

Dossier zur Nutzenbewertung gemäß § 35a SGB V

Acalabrutinib (Calquence®)

AstraZeneca GmbH

Modul 4 A – Anhang 4-G

Calquence® in Kombination mit Bendamustin und Rituximab (BR) ist zur Behandlung von erwachsenen Patienten mit nicht vorbehandeltem Mantelzell-Lymphom (MCL) indiziert, die nicht für eine autologe Stammzelltransplantation (ASCT) geeignet sind.

Weitere Analysen und Kaplan-Meier-Plots zu den
in Abschnitt 4.3.1.3 gezeigten Ergebnissen

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Table 1.1 ECHO: Summary of observation period (months) for efficacy endpoints
 (OS, PFS, TTR, DOR)
 Full Analysis Set, DC0 15FEB2024

		Acala+BR (N=299)	Placebo+BR (N=299)
Overall survival	n	299	299
	Mediane	46,92	45,70
	Min	0,0	0,0
	Max	80,4	81,3
Progression-free survival (IRC)	n	299	299
	Mediane	33,22	27,66
	Min	0,0	0,0
	Max	77,3	73,8
Time to Initial Response CR, PR (IRC)	n	299	299
	Mediane	2,79	2,79
	Min	0,0	0,0
	Max	66,3	66,3
Duration of response (IRC)	n	272	263
	Mediane	33,02	30,06
	Min	0,0	0,0
	Max	74,5	70,5
Overall survival - censoring covid death	n	299	299
	Mediane	46,92	45,70
	Min	0,0	0,0
	Max	80,4	81,3
Progression-free survival - censoring covid death (IRC)	n	299	299
	Mediane	33,22	27,66
	Min	0,0	0,0
	Max	77,3	73,8

Observation period for an efficacy endpoint is defined as the time from randomisation to the date of that event, if occurred or otherwise, to the date of the last evaluable assessment of that efficacy endpoint.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.1 ECHO: Summary of observation period (months) for PRO endpoints
 Full Analysis Set, DCO 15FEB2024

		Acala+BR (N=299)	Placebo+BR (N=299)
EORTC QLQ-C30	n	299	299
	Mediane	25,33	21,32
	Min	0,0	0,0
	Max	73,1	76,4
FACT-LYM	n	299	299
	Mediane	25,33	21,29
	Min	0,0	0,0
	Max	73,1	76,4
EQ-5D visuelle Analogskala	n	299	299
	Mediane	25,33	21,29
	Min	0,0	0,0
	Max	73,1	76,4

Observation period for PROs is defined as the time from randomisation to the earliest date of the last assessment of questionnaire or date of data cut-off (DCO). PRO assessments more than 1 day after study treatment discontinuation for any reason are not considered. Patients without any baseline or post baseline measurements are summarised with duration of 1 day.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab. PRO = Patient Reported Outcomes.

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Table 3.1 ECHO: Summary of observation period (months) for all safety outcomes
 Safety Analysis Set, DCO 15FEB2024

		Acala+BR (N=297)	Placebo+BR (N=297)
UE	n	297	297
	Mediane	29,77	26,28
	Min	0,2	0,1
	Max	80,4	77,6

Observation period for all safety outcomes is defined as the duration from the date of first dose of study treatment to the earliest of the date of data cut-off, end of safety follow-up period (30 days following discontinuation of study treatment +7 days for clinical laboratory tests), date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 1.1.3 ECHO Summary of analysis of time to initial response CR, PR (IRC)
 Full Analysis Set, DCO 15FEB2024

	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b] [95%-KI] [b]		2-seitiger p-Wert [c]
	Anzahl (%) der Patienten mit n Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		Anzahl (%) der Patienten mit n Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Zeit bis zum Ansprechen CR, PR (IRC)	299 272 (91,0)	2,8 [NE; NE]		299 263 (88,0)	2,8 [2,8; 2,8]		1,14 [0,96; 1,35]		0,1619

Stratification factors are as recorded in IXRS and selected as per pooling strategy described for PFS in the SAP (4.3.1.3).

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment, region and simplified MIPI score. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR. NC = not calculable.

[c] p-value is estimated using log-rank test stratified by region and simplified MIPI score. * p<0.05.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 1.1.4 ECHO Summary of analysis of duration of response (IRC)
 Full Analysis Set, DCO 15FEB2024

	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b] [95%-KI] [b]		2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Dauer des Ansprechens (IRC)	272	99 (36,4)	63,5 [52,5; NE]		263	117 (44,5)	53,8 [37,6;66,1]		0,74	[0,56; 0,96]	0,0247*

Stratification factors are as recorded in IXRS and selected as per pooling strategy described for PFS in the SAP (4.3.1.3).

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment and simplified MIPI score. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR. NC = not calculable.

[c] p-value is estimated using log-rank test stratified by simplified MIPI score. * p<0.05.

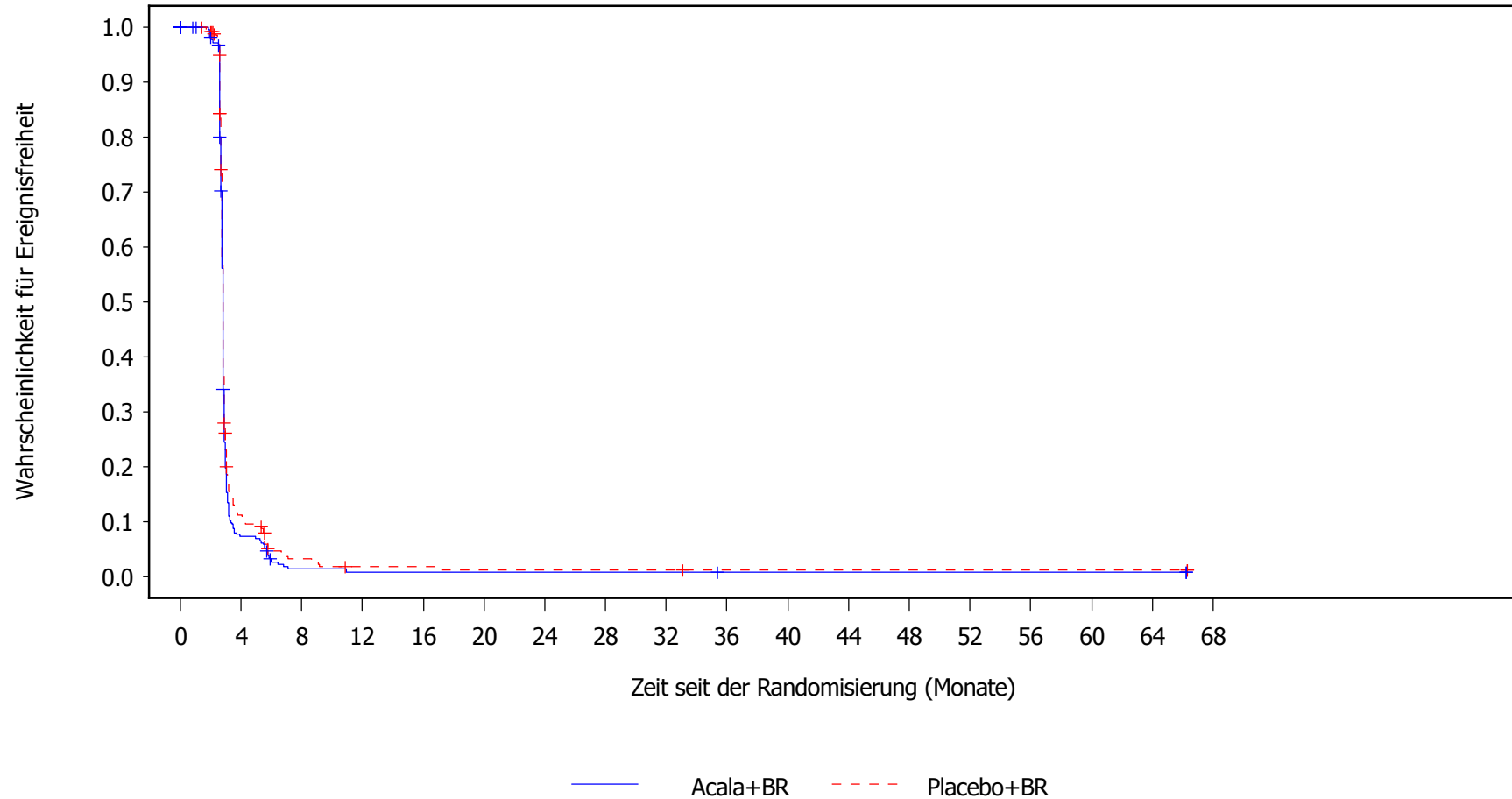
Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 1.2.3 ECHO: Kaplan-Meier plot of time to initial response CR, PR (IRC)
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

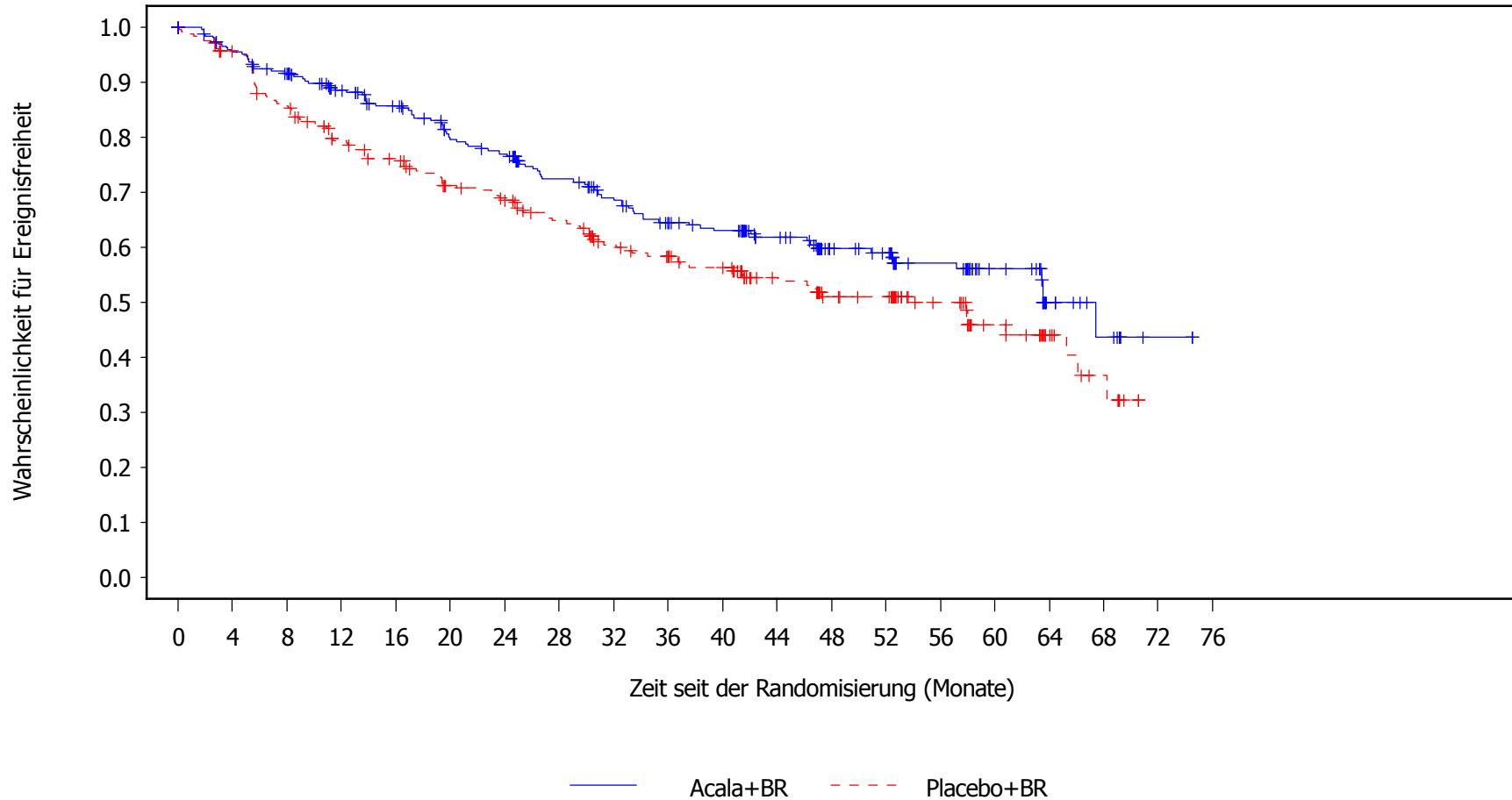
299	20	3	2	2	2	2	2	2	1	1	1	1	1	1	1	1	0	Acala+BR
299	29	7	3	3	2	2	2	2	1	1	1	1	1	1	1	1	0	Placebo+BR

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 1.2.4 ECHO: Kaplan-Meier plot of duration of response (IRC)
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

272	255	241	219	204	182	175	154	141	127	120	100	77	71	53	34	14	7	1	0	Acala+BR
263	239	213	189	177	159	151	137	120	112	102	83	64	61	42	27	15	8	0	0	Placebo+BR

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 1.3 ECHO: Objective response rate (ORR IRC)
 (odds ratio, relative risk and risk difference)
 Full Analysis Set, DC0 15FEB2024

	Behandlungseffekt															
	Acala + BR (N=299)				Placebo + BR (N=299)				Behandlungseffekt							
					Odds Ratio				Relatives Risiko				Risikodifferenz			
	Anzahl (%) der Patienten mit				Anzahl (%) der Patienten mit				Schätzer		2- seit- iger		Schätzer		2- seit- iger	
	n	Ereignis	n	Ereignis	[95%-KI]	p- Wert	[95%-KI]	p- Wert	[95%-KI]	p- Wert	[95%-KI]	p- Wert				
Objektive Ansprechrate [a][d][h]	299	272(91,0)	299	263(88,0)	1,38[0,82; 2,35]	0,2299	1,03[0,98; 1,09]	0,2299	0,03[-0,02; 0,08]	0,2299						

n = Number of patients in the FAS with measurable disease at baseline according to blinded independent central review.

Response did not require confirmation.

NC=not calculable. CI=confidence interval. PL=profile likelihood. LR=likelihood ratio test. All models include treatment only.

[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].

OR and RR <1, and RD <0 favours acalabrutinib. * p<0.05.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.4.1.1 ECHO: Summary of strata selection applied for time to first deterioration in PRO analysis
 Full Analysis Set, DCO 15FEB2024

Endpoint	Strata selection
EORTC QLQ-C30 Allgemeine Lebensqualität/Gesundheitsszustand	Region und Vereinfachter MIPI-Score
EORTC QLQ-C30 Funktionsskala: Körper	Region und Vereinfachter MIPI-Score
EORTC QLQ-C30 Funktionsskala: Rolle	Region und Vereinfachter MIPI-Score
EORTC QLQ-C30 Funktionsskala: Emotionalität	Vereinfachter MIPI-Score
EORTC QLQ-C30 Funktionsskala: Kognition	Vereinfachter MIPI-Score
EORTC QLQ-C30 Funktionsskala: Sozial	Region und Vereinfachter MIPI-Score
EORTC QLQ-C30 Fatigue	Region und Vereinfachter MIPI-Score
EORTC QLQ-C30 Übelkeit und Erbrechen	Vereinfachter MIPI-Score
EORTC QLQ-C30 Schmerzen	Vereinfachter MIPI-Score
EORTC QLQ-C30 Dyspnoe	Vereinfachter MIPI-Score
EORTC QLQ-C30 Schlaflosigkeit	Vereinfachter MIPI-Score
EORTC QLQ-C30 Appetitverlust	Vereinfachter MIPI-Score
EORTC QLQ-C30 Verstopfung	Vereinfachter MIPI-Score
EORTC QLQ-C30 Diarrhö	Vereinfachter MIPI-Score
EORTC QLQ-C30 Finanzielle Schwierigkeiten	Vereinfachter MIPI-Score
FACT-Lym Gesamtscore	Vereinfachter MIPI-Score
FACT-Lym Physisches Wohlbefinden (PWB)	Vereinfachter MIPI-Score
FACT-Lym Soziales Wohlbefinden (SWB)	Vereinfachter MIPI-Score
FACT-Lym Funktionales Wohlbefinden (FWB)	Region und Vereinfachter MIPI-Score
FACT-Lym Emotionales Wohlbefinden (EMB)	Vereinfachter MIPI-Score
FACT-Lym Lym-Subscala (LYMS)	Vereinfachter MIPI-Score
EQ-5D-5L Visuelle Analogskala	Vereinfachter MIPI-Score

Stratification factors tested were: region (North America, Western Europe, Other), Simplified Mantle Cell Lymphoma International Prognostic Index (MIPI) score (low risk [0 to 3], intermediate risk [4 to 5], high risk [6 to 11]).
 Pooling strategy described in SAP section 4.3.1.3 for PFS applied per endpoint.

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Table 2.4.2.1 ECHO: Summary of status at time of first deterioration in EORTC-QLQ-C30 questionnaire
 Full Analysis Set, DCO 15FEB2024

		Reason	Acala+BR (N=299)	Placebo+BR (N=299)
EORTC QLQ-C30 Allgemeine Lebensqualität/ Gesundheitsszustand	Deterioration	Total	146 (48,8)	117 (39,1)
	Censored	Total	153 (51,2)	182 (60,9)
		No evaluable baseline or post-baseline score	32 (10,7)	41 (13,7)
		Last evaluable assessment without deterioration [a]	76 (25,4)	88 (29,4)
		Missing 2 or more consecutive visits	12 (4,0)	21 (7,0)
		Death within 2 visits of the last evaluable PRO assessment	33 (11,0)	32 (10,7)
EORTC QLQ-C30 Funktionsskala: Körper	Deterioration	Total	147 (49,2)	138 (46,2)
	Censored	Total	152 (50,8)	161 (53,8)
		No evaluable baseline or post-baseline score	30 (10,0)	39 (13,0)
		Last evaluable assessment without deterioration [a]	77 (25,8)	74 (24,7)
		Missing 2 or more consecutive visits	16 (5,4)	17 (5,7)
		Death within 2 visits of the last evaluable PRO assessment	29 (9,7)	31 (10,4)
EORTC QLQ-C30 Funktionsskala: Rolle	Deterioration	Total	161 (53,8)	147 (49,2)
	Censored	Total	138 (46,2)	152 (50,8)
		No evaluable baseline or post-baseline score	30 (10,0)	39 (13,0)
		Last evaluable assessment without deterioration [a]	71 (23,7)	70 (23,4)
		Missing 2 or more consecutive visits	13 (4,3)	17 (5,7)
		Death within 2 visits of the last evaluable PRO assessment	24 (8,0)	26 (8,7)
EORTC QLQ-C30 Funktionsskala: Emotionalität	Deterioration	Total	95 (31,8)	96 (32,1)
	Censored	Total	204 (68,2)	203 (67,9)
		No evaluable baseline or post-baseline score	32 (10,7)	40 (13,4)
		Last evaluable assessment without deterioration [a]	109 (36,5)	104 (34,8)
		Missing 2 or more consecutive visits	24 (8,0)	22 (7,4)
		Death within 2 visits of the last evaluable PRO assessment	39 (13,0)	37 (12,4)
EORTC QLQ-C30 Funktionsskala: Kognition	Deterioration	Total	146 (48,8)	147 (49,2)

[a] Includes patients with baseline score too low/high to experience a deterioration.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.4.2.1 ECHO: Summary of status at time of first deterioration in EORTC-QLQ-C30 questionnaire
 Full Analysis Set, DCO 15FEB2024

		Reason	Acala+BR (N=299)	Placebo+BR (N=299)
EORTC QLQ-C30 Funktionsskala: Sozial	Censored	Total	153 (51,2)	152 (50,8)
		No evaluable baseline or post-baseline score	32 (10,7)	40 (13,4)
		Last evaluable assessment without deterioration [a]	79 (26,4)	75 (25,1)
		Missing 2 or more consecutive visits	13 (4,3)	17 (5,7)
		Death within 2 visits of the last evaluable PRO assessment	29 (9,7)	20 (6,7)
	Deterioration	Total	161 (53,8)	137 (45,8)
	Censored	Total	138 (46,2)	162 (54,2)
		No evaluable baseline or post-baseline score	32 (10,7)	40 (13,4)
		Last evaluable assessment without deterioration [a]	72 (24,1)	82 (27,4)
		Missing 2 or more consecutive visits	15 (5,0)	16 (5,4)
		Death within 2 visits of the last evaluable PRO assessment	19 (6,4)	24 (8,0)
EORTC QLQ-C30 Fatigue	Deterioration	Total	190 (63,5)	161 (53,8)
		No evaluable baseline or post-baseline score	30 (10,0)	39 (13,0)
		Last evaluable assessment without deterioration [a]	49 (16,4)	64 (21,4)
		Missing 2 or more consecutive visits	11 (3,7)	14 (4,7)
		Death within 2 visits of the last evaluable PRO assessment	19 (6,4)	21 (7,0)
	Censored	Total	109 (36,5)	138 (46,2)
		No evaluable baseline or post-baseline score	30 (10,0)	39 (13,0)
		Last evaluable assessment without deterioration [a]	49 (16,4)	64 (21,4)
		Missing 2 or more consecutive visits	11 (3,7)	14 (4,7)
		Death within 2 visits of the last evaluable PRO assessment	19 (6,4)	21 (7,0)
EORTC QLQ-C30 Übelkeit und Erbrechen	Deterioration	Total	110 (36,8)	105 (35,1)
		No evaluable baseline or post-baseline score	30 (10,0)	39 (13,0)
		Last evaluable assessment without deterioration [a]	102 (34,1)	104 (34,8)
		Missing 2 or more consecutive visits	20 (6,7)	20 (6,7)
		Death within 2 visits of the last evaluable PRO assessment	37 (12,4)	31 (10,4)
	Censored	Total	189 (63,2)	194 (64,9)
		No evaluable baseline or post-baseline score	30 (10,0)	39 (13,0)
		Last evaluable assessment without deterioration [a]	102 (34,1)	104 (34,8)
		Missing 2 or more consecutive visits	20 (6,7)	20 (6,7)
		Death within 2 visits of the last evaluable PRO assessment	37 (12,4)	31 (10,4)
EORTC QLQ-C30 Schmerzen	Deterioration	Total	157 (52,5)	119 (39,8)
		No evaluable baseline or post-baseline score	30 (10,0)	39 (13,0)
		Last evaluable assessment without deterioration [a]	71 (23,7)	89 (29,8)
		Missing 2 or more consecutive visits	15 (5,0)	17 (5,7)
		Death within 2 visits of the last evaluable PRO assessment	26 (8,7)	35 (11,7)
	Censored	Total	142 (47,5)	180 (60,2)
		No evaluable baseline or post-baseline score	30 (10,0)	39 (13,0)
		Last evaluable assessment without deterioration [a]	71 (23,7)	89 (29,8)
		Missing 2 or more consecutive visits	15 (5,0)	17 (5,7)
		Death within 2 visits of the last evaluable PRO assessment	26 (8,7)	35 (11,7)

[a] Includes patients with baseline score too low/high to experience a deterioration.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.4.2.1 ECHO: Summary of status at time of first deterioration in EORTC-QLQ-C30 questionnaire
 Full Analysis Set, DC0 15FEB2024

			Acala+BR (N=299)	Placebo+BR (N=299)
Reason				
EORTC QLQ-C30 Dyspnoe	Deterioration	Total	122 (40,8)	99 (33,1)
	Censored	Total	177 (59,2)	200 (66,9)
		No evaluable baseline or post-baseline score	30 (10,0)	40 (13,4)
		Last evaluable assessment without deterioration [a]	95 (31,8)	103 (34,4)
		Missing 2 or more consecutive visits	18 (6,0)	21 (7,0)
		Death within 2 visits of the last evaluable PRO assessment	34 (11,4)	36 (12,0)
EORTC QLQ-C30 Schlaflosigkeit	Deterioration	Total	126 (42,1)	103 (34,4)
	Censored	Total	173 (57,9)	196 (65,6)
		No evaluable baseline or post-baseline score	31 (10,4)	39 (13,0)
		Last evaluable assessment without deterioration [a]	88 (29,4)	109 (36,5)
		Missing 2 or more consecutive visits	22 (7,4)	19 (6,4)
		Death within 2 visits of the last evaluable PRO assessment	32 (10,7)	29 (9,7)
EORTC QLQ-C30 Appetitverlust	Deterioration	Total	129 (43,1)	105 (35,1)
	Censored	Total	170 (56,9)	194 (64,9)
		No evaluable baseline or post-baseline score	31 (10,4)	40 (13,4)
		Last evaluable assessment without deterioration [a]	98 (32,8)	96 (32,1)
		Missing 2 or more consecutive visits	17 (5,7)	23 (7,7)
		Death within 2 visits of the last evaluable PRO assessment	24 (8,0)	35 (11,7)
EORTC QLQ-C30 Verstopfung	Deterioration	Total	112 (37,5)	108 (36,1)
	Censored	Total	187 (62,5)	191 (63,9)
		No evaluable baseline or post-baseline score	31 (10,4)	41 (13,7)
		Last evaluable assessment without deterioration [a]	99 (33,1)	98 (32,8)
		Missing 2 or more consecutive visits	20 (6,7)	15 (5,0)
		Death within 2 visits of the last evaluable PRO assessment	37 (12,4)	37 (12,4)
EORTC QLQ-C30 Diarrhö	Deterioration	Total	119 (39,8)	85 (28,4)
	Censored	Total	180 (60,2)	214 (71,6)
		No evaluable baseline or post-baseline score	32 (10,7)	40 (13,4)
		Last evaluable assessment without deterioration [a]	101 (33,8)	110 (36,8)
		Missing 2 or more consecutive visits	14 (4,7)	23 (7,7)

[a] Includes patients with baseline score too low/high to experience a deterioration.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.4.2.1 ECHO: Summary of status at time of first deterioration in EORTC-QLQ-C30 questionnaire
 Full Analysis Set, DCO 15FEB2024

Reason			Acala+BR (N=299)	Placebo+BR (N=299)
Death within 2 visits of the last evaluable PRO assessment			33 (11,0)	41 (13,7)
EORTC QLQ-C30 Finanzielle Schwierigkeiten	Deterioration	Total	81 (27,1)	78 (26,1)
	Censored	Total	218 (72,9)	221 (73,9)
		No evaluable baseline or post-baseline score	32 (10,7)	40 (13,4)
		Last evaluable assessment without deterioration [a]	124 (41,5)	124 (41,5)
		Missing 2 or more consecutive visits	21 (7,0)	22 (7,4)
		Death within 2 visits of the last evaluable PRO assessment	41 (13,7)	35 (11,7)

[a] Includes patients with baseline score too low/high to experience a deterioration.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/ttereaspr.sas gtttereaspraa 19MAR2025:09:01 khcs324

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Table 2.4.2.2 ECHO: Summary of status at time of first deterioration in FACT-Lym questionnaire
 Full Analysis Set, DCO 15FEB2024

		Reason	Acala+BR (N=299)	Placebo+BR (N=299)
FACT-Lym Gesamtscore	Deterioration	Total	56 (18,7)	46 (15,4)
	Censored	Total	243 (81,3)	253 (84,6)
		No evaluable baseline or post-baseline score	36 (12,0)	41 (13,7)
		Last evaluable assessment without deterioration [a]	134 (44,8)	144 (48,2)
		Missing 2 or more consecutive visits	28 (9,4)	25 (8,4)
		Death within 2 visits of the last evaluable PRO assessment	45 (15,1)	43 (14,4)
FACT-Lym Physisches Wohlbefinden (PWB)	Deterioration	Total	100 (33,4)	106 (35,5)
	Censored	Total	199 (66,6)	193 (64,5)
		No evaluable baseline or post-baseline score	34 (11,4)	40 (13,4)
		Last evaluable assessment without deterioration [a]	108 (36,1)	99 (33,1)
		Missing 2 or more consecutive visits	20 (6,7)	18 (6,0)
		Death within 2 visits of the last evaluable PRO assessment	37 (12,4)	36 (12,0)
FACT-Lym Soziales Wohlbefinden (SWB)	Deterioration	Total	125 (41,8)	112 (37,5)
	Censored	Total	174 (58,2)	187 (62,5)
		No evaluable baseline or post-baseline score	34 (11,4)	40 (13,4)
		Last evaluable assessment without deterioration [a]	88 (29,4)	92 (30,8)
		Missing 2 or more consecutive visits	20 (6,7)	19 (6,4)
		Death within 2 visits of the last evaluable PRO assessment	32 (10,7)	36 (12,0)
FACT-Lym Funktionales Wohlbefinden (FWB)	Deterioration	Total	133 (44,5)	110 (36,8)
	Censored	Total	166 (55,5)	189 (63,2)
		No evaluable baseline or post-baseline score	35 (11,7)	40 (13,4)
		Last evaluable assessment without deterioration [a]	83 (27,8)	98 (32,8)
		Missing 2 or more consecutive visits	19 (6,4)	19 (6,4)
		Death within 2 visits of the last evaluable PRO assessment	29 (9,7)	32 (10,7)
FACT-Lym Emotionales Wohlbefinden (EMB)	Deterioration	Total	81 (27,1)	67 (22,4)
	Censored	Total	218 (72,9)	232 (77,6)
		No evaluable baseline or post-baseline score	35 (11,7)	40 (13,4)
		Last evaluable assessment without deterioration [a]	113 (37,8)	130 (43,5)

[a] Includes patients with baseline score too low/high to experience a deterioration.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.4.2.2 ECHO: Summary of status at time of first deterioration in FACT-Lym questionnaire
 Full Analysis Set, DCO 15FEB2024

			Acala+BR (N=299)	Placebo+BR (N=299)
Reason				
Missing 2 or more consecutive visits			23 (7,7)	24 (8,0)
Death within 2 visits of the last evaluable PRO assessment			47 (15,7)	38 (12,7)
FACT-Lym Lym-Subscala (LYMS)	Deterioration	Total	56 (18,7)	52 (17,4)
	Censored	Total	243 (81,3)	247 (82,6)
		No evaluable baseline or post-baseline score	36 (12,0)	41 (13,7)
		Last evaluable assessment without deterioration [a]	138 (46,2)	140 (46,8)
		Missing 2 or more consecutive visits	28 (9,4)	24 (8,0)
		Death within 2 visits of the last evaluable PRO assessment	41 (13,7)	42 (14,0)

[a] Includes patients with baseline score too low/high to experience a deterioration.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/ttereaspr.sas gtttereasprab 19MAR2025:09:01 khcs324

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Table 2.4.2.3 ECHO: Summary of status at time of first deterioration in EQ-5D-5L VAS
 Full Analysis Set, DCO 15FEB2024

			Acala+BR (N=299)	Placebo+BR (N=299)
		Reason		
EQ-5D-5L Visuelle Analogskala	Deterioration	Total	111 (37,1)	88 (29,4)
	Censored	Total	188 (62,9)	211 (70,6)
		No evaluable baseline or post-baseline score	37 (12,4)	47 (15,7)
		Last evaluable assessment without deterioration [a]	97 (32,4)	111 (37,1)
		Missing 2 or more consecutive visits	19 (6,4)	20 (6,7)
		Death within 2 visits of the last evaluable PRO assessment	35 (11,7)	33 (11,0)

[a] Includes patients with baseline score too low/high to experience a deterioration.

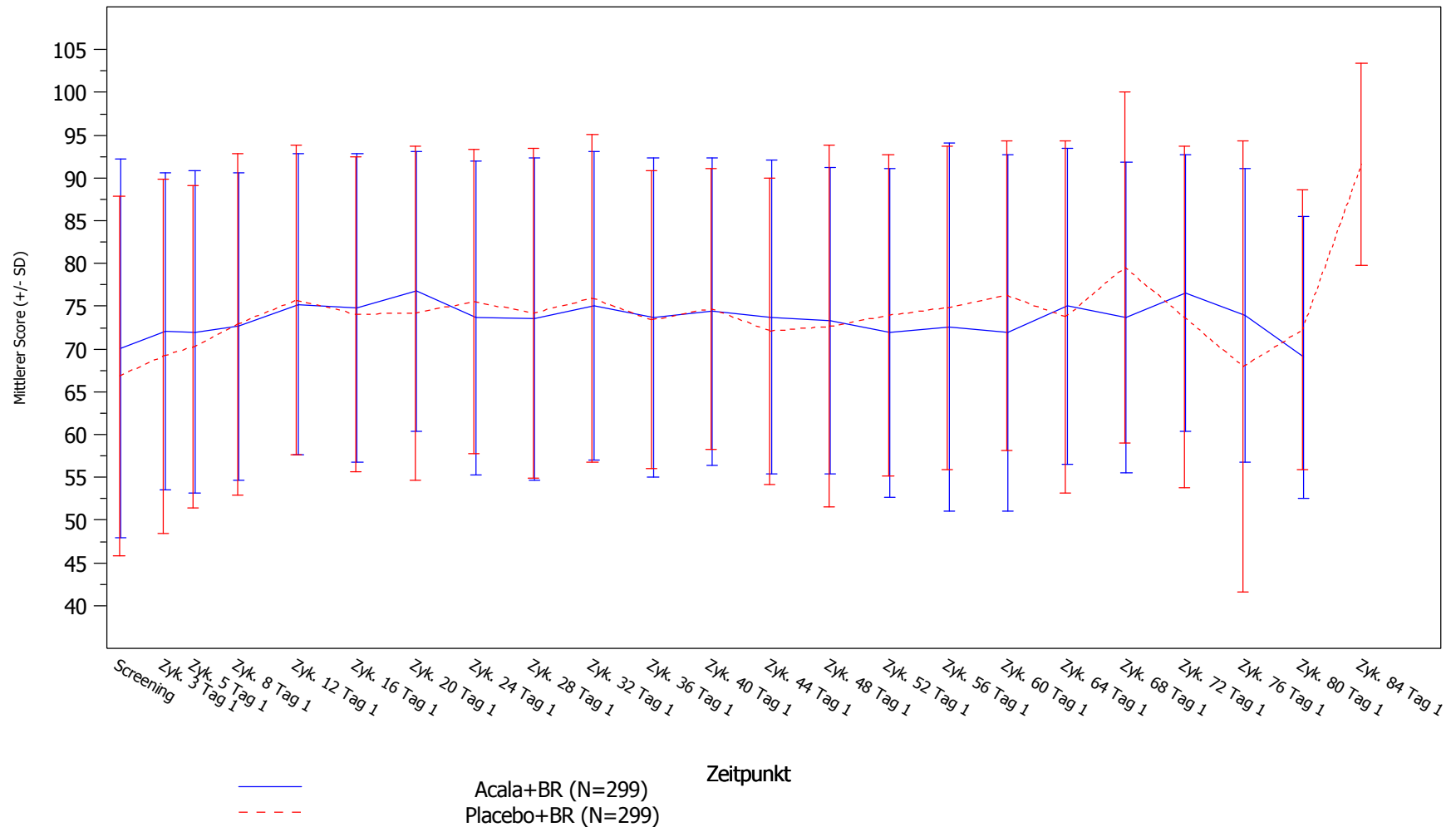
Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/ttereaspr.sas gtttereasprac 19MAR2025:09:01 khcs324

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Figure 2.5.1.1 ECHO: Mean (+/- SD) plot of EORTC QLQ-C30 Allgemeine Lebensqualität/Gesundheitsszustand across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



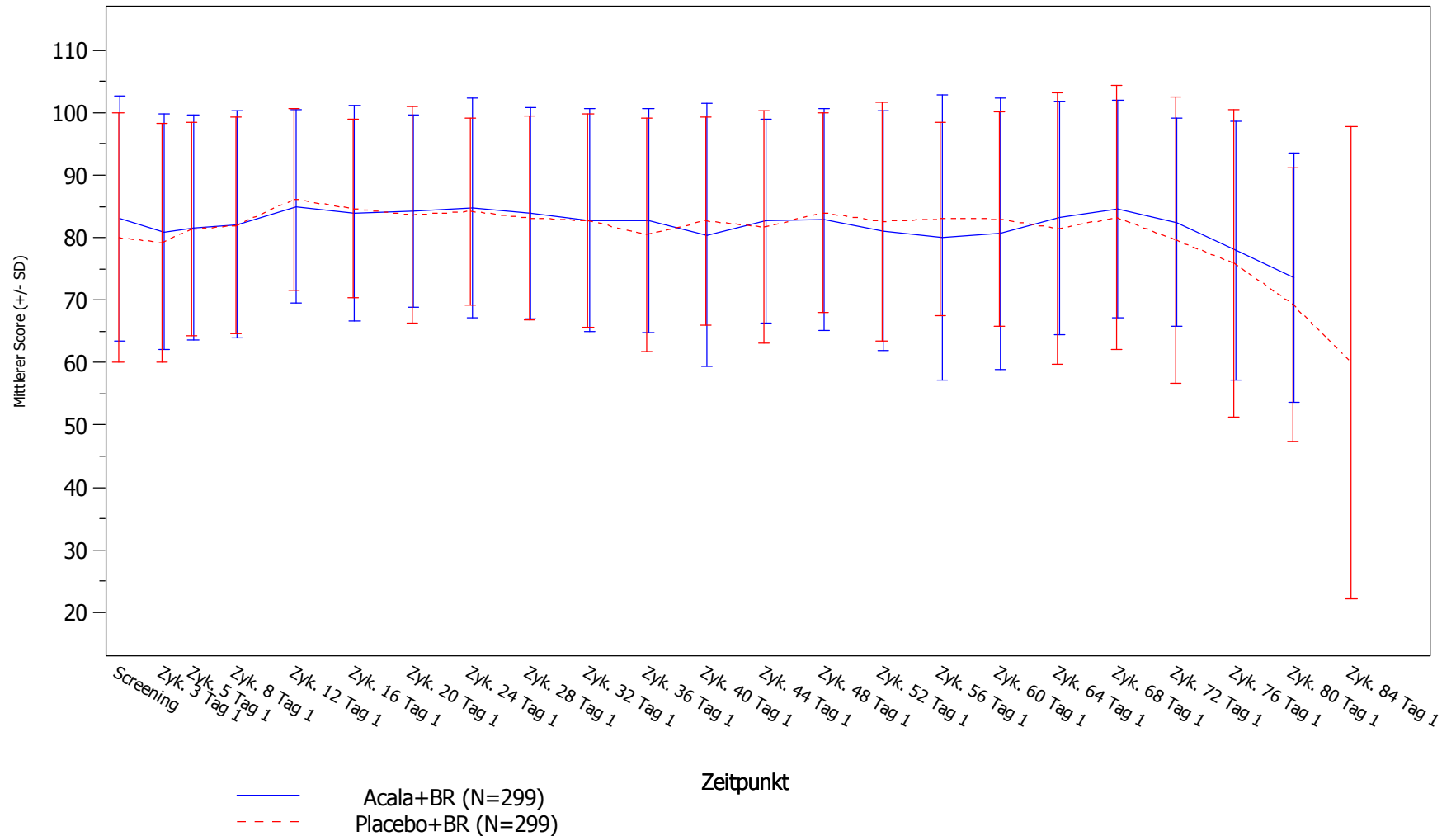
Anzahl an Patienten:

283	256	249	226	212	196	176	161	149	119	118	107	100	94	83	68	62	53	38	33	16	7	ND	Acala+BR
272	253	233	211	182	163	154	136	126	115	99	89	84	78	70	56	46	41	31	20	13	6	2	Placebo+BR

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Figure 2.5.1.2 ECHO: Mean (+/- SD) plot of EORTC QLQ-C30 Funktionsskala: Körper across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



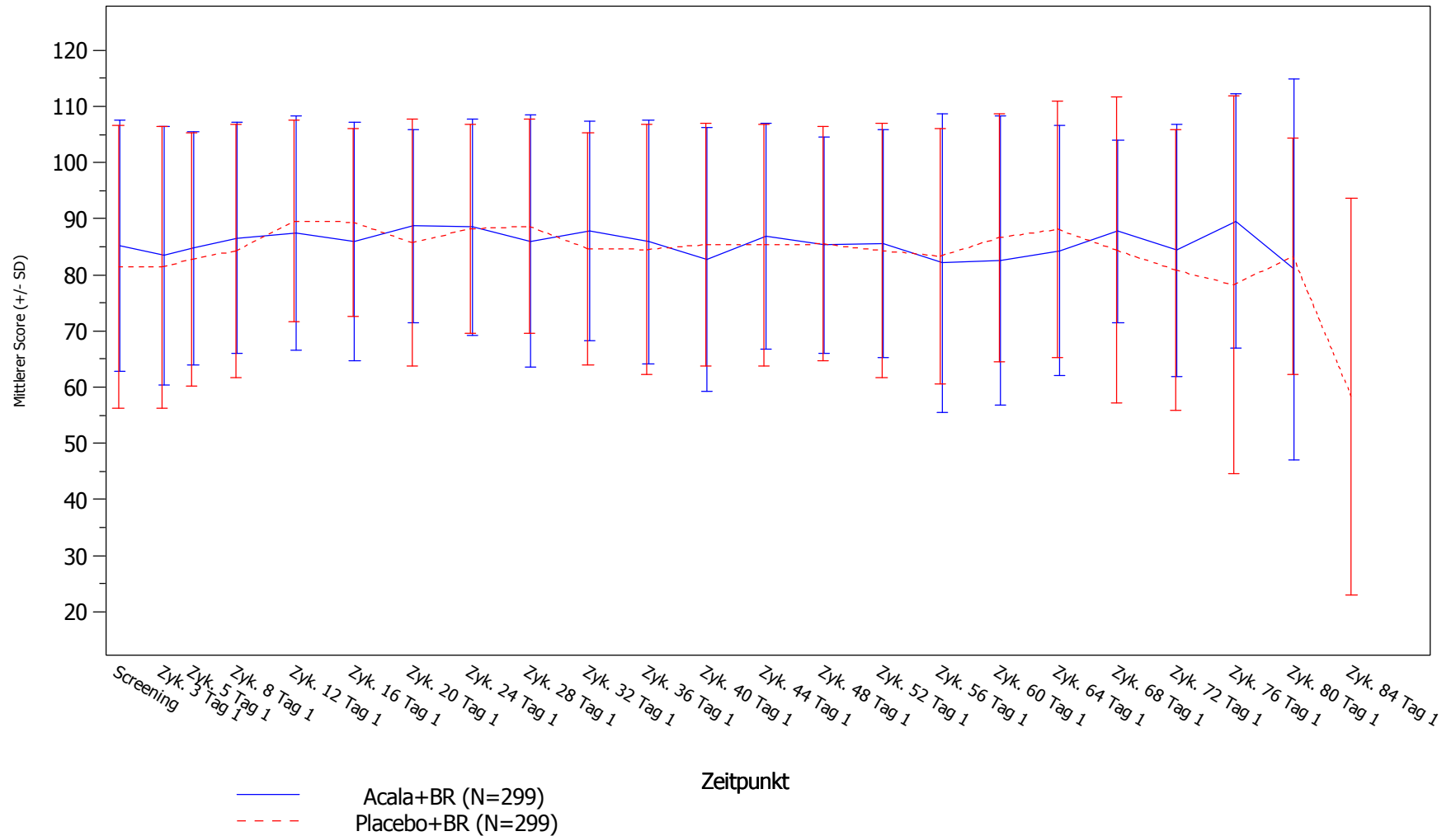
Anzahl an Patienten:

285	256	248	225	212	196	177	162	149	120	118	107	100	94	84	68	62	53	38	33	16	7	ND	Acala+BR
275	255	233	210	182	163	154	137	126	116	100	89	83	77	70	56	46	42	31	20	13	5	2	Placebo+BR

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Figure 2.5.1.3 ECHO: Mean ($\pm$ SD) plot of EORTC QLQ-C30 Funktionsskala: Rolle across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



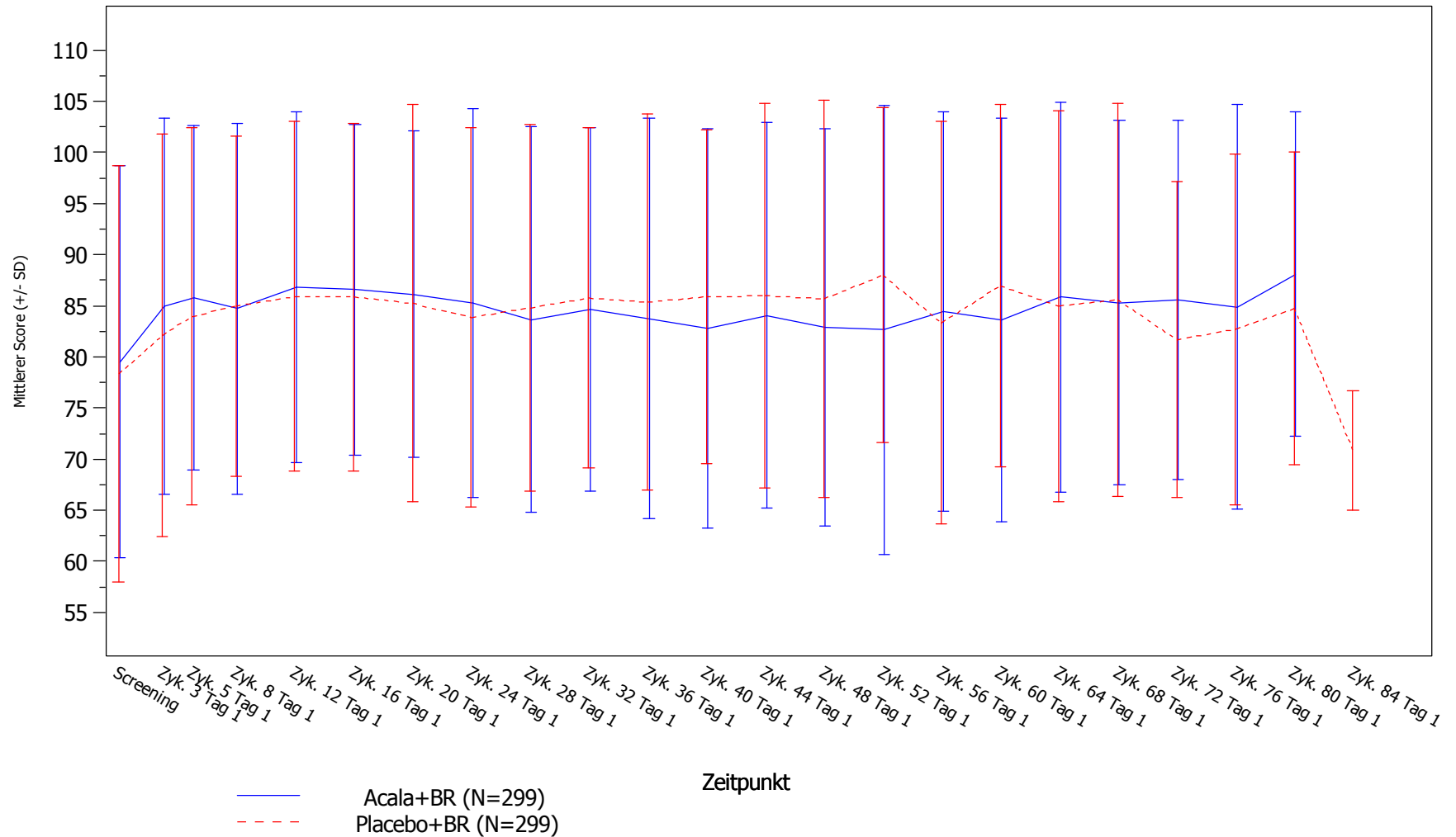
Anzahl an Patienten:

285	255	248	225	212	196	177	162	149	119	118	108	100	94	84	68	62	53	38	33	16	7	ND	Acala+BR
275	253	233	211	182	163	154	137	126	116	100	89	84	77	70	56	46	42	31	20	13	6	2	Placebo+BR

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Figure 2.5.1.4 ECHO: Mean ($\pm$ SD) plot of EORTC QLQ-C30 Funktionsskala: Emotionalität across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten:

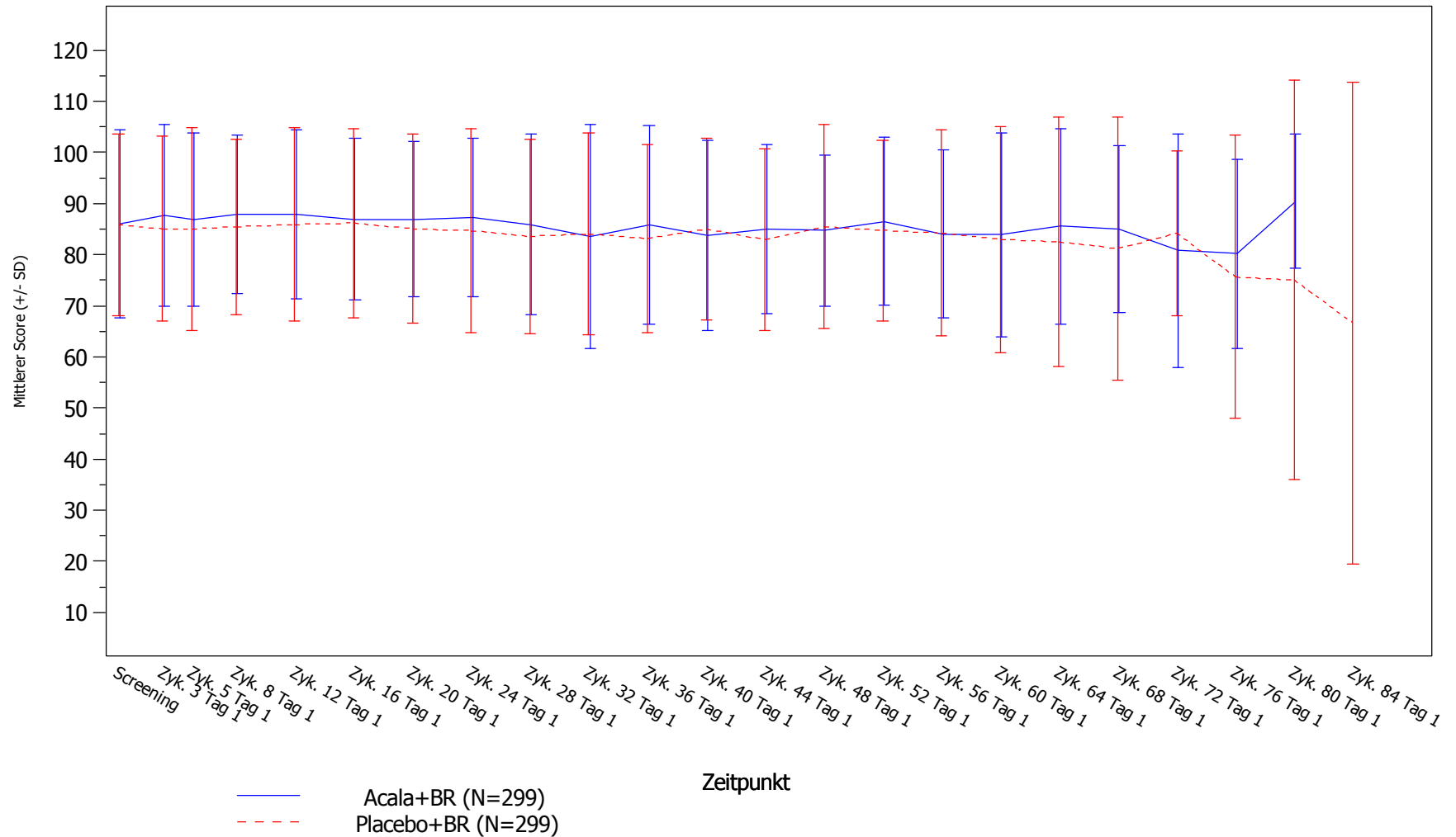
283	256	248	226	212	196	176	161	149	120	118	107	100	94	83	68	62	53	38	33	16	7	ND	Acala+BR
273	253	233	211	182	163	154	136	126	115	99	89	84	78	70	56	46	41	31	20	13	6	2	Placebo+BR

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 2.5.1.5 ECHO: Mean (+/- SD) plot of EORTC QLQ-C30 Funktionsskala: Kognition across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten:

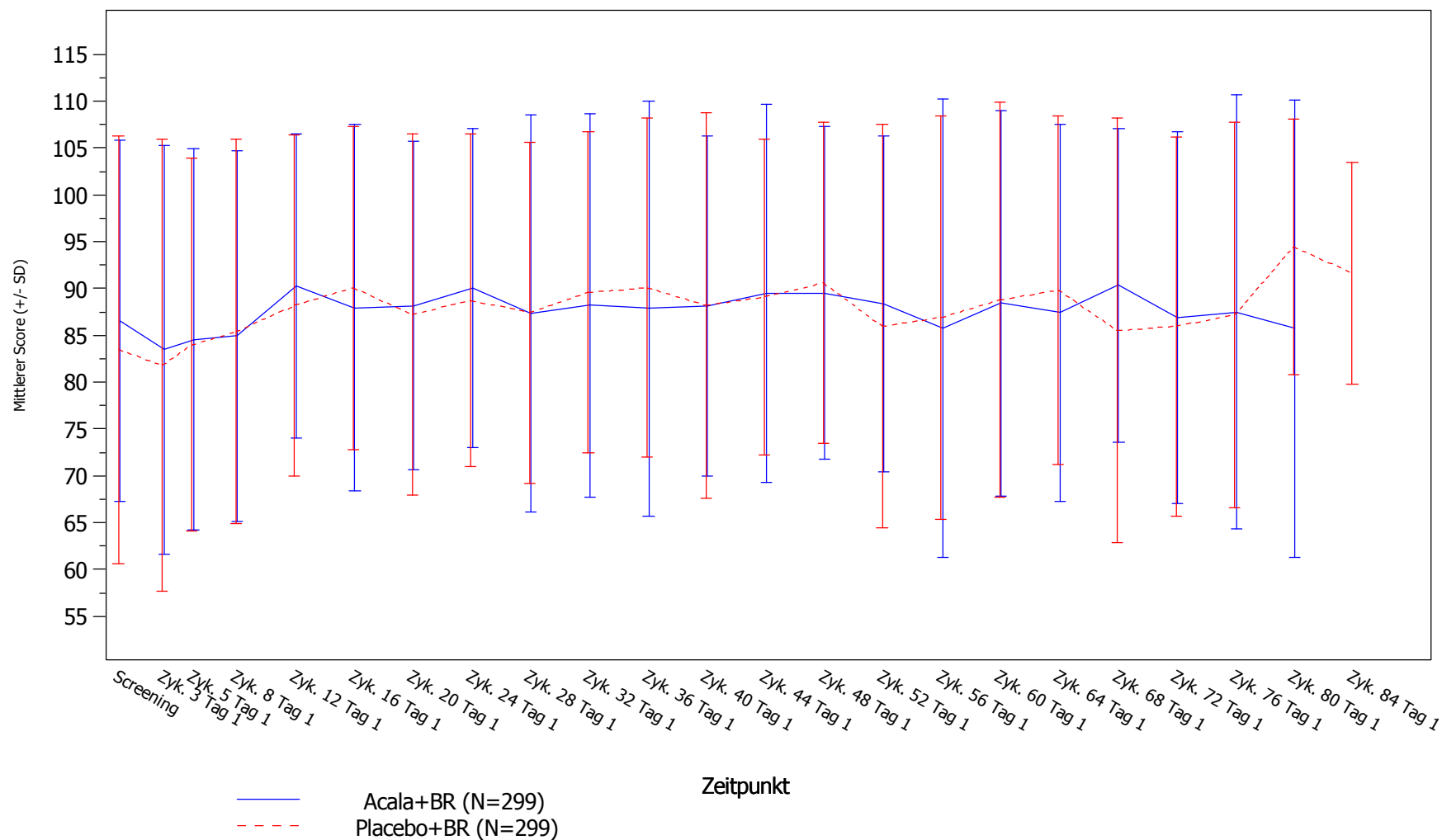
283	256	249	226	212	196	176	161	149	120	118	107	100	94	83	68	62	53	38	33	16	7	ND	Acala+BR
273	253	234	211	182	163	154	136	126	115	99	89	84	78	70	56	46	41	31	19	13	6	2	Placebo+BR

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 2.5.1.6 ECHO: Mean (+/- SD) plot of EORTC QLQ-C30 Funktionsskala: Sozial across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten:

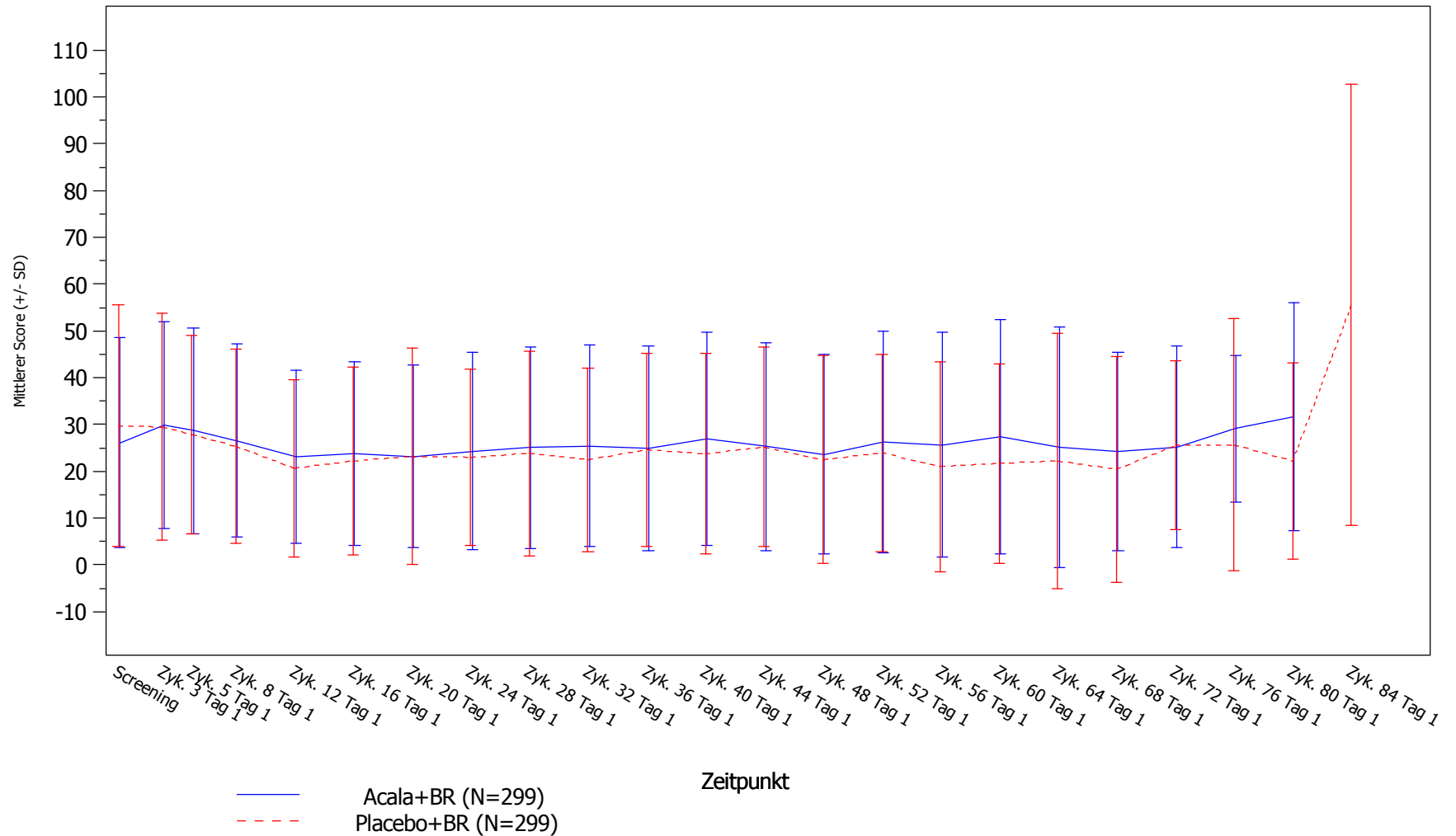
283	256	248	225	212	196	176	161	149	120	118	107	100	94	83	68	62	53	38	33	16	7	ND	Acala+BR
273	252	233	211	182	163	154	136	126	115	99	89	84	78	70	56	46	41	31	19	13	6	2	Placebo+BR

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 2.5.1.7 ECHO: Mean (+/- SD) plot of EORTC QLQ-C30 Fatigue across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten:

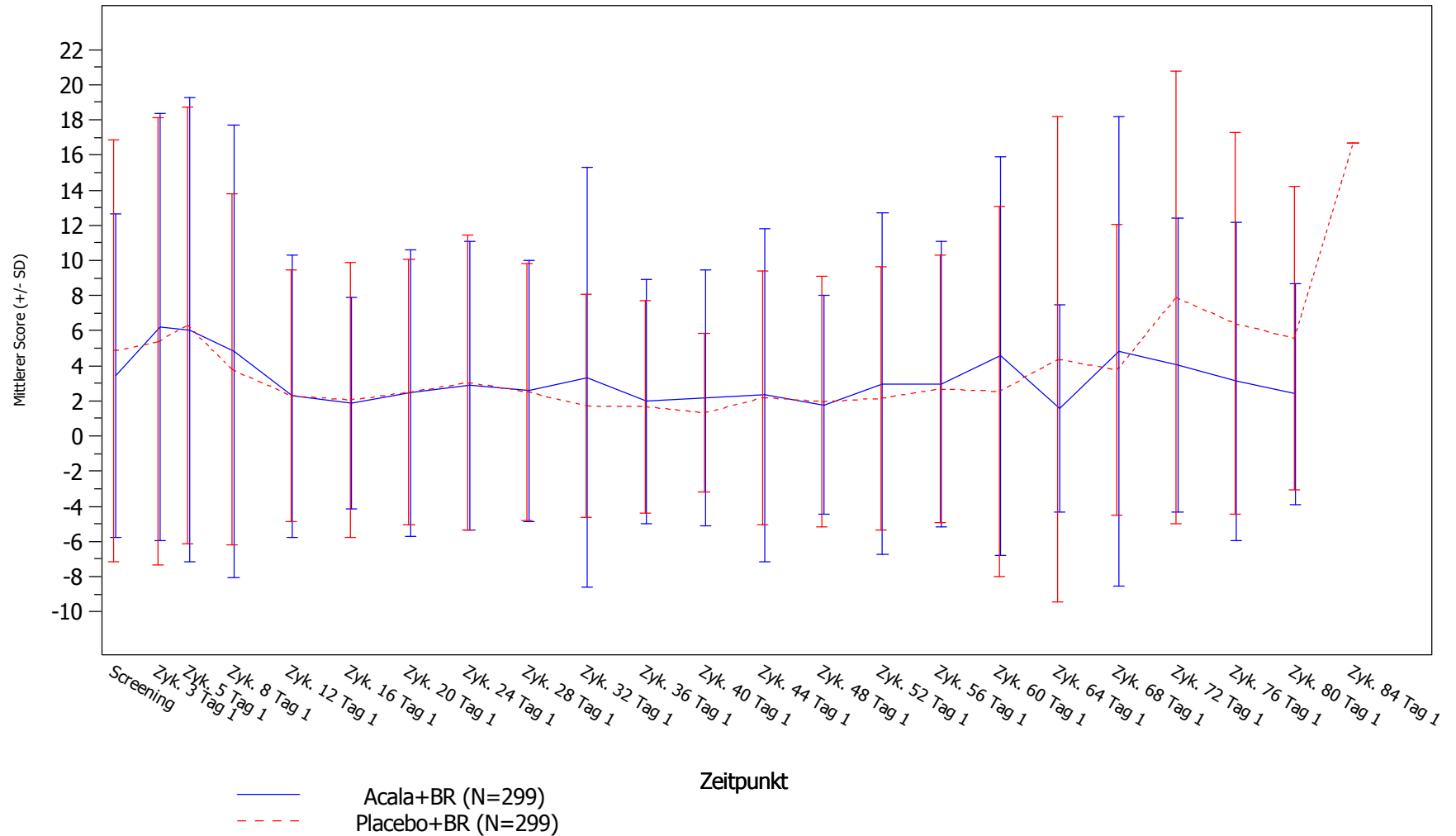
285	256	248	225	212	196	177	162	149	120	118	107	100	94	84	68	62	53	38	33	16	7	ND	Acala+BR
275	255	233	210	182	163	154	137	126	116	100	89	84	77	70	56	46	42	31	20	13	6	2	Placebo+BR

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 2.5.1.8 ECHO: Mean (+/- SD) plot of EORTC QLQ-C30 Übelkeit und Erbrechen across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten:

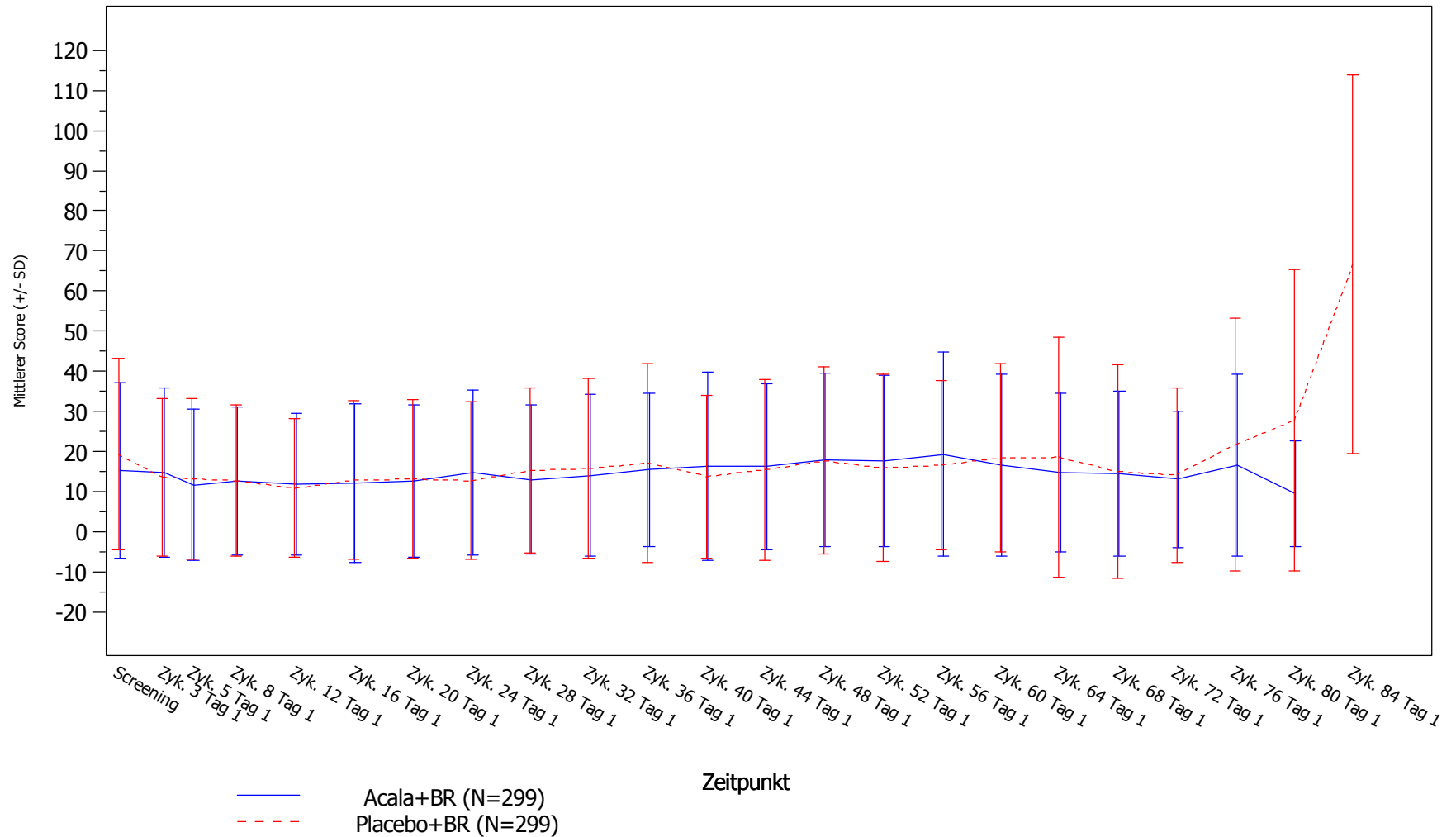
285	256	248	225	212	196	177	162	149	120	118	107	100	94	84	68	62	53	38	33	16	7	ND	Acala+BR
275	254	233	211	182	163	154	137	126	116	100	89	84	77	70	56	46	42	31	19	13	6	2	Placebo+BR

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 2.5.1.9 ECHO: Mean ($\pm$ SD) plot of EORTC QLQ-C30 Schmerzen across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten:

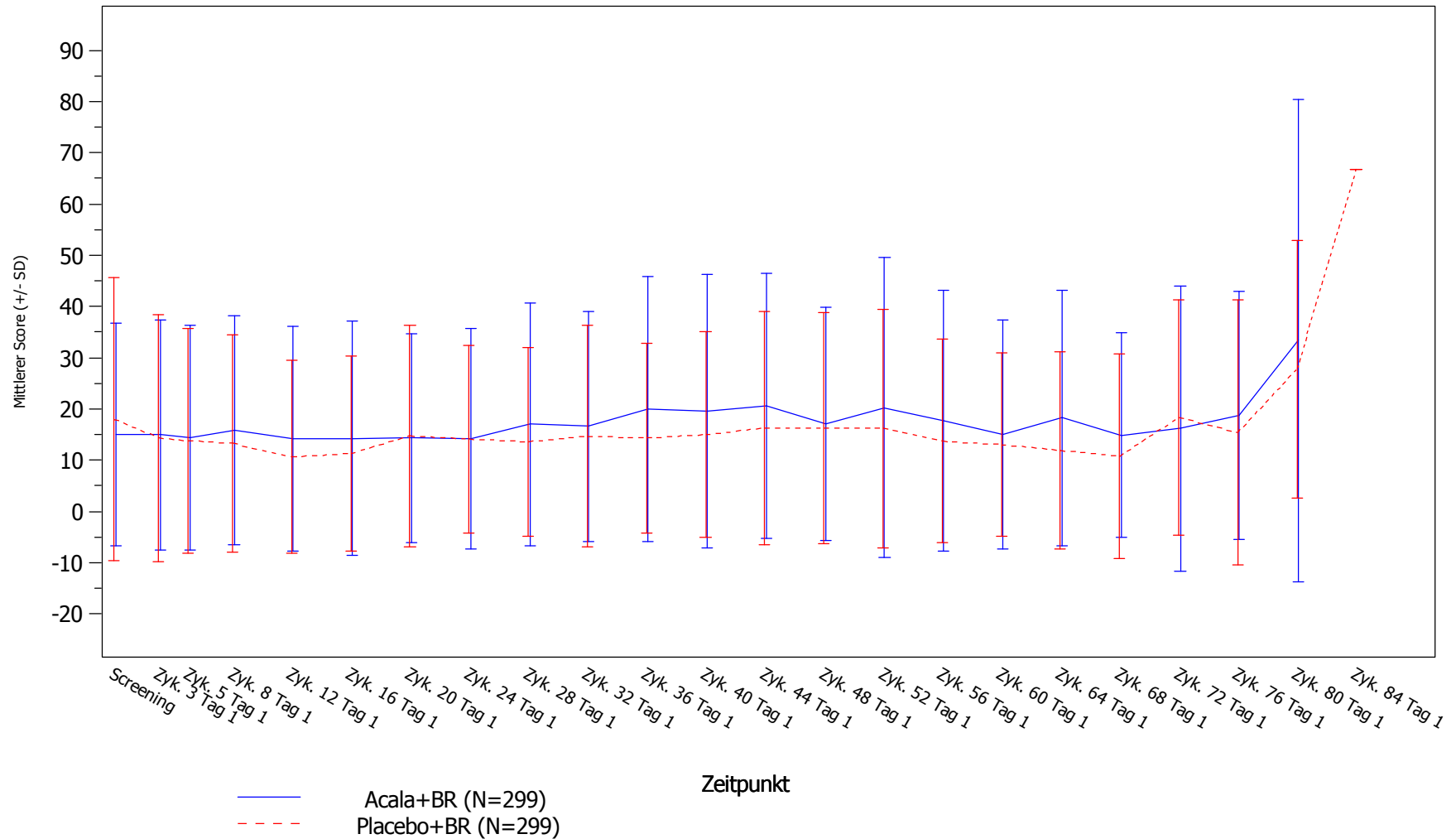
285	256	249	225	212	196	177	162	149	120	118	108	100	94	84	68	62	53	38	33	16	7	ND	Acala+BR
275	254	234	211	182	163	154	137	126	116	100	89	84	78	70	56	46	42	31	20	13	6	2	Placebo+BR

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 2.5.1.10 ECHO: Mean (+/- SD) plot of EORTC QLQ-C30 Dyspnoe across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten:

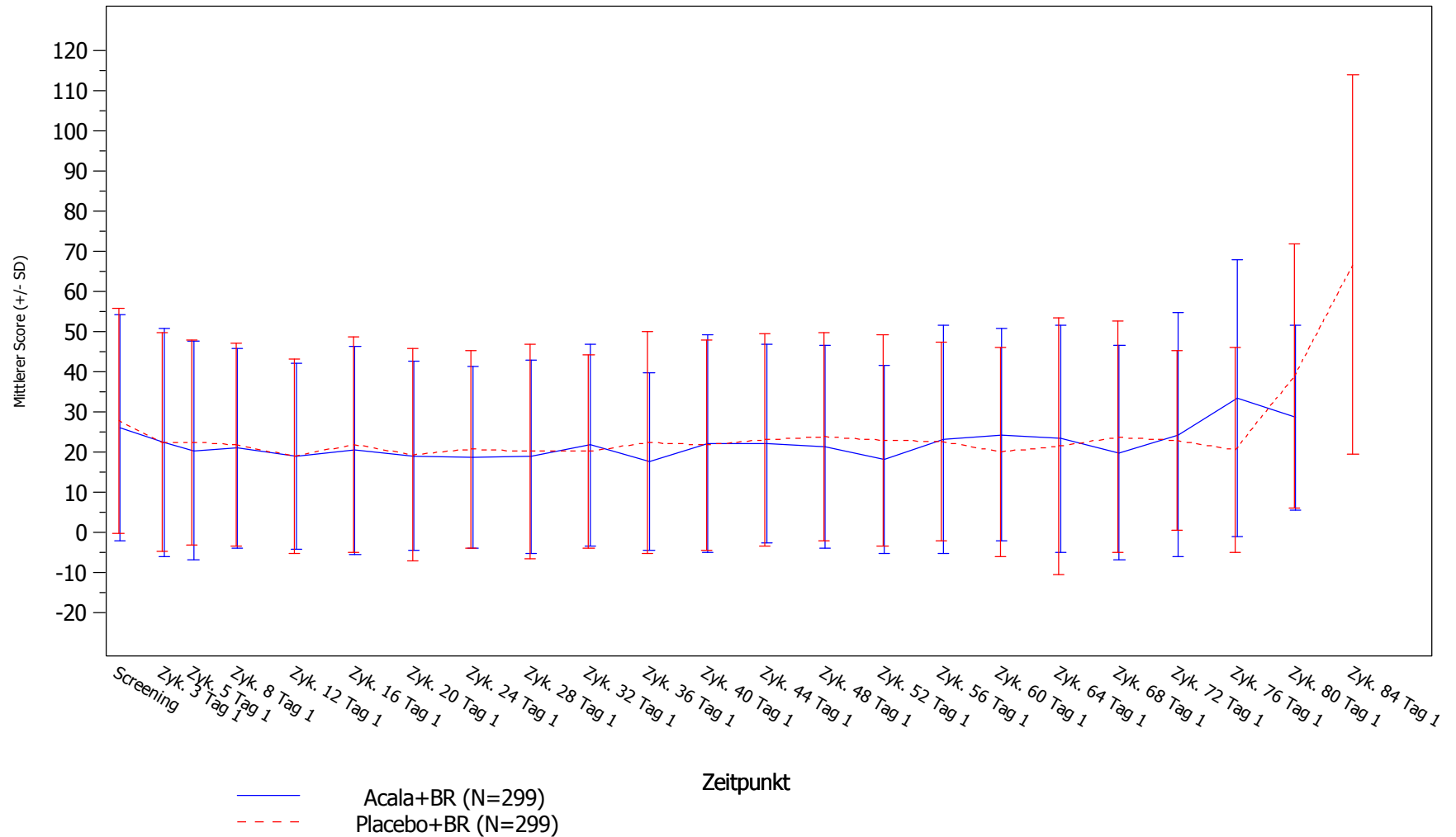
285	256	248	225	212	196	177	162	149	120	117	107	100	94	84	68	62	53	38	33	16	7	ND	Acala+BR
274	253	232	211	182	162	154	137	125	116	100	89	84	78	70	56	46	42	31	20	13	6	2	Placebo+BR

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 2.5.1.11 ECHO: Mean ($\pm$ SD) plot of EORTC QLQ-C30 Schlaflosigkeit across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten:

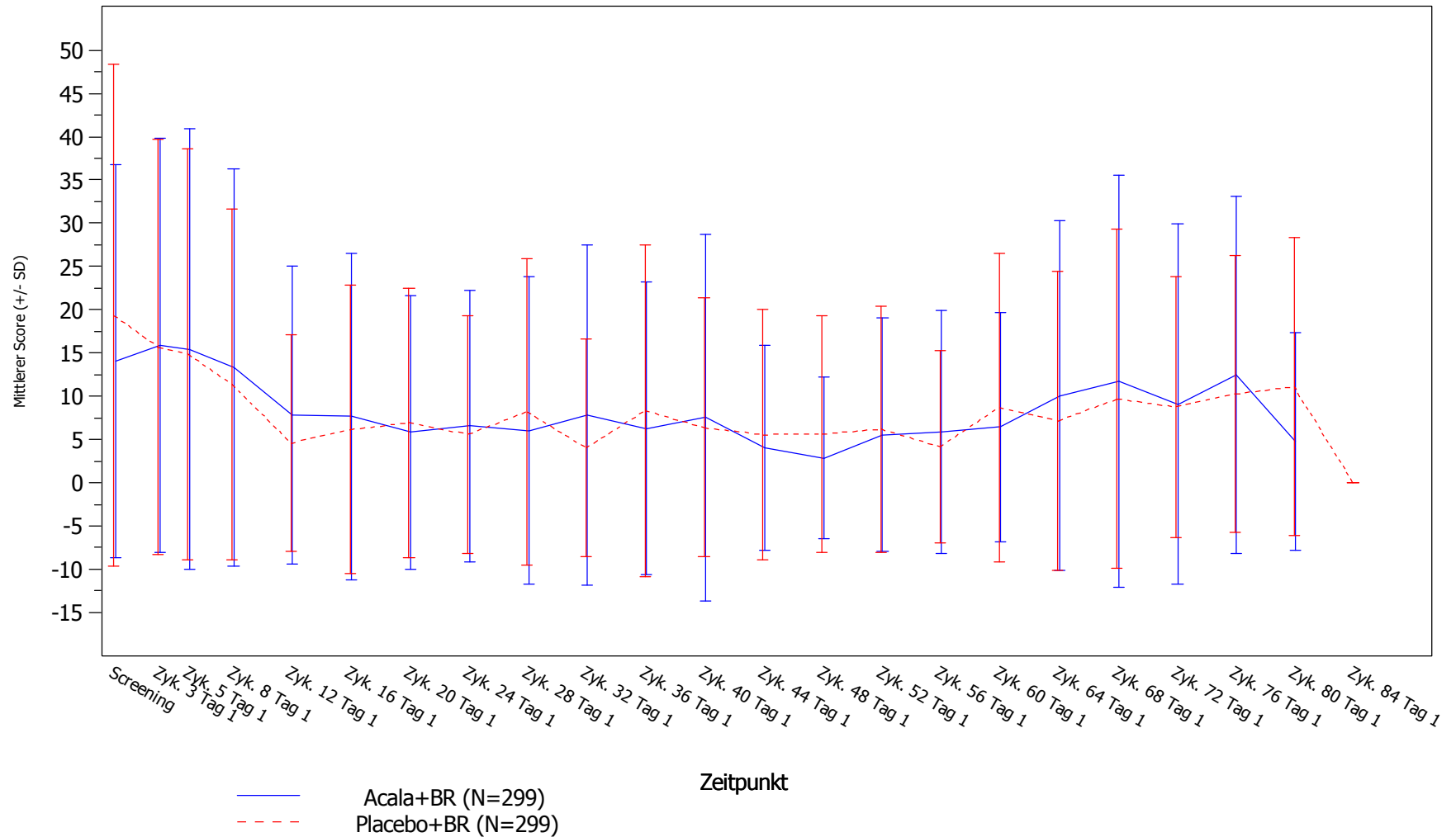
284	255	248	225	212	196	176	162	149	120	118	107	100	94	83	68	62	53	37	33	16	7	ND	Acala+BR
275	253	232	211	182	163	154	137	126	116	100	89	84	77	70	56	45	42	31	19	13	6	2	Placebo+BR

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 2.5.1.12 ECHO: Mean (+/- SD) plot of EORTC QLQ-C30 Appetitverlust across timepoints, by treatment group
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten:

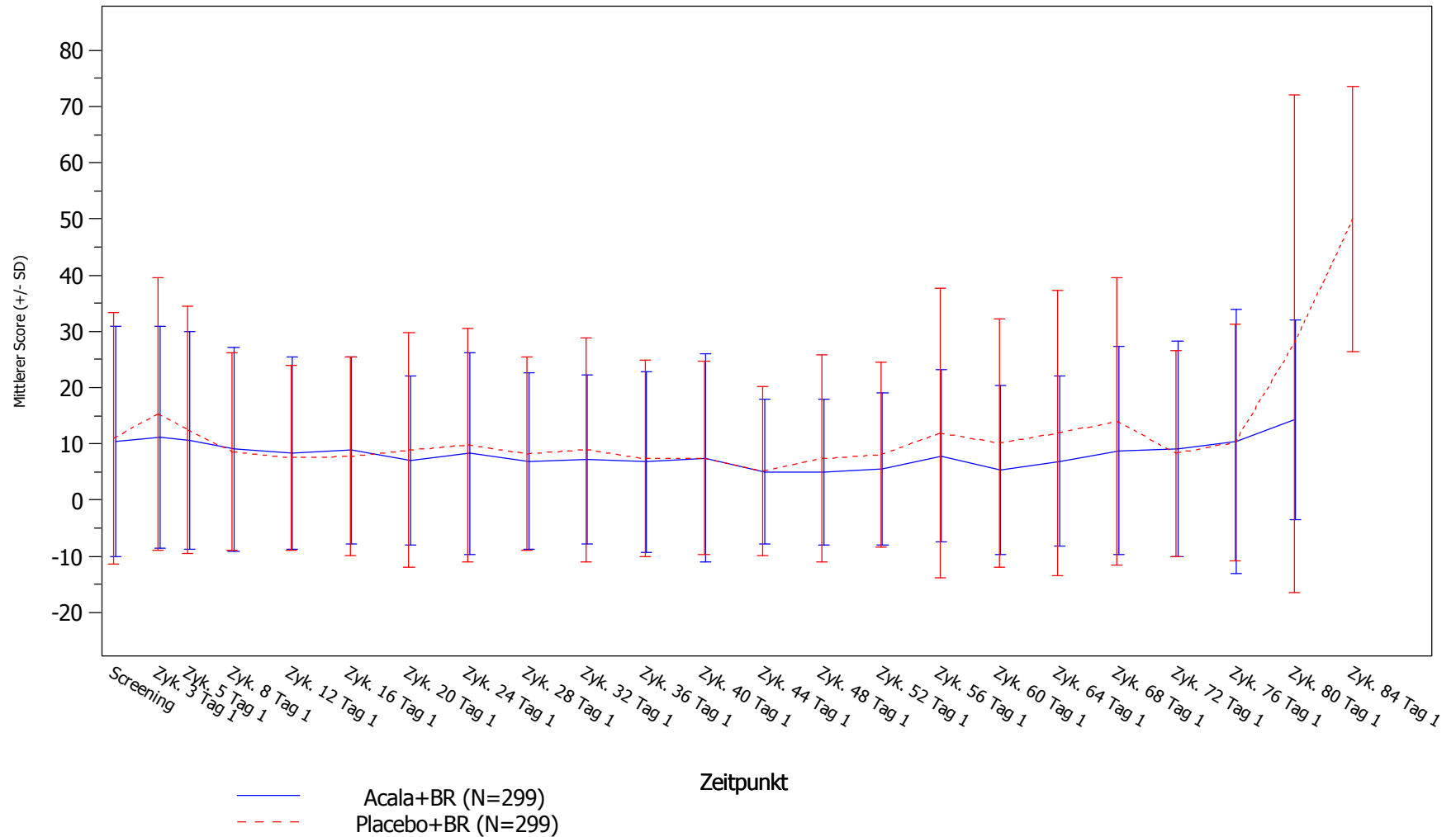
284	256	248	225	212	196	177	162	149	120	117	106	100	94	84	68	62	53	37	33	16	7	ND	Acala+BR
274	253	233	211	182	163	154	137	126	116	100	89	84	77	70	56	46	42	31	19	13	6	2	Placebo+BR

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 2.5.1.13 ECHO: Mean (+/- SD) plot of EORTC QLQ-C30 Verstopfung across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten:

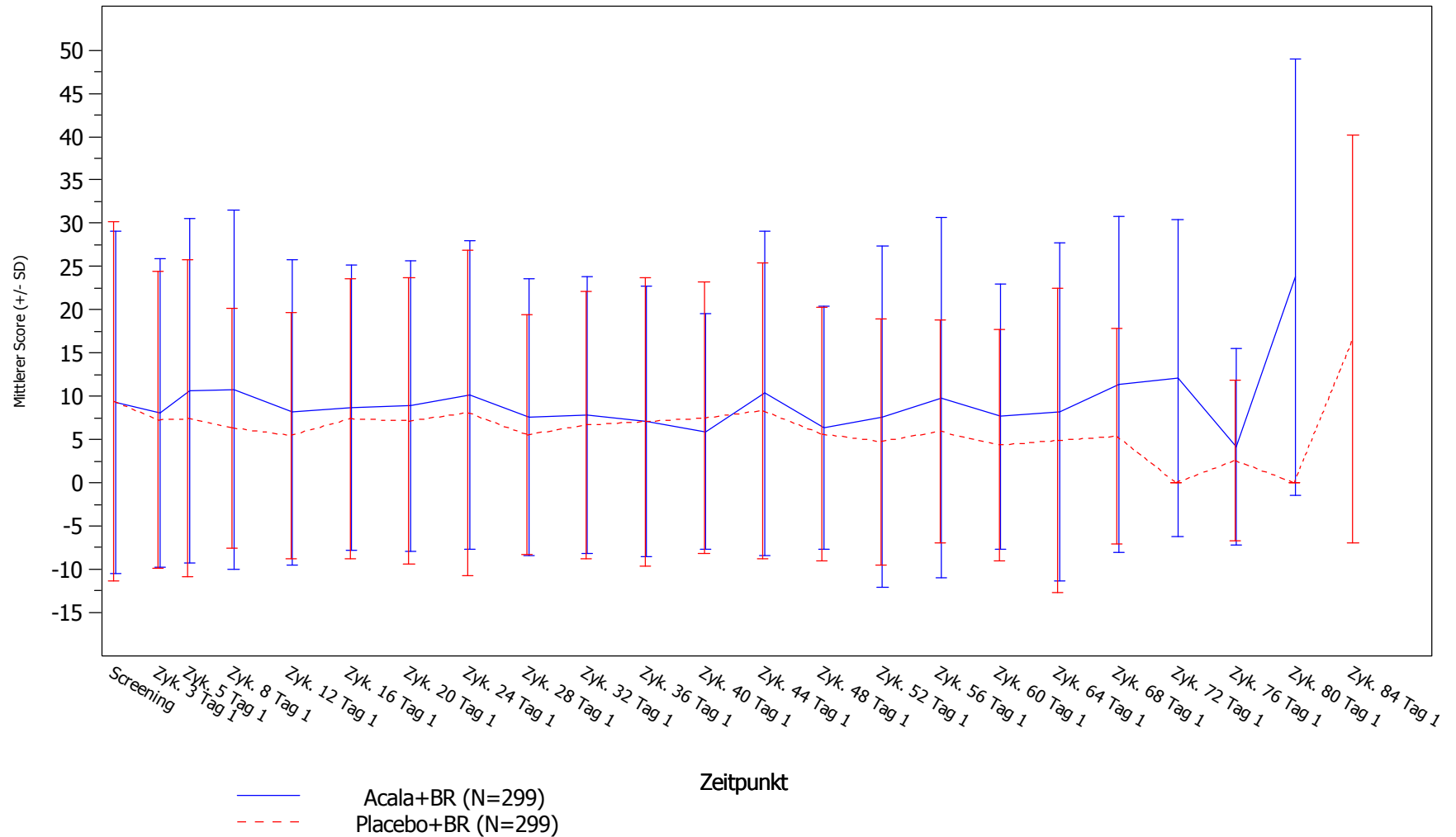
284	256	248	225	212	196	175	161	149	120	118	107	99	94	84	68	62	53	38	33	16	7	ND	Acala+BR
272	252	232	209	182	163	154	136	126	115	100	89	84	77	70	56	46	42	31	20	13	6	2	Placebo+BR

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 2.5.1.14 ECHO: Mean ($\pm$ SD) plot of EORTC QLQ-C30 Diarrhö across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten:

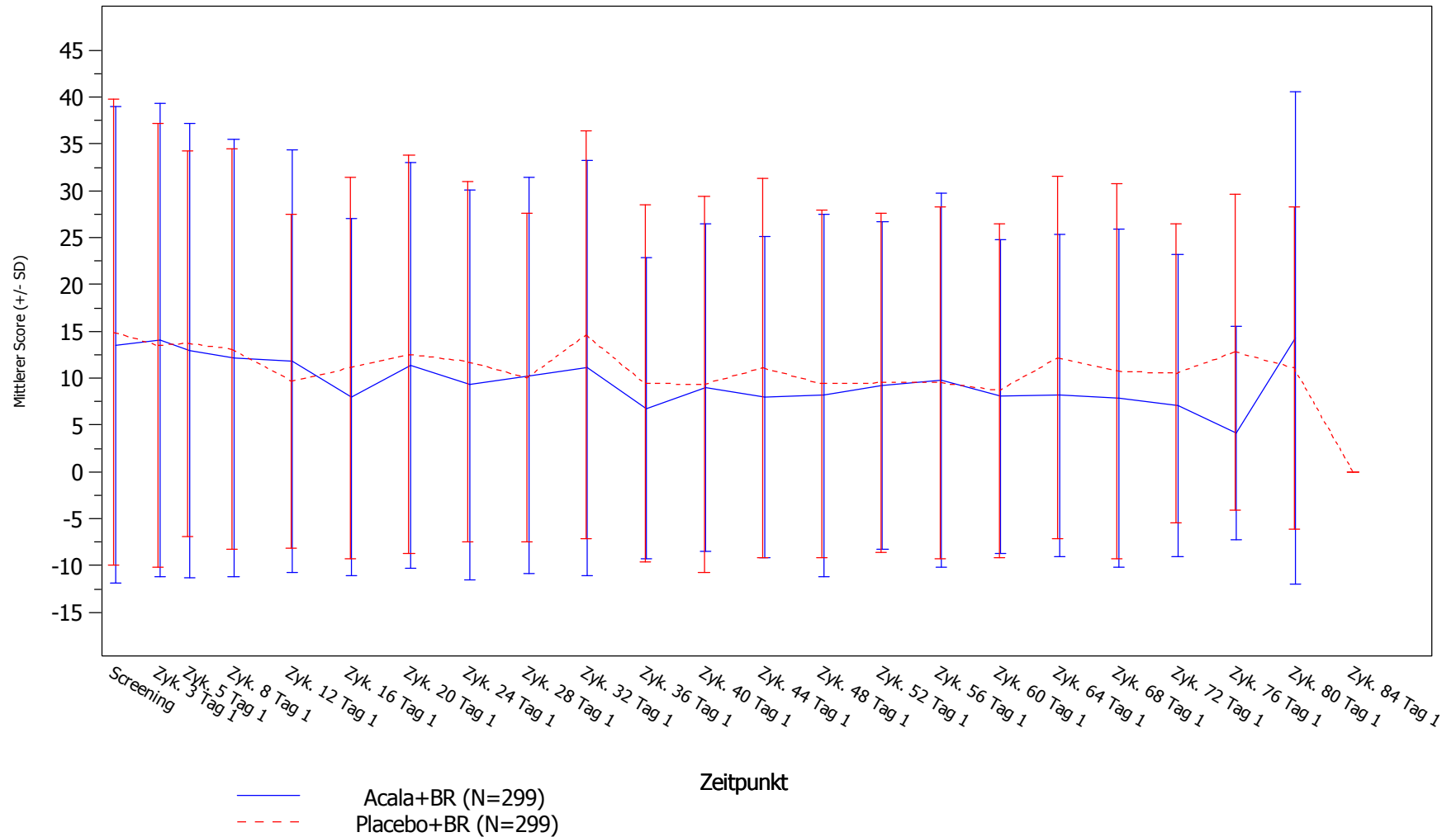
283	256	248	226	212	196	176	161	149	120	118	107	100	94	83	68	61	53	38	33	16	7	ND	Acala+BR
273	252	234	211	182	162	154	136	126	115	99	89	84	77	70	56	46	41	31	19	13	6	2	Placebo+BR

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 2.5.1.15 ECHO: Mean ($\pm$ SD) plot of EORTC QLQ-C30 Finanzielle Schwierigkeiten across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten:

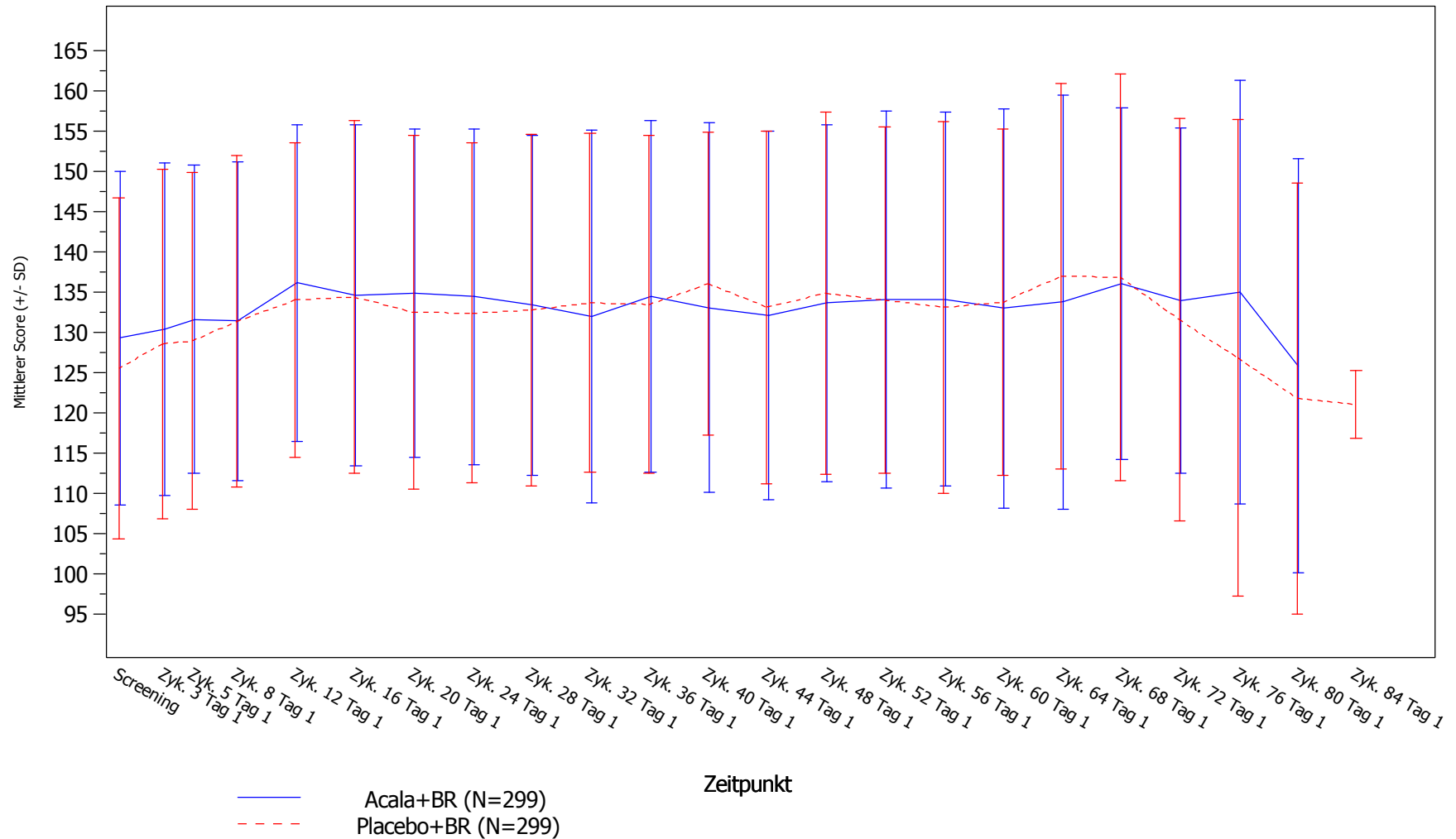
283	256	249	225	211	196	176	161	149	120	118	107	100	94	83	68	62	53	38	33	16	7	ND	Acala+BR
273	252	233	211	182	162	154	136	126	114	99	89	84	78	70	56	46	41	31	19	13	6	2	Placebo+BR

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 2.5.2.1 ECHO: Mean ($\pm$ SD) plot of FACT-Lym Gesamtscore across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



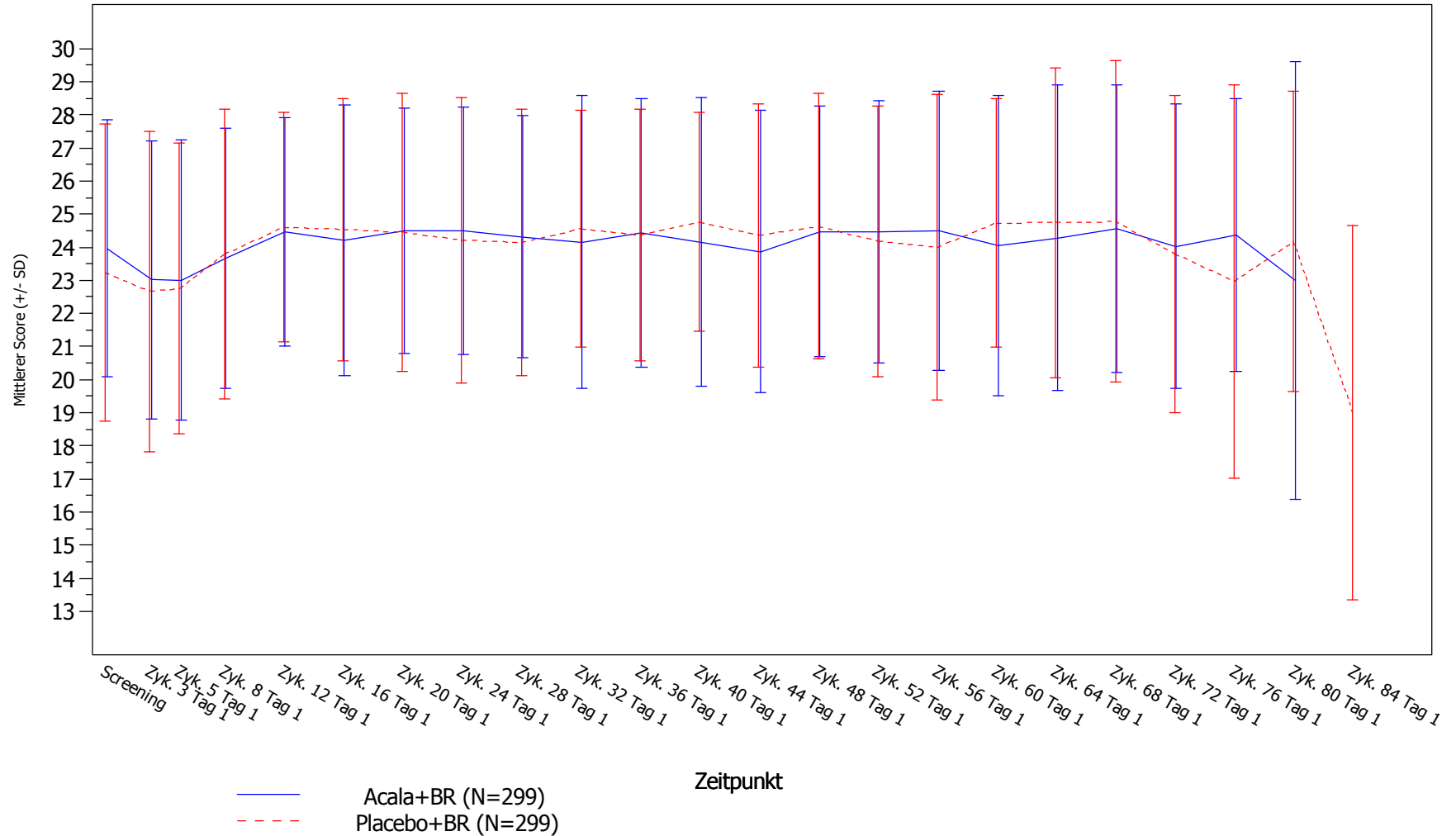
Anzahl an Patienten:

281	254	243	224	214	198	178	159	150	122	119	109	101	93	83	67	62	52	38	33	16	5	ND	Acala+BR
273	251	235	211	182	164	155	137	124	115	100	90	84	78	70	56	46	42	31	19	12	5	2	Placebo+BR

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Figure 2.5.2.2 ECHO: Mean ($\pm$ SD) plot of FACT-Lym Physisches Wohlbefinden (PWB) across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



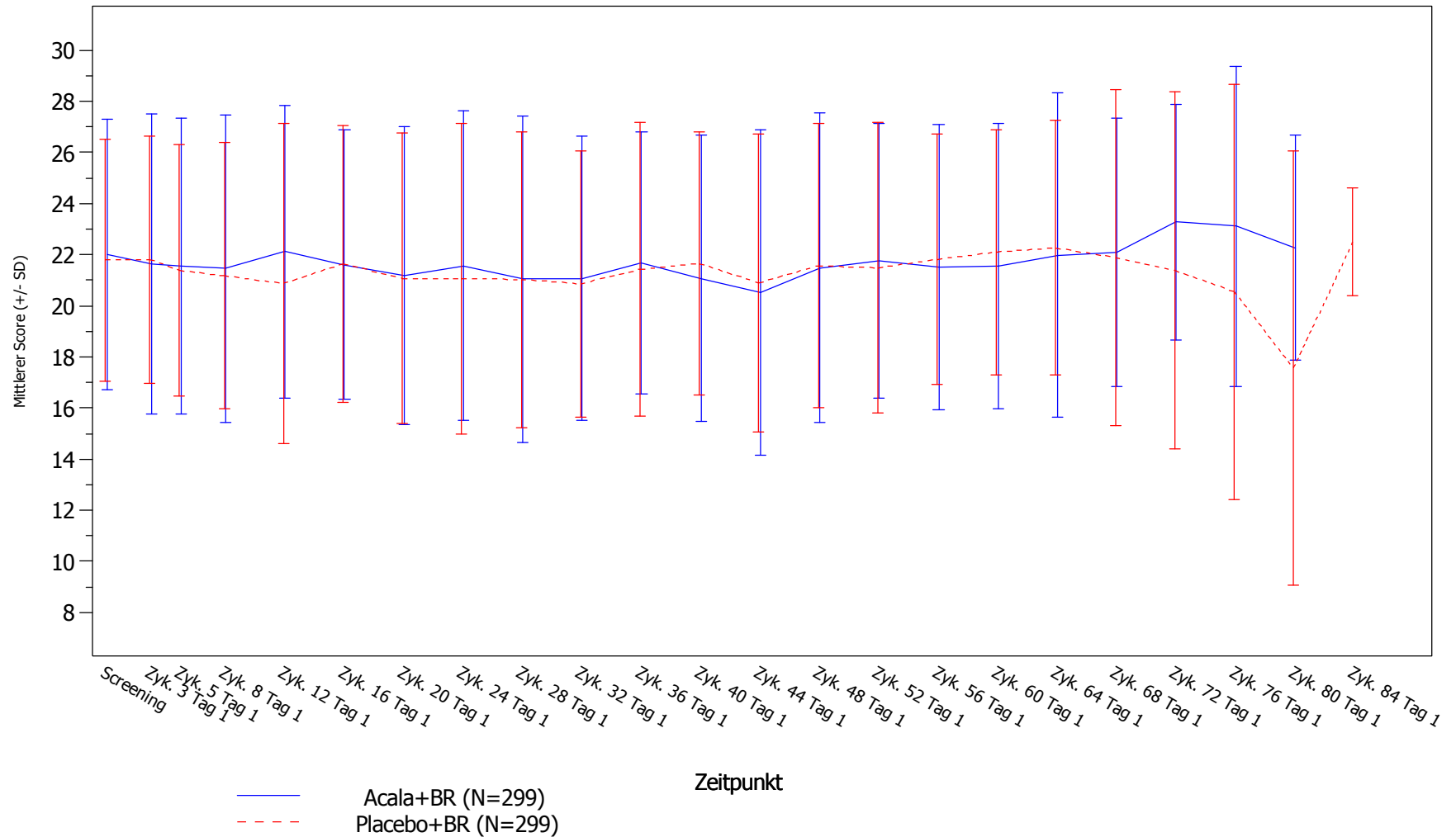
Anzahl an Patienten:

282	255	245	225	215	198	178	160	151	122	119	110	101	94	83	67	62	53	38	33	16	6	ND	Acala+BR
274	252	235	212	182	164	155	138	125	115	101	90	84	78	70	56	46	42	31	20	12	6	2	Placebo+BR

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Figure 2.5.2.3 ECHO: Mean ($\pm$ SD) plot of FACT-Lym Soziales Wohlbefinden (SWB) across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



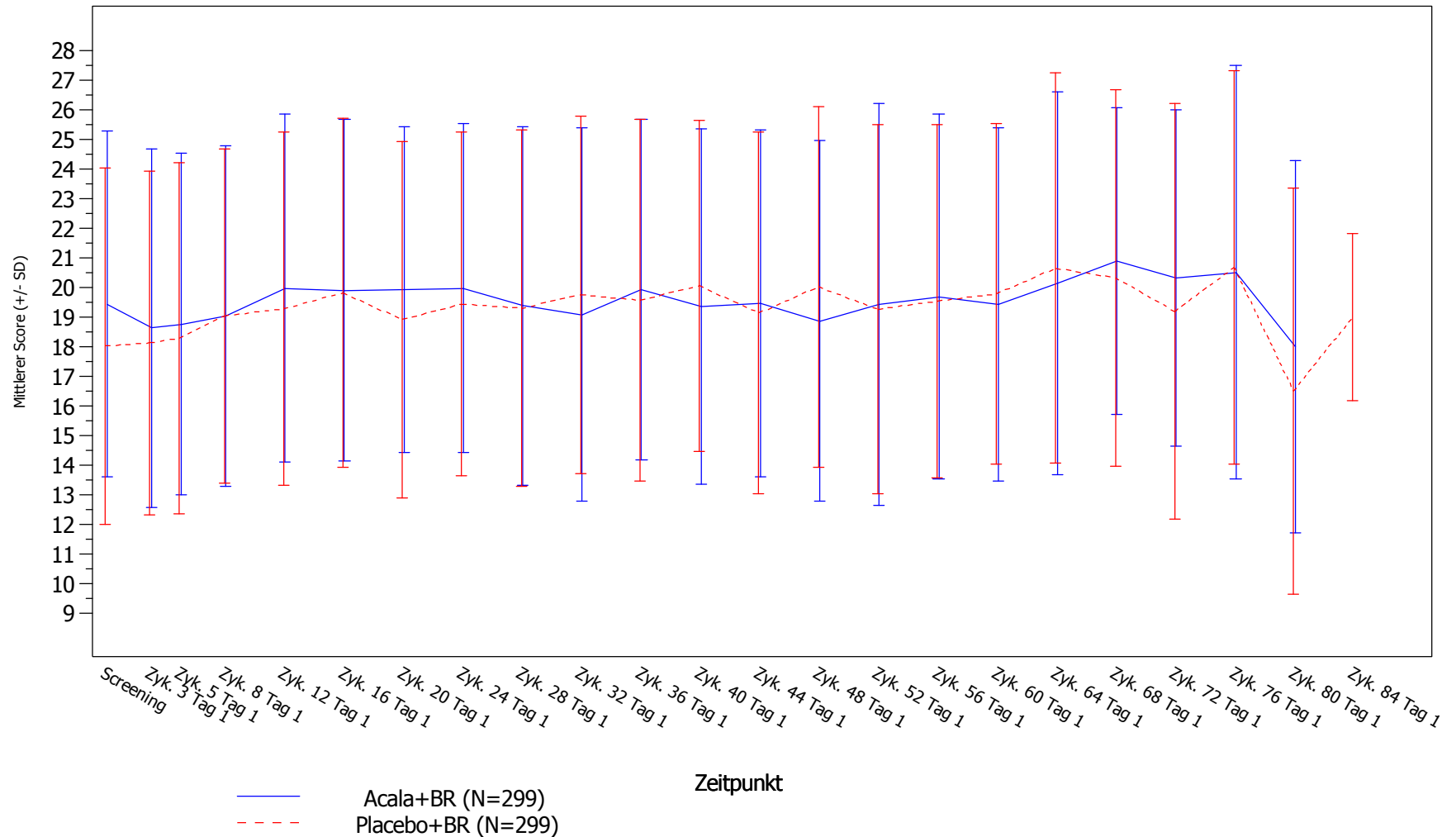
Anzahl an Patienten:

282	255	245	225	215	198	178	160	151	122	119	110	101	94	83	68	62	53	38	33	16	6	ND	Acala+BR
274	252	235	213	182	164	155	138	125	115	101	90	84	78	70	56	46	42	31	20	12	6	2	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 2.5.2.4 ECHO: Mean (+/- SD) plot of FACT-Lym Funktionales Wohlbefinden (FWB) across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



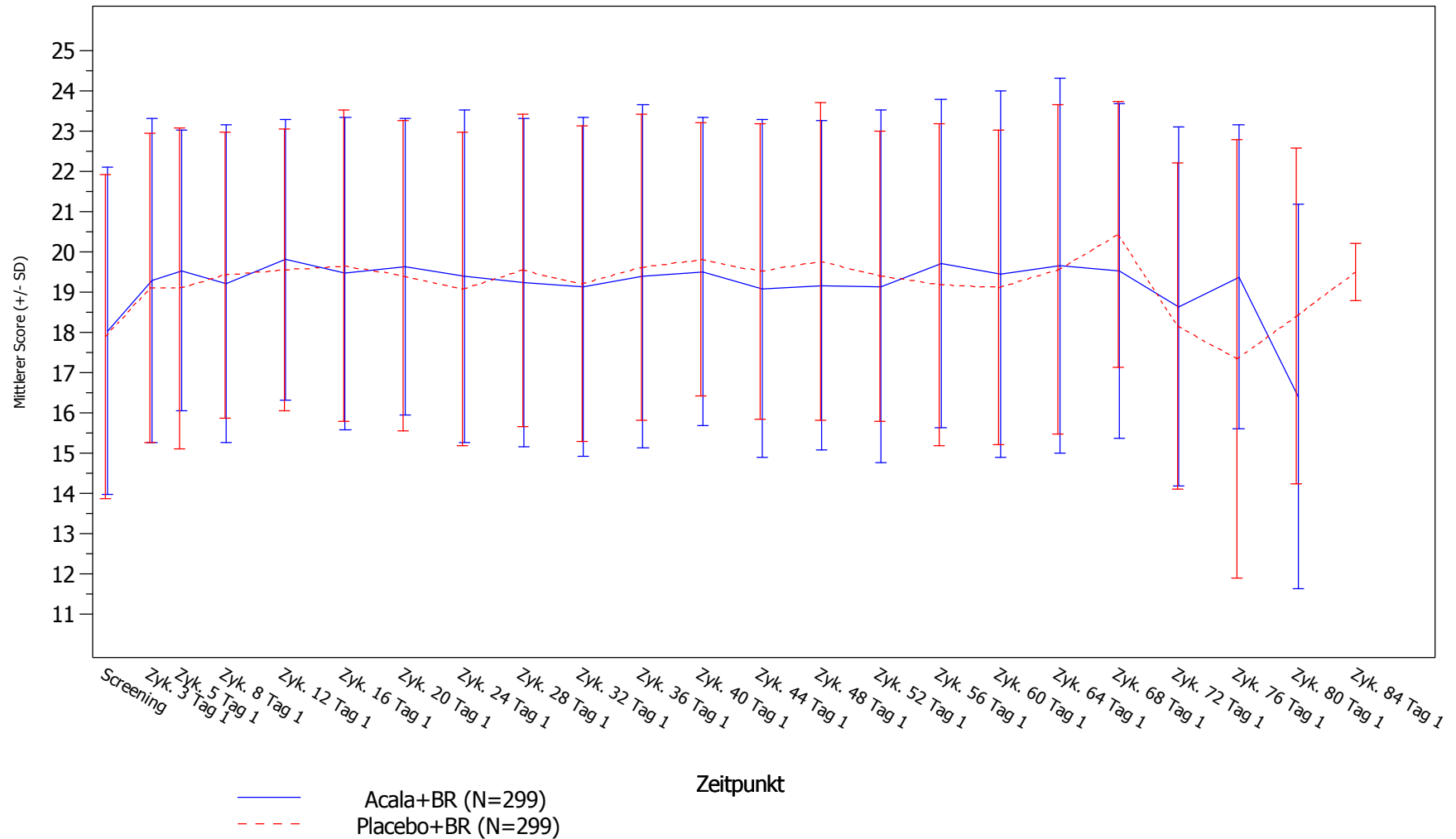
Anzahl an Patienten:

