Dossier zur Nutzenbewertung gemäß § 35a SGB V

Toripalimab (LOQTORZI®)

LEO Pharma GmbH

Separater Anhang 4-G zu Modul 4 B

Erstlinienbehandlung erwachsener Patienten mit inoperablem fortgeschrittenem, rezidivierendem oder metastasiertem Plattenepithelkarzinom des Ösophagus

Stand: 14.01.2026

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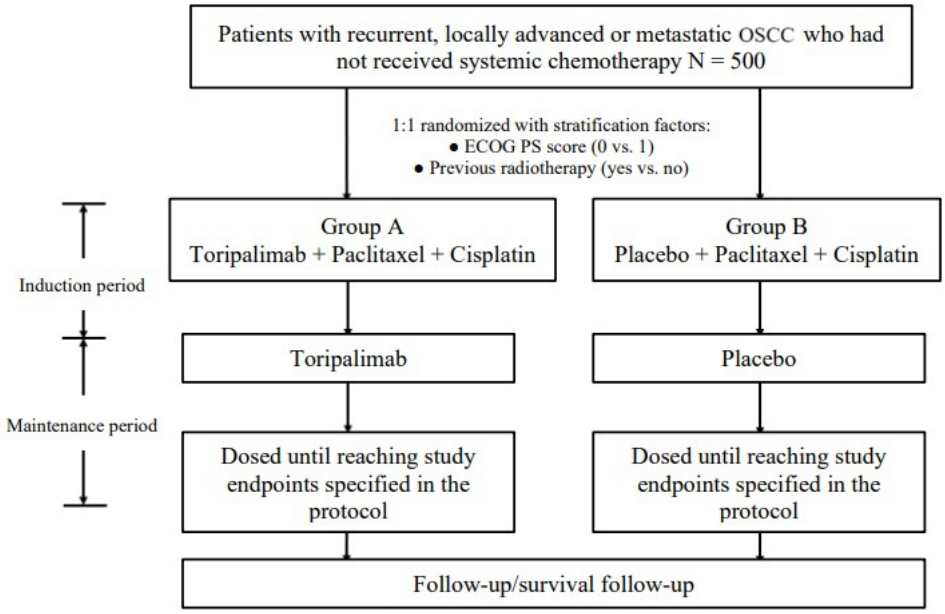


Abbildung 4-1: Schematische Darstellung des Studiendesigns der Studie JUPITER-06
ECOG: Eastern Cooperative Oncology Group; OSCC: Oesophageal squamous cell carcinoma (Plattenepithelkarzinom des Ösophagus); N: Anzahl der Studienteilnehmer; PS: Performance Status; vs.: versus.

Tabelle 4-1: Charakterisierung der Studienpopulationen aus RCT (JUPITER-06) mit dem zu bewertenden Arzneimittel, ITT-Population

Charakteristika zu Baseline	**Toripalimab + Chemotherapie (N=257)**	**Placebo + Chemotherapie (N=257)**	**Gesamt (N=514)**
Demographische Charakteristika			
Alter (Jahre)			
MW (StD)	61,3 (8,04)	60,9 (7,30)	61,1 (7,67)
Median	63,0	62,0	62,5
Spannweite: Min; Max	20 - 75	40 - 74	20 - 75
Alterskategorien			
< 65 Jahre, n (%)	156 (60,7)	163 (63,4)	319 (62,1)
≥ 65 Jahre, n (%)	101 (39,3)	94 (36,6)	195 (37,9)
Geschlecht			
Männlich, n (%)	217 (84,4)	220 (85,6)	437 (85,0)
Weiblich, n (%)	40 (15,6)	37 (14,4)	77 (15,0)
Ethnie			
Han-Chinesen, n (%)	245 (95,3)	243 (94,6)	488 (94,9)
Andere, n (%)	12 (4,7)	14 (5,4)	26 (5,1)
Größe (cm)			
MW (StD)	165,53 (7,363)	166,28 (7,698)	165,90 (7,534)
Median	167,00	167,00	167,00
Spannweite: Min; Max	140,0 - 183,0	145,0 - 186,0	140,0 - 186,0
Gewicht (kg)			
MW (StD)	59,58 (9,736)	59,41 (9,777)	59,50 (9,747)
Median	58,00	58,00	58,00
Spannweite: Min; Max	38,5 - 101,0	37,0 - 95,0	37,0 - 101,0
BMI (kg/m^2)[1]			
MW (StD)	21,701 (2,939)	21,453 (2,979)	21,578 (2,959)
Median	21,359	21,337	21,340
Spannweite: Min; Max	14,314 - 33,360	14,453 - 33,659	14,314 - 33,659
Krankheitscharakteristika			
ECOG-PS zu Baseline			
0, n (%)	66 (25,7)	68 (26,5)	134 (26,1)
1, n (%)	191 (74,3)	189 (73,5)	380 (73,9)
Vorangegangene Strahlentherapie			
Ja, n (%)	35 (13,6)	35 (13,6)	70 (13,6)
Nein, n (%)	222 (86,4)	222 (86,4)	444 (86,4)
Krankheitsstadium zu Baseline			
Fernmetastasen, n (%)	206 (80,2)	198 (77,0)	404 (78,6)
Lokalrezidiv/nicht resezierbar, n (%)	50 (19,5)	59 (23,0)	109 (21,2)
Nicht verfügbar oder nicht durchgeführt, n (%)	1 (0,4)	0	1 (0,2)

Charakteristika zu Baseline	**Toripalimab + Chemotherapie (N=257)**	**Placebo + Chemotherapie (N=257)**	**Gesamt (N=514)**
PD-L1 Expression			
CPS < 1, n (%)	43 (16,7)	44 (17,1)	87 (16,9)
CPS ≥ 1, n (%)	201 (78,2)	200 (77,8)	401 (78,0)
CPS < 10, n (%)	129 (50,2)	147 (57,2)	276 (53,7)
CPS ≥ 10, n (%)	115 (44,7)	97 (37,7)	212 (41,2)
Fehlend, n (%)	13 (5,1)	13 (5,1)	26 (5,1)
Biomarker: 11q13-Amplifikation			
Negativ, n (%)	129 (50,2)	105 (40,9)	234 (45,5)
Positiv, n (%)	113 (44,0)	139 (54,1)	252 (49,0)
Fehlend, n (%)	15 (5,8)	13 (5,1)	28 (5,4)
TMB			
TMB < 6, n (%)	191 (74,3)	185 (72,0)	376 (73,2)
TMB ≥ 6, n (%)	51 (19,8)	59 (23,0)	110 (21,4)
TMB < 8, n (%)	225 (87,5)	211 (82,1)	436 (84,8)
TMB ≥ 8, n (%)	17 (6,6)	33 (12,8)	50 (9,7)
Fehlend	15 (5,8)	13 (5,1)	28 (5,4)

1: BMI (kg/m^2) = Gewicht (kg)/Größe (m^2)

cm: Zentimeter; CPS: Combined Positive Score; CRF: Case Report Form; ECOG-PS: Eastern Cooperative Oncology Group-Performance Status; kg: Kilogramm; Max: Maximum; Min: Minimum; MW: Mittelwert; N: Anzahl der Patienten in der Analysepopulation; n: Anzahl der Patienten mit Ereignis; StD: Standardabweichung (Standard Deviation); TMB: Tumor Mutational Burden (Tumormutationslast)

