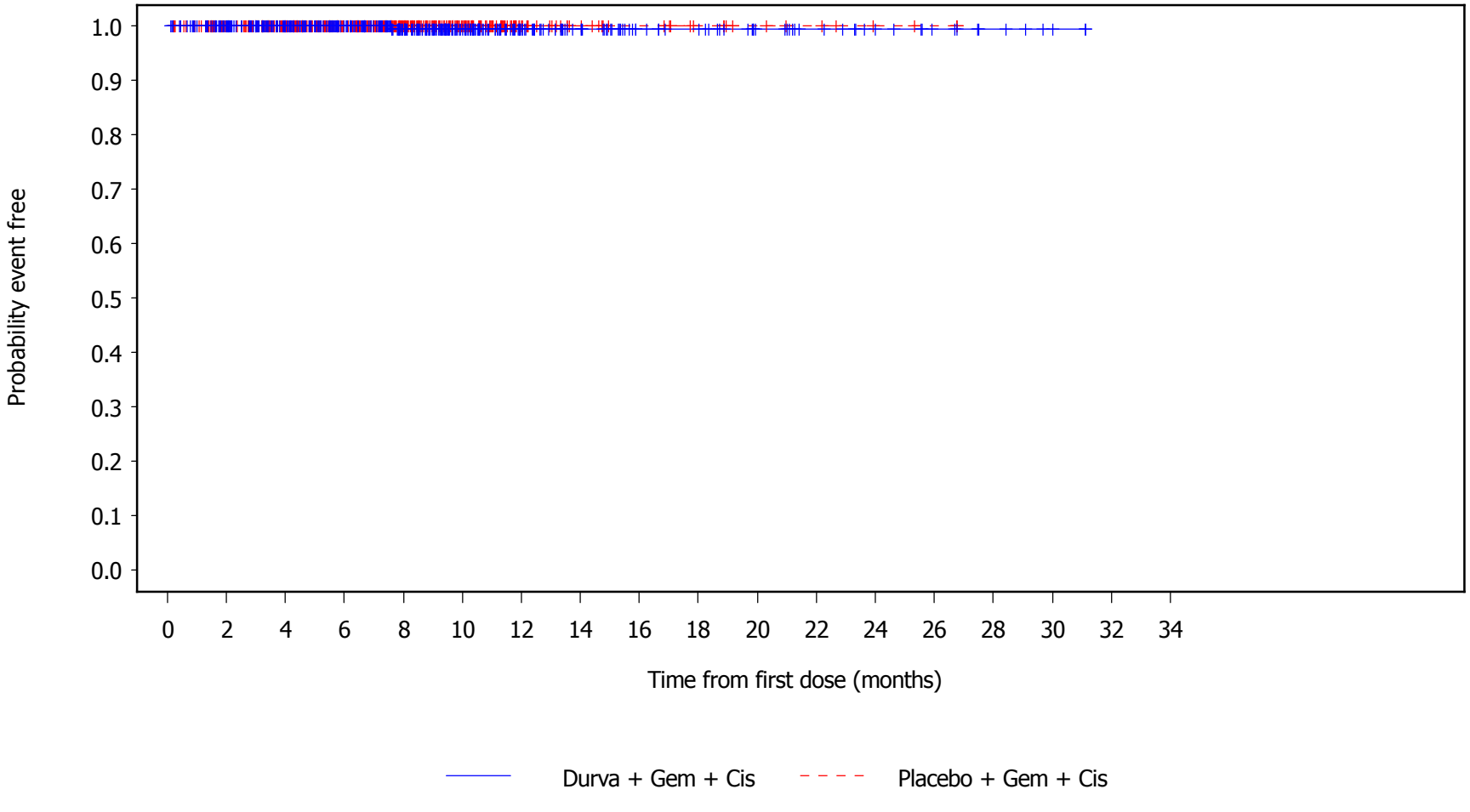
Figure 3.3.312 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Anaphylactic shock
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	231	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

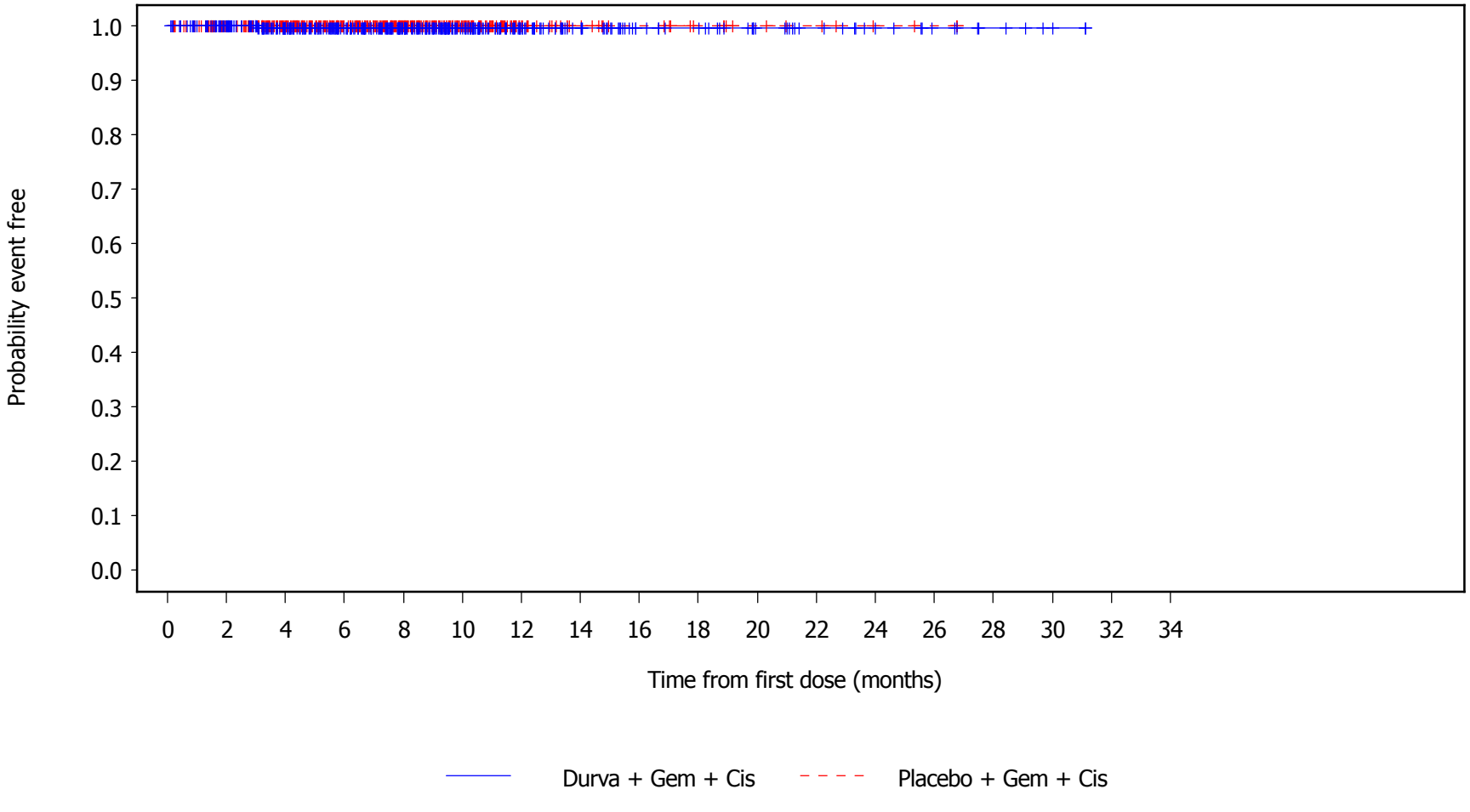
Figure 3.3.313 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Drug hypersensitivity
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	197	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

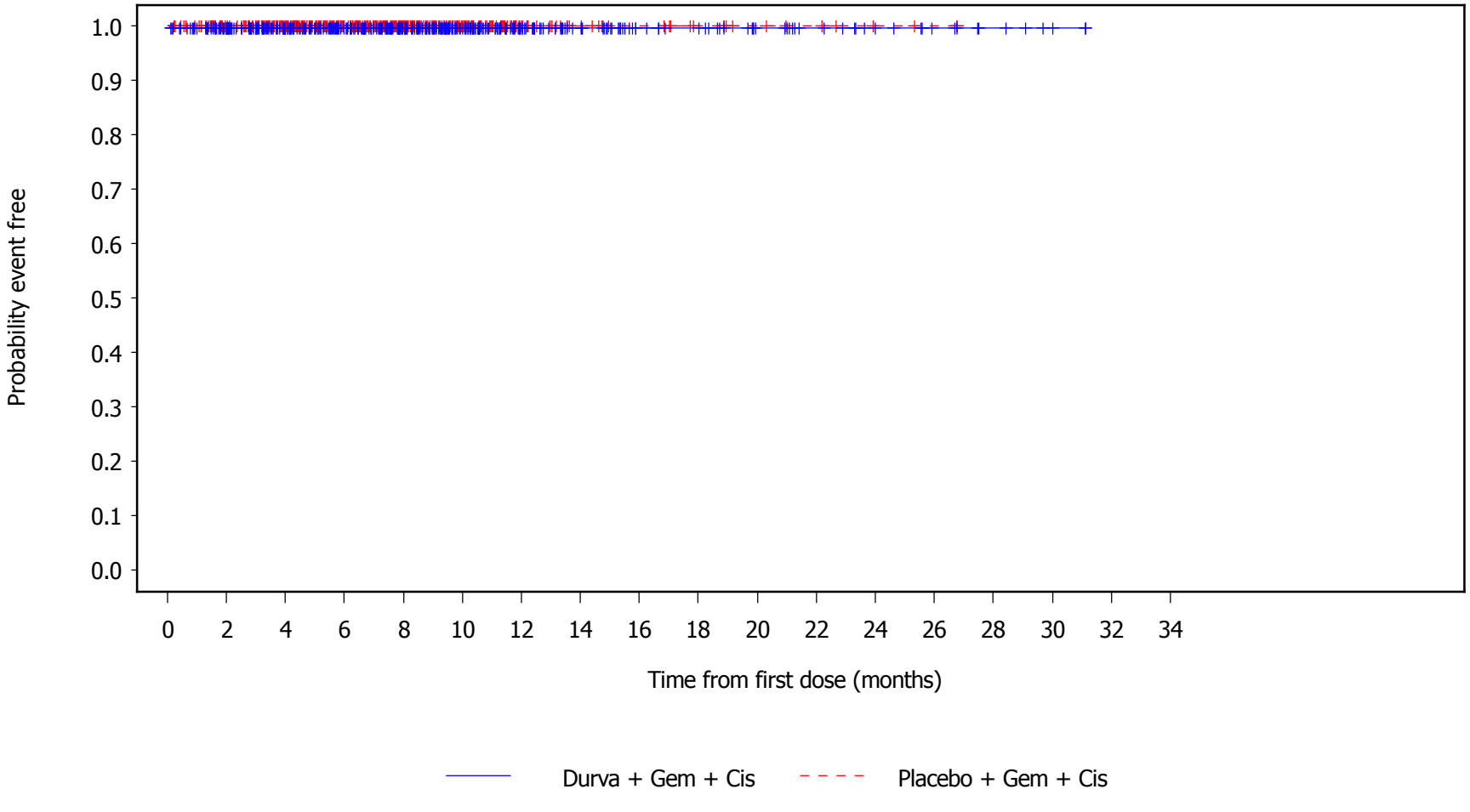
Figure 3.3.314 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Urticaria
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

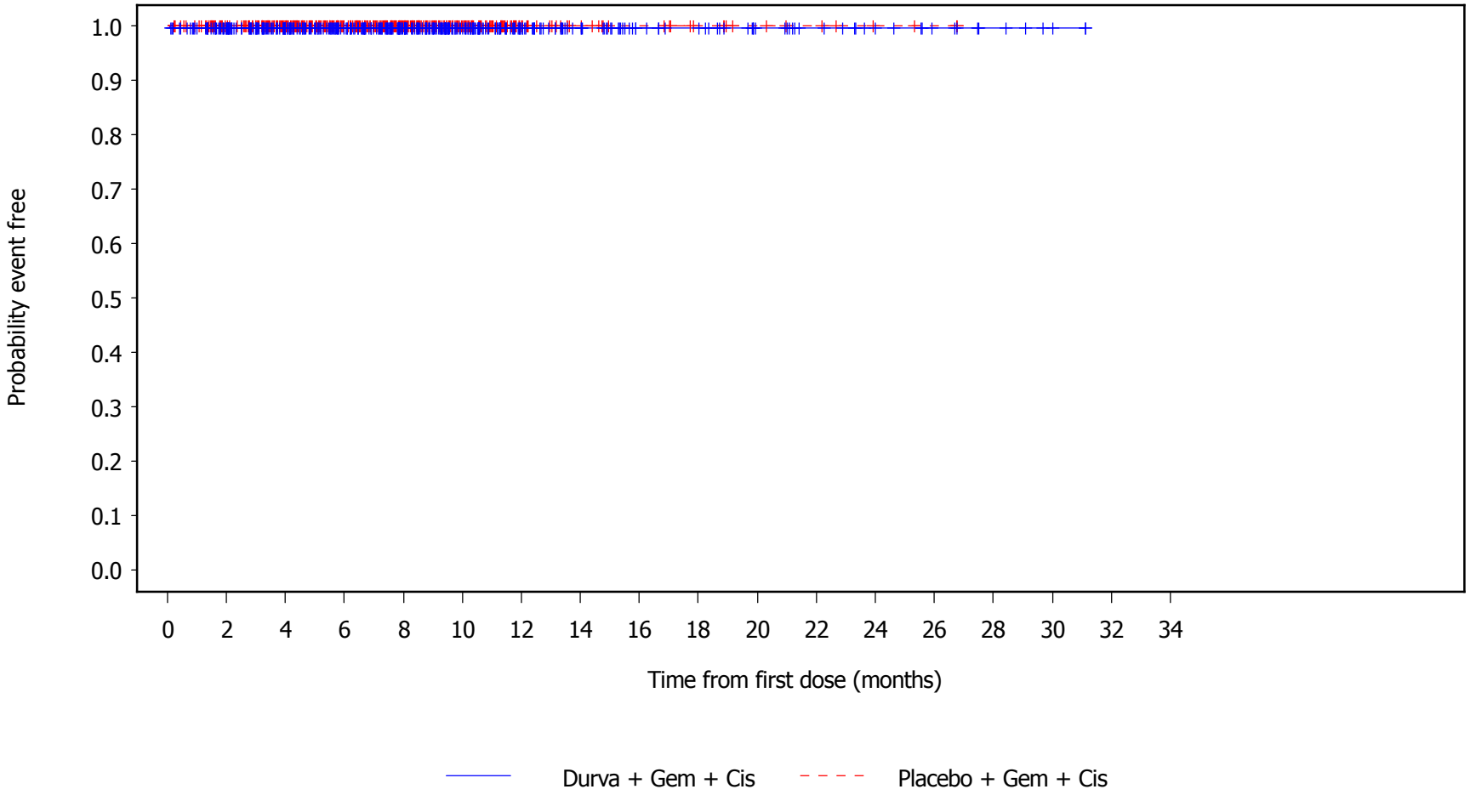
Figure 3.3.315 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Other rare/miscellaneous
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

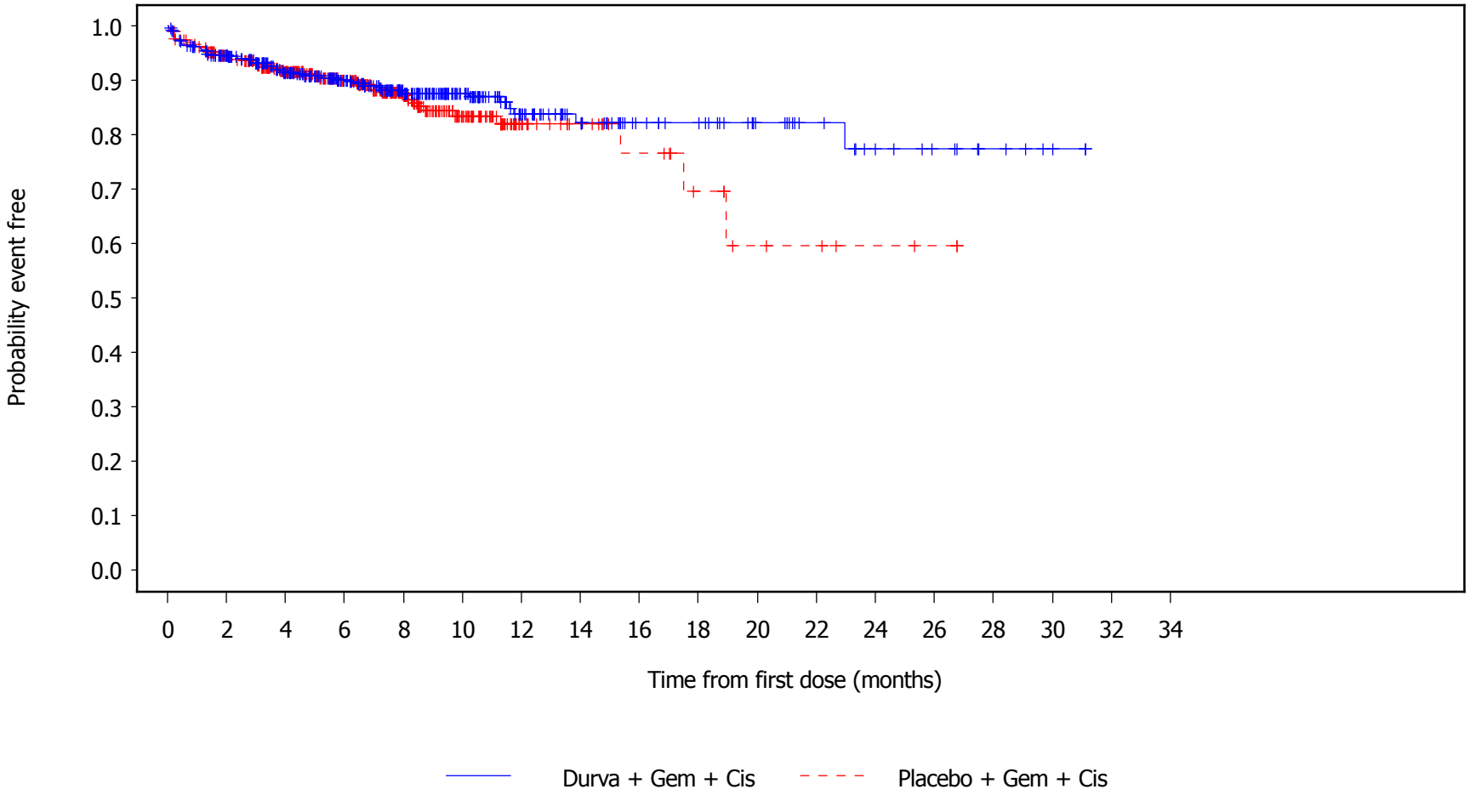
Figure 3.3.316 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Immune-mediated arthritis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

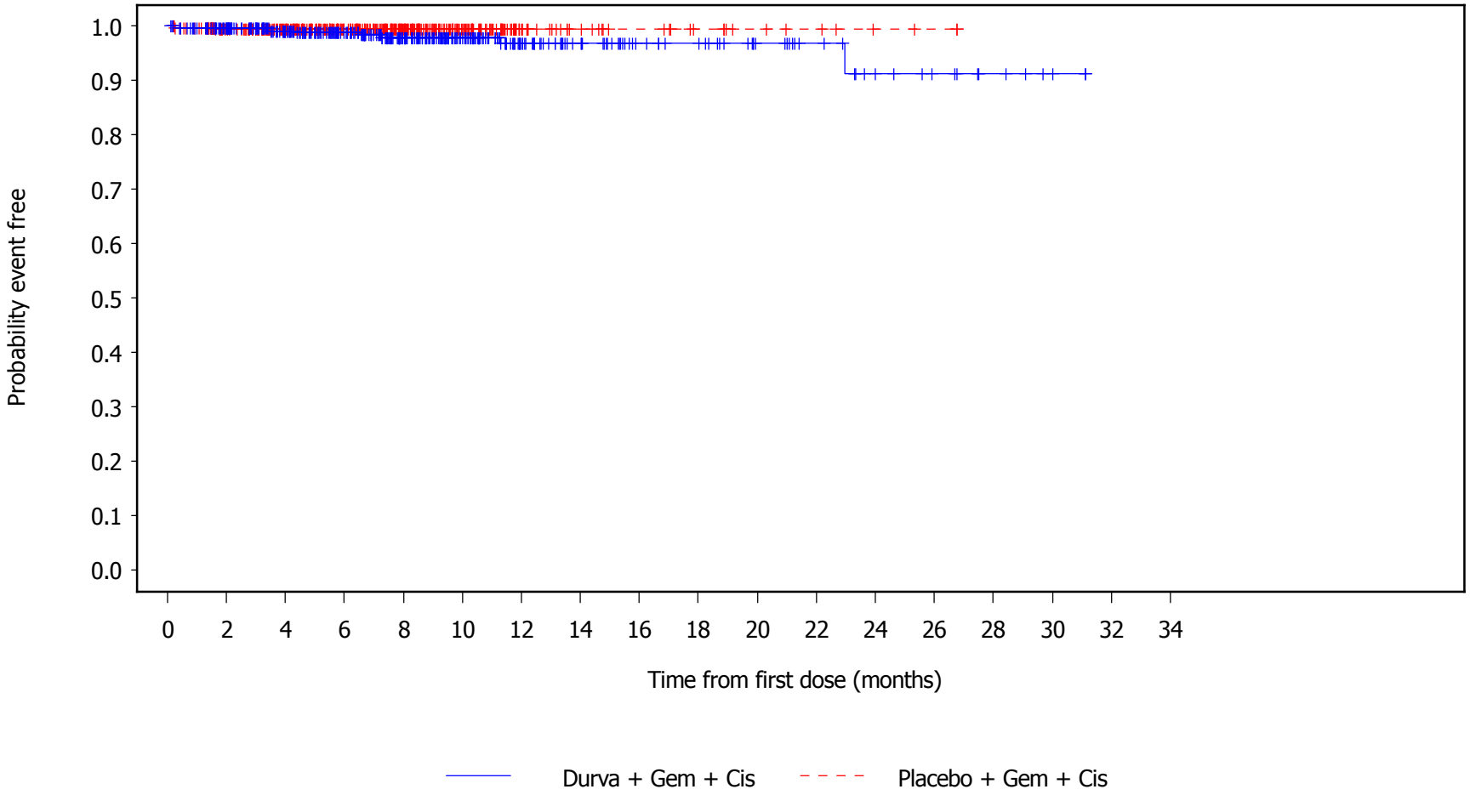
Figure 3.3.317 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Hepatic SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	357	296	249	184	122	74	52	38	34	24	18	13	9	5	2	0	0	Durva + Gem + Cis
403	353	293	217	146	82	31	21	14	9	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

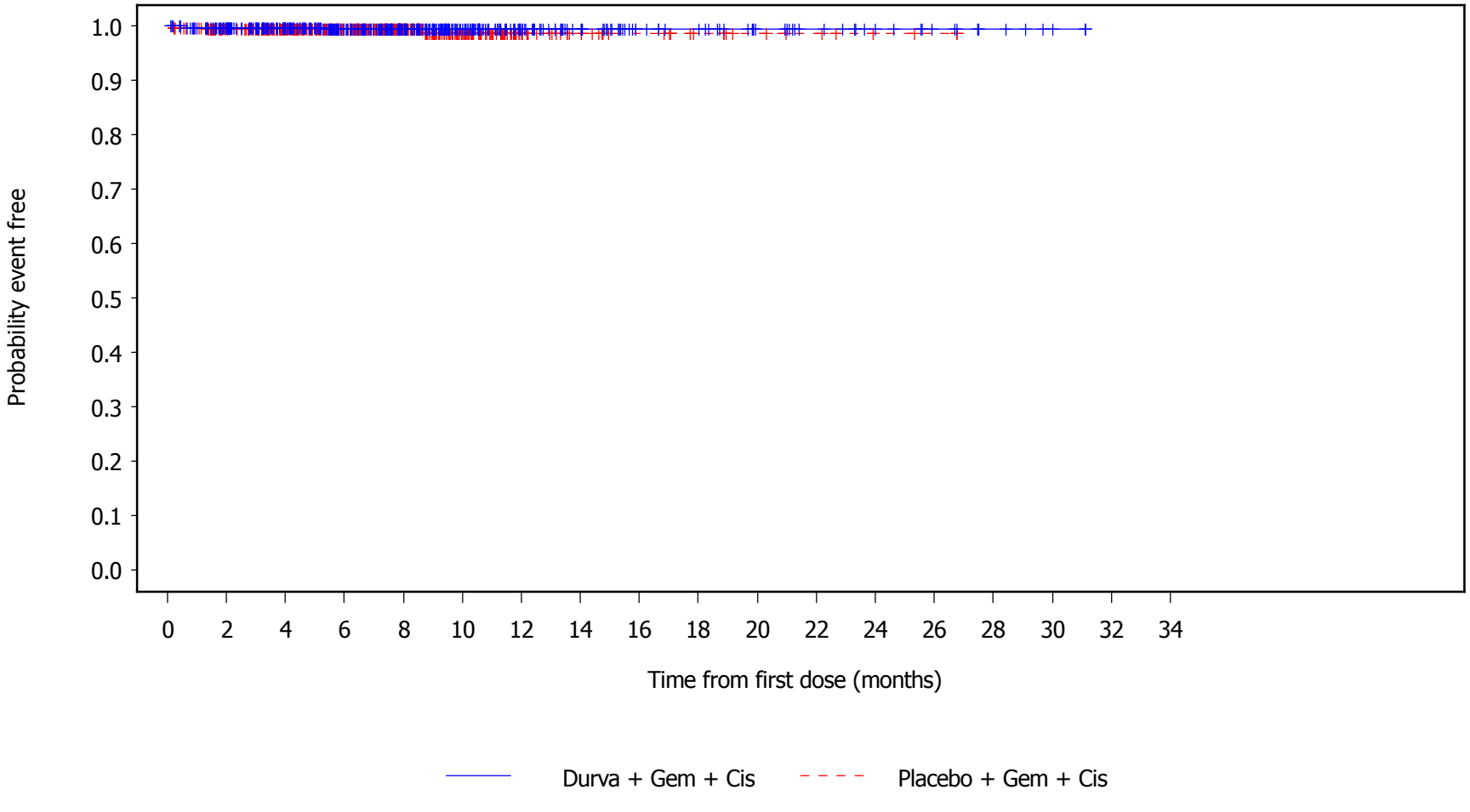
Figure 3.3.318 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Alanine aminotransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	312	261	194	130	78	56	40	36	25	19	13	9	5	2	0	0	Durva + Gem + Cis
403	369	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

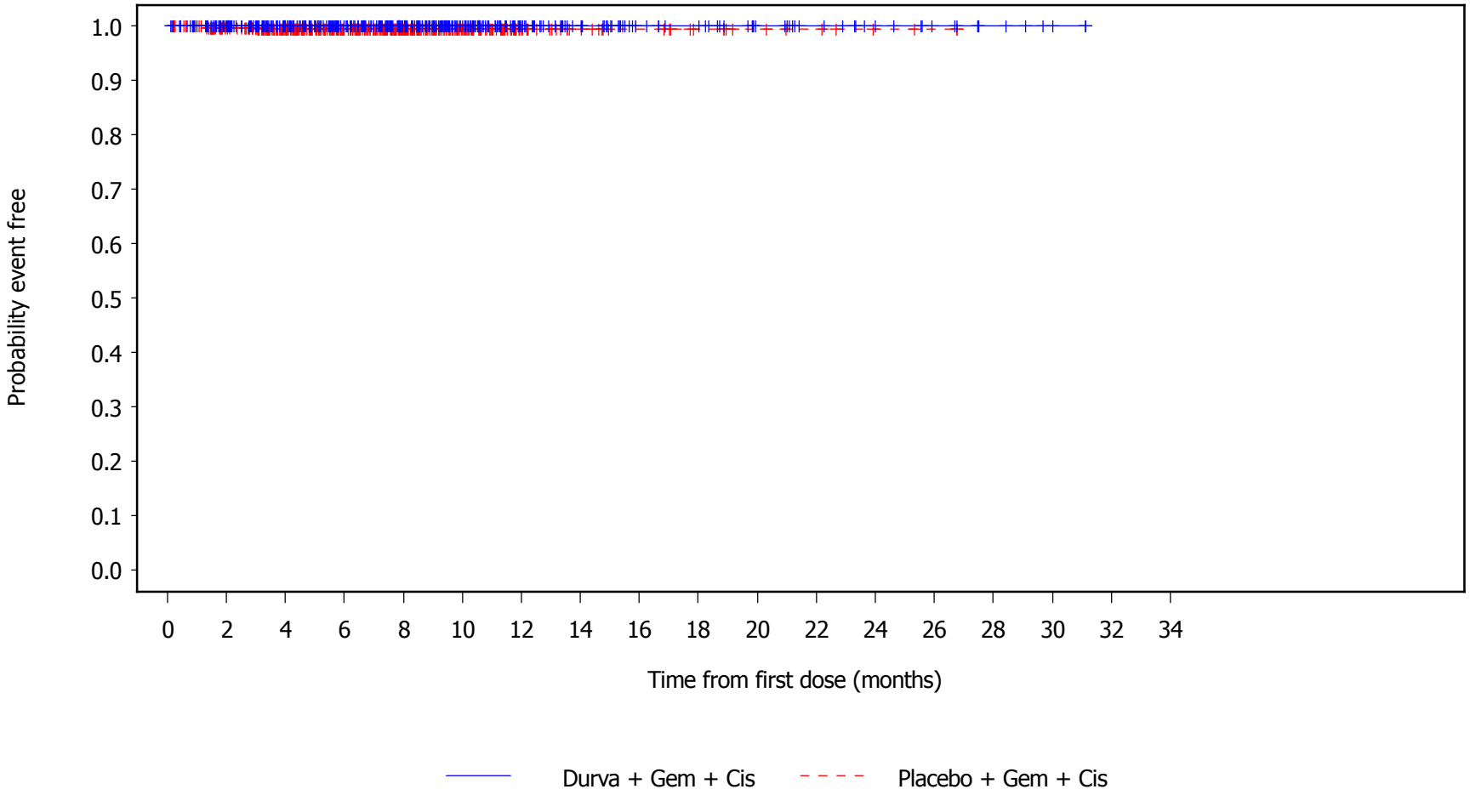
Figure 3.3.319 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Blood alkaline phosphatase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	263	197	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	312	231	158	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

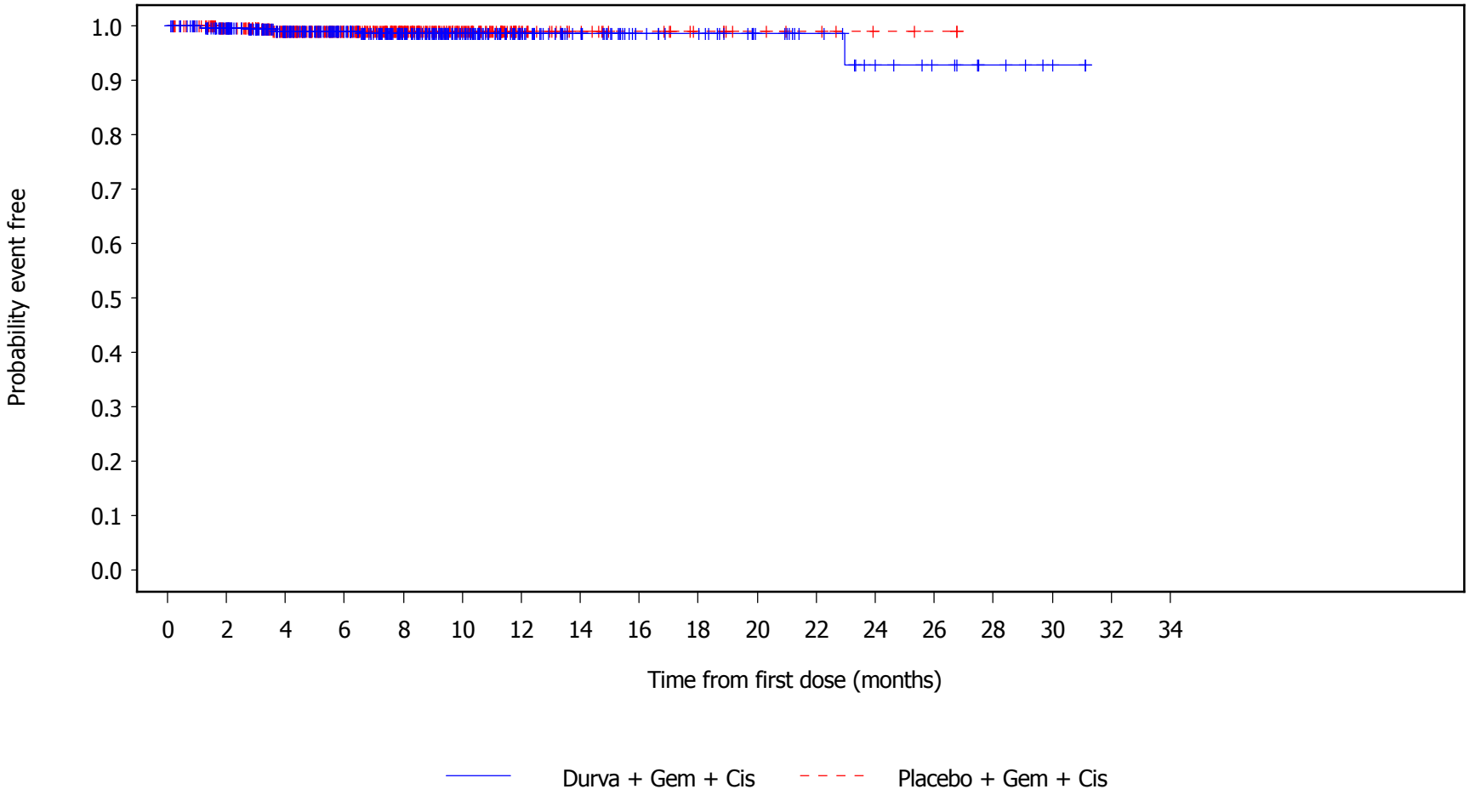
Figure 3.3.320 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

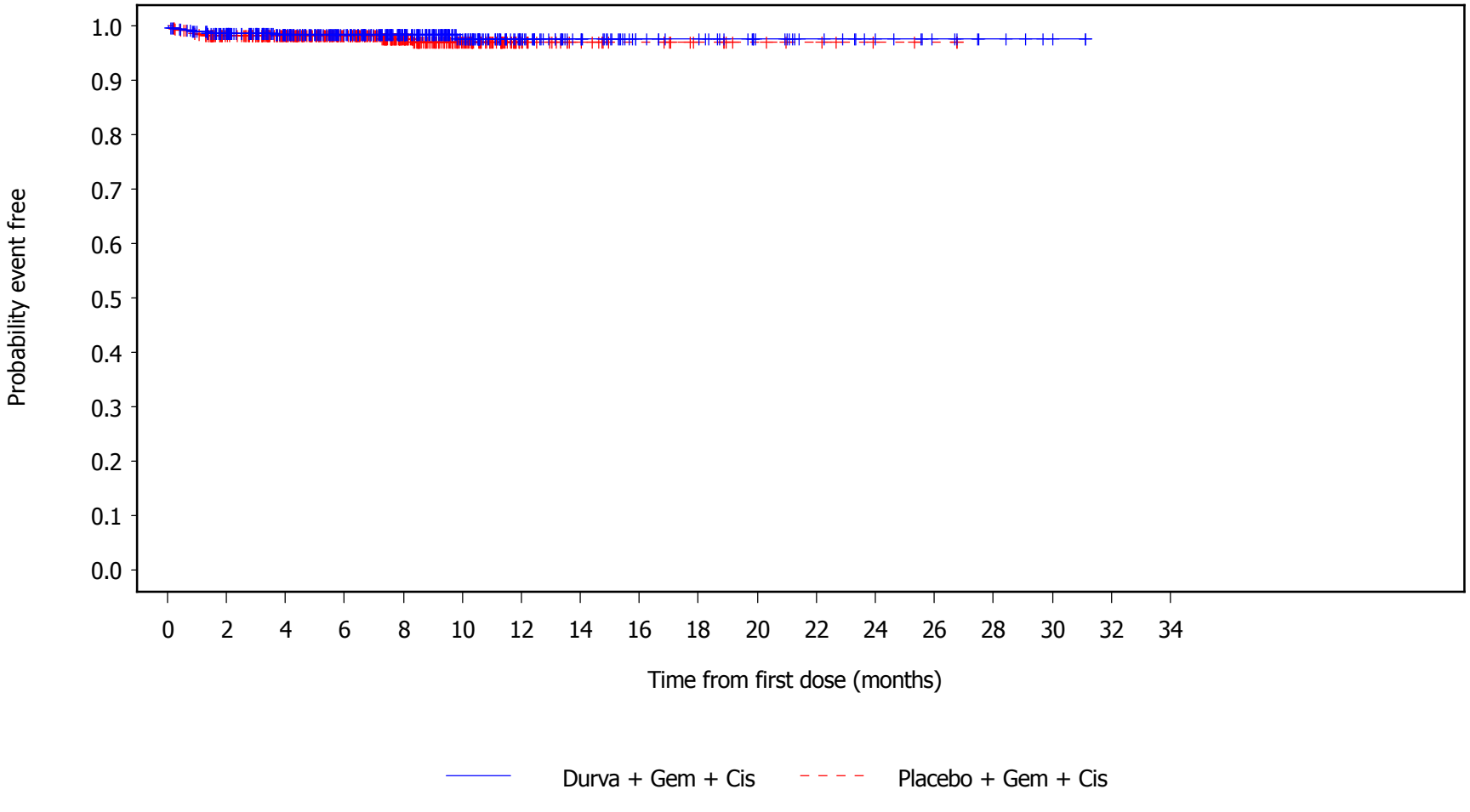
Figure 3.3.321 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Aspartate aminotransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	312	262	197	131	80	58	40	36	25	19	13	9	5	2	0	0	Durva + Gem + Cis
403	370	310	230	158	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

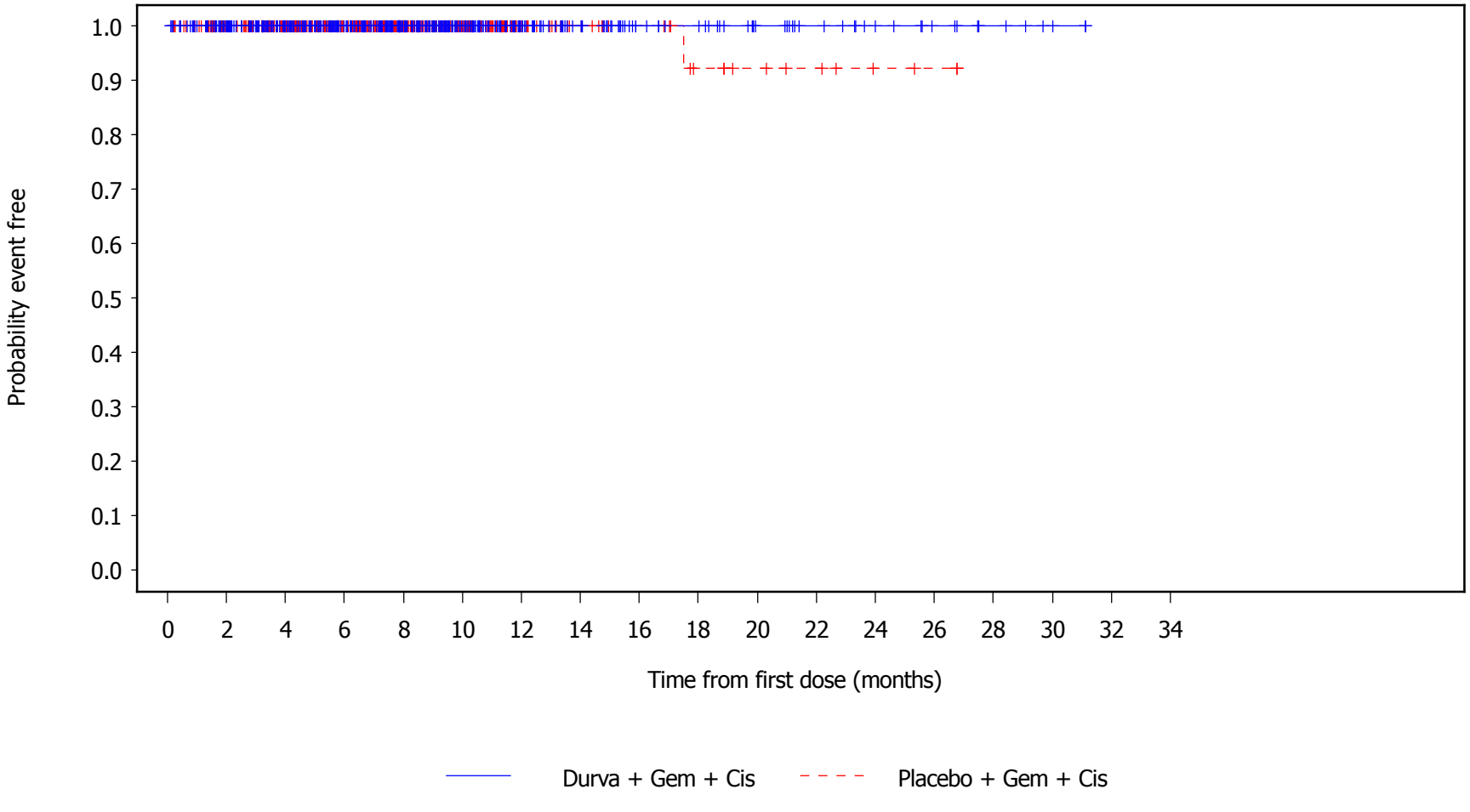
Figure 3.3.322 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Ascites
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	311	263	197	129	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	366	310	231	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

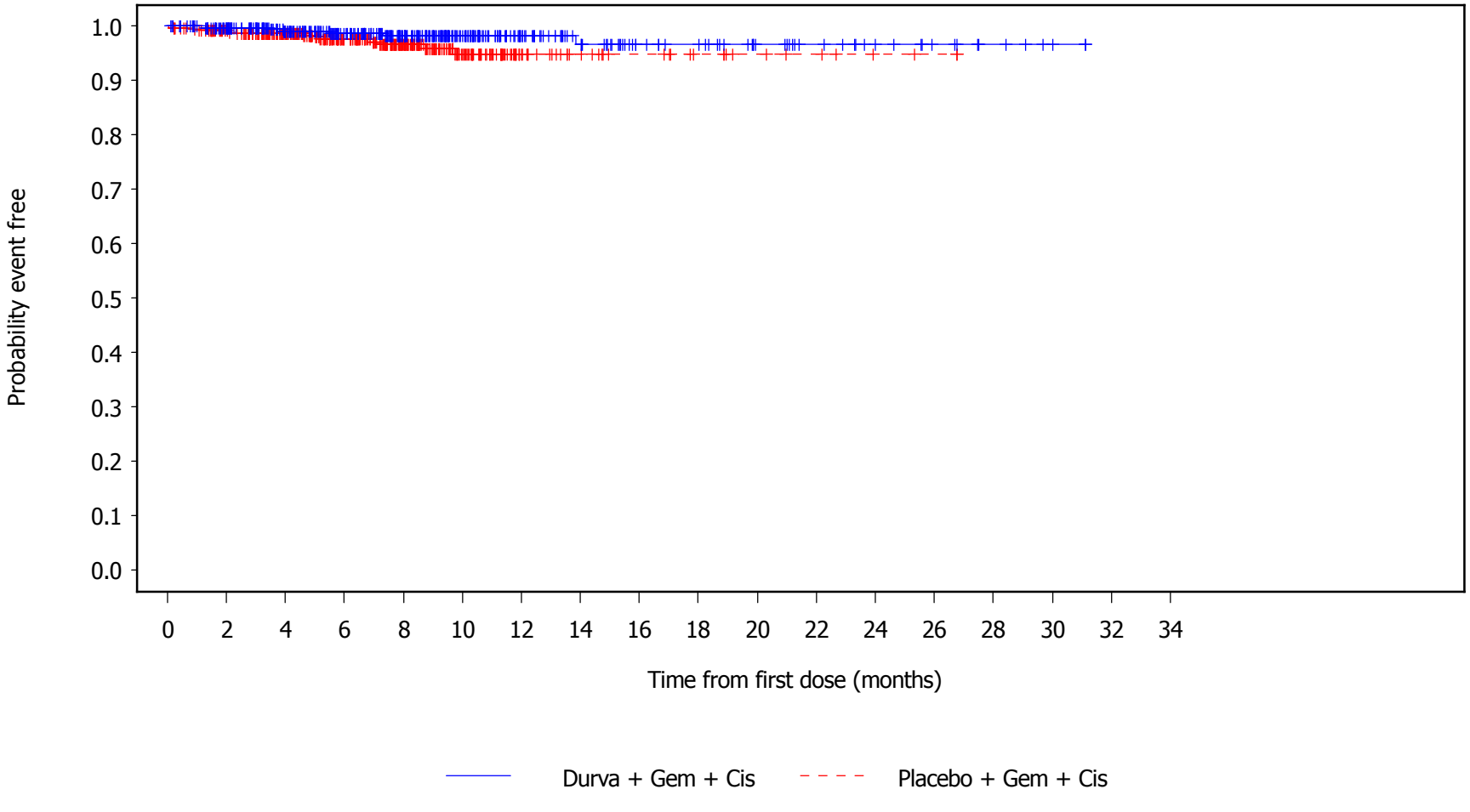
Figure 3.3.323 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

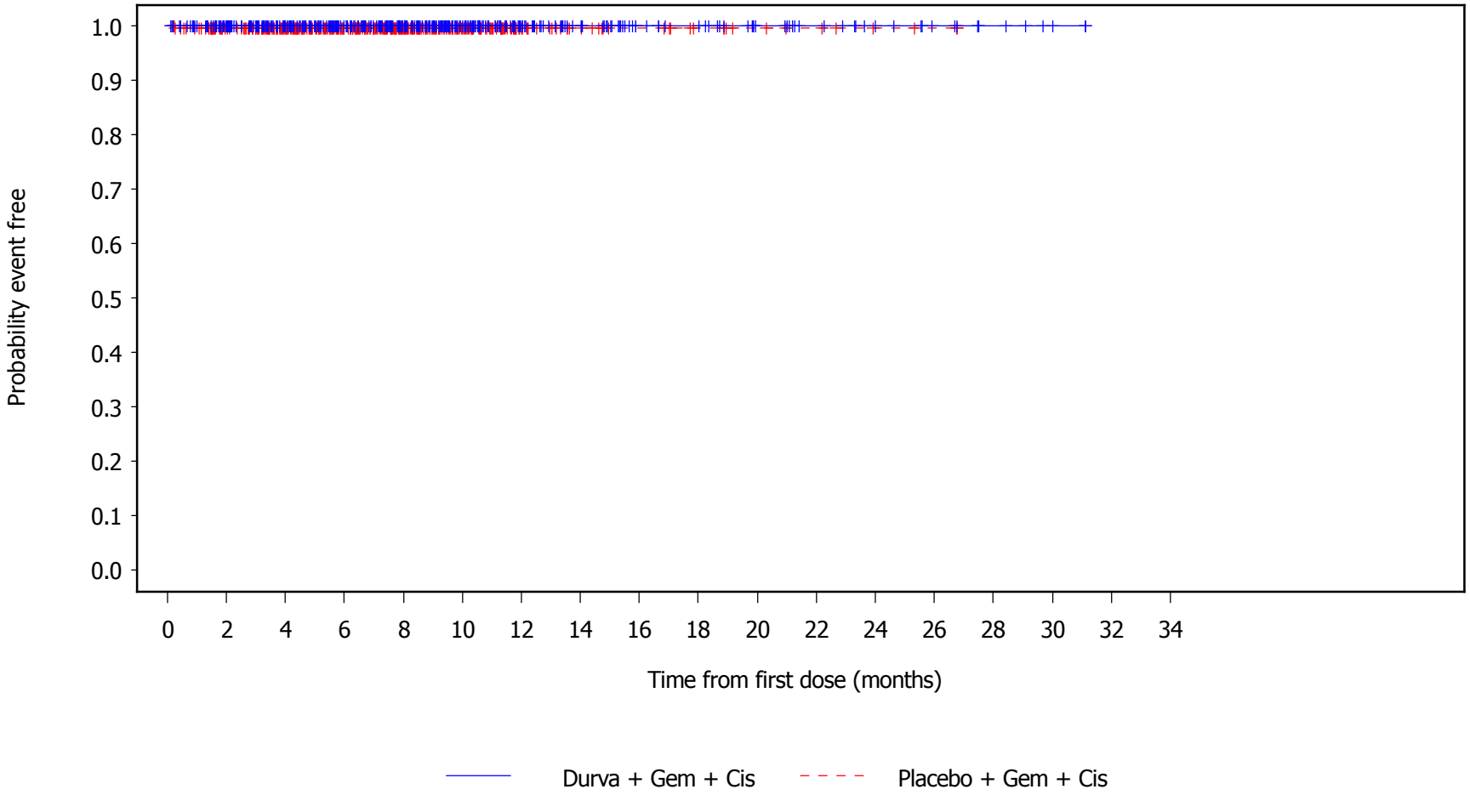
Figure 3.3.324 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	313	262	196	129	80	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	310	228	158	87	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

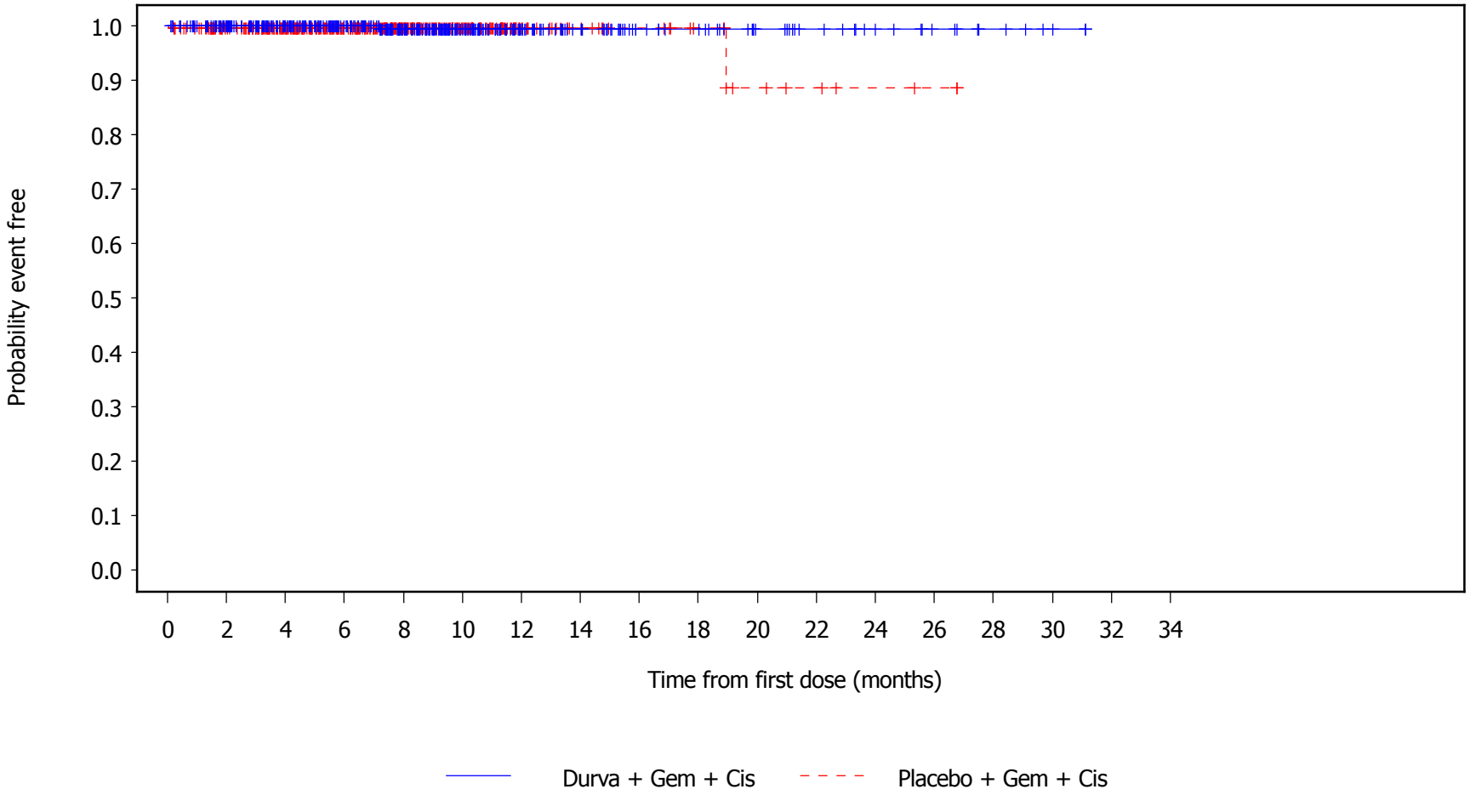
Figure 3.3.325 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Bilirubin conjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

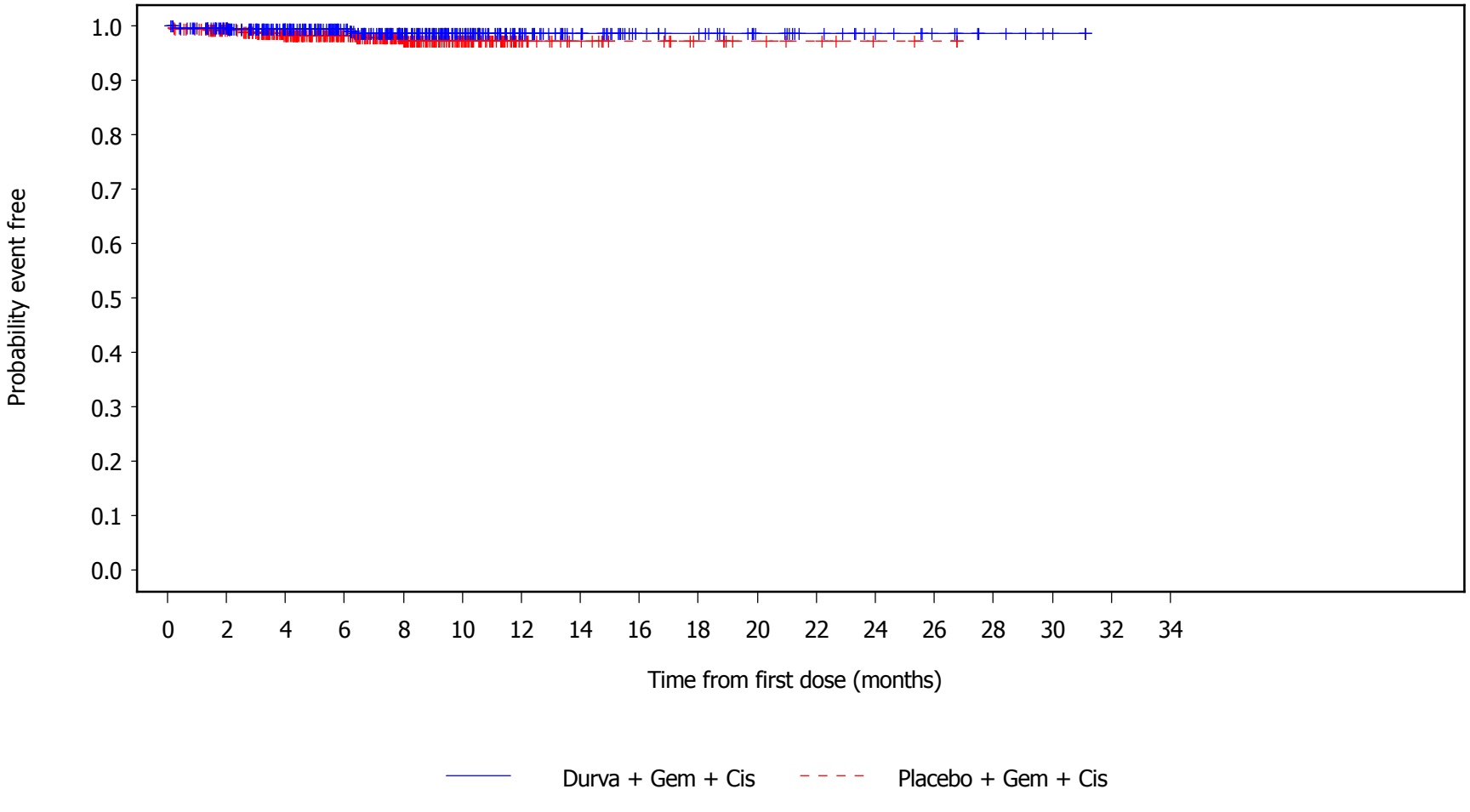
Figure 3.3.326 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	197	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	88	34	22	16	11	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

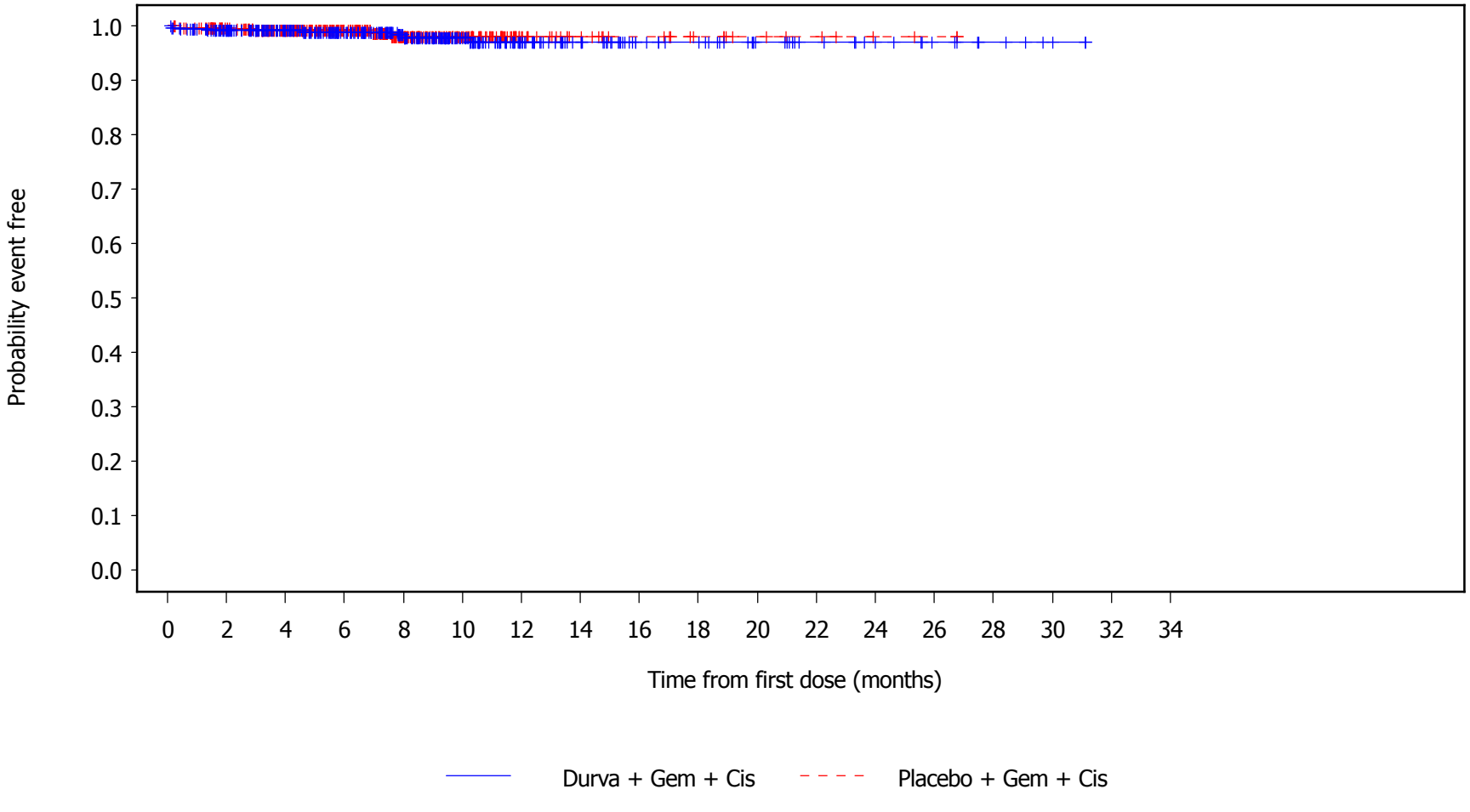
Figure 3.3.327 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Gamma-glutamyltransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	313	262	195	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	307	228	155	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

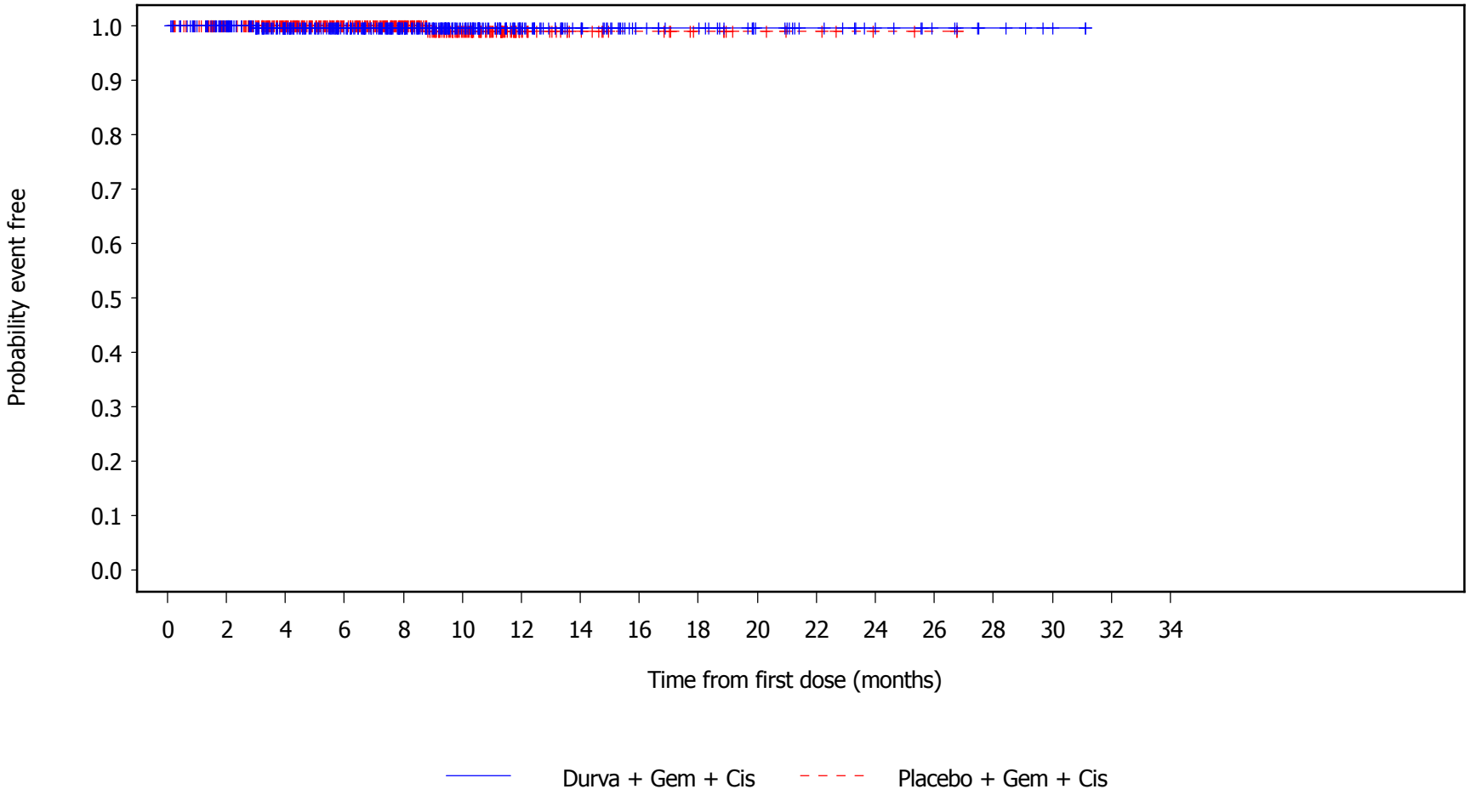
Figure 3.3.328 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	315	263	198	130	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	370	313	232	157	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

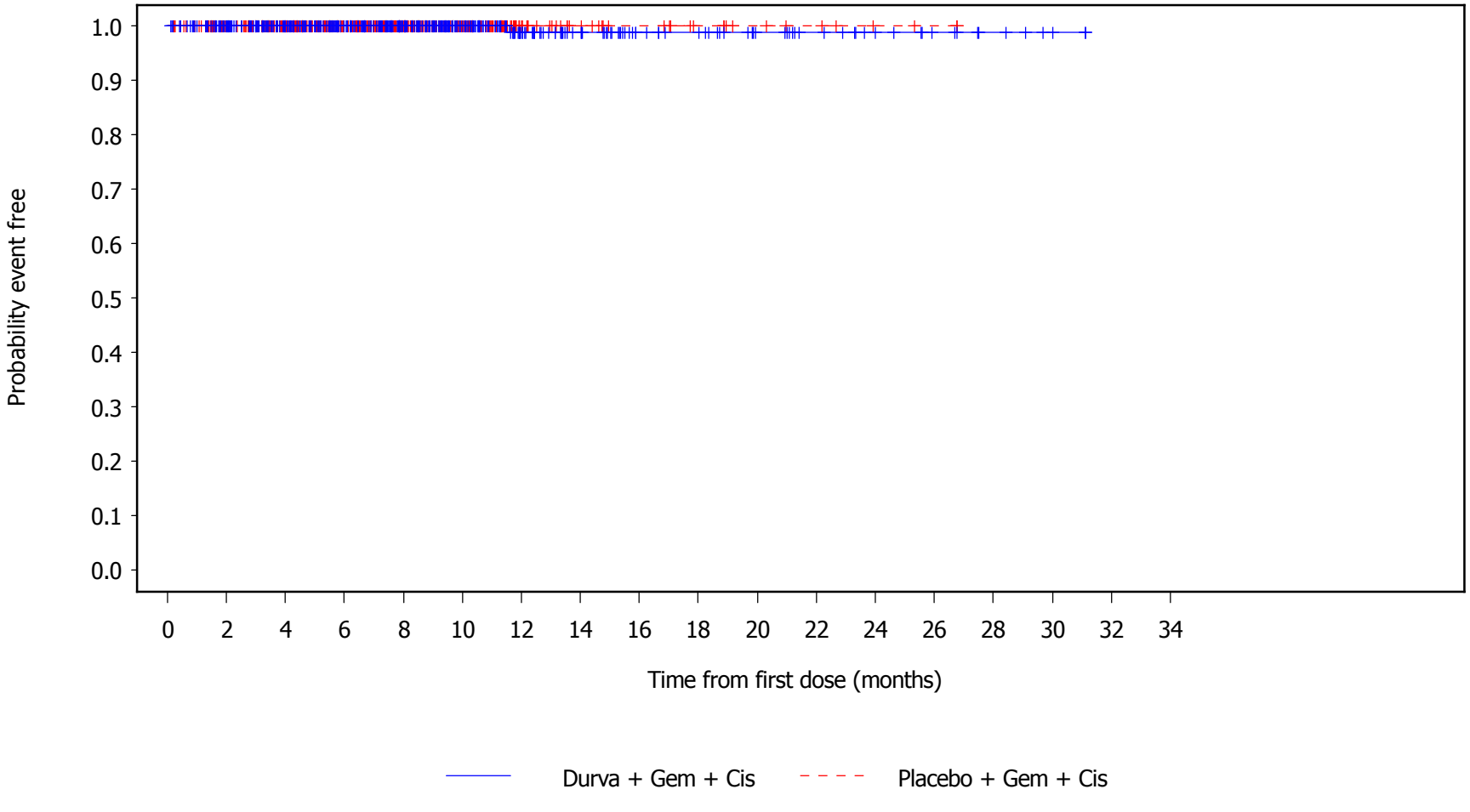
Figure 3.3.329 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Hepatic encephalopathy
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

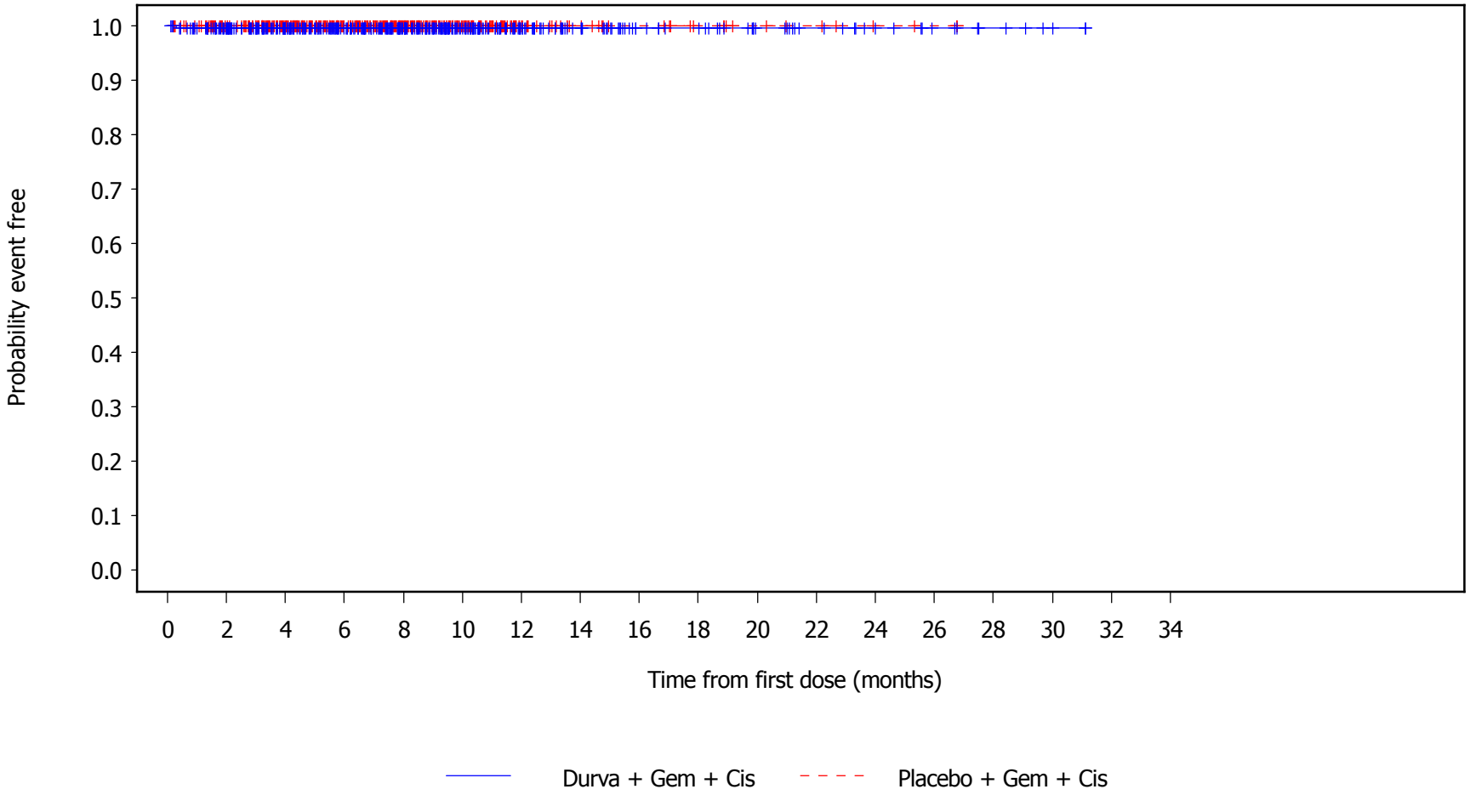
Figure 3.3.330 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Hepatic cytolysis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	79	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

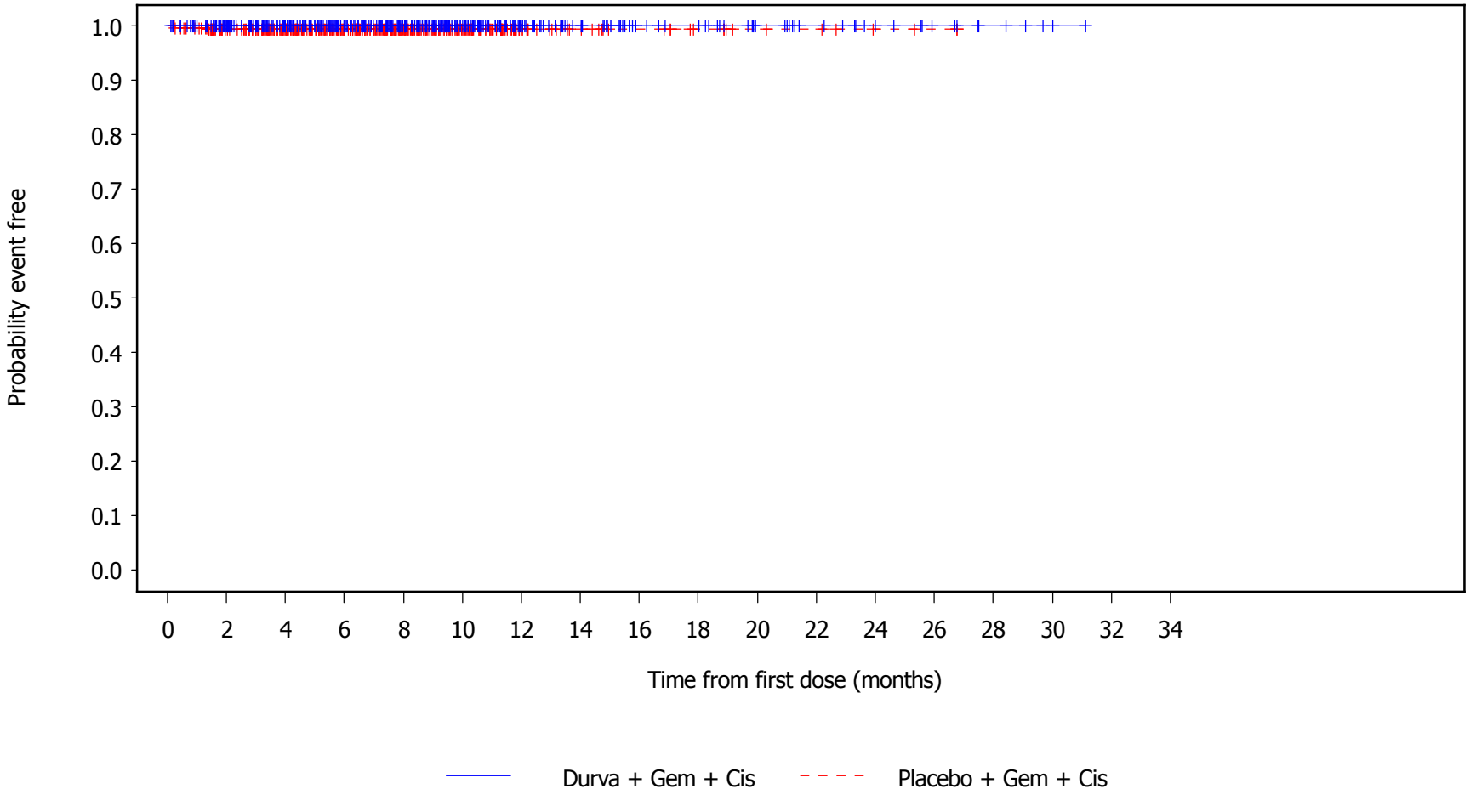
Figure 3.3.331 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

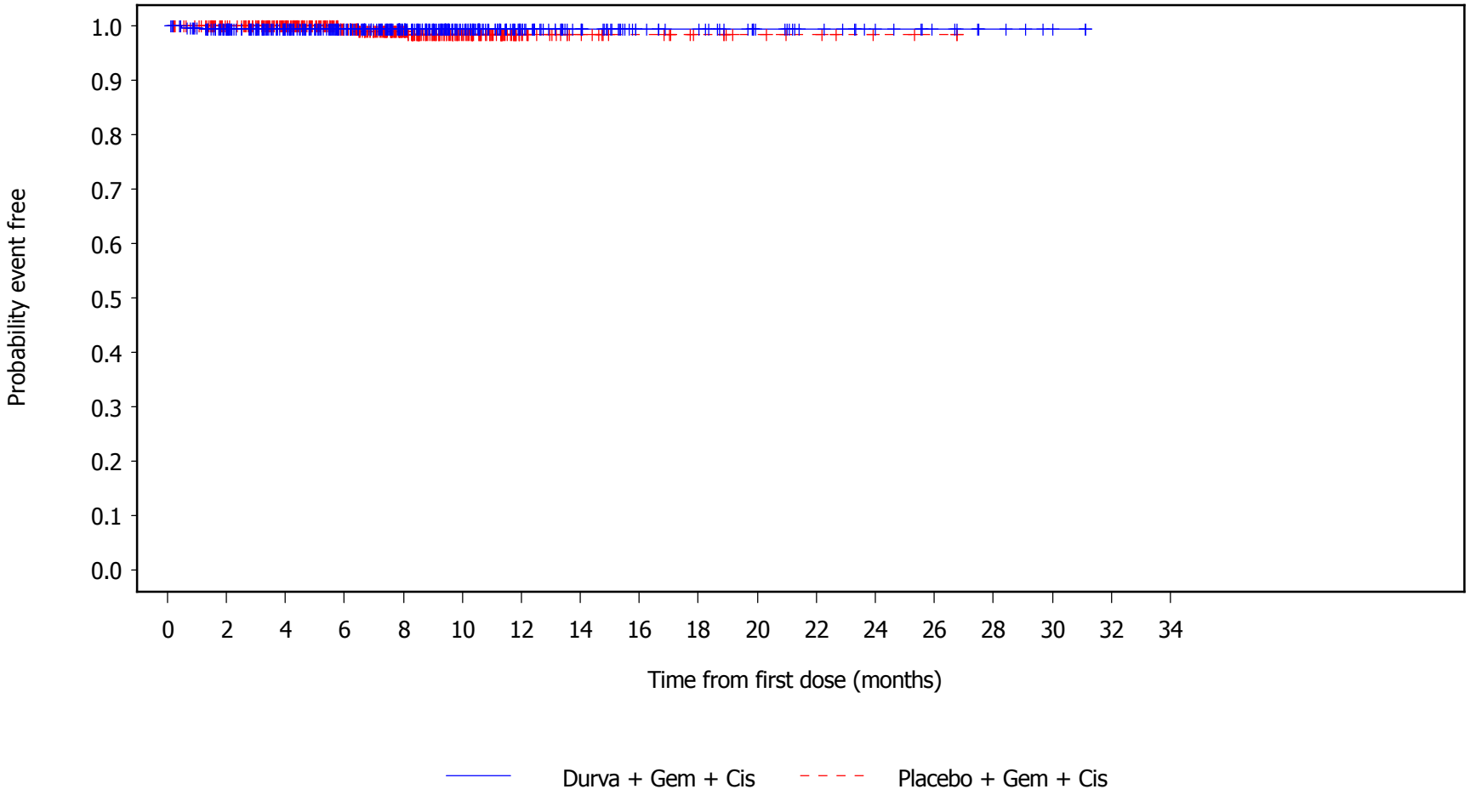
Figure 3.3.332 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Hypoalbuminaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	312	231	158	88	33	21	15	10	6	5	2	1	0	0	0	0	Placebo + Gem + Cis

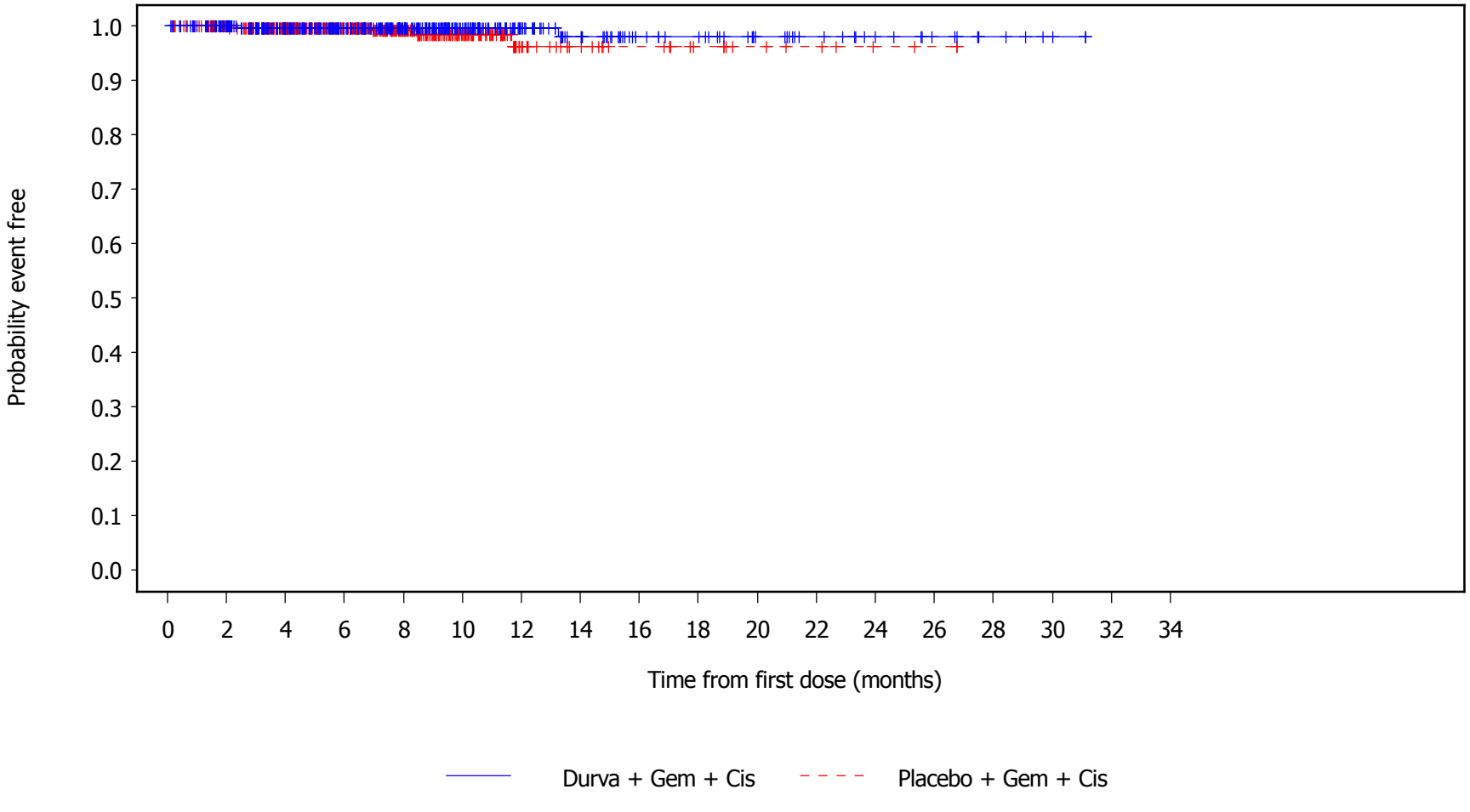
Figure 3.3.333 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	231	157	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

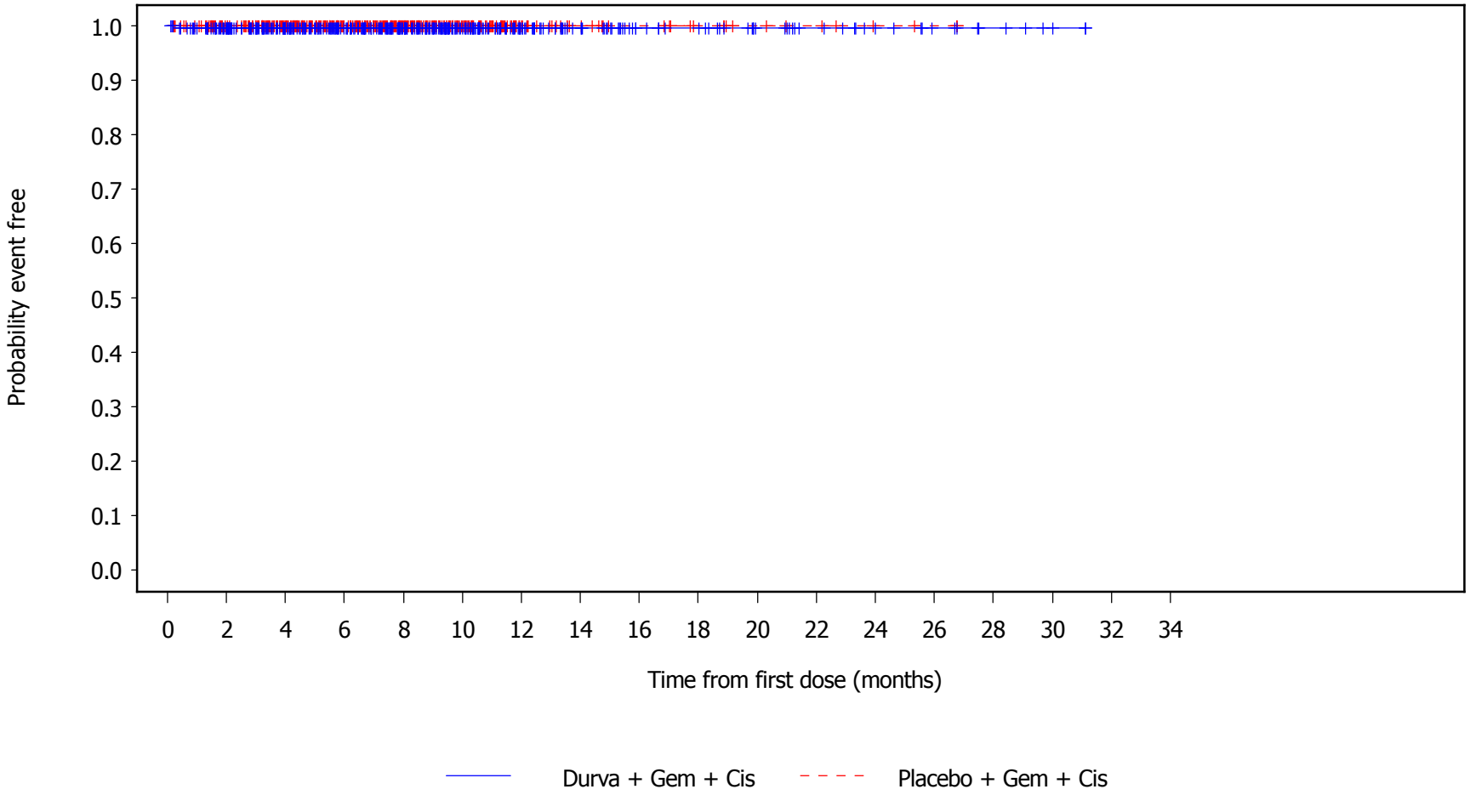
Figure 3.3.334 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	232	158	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

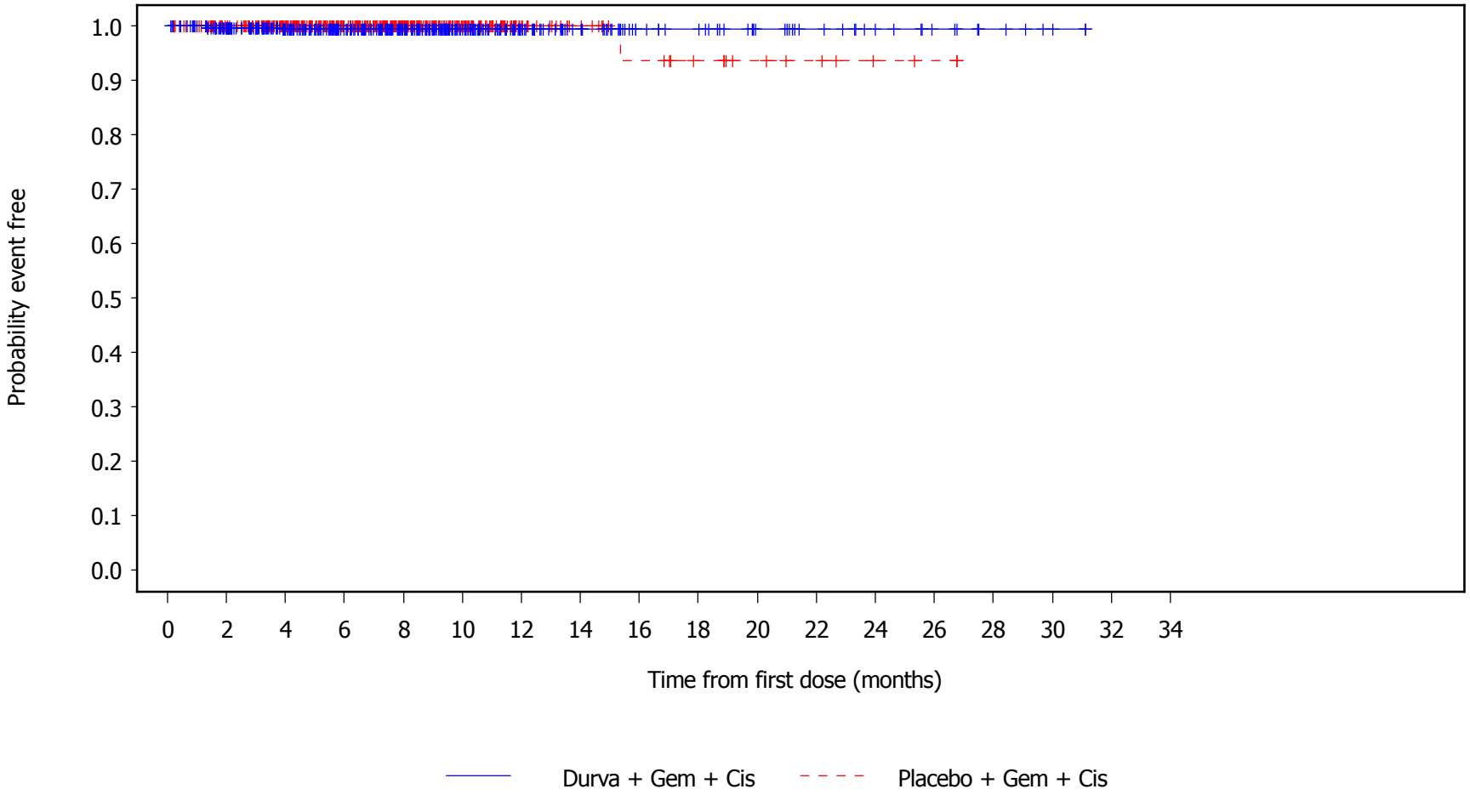
Figure 3.3.335 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Immune-mediated hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

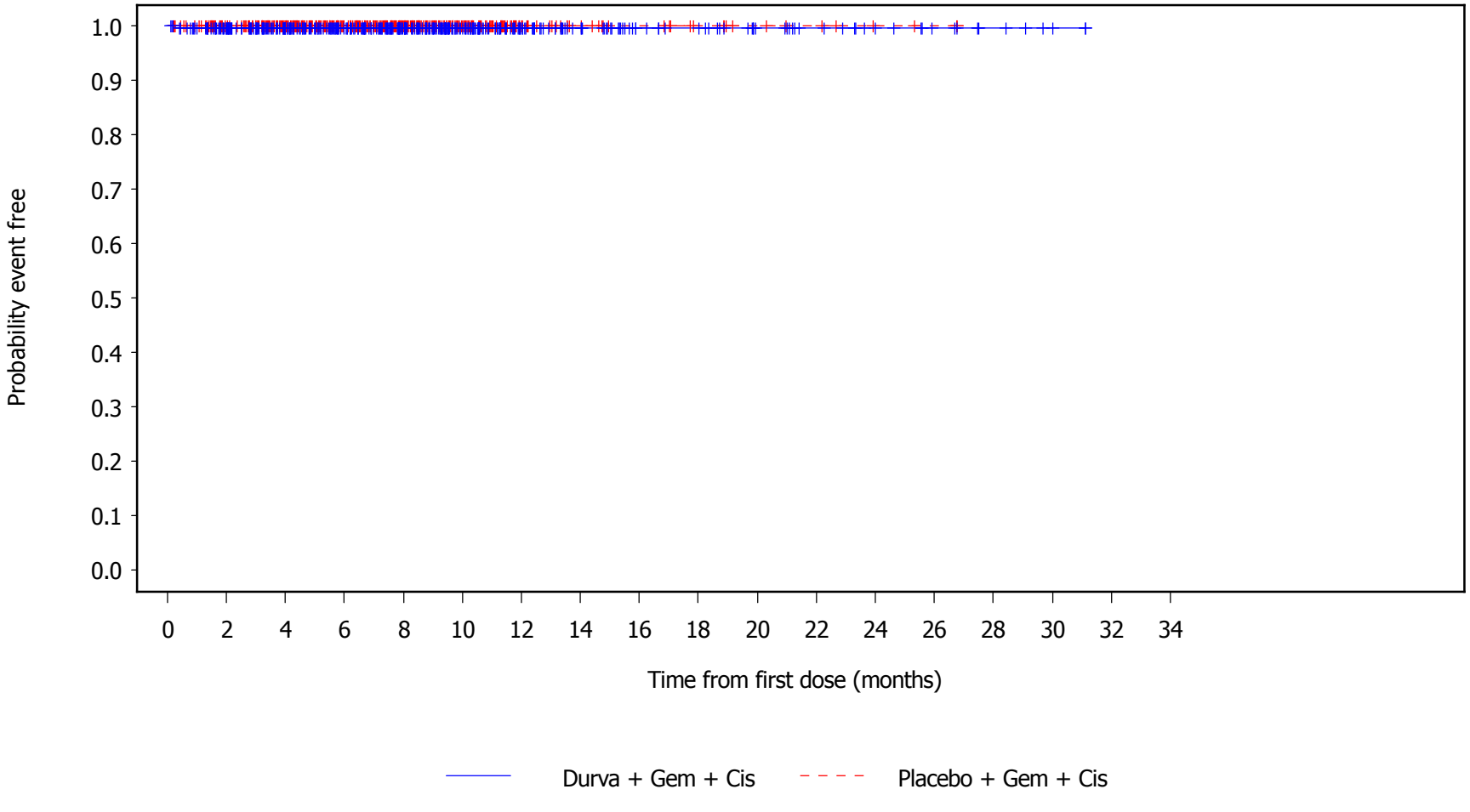
Figure 3.3.336 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Liver abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	313	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

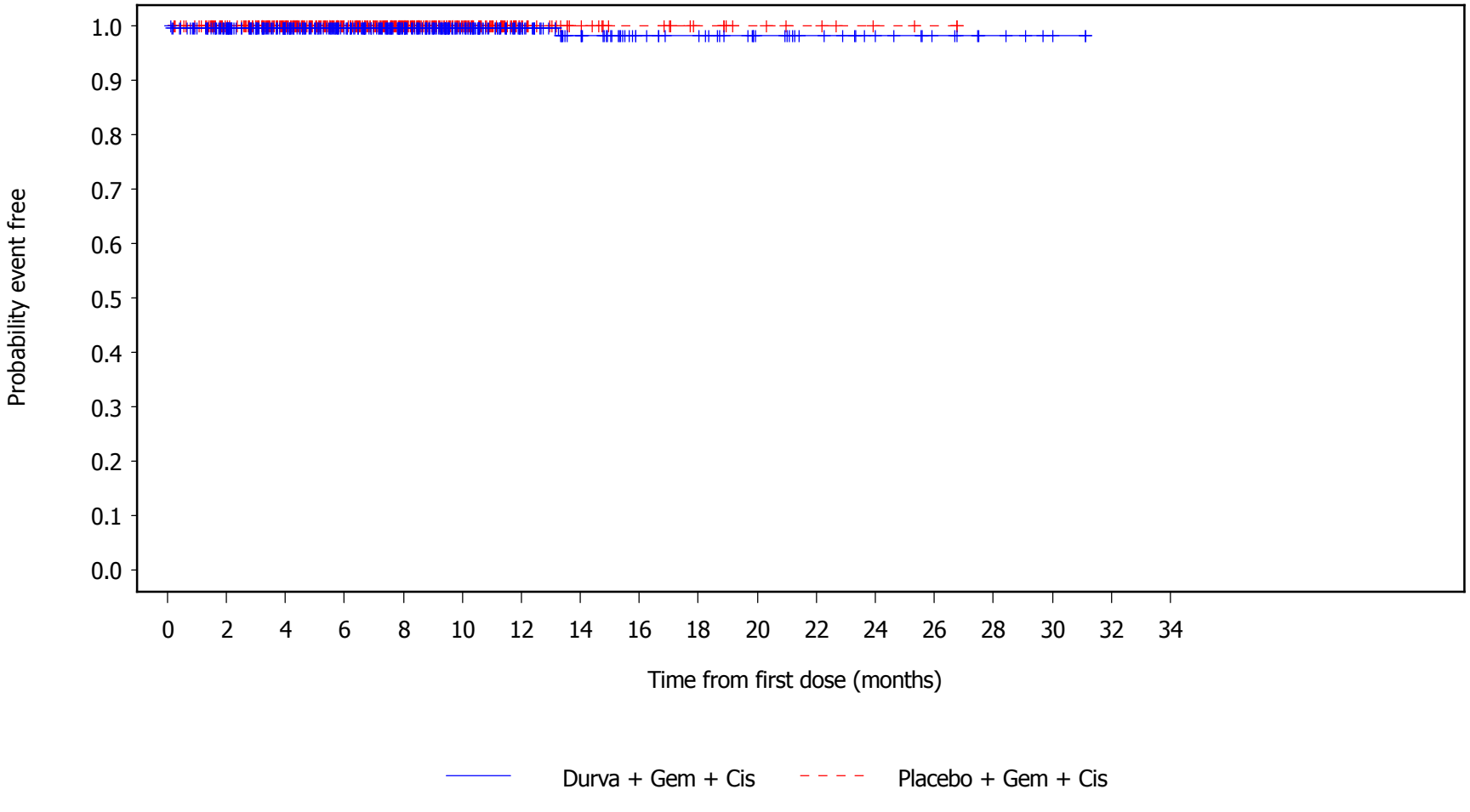
Figure 3.3.337 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Hepatic enzyme increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

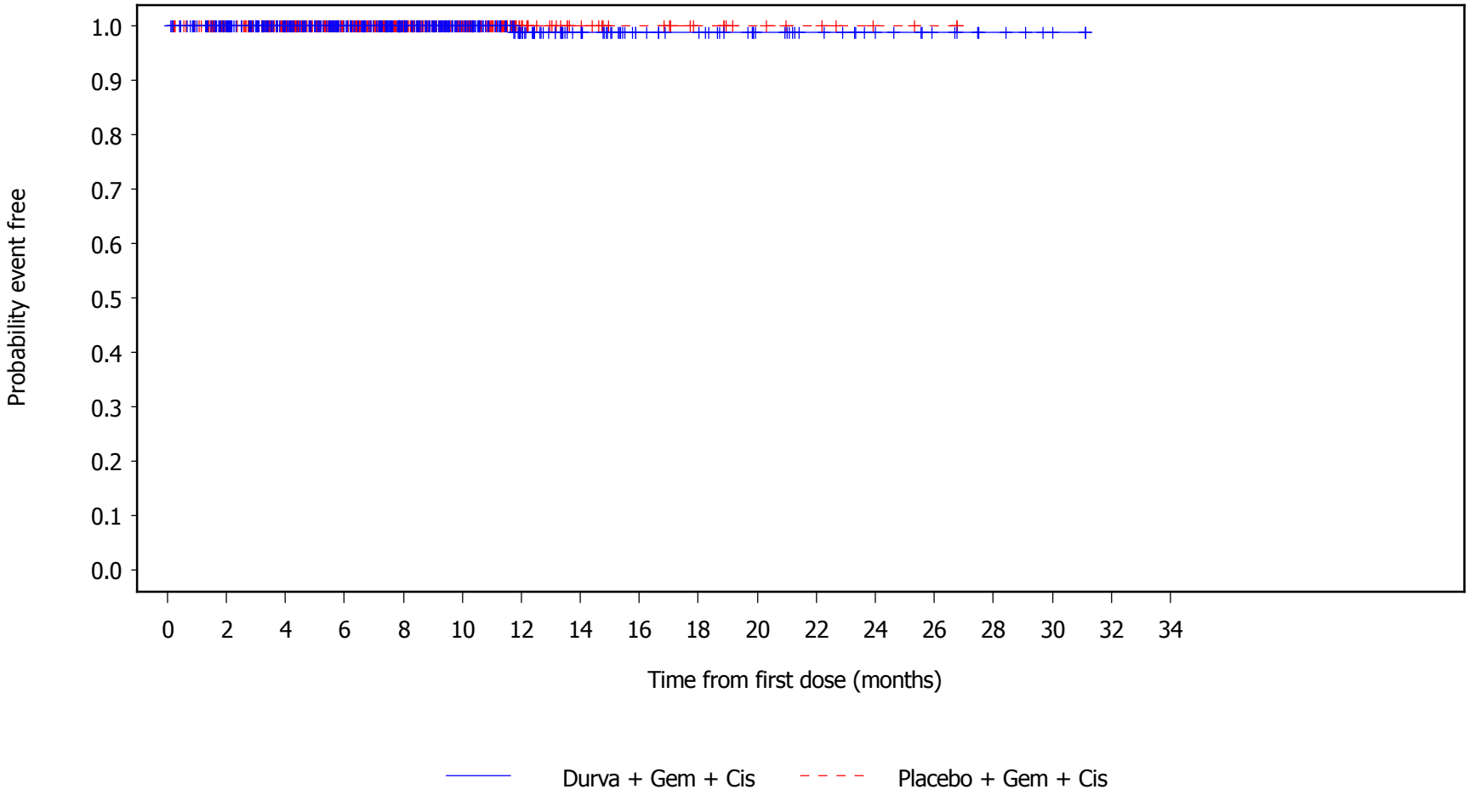
Figure 3.3.338 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Hepatic function abnormal
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

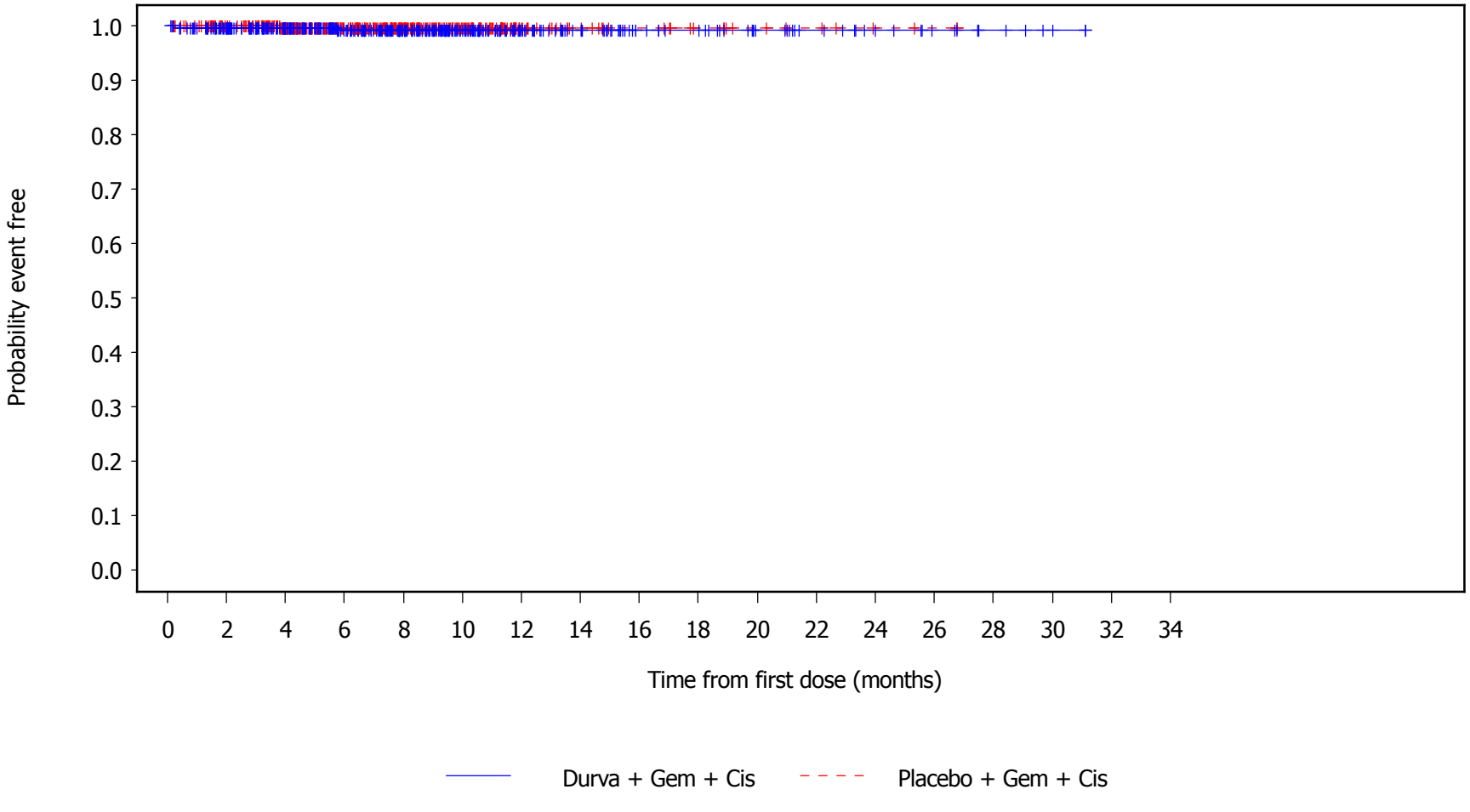
Figure 3.3.339 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Liver function test increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	79	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

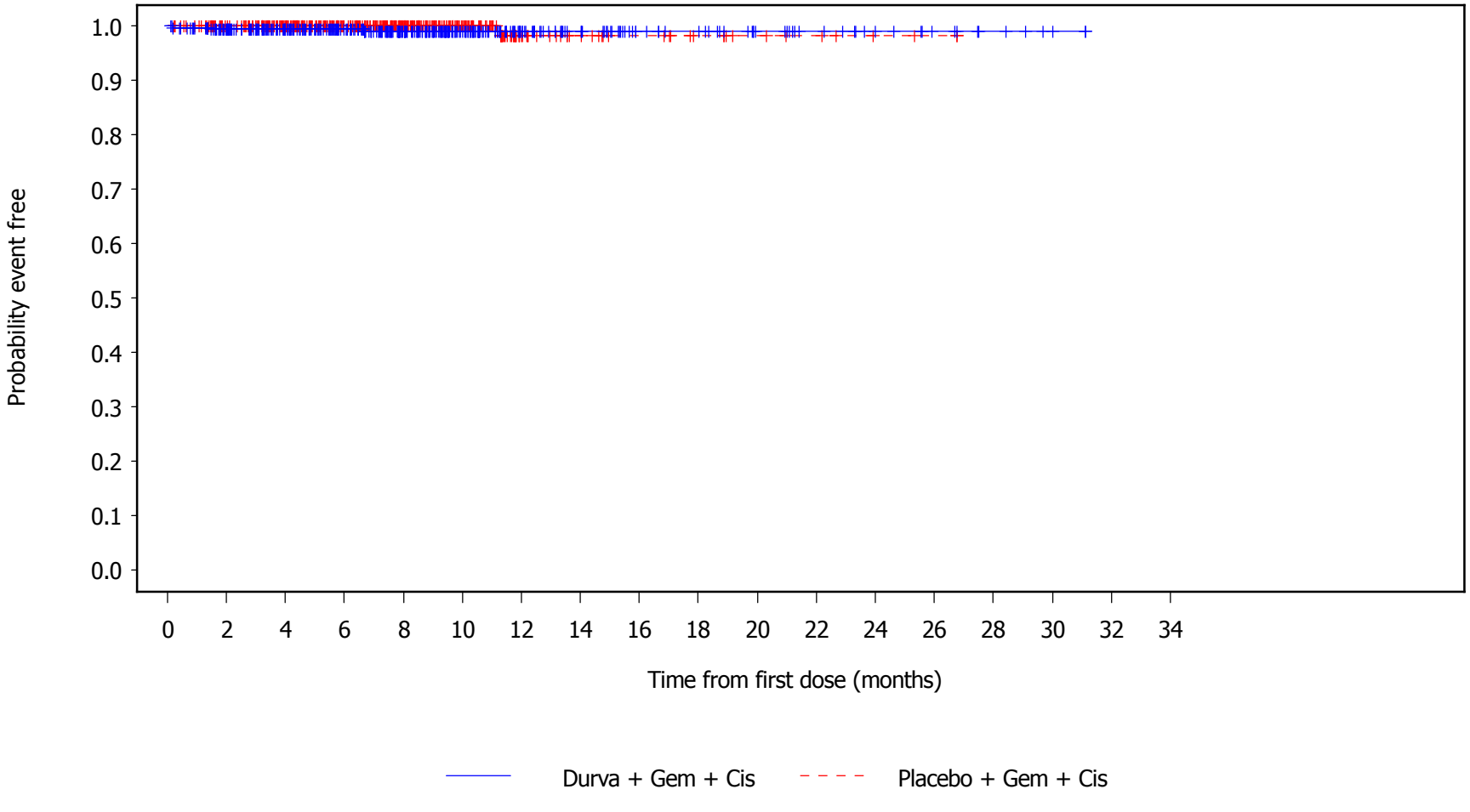
Figure 3.3.340 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	263	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	231	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

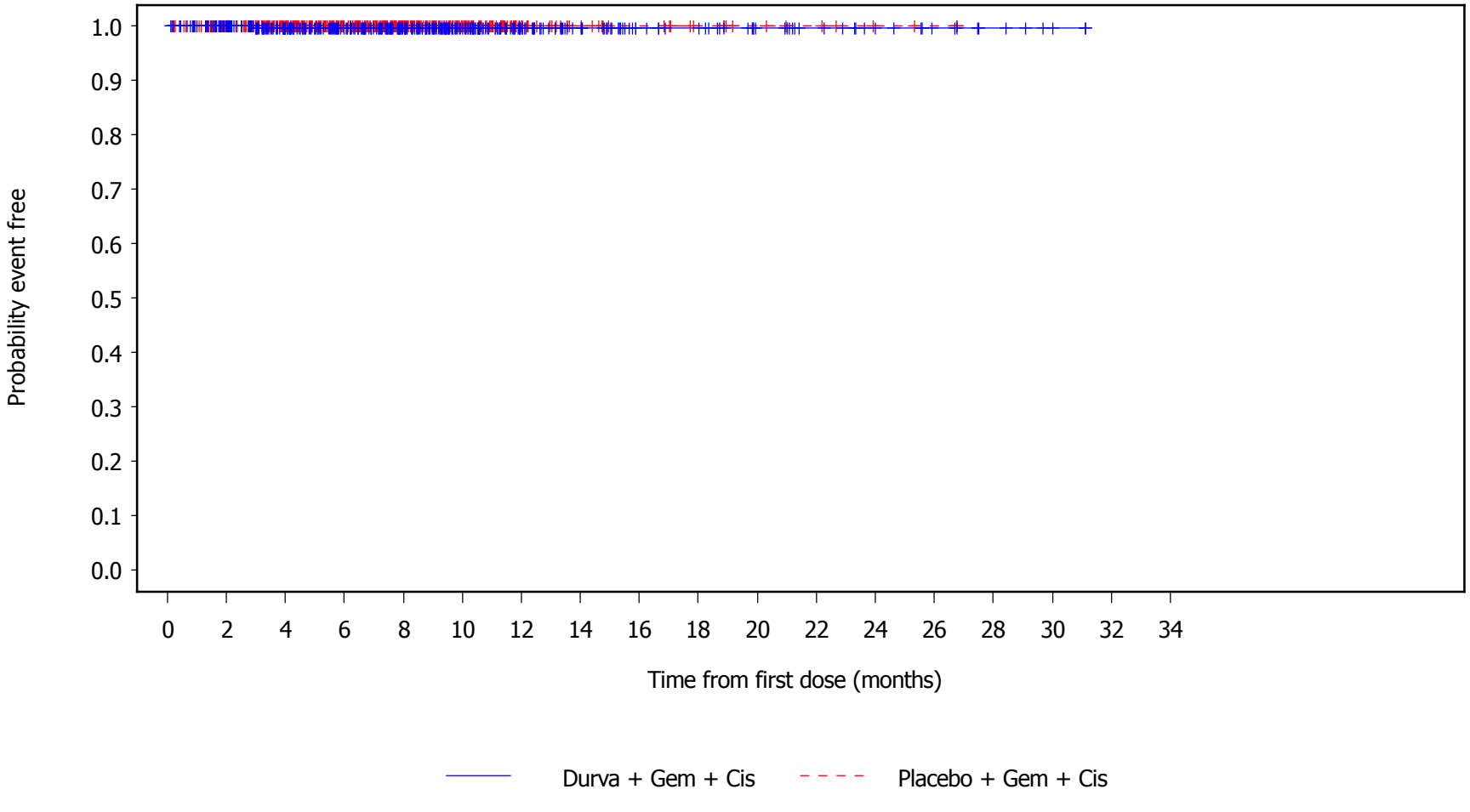
Figure 3.3.341 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Hepatic failure
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	197	130	79	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

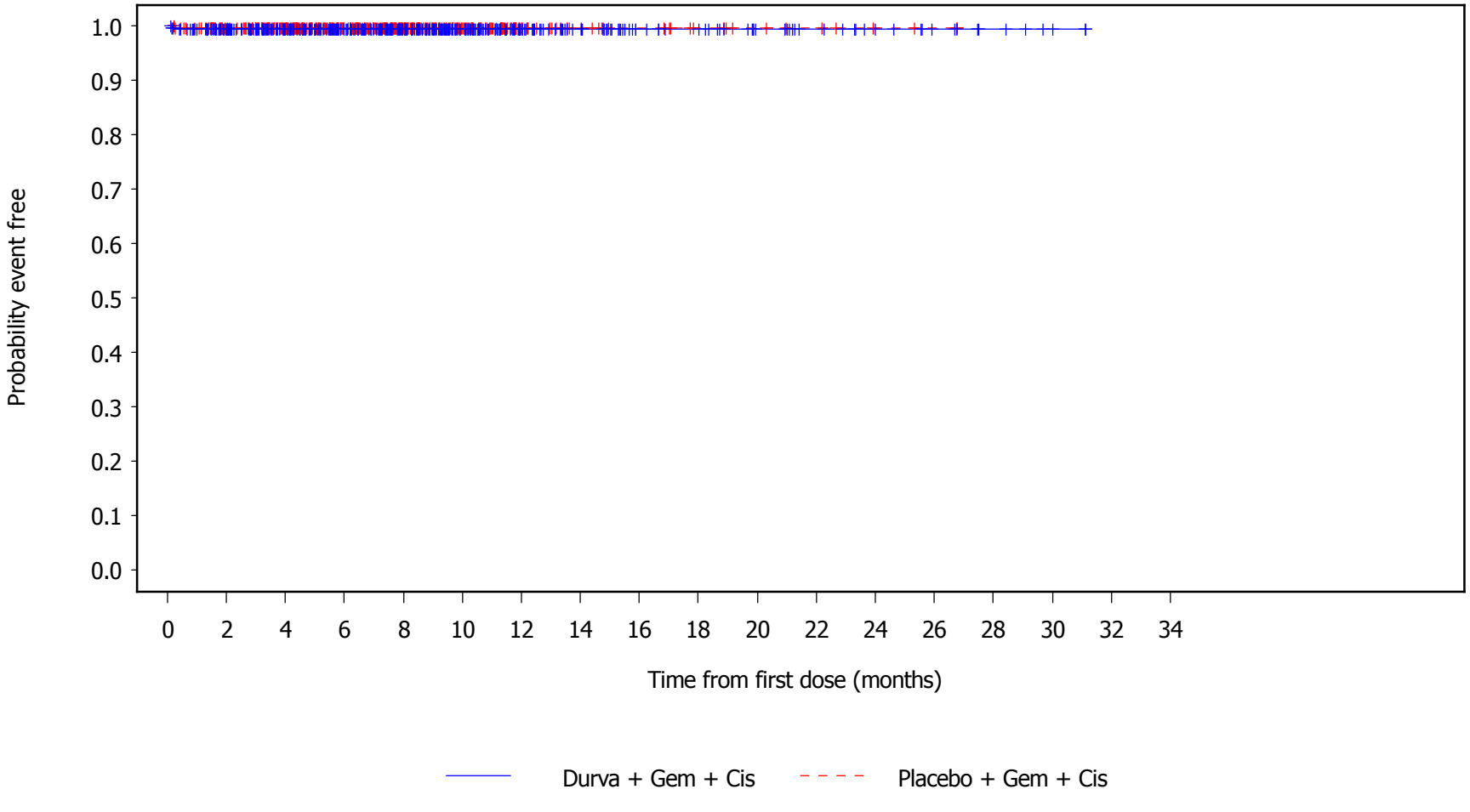
Figure 3.3.342 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Oesophageal varices haemorrhage
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

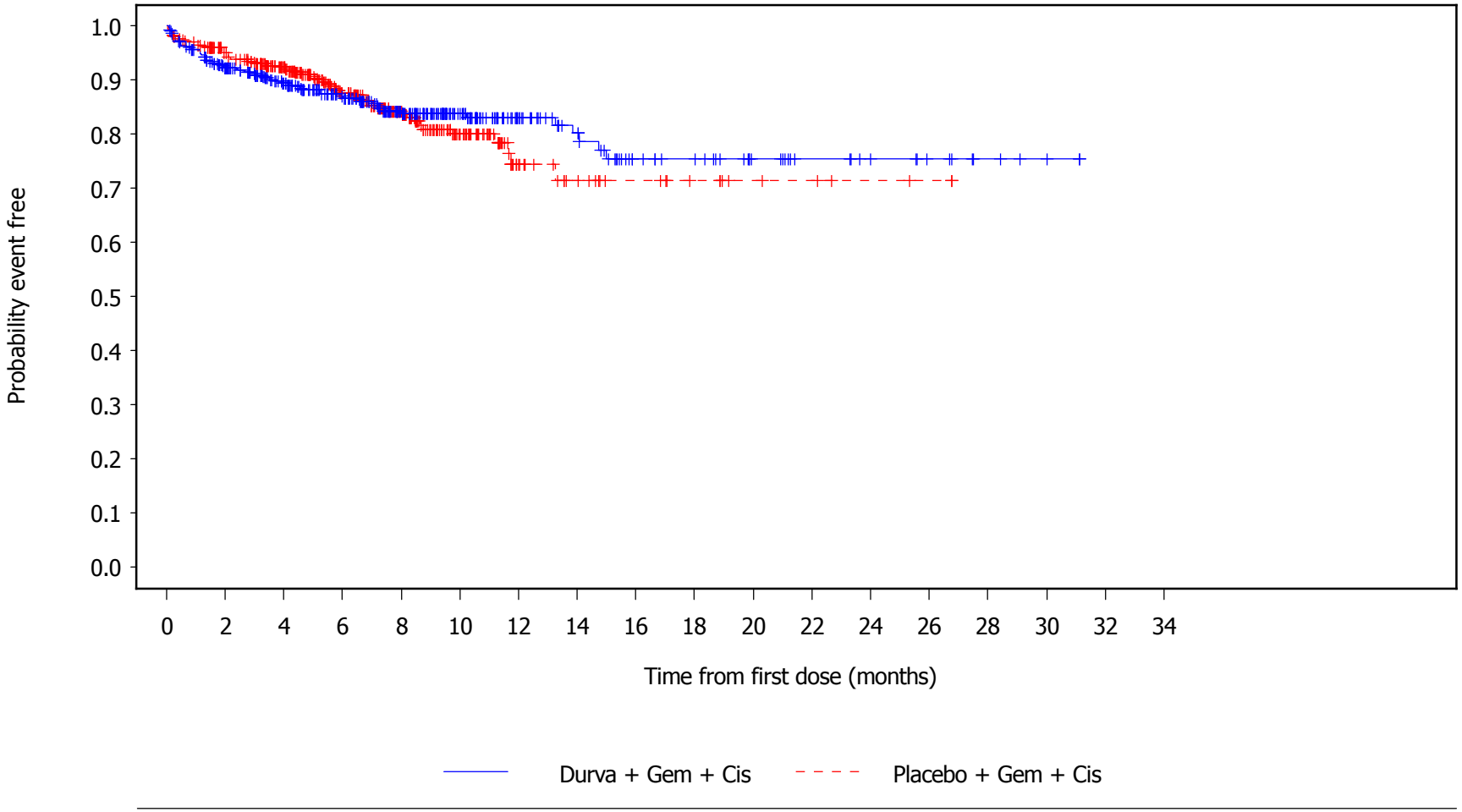
Figure 3.3.343 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Transaminases increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	263	197	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

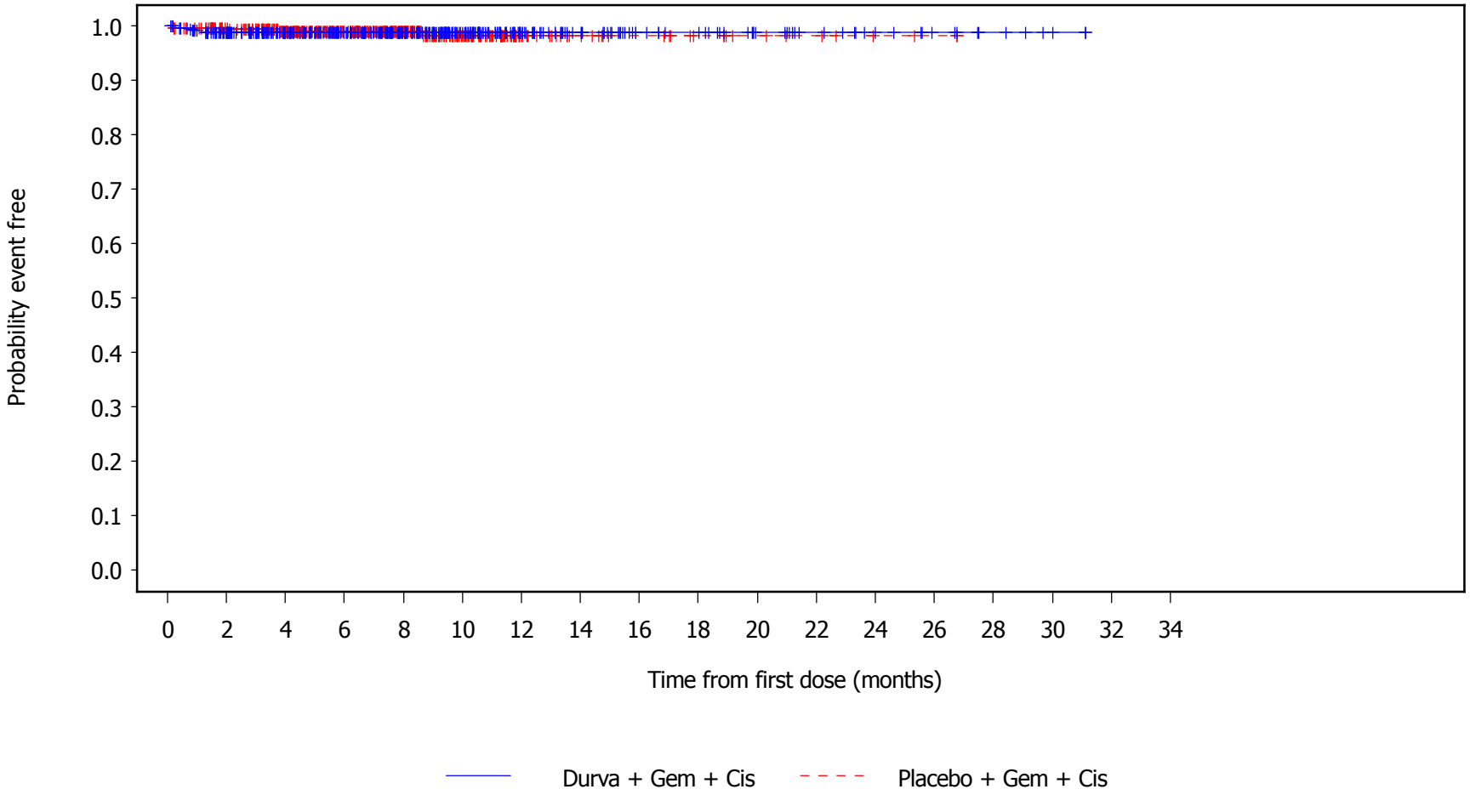
Figure 3.3.344 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Biliary SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	347	290	241	177	118	71	53	35	31	21	15	12	8	4	2	0	0	Durva + Gem + Cis
403	353	295	208	143	78	29	19	13	9	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

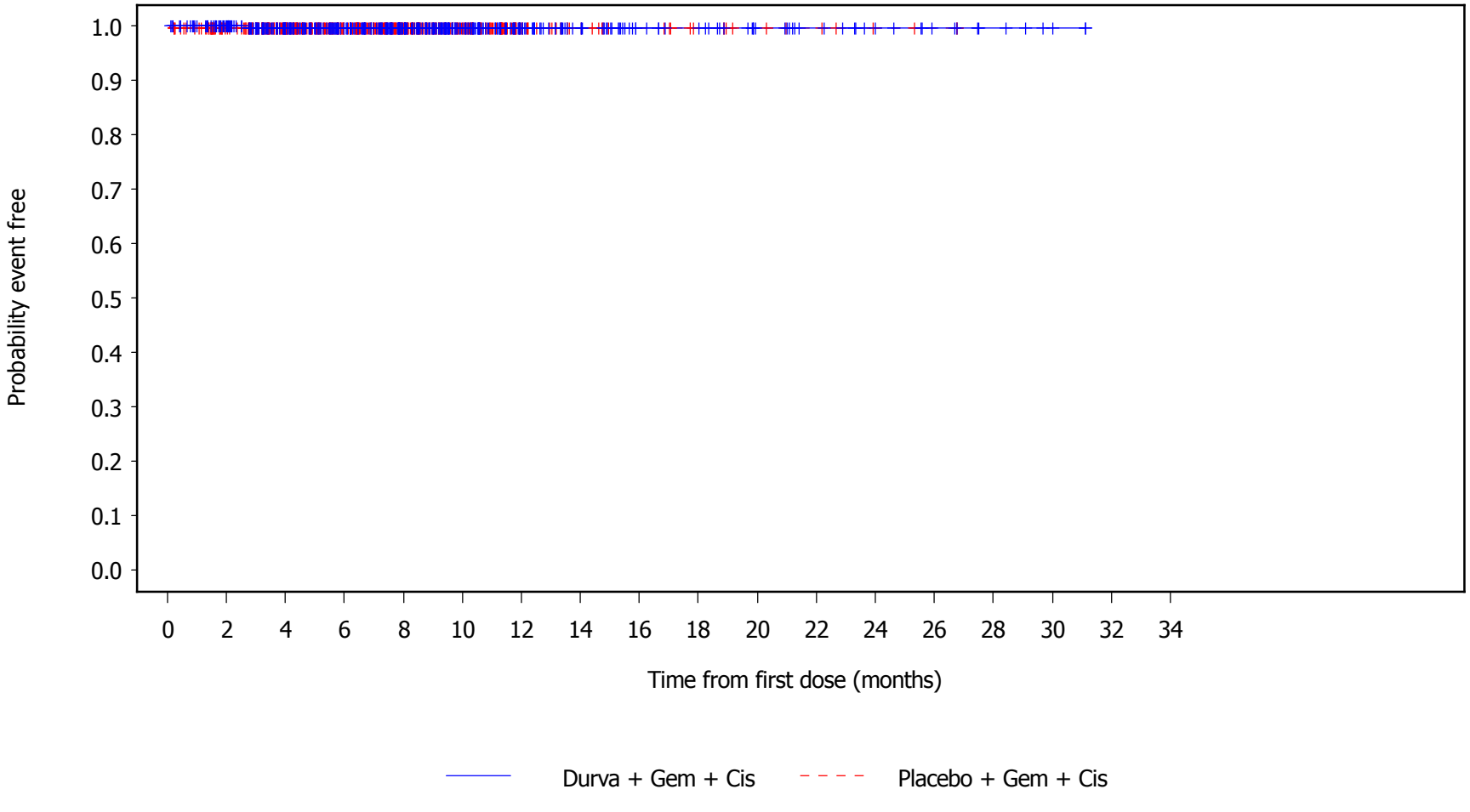
Figure 3.3.345 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Cholangitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	311	261	197	130	79	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	310	229	157	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

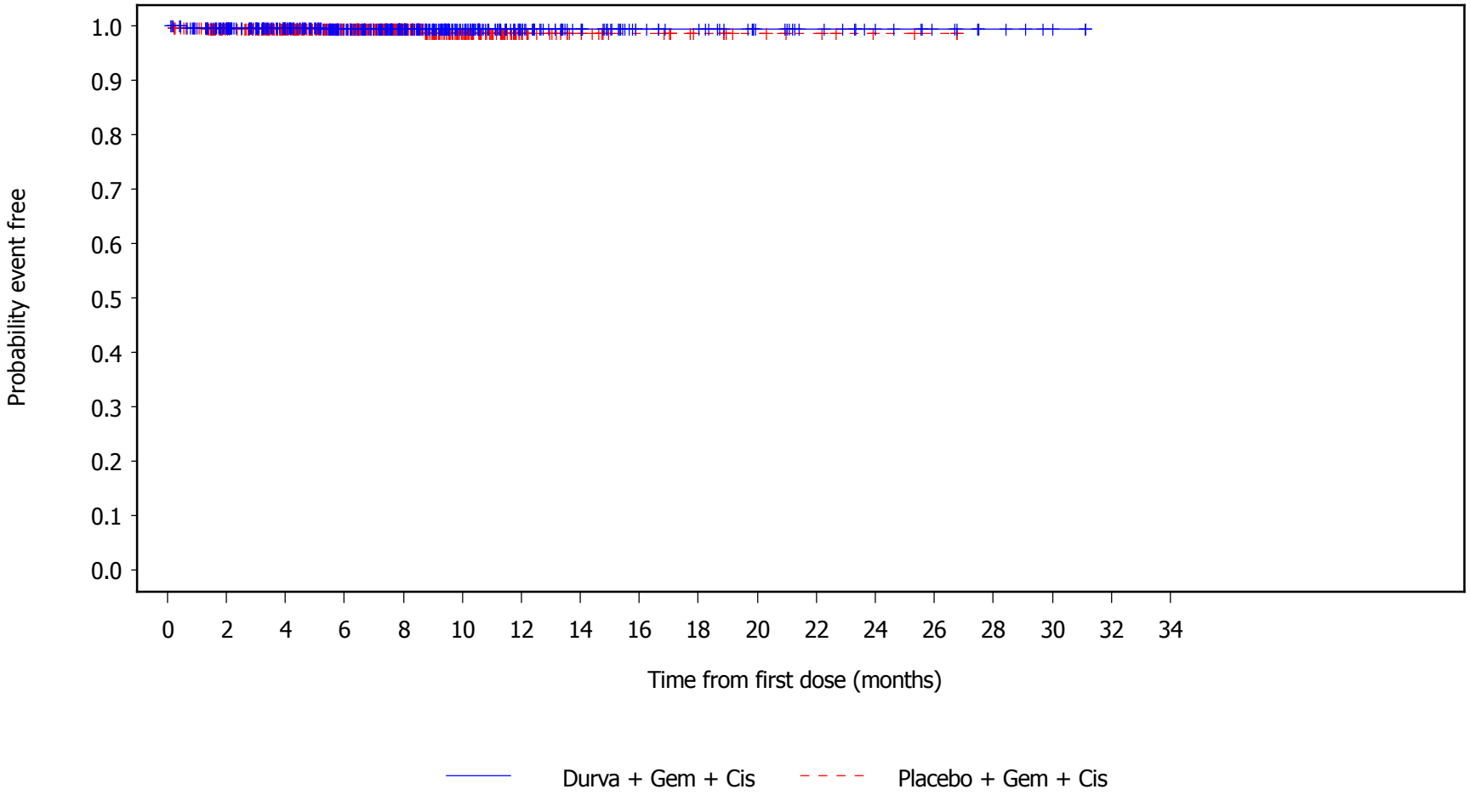
Figure 3.3.346 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Cholecystitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

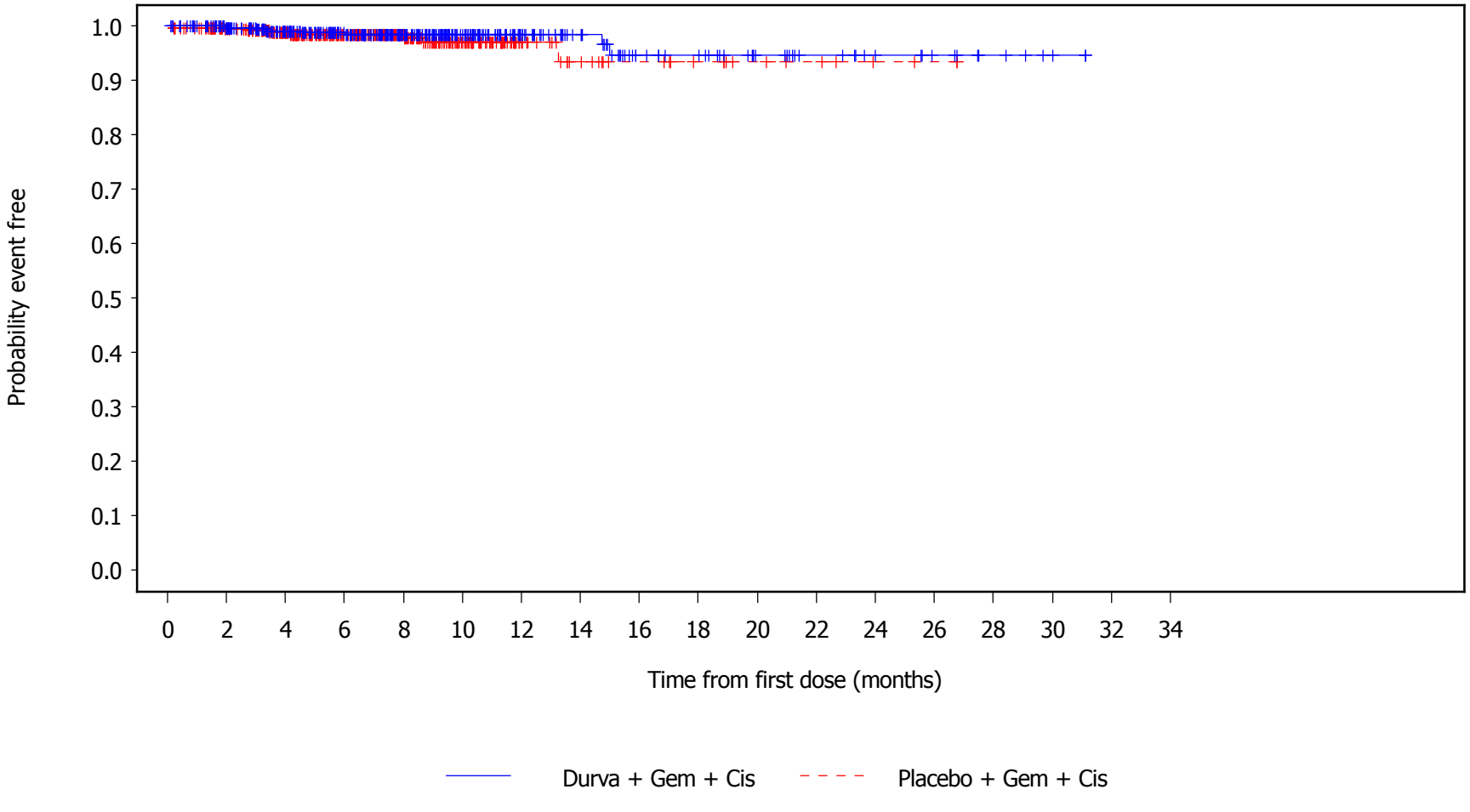
Figure 3.3.347 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Blood alkaline phosphatase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	263	197	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	312	231	158	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

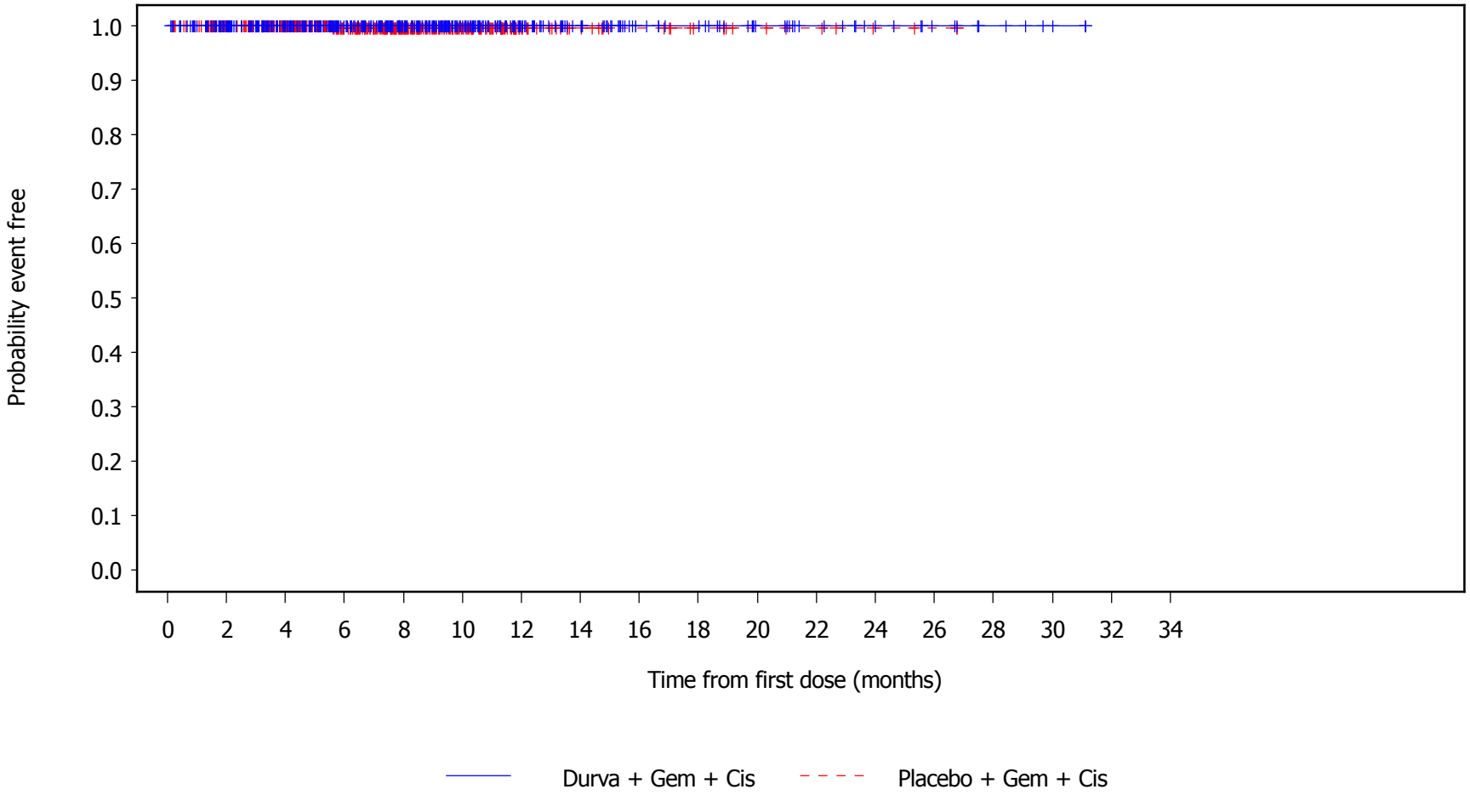
Figure 3.3.348 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Biliary obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	313	262	196	130	79	57	38	34	23	17	13	9	5	2	0	0	Durva + Gem + Cis
403	369	310	228	156	86	33	21	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

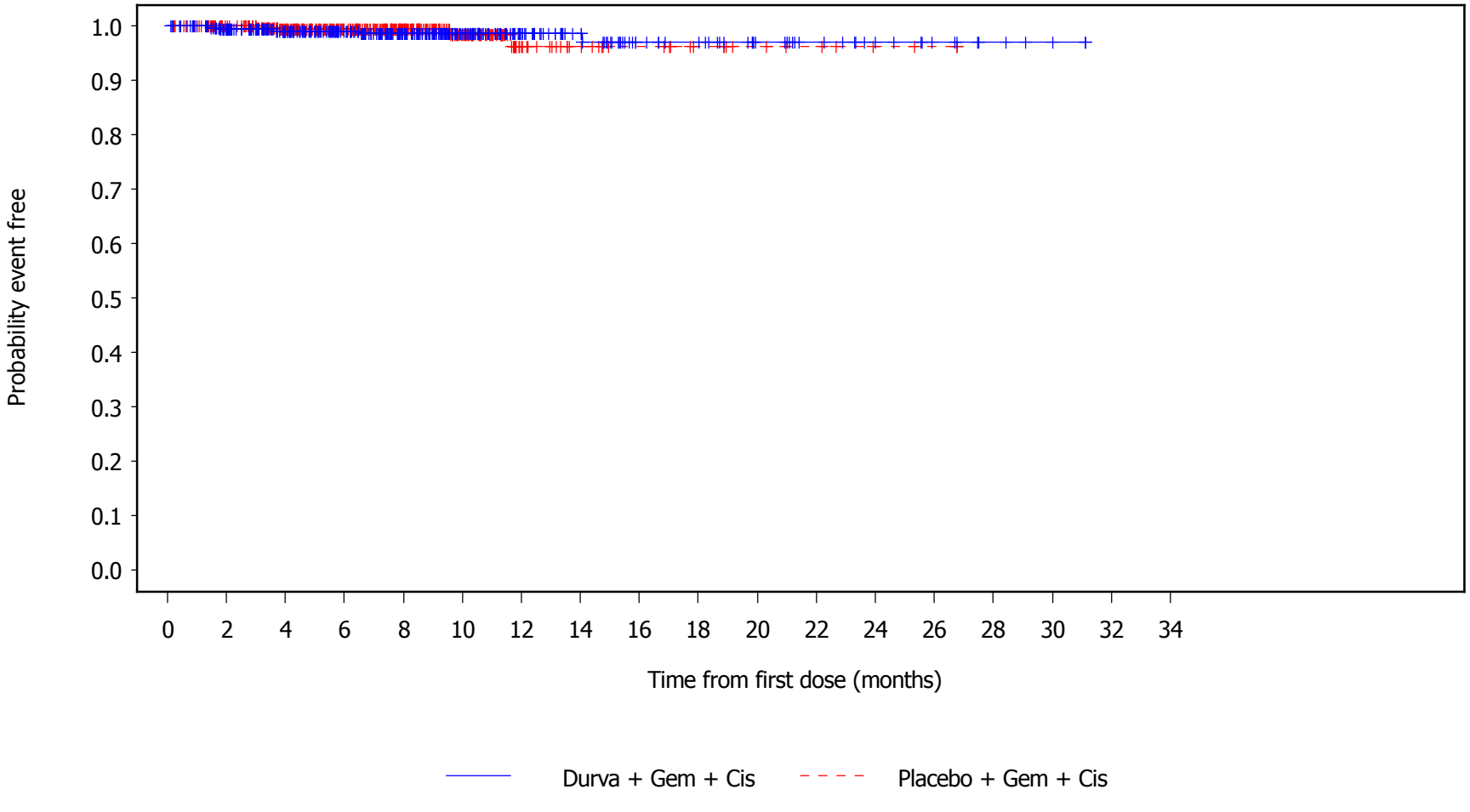
Figure 3.3.349 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Biliary abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	231	158	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

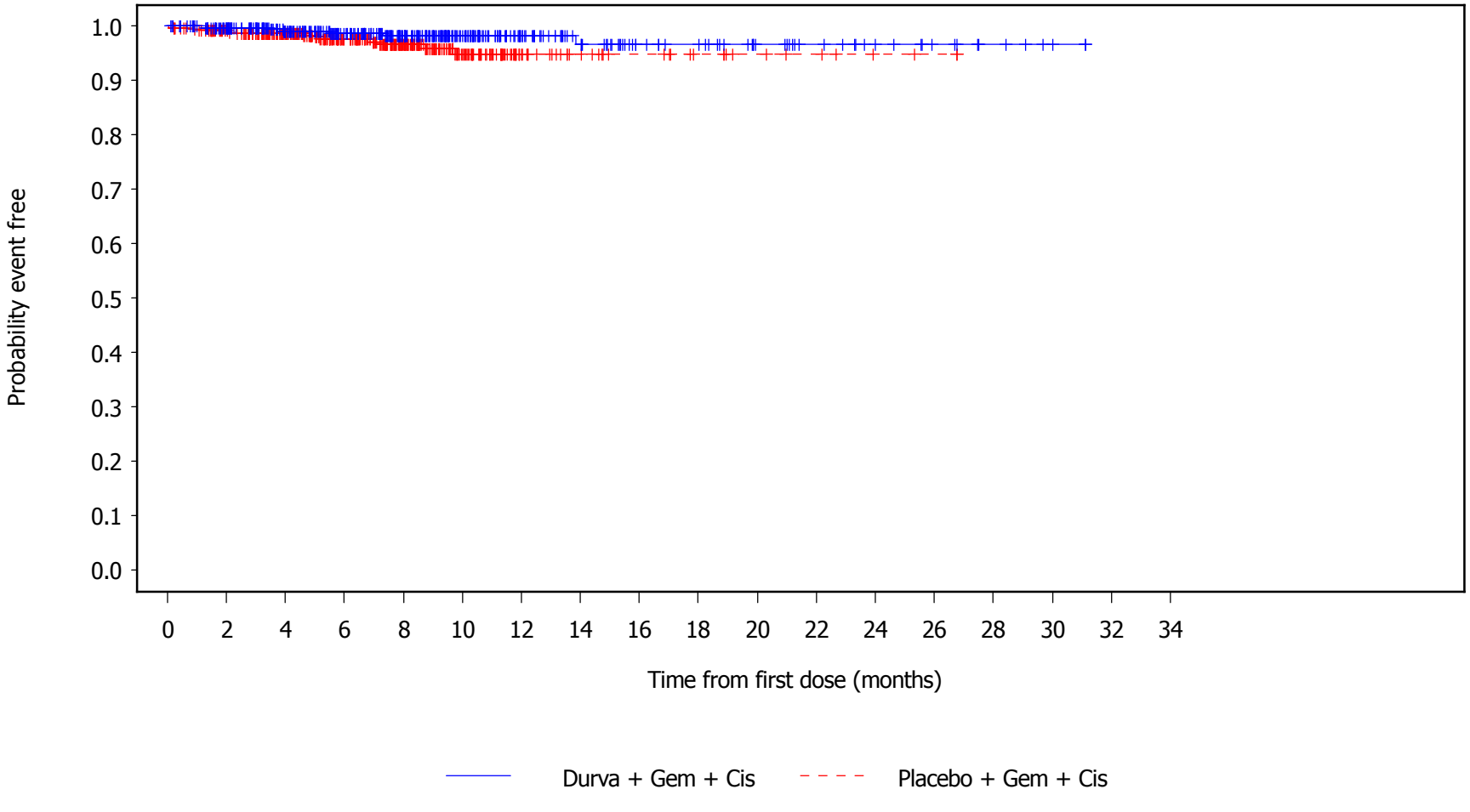
Figure 3.3.350 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Biliary sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	264	197	130	79	58	39	35	24	18	13	8	4	2	0	0	Durva + Gem + Cis
403	371	311	231	158	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

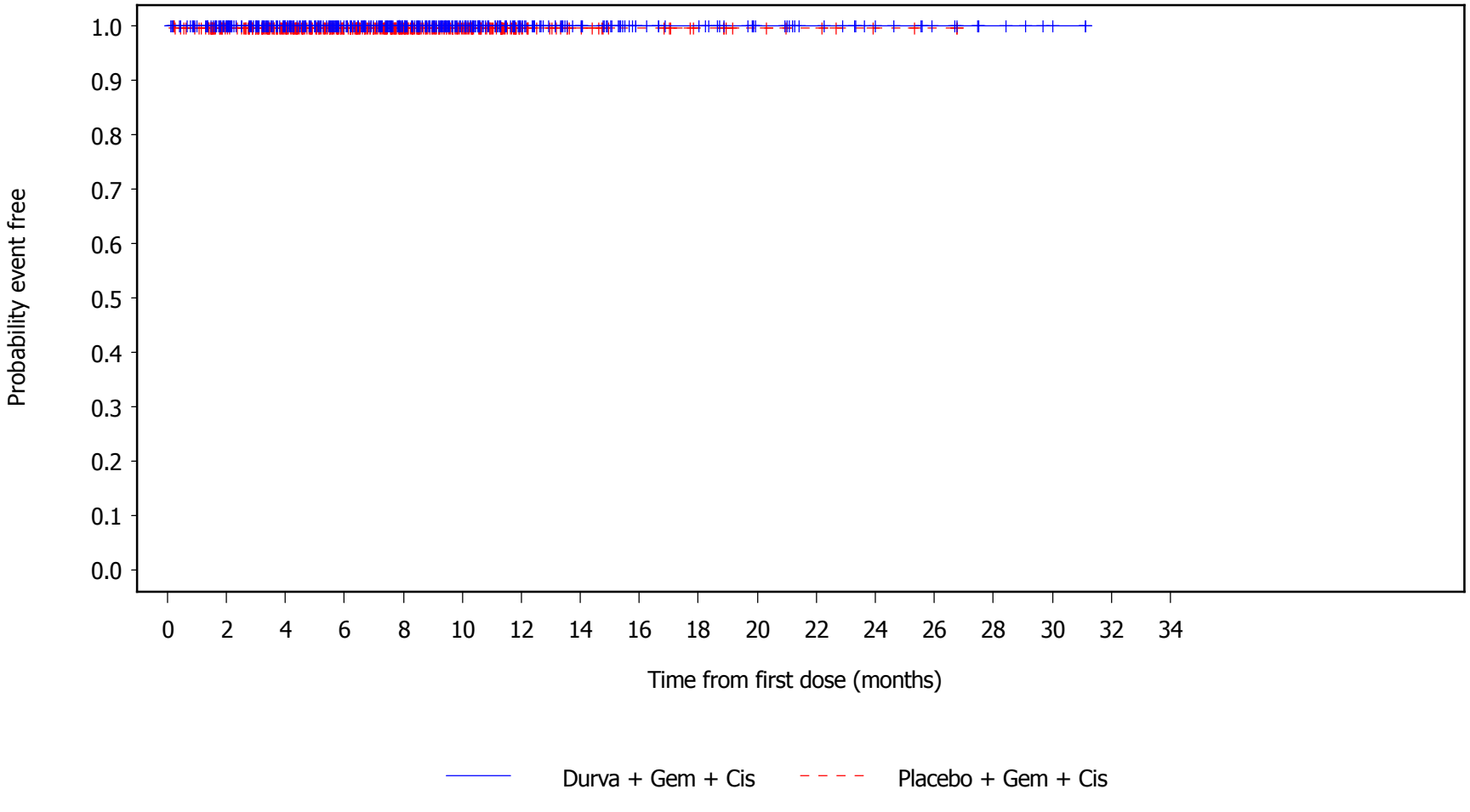
Figure 3.3.351 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	313	262	196	129	80	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	310	228	158	87	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

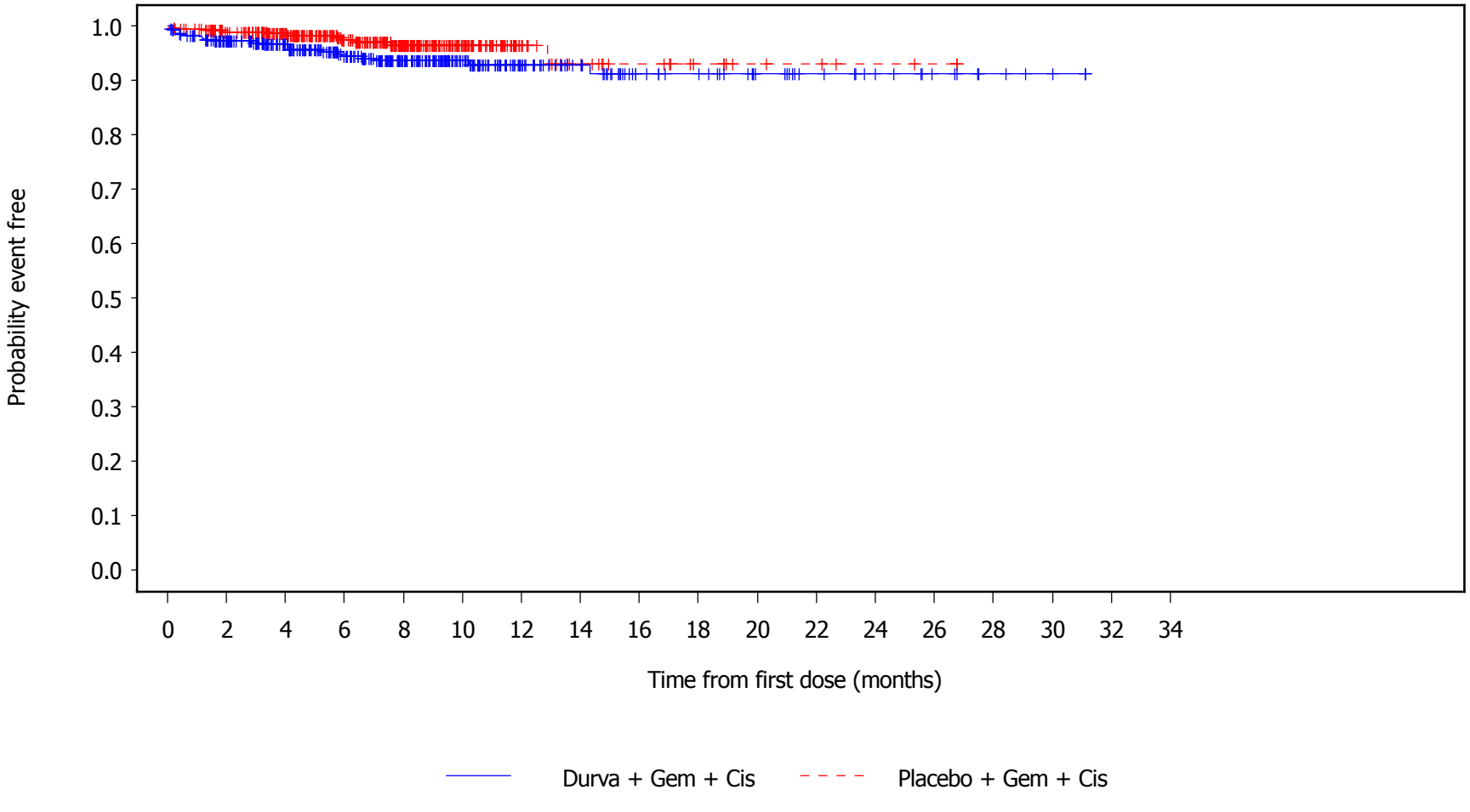
Figure 3.3.352 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Bilirubin conjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

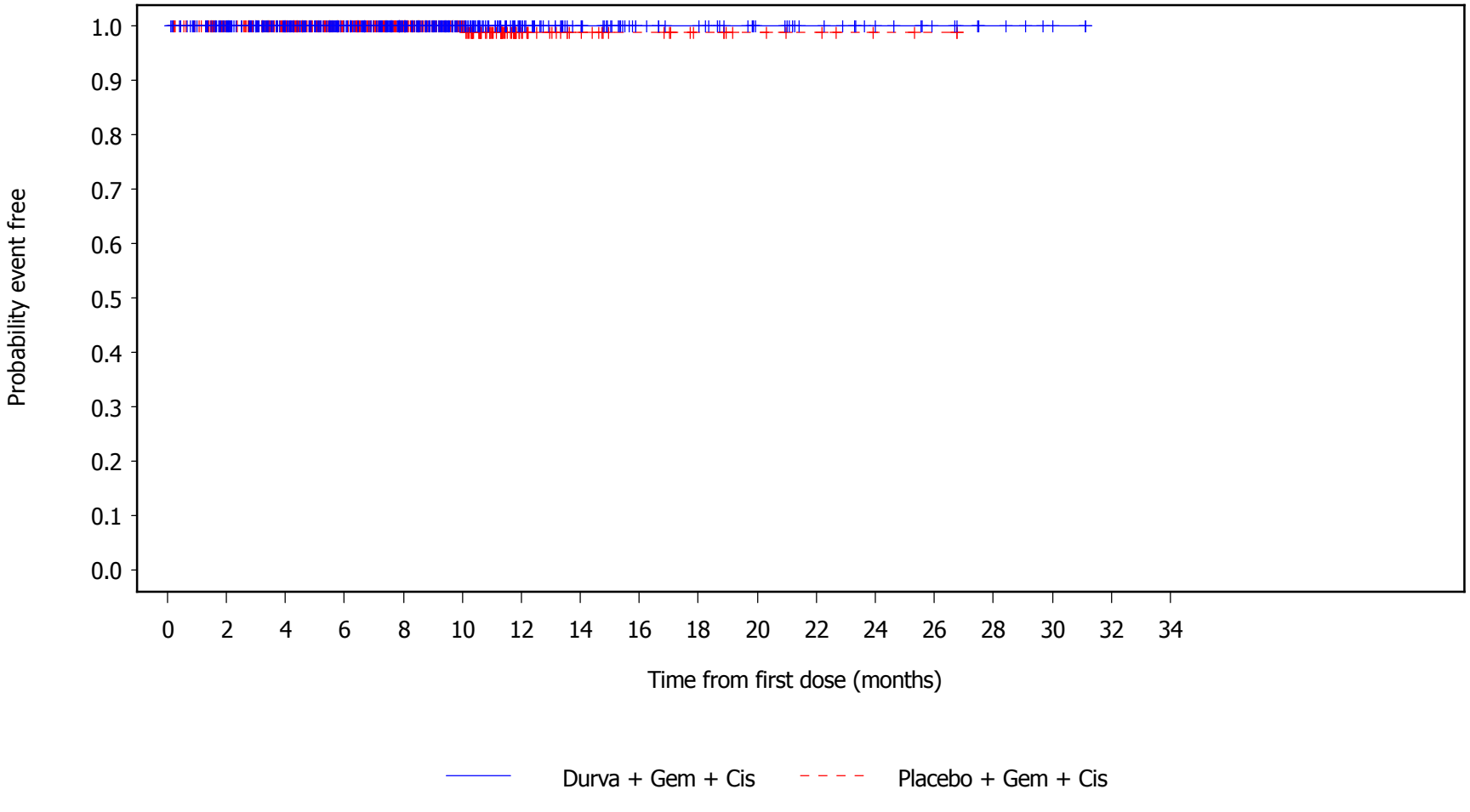
Figure 3.3.353 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Cholangitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	363	306	252	186	124	74	56	37	33	23	17	13	8	4	2	0	0	Durva + Gem + Cis
403	367	310	226	156	86	33	20	14	9	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

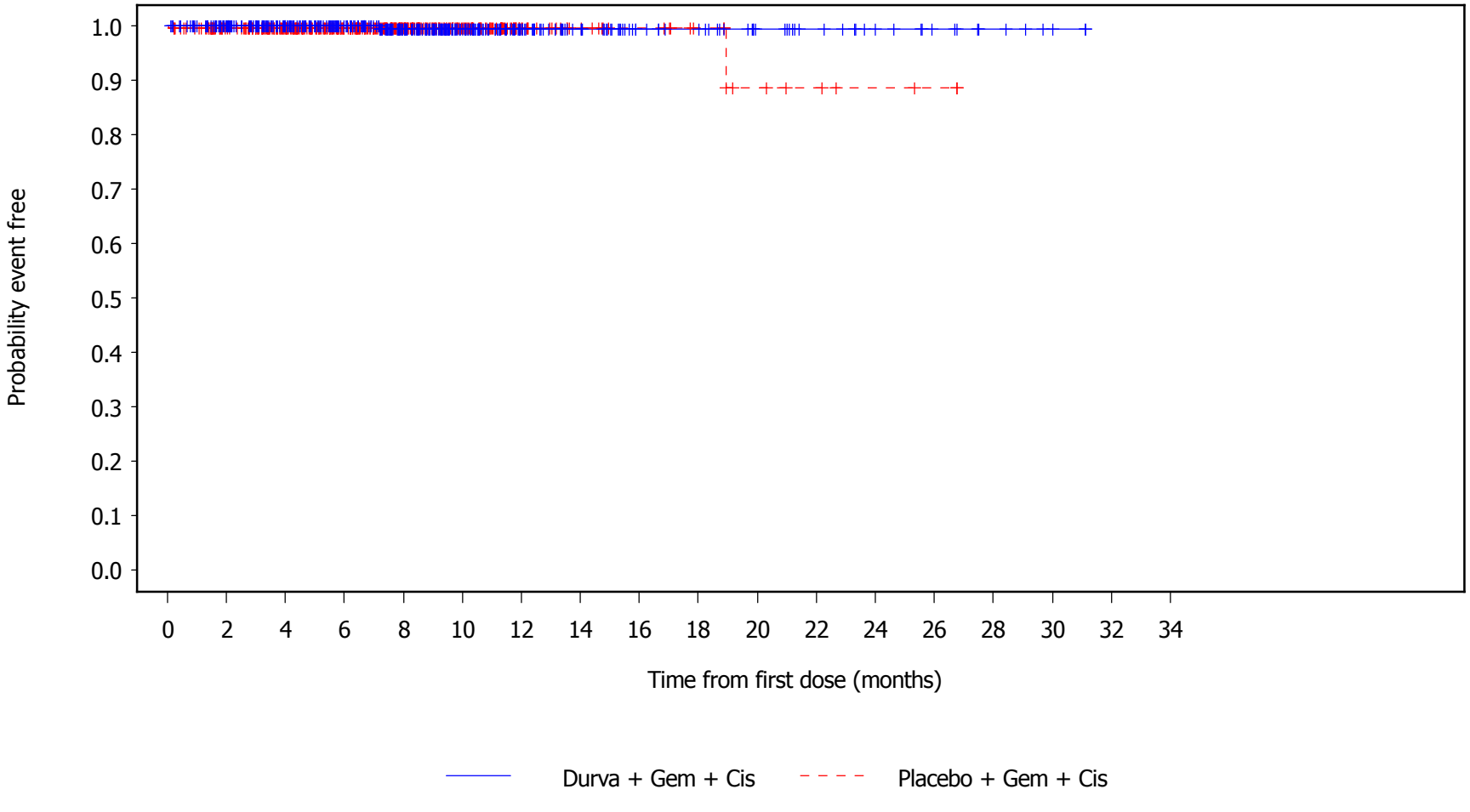
Figure 3.3.354 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Cholangitis infective
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

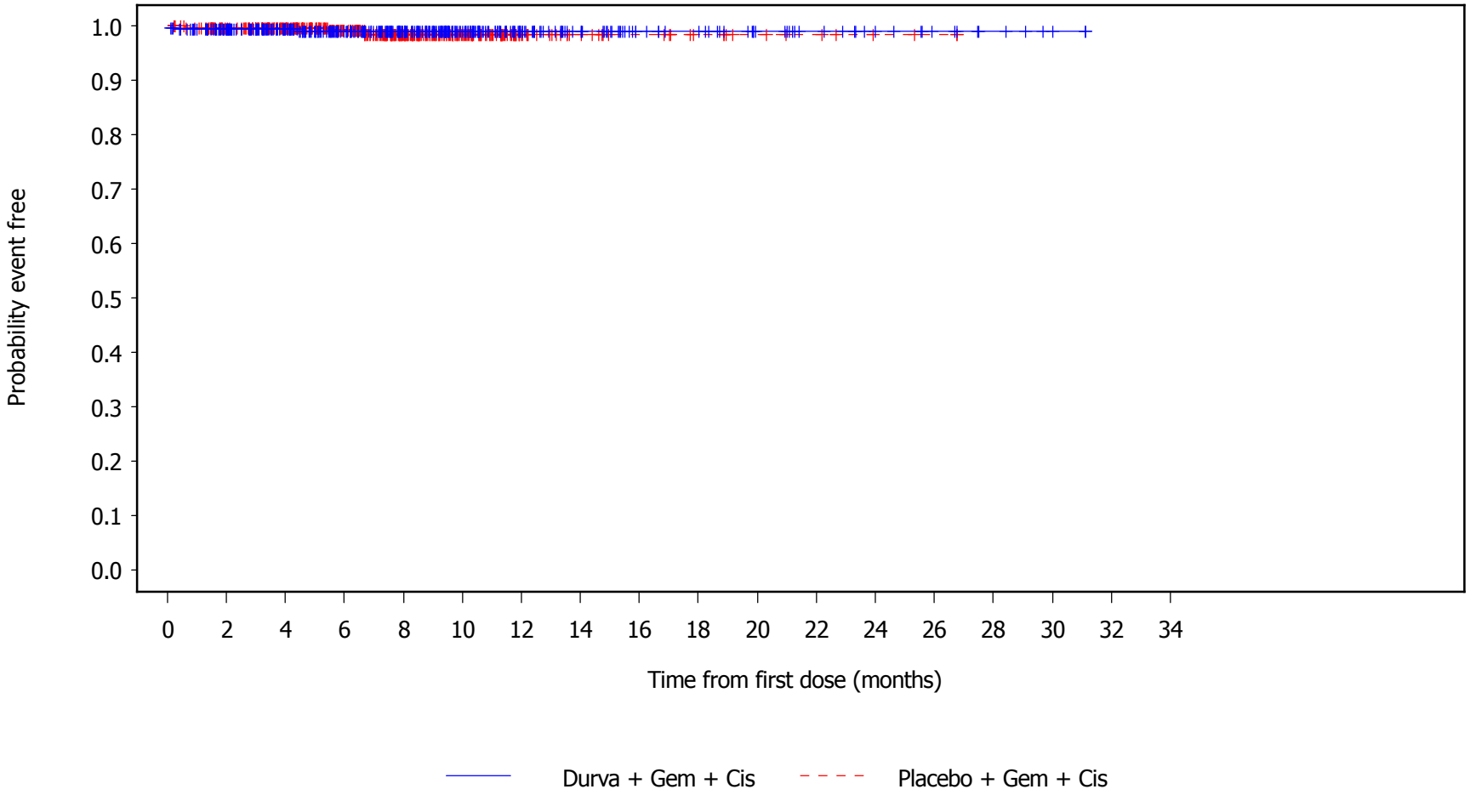
Figure 3.3.355 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	197	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	88	34	22	16	11	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

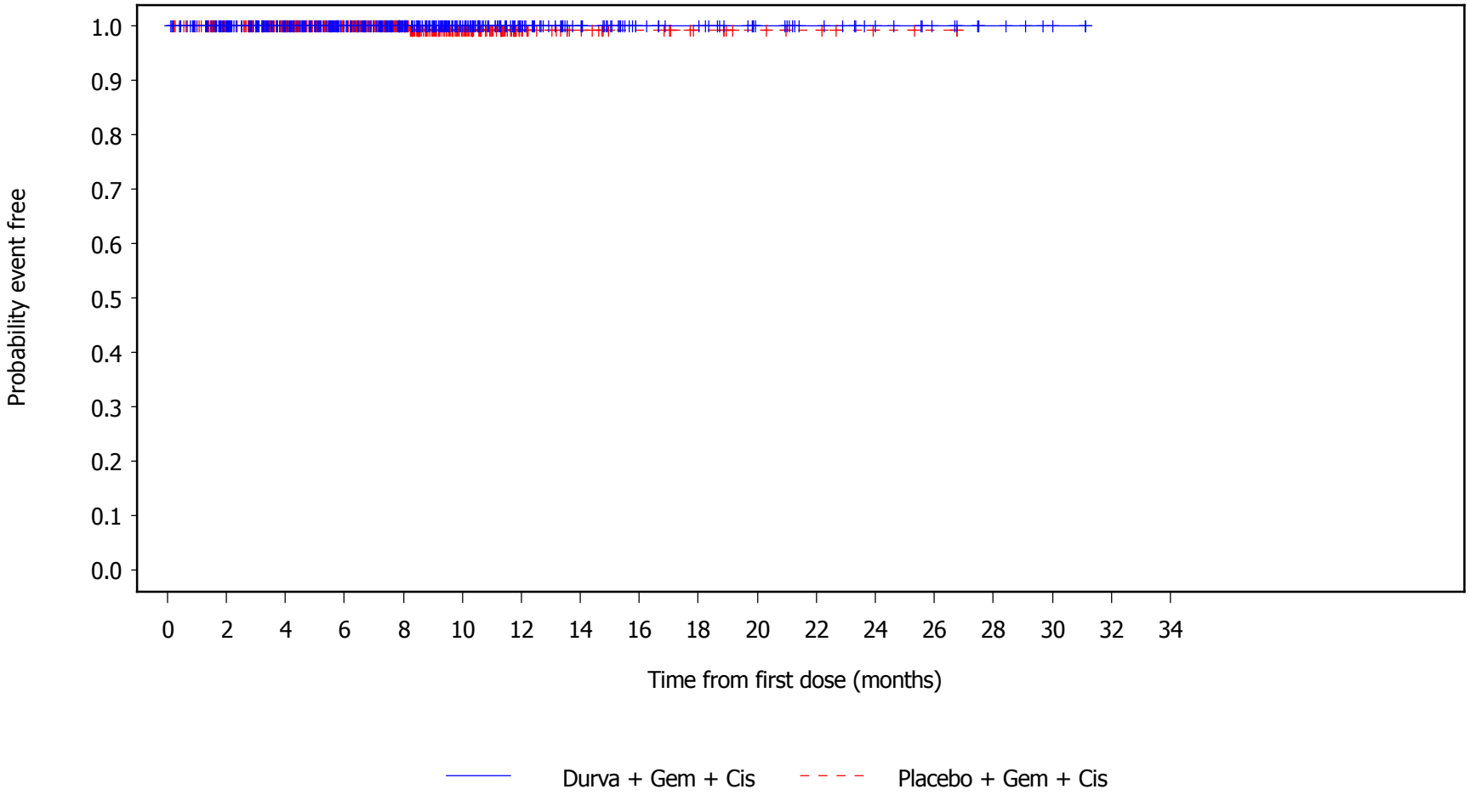
Figure 3.3.356 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Cholecystitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	313	263	197	130	79	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

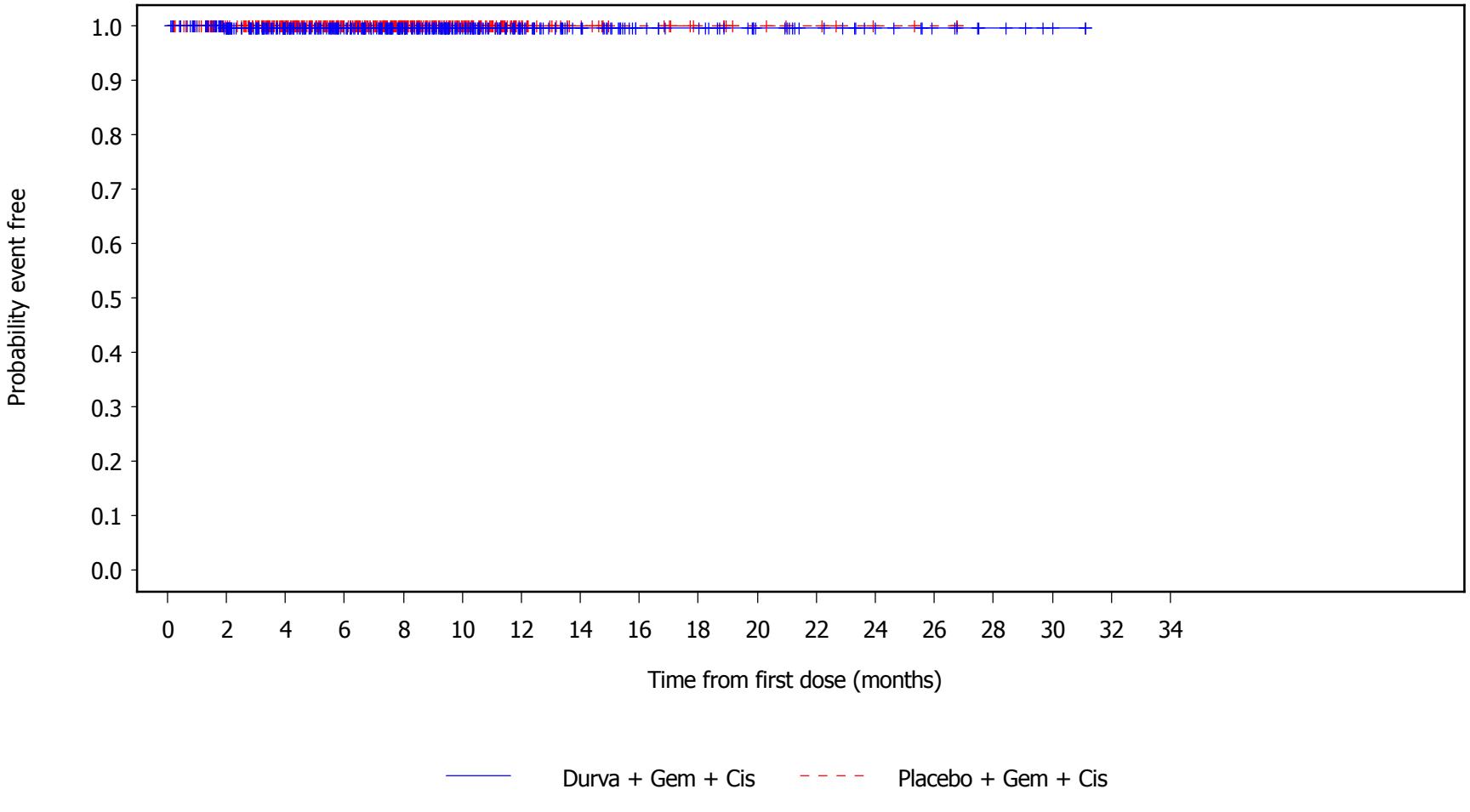
Figure 3.3.357 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Gallbladder empyema
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

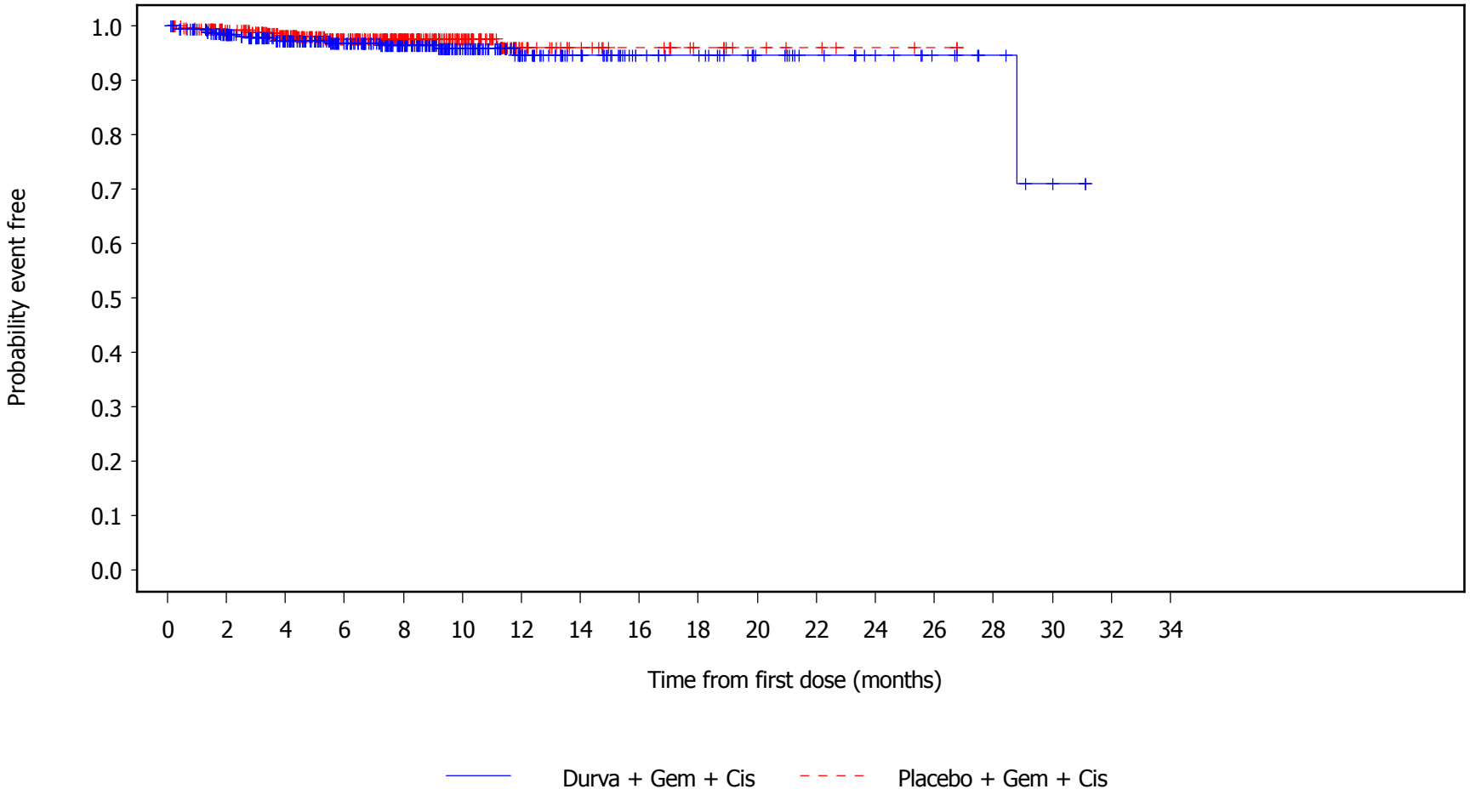
Figure 3.3.358 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Gallbladder obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

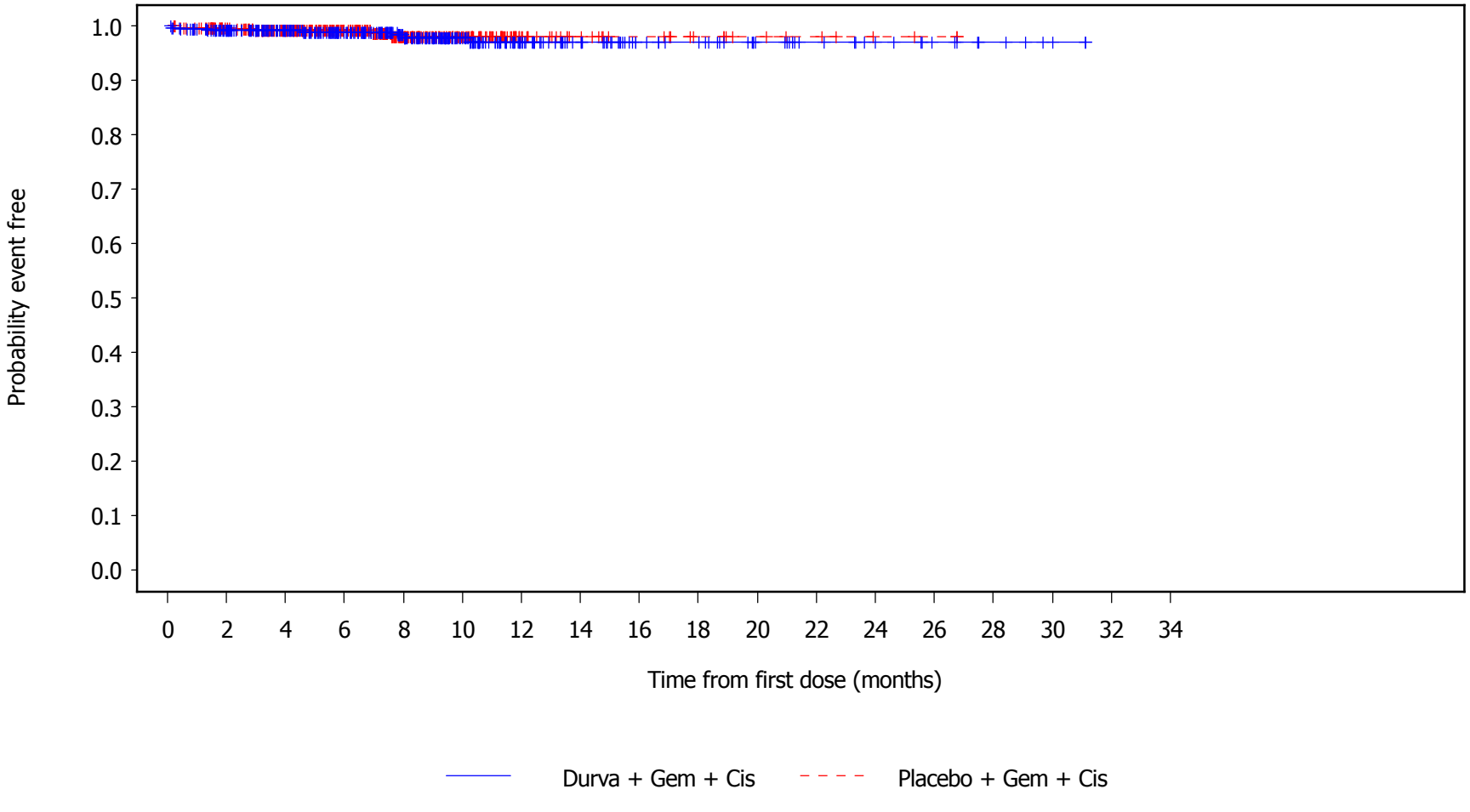
Figure 3.3.359 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Biliary tract infection
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	309	259	196	129	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	368	309	229	157	89	33	21	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