281	255	245	225	215	198	178	161	151	122	119	109	101	94	83	69	62	53	38	33	16	5	ND	Acala+BR
274	252	235	213	183	164	155	138	125	115	100	90	84	78	70	56	46	42	31	20	12	6	2	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 2.5.2.5 ECHO: Mean (+/- SD) plot of FACT-Lym Emotionales Wohlbefinden (EMB) across timepoints, by treatment group
 Full Analysis Set, DCO 15FEB2024



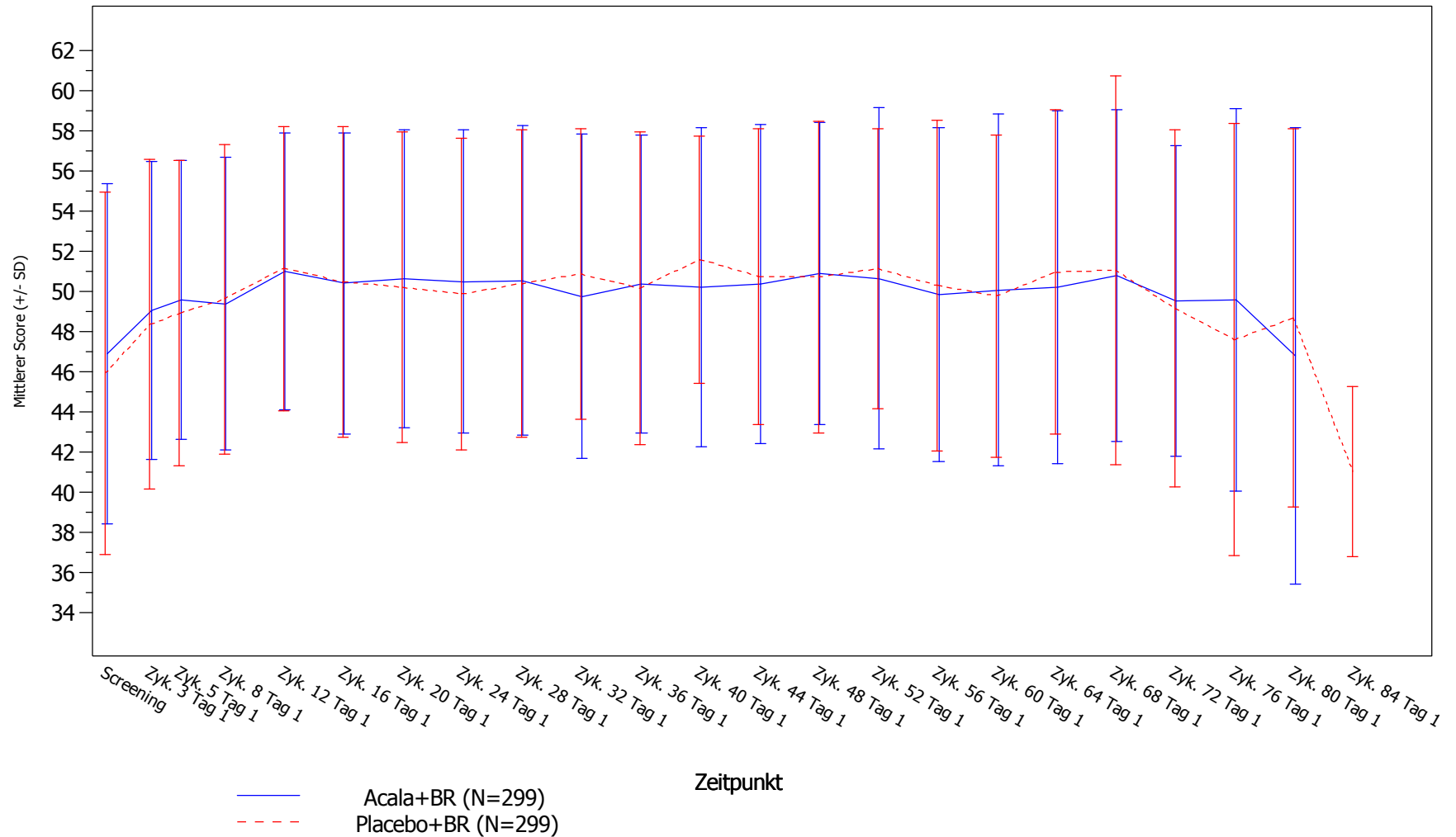
Anzahl an Patienten:

281	255	244	225	215	198	178	160	150	122	119	109	101	94	83	69	62	53	38	33	16	5	ND	Acala+BR
274	252	235	213	183	164	155	137	125	115	100	90	84	78	70	56	46	42	31	20	12	5	2	Placebo+BR

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Figure 2.5.2.6 ECHO: Mean (+/- SD) plot of FACT-Lym Lym-Subscala (LYMS) across timepoints, by treatment group
 Full Analysis Set, DCO 15FEB2024



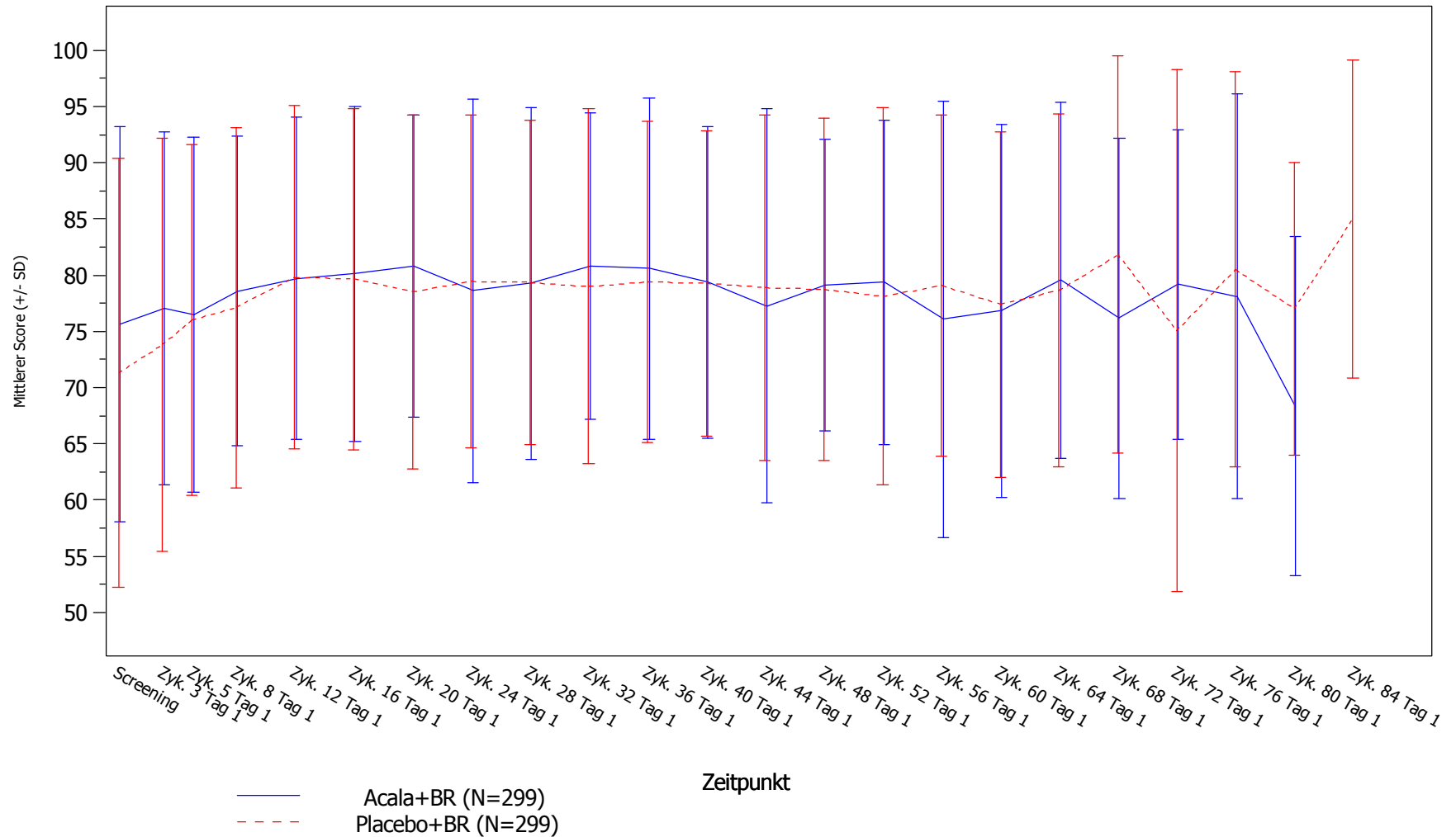
Anzahl an Patienten:

281	254	244	224	214	198	178	159	150	122	119	110	101	93	84	69	62	52	38	33	16	5	ND	Acala+BR
273	251	235	212	183	164	155	138	124	115	101	90	84	78	70	56	46	42	31	19	12	6	2	Placebo+BR

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Figure 2.5.3.1 ECHO: Mean (+/- SD) plot of EQ-5D-5L Visuelle Analogskala across timepoints, by treatment group
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten:

279	254	245	221	211	195	175	162	149	121	114	108	98	93	82	65	60	52	38	34	16	6	ND	Acala+BR
268	250	231	210	180	163	155	137	125	116	101	89	82	78	68	56	42	41	29	20	12	5	2	Placebo+BR

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DCO 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Allgemeine Lebensqualität/Gesundheitsszustand	Acala+BR (N=299)	Screening	283	70,08	22,140	0,0	75,00	100,0
		Zyklus 3 Tag 1	256	72,07	18,482	8,3	75,00	100,0
		Zyklus 5 Tag 1	249	71,99	18,865	16,7	75,00	100,0
		Zyklus 8 Tag 1	226	72,68	17,977	16,7	75,00	100,0
		Zyklus 12 Tag 1	212	75,24	17,622	16,7	83,30	100,0
		Zyklus 16 Tag 1	196	74,78	18,049	0,0	83,30	100,0
		Zyklus 20 Tag 1	176	76,75	16,365	33,3	83,30	100,0
		Zyklus 24 Tag 1	161	73,65	18,368	16,7	83,30	100,0
		Zyklus 28 Tag 1	149	73,54	18,849	16,7	83,30	100,0
		Zyklus 32 Tag 1	119	75,07	18,037	8,3	83,30	100,0
		Zyklus 36 Tag 1	118	73,73	18,665	16,7	75,00	100,0
		Zyklus 40 Tag 1	107	74,37	18,009	16,7	83,30	100,0
		Zyklus 44 Tag 1	100	73,74	18,361	0,0	83,30	100,0
		Zyklus 48 Tag 1	94	73,31	17,938	16,7	75,00	100,0
		Zyklus 52 Tag 1	83	71,89	19,198	0,0	66,70	100,0
		Zyklus 56 Tag 1	68	72,55	21,497	0,0	79,15	100,0
		Zyklus 60 Tag 1	62	71,90	20,868	8,3	79,15	100,0
		Zyklus 64 Tag 1	53	74,99	18,485	25,0	83,30	100,0
		Zyklus 68 Tag 1	38	73,68	18,126	33,3	83,30	100,0
		Zyklus 72 Tag 1	33	76,52	16,194	41,7	83,30	100,0
		Zyklus 76 Tag 1	16	73,96	17,172	41,7	83,30	100,0
		Zyklus 80 Tag 1	7	69,04	16,473	50,0	75,00	91,7
	Placebo+BR (N=299)	Screening	272	66,85	20,969	0,0	66,70	100,0
		Zyklus 3 Tag 1	253	69,20	20,712	0,0	75,00	100,0
		Zyklus 5 Tag 1	233	70,24	18,815	0,0	66,70	100,0
		Zyklus 8 Tag 1	211	72,90	19,932	0,0	75,00	100,0
		Zyklus 12 Tag 1	182	75,73	18,145	16,7	79,15	100,0
		Zyklus 16 Tag 1	163	74,08	18,445	16,7	75,00	100,0
		Zyklus 20 Tag 1	154	74,19	19,566	8,3	75,00	100,0
		Zyklus 24 Tag 1	136	75,55	17,775	16,7	83,30	100,0
		Zyklus 28 Tag 1	126	74,20	19,301	16,7	79,15	100,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Allgemeine Lebensqualität/Gesundheitsszustand	Placebo+BR (N=299)	Zyklus 32 Tag 1	115	75,94	19,138	16,7	83,30	100,0
		Zyklus 36 Tag 1	99	73,39	17,399	33,3	75,00	100,0
		Zyklus 40 Tag 1	89	74,71	16,445	41,7	83,30	100,0
		Zyklus 44 Tag 1	84	72,12	17,900	33,3	75,00	100,0
		Zyklus 48 Tag 1	78	72,64	21,142	0,0	83,30	100,0
		Zyklus 52 Tag 1	70	73,93	18,758	16,7	79,15	100,0
		Zyklus 56 Tag 1	56	74,84	18,901	33,3	79,15	100,0
		Zyklus 60 Tag 1	46	76,26	18,078	16,7	83,30	100,0
		Zyklus 64 Tag 1	41	73,77	20,544	25,0	83,30	100,0
		Zyklus 68 Tag 1	31	79,57	20,503	16,7	83,30	100,0
		Zyklus 72 Tag 1	20	73,75	19,920	33,3	79,15	100,0
		Zyklus 76 Tag 1	13	67,95	26,320	0,0	75,00	100,0
		Zyklus 80 Tag 1	6	72,22	16,358	41,7	79,15	83,3
		Zyklus 84 Tag 1	2	91,65	11,809	83,3	91,65	100,0
EORTC QLQ-C30 Funktionsskala: Körper	Acala+BR (N=299)	Screening	285	83,04	19,573	13,3	86,70	100,0
		Zyklus 3 Tag 1	256	80,94	18,850	0,0	86,70	100,0
		Zyklus 5 Tag 1	248	81,61	17,972	13,3	86,70	100,0
		Zyklus 8 Tag 1	225	82,12	18,227	20,0	86,70	100,0
		Zyklus 12 Tag 1	212	84,97	15,456	33,3	86,70	100,0
		Zyklus 16 Tag 1	196	83,88	17,287	6,7	86,70	100,0
		Zyklus 20 Tag 1	177	84,28	15,354	26,7	86,70	100,0
		Zyklus 24 Tag 1	162	84,70	17,551	26,7	90,00	100,0
		Zyklus 28 Tag 1	149	83,85	16,927	33,3	86,70	100,0
		Zyklus 32 Tag 1	120	82,77	17,828	20,0	86,70	100,0
		Zyklus 36 Tag 1	118	82,70	17,881	6,7	86,70	100,0
		Zyklus 40 Tag 1	107	80,37	21,058	0,0	86,70	100,0
		Zyklus 44 Tag 1	100	82,66	16,276	20,0	86,70	100,0
		Zyklus 48 Tag 1	94	82,91	17,798	6,7	86,70	100,0
		Zyklus 52 Tag 1	84	81,11	19,277	13,3	86,70	100,0
		Zyklus 56 Tag 1	68	79,95	22,849	0,0	86,70	100,0
		Zyklus 60 Tag 1	62	80,65	21,750	0,0	86,70	100,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Funktionsskala: Körper	Acala+BR (N=299)	Zyklus 64 Tag 1	53	83,15	18,738	26,7	86,70	100,0
		Zyklus 68 Tag 1	38	84,56	17,472	26,7	86,70	100,0
		Zyklus 72 Tag 1	33	82,42	16,645	40,0	86,70	100,0
		Zyklus 76 Tag 1	16	77,94	20,750	26,7	86,70	100,0
		Zyklus 80 Tag 1	7	73,57	20,021	33,3	75,00	93,3
	Placebo+BR (N=299)	Screening	275	79,99	19,969	6,7	86,70	100,0
		Zyklus 3 Tag 1	255	79,18	19,151	6,7	86,70	100,0
		Zyklus 5 Tag 1	233	81,34	17,126	20,0	86,70	100,0
		Zyklus 8 Tag 1	210	81,94	17,274	13,3	86,70	100,0
		Zyklus 12 Tag 1	182	86,15	14,540	20,0	86,70	100,0
		Zyklus 16 Tag 1	163	84,61	14,323	26,7	86,70	100,0
		Zyklus 20 Tag 1	154	83,64	17,298	20,0	86,70	100,0
		Zyklus 24 Tag 1	137	84,19	14,929	20,0	86,70	100,0
		Zyklus 28 Tag 1	126	83,12	16,301	26,7	86,70	100,0
		Zyklus 32 Tag 1	116	82,70	17,044	20,0	86,70	100,0
		Zyklus 36 Tag 1	100	80,47	18,644	20,0	86,70	100,0
		Zyklus 40 Tag 1	89	82,70	16,658	20,0	86,70	100,0
		Zyklus 44 Tag 1	83	81,69	18,560	26,7	86,70	100,0
		Zyklus 48 Tag 1	77	83,99	16,045	26,7	86,70	100,0
		Zyklus 52 Tag 1	70	82,57	19,169	20,0	86,70	100,0
		Zyklus 56 Tag 1	56	82,98	15,509	40,0	86,70	100,0
		Zyklus 60 Tag 1	46	82,97	17,133	33,3	86,70	100,0
		Zyklus 64 Tag 1	42	81,43	21,769	26,7	86,70	100,0
		Zyklus 68 Tag 1	31	83,22	21,143	20,0	93,30	100,0
		Zyklus 72 Tag 1	20	79,64	22,884	26,7	90,00	100,0
		Zyklus 76 Tag 1	13	75,89	24,573	33,3	80,00	100,0
		Zyklus 80 Tag 1	5	69,32	21,906	40,0	80,00	93,3
		Zyklus 84 Tag 1	2	60,00	37,760	33,3	60,00	86,7

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Funktionsskala: Rolle	Acala+BR (N=299)	Screening	285	85,21	22,385	0,0	100,00	100,0
		Zyklus 3 Tag 1	255	83,40	23,077	0,0	100,00	100,0
		Zyklus 5 Tag 1	248	84,75	20,756	0,0	100,00	100,0
		Zyklus 8 Tag 1	225	86,52	20,554	0,0	100,00	100,0
		Zyklus 12 Tag 1	212	87,42	20,882	0,0	100,00	100,0
		Zyklus 16 Tag 1	196	85,89	21,260	0,0	100,00	100,0
		Zyklus 20 Tag 1	177	88,70	17,158	33,3	100,00	100,0
		Zyklus 24 Tag 1	162	88,48	19,328	0,0	100,00	100,0
		Zyklus 28 Tag 1	149	86,02	22,431	0,0	100,00	100,0
		Zyklus 32 Tag 1	119	87,82	19,607	16,7	100,00	100,0
		Zyklus 36 Tag 1	118	85,88	21,749	0,0	100,00	100,0
		Zyklus 40 Tag 1	108	82,71	23,450	0,0	100,00	100,0
		Zyklus 44 Tag 1	100	86,83	20,137	0,0	100,00	100,0
		Zyklus 48 Tag 1	94	85,29	19,215	16,7	100,00	100,0
		Zyklus 52 Tag 1	84	85,52	20,331	0,0	100,00	100,0
		Zyklus 56 Tag 1	68	82,11	26,595	0,0	100,00	100,0
		Zyklus 60 Tag 1	62	82,53	25,684	0,0	100,00	100,0
		Zyklus 64 Tag 1	53	84,28	22,266	16,7	100,00	100,0
		Zyklus 68 Tag 1	38	87,73	16,283	50,0	100,00	100,0
		Zyklus 72 Tag 1	33	84,35	22,416	33,3	100,00	100,0
		Zyklus 76 Tag 1	16	89,59	22,658	16,7	100,00	100,0
		Zyklus 80 Tag 1	7	80,96	33,913	16,7	100,00	100,0
	Placebo+BR (N=299)	Screening	275	81,46	25,139	0,0	100,00	100,0
		Zyklus 3 Tag 1	253	81,36	25,073	0,0	100,00	100,0
		Zyklus 5 Tag 1	233	82,76	22,576	0,0	100,00	100,0
		Zyklus 8 Tag 1	211	84,28	22,515	0,0	100,00	100,0
		Zyklus 12 Tag 1	182	89,56	17,887	16,7	100,00	100,0
		Zyklus 16 Tag 1	163	89,37	16,749	33,3	100,00	100,0
		Zyklus 20 Tag 1	154	85,72	22,007	0,0	100,00	100,0
		Zyklus 24 Tag 1	137	88,20	18,645	0,0	100,00	100,0
		Zyklus 28 Tag 1	126	88,63	19,046	16,7	100,00	100,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Funktionsskala: Rolle	Placebo+BR (N=299)	Zyklus 32 Tag 1	116	84,63	20,629	0,0	100,00	100,0
		Zyklus 36 Tag 1	100	84,50	22,254	0,0	100,00	100,0
		Zyklus 40 Tag 1	89	85,39	21,587	16,7	100,00	100,0
		Zyklus 44 Tag 1	84	85,32	21,548	0,0	100,00	100,0
		Zyklus 48 Tag 1	77	85,50	20,827	0,0	100,00	100,0
		Zyklus 52 Tag 1	70	84,29	22,676	0,0	100,00	100,0
		Zyklus 56 Tag 1	56	83,33	22,696	16,7	100,00	100,0
		Zyklus 60 Tag 1	46	86,60	22,112	0,0	100,00	100,0
		Zyklus 64 Tag 1	42	88,10	22,776	16,7	100,00	100,0
		Zyklus 68 Tag 1	31	84,41	27,197	0,0	100,00	100,0
		Zyklus 72 Tag 1	20	80,84	24,936	16,7	91,65	100,0
		Zyklus 76 Tag 1	13	78,21	33,592	16,7	100,00	100,0
		Zyklus 80 Tag 1	6	83,33	21,077	50,0	91,65	100,0
		Zyklus 84 Tag 1	2	58,30	35,355	33,3	58,30	83,3
EORTC QLQ-C30 Funktionsskala: Emotionalität	Acala+BR (N=299)	Screening	283	79,49	19,170	0,0	83,30	100,0
		Zyklus 3 Tag 1	256	84,95	18,446	0,0	91,70	100,0
		Zyklus 5 Tag 1	248	85,76	16,824	0,0	91,70	100,0
		Zyklus 8 Tag 1	226	84,70	18,183	0,0	91,70	100,0
		Zyklus 12 Tag 1	212	86,84	17,168	0,0	91,70	100,0
		Zyklus 16 Tag 1	196	86,57	16,193	16,7	91,70	100,0
		Zyklus 20 Tag 1	176	86,13	16,002	25,0	91,70	100,0
		Zyklus 24 Tag 1	161	85,25	18,984	16,7	91,70	100,0
		Zyklus 28 Tag 1	149	83,62	18,867	16,7	91,70	100,0
		Zyklus 32 Tag 1	120	84,66	17,782	16,7	91,70	100,0
		Zyklus 36 Tag 1	118	83,76	19,548	8,3	91,70	100,0
		Zyklus 40 Tag 1	107	82,79	19,504	8,3	91,70	100,0
		Zyklus 44 Tag 1	100	84,06	18,832	0,0	91,70	100,0
		Zyklus 48 Tag 1	94	82,90	19,448	16,7	91,70	100,0
		Zyklus 52 Tag 1	83	82,63	21,977	8,3	91,70	100,0
		Zyklus 56 Tag 1	68	84,44	19,520	16,7	91,70	100,0
		Zyklus 60 Tag 1	62	83,61	19,730	16,7	91,70	100,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Funktionsskala: Emotionalität	Acala+BR (N=299)	Zyklus 64 Tag 1	53	85,85	19,108	33,3	100,00	100,0
		Zyklus 68 Tag 1	38	85,31	17,812	33,3	91,70	100,0
		Zyklus 72 Tag 1	33	85,61	17,586	33,3	91,70	100,0
		Zyklus 76 Tag 1	16	84,90	19,770	41,7	91,70	100,0
		Zyklus 80 Tag 1	7	88,10	15,866	58,3	91,70	100,0
	Placebo+BR (N=299)	Screening	273	78,33	20,384	0,0	83,30	100,0
		Zyklus 3 Tag 1	253	82,11	19,650	0,0	91,70	100,0
		Zyklus 5 Tag 1	233	83,95	18,453	0,0	91,70	100,0
		Zyklus 8 Tag 1	211	84,96	16,594	16,7	91,70	100,0
		Zyklus 12 Tag 1	182	85,90	17,108	8,3	91,70	100,0
		Zyklus 16 Tag 1	163	85,84	17,027	8,3	91,70	100,0
		Zyklus 20 Tag 1	154	85,23	19,423	0,0	91,70	100,0
		Zyklus 24 Tag 1	136	83,87	18,561	0,0	91,70	100,0
		Zyklus 28 Tag 1	126	84,79	17,921	16,7	91,70	100,0
		Zyklus 32 Tag 1	115	85,75	16,642	16,7	91,70	100,0
		Zyklus 36 Tag 1	99	85,36	18,412	25,0	91,70	100,0
		Zyklus 40 Tag 1	89	85,87	16,353	25,0	91,70	100,0
		Zyklus 44 Tag 1	84	85,98	18,830	8,3	91,70	100,0
		Zyklus 48 Tag 1	78	85,69	19,460	8,3	91,70	100,0
		Zyklus 52 Tag 1	70	87,98	16,400	33,3	100,00	100,0
		Zyklus 56 Tag 1	56	83,34	19,717	16,7	91,70	100,0
		Zyklus 60 Tag 1	46	86,96	17,714	8,3	91,70	100,0
		Zyklus 64 Tag 1	41	84,96	19,115	8,3	91,70	100,0
		Zyklus 68 Tag 1	31	85,58	19,190	16,7	91,70	100,0
		Zyklus 72 Tag 1	20	81,68	15,431	58,3	79,15	100,0
		Zyklus 76 Tag 1	13	82,70	17,160	58,3	75,00	100,0
		Zyklus 80 Tag 1	6	84,73	15,278	66,7	87,50	100,0
		Zyklus 84 Tag 1	2	70,85	5,869	66,7	70,85	75,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Funktionsskala: Kognition	Acala+BR (N=299)	Screening	283	86,04	18,419	0,0	100,00	100,0
		Zyklus 3 Tag 1	256	87,76	17,771	0,0	100,00	100,0
		Zyklus 5 Tag 1	249	86,94	16,939	0,0	100,00	100,0
		Zyklus 8 Tag 1	226	87,90	15,513	16,7	100,00	100,0
		Zyklus 12 Tag 1	212	87,89	16,472	16,7	100,00	100,0
		Zyklus 16 Tag 1	196	86,90	15,784	33,3	100,00	100,0
		Zyklus 20 Tag 1	176	86,92	15,210	33,3	83,30	100,0
		Zyklus 24 Tag 1	161	87,26	15,532	33,3	100,00	100,0
		Zyklus 28 Tag 1	149	85,90	17,727	16,7	83,30	100,0
		Zyklus 32 Tag 1	120	83,61	21,924	0,0	83,30	100,0
		Zyklus 36 Tag 1	118	85,87	19,444	0,0	100,00	100,0
		Zyklus 40 Tag 1	107	83,80	18,661	33,3	83,30	100,0
		Zyklus 44 Tag 1	100	85,00	16,492	33,3	83,30	100,0
		Zyklus 48 Tag 1	94	84,75	14,789	50,0	83,30	100,0
		Zyklus 52 Tag 1	83	86,54	16,346	33,3	100,00	100,0
		Zyklus 56 Tag 1	68	84,07	16,393	33,3	83,30	100,0
		Zyklus 60 Tag 1	62	83,87	20,005	0,0	83,30	100,0
		Zyklus 64 Tag 1	53	85,53	19,070	33,3	100,00	100,0
		Zyklus 68 Tag 1	38	85,09	16,334	50,0	83,30	100,0
		Zyklus 72 Tag 1	33	80,81	22,861	16,7	83,30	100,0
		Zyklus 76 Tag 1	16	80,21	18,469	50,0	83,30	100,0
		Zyklus 80 Tag 1	7	90,47	13,109	66,7	100,00	100,0
	Placebo+BR (N=299)	Screening	273	85,84	17,869	16,7	100,00	100,0
		Zyklus 3 Tag 1	253	85,04	18,101	0,0	83,30	100,0
		Zyklus 5 Tag 1	234	85,04	19,818	0,0	83,30	100,0
		Zyklus 8 Tag 1	211	85,46	17,112	0,0	83,30	100,0
		Zyklus 12 Tag 1	182	85,89	18,856	0,0	100,00	100,0
		Zyklus 16 Tag 1	163	86,19	18,477	0,0	83,30	100,0
		Zyklus 20 Tag 1	154	85,06	18,485	16,7	83,30	100,0
		Zyklus 24 Tag 1	136	84,68	19,875	0,0	100,00	100,0
		Zyklus 28 Tag 1	126	83,59	18,967	16,7	83,30	100,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Funktionsskala: Kognition	Placebo+BR (N=299)	Zyklus 32 Tag 1	115	84,05	19,666	0,0	83,30	100,0
		Zyklus 36 Tag 1	99	83,16	18,359	16,7	83,30	100,0
		Zyklus 40 Tag 1	89	85,01	17,769	16,7	83,30	100,0
		Zyklus 44 Tag 1	84	82,93	17,724	0,0	83,30	100,0
		Zyklus 48 Tag 1	78	85,47	19,979	0,0	100,00	100,0
		Zyklus 52 Tag 1	70	84,76	17,656	33,3	83,30	100,0
		Zyklus 56 Tag 1	56	84,23	20,200	0,0	91,65	100,0
		Zyklus 60 Tag 1	46	82,97	22,071	16,7	91,65	100,0
		Zyklus 64 Tag 1	41	82,52	24,415	0,0	83,30	100,0
		Zyklus 68 Tag 1	31	81,18	25,722	0,0	83,30	100,0
		Zyklus 72 Tag 1	19	84,21	16,162	50,0	83,30	100,0
		Zyklus 76 Tag 1	13	75,64	27,729	0,0	83,30	100,0
		Zyklus 80 Tag 1	6	75,00	39,084	0,0	91,65	100,0
		Zyklus 84 Tag 1	2	66,65	47,164	33,3	66,65	100,0
EORTC QLQ-C30 Funktionsskala: Sozial	Acala+BR (N=299)	Screening	283	86,57	19,252	0,0	100,00	100,0
		Zyklus 3 Tag 1	256	83,46	21,789	0,0	100,00	100,0
		Zyklus 5 Tag 1	248	84,54	20,360	0,0	100,00	100,0
		Zyklus 8 Tag 1	225	84,96	19,786	16,7	100,00	100,0
		Zyklus 12 Tag 1	212	90,25	16,202	33,3	100,00	100,0
		Zyklus 16 Tag 1	196	87,93	19,575	0,0	100,00	100,0
		Zyklus 20 Tag 1	176	88,17	17,552	16,7	100,00	100,0
		Zyklus 24 Tag 1	161	90,06	17,013	33,3	100,00	100,0
		Zyklus 28 Tag 1	149	87,36	21,191	0,0	100,00	100,0
		Zyklus 32 Tag 1	120	88,20	20,425	0,0	100,00	100,0
		Zyklus 36 Tag 1	118	87,86	22,184	0,0	100,00	100,0
		Zyklus 40 Tag 1	107	88,16	18,169	16,7	100,00	100,0
		Zyklus 44 Tag 1	100	89,50	20,191	0,0	100,00	100,0
		Zyklus 48 Tag 1	94	89,54	17,790	33,3	100,00	100,0
		Zyklus 52 Tag 1	83	88,35	17,981	33,3	100,00	100,0
		Zyklus 56 Tag 1	68	85,78	24,480	0,0	100,00	100,0
		Zyklus 60 Tag 1	62	88,44	20,601	33,3	100,00	100,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Funktionsskala: Sozial	Acala+BR (N=299)	Zyklus 64 Tag 1	53	87,42	20,126	33,3	100,00	100,0
		Zyklus 68 Tag 1	38	90,35	16,724	33,3	100,00	100,0
		Zyklus 72 Tag 1	33	86,87	19,875	33,3	100,00	100,0
		Zyklus 76 Tag 1	16	87,51	23,162	16,7	100,00	100,0
		Zyklus 80 Tag 1	7	85,71	24,398	50,0	100,00	100,0
	Placebo+BR (N=299)	Screening	273	83,46	22,862	0,0	100,00	100,0
		Zyklus 3 Tag 1	252	81,81	24,147	0,0	91,65	100,0
		Zyklus 5 Tag 1	233	83,98	19,893	0,0	100,00	100,0
		Zyklus 8 Tag 1	211	85,39	20,531	0,0	100,00	100,0
		Zyklus 12 Tag 1	182	88,19	18,184	16,7	100,00	100,0
		Zyklus 16 Tag 1	163	90,08	17,237	33,3	100,00	100,0
		Zyklus 20 Tag 1	154	87,23	19,317	16,7	100,00	100,0
		Zyklus 24 Tag 1	136	88,73	17,781	16,7	100,00	100,0
		Zyklus 28 Tag 1	126	87,43	18,212	16,7	100,00	100,0
		Zyklus 32 Tag 1	115	89,57	17,159	0,0	100,00	100,0
		Zyklus 36 Tag 1	99	90,07	18,115	16,7	100,00	100,0
		Zyklus 40 Tag 1	89	88,20	20,594	16,7	100,00	100,0
		Zyklus 44 Tag 1	84	89,09	16,859	33,3	100,00	100,0
		Zyklus 48 Tag 1	78	90,60	17,113	33,3	100,00	100,0
		Zyklus 52 Tag 1	70	85,96	21,539	0,0	100,00	100,0
		Zyklus 56 Tag 1	56	86,90	21,492	33,3	100,00	100,0
		Zyklus 60 Tag 1	46	88,77	21,098	0,0	100,00	100,0
		Zyklus 64 Tag 1	41	89,83	18,590	33,3	100,00	100,0
		Zyklus 68 Tag 1	31	85,49	22,659	16,7	100,00	100,0
		Zyklus 72 Tag 1	19	85,97	20,227	33,3	100,00	100,0
		Zyklus 76 Tag 1	13	87,18	20,589	33,3	100,00	100,0
		Zyklus 80 Tag 1	6	94,45	13,595	66,7	100,00	100,0
		Zyklus 84 Tag 1	2	91,65	11,809	83,3	91,65	100,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Fatigue	Acala+BR (N=299)	Screening	285	26,13	22,457	0,0	22,20	100,0
		Zyklus 3 Tag 1	256	29,93	22,077	0,0	33,30	100,0
		Zyklus 5 Tag 1	248	28,64	21,972	0,0	22,20	100,0
		Zyklus 8 Tag 1	225	26,60	20,707	0,0	22,20	100,0
		Zyklus 12 Tag 1	212	23,15	18,429	0,0	22,20	77,8
		Zyklus 16 Tag 1	196	23,74	19,672	0,0	22,20	100,0
		Zyklus 20 Tag 1	177	23,15	19,530	0,0	22,20	88,9
		Zyklus 24 Tag 1	162	24,27	21,063	0,0	22,20	100,0
		Zyklus 28 Tag 1	149	25,12	21,557	0,0	22,20	100,0
		Zyklus 32 Tag 1	120	25,45	21,581	0,0	22,20	100,0
		Zyklus 36 Tag 1	118	24,94	21,790	0,0	22,20	100,0
		Zyklus 40 Tag 1	107	26,89	22,811	0,0	22,20	100,0
		Zyklus 44 Tag 1	100	25,32	22,172	0,0	22,20	100,0
		Zyklus 48 Tag 1	94	23,63	21,258	0,0	22,20	100,0
		Zyklus 52 Tag 1	84	26,18	23,695	0,0	22,20	88,9
		Zyklus 56 Tag 1	68	25,65	24,004	0,0	22,20	100,0
		Zyklus 60 Tag 1	62	27,40	24,944	0,0	22,20	100,0
		Zyklus 64 Tag 1	53	25,15	25,619	0,0	22,20	100,0
		Zyklus 68 Tag 1	38	24,26	21,284	0,0	22,20	66,7
		Zyklus 72 Tag 1	33	25,25	21,575	0,0	22,20	66,7
		Zyklus 76 Tag 1	16	29,15	15,659	11,1	22,20	66,7
		Zyklus 80 Tag 1	7	31,73	24,374	0,0	22,20	77,8
	Placebo+BR (N=299)	Screening	275	29,71	25,788	0,0	33,30	100,0
		Zyklus 3 Tag 1	255	29,49	24,186	0,0	33,30	100,0
		Zyklus 5 Tag 1	233	27,83	21,174	0,0	33,30	100,0
		Zyklus 8 Tag 1	210	25,33	20,687	0,0	22,20	100,0
		Zyklus 12 Tag 1	182	20,68	18,933	0,0	22,20	77,8
		Zyklus 16 Tag 1	163	22,21	20,058	0,0	22,20	100,0
		Zyklus 20 Tag 1	154	23,22	23,022	0,0	22,20	100,0
		Zyklus 24 Tag 1	137	22,97	18,823	0,0	22,20	88,9
		Zyklus 28 Tag 1	126	23,89	21,870	0,0	22,20	88,9
		Zyklus 32 Tag 1	116	22,49	19,570	0,0	22,20	100,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DCO 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Fatigue	Placebo+BR (N=299)	Zyklus 36 Tag 1	100	24,60	20,547	0,0	22,20	88,9
		Zyklus 40 Tag 1	89	23,71	21,398	0,0	22,20	100,0
		Zyklus 44 Tag 1	84	25,25	21,360	0,0	22,20	88,9
		Zyklus 48 Tag 1	77	22,50	22,224	0,0	22,20	88,9
		Zyklus 52 Tag 1	70	23,96	21,041	0,0	22,20	77,8
		Zyklus 56 Tag 1	56	21,02	22,495	0,0	11,10	88,9
		Zyklus 60 Tag 1	46	21,73	21,337	0,0	22,20	77,8
		Zyklus 64 Tag 1	42	22,22	27,331	0,0	11,10	100,0
		Zyklus 68 Tag 1	31	20,42	24,193	0,0	11,10	88,9
		Zyklus 72 Tag 1	20	25,54	18,060	0,0	33,30	55,6
		Zyklus 76 Tag 1	13	25,64	26,991	0,0	22,20	77,8
		Zyklus 80 Tag 1	6	22,20	21,061	0,0	22,20	44,4
		Zyklus 84 Tag 1	2	55,55	47,164	22,2	55,55	88,9
EORTC QLQ-C30 Übelkeit und Erbrechen	Acala+BR (N=299)	Screening	285	3,45	9,215	0,0	0,00	50,0
		Zyklus 3 Tag 1	256	6,19	12,161	0,0	0,00	83,3
		Zyklus 5 Tag 1	248	6,05	13,221	0,0	0,00	66,7
		Zyklus 8 Tag 1	225	4,82	12,899	0,0	0,00	83,3
		Zyklus 12 Tag 1	212	2,28	8,034	0,0	0,00	50,0
		Zyklus 16 Tag 1	196	1,87	6,035	0,0	0,00	33,3
		Zyklus 20 Tag 1	177	2,45	8,162	0,0	0,00	66,7
		Zyklus 24 Tag 1	162	2,88	8,221	0,0	0,00	50,0
		Zyklus 28 Tag 1	149	2,57	7,436	0,0	0,00	33,3
		Zyklus 32 Tag 1	120	3,34	11,953	0,0	0,00	83,3
		Zyklus 36 Tag 1	118	1,98	6,947	0,0	0,00	33,3
		Zyklus 40 Tag 1	107	2,18	7,268	0,0	0,00	33,3
		Zyklus 44 Tag 1	100	2,33	9,485	0,0	0,00	66,7
		Zyklus 48 Tag 1	94	1,77	6,218	0,0	0,00	33,3
		Zyklus 52 Tag 1	84	2,98	9,740	0,0	0,00	66,7
		Zyklus 56 Tag 1	68	2,94	8,114	0,0	0,00	33,3
		Zyklus 60 Tag 1	62	4,57	11,355	0,0	0,00	50,0
		Zyklus 64 Tag 1	53	1,57	5,907	0,0	0,00	33,3

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Übelkeit und Erbrechen	Acala+BR (N=299)	Zyklus 68 Tag 1	38	4,83	13,374	0,0	0,00	66,7
		Zyklus 72 Tag 1	33	4,05	8,371	0,0	0,00	33,3
		Zyklus 76 Tag 1	16	3,13	9,061	0,0	0,00	33,3
		Zyklus 80 Tag 1	7	2,39	6,312	0,0	0,00	16,7
	Placebo+BR (N=299)	Screening	275	4,85	12,030	0,0	0,00	66,7
		Zyklus 3 Tag 1	254	5,38	12,730	0,0	0,00	83,3
		Zyklus 5 Tag 1	233	6,30	12,419	0,0	0,00	66,7
		Zyklus 8 Tag 1	211	3,79	9,967	0,0	0,00	50,0
		Zyklus 12 Tag 1	182	2,29	7,181	0,0	0,00	50,0
		Zyklus 16 Tag 1	163	2,05	7,814	0,0	0,00	66,7
		Zyklus 20 Tag 1	154	2,49	7,573	0,0	0,00	50,0
		Zyklus 24 Tag 1	137	3,04	8,389	0,0	0,00	50,0
		Zyklus 28 Tag 1	126	2,52	7,325	0,0	0,00	33,3
		Zyklus 32 Tag 1	116	1,73	6,362	0,0	0,00	33,3
		Zyklus 36 Tag 1	100	1,67	6,041	0,0	0,00	33,3
		Zyklus 40 Tag 1	89	1,31	4,521	0,0	0,00	16,7
		Zyklus 44 Tag 1	84	2,18	7,215	0,0	0,00	33,3
		Zyklus 48 Tag 1	77	1,95	7,145	0,0	0,00	50,0
		Zyklus 52 Tag 1	70	2,15	7,471	0,0	0,00	50,0
		Zyklus 56 Tag 1	56	2,68	7,640	0,0	0,00	33,3
		Zyklus 60 Tag 1	46	2,54	10,529	0,0	0,00	66,7
		Zyklus 64 Tag 1	42	4,37	13,806	0,0	0,00	66,7
		Zyklus 68 Tag 1	31	3,77	8,293	0,0	0,00	33,3
		Zyklus 72 Tag 1	19	7,89	12,865	0,0	0,00	33,3
		Zyklus 76 Tag 1	13	6,42	10,842	0,0	0,00	33,3
		Zyklus 80 Tag 1	6	5,57	8,624	0,0	0,00	16,7
		Zyklus 84 Tag 1	2	16,70	0,000	16,7	16,70	16,7

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Schmerzen	Acala+BR (N=299)	Screening	285	15,38	21,895	0,0	0,00	100,0
		Zyklus 3 Tag 1	256	14,71	21,040	0,0	0,00	100,0
		Zyklus 5 Tag 1	249	11,79	18,743	0,0	0,00	100,0
		Zyklus 8 Tag 1	225	12,74	18,447	0,0	0,00	83,3
		Zyklus 12 Tag 1	212	11,95	17,733	0,0	0,00	83,3
		Zyklus 16 Tag 1	196	12,25	19,692	0,0	0,00	100,0
		Zyklus 20 Tag 1	177	12,81	18,947	0,0	0,00	100,0
		Zyklus 24 Tag 1	162	14,82	20,599	0,0	0,00	100,0
		Zyklus 28 Tag 1	149	12,98	18,566	0,0	0,00	100,0
		Zyklus 32 Tag 1	120	14,03	20,153	0,0	0,00	83,3
		Zyklus 36 Tag 1	118	15,54	19,083	0,0	8,35	83,3
		Zyklus 40 Tag 1	108	16,36	23,457	0,0	0,00	100,0
		Zyklus 44 Tag 1	100	16,34	20,645	0,0	16,70	100,0
		Zyklus 48 Tag 1	94	17,91	21,612	0,0	16,70	83,3
		Zyklus 52 Tag 1	84	17,66	21,386	0,0	16,70	83,3
		Zyklus 56 Tag 1	68	19,36	25,366	0,0	16,70	100,0
		Zyklus 60 Tag 1	62	16,67	22,585	0,0	8,35	100,0
		Zyklus 64 Tag 1	53	14,79	19,789	0,0	16,70	83,3
		Zyklus 68 Tag 1	38	14,47	20,567	0,0	0,00	66,7
		Zyklus 72 Tag 1	33	13,13	17,052	0,0	0,00	50,0
		Zyklus 76 Tag 1	16	16,66	22,758	0,0	8,35	83,3
		Zyklus 80 Tag 1	7	9,53	13,109	0,0	0,00	33,3
	Placebo+BR (N=299)	Screening	275	19,40	23,859	0,0	16,70	100,0
		Zyklus 3 Tag 1	254	13,65	19,591	0,0	0,00	100,0
		Zyklus 5 Tag 1	234	13,25	19,953	0,0	0,00	100,0
		Zyklus 8 Tag 1	211	12,80	18,884	0,0	0,00	83,3
		Zyklus 12 Tag 1	182	10,90	17,217	0,0	0,00	100,0
		Zyklus 16 Tag 1	163	12,89	19,796	0,0	0,00	100,0
		Zyklus 20 Tag 1	154	13,21	19,770	0,0	0,00	100,0
		Zyklus 24 Tag 1	137	12,78	19,622	0,0	0,00	100,0
		Zyklus 28 Tag 1	126	15,34	20,503	0,0	0,00	83,3
		Zyklus 32 Tag 1	116	15,81	22,396	0,0	0,00	100,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Schmerzen	Placebo+BR (N=299)	Zyklus 36 Tag 1	100	17,17	24,782	0,0	0,00	100,0
		Zyklus 40 Tag 1	89	13,86	20,294	0,0	0,00	100,0
		Zyklus 44 Tag 1	84	15,48	22,521	0,0	0,00	100,0
		Zyklus 48 Tag 1	78	17,73	23,309	0,0	0,00	100,0
		Zyklus 52 Tag 1	70	15,95	23,301	0,0	0,00	100,0
		Zyklus 56 Tag 1	56	16,66	21,075	0,0	0,00	83,3
		Zyklus 60 Tag 1	46	18,48	23,366	0,0	8,35	83,3
		Zyklus 64 Tag 1	42	18,65	29,947	0,0	0,00	100,0
		Zyklus 68 Tag 1	31	15,05	26,640	0,0	0,00	83,3
		Zyklus 72 Tag 1	20	14,17	21,814	0,0	0,00	66,7
		Zyklus 76 Tag 1	13	21,79	31,465	0,0	0,00	100,0
		Zyklus 80 Tag 1	6	27,78	37,511	0,0	16,70	100,0
		Zyklus 84 Tag 1	2	66,65	47,164	33,3	66,65	100,0
EORTC QLQ-C30 Dyspnoe	Acala+BR (N=299)	Screening	285	14,96	21,708	0,0	0,00	100,0
		Zyklus 3 Tag 1	256	14,97	22,417	0,0	0,00	100,0
		Zyklus 5 Tag 1	248	14,37	21,919	0,0	0,00	100,0
		Zyklus 8 Tag 1	225	15,84	22,281	0,0	0,00	100,0
		Zyklus 12 Tag 1	212	14,14	21,982	0,0	0,00	100,0
		Zyklus 16 Tag 1	196	14,28	22,891	0,0	0,00	100,0
		Zyklus 20 Tag 1	177	14,30	20,310	0,0	0,00	66,7
		Zyklus 24 Tag 1	162	14,19	21,596	0,0	0,00	100,0
		Zyklus 28 Tag 1	149	17,00	23,765	0,0	0,00	100,0
		Zyklus 32 Tag 1	120	16,66	22,452	0,0	0,00	100,0
		Zyklus 36 Tag 1	117	19,94	25,917	0,0	0,00	100,0
		Zyklus 40 Tag 1	107	19,62	26,679	0,0	0,00	100,0
		Zyklus 44 Tag 1	100	20,66	25,854	0,0	0,00	100,0
		Zyklus 48 Tag 1	94	17,01	22,792	0,0	0,00	100,0
		Zyklus 52 Tag 1	84	20,23	29,279	0,0	0,00	100,0
		Zyklus 56 Tag 1	68	17,64	25,411	0,0	0,00	100,0
		Zyklus 60 Tag 1	62	15,05	22,317	0,0	0,00	100,0
		Zyklus 64 Tag 1	53	18,23	24,945	0,0	0,00	100,0
		Zyklus 68 Tag 1	38	14,90	20,050	0,0	0,00	66,7

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Dyspnoe	Acala+BR (N=299)	Zyklus 72 Tag 1	33	16,16	27,795	0,0	0,00	100,0
		Zyklus 76 Tag 1	16	18,74	24,250	0,0	0,00	66,7
		Zyklus 80 Tag 1	7	33,33	47,140	0,0	0,00	100,0
	Placebo+BR (N=299)	Screening	274	18,00	27,664	0,0	0,00	100,0
		Zyklus 3 Tag 1	253	14,36	24,127	0,0	0,00	100,0
		Zyklus 5 Tag 1	232	13,79	21,960	0,0	0,00	100,0
		Zyklus 8 Tag 1	211	13,26	21,148	0,0	0,00	100,0
		Zyklus 12 Tag 1	182	10,62	18,786	0,0	0,00	66,7
		Zyklus 16 Tag 1	162	11,31	18,999	0,0	0,00	66,7
		Zyklus 20 Tag 1	154	14,71	21,553	0,0	0,00	66,7
		Zyklus 24 Tag 1	137	14,10	18,391	0,0	0,00	66,7
		Zyklus 28 Tag 1	125	13,59	18,490	0,0	0,00	66,7
		Zyklus 32 Tag 1	116	14,65	21,661	0,0	0,00	100,0
		Zyklus 36 Tag 1	100	14,32	18,495	0,0	0,00	66,7
		Zyklus 40 Tag 1	89	14,97	20,102	0,0	0,00	66,7
		Zyklus 44 Tag 1	84	16,26	22,843	0,0	0,00	100,0
		Zyklus 48 Tag 1	78	16,23	22,630	0,0	0,00	66,7
		Zyklus 52 Tag 1	70	16,18	23,215	0,0	0,00	100,0
		Zyklus 56 Tag 1	56	13,68	19,870	0,0	0,00	66,7
		Zyklus 60 Tag 1	46	13,03	17,875	0,0	0,00	66,7
		Zyklus 64 Tag 1	42	11,90	19,223	0,0	0,00	66,7
		Zyklus 68 Tag 1	31	10,75	19,975	0,0	0,00	66,7
		Zyklus 72 Tag 1	20	18,33	22,877	0,0	0,00	66,7
		Zyklus 76 Tag 1	13	15,38	25,882	0,0	0,00	66,7
		Zyklus 80 Tag 1	6	27,77	25,098	0,0	33,30	66,7
		Zyklus 84 Tag 1	2	66,70	0,000	66,7	66,70	66,7
EORTC QLQ-C30 Schlaflosigkeit	Acala+BR (N=299)	Screening	284	26,05	28,197	0,0	33,30	100,0
		Zyklus 3 Tag 1	255	22,21	28,423	0,0	0,00	100,0
		Zyklus 5 Tag 1	248	20,29	27,249	0,0	0,00	100,0
		Zyklus 8 Tag 1	225	20,88	24,862	0,0	0,00	100,0
		Zyklus 12 Tag 1	212	18,86	23,183	0,0	0,00	100,0
		Zyklus 16 Tag 1	196	20,40	25,987	0,0	0,00	100,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Schlaflosigkeit	Acala+BR (N=299)	Zyklus 20 Tag 1	176	18,93	23,523	0,0	0,00	100,0
		Zyklus 24 Tag 1	162	18,71	22,577	0,0	0,00	100,0
		Zyklus 28 Tag 1	149	18,78	23,984	0,0	0,00	100,0
		Zyklus 32 Tag 1	120	21,66	25,069	0,0	16,65	100,0
		Zyklus 36 Tag 1	118	17,50	22,095	0,0	0,00	100,0
		Zyklus 40 Tag 1	107	22,11	27,067	0,0	0,00	100,0
		Zyklus 44 Tag 1	100	21,99	24,718	0,0	33,30	100,0
		Zyklus 48 Tag 1	94	21,27	25,328	0,0	16,65	100,0
		Zyklus 52 Tag 1	83	18,07	23,457	0,0	0,00	66,7
		Zyklus 56 Tag 1	68	23,04	28,370	0,0	0,00	100,0
		Zyklus 60 Tag 1	62	24,18	26,428	0,0	33,30	100,0
		Zyklus 64 Tag 1	53	23,26	28,185	0,0	0,00	100,0
		Zyklus 68 Tag 1	37	19,81	26,598	0,0	0,00	100,0
		Zyklus 72 Tag 1	33	24,24	30,368	0,0	0,00	100,0
		Zyklus 76 Tag 1	16	33,33	34,431	0,0	33,30	100,0
		Zyklus 80 Tag 1	7	28,56	23,007	0,0	33,30	66,7
	Placebo+BR (N=299)	Screening	275	27,75	27,930	0,0	33,30	100,0
		Zyklus 3 Tag 1	253	22,39	27,198	0,0	0,00	100,0
		Zyklus 5 Tag 1	232	22,40	25,493	0,0	33,30	100,0
		Zyklus 8 Tag 1	211	21,79	25,170	0,0	33,30	100,0
		Zyklus 12 Tag 1	182	18,86	24,113	0,0	0,00	100,0
		Zyklus 16 Tag 1	163	21,87	26,804	0,0	0,00	100,0
		Zyklus 20 Tag 1	154	19,26	26,343	0,0	0,00	100,0
		Zyklus 24 Tag 1	137	20,67	24,632	0,0	0,00	100,0
		Zyklus 28 Tag 1	126	20,10	26,692	0,0	0,00	100,0
		Zyklus 32 Tag 1	116	20,11	24,027	0,0	0,00	100,0
		Zyklus 36 Tag 1	100	22,33	27,650	0,0	0,00	100,0
		Zyklus 40 Tag 1	89	21,71	26,160	0,0	0,00	100,0
		Zyklus 44 Tag 1	84	23,01	26,375	0,0	33,30	100,0
		Zyklus 48 Tag 1	77	23,80	25,851	0,0	33,30	100,0
		Zyklus 52 Tag 1	70	22,85	26,342	0,0	33,30	100,0
		Zyklus 56 Tag 1	56	22,61	24,707	0,0	33,30	100,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Schlaflosigkeit	Placebo+BR (N=299)	Zyklus 60 Tag 1	45	19,99	26,011	0,0	0,00	100,0
		Zyklus 64 Tag 1	42	21,42	31,938	0,0	0,00	100,0
		Zyklus 68 Tag 1	31	23,65	28,794	0,0	33,30	100,0
		Zyklus 72 Tag 1	19	22,79	22,367	0,0	33,30	66,7
		Zyklus 76 Tag 1	13	20,51	25,603	0,0	0,00	66,7
		Zyklus 80 Tag 1	6	38,87	32,778	0,0	33,30	100,0
		Zyklus 84 Tag 1	2	66,65	47,164	33,3	66,65	100,0
EORTC QLQ-C30 Appetitverlust	Acala+BR (N=299)	Screening	284	14,08	22,702	0,0	0,00	100,0
		Zyklus 3 Tag 1	256	15,88	23,968	0,0	0,00	100,0
		Zyklus 5 Tag 1	248	15,45	25,420	0,0	0,00	100,0
		Zyklus 8 Tag 1	225	13,33	22,926	0,0	0,00	100,0
		Zyklus 12 Tag 1	212	7,86	17,199	0,0	0,00	100,0
		Zyklus 16 Tag 1	196	7,65	18,893	0,0	0,00	100,0
		Zyklus 20 Tag 1	177	5,84	15,802	0,0	0,00	100,0
		Zyklus 24 Tag 1	162	6,58	15,685	0,0	0,00	100,0
		Zyklus 28 Tag 1	149	6,04	17,775	0,0	0,00	100,0
		Zyklus 32 Tag 1	120	7,77	19,675	0,0	0,00	100,0
		Zyklus 36 Tag 1	117	6,26	16,910	0,0	0,00	100,0
		Zyklus 40 Tag 1	106	7,55	21,223	0,0	0,00	100,0
		Zyklus 44 Tag 1	100	4,00	11,866	0,0	0,00	66,7
		Zyklus 48 Tag 1	94	2,83	9,342	0,0	0,00	33,3
		Zyklus 52 Tag 1	84	5,55	13,518	0,0	0,00	66,7
		Zyklus 56 Tag 1	68	5,88	14,030	0,0	0,00	66,7
		Zyklus 60 Tag 1	62	6,45	13,264	0,0	0,00	33,3
		Zyklus 64 Tag 1	53	10,06	20,240	0,0	0,00	66,7
		Zyklus 68 Tag 1	37	11,71	23,851	0,0	0,00	100,0
		Zyklus 72 Tag 1	33	9,08	20,864	0,0	0,00	100,0
		Zyklus 76 Tag 1	16	12,49	20,635	0,0	0,00	66,7
		Zyklus 80 Tag 1	7	4,76	12,586	0,0	0,00	33,3

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Appetitverlust	Placebo+BR (N=299)	Screening	274	19,34	29,008	0,0	0,00	100,0
		Zyklus 3 Tag 1	253	15,67	24,034	0,0	0,00	100,0
		Zyklus 5 Tag 1	233	14,87	23,727	0,0	0,00	100,0
		Zyklus 8 Tag 1	211	11,37	20,236	0,0	0,00	100,0
		Zyklus 12 Tag 1	182	4,58	12,521	0,0	0,00	66,7
		Zyklus 16 Tag 1	163	6,13	16,657	0,0	0,00	100,0
		Zyklus 20 Tag 1	154	6,92	15,557	0,0	0,00	66,7
		Zyklus 24 Tag 1	137	5,59	13,742	0,0	0,00	66,7
		Zyklus 28 Tag 1	126	8,20	17,726	0,0	0,00	100,0
		Zyklus 32 Tag 1	116	4,02	12,550	0,0	0,00	66,7
		Zyklus 36 Tag 1	100	8,33	19,170	0,0	0,00	100,0
		Zyklus 40 Tag 1	89	6,36	14,966	0,0	0,00	66,7
		Zyklus 44 Tag 1	84	5,55	14,478	0,0	0,00	66,7
		Zyklus 48 Tag 1	77	5,62	13,675	0,0	0,00	66,7
		Zyklus 52 Tag 1	70	6,19	14,228	0,0	0,00	66,7
		Zyklus 56 Tag 1	56	4,16	11,113	0,0	0,00	33,3
		Zyklus 60 Tag 1	46	8,69	17,823	0,0	0,00	66,7
		Zyklus 64 Tag 1	42	7,14	17,321	0,0	0,00	66,7
		Zyklus 68 Tag 1	31	9,67	19,614	0,0	0,00	66,7
		Zyklus 72 Tag 1	19	8,76	15,065	0,0	0,00	33,3
		Zyklus 76 Tag 1	13	10,25	15,997	0,0	0,00	33,3
EORTC QLQ-C30 Verstopfung	Acala+BR (N=299)	Zyklus 80 Tag 1	6	11,10	17,196	0,0	0,00	33,3
		Zyklus 84 Tag 1	2	0,00	0,000	0,0	0,00	0,0
		Screening	284	10,44	20,503	0,0	0,00	100,0
		Zyklus 3 Tag 1	256	11,19	19,700	0,0	0,00	100,0
		Zyklus 5 Tag 1	248	10,61	19,415	0,0	0,00	100,0
		Zyklus 8 Tag 1	225	9,03	18,152	0,0	0,00	100,0
		Zyklus 12 Tag 1	212	8,33	17,128	0,0	0,00	100,0
		Zyklus 16 Tag 1	196	8,84	16,565	0,0	0,00	66,7
		Zyklus 20 Tag 1	175	7,04	14,980	0,0	0,00	66,7
		Zyklus 24 Tag 1	161	8,28	17,884	0,0	0,00	66,7
		Zyklus 28 Tag 1	149	6,93	15,623	0,0	0,00	100,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DCO 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Verstopfung	Acala+BR (N=299)	Zyklus 32 Tag 1	120	7,22	15,075	0,0	0,00	66,7
		Zyklus 36 Tag 1	118	6,78	16,045	0,0	0,00	66,7
		Zyklus 40 Tag 1	107	7,47	18,489	0,0	0,00	100,0
		Zyklus 44 Tag 1	99	5,05	12,914	0,0	0,00	66,7
		Zyklus 48 Tag 1	94	4,96	12,886	0,0	0,00	66,7
		Zyklus 52 Tag 1	84	5,55	13,518	0,0	0,00	66,7
		Zyklus 56 Tag 1	68	7,84	15,355	0,0	0,00	66,7
		Zyklus 60 Tag 1	62	5,37	15,019	0,0	0,00	66,7
		Zyklus 64 Tag 1	53	6,91	15,125	0,0	0,00	66,7
		Zyklus 68 Tag 1	38	8,77	18,475	0,0	0,00	66,7
		Zyklus 72 Tag 1	33	9,09	19,135	0,0	0,00	66,7
		Zyklus 76 Tag 1	16	10,42	23,480	0,0	0,00	66,7
		Zyklus 80 Tag 1	7	14,27	17,800	0,0	0,00	33,3
	Placebo+BR (N=299)	Screening	272	11,03	22,385	0,0	0,00	100,0
		Zyklus 3 Tag 1	252	15,34	24,225	0,0	0,00	100,0
		Zyklus 5 Tag 1	232	12,49	21,969	0,0	0,00	100,0
		Zyklus 8 Tag 1	209	8,61	17,604	0,0	0,00	100,0
		Zyklus 12 Tag 1	182	7,50	16,381	0,0	0,00	100,0
		Zyklus 16 Tag 1	163	7,77	17,592	0,0	0,00	100,0
		Zyklus 20 Tag 1	154	8,87	20,885	0,0	0,00	100,0
		Zyklus 24 Tag 1	136	9,80	20,730	0,0	0,00	100,0
		Zyklus 28 Tag 1	126	8,20	17,216	0,0	0,00	100,0
		Zyklus 32 Tag 1	115	8,98	19,899	0,0	0,00	100,0
		Zyklus 36 Tag 1	100	7,33	17,459	0,0	0,00	66,7
		Zyklus 40 Tag 1	89	7,49	17,220	0,0	0,00	100,0
		Zyklus 44 Tag 1	84	5,15	15,073	0,0	0,00	100,0
		Zyklus 48 Tag 1	77	7,36	18,432	0,0	0,00	100,0
		Zyklus 52 Tag 1	70	8,09	16,477	0,0	0,00	66,7
		Zyklus 56 Tag 1	56	11,90	25,761	0,0	0,00	100,0
		Zyklus 60 Tag 1	46	10,14	22,075	0,0	0,00	100,0
		Zyklus 64 Tag 1	42	11,90	25,310	0,0	0,00	100,0
		Zyklus 68 Tag 1	31	13,97	25,493	0,0	0,00	100,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanpraa 18MAR2025:14:24 khcs324

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DCO 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Verstopfung	Placebo+BR (N=299)	Zyklus 72 Tag 1	20	8,33	18,336	0,0	0,00	66,7
		Zyklus 76 Tag 1	13	10,25	21,016	0,0	0,00	66,7
		Zyklus 80 Tag 1	6	27,78	44,311	0,0	0,00	100,0
		Zyklus 84 Tag 1	2	50,00	23,617	33,3	50,00	66,7
EORTC QLQ-C30 Diarrhö	Acala+BR (N=299)	Screening	283	9,30	19,742	0,0	0,00	100,0
		Zyklus 3 Tag 1	256	8,07	17,826	0,0	0,00	100,0
		Zyklus 5 Tag 1	248	10,61	19,874	0,0	0,00	100,0
		Zyklus 8 Tag 1	226	10,76	20,774	0,0	0,00	100,0
		Zyklus 12 Tag 1	212	8,17	17,659	0,0	0,00	100,0
		Zyklus 16 Tag 1	196	8,67	16,484	0,0	0,00	66,7
		Zyklus 20 Tag 1	176	8,90	16,792	0,0	0,00	66,7
		Zyklus 24 Tag 1	161	10,14	17,881	0,0	0,00	100,0
		Zyklus 28 Tag 1	149	7,60	16,027	0,0	0,00	66,7
		Zyklus 32 Tag 1	120	7,77	16,003	0,0	0,00	100,0
		Zyklus 36 Tag 1	118	7,06	15,618	0,0	0,00	66,7
		Zyklus 40 Tag 1	107	5,91	13,583	0,0	0,00	66,7
		Zyklus 44 Tag 1	100	10,33	18,766	0,0	0,00	66,7
		Zyklus 48 Tag 1	94	6,38	14,054	0,0	0,00	66,7
		Zyklus 52 Tag 1	83	7,63	19,704	0,0	0,00	100,0
		Zyklus 56 Tag 1	68	9,80	20,810	0,0	0,00	100,0
		Zyklus 60 Tag 1	61	7,64	15,379	0,0	0,00	66,7
		Zyklus 64 Tag 1	53	8,17	19,504	0,0	0,00	100,0
		Zyklus 68 Tag 1	38	11,40	19,411	0,0	0,00	66,7
		Zyklus 72 Tag 1	33	12,11	18,283	0,0	0,00	66,7
		Zyklus 76 Tag 1	16	4,16	11,374	0,0	0,00	33,3
		Zyklus 80 Tag 1	7	23,80	25,201	0,0	33,30	66,7
	Placebo+BR (N=299)	Screening	273	9,40	20,739	0,0	0,00	100,0
		Zyklus 3 Tag 1	252	7,27	17,215	0,0	0,00	100,0
		Zyklus 5 Tag 1	234	7,40	18,325	0,0	0,00	100,0
		Zyklus 8 Tag 1	211	6,31	13,871	0,0	0,00	66,7
		Zyklus 12 Tag 1	182	5,49	14,237	0,0	0,00	100,0
		Zyklus 16 Tag 1	162	7,40	16,189	0,0	0,00	66,7

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Diarrhö	Placebo+BR (N=299)	Zyklus 20 Tag 1	154	7,14	16,591	0,0	0,00	100,0
		Zyklus 24 Tag 1	136	8,08	18,806	0,0	0,00	100,0
		Zyklus 28 Tag 1	126	5,55	13,818	0,0	0,00	66,7
		Zyklus 32 Tag 1	115	6,66	15,416	0,0	0,00	66,7
		Zyklus 36 Tag 1	99	7,07	16,680	0,0	0,00	66,7
		Zyklus 40 Tag 1	89	7,49	15,686	0,0	0,00	66,7
		Zyklus 44 Tag 1	84	8,33	17,059	0,0	0,00	66,7
		Zyklus 48 Tag 1	77	5,62	14,708	0,0	0,00	66,7
		Zyklus 52 Tag 1	70	4,76	14,226	0,0	0,00	66,7
		Zyklus 56 Tag 1	56	5,95	12,869	0,0	0,00	33,3
		Zyklus 60 Tag 1	46	4,35	13,346	0,0	0,00	66,7
		Zyklus 64 Tag 1	41	4,88	17,573	0,0	0,00	100,0
		Zyklus 68 Tag 1	31	5,37	12,450	0,0	0,00	33,3
		Zyklus 72 Tag 1	19	0,00	0,000	0,0	0,00	0,0
		Zyklus 76 Tag 1	13	2,56	9,236	0,0	0,00	33,3
		Zyklus 80 Tag 1	6	0,00	0,000	0,0	0,00	0,0
		Zyklus 84 Tag 1	2	16,65	23,547	0,0	16,65	33,3
EORTC QLQ-C30 Finanzielle Schwierigkeiten	Acala+BR (N=299)	Screening	283	13,54	25,441	0,0	0,00	100,0
		Zyklus 3 Tag 1	256	14,06	25,260	0,0	0,00	100,0
		Zyklus 5 Tag 1	249	12,98	24,245	0,0	0,00	100,0
		Zyklus 8 Tag 1	225	12,14	23,368	0,0	0,00	100,0
		Zyklus 12 Tag 1	211	11,84	22,573	0,0	0,00	100,0
		Zyklus 16 Tag 1	196	7,99	19,055	0,0	0,00	100,0
		Zyklus 20 Tag 1	176	11,36	21,606	0,0	0,00	100,0
		Zyklus 24 Tag 1	161	9,31	20,821	0,0	0,00	100,0
		Zyklus 28 Tag 1	149	10,29	21,187	0,0	0,00	100,0
		Zyklus 32 Tag 1	120	11,11	22,175	0,0	0,00	100,0
		Zyklus 36 Tag 1	118	6,78	16,045	0,0	0,00	66,7
		Zyklus 40 Tag 1	107	9,03	17,472	0,0	0,00	66,7
		Zyklus 44 Tag 1	100	8,00	17,158	0,0	0,00	66,7
		Zyklus 48 Tag 1	94	8,15	19,359	0,0	0,00	100,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.6.1 ECHO: Summary of absolute values of EORTC QLQ-C30 results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EORTC QLQ-C30 Finanzielle Schwierigkeiten	Acala+BR (N=299)	Zyklus 52 Tag 1	83	9,23	17,504	0,0	0,00	66,7
		Zyklus 56 Tag 1	68	9,80	19,994	0,0	0,00	100,0
		Zyklus 60 Tag 1	62	8,06	16,727	0,0	0,00	66,7
		Zyklus 64 Tag 1	53	8,17	17,175	0,0	0,00	66,7
		Zyklus 68 Tag 1	38	7,89	18,065	0,0	0,00	66,7
		Zyklus 72 Tag 1	33	7,07	16,149	0,0	0,00	66,7
		Zyklus 76 Tag 1	16	4,16	11,374	0,0	0,00	33,3
	Placebo+BR (N=299)	Zyklus 80 Tag 1	7	14,29	26,234	0,0	0,00	66,7
		Screening	273	14,89	24,874	0,0	0,00	100,0
		Zyklus 3 Tag 1	252	13,49	23,684	0,0	0,00	100,0
		Zyklus 5 Tag 1	233	13,73	20,576	0,0	0,00	100,0
		Zyklus 8 Tag 1	211	13,11	21,372	0,0	0,00	100,0
		Zyklus 12 Tag 1	182	9,70	17,786	0,0	0,00	66,7
		Zyklus 16 Tag 1	162	11,10	20,344	0,0	0,00	100,0
		Zyklus 20 Tag 1	154	12,55	21,244	0,0	0,00	100,0
		Zyklus 24 Tag 1	136	11,76	19,253	0,0	0,00	66,7
		Zyklus 28 Tag 1	126	10,05	17,515	0,0	0,00	66,7
		Zyklus 32 Tag 1	114	14,61	21,737	0,0	0,00	100,0
		Zyklus 36 Tag 1	99	9,42	19,067	0,0	0,00	100,0
		Zyklus 40 Tag 1	89	9,36	20,092	0,0	0,00	100,0
		Zyklus 44 Tag 1	84	11,10	20,257	0,0	0,00	100,0
		Zyklus 48 Tag 1	78	9,40	18,528	0,0	0,00	66,7
		Zyklus 52 Tag 1	70	9,52	18,069	0,0	0,00	66,7
		Zyklus 56 Tag 1	56	9,52	18,762	0,0	0,00	66,7
		Zyklus 60 Tag 1	46	8,69	17,823	0,0	0,00	66,7
		Zyklus 64 Tag 1	41	12,19	19,368	0,0	0,00	66,7
		Zyklus 68 Tag 1	31	10,75	19,975	0,0	0,00	66,7
		Zyklus 72 Tag 1	19	10,52	15,903	0,0	0,00	33,3
		Zyklus 76 Tag 1	13	12,81	16,862	0,0	0,00	33,3
		Zyklus 80 Tag 1	6	11,10	17,196	0,0	0,00	33,3
		Zyklus 84 Tag 1	2	0,00	0,000	0,0	0,00	0,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.6.2 ECHO: Summary of absolute values of FACT Lym results over time by treatment group
 Full Analysis Set, DCO 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
FACT-Lym Gesamtscore	Acala+BR (N=299)	Screening	281	129,25	20,683	66,0	133,00	167,0
		Zyklus 3 Tag 1	254	130,38	20,638	54,0	134,00	166,0
		Zyklus 5 Tag 1	243	131,61	19,187	58,0	134,00	168,0
		Zyklus 8 Tag 1	224	131,37	19,830	48,0	132,00	168,0
		Zyklus 12 Tag 1	214	136,10	19,680	70,0	139,00	168,0
		Zyklus 16 Tag 1	198	134,60	21,195	47,0	137,00	168,0
		Zyklus 20 Tag 1	178	134,84	20,427	73,0	136,50	167,0
		Zyklus 24 Tag 1	159	134,40	20,829	75,0	137,00	168,0
		Zyklus 28 Tag 1	150	133,36	21,142	62,0	135,50	166,0
		Zyklus 32 Tag 1	122	131,96	23,182	63,0	135,50	166,0
		Zyklus 36 Tag 1	119	134,44	21,848	65,0	138,00	168,0
		Zyklus 40 Tag 1	109	133,06	22,943	76,0	138,00	168,0
		Zyklus 44 Tag 1	101	132,10	22,860	74,0	135,00	168,0
		Zyklus 48 Tag 1	93	133,59	22,199	75,0	135,00	168,0
		Zyklus 52 Tag 1	83	134,08	23,412	70,0	138,00	168,0
		Zyklus 56 Tag 1	67	134,09	23,200	67,0	140,00	163,0
		Zyklus 60 Tag 1	62	132,98	24,793	70,0	138,50	166,0
		Zyklus 64 Tag 1	52	133,73	25,769	80,0	142,00	168,0
		Zyklus 68 Tag 1	38	136,03	21,848	83,0	142,00	165,0
		Zyklus 72 Tag 1	33	133,91	21,450	92,0	137,00	162,0
		Zyklus 76 Tag 1	16	134,94	26,310	84,0	144,50	161,0
		Zyklus 80 Tag 1	5	125,80	25,704	87,0	129,00	158,0
	Placebo+BR (N=299)	Screening	273	125,49	21,186	53,0	126,00	166,0
		Zyklus 3 Tag 1	251	128,57	21,700	67,0	131,00	168,0
		Zyklus 5 Tag 1	235	128,89	20,892	56,0	132,00	168,0
		Zyklus 8 Tag 1	211	131,33	20,567	51,0	133,00	168,0
		Zyklus 12 Tag 1	182	133,98	19,495	64,0	136,00	168,0
		Zyklus 16 Tag 1	164	134,37	21,852	59,0	139,00	168,0
		Zyklus 20 Tag 1	155	132,45	21,932	67,0	134,00	168,0
		Zyklus 24 Tag 1	137	132,36	21,130	73,0	134,00	168,0
		Zyklus 28 Tag 1	124	132,74	21,786	80,0	136,00	168,0
		Zyklus 32 Tag 1	115	133,63	21,058	69,0	136,00	167,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.6.2 ECHO: Summary of absolute values of FACT Lym results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Absolute Werte				
				Mittelwert	SD	Min	Median	Max
FACT-Lym Gesamtscore	Placebo+BR (N=299)	Zyklus 36 Tag 1	100	133,44	21,028	57,0	137,00	168,0
		Zyklus 40 Tag 1	90	136,00	18,826	85,0	140,00	168,0
		Zyklus 44 Tag 1	84	133,11	21,918	79,0	136,00	168,0
		Zyklus 48 Tag 1	78	134,83	22,513	78,0	140,00	168,0
		Zyklus 52 Tag 1	70	133,97	21,504	80,0	139,00	165,0
		Zyklus 56 Tag 1	56	133,07	23,095	80,0	140,50	164,0
		Zyklus 60 Tag 1	46	133,72	21,475	80,0	137,00	163,0
		Zyklus 64 Tag 1	42	136,98	23,910	77,0	144,00	167,0
		Zyklus 68 Tag 1	31	136,81	25,249	74,0	149,00	167,0
		Zyklus 72 Tag 1	19	131,53	24,963	92,0	140,00	167,0
		Zyklus 76 Tag 1	12	126,75	29,598	79,0	135,50	162,0
		Zyklus 80 Tag 1	5	121,80	26,771	87,0	120,00	155,0
		Zyklus 84 Tag 1	2	121,00	4,243	118,0	121,00	124,0
FACT-Lym Physisches Wohlbefinden (PWB)	Acala+BR (N=299)	Screening	282	23,97	3,872	9,0	25,00	28,0
		Zyklus 3 Tag 1	255	23,01	4,208	10,0	24,00	28,0
		Zyklus 5 Tag 1	245	23,01	4,239	6,0	24,00	28,0
		Zyklus 8 Tag 1	225	23,66	3,922	6,0	24,00	28,0
		Zyklus 12 Tag 1	215	24,47	3,454	10,0	26,00	28,0
		Zyklus 16 Tag 1	198	24,21	4,086	4,0	25,00	28,0
		Zyklus 20 Tag 1	178	24,49	3,700	8,0	25,00	28,0
		Zyklus 24 Tag 1	160	24,50	3,741	10,0	26,00	28,0
		Zyklus 28 Tag 1	151	24,32	3,651	10,0	25,00	28,0
		Zyklus 32 Tag 1	122	24,16	4,427	7,0	25,35	28,0
		Zyklus 36 Tag 1	119	24,44	4,055	7,0	26,00	28,0
		Zyklus 40 Tag 1	110	24,16	4,345	11,0	26,00	28,0
		Zyklus 44 Tag 1	101	23,87	4,258	10,0	25,00	28,0
		Zyklus 48 Tag 1	94	24,48	3,781	15,0	26,00	28,0
		Zyklus 52 Tag 1	83	24,47	3,964	14,0	26,00	28,0
		Zyklus 56 Tag 1	67	24,49	4,212	11,0	26,00	28,0
		Zyklus 60 Tag 1	62	24,05	4,546	10,0	26,00	28,0
		Zyklus 64 Tag 1	53	24,28	4,620	11,0	26,00	28,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/smeanpr.sas gsmeanprab 18MAR2025:14:24 khcs324

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Table 2.6.2 ECHO: Summary of absolute values of FACT Lym results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
FACT-Lym Physisches Wohlbefinden (PWB)	Acala+BR (N=299)	Zyklus 68 Tag 1	38	24,55	4,341	11,0	26,50	28,0
		Zyklus 72 Tag 1	33	24,03	4,305	11,0	26,00	28,0
		Zyklus 76 Tag 1	16	24,38	4,113	14,0	25,50	28,0
		Zyklus 80 Tag 1	6	23,00	6,603	10,0	25,00	28,0
	Placebo+BR (N=299)	Screening	274	23,23	4,483	5,0	25,00	28,0
		Zyklus 3 Tag 1	252	22,67	4,843	7,0	24,00	28,0
		Zyklus 5 Tag 1	235	22,75	4,399	3,0	24,00	28,0
		Zyklus 8 Tag 1	212	23,79	4,385	3,0	25,00	28,0
		Zyklus 12 Tag 1	182	24,60	3,471	7,0	25,00	28,0
		Zyklus 16 Tag 1	164	24,53	3,963	8,0	26,00	28,0
		Zyklus 20 Tag 1	155	24,45	4,194	9,0	26,00	28,0
		Zyklus 24 Tag 1	138	24,22	4,307	0,0	25,50	28,0
		Zyklus 28 Tag 1	125	24,14	4,019	10,0	26,00	28,0
		Zyklus 32 Tag 1	115	24,56	3,567	10,0	25,00	28,0
		Zyklus 36 Tag 1	101	24,36	3,801	9,0	25,70	28,0
		Zyklus 40 Tag 1	90	24,76	3,301	12,0	26,00	28,0
		Zyklus 44 Tag 1	84	24,36	3,972	9,0	26,00	28,0
		Zyklus 48 Tag 1	78	24,63	4,007	10,0	26,00	28,0
		Zyklus 52 Tag 1	70	24,18	4,100	12,0	26,00	28,0
		Zyklus 56 Tag 1	56	24,00	4,620	10,0	26,00	28,0
		Zyklus 60 Tag 1	46	24,73	3,742	14,0	26,00	28,0
		Zyklus 64 Tag 1	42	24,74	4,675	9,0	27,00	28,0
		Zyklus 68 Tag 1	31	24,77	4,849	12,0	27,00	28,0
		Zyklus 72 Tag 1	20	23,80	4,786	14,0	26,50	28,0
		Zyklus 76 Tag 1	12	22,98	5,943	12,0	25,50	28,0
		Zyklus 80 Tag 1	6	24,17	4,535	16,0	26,00	28,0
		Zyklus 84 Tag 1	2	19,00	5,657	15,0	19,00	23,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.6.2 ECHO: Summary of absolute values of FACT Lym results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
FACT-Lym Soziales Wohlbefinden (SWB)	Acala+BR (N=299)	Screening	282	22,01	5,293	0,0	22,30	28,0
		Zyklus 3 Tag 1	255	21,65	5,876	0,0	23,00	28,0
		Zyklus 5 Tag 1	245	21,56	5,786	0,0	23,00	28,0
		Zyklus 8 Tag 1	225	21,47	6,015	0,0	22,20	28,0
		Zyklus 12 Tag 1	215	22,12	5,730	0,0	23,30	28,0
		Zyklus 16 Tag 1	198	21,61	5,265	7,0	22,20	28,0
		Zyklus 20 Tag 1	178	21,17	5,843	0,0	22,00	28,0
		Zyklus 24 Tag 1	160	21,57	6,061	0,0	22,20	28,0
		Zyklus 28 Tag 1	151	21,04	6,401	0,0	22,20	28,0
		Zyklus 32 Tag 1	122	21,08	5,542	5,0	21,00	28,0
		Zyklus 36 Tag 1	119	21,68	5,137	7,0	22,20	28,0
		Zyklus 40 Tag 1	110	21,07	5,610	0,0	22,00	28,0
		Zyklus 44 Tag 1	101	20,51	6,360	0,0	21,00	28,0
		Zyklus 48 Tag 1	94	21,48	6,052	1,0	22,20	28,0
		Zyklus 52 Tag 1	83	21,77	5,383	9,0	22,00	28,0
		Zyklus 56 Tag 1	68	21,51	5,601	9,0	23,00	28,0
		Zyklus 60 Tag 1	62	21,55	5,571	10,5	21,50	28,0
		Zyklus 64 Tag 1	53	21,98	6,354	8,2	24,50	28,0
		Zyklus 68 Tag 1	38	22,09	5,250	10,0	22,00	28,0
		Zyklus 72 Tag 1	33	23,28	4,596	15,0	25,00	28,0
		Zyklus 76 Tag 1	16	23,11	6,255	12,0	27,50	28,0
		Zyklus 80 Tag 1	6	22,27	4,399	14,0	22,70	26,0
	Placebo+BR (N=299)	Screening	274	21,79	4,736	4,7	22,20	28,0
		Zyklus 3 Tag 1	252	21,82	4,836	5,0	22,20	28,0
		Zyklus 5 Tag 1	235	21,39	4,912	7,0	22,00	28,0
		Zyklus 8 Tag 1	213	21,17	5,217	0,0	22,00	28,0
		Zyklus 12 Tag 1	182	20,87	6,247	0,0	22,00	28,0
		Zyklus 16 Tag 1	164	21,64	5,421	4,0	22,20	28,0
		Zyklus 20 Tag 1	155	21,07	5,675	4,0	22,20	28,0
		Zyklus 24 Tag 1	138	21,06	6,075	0,0	22,30	28,0
		Zyklus 28 Tag 1	125	21,03	5,785	0,0	22,00	28,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.6.2 ECHO: Summary of absolute values of FACT Lym results over time by treatment group
 Full Analysis Set, DCO 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
FACT-Lym Soziales Wohlbefinden (SWB)	Placebo+BR (N=299)	Zyklus 32 Tag 1	115	20,86	5,217	6,0	22,00	28,0
		Zyklus 36 Tag 1	101	21,43	5,747	0,0	22,20	28,0
		Zyklus 40 Tag 1	90	21,65	5,156	8,0	22,20	28,0
		Zyklus 44 Tag 1	84	20,89	5,843	0,0	22,00	28,0
		Zyklus 48 Tag 1	78	21,57	5,555	6,0	22,60	28,0
		Zyklus 52 Tag 1	70	21,48	5,673	3,0	22,20	28,0
		Zyklus 56 Tag 1	56	21,82	4,893	9,3	22,00	28,0
		Zyklus 60 Tag 1	46	22,10	4,788	12,0	22,20	28,0
		Zyklus 64 Tag 1	42	22,27	4,991	8,2	23,00	28,0
		Zyklus 68 Tag 1	31	21,89	6,569	0,0	24,00	28,0
		Zyklus 72 Tag 1	20	21,39	6,985	0,0	23,15	28,0
		Zyklus 76 Tag 1	12	20,55	8,128	0,0	22,60	28,0
		Zyklus 80 Tag 1	6	17,57	8,512	4,7	17,85	28,0
		Zyklus 84 Tag 1	2	22,50	2,121	21,0	22,50	24,0
FACT-Lym Funktionales Wohlbefinden (FWB)	Acala+BR (N=299)	Screening	281	19,44	5,821	5,0	20,00	28,0
		Zyklus 3 Tag 1	255	18,62	6,046	0,0	19,00	28,0
		Zyklus 5 Tag 1	245	18,75	5,765	0,0	19,00	28,0
		Zyklus 8 Tag 1	225	19,02	5,752	0,0	19,00	28,0
		Zyklus 12 Tag 1	215	19,97	5,875	0,0	21,00	28,0
		Zyklus 16 Tag 1	198	19,90	5,779	3,0	21,00	28,0
		Zyklus 20 Tag 1	178	19,92	5,491	2,0	21,00	28,0
		Zyklus 24 Tag 1	161	19,96	5,553	6,0	20,00	28,0
		Zyklus 28 Tag 1	151	19,37	6,060	0,0	20,00	28,0
		Zyklus 32 Tag 1	122	19,07	6,312	1,0	20,00	28,0
		Zyklus 36 Tag 1	119	19,91	5,756	5,0	20,00	28,0
		Zyklus 40 Tag 1	109	19,37	5,999	0,0	20,00	28,0
		Zyklus 44 Tag 1	101	19,45	5,857	4,0	20,00	28,0
		Zyklus 48 Tag 1	94	18,86	6,097	4,0	19,00	28,0
		Zyklus 52 Tag 1	83	19,42	6,779	0,0	20,00	28,0
		Zyklus 56 Tag 1	69	19,68	6,161	2,0	19,00	28,0
		Zyklus 60 Tag 1	62	19,42	5,955	8,0	20,00	28,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.6.2 ECHO: Summary of absolute values of FACT Lym results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
FACT-Lym Funktionales Wohlbefinden (FWB)	Acala+BR (N=299)	Zyklus 64 Tag 1	53	20,14	6,457	6,0	21,00	28,0
		Zyklus 68 Tag 1	38	20,89	5,177	13,0	20,50	28,0
		Zyklus 72 Tag 1	33	20,30	5,682	10,0	20,00	28,0
		Zyklus 76 Tag 1	16	20,50	6,976	7,0	23,50	28,0
		Zyklus 80 Tag 1	5	18,00	6,285	12,0	15,00	27,0
	Placebo+BR (N=299)	Screening	274	18,02	6,009	0,0	18,00	28,0
		Zyklus 3 Tag 1	252	18,12	5,791	4,0	18,00	28,0
		Zyklus 5 Tag 1	235	18,28	5,918	1,0	19,00	28,0
		Zyklus 8 Tag 1	213	19,04	5,642	0,0	20,00	28,0
		Zyklus 12 Tag 1	183	19,27	5,953	0,0	20,00	28,0
		Zyklus 16 Tag 1	164	19,81	5,886	4,0	21,00	28,0
		Zyklus 20 Tag 1	155	18,90	6,004	1,0	19,00	28,0
		Zyklus 24 Tag 1	138	19,43	5,802	5,0	20,00	28,0
		Zyklus 28 Tag 1	125	19,29	6,019	2,0	20,00	28,0
		Zyklus 32 Tag 1	115	19,75	6,042	2,0	20,00	28,0
		Zyklus 36 Tag 1	100	19,56	6,114	1,0	20,50	28,0
		Zyklus 40 Tag 1	90	20,05	5,580	8,0	20,50	28,0
		Zyklus 44 Tag 1	84	19,13	6,117	2,0	19,50	28,0
		Zyklus 48 Tag 1	78	20,01	6,087	4,0	21,00	28,0
		Zyklus 52 Tag 1	70	19,26	6,220	0,0	20,00	28,0
		Zyklus 56 Tag 1	56	19,53	5,962	7,0	21,00	28,0
		Zyklus 60 Tag 1	46	19,78	5,736	8,0	21,00	28,0
		Zyklus 64 Tag 1	42	20,64	6,588	7,0	23,00	28,0
		Zyklus 68 Tag 1	31	20,32	6,353	7,0	21,00	28,0
		Zyklus 72 Tag 1	20	19,19	7,017	1,0	20,50	28,0
		Zyklus 76 Tag 1	12	20,67	6,638	10,0	23,00	28,0
		Zyklus 80 Tag 1	6	16,50	6,863	5,0	18,00	25,0
		Zyklus 84 Tag 1	2	19,00	2,828	17,0	19,00	21,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.6.2 ECHO: Summary of absolute values of FACT Lym results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
FACT-Lym Emotionales Wohlbefinden (EMB)	Acala+BR (N=299)	Screening	281	18,03	4,066	2,0	19,00	24,0
		Zyklus 3 Tag 1	255	19,29	4,024	6,0	20,00	24,0
		Zyklus 5 Tag 1	244	19,53	3,481	7,0	20,00	24,0
		Zyklus 8 Tag 1	225	19,21	3,955	6,0	20,00	24,0
		Zyklus 12 Tag 1	215	19,80	3,492	5,0	20,00	24,0
		Zyklus 16 Tag 1	198	19,45	3,878	0,0	20,00	24,0
		Zyklus 20 Tag 1	178	19,62	3,681	6,0	20,00	24,0
		Zyklus 24 Tag 1	160	19,38	4,134	4,0	20,00	24,0
		Zyklus 28 Tag 1	150	19,23	4,077	8,0	20,00	24,0
		Zyklus 32 Tag 1	122	19,12	4,206	7,0	20,00	24,0
		Zyklus 36 Tag 1	119	19,39	4,253	5,0	20,00	24,0
		Zyklus 40 Tag 1	109	19,50	3,824	6,0	20,00	24,0
		Zyklus 44 Tag 1	101	19,08	4,197	8,0	20,00	24,0
		Zyklus 48 Tag 1	94	19,16	4,083	7,0	20,00	24,0
		Zyklus 52 Tag 1	83	19,14	4,371	8,0	20,00	24,0
		Zyklus 56 Tag 1	69	19,71	4,084	8,0	20,00	24,0
		Zyklus 60 Tag 1	62	19,45	4,558	5,0	21,00	24,0
		Zyklus 64 Tag 1	53	19,64	4,658	7,0	21,00	24,0
		Zyklus 68 Tag 1	38	19,53	4,157	9,0	20,00	24,0
		Zyklus 72 Tag 1	33	18,64	4,450	8,0	20,00	24,0
	Placebo+BR (N=299)	Zyklus 76 Tag 1	16	19,38	3,775	11,0	19,50	24,0
		Zyklus 80 Tag 1	5	16,40	4,775	9,0	17,00	21,0
		Screening	274	17,89	4,032	3,0	18,00	24,0
		Zyklus 3 Tag 1	252	19,10	3,834	8,0	20,00	24,0
		Zyklus 5 Tag 1	235	19,09	3,985	2,0	20,00	24,0
		Zyklus 8 Tag 1	213	19,42	3,551	8,0	20,00	24,0
		Zyklus 12 Tag 1	183	19,54	3,495	7,0	20,00	24,0
		Zyklus 16 Tag 1	164	19,64	3,866	3,0	20,00	24,0
		Zyklus 20 Tag 1	155	19,40	3,850	2,0	20,00	24,0
		Zyklus 24 Tag 1	137	19,07	3,900	6,0	19,20	24,0
		Zyklus 28 Tag 1	125	19,54	3,874	7,0	20,00	24,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.6.2 ECHO: Summary of absolute values of FACT Lym results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
FACT-Lym Emotionales Wohlbefinden (EMB)	Placebo+BR (N=299)	Zyklus 32 Tag 1	115	19,20	3,925	2,0	20,00	24,0
		Zyklus 36 Tag 1	100	19,61	3,803	4,0	20,00	24,0
		Zyklus 40 Tag 1	90	19,80	3,395	8,0	20,00	24,0
		Zyklus 44 Tag 1	84	19,51	3,668	9,0	20,00	24,0
		Zyklus 48 Tag 1	78	19,76	3,948	8,0	21,00	24,0
		Zyklus 52 Tag 1	70	19,40	3,605	8,0	20,00	24,0
		Zyklus 56 Tag 1	56	19,18	4,005	8,0	20,00	24,0
		Zyklus 60 Tag 1	46	19,11	3,906	11,0	20,00	24,0
		Zyklus 64 Tag 1	42	19,55	4,092	5,0	20,00	24,0
		Zyklus 68 Tag 1	31	20,42	3,304	13,0	21,00	24,0
		Zyklus 72 Tag 1	20	18,15	4,043	8,0	19,50	24,0
		Zyklus 76 Tag 1	12	17,33	5,449	7,0	18,00	24,0
		Zyklus 80 Tag 1	5	18,40	4,159	13,0	19,00	24,0
		Zyklus 84 Tag 1	2	19,50	0,707	19,0	19,50	20,0
FACT-Lym Lym-Subscala (LYMS)	Acala+BR (N=299)	Screening	281	46,88	8,463	12,0	48,00	60,0
		Zyklus 3 Tag 1	254	49,03	7,429	16,0	51,00	60,0
		Zyklus 5 Tag 1	244	49,55	6,940	16,0	50,00	60,0
		Zyklus 8 Tag 1	224	49,38	7,275	14,0	50,50	60,0
		Zyklus 12 Tag 1	214	50,99	6,900	21,0	53,00	60,0
		Zyklus 16 Tag 1	198	50,38	7,514	20,0	53,00	60,0
		Zyklus 20 Tag 1	178	50,61	7,436	17,0	53,00	60,0
		Zyklus 24 Tag 1	159	50,48	7,566	20,4	52,00	60,0
		Zyklus 28 Tag 1	150	50,53	7,716	19,0	52,00	60,0
		Zyklus 32 Tag 1	122	49,75	8,061	18,0	52,00	60,0
		Zyklus 36 Tag 1	119	50,35	7,406	25,0	52,00	60,0
		Zyklus 40 Tag 1	110	50,19	7,933	26,0	52,00	60,0
		Zyklus 44 Tag 1	101	50,37	7,947	28,0	53,00	60,0
		Zyklus 48 Tag 1	93	50,88	7,512	29,0	53,00	60,0
		Zyklus 52 Tag 1	84	50,64	8,493	20,0	52,00	60,0
		Zyklus 56 Tag 1	69	49,83	8,322	22,0	52,00	60,0
		Zyklus 60 Tag 1	62	50,05	8,758	21,0	52,00	59,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.6.2 ECHO: Summary of absolute values of FACT Lym results over time by treatment group
 Full Analysis Set, DC0 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
FACT-Lym Lym-Subscala (LYMS)	Acala+BR (N=299)	Zyklus 64 Tag 1	52	50,20	8,793	27,0	53,00	60,0
		Zyklus 68 Tag 1	38	50,78	8,281	26,0	53,50	60,0
		Zyklus 72 Tag 1	33	49,52	7,730	31,0	51,00	59,0
		Zyklus 76 Tag 1	16	49,56	9,508	27,0	52,00	58,0
		Zyklus 80 Tag 1	5	46,80	11,367	28,0	50,00	58,0
	Placebo+BR (N=299)	Screening	273	45,91	9,019	8,0	48,00	60,0
		Zyklus 3 Tag 1	251	48,33	8,207	18,5	50,00	60,0
		Zyklus 5 Tag 1	235	48,91	7,591	18,0	50,00	60,0
		Zyklus 8 Tag 1	212	49,59	7,705	17,0	51,00	60,0
		Zyklus 12 Tag 1	183	51,12	7,098	20,4	53,00	60,0
		Zyklus 16 Tag 1	164	50,48	7,725	21,9	52,00	60,0
		Zyklus 20 Tag 1	155	50,20	7,722	16,0	52,00	60,0
		Zyklus 24 Tag 1	138	49,86	7,760	25,0	51,00	60,0
		Zyklus 28 Tag 1	124	50,38	7,668	29,0	52,00	60,0
		Zyklus 32 Tag 1	115	50,86	7,218	29,0	52,00	60,0
		Zyklus 36 Tag 1	101	50,15	7,786	23,0	52,00	60,0
		Zyklus 40 Tag 1	90	51,59	6,159	33,0	52,50	60,0
		Zyklus 44 Tag 1	84	50,74	7,358	29,0	53,00	60,0
		Zyklus 48 Tag 1	78	50,70	7,766	26,0	52,00	60,0
		Zyklus 52 Tag 1	70	51,13	6,957	30,0	52,00	60,0
		Zyklus 56 Tag 1	56	50,29	8,235	30,0	51,50	60,0
		Zyklus 60 Tag 1	46	49,76	8,036	25,0	51,50	60,0
		Zyklus 64 Tag 1	42	50,95	8,070	24,0	53,00	60,0
		Zyklus 68 Tag 1	31	51,05	9,679	20,0	55,00	60,0
		Zyklus 72 Tag 1	19	49,16	8,884	34,0	53,00	60,0
		Zyklus 76 Tag 1	12	47,58	10,749	32,0	51,50	60,0
		Zyklus 80 Tag 1	6	48,67	9,438	33,0	50,50	58,0
		Zyklus 84 Tag 1	2	41,00	4,243	38,0	41,00	44,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.6.3 ECHO: Summary of absolute values of EQ-5D-5L VAS scores over time by treatment group
 Full Analysis Set, DCO 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EQ-5D-5L Visuelle Analogskala	Acala+BR (N=299)	Screening	279	75,64	17,563	2,0	80,00	100,0
		Zyklus 3 Tag 1	254	77,00	15,692	20,0	80,00	100,0
		Zyklus 5 Tag 1	245	76,49	15,794	18,0	80,00	100,0
		Zyklus 8 Tag 1	221	78,59	13,753	27,0	80,00	100,0
		Zyklus 12 Tag 1	211	79,69	14,331	7,0	80,00	100,0
		Zyklus 16 Tag 1	195	80,14	14,890	10,0	81,00	100,0
		Zyklus 20 Tag 1	175	80,83	13,425	30,0	81,00	100,0
		Zyklus 24 Tag 1	162	78,63	17,050	3,0	82,50	100,0
		Zyklus 28 Tag 1	149	79,28	15,626	24,0	83,00	100,0
		Zyklus 32 Tag 1	121	80,81	13,638	30,0	83,00	100,0
		Zyklus 36 Tag 1	114	80,58	15,171	20,0	81,00	100,0
		Zyklus 40 Tag 1	108	79,35	13,851	32,0	80,00	100,0
		Zyklus 44 Tag 1	98	77,27	17,509	5,0	80,00	100,0
		Zyklus 48 Tag 1	93	79,12	12,974	49,0	80,00	100,0
		Zyklus 52 Tag 1	82	79,37	14,412	30,0	80,00	100,0
		Zyklus 56 Tag 1	65	76,06	19,366	0,0	80,00	100,0
		Zyklus 60 Tag 1	60	76,82	16,565	25,0	80,00	100,0
		Zyklus 64 Tag 1	52	79,56	15,840	29,0	80,00	100,0
		Zyklus 68 Tag 1	38	76,16	16,036	40,0	80,00	100,0
		Zyklus 72 Tag 1	34	79,18	13,739	47,0	80,00	100,0
		Zyklus 76 Tag 1	16	78,13	18,025	49,0	85,00	100,0
		Zyklus 80 Tag 1	6	68,33	15,055	50,0	72,50	85,0
	Placebo+BR (N=299)	Screening	268	71,31	19,092	1,0	75,00	100,0
		Zyklus 3 Tag 1	250	73,81	18,346	10,0	76,00	100,0
		Zyklus 5 Tag 1	231	75,99	15,613	14,0	80,00	100,0
		Zyklus 8 Tag 1	210	77,12	16,013	5,0	80,00	100,0
		Zyklus 12 Tag 1	180	79,79	15,252	20,0	80,00	100,0
		Zyklus 16 Tag 1	163	79,66	15,164	26,0	80,00	100,0
		Zyklus 20 Tag 1	155	78,50	15,749	20,0	80,00	100,0
		Zyklus 24 Tag 1	137	79,45	14,761	6,0	80,00	100,0
		Zyklus 28 Tag 1	125	79,34	14,457	35,0	80,00	100,0
		Zyklus 32 Tag 1	116	78,97	15,785	10,0	80,50	100,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.6.3 ECHO: Summary of absolute values of EQ-5D-5L VAS scores over time by treatment group
 Full Analysis Set, DCO 15FEB2024

Parameter	Gruppe	Zeitpunkt	n	Mittelwert	Absolute Werte			
					SD	Min	Median	Max
EQ-5D-5L Visuelle Analogskala	Placebo+BR (N=299)	Zyklus 36 Tag 1	101	79,40	14,268	33,0	80,00	100,0
		Zyklus 40 Tag 1	89	79,27	13,564	45,0	80,00	100,0
		Zyklus 44 Tag 1	82	78,89	15,343	25,0	84,00	100,0
		Zyklus 48 Tag 1	78	78,73	15,201	25,0	82,00	100,0
		Zyklus 52 Tag 1	68	78,10	16,793	30,0	80,00	100,0
		Zyklus 56 Tag 1	56	79,07	15,182	35,0	80,00	100,0
		Zyklus 60 Tag 1	42	77,40	15,375	40,0	80,00	100,0
		Zyklus 64 Tag 1	41	78,63	15,729	30,0	80,00	100,0
		Zyklus 68 Tag 1	29	81,79	17,662	30,0	90,00	100,0
		Zyklus 72 Tag 1	20	75,05	23,205	8,0	80,00	100,0
		Zyklus 76 Tag 1	12	80,50	17,558	50,0	83,00	100,0
		Zyklus 80 Tag 1	5	77,00	13,038	60,0	75,00	90,0
		Zyklus 84 Tag 1	2	85,00	14,142	75,0	85,00	95,0

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 2.7.1 ECHO: Summary of EORTC QLQ-C30 compliance over time and overall
 Full Analysis Set, DC0 15FEB2024

Time point	Treatment group	Expected [a]	Received [b]	Evaluable [c]	Compliance rate (%) [d]	Evaluability rate (%) [e]
Overall	Acala+BR (N=299)	297	270	270	90,9	100
	Placebo+BR (N=299)	298	261	261	87,6	100
Screening	Acala+BR (N=299)	299	285	285	95,3	100
	Placebo+BR (N=299)	299	275	275	92,0	100
Cycle 3 Day 1	Acala+BR (N=299)	297	257	257	86,5	100
	Placebo+BR (N=299)	298	256	256	85,9	100
Cycle 5 Day 1	Acala+BR (N=299)	283	250	250	88,3	100
	Placebo+BR (N=299)	280	234	234	83,6	100
Cycle 8 Day 1	Acala+BR (N=299)	270	226	226	83,7	100
	Placebo+BR (N=299)	259	212	212	81,9	100
Cycle 12 Day 1	Acala+BR (N=299)	247	212	212	85,8	100
	Placebo+BR (N=299)	236	183	183	77,5	100
Cycle 16 Day 1	Acala+BR (N=299)	232	197	197	84,9	100
	Placebo+BR (N=299)	203	165	165	81,3	100
Cycle 20 Day 1	Acala+BR (N=299)	213	177	177	83,1	100
	Placebo+BR (N=299)	185	154	154	83,2	100
Cycle 24 Day 1	Acala+BR (N=299)	196	162	162	82,7	100
	Placebo+BR (N=299)	172	137	137	79,7	100

[a] The number of patients who have not withdrawn from study and are expected to complete a questionnaire.

[b] The number of patients that have a completed questionnaire with completion date and at least one individual item completed.

[c] The number of patients that have a completed questionnaire with completion date and at least one non-missing subscale.

[d] The number of evaluable questionnaires divided by the number of expected questionnaires for the visit multiplied by 100.

[e] The number of evaluable questionnaires divided by the number of received questionnaires for the visit multiplied by 100.

In the overall row, patients are counted as Received/Evaluable if they have a Received/Evaluable baseline and at least one

Received/Evaluable post-baseline form.

NC = Not Calculated.

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Table 2.7.1 ECHO: Summary of EORTC QLQ-C30 compliance over time and overall
 Full Analysis Set, DC0 15FEB2024

Time point	Treatment group	Expected [a]	Received [b]	Evaluable [c]	Compliance rate (%) [d]	Evaluability rate (%) [e]
Cycle 28 Day 1	Acala+BR (N=299)	185	150	150	81,1	100
	Placebo+BR (N=299)	163	127	127	77,9	100
Cycle 32 Day 1	Acala+BR (N=299)	172	121	121	70,3	100
	Placebo+BR (N=299)	148	117	117	79,1	100
Cycle 36 Day 1	Acala+BR (N=299)	146	118	118	80,8	100
	Placebo+BR (N=299)	128	100	100	78,1	100
Cycle 40 Day 1	Acala+BR (N=299)	133	108	108	81,2	100
	Placebo+BR (N=299)	118	89	89	75,4	100
Cycle 44 Day 1	Acala+BR (N=299)	120	100	100	83,3	100
	Placebo+BR (N=299)	101	85	85	84,2	100
Cycle 48 Day 1	Acala+BR (N=299)	113	94	94	83,2	100
	Placebo+BR (N=299)	96	78	78	81,3	100
Cycle 52 Day 1	Acala+BR (N=299)	108	84	84	77,8	100
	Placebo+BR (N=299)	88	70	70	79,5	100
Cycle 56 Day 1	Acala+BR (N=299)	98	68	68	69,4	100
	Placebo+BR (N=299)	79	56	56	70,9	100
Cycle 60 Day 1	Acala+BR (N=299)	79	62	62	78,5	100
	Placebo+BR (N=299)	64	45	45	70,3	100

[a] The number of patients who have not withdrawn from study and are expected to complete a questionnaire.

[b] The number of patients that have a completed questionnaire with completion date and at least one individual item completed.

[c] The number of patients that have a completed questionnaire with completion date and at least one non-missing subscale.

[d] The number of evaluable questionnaires divided by the number of expected questionnaires for the visit multiplied by 100.

[e] The number of evaluable questionnaires divided by the number of received questionnaires for the visit multiplied by 100.

In the overall row, patients are counted as Received/Evaluable if they have a Received/Evaluable baseline and at least one

Received/Evaluable post-baseline form.

NC = Not Calculated.

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Table 2.7.1 ECHO: Summary of EORTC QLQ-C30 compliance over time and overall
Full Analysis Set, DC0 15FEB2024

Time point	Treatment group	Expected [a]	Received [b]	Evaluable [c]	Compliance rate (%) [d]	Evaluability rate (%) [e]
Cycle 64 Day 1	Acala+BR (N=299)	68	53	53	77,9	100
	Placebo+BR (N=299)	56	42	42	75,0	100
Cycle 68 Day 1	Acala+BR (N=299)	52	37	37	71,2	100
	Placebo+BR (N=299)	48	31	31	64,6	100
Cycle 72 Day 1	Acala+BR (N=299)	40	33	33	82,5	100
	Placebo+BR (N=299)	33	20	20	60,6	100
Cycle 76 Day 1	Acala+BR (N=299)	29	16	16	55,2	100
	Placebo+BR (N=299)	24	13	13	54,2	100
Cycle 80 Day 1	Acala+BR (N=299)	14	7	7	50,0	100
	Placebo+BR (N=299)	9	6	6	66,7	100
Cycle 84 Day 1	Acala+BR (N=299)	4	0	0	0	NC
	Placebo+BR (N=299)	5	2	2	40,0	100

[a] The number of patients who have not withdrawn from study and are expected to complete a questionnaire.

[b] The number of patients that have a completed questionnaire with completion date and at least one individual item completed.

[c] The number of patients that have a completed questionnaire with completion date and at least one non-missing subscale.

[d] The number of evaluable questionnaires divided by the number of expected questionnaires for the visit multiplied by 100.

[e] The number of evaluable questionnaires divided by the number of received questionnaires for the visit multiplied by 100.

In the overall row, patients are counted as Received/Evaluable if they have a Received/Evaluable baseline and at least one Received/Evaluable post-baseline form.

NC = Not Calculated.

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Table 2.7.2 ECHO: Summary of FACT-Lym compliance over time and overall
 Full Analysis Set, DC0 15FEB2024

Time point	Treatment group	Expected [a]	Received [b]	Evaluable [c]	Compliance rate (%) [d]	Evaluability rate (%) [e]
Overall	Acala+BR (N=299)	297	266	266	89,6	100
	Placebo+BR (N=299)	298	260	260	87,2	100
Screening	Acala+BR (N=299)	299	282	282	94,3	100
	Placebo+BR (N=299)	299	274	274	91,6	100
Cycle 3 Day 1	Acala+BR (N=299)	297	256	256	86,2	100
	Placebo+BR (N=299)	298	254	253	84,9	99,6
Cycle 5 Day 1	Acala+BR (N=299)	283	246	246	86,9	100
	Placebo+BR (N=299)	280	235	235	83,9	100
Cycle 8 Day 1	Acala+BR (N=299)	270	225	225	83,3	100
	Placebo+BR (N=299)	259	214	214	82,6	100
Cycle 12 Day 1	Acala+BR (N=299)	247	215	215	87,0	100
	Placebo+BR (N=299)	236	184	184	78,0	100
Cycle 16 Day 1	Acala+BR (N=299)	232	199	199	85,8	100
	Placebo+BR (N=299)	203	166	166	81,8	100
Cycle 20 Day 1	Acala+BR (N=299)	213	178	178	83,6	100
	Placebo+BR (N=299)	185	155	155	83,8	100
Cycle 24 Day 1	Acala+BR (N=299)	196	161	161	82,1	100
	Placebo+BR (N=299)	172	138	138	80,2	100

[a] The number of patients who have not withdrawn from study and are expected to complete a questionnaire.

[b] The number of patients that have a completed questionnaire with completion date and at least one individual item completed.

[c] The number of patients that have a completed questionnaire with completion date and at least one non-missing subscale.

[d] The number of evaluable questionnaires divided by the number of expected questionnaires for the visit multiplied by 100.

[e] The number of evaluable questionnaires divided by the number of received questionnaires for the visit multiplied by 100.

In the overall row, patients are counted as Received/Evaluable if they have a Received/Evaluable baseline and at least one

Received/Evaluable post-baseline form.

NC = Not Calculated.