Quelle: Shanghai Junshi Bioscience Co (2021) siehe Modul 4B, Referenz 8

2 Detaillierte Ergebnisse aus der Studie JUPITER-06

2.1 Mortalität

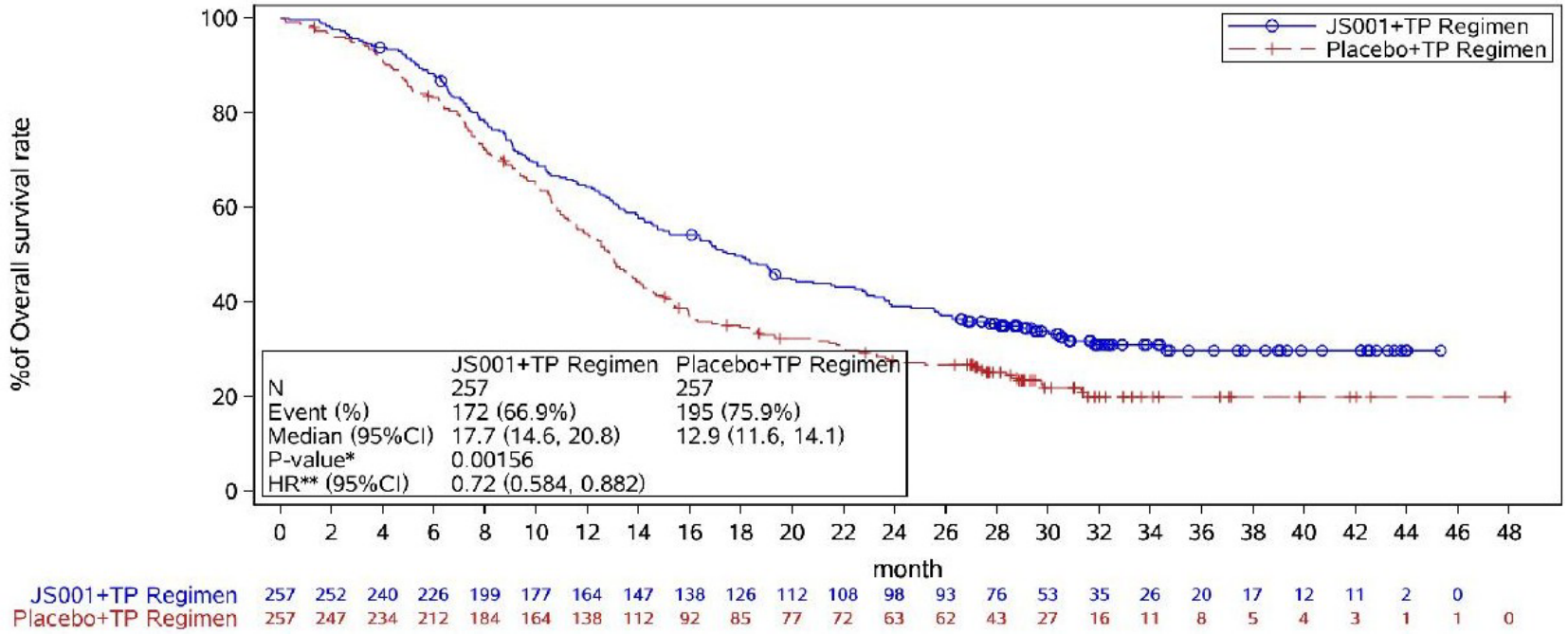
Tabelle 4-2: Detaillierte Ergebnisse für den Endpunkt Gesamtüberleben aus RCT (JUPITER-06) mit dem zu bewertenden Arzneimittel, ITT-Population

Table 14.4.2.1 Overall survival (OS) - Intent-to-Treat analysis set (ITT)

	JS001+TP Regimen (N=257) n (%)	Placebo +TP Regimen (N=257) n (%)	JS001+TP Regimen vs Placebo +TP Regimen
Number of death	172 (66.9)	195 (75.9)	
Number of censored subjects	85 (33.1)	62 (24.1)	
Overall survival (month)			
25% quantile (95% CI)	8.8 (7.5, 9.9)	7.5 (6.9, 8.7)	
Median (95% CI)	17.7 (14.6, 20.8)	12.9 (11.6, 14.1)	
75% quantile (95% CI)	NE (34.5, NE)	28.4 (21.8, NE)	
Minimum, Maximum	0.329, 45.339+	0.164, 47.836+	
12-month survival rate (95% CI)	64.4 (58.2, 69.9)	54.5 (48.1, 60.4)	
24-month survival rate (95% CI)	39.1 (33.1, 45.0)	27.1 (21.7, 32.7)	
Stratified analysis			
Hazard ratio (95% CI)			0.72 (0.584, 0.882)
p-value			0.00156
Unstratified analysis			
Hazard ratio (95% CI)			0.73 (0.591, 0.893)
p-value			0.00227

Data source: list 16.4.4.5
Note: CI = confidence interval, NE = not evaluable, + = censored observation;
Hazard ratios were estimated by the Cox proportional hazards model, and stratified analysis was performed by the stratified Cox proportional hazards model with the following stratification factors used for randomization: ECOG score (0 vs 1), previous radiotherapy (yes vs no);
Log-rank test was used for calculation of p-value (two-sided), and stratified log-rank test was used for stratified analysis using the same stratification factors for hazard ratio.

Figure 14.4.2.1 Kaplan-Meier plot of overall survival (OS) - Intent-to-Treat analysis set (ITT)



Note: Hazard ratios were estimated by the Cox proportional hazards model, and stratified analysis was performed by the stratified Cox proportional hazards model with the following stratification factors used for randomization: ECOG score (0 vs 1), previous radiotherapy (yes vs no); Log-rank test was used for calculation of p-value (two-sided), and stratified log-rank test was used for stratified analysis using the same stratification factors for hazard ratio.

Abbildung 4-2: Kaplan-Meier-Kurve für den Endpunkt Gesamtüberleben aus RCT (JUPITER-06) mit dem zu bewertenden Arzneimittel, ITT-Population

2.2 Morbidität

Tabelle 4-3: Detaillierte Ergebnisse für den Endpunkt Progressionsfreie Überleben aus RCT (JUPITER-06) mit dem zu bewertenden Arzneimittel, ITT-Population

Table 14.4.1.1 Progression-free survival evaluated by BICR in accordance with RECIST 1.1 (BICR-PFS) - Intent-to-Treat analysis set (ITT)

	JS001+TP Regimen (N=257) n (%)	Placebo+TP Regimen (N=257) n (%)	JS001+TP Regimen vs Placebo+TP Regimen
Number of PFS events	132 (51.4)	164 (63.8)	
Progressive Disease	117 (45.5)	152 (59.1)	
Death before first tumor evaluation	0	0	
Death between two tumor evaluations	15 (5.8)	12 (4.7)	
Number of censored subjects	125 (48.6)	93 (36.2)	
No death, no evaluation after randomization	4 (1.6)	3 (1.2)	
Missing baseline tumor evaluation	0	1 (0.4)	
PD/Death after missing >=2 consecutive tumor evaluations	6 (2.3)	16 (6.2)	
PD/Death after the start date of a new anti-tumor treatment	2 (0.8)	4 (1.6)	
No PD, no death, but starting a new anti-tumor treatment	19 (7.4)	10 (3.9)	
No PD, no death, and no new anti-tumor treatment	94 (36.6)	59 (23.0)	

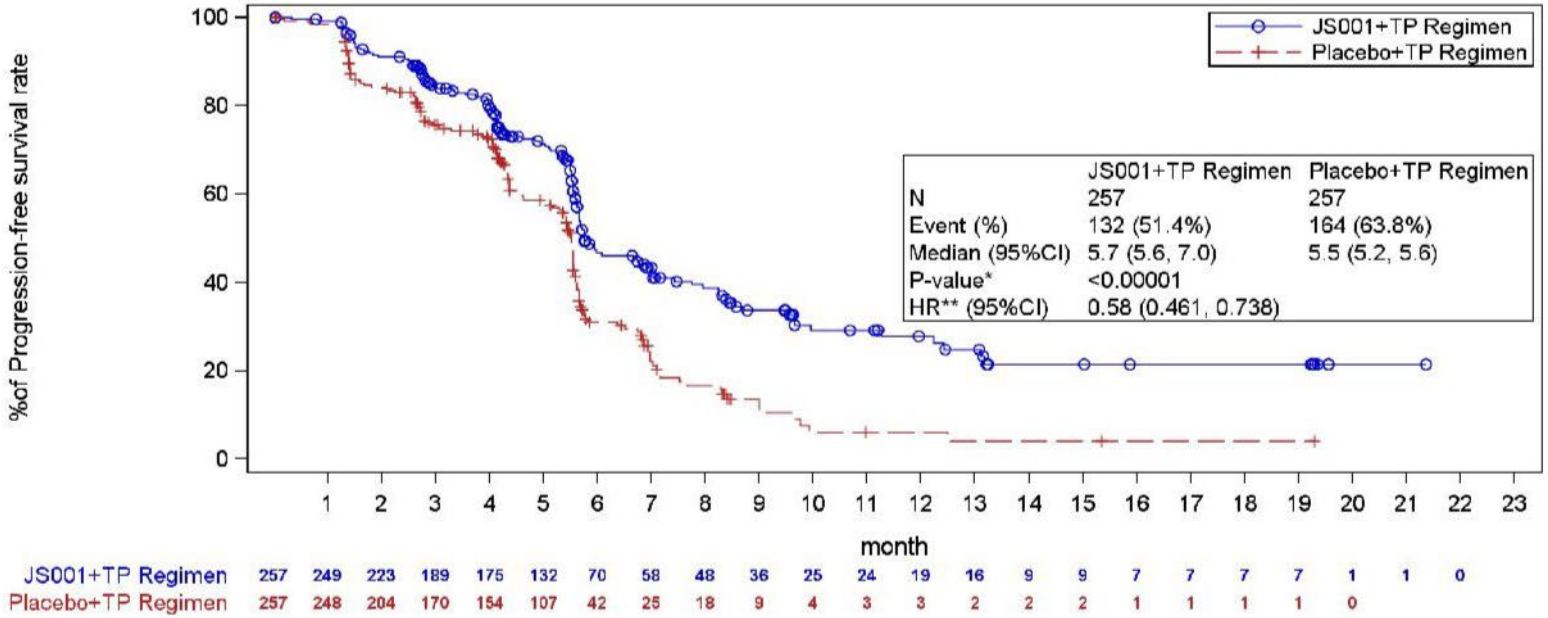
Data source: list 16.4.4.1
Note: CI = confidence interval, NE = not evaluable, + = censored observation;
Hazard ratios were estimated by the Cox proportional hazards model, and stratified analysis was performed by the stratified Cox proportional hazards model with the following stratification factors used for randomization: ECOG score (0 vs 1), previous radiotherapy (yes vs no);
Log-rank test was used for calculation of p-value (two-sided), and stratified log-rank test was used for stratified analysis using the same stratification factors for hazard ratio.