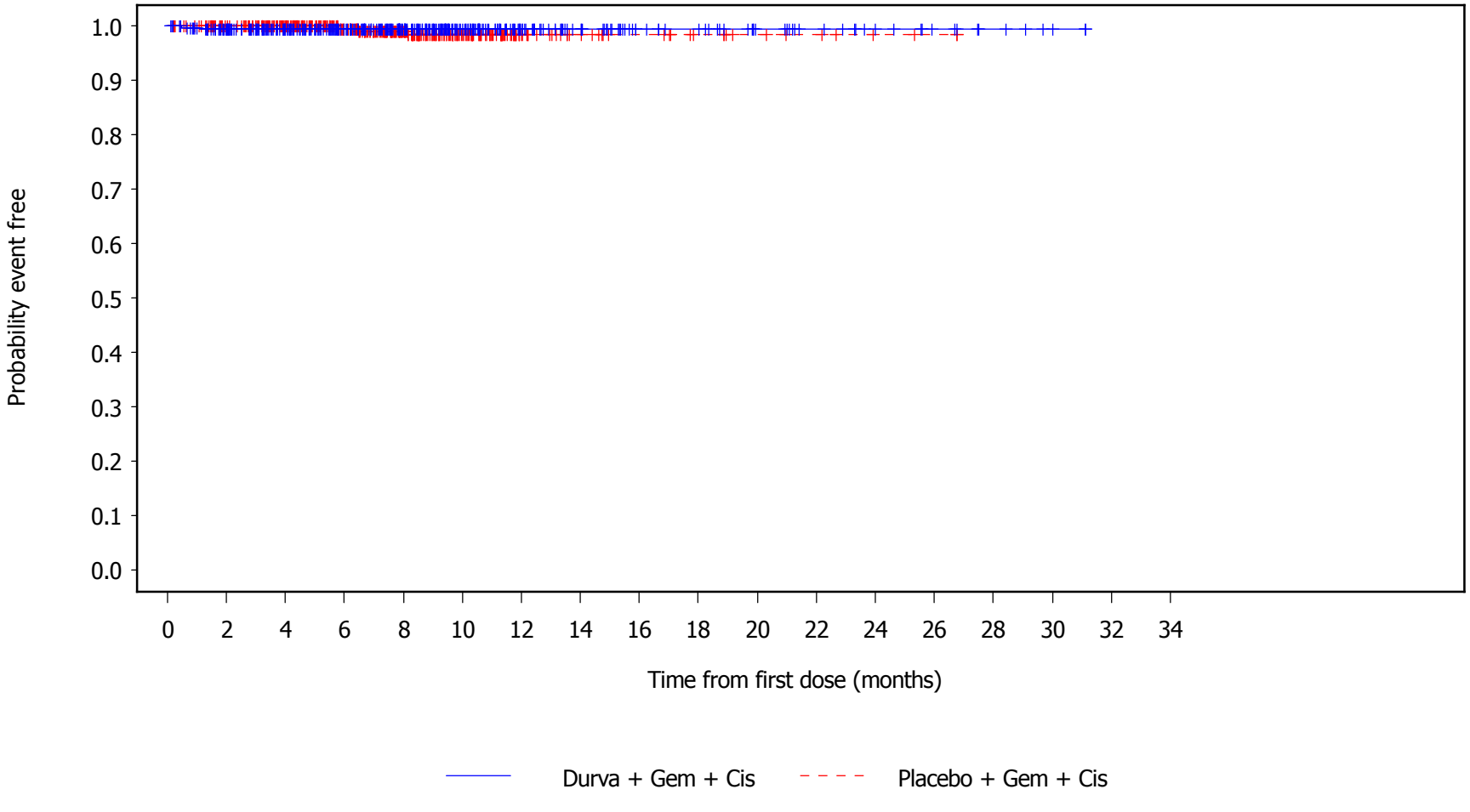
Figure 3.3.360 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	315	263	198	130	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	370	313	232	157	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

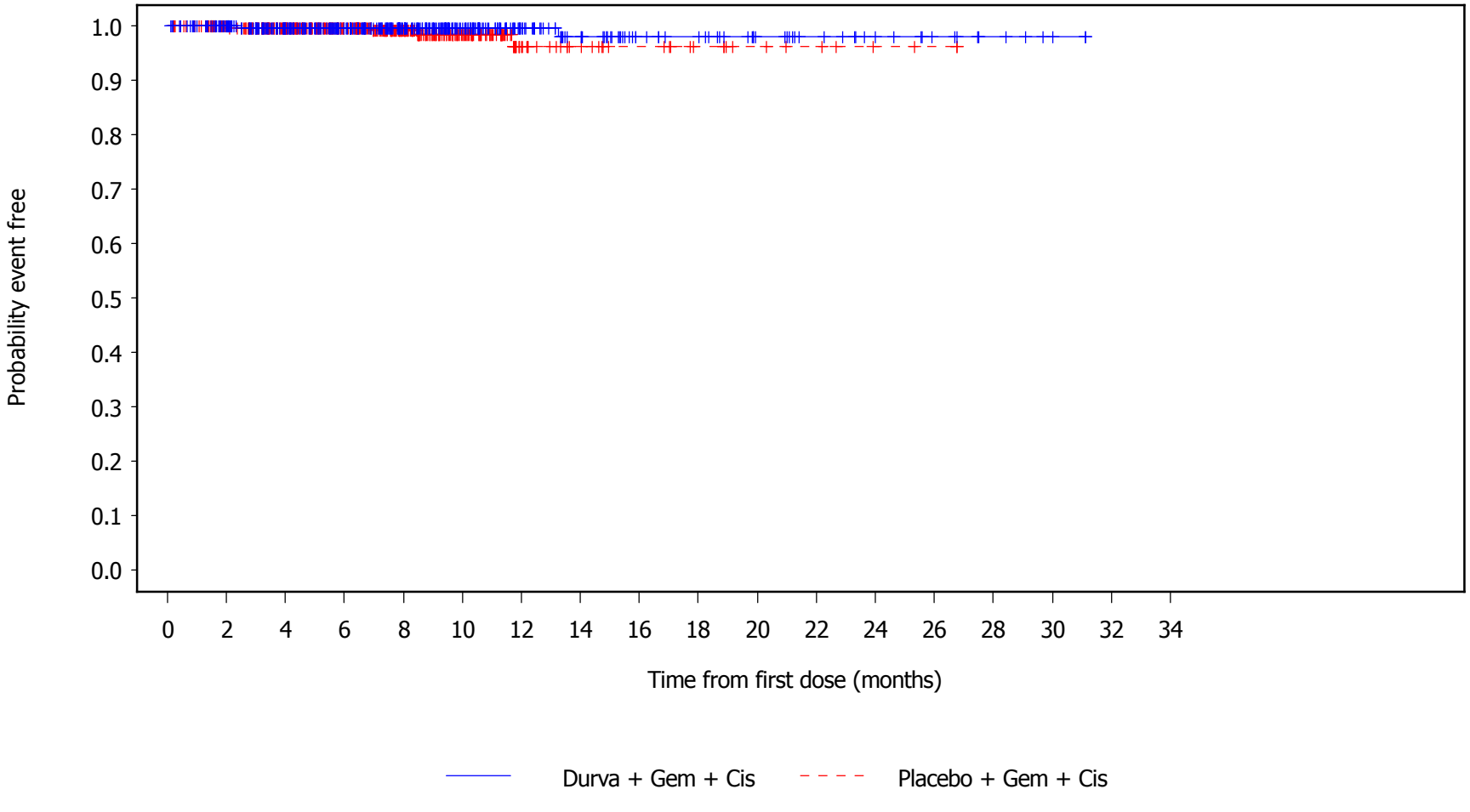
Figure 3.3.361 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	231	157	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

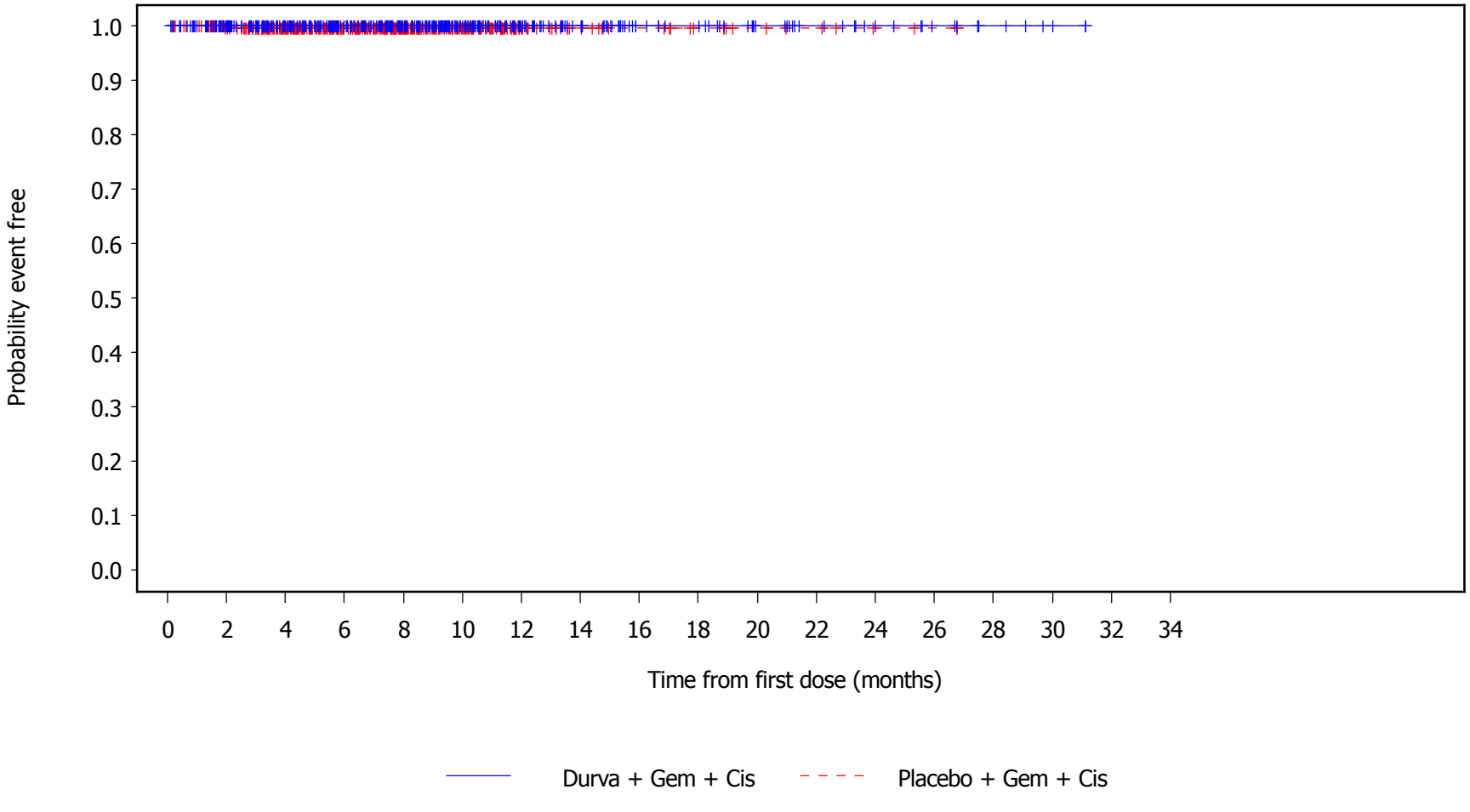
Figure 3.3.362 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	232	158	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

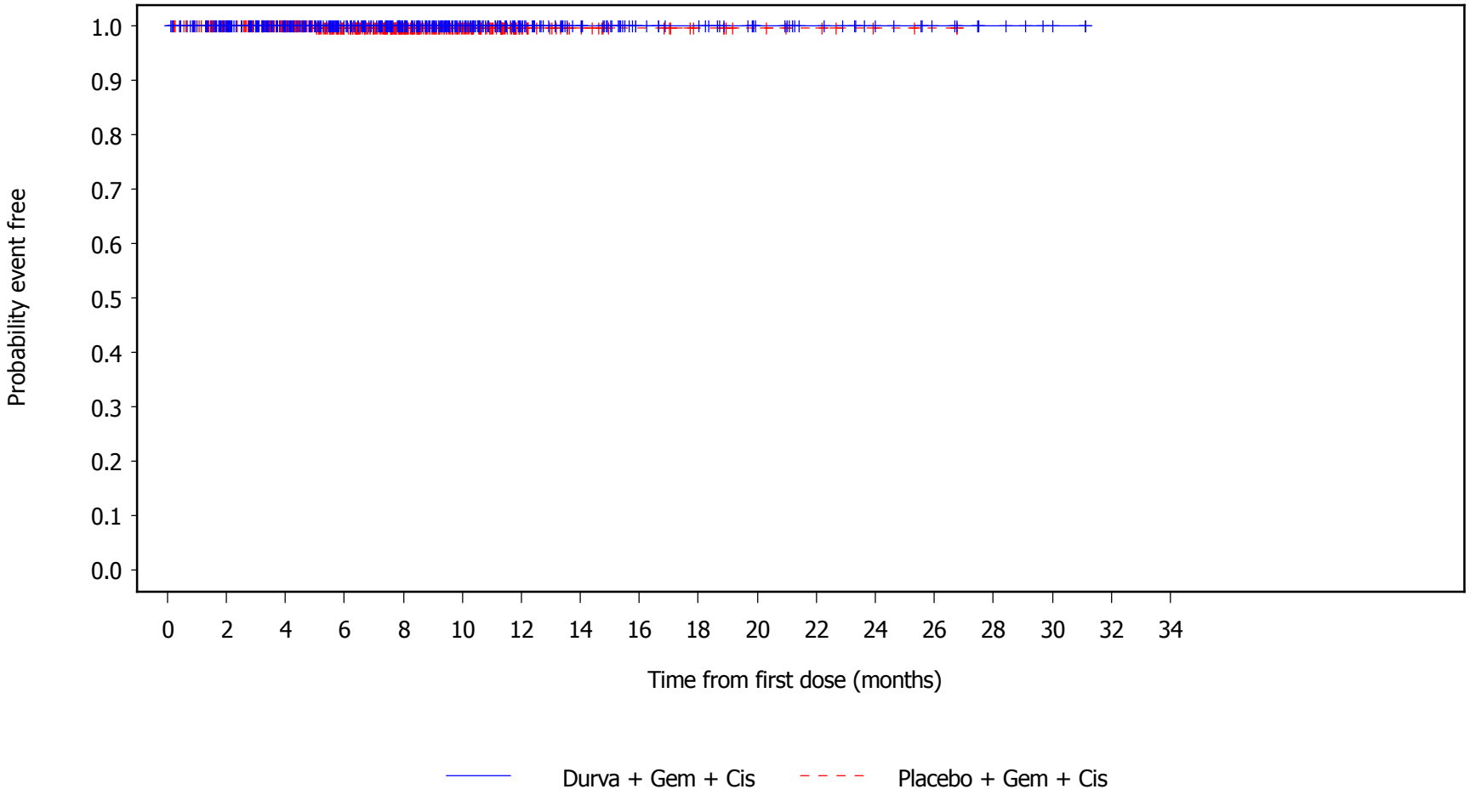
Figure 3.3.363 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Gallbladder rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

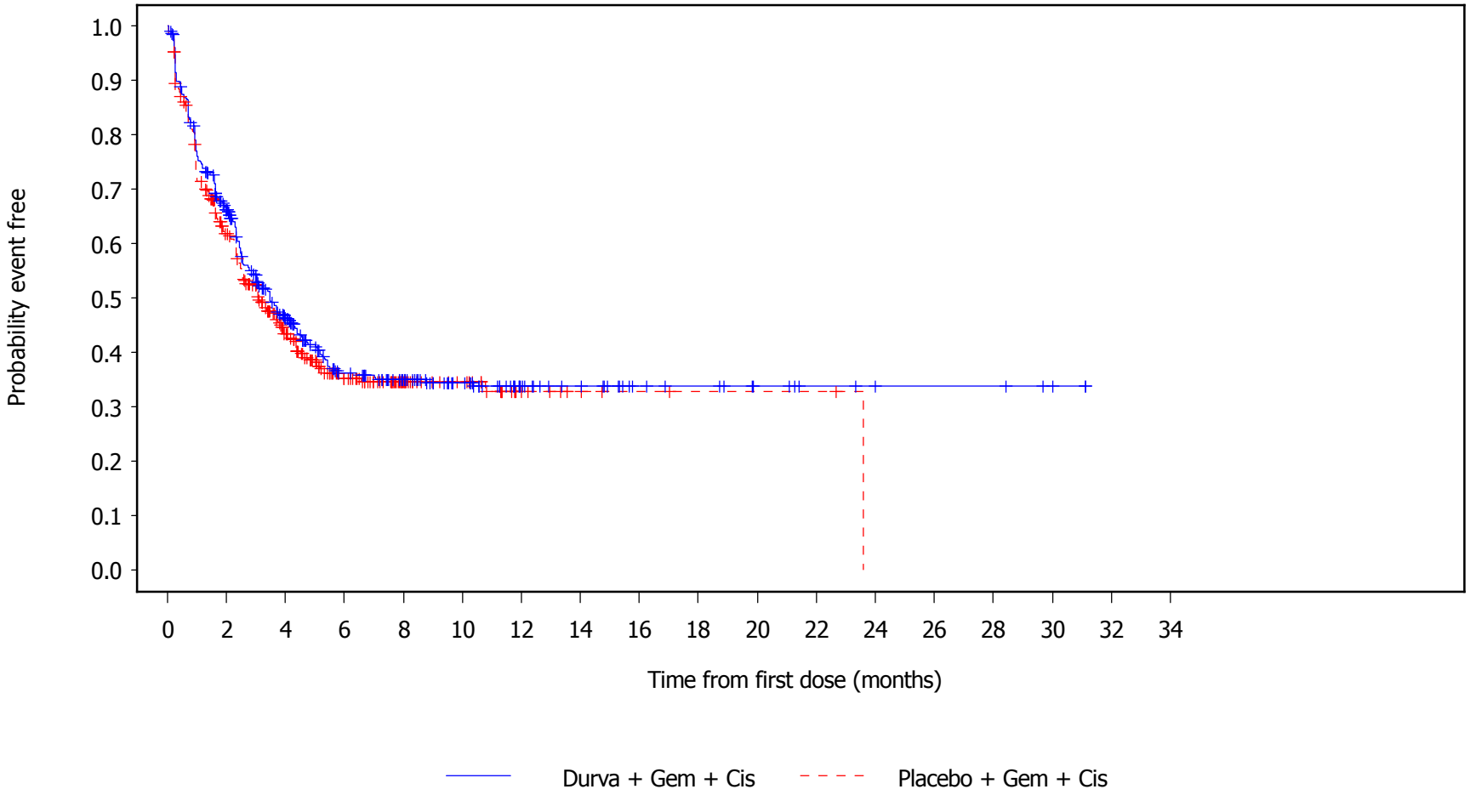
Figure 3.3.364 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Biloma rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

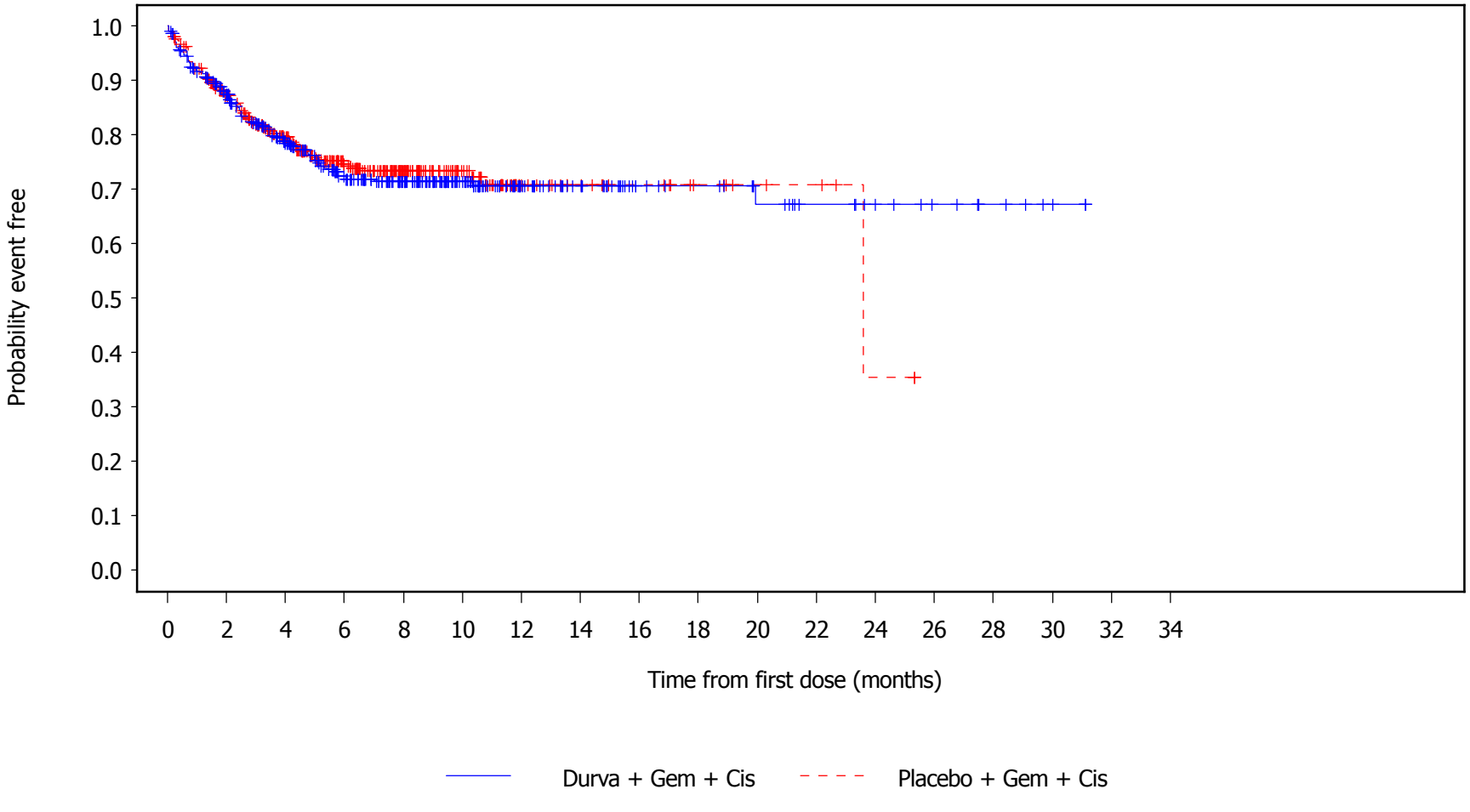
Figure 3.3.365 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Haematopoietic cytopenias SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	250	147	93	73	51	31	24	15	13	9	6	5	4	4	2	0	0	Durva + Gem + Cis
403	229	129	69	39	25	9	5	3	2	2	2	0	0	0	0	0	0	Placebo + Gem + Cis

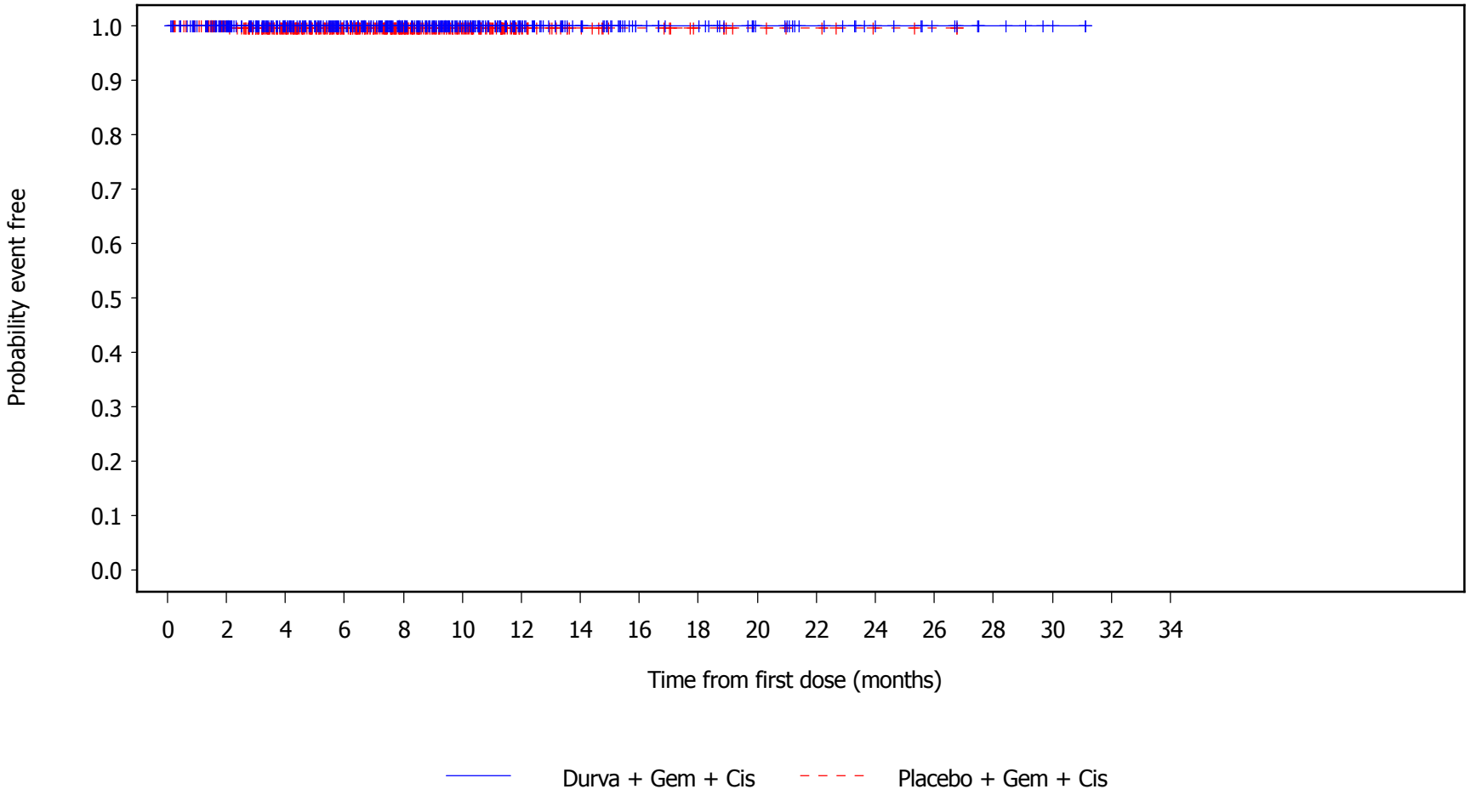
Figure 3.3.366 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Anaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	330	259	204	156	104	62	46	29	26	20	15	12	8	5	2	0	0	Durva + Gem + Cis
403	323	249	174	113	66	26	19	14	9	5	4	1	0	0	0	0	0	Placebo + Gem + Cis

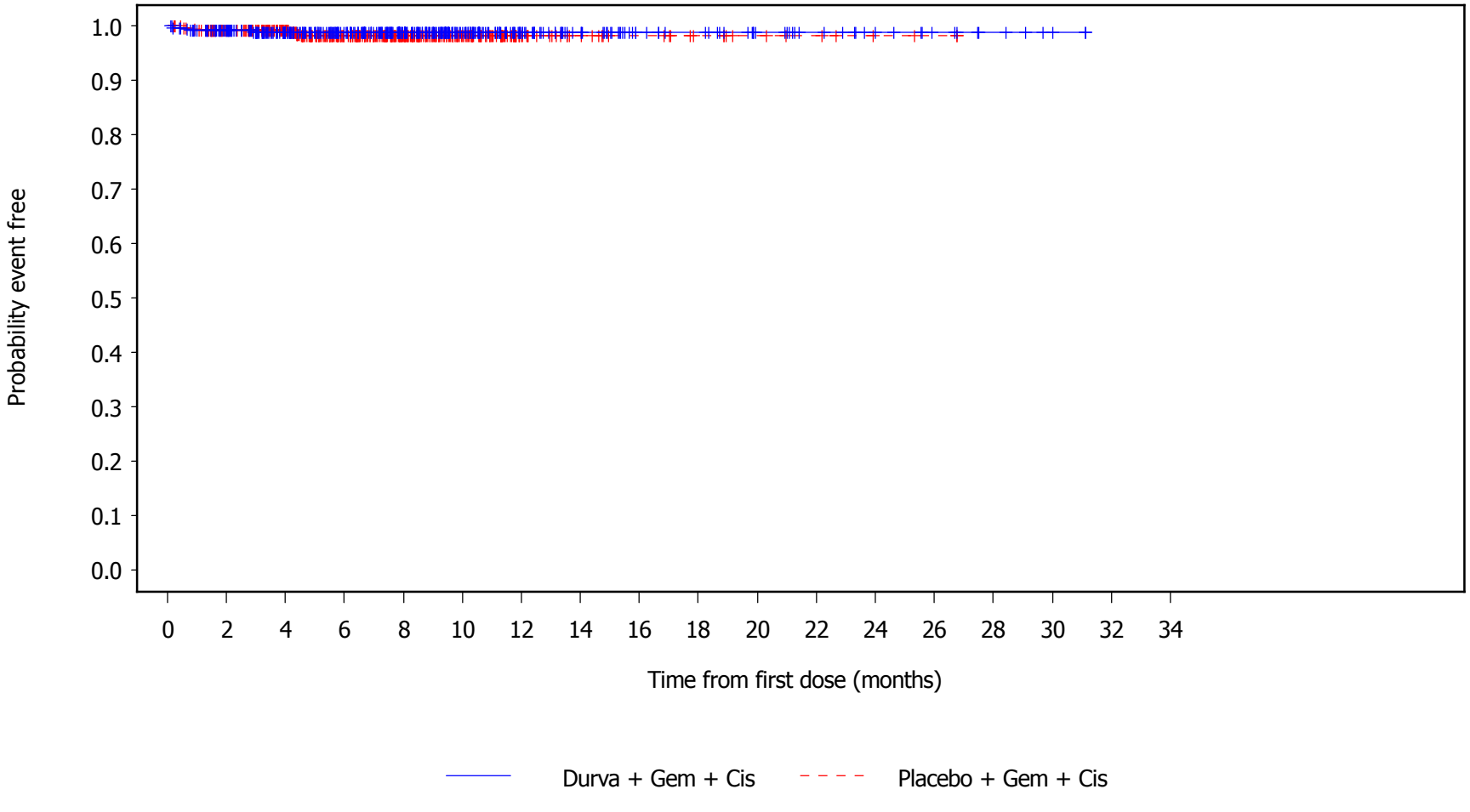
Figure 3.3.367 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Bicytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	231	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

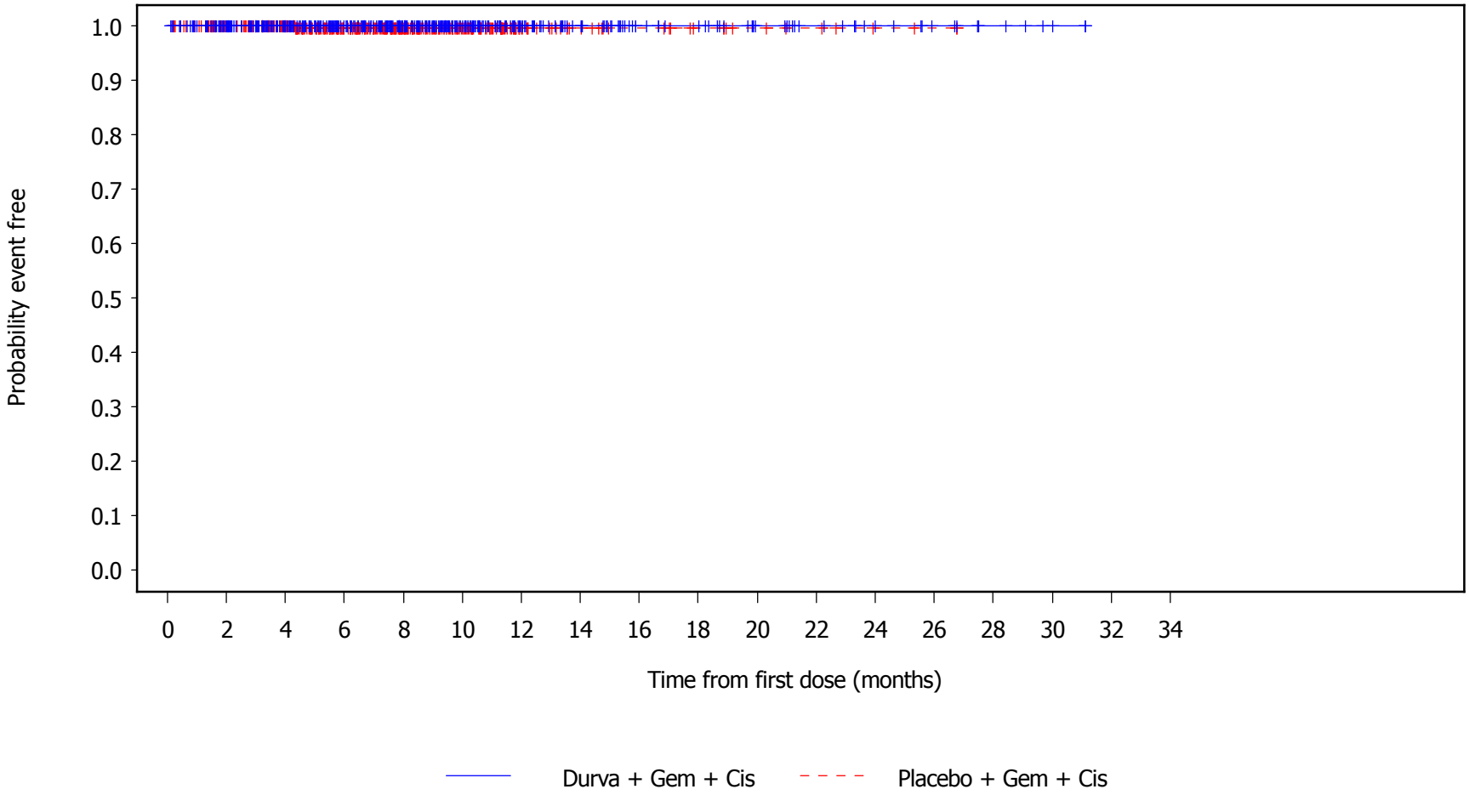
Figure 3.3.368 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Febrile neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	312	261	196	129	79	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	311	228	157	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

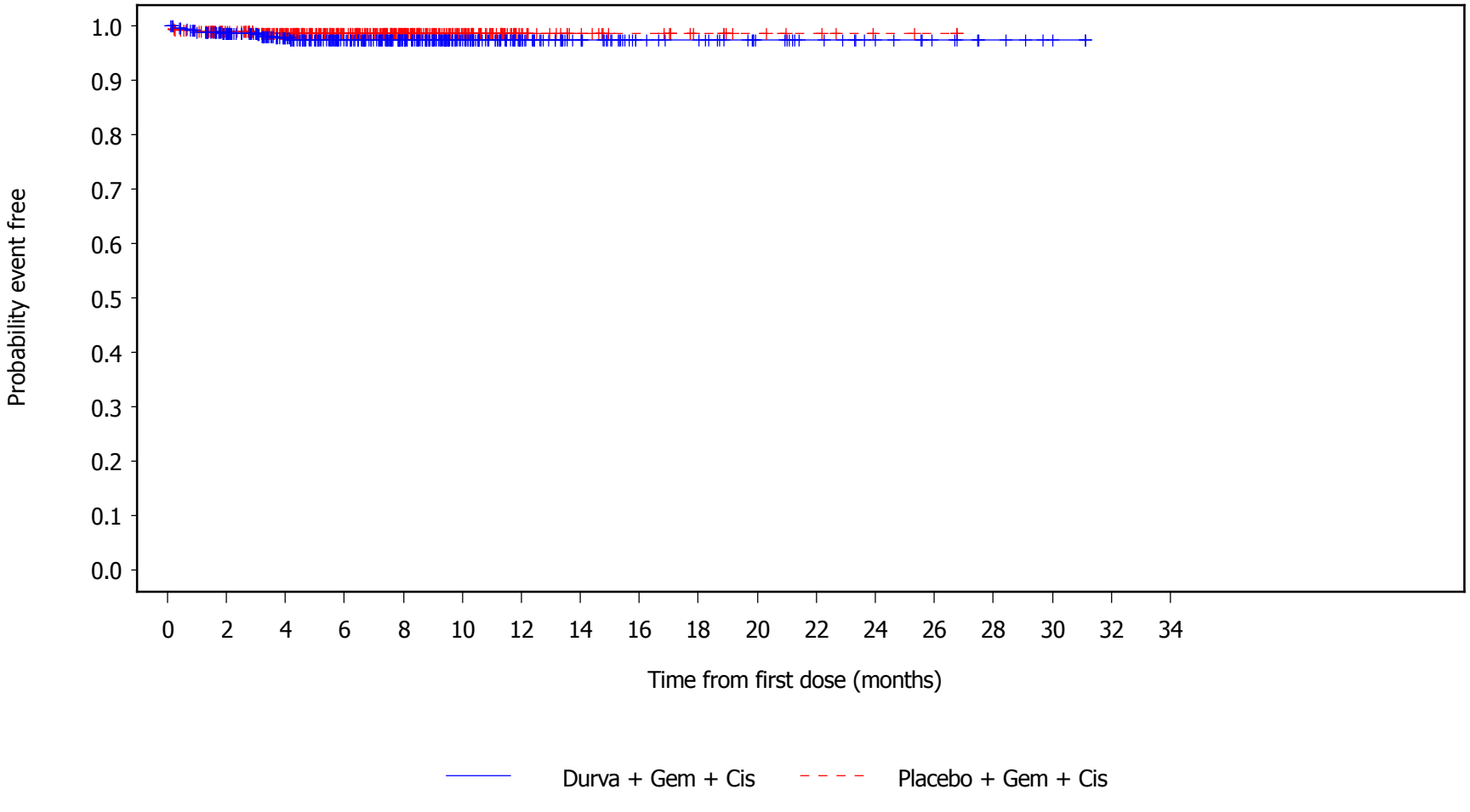
Figure 3.3.369 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Haemoglobin decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	231	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

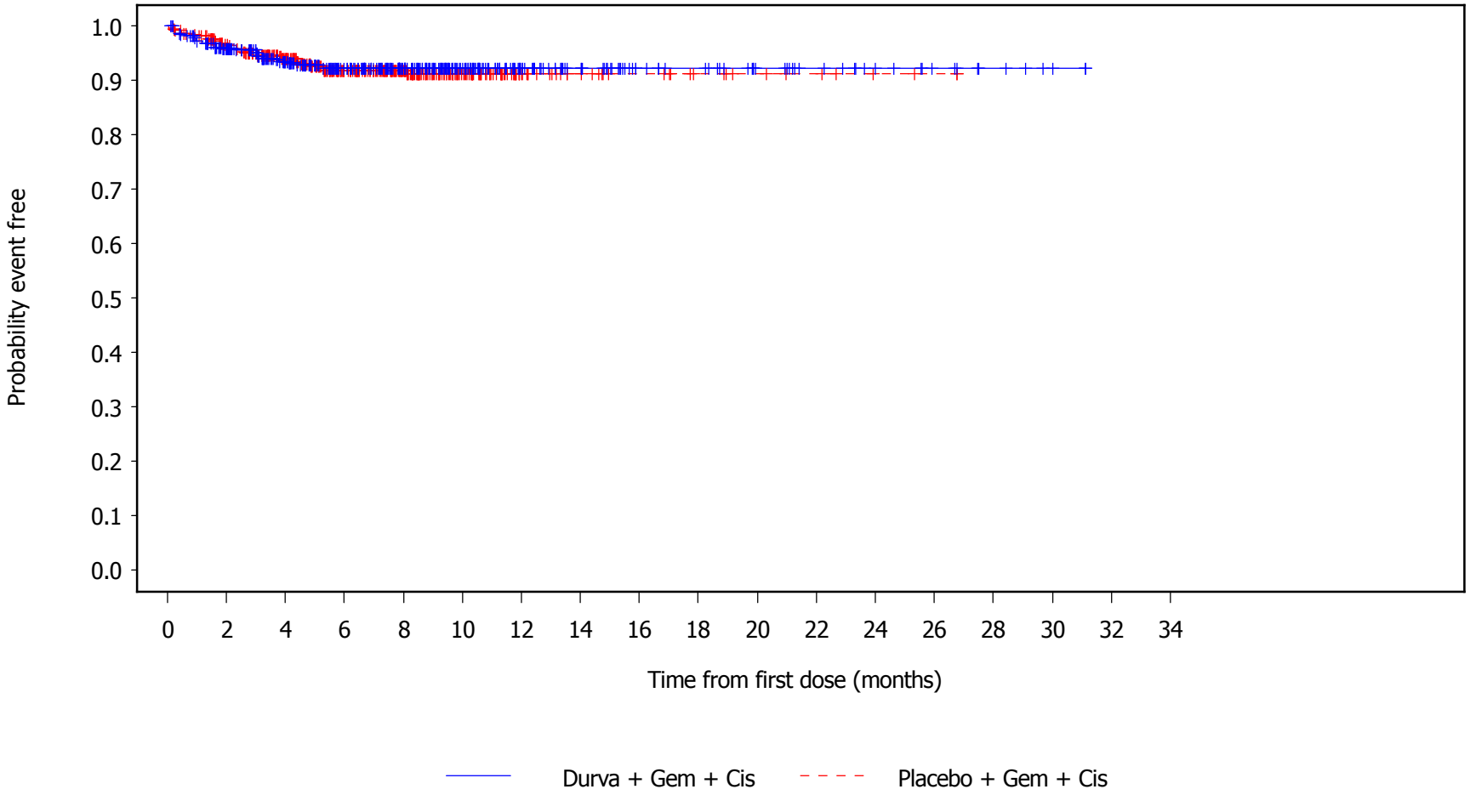
Figure 3.3.370 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Leukopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	368	308	256	192	126	79	57	39	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	309	228	155	87	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

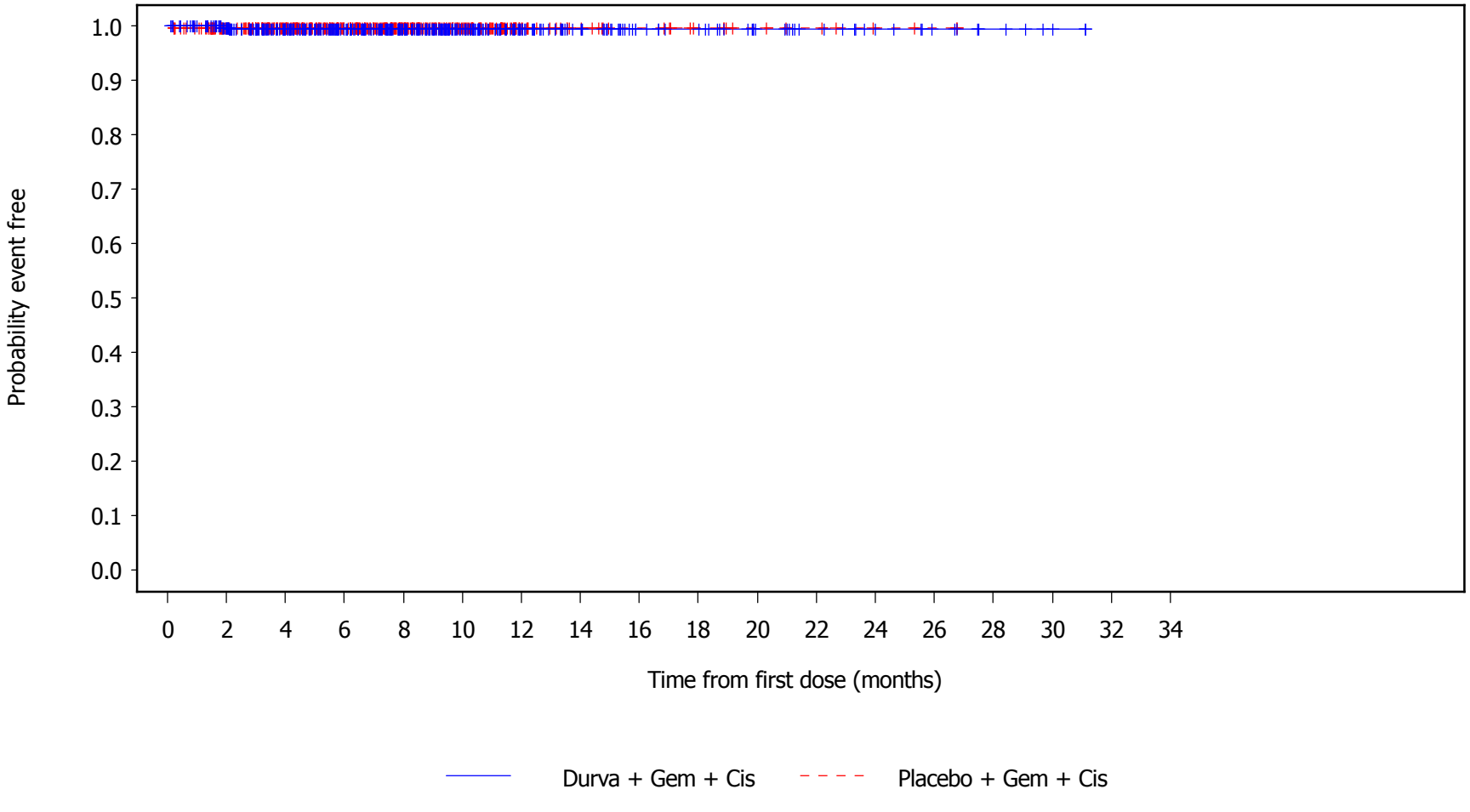
Figure 3.3.371 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: White blood cell count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	357	294	245	185	124	77	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	358	291	208	145	80	32	21	15	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

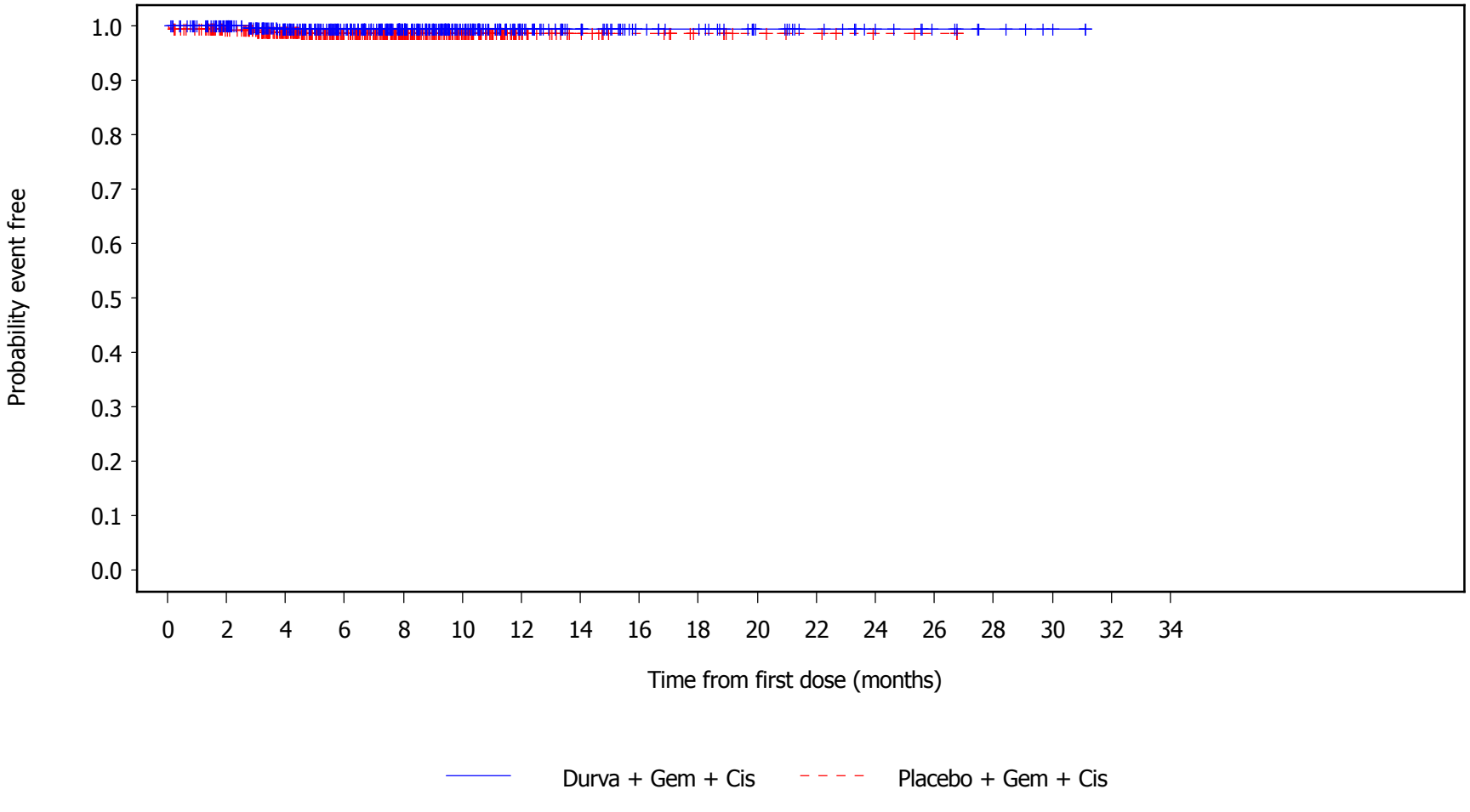
Figure 3.3.372 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Lymphopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	263	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

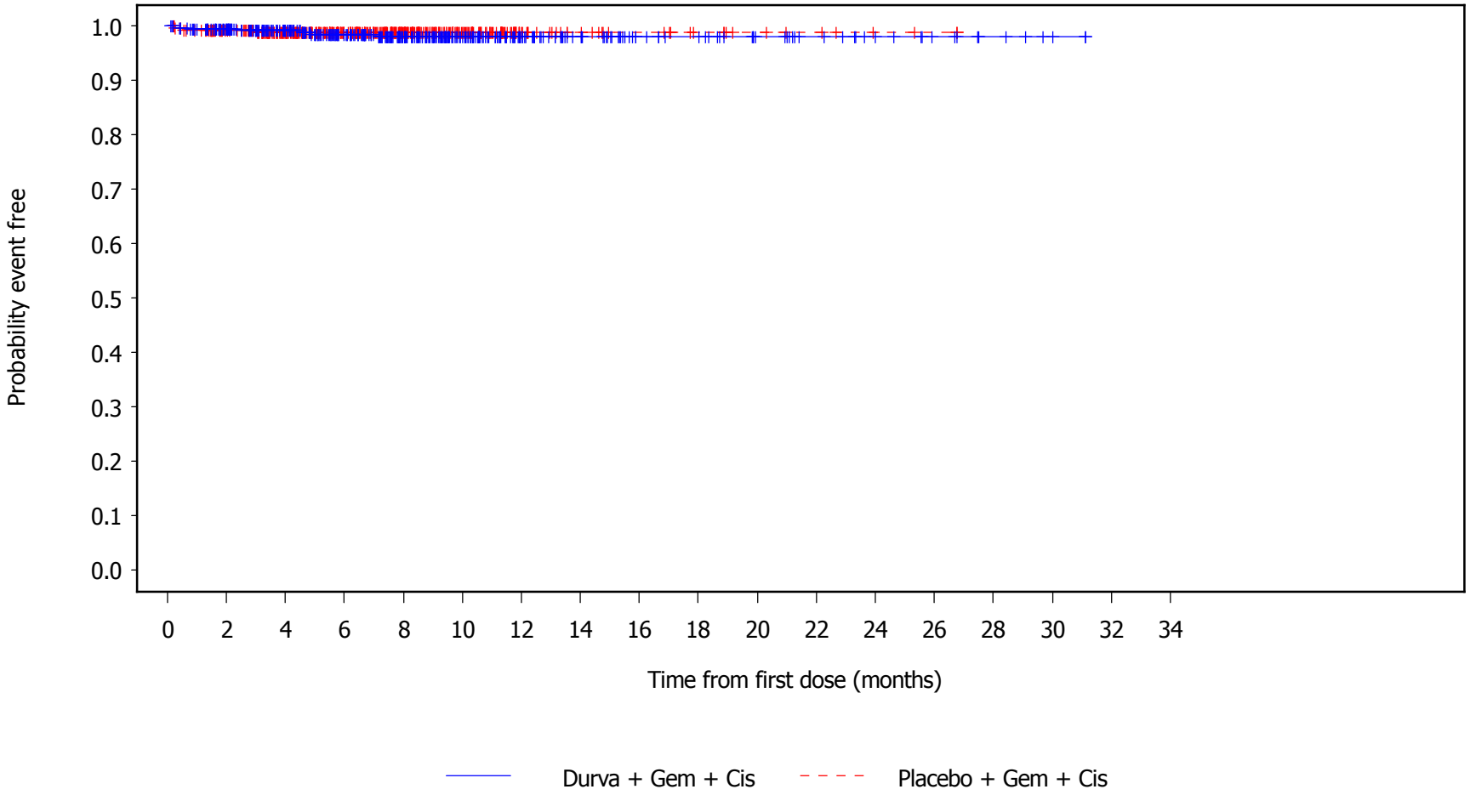
Figure 3.3.373 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Lymphocyte count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	197	130	79	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	311	230	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

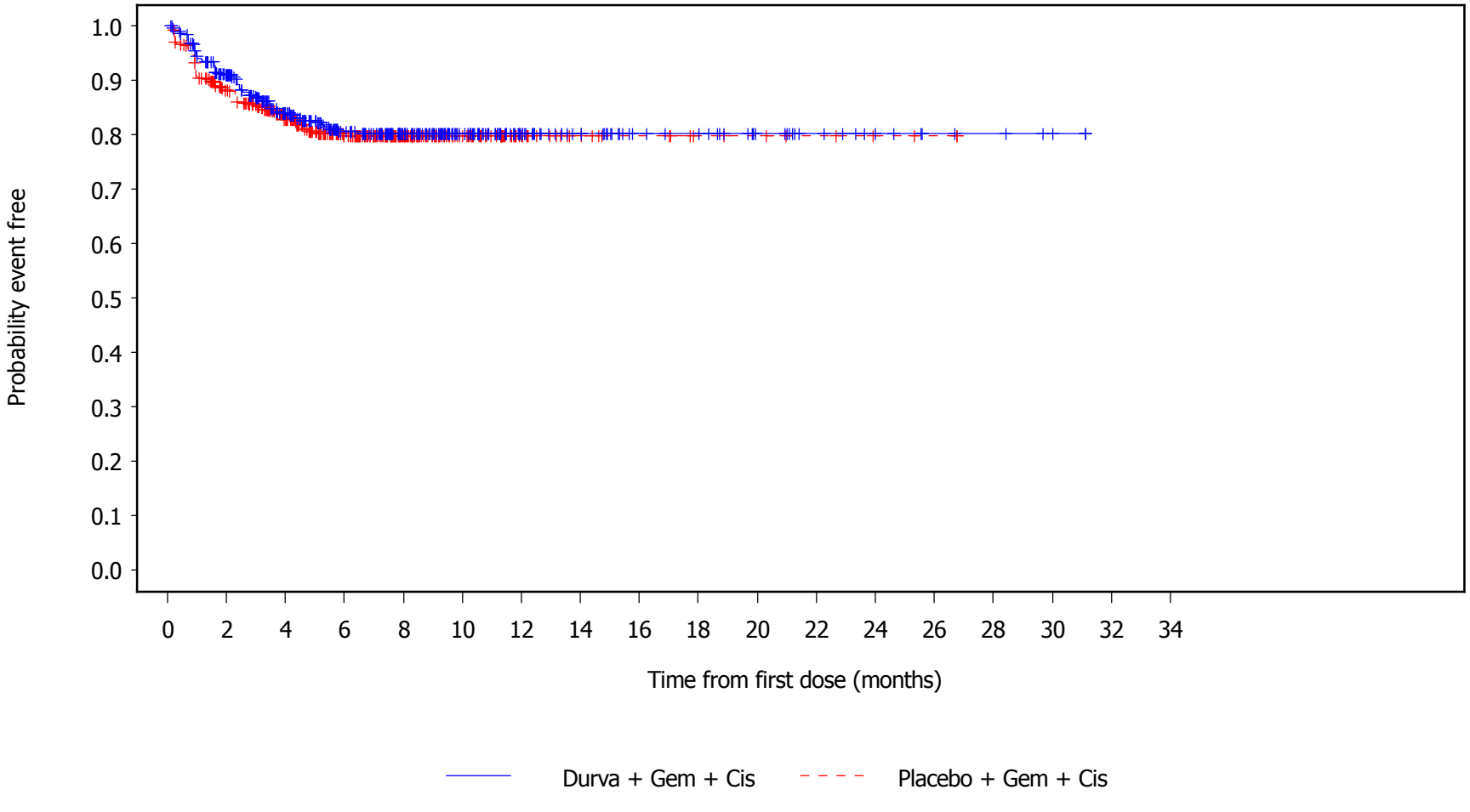
Figure 3.3.374 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Myelosuppression
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	312	260	195	129	79	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	310	229	157	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

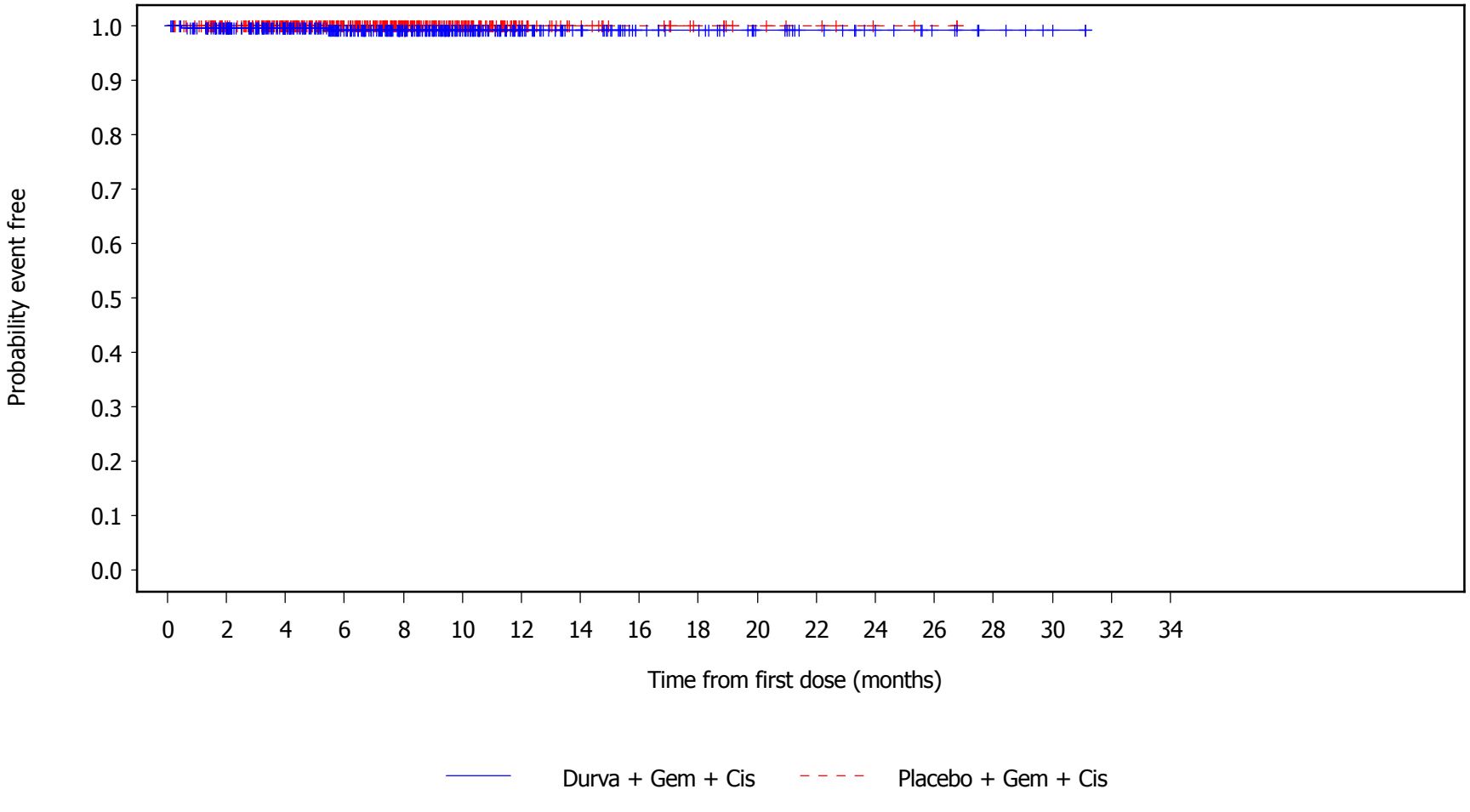
Figure 3.3.375 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	339	258	201	148	97	59	43	30	28	19	13	9	5	4	2	0	0	Durva + Gem + Cis
403	327	254	179	115	60	25	15	11	7	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

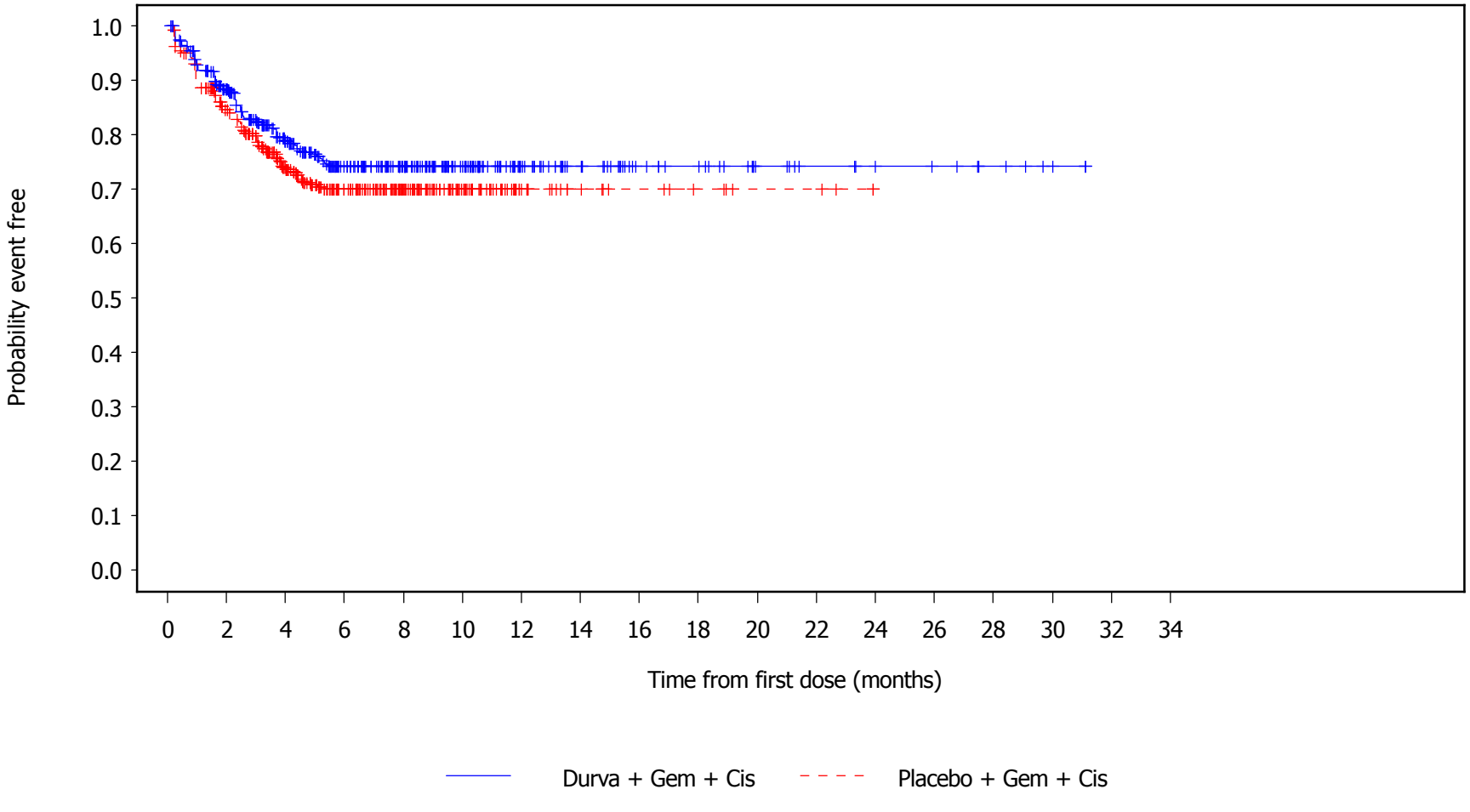
Figure 3.3.376 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Neutropenic sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	263	197	130	79	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

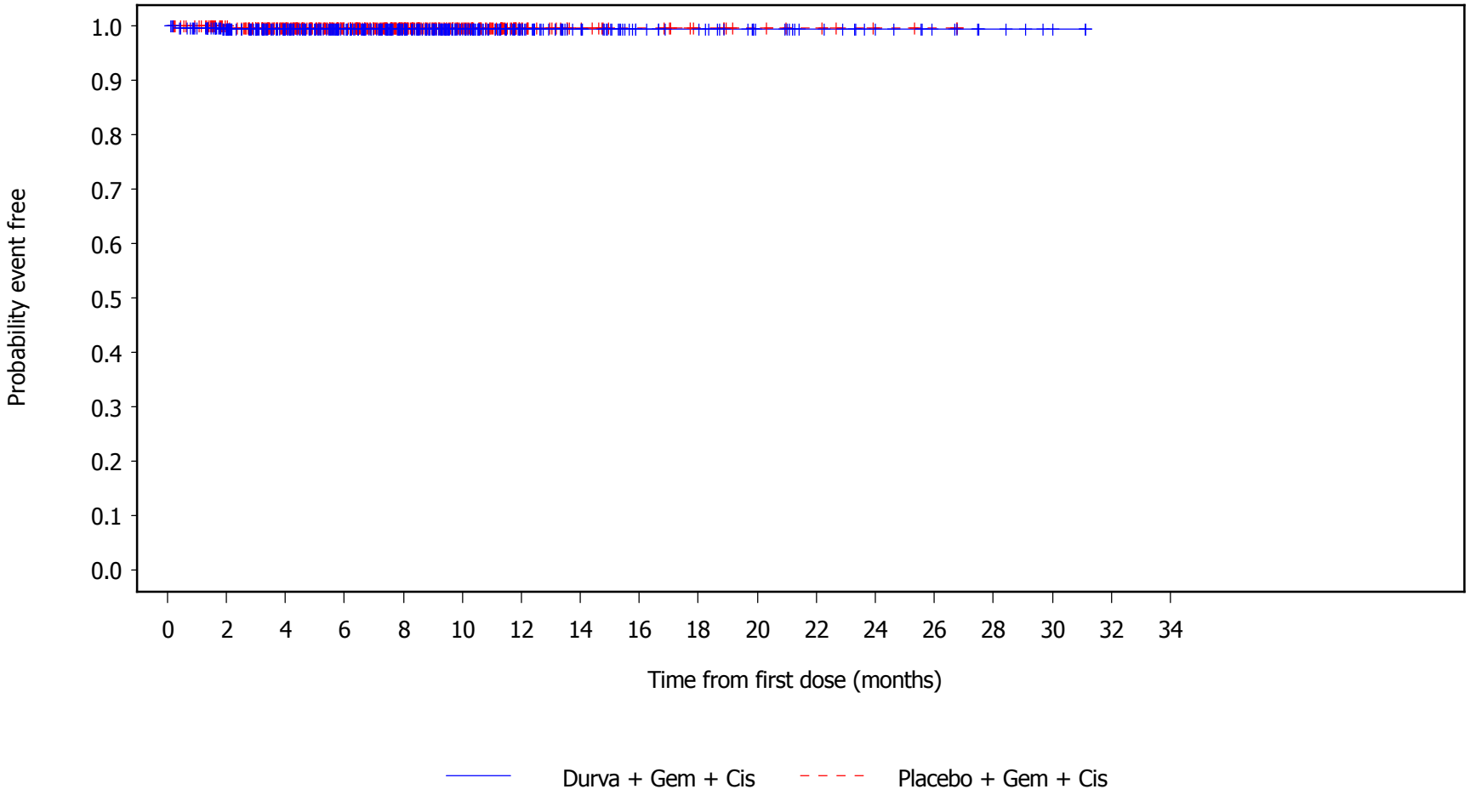
Figure 3.3.377 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Neutrophil count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	328	245	187	145	102	61	44	30	26	16	12	10	8	5	2	0	0	Durva + Gem + Cis
403	314	223	152	103	60	22	13	9	6	3	3	0	0	0	0	0	0	Placebo + Gem + Cis

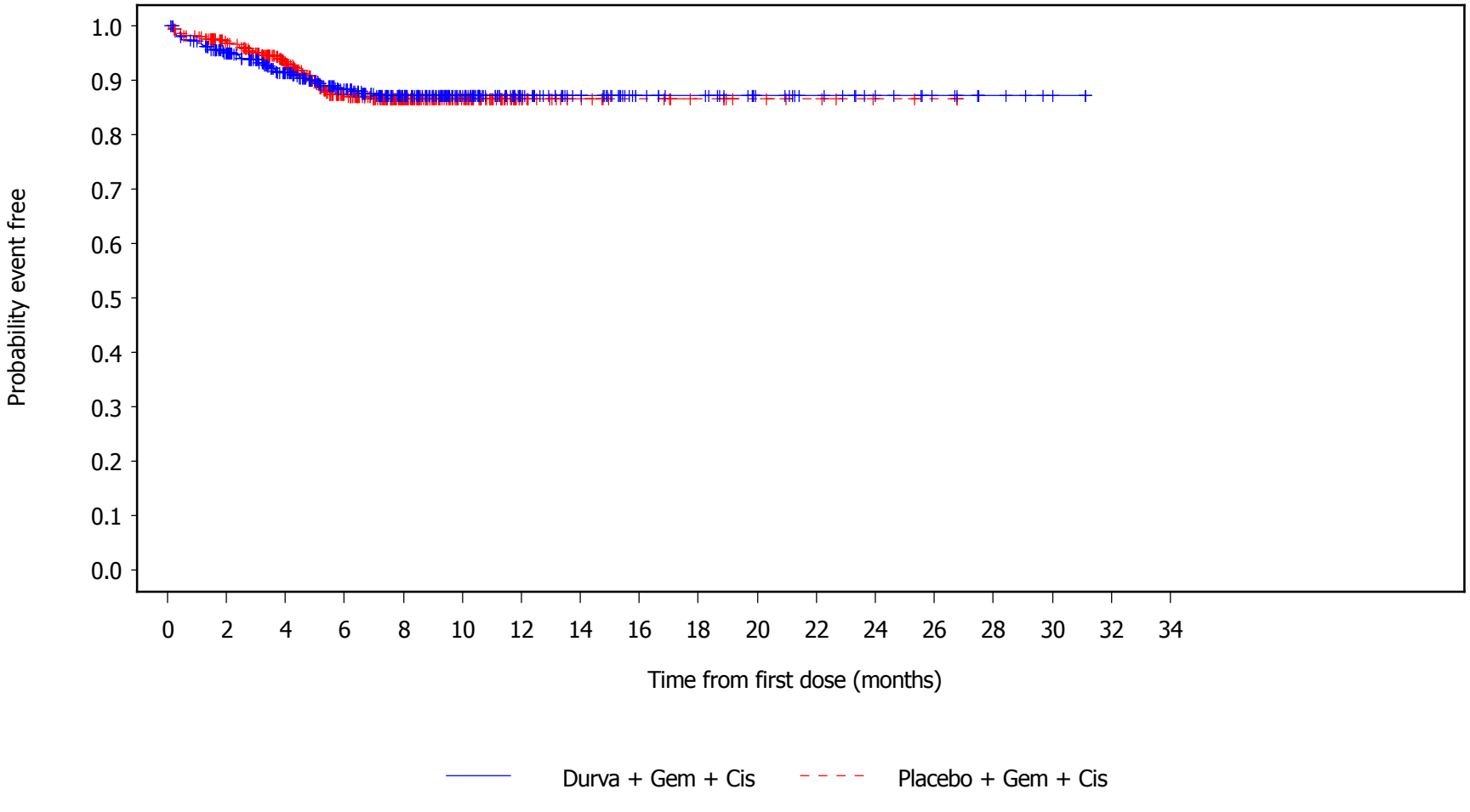
Figure 3.3.378 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Pancytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

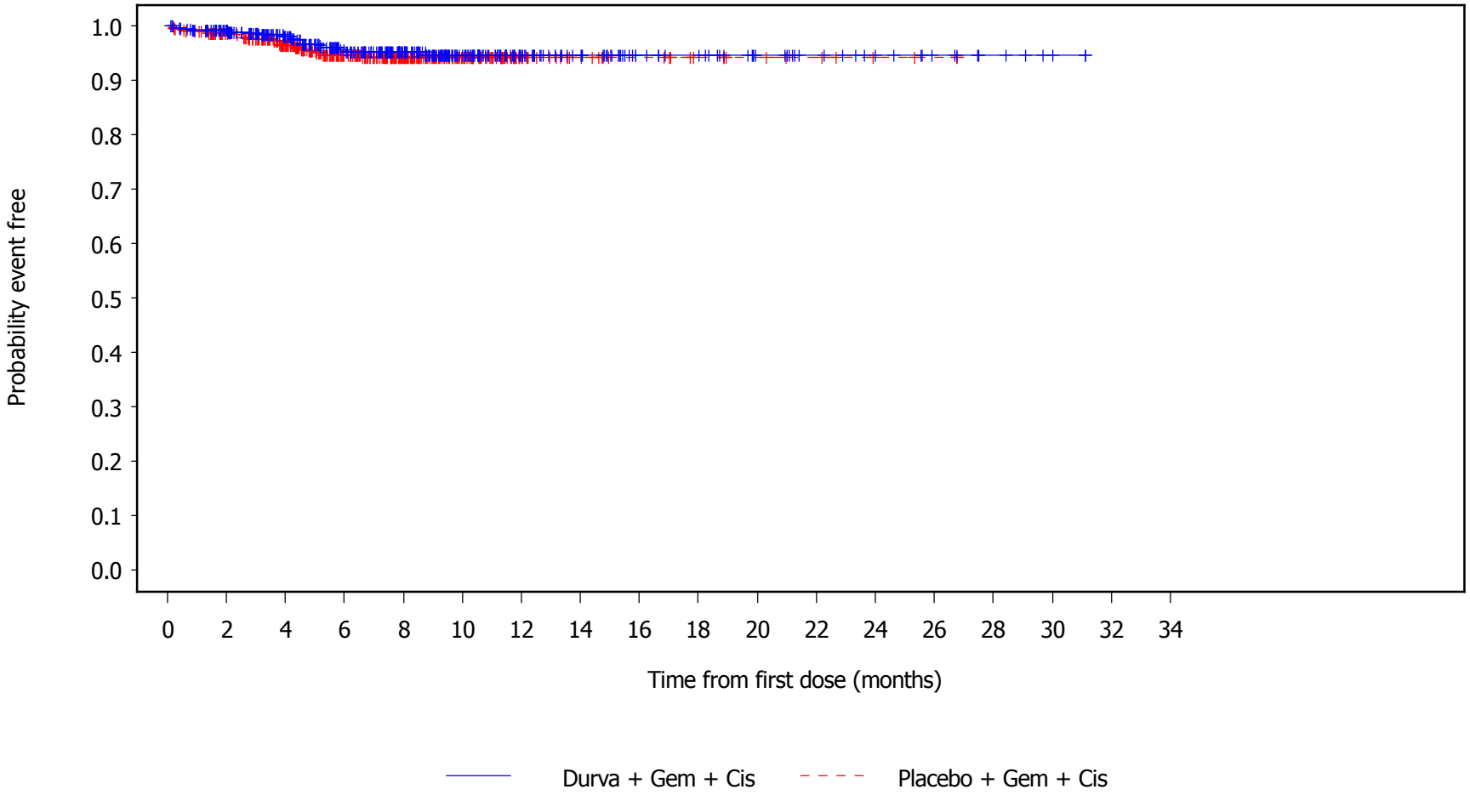
Figure 3.3.379 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Platelet count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	359	295	241	182	120	73	55	38	34	24	19	14	9	5	2	0	0	Durva + Gem + Cis
403	362	295	206	142	80	31	20	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

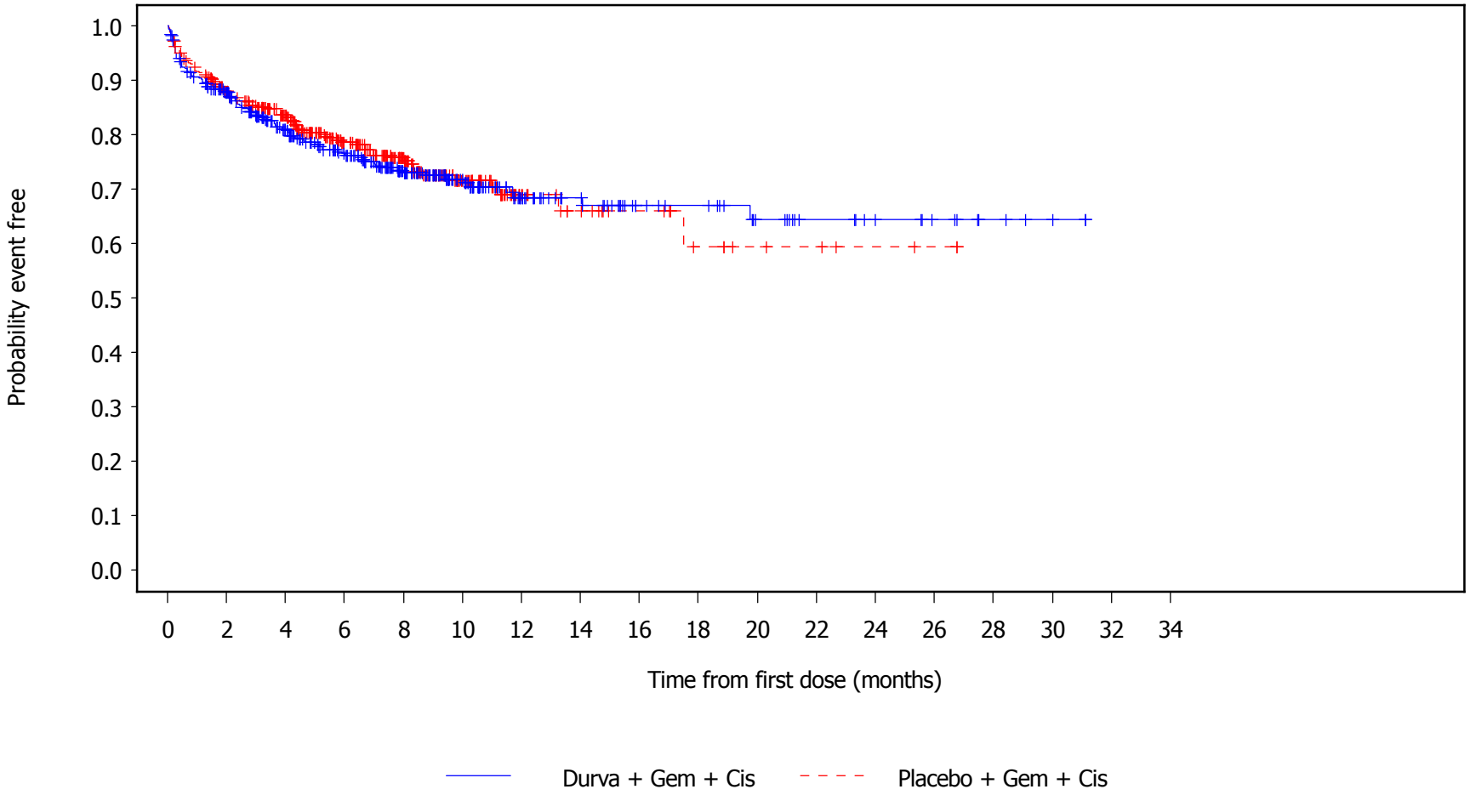
Figure 3.3.380 TOPAZ: Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Thrombocytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	310	253	190	125	77	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	368	305	220	150	84	32	21	15	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

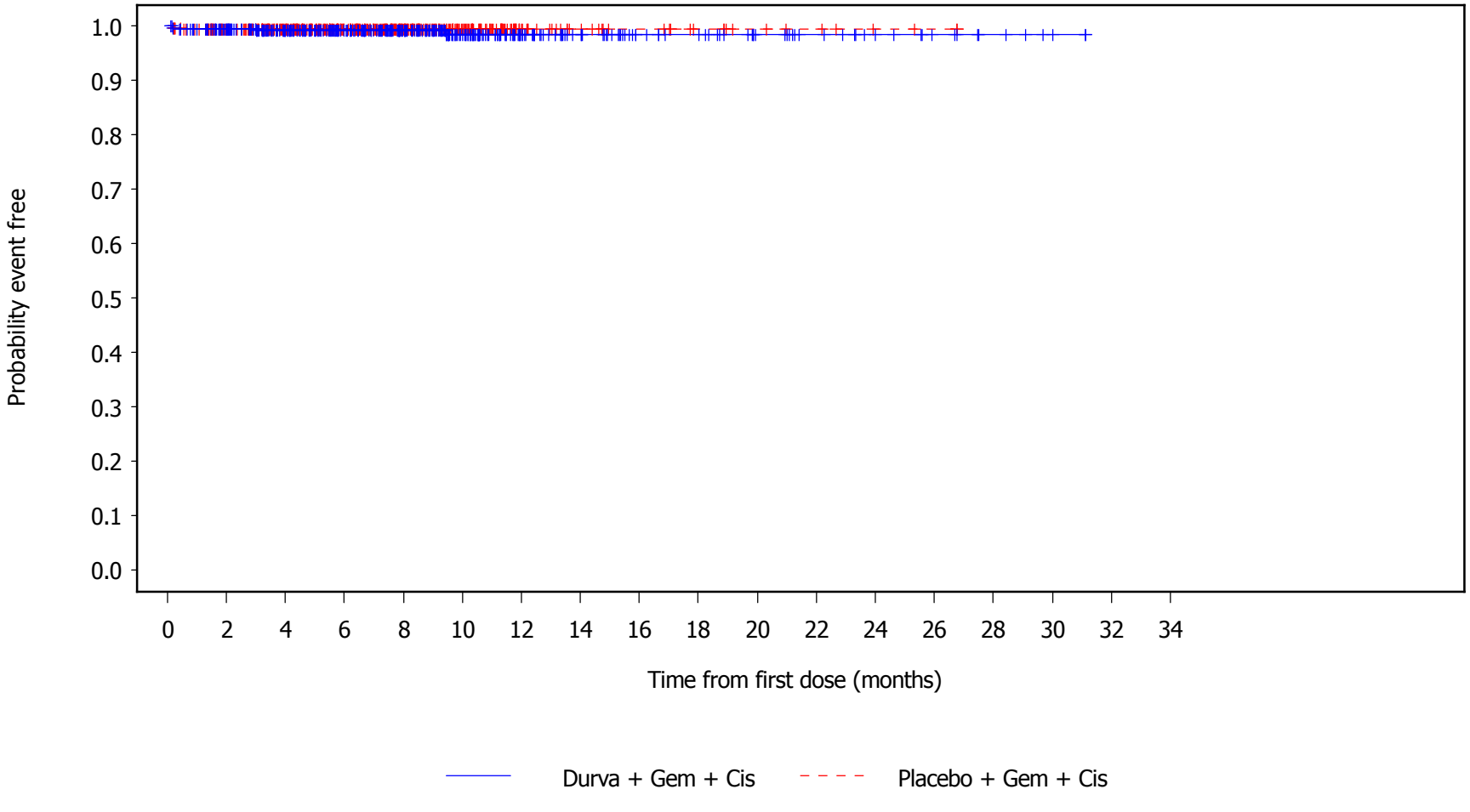
Figure 3.3.381 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	331	266	220	160	105	62	47	32	29	21	15	12	8	4	2	0	0	Durva + Gem + Cis
403	331	273	192	131	74	27	19	13	8	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

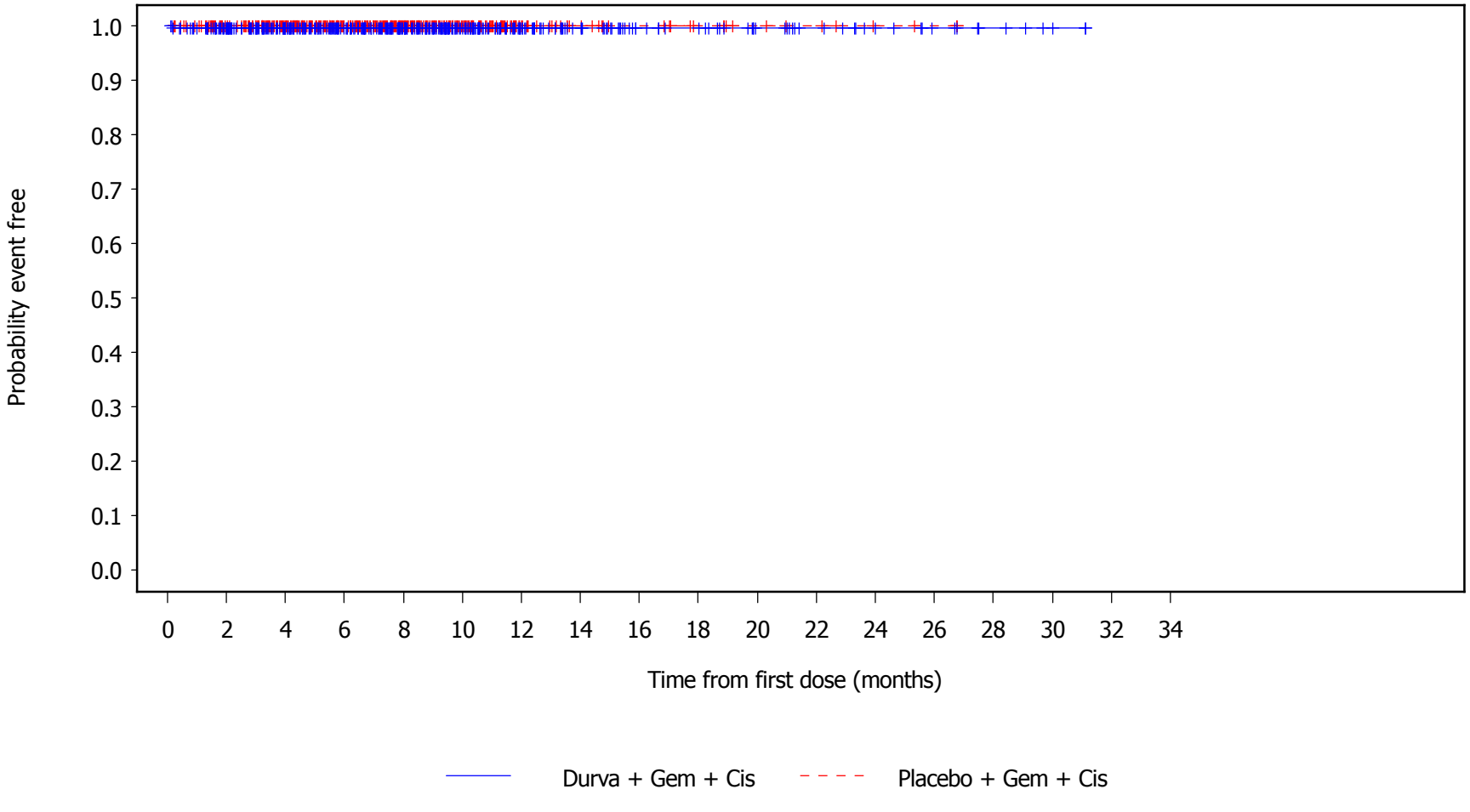
Figure 3.3.382 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI GT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	197	129	79	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

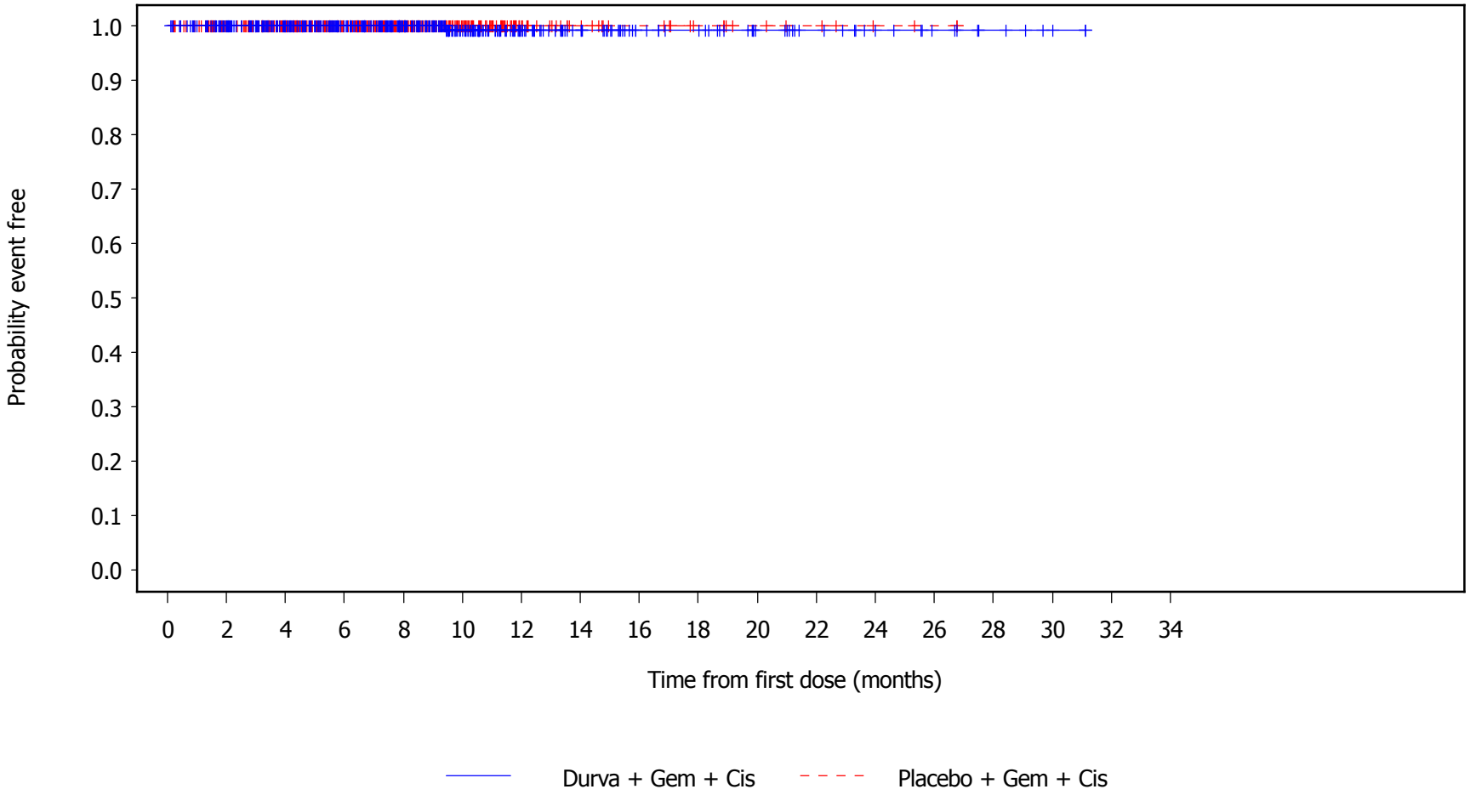
Figure 3.3.383 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Immune-mediated lung disease
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

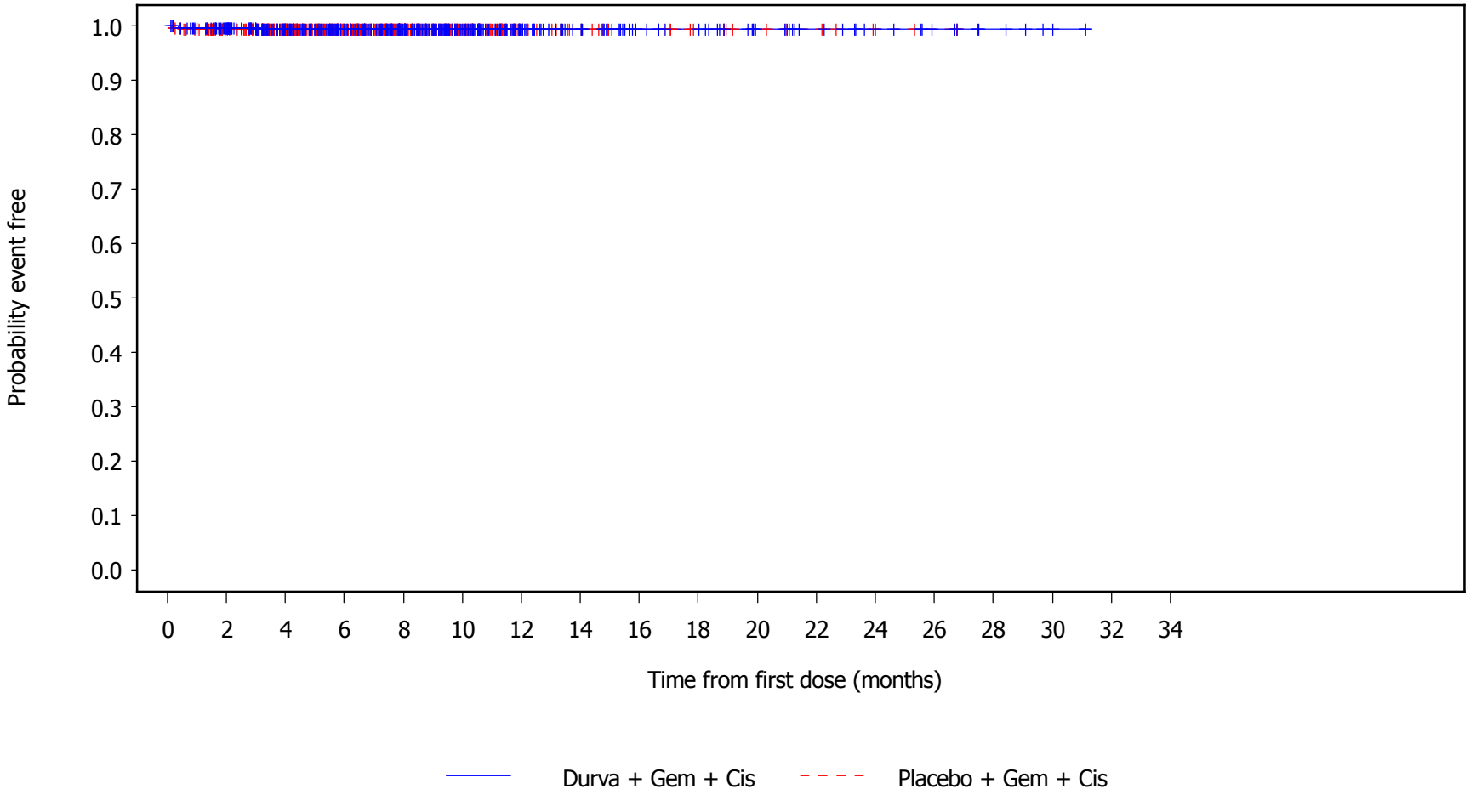
Figure 3.3.384 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Interstitial lung disease
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

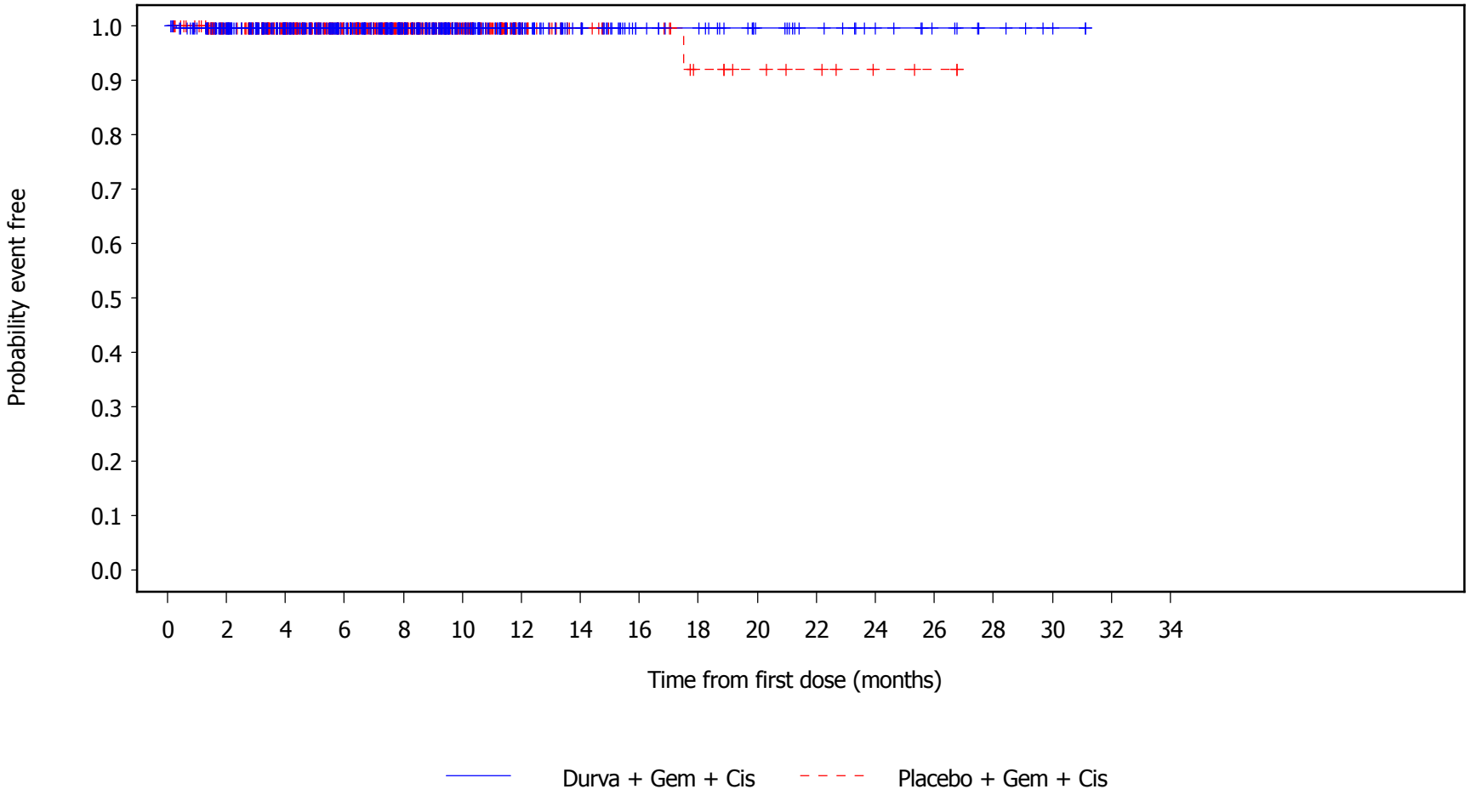
Figure 3.3.385 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	197	130	79	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

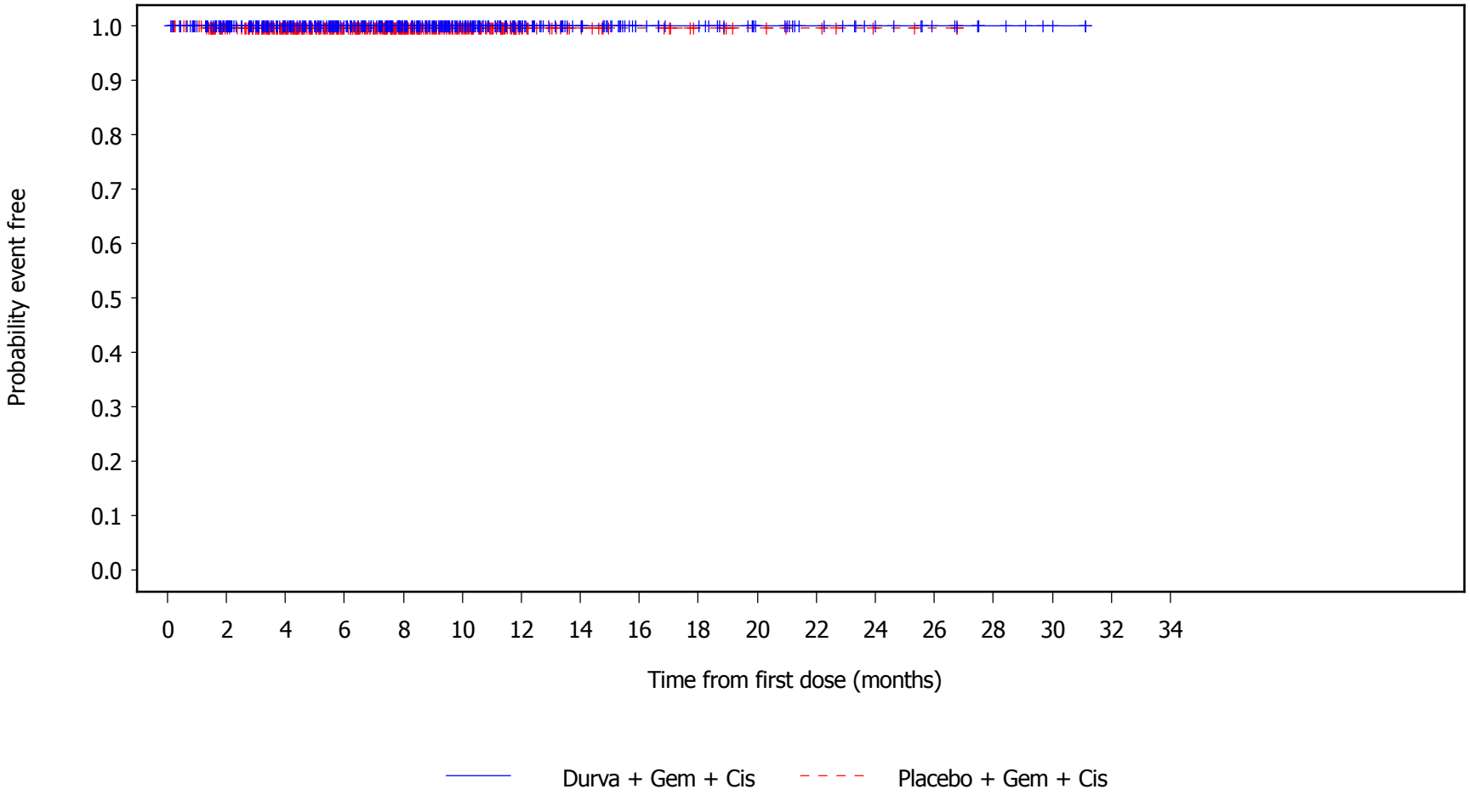
Figure 3.3.386 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI GT: Hepatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	313	232	159	89	34	22	16	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

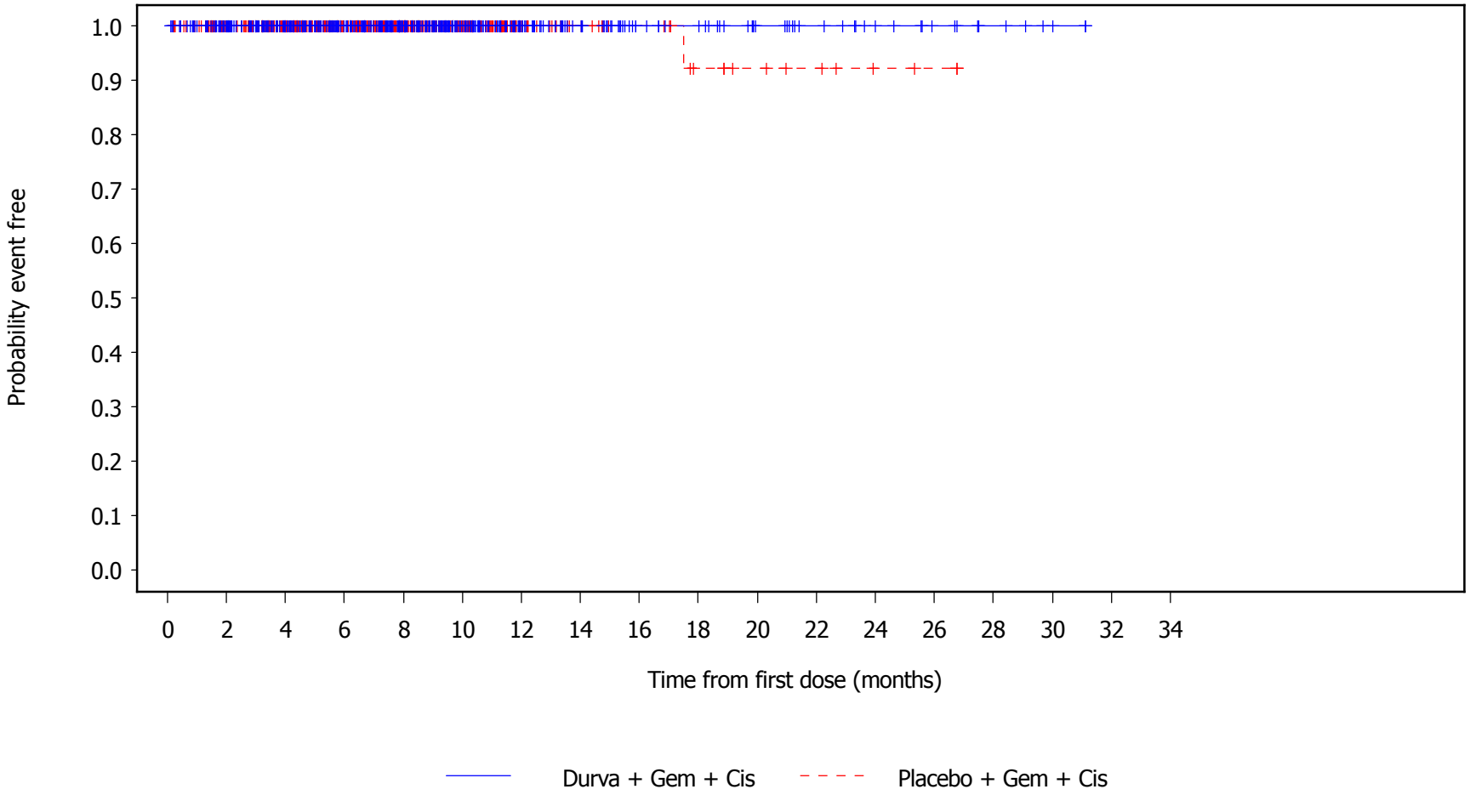
Figure 3.3.387 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

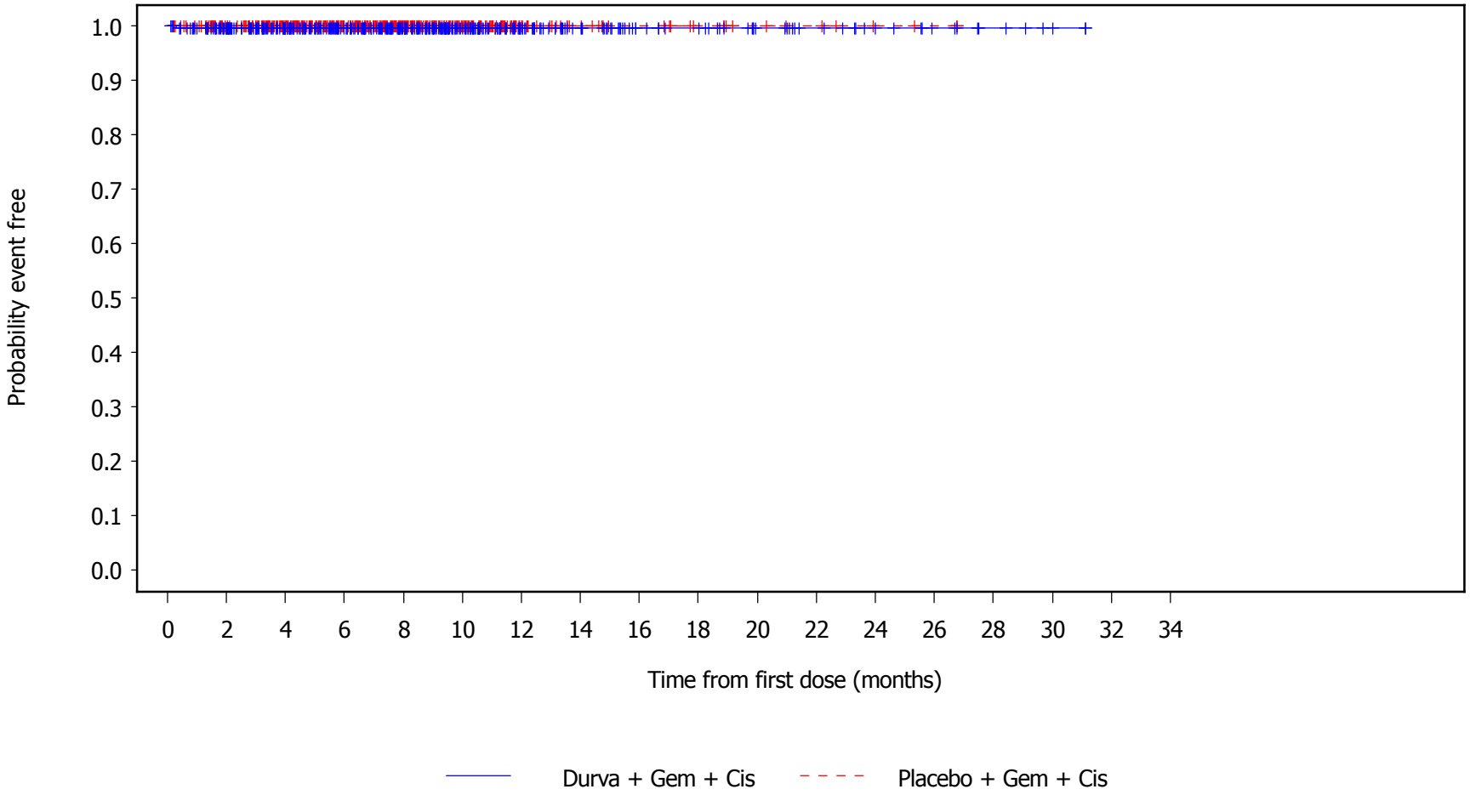
Figure 3.3.388 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

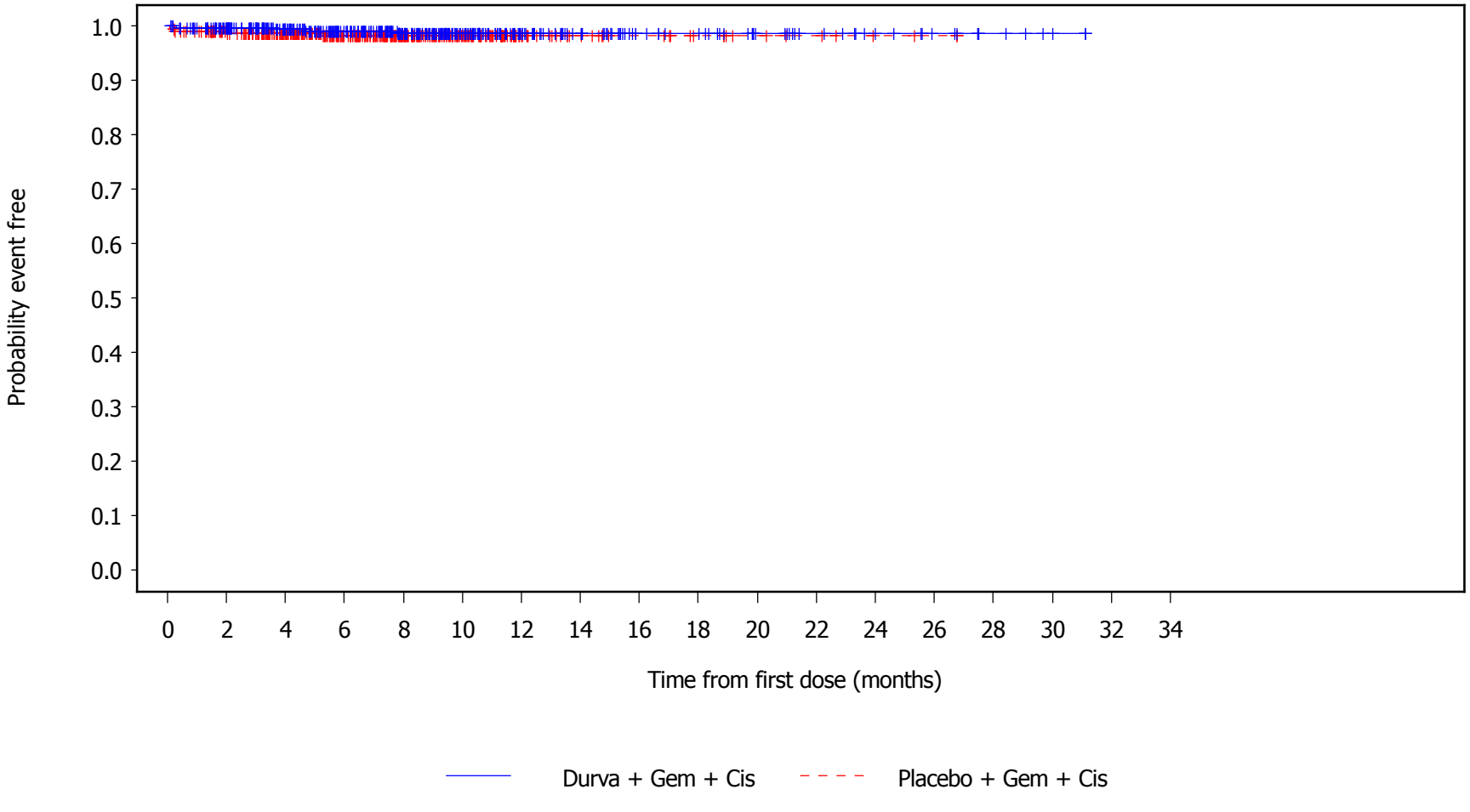
Figure 3.3.389 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

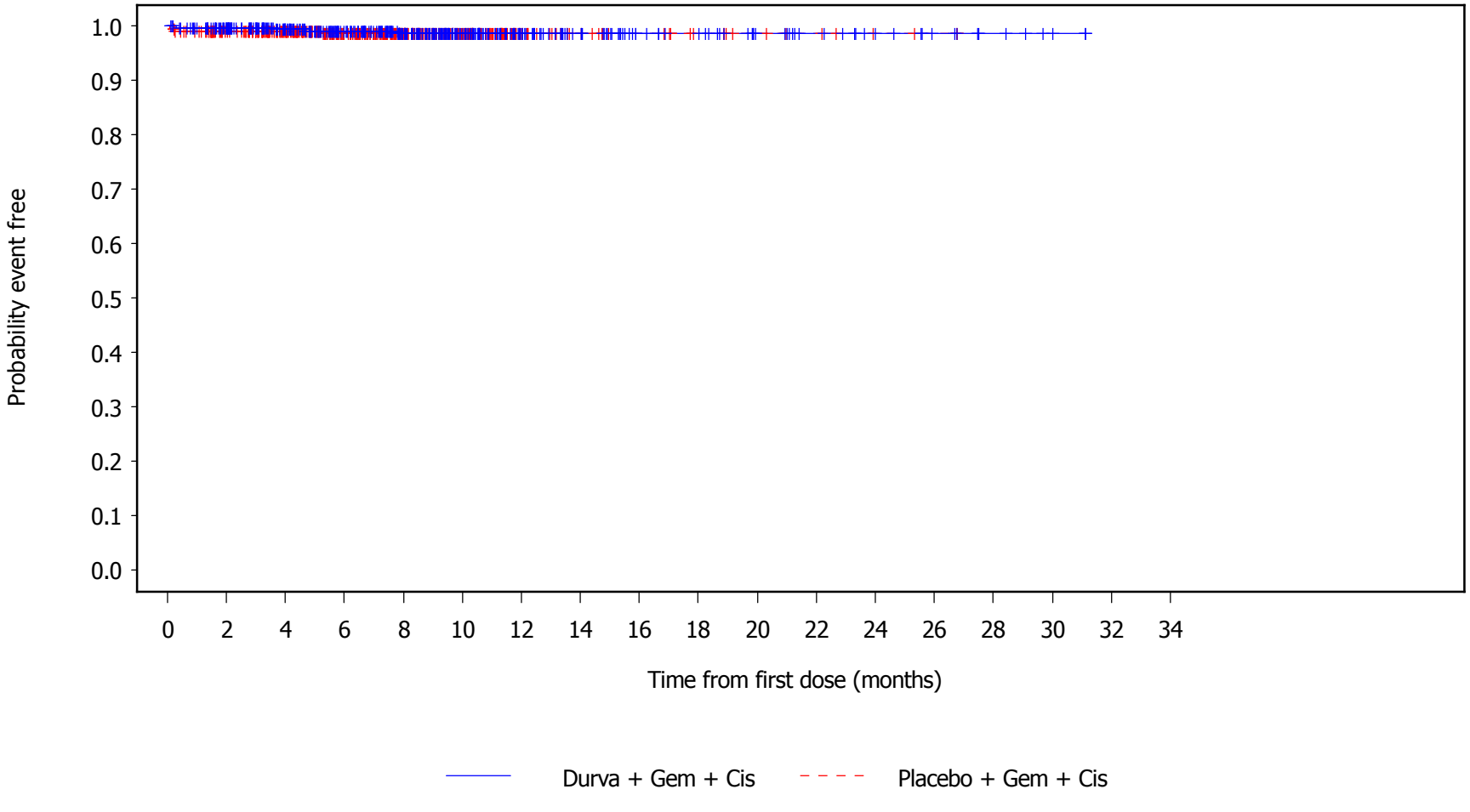
Figure 3.3.390 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI GT: Diarrhoea/Colitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	313	261	195	129	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	367	309	228	155	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

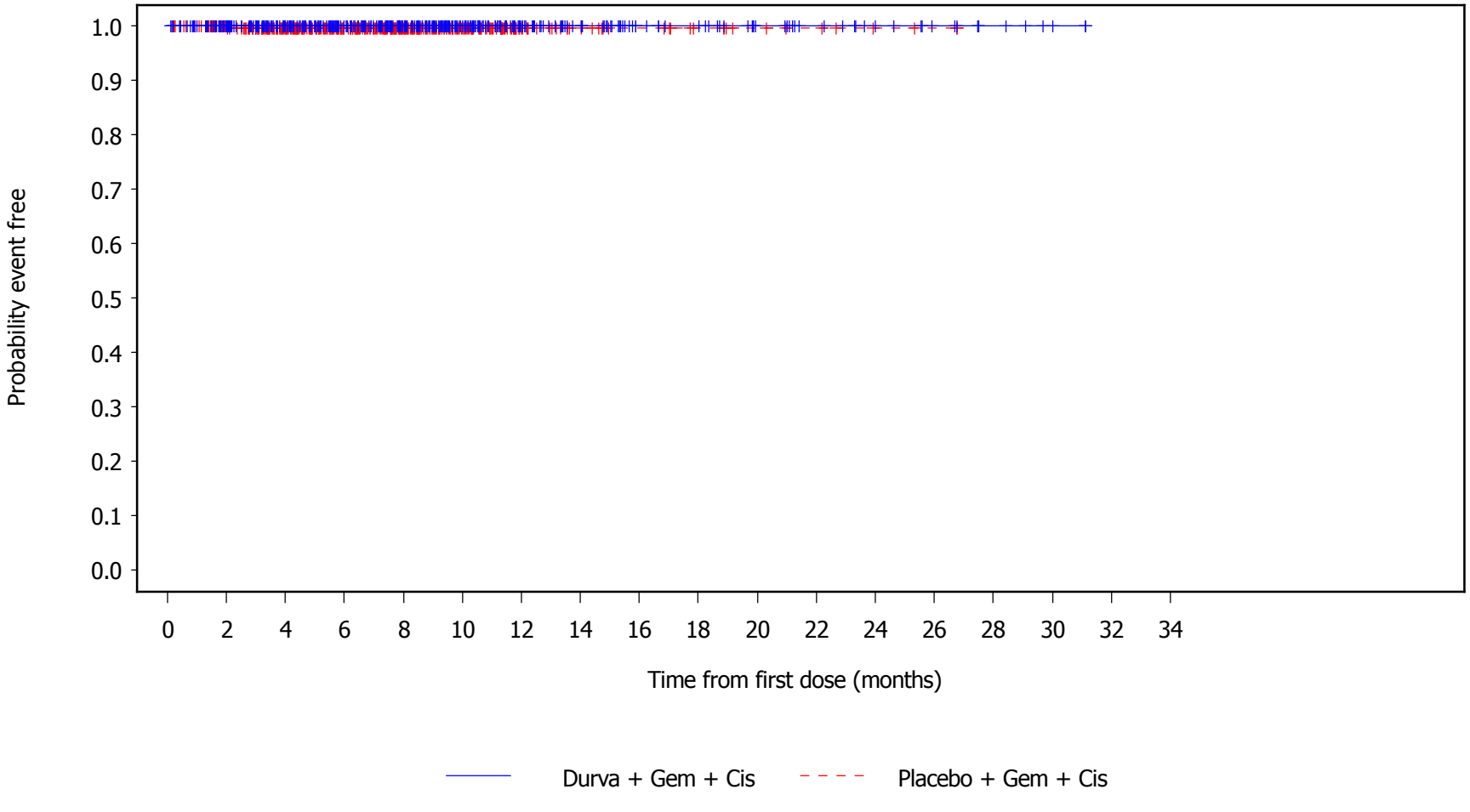
Figure 3.3.391 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Diarrhoea
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	313	261	195	129	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	367	310	228	155	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

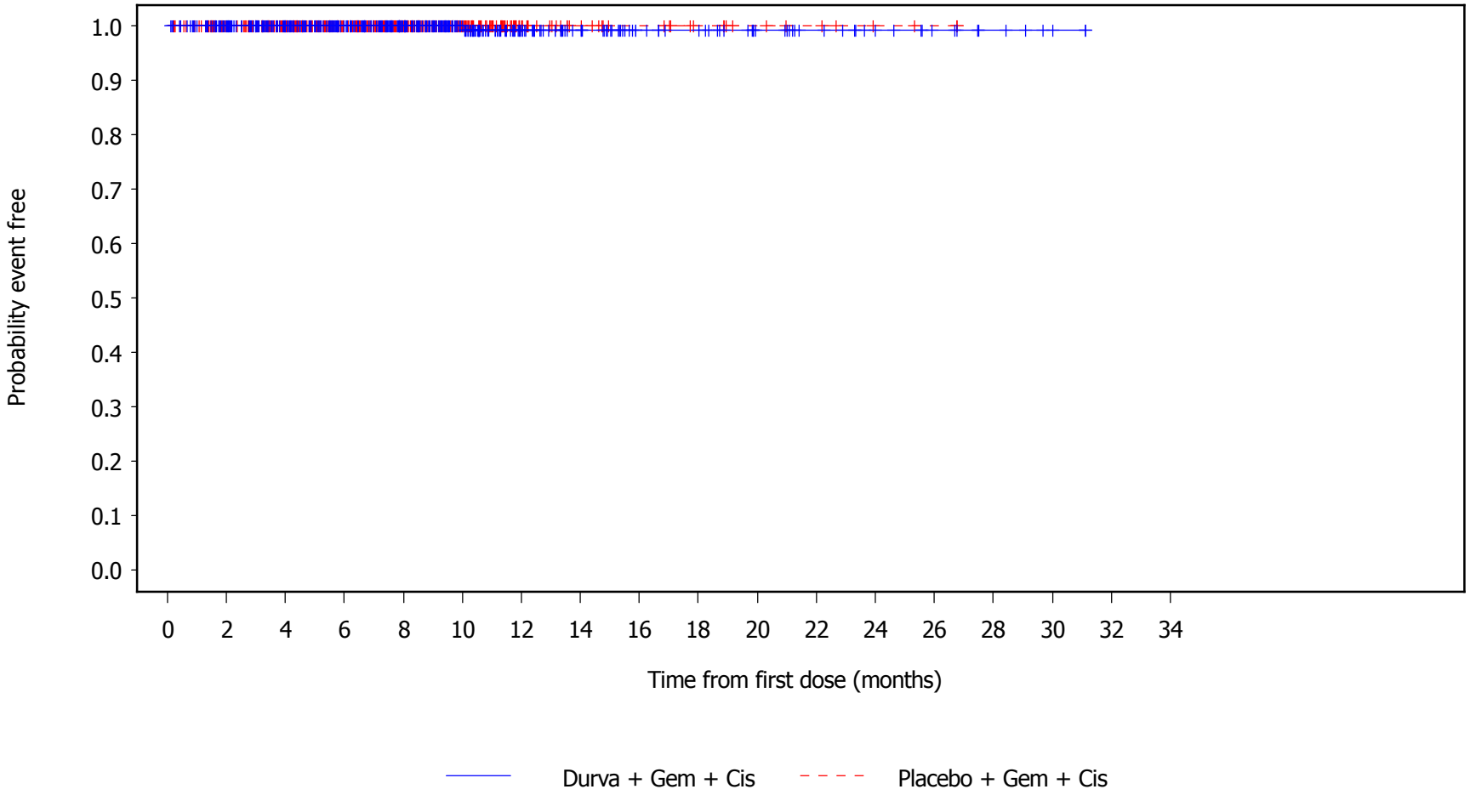
Figure 3.3.392 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Immune-mediated enterocolitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

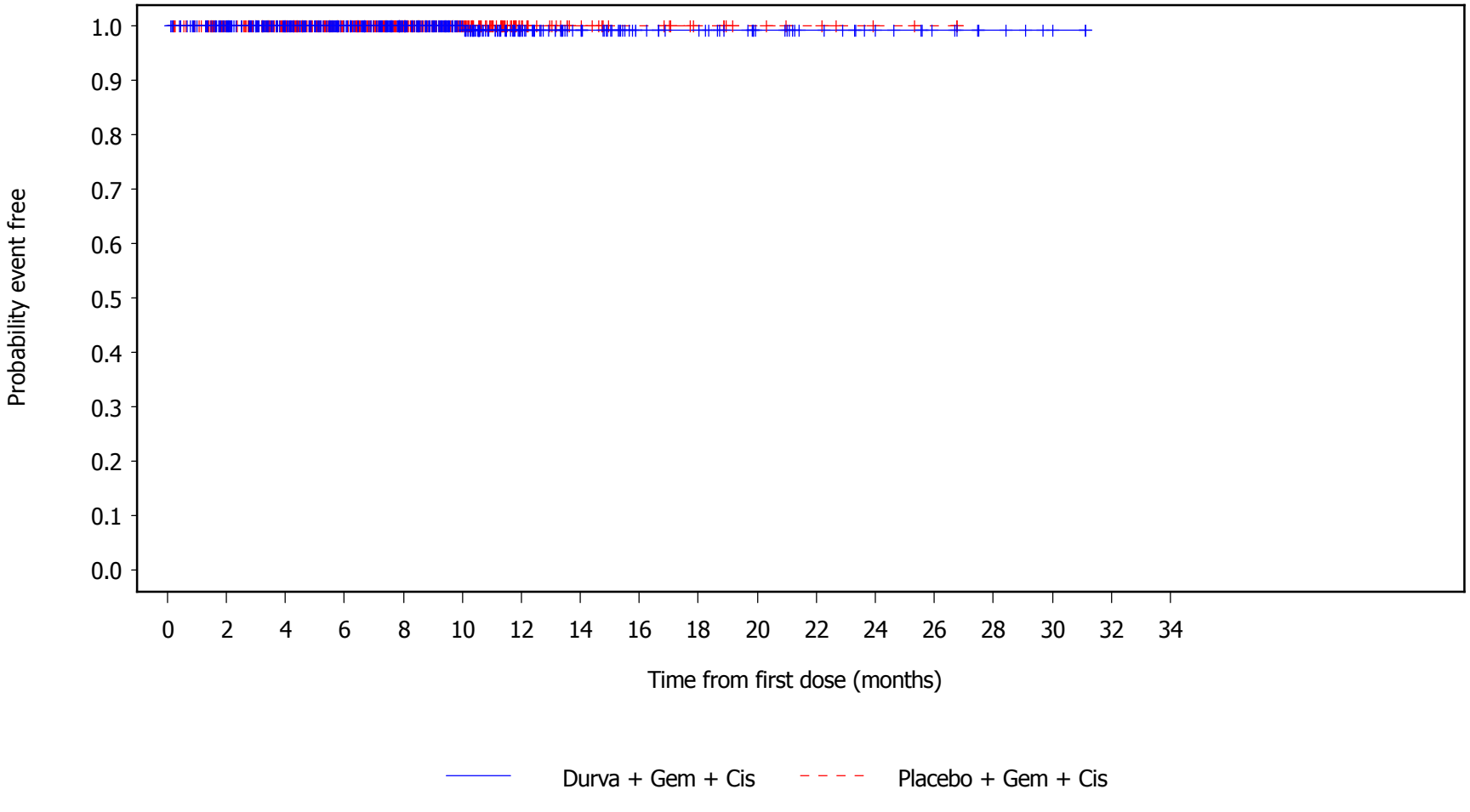
Figure 3.3.393 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI GT: Adrenal insufficiency
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

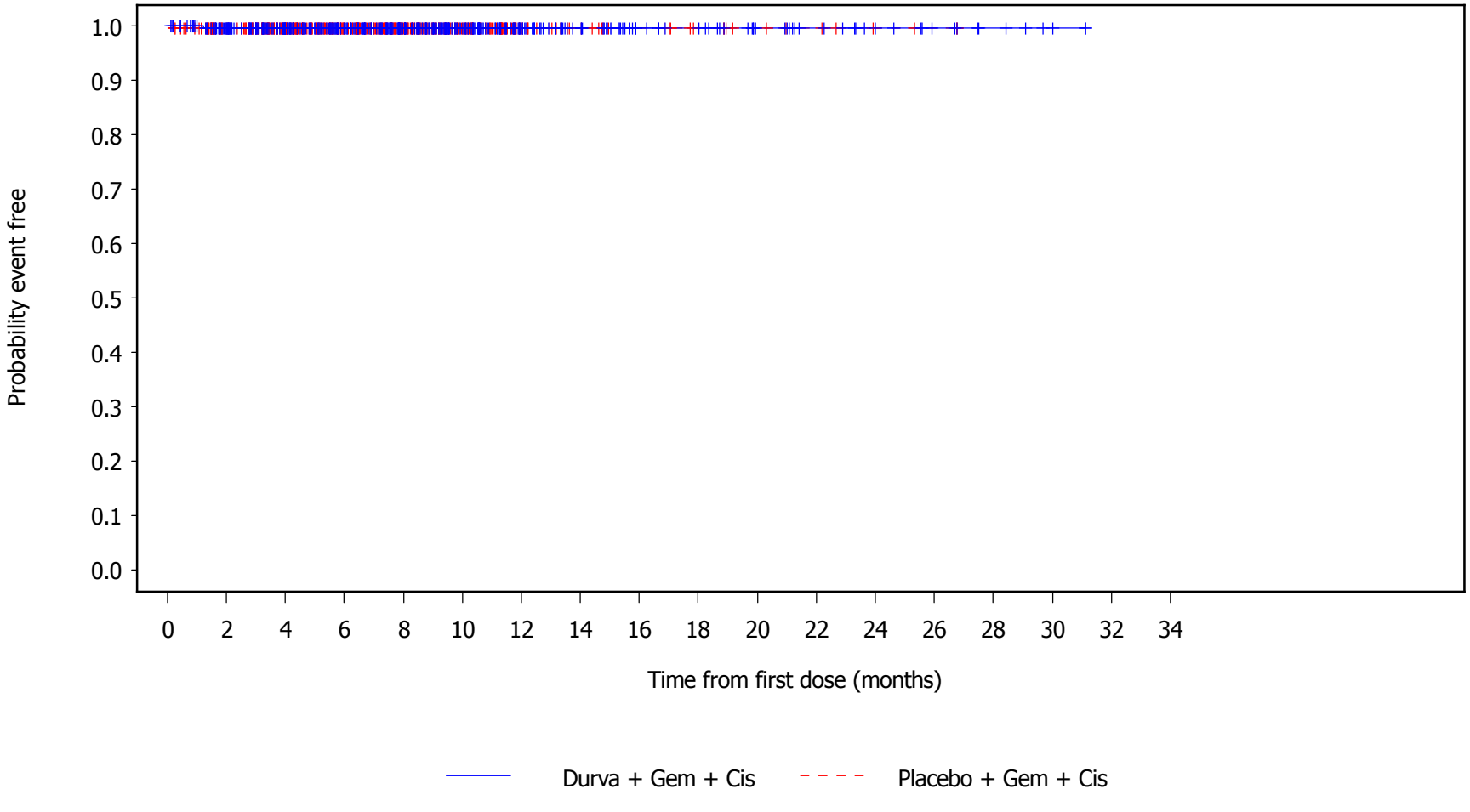
Figure 3.3.394 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Adrenal insufficiency
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

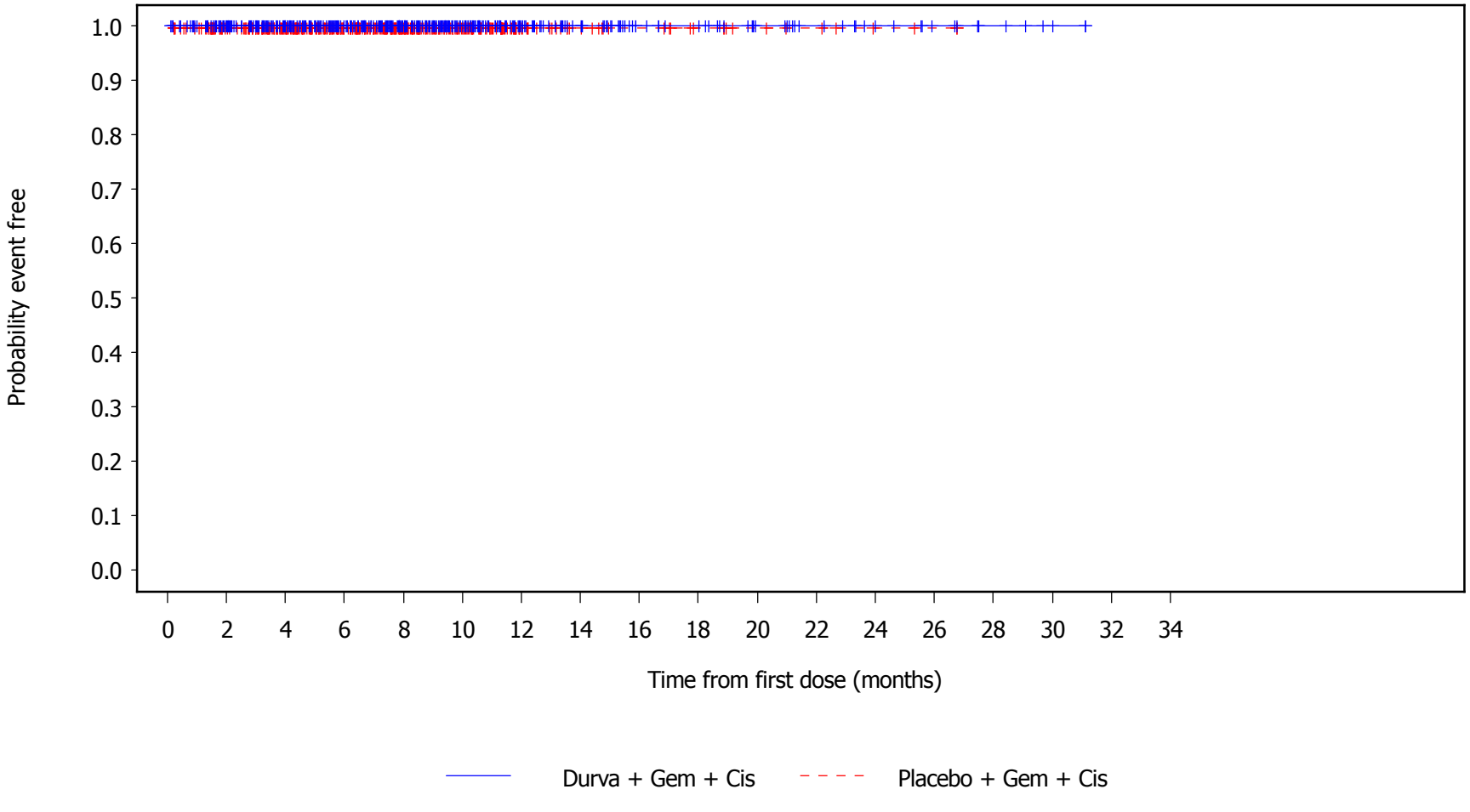
Figure 3.3.395 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI GT: Dermatitis/Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

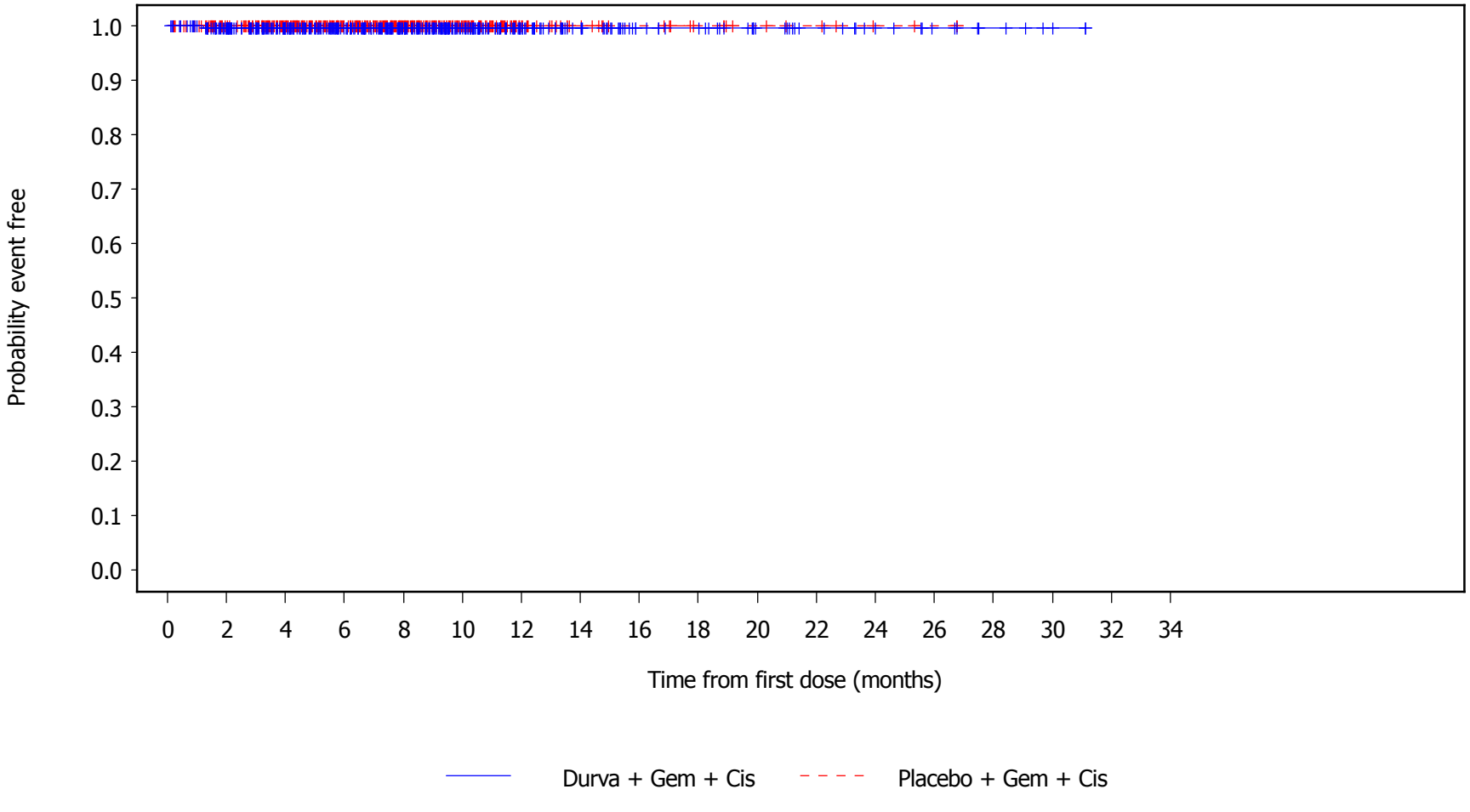
Figure 3.3.396 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

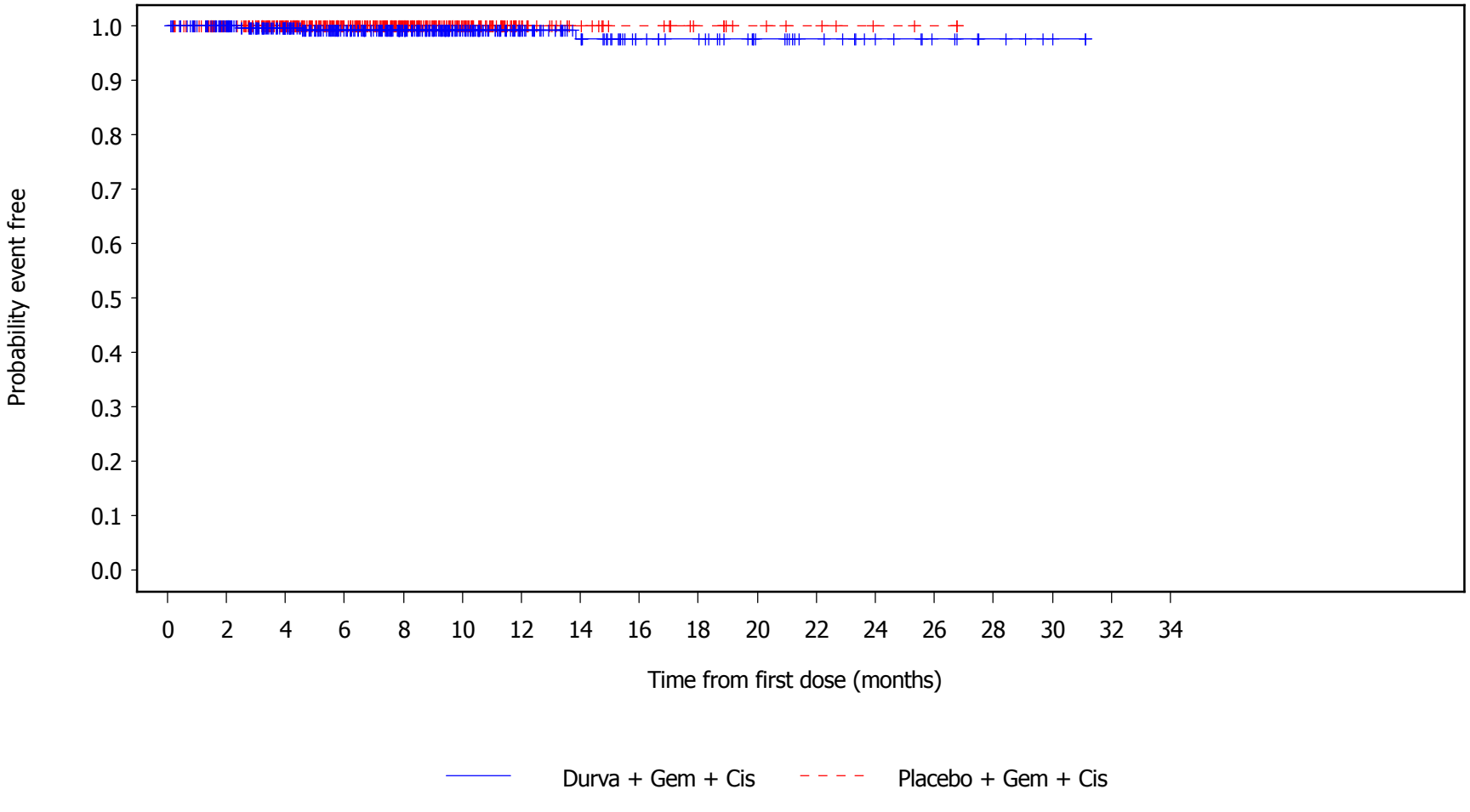
Figure 3.3.397 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Rash maculo-papular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

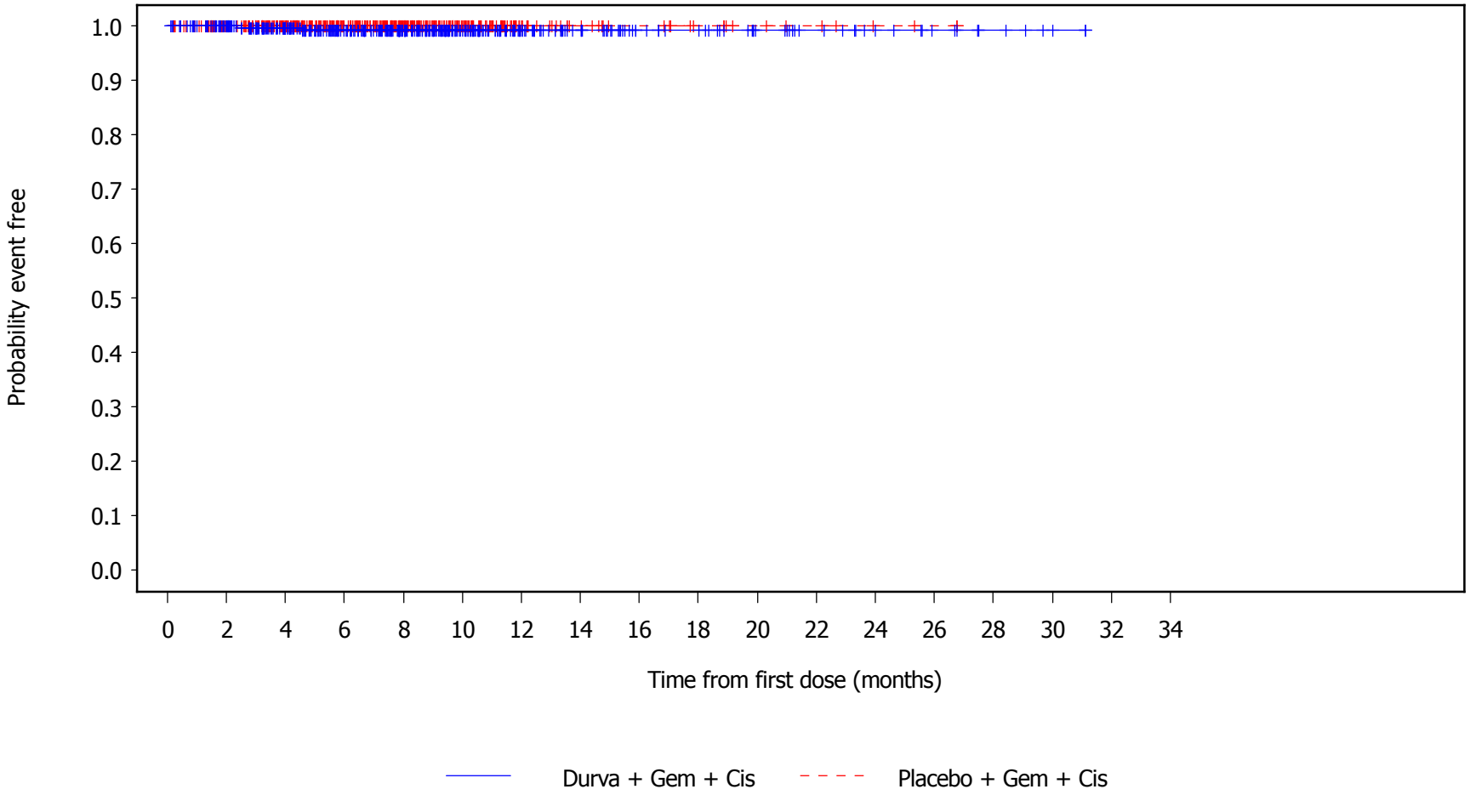
Figure 3.3.398 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI GT: Pancreatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	262	198	131	80	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

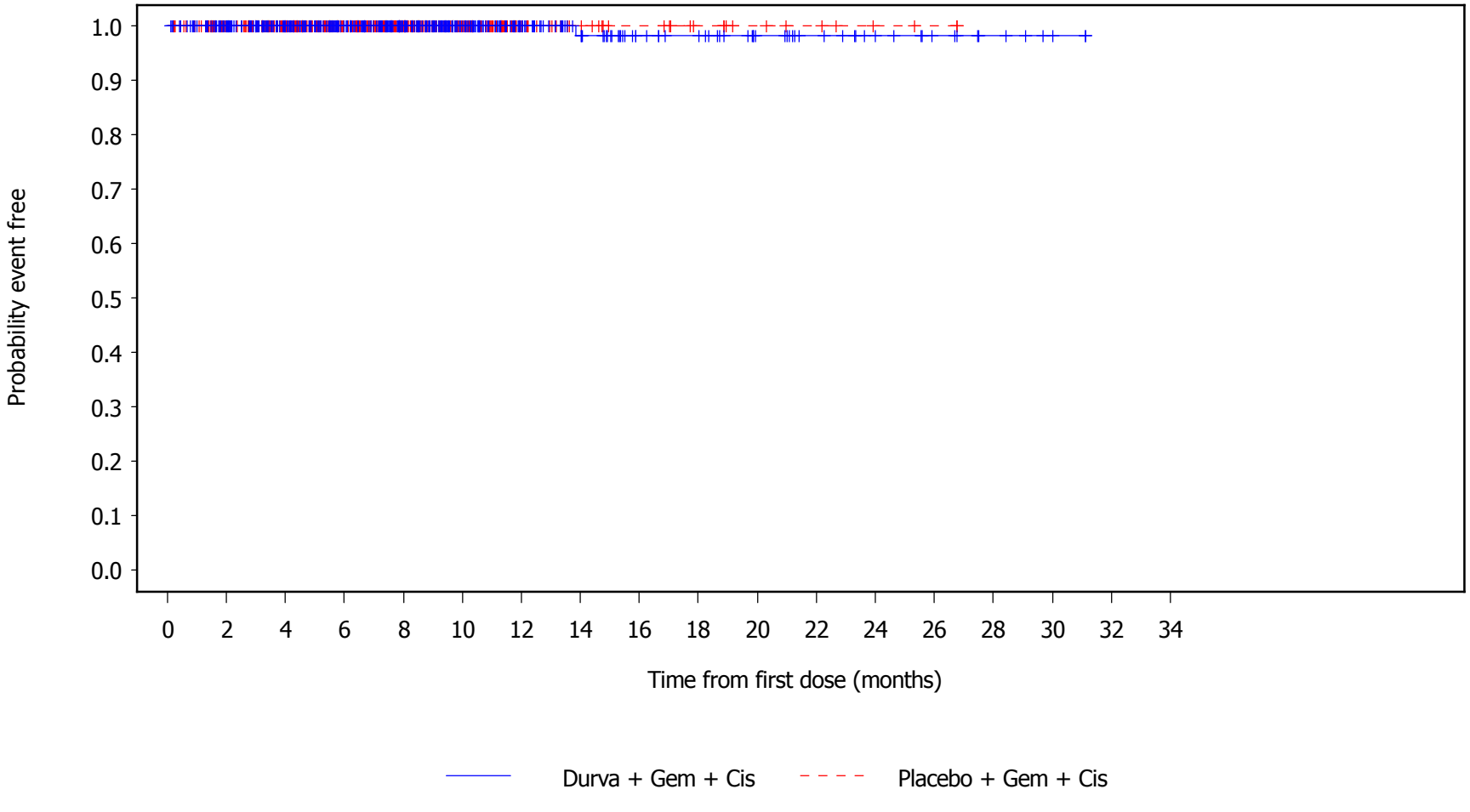
Figure 3.3.399 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Pancreatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	262	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

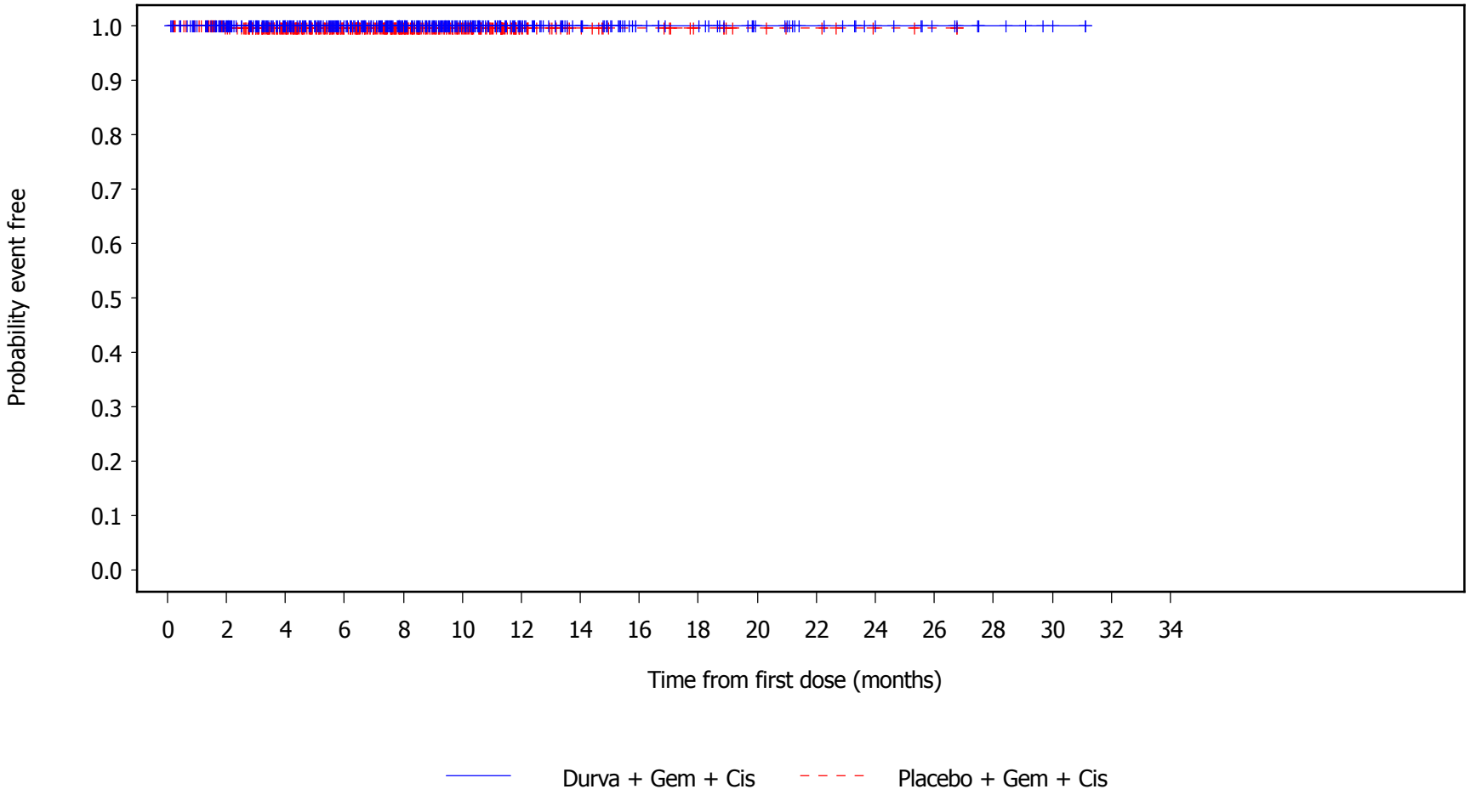
Figure 3.3.400 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Pancreatitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

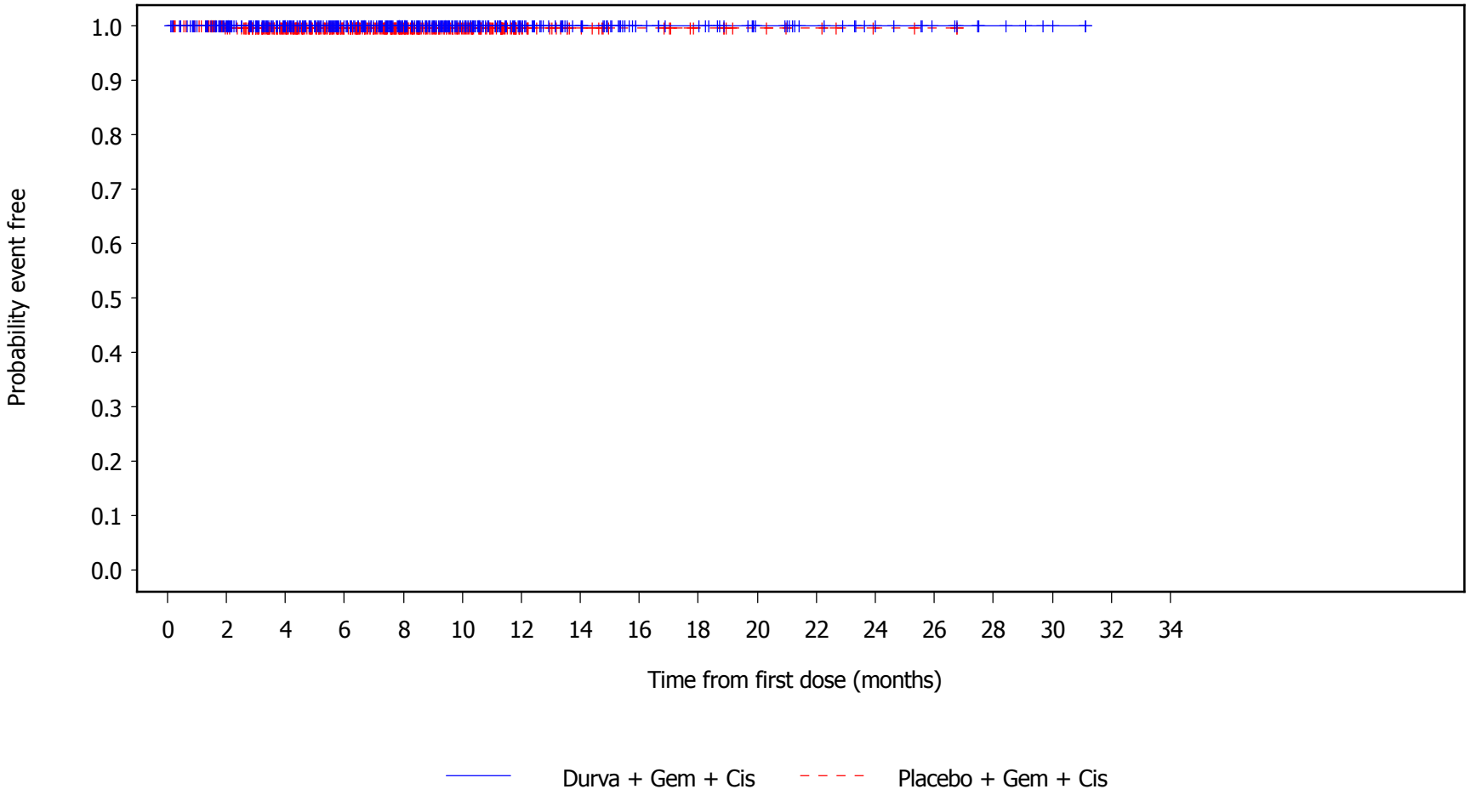
Figure 3.3.401 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI GT: Myositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

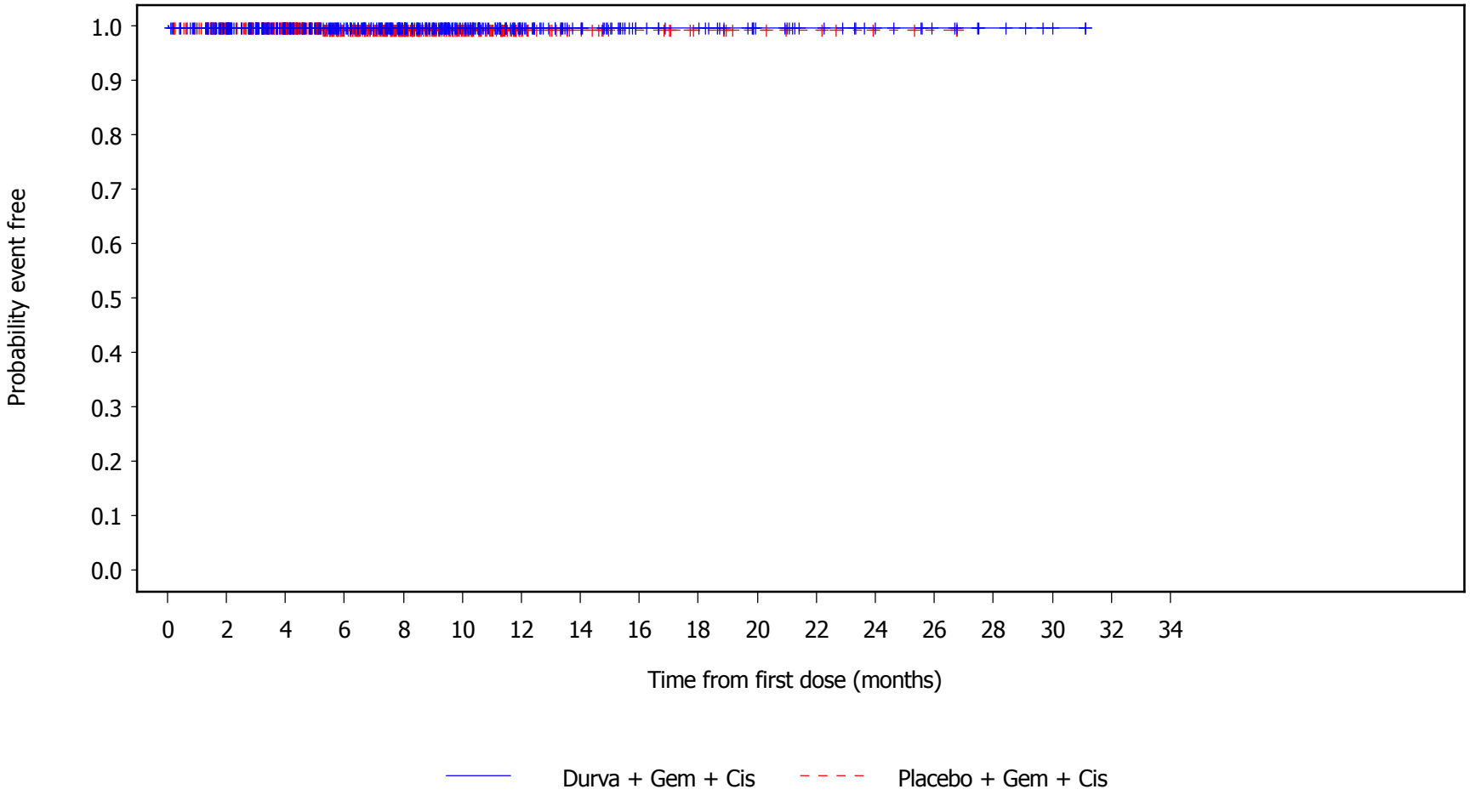
Figure 3.3.402 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Polymyositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

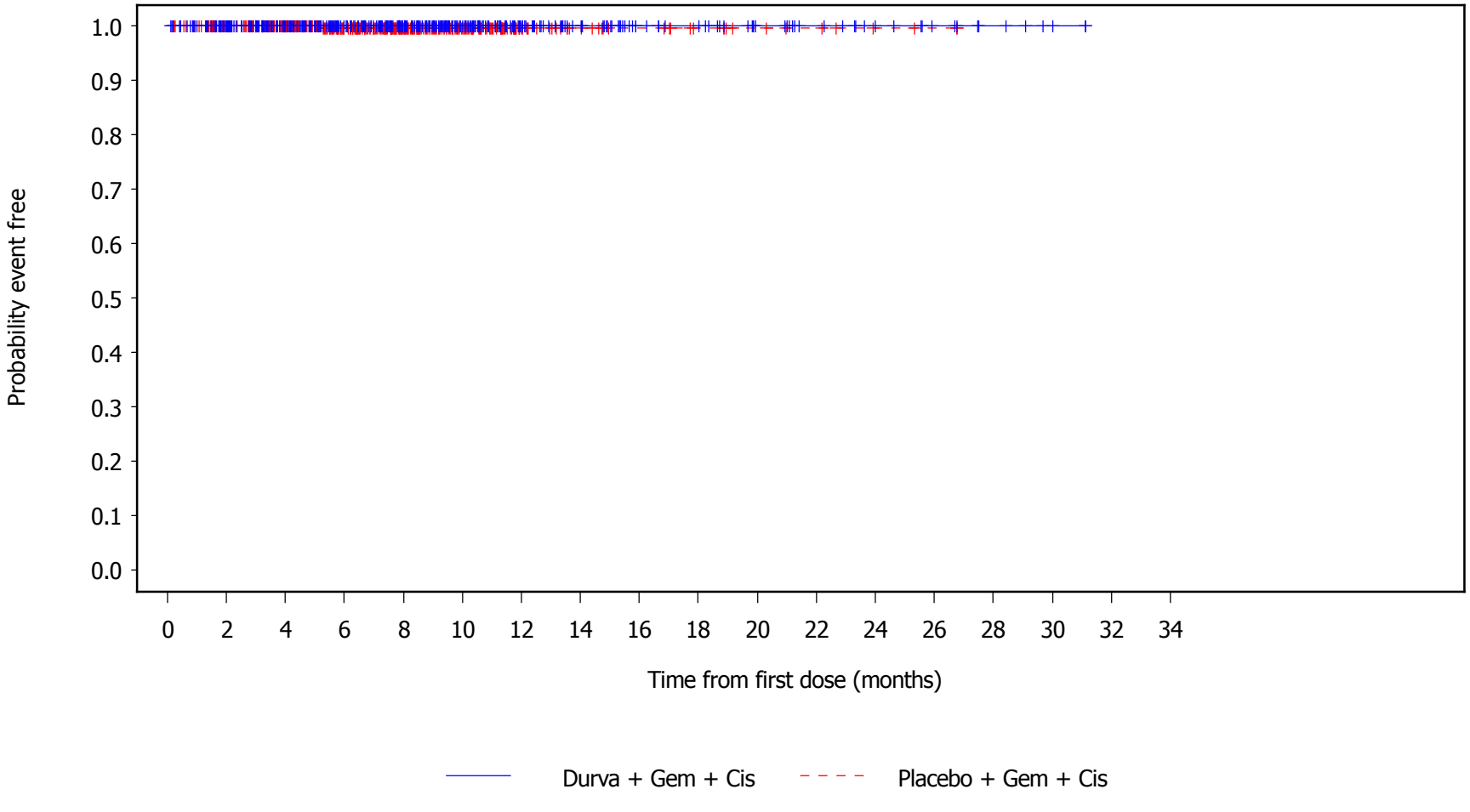
Figure 3.3.403 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI GT: Infusion/hypersensitivity reactions
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	263	197	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	230	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

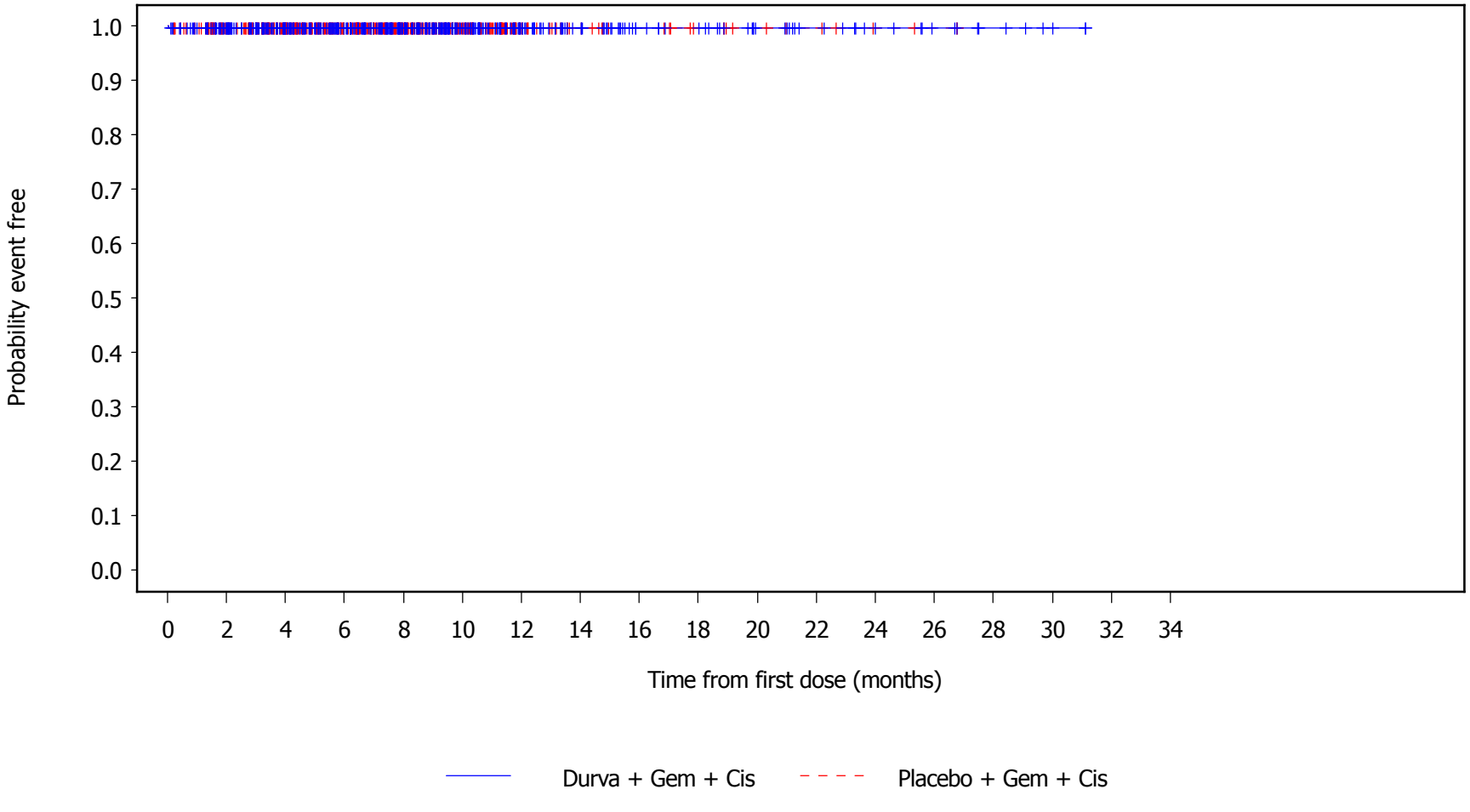
Figure 3.3.404 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Anaphylactic shock
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	231	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

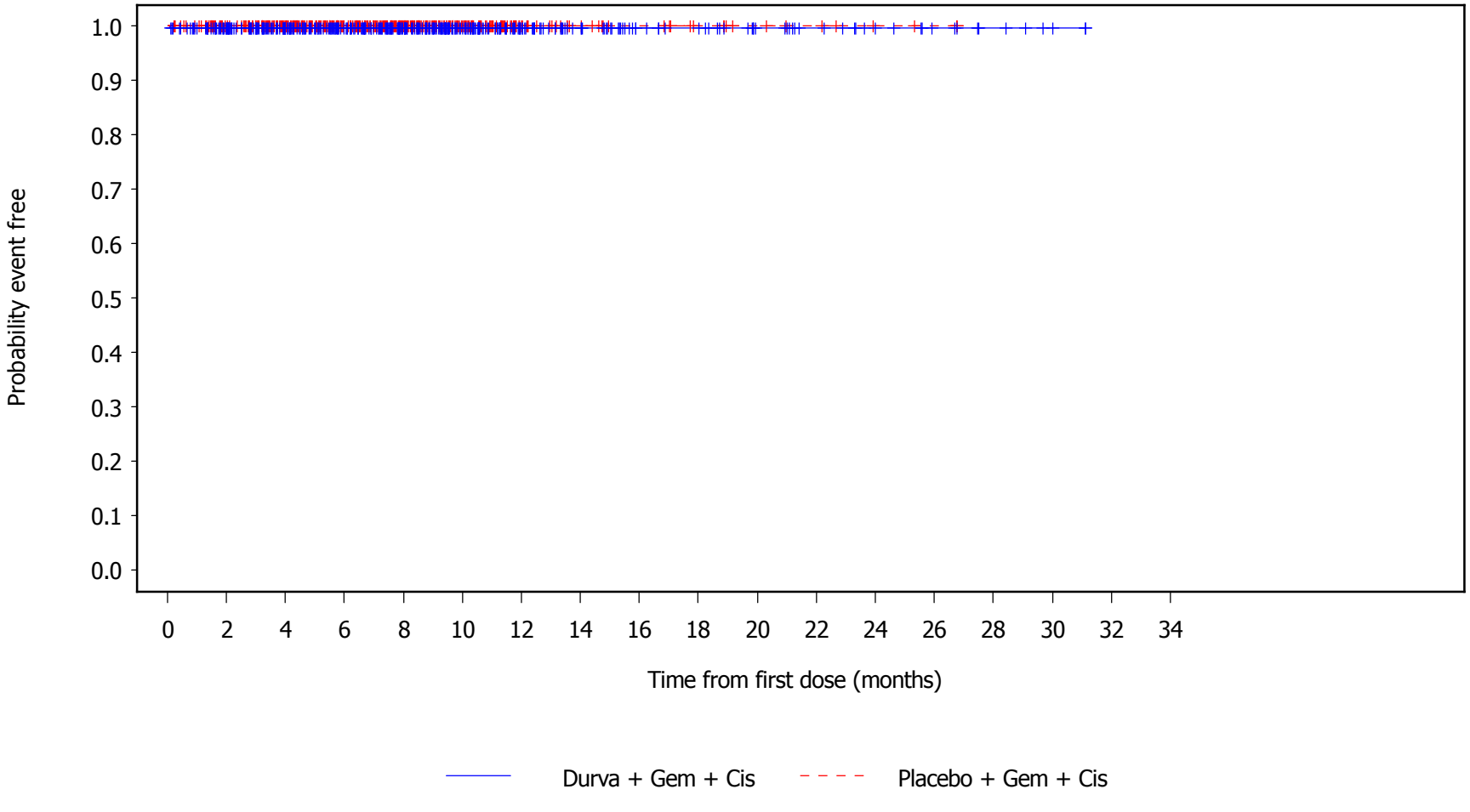
Figure 3.3.405 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Infusion related reaction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	263	197	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

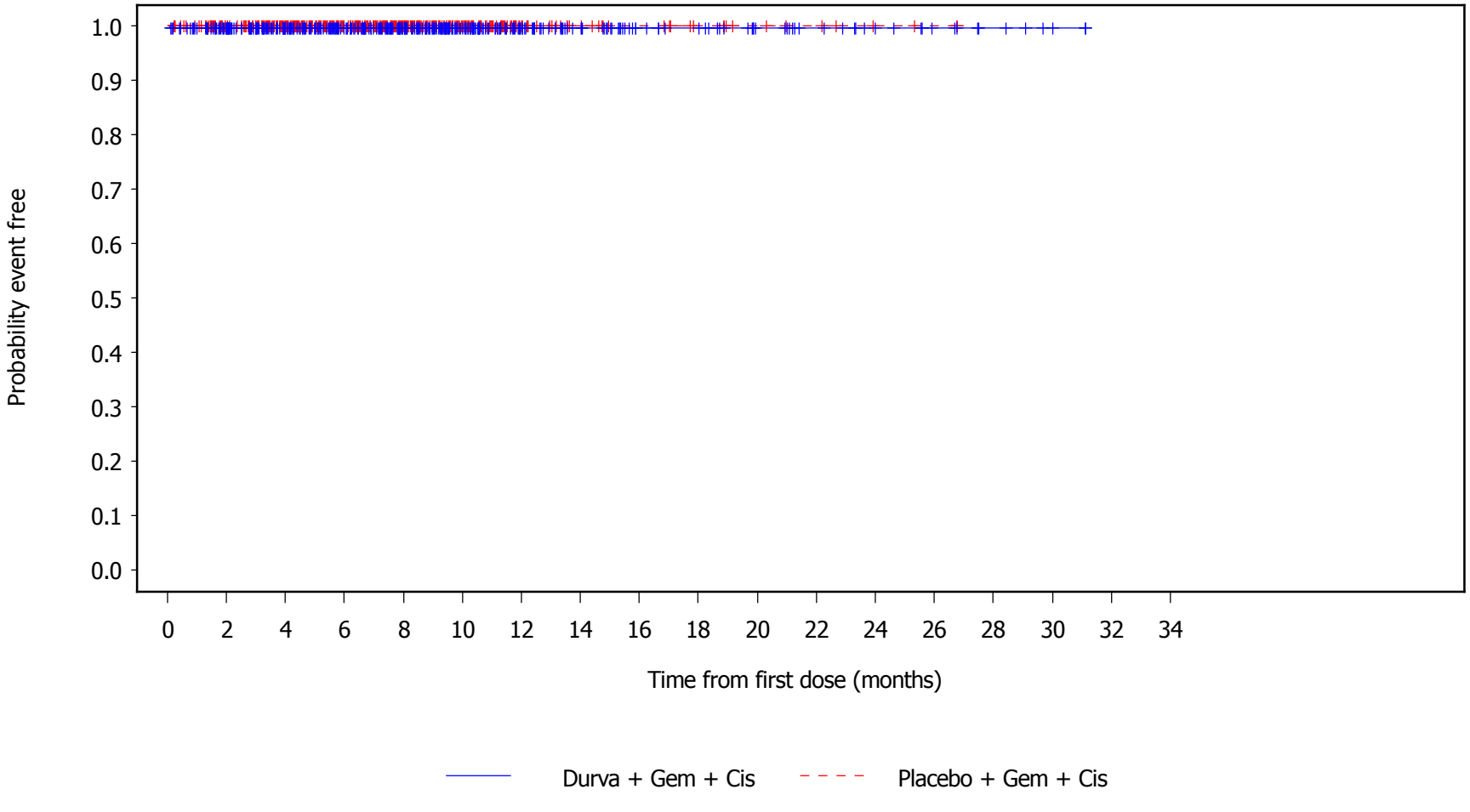
Figure 3.3.406 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI GT: Other rare/miscellaneous
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