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Table 2.7.2 ECHO: Summary of FACT-Lym compliance over time and overall
 Full Analysis Set, DC0 15FEB2024

Time point	Treatment group	Expected [a]	Received [b]	Evaluable [c]	Compliance rate (%) [d]	Evaluability rate (%) [e]
Cycle 28 Day 1	Acala+BR (N=299)	185	152	152	82,2	100
	Placebo+BR (N=299)	163	127	126	77,3	99,2
Cycle 32 Day 1	Acala+BR (N=299)	172	123	123	71,5	100
	Placebo+BR (N=299)	148	117	117	79,1	100
Cycle 36 Day 1	Acala+BR (N=299)	146	119	119	81,5	100
	Placebo+BR (N=299)	128	101	101	78,9	100
Cycle 40 Day 1	Acala+BR (N=299)	133	110	110	82,7	100
	Placebo+BR (N=299)	118	90	90	76,3	100
Cycle 44 Day 1	Acala+BR (N=299)	120	101	101	84,2	100
	Placebo+BR (N=299)	101	85	85	84,2	100
Cycle 48 Day 1	Acala+BR (N=299)	113	94	94	83,2	100
	Placebo+BR (N=299)	96	78	78	81,3	100
Cycle 52 Day 1	Acala+BR (N=299)	108	84	84	77,8	100
	Placebo+BR (N=299)	88	70	70	79,5	100
Cycle 56 Day 1	Acala+BR (N=299)	98	69	69	70,4	100
	Placebo+BR (N=299)	79	56	56	70,9	100
Cycle 60 Day 1	Acala+BR (N=299)	79	62	62	78,5	100
	Placebo+BR (N=299)	64	45	45	70,3	100

[a] The number of patients who have not withdrawn from study and are expected to complete a questionnaire.

[b] The number of patients that have a completed questionnaire with completion date and at least one individual item completed.

[c] The number of patients that have a completed questionnaire with completion date and at least one non-missing subscale.

[d] The number of evaluable questionnaires divided by the number of expected questionnaires for the visit multiplied by 100.

[e] The number of evaluable questionnaires divided by the number of received questionnaires for the visit multiplied by 100.

In the overall row, patients are counted as Received/Evaluable if they have a Received/Evaluable baseline and at least one

Received/Evaluable post-baseline form.

NC = Not Calculated.

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Table 2.7.2 ECHO: Summary of FACT-Lym compliance over time and overall
 Full Analysis Set, DC0 15FEB2024

Time point	Treatment group	Expected [a]	Received [b]	Evaluable [c]	Compliance rate (%) [d]	Evaluability rate (%) [e]
Cycle 64 Day 1	Acala+BR (N=299)	68	53	53	77,9	100
	Placebo+BR (N=299)	56	42	42	75,0	100
Cycle 68 Day 1	Acala+BR (N=299)	52	37	37	71,2	100
	Placebo+BR (N=299)	48	31	31	64,6	100
Cycle 72 Day 1	Acala+BR (N=299)	40	33	33	82,5	100
	Placebo+BR (N=299)	33	20	20	60,6	100
Cycle 76 Day 1	Acala+BR (N=299)	29	16	16	55,2	100
	Placebo+BR (N=299)	24	12	12	50,0	100
Cycle 80 Day 1	Acala+BR (N=299)	14	6	6	42,9	100
	Placebo+BR (N=299)	9	6	6	66,7	100
Cycle 84 Day 1	Acala+BR (N=299)	4	0	0	0	NC
	Placebo+BR (N=299)	5	2	2	40,0	100

[a] The number of patients who have not withdrawn from study and are expected to complete a questionnaire.

[b] The number of patients that have a completed questionnaire with completion date and at least one individual item completed.

[c] The number of patients that have a completed questionnaire with completion date and at least one non-missing subscale.

[d] The number of evaluable questionnaires divided by the number of expected questionnaires for the visit multiplied by 100.

[e] The number of evaluable questionnaires divided by the number of received questionnaires for the visit multiplied by 100.

In the overall row, patients are counted as Received/Evaluable if they have a Received/Evaluable baseline and at least one

Received/Evaluable post-baseline form.

NC = Not Calculated.

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Table 2.7.3 ECHO: Summary of EQ-5D-5L VAS compliance over time and overall
 Full Analysis Set, DCO 15FEB2024

Time point	Treatment group	Expected [a]	Received [b]	Evaluable [c]	Compliance rate (%) [d]	Evaluability rate (%) [e]
Overall	Acala+BR (N=299)	297	263	263	88,6	100
	Placebo+BR (N=299)	298	253	253	84,9	100
Screening	Acala+BR (N=299)	299	279	279	93,3	100
	Placebo+BR (N=299)	299	268	268	89,6	100
Cycle 3 Day 1	Acala+BR (N=299)	297	255	255	85,9	100
	Placebo+BR (N=299)	298	251	251	84,2	100
Cycle 5 Day 1	Acala+BR (N=299)	283	246	246	86,9	100
	Placebo+BR (N=299)	280	231	231	82,5	100
Cycle 8 Day 1	Acala+BR (N=299)	270	221	221	81,9	100
	Placebo+BR (N=299)	259	211	211	81,5	100
Cycle 12 Day 1	Acala+BR (N=299)	247	211	211	85,4	100
	Placebo+BR (N=299)	236	181	181	76,7	100
Cycle 16 Day 1	Acala+BR (N=299)	232	196	196	84,5	100
	Placebo+BR (N=299)	203	165	165	81,3	100
Cycle 20 Day 1	Acala+BR (N=299)	213	175	175	82,2	100
	Placebo+BR (N=299)	185	155	155	83,8	100
Cycle 24 Day 1	Acala+BR (N=299)	196	162	162	82,7	100
	Placebo+BR (N=299)	172	137	137	79,7	100

[a] The number of patients who have not withdrawn from study and are expected to complete a questionnaire.

[b] The number of patients that have a completed questionnaire with completion date and at least one individual item completed.

[c] The number of patients that have a completed questionnaire with completion date and at least one non-missing subscale.

[d] The number of evaluable questionnaires divided by the number of expected questionnaires for the visit multiplied by 100.

[e] The number of evaluable questionnaires divided by the number of received questionnaires for the visit multiplied by 100.

In the overall row, patients are counted as Received/Evaluable if they have a Received/Evaluable baseline and at least one

Received/Evaluable post-baseline form.

NC = Not Calculated.

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Table 2.7.3 ECHO: Summary of EQ-5D-5L VAS compliance over time and overall
Full Analysis Set, DCO 15FEB2024

Time point	Treatment group	Expected [a]	Received [b]	Evaluable [c]	Compliance rate (%) [d]	Evaluability rate (%) [e]
Cycle 28 Day 1	Acala+BR (N=299)	185	150	150	81,1	100
	Placebo+BR (N=299)	163	126	126	77,3	100
Cycle 32 Day 1	Acala+BR (N=299)	172	122	122	70,9	100
	Placebo+BR (N=299)	148	118	118	79,7	100
Cycle 36 Day 1	Acala+BR (N=299)	146	114	114	78,1	100
	Placebo+BR (N=299)	128	101	101	78,9	100
Cycle 40 Day 1	Acala+BR (N=299)	133	108	108	81,2	100
	Placebo+BR (N=299)	118	89	89	75,4	100
Cycle 44 Day 1	Acala+BR (N=299)	120	98	98	81,7	100
	Placebo+BR (N=299)	101	83	83	82,2	100
Cycle 48 Day 1	Acala+BR (N=299)	113	93	93	82,3	100
	Placebo+BR (N=299)	96	78	78	81,3	100
Cycle 52 Day 1	Acala+BR (N=299)	108	82	82	75,9	100
	Placebo+BR (N=299)	88	68	68	77,3	100
Cycle 56 Day 1	Acala+BR (N=299)	98	65	65	66,3	100
	Placebo+BR (N=299)	79	56	56	70,9	100
Cycle 60 Day 1	Acala+BR (N=299)	79	60	60	75,9	100
	Placebo+BR (N=299)	64	41	41	64,1	100

[a] The number of patients who have not withdrawn from study and are expected to complete a questionnaire.

[b] The number of patients that have a completed questionnaire with completion date and at least one individual item completed.

[c] The number of patients that have a completed questionnaire with completion date and at least one non-missing subscale.

[d] The number of evaluable questionnaires divided by the number of expected questionnaires for the visit multiplied by 100.

[e] The number of evaluable questionnaires divided by the number of received questionnaires for the visit multiplied by 100.

In the overall row, patients are counted as Received/Evaluable if they have a Received/Evaluable baseline and at least one

Received/Evaluable post-baseline form.

NC = Not Calculated.

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Table 2.7.3 ECHO: Summary of EQ-5D-5L VAS compliance over time and overall
 Full Analysis Set, DCO 15FEB2024

Time point	Treatment group	Expected [a]	Received [b]	Evaluable [c]	Compliance rate (%) [d]	Evaluability rate (%) [e]
Cycle 64 Day 1	Acala+BR (N=299)	68	52	52	76,5	100
	Placebo+BR (N=299)	56	41	41	73,2	100
Cycle 68 Day 1	Acala+BR (N=299)	52	37	37	71,2	100
	Placebo+BR (N=299)	48	29	29	60,4	100
Cycle 72 Day 1	Acala+BR (N=299)	40	34	34	85,0	100
	Placebo+BR (N=299)	33	20	20	60,6	100
Cycle 76 Day 1	Acala+BR (N=299)	29	16	16	55,2	100
	Placebo+BR (N=299)	24	12	12	50,0	100
Cycle 80 Day 1	Acala+BR (N=299)	14	6	6	42,9	100
	Placebo+BR (N=299)	9	5	5	55,6	100
Cycle 84 Day 1	Acala+BR (N=299)	4	0	0	0	NC
	Placebo+BR (N=299)	5	2	2	40,0	100

[a] The number of patients who have not withdrawn from study and are expected to complete a questionnaire.

[b] The number of patients that have a completed questionnaire with completion date and at least one individual item completed.

[c] The number of patients that have a completed questionnaire with completion date and at least one non-missing subscale.

[d] The number of evaluable questionnaires divided by the number of expected questionnaires for the visit multiplied by 100.

[e] The number of evaluable questionnaires divided by the number of received questionnaires for the visit multiplied by 100.

In the overall row, patients are counted as Received/Evaluable if they have a Received/Evaluable baseline and at least one Received/Evaluable post-baseline form.

NC = Not Calculated.

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Nutzenbewertung nach AMNOG

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Table 3.2.1 ECHO: Summary of analysis of time to first adverse event
 (total, and by SOC and PT occurring with >=10 patients frequency and at least 1% in either treatment arm)
 Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
UE	297	296 (99,7)	0,1 [0,1; 0,1]	297	294 (99,0)	0,1 [NE; NE]	0,98	[0,83; 1,15]	0,9695
SOC: Allgemeine Erkrankungen und Beschwerden am Verabreichungsort	297	183 (61,6)	5,6 [3,7; 9,0]	297	175 (58,9)	8,3 [4,4;17,4]	1,04	[0,84; 1,28]	0,7041
PT: Asthenie	297	31 (10,4)	NE [NE; NE]	297	29 (9,8)	NE [NE; NE]	1,03	[0,62; 1,72]	0,8950
PT: Ermuedung	297	87 (29,3)	NE [NE; NE]	297	72 (24,2)	NE [NE; NE]	1,22	[0,89; 1,67]	0,2173
PT: Fieber	297	86 (29,0)	NE [NE; NE]	297	72 (24,2)	NE [NE; NE]	1,18	[0,86; 1,61]	0,3088
PT: Oedem peripher	297	44 (14,8)	NE [NE; NE]	297	43 (14,5)	NE [NE; NE]	0,97	[0,63; 1,47]	0,8734
PT: Periphere Schwellung	297	11 (3,7)	NE [NE; NE]	297	9 (3,0)	NE [NE; NE]	1,15	[0,48; 2,85]	0,7573
PT: Schuettelfrost	297	20 (6,7)	NE [NE; NE]	297	29 (9,8)	NE [NE; NE]	0,66	[0,37; 1,16]	0,1503
PT: Thoraxschmerz nicht kardialen Ursprungs	297	9 (3,0)	NE [NE; NE]	297	10 (3,4)	NE [NE; NE]	0,84	[0,34; 2,10]	0,7133
PT: Unwohlsein	297	10 (3,4)	NE [NE; NE]	297	6 (2,0)	NE [NE; NE]	1,59	[0,59; 4,67]	0,3654
SOC: Augenerkrankungen	297	63 (21,2)	NE [NE; NE]	297	47 (15,8)	NE [NE; NE]	1,28	[0,88; 1,88]	0,1936

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.1 ECHO: Summary of analysis of time to first adverse event
(total, and by SOC and PT occurring with >=10 patients frequency and at least 1% in either treatment arm)
Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
PT: Katarakt	297	11 (3,7)	NE [NE; NE]	297	9 (3,0)	NE [NE; NE]	1,09	[0,45; 2,70]	0,8510
PT: Sehen verschwommen	297	13 (4,4)	NE [NE; NE]	297	13 (4,4)	NE [NE; NE]	0,96	[0,44; 2,09]	0,9116
PT: Trockenes Auge	297	11 (3,7)	NE [NE; NE]	297	8 (2,7)	NE [NE; NE]	1,35	[0,54; 3,48]	0,5212
SOC: Erkrankungen der Atemwege, des Brustraums und Mediastinums	297	150 (50,5)	23,2 [12,4;40,0]	297	124 (41,8)	46,2 [22,4; NE]	1,25	[0,99; 1,59]	0,0624
PT: Dyspnoe	297	45 (15,2)	76,3 [76,3; NE]	297	28 (9,4)	NE [NE; NE]	1,60	[1,002; 2,59]	0,0501
PT: Husten	297	80 (26,9)	NE [NE; NE]	297	60 (20,2)	NE [NE; NE]	1,29	[0,92; 1,80]	0,1405
PT: Husten mit Auswurf	297	14 (4,7)	NE [NE; NE]	297	7 (2,4)	NE [NE; NE]	1,84	[0,76; 4,85]	0,1815
PT: Nasenverstopfung	297	13 (4,4)	NE [NE; NE]	297	9 (3,0)	NE [NE; NE]	1,38	[0,59; 3,34]	0,4579
PT: Pleuraerguss	297	11 (3,7)	NE [NE; NE]	297	5 (1,7)	NE [NE; NE]	2,15	[0,78; 6,82]	0,1463
PT: Rhinorrhoe	297	7 (2,4)	NE [NE; NE]	297	12 (4,0)	NE [NE; NE]	0,53	[0,20; 1,33]	0,1798
PT: Schmerzen im Oropharynx	297	15 (5,1)	NE [NE; NE]	297	19 (6,4)	NE [NE; NE]	0,75	[0,37; 1,47]	0,4014

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.1 ECHO: Summary of analysis of time to first adverse event
(total, and by SOC and PT occurring with ≥ 10 patients frequency and at least 1% in either treatment arm)
Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
SOC: Erkrankungen der Geschlechtsorgane und der Brustdruese	297	36 (12,1)	NE [NE; NE]	297	27 (9,1)	NE [NE; NE]	1,22	[0,74; 2,03]	0,4308
SOC: Erkrankungen der Haut und des Unterhautgewebes	297	190 (64,0)	3,8 [2,3; 6,1]	297	140 (47,1)	29,3 [10,2; NE]	1,60	[1,29; 1,99]	<0,0001*
PT: Ausschlag	297	61 (20,5)	NE [NE; NE]	297	48 (16,2)	NE [NE; NE]	1,29	[0,88; 1,88]	0,1912
PT: Ausschlag makulo-papuloes	297	47 (15,8)	NE [NE; NE]	297	19 (6,4)	NE [NE; NE]	2,57	[1,53; 4,48]	0,0003*
PT: Ausschlag mit Juckreiz	297	11 (3,7)	NE [NE; NE]	297	12 (4,0)	NE [NE; NE]	0,89	[0,39; 2,04]	0,7895
PT: Erythem	297	14 (4,7)	NE [NE; NE]	297	9 (3,0)	NE [NE; NE]	1,51	[0,66; 3,62]	0,3336
PT: Hautlaesion	297	18 (6,1)	NE [NE; NE]	297	13 (4,4)	NE [NE; NE]	1,27	[0,62; 2,64]	0,5146
PT: Naechtliche Schweissausbrueche	297	11 (3,7)	NE [NE; NE]	297	7 (2,4)	NE [NE; NE]	1,49	[0,59; 4,04]	0,4089
PT: Pruritus	297	47 (15,8)	NE [NE; NE]	297	40 (13,5)	NE [NE; NE]	1,15	[0,76; 1,76]	0,5085
PT: Trockene Haut	297	13 (4,4)	NE [NE; NE]	297	11 (3,7)	NE [NE; NE]	1,14	[0,51; 2,59]	0,7549

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

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[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.1 ECHO: Summary of analysis of time to first adverse event
 (total, and by SOC and PT occurring with >=10 patients frequency and at least 1% in either treatment arm)
 Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]		2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
SOC: Erkrankungen der Nieren und Harnwege	297	58 (19,5)	NE [NE; NE]	297	54 (18,2)	NE [NE; NE]	1,03	[0,71; 1,50]	0,8567
PT: Akute Nierenschädigung	297	12 (4,0)	NE [NE; NE]	297	14 (4,7)	NE [NE; NE]	0,81	[0,37; 1,76]	0,5940
PT: Dysurie	297	11 (3,7)	NE [NE; NE]	297	10 (3,4)	NE [NE; NE]	1,01	[0,43; 2,43]	0,9815
PT: Haematurie	297	12 (4,0)	NE [NE; NE]	297	2 (0,7)	NE [NE; NE]	5,66	[1,54; 36,38]	0,0104*
PT: Pollakisurie	297	13 (4,4)	NE [NE; NE]	297	12 (4,0)	NE [NE; NE]	0,99	[0,45; 2,21]	0,9865
SOC: Erkrankungen des Blutes und des Lymphsystems	297	175 (58,9)	5,6 [4,6;10,2]	297	170 (57,2)	7,4 [5,3;13,9]	1,03	[0,83; 1,27]	0,7938
PT: Anaemie	297	68 (22,9)	NE [NE; NE]	297	60 (20,2)	NE [NE; NE]	1,11	[0,79; 1,58]	0,5519
PT: Febrile Neutropenie	297	16 (5,4)	NE [NE; NE]	297	7 (2,4)	NE [NE; NE]	2,20	[0,94; 5,72]	0,0747
PT: Leukopenie	297	23 (7,7)	NE [NE; NE]	297	23 (7,7)	NE [NE; NE]	0,97	[0,54; 1,73]	0,9074
PT: Lymphopenie	297	14 (4,7)	NE [NE; NE]	297	19 (6,4)	NE [NE; NE]	0,70	[0,35; 1,39]	0,3137
PT: Neutropenie	297	119 (40,1)	NE [NE; NE]	297	123 (41,4)	NE [NE; NE]	0,91	[0,71; 1,17]	0,4719

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

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[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.1 ECHO: Summary of analysis of time to first adverse event
(total, and by SOC and PT occurring with ≥ 10 patients frequency and at least 1% in either treatment arm)
Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
PT: Thrombozytopenie	297	38 (12,8)	NE [NE; NE]	297	34 (11,4)	NE [NE; NE]	1,10	[0,69; 1,75]	0,6946
SOC: Erkrankungen des Gastrointestinaltrakts	297	223 (75,1)	1,0 [0,3; 1,9]	297	211 (71,0)	1,2 [1,0; 2,3]	1,09	[0,90; 1,31]	0,4109
PT: Abdominalschmerz	297	23 (7,7)	NE [NE; NE]	297	25 (8,4)	NE [NE; NE]	0,86	[0,48; 1,51]	0,5921
PT: Bauch aufgetrieben	297	11 (3,7)	NE [NE; NE]	297	5 (1,7)	NE [NE; NE]	2,17	[0,79; 6,89]	0,1405
PT: Diarrhoe	297	111 (37,4)	66,2 [60,5; NE]	297	83 (27,9)	NE [NE; NE]	1,33	[1,01; 1,78]	0,0460*
PT: Dyspepsie	297	27 (9,1)	NE [NE; NE]	297	14 (4,7)	NE [NE; NE]	1,86	[0,99; 3,66]	0,0548
PT: Erbrechen	297	76 (25,6)	NE [NE; NE]	297	41 (13,8)	NE [NE; NE]	2,01	[1,38; 2,97]	0,0003*
PT: Gastroesophageale Refluxerkrankung	297	19 (6,4)	NE [NE; NE]	297	11 (3,7)	NE [NE; NE]	1,64	[0,79; 3,56]	0,1882
PT: Mundtrockenheit	297	11 (3,7)	NE [NE; NE]	297	7 (2,4)	NE [NE; NE]	1,51	[0,59; 4,10]	0,3932
PT: Obstipation	297	73 (24,6)	NE [NE; NE]	297	75 (25,3)	NE [NE; NE]	0,95	[0,69; 1,31]	0,7483
PT: Schmerzen Oberbauch	297	13 (4,4)	NE [NE; NE]	297	13 (4,4)	NE [NE; NE]	0,94	[0,43; 2,05]	0,8799
PT: Stomatitis	297	16 (5,4)	NE [NE; NE]	297	19 (6,4)	NE [NE; NE]	0,80	[0,41; 1,56]	0,5139

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

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[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.1 ECHO: Summary of analysis of time to first adverse event
 (total, and by SOC and PT occurring with ≥ 10 patients frequency and at least 1% in either treatment arm)
 Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)				Placebo+BR (N=297)				Hazard Ratio [b]		2-seitiger p-Wert [c]
	Anzahl (%) der Patienten mit			Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit			Mediane Zeit [95%-KI] (Monate) [a]			
	n	Ereignis			n	Ereignis					
PT: Uebelkeit	297	127 (42,8)	72,8 [40,1; NE]	297	112 (37,7)	NE [NE; NE]	1,19	[0,93; 1,54]	0,1852		
SOC: Erkrankungen des Immunsystems	297	28 (9,4)	NE [NE; NE]	297	14 (4,7)	NE [NE; NE]	1,92	[1,03; 3,76]	0,0418*		
PT: Hypogammaglobulinaemie	297	10 (3,4)	NE [NE; NE]	297	2 (0,7)	NE [NE; NE]	4,69	[1,24; 30,54]	0,0278*		
SOC: Erkrankungen des Nervensystems	297	154 (51,9)	24,8 [6,9;49,8]	297	124 (41,8)	39,2 [27,2; NE]	1,42	[1,12; 1,81]	0,0036*		
PT: Dysgeusie	297	15 (5,1)	NE [NE; NE]	297	11 (3,7)	NE [NE; NE]	1,36	[0,63; 3,03]	0,4413		
PT: Erinnerungsvermoegen eingeschraenkt	297	8 (2,7)	NE [NE; NE]	297	10 (3,4)	NE [NE; NE]	0,77	[0,29; 1,95]	0,5755		
PT: Kopfschmerzen	297	90 (30,3)	NE [NE; NE]	297	42 (14,1)	NE [NE; NE]	2,44	[1,70; 3,55]	<0,0001*		
PT: Paraesthesie	297	7 (2,4)	NE [NE; NE]	297	10 (3,4)	NE [NE; NE]	0,67	[0,24; 1,76]	0,4209		
PT: Periphere sensorische Neuropathie	297	9 (3,0)	NE [NE; NE]	297	13 (4,4)	NE [NE; NE]	0,64	[0,27; 1,49]	0,3059		
PT: Schwindelgefuehl	297	43 (14,5)	NE [NE; NE]	297	45 (15,2)	NE [NE; NE]	0,91	[0,60; 1,39]	0,6757		
PT: Synkope	297	12 (4,0)	NE [NE; NE]	297	6 (2,0)	NE [NE; NE]	1,88	[0,73; 5,40]	0,2001		

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

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[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.1 ECHO: Summary of analysis of time to first adverse event
(total, and by SOC and PT occurring with ≥ 10 patients frequency and at least 1% in either treatment arm)
Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b] [95%-KI] [b]		2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
SOC: Erkrankungen des Ohrs und des Labyrinths	297	31 (10,4)	NE [NE; NE]	297	19 (6,4)	NE [NE; NE]	1,55	[0,88; 2,79]	0,1299
PT: Vertigo	297	10 (3,4)	NE [NE; NE]	297	6 (2,0)	NE [NE; NE]	1,57	[0,58; 4,62]	0,3773
SOC: Gefaesserkrankungen	297	96 (32,3)	NE [NE; NE]	297	92 (31,0)	NE [NE; NE]	0,98	[0,74; 1,31]	0,9001
PT: Haematom	297	11 (3,7)	NE [NE; NE]	297	4 (1,3)	NE [NE; NE]	2,57	[0,88; 9,26]	0,0940
PT: Hypertonie	297	36 (12,1)	NE [NE; NE]	297	47 (15,8)	NE [NE; NE]	0,68	[0,44; 1,05]	0,0793
PT: Hypotonie	297	29 (9,8)	NE [NE; NE]	297	18 (6,1)	NE [NE; NE]	1,60	[0,90; 2,94]	0,1126
SOC: Gutartige, boesartige und nicht spezifizierte Neubildungen (einschl. Zysten und Polypen)	297	64 (21,5)	NE [NE; NE]	297	47 (15,8)	NE [NE; NE]	1,25	[0,86; 1,84]	0,2387
PT: Basalzellkarzinom	297	14 (4,7)	NE [NE; NE]	297	12 (4,0)	NE [NE; NE]	1,01	[0,46; 2,21]	0,9874
PT: Plattenepithelkarzinom der Haut	297	18 (6,1)	NE [NE; NE]	297	9 (3,0)	NE [NE; NE]	1,83	[0,84; 4,28]	0,1315
SOC: Herzerkrankungen	297	71 (23,9)	NE [NE; NE]	297	55 (18,5)	NE [NE; NE]	1,25	[0,88; 1,78]	0,2149

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * $p < 0.05$.

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Table 3.2.1 ECHO: Summary of analysis of time to first adverse event
(total, and by SOC and PT occurring with ≥ 10 patients frequency and at least 1% in either treatment arm)
Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
PT: Palpitationen	297	10 (3,4)	NE [NE; NE]	297	3 (1,0)	NE [NE; NE]	3,22	[0,98; 14,35]	0,0606
PT: Vorhofflimmern	297	18 (6,1)	NE [NE; NE]	297	13 (4,4)	NE [NE; NE]	1,29	[0,63; 2,69]	0,4867
SOC: Infektionen und parasitaere Erkrankungen	297	232 (78,1)	8,1 [6,9; 9,9]	297	211 (71,0)	9,7 [6,7;12,2]	1,15	[0,95; 1,39]	0,1398
PT: Atemwegsinfektion	297	15 (5,1)	NE [NE; NE]	297	14 (4,7)	NE [NE; NE]	1,00	[0,48; 2,10]	0,9994
PT: Bronchitis	297	19 (6,4)	NE [NE; NE]	297	18 (6,1)	NE [NE; NE]	0,97	[0,51; 1,86]	0,9206
PT: COVID-19	297	91 (30,6)	52,6 [47,5;71,0]	297	62 (20,9)	NE [NE; NE]	1,29	[0,93; 1,79]	0,1240
PT: COVID-19-Lungenentzuendun g	297	47 (15,8)	NE [NE; NE]	297	37 (12,5)	NE [NE; NE]	1,09	[0,71; 1,68]	0,7051
PT: Harnwegsinfektion	297	33 (11,1)	NE [NE; NE]	297	32 (10,8)	NE [NE; NE]	0,94	[0,57; 1,53]	0,7904
PT: Herpes zoster	297	29 (9,8)	NE [NE; NE]	297	15 (5,1)	NE [NE; NE]	1,81	[0,98; 3,46]	0,0588
PT: Infektion der oberen Atemwege	297	54 (18,2)	NE [NE; NE]	297	44 (14,8)	NE [NE; NE]	1,15	[0,77; 1,72]	0,4947
PT: Nasopharyngitis	297	16 (5,4)	NE [NE; NE]	297	18 (6,1)	NE [NE; NE]	0,85	[0,43; 1,66]	0,6274

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

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[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.1 ECHO: Summary of analysis of time to first adverse event
 (total, and by SOC and PT occurring with >=10 patients frequency and at least 1% in either treatment arm)
 Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]
	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]			
	n			n					
PT: Pneumonie	297	48 (16,2)	NE [NE; NE]	297	39 (13,1)	NE [NE; NE]	1,14	[0,75; 1,75]	0,5354
PT: Rhinitis	297	6 (2,0)	NE [NE; NE]	297	10 (3,4)	NE [NE; NE]	0,54	[0,18; 1,45]	0,2209
PT: Sinusitis	297	19 (6,4)	NE [NE; NE]	297	6 (2,0)	NE [NE; NE]	2,93	[1,24; 8,05]	0,0160*
PT: Zellulitis	297	15 (5,1)	NE [NE; NE]	297	9 (3,0)	NE [NE; NE]	1,55	[0,69; 3,69]	0,2967
SOC: Leber- und Gallenerkrankungen	297	13 (4,4)	NE [NE; NE]	297	12 (4,0)	NE [NE; NE]	1,02	[0,46; 2,27]	0,9598
SOC: Psychiatrische Erkrankungen	297	52 (17,5)	NE [NE; NE]	297	40 (13,5)	NE [NE; NE]	1,28	[0,85; 1,95]	0,2339
PT: Angst	297	12 (4,0)	NE [NE; NE]	297	11 (3,7)	NE [NE; NE]	1,03	[0,45; 2,37]	0,9472
PT: Schlaflosigkeit	297	30 (10,1)	NE [NE; NE]	297	20 (6,7)	NE [NE; NE]	1,47	[0,84; 2,63]	0,1767
SOC: Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen	297	145 (48,8)	27,2 [17,5;37,5]	297	117 (39,4)	43,0 [29,2; NE]	1,26	[0,99; 1,61]	0,0625
PT: Arthralgie	297	52 (17,5)	NE [NE; NE]	297	49 (16,5)	NE [NE; NE]	0,98	[0,66; 1,45]	0,9271
PT: Muskelspasmen	297	8 (2,7)	NE [NE; NE]	297	10 (3,4)	NE [NE; NE]	0,72	[0,27; 1,81]	0,4783

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.1 ECHO: Summary of analysis of time to first adverse event
 (total, and by SOC and PT occurring with ≥ 10 patients frequency and at least 1% in either treatment arm)
 Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
PT: Myalgie	297	40 (13,5)	NE [NE; NE]	297	29 (9,8)	NE [NE; NE]	1,33	[0,83; 2,17]	0,2382
PT: Nackenschmerzen	297	12 (4,0)	NE [NE; NE]	297	8 (2,7)	NE [NE; NE]	1,37	[0,57; 3,51]	0,4858
PT: Osteoarthritis	297	6 (2,0)	NE [NE; NE]	297	10 (3,4)	NE [NE; NE]	0,53	[0,18; 1,43]	0,2101
PT: Rueckenschmerzen	297	48 (16,2)	NE [NE; NE]	297	28 (9,4)	NE [NE; NE]	1,71	[1,08; 2,76]	0,0226*
PT: Schmerz in einer Extremitaet	297	29 (9,8)	NE [NE; NE]	297	22 (7,4)	NE [NE; NE]	1,25	[0,72; 2,21]	0,4229
SOC: Stoffwechsel- und Ernaehrungsstoerungen	297	148 (49,8)	28,2 [17,7;57,3]	297	131 (44,1)	42,7 [25,2; NE]	1,12	[0,89; 1,42]	0,3444
PT: Appetit vermindert	297	40 (13,5)	NE [NE; NE]	297	40 (13,5)	NE [NE; NE]	0,98	[0,63; 1,52]	0,9177
PT: Dehydratation	297	14 (4,7)	NE [NE; NE]	297	9 (3,0)	NE [NE; NE]	1,53	[0,67; 3,68]	0,3154
PT: Hypalbuminaemie	297	10 (3,4)	NE [NE; NE]	297	4 (1,3)	NE [NE; NE]	2,33	[0,78; 8,49]	0,1414
PT: Hyperglykaemie	297	19 (6,4)	NE [NE; NE]	297	20 (6,7)	NE [NE; NE]	0,88	[0,46; 1,65]	0,6790
PT: Hyperkaliaemie	297	17 (5,7)	NE [NE; NE]	297	13 (4,4)	NE [NE; NE]	1,24	[0,61; 2,61]	0,5573
PT: Hyperurikaemie	297	29 (9,8)	NE [NE; NE]	297	40 (13,5)	NE [NE; NE]	0,69	[0,42; 1,11]	0,1237

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.1 ECHO: Summary of analysis of time to first adverse event
(total, and by SOC and PT occurring with >=10 patients frequency and at least 1% in either treatment arm)
Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
PT: Hypokaliaemie	297	33 (11,1)	NE [NE; NE]	297	32 (10,8)	NE [NE; NE]	0,98	[0,60; 1,59]	0,9195
PT: Hypokalzaemie	297	15 (5,1)	NE [NE; NE]	297	5 (1,7)	NE [NE; NE]	2,87	[1,11; 8,84]	0,0325*
PT: Hypomagnesiaemie	297	12 (4,0)	NE [NE; NE]	297	13 (4,4)	NE [NE; NE]	0,88	[0,39; 1,93]	0,7410
PT: Hyponatriaemie	297	12 (4,0)	NE [NE; NE]	297	9 (3,0)	NE [NE; NE]	1,29	[0,54; 3,15]	0,5673
SOC: Untersuchungen	297	152 (51,2)	25,1 [8,3;48,9]	297	139 (46,8)	27,6 [17,5;42,6]	1,05	[0,83; 1,32]	0,6848
PT: Alaninaminotransferase erhoeht	297	27 (9,1)	NE [NE; NE]	297	16 (5,4)	NE [NE; NE]	1,64	[0,89; 3,11]	0,1145
PT: Aspartataminotransferase erhoeht	297	24 (8,1)	NE [NE; NE]	297	15 (5,1)	NE [NE; NE]	1,55	[0,82; 3,01]	0,1825
PT: Bilirubin im Blut erhoeht	297	10 (3,4)	NE [NE; NE]	297	7 (2,4)	NE [NE; NE]	1,36	[0,52; 3,75]	0,5302
PT: Gewicht erhoeht	297	7 (2,4)	NE [NE; NE]	297	16 (5,4)	NE [NE; NE]	0,41	[0,16; 0,96]	0,0434*
PT: Gewicht erniedrigt	297	31 (10,4)	NE [NE; NE]	297	19 (6,4)	NE [NE; NE]	1,56	[0,89; 2,81]	0,1237
PT: Kreatinin im Blut erhoeht	297	26 (8,8)	NE [NE; NE]	297	27 (9,1)	NE [NE; NE]	0,90	[0,52; 1,54]	0,6908

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.1 ECHO: Summary of analysis of time to first adverse event
 (total, and by SOC and PT occurring with ≥ 10 patients frequency and at least 1% in either treatment arm)
 Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
PT: Laktatdehydrogenase im Blut erhoeht	297	10 (3,4)	NE [NE; NE]	297	13 (4,4)	NE [NE; NE]	0,75	[0,32; 1,69]	0,4832
PT: Leukozytenzahl erniedrigt	297	41 (13,8)	NE [NE; NE]	297	31 (10,4)	NE [NE; NE]	1,30	[0,82; 2,08]	0,2717
PT: Lymphozytenzahl erniedrigt	297	22 (7,4)	NE [NE; NE]	297	29 (9,8)	NE [NE; NE]	0,74	[0,42; 1,27]	0,2801
PT: Neutrophilenzahl erniedrigt	297	53 (17,8)	NE [NE; NE]	297	46 (15,5)	NE [NE; NE]	1,11	[0,75; 1,66]	0,5990
PT: Thrombozytenzahl vermindert	297	30 (10,1)	NE [NE; NE]	297	30 (10,1)	NE [NE; NE]	0,98	[0,59; 1,63]	0,9332
SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen	297	121 (40,7)	66,1 [27,5; NE]	297	118 (39,7)	63,2 [39,2; NE]	0,96	[0,74; 1,24]	0,8405
PT: Kontusion	297	33 (11,1)	NE [NE; NE]	297	16 (5,4)	NE [NE; NE]	2,00	[1,12; 3,73]	0,0200*
PT: Reaktion im Zusammenhang mit einer Infusion	297	43 (14,5)	NE [NE; NE]	297	65 (21,9)	NE [NE; NE]	0,62	[0,42; 0,91]	0,0227*
PT: Sturz	297	17 (5,7)	NE [NE; NE]	297	9 (3,0)	NE [NE; NE]	1,73	[0,79; 4,07]	0,1762

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.2 ECHO: Summary of analysis of time to first serious adverse event
 (total, and by SOC and PT occurring with ≥ 10 patients frequency and at least 1% in either treatment arm)
 Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
SUE	297	205 (69,0)	15,5 [11,1;21,2]	297	184 (62,0)	22,9 [16,6;25,6]	1,12	[0,92; 1,37]	0,2478
SUE SOC: Allgemeine Erkrankungen und Beschwerden am Verabreichungsort	297	23 (7,7)	NE [NE; NE]	297	18 (6,1)	NE [NE; NE]	1,25	[0,68; 2,35]	0,4786
SUE PT: Fieber	297	17 (5,7)	NE [NE; NE]	297	15 (5,1)	NE [NE; NE]	1,11	[0,55; 2,25]	0,7671
SUE SOC: Erkrankungen der Atemwege, des Brustraums und Mediastinums	297	19 (6,4)	NE [NE; NE]	297	21 (7,1)	NE [NE; NE]	0,87	[0,46; 1,61]	0,6472
SUE SOC: Erkrankungen der Haut und des Unterhautgewebes	297	13 (4,4)	NE [NE; NE]	297	3 (1,0)	NE [NE; NE]	4,26	[1,37; 18,58]	0,0138*
SUE SOC: Erkrankungen des Blutes und des Lymphsystems	297	23 (7,7)	NE [NE; NE]	297	17 (5,7)	NE [NE; NE]	1,31	[0,70; 2,49]	0,3957
SUE PT: Febrile Neutropenie	297	10 (3,4)	NE [NE; NE]	297	3 (1,0)	NE [NE; NE]	3,20	[0,98; 14,28]	0,0615
SUE SOC: Erkrankungen des Gastrointestinaltrakts	297	18 (6,1)	NE [NE; NE]	297	18 (6,1)	NE [NE; NE]	0,92	[0,48; 1,79]	0,8133

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CIs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio < 1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * $p < 0.05$.

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Table 3.2.2 ECHO: Summary of analysis of time to first serious adverse event
 (total, and by SOC and PT occurring with >=10 patients frequency and at least 1% in either treatment arm)
 Safety Analysis Set, DCO 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b] [95%-KI] [b]		2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
SUE SOC: Erkrankungen des Nervensystems	297	13 (4,4)	NE [NE; NE]	297	15 (5,1)	NE [NE; NE]	0,78	[0,37; 1,65]	0,5181
SUE SOC: Gefaesserkrankungen	297	7 (2,4)	NE [NE; NE]	297	10 (3,4)	NE [NE; NE]	0,67	[0,24; 1,74]	0,4121
SUE SOC: Gutartige, boesartige und nicht spezifizierte Neubildungen (einschl. Zysten und Polypen)	297	22 (7,4)	NE [NE; NE]	297	20 (6,7)	NE [NE; NE]	0,97	[0,53; 1,78]	0,9089
SUE SOC: Herzerkrankungen	297	24 (8,1)	NE [NE; NE]	297	21 (7,1)	NE [NE; NE]	1,05	[0,59; 1,91]	0,8633
SUE SOC: Infektionen und parasitaere Erkrankungen	297	120 (40,4)	55,6 [37,5;67,6]	297	98 (33,0)	NE [NE; NE]	1,12	[0,86; 1,46]	0,4092
SUE PT: COVID-19	297	26 (8,8)	NE [NE; NE]	297	19 (6,4)	NE [NE; NE]	1,20	[0,67; 2,20]	0,5434
SUE PT: COVID-19-Lungenentzuendung	297	41 (13,8)	NE [NE; NE]	297	34 (11,4)	NE [NE; NE]	1,02	[0,65; 1,62]	0,9183
SUE PT: Pneumonie	297	28 (9,4)	NE [NE; NE]	297	21 (7,1)	NE [NE; NE]	1,22	[0,70; 2,17]	0,4914

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.2 ECHO: Summary of analysis of time to first serious adverse event
 (total, and by SOC and PT occurring with ≥ 10 patients frequency and at least 1% in either treatment arm)
 Safety Analysis Set, DCO 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)						2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]		
SUE SOC: Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen	297	10 (3,4)	NE [NE; NE]	297	5 (1,7)	NE [NE; NE]	1,85	[0,66; 5,93]	0,2556	
SUE SOC: Stoffwechsel- und Ernaehrungsstoerungen	297	11 (3,7)	NE [NE; NE]	297	9 (3,0)	NE [NE; NE]	1,20	[0,50; 2,97]	0,6896	
SUE SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen	297	7 (2,4)	NE [NE; NE]	297	18 (6,1)	NE [NE; NE]	0,37	[0,14; 0,84]	0,0188*	
SUE PT: Reaktion im Zusammenhang mit einer Infusion	297	2 (0,7)	NE [NE; NE]	297	10 (3,4)	NE [NE; NE]	0,19	[0,03; 0,74]	0,0183*	

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio < 1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * $p < 0.05$.

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Table 3.2.3 ECH0: Summary of analysis of time to first adverse event leading to discontinuation of ≥ 1 component of treatment
 Safety Analysis Set, DCO 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]
	Anzahl (%) der Patienten mit n Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		Anzahl (%) der Patienten mit n Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Therapieabbruch aufgrund von UE	297 150 (50,5)	37,3 [30,1;54,5]		297 105 (35,4)	NE [NE; NE]		1,38	[1,08; 1,78]	0,0107*

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio < 1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * $p < 0.05$.

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Table 3.2.4 ECHO: Summary of analysis of time to first adverse event with max. CTCAE grade 3 or higher (total, and by SOC and PT occurring with ≥ 10 patients frequency and at least 1% in either treatment arm)
 Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
UE mit CTCAE Grad ≥ 3	297	264 (88,9)	2,8 [1,9; 3,1]	297	262 (88,2)	2,8 [1,9; 3,6]	0,96	[0,81; 1,14]	0,6293
G ≥ 3 SOC: Allgemeine Erkrankungen und Beschwerden am Verabreichungsort	297	22 (7,4)	NE [NE; NE]	297	19 (6,4)	NE [NE; NE]	1,13	[0,61; 2,10]	0,7016
G ≥ 3 PT: Ermuedung	297	8 (2,7)	NE [NE; NE]	297	11 (3,7)	NE [NE; NE]	0,71	[0,28; 1,76]	0,4655
G ≥ 3 SOC: Erkrankungen der Atemwege, des Brustraums und Mediastinums	297	19 (6,4)	NE [NE; NE]	297	29 (9,8)	NE [NE; NE]	0,61	[0,34; 1,08]	0,0908
G ≥ 3 SOC: Erkrankungen der Haut und des Unterhautgewebes	297	47 (15,8)	NE [NE; NE]	297	12 (4,0)	NE [NE; NE]	4,07	[2,24; 8,04]	<0,0001*
G ≥ 3 PT: Ausschlag makulo-papuloes	297	21 (7,1)	NE [NE; NE]	297	2 (0,7)	NE [NE; NE]	10,69	[3,14; 66,82]	<0,0001*
G ≥ 3 SOC: Erkrankungen der Nieren und Harnwege	297	14 (4,7)	NE [NE; NE]	297	11 (3,7)	NE [NE; NE]	1,20	[0,54; 2,70]	0,6568
G ≥ 3 SOC: Erkrankungen des Blutes und des Lymphsystems	297	127 (42,8)	NE [NE; NE]	297	133 (44,8)	34,3 [15,6; NE]	0,91	[0,71; 1,16]	0,4311

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.4 ECHO: Summary of analysis of time to first adverse event with max. CTCAE grade 3 or higher (total, and by SOC and PT occurring with ≥ 10 patients frequency and at least 1% in either treatment arm)
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	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
G $\geq$ 3 PT: Anaemie	297	28 (9,4)	NE [NE; NE]	297	30 (10,1)	NE [NE; NE]	0,90	[0,54; 1,51]	0,6879
G $\geq$ 3 PT: Febrile Neutropenie	297	15 (5,1)	NE [NE; NE]	297	7 (2,4)	NE [NE; NE]	2,07	[0,87; 5,41]	0,1053
G $\geq$ 3 PT: Leukopenie	297	17 (5,7)	NE [NE; NE]	297	18 (6,1)	NE [NE; NE]	0,90	[0,46; 1,76]	0,7594
G $\geq$ 3 PT: Lymphopenie	297	8 (2,7)	NE [NE; NE]	297	16 (5,4)	NE [NE; NE]	0,48	[0,20; 1,10]	0,0855
G $\geq$ 3 PT: Neutropenie	297	105 (35,4)	NE [NE; NE]	297	110 (37,0)	NE [NE; NE]	0,90	[0,69; 1,18]	0,4623
G $\geq$ 3 PT: Thrombozytopenie	297	18 (6,1)	NE [NE; NE]	297	16 (5,4)	NE [NE; NE]	1,10	[0,56; 2,19]	0,7677
G $\geq$ 3 SOC: Erkrankungen des Gastrointestinaltrakts	297	35 (11,8)	NE [NE; NE]	297	28 (9,4)	NE [NE; NE]	1,20	[0,73; 1,99]	0,4687
G $\geq$ 3 SOC: Erkrankungen des Nervensystems	297	26 (8,8)	NE [NE; NE]	297	24 (8,1)	NE [NE; NE]	1,01	[0,58; 1,78]	0,9593
G $\geq$ 3 SOC: Gefaessserkrankungen	297	23 (7,7)	NE [NE; NE]	297	32 (10,8)	NE [NE; NE]	0,65	[0,38; 1,11]	0,1167
G $\geq$ 3 PT: Hypertonie	297	16 (5,4)	NE [NE; NE]	297	25 (8,4)	NE [NE; NE]	0,57	[0,30; 1,06]	0,0779

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * $p < 0.05$.

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Table 3.2.4 ECHO: Summary of analysis of time to first adverse event with max. CTCAE grade 3 or higher (total, and by SOC and PT occurring with ≥ 10 patients frequency and at least 1% in either treatment arm)
 Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)						
		Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]	
	n			n						
G>=3 SOC: Gutartige, boesartige und nicht spezifizierte Neubildungen (einschl. Zysten und Polypen)	297	22 (7,4)	NE [NE; NE]	297	22 (7,4)	NE [NE; NE]	0,88	[0,48; 1,59]	0,6669	
G>=3 SOC: Herzerkrankungen	297	23 (7,7)	NE [NE; NE]	297	18 (6,1)	NE [NE; NE]	1,18	[0,64; 2,21]	0,6041	
G>=3 PT: Vorhofflimmern	297	11 (3,7)	NE [NE; NE]	297	5 (1,7)	NE [NE; NE]	2,05	[0,75; 6,51]	0,1744	
G>=3 SOC: Infektionen und parasitaere Erkrankungen	297	122 (41,1)	47,4 [37,5;65,4]	297	101 (34,0)	59,3 [36,1; NE]	1,10	[0,85; 1,43]	0,4796	
G>=3 PT: COVID-19	297	26 (8,8)	NE [NE; NE]	297	21 (7,1)	NE [NE; NE]	1,09	[0,62; 1,96]	0,7628	
G>=3 PT: COVID-19-Lungenentzuendung	297	40 (13,5)	NE [NE; NE]	297	31 (10,4)	NE [NE; NE]	1,10	[0,69; 1,77]	0,6974	
G>=3 PT: Pneumonie	297	26 (8,8)	NE [NE; NE]	297	19 (6,4)	NE [NE; NE]	1,24	[0,69; 2,28]	0,4725	
G>=3 SOC: Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen	297	16 (5,4)	NE [NE; NE]	297	11 (3,7)	NE [NE; NE]	1,34	[0,63; 2,96]	0,4579	

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * $p < 0.05$.

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Table 3.2.4 ECHO: Summary of analysis of time to first adverse event with max. CTCAE grade 3 or higher (total, and by SOC and PT occurring with ≥ 10 patients frequency and at least 1% in either treatment arm)
Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
G $\geq$ 3 SOC: Stoffwechsel- und Ernährungsstörungen	297	45 (15,2)	NE [NE; NE]	297	36 (12,1)	NE [NE; NE]	1,22	[0,79; 1,90]	0,3799
G $\geq$ 3 PT: Hypokaliaemie	297	9 (3,0)	NE [NE; NE]	297	11 (3,7)	NE [NE; NE]	0,77	[0,31; 1,87]	0,5658
G $\geq$ 3 SOC: Untersuchungen	297	79 (26,6)	NE [NE; NE]	297	65 (21,9)	NE [NE; NE]	1,19	[0,85; 1,65]	0,3066
G $\geq$ 3 PT: Alaninaminotransferase erhoeht	297	13 (4,4)	NE [NE; NE]	297	1 (0,3)	NE [NE; NE]	12,54	[2,50;227,75]	0,0017*
G $\geq$ 3 PT: Leukozytenzahl erniedrigt	297	30 (10,1)	NE [NE; NE]	297	11 (3,7)	NE [NE; NE]	2,68	[1,38; 5,60]	0,0036*
G $\geq$ 3 PT: Lymphozytenzahl erniedrigt	297	19 (6,4)	NE [NE; NE]	297	29 (9,8)	NE [NE; NE]	0,63	[0,35; 1,12]	0,1186
G $\geq$ 3 PT: Neutrophilenzahl erniedrigt	297	46 (15,5)	NE [NE; NE]	297	30 (10,1)	NE [NE; NE]	1,50	[0,95; 2,39]	0,0840
G $\geq$ 3 PT: Thrombozytenzahl vermindert	297	11 (3,7)	NE [NE; NE]	297	8 (2,7)	NE [NE; NE]	1,34	[0,54; 3,46]	0,5263
G $\geq$ 3 SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen	297	13 (4,4)	NE [NE; NE]	297	14 (4,7)	NE [NE; NE]	0,86	[0,40; 1,83]	0,6880

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.5 ECHO: Summary of analysis of time to first event of clinical interest
 (by grouped term)
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	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b] [95%-KI] [b]		2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
EKI GT: Kardiale Ereignisse	297	71 (23,9)	NE [NE; NE]	297	55 (18,5)	NE [NE; NE]	1,25	[0,88; 1,78]	0,2149
EKI GT: Vorhofflimmern	297	20 (6,7)	NE [NE; NE]	297	13 (4,4)	NE [NE; NE]	1,42	[0,71; 2,93]	0,3232
EKI GT: Ventrikuläre Tachyarrhythmie	297	7 (2,4)	NE [NE; NE]	297	7 (2,4)	NE [NE; NE]	0,94	[0,32; 2,75]	0,9077
EKI GT: Anämie	297	72 (24,2)	NE [NE; NE]	297	62 (20,9)	NE [NE; NE]	1,15	[0,82; 1,61]	0,4329
EKI GT: Leukopenie	297	175 (58,9)	5,5 [4,6; 7,5]	297	182 (61,3)	5,0 [3,7; 6,8]	0,89	[0,72; 1,09]	0,2682
EKI GT: Neutropenie	297	163 (54,9)	6,5 [5,4;13,8]	297	166 (55,9)	6,8 [5,1;10,2]	0,93	[0,75; 1,15]	0,4898
EKI GT: Andere Leukopenie	297	74 (24,9)	NE [NE; NE]	297	75 (25,3)	NE [NE; NE]	0,94	[0,68; 1,30]	0,7197
EKI GT: Thrombozytopenie	297	68 (22,9)	NE [NE; NE]	297	61 (20,5)	NE [NE; NE]	1,10	[0,78; 1,55]	0,5989
EKI GT: Blutung	297	84 (28,3)	NE [NE; NE]	297	51 (17,2)	NE [NE; NE]	1,75	[1,24; 2,49]	0,0015*
EKI GT: Schwere Blutung	297	7 (2,4)	NE [NE; NE]	297	16 (5,4)	NE [NE; NE]	0,40	[0,15; 0,93]	0,0340*
EKI GT: Hepatotoxizität	297	42 (14,1)	NE [NE; NE]	297	38 (12,8)	NE [NE; NE]	1,06	[0,68; 1,64]	0,8081
EKI GT: Hypertonie	297	37 (12,5)	NE [NE; NE]	297	48 (16,2)	NE [NE; NE]	0,68	[0,44; 1,05]	0,0814

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.5 ECHO: Summary of analysis of time to first event of clinical interest
 (by grouped term)
 Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
EKI GT: Infektionen	297	232 (78,1)	8,1 [6,9; 9,9]	297	211 (71,0)	9,7 [6,7;12,2]	1,15	[0,95; 1,39]	0,1398
EKI GT: Interstitielle Lungenerkrankung/ Pneumonitis	297	10 (3,4)	NE [NE; NE]	297	10 (3,4)	NE [NE; NE]	0,92	[0,38; 2,24]	0,8477
EKI GT: Zweiter Primärtumor	297	53 (17,8)	NE [NE; NE]	297	43 (14,5)	NE [NE; NE]	1,09	[0,73; 1,64]	0,6672
EKI GT: Zweiter Primärtumor - ausgenommen nicht-melanotischer Hautkrebs	297	29 (9,8)	NE [NE; NE]	297	32 (10,8)	NE [NE; NE]	0,77	[0,46; 1,27]	0,3037
EKI GT: Tumorlysesyndrom	297	4 (1,3)	NE [NE; NE]	297	6 (2,0)	NE [NE; NE]	0,66	[0,17; 2,33]	0,5236

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.6 ECHO: Summary of analysis of time to first event of interest with max. CTCAE grade 3 or higher
 (by grouped term)
 Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]		2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
EKI G>=3 GT: Kardiale Ereignisse	297	23 (7,7)	NE [NE; NE]	297	18 (6,1)	NE [NE; NE]	1,18	[0,64; 2,21]	0,6041
EKI G>=3 GT: Vorhofflimmern	297	12 (4,0)	NE [NE; NE]	297	5 (1,7)	NE [NE; NE]	2,20	[0,81; 6,91]	0,1296
EKI G>=3 GT: Anämie	297	28 (9,4)	NE [NE; NE]	297	30 (10,1)	NE [NE; NE]	0,90	[0,54; 1,51]	0,6879
EKI G>=3 GT: Leukopenie	297	158 (53,2)	7,5 [5,6;16,6]	297	162 (54,5)	7,4 [5,1;15,6]	0,90	[0,72; 1,12]	0,3284
EKI G>=3 GT: Neutropenie	297	149 (50,2)	13,8 [7,1; NE]	297	138 (46,5)	21,3 [7,4; NE]	1,05	[0,84; 1,33]	0,6558
EKI G>=3 GT: Andere Leukopenie	297	62 (20,9)	NE [NE; NE]	297	60 (20,2)	NE [NE; NE]	0,98	[0,68; 1,40]	0,9067
EKI G>=3 GT: Thrombozytopenie	297	29 (9,8)	NE [NE; NE]	297	24 (8,1)	NE [NE; NE]	1,18	[0,69; 2,04]	0,5422
EKI G>=3 GT: Blutung	297	6 (2,0)	NE [NE; NE]	297	10 (3,4)	NE [NE; NE]	0,55	[0,19; 1,48]	0,2396
EKI G>=3 GT: Schwere Blutung	297	6 (2,0)	NE [NE; NE]	297	10 (3,4)	NE [NE; NE]	0,55	[0,19; 1,48]	0,2396
EKI G>=3 GT: Hepatotoxizität	297	20 (6,7)	NE [NE; NE]	297	6 (2,0)	NE [NE; NE]	3,21	[1,37; 8,77]	0,0081*

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.6 ECHO: Summary of analysis of time to first event of interest with max. CTCAE grade 3 or higher
(by grouped term)
Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b] [95%-KI] [b]			2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
EKI G>=3 GT: Hypertonie	297	17 (5,7)	NE [NE; NE]	297	25 (8,4)	NE [NE; NE]	0,61	[0,32; 1,12]	0,1115	
EKI G>=3 GT: Infektionen	297	122 (41,1)	47,4 [37,5;65,4]	297	101 (34,0)	59,3 [36,1; NE]	1,10	[0,85; 1,43]	0,4796	
EKI G>=3 GT: Interstitielle Lungenerkrankung/ Pneumonitis	297	2 (0,7)	NE [NE; NE]	297	4 (1,3)	NE [NE; NE]	0,47	[0,06; 2,39]	0,3675	
EKI G>=3 GT: Zweiter Primärtumor	297	22 (7,4)	NE [NE; NE]	297	22 (7,4)	NE [NE; NE]	0,88	[0,48; 1,59]	0,6669	
EKI G>=3 GT: Zweiter Primärtumor - ausgenommen nicht-melanotischer Hautkrebs	297	16 (5,4)	NE [NE; NE]	297	20 (6,7)	NE [NE; NE]	0,69	[0,35; 1,33]	0,2707	
EKI G>=3 GT: Tumorlysesyndrom	297	4 (1,3)	NE [NE; NE]	297	6 (2,0)	NE [NE; NE]	0,66	[0,17; 2,33]	0,5236	

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.7 ECHO: Summary of analysis of time to first serious event of clinical interest
 (by grouped term)
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	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
SEKI GT: Kardiale Ereignisse	297	24 (8,1)	NE [NE; NE]	297	21 (7,1)	NE [NE; NE]	1,05	[0,59; 1,91]	0,8633
SEKI GT: Vorhofflimmern	297	9 (3,0)	NE [NE; NE]	297	6 (2,0)	NE [NE; NE]	1,38	[0,50; 4,13]	0,5352
SEKI GT: Ventrikuläre Tachyarrhythmie	297	3 (1,0)	NE [NE; NE]	297	2 (0,7)	NE [NE; NE]	1,40	[0,23; 10,60]	0,7141
SEKI GT: Anämie	297	7 (2,4)	NE [NE; NE]	297	6 (2,0)	NE [NE; NE]	1,12	[0,37; 3,47]	0,8444
SEKI GT: Leukopenie	297	16 (5,4)	NE [NE; NE]	297	10 (3,4)	NE [NE; NE]	1,54	[0,71; 3,50]	0,2837
SEKI GT: Neutropenie	297	15 (5,1)	NE [NE; NE]	297	9 (3,0)	NE [NE; NE]	1,60	[0,71; 3,81]	0,2609
SEKI GT: Andere Leukopenie	297	2 (0,7)	NE [NE; NE]	297	1 (0,3)	NE [NE; NE]	1,92	[0,18; 41,37]	0,5865
SEKI GT: Thrombozytopenie	297	4 (1,3)	NE [NE; NE]	297	3 (1,0)	NE [NE; NE]	1,33	[0,29; 6,76]	0,7069
SEKI GT: Blutung	297	4 (1,3)	NE [NE; NE]	297	12 (4,0)	NE [NE; NE]	0,31	[0,09; 0,89]	0,0316*
SEKI GT: Schwere Blutung	297	4 (1,3)	NE [NE; NE]	297	12 (4,0)	NE [NE; NE]	0,31	[0,09; 0,89]	0,0316*
SEKI GT: Hepatotoxizität	297	5 (1,7)	NE [NE; NE]	297	1 (0,3)	NE [NE; NE]	4,88	[0,79; 93,43]	0,1091

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.2.7 ECHO: Summary of analysis of time to first serious event of clinical interest
 (by grouped term)
 Safety Analysis Set, DC0 15FEB2024

	Acala+BR (N=297)			Placebo+BR (N=297)						
	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [c]	
	n			n						
SEKI GT: Hypertonie	297	0	NE [NE; NE]	297	2 (0,7)	NE [NE; NE]	NC	NC	0,1378	
SEKI GT: Infektionen	297	120 (40,4)	55,6 [37,5;67,6]	297	98 (33,0)	NE [NE; NE]	1,12	[0,86; 1,46]	0,4092	
SEKI GT: Interstitielle Lungenerkrankung/ Pneumonitis	297	3 (1,0)	NE [NE; NE]	297	4 (1,3)	NE [NE; NE]	0,70	[0,14; 3,20]	0,6455	
SEKI GT: Zweiter Primärtumor	297	22 (7,4)	NE [NE; NE]	297	19 (6,4)	NE [NE; NE]	1,02	[0,55; 1,90]	0,9559	
SEKI GT: Zweiter Primärtumor - ausgenommen nicht-melanotischer Hautkrebs	297	16 (5,4)	NE [NE; NE]	297	16 (5,4)	NE [NE; NE]	0,87	[0,43; 1,75]	0,6912	
SEKI GT: Tumorlysesyndrom	297	1 (0,3)	NE [NE; NE]	297	5 (1,7)	NE [NE; NE]	0,20	[0,01; 1,23]	0,1006	

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE during the observation period as defined in Table 3.1.. Any patient that has not experienced the AE will be censored at the earliest of date of data cut-off, end of observation period, date of starting subsequent cancer therapy (including cross-over treatment start date) or date of death.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab. NC = not calculable.

[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.

[b] Estimated from Cox proportional hazards model including treatment only. Efron method for handling ties. 95% CI from profile likelihood estimation. Hazard ratio <1 favours Acala + BR.

[c] Determined using unstratified log-rank test. * p<0.05.

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Table 3.4 ECHO: Summary of adverse events leading to discontinuation of ≥ 1 component of treatment by SOC and PT
 Safety Analysis Set, DC0 15FEB2024

System organ class / MedDRA Preferred term	Number (%) of patients	
	Acala+BR (N=297)	Placebo+BR (N=297)
Patienten mit Abbruch wegen UE	150 (50,5)	105 (35,4)
Allgemeine Erkrankungen und Beschwerden am Verabreichungsort	6 (2,0)	4 (1,3)
Asthenie	1 (0,3)	0
Ermuedung	0	2 (0,7)
Fieber	2 (0,7)	2 (0,7)
Generelle Verschlechterung des physischen Gesundheitszustandes	1 (0,3)	0
Gesichtsoedem	1 (0,3)	0
Leistung vermindert	1 (0,3)	0
Erkrankungen der Atemwege, des Brustraums und Mediastinums	6 (2,0)	5 (1,7)
Dyspnoe	1 (0,3)	1 (0,3)
Husten	0	1 (0,3)
Interstitielle Lungenerkrankung	1 (0,3)	0
Lungenembolie	0	2 (0,7)
Lungeninfiltration	0	1 (0,3)
Pharynxhaematom	1 (0,3)	0
Pleuraerguss	1 (0,3)	0
Pneumonitis	2 (0,7)	1 (0,3)
Erkrankungen der Haut und des Unterhautgewebes	9 (3,0)	1 (0,3)
Ausschlag makulo-papuloes	1 (0,3)	0
Ausschlag mit Juckreiz	1 (0,3)	0
Dermatitis exfoliativa	1 (0,3)	0
Diabetischer Fuss	1 (0,3)	0
Erythema multiforme	1 (0,3)	0
Erythematoeser Hautausschlag	1 (0,3)	0
Medikamentenausschlag	1 (0,3)	0
Pruritus	1 (0,3)	0

Includes adverse events with onset date after first dose of study treatment until the end of the observation period as defined in Table 3.1. Discontinuation is defined as action taken with Acala/Placebo = 'DRUG WITHDRAWN' or action taken with Bendamustine or Rituximab = 'STUDY DRUG DISCONTINUED'.

Patients with multiple event are counted only once in each specific category.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 3.4 ECHO: Summary of adverse events leading to discontinuation of ≥ 1 component of treatment by SOC and PT
 Safety Analysis Set, DC0 15FEB2024

System organ class / MedDRA Preferred term	Number (%) of patients	
	Acala+BR (N=297)	Placebo+BR (N=297)
Urtikaria	1 (0,3)	1 (0,3)
Erkrankungen des Blutes und des Lymphsystems	31 (10,4)	26 (8,8)
Agranulozytose	0	1 (0,3)
Anaemie	2 (0,7)	0
Febrile Neutropenie	3 (1,0)	1 (0,3)
Leukopenie	2 (0,7)	0
Myelosuppression	0	1 (0,3)
Neutropenie	24 (8,1)	22 (7,4)
Panzytopenie	1 (0,3)	0
Thrombozytopenie	3 (1,0)	2 (0,7)
Erkrankungen des Gastrointestinaltrakts	6 (2,0)	1 (0,3)
Barrett-Ulkus	1 (0,3)	0
Diarrhoe	0	1 (0,3)
Dyspepsie	1 (0,3)	0
Erbrechen	1 (0,3)	0
Gastrooesophageale Refluxerkrankung	1 (0,3)	0
Stomatitis	1 (0,3)	0
Uebelkeit	1 (0,3)	0
Erkrankungen des Immunsystems	2 (0,7)	1 (0,3)
Anaphylaktische Reaktion	2 (0,7)	0
Serumkrankheit	0	1 (0,3)
Erkrankungen des Nervensystems	4 (1,3)	6 (2,0)
Apoplektischer Insult	0	1 (0,3)
Enzephalopathie	1 (0,3)	0
Epilepsie	1 (0,3)	1 (0,3)

Includes adverse events with onset date after first dose of study treatment until the end of the observation period as defined in Table 3.1. Discontinuation is defined as action taken with Acala/Placebo = 'DRUG WITHDRAWN' or action taken with Bendamustine or Rituximab = 'STUDY DRUG DISCONTINUED'.

Patients with multiple event are counted only once in each specific category.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 3.4 ECHO: Summary of adverse events leading to discontinuation of ≥ 1 component of treatment by SOC and PT
 Safety Analysis Set, DCO 15FEB2024

System organ class / MedDRA Preferred term	Number (%) of patients	
	Acala+BR (N=297)	Placebo+BR (N=297)
Intrakranielle Blutung	0	1 (0,3)
Ischaemischer Schlaganfall	0	1 (0,3)
Kognitive Störung	0	1 (0,3)
Kopfschmerzen	2 (0,7)	0
Morbus Parkinson	0	1 (0,3)
Gefäßerkrankungen	0	1 (0,3)
Aortenaneurysma Ruptur	0	1 (0,3)
Gutartige, boesartige und nicht spezifizierte Neubildungen (einschl. Zysten und Polypen)	15 (5,1)	15 (5,1)
Adenokarzinom der Lunge	0	1 (0,3)
Adenokarzinom des Magens	1 (0,3)	0
Anaplastisches grosszelliges Lymphom	1 (0,3)	0
Blasenkrebs	1 (0,3)	0
Boesartiges Melanom	0	1 (0,3)
Endometriumkarzinom	0	1 (0,3)
Glioblastom	0	1 (0,3)
Intestinales Adenokarzinom	1 (0,3)	0
Invasives Mammakarzinom	0	1 (0,3)
Kaposi-Sarkom	1 (0,3)	0
Karzinom der Tonsillen	0	1 (0,3)
Kolonkarzinom	1 (0,3)	0
Kolorektales Adenokarzinom	2 (0,7)	0
Lentigo maligna	0	1 (0,3)
Malignes Melanom mit Metastasen	1 (0,3)	0
Neuroendokrines Karzinom	1 (0,3)	0
Neuroendokrines Karzinom der Haut	0	1 (0,3)
Nicht-kleinzelliges Lungenkarzinom	1 (0,3)	0

Includes adverse events with onset date after first dose of study treatment until the end of the observation period as defined in Table 3.1. Discontinuation is defined as action taken with Acala/Placebo = 'DRUG WITHDRAWN' or action taken with Bendamustine or Rituximab = 'STUDY DRUG DISCONTINUED'.

Patients with multiple event are counted only once in each specific category.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 3.4 ECHO: Summary of adverse events leading to discontinuation of ≥ 1 component of treatment by SOC and PT
 Safety Analysis Set, DCO 15FEB2024

System organ class / MedDRA Preferred term	Number (%) of patients	
	Acala+BR (N=297)	Placebo+BR (N=297)
Nierenkrebs	1 (0,3)	0
Plasmazellmyelom	0	1 (0,3)
Plattenepithelkarzinom	1 (0,3)	0
Plattenepithelkarzinom der Haut	1 (0,3)	1 (0,3)
Plattenepithelkarzinom der Lunge	1 (0,3)	1 (0,3)
Prostatakarzinom	0	1 (0,3)
Rektales Adenokarzinom	0	1 (0,3)
Uebergangszellkarzinom	0	1 (0,3)
Urethrankarzinom	0	1 (0,3)
Herzerkrankungen	6 (2,0)	6 (2,0)
Akuter Myokardinfarkt	0	1 (0,3)
Arrhythmie	1 (0,3)	0
Herzinsuffizienz	0	1 (0,3)
Kardiopulmonales Versagen	1 (0,3)	0
Myokardinfarkt	1 (0,3)	2 (0,7)
Tachykardie supraventrikulaer	0	1 (0,3)
Vorhofflattern	1 (0,3)	0
Vorhofflimmern	2 (0,7)	1 (0,3)
Infektionen und parasitaere Erkrankungen	59 (19,9)	36 (12,1)
Akute Sinusitis	1 (0,3)	0
Arthritis bakteriell	1 (0,3)	0
Arthritis infektiöses	1 (0,3)	0
Ausschlag pustuloes	1 (0,3)	0
Bakterielle Hepatitis	0	1 (0,3)
COVID-19	16 (5,4)	9 (3,0)
COVID-19-Lungenentzündung	15 (5,1)	8 (2,7)
Clostridium difficile-Kolitis	1 (0,3)	0

Includes adverse events with onset date after first dose of study treatment until the end of the observation period as defined in Table 3.1. Discontinuation is defined as action taken with Acala/Placebo = 'DRUG WITHDRAWN' or action taken with Bendamustine or Rituximab = 'STUDY DRUG DISCONTINUED'.

Patients with multiple event are counted only once in each specific category.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 3.4 ECHO: Summary of adverse events leading to discontinuation of ≥ 1 component of treatment by SOC and PT
 Safety Analysis Set, DCO 15FEB2024

System organ class / MedDRA Preferred term	Number (%) of patients	
	Acala+BR (N=297)	Placebo+BR (N=297)
Diphyllobothriose	0	1 (0,3)
Divertikulitis	0	1 (0,3)
Enterokolitis durch Zytomegalievirus	1 (0,3)	0
Erysipel	0	1 (0,3)
Gastrointestinalinfektion	1 (0,3)	0
Hepatitis B	0	2 (0,7)
Infektion	1 (0,3)	0
Infektion in der Leiste	1 (0,3)	0
Meningitis	1 (0,3)	0
Nasopharyngitis	1 (0,3)	0
Osteomyelitis	1 (0,3)	0
Perinealabszess	1 (0,3)	0
Pneumonie	5 (1,7)	1 (0,3)
Pneumonie durch Haemophilus	0	1 (0,3)
Pneumonie durch Streptokokken	0	1 (0,3)
Pneumonie durch Zytomegalievirus	1 (0,3)	0
Reaktivierung einer Hepatitis B	4 (1,3)	5 (1,7)
Sepsis	1 (0,3)	3 (1,0)
Septischer Schock	0	1 (0,3)
Tuberkulose des maennlichen Genitaltrakts	0	1 (0,3)
Urosepsis	1 (0,3)	0
Weichteilinfektion	0	1 (0,3)
Zellulitis	2 (0,7)	0
Zytomegalievirus-Infektion	3 (1,0)	0
Leber- und Gallenerkrankungen	1 (0,3)	1 (0,3)
Leberfunktion anomal	1 (0,3)	0
Verdacht auf arzneimittelbedingten Leberschaden	0	1 (0,3)

Includes adverse events with onset date after first dose of study treatment until the end of the observation period as defined in Table 3.1. Discontinuation is defined as action taken with Acala/Placebo = 'DRUG WITHDRAWN' or action taken with Bendamustine or Rituximab = 'STUDY DRUG DISCONTINUED'.

Patients with multiple event are counted only once in each specific category.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 3.4 ECHO: Summary of adverse events leading to discontinuation of ≥ 1 component of treatment by SOC and PT
 Safety Analysis Set, DCO 15FEB2024

System organ class / MedDRA Preferred term	Number (%) of patients	
	Acala+BR (N=297)	Placebo+BR (N=297)
Psychiatrische Erkrankungen	0	1 (0,3)
Depression	0	1 (0,3)
Skelettmuskulatur-, Bindegewebs- und Knochenenerkrankungen	3 (1,0)	0
Arthralgie	1 (0,3)	0
Myalgie	1 (0,3)	0
Rueckenschmerzen	1 (0,3)	0
Stoffwechsel- und Ernaehrungsstoerungen	1 (0,3)	0
Tumorlysesyndrom	1 (0,3)	0
Untersuchungen	14 (4,7)	6 (2,0)
Alaninaminotransferase erhoeht	3 (1,0)	0
Aspartataminotransferase erhoeht	2 (0,7)	0
Bilirubin im Blut erhoeht	1 (0,3)	0
Fibrinogen im Blut erhoeht	0	1 (0,3)
Gamma-Glutamyltransferase erhoeht	2 (0,7)	0
Hepatitis B-DNS erhoeht	0	2 (0,7)
Leukozytenzahl erniedrigt	1 (0,3)	0
Lymphozytenzahl erniedrigt	0	1 (0,3)
Neutrophilenzahl erniedrigt	5 (1,7)	1 (0,3)
SARS-CoV-2-Test positiv	1 (0,3)	1 (0,3)
Thrombozytenzahl vermindert	2 (0,7)	0
Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen	0	3 (1,0)
Reaktion im Zusammenhang mit einer Infusion	0	2 (0,7)
Verkehrsunfall	0	1 (0,3)

Includes adverse events with onset date after first dose of study treatment until the end of the observation period as defined in Table 3.1. Discontinuation is defined as action taken with Acala/Placebo = 'DRUG WITHDRAWN' or action taken with Bendamustine or Rituximab = 'STUDY DRUG DISCONTINUED'.

Patients with multiple event are counted only once in each specific category.

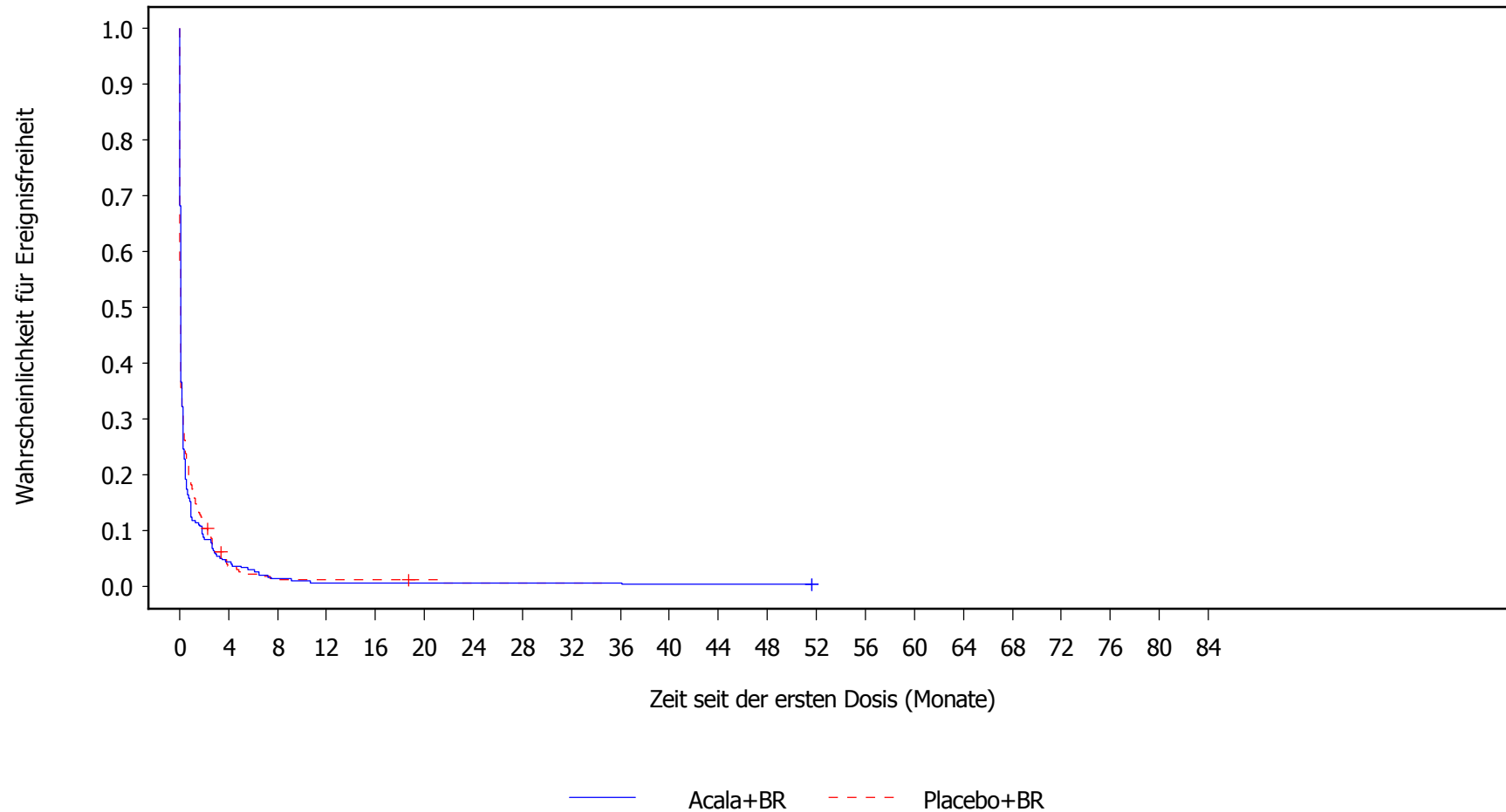
All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 3.3.1.1 ECHO: Kaplan-Meier plot of time to first occurrence of UE
 Safety Analysis Set, DC0 15FEB2024



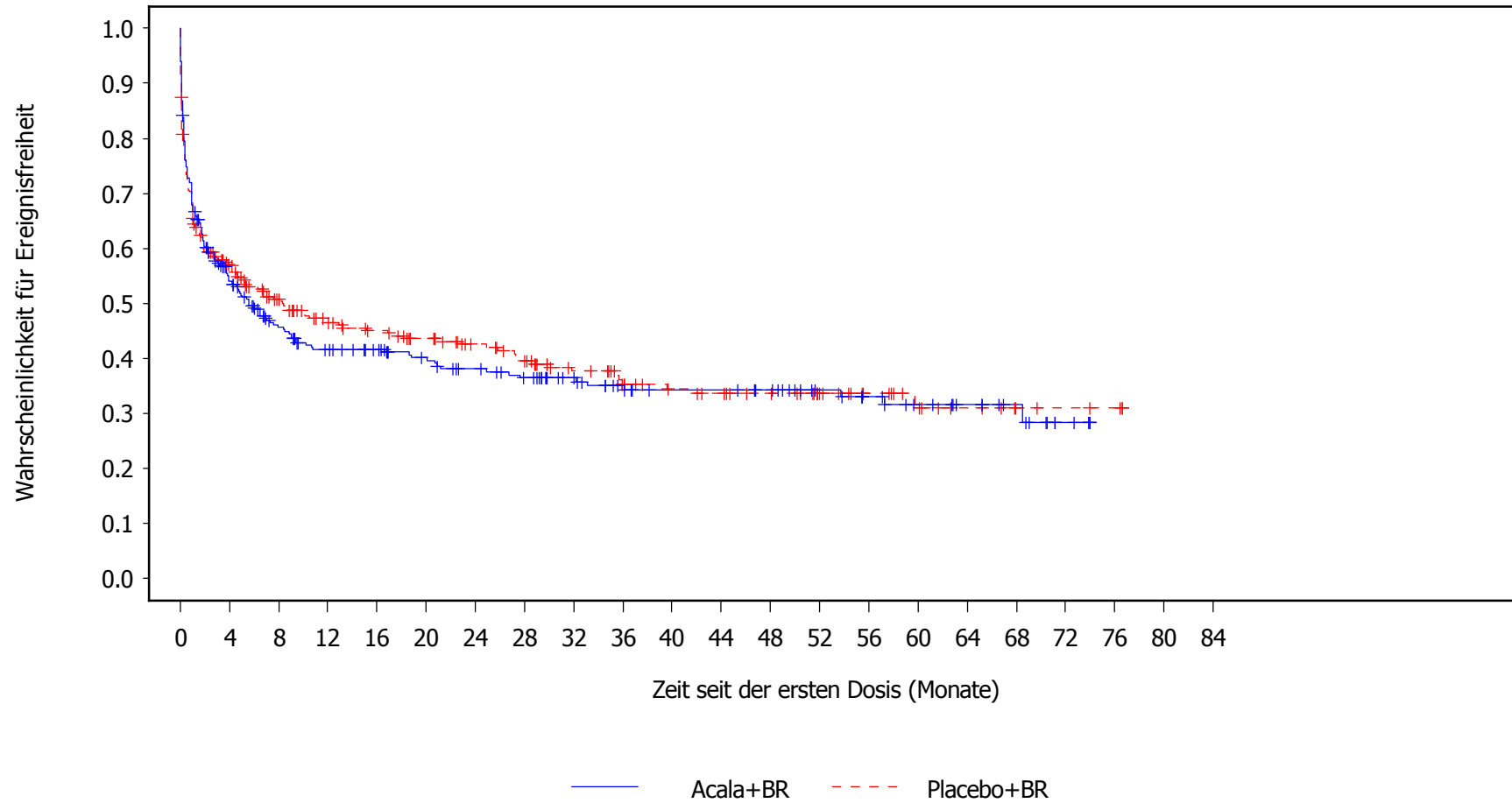
Anzahl an Patienten unter Risiko:

297	13	4	2	2	2	2	2	2	2	1	1	1	0	0	0	0	0	0	0	0	Acala+BR
297	10	3	3	3	2	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	Placebo+BR

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Figure 3.3.1.2 ECHO: Kaplan-Meier plot of time to first occurrence of SOC: Allgemeine Erkrankungen und Beschwerden am Verabreichungsort
 Safety Analysis Set, DCO 15FEB2024



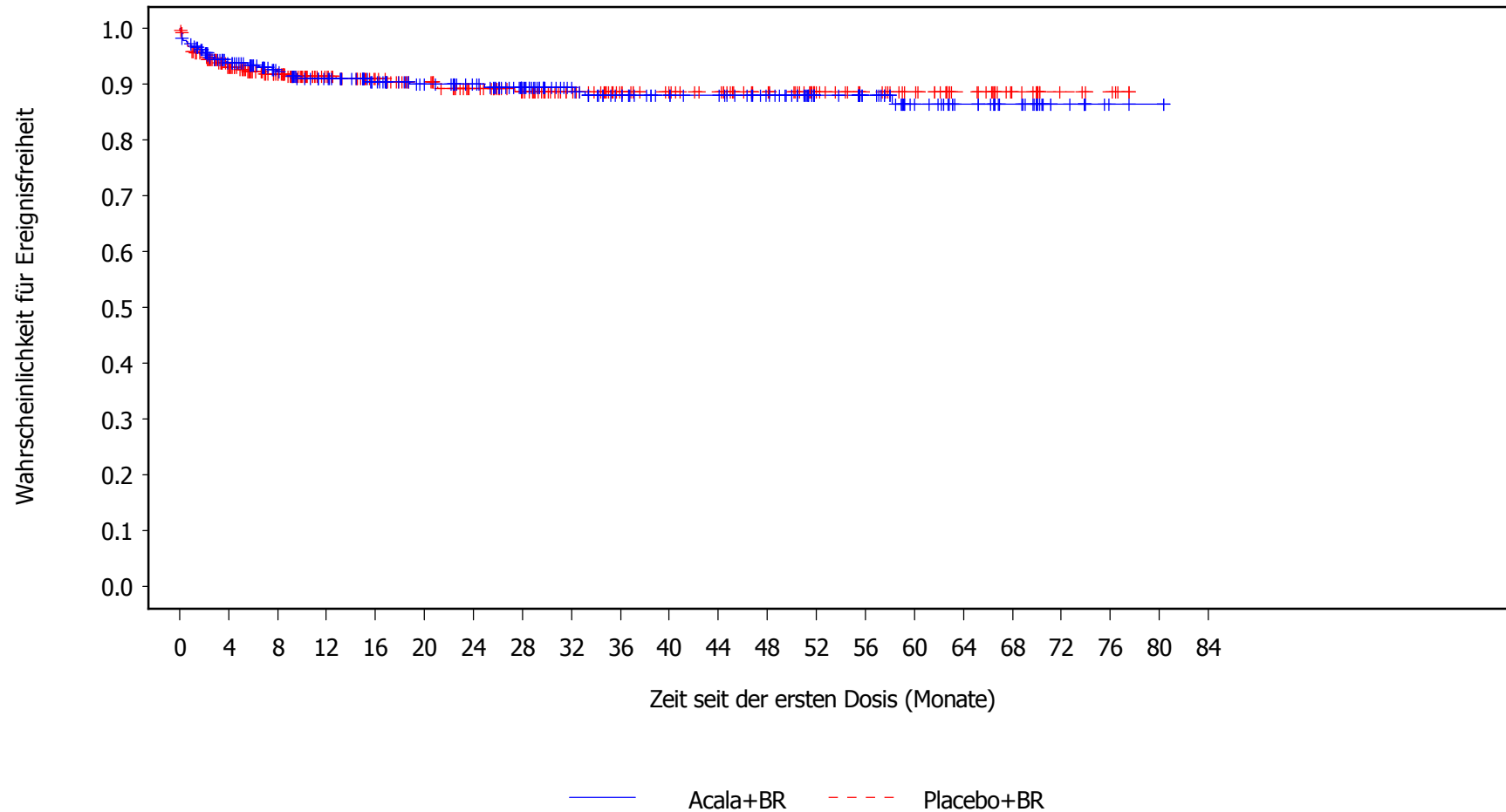
Anzahl an Patienten unter Risiko:

297	149	115	98	90	79	71	64	54	44	40	40	37	29	23	18	14	10	3	0	0	0	Acala+BR
297	156	124	106	95	86	75	67	54	45	39	36	32	24	17	12	8	4	3	2	0	0	Placebo+BR

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Figure 3.3.1.3 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Asthenie
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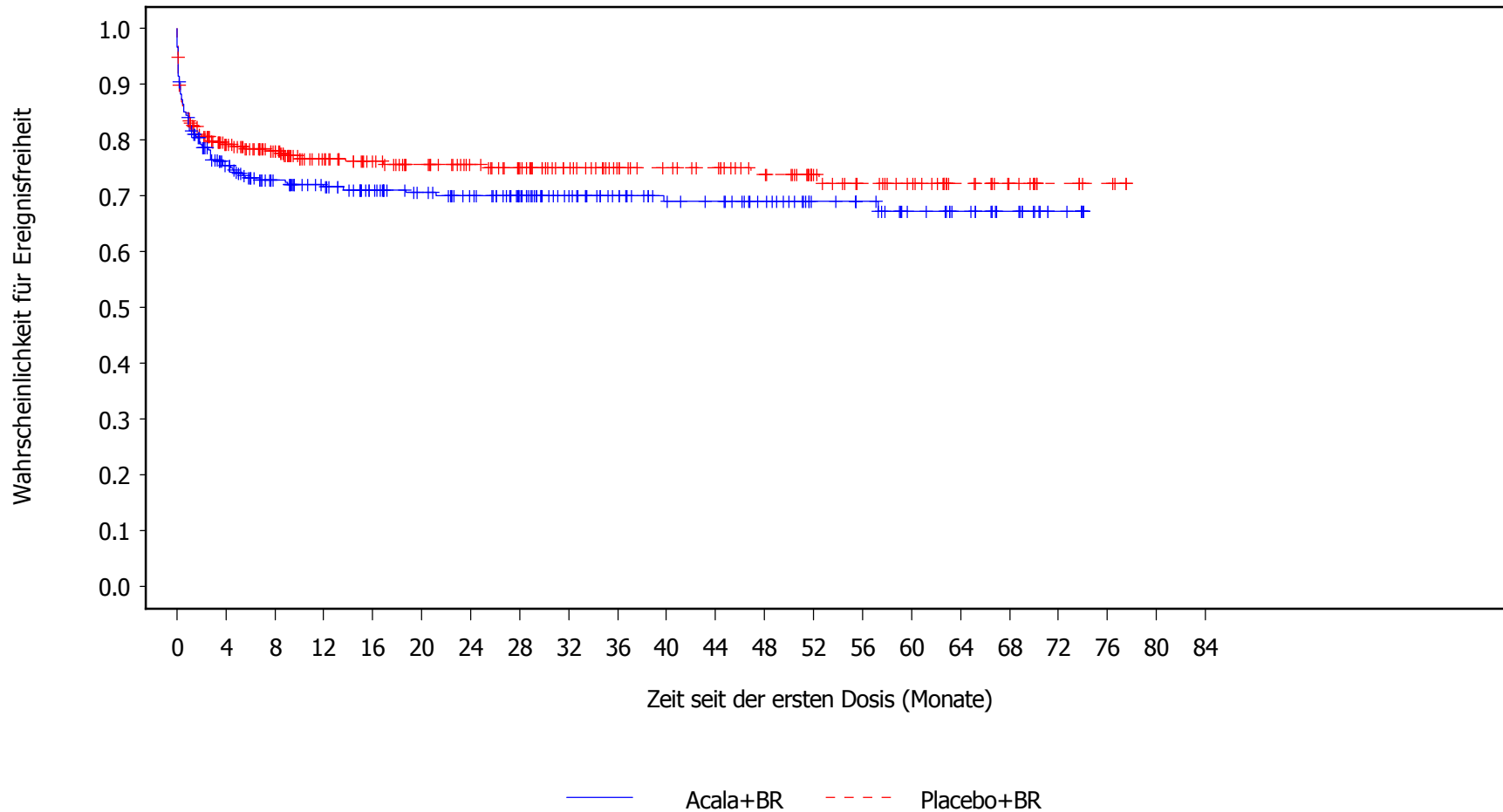
Anzahl an Patienten unter Risiko:

297	257	228	211	192	176	166	147	126	112	102	99	90	70	60	43	34	26	10	2	1	0	Acala+BR
297	252	223	192	173	161	146	131	112	98	90	85	75	58	49	42	29	17	6	4	0	0	Placebo+BR

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Figure 3.3.1.4 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Ermuedung
 Safety Analysis Set, DCO 15FEB2024



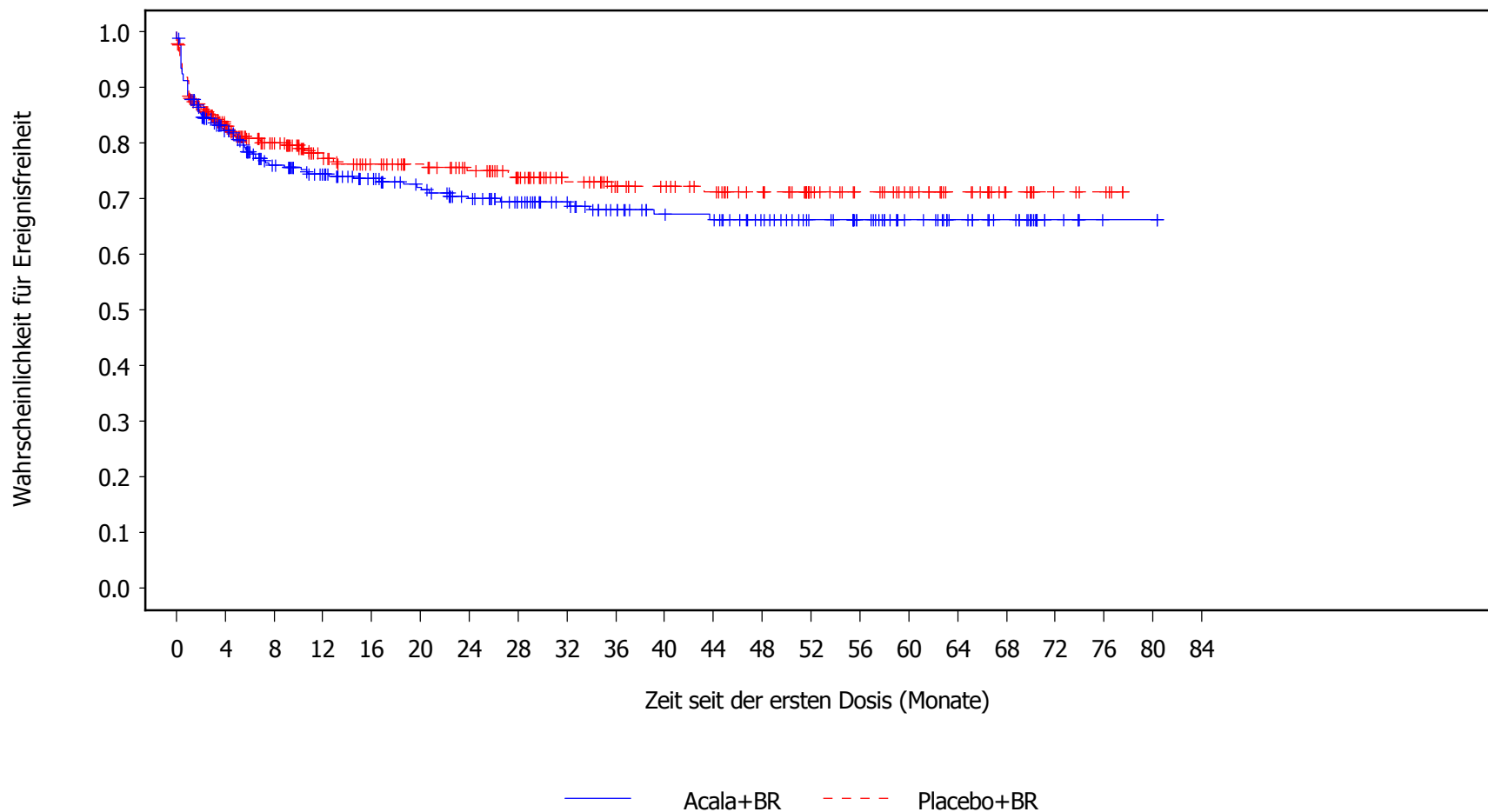
Anzahl an Patienten unter Risiko:

297	206	179	164	148	135	125	109	91	78	67	64	56	44	39	30	24	16	6	0	0	0	Acala+BR
297	212	186	158	144	132	120	110	95	83	77	73	64	50	41	35	22	14	6	3	0	0	Placebo+BR

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Figure 3.3.1.5 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Fieber
 Safety Analysis Set, DC0 15FEB2024



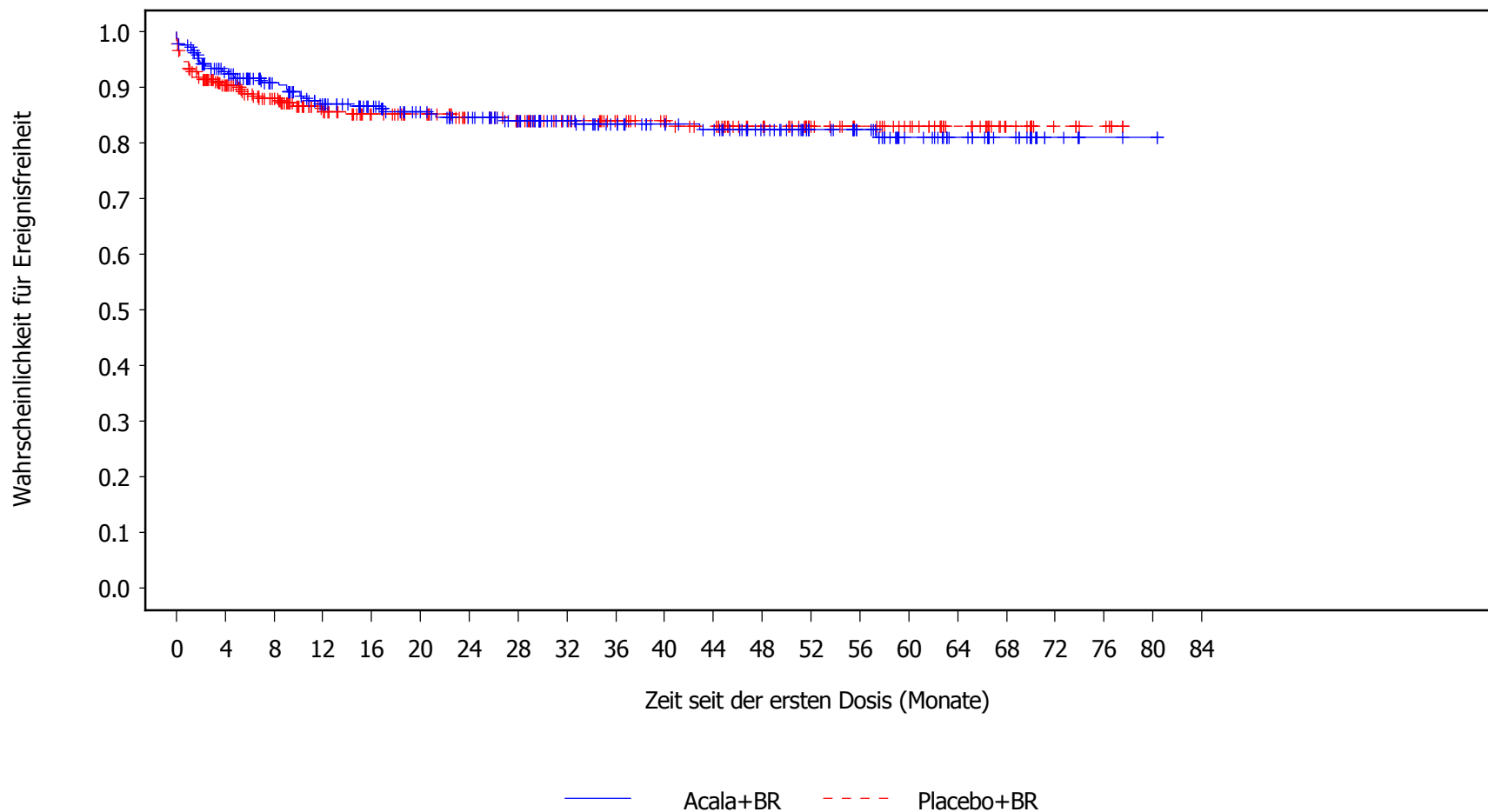
Anzahl an Patienten unter Risiko:

297	225	190	172	155	141	128	114	102	90	81	79	69	59	49	37	28	22	6	1	1	0	Acala+BR
297	222	188	161	146	137	125	112	95	85	78	72	64	49	41	34	24	13	6	4	0	0	Placebo+BR

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Figure 3.3.1.6 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Oedem peripher
 Safety Analysis Set, DCO 15FEB2024



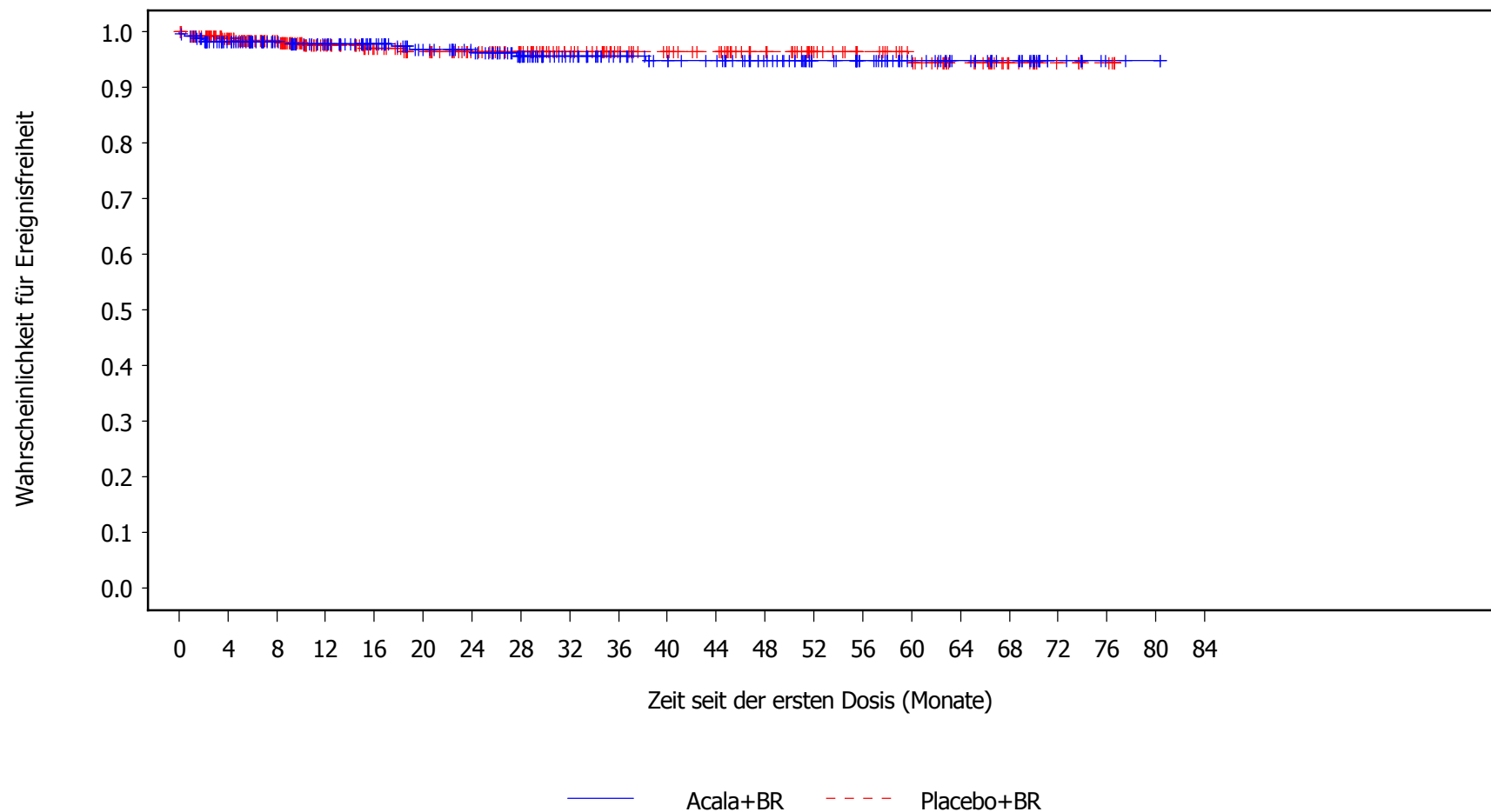
Anzahl an Patienten unter Risiko:

297	256	224	200	183	166	156	141	125	110	101	96	85	67	57	41	31	21	7	2	1	0	Acala+BR
297	241	211	178	161	152	137	126	110	100	91	86	74	58	50	43	30	17	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.7 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Periphere Schwellung
 Safety Analysis Set, DC0 15FEB2024



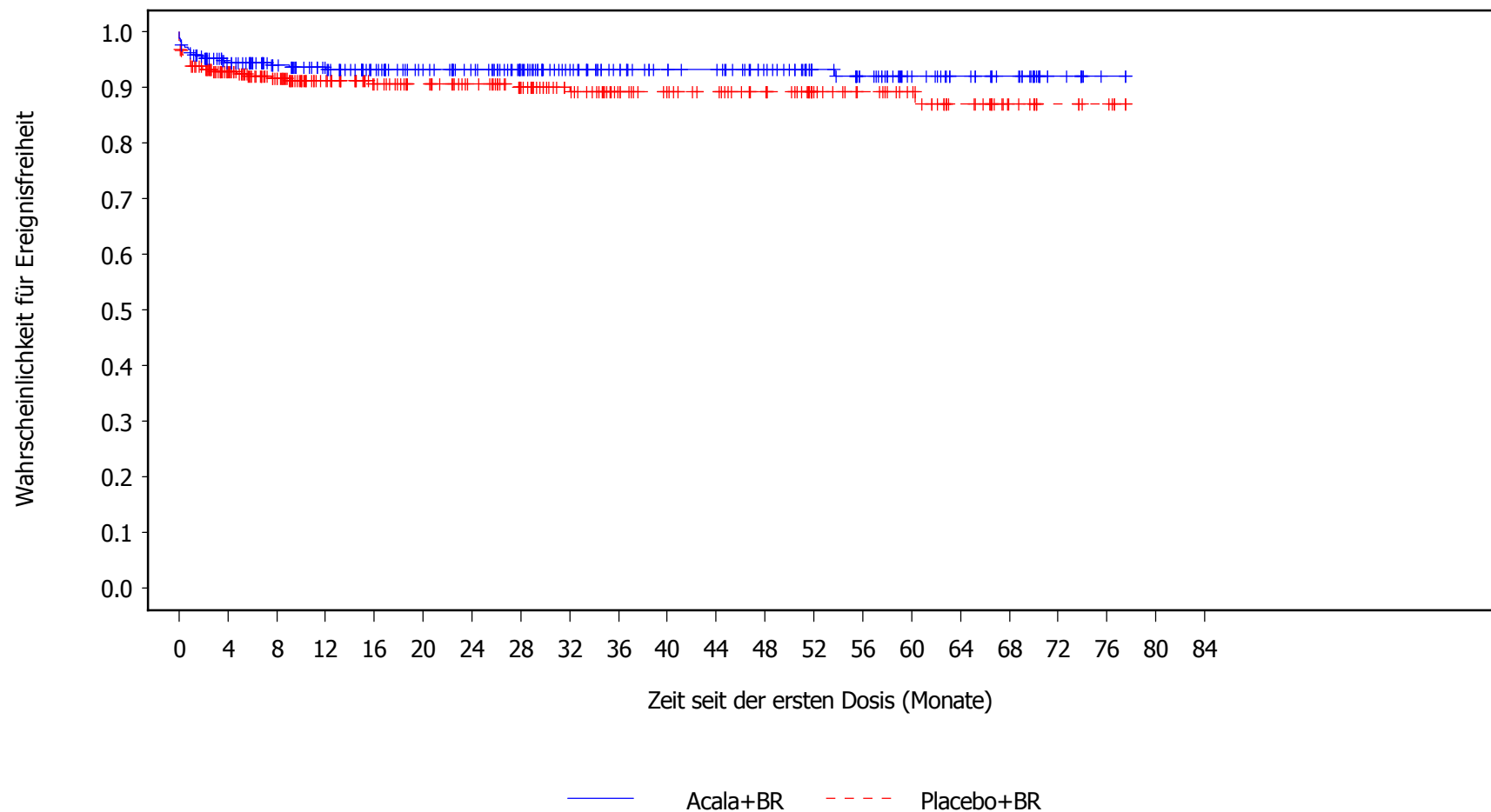
Anzahl an Patienten unter Risiko:

297	270	244	226	206	187	176	155	134	119	108	104	92	72	61	46	36	27	10	2	1	0	Acala+BR
297	265	235	198	178	166	153	137	118	104	95	90	78	62	53	44	31	18	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.8 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Schuettelfrost
 Safety Analysis Set, DC0 15FEB2024



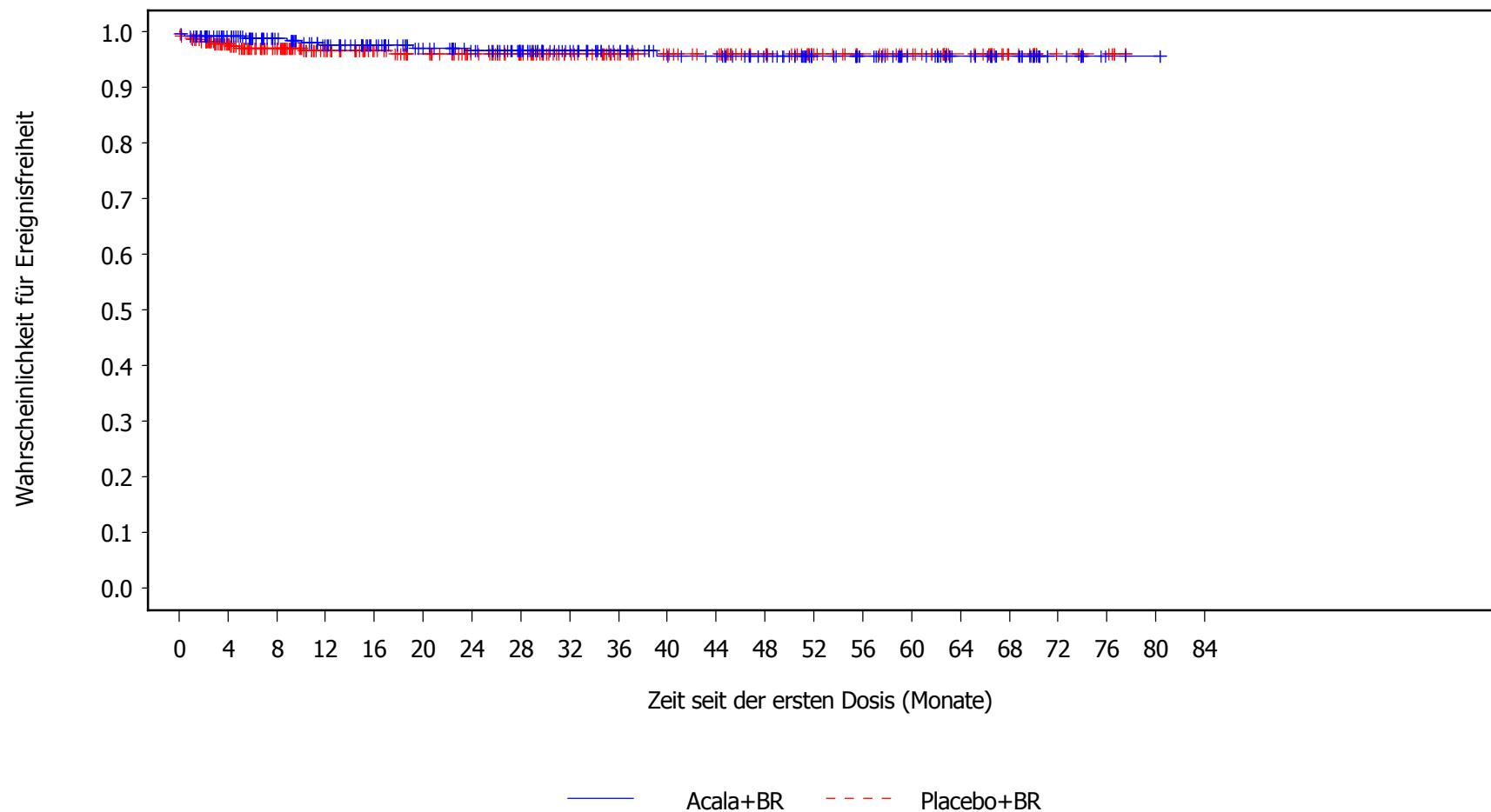
Anzahl an Patienten unter Risiko:

297	261	236	218	198	182	171	151	130	115	105	102	90	72	61	44	35	27	9	1	0	0	Acala+BR
297	249	217	186	167	155	143	128	111	95	87	82	74	58	50	43	29	16	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.9 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Thoraxschmerz nicht kardialen Ursprungs
 Safety Analysis Set, DC0 15FEB2024



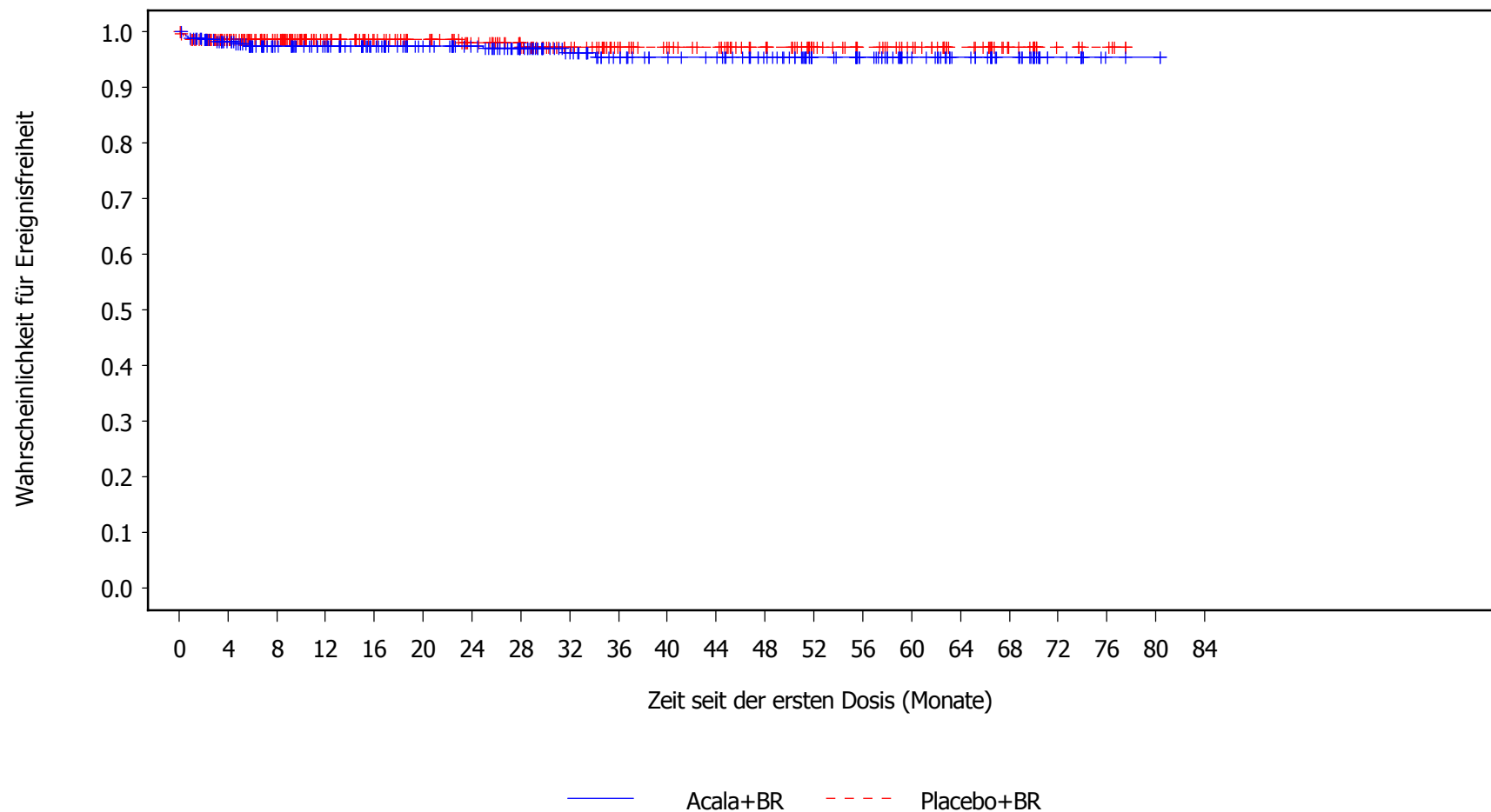
Anzahl an Patienten unter Risiko:

297	273	245	225	205	187	175	156	136	121	110	107	96	75	64	51	40	29	11	2	1	0	Acala+BR
297	261	230	198	179	167	153	138	119	105	96	91	79	65	56	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.10 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Unwohlsein
 Safety Analysis Set, DC0 15FEB2024



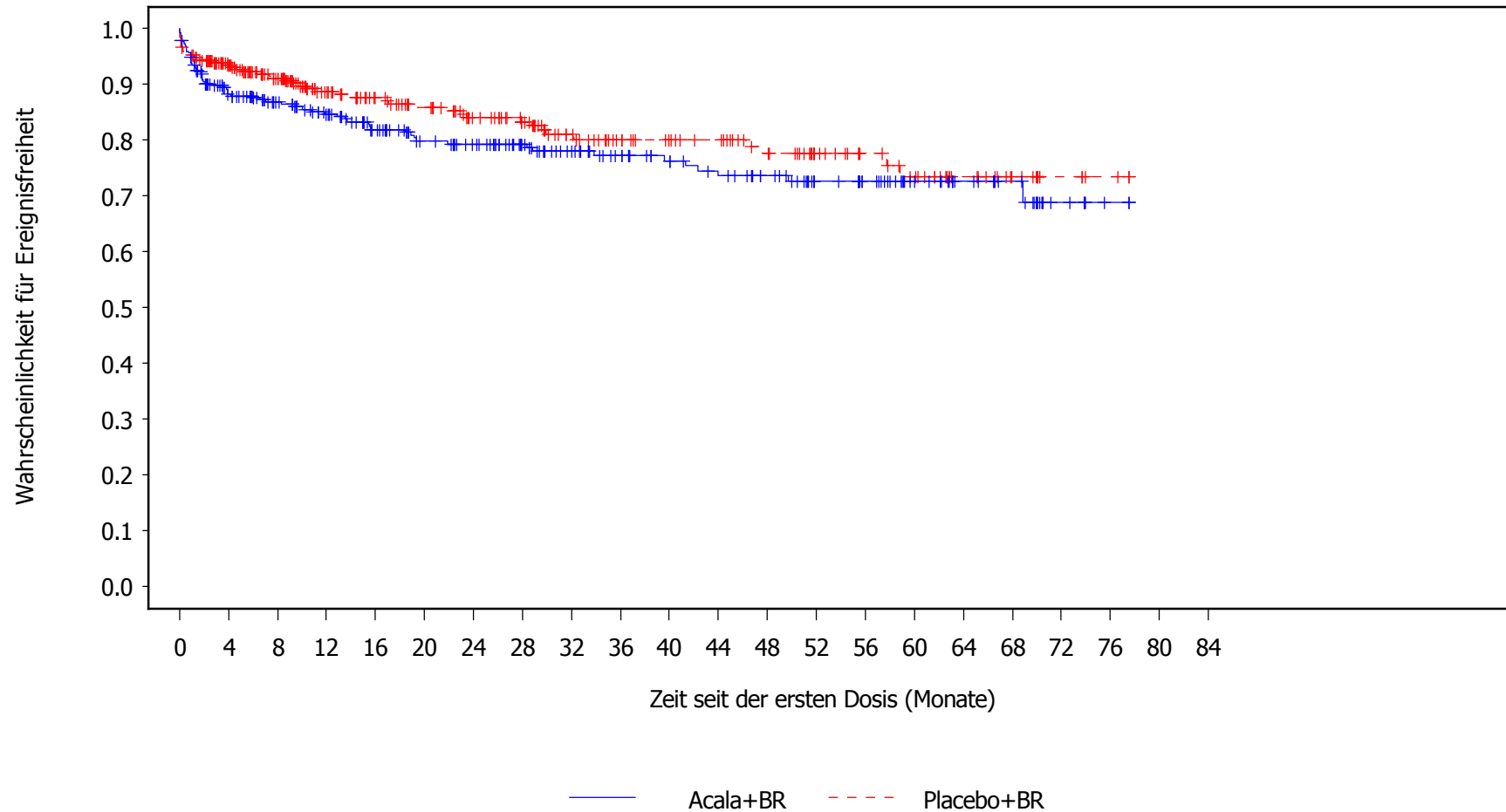
Anzahl an Patienten unter Risiko:

297	270	241	225	206	189	178	158	138	123	114	111	100	79	68	51	40	29	11	2	1	0	Acala+BR
297	263	235	200	181	169	154	138	120	106	97	92	80	63	54	46	32	18	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.11 ECH0: Kaplan-Meier plot of time to first occurrence of SOC: Augenerkrankungen
 Safety Analysis Set, DCO 15FEB2024



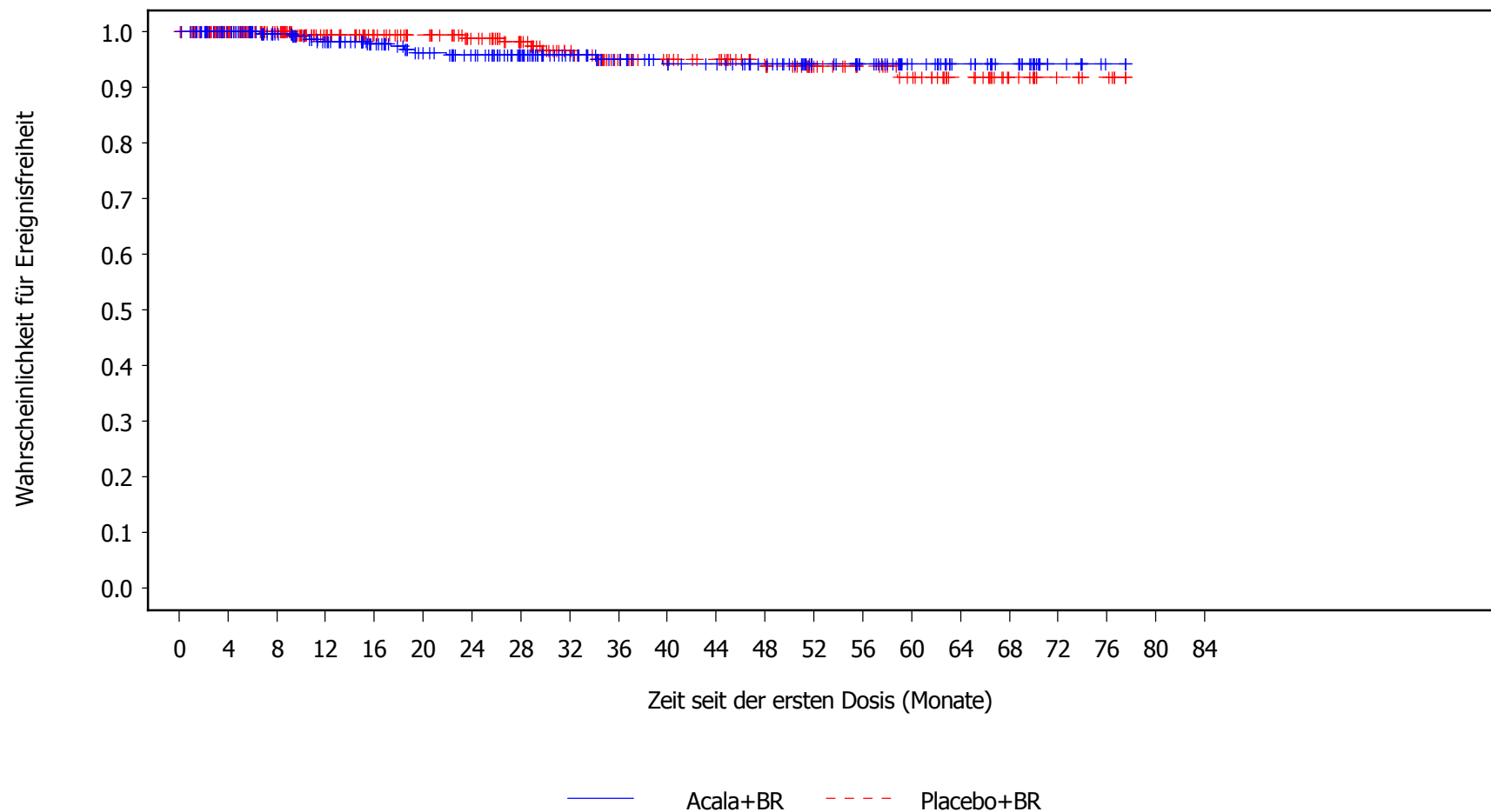
Anzahl an Patienten unter Risiko:

297	241	215	194	170	151	141	123	108	96	87	80	73	59	50	37	28	21	7	1	0	0	Acala+BR
297	248	214	176	157	143	126	113	94	82	75	71	61	47	39	33	21	13	5	2	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.12 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Katarakt
 Safety Analysis Set, DC0 15FEB2024



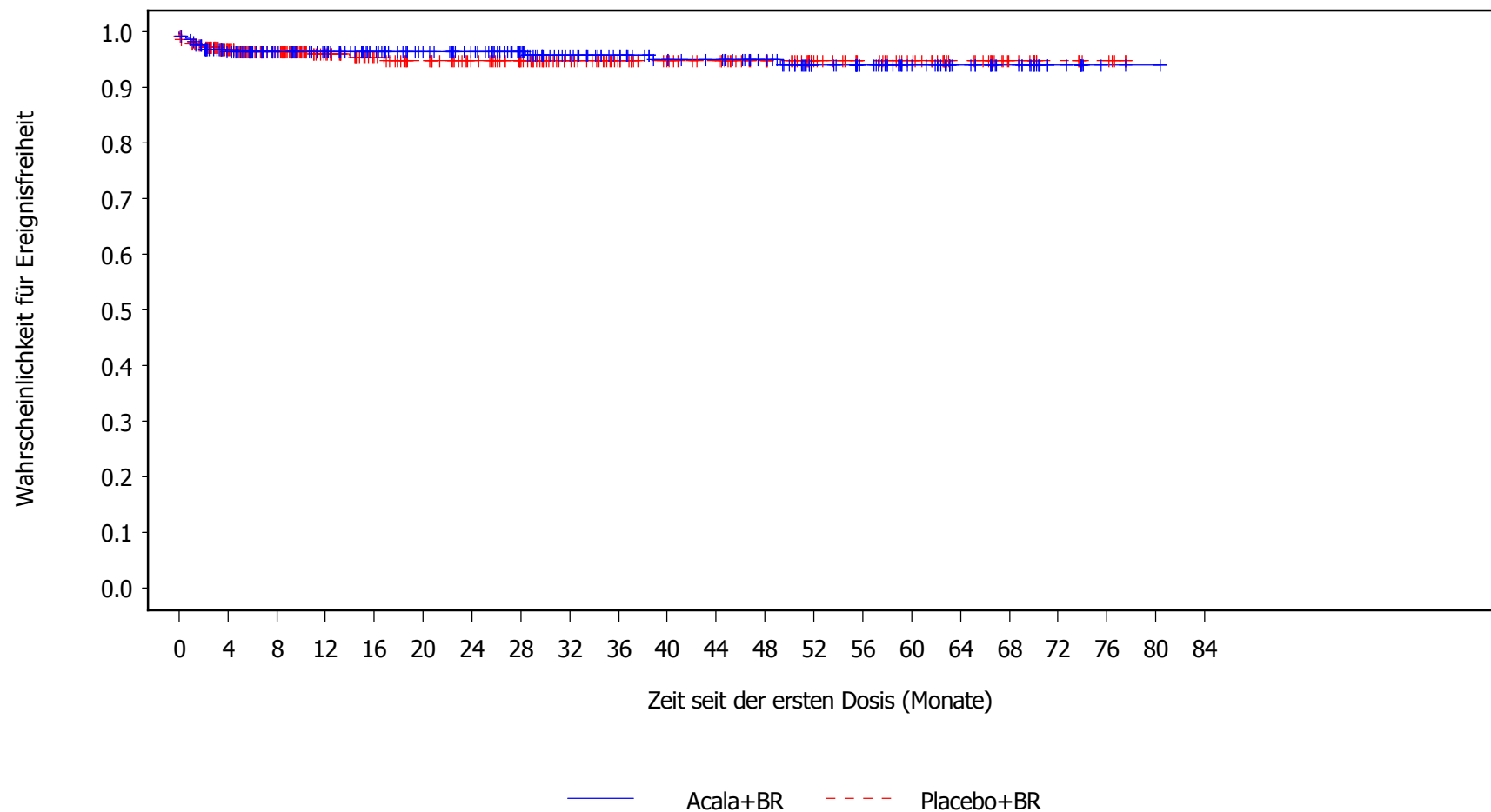
Anzahl an Patienten unter Risiko:

297	275	247	227	206	187	175	154	134	118	107	103	94	75	64	48	37	27	9	1	0	0	Acala+BR
297	267	238	202	183	171	156	139	118	102	93	88	76	60	51	43	29	17	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.13 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Sehen verschwommen
 Safety Analysis Set, DC0 15FEB2024



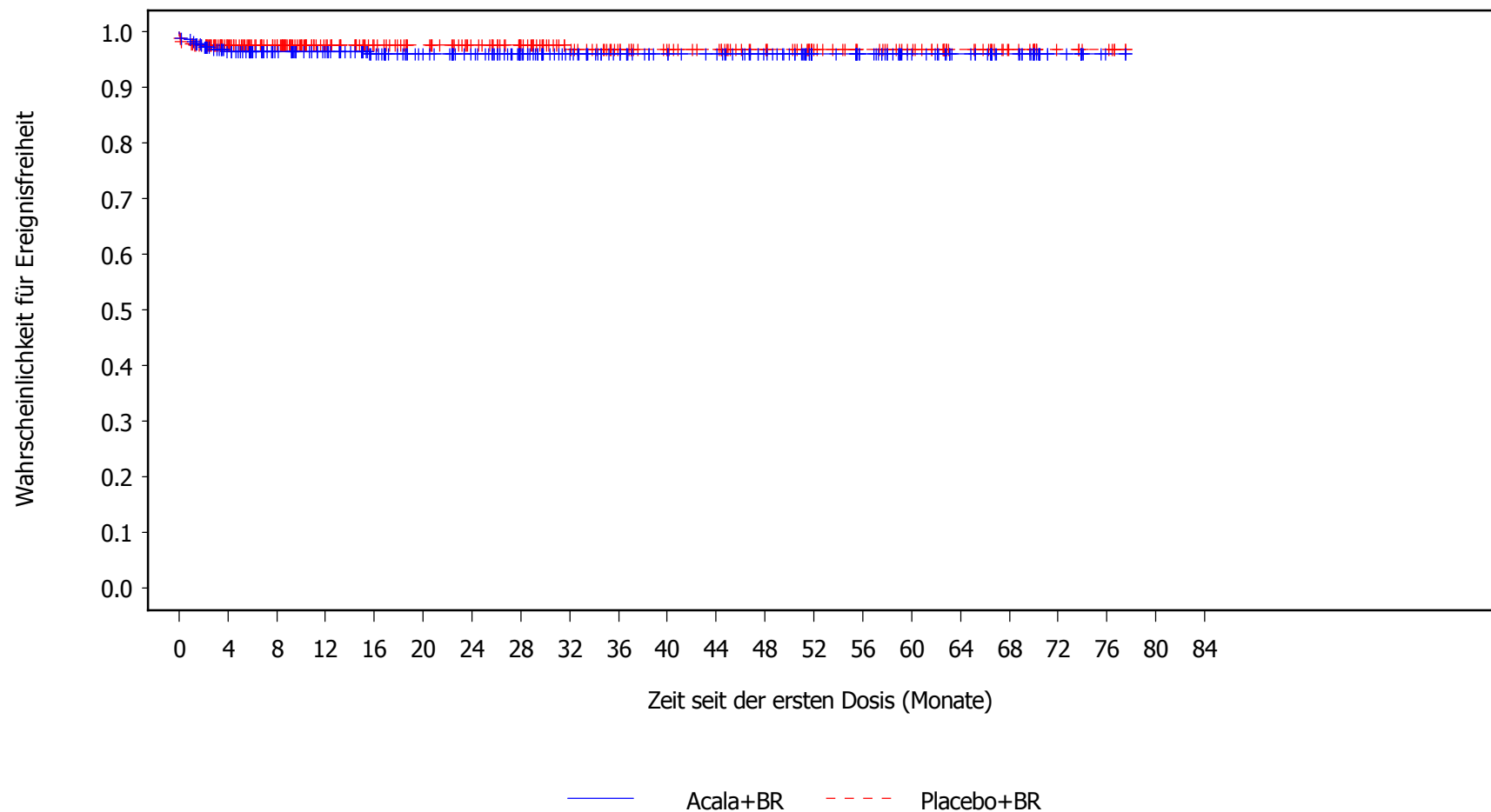
Anzahl an Patienten unter Risiko:

297	265	238	221	202	185	174	154	132	119	108	104	94	73	62	46	35	26	10	2	1	0	Acala+BR
297	258	229	193	174	161	147	133	114	100	91	86	75	58	49	41	28	16	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.14 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Trockenes Auge
 Safety Analysis Set, DC0 15FEB2024



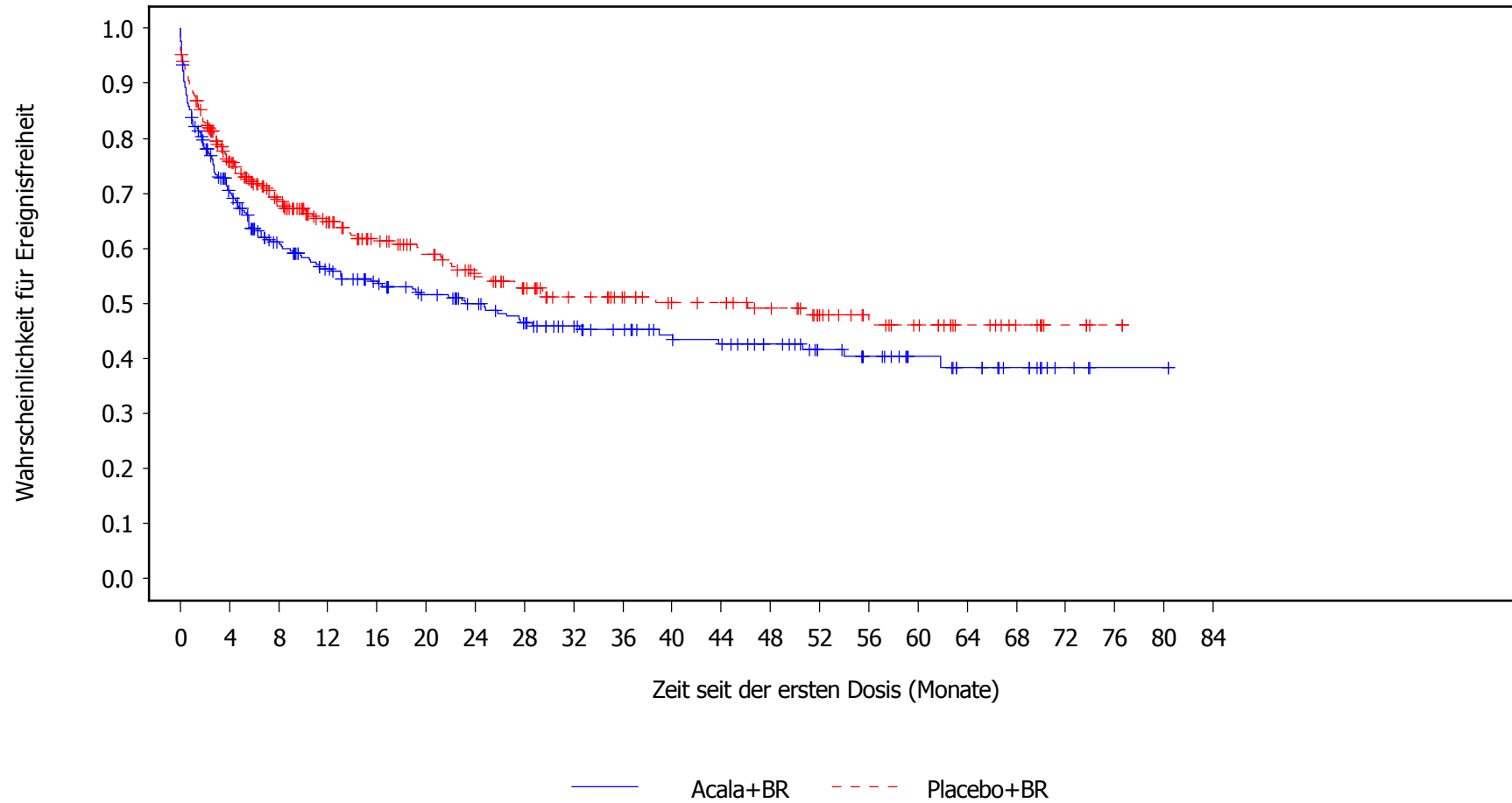
Anzahl an Patienten unter Risiko:

297	265	240	223	203	186	175	155	136	122	112	108	96	75	65	49	39	28	10	1	0	0	Acala+BR
297	260	232	197	178	166	152	137	117	104	95	90	79	63	54	46	31	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.15 ECH0: Kaplan-Meier plot of time to first occurrence of SOC: Erkrankungen der Atemwege, des Brustraums und Mediastinums
 Safety Analysis Set, DCO 15FEB2024



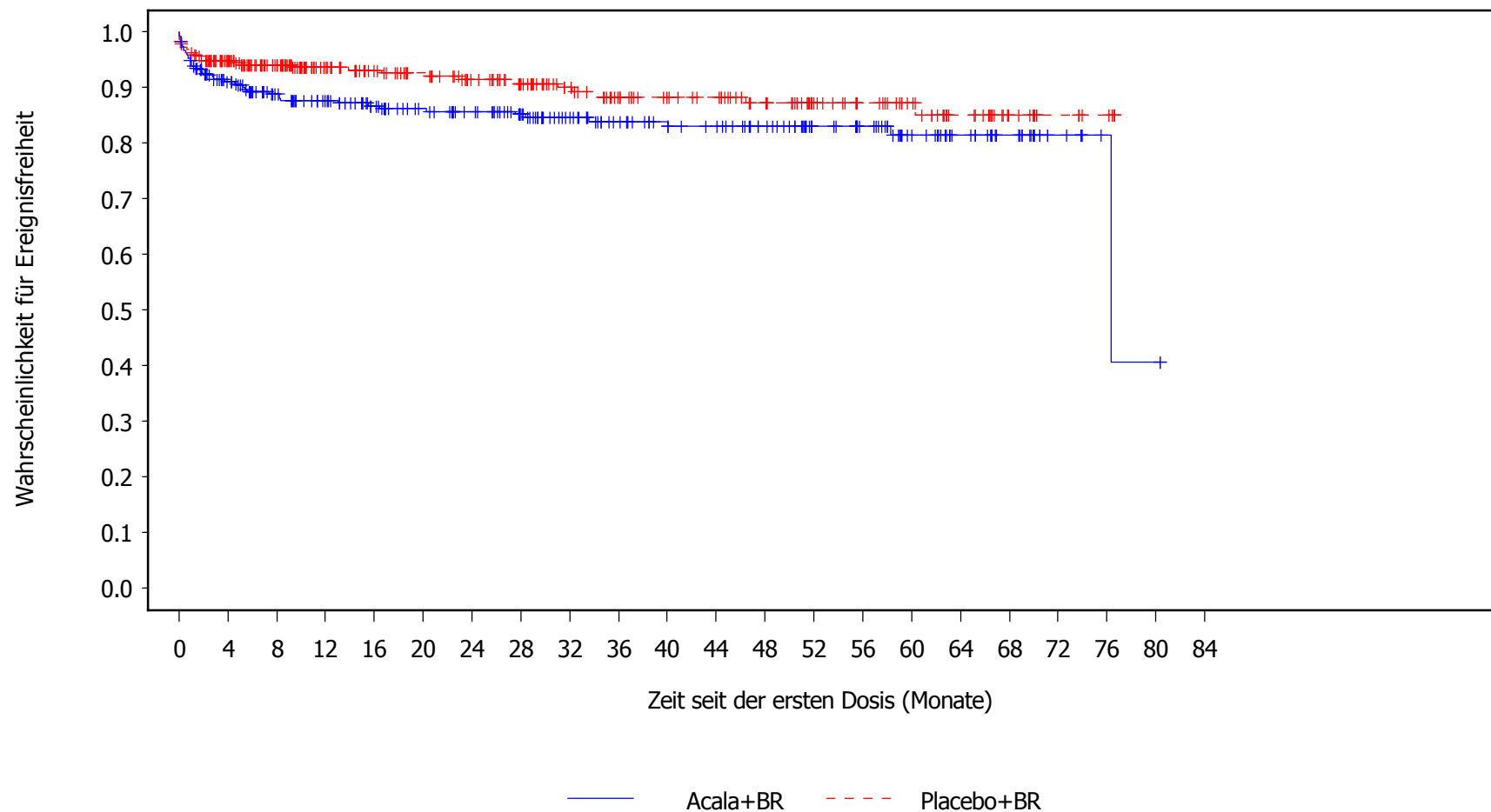
Anzahl an Patienten unter Risiko:

297	194	152	131	115	101	89	78	68	61	53	50	43	34	28	21	16	11	4	1	1	0	Acala+BR
297	206	166	135	113	101	86	74	63	57	50	49	43	34	27	22	14	9	4	1	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.16 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Dyspnoe
 Safety Analysis Set, DC0 15FEB2024



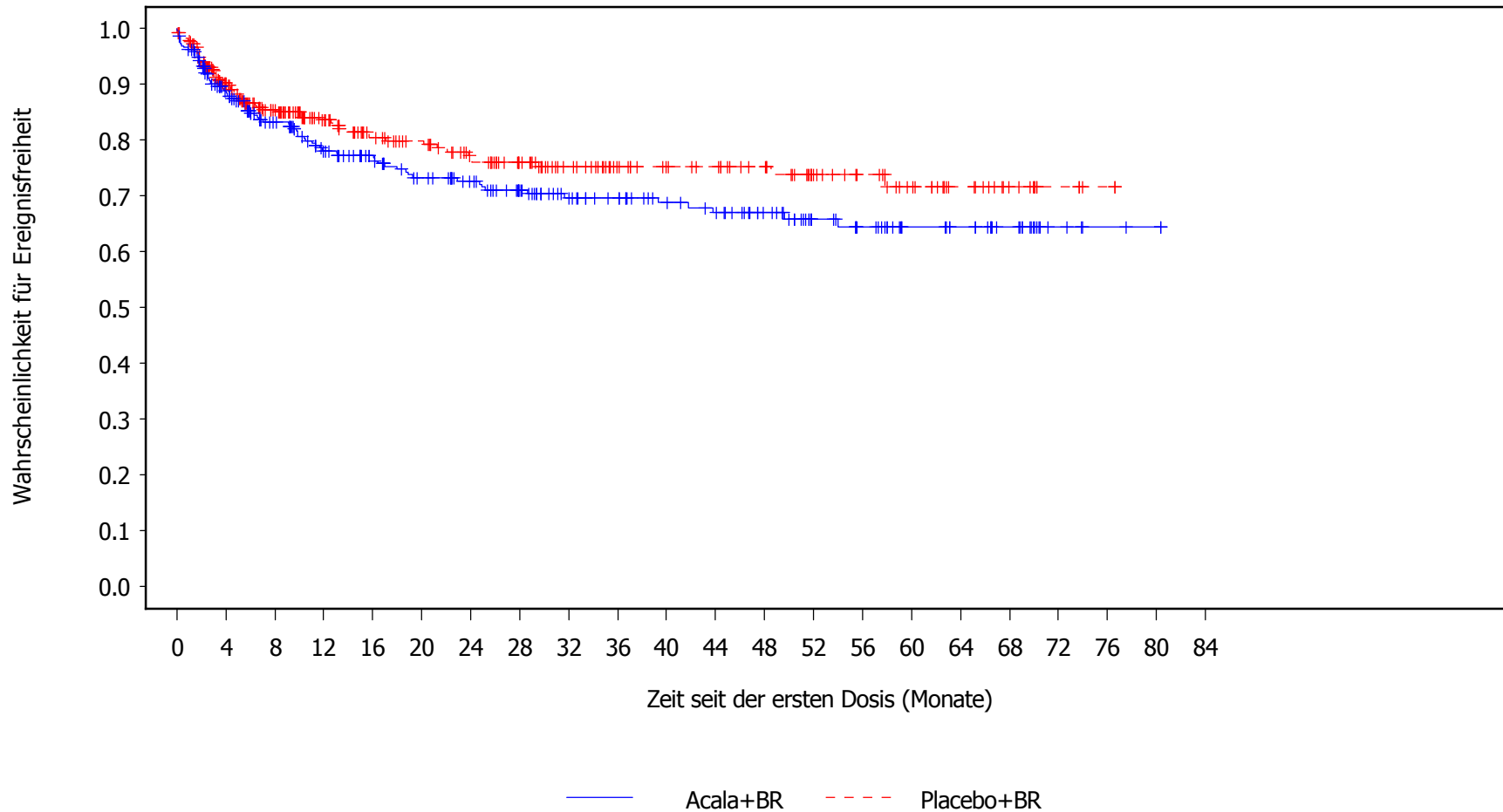
Anzahl an Patienten unter Risiko:

297	251	221	202	184	169	158	142	123	109	100	95	85	68	58	42	31	21	8	2	1	0	Acala+BR
297	255	224	190	173	161	146	131	113	100	91	87	76	60	51	43	28	16	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.17 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Husten
 Safety Analysis Set, DCO 15FEB2024



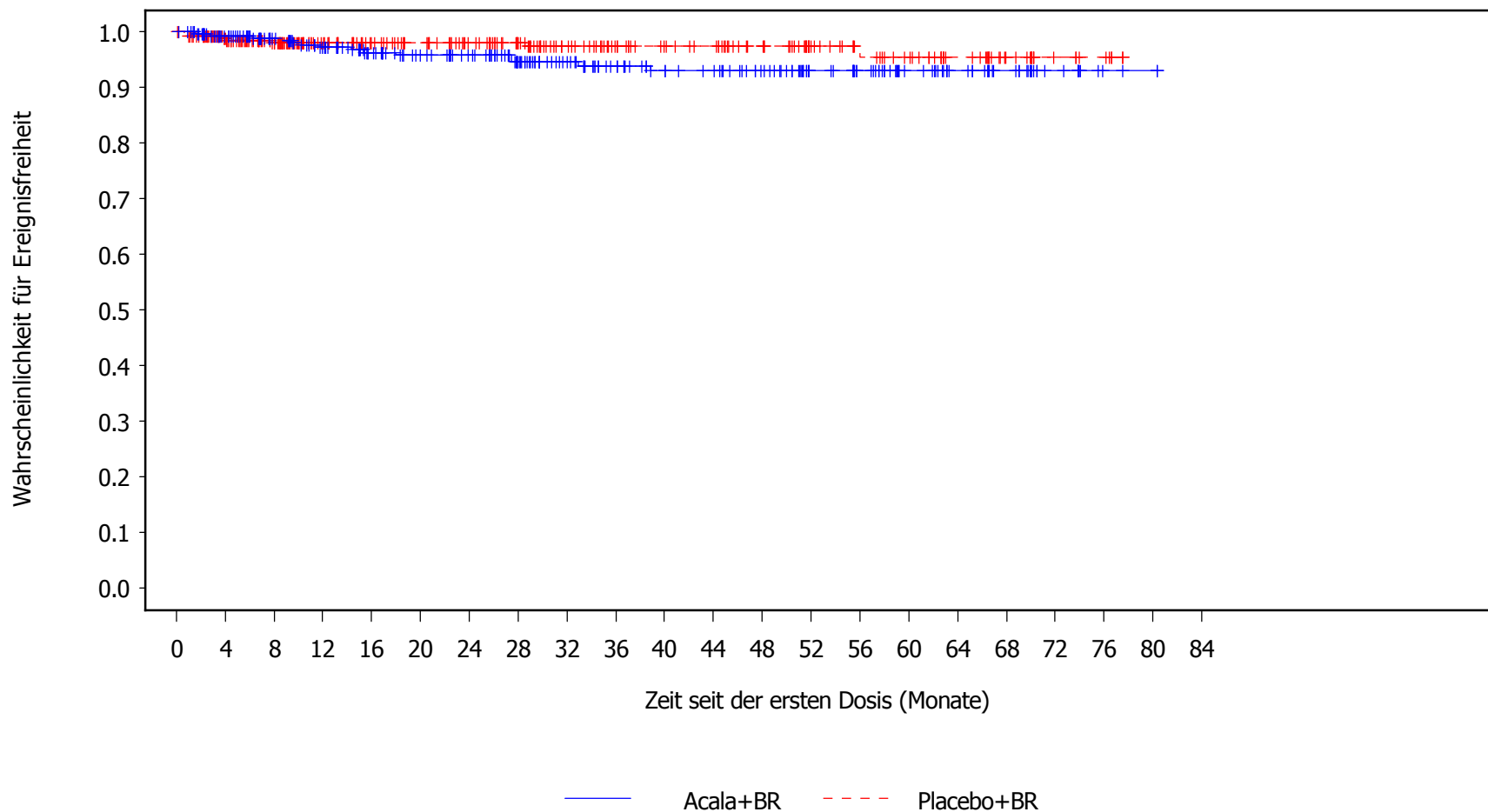
Anzahl an Patienten unter Risiko:

297	243	206	178	159	142	130	114	98	90	80	75	64	48	40	29	25	17	5	2	1	0	Acala+BR
297	239	200	166	142	132	116	102	87	74	67	64	57	44	37	29	19	11	4	1	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.18 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Husten mit Auswurf
 Safety Analysis Set, DC0 15FEB2024



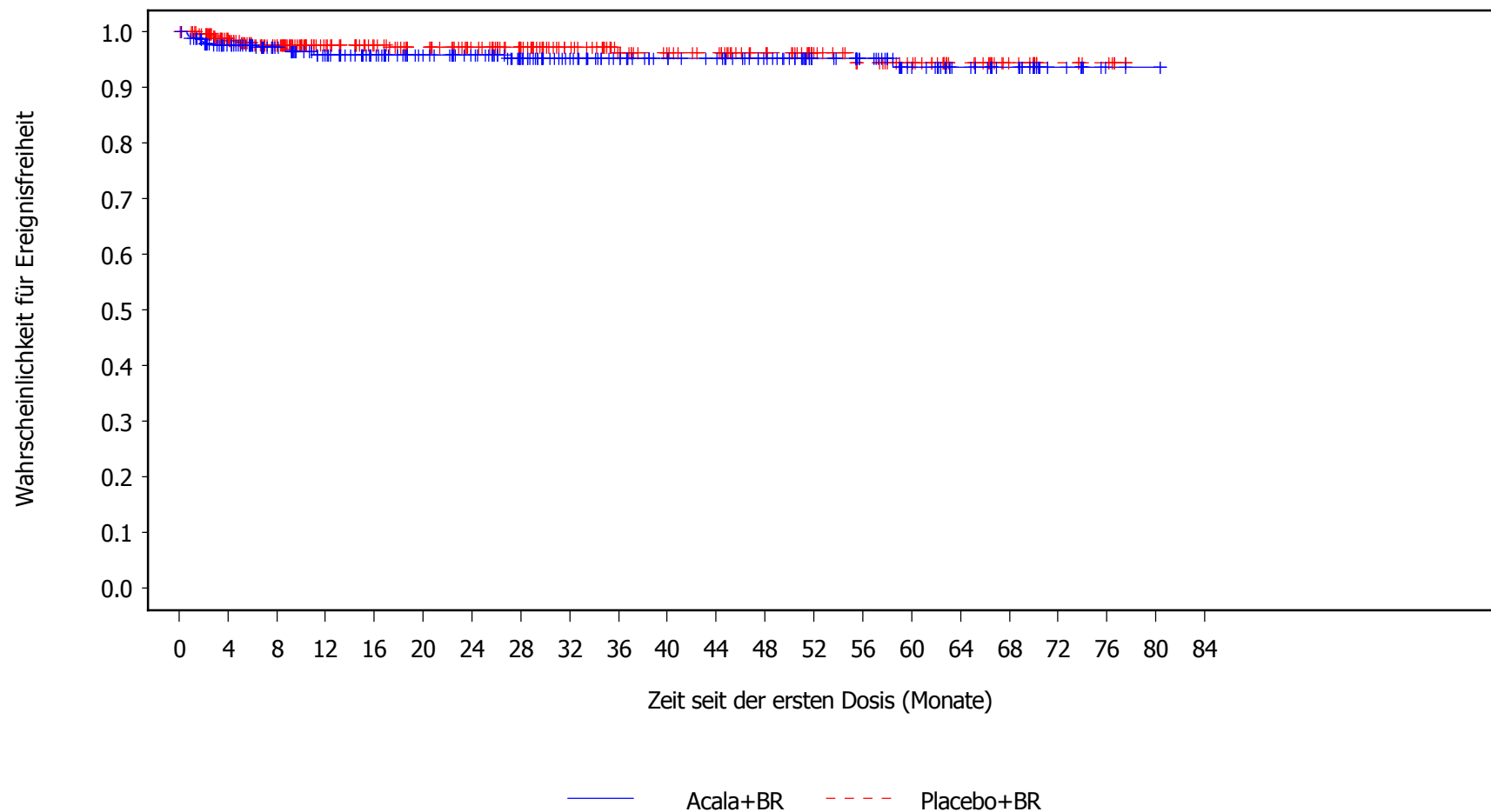
Anzahl an Patienten unter Risiko:

297	273	246	225	203	187	176	154	134	118	107	103	92	73	62	46	35	24	11	2	1	0	Acala+BR
297	264	233	198	180	168	154	138	118	104	95	91	79	62	53	46	32	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.19 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Nasenverstopfung
 Safety Analysis Set, DCO 15FEB2024



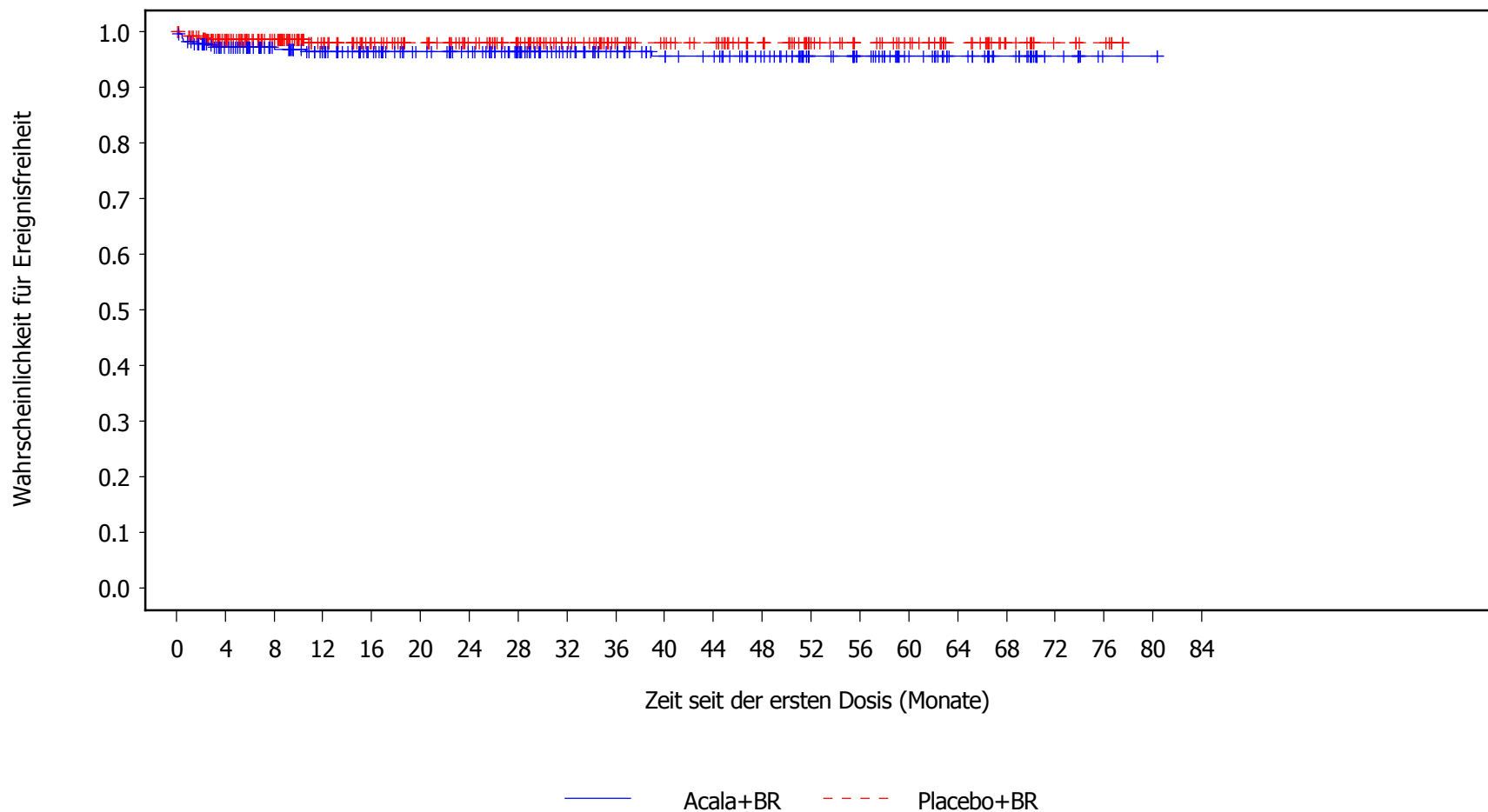
Anzahl an Patienten unter Risiko:

297	268	240	220	201	184	173	152	133	119	109	105	94	74	63	48	37	27	11	2	1	0	Acala+BR
297	264	233	198	181	168	154	138	119	104	95	90	78	61	52	45	30	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.20 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Pleuraerguss
 Safety Analysis Set, DC0 15FEB2024



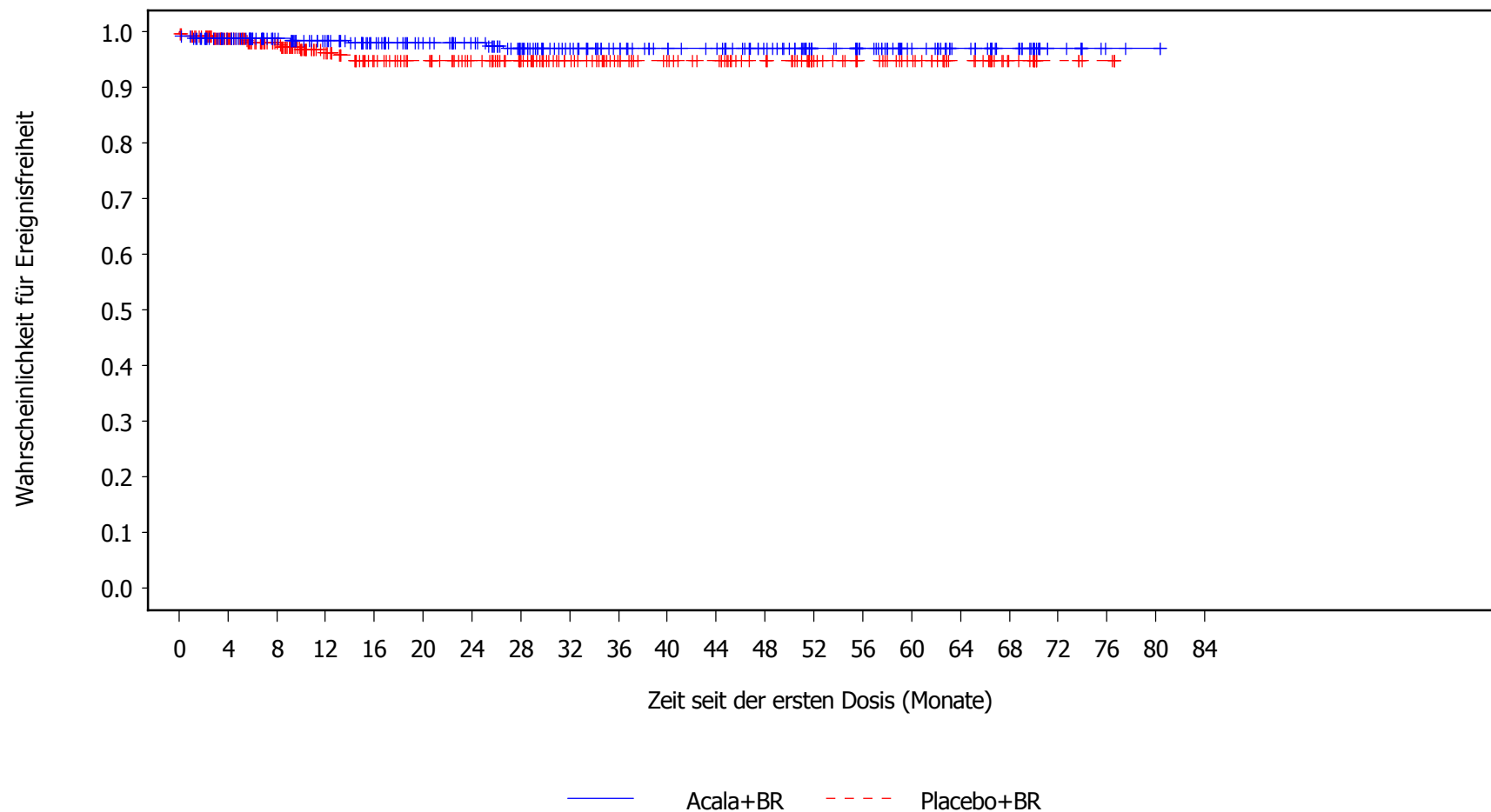
Anzahl an Patienten unter Risiko:

297	268	242	225	206	191	180	160	140	125	114	110	98	78	67	50	39	28	11	2	1	0	Acala+BR
297	264	236	201	183	171	157	141	122	107	98	93	81	64	55	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.21 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Rhinorrhoe
 Safety Analysis Set, DC0 15FEB2024



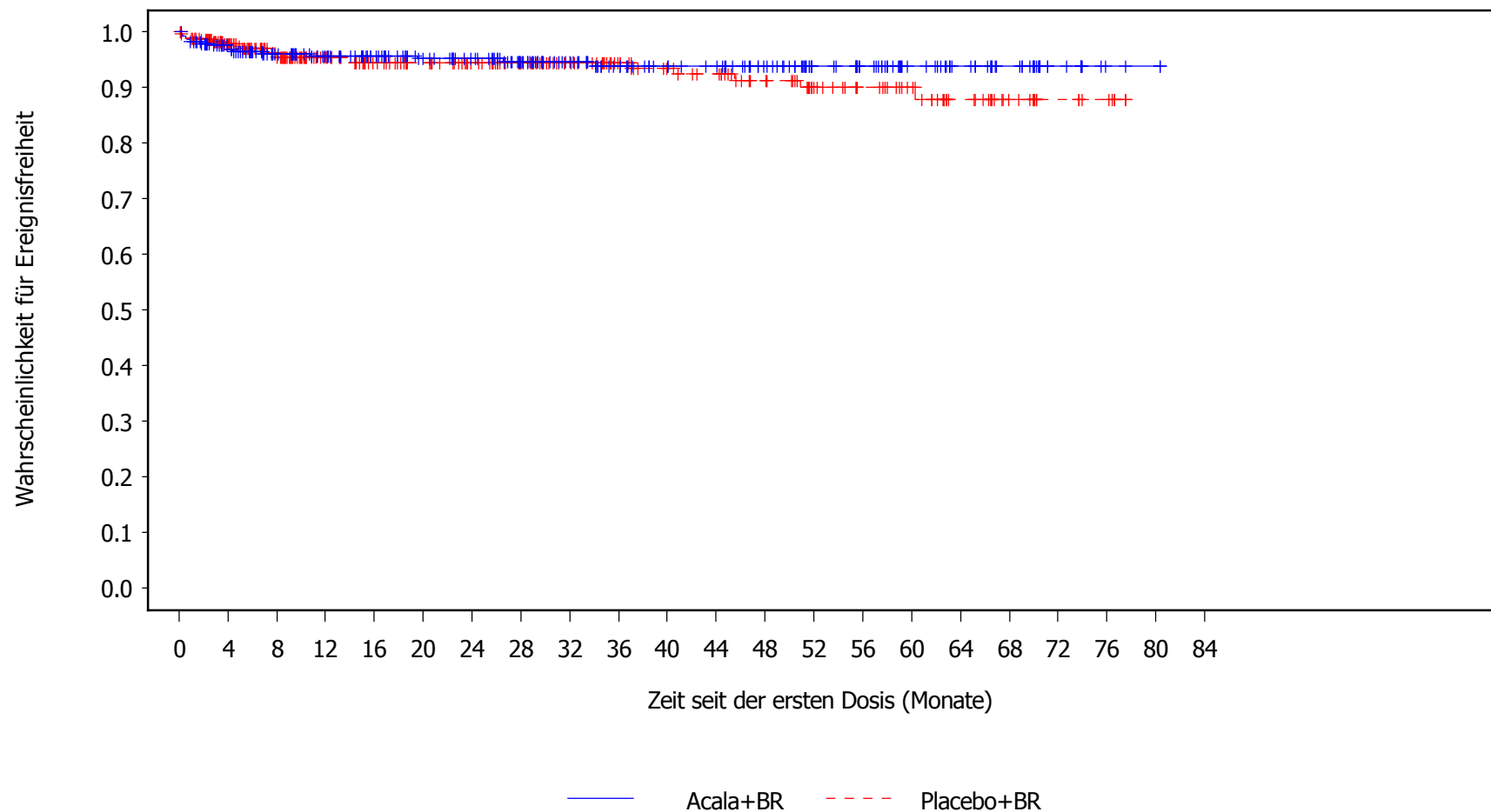
Anzahl an Patienten unter Risiko:

297	273	246	228	207	190	179	159	139	124	114	110	98	77	66	50	39	28	10	2	1	0	Acala+BR
297	264	233	195	173	162	149	134	115	101	92	87	76	59	50	42	29	16	6	3	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.22 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Schmerzen im Oropharynx
 Safety Analysis Set, DC0 15FEB2024



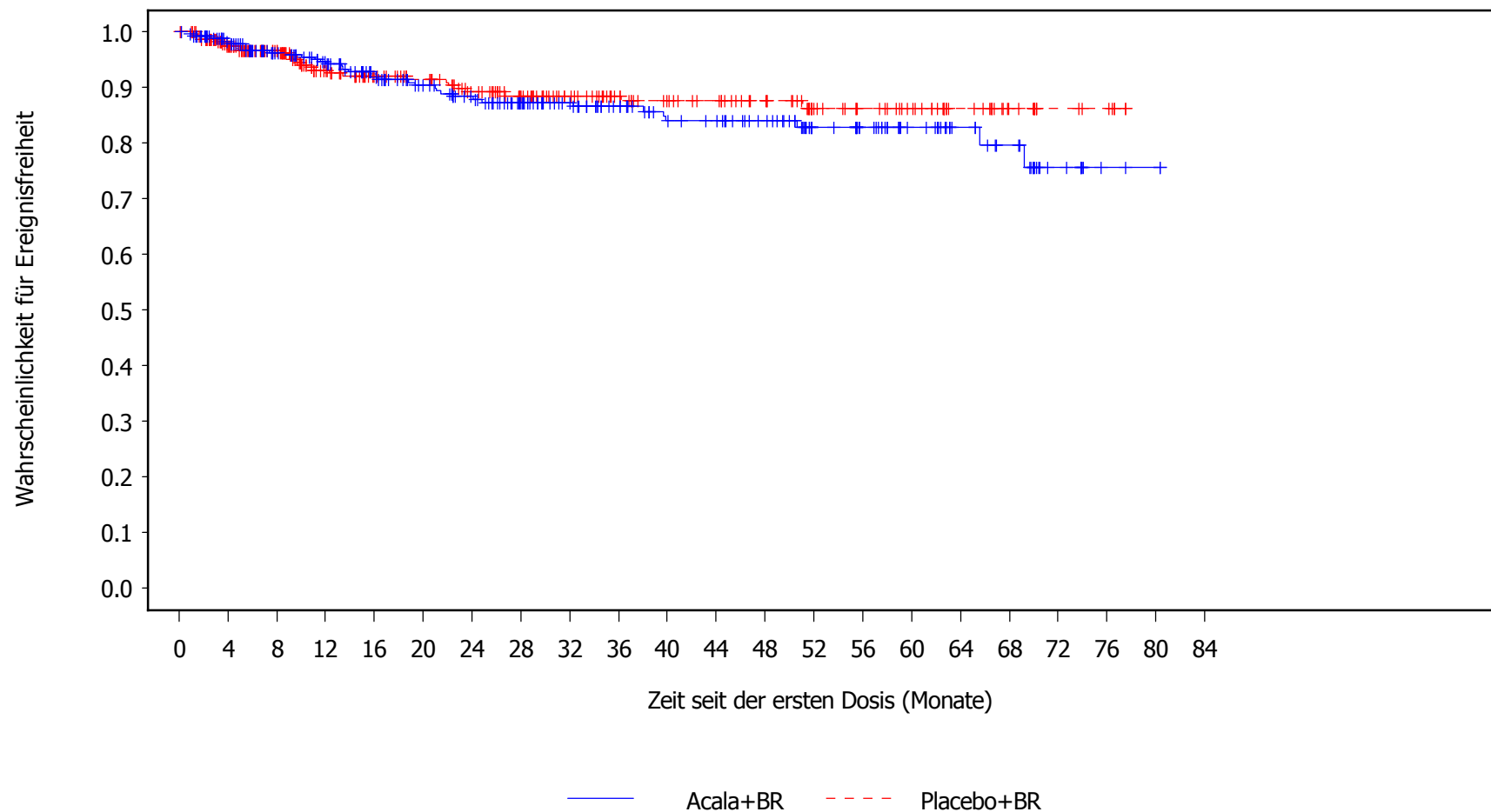
Anzahl an Patienten unter Risiko:

297	268	238	220	202	184	173	153	133	117	107	103	91	72	62	46	36	26	10	2	1	0	Acala+BR
297	261	228	196	176	165	152	136	117	103	93	88	77	62	53	45	29	17	8	5	0	0	Placebo+BR

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Figure 3.3.1.23 ECH0: Kaplan-Meier plot of time to first occurrence of SOC: Erkrankungen der Geschlechtsorgane und der Brustdruese
 Safety Analysis Set, DCO 15FEB2024



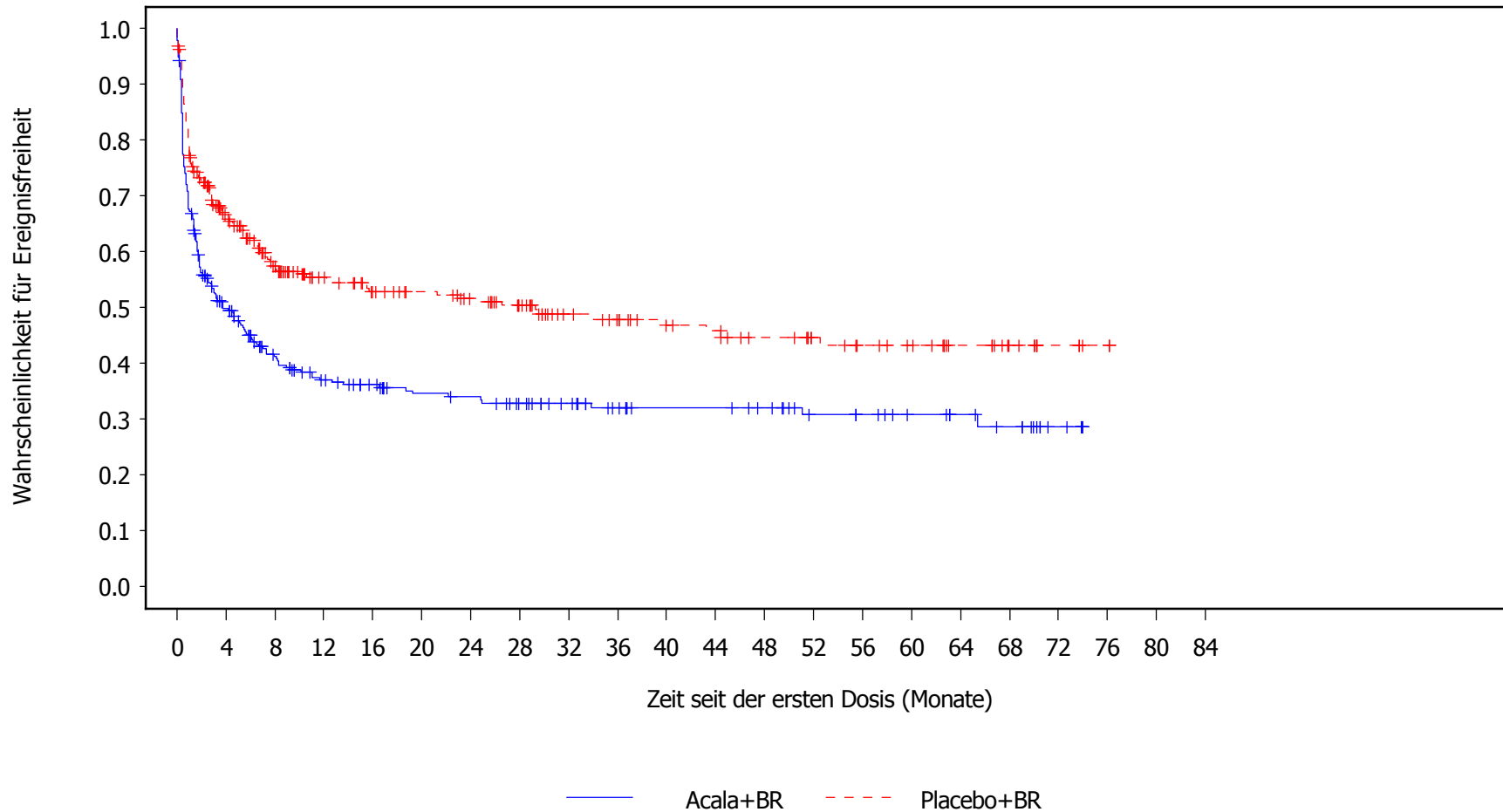
Anzahl an Patienten unter Risiko:

297	270	238	218	195	177	163	142	124	109	96	93	84	62	52	39	28	22	9	2	1	0	Acala+BR
297	261	231	191	173	161	144	128	110	97	87	82	73	56	48	41	27	16	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.24 ECHO: Kaplan-Meier plot of time to first occurrence of SOC: Erkrankungen der Haut und des Unterhautgewebes
 Safety Analysis Set, DC0 15FEB2024



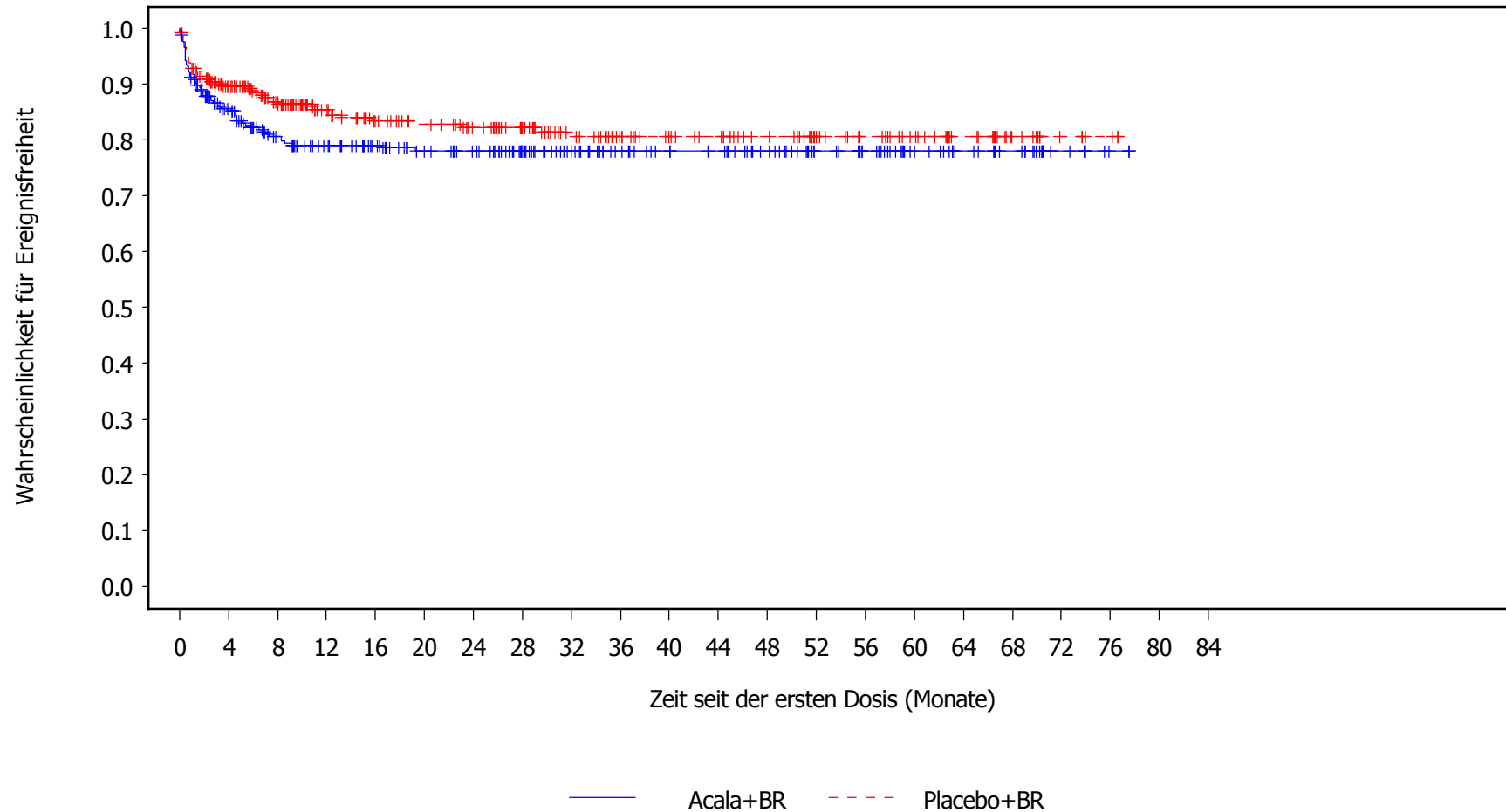
Anzahl an Patienten unter Risiko:

297	136	100	82	72	63	61	54	47	39	34	34	31	24	22	18	15	12	4	0	0	0	Acala+BR
297	175	134	108	96	89	82	71	56	51	44	42	36	30	26	23	16	10	4	1	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.25 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Ausschlag
 Safety Analysis Set, DC0 15FEB2024



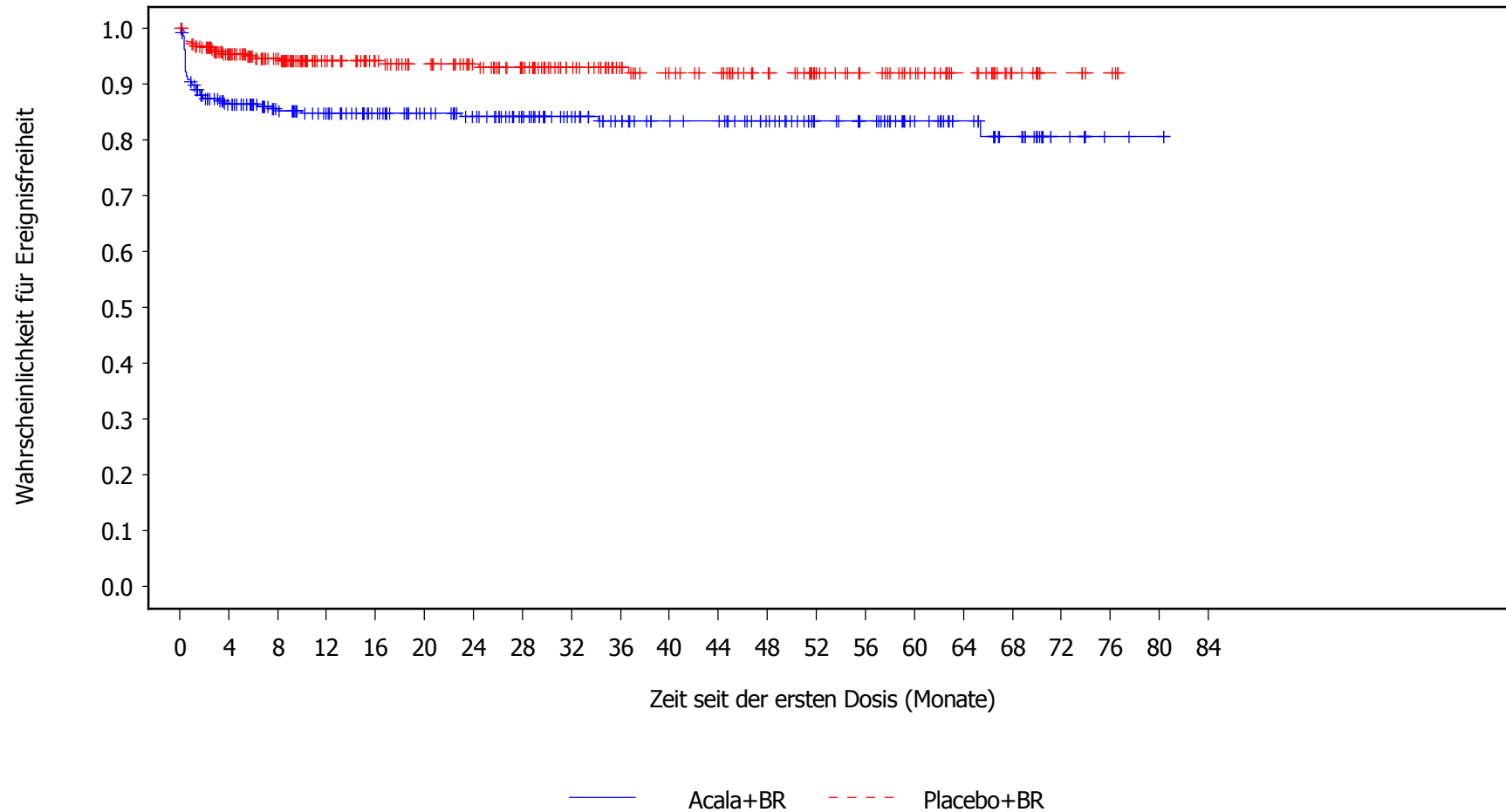
Anzahl an Patienten unter Risiko:

297	234	200	182	167	151	144	125	110	96	88	85	76	62	52	39	30	24	8	1	0	0	Acala+BR
297	238	207	172	154	143	133	119	101	89	80	76	67	54	46	39	27	15	5	2	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.26 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Ausschlag makulo-papuloes
 Safety Analysis Set, DCO 15FEB2024



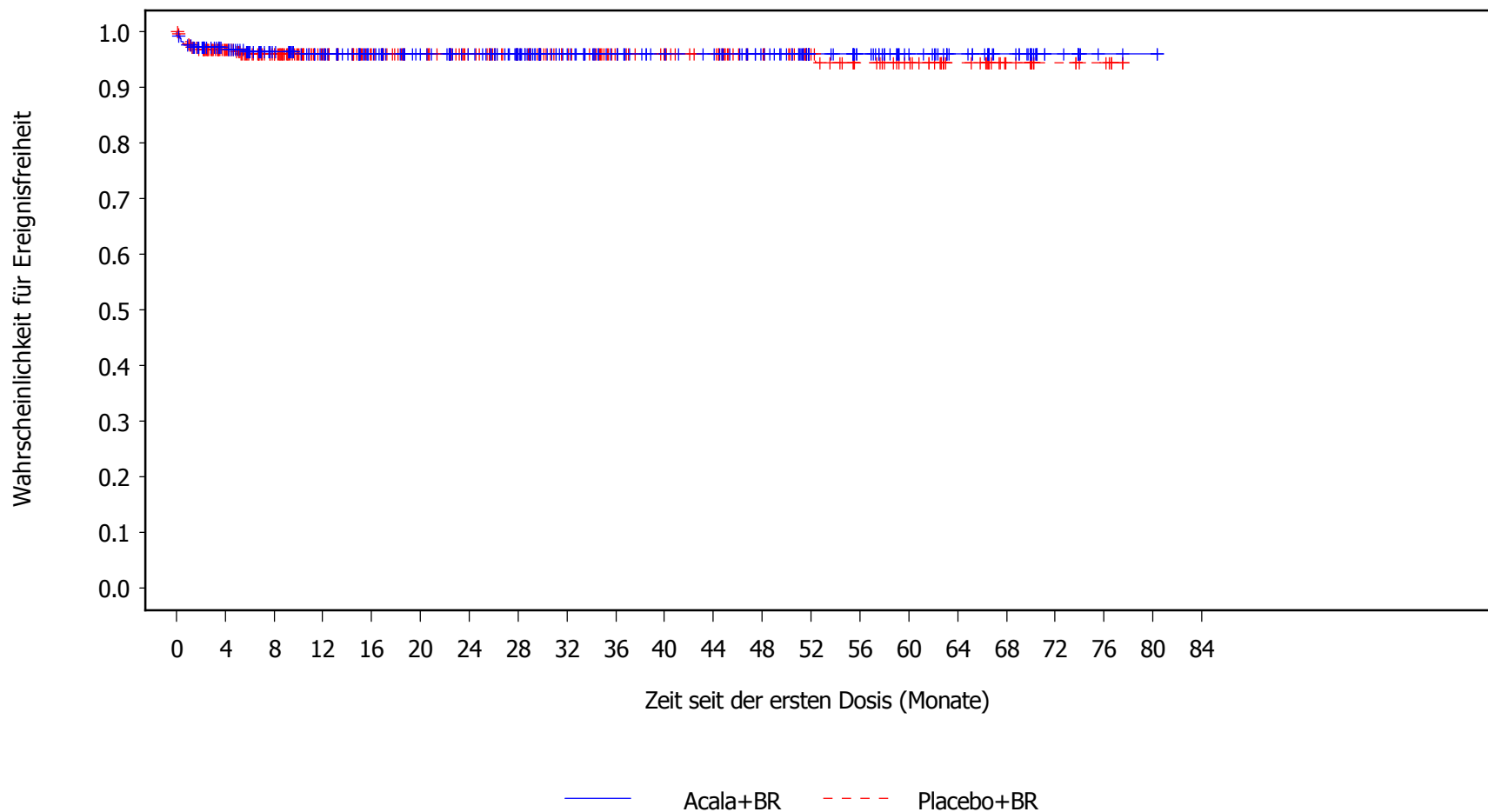
Anzahl an Patienten unter Risiko:

297	238	212	196	178	162	151	134	117	104	95	93	82	66	58	42	33	23	9	2	1	0	Acala+BR
297	255	225	189	172	160	146	130	111	97	87	83	72	59	51	43	29	16	6	3	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.27 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Ausschlag mit Juckreiz
 Safety Analysis Set, DC0 15FEB2024



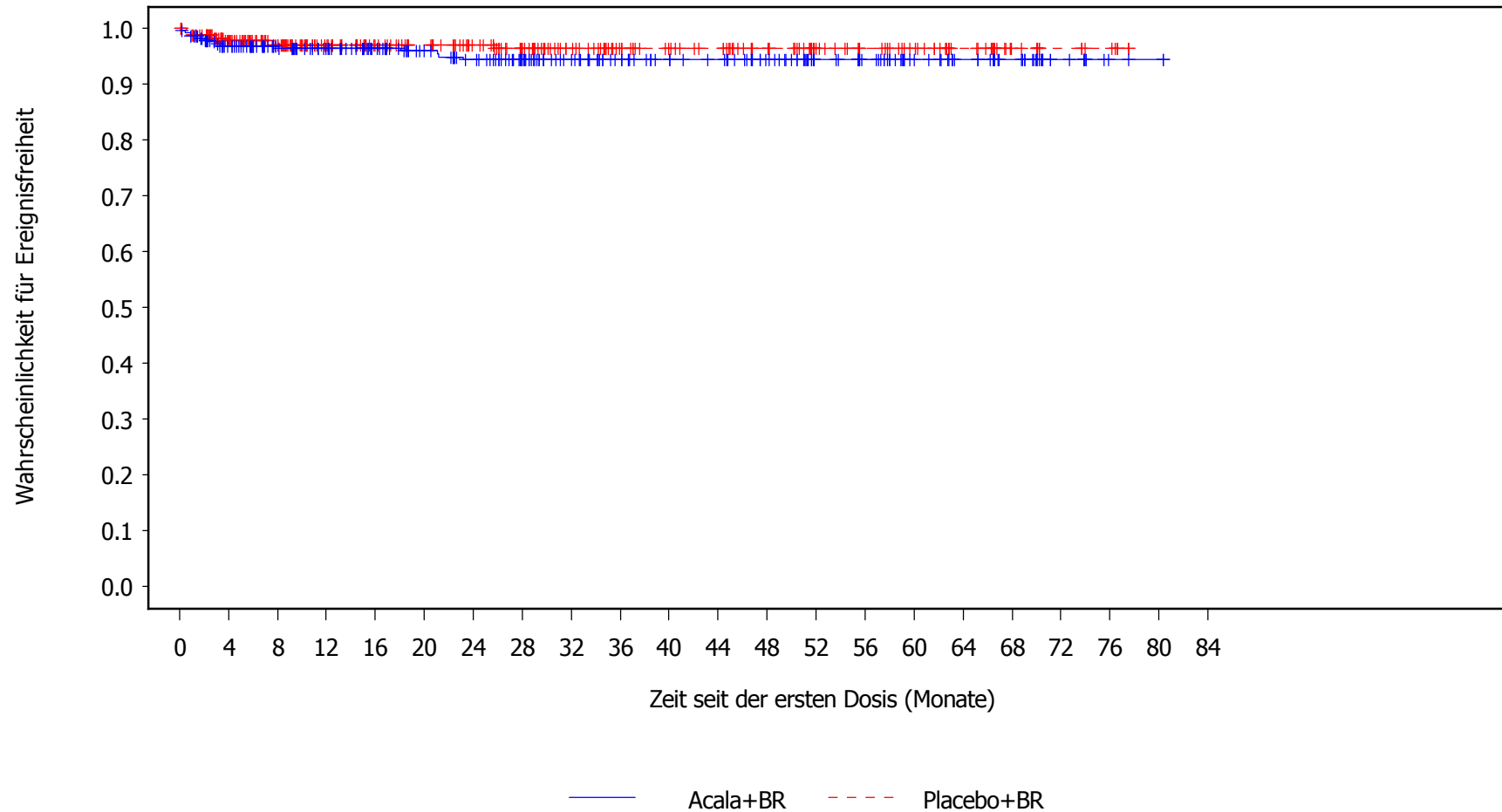
Anzahl an Patienten unter Risiko:

297	268	239	221	202	186	175	157	136	121	111	107	95	74	64	48	38	27	10	2	1	0	Acala+BR
297	258	227	194	175	163	149	133	116	102	95	90	78	61	51	43	29	16	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.28 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Erythem
 Safety Analysis Set, DC0 15FEB2024



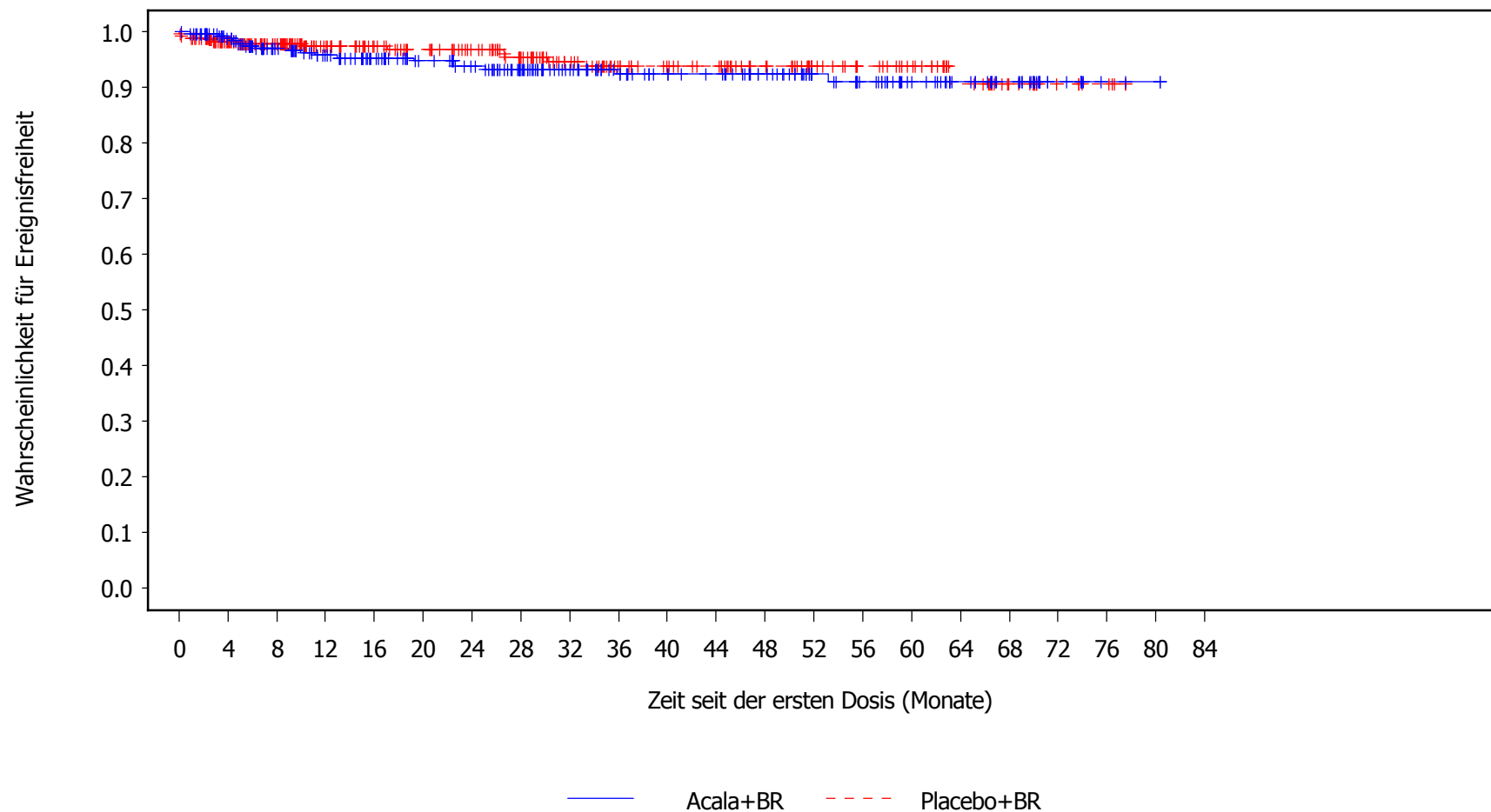
Anzahl an Patienten unter Risiko:

297	266	240	222	203	185	173	153	134	119	109	105	94	74	64	48	39	29	11	2	1	0	Acala+BR
297	261	230	198	179	167	153	137	118	103	94	89	78	61	52	44	30	16	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.29 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Hautlaesion
 Safety Analysis Set, DCO 15FEB2024



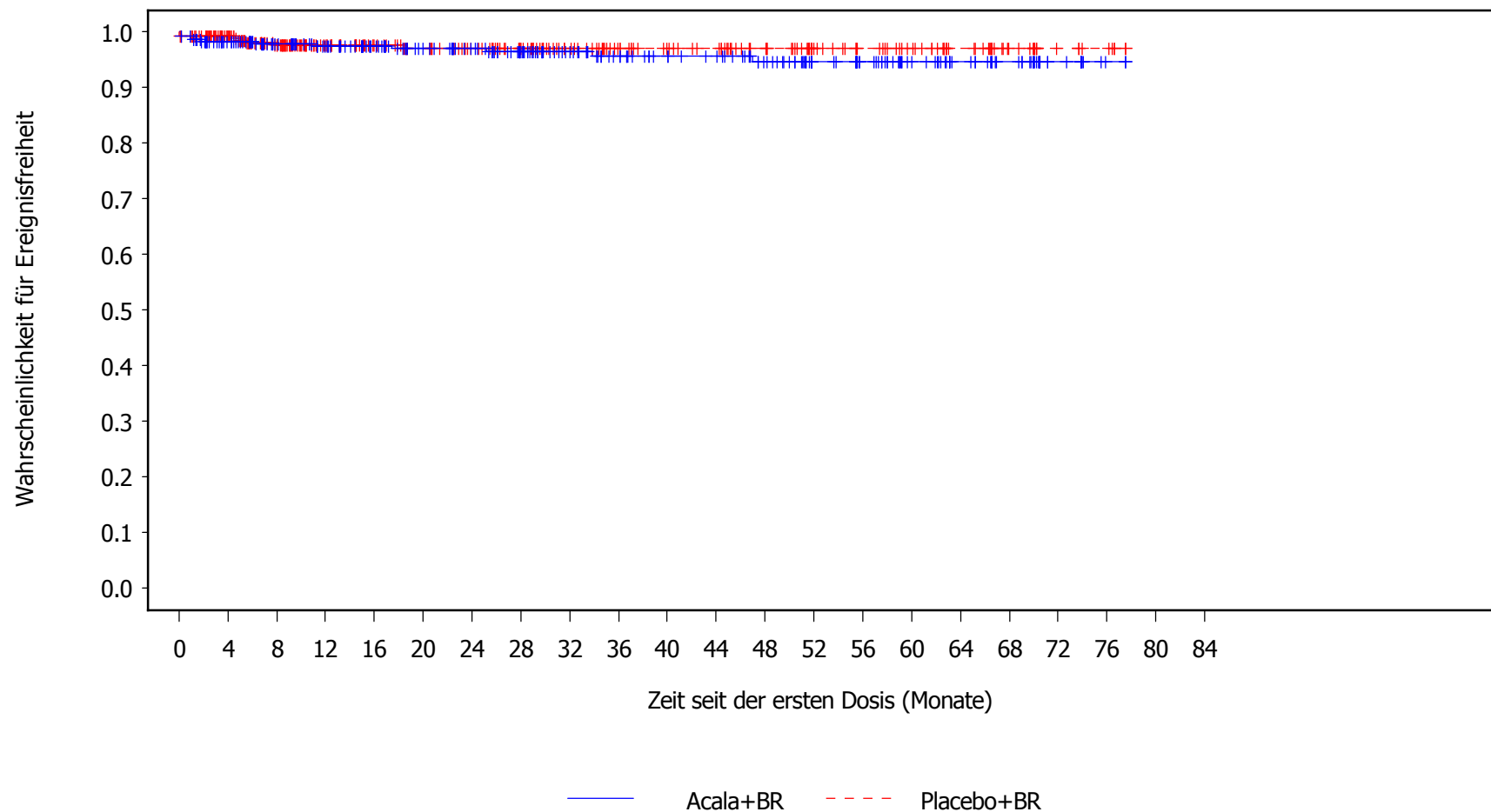
Anzahl an Patienten unter Risiko:

297	272	240	221	201	184	172	152	131	115	105	101	91	72	62	48	38	28	10	2	1	0	Acala+BR
297	262	232	196	178	165	152	134	114	98	90	85	73	58	50	43	28	17	7	4	0	0	Placebo+BR

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Figure 3.3.1.30 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Naechtliche Schweissausbrueche
 Safety Analysis Set, DCO 15FEB2024



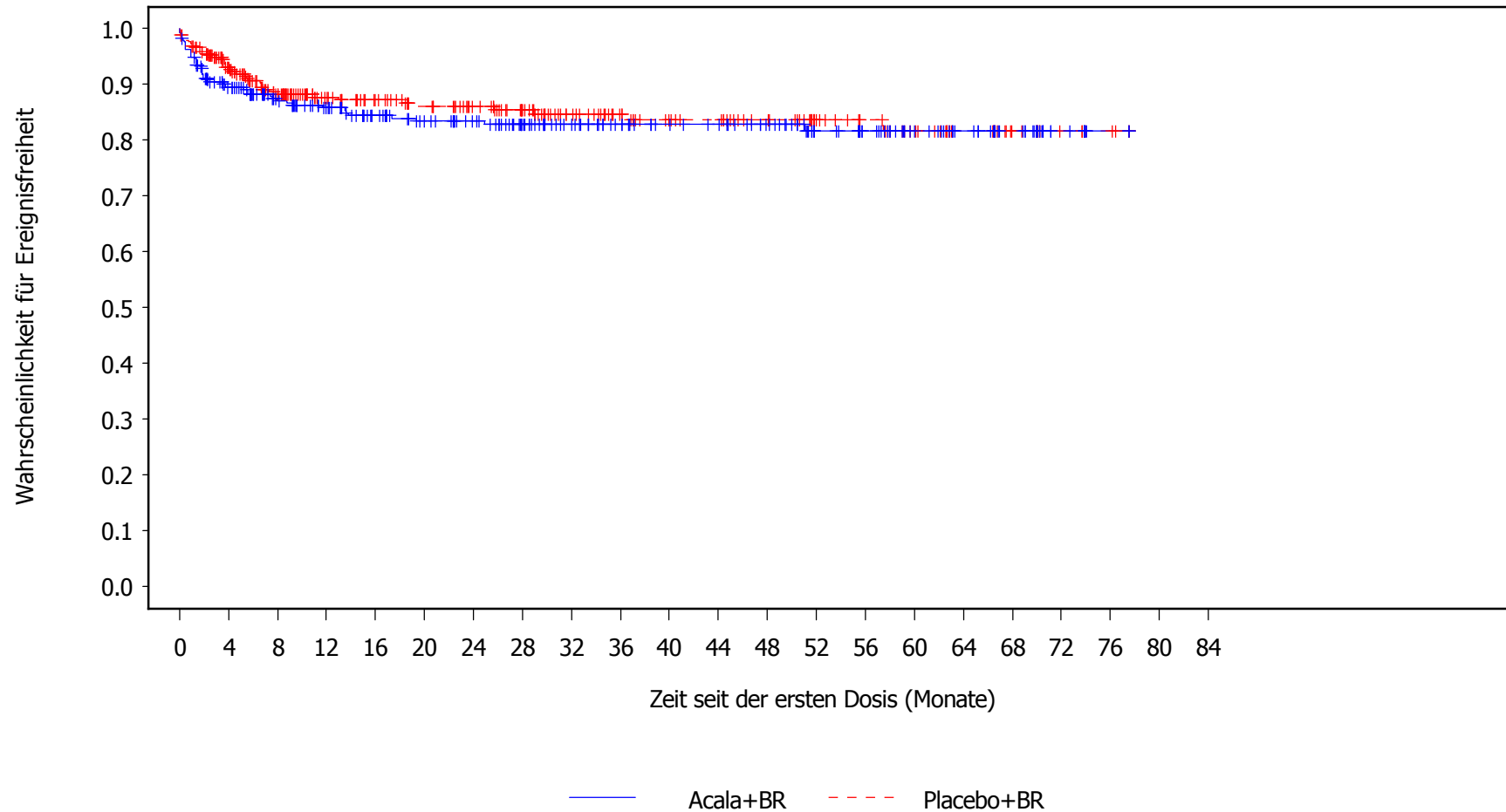
Anzahl an Patienten unter Risiko:

297	271	243	225	206	188	177	158	137	122	112	108	96	76	65	48	37	27	10	1	0	0	Acala+BR
297	265	232	198	180	168	156	140	121	107	98	93	81	64	55	47	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.31 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Pruritus
 Safety Analysis Set, DC0 15FEB2024



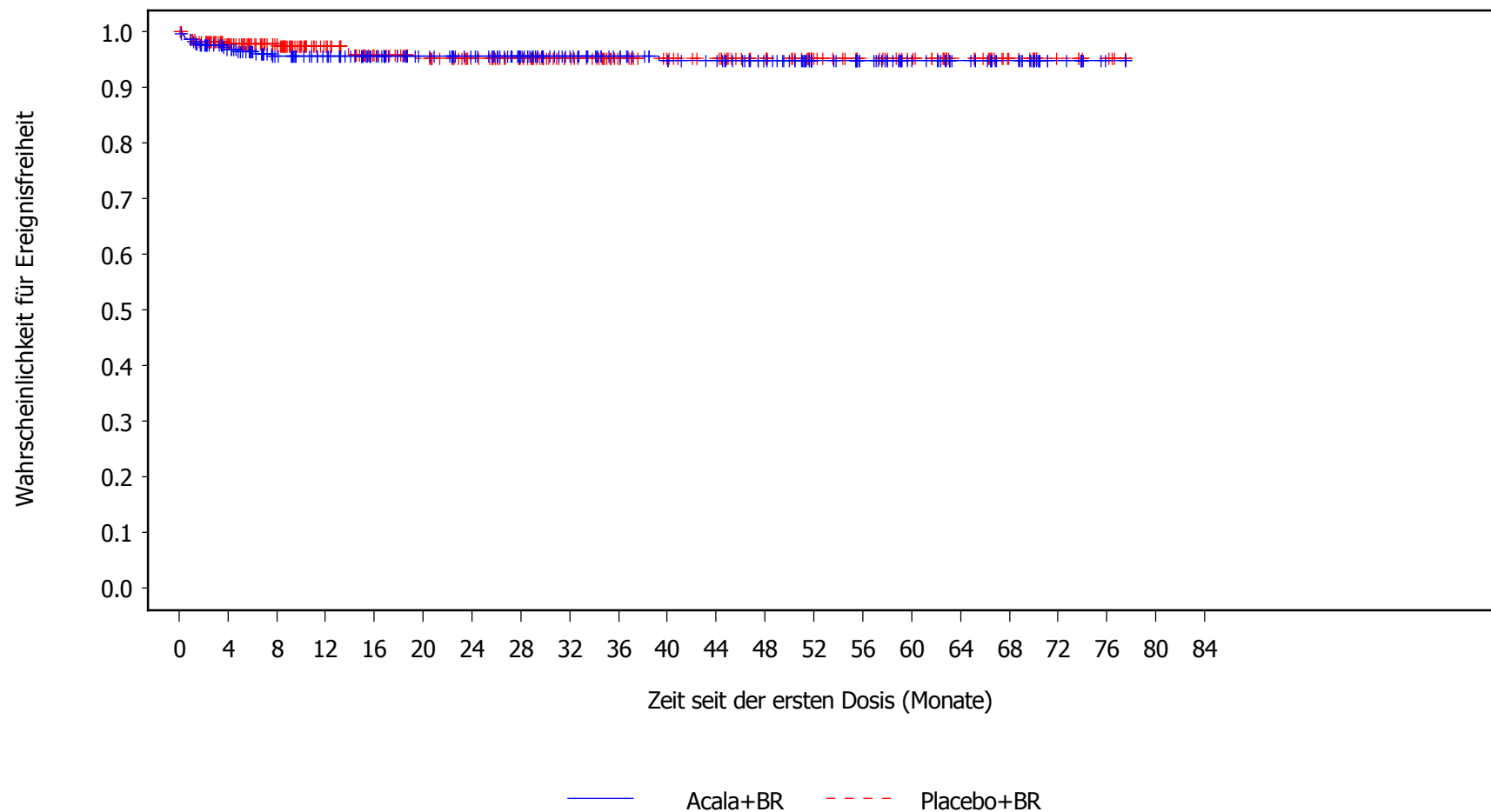
Anzahl an Patienten unter Risiko:

297	246	214	195	175	160	150	133	118	105	96	93	84	66	56	43	34	24	8	1	0	0	Acala+BR
297	248	208	175	160	147	135	120	100	87	77	74	65	51	44	36	25	15	6	3	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.32 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Trockene Haut
 Safety Analysis Set, DC0 15FEB2024



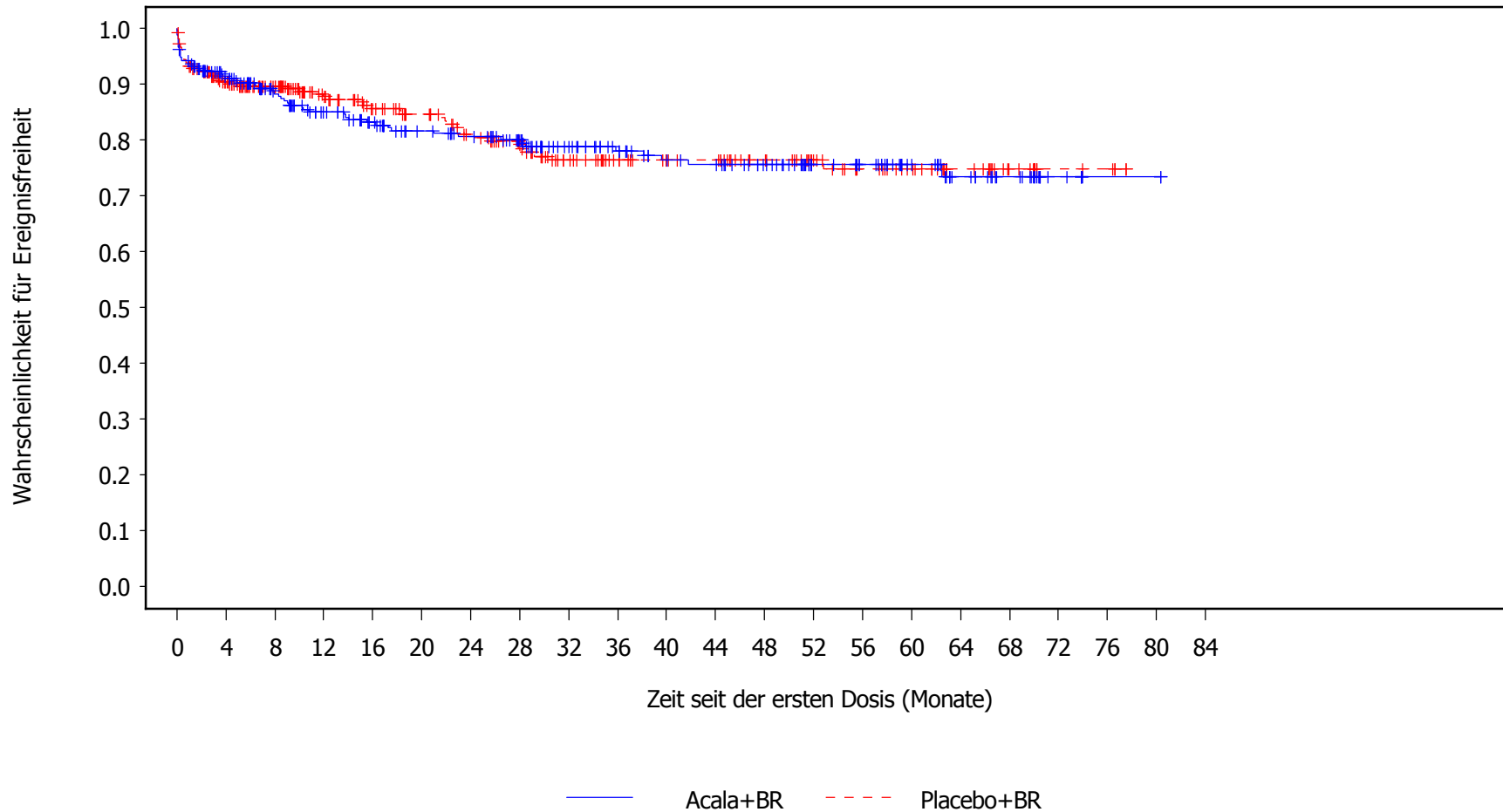
Anzahl an Patienten unter Risiko:

297	268	240	224	204	188	177	157	137	122	112	108	96	75	64	48	38	28	10	1	0	0	Acala+BR
297	261	232	198	177	164	150	135	117	102	93	88	77	61	52	44	31	18	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.33 ECHO: Kaplan-Meier plot of time to first occurrence of SOC: Erkrankungen der Nieren und Harnwege
 Safety Analysis Set, DCO 15FEB2024



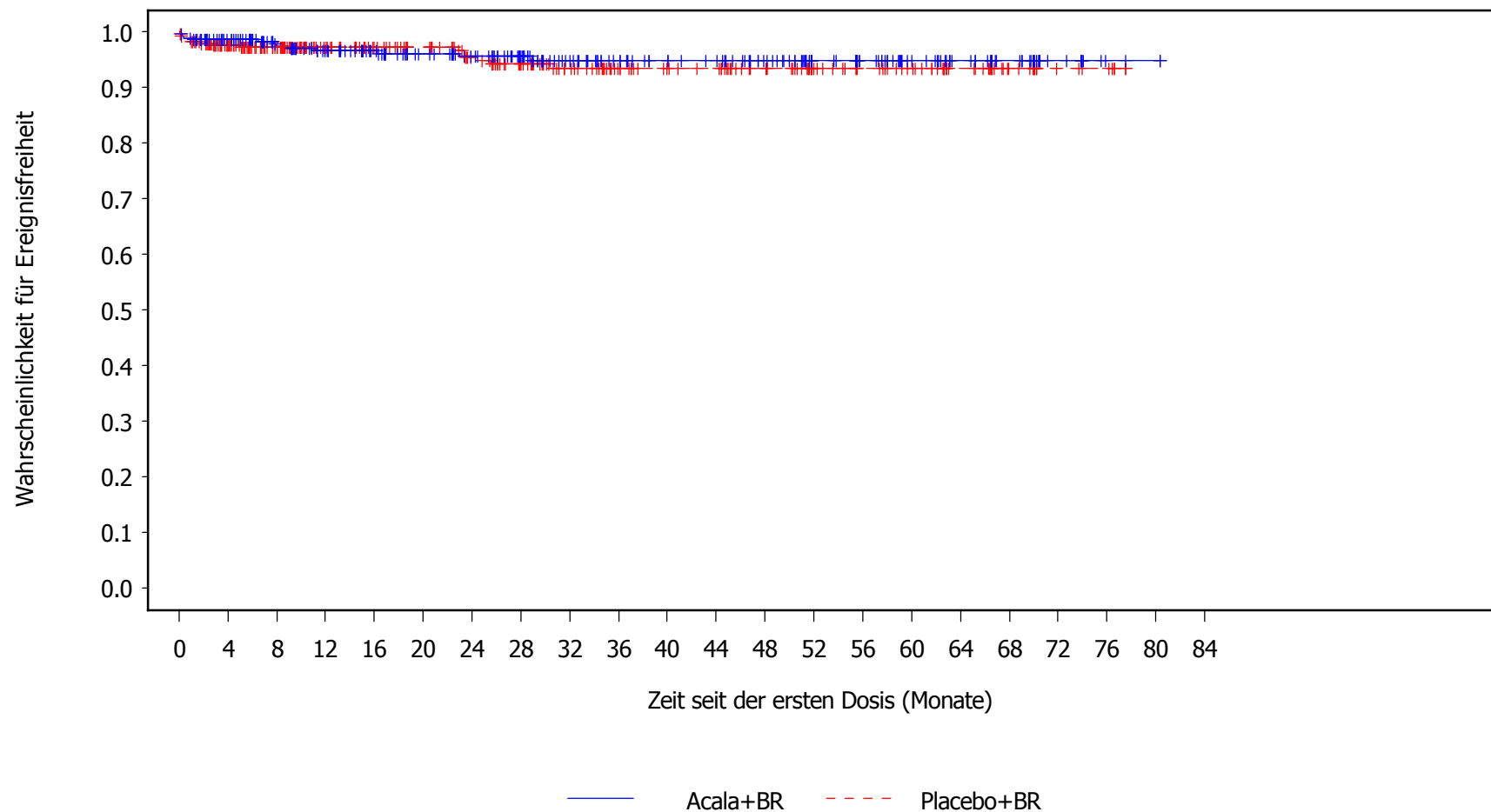
Anzahl an Patienten unter Risiko:

297	250	216	192	174	158	150	134	114	101	90	87	77	60	54	40	29	21	7	1	1	0	Acala+BR
297	245	216	182	162	149	134	119	99	87	79	77	66	54	44	37	24	14	5	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.34 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Akute Nierenschädigung
 Safety Analysis Set, DC0 15FEB2024



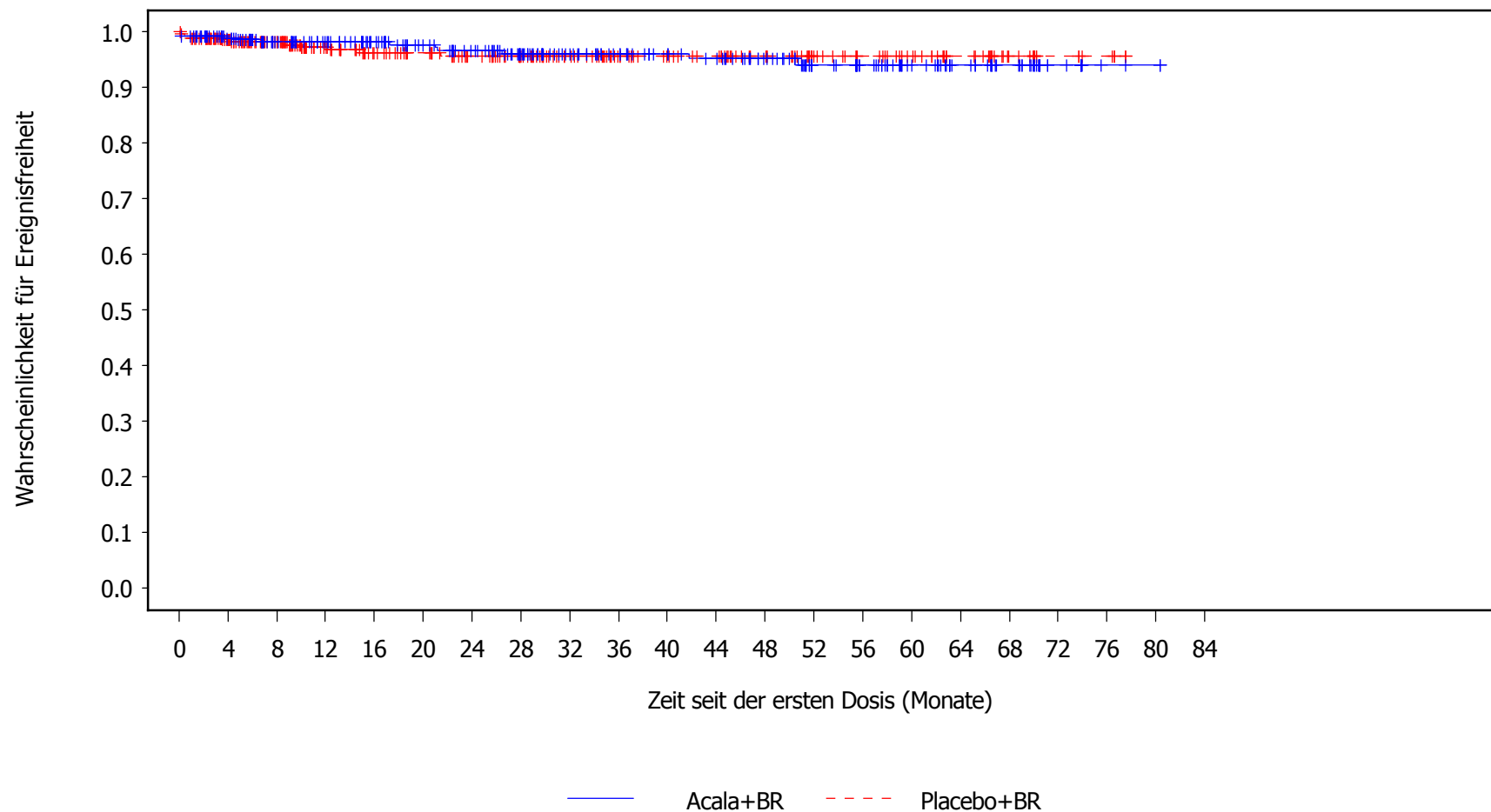
Anzahl an Patienten unter Risiko:

297	271	241	223	205	189	177	158	137	122	113	109	97	76	65	49	38	27	11	2	1	0	Acala+BR
297	263	234	201	184	172	155	138	119	104	95	92	80	63	54	47	32	18	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.35 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Dysurie
 Safety Analysis Set, DCO 15FEB2024



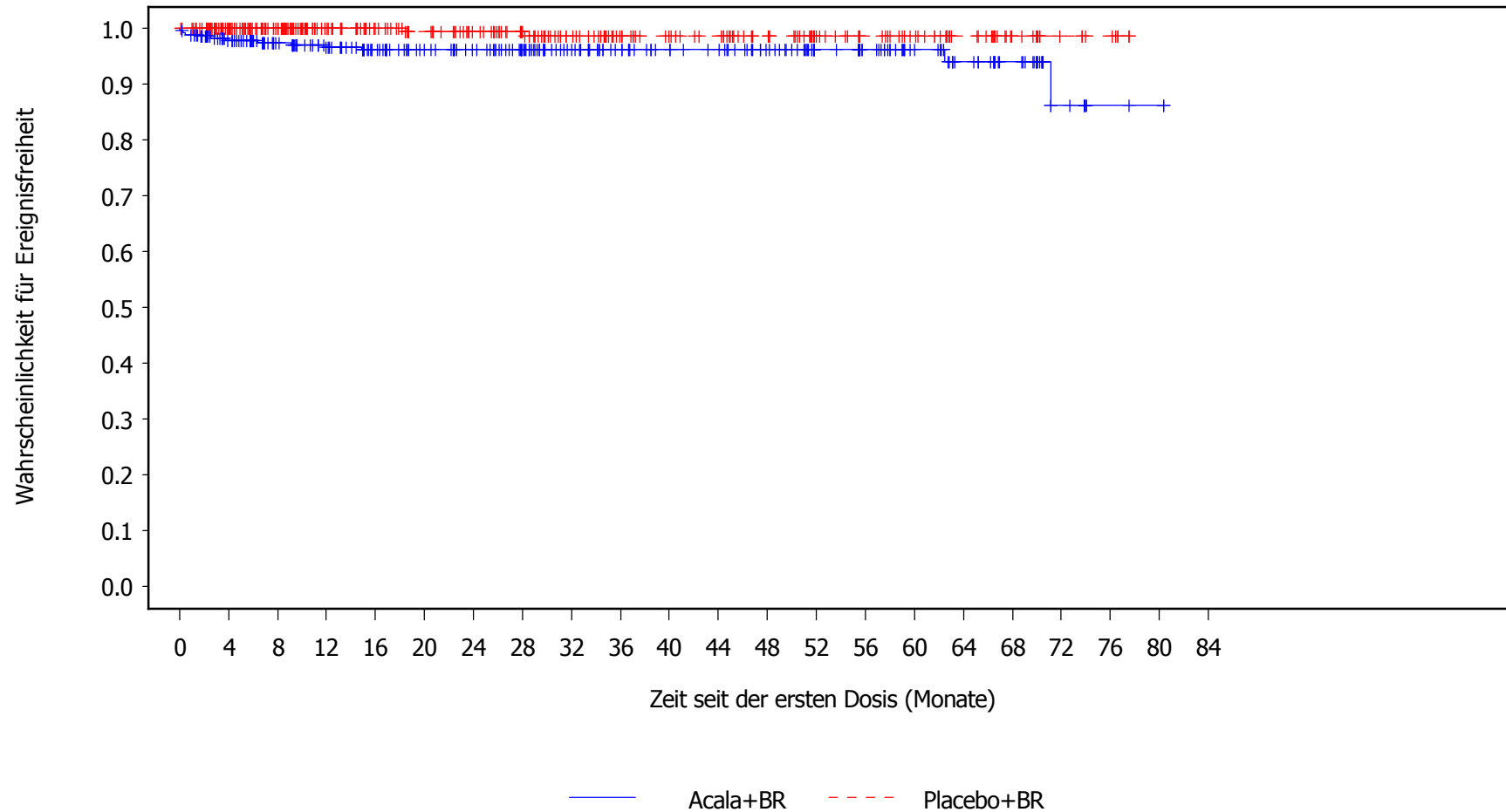
Anzahl an Patienten unter Risiko:

297	272	243	226	208	190	177	155	135	122	112	107	95	74	63	47	36	26	9	2	1	0	Acala+BR
297	263	233	198	178	166	152	138	119	104	95	90	78	61	52	44	30	16	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.36 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Haematurie
 Safety Analysis Set, DCO 15FEB2024



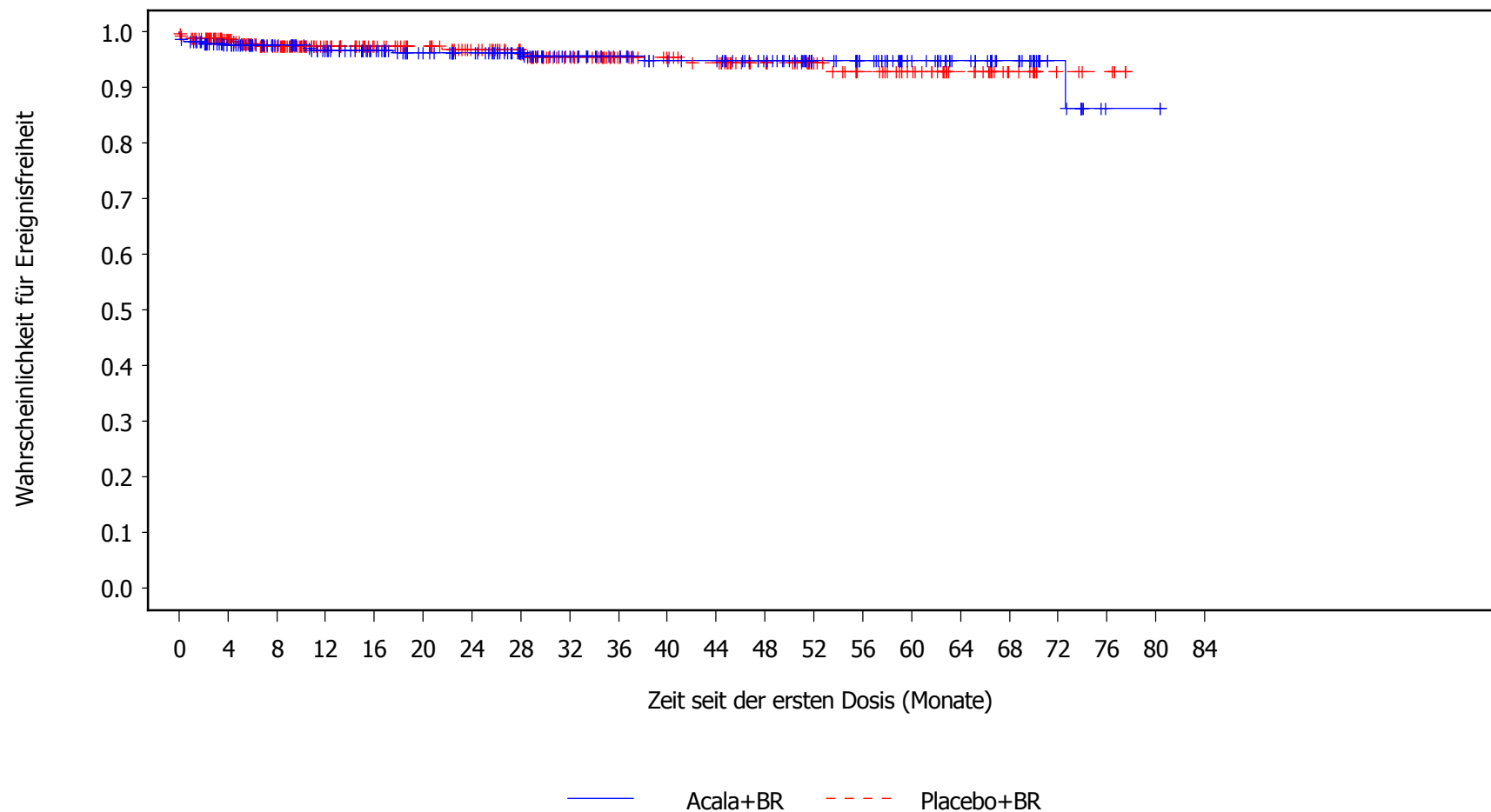
Anzahl an Patienten unter Risiko:

297	269	241	222	201	184	174	156	135	120	110	106	94	75	65	49	38	27	9	2	1	0	Acala+BR
297	267	238	203	184	171	157	141	122	107	98	93	81	64	55	47	32	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.37 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Pollakisurie
 Safety Analysis Set, DCO 15FEB2024



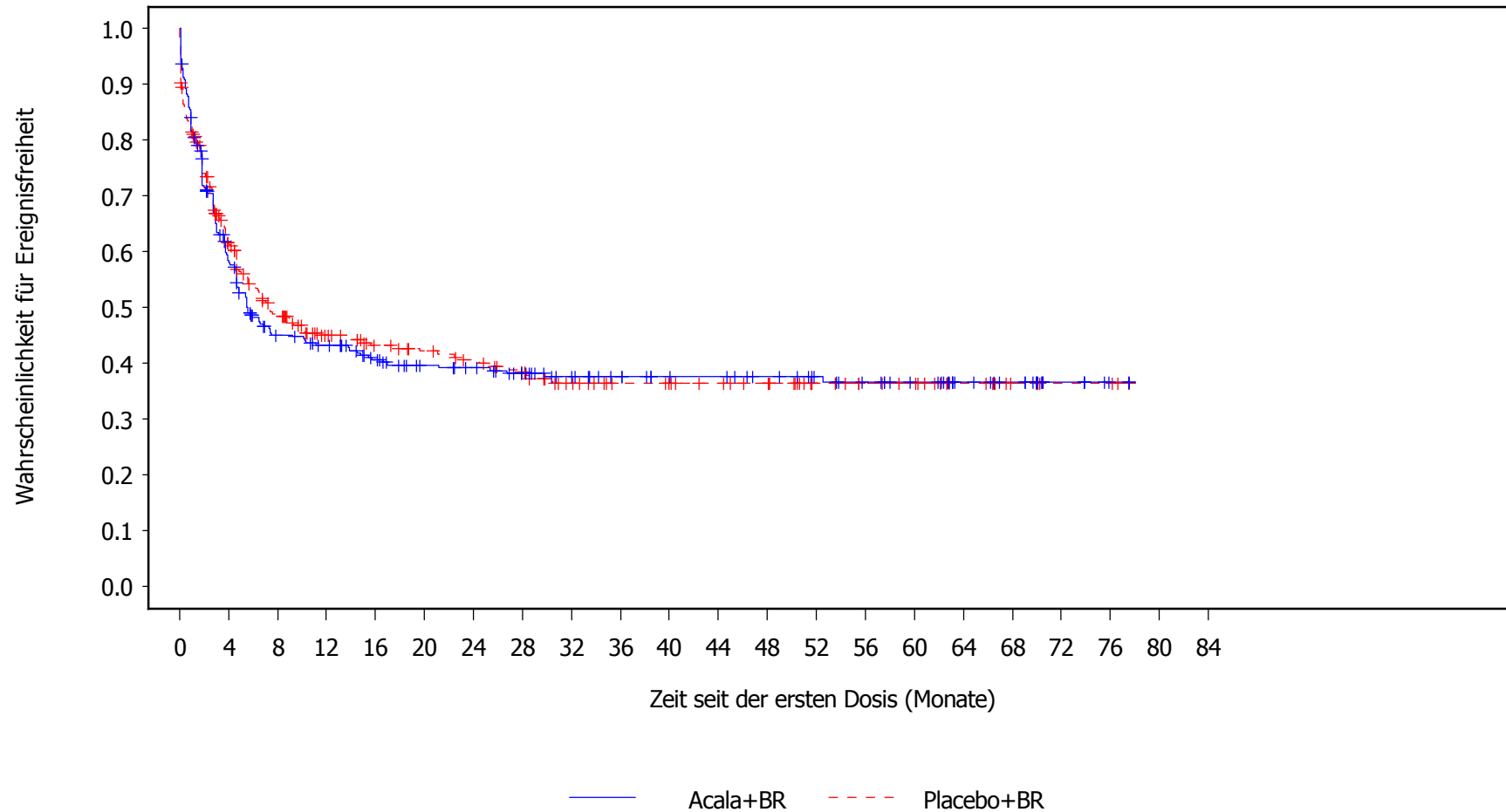
Anzahl an Patienten unter Risiko:

297	268	241	222	204	187	178	157	136	122	111	109	98	77	67	50	39	28	11	1	1	0	Acala+BR
297	263	231	197	179	168	154	138	119	104	95	90	78	62	52	44	29	17	6	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.38 ECH0: Kaplan-Meier plot of time to first occurrence of SOC: Erkrankungen des Blutes und des Lymphsystems
 Safety Analysis Set, DCO 15FEB2024



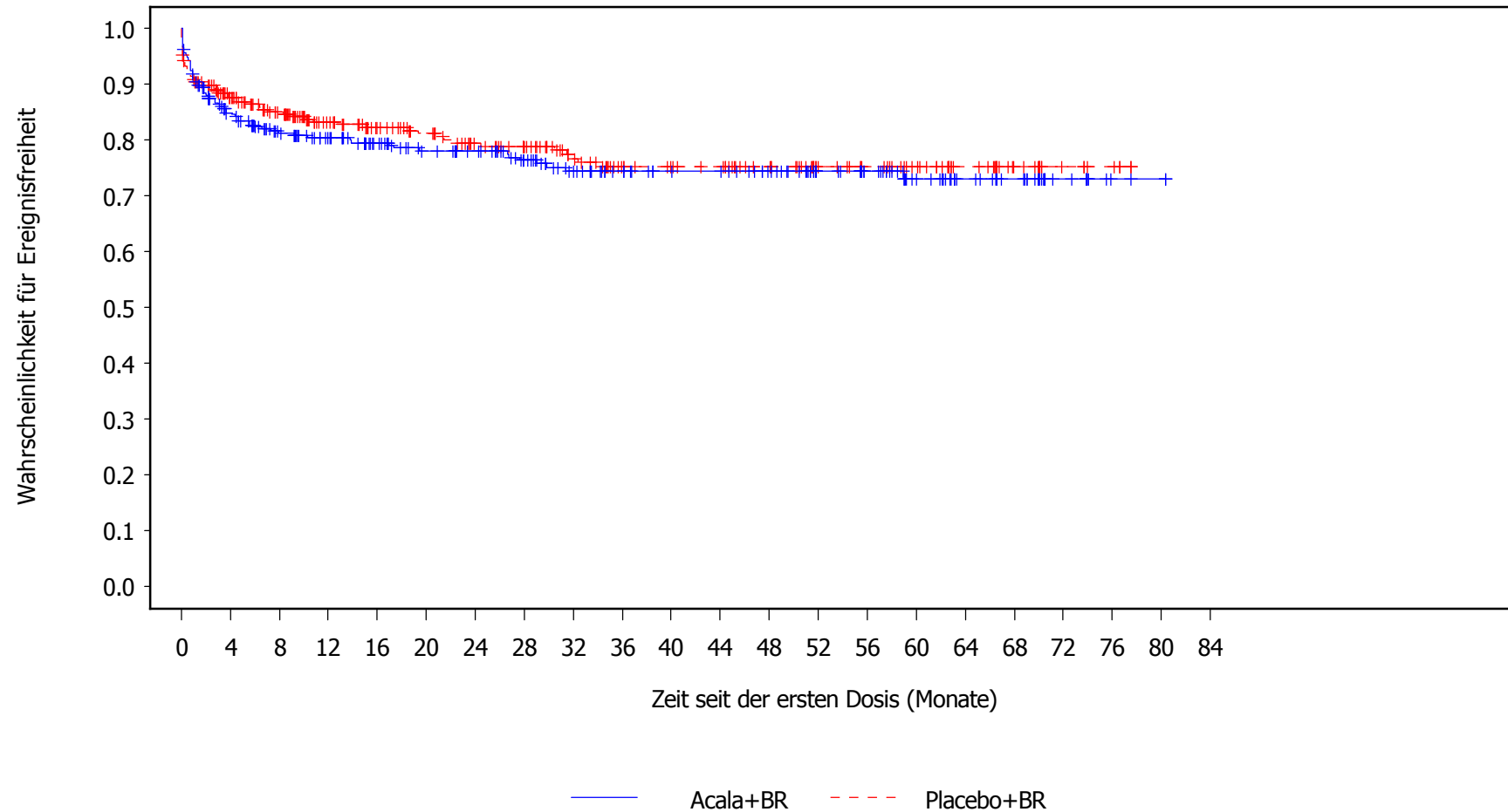
Anzahl an Patienten unter Risiko:

297	163	116	107	92	81	77	68	60	54	49	48	44	39	35	30	21	17	6	1	0	0	Acala+BR
297	168	125	100	87	81	75	65	55	48	46	43	40	29	25	23	15	8	3	3	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.39 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Anaemie
 Safety Analysis Set, DC0 15FEB2024



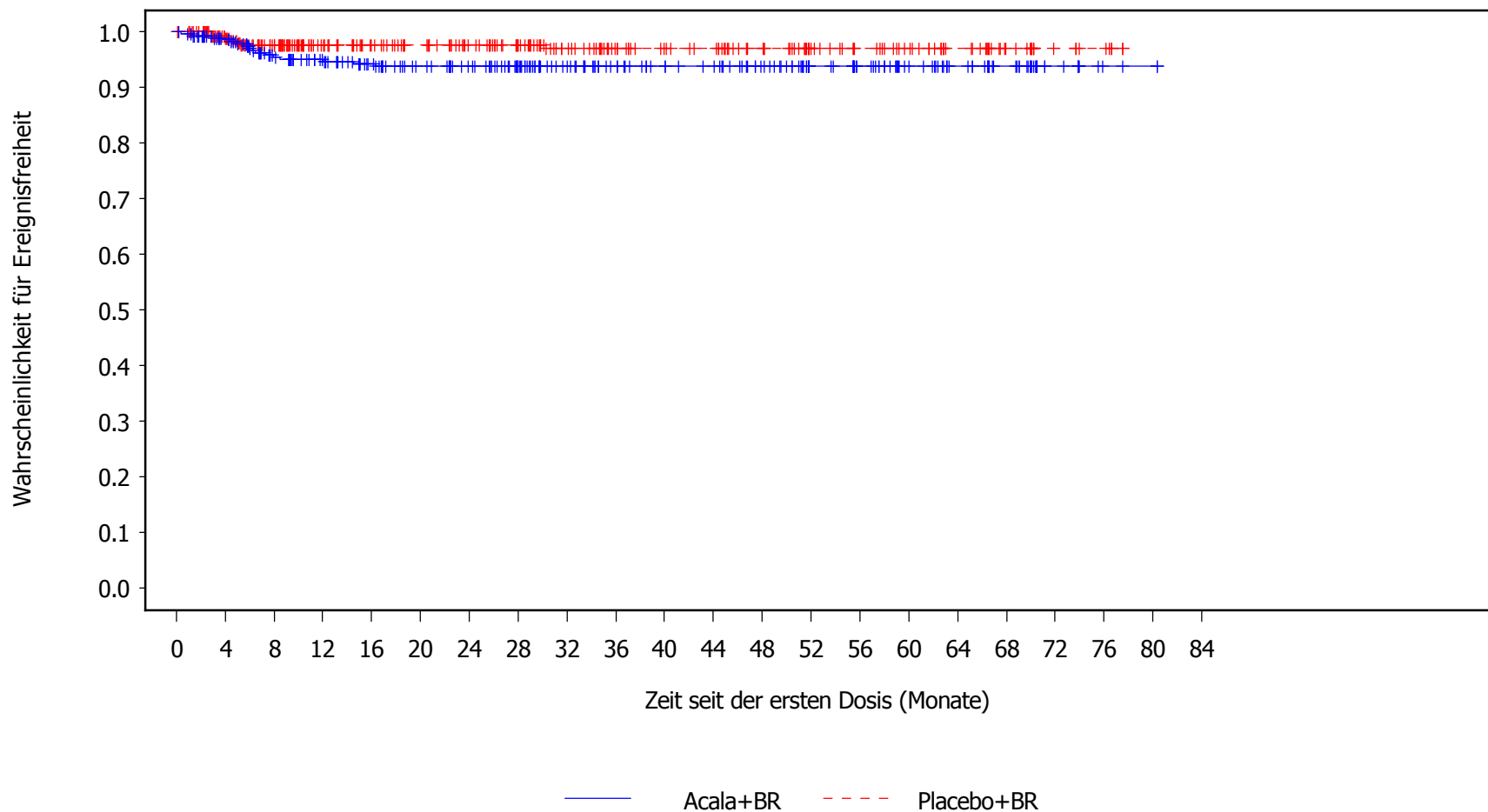
Anzahl an Patienten unter Risiko:

297	235	206	190	171	156	148	129	114	103	96	95	87	70	61	45	34	27	11	2	1	0	Acala+BR
297	238	210	178	160	147	132	122	104	90	85	82	72	57	50	42	29	17	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.40 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Febrile Neutropenie
 Safety Analysis Set, DCO 15FEB2024



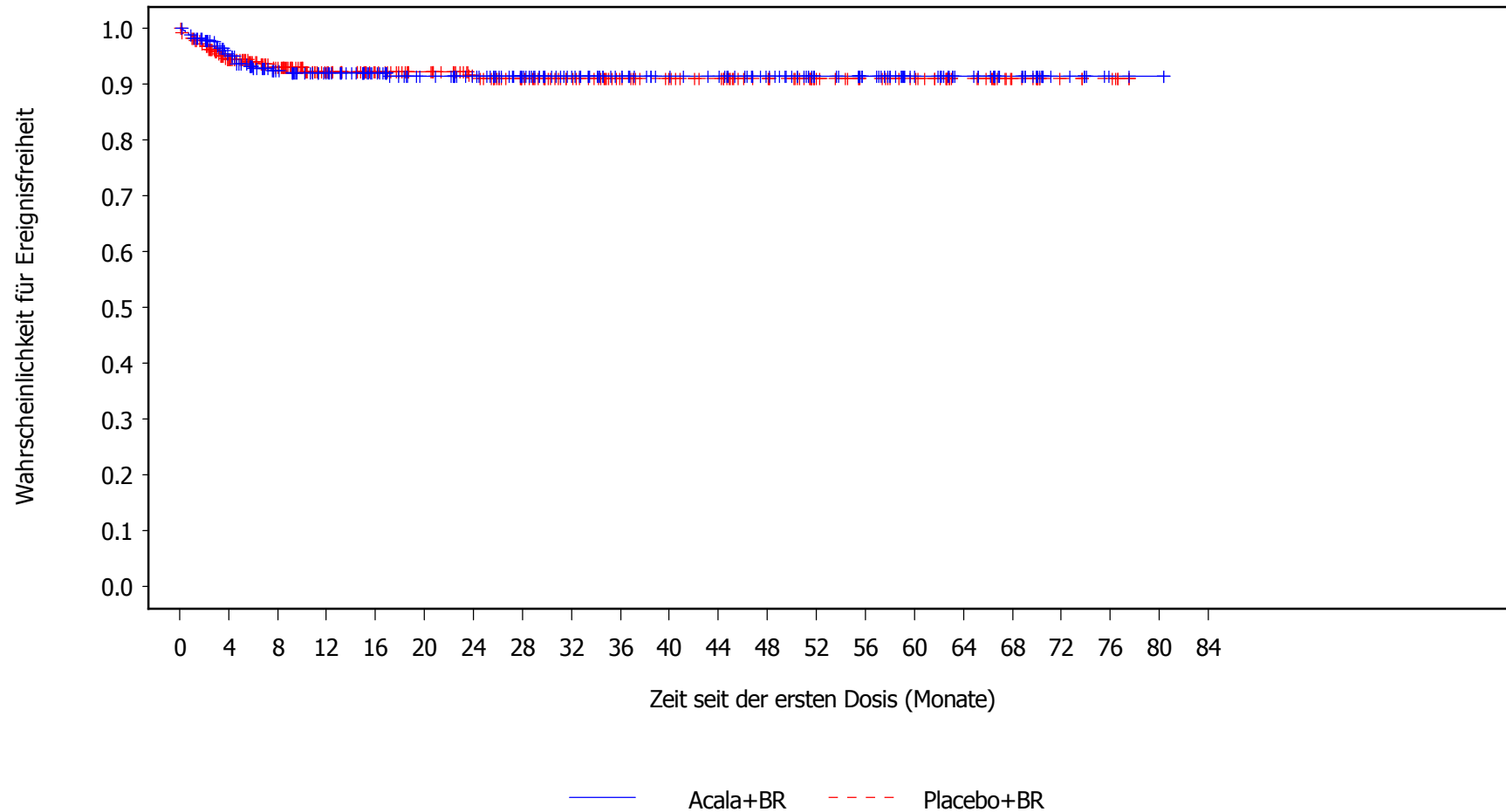
Anzahl an Patienten unter Risiko:

297	273	238	221	202	187	176	157	137	122	113	109	97	77	66	50	39	28	10	2	1	0	Acala+BR
297	266	234	200	183	171	157	141	121	106	97	93	81	64	55	47	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.41 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Leukopenie
 Safety Analysis Set, DCO 15FEB2024



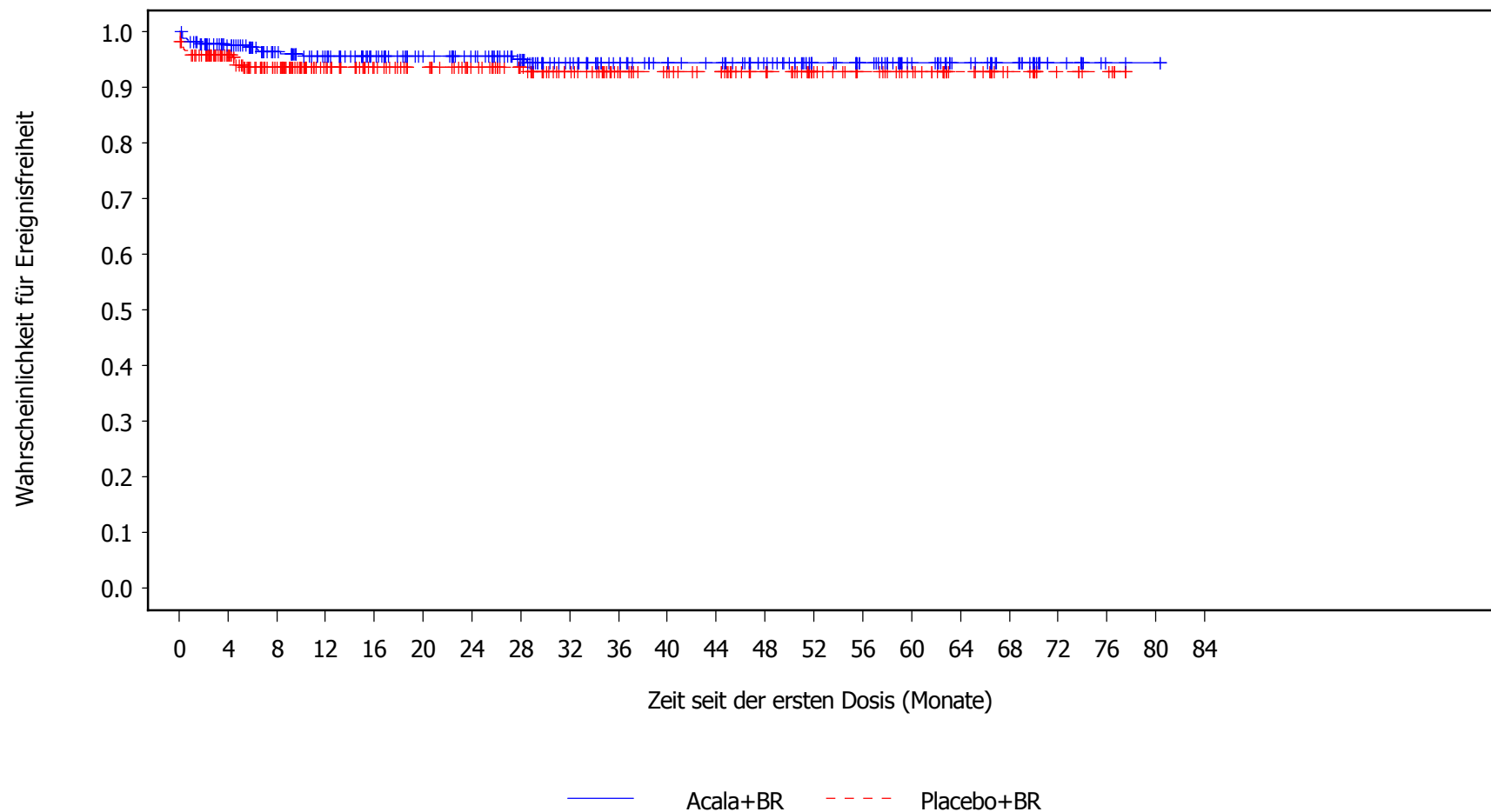
Anzahl an Patienten unter Risiko:

297	262	229	212	193	177	168	150	132	117	107	104	93	75	64	47	37	26	10	2	1	0	Acala+BR
297	252	220	188	171	159	143	128	112	98	91	86	75	59	51	45	32	18	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.42 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Lymphopenie
 Safety Analysis Set, DCO 15FEB2024



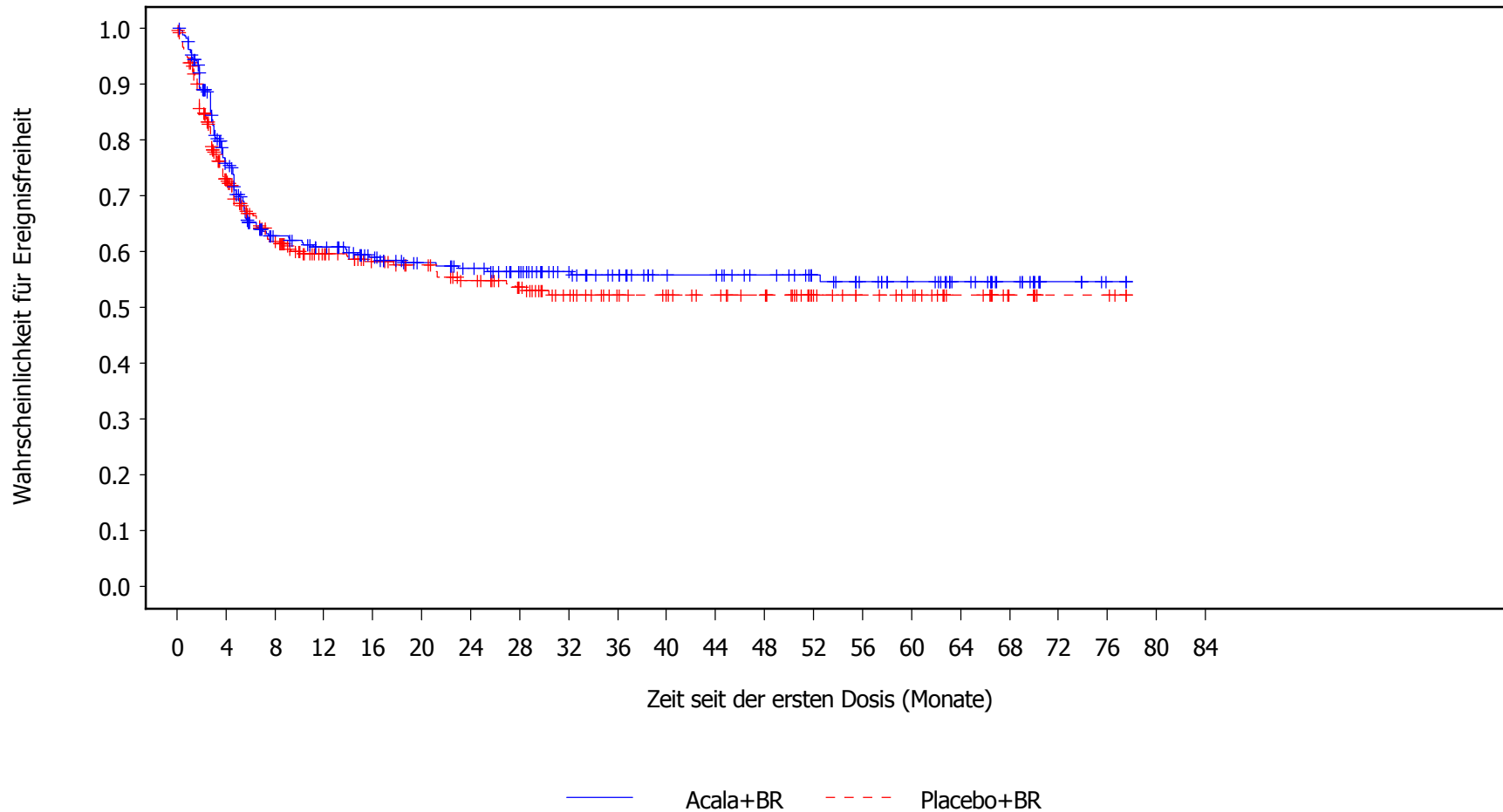
Anzahl an Patienten unter Risiko:

297	268	239	220	200	183	173	153	133	118	108	104	93	73	64	47	37	28	11	2	1	0	Acala+BR
297	255	221	190	172	161	148	134	117	102	93	88	77	61	52	44	29	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.43 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Neutropenie
 Safety Analysis Set, DCO 15FEB2024



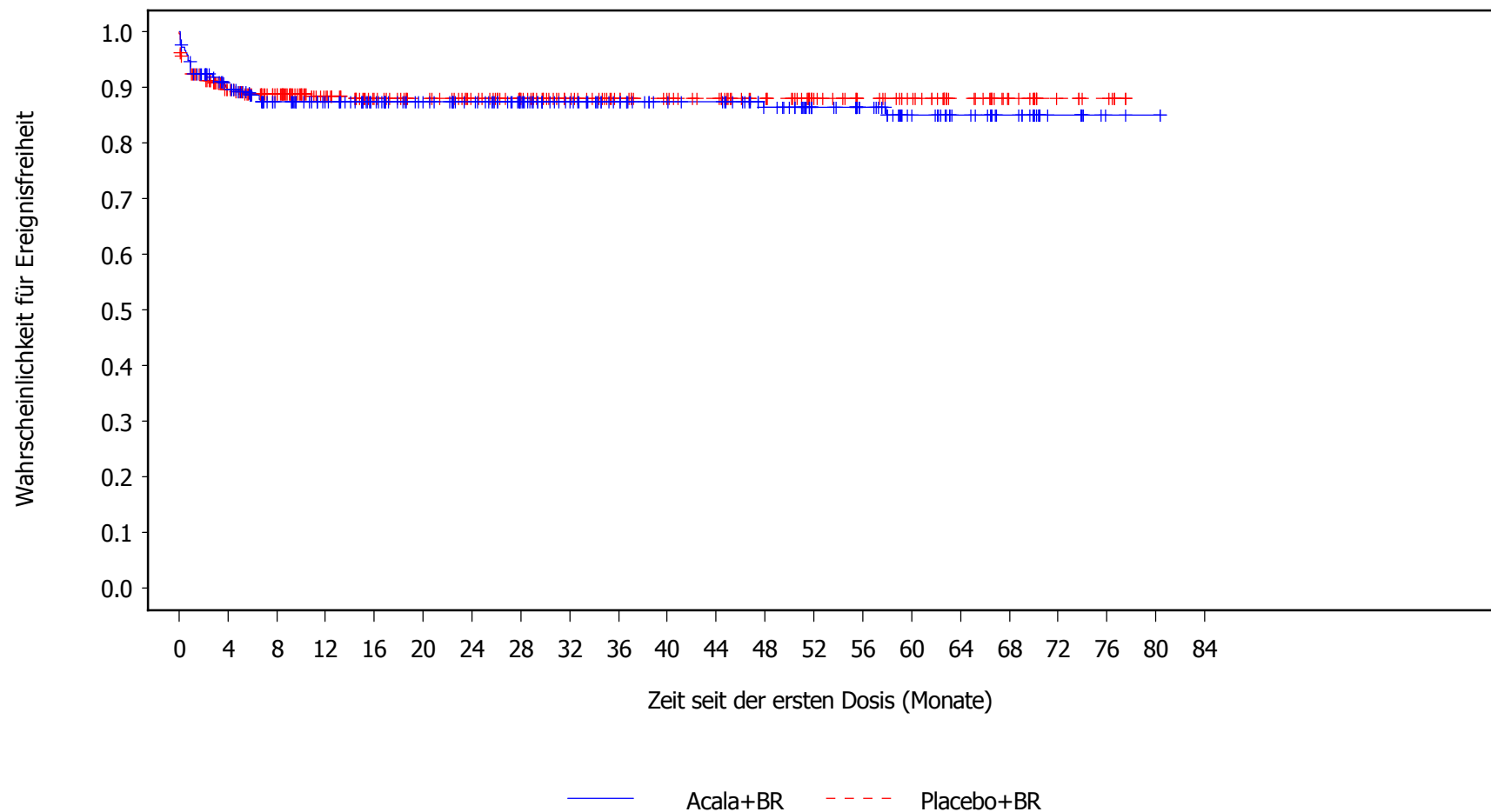
Anzahl an Patienten unter Risiko:

297	206	154	142	125	113	107	96	83	74	65	64	58	49	42	36	27	18	6	1	0	0	Acala+BR
297	194	149	125	112	106	95	83	70	61	57	53	49	36	30	27	17	9	3	3	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.44 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Thrombozytopenie
 Safety Analysis Set, DCO 15FEB2024



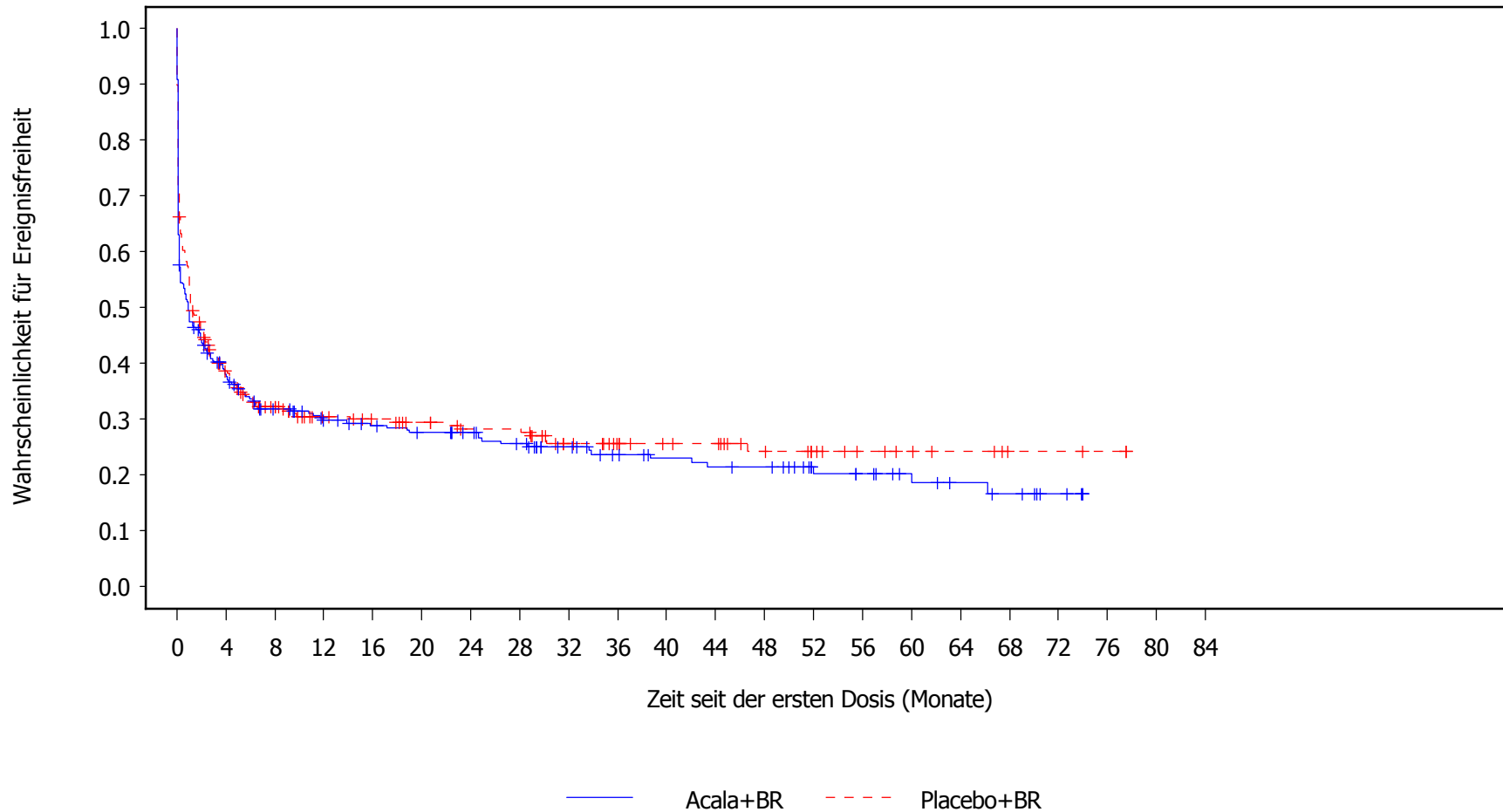
Anzahl an Patienten unter Risiko:

297	250	221	206	190	174	165	147	130	115	105	103	91	73	63	45	35	25	10	2	1	0	Acala+BR
297	242	218	186	166	155	144	131	114	102	94	89	78	62	53	46	31	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.45 ECH0: Kaplan-Meier plot of time to first occurrence of SOC: Erkrankungen des Gastrointestinaltrakts
 Safety Analysis Set, DCO 15FEB2024



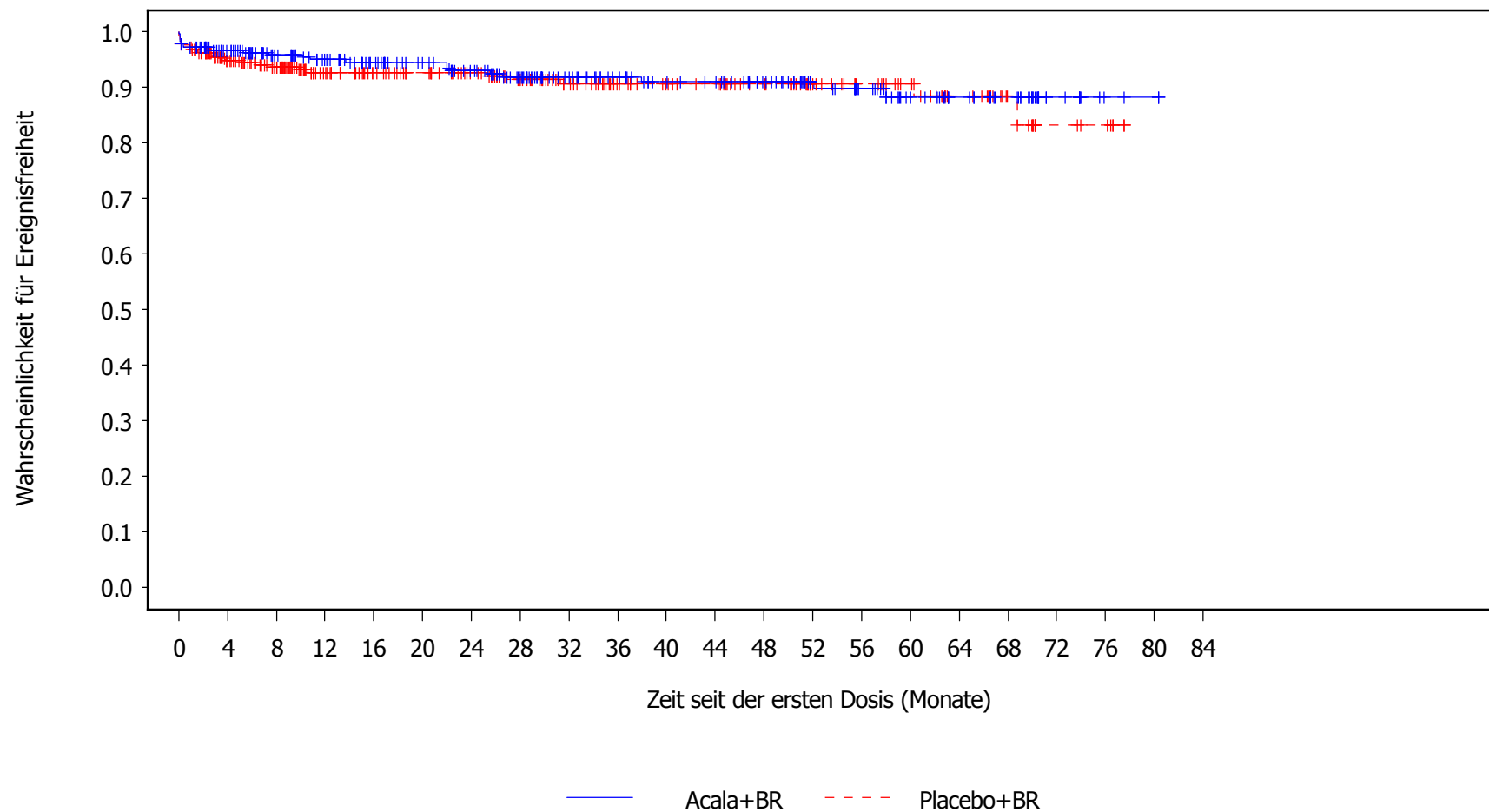
Anzahl an Patienten unter Risiko:

297	106	82	71	66	61	57	50	41	34	30	28	27	19	16	12	9	7	3	0	0	0	Acala+BR
297	105	79	63	58	53	47	47	34	28	24	23	17	13	9	7	5	2	2	1	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.46 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Abdominalschmerz
 Safety Analysis Set, DCO 15FEB2024



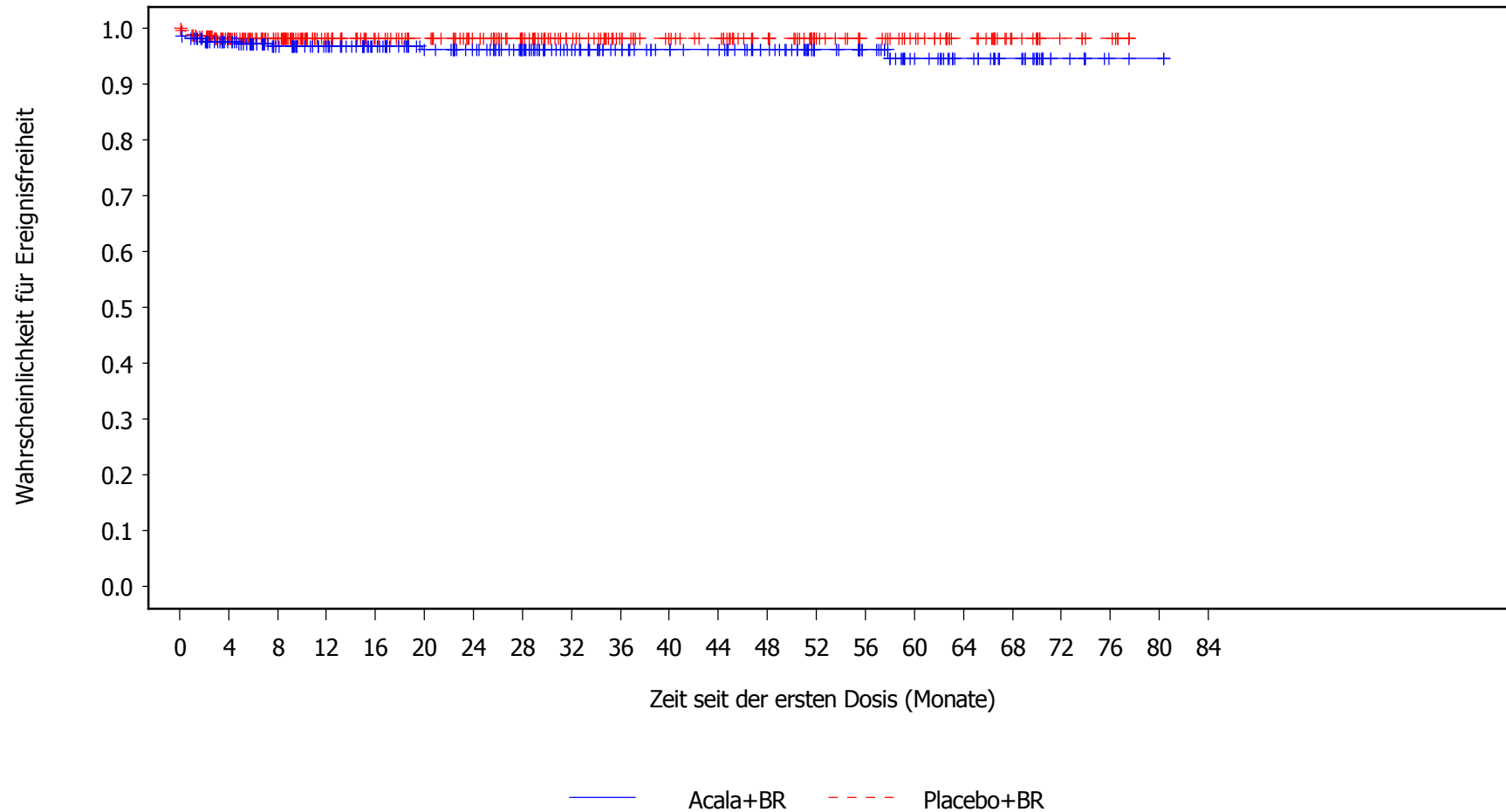
Anzahl an Patienten unter Risiko:

297	268	240	222	201	186	172	152	132	118	107	104	93	73	61	46	37	29	11	2	1	0	Acala+BR
297	254	227	191	175	163	150	132	113	99	91	87	77	61	52	45	30	17	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.47 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Bauch aufgetrieben
 Safety Analysis Set, DC0 15FEB2024



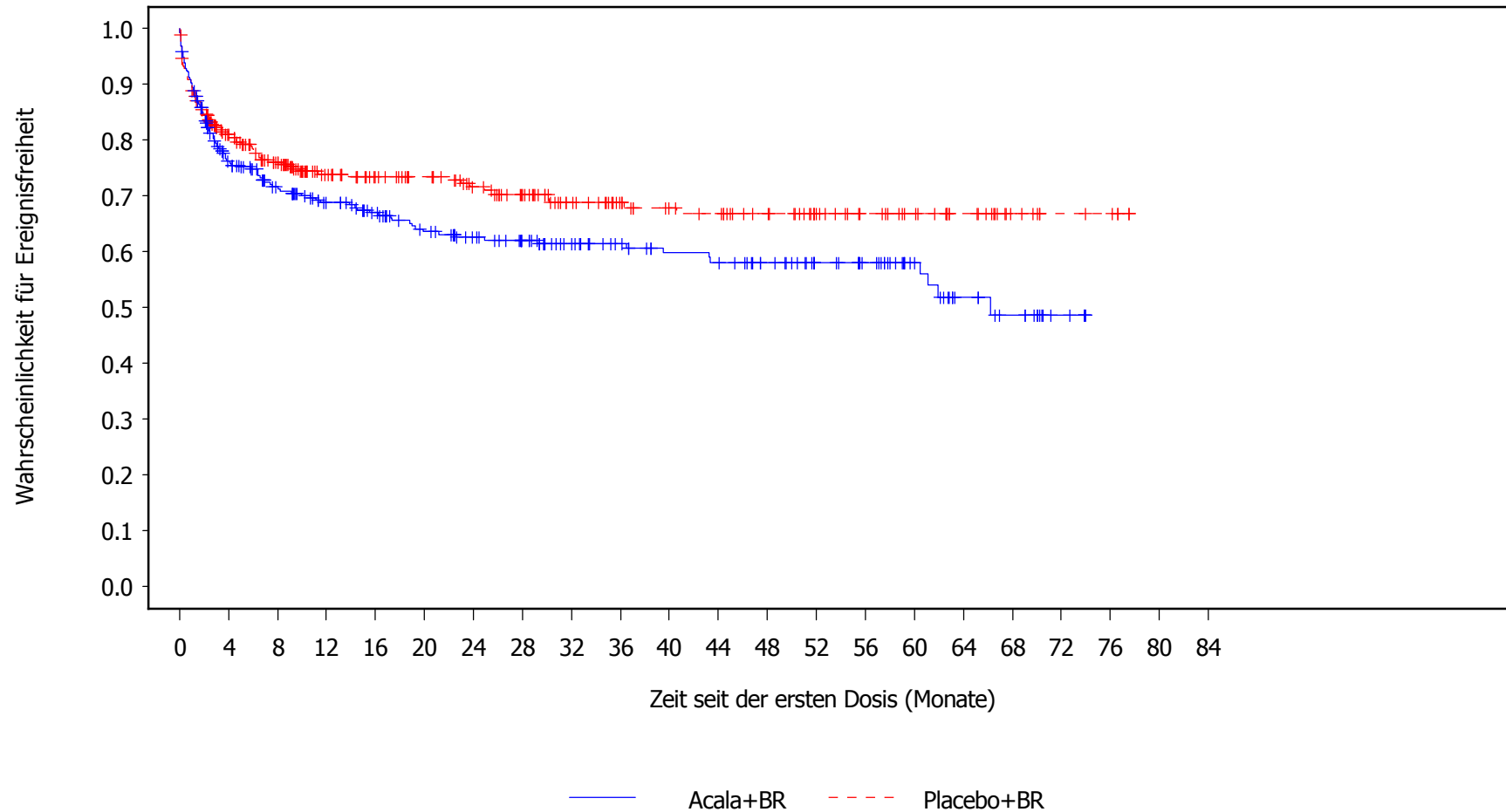
Anzahl an Patienten unter Risiko:

297	268	239	222	203	185	175	156	135	120	110	106	95	75	64	47	36	27	10	2	1	0	Acala+BR
297	264	235	200	183	171	157	141	122	107	98	93	81	64	55	47	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.48 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Diarrhoe
 Safety Analysis Set, DC0 15FEB2024



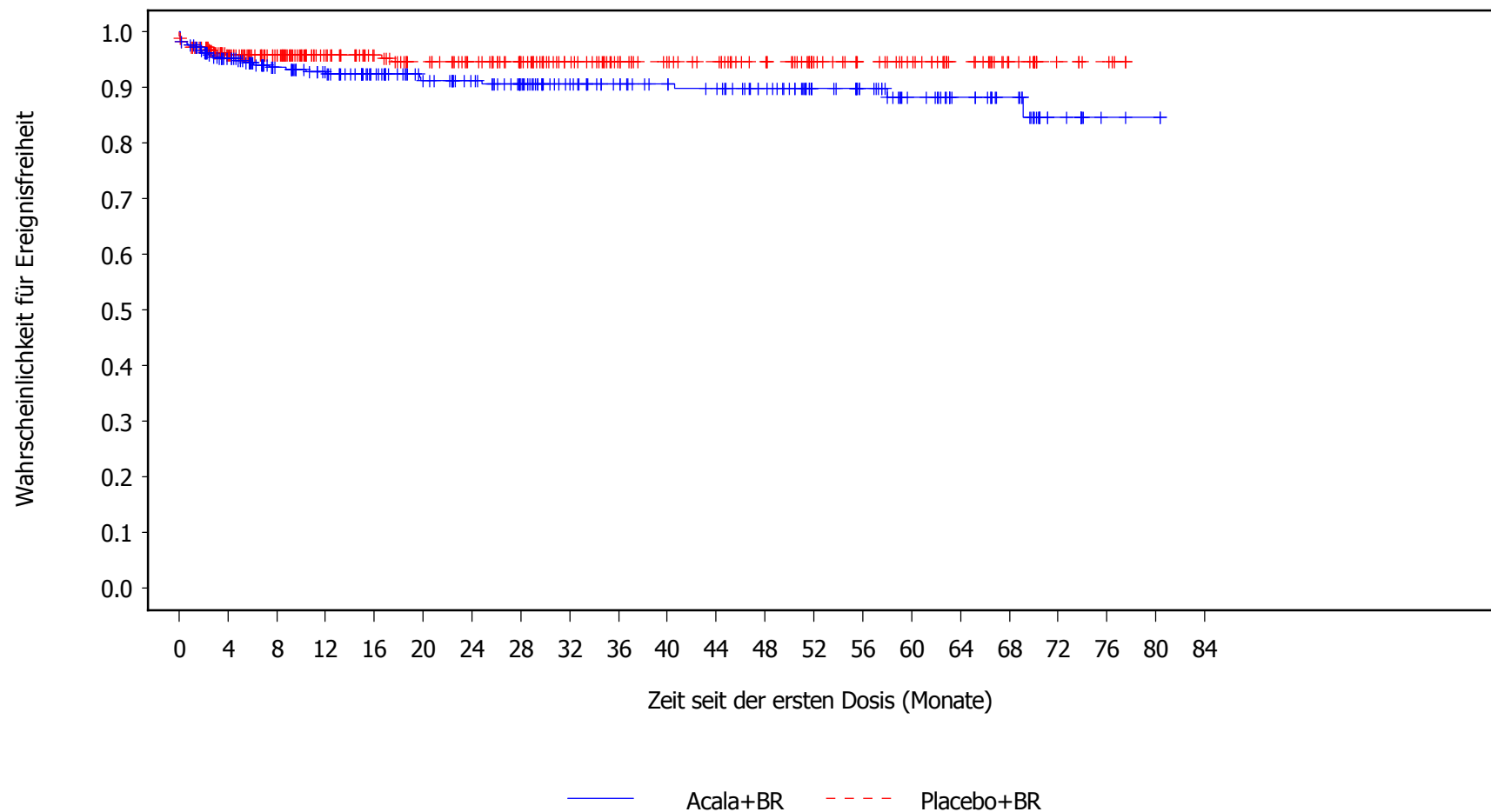
Anzahl an Patienten unter Risiko:

297	209	180	159	144	128	116	104	90	80	72	70	62	50	42	28	18	13	4	0	0	0	Acala+BR
297	219	187	153	138	128	114	102	84	73	65	62	54	43	35	29	20	10	5	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.49 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Dyspepsie
 Safety Analysis Set, DC0 15FEB2024



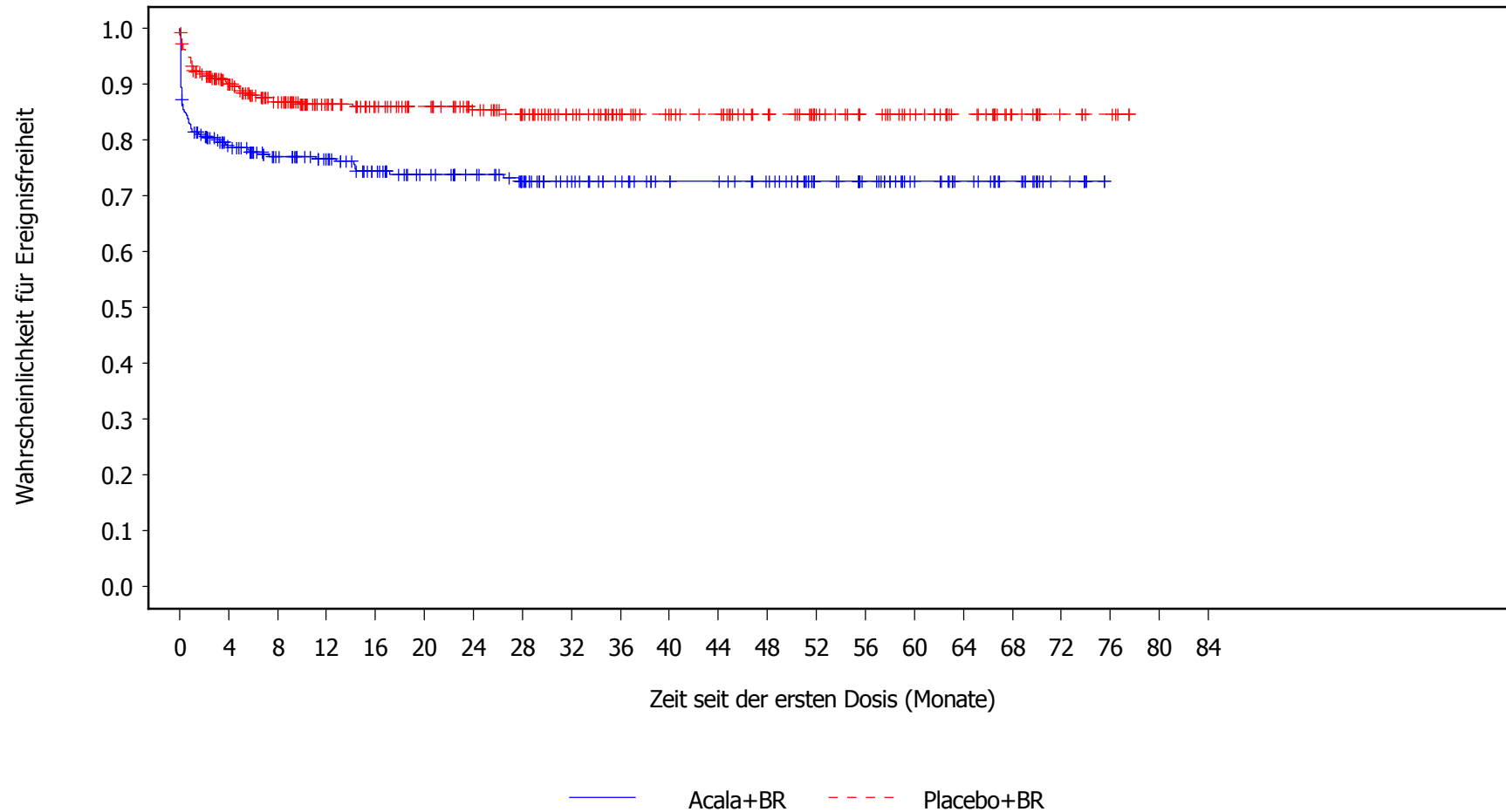
Anzahl an Patienten unter Risiko:

297	261	230	213	192	173	162	146	126	114	107	103	92	72	61	47	36	28	10	2	1	0	Acala+BR
297	256	228	193	174	161	149	134	115	100	91	86	76	60	51	44	30	18	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.50 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Erbrechen
 Safety Analysis Set, DC0 15FEB2024



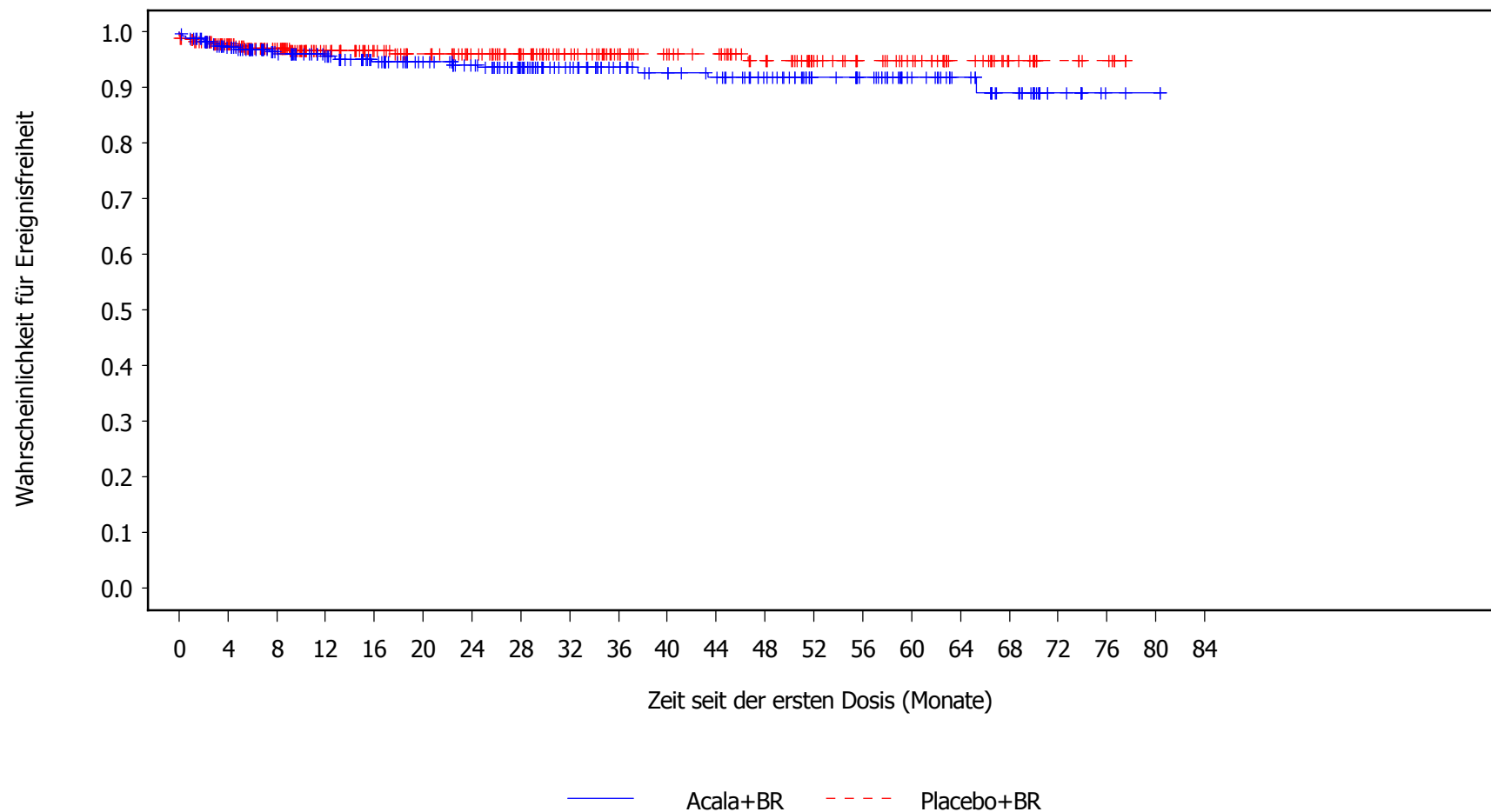
Anzahl an Patienten unter Risiko:

297	214	192	176	157	143	135	121	105	96	87	85	79	60	50	36	28	20	7	0	0	0	Acala+BR
297	243	212	182	165	153	138	125	109	95	87	83	72	59	50	42	30	17	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.51 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Gastrooesophageale Refluxerkrankung
 Safety Analysis Set, DCO 15FEB2024



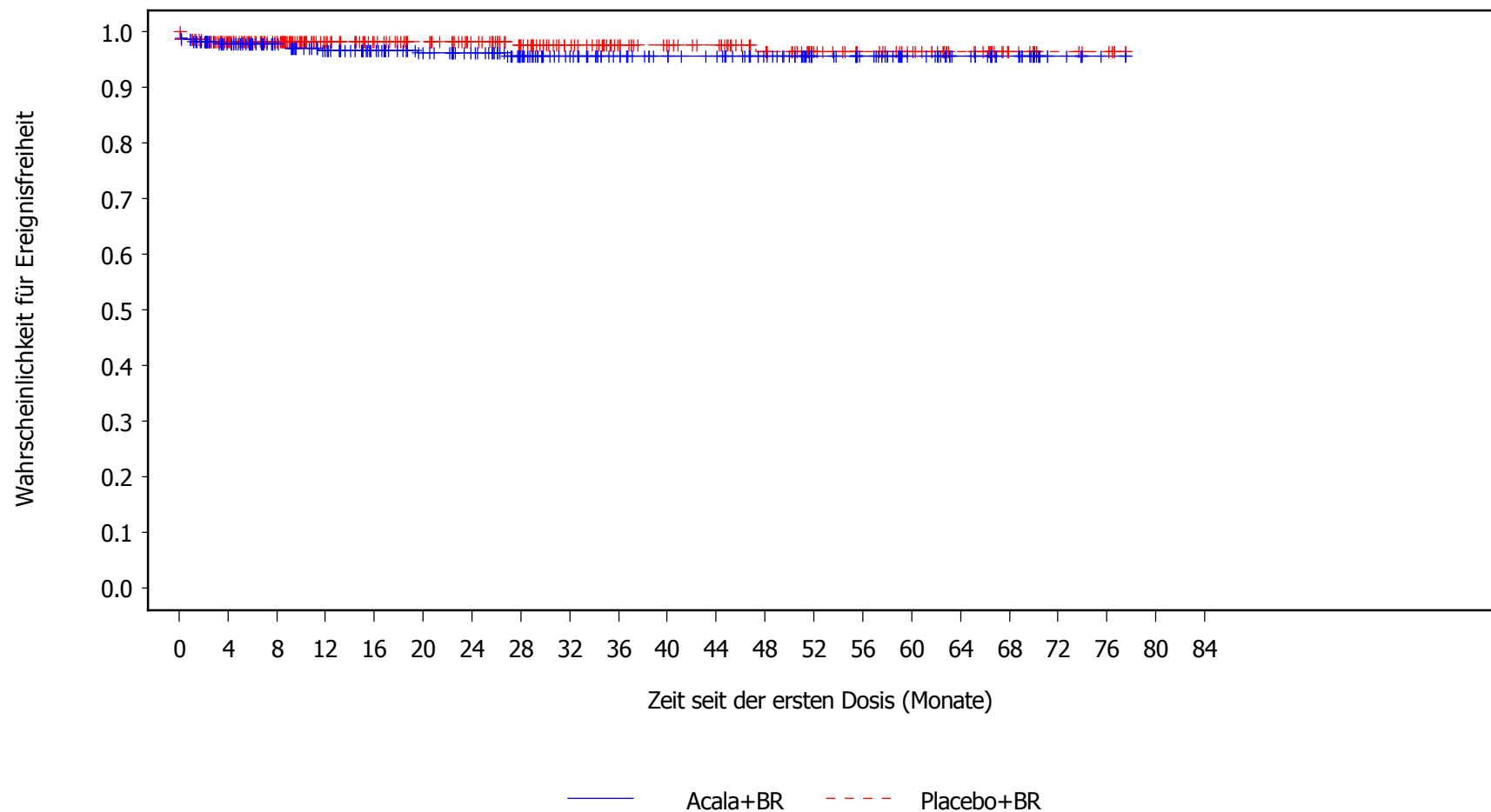
Anzahl an Patienten unter Risiko:

297	267	238	219	198	182	170	149	130	116	107	102	90	71	63	47	37	26	10	2	1	0	Acala+BR
297	262	231	195	178	165	152	136	118	103	94	90	77	60	51	44	29	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.52 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Mundtrockenheit
 Safety Analysis Set, DC0 15FEB2024



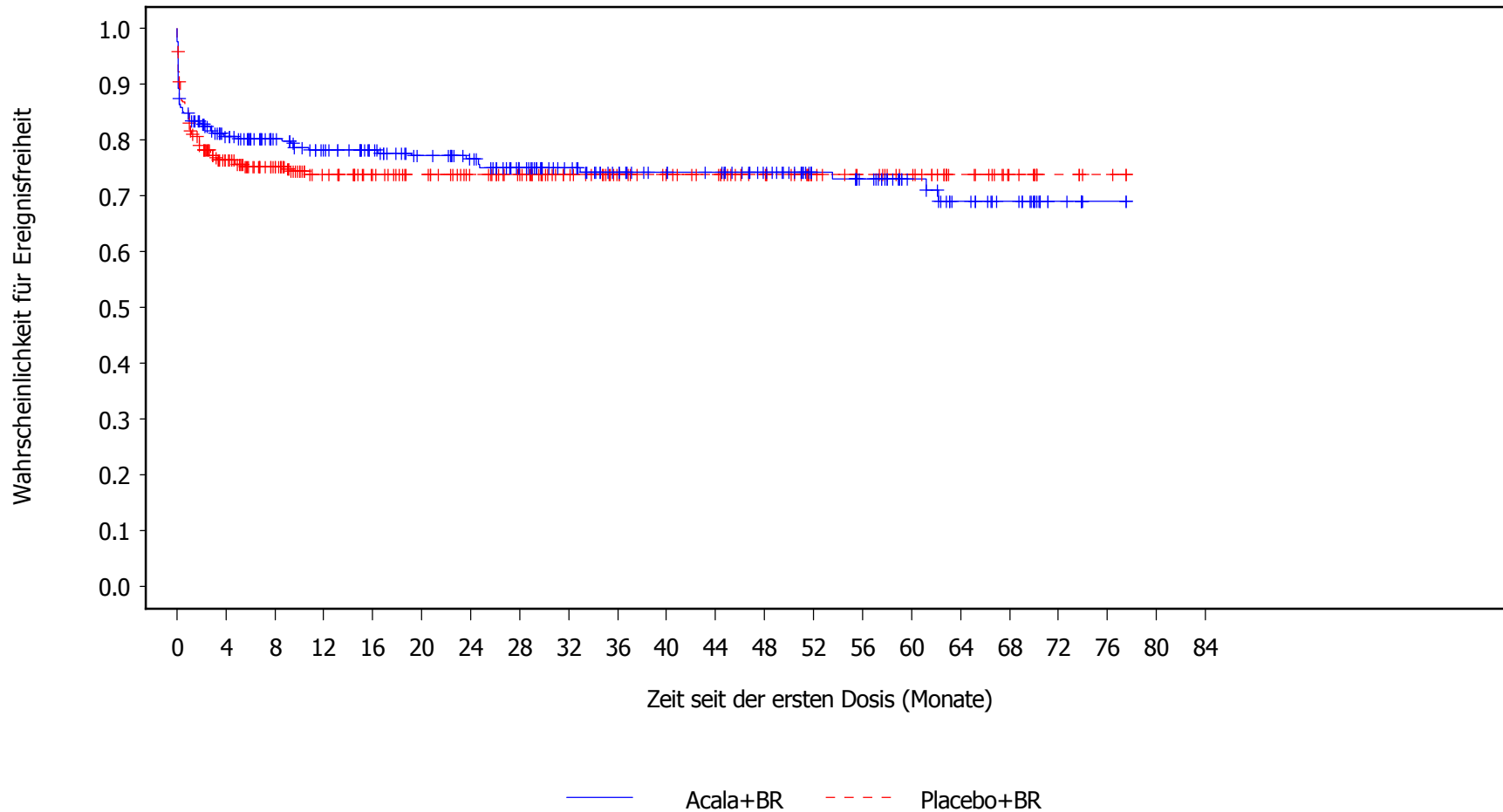
Anzahl an Patienten unter Risiko:

297	270	243	223	203	186	175	154	134	120	110	106	94	73	64	48	37	26	8	1	0	0	Acala+BR
297	264	235	200	182	170	156	139	121	106	97	92	79	62	53	46	31	17	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.53 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Obstipation
 Safety Analysis Set, DCO 15FEB2024



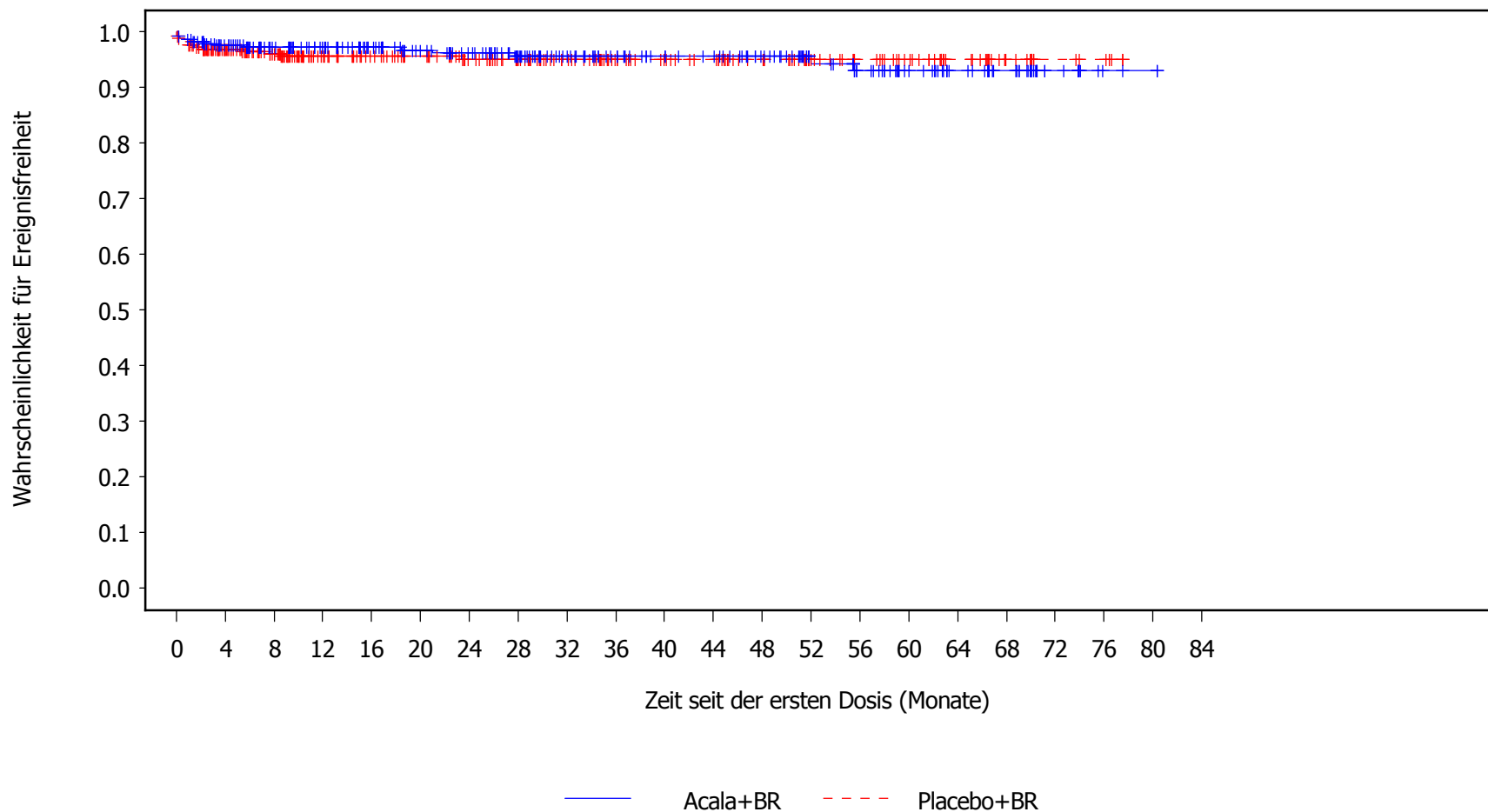
Anzahl an Patienten unter Risiko:

297	220	197	180	166	152	142	123	107	95	87	84	75	60	53	38	28	21	7	1	0	0	Acala+BR
297	202	176	149	137	127	116	107	90	79	72	68	59	45	40	34	21	12	5	2	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.54 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Schmerzen Oberbauch
 Safety Analysis Set, DC0 15FEB2024



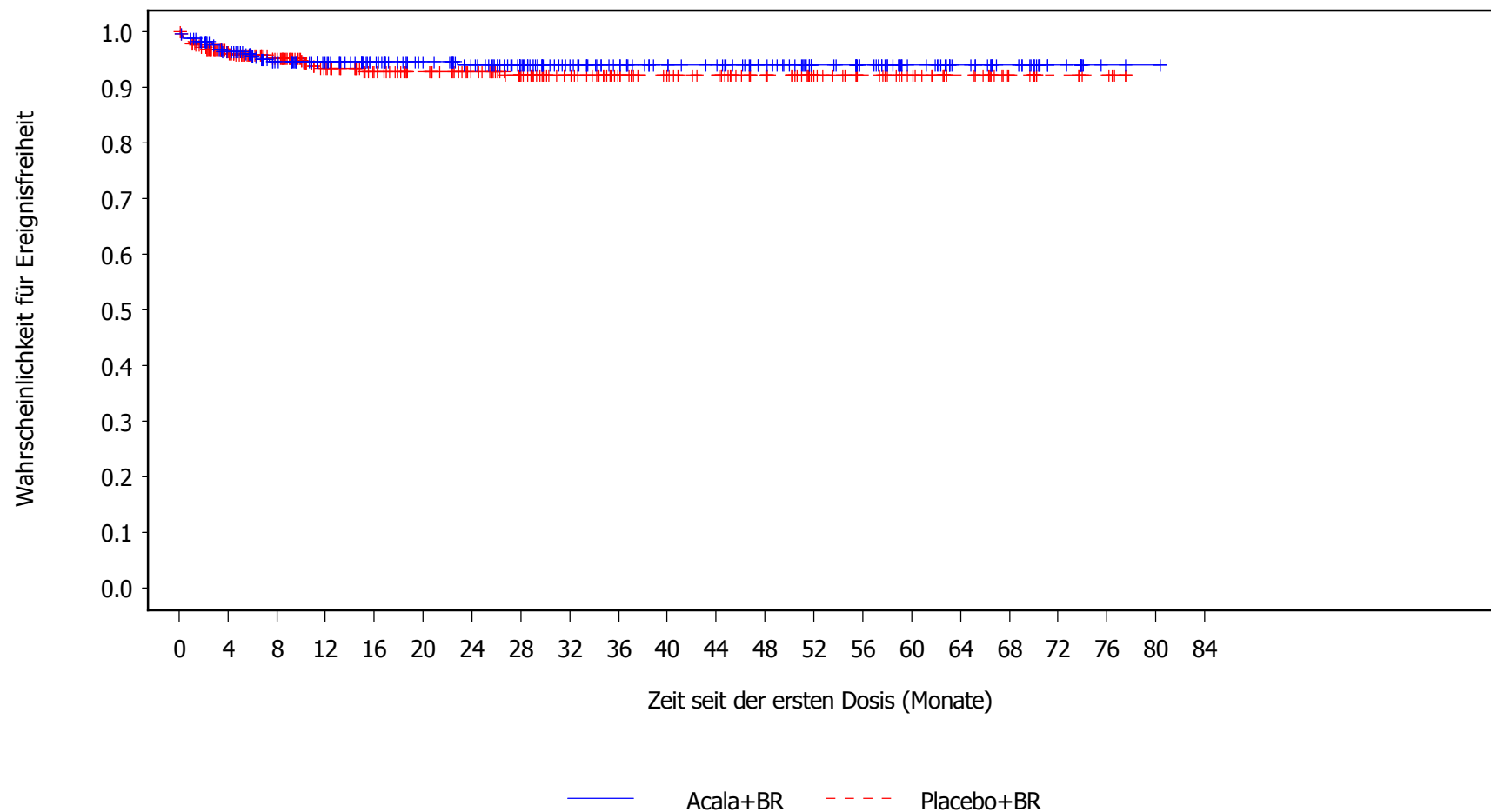
Anzahl an Patienten unter Risiko:

297	269	242	225	205	188	176	155	135	121	111	107	96	77	64	50	39	29	11	2	1	0	Acala+BR
297	258	229	193	175	164	149	134	117	102	93	88	77	60	51	43	28	15	6	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.55 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Stomatitis
 Safety Analysis Set, DCO 15FEB2024



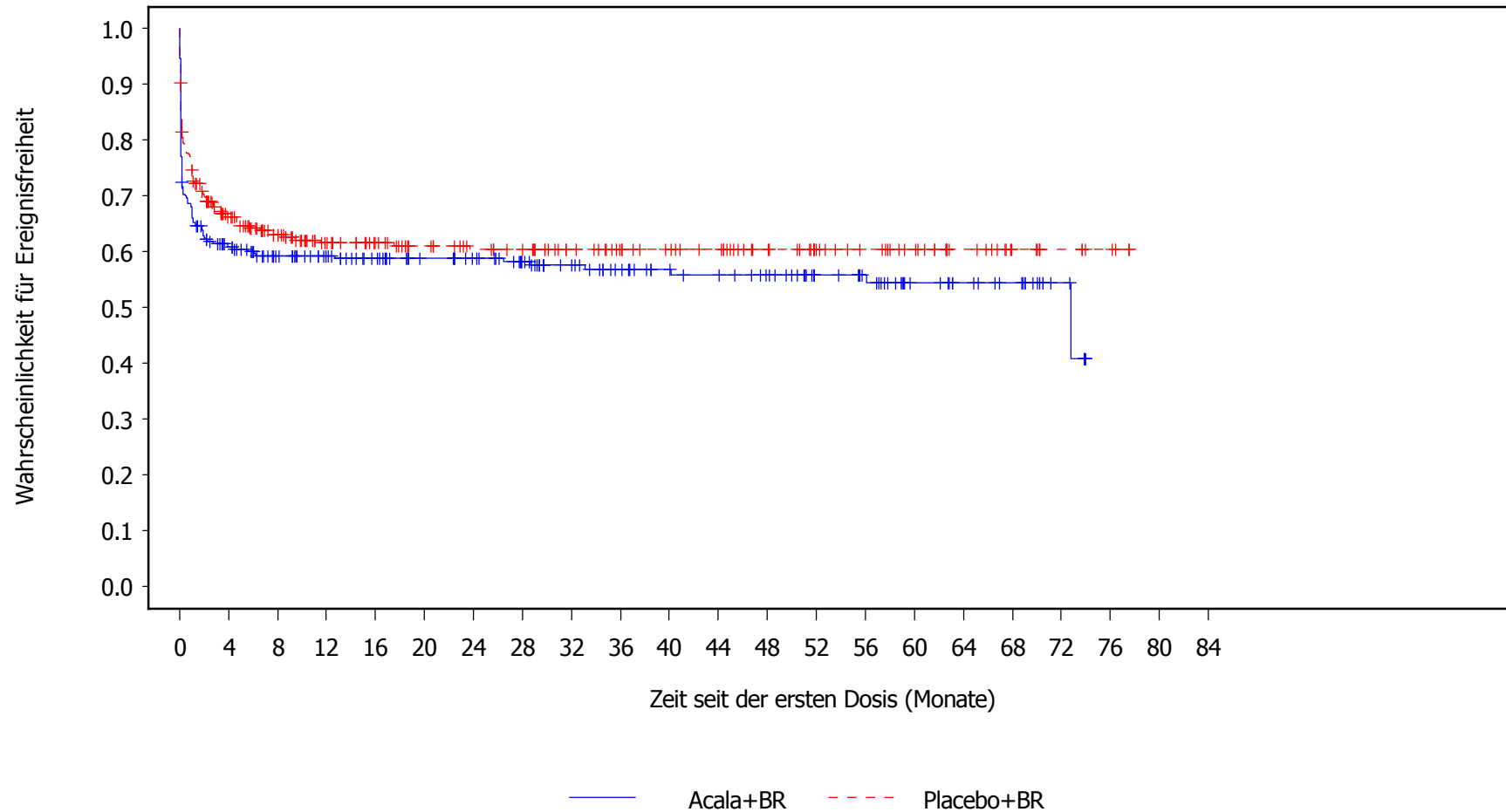
Anzahl an Patienten unter Risiko:

297	267	237	220	200	184	173	153	132	118	108	104	93	74	64	48	37	28	10	2	1	0	Acala+BR
297	257	226	189	171	159	145	129	112	98	89	84	73	56	47	39	27	15	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.56 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Uebelkeit
 Safety Analysis Set, DC0 15FEB2024



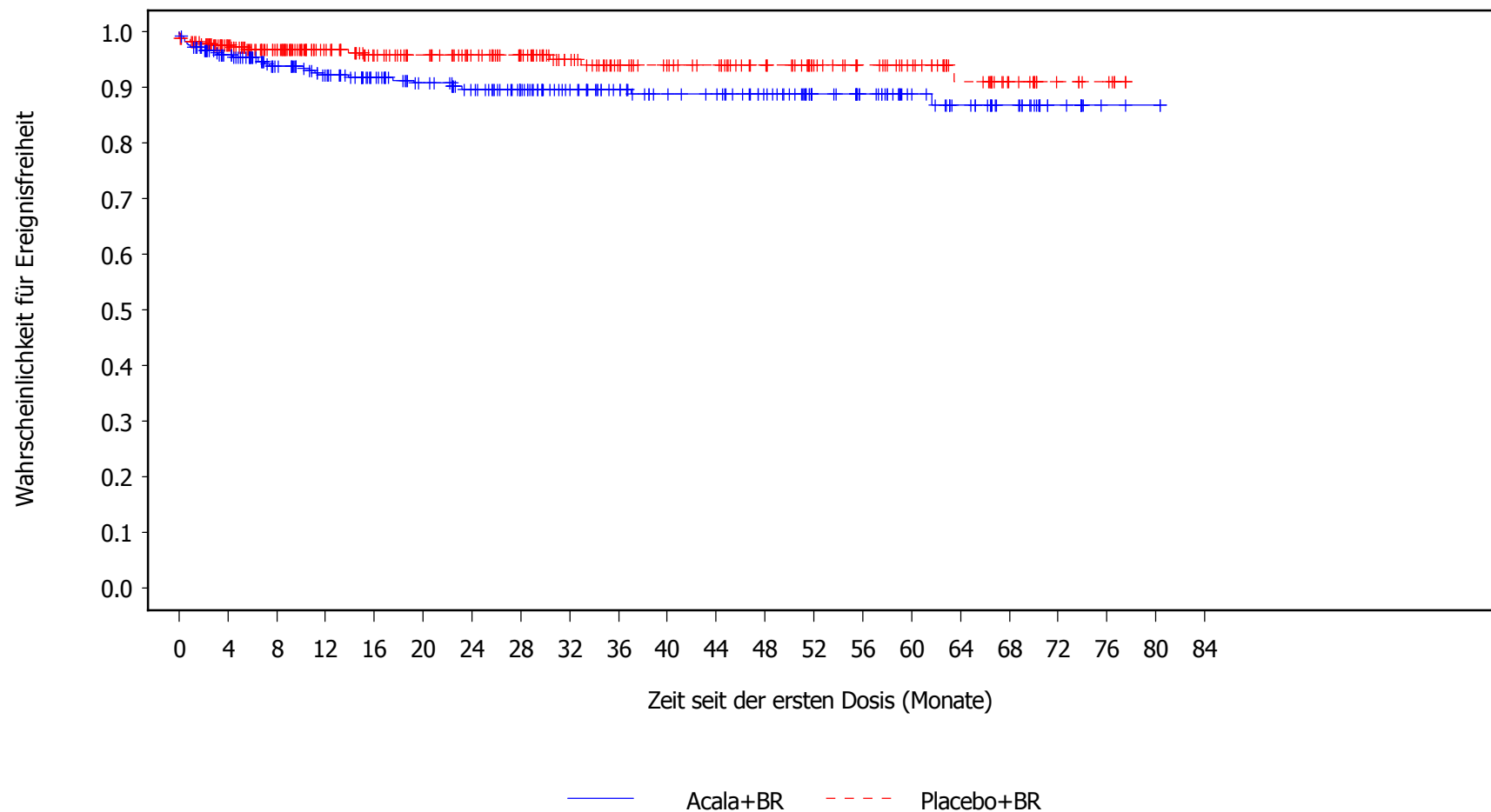
Anzahl an Patienten unter Risiko:

297	168	147	133	122	111	105	93	80	70	62	59	54	42	36	24	19	15	5	0	0	0	Acala+BR
297	175	147	124	113	102	94	90	78	70	65	61	51	41	35	29	19	11	6	3	0	0	Placebo+BR

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Figure 3.3.1.57 ECHO: Kaplan-Meier plot of time to first occurrence of SOC: Erkrankungen des Immunsystems
 Safety Analysis Set, DCO 15FEB2024



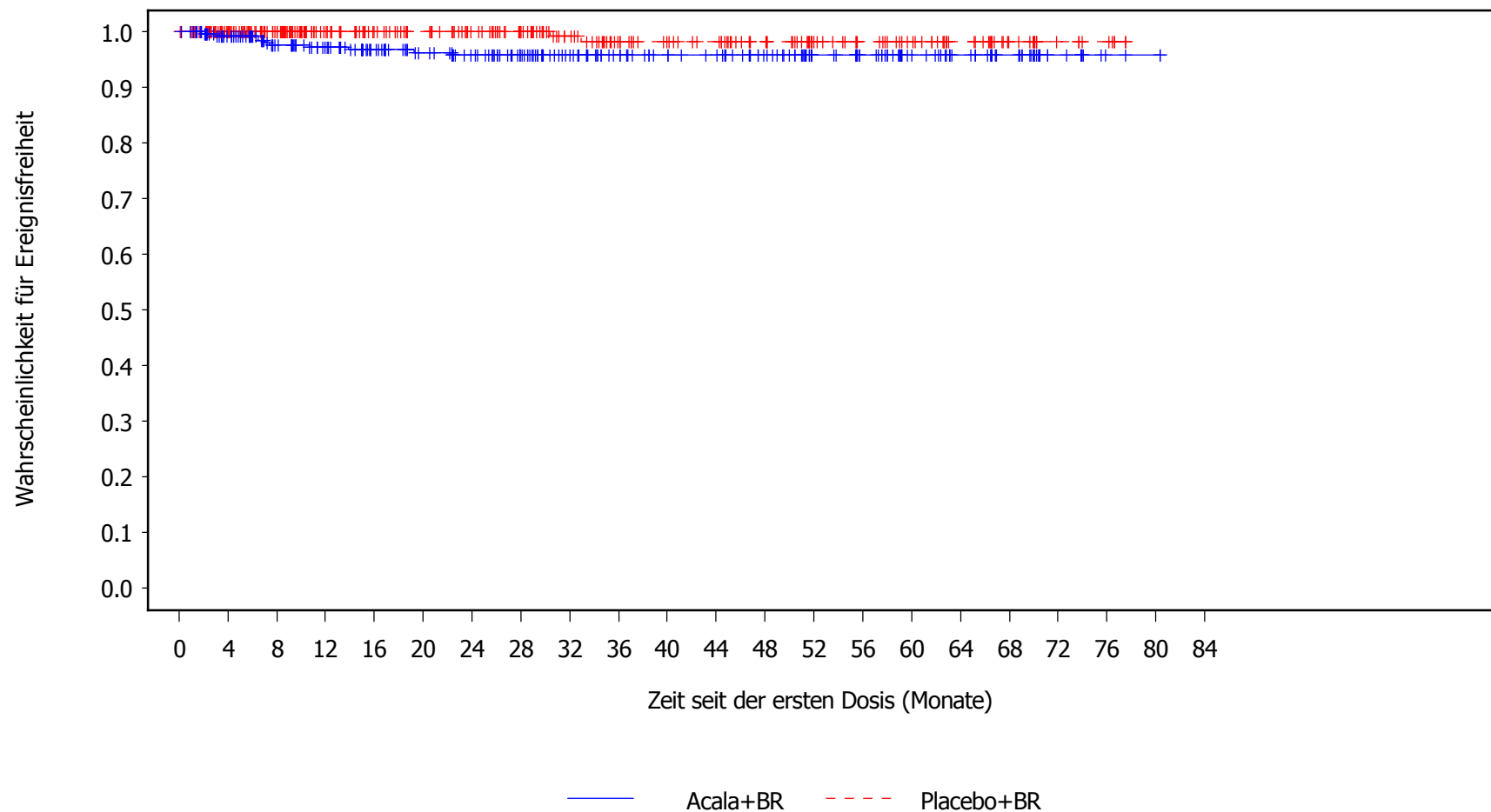
Anzahl an Patienten unter Risiko:

297	265	234	214	193	177	164	146	128	114	103	100	89	69	58	43	34	24	10	2	1	0	Acala+BR
297	261	230	196	176	164	150	136	116	101	92	87	76	62	53	45	30	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.58 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Hypogammaglobulinaemie
 Safety Analysis Set, DC0 15FEB2024



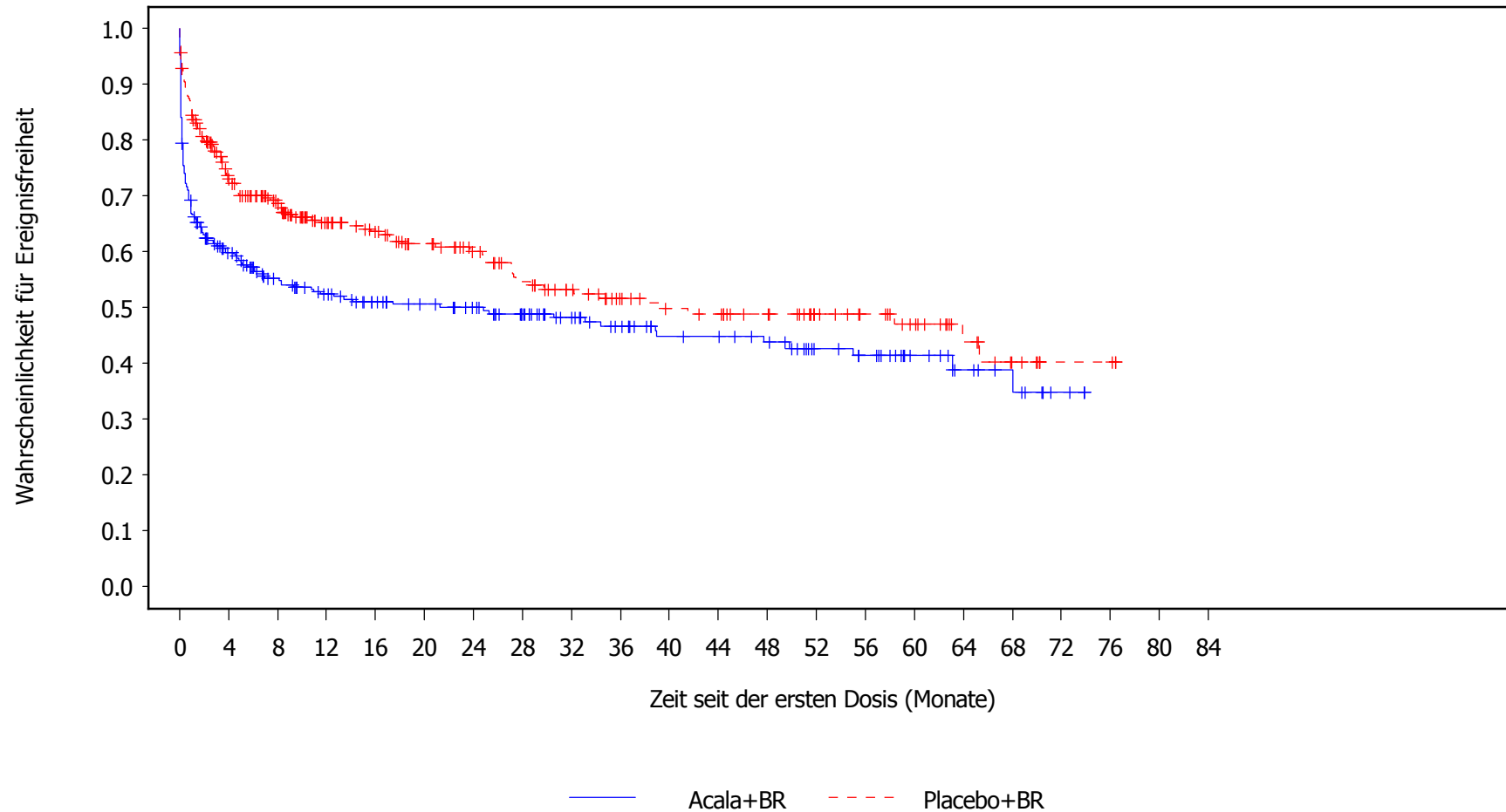
Anzahl an Patienten unter Risiko:

297	273	243	225	204	188	176	157	137	122	112	108	97	76	65	49	39	28	11	2	1	0	Acala+BR
297	267	238	203	184	172	158	142	122	106	97	92	80	64	55	47	33	19	8	5	0	0	Placebo+BR

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Figure 3.3.1.59 ECHO: Kaplan-Meier plot of time to first occurrence of SOC: Erkrankungen des Nervensystems
 Safety Analysis Set, DC0 15FEB2024



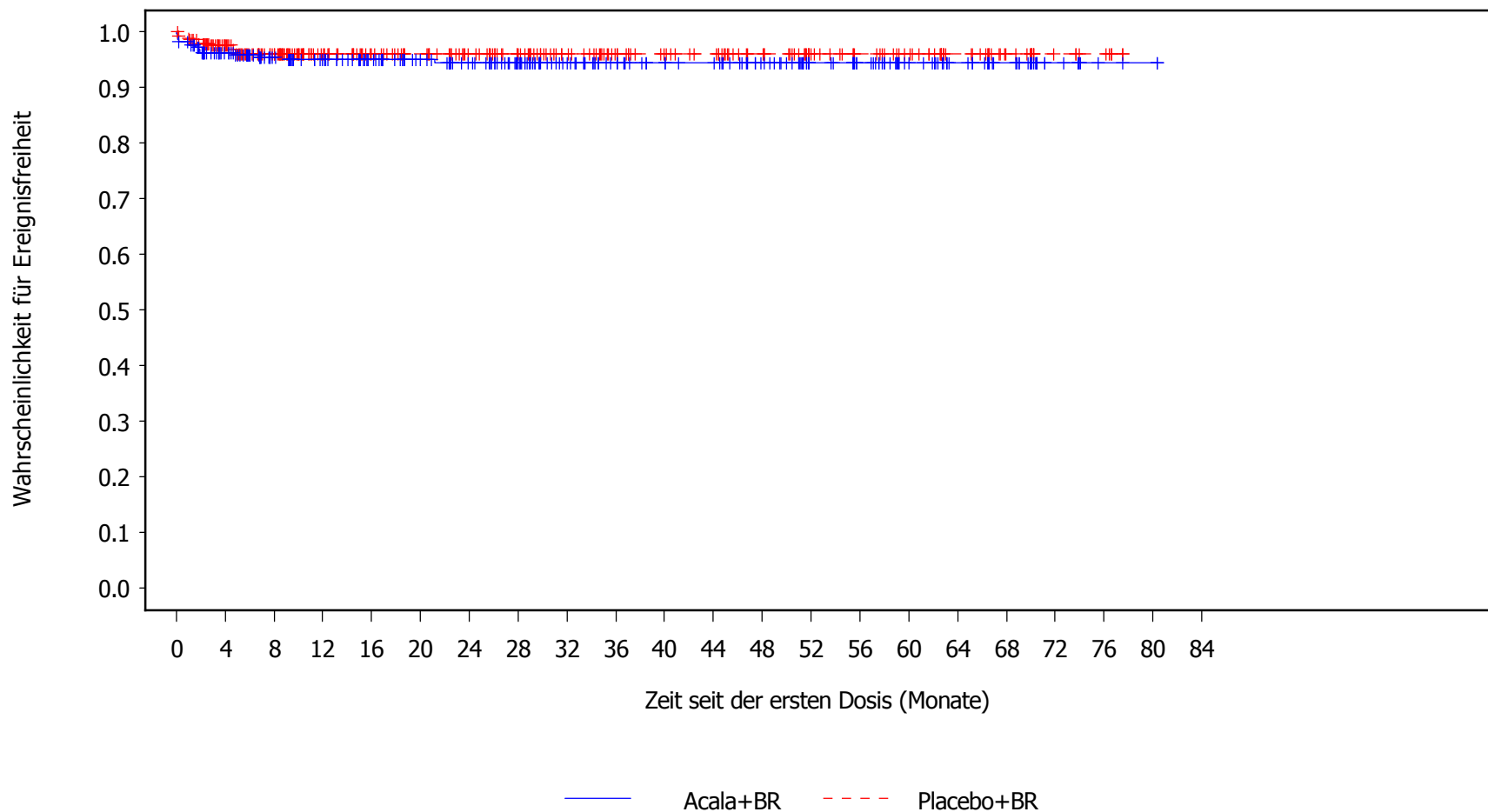
Anzahl an Patienten unter Risiko:

297	162	135	120	108	99	92	80	67	58	48	47	43	33	28	19	13	10	3	0	0	0	Acala+BR
297	196	165	131	118	104	92	79	69	59	53	51	45	34	29	23	14	8	2	2	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.60 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Dysgeusie
 Safety Analysis Set, DC0 15FEB2024



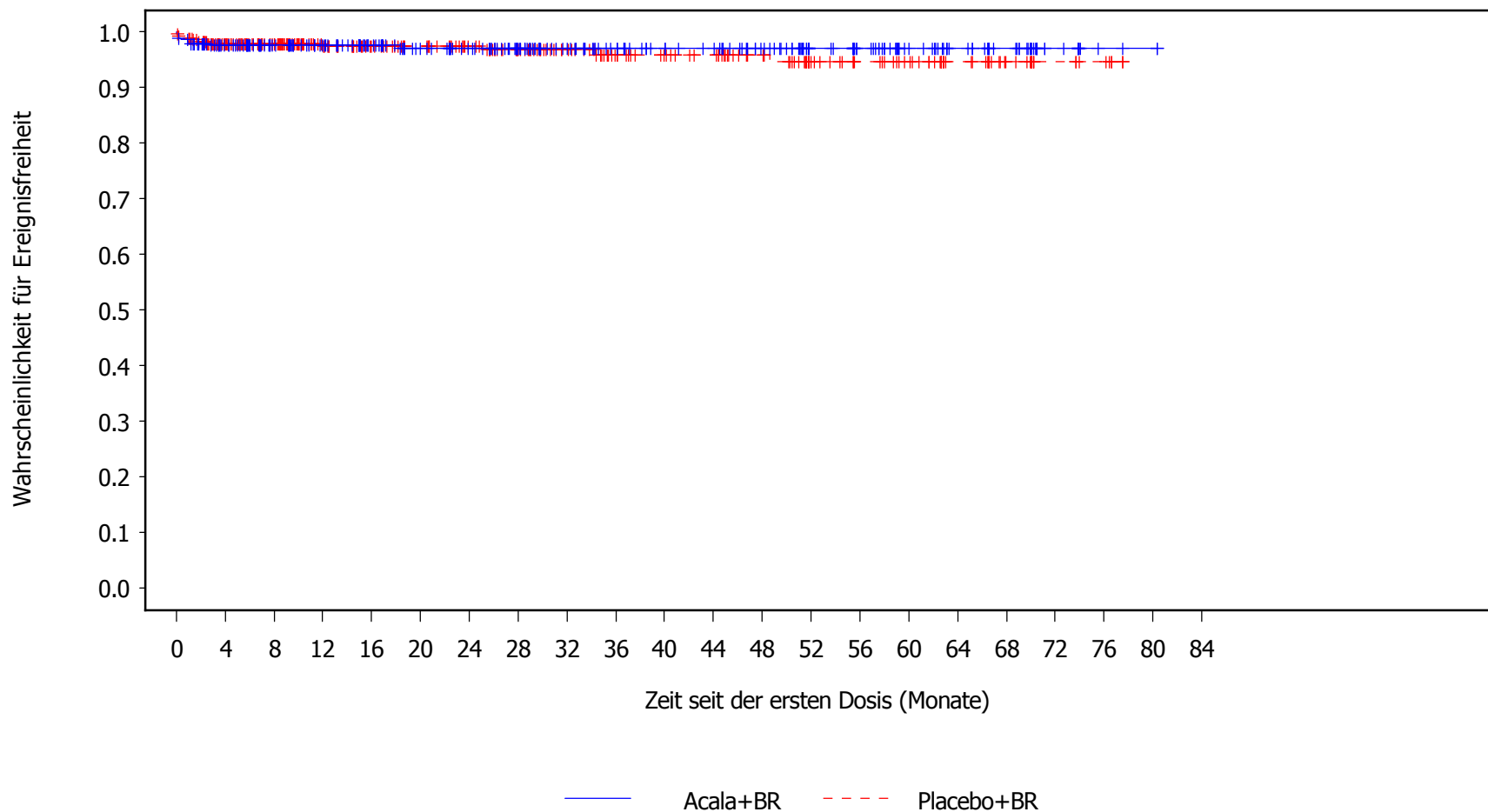
Anzahl an Patienten unter Risiko:

297	264	236	221	202	186	174	155	134	119	110	107	95	76	65	48	37	26	9	2	1	0	Acala+BR
297	262	230	195	178	166	152	138	120	106	97	92	80	64	55	47	32	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.61 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Erinnerungsvermoegen eingeschraenkt
 Safety Analysis Set, DCO 15FEB2024



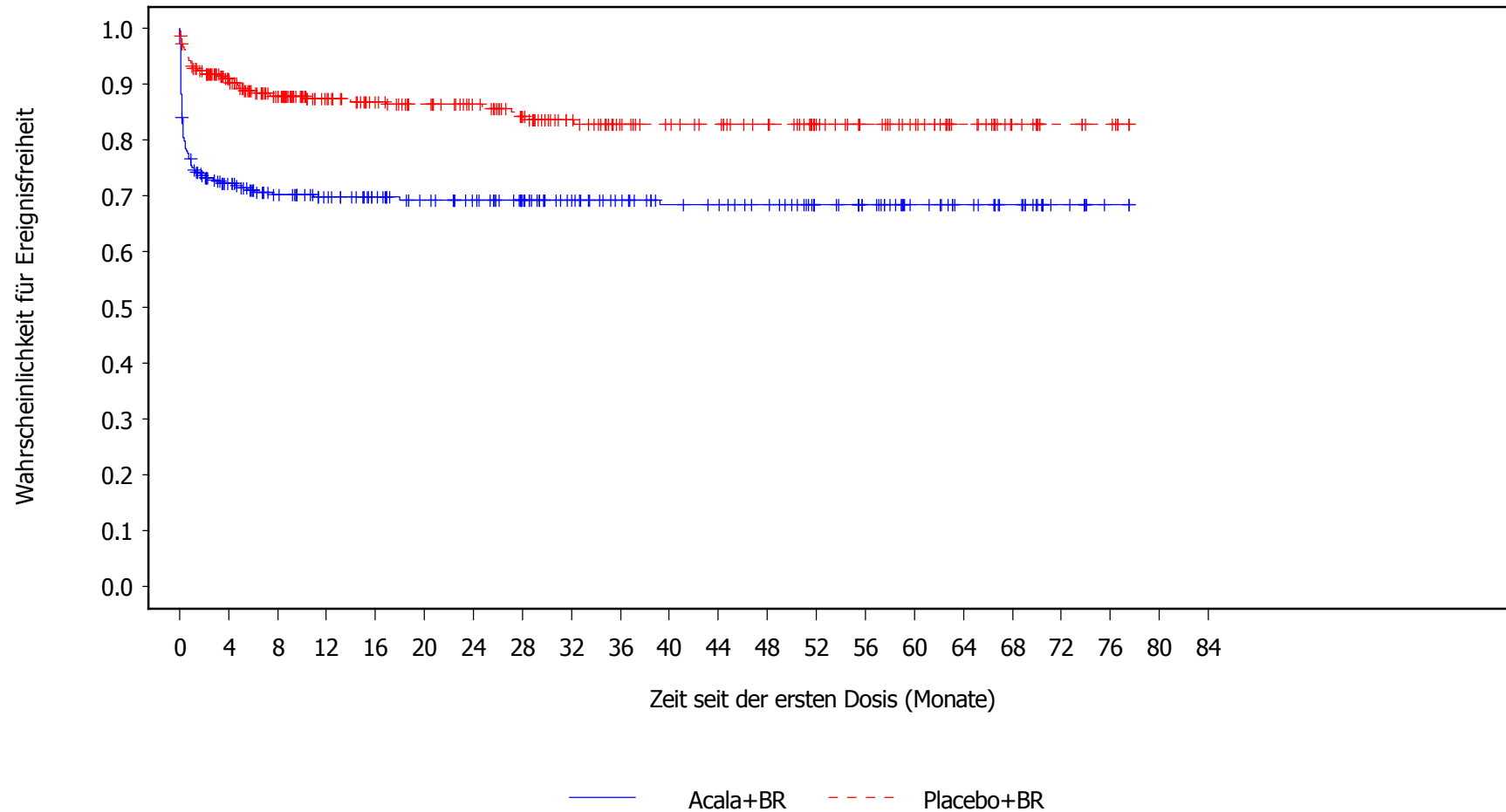
Anzahl an Patienten unter Risiko:

297	269	243	226	206	188	177	157	138	124	114	110	98	77	66	49	38	28	10	2	1	0	Acala+BR
297	261	232	197	180	168	154	137	118	103	95	90	78	61	52	45	30	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.62 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Kopfschmerzen
 Safety Analysis Set, DCO 15FEB2024



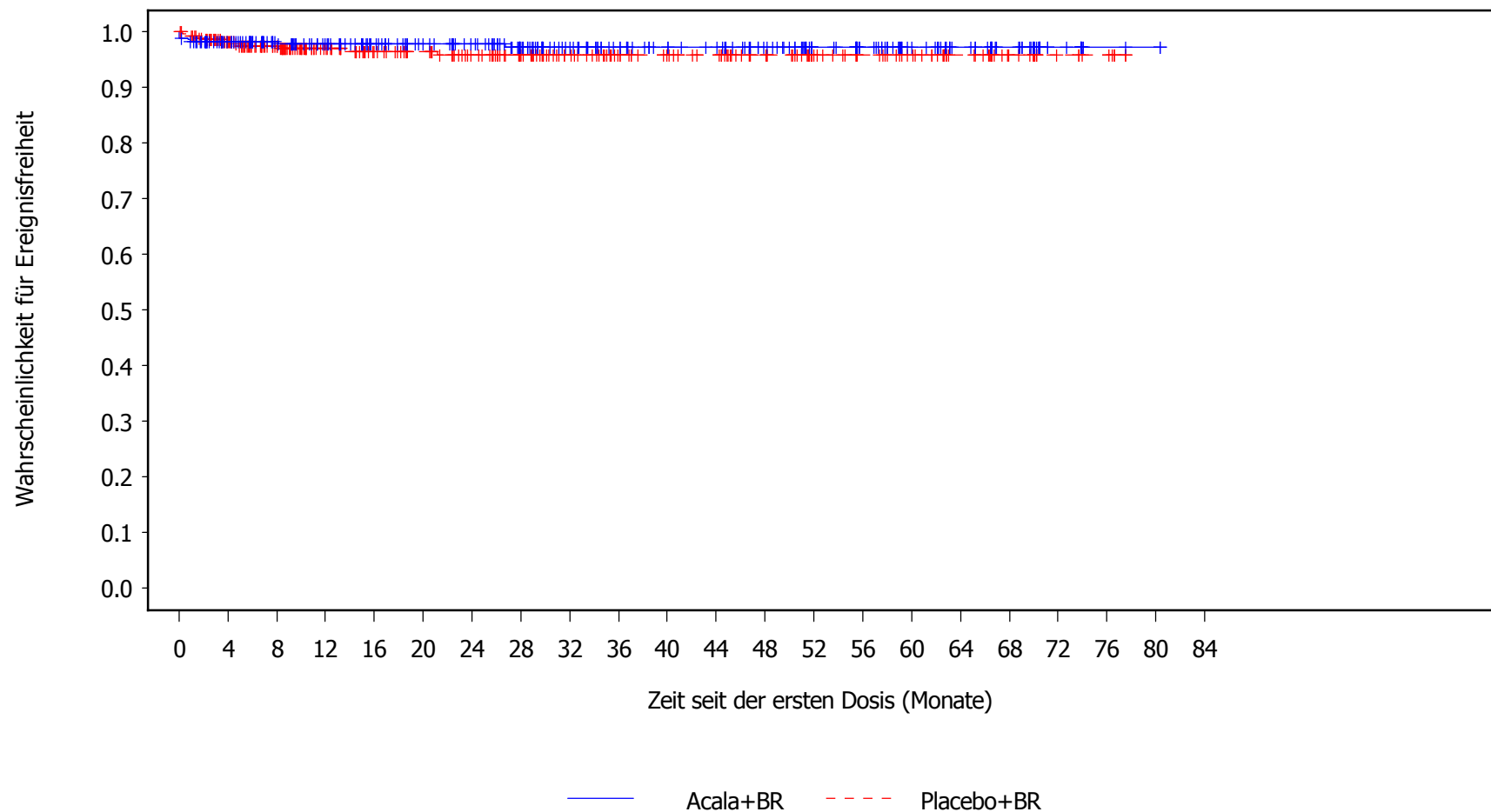
Anzahl an Patienten unter Risiko:

297	195	172	158	145	133	125	111	97	87	77	75	70	57	48	35	28	21	8	1	0	0	Acala+BR
297	241	206	173	158	146	134	120	102	88	82	78	71	57	48	41	28	17	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.63 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Paraesthesie
 Safety Analysis Set, DC0 15FEB2024



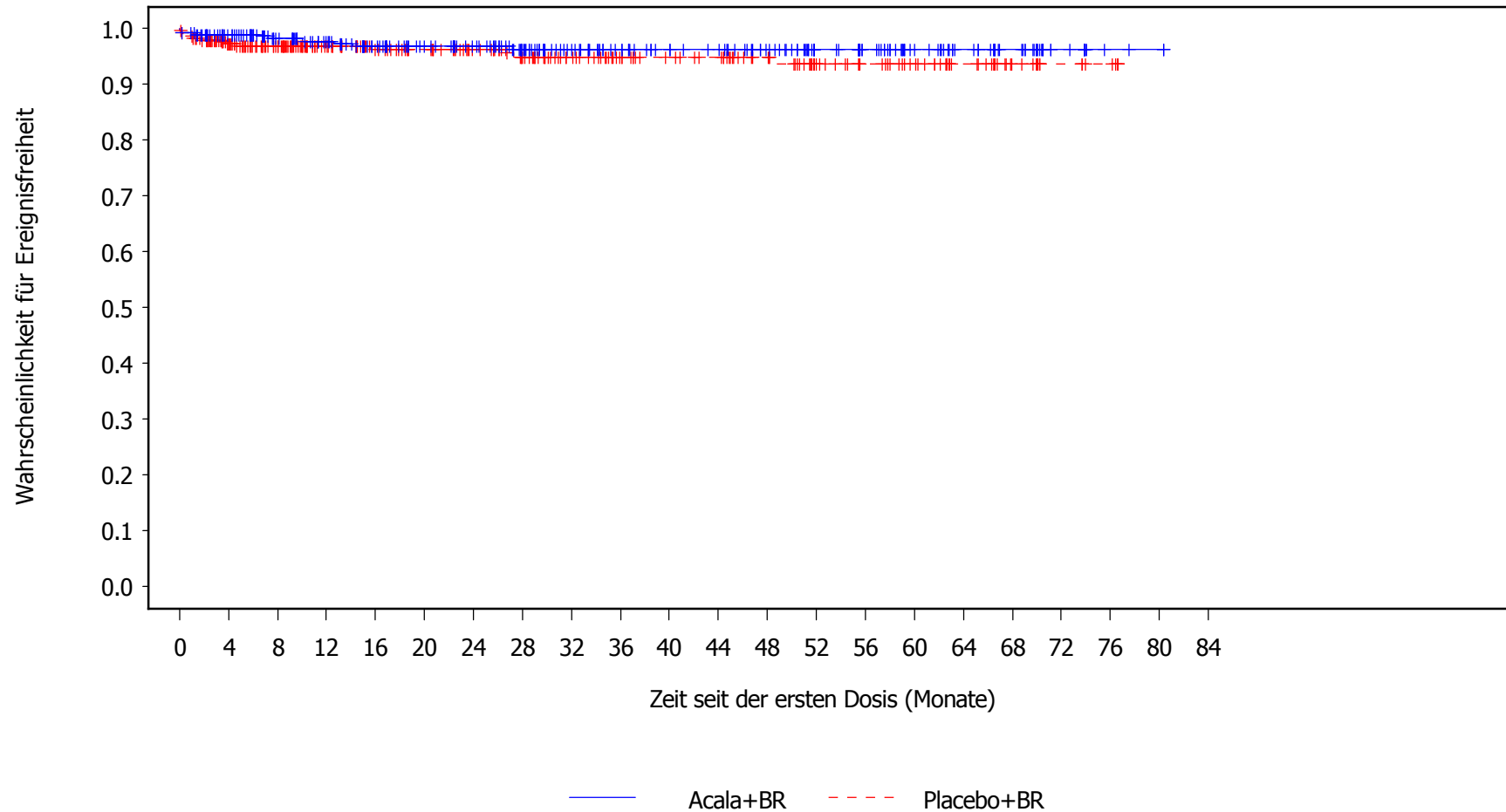
Anzahl an Patienten unter Risiko:

297	270	243	225	206	190	179	158	138	123	113	109	97	77	66	49	38	27	9	2	1	0	Acala+BR
297	263	232	197	178	167	153	137	119	105	97	92	80	63	54	46	32	19	8	5	0	0	Placebo+BR

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Figure 3.3.1.64 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Periphere sensorische Neuropathie
 Safety Analysis Set, DCO 15FEB2024



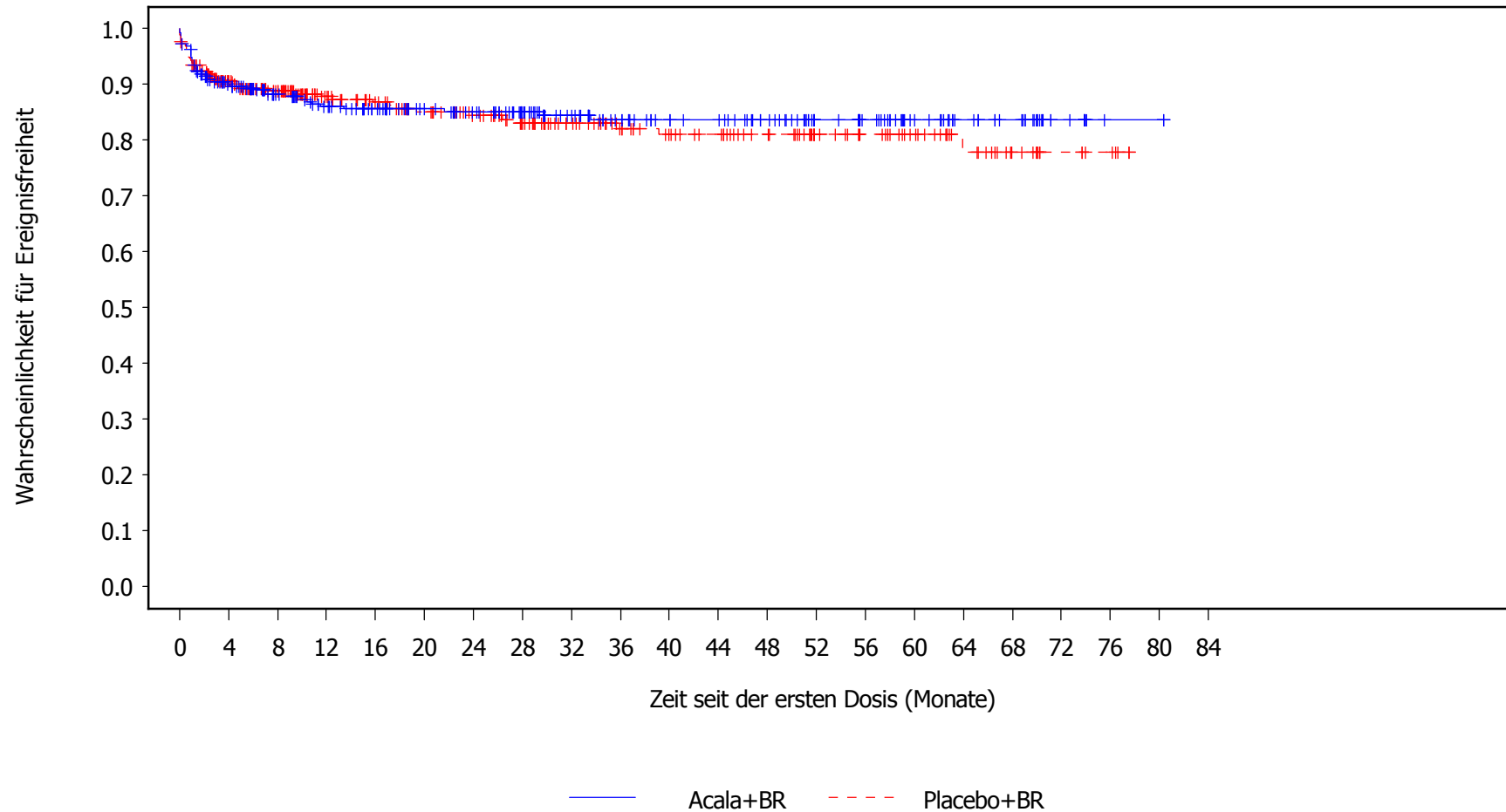
Anzahl an Patienten unter Risiko:

297	273	244	226	206	189	178	157	137	122	112	108	96	76	65	48	38	27	10	2	1	0	Acala+BR
297	259	230	196	177	165	151	136	118	104	96	92	80	62	53	45	30	17	7	4	0	0	Placebo+BR

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Figure 3.3.1.65 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Schwindelgefuehl
 Safety Analysis Set, DCO 15FEB2024



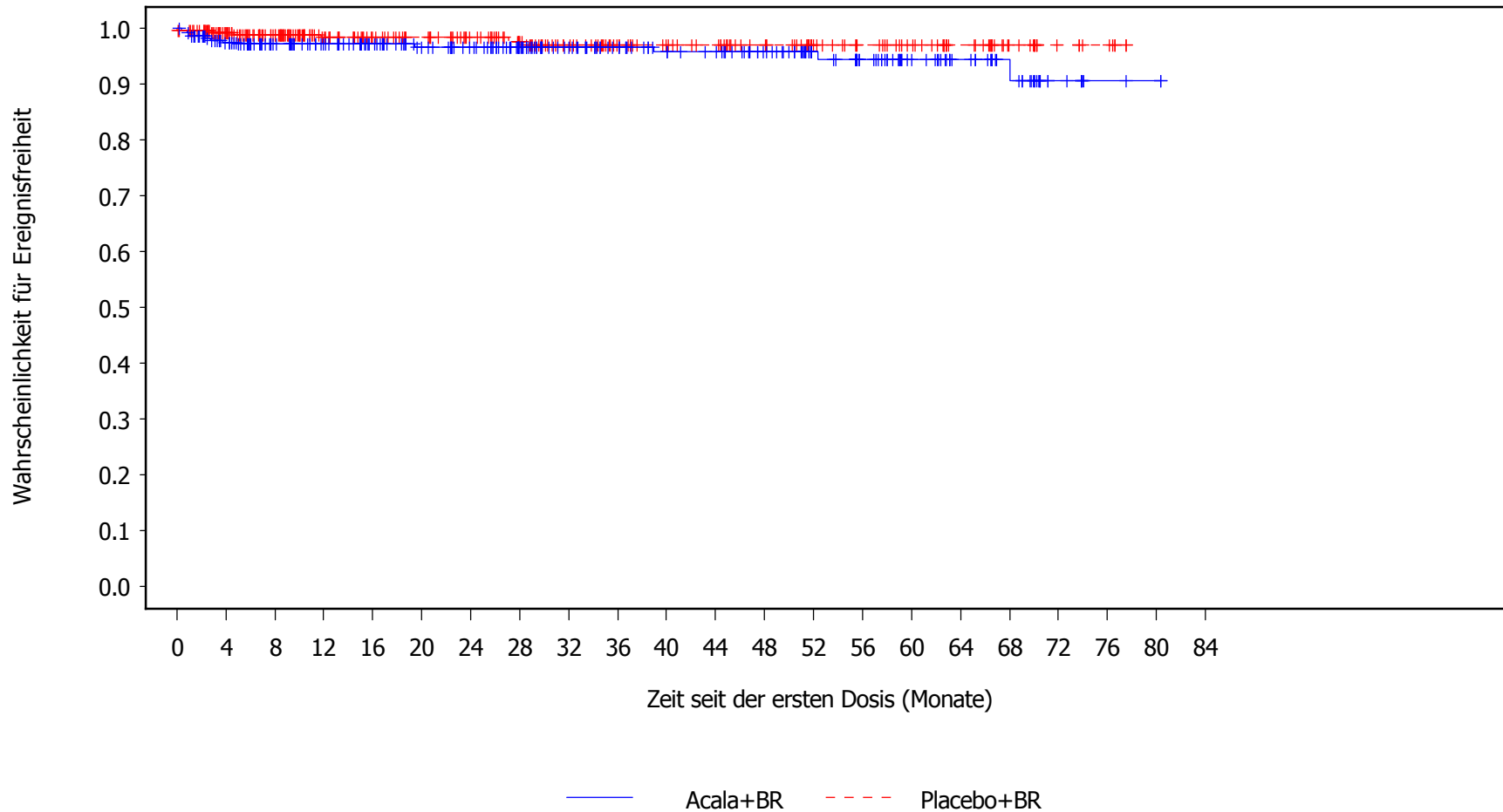
Anzahl an Patienten unter Risiko:

297	248	217	198	182	165	155	138	119	105	95	92	82	65	56	41	31	25	9	1	1	0	Acala+BR
297	240	209	174	158	144	131	118	101	88	79	74	65	50	43	35	24	15	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.66 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Synkope
 Safety Analysis Set, DC0 15FEB2024



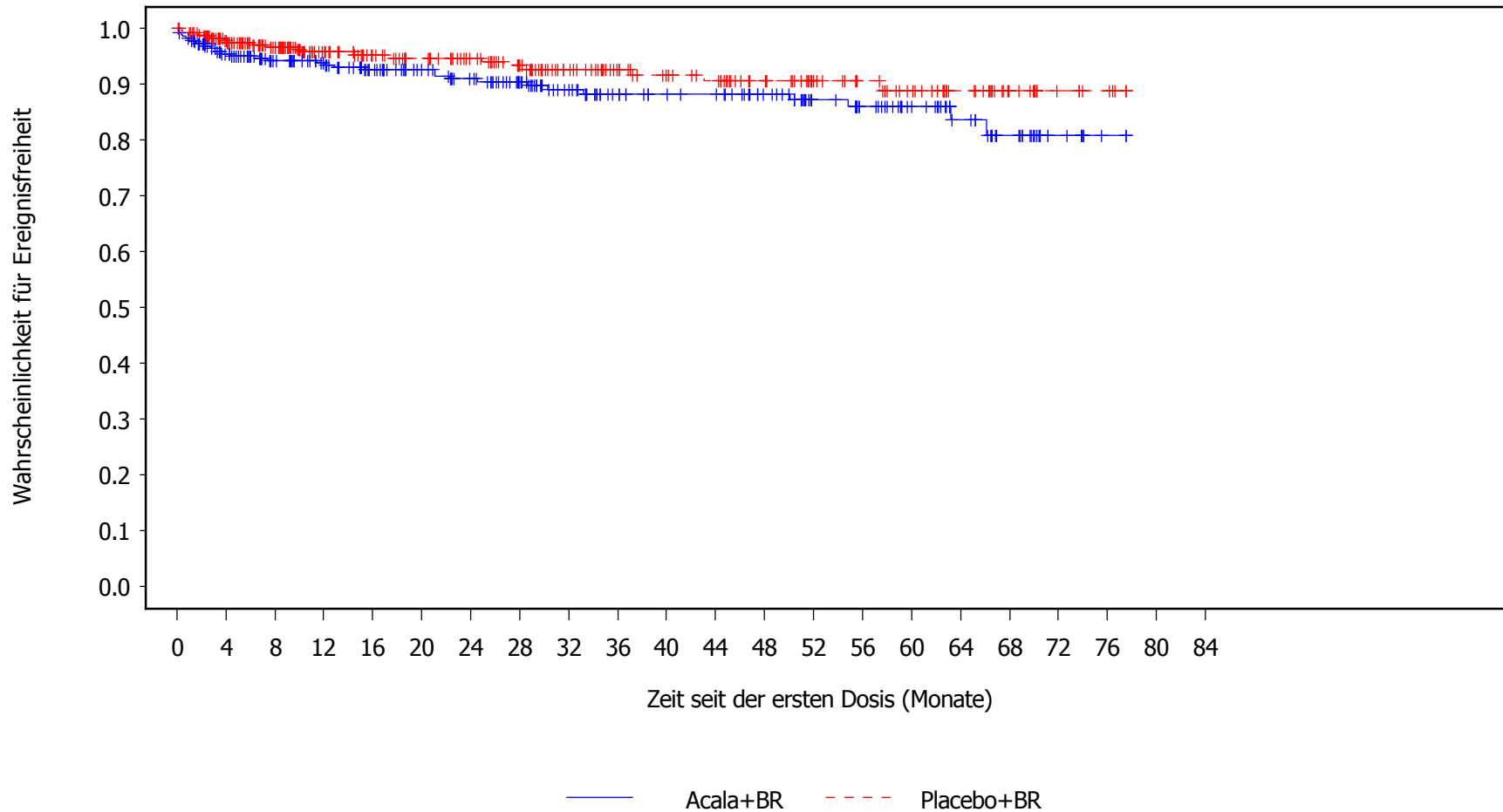
Anzahl an Patienten unter Risiko:

297	270	243	226	207	189	178	157	137	122	111	107	95	75	63	46	35	25	8	2	1	0	Acala+BR
297	266	237	201	183	171	157	140	120	105	96	91	80	64	55	47	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.67 ECH0: Kaplan-Meier plot of time to first occurrence of SOC: Erkrankungen des Ohrs und des Labyrinths
 Safety Analysis Set, DCO 15FEB2024



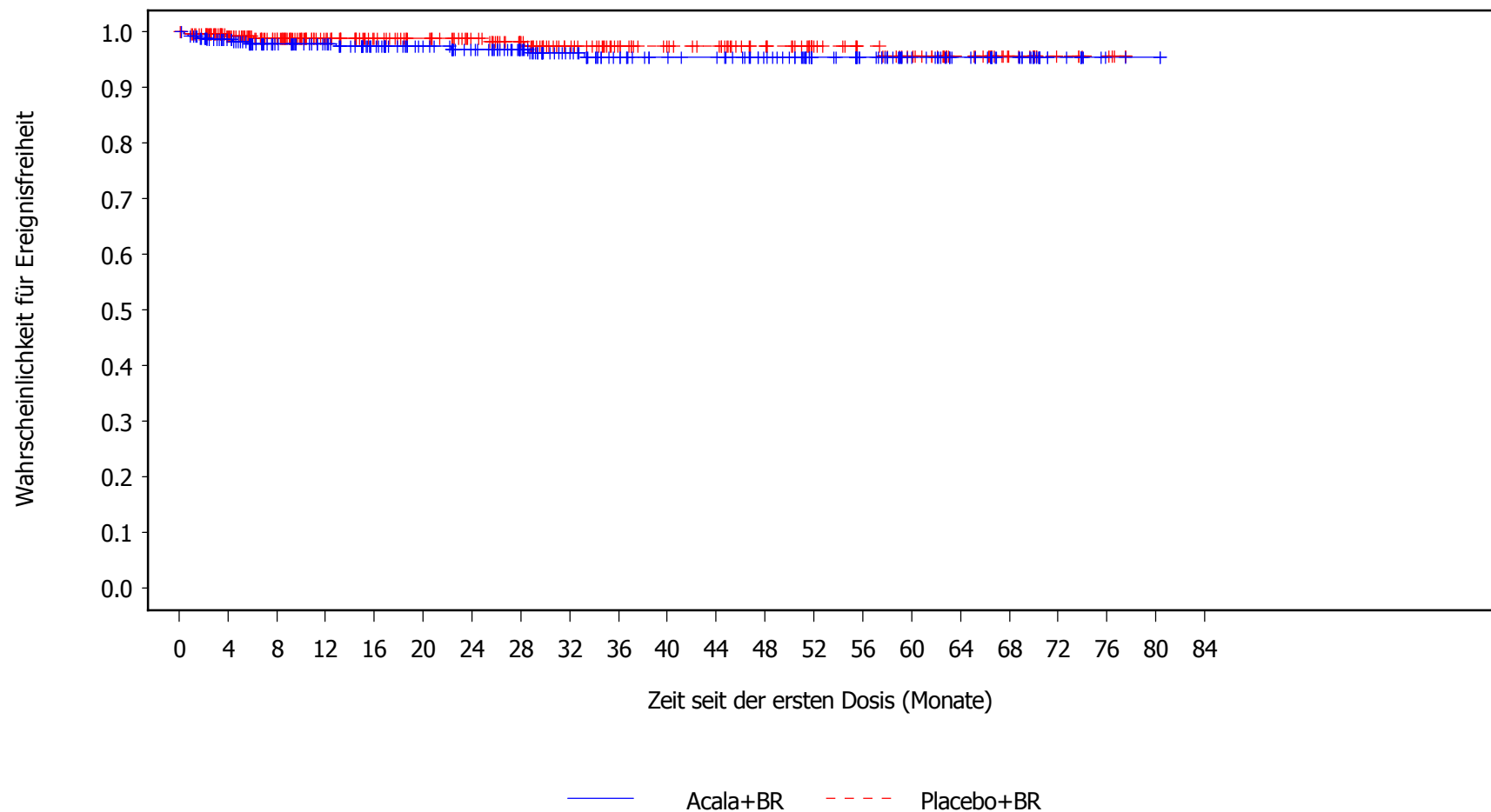
Anzahl an Patienten unter Risiko:

297	262	234	216	194	177	164	145	124	108	101	99	88	69	58	46	34	23	8	1	0	0	Acala+BR
297	262	231	195	175	163	150	134	114	100	91	86	74	60	52	44	30	18	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.68 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Vertigo
 Safety Analysis Set, DC0 15FEB2024



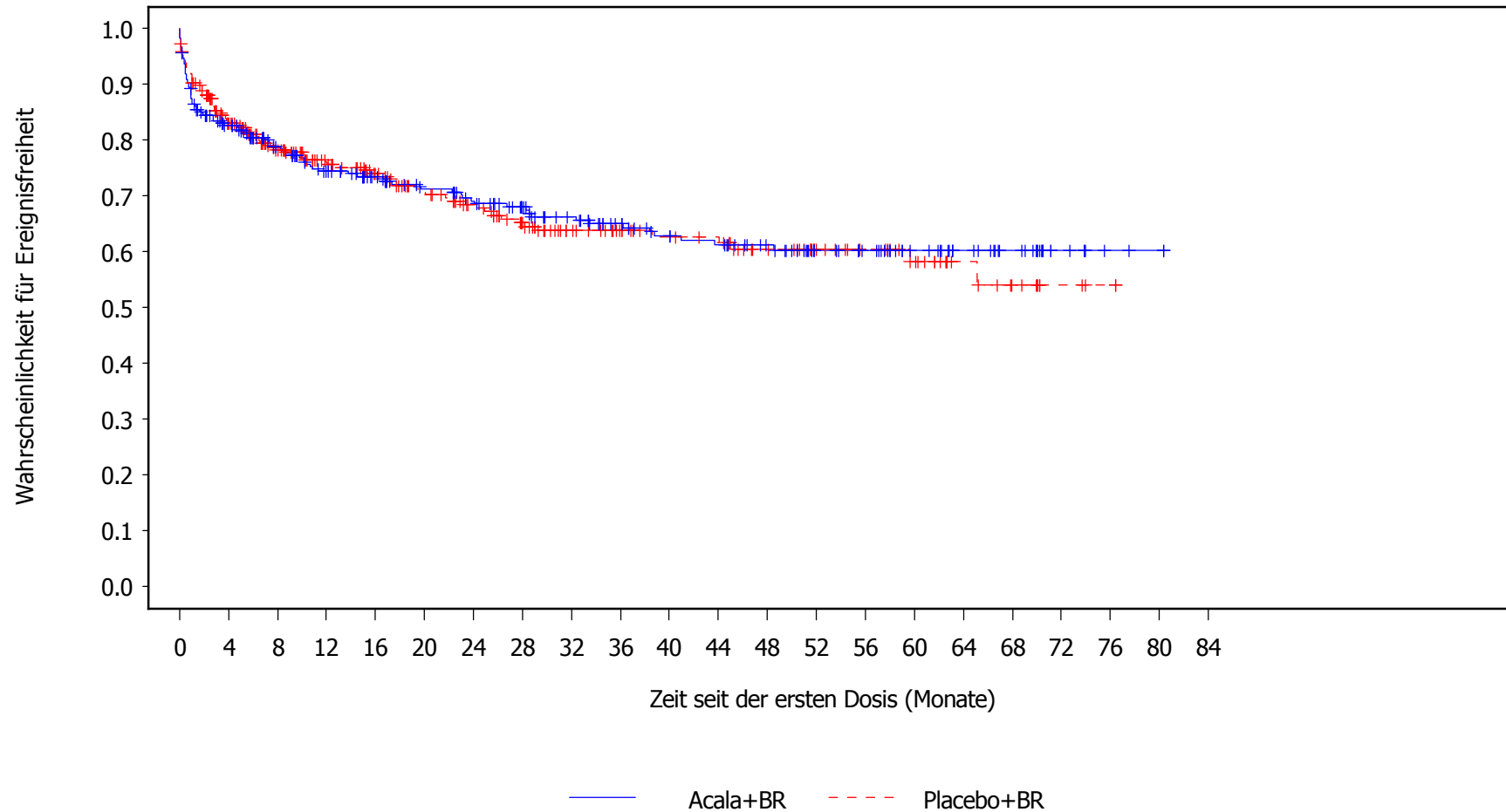
Anzahl an Patienten unter Risiko:

297	271	242	225	205	188	176	156	134	118	109	107	96	76	65	49	38	27	10	2	1	0	Acala+BR
297	265	235	201	182	170	156	139	119	104	95	91	79	64	56	47	32	18	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.69 ECHO: Kaplan-Meier plot of time to first occurrence of SOC: Gefaesserkrankungen
 Safety Analysis Set, DC0 15FEB2024



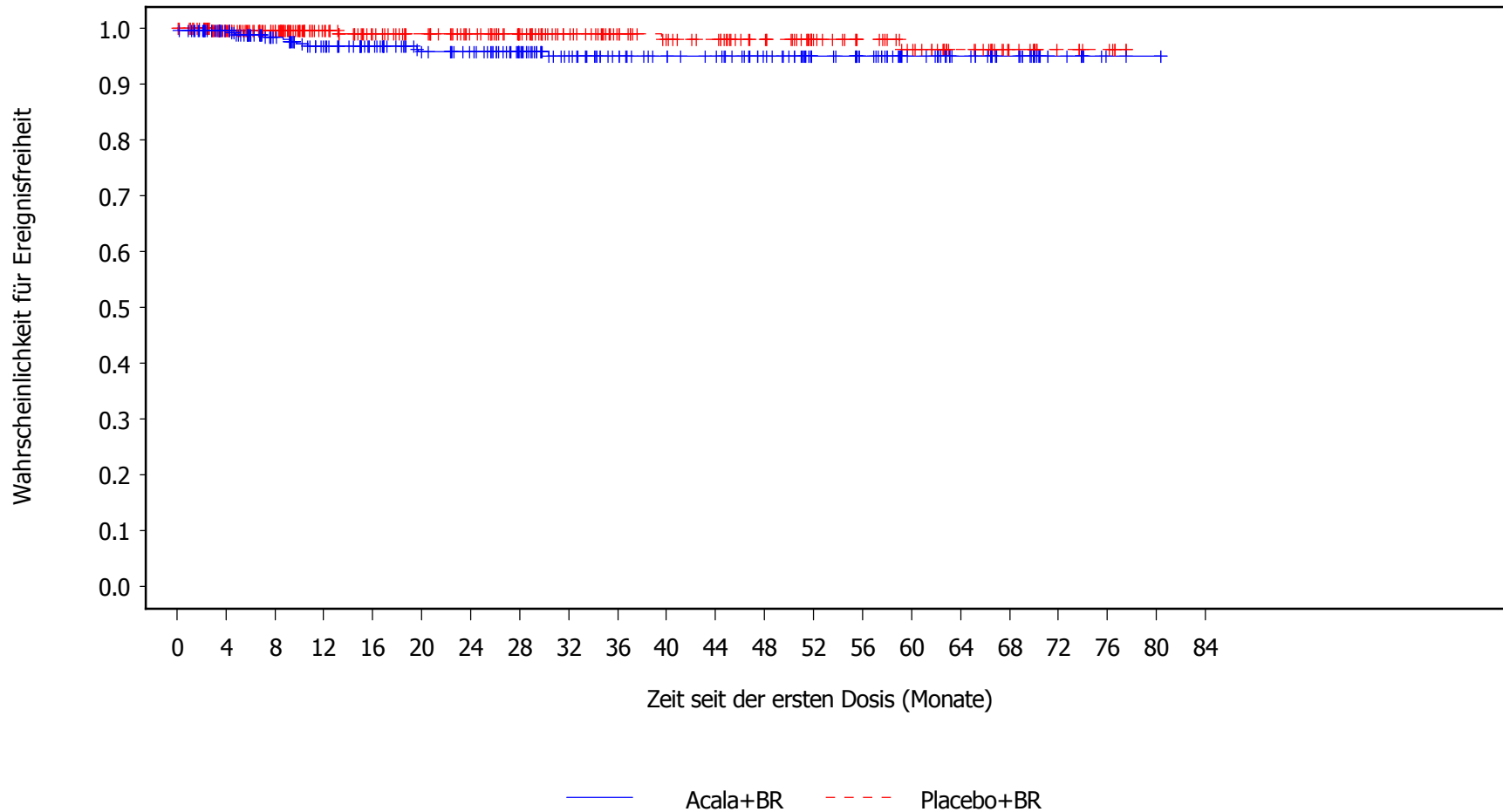
Anzahl an Patienten unter Risiko:

297	230	199	177	161	145	135	119	105	91	81	77	69	56	48	37	28	21	7	2	1	0	Acala+BR
297	223	188	160	142	125	110	94	77	68	61	59	49	38	31	25	14	9	3	1	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.70 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Haematom
 Safety Analysis Set, DC0 15FEB2024



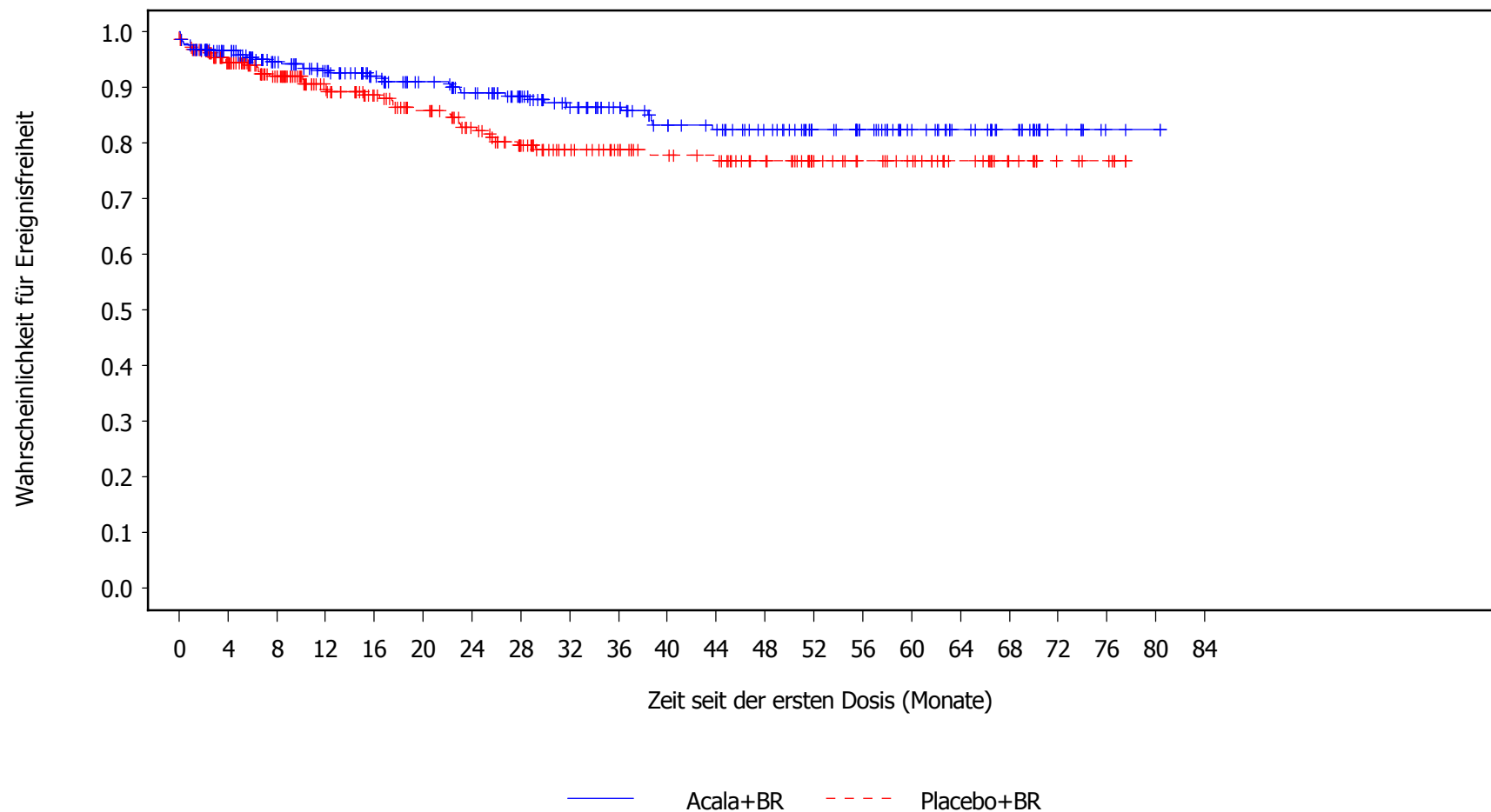
Anzahl an Patienten unter Risiko:

297	274	244	223	205	186	178	157	137	122	113	109	97	77	66	50	39	28	11	2	1	0	Acala+BR
297	266	238	203	184	172	158	142	123	108	98	93	81	65	56	47	32	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.71 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Hypertonie
 Safety Analysis Set, DCO 15FEB2024



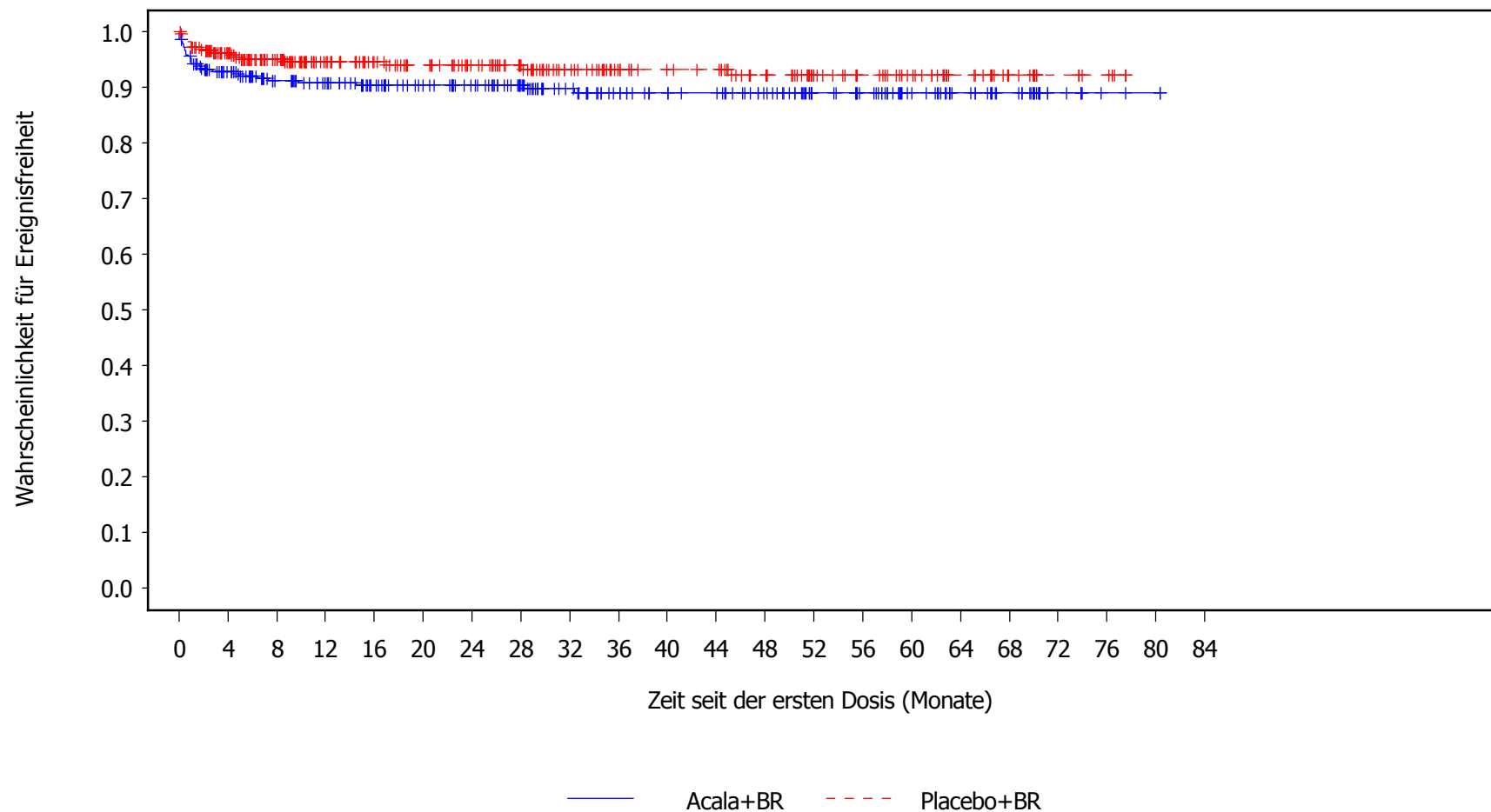
Anzahl an Patienten unter Risiko:

297	266	235	215	194	178	165	146	129	115	101	96	86	70	59	45	35	26	9	2	1	0	Acala+BR
297	253	221	188	167	150	132	113	95	85	77	74	63	48	41	36	25	15	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.72 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Hypotonie
 Safety Analysis Set, DC0 15FEB2024



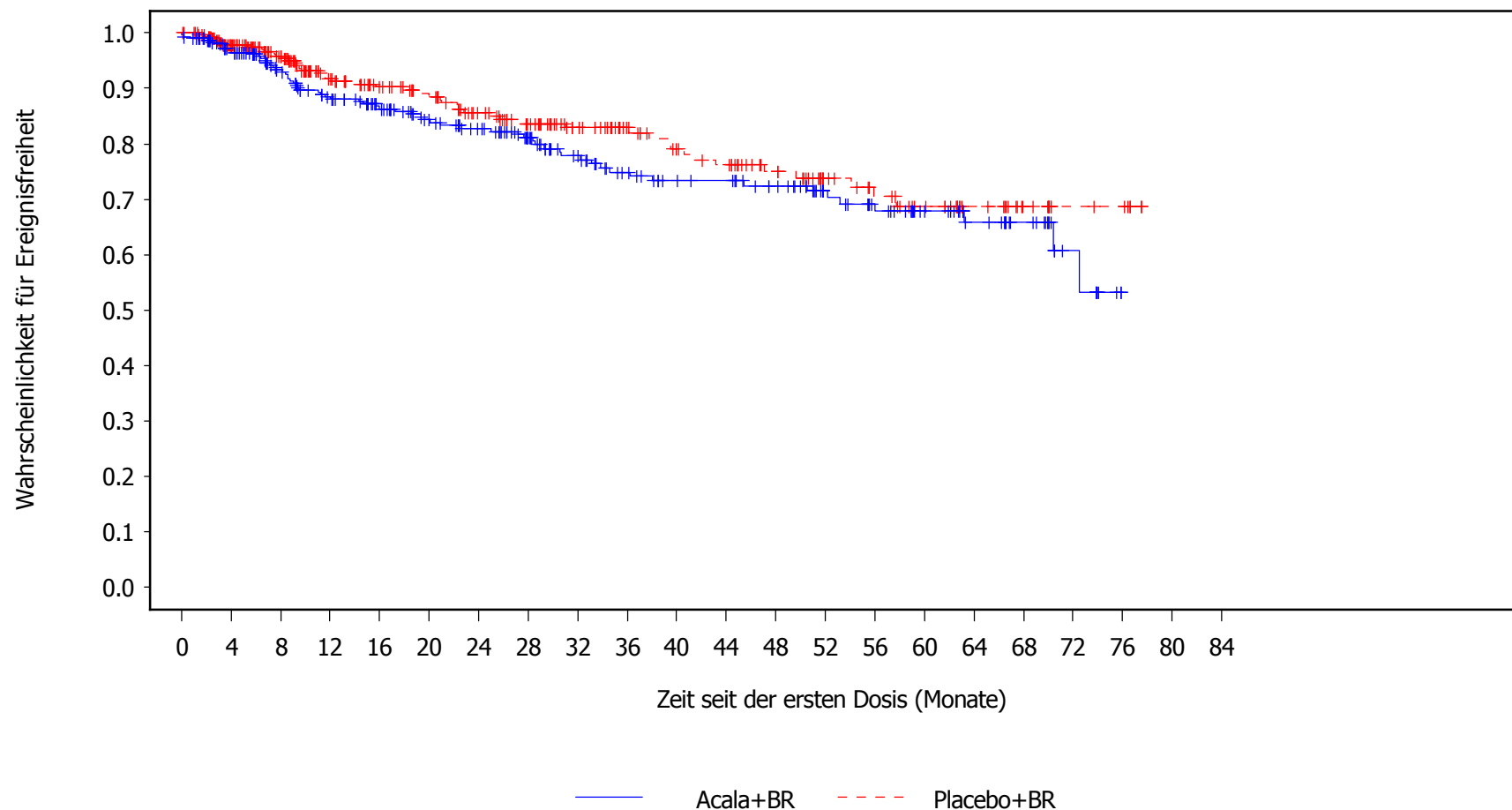
Anzahl an Patienten unter Risiko:

297	256	226	211	192	177	166	147	127	113	105	102	91	72	63	46	35	25	8	2	1	0	Acala+BR
297	257	226	192	175	162	148	132	112	97	90	88	76	60	51	43	28	17	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.73 ECH0: Kaplan-Meier plot of time to first occurrence of SOC: Gutartige, boesartige und nicht spezifizierte Neubildungen (einschl. Zysten und Polypen)
 Safety Analysis Set, DCO 15FEB2024



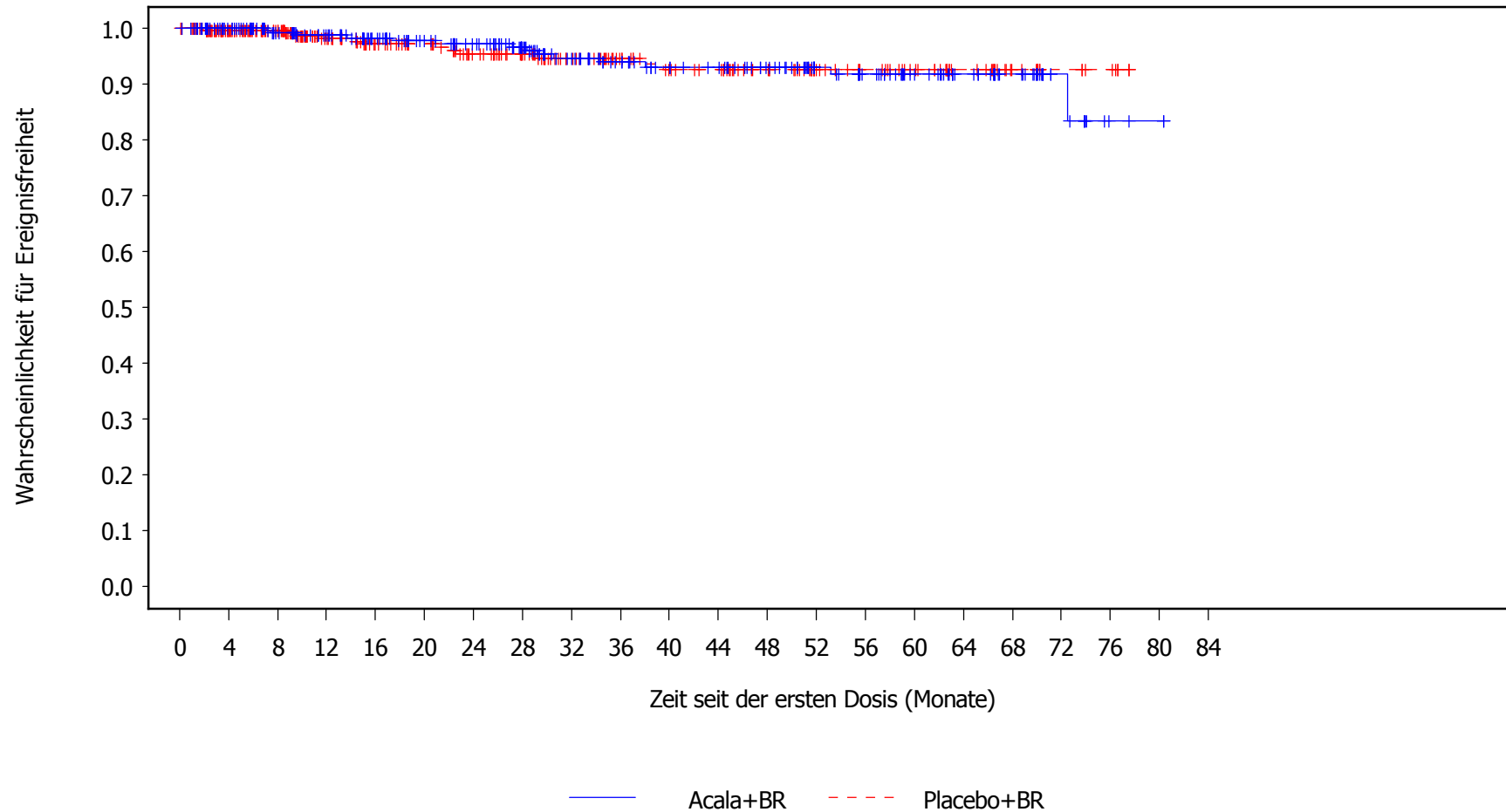
Anzahl an Patienten unter Risiko:

297	268	234	209	186	166	153	132	113	98	89	87	79	62	52	41	31	22	8	0	0	0	Acala+BR
297	262	228	188	169	156	138	123	105	92	81	76	64	49	42	34	23	14	6	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.74 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Basalzellkarzinom
 Safety Analysis Set, DCO 15FEB2024



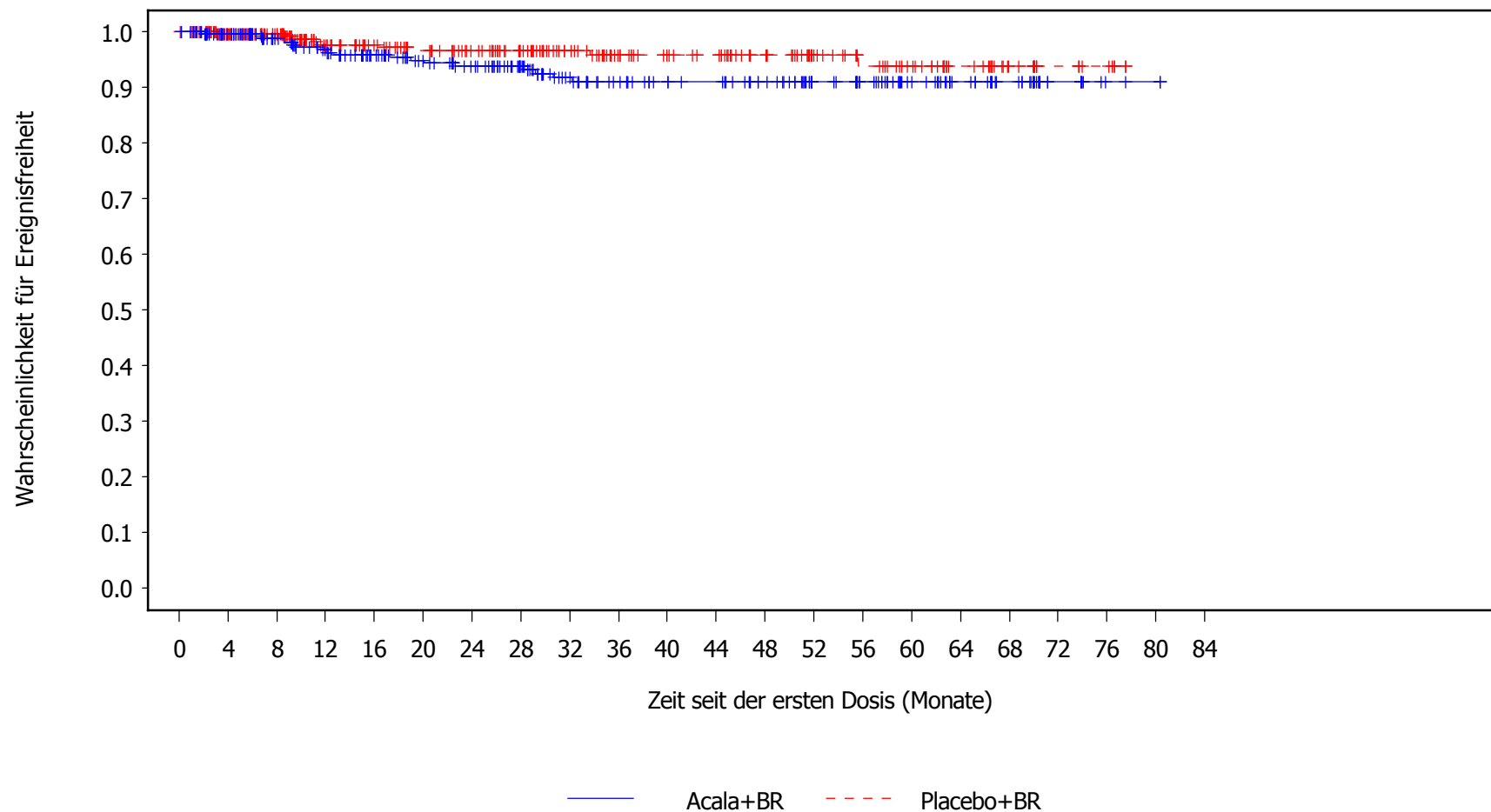
Anzahl an Patienten unter Risiko:

297	275	246	229	208	190	178	156	134	119	108	104	93	73	64	50	39	28	11	2	1	0	Acala+BR
297	266	237	199	178	166	149	133	113	98	88	84	72	57	49	41	29	17	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.75 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Plattenepithelkarzinom der Haut
 Safety Analysis Set, DCO 15FEB2024



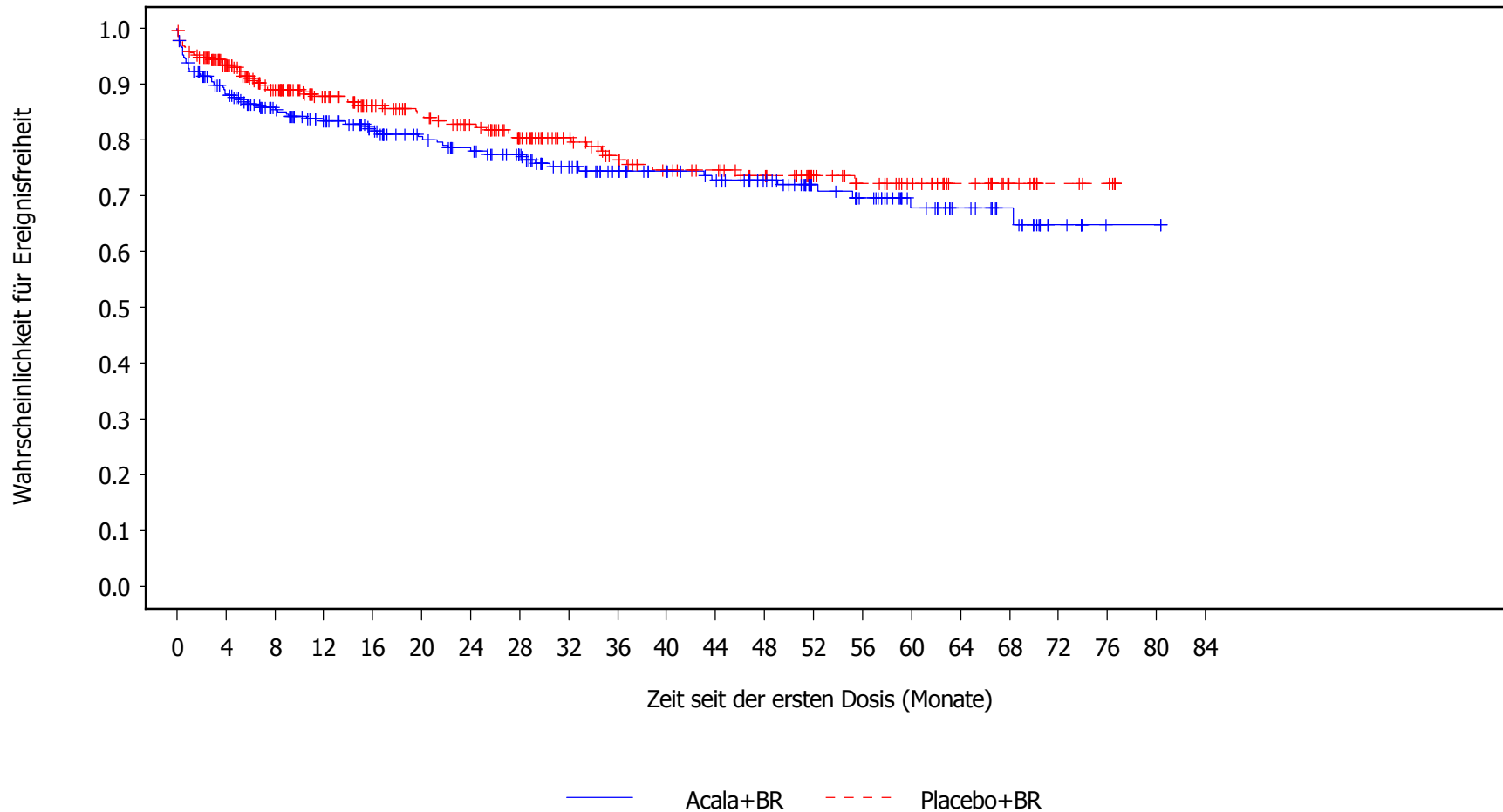
Anzahl an Patienten unter Risiko:

297	274	245	224	202	183	171	150	127	114	105	102	93	75	65	49	38	27	10	2	1	0	Acala+BR
297	266	237	198	180	166	153	137	119	103	94	90	78	61	51	43	29	17	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.76 ECHO: Kaplan-Meier plot of time to first occurrence of SOC: Herzerkrankungen
 Safety Analysis Set, DC0 15FEB2024



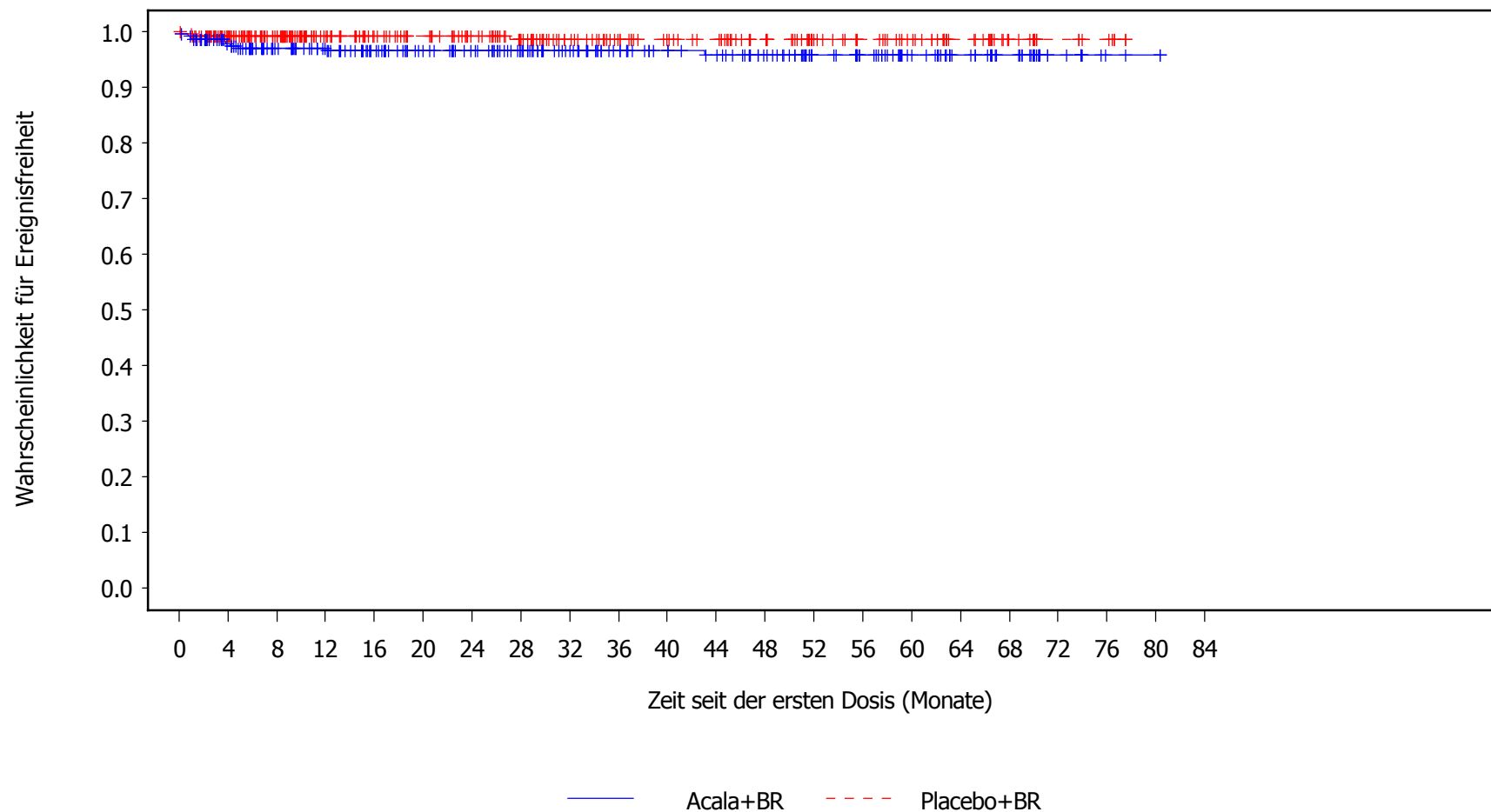
Anzahl an Patienten unter Risiko:

297	249	218	198	177	162	149	136	118	105	97	91	82	63	53	38	29	22	8	1	1	0	Acala+BR
297	253	216	187	166	152	140	122	104	91	82	78	70	55	46	39	26	16	6	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.77 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Palpitationen
 Safety Analysis Set, DC0 15FEB2024



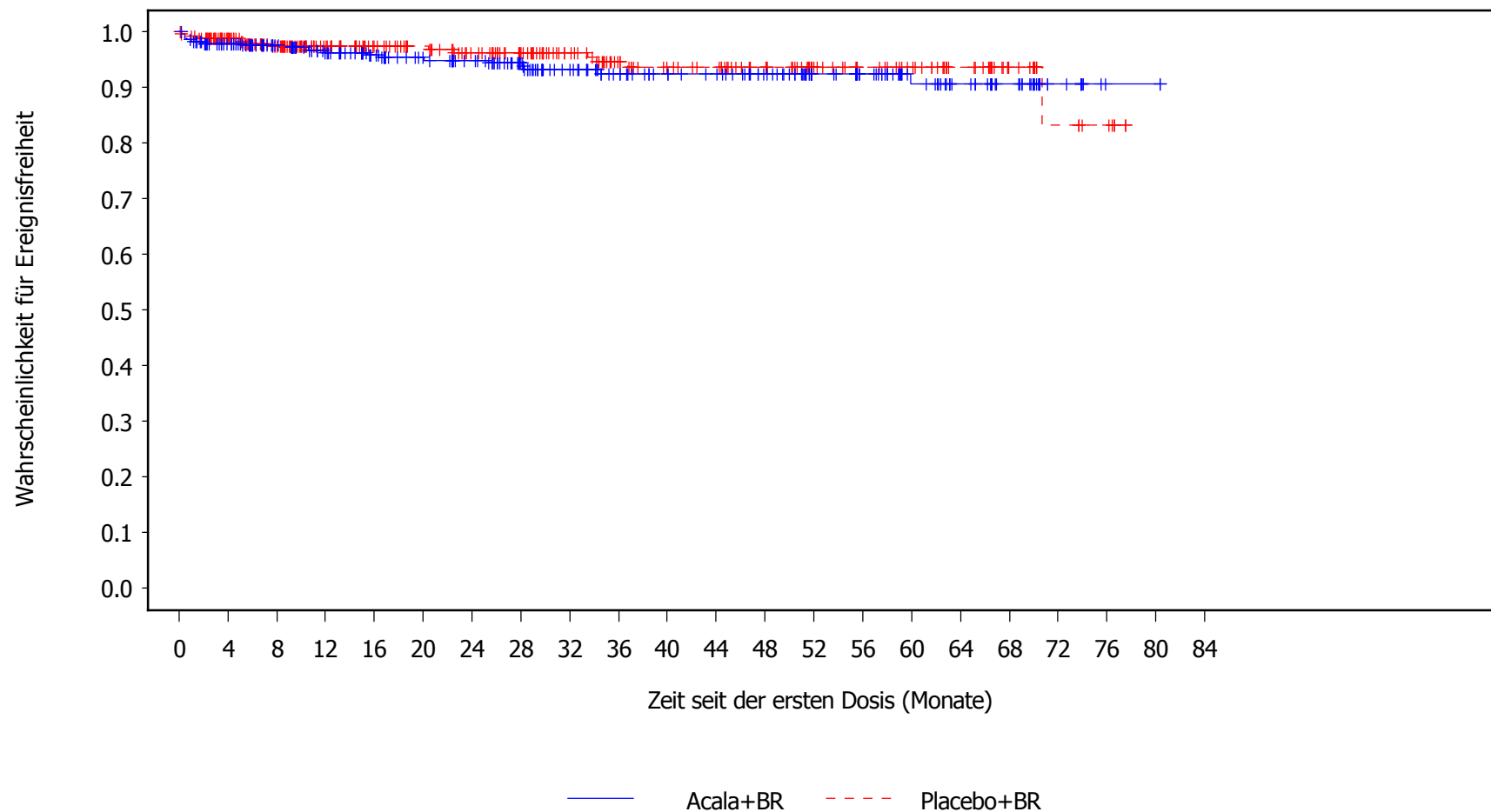
Anzahl an Patienten unter Risiko:

297	269	240	222	202	185	174	157	139	124	114	109	98	77	66	50	39	28	10	2	1	0	Acala+BR
297	265	236	201	182	170	156	139	120	107	98	93	81	64	55	47	32	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.78 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Vorhofflimmern
 Safety Analysis Set, DC0 15FEB2024



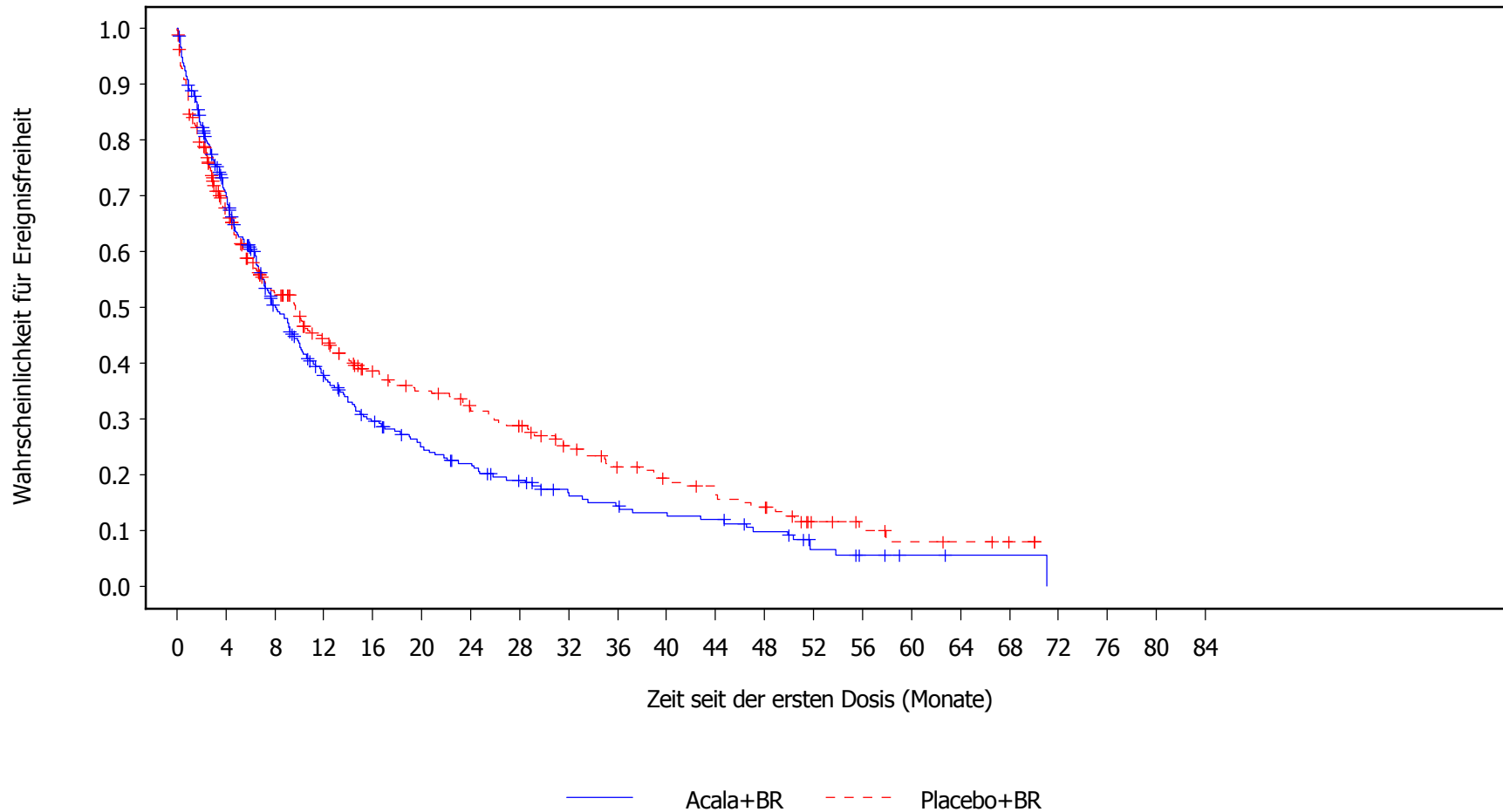
Anzahl an Patienten unter Risiko:

297	273	246	226	206	191	181	159	138	123	113	109	98	78	67	50	39	28	10	1	1	0	Acala+BR
297	266	235	202	183	171	157	141	122	105	95	91	80	63	54	47	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.79 ECH0: Kaplan-Meier plot of time to first occurrence of SOC: Infektionen und parasitaere Erkrankungen
 Safety Analysis Set, DCO 15FEB2024



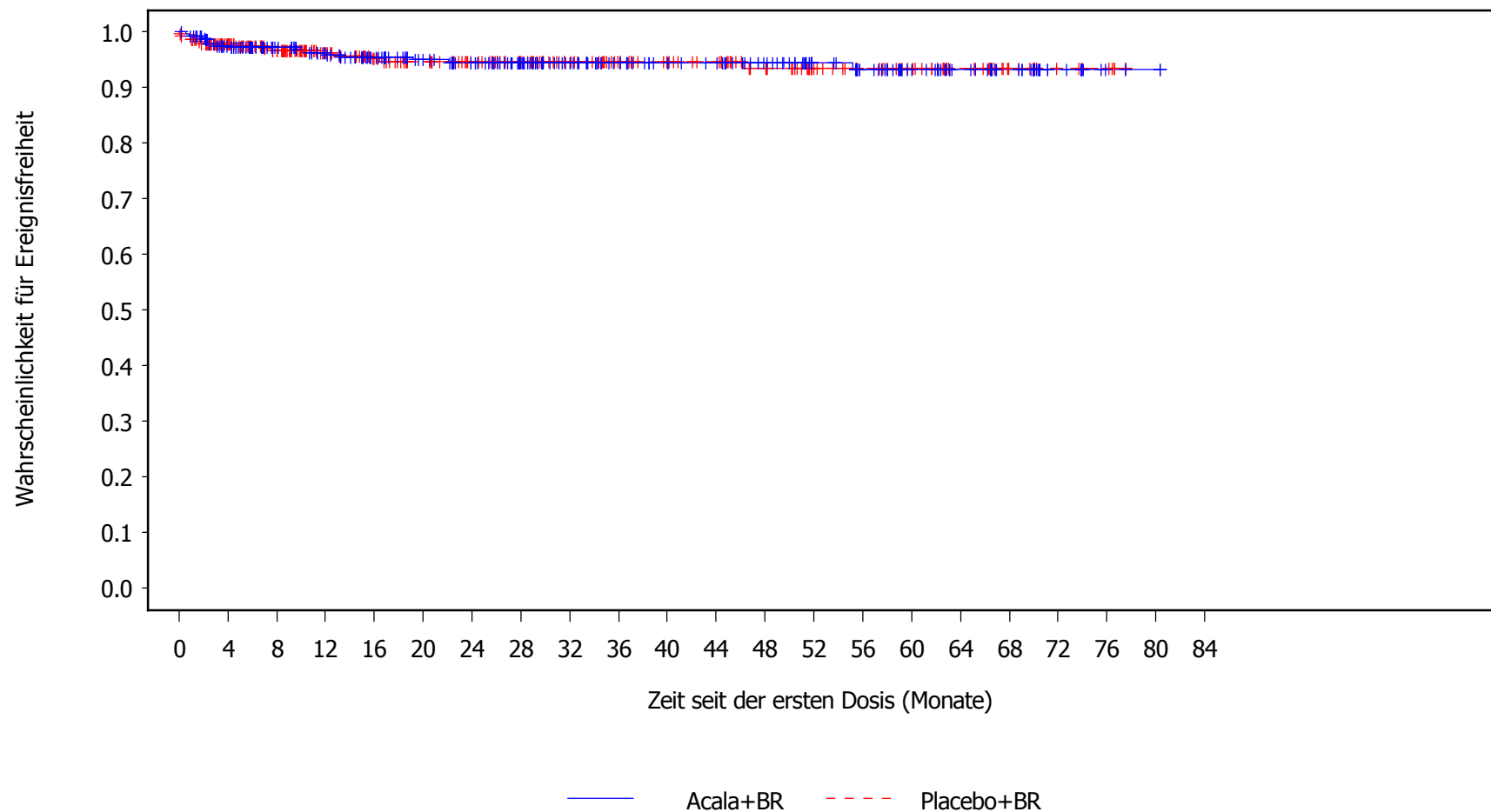
Anzahl an Patienten unter Risiko:

297	196	127	89	67	53	45	36	28	24	21	19	14	7	4	2	1	1	0	0	0	0	Acala+BR
297	184	131	101	79	69	59	52	41	32	27	22	19	9	6	4	3	1	0	0	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.80 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Atemwegsinfektion
 Safety Analysis Set, DC0 15FEB2024



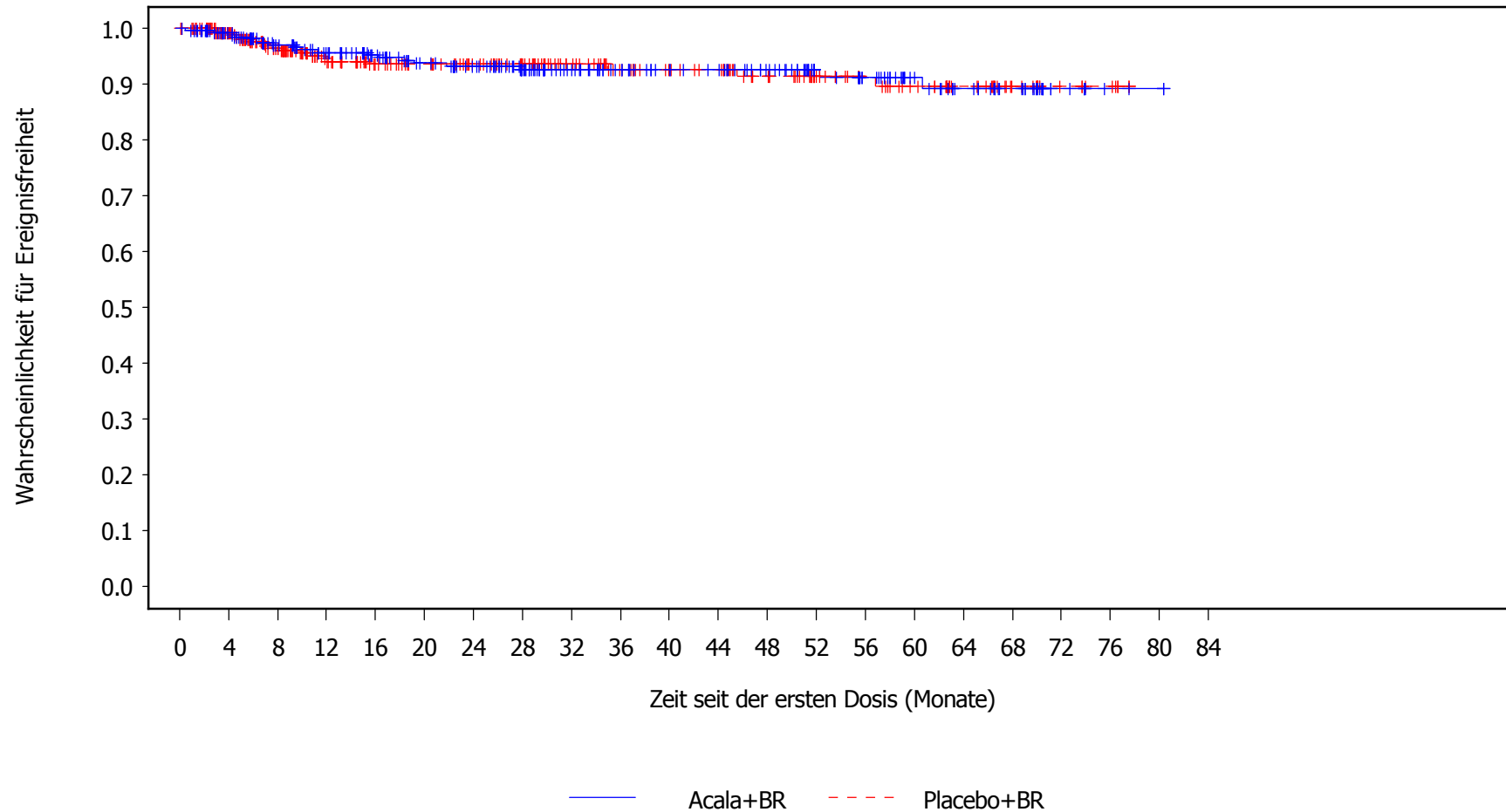
Anzahl an Patienten unter Risiko:

297	268	240	222	204	186	175	155	135	120	110	106	95	75	63	47	37	27	11	2	1	0	Acala+BR
297	261	232	198	177	164	150	134	116	103	94	89	77	61	52	44	29	15	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.81 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Bronchitis
 Safety Analysis Set, DCO 15FEB2024



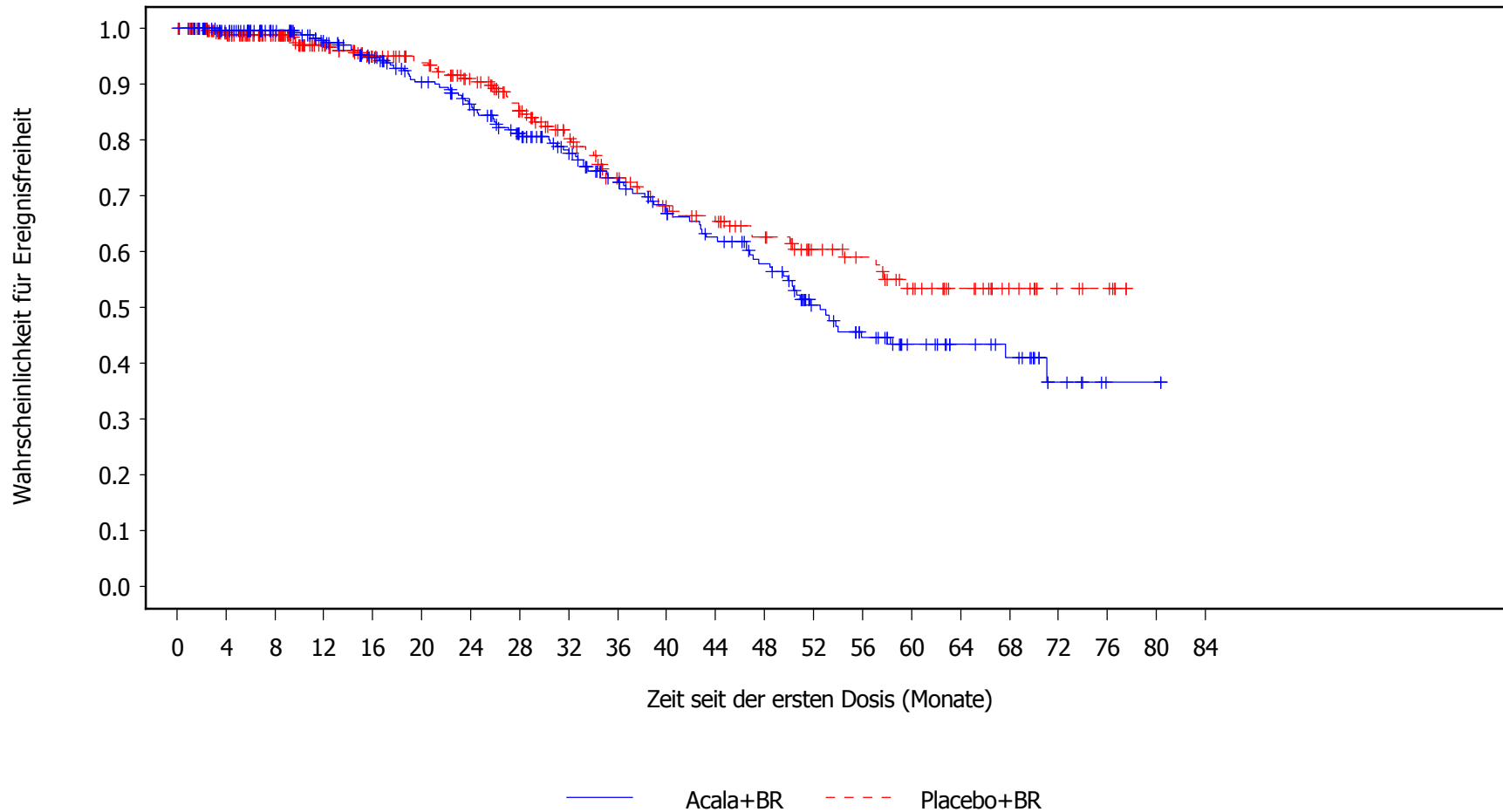
Anzahl an Patienten unter Risiko:

297	273	241	221	201	182	170	149	128	115	105	101	90	70	60	44	35	26	8	2	1	0	Acala+BR
297	265	229	192	172	161	148	133	114	100	92	88	76	59	51	43	31	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.82 ECHO: Kaplan-Meier plot of time to first occurrence of PT: COVID-19
 Safety Analysis Set, DC0 15FEB2024



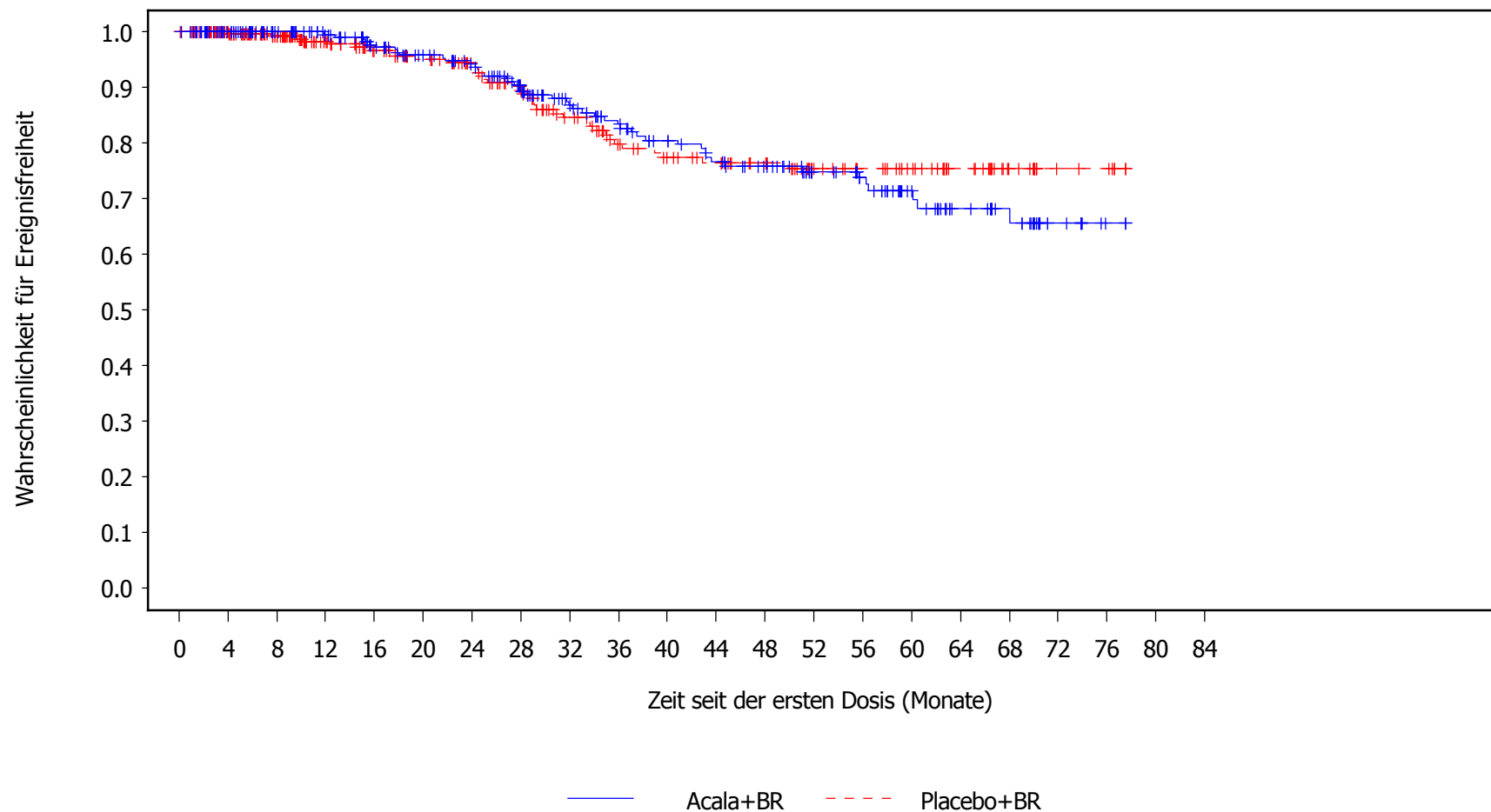
Anzahl an Patienten unter Risiko:

297	274	247	226	204	184	169	146	128	109	94	85	74	53	41	30	22	18	6	1	1	0	Acala+BR
297	267	238	201	180	168	151	128	107	89	78	72	62	49	43	33	24	15	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.83 ECHO: Kaplan-Meier plot of time to first occurrence of PT: COVID-19-Lungenentzündung
 Safety Analysis Set, DCO 15FEB2024



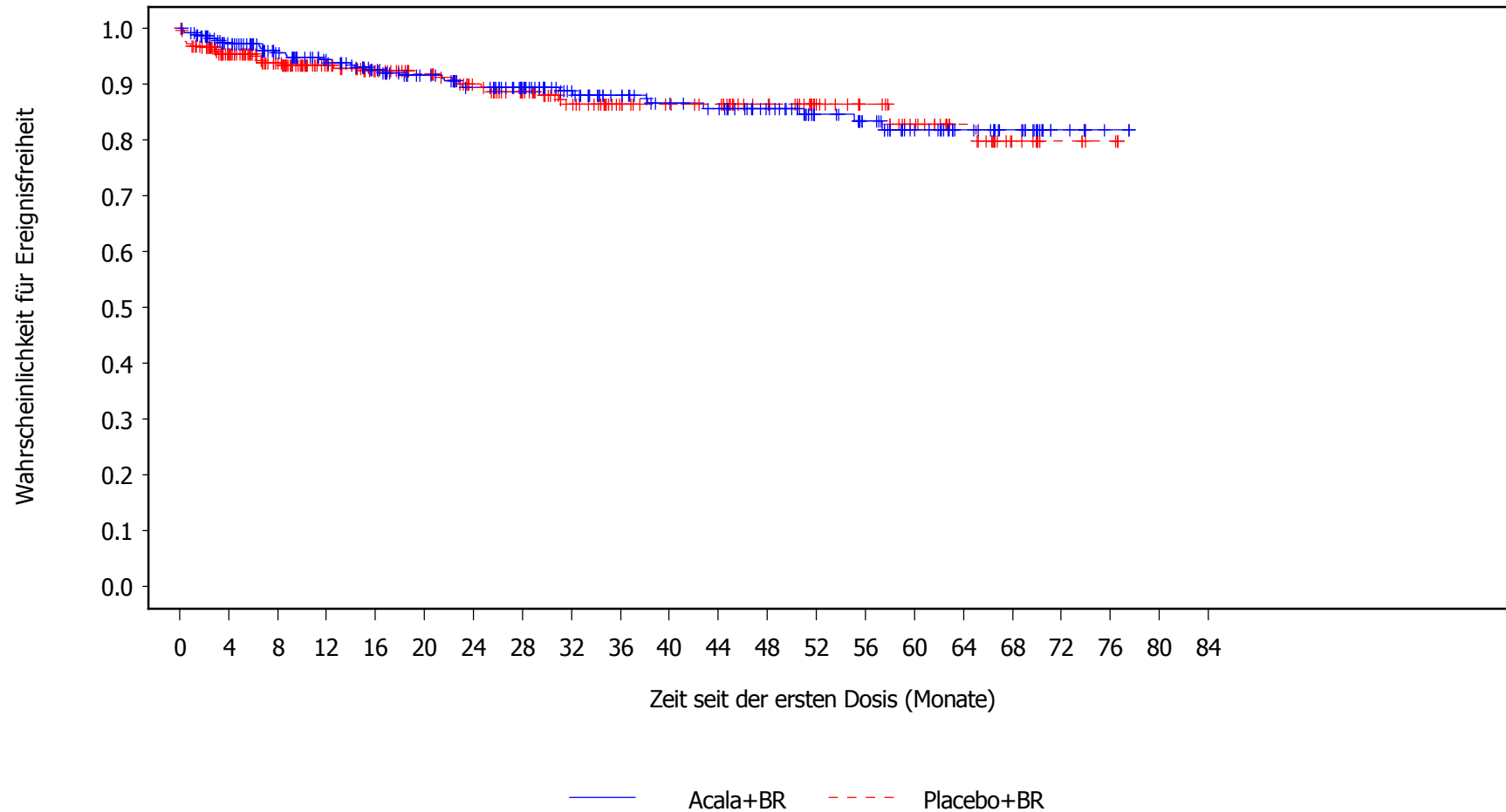
Anzahl an Patienten unter Risiko:

297	275	248	230	208	191	179	156	134	119	107	98	90	72	62	46	34	26	9	1	0	0	Acala+BR
297	267	237	202	182	169	152	134	114	97	89	84	76	59	51	44	30	17	6	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.84 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Harnwegsinfektion
 Safety Analysis Set, DC0 15FEB2024



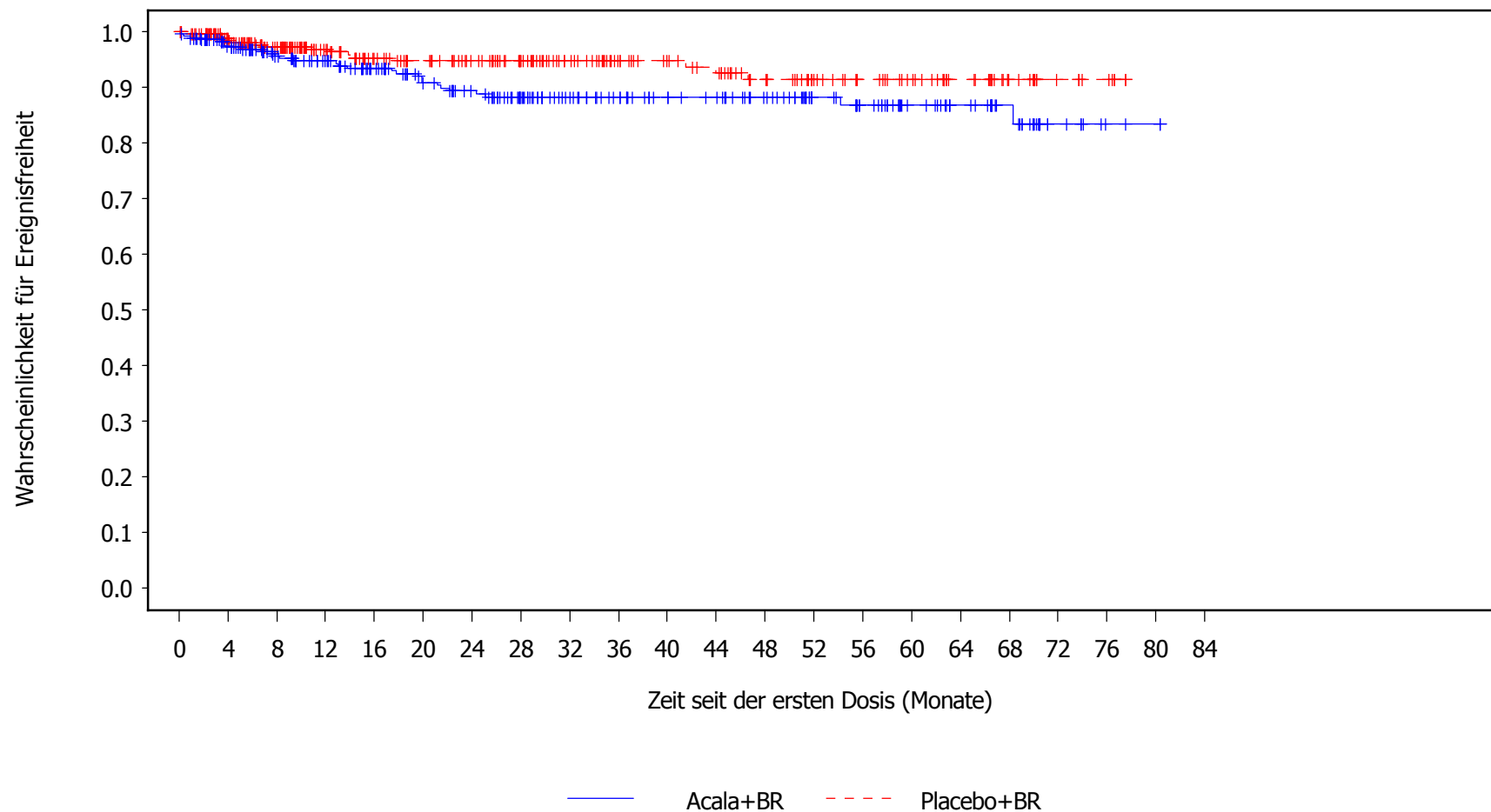
Anzahl an Patienten unter Risiko:

297	268	237	217	196	179	165	150	131	116	106	102	91	70	58	43	32	23	7	1	0	0	Acala+BR
297	255	222	190	171	158	141	127	108	94	88	85	74	59	51	41	28	15	6	3	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.85 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Herpes zoster
 Safety Analysis Set, DC0 15FEB2024



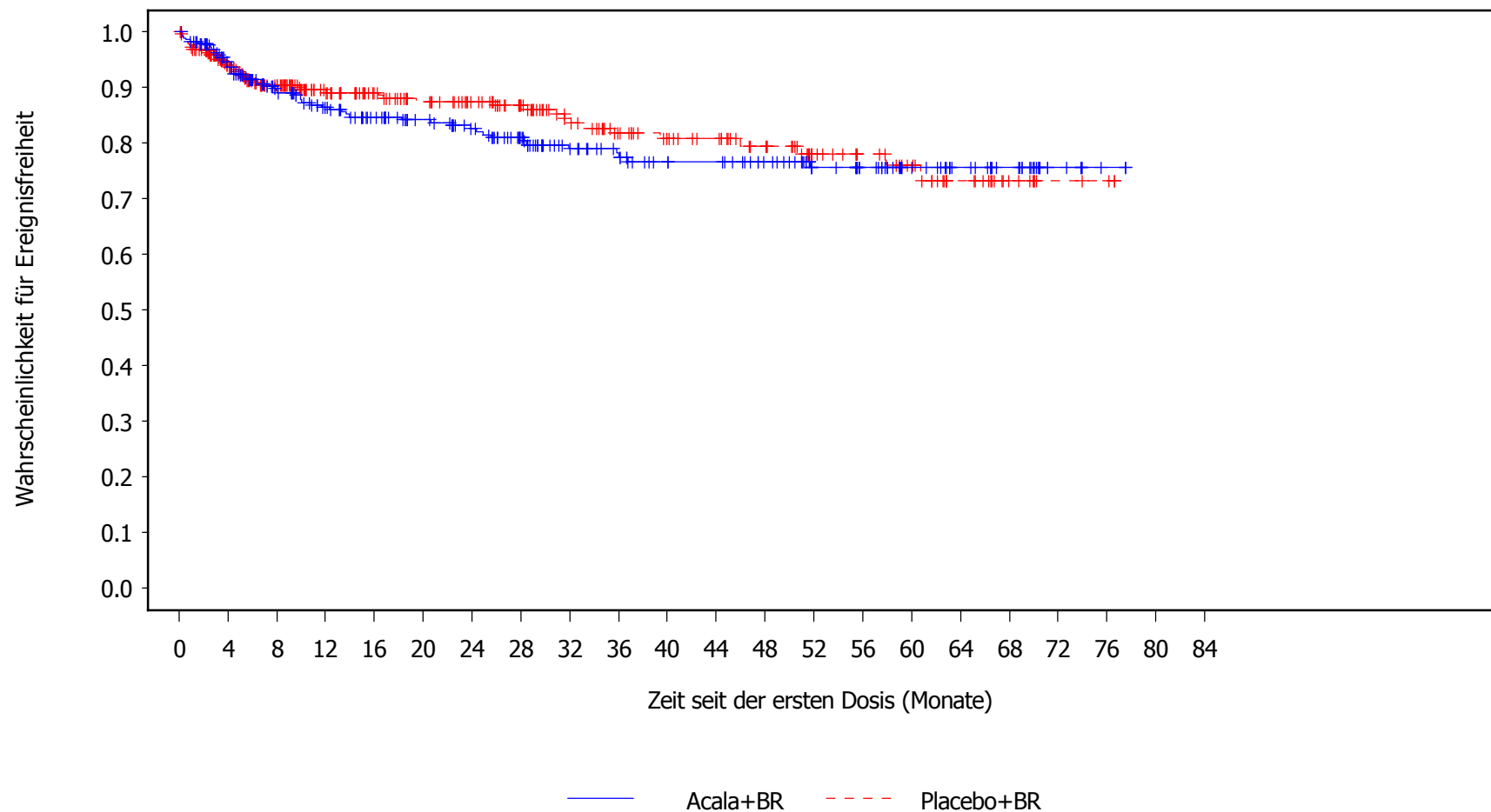
Anzahl an Patienten unter Risiko:

297	268	238	219	197	176	163	142	123	111	101	97	87	67	58	44	35	25	8	2	1	0	Acala+BR
297	264	233	197	175	163	150	134	116	101	93	87	75	61	52	45	32	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.86 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Infektion der oberen Atemwege
 Safety Analysis Set, DCO 15FEB2024



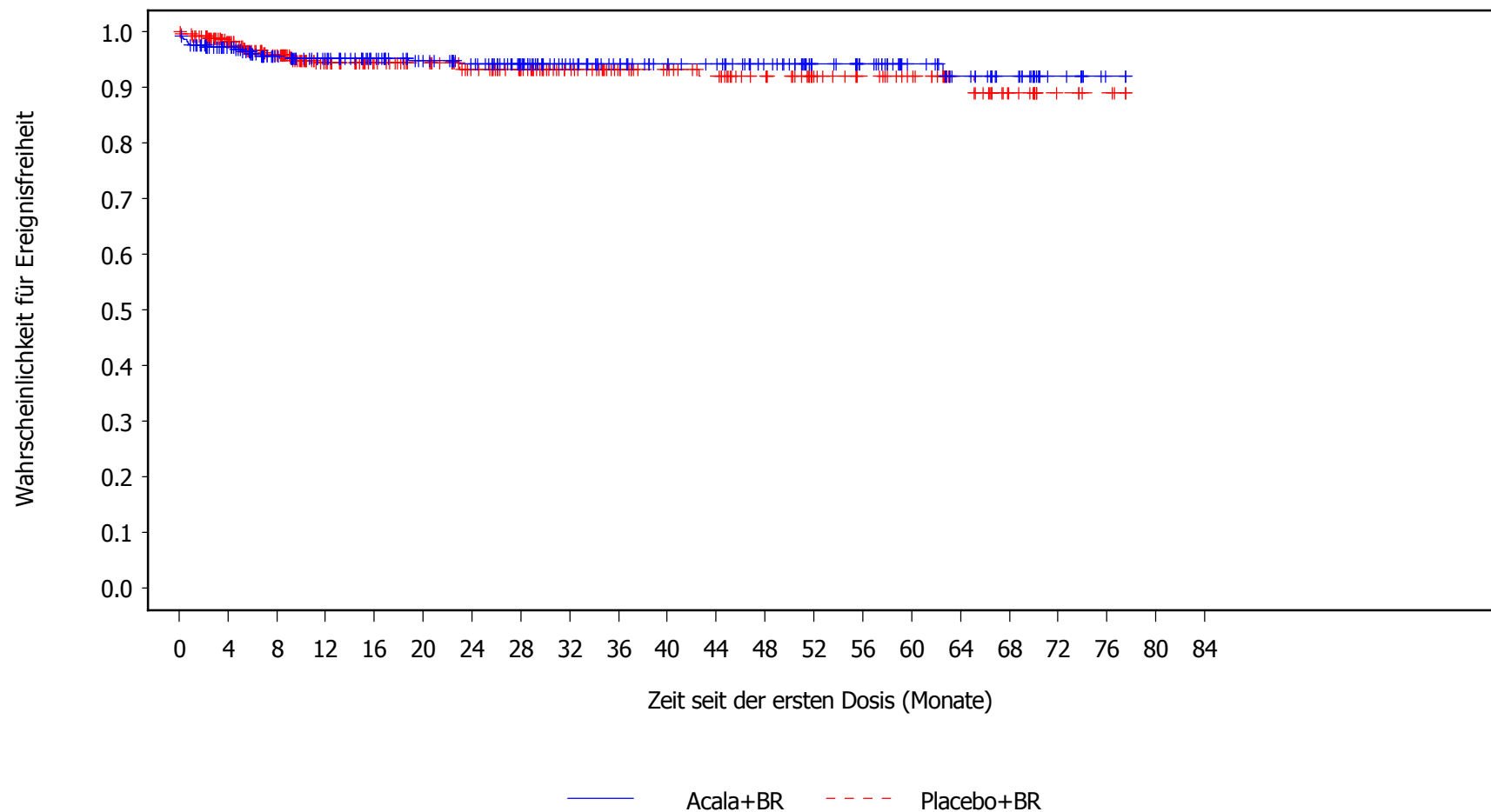
Anzahl an Patienten unter Risiko:

297	260	220	199	180	165	151	133	111	102	91	89	80	63	54	40	31	23	7	1	0	0	Acala+BR
297	250	216	184	164	149	137	120	101	87	78	73	63	45	38	31	19	9	3	2	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.87 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Nasopharyngitis
 Safety Analysis Set, DC0 15FEB2024



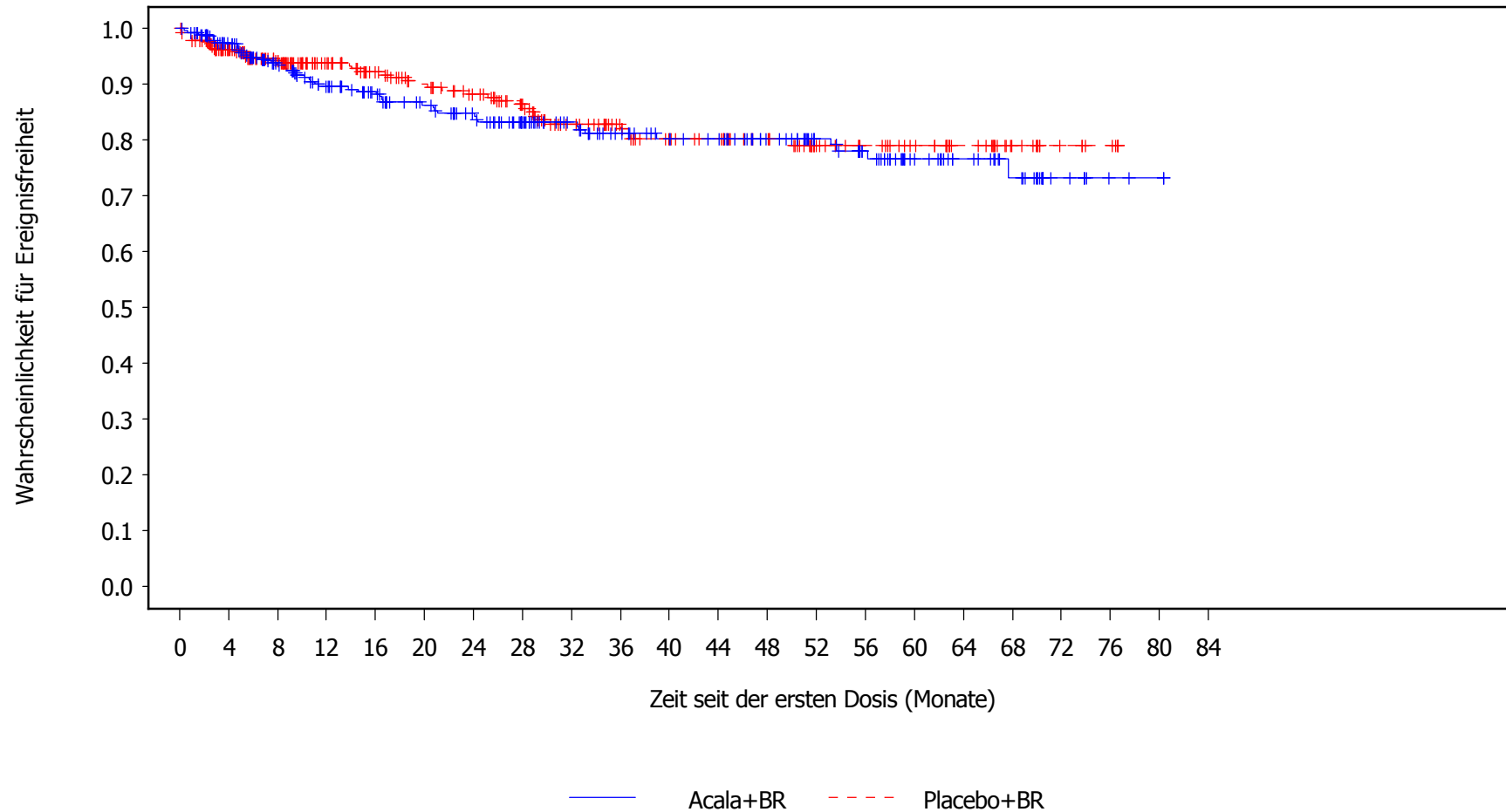
Anzahl an Patienten unter Risiko:

297	267	236	218	200	185	174	153	132	119	109	105	93	73	62	47	36	26	10	1	0	0	Acala+BR
297	262	227	190	171	161	147	133	114	100	91	85	74	59	51	44	30	17	6	3	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.88 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Pneumonie
 Safety Analysis Set, DC0 15FEB2024



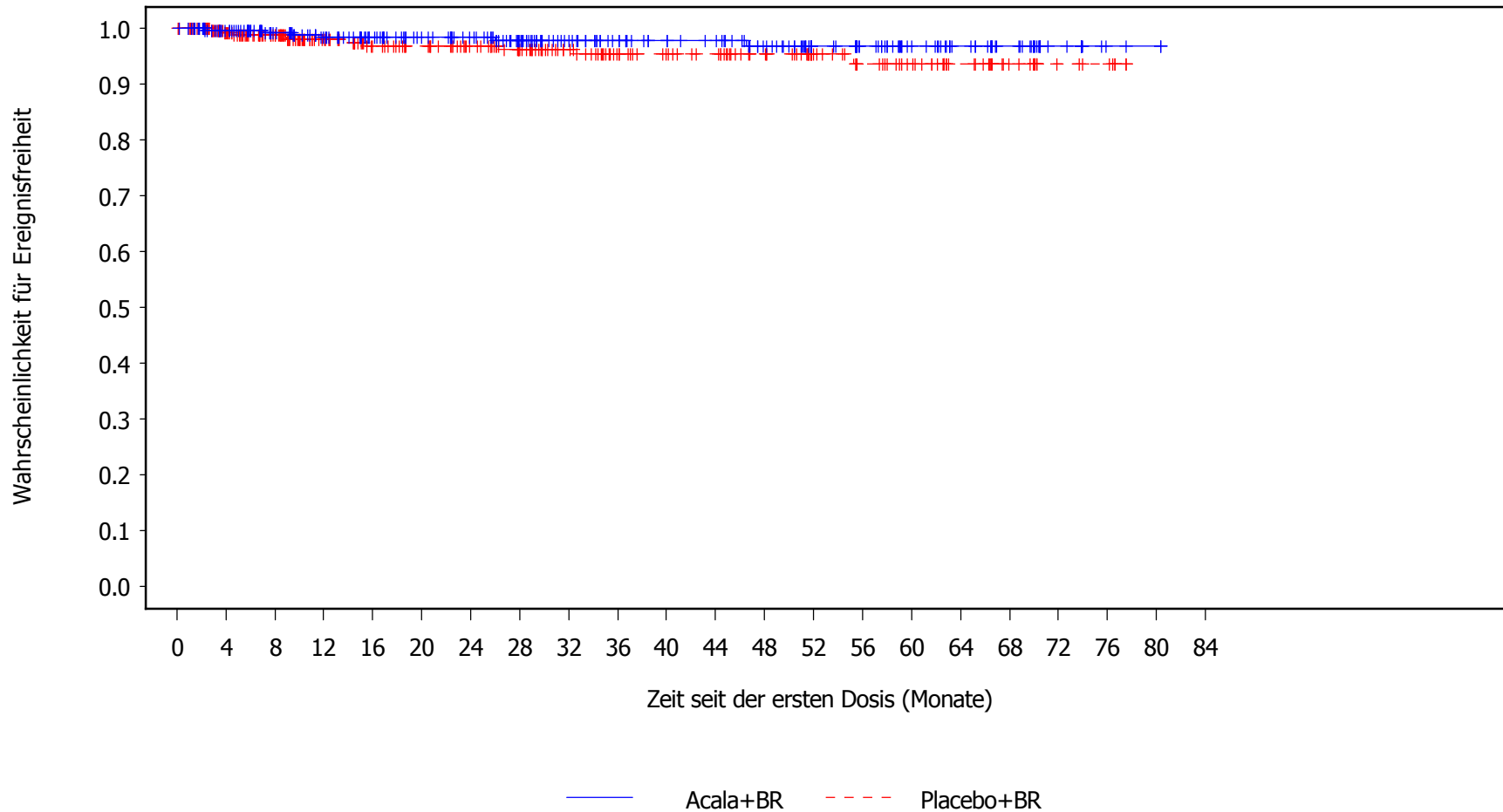
Anzahl an Patienten unter Risiko:

297	268	231	207	189	173	160	139	122	109	100	96	84	70	57	39	31	22	8	2	1	0	Acala+BR
297	259	226	193	173	158	146	128	107	95	83	79	70	53	45	38	27	15	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.89 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Rhinitis
 Safety Analysis Set, DC0 15FEB2024



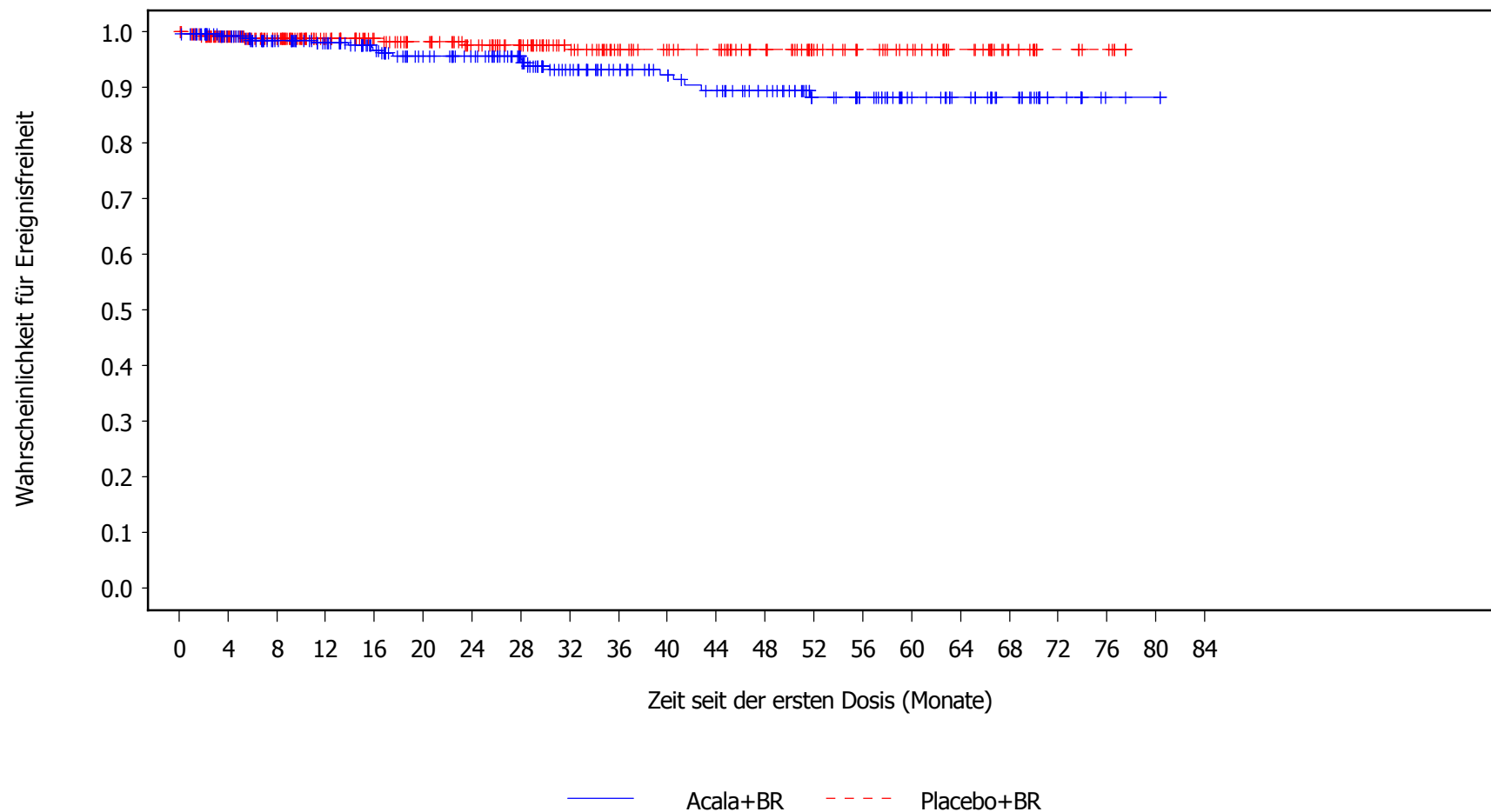
Anzahl an Patienten unter Risiko:

297	274	246	227	207	190	179	157	136	122	113	109	96	75	64	48	37	26	10	2	1	0	Acala+BR
297	265	236	200	179	168	154	138	119	103	95	90	78	62	52	44	30	18	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.90 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Sinusitis
 Safety Analysis Set, DC0 15FEB2024



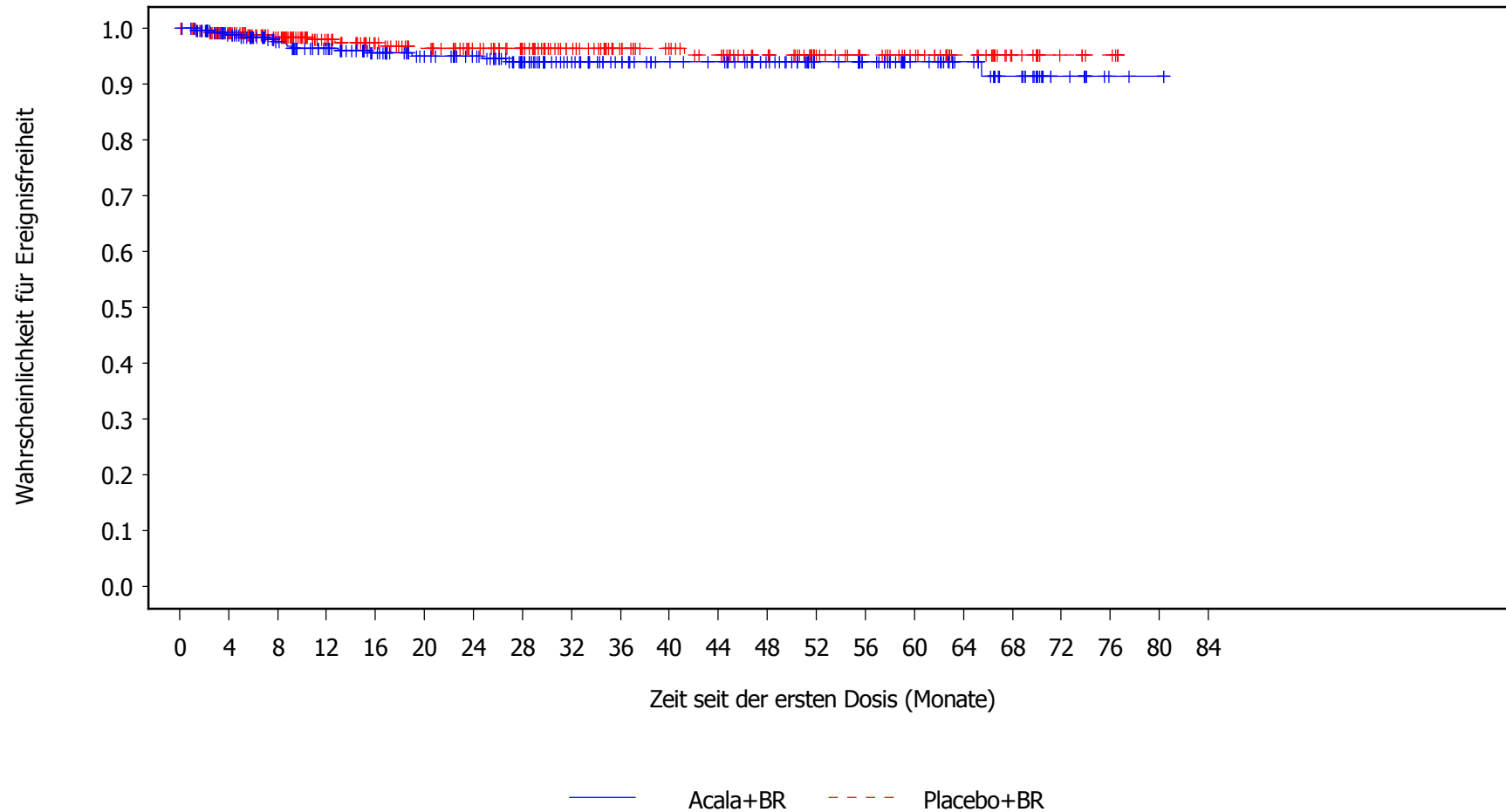
Anzahl an Patienten unter Risiko:

297	273	245	227	204	185	175	153	130	115	104	97	87	68	58	42	34	25	10	2	1	0	Acala+BR
297	265	235	200	182	170	155	139	120	104	95	91	79	62	53	46	31	17	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.91 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Zellulitis
 Safety Analysis Set, DCO 15FEB2024



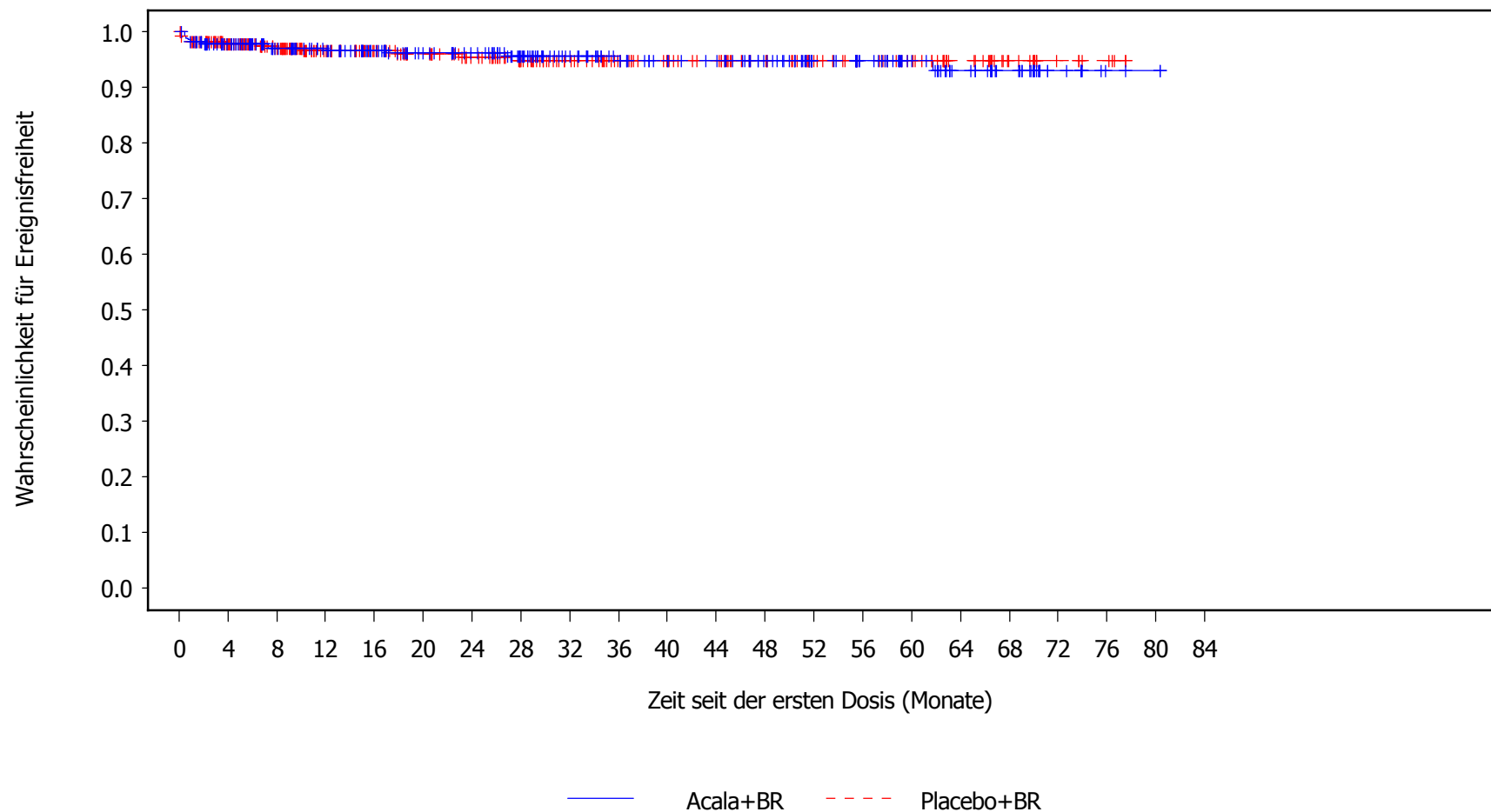
Anzahl an Patienten unter Risiko:

297	272	242	223	202	185	175	152	132	118	108	105	94	75	66	51	40	28	11	2	1	0	Acala+BR
297	267	236	201	181	167	153	139	120	106	97	91	80	63	54	46	31	17	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.92 ECH0: Kaplan-Meier plot of time to first occurrence of SOC: Leber- und Gallenerkrankungen
 Safety Analysis Set, DC0 15FEB2024



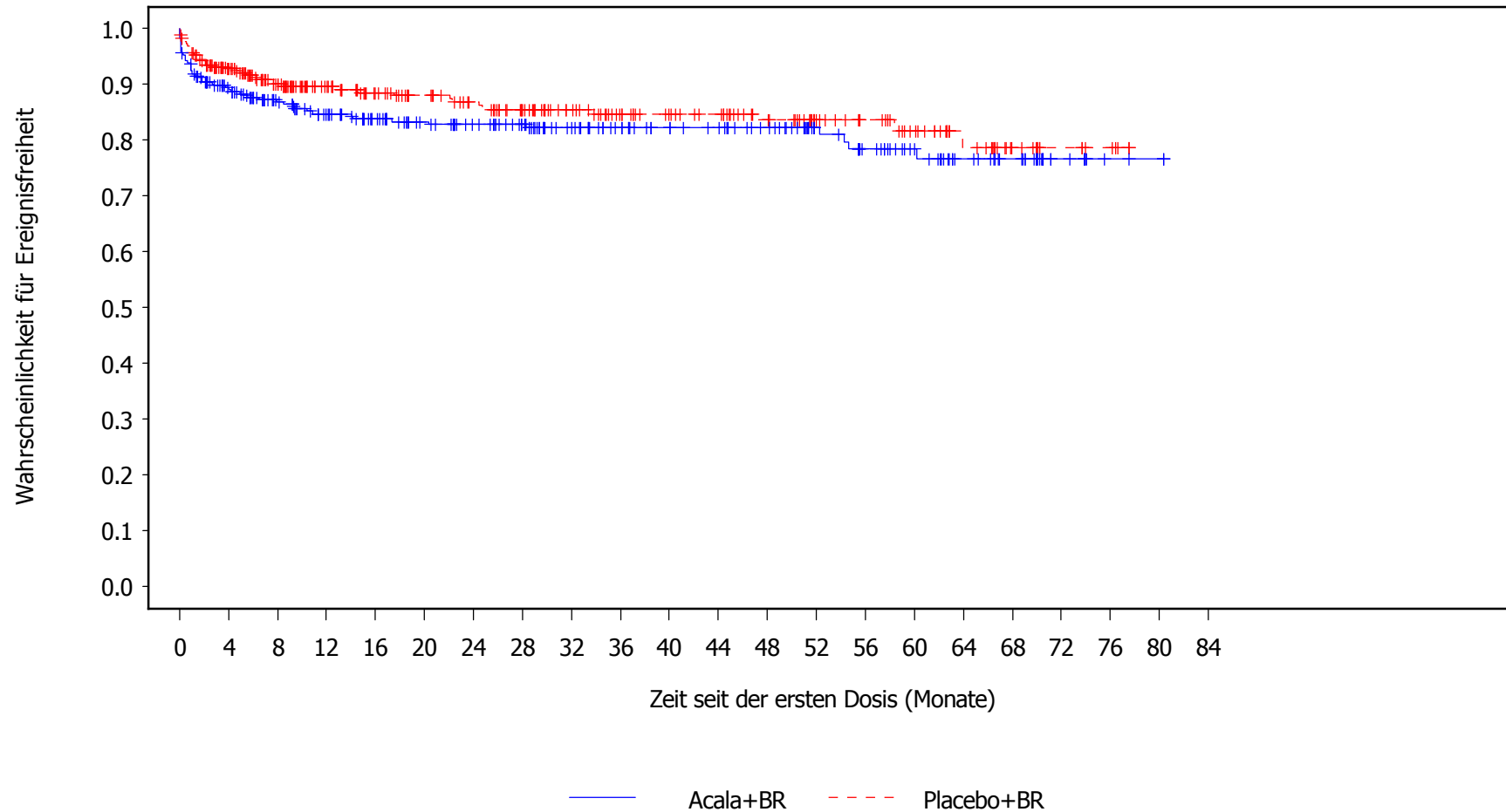
Anzahl an Patienten unter Risiko:

297	270	242	226	205	187	178	157	136	121	112	108	97	78	67	51	39	28	10	2	1	0	Acala+BR
297	263	233	198	179	166	153	136	118	105	96	91	80	64	55	47	32	18	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.93 ECH0: Kaplan-Meier plot of time to first occurrence of SOC: Psychiatrische Erkrankungen
 Safety Analysis Set, DCO 15FEB2024



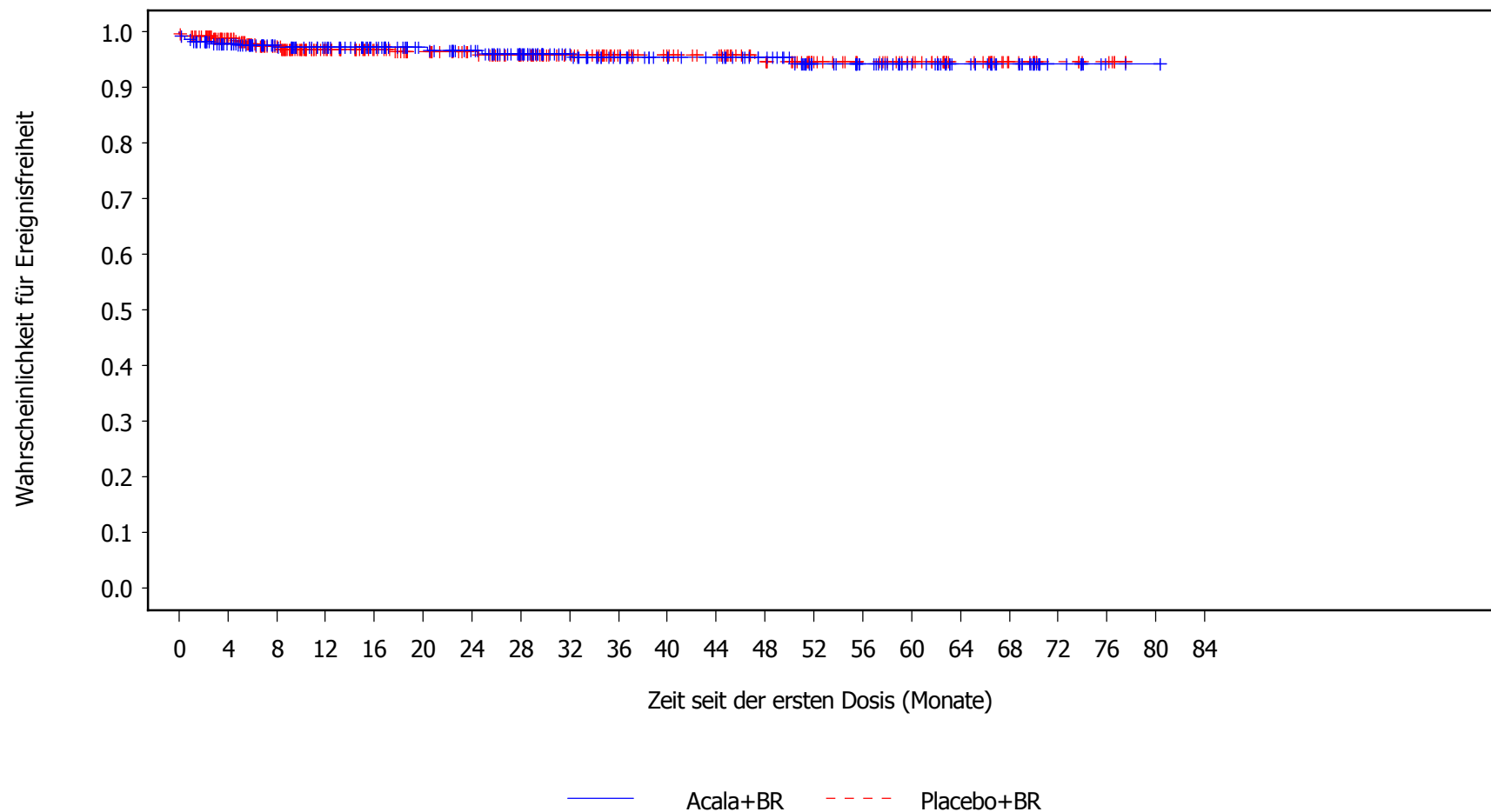
Anzahl an Patienten unter Risiko:

297	246	216	196	176	160	148	136	117	104	95	91	83	66	55	44	33	26	9	2	1	0	Acala+BR
297	248	213	184	164	151	140	127	111	97	88	83	71	57	49	40	26	14	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.94 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Angst
 Safety Analysis Set, DCO 15FEB2024



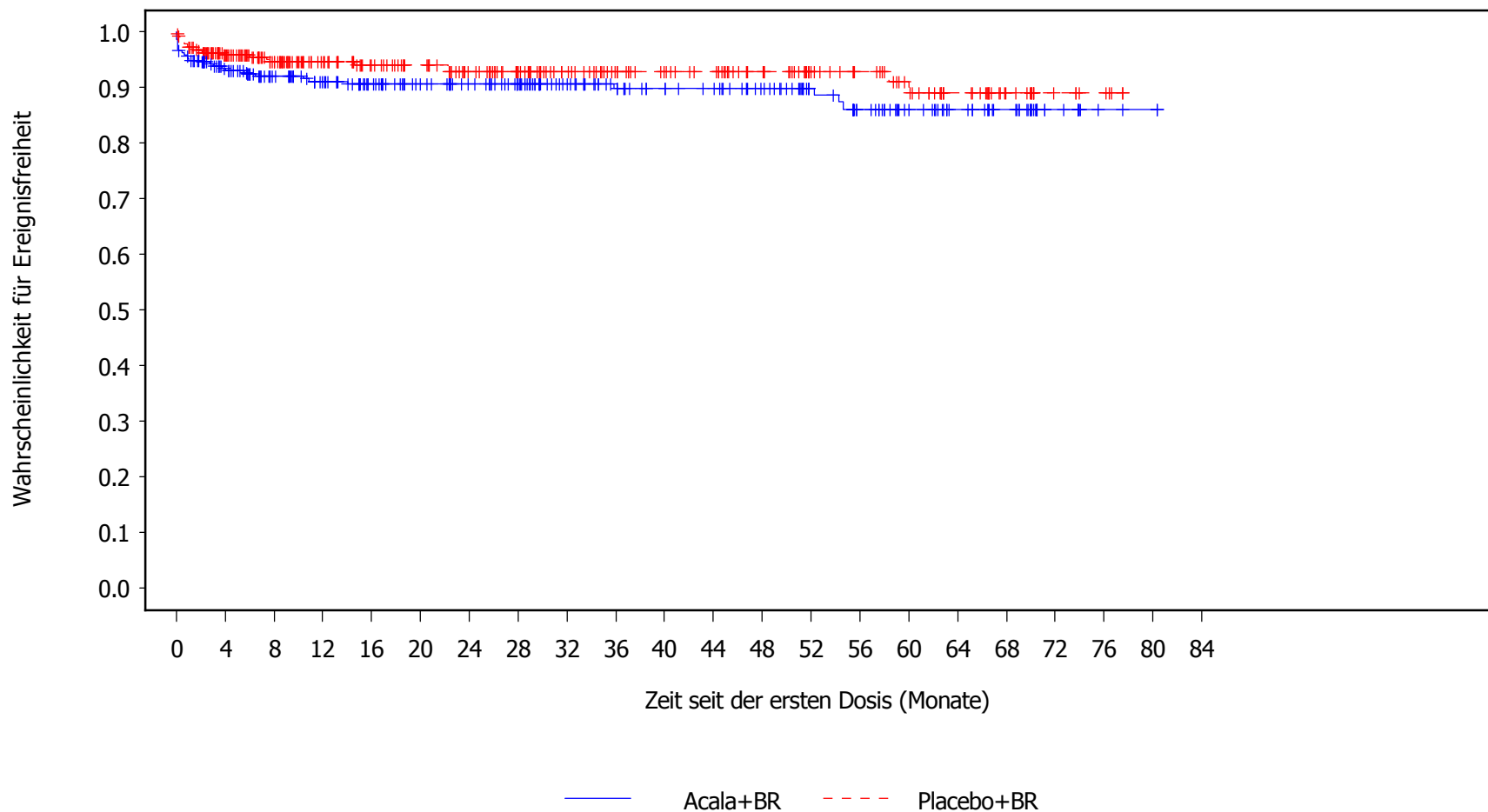
Anzahl an Patienten unter Risiko:

297	271	242	225	205	189	177	157	136	121	111	107	97	76	65	50	39	29	11	2	1	0	Acala+BR
297	264	232	197	178	165	154	139	121	106	97	92	79	62	53	45	30	17	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.95 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Schlaflosigkeit
 Safety Analysis Set, DC0 15FEB2024



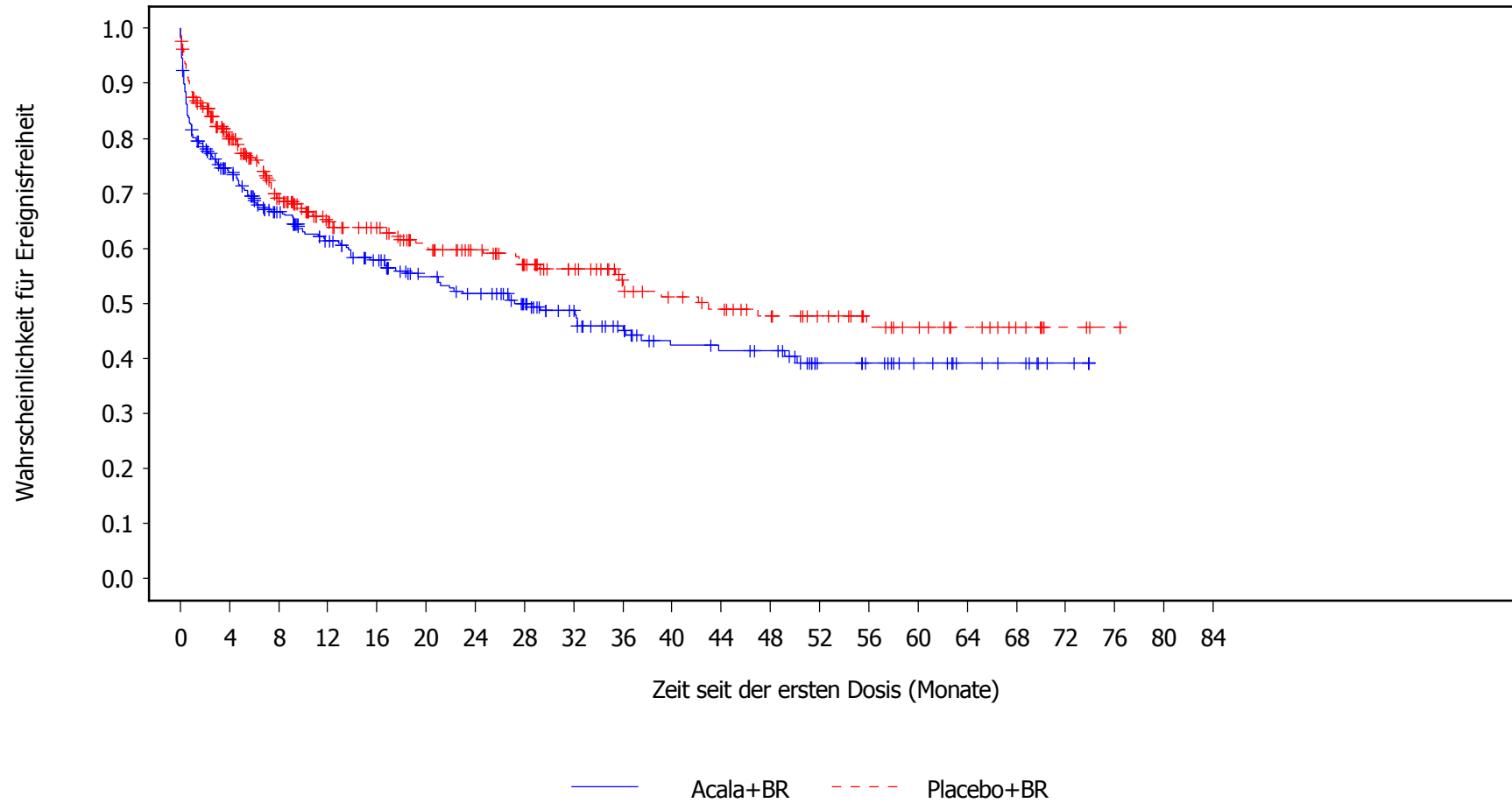
Anzahl an Patienten unter Risiko:

297	256	228	210	190	173	162	148	127	112	103	99	89	72	60	46	36	27	9	2	1	0	Acala+BR
297	255	223	194	175	163	147	133	116	103	94	89	77	62	54	45	31	17	7	4	0	0	Placebo+BR

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Figure 3.3.1.96 ECHO: Kaplan-Meier plot of time to first occurrence of SOC: Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen
 Safety Analysis Set, DC0 15FEB2024



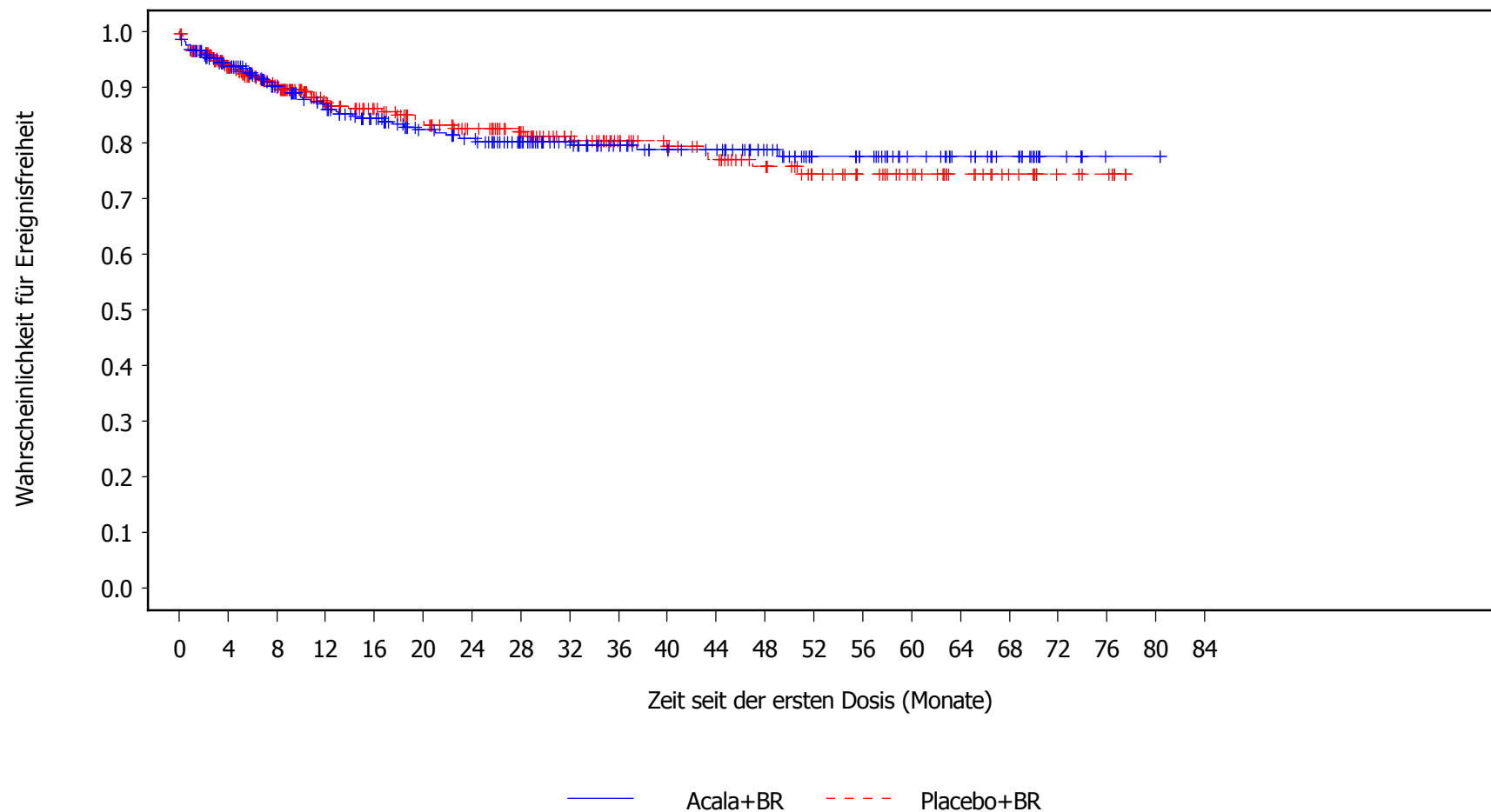
Anzahl an Patienten unter Risiko:

297	204	168	143	124	105	96	83	69	56	45	43	41	27	22	16	11	9	4	0	0	0	Acala+BR
297	212	162	131	119	103	90	78	66	54	47	43	37	31	23	19	14	9	3	1	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.97 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Arthralgie
 Safety Analysis Set, DCO 15FEB2024



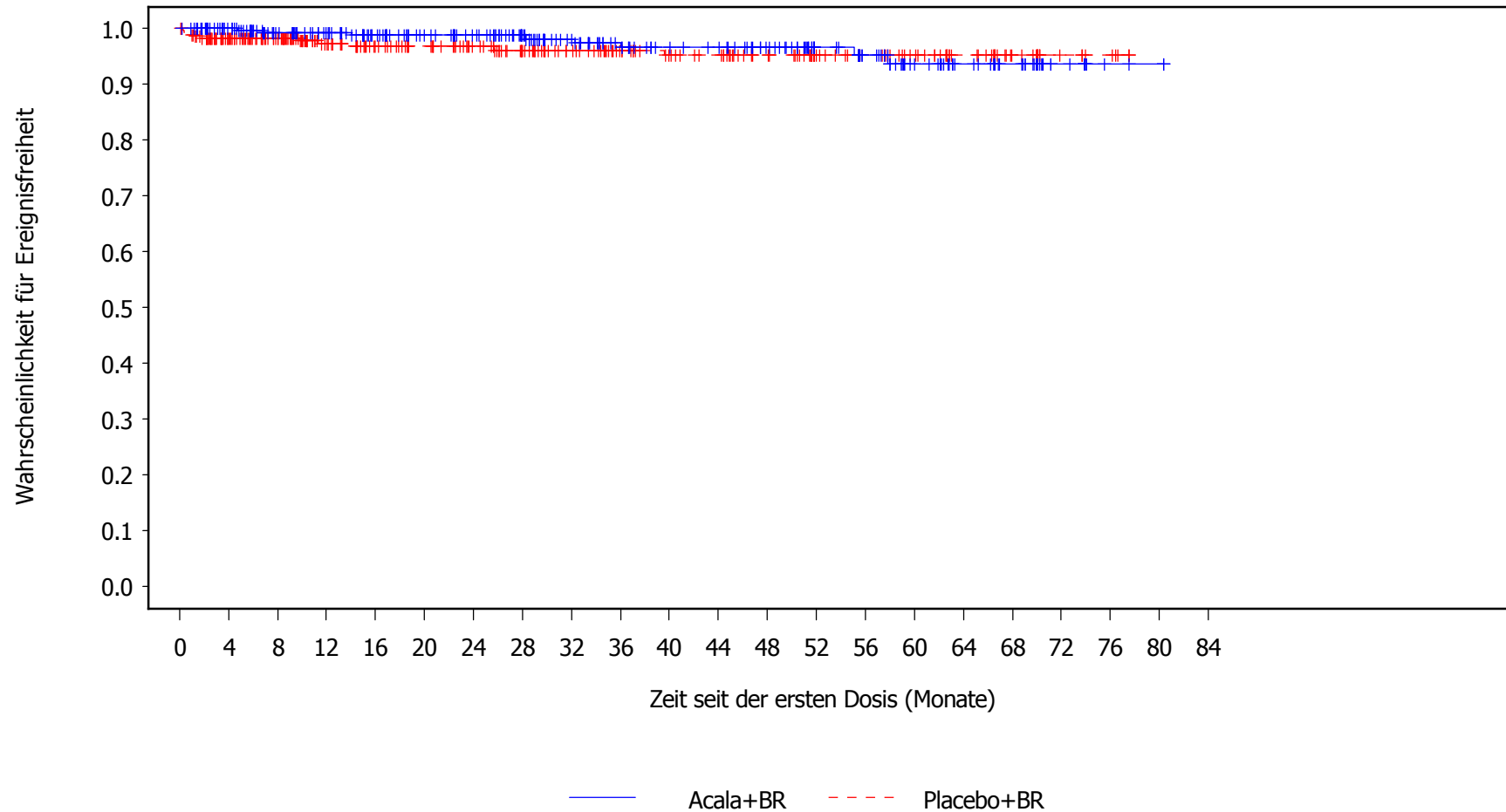
Anzahl an Patienten unter Risiko:

297	260	225	202	181	161	151	132	113	99	90	86	74	54	47	36	28	20	8	1	1	0	Acala+BR
297	249	214	176	158	143	129	114	98	84	75	69	59	47	40	33	22	15	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.98 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Muskelspasmen
 Safety Analysis Set, DC0 15FEB2024



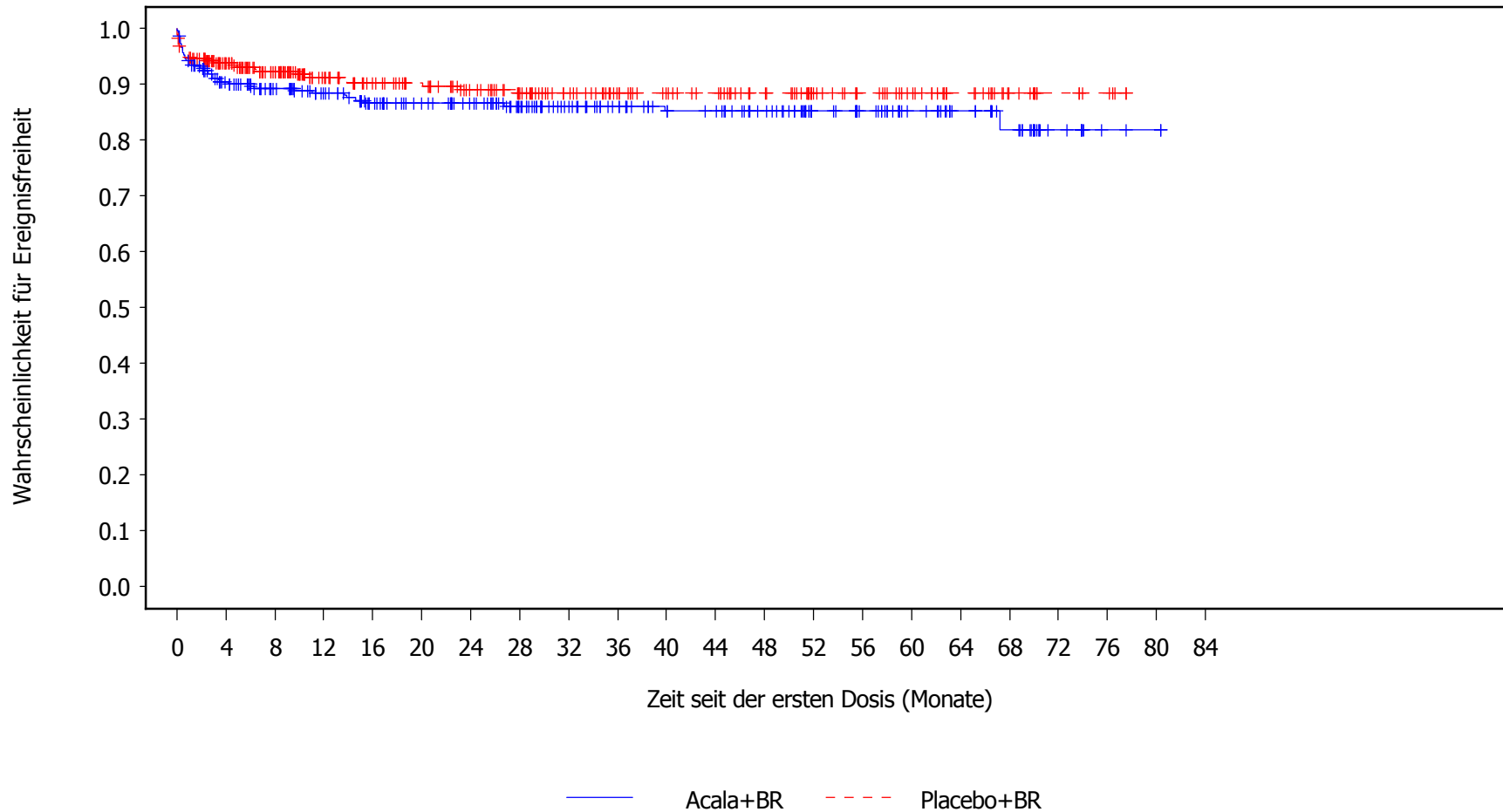
Anzahl an Patienten unter Risiko:

297	275	246	229	208	191	180	159	138	122	111	108	97	77	65	48	37	28	10	2	1	0	Acala+BR
297	263	234	198	179	167	153	136	119	104	94	89	77	61	52	44	31	18	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.99 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Myalgie
 Safety Analysis Set, DCO 15FEB2024



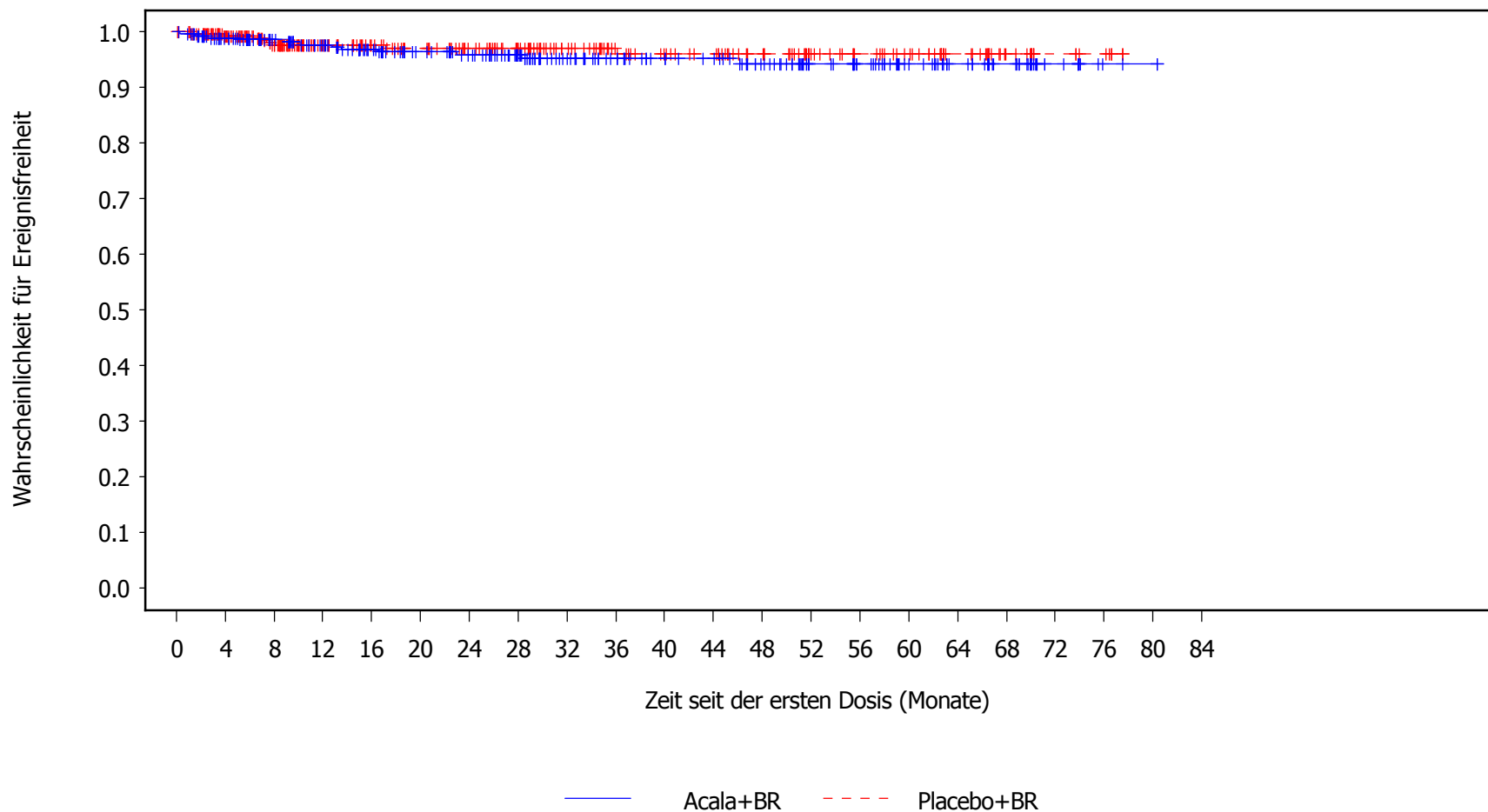
Anzahl an Patienten unter Risiko:

297	250	226	207	186	171	160	141	122	109	98	95	85	64	55	42	32	24	9	2	1	0	Acala+BR
297	249	218	183	165	154	139	126	110	97	88	83	72	56	47	39	27	16	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.100 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Nackenschmerzen
 Safety Analysis Set, DC0 15FEB2024



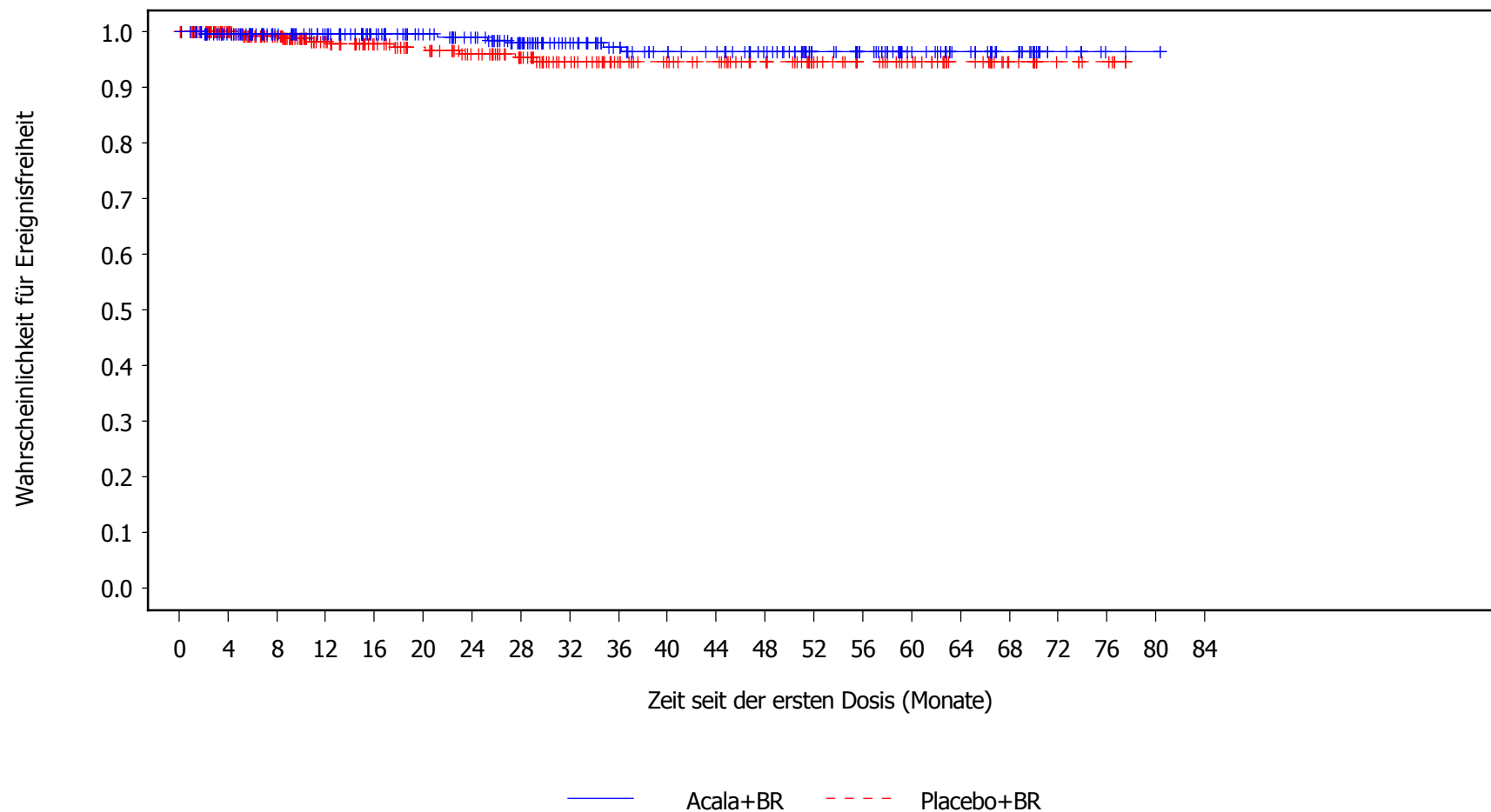
Anzahl an Patienten unter Risiko:

297	273	246	227	206	189	177	157	135	121	111	107	95	76	65	50	40	29	11	2	1	0	Acala+BR
297	265	232	197	179	166	152	136	117	102	94	89	78	63	54	47	32	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.101 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Osteoarthritis
 Safety Analysis Set, DC0 15FEB2024



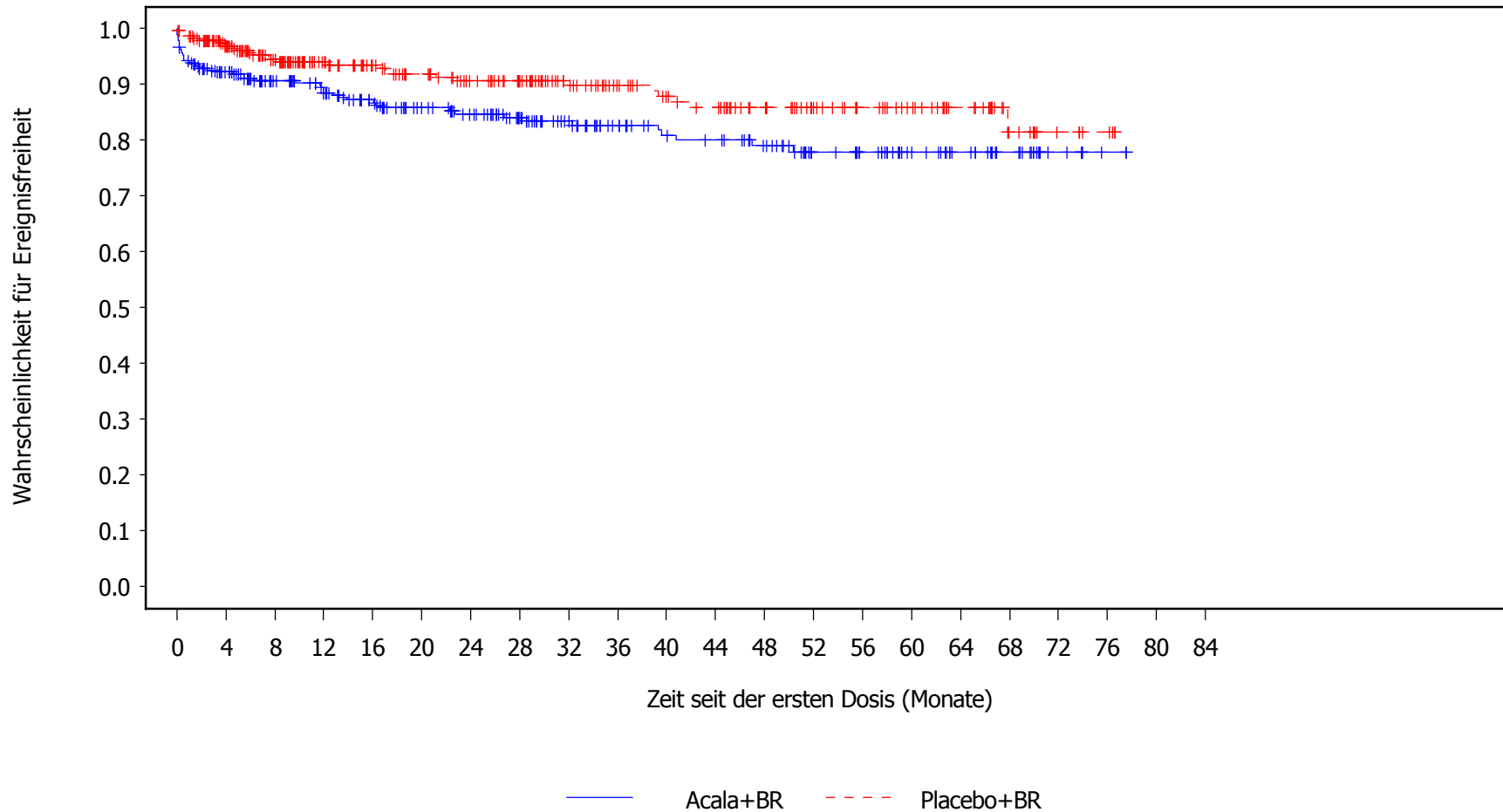
Anzahl an Patienten unter Risiko:

297	274	247	230	210	194	182	159	138	122	111	107	97	76	65	48	38	27	9	2	1	0	Acala+BR
297	267	237	200	181	168	153	136	116	102	93	88	78	62	53	45	31	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.102 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Rueckenschmerzen
 Safety Analysis Set, DC0 15FEB2024



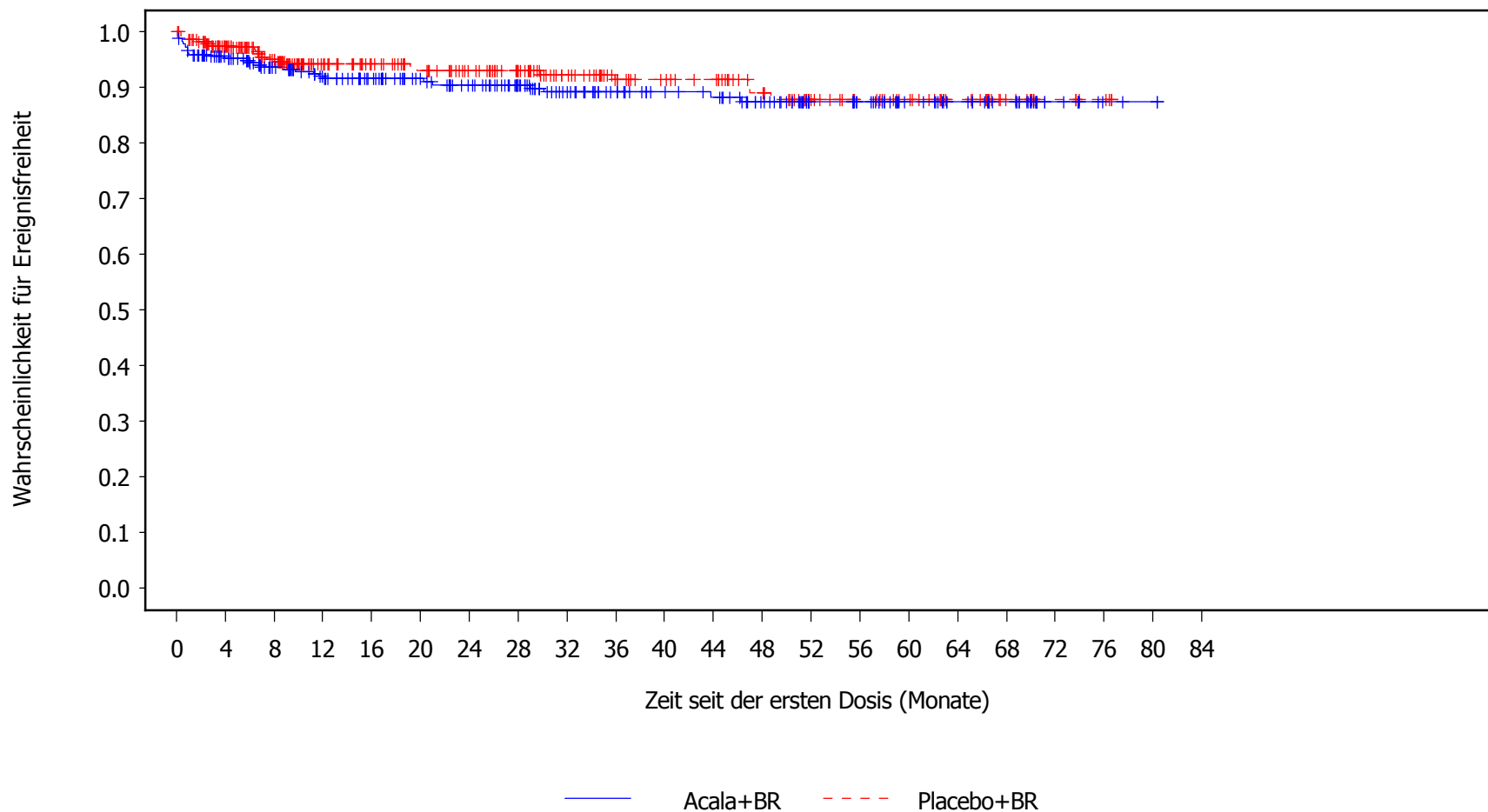
Anzahl an Patienten unter Risiko:

297	254	224	205	185	165	153	133	115	99	89	86	78	60	51	38	30	20	7	1	0	0	Acala+BR
297	259	225	192	173	159	145	132	112	99	90	85	73	60	51	44	31	16	6	3	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.103 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Schmerz in einer Extremität
 Safety Analysis Set, DCO 15FEB2024



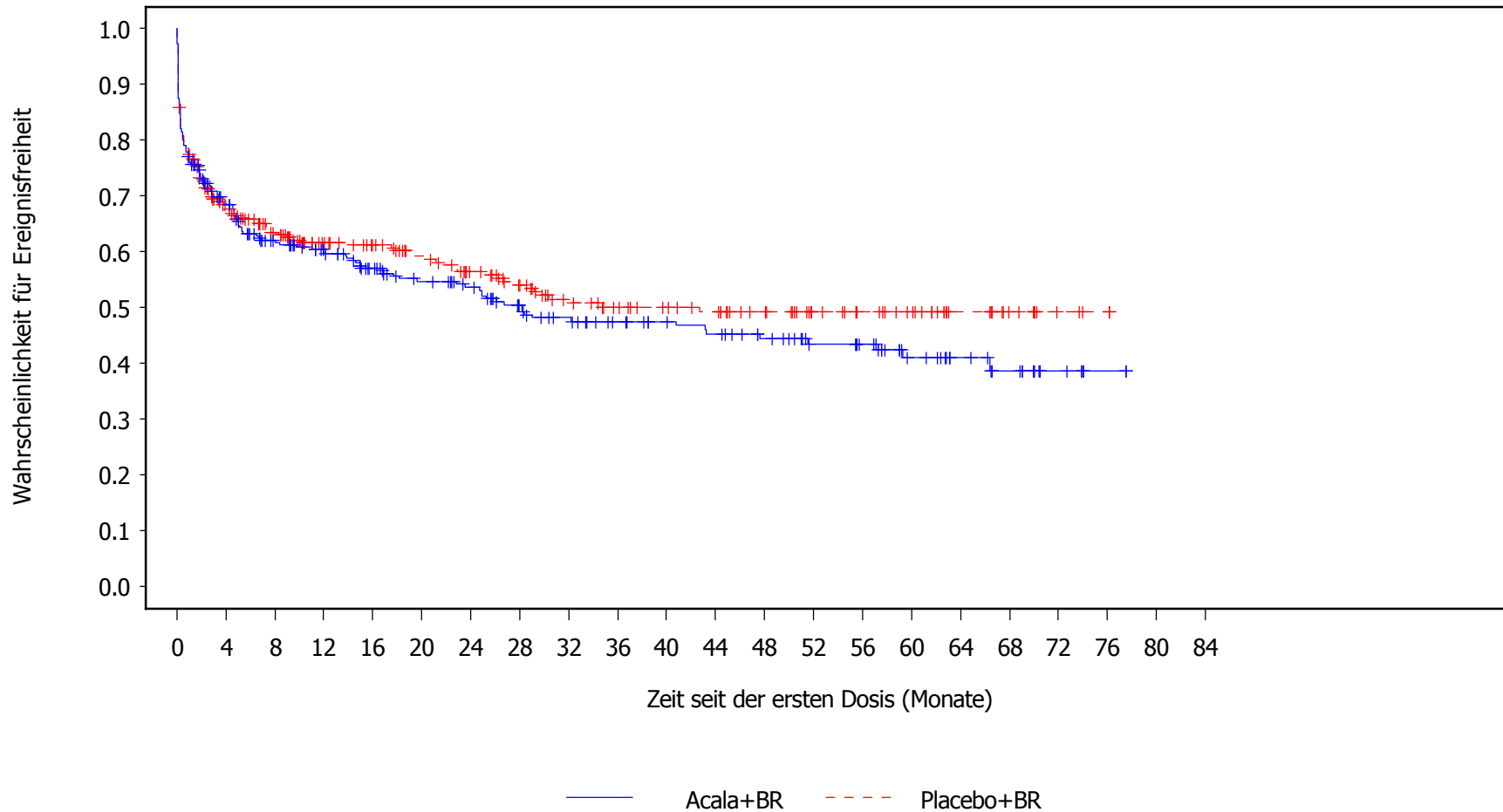
Anzahl an Patienten unter Risiko:

297	262	234	214	196	179	167	148	127	113	103	99	87	66	58	43	35	25	9	2	1	0	Acala+BR
297	261	226	189	173	160	147	133	113	98	90	86	74	57	48	41	28	16	6	3	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.104 ECHO: Kaplan-Meier plot of time to first occurrence of SOC: Stoffwechsel- und Ernährungsstörungen
 Safety Analysis Set, DC0 15FEB2024



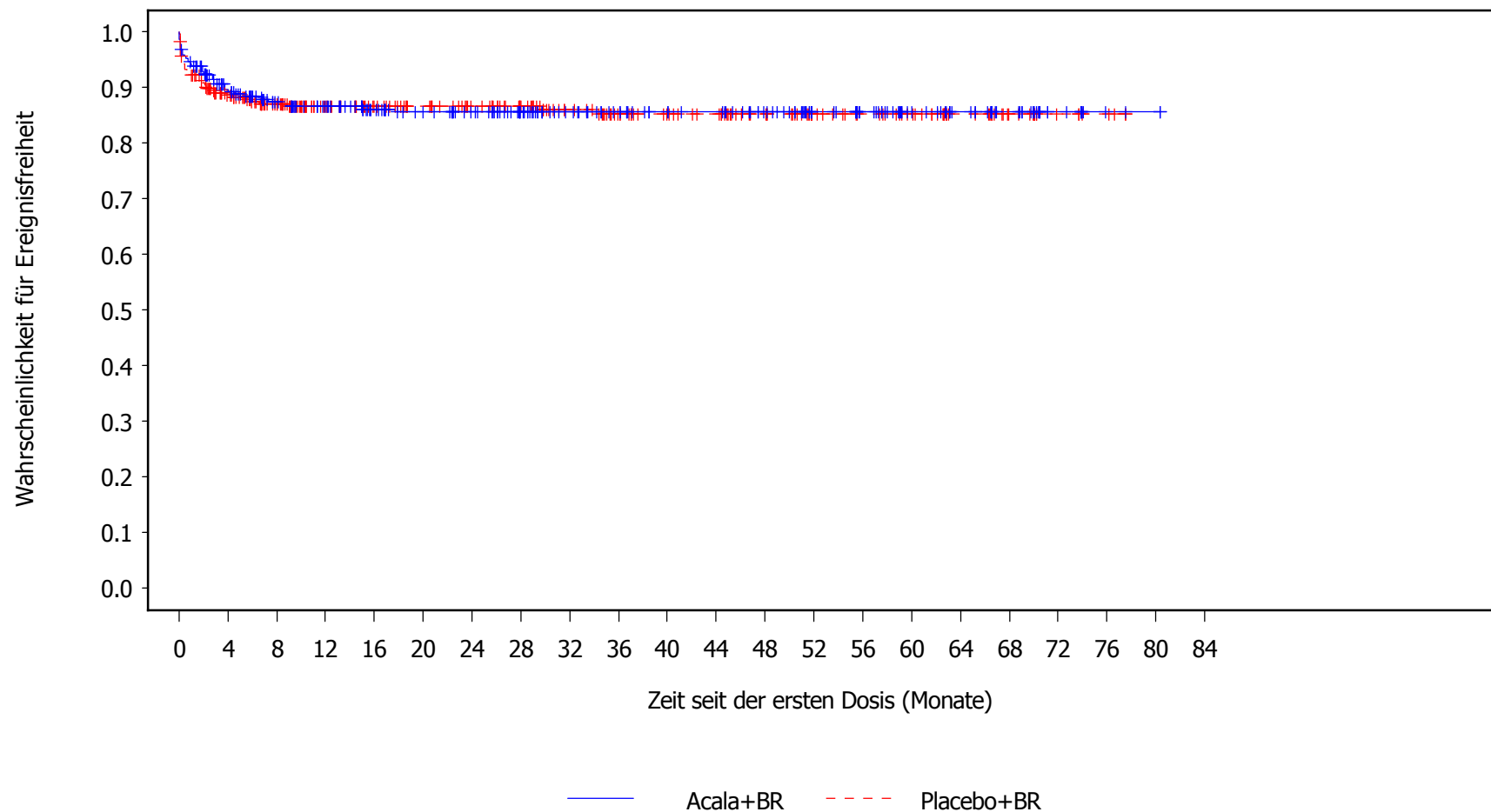
Anzahl an Patienten unter Risiko:

297	191	159	143	125	112	104	87	78	70	65	61	54	45	40	28	20	14	5	1	0	0	Acala+BR
297	186	157	134	125	112	99	87	73	65	60	56	48	37	32	27	16	9	3	1	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.105 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Appetit vermindert
 Safety Analysis Set, DC0 15FEB2024



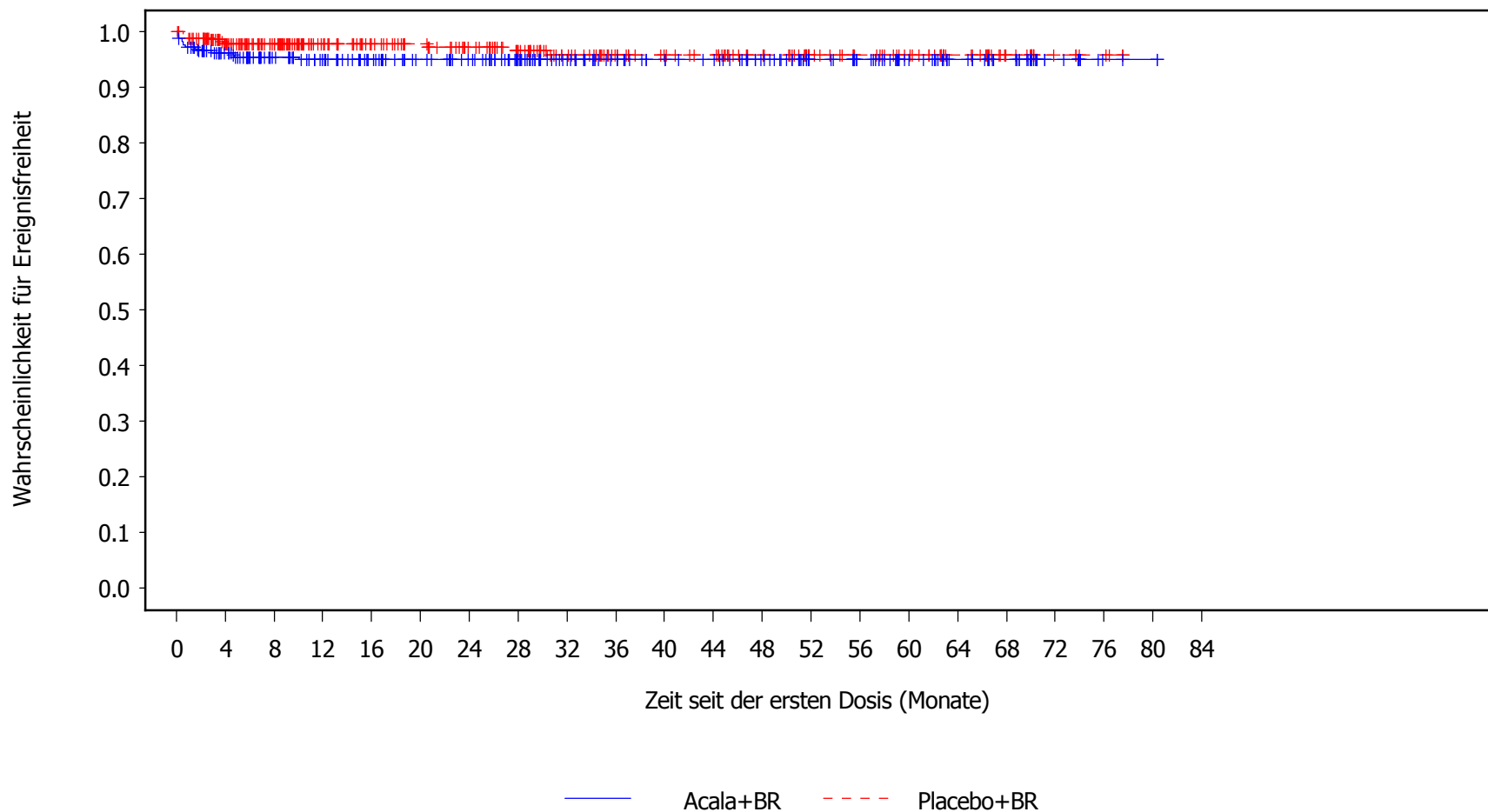
Anzahl an Patienten unter Risiko:

297	246	219	203	182	169	159	140	123	113	104	101	91	72	61	45	36	26	10	2	1	0	Acala+BR
297	240	212	181	165	153	141	127	110	97	88	83	71	56	49	42	27	16	6	3	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.106 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Dehydration
 Safety Analysis Set, DC0 15FEB2024



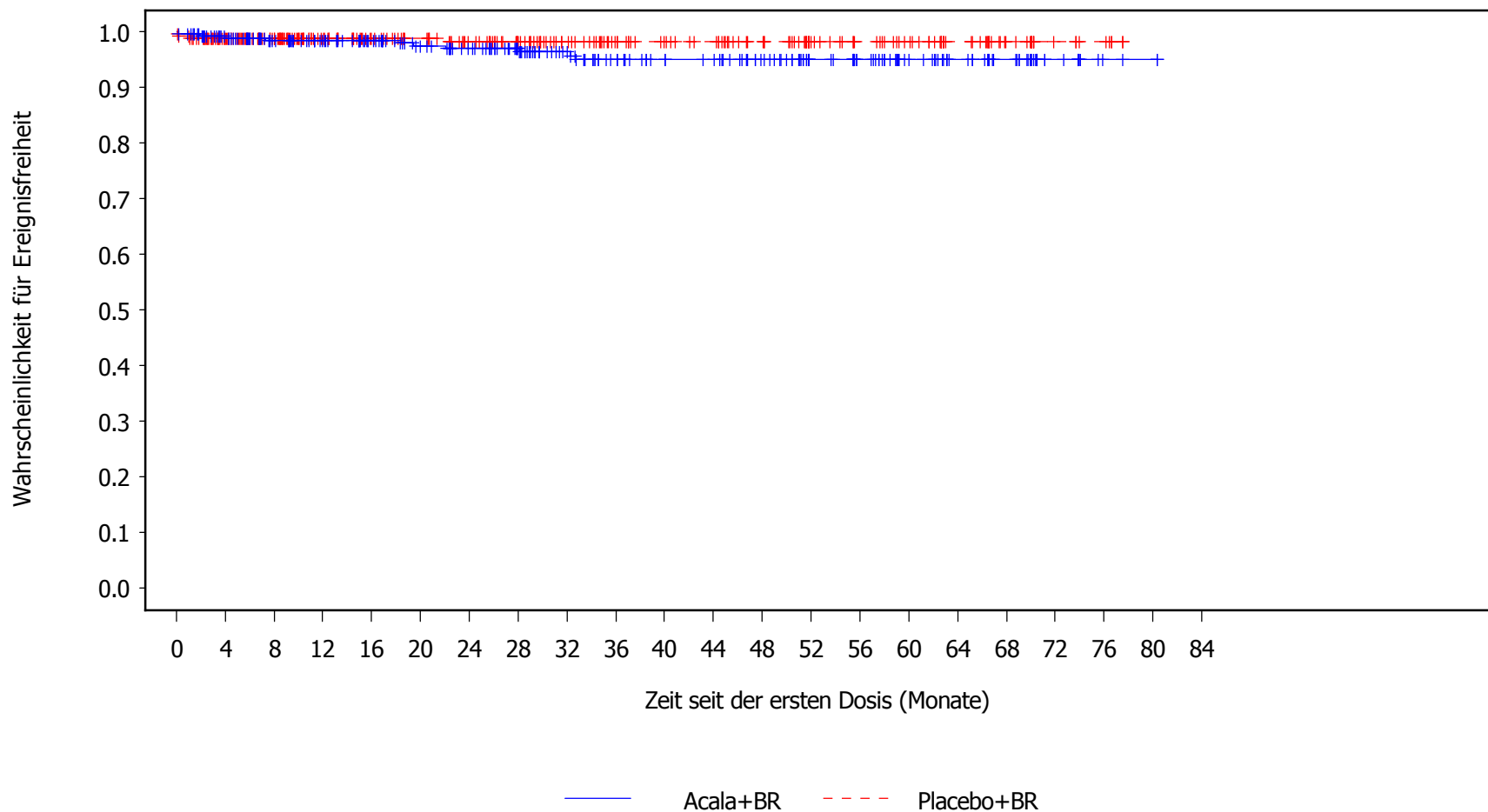
Anzahl an Patienten unter Risiko:

297	265	236	219	200	185	175	155	134	120	111	107	96	77	66	50	39	29	11	2	1	0	Acala+BR
297	261	232	197	179	167	153	137	117	102	94	90	78	62	54	46	31	17	6	3	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.107 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Hypalbuminaemie
 Safety Analysis Set, DC0 15FEB2024



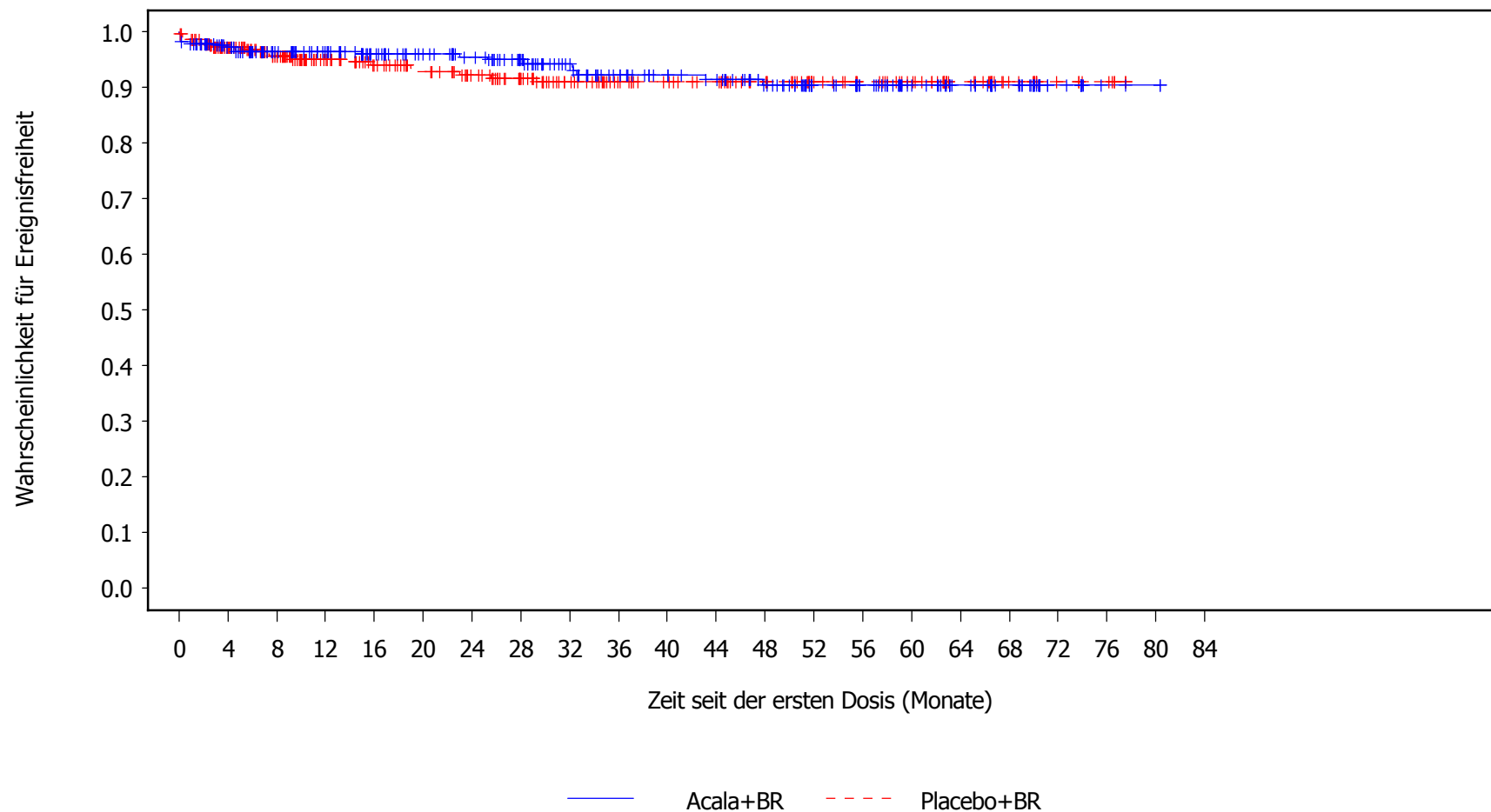
Anzahl an Patienten unter Risiko:

297	274	246	229	210	192	180	160	139	123	113	110	98	79	68	51	40	29	11	2	1	0	Acala+BR
297	265	237	202	183	171	157	141	123	108	99	94	82	65	56	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.108 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Hyperglykaemie
 Safety Analysis Set, DC0 15FEB2024



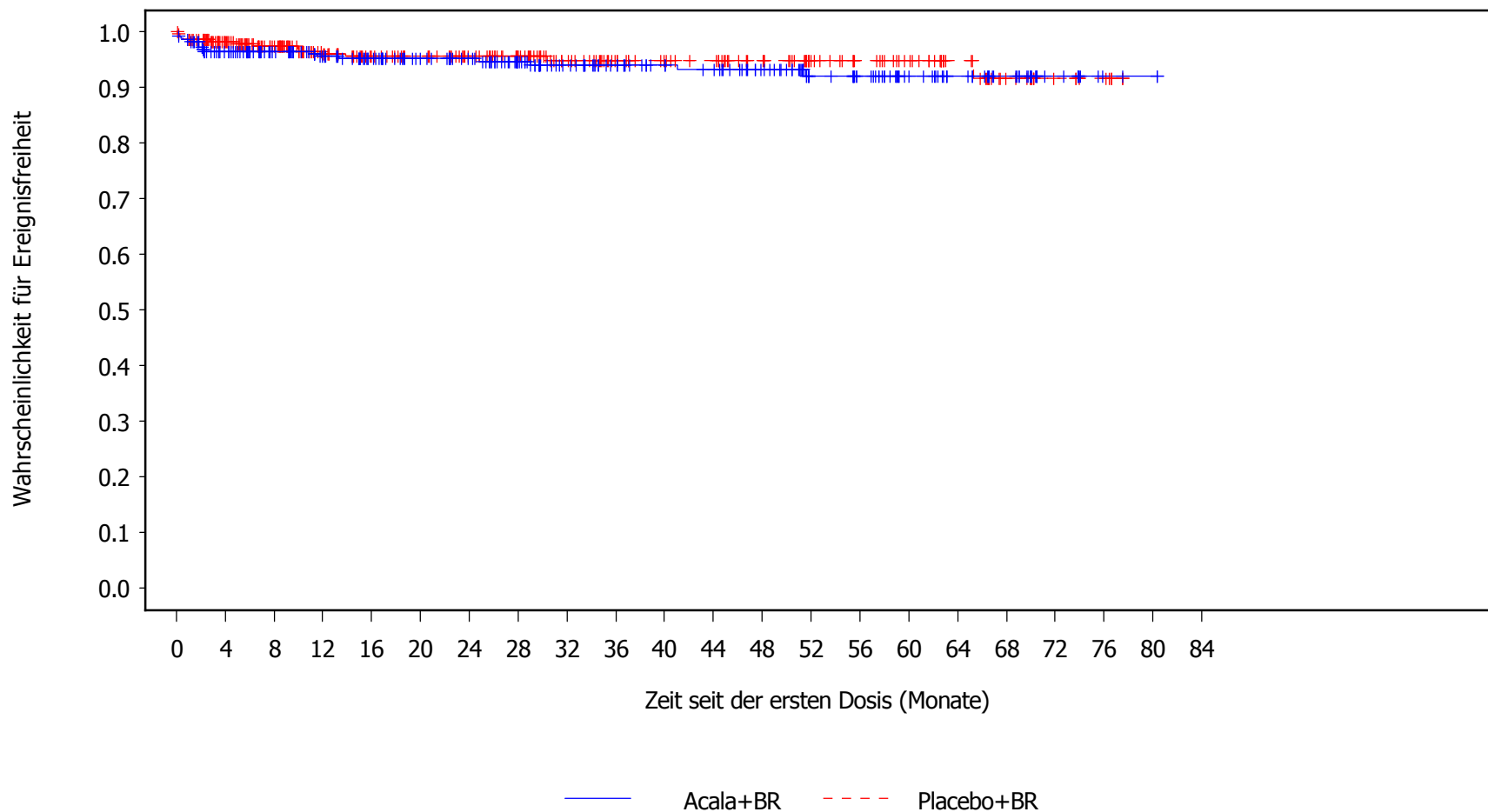
Anzahl an Patienten unter Risiko:

297	267	240	223	203	188	177	159	139	123	113	108	95	75	65	48	38	28	10	2	1	0	Acala+BR
297	259	228	194	175	161	149	133	115	101	94	89	78	61	53	45	30	17	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.109 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Hyperkaliaemie
 Safety Analysis Set, DCO 15FEB2024



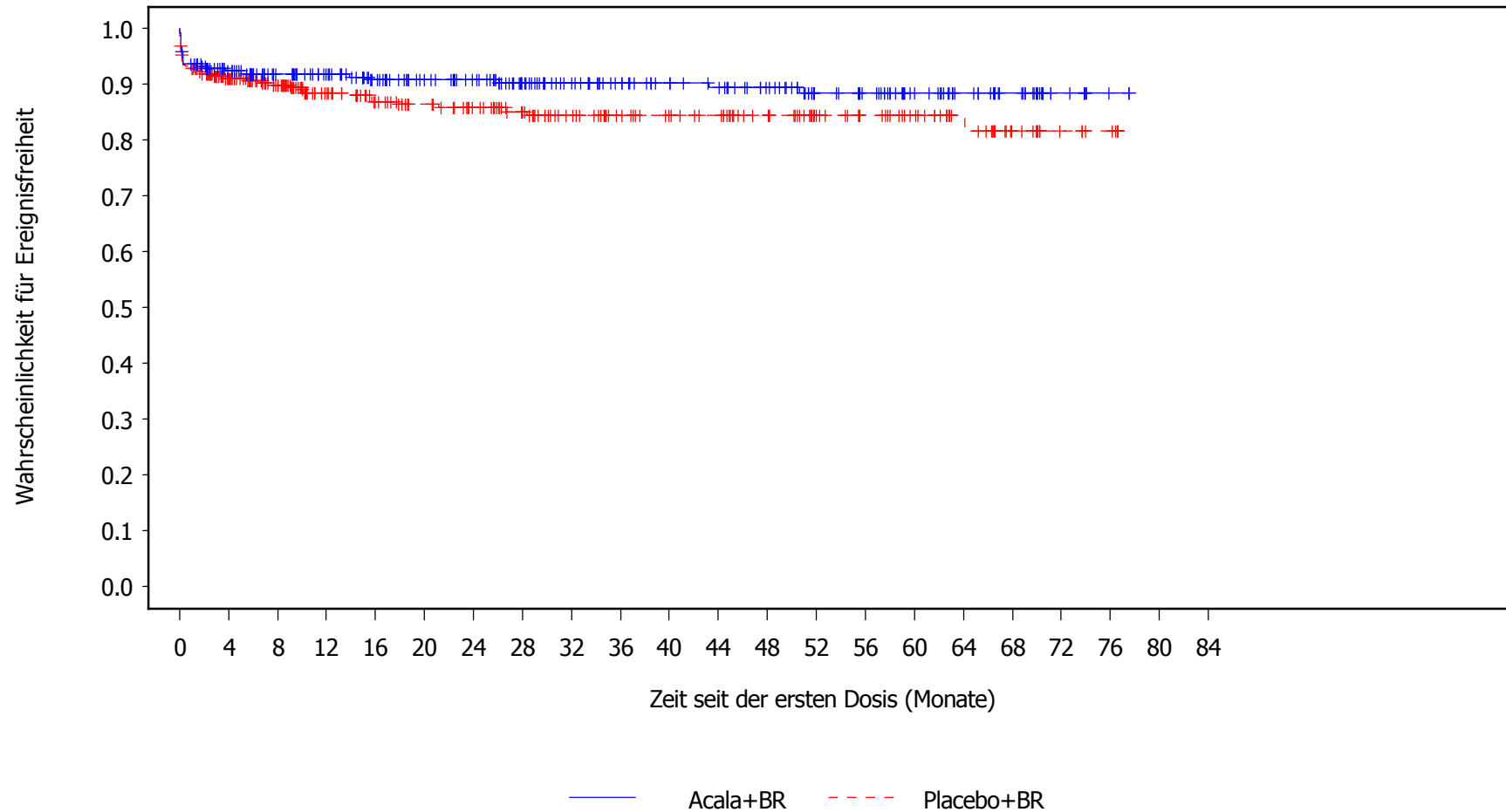
Anzahl an Patienten unter Risiko:

297	267	240	221	202	185	175	153	134	121	111	107	95	74	65	48	38	27	11	2	1	0	Acala+BR
297	262	232	198	178	167	154	138	118	103	95	91	80	64	55	47	32	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.110 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Hyperurikaemie
 Safety Analysis Set, DCO 15FEB2024



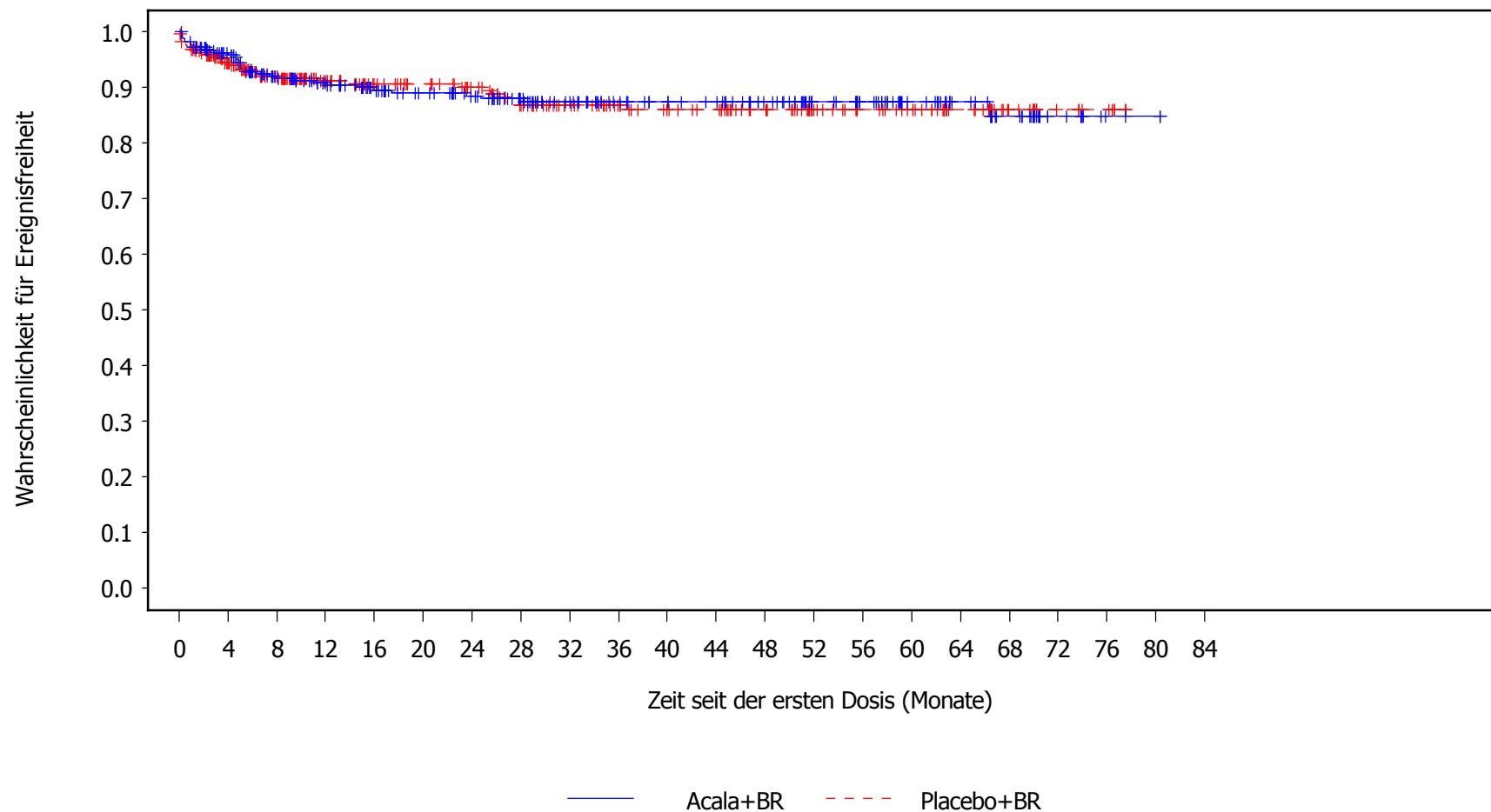
Anzahl an Patienten unter Risiko:

297	255	230	214	193	177	166	145	130	117	108	103	93	73	65	49	38	27	9	1	0	0	Acala+BR
297	243	213	180	161	149	138	123	108	97	90	86	75	60	52	44	30	17	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.111 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Hypokaliaemie
 Safety Analysis Set, DCO 15FEB2024



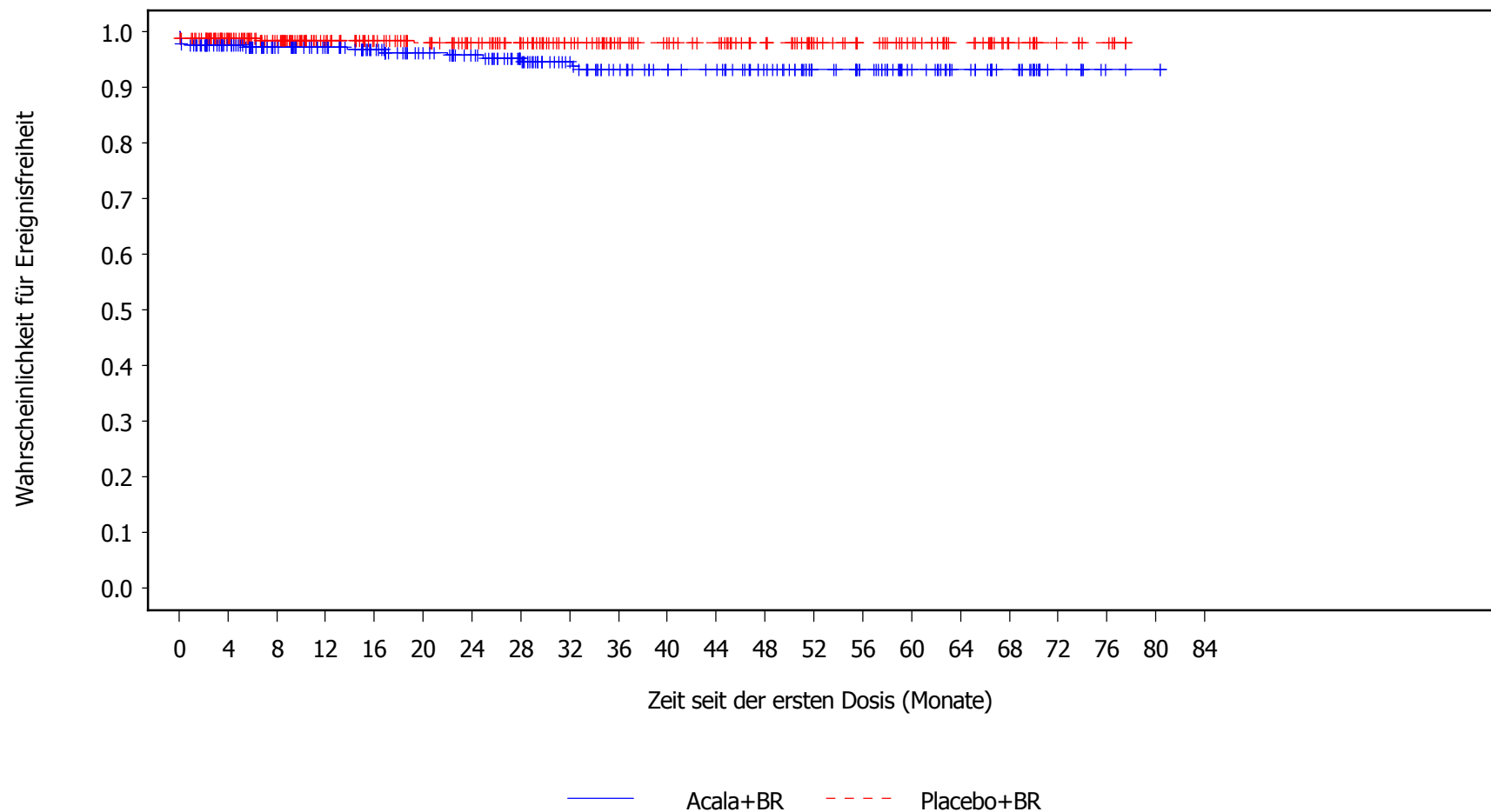
Anzahl an Patienten unter Risiko:

297	264	230	211	191	178	166	148	130	115	108	104	93	76	65	49	38	27	10	2	1	0	Acala+BR
297	253	221	185	168	159	147	130	115	103	95	91	79	63	54	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.112 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Hypokalzaemie
 Safety Analysis Set, DC0 15FEB2024



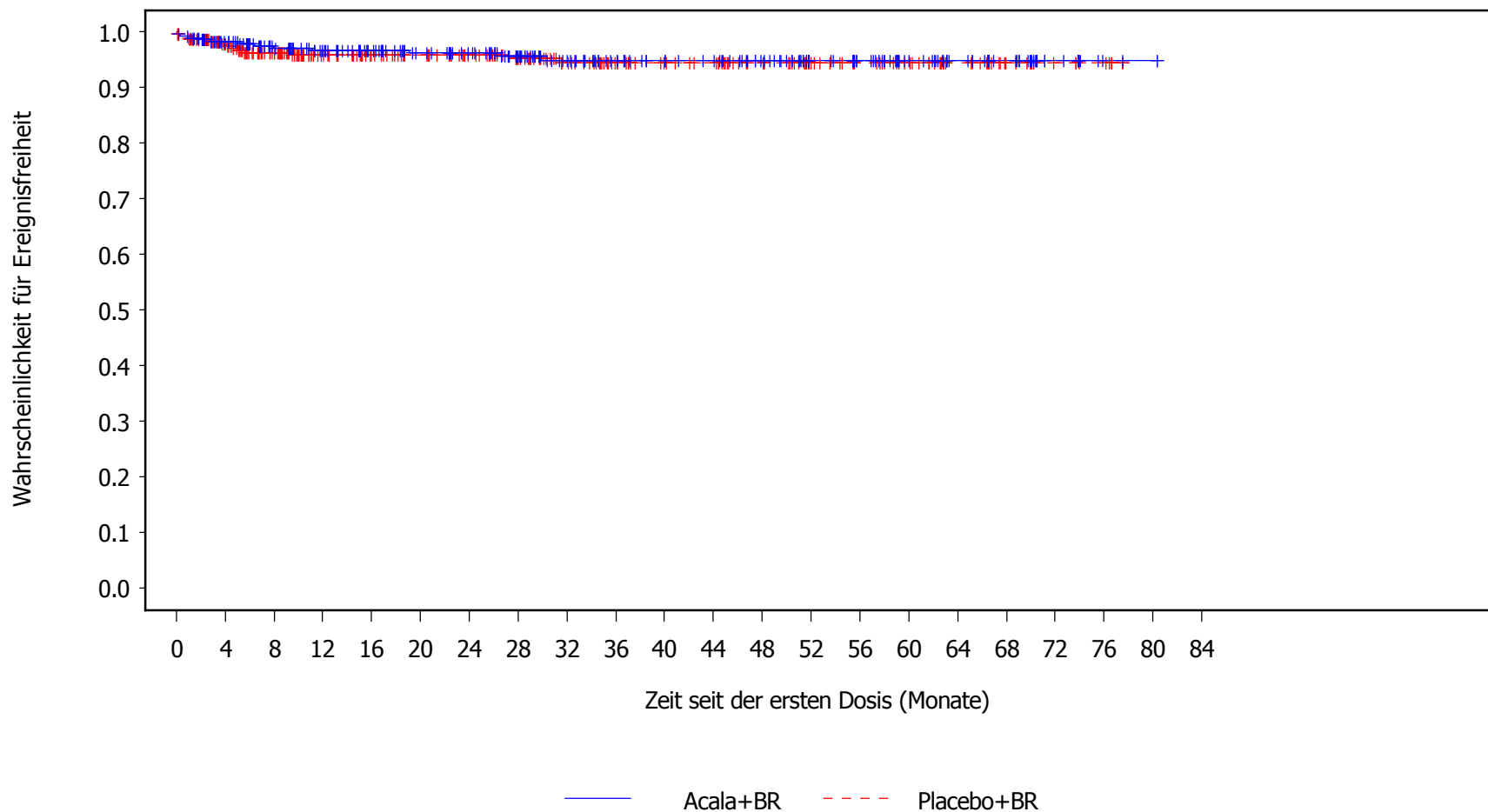
Anzahl an Patienten unter Risiko:

297	268	241	224	205	187	175	154	133	118	109	105	93	74	64	47	36	26	9	2	1	0	Acala+BR
297	264	235	201	182	169	155	141	123	108	99	94	82	65	56	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.113 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Hypomagnesiaemie
 Safety Analysis Set, DC0 15FEB2024



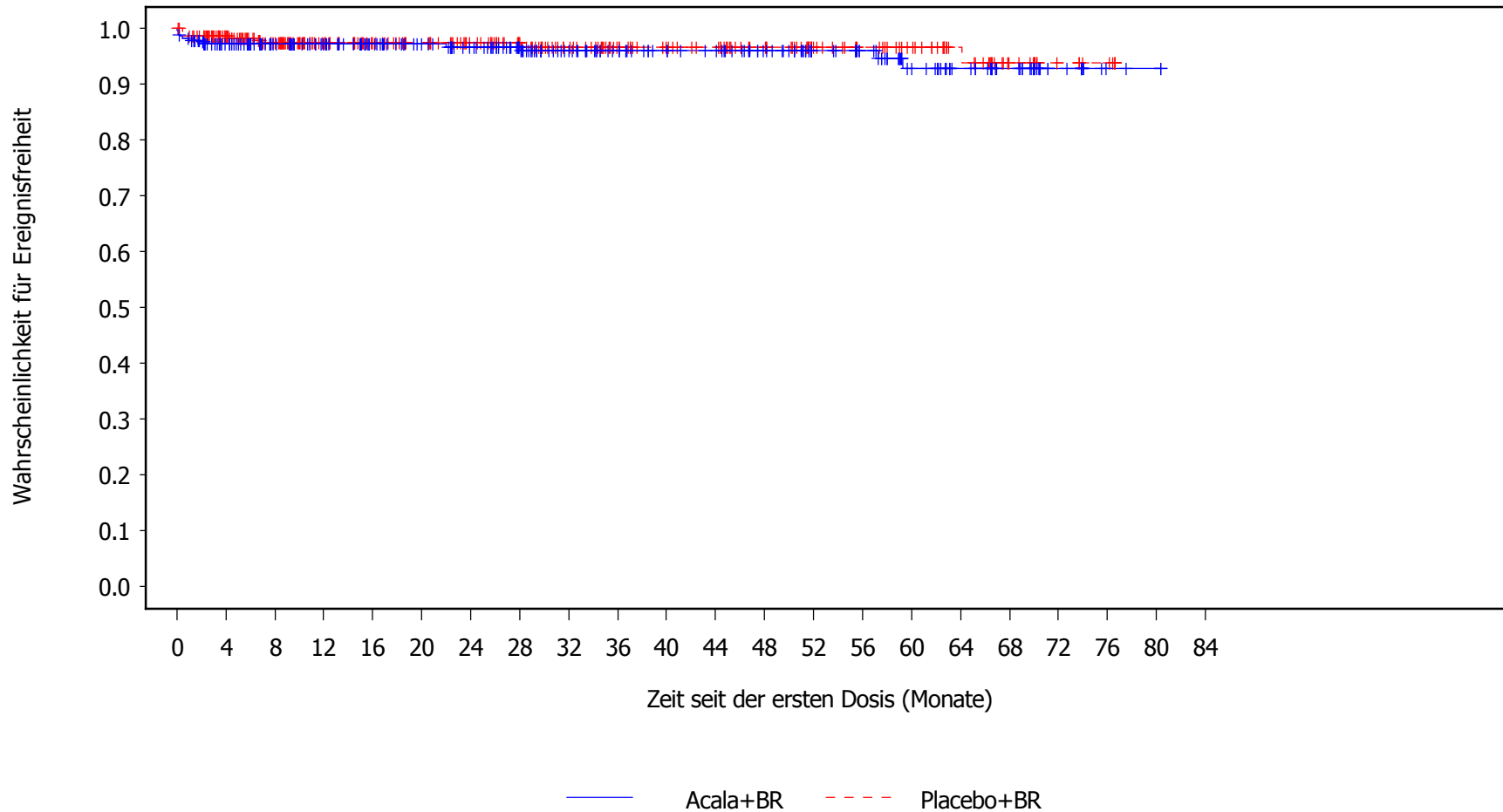
Anzahl an Patienten unter Risiko:

297	270	241	223	205	188	177	157	137	122	113	109	97	77	66	49	38	28	11	2	1	0	Acala+BR
297	261	229	195	179	167	154	139	120	105	96	92	80	63	54	46	31	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.114 ECH0: Kaplan-Meier plot of time to first occurrence of PT: Hyponatriaemie
 Safety Analysis Set, DC0 15FEB2024



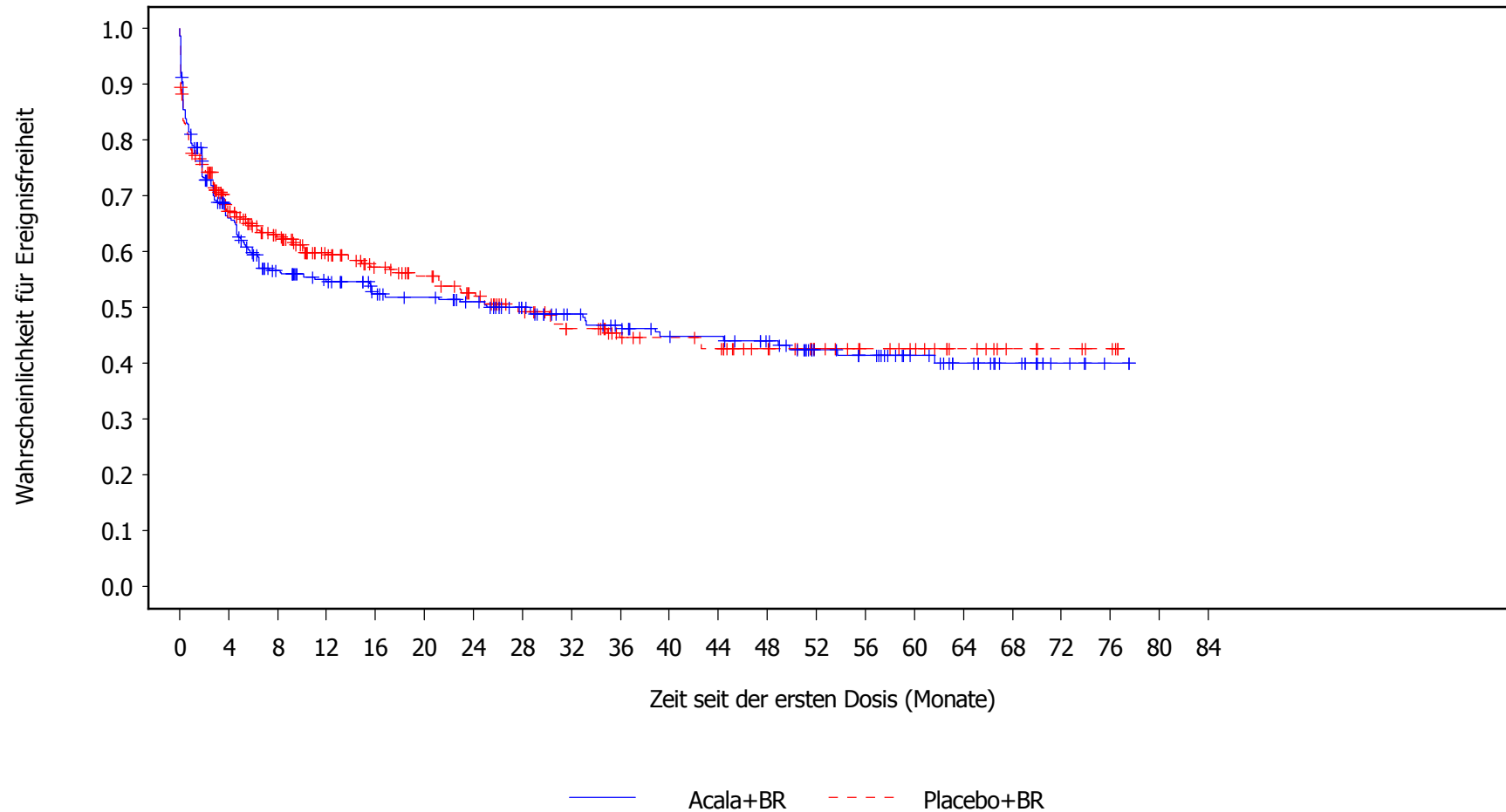
Anzahl an Patienten unter Risiko:

297	267	240	223	204	189	177	157	137	122	112	108	96	78	68	50	39	28	11	2	1	0	Acala+BR
297	265	235	202	183	171	157	141	122	107	98	93	81	64	55	47	33	18	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.115 ECHO: Kaplan-Meier plot of time to first occurrence of SOC: Untersuchungen
 Safety Analysis Set, DC0 15FEB2024



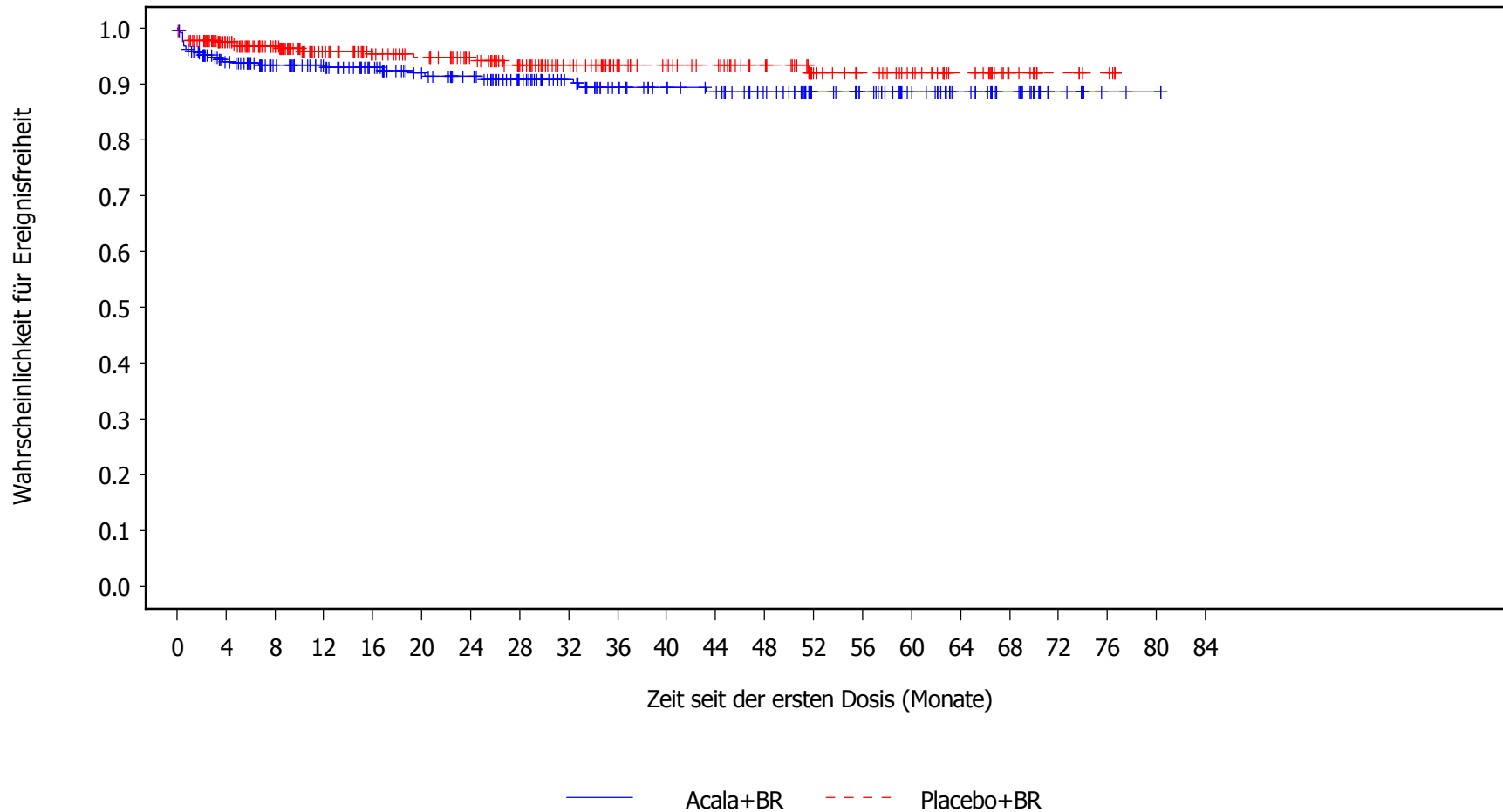
Anzahl an Patienten unter Risiko:

297	181	143	129	114	109	102	89	78	71	63	62	56	43	38	29	21	14	5	1	0	0	Acala+BR
297	179	149	122	105	95	83	70	59	50	47	44	36	26	21	18	12	7	5	3	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.116 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Alaninaminotransferase erhoeht
 Safety Analysis Set, DCO 15FEB2024



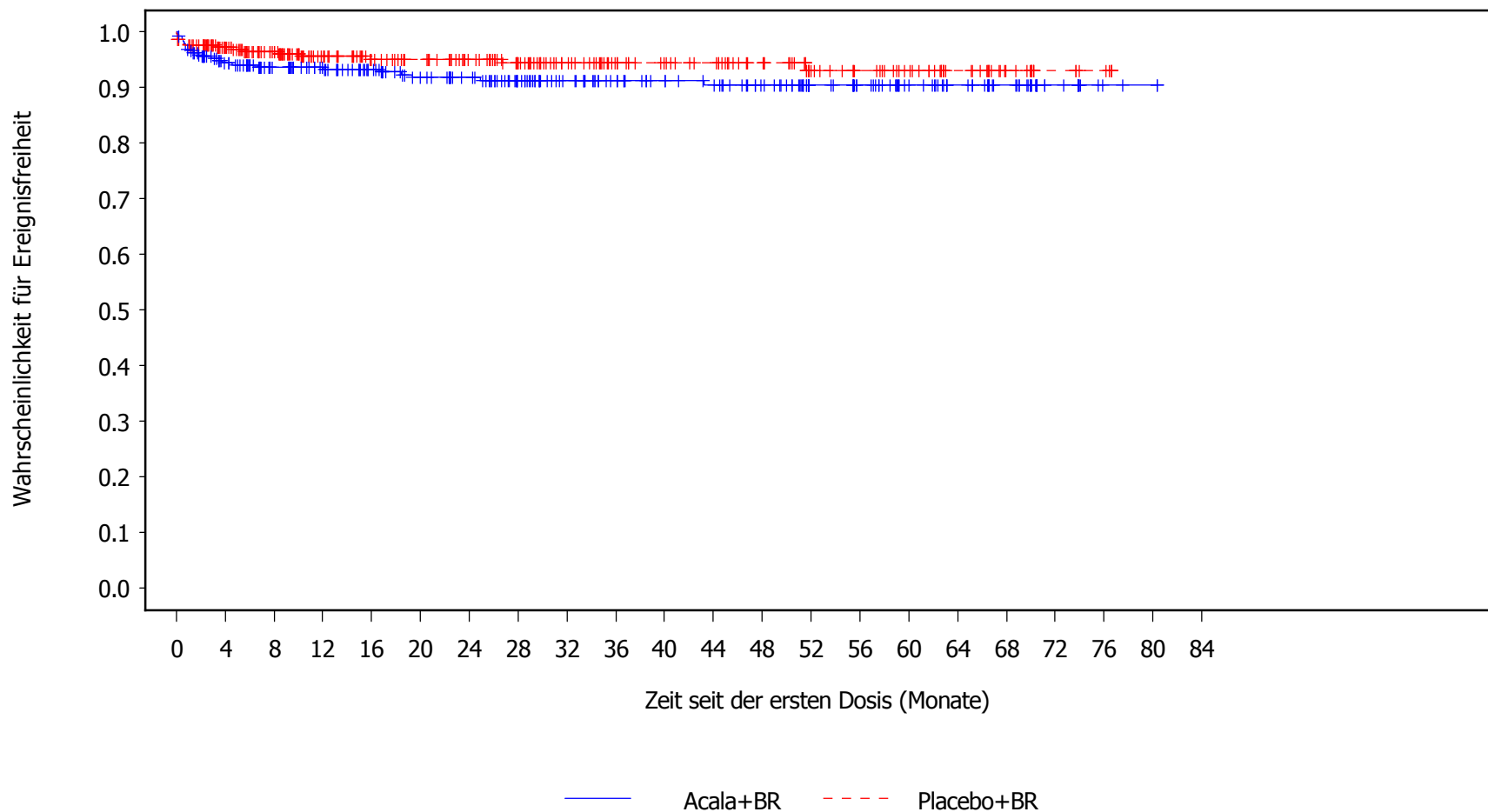
Anzahl an Patienten unter Risiko:

297	258	232	216	197	180	169	149	132	118	109	104	93	74	64	49	38	27	10	2	1	0	Acala+BR
297	260	231	196	177	166	152	135	117	102	94	89	78	61	53	45	30	16	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.117 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Aspartataminotransferase erhoeht
 Safety Analysis Set, DCO 15FEB2024



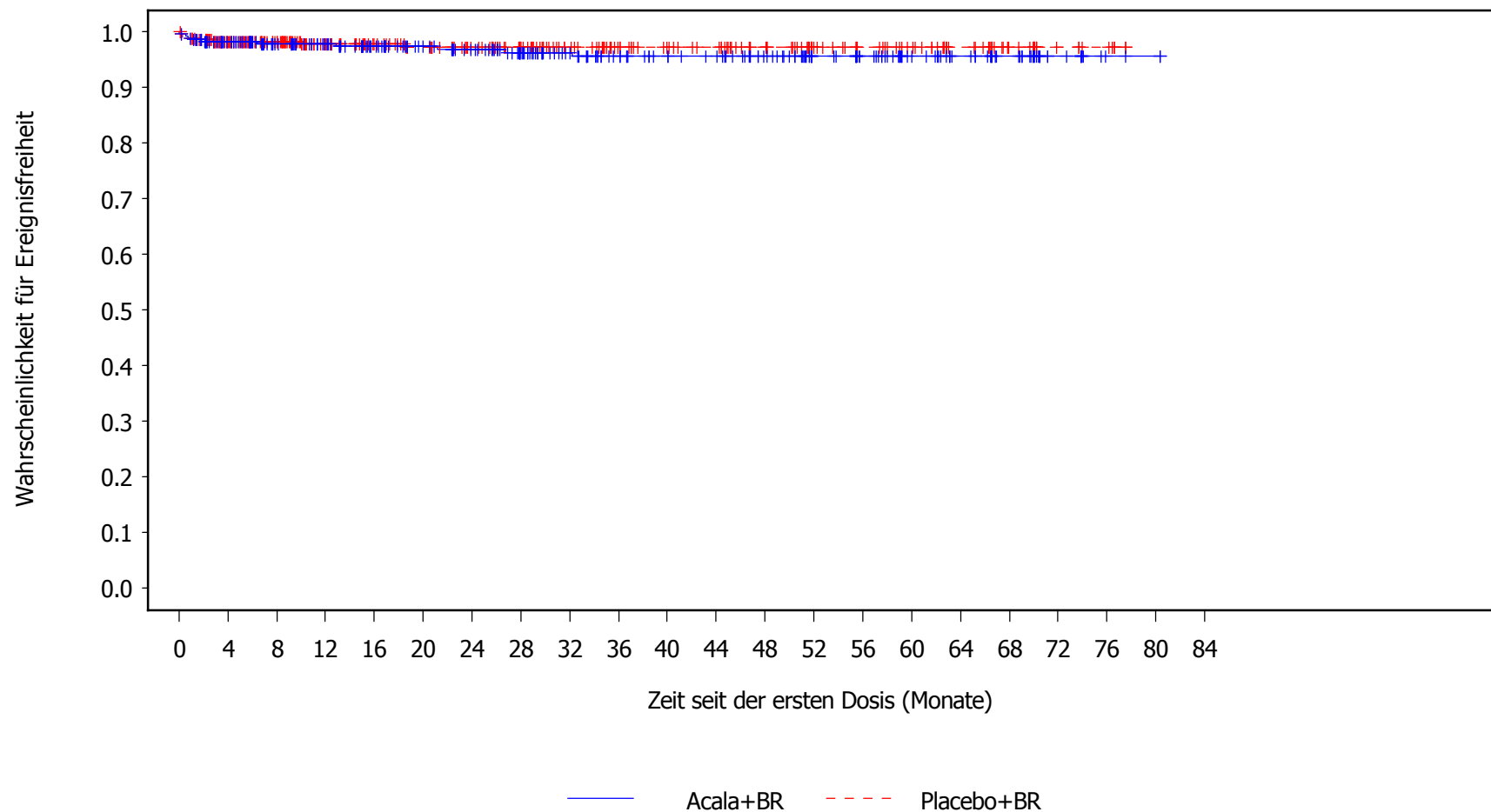
Anzahl an Patienten unter Risiko:

297	259	233	218	199	181	171	150	132	119	110	105	94	74	64	49	39	28	11	2	1	0	Acala+BR
297	259	230	196	176	166	152	135	116	101	93	88	77	60	52	44	30	17	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.118 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Bilirubin im Blut erhoeht
 Safety Analysis Set, DC0 15FEB2024