Table 14.4.1.1 Progression-free survival evaluated by BICR in accordance with RECIST 1.1 (BICR-PFS) - Intent-to-Treat analysis set (ITT)

	JS001+TP Regimen (N=257) n (%)	Placebo+TP Regimen (N=257) n (%)	JS001+TP Regimen vs Placebo+TP Regimen
Progression-free survival (month)			
25% quantile (95% CI)	4.2 (4.0, 5.4)	3.1 (2.7, 4.1)	
Median (95% CI)	5.7 (5.6, 7.0)	5.5 (5.2, 5.6)	
75% quantile (95% CI)	12.4 (9.7, NE)	7.0 (5.8, 7.5)	
Minimum, Maximum	0.033+, 21.355+	0.033+, 19.285+	
12-month PFS rate (95% CI)	27.8 (20.4, 35.8)	6.1 (2.2, 12.6)	
24-month PFS rate (95% CI)	NE (NE, NE)	NE (NE, NE)	
Stratified analysis			
Hazard ratio (95% CI)			0.58 (0.461, 0.738)
p-value			<0.00001
Unstratified analysis			
Hazard ratio (95% CI)			0.57 (0.451, 0.719)
p-value			<0.00001

Data source: list 16.4.4.1
Note: CI = confidence interval, NE = not evaluable, + = censored observation;
Hazard ratios were estimated by the Cox proportional hazards model, and stratified analysis was performed by the stratified Cox proportional hazards model with the following stratification factors used for randomization: ECOG score (0 vs 1), previous radiotherapy (yes vs no);
Log-rank test was used for calculation of p-value (two-sided), and stratified log-rank test was used for stratified analysis using the same stratification factors for hazard ratio.

Figure 14.4.1.1 Kaplan-Meier plot of progression-free survival evaluated by BICR (BICR-PFS) in accordance with RECIST 1.1 - Intent-to-Treat analysis set (ITT)



Note: Hazard ratios were estimated by the Cox proportional hazards model, and stratified analysis was performed by the stratified Cox proportional hazards model with the following stratification factors used for randomization: ECOG score (0 vs 1), previous radiotherapy (yes vs no); Log-rank test was used for calculation of p-value (two-sided), and stratified log-rank test was used for stratified analysis using the same stratification factors for hazard ratio.

Abbildung 4-3: Kaplan-Meier-Kurve für den Endpunkt progressionsfreies Überleben aus RCT (JUPITER-06) mit dem zu bewertenden Arzneimittel, ITT-Population

Tabelle 4-4: Detaillierte Ergebnisse für den Endpunkt Dauer des Ansprechens aus RCT (JUPITER-06) mit dem zu bewertenden Arzneimittel, ITT-Population

Table 14.4.5.1 Duration of response (BICR-DOR) evaluated by BICR in accordance with RECIST 1.1 - Intent-to-Treat analysis set (ITT)

	JS001+TP Regimen (N=257) n (%)	Placebo+TP Regimen (N=257) n (%)	JS001+TP Regimen vs Placebo+TP Regimen
Subjects with CR or PR	178	134	
Number of total events	77 (43.3)	73 (54.5)	
Progressive Disease	73 (41.0)	73 (54.5)	
Death before first tumor evaluation	0	0	
Death between two tumor evaluations	4 (2.2)	0	
Number of censored subjects	101 (56.7)	61 (45.5)	

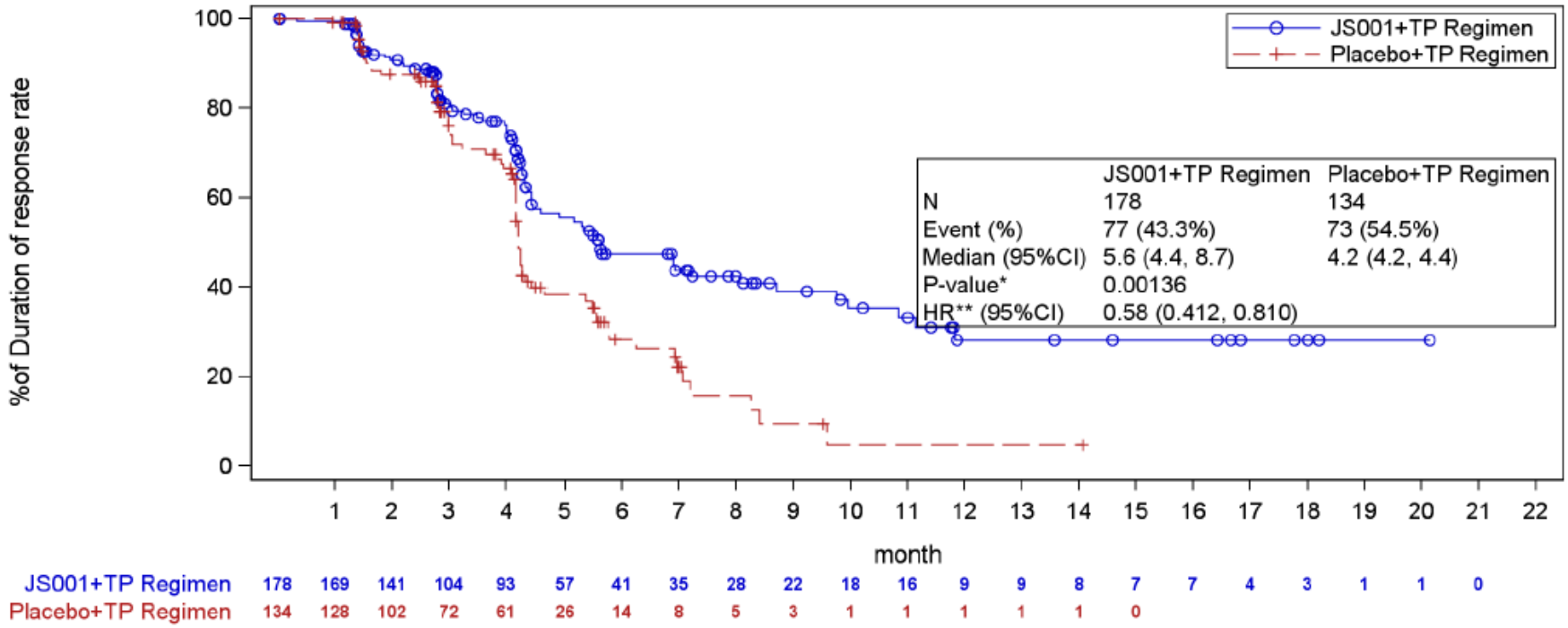
Data source: list 16.4.4.3
Note: CI = confidence interval, NE = not evaluable, + = censored observation;
The analysis was performed only in the subjects with the best overall response (BOR) of complete response (CR) or partial response (PR);
Hazard ratios were estimated by the Cox proportional hazards model, and stratified analysis was performed by the stratified Cox proportional hazards model with the following stratification factors used for randomization: ECOG score (0 vs 1), previous radiotherapy (yes vs no);
Log-rank test was used for calculation of p-value (two-sided), and stratified log-rank test was used for stratified analysis using the same stratification factors for hazard ratio.