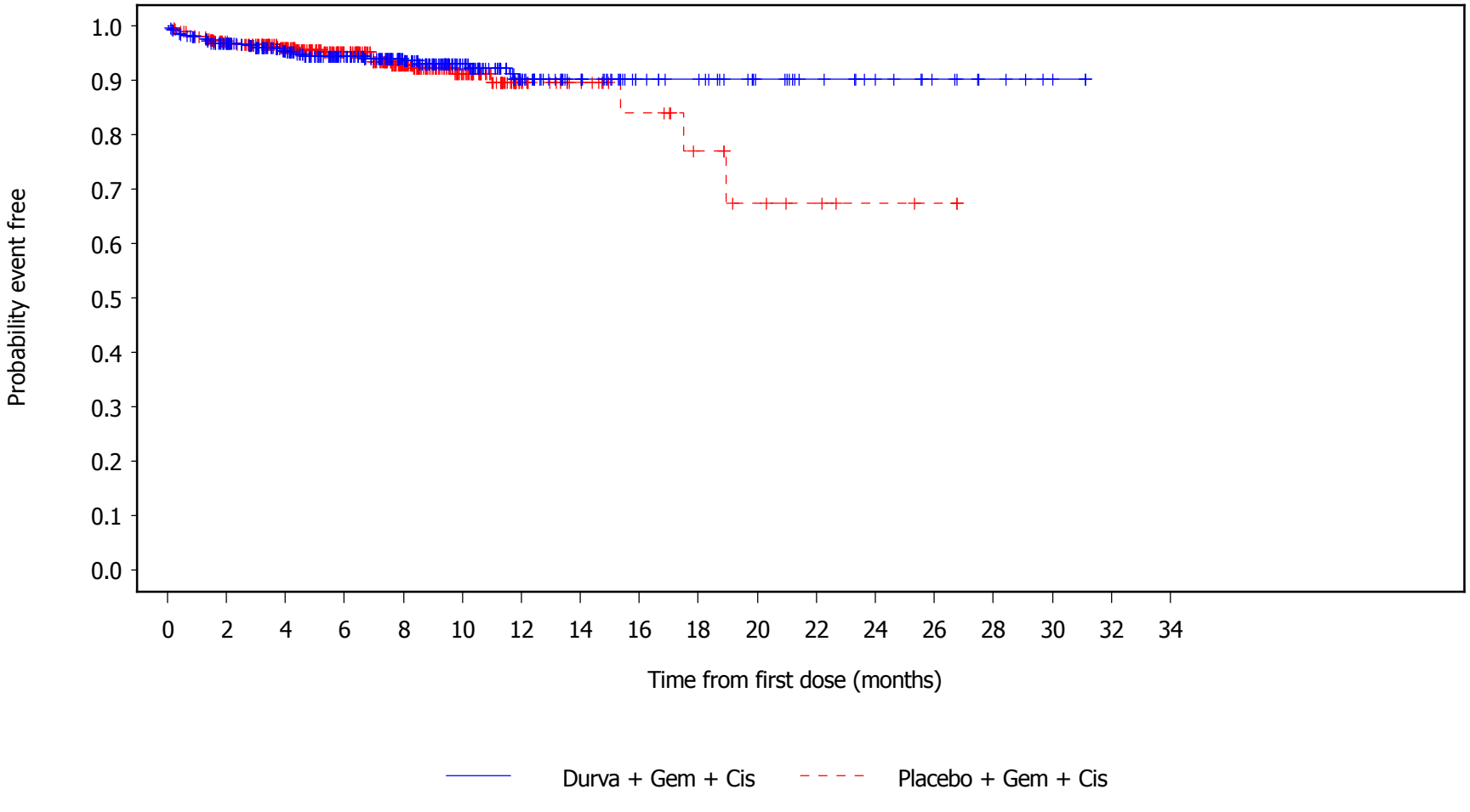
Figure 3.3.407 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Immune-mediated arthritis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

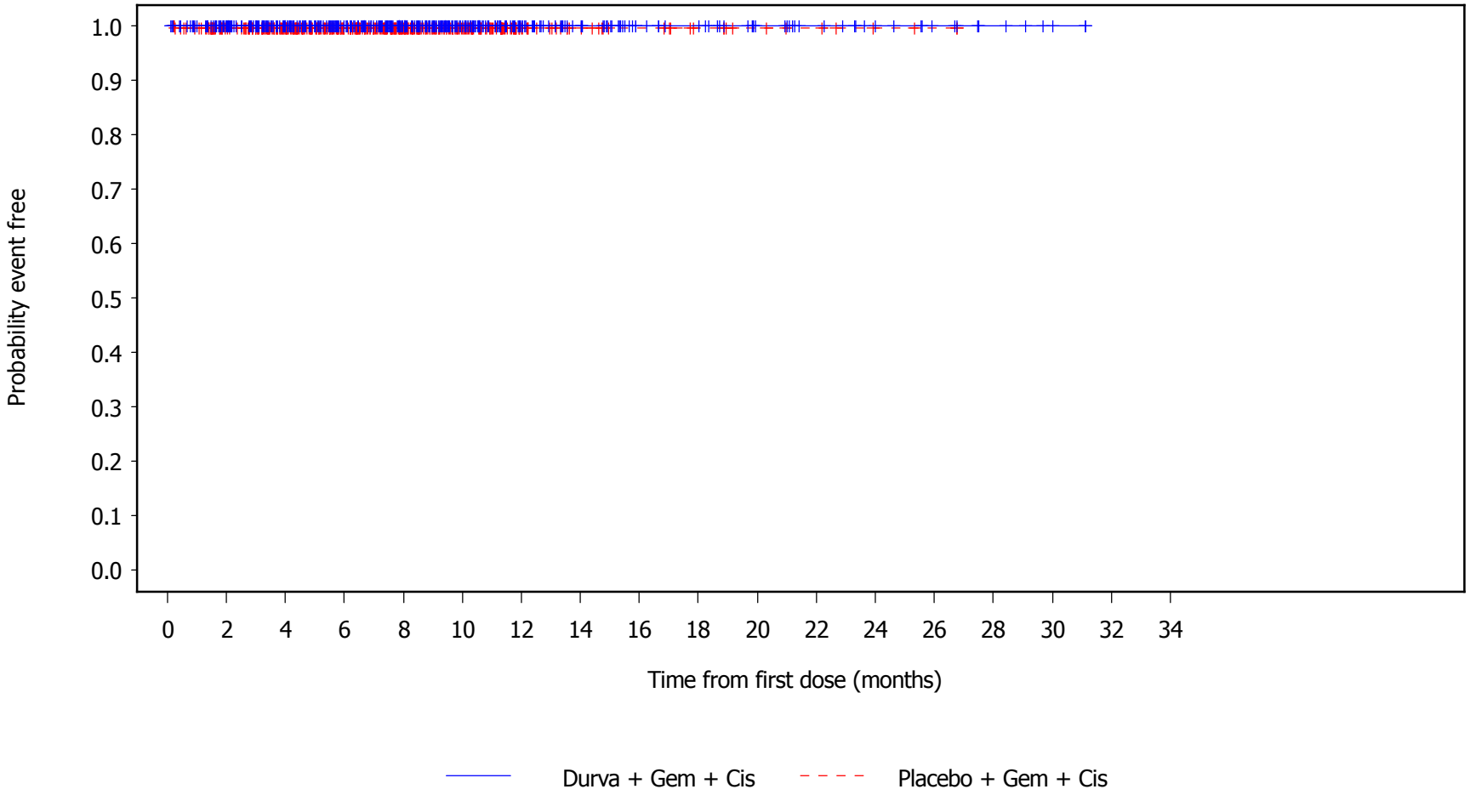
Figure 3.3.408 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI GT: Hepatic SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	364	307	259	194	127	75	55	38	34	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	361	306	227	153	85	32	22	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

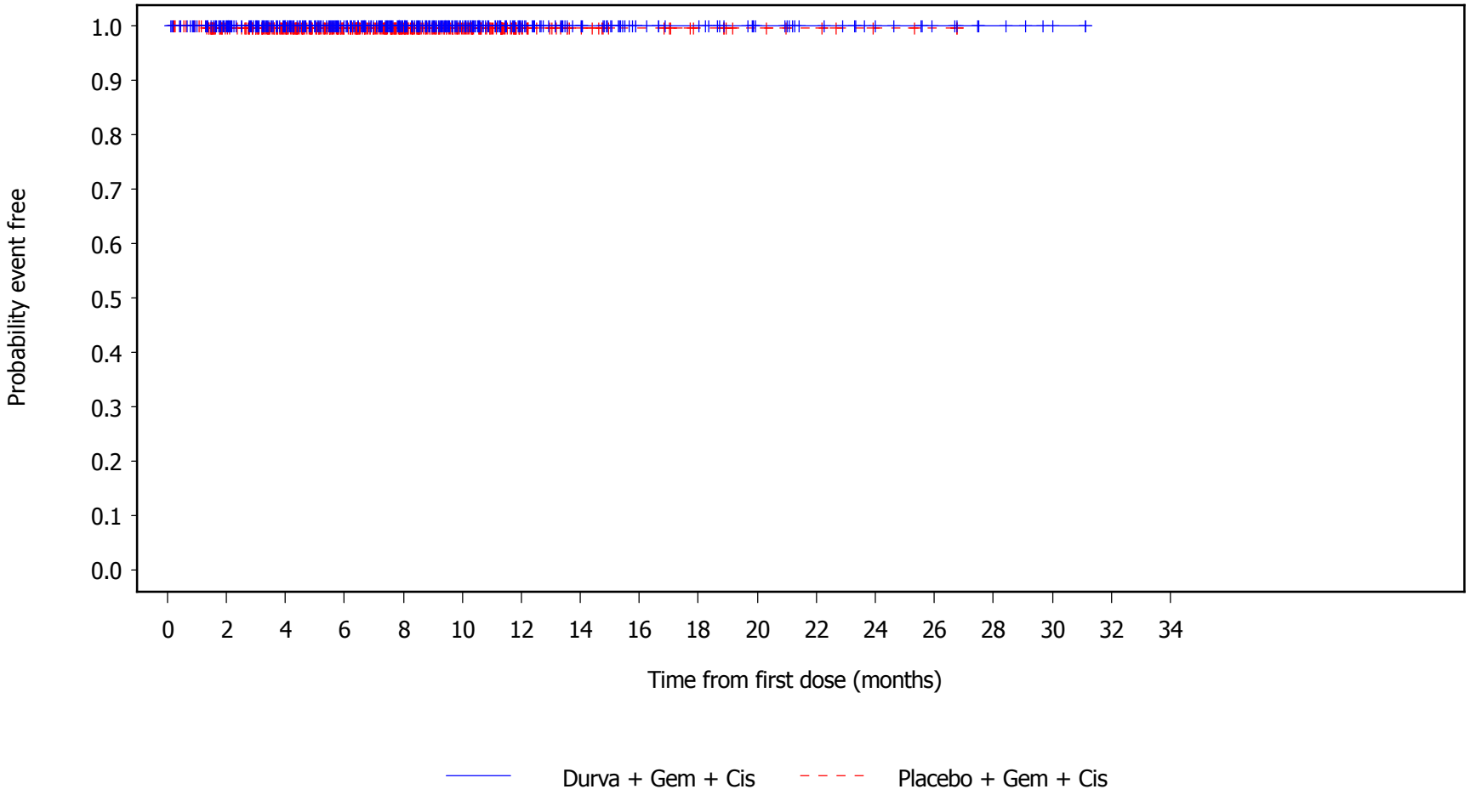
Figure 3.3.409 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Alanine aminotransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

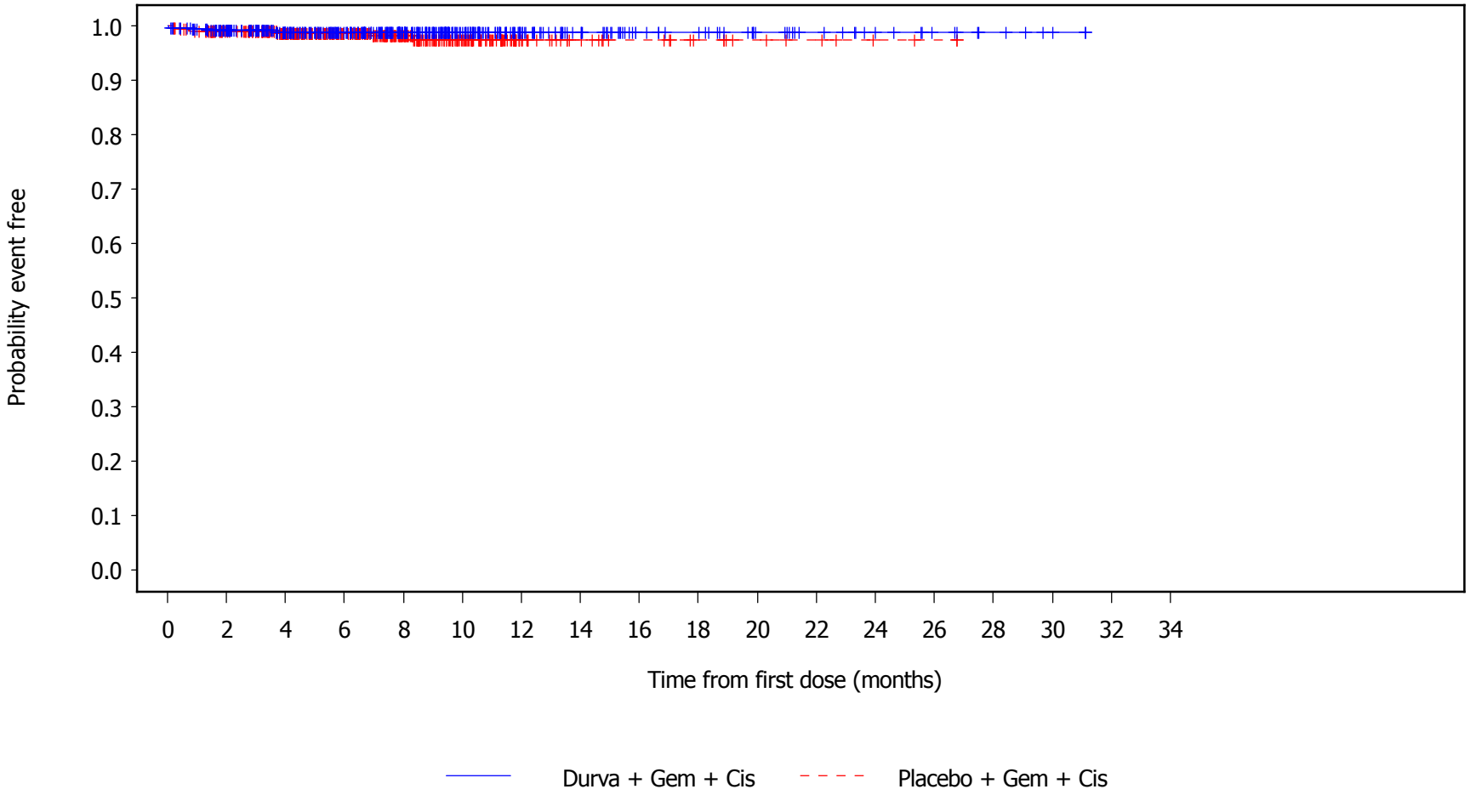
Figure 3.3.410 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

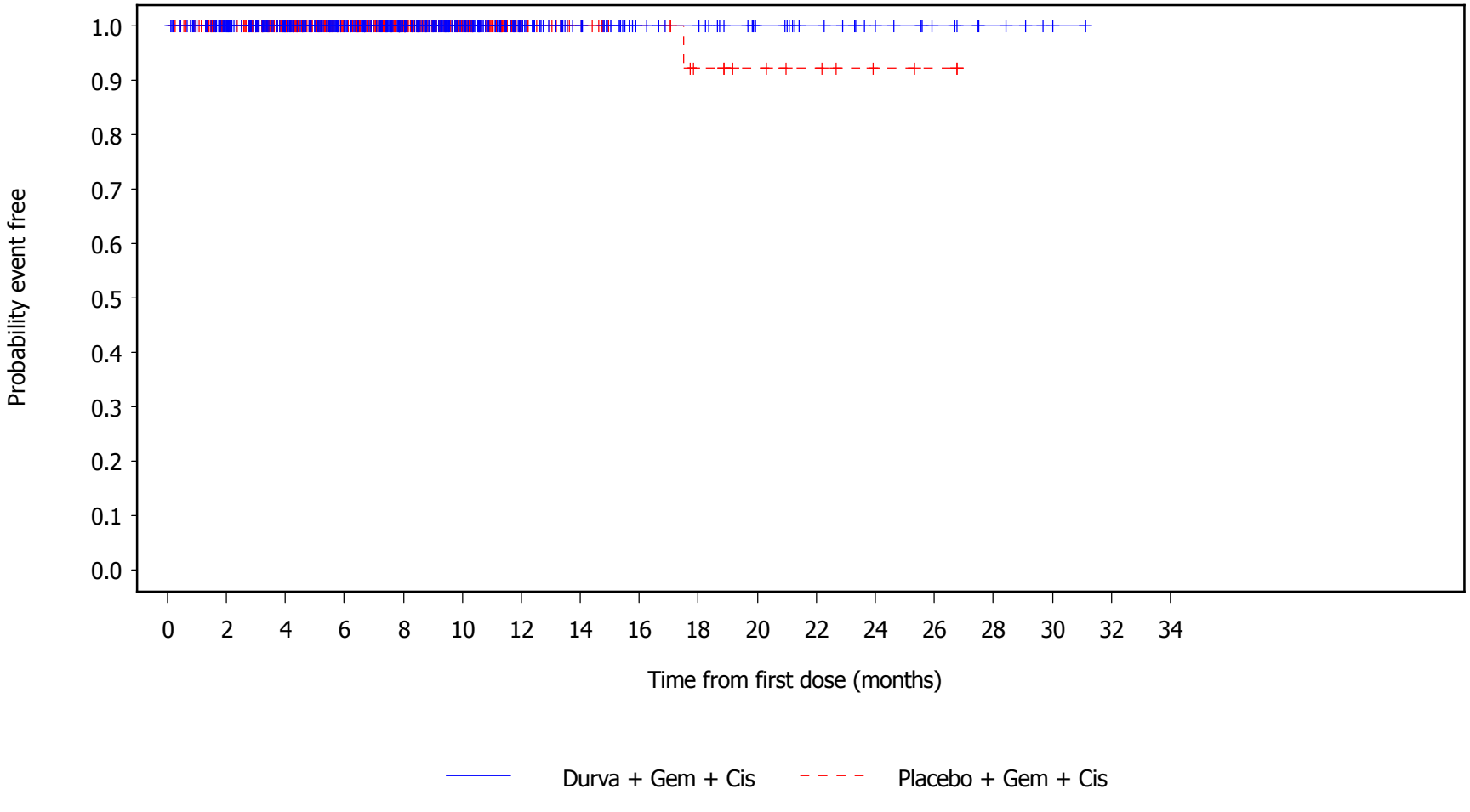
Figure 3.3.411 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Ascites
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	370	312	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	310	231	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

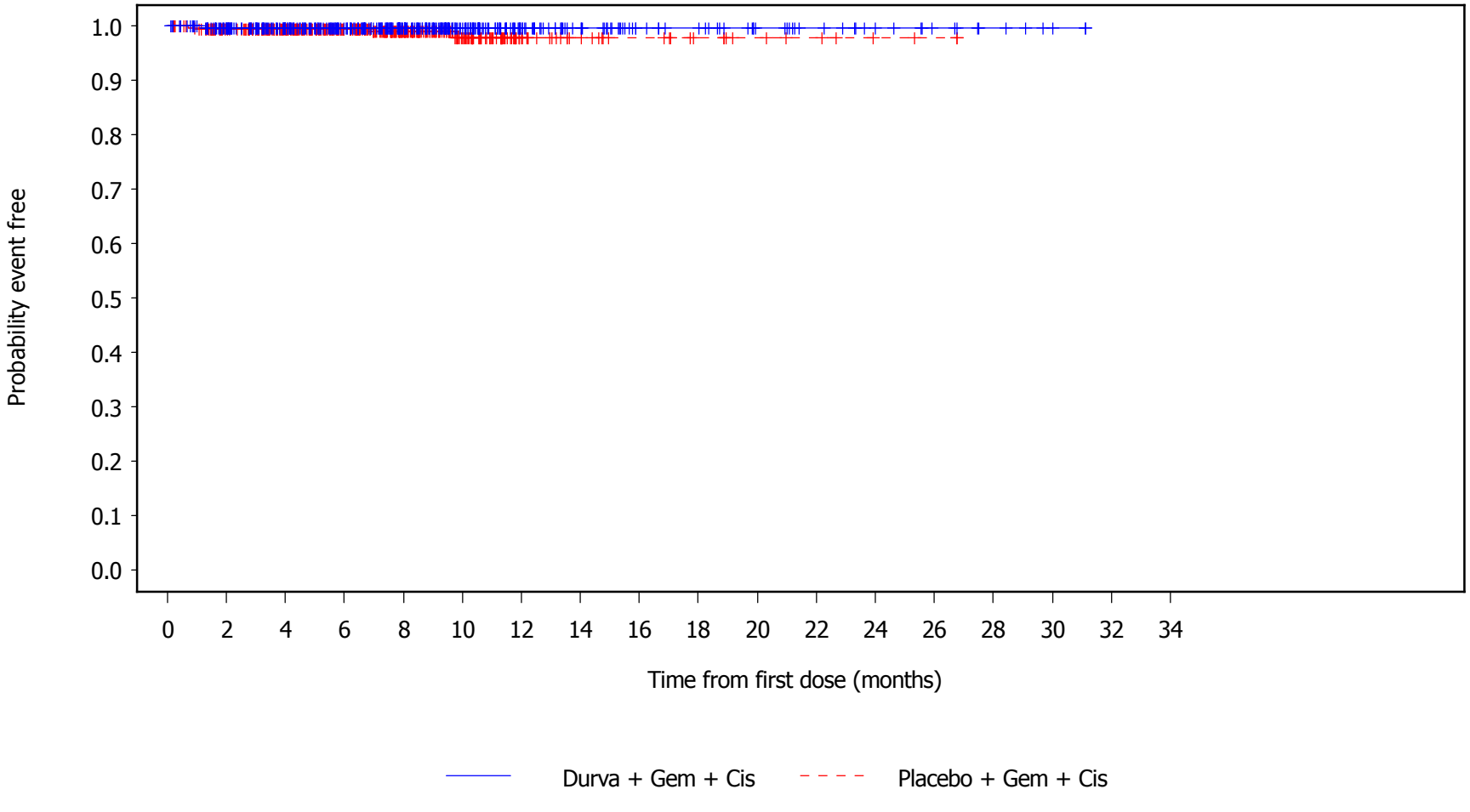
Figure 3.3.412 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	10	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

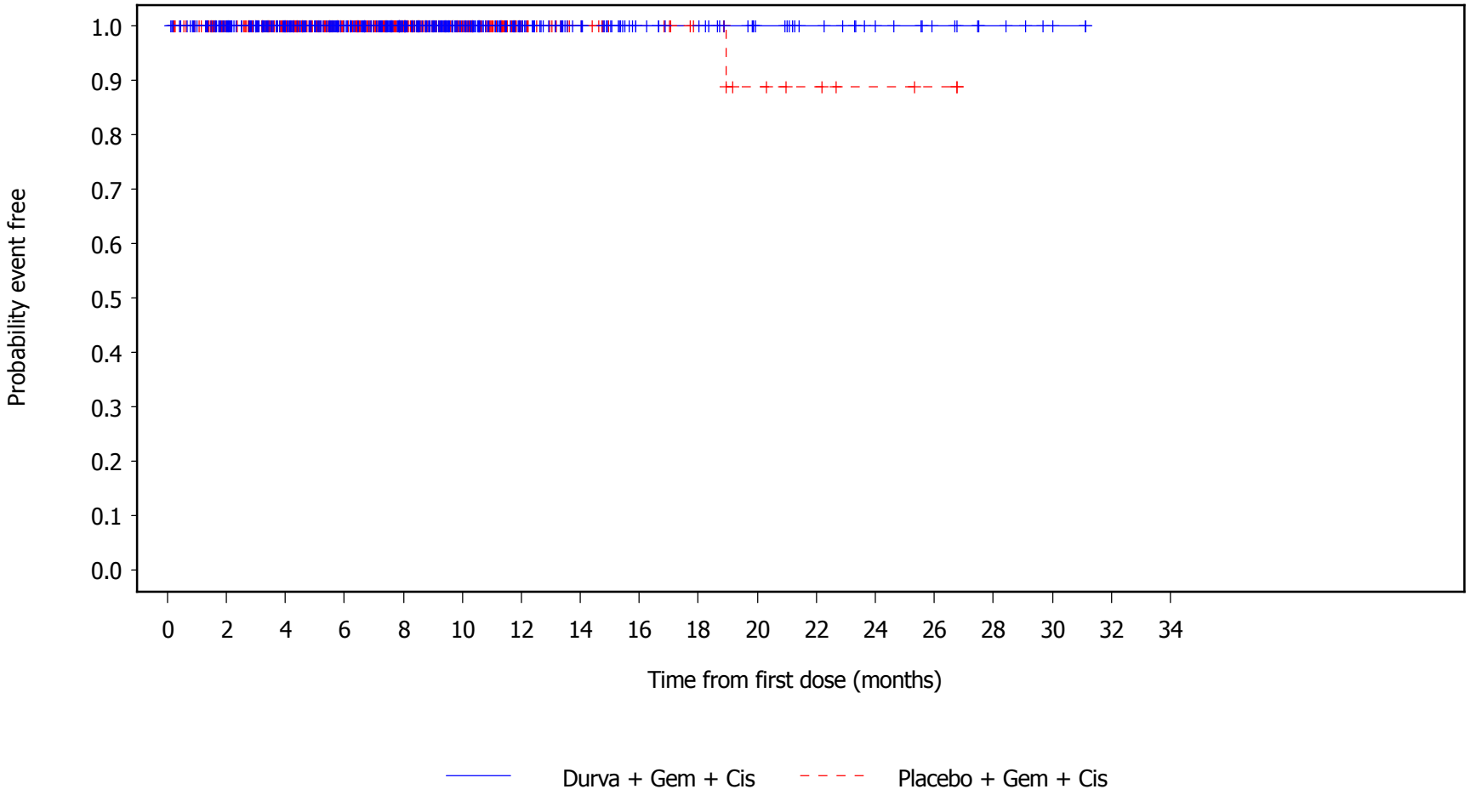
Figure 3.3.413 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	312	231	159	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

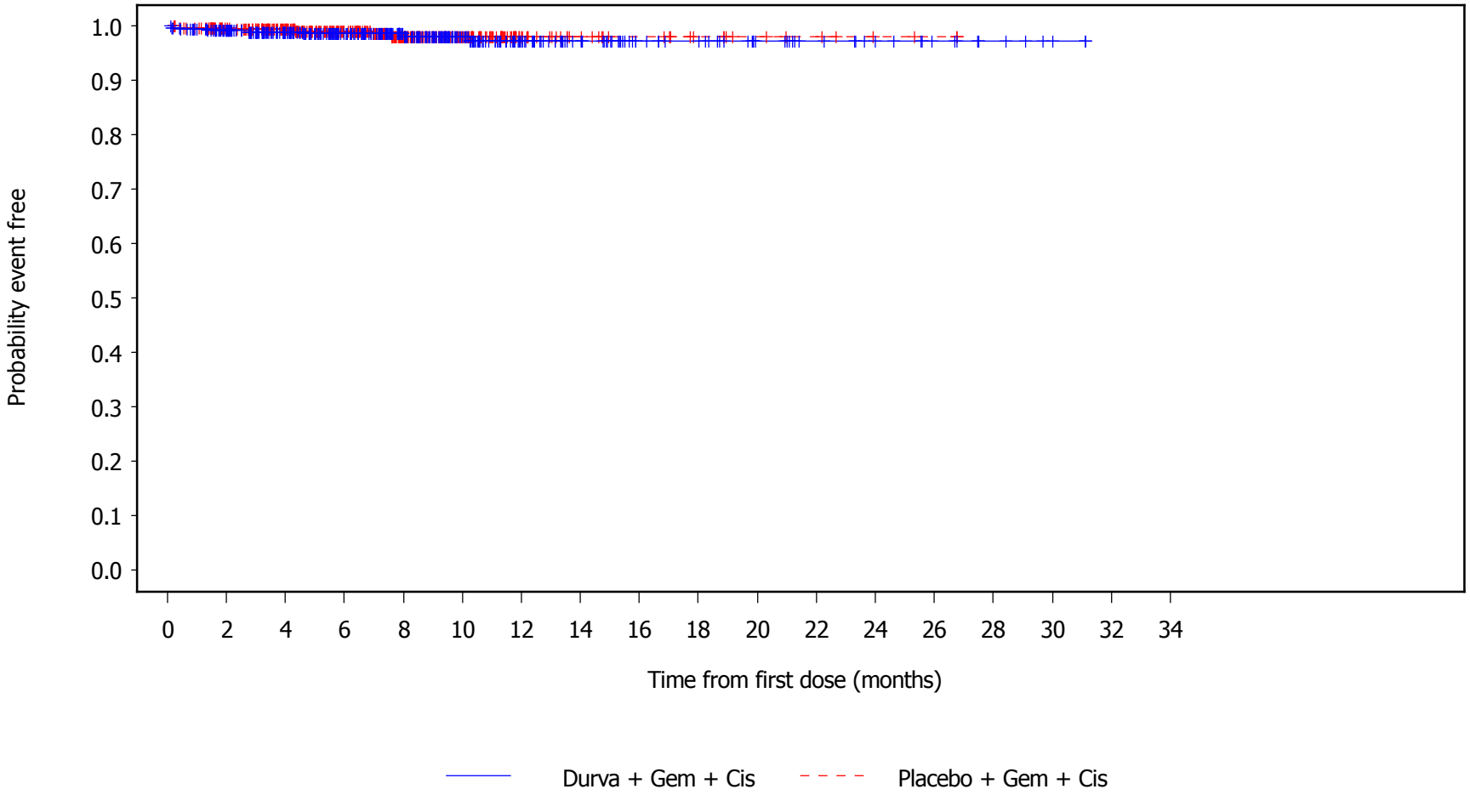
Figure 3.3.414 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

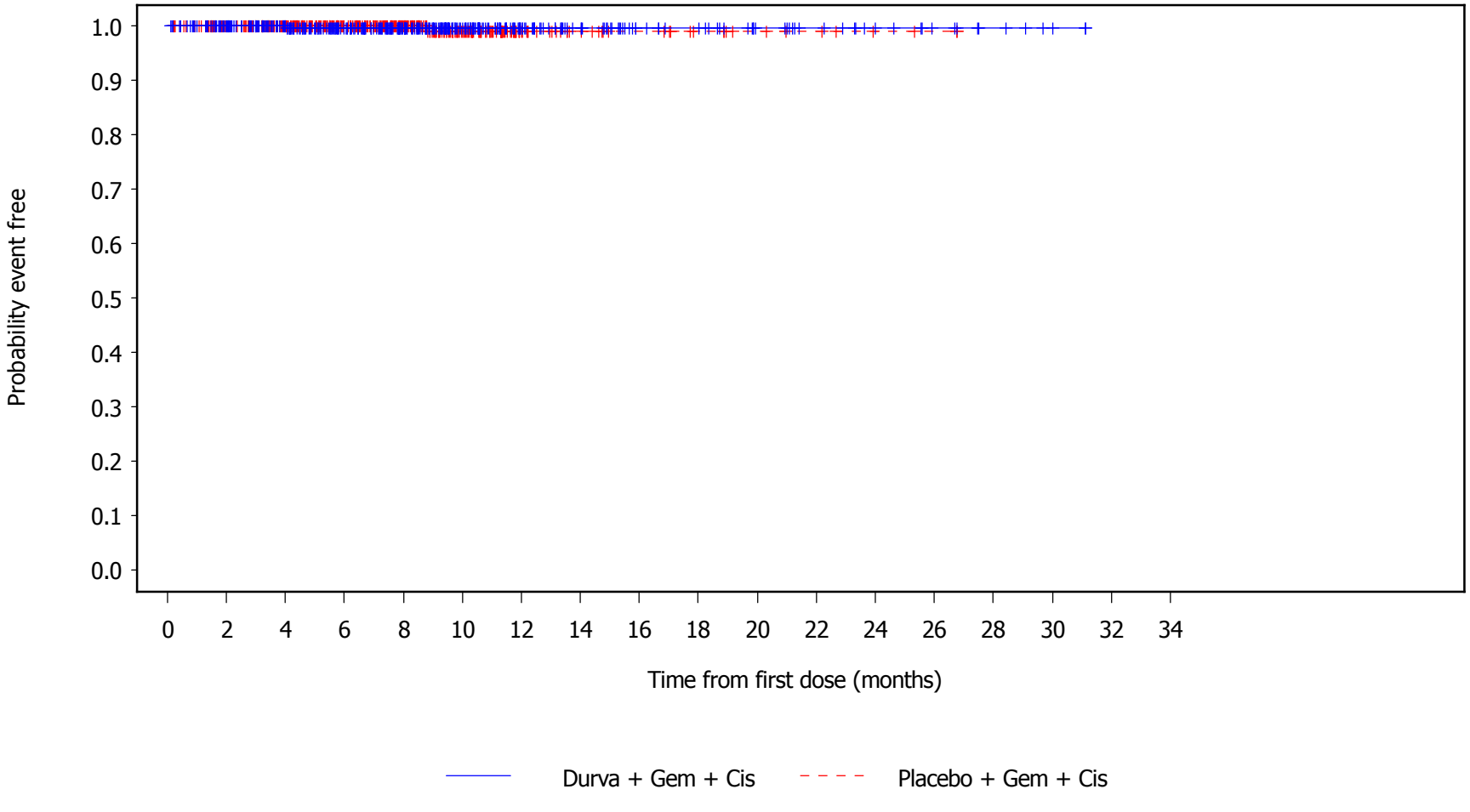
Figure 3.3.415 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	314	262	197	129	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	370	313	232	157	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

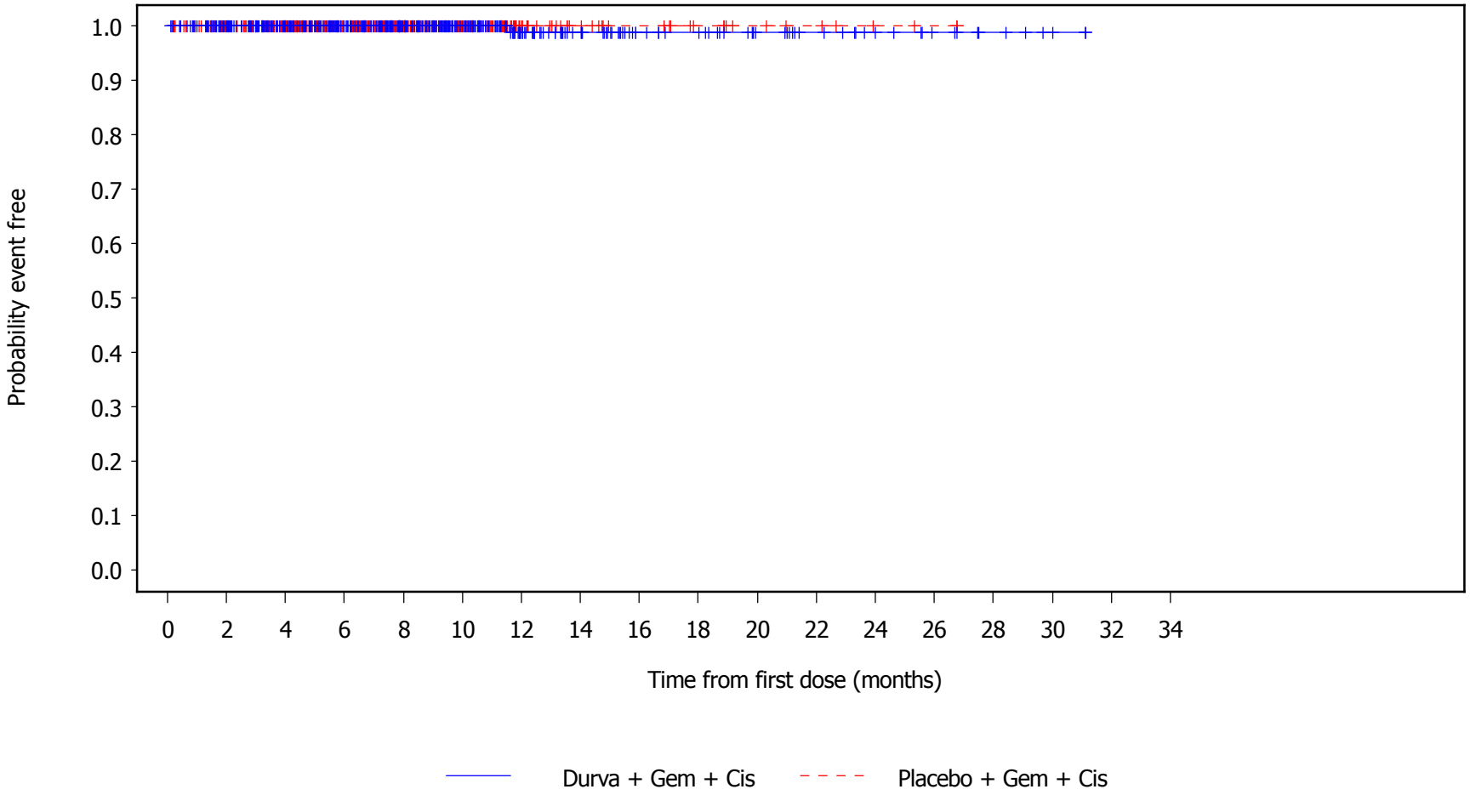
Figure 3.3.416 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Hepatic encephalopathy
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	263	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

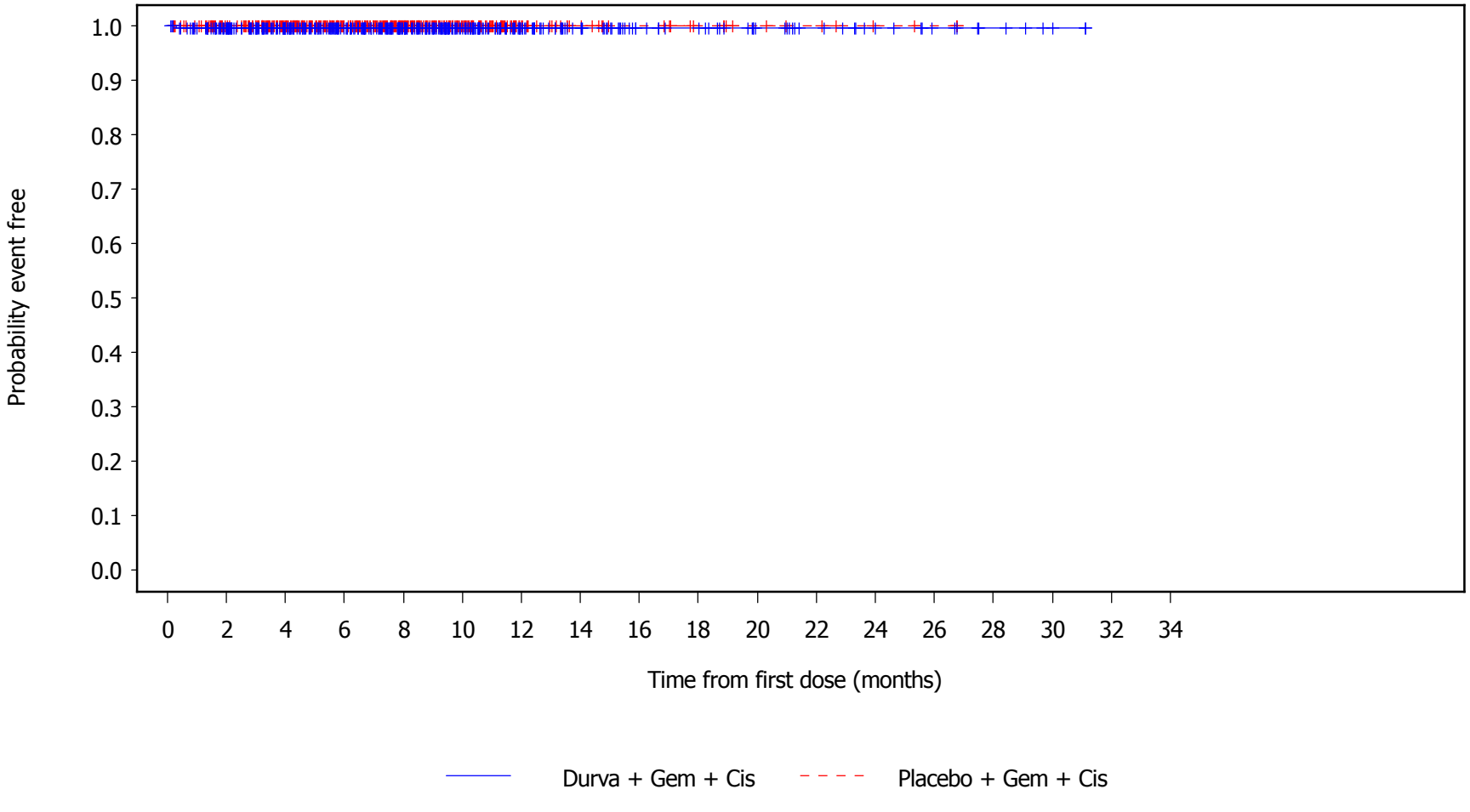
Figure 3.3.417 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Hepatic cytolysis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	79	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

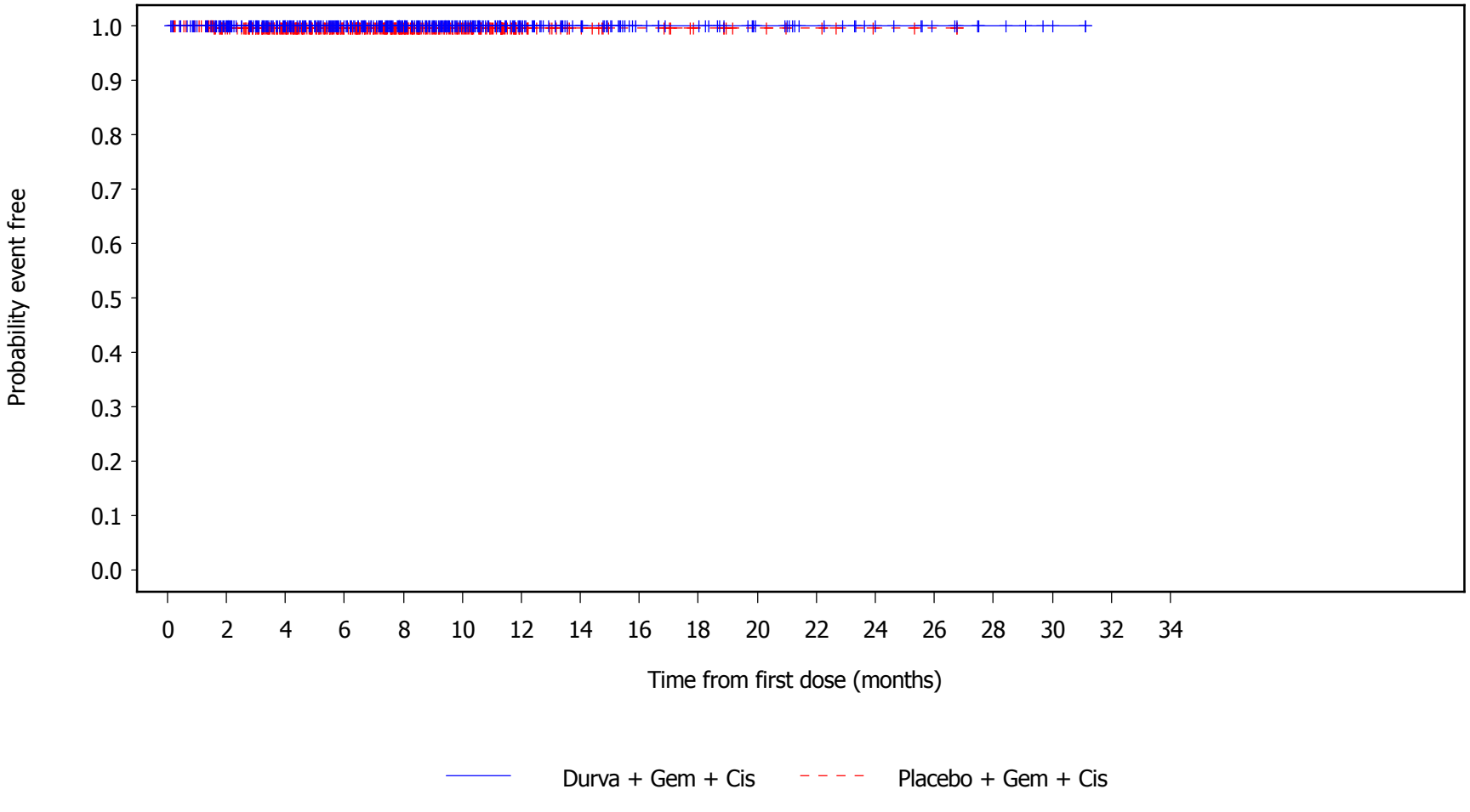
Figure 3.3.418 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

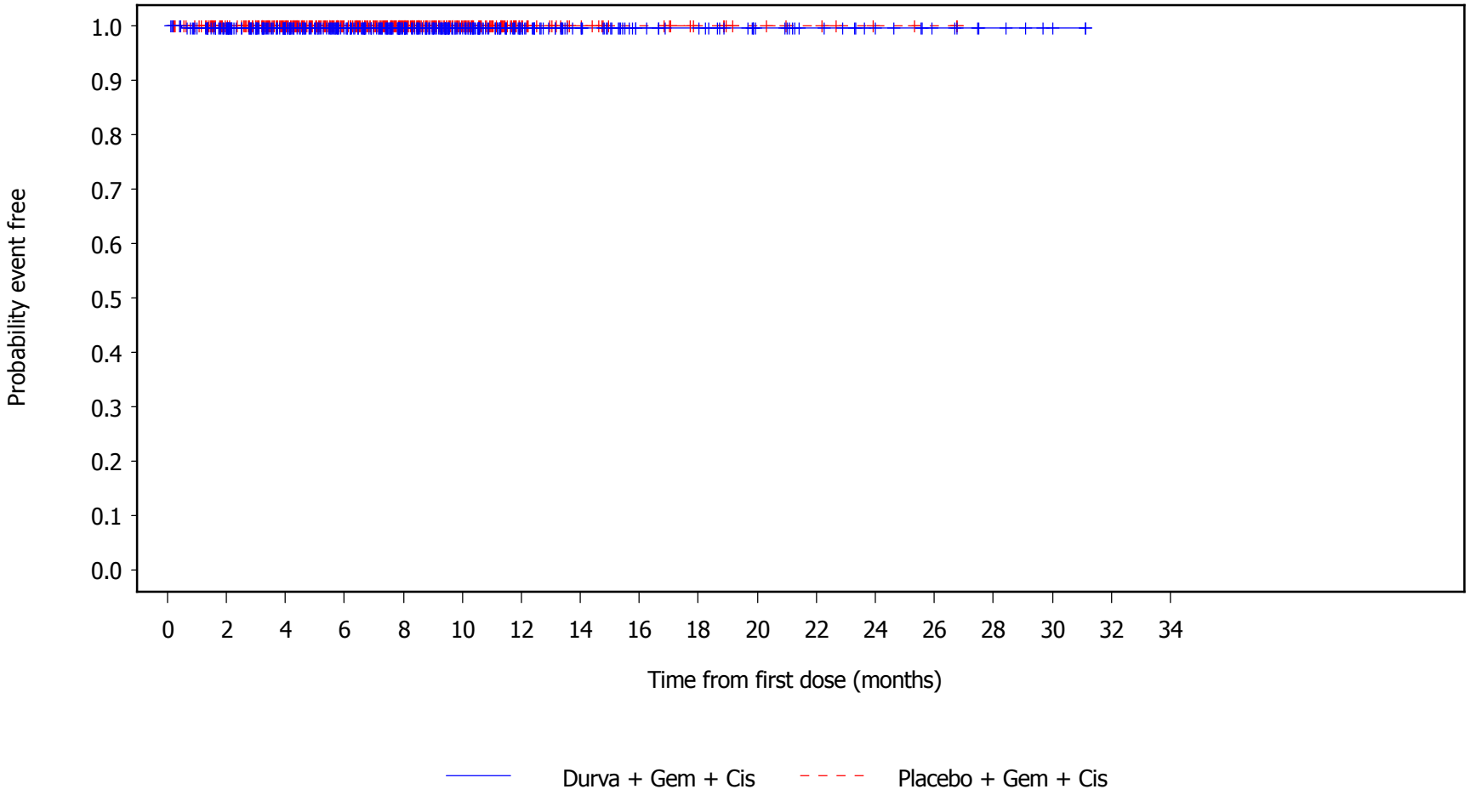
Figure 3.3.419 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Hypoalbuminaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

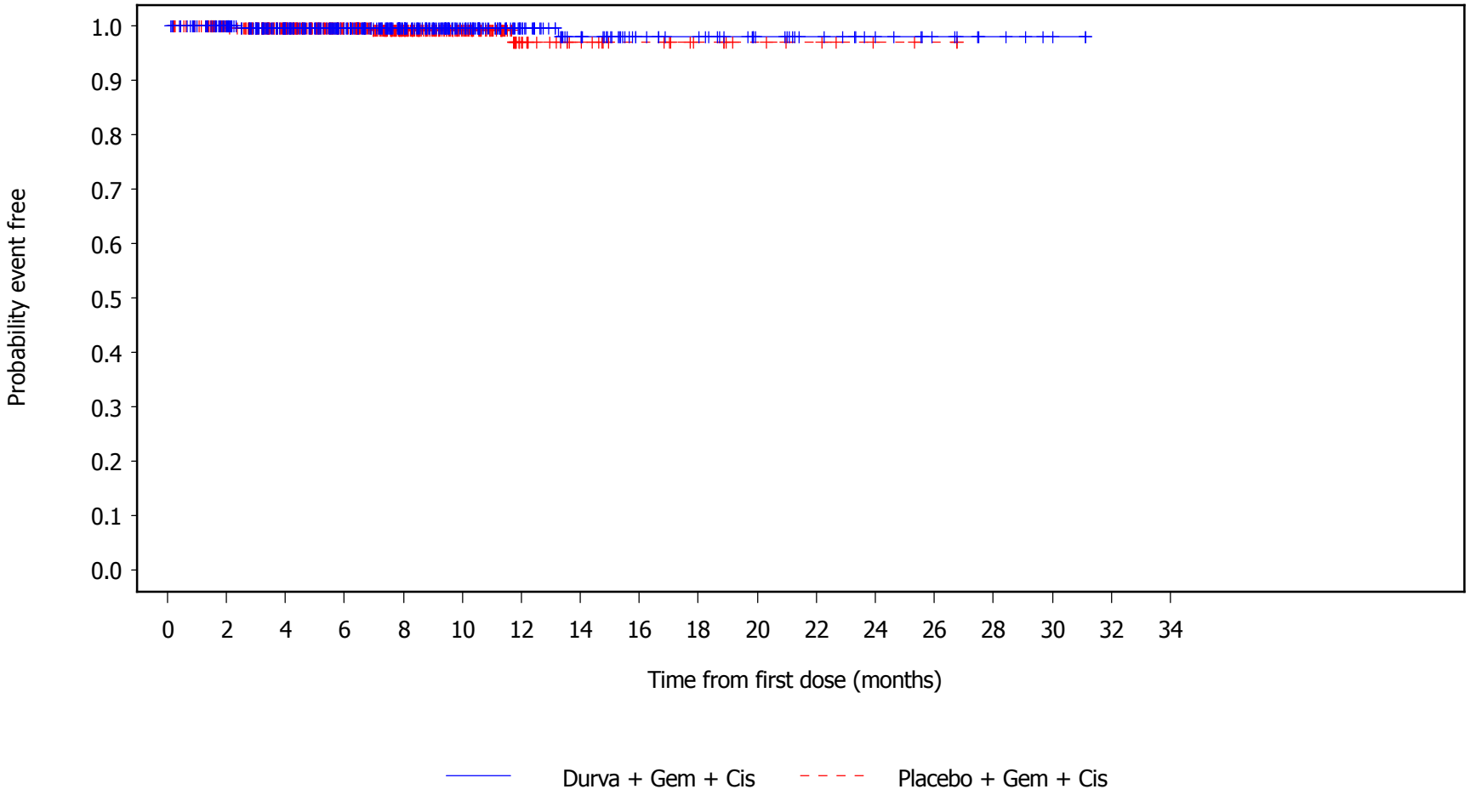
Figure 3.3.420 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

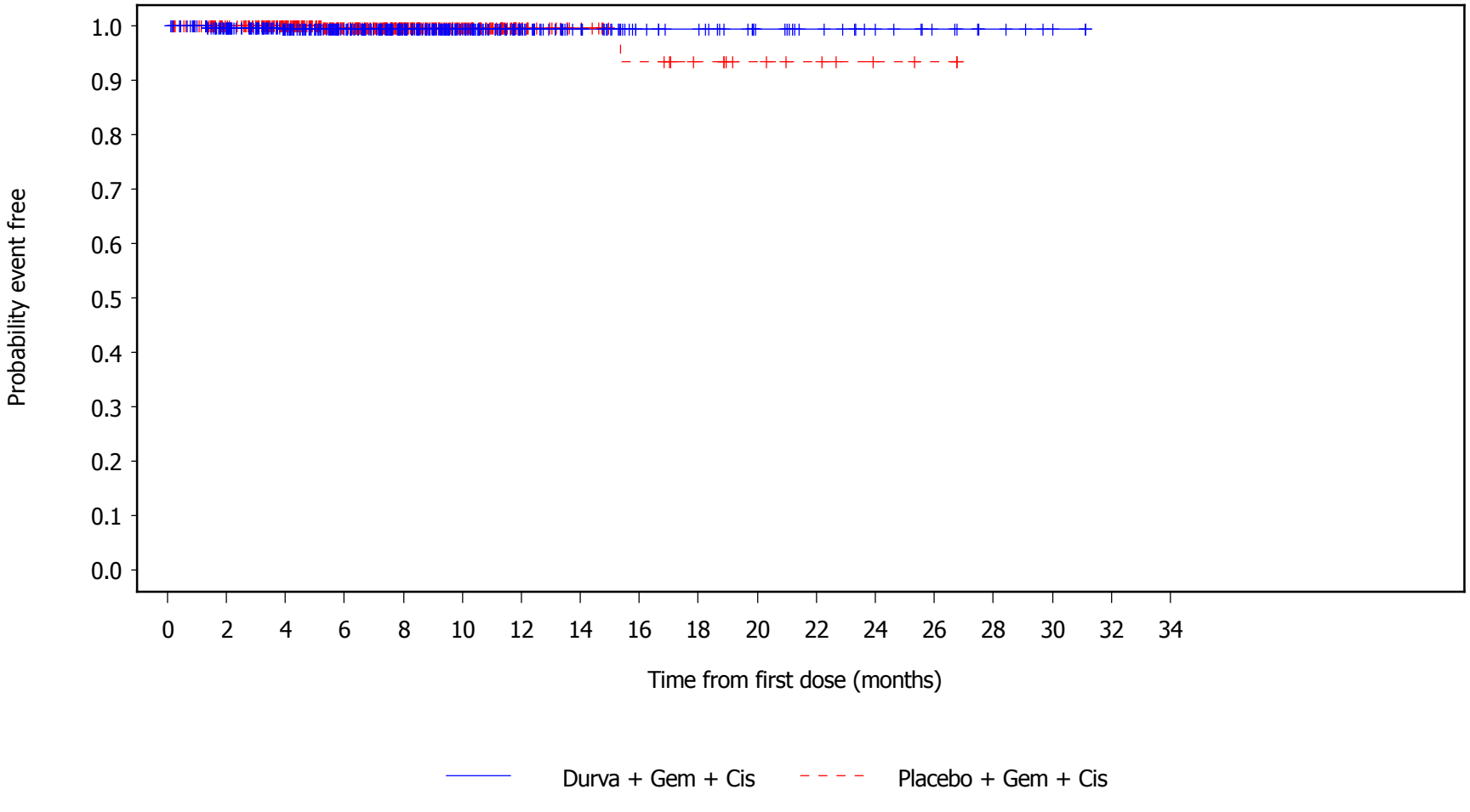
Figure 3.3.421 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	232	158	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

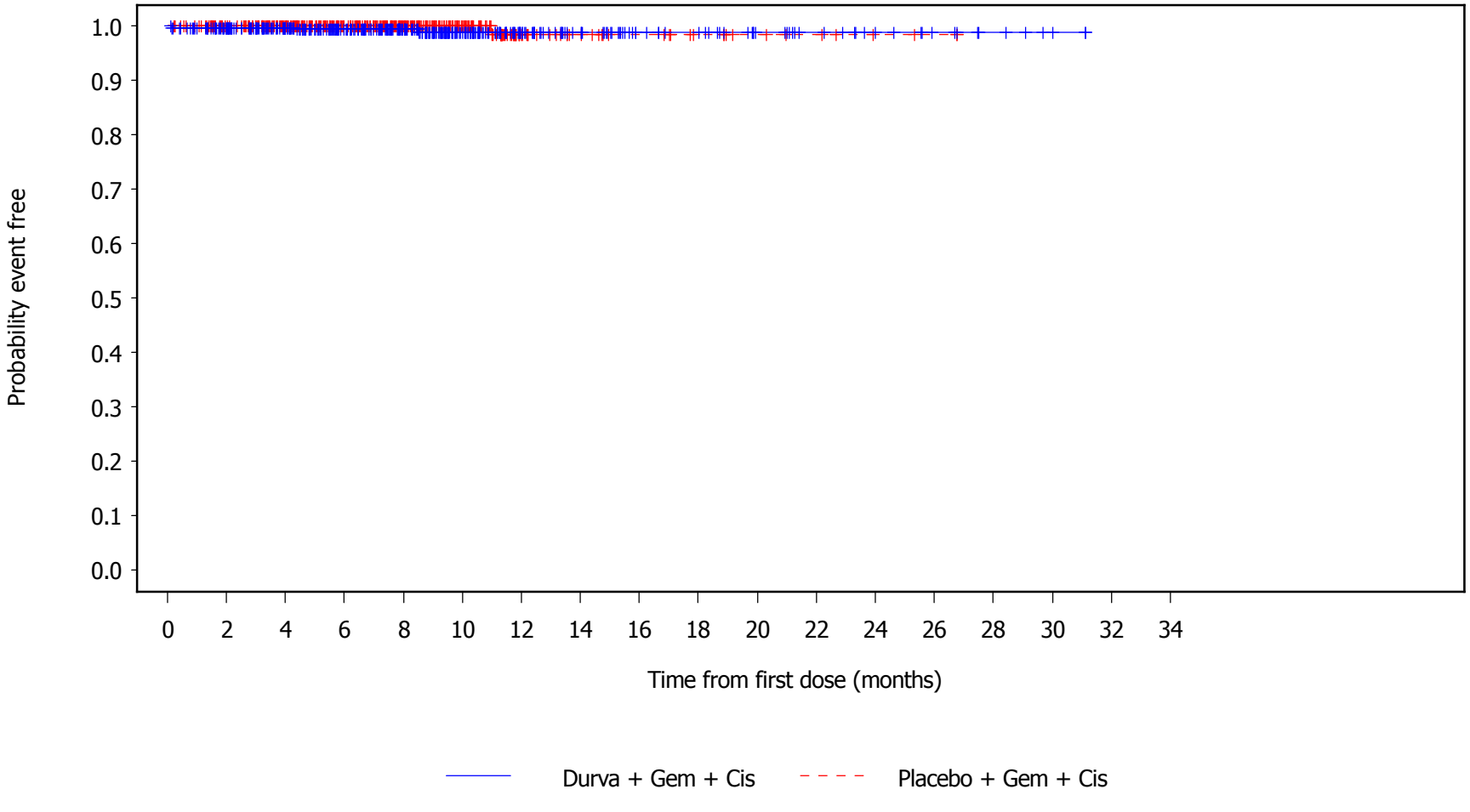
Figure 3.3.422 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Liver abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	313	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	231	159	89	34	22	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

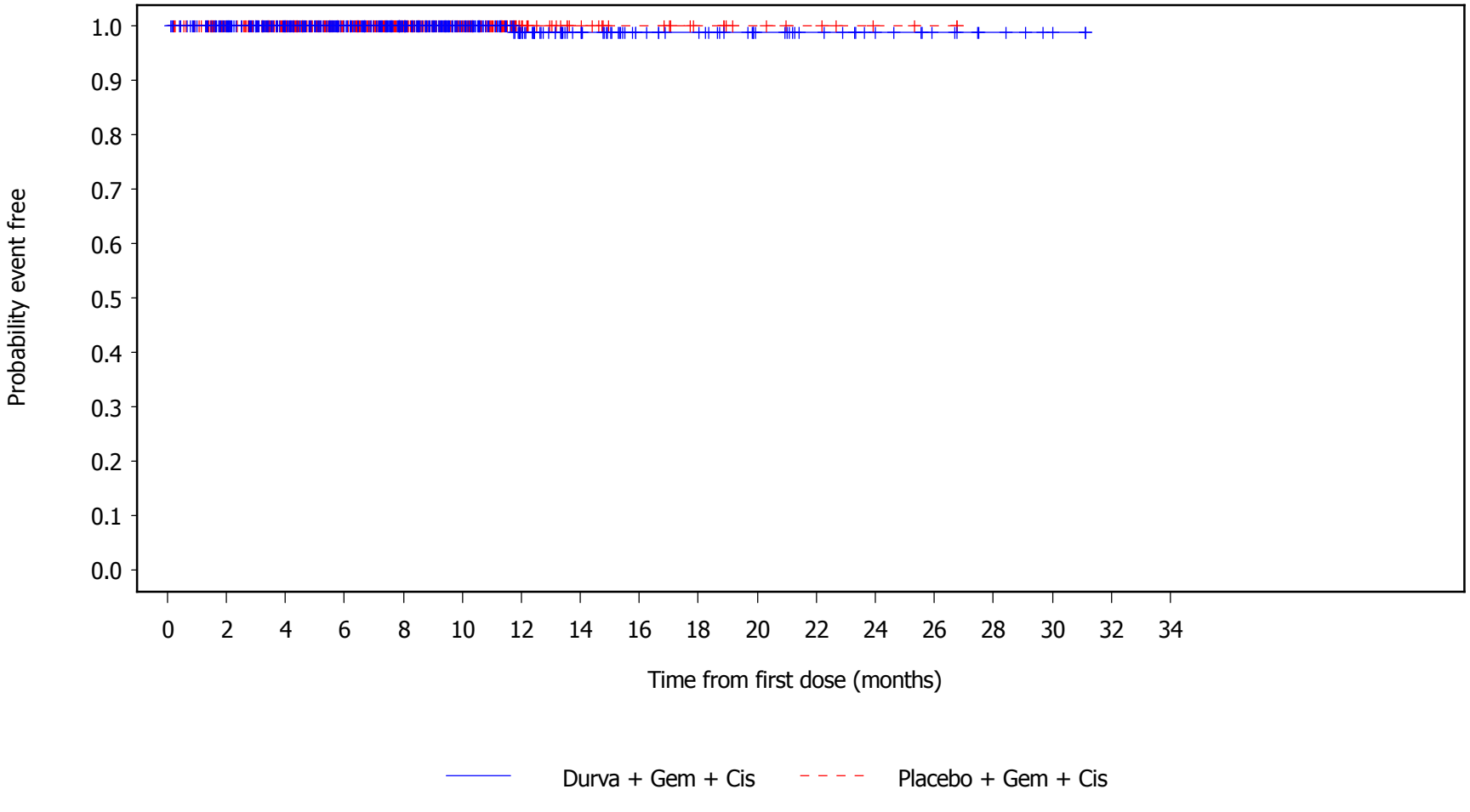
Figure 3.3.423 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Hepatic function abnormal
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	130	79	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

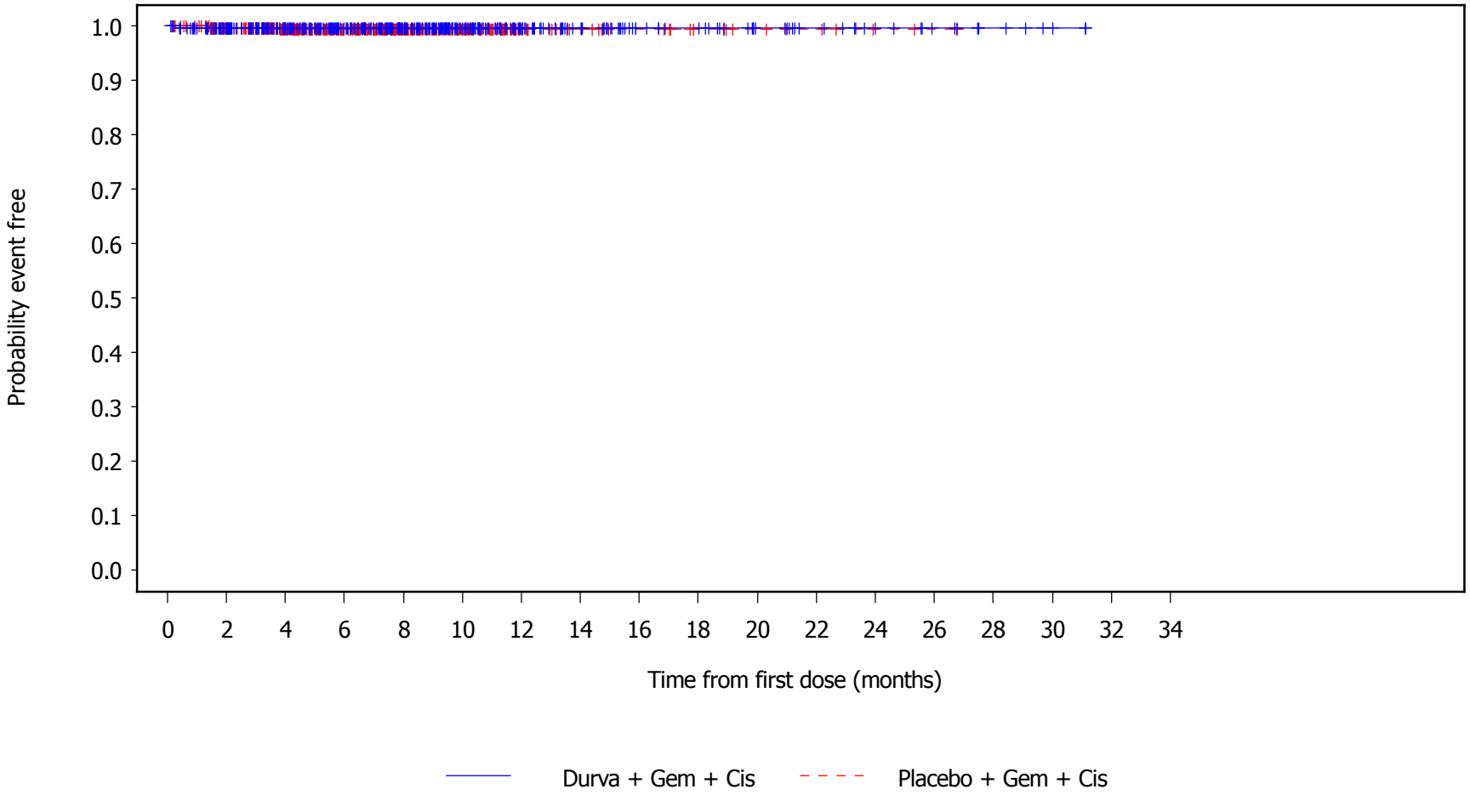
Figure 3.3.424 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Liver function test increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	79	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

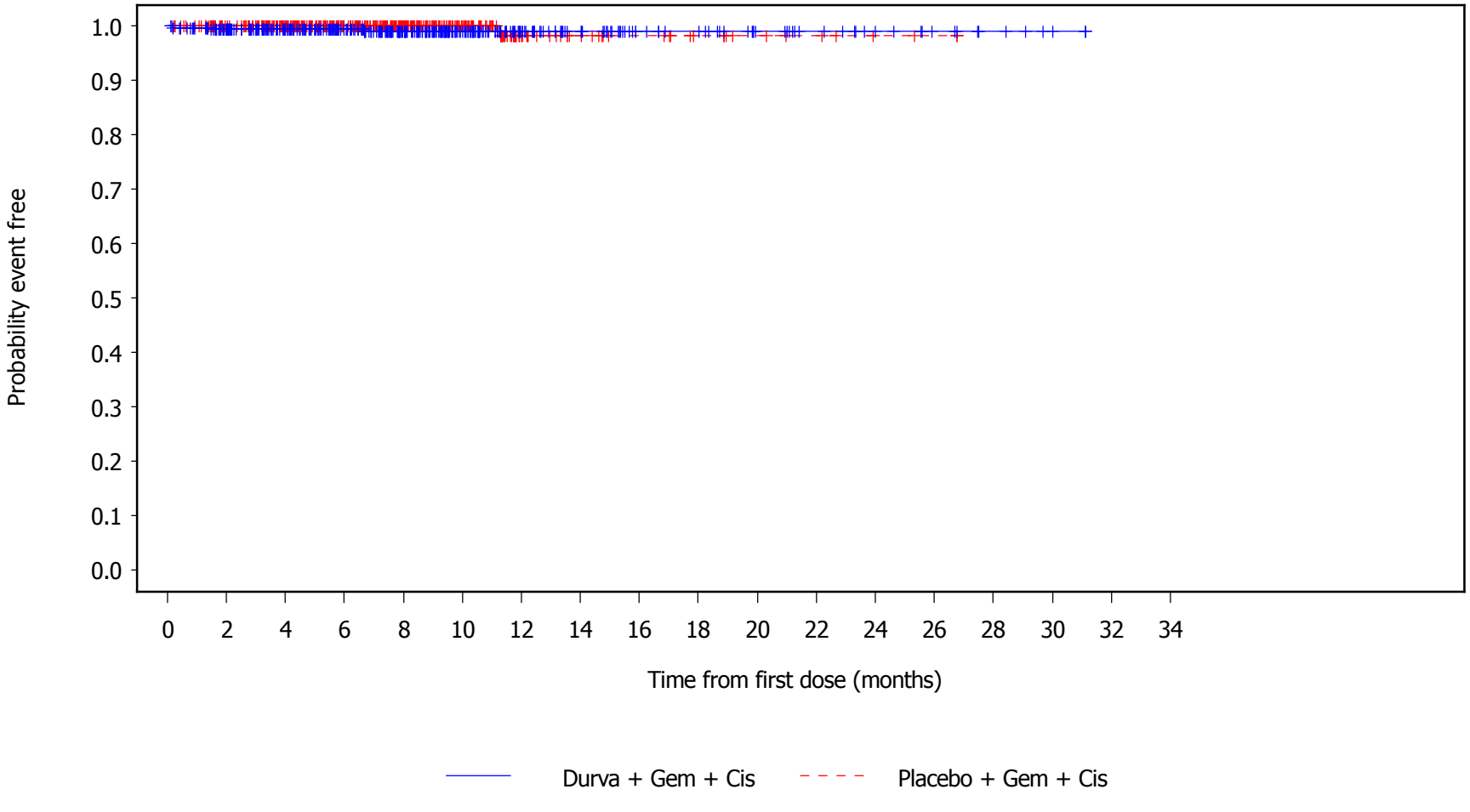
Figure 3.3.425 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	311	230	157	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

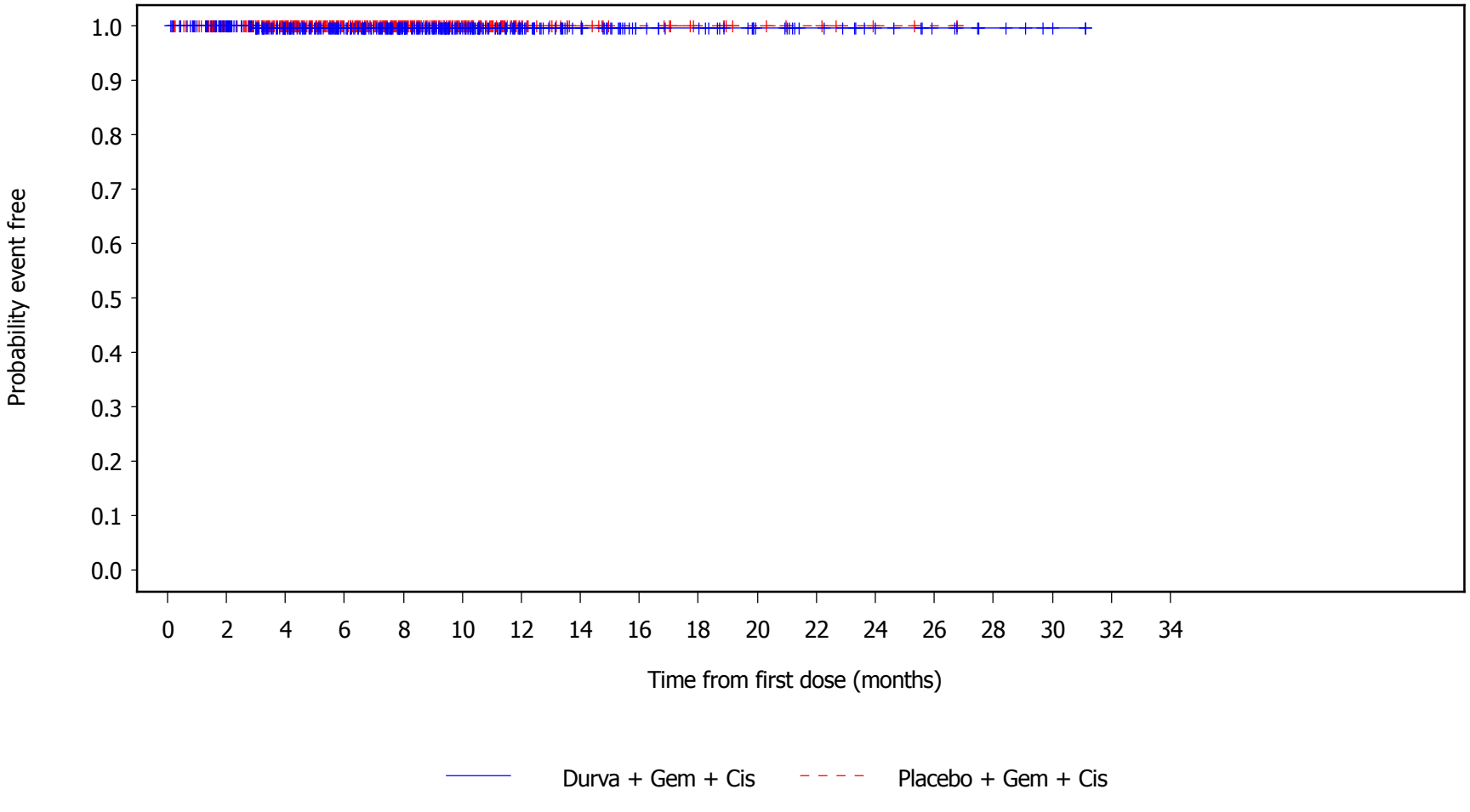
Figure 3.3.426 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Hepatic failure
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	197	130	79	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

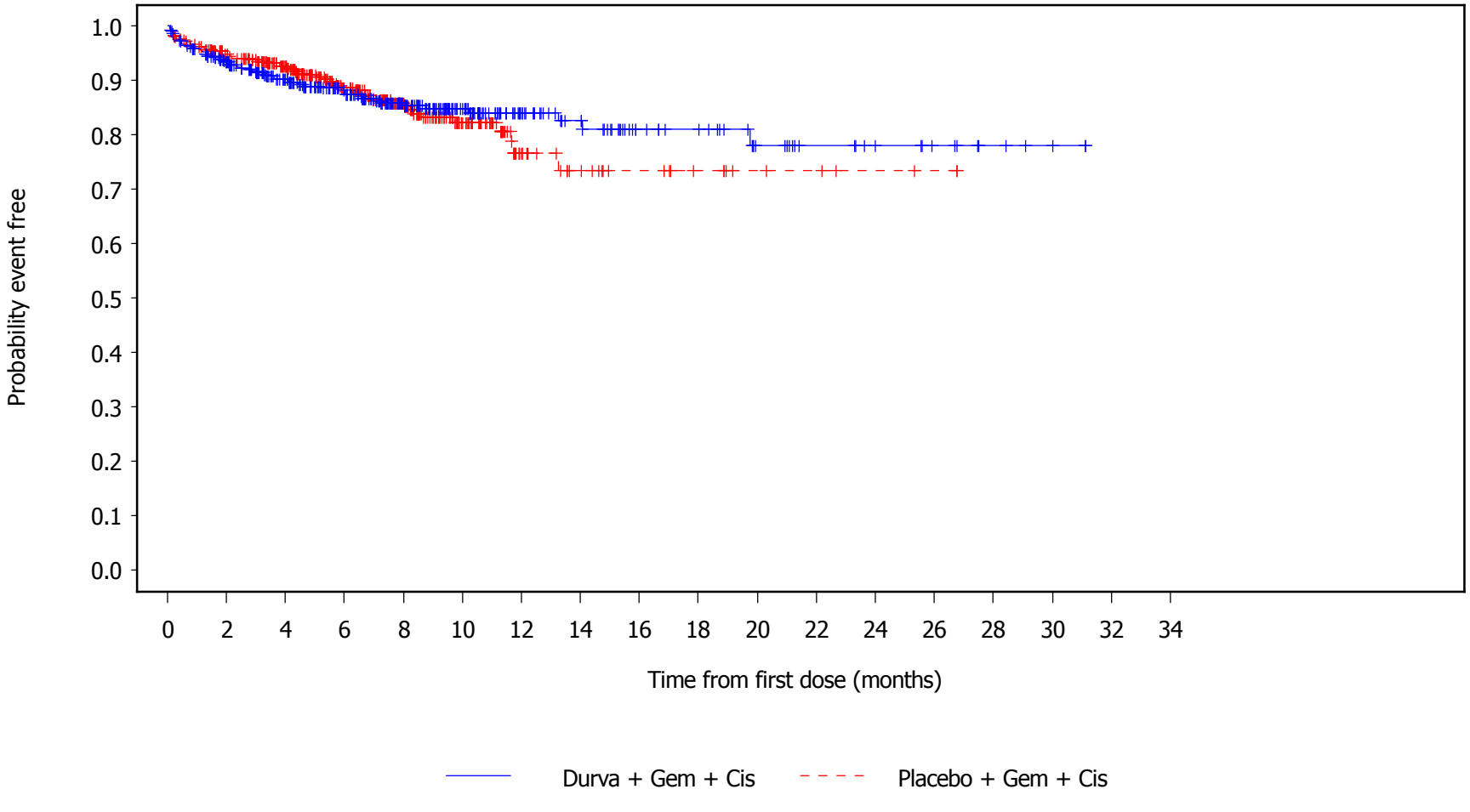
Figure 3.3.427 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Oesophageal varices haemorrhage
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

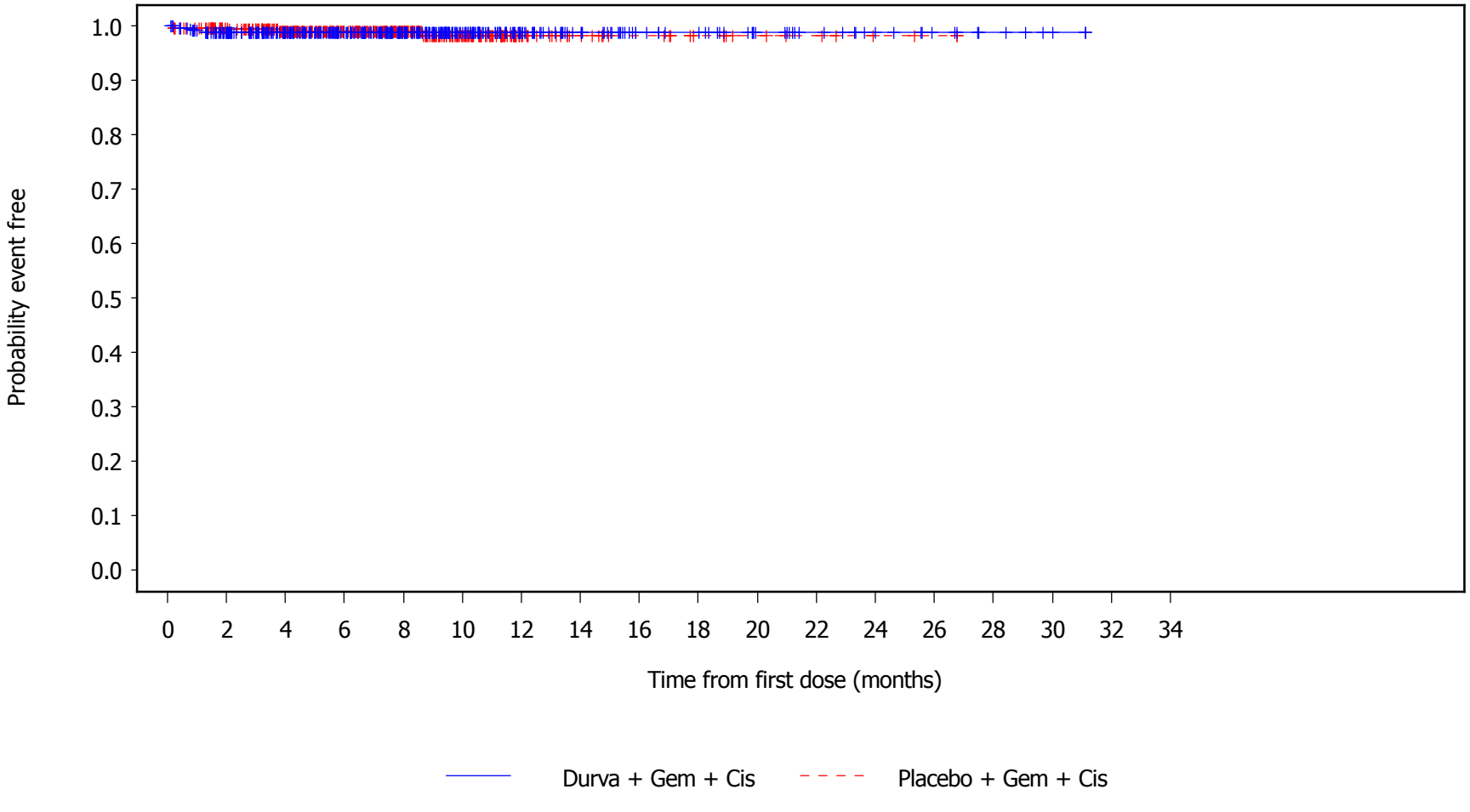
Figure 3.3.428 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI GT: Biliary SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	350	290	241	177	118	71	54	36	32	21	15	12	8	4	2	0	0	Durva + Gem + Cis
403	352	294	210	144	79	29	19	13	9	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

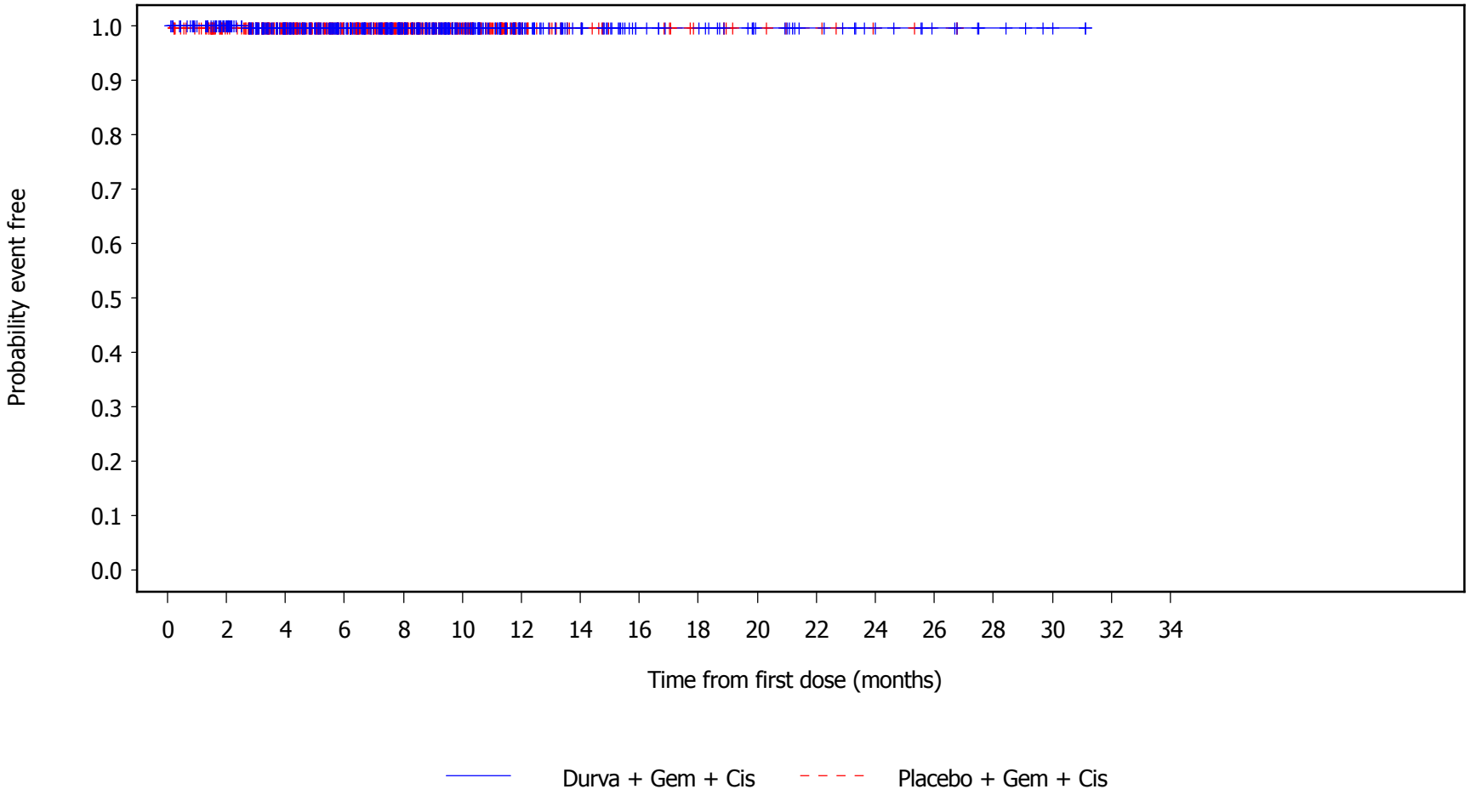
Figure 3.3.429 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Cholangitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	311	261	197	130	79	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	310	229	157	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

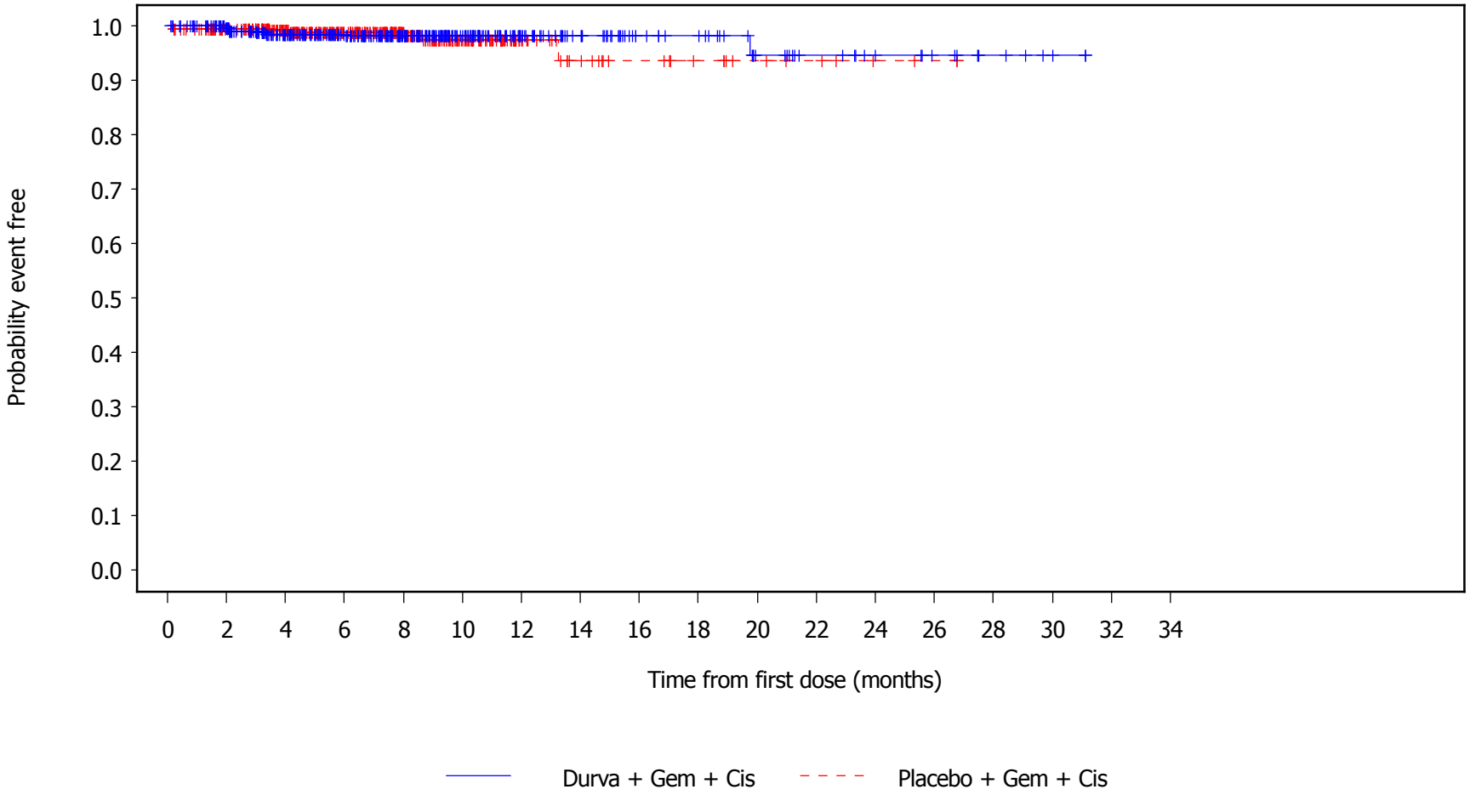
Figure 3.3.430 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Cholecystitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

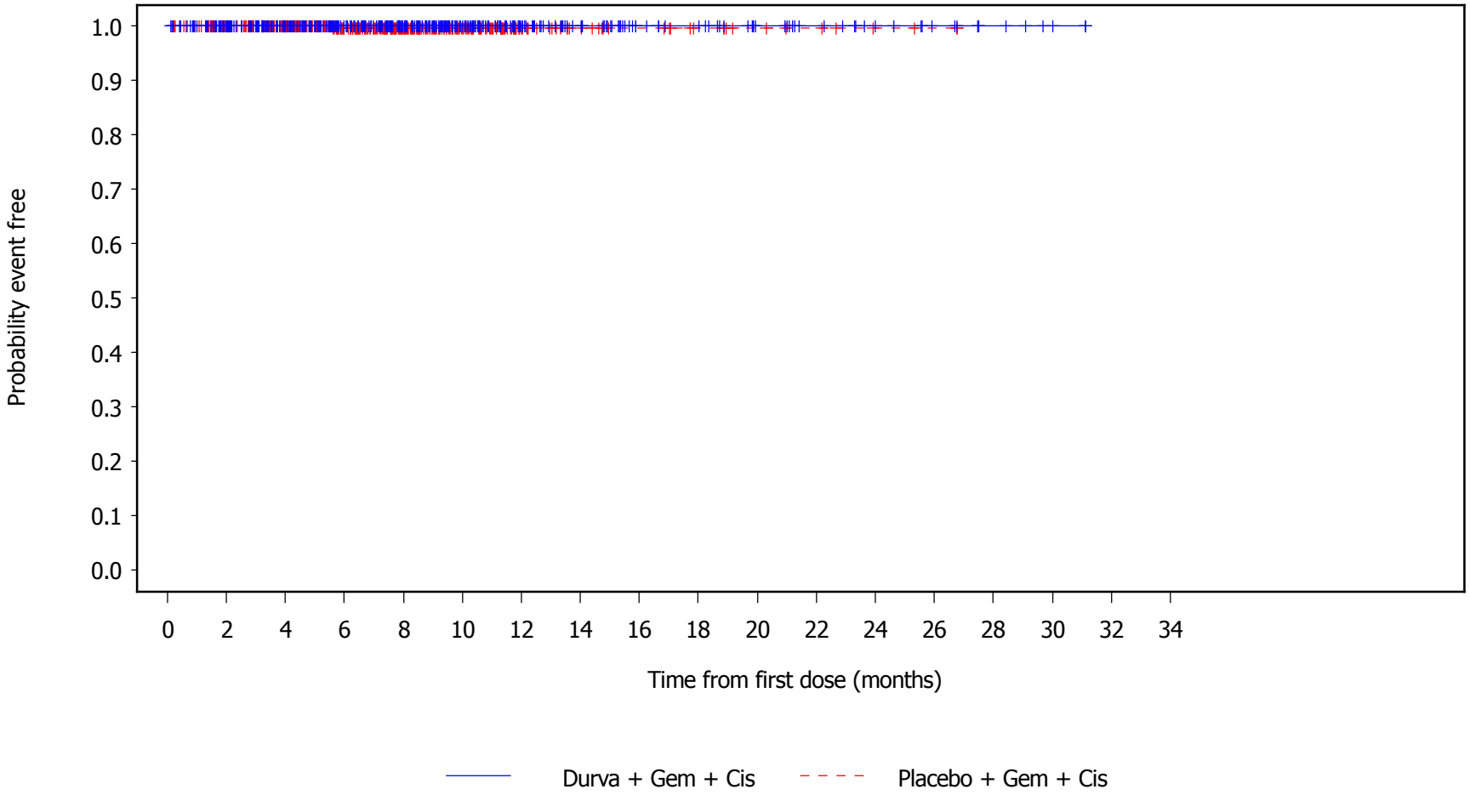
Figure 3.3.431 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Biliary obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	311	262	196	130	79	57	39	35	23	17	13	9	5	2	0	0	Durva + Gem + Cis
403	370	311	229	156	86	33	21	15	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

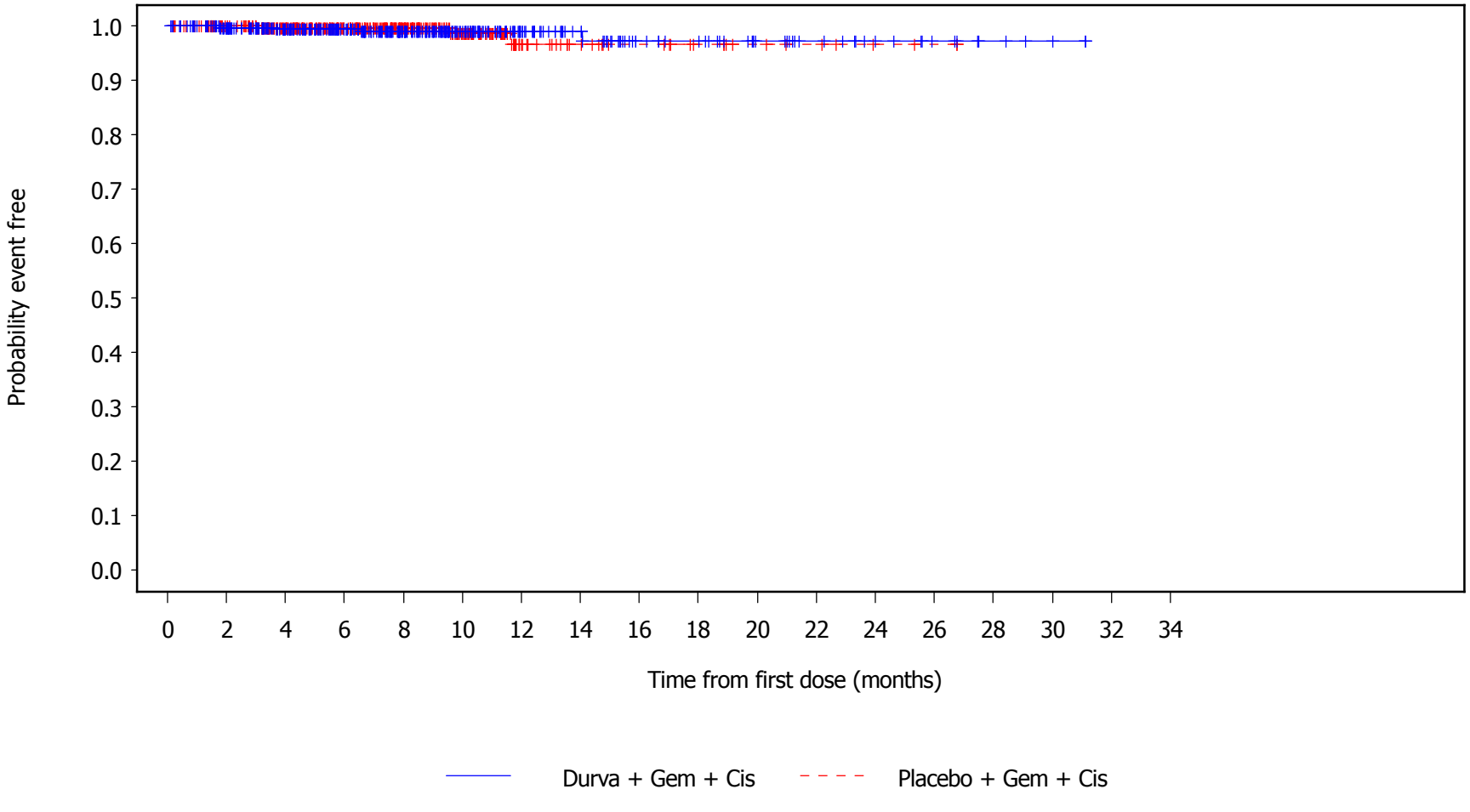
Figure 3.3.432 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Biliary abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	231	158	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

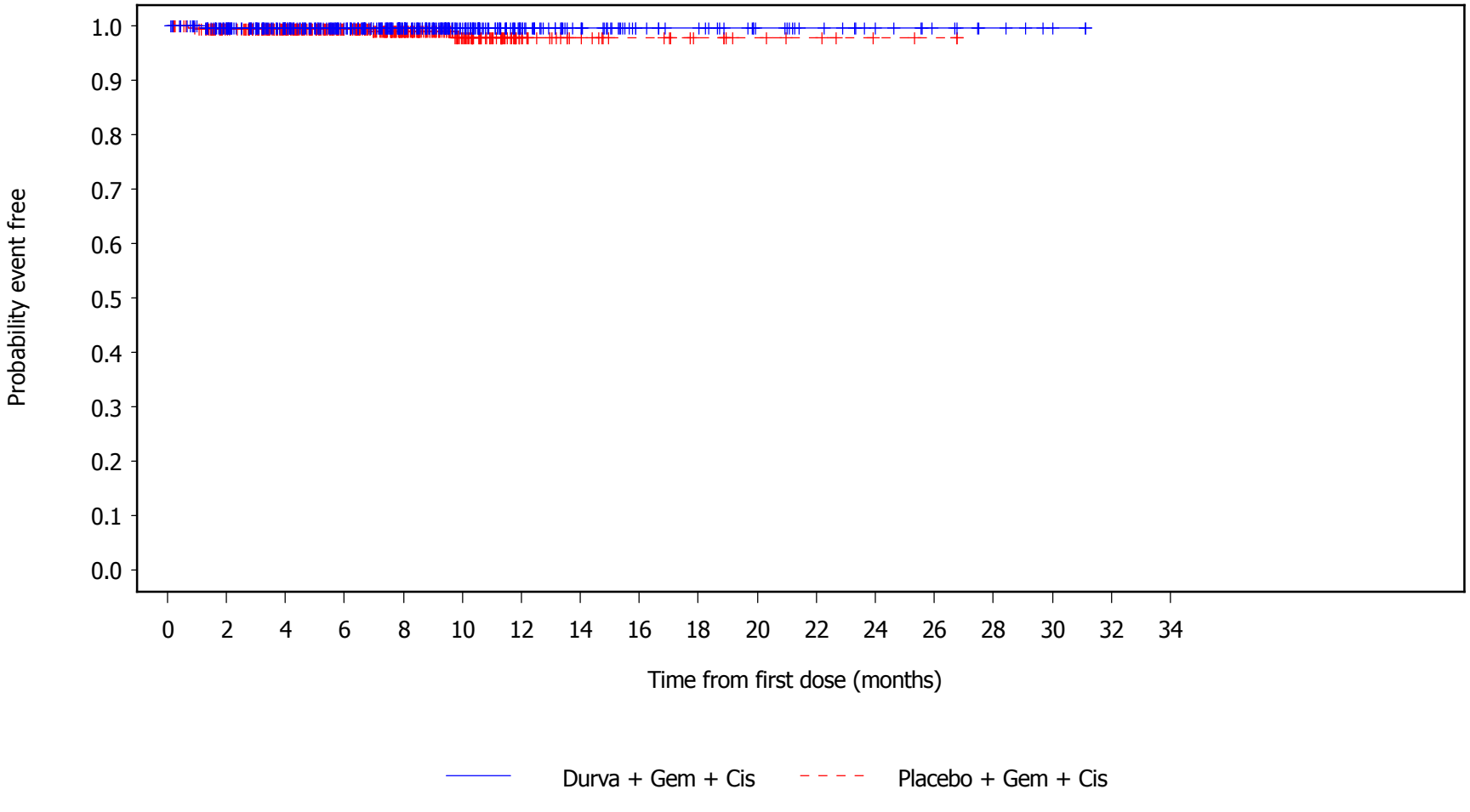
Figure 3.3.433 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Biliary sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	264	197	130	79	58	39	35	24	18	13	8	4	2	0	0	Durva + Gem + Cis
403	371	312	232	159	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

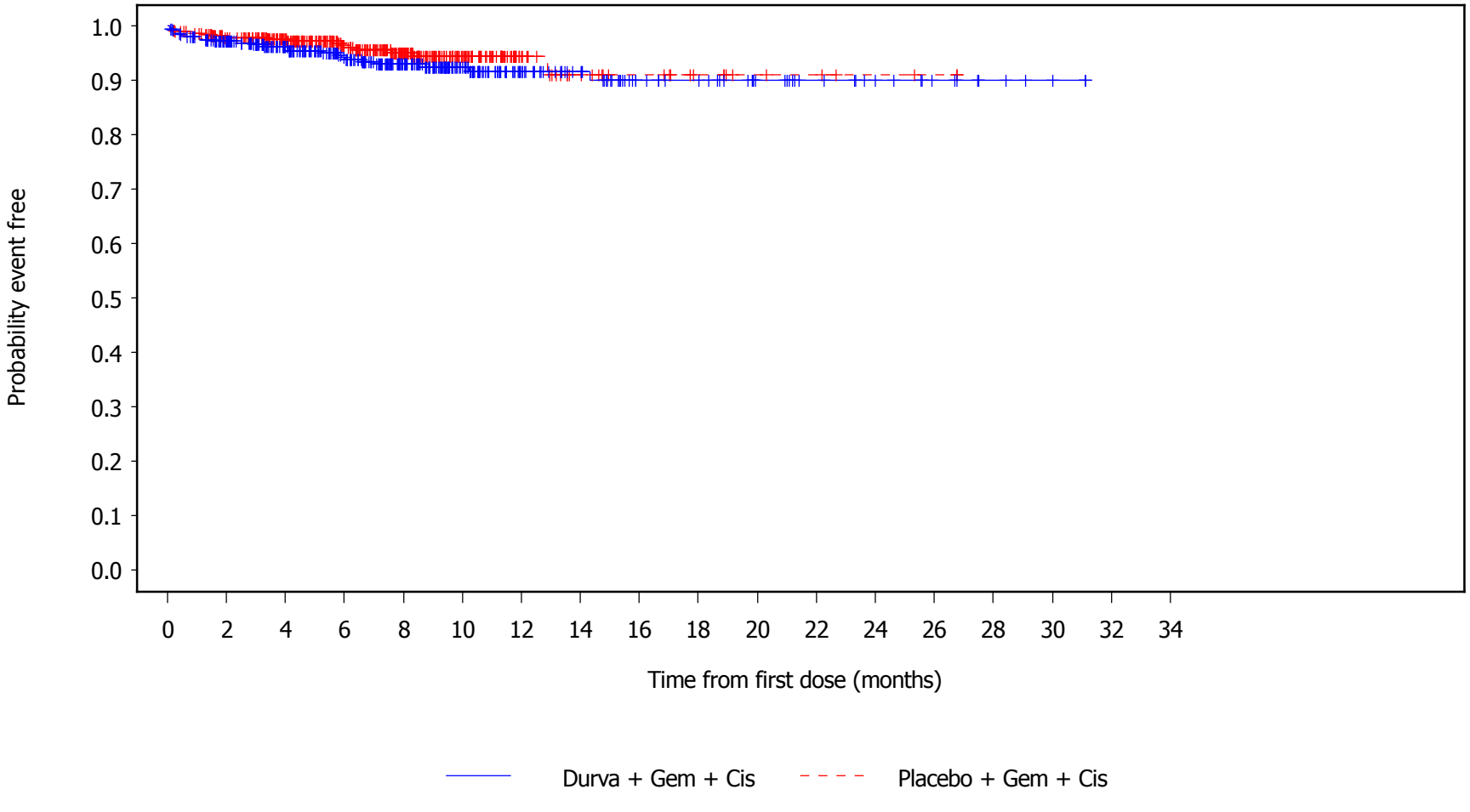
Figure 3.3.434 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	312	231	159	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

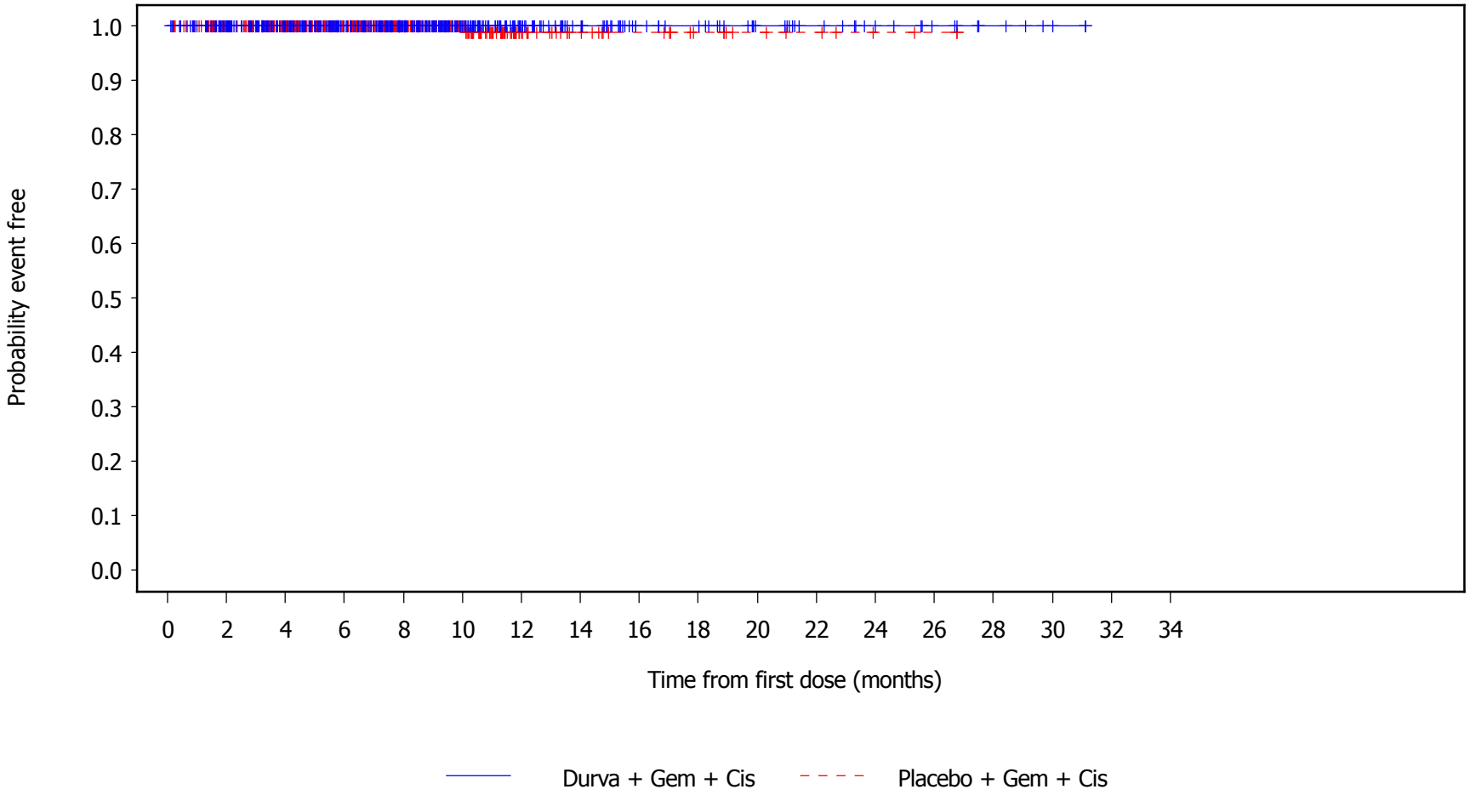
Figure 3.3.435 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Cholangitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	363	305	251	185	123	74	56	37	33	23	17	13	8	4	2	0	0	Durva + Gem + Cis
403	363	306	223	152	85	33	20	14	9	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

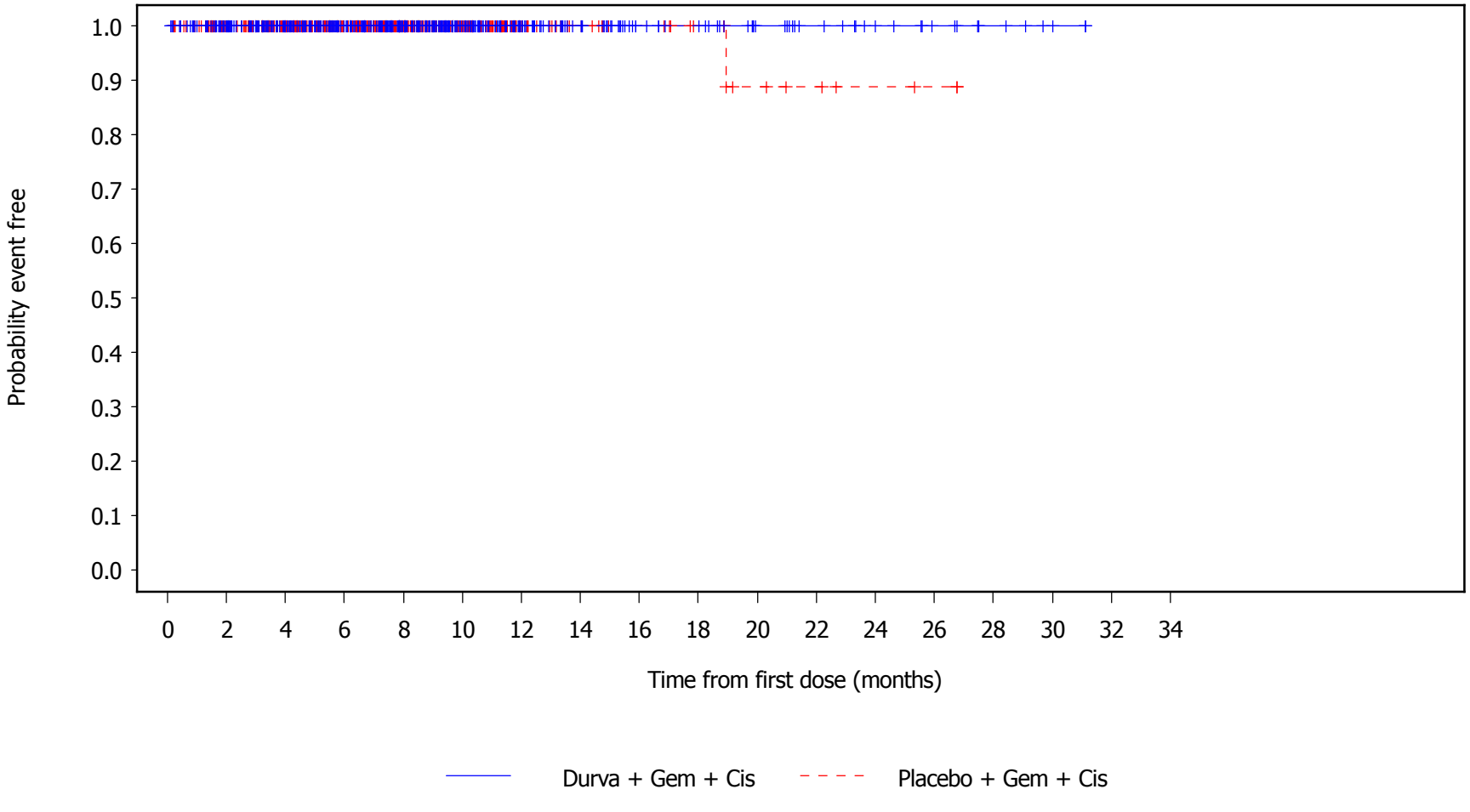
Figure 3.3.436 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Cholangitis infective
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

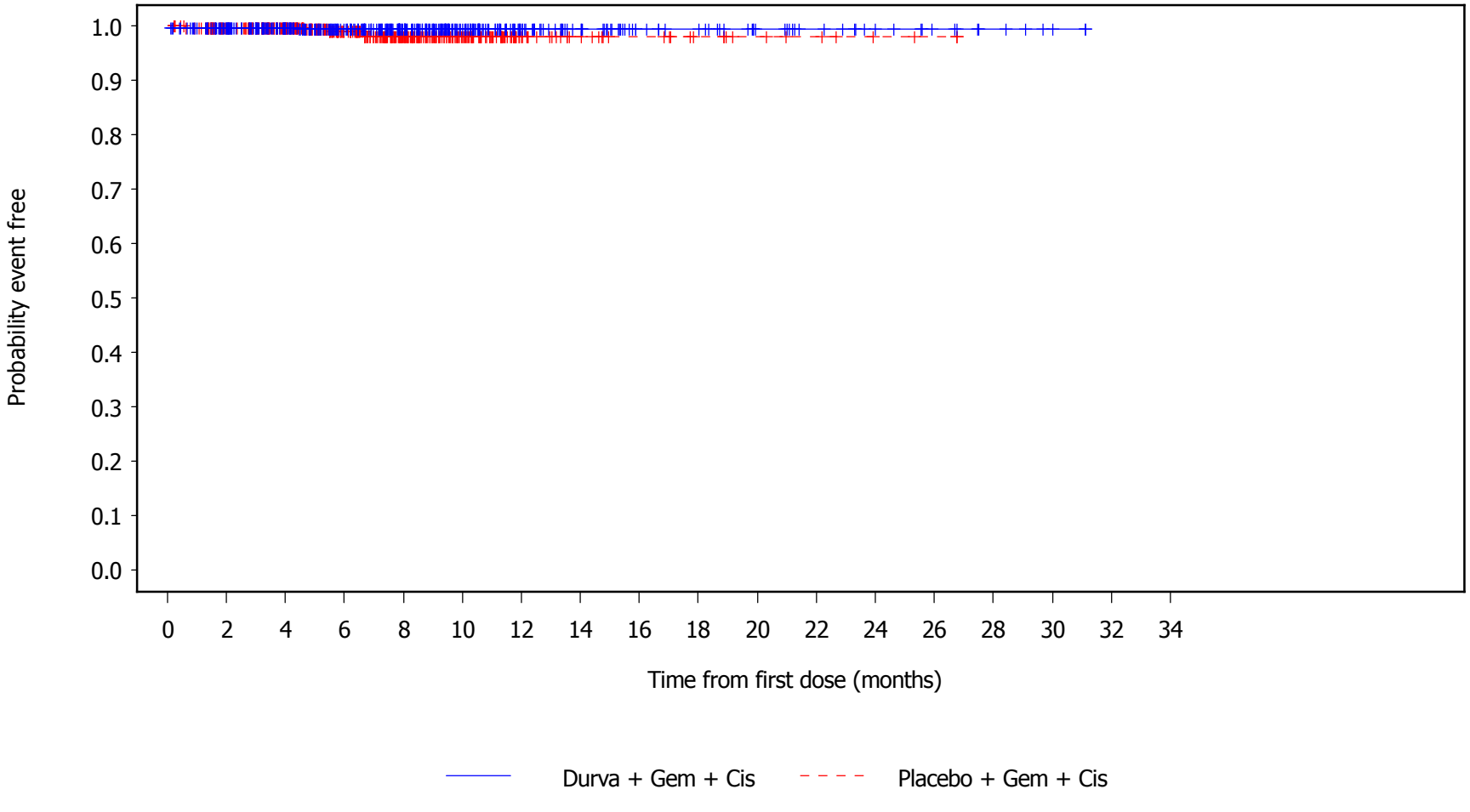
Figure 3.3.437 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

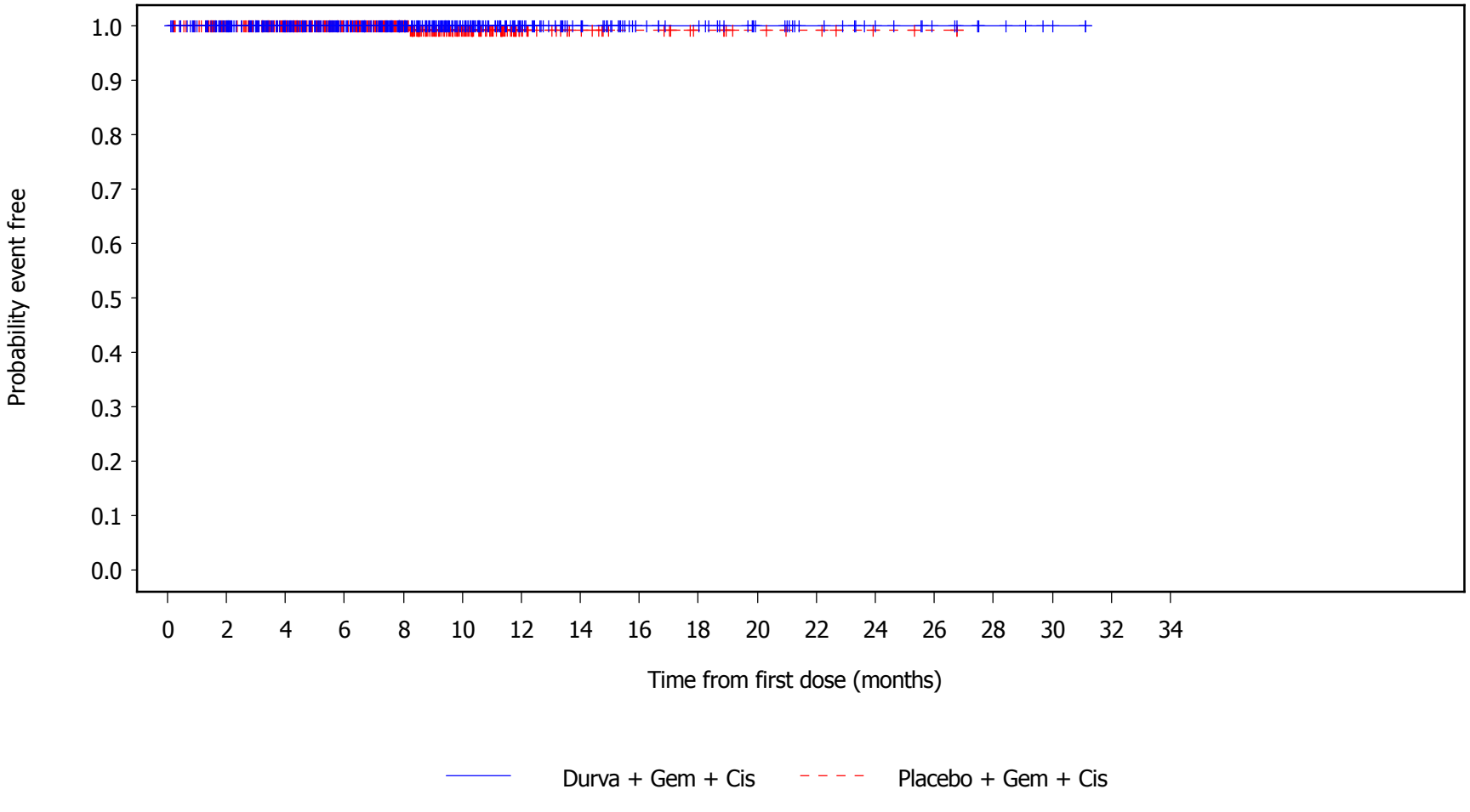
Figure 3.3.438 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Cholecystitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	263	197	130	79	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	230	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

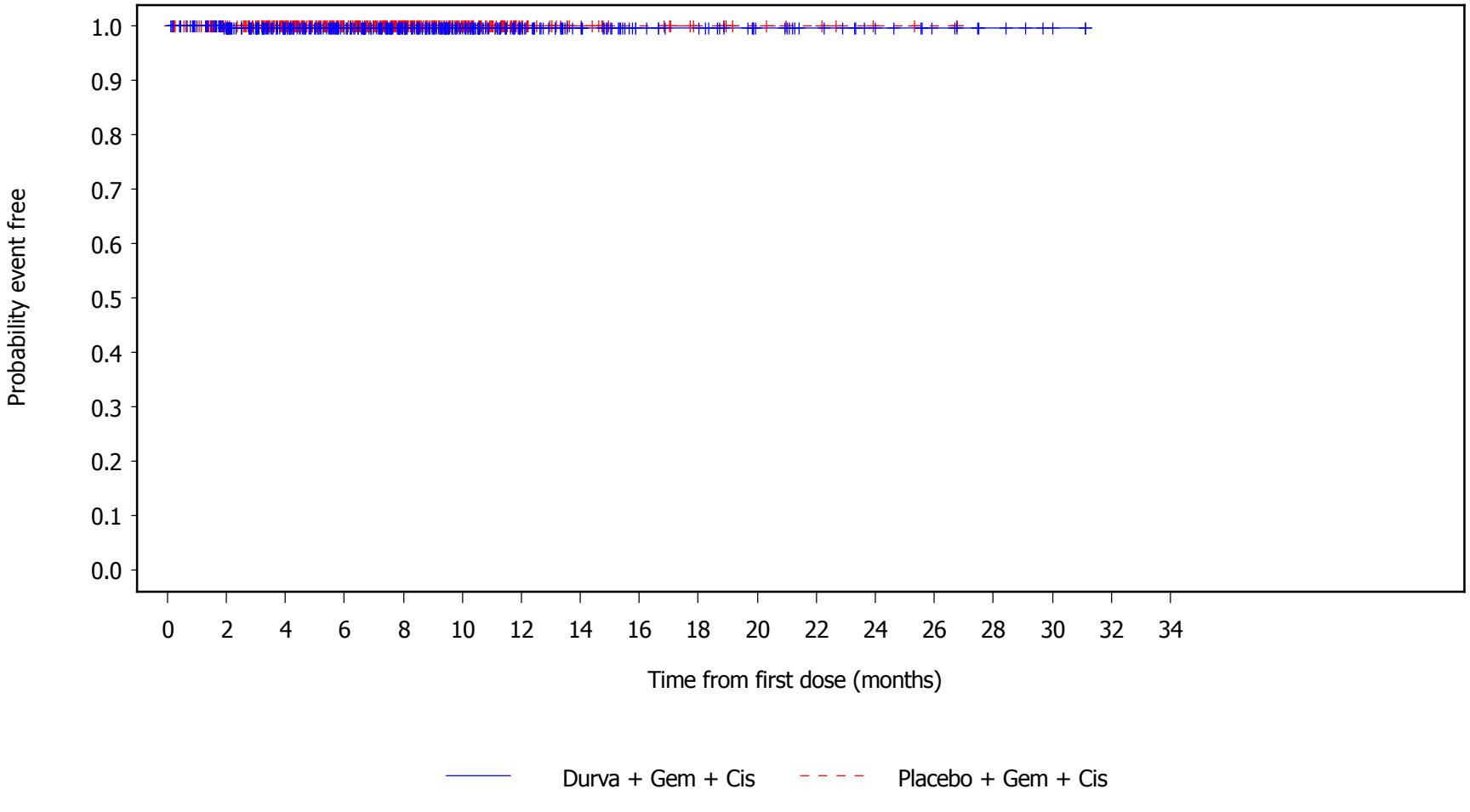
Figure 3.3.439 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Gallbladder empyema
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

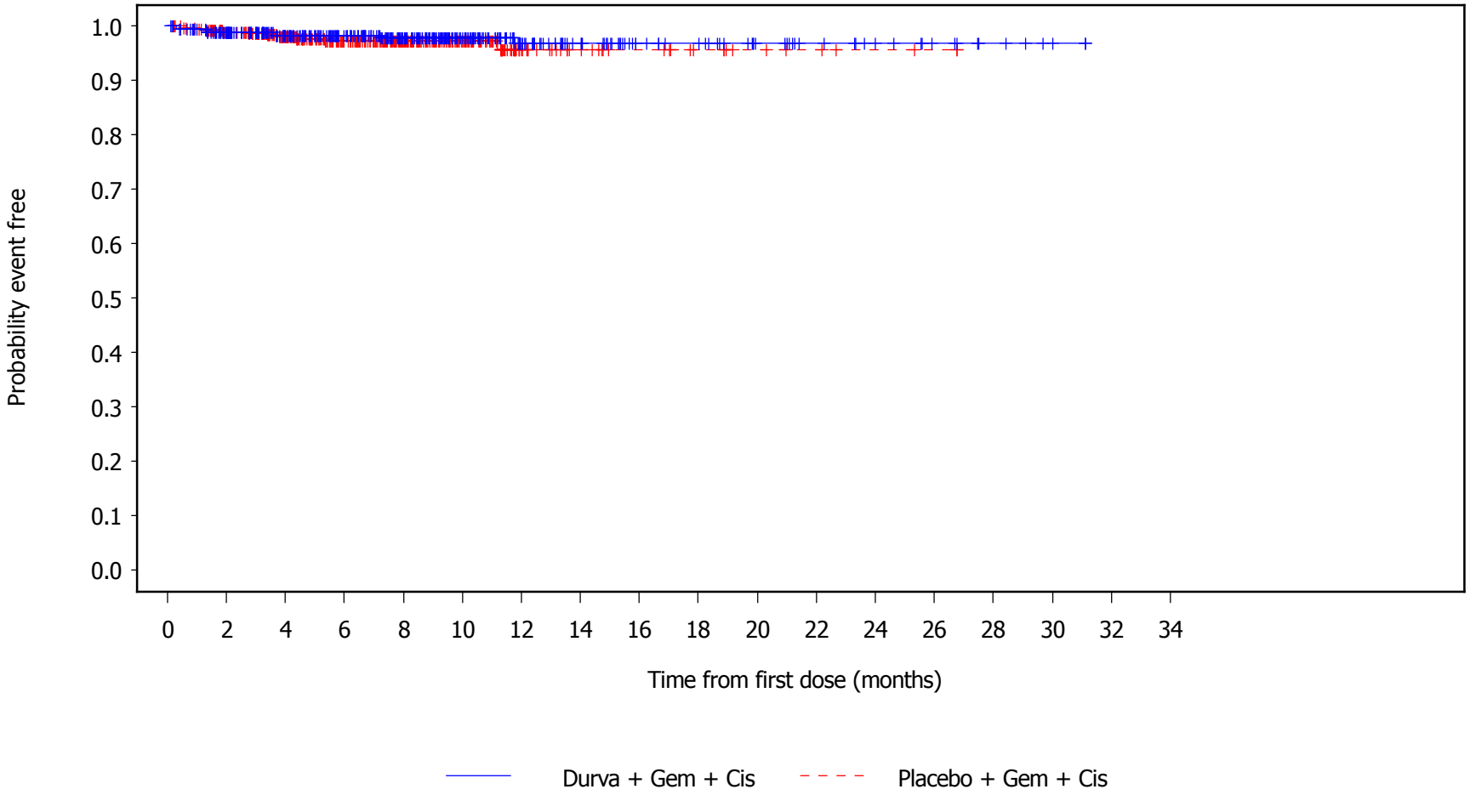
Figure 3.3.440 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Gallbladder obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

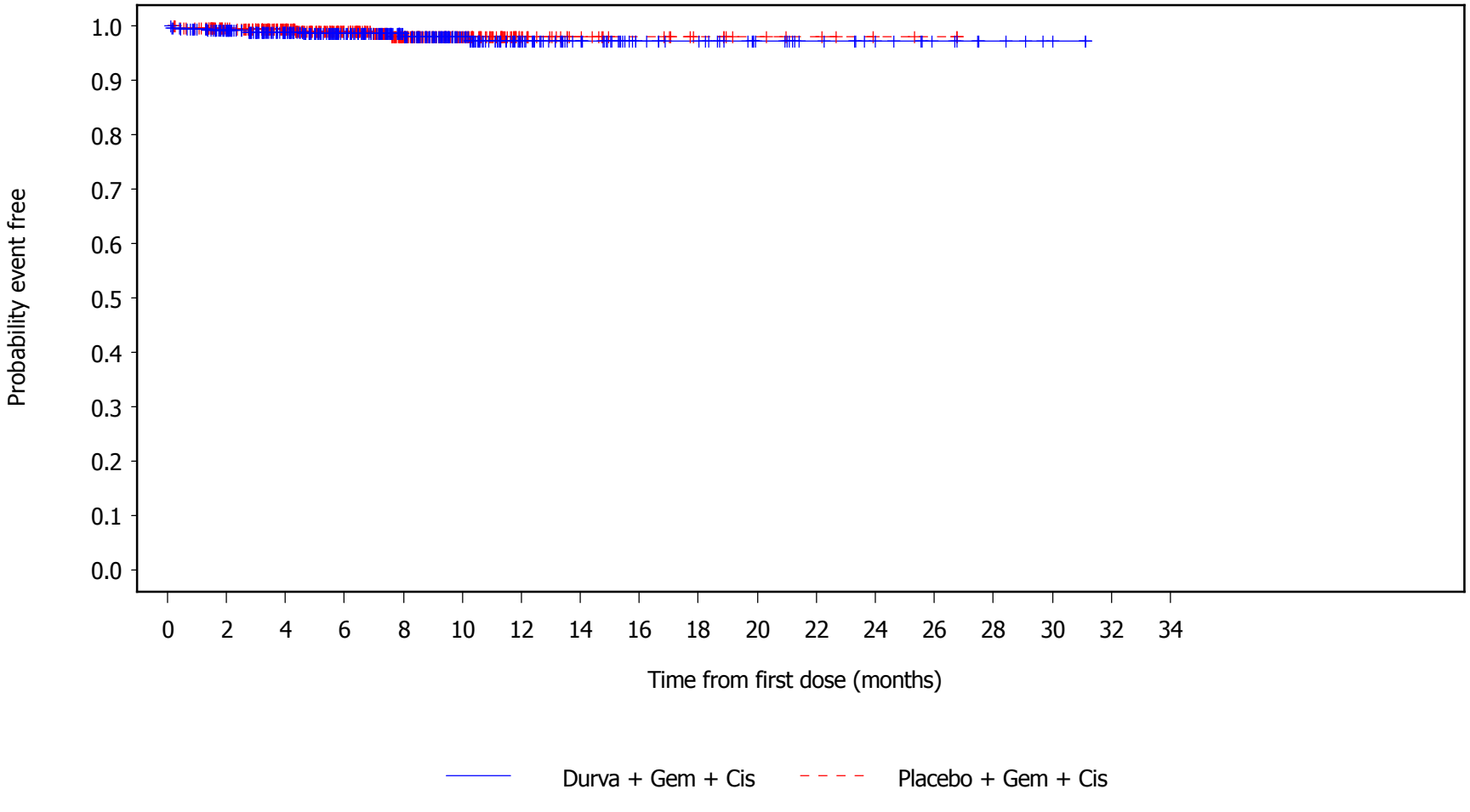
Figure 3.3.441 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Biliary tract infection
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	369	311	261	197	131	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	367	309	229	157	89	33	21	15	10	6	4	2	1	0	0	0	0	Placebo + Gem + Cis

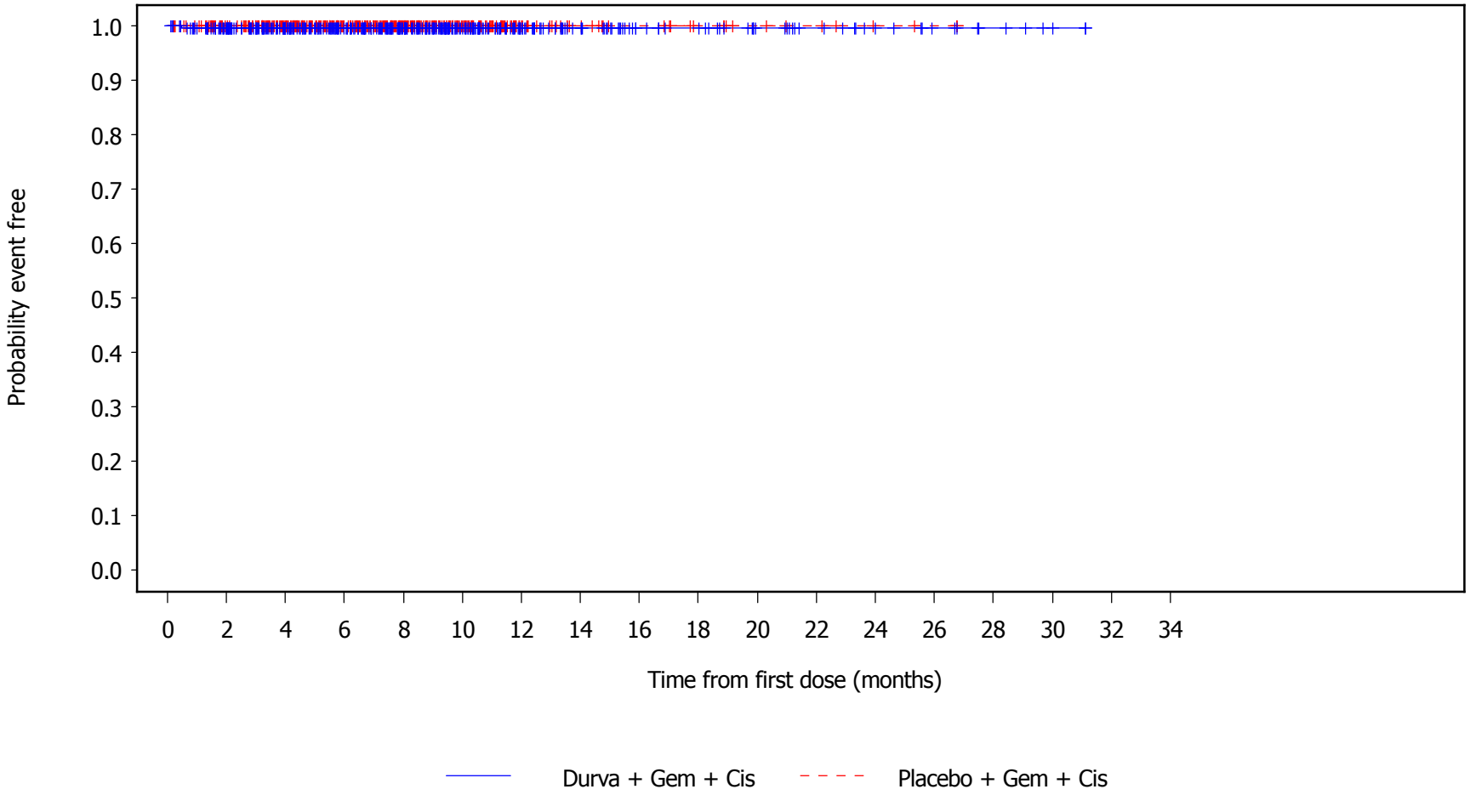
Figure 3.3.442 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	314	262	197	129	79	57	39	35	24	18	14	9	5	2	0	0	Durva + Gem + Cis
403	370	313	232	157	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

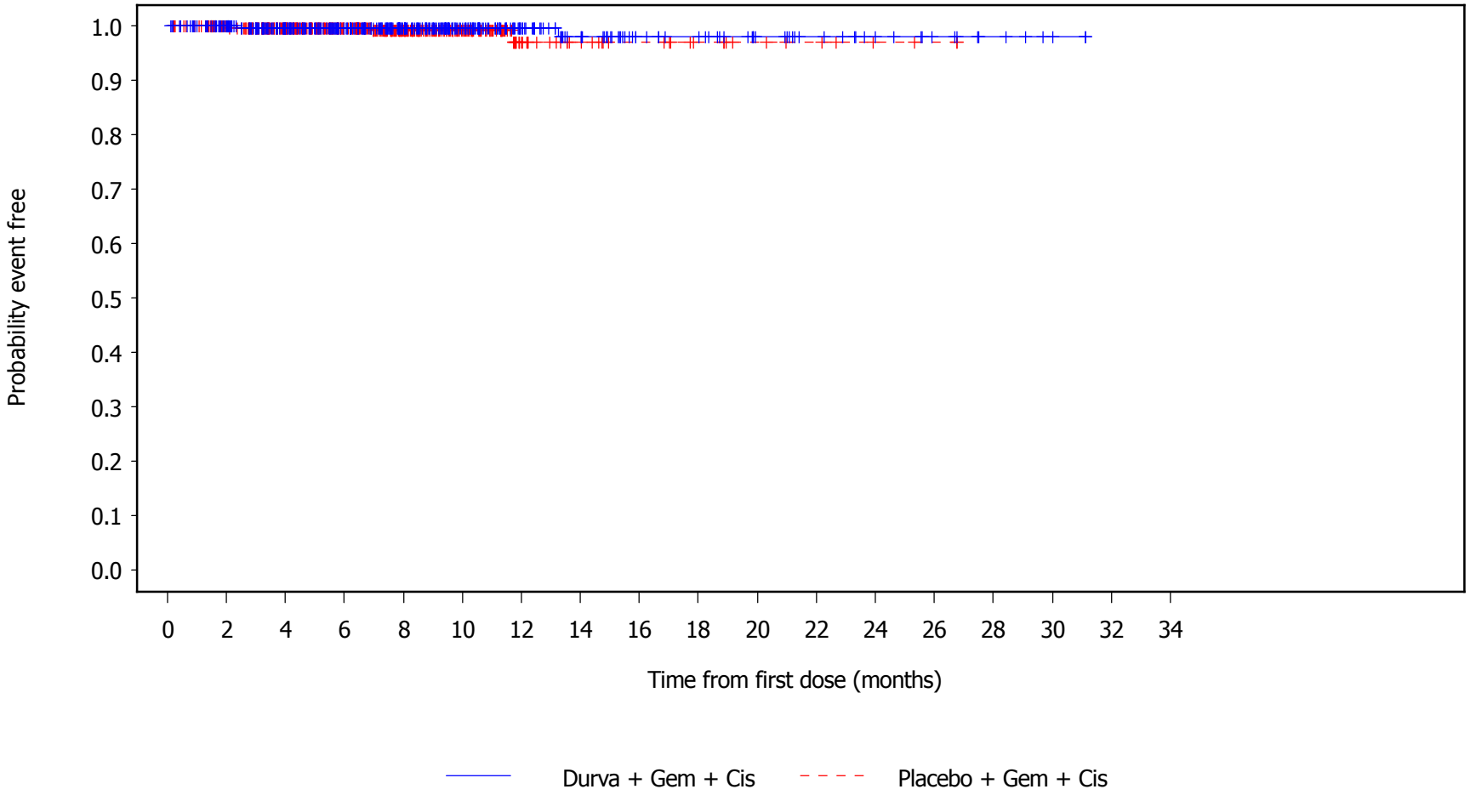
Figure 3.3.443 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

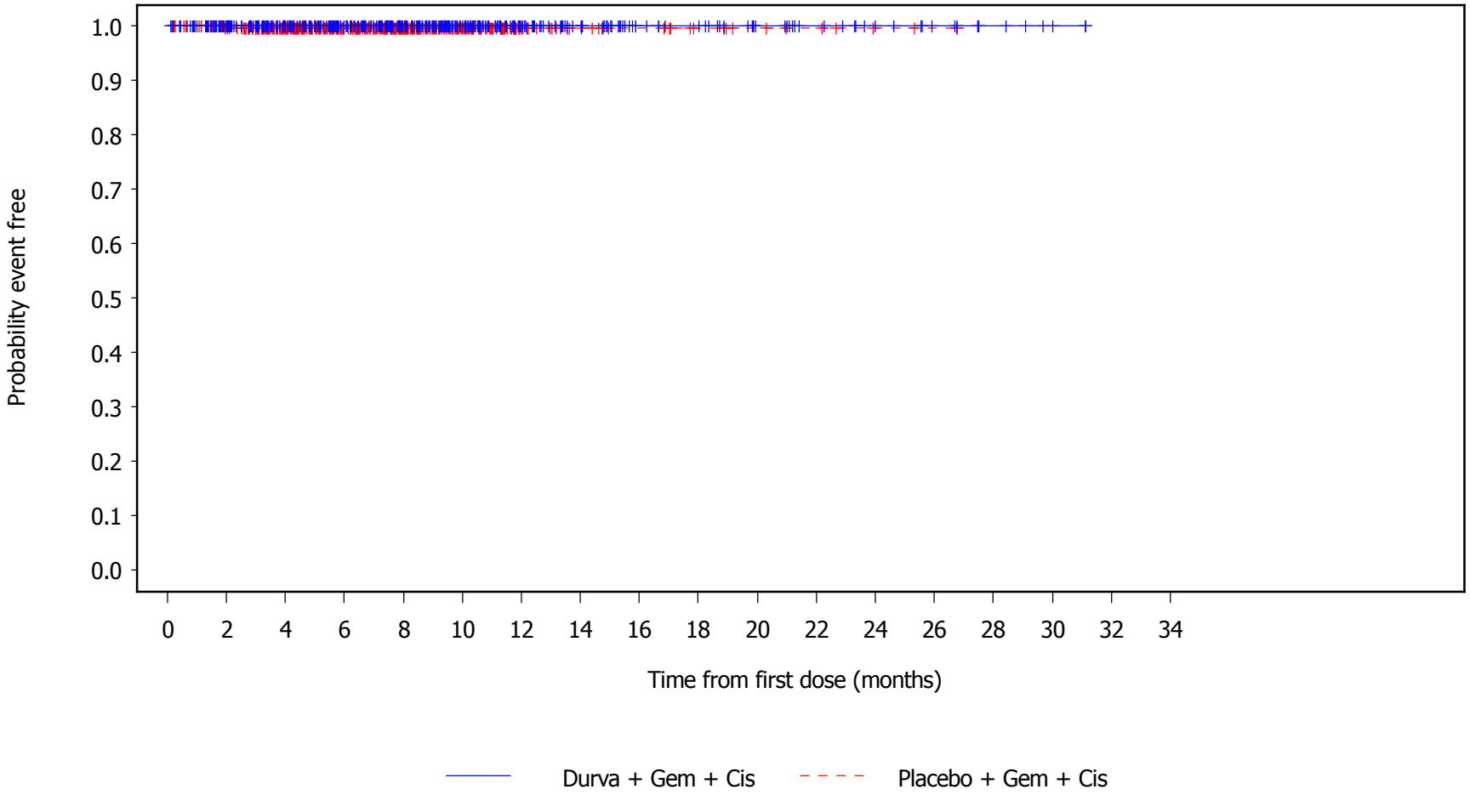
Figure 3.3.444 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	232	158	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

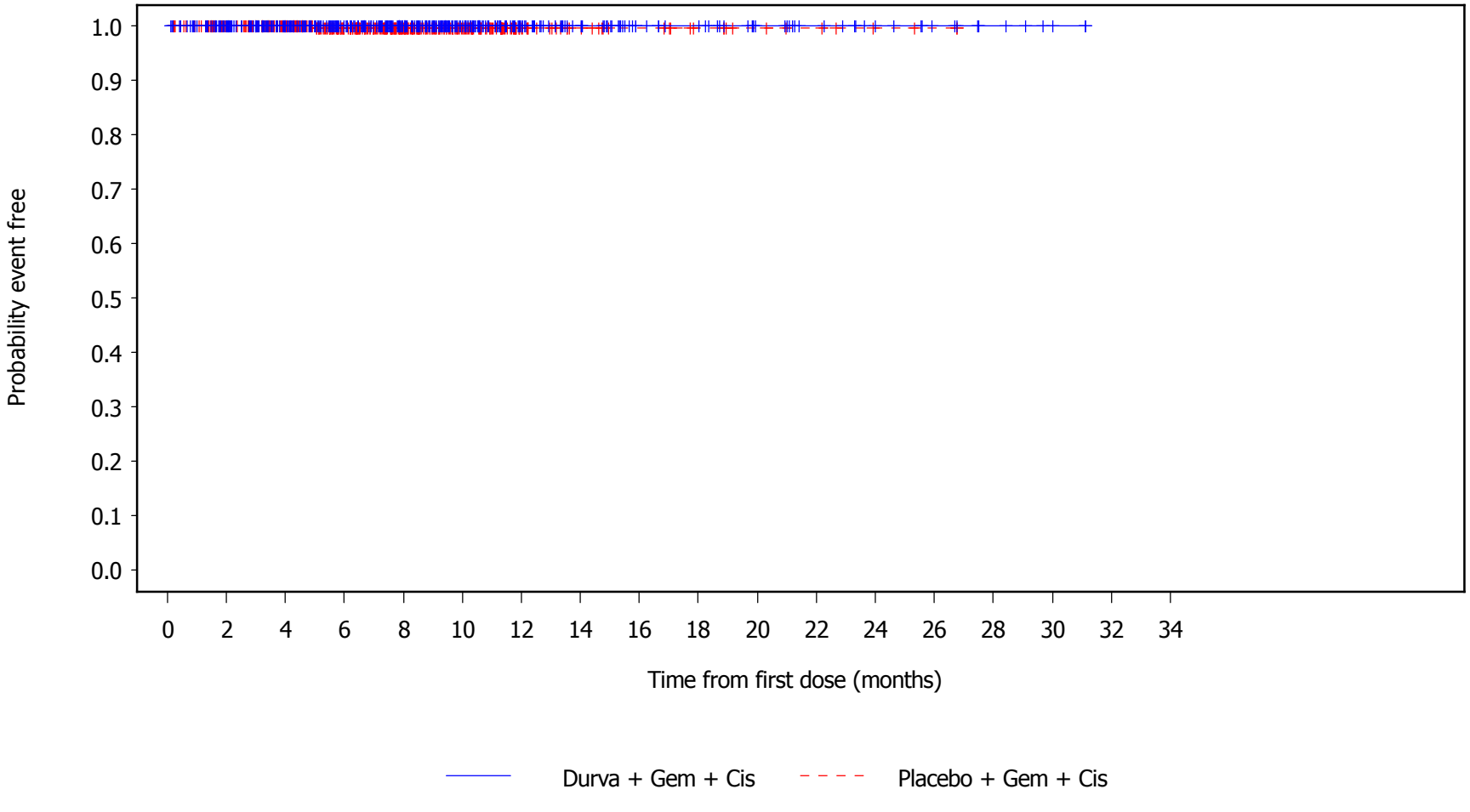
Figure 3.3.445 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Gallbladder rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

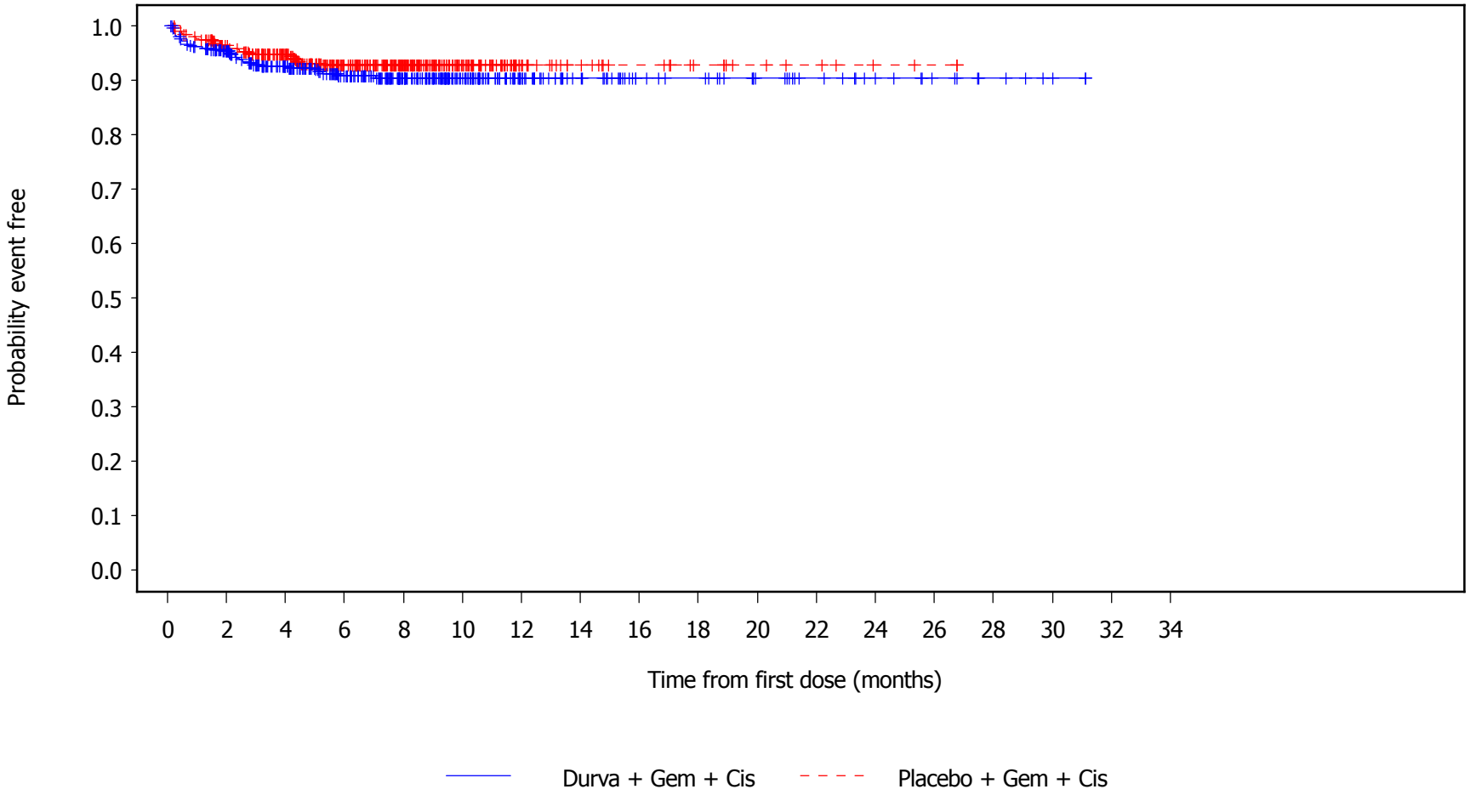
Figure 3.3.446 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Biloma rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

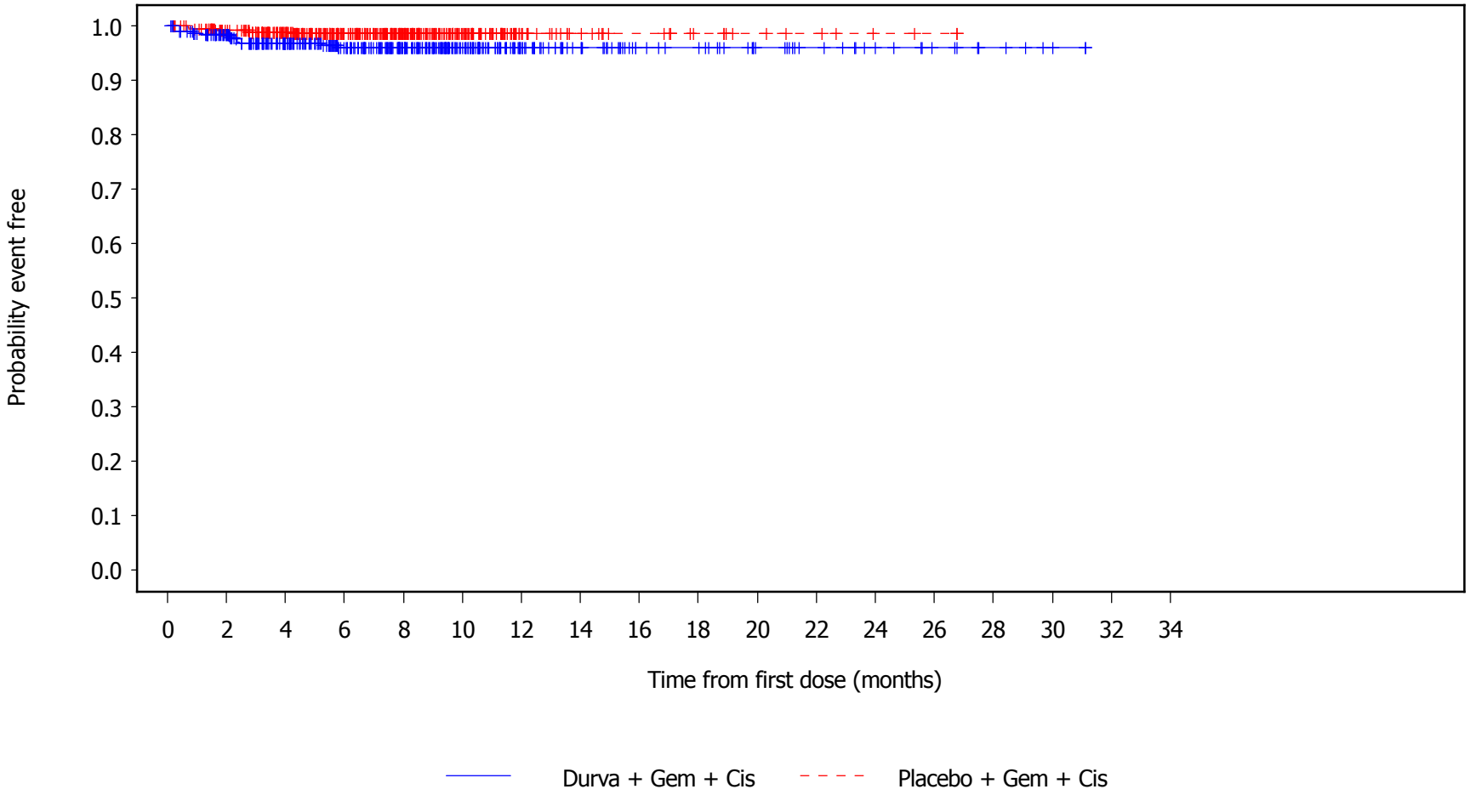
Figure 3.3.447 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI GT: Haematopoietic cytopenias SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	358	296	246	184	122	74	53	37	34	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	361	301	219	152	85	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

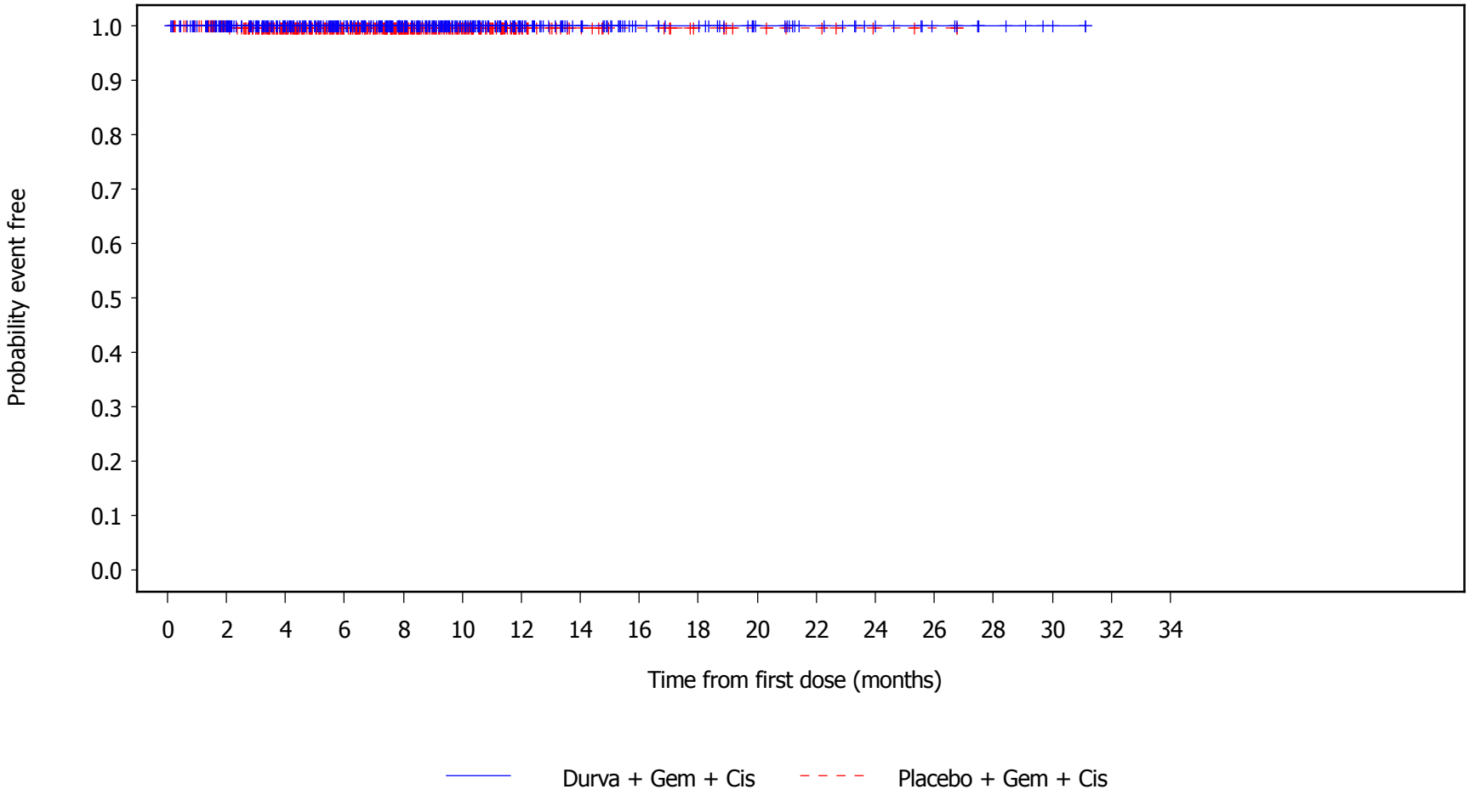
Figure 3.3.448 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Anaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	367	305	255	192	127	77	56	39	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	310	230	158	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

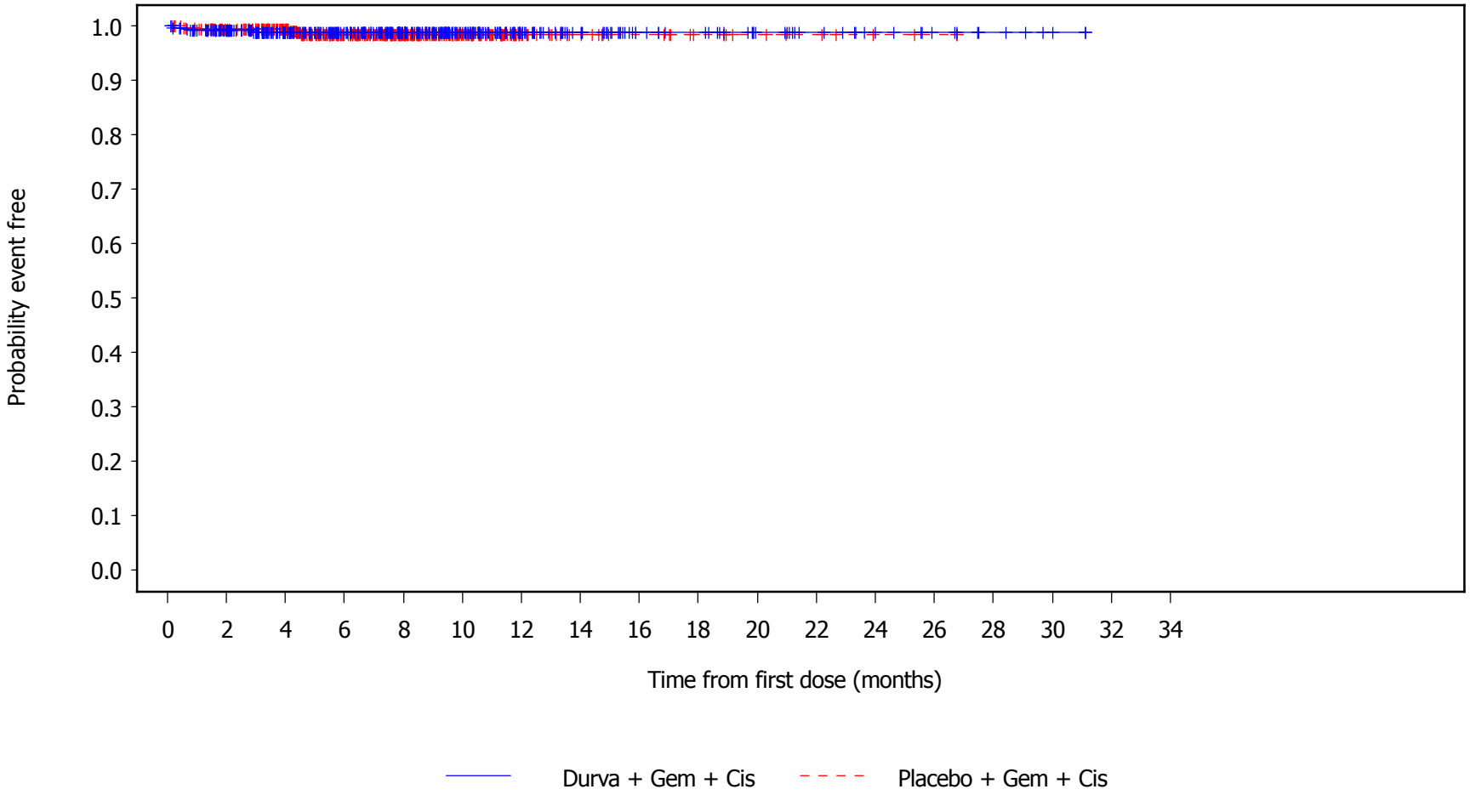
Figure 3.3.449 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Bicytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	231	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

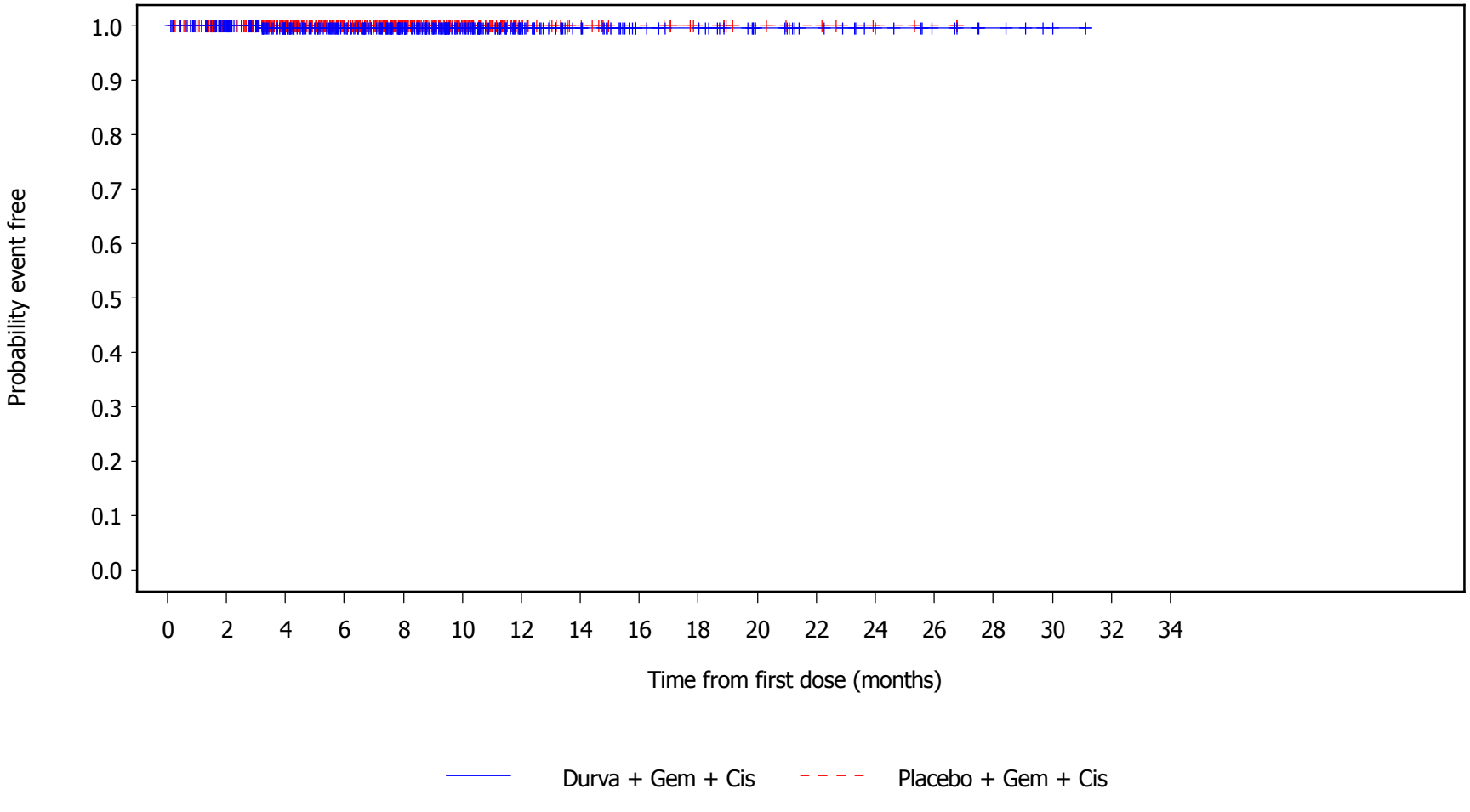
Figure 3.3.450 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Febrile neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	312	261	196	129	79	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	229	157	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

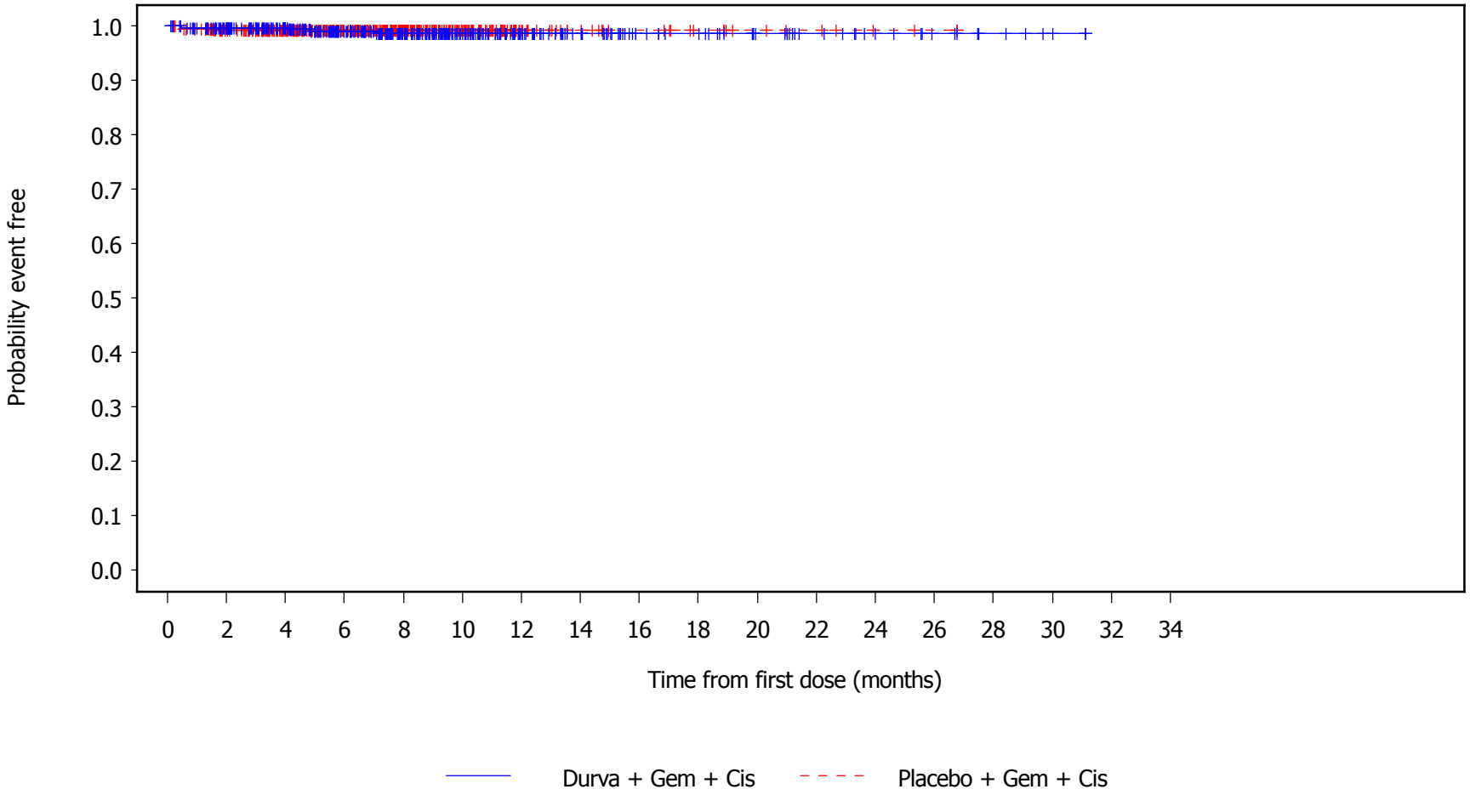
Figure 3.3.451 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: White blood cell count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	314	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

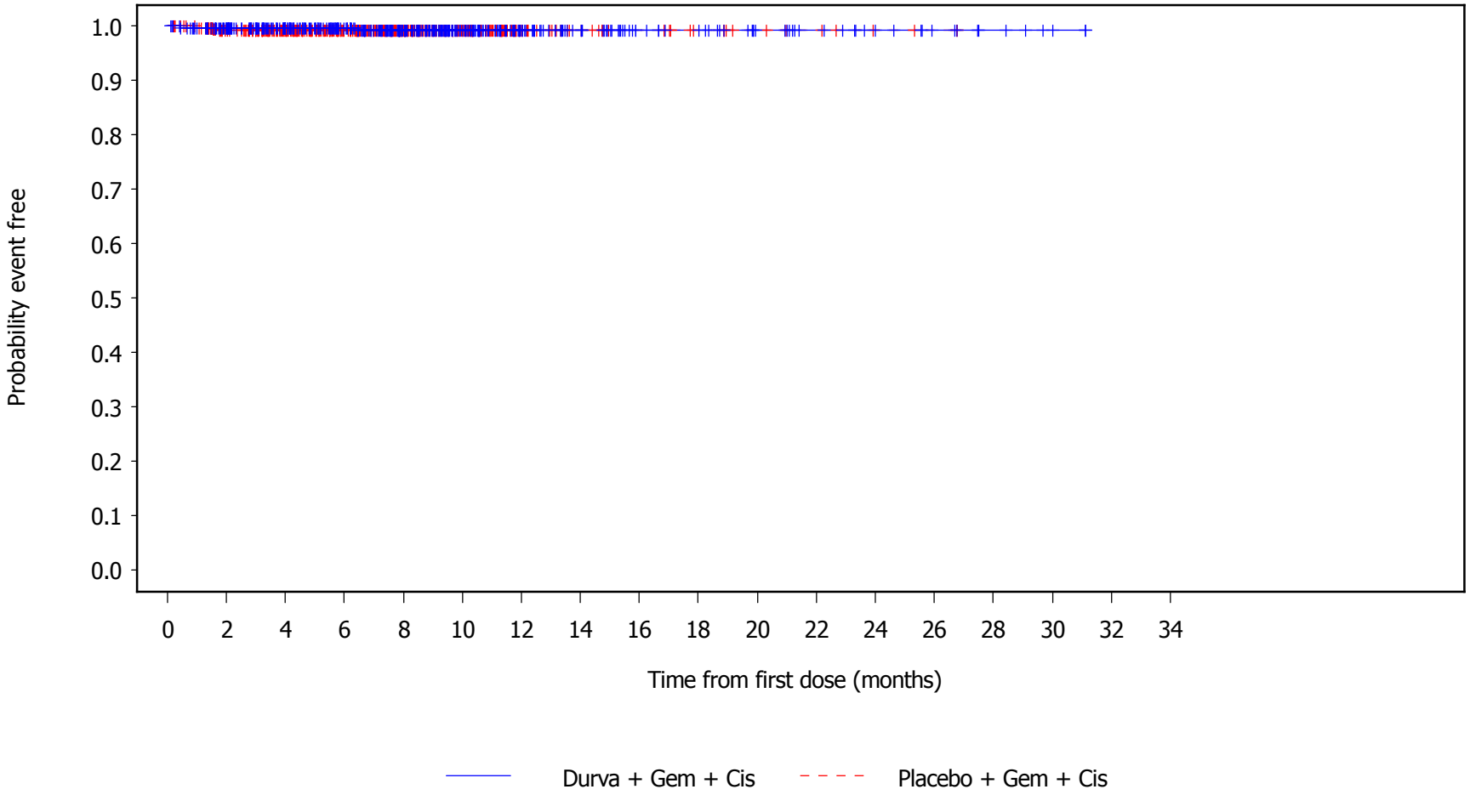
Figure 3.3.452 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Myelosuppression
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	262	195	129	79	57	39	35	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	369	311	230	158	88	33	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

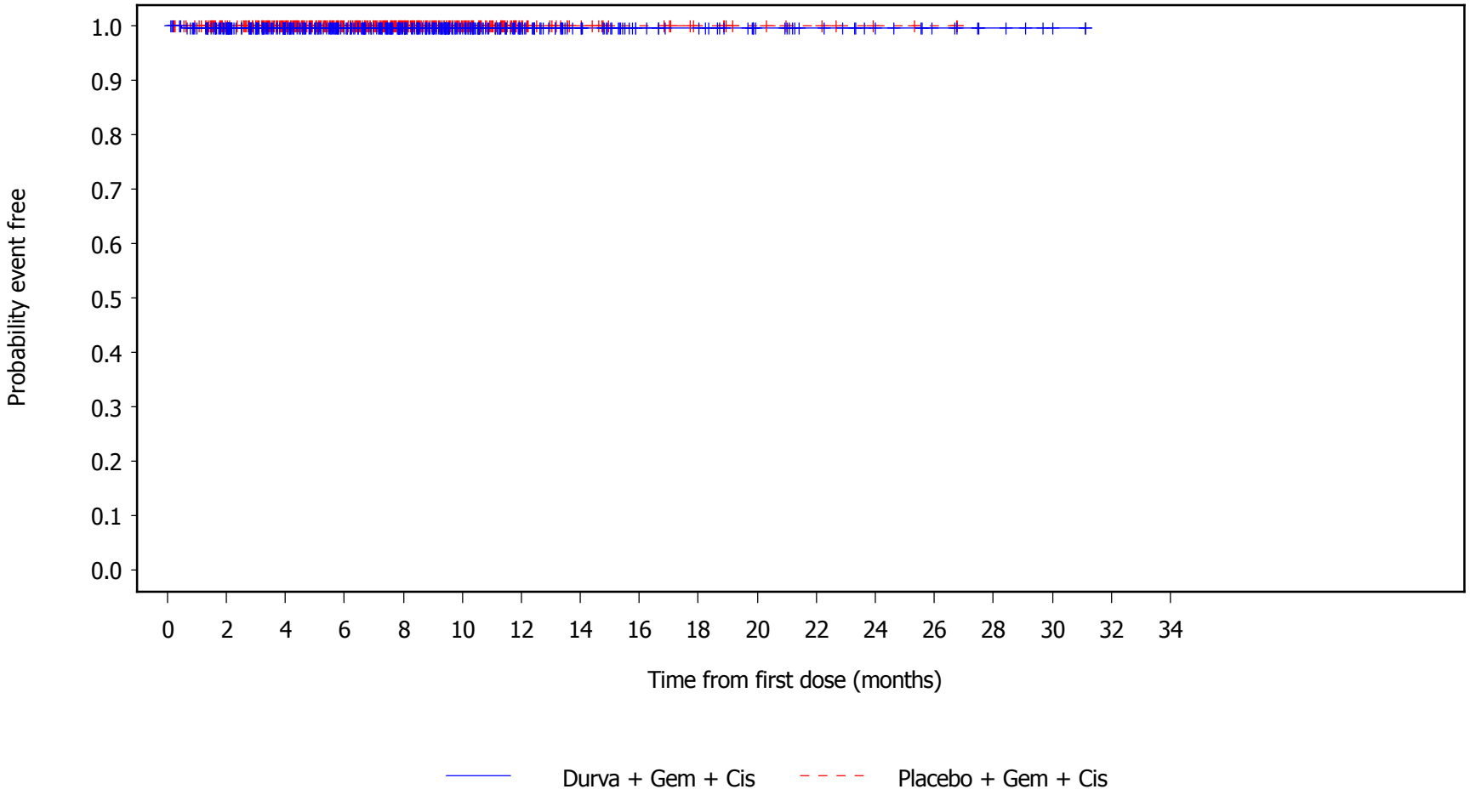
Figure 3.3.453 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	314	263	197	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	368	310	230	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

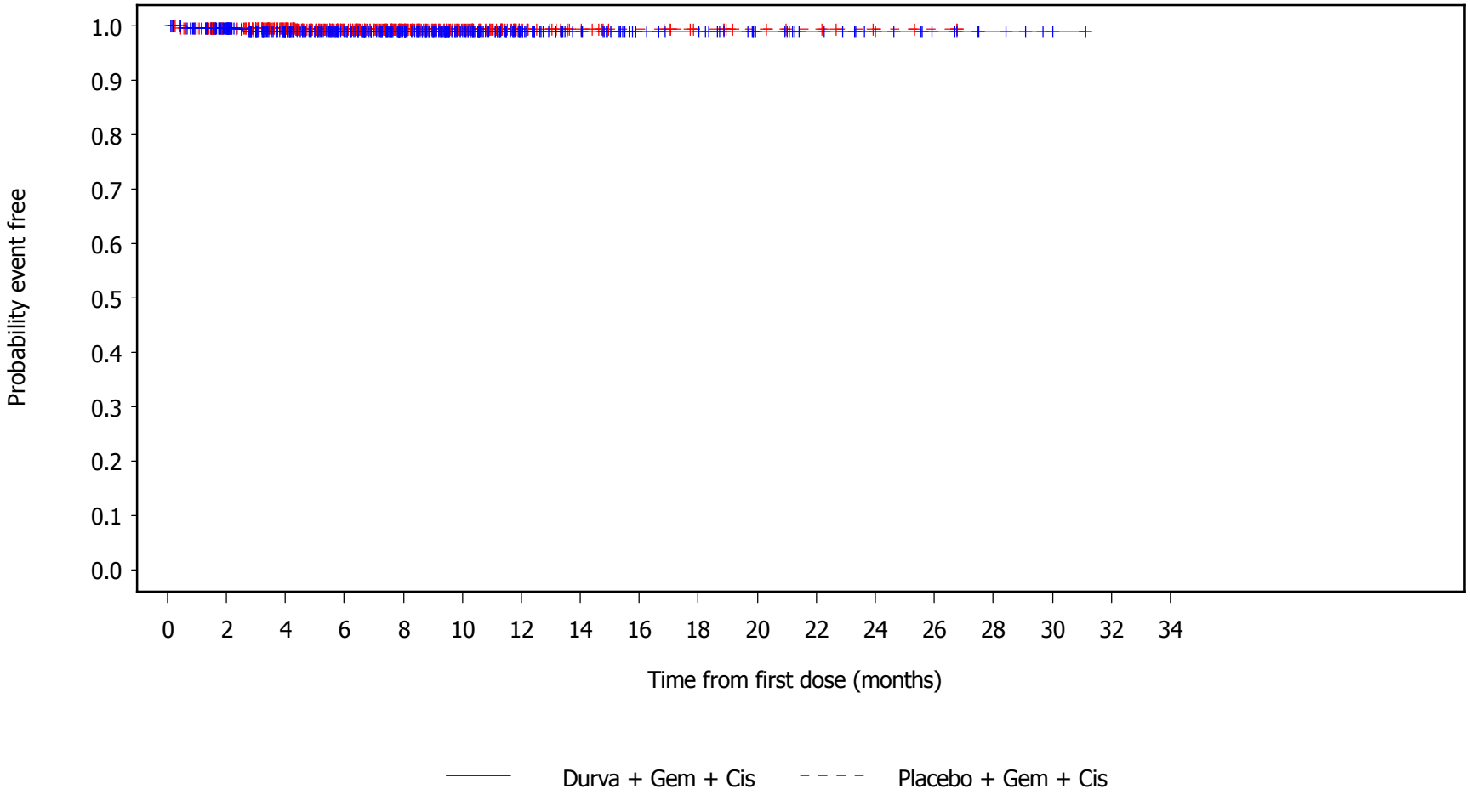
Figure 3.3.454 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Neutropenic sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