Table 14.4.5.1 Duration of response (BICR-DOR) evaluated by BICR in accordance with RECIST 1.1 - Intent-to-Treat analysis set (ITT)

	JS001+TP Regimen (N=257) n (%)	Placebo+TP Regimen (N=257) n (%)	JS001+TP Regimen vs Placebo+TP Regimen
Duration of response (month)			
25% quantile (95% CI)	4.0 (2.8, 4.3)	3.0 (2.8, 3.9)	
Median (95% CI)	5.6 (4.4, 8.7)	4.2 (4.2, 4.4)	
75% quantile (95% CI)	NE (10.8, NE)	6.9 (5.6, 8.2)	
Minimum, Maximum	0.033+, 20.140+	0.033+, 14.062+	
6-month DOR rate (95% CI)	47.4 (37.9, 56.2)	28.4 (18.7, 38.9)	
12-month DOR rate (95% CI)	28.2 (17.9, 39.3)	4.7 (0.5, 17.4)	
Stratified analysis			
Hazard ratio (95% CI)			0.58 (0.412, 0.810)
p-value			0.00136
Unstratified analysis			
Hazard ratio (95% CI)			0.57 (0.407, 0.786)
p-value			0.00063

Data source: list 16.4.4.3
Note: CI = confidence interval, NE = not evaluable, + = censored observation;
The analysis was performed only in the subjects with the best overall response (BOR) of complete response (CR) or partial response (PR);
Hazard ratios were estimated by the Cox proportional hazards model, and stratified analysis was performed by the stratified Cox proportional hazards model with the following stratification factors used for randomization: ECOG score (0 vs 1), previous radiotherapy (yes vs no);
Log-rank test was used for calculation of p-value (two-sided), and stratified log-rank test was used for stratified analysis using the same stratification factors for hazard ratio.

Figure 14.4.4.1 Kaplan-Meier plot of duration of response evaluated by the BICR (BICR-DOR) in accordance with RECIST 1.1 - Intent-to-Treat analysis set (ITT)



Note: Hazard ratios were estimated by the Cox proportional hazards model, and stratified analysis was performed by the stratified Cox proportional hazards model with the following stratification factors used for randomization: ECOG score (0 vs 1), previous radiotherapy (yes vs no); Log-rank test was used for calculation of p-value (two-sided), and stratified log-rank test was used for stratified analysis using the same stratification factors for hazard ratio.

Abbildung 4-4: Kaplan-Meier-Kurve für den Endpunkt Dauer des Ansprechens aus RCT (JUPITER-06) mit dem zu bewertenden Arzneimittel, ITT-Population

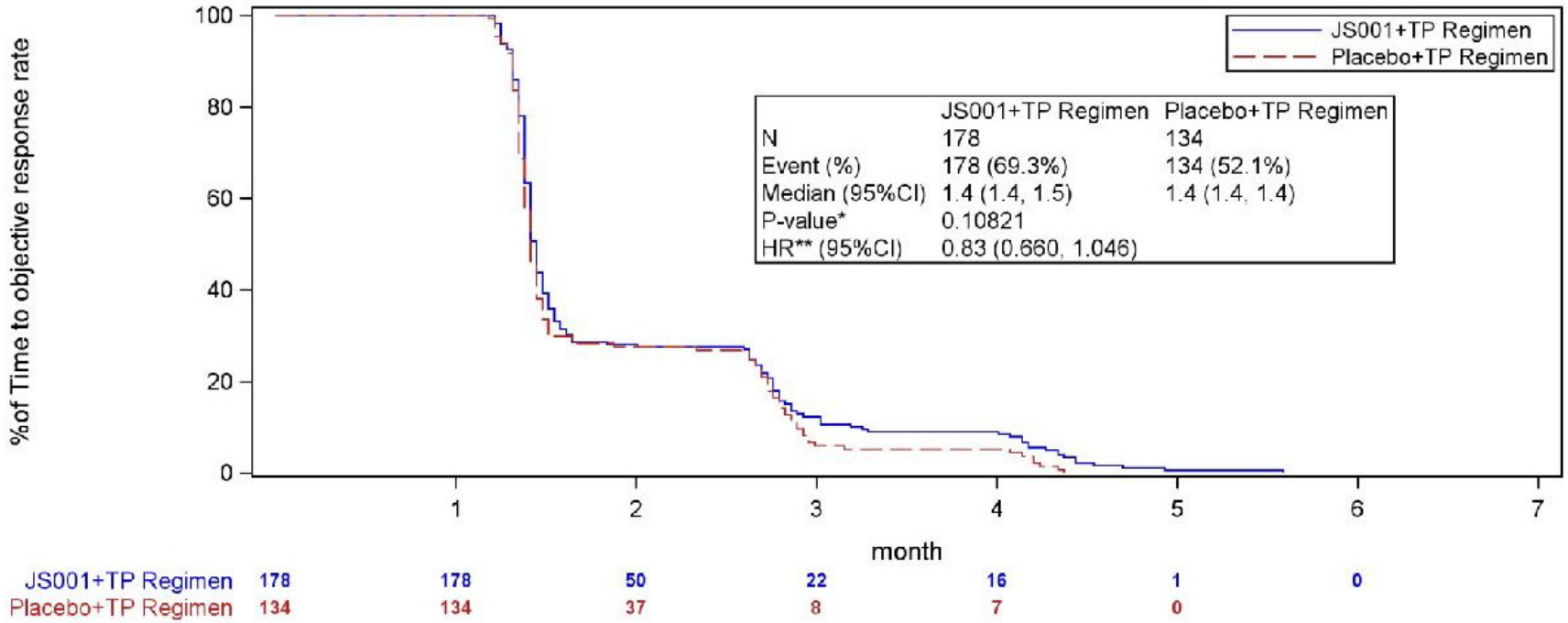
Tabelle 4-5: Detaillierte Ergebnisse für den Endpunkt Zeit bis zum Ansprechen aus RCT (JUPITER-06) mit dem zu bewertenden Arzneimittel, ITT-Population

Table 14.4.6.1 Time to objective response (BICR-TTR) evaluated by BICR in accordance with RECIST 1.1 - Intent-to-Treat analysis set (ITT)

	JS001+TP Regimen (N=257) n (%)	Placebo+TP Regimen (N=257) n (%)	JS001+TP Regimen vs Placebo+TP Regimen
Number of CR or PR events	178	134	
Complete Response (CR)	12 (6.7)	4 (3.0)	
Partial Response (PR)	166 (93.3)	130 (97.0)	
Time to objective response (month)			
25% quantile (95% CI)	1.4 (1.3, 1.4)	1.3 (1.3, 1.4)	
Median (95% CI)	1.4 (1.4, 1.5)	1.4 (1.4, 1.4)	
75% quantile (95% CI)	2.6 (1.6, 2.8)	2.6 (1.5, 2.7)	
Minimum, Maximum	1.216, 5.585	1.183, 4.370	
Stratified analysis			
Hazard ratio (95% CI)			0.83 (0.660, 1.046)
p-value			0.10821
Unstratified analysis			
Hazard ratio (95% CI)			0.84 (0.667, 1.050)
p-value			0.12149

Data source: list 16.4.4.4
Note: CI = confidence interval, NE = not evaluable, + = censored observation;
The analysis was performed only in the subjects with the best overall response (BOR) of complete response (CR) or partial response (PR);
Hazard ratios were estimated by the Cox proportional hazards model, and stratified analysis was performed by the stratified Cox proportional hazards model with the following stratification factors used for randomization: ECOG score (0 vs 1), previous radiotherapy (yes vs no);
Log-rank test was used for calculation of p-value (two-sided), and stratified log-rank test was used for stratified analysis using the same stratification factors for hazard ratio.

Figure 14.4.5.1 Kaplan-Meier plot of time to objective response evaluated by BICR (BICR-TTR) in accordance with RECIST 1.1 - Intent-to-Treat analysis set (ITT)



Note: Hazard ratios were estimated by the Cox proportional hazards model, and stratified analysis was performed by the stratified Cox proportional hazards model with the following stratification factors used for randomization: ECOG score (0 vs 1), previous radiotherapy (yes vs no); Log-rank test was used for calculation of p-value (two-sided), and stratified log-rank test was used for stratified analysis using the same stratification factors for hazard ratio.

Abbildung 4-5: Kaplan-Meier-Kurve für den Endpunkt Zeit bis zum Ansprechen aus RCT (JUPITER-06) mit dem zu bewertenden Arzneimittel, ITT-Population

2.3 Sicherheit

Tabelle 4-6: Unerwünschte Ereignisse nach SOC und PT aus RCT (JUPITER-06) mit dem zu bewertenden Arzneimittel, Safety-Population

Table 14.5.2.2.1.2 Treatment-emergent adverse events with an incidence of >=10% summarized by system organ class and preferred term - safety analysis set (SS)

System Organ Class Preferred Term	JS001+TP regimen N=257		Placebo+TP regimen N=257	
	No. of patients (%)	No. of events	No. of patients (%)	No. of events
Treatment-emergent adverse events with an incidence of >=10%	252 (98.1)	4800	253 (98.4)	3661
Blood and lymphatic system disorders	234 (91.1)	1900	226 (87.9)	1270
Anaemia	205 (79.8)	388	207 (80.5)	323
Leukopenia	175 (68.1)	625	138 (53.7)	414
Neutropenia	174 (67.7)	584	143 (55.6)	397
Thrombocytopenia	77 (30.0)	218	44 (17.1)	94
Lymphopenia	28 (10.9)	85	22 (8.6)	42
Gastrointestinal disorders	189 (73.5)	800	185 (72.0)	697
Nausea	113 (44.0)	260	119 (46.3)	257
Vomiting	106 (41.2)	233	97 (37.7)	208
Constipation	70 (27.2)	105	55 (21.4)	87
Diarrhoea	61 (23.7)	121	36 (14.0)	66
Abdominal pain	39 (15.2)	52	29 (11.3)	37

Data source: listing 16.5.2.1
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, this adverse event was only counted once for system organ class (SOC) and preferred term (PT), and the number of events can be counted as multiple times.

Table 14.5.2.2.1.2 Treatment-emergent adverse events with an incidence of >=10% summarized by system organ class and preferred term - safety analysis set (SS)

System Organ Class Preferred Term	JS001+TP regimen N=257		Placebo+TP regimen N=257	
	No. of patients (%)	No. of events	No. of patients (%)	No. of events
Dysphagia	24 (9.3)	29	35 (13.6)	42
Metabolism and nutrition disorders	187 (72.8)	777	191 (74.3)	718
Decreased appetite	105 (40.9)	235	120 (46.7)	222
Hypoproteinaemia	70 (27.2)	131	62 (24.1)	104
Hypokalaemia	47 (18.3)	81	51 (19.8)	103
Hyponatraemia	44 (17.1)	76	48 (18.7)	79
Hyperglycaemia	33 (12.8)	60	25 (9.7)	34
Hypomagnesaemia	33 (12.8)	63	35 (13.6)	56
Hyperuricaemia	30 (11.7)	65	32 (12.5)	62
Hyperlipidaemia	29 (11.3)	66	28 (10.9)	58
Skin and subcutaneous tissue disorders	136 (52.9)	230	118 (45.9)	155
Alopecia	91 (35.4)	92	104 (40.5)	106
Rash	64 (24.9)	92	27 (10.5)	36

Data source: listing 16.5.2.1
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, this adverse event was only counted once for system organ class (SOC) and preferred term (PT), and the number of events can be counted as multiple times.

Table 14.5.2.2.1.2 Treatment-emergent adverse events with an incidence of >=10% summarized by system organ class and preferred term - safety analysis set (SS)

	JS001+TP regimen N=257		Placebo+TP regimen N=257	
System Organ Class Preferred Term	No. of patients (%)	No. of events	No. of patients (%)	No. of events
Pruritus	33 (12.8)	46	7 (2.7)	13
General disorders and administration site conditions	131 (51.0)	297	117 (45.5)	205
Fatigue	112 (43.6)	233	103 (40.1)	163
Pyrexia	43 (16.7)	64	29 (11.3)	42
Investigations	127 (49.4)	273	112 (43.6)	199
Weight decreased	76 (29.6)	86	75 (29.2)	80
Blood creatinine increased	38 (14.8)	87	30 (11.7)	53
Aspartate aminotransferase increased	37 (14.4)	49	23 (8.9)	30
Alanine aminotransferase increased	33 (12.8)	51	24 (9.3)	36
Nervous system disorders	102 (39.7)	143	114 (44.4)	142
Neuropathy peripheral	72 (28.0)	87	90 (35.0)	105
Neurotoxicity	32 (12.5)	56	27 (10.5)	37

Data source: listing 16.5.2.1
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, this adverse event was only counted once for system organ class (SOC) and preferred term (PT), and the number of events can be counted as multiple times.

Table 14.5.2.2.1.2 Treatment-emergent adverse events with an incidence of >=10% summarized by system organ class and preferred term - safety analysis set (SS)

	JS001+TP regimen N=257		Placebo+TP regimen N=257	
System Organ Class Preferred Term	No. of patients (%)	No. of events	No. of patients (%)	No. of events
Respiratory, thoracic and mediastinal disorders	83 (32.3)	133	63 (24.5)	103
Cough	62 (24.1)	104	57 (22.2)	92
Pneumonitis	26 (10.1)	29	9 (3.5)	11
Musculoskeletal and connective tissue disorders	66 (25.7)	93	53 (20.6)	76
Musculoskeletal pain	66 (25.7)	93	53 (20.6)	76
Psychiatric disorders	31 (12.1)	38	26 (10.1)	34
Insomnia	31 (12.1)	38	26 (10.1)	34
Cardiac disorders	30 (11.7)	44	15 (5.8)	21
Arrhythmia	30 (11.7)	44	15 (5.8)	21
Endocrine disorders	29 (11.3)	39	16 (6.2)	18
Hypothyroidism	29 (11.3)	39	16 (6.2)	18

Data source: listing 16.5.2.1
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, this adverse event was only counted once for system organ class (SOC) and preferred term (PT), and the number of events can be counted as multiple times.

Table 14.5.2.2.1.2 Treatment-emergent adverse events with an incidence of >=10% summarized by system organ class and preferred term - safety analysis set (SS)

System Organ Class Preferred Term	JS001+TP regimen N=257		Placebo+TP regimen N=257	
	No. of patients (%)	No. of events	No. of patients (%)	No. of events
Infections and infestations	26 (10.1)	33	21 (8.2)	23
Pneumonia	26 (10.1)	33	21 (8.2)	23

Data source: listing 16.5.2.1
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, this adverse event was only counted once for system organ class (SOC) and preferred term (PT), and the number of events can be counted as multiple times.

Tabelle 4-7: Schwerwiegende Unerwünschte Ereignisse nach SOC und PT aus RCT (JUPITER-06) mit dem zu bewertenden Arzneimittel, Safety-Population

Table 14.5.2.4.2 Treatment-emergent serious adverse events summarized based on severity and by system organ class and preferred term - safety analysis set (SS)

	JS001+TP regimen N=257			Placebo+TP regimen N=257		
		Severity(CTCAE Grade)			Severity(CTCAE Grade)	
System Organ Class Preferred Term	No. of patients	Grade < 3	Grade ≥3	No. of patients	Grade < 3	Grade ≥3
Treatment-emergent serious adverse events	109 (42.4%)	19 (7.4%)	90 (35.0%)	79 (30.7%)	7 (2.7%)	72 (28.0%)
Gastrointestinal disorders	26 (10.1%)	7 (2.7%)	19 (7.4%)	25 (9.7%)	5 (1.9%)	20 (7.8%)
Vomiting	6 (2.3%)	2 (0.8%)	4 (1.6%)	3 (1.2%)	0	3 (1.2%)
Dysphagia	3 (1.2%)	1 (0.4%)	2 (0.8%)	4 (1.6%)	1 (0.4%)	3 (1.2%)
Gastrointestinal haemorrhage	3 (1.2%)	0	3 (1.2%)	7 (2.7%)	0	7 (2.7%)
Enteritis	2 (0.8%)	0	2 (0.8%)	0	0	0
Gastric fistula	2 (0.8%)	0	2 (0.8%)	0	0	0
Gastritis	2 (0.8%)	1 (0.4%)	1 (0.4%)	0	0	0
Nausea	2 (0.8%)	2 (0.8%)	0	0	0	0
Oesophageal obstruction	2 (0.8%)	0	2 (0.8%)	1 (0.4%)	0	1 (0.4%)
Colitis	1 (0.4%)	1 (0.4%)	0	0	0	0
Diarrhoea	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	0

Data source: listing 16.5.2.2
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, the event with the highest CTCAE grade will be counted.