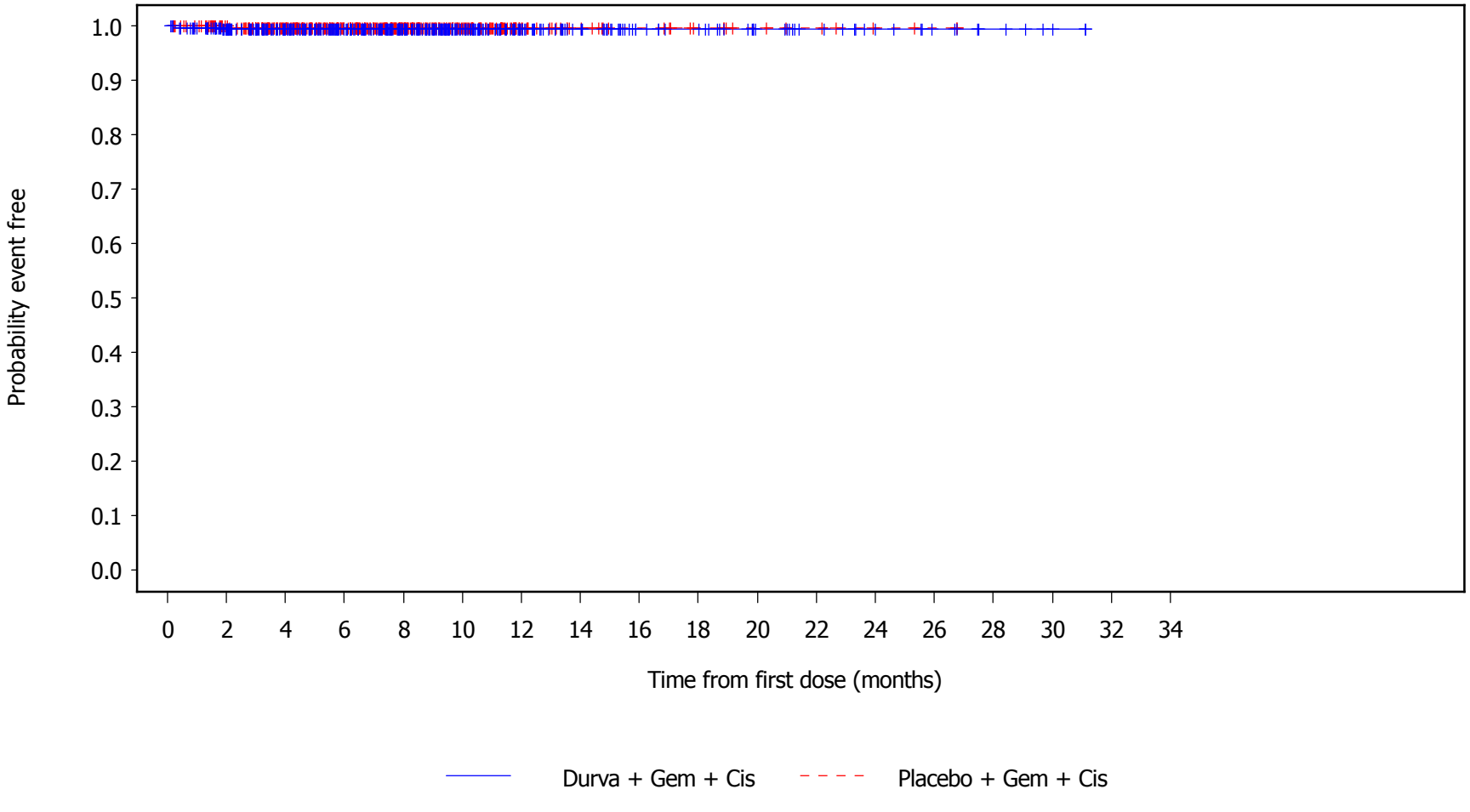
Figure 3.3.455 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Neutrophil count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	312	261	195	130	79	57	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	313	231	158	88	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

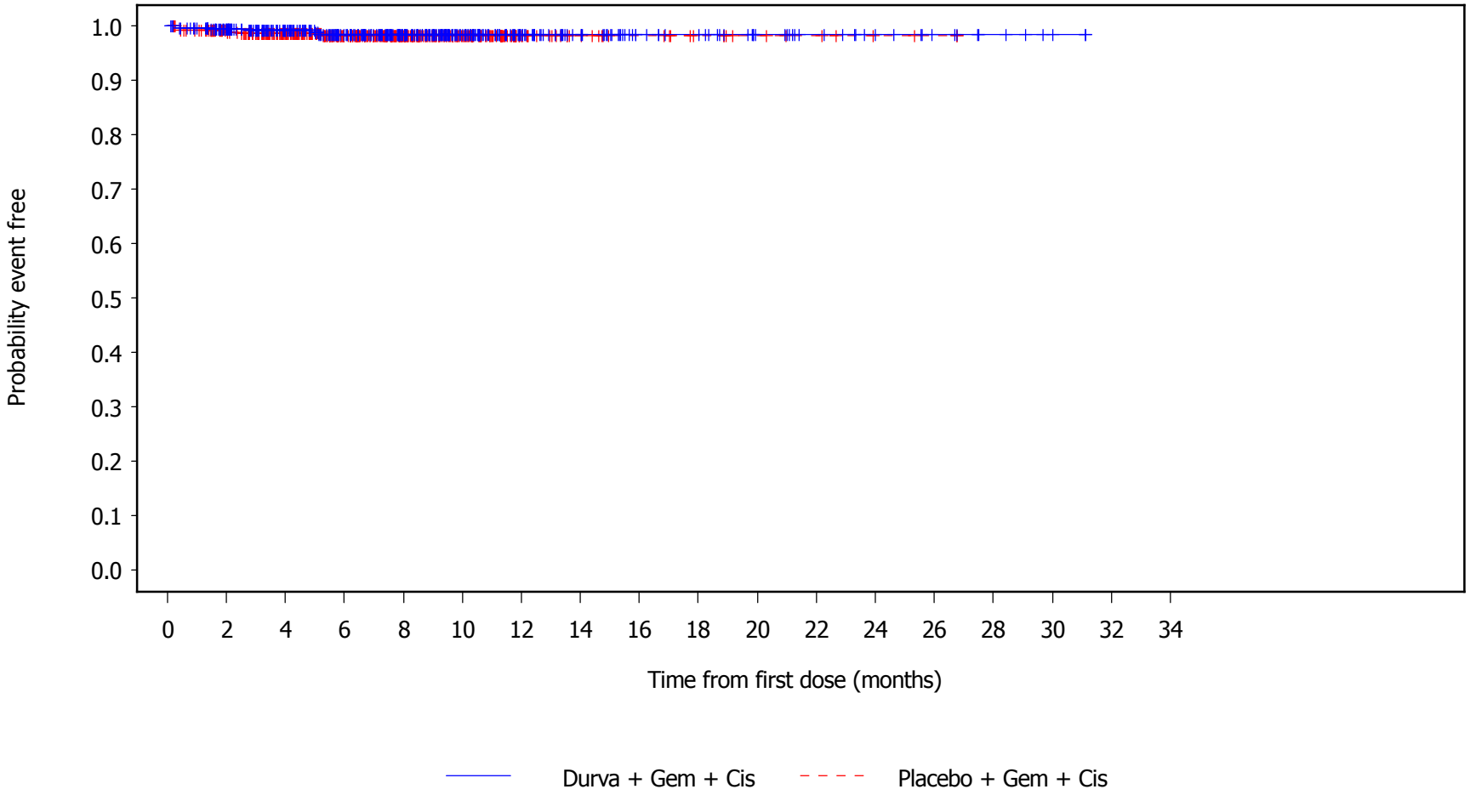
Figure 3.3.456 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Pancytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	371	315	264	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	232	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

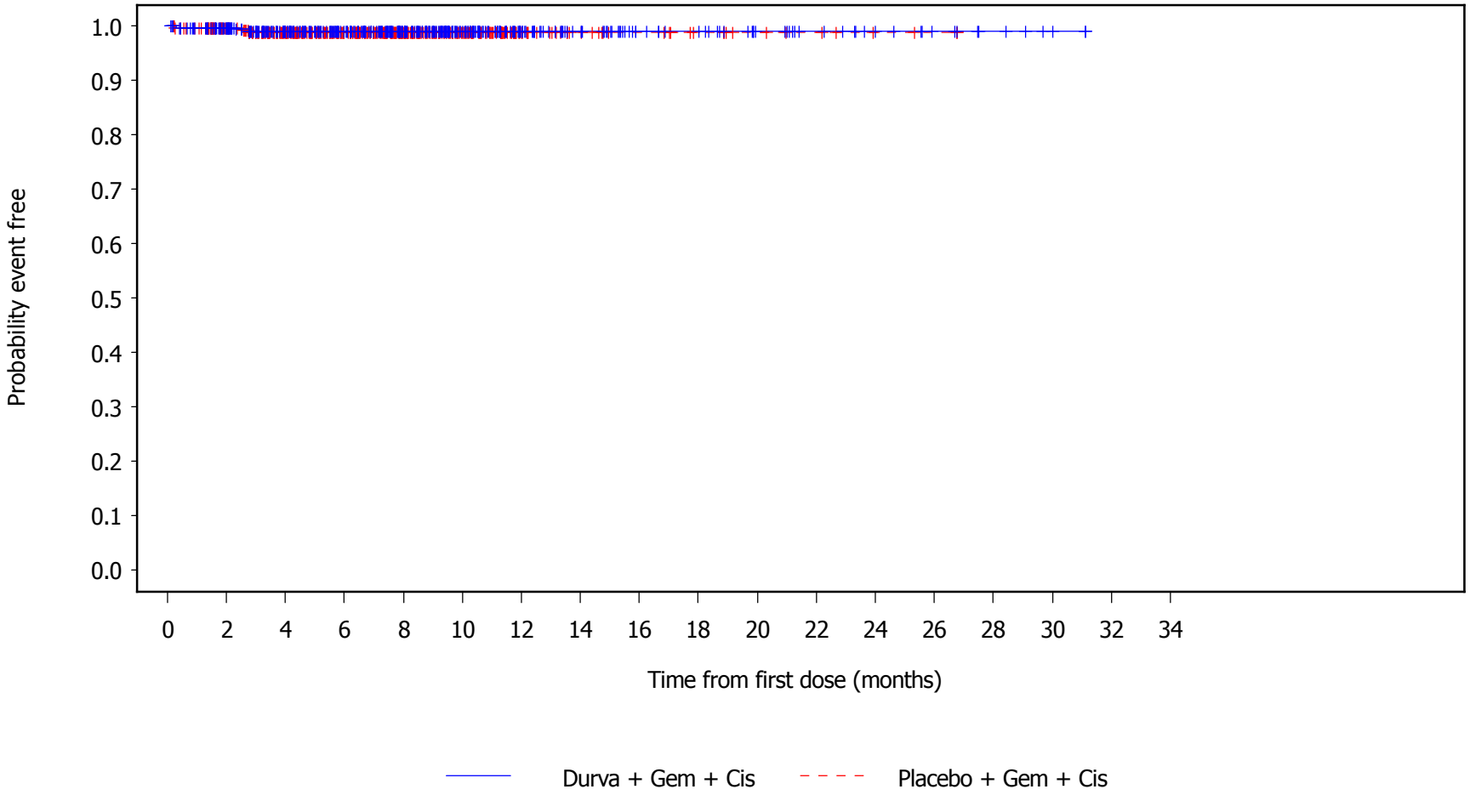
Figure 3.3.457 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Platelet count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	372	313	261	196	130	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	371	312	231	159	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

Figure 3.3.458 TOPAZ: Kaplan-Meier plot of time to first occurrence of SAESI PT: Thrombocytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

402	373	313	263	198	131	80	58	40	36	25	19	14	9	5	2	0	0	Durva + Gem + Cis
403	370	312	231	158	89	34	22	16	11	7	5	2	1	0	0	0	0	Placebo + Gem + Cis

Table 3.4.1.1 TOPAZ: Summary of subgroup analysis of time to first AE
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	324 (99.4)	0.2 (0.1, 0.2)	333	330 (99.1)	0.2 (0.1, 0.2)	0.99	0.85, 1.16	0.9288
Recurrent	76	75 (98.7)	0.2 (0.1, 0.3)	70	69 (98.6)	0.2 (0.2, 0.3)	0.92	0.67, 1.28	0.6339
Interaction p-value									0.6939
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	73 (100)	0.2 (0.1, 0.3)	71	70 (98.6)	0.2 (0.1, 0.3)	0.99	0.71, 1.38	0.9656
Intrahepatic CCA	234	231 (98.7)	0.2 (0.1, 0.2)	235	232 (98.7)	0.2 (0.1, 0.2)	0.98	0.82, 1.18	0.8408
Gallbladder cancer	95	95 (100)	0.2 (0.1, 0.3)	97	97 (100)	0.2 (0.1, 0.3)	0.96	0.72, 1.27	0.7710
Interaction p-value									0.9859
Age Group									
<65	219	216 (98.6)	0.2 (0.1, 0.2)	229	227 (99.1)	0.2 (0.1, 0.2)	0.93	0.77, 1.12	0.4644
>=65	183	183 (100)	0.2 (0.1, 0.2)	174	172 (98.9)	0.2 (0.1, 0.2)	1.04	0.84, 1.28	0.7435
Interaction p-value									0.4644
Region									
Asia	241	239 (99.2)	0.2 (0.1, 0.3)	257	253 (98.4)	0.2 (0.2, 0.2)	0.97	0.81, 1.15	0.7071
Rest of World	161	160 (99.4)	0.1 (0.1, 0.2)	146	146 (100)	0.1 (0.1, 0.2)	0.98	0.79, 1.23	0.8889
Interaction p-value									0.9021
PD-L1 Status									
High (>=1%)	239	236 (98.7)	0.2 (0.1, 0.2)	249	246 (98.8)	0.2 (0.1, 0.2)	1.02	0.86, 1.22	0.8008
Low (<1%)	118	118 (100)	0.2 (0.1, 0.3)	117	116 (99.1)	0.2 (0.1, 0.3)	0.92	0.71, 1.19	0.5393
Interaction p-value									0.5170
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.1.1 TOPAZ: Summary of subgroup analysis of time to first AE
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)						
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]		2-sided p-value [b]
Male	199	196 (98.5)	0.2 (0.1, 0.3)	207	204 (98.6)	0.2 (0.2, 0.2)	1.01	0.83,	1.22	0.9572
Female	203	203 (100)	0.2 (0.1, 0.2)	196	195 (99.5)	0.1 (0.1, 0.2)	0.94	0.77,	1.14	0.5257
Interaction p-value										0.6261
Race										
Asian	248	246 (99.2)	0.2 (0.1, 0.3)	262	258 (98.5)	0.2 (0.2, 0.2)	0.97	0.82,	1.16	0.7584
Non-Asian	154	153 (99.4)	0.2 (0.1, 0.2)	141	141 (100)	0.2 (0.1, 0.2)	0.98	0.78,	1.23	0.8454
Interaction p-value										0.9747
WHO ECOG Status at Screening										
0	186	185 (99.5)	0.2 (0.1, 0.2)	184	183 (99.5)	0.2 (0.1, 0.2)	0.98	0.80,	1.21	0.8655
1	216	214 (99.1)	0.2 (0.1, 0.3)	219	216 (98.6)	0.2 (0.1, 0.2)	0.97	0.80,	1.18	0.7725
Interaction p-value										0.9426
Disease Extent										
Locally Advanced	55	55 (100)	0.2 (0.1, 0.3)	73	73 (100)	0.2 (0.1, 0.2)	0.93	0.65,	1.32	0.6919
Metastatic	347	344 (99.1)	0.2 (0.1, 0.2)	330	326 (98.8)	0.2 (0.2, 0.2)	0.99	0.85,	1.15	0.8917
Interaction p-value										0.7571
MSI Status										
MSI High	3	3 (100)	0.1 (0.0, NE)	2	2 (100)	2.0 (0.0, NE)	NC	NC		NC
MSI Stable	166	164 (98.8)	0.2 (0.1, 0.3)	178	177 (99.4)	0.2 (0.1, 0.3)	0.98	0.79,	1.21	0.8489
Interaction p-value										NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.1.2 TOPAZ: Summary of subgroup analysis of time to first PT: Pyrexia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	67 (20.6)	NE (NE, NE)	333	53 (15.9)	NE (NE, NE)	1.26	0.88, 1.82	0.2017
Recurrent	76	22 (28.9)	NE (NE, NE)	70	9 (12.9)	20.1 (12.7, NE)	2.28	1.08, 5.22	0.0297*
Interaction p-value									0.1675
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	24 (32.9)	NE (NE, NE)	71	19 (26.8)	NE (NE, NE)	1.20	0.66, 2.22	0.5578
Intrahepatic CCA	234	42 (17.9)	NE (NE, NE)	235	33 (14.0)	NE (NE, NE)	1.24	0.79, 1.97	0.3486
Gallbladder cancer	95	23 (24.2)	NE (NE, NE)	97	10 (10.3)	NE (NE, NE)	2.38	1.16, 5.23	0.0168*
Interaction p-value									0.2732
Age Group									
<65	219	55 (25.1)	NE (NE, NE)	229	38 (16.6)	NE (NE, NE)	1.46	0.97, 2.23	0.0702
>=65	183	34 (18.6)	NE (NE, NE)	174	24 (13.8)	NE (NE, NE)	1.35	0.81, 2.31	0.2543
Interaction p-value									0.8192
Region									
Asia	241	65 (27.0)	NE (NE, NE)	257	45 (17.5)	20.1 (20.1, NE)	1.52	1.04, 2.24	0.0302*
Rest of World	161	24 (14.9)	NE (NE, NE)	146	17 (11.6)	NE (NE, NE)	1.26	0.68, 2.38	0.4633
Interaction p-value									0.6160
PD-L1 Status									
High (>=1%)	239	56 (23.4)	NE (NE, NE)	249	45 (18.1)	NE (NE, NE)	1.26	0.85, 1.87	0.2566
Low (<1%)	118	22 (18.6)	NE (NE, NE)	117	14 (12.0)	NE (NE, NE)	1.56	0.80, 3.11	0.1913
Interaction p-value									0.5871
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.1.2 TOPAZ: Summary of subgroup analysis of time to first PT: Pyrexia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	49 (24.6)	NE (NE, NE)	207	36 (17.4)	NE (NE, NE)	1.42	0.92, 2.19	0.1116
Female	203	40 (19.7)	NE (NE, NE)	196	26 (13.3)	NE (NE, NE)	1.44	0.88, 2.38	0.1474
Interaction p-value									0.9652
Race									
Asian	248	67 (27.0)	NE (NE, NE)	262	46 (17.6)	20.1 (20.1, NE)	1.53	1.05, 2.24	0.0260*
Non-Asian	154	22 (14.3)	NE (NE, NE)	141	16 (11.3)	NE (NE, NE)	1.22	0.65, 2.37	0.5356
Interaction p-value									0.5621
WHO ECOG Status at Screening									
0	186	38 (20.4)	NE (NE, NE)	184	33 (17.9)	20.1 (20.1, NE)	1.07	0.67, 1.72	0.7647
1	216	51 (23.6)	NE (NE, NE)	219	29 (13.2)	NE (NE, NE)	1.82	1.16, 2.91	0.0086*
Interaction p-value									0.1108
Disease Extent									
Locally Advanced	55	13 (23.6)	NE (NE, NE)	73	12 (16.4)	20.1 (12.7, NE)	1.37	0.62, 3.04	0.4368
Metastatic	347	76 (21.9)	NE (NE, NE)	330	50 (15.2)	NE (NE, NE)	1.43	1.001, 2.05	0.0496*
Interaction p-value									0.9221
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	166	34 (20.5)	NE (NE, NE)	178	32 (18.0)	20.1 (20.1, NE)	1.07	0.66, 1.74	0.7935
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeaab 01FEB2023:16:13 kjpc654

Table 3.4.1.3 TOPAZ: Summary of subgroup analysis of time to first SOC: Skin and subcutaneous tissue disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	128 (39.3)	13.6 (8.9,20.6)	333	82 (24.6)	NE (NE, NE)	1.65	1.25, 2.18	0.0004*
Recurrent	76	30 (39.5)	13.4 (11.2, NE)	70	20 (28.6)	NE (NE, NE)	1.28	0.73, 2.29	0.3893
Interaction p-value									0.4376
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	29 (39.7)	12.9 (9.1, NE)	71	17 (23.9)	NE (NE, NE)	1.58	0.88, 2.94	0.1271
Intrahepatic CCA	234	94 (40.2)	13.4 (7.6, NE)	235	66 (28.1)	NE (NE, NE)	1.44	1.06, 1.99	0.0212*
Gallbladder cancer	95	35 (36.8)	10.8 (7.6, NE)	97	19 (19.6)	NE (NE, NE)	1.97	1.14, 3.52	0.0145*
Interaction p-value									0.6301
Age Group									
<65	219	95 (43.4)	10.8 (7.3,14.3)	229	61 (26.6)	NE (NE, NE)	1.65	1.20, 2.28	0.0021*
>=65	183	63 (34.4)	20.6 (11.2, NE)	174	41 (23.6)	NE (NE, NE)	1.47	0.997, 2.20	0.0521
Interaction p-value									0.6614
Region									
Asia	241	96 (39.8)	12.9 (8.9, NE)	257	63 (24.5)	NE (NE, NE)	1.65	1.20, 2.28	0.0018*
Rest of World	161	62 (38.5)	13.6 (9.1, NE)	146	39 (26.7)	NE (NE, NE)	1.44	0.97, 2.17	0.0688
Interaction p-value									0.6090
PD-L1 Status									
High (>=1%)	239	88 (36.8)	13.4 (10.8, NE)	249	55 (22.1)	NE (NE, NE)	1.60	1.15, 2.26	0.0057*
Low (<1%)	118	50 (42.4)	10.0 (4.4, NE)	117	36 (30.8)	NE (NE, NE)	1.47	0.96, 2.27	0.0759
Interaction p-value									0.7599
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.1.3 TOPAZ: Summary of subgroup analysis of time to first SOC: Skin and subcutaneous tissue disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	80 (40.2)	12.9 (7.6,15.2)	207	46 (22.2)	NE (NE, NE)	1.98	1.39, 2.87	0.0002*
Female	203	78 (38.4)	13.6 (10.3, NE)	196	56 (28.6)	NE (NE, NE)	1.25	0.89, 1.77	0.2068
Interaction p-value									0.0688
Race									
Asian	248	101 (40.7)	12.9 (8.5,20.6)	262	66 (25.2)	NE (NE, NE)	1.65	1.21, 2.26	0.0014*
Non-Asian	154	57 (37.0)	13.6 (9.5, NE)	141	36 (25.5)	NE (NE, NE)	1.44	0.96, 2.21	0.0807
Interaction p-value									0.6193
WHO ECOG Status at Screening									
0	186	78 (41.9)	11.3 (8.9, NE)	184	47 (25.5)	NE (NE, NE)	1.61	1.12, 2.32	0.0093*
1	216	80 (37.0)	13.4 (10.3, NE)	219	55 (25.1)	NE (NE, NE)	1.53	1.09, 2.17	0.0144*
Interaction p-value									0.8484
Disease Extent									
Locally Advanced	55	25 (45.5)	13.8 (3.8, NE)	73	16 (21.9)	NE (NE, NE)	2.10	1.13, 4.02	0.0187*
Metastatic	347	133 (38.3)	11.3 (10.0,20.6)	330	86 (26.1)	NE (NE, NE)	1.48	1.13, 1.94	0.0044*
Interaction p-value									0.3090
MSI Status									
MSI High	3	2 (66.7)	20.6 (0.3, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	68 (41.0)	12.9 (9.5,15.2)	178	46 (25.8)	NE (NE, NE)	1.54	1.06, 2.25	0.0232*
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.1.4 TOPAZ: Summary of subgroup analysis of time to first PT: Alopecia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	26 (8.0)	NE (NE, NE)	333	13 (3.9)	NE (NE, NE)	2.10	1.10, 4.21	0.0247*
Recurrent	76	6 (7.9)	NE (NE, NE)	70	4 (5.7)	NE (NE, NE)	1.37	0.39, 5.34	0.6256
Interaction p-value									0.5617
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	7 (9.6)	NE (NE, NE)	71	2 (2.8)	NE (NE, NE)	3.59	0.87, 24.12	0.0794
Intrahepatic CCA	234	19 (8.1)	NE (NE, NE)	235	12 (5.1)	NE (NE, NE)	1.62	0.80, 3.43	0.1854
Gallbladder cancer	95	6 (6.3)	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	2.01	0.53, 9.55	0.3074
Interaction p-value									0.6388
Age Group									
<65	219	20 (9.1)	NE (NE, NE)	229	12 (5.2)	NE (NE, NE)	1.76	0.87, 3.70	0.1163
>=65	183	12 (6.6)	NE (NE, NE)	174	5 (2.9)	NE (NE, NE)	2.35	0.87, 7.38	0.0933
Interaction p-value									0.6515
Region									
Asia	241	13 (5.4)	NE (NE, NE)	257	5 (1.9)	NE (NE, NE)	2.79	1.05, 8.69	0.0388*
Rest of World	161	19 (11.8)	NE (NE, NE)	146	12 (8.2)	NE (NE, NE)	1.48	0.73, 3.14	0.2790
Interaction p-value									0.3184
PD-L1 Status									
High (>=1%)	239	18 (7.5)	NE (NE, NE)	249	9 (3.6)	NE (NE, NE)	2.10	0.97, 4.90	0.0609
Low (<1%)	118	13 (11.0)	NE (NE, NE)	117	6 (5.1)	NE (NE, NE)	2.23	0.88, 6.33	0.0925
Interaction p-value									0.9276
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.1.4 TOPAZ: Summary of subgroup analysis of time to first PT: Alopecia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	11 (5.5)	NE (NE, NE)	207	5 (2.4)	NE (NE, NE)	2.34	0.85, 7.42	0.1015
Female	203	21 (10.3)	NE (NE, NE)	196	12 (6.1)	NE (NE, NE)	1.71	0.86, 3.59	0.1304
Interaction p-value									0.6289
Race									
Asian	248	15 (6.0)	NE (NE, NE)	262	6 (2.3)	NE (NE, NE)	2.68	1.09, 7.51	0.0314*
Non-Asian	154	17 (11.0)	NE (NE, NE)	141	11 (7.8)	NE (NE, NE)	1.44	0.68, 3.18	0.3367
Interaction p-value									0.3136
WHO ECOG Status at Screening									
0	186	20 (10.8)	NE (NE, NE)	184	10 (5.4)	NE (NE, NE)	1.98	0.95, 4.42	0.0689
1	216	12 (5.6)	NE (NE, NE)	219	7 (3.2)	NE (NE, NE)	1.79	0.72, 4.81	0.2114
Interaction p-value									0.8694
Disease Extent									
Locally Advanced	55	5 (9.1)	NE (NE, NE)	73	4 (5.5)	NE (NE, NE)	1.69	0.45, 6.83	0.4316
Metastatic	347	27 (7.8)	NE (NE, NE)	330	13 (3.9)	NE (NE, NE)	2.00	1.05, 4.01	0.0337*
Interaction p-value									0.8222
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	17 (10.2)	NE (NE, NE)	178	9 (5.1)	NE (NE, NE)	2.11	0.96, 4.96	0.0621
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.1.5 TOPAZ: Summary of subgroup analysis of time to first SOC: Gastrointestinal disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	248 (76.1)	0.9 (0.7, 1.3)	333	226 (67.9)	1.3 (0.9, 1.7)	1.23	1.03, 1.47	0.0252*
Recurrent	76	61 (80.3)	1.0 (0.3, 2.8)	70	51 (72.9)	1.1 (0.6, 3.5)	1.11	0.77, 1.62	0.5813
Interaction p-value									0.6311
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	52 (71.2)	1.5 (0.7, 2.8)	71	49 (69.0)	1.6 (0.7, 4.2)	1.10	0.75, 1.63	0.6230
Intrahepatic CCA	234	176 (75.2)	1.0 (0.7, 1.5)	235	153 (65.1)	1.4 (0.8, 2.4)	1.26	1.02, 1.57	0.0348*
Gallbladder cancer	95	81 (85.3)	0.6 (0.3, 0.9)	97	75 (77.3)	0.9 (0.3, 1.6)	1.16	0.85, 1.59	0.3554
Interaction p-value									0.8055
Age Group									
<65	219	169 (77.2)	0.9 (0.5, 1.5)	229	163 (71.2)	1.0 (0.7, 1.4)	1.13	0.91, 1.40	0.2575
>=65	183	140 (76.5)	0.9 (0.7, 1.4)	174	114 (65.5)	1.6 (1.0, 3.5)	1.31	1.02, 1.68	0.0318*
Interaction p-value									0.3833
Region									
Asia	241	183 (75.9)	1.0 (0.7, 1.6)	257	170 (66.1)	1.4 (0.9, 2.7)	1.23	1.0001, 1.52	0.0499*
Rest of World	161	126 (78.3)	0.8 (0.3, 1.3)	146	107 (73.3)	1.0 (0.6, 1.6)	1.15	0.89, 1.49	0.2871
Interaction p-value									0.6831
PD-L1 Status									
High (>=1%)	239	184 (77.0)	0.9 (0.5, 1.1)	249	170 (68.3)	1.4 (0.9, 2.2)	1.24	1.01, 1.53	0.0407*
Low (<1%)	118	94 (79.7)	1.1 (0.5, 2.1)	117	80 (68.4)	1.0 (0.3, 2.3)	1.21	0.90, 1.64	0.2009
Interaction p-value									0.8995
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.1.5 TOPAZ: Summary of subgroup analysis of time to first SOC: Gastrointestinal disorders
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)						
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]		2-sided p-value [b]
Male	199	146 (73.4)	1.4 (0.7, 1.7)	207	133 (64.3)	1.6 (1.0, 3.5)	1.29	1.02,	1.63	0.0337*
Female	203	163 (80.3)	0.8 (0.5, 1.0)	196	144 (73.5)	0.9 (0.5, 1.4)	1.11	0.89,	1.39	0.3581
Interaction p-value										0.3672
Race										
Asian	248	189 (76.2)	1.0 (0.7, 1.5)	262	175 (66.8)	1.4 (0.8, 2.3)	1.22	0.99,	1.50	0.0609
Non-Asian	154	120 (77.9)	0.8 (0.3, 1.4)	141	102 (72.3)	1.1 (0.7, 1.8)	1.18	0.90,	1.54	0.2250
Interaction p-value										0.8445
WHO ECOG Status at Screening										
0	186	149 (80.1)	0.9 (0.4, 1.4)	184	124 (67.4)	1.4 (0.5, 2.5)	1.28	1.01,	1.63	0.0419*
1	216	160 (74.1)	0.9 (0.7, 1.5)	219	153 (69.9)	1.1 (0.8, 1.7)	1.14	0.92,	1.43	0.2327
Interaction p-value										0.5005
Disease Extent										
Locally Advanced	55	39 (70.9)	1.5 (0.7, 2.9)	73	53 (72.6)	1.0 (0.5, 3.5)	0.97	0.64,	1.46	0.8723
Metastatic	347	270 (77.8)	0.8 (0.6, 1.3)	330	224 (67.9)	1.3 (0.9, 1.7)	1.25	1.05,	1.50	0.0126*
Interaction p-value										0.2575
MSI Status										
MSI High	3	2 (66.7)	1.4 (0.1, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC		NC
MSI Stable	166	133 (80.1)	0.7 (0.3, 0.9)	178	123 (69.1)	1.0 (0.6, 1.8)	1.35	1.06,	1.73	0.0154*
Interaction p-value										NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeaae 01FEB2023:16:13 kjpc654

Table 3.4.1.6 TOPAZ: Summary of subgroup analysis of time to first PT: Dry mouth
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	10 (3.1)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	3 (4.1)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	5 (2.1)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	6 (2.7)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	4 (2.2)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	9 (5.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	3 (1.3)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	6 (5.1)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.1.6 TOPAZ: Summary of subgroup analysis of time to first PT: Dry mouth
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	5 (2.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	5 (2.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	7 (4.5)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	6 (3.2)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	4 (1.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	4 (7.3)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	6 (1.7)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	5 (3.0)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.1.7 TOPAZ: Summary of subgroup analysis of time to first SOC: Investigations
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	195 (59.8)	3.6 (2.4, 4.4)	333	217 (65.2)	2.4 (1.8, 3.1)	0.84	0.69, 1.02	0.0807
Recurrent	76	48 (63.2)	2.7 (1.6, 5.2)	70	48 (68.6)	1.7 (0.9, 3.4)	0.78	0.52, 1.16	0.2181
Interaction p-value									0.7250
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	42 (57.5)	3.8 (1.8,10.4)	71	47 (66.2)	2.1 (1.4, 3.4)	0.79	0.52, 1.20	0.2700
Intrahepatic CCA	234	143 (61.1)	3.0 (2.3, 4.1)	235	153 (65.1)	2.3 (1.6, 3.3)	0.86	0.69, 1.09	0.2110
Gallbladder cancer	95	58 (61.1)	4.0 (2.3, 4.9)	97	65 (67.0)	2.4 (1.0, 3.6)	0.78	0.55, 1.11	0.1670
Interaction p-value									0.8623
Age Group									
<65	219	129 (58.9)	4.0 (2.8, 5.1)	229	147 (64.2)	2.3 (1.6, 3.7)	0.79	0.62, 1.003	0.0529
>=65	183	114 (62.3)	2.6 (1.9, 3.9)	174	118 (67.8)	2.3 (1.6, 3.0)	0.88	0.68, 1.14	0.3204
Interaction p-value									0.5633
Region									
Asia	241	165 (68.5)	1.9 (1.2, 2.8)	257	187 (72.8)	1.7 (1.0, 2.3)	0.87	0.71, 1.07	0.1985
Rest of World	161	78 (48.4)	6.1 (4.3, NE)	146	78 (53.4)	4.2 (3.0, 8.0)	0.81	0.59, 1.11	0.1805
Interaction p-value									0.6879
PD-L1 Status									
High (>=1%)	239	143 (59.8)	3.5 (2.3, 4.9)	249	172 (69.1)	1.8 (1.4, 2.6)	0.74	0.59, 0.92	0.0073*
Low (<1%)	118	75 (63.6)	3.5 (2.3, 4.4)	117	70 (59.8)	3.1 (1.9, 4.6)	1.07	0.78, 1.49	0.6659
Interaction p-value									0.0619
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.1.7 TOPAZ: Summary of subgroup analysis of time to first SOC: Investigations
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)						
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]		2-sided p-value [b]
Male	199	120 (60.3)	3.5 (2.3, 4.6)	207	137 (66.2)	2.1 (1.6, 3.1)	0.81	0.63,	1.03	0.0883
Female	203	123 (60.6)	3.6 (2.3, 4.5)	196	128 (65.3)	2.4 (1.6, 3.3)	0.85	0.67,	1.09	0.2088
Interaction p-value										0.7604
Race										
Asian	248	169 (68.1)	2.1 (1.2, 2.8)	262	190 (72.5)	1.7 (1.2, 2.3)	0.87	0.71,	1.07	0.1983
Non-Asian	154	74 (48.1)	6.3 (4.3, NE)	141	75 (53.2)	4.2 (3.0, 8.0)	0.80	0.58,	1.10	0.1661
Interaction p-value										0.6409
WHO ECOG Status at Screening										
0	186	108 (58.1)	4.1 (2.8, 6.0)	184	120 (65.2)	2.9 (1.8, 3.5)	0.75	0.58,	0.97	0.0291*
1	216	135 (62.5)	2.6 (1.6, 3.8)	219	145 (66.2)	2.1 (1.4, 2.7)	0.91	0.72,	1.15	0.4499
Interaction p-value										0.2642
Disease Extent										
Locally Advanced	55	39 (70.9)	2.5 (0.9, 4.2)	73	51 (69.9)	2.1 (1.0, 3.1)	0.91	0.60,	1.38	0.6714
Metastatic	347	204 (58.8)	3.6 (2.6, 4.5)	330	214 (64.8)	2.4 (1.8, 3.2)	0.82	0.67,	0.99	0.0406*
Interaction p-value										0.6376
MSI Status										
MSI High	3	2 (66.7)	1.7 (0.3, NE)	2	2 (100)	9.1 (1.9, NE)	NC	NC		NC
MSI Stable	166	98 (59.0)	4.1 (2.4, 5.2)	178	120 (67.4)	2.3 (1.6, 3.5)	0.75	0.57,	0.98	0.0343*
Interaction p-value										NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.1.8 TOPAZ: Summary of subgroup analysis of time to first PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	17 (5.2)	NE (NE, NE)	333	27 (8.1)	NE (NE, NE)	0.58	0.31, 1.06	0.0757
Recurrent	76	1 (1.3)	NE (NE, NE)	70	6 (8.6)	NE (NE, NE)	0.13	0.01, 0.75	0.0199*
Interaction p-value									0.1227
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	3 (4.1)	NE (NE, NE)	71	7 (9.9)	NE (NE, NE)	0.33	0.07, 1.20	0.0945
Intrahepatic CCA	234	13 (5.6)	NE (NE, NE)	235	21 (8.9)	NE (NE, NE)	0.56	0.27, 1.11	0.0960
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	5 (5.2)	NE (NE, NE)	0.38	0.05, 1.75	0.2203
Interaction p-value									0.7519
Age Group									
<65	219	7 (3.2)	NE (NE, NE)	229	24 (10.5)	NE (NE, NE)	0.26	0.10, 0.57	0.0006*
>=65	183	11 (6.0)	NE (NE, NE)	174	9 (5.2)	NE (NE, NE)	1.08	0.45, 2.69	0.8586
Interaction p-value									0.0185*
Region									
Asia	241	12 (5.0)	NE (NE, NE)	257	20 (7.8)	NE (NE, NE)	0.56	0.27, 1.14	0.1102
Rest of World	161	6 (3.7)	NE (NE, NE)	146	13 (8.9)	NE (NE, NE)	0.38	0.13, 0.96	0.0409*
Interaction p-value									0.5202
PD-L1 Status									
High (>=1%)	239	12 (5.0)	NE (NE, NE)	249	20 (8.0)	NE (NE, NE)	0.55	0.26, 1.10	0.0927
Low (<1%)	118	5 (4.2)	NE (NE, NE)	117	10 (8.5)	NE (NE, NE)	0.46	0.14, 1.30	0.1443
Interaction p-value									0.7964
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeaah 01FEB2023:16:13 kjpc654

Table 3.4.1.8 TOPAZ: Summary of subgroup analysis of time to first PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	8 (4.0)	NE (NE, NE)	207	19 (9.2)	NE (NE, NE)	0.39	0.16, 0.87	0.0205*
Female	203	10 (4.9)	NE (NE, NE)	196	14 (7.1)	NE (NE, NE)	0.61	0.26, 1.36	0.2238
Interaction p-value									0.4639
Race									
Asian	248	13 (5.2)	NE (NE, NE)	262	21 (8.0)	NE (NE, NE)	0.57	0.28, 1.14	0.1127
Non-Asian	154	5 (3.2)	NE (NE, NE)	141	12 (8.5)	NE (NE, NE)	0.35	0.11, 0.93	0.0357*
Interaction p-value									0.4214
WHO ECOG Status at Screening									
0	186	6 (3.2)	NE (NE, NE)	184	6 (3.3)	NE (NE, NE)	0.87	0.27, 2.79	0.8134
1	216	12 (5.6)	NE (NE, NE)	219	27 (12.3)	NE (NE, NE)	0.39	0.19, 0.76	0.0054*
Interaction p-value									0.2401
Disease Extent									
Locally Advanced	55	5 (9.1)	NE (NE, NE)	73	6 (8.2)	NE (NE, NE)	0.92	0.26, 3.07	0.8910
Metastatic	347	13 (3.7)	NE (NE, NE)	330	27 (8.2)	NE (NE, NE)	0.41	0.20, 0.78	0.0064*
Interaction p-value									0.2503
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	166	5 (3.0)	NE (NE, NE)	178	9 (5.1)	NE (NE, NE)	0.52	0.16, 1.52	0.2366
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.1.9 TOPAZ: Summary of subgroup analysis of time to first PT: Blood creatinine increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	10 (3.1)	NE (NE, NE)	333	32 (9.6)	NE (NE, NE)	0.30	0.14, 0.59	0.0003*
Recurrent	76	3 (3.9)	NE (NE, NE)	70	6 (8.6)	NE (NE, NE)	0.42	0.09, 1.58	0.2006
Interaction p-value									0.6788
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	3 (4.1)	NE (NE, NE)	71	4 (5.6)	NE (NE, NE)	0.70	0.14, 3.16	0.6347
Intrahepatic CCA	234	8 (3.4)	NE (NE, NE)	235	25 (10.6)	NE (NE, NE)	0.30	0.13, 0.63	0.0013*
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	9 (9.3)	NE (NE, NE)	0.20	0.03, 0.79	0.0198*
Interaction p-value									0.5043
Age Group									
<65	219	5 (2.3)	NE (NE, NE)	229	17 (7.4)	NE (NE, NE)	0.29	0.09, 0.72	0.0069*
>=65	183	8 (4.4)	NE (NE, NE)	174	21 (12.1)	NE (NE, NE)	0.34	0.14, 0.73	0.0052*
Interaction p-value									0.8029
Region									
Asia	241	7 (2.9)	NE (NE, NE)	257	22 (8.6)	NE (NE, NE)	0.32	0.13, 0.71	0.0042*
Rest of World	161	6 (3.7)	NE (NE, NE)	146	16 (11.0)	NE (NE, NE)	0.31	0.11, 0.76	0.0094*
Interaction p-value									0.9789
PD-L1 Status									
High (>=1%)	239	10 (4.2)	NE (NE, NE)	249	23 (9.2)	NE (NE, NE)	0.42	0.19, 0.85	0.0158*
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	14 (12.0)	NE (NE, NE)	0.20	0.05, 0.60	0.0031*
Interaction p-value									0.2897
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeaai 01FEB2023:16:13 kjpc654

Table 3.4.1.9 TOPAZ: Summary of subgroup analysis of time to first PT: Blood creatinine increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	8 (4.0)	NE (NE, NE)	207	25 (12.1)	NE (NE, NE)	0.31	0.13, 0.65	0.0016*
Female	203	5 (2.5)	NE (NE, NE)	196	13 (6.6)	NE (NE, NE)	0.35	0.11, 0.92	0.0332*
Interaction p-value									0.8489
Race									
Asian	248	7 (2.8)	NE (NE, NE)	262	22 (8.4)	NE (NE, NE)	0.31	0.12, 0.70	0.0040*
Non-Asian	154	6 (3.9)	NE (NE, NE)	141	16 (11.3)	NE (NE, NE)	0.31	0.11, 0.76	0.0097*
Interaction p-value									0.9933
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	18 (9.8)	NE (NE, NE)	0.15	0.03, 0.43	0.0002*
1	216	10 (4.6)	NE (NE, NE)	219	20 (9.1)	NE (NE, NE)	0.49	0.22, 1.02	0.0562
Interaction p-value									0.0839
Disease Extent									
Locally Advanced	55	2 (3.6)	NE (NE, NE)	73	5 (6.8)	NE (NE, NE)	0.48	0.07, 2.24	0.3638
Metastatic	347	11 (3.2)	NE (NE, NE)	330	33 (10.0)	NE (NE, NE)	0.29	0.14, 0.56	0.0001*
Interaction p-value									0.5930
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	166	7 (4.2)	NE (NE, NE)	178	19 (10.7)	NE (NE, NE)	0.36	0.14, 0.81	0.0133*
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeaai 01FEB2023:16:13 kjpc654

Table 3.4.2.1 TOPAZ: Summary of subgroup analysis of time to first SAE
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	156 (47.9)	8.8 (6.2, NE)	333	152 (45.6)	9.5 (6.7,17.1)	1.01	0.80, 1.26	0.9615
Recurrent	76	34 (44.7)	16.2 (6.8, NE)	70	19 (27.1)	NE (NE, NE)	1.60	0.92, 2.85	0.0971
Interaction p-value									0.1291
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	38 (52.1)	8.1 (3.6, NE)	71	31 (43.7)	NE (NE, NE)	1.09	0.68, 1.77	0.7098
Intrahepatic CCA	234	99 (42.3)	12.0 (9.2, NE)	235	94 (40.0)	15.3 (9.5, NE)	0.99	0.75, 1.31	0.9442
Gallbladder cancer	95	53 (55.8)	5.8 (2.8, 8.7)	97	46 (47.4)	8.3 (5.4,17.1)	1.25	0.84, 1.86	0.2691
Interaction p-value									0.6413
Age Group									
<65	219	105 (47.9)	10.2 (6.2, NE)	229	86 (37.6)	15.3 (11.0, NE)	1.26	0.95, 1.68	0.1110
>=65	183	85 (46.4)	9.2 (6.0, NE)	174	85 (48.9)	8.3 (4.4, NE)	0.88	0.65, 1.19	0.3921
Interaction p-value									0.0858
Region									
Asia	241	113 (46.9)	9.5 (6.7, NE)	257	105 (40.9)	11.2 (8.0, NE)	1.09	0.84, 1.42	0.5244
Rest of World	161	77 (47.8)	9.2 (5.9, NE)	146	66 (45.2)	15.3 (6.2,17.5)	1.03	0.74, 1.44	0.8405
Interaction p-value									0.8071
PD-L1 Status									
High (>=1%)	239	115 (48.1)	9.0 (6.7,16.2)	249	102 (41.0)	15.3 (9.8,17.5)	1.12	0.86, 1.46	0.4173
Low (<1%)	118	55 (46.6)	9.2 (5.8, NE)	117	49 (41.9)	11.2 (6.2, NE)	1.08	0.74, 1.59	0.6885
Interaction p-value									0.8943
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.2.1 TOPAZ: Summary of subgroup analysis of time to first SAE
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	95 (47.7)	8.8 (6.4, NE)	207	94 (45.4)	9.8 (6.9,17.5)	1.03	0.78, 1.37	0.8279
Female	203	95 (46.8)	10.2 (6.0, NE)	196	77 (39.3)	17.1 (11.0, NE)	1.12	0.83, 1.51	0.4712
Interaction p-value									0.7095
Race									
Asian	248	117 (47.2)	9.5 (6.7, NE)	262	108 (41.2)	11.2 (8.0, NE)	1.09	0.84, 1.42	0.5243
Non-Asian	154	73 (47.4)	9.6 (5.9, NE)	141	63 (44.7)	15.3 (6.2,17.5)	1.04	0.74, 1.46	0.8356
Interaction p-value									0.8203
WHO ECOG Status at Screening									
0	186	92 (49.5)	9.5 (6.0,12.0)	184	75 (40.8)	13.2 (9.5, NE)	1.19	0.88, 1.61	0.2707
1	216	98 (45.4)	16.2 (6.6, NE)	219	96 (43.8)	9.8 (6.9, NE)	0.98	0.74, 1.30	0.8670
Interaction p-value									0.3568
Disease Extent									
Locally Advanced	55	21 (38.2)	NE (NE, NE)	73	33 (45.2)	8.9 (5.3, NE)	0.72	0.41, 1.24	0.2403
Metastatic	347	169 (48.7)	9.0 (6.4,14.6)	330	138 (41.8)	13.2 (9.5,17.5)	1.14	0.91, 1.43	0.2587
Interaction p-value									0.1285
MSI Status									
MSI High	3	1 (33.3)	NE (NE, NE)	2	2 (100)	9.0 (0.4, NE)	NC	NC	NC
MSI Stable	166	78 (47.0)	9.5 (6.8, NE)	178	75 (42.1)	11.0 (8.3, NE)	1.07	0.78, 1.47	0.6747
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.2.2 TOPAZ: Summary of subgroup analysis of time to first SAE PT: Anaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	13 (4.0)	NE (NE, NE)	333	5 (1.5)	NE (NE, NE)	2.72	1.02, 8.47	0.0443*
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	7 (3.0)	NE (NE, NE)	235	5 (2.1)	NE (NE, NE)	1.43	0.46, 4.84	0.5363
Gallbladder cancer	95	5 (5.3)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	9 (4.1)	NE (NE, NE)	229	3 (1.3)	NE (NE, NE)	3.17	0.95, 14.30	0.0619
>=65	183	5 (2.7)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	2.43	0.52, 16.95	0.2650
Interaction p-value									0.8034
Region									
Asia	241	4 (1.7)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	4.29	0.63, 83.87	0.1432
Rest of World	161	10 (6.2)	NE (NE, NE)	146	4 (2.7)	NE (NE, NE)	2.34	0.78, 8.53	0.1317
Interaction p-value									0.6208
PD-L1 Status									
High (>=1%)	239	8 (3.3)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	2.77	0.80, 12.65	0.1100
Low (<1%)	118	6 (5.1)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	6.24	1.07,117.85	0.0414*
Interaction p-value									0.5082
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.2.2 TOPAZ: Summary of subgroup analysis of time to first SAE PT: Anaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	14 (6.9)	NE (NE, NE)	196	4 (2.0)	NE (NE, NE)	3.46	1.24, 12.19	0.0164*
Interaction p-value									NC
Race									
Asian	248	4 (1.6)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	2.13	0.42, 15.34	0.3686
Non-Asian	154	10 (6.5)	NE (NE, NE)	141	3 (2.1)	NE (NE, NE)	3.15	0.96, 14.04	0.0582
Interaction p-value									0.7199
WHO ECOG Status at Screening									
0	186	9 (4.8)	NE (NE, NE)	184	4 (2.2)	NE (NE, NE)	2.24	0.73, 8.26	0.1627
1	216	5 (2.3)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	5.20	0.84, 99.53	0.0798
Interaction p-value									0.4806
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	1.31	0.05, 33.18	0.8474
Metastatic	347	13 (3.7)	NE (NE, NE)	330	4 (1.2)	NE (NE, NE)	3.14	1.11, 11.17	0.0297*
Interaction p-value									0.5704
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	9 (5.4)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	4.93	1.27, 32.36	0.0192*
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.3.1 TOPAZ: Summary of subgroup analysis of time to first AE leading to discontinuation of treatment
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	48 (14.7)	NE (NE, NE)	333	46 (13.8)	NE (NE, NE)	1.03	0.69, 1.55	0.8734
Recurrent	76	8 (10.5)	NE (NE, NE)	70	11 (15.7)	NE (NE, NE)	0.60	0.23, 1.49	0.2723
Interaction p-value									0.2857
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	12 (16.4)	NE (NE, NE)	71	5 (7.0)	NE (NE, NE)	2.25	0.83, 7.07	0.1121
Intrahepatic CCA	234	35 (15.0)	NE (NE, NE)	235	37 (15.7)	NE (NE, NE)	0.91	0.57, 1.45	0.7042
Gallbladder cancer	95	9 (9.5)	NE (NE, NE)	97	15 (15.5)	NE (NE, NE)	0.57	0.24, 1.27	0.1714
Interaction p-value									0.1089
Age Group									
<65	219	32 (14.6)	NE (NE, NE)	229	32 (14.0)	NE (NE, NE)	0.98	0.60, 1.60	0.9211
>=65	183	24 (13.1)	NE (NE, NE)	174	25 (14.4)	NE (NE, NE)	0.89	0.51, 1.57	0.6926
Interaction p-value									0.8162
Region									
Asia	241	30 (12.4)	NE (NE, NE)	257	31 (12.1)	NE (NE, NE)	0.98	0.59, 1.62	0.9396
Rest of World	161	26 (16.1)	NE (NE, NE)	146	26 (17.8)	NE (NE, NE)	0.87	0.50, 1.50	0.6175
Interaction p-value									0.7522
PD-L1 Status									
High (>=1%)	239	29 (12.1)	NE (NE, NE)	249	39 (15.7)	NE (NE, NE)	0.71	0.44, 1.15	0.1672
Low (<1%)	118	23 (19.5)	NE (NE, NE)	117	12 (10.3)	NE (NE, NE)	1.93	0.98, 4.01	0.0578
Interaction p-value									0.0189*
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaecaa 01FEB2023:16:13 kjpc654

Table 3.4.3.1 TOPAZ: Summary of subgroup analysis of time to first AE leading to discontinuation of treatment
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	29 (14.6)	NE (NE, NE)	207	33 (15.9)	NE (NE, NE)	0.88	0.53, 1.45	0.6079
Female	203	27 (13.3)	NE (NE, NE)	196	24 (12.2)	NE (NE, NE)	1.03	0.59, 1.79	0.9201
Interaction p-value									0.6749
Race									
Asian	248	32 (12.9)	NE (NE, NE)	262	31 (11.8)	NE (NE, NE)	1.04	0.63, 1.71	0.8826
Non-Asian	154	24 (15.6)	NE (NE, NE)	141	26 (18.4)	NE (NE, NE)	0.81	0.46, 1.41	0.4534
Interaction p-value									0.5102
WHO ECOG Status at Screening									
0	186	20 (10.8)	NE (NE, NE)	184	29 (15.8)	NE (NE, NE)	0.62	0.35, 1.09	0.0987
1	216	36 (16.7)	NE (NE, NE)	219	28 (12.8)	NE (NE, NE)	1.29	0.79, 2.14	0.3033
Interaction p-value									0.0546
Disease Extent									
Locally Advanced	55	6 (10.9)	NE (NE, NE)	73	7 (9.6)	NE (NE, NE)	1.06	0.34, 3.21	0.9101
Metastatic	347	50 (14.4)	NE (NE, NE)	330	50 (15.2)	NE (NE, NE)	0.90	0.61, 1.34	0.6120
Interaction p-value									0.7813
MSI Status									
MSI High	3	0	NE (NE, NE)	2	2 (100)	10.5 (3.5, NE)	NC	NC	NC
MSI Stable	166	21 (12.7)	NE (NE, NE)	178	22 (12.4)	NE (NE, NE)	0.98	0.53, 1.78	0.9412
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaecaa 01FEB2023:16:13 kjpc654

Table 3.4.4.1 TOPAZ: Summary of subgroup analysis of time to first AE max CTCAE grade >=3
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	251 (77.0)	2.0 (1.6, 2.4)	333	256 (76.9)	1.6 (1.2, 2.2)	0.91	0.76, 1.08	0.2902
Recurrent	76	62 (81.6)	2.3 (1.0, 2.8)	70	59 (84.3)	1.7 (1.0, 2.3)	0.79	0.55, 1.13	0.1970
Interaction p-value									0.4836
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	55 (75.3)	1.7 (1.0, 3.7)	71	59 (83.1)	1.0 (0.8, 1.7)	0.67	0.47, 0.98	0.0365*
Intrahepatic CCA	234	176 (75.2)	2.3 (1.6, 2.7)	235	180 (76.6)	2.1 (1.4, 2.3)	0.89	0.72, 1.09	0.2533
Gallbladder cancer	95	82 (86.3)	2.0 (1.3, 2.5)	97	76 (78.4)	1.7 (1.0, 2.6)	1.08	0.79, 1.48	0.6348
Interaction p-value									0.1621
Age Group									
<65	219	172 (78.5)	2.1 (1.6, 2.6)	229	169 (73.8)	2.1 (1.5, 2.5)	0.98	0.79, 1.22	0.8732
>=65	183	141 (77.0)	2.0 (1.3, 2.5)	174	146 (83.9)	1.4 (1.0, 1.7)	0.77	0.61, 0.98	0.0300*
Interaction p-value									0.1347
Region									
Asia	241	192 (79.7)	1.8 (1.6, 2.3)	257	199 (77.4)	1.7 (1.2, 2.3)	0.95	0.78, 1.16	0.5985
Rest of World	161	121 (75.2)	2.4 (1.5, 3.5)	146	116 (79.5)	1.6 (1.0, 2.1)	0.80	0.62, 1.04	0.0935
Interaction p-value									0.3159
PD-L1 Status									
High (>=1%)	239	188 (78.7)	1.7 (1.5, 2.4)	249	191 (76.7)	1.7 (1.2, 2.3)	0.93	0.76, 1.14	0.4860
Low (<1%)	118	92 (78.0)	2.4 (1.4, 3.7)	117	92 (78.6)	1.4 (1.0, 2.3)	0.86	0.65, 1.15	0.3218
Interaction p-value									0.6792
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.4.1 TOPAZ: Summary of subgroup analysis of time to first AE max CTCAE grade >=3
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	160 (80.4)	2.0 (1.4, 2.5)	207	163 (78.7)	1.9 (1.2, 2.3)	0.98	0.79, 1.22	0.8351
Female	203	153 (75.4)	2.1 (1.6, 2.6)	196	152 (77.6)	1.6 (1.0, 2.1)	0.81	0.64, 1.01	0.0604
Interaction p-value									0.2277
Race									
Asian	248	198 (79.8)	1.8 (1.6, 2.3)	262	201 (76.7)	1.8 (1.2, 2.3)	0.96	0.79, 1.17	0.7037
Non-Asian	154	115 (74.7)	2.4 (1.5, 3.5)	141	114 (80.9)	1.6 (0.9, 2.1)	0.77	0.60, 1.005	0.0545
Interaction p-value									0.1915
WHO ECOG Status at Screening									
0	186	141 (75.8)	2.4 (1.7, 3.1)	184	140 (76.1)	2.2 (1.6, 2.5)	0.89	0.70, 1.12	0.3238
1	216	172 (79.6)	1.6 (1.1, 2.3)	219	175 (79.9)	1.2 (1.0, 1.7)	0.89	0.72, 1.10	0.2660
Interaction p-value									0.9914
Disease Extent									
Locally Advanced	55	44 (80.0)	2.4 (1.1, 4.3)	73	60 (82.2)	1.4 (0.9, 2.1)	0.75	0.50, 1.10	0.1457
Metastatic	347	269 (77.5)	2.1 (1.6, 2.4)	330	255 (77.3)	1.7 (1.3, 2.3)	0.92	0.77, 1.09	0.3213
Interaction p-value									0.3526
MSI Status									
MSI High	3	2 (66.7)	5.8 (1.6, NE)	2	2 (100)	2.2 (0.4, NE)	NC	NC	NC
MSI Stable	166	127 (76.5)	1.9 (1.3, 2.5)	178	139 (78.1)	1.6 (1.0, 2.3)	0.88	0.69, 1.12	0.2818
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.1 TOPAZ: Summary of subgroup analysis of time to first AESI
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	291 (89.3)	0.7 (0.7, 0.9)	333	299 (89.8)	0.9 (0.7, 1.0)	0.98	0.84, 1.15	0.8259
Recurrent	76	70 (92.1)	0.8 (0.6, 1.0)	70	63 (90.0)	0.7 (0.3, 1.0)	0.89	0.63, 1.26	0.5070
Interaction p-value									0.6123
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	65 (89.0)	0.8 (0.4, 1.4)	71	63 (88.7)	0.8 (0.3, 1.0)	0.86	0.61, 1.22	0.4122
Intrahepatic CCA	234	208 (88.9)	0.7 (0.5, 0.9)	235	213 (90.6)	0.7 (0.6, 0.9)	0.95	0.78, 1.15	0.6020
Gallbladder cancer	95	88 (92.6)	0.9 (0.7, 1.1)	97	86 (88.7)	1.0 (0.7, 1.3)	1.08	0.80, 1.46	0.6110
Interaction p-value									0.6187
Age Group									
<65	219	200 (91.3)	0.9 (0.7, 1.0)	229	205 (89.5)	0.8 (0.7, 0.9)	0.94	0.77, 1.14	0.5046
>=65	183	161 (88.0)	0.7 (0.5, 0.9)	174	157 (90.2)	1.0 (0.7, 1.0)	1.00	0.80, 1.25	0.9958
Interaction p-value									0.6556
Region									
Asia	241	220 (91.3)	0.7 (0.5, 0.9)	257	229 (89.1)	0.8 (0.7, 1.0)	1.04	0.87, 1.26	0.6587
Rest of World	161	141 (87.6)	0.9 (0.7, 1.0)	146	133 (91.1)	0.8 (0.7, 1.0)	0.85	0.67, 1.08	0.1888
Interaction p-value									0.1901
PD-L1 Status									
High (>=1%)	239	217 (90.8)	0.7 (0.6, 0.9)	249	222 (89.2)	0.7 (0.5, 0.9)	0.97	0.80, 1.17	0.7313
Low (<1%)	118	106 (89.8)	0.9 (0.7, 1.2)	117	105 (89.7)	1.0 (0.8, 1.2)	1.03	0.79, 1.35	0.8340
Interaction p-value									0.7126
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.1 TOPAZ: Summary of subgroup analysis of time to first AESI
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)						
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]		2-sided p-value [b]
Male	199	173 (86.9)	0.8 (0.7, 1.0)	207	182 (87.9)	0.9 (0.7, 1.0)	0.91	0.74,	1.12	0.3731
Female	203	188 (92.6)	0.7 (0.5, 0.9)	196	180 (91.8)	0.7 (0.5, 1.0)	1.02	0.83,	1.25	0.8547
Interaction p-value										0.4439
Race										
Asian	248	227 (91.5)	0.7 (0.5, 0.9)	262	234 (89.3)	0.8 (0.7, 1.0)	1.04	0.87,	1.25	0.6726
Non-Asian	154	134 (87.0)	0.9 (0.7, 1.0)	141	128 (90.8)	0.8 (0.7, 1.0)	0.85	0.67,	1.08	0.1883
Interaction p-value										0.1910
WHO ECOG Status at Screening										
0	186	168 (90.3)	0.9 (0.7, 1.0)	184	164 (89.1)	0.7 (0.6, 1.0)	0.94	0.76,	1.17	0.5930
1	216	193 (89.4)	0.7 (0.5, 0.9)	219	198 (90.4)	0.9 (0.7, 1.0)	0.98	0.81,	1.20	0.8785
Interaction p-value										0.7724
Disease Extent										
Locally Advanced	55	52 (94.5)	0.8 (0.3, 1.6)	73	69 (94.5)	0.7 (0.3, 1.0)	0.83	0.58,	1.19	0.3199
Metastatic	347	309 (89.0)	0.8 (0.7, 0.9)	330	293 (88.8)	0.9 (0.7, 1.0)	0.99	0.85,	1.17	0.9415
Interaction p-value										0.3794
MSI Status										
MSI High	3	3 (100)	1.6 (0.3, NE)	2	2 (100)	2.6 (1.2, NE)	NC	NC		NC
MSI Stable	166	146 (88.0)	0.8 (0.7, 1.0)	178	159 (89.3)	0.8 (0.7, 1.0)	0.90	0.72,	1.13	0.3489
Interaction p-value										NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.2 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	6 (1.8)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	1.37	0.39, 5.41	0.6256
Recurrent	76	0	NE (NE, NE)	70	2 (2.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	4 (1.7)	NE (NE, NE)	235	4 (1.7)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	4 (1.8)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	5 (2.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	5 (2.1)	NE (NE, NE)	257	3 (1.2)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	5 (2.0)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.2 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	4 (2.0)	NE (NE, NE)	207	4 (1.9)	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	5 (2.0)	NE (NE, NE)	262	3 (1.1)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	5 (2.7)	NE (NE, NE)	NC	NC	NC
1	216	4 (1.9)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	6 (1.7)	NE (NE, NE)	330	6 (1.8)	NE (NE, NE)	0.82	0.25, 2.64	0.7270
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.3 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Immune-mediated lung disease
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.3 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Immune-mediated lung disease
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeac 01FEB2023:16:13 kjpc654

Table 3.4.5.4 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Interstitial lung disease
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.4 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Interstitial lung disease
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeead 01FEB2023:16:13 kjpc654

Table 3.4.5.5 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	3 (0.9)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	3 (1.3)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	4 (2.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	3 (1.2)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	4 (1.6)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.5 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	3 (1.4)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	3 (1.1)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	4 (2.2)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	5 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.6 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Hepatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	3 (0.9)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	2 (2.6)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	3 (1.3)	NE (NE, NE)	235	3 (1.3)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	5 (2.3)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	3 (1.9)	NE (NE, NE)	146	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeaf 01FEB2023:16:13 kjpc654

Table 3.4.5.6 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Hepatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	3 (1.4)	NE (NE, NE)	NC	NC	NC
Female	203	4 (2.0)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	3 (1.9)	NE (NE, NE)	141	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	5 (1.4)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	17.5 (NE, NE)	NC	NC	NC
MSI Stable	166	3 (1.8)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeaf 01FEB2023:16:13 kjpc654

Table 3.4.5.7 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	Number (%) of patients n with events		Median time (95% CI) (months) [a]	Number (%) of patients n with events		Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeag 01FEB2023:16:13 kjpc654

Table 3.4.5.7 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeag 01FEB2023:16:13 kjpc654

Table 3.4.5.8 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeah 01FEB2023:16:13 kjpc654

Table 3.4.5.8 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	17.5 (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeah 01FEB2023:16:13 kjpc654

Table 3.4.5.9 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	2 (2.6)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	3 (1.4)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.9 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.10 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Immune-mediated hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeaj 01FEB2023:16:13 kjpc654

Table 3.4.5.10 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Immune-mediated hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeaj 01FEB2023:16:13 kjpc654

Table 3.4.5.11 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Diarrhoea/Colitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	56 (17.2)	NE (NE, NE)	333	44 (13.2)	NE (NE, NE)	1.29	0.87, 1.93	0.2009
Recurrent	76	9 (11.8)	NE (NE, NE)	70	13 (18.6)	20.2 (20.2, NE)	0.56	0.23, 1.30	0.1759
Interaction p-value									0.0768
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	11 (15.1)	NE (NE, NE)	71	14 (19.7)	NE (NE, NE)	0.68	0.30, 1.49	0.3345
Intrahepatic CCA	234	37 (15.8)	NE (NE, NE)	235	25 (10.6)	NE (NE, NE)	1.50	0.91, 2.51	0.1163
Gallbladder cancer	95	17 (17.9)	NE (NE, NE)	97	18 (18.6)	NE (NE, NE)	0.90	0.46, 1.76	0.7622
Interaction p-value									0.1995
Age Group									
<65	219	32 (14.6)	NE (NE, NE)	229	35 (15.3)	NE (NE, NE)	0.90	0.56, 1.46	0.6747
>=65	183	33 (18.0)	NE (NE, NE)	174	22 (12.6)	NE (NE, NE)	1.42	0.84, 2.48	0.1946
Interaction p-value									0.2129
Region									
Asia	241	35 (14.5)	NE (NE, NE)	257	20 (7.8)	NE (NE, NE)	1.82	1.06, 3.21	0.0292*
Rest of World	161	30 (18.6)	NE (NE, NE)	146	37 (25.3)	NE (NE, NE)	0.70	0.43, 1.13	0.1421
Interaction p-value									0.0092*
PD-L1 Status									
High (>=1%)	239	36 (15.1)	NE (NE, NE)	249	36 (14.5)	NE (NE, NE)	0.97	0.61, 1.54	0.8880
Low (<1%)	118	18 (15.3)	NE (NE, NE)	117	13 (11.1)	NE (NE, NE)	1.39	0.69, 2.91	0.3590
Interaction p-value									0.3982
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeak 01FEB2023:16:13 kjpc654

Table 3.4.5.11 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Diarrhoea/Colitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	34 (17.1)	NE (NE, NE)	207	27 (13.0)	NE (NE, NE)	1.31	0.79, 2.18	0.2988
Female	203	31 (15.3)	NE (NE, NE)	196	30 (15.3)	NE (NE, NE)	0.94	0.57, 1.56	0.8027
Interaction p-value									0.3619
Race									
Asian	248	36 (14.5)	NE (NE, NE)	262	22 (8.4)	NE (NE, NE)	1.68	0.998, 2.90	0.0511
Non-Asian	154	29 (18.8)	NE (NE, NE)	141	35 (24.8)	NE (NE, NE)	0.72	0.44, 1.18	0.1968
Interaction p-value									0.0211*
WHO ECOG Status at Screening									
0	186	28 (15.1)	NE (NE, NE)	184	21 (11.4)	NE (NE, NE)	1.27	0.72, 2.26	0.4114
1	216	37 (17.1)	NE (NE, NE)	219	36 (16.4)	NE (NE, NE)	1.02	0.64, 1.61	0.9447
Interaction p-value									0.5534
Disease Extent									
Locally Advanced	55	11 (20.0)	NE (NE, NE)	73	9 (12.3)	NE (NE, NE)	1.57	0.65, 3.91	0.3112
Metastatic	347	54 (15.6)	NE (NE, NE)	330	48 (14.5)	NE (NE, NE)	1.03	0.70, 1.53	0.8800
Interaction p-value									0.3870
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	26 (15.7)	NE (NE, NE)	178	23 (12.9)	NE (NE, NE)	1.18	0.67, 2.09	0.5606
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeak 01FEB2023:16:13 kjpc654

Table 3.4.5.12 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Diarrhoea
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	55 (16.9)	NE (NE, NE)	333	44 (13.2)	NE (NE, NE)	1.27	0.85, 1.89	0.2398
Recurrent	76	9 (11.8)	NE (NE, NE)	70	13 (18.6)	20.2 (20.2, NE)	0.56	0.23, 1.30	0.1753
Interaction p-value									0.0839
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	11 (15.1)	NE (NE, NE)	71	14 (19.7)	NE (NE, NE)	0.68	0.30, 1.49	0.3327
Intrahepatic CCA	234	37 (15.8)	NE (NE, NE)	235	25 (10.6)	NE (NE, NE)	1.50	0.91, 2.51	0.1168
Gallbladder cancer	95	16 (16.8)	NE (NE, NE)	97	18 (18.6)	NE (NE, NE)	0.85	0.43, 1.66	0.6264
Interaction p-value									0.1772
Age Group									
<65	219	32 (14.6)	NE (NE, NE)	229	35 (15.3)	NE (NE, NE)	0.90	0.56, 1.46	0.6724
>=65	183	32 (17.5)	NE (NE, NE)	174	22 (12.6)	NE (NE, NE)	1.38	0.81, 2.40	0.2435
Interaction p-value									0.2491
Region									
Asia	241	34 (14.1)	NE (NE, NE)	257	20 (7.8)	NE (NE, NE)	1.77	1.03, 3.12	0.0401*
Rest of World	161	30 (18.6)	NE (NE, NE)	146	37 (25.3)	NE (NE, NE)	0.70	0.43, 1.13	0.1417
Interaction p-value									0.0120*
PD-L1 Status									
High (>=1%)	239	35 (14.6)	NE (NE, NE)	249	36 (14.5)	NE (NE, NE)	0.94	0.59, 1.50	0.7888
Low (<1%)	118	18 (15.3)	NE (NE, NE)	117	13 (11.1)	NE (NE, NE)	1.39	0.69, 2.90	0.3603
Interaction p-value									0.3620
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.12 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Diarrhoea
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	33 (16.6)	NE (NE, NE)	207	27 (13.0)	NE (NE, NE)	1.26	0.76, 2.12	0.3650
Female	203	31 (15.3)	NE (NE, NE)	196	30 (15.3)	NE (NE, NE)	0.94	0.57, 1.56	0.8015
Interaction p-value									0.4119
Race									
Asian	248	35 (14.1)	NE (NE, NE)	262	22 (8.4)	NE (NE, NE)	1.63	0.96, 2.82	0.0681
Non-Asian	154	29 (18.8)	NE (NE, NE)	141	35 (24.8)	NE (NE, NE)	0.72	0.44, 1.18	0.1962
Interaction p-value									0.0266*
WHO ECOG Status at Screening									
0	186	28 (15.1)	NE (NE, NE)	184	21 (11.4)	NE (NE, NE)	1.27	0.72, 2.26	0.4128
1	216	36 (16.7)	NE (NE, NE)	219	36 (16.4)	NE (NE, NE)	0.99	0.62, 1.57	0.9549
Interaction p-value									0.5035
Disease Extent									
Locally Advanced	55	11 (20.0)	NE (NE, NE)	73	9 (12.3)	NE (NE, NE)	1.57	0.65, 3.90	0.3124
Metastatic	347	53 (15.3)	NE (NE, NE)	330	48 (14.5)	NE (NE, NE)	1.01	0.68, 1.50	0.9610
Interaction p-value									0.3663
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	26 (15.7)	NE (NE, NE)	178	23 (12.9)	NE (NE, NE)	1.18	0.67, 2.09	0.5606
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.13 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Enterocolitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.13 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Enterocolitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.14 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Immune-mediated enterocolitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.14 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Immune-mediated enterocolitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeean 01FEB2023:16:13 kjpc654

Table 3.4.5.15 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Colitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.15 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Colitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeao 01FEB2023:16:13 kjpc654

Table 3.4.5.16 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Adrenal insufficiency
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	3 (3.9)	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	3 (3.2)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	3 (1.2)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	3 (1.3)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.16 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Adrenal insufficiency
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	3 (1.4)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	3 (1.8)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.17 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Adrenal insufficiency
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	3 (3.9)	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	3 (3.2)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	3 (1.2)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	3 (1.3)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.17 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Adrenal insufficiency
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	3 (1.4)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	3 (1.8)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.18 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Type 1 diabetes mellitus
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.18 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Type 1 diabetes mellitus
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeear 01FEB2023:16:13 kjpc654

Table 3.4.5.19 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Type 1 diabetes mellitus
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeas 01FEB2023:16:13 kjpc654

Table 3.4.5.19 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Type 1 diabetes mellitus
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeas 01FEB2023:16:13 kjpc654

Table 3.4.5.20 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Hyperthyroid events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	8 (2.5)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	2.57	0.74, 11.73	0.1415
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	3 (1.3)	NE (NE, NE)	235	3 (1.3)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	4 (4.2)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	5 (2.3)	NE (NE, NE)	229	3 (1.3)	NE (NE, NE)	NC	NC	NC
>=65	183	4 (2.2)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	3 (1.2)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	6 (3.7)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	5 (2.1)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeat 01FEB2023:16:13 kjpc654

Table 3.4.5.20 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Hyperthyroid events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	4 (2.0)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	5 (2.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	6 (3.9)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	4 (2.2)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	5 (2.3)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	2 (3.6)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	7 (2.0)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	2.13	0.59, 9.89	0.2541
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.21 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hyperthyroidism
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	7 (2.1)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	2.26	0.63, 10.52	0.2175
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	3 (1.3)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	4 (4.2)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	4 (1.8)	NE (NE, NE)	229	3 (1.3)	NE (NE, NE)	NC	NC	NC
>=65	183	4 (2.2)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	3 (1.2)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	5 (3.1)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	4 (1.7)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.21 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hyperthyroidism
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	4 (2.0)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	4 (2.0)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	5 (3.2)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	5 (2.3)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	7 (2.0)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	2.13	0.59, 9.89	0.2541
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.22 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Immune-mediated hyperthyroidism
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.22 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Immune-mediated hyperthyroidism
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeav 01FEB2023:16:13 kjpc654

Table 3.4.5.23 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Hypophysitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.23 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Hypophysitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeaw 01FEB2023:16:13 kjpc654

Table 3.4.5.24 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hypothalamic pituitary adrenal axis suppression
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeax 01FEB2023:16:13 kjpc654

Table 3.4.5.24 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hypothalamic pituitary adrenal axis suppression
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeax 01FEB2023:16:13 kjpc654

Table 3.4.5.25 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Hypothyroid events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	23 (7.1)	NE (NE, NE)	333	12 (3.6)	NE (NE, NE)	1.82	0.92, 3.79	0.0854
Recurrent	76	6 (7.9)	NE (NE, NE)	70	2 (2.9)	NE (NE, NE)	2.49	0.57, 17.01	0.2343
Interaction p-value									0.7206
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	3 (4.2)	NE (NE, NE)	0.26	0.01, 2.04	0.2069
Intrahepatic CCA	234	17 (7.3)	NE (NE, NE)	235	9 (3.8)	NE (NE, NE)	1.77	0.81, 4.16	0.1577
Gallbladder cancer	95	11 (11.6)	NE (NE, NE)	97	2 (2.1)	NE (NE, NE)	5.50	1.48, 35.56	0.0088*
Interaction p-value									0.0498*
Age Group									
<65	219	18 (8.2)	NE (NE, NE)	229	8 (3.5)	NE (NE, NE)	2.15	0.97, 5.26	0.0611
>=65	183	11 (6.0)	NE (NE, NE)	174	6 (3.4)	NE (NE, NE)	1.62	0.61, 4.70	0.3352
Interaction p-value									0.6655
Region									
Asia	241	15 (6.2)	NE (NE, NE)	257	6 (2.3)	NE (NE, NE)	2.44	0.99, 6.84	0.0534
Rest of World	161	14 (8.7)	NE (NE, NE)	146	8 (5.5)	NE (NE, NE)	1.49	0.64, 3.73	0.3608
Interaction p-value									0.4524
PD-L1 Status									
High (>=1%)	239	22 (9.2)	NE (NE, NE)	249	8 (3.2)	NE (NE, NE)	2.59	1.20, 6.22	0.0148*
Low (<1%)	118	6 (5.1)	NE (NE, NE)	117	4 (3.4)	NE (NE, NE)	1.41	0.40, 5.51	0.5934
Interaction p-value									0.4295
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.25 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Hypothyroid events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	11 (5.5)	NE (NE, NE)	207	6 (2.9)	NE (NE, NE)	1.81	0.69, 5.27	0.2305
Female	203	18 (8.9)	NE (NE, NE)	196	8 (4.1)	NE (NE, NE)	1.94	0.87, 4.74	0.1067
Interaction p-value									0.9180
Race									
Asian	248	15 (6.0)	NE (NE, NE)	262	6 (2.3)	NE (NE, NE)	2.42	0.98, 6.79	0.0557
Non-Asian	154	14 (9.1)	NE (NE, NE)	141	8 (5.7)	NE (NE, NE)	1.50	0.64, 3.76	0.3522
Interaction p-value									0.4666
WHO ECOG Status at Screening									
0	186	15 (8.1)	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	4.59	1.51, 19.81	0.0055*
1	216	14 (6.5)	NE (NE, NE)	219	11 (5.0)	NE (NE, NE)	1.18	0.53, 2.66	0.6870
Interaction p-value									0.0543
Disease Extent									
Locally Advanced	55	4 (7.3)	NE (NE, NE)	73	4 (5.5)	NE (NE, NE)	1.06	0.25, 4.48	0.9391
Metastatic	347	25 (7.2)	NE (NE, NE)	330	10 (3.0)	NE (NE, NE)	2.24	1.11, 4.90	0.0240*
Interaction p-value									0.3485
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	12 (7.2)	NE (NE, NE)	178	7 (3.9)	NE (NE, NE)	1.67	0.67, 4.51	0.2733
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.26 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hypothyroidism
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	21 (6.4)	NE (NE, NE)	333	12 (3.6)	NE (NE, NE)	1.66	0.83, 3.48	0.1569
Recurrent	76	6 (7.9)	NE (NE, NE)	70	2 (2.9)	NE (NE, NE)	2.50	0.57, 17.08	0.2323
Interaction p-value									0.6375
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	3 (4.2)	NE (NE, NE)	0.26	0.01, 2.06	0.2100
Intrahepatic CCA	234	15 (6.4)	NE (NE, NE)	235	9 (3.8)	NE (NE, NE)	1.55	0.69, 3.69	0.2928
Gallbladder cancer	95	11 (11.6)	NE (NE, NE)	97	2 (2.1)	NE (NE, NE)	5.50	1.48, 35.53	0.0089*
Interaction p-value									0.0463*
Age Group									
<65	219	16 (7.3)	NE (NE, NE)	229	8 (3.5)	NE (NE, NE)	1.90	0.84, 4.70	0.1271
>=65	183	11 (6.0)	NE (NE, NE)	174	6 (3.4)	NE (NE, NE)	1.62	0.62, 4.71	0.3331
Interaction p-value									0.8091
Region									
Asia	241	15 (6.2)	NE (NE, NE)	257	6 (2.3)	NE (NE, NE)	2.44	0.99, 6.85	0.0530
Rest of World	161	12 (7.5)	NE (NE, NE)	146	8 (5.5)	NE (NE, NE)	1.27	0.52, 3.24	0.5999
Interaction p-value									0.3230
PD-L1 Status									
High (>=1%)	239	21 (8.8)	NE (NE, NE)	249	8 (3.2)	NE (NE, NE)	2.47	1.13, 5.96	0.0220*
Low (<1%)	118	5 (4.2)	NE (NE, NE)	117	4 (3.4)	NE (NE, NE)	1.16	0.31, 4.71	0.8198
Interaction p-value									0.3437
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.26 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hypothyroidism
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	11 (5.5)	NE (NE, NE)	207	6 (2.9)	NE (NE, NE)	1.82	0.69, 5.28	0.2295
Female	203	16 (7.9)	NE (NE, NE)	196	8 (4.1)	NE (NE, NE)	1.72	0.75, 4.24	0.2021
Interaction p-value									0.9326
Race									
Asian	248	15 (6.0)	NE (NE, NE)	262	6 (2.3)	NE (NE, NE)	2.42	0.98, 6.80	0.0553
Non-Asian	154	12 (7.8)	NE (NE, NE)	141	8 (5.7)	NE (NE, NE)	1.28	0.53, 3.26	0.5889
Interaction p-value									0.3345
WHO ECOG Status at Screening									
0	186	13 (7.0)	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	3.95	1.27, 17.25	0.0156*
1	216	14 (6.5)	NE (NE, NE)	219	11 (5.0)	NE (NE, NE)	1.18	0.53, 2.66	0.6889
Interaction p-value									0.0917
Disease Extent									
Locally Advanced	55	3 (5.5)	NE (NE, NE)	73	4 (5.5)	NE (NE, NE)	0.79	0.15, 3.60	0.7569
Metastatic	347	24 (6.9)	NE (NE, NE)	330	10 (3.0)	NE (NE, NE)	2.15	1.05, 4.71	0.0347*
Interaction p-value									0.2376
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	11 (6.6)	NE (NE, NE)	178	7 (3.9)	NE (NE, NE)	1.51	0.59, 4.13	0.3885
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeaz 01FEB2023:16:13 kjpc654

Table 3.4.5.27 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Immune-mediated hypothyroidism
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeba 01FEB2023:16:13 kjpc654

Table 3.4.5.27 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Immune-mediated hypothyroidism
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeba 01FEB2023:16:13 kjpc654

Table 3.4.5.28 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Thyroiditis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebb 01FEB2023:16:13 kjpc654

Table 3.4.5.28 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Thyroiditis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebb 01FEB2023:16:13 kjpc654

Table 3.4.5.29 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Autoimmune thyroiditis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebc 01FEB2023:16:13 kjpc654

Table 3.4.5.29 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Autoimmune thyroiditis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebc 01FEB2023:16:13 kjpc654

Table 3.4.5.30 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Renal events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	2 (2.9)	20.2 (20.2, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebd 01FEB2023:16:13 kjpc654

Table 3.4.5.30 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Renal events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	2 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebd 01FEB2023:16:13 kjpc654

Table 3.4.5.31 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Nephritis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	2 (2.9)	20.2 (20.2, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.31 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Nephritis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	2 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebe 01FEB2023:16:13 kjpc654

Table 3.4.5.32 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Dermatitis/Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	70 (21.5)	NE (NE, NE)	333	38 (11.4)	NE (NE, NE)	1.90	1.29, 2.84	0.0011*
Recurrent	76	11 (14.5)	NE (NE, NE)	70	13 (18.6)	NE (NE, NE)	0.69	0.30, 1.54	0.3599
Interaction p-value									0.0263*
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	17 (23.3)	NE (NE, NE)	71	6 (8.5)	NE (NE, NE)	2.72	1.13, 7.54	0.0251*
Intrahepatic CCA	234	47 (20.1)	NE (NE, NE)	235	37 (15.7)	NE (NE, NE)	1.25	0.81, 1.94	0.3062
Gallbladder cancer	95	17 (17.9)	NE (NE, NE)	97	8 (8.2)	NE (NE, NE)	2.12	0.94, 5.20	0.0694
Interaction p-value									0.2225
Age Group									
<65	219	50 (22.8)	NE (NE, NE)	229	38 (16.6)	NE (NE, NE)	1.30	0.86, 2.00	0.2182
>=65	183	31 (16.9)	NE (NE, NE)	174	13 (7.5)	NE (NE, NE)	2.32	1.24, 4.60	0.0076*
Interaction p-value									0.1359
Region									
Asia	241	51 (21.2)	NE (NE, NE)	257	34 (13.2)	NE (NE, NE)	1.56	1.02, 2.43	0.0418*
Rest of World	161	30 (18.6)	NE (NE, NE)	146	17 (11.6)	NE (NE, NE)	1.59	0.89, 2.94	0.1222
Interaction p-value									0.9684
PD-L1 Status									
High (>=1%)	239	46 (19.2)	NE (NE, NE)	249	27 (10.8)	NE (NE, NE)	1.70	1.06, 2.77	0.0263*
Low (<1%)	118	28 (23.7)	NE (NE, NE)	117	20 (17.1)	NE (NE, NE)	1.40	0.79, 2.52	0.2486
Interaction p-value									0.6089
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebf 01FEB2023:16:13 kjpc654

Table 3.4.5.32 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Dermatitis/Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	43 (21.6)	NE (NE, NE)	207	25 (12.1)	NE (NE, NE)	1.82	1.12, 3.02	0.0154*
Female	203	38 (18.7)	NE (NE, NE)	196	26 (13.3)	NE (NE, NE)	1.34	0.82, 2.23	0.2503
Interaction p-value									0.3912
Race									
Asian	248	54 (21.8)	NE (NE, NE)	262	36 (13.7)	NE (NE, NE)	1.55	1.02, 2.38	0.0396*
Non-Asian	154	27 (17.5)	NE (NE, NE)	141	15 (10.6)	NE (NE, NE)	1.63	0.88, 3.14	0.1224
Interaction p-value									0.8982
WHO ECOG Status at Screening									
0	186	39 (21.0)	NE (NE, NE)	184	23 (12.5)	NE (NE, NE)	1.61	0.97, 2.73	0.0671
1	216	42 (19.4)	NE (NE, NE)	219	28 (12.8)	NE (NE, NE)	1.53	0.95, 2.49	0.0804
Interaction p-value									0.8855
Disease Extent									
Locally Advanced	55	14 (25.5)	NE (NE, NE)	73	10 (13.7)	NE (NE, NE)	1.73	0.77, 4.01	0.1841
Metastatic	347	67 (19.3)	NE (NE, NE)	330	41 (12.4)	NE (NE, NE)	1.54	1.05, 2.28	0.0280*
Interaction p-value									0.8005
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	34 (20.5)	NE (NE, NE)	178	22 (12.4)	NE (NE, NE)	1.61	0.95, 2.79	0.0789
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebf 01FEB2023:16:13 kjpc654

Table 3.4.5.33 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	39 (12.0)	NE (NE, NE)	333	24 (7.2)	NE (NE, NE)	1.63	0.99, 2.74	0.0566
Recurrent	76	8 (10.5)	NE (NE, NE)	70	10 (14.3)	NE (NE, NE)	0.67	0.26, 1.71	0.4056
Interaction p-value									0.1020
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	11 (15.1)	NE (NE, NE)	71	5 (7.0)	NE (NE, NE)	2.06	0.75, 6.53	0.1663
Intrahepatic CCA	234	25 (10.7)	NE (NE, NE)	235	23 (9.8)	NE (NE, NE)	1.06	0.60, 1.87	0.8520
Gallbladder cancer	95	11 (11.6)	NE (NE, NE)	97	6 (6.2)	NE (NE, NE)	1.82	0.69, 5.28	0.2286
Interaction p-value									0.4252
Age Group									
<65	219	32 (14.6)	NE (NE, NE)	229	27 (11.8)	NE (NE, NE)	1.17	0.70, 1.96	0.5588
>=65	183	15 (8.2)	NE (NE, NE)	174	7 (4.0)	NE (NE, NE)	2.04	0.86, 5.34	0.1075
Interaction p-value									0.2808
Region									
Asia	241	31 (12.9)	NE (NE, NE)	257	25 (9.7)	NE (NE, NE)	1.27	0.75, 2.17	0.3708
Rest of World	161	16 (9.9)	NE (NE, NE)	146	9 (6.2)	NE (NE, NE)	1.58	0.71, 3.73	0.2662
Interaction p-value									0.6628
PD-L1 Status									
High (>=1%)	239	28 (11.7)	NE (NE, NE)	249	20 (8.0)	NE (NE, NE)	1.39	0.79, 2.50	0.2610
Low (<1%)	118	16 (13.6)	NE (NE, NE)	117	12 (10.3)	NE (NE, NE)	1.33	0.63, 2.86	0.4590
Interaction p-value									0.9242
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.33 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	22 (11.1)	NE (NE, NE)	207	17 (8.2)	NE (NE, NE)	1.32	0.70, 2.53	0.3852
Female	203	25 (12.3)	NE (NE, NE)	196	17 (8.7)	NE (NE, NE)	1.35	0.73, 2.55	0.3346
Interaction p-value									0.9612
Race									
Asian	248	32 (12.9)	NE (NE, NE)	262	26 (9.9)	NE (NE, NE)	1.25	0.74, 2.11	0.4016
Non-Asian	154	15 (9.7)	NE (NE, NE)	141	8 (5.7)	NE (NE, NE)	1.69	0.73, 4.19	0.2233
Interaction p-value									0.5533
WHO ECOG Status at Screening									
0	186	25 (13.4)	NE (NE, NE)	184	14 (7.6)	NE (NE, NE)	1.70	0.90, 3.36	0.1040
1	216	22 (10.2)	NE (NE, NE)	219	20 (9.1)	NE (NE, NE)	1.08	0.59, 2.00	0.8006
Interaction p-value									0.3158
Disease Extent									
Locally Advanced	55	7 (12.7)	NE (NE, NE)	73	6 (8.2)	NE (NE, NE)	1.42	0.47, 4.41	0.5312
Metastatic	347	40 (11.5)	NE (NE, NE)	330	28 (8.5)	NE (NE, NE)	1.32	0.82, 2.17	0.2520
Interaction p-value									0.9114
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	20 (12.0)	NE (NE, NE)	178	11 (6.2)	NE (NE, NE)	1.90	0.93, 4.12	0.0801
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.34 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Rash maculo-papular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	18 (5.5)	NE (NE, NE)	333	8 (2.4)	NE (NE, NE)	2.19	0.98, 5.36	0.0557
Recurrent	76	2 (2.6)	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	1.63	0.16, 35.18	0.6828
Interaction p-value									0.8223
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	5 (6.8)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	13 (5.6)	NE (NE, NE)	235	8 (3.4)	NE (NE, NE)	1.62	0.68, 4.11	0.2732
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	2.01	0.19, 43.32	0.5558
Interaction p-value									0.8680
Age Group									
<65	219	10 (4.6)	NE (NE, NE)	229	4 (1.7)	NE (NE, NE)	2.44	0.81, 8.92	0.1136
>=65	183	10 (5.5)	NE (NE, NE)	174	5 (2.9)	NE (NE, NE)	1.82	0.65, 5.85	0.2627
Interaction p-value									0.7146
Region									
Asia	241	11 (4.6)	NE (NE, NE)	257	6 (2.3)	NE (NE, NE)	1.81	0.69, 5.28	0.2336
Rest of World	161	9 (5.6)	NE (NE, NE)	146	3 (2.1)	NE (NE, NE)	2.65	0.79, 11.95	0.1186
Interaction p-value									0.6469
PD-L1 Status									
High (>=1%)	239	9 (3.8)	NE (NE, NE)	249	4 (1.6)	NE (NE, NE)	2.13	0.69, 7.90	0.1929
Low (<1%)	118	8 (6.8)	NE (NE, NE)	117	5 (4.3)	NE (NE, NE)	1.53	0.51, 5.07	0.4510
Interaction p-value									0.6881
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.34 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Rash maculo-papular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	14 (7.0)	NE (NE, NE)	207	5 (2.4)	NE (NE, NE)	2.82	1.08, 8.75	0.0339*
Female	203	6 (3.0)	NE (NE, NE)	196	4 (2.0)	NE (NE, NE)	1.32	0.38, 5.19	0.6643
Interaction p-value									0.3621
Race									
Asian	248	14 (5.6)	NE (NE, NE)	262	6 (2.3)	NE (NE, NE)	2.30	0.92, 6.52	0.0764
Non-Asian	154	6 (3.9)	NE (NE, NE)	141	3 (2.1)	NE (NE, NE)	1.77	0.47, 8.38	0.4093
Interaction p-value									0.7600
WHO ECOG Status at Screening									
0	186	7 (3.8)	NE (NE, NE)	184	4 (2.2)	NE (NE, NE)	1.60	0.48, 6.12	0.4471
1	216	13 (6.0)	NE (NE, NE)	219	5 (2.3)	NE (NE, NE)	2.53	0.95, 7.89	0.0643
Interaction p-value									0.5778
Disease Extent									
Locally Advanced	55	4 (7.3)	NE (NE, NE)	73	2 (2.7)	NE (NE, NE)	2.36	0.46, 17.08	0.3071
Metastatic	347	16 (4.6)	NE (NE, NE)	330	7 (2.1)	NE (NE, NE)	2.08	0.88, 5.41	0.0953
Interaction p-value									0.8952
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	9 (5.4)	NE (NE, NE)	178	7 (3.9)	NE (NE, NE)	1.26	0.46, 3.54	0.6528
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.35 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Rash pruritic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.35 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Rash pruritic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebi 01FEB2023:16:13 kjpc654

Table 3.4.5.36 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Rash morbilliform
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebj 01FEB2023:16:13 kjpc654

Table 3.4.5.36 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Rash morbilliform
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebj 01FEB2023:16:13 kjpc654

Table 3.4.5.37 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Rash papular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.37 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Rash papular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.38 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Rash pustular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	3 (0.9)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	2 (2.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	3 (1.4)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebl 01FEB2023:16:13 kjpc654

Table 3.4.5.38 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Rash pustular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebl 01FEB2023:16:13 kjpc654

Table 3.4.5.39 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Dermatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	6 (1.8)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	5 (2.1)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	4 (1.8)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	3 (1.6)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	5 (2.1)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	5 (2.1)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebm 01FEB2023:16:13 kjpc654

Table 3.4.5.39 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Dermatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	4 (2.0)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	5 (2.0)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	4 (2.2)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	3 (1.4)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	6 (1.7)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebm 01FEB2023:16:13 kjpc654

Table 3.4.5.40 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Dermatitis bullous
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebn 01FEB2023:16:13 kjpc654

Table 3.4.5.40 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Dermatitis bullous
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebn 01FEB2023:16:13 kjpc654

Table 3.4.5.41 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Eczema
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	6 (1.8)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	4 (4.2)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	4 (1.8)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	4 (1.7)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	4 (1.7)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebo 01FEB2023:16:13 kjpc654

Table 3.4.5.41 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Eczema
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	3 (1.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	4 (1.6)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	4 (1.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	5 (1.4)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	4 (2.4)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebo 01FEB2023:16:13 kjpc654

Table 3.4.5.42 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Rash erythematous
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.42 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Rash erythematous
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebp 01FEB2023:16:13 kjpc654

Table 3.4.5.43 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Rash macular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebq 01FEB2023:16:13 kjpc654

Table 3.4.5.43 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Rash macular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebq 01FEB2023:16:13 kjpc654

Table 3.4.5.44 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Dermatitis psoriasiform
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebr 01FEB2023:16:13 kjpc654

Table 3.4.5.44 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Dermatitis psoriasiform
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebr 01FEB2023:16:13 kjpc654

Table 3.4.5.45 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Psoriasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebs 01FEB2023:16:13 kjpc654

Table 3.4.5.45 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Psoriasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebs 01FEB2023:16:13 kjpc654

Table 3.4.5.46 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Urticarial dermatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebt 01FEB2023:16:13 kjpc654

Table 3.4.5.46 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Urticarial dermatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebt 01FEB2023:16:13 kjpc654

Table 3.4.5.47 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Pancreatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	4 (5.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	2 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	3 (1.6)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	3 (1.2)	NE (NE, NE)	257	3 (1.2)	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebu 01FEB2023:16:13 kjpc654

Table 3.4.5.47 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Pancreatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	5 (2.5)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	3 (1.1)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	4 (1.2)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebu 01FEB2023:16:13 kjpc654

Table 3.4.5.48 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Pancreatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	3 (3.9)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	2 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	3 (1.6)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	3 (1.2)	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebv 01FEB2023:16:13 kjpc654

Table 3.4.5.48 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Pancreatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	4 (2.0)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	3 (1.1)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebv 01FEB2023:16:13 kjpc654

Table 3.4.5.49 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Pancreatitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebw 01FEB2023:16:13 kjpc654

Table 3.4.5.49 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Pancreatitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebw 01FEB2023:16:13 kjpc654

Table 3.4.5.50 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Myositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.50 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Myositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebx 01FEB2023:16:13 kjpc654

Table 3.4.5.51 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Polymyositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeby 01FEB2023:16:13 kjpc654

Table 3.4.5.51 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Polymyositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeby 01FEB2023:16:13 kjpc654

Table 3.4.5.52 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Infusion/hypersensitivity reactions
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	13 (4.0)	NE (NE, NE)	333	8 (2.4)	NE (NE, NE)	1.55	0.65, 3.93	0.3234
Recurrent	76	2 (2.6)	NE (NE, NE)	70	2 (2.9)	NE (NE, NE)	0.81	0.10, 6.74	0.8307
Interaction p-value									0.5528
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	4 (5.5)	NE (NE, NE)	71	5 (7.0)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	6 (2.6)	NE (NE, NE)	235	3 (1.3)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	5 (5.3)	NE (NE, NE)	97	2 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	10 (4.6)	NE (NE, NE)	229	4 (1.7)	NE (NE, NE)	2.42	0.81, 8.82	0.1184
>=65	183	5 (2.7)	NE (NE, NE)	174	6 (3.4)	NE (NE, NE)	0.73	0.21, 2.43	0.6034
Interaction p-value									0.1505
Region									
Asia	241	12 (5.0)	NE (NE, NE)	257	6 (2.3)	NE (NE, NE)	1.97	0.76, 5.69	0.1639
Rest of World	161	3 (1.9)	NE (NE, NE)	146	4 (2.7)	NE (NE, NE)	0.63	0.12, 2.85	0.5385
Interaction p-value									0.2051
PD-L1 Status									
High (>=1%)	239	9 (3.8)	NE (NE, NE)	249	9 (3.6)	NE (NE, NE)	0.94	0.36, 2.41	0.8922
Low (<1%)	118	5 (4.2)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	4.73	0.76, 90.53	0.1011
Interaction p-value									0.1325
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebz 01FEB2023:16:13 kjpc654

Table 3.4.5.52 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Infusion/hypersensitivity reactions
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	7 (3.5)	NE (NE, NE)	207	6 (2.9)	NE (NE, NE)	1.13	0.38, 3.53	0.8205
Female	203	8 (3.9)	NE (NE, NE)	196	4 (2.0)	NE (NE, NE)	1.76	0.55, 6.61	0.3456
Interaction p-value									0.5944
Race									
Asian	248	12 (4.8)	NE (NE, NE)	262	6 (2.3)	NE (NE, NE)	1.96	0.76, 5.64	0.1696
Non-Asian	154	3 (1.9)	NE (NE, NE)	141	4 (2.8)	NE (NE, NE)	0.63	0.12, 2.87	0.5461
Interaction p-value									0.2121
WHO ECOG Status at Screening									
0	186	5 (2.7)	NE (NE, NE)	184	5 (2.7)	NE (NE, NE)	0.91	0.25, 3.26	0.8760
1	216	10 (4.6)	NE (NE, NE)	219	5 (2.3)	NE (NE, NE)	1.88	0.67, 6.06	0.2373
Interaction p-value									0.3801
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	3 (4.1)	NE (NE, NE)	NC	NC	NC
Metastatic	347	15 (4.3)	NE (NE, NE)	330	7 (2.1)	NE (NE, NE)	1.89	0.79, 4.96	0.1544
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	5 (3.0)	NE (NE, NE)	178	4 (2.2)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeebz 01FEB2023:16:13 kjpc654

Table 3.4.5.53 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Anaphylactic shock
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	Number (%) of patients n with events		Median time (95% CI) (months) [a]	Number (%) of patients n with events		Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeca 01FEB2023:16:13 kjpc654

Table 3.4.5.53 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Anaphylactic shock
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeca 01FEB2023:16:13 kjpc654

Table 3.4.5.54 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Drug hypersensitivity
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecb 01FEB2023:16:13 kjpc654

Table 3.4.5.54 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Drug hypersensitivity
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecb 01FEB2023:16:13 kjpc654

Table 3.4.5.55 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Drug eruption
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecc 01FEB2023:16:13 kjpc654

Table 3.4.5.55 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Drug eruption
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecc 01FEB2023:16:13 kjpc654

Table 3.4.5.56 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Infusion related reaction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	5 (1.5)	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	3 (3.2)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	3 (1.4)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	3 (1.9)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	3 (1.3)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.56 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Infusion related reaction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	3 (1.4)	NE (NE, NE)	NC	NC	NC
Female	203	3 (1.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	3 (1.9)	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	5 (1.4)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecd 01FEB2023:16:13 kjpc654

Table 3.4.5.57 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Type I hypersensitivity
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.57 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Type I hypersensitivity
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeece 01FEB2023:16:13 kjpc654

Table 3.4.5.58 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Urticaria
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	7 (2.1)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	2.14	0.59, 9.98	0.2533
Recurrent	76	2 (2.6)	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	1.54	0.15, 33.26	0.7198
Interaction p-value									0.8167
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	4 (5.5)	NE (NE, NE)	71	2 (2.8)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	3 (1.3)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	6 (2.7)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	3 (1.6)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	9 (3.7)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	4.27	1.09, 28.20	0.0368*
Rest of World	161	0	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	6 (2.5)	NE (NE, NE)	249	4 (1.6)	NE (NE, NE)	1.27	0.36, 5.02	0.7150
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecf 01FEB2023:16:13 kjpc654

Table 3.4.5.58 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Urticaria
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	4 (2.0)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	5 (2.5)	NE (NE, NE)	196	3 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	9 (3.6)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	4.24	1.08, 27.96	0.0381*
Non-Asian	154	0	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	0.43	0.02, 4.55	0.4830
1	216	8 (3.7)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	3.55	0.88, 23.67	0.0781
Interaction p-value									0.1327
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	9 (2.6)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	2.52	0.74, 11.41	0.1440
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	3 (1.8)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecf 01FEB2023:16:13 kjpc654

Table 3.4.5.59 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Other rare/miscellaneous
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecg 01FEB2023:16:13 kjpc654

Table 3.4.5.59 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Other rare/miscellaneous
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecg 01FEB2023:16:13 kjpc654

Table 3.4.5.60 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Immune-mediated arthritis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeech 01FEB2023:16:13 kjpc654

Table 3.4.5.60 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Immune-mediated arthritis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeech 01FEB2023:16:13 kjpc654

Table 3.4.5.61 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Vitiligo
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeci 01FEB2023:16:13 kjpc654

Table 3.4.5.61 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Vitiligo
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.62 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Hepatic SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	111 (34.0)	NE (NE, NE)	333	114 (34.2)	17.5 (13.5, NE)	0.94	0.72, 1.22	0.6406
Recurrent	76	27 (35.5)	NE (NE, NE)	70	16 (22.9)	NE (NE, NE)	1.49	0.81, 2.83	0.1989
Interaction p-value									0.1718
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	27 (37.0)	19.8 (11.6, NE)	71	25 (35.2)	NE (NE, NE)	0.98	0.57, 1.70	0.9402
Intrahepatic CCA	234	77 (32.9)	NE (NE, NE)	235	74 (31.5)	17.5 (13.5, NE)	0.99	0.72, 1.37	0.9724
Gallbladder cancer	95	34 (35.8)	15.7 (8.5, NE)	97	31 (32.0)	15.4 (15.4, NE)	1.06	0.65, 1.73	0.8217
Interaction p-value									0.9729
Age Group									
<65	219	78 (35.6)	23.0 (15.7, NE)	229	91 (39.7)	17.5 (8.7, NE)	0.80	0.59, 1.08	0.1429
>=65	183	60 (32.8)	NE (NE, NE)	174	39 (22.4)	NE (NE, NE)	1.49	0.999, 2.25	0.0508
Interaction p-value									0.0144*
Region									
Asia	241	90 (37.3)	NE (NE, NE)	257	82 (31.9)	15.4 (13.5, NE)	1.12	0.83, 1.51	0.4696
Rest of World	161	48 (29.8)	23.0 (15.7, NE)	146	48 (32.9)	NE (NE, NE)	0.85	0.57, 1.27	0.4282
Interaction p-value									0.2851
PD-L1 Status									
High (>=1%)	239	81 (33.9)	NE (NE, NE)	249	87 (34.9)	NE (NE, NE)	0.88	0.65, 1.19	0.3941
Low (<1%)	118	45 (38.1)	23.0 (7.3, NE)	117	28 (23.9)	NE (NE, NE)	1.68	1.06, 2.73	0.0279*
Interaction p-value									0.0210*
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.62 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Hepatic SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	62 (31.2)	NE (NE, NE)	207	67 (32.4)	17.5 (13.5, NE)	0.90	0.64, 1.27	0.5517
Female	203	76 (37.4)	19.8 (12.6, NE)	196	63 (32.1)	NE (NE, NE)	1.11	0.80, 1.56	0.5232
Interaction p-value									0.3825
Race									
Asian	248	92 (37.1)	NE (NE, NE)	262	83 (31.7)	15.4 (13.5, NE)	1.12	0.83, 1.51	0.4649
Non-Asian	154	46 (29.9)	23.0 (15.7, NE)	141	47 (33.3)	NE (NE, NE)	0.84	0.56, 1.26	0.3994
Interaction p-value									0.2657
WHO ECOG Status at Screening									
0	186	59 (31.7)	NE (NE, NE)	184	52 (28.3)	NE (NE, NE)	1.06	0.73, 1.54	0.7636
1	216	79 (36.6)	NE (NE, NE)	219	78 (35.6)	17.5 (9.8, NE)	0.97	0.71, 1.33	0.8711
Interaction p-value									0.7375
Disease Extent									
Locally Advanced	55	18 (32.7)	23.0 (14.1, NE)	73	31 (42.5)	NE (NE, NE)	0.66	0.36, 1.17	0.1574
Metastatic	347	120 (34.6)	NE (NE, NE)	330	99 (30.0)	17.5 (15.4, NE)	1.11	0.85, 1.45	0.4496
Interaction p-value									0.1087
MSI Status									
MSI High	3	0	NE (NE, NE)	2	2 (100)	9.7 (1.9, NE)	NC	NC	NC
MSI Stable	166	44 (26.5)	NE (NE, NE)	178	43 (24.2)	NE (NE, NE)	1.01	0.66, 1.55	0.9524
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.63 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Alanine aminotransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	39 (12.0)	NE (NE, NE)	333	42 (12.6)	NE (NE, NE)	0.89	0.57, 1.38	0.5931
Recurrent	76	9 (11.8)	NE (NE, NE)	70	8 (11.4)	NE (NE, NE)	0.96	0.36, 2.55	0.9266
Interaction p-value									0.8897
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	11 (15.1)	NE (NE, NE)	71	9 (12.7)	NE (NE, NE)	1.08	0.45, 2.70	0.8614
Intrahepatic CCA	234	28 (12.0)	NE (NE, NE)	235	26 (11.1)	NE (NE, NE)	1.03	0.60, 1.76	0.9252
Gallbladder cancer	95	9 (9.5)	NE (NE, NE)	97	15 (15.5)	NE (NE, NE)	0.56	0.24, 1.26	0.1630
Interaction p-value									0.4287
Age Group									
<65	219	30 (13.7)	NE (NE, NE)	229	40 (17.5)	NE (NE, NE)	0.71	0.44, 1.14	0.1529
>=65	183	18 (9.8)	NE (NE, NE)	174	10 (5.7)	NE (NE, NE)	1.65	0.78, 3.72	0.1957
Interaction p-value									0.0627
Region									
Asia	241	36 (14.9)	NE (NE, NE)	257	35 (13.6)	NE (NE, NE)	1.03	0.64, 1.65	0.9054
Rest of World	161	12 (7.5)	NE (NE, NE)	146	15 (10.3)	NE (NE, NE)	0.67	0.31, 1.44	0.3042
Interaction p-value									0.3479
PD-L1 Status									
High (>=1%)	239	29 (12.1)	NE (NE, NE)	249	34 (13.7)	NE (NE, NE)	0.81	0.49, 1.32	0.3939
Low (<1%)	118	15 (12.7)	23.0 (18.1, NE)	117	10 (8.5)	NE (NE, NE)	1.46	0.66, 3.37	0.3469
Interaction p-value									0.2105
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.63 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Alanine aminotransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	21 (10.6)	NE (NE, NE)	207	23 (11.1)	NE (NE, NE)	0.90	0.49, 1.62	0.7152
Female	203	27 (13.3)	NE (NE, NE)	196	27 (13.8)	NE (NE, NE)	0.89	0.52, 1.52	0.6692
Interaction p-value									0.9872
Race									
Asian	248	36 (14.5)	NE (NE, NE)	262	36 (13.7)	NE (NE, NE)	0.99	0.62, 1.57	0.9579
Non-Asian	154	12 (7.8)	NE (NE, NE)	141	14 (9.9)	NE (NE, NE)	0.73	0.33, 1.58	0.4255
Interaction p-value									0.5114
WHO ECOG Status at Screening									
0	186	23 (12.4)	NE (NE, NE)	184	20 (10.9)	NE (NE, NE)	1.07	0.59, 1.97	0.8205
1	216	25 (11.6)	NE (NE, NE)	219	30 (13.7)	NE (NE, NE)	0.78	0.45, 1.33	0.3585
Interaction p-value									0.4349
Disease Extent									
Locally Advanced	55	8 (14.5)	NE (NE, NE)	73	12 (16.4)	NE (NE, NE)	0.77	0.30, 1.87	0.5682
Metastatic	347	40 (11.5)	NE (NE, NE)	330	38 (11.5)	NE (NE, NE)	0.94	0.60, 1.48	0.7975
Interaction p-value									0.6921
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	166	17 (10.2)	NE (NE, NE)	178	20 (11.2)	NE (NE, NE)	0.84	0.44, 1.62	0.6087
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.64 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Blood alkaline phosphatase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	17 (5.2)	NE (NE, NE)	333	22 (6.6)	NE (NE, NE)	0.72	0.38, 1.36	0.3089
Recurrent	76	3 (3.9)	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	2.41	0.31, 48.79	0.4188
Interaction p-value									0.2812
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	6 (8.2)	NE (NE, NE)	71	3 (4.2)	NE (NE, NE)	1.65	0.43, 7.88	0.4721
Intrahepatic CCA	234	11 (4.7)	NE (NE, NE)	235	14 (6.0)	NE (NE, NE)	0.73	0.32, 1.61	0.4361
Gallbladder cancer	95	3 (3.2)	NE (NE, NE)	97	6 (6.2)	NE (NE, NE)	0.47	0.10, 1.79	0.2723
Interaction p-value									0.4191
Age Group									
<65	219	11 (5.0)	NE (NE, NE)	229	15 (6.6)	NE (NE, NE)	0.68	0.30, 1.48	0.3301
>=65	183	9 (4.9)	NE (NE, NE)	174	8 (4.6)	NE (NE, NE)	1.00	0.38, 2.66	0.9918
Interaction p-value									0.5428
Region									
Asia	241	9 (3.7)	NE (NE, NE)	257	14 (5.4)	NE (NE, NE)	0.62	0.26, 1.41	0.2549
Rest of World	161	11 (6.8)	NE (NE, NE)	146	9 (6.2)	NE (NE, NE)	1.02	0.42, 2.53	0.9678
Interaction p-value									0.4174
PD-L1 Status									
High (>=1%)	239	13 (5.4)	NE (NE, NE)	249	14 (5.6)	NE (NE, NE)	0.86	0.40, 1.85	0.6990
Low (<1%)	118	5 (4.2)	NE (NE, NE)	117	7 (6.0)	NE (NE, NE)	0.66	0.20, 2.08	0.4772
Interaction p-value									0.7061
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.64 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Blood alkaline phosphatase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	5 (2.5)	NE (NE, NE)	207	15 (7.2)	NE (NE, NE)	0.31	0.10, 0.81	0.0161*
Female	203	15 (7.4)	NE (NE, NE)	196	8 (4.1)	NE (NE, NE)	1.64	0.71, 4.10	0.2487
Interaction p-value									0.0104*
Race									
Asian	248	9 (3.6)	NE (NE, NE)	262	14 (5.3)	NE (NE, NE)	0.61	0.25, 1.40	0.2462
Non-Asian	154	11 (7.1)	NE (NE, NE)	141	9 (6.4)	NE (NE, NE)	1.03	0.42, 2.55	0.9535
Interaction p-value									0.4016
WHO ECOG Status at Screening									
0	186	13 (7.0)	NE (NE, NE)	184	11 (6.0)	NE (NE, NE)	1.06	0.47, 2.43	0.8808
1	216	7 (3.2)	NE (NE, NE)	219	12 (5.5)	NE (NE, NE)	0.54	0.20, 1.34	0.1829
Interaction p-value									0.2708
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	3 (4.1)	NE (NE, NE)	0.36	0.02, 2.80	0.3394
Metastatic	347	19 (5.5)	NE (NE, NE)	330	20 (6.1)	NE (NE, NE)	0.83	0.44, 1.56	0.5574
Interaction p-value									0.4596
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	7 (4.2)	NE (NE, NE)	178	9 (5.1)	NE (NE, NE)	0.76	0.27, 2.05	0.5826
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.65 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecm 01FEB2023:16:13 kjpc654

Table 3.4.5.65 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecm 01FEB2023:16:13 kjpc654

Table 3.4.5.66 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Aspartate aminotransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	35 (10.7)	NE (NE, NE)	333	39 (11.7)	NE (NE, NE)	0.85	0.54, 1.34	0.4880
Recurrent	76	7 (9.2)	NE (NE, NE)	70	8 (11.4)	NE (NE, NE)	0.74	0.26, 2.06	0.5571
Interaction p-value									0.8017
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	9 (12.3)	NE (NE, NE)	71	9 (12.7)	NE (NE, NE)	0.86	0.33, 2.22	0.7525
Intrahepatic CCA	234	25 (10.7)	NE (NE, NE)	235	27 (11.5)	NE (NE, NE)	0.88	0.50, 1.51	0.6326
Gallbladder cancer	95	8 (8.4)	NE (NE, NE)	97	11 (11.3)	NE (NE, NE)	0.68	0.26, 1.68	0.4056
Interaction p-value									0.8934
Age Group									
<65	219	25 (11.4)	NE (NE, NE)	229	36 (15.7)	NE (NE, NE)	0.65	0.39, 1.08	0.0965
>=65	183	17 (9.3)	NE (NE, NE)	174	11 (6.3)	NE (NE, NE)	1.41	0.67, 3.11	0.3710
Interaction p-value									0.0932
Region									
Asia	241	31 (12.9)	NE (NE, NE)	257	34 (13.2)	NE (NE, NE)	0.90	0.55, 1.47	0.6684
Rest of World	161	11 (6.8)	NE (NE, NE)	146	13 (8.9)	NE (NE, NE)	0.71	0.31, 1.59	0.4072
Interaction p-value									0.6272
PD-L1 Status									
High (>=1%)	239	26 (10.9)	NE (NE, NE)	249	35 (14.1)	NE (NE, NE)	0.70	0.41, 1.15	0.1604
Low (<1%)	118	14 (11.9)	NE (NE, NE)	117	8 (6.8)	NE (NE, NE)	1.70	0.73, 4.26	0.2231
Interaction p-value									0.0767
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecn 01FEB2023:16:13 kjpc654

Table 3.4.5.66 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Aspartate aminotransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	15 (7.5)	NE (NE, NE)	207	20 (9.7)	NE (NE, NE)	0.73	0.37, 1.42	0.3572
Female	203	27 (13.3)	NE (NE, NE)	196	27 (13.8)	NE (NE, NE)	0.88	0.51, 1.51	0.6376
Interaction p-value									0.6720
Race									
Asian	248	32 (12.9)	NE (NE, NE)	262	35 (13.4)	NE (NE, NE)	0.89	0.55, 1.45	0.6436
Non-Asian	154	10 (6.5)	NE (NE, NE)	141	12 (8.5)	NE (NE, NE)	0.71	0.30, 1.65	0.4213
Interaction p-value									0.6404
WHO ECOG Status at Screening									
0	186	17 (9.1)	NE (NE, NE)	184	22 (12.0)	NE (NE, NE)	0.70	0.37, 1.32	0.2685
1	216	25 (11.6)	NE (NE, NE)	219	25 (11.4)	NE (NE, NE)	0.95	0.54, 1.66	0.8448
Interaction p-value									0.4833
Disease Extent									
Locally Advanced	55	8 (14.5)	NE (NE, NE)	73	8 (11.0)	NE (NE, NE)	1.19	0.44, 3.25	0.7262
Metastatic	347	34 (9.8)	NE (NE, NE)	330	39 (11.8)	NE (NE, NE)	0.77	0.48, 1.22	0.2640
Interaction p-value									0.4286
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	166	14 (8.4)	NE (NE, NE)	178	16 (9.0)	NE (NE, NE)	0.87	0.42, 1.79	0.7046
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecn 01FEB2023:16:13 kjpc654

Table 3.4.5.67 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Ascites
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	15 (4.6)	NE (NE, NE)	333	13 (3.9)	NE (NE, NE)	1.12	0.53, 2.39	0.7698
Recurrent	76	2 (2.6)	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	1.69	0.16, 36.37	0.6609
Interaction p-value									0.7428
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	3 (4.1)	NE (NE, NE)	71	4 (5.6)	NE (NE, NE)	0.65	0.13, 2.95	0.5659
Intrahepatic CCA	234	12 (5.1)	NE (NE, NE)	235	10 (4.3)	NE (NE, NE)	1.16	0.50, 2.74	0.7336
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									0.5036
Age Group									
<65	219	10 (4.6)	NE (NE, NE)	229	8 (3.5)	NE (NE, NE)	1.21	0.48, 3.19	0.6823
>=65	183	7 (3.8)	NE (NE, NE)	174	6 (3.4)	NE (NE, NE)	1.07	0.35, 3.31	0.9094
Interaction p-value									0.8581
Region									
Asia	241	7 (2.9)	NE (NE, NE)	257	3 (1.2)	NE (NE, NE)	2.34	0.65, 10.87	0.1987
Rest of World	161	10 (6.2)	NE (NE, NE)	146	11 (7.5)	NE (NE, NE)	0.79	0.33, 1.87	0.5859
Interaction p-value									0.1705
PD-L1 Status									
High (>=1%)	239	9 (3.8)	NE (NE, NE)	249	10 (4.0)	NE (NE, NE)	0.86	0.34, 2.14	0.7450
Low (<1%)	118	7 (5.9)	NE (NE, NE)	117	3 (2.6)	NE (NE, NE)	2.23	0.62, 10.36	0.2254
Interaction p-value									0.2390
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeco 01FEB2023:16:13 kjpc654

Table 3.4.5.67 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Ascites
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	10 (5.0)	NE (NE, NE)	207	6 (2.9)	NE (NE, NE)	1.67	0.62, 4.92	0.3126
Female	203	7 (3.4)	NE (NE, NE)	196	8 (4.1)	NE (NE, NE)	0.78	0.27, 2.17	0.6285
Interaction p-value									0.2925
Race									
Asian	248	7 (2.8)	NE (NE, NE)	262	3 (1.1)	NE (NE, NE)	2.32	0.64, 10.78	0.2034
Non-Asian	154	10 (6.5)	NE (NE, NE)	141	11 (7.8)	NE (NE, NE)	0.79	0.33, 1.89	0.5981
Interaction p-value									0.1772
WHO ECOG Status at Screening									
0	186	8 (4.3)	NE (NE, NE)	184	7 (3.8)	NE (NE, NE)	1.06	0.38, 3.02	0.9136
1	216	9 (4.2)	NE (NE, NE)	219	7 (3.2)	NE (NE, NE)	1.24	0.46, 3.47	0.6705
Interaction p-value									0.8270
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	5 (6.8)	NE (NE, NE)	0.22	0.01, 1.40	0.1164
Metastatic	347	16 (4.6)	NE (NE, NE)	330	9 (2.7)	NE (NE, NE)	1.62	0.73, 3.83	0.2400
Interaction p-value									0.0543
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	8 (4.8)	NE (NE, NE)	178	4 (2.2)	NE (NE, NE)	2.14	0.67, 8.02	0.2002
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeco 01FEB2023:16:13 kjpc654

Table 3.4.5.68 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.68 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	17.5 (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecp 01FEB2023:16:13 kjpc654

Table 3.4.5.69 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	Number (%) of patients n with events	Median time (95% CI) (months) [a]		Number (%) of patients n with events	Median time (95% CI) (months) [a]		Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326 17 (5.2)	NE (NE, NE)		333 27 (8.1)	NE (NE, NE)		0.58	0.31, 1.06	0.0757
Recurrent	76 1 (1.3)	NE (NE, NE)		70 6 (8.6)	NE (NE, NE)		0.13	0.01, 0.75	0.0199*
Interaction p-value									0.1227
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73 3 (4.1)	NE (NE, NE)		71 7 (9.9)	NE (NE, NE)		0.33	0.07, 1.20	0.0945
Intrahepatic CCA	234 13 (5.6)	NE (NE, NE)		235 21 (8.9)	NE (NE, NE)		0.56	0.27, 1.11	0.0960
Gallbladder cancer	95 2 (2.1)	NE (NE, NE)		97 5 (5.2)	NE (NE, NE)		0.38	0.05, 1.75	0.2203
Interaction p-value									0.7519
Age Group									
<65	219 7 (3.2)	NE (NE, NE)		229 24 (10.5)	NE (NE, NE)		0.26	0.10, 0.57	0.0006*
>=65	183 11 (6.0)	NE (NE, NE)		174 9 (5.2)	NE (NE, NE)		1.08	0.45, 2.69	0.8586
Interaction p-value									0.0185*
Region									
Asia	241 12 (5.0)	NE (NE, NE)		257 20 (7.8)	NE (NE, NE)		0.56	0.27, 1.14	0.1102
Rest of World	161 6 (3.7)	NE (NE, NE)		146 13 (8.9)	NE (NE, NE)		0.38	0.13, 0.96	0.0409*
Interaction p-value									0.5202
PD-L1 Status									
High (>=1%)	239 12 (5.0)	NE (NE, NE)		249 20 (8.0)	NE (NE, NE)		0.55	0.26, 1.10	0.0927
Low (<1%)	118 5 (4.2)	NE (NE, NE)		117 10 (8.5)	NE (NE, NE)		0.46	0.14, 1.30	0.1443
Interaction p-value									0.7964
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecq 01FEB2023:16:13 kjpc654

Table 3.4.5.69 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	8 (4.0)	NE (NE, NE)	207	19 (9.2)	NE (NE, NE)	0.39	0.16, 0.87	0.0205*
Female	203	10 (4.9)	NE (NE, NE)	196	14 (7.1)	NE (NE, NE)	0.61	0.26, 1.36	0.2238
Interaction p-value									0.4639
Race									
Asian	248	13 (5.2)	NE (NE, NE)	262	21 (8.0)	NE (NE, NE)	0.57	0.28, 1.14	0.1127
Non-Asian	154	5 (3.2)	NE (NE, NE)	141	12 (8.5)	NE (NE, NE)	0.35	0.11, 0.93	0.0357*
Interaction p-value									0.4214
WHO ECOG Status at Screening									
0	186	6 (3.2)	NE (NE, NE)	184	6 (3.3)	NE (NE, NE)	0.87	0.27, 2.79	0.8134
1	216	12 (5.6)	NE (NE, NE)	219	27 (12.3)	NE (NE, NE)	0.39	0.19, 0.76	0.0054*
Interaction p-value									0.2401
Disease Extent									
Locally Advanced	55	5 (9.1)	NE (NE, NE)	73	6 (8.2)	NE (NE, NE)	0.92	0.26, 3.07	0.8910
Metastatic	347	13 (3.7)	NE (NE, NE)	330	27 (8.2)	NE (NE, NE)	0.41	0.20, 0.78	0.0064*
Interaction p-value									0.2503
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	166	5 (3.0)	NE (NE, NE)	178	9 (5.1)	NE (NE, NE)	0.52	0.16, 1.52	0.2366
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecq 01FEB2023:16:13 kjpc654

Table 3.4.5.70 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Blood bilirubin unconjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecr 01FEB2023:16:13 kjpc654

Table 3.4.5.70 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Blood bilirubin unconjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecr 01FEB2023:16:13 kjpc654

Table 3.4.5.71 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Bilirubin conjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	4 (1.7)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	4 (1.6)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecs 01FEB2023:16:13 kjpc654

Table 3.4.5.71 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Bilirubin conjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	4 (1.5)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	4 (1.2)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecs 01FEB2023:16:13 kjpc654

Table 3.4.5.72 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.72 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeect 01FEB2023:16:13 kjpc654

Table 3.4.5.73 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Blood cholinesterase decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.73 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Blood cholinesterase decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecu 01FEB2023:16:13 kjpc654

Table 3.4.5.74 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Total bile acids increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	3 (0.9)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	3 (1.2)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.74 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Total bile acids increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	3 (1.4)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	2 (3.6)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecv 01FEB2023:16:13 kjpc654

Table 3.4.5.75 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Gamma-glutamyltransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	16 (4.9)	NE (NE, NE)	333	21 (6.3)	NE (NE, NE)	0.70	0.36, 1.35	0.2878
Recurrent	76	4 (5.3)	NE (NE, NE)	70	2 (2.9)	NE (NE, NE)	1.56	0.30, 11.32	0.6008
Interaction p-value									0.3773
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	5 (6.8)	NE (NE, NE)	71	3 (4.2)	NE (NE, NE)	1.31	0.32, 6.45	0.7126
Intrahepatic CCA	234	11 (4.7)	NE (NE, NE)	235	16 (6.8)	NE (NE, NE)	0.62	0.28, 1.33	0.2240
Gallbladder cancer	95	4 (4.2)	NE (NE, NE)	97	4 (4.1)	NE (NE, NE)	0.96	0.23, 4.07	0.9576
Interaction p-value									0.6249
Age Group									
<65	219	14 (6.4)	NE (NE, NE)	229	15 (6.6)	NE (NE, NE)	0.86	0.41, 1.79	0.6764
>=65	183	6 (3.3)	NE (NE, NE)	174	8 (4.6)	NE (NE, NE)	0.64	0.21, 1.86	0.4150
Interaction p-value									0.6661
Region									
Asia	241	13 (5.4)	NE (NE, NE)	257	13 (5.1)	NE (NE, NE)	0.96	0.44, 2.09	0.9098
Rest of World	161	7 (4.3)	NE (NE, NE)	146	10 (6.8)	NE (NE, NE)	0.56	0.20, 1.47	0.2394
Interaction p-value									0.3964
PD-L1 Status									
High (>=1%)	239	14 (5.9)	NE (NE, NE)	249	16 (6.4)	NE (NE, NE)	0.80	0.38, 1.66	0.5518
Low (<1%)	118	6 (5.1)	NE (NE, NE)	117	3 (2.6)	NE (NE, NE)	1.83	0.48, 8.69	0.3795
Interaction p-value									0.2893
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecw 01FEB2023:16:13 kjpc654

Table 3.4.5.75 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Gamma-glutamyltransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	5 (2.5)	NE (NE, NE)	207	17 (8.2)	NE (NE, NE)	0.27	0.09, 0.69	0.0049*
Female	203	15 (7.4)	NE (NE, NE)	196	6 (3.1)	NE (NE, NE)	2.18	0.88, 6.13	0.0937
Interaction p-value									0.0015*
Race									
Asian	248	13 (5.2)	NE (NE, NE)	262	13 (5.0)	NE (NE, NE)	0.95	0.43, 2.07	0.8874
Non-Asian	154	7 (4.5)	NE (NE, NE)	141	10 (7.1)	NE (NE, NE)	0.57	0.21, 1.49	0.2490
Interaction p-value									0.4173
WHO ECOG Status at Screening									
0	186	8 (4.3)	NE (NE, NE)	184	13 (7.1)	NE (NE, NE)	0.53	0.21, 1.27	0.1585
1	216	12 (5.6)	NE (NE, NE)	219	10 (4.6)	NE (NE, NE)	1.10	0.47, 2.62	0.8224
Interaction p-value									0.2410
Disease Extent									
Locally Advanced	55	2 (3.6)	NE (NE, NE)	73	3 (4.1)	NE (NE, NE)	0.73	0.10, 4.43	0.7286
Metastatic	347	18 (5.2)	NE (NE, NE)	330	20 (6.1)	NE (NE, NE)	0.76	0.40, 1.45	0.4075
Interaction p-value									0.9641
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	166	6 (3.6)	NE (NE, NE)	178	8 (4.5)	NE (NE, NE)	0.73	0.24, 2.13	0.5688
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecw 01FEB2023:16:13 kjpc654

Table 3.4.5.76 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	6 (1.8)	NE (NE, NE)	333	6 (1.8)	NE (NE, NE)	0.97	0.30, 3.10	0.9547
Recurrent	76	2 (2.6)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	5 (2.1)	NE (NE, NE)	235	3 (1.3)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	3 (3.2)	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	6 (2.7)	NE (NE, NE)	229	5 (2.2)	NE (NE, NE)	1.13	0.34, 3.93	0.8418
>=65	183	2 (1.1)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	1.80	0.17, 38.77	0.6215
Interaction p-value									0.7282
Region									
Asia	241	8 (3.3)	NE (NE, NE)	257	6 (2.3)	NE (NE, NE)	1.30	0.45, 3.97	0.6222
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	5 (2.1)	NE (NE, NE)	249	4 (1.6)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecx 01FEB2023:16:13 kjpc654

Table 3.4.5.76 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	5 (2.5)	NE (NE, NE)	207	5 (2.4)	NE (NE, NE)	0.98	0.27, 3.52	0.9715
Female	203	3 (1.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	2.61	0.33, 52.84	0.3746
Interaction p-value									0.4370
Race									
Asian	248	8 (3.2)	NE (NE, NE)	262	6 (2.3)	NE (NE, NE)	1.30	0.45, 3.95	0.6281
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	2.65	0.34, 53.57	0.3674
1	216	5 (2.3)	NE (NE, NE)	219	5 (2.3)	NE (NE, NE)	0.96	0.27, 3.45	0.9465
Interaction p-value									0.4210
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	8 (2.3)	NE (NE, NE)	330	6 (1.8)	NE (NE, NE)	1.19	0.41, 3.62	0.7464
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	3 (1.8)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecx 01FEB2023:16:13 kjpc654

Table 3.4.5.77 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatic encephalopathy
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.77 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatic encephalopathy
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.78 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatic cytolysis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	3 (0.9)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	3 (1.3)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	4 (2.5)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	3 (1.3)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecz 01FEB2023:16:13 kjpc654

Table 3.4.5.78 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatic cytolysis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	3 (1.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	4 (2.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	4 (2.2)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeecz 01FEB2023:16:13 kjpc654

Table 3.4.5.79 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	2 (2.6)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	3 (1.4)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.79 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.80 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatitis B
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	Number (%) of patients n with events		Median time (95% CI) (months) [a]	Number (%) of patients n with events		Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.80 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatitis B
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedb 01FEB2023:16:13 kjpc654

Table 3.4.5.81 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatitis E
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedc 01FEB2023:16:13 kjpc654

Table 3.4.5.81 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatitis E
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedc 01FEB2023:16:13 kjpc654

Table 3.4.5.82 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatorenal failure
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedd 01FEB2023:16:13 kjpc654

Table 3.4.5.82 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatorenal failure
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedd 01FEB2023:16:13 kjpc654

Table 3.4.5.83 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hypoalbuminaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	24 (7.4)	NE (NE, NE)	333	21 (6.3)	NE (NE, NE)	1.12	0.62, 2.03	0.6993
Recurrent	76	5 (6.6)	NE (NE, NE)	70	4 (5.7)	NE (NE, NE)	1.07	0.28, 4.34	0.9155
Interaction p-value									0.9519
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	4 (5.6)	NE (NE, NE)	0.44	0.06, 2.26	0.3278
Intrahepatic CCA	234	17 (7.3)	NE (NE, NE)	235	16 (6.8)	NE (NE, NE)	1.03	0.52, 2.05	0.9380
Gallbladder cancer	95	10 (10.5)	NE (NE, NE)	97	5 (5.2)	NE (NE, NE)	1.98	0.70, 6.37	0.1984
Interaction p-value									0.2933
Age Group									
<65	219	14 (6.4)	NE (NE, NE)	229	18 (7.9)	NE (NE, NE)	0.76	0.37, 1.52	0.4331
>=65	183	15 (8.2)	NE (NE, NE)	174	7 (4.0)	NE (NE, NE)	2.01	0.85, 5.26	0.1161
Interaction p-value									0.0865
Region									
Asia	241	24 (10.0)	NE (NE, NE)	257	15 (5.8)	NE (NE, NE)	1.64	0.87, 3.19	0.1296
Rest of World	161	5 (3.1)	NE (NE, NE)	146	10 (6.8)	NE (NE, NE)	0.43	0.13, 1.21	0.1113
Interaction p-value									0.0312*
PD-L1 Status									
High (>=1%)	239	19 (7.9)	NE (NE, NE)	249	14 (5.6)	NE (NE, NE)	1.34	0.67, 2.72	0.4066
Low (<1%)	118	8 (6.8)	NE (NE, NE)	117	5 (4.3)	NE (NE, NE)	1.54	0.51, 5.10	0.4417
Interaction p-value									0.8321
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.83 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hypoalbuminaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	12 (6.0)	NE (NE, NE)	207	15 (7.2)	NE (NE, NE)	0.79	0.36, 1.69	0.5497
Female	203	17 (8.4)	NE (NE, NE)	196	10 (5.1)	NE (NE, NE)	1.57	0.73, 3.56	0.2515
Interaction p-value									0.2161
Race									
Asian	248	24 (9.7)	NE (NE, NE)	262	15 (5.7)	NE (NE, NE)	1.62	0.86, 3.17	0.1365
Non-Asian	154	5 (3.2)	NE (NE, NE)	141	10 (7.1)	NE (NE, NE)	0.43	0.13, 1.22	0.1145
Interaction p-value									0.0334*
WHO ECOG Status at Screening									
0	186	5 (2.7)	NE (NE, NE)	184	9 (4.9)	NE (NE, NE)	0.51	0.16, 1.47	0.2140
1	216	24 (11.1)	NE (NE, NE)	219	16 (7.3)	NE (NE, NE)	1.49	0.80, 2.86	0.2142
Interaction p-value									0.0884
Disease Extent									
Locally Advanced	55	3 (5.5)	NE (NE, NE)	73	5 (6.8)	NE (NE, NE)	0.72	0.15, 2.92	0.6440
Metastatic	347	26 (7.5)	NE (NE, NE)	330	20 (6.1)	NE (NE, NE)	1.19	0.67, 2.16	0.5603
Interaction p-value									0.5153
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	166	4 (2.4)	NE (NE, NE)	178	7 (3.9)	NE (NE, NE)	0.60	0.16, 1.98	0.4021
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.84 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	3 (0.9)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	3 (1.3)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	4 (1.6)	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedf 01FEB2023:16:13 kjpc654

Table 3.4.5.84 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	3 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	4 (1.5)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	4 (1.2)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedf 01FEB2023:16:13 kjpc654

Table 3.4.5.85 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hypertransaminasaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedg 01FEB2023:16:13 kjpc654

Table 3.4.5.85 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hypertransaminasaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedg 01FEB2023:16:13 kjpc654

Table 3.4.5.86 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	5 (1.5)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	4 (5.6)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	6 (2.6)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	4 (1.6)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	5 (2.0)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.86 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	4 (2.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	4 (1.5)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	5 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedh 01FEB2023:16:13 kjpc654

Table 3.4.5.87 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Immune-mediated hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedi 01FEB2023:16:13 kjpc654

Table 3.4.5.87 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Immune-mediated hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedi 01FEB2023:16:13 kjpc654

Table 3.4.5.88 TOPAZ: Summary of subgroup analysis of time to first AESI PT: International normalised ratio increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	Number (%) of patients n with events	Median time (95% CI) (months) [a]		Number (%) of patients n with events	Median time (95% CI) (months) [a]		Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326 1 (0.3)	NE (NE, NE)		333 1 (0.3)	NE (NE, NE)		NC	NC	NC
Recurrent	76 0	NE (NE, NE)		70 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73 0	NE (NE, NE)		71 0	NE (NE, NE)		NC	NC	NC
Intrahepatic CCA	234 0	NE (NE, NE)		235 1 (0.4)	NE (NE, NE)		NC	NC	NC
Gallbladder cancer	95 1 (1.1)	NE (NE, NE)		97 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219 1 (0.5)	NE (NE, NE)		229 1 (0.4)	NE (NE, NE)		NC	NC	NC
>=65	183 0	NE (NE, NE)		174 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Region									
Asia	241 1 (0.4)	NE (NE, NE)		257 1 (0.4)	NE (NE, NE)		NC	NC	NC
Rest of World	161 0	NE (NE, NE)		146 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239 1 (0.4)	NE (NE, NE)		249 1 (0.4)	NE (NE, NE)		NC	NC	NC
Low (<1%)	118 0	NE (NE, NE)		117 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedj 01FEB2023:16:13 kjpc654

Table 3.4.5.88 TOPAZ: Summary of subgroup analysis of time to first AESI PT: International normalised ratio increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedj 01FEB2023:16:13 kjpc654

Table 3.4.5.89 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Liver abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	2 (2.6)	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedk 01FEB2023:16:13 kjpc654

Table 3.4.5.89 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Liver abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	2 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedk 01FEB2023:16:13 kjpc654

Table 3.4.5.90 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatic enzyme increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedl 01FEB2023:16:13 kjpc654

Table 3.4.5.90 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatic enzyme increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedl 01FEB2023:16:13 kjpc654

Table 3.4.5.91 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatic function abnormal
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	5 (1.5)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	2 (2.6)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	3 (1.3)	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	3 (3.2)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	3 (1.4)	NE (NE, NE)	229	3 (1.3)	NE (NE, NE)	NC	NC	NC
>=65	183	4 (2.2)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	7 (2.9)	NE (NE, NE)	257	3 (1.2)	NE (NE, NE)	1.95	0.52, 9.21	0.3268
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	5 (2.1)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.91 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatic function abnormal
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	3 (1.4)	NE (NE, NE)	NC	NC	NC
Female	203	4 (2.0)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	7 (2.8)	NE (NE, NE)	262	3 (1.1)	NE (NE, NE)	1.93	0.52, 9.12	0.3350
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	4 (2.2)	NE (NE, NE)	NC	NC	NC
1	216	4 (1.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	2 (3.6)	NE (NE, NE)	73	2 (2.7)	NE (NE, NE)	NC	NC	NC
Metastatic	347	5 (1.4)	NE (NE, NE)	330	2 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedm 01FEB2023:16:13 kjpc654

Table 3.4.5.92 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Liver function test abnormal
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedn 01FEB2023:16:13 kjpc654

Table 3.4.5.92 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Liver function test abnormal
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedn 01FEB2023:16:13 kjpc654

Table 3.4.5.93 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Liver function test increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.93 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Liver function test increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedo 01FEB2023:16:13 kjpc654

Table 3.4.5.94 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatotoxicity
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.94 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatotoxicity
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedp 01FEB2023:16:13 kjpc654

Table 3.4.5.95 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	2 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	3 (1.3)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	3 (1.2)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedq 01FEB2023:16:13 kjpc654

Table 3.4.5.95 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	3 (1.1)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	2 (2.7)	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedq 01FEB2023:16:13 kjpc654

Table 3.4.5.96 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatic failure
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	3 (0.9)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedr 01FEB2023:16:13 kjpc654

Table 3.4.5.96 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatic failure
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedr 01FEB2023:16:13 kjpc654

Table 3.4.5.97 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Oesophageal varices haemorrhage
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeds 01FEB2023:16:13 kjpc654

Table 3.4.5.97 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Oesophageal varices haemorrhage
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeds 01FEB2023:16:13 kjpc654

Table 3.4.5.98 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Prothrombin level decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedt 01FEB2023:16:13 kjpc654

Table 3.4.5.98 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Prothrombin level decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedt 01FEB2023:16:13 kjpc654

Table 3.4.5.99 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Prothrombin time prolonged
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedu 01FEB2023:16:13 kjpc654

Table 3.4.5.99 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Prothrombin time prolonged
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedu 01FEB2023:16:13 kjpc654

Table 3.4.5.100 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Prothrombin time ratio increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedv 01FEB2023:16:13 kjpc654

Table 3.4.5.100 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Prothrombin time ratio increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedv 01FEB2023:16:13 kjpc654

Table 3.4.5.101 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatitis B reactivation
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.101 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hepatitis B reactivation
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedw 01FEB2023:16:13 kjpc654

Table 3.4.5.102 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Transaminases increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	4 (1.2)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	3 (1.3)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	4 (1.8)	NE (NE, NE)	229	4 (1.7)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	4 (1.7)	NE (NE, NE)	257	4 (1.6)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeedx 01FEB2023:16:13 kjpc654

Table 3.4.5.102 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Transaminases increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	3 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	4 (1.6)	NE (NE, NE)	262	4 (1.5)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	NC	NC	NC
1	216	5 (2.3)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	5 (1.4)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.103 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Biliary SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	88 (27.0)	NE (NE, NE)	333	85 (25.5)	NE (NE, NE)	0.98	0.73, 1.33	0.9186
Recurrent	76	18 (23.7)	NE (NE, NE)	70	16 (22.9)	NE (NE, NE)	0.89	0.45, 1.76	0.7233
Interaction p-value									0.7770
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	30 (41.1)	19.8 (7.2, NE)	71	26 (36.6)	8.7 (7.0, NE)	0.96	0.56, 1.64	0.8728
Intrahepatic CCA	234	46 (19.7)	NE (NE, NE)	235	49 (20.9)	NE (NE, NE)	0.86	0.57, 1.28	0.4462
Gallbladder cancer	95	30 (31.6)	NE (NE, NE)	97	26 (26.8)	NE (NE, NE)	1.15	0.68, 1.96	0.5943
Interaction p-value									0.6745
Age Group									
<65	219	52 (23.7)	NE (NE, NE)	229	60 (26.2)	NE (NE, NE)	0.79	0.54, 1.15	0.2146
>=65	183	54 (29.5)	NE (NE, NE)	174	41 (23.6)	NE (NE, NE)	1.21	0.81, 1.83	0.3508
Interaction p-value									0.1258
Region									
Asia	241	74 (30.7)	NE (NE, NE)	257	73 (28.4)	15.2 (13.2, NE)	0.98	0.71, 1.36	0.9103
Rest of World	161	32 (19.9)	NE (NE, NE)	146	28 (19.2)	NE (NE, NE)	0.96	0.58, 1.60	0.8760
Interaction p-value									0.9436
PD-L1 Status									
High (>=1%)	239	62 (25.9)	NE (NE, NE)	249	63 (25.3)	NE (NE, NE)	0.90	0.63, 1.28	0.5576
Low (<1%)	118	34 (28.8)	NE (NE, NE)	117	28 (23.9)	NE (NE, NE)	1.18	0.72, 1.97	0.5059
Interaction p-value									0.3771
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.103 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Biliary SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	46 (23.1)	NE (NE, NE)	207	58 (28.0)	NE (NE, NE)	0.73	0.49, 1.07	0.1055
Female	203	60 (29.6)	NE (NE, NE)	196	43 (21.9)	NE (NE, NE)	1.28	0.86, 1.90	0.2198
Interaction p-value									0.0437*
Race									
Asian	248	78 (31.5)	NE (NE, NE)	262	75 (28.6)	15.2 (11.7, NE)	1.00	0.73, 1.38	0.9921
Non-Asian	154	28 (18.2)	NE (NE, NE)	141	26 (18.4)	NE (NE, NE)	0.91	0.53, 1.55	0.7190
Interaction p-value									0.7529
WHO ECOG Status at Screening									
0	186	47 (25.3)	NE (NE, NE)	184	44 (23.9)	NE (NE, NE)	0.94	0.62, 1.43	0.7831
1	216	59 (27.3)	NE (NE, NE)	219	57 (26.0)	NE (NE, NE)	0.98	0.68, 1.41	0.9086
Interaction p-value									0.8965
Disease Extent									
Locally Advanced	55	14 (25.5)	NE (NE, NE)	73	22 (30.1)	NE (NE, NE)	0.67	0.33, 1.30	0.2400
Metastatic	347	92 (26.5)	NE (NE, NE)	330	79 (23.9)	NE (NE, NE)	1.03	0.77, 1.40	0.8283
Interaction p-value									0.2453
MSI Status									
MSI High	3	1 (33.3)	NE (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	166	39 (23.5)	NE (NE, NE)	178	42 (23.6)	NE (NE, NE)	0.90	0.58, 1.40	0.6417
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.104 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Cholangitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	4 (1.2)	NE (NE, NE)	333	5 (1.5)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	3 (4.2)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	3 (1.3)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	3 (1.4)	NE (NE, NE)	229	3 (1.3)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	3 (1.2)	NE (NE, NE)	257	6 (2.3)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	4 (1.6)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.104 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Cholangitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	4 (1.9)	NE (NE, NE)	NC	NC	NC
Female	203	3 (1.5)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	6 (2.3)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	4 (2.2)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	4 (1.2)	NE (NE, NE)	330	5 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	3 (1.8)	NE (NE, NE)	178	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.105 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Cholecystitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.105 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Cholecystitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.106 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Blood alkaline phosphatase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	17 (5.2)	NE (NE, NE)	333	22 (6.6)	NE (NE, NE)	0.72	0.38, 1.36	0.3089
Recurrent	76	3 (3.9)	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	2.41	0.31, 48.79	0.4188
Interaction p-value									0.2812
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	6 (8.2)	NE (NE, NE)	71	3 (4.2)	NE (NE, NE)	1.65	0.43, 7.88	0.4721
Intrahepatic CCA	234	11 (4.7)	NE (NE, NE)	235	14 (6.0)	NE (NE, NE)	0.73	0.32, 1.61	0.4361
Gallbladder cancer	95	3 (3.2)	NE (NE, NE)	97	6 (6.2)	NE (NE, NE)	0.47	0.10, 1.79	0.2723
Interaction p-value									0.4191
Age Group									
<65	219	11 (5.0)	NE (NE, NE)	229	15 (6.6)	NE (NE, NE)	0.68	0.30, 1.48	0.3301
>=65	183	9 (4.9)	NE (NE, NE)	174	8 (4.6)	NE (NE, NE)	1.00	0.38, 2.66	0.9918
Interaction p-value									0.5428
Region									
Asia	241	9 (3.7)	NE (NE, NE)	257	14 (5.4)	NE (NE, NE)	0.62	0.26, 1.41	0.2549
Rest of World	161	11 (6.8)	NE (NE, NE)	146	9 (6.2)	NE (NE, NE)	1.02	0.42, 2.53	0.9678
Interaction p-value									0.4174
PD-L1 Status									
High (>=1%)	239	13 (5.4)	NE (NE, NE)	249	14 (5.6)	NE (NE, NE)	0.86	0.40, 1.85	0.6990
Low (<1%)	118	5 (4.2)	NE (NE, NE)	117	7 (6.0)	NE (NE, NE)	0.66	0.20, 2.08	0.4772
Interaction p-value									0.7061
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeeb 01FEB2023:16:13 kjpc654

Table 3.4.5.106 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Blood alkaline phosphatase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	5 (2.5)	NE (NE, NE)	207	15 (7.2)	NE (NE, NE)	0.31	0.10, 0.81	0.0161*
Female	203	15 (7.4)	NE (NE, NE)	196	8 (4.1)	NE (NE, NE)	1.64	0.71, 4.10	0.2487
Interaction p-value									0.0104*
Race									
Asian	248	9 (3.6)	NE (NE, NE)	262	14 (5.3)	NE (NE, NE)	0.61	0.25, 1.40	0.2462
Non-Asian	154	11 (7.1)	NE (NE, NE)	141	9 (6.4)	NE (NE, NE)	1.03	0.42, 2.55	0.9535
Interaction p-value									0.4016
WHO ECOG Status at Screening									
0	186	13 (7.0)	NE (NE, NE)	184	11 (6.0)	NE (NE, NE)	1.06	0.47, 2.43	0.8808
1	216	7 (3.2)	NE (NE, NE)	219	12 (5.5)	NE (NE, NE)	0.54	0.20, 1.34	0.1829
Interaction p-value									0.2708
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	3 (4.1)	NE (NE, NE)	0.36	0.02, 2.80	0.3394
Metastatic	347	19 (5.5)	NE (NE, NE)	330	20 (6.1)	NE (NE, NE)	0.83	0.44, 1.56	0.5574
Interaction p-value									0.4596
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	7 (4.2)	NE (NE, NE)	178	9 (5.1)	NE (NE, NE)	0.76	0.27, 2.05	0.5826
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.107 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Biliary obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

		Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)				
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	10 (3.1)	NE (NE, NE)	333	8 (2.4)	NE (NE, NE)	1.04	0.41, 2.76	0.9308
Recurrent	76	2 (2.6)	NE (NE, NE)	70	2 (2.9)	NE (NE, NE)	0.67	0.08, 5.66	0.6964
Interaction p-value									0.6950
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	3 (4.1)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	1.87	0.23, 38.33	0.5737
Intrahepatic CCA	234	5 (2.1)	NE (NE, NE)	235	6 (2.6)	NE (NE, NE)	0.71	0.20, 2.35	0.5648
Gallbladder cancer	95	4 (4.2)	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	1.15	0.25, 5.88	0.8503
Interaction p-value									0.7096
Age Group									
<65	219	4 (1.8)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	1.65	0.32, 11.96	0.5556
>=65	183	8 (4.4)	NE (NE, NE)	174	8 (4.6)	NE (NE, NE)	0.78	0.28, 2.15	0.6275
Interaction p-value									0.4470
Region									
Asia	241	7 (2.9)	NE (NE, NE)	257	8 (3.1)	NE (NE, NE)	0.72	0.25, 2.03	0.5255
Rest of World	161	5 (3.1)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	1.90	0.41, 13.29	0.4270
Interaction p-value									0.3077
PD-L1 Status									
High (>=1%)	239	4 (1.7)	NE (NE, NE)	249	6 (2.4)	NE (NE, NE)	0.52	0.13, 1.84	0.3083
Low (<1%)	118	6 (5.1)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	2.68	0.61, 18.32	0.1981
Interaction p-value									0.0992
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.107 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Biliary obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	5 (2.4)	NE (NE, NE)	0.52	0.11, 2.14	0.3663
Female	203	9 (4.4)	NE (NE, NE)	196	5 (2.6)	NE (NE, NE)	1.34	0.46, 4.41	0.6013
Interaction p-value									0.2975
Race									
Asian	248	7 (2.8)	NE (NE, NE)	262	8 (3.1)	NE (NE, NE)	0.71	0.24, 2.01	0.5146
Non-Asian	154	5 (3.2)	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	1.92	0.41, 13.44	0.4184
Interaction p-value									0.2975
WHO ECOG Status at Screening									
0	186	5 (2.7)	NE (NE, NE)	184	6 (3.3)	NE (NE, NE)	0.65	0.19, 2.19	0.4851
1	216	7 (3.2)	NE (NE, NE)	219	4 (1.8)	NE (NE, NE)	1.43	0.43, 5.52	0.5666
Interaction p-value									0.3652
Disease Extent									
Locally Advanced	55	2 (3.6)	NE (NE, NE)	73	2 (2.7)	NE (NE, NE)	0.89	0.11, 7.46	0.9042
Metastatic	347	10 (2.9)	NE (NE, NE)	330	8 (2.4)	NE (NE, NE)	0.97	0.38, 2.58	0.9575
Interaction p-value									0.9312
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	3 (1.8)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.108 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Biliary abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.108 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Biliary abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.109 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Biliary sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	4 (1.2)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	3 (3.2)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	3 (1.3)	NE (NE, NE)	NC	NC	NC
>=65	183	3 (1.6)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	4 (2.5)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	3 (1.3)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.109 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Biliary sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	3 (1.4)	NE (NE, NE)	NC	NC	NC
Female	203	3 (1.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	3 (1.1)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	2 (3.6)	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeee 01FEB2023:16:13 kjpc654

Table 3.4.5.110 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	17 (5.2)	NE (NE, NE)	333	27 (8.1)	NE (NE, NE)	0.58	0.31, 1.06	0.0757
Recurrent	76	1 (1.3)	NE (NE, NE)	70	6 (8.6)	NE (NE, NE)	0.13	0.01, 0.75	0.0199*
Interaction p-value									0.1227
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	3 (4.1)	NE (NE, NE)	71	7 (9.9)	NE (NE, NE)	0.33	0.07, 1.20	0.0945
Intrahepatic CCA	234	13 (5.6)	NE (NE, NE)	235	21 (8.9)	NE (NE, NE)	0.56	0.27, 1.11	0.0960
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	5 (5.2)	NE (NE, NE)	0.38	0.05, 1.75	0.2203
Interaction p-value									0.7519
Age Group									
<65	219	7 (3.2)	NE (NE, NE)	229	24 (10.5)	NE (NE, NE)	0.26	0.10, 0.57	0.0006*
>=65	183	11 (6.0)	NE (NE, NE)	174	9 (5.2)	NE (NE, NE)	1.08	0.45, 2.69	0.8586
Interaction p-value									0.0185*
Region									
Asia	241	12 (5.0)	NE (NE, NE)	257	20 (7.8)	NE (NE, NE)	0.56	0.27, 1.14	0.1102
Rest of World	161	6 (3.7)	NE (NE, NE)	146	13 (8.9)	NE (NE, NE)	0.38	0.13, 0.96	0.0409*
Interaction p-value									0.5202
PD-L1 Status									
High (>=1%)	239	12 (5.0)	NE (NE, NE)	249	20 (8.0)	NE (NE, NE)	0.55	0.26, 1.10	0.0927
Low (<1%)	118	5 (4.2)	NE (NE, NE)	117	10 (8.5)	NE (NE, NE)	0.46	0.14, 1.30	0.1443
Interaction p-value									0.7964
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.110 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	8 (4.0)	NE (NE, NE)	207	19 (9.2)	NE (NE, NE)	0.39	0.16, 0.87	0.0205*
Female	203	10 (4.9)	NE (NE, NE)	196	14 (7.1)	NE (NE, NE)	0.61	0.26, 1.36	0.2238
Interaction p-value									0.4639
Race									
Asian	248	13 (5.2)	NE (NE, NE)	262	21 (8.0)	NE (NE, NE)	0.57	0.28, 1.14	0.1127
Non-Asian	154	5 (3.2)	NE (NE, NE)	141	12 (8.5)	NE (NE, NE)	0.35	0.11, 0.93	0.0357*
Interaction p-value									0.4214
WHO ECOG Status at Screening									
0	186	6 (3.2)	NE (NE, NE)	184	6 (3.3)	NE (NE, NE)	0.87	0.27, 2.79	0.8134
1	216	12 (5.6)	NE (NE, NE)	219	27 (12.3)	NE (NE, NE)	0.39	0.19, 0.76	0.0054*
Interaction p-value									0.2401
Disease Extent									
Locally Advanced	55	5 (9.1)	NE (NE, NE)	73	6 (8.2)	NE (NE, NE)	0.92	0.26, 3.07	0.8910
Metastatic	347	13 (3.7)	NE (NE, NE)	330	27 (8.2)	NE (NE, NE)	0.41	0.20, 0.78	0.0064*
Interaction p-value									0.2503
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	166	5 (3.0)	NE (NE, NE)	178	9 (5.1)	NE (NE, NE)	0.52	0.16, 1.52	0.2366
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.111 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Blood bilirubin unconjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.111 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Blood bilirubin unconjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeeg 01FEB2023:16:13 kjpc654

Table 3.4.5.112 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Bilirubin conjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	4 (1.7)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	4 (1.6)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeeh 01FEB2023:16:13 kjpc654

Table 3.4.5.112 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Bilirubin conjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	4 (1.5)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	4 (1.2)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeeh 01FEB2023:16:13 kjpc654

Table 3.4.5.113 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Cholangitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	24 (7.4)	NE (NE, NE)	333	12 (3.6)	NE (NE, NE)	1.92	0.98, 3.97	0.0592
Recurrent	76	6 (7.9)	NE (NE, NE)	70	7 (10.0)	NE (NE, NE)	0.68	0.22, 2.04	0.4830
Interaction p-value									0.1135
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	11 (15.1)	NE (NE, NE)	71	10 (14.1)	NE (NE, NE)	0.88	0.37, 2.12	0.7628
Intrahepatic CCA	234	9 (3.8)	NE (NE, NE)	235	4 (1.7)	NE (NE, NE)	2.10	0.68, 7.77	0.1988
Gallbladder cancer	95	10 (10.5)	NE (NE, NE)	97	5 (5.2)	NE (NE, NE)	1.97	0.70, 6.32	0.2032
Interaction p-value									0.3662
Age Group									
<65	219	14 (6.4)	NE (NE, NE)	229	8 (3.5)	NE (NE, NE)	1.65	0.71, 4.14	0.2511
>=65	183	16 (8.7)	NE (NE, NE)	174	11 (6.3)	NE (NE, NE)	1.29	0.61, 2.87	0.5079
Interaction p-value									0.6812
Region									
Asia	241	22 (9.1)	NE (NE, NE)	257	17 (6.6)	NE (NE, NE)	1.24	0.66, 2.38	0.5036
Rest of World	161	8 (5.0)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	3.41	0.85, 22.58	0.0856
Interaction p-value									0.2080
PD-L1 Status									
High (>=1%)	239	16 (6.7)	NE (NE, NE)	249	14 (5.6)	NE (NE, NE)	1.05	0.51, 2.18	0.9001
Low (<1%)	118	10 (8.5)	NE (NE, NE)	117	4 (3.4)	NE (NE, NE)	2.33	0.78, 8.51	0.1334
Interaction p-value									0.2388
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeei 01FEB2023:16:13 kjpc654

Table 3.4.5.113 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Cholangitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	14 (7.0)	NE (NE, NE)	207	14 (6.8)	NE (NE, NE)	0.96	0.45, 2.03	0.9106
Female	203	16 (7.9)	NE (NE, NE)	196	5 (2.6)	NE (NE, NE)	2.82	1.10, 8.62	0.0298*
Interaction p-value									0.0805
Race									
Asian	248	23 (9.3)	NE (NE, NE)	262	17 (6.5)	NE (NE, NE)	1.29	0.69, 2.46	0.4310
Non-Asian	154	7 (4.5)	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	3.01	0.73, 20.20	0.1349
Interaction p-value									0.3011
WHO ECOG Status at Screening									
0	186	14 (7.5)	NE (NE, NE)	184	13 (7.1)	NE (NE, NE)	0.95	0.44, 2.06	0.9002
1	216	16 (7.4)	NE (NE, NE)	219	6 (2.7)	NE (NE, NE)	2.55	1.05, 7.12	0.0393*
Interaction p-value									0.1023
Disease Extent									
Locally Advanced	55	2 (3.6)	NE (NE, NE)	73	4 (5.5)	NE (NE, NE)	0.51	0.07, 2.63	0.4266
Metastatic	347	28 (8.1)	NE (NE, NE)	330	15 (4.5)	NE (NE, NE)	1.67	0.90, 3.21	0.1029
Interaction p-value									0.1855
MSI Status									
MSI High	3	1 (33.3)	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	18 (10.8)	NE (NE, NE)	178	13 (7.3)	NE (NE, NE)	1.43	0.71, 2.99	0.3205
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeei 01FEB2023:16:13 kjpc654

Table 3.4.5.114 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Cholangitis infective
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.114 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Cholangitis infective
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.115 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Cholelithiasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.115 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Cholelithiasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.116 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	Number (%) of patients n with events		Median time (95% CI) (months) [a]	Number (%) of patients n with events		Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.116 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.117 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Cholecystitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	7 (2.1)	NE (NE, NE)	333	5 (1.5)	NE (NE, NE)	1.40	0.45, 4.73	0.5643
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	4 (1.7)	NE (NE, NE)	235	3 (1.3)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	3 (3.2)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	5 (2.3)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	7 (2.9)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	3 (1.3)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeem 01FEB2023:16:13 kjpc654

Table 3.4.5.117 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Cholecystitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	4 (2.0)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	3 (1.5)	NE (NE, NE)	196	3 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	7 (2.8)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	NC	NC	NC
1	216	6 (2.8)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	3 (4.1)	NE (NE, NE)	NC	NC	NC
Metastatic	347	6 (1.7)	NE (NE, NE)	330	2 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeem 01FEB2023:16:13 kjpc654

Table 3.4.5.118 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Gallbladder empyema
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeen 01FEB2023:16:13 kjpc654

Table 3.4.5.118 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Gallbladder empyema
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.119 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Gallbladder obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.119 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Gallbladder obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.120 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Biliary tract infection
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	13 (4.0)	28.8 (28.8, NE)	333	9 (2.7)	NE (NE, NE)	1.37	0.59, 3.32	0.4713
Recurrent	76	6 (7.9)	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	4.54	0.76, 86.22	0.1036
Interaction p-value									0.2587
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	7 (9.6)	NE (NE, NE)	71	2 (2.8)	NE (NE, NE)	2.70	0.63, 18.36	0.1918
Intrahepatic CCA	234	10 (4.3)	NE (NE, NE)	235	7 (3.0)	NE (NE, NE)	1.35	0.52, 3.72	0.5401
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	1.94	0.19, 41.71	0.5778
Interaction p-value									0.7503
Age Group									
<65	219	7 (3.2)	28.8 (28.8, NE)	229	7 (3.1)	NE (NE, NE)	0.92	0.31, 2.70	0.8770
>=65	183	12 (6.6)	NE (NE, NE)	174	3 (1.7)	NE (NE, NE)	3.47	1.09, 15.29	0.0338*
Interaction p-value									0.1010
Region									
Asia	241	14 (5.8)	NE (NE, NE)	257	9 (3.5)	NE (NE, NE)	1.47	0.64, 3.56	0.3656
Rest of World	161	5 (3.1)	28.8 (28.8, NE)	146	1 (0.7)	NE (NE, NE)	4.05	0.65, 77.79	0.1453
Interaction p-value									0.3535
PD-L1 Status									
High (>=1%)	239	12 (5.0)	NE (NE, NE)	249	6 (2.4)	NE (NE, NE)	1.76	0.67, 5.12	0.2567
Low (<1%)	118	6 (5.1)	NE (NE, NE)	117	3 (2.6)	NE (NE, NE)	1.91	0.50, 9.04	0.3484
Interaction p-value									0.9265
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.120 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Biliary tract infection
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	10 (5.0)	28.8 (28.8, NE)	207	6 (2.9)	NE (NE, NE)	1.56	0.58, 4.62	0.3828
Female	203	9 (4.4)	NE (NE, NE)	196	4 (2.0)	NE (NE, NE)	1.92	0.62, 7.12	0.2645
Interaction p-value									0.7959
Race									
Asian	248	15 (6.0)	NE (NE, NE)	262	9 (3.4)	NE (NE, NE)	1.55	0.68, 3.72	0.3014
Non-Asian	154	4 (2.6)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	3.39	0.50, 66.41	0.2259
Interaction p-value									0.4881
WHO ECOG Status at Screening									
0	186	11 (5.9)	28.8 (NE, NE)	184	2 (1.1)	NE (NE, NE)	4.96	1.33, 32.09	0.0149*
1	216	8 (3.7)	NE (NE, NE)	219	8 (3.7)	NE (NE, NE)	0.88	0.32, 2.42	0.7973
Interaction p-value									0.0419*
Disease Extent									
Locally Advanced	55	4 (7.3)	28.8 (NE, NE)	73	4 (5.5)	NE (NE, NE)	1.08	0.25, 4.60	0.9169
Metastatic	347	15 (4.3)	NE (NE, NE)	330	6 (1.8)	NE (NE, NE)	2.16	0.87, 6.08	0.0983
Interaction p-value									0.4171
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	6 (3.6)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.121 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Post procedural bile leak
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.121 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Post procedural bile leak
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.122 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	6 (1.8)	NE (NE, NE)	333	6 (1.8)	NE (NE, NE)	0.97	0.30, 3.10	0.9547
Recurrent	76	2 (2.6)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	5 (2.1)	NE (NE, NE)	235	3 (1.3)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	3 (3.2)	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	6 (2.7)	NE (NE, NE)	229	5 (2.2)	NE (NE, NE)	1.13	0.34, 3.93	0.8418
>=65	183	2 (1.1)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	1.80	0.17, 38.77	0.6215
Interaction p-value									0.7282
Region									
Asia	241	8 (3.3)	NE (NE, NE)	257	6 (2.3)	NE (NE, NE)	1.30	0.45, 3.97	0.6222
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	5 (2.1)	NE (NE, NE)	249	4 (1.6)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.122 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	5 (2.5)	NE (NE, NE)	207	5 (2.4)	NE (NE, NE)	0.98	0.27, 3.52	0.9715
Female	203	3 (1.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	2.61	0.33, 52.84	0.3746
Interaction p-value									0.4370
Race									
Asian	248	8 (3.2)	NE (NE, NE)	262	6 (2.3)	NE (NE, NE)	1.30	0.45, 3.95	0.6281
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	2.65	0.34, 53.57	0.3674
1	216	5 (2.3)	NE (NE, NE)	219	5 (2.3)	NE (NE, NE)	0.96	0.27, 3.45	0.9465
Interaction p-value									0.4210
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	8 (2.3)	NE (NE, NE)	330	6 (1.8)	NE (NE, NE)	1.19	0.41, 3.62	0.7464
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	3 (1.8)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.123 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	3 (0.9)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	3 (1.3)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	4 (1.6)	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.123 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	3 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	4 (1.5)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	4 (1.2)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.124 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	5 (1.5)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	4 (5.6)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	6 (2.6)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	4 (1.6)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	5 (2.0)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.124 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	4 (2.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	4 (1.5)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	5 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.125 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Gallbladder rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	Number (%) of patients n with events		Median time (95% CI) (months) [a]	Number (%) of patients n with events		Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.125 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Gallbladder rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeeu 01FEB2023:16:13 kjpc654

Table 3.4.5.126 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Biloma rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.126 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Biloma rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.127 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Haematopoietic cytopenias SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	258 (79.1)	1.4 (1.1, 1.7)	333	262 (78.7)	1.2 (1.0, 1.6)	0.97	0.82, 1.15	0.7127
Recurrent	76	66 (86.8)	1.0 (0.7, 1.6)	70	61 (87.1)	1.0 (0.7, 1.3)	0.92	0.65, 1.31	0.6529
Interaction p-value									0.8097
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	57 (78.1)	1.7 (1.0, 2.6)	71	57 (80.3)	1.0 (0.9, 1.9)	0.83	0.57, 1.20	0.3103
Intrahepatic CCA	234	186 (79.5)	1.0 (0.9, 1.4)	235	193 (82.1)	1.0 (0.9, 1.6)	0.95	0.78, 1.16	0.6321
Gallbladder cancer	95	81 (85.3)	1.6 (1.0, 2.0)	97	73 (75.3)	1.0 (1.0, 2.3)	1.12	0.82, 1.54	0.4798
Interaction p-value									0.4585
Age Group									
<65	219	178 (81.3)	1.6 (1.0, 1.8)	229	181 (79.0)	1.0 (0.9, 1.6)	0.95	0.77, 1.17	0.6476
>=65	183	146 (79.8)	1.0 (0.9, 1.4)	174	142 (81.6)	1.0 (1.0, 1.6)	0.98	0.77, 1.23	0.8319
Interaction p-value									0.8834
Region									
Asia	241	202 (83.8)	1.0 (0.9, 1.4)	257	209 (81.3)	1.0 (1.0, 1.6)	1.02	0.84, 1.24	0.8485
Rest of World	161	122 (75.8)	1.6 (1.0, 2.3)	146	114 (78.1)	1.5 (1.0, 1.9)	0.90	0.70, 1.16	0.4135
Interaction p-value									0.4426
PD-L1 Status									
High (>=1%)	239	199 (83.3)	1.0 (0.9, 1.6)	249	198 (79.5)	1.0 (1.0, 1.6)	1.07	0.88, 1.30	0.5176
Low (<1%)	118	92 (78.0)	1.7 (1.0, 2.4)	117	92 (78.6)	1.4 (1.0, 1.7)	0.90	0.67, 1.20	0.4668
Interaction p-value									0.3344
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.127 TOPAZ: Summary of subgroup analysis of time to first AESI GT: Haematopoietic cytopenias SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)						
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]		2-sided p-value [b]
Male	199	156 (78.4)	1.4 (1.0, 1.8)	207	166 (80.2)	1.0 (1.0, 1.6)	0.90	0.72,	1.12	0.3282
Female	203	168 (82.8)	1.2 (1.0, 1.6)	196	157 (80.1)	1.0 (1.0, 1.7)	1.03	0.83,	1.29	0.7639
Interaction p-value										0.3653
Race										
Asian	248	206 (83.1)	1.0 (0.9, 1.6)	262	212 (80.9)	1.0 (1.0, 1.6)	1.01	0.83,	1.22	0.9165
Non-Asian	154	118 (76.6)	1.6 (1.0, 2.3)	141	111 (78.7)	1.3 (0.9, 1.8)	0.90	0.70,	1.17	0.4332
Interaction p-value										0.4884
WHO ECOG Status at Screening										
0	186	154 (82.8)	1.4 (0.9, 1.7)	184	149 (81.0)	1.4 (1.0, 1.7)	1.01	0.81,	1.27	0.9226
1	216	170 (78.7)	1.2 (1.0, 1.7)	219	174 (79.5)	1.0 (0.9, 1.6)	0.92	0.75,	1.14	0.4539
Interaction p-value										0.5594
Disease Extent										
Locally Advanced	55	49 (89.1)	1.0 (0.7, 2.3)	73	63 (86.3)	1.0 (0.9, 1.8)	0.96	0.66,	1.39	0.8246
Metastatic	347	275 (79.3)	1.4 (1.0, 1.6)	330	260 (78.8)	1.0 (1.0, 1.6)	0.97	0.82,	1.15	0.7129
Interaction p-value										0.9603
MSI Status										
MSI High	3	3 (100)	1.6 (0.3, NE)	2	2 (100)	2.6 (1.2, NE)	NC	NC		NC
MSI Stable	166	132 (79.5)	1.4 (1.0, 2.0)	178	143 (80.3)	1.6 (1.0, 1.7)	0.92	0.72,	1.16	0.4765
Interaction p-value										NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.128 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Anaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	171 (52.5)	4.0 (3.2, 5.8)	333	169 (50.8)	4.4 (3.2, 7.2)	1.03	0.84, 1.28	0.7605
Recurrent	76	41 (53.9)	5.0 (2.6, NE)	70	27 (38.6)	NE (NE, NE)	1.46	0.90, 2.39	0.1256
Interaction p-value									0.2020
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	39 (53.4)	4.2 (2.8, NE)	71	28 (39.4)	NE (NE, NE)	1.35	0.83, 2.21	0.2234
Intrahepatic CCA	234	123 (52.6)	3.9 (2.5,10.5)	235	125 (53.2)	4.4 (2.8, 6.9)	1.02	0.79, 1.30	0.9055
Gallbladder cancer	95	50 (52.6)	4.7 (3.5, NE)	97	43 (44.3)	5.1 (3.3, NE)	1.15	0.76, 1.73	0.5052
Interaction p-value									0.5696
Age Group									
<65	219	112 (51.1)	5.3 (3.5, NE)	229	113 (49.3)	4.8 (3.2, NE)	0.99	0.76, 1.29	0.9481
>=65	183	100 (54.6)	3.7 (2.4, 5.4)	174	83 (47.7)	6.0 (3.5, NE)	1.23	0.92, 1.65	0.1658
Interaction p-value									0.2830
Region									
Asia	241	131 (54.4)	4.0 (2.8, 6.1)	257	136 (52.9)	4.0 (2.8, 6.1)	0.99	0.78, 1.26	0.9449
Rest of World	161	81 (50.3)	5.2 (3.2, NE)	146	60 (41.1)	16.3 (4.4, NE)	1.32	0.95, 1.85	0.1005
Interaction p-value									0.1704
PD-L1 Status									
High (>=1%)	239	129 (54.0)	4.7 (3.3, 6.3)	249	120 (48.2)	5.2 (3.5, NE)	1.13	0.88, 1.44	0.3527
Low (<1%)	118	64 (54.2)	3.9 (2.6,10.5)	117	58 (49.6)	6.1 (2.8, NE)	1.13	0.80, 1.62	0.4864
Interaction p-value									0.9711
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.128 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Anaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	98 (49.2)	5.4 (3.4, NE)	207	99 (47.8)	6.0 (3.5, NE)	1.00	0.76, 1.33	0.9865
Female	203	114 (56.2)	3.9 (2.8, 5.6)	196	97 (49.5)	4.4 (3.2, NE)	1.18	0.90, 1.55	0.2296
Interaction p-value									0.4102
Race									
Asian	248	132 (53.2)	4.2 (3.4, 6.4)	262	138 (52.7)	4.0 (2.8, 7.2)	0.97	0.76, 1.23	0.8002
Non-Asian	154	80 (51.9)	4.4 (3.0, NE)	141	58 (41.1)	16.3 (4.4, NE)	1.38	0.99, 1.94	0.0604
Interaction p-value									0.0937
WHO ECOG Status at Screening									
0	186	92 (49.5)	5.8 (3.3, NE)	184	77 (41.8)	16.3 (5.3, NE)	1.22	0.90, 1.65	0.1984
1	216	120 (55.6)	3.9 (2.8, 5.3)	219	119 (54.3)	3.5 (2.8, 5.1)	1.00	0.78, 1.30	0.9695
Interaction p-value									0.3370
Disease Extent									
Locally Advanced	55	31 (56.4)	5.6 (2.8, NE)	73	38 (52.1)	4.1 (2.5, NE)	1.02	0.63, 1.63	0.9416
Metastatic	347	181 (52.2)	4.0 (3.3, 5.8)	330	158 (47.9)	5.3 (3.6, NE)	1.11	0.89, 1.37	0.3484
Interaction p-value									0.7505
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	166	82 (49.4)	5.4 (4.2, NE)	178	77 (43.3)	16.3 (4.4, NE)	1.16	0.85, 1.58	0.3521
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.129 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Bicytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	Number (%) of patients n with events		Median time (95% CI) (months) [a]	Number (%) of patients n with events		Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.129 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Bicytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.130 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Red blood cell count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeeez 01FEB2023:16:13 kjpc654

Table 3.4.5.130 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Red blood cell count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	2 (3.6)	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.131 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Febrile neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	4 (1.2)	NE (NE, NE)	333	6 (1.8)	NE (NE, NE)	0.68	0.17, 2.39	0.5512
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	3 (1.3)	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	4 (2.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	4 (1.7)	NE (NE, NE)	257	4 (1.6)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	3 (2.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.131 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Febrile neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	5 (2.4)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	4 (1.6)	NE (NE, NE)	262	4 (1.5)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	4 (1.8)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	4 (1.2)	NE (NE, NE)	330	5 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefa 01FEB2023:16:13 kjpc654

Table 3.4.5.132 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Granulocyte count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.132 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Granulocyte count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefb 01FEB2023:16:13 kjpc654

Table 3.4.5.133 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Haematocrit decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefc 01FEB2023:16:13 kjpc654

Table 3.4.5.133 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Haematocrit decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	2 (2.7)	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefc 01FEB2023:16:13 kjpc654

Table 3.4.5.134 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Haemoglobin decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	2 (2.6)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	3 (1.3)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefd 01FEB2023:16:13 kjpc654

Table 3.4.5.134 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Haemoglobin decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.135 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Leukopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	22 (6.7)	NE (NE, NE)	333	17 (5.1)	NE (NE, NE)	1.33	0.71, 2.53	0.3786
Recurrent	76	4 (5.3)	NE (NE, NE)	70	4 (5.7)	NE (NE, NE)	0.91	0.22, 3.85	0.8947
Interaction p-value									0.6285
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	3 (4.2)	NE (NE, NE)	0.65	0.09, 3.89	0.6277
Intrahepatic CCA	234	18 (7.7)	NE (NE, NE)	235	14 (6.0)	NE (NE, NE)	1.29	0.65, 2.65	0.4689
Gallbladder cancer	95	6 (6.3)	NE (NE, NE)	97	4 (4.1)	NE (NE, NE)	1.53	0.44, 6.00	0.5036
Interaction p-value									0.7230
Age Group									
<65	219	15 (6.8)	NE (NE, NE)	229	15 (6.6)	NE (NE, NE)	1.03	0.50, 2.12	0.9398
>=65	183	11 (6.0)	NE (NE, NE)	174	6 (3.4)	NE (NE, NE)	1.78	0.68, 5.17	0.2447
Interaction p-value									0.3744
Region									
Asia	241	16 (6.6)	NE (NE, NE)	257	9 (3.5)	NE (NE, NE)	1.92	0.86, 4.53	0.1103
Rest of World	161	10 (6.2)	NE (NE, NE)	146	12 (8.2)	NE (NE, NE)	0.74	0.31, 1.72	0.4827
Interaction p-value									0.1082
PD-L1 Status									
High (>=1%)	239	17 (7.1)	NE (NE, NE)	249	10 (4.0)	NE (NE, NE)	1.78	0.83, 4.04	0.1389
Low (<1%)	118	6 (5.1)	NE (NE, NE)	117	6 (5.1)	NE (NE, NE)	0.99	0.31, 3.17	0.9892
Interaction p-value									0.4028
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.135 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Leukopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	11 (5.5)	NE (NE, NE)	207	11 (5.3)	NE (NE, NE)	1.03	0.44, 2.40	0.9501
Female	203	15 (7.4)	NE (NE, NE)	196	10 (5.1)	NE (NE, NE)	1.47	0.67, 3.37	0.3428
Interaction p-value									0.5447
Race									
Asian	248	16 (6.5)	NE (NE, NE)	262	9 (3.4)	NE (NE, NE)	1.90	0.86, 4.50	0.1145
Non-Asian	154	10 (6.5)	NE (NE, NE)	141	12 (8.5)	NE (NE, NE)	0.74	0.31, 1.73	0.4901
Interaction p-value									0.1130
WHO ECOG Status at Screening									
0	186	13 (7.0)	NE (NE, NE)	184	15 (8.2)	NE (NE, NE)	0.84	0.39, 1.77	0.6491
1	216	13 (6.0)	NE (NE, NE)	219	6 (2.7)	NE (NE, NE)	2.23	0.88, 6.35	0.0913
Interaction p-value									0.1102
Disease Extent									
Locally Advanced	55	3 (5.5)	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	4.12	0.53, 83.33	0.1817
Metastatic	347	23 (6.6)	NE (NE, NE)	330	20 (6.1)	NE (NE, NE)	1.08	0.59, 1.99	0.7939
Interaction p-value									0.2287
MSI Status									
MSI High	3	2 (66.7)	4.0 (1.2, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	8 (4.8)	NE (NE, NE)	178	7 (3.9)	NE (NE, NE)	1.22	0.44, 3.49	0.6966
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.136 TOPAZ: Summary of subgroup analysis of time to first AESI PT: White blood cell count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	58 (17.8)	NE (NE, NE)	333	65 (19.5)	NE (NE, NE)	0.90	0.63, 1.29	0.5700
Recurrent	76	11 (14.5)	NE (NE, NE)	70	16 (22.9)	NE (NE, NE)	0.58	0.26, 1.24	0.1634
Interaction p-value									0.3070
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	10 (13.7)	NE (NE, NE)	71	15 (21.1)	NE (NE, NE)	0.60	0.26, 1.31	0.2002
Intrahepatic CCA	234	48 (20.5)	NE (NE, NE)	235	48 (20.4)	NE (NE, NE)	1.03	0.69, 1.53	0.8972
Gallbladder cancer	95	11 (11.6)	NE (NE, NE)	97	18 (18.6)	NE (NE, NE)	0.57	0.26, 1.19	0.1346
Interaction p-value									0.2539
Age Group									
<65	219	43 (19.6)	NE (NE, NE)	229	44 (19.2)	NE (NE, NE)	1.00	0.65, 1.52	0.9913
>=65	183	26 (14.2)	NE (NE, NE)	174	37 (21.3)	NE (NE, NE)	0.65	0.39, 1.07	0.0909
Interaction p-value									0.2000
Region									
Asia	241	60 (24.9)	NE (NE, NE)	257	73 (28.4)	NE (NE, NE)	0.84	0.60, 1.19	0.3306
Rest of World	161	9 (5.6)	NE (NE, NE)	146	8 (5.5)	NE (NE, NE)	1.02	0.39, 2.73	0.9613
Interaction p-value									0.7085
PD-L1 Status									
High (>=1%)	239	40 (16.7)	NE (NE, NE)	249	53 (21.3)	NE (NE, NE)	0.75	0.50, 1.13	0.1690
Low (<1%)	118	22 (18.6)	NE (NE, NE)	117	22 (18.8)	NE (NE, NE)	0.99	0.54, 1.79	0.9651
Interaction p-value									0.4561
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.136 TOPAZ: Summary of subgroup analysis of time to first AESI PT: White blood cell count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	40 (20.1)	NE (NE, NE)	207	43 (20.8)	NE (NE, NE)	0.95	0.62, 1.47	0.8316
Female	203	29 (14.3)	NE (NE, NE)	196	38 (19.4)	NE (NE, NE)	0.71	0.44, 1.15	0.1656
Interaction p-value									0.3736
Race									
Asian	248	61 (24.6)	NE (NE, NE)	262	73 (27.9)	NE (NE, NE)	0.85	0.61, 1.20	0.3611
Non-Asian	154	8 (5.2)	NE (NE, NE)	141	8 (5.7)	NE (NE, NE)	0.91	0.34, 2.48	0.8563
Interaction p-value									0.8982
WHO ECOG Status at Screening									
0	186	24 (12.9)	NE (NE, NE)	184	34 (18.5)	NE (NE, NE)	0.67	0.39, 1.13	0.1309
1	216	45 (20.8)	NE (NE, NE)	219	47 (21.5)	NE (NE, NE)	0.96	0.64, 1.45	0.8469
Interaction p-value									0.2873
Disease Extent									
Locally Advanced	55	15 (27.3)	NE (NE, NE)	73	20 (27.4)	NE (NE, NE)	0.98	0.49, 1.90	0.9439
Metastatic	347	54 (15.6)	NE (NE, NE)	330	61 (18.5)	NE (NE, NE)	0.82	0.57, 1.18	0.2880
Interaction p-value									0.6552
MSI Status									
MSI High	3	2 (66.7)	1.7 (0.3, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	18 (10.8)	NE (NE, NE)	178	28 (15.7)	NE (NE, NE)	0.68	0.37, 1.22	0.1932
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.137 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Lymphopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	3 (3.9)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	4 (1.7)	NE (NE, NE)	235	3 (1.3)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	3 (1.3)	NE (NE, NE)	NC	NC	NC
>=65	183	3 (1.6)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	3 (1.9)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	3 (1.3)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefg 01FEB2023:16:13 kjpc654