Table 14.5.2.4.2 Treatment-emergent serious adverse events summarized based on severity and by system organ class and preferred term - safety analysis set (SS)

	JS001+TP regimen N=257			Placebo+TP regimen N=257		
		Severity(CTCAE Grade)			Severity(CTCAE Grade)	
System Organ Class Preferred Term	No. of patients	Grade < 3	Grade ≥3	No. of patients	Grade < 3	Grade ≥3
Gastrointestinal disorder	1 (0.4%)	1 (0.4%)	0	0	0	0
Impaired gastric emptying	1 (0.4%)	0	1 (0.4%)	0	0	0
Oesophageal fistula	1 (0.4%)	0	1 (0.4%)	8 (3.1%)	2 (0.8%)	6 (2.3%)
Oesophageal stenosis	1 (0.4%)	0	1 (0.4%)	0	0	0
Pancreatitis	1 (0.4%)	0	1 (0.4%)	0	0	0
Abdominal pain	0	0	0	1 (0.4%)	1 (0.4%)	0
Intestinal obstruction	0	0	0	1 (0.4%)	0	1 (0.4%)
Infections and infestations	20 (7.8%)	3 (1.2%)	17 (6.6%)	11 (4.3%)	1 (0.4%)	10 (3.9%)
Pneumonia	13 (5.1%)	3 (1.2%)	10 (3.9%)	8 (3.1%)	1 (0.4%)	7 (2.7%)
Gastroenteritis	2 (0.8%)	0	2 (0.8%)	0	0	0
Urinary tract infection	2 (0.8%)	0	2 (0.8%)	0	0	0
Catheter site infection	1 (0.4%)	0	1 (0.4%)	0	0	0

Data source: listing 16.5.2.2
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, the event with the highest CTCAE grade will be counted.

Table 14.5.2.4.2 Treatment-emergent serious adverse events summarized based on severity and by system organ class and preferred term - safety analysis set (SS)

	JS001+TP regimen N=257			Placebo+TP regimen N=257		
		Severity(CTCAE Grade)			Severity(CTCAE Grade)	
System Organ Class Preferred Term	No. of patients	Grade < 3	Grade ≥3	No. of patients	Grade < 3	Grade ≥3
Infected dermal cyst	1 (0.4%)	0	1 (0.4%)	0	0	0
Muscle abscess	1 (0.4%)	0	1 (0.4%)	0	0	0
Ophthalmic herpes zoster	1 (0.4%)	0	1 (0.4%)	0	0	0
Appendicitis	0	0	0	1 (0.4%)	0	1 (0.4%)
Device related infection	0	0	0	1 (0.4%)	0	1 (0.4%)
Upper respiratory tract infection	0	0	0	2 (0.8%)	1 (0.4%)	1 (0.4%)
Blood and lymphatic system disorders	19 (7.4%)	3 (1.2%)	16 (6.2%)	14 (5.4%)	0	14 (5.4%)
Neutropenia	8 (3.1%)	0	8 (3.1%)	10 (3.9%)	0	10 (3.9%)
Leukopenia	6 (2.3%)	1 (0.4%)	5 (1.9%)	5 (1.9%)	1 (0.4%)	4 (1.6%)
Thrombocytopenia	4 (1.6%)	2 (0.8%)	2 (0.8%)	2 (0.8%)	0	2 (0.8%)
Anaemia	3 (1.2%)	0	3 (1.2%)	1 (0.4%)	0	1 (0.4%)
Myelosuppression	3 (1.2%)	0	3 (1.2%)	2 (0.8%)	0	2 (0.8%)

Data source: listing 16.5.2.2
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, the event with the highest CTCAE grade will be counted.

Table 14.5.2.4.2 Treatment-emergent serious adverse events summarized based on severity and by system organ class and preferred term - safety analysis set (SS)

	JS001+TP regimen N=257			Placebo+TP regimen N=257		
		Severity(CTCAE Grade)			Severity(CTCAE Grade)	
System Organ Class Preferred Term	No. of patients	Grade < 3	Grade ≥3	No. of patients	Grade < 3	Grade ≥3
General disorders and administration site conditions	17 (6.6%)	3 (1.2%)	14 (5.4%)	13 (5.1%)	0	13 (5.1%)
Disease progression	10 (3.9%)	0	10 (3.9%)	9 (3.5%)	0	9 (3.5%)
Fatigue	3 (1.2%)	2 (0.8%)	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Pyrexia	2 (0.8%)	1 (0.4%)	1 (0.4%)	0	0	0
Chest discomfort	1 (0.4%)	1 (0.4%)	0	0	0	0
Death	1 (0.4%)	0	1 (0.4%)	2 (0.8%)	0	2 (0.8%)
Multiple organ dysfunction syndrome	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Respiratory, thoracic and mediastinal disorders	16 (6.2%)	5 (1.9%)	11 (4.3%)	10 (3.9%)	5 (1.9%)	5 (1.9%)
Pneumonitis	9 (3.5%)	4 (1.6%)	5 (1.9%)	4 (1.6%)	3 (1.2%)	1 (0.4%)
Pulmonary embolism	2 (0.8%)	0	2 (0.8%)	0	0	0
Respiratory failure	2 (0.8%)	0	2 (0.8%)	0	0	0

Data source: listing 16.5.2.2
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, the event with the highest CTCAE grade will be counted.

Table 14.5.2.4.2 Treatment-emergent serious adverse events summarized based on severity and by system organ class and preferred term - safety analysis set (SS)

	JS001+TP regimen N=257			Placebo+TP regimen N=257		
		Severity(CTCAE Grade)			Severity(CTCAE Grade)	
System Organ Class Preferred Term	No. of patients	Grade < 3	Grade ≥ 3	No. of patients	Grade < 3	Grade ≥ 3
Tracheo-oesophageal fistula	2 (0.8%)	0	2 (0.8%)	0	0	0
Asphyxia	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Dyspnoea	1 (0.4%)	1 (0.4%)	0	0	0	0
Pleural effusion	1 (0.4%)	0	1 (0.4%)	0	0	0
Haemoptysis	0	0	0	3 (1.2%)	2 (0.8%)	1 (0.4%)
Obstructive airways disorder	0	0	0	1 (0.4%)	0	1 (0.4%)
Pneumothorax	0	0	0	1 (0.4%)	0	1 (0.4%)
Hepatobiliary disorders	8 (3.1%)	2 (0.8%)	6 (2.3%)	5 (1.9%)	2 (0.8%)	3 (1.2%)
Hepatic function abnormal	4 (1.6%)	2 (0.8%)	2 (0.8%)	3 (1.2%)	1 (0.4%)	2 (0.8%)
Hepatitis	2 (0.8%)	0	2 (0.8%)	2 (0.8%)	1 (0.4%)	1 (0.4%)
Cholecystitis acute	1 (0.4%)	0	1 (0.4%)	0	0	0
Jaundice cholestatic	1 (0.4%)	0	1 (0.4%)	0	0	0

Data source: listing 16.5.2.2
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, the event with the highest CTCAE grade will be counted.

Table 14.5.2.4.2 Treatment-emergent serious adverse events summarized based on severity and by system organ class and preferred term - safety analysis set (SS)

	JS001+TP regimen N=257			Placebo+TP regimen N=257		
		Severity(CTCAE Grade)			Severity(CTCAE Grade)	
System Organ Class Preferred Term	No. of patients	Grade < 3	Grade ≥3	No. of patients	Grade < 3	Grade ≥3
Cardiac disorders	5 (1.9%)	1 (0.4%)	4 (1.6%)	1 (0.4%)	0	1 (0.4%)
Arteriosclerosis coronary artery	2 (0.8%)	0	2 (0.8%)	0	0	0
Arrhythmia	1 (0.4%)	1 (0.4%)	0	0	0	0
Immune-mediated myocarditis	1 (0.4%)	0	1 (0.4%)	0	0	0
Myocardial injury	1 (0.4%)	0	1 (0.4%)	0	0	0
Cardiac failure	0	0	0	1 (0.4%)	0	1 (0.4%)
Metabolism and nutrition disorders	5 (1.9%)	0	5 (1.9%)	10 (3.9%)	0	10 (3.9%)
Hyponatraemia	2 (0.8%)	0	2 (0.8%)	2 (0.8%)	0	2 (0.8%)
Decreased appetite	1 (0.4%)	0	1 (0.4%)	2 (0.8%)	0	2 (0.8%)
Electrolyte imbalance	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Hypokalaemia	1 (0.4%)	0	1 (0.4%)	3 (1.2%)	0	3 (1.2%)

Data source: listing 16.5.2.2
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, the event with the highest CTCAE grade will be counted.