Table 3.4.5.137 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Lymphopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	3 (1.9)	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	NC	NC	NC
1	216	3 (1.4)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	5 (1.4)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	3 (1.8)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefg 01FEB2023:16:13 kjpc654

Table 3.4.5.138 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Lymphocyte percentage decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefh 01FEB2023:16:13 kjpc654

Table 3.4.5.138 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Lymphocyte percentage decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefh 01FEB2023:16:13 kjpc654

Table 3.4.5.139 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Lymphocyte count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	6 (1.8)	NE (NE, NE)	333	12 (3.6)	NE (NE, NE)	0.50	0.17, 1.28	0.1486
Recurrent	76	4 (5.3)	NE (NE, NE)	70	2 (2.9)	NE (NE, NE)	1.71	0.33, 12.38	0.5273
Interaction p-value									0.2024
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	3 (4.1)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	2.72	0.35, 55.22	0.3557
Intrahepatic CCA	234	5 (2.1)	NE (NE, NE)	235	12 (5.1)	NE (NE, NE)	0.40	0.13, 1.08	0.0715
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	1.99	0.19, 42.90	0.5614
Interaction p-value									0.1659
Age Group									
<65	219	4 (1.8)	NE (NE, NE)	229	10 (4.4)	NE (NE, NE)	0.39	0.11, 1.18	0.0990
>=65	183	6 (3.3)	NE (NE, NE)	174	4 (2.3)	NE (NE, NE)	1.38	0.39, 5.41	0.6148
Interaction p-value									0.1434
Region									
Asia	241	9 (3.7)	NE (NE, NE)	257	8 (3.1)	NE (NE, NE)	1.14	0.43, 3.04	0.7891
Rest of World	161	1 (0.6)	NE (NE, NE)	146	6 (4.1)	NE (NE, NE)	0.15	0.01, 0.86	0.0312*
Interaction p-value									0.0474*
PD-L1 Status									
High (>=1%)	239	7 (2.9)	NE (NE, NE)	249	10 (4.0)	NE (NE, NE)	0.68	0.25, 1.79	0.4372
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	4 (3.4)	NE (NE, NE)	0.74	0.15, 3.34	0.6879
Interaction p-value									0.9331
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefi 01FEB2023:16:13 kjpc654

Table 3.4.5.139 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Lymphocyte count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	4 (2.0)	NE (NE, NE)	207	7 (3.4)	NE (NE, NE)	0.57	0.15, 1.89	0.3617
Female	203	6 (3.0)	NE (NE, NE)	196	7 (3.6)	NE (NE, NE)	0.79	0.25, 2.37	0.6658
Interaction p-value									0.7003
Race									
Asian	248	9 (3.6)	NE (NE, NE)	262	8 (3.1)	NE (NE, NE)	1.13	0.43, 3.02	0.8019
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	6 (4.3)	NE (NE, NE)	0.15	0.01, 0.86	0.0320*
Interaction p-value									0.0495*
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	10 (5.4)	NE (NE, NE)	0.28	0.06, 0.91	0.0342*
1	216	7 (3.2)	NE (NE, NE)	219	4 (1.8)	NE (NE, NE)	1.73	0.52, 6.61	0.3759
Interaction p-value									0.0354*
Disease Extent									
Locally Advanced	55	2 (3.6)	NE (NE, NE)	73	3 (4.1)	NE (NE, NE)	0.81	0.11, 4.90	0.8167
Metastatic	347	8 (2.3)	NE (NE, NE)	330	11 (3.3)	NE (NE, NE)	0.66	0.26, 1.64	0.3762
Interaction p-value									0.8469
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	17.5 (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	4 (2.2)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.140 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Monocyte count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.140 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Monocyte count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefj 01FEB2023:16:13 kjpc654

Table 3.4.5.141 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Myelosuppression
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	8 (2.5)	NE (NE, NE)	333	7 (2.1)	NE (NE, NE)	1.16	0.42, 3.31	0.7739
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	7 (3.0)	NE (NE, NE)	235	6 (2.6)	NE (NE, NE)	1.16	0.39, 3.61	0.7863
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	2 (2.1)	NE (NE, NE)	0.50	0.02, 5.21	0.5592
Interaction p-value									0.5196
Age Group									
<65	219	4 (1.8)	NE (NE, NE)	229	6 (2.6)	NE (NE, NE)	0.68	0.17, 2.39	0.5499
>=65	183	4 (2.2)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	1.91	0.37, 13.78	0.4416
Interaction p-value									0.3298
Region									
Asia	241	8 (3.3)	NE (NE, NE)	257	8 (3.1)	NE (NE, NE)	1.05	0.39, 2.87	0.9148
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	6 (2.5)	NE (NE, NE)	249	6 (2.4)	NE (NE, NE)	1.02	0.32, 3.27	0.9686
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	0.99	0.12, 8.26	0.9932
Interaction p-value									0.9784
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefk 01FEB2023:16:13 kjpc654

Table 3.4.5.141 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Myelosuppression
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	3 (1.4)	NE (NE, NE)	0.35	0.02, 2.69	0.3227
Female	203	7 (3.4)	NE (NE, NE)	196	5 (2.6)	NE (NE, NE)	1.33	0.43, 4.50	0.6221
Interaction p-value									0.2698
Race									
Asian	248	8 (3.2)	NE (NE, NE)	262	8 (3.1)	NE (NE, NE)	1.05	0.38, 2.84	0.9278
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	5 (2.7)	NE (NE, NE)	NC	NC	NC
1	216	6 (2.8)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	4 (7.3)	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	5.32	0.79,104.12	0.0894
Metastatic	347	4 (1.2)	NE (NE, NE)	330	7 (2.1)	NE (NE, NE)	0.54	0.14, 1.78	0.3099
Interaction p-value									0.0480*
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefk 01FEB2023:16:13 kjpc654

Table 3.4.5.142 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	88 (27.0)	NE (NE, NE)	333	84 (25.2)	NE (NE, NE)	1.07	0.79, 1.44	0.6789
Recurrent	76	23 (30.3)	NE (NE, NE)	70	20 (28.6)	NE (NE, NE)	1.07	0.59, 1.96	0.8318
Interaction p-value									0.9959
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	18 (24.7)	NE (NE, NE)	71	20 (28.2)	NE (NE, NE)	0.82	0.43, 1.56	0.5476
Intrahepatic CCA	234	64 (27.4)	NE (NE, NE)	235	62 (26.4)	NE (NE, NE)	1.04	0.73, 1.47	0.8369
Gallbladder cancer	95	29 (30.5)	NE (NE, NE)	97	22 (22.7)	NE (NE, NE)	1.39	0.80, 2.45	0.2417
Interaction p-value									0.4608
Age Group									
<65	219	71 (32.4)	NE (NE, NE)	229	62 (27.1)	NE (NE, NE)	1.19	0.85, 1.68	0.3062
>=65	183	40 (21.9)	NE (NE, NE)	174	42 (24.1)	NE (NE, NE)	0.90	0.58, 1.40	0.6478
Interaction p-value									0.3216
Region									
Asia	241	48 (19.9)	NE (NE, NE)	257	38 (14.8)	NE (NE, NE)	1.38	0.91, 2.13	0.1337
Rest of World	161	63 (39.1)	NE (NE, NE)	146	66 (45.2)	NE (NE, NE)	0.79	0.56, 1.12	0.1914
Interaction p-value									0.0468*
PD-L1 Status									
High (>=1%)	239	70 (29.3)	NE (NE, NE)	249	55 (22.1)	NE (NE, NE)	1.37	0.96, 1.95	0.0823
Low (<1%)	118	33 (28.0)	NE (NE, NE)	117	34 (29.1)	NE (NE, NE)	0.94	0.58, 1.52	0.7950
Interaction p-value									0.2163
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefl 01FEB2023:16:13 kjpc654

Table 3.4.5.142 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	55 (27.6)	NE (NE, NE)	207	51 (24.6)	NE (NE, NE)	1.13	0.77, 1.65	0.5381
Female	203	56 (27.6)	NE (NE, NE)	196	53 (27.0)	NE (NE, NE)	1.01	0.69, 1.47	0.9679
Interaction p-value									0.6818
Race									
Asian	248	49 (19.8)	NE (NE, NE)	262	40 (15.3)	NE (NE, NE)	1.33	0.88, 2.03	0.1807
Non-Asian	154	62 (40.3)	NE (NE, NE)	141	64 (45.4)	NE (NE, NE)	0.81	0.57, 1.15	0.2421
Interaction p-value									0.0755
WHO ECOG Status at Screening									
0	186	68 (36.6)	NE (NE, NE)	184	54 (29.3)	NE (NE, NE)	1.27	0.89, 1.83	0.1840
1	216	43 (19.9)	NE (NE, NE)	219	50 (22.8)	NE (NE, NE)	0.85	0.56, 1.28	0.4371
Interaction p-value									0.1445
Disease Extent									
Locally Advanced	55	15 (27.3)	NE (NE, NE)	73	19 (26.0)	NE (NE, NE)	1.05	0.53, 2.06	0.8890
Metastatic	347	96 (27.7)	NE (NE, NE)	330	85 (25.8)	NE (NE, NE)	1.07	0.80, 1.43	0.6688
Interaction p-value									0.9673
MSI Status									
MSI High	3	2 (66.7)	1.7 (1.6, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	166	50 (30.1)	NE (NE, NE)	178	43 (24.2)	NE (NE, NE)	1.26	0.84, 1.90	0.2630
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefl 01FEB2023:16:13 kjpc654

Table 3.4.5.143 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Neutropenic sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefm 01FEB2023:16:13 kjpc654

Table 3.4.5.143 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Neutropenic sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefm 01FEB2023:16:13 kjpc654

Table 3.4.5.144 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Neutrophil count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	86 (26.4)	NE (NE, NE)	333	108 (32.4)	NE (NE, NE)	0.78	0.59, 1.04	0.0858
Recurrent	76	33 (43.4)	NE (NE, NE)	70	35 (50.0)	4.9 (2.4, NE)	0.83	0.52, 1.34	0.4477
Interaction p-value									0.8229
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	22 (30.1)	NE (NE, NE)	71	27 (38.0)	NE (NE, NE)	0.78	0.44, 1.37	0.3863
Intrahepatic CCA	234	70 (29.9)	NE (NE, NE)	235	77 (32.8)	NE (NE, NE)	0.90	0.65, 1.24	0.5150
Gallbladder cancer	95	27 (28.4)	NE (NE, NE)	97	39 (40.2)	NE (NE, NE)	0.63	0.38, 1.02	0.0603
Interaction p-value									0.4847
Age Group									
<65	219	61 (27.9)	NE (NE, NE)	229	75 (32.8)	NE (NE, NE)	0.82	0.59, 1.15	0.2617
>=65	183	58 (31.7)	NE (NE, NE)	174	68 (39.1)	NE (NE, NE)	0.77	0.54, 1.09	0.1381
Interaction p-value									0.7735
Region									
Asia	241	92 (38.2)	NE (NE, NE)	257	117 (45.5)	5.7 (3.8, NE)	0.80	0.61, 1.05	0.1065
Rest of World	161	27 (16.8)	NE (NE, NE)	146	26 (17.8)	NE (NE, NE)	0.93	0.54, 1.60	0.7834
Interaction p-value									0.6291
PD-L1 Status									
High (>=1%)	239	64 (26.8)	NE (NE, NE)	249	94 (37.8)	NE (NE, NE)	0.65	0.47, 0.89	0.0073*
Low (<1%)	118	39 (33.1)	NE (NE, NE)	117	40 (34.2)	NE (NE, NE)	0.96	0.62, 1.50	0.8696
Interaction p-value									0.1557
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefn 01FEB2023:16:13 kjpc654

Table 3.4.5.144 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Neutrophil count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	56 (28.1)	NE (NE, NE)	207	71 (34.3)	NE (NE, NE)	0.78	0.55, 1.10	0.1566
Female	203	63 (31.0)	NE (NE, NE)	196	72 (36.7)	NE (NE, NE)	0.82	0.59, 1.15	0.2602
Interaction p-value									0.8143
Race									
Asian	248	94 (37.9)	NE (NE, NE)	262	117 (44.7)	7.6 (3.9, NE)	0.81	0.62, 1.07	0.1339
Non-Asian	154	25 (16.2)	NE (NE, NE)	141	26 (18.4)	NE (NE, NE)	0.86	0.49, 1.49	0.5885
Interaction p-value									0.8587
WHO ECOG Status at Screening									
0	186	52 (28.0)	NE (NE, NE)	184	72 (39.1)	NE (NE, NE)	0.66	0.46, 0.94	0.0201*
1	216	67 (31.0)	NE (NE, NE)	219	71 (32.4)	NE (NE, NE)	0.96	0.68, 1.33	0.7887
Interaction p-value									0.1325
Disease Extent									
Locally Advanced	55	20 (36.4)	NE (NE, NE)	73	32 (43.8)	NE (NE, NE)	0.79	0.44, 1.36	0.3966
Metastatic	347	99 (28.5)	NE (NE, NE)	330	111 (33.6)	NE (NE, NE)	0.82	0.62, 1.07	0.1418
Interaction p-value									0.9072
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	50 (30.1)	NE (NE, NE)	178	78 (43.8)	NE (NE, NE)	0.61	0.43, 0.87	0.0061*
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefn 01FEB2023:16:13 kjpc654

Table 3.4.5.145 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Pancytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefo 01FEB2023:16:13 kjpc654

Table 3.4.5.145 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Pancytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaeefo 01FEB2023:16:13 kjpc654

Table 3.4.5.146 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Platelet count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	78 (23.9)	NE (NE, NE)	333	85 (25.5)	NE (NE, NE)	0.89	0.65, 1.21	0.4450
Recurrent	76	21 (27.6)	NE (NE, NE)	70	26 (37.1)	NE (NE, NE)	0.66	0.37, 1.18	0.1596
Interaction p-value									0.3797
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	16 (21.9)	NE (NE, NE)	71	21 (29.6)	NE (NE, NE)	0.68	0.35, 1.30	0.2481
Intrahepatic CCA	234	62 (26.5)	NE (NE, NE)	235	69 (29.4)	NE (NE, NE)	0.85	0.60, 1.19	0.3425
Gallbladder cancer	95	21 (22.1)	NE (NE, NE)	97	21 (21.6)	21.2 (10.5, NE)	0.95	0.52, 1.76	0.8797
Interaction p-value									0.7542
Age Group									
<65	219	39 (17.8)	NE (NE, NE)	229	56 (24.5)	NE (NE, NE)	0.65	0.43, 0.98	0.0394*
>=65	183	60 (32.8)	NE (NE, NE)	174	55 (31.6)	21.2 (21.2, NE)	1.02	0.71, 1.47	0.9121
Interaction p-value									0.1091
Region									
Asia	241	81 (33.6)	NE (NE, NE)	257	83 (32.3)	NE (NE, NE)	0.97	0.71, 1.32	0.8567
Rest of World	161	18 (11.2)	NE (NE, NE)	146	28 (19.2)	21.2 (21.2, NE)	0.55	0.30, 0.99	0.0454*
Interaction p-value									0.0920
PD-L1 Status									
High (>=1%)	239	59 (24.7)	NE (NE, NE)	249	76 (30.5)	21.2 (21.2, NE)	0.74	0.52, 1.03	0.0752
Low (<1%)	118	27 (22.9)	NE (NE, NE)	117	30 (25.6)	NE (NE, NE)	0.83	0.49, 1.40	0.4945
Interaction p-value									0.6895
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.146 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Platelet count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	49 (24.6)	NE (NE, NE)	207	58 (28.0)	NE (NE, NE)	0.83	0.57, 1.21	0.3355
Female	203	50 (24.6)	NE (NE, NE)	196	53 (27.0)	21.2 (21.2, NE)	0.84	0.57, 1.24	0.3892
Interaction p-value									0.9515
Race									
Asian	248	82 (33.1)	NE (NE, NE)	262	84 (32.1)	NE (NE, NE)	0.96	0.71, 1.31	0.8118
Non-Asian	154	17 (11.0)	NE (NE, NE)	141	27 (19.1)	21.2 (21.2, NE)	0.54	0.29, 0.99	0.0459*
Interaction p-value									0.0954
WHO ECOG Status at Screening									
0	186	37 (19.9)	NE (NE, NE)	184	47 (25.5)	21.2 (21.2, NE)	0.72	0.46, 1.10	0.1270
1	216	62 (28.7)	NE (NE, NE)	219	64 (29.2)	NE (NE, NE)	0.93	0.66, 1.33	0.6997
Interaction p-value									0.3479
Disease Extent									
Locally Advanced	55	18 (32.7)	NE (NE, NE)	73	24 (32.9)	NE (NE, NE)	0.88	0.47, 1.62	0.6867
Metastatic	347	81 (23.3)	NE (NE, NE)	330	87 (26.4)	21.2 (21.2, NE)	0.83	0.61, 1.13	0.2382
Interaction p-value									0.8708
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	42 (25.3)	NE (NE, NE)	178	50 (28.1)	NE (NE, NE)	0.86	0.57, 1.29	0.4569
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.5.147 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Thrombocytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	38 (11.7)	NE (NE, NE)	333	43 (12.9)	NE (NE, NE)	0.87	0.56, 1.35	0.5425
Recurrent	76	7 (9.2)	NE (NE, NE)	70	6 (8.6)	NE (NE, NE)	1.02	0.34, 3.17	0.9722
Interaction p-value									0.7958
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	8 (11.0)	NE (NE, NE)	71	6 (8.5)	NE (NE, NE)	1.26	0.44, 3.82	0.6701
Intrahepatic CCA	234	27 (11.5)	NE (NE, NE)	235	32 (13.6)	NE (NE, NE)	0.83	0.49, 1.38	0.4629
Gallbladder cancer	95	10 (10.5)	NE (NE, NE)	97	11 (11.3)	NE (NE, NE)	0.86	0.36, 2.04	0.7301
Interaction p-value									0.7778
Age Group									
<65	219	28 (12.8)	NE (NE, NE)	229	28 (12.2)	NE (NE, NE)	1.01	0.60, 1.71	0.9728
>=65	183	17 (9.3)	NE (NE, NE)	174	21 (12.1)	NE (NE, NE)	0.74	0.38, 1.39	0.3469
Interaction p-value									0.4544
Region									
Asia	241	13 (5.4)	NE (NE, NE)	257	14 (5.4)	NE (NE, NE)	0.97	0.45, 2.07	0.9273
Rest of World	161	32 (19.9)	NE (NE, NE)	146	35 (24.0)	NE (NE, NE)	0.77	0.47, 1.24	0.2839
Interaction p-value									0.6191
PD-L1 Status									
High (>=1%)	239	26 (10.9)	NE (NE, NE)	249	24 (9.6)	NE (NE, NE)	1.10	0.63, 1.92	0.7454
Low (<1%)	118	18 (15.3)	NE (NE, NE)	117	15 (12.8)	NE (NE, NE)	1.16	0.58, 2.33	0.6757
Interaction p-value									0.9042
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.5.147 TOPAZ: Summary of subgroup analysis of time to first AESI PT: Thrombocytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	21 (10.6)	NE (NE, NE)	207	21 (10.1)	NE (NE, NE)	1.00	0.55, 1.85	0.9881
Female	203	24 (11.8)	NE (NE, NE)	196	28 (14.3)	NE (NE, NE)	0.79	0.46, 1.37	0.4030
Interaction p-value									0.5684
Race									
Asian	248	13 (5.2)	NE (NE, NE)	262	16 (6.1)	NE (NE, NE)	0.84	0.39, 1.74	0.6295
Non-Asian	154	32 (20.8)	NE (NE, NE)	141	33 (23.4)	NE (NE, NE)	0.83	0.51, 1.35	0.4402
Interaction p-value									0.9786
WHO ECOG Status at Screening									
0	186	29 (15.6)	NE (NE, NE)	184	29 (15.8)	NE (NE, NE)	0.93	0.56, 1.57	0.7908
1	216	16 (7.4)	NE (NE, NE)	219	20 (9.1)	NE (NE, NE)	0.79	0.41, 1.53	0.4912
Interaction p-value									0.7061
Disease Extent									
Locally Advanced	55	6 (10.9)	NE (NE, NE)	73	11 (15.1)	NE (NE, NE)	0.66	0.23, 1.73	0.3996
Metastatic	347	39 (11.2)	NE (NE, NE)	330	38 (11.5)	NE (NE, NE)	0.95	0.60, 1.48	0.8068
Interaction p-value									0.5077
MSI Status									
MSI High	3	1 (33.3)	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	21 (12.7)	NE (NE, NE)	178	16 (9.0)	NE (NE, NE)	1.39	0.73, 2.70	0.3241
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.1 TOPAZ: Summary of subgroup analysis of time to first AESI max CTCAE grade >=3
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	211 (64.7)	3.0 (2.4, 3.7)	333	209 (62.8)	2.7 (2.3, 3.7)	1.00	0.82, 1.21	0.9713
Recurrent	76	54 (71.1)	2.5 (1.6, 3.9)	70	55 (78.6)	2.0 (1.0, 3.0)	0.74	0.51, 1.08	0.1197
Interaction p-value									0.1695
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	46 (63.0)	3.7 (1.7, 5.2)	71	53 (74.6)	1.8 (1.0, 2.8)	0.66	0.44, 0.98	0.0380*
Intrahepatic CCA	234	147 (62.8)	3.1 (2.4, 3.9)	235	149 (63.4)	3.0 (2.3, 3.8)	0.94	0.75, 1.18	0.5978
Gallbladder cancer	95	72 (75.8)	2.4 (1.6, 3.0)	97	62 (63.9)	2.6 (1.8, 4.4)	1.24	0.89, 1.75	0.2071
Interaction p-value									0.0563
Age Group									
<65	219	146 (66.7)	3.0 (2.4, 3.7)	229	144 (62.9)	3.0 (2.2, 3.7)	0.97	0.77, 1.22	0.8085
>=65	183	119 (65.0)	2.6 (2.2, 3.7)	174	120 (69.0)	2.4 (1.9, 3.6)	0.91	0.71, 1.18	0.4754
Interaction p-value									0.7146
Region									
Asia	241	169 (70.1)	2.4 (1.9, 3.0)	257	172 (66.9)	2.5 (2.3, 3.1)	1.02	0.82, 1.26	0.8793
Rest of World	161	96 (59.6)	3.8 (2.6, 5.4)	146	92 (63.0)	3.0 (1.9, 4.3)	0.86	0.64, 1.14	0.2861
Interaction p-value									0.3430
PD-L1 Status									
High (>=1%)	239	161 (67.4)	2.5 (2.0, 3.3)	249	157 (63.1)	2.7 (2.3, 3.3)	1.02	0.82, 1.27	0.8457
Low (<1%)	118	79 (66.9)	3.5 (2.5, 4.4)	117	80 (68.4)	2.5 (1.6, 3.8)	0.90	0.66, 1.23	0.5010
Interaction p-value									0.5079
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.1 TOPAZ: Summary of subgroup analysis of time to first AESI max CTCAE grade >=3
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)						
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]		2-sided p-value [b]
Male	199	129 (64.8)	3.0 (2.4, 3.8)	207	134 (64.7)	2.6 (2.2, 3.7)	0.94	0.74,	1.20	0.6065
Female	203	136 (67.0)	2.6 (2.1, 3.7)	196	130 (66.3)	2.5 (1.9, 3.3)	0.95	0.75,	1.21	0.6821
Interaction p-value										0.9390
Race										
Asian	248	175 (70.6)	2.4 (1.9, 3.0)	262	174 (66.4)	2.5 (2.3, 3.1)	1.03	0.84,	1.28	0.7520
Non-Asian	154	90 (58.4)	3.8 (2.6, 5.4)	141	90 (63.8)	2.5 (1.9, 3.9)	0.82	0.61,	1.10	0.1829
Interaction p-value										0.2050
WHO ECOG Status at Screening										
0	186	119 (64.0)	3.4 (2.5, 4.4)	184	114 (62.0)	3.0 (2.3, 4.2)	0.95	0.73,	1.22	0.6719
1	216	146 (67.6)	2.5 (1.9, 3.5)	219	150 (68.5)	2.4 (1.8, 3.0)	0.95	0.76,	1.19	0.6576
Interaction p-value										0.9820
Disease Extent										
Locally Advanced	55	38 (69.1)	3.7 (1.6, 5.4)	73	53 (72.6)	2.3 (1.6, 3.3)	0.81	0.53,	1.22	0.3152
Metastatic	347	227 (65.4)	2.6 (2.3, 3.5)	330	211 (63.9)	2.7 (2.3, 3.4)	0.98	0.81,	1.18	0.7974
Interaction p-value										0.4178
MSI Status										
MSI High	3	2 (66.7)	5.8 (1.6, NE)	2	2 (100)	2.6 (1.2, NE)	NC	NC		NC
MSI Stable	166	116 (69.9)	2.5 (1.7, 3.6)	178	119 (66.9)	2.5 (1.9, 3.1)	0.99	0.76,	1.28	0.9244
Interaction p-value										NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefaa 01FEB2023:16:13 kjpc654

Table 3.4.6.2 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefab 01FEB2023:16:13 kjpc654

Table 3.4.6.2 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefab 01FEB2023:16:13 kjpc654

Table 3.4.6.3 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefac 01FEB2023:16:13 kjpc654

Table 3.4.6.3 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefac 01FEB2023:16:13 kjpc654

Table 3.4.6.4 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Hepatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.4 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Hepatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	3 (1.4)	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	2 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	17.5 (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefad 01FEB2023:16:13 kjpc654

Table 3.4.6.5 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefae 01FEB2023:16:13 kjpc654

Table 3.4.6.5 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefae 01FEB2023:16:13 kjpc654

Table 3.4.6.6 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefaf 01FEB2023:16:13 kjpc654

Table 3.4.6.6 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	17.5 (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.7 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.7 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefag 01FEB2023:16:13 kjpc654

Table 3.4.6.8 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Immune-mediated hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefah 01FEB2023:16:13 kjpc654

Table 3.4.6.8 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Immune-mediated hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefah 01FEB2023:16:13 kjpc654

Table 3.4.6.9 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Diarrhoea/Colitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	5 (1.5)	NE (NE, NE)	333	5 (1.5)	NE (NE, NE)	1.02	0.28, 3.65	0.9811
Recurrent	76	0	NE (NE, NE)	70	2 (2.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	4 (4.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	5 (2.2)	NE (NE, NE)	NC	NC	NC
>=65	183	3 (1.6)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	4 (1.6)	NE (NE, NE)	NC	NC	NC
Rest of World	161	3 (1.9)	NE (NE, NE)	146	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	3 (1.3)	NE (NE, NE)	249	5 (2.0)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.9 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Diarrhoea/Colitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	5 (2.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	5 (1.9)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	3 (1.9)	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	3 (1.4)	NE (NE, NE)	219	6 (2.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	5 (1.4)	NE (NE, NE)	330	7 (2.1)	NE (NE, NE)	0.67	0.20, 2.09	0.4836
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefai 01FEB2023:16:13 kjpc654

Table 3.4.6.10 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Diarrhoea
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	4 (1.2)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	2 (2.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	4 (4.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	4 (1.7)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	4 (1.6)	NE (NE, NE)	NC	NC	NC
Rest of World	161	3 (1.9)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	4 (1.6)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefaj 01FEB2023:16:13 kjpc654

Table 3.4.6.10 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Diarrhoea
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	4 (2.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	5 (1.9)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	3 (1.9)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	5 (2.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	4 (1.2)	NE (NE, NE)	330	6 (1.8)	NE (NE, NE)	0.62	0.16, 2.17	0.4543
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefaj 01FEB2023:16:13 kjpc654

Table 3.4.6.11 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Immune-mediated enterocolitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefak 01FEB2023:16:13 kjpc654

Table 3.4.6.11 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Immune-mediated enterocolitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefak 01FEB2023:16:13 kjpc654

Table 3.4.6.12 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Colitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefal 01FEB2023:16:13 kjpc654

Table 3.4.6.12 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Colitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefal 01FEB2023:16:13 kjpc654

Table 3.4.6.13 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Dermatitis/Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	3 (0.9)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefam 01FEB2023:16:13 kjpc654

Table 3.4.6.13 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Dermatitis/Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefam 01FEB2023:16:13 kjpc654

Table 3.4.6.14 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.14 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefan 01FEB2023:16:13 kjpc654

Table 3.4.6.15 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Rash maculo-papular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	3 (0.9)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefao 01FEB2023:16:13 kjpc654

Table 3.4.6.15 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Rash maculo-papular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefao 01FEB2023:16:13 kjpc654

Table 3.4.6.16 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Pancreatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	2 (2.6)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefap 01FEB2023:16:13 kjpc654

Table 3.4.6.16 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Pancreatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefap 01FEB2023:16:13 kjpc654

Table 3.4.6.17 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Pancreatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	2 (2.6)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.17 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Pancreatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefaq 01FEB2023:16:13 kjpc654

Table 3.4.6.18 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Myositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefar 01FEB2023:16:13 kjpc654

Table 3.4.6.18 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Myositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefar 01FEB2023:16:13 kjpc654

Table 3.4.6.19 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Polymyositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefas 01FEB2023:16:13 kjpc654

Table 3.4.6.19 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Polymyositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefas 01FEB2023:16:13 kjpc654

Table 3.4.6.20 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Infusion/hypersensitivity reactions
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefat 01FEB2023:16:13 kjpc654

Table 3.4.6.20 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Infusion/hypersensitivity reactions
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefat 01FEB2023:16:13 kjpc654

Table 3.4.6.21 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Anaphylactic shock
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefau 01FEB2023:16:13 kjpc654

Table 3.4.6.21 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Anaphylactic shock
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefau 01FEB2023:16:13 kjpc654

Table 3.4.6.22 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Drug hypersensitivity
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefav 01FEB2023:16:13 kjpc654

Table 3.4.6.22 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Drug hypersensitivity
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefav 01FEB2023:16:13 kjpc654

Table 3.4.6.23 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Urticaria
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefaw 01FEB2023:16:13 kjpc654

Table 3.4.6.23 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Urticaria
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.24 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Other rare/miscellaneous
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.24 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Other rare/miscellaneous
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefax 01FEB2023:16:13 kjpc654

Table 3.4.6.25 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Immune-mediated arthritis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.25 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Immune-mediated arthritis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.26 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Hepatic SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	41 (12.6)	NE (NE, NE)	333	45 (13.5)	18.9 (17.5, NE)	0.84	0.55, 1.28	0.4153
Recurrent	76	7 (9.2)	NE (NE, NE)	70	6 (8.6)	NE (NE, NE)	0.87	0.29, 2.72	0.8074
Interaction p-value									0.9458
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	11 (15.1)	NE (NE, NE)	71	10 (14.1)	NE (NE, NE)	0.84	0.35, 2.02	0.6871
Intrahepatic CCA	234	23 (9.8)	NE (NE, NE)	235	26 (11.1)	NE (NE, NE)	0.80	0.46, 1.41	0.4477
Gallbladder cancer	95	14 (14.7)	NE (NE, NE)	97	15 (15.5)	NE (NE, NE)	0.87	0.41, 1.81	0.7048
Interaction p-value									0.9864
Age Group									
<65	219	32 (14.6)	NE (NE, NE)	229	36 (15.7)	18.9 (17.5, NE)	0.80	0.49, 1.29	0.3595
>=65	183	16 (8.7)	NE (NE, NE)	174	15 (8.6)	NE (NE, NE)	0.92	0.45, 1.87	0.8074
Interaction p-value									0.7533
Region									
Asia	241	31 (12.9)	NE (NE, NE)	257	25 (9.7)	NE (NE, NE)	1.17	0.69, 2.00	0.5610
Rest of World	161	17 (10.6)	NE (NE, NE)	146	26 (17.8)	NE (NE, NE)	0.52	0.28, 0.96	0.0353*
Interaction p-value									0.0484*
PD-L1 Status									
High (>=1%)	239	32 (13.4)	NE (NE, NE)	249	31 (12.4)	NE (NE, NE)	0.94	0.57, 1.55	0.8020
Low (<1%)	118	13 (11.0)	NE (NE, NE)	117	15 (12.8)	18.9 (18.9, NE)	0.78	0.37, 1.65	0.5205
Interaction p-value									0.6933
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefaz 01FEB2023:16:13 kjpc654

Table 3.4.6.26 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Hepatic SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	27 (13.6)	NE (NE, NE)	207	28 (13.5)	NE (NE, NE)	0.90	0.53, 1.54	0.6996
Female	203	21 (10.3)	NE (NE, NE)	196	23 (11.7)	NE (NE, NE)	0.76	0.42, 1.38	0.3719
Interaction p-value									0.6818
Race									
Asian	248	31 (12.5)	NE (NE, NE)	262	25 (9.5)	NE (NE, NE)	1.16	0.68, 1.98	0.5885
Non-Asian	154	17 (11.0)	NE (NE, NE)	141	26 (18.4)	NE (NE, NE)	0.53	0.28, 0.97	0.0385*
Interaction p-value									0.0549
WHO ECOG Status at Screening									
0	186	21 (11.3)	NE (NE, NE)	184	17 (9.2)	NE (NE, NE)	1.07	0.56, 2.06	0.8377
1	216	27 (12.5)	NE (NE, NE)	219	34 (15.5)	NE (NE, NE)	0.71	0.42, 1.18	0.1908
Interaction p-value									0.3281
Disease Extent									
Locally Advanced	55	4 (7.3)	NE (NE, NE)	73	13 (17.8)	NE (NE, NE)	0.30	0.08, 0.86	0.0235*
Metastatic	347	44 (12.7)	NE (NE, NE)	330	38 (11.5)	18.9 (17.5, NE)	1.00	0.64, 1.55	0.9878
Interaction p-value									0.0382*
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	17.5 (NE, NE)	NC	NC	NC
MSI Stable	166	16 (9.6)	NE (NE, NE)	178	21 (11.8)	NE (NE, NE)	0.71	0.36, 1.35	0.2937
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefaz 01FEB2023:16:13 kjpc654

Table 3.4.6.27 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Alanine aminotransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	8 (2.5)	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	3.47	0.85, 23.15	0.0845
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	3 (1.3)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	3 (3.2)	NE (NE, NE)	97	2 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	6 (2.7)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	5 (2.1)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	3 (1.9)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	5 (2.1)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefba 01FEB2023:16:13 kjpc654

Table 3.4.6.27 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Alanine aminotransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	6 (3.0)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	5 (2.0)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	3 (1.9)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	5 (2.3)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	7 (2.0)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	4 (2.4)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefba 01FEB2023:16:13 kjpc654

Table 3.4.6.28 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Blood alkaline phosphatase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	3 (2.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbb 01FEB2023:16:13 kjpc654

Table 3.4.6.28 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Blood alkaline phosphatase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbb 01FEB2023:16:13 kjpc654

Table 3.4.6.29 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	Number (%) of patients n with events		Median time (95% CI) (months) [a]	Number (%) of patients n with events		Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbc 01FEB2023:16:13 kjpc654

Table 3.4.6.29 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbc 01FEB2023:16:13 kjpc654

Table 3.4.6.30 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Aspartate aminotransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	4 (1.2)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	2 (2.8)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	3 (3.2)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	3 (1.4)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	4 (1.7)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	4 (1.7)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbd 01FEB2023:16:13 kjpc654

Table 3.4.6.30 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Aspartate aminotransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	4 (2.0)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	4 (1.6)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	4 (1.9)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	4 (1.2)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbd 01FEB2023:16:13 kjpc654

Table 3.4.6.31 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Ascites
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	7 (2.1)	NE (NE, NE)	333	8 (2.4)	NE (NE, NE)	0.85	0.30, 2.37	0.7512
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	2 (2.8)	NE (NE, NE)	0.44	0.02, 4.55	0.4831
Intrahepatic CCA	234	5 (2.1)	NE (NE, NE)	235	7 (3.0)	NE (NE, NE)	0.69	0.20, 2.16	0.5238
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									0.7305
Age Group									
<65	219	4 (1.8)	NE (NE, NE)	229	7 (3.1)	NE (NE, NE)	0.56	0.15, 1.85	0.3436
>=65	183	3 (1.6)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	1.39	0.23, 10.54	0.7171
Interaction p-value									0.4050
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	1.02	0.12, 8.51	0.9830
Rest of World	161	5 (3.1)	NE (NE, NE)	146	7 (4.8)	NE (NE, NE)	0.61	0.18, 1.92	0.3998
Interaction p-value									0.6600
PD-L1 Status									
High (>=1%)	239	4 (1.7)	NE (NE, NE)	249	7 (2.8)	NE (NE, NE)	0.56	0.15, 1.85	0.3418
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	0.95	0.11, 7.95	0.9619
Interaction p-value									0.6491
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbe 01FEB2023:16:13 kjpc654

Table 3.4.6.31 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Ascites
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	5 (2.5)	NE (NE, NE)	207	4 (1.9)	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	5 (2.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	1.01	0.12, 8.45	0.9892
Non-Asian	154	5 (3.2)	NE (NE, NE)	141	7 (5.0)	NE (NE, NE)	0.62	0.18, 1.93	0.4039
Interaction p-value									0.6674
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	4 (2.2)	NE (NE, NE)	0.47	0.06, 2.39	0.3623
1	216	5 (2.3)	NE (NE, NE)	219	5 (2.3)	NE (NE, NE)	0.97	0.27, 3.51	0.9672
Interaction p-value									0.4848
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	4 (5.5)	NE (NE, NE)	0.29	0.01, 1.98	0.2224
Metastatic	347	6 (1.7)	NE (NE, NE)	330	5 (1.5)	NE (NE, NE)	1.10	0.33, 3.82	0.8751
Interaction p-value									0.2649
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbe 01FEB2023:16:13 kjpc654

Table 3.4.6.32 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	Number (%) of patients n with events		Median time (95% CI) (months) [a]	Number (%) of patients n with events		Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.32 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	17.5 (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbf 01FEB2023:16:13 kjpc654

Table 3.4.6.33 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	6 (1.8)	NE (NE, NE)	333	10 (3.0)	NE (NE, NE)	0.54	0.18, 1.46	0.2282
Recurrent	76	0	NE (NE, NE)	70	2 (2.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	4 (5.6)	NE (NE, NE)	0.18	0.01, 1.27	0.0886
Intrahepatic CCA	234	4 (1.7)	NE (NE, NE)	235	7 (3.0)	NE (NE, NE)	0.51	0.13, 1.69	0.2710
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	0.91	0.04, 22.96	0.9458
Interaction p-value									0.6048
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	8 (3.5)	NE (NE, NE)	0.22	0.03, 0.88	0.0309*
>=65	183	4 (2.2)	NE (NE, NE)	174	4 (2.3)	NE (NE, NE)	0.85	0.20, 3.62	0.8245
Interaction p-value									0.1856
Region									
Asia	241	4 (1.7)	NE (NE, NE)	257	5 (1.9)	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	7 (4.8)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	6 (2.5)	NE (NE, NE)	249	7 (2.8)	NE (NE, NE)	0.75	0.24, 2.28	0.6073
Low (<1%)	118	0	NE (NE, NE)	117	5 (4.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbg 01FEB2023:16:13 kjpc654

Table 3.4.6.33 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	4 (1.9)	NE (NE, NE)	0.70	0.14, 3.20	0.6455
Female	203	3 (1.5)	NE (NE, NE)	196	8 (4.1)	NE (NE, NE)	0.30	0.07, 1.05	0.0594
Interaction p-value									0.4037
Race									
Asian	248	4 (1.6)	NE (NE, NE)	262	5 (1.9)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	7 (5.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	4 (1.9)	NE (NE, NE)	219	12 (5.5)	NE (NE, NE)	0.31	0.09, 0.89	0.0291*
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	4 (5.5)	NE (NE, NE)	0.25	0.01, 1.69	0.1651
Metastatic	347	5 (1.4)	NE (NE, NE)	330	8 (2.4)	NE (NE, NE)	0.53	0.16, 1.58	0.2546
Interaction p-value									0.5331
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	6 (3.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.34 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Bilirubin conjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.34 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Bilirubin conjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbh 01FEB2023:16:13 kjpc654

Table 3.4.6.35 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbi 01FEB2023:16:13 kjpc654

Table 3.4.6.35 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbi 01FEB2023:16:13 kjpc654

Table 3.4.6.36 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Gamma-glutamyltransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	4 (1.2)	NE (NE, NE)	333	6 (1.8)	NE (NE, NE)	0.66	0.17, 2.30	0.5115
Recurrent	76	0	NE (NE, NE)	70	2 (2.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	4 (1.7)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	3 (1.4)	NE (NE, NE)	229	5 (2.2)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	6 (4.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	4 (1.6)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbj 01FEB2023:16:13 kjpc654

Table 3.4.6.36 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Gamma-glutamyltransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	7 (3.4)	NE (NE, NE)	NC	NC	NC
Female	203	3 (1.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	6 (4.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	5 (2.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	4 (1.2)	NE (NE, NE)	330	7 (2.1)	NE (NE, NE)	0.52	0.14, 1.74	0.2923
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbj 01FEB2023:16:13 kjpc654

Table 3.4.6.37 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	Number (%) of patients n with events	Median time (95% CI) (months) [a]		Number (%) of patients n with events	Median time (95% CI) (months) [a]		Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326 5 (1.5)	NE (NE, NE)		333 5 (1.5)	NE (NE, NE)		0.95	0.26, 3.43	0.9373
Recurrent	76 2 (2.6)	NE (NE, NE)		70 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73 0	NE (NE, NE)		71 0	NE (NE, NE)		NC	NC	NC
Intrahepatic CCA	234 5 (2.1)	NE (NE, NE)		235 2 (0.9)	NE (NE, NE)		NC	NC	NC
Gallbladder cancer	95 2 (2.1)	NE (NE, NE)		97 3 (3.1)	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219 6 (2.7)	NE (NE, NE)		229 5 (2.2)	NE (NE, NE)		1.09	0.33, 3.81	0.8814
>=65	183 1 (0.5)	NE (NE, NE)		174 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Region									
Asia	241 7 (2.9)	NE (NE, NE)		257 5 (1.9)	NE (NE, NE)		1.35	0.43, 4.56	0.6106
Rest of World	161 0	NE (NE, NE)		146 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239 5 (2.1)	NE (NE, NE)		249 3 (1.2)	NE (NE, NE)		NC	NC	NC
Low (<1%)	118 2 (1.7)	NE (NE, NE)		117 2 (1.7)	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbk 01FEB2023:16:13 kjpc654

Table 3.4.6.37 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	5 (2.5)	NE (NE, NE)	207	4 (1.9)	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	7 (2.8)	NE (NE, NE)	262	5 (1.9)	NE (NE, NE)	1.34	0.43, 4.54	0.6161
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	4 (1.9)	NE (NE, NE)	219	4 (1.8)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	7 (2.0)	NE (NE, NE)	330	5 (1.5)	NE (NE, NE)	1.23	0.39, 4.17	0.7197
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbk 01FEB2023:16:13 kjpc654

Table 3.4.6.38 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hepatic encephalopathy
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	Number (%) of patients n with events	Median time (95% CI) (months) [a]		Number (%) of patients n with events	Median time (95% CI) (months) [a]		Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326 1 (0.3)	NE (NE, NE)		333 1 (0.3)	NE (NE, NE)		NC	NC	NC
Recurrent	76 0	NE (NE, NE)		70 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73 0	NE (NE, NE)		71 0	NE (NE, NE)		NC	NC	NC
Intrahepatic CCA	234 1 (0.4)	NE (NE, NE)		235 1 (0.4)	NE (NE, NE)		NC	NC	NC
Gallbladder cancer	95 0	NE (NE, NE)		97 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219 1 (0.5)	NE (NE, NE)		229 0	NE (NE, NE)		NC	NC	NC
>=65	183 0	NE (NE, NE)		174 1 (0.6)	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Region									
Asia	241 1 (0.4)	NE (NE, NE)		257 0	NE (NE, NE)		NC	NC	NC
Rest of World	161 0	NE (NE, NE)		146 1 (0.7)	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239 1 (0.4)	NE (NE, NE)		249 1 (0.4)	NE (NE, NE)		NC	NC	NC
Low (<1%)	118 0	NE (NE, NE)		117 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbl 01FEB2023:16:13 kjpc654

Table 3.4.6.38 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hepatic encephalopathy
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbl 01FEB2023:16:13 kjpc654

Table 3.4.6.39 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hepatic cytolysis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.39 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hepatic cytolysis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbm 01FEB2023:16:13 kjpc654

Table 3.4.6.40 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.40 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.41 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hypoalbuminaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.41 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hypoalbuminaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbo 01FEB2023:16:13 kjpc654

Table 3.4.6.42 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	2 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	3 (1.2)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbp 01FEB2023:16:13 kjpc654

Table 3.4.6.42 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	3 (1.1)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbp 01FEB2023:16:13 kjpc654

Table 3.4.6.43 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	2 (2.8)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	4 (1.7)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.43 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	4 (1.2)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbq 01FEB2023:16:13 kjpc654

Table 3.4.6.44 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Immune-mediated hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbr 01FEB2023:16:13 kjpc654

Table 3.4.6.44 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Immune-mediated hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbr 01FEB2023:16:13 kjpc654

Table 3.4.6.45 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Liver abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	2 (2.6)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.45 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Liver abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbs 01FEB2023:16:13 kjpc654

Table 3.4.6.46 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hepatic enzyme increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.46 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hepatic enzyme increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbt 01FEB2023:16:13 kjpc654

Table 3.4.6.47 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hepatic function abnormal
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbu 01FEB2023:16:13 kjpc654

Table 3.4.6.47 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hepatic function abnormal
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbu 01FEB2023:16:13 kjpc654

Table 3.4.6.48 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Liver function test increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.48 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Liver function test increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.49 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbw 01FEB2023:16:13 kjpc654

Table 3.4.6.49 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbw 01FEB2023:16:13 kjpc654

Table 3.4.6.50 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hepatic failure
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	3 (0.9)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbx 01FEB2023:16:13 kjpc654

Table 3.4.6.50 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hepatic failure
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbx 01FEB2023:16:13 kjpc654

Table 3.4.6.51 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Oesophageal varices haemorrhage
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefby 01FEB2023:16:13 kjpc654

Table 3.4.6.51 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Oesophageal varices haemorrhage
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefby 01FEB2023:16:13 kjpc654

Table 3.4.6.52 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Transaminases increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefbz 01FEB2023:16:13 kjpc654

Table 3.4.6.52 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Transaminases increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.53 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Biliary SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	52 (16.0)	NE (NE, NE)	333	52 (15.6)	NE (NE, NE)	0.94	0.64, 1.38	0.7442
Recurrent	76	9 (11.8)	NE (NE, NE)	70	7 (10.0)	NE (NE, NE)	1.00	0.37, 2.79	0.9950
Interaction p-value									0.9099
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	17 (23.3)	NE (NE, NE)	71	17 (23.9)	NE (NE, NE)	0.79	0.40, 1.57	0.4972
Intrahepatic CCA	234	22 (9.4)	NE (NE, NE)	235	26 (11.1)	NE (NE, NE)	0.77	0.43, 1.35	0.3565
Gallbladder cancer	95	22 (23.2)	NE (NE, NE)	97	16 (16.5)	NE (NE, NE)	1.38	0.73, 2.67	0.3281
Interaction p-value									0.3469
Age Group									
<65	219	31 (14.2)	NE (NE, NE)	229	35 (15.3)	NE (NE, NE)	0.81	0.50, 1.32	0.3935
>=65	183	30 (16.4)	NE (NE, NE)	174	24 (13.8)	NE (NE, NE)	1.11	0.65, 1.92	0.6934
Interaction p-value									0.3855
Region									
Asia	241	44 (18.3)	NE (NE, NE)	257	40 (15.6)	NE (NE, NE)	1.05	0.68, 1.63	0.8110
Rest of World	161	17 (10.6)	NE (NE, NE)	146	19 (13.0)	NE (NE, NE)	0.74	0.38, 1.42	0.3645
Interaction p-value									0.3729
PD-L1 Status									
High (>=1%)	239	33 (13.8)	NE (NE, NE)	249	32 (12.9)	NE (NE, NE)	0.94	0.57, 1.54	0.8022
Low (<1%)	118	21 (17.8)	NE (NE, NE)	117	21 (17.9)	NE (NE, NE)	0.93	0.50, 1.71	0.8095
Interaction p-value									0.9760
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.53 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Biliary SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	29 (14.6)	NE (NE, NE)	207	34 (16.4)	NE (NE, NE)	0.80	0.49, 1.32	0.3846
Female	203	32 (15.8)	NE (NE, NE)	196	25 (12.8)	NE (NE, NE)	1.11	0.66, 1.90	0.6905
Interaction p-value									0.3732
Race									
Asian	248	47 (19.0)	NE (NE, NE)	262	41 (15.6)	NE (NE, NE)	1.09	0.72, 1.67	0.6797
Non-Asian	154	14 (9.1)	NE (NE, NE)	141	18 (12.8)	NE (NE, NE)	0.64	0.31, 1.29	0.2134
Interaction p-value									0.2004
WHO ECOG Status at Screening									
0	186	29 (15.6)	NE (NE, NE)	184	24 (13.0)	NE (NE, NE)	1.06	0.62, 1.83	0.8423
1	216	32 (14.8)	NE (NE, NE)	219	35 (16.0)	NE (NE, NE)	0.85	0.52, 1.38	0.5108
Interaction p-value									0.5566
Disease Extent									
Locally Advanced	55	6 (10.9)	NE (NE, NE)	73	16 (21.9)	NE (NE, NE)	0.37	0.13, 0.91	0.0293*
Metastatic	347	55 (15.9)	NE (NE, NE)	330	43 (13.0)	NE (NE, NE)	1.13	0.76, 1.70	0.5454
Interaction p-value									0.0253*
MSI Status									
MSI High	3	1 (33.3)	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	26 (15.7)	NE (NE, NE)	178	27 (15.2)	NE (NE, NE)	0.93	0.54, 1.61	0.7986
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.54 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Cholangitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	4 (1.2)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	2 (2.8)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	3 (1.4)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	3 (1.2)	NE (NE, NE)	257	4 (1.6)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.54 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Cholangitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	3 (1.4)	NE (NE, NE)	NC	NC	NC
Female	203	3 (1.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	4 (1.5)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	4 (1.2)	NE (NE, NE)	330	4 (1.2)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	3 (1.8)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.55 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Cholecystitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.55 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Cholecystitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcc 01FEB2023:16:13 kjpc654

Table 3.4.6.56 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Blood alkaline phosphatase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	3 (2.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcd 01FEB2023:16:13 kjpc654

Table 3.4.6.56 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Blood alkaline phosphatase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.57 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Biliary obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	7 (2.1)	NE (NE, NE)	333	6 (1.8)	NE (NE, NE)	0.91	0.29, 2.88	0.8666
Recurrent	76	0	NE (NE, NE)	70	2 (2.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	4 (1.7)	NE (NE, NE)	235	4 (1.7)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	0.79	0.09, 6.63	0.8128
>=65	183	5 (2.7)	NE (NE, NE)	174	6 (3.4)	NE (NE, NE)	0.63	0.18, 2.13	0.4548
Interaction p-value									0.8520
Region									
Asia	241	4 (1.7)	NE (NE, NE)	257	6 (2.3)	NE (NE, NE)	0.52	0.13, 1.86	0.3138
Rest of World	161	3 (1.9)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	1.11	0.18, 8.49	0.9061
Interaction p-value									0.4911
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	6 (2.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	4 (3.4)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.57 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Biliary obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	4 (1.9)	NE (NE, NE)	NC	NC	NC
Female	203	5 (2.5)	NE (NE, NE)	196	4 (2.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	4 (1.6)	NE (NE, NE)	262	6 (2.3)	NE (NE, NE)	0.51	0.13, 1.85	0.3082
Non-Asian	154	3 (1.9)	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	1.13	0.19, 8.58	0.8966
Interaction p-value									0.4805
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	4 (2.2)	NE (NE, NE)	NC	NC	NC
1	216	4 (1.9)	NE (NE, NE)	219	4 (1.8)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	2 (2.7)	NE (NE, NE)	0.42	0.02, 4.50	0.4721
Metastatic	347	6 (1.7)	NE (NE, NE)	330	6 (1.8)	NE (NE, NE)	0.75	0.23, 2.44	0.6264
Interaction p-value									0.6669
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.58 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Biliary abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.58 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Biliary abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcf 01FEB2023:16:13 kjpc654

Table 3.4.6.59 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Biliary sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	4 (1.2)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	3 (3.2)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	3 (1.3)	NE (NE, NE)	NC	NC	NC
>=65	183	3 (1.6)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	4 (2.5)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	3 (1.3)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcg 01FEB2023:16:13 kjpc654

Table 3.4.6.59 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Biliary sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	3 (1.4)	NE (NE, NE)	NC	NC	NC
Female	203	3 (1.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	3 (1.1)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	2 (3.6)	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcg 01FEB2023:16:13 kjpc654

Table 3.4.6.60 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	6 (1.8)	NE (NE, NE)	333	10 (3.0)	NE (NE, NE)	0.54	0.18, 1.46	0.2282
Recurrent	76	0	NE (NE, NE)	70	2 (2.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	4 (5.6)	NE (NE, NE)	0.18	0.01, 1.27	0.0886
Intrahepatic CCA	234	4 (1.7)	NE (NE, NE)	235	7 (3.0)	NE (NE, NE)	0.51	0.13, 1.69	0.2710
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	0.91	0.04, 22.96	0.9458
Interaction p-value									0.6048
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	8 (3.5)	NE (NE, NE)	0.22	0.03, 0.88	0.0309*
>=65	183	4 (2.2)	NE (NE, NE)	174	4 (2.3)	NE (NE, NE)	0.85	0.20, 3.62	0.8245
Interaction p-value									0.1856
Region									
Asia	241	4 (1.7)	NE (NE, NE)	257	5 (1.9)	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	7 (4.8)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	6 (2.5)	NE (NE, NE)	249	7 (2.8)	NE (NE, NE)	0.75	0.24, 2.28	0.6073
Low (<1%)	118	0	NE (NE, NE)	117	5 (4.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefch 01FEB2023:16:13 kjpc654

Table 3.4.6.60 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	4 (1.9)	NE (NE, NE)	0.70	0.14, 3.20	0.6455
Female	203	3 (1.5)	NE (NE, NE)	196	8 (4.1)	NE (NE, NE)	0.30	0.07, 1.05	0.0594
Interaction p-value									0.4037
Race									
Asian	248	4 (1.6)	NE (NE, NE)	262	5 (1.9)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	7 (5.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	4 (1.9)	NE (NE, NE)	219	12 (5.5)	NE (NE, NE)	0.31	0.09, 0.89	0.0291*
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	4 (5.5)	NE (NE, NE)	0.25	0.01, 1.69	0.1651
Metastatic	347	5 (1.4)	NE (NE, NE)	330	8 (2.4)	NE (NE, NE)	0.53	0.16, 1.58	0.2546
Interaction p-value									0.5331
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	6 (3.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.61 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Bilirubin conjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.61 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Bilirubin conjugated increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.62 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Cholangitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	19 (5.8)	NE (NE, NE)	333	8 (2.4)	NE (NE, NE)	2.30	1.04, 5.58	0.0398*
Recurrent	76	4 (5.3)	NE (NE, NE)	70	3 (4.3)	NE (NE, NE)	1.08	0.24, 5.47	0.9241
Interaction p-value									0.3912
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	7 (9.6)	NE (NE, NE)	71	6 (8.5)	NE (NE, NE)	0.96	0.32, 3.02	0.9494
Intrahepatic CCA	234	6 (2.6)	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	2.83	0.65, 19.29	0.1730
Gallbladder cancer	95	10 (10.5)	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	3.32	1.02, 14.82	0.0469*
Interaction p-value									0.2925
Age Group									
<65	219	12 (5.5)	NE (NE, NE)	229	5 (2.2)	NE (NE, NE)	2.29	0.85, 7.22	0.1040
>=65	183	11 (6.0)	NE (NE, NE)	174	6 (3.4)	NE (NE, NE)	1.66	0.63, 4.81	0.3119
Interaction p-value									0.6573
Region									
Asia	241	18 (7.5)	NE (NE, NE)	257	10 (3.9)	NE (NE, NE)	1.76	0.83, 3.99	0.1446
Rest of World	161	5 (3.1)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	4.28	0.69, 81.94	0.1276
Interaction p-value									0.4148
PD-L1 Status									
High (>=1%)	239	11 (4.6)	NE (NE, NE)	249	7 (2.8)	NE (NE, NE)	1.47	0.58, 4.01	0.4243
Low (<1%)	118	8 (6.8)	NE (NE, NE)	117	4 (3.4)	NE (NE, NE)	1.87	0.59, 7.01	0.2942
Interaction p-value									0.7561
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcj 01FEB2023:16:13 kjpc654

Table 3.4.6.62 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Cholangitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	10 (5.0)	NE (NE, NE)	207	9 (4.3)	NE (NE, NE)	1.09	0.44, 2.74	0.8566
Female	203	13 (6.4)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	5.77	1.59, 36.95	0.0054*
Interaction p-value									0.0403*
Race									
Asian	248	19 (7.7)	NE (NE, NE)	262	10 (3.8)	NE (NE, NE)	1.84	0.87, 4.15	0.1108
Non-Asian	154	4 (2.6)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	3.45	0.51, 67.57	0.2184
Interaction p-value									0.5791
WHO ECOG Status at Screening									
0	186	11 (5.9)	NE (NE, NE)	184	8 (4.3)	NE (NE, NE)	1.24	0.50, 3.21	0.6399
1	216	12 (5.6)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	3.85	1.22, 16.93	0.0199*
Interaction p-value									0.1402
Disease Extent									
Locally Advanced	55	2 (3.6)	NE (NE, NE)	73	3 (4.1)	NE (NE, NE)	0.70	0.09, 4.25	0.6953
Metastatic	347	21 (6.1)	NE (NE, NE)	330	8 (2.4)	NE (NE, NE)	2.38	1.09, 5.72	0.0285*
Interaction p-value									0.2177
MSI Status									
MSI High	3	1 (33.3)	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	13 (7.8)	NE (NE, NE)	178	8 (4.5)	NE (NE, NE)	1.75	0.74, 4.41	0.2078
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcj 01FEB2023:16:13 kjpc654

Table 3.4.6.63 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Cholangitis infective
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefck 01FEB2023:16:13 kjpc654

Table 3.4.6.63 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Cholangitis infective
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefck 01FEB2023:16:13 kjpc654

Table 3.4.6.64 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcl 01FEB2023:16:13 kjpc654

Table 3.4.6.64 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.65 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Cholecystitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	3 (0.9)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	3 (1.2)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.65 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Cholecystitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	3 (4.1)	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcm 01FEB2023:16:13 kjpc654

Table 3.4.6.66 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Gallbladder empyema
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcn 01FEB2023:16:13 kjpc654

Table 3.4.6.66 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Gallbladder empyema
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcn 01FEB2023:16:13 kjpc654

Table 3.4.6.67 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Gallbladder obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefco 01FEB2023:16:13 kjpc654

Table 3.4.6.67 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Gallbladder obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefco 01FEB2023:16:13 kjpc654

Table 3.4.6.68 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Biliary tract infection
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	11 (3.4)	28.8 (28.8, NE)	333	8 (2.4)	NE (NE, NE)	1.27	0.51, 3.30	0.6051
Recurrent	76	4 (5.3)	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	2.85	0.41, 56.16	0.3116
Interaction p-value									0.4855
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	5 (6.8)	NE (NE, NE)	71	2 (2.8)	NE (NE, NE)	1.76	0.36, 12.64	0.4973
Intrahepatic CCA	234	8 (3.4)	NE (NE, NE)	235	6 (2.6)	NE (NE, NE)	1.24	0.43, 3.79	0.6861
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	1.93	0.18, 41.42	0.5820
Interaction p-value									0.9097
Age Group									
<65	219	6 (2.7)	28.8 (28.8, NE)	229	6 (2.6)	NE (NE, NE)	0.90	0.28, 2.89	0.8528
>=65	183	9 (4.9)	NE (NE, NE)	174	3 (1.7)	NE (NE, NE)	2.53	0.75, 11.48	0.1417
Interaction p-value									0.2300
Region									
Asia	241	11 (4.6)	NE (NE, NE)	257	8 (3.1)	NE (NE, NE)	1.27	0.51, 3.30	0.6149
Rest of World	161	4 (2.5)	28.8 (28.8, NE)	146	1 (0.7)	NE (NE, NE)	3.15	0.46, 61.86	0.2596
Interaction p-value									0.4250
PD-L1 Status									
High (>=1%)	239	9 (3.8)	NE (NE, NE)	249	5 (2.0)	NE (NE, NE)	1.51	0.50, 5.01	0.4657
Low (<1%)	118	5 (4.2)	NE (NE, NE)	117	3 (2.6)	NE (NE, NE)	1.58	0.39, 7.69	0.5276
Interaction p-value									0.9632
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcp 01FEB2023:16:13 kjpc654

Table 3.4.6.68 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Biliary tract infection
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	8 (4.0)	28.8 (28.8, NE)	207	5 (2.4)	NE (NE, NE)	1.46	0.48, 4.88	0.5034
Female	203	7 (3.4)	NE (NE, NE)	196	4 (2.0)	NE (NE, NE)	1.45	0.43, 5.59	0.5484
Interaction p-value									0.9935
Race									
Asian	248	12 (4.8)	NE (NE, NE)	262	8 (3.1)	NE (NE, NE)	1.35	0.55, 3.49	0.5148
Non-Asian	154	3 (1.9)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	2.50	0.32, 50.61	0.3978
Interaction p-value									0.6079
WHO ECOG Status at Screening									
0	186	9 (4.8)	28.8 (NE, NE)	184	2 (1.1)	NE (NE, NE)	3.96	1.02, 26.05	0.0471*
1	216	6 (2.8)	NE (NE, NE)	219	7 (3.2)	NE (NE, NE)	0.73	0.23, 2.23	0.5722
Interaction p-value									0.0604
Disease Extent									
Locally Advanced	55	2 (3.6)	28.8 (NE, NE)	73	4 (5.5)	NE (NE, NE)	0.51	0.07, 2.65	0.4286
Metastatic	347	13 (3.7)	NE (NE, NE)	330	5 (1.5)	NE (NE, NE)	2.19	0.81, 6.86	0.1232
Interaction p-value									0.1377
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	5 (3.0)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.69 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	Number (%) of patients n with events	Median time (95% CI) (months) [a]		Number (%) of patients n with events	Median time (95% CI) (months) [a]		Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326 5 (1.5)	NE (NE, NE)		333 5 (1.5)	NE (NE, NE)		0.95	0.26, 3.43	0.9373
Recurrent	76 2 (2.6)	NE (NE, NE)		70 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73 0	NE (NE, NE)		71 0	NE (NE, NE)		NC	NC	NC
Intrahepatic CCA	234 5 (2.1)	NE (NE, NE)		235 2 (0.9)	NE (NE, NE)		NC	NC	NC
Gallbladder cancer	95 2 (2.1)	NE (NE, NE)		97 3 (3.1)	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219 6 (2.7)	NE (NE, NE)		229 5 (2.2)	NE (NE, NE)		1.09	0.33, 3.81	0.8814
>=65	183 1 (0.5)	NE (NE, NE)		174 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Region									
Asia	241 7 (2.9)	NE (NE, NE)		257 5 (1.9)	NE (NE, NE)		1.35	0.43, 4.56	0.6106
Rest of World	161 0	NE (NE, NE)		146 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239 5 (2.1)	NE (NE, NE)		249 3 (1.2)	NE (NE, NE)		NC	NC	NC
Low (<1%)	118 2 (1.7)	NE (NE, NE)		117 2 (1.7)	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.69 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	5 (2.5)	NE (NE, NE)	207	4 (1.9)	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	7 (2.8)	NE (NE, NE)	262	5 (1.9)	NE (NE, NE)	1.34	0.43, 4.54	0.6161
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	4 (1.9)	NE (NE, NE)	219	4 (1.8)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	7 (2.0)	NE (NE, NE)	330	5 (1.5)	NE (NE, NE)	1.23	0.39, 4.17	0.7197
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.70 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	2 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	3 (1.2)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.70 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	3 (1.1)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcr 01FEB2023:16:13 kjpc654

Table 3.4.6.71 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	2 (2.8)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	4 (1.7)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcs 01FEB2023:16:13 kjpc654

Table 3.4.6.71 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	4 (1.2)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcs 01FEB2023:16:13 kjpc654

Table 3.4.6.72 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Gallbladder rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefct 01FEB2023:16:13 kjpc654

Table 3.4.6.72 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Gallbladder rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.73 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Biloma rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.73 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Biloma rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.74 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Haematopoietic cytopenias SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	187 (57.4)	3.6 (3.0, 4.4)	333	187 (56.2)	3.5 (2.7, 4.4)	0.98	0.80, 1.20	0.8255
Recurrent	76	49 (64.5)	2.6 (1.6, 4.7)	70	51 (72.9)	2.2 (1.2, 3.0)	0.74	0.50, 1.10	0.1385
Interaction p-value									0.2236
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	37 (50.7)	5.1 (2.6, NE)	71	47 (66.2)	2.3 (1.2, 4.2)	0.59	0.38, 0.91	0.0167*
Intrahepatic CCA	234	135 (57.7)	3.5 (2.6, 4.8)	235	138 (58.7)	3.4 (2.5, 4.4)	0.95	0.75, 1.21	0.6939
Gallbladder cancer	95	64 (67.4)	2.9 (2.4, 3.7)	97	53 (54.6)	3.3 (2.4, 6.6)	1.22	0.85, 1.76	0.2815
Interaction p-value									0.0396*
Age Group									
<65	219	128 (58.4)	3.5 (2.8, 4.5)	229	129 (56.3)	3.2 (2.5, 4.4)	0.96	0.75, 1.23	0.7560
>=65	183	108 (59.0)	3.5 (2.4, 5.0)	174	109 (62.6)	2.8 (2.3, 3.9)	0.89	0.68, 1.17	0.4027
Interaction p-value									0.6843
Region									
Asia	241	154 (63.9)	2.8 (2.3, 3.5)	257	160 (62.3)	2.8 (2.3, 3.5)	0.98	0.79, 1.23	0.8874
Rest of World	161	82 (50.9)	5.2 (3.7,10.4)	146	78 (53.4)	3.9 (2.5, 6.0)	0.87	0.64, 1.19	0.3946
Interaction p-value									0.5410
PD-L1 Status									
High (>=1%)	239	143 (59.8)	3.0 (2.3, 4.4)	249	142 (57.0)	3.3 (2.5, 4.4)	1.02	0.81, 1.28	0.8901
Low (<1%)	118	70 (59.3)	4.0 (3.0, 4.6)	117	71 (60.7)	3.1 (2.3, 3.9)	0.88	0.64, 1.23	0.4680
Interaction p-value									0.5011
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.74 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 GT: Haematopoietic cytopenias SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	114 (57.3)	3.5 (2.6, 4.5)	207	120 (58.0)	3.4 (2.3, 4.4)	0.93	0.72, 1.20	0.5731
Female	203	122 (60.1)	3.5 (2.5, 4.5)	196	118 (60.2)	3.0 (2.4, 3.8)	0.93	0.72, 1.20	0.5876
Interaction p-value									0.9842
Race									
Asian	248	158 (63.7)	2.9 (2.3, 3.5)	262	161 (61.5)	3.0 (2.4, 3.7)	1.00	0.80, 1.25	0.9905
Non-Asian	154	78 (50.6)	5.2 (3.5,10.4)	141	77 (54.6)	3.8 (2.3, 6.0)	0.84	0.61, 1.15	0.2679
Interaction p-value									0.3595
WHO ECOG Status at Screening									
0	186	104 (55.9)	4.3 (2.9, 5.1)	184	104 (56.5)	3.7 (2.5, 5.1)	0.92	0.70, 1.21	0.5448
1	216	132 (61.1)	3.1 (2.4, 4.0)	219	134 (61.2)	3.0 (2.3, 3.7)	0.94	0.74, 1.20	0.6350
Interaction p-value									0.8896
Disease Extent									
Locally Advanced	55	36 (65.5)	3.9 (1.7, 6.3)	73	46 (63.0)	2.5 (1.8, 4.6)	0.96	0.62, 1.49	0.8688
Metastatic	347	200 (57.6)	3.5 (2.6, 4.3)	330	192 (58.2)	3.2 (2.5, 3.9)	0.93	0.76, 1.13	0.4471
Interaction p-value									0.8699
MSI Status									
MSI High	3	2 (66.7)	5.8 (1.6, NE)	2	2 (100)	2.6 (1.2, NE)	NC	NC	NC
MSI Stable	166	106 (63.9)	3.0 (2.4, 4.2)	178	113 (63.5)	2.6 (2.3, 3.8)	0.94	0.72, 1.22	0.6280
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.75 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Anaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	82 (25.2)	NE (NE, NE)	333	80 (24.0)	23.6 (23.6, NE)	1.02	0.75, 1.40	0.8763
Recurrent	76	22 (28.9)	NE (NE, NE)	70	17 (24.3)	NE (NE, NE)	1.09	0.58, 2.07	0.7992
Interaction p-value									0.8725
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	18 (24.7)	NE (NE, NE)	71	18 (25.4)	NE (NE, NE)	0.88	0.45, 1.70	0.6976
Intrahepatic CCA	234	61 (26.1)	NE (NE, NE)	235	59 (25.1)	23.6 (23.6, NE)	1.03	0.72, 1.48	0.8625
Gallbladder cancer	95	25 (26.3)	NE (NE, NE)	97	20 (20.6)	NE (NE, NE)	1.20	0.67, 2.18	0.5485
Interaction p-value									0.7874
Age Group									
<65	219	53 (24.2)	NE (NE, NE)	229	55 (24.0)	23.6 (NE, NE)	0.95	0.65, 1.38	0.7692
>=65	183	51 (27.9)	NE (NE, NE)	174	42 (24.1)	NE (NE, NE)	1.15	0.76, 1.74	0.5029
Interaction p-value									0.4891
Region									
Asia	241	74 (30.7)	NE (NE, NE)	257	78 (30.4)	23.6 (23.6, NE)	0.96	0.70, 1.32	0.7925
Rest of World	161	30 (18.6)	NE (NE, NE)	146	19 (13.0)	NE (NE, NE)	1.43	0.81, 2.58	0.2175
Interaction p-value									0.2285
PD-L1 Status									
High (>=1%)	239	59 (24.7)	NE (NE, NE)	249	57 (22.9)	NE (NE, NE)	1.01	0.70, 1.46	0.9451
Low (<1%)	118	35 (29.7)	19.9 (19.9, NE)	117	31 (26.5)	23.6 (23.6, NE)	1.12	0.69, 1.83	0.6400
Interaction p-value									0.7403
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcw 01FEB2023:16:13 kjpc654

Table 3.4.6.75 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Anaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	43 (21.6)	NE (NE, NE)	207	47 (22.7)	23.6 (NE, NE)	0.90	0.59, 1.36	0.6151
Female	203	61 (30.0)	NE (NE, NE)	196	50 (25.5)	NE (NE, NE)	1.16	0.80, 1.69	0.4424
Interaction p-value									0.3740
Race									
Asian	248	75 (30.2)	NE (NE, NE)	262	78 (29.8)	23.6 (23.6, NE)	0.96	0.70, 1.33	0.8226
Non-Asian	154	29 (18.8)	NE (NE, NE)	141	19 (13.5)	NE (NE, NE)	1.39	0.79, 2.52	0.2584
Interaction p-value									0.2726
WHO ECOG Status at Screening									
0	186	35 (18.8)	NE (NE, NE)	184	32 (17.4)	23.6 (NE, NE)	1.02	0.63, 1.65	0.9393
1	216	69 (31.9)	NE (NE, NE)	219	65 (29.7)	NE (NE, NE)	1.06	0.76, 1.49	0.7302
Interaction p-value									0.8908
Disease Extent									
Locally Advanced	55	16 (29.1)	NE (NE, NE)	73	17 (23.3)	NE (NE, NE)	1.24	0.62, 2.46	0.5407
Metastatic	347	88 (25.4)	NE (NE, NE)	330	80 (24.2)	23.6 (23.6, NE)	1.00	0.74, 1.35	0.9940
Interaction p-value									0.5732
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	166	50 (30.1)	NE (NE, NE)	178	38 (21.3)	NE (NE, NE)	1.44	0.94, 2.20	0.0904
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcw 01FEB2023:16:13 kjpc654

Table 3.4.6.76 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Bicytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.76 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Bicytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.77 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Febrile neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	4 (1.2)	NE (NE, NE)	333	6 (1.8)	NE (NE, NE)	0.68	0.17, 2.39	0.5512
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	3 (1.3)	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	4 (2.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	4 (1.7)	NE (NE, NE)	257	4 (1.6)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	3 (2.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.77 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Febrile neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	5 (2.4)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	4 (1.6)	NE (NE, NE)	262	4 (1.5)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	4 (1.8)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	4 (1.2)	NE (NE, NE)	330	5 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcy 01FEB2023:16:13 kjpc654

Table 3.4.6.78 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Haemoglobin decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	Number (%) of patients n with events	Median time (95% CI) (months) [a]		Number (%) of patients n with events	Median time (95% CI) (months) [a]		Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326 0	NE (NE, NE)		333 1 (0.3)	NE (NE, NE)		NC	NC	NC
Recurrent	76 0	NE (NE, NE)		70 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73 0	NE (NE, NE)		71 0	NE (NE, NE)		NC	NC	NC
Intrahepatic CCA	234 0	NE (NE, NE)		235 0	NE (NE, NE)		NC	NC	NC
Gallbladder cancer	95 0	NE (NE, NE)		97 1 (1.0)	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219 0	NE (NE, NE)		229 1 (0.4)	NE (NE, NE)		NC	NC	NC
>=65	183 0	NE (NE, NE)		174 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Region									
Asia	241 0	NE (NE, NE)		257 1 (0.4)	NE (NE, NE)		NC	NC	NC
Rest of World	161 0	NE (NE, NE)		146 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239 0	NE (NE, NE)		249 1 (0.4)	NE (NE, NE)		NC	NC	NC
Low (<1%)	118 0	NE (NE, NE)		117 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.78 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Haemoglobin decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefcz 01FEB2023:16:13 kjpc654

Table 3.4.6.79 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Leukopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	6 (1.8)	NE (NE, NE)	333	5 (1.5)	NE (NE, NE)	1.23	0.37, 4.28	0.7272
Recurrent	76	3 (3.9)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	6 (2.6)	NE (NE, NE)	235	5 (2.1)	NE (NE, NE)	1.21	0.36, 4.19	0.7541
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	6 (2.7)	NE (NE, NE)	229	5 (2.2)	NE (NE, NE)	1.25	0.38, 4.35	0.7084
>=65	183	3 (1.6)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	6 (2.5)	NE (NE, NE)	257	3 (1.2)	NE (NE, NE)	NC	NC	NC
Rest of World	161	3 (1.9)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	6 (2.5)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefda 01FEB2023:16:13 kjpc654

Table 3.4.6.79 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Leukopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	5 (2.5)	NE (NE, NE)	207	3 (1.4)	NE (NE, NE)	NC	NC	NC
Female	203	4 (2.0)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	6 (2.4)	NE (NE, NE)	262	3 (1.1)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	3 (1.9)	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	5 (2.7)	NE (NE, NE)	184	4 (2.2)	NE (NE, NE)	NC	NC	NC
1	216	4 (1.9)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	9 (2.6)	NE (NE, NE)	330	5 (1.5)	NE (NE, NE)	1.71	0.59, 5.58	0.3247
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	4 (2.4)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefda 01FEB2023:16:13 kjpc654

Table 3.4.6.80 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: White blood cell count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	23 (7.1)	NE (NE, NE)	333	22 (6.6)	NE (NE, NE)	1.08	0.60, 1.94	0.8023
Recurrent	76	5 (6.6)	NE (NE, NE)	70	7 (10.0)	NE (NE, NE)	0.62	0.18, 1.96	0.4177
Interaction p-value									0.4037
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	8 (11.3)	NE (NE, NE)	0.23	0.03, 0.92	0.0365*
Intrahepatic CCA	234	21 (9.0)	NE (NE, NE)	235	15 (6.4)	NE (NE, NE)	1.44	0.75, 2.84	0.2803
Gallbladder cancer	95	5 (5.3)	NE (NE, NE)	97	6 (6.2)	NE (NE, NE)	0.83	0.24, 2.75	0.7533
Interaction p-value									0.0601
Age Group									
<65	219	17 (7.8)	NE (NE, NE)	229	14 (6.1)	NE (NE, NE)	1.27	0.63, 2.62	0.5080
>=65	183	11 (6.0)	NE (NE, NE)	174	15 (8.6)	NE (NE, NE)	0.69	0.31, 1.49	0.3471
Interaction p-value									0.2540
Region									
Asia	241	25 (10.4)	NE (NE, NE)	257	25 (9.7)	NE (NE, NE)	1.06	0.61, 1.86	0.8269
Rest of World	161	3 (1.9)	NE (NE, NE)	146	4 (2.7)	NE (NE, NE)	0.68	0.13, 3.08	0.6095
Interaction p-value									0.5789
PD-L1 Status									
High (>=1%)	239	14 (5.9)	NE (NE, NE)	249	18 (7.2)	NE (NE, NE)	0.79	0.39, 1.59	0.5089
Low (<1%)	118	10 (8.5)	NE (NE, NE)	117	6 (5.1)	NE (NE, NE)	1.70	0.63, 5.00	0.2950
Interaction p-value									0.2162
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefdb 01FEB2023:16:13 kjpc654

Table 3.4.6.80 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: White blood cell count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	19 (9.5)	NE (NE, NE)	207	14 (6.8)	NE (NE, NE)	1.45	0.73, 2.95	0.2867
Female	203	9 (4.4)	NE (NE, NE)	196	15 (7.7)	NE (NE, NE)	0.56	0.23, 1.26	0.1603
Interaction p-value									0.0784
Race									
Asian	248	25 (10.1)	NE (NE, NE)	262	25 (9.5)	NE (NE, NE)	1.06	0.60, 1.85	0.8459
Non-Asian	154	3 (1.9)	NE (NE, NE)	141	4 (2.8)	NE (NE, NE)	0.68	0.13, 3.09	0.6138
Interaction p-value									0.5887
WHO ECOG Status at Screening									
0	186	11 (5.9)	NE (NE, NE)	184	14 (7.6)	NE (NE, NE)	0.76	0.34, 1.66	0.4864
1	216	17 (7.9)	NE (NE, NE)	219	15 (6.8)	NE (NE, NE)	1.17	0.58, 2.37	0.6604
Interaction p-value									0.4164
Disease Extent									
Locally Advanced	55	9 (16.4)	NE (NE, NE)	73	6 (8.2)	NE (NE, NE)	2.01	0.73, 6.01	0.1783
Metastatic	347	19 (5.5)	NE (NE, NE)	330	23 (7.0)	NE (NE, NE)	0.78	0.42, 1.43	0.4166
Interaction p-value									0.1159
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	8 (4.8)	NE (NE, NE)	178	15 (8.4)	NE (NE, NE)	0.56	0.23, 1.30	0.1794
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefdb 01FEB2023:16:13 kjpc654

Table 3.4.6.81 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Lymphopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	Number (%) of patients n with events	Median time (95% CI) (months) [a]		Number (%) of patients n with events	Median time (95% CI) (months) [a]		Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326 0	NE (NE, NE)		333 1 (0.3)	NE (NE, NE)		NC	NC	NC
Recurrent	76 2 (2.6)	NE (NE, NE)		70 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73 1 (1.4)	NE (NE, NE)		71 0	NE (NE, NE)		NC	NC	NC
Intrahepatic CCA	234 1 (0.4)	NE (NE, NE)		235 1 (0.4)	NE (NE, NE)		NC	NC	NC
Gallbladder cancer	95 0	NE (NE, NE)		97 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219 1 (0.5)	NE (NE, NE)		229 1 (0.4)	NE (NE, NE)		NC	NC	NC
>=65	183 1 (0.5)	NE (NE, NE)		174 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Region									
Asia	241 2 (0.8)	NE (NE, NE)		257 0	NE (NE, NE)		NC	NC	NC
Rest of World	161 0	NE (NE, NE)		146 1 (0.7)	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239 2 (0.8)	NE (NE, NE)		249 1 (0.4)	NE (NE, NE)		NC	NC	NC
Low (<1%)	118 0	NE (NE, NE)		117 0	NE (NE, NE)		NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.81 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Lymphopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefdc 01FEB2023:16:13 kjpc654

Table 3.4.6.82 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Lymphocyte count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	5 (1.5)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	5 (2.1)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	4 (1.7)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	3 (1.2)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.6.82 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Lymphocyte count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	3 (1.4)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	3 (1.1)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	2 (2.7)	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefdd 01FEB2023:16:13 kjpc654

Table 3.4.6.83 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Myelosuppression
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	6 (1.8)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	5 (2.1)	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	2 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	3 (1.4)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	3 (1.6)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	6 (2.5)	NE (NE, NE)	257	4 (1.6)	NE (NE, NE)	1.57	0.45, 6.14	0.4810
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	5 (2.1)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefde 01FEB2023:16:13 kjpc654

Table 3.4.6.83 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Myelosuppression
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	6 (3.0)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	6 (2.4)	NE (NE, NE)	262	4 (1.5)	NE (NE, NE)	1.56	0.44, 6.09	0.4889
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	5 (2.3)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	4 (7.3)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	4 (1.2)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefde 01FEB2023:16:13 kjpc654

Table 3.4.6.84 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	56 (17.2)	NE (NE, NE)	333	59 (17.7)	NE (NE, NE)	0.95	0.66, 1.37	0.7795
Recurrent	76	13 (17.1)	NE (NE, NE)	70	14 (20.0)	NE (NE, NE)	0.85	0.39, 1.81	0.6646
Interaction p-value									0.7886
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	8 (11.0)	NE (NE, NE)	71	16 (22.5)	NE (NE, NE)	0.45	0.18, 1.02	0.0558
Intrahepatic CCA	234	39 (16.7)	NE (NE, NE)	235	43 (18.3)	NE (NE, NE)	0.90	0.58, 1.38	0.6193
Gallbladder cancer	95	22 (23.2)	NE (NE, NE)	97	14 (14.4)	NE (NE, NE)	1.63	0.84, 3.26	0.1475
Interaction p-value									0.0546
Age Group									
<65	219	47 (21.5)	NE (NE, NE)	229	43 (18.8)	NE (NE, NE)	1.12	0.74, 1.70	0.5948
>=65	183	22 (12.0)	NE (NE, NE)	174	30 (17.2)	NE (NE, NE)	0.68	0.39, 1.18	0.1745
Interaction p-value									0.1606
Region									
Asia	241	32 (13.3)	NE (NE, NE)	257	27 (10.5)	NE (NE, NE)	1.27	0.76, 2.14	0.3557
Rest of World	161	37 (23.0)	NE (NE, NE)	146	46 (31.5)	NE (NE, NE)	0.67	0.43, 1.04	0.0716
Interaction p-value									0.0618
PD-L1 Status									
High (>=1%)	239	47 (19.7)	NE (NE, NE)	249	33 (13.3)	NE (NE, NE)	1.52	0.98, 2.39	0.0625
Low (<1%)	118	19 (16.1)	NE (NE, NE)	117	27 (23.1)	NE (NE, NE)	0.66	0.36, 1.18	0.1580
Interaction p-value									0.0244*
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefdf 01FEB2023:16:13 kjpc654

Table 3.4.6.84 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	38 (19.1)	NE (NE, NE)	207	33 (15.9)	NE (NE, NE)	1.22	0.76, 1.95	0.4071
Female	203	31 (15.3)	NE (NE, NE)	196	40 (20.4)	NE (NE, NE)	0.71	0.44, 1.12	0.1426
Interaction p-value									0.1045
Race									
Asian	248	33 (13.3)	NE (NE, NE)	262	28 (10.7)	NE (NE, NE)	1.26	0.76, 2.09	0.3711
Non-Asian	154	36 (23.4)	NE (NE, NE)	141	45 (31.9)	NE (NE, NE)	0.67	0.43, 1.04	0.0716
Interaction p-value									0.0634
WHO ECOG Status at Screening									
0	186	37 (19.9)	NE (NE, NE)	184	35 (19.0)	NE (NE, NE)	1.02	0.64, 1.63	0.9254
1	216	32 (14.8)	NE (NE, NE)	219	38 (17.4)	NE (NE, NE)	0.84	0.52, 1.34	0.4603
Interaction p-value									0.5541
Disease Extent									
Locally Advanced	55	8 (14.5)	NE (NE, NE)	73	13 (17.8)	NE (NE, NE)	0.79	0.31, 1.88	0.5982
Metastatic	347	61 (17.6)	NE (NE, NE)	330	60 (18.2)	NE (NE, NE)	0.94	0.66, 1.35	0.7553
Interaction p-value									0.7118
MSI Status									
MSI High	3	2 (66.7)	5.8 (1.6, NE)	2	1 (50.0)	NE (NE, NE)	NC	NC	NC
MSI Stable	166	35 (21.1)	NE (NE, NE)	178	29 (16.3)	NE (NE, NE)	1.33	0.81, 2.19	0.2571
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefdf 01FEB2023:16:13 kjpc654

Table 3.4.6.85 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Neutropenic sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefdg 01FEB2023:16:13 kjpc654

Table 3.4.6.85 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Neutropenic sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefdg 01FEB2023:16:13 kjpc654

Table 3.4.6.86 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Neutrophil count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	64 (19.6)	NE (NE, NE)	333	78 (23.4)	NE (NE, NE)	0.82	0.59, 1.14	0.2392
Recurrent	76	27 (35.5)	NE (NE, NE)	70	30 (42.9)	NE (NE, NE)	0.75	0.44, 1.26	0.2693
Interaction p-value									0.7628
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	17 (23.3)	NE (NE, NE)	71	22 (31.0)	NE (NE, NE)	0.71	0.37, 1.32	0.2780
Intrahepatic CCA	234	53 (22.6)	NE (NE, NE)	235	57 (24.3)	NE (NE, NE)	0.93	0.64, 1.35	0.7055
Gallbladder cancer	95	21 (22.1)	NE (NE, NE)	97	29 (29.9)	NE (NE, NE)	0.67	0.38, 1.18	0.1673
Interaction p-value									0.5724
Age Group									
<65	219	45 (20.5)	NE (NE, NE)	229	53 (23.1)	NE (NE, NE)	0.86	0.58, 1.28	0.4596
>=65	183	46 (25.1)	NE (NE, NE)	174	55 (31.6)	NE (NE, NE)	0.76	0.51, 1.13	0.1714
Interaction p-value									0.6657
Region									
Asia	241	74 (30.7)	NE (NE, NE)	257	88 (34.2)	NE (NE, NE)	0.86	0.63, 1.18	0.3562
Rest of World	161	17 (10.6)	NE (NE, NE)	146	20 (13.7)	NE (NE, NE)	0.75	0.39, 1.44	0.3919
Interaction p-value									0.7087
PD-L1 Status									
High (>=1%)	239	52 (21.8)	NE (NE, NE)	249	72 (28.9)	NE (NE, NE)	0.71	0.49, 1.01	0.0564
Low (<1%)	118	27 (22.9)	NE (NE, NE)	117	28 (23.9)	NE (NE, NE)	0.95	0.56, 1.61	0.8366
Interaction p-value									0.3739
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefdh 01FEB2023:16:13 kjpc654

Table 3.4.6.86 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Neutrophil count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	44 (22.1)	NE (NE, NE)	207	55 (26.6)	NE (NE, NE)	0.80	0.54, 1.19	0.2730
Female	203	47 (23.2)	NE (NE, NE)	196	53 (27.0)	NE (NE, NE)	0.83	0.56, 1.23	0.3506
Interaction p-value									0.9042
Race									
Asian	248	74 (29.8)	NE (NE, NE)	262	88 (33.6)	NE (NE, NE)	0.86	0.63, 1.17	0.3348
Non-Asian	154	17 (11.0)	NE (NE, NE)	141	20 (14.2)	NE (NE, NE)	0.76	0.39, 1.45	0.3982
Interaction p-value									0.7298
WHO ECOG Status at Screening									
0	186	40 (21.5)	NE (NE, NE)	184	52 (28.3)	NE (NE, NE)	0.72	0.47, 1.08	0.1122
1	216	51 (23.6)	NE (NE, NE)	219	56 (25.6)	NE (NE, NE)	0.91	0.62, 1.33	0.6337
Interaction p-value									0.4002
Disease Extent									
Locally Advanced	55	13 (23.6)	NE (NE, NE)	73	24 (32.9)	NE (NE, NE)	0.67	0.33, 1.29	0.2363
Metastatic	347	78 (22.5)	NE (NE, NE)	330	84 (25.5)	NE (NE, NE)	0.86	0.63, 1.17	0.3248
Interaction p-value									0.5121
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	41 (24.7)	NE (NE, NE)	178	65 (36.5)	NE (NE, NE)	0.60	0.40, 0.88	0.0094*
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefdh 01FEB2023:16:13 kjpc654

Table 3.4.6.87 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Pancytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefdi 01FEB2023:16:13 kjpc654

Table 3.4.6.87 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Pancytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefdi 01FEB2023:16:13 kjpc654

Table 3.4.6.88 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Platelet count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	36 (11.0)	NE (NE, NE)	333	35 (10.5)	NE (NE, NE)	1.04	0.65, 1.67	0.8596
Recurrent	76	8 (10.5)	NE (NE, NE)	70	8 (11.4)	NE (NE, NE)	0.87	0.32, 2.38	0.7893
Interaction p-value									0.7510
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	7 (9.6)	NE (NE, NE)	71	10 (14.1)	NE (NE, NE)	0.67	0.24, 1.76	0.4196
Intrahepatic CCA	234	26 (11.1)	NE (NE, NE)	235	25 (10.6)	NE (NE, NE)	1.03	0.59, 1.79	0.9152
Gallbladder cancer	95	11 (11.6)	NE (NE, NE)	97	8 (8.2)	NE (NE, NE)	1.36	0.55, 3.50	0.5098
Interaction p-value									0.5780
Age Group									
<65	219	14 (6.4)	NE (NE, NE)	229	21 (9.2)	NE (NE, NE)	0.67	0.33, 1.31	0.2466
>=65	183	30 (16.4)	NE (NE, NE)	174	22 (12.6)	NE (NE, NE)	1.30	0.75, 2.28	0.3493
Interaction p-value									0.1363
Region									
Asia	241	33 (13.7)	NE (NE, NE)	257	36 (14.0)	NE (NE, NE)	0.96	0.59, 1.53	0.8525
Rest of World	161	11 (6.8)	NE (NE, NE)	146	7 (4.8)	NE (NE, NE)	1.41	0.56, 3.84	0.4690
Interaction p-value									0.4654
PD-L1 Status									
High (>=1%)	239	22 (9.2)	NE (NE, NE)	249	29 (11.6)	NE (NE, NE)	0.75	0.43, 1.31	0.3134
Low (<1%)	118	14 (11.9)	NE (NE, NE)	117	11 (9.4)	NE (NE, NE)	1.25	0.57, 2.83	0.5721
Interaction p-value									0.2976
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefdj 01FEB2023:16:13 kjpc654

Table 3.4.6.88 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Platelet count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	20 (10.1)	NE (NE, NE)	207	22 (10.6)	NE (NE, NE)	0.94	0.51, 1.72	0.8298
Female	203	24 (11.8)	NE (NE, NE)	196	21 (10.7)	NE (NE, NE)	1.08	0.60, 1.95	0.8072
Interaction p-value									0.7457
Race									
Asian	248	34 (13.7)	NE (NE, NE)	262	36 (13.7)	NE (NE, NE)	0.98	0.61, 1.57	0.9273
Non-Asian	154	10 (6.5)	NE (NE, NE)	141	7 (5.0)	NE (NE, NE)	1.29	0.50, 3.56	0.6008
Interaction p-value									0.6101
WHO ECOG Status at Screening									
0	186	15 (8.1)	NE (NE, NE)	184	15 (8.2)	NE (NE, NE)	0.96	0.46, 1.97	0.9024
1	216	29 (13.4)	NE (NE, NE)	219	28 (12.8)	NE (NE, NE)	1.05	0.62, 1.77	0.8630
Interaction p-value									0.8410
Disease Extent									
Locally Advanced	55	8 (14.5)	NE (NE, NE)	73	9 (12.3)	NE (NE, NE)	1.14	0.43, 2.98	0.7909
Metastatic	347	36 (10.4)	NE (NE, NE)	330	34 (10.3)	NE (NE, NE)	0.99	0.62, 1.58	0.9567
Interaction p-value									0.7934
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	18 (10.8)	NE (NE, NE)	178	19 (10.7)	NE (NE, NE)	0.99	0.52, 1.90	0.9787
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaefdj 01FEB2023:16:13 kjpc654

Table 3.4.6.89 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Thrombocytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	12 (3.7)	NE (NE, NE)	333	17 (5.1)	NE (NE, NE)	0.70	0.33, 1.45	0.3368
Recurrent	76	4 (5.3)	NE (NE, NE)	70	2 (2.9)	NE (NE, NE)	1.76	0.34, 12.68	0.5039
Interaction p-value									0.3149
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	4 (5.5)	NE (NE, NE)	71	2 (2.8)	NE (NE, NE)	1.89	0.37, 13.65	0.4492
Intrahepatic CCA	234	9 (3.8)	NE (NE, NE)	235	13 (5.5)	NE (NE, NE)	0.68	0.28, 1.57	0.3630
Gallbladder cancer	95	3 (3.2)	NE (NE, NE)	97	4 (4.1)	NE (NE, NE)	0.72	0.14, 3.24	0.6590
Interaction p-value									0.5414
Age Group									
<65	219	12 (5.5)	NE (NE, NE)	229	11 (4.8)	NE (NE, NE)	1.10	0.48, 2.54	0.8131
>=65	183	4 (2.2)	NE (NE, NE)	174	8 (4.6)	NE (NE, NE)	0.45	0.12, 1.44	0.1838
Interaction p-value									0.2230
Region									
Asia	241	3 (1.2)	NE (NE, NE)	257	7 (2.7)	NE (NE, NE)	0.44	0.09, 1.58	0.2115
Rest of World	161	13 (8.1)	NE (NE, NE)	146	12 (8.2)	NE (NE, NE)	0.95	0.43, 2.12	0.9054
Interaction p-value									0.3175
PD-L1 Status									
High (>=1%)	239	9 (3.8)	NE (NE, NE)	249	9 (3.6)	NE (NE, NE)	1.00	0.39, 2.57	0.9966
Low (<1%)	118	7 (5.9)	NE (NE, NE)	117	7 (6.0)	NE (NE, NE)	0.95	0.33, 2.79	0.9301
Interaction p-value									0.9453
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.6.89 TOPAZ: Summary of subgroup analysis of time to first AESI G>=3 PT: Thrombocytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	7 (3.5)	NE (NE, NE)	207	8 (3.9)	NE (NE, NE)	0.88	0.31, 2.45	0.8036
Female	203	9 (4.4)	NE (NE, NE)	196	11 (5.6)	NE (NE, NE)	0.76	0.31, 1.83	0.5383
Interaction p-value									0.8299
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	7 (2.7)	NE (NE, NE)	0.44	0.09, 1.57	0.2079
Non-Asian	154	13 (8.4)	NE (NE, NE)	141	12 (8.5)	NE (NE, NE)	0.96	0.43, 2.13	0.9137
Interaction p-value									0.3108
WHO ECOG Status at Screening									
0	186	9 (4.8)	NE (NE, NE)	184	11 (6.0)	NE (NE, NE)	0.76	0.31, 1.85	0.5487
1	216	7 (3.2)	NE (NE, NE)	219	8 (3.7)	NE (NE, NE)	0.87	0.31, 2.43	0.7896
Interaction p-value									0.8486
Disease Extent									
Locally Advanced	55	2 (3.6)	NE (NE, NE)	73	5 (6.8)	NE (NE, NE)	0.48	0.07, 2.24	0.3622
Metastatic	347	14 (4.0)	NE (NE, NE)	330	14 (4.2)	NE (NE, NE)	0.92	0.44, 1.95	0.8289
Interaction p-value									0.4677
MSI Status									
MSI High	3	1 (33.3)	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	7 (4.2)	NE (NE, NE)	178	9 (5.1)	NE (NE, NE)	0.79	0.28, 2.13	0.6447
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.1 TOPAZ: Summary of subgroup analysis of time to first SAESI
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	85 (26.1)	NE (NE, NE)	333	83 (24.9)	NE (NE, NE)	1.01	0.75, 1.37	0.9415
Recurrent	76	18 (23.7)	NE (NE, NE)	70	11 (15.7)	NE (NE, NE)	1.37	0.66, 3.00	0.4050
Interaction p-value									0.4573
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	22 (30.1)	NE (NE, NE)	71	21 (29.6)	NE (NE, NE)	0.89	0.49, 1.63	0.7066
Intrahepatic CCA	234	47 (20.1)	NE (NE, NE)	235	46 (19.6)	NE (NE, NE)	0.97	0.65, 1.46	0.8949
Gallbladder cancer	95	34 (35.8)	NE (NE, NE)	97	27 (27.8)	NE (NE, NE)	1.33	0.81, 2.23	0.2636
Interaction p-value									0.5269
Age Group									
<65	219	55 (25.1)	NE (NE, NE)	229	50 (21.8)	17.5 (17.5, NE)	1.08	0.74, 1.59	0.6947
>=65	183	48 (26.2)	NE (NE, NE)	174	44 (25.3)	NE (NE, NE)	1.01	0.67, 1.52	0.9674
Interaction p-value									0.8111
Region									
Asia	241	68 (28.2)	NE (NE, NE)	257	62 (24.1)	NE (NE, NE)	1.11	0.79, 1.58	0.5410
Rest of World	161	35 (21.7)	NE (NE, NE)	146	32 (21.9)	NE (NE, NE)	0.95	0.59, 1.55	0.8422
Interaction p-value									0.6037
PD-L1 Status									
High (>=1%)	239	62 (25.9)	NE (NE, NE)	249	55 (22.1)	NE (NE, NE)	1.09	0.76, 1.57	0.6373
Low (<1%)	118	31 (26.3)	NE (NE, NE)	117	29 (24.8)	NE (NE, NE)	1.05	0.63, 1.76	0.8384
Interaction p-value									0.9127
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegaa 01FEB2023:16:13 kjpc654

Table 3.4.7.1 TOPAZ: Summary of subgroup analysis of time to first SAESI
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	45 (22.6)	NE (NE, NE)	207	52 (25.1)	NE (NE, NE)	0.85	0.57, 1.26	0.4104
Female	203	58 (28.6)	NE (NE, NE)	196	42 (21.4)	NE (NE, NE)	1.29	0.87, 1.93	0.2050
Interaction p-value									0.1390
Race									
Asian	248	72 (29.0)	NE (NE, NE)	262	64 (24.4)	NE (NE, NE)	1.13	0.81, 1.59	0.4801
Non-Asian	154	31 (20.1)	NE (NE, NE)	141	30 (21.3)	NE (NE, NE)	0.91	0.55, 1.51	0.7169
Interaction p-value									0.4867
WHO ECOG Status at Screening									
0	186	52 (28.0)	NE (NE, NE)	184	43 (23.4)	NE (NE, NE)	1.15	0.77, 1.72	0.5084
1	216	51 (23.6)	NE (NE, NE)	219	51 (23.3)	NE (NE, NE)	0.96	0.65, 1.42	0.8520
Interaction p-value									0.5443
Disease Extent									
Locally Advanced	55	11 (20.0)	NE (NE, NE)	73	24 (32.9)	NE (NE, NE)	0.49	0.23, 0.98	0.0450*
Metastatic	347	92 (26.5)	NE (NE, NE)	330	70 (21.2)	NE (NE, NE)	1.22	0.90, 1.68	0.2010
Interaction p-value									0.0183*
MSI Status									
MSI High	3	1 (33.3)	NE (NE, NE)	2	1 (50.0)	17.5 (NE, NE)	NC	NC	NC
MSI Stable	166	45 (27.1)	NE (NE, NE)	178	38 (21.3)	NE (NE, NE)	1.26	0.82, 1.95	0.2985
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegaa 01FEB2023:16:13 kjpc654

Table 3.4.7.2 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	4 (1.2)	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	3 (1.3)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	3 (1.2)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegab 01FEB2023:16:13 kjpc654

Table 3.4.7.2 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	4 (1.2)	NE (NE, NE)	330	2 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegab 01FEB2023:16:13 kjpc654

Table 3.4.7.3 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Immune-mediated lung disease
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegac 01FEB2023:16:13 kjpc654

Table 3.4.7.3 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Immune-mediated lung disease
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegac 01FEB2023:16:13 kjpc654

Table 3.4.7.4 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Interstitial lung disease
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.4 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Interstitial lung disease
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.5 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.5 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Pneumonitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	2 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegae 01FEB2023:16:13 kjpc654

Table 3.4.7.6 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Hepatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegaf 01FEB2023:16:13 kjpc654

Table 3.4.7.6 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Hepatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	2 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	17.5 (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegaf 01FEB2023:16:13 kjpc654

Table 3.4.7.7 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.7 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegag 01FEB2023:16:13 kjpc654

Table 3.4.7.8 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.8 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	17.5 (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegah 01FEB2023:16:13 kjpc654

Table 3.4.7.9 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.9 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegai 01FEB2023:16:13 kjpc654

Table 3.4.7.10 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Diarrhoea/Colitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	3 (0.9)	NE (NE, NE)	333	5 (1.5)	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	5 (2.2)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	3 (1.2)	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	4 (1.7)	NE (NE, NE)	249	4 (1.6)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegaj 01FEB2023:16:13 kjpc654

Table 3.4.7.10 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Diarrhoea/Colitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	5 (2.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	4 (1.5)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	6 (2.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	4 (1.2)	NE (NE, NE)	330	5 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegaj 01FEB2023:16:13 kjpc654

Table 3.4.7.11 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Diarrhoea
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	3 (0.9)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	4 (1.7)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	3 (1.2)	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	4 (1.7)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.11 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Diarrhoea
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	4 (2.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	4 (1.5)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	5 (2.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	4 (1.2)	NE (NE, NE)	330	4 (1.2)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.12 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Immune-mediated enterocolitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.12 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Immune-mediated enterocolitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegal 01FEB2023:16:13 kjpc654

Table 3.4.7.13 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Adrenal insufficiency
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.13 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Adrenal insufficiency
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.14 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Adrenal insufficiency
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.14 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Adrenal insufficiency
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.15 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Dermatitis/Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegao 01FEB2023:16:13 kjpc654

Table 3.4.7.15 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Dermatitis/Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.16 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.16 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Rash
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.17 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Rash maculo-papular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.17 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Rash maculo-papular
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.18 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Pancreatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	3 (3.9)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	3 (1.2)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegar 01FEB2023:16:13 kjpc654

Table 3.4.7.18 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Pancreatic events
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	3 (1.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegar 01FEB2023:16:13 kjpc654

Table 3.4.7.19 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Pancreatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	2 (2.6)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegas 01FEB2023:16:13 kjpc654

Table 3.4.7.19 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Pancreatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegas 01FEB2023:16:13 kjpc654

Table 3.4.7.20 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Pancreatitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.20 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Pancreatitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.21 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Myositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.21 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Myositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.22 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Polymyositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.22 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Polymyositis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.23 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Infusion/hypersensitivity reactions
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegaw 01FEB2023:16:13 kjpc654

Table 3.4.7.23 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Infusion/hypersensitivity reactions
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegaw 01FEB2023:16:13 kjpc654

Table 3.4.7.24 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Anaphylactic shock
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegax 01FEB2023:16:13 kjpc654

Table 3.4.7.24 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Anaphylactic shock
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegax 01FEB2023:16:13 kjpc654

Table 3.4.7.25 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Infusion related reaction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.25 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Infusion related reaction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegay 01FEB2023:16:13 kjpc654

Table 3.4.7.26 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Other rare/miscellaneous
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.26 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Other rare/miscellaneous
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegaz 01FEB2023:16:13 kjpc654

Table 3.4.7.27 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Immune-mediated arthritis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegba 01FEB2023:16:13 kjpc654

Table 3.4.7.27 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Immune-mediated arthritis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegba 01FEB2023:16:13 kjpc654

Table 3.4.7.28 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Hepatic SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	20 (6.1)	NE (NE, NE)	333	24 (7.2)	NE (NE, NE)	0.75	0.41, 1.37	0.3521
Recurrent	76	6 (7.9)	NE (NE, NE)	70	4 (5.7)	NE (NE, NE)	1.14	0.33, 4.48	0.8365
Interaction p-value									0.5570
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	6 (8.2)	NE (NE, NE)	71	7 (9.9)	NE (NE, NE)	0.62	0.20, 1.90	0.4003
Intrahepatic CCA	234	13 (5.6)	NE (NE, NE)	235	12 (5.1)	NE (NE, NE)	0.97	0.44, 2.16	0.9409
Gallbladder cancer	95	7 (7.4)	NE (NE, NE)	97	9 (9.3)	NE (NE, NE)	0.73	0.26, 1.97	0.5374
Interaction p-value									0.7933
Age Group									
<65	219	16 (7.3)	NE (NE, NE)	229	18 (7.9)	18.9 (17.5, NE)	0.79	0.39, 1.55	0.4838
>=65	183	10 (5.5)	NE (NE, NE)	174	10 (5.7)	NE (NE, NE)	0.86	0.35, 2.09	0.7277
Interaction p-value									0.8790
Region									
Asia	241	20 (8.3)	NE (NE, NE)	257	17 (6.6)	NE (NE, NE)	1.08	0.56, 2.10	0.8099
Rest of World	161	6 (3.7)	NE (NE, NE)	146	11 (7.5)	NE (NE, NE)	0.44	0.15, 1.15	0.0956
Interaction p-value									0.1287
PD-L1 Status									
High (>=1%)	239	16 (6.7)	NE (NE, NE)	249	20 (8.0)	NE (NE, NE)	0.71	0.36, 1.38	0.3174
Low (<1%)	118	7 (5.9)	NE (NE, NE)	117	6 (5.1)	18.9 (18.9, NE)	1.07	0.35, 3.32	0.9071
Interaction p-value									0.5359
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbb 01FEB2023:16:13 kjpc654

Table 3.4.7.28 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Hepatic SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	16 (8.0)	NE (NE, NE)	207	15 (7.2)	NE (NE, NE)	1.00	0.49, 2.06	0.9901
Female	203	10 (4.9)	NE (NE, NE)	196	13 (6.6)	NE (NE, NE)	0.62	0.26, 1.42	0.2576
Interaction p-value									0.3841
Race									
Asian	248	20 (8.1)	NE (NE, NE)	262	17 (6.5)	NE (NE, NE)	1.07	0.56, 2.08	0.8306
Non-Asian	154	6 (3.9)	NE (NE, NE)	141	11 (7.8)	NE (NE, NE)	0.44	0.15, 1.17	0.0997
Interaction p-value									0.1371
WHO ECOG Status at Screening									
0	186	11 (5.9)	NE (NE, NE)	184	9 (4.9)	NE (NE, NE)	1.06	0.44, 2.63	0.9005
1	216	15 (6.9)	NE (NE, NE)	219	19 (8.7)	NE (NE, NE)	0.69	0.34, 1.36	0.2817
Interaction p-value									0.4472
Disease Extent									
Locally Advanced	55	2 (3.6)	NE (NE, NE)	73	6 (8.2)	NE (NE, NE)	0.33	0.05, 1.43	0.1427
Metastatic	347	24 (6.9)	NE (NE, NE)	330	22 (6.7)	NE (NE, NE)	0.92	0.51, 1.66	0.7883
Interaction p-value									0.2074
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	17.5 (NE, NE)	NC	NC	NC
MSI Stable	166	7 (4.2)	NE (NE, NE)	178	9 (5.1)	NE (NE, NE)	0.68	0.24, 1.84	0.4433
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbb 01FEB2023:16:13 kjpc654

Table 3.4.7.29 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Alanine aminotransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.29 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Alanine aminotransferase increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.30 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.30 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Drug-induced liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbd 01FEB2023:16:13 kjpc654

Table 3.4.7.31 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Ascites
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	4 (1.2)	NE (NE, NE)	333	6 (1.8)	NE (NE, NE)	0.65	0.17, 2.29	0.5063
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	3 (4.2)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	3 (1.3)	NE (NE, NE)	235	4 (1.7)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	4 (1.7)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	3 (1.9)	NE (NE, NE)	146	6 (4.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	5 (2.0)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.31 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Ascites
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	5 (2.4)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	3 (1.9)	NE (NE, NE)	141	6 (4.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	4 (1.8)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	2 (2.7)	NE (NE, NE)	NC	NC	NC
Metastatic	347	4 (1.2)	NE (NE, NE)	330	5 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbe 01FEB2023:16:13 kjpc654

Table 3.4.7.32 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbf 01FEB2023:16:13 kjpc654

Table 3.4.7.32 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Autoimmune hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	1 (50.0)	17.5 (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbf 01FEB2023:16:13 kjpc654

Table 3.4.7.33 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	3 (1.3)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbg 01FEB2023:16:13 kjpc654

Table 3.4.7.33 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	3 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	4 (1.8)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	2 (2.7)	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	2 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbg 01FEB2023:16:13 kjpc654

Table 3.4.7.34 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbh 01FEB2023:16:13 kjpc654

Table 3.4.7.34 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbh 01FEB2023:16:13 kjpc654

Table 3.4.7.35 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	5 (1.5)	NE (NE, NE)	333	5 (1.5)	NE (NE, NE)	0.98	0.27, 3.51	0.9697
Recurrent	76	2 (2.6)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	4 (1.7)	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	3 (3.2)	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	5 (2.3)	NE (NE, NE)	229	4 (1.7)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	7 (2.9)	NE (NE, NE)	257	5 (1.9)	NE (NE, NE)	1.38	0.44, 4.66	0.5836
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	4 (1.7)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbi 01FEB2023:16:13 kjpc654

Table 3.4.7.35 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	4 (2.0)	NE (NE, NE)	207	4 (1.9)	NE (NE, NE)	NC	NC	NC
Female	203	3 (1.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	7 (2.8)	NE (NE, NE)	262	5 (1.9)	NE (NE, NE)	1.37	0.44, 4.64	0.5889
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	4 (1.9)	NE (NE, NE)	219	4 (1.8)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	7 (2.0)	NE (NE, NE)	330	5 (1.5)	NE (NE, NE)	1.26	0.40, 4.25	0.6966
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	3 (1.8)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbi 01FEB2023:16:13 kjpc654

Table 3.4.7.36 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hepatic encephalopathy
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbj 01FEB2023:16:13 kjpc654

Table 3.4.7.36 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hepatic encephalopathy
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbj 01FEB2023:16:13 kjpc654

Table 3.4.7.37 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hepatic cytolysis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbk 01FEB2023:16:13 kjpc654

Table 3.4.7.37 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hepatic cytolysis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbk 01FEB2023:16:13 kjpc654

Table 3.4.7.38 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbl 01FEB2023:16:13 kjpc654

Table 3.4.7.38 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hepatitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbl 01FEB2023:16:13 kjpc654

Table 3.4.7.39 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hypoalbuminaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.39 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hypoalbuminaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbm 01FEB2023:16:13 kjpc654

Table 3.4.7.40 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbn 01FEB2023:16:13 kjpc654

Table 3.4.7.40 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbn 01FEB2023:16:13 kjpc654

Table 3.4.7.41 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	3 (1.3)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbo 01FEB2023:16:13 kjpc654

Table 3.4.7.41 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbo 01FEB2023:16:13 kjpc654

Table 3.4.7.42 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Liver abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	2 (2.6)	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.42 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Liver abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	2 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbp 01FEB2023:16:13 kjpc654

Table 3.4.7.43 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hepatic function abnormal
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	3 (0.9)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	3 (1.2)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.43 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hepatic function abnormal
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbq 01FEB2023:16:13 kjpc654

Table 3.4.7.44 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Liver function test increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.44 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Liver function test increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbr 01FEB2023:16:13 kjpc654

Table 3.4.7.45 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	2 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.45 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Liver injury
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.46 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hepatic failure
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	3 (0.9)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.46 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hepatic failure
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.47 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Oesophageal varices haemorrhage
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.47 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Oesophageal varices haemorrhage
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbu 01FEB2023:16:13 kjpc654

Table 3.4.7.48 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Biliary SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	47 (14.4)	NE (NE, NE)	333	46 (13.8)	NE (NE, NE)	0.97	0.65, 1.47	0.8999
Recurrent	76	8 (10.5)	NE (NE, NE)	70	8 (11.4)	NE (NE, NE)	0.77	0.28, 2.11	0.6099
Interaction p-value									0.6714
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	16 (21.9)	NE (NE, NE)	71	16 (22.5)	NE (NE, NE)	0.79	0.39, 1.60	0.5039
Intrahepatic CCA	234	19 (8.1)	NE (NE, NE)	235	23 (9.8)	NE (NE, NE)	0.76	0.41, 1.40	0.3758
Gallbladder cancer	95	20 (21.1)	NE (NE, NE)	97	15 (15.5)	NE (NE, NE)	1.35	0.69, 2.68	0.3793
Interaction p-value									0.3993
Age Group									
<65	219	27 (12.3)	NE (NE, NE)	229	28 (12.2)	NE (NE, NE)	0.90	0.53, 1.53	0.6978
>=65	183	28 (15.3)	NE (NE, NE)	174	26 (14.9)	NE (NE, NE)	0.96	0.56, 1.65	0.8862
Interaction p-value									0.8632
Region									
Asia	241	42 (17.4)	NE (NE, NE)	257	43 (16.7)	NE (NE, NE)	0.94	0.61, 1.44	0.7751
Rest of World	161	13 (8.1)	NE (NE, NE)	146	11 (7.5)	NE (NE, NE)	1.00	0.45, 2.27	0.9923
Interaction p-value									0.8996
PD-L1 Status									
High (>=1%)	239	29 (12.1)	NE (NE, NE)	249	32 (12.9)	NE (NE, NE)	0.83	0.50, 1.37	0.4666
Low (<1%)	118	19 (16.1)	NE (NE, NE)	117	16 (13.7)	NE (NE, NE)	1.13	0.58, 2.24	0.7105
Interaction p-value									0.4605
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbv 01FEB2023:16:13 kjpc654

Table 3.4.7.48 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Biliary SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	25 (12.6)	NE (NE, NE)	207	31 (15.0)	NE (NE, NE)	0.76	0.44, 1.29	0.3091
Female	203	30 (14.8)	NE (NE, NE)	196	23 (11.7)	NE (NE, NE)	1.16	0.67, 2.02	0.5970
Interaction p-value									0.2751
Race									
Asian	248	45 (18.1)	NE (NE, NE)	262	44 (16.8)	NE (NE, NE)	0.98	0.64, 1.49	0.9201
Non-Asian	154	10 (6.5)	NE (NE, NE)	141	10 (7.1)	NE (NE, NE)	0.84	0.35, 2.06	0.7055
Interaction p-value									0.7654
WHO ECOG Status at Screening									
0	186	24 (12.9)	NE (NE, NE)	184	26 (14.1)	NE (NE, NE)	0.81	0.46, 1.42	0.4592
1	216	31 (14.4)	NE (NE, NE)	219	28 (12.8)	NE (NE, NE)	1.05	0.63, 1.77	0.8448
Interaction p-value									0.4974
Disease Extent									
Locally Advanced	55	5 (9.1)	NE (NE, NE)	73	15 (20.5)	NE (NE, NE)	0.34	0.11, 0.88	0.0257*
Metastatic	347	50 (14.4)	NE (NE, NE)	330	39 (11.8)	NE (NE, NE)	1.14	0.75, 1.75	0.5308
Interaction p-value									0.0218*
MSI Status									
MSI High	3	1 (33.3)	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	25 (15.1)	NE (NE, NE)	178	29 (16.3)	NE (NE, NE)	0.85	0.49, 1.46	0.5572
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbv 01FEB2023:16:13 kjpc654

Table 3.4.7.49 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Cholangitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	4 (1.2)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	2 (2.8)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	3 (1.4)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	3 (1.2)	NE (NE, NE)	257	4 (1.6)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbw 01FEB2023:16:13 kjpc654

Table 3.4.7.49 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Cholangitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	3 (1.4)	NE (NE, NE)	NC	NC	NC
Female	203	3 (1.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	4 (1.5)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	4 (1.2)	NE (NE, NE)	330	4 (1.2)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	3 (1.8)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbw 01FEB2023:16:13 kjpc654

Table 3.4.7.50 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Cholecystitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbx 01FEB2023:16:13 kjpc654

Table 3.4.7.50 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Cholecystitis acute
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbx 01FEB2023:16:13 kjpc654

Table 3.4.7.51 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Biliary obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	7 (2.1)	NE (NE, NE)	333	6 (1.8)	NE (NE, NE)	1.00	0.33, 3.16	0.9945
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	4 (1.7)	NE (NE, NE)	235	4 (1.7)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	0.83	0.10, 7.00	0.8553
>=65	183	5 (2.7)	NE (NE, NE)	174	5 (2.9)	NE (NE, NE)	0.82	0.23, 2.99	0.7621
Interaction p-value									0.9937
Region									
Asia	241	5 (2.1)	NE (NE, NE)	257	6 (2.3)	NE (NE, NE)	0.72	0.20, 2.44	0.5979
Rest of World	161	2 (1.2)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	1.49	0.14, 32.29	0.7389
Interaction p-value									0.5880
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	4 (1.6)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	4 (3.4)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegby 01FEB2023:16:13 kjpc654

Table 3.4.7.51 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Biliary obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	4 (1.9)	NE (NE, NE)	NC	NC	NC
Female	203	5 (2.5)	NE (NE, NE)	196	3 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	5 (2.0)	NE (NE, NE)	262	6 (2.3)	NE (NE, NE)	0.72	0.20, 2.42	0.5857
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	1.51	0.14, 32.67	0.7311
Interaction p-value									0.5758
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	4 (2.2)	NE (NE, NE)	NC	NC	NC
1	216	5 (2.3)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	2 (2.7)	NE (NE, NE)	0.46	0.02, 4.92	0.5211
Metastatic	347	6 (1.7)	NE (NE, NE)	330	5 (1.5)	NE (NE, NE)	0.96	0.28, 3.37	0.9453
Interaction p-value									0.5882
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegby 01FEB2023:16:13 kjpc654

Table 3.4.7.52 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Biliary abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.52 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Biliary abscess
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegbz 01FEB2023:16:13 kjpc654

Table 3.4.7.53 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Biliary sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	3 (0.9)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	3 (1.9)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	3 (1.3)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.53 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Biliary sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	3 (1.2)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	2 (1.1)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	2 (3.6)	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	2 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegca 01FEB2023:16:13 kjpc654

Table 3.4.7.54 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	3 (1.3)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcb 01FEB2023:16:13 kjpc654

Table 3.4.7.54 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Blood bilirubin increased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	3 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	4 (1.8)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	2 (2.7)	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	2 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcb 01FEB2023:16:13 kjpc654

Table 3.4.7.55 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Cholangitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	21 (6.4)	NE (NE, NE)	333	12 (3.6)	NE (NE, NE)	1.68	0.84, 3.53	0.1454
Recurrent	76	5 (6.6)	NE (NE, NE)	70	5 (7.1)	NE (NE, NE)	0.80	0.22, 2.87	0.7186
Interaction p-value									0.3069
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	9 (12.3)	NE (NE, NE)	71	9 (12.7)	NE (NE, NE)	0.80	0.31, 2.07	0.6423
Intrahepatic CCA	234	7 (3.0)	NE (NE, NE)	235	3 (1.3)	NE (NE, NE)	2.19	0.61, 10.17	0.2368
Gallbladder cancer	95	10 (10.5)	NE (NE, NE)	97	5 (5.2)	NE (NE, NE)	1.97	0.70, 6.34	0.2013
Interaction p-value									0.3304
Age Group									
<65	219	13 (5.9)	NE (NE, NE)	229	6 (2.6)	NE (NE, NE)	2.05	0.81, 5.85	0.1326
>=65	183	13 (7.1)	NE (NE, NE)	174	11 (6.3)	NE (NE, NE)	1.06	0.47, 2.41	0.8934
Interaction p-value									0.2960
Region									
Asia	241	19 (7.9)	NE (NE, NE)	257	16 (6.2)	NE (NE, NE)	1.15	0.59, 2.26	0.6890
Rest of World	161	7 (4.3)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	5.98	1.06,111.75	0.0414*
Interaction p-value									0.0878
PD-L1 Status									
High (>=1%)	239	14 (5.9)	NE (NE, NE)	249	12 (4.8)	NE (NE, NE)	1.08	0.50, 2.38	0.8499
Low (<1%)	118	8 (6.8)	NE (NE, NE)	117	4 (3.4)	NE (NE, NE)	1.86	0.59, 6.97	0.2985
Interaction p-value									0.4485
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcc 01FEB2023:16:13 kjpc654

Table 3.4.7.55 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Cholangitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	12 (6.0)	NE (NE, NE)	207	13 (6.3)	NE (NE, NE)	0.89	0.40, 1.97	0.7712
Female	203	14 (6.9)	NE (NE, NE)	196	4 (2.0)	NE (NE, NE)	3.09	1.11, 10.92	0.0303*
Interaction p-value									0.0614
Race									
Asian	248	20 (8.1)	NE (NE, NE)	262	16 (6.1)	NE (NE, NE)	1.20	0.62, 2.35	0.5957
Non-Asian	154	6 (3.9)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	5.17	0.88, 97.71	0.0711
Interaction p-value									0.1419
WHO ECOG Status at Screening									
0	186	13 (7.0)	NE (NE, NE)	184	11 (6.0)	NE (NE, NE)	1.05	0.47, 2.39	0.9108
1	216	13 (6.0)	NE (NE, NE)	219	6 (2.7)	NE (NE, NE)	2.08	0.82, 5.94	0.1239
Interaction p-value									0.2781
Disease Extent									
Locally Advanced	55	2 (3.6)	NE (NE, NE)	73	4 (5.5)	NE (NE, NE)	0.52	0.07, 2.66	0.4336
Metastatic	347	24 (6.9)	NE (NE, NE)	330	13 (3.9)	NE (NE, NE)	1.66	0.86, 3.36	0.1344
Interaction p-value									0.1962
MSI Status									
MSI High	3	1 (33.3)	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	15 (9.0)	NE (NE, NE)	178	13 (7.3)	NE (NE, NE)	1.19	0.56, 2.54	0.6476
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcc 01FEB2023:16:13 kjpc654

Table 3.4.7.56 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Cholangitis infective
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcd 01FEB2023:16:13 kjpc654

Table 3.4.7.56 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Cholangitis infective
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcd 01FEB2023:16:13 kjpc654

Table 3.4.7.57 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.57 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Cholestasis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.58 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Cholecystitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	5 (1.5)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	3 (1.3)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.58 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Cholecystitis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	3 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	3 (4.1)	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	2 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.59 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Gallbladder empyema
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.59 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Gallbladder empyema
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcg 01FEB2023:16:13 kjpc654

Table 3.4.7.60 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Gallbladder obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegch 01FEB2023:16:13 kjpc654

Table 3.4.7.60 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Gallbladder obstruction
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegch 01FEB2023:16:13 kjpc654

Table 3.4.7.61 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Biliary tract infection
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	6 (1.8)	NE (NE, NE)	333	9 (2.7)	NE (NE, NE)	0.64	0.21, 1.77	0.3905
Recurrent	76	2 (2.6)	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	1.60	0.15, 34.57	0.6935
Interaction p-value									0.4775
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	2 (2.8)	NE (NE, NE)	0.82	0.10, 6.89	0.8436
Intrahepatic CCA	234	5 (2.1)	NE (NE, NE)	235	7 (3.0)	NE (NE, NE)	0.67	0.20, 2.12	0.4973
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	0.96	0.04, 24.23	0.9762
Interaction p-value									0.9659
Age Group									
<65	219	3 (1.4)	NE (NE, NE)	229	7 (3.1)	NE (NE, NE)	0.40	0.09, 1.46	0.1712
>=65	183	5 (2.7)	NE (NE, NE)	174	3 (1.7)	NE (NE, NE)	1.49	0.37, 7.29	0.5780
Interaction p-value									0.1820
Region									
Asia	241	8 (3.3)	NE (NE, NE)	257	9 (3.5)	NE (NE, NE)	0.85	0.32, 2.24	0.7403
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	4 (1.7)	NE (NE, NE)	249	6 (2.4)	NE (NE, NE)	0.62	0.16, 2.19	0.4580
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	3 (2.6)	NE (NE, NE)	0.93	0.17, 5.05	0.9319
Interaction p-value									0.6964
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegci 01FEB2023:16:13 kjpc654

Table 3.4.7.61 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Biliary tract infection
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	6 (2.9)	NE (NE, NE)	NC	NC	NC
Female	203	5 (2.5)	NE (NE, NE)	196	4 (2.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	8 (3.2)	NE (NE, NE)	262	9 (3.4)	NE (NE, NE)	0.84	0.31, 2.22	0.7286
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	4 (2.2)	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	1.82	0.35, 13.14	0.4784
1	216	4 (1.9)	NE (NE, NE)	219	8 (3.7)	NE (NE, NE)	0.46	0.12, 1.48	0.1971
Interaction p-value									0.1839
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	4 (5.5)	NE (NE, NE)	NC	NC	NC
Metastatic	347	8 (2.3)	NE (NE, NE)	330	6 (1.8)	NE (NE, NE)	1.16	0.40, 3.53	0.7855
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.62 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	5 (1.5)	NE (NE, NE)	333	5 (1.5)	NE (NE, NE)	0.98	0.27, 3.51	0.9697
Recurrent	76	2 (2.6)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	4 (1.7)	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	3 (3.2)	NE (NE, NE)	97	3 (3.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	5 (2.3)	NE (NE, NE)	229	4 (1.7)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	7 (2.9)	NE (NE, NE)	257	5 (1.9)	NE (NE, NE)	1.38	0.44, 4.66	0.5836
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	4 (1.7)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	3 (2.5)	NE (NE, NE)	117	2 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.62 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Jaundice cholestatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	4 (2.0)	NE (NE, NE)	207	4 (1.9)	NE (NE, NE)	NC	NC	NC
Female	203	3 (1.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	7 (2.8)	NE (NE, NE)	262	5 (1.9)	NE (NE, NE)	1.37	0.44, 4.64	0.5889
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	4 (1.9)	NE (NE, NE)	219	4 (1.8)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	7 (2.0)	NE (NE, NE)	330	5 (1.5)	NE (NE, NE)	1.26	0.40, 4.25	0.6966
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	3 (1.8)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.63 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.63 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Hyperbilirubinaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegck 01FEB2023:16:13 kjpc654

Table 3.4.7.64 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	3 (1.3)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	2 (0.8)	NE (NE, NE)	257	2 (0.8)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.64 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Jaundice
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	2 (0.8)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcl 01FEB2023:16:13 kjpc654

Table 3.4.7.65 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Gallbladder rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcm 01FEB2023:16:13 kjpc654

Table 3.4.7.65 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Gallbladder rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcm 01FEB2023:16:13 kjpc654

Table 3.4.7.66 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Biloma rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.66 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Biloma rupture
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcn 01FEB2023:16:13 kjpc654

Table 3.4.7.67 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Haematopoietic cytopenias SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	28 (8.6)	NE (NE, NE)	333	25 (7.5)	NE (NE, NE)	1.16	0.68, 2.01	0.5832
Recurrent	76	6 (7.9)	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	5.57	0.95,105.24	0.0577
Interaction p-value									0.1050
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	5 (6.8)	NE (NE, NE)	71	3 (4.2)	NE (NE, NE)	1.66	0.41, 8.11	0.4789
Intrahepatic CCA	234	18 (7.7)	NE (NE, NE)	235	16 (6.8)	NE (NE, NE)	1.14	0.58, 2.27	0.6967
Gallbladder cancer	95	11 (11.6)	NE (NE, NE)	97	7 (7.2)	NE (NE, NE)	1.62	0.64, 4.40	0.3135
Interaction p-value									0.7966
Age Group									
<65	219	18 (8.2)	NE (NE, NE)	229	13 (5.7)	NE (NE, NE)	1.47	0.72, 3.06	0.2903
>=65	183	16 (8.7)	NE (NE, NE)	174	13 (7.5)	NE (NE, NE)	1.19	0.57, 2.51	0.6462
Interaction p-value									0.6855
Region									
Asia	241	17 (7.1)	NE (NE, NE)	257	14 (5.4)	NE (NE, NE)	1.30	0.64, 2.69	0.4612
Rest of World	161	17 (10.6)	NE (NE, NE)	146	12 (8.2)	NE (NE, NE)	1.31	0.63, 2.82	0.4652
Interaction p-value									0.9871
PD-L1 Status									
High (>=1%)	239	23 (9.6)	NE (NE, NE)	249	14 (5.6)	NE (NE, NE)	1.72	0.89, 3.42	0.1052
Low (<1%)	118	11 (9.3)	NE (NE, NE)	117	10 (8.5)	NE (NE, NE)	1.13	0.48, 2.72	0.7734
Interaction p-value									0.4534
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.67 TOPAZ: Summary of subgroup analysis of time to first SAESI GT: Haematopoietic cytopenias SMQ AEs
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	12 (6.0)	NE (NE, NE)	207	15 (7.2)	NE (NE, NE)	0.83	0.38, 1.77	0.6338
Female	203	22 (10.8)	NE (NE, NE)	196	11 (5.6)	NE (NE, NE)	1.98	0.98, 4.25	0.0561
Interaction p-value									0.1004
Race									
Asian	248	19 (7.7)	NE (NE, NE)	262	15 (5.7)	NE (NE, NE)	1.35	0.69, 2.70	0.3804
Non-Asian	154	15 (9.7)	NE (NE, NE)	141	11 (7.8)	NE (NE, NE)	1.27	0.59, 2.84	0.5441
Interaction p-value									0.9061
WHO ECOG Status at Screening									
0	186	19 (10.2)	NE (NE, NE)	184	13 (7.1)	NE (NE, NE)	1.46	0.73, 3.03	0.2879
1	216	15 (6.9)	NE (NE, NE)	219	13 (5.9)	NE (NE, NE)	1.19	0.56, 2.54	0.6476
Interaction p-value									0.6930
Disease Extent									
Locally Advanced	55	5 (9.1)	NE (NE, NE)	73	5 (6.8)	NE (NE, NE)	1.31	0.36, 4.71	0.6705
Metastatic	347	29 (8.4)	NE (NE, NE)	330	21 (6.4)	NE (NE, NE)	1.33	0.76, 2.36	0.3139
Interaction p-value									0.9800
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	17 (10.2)	NE (NE, NE)	178	9 (5.1)	NE (NE, NE)	2.11	0.96, 4.96	0.0623
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.68 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Anaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	13 (4.0)	NE (NE, NE)	333	5 (1.5)	NE (NE, NE)	2.72	1.02, 8.47	0.0443*
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	2 (2.7)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	7 (3.0)	NE (NE, NE)	235	5 (2.1)	NE (NE, NE)	1.43	0.46, 4.84	0.5363
Gallbladder cancer	95	5 (5.3)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	9 (4.1)	NE (NE, NE)	229	3 (1.3)	NE (NE, NE)	3.17	0.95, 14.30	0.0619
>=65	183	5 (2.7)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	2.43	0.52, 16.95	0.2650
Interaction p-value									0.8034
Region									
Asia	241	4 (1.7)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	4.29	0.63, 83.87	0.1432
Rest of World	161	10 (6.2)	NE (NE, NE)	146	4 (2.7)	NE (NE, NE)	2.34	0.78, 8.53	0.1317
Interaction p-value									0.6208
PD-L1 Status									
High (>=1%)	239	8 (3.3)	NE (NE, NE)	249	3 (1.2)	NE (NE, NE)	2.77	0.80, 12.65	0.1100
Low (<1%)	118	6 (5.1)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	6.24	1.07,117.85	0.0414*
Interaction p-value									0.5082
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcp 01FEB2023:16:13 kjpc654

Table 3.4.7.68 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Anaemia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	14 (6.9)	NE (NE, NE)	196	4 (2.0)	NE (NE, NE)	3.46	1.24, 12.19	0.0164*
Interaction p-value									NC
Race									
Asian	248	4 (1.6)	NE (NE, NE)	262	2 (0.8)	NE (NE, NE)	2.13	0.42, 15.34	0.3686
Non-Asian	154	10 (6.5)	NE (NE, NE)	141	3 (2.1)	NE (NE, NE)	3.15	0.96, 14.04	0.0582
Interaction p-value									0.7199
WHO ECOG Status at Screening									
0	186	9 (4.8)	NE (NE, NE)	184	4 (2.2)	NE (NE, NE)	2.24	0.73, 8.26	0.1627
1	216	5 (2.3)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	5.20	0.84, 99.53	0.0798
Interaction p-value									0.4806
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	1.31	0.05, 33.18	0.8474
Metastatic	347	13 (3.7)	NE (NE, NE)	330	4 (1.2)	NE (NE, NE)	3.14	1.11, 11.17	0.0297*
Interaction p-value									0.5704
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	9 (5.4)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	4.93	1.27, 32.36	0.0192*
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcp 01FEB2023:16:13 kjpc654

Table 3.4.7.69 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Bicytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	0	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	0	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.69 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Bicytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	0	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcq 01FEB2023:16:13 kjpc654

Table 3.4.7.70 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Febrile neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	4 (1.2)	NE (NE, NE)	333	5 (1.5)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	3 (1.3)	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	2 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	4 (1.7)	NE (NE, NE)	257	4 (1.6)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	3 (2.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcr 01FEB2023:16:13 kjpc654

Table 3.4.7.70 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Febrile neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	3 (1.5)	NE (NE, NE)	207	4 (1.9)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	4 (1.6)	NE (NE, NE)	262	4 (1.5)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	3 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	4 (1.2)	NE (NE, NE)	330	4 (1.2)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	3 (1.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcr 01FEB2023:16:13 kjpc654

Table 3.4.7.71 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: White blood cell count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcs 01FEB2023:16:13 kjpc654

Table 3.4.7.71 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: White blood cell count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	0	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcs 01FEB2023:16:13 kjpc654

Table 3.4.7.72 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Myelosuppression
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	4 (1.2)	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	1 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	4 (1.7)	NE (NE, NE)	235	2 (0.9)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	3 (1.6)	NE (NE, NE)	174	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	4 (1.7)	NE (NE, NE)	257	3 (1.2)	NE (NE, NE)	NC	NC	NC
Rest of World	161	0	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	3 (1.3)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	1 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.72 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Myelosuppression
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	3 (1.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	4 (1.6)	NE (NE, NE)	262	3 (1.1)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	4 (1.9)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	2 (3.6)	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	2 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegct 01FEB2023:16:13 kjpc654

Table 3.4.7.73 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	3 (0.9)	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	2 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	2 (0.9)	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	1 (0.8)	NE (NE, NE)	117	3 (2.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.73 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Neutropenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	0	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	2 (1.0)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	2 (1.4)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	1 (0.5)	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	3 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcu 01FEB2023:16:13 kjpc654

Table 3.4.7.74 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Neutropenic sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	0	NE (NE, NE)	333	0	NE (NE, NE)	NC	NC	NC
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	0	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	0	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	0	NE (NE, NE)	NC	NC	NC
>=65	183	0	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	0	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	0	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcv 01FEB2023:16:13 kjpc654

Table 3.4.7.74 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Neutropenic sepsis
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	0	NE (NE, NE)	NC	NC	NC
Female	203	0	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	0	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	1 (0.3)	NE (NE, NE)	330	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	0	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcv 01FEB2023:16:13 kjpc654

Table 3.4.7.75 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Neutrophil count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	2 (0.6)	NE (NE, NE)	NC	NC	NC
Recurrent	76	2 (2.6)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	0	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	3 (3.2)	NE (NE, NE)	97	1 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	3 (1.3)	NE (NE, NE)	249	2 (0.8)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.75 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Neutrophil count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	2 (1.1)	NE (NE, NE)	NC	NC	NC
1	216	0	NE (NE, NE)	219	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	1 (1.4)	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	2 (1.2)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
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Table 3.4.7.76 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Pancytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	2 (0.6)	NE (NE, NE)	333	1 (0.3)	NE (NE, NE)	NC	NC	NC
Recurrent	76	0	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	0	NE (NE, NE)	71	0	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	1 (0.4)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	1 (0.5)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	0	NE (NE, NE)	NC	NC	NC
Rest of World	161	1 (0.6)	NE (NE, NE)	146	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	2 (0.8)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	0	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.76 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Pancytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	1 (0.5)	NE (NE, NE)	207	1 (0.5)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	0	NE (NE, NE)	NC	NC	NC
Non-Asian	154	1 (0.6)	NE (NE, NE)	141	1 (0.7)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	0	NE (NE, NE)	NC	NC	NC
1	216	1 (0.5)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	0	NE (NE, NE)	NC	NC	NC
Metastatic	347	2 (0.6)	NE (NE, NE)	330	1 (0.3)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcx 01FEB2023:16:13 kjpc654

Table 3.4.7.77 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Platelet count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	4 (1.2)	NE (NE, NE)	333	6 (1.8)	NE (NE, NE)	0.68	0.17, 2.39	0.5497
Recurrent	76	1 (1.3)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	2 (0.9)	NE (NE, NE)	235	3 (1.3)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	2 (2.1)	NE (NE, NE)	97	2 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	3 (1.4)	NE (NE, NE)	229	1 (0.4)	NE (NE, NE)	NC	NC	NC
>=65	183	2 (1.1)	NE (NE, NE)	174	5 (2.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	4 (1.7)	NE (NE, NE)	257	6 (2.3)	NE (NE, NE)	0.70	0.18, 2.47	0.5837
Rest of World	161	1 (0.6)	NE (NE, NE)	146	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	3 (1.3)	NE (NE, NE)	249	6 (2.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.

Table 3.4.7.77 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Platelet count decreased
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	3 (1.4)	NE (NE, NE)	NC	NC	NC
Female	203	3 (1.5)	NE (NE, NE)	196	3 (1.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	5 (2.0)	NE (NE, NE)	262	6 (2.3)	NE (NE, NE)	0.87	0.25, 2.90	0.8243
Non-Asian	154	0	NE (NE, NE)	141	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	3 (1.6)	NE (NE, NE)	184	4 (2.2)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	2 (0.9)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	1 (1.8)	NE (NE, NE)	73	2 (2.7)	NE (NE, NE)	NC	NC	NC
Metastatic	347	4 (1.2)	NE (NE, NE)	330	4 (1.2)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	3 (1.8)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcy 01FEB2023:16:13 kjpc654

Table 3.4.7.78 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Thrombocytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Disease Status [eCRF]									
Initially unresectable	326	1 (0.3)	NE (NE, NE)	333	4 (1.2)	NE (NE, NE)	NC	NC	NC
Recurrent	76	2 (2.6)	NE (NE, NE)	70	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Primary Tumor Location [eCRF]									
Extrahepatic CCA	73	1 (1.4)	NE (NE, NE)	71	1 (1.4)	NE (NE, NE)	NC	NC	NC
Intrahepatic CCA	234	1 (0.4)	NE (NE, NE)	235	3 (1.3)	NE (NE, NE)	NC	NC	NC
Gallbladder cancer	95	1 (1.1)	NE (NE, NE)	97	0	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Age Group									
<65	219	2 (0.9)	NE (NE, NE)	229	3 (1.3)	NE (NE, NE)	NC	NC	NC
>=65	183	1 (0.5)	NE (NE, NE)	174	1 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Region									
Asia	241	1 (0.4)	NE (NE, NE)	257	1 (0.4)	NE (NE, NE)	NC	NC	NC
Rest of World	161	2 (1.2)	NE (NE, NE)	146	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
PD-L1 Status									
High (>=1%)	239	1 (0.4)	NE (NE, NE)	249	1 (0.4)	NE (NE, NE)	NC	NC	NC
Low (<1%)	118	2 (1.7)	NE (NE, NE)	117	3 (2.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Sex									

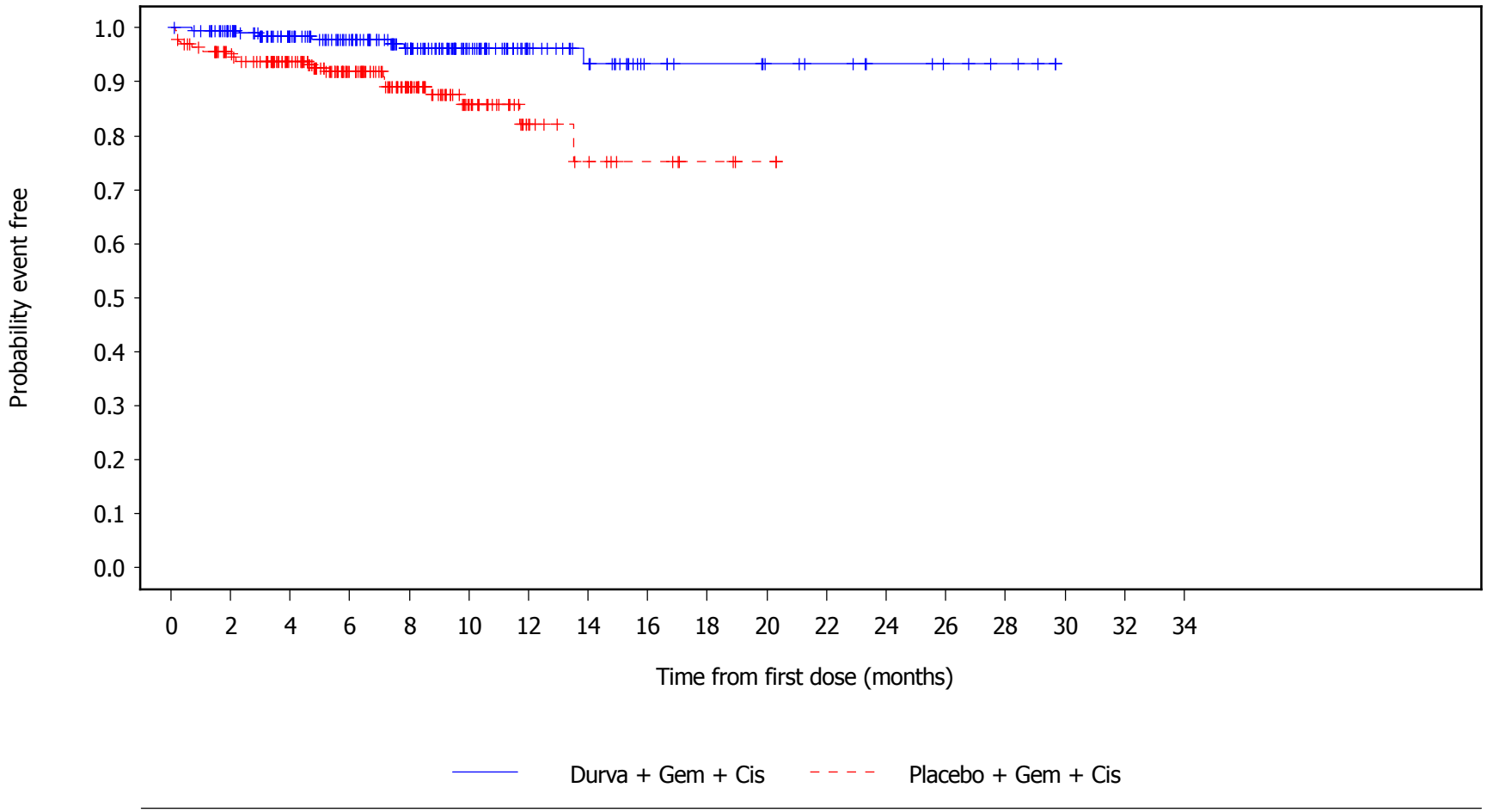
Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcz 01FEB2023:16:13 kjpc654

Table 3.4.7.78 TOPAZ: Summary of subgroup analysis of time to first SAESI PT: Thrombocytopenia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)			Placebo + Gem + Cis (N=403)					
Subgroup	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	n	Number (%) of patients with events	Median time (95% CI) (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Male	199	2 (1.0)	NE (NE, NE)	207	2 (1.0)	NE (NE, NE)	NC	NC	NC
Female	203	1 (0.5)	NE (NE, NE)	196	2 (1.0)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Race									
Asian	248	1 (0.4)	NE (NE, NE)	262	1 (0.4)	NE (NE, NE)	NC	NC	NC
Non-Asian	154	2 (1.3)	NE (NE, NE)	141	3 (2.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
WHO ECOG Status at Screening									
0	186	1 (0.5)	NE (NE, NE)	184	3 (1.6)	NE (NE, NE)	NC	NC	NC
1	216	2 (0.9)	NE (NE, NE)	219	1 (0.5)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
Disease Extent									
Locally Advanced	55	0	NE (NE, NE)	73	2 (2.7)	NE (NE, NE)	NC	NC	NC
Metastatic	347	3 (0.9)	NE (NE, NE)	330	2 (0.6)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC
MSI Status									
MSI High	3	0	NE (NE, NE)	2	0	NE (NE, NE)	NC	NC	NC
MSI Stable	166	1 (0.6)	NE (NE, NE)	178	2 (1.1)	NE (NE, NE)	NC	NC	NC
Interaction p-value									NC

Time to first AE or censoring if AE has not occurred by 30 days after last dose of durvalumab/placebo. Includes AEs with an onset date >=first dose plus <first dose which worsen after dosing, and <= 90 days after last dose or up to first subsequent therapy (whichever comes first). [a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached. [b] HR, 95% profile likelihood CIs and likelihood-ratio test p-values estimated from Cox PH model. Efron method for handling ties. If >=10 patients for all subgroup levels, >=10 events for 1 subgroup level, >0 events for all subgroup levels/ treatments, results from model including treatment, subgroup, treatment by subgroup interaction. For subgroups with >2 levels, levels with insufficient data were dropped and, if appropriate, interaction model re-fitted. If interaction model conditions not met but 1 level had >=10 events, and >0 events for both treatments, results from model for 1 level including treatment only.
* Interaction p-value <0.05. HR <1 favours durvalumab. NC = not calculable. MedDRA version 24.0.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/ttesubae.sas ettesubaegcz 01FEB2023:16:13 kjpc654

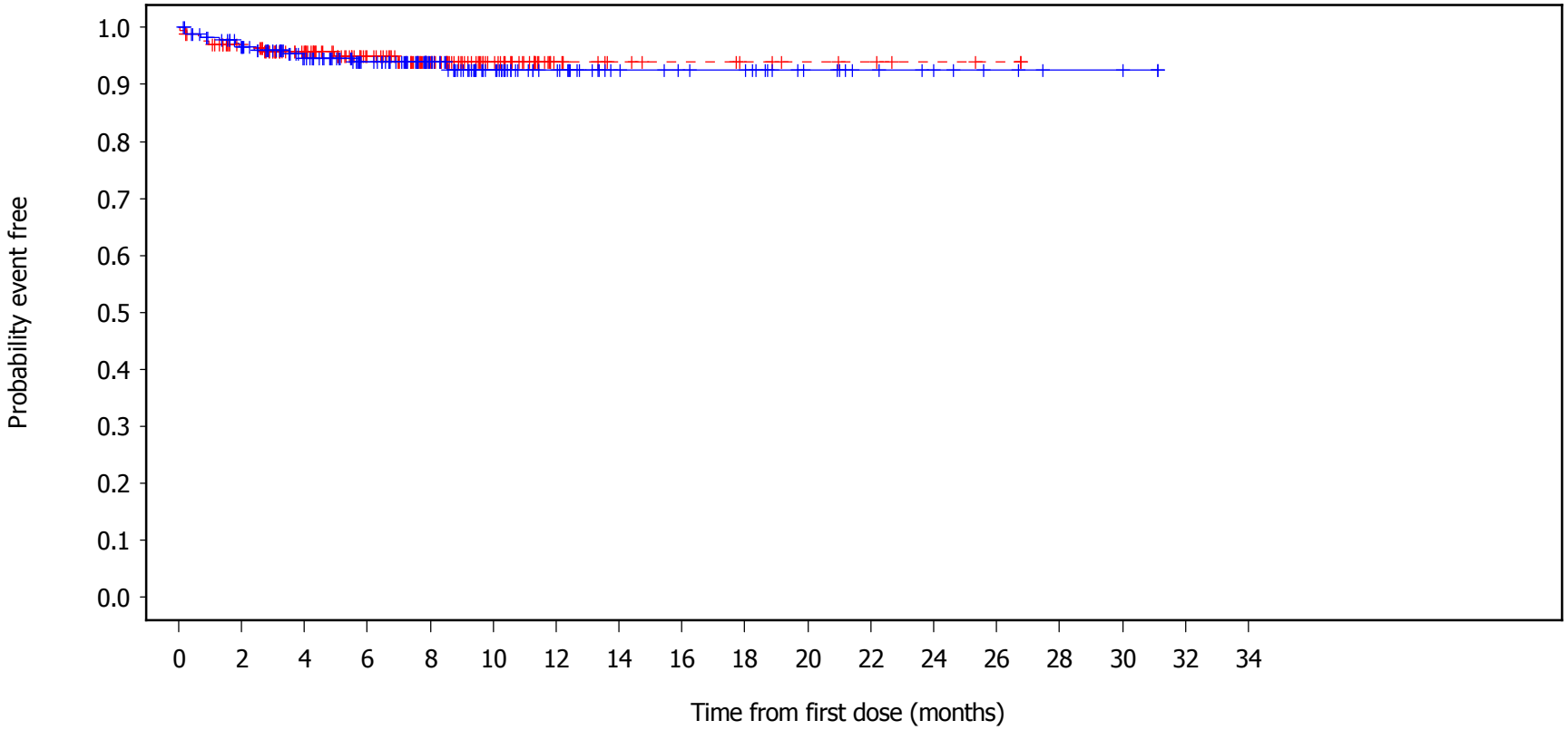
Figure 3.5.1.1 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of PT: Blood bilirubin increased for Age Group=<65
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

219	203	170	144	110	71	41	31	18	15	12	10	7	5	3	0	0	0	Durva + Gem + Cis
229	201	169	121	79	42	16	10	6	3	1	0	0	0	0	0	0	0	Placebo + Gem + Cis

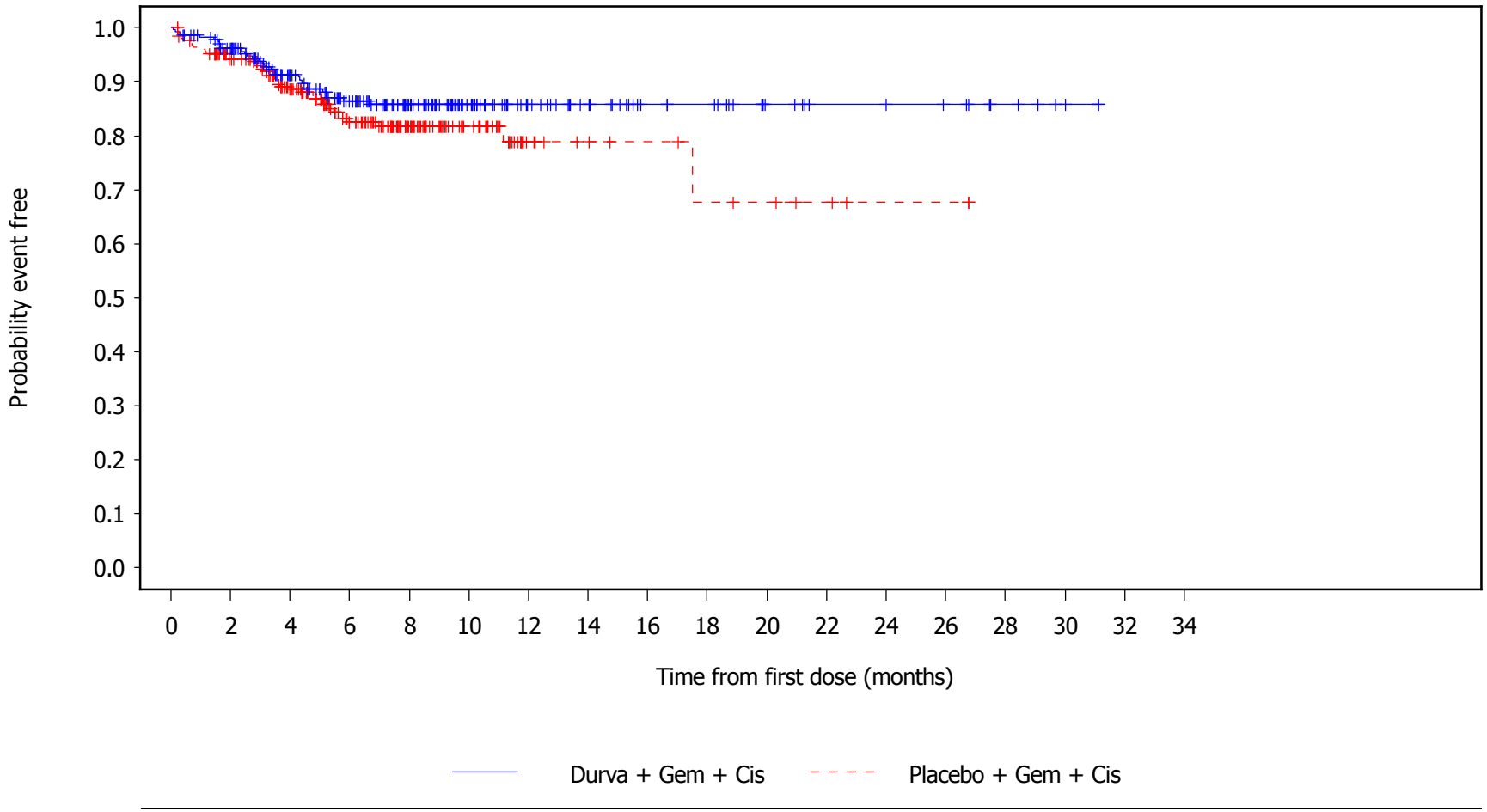
Figure 3.5.1.2 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of PT: Blood bilirubin increased for Age Group=>=65
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

183	165	137	114	83	54	38	25	22	21	13	9	7	4	2	2	0	0	Durva + Gem + Cis
174	157	131	100	71	41	16	11	9	7	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

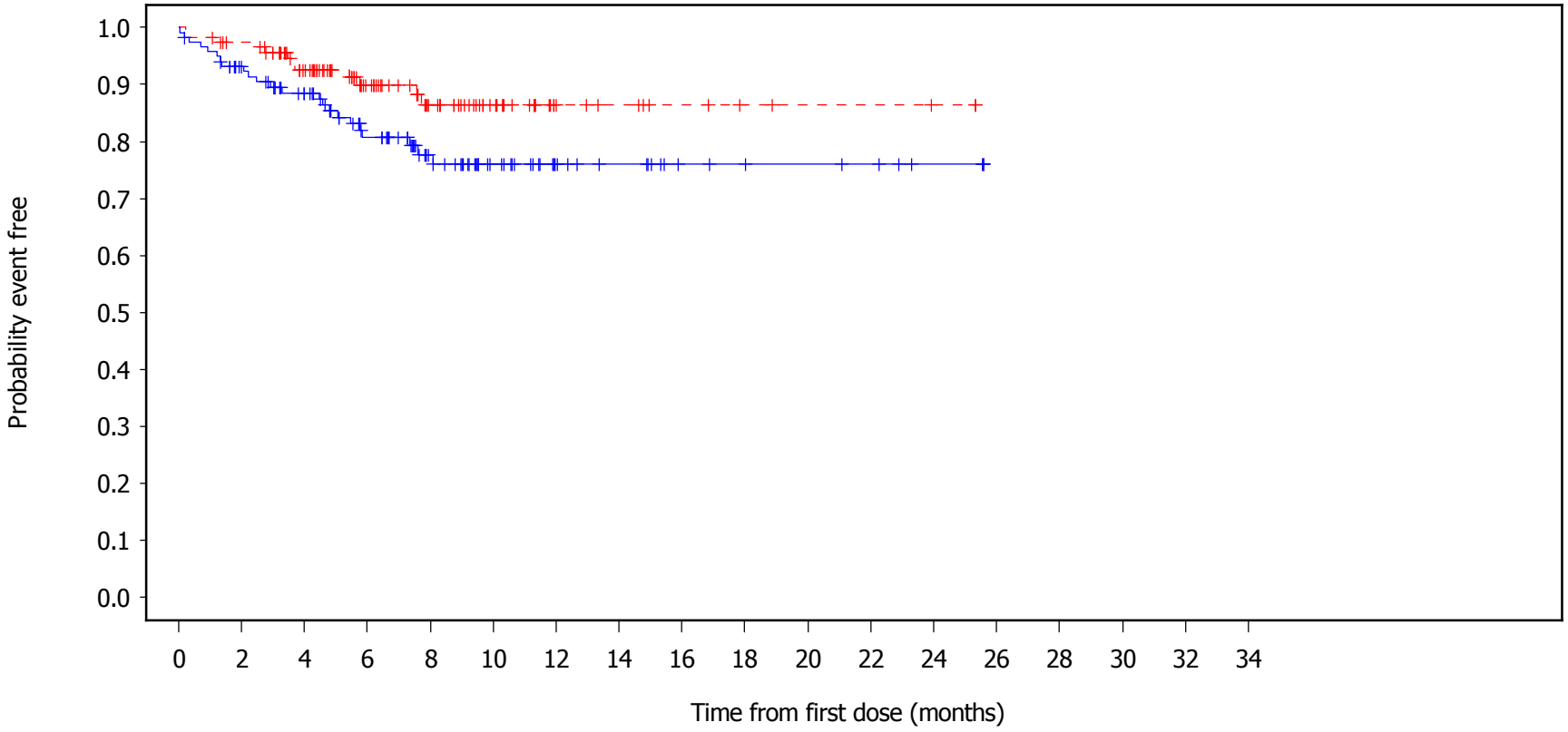
Figure 3.5.3.1 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AE leading to discontinuation of treatment for PD-L1 Status=High (>=1%)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

239	218	176	144	107	71	45	36	26	24	15	11	11	9	5	2	0	0	Durva + Gem + Cis
249	216	174	122	79	44	14	10	8	6	5	3	1	1	0	0	0	0	Placebo + Gem + Cis

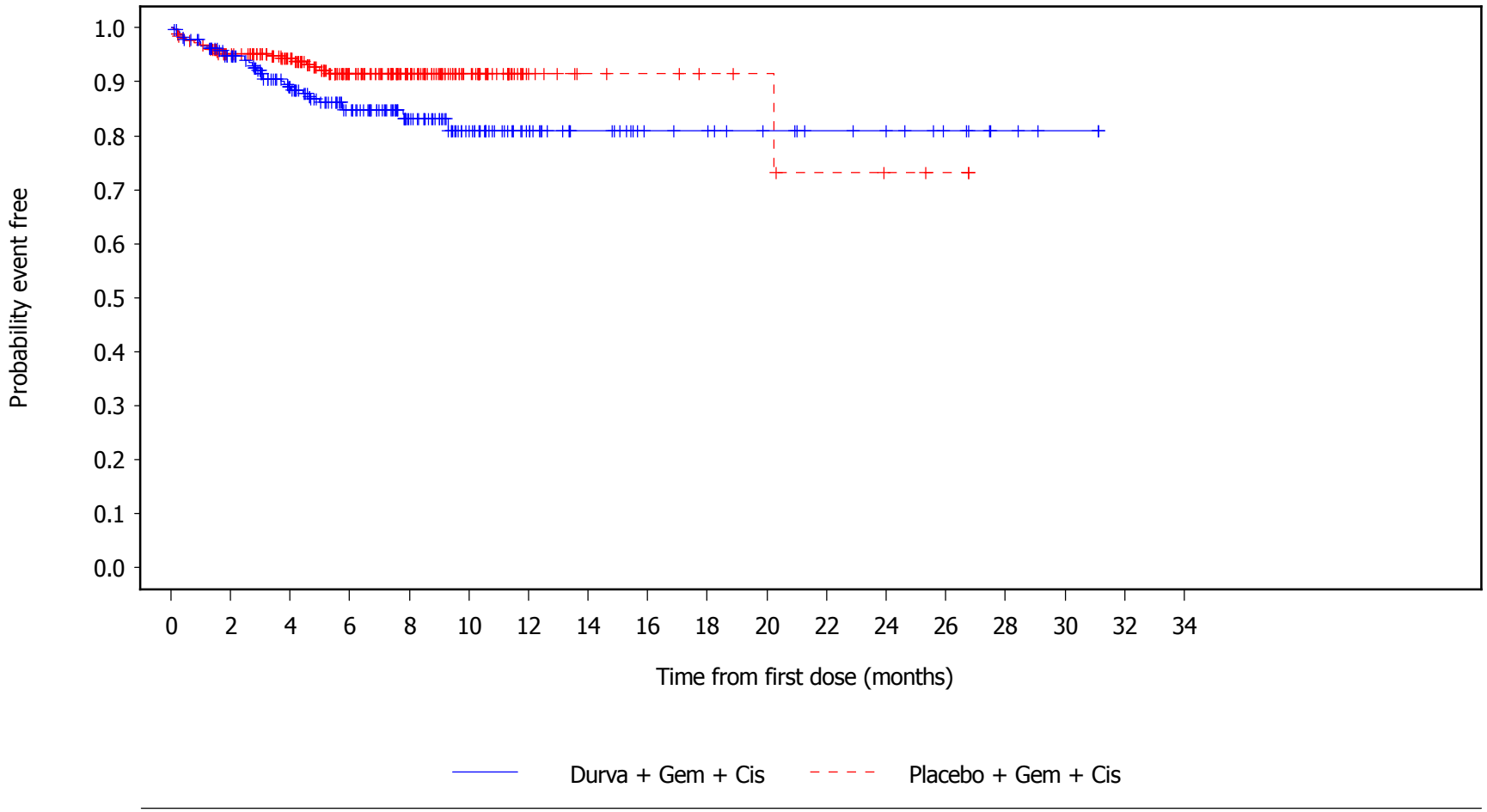
Figure 3.5.3.2 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AE leading to discontinuation of treatment for PD-L1 Status=Low (<1%)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

118	103	87	67	46	30	18	14	8	7	6	5	2	0	0	0	0	0	Durva + Gem + Cis
117	110	88	61	43	27	10	8	5	3	2	2	1	0	0	0	0	0	Placebo + Gem + Cis

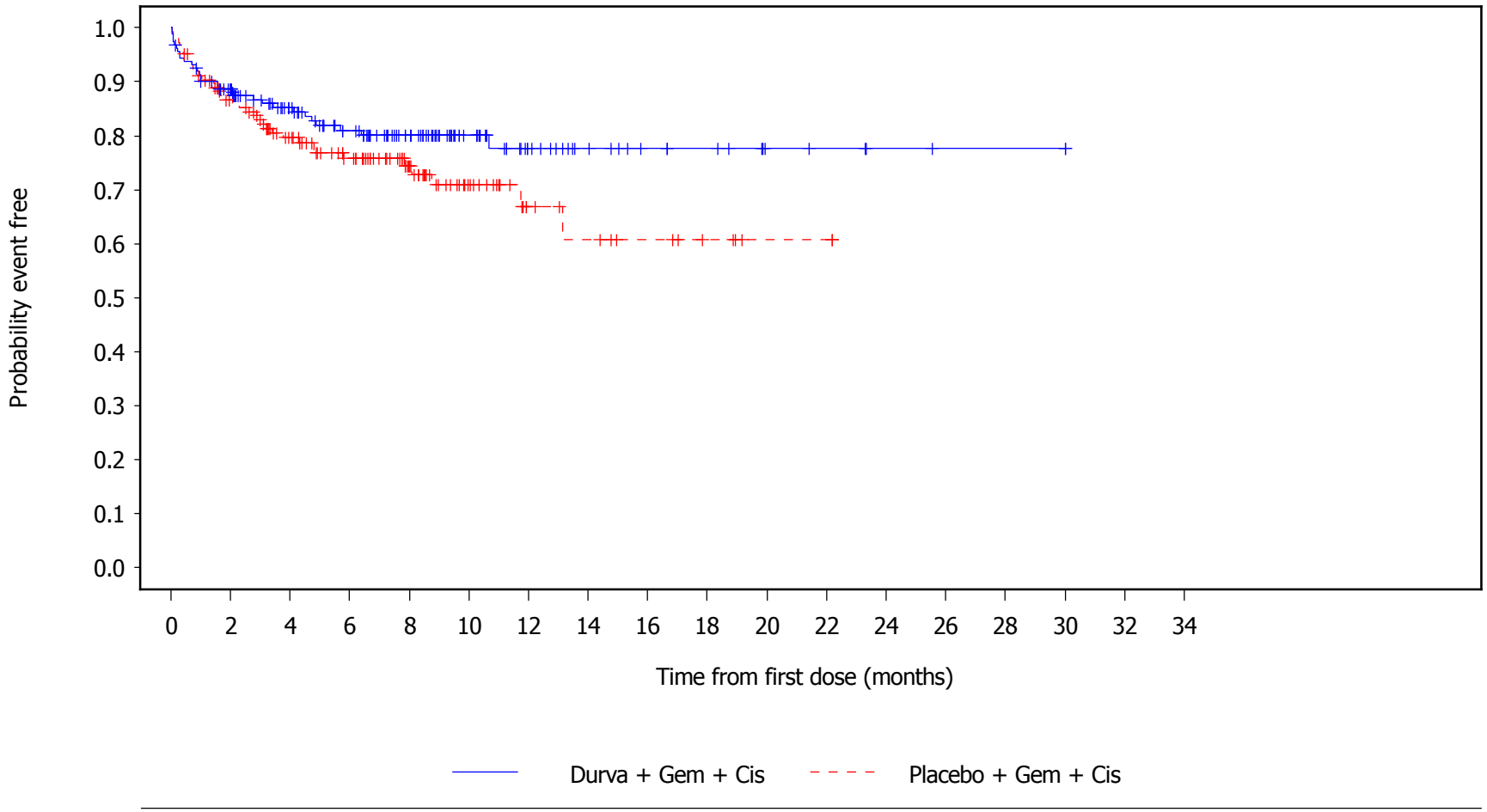
Figure 3.5.5.1 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI GT: Diarrhoea/Colitis for Region=Asia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

241	210	165	130	91	62	39	28	20	19	15	12	11	7	3	1	0	0	Durva + Gem + Cis
257	224	187	128	88	50	14	9	8	6	5	3	2	1	0	0	0	0	Placebo + Gem + Cis

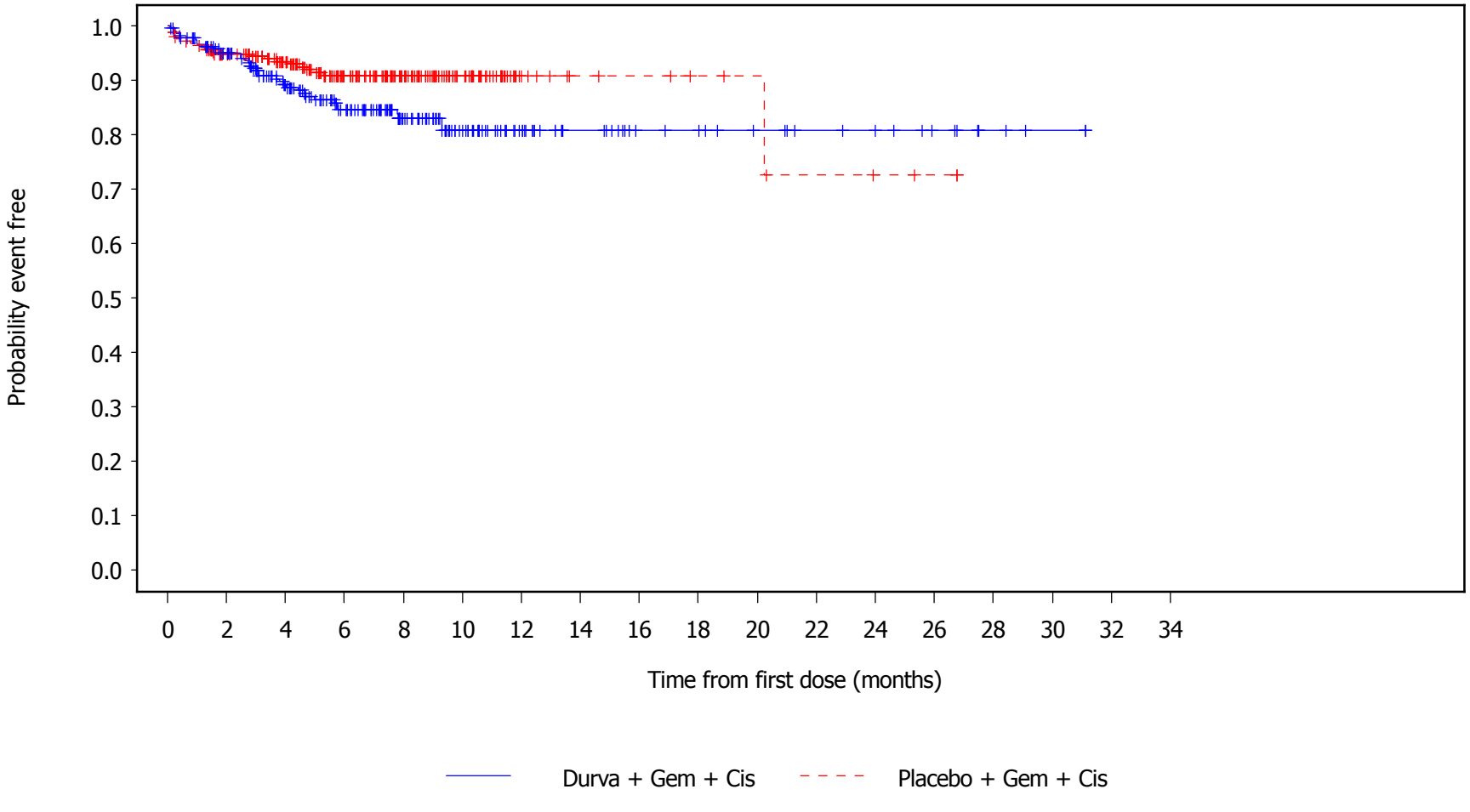
Figure 3.5.5.2 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI GT: Diarrhoea/Colitis for Region=Rest of World
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

161	135	108	89	68	42	25	17	12	10	5	4	2	1	1	1	0	0	Durva + Gem + Cis
146	116	92	73	48	27	13	10	7	4	1	1	0	0	0	0	0	0	Placebo + Gem + Cis

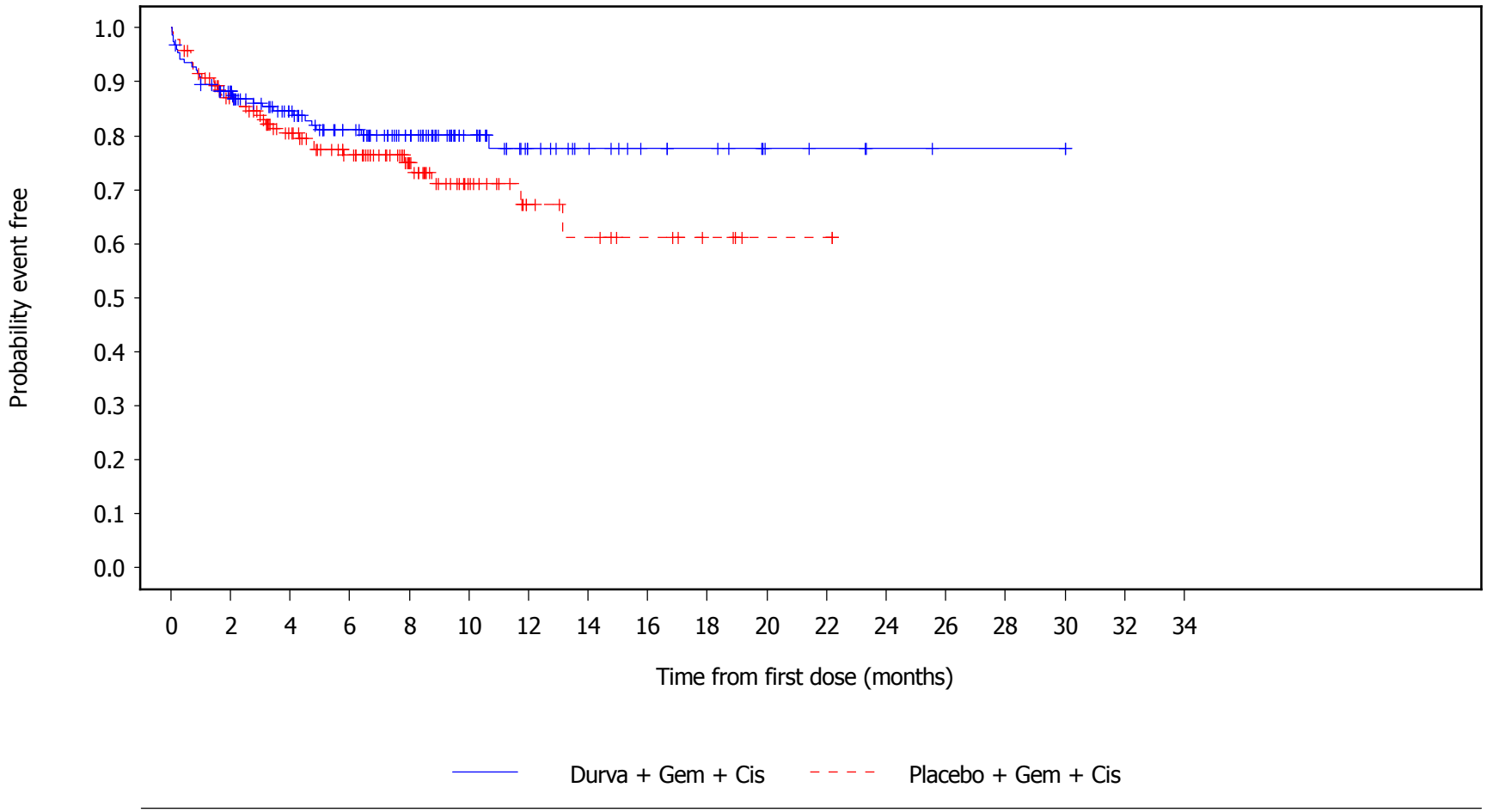
Figure 3.5.5.3 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI GT: Diarrhoea/Colitis for Race=Asian
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

248	216	170	134	94	64	41	28	20	19	15	12	11	7	3	1	0	0	Durva + Gem + Cis
262	228	190	130	90	52	14	9	8	6	5	3	2	1	0	0	0	0	Placebo + Gem + Cis

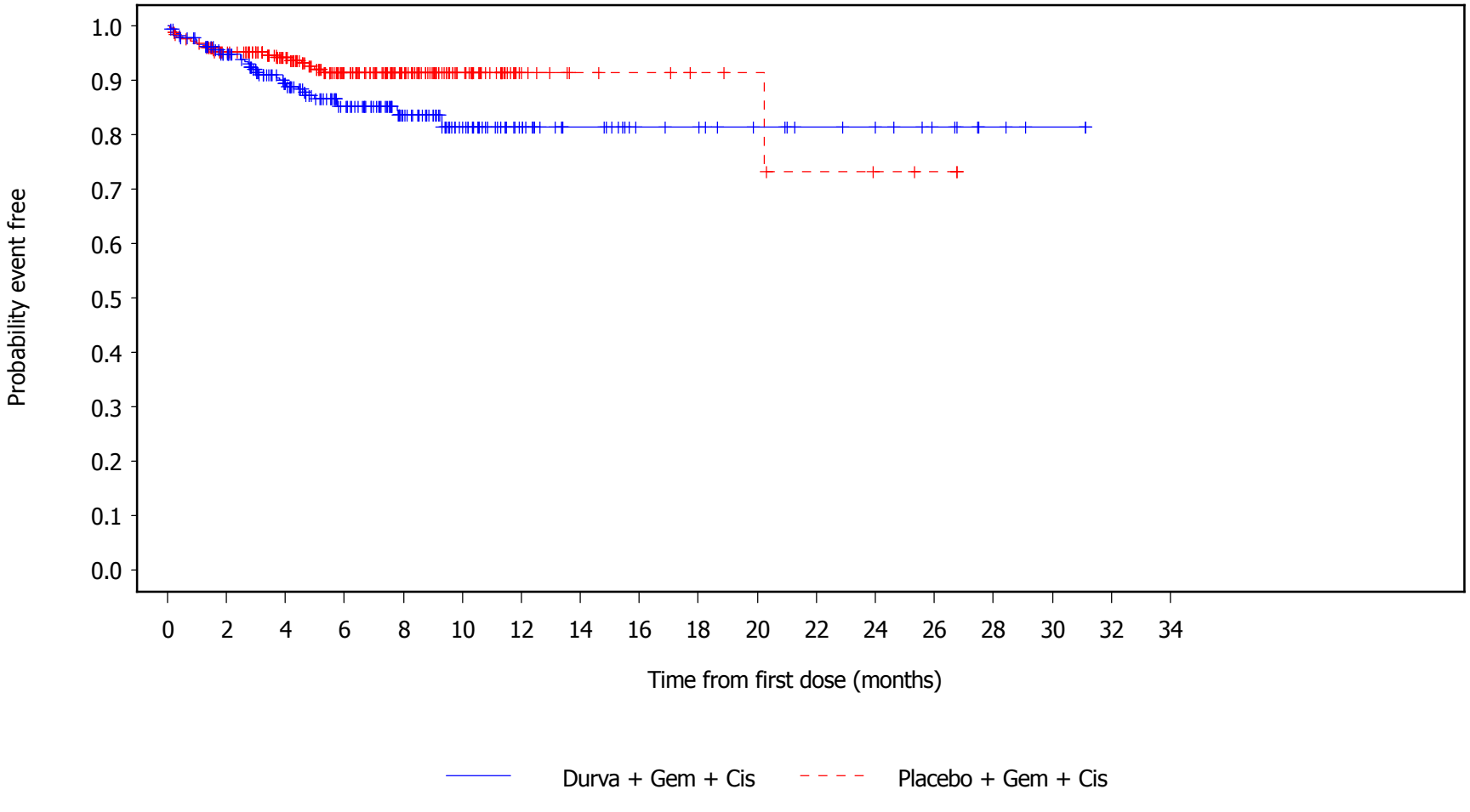
Figure 3.5.5.4 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI GT: Diarrhoea/Colitis for Race=Non-Asian
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

154	129	103	85	65	40	23	17	12	10	5	4	2	1	1	1	0	0	Durva + Gem + Cis
141	112	89	71	46	25	13	10	7	4	1	1	0	0	0	0	0	0	Placebo + Gem + Cis

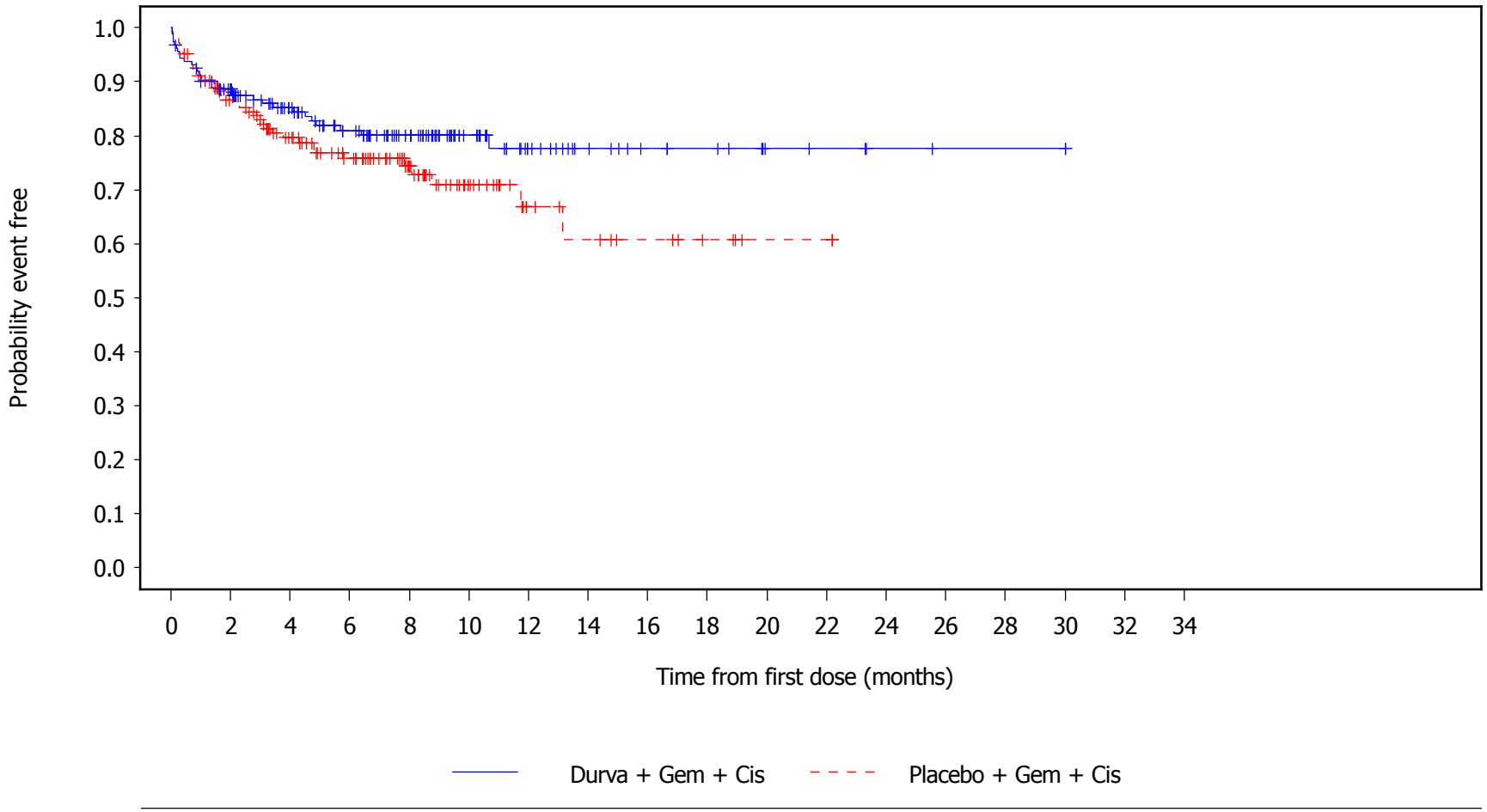
Figure 3.5.5.5 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Diarrhoea for Region=Asia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

241	210	166	130	91	62	39	28	20	19	15	12	11	7	3	1	0	0	Durva + Gem + Cis
257	224	187	128	88	50	14	9	8	6	5	3	2	1	0	0	0	0	Placebo + Gem + Cis

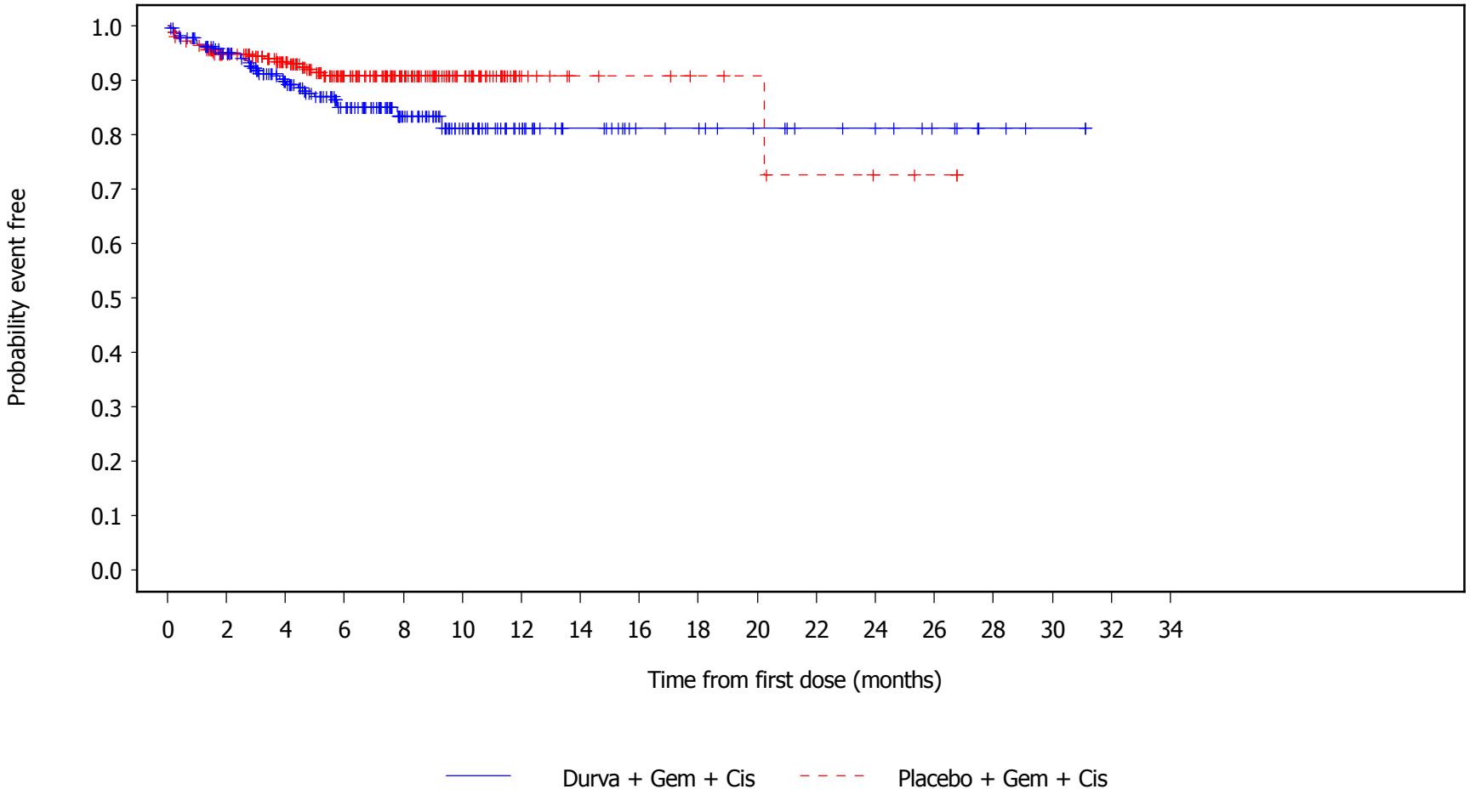
Figure 3.5.5.6 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Diarrhoea for Region=Rest of World
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

161	135	108	89	68	42	25	17	12	10	5	4	2	1	1	1	0	0	Durva + Gem + Cis
146	116	92	73	48	27	13	10	7	4	1	1	0	0	0	0	0	0	Placebo + Gem + Cis

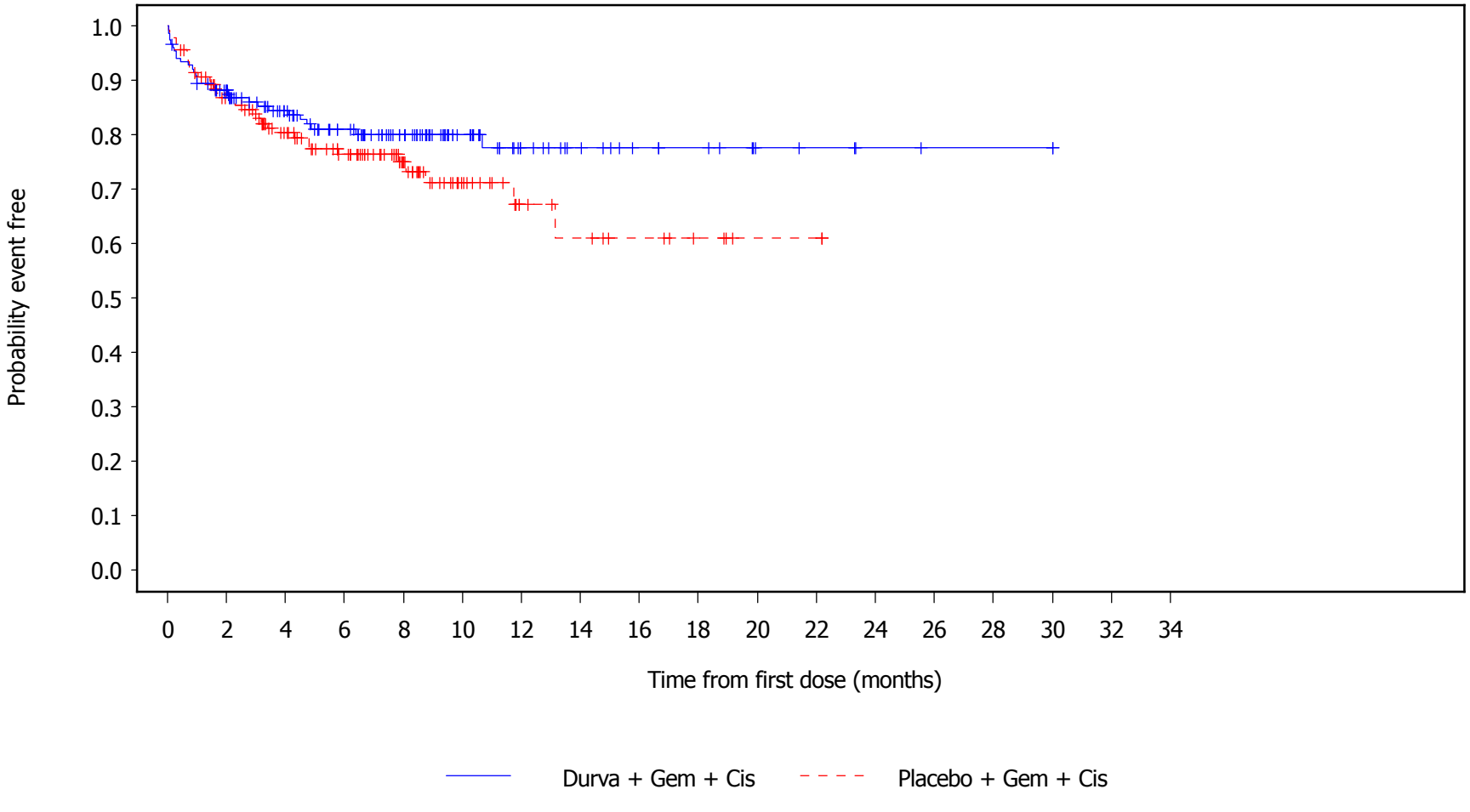
Figure 3.5.5.7 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Diarrhoea for Race=Asian
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

248	216	171	134	94	64	41	28	20	19	15	12	11	7	3	1	0	0	Durva + Gem + Cis
262	228	190	130	90	52	14	9	8	6	5	3	2	1	0	0	0	0	Placebo + Gem + Cis

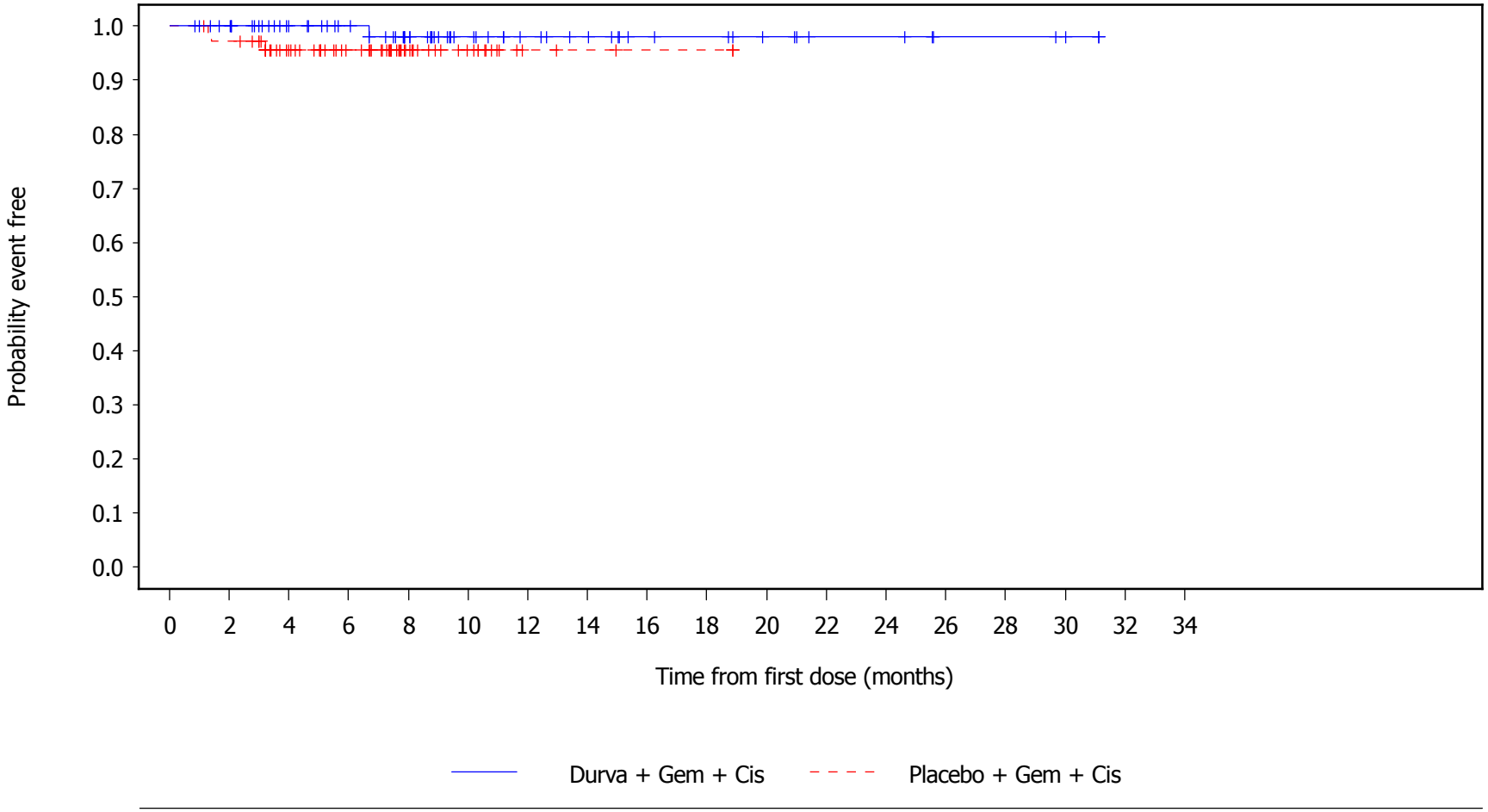
Figure 3.5.5.8 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Diarrhoea for Race=Non-Asian
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

154	129	103	85	65	40	23	17	12	10	5	4	2	1	1	1	0	0	Durva + Gem + Cis
141	112	89	71	46	25	13	10	7	4	1	1	0	0	0	0	0	0	Placebo + Gem + Cis

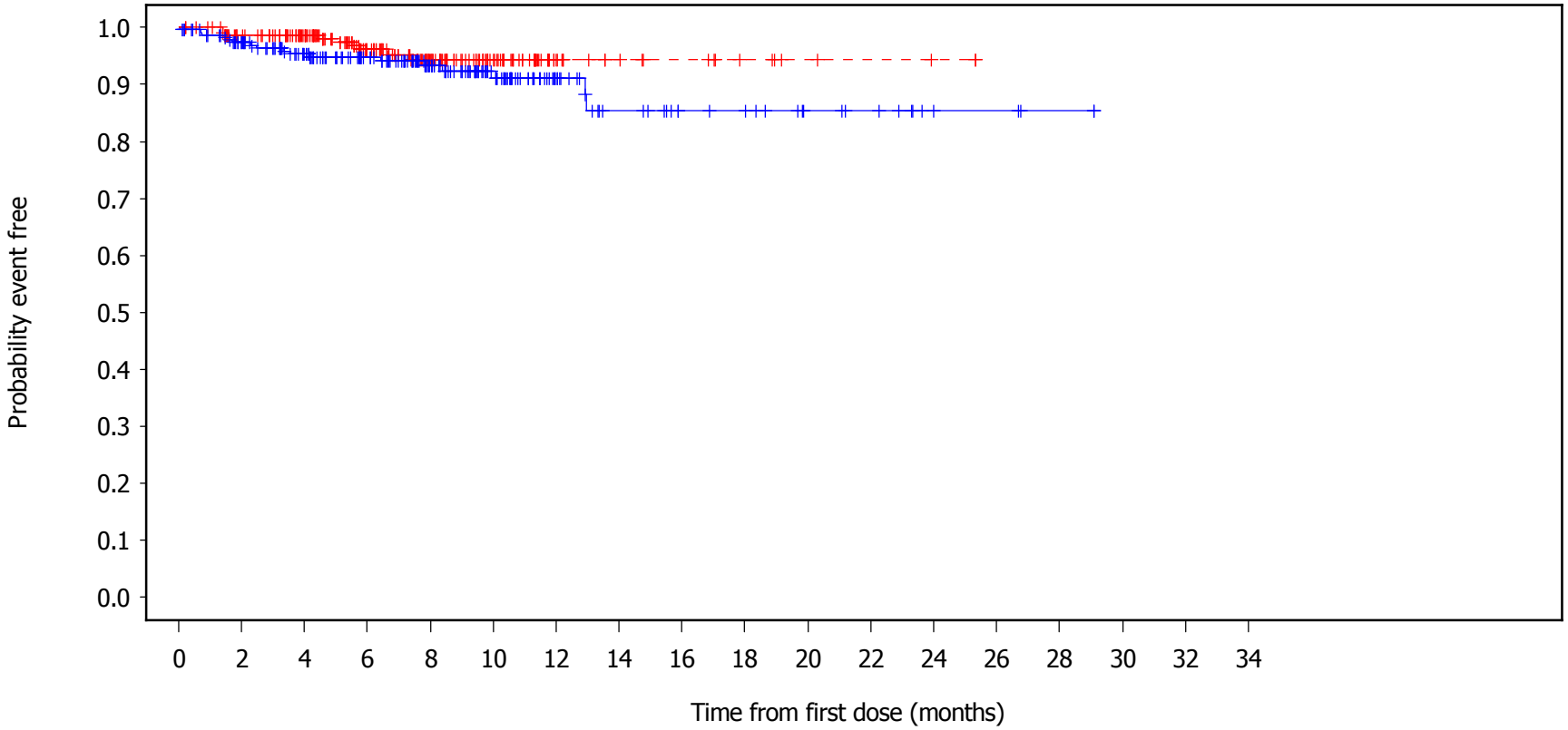
Figure 3.5.5.9 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI GT: Hypothyroid events for Primary Tumor Location [eCRF]=Extrahepatic CCA
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

73	69	58	51	39	27	21	18	13	12	9	6	6	3	3	2	0	0	Durva + Gem + Cis
71	68	52	40	22	13	3	2	1	1	0	0	0	0	0	0	0	0	Placebo + Gem + Cis

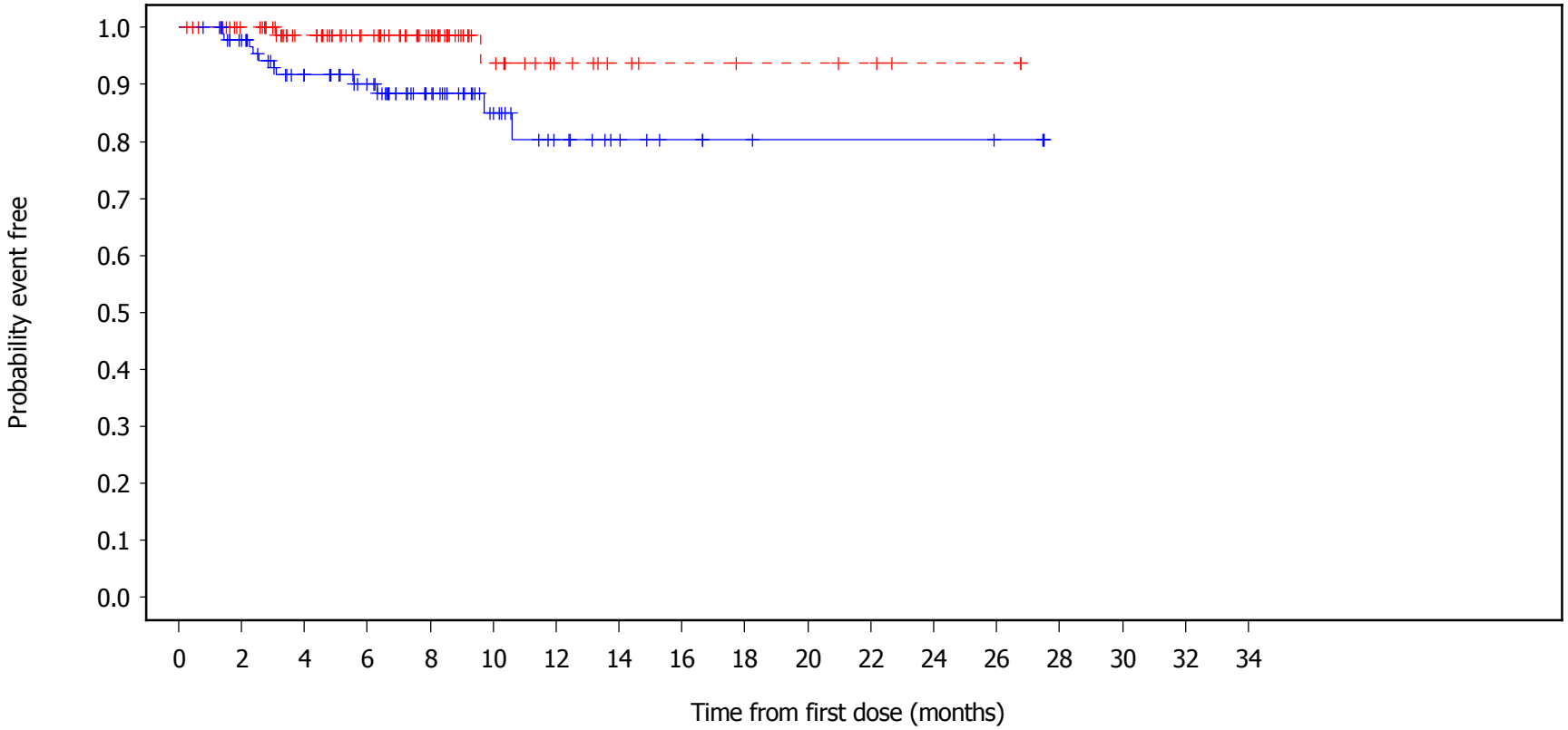
Figure 3.5.5.10 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI GT: Hypothyroid events for Primary Tumor Location [eCRF]=Intrahepatic CCA
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

234	211	177	145	109	73	39	25	18	17	11	9	4	3	1	0	0	0	Durva + Gem + Cis
235	211	183	129	91	55	20	13	10	6	3	2	1	0	0	0	0	0	Placebo + Gem + Cis

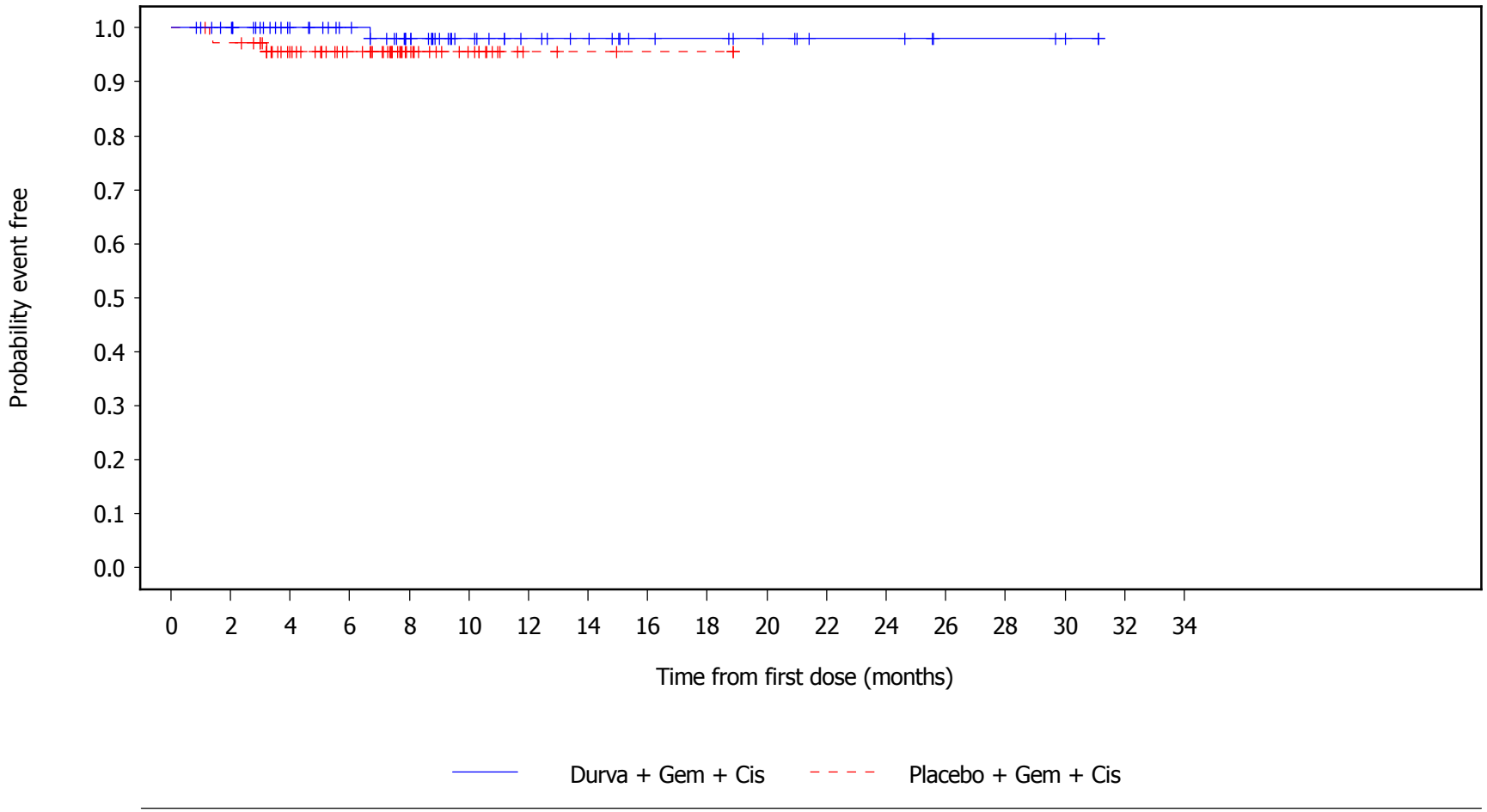
Figure 3.5.5.11 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI GT: Hypothyroid events for Primary Tumor Location [eCRF]=Gallbladder cancer
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

95	85	67	57	38	23	14	9	6	4	3	3	3	2	0	0	0	0	Durva + Gem + Cis
97	87	71	55	40	19	11	7	5	4	4	3	1	1	0	0	0	0	Placebo + Gem + Cis

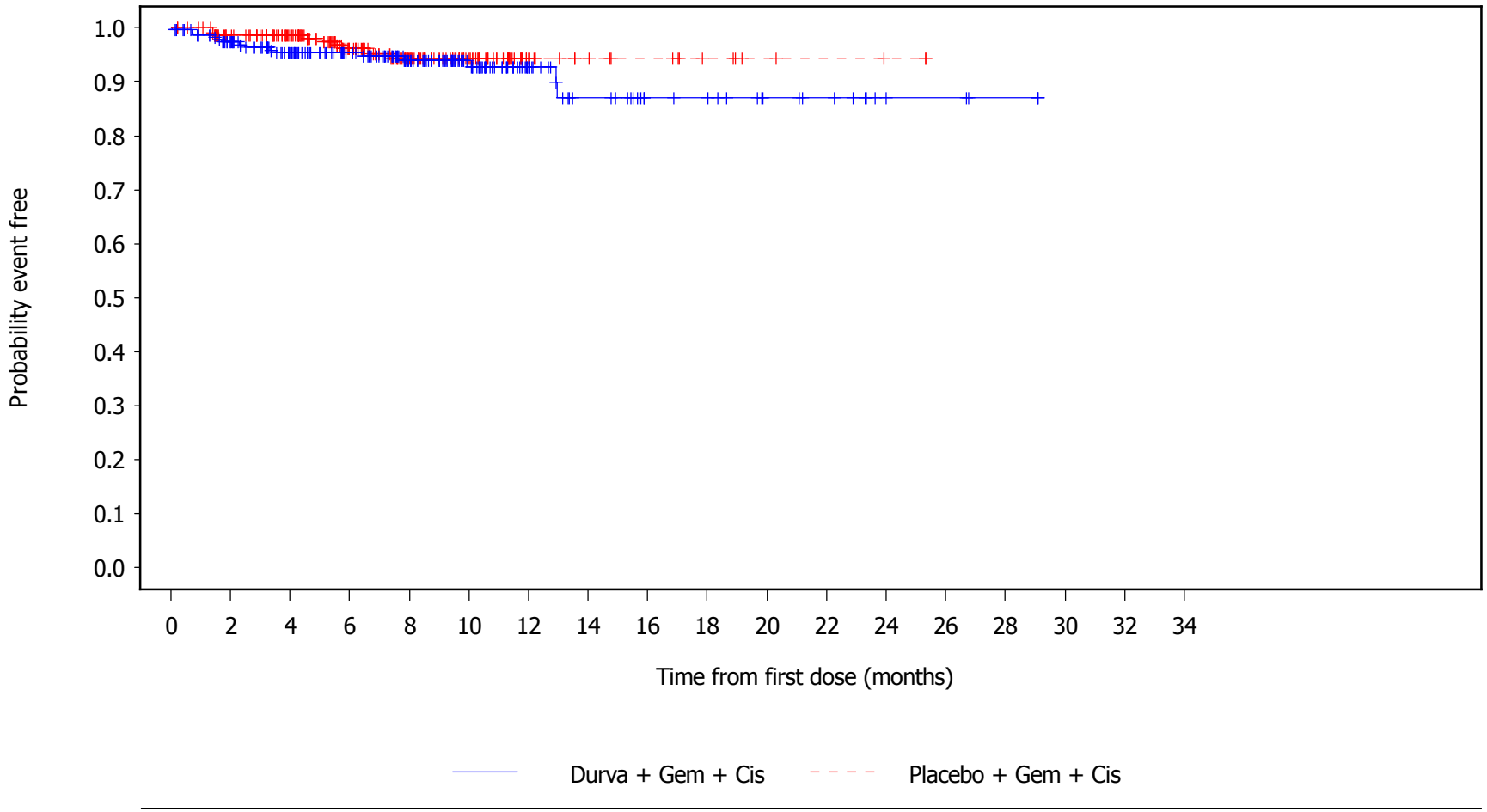
Figure 3.5.5.12 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Hypothyroidism for Primary Tumor Location [eCRF]=Extrahepatic CCA
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

73	69	58	51	39	27	21	18	13	12	9	6	6	3	3	2	0	0	Durva + Gem + Cis
71	68	52	40	22	13	3	2	1	1	0	0	0	0	0	0	0	0	Placebo + Gem + Cis

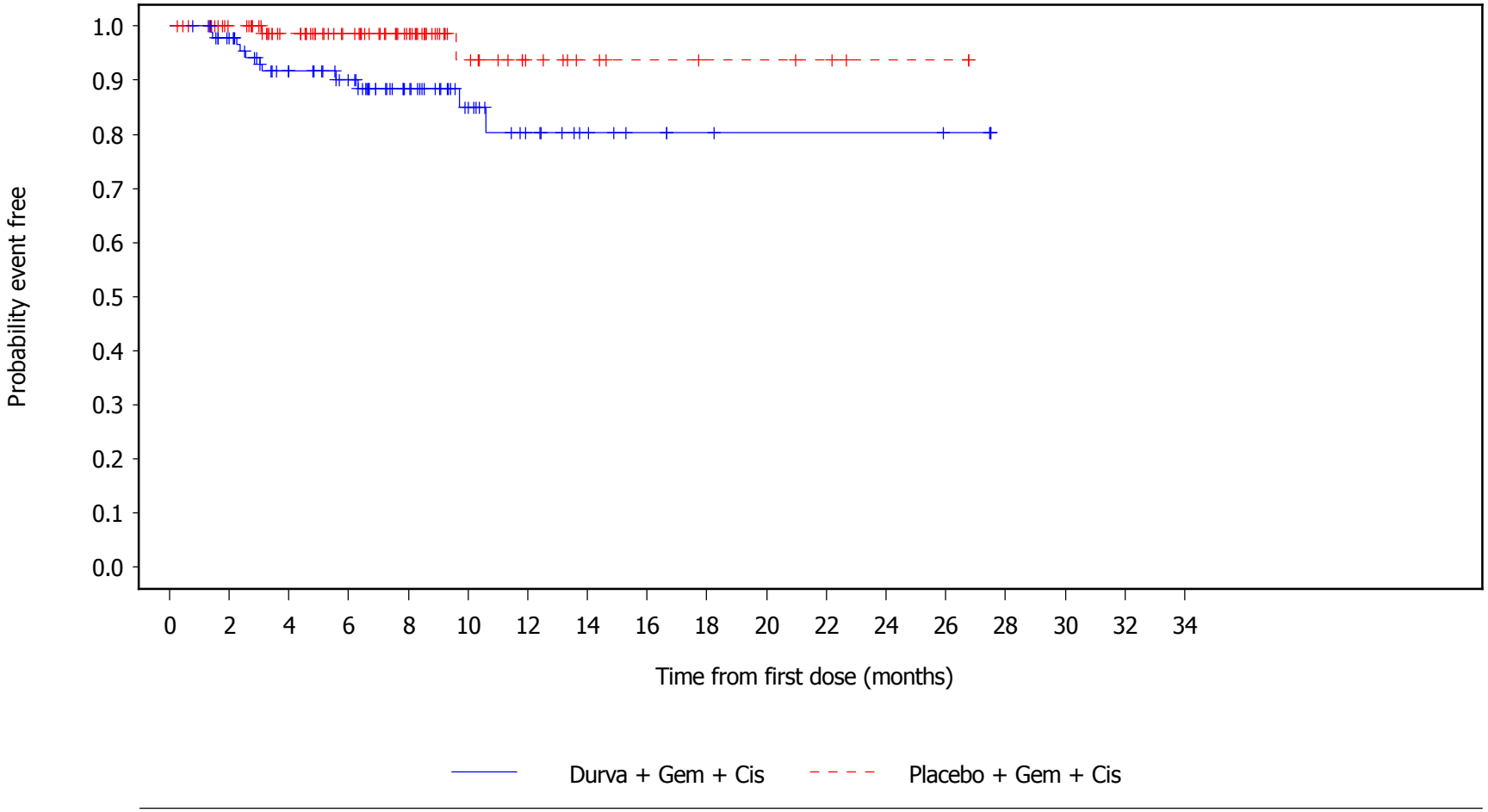
Figure 3.5.5.13 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Hypothyroidism for Primary Tumor Location [eCRF]=Intrahepatic CCA
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

234	211	177	146	110	75	41	27	18	17	11	9	4	3	1	0	0	0	Durva + Gem + Cis
235	211	183	129	91	55	20	13	10	6	3	2	1	0	0	0	0	0	Placebo + Gem + Cis

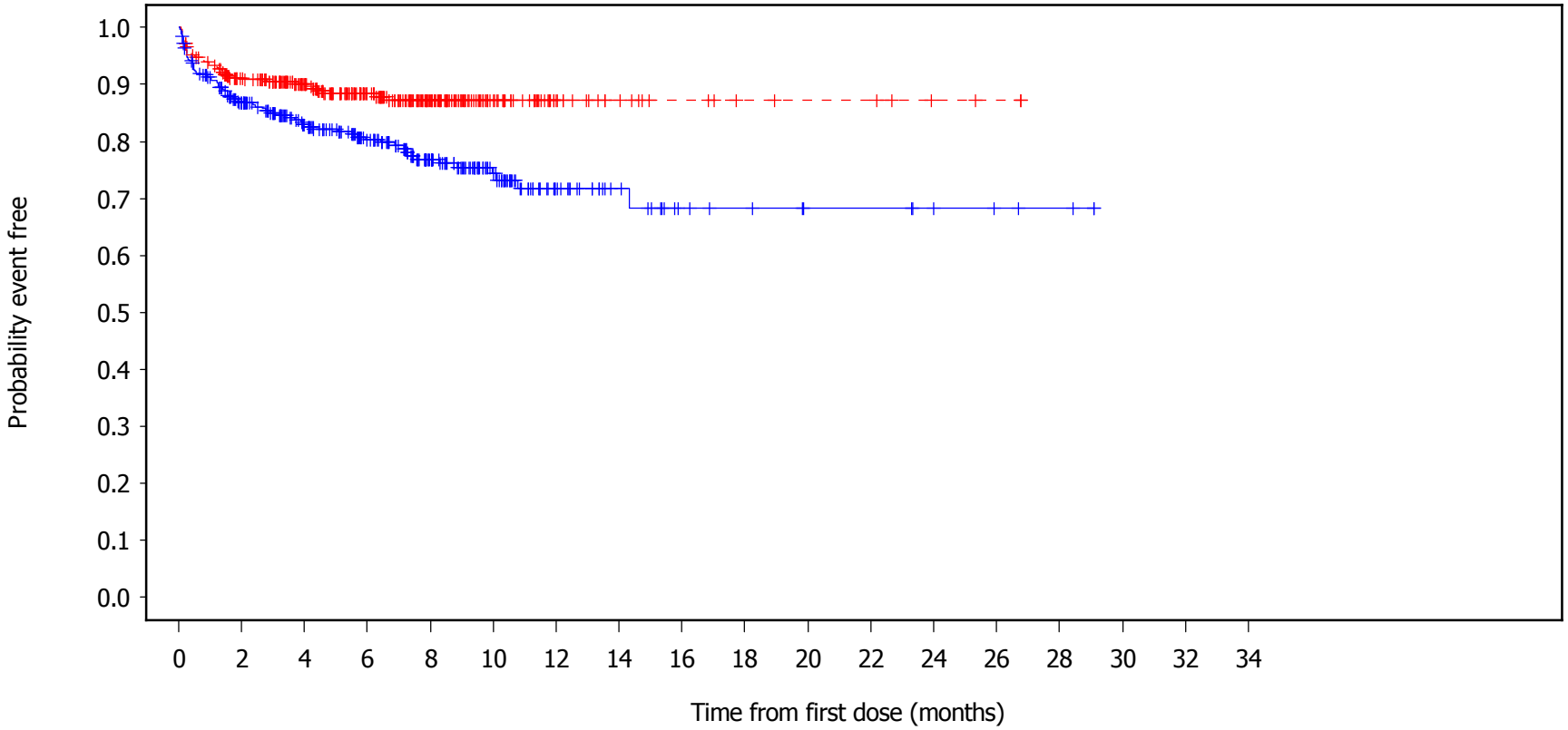
Figure 3.5.5.14 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Hypothyroidism for Primary Tumor Location [eCRF]=Gallbladder cancer
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

95	85	67	57	38	23	14	9	6	4	3	3	3	2	0	0	0	0	Durva + Gem + Cis
97	87	71	55	40	19	11	7	5	4	4	3	1	1	0	0	0	0	Placebo + Gem + Cis

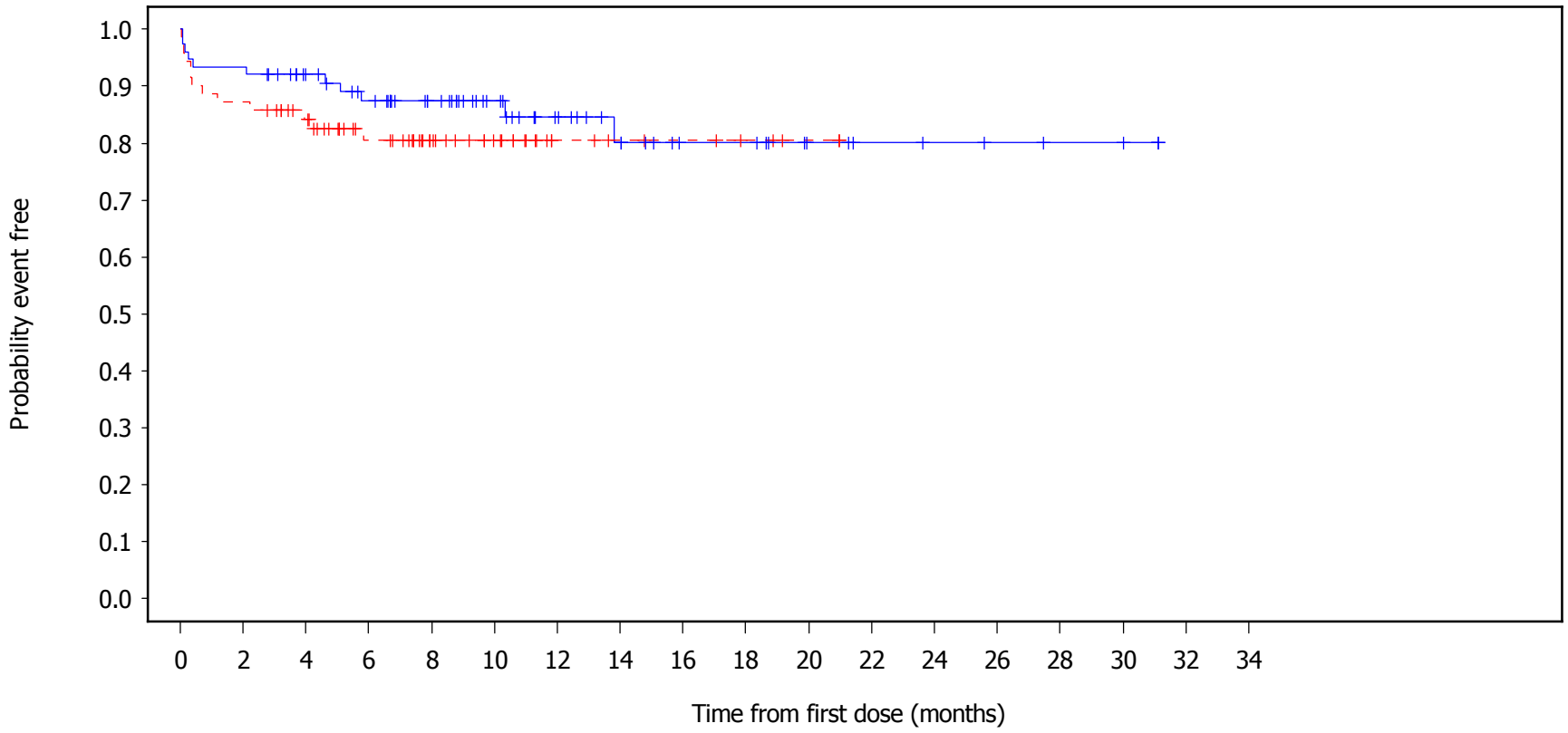
Figure 3.5.5.15 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI GT: Dermatitis/Rash for Disease Status [eCRF]=Initially unresectable
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

326	257	202	162	112	70	35	21	12	10	7	7	5	3	2	0	0	0	Durva + Gem + Cis
333	275	224	159	103	53	23	14	9	6	5	5	2	1	0	0	0	0	Placebo + Gem + Cis

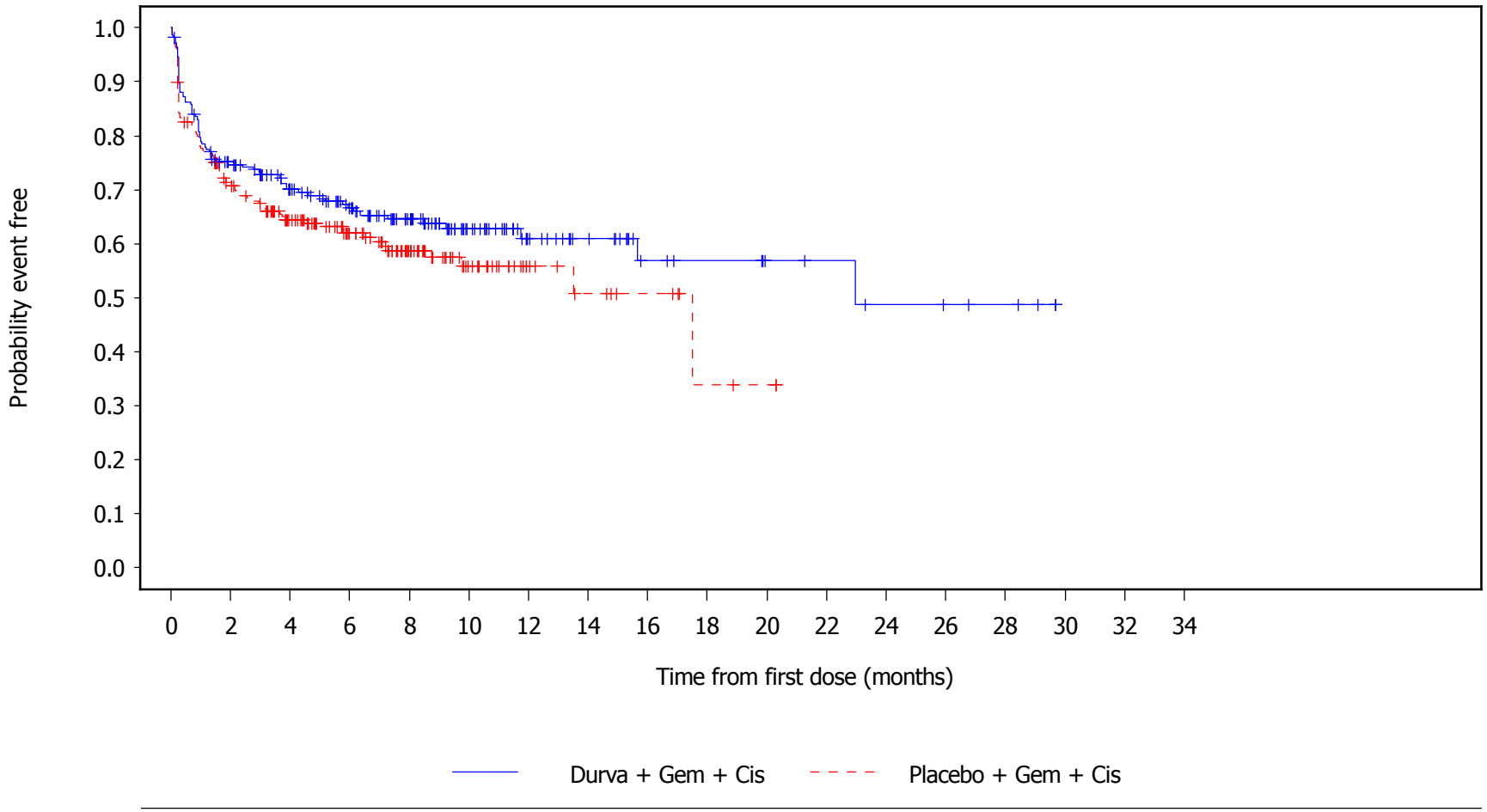
Figure 3.5.5.16 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI GT: Dermatitis/Rash for Disease Status [eCRF]=Recurrent
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

76	71	63	55	44	33	24	18	12	12	7	5	4	3	2	2	0	0	Durva + Gem + Cis
70	61	53	39	27	19	8	6	5	3	1	0	0	0	0	0	0	0	Placebo + Gem + Cis

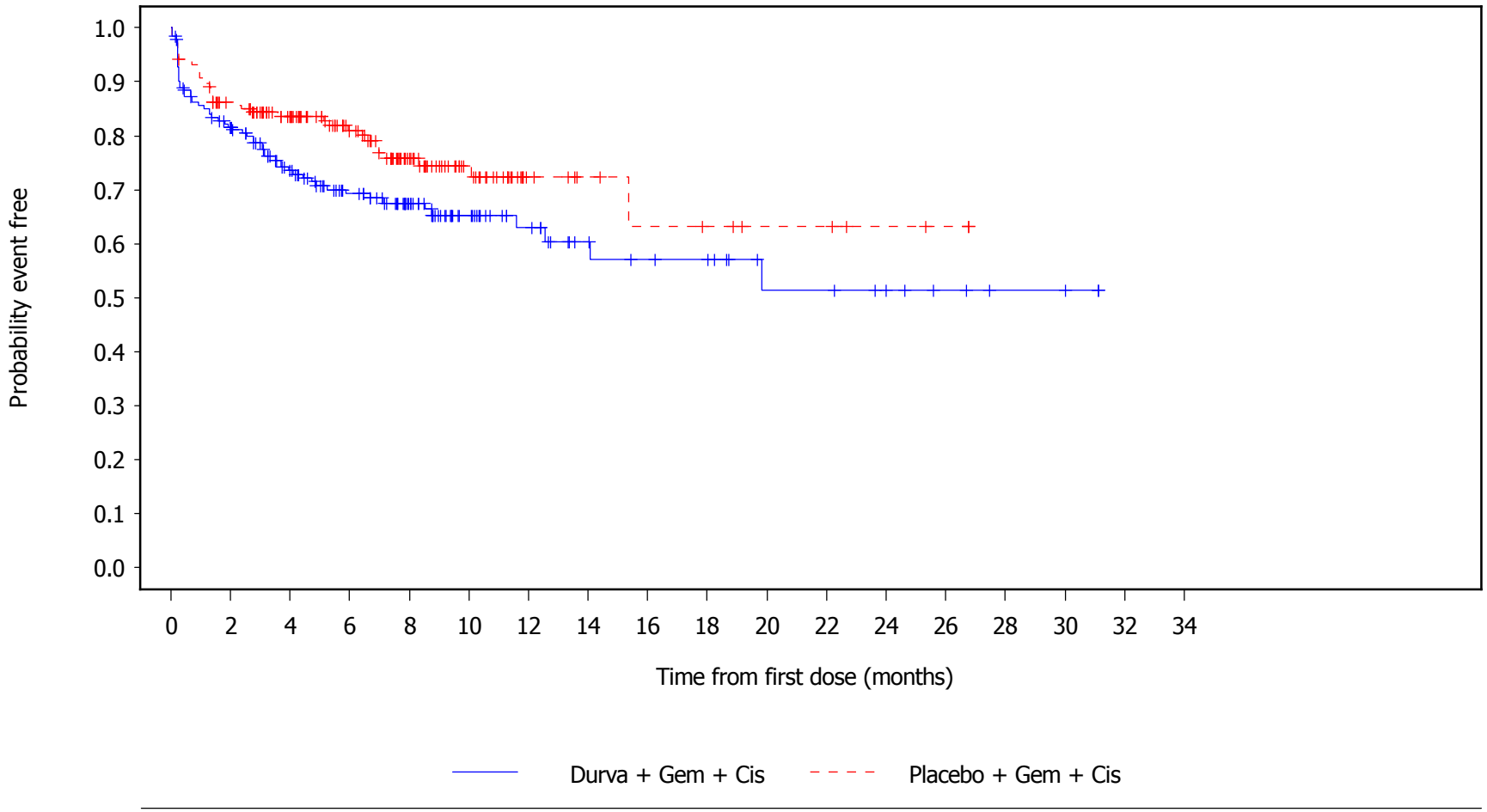
Figure 3.5.5.17 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI GT: Hepatic SMQ AEs for Age Group=<65
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

219	156	130	108	83	52	31	23	13	11	8	7	5	4	3	0	0	0	Durva + Gem + Cis
229	152	118	86	57	30	14	9	6	2	1	0	0	0	0	0	0	0	Placebo + Gem + Cis

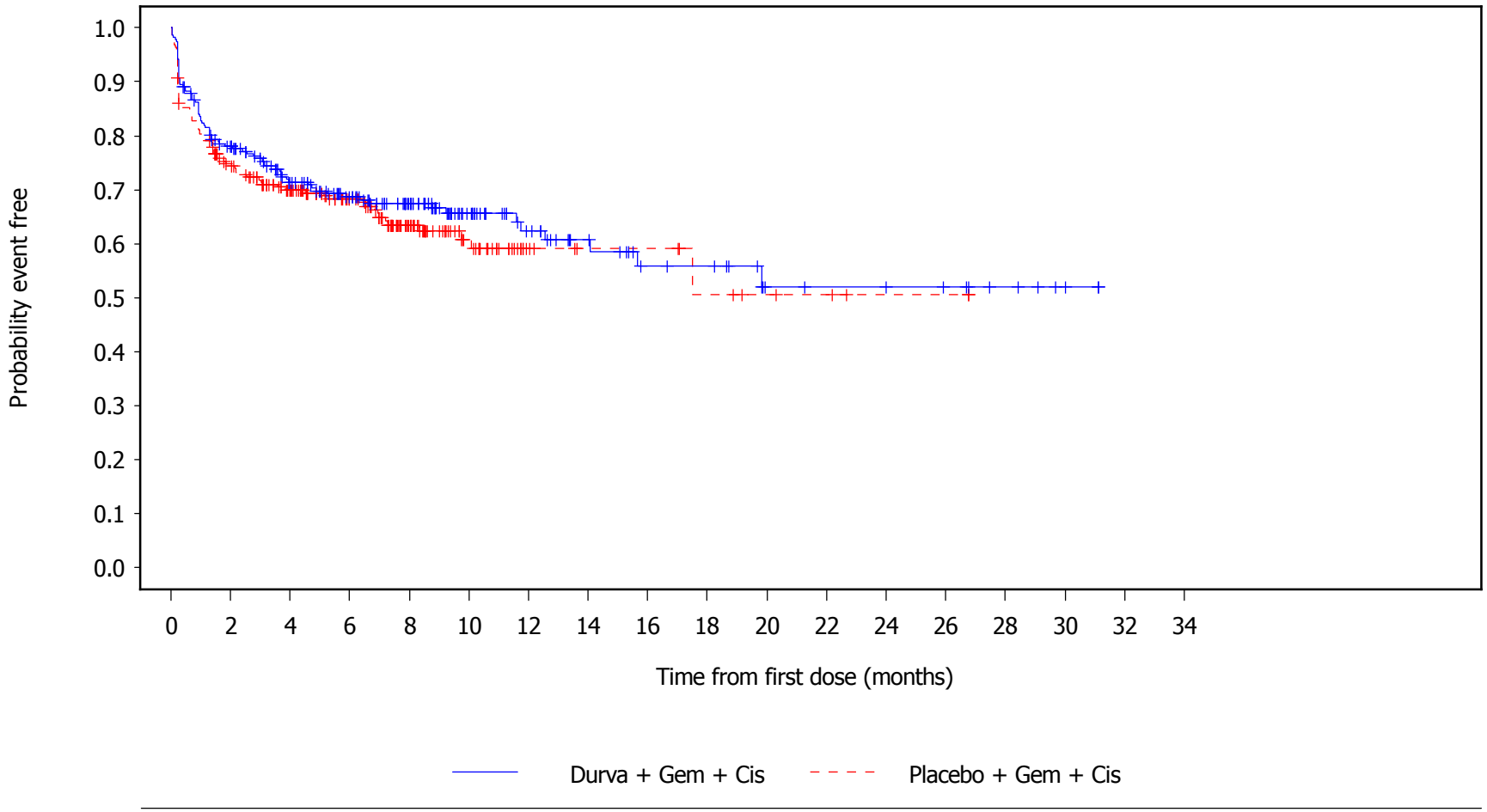
Figure 3.5.5.18 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI GT: Hepatic SMQ AEs for Age Group=>=65
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

183	142	110	88	63	40	28	19	16	15	9	9	7	4	2	2	0	0	Durva + Gem + Cis
174	141	115	86	58	34	13	9	7	6	4	4	2	1	0	0	0	0	Placebo + Gem + Cis

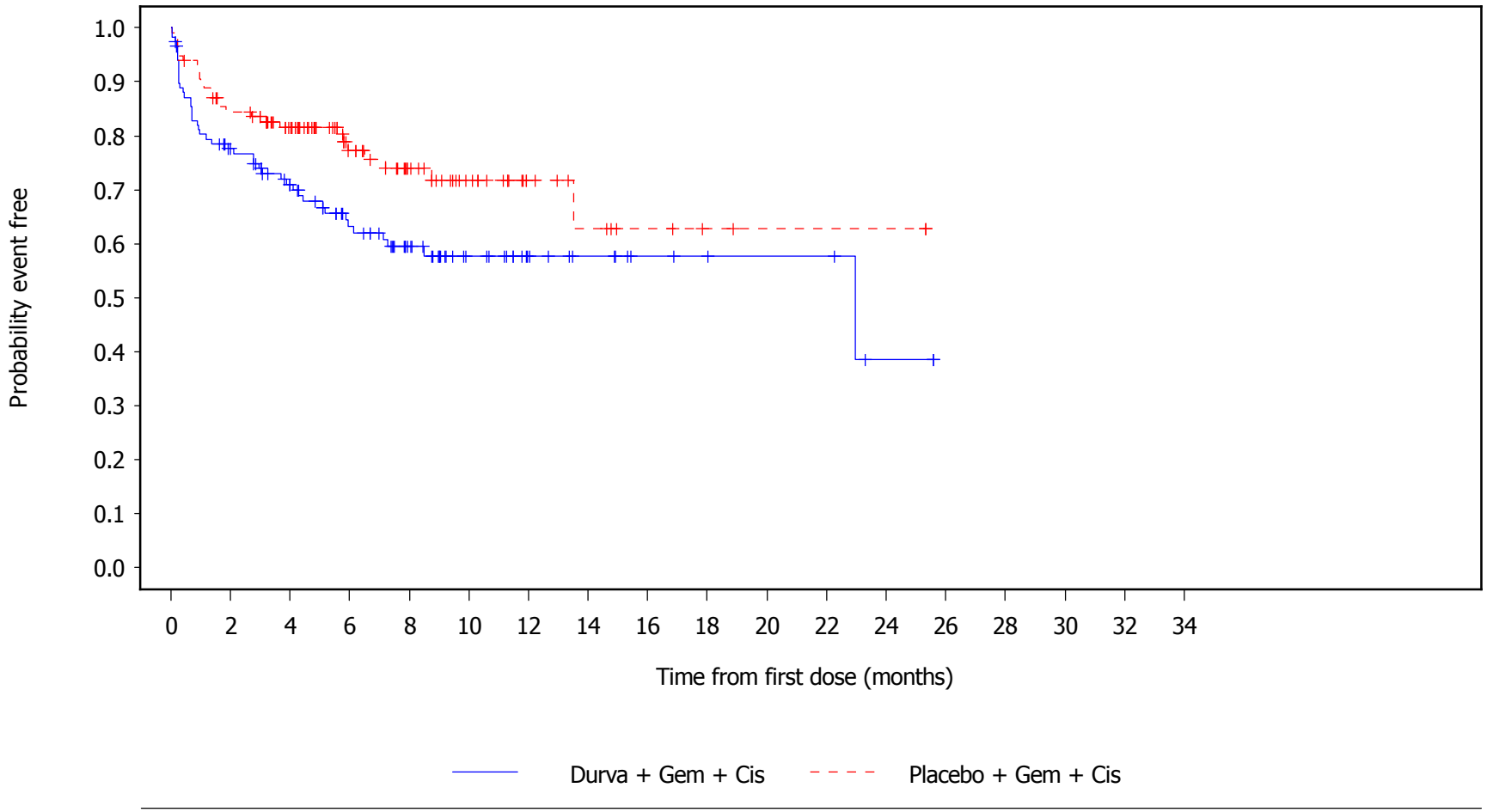
Figure 3.5.5.19 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI GT: Hepatic SMQ AEs for PD-L1 Status=High (>=1%)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

239	178	143	118	90	56	38	28	20	19	11	10	10	8	5	2	0	0	Durva + Gem + Cis
249	173	140	107	68	35	13	9	9	6	4	3	1	1	0	0	0	0	Placebo + Gem + Cis

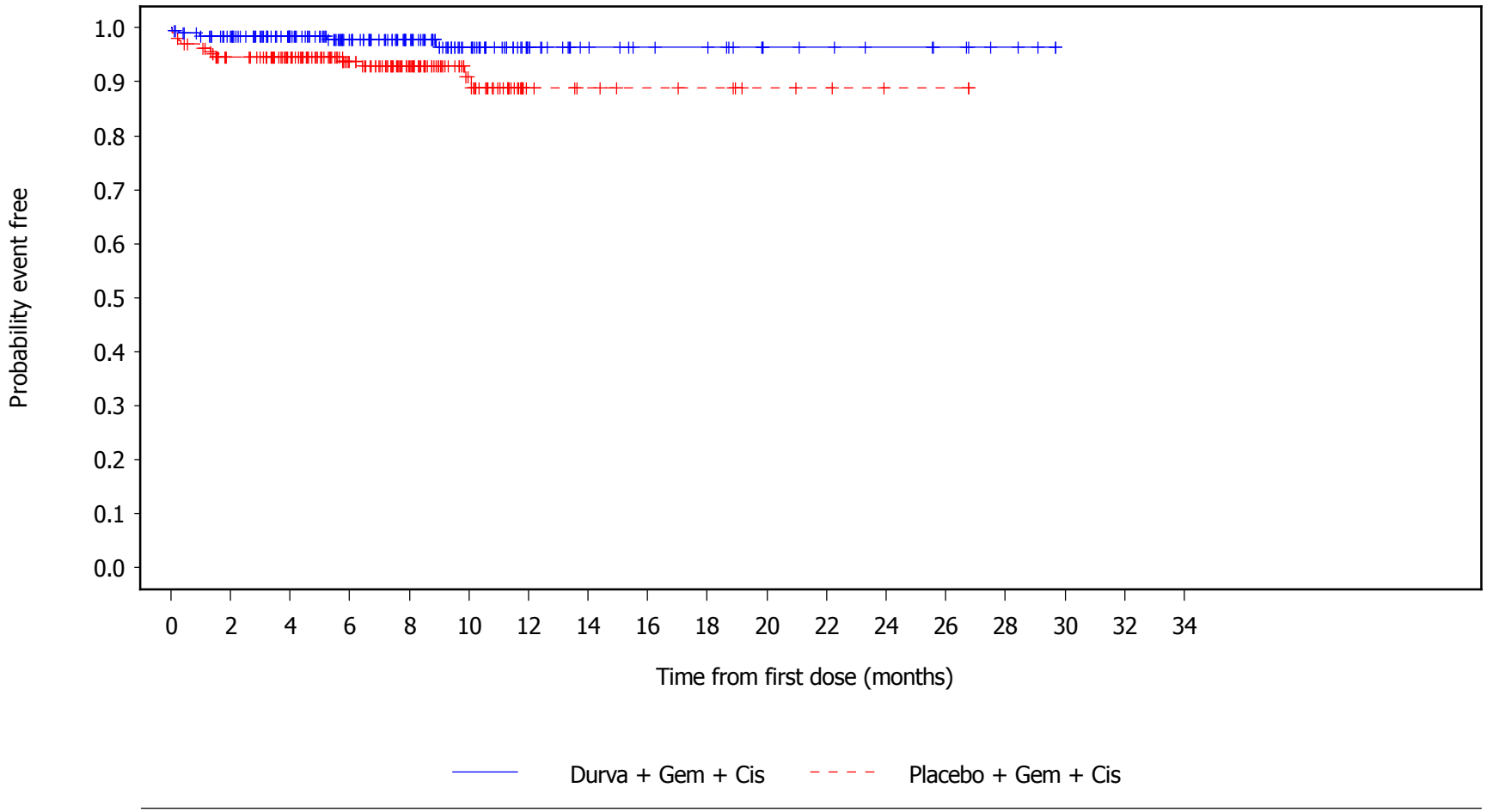
Figure 3.5.5.20 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI GT: Hepatic SMQ AEs for PD-L1 Status=Low (<1%)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

118	86	69	53	38	23	14	10	6	5	4	4	1	0	0	0	0	0	Durva + Gem + Cis
117	95	77	51	36	23	11	7	4	2	1	1	1	0	0	0	0	0	Placebo + Gem + Cis

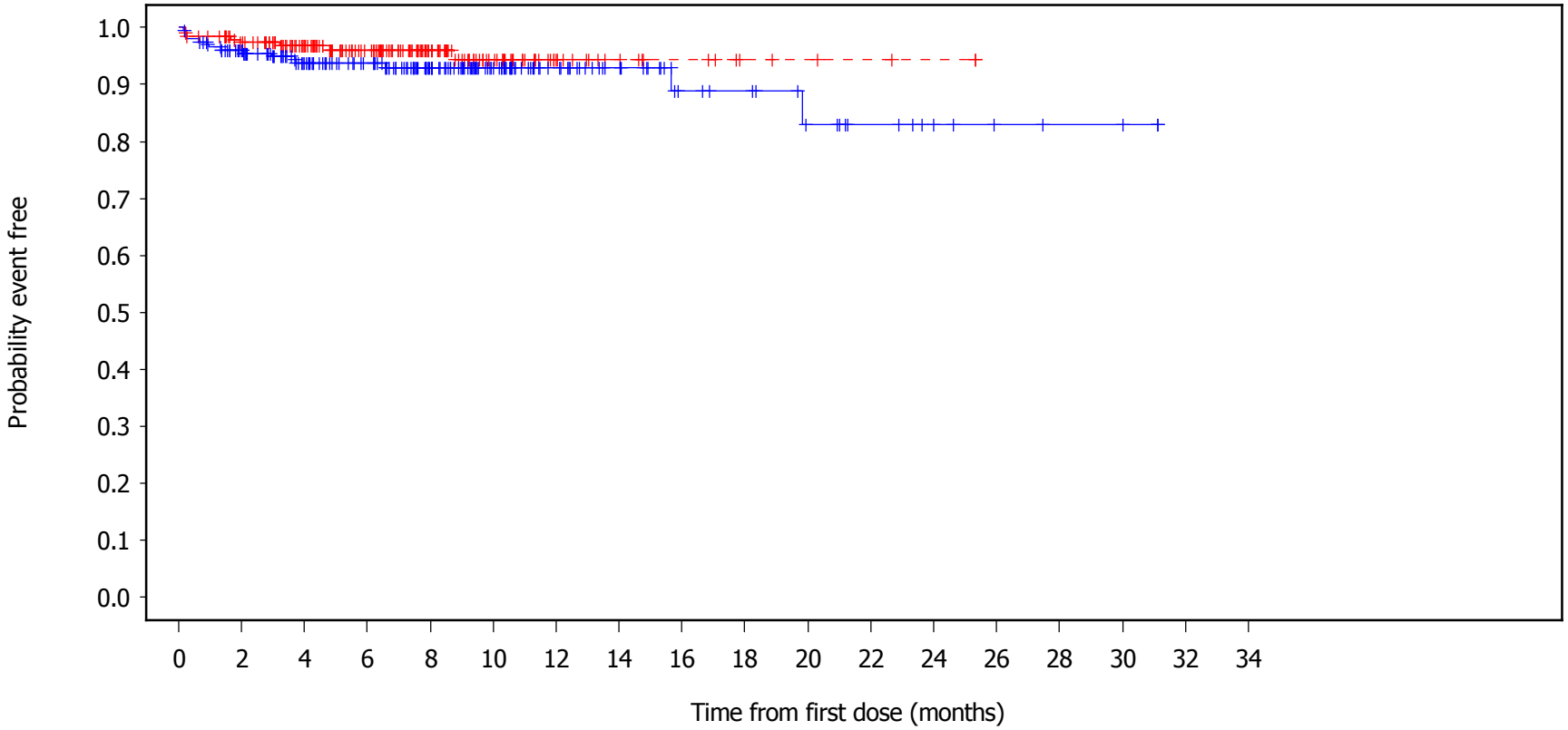
Figure 3.5.5.21 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Blood alkaline phosphatase increased for Sex=Male
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

199	183	153	122	91	58	33	23	19	18	11	10	8	6	3	0	0	0	Durva + Gem + Cis
207	179	152	108	78	43	13	10	8	7	4	3	1	1	0	0	0	0	Placebo + Gem + Cis

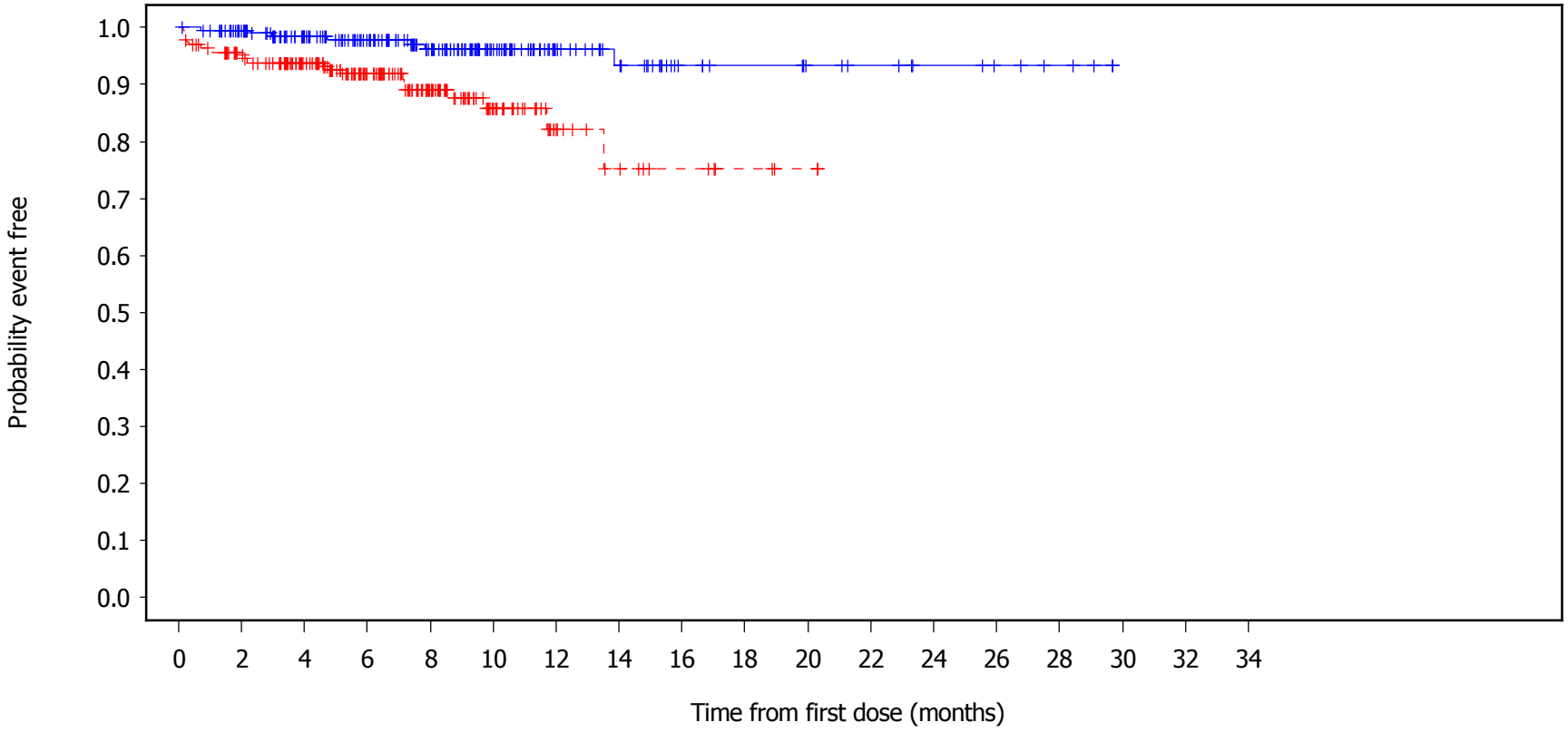
Figure 3.5.5.22 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Blood alkaline phosphatase increased for Sex=Female
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

203	180	151	130	97	66	44	32	20	18	13	9	6	3	2	2	0	0	Durva + Gem + Cis
196	177	146	113	73	41	19	12	8	4	3	2	1	0	0	0	0	0	Placebo + Gem + Cis

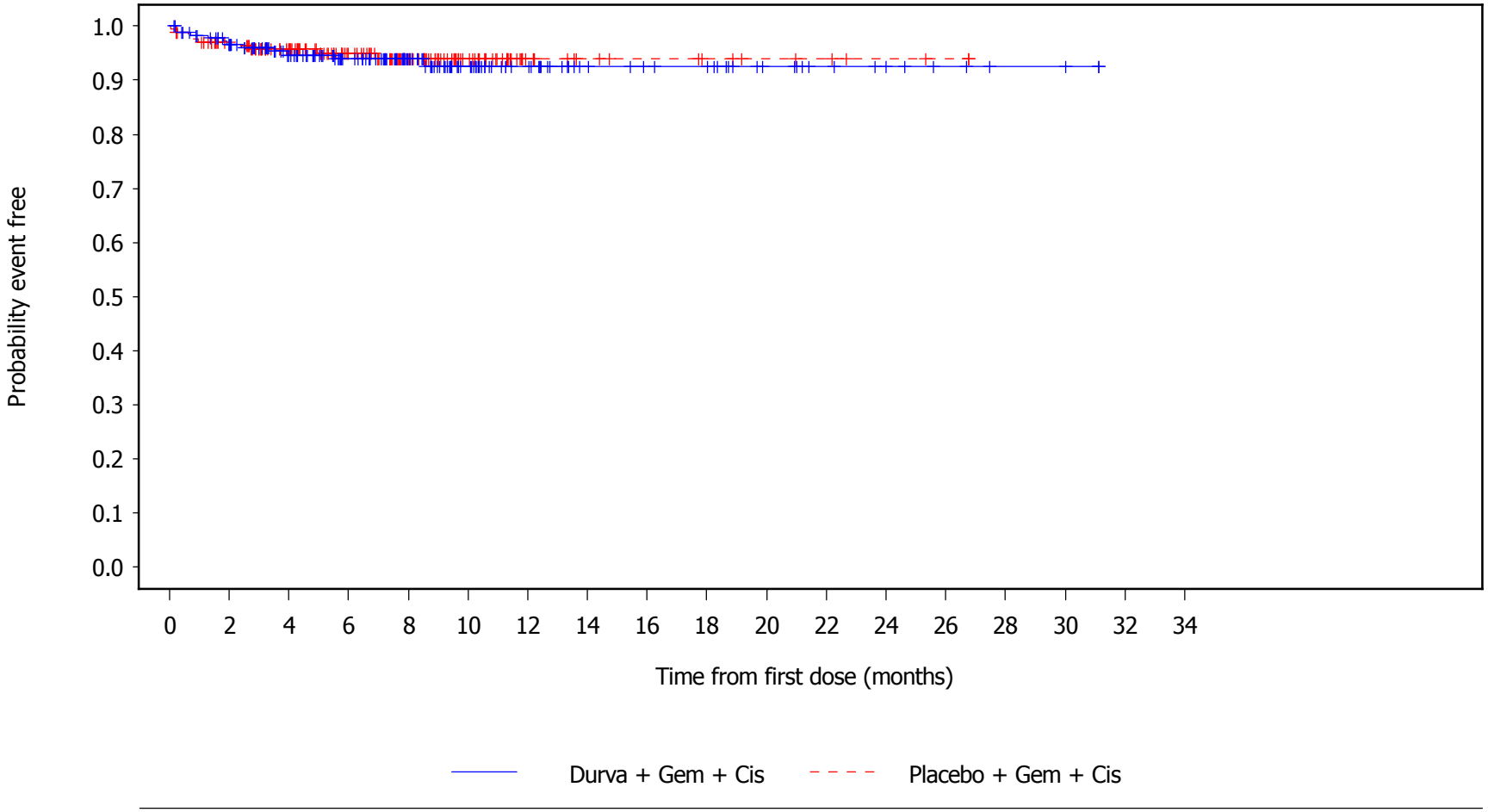
Figure 3.5.5.23 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Blood bilirubin increased for Age Group=<65
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

219	203	170	144	110	71	41	31	18	15	12	10	7	5	3	0	0	0	Durva + Gem + Cis
229	201	169	121	79	42	16	10	6	3	1	0	0	0	0	0	0	0	Placebo + Gem + Cis

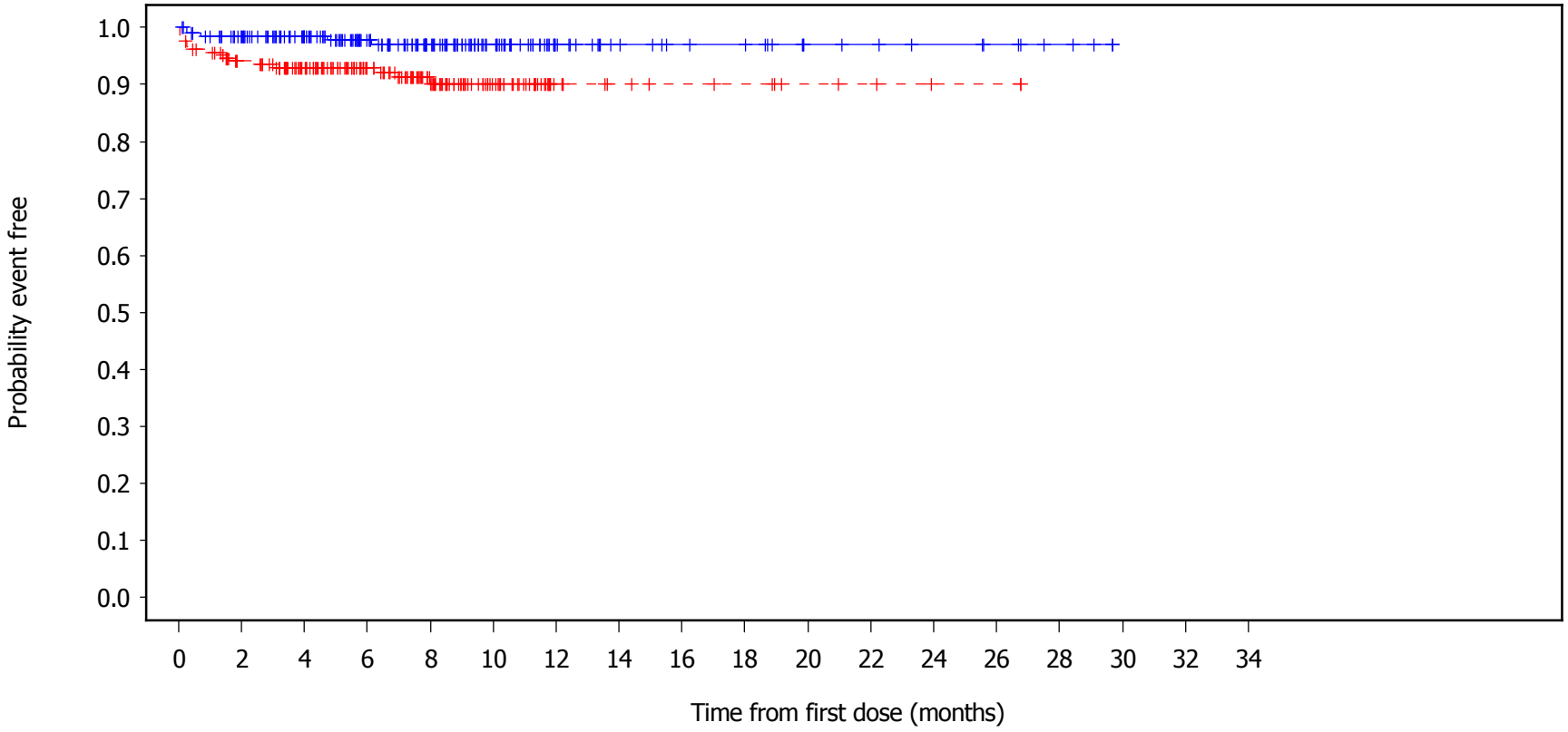
Figure 3.5.5.24 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Blood bilirubin increased for Age Group=>=65
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

183	165	137	114	83	54	38	25	22	21	13	9	7	4	2	2	0	0	Durva + Gem + Cis
174	157	131	100	71	41	16	11	9	7	5	4	2	1	0	0	0	0	Placebo + Gem + Cis

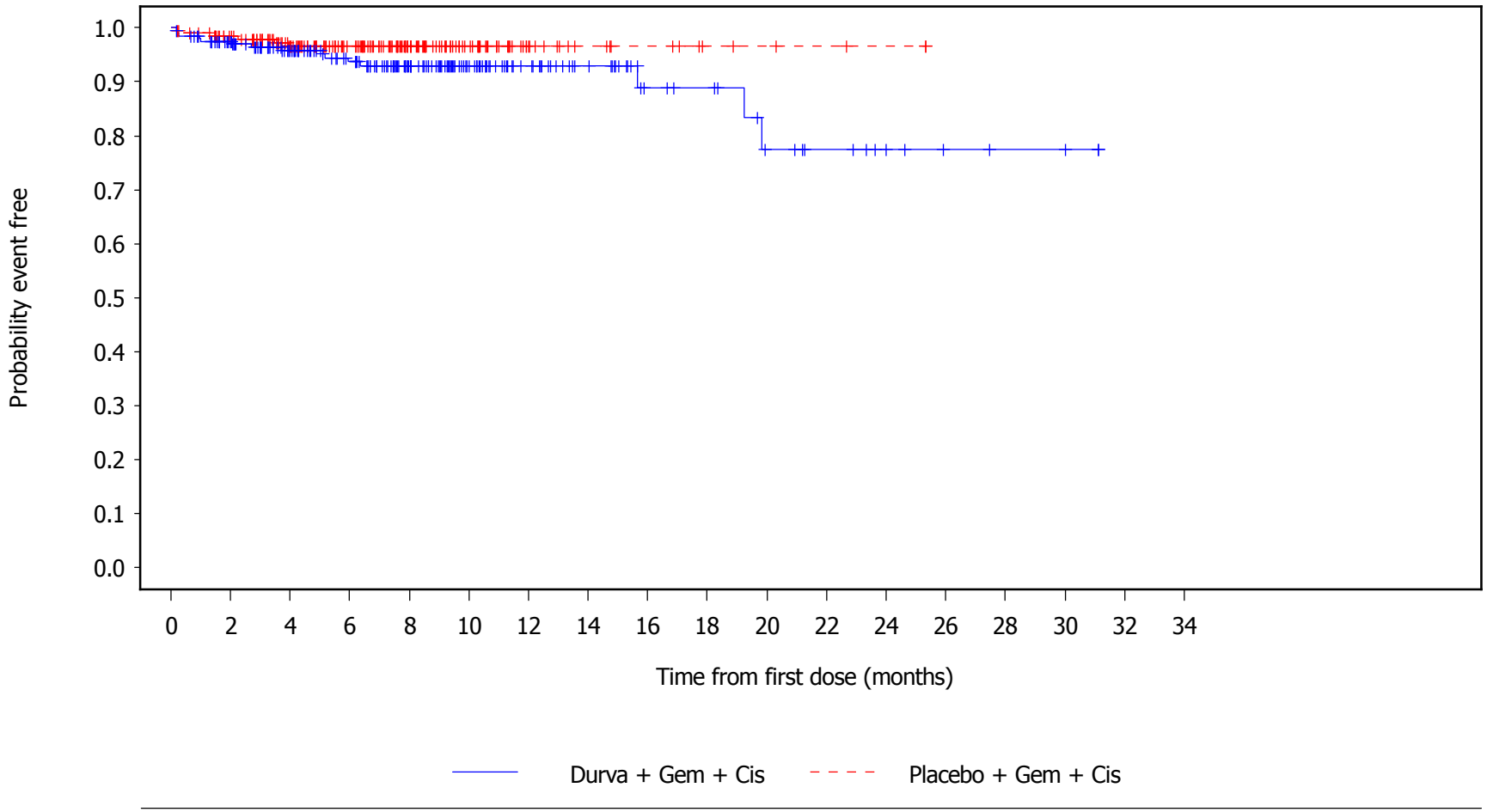
Figure 3.5.5.25 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Gamma-glutamyltransferase increased for Sex=Male
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

199	183	153	122	90	58	32	23	19	18	11	10	8	6	3	0	0	0	Durva + Gem + Cis
207	178	148	107	77	43	14	10	8	7	4	3	1	1	0	0	0	0	Placebo + Gem + Cis

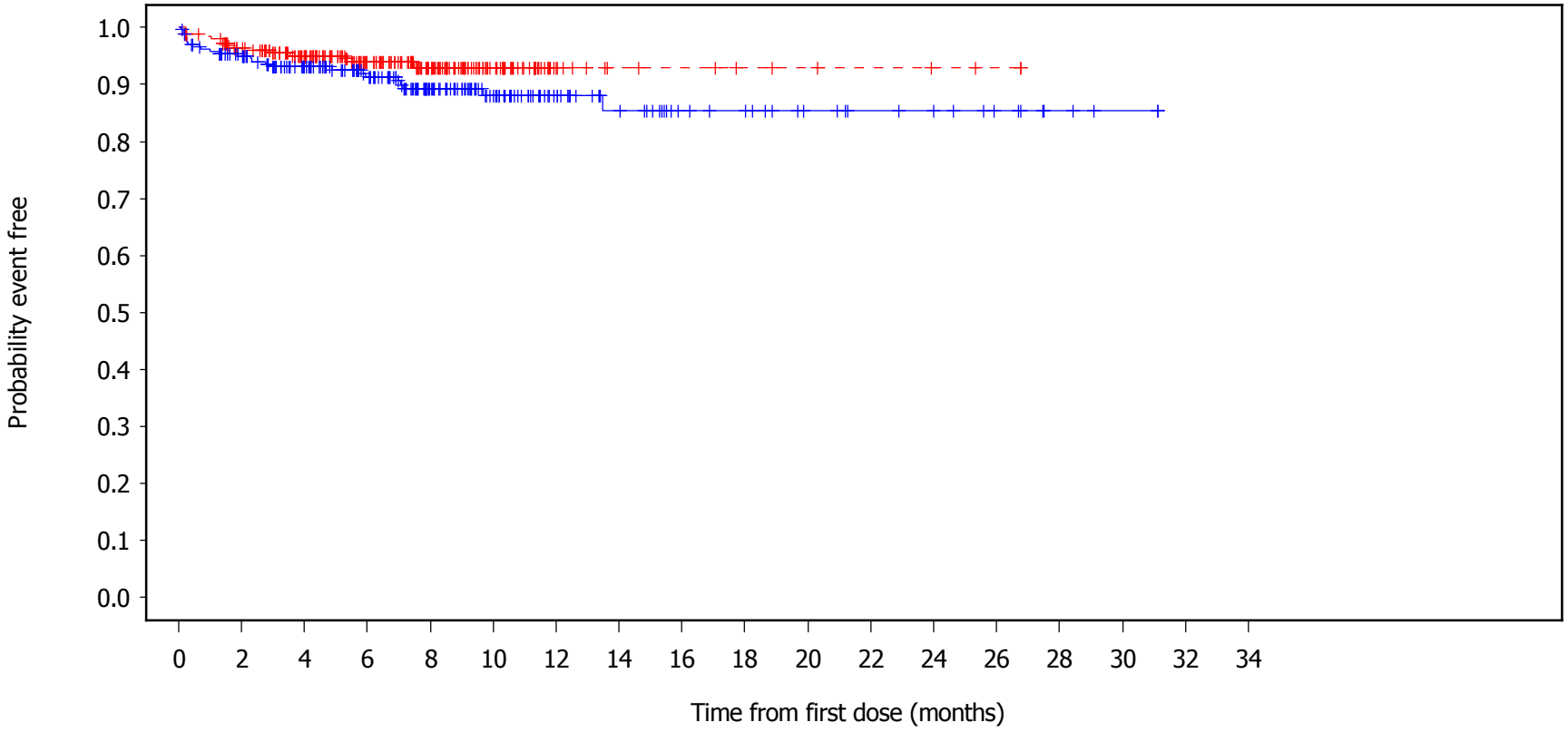
Figure 3.5.5.26 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Gamma-glutamyltransferase increased for Sex=Female
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

203	182	154	130	96	65	45	33	20	18	12	9	6	3	2	2	0	0	Durva + Gem + Cis
196	179	146	112	73	42	18	11	8	4	3	2	1	0	0	0	0	0	Placebo + Gem + Cis

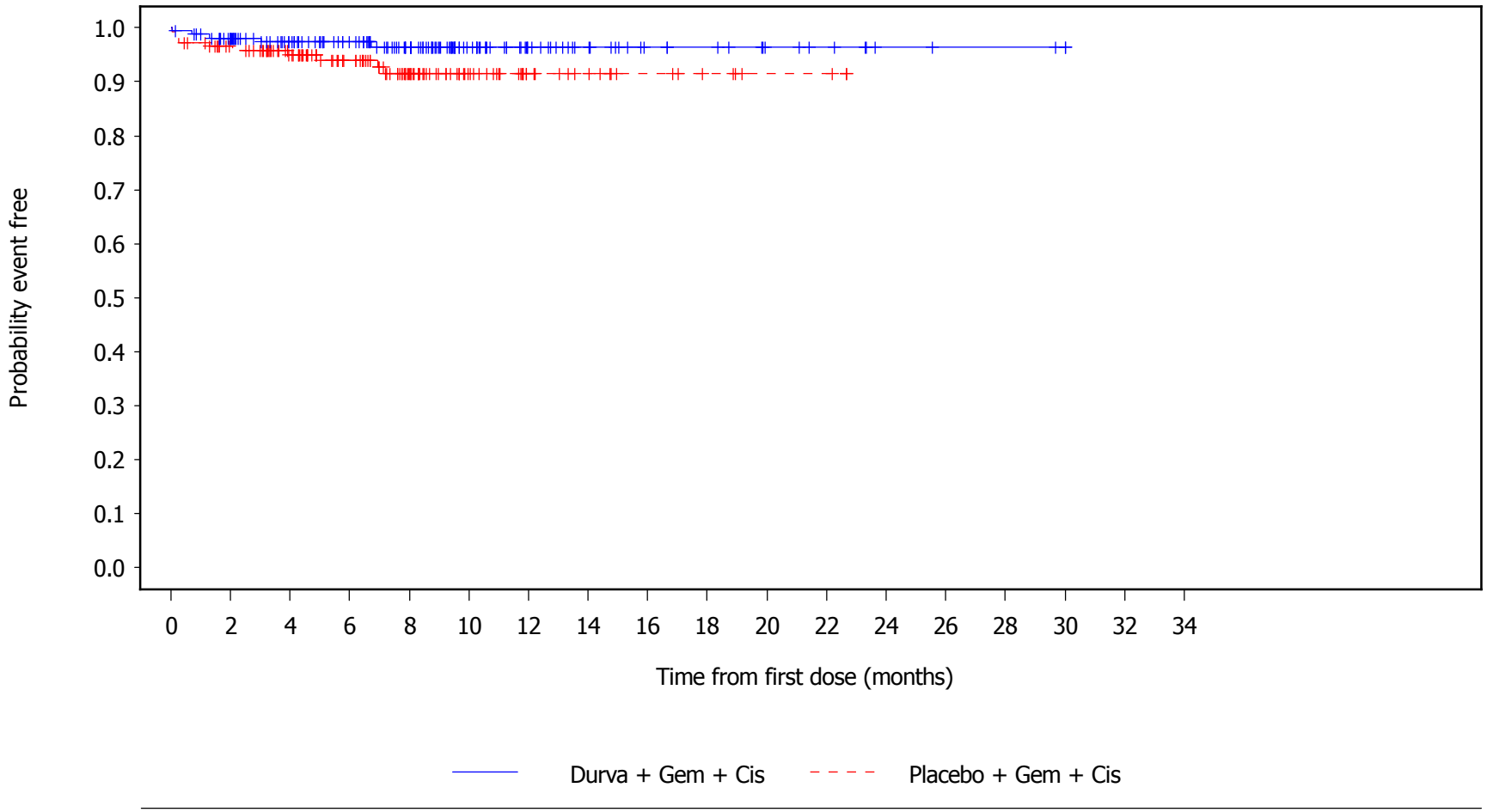
Figure 3.5.5.27 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Hypoalbuminaemia for Region=Asia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

241	215	181	149	105	73	46	33	23	21	15	12	11	7	3	1	0	0	Durva + Gem + Cis
257	229	191	138	94	51	14	8	7	5	4	3	2	1	0	0	0	0	Placebo + Gem + Cis

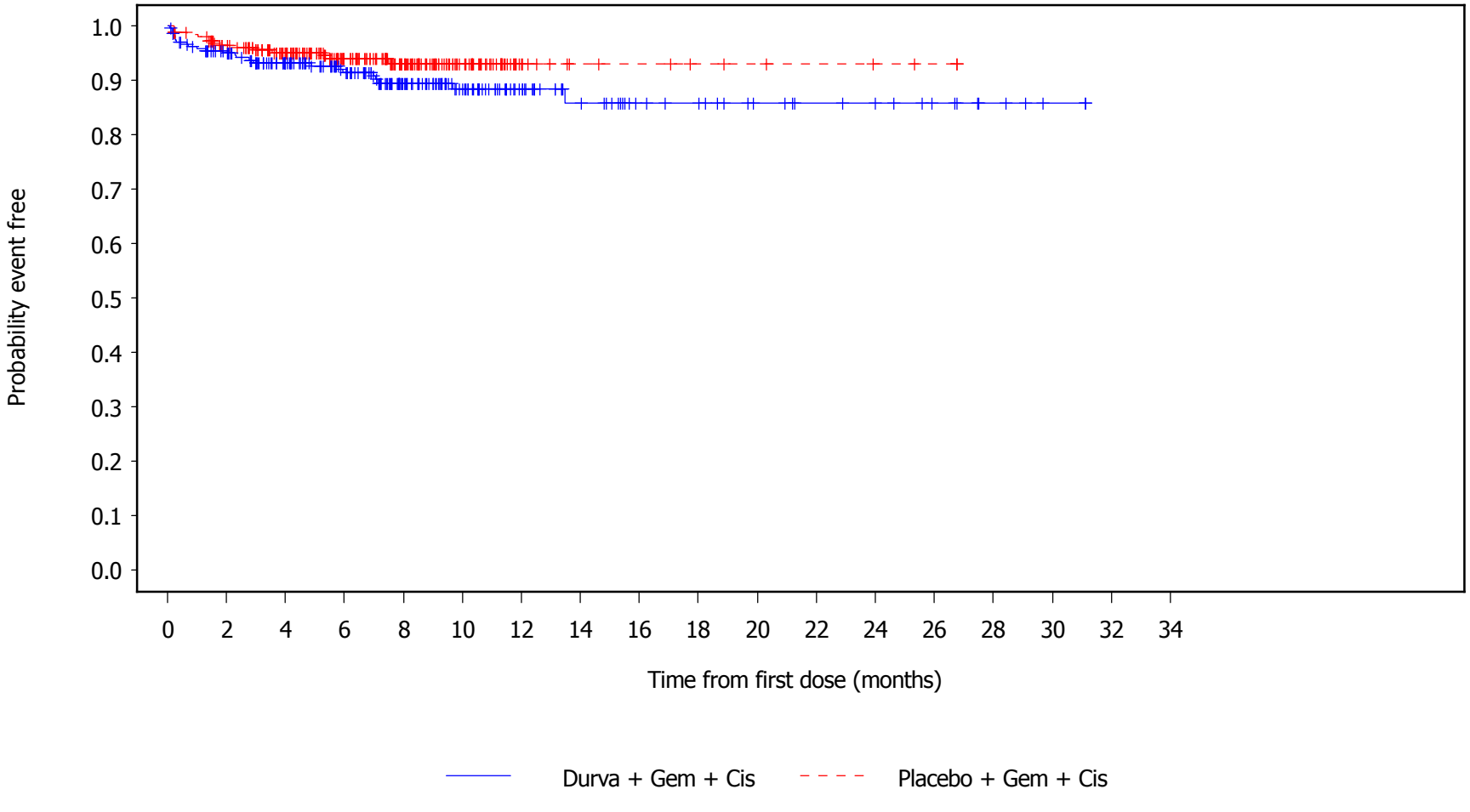
Figure 3.5.5.28 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Hypoalbuminaemia for Region=Rest of World
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

161	148	125	107	85	52	33	24	16	14	9	7	3	2	2	1	0	0	Durva + Gem + Cis
146	131	111	86	58	33	18	13	8	5	2	2	0	0	0	0	0	0	Placebo + Gem + Cis

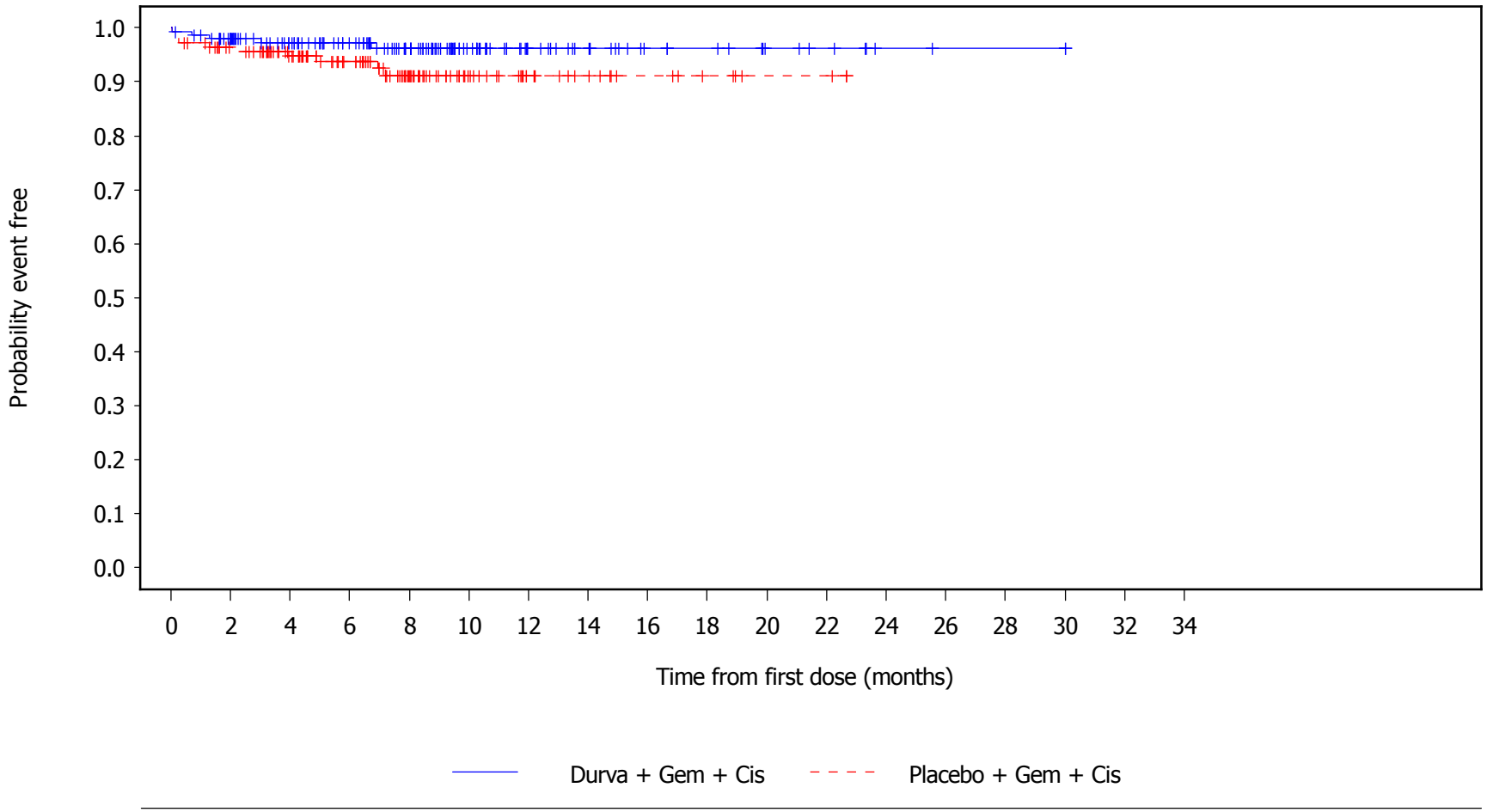
Figure 3.5.5.29 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Hypoalbuminaemia for Race=Asian
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

248	221	186	154	109	76	49	34	24	22	16	13	12	8	4	1	0	0	Durva + Gem + Cis
262	234	196	141	97	54	14	8	7	5	4	3	2	1	0	0	0	0	Placebo + Gem + Cis

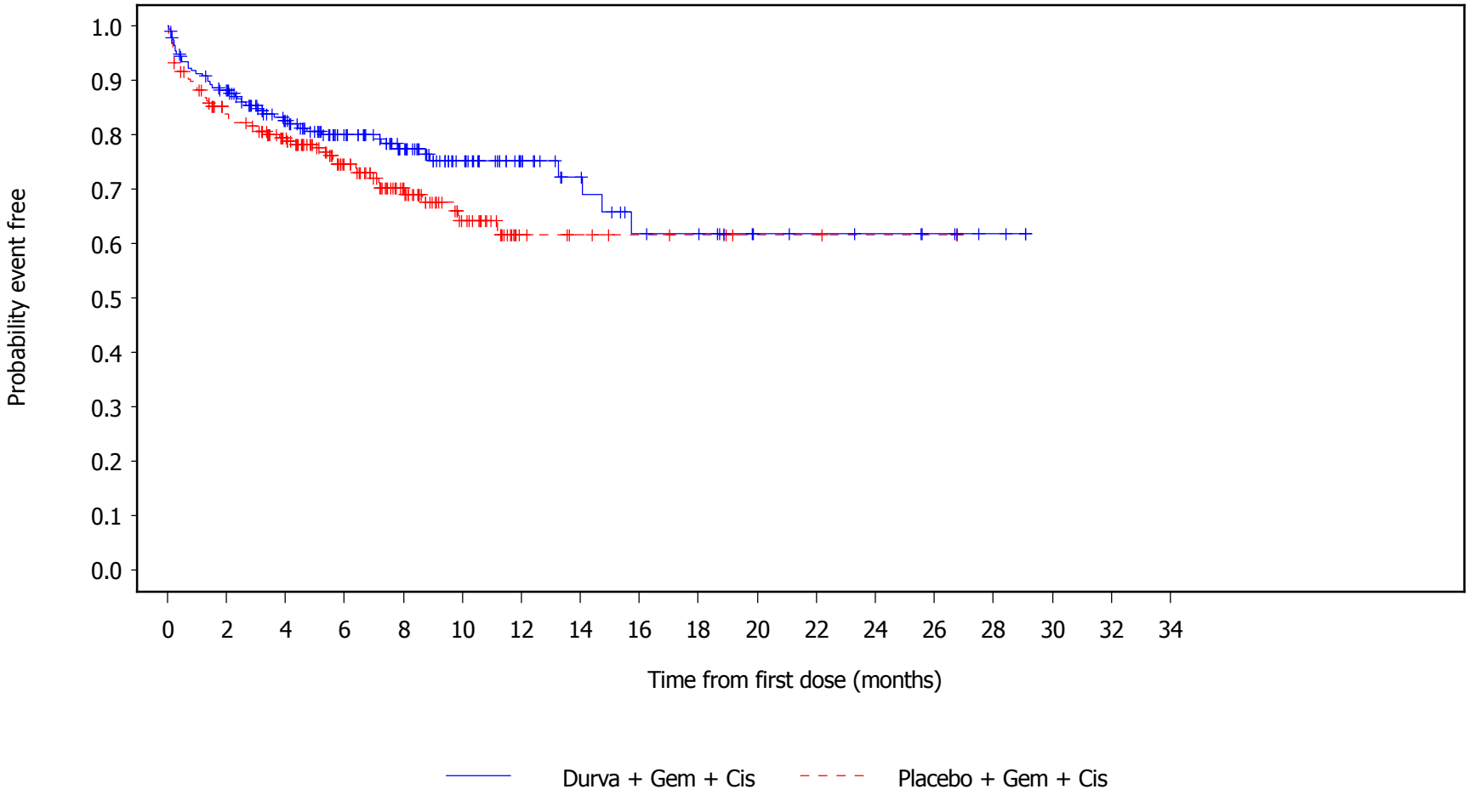
Figure 3.5.5.30 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Hypoalbuminaemia for Race=Non-Asian
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

154	142	120	102	81	49	30	23	15	13	8	6	2	1	1	1	0	0	Durva + Gem + Cis
141	126	106	83	55	30	18	13	8	5	2	2	0	0	0	0	0	0	Placebo + Gem + Cis

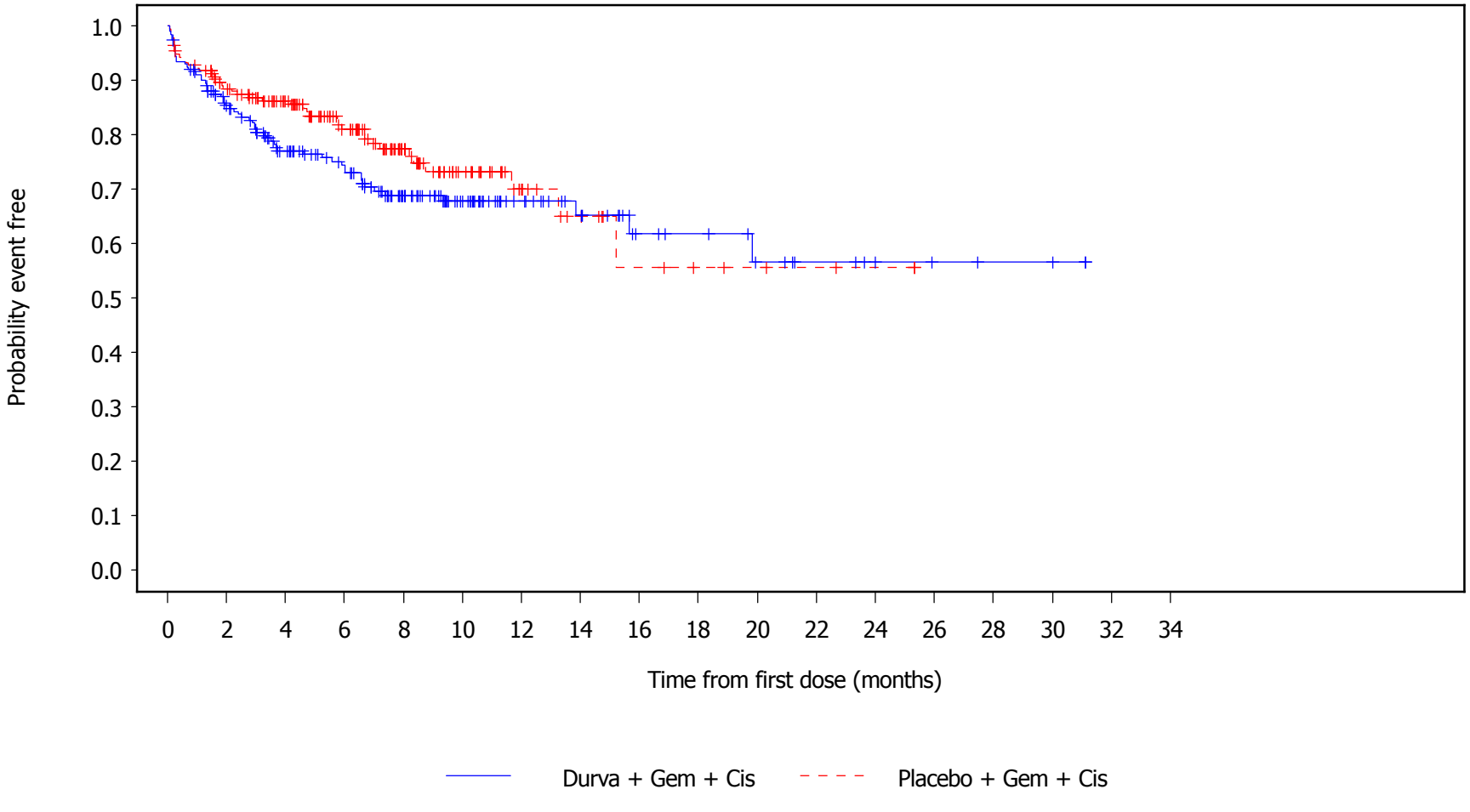
Figure 3.5.5.31 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI GT: Biliary SMQ AEs for Sex=Male
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

199	169	136	108	81	53	32	23	16	15	9	8	7	5	2	0	0	0	Durva + Gem + Cis
207	160	133	91	63	34	11	8	6	5	2	2	1	1	0	0	0	0	Placebo + Gem + Cis

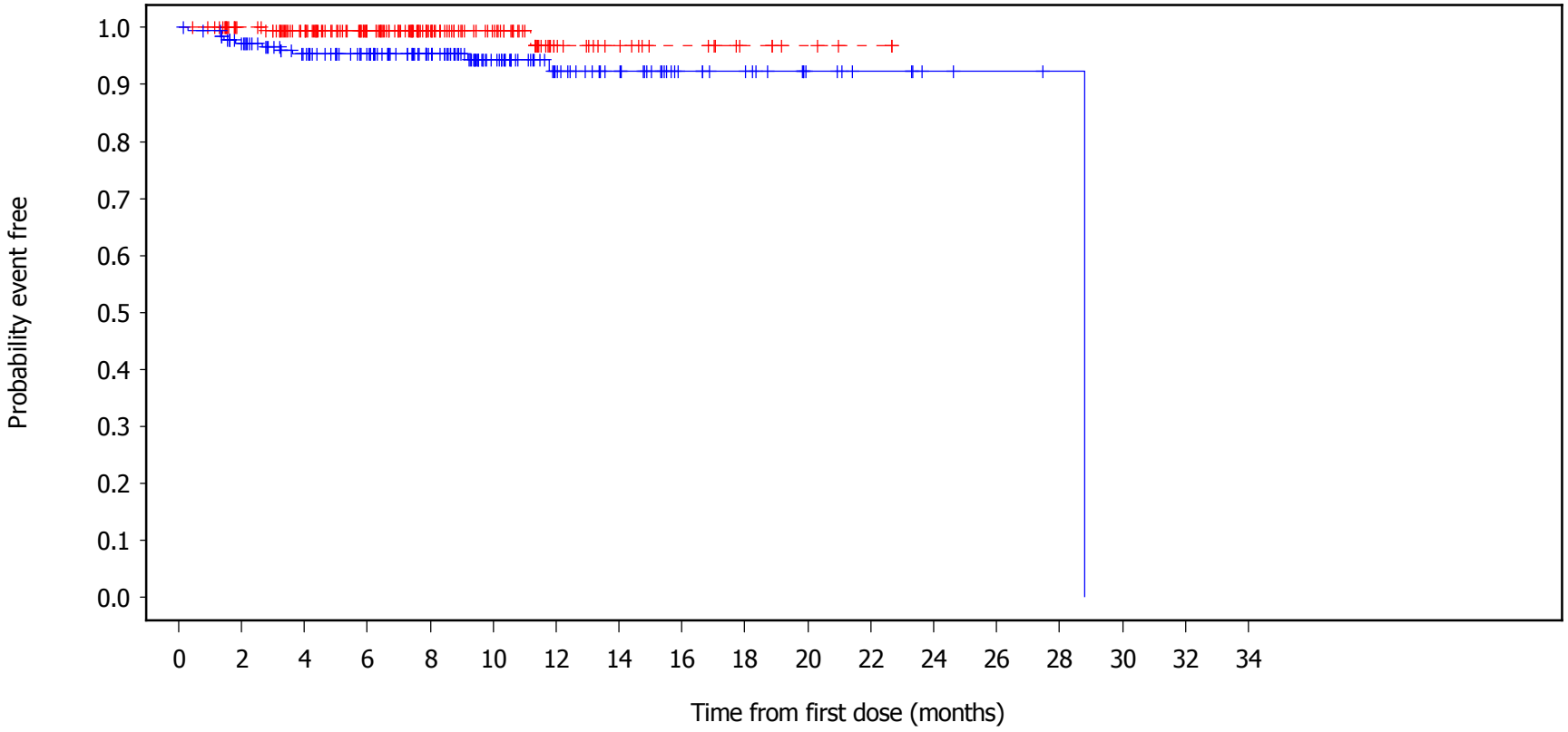
Figure 3.5.5.32 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI GT: Biliary SMQ AEs for Sex=Female
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

203	161	129	112	80	54	35	26	16	14	10	7	5	3	2	2	0	0	Durva + Gem + Cis
196	162	134	100	64	36	17	11	6	4	3	2	1	0	0	0	0	0	Placebo + Gem + Cis

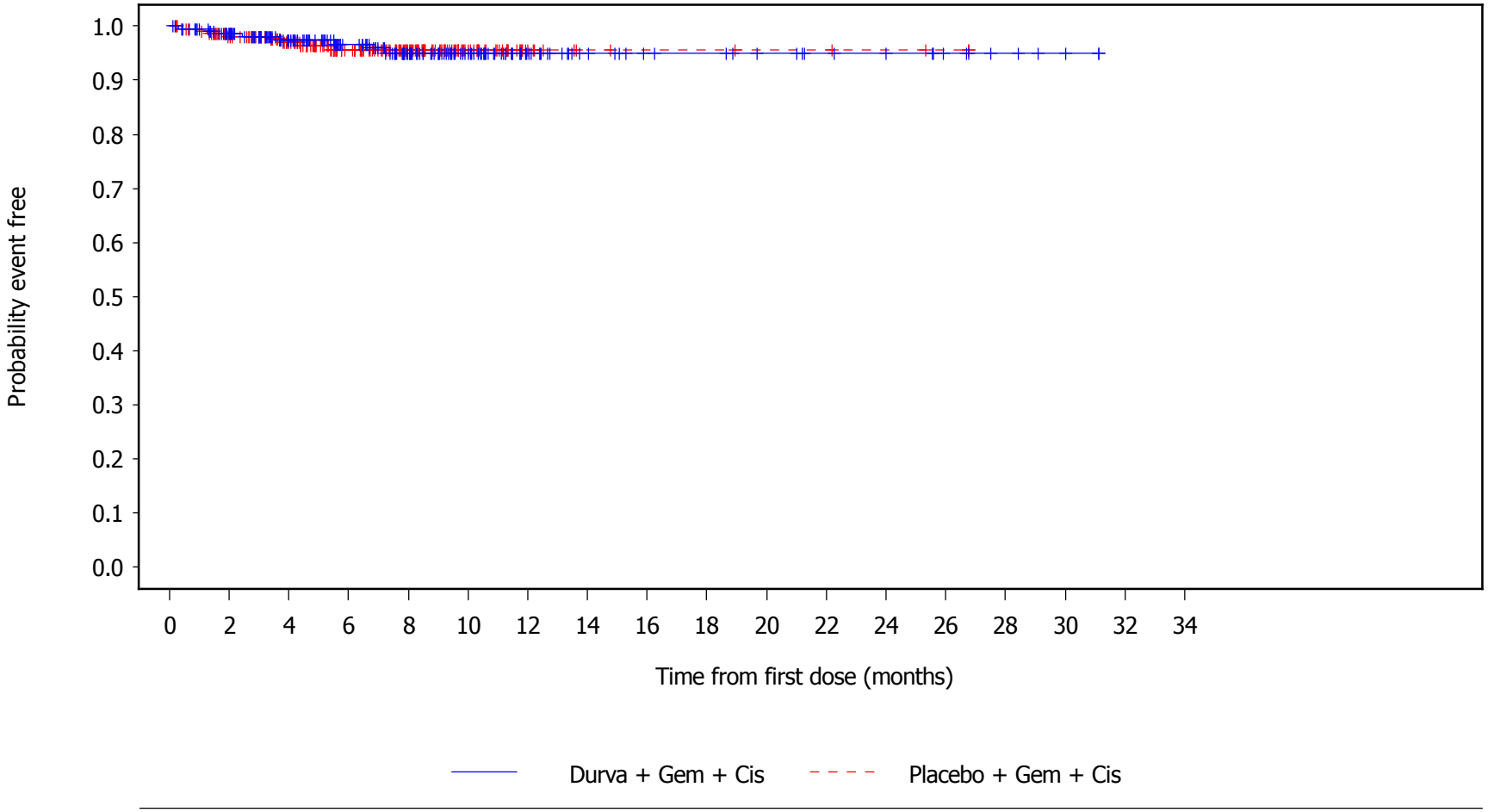
Figure 3.5.5.33 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Biliary tract infection for WHO ECOG Status at Screening=0
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

186	171	150	132	102	66	43	33	20	17	9	6	3	2	1	0	0	0	Durva + Gem + Cis
184	169	149	113	75	51	23	16	11	6	3	1	0	0	0	0	0	0	Placebo + Gem + Cis

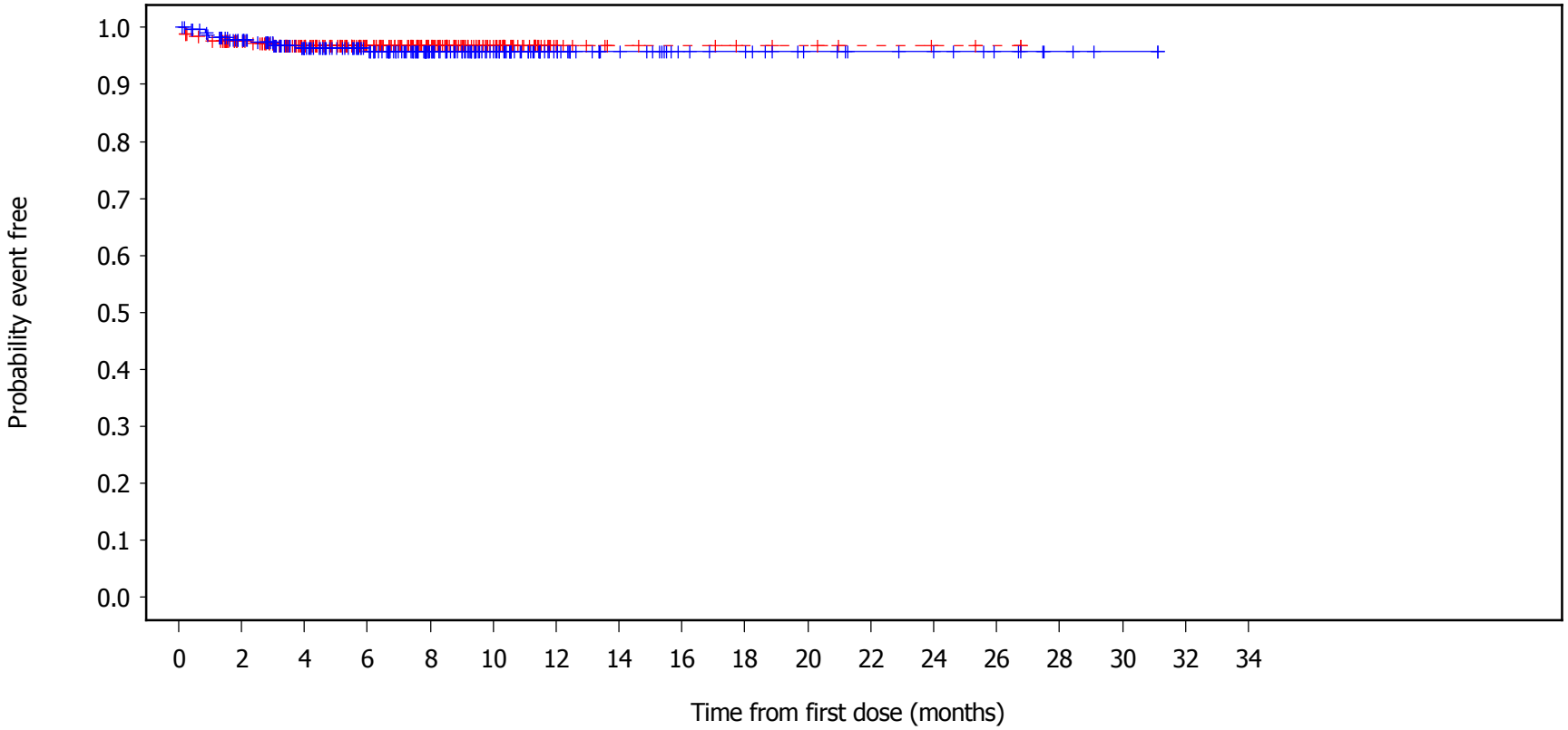
Figure 3.5.5.34 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Biliary tract infection for WHO ECOG Status at Screening=1
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

216	194	158	126	93	63	36	24	19	18	15	12	11	7	4	2	0	0	Durva + Gem + Cis
219	198	160	116	82	38	10	5	4	4	3	3	2	1	0	0	0	0	Placebo + Gem + Cis

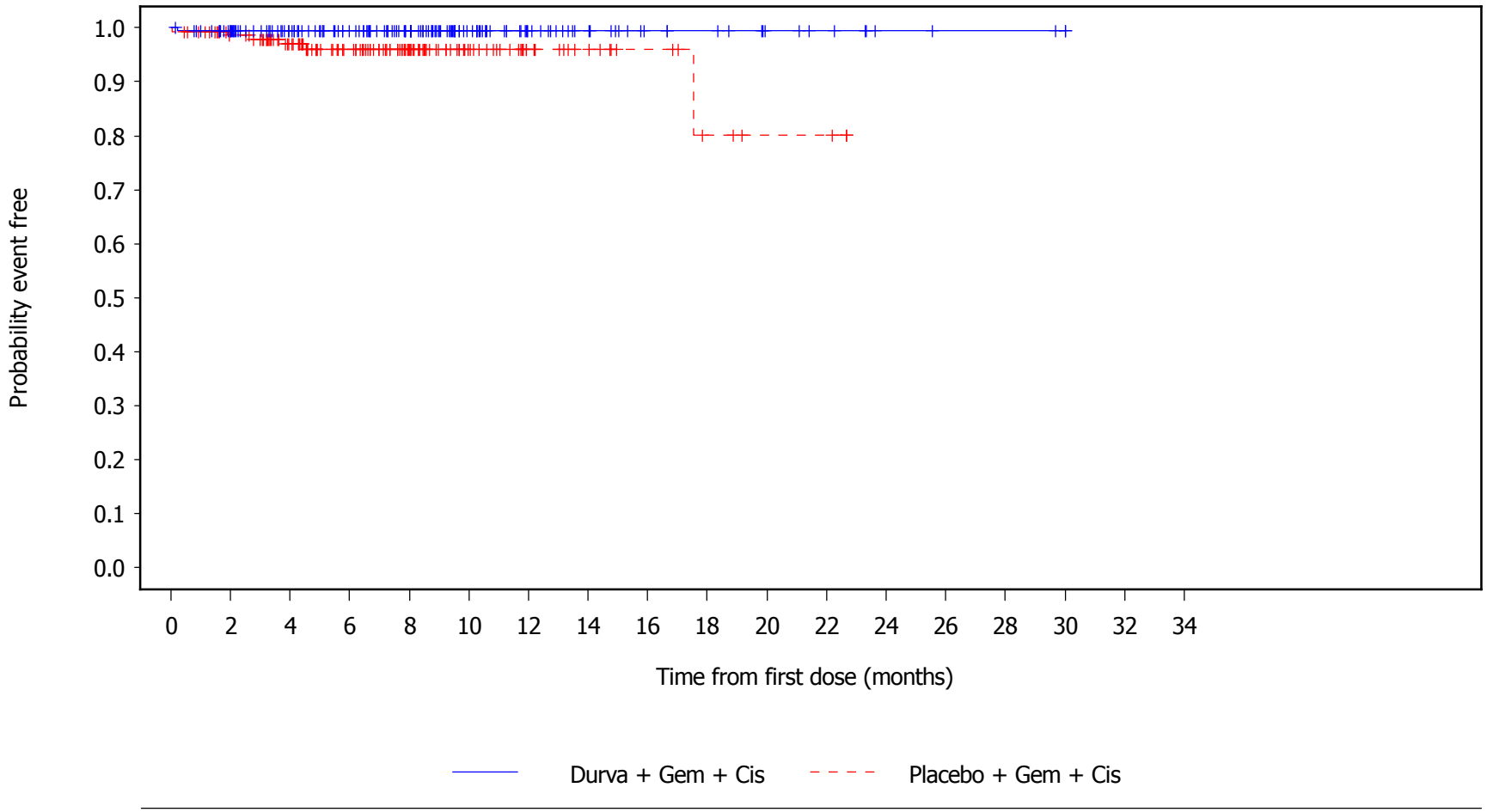
Figure 3.5.5.35 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Lymphocyte count decreased for Region=Asia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

241	217	181	150	106	73	44	32	23	21	15	12	11	7	3	1	0	0	Durva + Gem + Cis
257	231	191	138	97	54	15	9	8	6	5	3	2	1	0	0	0	0	Placebo + Gem + Cis

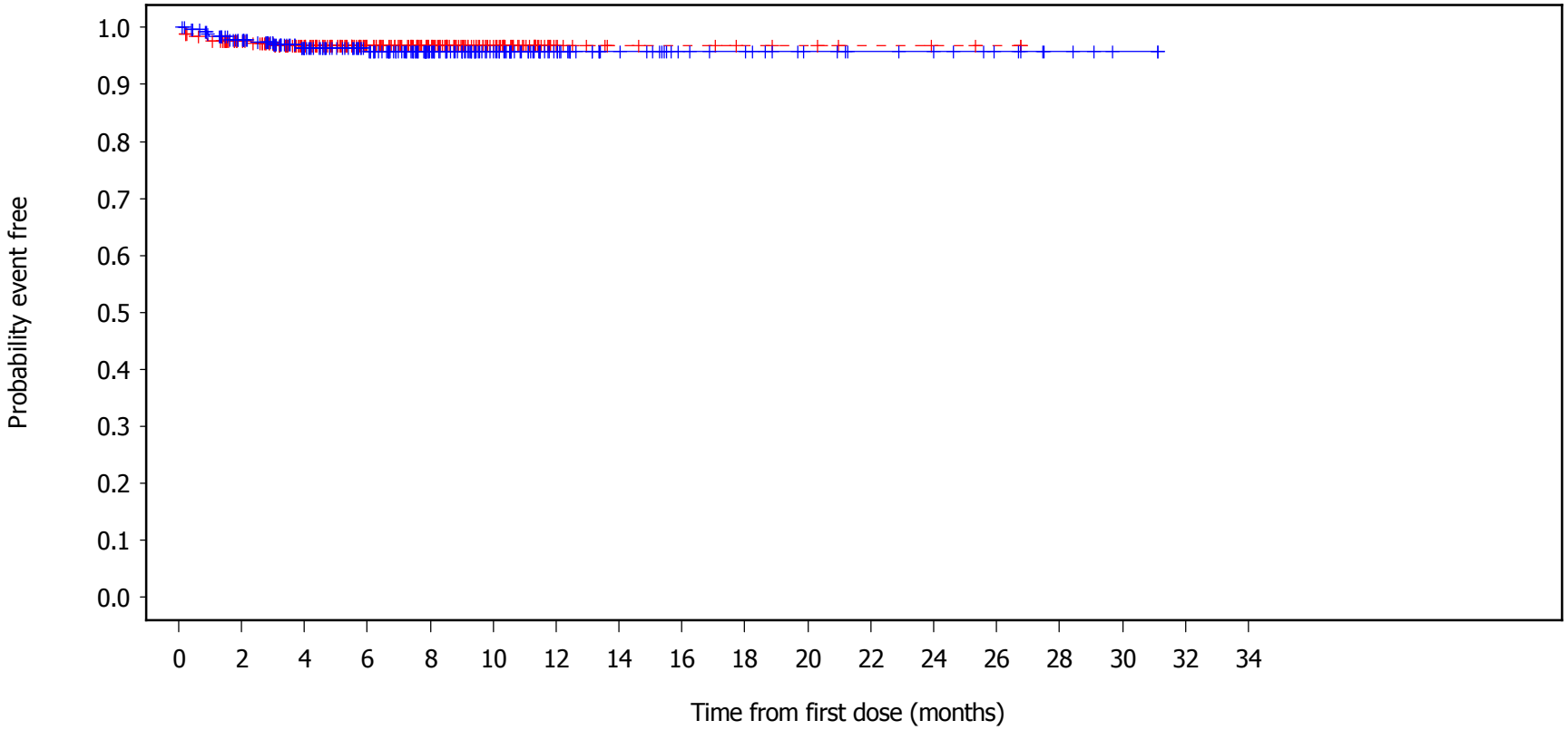
Figure 3.5.5.36 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Lymphocyte count decreased for Region=Rest of World
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

161	150	126	107	85	53	33	24	16	14	9	7	3	2	2	1	0	0	Durva + Gem + Cis
146	133	113	87	59	34	19	13	8	4	2	2	0	0	0	0	0	0	Placebo + Gem + Cis

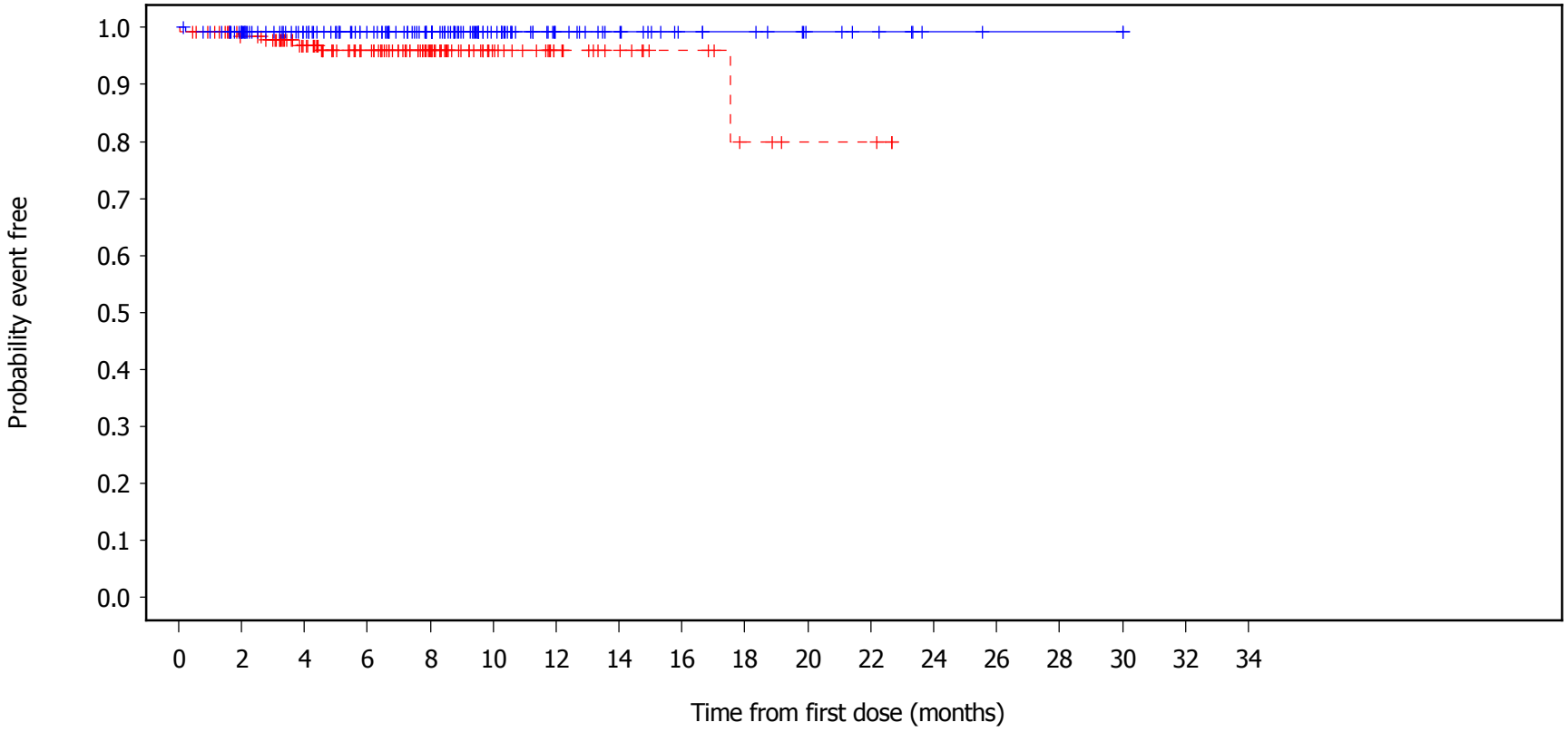
Figure 3.5.5.37 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Lymphocyte count decreased for Race=Asian
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

248	223	186	155	110	76	47	33	24	22	16	13	12	8	4	1	0	0	Durva + Gem + Cis
262	236	196	141	100	57	15	9	8	6	5	3	2	1	0	0	0	0	Placebo + Gem + Cis

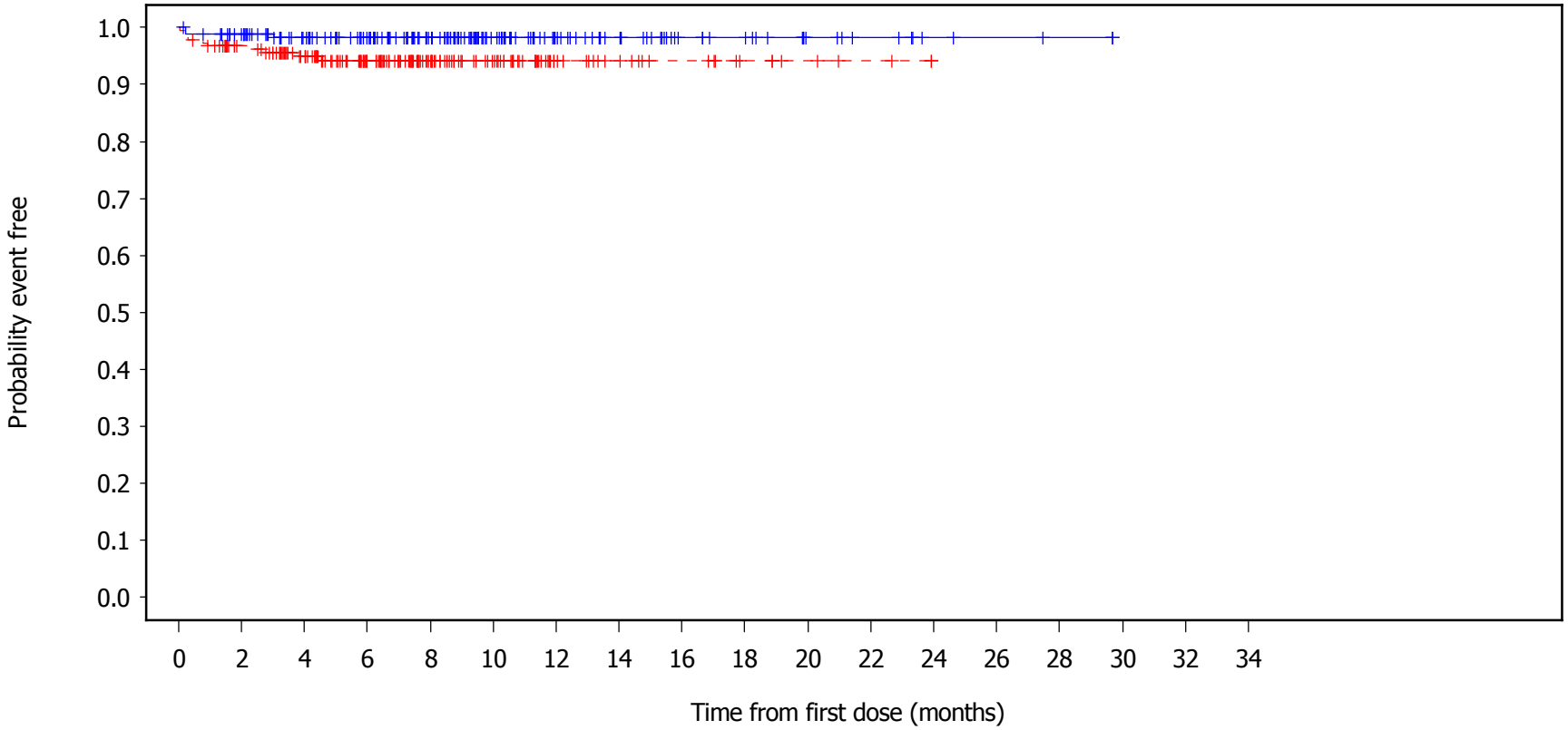
Figure 3.5.5.38 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Lymphocyte count decreased for Race=Non-Asian
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

154	144	121	102	81	50	30	23	15	13	8	6	2	1	1	1	0	0	Durva + Gem + Cis
141	128	108	84	56	31	19	13	8	4	2	2	0	0	0	0	0	0	Placebo + Gem + Cis

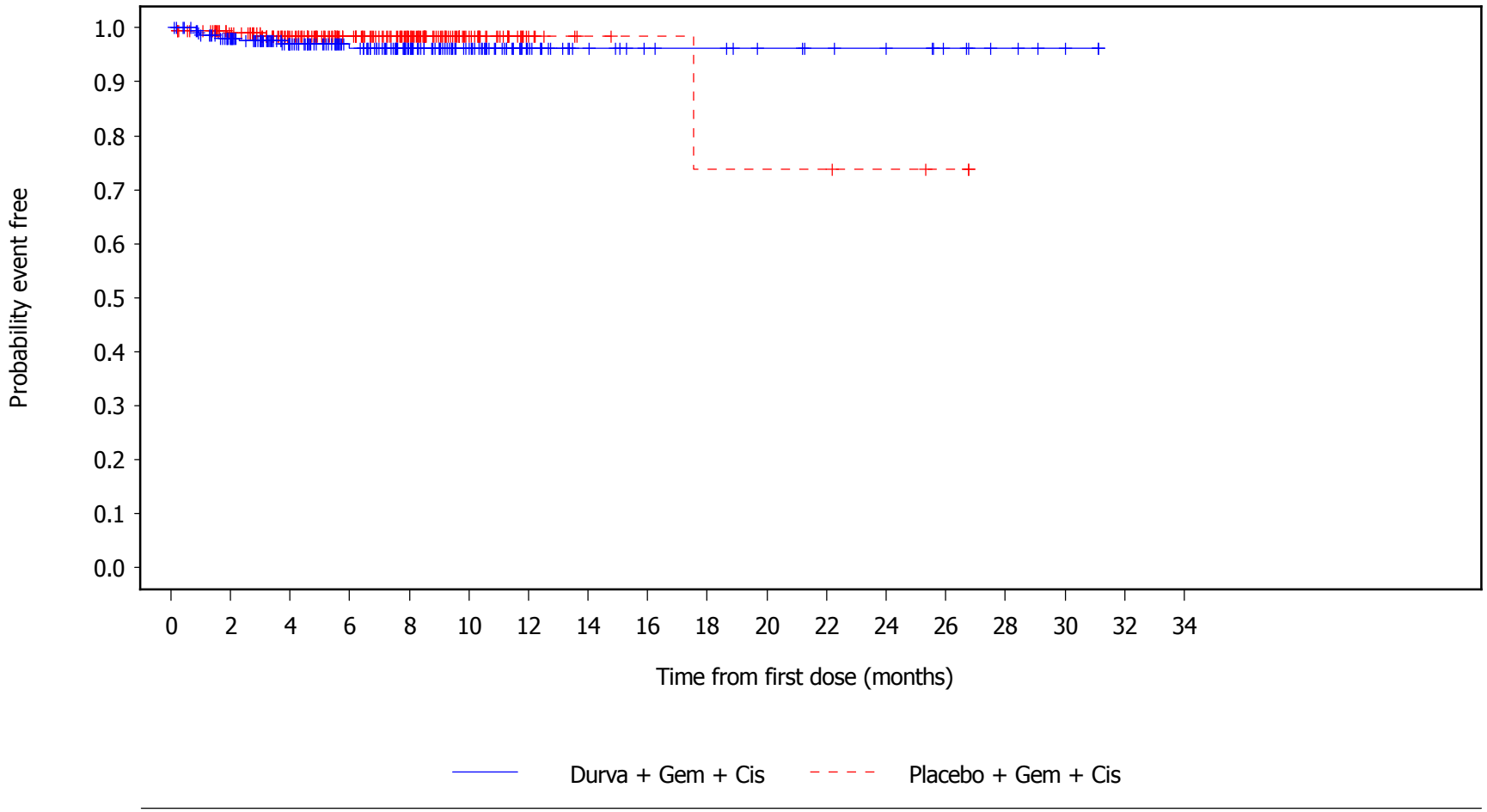
Figure 3.5.5.39 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Lymphocyte count decreased for WHO ECOG Status at Screening=0
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

186	174	152	133	101	65	43	33	21	18	10	7	3	2	1	0	0	0	Durva + Gem + Cis
184	164	142	107	72	50	24	17	12	7	4	2	0	0	0	0	0	0	Placebo + Gem + Cis

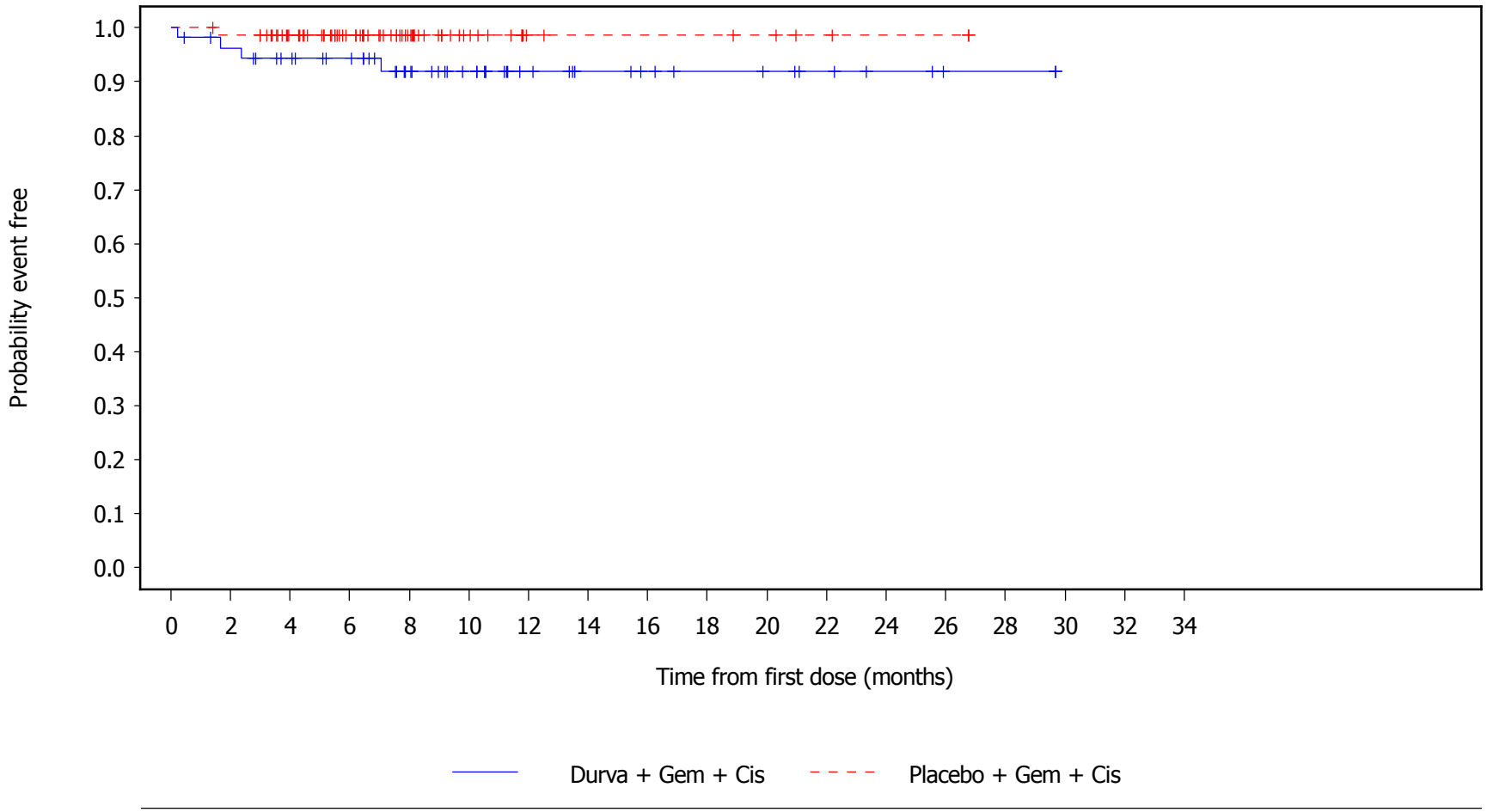
Figure 3.5.5.40 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Lymphocyte count decreased for WHO ECOG Status at Screening=1
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

216	193	155	124	90	61	34	23	18	17	14	12	11	7	4	2	0	0	Durva + Gem + Cis
219	200	162	118	84	38	10	5	4	3	3	3	2	1	0	0	0	0	Placebo + Gem + Cis

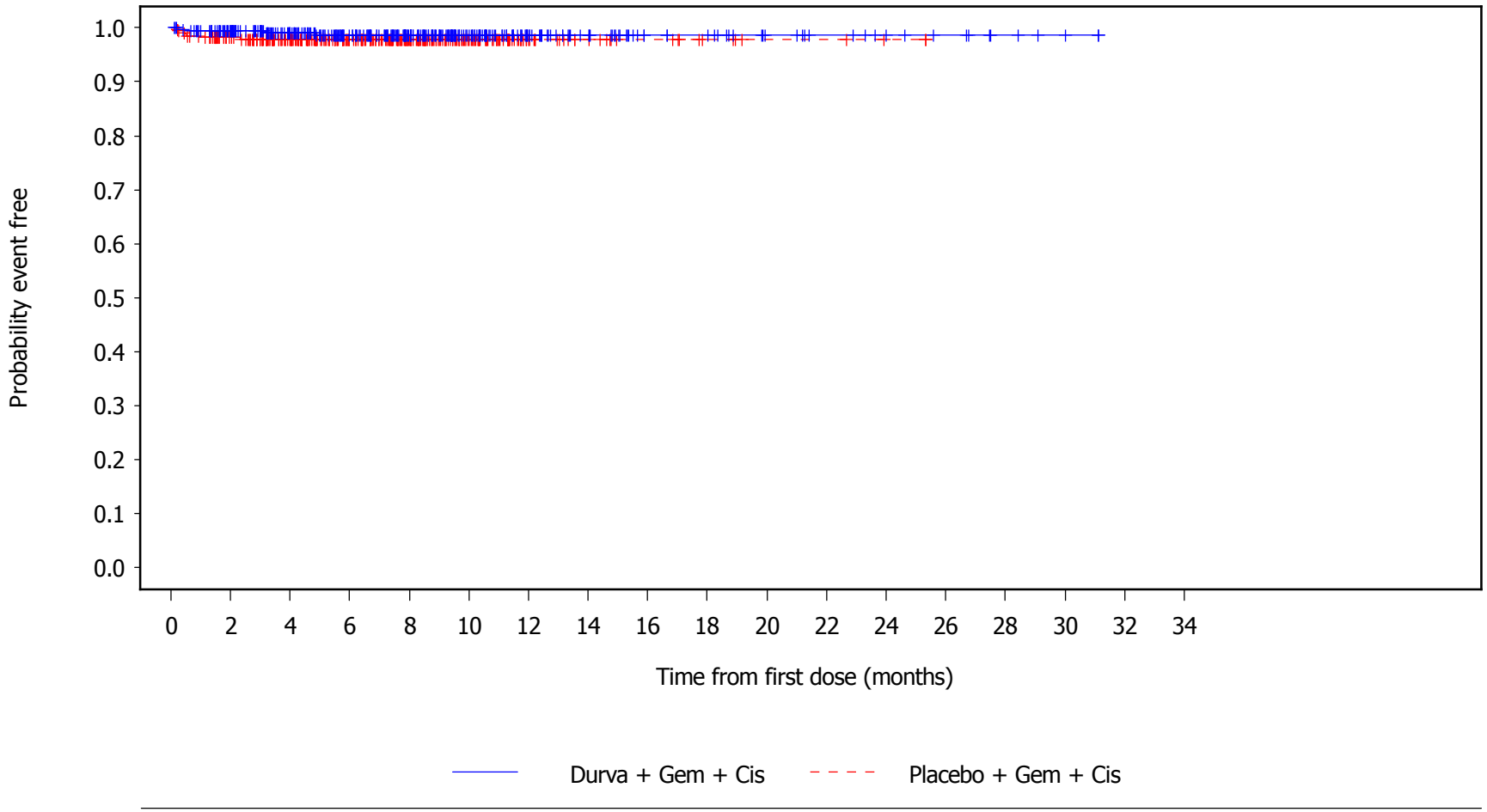
Figure 3.5.5.41 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Myelosuppression for Disease Extent=Locally Advanced
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

55	51	46	42	32	25	16	12	10	8	7	5	3	1	1	0	0	0	Durva + Gem + Cis
73	71	60	44	27	14	6	5	5	5	4	2	1	1	0	0	0	0	Placebo + Gem + Cis

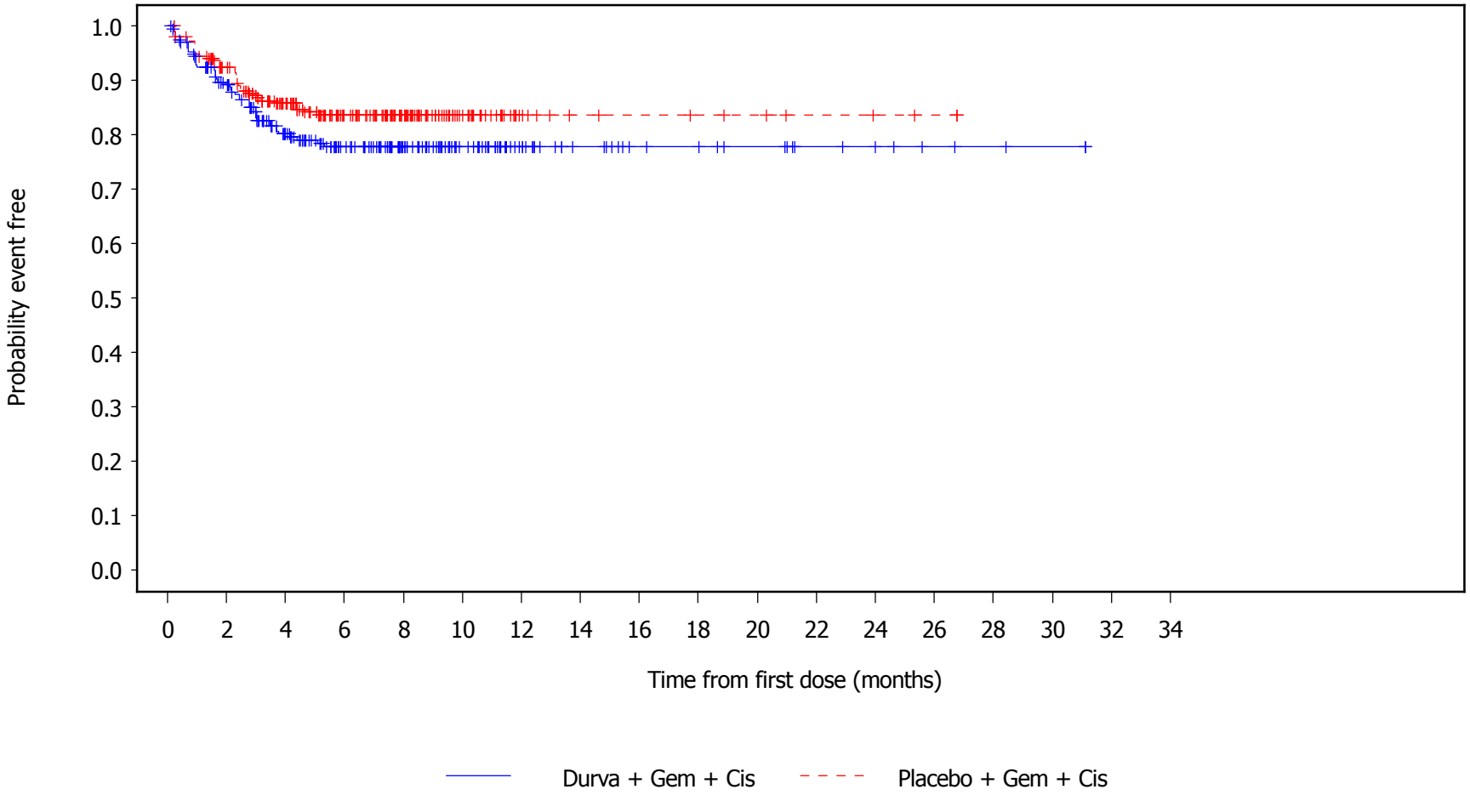
Figure 3.5.5.42 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Myelosuppression for Disease Extent=Metastatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

347	318	264	218	163	104	63	45	29	27	18	14	11	8	4	2	0	0	Durva + Gem + Cis
330	295	247	183	130	74	27	17	11	6	3	3	1	0	0	0	0	0	Placebo + Gem + Cis

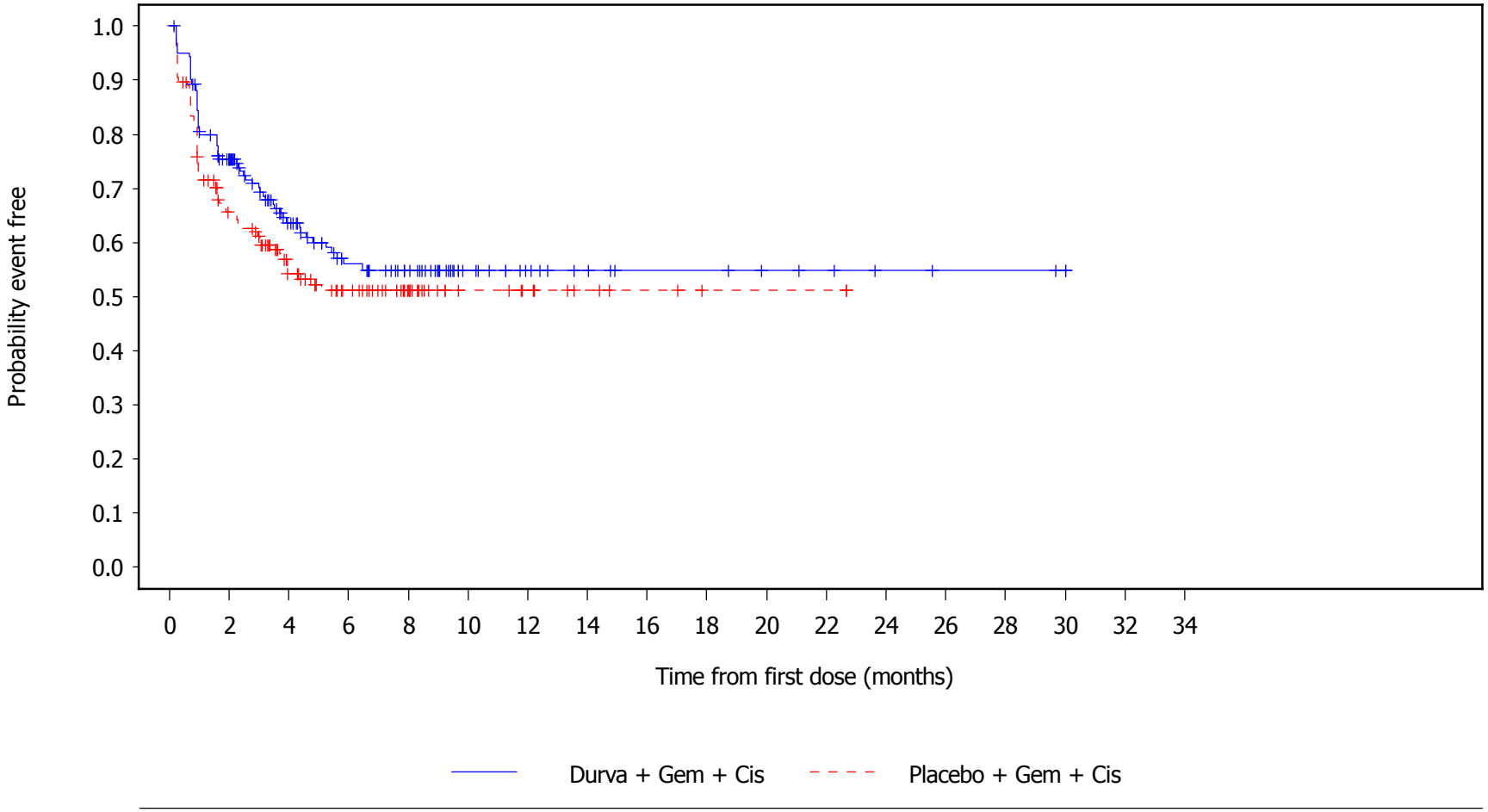
Figure 3.5.5.43 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Neutropenia for Region=Asia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

241	199	149	114	79	53	32	21	15	14	11	7	6	3	2	1	0	0	Durva + Gem + Cis
257	218	168	113	75	39	13	8	7	6	5	3	2	1	0	0	0	0	Placebo + Gem + Cis

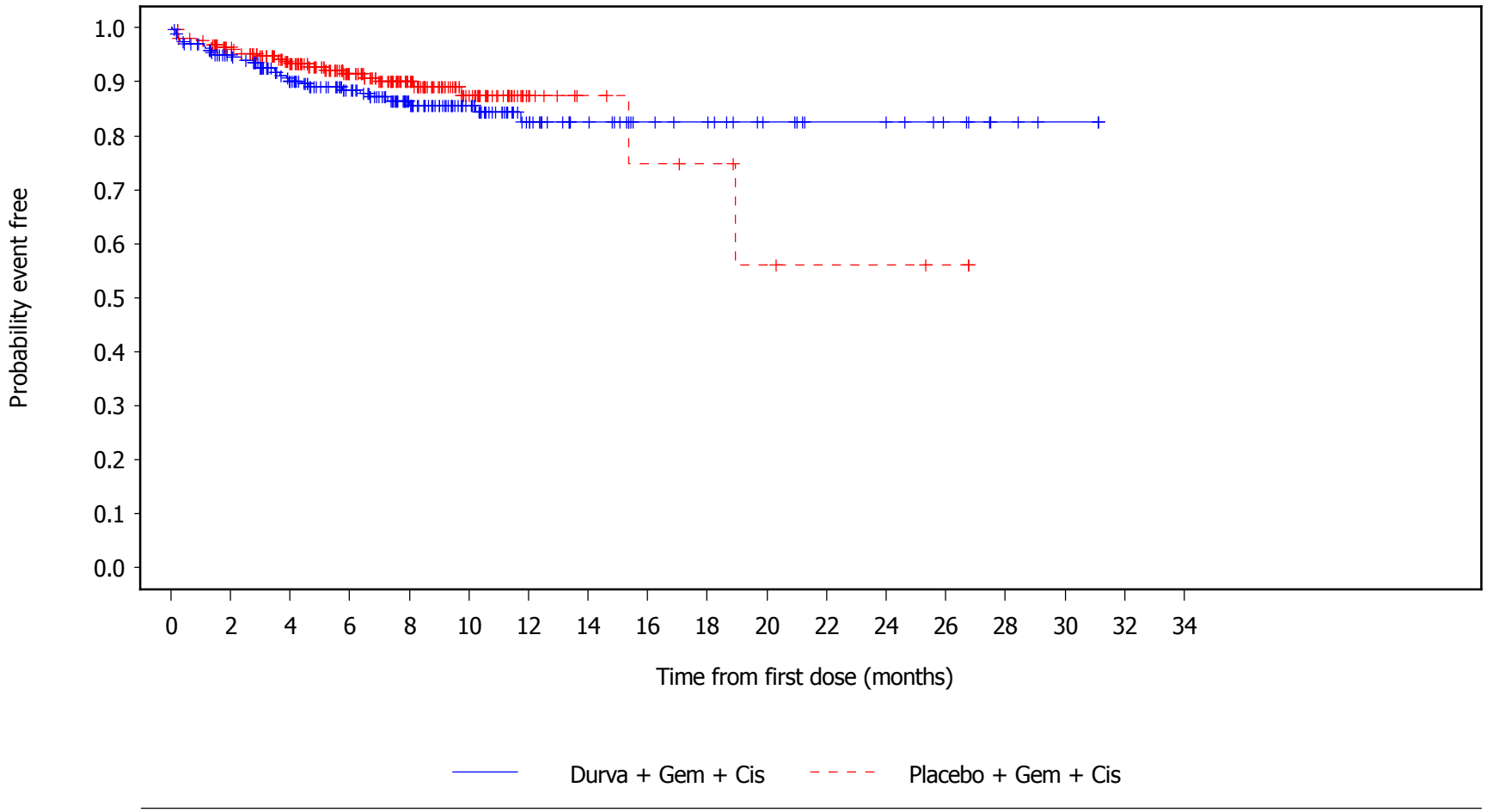
Figure 3.5.5.44 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI PT: Neutropenia for Region=Rest of World
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

161	112	74	53	41	22	15	11	8	8	6	5	3	2	2	1	0	0	Durva + Gem + Cis
146	87	58	42	26	12	9	5	3	1	1	1	0	0	0	0	0	0	Placebo + Gem + Cis

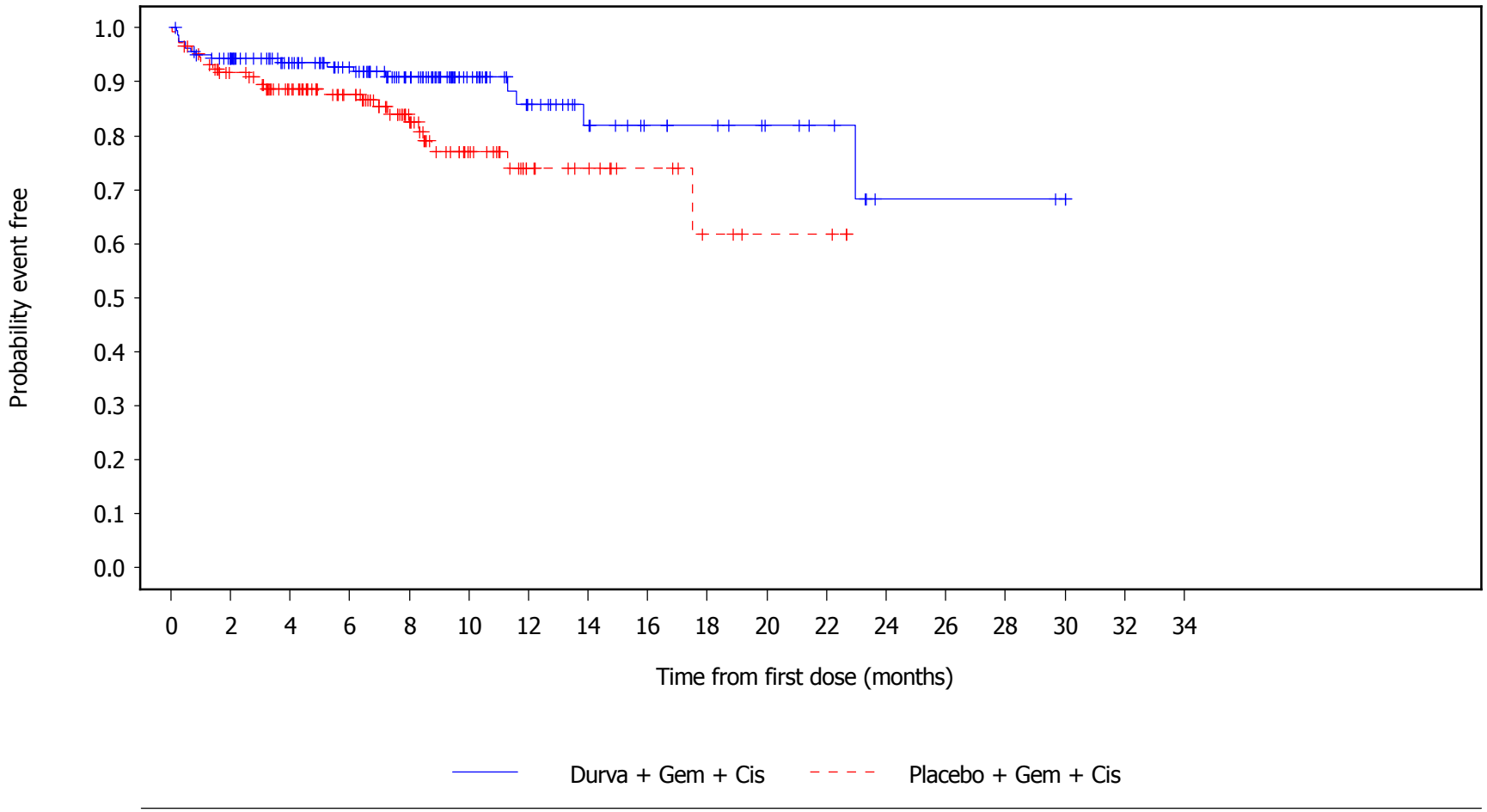
Figure 3.5.6.1 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Hepatic SMQ AEs for Region=Asia
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

241	212	175	145	104	73	43	31	23	21	15	11	11	7	3	1	0	0	Durva + Gem + Cis
257	229	189	134	91	50	14	8	6	5	3	2	2	1	0	0	0	0	Placebo + Gem + Cis

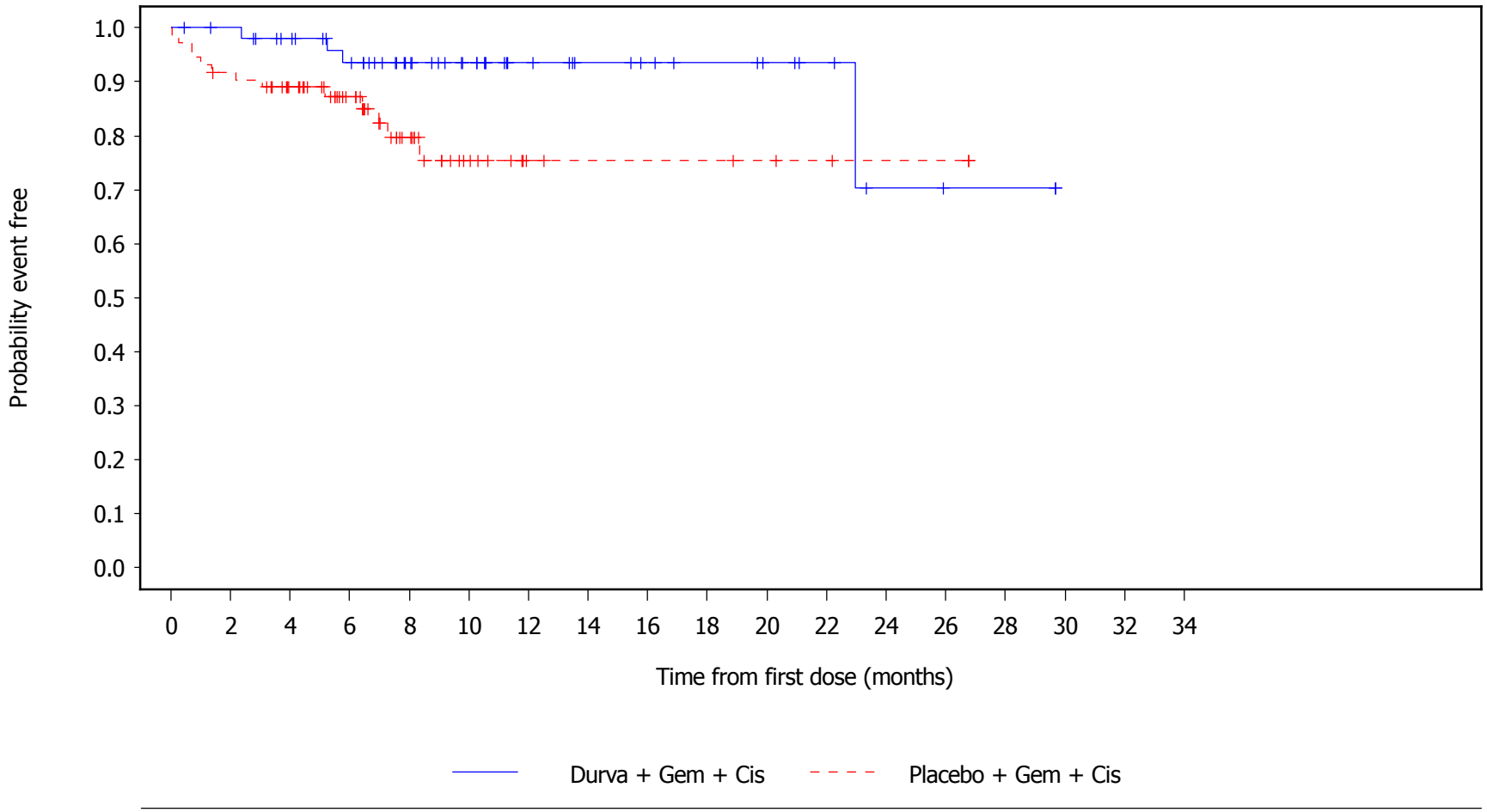
Figure 3.5.6.2 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Hepatic SMQ AEs for Region=Rest of World
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

161	145	121	104	80	49	31	21	15	13	9	7	2	2	2	1	0	0	Durva + Gem + Cis
146	124	104	83	55	32	17	13	8	4	2	2	0	0	0	0	0	0	Placebo + Gem + Cis

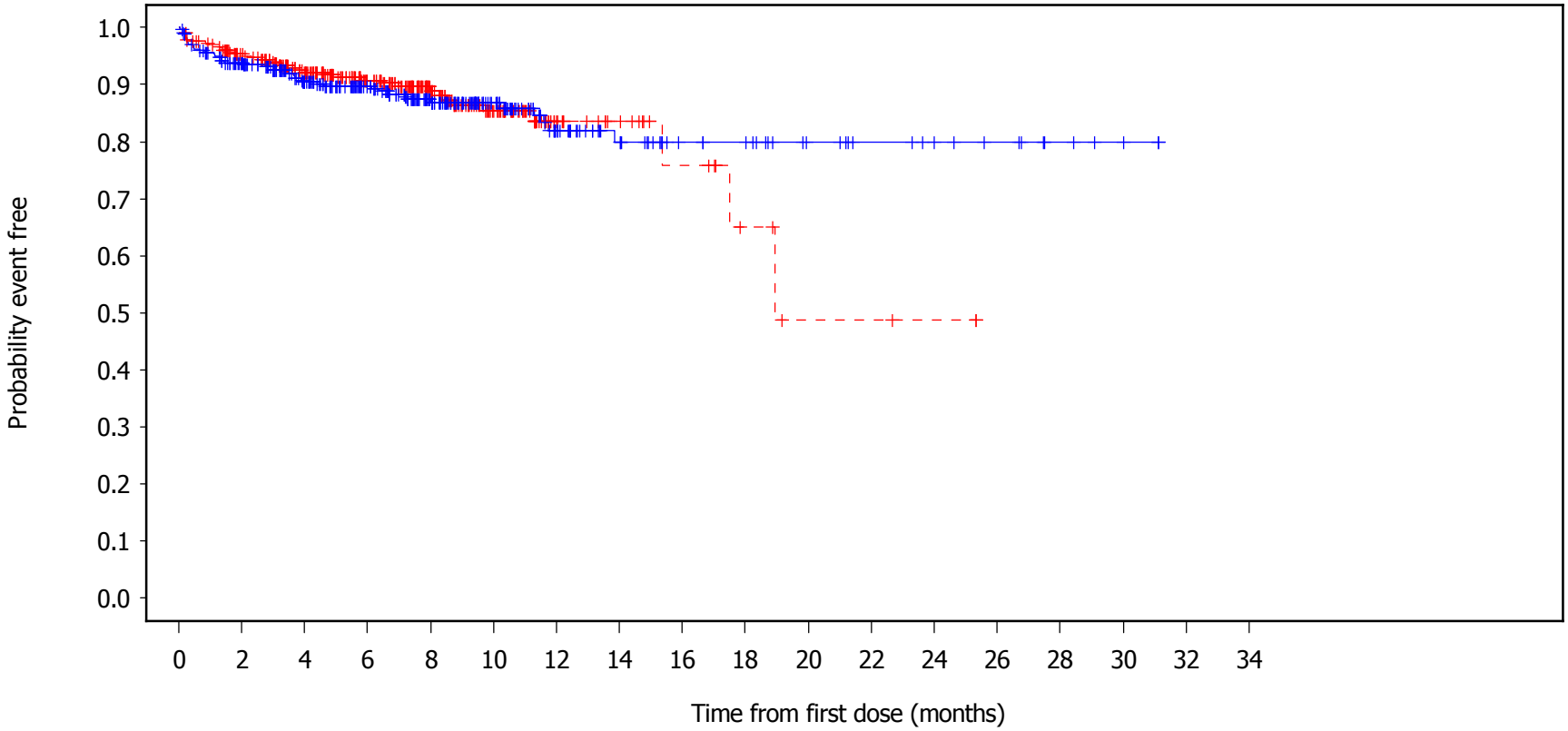
Figure 3.5.6.3 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Hepatic SMQ AEs for Disease Extent=Locally Advanced
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

55	53	48	42	32	25	17	13	11	9	7	5	2	1	1	0	0	0	Durva + Gem + Cis
73	66	57	42	24	12	5	4	4	4	3	2	1	1	0	0	0	0	Placebo + Gem + Cis

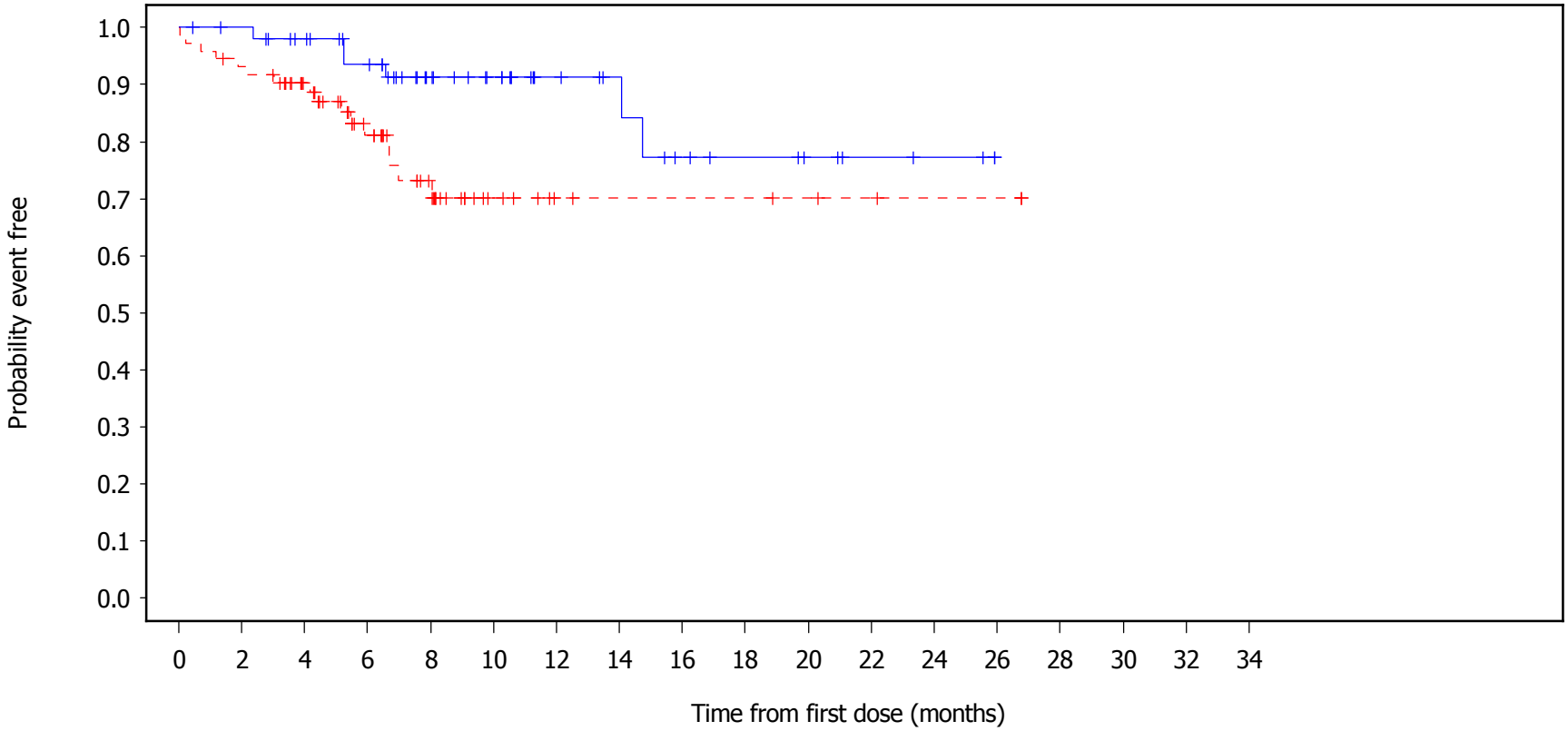
Figure 3.5.6.4 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Hepatic SMQ AEs for Disease Extent=Metastatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

347	304	248	207	152	97	57	39	27	25	17	13	11	8	4	2	0	0	Durva + Gem + Cis
330	287	236	175	122	70	26	17	10	5	2	2	1	0	0	0	0	0	Placebo + Gem + Cis