Table 14.5.2.4.2 Treatment-emergent serious adverse events summarized based on severity and by system organ class and preferred term - safety analysis set (SS)

	JS001+TP regimen N=257			Placebo+TP regimen N=257		
		Severity(CTCAE Grade)			Severity(CTCAE Grade)	
System Organ Class Preferred Term	No. of patients	Grade < 3	Grade ≥3	No. of patients	Grade < 3	Grade ≥3
Hypercalcaemia	0	0	0	1 (0.4%)	0	1 (0.4%)
Hypochloraemia	0	0	0	1 (0.4%)	0	1 (0.4%)
Hypomagnesaemia	0	0	0	1 (0.4%)	0	1 (0.4%)
Endocrine disorders	4 (1.6%)	2 (0.8%)	2 (0.8%)	0	0	0
Adrenal insufficiency	2 (0.8%)	0	2 (0.8%)	0	0	0
Hypothyroidism	1 (0.4%)	1 (0.4%)	0	0	0	0
Thyroiditis	1 (0.4%)	1 (0.4%)	0	0	0	0
Injury, poisoning and procedural complications	4 (1.6%)	1 (0.4%)	3 (1.2%)	2 (0.8%)	1 (0.4%)	1 (0.4%)
Carbon monoxide poisoning	1 (0.4%)	0	1 (0.4%)	0	0	0
Infusion related reaction	1 (0.4%)	0	1 (0.4%)	0	0	0
Limb injury	1 (0.4%)	0	1 (0.4%)	0	0	0

Data source: listing 16.5.2.2
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, the event with the highest CTCAE grade will be counted.

Table 14.5.2.4.2 Treatment-emergent serious adverse events summarized based on severity and by system organ class and preferred term - safety analysis set (SS)

	JS001+TP regimen N=257			Placebo+TP regimen N=257		
		Severity(CTCAE Grade)			Severity(CTCAE Grade)	
System Organ Class Preferred Term	No. of patients	Grade < 3	Grade ≥3	No. of patients	Grade < 3	Grade ≥3
Rib fracture	1 (0.4%)	1 (0.4%)	0	0	0	0
Pelvic fracture	0	0	0	1 (0.4%)	1 (0.4%)	0
Spinal fracture	0	0	0	1 (0.4%)	0	1 (0.4%)
Renal and urinary disorders	4 (1.6%)	1 (0.4%)	3 (1.2%)	1 (0.4%)	1 (0.4%)	0
Renal injury	2 (0.8%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	0
Cystitis haemorrhagic	1 (0.4%)	0	1 (0.4%)	0	0	0
Renal hydrocele	1 (0.4%)	0	1 (0.4%)	0	0	0
Ureterolithiasis	1 (0.4%)	0	1 (0.4%)	0	0	0
Skin and subcutaneous tissue disorders	4 (1.6%)	0	4 (1.6%)	1 (0.4%)	1 (0.4%)	0
Rash	3 (1.2%)	0	3 (1.2%)	0	0	0
Psoriasis	1 (0.4%)	0	1 (0.4%)	0	0	0

Data source: listing 16.5.2.2
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, the event with the highest CTCAE grade will be counted.

Table 14.5.2.4.2 Treatment-emergent serious adverse events summarized based on severity and by system organ class and preferred term - safety analysis set (SS)

	JS001+TP regimen N=257			Placebo+TP regimen N=257		
		Severity(CTCAE Grade)			Severity(CTCAE Grade)	
System Organ Class Preferred Term	No. of patients	Grade < 3	Grade ≥3	No. of patients	Grade < 3	Grade ≥3
Skin mass	0	0	0	1 (0.4%)	1 (0.4%)	0
Investigations	3 (1.2%)	2 (0.8%)	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Alanine aminotransferase increased	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Aspartate aminotransferase increased	1 (0.4%)	0	1 (0.4%)	0	0	0
Blood creatine phosphokinaseincreased	1 (0.4%)	1 (0.4%)	0	0	0	0
Blood creatinine increased	1 (0.4%)	1 (0.4%)	0	0	0	0
Musculoskeletal and connective tissue disorders	3 (1.2%)	0	3 (1.2%)	3 (1.2%)	0	3 (1.2%)
Arthritis	1 (0.4%)	0	1 (0.4%)	0	0	0
Carcinomatous polyarthritis	1 (0.4%)	0	1 (0.4%)	0	0	0
Myositis	1 (0.4%)	0	1 (0.4%)	0	0	0
Musculoskeletal pain	0	0	0	3 (1.2%)	0	3 (1.2%)

Data source: listing 16.5.2.2
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, the event with the highest CTCAE grade will be counted.

Table 14.5.2.4.2 Treatment-emergent serious adverse events summarized based on severity and by system organ class and preferred term - safety analysis set (SS)

	JS001+TP regimen N=257			Placebo+TP regimen N=257		
		Severity(CTCAE Grade)			Severity(CTCAE Grade)	
System Organ Class Preferred Term	No. of patients	Grade < 3	Grade ≥ 3	No. of patients	Grade < 3	Grade ≥ 3
Nervous system disorders	3 (1.2%)	1 (0.4%)	2 (0.8%)	5 (1.9%)	0	5 (1.9%)
Cerebral infarction	1 (0.4%)	0	1 (0.4%)	2 (0.8%)	0	2 (0.8%)
Epilepsy	1 (0.4%)	1 (0.4%)	0	0	0	0
Neuropathy peripheral	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Cerebral ischaemia	0	0	0	1 (0.4%)	0	1 (0.4%)
Syncope	0	0	0	1 (0.4%)	0	1 (0.4%)
Vascular disorders	3 (1.2%)	1 (0.4%)	2 (0.8%)	2 (0.8%)	0	2 (0.8%)
Embolism	1 (0.4%)	1 (0.4%)	0	0	0	0
Haemorrhage	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Hypertension	1 (0.4%)	0	1 (0.4%)	0	0	0
Shock haemorrhagic	0	0	0	1 (0.4%)	0	1 (0.4%)

Data source: listing 16.5.2.2
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, the event with the highest CTCAE grade will be counted.

Table 14.5.2.4.2 Treatment-emergent serious adverse events summarized based on severity and by system organ class and preferred term - safety analysis set (SS)

	JS001+TP regimen N=257			Placebo+TP regimen N=257		
		Severity(CTCAE Grade)			Severity(CTCAE Grade)	
System Organ Class Preferred Term	No. of patients	Grade < 3	Grade ≥3	No. of patients	Grade < 3	Grade ≥3
Immune system disorders	1 (0.4%)	0	1 (0.4%)	0	0	0
Hypersensitivity	1 (0.4%)	0	1 (0.4%)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Adenocarcinoma gastric	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)

Data source: listing 16.5.2.2
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, the event with the highest CTCAE grade will be counted.

Tabelle 4-8: Unerwünschte Ereignisse, die zum Therapieabbruch führten nach SOC und PT aus RCT (JUPITER-06) mit dem zu bewertenden Arzneimittel, Safety-Population

Table 14.5.2.7.1 Treatment-emergent adverse events leading to permanent discontinuation of study drug (JS001/placebo), summarized by system organ class and preferred term - safety analysis set (SS)

System Organ Class	JS001+TP regimen N=257		Placebo+TP regimen N=257	
Preferred Term	No. of patients (%)	No. of events	No. of patients (%)	No. of events
Treatment-emergent adverse events leading to permanent discontinuation of study drug (JS001/placebo)	38 (14.8)	44	21 (8.2)	23
Respiratory, thoracic and mediastinal disorders	7 (2.7)	7	2 (0.8)	2
Pneumonitis	5 (1.9)	5	1 (0.4)	1
Pleural effusion	1 (0.4)	1	0	0
Tracheo-oesophageal fistula	1 (0.4)	1	0	0
Haemoptysis	0	0	1 (0.4)	1
Gastrointestinal disorders	6 (2.3)	6	7 (2.7)	8
Enteritis	2 (0.8)	2	0	0
Dysphagia	1 (0.4)	1	1 (0.4)	1
Gastric fistula	1 (0.4)	1	0	0
Oesophageal fistula	1 (0.4)	1	5 (1.9)	5
Oesophageal obstruction	1 (0.4)	1	1 (0.4)	1
Gastrooesophageal reflux disease	0	0	1 (0.4)	1

Data source: listing 16.5.2.4
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, this adverse event was only counted once for system organ class (SOC) and preferred term (PT), and the number of events can be counted as multiple times.