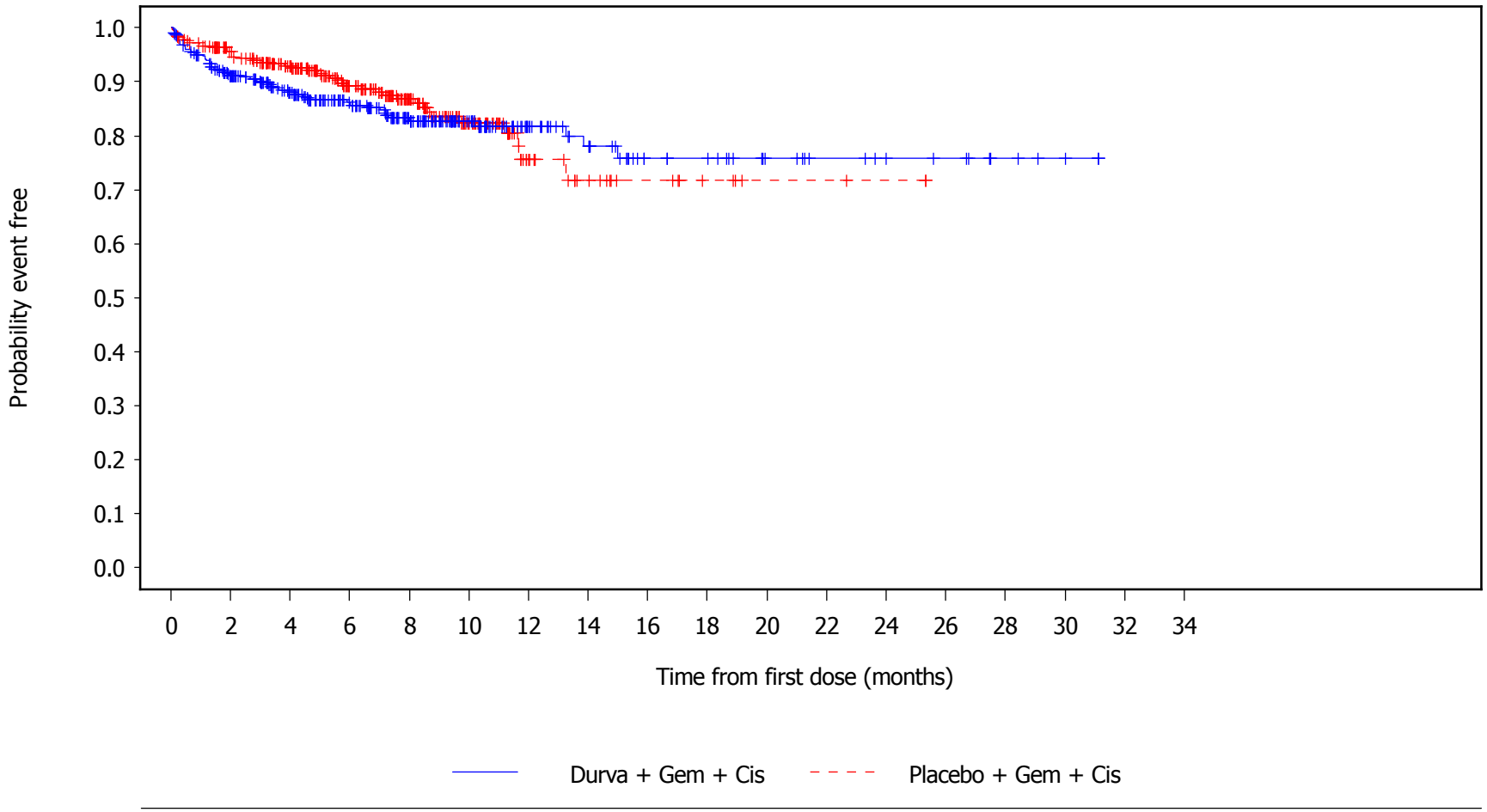
Figure 3.5.6.5 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Biliary SMQ AEs for Disease Extent=Locally Advanced
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

55	53	48	42	30	24	16	13	9	7	5	3	2	0	0	0	0	0	Durva + Gem + Cis
73	67	56	38	24	10	5	4	4	4	3	2	1	1	0	0	0	0	Placebo + Gem + Cis

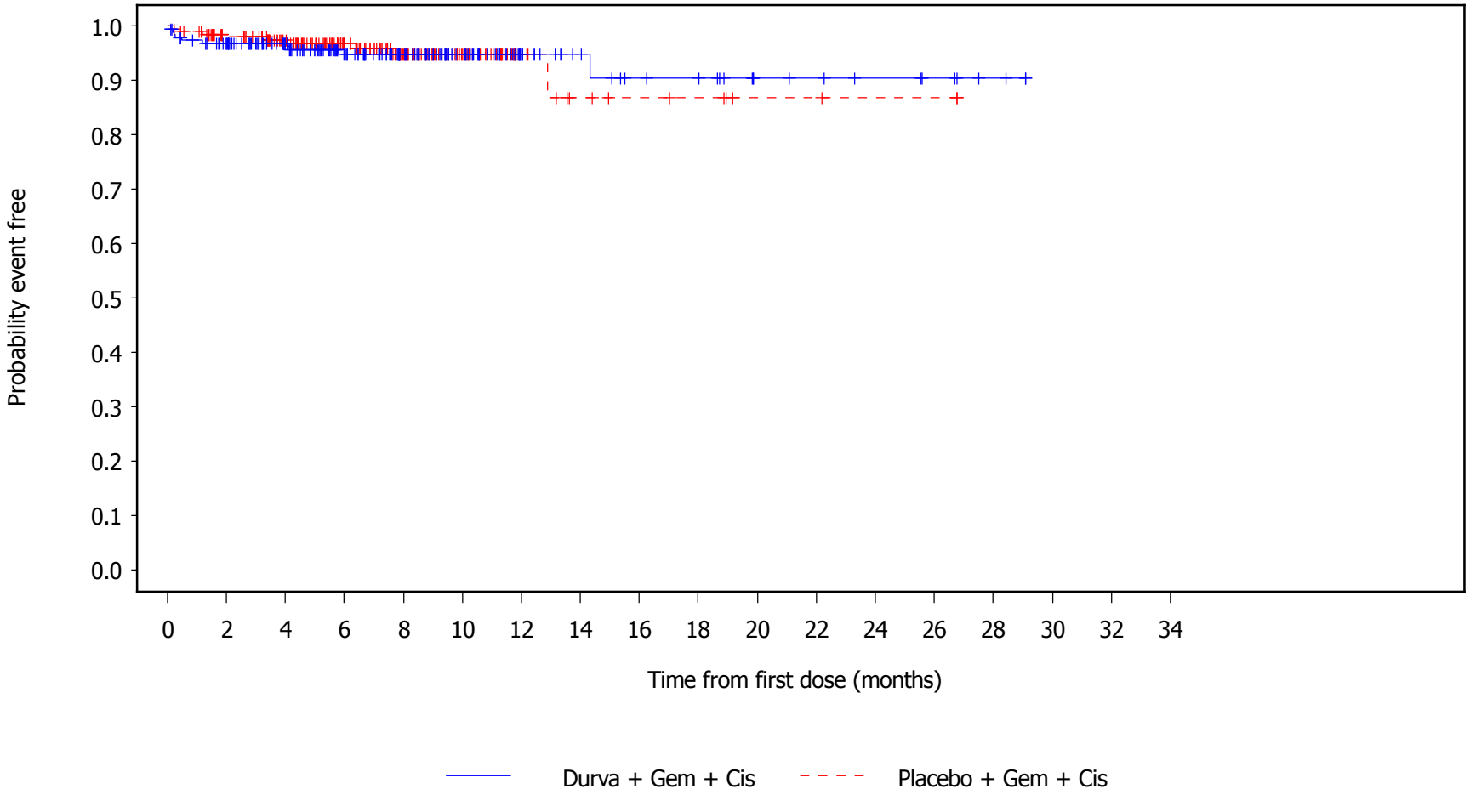
Figure 3.5.6.6 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Biliary SMQ AEs for Disease Extent=Metastatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

347	294	242	199	147	94	55	40	26	24	16	12	10	8	4	2	0	0	Durva + Gem + Cis
330	286	239	170	119	68	24	15	9	5	2	2	1	0	0	0	0	0	Placebo + Gem + Cis

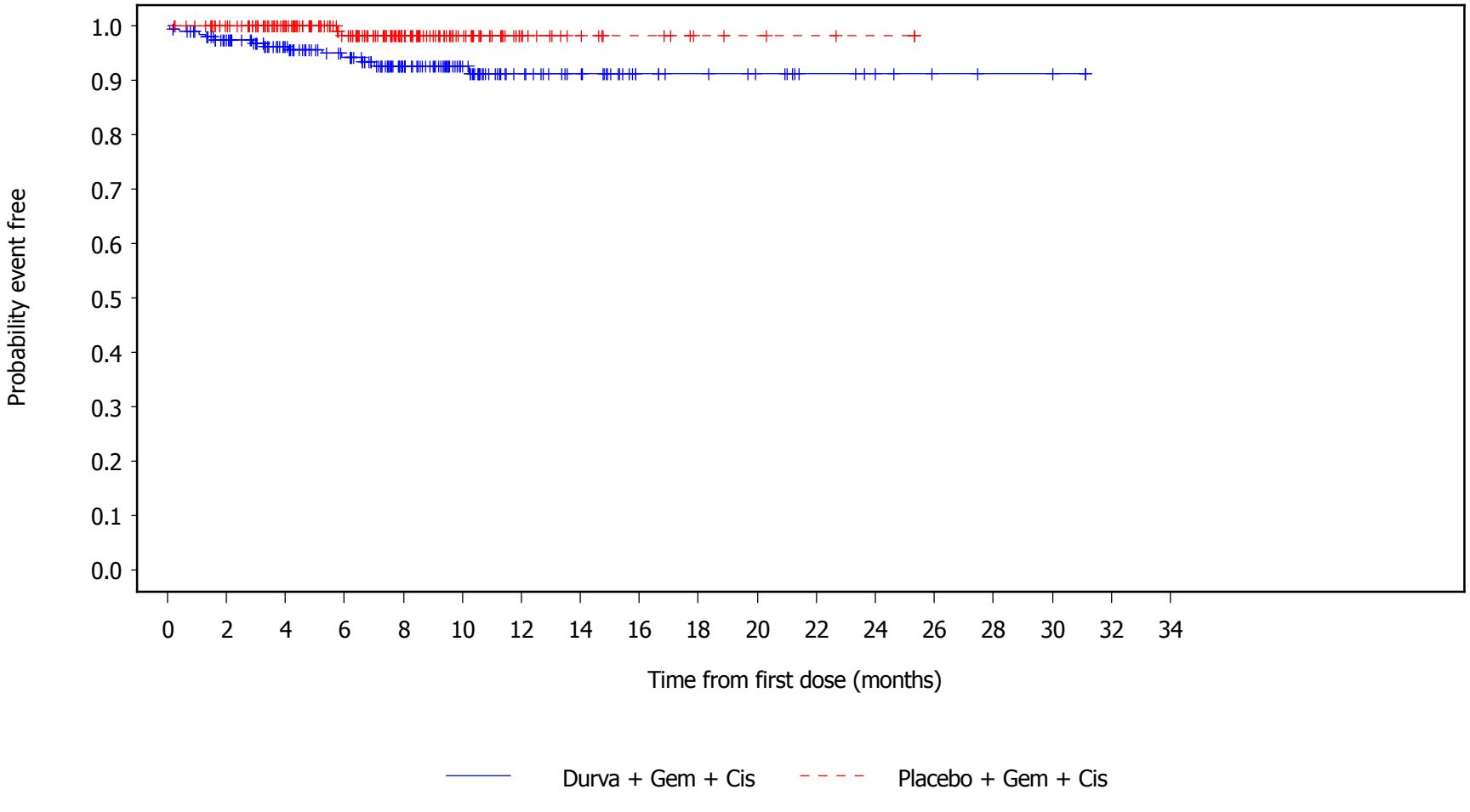
Figure 3.5.6.7 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Cholangitis for Sex=Male
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

199	181	151	119	89	58	32	23	18	17	10	9	7	5	2	0	0	0	Durva + Gem + Cis
207	185	158	111	81	44	14	8	6	5	2	2	1	1	0	0	0	0	Placebo + Gem + Cis

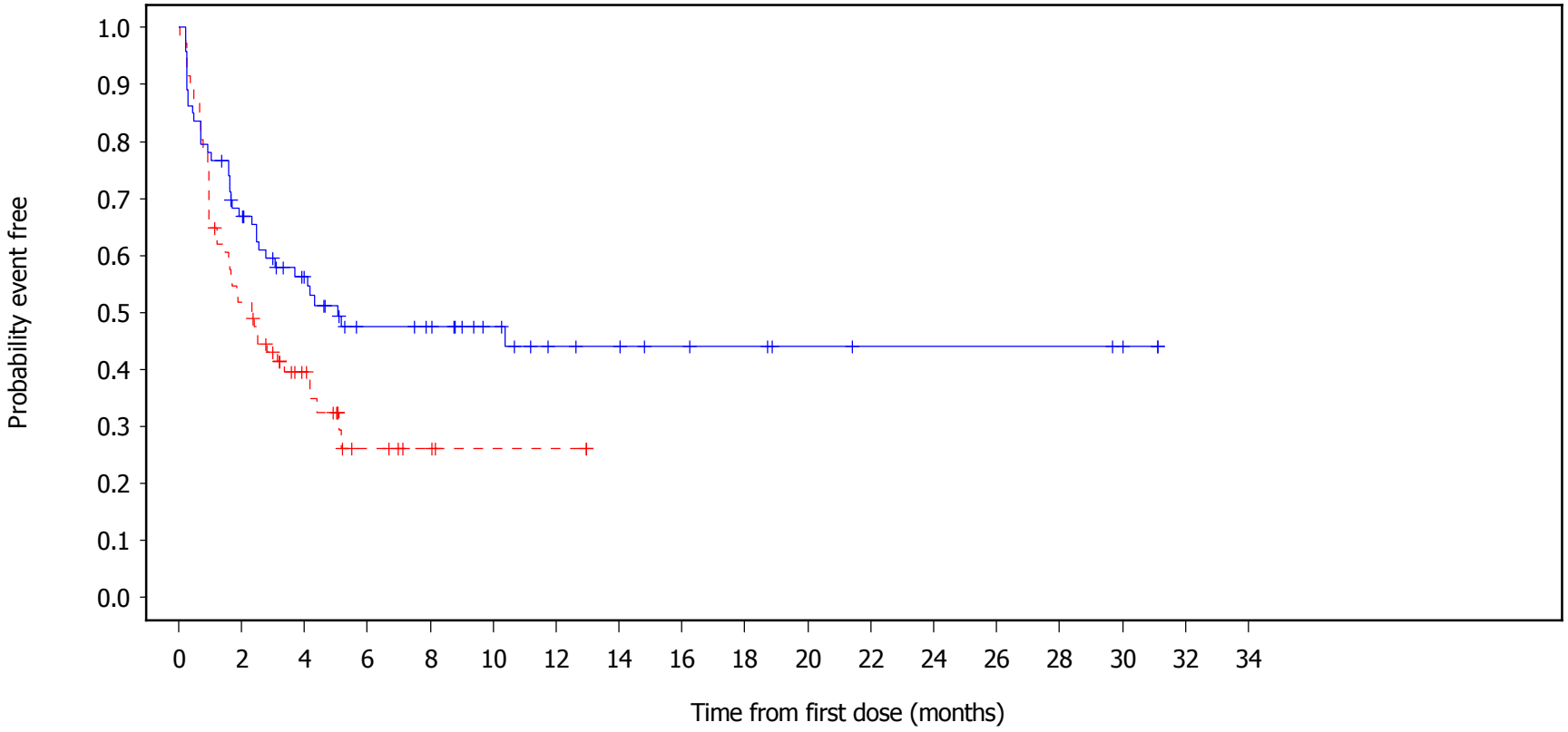
Figure 3.5.6.8 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Cholangitis for Sex=Female
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

203	182	155	133	97	66	42	33	19	16	13	8	6	3	2	2	0	0	Durva + Gem + Cis
196	182	152	115	75	42	19	12	8	4	3	2	1	0	0	0	0	0	Placebo + Gem + Cis

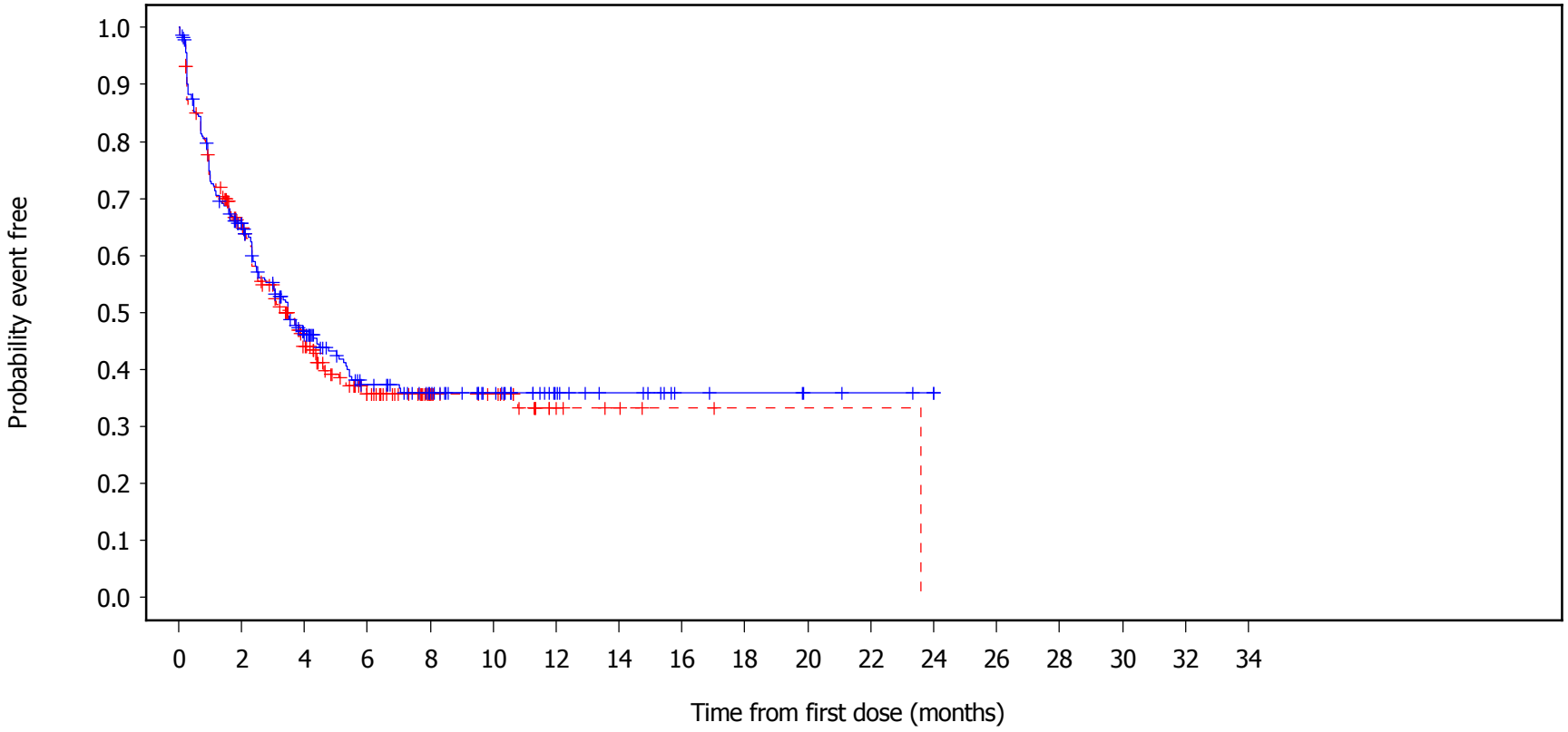
Figure 3.5.6.9 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Haematopoietic cytopenias SMQ AEs for Primary Tumor Location [eCRF]=Extrahepatic CCA
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

73	47	34	23	21	15	10	9	7	6	4	3	3	3	3	2	0	0	Durva + Gem + Cis
71	36	18	6	3	1	1	0	0	0	0	0	0	0	0	0	0	0	Placebo + Gem + Cis

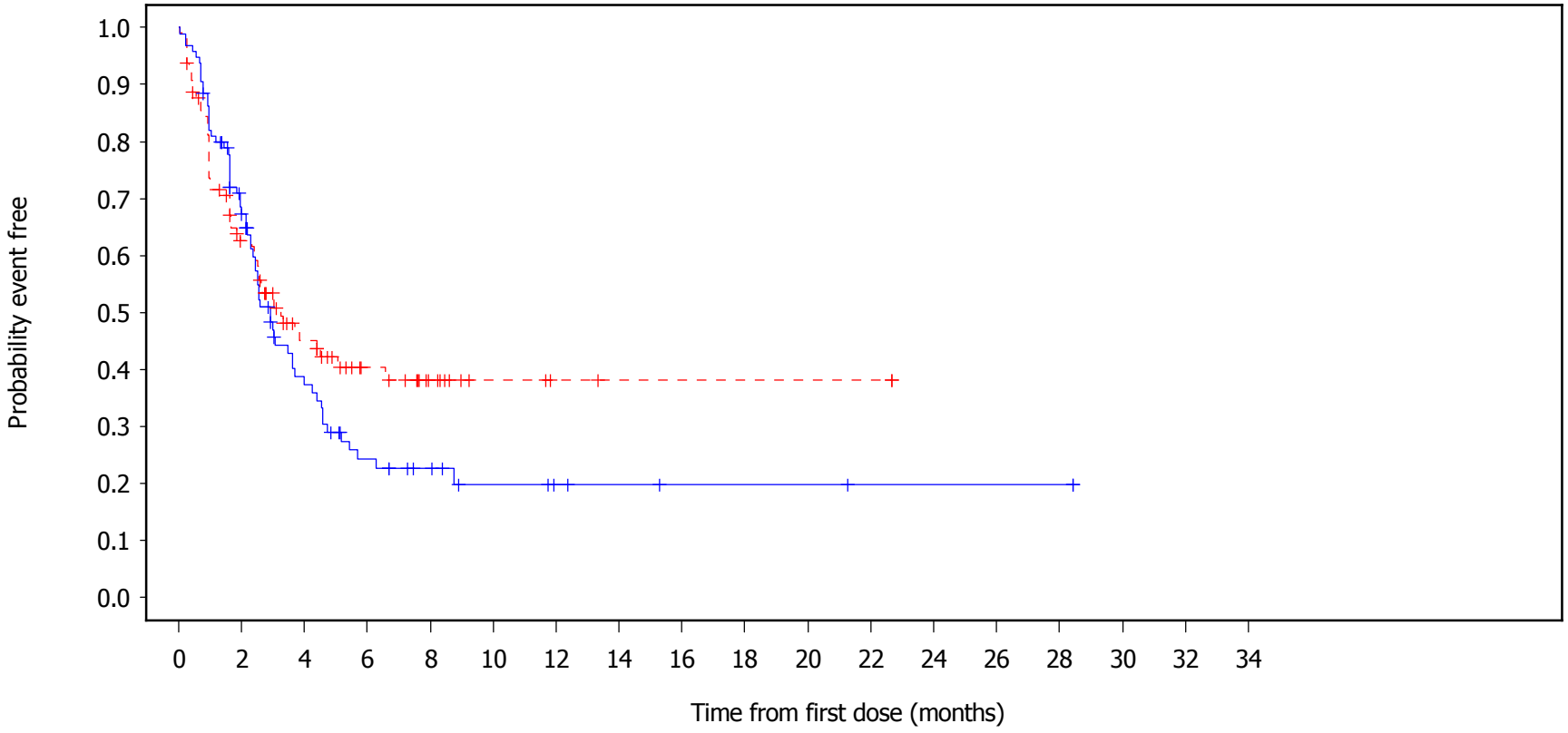
Figure 3.5.6.10 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Haematopoietic cytopenias
SMQ AEs for Primary Tumor Location [eCRF]=Intrahepatic CCA
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

234	145	85	55	42	30	17	12	6	5	3	2	1	0	0	0	0	0	Durva + Gem + Cis
235	139	80	45	26	20	6	4	2	1	1	1	0	0	0	0	0	0	Placebo + Gem + Cis

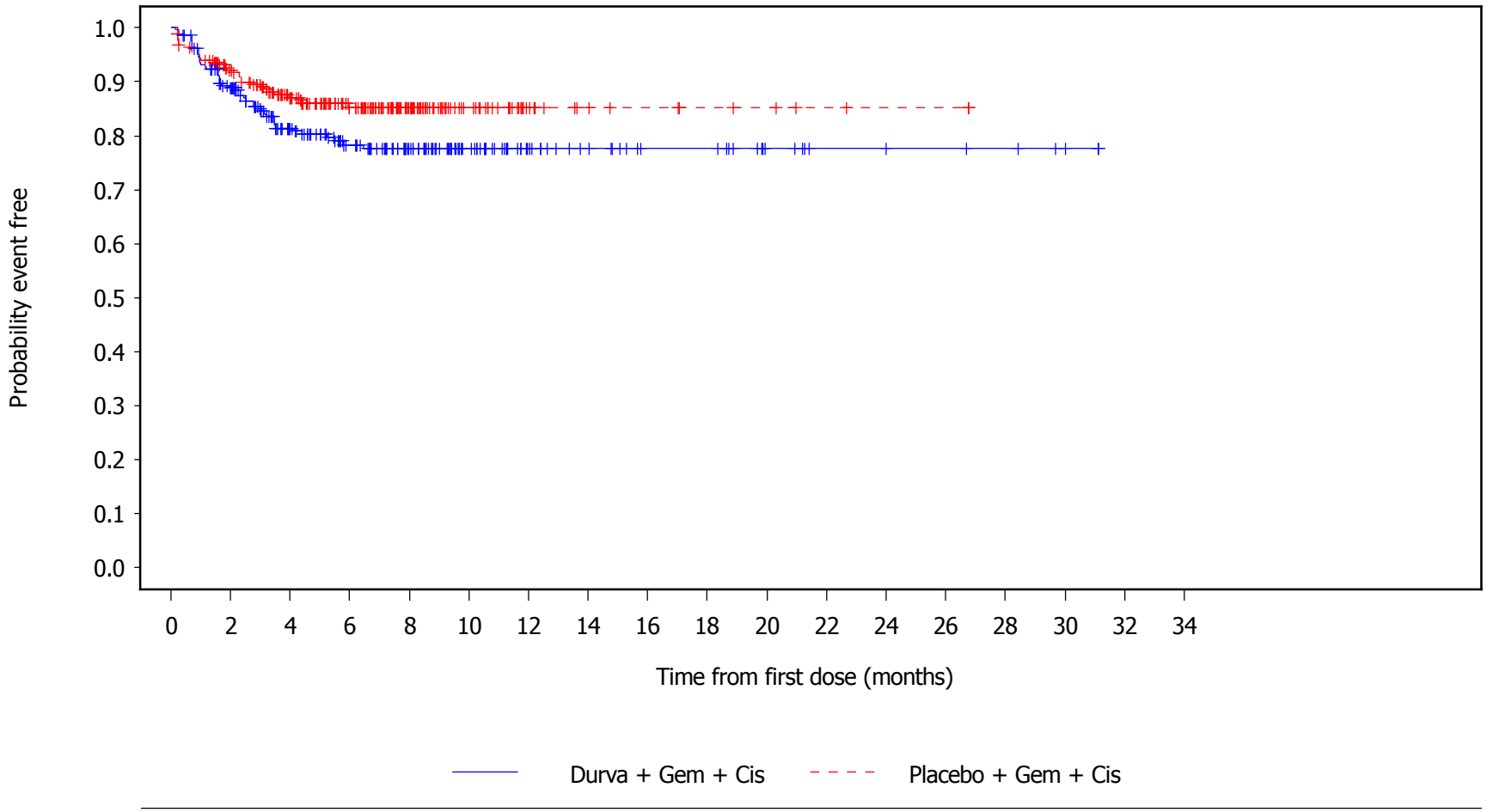
Figure 3.5.6.11 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI G>=3 GT: Haematopoietic cytopenias
SMQ AEs for Primary Tumor Location [eCRF]=Gallbladder cancer
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

95	58	28	15	10	6	4	3	2	2	2	1	1	1	1	0	0	0	Durva + Gem + Cis
97	54	31	18	10	4	2	1	1	1	1	1	0	0	0	0	0	0	Placebo + Gem + Cis

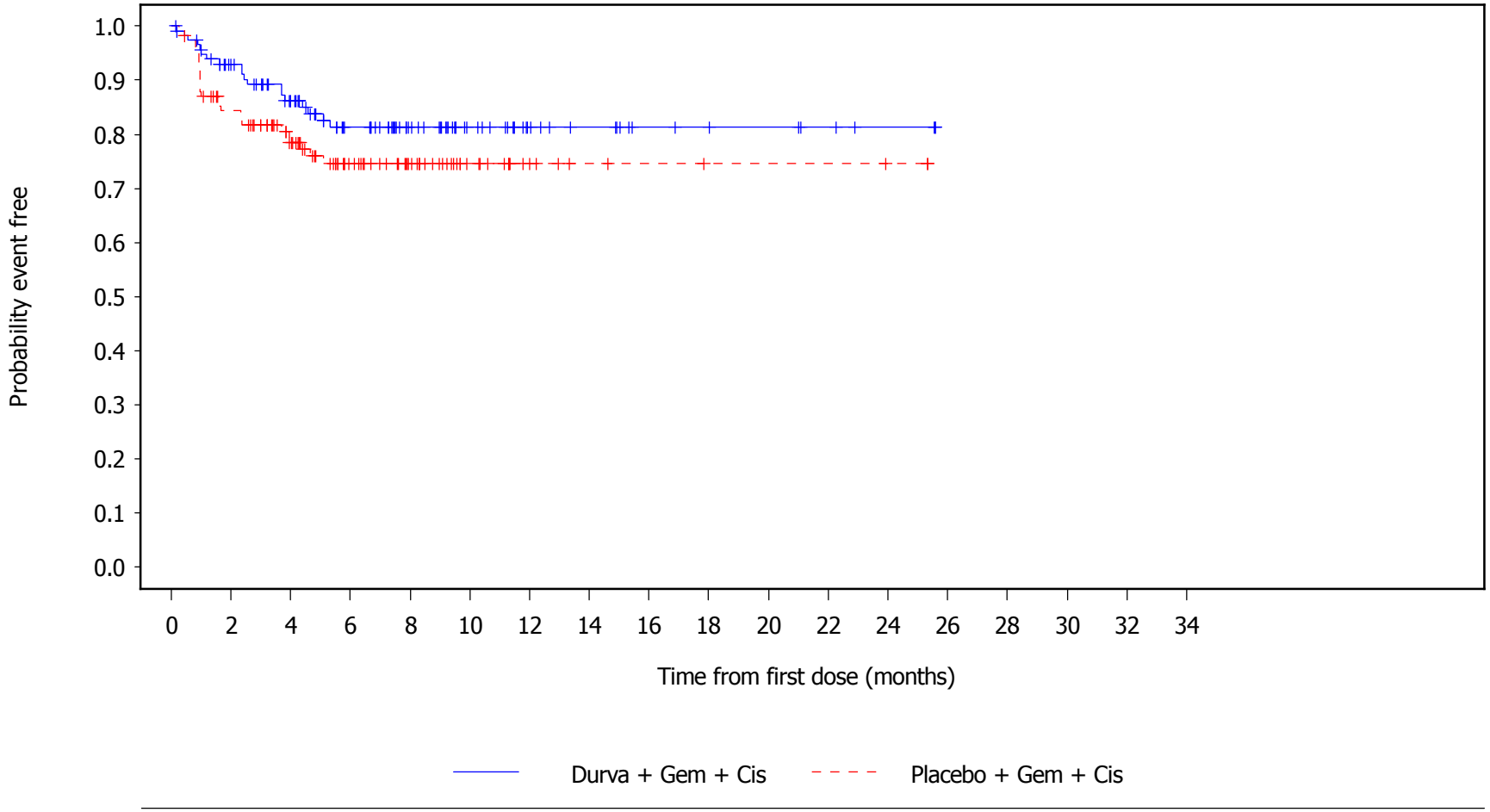
Figure 3.5.6.12 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Neutropenia for PD-L1 Status=High (>=1%)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

239	199	146	115	86	55	33	25	18	18	10	6	6	5	4	2	0	0	Durva + Gem + Cis
249	209	165	119	72	36	15	9	7	5	4	2	1	1	0	0	0	0	Placebo + Gem + Cis

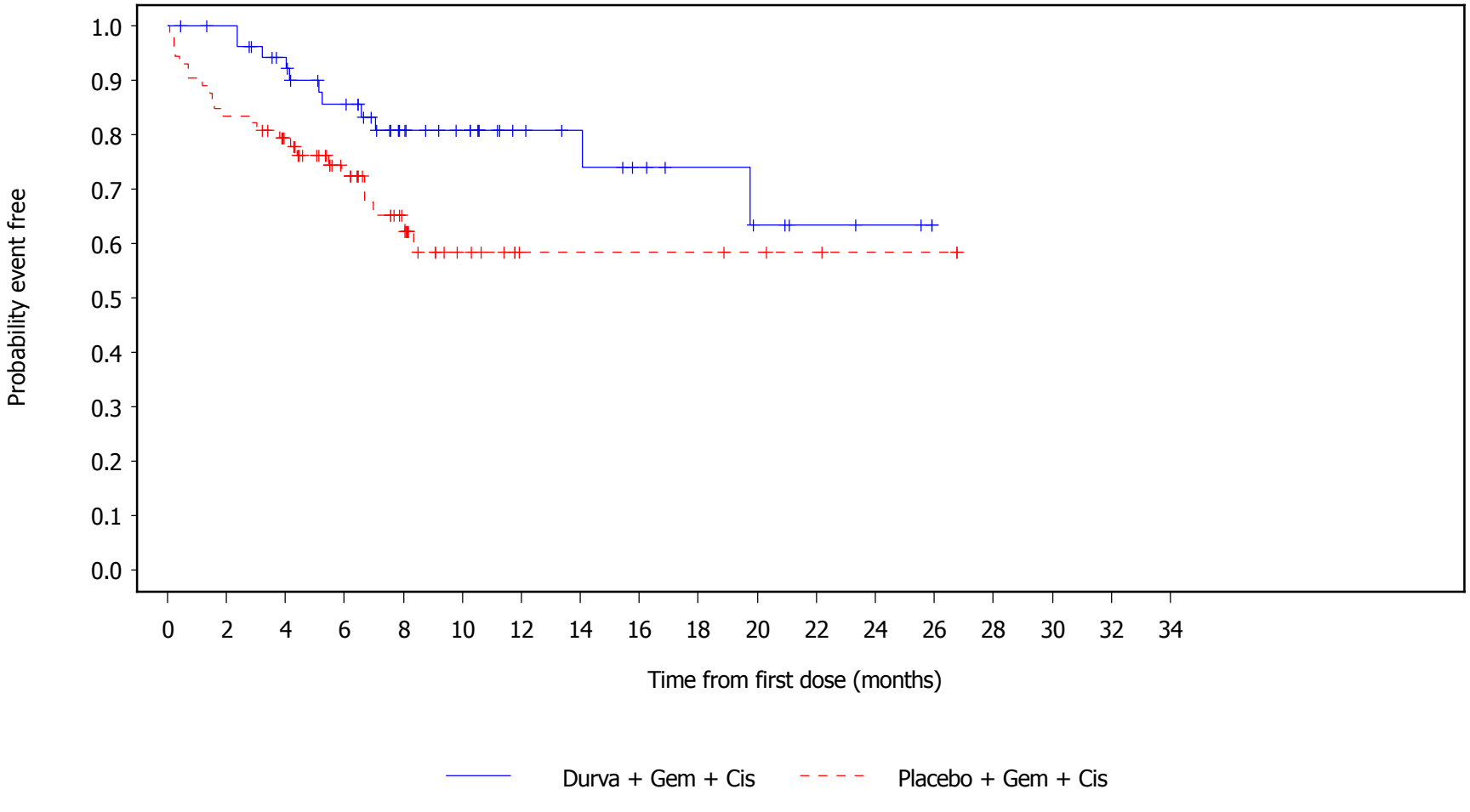
Figure 3.5.6.13 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of AESI G>=3 PT: Neutropenia for PD-L1 Status=Low (<1%)
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

118	100	80	60	43	28	17	13	8	7	6	4	2	0	0	0	0	0	Durva + Gem + Cis
117	93	71	47	33	17	7	4	3	2	2	2	1	0	0	0	0	0	Placebo + Gem + Cis

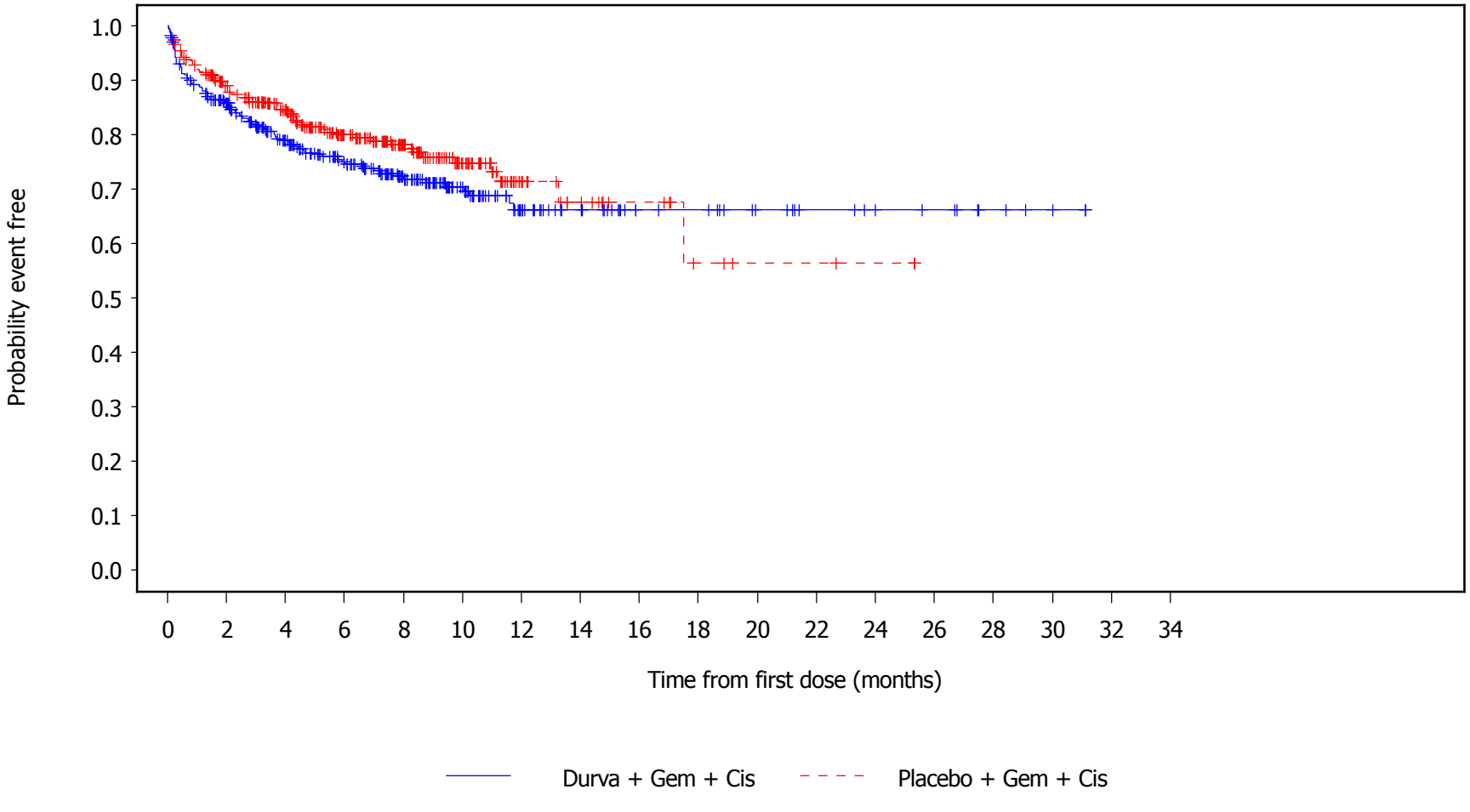
Figure 3.5.7.1 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of SAESI for Disease Extent=Locally Advanced
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

55	53	46	39	27	22	14	12	9	7	5	3	2	0	0	0	0	0	Durva + Gem + Cis
73	61	53	36	22	10	4	4	4	4	3	2	1	1	0	0	0	0	Placebo + Gem + Cis

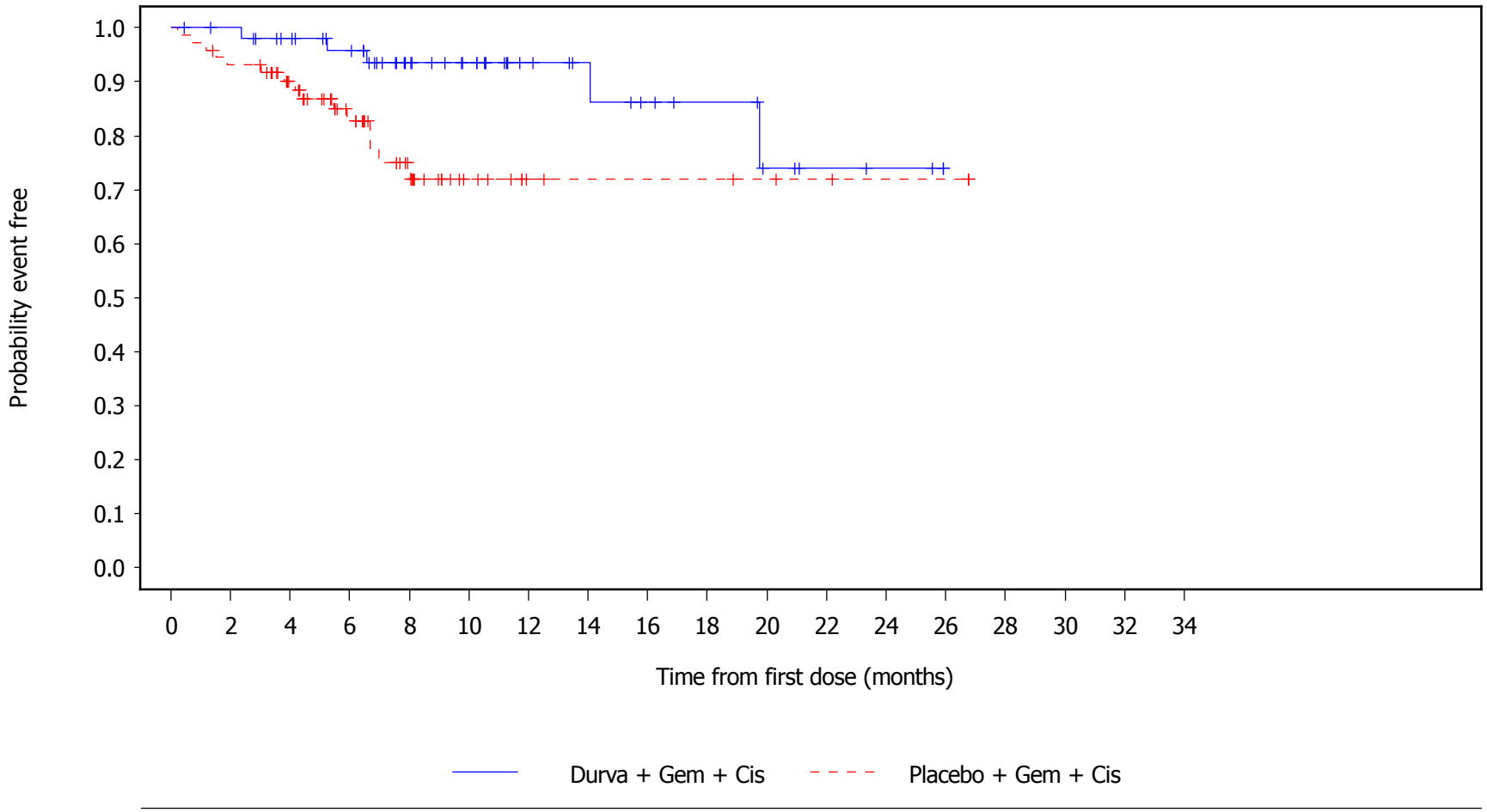
Figure 3.5.7.2 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of SAESI for Disease Extent=Metastatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

347	278	220	181	133	83	48	35	23	22	16	12	10	8	4	2	0	0	Durva + Gem + Cis
330	270	220	156	109	64	23	15	9	4	2	2	1	0	0	0	0	0	Placebo + Gem + Cis

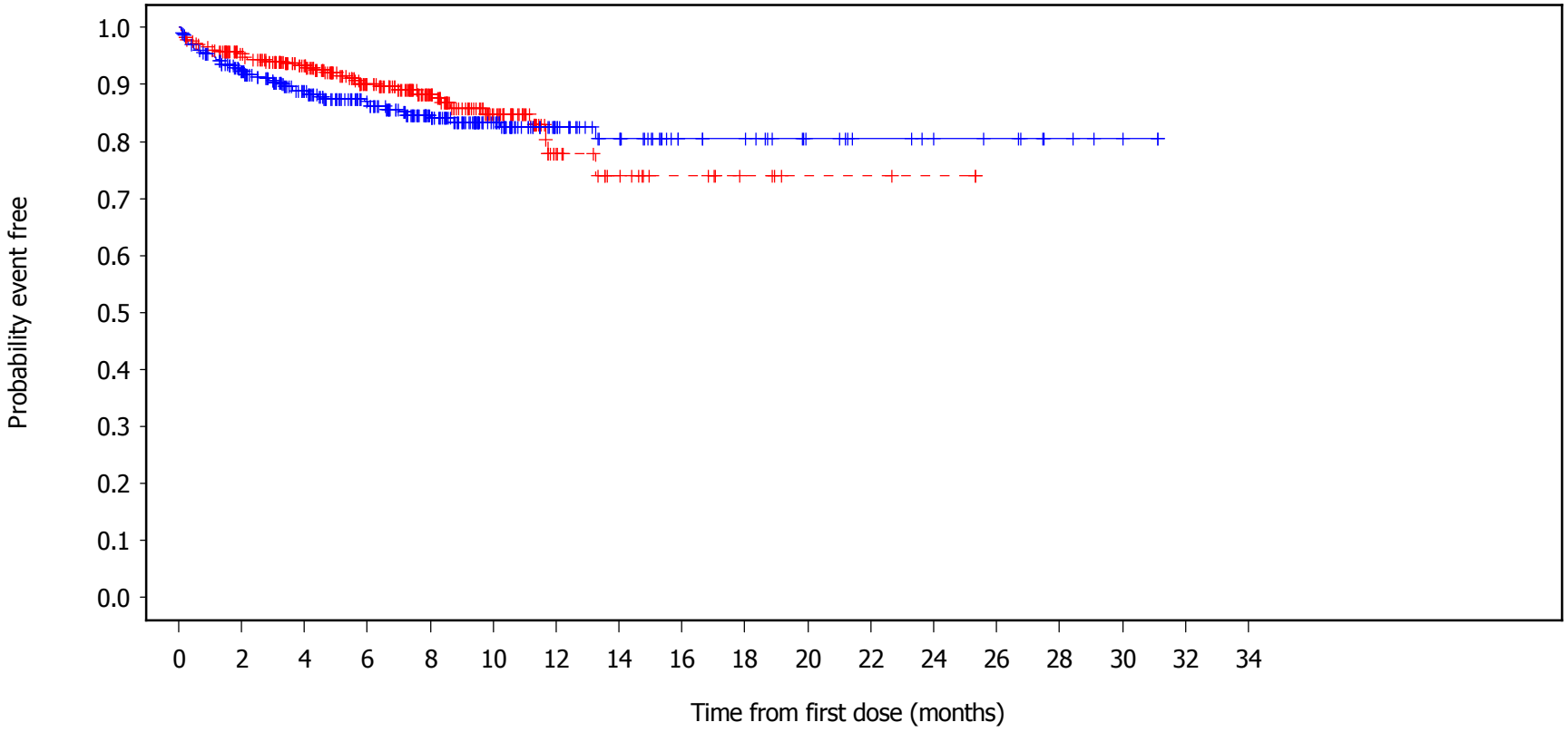
Figure 3.5.7.3 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of SAESI GT: Biliary SMQ AEs for Disease Extent=Locally Advanced
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

55	53	48	43	31	25	16	13	10	8	5	3	2	0	0	0	0	0	Durva + Gem + Cis
73	67	56	39	24	11	5	4	4	4	3	2	1	1	0	0	0	0	Placebo + Gem + Cis

Figure 3.5.7.4 TOPAZ: Subgroup analysis Kaplan-Meier plot of time to first occurrence of SAESI GT: Biliary SMQ AEs for Disease Extent=Metastatic
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients



Number of patients at risk:

347	297	242	198	146	93	55	41	26	24	16	12	10	8	4	2	0	0	Durva + Gem + Cis
330	285	238	171	120	68	24	15	9	5	2	2	1	0	0	0	0	0	Placebo + Gem + Cis

Table 3.6.1 TOPAZ: Summary of analysis of PRO-CTCAE
(odds ratio, relative risk and risk difference)
Safety Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)		Placebo + Gem + Cis (N=403)		Treatment effect					
					Odds Ratio		Relative Risk		Risk Difference	
	n	Number (%) of patients with events	n	Number (%) of patients with events	Estimate (95% CI)	2-sided p-value	Estimate (95% CI)	2-sided p-value	Estimate (95% CI)	2-sided p-value
Severity/ Intensity-Mouth And Throat Sores [a][d][h]	199	21(10.6)	197	19(9.6)	1.11(0.57, 2.14)	0.7643	1.09(0.61, 1.99)	0.7643	0.01(-0.05, 0.07)	0.7643
Interfere with Usual or Daily Activities-Mouth And Throat Sores [b][f][i]	20	5(25.0)	11	0	8.16(0.79,1112.22)	0.0841	6.17(0.37,101.84)	0.2033	0.25(-0.04, 0.43)	0.0911
Severity/ Intensity-Shortness Of Breath [a][d][h]	199	38(19.1)	197	31(15.7)	1.26(0.75, 2.14)	0.3778	1.21(0.79, 1.88)	0.3778	0.03(-0.04, 0.11)	0.3778
Interfere with Usual or Daily Activities-Shortness Of Breath [a][d][h]	59	16(27.1)	44	11(25.0)	1.12(0.46, 2.78)	0.8086	1.08(0.57, 2.18)	0.8086	0.02(-0.15, 0.19)	0.8086
Severity/ Intensity-Cough [a][d][h]	199	17(8.5)	197	22(11.2)	0.74(0.38, 1.44)	0.3802	0.76(0.41, 1.39)	0.3802	-0.03(-0.09, 0.03)	0.3802
Interfere with Usual or Daily Activities-Cough [a][d][h]	41	8(19.5)	25	2(8.0)	2.79(0.63, 19.60)	0.1881	2.44(0.67, 15.32)	0.1881	0.12(-0.06, 0.28)	0.1881

NC=Not calculable. CI=Confidence interval. PL=Profile likelihood. LR=Likelihood ratio test.
[a] Odds ratio (OR), 95% PL CI, LR p-value via logistic regression. [b] As [a] but with Firth method. [c] OR NC via [a] or [b].
[d] Relative risk (RR), 95% PL CI, LR p-value via log-binomial regression.
[e] RR, 95% CI, p-value via modified Poisson regression. [f] RR, 95% CI, p-value via modified Wald method.
[g] RR NC via [d], [e] or [f]. [h] Risk difference (RD), 95% PL CI, LR p-value via binomial regression.
[i] RD, 95% CI, p-value via Agresti-Caffo method. [j] RD NC via [h] or [i].
Odds ratio and relative risk <1, and risk difference <0 favours durvalumab. * p<0.05.
For occurrence of rash, event is defined as a post-baseline occurrence when not present at baseline.
For all other items, event is defined as maximum post-baseline score >=3 and worse than baseline score.

Table 3.6.1 TOPAZ: Summary of analysis of PRO-CTCAE
(odds ratio, relative risk and risk difference)
Safety Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Durva + Gem + Cis (N=402)		Placebo + Gem + Cis (N=403)		Treatment effect					
					Odds Ratio		Relative Risk		Risk Difference	
	n	Number (%) of patients with events	n	Number (%) of patients with events	Estimate (95% CI)	2-sided p-value	Estimate (95% CI)	2-sided p-value	Estimate (95% CI)	2-sided p-value
Occurrence-Rash [a][d][h]	199	64(32.2)	197	53(26.9)	1.29(0.84, 1.99)	0.2513	1.20(0.88, 1.63)	0.2513	0.05(-0.04, 0.14)	0.2513
Amount-Hair Loss [a][d][h]	199	65(32.7)	197	54(27.4)	1.28(0.84, 1.98)	0.2541	1.19(0.88, 1.62)	0.2541	0.05(-0.04, 0.14)	0.2541
Severity/ Intensity-Numbness Or Tingling In Hands Or Feet [a][d][h]	199	43(21.6)	197	27(13.7)	1.74(1.03, 2.97)	0.0385 *	1.58(1.02, 2.48)	0.0385 *	0.08(0.004, 0.15)	0.0385 *
Interfere with Usual or Daily Activities-Numbness Or Tingling In Hands Or Feet [a][d][h]	19	5(26.3)	28	6(21.4)	1.31(0.32, 5.18)	0.6989	1.23(0.40, 3.54)	0.6989	0.05(-0.19, 0.31)	0.6989

NC=Not calculable. CI=Confidence interval. PL=Profile likelihood. LR=Likelihood ratio test.
[a] Odds ratio (OR), 95% PL CI, LR p-value via logistic regression. [b] As [a] but with Firth method. [c] OR NC via [a] or [b].
[d] Relative risk (RR), 95% PL CI, LR p-value via log-binomial regression.
[e] RR, 95% CI, p-value via modified Poisson regression. [f] RR, 95% CI, p-value via modified Wald method.
[g] RR NC via [d], [e] or [f]. [h] Risk difference (RD), 95% PL CI, LR p-value via binomial regression.
[i] RD, 95% CI, p-value via Agresti-Caffo method. [j] RD NC via [h] or [i].
Odds ratio and relative risk <1, and risk difference <0 favours durvalumab. * p<0.05.
For occurrence of rash, event is defined as a post-baseline occurrence when not present at baseline.
For all other items, event is defined as maximum post-baseline score >=3 and worse than baseline score.
root/cdar/d419/_Payer/ar/restricted_topaz_payer1_germany/tlf/prod/program/orrrardae.sas eorrrardaeaa 20JAN2023:04:45 kjpc654

Table 3.7.1 TOPAZ: Summary of compliance with PRO-CTCAE by visit
Safety Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=402)	Placebo + Gem + Cis (N=403)
Baseline	Expected forms [a]	255	251
	Received forms [b]	199	197
	Evaluable forms [c]	199	197
	Compliance rate (%) [d]	78.0	78.5
	Evaluability rate (%) [e]	100	100
Cycle 02 Day 01	Expected forms [a]	240	233
	Received forms [b]	205	208
	Evaluable forms [c]	205	208
	Compliance rate (%) [d]	85.4	89.3
	Evaluability rate (%) [e]	100	100
Cycle 03 Day 01	Expected forms [a]	220	201
	Received forms [b]	180	157
	Evaluable forms [c]	180	157
	Compliance rate (%) [d]	81.8	78.1
	Evaluability rate (%) [e]	100	100
Cycle 04 Day 01	Expected forms [a]	208	190
	Received forms [b]	173	157
	Evaluable forms [c]	173	157
	Compliance rate (%) [d]	83.2	82.6
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 3.7.1 TOPAZ: Summary of compliance with PRO-CTCAE by visit
Safety Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=402)	Placebo + Gem + Cis (N=403)
Cycle 05 Day 01	Expected forms [a]	197	171
	Received forms [b]	165	135
	Evaluable forms [c]	165	135
	Compliance rate (%) [d]	83.8	78.9
	Evaluability rate (%) [e]	100	100
Cycle 06 Day 01	Expected forms [a]	186	162
	Received forms [b]	149	129
	Evaluable forms [c]	149	129
	Compliance rate (%) [d]	80.1	79.6
	Evaluability rate (%) [e]	100	100
Cycle 07 Day 01	Expected forms [a]	171	138
	Received forms [b]	128	115
	Evaluable forms [c]	128	115
	Compliance rate (%) [d]	74.9	83.3
	Evaluability rate (%) [e]	100	100
Cycle 08 Day 01	Expected forms [a]	163	127
	Received forms [b]	129	98
	Evaluable forms [c]	129	98
	Compliance rate (%) [d]	79.1	77.2
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 3.7.1 TOPAZ: Summary of compliance with PRO-CTCAE by visit
Safety Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=402)	Placebo + Gem + Cis (N=403)
Cycle 09 Day 01	Expected forms [a]	142	102
	Received forms [b]	105	80
	Evaluable forms [c]	105	80
	Compliance rate (%) [d]	73.9	78.4
	Evaluability rate (%) [e]	100	100
Cycle 10 Day 01	Expected forms [a]	124	88
	Received forms [b]	107	76
	Evaluable forms [c]	107	76
	Compliance rate (%) [d]	86.3	86.4
	Evaluability rate (%) [e]	100	100
Cycle 11 Day 01	Expected forms [a]	91	62
	Received forms [b]	76	52
	Evaluable forms [c]	76	52
	Compliance rate (%) [d]	83.5	83.9
	Evaluability rate (%) [e]	100	100
Cycle 12 Day 01	Expected forms [a]	78	48
	Received forms [b]	66	43
	Evaluable forms [c]	66	43
	Compliance rate (%) [d]	84.6	89.6
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 3.7.1 TOPAZ: Summary of compliance with PRO-CTCAE by visit
Safety Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=402)	Placebo + Gem + Cis (N=403)
Cycle 13 Day 01	Expected forms [a]	54	26
	Received forms [b]	44	22
	Evaluable forms [c]	44	22
	Compliance rate (%) [d]	81.5	84.6
	Evaluability rate (%) [e]	100	100
Cycle 14 Day 01	Expected forms [a]	48	23
	Received forms [b]	38	21
	Evaluable forms [c]	38	21
	Compliance rate (%) [d]	79.2	91.3
	Evaluability rate (%) [e]	100	100
Cycle 15 Day 01	Expected forms [a]	37	13
	Received forms [b]	27	12
	Evaluable forms [c]	27	12
	Compliance rate (%) [d]	73.0	92.3
	Evaluability rate (%) [e]	100	100
Cycle 16 Day 01	Expected forms [a]	36	11
	Received forms [b]	32	10
	Evaluable forms [c]	32	10
	Compliance rate (%) [d]	88.9	90.9
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 3.7.1 TOPAZ: Summary of compliance with PRO-CTCAE by visit
Safety Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=402)	Placebo + Gem + Cis (N=403)
Cycle 18 Day 01	Expected forms [a]	26	10
	Received forms [b]	20	8
	Evaluable forms [c]	20	8
	Compliance rate (%) [d]	76.9	80.0
	Evaluability rate (%) [e]	100	100
Cycle 20 Day 01	Expected forms [a]	22	6
	Received forms [b]	18	6
	Evaluable forms [c]	18	6
	Compliance rate (%) [d]	81.8	100
	Evaluability rate (%) [e]	100	100
Cycle 22 Day 01	Expected forms [a]	17	4
	Received forms [b]	15	4
	Evaluable forms [c]	15	4
	Compliance rate (%) [d]	88.2	100
	Evaluability rate (%) [e]	100	100
Cycle 24 Day 01	Expected forms [a]	10	3
	Received forms [b]	9	2
	Evaluable forms [c]	9	2
	Compliance rate (%) [d]	90.0	66.7
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 3.7.1 TOPAZ: Summary of compliance with PRO-CTCAE by visit
Safety Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=402)	Placebo + Gem + Cis (N=403)
Cycle 26 Day 01	Expected forms [a]	5	2
	Received forms [b]	4	2
	Evaluable forms [c]	4	2
	Compliance rate (%) [d]	80.0	100
	Evaluability rate (%) [e]	100	100
Cycle 28 Day 01	Expected forms [a]	3	NC
	Received forms [b]	2	NC
	Evaluable forms [c]	2	NC
	Compliance rate (%) [d]	66.7	NC
	Evaluability rate (%) [e]	100	NC
Follow-up Day 30	Expected forms [a]	181	197
	Received forms [b]	61	69
	Evaluable forms [c]	61	69
	Compliance rate (%) [d]	33.7	35.0
	Evaluability rate (%) [e]	100	100
Follow-up Month 2	Expected forms [a]	149	156
	Received forms [b]	23	19
	Evaluable forms [c]	23	19
	Compliance rate (%) [d]	15.4	12.2
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 3.7.1 TOPAZ: Summary of compliance with PRO-CTCAE by visit
Safety Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Timepoint	Compliance	Durva + Gem + Cis (N=402)	Placebo + Gem + Cis (N=403)
Follow-up Month 3	Expected forms [a]	125	136
	Received forms [b]	17	14
	Evaluable forms [c]	17	14
	Compliance rate (%) [d]	13.6	10.3
	Evaluability rate (%) [e]	100	100

Baseline is defined as last evaluable assessment on or prior to start of treatment start time.
[a] Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint.
[b] Received forms = number of subjects who completed the form at a given timepoint.
[c] Evaluable forms = forms where at least one subscale can be determined.
[d] Compliance Rate = Evaluable/Expected * 100.
[e] Evaluability Rate = Evaluable/Received * 100.
Timepoints are reported by visit for each treatment arm.
NC = Not Calculable

Table 3.8.1 TOPAZ: Adverse events leading to discontinuation of any study medication, by system organ class and preferred term
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

System organ class / MedDRA Preferred term	Number (%) of subjects [a] Durva + Gem + Cis (N=402)	Placebo + Gem + Cis (N=403)	Total (N=805)
Subjects with any AE leading to discontinuation of any study medication [b]	56 (13.9)	57 (14.1)	113 (14.0)
INFECTIONS AND INFESTATIONS	8 (2.0)	5 (1.2)	13 (1.6)
Sepsis	3 (0.7)	0	3 (0.4)
Biliary tract infection	1 (0.2)	0	1 (0.1)
COVID-19	1 (0.2)	0	1 (0.1)
Gastroenteritis Escherichia coli	1 (0.2)	0	1 (0.1)
Pyuria	1 (0.2)	0	1 (0.1)
Urinary tract infection	1 (0.2)	0	1 (0.1)
Appendicitis	0	1 (0.2)	1 (0.1)
Gingivitis	0	1 (0.2)	1 (0.1)
Klebsiella infection	0	1 (0.2)	1 (0.1)
Pneumonia	0	1 (0.2)	1 (0.1)
Septic shock	0	1 (0.2)	1 (0.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	11 (2.7)	10 (2.5)	21 (2.6)
Anaemia	5 (1.2)	3 (0.7)	8 (1.0)
Thrombocytopenia	4 (1.0)	2 (0.5)	6 (0.7)
Neutropenia	3 (0.7)	2 (0.5)	5 (0.6)
Myelosuppression	1 (0.2)	0	1 (0.1)
Bicytopenia	0	1 (0.2)	1 (0.1)
Febrile neutropenia	0	1 (0.2)	1 (0.1)
Leukopenia	0	1 (0.2)	1 (0.1)
Pancytopenia	0	1 (0.2)	1 (0.1)

[a] Number (%) subjects with an AE leading to discontinuation of study medication, sorted by international order for system organ class and descending frequency for preferred term (Durva + Gem + Cis group).
Subjects with multiple AEs leading to discontinuation are counted once for each system organ class.
[b] Action taken: drug permanently discontinued.
Note: AEs with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing;
Includes AEs occurring up to 90 days following date of last dose or up to first subsequent therapy (whichever comes first).
MedDRA version 24.0.

Table 3.8.1 TOPAZ: Adverse events leading to discontinuation of any study medication, by system organ class and preferred term
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

System organ class / MedDRA Preferred term	Number (%) of subjects [a] Durva + Gem + Cis (N=402)	Placebo + Gem + Cis (N=403)	Total (N=805)
IMMUNE SYSTEM DISORDERS	1 (0.2)	0	1 (0.1)
Drug hypersensitivity	1 (0.2)	0	1 (0.1)
METABOLISM AND NUTRITION DISORDERS	1 (0.2)	2 (0.5)	3 (0.4)
Hyponatraemia	1 (0.2)	0	1 (0.1)
Decreased appetite	0	1 (0.2)	1 (0.1)
Hypokalaemia	0	1 (0.2)	1 (0.1)
PSYCHIATRIC DISORDERS	1 (0.2)	0	1 (0.1)
Suicide attempt	1 (0.2)	0	1 (0.1)
NERVOUS SYSTEM DISORDERS	3 (0.7)	2 (0.5)	5 (0.6)
Ischaemic stroke	2 (0.5)	0	2 (0.2)
Neuropathy peripheral	1 (0.2)	0	1 (0.1)
Altered state of consciousness	0	1 (0.2)	1 (0.1)
Peripheral sensory neuropathy	0	1 (0.2)	1 (0.1)
EAR AND LABYRINTH DISORDERS	0	1 (0.2)	1 (0.1)
Tinnitus	0	1 (0.2)	1 (0.1)
CARDIAC DISORDERS	1 (0.2)	0	1 (0.1)
Acute coronary syndrome	1 (0.2)	0	1 (0.1)

[a] Number (%) subjects with an AE leading to discontinuation of study medication, sorted by international order for system organ class and descending frequency for preferred term (Durva + Gem + Cis group).
Subjects with multiple AEs leading to discontinuation are counted once for each system organ class.
[b] Action taken: drug permanently discontinued.
Note: AEs with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing;
Includes AEs occurring up to 90 days following date of last dose or up to first subsequent therapy (whichever comes first).
MedDRA version 24.0.

Table 3.8.1 TOPAZ: Adverse events leading to discontinuation of any study medication, by system organ class and preferred term
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

System organ class / MedDRA Preferred term	Number (%) of subjects [a] Durva + Gem + Cis (N=402)	Placebo + Gem + Cis (N=403)	Total (N=805)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (0.5)	2 (0.5)	4 (0.5)
Immune-mediated lung disease	1 (0.2)	0	1 (0.1)
Interstitial lung disease	1 (0.2)	0	1 (0.1)
Pneumonitis	0	1 (0.2)	1 (0.1)
Respiratory failure	0	1 (0.2)	1 (0.1)
GASTROINTESTINAL DISORDERS	8 (2.0)	6 (1.5)	14 (1.7)
Vomiting	3 (0.7)	1 (0.2)	4 (0.5)
Ascites	1 (0.2)	2 (0.5)	3 (0.4)
Melaena	1 (0.2)	0	1 (0.1)
Oesophageal varices haemorrhage	1 (0.2)	0	1 (0.1)
Pancreatitis	1 (0.2)	0	1 (0.1)
Upper gastrointestinal haemorrhage	1 (0.2)	0	1 (0.1)
Gastric perforation	0	1 (0.2)	1 (0.1)
Nausea	0	2 (0.5)	2 (0.2)
HEPATOBILIARY DISORDERS	5 (1.2)	5 (1.2)	10 (1.2)
Hepatic failure	2 (0.5)	0	2 (0.2)
Hepatic function abnormal	2 (0.5)	0	2 (0.2)
Biliary obstruction	1 (0.2)	1 (0.2)	2 (0.2)
Jaundice cholestatic	1 (0.2)	1 (0.2)	2 (0.2)
Autoimmune hepatitis	0	1 (0.2)	1 (0.1)
Cholangitis	0	1 (0.2)	1 (0.1)
Drug-induced liver injury	0	1 (0.2)	1 (0.1)

[a] Number (%) subjects with an AE leading to discontinuation of study medication, sorted by international order for system organ class and descending frequency for preferred term (Durva + Gem + Cis group).
Subjects with multiple AEs leading to discontinuation are counted once for each system organ class.
[b] Action taken: drug permanently discontinued.
Note: AEs with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing;
Includes AEs occurring up to 90 days following date of last dose or up to first subsequent therapy (whichever comes first).
MedDRA version 24.0.

Table 3.8.1 TOPAZ: Adverse events leading to discontinuation of any study medication, by system organ class and preferred term
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

System organ class / MedDRA Preferred term	Number (%) of subjects [a] Durva + Gem + Cis (N=402)	Placebo + Gem + Cis (N=403)	Total (N=805)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (0.5)	0	2 (0.2)
Pruritus	1 (0.2)	0	1 (0.1)
Rash maculo-papular	1 (0.2)	0	1 (0.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	2 (0.5)	2 (0.2)
Arthralgia	0	1 (0.2)	1 (0.1)
Polymyositis	0	1 (0.2)	1 (0.1)
RENAL AND URINARY DISORDERS	5 (1.2)	3 (0.7)	8 (1.0)
Acute kidney injury	2 (0.5)	0	2 (0.2)
Chronic kidney disease	1 (0.2)	2 (0.5)	3 (0.4)
IgM nephropathy	1 (0.2)	0	1 (0.1)
Renal failure	1 (0.2)	0	1 (0.1)
Renal impairment	0	1 (0.2)	1 (0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (1.0)	0	4 (0.5)
Fatigue	3 (0.7)	0	3 (0.4)
Asthenia	1 (0.2)	0	1 (0.1)
INVESTIGATIONS	11 (2.7)	23 (5.7)	34 (4.2)
Blood creatinine increased	3 (0.7)	10 (2.5)	13 (1.6)
Neutrophil count decreased	3 (0.7)	8 (2.0)	11 (1.4)
Alanine aminotransferase increased	2 (0.5)	1 (0.2)	3 (0.4)
Platelet count decreased	2 (0.5)	4 (1.0)	6 (0.7)
Aspartate aminotransferase increased	1 (0.2)	0	1 (0.1)

[a] Number (%) subjects with an AE leading to discontinuation of study medication, sorted by international order for system organ class and descending frequency for preferred term (Durva + Gem + Cis group).
Subjects with multiple AEs leading to discontinuation are counted once for each system organ class.
[b] Action taken: drug permanently discontinued.
Note: AEs with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing;
Includes AEs occurring up to 90 days following date of last dose or up to first subsequent therapy (whichever comes first).
MedDRA version 24.0.

Table 3.8.1 TOPAZ: Adverse events leading to discontinuation of any study medication, by system organ class and preferred term
Safety Analysis Set, DCO 25FEB2022 and 14OCT2022 for China Patients

System organ class / MedDRA Preferred term	Number (%) of subjects [a] Durva + Gem + Cis (N=402)	Placebo + Gem + Cis (N=403)	Total (N=805)
Lipase increased	1 (0.2)	0	1 (0.1)
Myocardial necrosis marker increased	1 (0.2)	0	1 (0.1)
Weight decreased	1 (0.2)	0	1 (0.1)
Glomerular filtration rate decreased	0	1 (0.2)	1 (0.1)
White blood cell count decreased	0	2 (0.5)	2 (0.2)

[a] Number (%) subjects with an AE leading to discontinuation of study medication, sorted by international order for system organ class and descending frequency for preferred term (Durva + Gem + Cis group).
Subjects with multiple AEs leading to discontinuation are counted once for each system organ class.
[b] Action taken: drug permanently discontinued.
Note: AEs with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing;
Includes AEs occurring up to 90 days following date of last dose or up to first subsequent therapy (whichever comes first).
MedDRA version 24.0.

Table 4.1 TOPAZ: Subject disposition
All Subjects, DCO 25FEB2022 and 14OCT2022 for China Patients

	Number (%) of subjects		
	Durva + Gem + Cis	Placebo + Gem + Cis	Total
Subjects enrolled [a]			1069
Subjects randomized	405 (100)	405 (100)	810 (100)
Subjects who were not randomized			259
Screen failure			243
Death			1
Withdrawal by subject			13
Other			2
Full analysis set [b]	405 (100)	405 (100)	810 (100)
Subjects who received treatment	402 (99.3)	403 (99.5)	805 (99.4)
Subjects who received Durvalumab / Placebo	402 (99.3)	403 (99.5)	805 (99.4)
Subjects who received Gemcitabine	401 (99.0)	402 (99.3)	803 (99.1)
Subjects who received Cisplatin	400 (98.8)	402 (99.3)	802 (99.0)

[a] Informed consent received.
[b] Full analysis set - all subjects randomized regardless of study drug administration.
[c] Percentages are calculated from number of subjects who received any treatment.
[d] Percentages are calculated from number of subjects who received relevant treatment.
[e] RECIST 1.1-defined radiological progression of disease.
[f] Clinical progression without RECIST 1.1-defined radiological progression of disease.
[g] May include subjects who never received study treatment.
[h] Percentages are calculated from number of subjects randomized.
COVID-19 = Coronavirus Disease 2019. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.1 TOPAZ: Subject disposition
All Subjects, DCO 25FEB2022 and 14OCT2022 for China Patients

	Number (%) of subjects		
	Durva + Gem + Cis	Placebo + Gem + Cis	Total
Subjects who did not receive treatment	3 (0.7)	2 (0.5)	5 (0.6)
Death	3 (0.7)	1 (0.2)	4 (0.5)
Withdrawal by subject	0	1 (0.2)	1 (0.1)
Subjects ongoing study treatment at data cut-off [c]	63 (15.7)	20 (5.0)	83 (10.3)
Subjects who discontinued Durvalumab / Placebo [d]	336 (83.6)	380 (94.3)	716 (88.9)
Condition under investigation worsened [e]	215 (53.5)	271 (67.2)	486 (60.4)
Subjective disease progression [f]	52 (12.9)	51 (12.7)	103 (12.8)
Adverse event	28 (7.0)	22 (5.5)	50 (6.2)
Subject decision	25 (6.2)	29 (7.2)	54 (6.7)
Severe non-compliance to protocol	1 (0.2)	0	1 (0.1)
Condition under investigation improved / Subject recovered	3 (0.7)	1 (0.2)	4 (0.5)
Due to COVID-19 pandemic	1 (0.2)	2 (0.5)	3 (0.4)
Other	11 (2.7)	4 (1.0)	15 (1.9)

[a] Informed consent received.
[b] Full analysis set - all subjects randomized regardless of study drug administration.
[c] Percentages are calculated from number of subjects who received any treatment.
[d] Percentages are calculated from number of subjects who received relevant treatment.
[e] RECIST 1.1-defined radiological progression of disease.
[f] Clinical progression without RECIST 1.1-defined radiological progression of disease.
[g] May include subjects who never received study treatment.
[h] Percentages are calculated from number of subjects randomized.
COVID-19 = Coronavirus Disease 2019. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.1 TOPAZ: Subject disposition
All Subjects, DCO 25FEB2022 and 14OCT2022 for China Patients

	Number (%) of subjects		
	Durva + Gem + Cis	Placebo + Gem + Cis	Total
Subjects who discontinued Gemcitabine [d]	401 (100)	401 (99.8)	802 (99.9)
Condition under investigation worsened [e]	92 (22.9)	128 (31.8)	220 (27.4)
Subjective disease progression [f]	39 (9.7)	36 (9.0)	75 (9.3)
Development of study specific discontinuation criteria	1 (0.2)	0	1 (0.1)
Adverse event	47 (11.7)	37 (9.2)	84 (10.5)
Subject decision	19 (4.7)	23 (5.7)	42 (5.2)
Condition under investigation improved / Subject recovered	1 (0.2)	1 (0.2)	2 (0.2)
Maximum cycle of chemotherapy reached	192 (47.9)	171 (42.5)	363 (45.2)
Other	10 (2.5)	5 (1.2)	15 (1.9)
Subjects who discontinued Cisplatin [d]	400 (100)	401 (99.8)	801 (99.9)
Condition under investigation worsened [e]	92 (23.0)	123 (30.6)	215 (26.8)
Subjective disease progression [f]	39 (9.8)	33 (8.2)	72 (9.0)
Development of study specific discontinuation criteria	1 (0.3)	0	1 (0.1)
Adverse event	53 (13.3)	50 (12.4)	103 (12.8)
Subject decision	18 (4.5)	24 (6.0)	42 (5.2)
Condition under investigation improved / Subject recovered	2 (0.5)	1 (0.2)	3 (0.4)

[a] Informed consent received.
[b] Full analysis set - all subjects randomized regardless of study drug administration.
[c] Percentages are calculated from number of subjects who received any treatment.
[d] Percentages are calculated from number of subjects who received relevant treatment.
[e] RECIST 1.1-defined radiological progression of disease.
[f] Clinical progression without RECIST 1.1-defined radiological progression of disease.
[g] May include subjects who never received study treatment.
[h] Percentages are calculated from number of subjects randomized.
COVID-19 = Coronavirus Disease 2019. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.1 TOPAZ: Subject disposition
All Subjects, DCO 25FEB2022 and 14OCT2022 for China Patients

	Number (%) of subjects		
	Durva + Gem + Cis	Placebo + Gem + Cis	Total
Maximum cycle of chemotherapy reached	185 (46.3)	164 (40.8)	349 (43.5)
Other	10 (2.5)	6 (1.5)	16 (2.0)
Subjects continuing study off treatment [g][h] at data cut-off	77 (19.0)	90 (22.2)	167 (20.6)
Subjects who terminated study [g]	245 (60.5)	282 (69.6)	527 (65.1)
Death	240 (59.3)	271 (66.9)	511 (63.1)
Lost to follow-up	2 (0.5)	1 (0.2)	3 (0.4)
Withdrawal by subject	3 (0.7)	10 (2.5)	13 (1.6)

[a] Informed consent received.
[b] Full analysis set - all subjects randomized regardless of study drug administration.
[c] Percentages are calculated from number of subjects who received any treatment.
[d] Percentages are calculated from number of subjects who received relevant treatment.
[e] RECIST 1.1-defined radiological progression of disease.
[f] Clinical progression without RECIST 1.1-defined radiological progression of disease.
[g] May include subjects who never received study treatment.
[h] Percentages are calculated from number of subjects randomized.
COVID-19 = Coronavirus Disease 2019. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.2 TOPAZ: Subject recruitment by region, country and center
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

			Number (%) of subjects		
Region	Country	Center	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Asia	China	01326	11 (2.7)	7 (1.7)	18 (2.2)
		01310	5 (1.2)	4 (1.0)	9 (1.1)
		01322	5 (1.2)	4 (1.0)	9 (1.1)
		01327	5 (1.2)	4 (1.0)	9 (1.1)
		01304	6 (1.5)	2 (0.5)	8 (1.0)
		01308	2 (0.5)	6 (1.5)	8 (1.0)
		01314	1 (0.2)	7 (1.7)	8 (1.0)
		01317	5 (1.2)	3 (0.7)	8 (1.0)
		01307	2 (0.5)	4 (1.0)	6 (0.7)
		01320	4 (1.0)	2 (0.5)	6 (0.7)
		01301	2 (0.5)	3 (0.7)	5 (0.6)
		01305	2 (0.5)	3 (0.7)	5 (0.6)
		01313	2 (0.5)	3 (0.7)	5 (0.6)
		01318	3 (0.7)	2 (0.5)	5 (0.6)
		01321	2 (0.5)	3 (0.7)	5 (0.6)
		01324	2 (0.5)	3 (0.7)	5 (0.6)
		01302	3 (0.7)	0	3 (0.4)
		01312	1 (0.2)	2 (0.5)	3 (0.4)
		01319	0	2 (0.5)	2 (0.2)

N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.2 TOPAZ: Subject recruitment by region, country and center
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

			Number (%) of subjects		
Region	Country	Center	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Asia	China	01303	1 (0.2)	0	1 (0.1)
		01316	0	1 (0.2)	1 (0.1)
		01323	1 (0.2)	0	1 (0.1)
		Total	65 (16.0)	65 (16.0)	130 (16.0)
	South Korea	06005	19 (4.7)	15 (3.7)	34 (4.2)
		06001	10 (2.5)	14 (3.5)	24 (3.0)
		06004	11 (2.7)	11 (2.7)	22 (2.7)
		06003	6 (1.5)	8 (2.0)	14 (1.7)
		06002	10 (2.5)	3 (0.7)	13 (1.6)
		06006	4 (1.0)	9 (2.2)	13 (1.6)
		Total	60 (14.8)	60 (14.8)	120 (14.8)
	Thailand	07501	15 (3.7)	18 (4.4)	33 (4.1)
		07503	7 (1.7)	11 (2.7)	18 (2.2)
		07505	5 (1.2)	7 (1.7)	12 (1.5)
		07504	4 (1.0)	5 (1.2)	9 (1.1)
		07502	2 (0.5)	5 (1.2)	7 (0.9)

N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.2 TOPAZ: Subject recruitment by region, country and center
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

			Number (%) of subjects		
Region	Country	Center	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Asia	Thailand	07506	2 (0.5)	2 (0.5)	4 (0.5)
		Total	35 (8.6)	48 (11.9)	83 (10.2)
	Japan	04307	9 (2.2)	9 (2.2)	18 (2.2)
		04305	4 (1.0)	13 (3.2)	17 (2.1)
		04302	8 (2.0)	4 (1.0)	12 (1.5)
		04306	5 (1.2)	5 (1.2)	10 (1.2)
		04303	6 (1.5)	3 (0.7)	9 (1.1)
		04308	1 (0.2)	4 (1.0)	5 (0.6)
		04301	2 (0.5)	2 (0.5)	4 (0.5)
		04304	2 (0.5)	1 (0.2)	3 (0.4)
		Total	37 (9.1)	41 (10.1)	78 (9.6)
	Taiwan	07401	8 (2.0)	9 (2.2)	17 (2.1)
		07405	8 (2.0)	7 (1.7)	15 (1.9)
		07403	5 (1.2)	4 (1.0)	9 (1.1)
		07406	6 (1.5)	3 (0.7)	9 (1.1)
		07402	0	3 (0.7)	3 (0.4)
		07404	2 (0.5)	1 (0.2)	3 (0.4)

N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.2 TOPAZ: Subject recruitment by region, country and center
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

			Number (%) of subjects		
Region	Country	Center	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Asia	Taiwan	07408	0	3 (0.7)	3 (0.4)
		07407	1 (0.2)	0	1 (0.1)
		Total	30 (7.4)	30 (7.4)	60 (7.4)
	India	03502	10 (2.5)	5 (1.2)	15 (1.9)
		03504	3 (0.7)	4 (1.0)	7 (0.9)
		03507	1 (0.2)	0	1 (0.1)
		03508	0	1 (0.2)	1 (0.1)
		Total	14 (3.5)	10 (2.5)	24 (3.0)
	Hong Kong	03202	1 (0.2)	1 (0.2)	2 (0.2)
		03201	0	1 (0.2)	1 (0.1)
		03203	0	1 (0.2)	1 (0.1)
		Total	1 (0.2)	3 (0.7)	4 (0.5)
Europe	France	02309	5 (1.2)	5 (1.2)	10 (1.2)
		02303	7 (1.7)	1 (0.2)	8 (1.0)
		02304	4 (1.0)	4 (1.0)	8 (1.0)
		02307	2 (0.5)	6 (1.5)	8 (1.0)

N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.2 TOPAZ: Subject recruitment by region, country and center
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

			Number (%) of subjects		
Region	Country	Center	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Europe	France	02306	4 (1.0)	1 (0.2)	5 (0.6)
		02301	3 (0.7)	1 (0.2)	4 (0.5)
		02302	1 (0.2)	3 (0.7)	4 (0.5)
		Total	26 (6.4)	21 (5.2)	47 (5.8)
	United Kingdom	02801	3 (0.7)	11 (2.7)	14 (1.7)
		02810	3 (0.7)	7 (1.7)	10 (1.2)
		02802	4 (1.0)	2 (0.5)	6 (0.7)
		02803	4 (1.0)	2 (0.5)	6 (0.7)
		02807	2 (0.5)	2 (0.5)	4 (0.5)
		02811	3 (0.7)	1 (0.2)	4 (0.5)
		02809	1 (0.2)	1 (0.2)	2 (0.2)
		02804	0	1 (0.2)	1 (0.1)
		Total	20 (4.9)	27 (6.7)	47 (5.8)
	Poland	05701	8 (2.0)	5 (1.2)	13 (1.6)
		05702	5 (1.2)	6 (1.5)	11 (1.4)
		05708	2 (0.5)	2 (0.5)	4 (0.5)
		05705	3 (0.7)	0	3 (0.4)

N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.2 TOPAZ: Subject recruitment by region, country and center
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Region	Country	Center	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Europe	Poland	05707	1 (0.2)	1 (0.2)	2 (0.2)
		05703	0	1 (0.2)	1 (0.1)
		Total	19 (4.7)	15 (3.7)	34 (4.2)
	Italy	04101	3 (0.7)	5 (1.2)	8 (1.0)
		04106	3 (0.7)	5 (1.2)	8 (1.0)
		04102	3 (0.7)	2 (0.5)	5 (0.6)
		04104	3 (0.7)	1 (0.2)	4 (0.5)
		04105	2 (0.5)	1 (0.2)	3 (0.4)
		04107	2 (0.5)	1 (0.2)	3 (0.4)
		Total	16 (4.0)	15 (3.7)	31 (3.8)
	Russian Federation	06201	6 (1.5)	7 (1.7)	13 (1.6)
		06204	1 (0.2)	3 (0.7)	4 (0.5)
		06208	2 (0.5)	1 (0.2)	3 (0.4)
		06206	1 (0.2)	1 (0.2)	2 (0.2)
		06202	0	1 (0.2)	1 (0.1)
		06207	0	1 (0.2)	1 (0.1)

N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.2 TOPAZ: Subject recruitment by region, country and center
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

			Number (%) of subjects		
Region	Country	Center	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Europe	Russian Federation	06209	0	1 (0.2)	1 (0.1)
		Total	10 (2.5)	15 (3.7)	25 (3.1)
	Turkey	07604	4 (1.0)	5 (1.2)	9 (1.1)
		07602	3 (0.7)	2 (0.5)	5 (0.6)
		07603	2 (0.5)	1 (0.2)	3 (0.4)
		07601	0	1 (0.2)	1 (0.1)
		Total	9 (2.2)	9 (2.2)	18 (2.2)
	Bulgaria	00904	4 (1.0)	4 (1.0)	8 (1.0)
		00903	1 (0.2)	1 (0.2)	2 (0.2)
		00907	2 (0.5)	0	2 (0.2)
		00905	1 (0.2)	0	1 (0.1)
		Total	8 (2.0)	5 (1.2)	13 (1.6)
North America	United States of America	07822	5 (1.2)	8 (2.0)	13 (1.6)
		07806	7 (1.7)	5 (1.2)	12 (1.5)
		07805	3 (0.7)	3 (0.7)	6 (0.7)
		07804	4 (1.0)	1 (0.2)	5 (0.6)

N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.2 TOPAZ: Subject recruitment by region, country and center
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

			Number (%) of subjects		
Region	Country	Center	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
North America	United States of America	07808	3 (0.7)	2 (0.5)	5 (0.6)
		07826	4 (1.0)	1 (0.2)	5 (0.6)
		07809	2 (0.5)	1 (0.2)	3 (0.4)
		07813	2 (0.5)	1 (0.2)	3 (0.4)
		07817	3 (0.7)	0	3 (0.4)
		07818	2 (0.5)	1 (0.2)	3 (0.4)
		07801	1 (0.2)	1 (0.2)	2 (0.2)
		07816	1 (0.2)	1 (0.2)	2 (0.2)
		07802	0	1 (0.2)	1 (0.1)
		07810	0	1 (0.2)	1 (0.1)
		07823	0	1 (0.2)	1 (0.1)
		Total	37 (9.1)	28 (6.9)	65 (8.0)
South America	Argentina	00209	5 (1.2)	4 (1.0)	9 (1.1)
		00201	2 (0.5)	3 (0.7)	5 (0.6)
		00202	2 (0.5)	3 (0.7)	5 (0.6)
		00206	2 (0.5)	0	2 (0.2)
		00211	1 (0.2)	0	1 (0.1)
		Total	12 (3.0)	10 (2.5)	22 (2.7)

N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.2 TOPAZ: Subject recruitment by region, country and center
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

			Number (%) of subjects		
Region	Country	Center	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
South America	Chile	01202	4 (1.0)	3 (0.7)	7 (0.9)
		01201	2 (0.5)	0	2 (0.2)
		Total	6 (1.5)	3 (0.7)	9 (1.1)

N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.3 TOPAZ: Demographic characteristics
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Demographic characteristic		Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Age (years)	n	405	405	810
	Mean	61.8	61.7	61.7
	SD	10.54	10.91	10.72
	Median	64.0	63.0	63.0
	Min	20	27	20
	Max	84	85	85
Age group (years) n (%)	<65	220 (54.3)	230 (56.8)	450 (55.6)
	>=65 - <75	142 (35.1)	128 (31.6)	270 (33.3)
	>=75	43 (10.6)	47 (11.6)	90 (11.1)
Sex n (%)	Male	199 (49.1)	208 (51.4)	407 (50.2)
	Female	206 (50.9)	197 (48.6)	403 (49.8)
Race n (%)	Black or African American	8 (2.0)	6 (1.5)	14 (1.7)
	American Indian or Alaska Native	0	1 (0.2)	1 (0.1)
	Asian	249 (61.5)	262 (64.7)	511 (63.1)
	White	131 (32.3)	124 (30.6)	255 (31.5)
	Other	17 (4.2)	12 (3.0)	29 (3.6)

[a] Region is defined by randomization center location.
N = Number of subjects in treatment group. n = Number of subjects in category or analysis.
SD = Standard deviation. Min = Minimum. Max = Maximum.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.3 TOPAZ: Demographic characteristics
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Demographic characteristic		Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Ethnic group n (%)	Hispanic or Latino	27 (6.7)	19 (4.7)	46 (5.7)
	Not Hispanic or Latino	377 (93.1)	386 (95.3)	763 (94.2)
	Missing	1 (0.2)	0	1 (0.1)
Region n (%) [a]	Asia	242 (59.8)	257 (63.5)	499 (61.6)
	Rest of the World	163 (40.2)	148 (36.5)	311 (38.4)

[a] Region is defined by randomization center location.
N = Number of subjects in treatment group. n = Number of subjects in category or analysis.
SD = Standard deviation. Min = Minimum. Max = Maximum.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.4 TOPAZ: Subject Characteristics at baseline
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Subject characteristic		Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Height (cm)	n	402	402	804
	Mean	163.3	163.8	163.6
	SD	9.70	9.49	9.59
	Median	163.0	163.0	163.0
	Min	140	135	135
	Max	188	190	190
Weight (kg)	n	405	404	809
	Mean	65.3	66.1	65.7
	SD	15.33	15.78	15.56
	Median	62.5	63.9	63.0
	Min	35	38	35
	Max	127	131	131
Weight group (kg) n (%)	< 70	277 (68.4)	264 (65.2)	541 (66.8)
	>= 70 - <= 90	101 (24.9)	109 (26.9)	210 (25.9)
	> 90	27 (6.7)	31 (7.7)	58 (7.2)
	Missing	0	1 (0.2)	1 (0.1)
Body Mass Index (kg/m2)	n	402	402	804
	Mean	24.4	24.5	24.4
	SD	4.94	4.86	4.89
	Median	23.5	23.6	23.5
	Min	15	15	15
	Max	55	47	55

MSI status missing includes MSI-unknown and not tested.
N = Number of subjects in treatment group. n = Number of subjects in category or analysis.
SD = Standard deviation. Min = Minimum. Max = Maximum.
MSI = Microsatellite instability. PD-L1 = Programmed cell death ligand 1. TIP = Tumor and/or immune cell positivity.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.4 TOPAZ: Subject Characteristics at baseline
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Subject characteristic		Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Body Mass Index group (kg/m2) n (%)	Underweight [<18.5]	26 (6.4)	22 (5.4)	48 (5.9)
	Normal [18.5 - <25.0]	231 (57.0)	227 (56.0)	458 (56.5)
	Overweight [25.0 - <30.0]	99 (24.4)	106 (26.2)	205 (25.3)
	Obese [>=30.0]	46 (11.4)	47 (11.6)	93 (11.5)
	Missing	3 (0.7)	3 (0.7)	6 (0.7)
MSI status n (%)	High	3 (0.7)	2 (0.5)	5 (0.6)
	Stable	160 (39.5)	168 (41.5)	328 (40.5)
	Missing	242 (59.8)	235 (58.0)	477 (58.9)
PD-L1 expression n (%)	High (TIP >=1%)	239 (59.0)	251 (62.0)	490 (60.5)
	Low/Negative (TIP <1%)	119 (29.4)	117 (28.9)	236 (29.1)
	Missing	47 (11.6)	37 (9.1)	84 (10.4)

MSI status missing includes MSI-unknown and not tested.
N = Number of subjects in treatment group. n = Number of subjects in category or analysis.
SD = Standard deviation. Min = Minimum. Max = Maximum.
MSI = Microsatellite instability. PD-L1 = Programmed cell death ligand 1. TIP = Tumor and/or immune cell positivity.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.5 TOPAZ: Stratification factors recorded at randomization on the eCRF
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

		Number (%) of subjects}		
Disease status	Primary tumor location	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Initially unresectable	IHCC	211 (52.1)	214 (52.8)	425 (52.5)
	EHCC	39 (9.6)	39 (9.6)	78 (9.6)
	GB	79 (19.5)	81 (20.0)	160 (19.8)
	Total	329 (81.2)	334 (82.5)	663 (81.9)
Recurrent	IHCC	25 (6.2)	21 (5.2)	46 (5.7)
	EHCC	34 (8.4)	32 (7.9)	66 (8.1)
	GB	17 (4.2)	17 (4.2)	34 (4.2)
	Total	76 (18.8)	70 (17.3)	146 (18.0)
Missing	EHCC	0	1 (0.2)	1 (0.1)
	Total	0	1 (0.2)	1 (0.1)
Total	IHCC	236 (58.3)	235 (58.0)	471 (58.1)
	EHCC	73 (18.0)	72 (17.8)	145 (17.9)
	GB	96 (23.7)	98 (24.2)	194 (24.0)

IHCC = Intrahepatic cholangiocarcinoma. EHCC = Extrahepatic cholangiocarcinoma. GB = Gallbladder cancer.
N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.6 TOPAZ: Previous disease related treatment modalities
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Number (%) of subjects}		
Previous treatment modalities	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Chemotherapy	24 (5.9)	33 (8.1)	57 (7.0)
Cytotoxic chemotherapy	24 (5.9)	33 (8.1)	57 (7.0)
Other	2 (0.5)	0	2 (0.2)
Radiotherapy	11 (2.7)	8 (2.0)	19 (2.3)

Subjects may appear under more than one previous treatment type, if they received more than one treatment.
N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.7 TOPAZ: Number of regimens of previous chemotherapy at baseline
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Number (%) of subjects}		
Number of regimens	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
0	381 (94.1)	372 (91.9)	753 (93.0)
1	23 (5.7)	31 (7.7)	54 (6.7)
2	1 (0.2)	2 (0.5)	3 (0.4)
n	24	33	57
Mean	1.0	1.1	1.1
SD	0.20	0.24	0.23
Median	1.0	1.0	1.0
Min	1	1	1
Max	2	2	2

Only subjects with previous chemotherapy are included in summary statistics.
N = Number of subjects in treatment group. n = Number of subjects in category or analysis.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.8 TOPAZ: Disease characteristics at initial diagnosis or screening
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Number (%) of subjects		
	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
WHO / ECOG performance status			
(0) Normal activity	189 (46.7)	185 (45.7)	374 (46.2)
(1) Restricted activity	216 (53.3)	220 (54.3)	436 (53.8)
Missing	0	0	0
Primary tumor location - category 1			
Intrahepatic Bile Duct	236 (58.3)	235 (58.0)	471 (58.1)
Perihilar Bile Duct	41 (10.1)	32 (7.9)	73 (9.0)
Distal Common Bile Duct	32 (7.9)	40 (9.9)	72 (8.9)
Gallbladder	96 (23.7)	98 (24.2)	194 (24.0)
Missing	0	0	0
Primary tumor location - category 2			
Intrahepatic Bile Duct	236 (58.3)	235 (58.0)	471 (58.1)
Extrahepatic Bile Duct (Perihilar and Distal)	73 (18.0)	72 (17.8)	145 (17.9)
Gallbladder	96 (23.7)	98 (24.2)	194 (24.0)
Missing	0	0	0

[a] Stages according to version 8 of the IASLC Staging Manual in Thoracic Oncology.
[b] Metastatic disease - subject has any metastatic site of disease.
[c] Locally advanced - subject has only locally advanced sites of disease.
[d] No evidence of disease - subject has neither locally advanced nor metastatic sites of disease.
WHO / ECOG performance status are based at study entry and overall disease classification and other parameters are based at time of initial diagnosis, apart from virology status which is measured at baseline.
WHO = World Health Organization. ECOG = The Eastern Cooperative Oncology Group.
N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.8 TOPAZ: Disease characteristics at initial diagnosis or screening
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Number (%) of subjects		
	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Histology type			
Adenocarcinoma	372 (91.9)	373 (92.1)	745 (92.0)
Adenosquamous carcinoma	3 (0.7)	3 (0.7)	6 (0.7)
Papillary adenocarcinoma	2 (0.5)	0	2 (0.2)
Mucinous adenocarcinoma	1 (0.2)	1 (0.2)	2 (0.2)
Bile duct cystadenocarcinoma	6 (1.5)	2 (0.5)	8 (1.0)
Other	16 (4.0)	22 (5.4)	38 (4.7)
Missing	5 (1.2)	4 (1.0)	9 (1.1)
Tumor grade			
Well Differentiated (G1)	38 (9.4)	45 (11.1)	83 (10.2)
Mod. Differentiated (G2)	114 (28.1)	122 (30.1)	236 (29.1)
Poorly Differentiated (G3)	103 (25.4)	100 (24.7)	203 (25.1)
Undifferentiated (G4)	0	0	0
Unassessable (GX)	150 (37.0)	137 (33.8)	287 (35.4)
Not done	0	0	0
Missing	0	1 (0.2)	1 (0.1)

[a] Stages according to version 8 of the IASLC Staging Manual in Thoracic Oncology.
[b] Metastatic disease - subject has any metastatic site of disease.
[c] Locally advanced - subject has only locally advanced sites of disease.
[d] No evidence of disease - subject has neither locally advanced nor metastatic sites of disease.
WHO / ECOG performance status are based at study entry and overall disease classification and other parameters are based at time of initial diagnosis, apart from virology status which is measured at baseline.
WHO = World Health Organization. ECOG = The Eastern Cooperative Oncology Group.
N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.
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Table 4.8 TOPAZ: Disease characteristics at initial diagnosis or screening
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Number (%) of subjects		
	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
TNM classification - initially unresectable			
Primary tumor			
T0	1 (0.2)	2 (0.5)	3 (0.4)
Tis	0	0	0
TX	40 (9.9)	43 (10.6)	83 (10.2)
T1	4 (1.0)	3 (0.7)	7 (0.9)
T1a	8 (2.0)	6 (1.5)	14 (1.7)
T1b	12 (3.0)	7 (1.7)	19 (2.3)
T2	82 (20.2)	85 (21.0)	167 (20.6)
T2a	5 (1.2)	5 (1.2)	10 (1.2)
T2b	7 (1.7)	6 (1.5)	13 (1.6)
T3	81 (20.0)	92 (22.7)	173 (21.4)
T4	89 (22.0)	85 (21.0)	174 (21.5)

[a] Stages according to version 8 of the IASLC Staging Manual in Thoracic Oncology.
[b] Metastatic disease - subject has any metastatic site of disease.
[c] Locally advanced - subject has only locally advanced sites of disease.
[d] No evidence of disease - subject has neither locally advanced nor metastatic sites of disease.
WHO / ECOG performance status are based at study entry and overall disease classification and other parameters are based at time of initial diagnosis, apart from virology status which is measured at baseline.
WHO = World Health Organization. ECOG = The Eastern Cooperative Oncology Group.
N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.8 TOPAZ: Disease characteristics at initial diagnosis or screening
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Number (%) of subjects		
	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Regional lymph nodes			
N0	77 (19.0)	74 (18.3)	151 (18.6)
N1	177 (43.7)	181 (44.7)	358 (44.2)
N2	23 (5.7)	28 (6.9)	51 (6.3)
NX	52 (12.8)	51 (12.6)	103 (12.7)
Distant metastases			
M0	53 (13.1)	67 (16.5)	120 (14.8)
MX	5 (1.2)	5 (1.2)	10 (1.2)
M1	271 (66.9)	262 (64.7)	533 (65.8)
Missing	0	0	0

[a] Stages according to version 8 of the IASLC Staging Manual in Thoracic Oncology.
[b] Metastatic disease - subject has any metastatic site of disease.
[c] Locally advanced - subject has only locally advanced sites of disease.
[d] No evidence of disease - subject has neither locally advanced nor metastatic sites of disease.
WHO / ECOG performance status are based at study entry and overall disease classification and other parameters are based at time of initial diagnosis, apart from virology status which is measured at baseline.
WHO = World Health Organization. ECOG = The Eastern Cooperative Oncology Group.
N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.8 TOPAZ: Disease characteristics at initial diagnosis or screening
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Number (%) of subjects		
	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
TNM classification - recurrent			
Primary tumor			
T0	0	0	0
Tis	0	0	0
TX	5 (1.2)	6 (1.5)	11 (1.4)
T1	8 (2.0)	3 (0.7)	11 (1.4)
T1a	6 (1.5)	4 (1.0)	10 (1.2)
T1b	5 (1.2)	3 (0.7)	8 (1.0)
T2	9 (2.2)	13 (3.2)	22 (2.7)
T2a	13 (3.2)	8 (2.0)	21 (2.6)
T2b	2 (0.5)	8 (2.0)	10 (1.2)
T3	25 (6.2)	22 (5.4)	47 (5.8)
T4	3 (0.7)	3 (0.7)	6 (0.7)

[a] Stages according to version 8 of the IASLC Staging Manual in Thoracic Oncology.
[b] Metastatic disease - subject has any metastatic site of disease.
[c] Locally advanced - subject has only locally advanced sites of disease.
[d] No evidence of disease - subject has neither locally advanced nor metastatic sites of disease.
WHO / ECOG performance status are based at study entry and overall disease classification and other parameters are based at time of initial diagnosis, apart from virology status which is measured at baseline.
WHO = World Health Organization. ECOG = The Eastern Cooperative Oncology Group.
N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.8 TOPAZ: Disease characteristics at initial diagnosis or screening
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Number (%) of subjects		
	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Regional lymph nodes			
N0	44 (10.9)	33 (8.1)	77 (9.5)
N1	17 (4.2)	27 (6.7)	44 (5.4)
N2	3 (0.7)	3 (0.7)	6 (0.7)
NX	12 (3.0)	7 (1.7)	19 (2.3)
Distant metastases			
M0	61 (15.1)	62 (15.3)	123 (15.2)
MX	7 (1.7)	4 (1.0)	11 (1.4)
M1	8 (2.0)	4 (1.0)	12 (1.5)
Missing	0	0	0

[a] Stages according to version 8 of the IASLC Staging Manual in Thoracic Oncology.
[b] Metastatic disease - subject has any metastatic site of disease.
[c] Locally advanced - subject has only locally advanced sites of disease.
[d] No evidence of disease - subject has neither locally advanced nor metastatic sites of disease.
WHO / ECOG performance status are based at study entry and overall disease classification and other parameters are based at time of initial diagnosis, apart from virology status which is measured at baseline.
WHO = World Health Organization. ECOG = The Eastern Cooperative Oncology Group.
N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.8 TOPAZ: Disease characteristics at initial diagnosis or screening
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Number (%) of subjects		
	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
AJCC staging - initially unresectable [a]			
Stage 0	0	0	0
Stage I	1 (0.2)	0	1 (0.1)
Stage IA	0	0	0
Stage IB	0	1 (0.2)	1 (0.1)
Stage II	8 (2.0)	15 (3.7)	23 (2.8)
Stage IIA	1 (0.2)	0	1 (0.1)
Stage IIB	0	1 (0.2)	1 (0.1)
Stage IIIA	8 (2.0)	5 (1.2)	13 (1.6)
Stage IIIB	33 (8.1)	32 (7.9)	65 (8.0)
Stage IIIC	3 (0.7)	5 (1.2)	8 (1.0)
Stage IV	184 (45.4)	184 (45.4)	368 (45.4)
Stage IVA	10 (2.5)	10 (2.5)	20 (2.5)
Stage IVB	81 (20.0)	81 (20.0)	162 (20.0)
Missing	0	0	0

[a] Stages according to version 8 of the IASLC Staging Manual in Thoracic Oncology.
[b] Metastatic disease - subject has any metastatic site of disease.
[c] Locally advanced - subject has only locally advanced sites of disease.
[d] No evidence of disease - subject has neither locally advanced nor metastatic sites of disease.
WHO / ECOG performance status are based at study entry and overall disease classification and other parameters are based at time of initial diagnosis, apart from virology status which is measured at baseline.
WHO = World Health Organization. ECOG = The Eastern Cooperative Oncology Group.
N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.8 TOPAZ: Disease characteristics at initial diagnosis or screening
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Number (%) of subjects		
	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
AJCC staging - recurrent [a]			
Stage 0	0	0	0
Stage I	12 (3.0)	5 (1.2)	17 (2.1)
Stage IA	5 (1.2)	2 (0.5)	7 (0.9)
Stage IB	0	2 (0.5)	2 (0.2)
Stage II	10 (2.5)	7 (1.7)	17 (2.1)
Stage IIA	6 (1.5)	6 (1.5)	12 (1.5)
Stage IIB	7 (1.7)	12 (3.0)	19 (2.3)
Stage IIIA	10 (2.5)	8 (2.0)	18 (2.2)
Stage IIIB	12 (3.0)	16 (4.0)	28 (3.5)
Stage IIIC	3 (0.7)	5 (1.2)	8 (1.0)
Stage IV	7 (1.7)	3 (0.7)	10 (1.2)
Stage IVA	1 (0.2)	1 (0.2)	2 (0.2)
Stage IVB	2 (0.5)	3 (0.7)	5 (0.6)
Missing	1 (0.2)	0	1 (0.1)

[a] Stages according to version 8 of the IASLC Staging Manual in Thoracic Oncology.
[b] Metastatic disease - subject has any metastatic site of disease.
[c] Locally advanced - subject has only locally advanced sites of disease.
[d] No evidence of disease - subject has neither locally advanced nor metastatic sites of disease.
WHO / ECOG performance status are based at study entry and overall disease classification and other parameters are based at time of initial diagnosis, apart from virology status which is measured at baseline.
WHO = World Health Organization. ECOG = The Eastern Cooperative Oncology Group.
N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.8 TOPAZ: Disease characteristics at initial diagnosis or screening
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Number (%) of subjects		
	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Extent of resection			
R0	47 (11.6)	51 (12.6)	98 (12.1)
R1	16 (4.0)	14 (3.5)	30 (3.7)
R2	8 (2.0)	8 (2.0)	16 (2.0)
Not applicable	333 (82.2)	332 (82.0)	665 (82.1)
Missing	1 (0.2)	0	1 (0.1)
Overall disease classification			
Metastatic [b]	350 (86.4)	331 (81.7)	681 (84.1)
Locally advanced [c]	55 (13.6)	73 (18.0)	128 (15.8)
No evidence of disease [d]	0	0	0
Missing	0	1 (0.2)	1 (0.1)
Virology status			
No Viral Hepatitis	212 (52.3)	204 (50.4)	416 (51.4)
Any Viral Hepatitis B	106 (26.2)	111 (27.4)	217 (26.8)
Active Viral Hepatitis B	18 (4.4)	26 (6.4)	44 (5.4)
Prior Hepatitis C	8 (2.0)	11 (2.7)	19 (2.3)
Missing	84 (20.7)	83 (20.5)	167 (20.6)

[a] Stages according to version 8 of the IASLC Staging Manual in Thoracic Oncology.
[b] Metastatic disease - subject has any metastatic site of disease.
[c] Locally advanced - subject has only locally advanced sites of disease.
[d] No evidence of disease - subject has neither locally advanced nor metastatic sites of disease.
WHO / ECOG performance status are based at study entry and overall disease classification and other parameters are based at time of initial diagnosis, apart from virology status which is measured at baseline.
WHO = World Health Organization. ECOG = The Eastern Cooperative Oncology Group.
N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.9 TOPAZ: Extent of Disease at baseline
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

		Number (%) of subjects		
Extent of disease	Site of disease	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Locally advanced [a]	Total	260 (64.2)	263 (64.9)	523 (64.6)
	Respiratory	3 (0.7)	2 (0.5)	5 (0.6)
	Ascites	0	2 (0.5)	2 (0.2)
	Gastrointestinal	1 (0.2)	1 (0.2)	2 (0.2)
	Hepatic (including Gall Bladder)	50 (12.3)	26 (6.4)	76 (9.4)
	Genitourinary	1 (0.2)	0	1 (0.1)
	Bone and Locomotor	1 (0.2)	0	1 (0.1)
	Peritoneum	7 (1.7)	7 (1.7)	14 (1.7)
	Pancreas	2 (0.5)	3 (0.7)	5 (0.6)
	Liver	125 (30.9)	145 (35.8)	270 (33.3)
	Gallbladder	55 (13.6)	57 (14.1)	112 (13.8)
	Distant Lymph Nodes	2 (0.5)	1 (0.2)	3 (0.4)
	Regional Lymph Nodes	85 (21.0)	100 (24.7)	185 (22.8)
	Other Locally Advanced Sites	56 (13.8)	52 (12.8)	108 (13.3)
	Lymph Nodes (Regional or Distant)	87 (21.5)	101 (24.9)	188 (23.2)

[a] Locally advanced disease - subject has any locally advanced site of disease.
[b] Metastatic - subject has any metastatic site of disease.
A subject can have one or more sites of disease.
Baseline is defined as the last result obtained prior to the start of study treatment.
N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.9 TOPAZ: Extent of Disease at baseline
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

		Number (%) of subjects		
Extent of disease	Site of disease	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Metastatic [b]	Total	350 (86.4)	331 (81.7)	681 (84.1)
	Cardiovascular	2 (0.5)	0	2 (0.2)
	Pleural Effusion	9 (2.2)	14 (3.5)	23 (2.8)
	Respiratory	96 (23.7)	89 (22.0)	185 (22.8)
	Ascites	28 (6.9)	27 (6.7)	55 (6.8)
	Breast	1 (0.2)	0	1 (0.1)
	Gastrointestinal	10 (2.5)	7 (1.7)	17 (2.1)
	Hepatic (including Gall Bladder)	34 (8.4)	42 (10.4)	76 (9.4)
	Genitourinary	6 (1.5)	9 (2.2)	15 (1.9)
	Skin/Soft Tissue	5 (1.2)	3 (0.7)	8 (1.0)
	Bone and Locomotor	34 (8.4)	24 (5.9)	58 (7.2)
	Pericardial Effusion	1 (0.2)	2 (0.5)	3 (0.4)
	Peritoneum	95 (23.5)	87 (21.5)	182 (22.5)
	Pancreas	4 (1.0)	8 (2.0)	12 (1.5)
	Spleen	4 (1.0)	3 (0.7)	7 (0.9)
	Esophagus	2 (0.5)	1 (0.2)	3 (0.4)
	Colon	4 (1.0)	5 (1.2)	9 (1.1)
	Liver	180 (44.4)	149 (36.8)	329 (40.6)
	Gallbladder	5 (1.2)	7 (1.7)	12 (1.5)
	Distant Lymph Nodes	163 (40.2)	165 (40.7)	328 (40.5)
	Trachea	1 (0.2)	2 (0.5)	3 (0.4)
	Regional Lymph Nodes	102 (25.2)	85 (21.0)	187 (23.1)
	Other Metastatic Sites	47 (11.6)	47 (11.6)	94 (11.6)
	Lymph Nodes (Regional or Distant)	217 (53.6)	200 (49.4)	417 (51.5)

[a] Locally advanced disease - subject has any locally advanced site of disease.
[b] Metastatic - subject has any metastatic site of disease.
A subject can have one or more sites of disease.
Baseline is defined as the last result obtained prior to the start of study treatment.
N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.10 TOPAZ: Time from most recent disease progression to randomization
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Time (days)		Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Most recent progression to start of randomization	n	394	395	789
	Mean	20.1	20.3	20.2
	SD	20.19	19.83	20.00
	Median	14.0	15.0	14.0
	Min	1	1	1
	Max	166	133	166

N = Number of subjects in treatment group. n = Number of subjects in category or analysis.
SD = Standard deviation. Min = Minimum. Max = Maximum. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.11 TOPAZ: Post-discontinuation disease-related anti-cancer therapy
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Number (%) of subjects}		
Anti-cancer therapy[a]	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Number of subjects with subsequent anti-cancer therapy	171 (42.2)	192 (47.4)	363 (44.8)
Immunotherapy	19 (4.7)	26 (6.4)	45 (5.6)
Cytotoxic Chemotherapy	152 (37.5)	165 (40.7)	317 (39.1)
Targeted Therapy	26 (6.4)	31 (7.7)	57 (7.0)
Antiangiogenic Therapy	4 (1.0)	2 (0.5)	6 (0.7)
Taxane Chemotherapy	10 (2.5)	17 (4.2)	27 (3.3)
Other	23 (5.7)	35 (8.6)	58 (7.2)

[a] Therapies post-discontinuation of study treatment.
Subjects may have more than 1 cancer therapy.
N = Number of subjects in treatment group. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.12 TOPAZ: Concomitant surgical procedures related to biliary tract by preferred term
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

MedDRA Preferred term	Number (%) of subjects [a] Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Stenting and drainage			
Subjects with at least one procedure	66 (16.3)	71 (17.5)	137 (16.9)
Bile duct stent insertion	36 (8.9)	32 (7.9)	68 (8.4)
Biliary catheter insertion	34 (8.4)	33 (8.1)	67 (8.3)
Cholangiostomy	9 (2.2)	25 (6.2)	34 (4.2)
Biliary catheter removal	4 (1.0)	6 (1.5)	10 (1.2)
Biliary sphincterotomy	1 (0.2)	0	1 (0.1)
Bile duct stent removal	0	1 (0.2)	1 (0.1)
Pancreatic duct drainage	0	1 (0.2)	1 (0.1)
Pancreatic stent placement	0	1 (0.2)	1 (0.1)
Surgery related to disease under study			
Subjects with at least one procedure	7 (1.7)	6 (1.5)	13 (1.6)
Hepatectomy	5 (1.2)	4 (1.0)	9 (1.1)
Cholecystectomy	3 (0.7)	3 (0.7)	6 (0.7)
Hepaticojejunostomy	1 (0.2)	0	1 (0.1)
Choledochectomy	0	1 (0.2)	1 (0.1)

[a] Number (%) of subjects with surgical procedures, sorted in descending frequency of preferred term in the Durva + Gem + Cis treatment group. Subjects with multiple procedures in the same preferred term are counted only once in that preferred term. Subjects with procedures in more than one preferred term are counted once in each of those preferred terms.
Percentages are based on the total number of subjects in the treatment group (N).
MedDRA version 24.0.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.13 TOPAZ: Duration of Durvalumab/Placebo exposure
Safety Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Treatment duration (months)		Durva + Gem + Cis (N=402)	Placebo + Gem + Cis (N=403)	Total (N=805)
Durva/Placebo (combination) total treatment duration (months) [a]	n	402	403	805
	Mean	4.72	4.56	4.64
	SD	1.997	1.980	1.989
	Median	5.55	5.52	5.52
	Min	0.1	0.2	0.1
	Max	9.0	9.4	9.4
	Total treatment years	158.09	153.13	311.21
Durva/Placebo (combination) actual treatment duration (months) [b]	n	402	403	805
	Mean	4.44	4.25	4.34
	SD	1.841	1.784	1.814
	Median	5.52	5.49	5.52
	Min	0.1	0.2	0.1
	Max	9.0	8.1	9.0
	Total treatment years	148.73	142.61	291.34

[a] Total treatment duration = (min(last dose date period 1 where dose > 0 + 20, date of death, date of DCO) - first dose date +1) / (365.25/12). [b] Actual treatment duration = total treatment duration minus the total duration of delays. [c] Total treatment duration = (min(last dose date period 2 where dose > 0 + 27, date of death, date of DCO) - first dose date period 2 +1) / (365.25/12). [d] Total treatment duration = (min(last dose date where dose > 0 + [20 if last dose in period 1 (combination) or 27 if last dose in period 2 (maintenance], date of death, date of DCO) - first dose date +1) / (365.25/12). N = Number of subjects in treatment group. n = number of subjects in category or analysis. Period 1 = Combination therapy. Period 2 = Maintenance monotherapy only.
SD = Standard deviation. Min = Minimum. Max = Maximum. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.13 TOPAZ: Duration of Durvalumab/Placebo exposure
Safety Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Treatment duration (months)		Durva + Gem + Cis (N=402)	Placebo + Gem + Cis (N=403)	Total (N=805)
Durva/Placebo (maintenance) total treatment duration (months) [c]	n	217	183	400
	Mean	4.54	3.35	4.00
	SD	4.004	2.810	3.554
	Median	3.15	2.53	2.76
	Min	0.2	0.6	0.2
	Max	18.9	16.6	18.9
	Total treatment years	82.09	51.13	133.22
Durva/Placebo (maintenance) actual treatment duration (months) [b]	n	217	183	400
	Mean	4.40	3.24	3.87
	SD	3.816	2.617	3.368
	Median	3.02	2.53	2.76
	Min	0.2	0.6	0.2
	Max	18.9	16.0	18.9
	Total treatment years	79.53	49.38	128.91

[a] Total treatment duration = (min(last dose date period 1 where dose > 0 + 20, date of death, date of DCO) - first dose date +1) / (365.25/12). [b] Actual treatment duration = total treatment duration minus the total duration of delays. [c] Total treatment duration = (min(last dose date period 2 where dose > 0 + 27, date of death, date of DCO) - first dose date period 2 +1) / (365.25/12). [d] Total treatment duration = (min(last dose date where dose > 0 + [20 if last dose in period 1 (combination) or 27 if last dose in period 2 (maintenance], date of death, date of DCO) - first dose date +1) / (365.25/12). N = Number of subjects in treatment group. n = number of subjects in category or analysis.
Period 1 = Combination therapy. Period 2 = Maintenance monotherapy only.
SD = Standard deviation. Min = Minimum. Max = Maximum. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.13 TOPAZ: Duration of Durvalumab/Placebo exposure
Safety Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

Treatment duration (months)		Durva + Gem + Cis (N=402)	Placebo + Gem + Cis (N=403)	Total (N=805)
Durva/Placebo total treatment duration (months) [d]	n	402	403	805
	Mean	7.26	6.13	6.69
	SD	4.934	3.836	4.452
	Median	7.15	5.78	6.47
	Min	0.1	0.2	0.1
	Max	24.6	22.1	24.6
	Total treatment years	243.12	205.97	449.09
Durva/Placebo actual treatment duration (months) [b]	n	402	403	805
	Mean	6.87	5.76	6.31
	SD	4.691	3.605	4.217
	Median	6.67	5.59	5.78
	Min	0.1	0.2	0.1
	Max	24.5	21.5	24.5
	Total treatment years	230.02	193.30	423.32

[a] Total treatment duration = (min(last dose date period 1 where dose > 0 + 20, date of death, date of DCO) - first dose date +1) / (365.25/12). [b] Actual treatment duration = total treatment duration minus the total duration of delays. [c] Total treatment duration = (min(last dose date period 2 where dose > 0 + 27, date of death, date of DCO) - first dose date period 2 +1) / (365.25/12). [d] Total treatment duration = (min(last dose date where dose > 0 + [20 if last dose in period 1 (combination) or 27 if last dose in period 2 (maintenance], date of death, date of DCO) - first dose date +1) / (365.25/12). N = Number of subjects in treatment group. n = number of subjects in category or analysis. Period 1 = Combination therapy. Period 2 = Maintenance monotherapy only.
SD = Standard deviation. Min = Minimum. Max = Maximum. Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.14 TOPAZ: Previous surgical therapy related to disease under study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Number (%) of subjects [a]		
	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Previous surgical therapy related to disease under study (except biliary stenting or drainage)	100 (24.7)	105 (25.9)	205 (25.3)
Curative surgery	75 (18.5)	70 (17.3)	145 (17.9)
Hepatectomy	47 (11.6)	32 (7.9)	79 (9.8)
Cholecystectomy	33 (8.1)	27 (6.7)	60 (7.4)
Choledochectomy	13 (3.2)	6 (1.5)	19 (2.3)
Pancreaticoduodenectomy	12 (3.0)	22 (5.4)	34 (4.2)
Hepaticojejunostomy	10 (2.5)	3 (0.7)	13 (1.6)
Choledochoenterostomy	3 (0.7)	2 (0.5)	5 (0.6)
Biliary tract operation	2 (0.5)	4 (1.0)	6 (0.7)
Liver operation	2 (0.5)	0	2 (0.2)
Duodenectomy	1 (0.2)	0	1 (0.1)
Gallbladder operation	0	2 (0.5)	2 (0.2)
Non-curative surgery	25 (6.2)	35 (8.6)	60 (7.4)
Cholecystectomy	18 (4.4)	26 (6.4)	44 (5.4)
Hepatectomy	10 (2.5)	10 (2.5)	20 (2.5)
Choledochectomy	1 (0.2)	3 (0.7)	4 (0.5)
Duodenectomy	1 (0.2)	0	1 (0.1)
Hepaticojejunostomy	1 (0.2)	0	1 (0.1)
Liver operation	1 (0.2)	0	1 (0.1)
Pancreaticoduodenectomy	1 (0.2)	0	1 (0.1)
Choledochoenterostomy	0	1 (0.2)	1 (0.1)

[a] Number (%) of subjects with surgical procedures, sorted in descending frequency of preferred term in the Durva + Gem + Cis treatment group. Subjects with multiple procedures in the same preferred term are counted only once in that preferred term. Subjects with procedures in more than one preferred term are counted once in each of those preferred terms.
Percentages are based on the total number of subjects in the treatment group (N).
MedDRA version 24.0.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.14 TOPAZ: Previous surgical therapy related to disease under study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

	Number (%) of subjects [a]		
	Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Previous history of biliary stenting or drainage (previous or on-going)	63 (15.6)	61 (15.1)	124 (15.3)
Bile duct stent insertion	38 (9.4)	29 (7.2)	67 (8.3)
Biliary catheter insertion	17 (4.2)	22 (5.4)	39 (4.8)
Cholangiostomy	10 (2.5)	17 (4.2)	27 (3.3)
Biliary sphincterotomy	4 (1.0)	3 (0.7)	7 (0.9)
Pancreatobiliary sphincterotomy	2 (0.5)	0	2 (0.2)
Biliary tract dilation procedure	1 (0.2)	1 (0.2)	2 (0.2)
Cholecystostomy	1 (0.2)	0	1 (0.1)
Choledochostomy	1 (0.2)	0	1 (0.1)
Bile duct stent removal	0	1 (0.2)	1 (0.1)
Biliary anastomosis	0	1 (0.2)	1 (0.1)
Biliary catheter removal	0	2 (0.5)	2 (0.2)
Pancreatic stent placement	0	1 (0.2)	1 (0.1)

[a] Number (%) of subjects with surgical procedures, sorted in descending frequency of preferred term in the Durva + Gem + Cis treatment group. Subjects with multiple procedures in the same preferred term are counted only once in that preferred term. Subjects with procedures in more than one preferred term are counted once in each of those preferred terms.
Percentages are based on the total number of subjects in the treatment group (N).
MedDRA version 24.0.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Number of subjects with allowed concomitant medication	404 (99.8)	404 (99.8)	808 (99.8)
SEROTONIN (5HT3) ANTAGONISTS	350 (86.4)	343 (84.7)	693 (85.6)
Ondansetron	133 (32.8)	127 (31.4)	260 (32.1)
Palonosetron hydrochloride	91 (22.5)	110 (27.2)	201 (24.8)
Palonosetron	49 (12.1)	35 (8.6)	84 (10.4)
Ondansetron hydrochloride	40 (9.9)	37 (9.1)	77 (9.5)
Tropisetron hydrochloride	25 (6.2)	18 (4.4)	43 (5.3)
Netupitant;palonosetron hydrochloride	24 (5.9)	21 (5.2)	45 (5.6)
Ramosetron hydrochloride	18 (4.4)	18 (4.4)	36 (4.4)
Granisetron hydrochloride	15 (3.7)	13 (3.2)	28 (3.5)
Granisetron	14 (3.5)	29 (7.2)	43 (5.3)
Tropisetron	5 (1.2)	4 (1.0)	9 (1.1)
Azasetron hydrochloride	4 (1.0)	6 (1.5)	10 (1.2)
Azasetron hydrochloride;sodium chloride	4 (1.0)	8 (2.0)	12 (1.5)
Dolasetron mesilate	2 (0.5)	2 (0.5)	4 (0.5)
Netupitant;palonosetron	2 (0.5)	3 (0.7)	5 (0.6)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Sodium chloride;tropisetron hydrochloride	2 (0.5)	3 (0.7)	5 (0.6)
Tropisetron mesylate	2 (0.5)	0	2 (0.2)
Glucose;granisetron hydrochloride	0	2 (0.5)	2 (0.2)
Ondansetron hydrochloride dihydrate	0	1 (0.2)	1 (0.1)
Ondansetron;sodium chloride	0	1 (0.2)	1 (0.1)
Ramosetron	0	1 (0.2)	1 (0.1)
GLUCOCORTICOIDS	292 (72.1)	276 (68.1)	568 (70.1)
Dexamethasone	176 (43.5)	176 (43.5)	352 (43.5)
Dexamethasone sodium phosphate	85 (21.0)	83 (20.5)	168 (20.7)
Methylprednisolone	28 (6.9)	16 (4.0)	44 (5.4)
Prednisolone	19 (4.7)	16 (4.0)	35 (4.3)
Hydrocortisone sodium succinate	18 (4.4)	11 (2.7)	29 (3.6)
Hydrocortisone	11 (2.7)	4 (1.0)	15 (1.9)
Methylprednisolone sodium succinate	11 (2.7)	7 (1.7)	18 (2.2)
Dexamethasone phosphate	9 (2.2)	7 (1.7)	16 (2.0)
Prednisone	9 (2.2)	11 (2.7)	20 (2.5)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Betamethasone sodium phosphate	3 (0.7)	3 (0.7)	6 (0.7)
Budesonide	3 (0.7)	4 (1.0)	7 (0.9)
Dexamethasone acetate	3 (0.7)	1 (0.2)	4 (0.5)
Dexamethasone palmitate	3 (0.7)	3 (0.7)	6 (0.7)
Deflazacort	2 (0.5)	1 (0.2)	3 (0.4)
Beclometasone dipropionate	1 (0.2)	0	1 (0.1)
Betamethasone	1 (0.2)	4 (1.0)	5 (0.6)
Ciclesonide	1 (0.2)	0	1 (0.1)
Cortisone acetate	1 (0.2)	0	1 (0.1)
Fluticasone propionate	1 (0.2)	1 (0.2)	2 (0.2)
Prednisone acetate	1 (0.2)	2 (0.5)	3 (0.4)
Triamcinolone	1 (0.2)	0	1 (0.1)
Beclometasone	0	1 (0.2)	1 (0.1)
Betamethasone dipropionate	0	1 (0.2)	1 (0.1)
Dexamethasone sodium succinate	0	1 (0.2)	1 (0.1)
Meprednisone	0	2 (0.5)	2 (0.2)
Triamcinolone acetonide	0	2 (0.5)	2 (0.2)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
PROTON PUMP INHIBITORS	214 (52.8)	216 (53.3)	430 (53.1)
Omeprazole	68 (16.8)	56 (13.8)	124 (15.3)
Pantoprazole sodium sesquihydrate	38 (9.4)	38 (9.4)	76 (9.4)
Esomeprazole magnesium	33 (8.1)	39 (9.6)	72 (8.9)
Lansoprazole	30 (7.4)	33 (8.1)	63 (7.8)
Omeprazole sodium	25 (6.2)	26 (6.4)	51 (6.3)
Pantoprazole	25 (6.2)	25 (6.2)	50 (6.2)
Esomeprazole sodium	24 (5.9)	23 (5.7)	47 (5.8)
Rabeprazole sodium	22 (5.4)	22 (5.4)	44 (5.4)
Esomeprazole	21 (5.2)	14 (3.5)	35 (4.3)
Vonoprazan fumarate	6 (1.5)	7 (1.7)	13 (1.6)
Ilaprazole	5 (1.2)	2 (0.5)	7 (0.9)
Dexlansoprazole	3 (0.7)	4 (1.0)	7 (0.9)
Rabeprazole	3 (0.7)	2 (0.5)	5 (0.6)
Domperidone;pantoprazole sodium sesquihydrate	2 (0.5)	2 (0.5)	4 (0.5)
Omeprazole magnesium	2 (0.5)	1 (0.2)	3 (0.4)
Domperidone;rabeprazole	1 (0.2)	0	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Esomeprazole magnesium dihydrate	1 (0.2)	1 (0.2)	2 (0.2)
Ilaprazole sodium	1 (0.2)	0	1 (0.1)
Levosulpiride;rabeprazole	1 (0.2)	0	1 (0.1)
Tegoprazan	1 (0.2)	1 (0.2)	2 (0.2)
Domperidone;pantoprazole	0	1 (0.2)	1 (0.1)
Domperidone;rabeprazole sodium	0	1 (0.2)	1 (0.1)
PROPULSIVES	210 (51.9)	199 (49.1)	409 (50.5)
Metoclopramide	103 (25.4)	96 (23.7)	199 (24.6)
Metoclopramide hydrochloride	58 (14.3)	57 (14.1)	115 (14.2)
Domperidone	46 (11.4)	36 (8.9)	82 (10.1)
Metoclopramide dihydrochloride	18 (4.4)	13 (3.2)	31 (3.8)
Mosapride citrate	14 (3.5)	23 (5.7)	37 (4.6)
Itopride hydrochloride	8 (2.0)	3 (0.7)	11 (1.4)
Mosapride	4 (1.0)	6 (1.5)	10 (1.2)
Levosulpiride	2 (0.5)	0	2 (0.2)
Cisapride	1 (0.2)	0	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Itopride	1 (0.2)	1 (0.2)	2 (0.2)
Domperidone maleate	0	1 (0.2)	1 (0.1)
ELECTROLYTE SOLUTIONS	160 (39.5)	138 (34.1)	298 (36.8)
Potassium chloride	79 (19.5)	63 (15.6)	142 (17.5)
Magnesium sulfate	75 (18.5)	68 (16.8)	143 (17.7)
Sodium chloride	66 (16.3)	63 (15.6)	129 (15.9)
Calcium gluconate	12 (3.0)	12 (3.0)	24 (3.0)
Calcium chloride;potassium chloride;sodium chloride	11 (2.7)	8 (2.0)	19 (2.3)
Sodium bicarbonate	11 (2.7)	10 (2.5)	21 (2.6)
Chromic chloride hexahydrate;copper chloride dihydrate;ferric chloride hexahydrate;manganese chloride tetrahydrate;potassium iodide;sodium fluoride;sodium molybdate dihydrate;sodium selenite pentahydrate;zinc chloride	5 (1.2)	0	5 (0.6)
Potassium chloride;sodium chloride	5 (1.2)	4 (1.0)	9 (1.1)
Potassium phosphate monobasic	5 (1.2)	5 (1.2)	10 (1.2)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Calcium chloride;potassium chloride;sodium acetate;sodium chloride	4 (1.0)	2 (0.5)	6 (0.7)
Potassium	4 (1.0)	0	4 (0.5)
Chromic chloride;copper sulfate;manganese sulfate;zinc sulfate	3 (0.7)	0	3 (0.4)
Glucose;magnesium chloride hexahydrate;potassium acetate;potassium phosphate monobasic;sodium acetate;sodium chloride	3 (0.7)	1 (0.2)	4 (0.5)
Calcium chloride dihydrate;potassium chloride;sodium chloride	2 (0.5)	4 (1.0)	6 (0.7)
Sodium glycerophosphate	2 (0.5)	0	2 (0.2)
Amino acids nos;electrolytes nos;glucose	1 (0.2)	3 (0.7)	4 (0.5)
Calcium chloride dihydrate;magnesium chloride hexahydrate;potassium chloride;sodium acetate trihydrate;sodium chloride;sodium citrate dihydrate	1 (0.2)	2 (0.5)	3 (0.4)
Calcium chloride;magnesium chloride;potassium chloride;sodium acetate;sodium chloride	1 (0.2)	0	1 (0.1)
Calcium chloride;magnesium chloride;potassium chloride;sodium acetate;sodium chloride;sodium citrate	1 (0.2)	0	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Glucose monohydrate;magnesium chloride hexahydrate;potassium acetate;potassium phosphate monobasic;sodium acetate;sodium chloride	1 (0.2)	0	1 (0.1)
Glucose;magnesium chloride;potassium chloride;potassium phosphate monobasic;sodium acetate;sodium chloride	1 (0.2)	0	1 (0.1)
Magnesium sulfate;potassium chloride;sodium chloride	1 (0.2)	2 (0.5)	3 (0.4)
Potassium phosphate dibasic;potassium phosphate monobasic	1 (0.2)	0	1 (0.1)
Zinc sulfate	1 (0.2)	0	1 (0.1)
Calcium chloride;potassium chloride	0	1 (0.2)	1 (0.1)
Chromic chloride;copper sulfate;manganese sulfate;selenious acid;zinc sulfate	0	1 (0.2)	1 (0.1)
Magnesium chloride	0	3 (0.7)	3 (0.4)
Potassium phosphate dibasic	0	1 (0.2)	1 (0.1)
ANILIDES	157 (38.8)	144 (35.6)	301 (37.2)
Paracetamol	149 (36.8)	135 (33.3)	284 (35.1)
Propacetamol hydrochloride	11 (2.7)	10 (2.5)	21 (2.6)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Bidens biternata;caffeine;chlorphenamine maleate;chrysanthemum indicum flower;ilex asprella root;melicope pteleifolia;mentha canadensis oil;paracetamol	2 (0.5)	1 (0.2)	3 (0.4)
Propacetamol	2 (0.5)	1 (0.2)	3 (0.4)
Acetylsalicylic acid;caffeine;orphenadrine citrate;phenacetin	1 (0.2)	0	1 (0.1)
Acetylsalicylic acid;paracetamol	1 (0.2)	0	1 (0.1)
Caffeine;chlorphenamine maleate;cow bezoar;paracetamol	1 (0.2)	0	1 (0.1)
Caffeine;chlorphenamine maleate;ethenzamide;methylephedrine hydrochloride-dl;noscapine;paracetamol	1 (0.2)	0	1 (0.1)
Diclofenac sodium;paracetamol	1 (0.2)	0	1 (0.1)
Paracetamol;phenylephrine	1 (0.2)	0	1 (0.1)
Amantadine hydrochloride;paracetamol	0	2 (0.5)	2 (0.2)
Ascorbic acid;paracetamol;pheniramine maleate	0	1 (0.2)	1 (0.1)
Chlorphenamine maleate;dextromethorphan hydrobromide;paracetamol;pseudoephedrine hydrochloride	0	1 (0.2)	1 (0.1)
Ibuprofen;paracetamol	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OSMOTICALLY ACTING LAXATIVES	148 (36.5)	152 (37.5)	300 (37.0)
Lactulose	78 (19.3)	73 (18.0)	151 (18.6)
Magnesium oxide	51 (12.6)	52 (12.8)	103 (12.7)
Macrogol 3350;potassium chloride;sodium bicarbonate;sodium chloride	14 (3.5)	7 (1.7)	21 (2.6)
Macrogol 3350	8 (2.0)	11 (2.7)	19 (2.3)
Magnesium hydroxide	7 (1.7)	20 (4.9)	27 (3.3)
Macrogol;potassium chloride;sodium bicarbonate;sodium chloride	6 (1.5)	10 (2.5)	16 (2.0)
Galactose;lactose;lactulose	2 (0.5)	1 (0.2)	3 (0.4)
Macrogol	2 (0.5)	2 (0.5)	4 (0.5)
Macrogol 4000;potassium chloride;sodium bicarbonate;sodium chloride	2 (0.5)	4 (1.0)	6 (0.7)
Ascorbic acid;macrogol 3350;potassium chloride;sodium ascorbate;sodium chloride;sodium sulfate	1 (0.2)	0	1 (0.1)
Ascorbic acid;macrogol 3350;potassium chloride;sodium ascorbate;sodium chloride;sodium sulfate anhydrous	1 (0.2)	0	1 (0.1)
Lactitol	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Macrogol 4000	1 (0.2)	0	1 (0.1)
Macrogol;potassium chloride;sodium bicarbonate;sodium chloride;sodium sulfate anhydrous	1 (0.2)	0	1 (0.1)
Magnesium sulfate;potassium sulfate;simeticone;sodium sulfate	1 (0.2)	0	1 (0.1)
Potassium sulfate	1 (0.2)	1 (0.2)	2 (0.2)
Ascorbic acid;macrogol 4000;potassium chloride;sodium ascorbate;sodium chloride;sodium sulfate anhydrous	0	1 (0.2)	1 (0.1)
Macrogol 3350;potassium;sodium bicarbonate;sodium chloride	0	2 (0.5)	2 (0.2)
Magnesium citrate	0	1 (0.2)	1 (0.1)
Magnesium sulfate	0	1 (0.2)	1 (0.1)
OTHER ANTIEMETICS	144 (35.6)	140 (34.6)	284 (35.1)
Aprepitant	71 (17.5)	73 (18.0)	144 (17.8)
Prochlorperazine	31 (7.7)	22 (5.4)	53 (6.5)
Fosaprepitant meglumine	22 (5.4)	31 (7.7)	53 (6.5)
Fosaprepitant	9 (2.2)	5 (1.2)	14 (1.7)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Diphenhydramine hydrochloride	6 (1.5)	2 (0.5)	8 (1.0)
Promethazine hydrochloride	5 (1.2)	4 (1.0)	9 (1.1)
Cyclizine	4 (1.0)	5 (1.2)	9 (1.1)
Dronabinol	4 (1.0)	2 (0.5)	6 (0.7)
Metopimazine	4 (1.0)	2 (0.5)	6 (0.7)
Prochlorperazine maleate	4 (1.0)	5 (1.2)	9 (1.1)
Promethazine	3 (0.7)	3 (0.7)	6 (0.7)
Cyanocobalamin;pyridoxine hydrochloride;thiamine hydrochloride	1 (0.2)	0	1 (0.1)
Cyclizine hydrochloride	1 (0.2)	0	1 (0.1)
Difenidol	1 (0.2)	1 (0.2)	2 (0.2)
Dimenhydrinate	1 (0.2)	3 (0.7)	4 (0.5)
Diphenhydramine	1 (0.2)	2 (0.5)	3 (0.4)
Prochlorperazine mesilate	1 (0.2)	1 (0.2)	2 (0.2)
Bromisoval;procaine	0	2 (0.5)	2 (0.2)
Diphenhydramine hydrochloride;diprophylline	0	1 (0.2)	1 (0.1)
Diphenhydramine salicylate;diprophylline	0	3 (0.7)	3 (0.4)
Hydroxyzine	0	1 (0.2)	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Hyoscine	0	1 (0.2)	1 (0.1)
Promethazine teoclate	0	1 (0.2)	1 (0.1)
COLONY STIMULATING FACTORS	142 (35.1)	156 (38.5)	298 (36.8)
Filgrastim	82 (20.2)	87 (21.5)	169 (20.9)
Granulocyte colony stimulating factor	45 (11.1)	51 (12.6)	96 (11.9)
Pegfilgrastim	9 (2.2)	13 (3.2)	22 (2.7)
Peg granulocyte colony stimulating factor	7 (1.7)	4 (1.0)	11 (1.4)
Filgrastim sndz	6 (1.5)	3 (0.7)	9 (1.1)
Lenograstim	3 (0.7)	10 (2.5)	13 (1.6)
Mecapegfilgrastim	2 (0.5)	2 (0.5)	4 (0.5)
Granulocyte macrophage colony stim factor	1 (0.2)	1 (0.2)	2 (0.2)
Empegfilgrastim	0	1 (0.2)	1 (0.1)
Filgrastim aafi	0	1 (0.2)	1 (0.1)
Pegfilgrastim bmez	0	1 (0.2)	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
NATURAL OPIUM ALKALOIDS	121 (29.9)	134 (33.1)	255 (31.5)
Oxycodone hydrochloride	49 (12.1)	52 (12.8)	101 (12.5)
Morphine sulfate	41 (10.1)	38 (9.4)	79 (9.8)
Morphine	20 (4.9)	27 (6.7)	47 (5.8)
Morphine hydrochloride	20 (4.9)	14 (3.5)	34 (4.2)
Oxycodone	20 (4.9)	26 (6.4)	46 (5.7)
Naloxone hydrochloride;oxycodone hydrochloride	12 (3.0)	13 (3.2)	25 (3.1)
Hydromorphone hydrochloride	9 (2.2)	12 (3.0)	21 (2.6)
Codeine	7 (1.7)	5 (1.2)	12 (1.5)
Codeine phosphate	3 (0.7)	5 (1.2)	8 (1.0)
Hydromorphone	3 (0.7)	0	3 (0.4)
Hydrocodone	2 (0.5)	0	2 (0.2)
Hydrocodone hydrochloride	1 (0.2)	0	1 (0.1)
Naloxone;oxycodone	0	1 (0.2)	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER BLOOD PRODUCTS	119 (29.4)	99 (24.4)	218 (26.9)
Red blood cells, concentrated	52 (12.8)	51 (12.6)	103 (12.7)
Red blood cells	34 (8.4)	29 (7.2)	63 (7.8)
Blood, whole	22 (5.4)	15 (3.7)	37 (4.6)
Platelets, concentrated	15 (3.7)	12 (3.0)	27 (3.3)
Red blood cells, leucocyte depleted	9 (2.2)	5 (1.2)	14 (1.7)
Platelets	8 (2.0)	12 (3.0)	20 (2.5)
Plasma	7 (1.7)	12 (3.0)	19 (2.3)
Platelets, human blood	1 (0.2)	2 (0.5)	3 (0.4)
Blood plasma	0	1 (0.2)	1 (0.1)
SULFONAMIDES, PLAIN	112 (27.7)	98 (24.2)	210 (25.9)
Furosemide	99 (24.4)	89 (22.0)	188 (23.2)
Torasemide	14 (3.5)	8 (2.0)	22 (2.7)
Indapamide	5 (1.2)	6 (1.5)	11 (1.4)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Furosemide sodium	1 (0.2)	0	1 (0.1)
Chlortalidone	0	1 (0.2)	1 (0.1)
THIRD-GENERATION CEPHALOSPORINS	104 (25.7)	93 (23.0)	197 (24.3)
Ceftriaxone	33 (8.1)	31 (7.7)	64 (7.9)
Cefoperazone sodium;sulbactam sodium	32 (7.9)	25 (6.2)	57 (7.0)
Ceftriaxone sodium	17 (4.2)	21 (5.2)	38 (4.7)
Cefixime	11 (2.7)	8 (2.0)	19 (2.3)
Cefpodoxime proxetil	10 (2.5)	2 (0.5)	12 (1.5)
Ceftazidime	9 (2.2)	10 (2.5)	19 (2.3)
Cefdinir	5 (1.2)	3 (0.7)	8 (1.0)
Cefditoren pivoxil	5 (1.2)	11 (2.7)	16 (2.0)
Ceftriaxone sodium sesquaterhydrate	4 (1.0)	1 (0.2)	5 (0.6)
Cefotaxime sodium	3 (0.7)	3 (0.7)	6 (0.7)
Cefoperazone	2 (0.5)	0	2 (0.2)
Cefpodoxime	2 (0.5)	2 (0.5)	4 (0.5)
Ceftazidime pentahydrate	2 (0.5)	0	2 (0.2)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Ceftriaxone sodium sesquaterhydrate;sodium chloride	2 (0.5)	1 (0.2)	3 (0.4)
Ceftriaxone sodium;tazobactam sodium	2 (0.5)	0	2 (0.2)
Avibactam sodium;ceftazidime pentahydrate	1 (0.2)	0	1 (0.1)
Cefcapene pivoxil hydrochloride	1 (0.2)	2 (0.5)	3 (0.4)
Cefditoren	1 (0.2)	0	1 (0.1)
Cefixime trihydrate	1 (0.2)	0	1 (0.1)
Cefodizime disodium	1 (0.2)	0	1 (0.1)
Cefoperazone sodium;tazobactam sodium	1 (0.2)	1 (0.2)	2 (0.2)
Cefoperazone;sulbactam	1 (0.2)	0	1 (0.1)
Cefotaxime	1 (0.2)	3 (0.7)	4 (0.5)
Ceftibuten	1 (0.2)	0	1 (0.1)
Ceftibuten dihydrate	1 (0.2)	1 (0.2)	2 (0.2)
Ceftriaxone sodium;tazobactam	1 (0.2)	0	1 (0.1)
Latamoxef sodium	1 (0.2)	2 (0.5)	3 (0.4)
Cefcapene pivoxil	0	1 (0.2)	1 (0.1)
Cefoperazone sodium	0	2 (0.5)	2 (0.2)
Cefotaxime sodium;lidocaine hydrochloride	0	1 (0.2)	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
FLUOROQUINOLONES	101 (24.9)	95 (23.5)	196 (24.2)
Levofloxacin	46 (11.4)	46 (11.4)	92 (11.4)
Ciprofloxacin	33 (8.1)	34 (8.4)	67 (8.3)
Ciprofloxacin hydrochloride	8 (2.0)	6 (1.5)	14 (1.7)
Ciprofloxacin lactate	4 (1.0)	3 (0.7)	7 (0.9)
Levofloxacin hydrochloride	4 (1.0)	0	4 (0.5)
Moxifloxacin hydrochloride	3 (0.7)	8 (2.0)	11 (1.4)
Norfloxacin	3 (0.7)	3 (0.7)	6 (0.7)
Levofloxacin hydrochloride;sodium chloride	2 (0.5)	1 (0.2)	3 (0.4)
Moxifloxacin	2 (0.5)	2 (0.5)	4 (0.5)
Ofloxacin	2 (0.5)	6 (1.5)	8 (1.0)
Ciprofloxacin;ciprofloxacin hydrochloride	1 (0.2)	0	1 (0.1)
Garenoxacin mesilate	1 (0.2)	0	1 (0.1)
Gatifloxacin	1 (0.2)	0	1 (0.1)
Levofloxacin lactate;sodium chloride	1 (0.2)	0	1 (0.1)
Levofloxacin;sodium chloride	1 (0.2)	1 (0.2)	2 (0.2)

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Levofloxacin hemihydrate	0	1 (0.2)	1 (0.1)
Levofloxacin mesylate	0	1 (0.2)	1 (0.1)
OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	98 (24.2)	89 (22.0)	187 (23.1)
Paracetamol;tramadol hydrochloride	46 (11.4)	49 (12.1)	95 (11.7)
Codeine phosphate;paracetamol	11 (2.7)	7 (1.7)	18 (2.2)
Codeine phosphate;ibuprofen;paracetamol	9 (2.2)	6 (1.5)	15 (1.9)
Domperidone;paracetamol;tramadol hydrochloride	7 (1.7)	5 (1.2)	12 (1.5)
Hydrocodone bitartrate;paracetamol	6 (1.5)	6 (1.5)	12 (1.5)
Oxycodone hydrochloride;paracetamol	5 (1.2)	0	5 (0.6)
Oxycodone;paracetamol	5 (1.2)	4 (1.0)	9 (1.1)
Paracetamol;tramadol	5 (1.2)	6 (1.5)	11 (1.4)
Hydrocodone;paracetamol	3 (0.7)	2 (0.5)	5 (0.6)
Codeine phosphate;diclofenac sodium	2 (0.5)	0	2 (0.2)
Codeine phosphate;ibuprofen	2 (0.5)	2 (0.5)	4 (0.5)
Caffeine;codeine phosphate;paracetamol	1 (0.2)	1 (0.2)	2 (0.2)
Codeine;paracetamol	1 (0.2)	2 (0.5)	3 (0.4)

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Gymnopus androsaceus;tramadol hydrochloride	1 (0.2)	0	1 (0.1)
Caffeine;chlorphenamine maleate;dihydrocodeine phosphate;ibuprofen;pseudoephedrine hydrochloride	0	1 (0.2)	1 (0.1)
Codeine phosphate;naproxen sodium	0	1 (0.2)	1 (0.1)
Codeine;naproxen	0	2 (0.5)	2 (0.2)
Dihydrocodeine bitartrate;paracetamol	0	1 (0.2)	1 (0.1)
BENZODIAZEPINE DERIVATIVES	96 (23.7)	89 (22.0)	185 (22.8)
Lorazepam	44 (10.9)	44 (10.9)	88 (10.9)
Alprazolam	19 (4.7)	13 (3.2)	32 (4.0)
Midazolam	14 (3.5)	12 (3.0)	26 (3.2)
Clonazepam	9 (2.2)	8 (2.0)	17 (2.1)
Estazolam	8 (2.0)	9 (2.2)	17 (2.1)
Brotizolam	7 (1.7)	4 (1.0)	11 (1.4)
Diazepam	5 (1.2)	7 (1.7)	12 (1.5)
Etizolam	3 (0.7)	0	3 (0.4)
Nitrazepam	3 (0.7)	2 (0.5)	5 (0.6)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Bromazepam	2 (0.5)	2 (0.5)	4 (0.5)
Clotiazepam	1 (0.2)	0	1 (0.1)
Delorazepam	1 (0.2)	0	1 (0.1)
Temazepam	1 (0.2)	0	1 (0.1)
Tofisopam	1 (0.2)	0	1 (0.1)
Triazolam	1 (0.2)	0	1 (0.1)
Clorazepate dipotassium	0	1 (0.2)	1 (0.1)
Flurazepam hydrochloride	0	1 (0.2)	1 (0.1)
Midazolam hydrochloride	0	2 (0.5)	2 (0.2)
Oxazepam	0	1 (0.2)	1 (0.1)
CONTACT LAXATIVES	94 (23.2)	100 (24.7)	194 (24.0)
Sennoside a+b	56 (13.8)	61 (15.1)	117 (14.4)
Sennoside a+b calcium	10 (2.5)	8 (2.0)	18 (2.2)
Bisacodyl	9 (2.2)	15 (3.7)	24 (3.0)
Senna spp.	9 (2.2)	6 (1.5)	15 (1.9)
Sodium picosulfate	9 (2.2)	3 (0.7)	12 (1.5)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Senna alexandrina leaf	3 (0.7)	3 (0.7)	6 (0.7)
Bisacodyl;docusate sodium;sennoside a+b	2 (0.5)	2 (0.5)	4 (0.5)
Citric acid;magnesium oxide;sodium picosulfate	2 (0.5)	1 (0.2)	3 (0.4)
Docusate sodium;sennoside a+b	2 (0.5)	1 (0.2)	3 (0.4)
Docusate sodium;senna alexandrina	1 (0.2)	0	1 (0.1)
Docusate;senna alexandrina	1 (0.2)	0	1 (0.1)
Ricinus communis oil	1 (0.2)	0	1 (0.1)
Senna alexandrina extract	1 (0.2)	3 (0.7)	4 (0.5)
Senna spp. extract	1 (0.2)	4 (1.0)	5 (0.6)
Aloe vera dry leaf juice;aucklandia costus root;pearl	0	1 (0.2)	1 (0.1)
Bisacodyl;docusate sodium	0	1 (0.2)	1 (0.1)
Bisacodyl;sennoside a+b	0	1 (0.2)	1 (0.1)
Bisacodyl;sennoside b	0	1 (0.2)	1 (0.1)
Rheum officinale	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER OPIOIDS	93 (23.0)	83 (20.5)	176 (21.7)
Tramadol	50 (12.3)	39 (9.6)	89 (11.0)
Tramadol hydrochloride	36 (8.9)	41 (10.1)	77 (9.5)
Bucinnazine hydrochloride	3 (0.7)	2 (0.5)	5 (0.6)
Tapentadol	3 (0.7)	1 (0.2)	4 (0.5)
Dezocine	2 (0.5)	3 (0.7)	5 (0.6)
Tapentadol hydrochloride	2 (0.5)	1 (0.2)	3 (0.4)
Bucinnazine	1 (0.2)	0	1 (0.1)
PROPIONIC ACID DERIVATIVES	87 (21.5)	72 (17.8)	159 (19.6)
Ibuprofen	35 (8.6)	17 (4.2)	52 (6.4)
Loxoprofen	14 (3.5)	14 (3.5)	28 (3.5)
Naproxen	13 (3.2)	14 (3.5)	27 (3.3)
Flurbiprofen axetil	11 (2.7)	8 (2.0)	19 (2.3)
Loxoprofen sodium	8 (2.0)	6 (1.5)	14 (1.7)
Ketoprofen	5 (1.2)	5 (1.2)	10 (1.2)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Loxoprofen sodium dihydrate	5 (1.2)	9 (2.2)	14 (1.7)
Arginine hydrochloride;ibuprofen	2 (0.5)	0	2 (0.2)
Dexketoprofen trometamol	2 (0.5)	1 (0.2)	3 (0.4)
Naproxen sodium	2 (0.5)	1 (0.2)	3 (0.4)
Bromisoval;caffeine;ethenzamide;ibuprofen	1 (0.2)	0	1 (0.1)
Ibuprofen arginine	1 (0.2)	0	1 (0.1)
Dexibuprofen	0	1 (0.2)	1 (0.1)
Dexketoprofen	0	1 (0.2)	1 (0.1)
Flurbiprofen	0	3 (0.7)	3 (0.4)
Pelubiprofen	0	1 (0.2)	1 (0.1)
Zaltoprofen	0	1 (0.2)	1 (0.1)
DIHYDROPYRIDINE DERIVATIVES	85 (21.0)	76 (18.8)	161 (19.9)
Amlodipine	33 (8.1)	38 (9.4)	71 (8.8)
Amlodipine besilate	26 (6.4)	18 (4.4)	44 (5.4)
Nifedipine	9 (2.2)	15 (3.7)	24 (3.0)
Amlodipine orotate	6 (1.5)	1 (0.2)	7 (0.9)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Lercanidipine	3 (0.7)	1 (0.2)	4 (0.5)
Felodipine	2 (0.5)	2 (0.5)	4 (0.5)
Nicardipine hydrochloride	2 (0.5)	3 (0.7)	5 (0.6)
Azelnidipine	1 (0.2)	0	1 (0.1)
Barnidipine hydrochloride	1 (0.2)	0	1 (0.1)
Benidipine hydrochloride	1 (0.2)	0	1 (0.1)
Levamlodipine besilate	1 (0.2)	1 (0.2)	2 (0.2)
Levamlodipine maleate	1 (0.2)	1 (0.2)	2 (0.2)
Manidipine	1 (0.2)	0	1 (0.1)
Manidipine hydrochloride	1 (0.2)	0	1 (0.1)
S amlodipine nicotinate	1 (0.2)	0	1 (0.1)
Amlodipine camsilate	0	1 (0.2)	1 (0.1)
Lacidipine	0	2 (0.5)	2 (0.2)
Nicardipine	0	1 (0.2)	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
SOLUTIONS FOR PARENTERAL NUTRITION	81 (20.0)	69 (17.0)	150 (18.5)
Glucose	25 (6.2)	35 (8.6)	60 (7.4)
Amino acids nos;electrolytes nos;glucose;thiamine hydrochloride	12 (3.0)	4 (1.0)	16 (2.0)
Fish oil;glycine max seed oil;olea europaea oil;triglycerides	9 (2.2)	14 (3.5)	23 (2.8)
Alanine;arginine;calcium chloride dihydrate;fish oil;glucose monohydrate;glycine;glycine max oil;histidine;isoleucine;leucine;lysine hydrochloride;magnesium sulfate heptahydrate;medium-chain triglycerides;methionine;olea europaea oil;phenylalanine;potassium chloride;proline;serine;sodium acetate trihydrate;sodium glycerophosphate;threonine;tryptophan, l-;tyrosine;valine;zinc sulfate heptahydrate	8 (2.0)	9 (2.2)	17 (2.1)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Alanine;arginine;calcium chloride;fish oil;glucose monohydrate;glycine;glycine max seed oil;histidine;isoleucine;leucine;lysine acetate;magnesium sulfate;medium-chain triglycerides;methionine;olea europaea oil;phenylalanine;potassium chloride;proline;serine;sodium acetate;sodium glycerophosphate;taurine;threonine;tryptophan, l-;tyrosine;valine;zinc sulfate	8 (2.0)	12 (3.0)	20 (2.5)
Amino acids nos	7 (1.7)	11 (2.7)	18 (2.2)
Alanine;arginine hydrochloride;cysteine hydrochloride;glycine;histidine hydrochloride;isoleucine;leucine;lysine acetate;methionine;phenylalanine;proline;serine;threonine; tryptophan, l-;valine	6 (1.5)	6 (1.5)	12 (1.5)
Fish oil;glycerol;phospholipids egg	5 (1.2)	0	5 (0.6)
Solutions for parenteral nutrition	5 (1.2)	0	5 (0.6)
Amino acids nos;electrolytes nos;glucose;lipids nos	4 (1.0)	4 (1.0)	8 (1.0)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Arginine;beta-alanine;cysteine hydrochloride;glycine;histidine;isoleucine;leucine;lysine; methionine;phenylalanine;proline;serine;threonine;tryptoph an, l-;valine	4 (1.0)	4 (1.0)	8 (1.0)
Dl-alpha tocopheryl acetate;glycerol;glycine max seed oil;lecithin;medium-chain triglycerides	4 (1.0)	5 (1.2)	9 (1.1)
Acetic acid;alanine;arginine;aspartic acid;calcium;calcium chloride;chloride;glucose;glutamate sodium;glycerol;glycine;glycine max seed oil;histidine;isoleucine;lecithin;leucine;lysine hydrochloride;magnesium;magnesium sulfate;methionine;phenylalanine;phosphorus;potassium;pota ssium chloride;proline;serine;sodium;sodium acetate;sodium glycerophosphate;sodium hydroxide;threonine;tryptophan, l-;tyrosine;valine	3 (0.7)	2 (0.5)	5 (0.6)
Amino acids nos;fats nos;glucose	3 (0.7)	7 (1.7)	10 (1.2)
Glycine max seed oil;lecithin	3 (0.7)	1 (0.2)	4 (0.5)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Alanine;arginine hydrochloride;aspartic acid;cysteine hydrochloride;glutamic acid;glycine;histidine hydrochloride;isoleucine;leucine;lysine hydrochloride;methionine;phenylalanine;proline;serine;threonine;tryptophan, l-;tyrosine;valine;xylitol	2 (0.5)	0	2 (0.2)
Alanine;arginine;aspartic acid;calcium chloride;glucose;glutamic acid;glycine;glycine max oil;histidine;isoleucine;leucine;lysine hydrochloride;magnesium sulfate;methionine;phenylalanine;potassium chloride;proline;serine;sodium acetate;sodium glycerophosphate;threonine;tryptophan, l-;tyrosine;valine	2 (0.5)	0	2 (0.2)
Alanine;arginine;aspartic acid;cysteine;glutamic acid;glycine;histidine;isoleucine;leucine;lysine acetate;methionine;phenylalanine;proline;serine;threonine;tryptophan, l-;tyrosine;valine	2 (0.5)	1 (0.2)	3 (0.4)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Alanine;arginine;calcium hydroxide;glucose monohydrate;glycine;glycine max seed oil;histidine;isoleucine;leucine;lysine hydrochloride;magnesium chloride;methionine;phenylalanine;potassium phosphate dibasic;proline;serine;sodium acetate trihydrate;sodium chloride;threonine;tryptophan, l-;tyrosine;valine	2 (0.5)	0	2 (0.2)
Cysteine hydrochloride;glycine;glycyrrhizic acid, ammonium salt	2 (0.5)	0	2 (0.2)
Glycerol;glycine max oil;lecithin;olea europaea oil;sodium oleate	2 (0.5)	0	2 (0.2)
Glycerol;glycine max seed oil;lecithin;medium-chain triglycerides	2 (0.5)	1 (0.2)	3 (0.4)
Alanine;allysine;arginine;aspartic acid;cystine;glutamic acid;glycine;histidine;isoleucine;leucine;methionine;phenylalanine;proline;serine;sorbitol;threonine;tryptophan, l-;tyrosine;valine	1 (0.2)	0	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Alanine;arginine hydrochloride;aspartic acid;cysteine hydrochloride;glutamic acid;glycine;histidine hydrochloride;isoleucine;leucine;lysine hydrochloride;methionine;phenylalanine;proline;serine;sorbitol;threonine;tryptophan, l-;tyrosine;valine	1 (0.2)	0	1 (0.1)
Alanine;arginine hydrochloride;aspartic acid;cysteine;glutamic acid;histidine;isoleucine;leucine;lysine acetate;methionine;phenylalanine;proline;serine;threonine;tryptophan, l-;tyrosine;valine	1 (0.2)	0	1 (0.1)
Alanine;arginine hydrochloride;calcium chloride dihydrate;glucose;glycine;histidine hydrochloride;isoleucine;leucine;lysine hydrochloride;magnesium chloride;methionine;phenylalanine;potassium phosphate dibasic;proline;serine;sodium acetate;sodium chloride;threonine;tryptophan, l-;tyrosine;valine	1 (0.2)	0	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Alanine;arginine;aspartic acid;calcium chloride;cysteine hydrochloride;glutamic acid;glycine;histidine;isoleucine;leucine;lysine hydrochloride;magnesium sulfate;methionine;phenylalanine;potassium chloride;potassium hydroxide;proline;serine;sodium hydroxide;threonine;tryptophan, l-;tyrosine;valine	1 (0.2)	0	1 (0.1)
Alanine;arginine;aspartic acid;cystine;glutamic acid;glycine;histidine;isoleucine;leucine;lysine acetate;methionine;phenylalanine;proline;serine;threonine; tryptophan, l-;tyrosine;valine	1 (0.2)	1 (0.2)	2 (0.2)
Alanine;arginine;aspartic acid;glutamic acid;glycine;histidine;isoleucine;leucine;lysine acetate;lysine monohydrate;methionine;phenylalanine;proline;serine;threonine;tryptophan, l-;tyrosine;valine	1 (0.2)	0	1 (0.1)
Alanine;arginine;aspartic acid;glutamic acid;glycylglutamine;glycyltyrosine;histidine;isoleucine;leucine;lysine acetate;methionine;phenylalanine;proline;serine;threonine; tryptophan, l-;valine	1 (0.2)	0	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Alanine;arginine;calcium chloride;cysteine hydrochloride;glucose;glycine;histidine;isoleucine;leucine ;lysine acetate;magnesium chloride;methionine;phenylalanine;potassium chloride;potassium phosphate monobasic;proline;serine;sodium acetate;sodium chloride;threonine;tryptophan, l-;valine	1 (0.2)	0	1 (0.1)
Alanine;arginine;cysteine hydrochloride;glycine;histidine;isoleucine;leucine;lysine acetate;methionine;phenylalanine;proline;serine;threonine; tryptophan, l-;valine	1 (0.2)	1 (0.2)	2 (0.2)
Amino acids nos;carbohydrates nos;electrolytes nos	1 (0.2)	0	1 (0.1)
Amino acids nos;carbohydrates nos;minerals nos;vitamins nos	1 (0.2)	0	1 (0.1)
Amino acids nos;electrolytes nos	1 (0.2)	0	1 (0.1)
Amino acids nos;glucose;lipids nos	1 (0.2)	0	1 (0.1)
Amino acids nos;oxycodone;oxycodone terephthalate;paracetamol	1 (0.2)	1 (0.2)	2 (0.2)

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Ammonium molybdate;chromic chloride;cobalt gluconate;copper gluconate;ferrous gluconate;manganese gluconate;sodium fluoride;sodium iodide;sodium selenite;zinc gluconate	1 (0.2)	2 (0.5)	3 (0.4)
Glycerol;glycine max seed oil;medium-chain triglycerides;phospholipids egg	1 (0.2)	0	1 (0.1)
Isoleucine;leucine;valine	1 (0.2)	0	1 (0.1)
Triglycerides	1 (0.2)	2 (0.5)	3 (0.4)
Alanine;arginine glutamate;aspartic acid;calcium chloride dihydrate;glucose monohydrate;glutamic acid;glycine;histidine hydrochloride;isoleucine;leucine;lysine hydrochloride;magnesium acetate tetrahydrate;methionine;phenylalanine;potassium hydroxide;potassium phosphate monobasic;proline;serine;sodium acetate trihydrate;sodium chloride;sodium hydroxide;threonine;tryptophan, l-;valine	0	1 (0.2)	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Alanine;arginine hydrochloride;aspartic acid;cysteine;glutamic acid;glycerol;glycine;glycine max seed oil;histidine;isoleucine;lecithin;leucine;lysine hydrochloride;methionine;phenylalanine;proline;serine;sodium bisulfite;sorbitol;threonine;tryptophan, l-;tyrosine;valine	0	1 (0.2)	1 (0.1)
Alanine;arginine hydrochloride;glycine;histidine hydrochloride;isoleucine;leucine;lysine hydrochloride;malic acid;methionine;n-acetyltyrosin;phenylalanine;proline;serine;taurine;threonine;tryptophan, l-;valine	0	1 (0.2)	1 (0.1)
Alanine;arginine;aspartic acid;calcium chloride dihydrate;glucose monohydrate;glutamic acid;glycine;glycine max oil;histidine;isoleucine;leucine;lysine acetate;magnesium chloride hexahydrate;methionine;olea europaea oil;phenylalanine;potassium chloride;proline;serine;sodium acetate;sodium glycerophosphate;threonine;tryptophan, l-;tyrosine;valine	0	3 (0.7)	3 (0.4)
Amino acids nos;calcium;glucose;magnesium;potassium;sodium	0	1 (0.2)	1 (0.1)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Amino acids nos;copper;electrolytes nos;glucose;iodine;iron;manganese;vitamins nos;zinc	0	1 (0.2)	1 (0.1)
Glycine max seed oil	0	1 (0.2)	1 (0.1)
SUBSTITUTED ALKYLAMINES	80 (19.8)	56 (13.8)	136 (16.8)
Chlorphenamine	36 (8.9)	24 (5.9)	60 (7.4)
Chlorphenamine maleate	21 (5.2)	19 (4.7)	40 (4.9)
Pheniramine	17 (4.2)	11 (2.7)	28 (3.5)
Dexchlorpheniramine maleate	5 (1.2)	2 (0.5)	7 (0.9)
Pheniramine maleate	2 (0.5)	4 (1.0)	6 (0.7)
Dexchlorpheniramine	1 (0.2)	0	1 (0.1)
Pheniramine aminosalicylate	1 (0.2)	0	1 (0.1)
COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS	79 (19.5)	80 (19.8)	159 (19.6)
Piperacillin sodium;tazobactam sodium	47 (11.6)	44 (10.9)	91 (11.2)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Piperacillin;tazobactam	14 (3.5)	5 (1.2)	19 (2.3)
Amoxicillin;clavulanic acid	13 (3.2)	16 (4.0)	29 (3.6)
Amoxicillin;clavulanate potassium	11 (2.7)	13 (3.2)	24 (3.0)
Amoxicillin trihydrate;clavulanate potassium	7 (1.7)	3 (0.7)	10 (1.2)
Ampicillin sodium;sulbactam sodium	5 (1.2)	9 (2.2)	14 (1.7)
Amoxicillin sodium;clavulanate potassium	3 (0.7)	1 (0.2)	4 (0.5)
Sultamicillin	2 (0.5)	1 (0.2)	3 (0.4)
Amoxicillin;sulbactam	1 (0.2)	0	1 (0.1)
Piperacillin sodium;sulbactam sodium	1 (0.2)	0	1 (0.1)
Ampicillin;sulbactam	0	2 (0.5)	2 (0.2)
Sultamicillin tosilate	0	2 (0.5)	2 (0.2)
SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	78 (19.3)	74 (18.3)	152 (18.8)
Glucose;sodium chloride	23 (5.7)	25 (6.2)	48 (5.9)
Calcium chloride dihydrate;potassium chloride;sodium chloride;sodium lactate	11 (2.7)	8 (2.0)	19 (2.3)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Calcium gluconate;glucose;magnesium chloride;potassium chloride;sodium acetate;sodium chloride;sodium citrate	10 (2.5)	10 (2.5)	20 (2.5)
Gluconate sodium;magnesium chloride;potassium chloride;sodium acetate;sodium chloride	9 (2.2)	8 (2.0)	17 (2.1)
Calcium chloride;potassium chloride;sodium chloride;sodium lactate	8 (2.0)	3 (0.7)	11 (1.4)
Glucose;potassium chloride;sodium chloride;sodium lactate	7 (1.7)	10 (2.5)	17 (2.1)
Calcium chloride;potassium chloride;sodium lactate	5 (1.2)	4 (1.0)	9 (1.1)
Calcium chloride;potassium chloride;sodium chloride;sodium lactate;sorbitol	4 (1.0)	1 (0.2)	5 (0.6)
Calcium chloride dihydrate;glucose;potassium chloride;sodium acetate;sodium chloride	3 (0.7)	3 (0.7)	6 (0.7)
Calcium chloride dihydrate;glucose;potassium chloride;sodium chloride;sodium lactate	3 (0.7)	1 (0.2)	4 (0.5)
Electrolytes nos	3 (0.7)	6 (1.5)	9 (1.1)
Glucose;potassium;sodium	3 (0.7)	3 (0.7)	6 (0.7)
Calcium chloride dihydrate;magnesium chloride hexahydrate;potassium chloride;sodium chloride;sodium lactate	2 (0.5)	1 (0.2)	3 (0.4)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Calcium chloride dihydrate;potassium chloride;sodium acetate trihydrate;sodium chloride	2 (0.5)	8 (2.0)	10 (1.2)
Glucose;sodium chloride;sodium lactate	2 (0.5)	1 (0.2)	3 (0.4)
Calcium chloride dihydrate;maltose monohydrate;potassium chloride;sodium chloride;sodium lactate	1 (0.2)	0	1 (0.1)
Calcium chloride;citric acid;magnesium chloride;potassium chloride;sodium bicarbonate;sodium chloride;sodium citrate	1 (0.2)	1 (0.2)	2 (0.2)
Calcium chloride;potassium;sodium chloride;sodium lactate	1 (0.2)	0	1 (0.1)
Electrolytes nos;glucose	1 (0.2)	0	1 (0.1)
Fructose;glucose;magnesium chloride;potassium chloride;sodium chloride;sodium lactate;sodium phosphate monobasic	1 (0.2)	1 (0.2)	2 (0.2)
Gluconate sodium;magnesium chloride hexahydrate;potassium chloride;sodium acetate trihydrate;sodium chloride	1 (0.2)	1 (0.2)	2 (0.2)
Gluconate sodium;magnesium chloride hexahydrate;potassium chloride;sodium acetate;sodium chloride	1 (0.2)	2 (0.5)	3 (0.4)
Glucose 1-phosphate disodium	1 (0.2)	0	1 (0.1)
Glucose;magnesium sulfate	1 (0.2)	1 (0.2)	2 (0.2)
Glucose;potassium chloride	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Glucose;potassium chloride;sodium chloride;sodium citrate dihydrate	1 (0.2)	0	1 (0.1)
Magnesium sulfate	1 (0.2)	2 (0.5)	3 (0.4)
Sodium lactate	1 (0.2)	1 (0.2)	2 (0.2)
Calcium chloride;fructose;glucose;magnesium chloride;potassium phosphate dibasic;sodium acetate;sodium chloride;xylitol;zinc sulfate	0	1 (0.2)	1 (0.1)
Calcium chloride;potassium chloride;sodium acetate	0	1 (0.2)	1 (0.1)
Electrolytes with carbohydrates	0	1 (0.2)	1 (0.1)
Glucose;magnesium chloride hexahydrate;potassium chloride;potassium phosphate monobasic;sodium acetate trihydrate;sodium chloride	0	1 (0.2)	1 (0.1)
Glucose;potassium chloride;sodium chloride	0	1 (0.2)	1 (0.1)
Sodium chloride	0	1 (0.2)	1 (0.1)
HEPARIN GROUP	75 (18.5)	59 (14.6)	134 (16.5)
Enoxaparin sodium	23 (5.7)	21 (5.2)	44 (5.4)
Heparin	11 (2.7)	6 (1.5)	17 (2.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Heparin sodium	11 (2.7)	6 (1.5)	17 (2.1)
Enoxaparin	9 (2.2)	7 (1.7)	16 (2.0)
Nadroparin calcium	9 (2.2)	6 (1.5)	15 (1.9)
Tinzaparin sodium	6 (1.5)	6 (1.5)	12 (1.5)
Dalteparin sodium	4 (1.0)	2 (0.5)	6 (0.7)
Heparin calcium	4 (1.0)	2 (0.5)	6 (0.7)
Tinzaparin	4 (1.0)	4 (1.0)	8 (1.0)
Dalteparin	3 (0.7)	4 (1.0)	7 (0.9)
Low molecular weight heparin, sodium salt	3 (0.7)	2 (0.5)	5 (0.6)
Heparin porcine	0	1 (0.2)	1 (0.1)
Heparin;sodium chloride	0	1 (0.2)	1 (0.1)
Parnaparin	0	1 (0.2)	1 (0.1)
BILE ACIDS AND DERIVATIVES	74 (18.3)	81 (20.0)	155 (19.1)
Ursodeoxycholic acid	73 (18.0)	81 (20.0)	154 (19.0)
Chenodeoxycholic acid;ursodeoxycholic acid	2 (0.5)	0	2 (0.2)
Bear bile	0	1 (0.2)	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
LIVER THERAPY	72 (17.8)	67 (16.5)	139 (17.2)
Magnesium isoglycyrrhizinate	17 (4.2)	17 (4.2)	34 (4.2)
Diammonium glycyrrhizinate	16 (4.0)	10 (2.5)	26 (3.2)
Silybum marianum	14 (3.5)	15 (3.7)	29 (3.6)
Polyene phosphatidylcholine	12 (3.0)	6 (1.5)	18 (2.2)
Adenine hydrochloride;bifendate;carnitine orotate;cyanocobalamin;liver extract;pyridoxine hydrochloride;riboflavin	9 (2.2)	6 (1.5)	15 (1.9)
Dl-methionine;glycine;glycyrrhizic acid, ammonium salt	9 (2.2)	7 (1.7)	16 (2.0)
Ornithine aspartate	9 (2.2)	12 (3.0)	21 (2.6)
Cysteine hydrochloride;glycine;glycyrrhizic acid, ammonium salt	7 (1.7)	5 (1.2)	12 (1.5)
Tiopronin	4 (1.0)	3 (0.7)	7 (0.9)
Glycyrrhizic acid	3 (0.7)	0	3 (0.4)
Hepatocyte growth factor	3 (0.7)	4 (1.0)	7 (0.9)
Ornithine	3 (0.7)	2 (0.5)	5 (0.6)
Ornithine oxoglurate	3 (0.7)	4 (1.0)	7 (0.9)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Lactulose	2 (0.5)	4 (1.0)	6 (0.7)
Rifaximin	2 (0.5)	0	2 (0.2)
Choline citrate;dl-alpha tocopheryl acetate;folic acid;silybum marianum;uridine phosphate;vitamin b12 nos	1 (0.2)	0	1 (0.1)
Coenzyme a	1 (0.2)	0	1 (0.1)
Cysteine hydrochloride;glycyrrhizic acid, ammonium salt	1 (0.2)	3 (0.7)	4 (0.5)
Flavine adenine dinucleotide disodium;liver extract	1 (0.2)	0	1 (0.1)
Glycyrrhiza glabra	1 (0.2)	0	1 (0.1)
Liver therapy	1 (0.2)	2 (0.5)	3 (0.4)
Ornithine aspartate;pancreatin	1 (0.2)	0	1 (0.1)
Phospholipids	1 (0.2)	1 (0.2)	2 (0.2)
Tiopronin sodium	1 (0.2)	0	1 (0.1)
Allium sativum oil;dimethyl 4,4'-biphenyldicarboxylate	0	1 (0.2)	1 (0.1)
Bupleurum spp. root;ganoderma spp. sporocarp;salvia miltiorrhiza root with rhizome;schisandra chinensis fruit	0	1 (0.2)	1 (0.1)
Glycine;glycyrrhizic acid;methionine	0	1 (0.2)	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
HMG COA REDUCTASE INHIBITORS	65 (16.0)	64 (15.8)	129 (15.9)
Atorvastatin	19 (4.7)	18 (4.4)	37 (4.6)
Simvastatin	16 (4.0)	13 (3.2)	29 (3.6)
Atorvastatin calcium	14 (3.5)	16 (4.0)	30 (3.7)
Rosuvastatin calcium	10 (2.5)	9 (2.2)	19 (2.3)
Pitavastatin	3 (0.7)	0	3 (0.4)
Rosuvastatin	3 (0.7)	6 (1.5)	9 (1.1)
Pravastatin	2 (0.5)	2 (0.5)	4 (0.5)
Atorvastatin calcium trihydrate	1 (0.2)	0	1 (0.1)
Pitavastatin calcium	1 (0.2)	1 (0.2)	2 (0.2)
Pravastatin sodium	0	2 (0.5)	2 (0.2)
H2-RECEPTOR ANTAGONISTS	63 (15.6)	65 (16.0)	128 (15.8)
Famotidine	39 (9.6)	35 (8.6)	74 (9.1)
Ranitidine	15 (3.7)	19 (4.7)	34 (4.2)
Ranitidine hydrochloride	9 (2.2)	9 (2.2)	18 (2.2)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Cimetidine	6 (1.5)	9 (2.2)	15 (1.9)
Lafutidine	2 (0.5)	0	2 (0.2)
POTASSIUM	56 (13.8)	40 (9.9)	96 (11.9)
Potassium chloride	34 (8.4)	27 (6.7)	61 (7.5)
Potassium gluconate	6 (1.5)	5 (1.2)	11 (1.4)
Potassium	5 (1.2)	1 (0.2)	6 (0.7)
Potassium aspartate	4 (1.0)	5 (1.2)	9 (1.1)
Potassium citrate	4 (1.0)	0	4 (0.5)
Citric acid;potassium bicarbonate;potassium citrate	2 (0.5)	0	2 (0.2)
Magnesium aspartate;potassium aspartate	2 (0.5)	2 (0.5)	4 (0.5)
Phosphorus;potassium	1 (0.2)	0	1 (0.1)
Potassium bicarbonate;potassium chloride	1 (0.2)	1 (0.2)	2 (0.2)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
APPETITE STIMULANTS	51 (12.6)	54 (13.3)	105 (13.0)
Megestrol acetate	35 (8.6)	37 (9.1)	72 (8.9)
Megestrol	13 (3.2)	14 (3.5)	27 (3.3)
Cyproheptadine	2 (0.5)	0	2 (0.2)
Carnitine hydrochloride;cyanocobalamin;cyproheptadine orotate;lysine hydrochloride	1 (0.2)	1 (0.2)	2 (0.2)
Cyproheptadine hydrochloride	0	2 (0.5)	2 (0.2)
Dronabinol	0	1 (0.2)	1 (0.1)
INSULINS AND ANALOGUES FOR INJECTION, FAST-ACTING	50 (12.3)	51 (12.6)	101 (12.5)
Insulin	27 (6.7)	28 (6.9)	55 (6.8)
Insulin human	14 (3.5)	18 (4.4)	32 (4.0)
Insulin aspart	10 (2.5)	4 (1.0)	14 (1.7)
Insulin lispro	9 (2.2)	4 (1.0)	13 (1.6)
Insulin glulisine	3 (0.7)	6 (1.5)	9 (1.1)
Insulin porcine	1 (0.2)	0	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Insulin human biosynthetic	0	2 (0.5)	2 (0.2)
OTHER ANTIHISTAMINES FOR SYSTEMIC USE	49 (12.1)	29 (7.2)	78 (9.6)
Loratadine	15 (3.7)	6 (1.5)	21 (2.6)
Fexofenadine hydrochloride	14 (3.5)	9 (2.2)	23 (2.8)
Fexofenadine	7 (1.7)	2 (0.5)	9 (1.1)
Desloratadine	4 (1.0)	1 (0.2)	5 (0.6)
Azelastine hydrochloride	2 (0.5)	0	2 (0.2)
Bilastine	2 (0.5)	3 (0.7)	5 (0.6)
Cyproheptadine hydrochloride	2 (0.5)	1 (0.2)	3 (0.4)
Ebastine	2 (0.5)	0	2 (0.2)
Olopatadine hydrochloride	2 (0.5)	1 (0.2)	3 (0.4)
Bepotastine besilate	1 (0.2)	2 (0.5)	3 (0.4)
Cyproheptadine	1 (0.2)	0	1 (0.1)
Desloratadine citrate disodium	1 (0.2)	1 (0.2)	2 (0.2)
Ketotifen	1 (0.2)	0	1 (0.1)
Rupatadine fumarate	1 (0.2)	0	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Cyanocobalamin;cyproheptadine	0	1 (0.2)	1 (0.1)
Epinastine hydrochloride	0	3 (0.7)	3 (0.4)
BETA BLOCKING AGENTS, SELECTIVE	48 (11.9)	50 (12.3)	98 (12.1)
Bisoprolol	13 (3.2)	13 (3.2)	26 (3.2)
Bisoprolol fumarate	8 (2.0)	8 (2.0)	16 (2.0)
Metoprolol tartrate	8 (2.0)	6 (1.5)	14 (1.7)
Metoprolol succinate	7 (1.7)	2 (0.5)	9 (1.1)
Metoprolol	6 (1.5)	5 (1.2)	11 (1.4)
Nebivolol hydrochloride	5 (1.2)	5 (1.2)	10 (1.2)
Atenolol	4 (1.0)	7 (1.7)	11 (1.4)
Nebivolol	1 (0.2)	4 (1.0)	5 (0.6)
DIAZEPINES, OXAZEPINES, THIAZEPINES AND OXEPINES	48 (11.9)	52 (12.8)	100 (12.3)
Olanzapine	43 (10.6)	45 (11.1)	88 (10.9)
Quetiapine	4 (1.0)	3 (0.7)	7 (0.9)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Clozapine	1 (0.2)	0	1 (0.1)
Quetiapine fumarate	1 (0.2)	4 (1.0)	5 (0.6)
ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	46 (11.4)	31 (7.7)	77 (9.5)
Indometacin	12 (3.0)	4 (1.0)	16 (2.0)
Diclofenac sodium	11 (2.7)	10 (2.5)	21 (2.6)
Diclofenac	9 (2.2)	5 (1.2)	14 (1.7)
Ketorolac tromethamine	6 (1.5)	2 (0.5)	8 (1.0)
Diclofenac potassium	4 (1.0)	1 (0.2)	5 (0.6)
Ketorolac	3 (0.7)	3 (0.7)	6 (0.7)
Diclofenac sodium;lidocaine	2 (0.5)	0	2 (0.2)
Diclofenac sodium;lidocaine hydrochloride	2 (0.5)	2 (0.5)	4 (0.5)
Aceclofenac	1 (0.2)	3 (0.7)	4 (0.5)
Acemetacin	1 (0.2)	0	1 (0.1)
Diclofenac;lidocaine	1 (0.2)	0	1 (0.1)
Etodolac	0	3 (0.7)	3 (0.4)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
ANGIOTENSIN II RECEPTOR BLOCKERS (ARBS), PLAIN	46 (11.4)	37 (9.1)	83 (10.2)
Losartan	11 (2.7)	13 (3.2)	24 (3.0)
Valsartan	11 (2.7)	8 (2.0)	19 (2.3)
Losartan potassium	6 (1.5)	4 (1.0)	10 (1.2)
Irbesartan	4 (1.0)	3 (0.7)	7 (0.9)
Olmesartan medoxomil	4 (1.0)	3 (0.7)	7 (0.9)
Candesartan cilexetil	3 (0.7)	4 (1.0)	7 (0.9)
Telmisartan	3 (0.7)	4 (1.0)	7 (0.9)
Azilsartan	1 (0.2)	1 (0.2)	2 (0.2)
Azilsartan kamedoxomil	1 (0.2)	0	1 (0.1)
Fimasartan potassium trihydrate	1 (0.2)	0	1 (0.1)
Olmesartan	1 (0.2)	0	1 (0.1)
Candesartan	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
PHENYLPIPERIDINE DERIVATIVES	46 (11.4)	45 (11.1)	91 (11.2)
Fentanyl	24 (5.9)	24 (5.9)	48 (5.9)
Pethidine hydrochloride	19 (4.7)	15 (3.7)	34 (4.2)
Fentanyl citrate	10 (2.5)	12 (3.0)	22 (2.7)
Pethidine	5 (1.2)	9 (2.2)	14 (1.7)
IMIDAZOLE DERIVATIVES	44 (10.9)	36 (8.9)	80 (9.9)
Metronidazole	41 (10.1)	33 (8.1)	74 (9.1)
Clotrimazole	1 (0.2)	0	1 (0.1)
Metronidazole;sodium chloride	1 (0.2)	0	1 (0.1)
Ornidazole	1 (0.2)	1 (0.2)	2 (0.2)
Morinidazole	0	2 (0.5)	2 (0.2)
Ornidazole;sodium chloride	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	44 (10.9)	50 (12.3)	94 (11.6)
Acetylsalicylic acid	30 (7.4)	41 (10.1)	71 (8.8)
Clopidogrel	5 (1.2)	6 (1.5)	11 (1.4)
Clopidogrel bisulfate	5 (1.2)	8 (2.0)	13 (1.6)
Ticagrelor	4 (1.0)	1 (0.2)	5 (0.6)
Acetylsalicylate lysine	3 (0.7)	0	3 (0.4)
Sarpogrelate hydrochloride	2 (0.5)	0	2 (0.2)
Alprostadil	1 (0.2)	0	1 (0.1)
Beraprost sodium	1 (0.2)	0	1 (0.1)
Clopidogrel resinate	1 (0.2)	2 (0.5)	3 (0.4)
Prasugrel hydrochloride	1 (0.2)	0	1 (0.1)
Ticlopidine hydrochloride	1 (0.2)	0	1 (0.1)
Cilostazol	0	2 (0.5)	2 (0.2)
Limaprost alfadex	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
ANTIPROPULSIVES	42 (10.4)	35 (8.6)	77 (9.5)
Loperamide hydrochloride	23 (5.7)	23 (5.7)	46 (5.7)
Loperamide	17 (4.2)	13 (3.2)	30 (3.7)
Atropine sulfate;diphenoxylate hydrochloride	1 (0.2)	1 (0.2)	2 (0.2)
Loperamide;simeticone	1 (0.2)	0	1 (0.1)
Morphine	1 (0.2)	0	1 (0.1)
Papaver somniferum tincture	1 (0.2)	0	1 (0.1)
BIGUANIDES	42 (10.4)	49 (12.1)	91 (11.2)
Metformin	22 (5.4)	28 (6.9)	50 (6.2)
Metformin hydrochloride	19 (4.7)	23 (5.7)	42 (5.2)
Metformin embonate	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
MUCOLYTICS	42 (10.4)	36 (8.9)	78 (9.6)
Acetylcysteine	21 (5.2)	16 (4.0)	37 (4.6)
Ambroxol hydrochloride	11 (2.7)	11 (2.7)	22 (2.7)
Carbocisteine	6 (1.5)	2 (0.5)	8 (1.0)
Ambroxol	5 (1.2)	3 (0.7)	8 (1.0)
Bromhexine hydrochloride	3 (0.7)	2 (0.5)	5 (0.6)
Bromhexine	2 (0.5)	2 (0.5)	4 (0.5)
L-carbocisteine	1 (0.2)	0	1 (0.1)
Mesna	1 (0.2)	0	1 (0.1)
Chymotrypsin	0	1 (0.2)	1 (0.1)
Erdosteine	0	5 (1.2)	5 (0.6)
BLOOD SUBSTITUTES AND PLASMA PROTEIN FRACTIONS	41 (10.1)	33 (8.1)	74 (9.1)
Albumin human	40 (9.9)	33 (8.1)	73 (9.0)
Succinylated gelatin	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
THYROID HORMONES	40 (9.9)	24 (5.9)	64 (7.9)
Levothyroxine sodium	24 (5.9)	16 (4.0)	40 (4.9)
Levothyroxine	17 (4.2)	8 (2.0)	25 (3.1)
ENEMAS	39 (9.6)	30 (7.4)	69 (8.5)
Glycerol	16 (4.0)	17 (4.2)	33 (4.1)
Bisacodyl	8 (2.0)	6 (1.5)	14 (1.7)
Phosphoric acid sodium;sodium phosphate dibasic	3 (0.7)	0	3 (0.4)
Sodium chloride	3 (0.7)	4 (1.0)	7 (0.9)
Sodium phosphate	2 (0.5)	2 (0.5)	4 (0.5)
Sodium phosphate dibasic;sodium phosphate monobasic	2 (0.5)	0	2 (0.2)
Sodium phosphate dibasic;sodium phosphate monobasic (anhydrous)	2 (0.5)	0	2 (0.2)
Sodium phosphate;sodium phosphate dibasic	2 (0.5)	0	2 (0.2)
Docusate sodium;sorbitol	1 (0.2)	0	1 (0.1)
Gelatin;glycerol	1 (0.2)	0	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Sodium citrate;sorbitol	1 (0.2)	0	1 (0.1)
Sodium phosphate dibasic (heptahydrate);sodium phosphate monobasic (monohydrate)	1 (0.2)	2 (0.5)	3 (0.4)
Glycerol;polysorbate 80;sodium citrate;sorbitol	0	1 (0.2)	1 (0.1)
Macrogol;sodium citrate;sodium lauryl sulfate;sorbic acid	0	1 (0.2)	1 (0.1)
IRON BIVALENT, ORAL PREPARATIONS	39 (9.6)	35 (8.6)	74 (9.1)
Ferrous sulfate	19 (4.7)	19 (4.7)	38 (4.7)
Ferrous fumarate	5 (1.2)	4 (1.0)	9 (1.1)
Ferrous sodium citrate	5 (1.2)	4 (1.0)	9 (1.1)
Iron	4 (1.0)	1 (0.2)	5 (0.6)
Ferrous succinate	3 (0.7)	6 (1.5)	9 (1.1)
Iron polysaccharide complex	3 (0.7)	1 (0.2)	4 (0.5)
Ferrous gluconate	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER ANALGESICS AND ANTIPYRETICS	39 (9.6)	33 (8.1)	72 (8.9)
Gabapentin	18 (4.4)	16 (4.0)	34 (4.2)
Pregabalin	16 (4.0)	13 (3.2)	29 (3.6)
Amitriptyline hydrochloride	2 (0.5)	0	2 (0.2)
Nefopam hydrochloride	2 (0.5)	0	2 (0.2)
Arctium lappa fruit;ascorbic acid;chlorphenamine maleate;forsythia suspensa fruit;forsythia suspensa fruit essential oil;glycine max fermented seed;glycyrrhiza spp. root with rhizome;lonicera japonicaflower;lophatherum gracile leaf with stem;mentha canadensis herb essential oil;paracetamol;phragmites communis rhizome;platycodon grandiflorus root;schizonepeta tenuifolia herb;schizonepeta tenuifolia herb essential oil	1 (0.2)	0	1 (0.1)
Duloxetine hydrochloride	1 (0.2)	1 (0.2)	2 (0.2)
Mecobalamin;pregabalin	1 (0.2)	0	1 (0.1)
Amitriptyline	0	2 (0.5)	2 (0.2)
Cannabinoids nos	0	1 (0.2)	1 (0.1)
Duloxetine	0	2 (0.5)	2 (0.2)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Gabapentin;nortriptyline hydrochloride	0	1 (0.2)	1 (0.1)
Oxcarbazepine	0	1 (0.2)	1 (0.1)
OTHER DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	39 (9.6)	26 (6.4)	65 (8.0)
Simeticone	16 (4.0)	15 (3.7)	31 (3.8)
Dimeticone	10 (2.5)	6 (1.5)	16 (2.0)
Phloroglucinol	5 (1.2)	1 (0.2)	6 (0.7)
Pinaverium bromide	5 (1.2)	3 (0.7)	8 (1.0)
Alverine citrate;simeticone	1 (0.2)	1 (0.2)	2 (0.2)
Dimeticone;guaiazulene	1 (0.2)	0	1 (0.1)
Phloroglucinol;trimethylphloroglucinol	1 (0.2)	0	1 (0.1)
Sodium butyrate	1 (0.2)	0	1 (0.1)
PIPERAZINE DERIVATIVES	39 (9.6)	35 (8.6)	74 (9.1)
Levocetirizine dihydrochloride	13 (3.2)	12 (3.0)	25 (3.1)
Hydroxyzine	12 (3.0)	9 (2.2)	21 (2.6)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Levocetirizine	7 (1.7)	1 (0.2)	8 (1.0)
Cetirizine	6 (1.5)	5 (1.2)	11 (1.4)
Cetirizine hydrochloride	5 (1.2)	7 (1.7)	12 (1.5)
Hydroxyzine hydrochloride	2 (0.5)	3 (0.7)	5 (0.6)
Cyclizine	0	1 (0.2)	1 (0.1)
CARBAPENEMS	38 (9.4)	31 (7.7)	69 (8.5)
Meropenem	21 (5.2)	25 (6.2)	46 (5.7)
Meropenem trihydrate	7 (1.7)	3 (0.7)	10 (1.2)
Ertapenem	6 (1.5)	2 (0.5)	8 (1.0)
Ertapenem sodium	4 (1.0)	4 (1.0)	8 (1.0)
Imipenem	4 (1.0)	2 (0.5)	6 (0.7)
Cilastatin sodium;imipenem	2 (0.5)	0	2 (0.2)
Biapenem	1 (0.2)	0	1 (0.1)
Cilastatin sodium;imipenem monohydrate	1 (0.2)	0	1 (0.1)
Cilastatin;imipenem	1 (0.2)	0	1 (0.1)
Meropenem sodium carbonate	1 (0.2)	1 (0.2)	2 (0.2)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
SOLUTIONS PRODUCING OSMOTIC DIURESIS	37 (9.1)	23 (5.7)	60 (7.4)
Mannitol	36 (8.9)	23 (5.7)	59 (7.3)
Fructose;glycerol	1 (0.2)	0	1 (0.1)
Glucose;mannitol;sodium chloride	1 (0.2)	0	1 (0.1)
ALDOSTERONE ANTAGONISTS	36 (8.9)	27 (6.7)	63 (7.8)
Spironolactone	32 (7.9)	27 (6.7)	59 (7.3)
Potassium canrenoate	3 (0.7)	0	3 (0.4)
Canrenone	1 (0.2)	0	1 (0.1)
ANTIDOTES	36 (8.9)	30 (7.4)	66 (8.1)
Glutathione	24 (5.9)	20 (4.9)	44 (5.4)
Acetylcysteine	7 (1.7)	3 (0.7)	10 (1.2)
Flumazenil	5 (1.2)	4 (1.0)	9 (1.1)
Naloxone hydrochloride	2 (0.5)	2 (0.5)	4 (0.5)

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Glutathione sodium	1 (0.2)	0	1 (0.1)
Naloxone	0	1 (0.2)	1 (0.1)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	36 (8.9)	36 (8.9)	72 (8.9)
Unspecified herbal and traditional medicine	6 (1.5)	2 (0.5)	8 (1.0)
Cordyceps sinensis mycelium	4 (1.0)	2 (0.5)	6 (0.7)
Herbal preparation	4 (1.0)	3 (0.7)	7 (0.9)
Sanguisorba officinalis	4 (1.0)	5 (1.2)	9 (1.1)
Cordyceps sinensis	3 (0.7)	1 (0.2)	4 (0.5)
Traditional medicine	3 (0.7)	8 (2.0)	11 (1.4)
Aconitum carmichaelii root;angelica sinensis root;astragalus mongholicus root;cullen corylifolium fruit;epimedium brevicornu herb;glycyrrhiza uralensis root with rhizome;lycium barbarum fruit;ophiopogon japonicus root tuber;phragmites communis rhizome;rubia cordifolia root;spatholobus suberectus stem	2 (0.5)	1 (0.2)	3 (0.4)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Anemarrhena asphodeloides rhizome;angelica sinensis root;animal bone marrow;arachis hypogaea seed coat;asini corii colla;astragalus spp. root;atractylodes macrocephala, rhizoma;blood, deer;chicken's gizzard-membrane;codonopsis spp. root;crataegus pinnatifida fruit;deer horn;deer velvet;fallopia multiflora root tuber;hordeum vulgare malt;paeonia lactiflora root;placenta;poria cocos sclerotium;rehmannia glutinosa root;rheum spp. root with rhizome;turtle carapace;ziziphus jujuba fruit	2 (0.5)	0	2 (0.2)
Angelica sinensis root;asini corii colla;astragalus mongholicus root;epimedium brevicornu herb;lespedeza buergeri;sophora flavescens root;ziziphus jujuba fruit	2 (0.5)	5 (1.2)	7 (0.9)
Artemisia capillaris herb;baicalin;ganoderma lucidum sporocarp;gardenia jasminoides fruit;isatis tinctoria root	2 (0.5)	1 (0.2)	3 (0.4)
Astragalus spp. root polysaccharide extract	2 (0.5)	0	2 (0.2)
Ophiopogon japonicus root tuber;panax ginseng	2 (0.5)	0	2 (0.2)
Smilax spp. tuber;sophora flavescens root	2 (0.5)	0	2 (0.2)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Aconitum kusnezoffii root tuber;angelica sinensis root;boswellia spp. resin;commiphora myrrha resin;flying squirrel feces;herbal nos;liquidambar formosana resin;momordica cochinchinensis seed;musk;pheretima spp.	1 (0.2)	0	1 (0.1)
Adenophora triphylla root;glehnia littoralis root;glycyrrhiza uralensis root;lablab purpureus seed;morus alba leaf;ophiopogon japonicus tube;polygonatum odoratum rhizome;trichosanthes kirilowii root	1 (0.2)	0	1 (0.1)
Agrimonia pilosa herb;forsythia suspensa fruit;glycyrrhiza spp. root with rhizome;indigo;paeonia x suffruticosa root bark	1 (0.2)	3 (0.7)	4 (0.5)
Allium sativum oil	1 (0.2)	0	1 (0.1)
Aloe vera;calcium;camellia sinensis leaf;cordyceps sinensis;ginkgo biloba leaf;glycyrrhiza spp. root;nicotinamide;ornithine oxoglurate;piper nigrum fruit;prunus avium;pyridoxine hydrochloride;rhodiolacrenulata root;scutellaria baicalensis root;senegalia catechu heartwood;thioctic acid;vaccinium corymbosum;vaccinium macrocarpon;vitis labrusca;zea mays;ziziphus jujuba fruit	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Angelica sinensis root;bombyx mori;centipede;corydalis yanhusuo tuber;drynaria roosii rhizome;eupolyphaga sinensis;gekko gecko;glycyrrhiza spp. root with rhizome;honeycomb;leech;manis pentadactyla;musk;pheretima spp.;ptyas dhumnades;salvia miltiorrhiza root with rhizome;smilax glabra rhizome;strychnos nux-vomica seed;tabanus mandarinus;toad venom	1 (0.2)	0	1 (0.1)
Asparagus cochinchinensis root tuber;borneol;epimedium brevicornu herb;ophiopogon japonicus root tuber;panax ginseng root;polygonatum odoratum rhizome;sesamum indicum seed;smilax glabra rhizome;sophora flavescens root	1 (0.2)	0	1 (0.1)
Astragalus mongholicus root;cibotium barometz rhizome;eclipta prostrata herb;fallopia multiflora root tuber;ligustrum lucidum fruit;morus alba fruit;paeonia lactiflora root	1 (0.2)	2 (0.5)	3 (0.4)
Astragalus mongholicus root;citrus medica fruit;codonopsis pilosula root;drynaria roosii rhizome;fallopia multiflora root tuber;hordeum vulgare sprout;ligustrum lucidum fruit;spatholobus suberectus stem	1 (0.2)	0	1 (0.1)
Astragalus mongholicus root;codonopsis pilosula root	1 (0.2)	0	1 (0.1)

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Astragalus mongholicus root;oxymatrine;panax ginseng dry extract	1 (0.2)	0	1 (0.1)
Astragalus spp.	1 (0.2)	0	1 (0.1)
Astragalus spp. root;atractylodes macrocephala, rhizoma;fallopia multiflora root tuber;morus alba root bark;paeonia lactiflora root;plantago spp. herb;poria cocos sclerotium;rheum spp. root with rhizome;salvia miltiorrhiza root with rhizome;sophora flavescens root	1 (0.2)	1 (0.2)	2 (0.2)
Boswellia sacra;commiphora myrrha resin;cow bezoar;musk	1 (0.2)	0	1 (0.1)
Camellia sinensis	1 (0.2)	0	1 (0.1)
Forsythia suspensa fruit;glycyrrhiza uralensis root with rhizome;lonicera japonica flower bud;platycodon grandiflorus root;saposhnikovia divaricata root	1 (0.2)	0	1 (0.1)
Ganoderma capense	1 (0.2)	0	1 (0.1)
Ginkgo biloba	1 (0.2)	0	1 (0.1)
Ginkgo biloba extract	1 (0.2)	0	1 (0.1)
Ginseng nos	1 (0.2)	1 (0.2)	2 (0.2)
Herbal nos	1 (0.2)	2 (0.5)	3 (0.4)
Monascus purpureus	1 (0.2)	0	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Phellinus linteus polysaccharide extract	1 (0.2)	0	1 (0.1)
Thymus spp.	1 (0.2)	0	1 (0.1)
Achyranthes bidentata root;carthamus tinctorius flower;citrus aurantium pericarp;coptis spp. rhizome;glycyrrhiza spp. root with rhizome;pinellia ternata tuber;poria cocos sclerotium;pseudostellaria heterophylla root tuber;rheum spp. root with rhizome;salvia miltiorrhiza root with rhizome	0	1 (0.2)	1 (0.1)
Aesculus hippocastanum	0	1 (0.2)	1 (0.1)
Andrographis paniculata herb;isodon lophanthoides herb;picrasma quassioides leaf with twig	0	1 (0.2)	1 (0.1)
Angelica acutiloba root;astragalus spp. root;atractylodes spp. rhizome;bupleurum falcatum root;cimicifuga spp. rhizome;citrus aurantium peel;glycyrrhiza spp. root;panax ginseng root;zingiber officinale fresh rhizome;ziziphus jujuba fruit	0	1 (0.2)	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Angelica sinensis root;atractylodes macrocephala, rhizoma;bupleurum chinense, root;glycyrrhiza uralensis root with rhizome;mentha canadensis herb;paeonia lactiflora root;poria cocos sclerotium;zingiber officinale rhizome	0	1 (0.2)	1 (0.1)
Arctium lappa root;rheum officinale root;rumex acetosella leaf;ulmus rubra bark	0	1 (0.2)	1 (0.1)
Ardisia japonica herb;cow bezoar;indometacin;panax notoginseng root;pearl;urena lobata	0	1 (0.2)	1 (0.1)
Artemisia annua herb;boswellia serrata gum;curcuma longa rhizome	0	1 (0.2)	1 (0.1)
Artemisia capillaris herb;bupleurum chinense, root;isatis tinctoria dry leaf;rheum palmatum root with rhizome;sophora flavescens root	0	1 (0.2)	1 (0.1)
Astragalus mongholicus root;atractylodes macrocephala, rhizoma;citrus aurantium fruit peel;epimedium spp. leaf;ligustrum lucidum ripe fruit;panax ginseng root;turtle carapace	0	1 (0.2)	1 (0.1)
Astragalus mongholicus root;atractylodes macrocephala, rhizoma;saposhnikovia divaricata root	0	1 (0.2)	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Bidens biternata;caffeine;chlorphenamine maleate;chrysanthemum indicum flower;ilex asprella root;melicope pteleifolia;mentha canadensis oil;paracetamol	0	2 (0.5)	2 (0.2)
Borneol;panax notoginseng root;salvia miltiorrhiza root	0	1 (0.2)	1 (0.1)
Cistanche spp.	0	1 (0.2)	1 (0.1)
Fagopyrum esculentum	0	1 (0.2)	1 (0.1)
Linum usitatissimum oil	0	1 (0.2)	1 (0.1)
Matricaria recutita	0	1 (0.2)	1 (0.1)
Menthol;peucedanum praeruptorum root;platycodon grandiflorus root;prunus mume smoke treated unripe fruit;pueraria lobata root;santalum album heartwood;trichosanthes kirilowii root	0	1 (0.2)	1 (0.1)
Ophiopogon japonicus root tuber;panax ginseng root;schisandra chinensis fruit	0	1 (0.2)	1 (0.1)
Plantago ovata	0	1 (0.2)	1 (0.1)
Salvia miltiorrhiza root	0	1 (0.2)	1 (0.1)
Sambucus nigra fruit	0	1 (0.2)	1 (0.1)
Trametes robiniophila	0	1 (0.2)	1 (0.1)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Unspecified traditional medicine	0	3 (0.7)	3 (0.4)
ACE INHIBITORS, PLAIN	35 (8.6)	39 (9.6)	74 (9.1)
Ramipril	13 (3.2)	12 (3.0)	25 (3.1)
Lisinopril	11 (2.7)	11 (2.7)	22 (2.7)
Enalapril	6 (1.5)	6 (1.5)	12 (1.5)
Captopril	2 (0.5)	4 (1.0)	6 (0.7)
Enalapril maleate	1 (0.2)	3 (0.7)	4 (0.5)
Fosinopril sodium	1 (0.2)	0	1 (0.1)
Perindopril	1 (0.2)	2 (0.5)	3 (0.4)
Benazepril	0	1 (0.2)	1 (0.1)
Benazepril hydrochloride	0	1 (0.2)	1 (0.1)
Quinapril hydrochloride	0	1 (0.2)	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
ASCORBIC ACID (VITAMIN C), PLAIN	34 (8.4)	33 (8.1)	67 (8.3)
Ascorbic acid	34 (8.4)	33 (8.1)	67 (8.3)
MAGNESIUM	34 (8.4)	31 (7.7)	65 (8.0)
Magnesium	12 (3.0)	10 (2.5)	22 (2.7)
Magnesium oxide	6 (1.5)	6 (1.5)	12 (1.5)
Magnesium chelate	5 (1.2)	4 (1.0)	9 (1.1)
Magnesium lactate;pyridoxine hydrochloride	3 (0.7)	0	3 (0.4)
Magnesium sulfate	3 (0.7)	1 (0.2)	4 (0.5)
Magnesium chloride	2 (0.5)	5 (1.2)	7 (0.9)
Magnesium citrate	2 (0.5)	0	2 (0.2)
Magnesium;pyridoxine	2 (0.5)	0	2 (0.2)
Magnesium aspartate	1 (0.2)	0	1 (0.1)
Magnesium glycinate	1 (0.2)	2 (0.5)	3 (0.4)
Magnesium orotate	1 (0.2)	0	1 (0.1)
Magnesium carbonate	0	1 (0.2)	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Magnesium hydroxide	0	1 (0.2)	1 (0.1)
Magnesium lactate	0	1 (0.2)	1 (0.1)
Magnesium orotate dihydrate	0	1 (0.2)	1 (0.1)
Magnesium pidolate	0	1 (0.2)	1 (0.1)
OTHER SYSTEMIC HEMOSTATICS	33 (8.1)	35 (8.6)	68 (8.4)
Recombinant human thrombopoietin	14 (3.5)	20 (4.9)	34 (4.2)
Leucogen	10 (2.5)	10 (2.5)	20 (2.5)
Etamsilate	5 (1.2)	4 (1.0)	9 (1.1)
Agrimonia pilosa herb;forsythia suspensa fruit;glycyrrhiza spp. root with rhizome;indigo;paeonia x suffruticosa root bark	4 (1.0)	6 (1.5)	10 (1.2)
Haemocoagulase	4 (1.0)	2 (0.5)	6 (0.7)
Carbazochrome sodium sulfonate	3 (0.7)	2 (0.5)	5 (0.6)
Avatrombopag	2 (0.5)	2 (0.5)	4 (0.5)
Caffeic acid	2 (0.5)	1 (0.2)	3 (0.4)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Agrimonia pilosa;forsythia suspensa;glycyrrhiza spp.;indigo;paeonia x suffruticosa	1 (0.2)	0	1 (0.1)
Avatrombopag maleate	1 (0.2)	1 (0.2)	2 (0.2)
Callicarpa nudiflora leaf	1 (0.2)	0	1 (0.1)
Romiplostim	1 (0.2)	1 (0.2)	2 (0.2)
Anemarrhena asphodeloides rhizome;angelica sinensis root;animal bone marrow;arachis hypogaea seed coat;asini corii colla;astragalus spp. root;atractylodes macrocephala, rhizoma;blood, deer;chicken's gizzard-membrane;codonopsis spp. root;crataegus pinnatifida fruit;deer horn;deer velvet;fallopia multiflora root tuber;hordeum vulgare malt;paeonia lactiflora root;placenta;poria cocos sclerotium;rehmannia glutinosa root;rheum spp. root with rhizome;turtle carapace;ziziphus jujuba fruit	0	2 (0.5)	2 (0.2)
Carbazochrome sodium sulfonate;sodium chloride	0	1 (0.2)	1 (0.1)
Desmopressin acetate	0	1 (0.2)	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
DIRECT FACTOR XA INHIBITORS	32 (7.9)	28 (6.9)	60 (7.4)
Apixaban	15 (3.7)	7 (1.7)	22 (2.7)
Rivaroxaban	13 (3.2)	17 (4.2)	30 (3.7)
Edoxaban tosilate	3 (0.7)	3 (0.7)	6 (0.7)
Edoxaban	2 (0.5)	1 (0.2)	3 (0.4)
OTHER DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	32 (7.9)	46 (11.4)	78 (9.6)
Rebamipide	16 (4.0)	19 (4.7)	35 (4.3)
Sucralfate	7 (1.7)	5 (1.2)	12 (1.5)
Sodium alginate	4 (1.0)	6 (1.5)	10 (1.2)
Calcium carbonate;magnesium carbonate;sodium alginate	2 (0.5)	0	2 (0.2)
Calcium carbonate;sodium alginate;sodium bicarbonate	2 (0.5)	3 (0.7)	5 (0.6)
Sulpiride	2 (0.5)	2 (0.5)	4 (0.5)
Alginic acid;aluminium hydroxide gel, dried;magnesium carbonate	1 (0.2)	0	1 (0.1)

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Polaprezinc	1 (0.2)	0	1 (0.1)
Sodium gualenate hydrate	1 (0.2)	0	1 (0.1)
Bismuth pectin	0	2 (0.5)	2 (0.2)
Calcium carbonate;sodium alginate	0	1 (0.2)	1 (0.1)
Gefarnate	0	1 (0.2)	1 (0.1)
Irsogladine maleate	0	1 (0.2)	1 (0.1)
Levoglutamide;sodium gualenate	0	4 (1.0)	4 (0.5)
Levoglutamide;sodium gualenate hydrate	0	1 (0.2)	1 (0.1)
Sulglicotide	0	1 (0.2)	1 (0.1)
AMIDES	31 (7.7)	23 (5.7)	54 (6.7)
Lidocaine hydrochloride	18 (4.4)	12 (3.0)	30 (3.7)
Lidocaine	6 (1.5)	4 (1.0)	10 (1.2)
Lidocaine;prilocaine	3 (0.7)	5 (1.2)	8 (1.0)
Epinephrine;lidocaine	1 (0.2)	0	1 (0.1)
Epinephrine;lidocaine hydrochloride	1 (0.2)	0	1 (0.1)
Levobupivacaine hydrochloride	1 (0.2)	0	1 (0.1)

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Lidocaine;sodium chloride	1 (0.2)	0	1 (0.1)
Oxetacaine	1 (0.2)	0	1 (0.1)
Chlorhexidine;lidocaine	0	1 (0.2)	1 (0.1)
Prilocaine hydrochloride	0	1 (0.2)	1 (0.1)
ENZYME PREPARATIONS	31 (7.7)	34 (8.4)	65 (8.0)
Pancreatin	19 (4.7)	21 (5.2)	40 (4.9)
Bromelains;dimeticone;pancreatin	4 (1.0)	5 (1.2)	9 (1.1)
Pancreatin;simeticone;ursodeoxycholic acid	3 (0.7)	1 (0.2)	4 (0.5)
Tilactase	2 (0.5)	0	2 (0.2)
Alpha-d-galactosidase	1 (0.2)	0	1 (0.1)
Amylase;lipase;protease nos	1 (0.2)	0	1 (0.1)
Azintamide;cellulase;dimeticone;pancreatin	1 (0.2)	1 (0.2)	2 (0.2)
Diastase;pepsin	1 (0.2)	0	1 (0.1)
Pancrelipase	1 (0.2)	3 (0.7)	4 (0.5)
Aspergillus oryzae enzyme;pancreatin	0	4 (1.0)	4 (0.5)

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Cellulase;diastase;hemicellulase;lipase;pancreatin;protease nos;trypsin	0	1 (0.2)	1 (0.1)
Enzymes nos	0	1 (0.2)	1 (0.1)
Hemicellulase;ox bile extract;pancreatin	0	1 (0.2)	1 (0.1)
Pancreatin;simeticone	0	1 (0.2)	1 (0.1)
ANTIEMETICS AND ANTINAUSEANTS	29 (7.2)	30 (7.4)	59 (7.3)
Metoclopramide hydrochloride	16 (4.0)	14 (3.5)	30 (3.7)
Metoclopramide	8 (2.0)	11 (2.7)	19 (2.3)
Antiemetics and antinauseants	7 (1.7)	5 (1.2)	12 (1.5)
FAT/CARBOHYDRATES/PROTEINS/MINERALS/VITAMINS, COMBINATIONS	29 (7.2)	21 (5.2)	50 (6.2)
Casein;fats nos;fibre, dietary;maltodextrin;minerals nos;vitamins nos	7 (1.7)	4 (1.0)	11 (1.4)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Ascorbic acid;biotin;calcium;carbohydrates nos;chloride;colecalciferol;copper;cyanocobalamin;fats nos;folic acid;iron;magnesium;manganese;nicotinamide;pantothenic acid;phosphorus;potassium;proteins nos;pyridoxine;retinol;riboflavin;sodium;thiamine;tocopherol;zinc	6 (1.5)	6 (1.5)	12 (1.5)
Ascorbic acid;biotin;calcium citrate;calcium pantothenate;cyanocobalamin;ferrous sulfate;fibre, dietary;folic acid;glycine max seed oil;magnesium carbonate;maltodextrin;nicotinamide;potassium citrate;proteins nos;pyridoxine hydrochloride;retinol;riboflavin;sodium chloride;sucrose;thiamine hydrochloride;tocopheryl acetate;whey protein;zea mays starch	5 (1.2)	5 (1.2)	10 (1.2)
Carbohydrates nos;fatty acids nos;minerals nos;proteins nos;vitamins nos	4 (1.0)	2 (0.5)	6 (0.7)
Carbohydrates nos;fats nos;minerals nos;proteins nos;vitamins nos	3 (0.7)	2 (0.5)	5 (0.6)
Carbohydrates nos;fats nos;minerals nos;protein;vitamins nos	2 (0.5)	0	2 (0.2)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Casein;herbal oil nos;maltodextrin;minerals nos;trace elements nos;vitamins nos	2 (0.5)	0	2 (0.2)
Calcium caseinate;fructooligosaccharides;fructose;glycine max fibre;glycine max oil;helianthus annuus oil;inositol;levocarnitine;maltodextrin;minerals nos;taurine;vitamins nos	1 (0.2)	0	1 (0.1)
Carbohydrates nos;electrolytes nos;lipids nos;proteins nos;vitamins nos	0	2 (0.5)	2 (0.2)
Fat/carbohydrates/proteins/minerals/vitamins, combinations	0	1 (0.2)	1 (0.1)
OTHER ANTIANEMIC PREPARATIONS	29 (7.2)	18 (4.4)	47 (5.8)
Darbepoetin alfa	13 (3.2)	5 (1.2)	18 (2.2)
Erythropoietin human	10 (2.5)	10 (2.5)	20 (2.5)
Epoetin alfa	4 (1.0)	2 (0.5)	6 (0.7)
Erythropoietin	2 (0.5)	1 (0.2)	3 (0.4)
Astragalus mongholicus root;blood, pig;ziziphus jujuba fruit	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
AMINO ACIDS	27 (6.7)	21 (5.2)	48 (5.9)
Tranexamic acid	9 (2.2)	12 (3.0)	21 (2.6)
Alanine;arginine;aspartic acid;cystine;glutamic acid;glycine;histidine;isoleucine;leucine;lysine acetate;methionine;phenylalanine;proline;serine;threonine; tryptophan, l-;tyrosine;valine	6 (1.5)	1 (0.2)	7 (0.9)
Alanyl glutamine	5 (1.2)	3 (0.7)	8 (1.0)
Amino acids nos	5 (1.2)	3 (0.7)	8 (1.0)
Aminomethylbenzoic acid	2 (0.5)	1 (0.2)	3 (0.4)
Alanine;arginine;aspartic acid;cysteine;glycine;histidine;isoleucine;leucine;lysine acetate;methionine;phenylalanine;proline;serine;threonine; tryptophan, l-;tyrosine;valine	1 (0.2)	0	1 (0.1)
Arginine	1 (0.2)	0	1 (0.1)
Alanine;arginine;aspartic acid;cysteine;glutamic acid;glycine;histidine;isoleucine;leucine;lysine acetate;methionine;phenylalanine;proline;serine;threonine; tryptophan, l-;tyrosine;valine	0	3 (0.7)	3 (0.4)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Arginine hydrochloride	0	1 (0.2)	1 (0.1)
OTHER PLAIN VITAMIN PREPARATIONS	26 (6.4)	27 (6.7)	53 (6.5)
Pyridoxine hydrochloride	20 (4.9)	21 (5.2)	41 (5.1)
Pyridoxine	2 (0.5)	0	2 (0.2)
Biotin	1 (0.2)	0	1 (0.1)
Flavine adenine dinucleotide	1 (0.2)	2 (0.5)	3 (0.4)
Nicotinamide	1 (0.2)	0	1 (0.1)
Panthenol	1 (0.2)	0	1 (0.1)
Riboflavin tetrabutyrate	0	1 (0.2)	1 (0.1)
Tocopherol	0	1 (0.2)	1 (0.1)
Tocopheryl acetate	0	1 (0.2)	1 (0.1)
Vitamin e nos	0	1 (0.2)	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
CORTICOSTEROIDS, POTENT (GROUP III)	25 (6.2)	11 (2.7)	36 (4.4)
Fluocinonide	5 (1.2)	2 (0.5)	7 (0.9)
Prednicarbate	5 (1.2)	2 (0.5)	7 (0.9)
Betamethasone butyrate propionate	3 (0.7)	3 (0.7)	6 (0.7)
Difluprednate	3 (0.7)	2 (0.5)	5 (0.6)
Methylprednisolone aceponate	3 (0.7)	0	3 (0.4)
Mometasone furoate	2 (0.5)	1 (0.2)	3 (0.4)
Betamethasone	1 (0.2)	0	1 (0.1)
Betamethasone valerate	1 (0.2)	2 (0.5)	3 (0.4)
Diflucortolone	1 (0.2)	0	1 (0.1)
Diflucortolone valerate	1 (0.2)	1 (0.2)	2 (0.2)
Hydrocortisone	1 (0.2)	0	1 (0.1)
Ulobetasol	1 (0.2)	0	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
BENZODIAZEPINE RELATED DRUGS	24 (5.9)	31 (7.7)	55 (6.8)
Zolpidem tartrate	11 (2.7)	15 (3.7)	26 (3.2)
Zolpidem	8 (2.0)	5 (1.2)	13 (1.6)
Zopiclone	5 (1.2)	7 (1.7)	12 (1.5)
Eszopiclone	1 (0.2)	5 (1.2)	6 (0.7)
OPIUM ALKALOIDS AND DERIVATIVES	24 (5.9)	19 (4.7)	43 (5.3)
Ammonium chloride;chlorphenamine maleate;dihydrocodeine bitartrate;methylephedrine hydrochloride-dl	10 (2.5)	7 (1.7)	17 (2.1)
Codeine	3 (0.7)	0	3 (0.4)
Codeine phosphate	3 (0.7)	5 (1.2)	8 (1.0)
Chlorphenamine;codeine	2 (0.5)	0	2 (0.2)
Dextromethorphan	2 (0.5)	1 (0.2)	3 (0.4)
Dextromethorphan hydrobromide;lysozyme chloride;potassium cresolsulfonate	2 (0.5)	0	2 (0.2)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Dextromethorphan hydrobromide;pseudoephedrine hydrochloride	2 (0.5)	0	2 (0.2)
Codeine phosphate;promethazine hydrochloride	1 (0.2)	0	1 (0.1)
Dextromethorphan hydrobromide	1 (0.2)	2 (0.5)	3 (0.4)
Dextromethorphan hydrobromide;lysozyme hydrochloride;potassium cresolsulfonate	1 (0.2)	0	1 (0.1)
Chlorphenamine maleate;dextromethorphan hydrobromide	0	1 (0.2)	1 (0.1)
Chlorphenamine maleate;dihydrocodeine phosphate;methylephedrine hydrochloride-dl	0	1 (0.2)	1 (0.1)
Codeine phosphate;pseudoephedrine hydrochloride;triprolidine hydrochloride	0	1 (0.2)	1 (0.1)
Codeine;ethylmorphine hydrochloride	0	1 (0.2)	1 (0.1)
Dextromethorphan;lysozyme;potassium cresolsulfonate	0	1 (0.2)	1 (0.1)
Dimemorfan phosphate	0	1 (0.2)	1 (0.1)
ADRENERGIC AND DOPAMINERGIC AGENTS	23 (5.7)	12 (3.0)	35 (4.3)
Norepinephrine	11 (2.7)	5 (1.2)	16 (2.0)
Epinephrine	5 (1.2)	5 (1.2)	10 (1.2)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Norepinephrine bitartrate	4 (1.0)	2 (0.5)	6 (0.7)
Epinephrine hydrochloride	2 (0.5)	1 (0.2)	3 (0.4)
Dobutamine hydrochloride	1 (0.2)	0	1 (0.1)
Dopamine	1 (0.2)	0	1 (0.1)
Dopamine hydrochloride	1 (0.2)	1 (0.2)	2 (0.2)
Methoxamine hydrochloride	1 (0.2)	0	1 (0.1)
Phenylephrine	1 (0.2)	1 (0.2)	2 (0.2)
Dobutamine	0	1 (0.2)	1 (0.1)
Midodrine hydrochloride	0	1 (0.2)	1 (0.1)
Phenylephrine hydrochloride	0	1 (0.2)	1 (0.1)
AMINOALKYL ETHERS	23 (5.7)	24 (5.9)	47 (5.8)
Diphenhydramine hydrochloride	15 (3.7)	9 (2.2)	24 (3.0)
Diphenhydramine	6 (1.5)	12 (3.0)	18 (2.2)
Clemastine fumarate	1 (0.2)	1 (0.2)	2 (0.2)
Piprinhydrinate	1 (0.2)	0	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Clemastine	0	1 (0.2)	1 (0.1)
Dimenhydrinate	0	1 (0.2)	1 (0.1)
COXIBS	23 (5.7)	27 (6.7)	50 (6.2)
Celecoxib	17 (4.2)	19 (4.7)	36 (4.4)
Etoricoxib	5 (1.2)	7 (1.7)	12 (1.5)
Imrecoxib	2 (0.5)	3 (0.7)	5 (0.6)
Parecoxib sodium	2 (0.5)	1 (0.2)	3 (0.4)
AMINO ACIDS AND DERIVATIVES	22 (5.4)	25 (6.2)	47 (5.8)
Ademetionine 1,4-butanedisulfonate	13 (3.2)	10 (2.5)	23 (2.8)
Ademetionine	9 (2.2)	12 (3.0)	21 (2.6)
Acetylcysteine	2 (0.5)	3 (0.7)	5 (0.6)
Levoglutamide	1 (0.2)	1 (0.2)	2 (0.2)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
GLYCOPEPTIDE ANTIBACTERIALS	22 (5.4)	19 (4.7)	41 (5.1)
Teicoplanin	11 (2.7)	8 (2.0)	19 (2.3)
Vancomycin hydrochloride	7 (1.7)	1 (0.2)	8 (1.0)
Vancomycin	5 (1.2)	9 (2.2)	14 (1.7)
Sodium chloride;vancomycin hydrochloride	0	1 (0.2)	1 (0.1)
OTHER VIRAL VACCINES	22 (5.4)	19 (4.7)	41 (5.1)
Tozinameran	12 (3.0)	6 (1.5)	18 (2.2)
Covid-19 vaccine nrvv ad (chadox1 ncov-19)	6 (1.5)	8 (2.0)	14 (1.7)
Covid-19 vaccine	1 (0.2)	3 (0.7)	4 (0.5)
Covid-19 vaccine inact (vero) cz02	1 (0.2)	1 (0.2)	2 (0.2)
Covid-19 vaccine mrna (mrna 1273)	1 (0.2)	2 (0.5)	3 (0.4)
Covid-19 vaccine nrvv ad26 (gam-covid-vac)	1 (0.2)	1 (0.2)	2 (0.2)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
PENICILLINS WITH EXTENDED SPECTRUM	22 (5.4)	23 (5.7)	45 (5.6)
Amoxicillin	16 (4.0)	20 (4.9)	36 (4.4)
Piperacillin	2 (0.5)	0	2 (0.2)
Piperacillin sodium	2 (0.5)	0	2 (0.2)
Ampicillin	1 (0.2)	2 (0.5)	3 (0.4)
Mezlocillin sodium	1 (0.2)	0	1 (0.1)
Pivmecillinam	1 (0.2)	0	1 (0.1)
Temocillin	1 (0.2)	0	1 (0.1)
Amoxicillin trihydrate	0	1 (0.2)	1 (0.1)
SECOND-GENERATION CEPHALOSPORINS	22 (5.4)	15 (3.7)	37 (4.6)
Cefuroxime	6 (1.5)	4 (1.0)	10 (1.2)
Flomoxef	4 (1.0)	1 (0.2)	5 (0.6)
Cefuroxime axetil	3 (0.7)	5 (1.2)	8 (1.0)
Cefmetazole	2 (0.5)	1 (0.2)	3 (0.4)
Cefuroxime sodium	2 (0.5)	1 (0.2)	3 (0.4)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Cefaclor monohydrate	1 (0.2)	0	1 (0.1)
Cefmetazole sodium	1 (0.2)	2 (0.5)	3 (0.4)
Cefotetan disodium	1 (0.2)	0	1 (0.1)
Cefotiam hydrochloride	1 (0.2)	0	1 (0.1)
Cefoxitin	1 (0.2)	0	1 (0.1)
Cefoxitin sodium	1 (0.2)	0	1 (0.1)
Cefaclor	0	3 (0.7)	3 (0.4)
Flomoxef sodium	0	1 (0.2)	1 (0.1)
IRON, PARENTERAL PREPARATIONS	21 (5.2)	17 (4.2)	38 (4.7)
Ferric carboxymaltose	9 (2.2)	2 (0.5)	11 (1.4)
Iron	6 (1.5)	1 (0.2)	7 (0.9)
Saccharated iron oxide	6 (1.5)	11 (2.7)	17 (2.1)
Iron isomaltoside 1000	1 (0.2)	0	1 (0.1)
Ferric hydroxide polymaltose complex	0	1 (0.2)	1 (0.1)
Iron polysaccharide complex	0	1 (0.2)	1 (0.1)
Iron;sucrose	0	2 (0.5)	2 (0.2)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
ANTIINFLAMMATORY PREPARATIONS, NON-STEROIDS FOR TOPICAL USE	20 (4.9)	19 (4.7)	39 (4.8)
Ketoprofen	9 (2.2)	5 (1.2)	14 (1.7)
Loxoprofen sodium	3 (0.7)	2 (0.5)	5 (0.6)
Diclofenac	2 (0.5)	3 (0.7)	5 (0.6)
Indometacin	2 (0.5)	2 (0.5)	4 (0.5)
Diclofenac diethylamine;linum usitatissimum seed oil;menthol;methyl salicylate	1 (0.2)	0	1 (0.1)
Diclofenac sodium	1 (0.2)	0	1 (0.1)
Etofenamate	1 (0.2)	2 (0.5)	3 (0.4)
Felbinac	1 (0.2)	1 (0.2)	2 (0.2)
Flurbiprofen	1 (0.2)	3 (0.7)	4 (0.5)
Loxoprofen sodium dihydrate	1 (0.2)	1 (0.2)	2 (0.2)
Ufenamate	1 (0.2)	0	1 (0.1)
Diclofenac diethylamine	0	1 (0.2)	1 (0.1)
Piroxicam	0	1 (0.2)	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS	20 (4.9)	30 (7.4)	50 (6.2)
Entecavir	15 (3.7)	20 (4.9)	35 (4.3)
Lamivudine	3 (0.7)	2 (0.5)	5 (0.6)
Tenofovir disoproxil fumarate	3 (0.7)	2 (0.5)	5 (0.6)
Tenofovir	0	1 (0.2)	1 (0.1)
Tenofovir alafenamide	0	1 (0.2)	1 (0.1)
Tenofovir alafenamide fumarate	0	4 (1.0)	4 (0.5)
VITAMIN D AND ANALOGUES	19 (4.7)	18 (4.4)	37 (4.6)
Colecalciferol	15 (3.7)	11 (2.7)	26 (3.2)
Alfacalcidol	2 (0.5)	2 (0.5)	4 (0.5)
Calcitriol	2 (0.5)	1 (0.2)	3 (0.4)
Ergocalciferol	1 (0.2)	1 (0.2)	2 (0.2)
Vitamin d nos	1 (0.2)	3 (0.7)	4 (0.5)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
BISPHOSPHONATES	18 (4.4)	12 (3.0)	30 (3.7)
Zoledronic acid	9 (2.2)	4 (1.0)	13 (1.6)
Zoledronic acid monohydrate	6 (1.5)	1 (0.2)	7 (0.9)
Alendronic acid	1 (0.2)	0	1 (0.1)
Clodronic acid	1 (0.2)	0	1 (0.1)
Disodium incadronate	1 (0.2)	0	1 (0.1)
Pamidronate disodium	1 (0.2)	6 (1.5)	7 (0.9)
Alendronate sodium	0	1 (0.2)	1 (0.1)
Ibandronate sodium	0	1 (0.2)	1 (0.1)
FOURTH-GENERATION CEPHALOSPORINS	18 (4.4)	6 (1.5)	24 (3.0)
Cefepime hydrochloride	11 (2.7)	4 (1.0)	15 (1.9)
Cefepime	7 (1.7)	2 (0.5)	9 (1.1)
Cefepime hydrochloride;glucose	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER AGENTS FOR LOCAL ORAL TREATMENT	18 (4.4)	21 (5.2)	39 (4.8)
Benzydamine hydrochloride	10 (2.5)	16 (4.0)	26 (3.2)
Lidocaine	2 (0.5)	0	2 (0.2)
Sodium gualenate hydrate	2 (0.5)	4 (1.0)	6 (0.7)
Benzalkonium chloride;calcium chloride;sodium phosphate dibasic;sodium phosphate monobasic (anhydrous)	1 (0.2)	0	1 (0.1)
Glucose oxidase;lactoferrin;lactoperoxidase;lysozyme	1 (0.2)	0	1 (0.1)
Iodine;menthol;potassium iodide;tannic acid;thymol	1 (0.2)	0	1 (0.1)
Lidocaine hydrochloride	1 (0.2)	0	1 (0.1)
Other agents for local oral treatment	1 (0.2)	0	1 (0.1)
Sodium chloride	1 (0.2)	0	1 (0.1)
Benzydamine	0	1 (0.2)	1 (0.1)
Diclofenac	0	1 (0.2)	1 (0.1)
Sodium bicarbonate;sodium chloride	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
SULFONYLUREAS	18 (4.4)	24 (5.9)	42 (5.2)
Glimepiride	11 (2.7)	11 (2.7)	22 (2.7)
Gliclazide	5 (1.2)	7 (1.7)	12 (1.5)
Glipizide	2 (0.5)	5 (1.2)	7 (0.9)
Glibenclamide	0	2 (0.5)	2 (0.2)
VITAMIN K	18 (4.4)	18 (4.4)	36 (4.4)
Phytomenadione	12 (3.0)	7 (1.7)	19 (2.3)
Vitamin k nos	4 (1.0)	9 (2.2)	13 (1.6)
Menatetrenone	2 (0.5)	2 (0.5)	4 (0.5)
Menadione	0	1 (0.2)	1 (0.1)
VITAMINS	18 (4.4)	21 (5.2)	39 (4.8)
Vitamins nos	14 (3.5)	19 (4.7)	33 (4.1)
Fat soluble vitamins nos	2 (0.5)	2 (0.5)	4 (0.5)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Water soluble vitamins nos	2 (0.5)	2 (0.5)	4 (0.5)
Ascorbic acid;biotin;cocarboxylase tetrahydrate;colecalciferol;cyanocobalamin;dexpanthenol;dl -alpha tocopherol;folic acid;nicotinamide;pyridoxine hydrochloride;retinol palmitate;riboflavin sodium phosphate	1 (0.2)	0	1 (0.1)
ALPHA-ADRENORECEPTOR ANTAGONISTS	17 (4.2)	22 (5.4)	39 (4.8)
Tamsulosin	7 (1.7)	1 (0.2)	8 (1.0)
Tamsulosin hydrochloride	6 (1.5)	9 (2.2)	15 (1.9)
Silodosin	2 (0.5)	2 (0.5)	4 (0.5)
Alfuzosin	1 (0.2)	2 (0.5)	3 (0.4)
Naftopidil	1 (0.2)	0	1 (0.1)
Alfuzosin hydrochloride	0	1 (0.2)	1 (0.1)
Doxazosin	0	2 (0.5)	2 (0.2)
Doxazosin mesilate	0	1 (0.2)	1 (0.1)
Terazosin	0	2 (0.5)	2 (0.2)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Terazosin hydrochloride	0	1 (0.2)	1 (0.1)
Urapidil hydrochloride	0	1 (0.2)	1 (0.1)
ANTIDIARRHEAL MICROORGANISMS	17 (4.2)	18 (4.4)	35 (4.3)
Bifidobacterium longum;enterococcus faecalis;lactobacillus acidophilus	4 (1.0)	2 (0.5)	6 (0.7)
Bifidobacterium bifidum	3 (0.7)	0	3 (0.4)
Bifidobacterium nos	3 (0.7)	1 (0.2)	4 (0.5)
Lactobacillus nos	3 (0.7)	2 (0.5)	5 (0.6)
Saccharomyces boulardii	2 (0.5)	4 (1.0)	6 (0.7)
Bifidobacterium lactis;fructooligosaccharides;inulin;lactobacillus acidophilus	1 (0.2)	1 (0.2)	2 (0.2)
Fructooligosaccharides;lactobacillus rhamnosus	1 (0.2)	0	1 (0.1)
Lactobacillus acidophilus	1 (0.2)	3 (0.7)	4 (0.5)
Lactobacillus reuteri	1 (0.2)	0	1 (0.1)
Bifidobacterium bifidum;bifidobacterium infantis	0	1 (0.2)	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Enterococcus faecalis	0	3 (0.7)	3 (0.4)
Lactobacillus helveticus;lactobacillus rhamnosus	0	1 (0.2)	1 (0.1)
BELLADONNA ALKALOIDS, SEMISYNTHETIC, QUATERNARY AMMONIUM COMPOUNDS	17 (4.2)	20 (4.9)	37 (4.6)
Hyoscine butylbromide	12 (3.0)	15 (3.7)	27 (3.3)
Cimetropium bromide	3 (0.7)	3 (0.7)	6 (0.7)
Hyoscine	3 (0.7)	2 (0.5)	5 (0.6)
Cimetropium	0	1 (0.2)	1 (0.1)
FOLIC ACID AND DERIVATIVES	17 (4.2)	18 (4.4)	35 (4.3)
Folic acid	17 (4.2)	17 (4.2)	34 (4.2)
Amylase;ascorbic acid;cellulase;folic acid;lipase;protease nos	0	1 (0.2)	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER CENTRALLY ACTING AGENTS	17 (4.2)	10 (2.5)	27 (3.3)
Baclofen	8 (2.0)	4 (1.0)	12 (1.5)
Eperisone hydrochloride	3 (0.7)	3 (0.7)	6 (0.7)
Cyclobenzaprine hydrochloride	2 (0.5)	1 (0.2)	3 (0.4)
Diazepam	2 (0.5)	0	2 (0.2)
Cyclobenzaprine	1 (0.2)	1 (0.2)	2 (0.2)
Thiocolchicoside	1 (0.2)	0	1 (0.1)
Tizanidine	1 (0.2)	1 (0.2)	2 (0.2)
Tolperisone	0	1 (0.2)	1 (0.1)
OTHER DRUGS FOR CONSTIPATION	17 (4.2)	14 (3.5)	31 (3.8)
Sodium bicarbonate;sodium phosphate monobasic (anhydrous)	5 (1.2)	4 (1.0)	9 (1.1)
Prucalopride succinate	4 (1.0)	0	4 (0.5)
Lubiprostone	3 (0.7)	2 (0.5)	5 (0.6)
Panax ginseng root;zanthoxylum piperitum pericarp;zingiber officinale processed rhizome	3 (0.7)	3 (0.7)	6 (0.7)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Aloe spp. leaf;amber (fossilized tree resin);isatis tinctoria leaf	1 (0.2)	0	1 (0.1)
Linaclotide	1 (0.2)	2 (0.5)	3 (0.4)
Potassium bitartrate;sodium bicarbonate	1 (0.2)	0	1 (0.1)
Aloe vera;asini corii colla;atractylodes macrocephala;citrus spp. unripe fruit;fallopia multiflora;lycium barbarum fruit;panax ginseng;senna tora seed	0	1 (0.2)	1 (0.1)
Angelica acutiloba root;atractylodes spp. rhizome;calcium sulfate;cnidium officinale rhizome;ephedra spp. herb;forsythia spp. fruit;gardenia jasminoides fruit;glycyrrhiza spp. root;mentha canadensis herb;paeonia lactiflora root;platycodon grandiflorus root;rheum spp. rhizome;saposhnikovia divaricata root;schizonepeta tenuifolia spike;scutellaria baicalensis root;sodium sulfate;talc;zingiber officinale rhizome	0	1 (0.2)	1 (0.1)
Elobixibat	0	2 (0.5)	2 (0.2)
Glycerol	0	1 (0.2)	1 (0.1)
Glycyrrhiza glabra extract;rheum palmatum extract	0	1 (0.2)	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	17 (4.2)	13 (3.2)	30 (3.7)
Salbutamol	9 (2.2)	6 (1.5)	15 (1.9)
Salbutamol sulfate	6 (1.5)	0	6 (0.7)
Formoterol	1 (0.2)	1 (0.2)	2 (0.2)
Procaterol hydrochloride	1 (0.2)	0	1 (0.1)
Indacaterol maleate	0	1 (0.2)	1 (0.1)
Salmeterol xinafoate	0	1 (0.2)	1 (0.1)
Terbutaline sulfate	0	3 (0.7)	3 (0.4)
Tulobuterol	0	1 (0.2)	1 (0.1)
SOFTENERS, EMOLLIENTS	17 (4.2)	24 (5.9)	41 (5.1)
Docusate sodium	10 (2.5)	15 (3.7)	25 (3.1)
Magnesium hydroxide;paraffin, liquid	6 (1.5)	2 (0.5)	8 (1.0)
Magnesium hydroxide;paraffin, liquid;sodium picosulfate	2 (0.5)	1 (0.2)	3 (0.4)
Docusate	0	3 (0.7)	3 (0.4)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Light liquid paraffin	0	1 (0.2)	1 (0.1)
Paraffin	0	2 (0.5)	2 (0.2)
CORTICOSTEROIDS, MODERATELY POTENT (GROUP II)	16 (4.0)	10 (2.5)	26 (3.2)
Desonide	5 (1.2)	2 (0.5)	7 (0.9)
Triamcinolone	4 (1.0)	3 (0.7)	7 (0.9)
Dexamethasone	3 (0.7)	2 (0.5)	5 (0.6)
Triamcinolone acetonide	3 (0.7)	3 (0.7)	6 (0.7)
Hydrocortisone butyrate	2 (0.5)	0	2 (0.2)
Dexamethasone sodium phosphate	1 (0.2)	0	1 (0.1)
Dexamethasone valerate	1 (0.2)	0	1 (0.1)
Hydrocortisone probutat	1 (0.2)	0	1 (0.1)
INTERLEUKINS	16 (4.0)	16 (4.0)	32 (4.0)
Oprelvekin	14 (3.5)	16 (4.0)	30 (3.7)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Interleukin-2	1 (0.2)	0	1 (0.1)
Interleukins	1 (0.2)	0	1 (0.1)
ANTIINFECTIVES AND ANTISEPTICS FOR LOCAL ORAL TREATMENT	15 (3.7)	12 (3.0)	27 (3.3)
Chlorhexidine gluconate	9 (2.2)	7 (1.7)	16 (2.0)
Clotrimazole	4 (1.0)	2 (0.5)	6 (0.7)
Nystatin	2 (0.5)	1 (0.2)	3 (0.4)
Benzydamine;chlorhexidine	1 (0.2)	0	1 (0.1)
Chlorhexidine	1 (0.2)	0	1 (0.1)
Magic mouthwash	1 (0.2)	1 (0.2)	2 (0.2)
Povidone-iodine	1 (0.2)	1 (0.2)	2 (0.2)
Azulene sodium sulfonate	0	1 (0.2)	1 (0.1)
FIRST-GENERATION CEPHALOSPORINS	15 (3.7)	16 (4.0)	31 (3.8)
Cefalexin	5 (1.2)	4 (1.0)	9 (1.1)
Cefadroxil	3 (0.7)	1 (0.2)	4 (0.5)

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Cefadroxil monohydrate	2 (0.5)	0	2 (0.2)
Cefazolin	2 (0.5)	1 (0.2)	3 (0.4)
Cefazolin sodium	2 (0.5)	6 (1.5)	8 (1.0)
Cefazolin;glucose	2 (0.5)	2 (0.5)	4 (0.5)
Cefradine	1 (0.2)	0	1 (0.1)
Methylol cefalexin lysinate	1 (0.2)	1 (0.2)	2 (0.2)
Cefalexin monohydrate	0	1 (0.2)	1 (0.1)
Cefazedone sodium	0	1 (0.2)	1 (0.1)
MULTIVITAMINS, PLAIN	15 (3.7)	15 (3.7)	30 (3.7)
Vitamins nos	12 (3.0)	12 (3.0)	24 (3.0)
Ascorbic acid;dexpanthenol;ergocalciferol;nicotinamide;pyridoxine hydrochloride;retinol;riboflavin sodium phosphate;thiamine hydrochloride;tocopherol	3 (0.7)	0	3 (0.4)

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Ascorbic acid;biotin;colecalciferol;dexpanthenol;folic acid;nicotinamide;pyridoxine hydrochloride;retinol palmitate;riboflavin sodium phosphate;tocopherol;vitamin b1 nos;vitamin b12 nos	0	1 (0.2)	1 (0.1)
Ascorbic acid;calcium pantothenate;colecalciferol;cyanocobalamin;nicotinamide;pyridoxine hydrochloride;retinol;riboflavin;thiamine hydrochloride;tocopheryl acetate	0	1 (0.2)	1 (0.1)
Ascorbic acid;calcium pantothenate;cyanocobalamin;ergocalciferol;folic acid;nicotinamide;pyridoxine hydrochloride;retinol palmitate;riboflavin;thiamine mononitrate;tocopheryl acetate	0	1 (0.2)	1 (0.1)
Ascorbic acid;nicotinamide;retinol;riboflavin;vitamin b1 nos;vitamin d nos	0	1 (0.2)	1 (0.1)
CALCIUM, COMBINATIONS WITH VITAMIN D AND/OR OTHER DRUGS	14 (3.5)	13 (3.2)	27 (3.3)
Calcium carbonate;colecalciferol	6 (1.5)	5 (1.2)	11 (1.4)
Calcium citrate;colecalciferol	2 (0.5)	0	2 (0.2)

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Calcium;colecalciferol	2 (0.5)	0	2 (0.2)
Calcium;vitamin d nos	2 (0.5)	1 (0.2)	3 (0.4)
Calcium carbonate;colecalciferol;magnesium carbonate	1 (0.2)	2 (0.5)	3 (0.4)
Calcium citrate malate;colecalciferol;folic acid	1 (0.2)	0	1 (0.1)
Calcium;calcium carbonate;colecalciferol	1 (0.2)	0	1 (0.1)
Calcium;colecalciferol;phosphorus	1 (0.2)	0	1 (0.1)
Calcium carbonate;calcium gluconate;calcium lactate;ergocalciferol	0	1 (0.2)	1 (0.1)
Calcium carbonate;colecalciferol;copper;magnesium oxide;manganese;zinc	0	1 (0.2)	1 (0.1)
Calcium carbonate;colecalciferol;magnesium oxide;zinc oxide	0	1 (0.2)	1 (0.1)
Calcium phosphate;colecalciferol;retinol	0	1 (0.2)	1 (0.1)
Calcium;colecalciferol;menaquinone	0	1 (0.2)	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
COMBINATIONS AND COMPLEXES OF ALUMINIUM, CALCIUM AND MAGNESIUM COMPOUNDS	14 (3.5)	13 (3.2)	27 (3.3)
Almagate	6 (1.5)	6 (1.5)	12 (1.5)
Aluminium hydroxide;calcium carbonate;magnesium carbonate;oxetacaine	2 (0.5)	2 (0.5)	4 (0.5)
Magaldrate	2 (0.5)	0	2 (0.2)
Algeldrate;magnesium hydroxide	1 (0.2)	0	1 (0.1)
Aluminium hydroxide;calcium carbonate;magnesium carbonate	1 (0.2)	0	1 (0.1)
Aluminium hydroxide;magnesium hydroxide	1 (0.2)	0	1 (0.1)
Aluminium hydroxide;magnesium oxide;oxetacaine	1 (0.2)	0	1 (0.1)
Calcium carbonate;magnesium carbonate	1 (0.2)	0	1 (0.1)
Aluminium hydroxide gel;magnesium trisilicate	0	1 (0.2)	1 (0.1)
Aluminium hydroxide-magnesium carbonate gel	0	1 (0.2)	1 (0.1)
Aluminium hydroxide;magnesium carbonate;oxetacaine	0	2 (0.5)	2 (0.2)
Aluminium hydroxide;magnesium hydroxide;montmorillonite	0	1 (0.2)	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS	14 (3.5)	18 (4.4)	32 (4.0)
Linagliptin	4 (1.0)	6 (1.5)	10 (1.2)
Vildagliptin	4 (1.0)	3 (0.7)	7 (0.9)
Sitagliptin phosphate	3 (0.7)	4 (1.0)	7 (0.9)
Gemigliptin tartrate	1 (0.2)	3 (0.7)	4 (0.5)
Saxagliptin	1 (0.2)	1 (0.2)	2 (0.2)
Sitagliptin	1 (0.2)	0	1 (0.1)
Sitagliptin phosphate monohydrate	1 (0.2)	0	1 (0.1)
Alogliptin	0	1 (0.2)	1 (0.1)
Teneligliptin hydrobromide	0	1 (0.2)	1 (0.1)
MACROLIDES	14 (3.5)	7 (1.7)	21 (2.6)
Azithromycin	10 (2.5)	4 (1.0)	14 (1.7)
Clarithromycin	2 (0.5)	2 (0.5)	4 (0.5)
Roxithromycin	2 (0.5)	0	2 (0.2)
Erythromycin	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OPIUM DERIVATIVES AND EXPECTORANTS	14 (3.5)	7 (1.7)	21 (2.6)
Antimony potassium tartrate;glycyrrhiza spp.;papaver somniferum tincture	4 (1.0)	1 (0.2)	5 (0.6)
Ammonium chloride;chlorphenamine maleate;dextromethorphan hydrobromide;guaifenesin	2 (0.5)	0	2 (0.2)
Camphor;glycyrrhiza glabra;illicium verum oil;papaver somniferum;sodium benzoate	2 (0.5)	1 (0.2)	3 (0.4)
Dextromethorphan hydrobromide;guaifenesin	2 (0.5)	1 (0.2)	3 (0.4)
Antimony potassium tartrate;glycyrrhiza spp.;papaver somniferum	1 (0.2)	0	1 (0.1)
Codeine phosphate;ephedrine hydrochloride;sulfogaiacol;triprolidine hydrochloride	1 (0.2)	0	1 (0.1)
Codeine phosphate;sulfogaiacol	1 (0.2)	0	1 (0.1)
Codeine;platycodon grandiflorus	1 (0.2)	0	1 (0.1)
Dextromethorphan;guaifenesin	1 (0.2)	0	1 (0.1)
Antimony potassium tartrate;glycerol;glycyrrhiza glabra;nitrous ether spirit;papaver somniferum	0	1 (0.2)	1 (0.1)
Antimony potassium tartrate;glycyrrhiza glabra;papaver somniferum tincture	0	1 (0.2)	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Ascorbic acid;guaifenesin;paracetamol;pentoxyverine citrate	0	1 (0.2)	1 (0.1)
Codeine phosphate;guaifenesin	0	1 (0.2)	1 (0.1)
OTHER ANTIBIOTICS FOR TOPICAL USE	14 (3.5)	14 (3.5)	28 (3.5)
Mupirocin	4 (1.0)	6 (1.5)	10 (1.2)
Gentamicin sulfate	3 (0.7)	0	3 (0.4)
Fusidate sodium	2 (0.5)	0	2 (0.2)
Neomycin	2 (0.5)	1 (0.2)	3 (0.4)
Neomycin;tyrothricin	2 (0.5)	2 (0.5)	4 (0.5)
Neomycin sulfate;polymyxin b sulfate	1 (0.2)	0	1 (0.1)
Bacitracin;polymyxin b sulfate	0	1 (0.2)	1 (0.1)
Chloramphenicol	0	1 (0.2)	1 (0.1)
Fusidic acid	0	3 (0.7)	3 (0.4)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER ANTIDEPRESSANTS	14 (3.5)	6 (1.5)	20 (2.5)
Trazodone	5 (1.2)	2 (0.5)	7 (0.9)
Mirtazapine	4 (1.0)	2 (0.5)	6 (0.7)
Venlafaxine hydrochloride	2 (0.5)	0	2 (0.2)
Ademetionine 1,4-butanedisulfonate	1 (0.2)	0	1 (0.1)
Bupropion hydrochloride	1 (0.2)	0	1 (0.1)
Tianeptine sodium	1 (0.2)	1 (0.2)	2 (0.2)
Vortioxetine	1 (0.2)	0	1 (0.1)
Duloxetine hydrochloride	0	1 (0.2)	1 (0.1)
Trazodone hydrochloride	0	1 (0.2)	1 (0.1)
PYRAZOLONES	14 (3.5)	2 (0.5)	16 (2.0)
Metamizole	5 (1.2)	0	5 (0.6)
Metamizole sodium	4 (1.0)	2 (0.5)	6 (0.7)
Aminophenazone;barbital;phenazone	3 (0.7)	0	3 (0.4)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Fenpiverinium bromide;metamizole sodium;pitofenone hydrochloride	3 (0.7)	0	3 (0.4)
Metamizole sodium monohydrate	1 (0.2)	0	1 (0.1)
VITAMIN B12 (CYANOCOBALAMIN AND ANALOGUES)	14 (3.5)	12 (3.0)	26 (3.2)
Cyanocobalamin	6 (1.5)	3 (0.7)	9 (1.1)
Mecobalamin	5 (1.2)	4 (1.0)	9 (1.1)
Vitamin b12 nos	3 (0.7)	5 (1.2)	8 (1.0)
Cobamamide	1 (0.2)	0	1 (0.1)
Hydroxocobalamin	1 (0.2)	0	1 (0.1)
Folic acid;nicotinamide;vitamin b12 nos	0	1 (0.2)	1 (0.1)
COMBINATIONS OF ORAL BLOOD GLUCOSE LOWERING DRUGS	13 (3.2)	12 (3.0)	25 (3.1)
Metformin hydrochloride;sitagliptin phosphate monohydrate	5 (1.2)	1 (0.2)	6 (0.7)
Glimepiride;metformin hydrochloride	3 (0.7)	0	3 (0.4)
Alogliptin benzoate;metformin hydrochloride	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Canagliflozin hemihydrate;teneligliptin hydrobromide	1 (0.2)	0	1 (0.1)
Gemigliptin tartrate;metformin hydrochloride	1 (0.2)	3 (0.7)	4 (0.5)
Glibenclamide;metformin hydrochloride	1 (0.2)	2 (0.5)	3 (0.4)
Metformin hydrochloride;vildagliptin	1 (0.2)	0	1 (0.1)
Metformin;vildagliptin	1 (0.2)	0	1 (0.1)
Empagliflozin;metformin hydrochloride	0	1 (0.2)	1 (0.1)
Evogliptin tartrate;metformin hydrochloride	0	1 (0.2)	1 (0.1)
Linagliptin;metformin hydrochloride	0	1 (0.2)	1 (0.1)
Metformin hydrochloride;pioglitazone hydrochloride	0	1 (0.2)	1 (0.1)
Metformin hydrochloride;teneligliptin hydrobromide hydrate	0	1 (0.2)	1 (0.1)
Metformin;sitagliptin	0	1 (0.2)	1 (0.1)
OPIOID ANESTHETICS	13 (3.2)	11 (2.7)	24 (3.0)
Fentanyl citrate	8 (2.0)	6 (1.5)	14 (1.7)
Fentanyl	6 (1.5)	5 (1.2)	11 (1.4)
Alfentanil	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER ANTIPRURITICS	13 (3.2)	6 (1.5)	19 (2.3)
Calamine	3 (0.7)	0	3 (0.4)
Calamine;glycerol;zinc oxide	3 (0.7)	3 (0.7)	6 (0.7)
Doxepin	3 (0.7)	1 (0.2)	4 (0.5)
Doxepin hydrochloride	2 (0.5)	2 (0.5)	4 (0.5)
Calamine;zinc oxide	1 (0.2)	0	1 (0.1)
Other antipruritics	1 (0.2)	0	1 (0.1)
Camphor;menthol	0	1 (0.2)	1 (0.1)
INSULINS AND ANALOGUES FOR INJECTION, LONG-ACTING	12 (3.0)	10 (2.5)	22 (2.7)
Insulin glargine	10 (2.5)	7 (1.7)	17 (2.1)
Insulin degludec	1 (0.2)	3 (0.7)	4 (0.5)
Insulin detemir	1 (0.2)	1 (0.2)	2 (0.2)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
IRON IN OTHER COMBINATIONS	12 (3.0)	5 (1.2)	17 (2.1)
Ascorbic acid;cyanocobalamin;ferrous fumarate;folic acid	3 (0.7)	1 (0.2)	4 (0.5)
Ascorbic acid;ferrous gluconate;thiamine	3 (0.7)	2 (0.5)	5 (0.6)
Ascorbic acid;calcium phosphate;ferrous fumarate;folic acid;nicotinic acid;riboflavin;thiamine;vitamin b12 nos	2 (0.5)	0	2 (0.2)
Ascorbic acid;cyanocobalamin;ferrous fumarate	1 (0.2)	0	1 (0.1)
Ascorbic acid;ferric pyrophosphate;vitamin b12 nos	1 (0.2)	0	1 (0.1)
Ferrous fumarate;folic acid;zinc sulfate monohydrate	1 (0.2)	0	1 (0.1)
Folic acid;iron;mecobalamin;zinc	1 (0.2)	0	1 (0.1)
Ascorbic acid;ferric pyrophosphate	0	1 (0.2)	1 (0.1)
Ferrous fumarate;folic acid;pyridoxine hydrochloride	0	1 (0.2)	1 (0.1)
OTHER EMOLLIENTS AND PROTECTIVES	12 (3.0)	19 (4.7)	31 (3.8)
Mucopolysaccharide polysulfuric acid ester	5 (1.2)	9 (2.2)	14 (1.7)
Heparinoid	4 (1.0)	3 (0.7)	7 (0.9)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Aloe spp.;glycerol;mangifera indica;propylene glycol;theobroma cacao oil;vitellaria paradoxa	1 (0.2)	0	1 (0.1)
Boric acid	1 (0.2)	0	1 (0.1)
Glycerol	1 (0.2)	0	1 (0.1)
Glycerol;paraffin, liquid;white soft paraffin	1 (0.2)	1 (0.2)	2 (0.2)
Allantoin;diethylene glycol monostearate;dimeticone;isopropyl myristate;lanolin oil;paraffin, liquid;propylene glycol;stearic acid;tocopheryl acetate;trolamine	0	1 (0.2)	1 (0.1)
Emulsifying wax;paraffin soft	0	1 (0.2)	1 (0.1)
Glycerol;glyceryl monostearate;paraffin, liquid;simeticone;wool alcohols	0	1 (0.2)	1 (0.1)
Other emollients and protectives	0	2 (0.5)	2 (0.2)
Vitamin e nos	0	1 (0.2)	1 (0.1)
PREPARATIONS INHIBITING URIC ACID PRODUCTION	12 (3.0)	13 (3.2)	25 (3.1)
Allopurinol	7 (1.7)	9 (2.2)	16 (2.0)
Febuxostat	5 (1.2)	4 (1.0)	9 (1.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
SOFT PARAFFIN AND FAT PRODUCTS	12 (3.0)	9 (2.2)	21 (2.6)
White soft paraffin	8 (2.0)	4 (1.0)	12 (1.5)
Emulsifying wax;paraffin, liquid;white soft paraffin	2 (0.5)	2 (0.5)	4 (0.5)
Paraffin soft;paraffin, liquid;wool fat	1 (0.2)	1 (0.2)	2 (0.2)
Paraffin, liquid;white soft paraffin	1 (0.2)	0	1 (0.1)
Mineral oil light;paraffin;petrolatum;wool alcohols	0	1 (0.2)	1 (0.1)
Paraffin, liquid;white soft paraffin;wool fat	0	1 (0.2)	1 (0.1)
THIAZIDES, PLAIN	12 (3.0)	11 (2.7)	23 (2.8)
Hydrochlorothiazide	12 (3.0)	9 (2.2)	21 (2.6)
Bendroflumethiazide	0	2 (0.5)	2 (0.2)
ANTIBIOTICS	11 (2.7)	17 (4.2)	28 (3.5)
Nystatin	7 (1.7)	10 (2.5)	17 (2.1)
Vancomycin	2 (0.5)	2 (0.5)	4 (0.5)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Rifaximin	1 (0.2)	0	1 (0.1)
Tobramycin	1 (0.2)	1 (0.2)	2 (0.2)
Vancomycin hydrochloride	1 (0.2)	2 (0.5)	3 (0.4)
Antibiotics	0	1 (0.2)	1 (0.1)
Fidaxomicin	0	1 (0.2)	1 (0.1)
Griseofulvin	0	1 (0.2)	1 (0.1)
Rifampicin	0	1 (0.2)	1 (0.1)
BILE AND LIVER THERAPY	11 (2.7)	22 (5.4)	33 (4.1)
Bicyclol	11 (2.7)	22 (5.4)	33 (4.1)
Artemisia spp. herb;baicalin;gardenia jasminoides fruit;lonicera japonica flower bud	1 (0.2)	0	1 (0.1)
COMBINATIONS OF SULFONAMIDES AND TRIMETHOPRIM, INCL. DERIVATIVES	11 (2.7)	4 (1.0)	15 (1.9)
Sulfamethoxazole;trimethoprim	11 (2.7)	4 (1.0)	15 (1.9)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
CORTICOSTEROIDS	11 (2.7)	11 (2.7)	22 (2.7)
Fluticasone propionate	3 (0.7)	3 (0.7)	6 (0.7)
Escherichia coli;hydrocortisone	2 (0.5)	4 (1.0)	6 (0.7)
Fluticasone	2 (0.5)	0	2 (0.2)
Aluminium acetate;hydrocortisone acetate;lidocaine;zinc oxide	1 (0.2)	1 (0.2)	2 (0.2)
Fluticasone furoate	1 (0.2)	0	1 (0.1)
Hydrocortisone acetate	1 (0.2)	0	1 (0.1)
Hydrocortisone acetate;lidocaine	1 (0.2)	0	1 (0.1)
Mometasone	1 (0.2)	0	1 (0.1)
Mometasone furoate	1 (0.2)	1 (0.2)	2 (0.2)
Triamcinolone acetonide	1 (0.2)	0	1 (0.1)
Budesonide	0	1 (0.2)	1 (0.1)
Cinchocaine hydrochloride;hydrocortisone	0	1 (0.2)	1 (0.1)
Dexamethasone	0	1 (0.2)	1 (0.1)
Lidocaine;prednisolone	0	1 (0.2)	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
DRUGS FOR TREATMENT OF HYPERKALEMIA AND HYPERPHOSPHATEMIA	11 (2.7)	17 (4.2)	28 (3.5)
Calcium polystyrene sulfonate	9 (2.2)	16 (4.0)	25 (3.1)
Sodium polystyrene sulfonate	2 (0.5)	1 (0.2)	3 (0.4)
OTHER AMINOGLYCOSIDES	11 (2.7)	9 (2.2)	20 (2.5)
Gentamicin	4 (1.0)	3 (0.7)	7 (0.9)
Amikacin	3 (0.7)	4 (1.0)	7 (0.9)
Amikacin sulfate	2 (0.5)	0	2 (0.2)
Gentamicin sulfate	2 (0.5)	0	2 (0.2)
Etimicin sulfate	0	1 (0.2)	1 (0.1)
Netilmicin sulfate	0	1 (0.2)	1 (0.1)
PHENOTHIAZINE DERIVATIVES	11 (2.7)	6 (1.5)	17 (2.1)
Promethazine hydrochloride	6 (1.5)	5 (1.2)	11 (1.4)
Mequitazine	2 (0.5)	0	2 (0.2)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Promethazine	2 (0.5)	0	2 (0.2)
Thiethylperazine maleate	1 (0.2)	1 (0.2)	2 (0.2)
SELECTIVE SEROTONIN REUPTAKE INHIBITORS	11 (2.7)	13 (3.2)	24 (3.0)
Escitalopram	4 (1.0)	1 (0.2)	5 (0.6)
Sertraline	3 (0.7)	0	3 (0.4)
Sertraline hydrochloride	2 (0.5)	2 (0.5)	4 (0.5)
Citalopram	1 (0.2)	1 (0.2)	2 (0.2)
Fluoxetine	1 (0.2)	2 (0.5)	3 (0.4)
Citalopram hydrobromide	0	4 (1.0)	4 (0.5)
Escitalopram oxalate	0	4 (1.0)	4 (0.5)
STOMATOLOGICAL PREPARATIONS	11 (2.7)	7 (1.7)	18 (2.2)
Sodium bicarbonate	8 (2.0)	6 (1.5)	14 (1.7)
Stomatological preparations	2 (0.5)	1 (0.2)	3 (0.4)
Cetalkonium chloride;choline salicylate	1 (0.2)	0	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
IRON TRIVALENT, ORAL PREPARATIONS	10 (2.5)	14 (3.5)	24 (3.0)
Iron polysaccharide complex	4 (1.0)	5 (1.2)	9 (1.1)
Iron succinyl-protein complex	4 (1.0)	2 (0.5)	6 (0.7)
Ferric hydroxide	1 (0.2)	0	1 (0.1)
Ferric hydroxide polymaltose complex	1 (0.2)	6 (1.5)	7 (0.9)
Saccharated iron oxide	1 (0.2)	0	1 (0.1)
Ferric acetyl transferrin	0	1 (0.2)	1 (0.1)
OTHER INTESTINAL ADSORBENTS	10 (2.5)	9 (2.2)	19 (2.3)
Diosmectite	10 (2.5)	8 (2.0)	18 (2.2)
Montmorillonite	0	1 (0.2)	1 (0.1)
VITAMIN B-COMPLEX, PLAIN	10 (2.5)	7 (1.7)	17 (2.1)
Vitamin b complex	5 (1.2)	5 (1.2)	10 (1.2)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Cyanocobalamin;dexpanthenol;nicotinamide;pyridoxine hydrochloride;riboflavin;thiamine hydrochloride	2 (0.5)	1 (0.2)	3 (0.4)
Calcium pantothenate;cyanocobalamin;nicotinamide;pyridoxine hydrochloride;riboflavin;thiamine mononitrate	1 (0.2)	0	1 (0.1)
Nicotinamide;pyridoxine hydrochloride;riboflavin;thiamine hydrochloride	1 (0.2)	0	1 (0.1)
Vitamin b nos	1 (0.2)	0	1 (0.1)
Calcium pantothenate;nicotinamide;pyridoxine hydrochloride;riboflavin;thiamine hydrochloride	0	1 (0.2)	1 (0.1)
ADRENERGICS IN COMBINATION WITH CORTICOSTEROIDS OR OTHER DRUGS, EXCL. ANTICHOLINERGICS	9 (2.2)	4 (1.0)	13 (1.6)
Fluticasone propionate;salmeterol xinafoate	3 (0.7)	0	3 (0.4)
Budesonide;formoterol fumarate	2 (0.5)	2 (0.5)	4 (0.5)
Beclometasone dipropionate;formoterol fumarate	1 (0.2)	2 (0.5)	3 (0.4)
Fluticasone furoate;vilanterol trifenatate	1 (0.2)	0	1 (0.1)
Fluticasone;salmeterol	1 (0.2)	0	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Fluticasone;vilanterol	1 (0.2)	0	1 (0.1)
ANGIOTENSIN II RECEPTOR BLOCKERS (ARBS) AND CALCIUM CHANNEL BLOCKERS	9 (2.2)	10 (2.5)	19 (2.3)
Amlodipine;valsartan	3 (0.7)	2 (0.5)	5 (0.6)
Amlodipine besilate;candesartan cilexetil	1 (0.2)	2 (0.5)	3 (0.4)
Amlodipine besilate;irbesartan	1 (0.2)	0	1 (0.1)
Amlodipine besilate;olmesartan medoxomil	1 (0.2)	1 (0.2)	2 (0.2)
Amlodipine besilate;telmisartan	1 (0.2)	2 (0.5)	3 (0.4)
Amlodipine besilate;valsartan	1 (0.2)	1 (0.2)	2 (0.2)
Azelnidipine;olmesartan medoxomil	1 (0.2)	0	1 (0.1)
Amlodipine;telmisartan	0	1 (0.2)	1 (0.1)
Levamlodipine besilate;telmisartan	0	1 (0.2)	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
ANGIOTENSIN II RECEPTOR BLOCKERS (ARBS) AND DIURETICS	9 (2.2)	4 (1.0)	13 (1.6)
Hydrochlorothiazide;losartan potassium	4 (1.0)	0	4 (0.5)
Candesartan cilexetil;hydrochlorothiazide	2 (0.5)	2 (0.5)	4 (0.5)
Hydrochlorothiazide;irbesartan	2 (0.5)	1 (0.2)	3 (0.4)
Hydrochlorothiazide;telmisartan	1 (0.2)	0	1 (0.1)
Hydrochlorothiazide;olmesartan medoxomil	0	1 (0.2)	1 (0.1)
ANTICHOLINERGICS	9 (2.2)	8 (2.0)	17 (2.1)
Ipratropium bromide	3 (0.7)	2 (0.5)	5 (0.6)
Phenylephrine hydrochloride;tropicamide	2 (0.5)	4 (1.0)	6 (0.7)
Tiotropium bromide monohydrate	2 (0.5)	2 (0.5)	4 (0.5)
Tiotropium	1 (0.2)	0	1 (0.1)
Umeclidinium bromide	1 (0.2)	0	1 (0.1)
Atropine sulfate monohydrate	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
CORTICOSTEROIDS, VERY POTENT (GROUP IV)	9 (2.2)	3 (0.7)	12 (1.5)
Clobetasol propionate	7 (1.7)	2 (0.5)	9 (1.1)
Clobetasol	2 (0.5)	1 (0.2)	3 (0.4)
CORTICOSTEROIDS, WEAK (GROUP I)	9 (2.2)	7 (1.7)	16 (2.0)
Hydrocortisone	7 (1.7)	6 (1.5)	13 (1.6)
Prednisolone valeroacetate	2 (0.5)	1 (0.2)	3 (0.4)
Prednisolone	1 (0.2)	0	1 (0.1)
GENERAL NUTRIENTS	9 (2.2)	17 (4.2)	26 (3.2)
Nutrients nos	6 (1.5)	12 (3.0)	18 (2.2)
General nutrients	2 (0.5)	3 (0.7)	5 (0.6)
Trace elements nos	1 (0.2)	2 (0.5)	3 (0.4)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
IMIDAZOLE AND TRIAZOLE DERIVATIVES	9 (2.2)	4 (1.0)	13 (1.6)
Ketoconazole	4 (1.0)	0	4 (0.5)
Econazole;triamcinolone acetonide	2 (0.5)	0	2 (0.2)
Efinaconazole	2 (0.5)	0	2 (0.2)
Flutrimazole	1 (0.2)	0	1 (0.1)
Luliconazole	1 (0.2)	0	1 (0.1)
Clotrimazole	0	2 (0.5)	2 (0.2)
Econazole	0	1 (0.2)	1 (0.1)
Econazole nitrate;triamcinolone acetonide	0	1 (0.2)	1 (0.1)
ADRENERGICS IN COMBINATIONS WITH ANTICHOLINERGICS INCL. TRIPLE COMBINATIONS WITH CORTICOSTEROIDS	8 (2.0)	10 (2.5)	18 (2.2)
Ipratropium bromide;salbutamol sulfate	3 (0.7)	1 (0.2)	4 (0.5)
Fenoterol hydrobromide;ipratropium bromide	2 (0.5)	2 (0.5)	4 (0.5)
Ipratropium bromide;salbutamol	2 (0.5)	2 (0.5)	4 (0.5)
Ipratropium;salbutamol	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Fluticasone furoate;umeclidinium bromide;vilanterol trifenatate	0	1 (0.2)	1 (0.1)
Glycopyrronium bromide;indacaterol maleate	0	2 (0.5)	2 (0.2)
Olodaterol hydrochloride;tiotropium bromide	0	1 (0.2)	1 (0.1)
Umeclidinium bromide;vilanterol trifenatate	0	1 (0.2)	1 (0.1)
ALPHA AND BETA BLOCKING AGENTS	8 (2.0)	7 (1.7)	15 (1.9)
Carvedilol	6 (1.5)	7 (1.7)	13 (1.6)
Labetalol hydrochloride	2 (0.5)	0	2 (0.2)
BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	8 (2.0)	10 (2.5)	18 (2.2)
Carbohydrates nos;potassium chloride;sodium chloride;sodium lactate	8 (2.0)	10 (2.5)	18 (2.2)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
BUTYROPHENONE DERIVATIVES	8 (2.0)	6 (1.5)	14 (1.7)
Haloperidol	8 (2.0)	6 (1.5)	14 (1.7)
CALCIUM	8 (2.0)	6 (1.5)	14 (1.7)
Calcium carbonate	5 (1.2)	3 (0.7)	8 (1.0)
Calcium	1 (0.2)	1 (0.2)	2 (0.2)
Calcium citrate malate	1 (0.2)	0	1 (0.1)
Calcium gluconate	1 (0.2)	0	1 (0.1)
Calcium lactate	0	1 (0.2)	1 (0.1)
Calcium laevulinate	0	1 (0.2)	1 (0.1)
CORTICOSTEROIDS FOR LOCAL ORAL TREATMENT	8 (2.0)	9 (2.2)	17 (2.1)
Dexamethasone	5 (1.2)	7 (1.7)	12 (1.5)
Triamcinolone	4 (1.0)	2 (0.5)	6 (0.7)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
DRUGS FOR URINARY FREQUENCY AND INCONTINENCE	8 (2.0)	4 (1.0)	12 (1.5)
Mirabegron	4 (1.0)	2 (0.5)	6 (0.7)
Solifenacin succinate	3 (0.7)	0	3 (0.4)
Solifenacin	1 (0.2)	1 (0.2)	2 (0.2)
Tolterodine	0	1 (0.2)	1 (0.1)
ORIPAVINE DERIVATIVES	8 (2.0)	5 (1.2)	13 (1.6)
Buprenorphine	7 (1.7)	5 (1.2)	12 (1.5)
Buprenorphine hydrochloride	1 (0.2)	0	1 (0.1)
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	8 (2.0)	5 (1.2)	13 (1.6)
Clostridium butyricum	7 (1.7)	4 (1.0)	11 (1.4)
Calcium chloride dihydrate;magnesium chloride hexahydrate;potassium chloride;potassium phosphate dibasic;potassium phosphate monobasic;sodium chloride	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Ulinastatin	0	1 (0.2)	1 (0.1)
OTHER COMBINATIONS OF NUTRIENTS	8 (2.0)	3 (0.7)	11 (1.4)
Fish oil	4 (1.0)	1 (0.2)	5 (0.6)
Carbohydrates nos;fats nos;fibre, dietary;minerals nos;proteins nos;vitamins nos	2 (0.5)	2 (0.5)	4 (0.5)
Carbohydrates nos;electrolytes nos;fatty acids nos;minerals nos;proteins nos;vitamins nos	1 (0.2)	0	1 (0.1)
Glucose;herbal nos;minerals nos;sucrose;vitamins nos;whey protein	1 (0.2)	0	1 (0.1)
Herbal nos;minerals nos;vitamins nos	1 (0.2)	0	1 (0.1)
PROTEINASE INHIBITORS	8 (2.0)	11 (2.7)	19 (2.3)
Ulinastatin	4 (1.0)	2 (0.5)	6 (0.7)
Camostat mesilate	3 (0.7)	4 (1.0)	7 (0.9)
Gabexate mesilate	2 (0.5)	3 (0.7)	5 (0.6)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Nafamostat	1 (0.2)	0	1 (0.1)
Camostat	0	1 (0.2)	1 (0.1)
Nafamostat mesilate	0	2 (0.5)	2 (0.2)
SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS	8 (2.0)	10 (2.5)	18 (2.2)
Dapagliflozin	3 (0.7)	2 (0.5)	5 (0.6)
Empagliflozin	2 (0.5)	3 (0.7)	5 (0.6)
Canagliflozin	1 (0.2)	1 (0.2)	2 (0.2)
Dapagliflozin propanediol monohydrate	1 (0.2)	4 (1.0)	5 (0.6)
Ipragliflozin l-proline	1 (0.2)	0	1 (0.1)
TETRACYCLINES	8 (2.0)	7 (1.7)	15 (1.9)
Doxycycline	4 (1.0)	3 (0.7)	7 (0.9)
Doxycycline monohydrate	2 (0.5)	0	2 (0.2)
Lymecycline	1 (0.2)	0	1 (0.1)
Tigecycline	1 (0.2)	1 (0.2)	2 (0.2)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Doxycycline hyclate	0	2 (0.5)	2 (0.2)
Doxycycline hydrochloride	0	1 (0.2)	1 (0.1)
TRIAZOLE DERIVATIVES	8 (2.0)	12 (3.0)	20 (2.5)
Fluconazole	8 (2.0)	12 (3.0)	20 (2.5)
VITAMIN B1 IN COMBINATION WITH VITAMIN B6 AND/OR VITAMIN B12	8 (2.0)	9 (2.2)	17 (2.1)
Cyanocobalamin;pyridoxine hydrochloride;thiamine hydrochloride	4 (1.0)	6 (1.5)	10 (1.2)
Cyanocobalamin;pyridoxine;thiamine	2 (0.5)	0	2 (0.2)
Cyanocobalamin;pyridoxine hydrochloride;riboflavin;thiamine disulfide	1 (0.2)	0	1 (0.1)
Pyridoxine hydrochloride;thiamine mononitrate;vitamin b12 nos	1 (0.2)	1 (0.2)	2 (0.2)
Cyanocobalamin;octotiamine;pyridoxine hydrochloride;riboflavin	0	1 (0.2)	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Cyanocobalamin;pyridoxine hydrochloride;thiamine disulfide	0	1 (0.2)	1 (0.1)
Fursultiamine;hydroxocobalamin;pyridoxal phosphate	0	2 (0.5)	2 (0.2)
Hydroxocobalamin acetate;pyridoxine hydrochloride;thiamine disulfide	0	1 (0.2)	1 (0.1)
WATERSOLUBLE, NEPHROTROPIC, LOW OSMOLAR X-RAY CONTRAST MEDIA	8 (2.0)	3 (0.7)	11 (1.4)
Iohexol	3 (0.7)	2 (0.5)	5 (0.6)
Iodixanol	2 (0.5)	0	2 (0.2)
Iopromide	2 (0.5)	1 (0.2)	3 (0.4)
Ioversol	1 (0.2)	1 (0.2)	2 (0.2)
BETA-LACTAMASE INHIBITORS	7 (1.7)	5 (1.2)	12 (1.5)
Clavulanic acid	3 (0.7)	4 (1.0)	7 (0.9)
Tazobactam	2 (0.5)	0	2 (0.2)
Sulbactam	1 (0.2)	0	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Sulbactam sodium	1 (0.2)	0	1 (0.1)
Clavulanate potassium	0	1 (0.2)	1 (0.1)
CORTICOSTEROIDS, POTENT, COMBINATIONS WITH ANTIBIOTICS	7 (1.7)	3 (0.7)	10 (1.2)
Betamethasone valerate;gentamicin sulfate	4 (1.0)	0	4 (0.5)
Betamethasone;gentamicin	2 (0.5)	1 (0.2)	3 (0.4)
Betamethasone;fusidic acid	1 (0.2)	0	1 (0.1)
Betamethasone;neomycin	0	1 (0.2)	1 (0.1)
Fluocinolone acetonide;neomycin	0	1 (0.2)	1 (0.1)
INFLUENZA VACCINES	7 (1.7)	10 (2.5)	17 (2.1)
Influenza vaccine	6 (1.5)	10 (2.5)	16 (2.0)
Influenza vaccine inact sag 3v	1 (0.2)	0	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
IRON PREPARATIONS	7 (1.7)	3 (0.7)	10 (1.2)
Iron polysaccharide complex	4 (1.0)	1 (0.2)	5 (0.6)
Iron	2 (0.5)	0	2 (0.2)
Iron dextran	1 (0.2)	1 (0.2)	2 (0.2)
Ferumoxytol	0	1 (0.2)	1 (0.1)
MULTIVITAMINS WITH MINERALS	7 (1.7)	1 (0.2)	8 (1.0)
Iron;minerals nos;vitamins nos	2 (0.5)	0	2 (0.2)
Minerals nos;vitamins nos	2 (0.5)	0	2 (0.2)
Ascorbic acid;betacarotene;biotin;calcium;chromium;colecalciferol;copper;folic acid;iodine;iron;lycopene;magnesium;manganese;nicotinamide;pantothenic acid;phosphorus;phytomenadione;potassium;pyridoxine hydrochloride;retinol;riboflavin;selenium;vitamin b1 nos;vitamin b12 nos;vitamin e nos;xantofyl;zinc	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Ascorbic acid;colecalciferol;cyanocobalamin;folic acid;nicotinamide;pyridoxine hydrochloride;retinol;riboflavin;sodium ascorbate;sodium fluoride;thiamine mononitrate;tocopheryl acetate	1 (0.2)	0	1 (0.1)
Folic acid;minerals nos;vitamins nos	1 (0.2)	0	1 (0.1)
Ascorbic acid;calcium pantothenate;chromium picolinate;colecalciferol;copper sulfate;folic acid;magnesium oxide;manganese sulfate monohydrate;nicotinamide;potassium iodide;pyridoxine hydrochloride;retinol acetate;riboflavin;selenium oxide;silicon dioxide;sodium borate;sodium molybdate;thiamine mononitrate;tocopheryl acetate;zinc sulfate	0	1 (0.2)	1 (0.1)
OTHER ANXIOLYTICS	7 (1.7)	9 (2.2)	16 (2.0)
Escitalopram oxalate	2 (0.5)	1 (0.2)	3 (0.4)
Paroxetine	2 (0.5)	1 (0.2)	3 (0.4)
Amitriptyline	1 (0.2)	2 (0.5)	3 (0.4)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Escitalopram	1 (0.2)	0	1 (0.1)
Paroxetine hydrochloride	1 (0.2)	1 (0.2)	2 (0.2)
Pregabalin	0	3 (0.7)	3 (0.4)
Propranolol	0	1 (0.2)	1 (0.1)
Sertraline hydrochloride	0	1 (0.2)	1 (0.1)
OTHER COUGH SUPPRESSANTS	7 (1.7)	3 (0.7)	10 (1.2)
Benzonatate	4 (1.0)	2 (0.5)	6 (0.7)
Benproperine phosphate	1 (0.2)	0	1 (0.1)
Glycyrrhiza glabra extract;papaver somniferum powder	1 (0.2)	0	1 (0.1)
Levodropropizine	1 (0.2)	0	1 (0.1)
Cloperastine hydrochloride	0	1 (0.2)	1 (0.1)
PAPAVERINE AND DERIVATIVES	7 (1.7)	12 (3.0)	19 (2.3)
Drotaverine hydrochloride	6 (1.5)	7 (1.7)	13 (1.6)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Drotaverine	2 (0.5)	5 (1.2)	7 (0.9)
Papaverine hydrochloride	1 (0.2)	1 (0.2)	2 (0.2)
SOMATOSTATIN AND ANALOGUES	7 (1.7)	7 (1.7)	14 (1.7)
Octreotide acetate	4 (1.0)	6 (1.5)	10 (1.2)
Octreotide	2 (0.5)	0	2 (0.2)
Somatostatin	1 (0.2)	1 (0.2)	2 (0.2)
SYNTHETIC ANTICHOLINERGICS, ESTERS WITH TERTIARY AMINO GROUP	7 (1.7)	7 (1.7)	14 (1.7)
Trimebutine	3 (0.7)	0	3 (0.4)
Trimebutine maleate	2 (0.5)	3 (0.7)	5 (0.6)
Dicycloverine	1 (0.2)	1 (0.2)	2 (0.2)
Pargeverine	1 (0.2)	1 (0.2)	2 (0.2)
Dicycloverine hydrochloride	0	2 (0.5)	2 (0.2)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
VARIOUS ALIMENTARY TRACT AND METABOLISM PRODUCTS	7 (1.7)	3 (0.7)	10 (1.2)
Ubidecarenone	4 (1.0)	0	4 (0.5)
Thioctic acid tromethamine	2 (0.5)	0	2 (0.2)
Thioctic acid	1 (0.2)	2 (0.5)	3 (0.4)
Zinc acetate	1 (0.2)	1 (0.2)	2 (0.2)
ACE INHIBITORS AND DIURETICS	6 (1.5)	1 (0.2)	7 (0.9)
Hydrochlorothiazide;lisinopril	2 (0.5)	0	2 (0.2)
Enalapril maleate;hydrochlorothiazide	1 (0.2)	0	1 (0.1)
Hydrochlorothiazide;zofenopril calcium	1 (0.2)	0	1 (0.1)
Indapamide;perindopril	1 (0.2)	0	1 (0.1)
Indapamide;perindopril arginine	1 (0.2)	0	1 (0.1)
Indapamide;perindopril erbumine	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
ANESTHETICS FOR TOPICAL USE	6 (1.5)	1 (0.2)	7 (0.9)
Lidocaine	2 (0.5)	1 (0.2)	3 (0.4)
Allantoin;diphenhydramine hydrochloride;menthol;o-cymen-5y-ol;panthenol;prednisolone valeroacetate	1 (0.2)	0	1 (0.1)
Benzocaine	1 (0.2)	0	1 (0.1)
Benzocaine;chlorphenamine maleate	1 (0.2)	0	1 (0.1)
Cinchocaine hydrochloride;diphenhydramine;zinc oxide	1 (0.2)	0	1 (0.1)
Lidocaine;prilocaine	1 (0.2)	0	1 (0.1)
CARBAMIDE PRODUCTS	6 (1.5)	5 (1.2)	11 (1.4)
Urea	6 (1.5)	5 (1.2)	11 (1.4)
COMBINATIONS OF VITAMINS	6 (1.5)	5 (1.2)	11 (1.4)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Ergocalciferol;phytomenadione;retinol palmitate;vitamin e nos	5 (1.2)	2 (0.5)	7 (0.9)
Ascorbic acid;cyanocobalamin;folic acid;nicotinamide	1 (0.2)	1 (0.2)	2 (0.2)
Colecalciferol;folic acid	0	1 (0.2)	1 (0.1)
Prosultiamine;riboflavin	0	1 (0.2)	1 (0.1)
DIPHENYLMETHANE DERIVATIVES	6 (1.5)	7 (1.7)	13 (1.6)
Hydroxyzine	5 (1.2)	4 (1.0)	9 (1.1)
Hydroxyzine hydrochloride	2 (0.5)	3 (0.7)	5 (0.6)
HERBAL ANTIANEMIC PREPARATIONS	6 (1.5)	6 (1.5)	12 (1.5)
Astragalus mongholicus root;cibotium barometz rhizome;eclipta prostrata herb;fallopia multiflora root tuber;ligustrum lucidum fruit;morus alba fruit;paeonia lactiflora root	6 (1.5)	5 (1.2)	11 (1.4)
Animal feces nos;bombyx mori	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Herbal antianemic preparations	0	1 (0.2)	1 (0.1)
MEDICAL GASES	6 (1.5)	2 (0.5)	8 (1.0)
Oxygen	6 (1.5)	2 (0.5)	8 (1.0)
MELATONIN RECEPTOR AGONISTS	6 (1.5)	4 (1.0)	10 (1.2)
Melatonin	5 (1.2)	2 (0.5)	7 (0.9)
Ramelteon	1 (0.2)	2 (0.5)	3 (0.4)
ORAL REHYDRATION SALT FORMULATIONS	6 (1.5)	5 (1.2)	11 (1.4)
Glucose;potassium chloride;sodium chloride;sodium citrate	3 (0.7)	1 (0.2)	4 (0.5)
Glucose;potassium chloride;sodium bicarbonate;sodium chloride	2 (0.5)	3 (0.7)	5 (0.6)
Carbohydrates nos;electrolytes nos	1 (0.2)	1 (0.2)	2 (0.2)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Glucose;potassium chloride;sodium chloride;sodium citrate acid	1 (0.2)	0	1 (0.1)
Glucose;potassium chloride;sodium bicarbonate	0	1 (0.2)	1 (0.1)
OTHER ANTIBACTERIALS	6 (1.5)	7 (1.7)	13 (1.6)
Fosfomycin	2 (0.5)	1 (0.2)	3 (0.4)
Linezolid	2 (0.5)	1 (0.2)	3 (0.4)
Fosfomycin trometamol	1 (0.2)	4 (1.0)	5 (0.6)
Other antibacterials	1 (0.2)	0	1 (0.1)
Rifampicin	0	1 (0.2)	1 (0.1)
OTHER LIPID MODIFYING AGENTS	6 (1.5)	6 (1.5)	12 (1.5)
Ezetimibe	4 (1.0)	3 (0.7)	7 (0.9)
Eicosapentaenoic acid ethyl ester	1 (0.2)	1 (0.2)	2 (0.2)
Omega-3-acid ethyl ester	1 (0.2)	0	1 (0.1)
Eicosapentaenoic acid	0	1 (0.2)	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Omega-3 triglycerides	0	1 (0.2)	1 (0.1)
OTHER OPHTHALMOLOGICALS	6 (1.5)	12 (3.0)	18 (2.2)
Hyaluronate sodium	4 (1.0)	2 (0.5)	6 (0.7)
Pirenoxine sodium	2 (0.5)	0	2 (0.2)
Hypromellose	1 (0.2)	2 (0.5)	3 (0.4)
Macrogol 400;propylene glycol	1 (0.2)	0	1 (0.1)
Retinol palmitate	1 (0.2)	0	1 (0.1)
Ascorbic acid;cupric oxide;dl-alpha tocopheryl acetate;xantofyl;zeaxanthin;zinc oxide	0	1 (0.2)	1 (0.1)
Boric acid;potassium chloride;sodium bicarbonate;sodium chloride;sodium phosphate	0	1 (0.2)	1 (0.1)
Calcium chloride dihydrate;glucose;glutathione;magnesium chloride;potassium chloride;sodium bicarbonate;sodium chloride;sodium phosphate	0	1 (0.2)	1 (0.1)
Carbomer	0	1 (0.2)	1 (0.1)
Cyanocobalamin	0	1 (0.2)	1 (0.1)
Other ophthalmologicals	0	2 (0.5)	2 (0.2)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Pirenoxine	0	1 (0.2)	1 (0.1)
Rebamipide	0	1 (0.2)	1 (0.1)
SALICYLIC ACID AND DERIVATIVES	6 (1.5)	8 (2.0)	14 (1.7)
Acetylsalicylate lysine	4 (1.0)	3 (0.7)	7 (0.9)
Acetylsalicylic acid	1 (0.2)	5 (1.2)	6 (0.7)
Calcium bromide;cinchocaine hydrochloride;salicylate sodium	1 (0.2)	0	1 (0.1)
ALPHA GLUCOSIDASE INHIBITORS	5 (1.2)	2 (0.5)	7 (0.9)
Acarbose	3 (0.7)	1 (0.2)	4 (0.5)
Miglitol	1 (0.2)	0	1 (0.1)
Voglibose	1 (0.2)	1 (0.2)	2 (0.2)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
BELLADONNA ALKALOIDS, TERTIARY AMINES	5 (1.2)	4 (1.0)	9 (1.1)
Raceanisodamine hydrochloride	3 (0.7)	1 (0.2)	4 (0.5)
Atropine sulfate	2 (0.5)	1 (0.2)	3 (0.4)
Anisodamine hydrobromide	1 (0.2)	1 (0.2)	2 (0.2)
Anisodamine	0	1 (0.2)	1 (0.1)
Hyoscyamine	0	1 (0.2)	1 (0.1)
BENZOTHIAZEPINE DERIVATIVES	5 (1.2)	4 (1.0)	9 (1.1)
Diltiazem hydrochloride	3 (0.7)	2 (0.5)	5 (0.6)
Diltiazem	2 (0.5)	2 (0.5)	4 (0.5)
HERBAL EXPECTORANTS AND EMOLLIENTS	5 (1.2)	2 (0.5)	7 (0.9)
Coptis spp. rhizome;hedera helix leaf	3 (0.7)	0	3 (0.4)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Adenophora spp. root;citrus maxima peel;eriobotrya japonica leaf;fritillaria cirrhosa bulb;glycyrrhiza uralensis root;honey;menthol;pinellia ternata rhizome;platycodon grandiflorus root;polygala spp. root;poria cocos sclerotium;prunus armeniaca seed;schisandra chinensis fruit;trichosanthes spp. seed;tussilago farfara flower bud;zingiber officinale fresh rhizome	1 (0.2)	0	1 (0.1)
Thymus spp.	1 (0.2)	0	1 (0.1)
Arctium lappa fruit;cicada slough;ephedra spp. herb;eriobotrya japonica leaf;perilla frutescens fruit;perilla frutescens leaf;peucedanum praeruptorum root;pheretima spp.;schisandra chinensis fruit	0	1 (0.2)	1 (0.1)
Glycyrrhiza glabra	0	1 (0.2)	1 (0.1)
INSULINS AND ANALOGUES FOR INJECTION, INTERMEDIATE-ACTING	5 (1.2)	5 (1.2)	10 (1.2)
Insulin human injection, isophane	3 (0.7)	3 (0.7)	6 (0.7)
Isophane insulin	2 (0.5)	1 (0.2)	3 (0.4)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Insulin isophane porcine	1 (0.2)	1 (0.2)	2 (0.2)
NITROFURAN DERIVATIVES	5 (1.2)	5 (1.2)	10 (1.2)
Nitrofurantoin	3 (0.7)	3 (0.7)	6 (0.7)
Furazidin	2 (0.5)	2 (0.5)	4 (0.5)
OTHER CARDIAC PREPARATIONS	5 (1.2)	5 (1.2)	10 (1.2)
Trimetazidine hydrochloride	2 (0.5)	1 (0.2)	3 (0.4)
Adenosine triphosphate, disodium salt	1 (0.2)	3 (0.7)	4 (0.5)
Ivabradine hydrobromide	1 (0.2)	0	1 (0.1)
Ubidecarenone	1 (0.2)	1 (0.2)	2 (0.2)
OTHER DERMATOLOGICALS	5 (1.2)	7 (1.7)	12 (1.5)
Guaiazulene	2 (0.5)	3 (0.7)	5 (0.6)
Magnesium sulfate	1 (0.2)	1 (0.2)	2 (0.2)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Other dermatologicals	1 (0.2)	1 (0.2)	2 (0.2)
Sodium bicarbonate	1 (0.2)	0	1 (0.1)
Ananas comosus;copper;oenothera biennis oil;omega-3 fatty acids;retinol;vitamin e nos	0	1 (0.2)	1 (0.1)
Minoxidil	0	2 (0.5)	2 (0.2)
OTHER DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	5 (1.2)	2 (0.5)	7 (0.9)
Denosumab	5 (1.2)	2 (0.5)	7 (0.9)
OTHER HYPNOTICS AND SEDATIVES	5 (1.2)	6 (1.5)	11 (1.4)
Diphenhydramine	1 (0.2)	0	1 (0.1)
Diphenhydramine hydrochloride	1 (0.2)	2 (0.5)	3 (0.4)
Doxylamine succinate	1 (0.2)	1 (0.2)	2 (0.2)
Hyoscine	1 (0.2)	0	1 (0.1)
Suvorexant	1 (0.2)	1 (0.2)	2 (0.2)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Coptis spp. rhizome;gardenia jasminoides fruit;phellodendron spp. bark;scutellaria baicalensis root	0	1 (0.2)	1 (0.1)
Lemborexant	0	1 (0.2)	1 (0.1)
Podosordaria nigripes mycelium	0	1 (0.2)	1 (0.1)
OTHER NERVOUS SYSTEM DRUGS	5 (1.2)	3 (0.7)	8 (1.0)
Gabapentin	2 (0.5)	1 (0.2)	3 (0.4)
Mecobalamin	2 (0.5)	1 (0.2)	3 (0.4)
Gabapentin enacarbil	1 (0.2)	0	1 (0.1)
Methylethylpiridinol succinate	0	1 (0.2)	1 (0.1)
PERIPHERAL OPIOID RECEPTOR ANTAGONISTS	5 (1.2)	6 (1.5)	11 (1.4)
Naldemedine tosilate	5 (1.2)	5 (1.2)	10 (1.2)
Naloxegol oxalate	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
SODIUM	5 (1.2)	8 (2.0)	13 (1.6)
Sodium chloride	5 (1.2)	8 (2.0)	13 (1.6)
VITAMIN B1, PLAIN	5 (1.2)	14 (3.5)	19 (2.3)
Thiamine hydrochloride	5 (1.2)	8 (2.0)	13 (1.6)
Thiamine	0	5 (1.2)	5 (0.6)
Vitamin b nos	0	3 (0.7)	3 (0.4)
VITAMINS, OTHER COMBINATIONS	5 (1.2)	4 (1.0)	9 (1.1)
Ascorbic acid;biotin;chromium;colecalciferol;copper;folic acid;iodine;magnesium;manganese;nicotinamide;pantothenic acid;pyridoxine hydrochloride;retinol;riboflavin;selenium;vitamin b1 nos;vitamin b12 nos;vitamin e nos;vitis vinifera seed;zinc	1 (0.2)	0	1 (0.1)
Ascorbic acid;carbazochrome;lysozyme chloride;tocopherol calcium succinate	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Cod-liver oil;vitamins nos	1 (0.2)	0	1 (0.1)
Dl-alpha tocopheryl acetate;omega-3 fatty acids	1 (0.2)	0	1 (0.1)
Vitamins, other combinations	1 (0.2)	1 (0.2)	2 (0.2)
Ascorbic acid;malpighia glabra	0	1 (0.2)	1 (0.1)
Minerals nos;vitamins nos	0	1 (0.2)	1 (0.1)
Minerals nos;vitamins nos;xantofyl	0	1 (0.2)	1 (0.1)
ACE INHIBITORS AND CALCIUM CHANNEL BLOCKERS	4 (1.0)	3 (0.7)	7 (0.9)
Amlodipine besilate;benazepril hydrochloride	1 (0.2)	1 (0.2)	2 (0.2)
Amlodipine besilate;lisinopril dihydrate	1 (0.2)	0	1 (0.1)
Amlodipine besilate;perindopril tosilate	1 (0.2)	0	1 (0.1)
Amlodipine besilate;ramipril	1 (0.2)	1 (0.2)	2 (0.2)
Amlodipine besilate;perindopril arginine	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
ACTH	4 (1.0)	2 (0.5)	6 (0.7)
Tetracosactide acetate	4 (1.0)	2 (0.5)	6 (0.7)
ANTACIDS WITH SODIUM BICARBONATE	4 (1.0)	5 (1.2)	9 (1.1)
Sodium alginate;sodium bicarbonate	2 (0.5)	0	2 (0.2)
Sodium bicarbonate	2 (0.5)	4 (1.0)	6 (0.7)
Algeldrate;alginic acid;magnesium trisilicate;sodium bicarbonate	0	1 (0.2)	1 (0.1)
BETA BLOCKING AGENTS, NON-SELECTIVE	4 (1.0)	4 (1.0)	8 (1.0)
Propranolol	4 (1.0)	2 (0.5)	6 (0.7)
Propranolol hydrochloride	0	2 (0.5)	2 (0.2)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
BULK-FORMING LAXATIVES	4 (1.0)	6 (1.5)	10 (1.2)
Plantago ovata	2 (0.5)	1 (0.2)	3 (0.4)
Polycarbophil calcium	2 (0.5)	4 (1.0)	6 (0.7)
Plantago ovata husk	1 (0.2)	0	1 (0.1)
Psyllium hydrophilic mucilloid	0	1 (0.2)	1 (0.1)
CALCITONIN PREPARATIONS	4 (1.0)	0	4 (0.5)
Calcitonin	3 (0.7)	0	3 (0.4)
Elcatonin	1 (0.2)	0	1 (0.1)
CORTICOSTEROIDS, PLAIN	4 (1.0)	7 (1.7)	11 (1.4)
Betamethasone sodium phosphate	1 (0.2)	0	1 (0.1)
Desonide	1 (0.2)	0	1 (0.1)
Fluorometholone	1 (0.2)	2 (0.5)	3 (0.4)
Prednisolone	1 (0.2)	0	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Betamethasone phosphate	0	1 (0.2)	1 (0.1)
Dexamethasone sodium phosphate	0	1 (0.2)	1 (0.1)
Prednisolone acetate	0	3 (0.7)	3 (0.4)
Prednisone	0	1 (0.2)	1 (0.1)
Triamcinolone	0	1 (0.2)	1 (0.1)
Triamcinolone acetonide	0	1 (0.2)	1 (0.1)
ENZYMES	4 (1.0)	1 (0.2)	5 (0.6)
Bromelains;cysteine	2 (0.5)	0	2 (0.2)
Alteplase	1 (0.2)	0	1 (0.1)
Serrapeptase	1 (0.2)	0	1 (0.1)
Kallidinogenase	0	1 (0.2)	1 (0.1)
FIBRATES	4 (1.0)	4 (1.0)	8 (1.0)
Fenofibrate	4 (1.0)	4 (1.0)	8 (1.0)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
HERBAL CARMINATIVES	4 (1.0)	1 (0.2)	5 (0.6)
Mentha x piperita oil	3 (0.7)	0	3 (0.4)
Curcuma longa	1 (0.2)	0	1 (0.1)
Aucklandia costus root;citrus aurantium submature fruit;magnolia officinalis bark;rheum spp. root with rhizome	0	1 (0.2)	1 (0.1)
IMIDAZOLINE RECEPTOR AGONISTS	4 (1.0)	2 (0.5)	6 (0.7)
Clonidine	2 (0.5)	1 (0.2)	3 (0.4)
Moxonidine	2 (0.5)	1 (0.2)	3 (0.4)
Clonidine hydrochloride	1 (0.2)	0	1 (0.1)
LINCOSAMIDES	4 (1.0)	2 (0.5)	6 (0.7)
Clindamycin	4 (1.0)	2 (0.5)	6 (0.7)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
LIPID MODIFYING AGENTS IN COMBINATION WITH OTHER DRUGS	4 (1.0)	2 (0.5)	6 (0.7)
Amlodipine besilate;atorvastatin calcium	2 (0.5)	1 (0.2)	3 (0.4)
Acetylsalicylic acid;atorvastatin	1 (0.2)	0	1 (0.1)
Rosuvastatin calcium;telmisartan	1 (0.2)	0	1 (0.1)
Pitavastatin calcium;valsartan	0	1 (0.2)	1 (0.1)
MULTIVITAMINS, OTHER COMBINATIONS	4 (1.0)	3 (0.7)	7 (0.9)
Ascorbic acid;betacarotene;biotin;calcium carbonate;calcium pantothenate;calcium phosphate dibasic;chromic chloride;colecalciferol;copper sulfate;cyanocobalamin;ferrous fumarate;folic acid;magnesium oxide;manganese sulfate;nicotinamide;phytomenadione;potassium iodide;pyridoxine hydrochloride;retinol acetate;riboflavin;sodium molybdate;sodium selenate;thiamine mononitrate;tocopheryl acetate;zinc oxide	3 (0.7)	2 (0.5)	5 (0.6)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Multivitamins, other combinations	1 (0.2)	0	1 (0.1)
Ascorbic acid;biotin;calcium chloride;calcium pantothenate;choline chloride;chromic chloride;citric acid;colecalciferol;copper gluconate;cyanocobalamin;ferrous lactate;folic acid;glucose;magnesium chloride;maltodextrin;manganese sulfate;nicotinamide;phytomenadione;polysorbate 80;potassium chloride;potassium iodide;proteins nos;pyridoxine hydrochloride;retinol palmitate;riboflavin;sodium chloride;sodium fluoride;sodium molybdate;sodium selenite;sucrose;thiamine hydrochloride;tocopheryl acetate;zinc sulfate	0	1 (0.2)	1 (0.1)
NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS	4 (1.0)	4 (1.0)	8 (1.0)
Aciclovir	2 (0.5)	2 (0.5)	4 (0.5)
Famciclovir	2 (0.5)	2 (0.5)	4 (0.5)
Ganciclovir sodium	0	1 (0.2)	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
ORGANIC NITRATES	4 (1.0)	8 (2.0)	12 (1.5)
Glyceryl trinitrate	3 (0.7)	3 (0.7)	6 (0.7)
Isosorbide mononitrate	2 (0.5)	3 (0.7)	5 (0.6)
Isosorbide dinitrate	0	2 (0.5)	2 (0.2)
OTHER ANTIALLERGICS	4 (1.0)	3 (0.7)	7 (0.9)
Olopatadine hydrochloride	3 (0.7)	0	3 (0.4)
Olopatadine	1 (0.2)	0	1 (0.1)
Cromoglicate sodium	0	2 (0.5)	2 (0.2)
Epinastine hydrochloride	0	1 (0.2)	1 (0.1)
OTHER ANTIINFLAMMATORY AND ANTIRHEUMATIC AGENTS, NON-STEROIDS	4 (1.0)	3 (0.7)	7 (0.9)
Glucosamine	2 (0.5)	0	2 (0.2)
Benzydamine hydrochloride	1 (0.2)	0	1 (0.1)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Nimesulide	1 (0.2)	1 (0.2)	2 (0.2)
Diacerein;glucosamine	0	1 (0.2)	1 (0.1)
Morniflumate	0	1 (0.2)	1 (0.1)
OTHER ANTITHROMBOTIC AGENTS	4 (1.0)	5 (1.2)	9 (1.1)
Fondaparinux sodium	2 (0.5)	3 (0.7)	5 (0.6)
Coumarin	1 (0.2)	0	1 (0.1)
Thrombomodulin alfa	1 (0.2)	1 (0.2)	2 (0.2)
Fondaparinux	0	2 (0.5)	2 (0.2)
OTHER GENERAL ANESTHETICS	4 (1.0)	3 (0.7)	7 (0.9)
Propofol	4 (1.0)	3 (0.7)	7 (0.9)
Ketamine	0	1 (0.2)	1 (0.1)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER I.V. SOLUTION ADDITIVES	4 (1.0)	2 (0.5)	6 (0.7)
Biotin;cyanocobalamin;folic acid;glycine;nicotinamide;pantothenate sodium;pyridoxine hydrochloride;riboflavin sodium phosphate;sodium ascorbate;thiamine mononitrate	4 (1.0)	2 (0.5)	6 (0.7)
OTHER THERAPEUTIC PRODUCTS	4 (1.0)	2 (0.5)	6 (0.7)
Polypeptide	2 (0.5)	0	2 (0.2)
Ethylene glycol	1 (0.2)	0	1 (0.1)
Inosine	1 (0.2)	0	1 (0.1)
Armillarisin a	0	1 (0.2)	1 (0.1)
Nucleosides	0	1 (0.2)	1 (0.1)
PHENOTHIAZINES WITH ALIPHATIC SIDE-CHAIN	4 (1.0)	6 (1.5)	10 (1.2)
Chlorpromazine	4 (1.0)	3 (0.7)	7 (0.9)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Levomepromazine	0	3 (0.7)	3 (0.4)
PROSTAGLANDIN ANALOGUES	4 (1.0)	7 (1.7)	11 (1.4)
Latanoprost	4 (1.0)	2 (0.5)	6 (0.7)
Bimatoprost	0	2 (0.5)	2 (0.2)
Tafluprost	0	1 (0.2)	1 (0.1)
Travoprost	0	2 (0.5)	2 (0.2)
SULFONAMIDES	4 (1.0)	2 (0.5)	6 (0.7)
Sulfadiazine silver	3 (0.7)	2 (0.5)	5 (0.6)
Sulfamethoxazole	1 (0.2)	0	1 (0.1)
SULFUR-CONTAINING IMIDAZOLE DERIVATIVES	4 (1.0)	1 (0.2)	5 (0.6)
Thiamazole	3 (0.7)	1 (0.2)	4 (0.5)
Carbimazole	1 (0.2)	0	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
TONICS	4 (1.0)	0	4 (0.5)
Citrulline malate	2 (0.5)	0	2 (0.2)
Arginine hydrochloride;hydroxocobalamin hydrochloride;levoglutamide;serine phosphate;threonine phosphate;tryptophan, l-	1 (0.2)	0	1 (0.1)
Dietary supplement	1 (0.2)	0	1 (0.1)
ALUMINIUM COMPOUNDS	3 (0.7)	1 (0.2)	4 (0.5)
Aldioxa;aluminium magnesium silicate	3 (0.7)	0	3 (0.4)
Aluminium hydroxide	0	1 (0.2)	1 (0.1)
AMINO ACIDS, INCL. COMBINATIONS WITH POLYPEPTIDES	3 (0.7)	2 (0.5)	5 (0.6)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
(rs)-3 methyl-2-oxovalerianic acid calcium;(rs)-3-methyl-2-oxobutyric acid calcium;calcium (rs)-4-methyl-2-oxovalerianat;calcium 2-oxo-3-phenylpropionat;desmeninol calcium;histidine;lysine acetate;threonine;tryptophan, l-;tyrosine	2 (0.5)	0	2 (0.2)
Arginine;beta-hydroxy-beta-methylbutyrate;levoglutamide	1 (0.2)	0	1 (0.1)
Cysteine hydrochloride;histidine;isoleucine;leucine;lysine acetate;methionine;phenylalanine;threonine;tryptophan, l-;valine	0	1 (0.2)	1 (0.1)
Isoleucine;leucine;valine	0	1 (0.2)	1 (0.1)
ANTACIDS WITH ANTIFLATULENTS	3 (0.7)	1 (0.2)	4 (0.5)
Aluminium hydroxide;dicycloverine hydrochloride;magnesium oxide;simeticone	1 (0.2)	0	1 (0.1)
Aluminium hydroxide;magnesium hydroxide;simeticone	1 (0.2)	1 (0.2)	2 (0.2)
Benzocaine;magaldrate;simeticone	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
ANTACIDS, OTHER COMBINATIONS	3 (0.7)	5 (1.2)	8 (1.0)
Aluminium hydroxide gel;magnesium hydroxide;oxetacaine	2 (0.5)	3 (0.7)	5 (0.6)
Aluminium hydroxide;magnesium hydroxide;oxetacaine	2 (0.5)	1 (0.2)	3 (0.4)
Bismuth aluminate;foeniculum vulgare;glycyrrhiza glabra;magnesium carbonate;rhamnus frangula;sodium bicarbonate	0	1 (0.2)	1 (0.1)
ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.	3 (0.7)	0	3 (0.4)
Diphenhydramine	3 (0.7)	0	3 (0.4)
ANTIVIRALS	3 (0.7)	1 (0.2)	4 (0.5)
Aciclovir	2 (0.5)	1 (0.2)	3 (0.4)
Docosanol	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
BETA BLOCKING AGENTS AND CALCIUM CHANNEL BLOCKERS	3 (0.7)	0	3 (0.4)
Amlodipine besilate;atenolol	1 (0.2)	0	1 (0.1)
Amlodipine;atenolol	1 (0.2)	0	1 (0.1)
Felodipine;metoprolol succinate	1 (0.2)	0	1 (0.1)
CALCIUM COMPOUNDS	3 (0.7)	1 (0.2)	4 (0.5)
Calcium carbonate	3 (0.7)	1 (0.2)	4 (0.5)
CORTICOSTEROIDS, WEAK, OTHER COMBINATIONS	3 (0.7)	0	3 (0.4)
Crotamiton;hydrocortisone	2 (0.5)	0	2 (0.2)
Hydrocortisone;urea	1 (0.2)	0	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
DRUGS USED IN ERECTILE DYSFUNCTION	3 (0.7)	1 (0.2)	4 (0.5)
Sildenafil	2 (0.5)	0	2 (0.2)
Tadalafil	1 (0.2)	1 (0.2)	2 (0.2)
ENZYME AND ACID PREPARATIONS, COMBINATIONS	3 (0.7)	5 (1.2)	8 (1.0)
Alpha-amylase swine pancreas;amylase;cellulase;pancrelipase;papain;pepsin;trypsin;ursodeoxycholic acid	3 (0.7)	5 (1.2)	8 (1.0)
EXPECTORANTS	3 (0.7)	0	3 (0.4)
Guaifenesin	2 (0.5)	0	2 (0.2)
Ammonium chloride;glycyrrhiza glabra	1 (0.2)	0	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
HEPARINS OR HEPARINOIDS FOR TOPICAL USE	3 (0.7)	3 (0.7)	6 (0.7)
Benzyl nicotinate;heparin sodium	1 (0.2)	2 (0.5)	3 (0.4)
Heparin sodium	1 (0.2)	0	1 (0.1)
Mucopolysaccharide polysulfuric acid ester	1 (0.2)	1 (0.2)	2 (0.2)
HERBAL ANTISPASMODIC AGENTS, OTHER	3 (0.7)	1 (0.2)	4 (0.5)
Corydalis yanhusuo tuber;ipomoea nil seed	3 (0.7)	1 (0.2)	4 (0.5)
LEUKOTRIENE RECEPTOR ANTAGONISTS	3 (0.7)	3 (0.7)	6 (0.7)
Montelukast	1 (0.2)	2 (0.5)	3 (0.4)
Montelukast sodium	1 (0.2)	1 (0.2)	2 (0.2)
Pranlukast	1 (0.2)	0	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
LOCAL ANESTHETICS	3 (0.7)	5 (1.2)	8 (1.0)
Benzocaine;bismuth subgallate;diphenhydramine hydrochloride;zinc oxide	1 (0.2)	0	1 (0.1)
Benzocaine;bismuth subnitrate;chlorhexidine diacetate;enoxolone;lidocaine;phenylephrine hydrochloride	1 (0.2)	0	1 (0.1)
Cinchocaine hydrochloride;policresulen	1 (0.2)	0	1 (0.1)
Proxymetacaine hydrochloride	1 (0.2)	2 (0.5)	3 (0.4)
Bupivacaine hydrochloride	0	1 (0.2)	1 (0.1)
Lidocaine	0	1 (0.2)	1 (0.1)
Lidocaine hydrochloride	0	1 (0.2)	1 (0.1)
Oxybuprocaine hydrochloride	0	1 (0.2)	1 (0.1)
Pramocaine hydrochloride	0	1 (0.2)	1 (0.1)
OTHER ANTIDIARRHEALS	3 (0.7)	4 (1.0)	7 (0.9)
Racecadotril	2 (0.5)	1 (0.2)	3 (0.4)
Berberine hydrochloride	1 (0.2)	1 (0.2)	2 (0.2)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Other antidiarrheals	0	1 (0.2)	1 (0.1)
Saccharomyces cerevisiae	0	1 (0.2)	1 (0.1)
OTHER ANTIPSYCHOTICS	3 (0.7)	1 (0.2)	4 (0.5)
Risperidone	3 (0.7)	1 (0.2)	4 (0.5)
Perospirone hydrochloride	0	1 (0.2)	1 (0.1)
OTHER CARDIAC STIMULANTS	3 (0.7)	1 (0.2)	4 (0.5)
Atropine sulfate	2 (0.5)	1 (0.2)	3 (0.4)
Atropine	1 (0.2)	0	1 (0.1)
OTHER HEMATOLOGICAL AGENTS	3 (0.7)	1 (0.2)	4 (0.5)
Haemagglutinin	2 (0.5)	0	2 (0.2)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Cinnamomum cassia stem bark;ferrous sulfate;juglans regia seed;panax quinquefolius root;sea horse;ziziphus jujuba fruit	1 (0.2)	1 (0.2)	2 (0.2)
OTHER MINERAL PRODUCTS	3 (0.7)	3 (0.7)	6 (0.7)
Magnesium aspartate;potassium aspartate	1 (0.2)	0	1 (0.1)
Molybdenum	1 (0.2)	0	1 (0.1)
Sodium phosphate monobasic (anhydrous)	1 (0.2)	1 (0.2)	2 (0.2)
Calcium phosphate monobasic;magnesium glycerophosphate;phosphoric acid;sodium phosphate dibasic	0	1 (0.2)	1 (0.1)
Potassium phosphate monobasic;sodium phosphate	0	1 (0.2)	1 (0.1)
Sodium phosphate	0	1 (0.2)	1 (0.1)
OTHER VASODILATORS USED IN CARDIAC DISEASES	3 (0.7)	4 (1.0)	7 (0.9)
Nicorandil	2 (0.5)	3 (0.7)	5 (0.6)
Molsidomine	1 (0.2)	1 (0.2)	2 (0.2)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
POLYMYXINS	3 (0.7)	0	3 (0.4)
Colistin	3 (0.7)	0	3 (0.4)
PREPARATIONS INCREASING URIC ACID EXCRETION	3 (0.7)	0	3 (0.4)
Benzbromarone	3 (0.7)	0	3 (0.4)
PREPARATIONS WITH NO EFFECT ON URIC ACID METABOLISM	3 (0.7)	7 (1.7)	10 (1.2)
Colchicine	3 (0.7)	7 (1.7)	10 (1.2)
PROTEIN SUPPLEMENTS	3 (0.7)	1 (0.2)	4 (0.5)
Carbohydrates nos;lipids nos;minerals nos;proteins nos	1 (0.2)	0	1 (0.1)
Protein hydrolysate	1 (0.2)	0	1 (0.1)
Proteins nos	1 (0.2)	1 (0.2)	2 (0.2)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
SYMPATHOMIMETICS	3 (0.7)	5 (1.2)	8 (1.0)
Pseudoephedrine hydrochloride;triprolidine hydrochloride	2 (0.5)	3 (0.7)	5 (0.6)
Ebastine;pseudoephedrine hydrochloride	1 (0.2)	0	1 (0.1)
Pseudoephedrine hydrochloride	1 (0.2)	0	1 (0.1)
Chlorphenamine maleate;pseudoephedrine hydrochloride	0	2 (0.5)	2 (0.2)
ZINC PRODUCTS	3 (0.7)	5 (1.2)	8 (1.0)
Boric acid;zinc oxide	1 (0.2)	0	1 (0.1)
Dimeticone;zinc oxide	1 (0.2)	0	1 (0.1)
Zinc oxide	1 (0.2)	4 (1.0)	5 (0.6)
Benzyl alcohol;benzyl benzoate;benzyl cinnamate;wool fat;zinc oxide	0	1 (0.2)	1 (0.1)
ALPHA- AND BETA-ADRENORECEPTOR AGONISTS	2 (0.5)	0	2 (0.2)
Ephedrine sulfate	1 (0.2)	0	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Epinephrine hydrochloride	1 (0.2)	0	1 (0.1)
ANTIHISTAMINES FOR TOPICAL USE	2 (0.5)	6 (1.5)	8 (1.0)
Diphenhydramine	2 (0.5)	3 (0.7)	5 (0.6)
Calamine;camphor;diphenhydramine hydrochloride	0	1 (0.2)	1 (0.1)
Calamine;diphenhydramine hydrochloride	0	2 (0.5)	2 (0.2)
Diphenhydramine hydrochloride	0	1 (0.2)	1 (0.1)
ANTIVERTIGO PREPARATIONS	2 (0.5)	4 (1.0)	6 (0.7)
Acetylleucine	1 (0.2)	0	1 (0.1)
Meclozine	1 (0.2)	1 (0.2)	2 (0.2)
Betahistine hydrochloride	0	1 (0.2)	1 (0.1)
Betahistine mesilate	0	2 (0.5)	2 (0.2)
Flunarizine dihydrochloride	0	1 (0.2)	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
AVERMECTINES	2 (0.5)	1 (0.2)	3 (0.4)
Ivermectin	2 (0.5)	1 (0.2)	3 (0.4)
BENZOMORPHAN DERIVATIVES	2 (0.5)	3 (0.7)	5 (0.6)
Pentazocine	2 (0.5)	2 (0.5)	4 (0.5)
Naloxone hydrochloride;pentazocine hydrochloride	0	1 (0.2)	1 (0.1)
BETA BLOCKING AGENTS	2 (0.5)	6 (1.5)	8 (1.0)
Dorzolamide hydrochloride;timolol maleate	1 (0.2)	2 (0.5)	3 (0.4)
Timolol	1 (0.2)	1 (0.2)	2 (0.2)
Betaxolol	0	1 (0.2)	1 (0.1)
Brimonidine;timolol	0	1 (0.2)	1 (0.1)
Carteolol hydrochloride;latanoprost	0	1 (0.2)	1 (0.1)

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BIOFLAVONOIDS	2 (0.5)	6 (1.5)	8 (1.0)
Diosmin	1 (0.2)	1 (0.2)	2 (0.2)
Diosmin;hesperidin	1 (0.2)	3 (0.7)	4 (0.5)
Ascorbic acid;hesperidin methyl chalcone;ruscus aculeatus	0	2 (0.5)	2 (0.2)
CARBAMIC ACID ESTERS	2 (0.5)	0	2 (0.2)
Methocarbamol	2 (0.5)	0	2 (0.2)
CARBOHYDRATES	2 (0.5)	0	2 (0.2)
Dextrin	1 (0.2)	0	1 (0.1)
Glucose	1 (0.2)	0	1 (0.1)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
CORTICOSTEROIDS FOR SYSTEMIC USE, COMBINATIONS	2 (0.5)	2 (0.5)	4 (0.5)
Betamethasone;dexchlorpheniramine maleate	1 (0.2)	0	1 (0.1)
Methylprednisolone;succinate sodium	1 (0.2)	0	1 (0.1)
Betamethasone;chlorphenamine maleate	0	1 (0.2)	1 (0.1)
Lidocaine hydrochloride;methylprednisolone acetate	0	1 (0.2)	1 (0.1)
COUGH AND COLD PREPARATIONS	2 (0.5)	0	2 (0.2)
Cough and cold preparations	1 (0.2)	0	1 (0.1)
Phyllanthus emblica	1 (0.2)	0	1 (0.1)
DETOXIFYING AGENTS FOR ANTINEOPLASTIC TREATMENT	2 (0.5)	0	2 (0.2)
Calcium folinate	1 (0.2)	0	1 (0.1)
Calcium levofolinate pentahydrate	1 (0.2)	0	1 (0.1)

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DIPHENYLPROPYLAMINE DERIVATIVES	2 (0.5)	2 (0.5)	4 (0.5)
Methadone hydrochloride	2 (0.5)	0	2 (0.2)
Methadone	1 (0.2)	2 (0.5)	3 (0.4)
GINKGO REMEDIES	2 (0.5)	3 (0.7)	5 (0.6)
Ginkgo biloba extract	1 (0.2)	1 (0.2)	2 (0.2)
Ginkgo biloba leaf extract	1 (0.2)	2 (0.5)	3 (0.4)
HERBAL ANTIINFLAMMATORY AND ANTIRHEUMATIC REMEDIES	2 (0.5)	3 (0.7)	5 (0.6)
Ardisia japonica herb;cow bezoar;indometacin;panax notoginseng root;pearl;urena lobata	2 (0.5)	0	2 (0.2)
Arnica montana	0	1 (0.2)	1 (0.1)
Glycyrrhiza spp. root;paeonia lactiflora root	0	2 (0.5)	2 (0.2)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
HERBAL ANTIVERTIGO PREPARATIONS	2 (0.5)	1 (0.2)	3 (0.4)
Ginkgo biloba extract	2 (0.5)	0	2 (0.2)
Atractylodes spp. rhizome;cinnamomum cassia bark;glycyrrhiza spp. root;poria cocos sclerotium	0	1 (0.2)	1 (0.1)
HIGH-CEILING DIURETICS AND POTASSIUM-SPARING AGENTS	2 (0.5)	1 (0.2)	3 (0.4)
Furosemide;spironolactone	2 (0.5)	1 (0.2)	3 (0.4)
HYDRAZINOPHTHALAZINE DERIVATIVES	2 (0.5)	4 (1.0)	6 (0.7)
Hydralazine	2 (0.5)	4 (1.0)	6 (0.7)
HYPNOTICS AND SEDATIVES	2 (0.5)	2 (0.5)	4 (0.5)
Promethazine	1 (0.2)	1 (0.2)	2 (0.2)
Promethazine hydrochloride	1 (0.2)	1 (0.2)	2 (0.2)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
INSULINS AND ANALOGUES FOR INJECTION, INTERMEDIATE- OR LONG-ACTING COMBINED WITH FAST-ACTING	2 (0.5)	3 (0.7)	5 (0.6)
Insulin aspart;insulin aspart protamine (crystalline)	2 (0.5)	2 (0.5)	4 (0.5)
Insulin aspart;insulin degludec	0	1 (0.2)	1 (0.1)
MAGNESIUM COMPOUNDS	2 (0.5)	1 (0.2)	3 (0.4)
Magnesium oxide	2 (0.5)	1 (0.2)	3 (0.4)
NON-SELECTIVE MONOAMINE REUPTAKE INHIBITORS	2 (0.5)	2 (0.5)	4 (0.5)
Amitriptyline	1 (0.2)	0	1 (0.1)
Clomipramine	1 (0.2)	0	1 (0.1)
Nortriptyline	0	2 (0.5)	2 (0.2)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER AGENTS FOR TREATMENT OF HEMORRHOIDS AND ANAL FISSURES FOR TOPICAL USE	2 (0.5)	2 (0.5)	4 (0.5)
Paraffin, liquid;petrolatum;phenylephrine hydrochloride	1 (0.2)	0	1 (0.1)
Phenylephrine	1 (0.2)	0	1 (0.1)
Chondrus crispus;titanium dioxide;zinc oxide	0	2 (0.5)	2 (0.2)
OTHER ANTIEPILEPTICS	2 (0.5)	6 (1.5)	8 (1.0)
Gabapentin	1 (0.2)	0	1 (0.1)
Levetiracetam	1 (0.2)	5 (1.2)	6 (0.7)
Magnesium sulfate	0	1 (0.2)	1 (0.1)
Sultiame	0	1 (0.2)	1 (0.1)
OTHER ANTIMIGRAINE PREPARATIONS	2 (0.5)	0	2 (0.2)
Botulinum toxin type a	1 (0.2)	0	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Topiramate	1 (0.2)	0	1 (0.1)
Verapamil	1 (0.2)	0	1 (0.1)
OTHER ANTISEPTICS AND DISINFECTANTS	2 (0.5)	1 (0.2)	3 (0.4)
Lactic acid;sodium pidolate	2 (0.5)	0	2 (0.2)
Potassium permanganate	0	1 (0.2)	1 (0.1)
OTHER ANTIVIRALS	2 (0.5)	3 (0.7)	5 (0.6)
Lysozyme chloride	1 (0.2)	0	1 (0.1)
Thymalfasin	1 (0.2)	0	1 (0.1)
Favipiravir	0	1 (0.2)	1 (0.1)
Inosine pranobex	0	1 (0.2)	1 (0.1)
Umifenovir	0	1 (0.2)	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	2 (0.5)	3 (0.7)	5 (0.6)
Repaglinide	2 (0.5)	1 (0.2)	3 (0.4)
Glycyrrhiza glabra;mentha pulegium;morus nigra;olea europaea;trigonella foenum-graecum	0	1 (0.2)	1 (0.1)
Mitiglinide	0	1 (0.2)	1 (0.1)
OTHER CARDIAC COMBINATION PRODUCTS	2 (0.5)	1 (0.2)	3 (0.4)
Aspartic acid;magnesium oxide;potassium hydroxide	1 (0.2)	0	1 (0.1)
Ginkgo biloba extract;ligustrazine	1 (0.2)	0	1 (0.1)
Amber (fossilized tree resin);codonopsis pilosula root;nardostachys jatamansi root with rhizome;panax notoginseng root;polygonatum sibiricum root	0	1 (0.2)	1 (0.1)
OTHER DRUGS FOR BILE THERAPY	2 (0.5)	4 (1.0)	6 (0.7)
Borneol;camphene;cineole;menthol;menthone;pinene	2 (0.5)	2 (0.5)	4 (0.5)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Borneol;camphene;cineole;menthol;menthone;olea europaea;pinene	0	1 (0.2)	1 (0.1)
Hymecromone	0	1 (0.2)	1 (0.1)
OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM	2 (0.5)	1 (0.2)	3 (0.4)
Hyaluronate sodium	2 (0.5)	1 (0.2)	3 (0.4)
OTHER IMMUNOSUPPRESSANTS	2 (0.5)	2 (0.5)	4 (0.5)
Azathioprine	1 (0.2)	1 (0.2)	2 (0.2)
Thalidomide	1 (0.2)	0	1 (0.1)
Hydroxychloroquine	0	1 (0.2)	1 (0.1)
OTHER NASAL PREPARATIONS	2 (0.5)	0	2 (0.2)
Ipratropium bromide	1 (0.2)	0	1 (0.1)
Sodium chloride	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER PERIPHERAL VASODILATORS	2 (0.5)	0	2 (0.2)
Ifenprodil tartrate	1 (0.2)	0	1 (0.1)
Naftidrofuryl oxalate	1 (0.2)	0	1 (0.1)
OXICAMS	2 (0.5)	3 (0.7)	5 (0.6)
Lornoxicam	1 (0.2)	0	1 (0.1)
Meloxicam	1 (0.2)	3 (0.7)	4 (0.5)
PARAMAGNETIC CONTRAST MEDIA	2 (0.5)	1 (0.2)	3 (0.4)
Gadoteridol	2 (0.5)	1 (0.2)	3 (0.4)
PHENYLALKYLAMINE DERIVATIVES	2 (0.5)	0	2 (0.2)
Verapamil hydrochloride	2 (0.5)	0	2 (0.2)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
PREPARATIONS WITH SALICYLIC ACID DERIVATIVES	2 (0.5)	3 (0.7)	5 (0.6)
Methyl salicylate	1 (0.2)	2 (0.5)	3 (0.4)
Trolamine salicylate	1 (0.2)	0	1 (0.1)
Menthol;methyl salicylate	0	1 (0.2)	1 (0.1)
SELECTIVE ESTROGEN RECEPTOR MODULATORS	2 (0.5)	1 (0.2)	3 (0.4)
Raloxifene hydrochloride	2 (0.5)	0	2 (0.2)
Bazedoxifene acetate	0	1 (0.2)	1 (0.1)
SELECTIVE IMMUNOSUPPRESSANTS	2 (0.5)	1 (0.2)	3 (0.4)
Mycophenolate mofetil	1 (0.2)	1 (0.2)	2 (0.2)
Mycophenolic acid	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
SELECTIVE SEROTONIN (5HT1) AGONISTS	2 (0.5)	0	2 (0.2)
Sumatriptan	2 (0.5)	0	2 (0.2)
VASOPRESSIN AND ANALOGUES	2 (0.5)	2 (0.5)	4 (0.5)
Terlipressin acetate	1 (0.2)	0	1 (0.1)
Vasopressin	1 (0.2)	1 (0.2)	2 (0.2)
Terlipressin	0	1 (0.2)	1 (0.1)
VITAMIN B-COMPLEX WITH VITAMIN C	2 (0.5)	1 (0.2)	3 (0.4)
Ascorbic acid;calcium pantothenate;cyanocobalamin;nicotinamide;pyridoxine hydrochloride;riboflavin;thiamine hydrochloride	1 (0.2)	1 (0.2)	2 (0.2)
Ascorbic acid;vitamin b complex	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
3-OXOANDROSTEN (4) DERIVATIVES	1 (0.2)	0	1 (0.1)
Testosterone cipionate	1 (0.2)	0	1 (0.1)
ADRENERGICS AND OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	1 (0.2)	0	1 (0.1)
Ipratropium bromide monohydrate;salbutamol sulfate	1 (0.2)	0	1 (0.1)
Ipratropium bromide;salbutamol sulfate	1 (0.2)	0	1 (0.1)
AGENTS FOR DERMATITIS, EXCLUDING CORTICOSTEROIDS	1 (0.2)	1 (0.2)	2 (0.2)
Tacrolimus	1 (0.2)	0	1 (0.1)
Pimecrolimus	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
ALL OTHER THERAPEUTIC PRODUCTS	1 (0.2)	0	1 (0.1)
All other therapeutic products	1 (0.2)	0	1 (0.1)
ALLERGEN EXTRACTS	1 (0.2)	0	1 (0.1)
Allergens, insect venom	1 (0.2)	0	1 (0.1)
ANESTHETICS, LOCAL	1 (0.2)	0	1 (0.1)
Ambroxol hydrochloride	1 (0.2)	0	1 (0.1)
ANTIARRHYTHMICS, CLASS IC	1 (0.2)	1 (0.2)	2 (0.2)
Propafenone hydrochloride	1 (0.2)	1 (0.2)	2 (0.2)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
ANTIINFECTIVES FOR TREATMENT OF ACNE	1 (0.2)	0	1 (0.1)
Clindamycin phosphate	1 (0.2)	0	1 (0.1)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	1 (0.2)	0	1 (0.1)
Talniflumate	1 (0.2)	0	1 (0.1)
ANTIINFLAMMATORY/ANTIRHEUMATIC AGENTS IN COMBINATION WITH CORTICOSTEROIDS	1 (0.2)	0	1 (0.1)
Betamethasone;cyanocobalamin;diclofenac potassium	1 (0.2)	0	1 (0.1)
ANTISEPTICS	1 (0.2)	3 (0.7)	4 (0.5)
Sodium bicarbonate;sodium gualenate	1 (0.2)	0	1 (0.1)
Benzethonium chloride	0	1 (0.2)	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Ethanol;eucalyptus spp. oil;menthol;methyl salicylate;pinus spp. oil;salicylate sodium;thymol	0	1 (0.2)	1 (0.1)
Sodium bicarbonate;sodium gualenate hydrate	0	1 (0.2)	1 (0.1)
ASCORBIC ACID (VITAMIN C), COMBINATIONS	1 (0.2)	1 (0.2)	2 (0.2)
Ascorbic acid;calcium pantothenate	1 (0.2)	1 (0.2)	2 (0.2)
BARBITURATES AND DERIVATIVES	1 (0.2)	1 (0.2)	2 (0.2)
Phenobarbital sodium	1 (0.2)	0	1 (0.1)
Primidone	0	1 (0.2)	1 (0.1)
BARBITURATES, COMBINATIONS	1 (0.2)	0	1 (0.1)
Barbiturates, combinations	1 (0.2)	0	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
BENZAMIDES	1 (0.2)	1 (0.2)	2 (0.2)
Levosulpiride	1 (0.2)	0	1 (0.1)
Amisulpride	0	1 (0.2)	1 (0.1)
BENZIMIDAZOLE DERIVATIVES	1 (0.2)	0	1 (0.1)
Albendazole	1 (0.2)	0	1 (0.1)
BETA BLOCKING AGENTS, SELECTIVE, AND THIAZIDES	1 (0.2)	1 (0.2)	2 (0.2)
Bisoprolol fumarate;hydrochlorothiazide	1 (0.2)	1 (0.2)	2 (0.2)
BETA-LACTAMASE SENSITIVE PENICILLINS	1 (0.2)	1 (0.2)	2 (0.2)
Benzylpenicillin sodium	1 (0.2)	0	1 (0.1)
Benzylpenicillin	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
BILE ACID SEQUESTRANTS	1 (0.2)	1 (0.2)	2 (0.2)
Colestyramine	1 (0.2)	1 (0.2)	2 (0.2)
CARBONIC ANHYDRASE INHIBITORS	1 (0.2)	1 (0.2)	2 (0.2)
Brinzolamide	1 (0.2)	1 (0.2)	2 (0.2)
CHOLINE ESTERS	1 (0.2)	0	1 (0.1)
Bethanechol chloride	1 (0.2)	0	1 (0.1)
COMBINATIONS OF VARIOUS LIPID MODIFYING AGENTS	1 (0.2)	3 (0.7)	4 (0.5)
Fenofibrate;pravastatin sodium	1 (0.2)	1 (0.2)	2 (0.2)
Atorvastatin calcium;ezetimibe	0	1 (0.2)	1 (0.1)
Ezetimibe;rosuvastatin calcium	0	1 (0.2)	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION	1 (0.2)	1 (0.2)	2 (0.2)
Chloramphenicol;dexamethasone sodium phosphate	1 (0.2)	0	1 (0.1)
Dexamethasone;neomycin sulfate;polymyxin b sulfate	0	1 (0.2)	1 (0.1)
DIGITALIS GLYCOSIDES	1 (0.2)	4 (1.0)	5 (0.6)
Digoxin	1 (0.2)	4 (1.0)	5 (0.6)
DIRECT THROMBIN INHIBITORS	1 (0.2)	1 (0.2)	2 (0.2)
Dabigatran etexilate mesilate	1 (0.2)	1 (0.2)	2 (0.2)
DIURETICS	1 (0.2)	0	1 (0.1)
Acetazolamide sodium	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
DRUGS FOR CONSTIPATION	1 (0.2)	1 (0.2)	2 (0.2)
Fraxinus ornus;mannitol	1 (0.2)	0	1 (0.1)
Cistanche spp. stem;citrus aurantium submature fruit;fallopia multiflora root tuber;honey	0	1 (0.2)	1 (0.1)
DRUGS USED IN NICOTINE DEPENDENCE	1 (0.2)	1 (0.2)	2 (0.2)
Nicotine	1 (0.2)	1 (0.2)	2 (0.2)
ERGOT ALKALOIDS	1 (0.2)	0	1 (0.1)
Aminophenazone;caffeine;cyclizine hydrochloride;cyclobarbital;ergotamine tartrate;phenacetin	1 (0.2)	0	1 (0.1)
ESTERS OF AMINOBENZOIC ACID	1 (0.2)	2 (0.5)	3 (0.4)
Oxybuprocaine hydrochloride	1 (0.2)	0	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Procaine hydrochloride	0	2 (0.5)	2 (0.2)
GLUCAGON-LIKE PEPTIDE-1 (GLP-1) ANALOGUES	1 (0.2)	2 (0.5)	3 (0.4)
Liraglutide	1 (0.2)	1 (0.2)	2 (0.2)
Semaglutide	0	1 (0.2)	1 (0.1)
HERBAL ANTIVIRALS FOR SYSTEMIC USE	1 (0.2)	0	1 (0.1)
Calcium sulfate dihydrate;dryopteris crassirhizoma rhizome;ephedra spp. herb;forsythia suspensa;glycyrrhiza spp. root with rhizome;houttuynia cordata herb;isatis tinctoria root;lonicera japonica flower;menthol;pogostemon cablin herb;prunus spp. seed;rheum spp. root with rhizome;rhodiola crenulata root with rhizome	1 (0.2)	0	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
HERBAL CHOLAGOGUES AND CHOLERETICS	1 (0.2)	0	1 (0.1)
Artemisia capillaris flower;gardenia jasminoides fruit;rheum spp. rhizome	1 (0.2)	0	1 (0.1)
HERBAL DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY	1 (0.2)	0	1 (0.1)
Serenoa repens extract	1 (0.2)	0	1 (0.1)
HERBAL REMEDIES FOR TREATMENT OF PREMENSTRUAL SYNDROME OR DYSMENORRHOEA	1 (0.2)	0	1 (0.1)
Cinnamomum cassia bark;paeonia lactiflora root;paeonia x suffruticosa root bark;poria cocos sclerotium;prunus spp. seed	1 (0.2)	0	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
HERBAL TONICS, OTHER	1 (0.2)	1 (0.2)	2 (0.2)
Angelica sinensis root;astragalus mongholicus root;atractylodes macrocephala, rhizoma;bupleurum spp. root;cimicifuga spp. rhizome;citrus aurantium fruit peel;codonopsis pilosula root;glycyrrhiza spp. root with rhizome;zingiber officinale fresh rhizome;ziziphus jujuba fruit	1 (0.2)	0	1 (0.1)
Cuminum cyminum;cyperus scariosus;piper longum	0	1 (0.2)	1 (0.1)
HERBAL TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN CONTAINING OR CONSTITUTING ESSENTIAL OILS	1 (0.2)	0	1 (0.1)
Pinus spp. oil	1 (0.2)	0	1 (0.1)
HYDANTOIN DERIVATIVES	1 (0.2)	1 (0.2)	2 (0.2)
Phenytoin	1 (0.2)	1 (0.2)	2 (0.2)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
I.V. SOLUTION ADDITIVES	1 (0.2)	4 (1.0)	5 (0.6)
Biotin;cyanocobalamin;ergocalciferol;folic acid;glycine;nicotinamide;pantothenate sodium;phytomenadione;pyridoxine hydrochloride;retinol;riboflavin sodium phosphate;sodium ascorbate;thiamine mononitrate;vitamin e nos	1 (0.2)	0	1 (0.1)
Minerals nos	0	2 (0.5)	2 (0.2)
Selenious acid	0	2 (0.5)	2 (0.2)
IMIDAZOLINE RECEPTOR AGONISTS IN COMBINATION WITH DIURETICS	1 (0.2)	0	1 (0.1)
Chrysanthemum indicum;clonidine hydrochloride;concha margaritifera;hydrochlorothiazide;rutoside	1 (0.2)	0	1 (0.1)
IODINE PRODUCTS	1 (0.2)	0	1 (0.1)
Povidone-iodine	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
IRON IN COMBINATION WITH FOLIC ACID	1 (0.2)	0	1 (0.1)
Angelica sinensis;astragalus spp.;atractylodes macrocephala;ferrous sulfate;folic acid;yeast dried	1 (0.2)	0	1 (0.1)
LIVER THERAPY, LIPOTROPICS	1 (0.2)	0	1 (0.1)
Cysteine hydrochloride;glycyrrhizic acid, ammonium salt	1 (0.2)	0	1 (0.1)
LOCAL HEMOSTATICS	1 (0.2)	1 (0.2)	2 (0.2)
Bovine basic fibroblast growth factor	1 (0.2)	0	1 (0.1)
Epinephrine	0	1 (0.2)	1 (0.1)
MEDICATED DRESSINGS WITH ANTIINFECTIVES	1 (0.2)	0	1 (0.1)
Nitrofural	1 (0.2)	0	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
MORPHINAN DERIVATIVES	1 (0.2)	0	1 (0.1)
Butorphanol	1 (0.2)	0	1 (0.1)
MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS	1 (0.2)	0	1 (0.1)
Muscle relaxants, centrally acting agents	1 (0.2)	0	1 (0.1)
NATURAL AND SEMISYNTHETIC ESTROGENS, PLAIN	1 (0.2)	2 (0.5)	3 (0.4)
Estradiol	1 (0.2)	0	1 (0.1)
Estriol	0	1 (0.2)	1 (0.1)
Ethinylestradiol	0	1 (0.2)	1 (0.1)
NEURAMINIDASE INHIBITORS	1 (0.2)	1 (0.2)	2 (0.2)
Peramivir	1 (0.2)	0	1 (0.1)
Oseltamivir phosphate	0	1 (0.2)	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER AGENTS AGAINST LEISHMANIASIS AND TRYPANOSOMIASIS	1 (0.2)	0	1 (0.1)
Pentamidine isethionate	1 (0.2)	0	1 (0.1)
OTHER ANTI-DEMENTIA DRUGS	1 (0.2)	0	1 (0.1)
Nimodipine	1 (0.2)	0	1 (0.1)
OTHER ANTIFUNGALS FOR TOPICAL USE	1 (0.2)	1 (0.2)	2 (0.2)
Terbinafine hydrochloride	1 (0.2)	0	1 (0.1)
Amorolfine hydrochloride	0	1 (0.2)	1 (0.1)
OTHER ANTIINFECTIVES	1 (0.2)	1 (0.2)	2 (0.2)
Boric acid;sodium borate	1 (0.2)	0	1 (0.1)
Propamidine isetionate	0	1 (0.2)	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER ANTIINFLAMMATORY/ANTIRHEUMATIC AGENTS IN COMBINATION WITH OTHER DRUGS	1 (0.2)	0	1 (0.1)
Aceclofenac;paracetamol;serrapeptase	1 (0.2)	0	1 (0.1)
OTHER ANTIPSORIATICS FOR TOPICAL USE	1 (0.2)	0	1 (0.1)
Betamethasone dipropionate;calcipotriol	1 (0.2)	0	1 (0.1)
Calcipotriol	1 (0.2)	0	1 (0.1)
Maxacalcitol	1 (0.2)	0	1 (0.1)
OTHER CAPILLARY STABILIZING AGENTS	1 (0.2)	1 (0.2)	2 (0.2)
Escin sodium	1 (0.2)	1 (0.2)	2 (0.2)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER CEPHALOSPORINS AND PENEMS	1 (0.2)	0	1 (0.1)
Faropenem sodium	1 (0.2)	0	1 (0.1)
OTHER CHEMOTHERAPEUTICS	1 (0.2)	0	1 (0.1)
Metronidazole	1 (0.2)	0	1 (0.1)
OTHER CICATRIZANTS	1 (0.2)	1 (0.2)	2 (0.2)
Dexpanthenol	1 (0.2)	1 (0.2)	2 (0.2)
OTHER COLD PREPARATIONS	1 (0.2)	1 (0.2)	2 (0.2)
Menthol	1 (0.2)	0	1 (0.1)
Caffeine;chlorphenamine maleate;paracetamol;salicylamide	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER DERMATOLOGICAL PREPARATIONS	1 (0.2)	0	1 (0.1)
Other dermatological preparations	1 (0.2)	0	1 (0.1)
OTHER DIAGNOSTIC AGENTS	1 (0.2)	1 (0.2)	2 (0.2)
Indocyanine green	1 (0.2)	1 (0.2)	2 (0.2)
OTHER DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY	1 (0.2)	0	1 (0.1)
Other drugs used in benign prostatic hypertrophy	1 (0.2)	0	1 (0.1)
OTHER IMMUNOSTIMULANTS	1 (0.2)	1 (0.2)	2 (0.2)
Lentinan	1 (0.2)	0	1 (0.1)
Deoxyribonucleotide sodium	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER LOCAL ANESTHETICS	1 (0.2)	0	1 (0.1)
Dyclonine hydrochloride	1 (0.2)	0	1 (0.1)
OTHER NON-THERAPEUTIC AUXILIARY PRODUCTS	1 (0.2)	0	1 (0.1)
Medronic acid;stannous chloride	1 (0.2)	0	1 (0.1)
OTHER PLANT ALKALOIDS AND NATURAL PRODUCTS	1 (0.2)	0	1 (0.1)
Beta elemene;delta elemene;gamma elemene	1 (0.2)	0	1 (0.1)
OTHER POTASSIUM-SPARING AGENTS	1 (0.2)	0	1 (0.1)
Amiloride	1 (0.2)	0	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER PSYCHOSTIMULANTS AND NOOTROPICS	1 (0.2)	3 (0.7)	4 (0.5)
Citicoline sodium	1 (0.2)	0	1 (0.1)
Piracetam	0	2 (0.5)	2 (0.2)
Vinpocetine	0	1 (0.2)	1 (0.1)
OTHER TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	1 (0.2)	0	1 (0.1)
Mucopolysaccharide polysulfuric acid ester	1 (0.2)	0	1 (0.1)
OTHER UROLOGICALS	1 (0.2)	1 (0.2)	2 (0.2)
Piperazine ferulate	1 (0.2)	0	1 (0.1)
Sodium citrate acid	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
PARASYMPATHOMIMETICS	1 (0.2)	2 (0.5)	3 (0.4)
Pilocarpine	1 (0.2)	0	1 (0.1)
Carbachol	0	2 (0.5)	2 (0.2)
PARATHYROID HORMONES AND ANALOGUES	1 (0.2)	0	1 (0.1)
Teriparatide	1 (0.2)	0	1 (0.1)
PIPERIDINEDIONE DERIVATIVES	1 (0.2)	0	1 (0.1)
Piperidinedione derivatives	1 (0.2)	0	1 (0.1)
PNEUMOCOCCAL VACCINES	1 (0.2)	0	1 (0.1)
Pneumococcal vaccine	1 (0.2)	0	1 (0.1)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
PROTEOLYTIC ENZYMES	1 (0.2)	0	1 (0.1)
Bromelains	1 (0.2)	0	1 (0.1)
PURINE DERIVATIVES	1 (0.2)	2 (0.5)	3 (0.4)
Pentoxifylline	1 (0.2)	2 (0.5)	3 (0.4)
SOLVENTS AND DILUTING AGENTS, INCL. IRRIGATING SOLUTIONS	1 (0.2)	0	1 (0.1)
Sodium chloride	1 (0.2)	0	1 (0.1)
SUBSTITUTED ETHYLENE DIAMINES	1 (0.2)	1 (0.2)	2 (0.2)
Chloropyramine hydrochloride	1 (0.2)	0	1 (0.1)
Chloropyramine	0	1 (0.2)	1 (0.1)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
SYMPATHOMIMETICS IN GLAUCOMA THERAPY	1 (0.2)	3 (0.7)	4 (0.5)
Brimonidine tartrate	1 (0.2)	3 (0.7)	4 (0.5)
SYMPATHOMIMETICS USED AS DECONGESTANTS	1 (0.2)	1 (0.2)	2 (0.2)
Phenylephrine	1 (0.2)	0	1 (0.1)
Glycerol;naphazoline hydrochloride;zinc sulfate	0	1 (0.2)	1 (0.1)
SYNTHETIC ANTICHOLINERGIC AGENTS IN COMBINATION WITH ANALGESICS	1 (0.2)	0	1 (0.1)
Ciclonium bromide;codeine phosphate;paracetamol	1 (0.2)	0	1 (0.1)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
SYNTHETIC ANTICHOLINERGIC AGENTS IN COMBINATION WITH PSYCHOLEPTICS	1 (0.2)	0	1 (0.1)
Medazepam;trimebutine maleate	1 (0.2)	0	1 (0.1)
SYNTHETIC ANTICHOLINERGICS, QUATERNARY AMMONIUM COMPOUNDS	1 (0.2)	2 (0.5)	3 (0.4)
Glycopyrronium bromide	1 (0.2)	0	1 (0.1)
Glycopyrronium	0	1 (0.2)	1 (0.1)
Timepidium	0	1 (0.2)	1 (0.1)
UROLOGICALS	1 (0.2)	0	1 (0.1)
Urologicals	1 (0.2)	0	1 (0.1)

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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
VASOPRESSIN ANTAGONISTS	1 (0.2)	0	1 (0.1)
Tolvaptan	1 (0.2)	0	1 (0.1)
VITAMIN K ANTAGONISTS	1 (0.2)	6 (1.5)	7 (0.9)
Warfarin	1 (0.2)	4 (1.0)	5 (0.6)
Acenocoumarol	0	1 (0.2)	1 (0.1)
Warfarin sodium	0	1 (0.2)	1 (0.1)
VITAMINS WITH MINERALS	1 (0.2)	4 (1.0)	5 (0.6)
Ascorbic acid;betacarotene;cupric oxide;tocopheryl acetate;zinc oxide	1 (0.2)	0	1 (0.1)
Ascorbic acid;biotin;cyanocobalamin;ferrous fumarate;folic acid;fursultiamine hydrochloride;nicotinamide;pyridoxine hydrochloride;riboflavin tetrabutyrate;selenium;tocopheryl acetate;zinc oxide	0	2 (0.5)	2 (0.2)

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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
Ascorbic acid;calcium pantothenate;cyanocobalamin;folic acid;nicotinamide;pyridoxine hydrochloride;riboflavin;thiamine mononitrate;vitamin e nos;zinc sulfate	0	1 (0.2)	1 (0.1)
Magnesium oxide;pyridoxine hydrochloride	0	1 (0.2)	1 (0.1)
Magnesium;pyridoxine hydrochloride	0	1 (0.2)	1 (0.1)
XANTHINES	1 (0.2)	3 (0.7)	4 (0.5)
Ambroxol acefyllinate	1 (0.2)	0	1 (0.1)
Aminophylline	0	1 (0.2)	1 (0.1)
Theobromine	0	1 (0.2)	1 (0.1)
Theophylline	0	1 (0.2)	1 (0.1)
ACE INHIBITORS, OTHER COMBINATIONS	0	4 (1.0)	4 (0.5)
Amlodipine besilate;indapamide;perindopril arginine	0	4 (1.0)	4 (0.5)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
AGENTS FOR TREATMENT OF HEMORRHOIDS AND ANAL FISSURES FOR TOPICAL USE	0	1 (0.2)	1 (0.1)
Agents for treatment of hemorrhoids and anal fissures for topical use	0	1 (0.2)	1 (0.1)
AMINO ACIDS/CARBOHYDRATES/MINERALS/VITAMINS, COMBINATIONS	0	1 (0.2)	1 (0.1)
Amino acids nos;carbohydrates nos;fats nos;minerals nos;vitamins nos	0	1 (0.2)	1 (0.1)
AMINOQUINOLINES	0	1 (0.2)	1 (0.1)
Hydroxychloroquine	0	1 (0.2)	1 (0.1)
ANALGESICS	0	1 (0.2)	1 (0.1)
Analgesics	0	1 (0.2)	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
WHODrug Global B3-format March 2021.
Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
ANTIARRHYTHMICS, CLASS III	0	1 (0.2)	1 (0.1)
Dofetilide	0	1 (0.2)	1 (0.1)
ANTICHOLINESTERASES	0	1 (0.2)	1 (0.1)
Donepezil hydrochloride	0	1 (0.2)	1 (0.1)
ANTIHEMORRHAGICS	0	1 (0.2)	1 (0.1)
Aconitum kusnezoffii root;herbal nos	0	1 (0.2)	1 (0.1)
ANTIHISTAMINES FOR SYSTEMIC USE	0	1 (0.2)	1 (0.1)
Antihistamines	0	1 (0.2)	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
ANTIINFECTIVES	0	3 (0.7)	3 (0.4)
Acetic acid	0	1 (0.2)	1 (0.1)
Boric acid	0	1 (0.2)	1 (0.1)
Ciprofloxacin hydrochloride	0	1 (0.2)	1 (0.1)
Ofloxacin	0	1 (0.2)	1 (0.1)
ANTIINFLAMMATORY AGENTS, NON-STEROIDS	0	4 (1.0)	4 (0.5)
Bromfenac sodium	0	4 (1.0)	4 (0.5)
ANTINEOVASCULARISATION AGENTS	0	2 (0.5)	2 (0.2)
Aflibercept	0	1 (0.2)	1 (0.1)
Bevacizumab	0	1 (0.2)	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
ARTEMISININ AND DERIVATIVES, PLAIN	0	1 (0.2)	1 (0.1)
Artesunate	0	1 (0.2)	1 (0.1)
BARIUM SULFATE CONTAINING X-RAY CONTRAST MEDIA	0	1 (0.2)	1 (0.1)
Barium sulfate	0	1 (0.2)	1 (0.1)
BETA-LACTAMASE RESISTANT PENICILLINS	0	1 (0.2)	1 (0.1)
Oxacillin	0	1 (0.2)	1 (0.1)
BILE THERAPY	0	2 (0.5)	2 (0.2)
Timonacic	0	2 (0.5)	2 (0.2)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
BISMUTH PREPARATIONS	0	1 (0.2)	1 (0.1)
Bismuth subsalicylate	0	1 (0.2)	1 (0.1)
CARBOXAMIDE DERIVATIVES	0	1 (0.2)	1 (0.1)
Carbamazepine	0	1 (0.2)	1 (0.1)
CENTRALLY ACTING SYMPATHOMIMETICS	0	2 (0.5)	2 (0.2)
Amfetamine	0	1 (0.2)	1 (0.1)
Amfetamine aspartate;amfetamine sulfate;dexamfetamine saccharate;dexamfetamine sulfate	0	1 (0.2)	1 (0.1)
CORTICOSTEROIDS, WEAK, COMBINATIONS WITH ANTIBIOTICS	0	2 (0.5)	2 (0.2)
Hydrocortisone;natamycin;neomycin	0	1 (0.2)	1 (0.1)
Hydrocortisone;oxytetracycline hydrochloride	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Durva = Durvalumab. Gem = Gemcitabine. Cis = Cisplatin.

Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
DOPA AND DOPA DERIVATIVES	0	1 (0.2)	1 (0.1)
Benserazide hydrochloride;levodopa	0	1 (0.2)	1 (0.1)
DOPAMINE AGONISTS	0	2 (0.5)	2 (0.2)
Pramipexole dihydrochloride monohydrate	0	1 (0.2)	1 (0.1)
Ropinirole	0	1 (0.2)	1 (0.1)
DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	0	3 (0.7)	3 (0.4)
Teprenone	0	3 (0.7)	3 (0.4)
ESTROGENS, COMBINATIONS WITH OTHER DRUGS	0	1 (0.2)	1 (0.1)
Estriol;lactobacillus acidophilus	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
ETHERS, CHEMICALLY CLOSE TO ANTIHISTAMINES	0	1 (0.2)	1 (0.1)
Acetylsalicylic acid;caffeine;orphenadrine citrate	0	1 (0.2)	1 (0.1)
FATTY ACID DERIVATIVES	0	2 (0.5)	2 (0.2)
Valproate sodium	0	2 (0.5)	2 (0.2)
FENAMATES	0	1 (0.2)	1 (0.1)
Mefenamic acid	0	1 (0.2)	1 (0.1)
HERBAL ANTIVARICOSE REMEDIES	0	1 (0.2)	1 (0.1)
Aesculus hippocastanum extract	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
HERBAL APPETITE STIMULANTS	0	1 (0.2)	1 (0.1)
Atractylodes lancea rhizome;citrus aurantium peel;glycyrrhiza spp. root;panax ginseng root;pinellia ternata tuber;poria cocos sclerotium;zingiber officinale rhizome;ziziphus jujuba fruit	0	1 (0.2)	1 (0.1)
HERBAL COUGH AND COLD REMEDIES, OTHER	0	2 (0.5)	2 (0.2)
Calcium sulfate dihydrate;chrysanthemum x morifolium flower;ephedra spp. stem;glycyrrhiza spp. root with rhizome;lonicera japonica flower bud;mentha canadensis herb;morus alba leaf;perilla frutescens leaf;peucedanum praeruptorum root;platycodon grandiflorus root;prunus spp. seed;scutellaria baicalensis root	0	1 (0.2)	1 (0.1)
Herbal cough and cold remedies, other	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
HERBAL DIAPHORETICS AND OTHER HERBAL COUGH AND COLD REMEDIES	0	1 (0.2)	1 (0.1)
Angelica dahurica root;bupleurum spp. root;corydalis bungeana herb;mentha canadensis herb;perilla frutescens leaf;phragmites communis rhizome;platycodon grandiflorus root;prunus spp. seed;pueraria lobata root;saposhnikovia divaricata root;schizonepeta tenuifolia spike	0	1 (0.2)	1 (0.1)
HERBAL DIURETICS, OTHER	0	2 (0.5)	2 (0.2)
Alisma orientale tuber;atractylodes lancea rhizome;cinnamomum cassia bark;polyporus umbellatus sclerotium;poria cocos sclerotium	0	1 (0.2)	1 (0.1)
Alisma orientale tuber;atractylodes spp. rhizome;cinnamomum cassia bark;polyporus umbellatus sclerotium;poria cocos sclerotium	0	1 (0.2)	1 (0.1)
Lespedeza bicolor	0	1 (0.2)	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
HERBAL EMOLLIENTS AND PROTECTIVES, OTHER	0	1 (0.2)	1 (0.1)
Avena sativa fluid extract	0	1 (0.2)	1 (0.1)
HERBAL PREPARATIONS FOR TREATMENT OF WOUNDS AND ULCERS, OTHER	0	1 (0.2)	1 (0.1)
Centipede;forsythia suspensa;lonicera japonica flower;phellodendron chinense;taraxacum mongolicum herb	0	1 (0.2)	1 (0.1)
HERBAL REMEDIES FOR TREATMENT OF PEPTIC ULCER, OTHER	0	2 (0.5)	2 (0.2)
Artemisia argyi leaf	0	1 (0.2)	1 (0.1)
Periplaneta americana	0	1 (0.2)	1 (0.1)
HYDRAZIDES	0	1 (0.2)	1 (0.1)
Isoniazid	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
IMMUNOGLOBULINS, NORMAL HUMAN	0	2 (0.5)	2 (0.2)
Immunoglobulin g human	0	1 (0.2)	1 (0.1)
Immunoglobulin human normal	0	1 (0.2)	1 (0.1)
INTERFERONS	0	1 (0.2)	1 (0.1)
Interferon alfa-2b	0	1 (0.2)	1 (0.1)
LOW-CEILING DIURETICS AND POTASSIUM-SPARING AGENTS	0	1 (0.2)	1 (0.1)
Amiloride hydrochloride;hydrochlorothiazide	0	1 (0.2)	1 (0.1)
MONOBACTAMS	0	1 (0.2)	1 (0.1)
Aztreonam	0	1 (0.2)	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
NASAL PREPARATIONS	0	1 (0.2)	1 (0.1)
Nasal preparations	0	1 (0.2)	1 (0.1)
OTHER ANTI-PARATHYROID AGENTS	0	1 (0.2)	1 (0.1)
Cinacalcet	0	1 (0.2)	1 (0.1)
OTHER ANTIMYCOTICS FOR SYSTEMIC USE	0	3 (0.7)	3 (0.4)
Caspofungin	0	1 (0.2)	1 (0.1)
Micafungin sodium	0	2 (0.5)	2 (0.2)
OTHER DRUGS FOR TREATMENT OF TUBERCULOSIS	0	2 (0.5)	2 (0.2)
Ethambutol	0	1 (0.2)	1 (0.1)
Ethambutol dihydrochloride	0	1 (0.2)	1 (0.1)
Pyrazinamide	0	1 (0.2)	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
OTHER MUSCLE RELAXANTS, PERIPHERALLY ACTING AGENTS	0	1 (0.2)	1 (0.1)
Botulinum toxin type a	0	1 (0.2)	1 (0.1)
OTHER PARASYMPATHOMIMETICS	0	2 (0.5)	2 (0.2)
Choline alfoscerate	0	2 (0.5)	2 (0.2)
OTHER SURGICAL AIDS	0	2 (0.5)	2 (0.2)
Calcium chloride dihydrate;magnesium chloride hexahydrate;potassium chloride;sodium acetate trihydrate;sodium chloride;sodium citrate dihydrate	0	2 (0.5)	2 (0.2)
PROGESTOGENS	0	2 (0.5)	2 (0.2)
Drospirenone	0	1 (0.2)	1 (0.1)
Medroxyprogesterone	0	1 (0.2)	1 (0.1)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
RETINOIDS FOR TOPICAL USE IN ACNE	0	1 (0.2)	1 (0.1)
Tretinoin	0	1 (0.2)	1 (0.1)
SYMPATHOMIMETICS EXCL. ANTIGLAUCOMA PREPARATIONS	0	1 (0.2)	1 (0.1)
Ephedrine hydrochloride	0	1 (0.2)	1 (0.1)
TESTOSTERONE-5-ALPHA REDUCTASE INHIBITORS	0	4 (1.0)	4 (0.5)
Dutasteride	0	1 (0.2)	1 (0.1)
Finasteride	0	3 (0.7)	3 (0.4)
THIAZOLIDINEDIONES	0	7 (1.7)	7 (0.9)
Lobeglitazone sulfate	0	2 (0.5)	2 (0.2)
Pioglitazone	0	3 (0.7)	3 (0.4)
Pioglitazone hydrochloride	0	2 (0.5)	2 (0.2)

A subject can have one or more generic term reported under a given ATC text. Number (%) of subjects are sorted by descending frequency of ATC followed by generic term in the Durva + Gem + Cis group. Medications starting prior to randomization but still ongoing are also included.
N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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Table 4.15 TOPAZ: All allowed concomitant medications during study
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ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
TRIMETHOPRIM AND DERIVATIVES	0	1 (0.2)	1 (0.1)
Trimethoprim	0	1 (0.2)	1 (0.1)
VISCOELASTIC SUBSTANCES	0	2 (0.5)	2 (0.2)
Hyaluronate sodium	0	2 (0.5)	2 (0.2)
VITAMIN B-COMPLEX WITH MINERALS	0	1 (0.2)	1 (0.1)
Minerals nos;vitamin b nos	0	1 (0.2)	1 (0.1)
XANTHINES AND ADRENERGICS	0	1 (0.2)	1 (0.1)
Aminophylline;chlorphenamine maleate;methoxyphenamine hydrochloride;noscapine	0	1 (0.2)	1 (0.1)

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Table 4.15 TOPAZ: All allowed concomitant medications during study
Full Analysis Set, DCO 11AUG2021 and 14OCT2022 for China Patients

ATC Classification / Generic term	Number (%) of subjects Durva + Gem + Cis (N=405)	Placebo + Gem + Cis (N=405)	Total (N=810)
ZINC	0	1 (0.2)	1 (0.1)
Zinc	0	1 (0.2)	1 (0.1)

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N = Number of subjects in treatment group. ATC = Anatomical Therapeutic Chemical. WHO = World Health Organization.
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