Table 14.5.2.7.1 Treatment-emergent adverse events leading to permanent discontinuation of study drug (JS001/placebo), summarized by system organ class and preferred term - safety analysis set (SS)

System Organ Class	JS001+TP regimen N=257		Placebo+TP regimen N=257	
Preferred Term	No. of patients (%)	No. of events	No. of patients (%)	No. of events
General disorders and administration site conditions	4 (1.6)	4	3 (1.2)	3
Disease progression	2 (0.8)	2	2 (0.8)	2
Death	1 (0.4)	1	1 (0.4)	1
Fatigue	1 (0.4)	1	0	0
Renal and urinary disorders	4 (1.6)	4	1 (0.4)	1
Renal injury	3 (1.2)	3	1 (0.4)	1
Cystitis haemorrhagic	1 (0.4)	1	0	0
Endocrine disorders	3 (1.2)	3	0	0
Adrenal insufficiency	2 (0.8)	2	0	0
Immune-mediated thyroiditis	1 (0.4)	1	0	0
Hepatobiliary disorders	3 (1.2)	3	0	0
Hepatic function abnormal	2 (0.8)	2	0	0
Hepatitis	1 (0.4)	1	0	0

Data source: listing 16.5.2.4
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, this adverse event was only counted once for system organ class (SOC) and preferred term (PT), and the number of events can be counted as multiple times.

Table 14.5.2.7.1 Treatment-emergent adverse events leading to permanent discontinuation of study drug (JS001/placebo), summarized by system organ class and preferred term - safety analysis set (SS)

System Organ Class	JS001+TP regimen N=257		Placebo+TP regimen N=257	
Preferred Term	No. of patients (%)	No. of events	No. of patients (%)	No. of events
Skin and subcutaneous tissue disorders	3 (1.2)	3	0	0
Rash	2 (0.8)	2	0	0
Psoriasis	1 (0.4)	1	0	0
Cardiac disorders	2 (0.8)	2	2 (0.8)	2
Immune-mediated myocarditis	1 (0.4)	1	0	0
Myocardial injury	1 (0.4)	1	1 (0.4)	1
Arrhythmia	0	0	1 (0.4)	1
Investigations	2 (0.8)	5	0	0
Alanine aminotransferase increased	1 (0.4)	2	0	0
Aspartate aminotransferase increased	1 (0.4)	1	0	0
Blood urea increased	1 (0.4)	1	0	0
Creatinine renal clearance decreased	1 (0.4)	1	0	0

Data source: listing 16.5.2.4
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, this adverse event was only counted once for system organ class (SOC) and preferred term (PT), and the number of events can be counted as multiple times.

Table 14.5.2.7.1 Treatment-emergent adverse events leading to permanent discontinuation of study drug (JS001/placebo), summarized by system organ class and preferred term - safety analysis set (SS)

System Organ Class	JS001+TP regimen N=257		Placebo+TP regimen N=257	
Preferred Term	No. of patients (%)	No. of events	No. of patients (%)	No. of events
Musculoskeletal and connective tissue disorders	2 (0.8)	2	1 (0.4)	1
Arthritis	1 (0.4)	1	0	0
Myositis	1 (0.4)	1	0	0
Musculoskeletal pain	0	0	1 (0.4)	1
Immune system disorders	1 (0.4)	1	0	0
Hypersensitivity	1 (0.4)	1	0	0
Infections and infestations	1 (0.4)	1	1 (0.4)	1
Pneumonia	1 (0.4)	1	1 (0.4)	1
Injury, poisoning and procedural complications	1 (0.4)	1	0	0
Infusion related reaction	1 (0.4)	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	1	2 (0.8)	2
Adenocarcinoma gastric	1 (0.4)	1	1 (0.4)	1

Data source: listing 16.5.2.4
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, this adverse event was only counted once for system organ class (SOC) and preferred term (PT), and the number of events can be counted as multiple times.

Table 14.5.2.7.1 Treatment-emergent adverse events leading to permanent discontinuation of study drug (JS001/placebo), summarized by system organ class and preferred term - safety analysis set (SS)

System Organ Class	JS001+TP regimen N=257		Placebo+TP regimen N=257	
Preferred Term	No. of patients (%)	No. of events	No. of patients (%)	No. of events
Cancer pain	0	0	1 (0.4)	1
Vascular disorders	1 (0.4)	1	2 (0.8)	2
Haemorrhage	1 (0.4)	1	1 (0.4)	1
Shock haemorrhagic	0	0	1 (0.4)	1
Nervous system disorders	0	0	1 (0.4)	1
Syncope	0	0	1 (0.4)	1

Data source: listing 16.5.2.4
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, this adverse event was only counted once for system organ class (SOC) and preferred term (PT), and the number of events can be counted as multiple times.

Tabelle 4-9: Unerwünschte Ereignisse, die zum Tod führten nach SOC und PT aus RCT (JUPITER-06) mit dem zu bewertenden Arzneimittel, Safety-Population

Table 14.5.2.9.1 Treatment-emergent adverse events with fatal outcome

System Organ Class	JS001+TP regimen N=257		Placebo+TP regimen N=257	
Preferred Term	No. of patients (%)	No. of events	No. of patients (%)	No. of events
Treatment-emergent adverse events with fatal outcome	24 (9.3)	24	24 (9.3)	24
General disorders and administration site conditions	12 (4.7)	12	12 (4.7)	12
Disease progression	10 (3.9)	10	9 (3.5)	9
Death	1 (0.4)	1	2 (0.8)	2
Multiple organ dysfunction syndrome	1 (0.4)	1	1 (0.4)	1
Gastrointestinal disorders	4 (1.6)	4	5 (1.9)	5
Gastrointestinal haemorrhage	2 (0.8)	2	2 (0.8)	2
Gastric fistula	1 (0.4)	1	0	0
Oesophageal fistula	1 (0.4)	1	2 (0.8)	2
Intestinal obstruction	0	0	1 (0.4)	1
Respiratory, thoracic and mediastinal disorders	3 (1.2)	3	2 (0.8)	2
Asphyxia	1 (0.4)	1	1 (0.4)	1
Pulmonary embolism	1 (0.4)	1	0	0

Data source: listing 16.5.2.6
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, this adverse event was only counted once for system organ class (SOC) and preferred term (PT), and the number of events can be counted as multiple times.

Table 14.5.2.9.1 Treatment-emergent adverse events with fatal outcome

System Organ Class Preferred Term	JS001+TP regimen N=257 No. of patients (%)	 No. of events	Placebo+TP regimen N=257 No. of patients (%)	 No. of events
Respiratory failure	1 (0.4)	1	0	0
Pneumonitis	0	0	1 (0.4)	1
Infections and infestations	2 (0.8)	2	1 (0.4)	1
Pneumonia	2 (0.8)	2	1 (0.4)	1
Injury, poisoning and procedural complications	1 (0.4)	1	0	0
Carbon monoxide poisoning	1 (0.4)	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	1	0	0
Adenocarcinoma gastric	1 (0.4)	1	0	0
Vascular disorders	1 (0.4)	1	2 (0.8)	2
Haemorrhage	1 (0.4)	1	1 (0.4)	1
Shock haemorrhagic	0	0	1 (0.4)	1

Data source: listing 16.5.2.6
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, this adverse event was only counted once for system organ class (SOC) and preferred term (PT), and the number of events can be counted as multiple times.

Table 14.5.2.9.1 Treatment-emergent adverse events with fatal outcome

System Organ Class Preferred Term	JS001+TP regimen N=257 No. of patients (%)	 No. of events	Placebo+TP regimen N=257 No. of patients (%)	 No. of events
Cardiac disorders	0	0	1 (0.4)	1
Cardiac failure	0	0	1 (0.4)	1
Nervous system disorders	0	0	1 (0.4)	1
Cerebral infarction	0	0	1 (0.4)	1

Data source: listing 16.5.2.6
Note: Coding of adverse events: MedDRA25.1.
Note: A treatment-emergent adverse event was defined as any adverse event occurring between the first dose to 60 days after the last dose of study drug or prior to start of a new systemic antitumor therapy, whichever came first.
If an adverse event occurred in the same patient more than once, this adverse event was only counted once for system organ class (SOC) and preferred term (PT), and the number of events can be counted as multiple times.