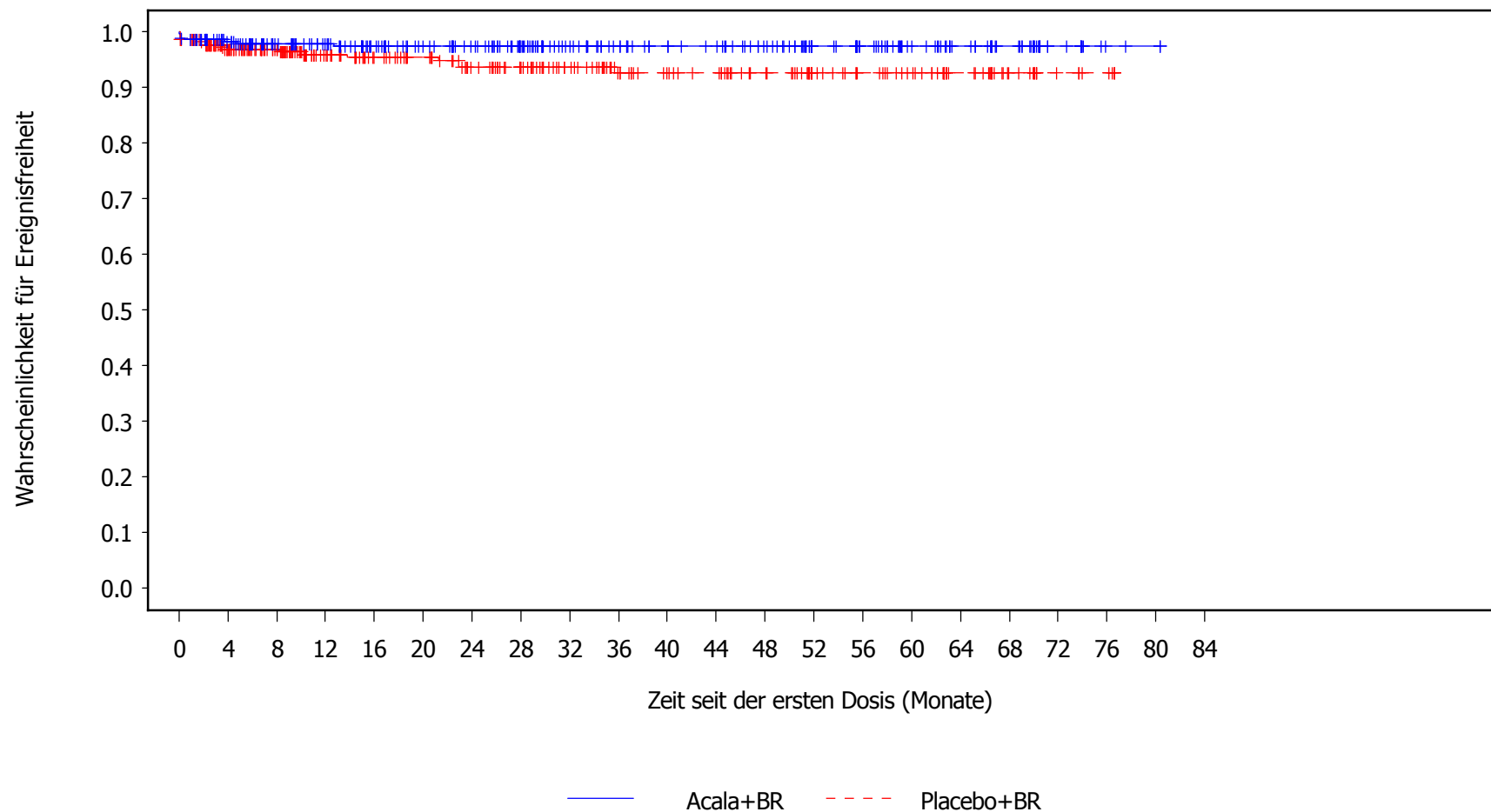
Anzahl an Patienten unter Risiko:

297	270	242	225	205	188	177	157	137	122	113	109	97	76	66	50	40	29	11	2	1	0	Acala+BR
297	263	234	199	180	168	155	139	120	106	97	92	80	64	55	47	32	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.119 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Gewicht erhoeht
 Safety Analysis Set, DC0 15FEB2024



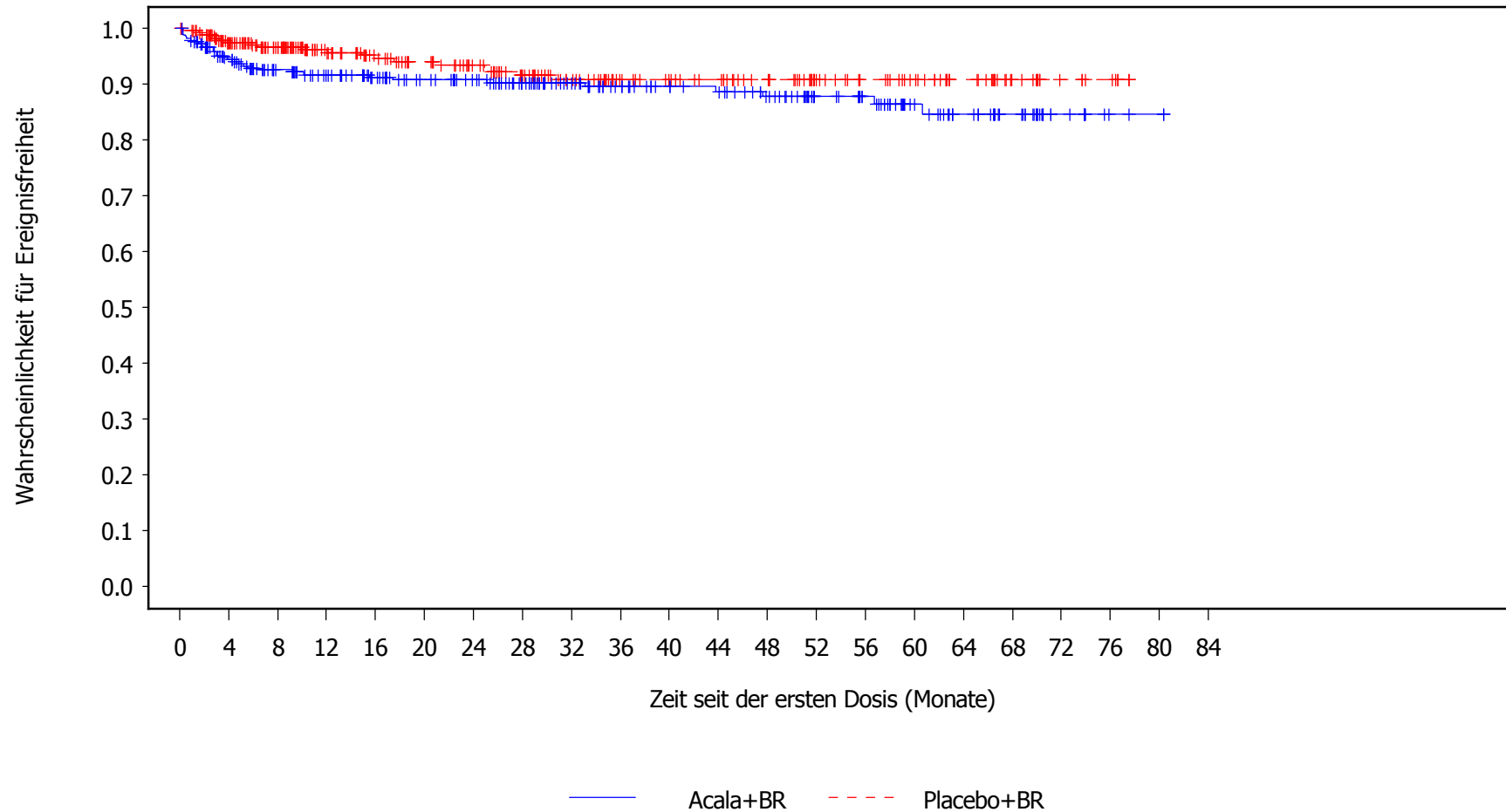
Anzahl an Patienten unter Risiko:

297	271	243	226	205	189	178	158	137	124	115	111	100	79	68	51	40	29	11	2	1	0	Acala+BR
297	259	230	194	175	164	148	134	117	101	92	88	77	61	53	46	31	17	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.120 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Gewicht erniedrigt
 Safety Analysis Set, DCO 15FEB2024



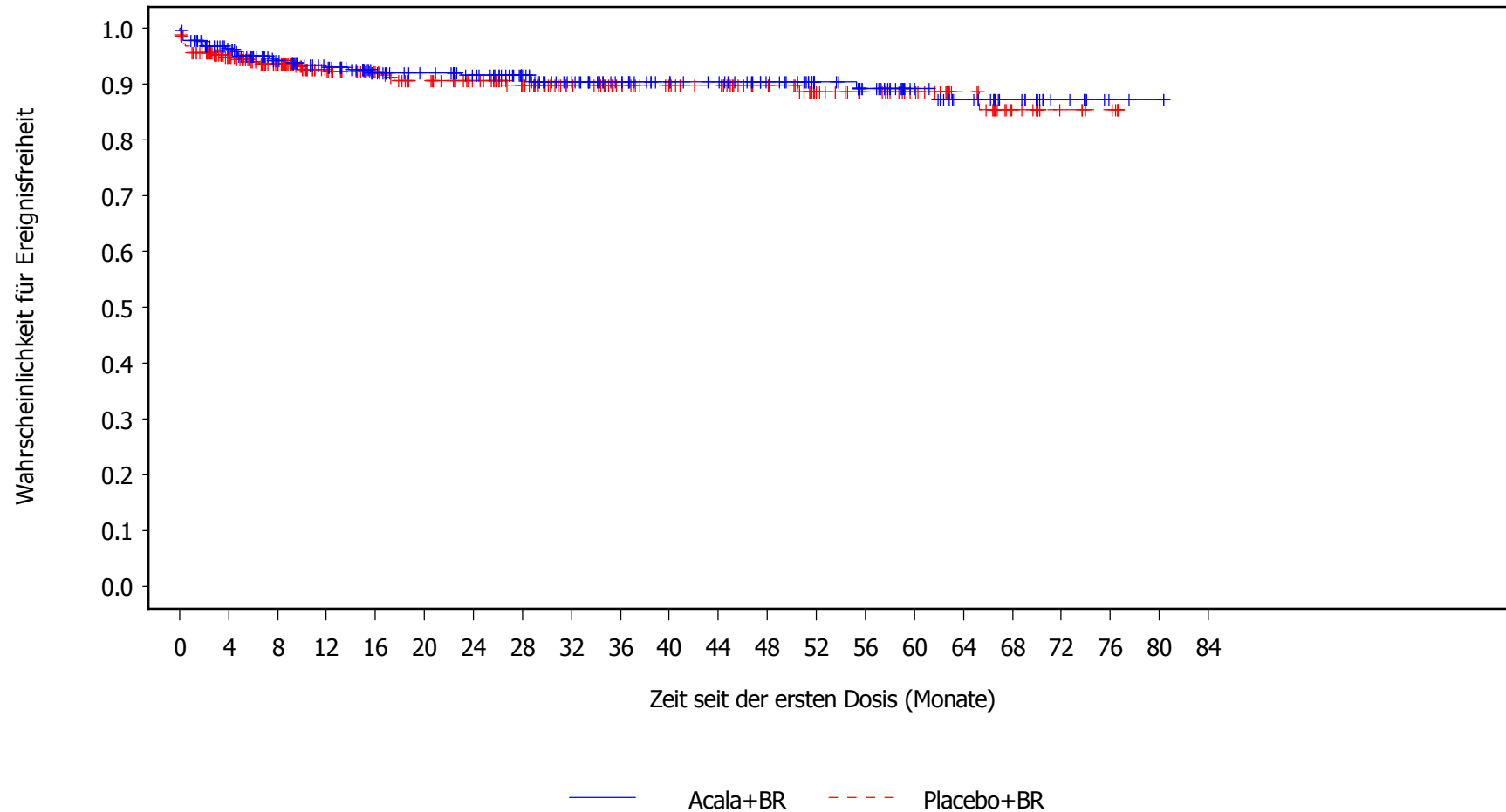
Anzahl an Patienten unter Risiko:

297	260	233	217	198	183	172	152	133	118	108	104	94	75	65	47	37	27	10	2	1	0	Acala+BR
297	261	231	196	175	163	149	132	114	99	93	88	79	62	54	47	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.121 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Kreatinin im Blut erhoeht
 Safety Analysis Set, DCO 15FEB2024



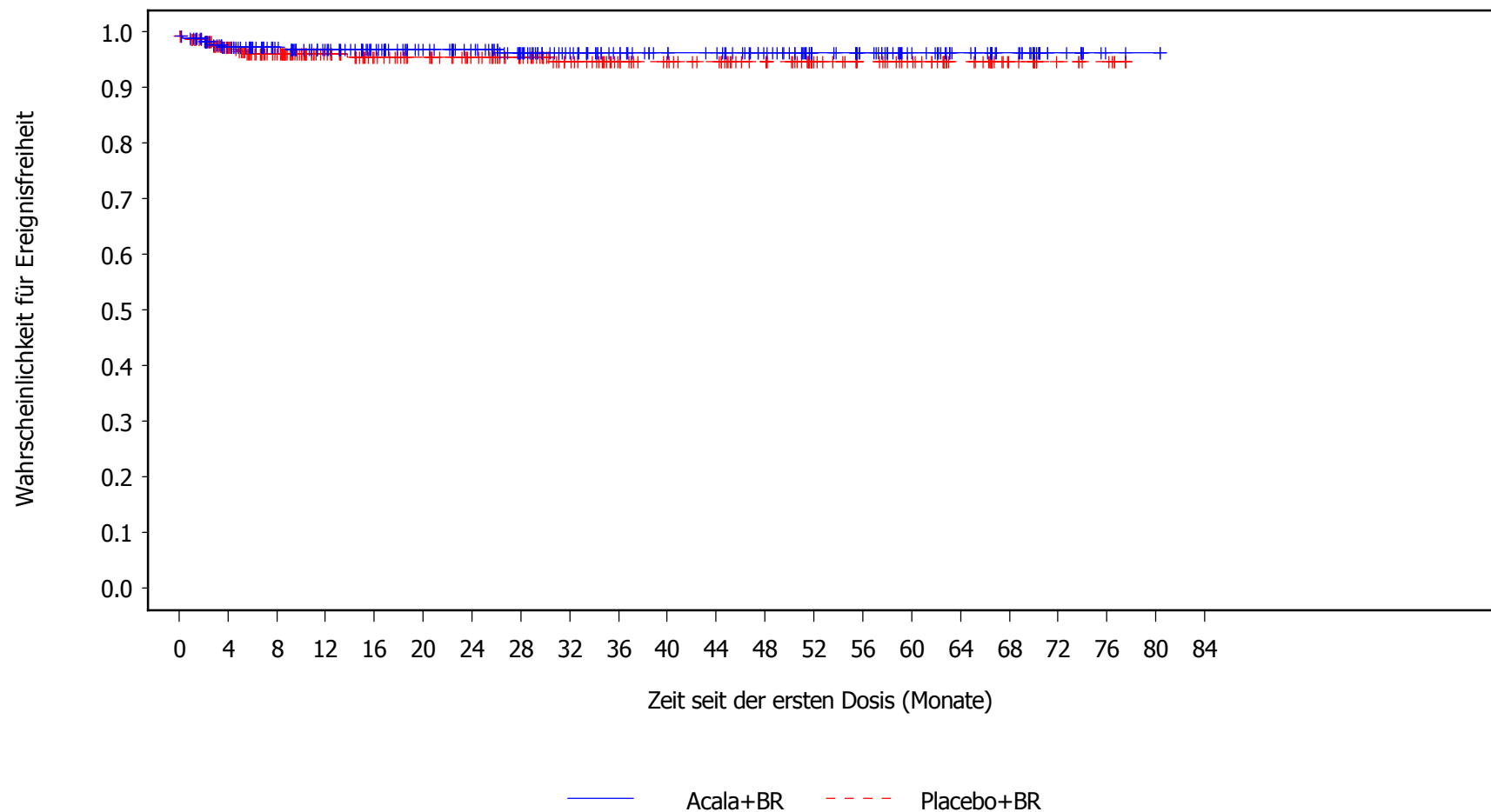
Anzahl an Patienten unter Risiko:

297	266	235	216	194	184	173	153	133	118	108	104	94	76	64	47	36	25	11	2	1	0	Acala+BR
297	252	223	188	170	157	144	130	113	103	94	90	78	60	52	44	30	17	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.122 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Laktatdehydrogenase im Blut erhoeht
 Safety Analysis Set, DCO 15FEB2024



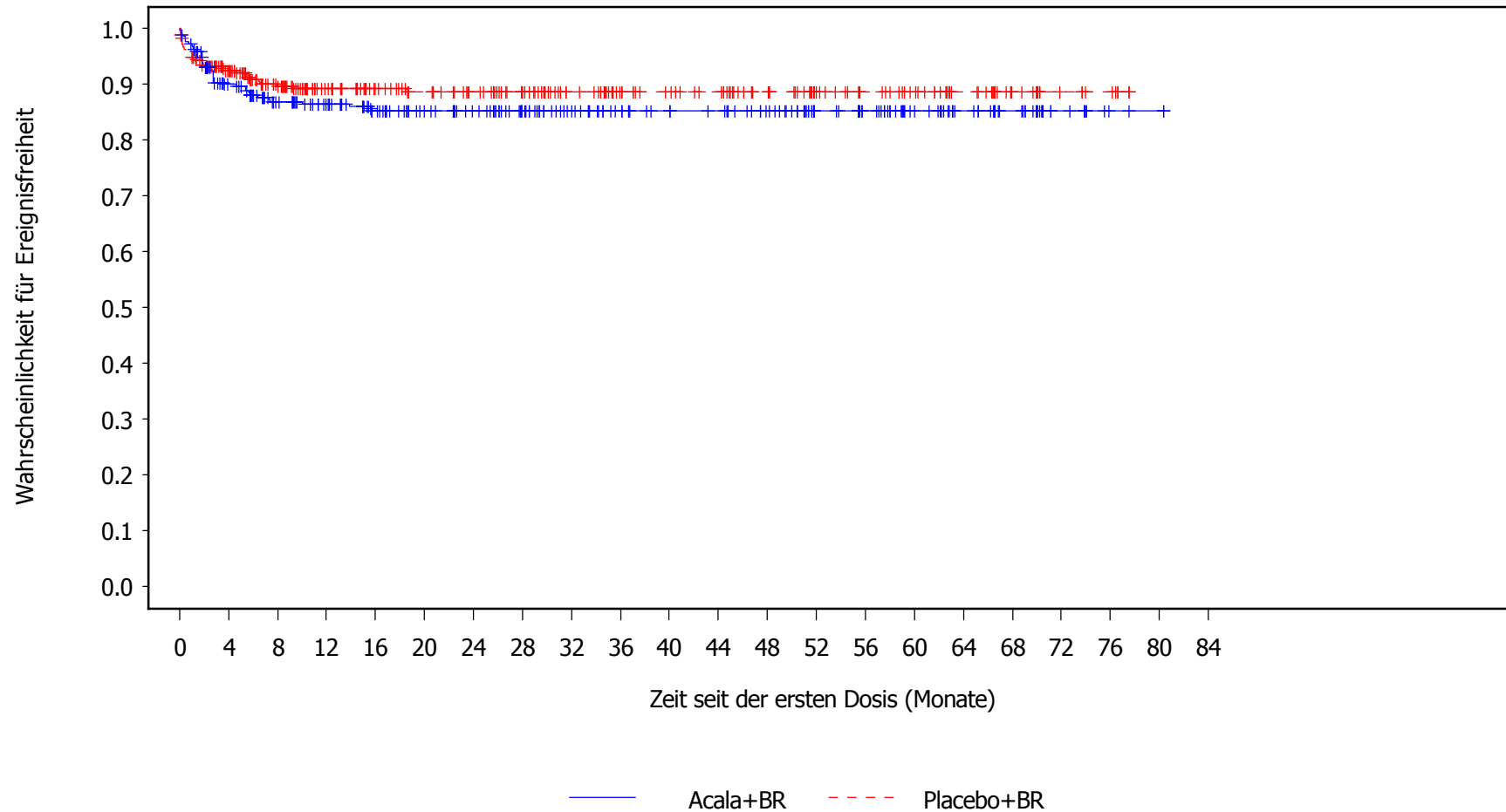
Anzahl an Patienten unter Risiko:

297	267	242	224	205	188	177	157	139	124	114	111	99	78	68	51	40	29	11	2	1	0	Acala+BR
297	259	227	195	177	167	155	139	121	106	97	92	81	64	55	47	32	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.123 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Leukozytenzahl erniedrigt
 Safety Analysis Set, DC0 15FEB2024



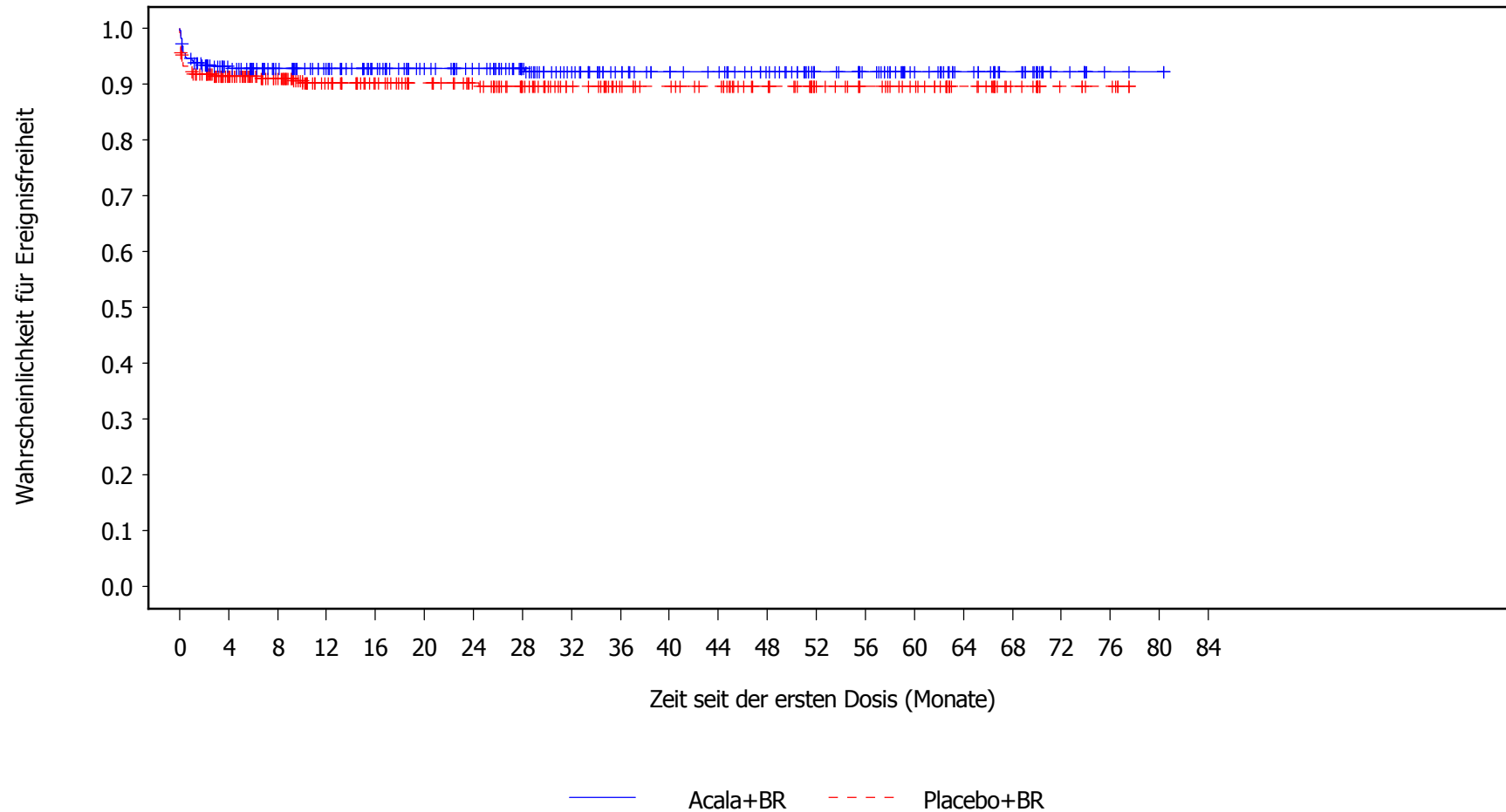
Anzahl an Patienten unter Risiko:

297	246	218	202	183	168	158	140	125	113	106	103	94	75	65	48	37	26	10	2	1	0	Acala+BR
297	248	213	183	165	154	144	130	113	101	94	89	77	63	54	47	32	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.124 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Lymphozytenzahl erniedrigt
 Safety Analysis Set, DCO 15FEB2024



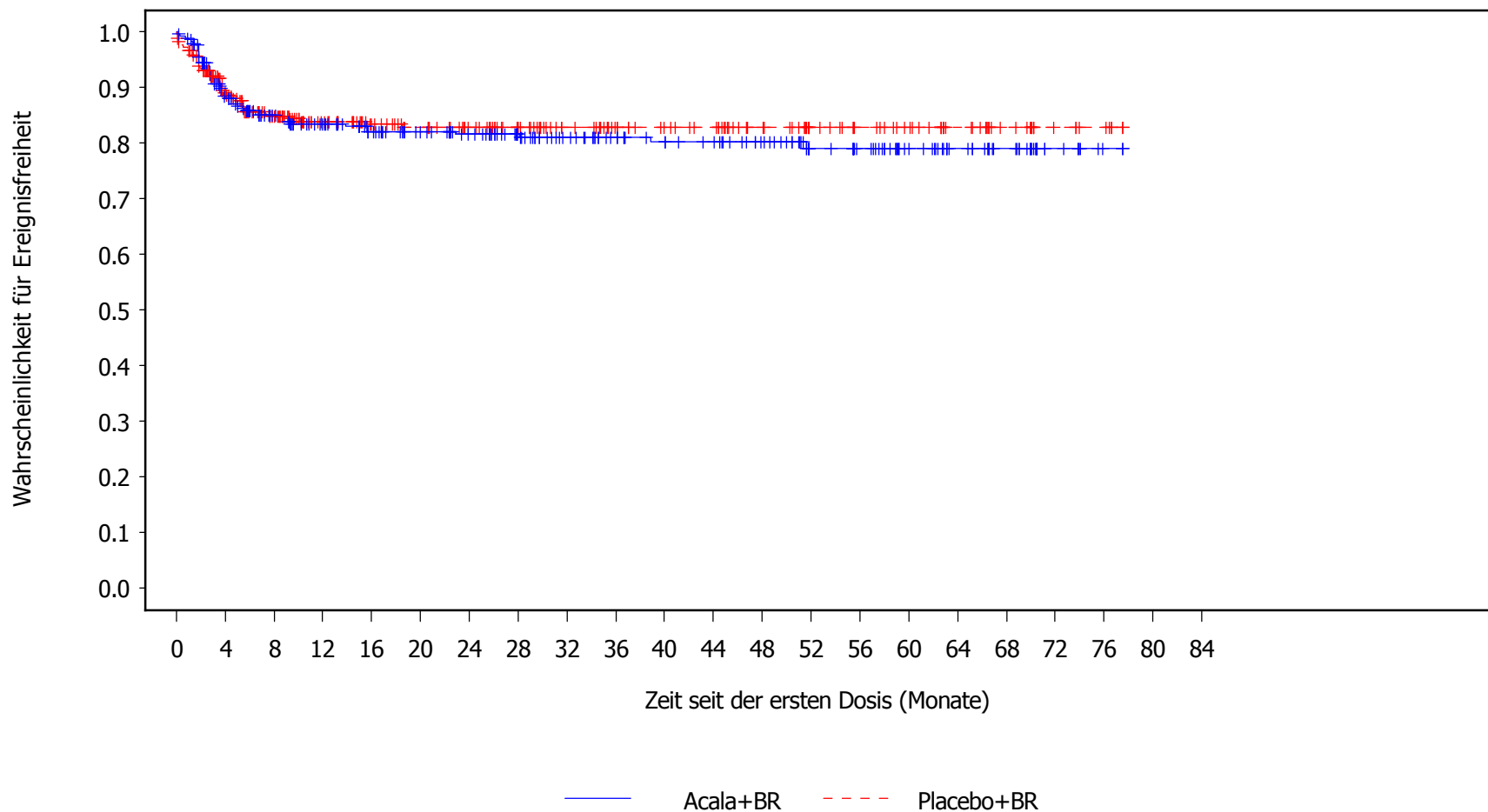
Anzahl an Patienten unter Risiko:

297	255	231	215	197	182	171	151	133	118	109	105	95	76	67	50	39	28	10	2	1	0	Acala+BR
297	243	215	184	167	155	144	127	110	98	93	88	76	62	54	47	32	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.125 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Neutrophilenzahl erniedrigt
 Safety Analysis Set, DCO 15FEB2024



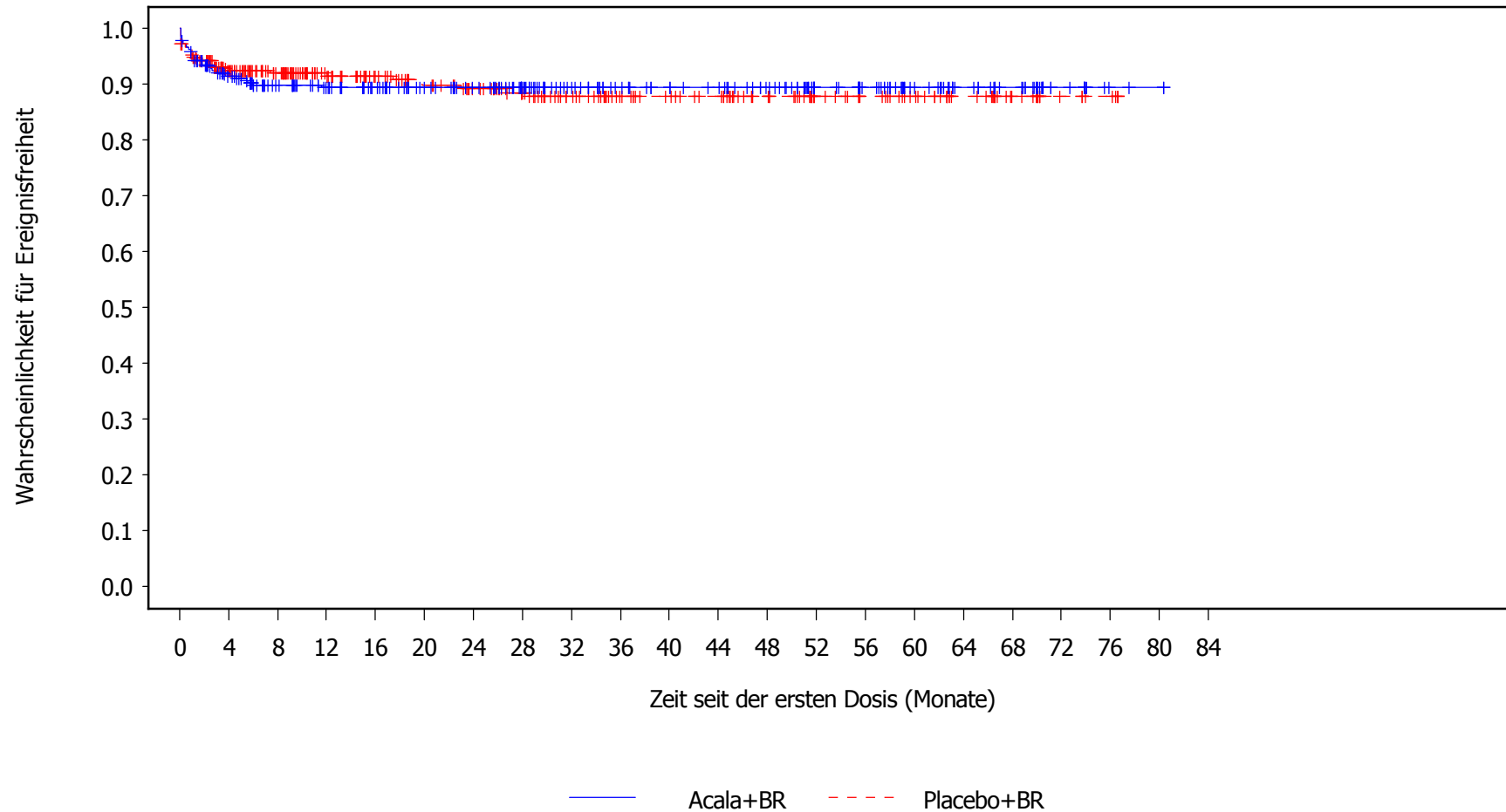
Anzahl an Patienten unter Risiko:

297	243	213	195	177	164	152	135	120	109	102	98	88	70	62	46	35	25	8	1	0	0	Acala+BR
297	239	202	171	152	141	130	115	100	90	83	79	67	53	46	40	28	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.126 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Thrombozytenzahl vermindert
 Safety Analysis Set, DCO 15FEB2024



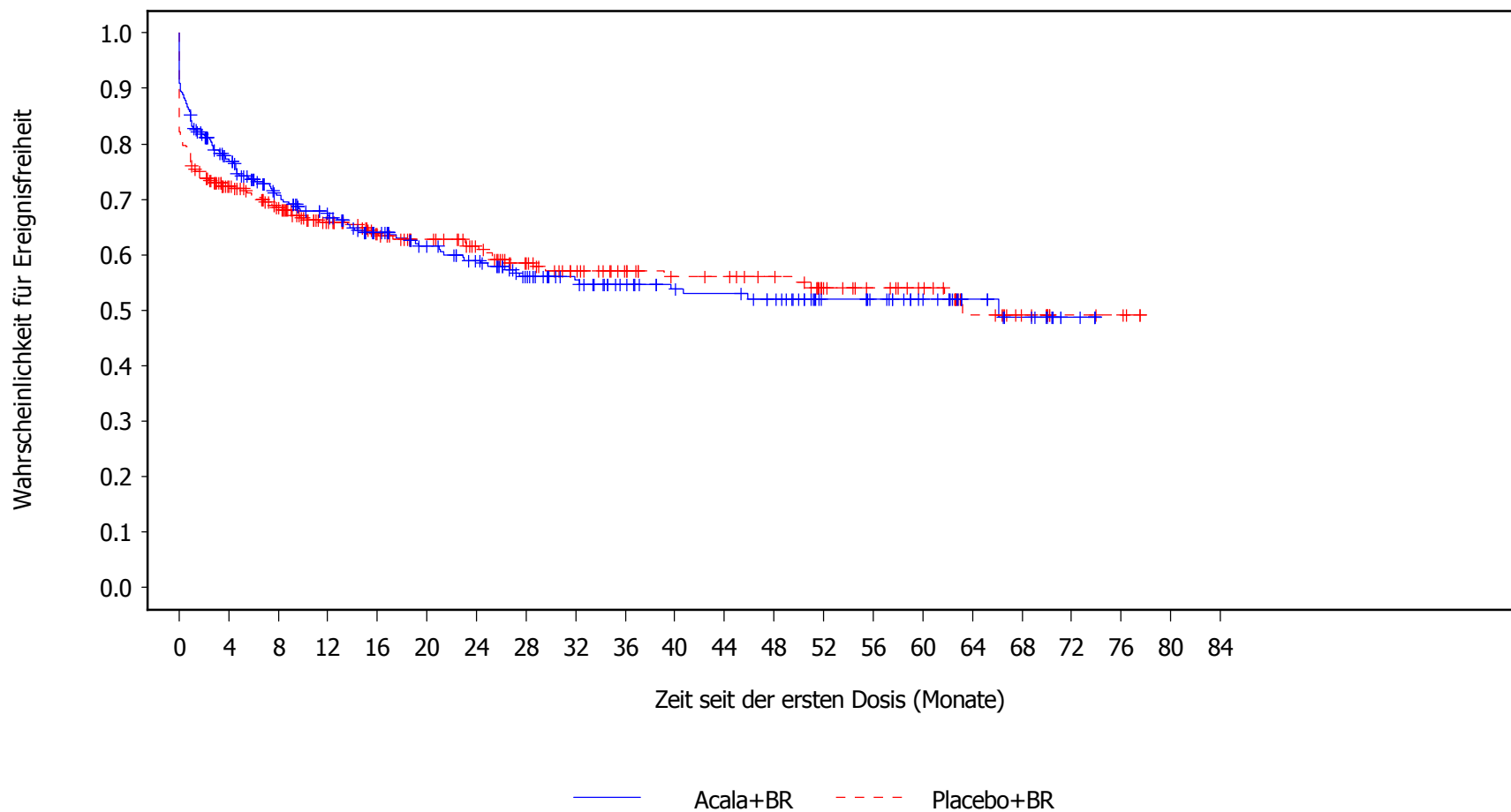
Anzahl an Patienten unter Risiko:

297	251	225	210	195	178	168	149	130	117	110	106	96	75	65	48	37	29	11	2	1	0	Acala+BR
297	248	220	188	169	154	143	127	111	97	90	85	73	57	50	42	29	17	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.127 ECHO: Kaplan-Meier plot of time to first occurrence of SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen
 Safety Analysis Set, DCO 15FEB2024



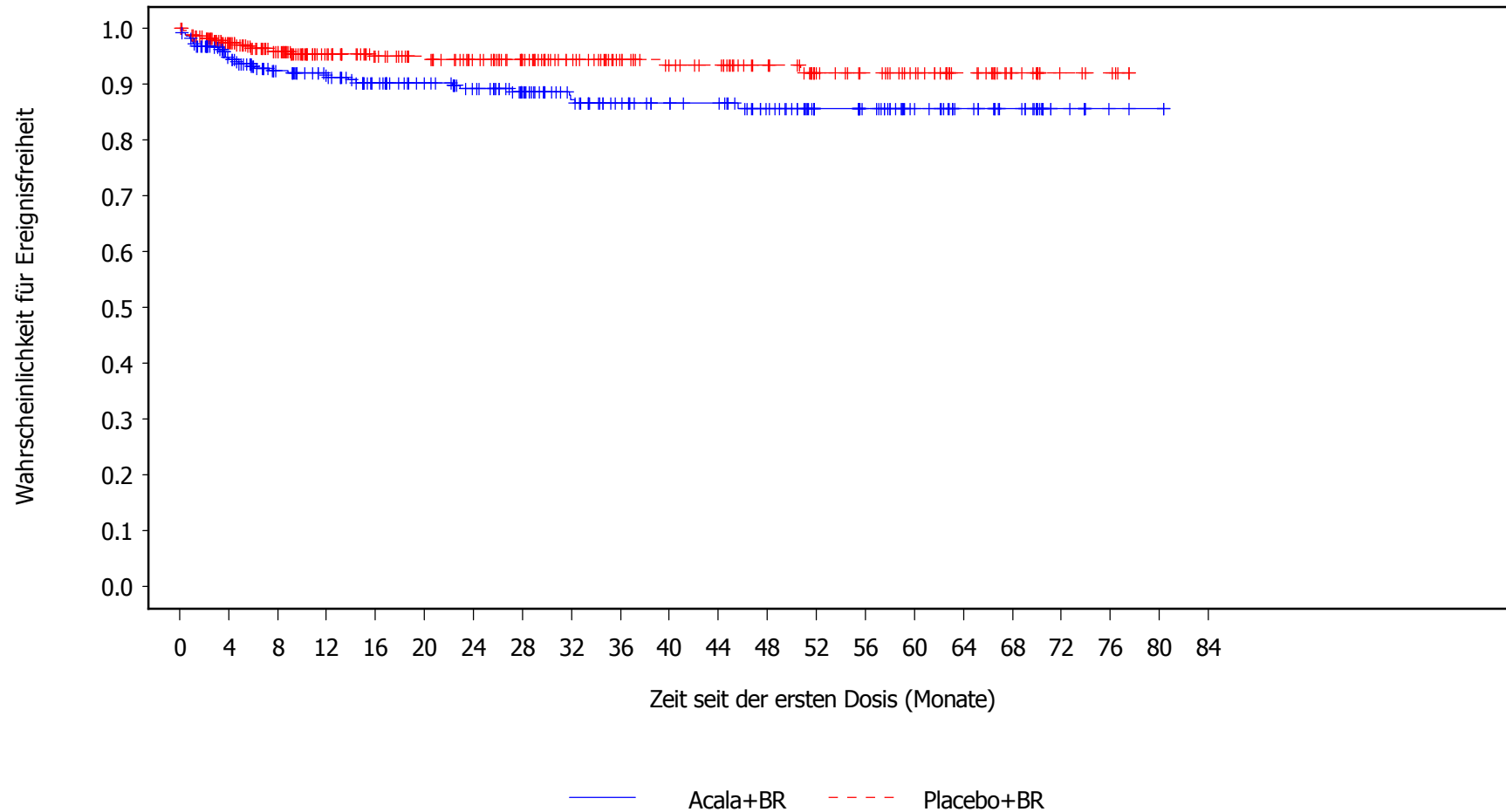
Anzahl an Patienten unter Risiko:

297	213	178	158	137	121	110	93	79	68	61	59	54	40	36	27	18	13	4	0	0	0	Acala+BR
297	195	169	142	125	113	101	86	74	65	58	57	53	41	35	30	18	11	4	3	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.128 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Kontusion
 Safety Analysis Set, DC0 15FEB2024



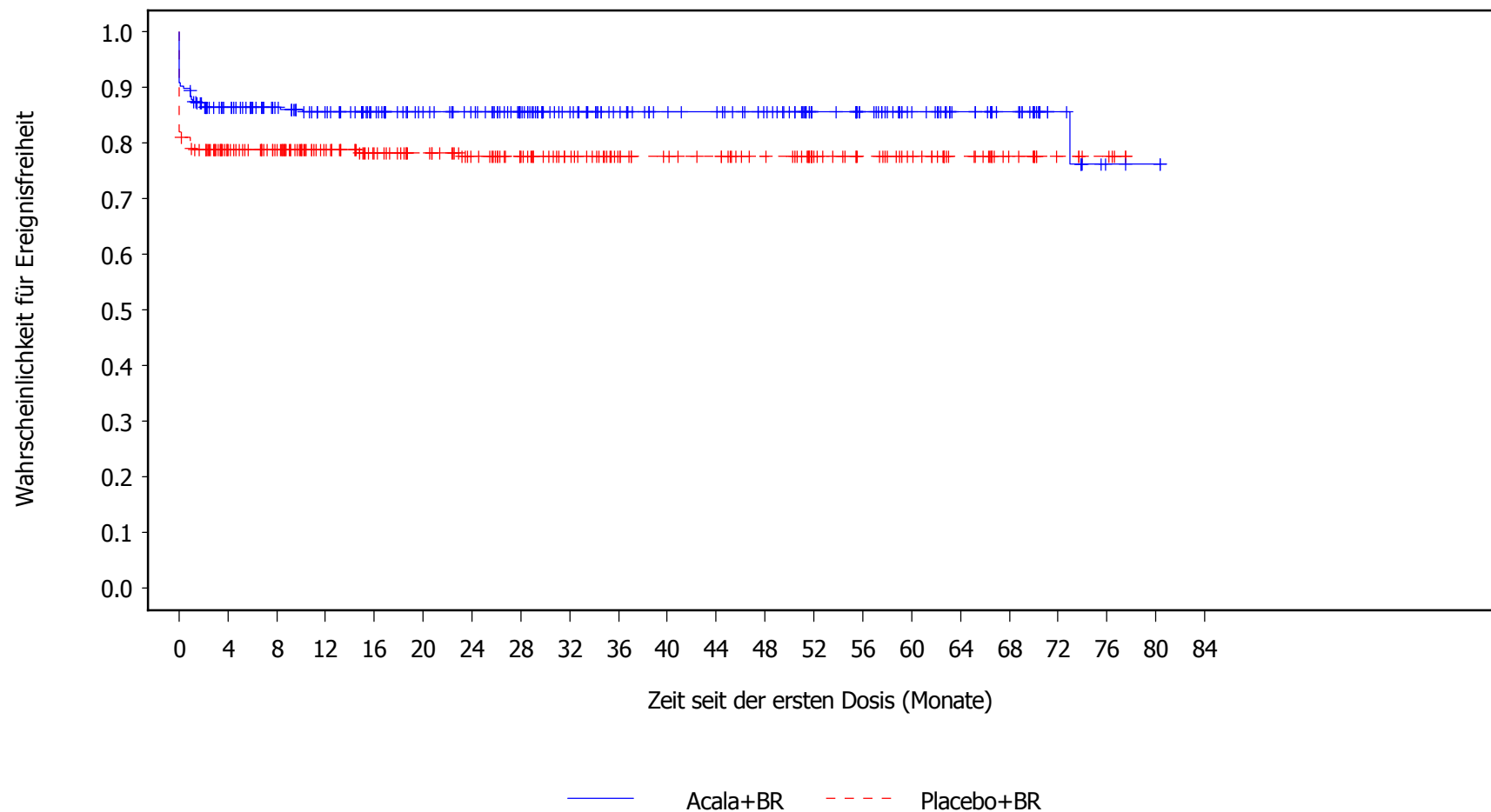
Anzahl an Patienten unter Risiko:

297	260	228	211	191	177	164	145	125	111	103	100	87	68	60	44	34	25	8	2	1	0	Acala+BR
297	260	229	194	176	164	151	135	117	102	92	88	76	60	53	45	30	17	6	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.129 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Reaktion im Zusammenhang mit einer Infusion
 Safety Analysis Set, DCO 15FEB2024



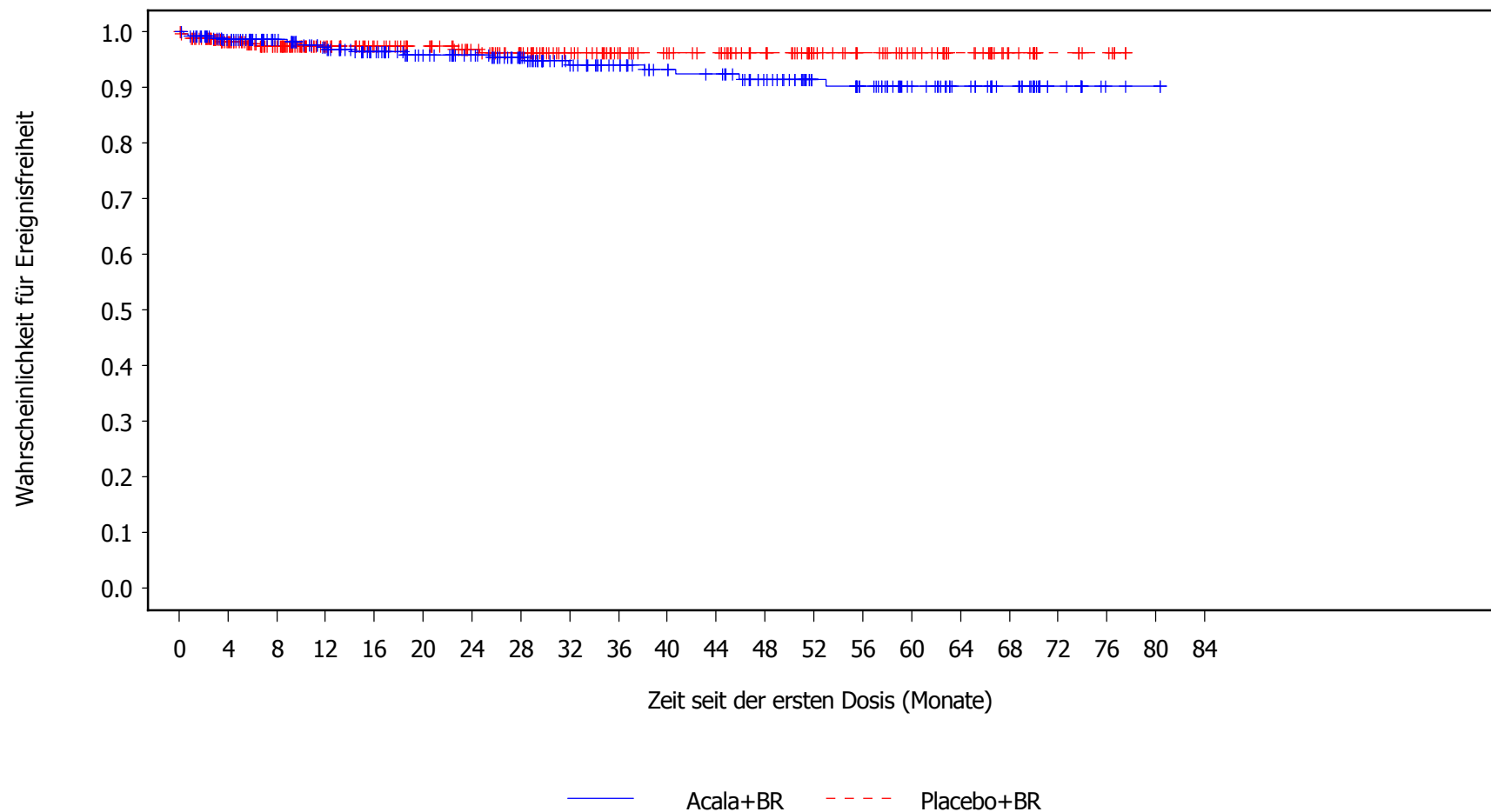
Anzahl an Patienten unter Risiko:

297	239	218	201	183	168	160	143	124	109	100	98	89	70	62	47	36	27	10	2	1	0	Acala+BR
297	211	194	167	150	139	126	114	100	86	80	77	69	55	46	38	26	15	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.130 ECHO: Kaplan-Meier plot of time to first occurrence of PT: Sturz
 Safety Analysis Set, DCO 15FEB2024



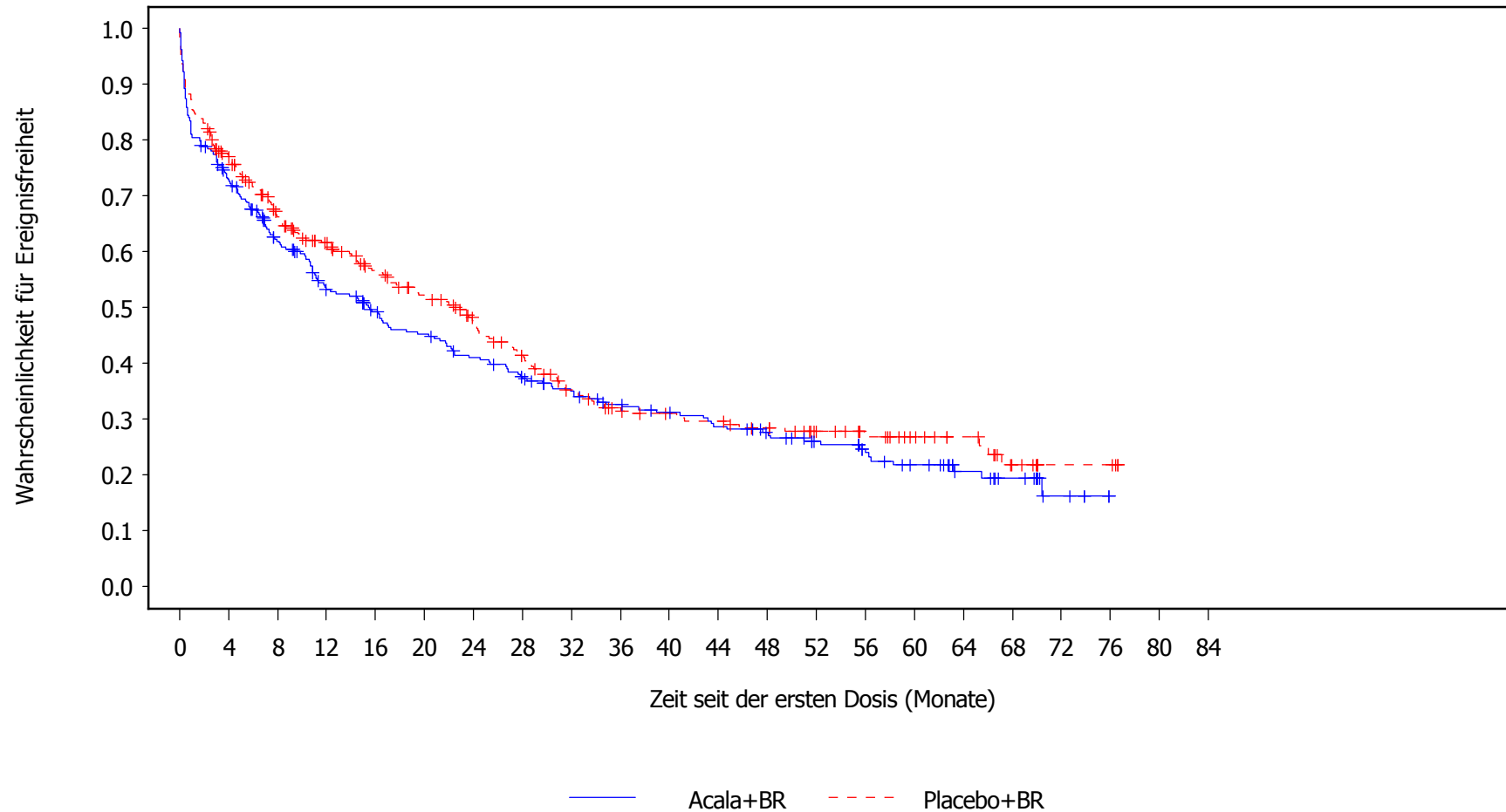
Anzahl an Patienten unter Risiko:

297	271	244	225	205	187	176	155	134	121	110	106	94	73	64	48	37	28	10	2	1	0	Acala+BR
297	263	233	199	181	169	154	137	118	104	95	91	79	63	54	46	32	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.131 ECHO: Kaplan-Meier plot of time to first occurrence of SUE
 Safety Analysis Set, DC0 15FEB2024



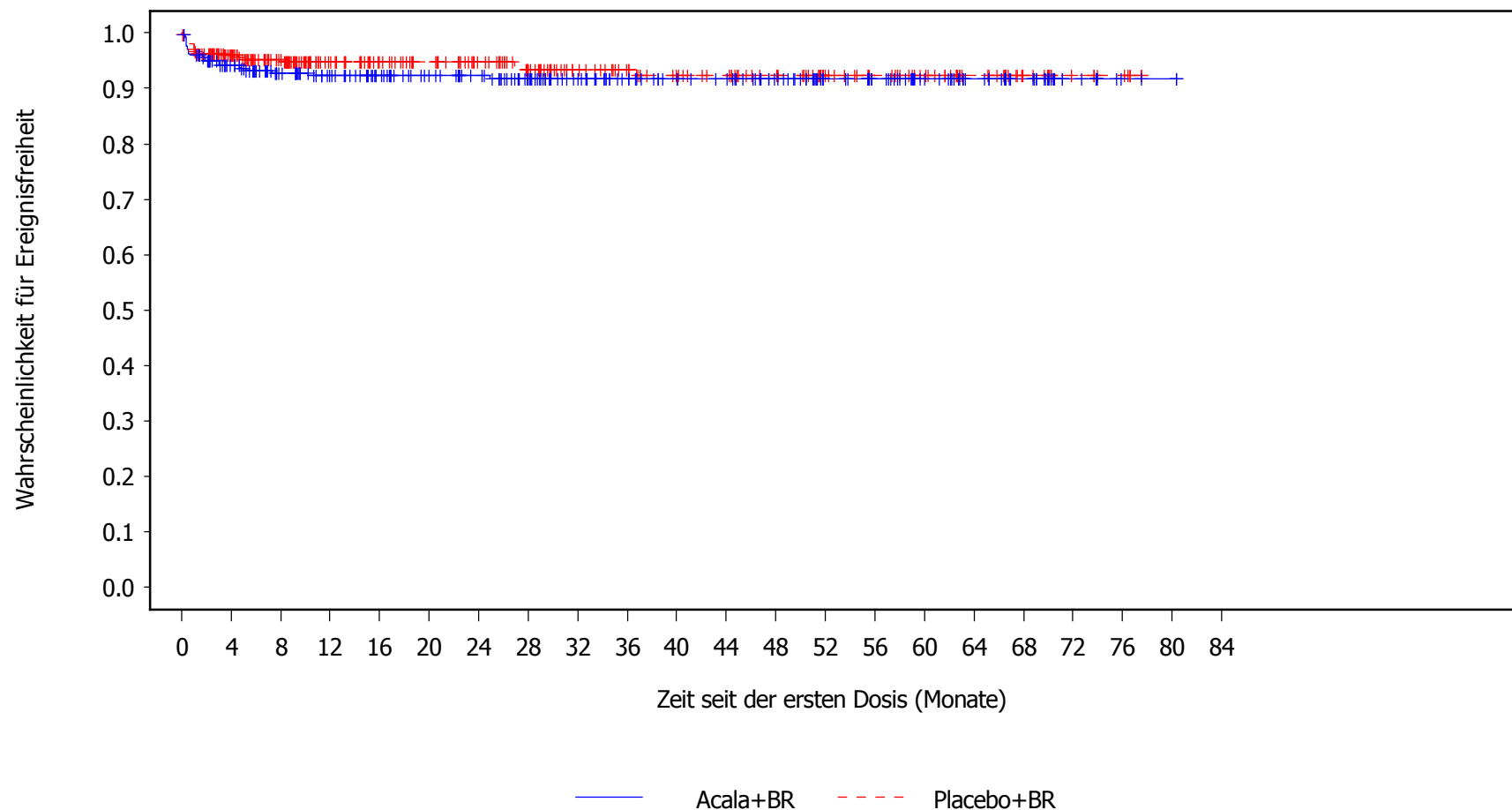
Anzahl an Patienten unter Risiko:

297	211	168	138	121	110	98	86	76	68	63	57	51	42	33	27	18	13	4	0	0	0	Acala+BR
297	222	177	154	133	117	98	83	66	56	51	49	44	36	29	23	18	9	3	3	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.132 ECH0: Kaplan-Meier plot of time to first occurrence of SUE SOC: Allgemeine Erkrankungen und Beschwerden am Verabreichungsort
 Safety Analysis Set, DCO 15FEB2024



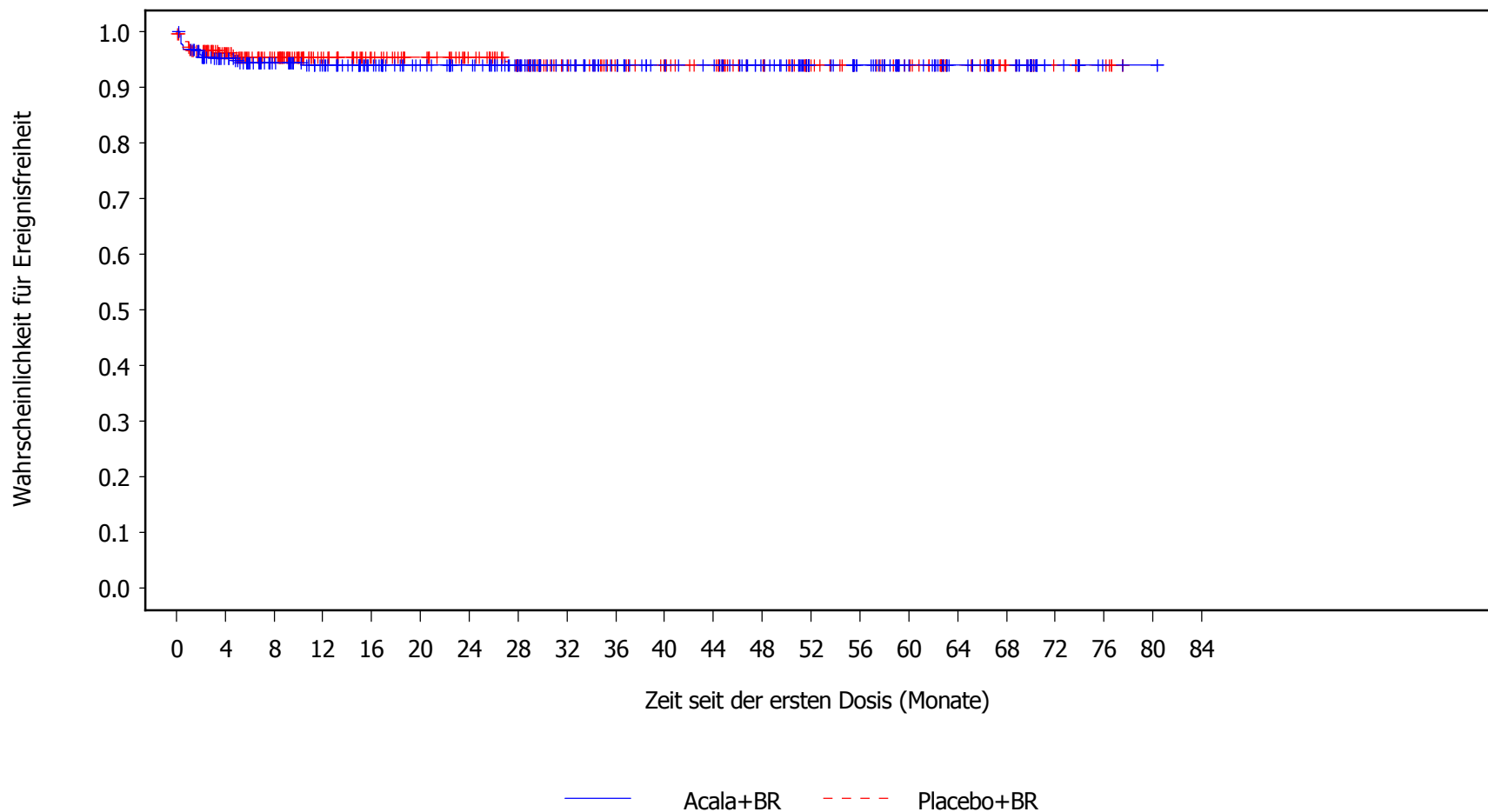
Anzahl an Patienten unter Risiko:

297	260	232	214	196	181	171	152	133	119	109	105	93	75	65	50	39	28	10	2	1	0	Acala+BR
297	256	227	192	174	162	148	131	112	102	93	88	79	62	53	45	31	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.133 ECHO: Kaplan-Meier plot of time to first occurrence of SUE PT: Fieber
 Safety Analysis Set, DC0 15FEB2024



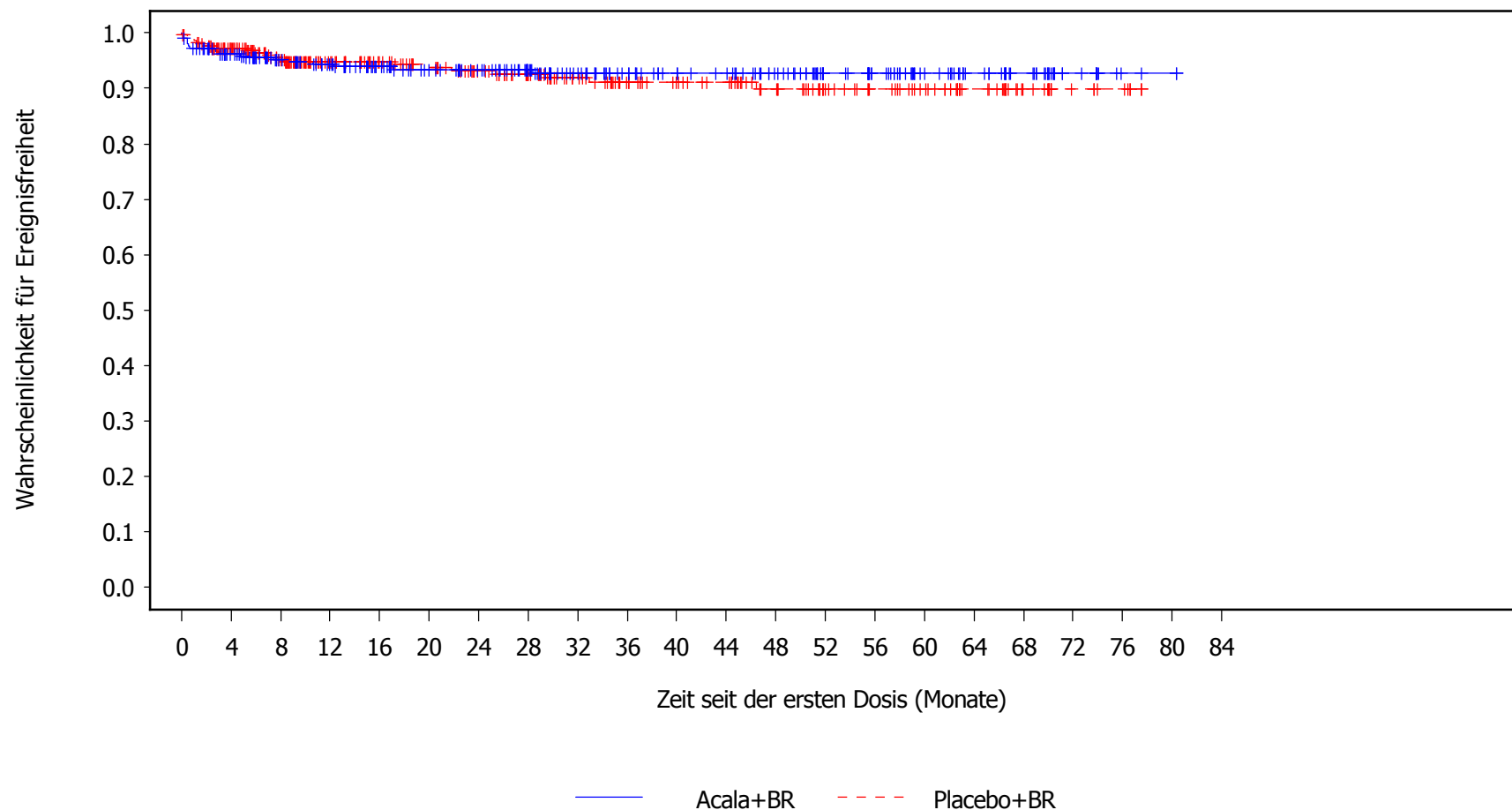
Anzahl an Patienten unter Risiko:

297	262	236	218	198	182	172	153	134	120	110	106	94	76	66	50	39	28	10	2	1	0	Acala+BR
297	257	228	194	176	164	150	132	113	102	94	89	79	62	53	45	31	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.134 ECHO: Kaplan-Meier plot of time to first occurrence of SUE SOC: Erkrankungen der Atemwege, des Brustraums und Mediastinums
 Safety Analysis Set, DCO 15FEB2024



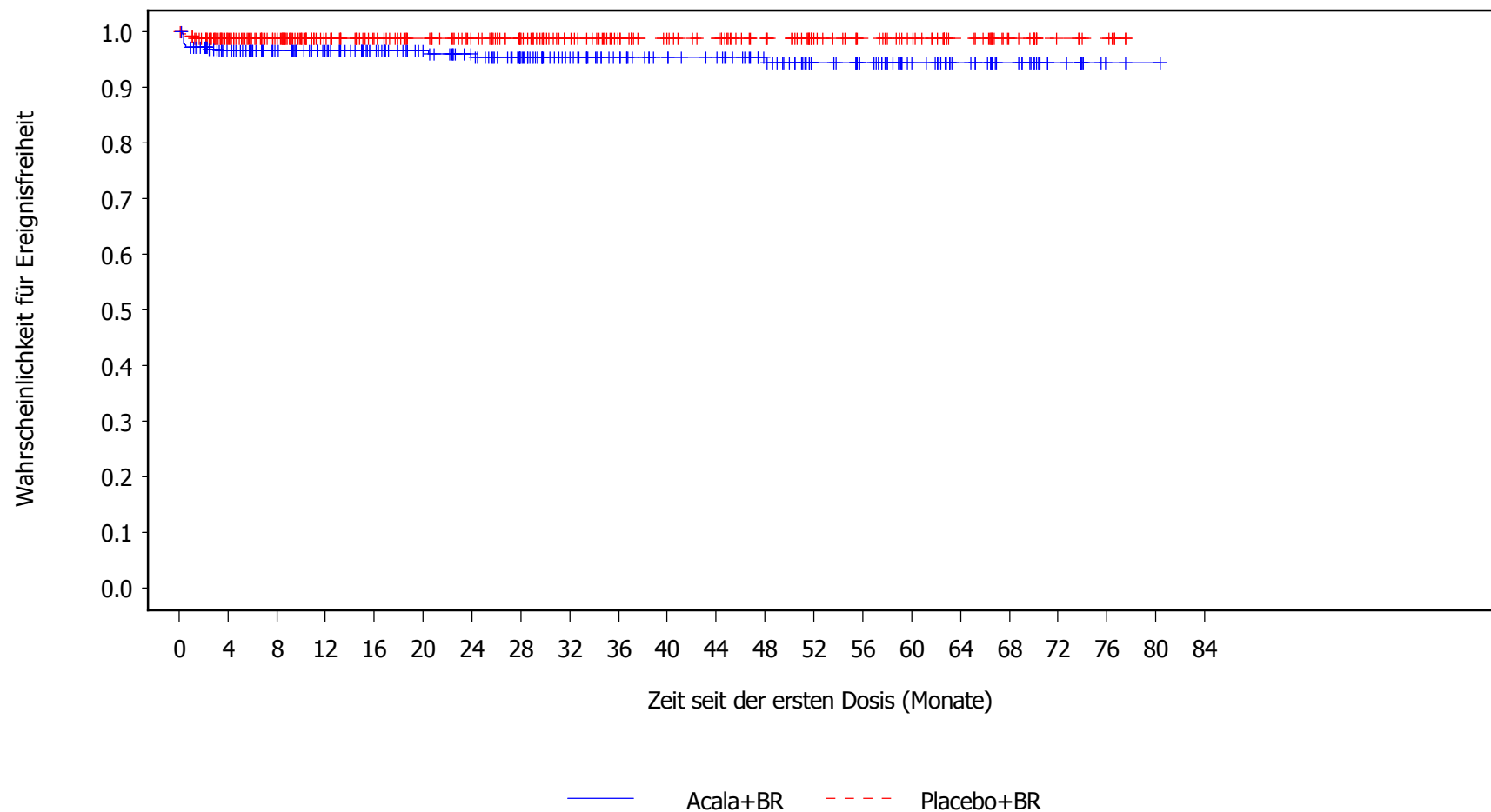
Anzahl an Patienten unter Risiko:

297	268	240	224	204	188	177	159	139	125	115	111	99	78	67	50	39	28	11	2	1	0	Acala+BR
297	264	232	198	179	165	152	137	119	105	96	91	78	64	55	47	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.135 ECH0: Kaplan-Meier plot of time to first occurrence of SUE SOC: Erkrankungen der Haut und des Unterhautgewebes
 Safety Analysis Set, DC0 15FEB2024



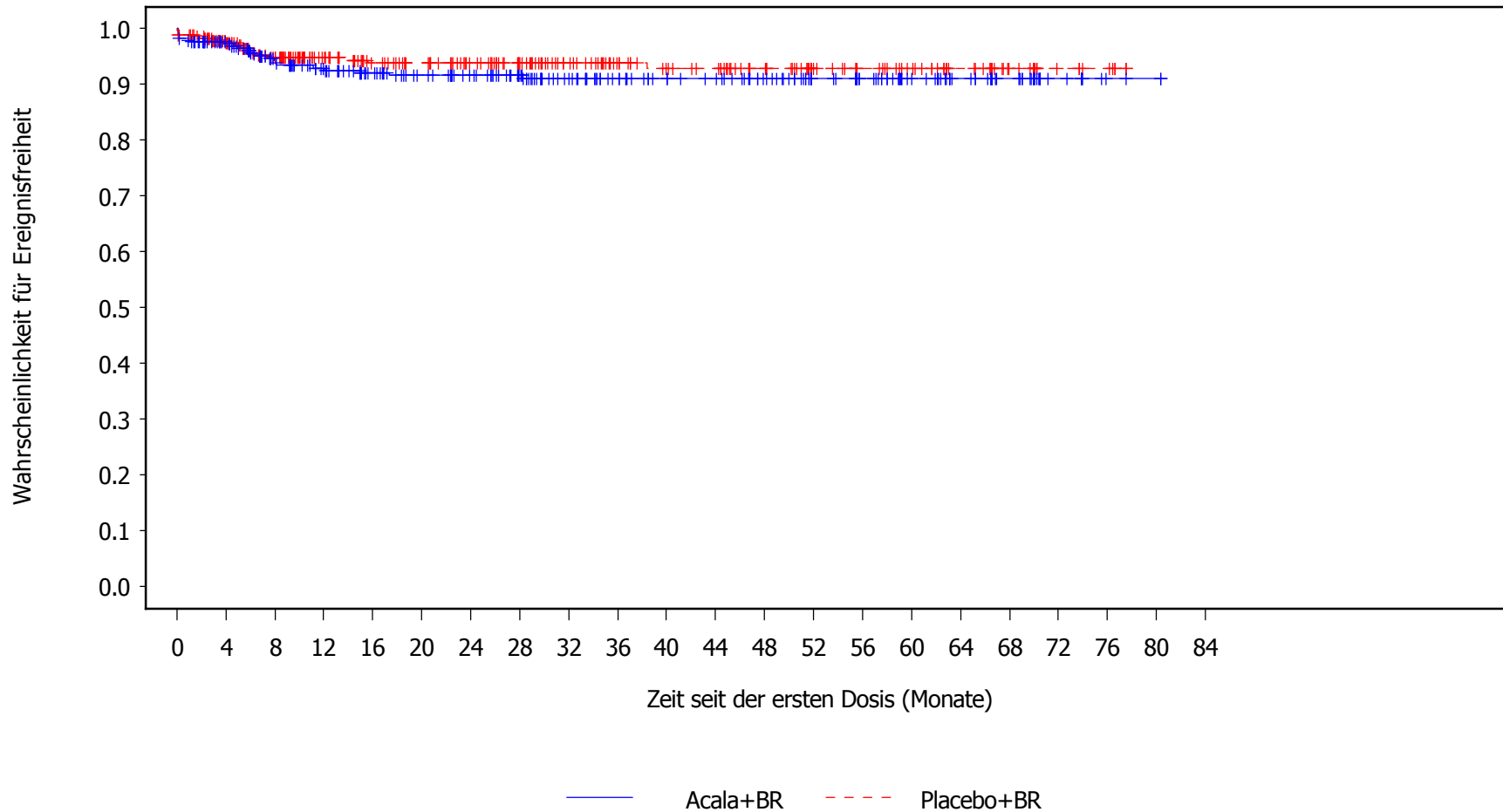
Anzahl an Patienten unter Risiko:

297	266	242	225	206	189	178	159	138	123	113	109	97	76	67	51	40	29	11	2	1	0	Acala+BR
297	265	236	201	184	172	158	142	123	108	99	94	82	65	56	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.136 ECHO: Kaplan-Meier plot of time to first occurrence of SUE SOC: Erkrankungen des Blutes und des Lymphsystems
 Safety Analysis Set, DCO 15FEB2024



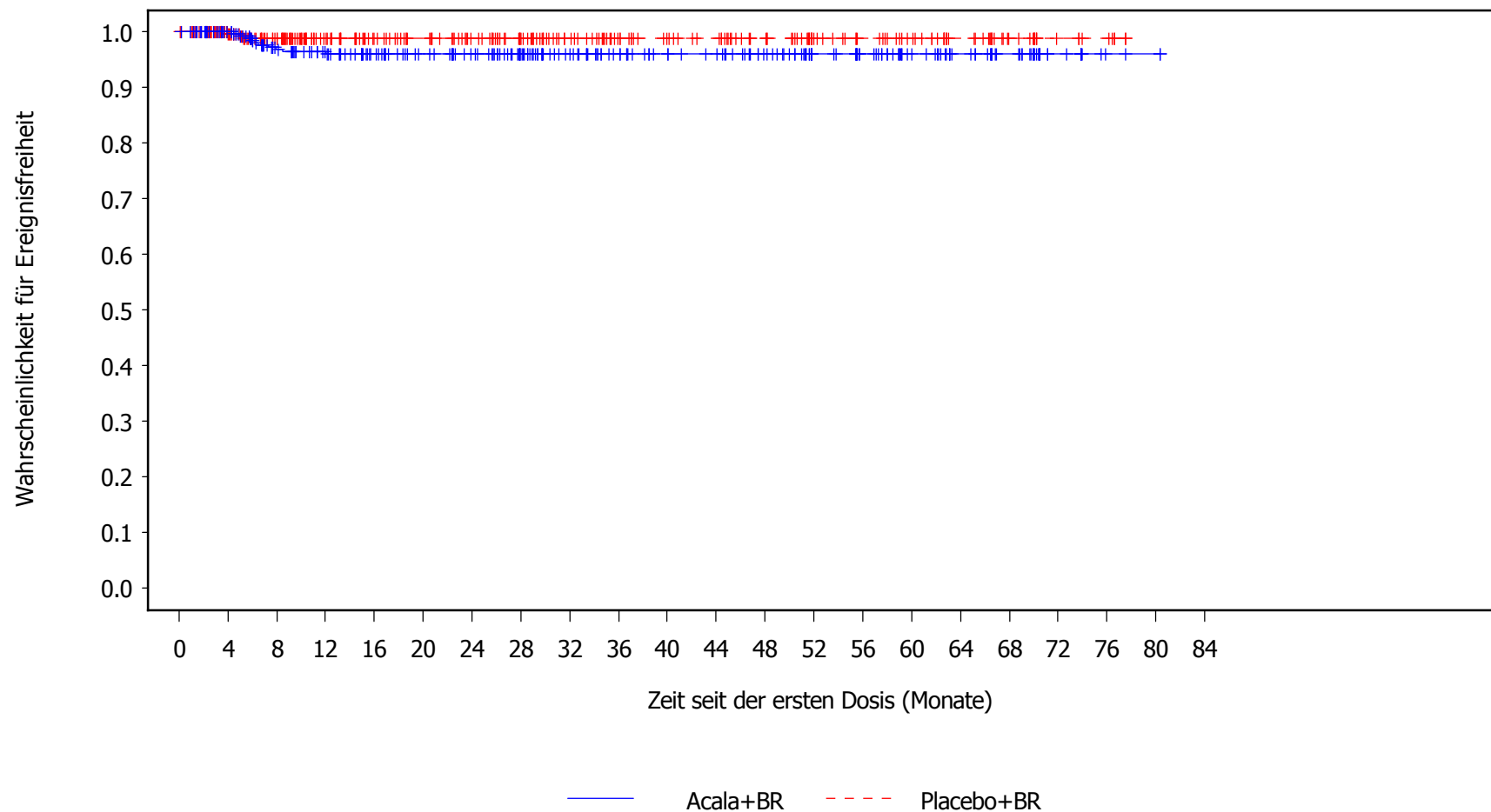
Anzahl an Patienten unter Risiko:

297	269	234	215	195	181	170	155	135	120	110	106	95	76	65	49	38	27	10	2	1	0	Acala+BR
297	264	231	198	177	167	153	137	119	104	95	91	79	62	54	46	32	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.137 ECHO: Kaplan-Meier plot of time to first occurrence of SUE PT: Febrile Neutropenie
 Safety Analysis Set, DC0 15FEB2024



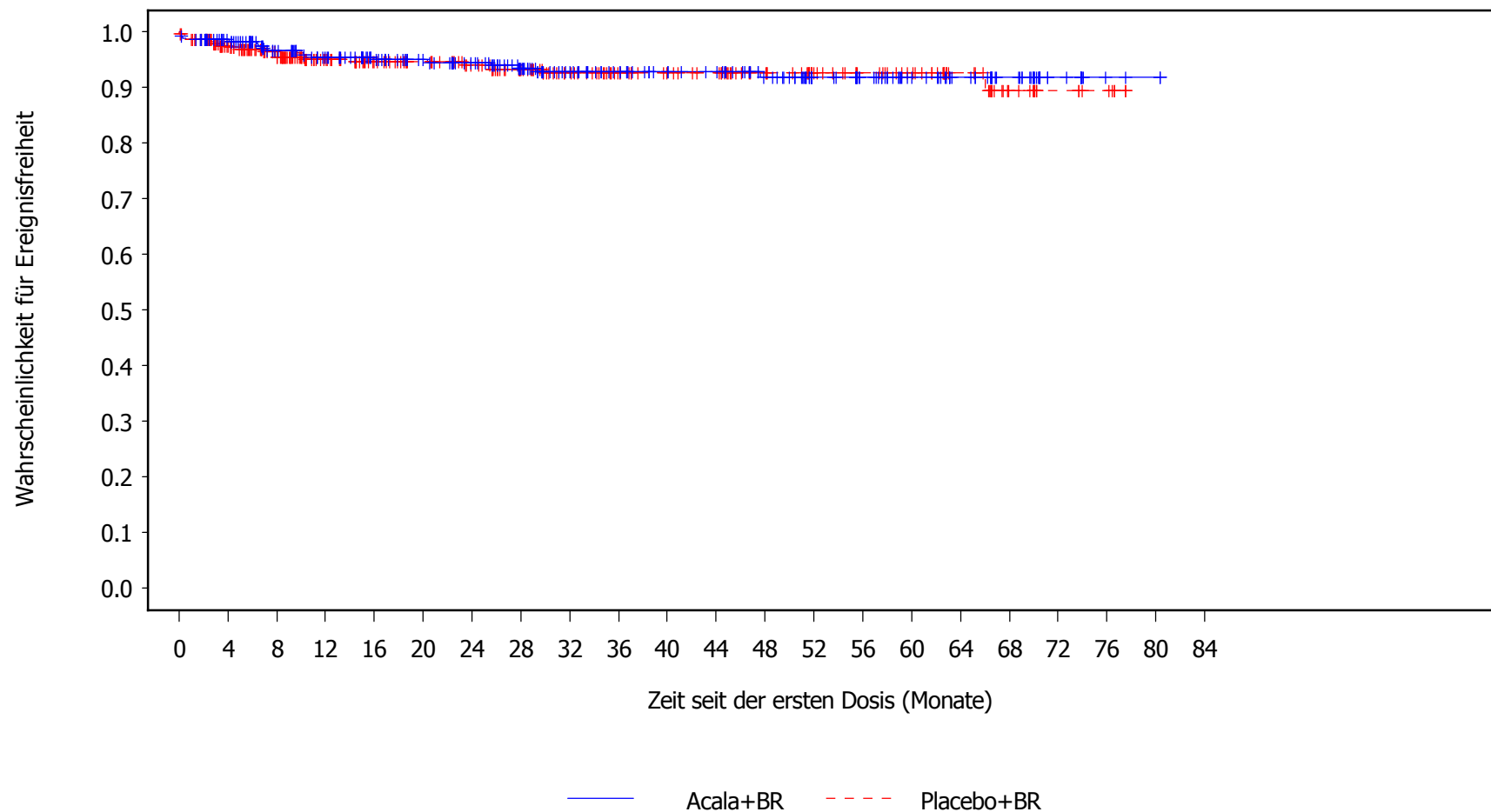
Anzahl an Patienten unter Risiko:

297	275	240	223	203	189	178	158	138	123	113	109	97	77	66	50	39	28	10	2	1	0	Acala+BR
297	267	236	202	183	171	157	141	122	107	98	93	81	64	55	47	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.138 ECHO: Kaplan-Meier plot of time to first occurrence of SUE SOC: Erkrankungen des Gastrointestinaltrakts
 Safety Analysis Set, DCO 15FEB2024



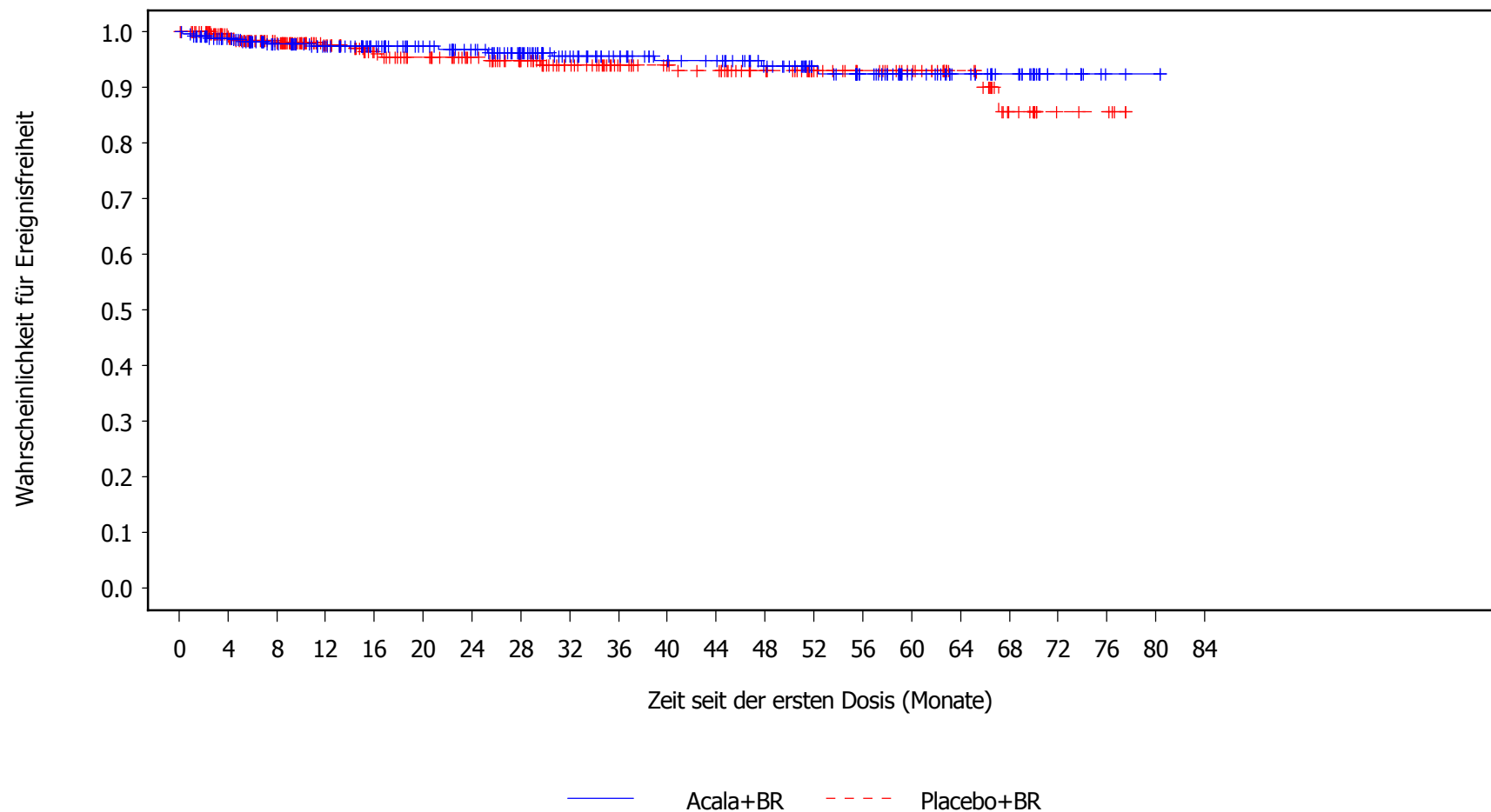
Anzahl an Patienten unter Risiko:

297	274	243	225	205	190	178	156	135	122	112	108	95	75	64	49	39	28	10	2	1	0	Acala+BR
297	262	230	195	176	164	151	134	115	101	93	89	77	64	55	48	33	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.139 ECHO: Kaplan-Meier plot of time to first occurrence of SUE SOC: Erkrankungen des Nervensystems
 Safety Analysis Set, DCO 15FEB2024



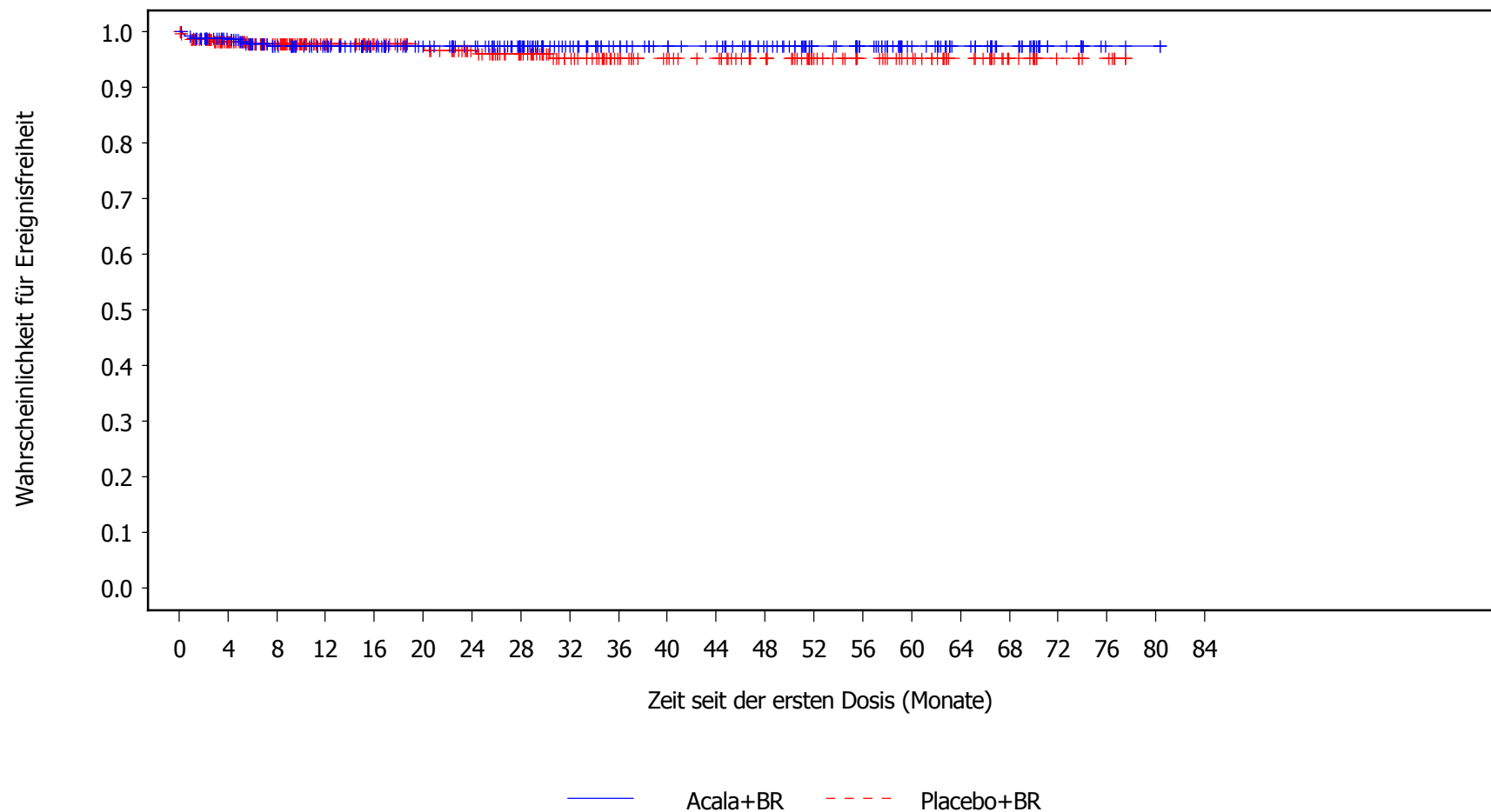
Anzahl an Patienten unter Risiko:

297	274	245	227	208	191	179	157	135	122	111	107	94	75	63	46	36	27	10	2	1	0	Acala+BR
297	266	235	199	179	166	152	137	119	104	95	91	80	64	55	47	32	16	5	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.140 ECH0: Kaplan-Meier plot of time to first occurrence of SUE SOC: Gefaesserkrankungen
 Safety Analysis Set, DC0 15FEB2024



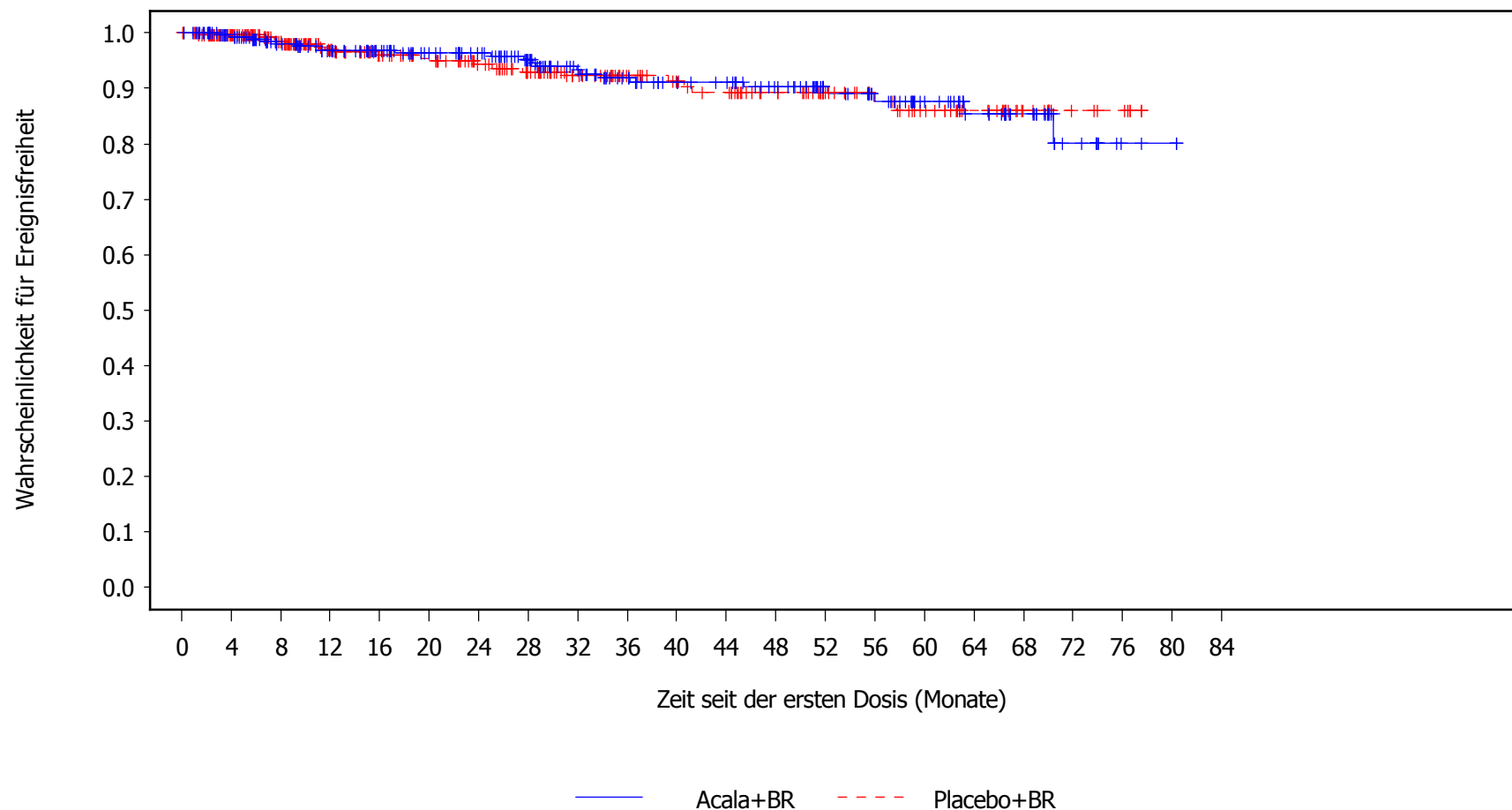
Anzahl an Patienten unter Risiko:

297	272	243	226	206	190	180	160	139	124	115	111	99	79	68	51	40	29	11	2	1	0	Acala+BR
297	263	234	199	181	169	155	138	118	103	94	90	80	63	54	46	32	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.141 ECHO: Kaplan-Meier plot of time to first occurrence of SUE SOC: Gutartige, boesartige und nicht spezifizierte Neubildungen (einschl. Zysten und Polypen)
 Safety Analysis Set, DCO 15FEB2024



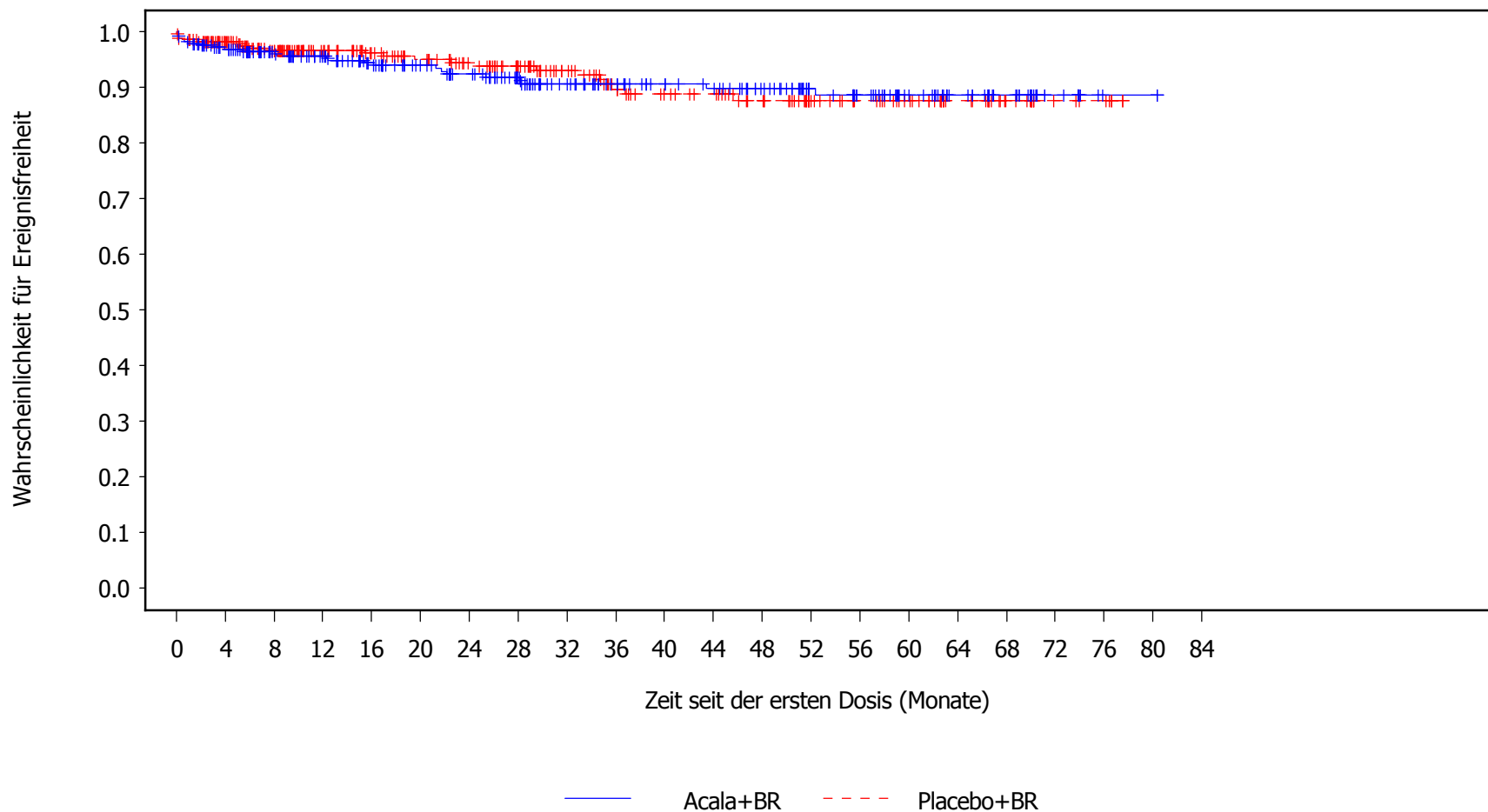
Anzahl an Patienten unter Risiko:

297	274	245	226	208	190	179	157	135	120	110	106	95	75	63	49	38	28	11	2	1	0	Acala+BR
297	267	235	200	180	168	153	137	118	104	95	90	78	63	53	44	30	17	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.142 ECHO: Kaplan-Meier plot of time to first occurrence of SUE SOC: Herzerkrankungen
 Safety Analysis Set, DC0 15FEB2024



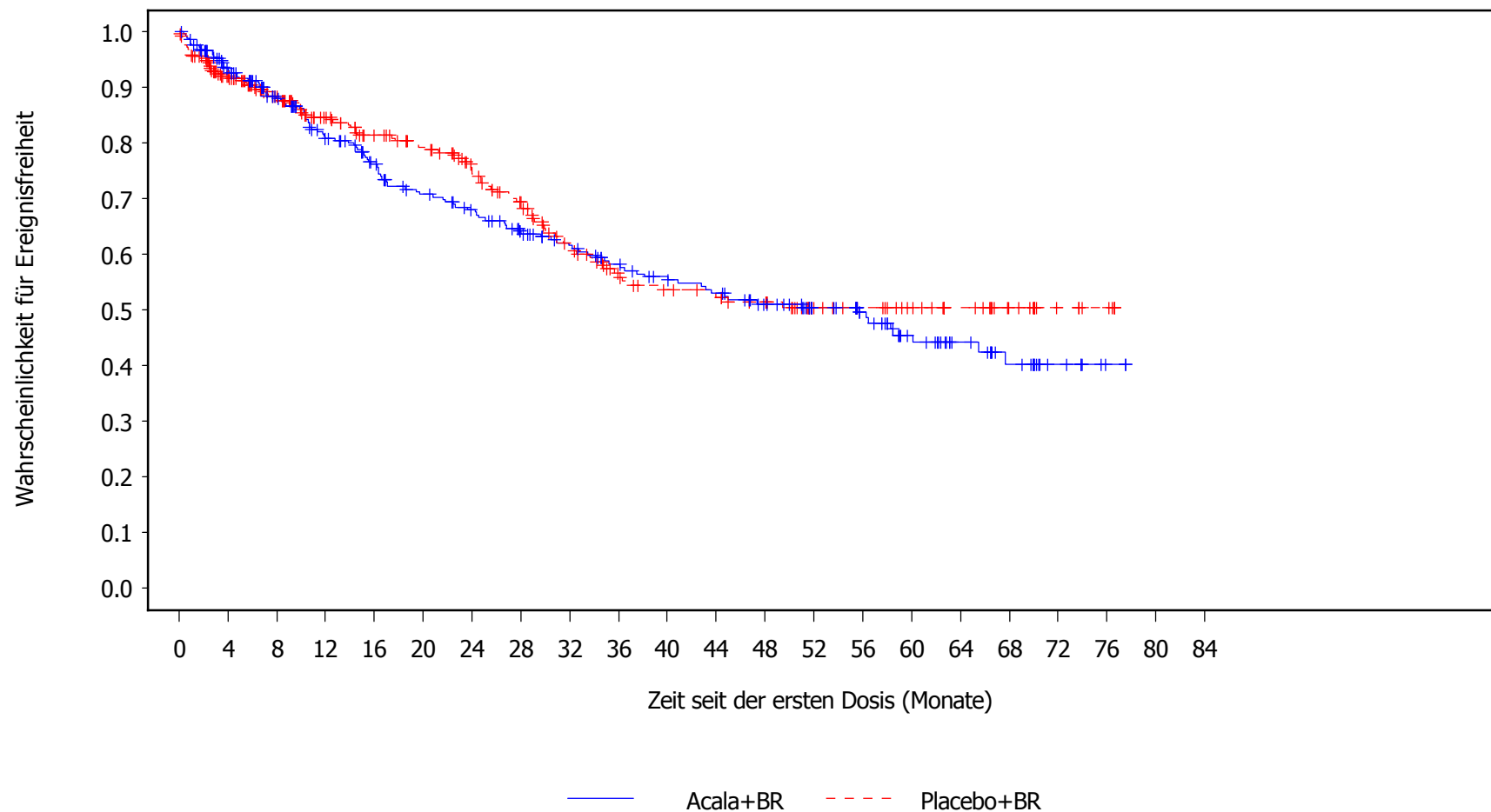
Anzahl an Patienten unter Risiko:

297	272	244	226	204	187	175	155	135	121	111	106	95	75	64	47	36	26	10	1	1	0	Acala+BR
297	264	233	199	180	166	153	137	118	101	92	88	78	61	52	44	30	18	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.143 ECHO: Kaplan-Meier plot of time to first occurrence of SUE SOC: Infektionen und parasitaere Erkrankungen
 Safety Analysis Set, DCO 15FEB2024



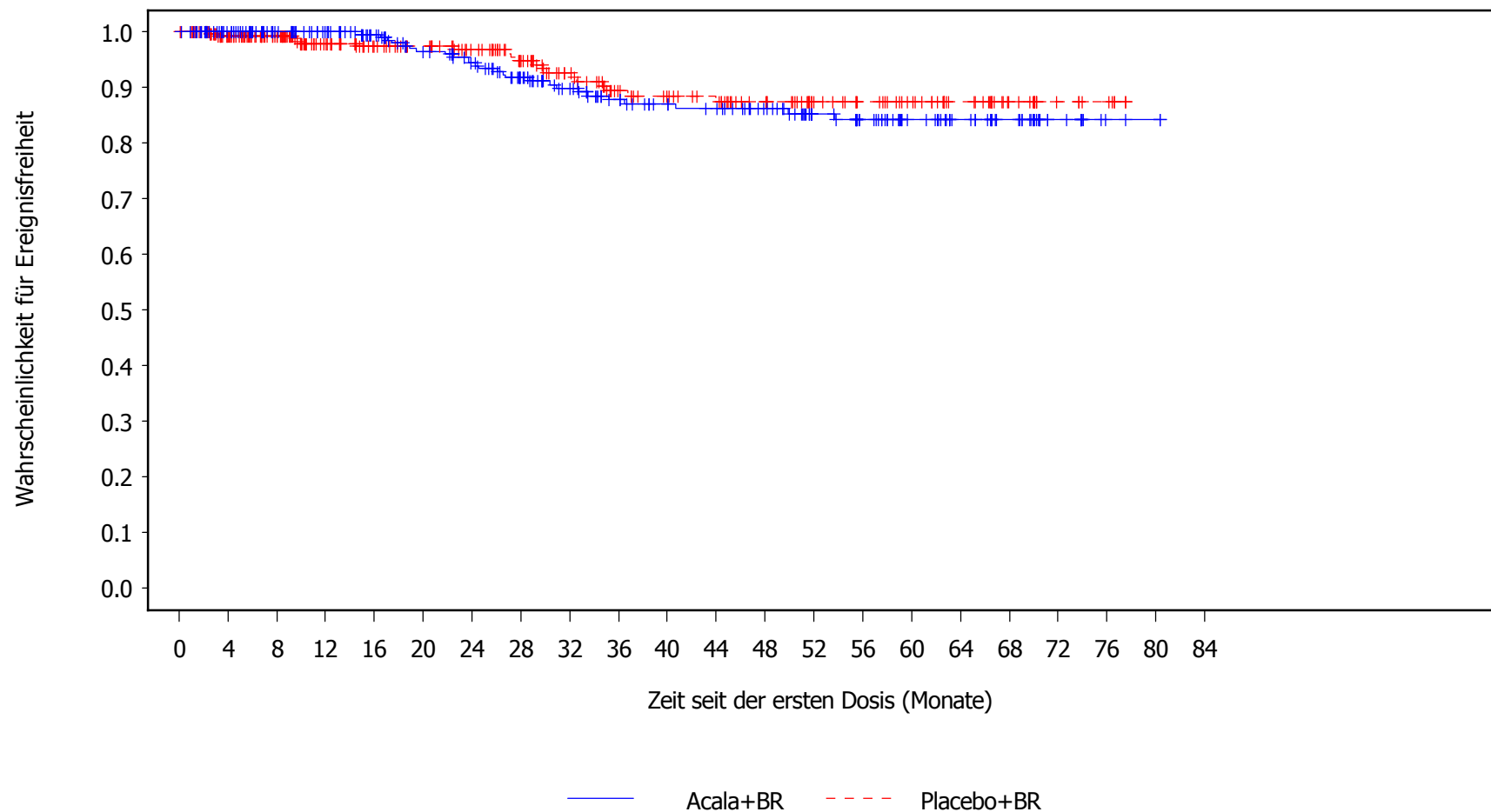
Anzahl an Patienten unter Risiko:

297	259	226	196	173	155	144	126	114	103	95	89	79	65	53	37	26	17	7	1	0	0	Acala+BR
297	250	216	186	167	155	135	118	96	79	71	67	62	46	39	33	25	16	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.144 ECH0: Kaplan-Meier plot of time to first occurrence of SUE PT: COVID-19
 Safety Analysis Set, DCO 15FEB2024



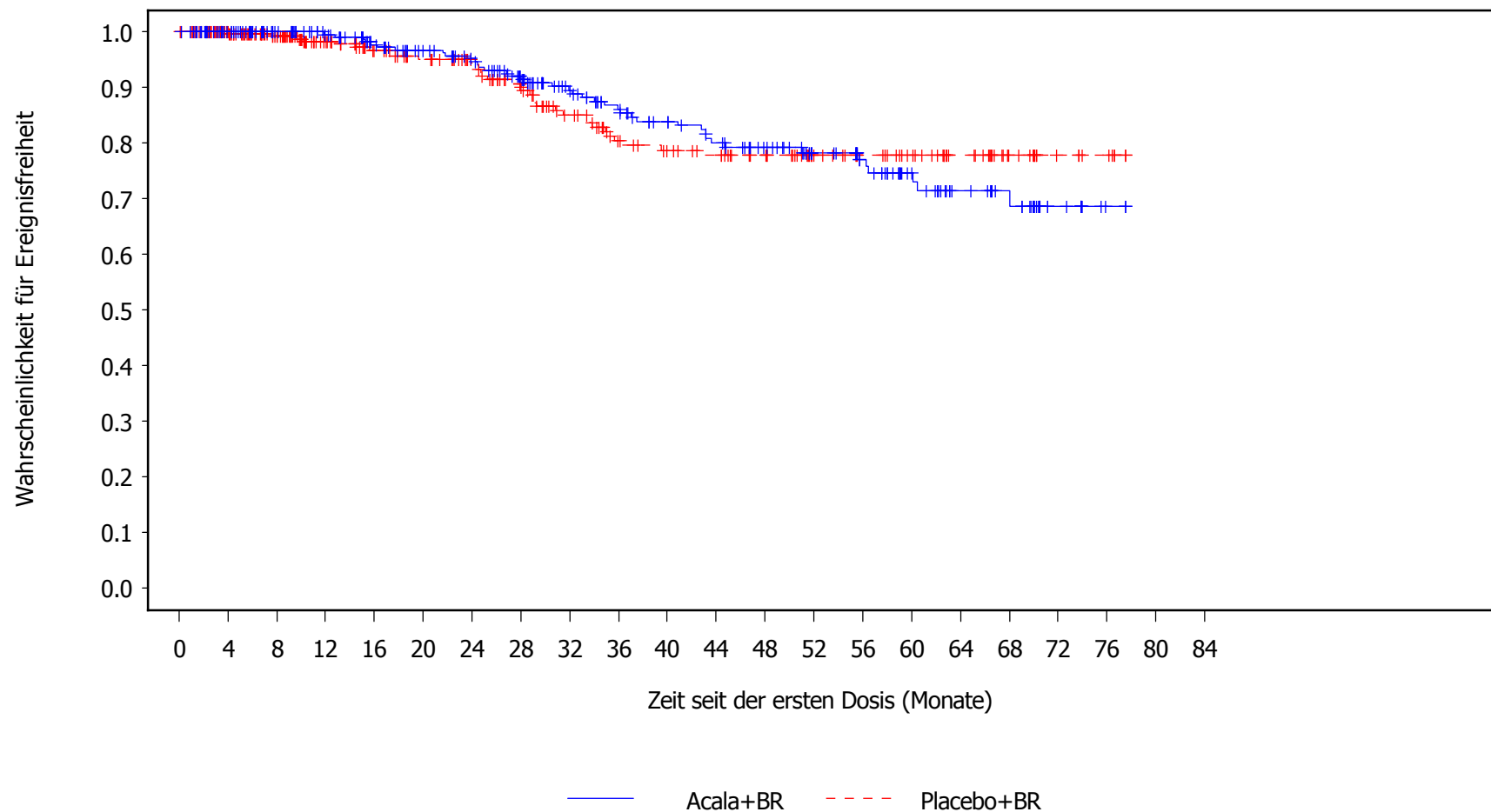
Anzahl an Patienten unter Risiko:

297	275	248	231	210	191	179	157	138	121	112	108	98	79	67	51	40	29	11	2	1	0	Acala+BR
297	267	238	202	183	172	158	140	120	102	94	88	77	62	54	46	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.145 ECHO: Kaplan-Meier plot of time to first occurrence of SUE PT: COVID-19-Lungenentzündung
 Safety Analysis Set, DCO 15FEB2024



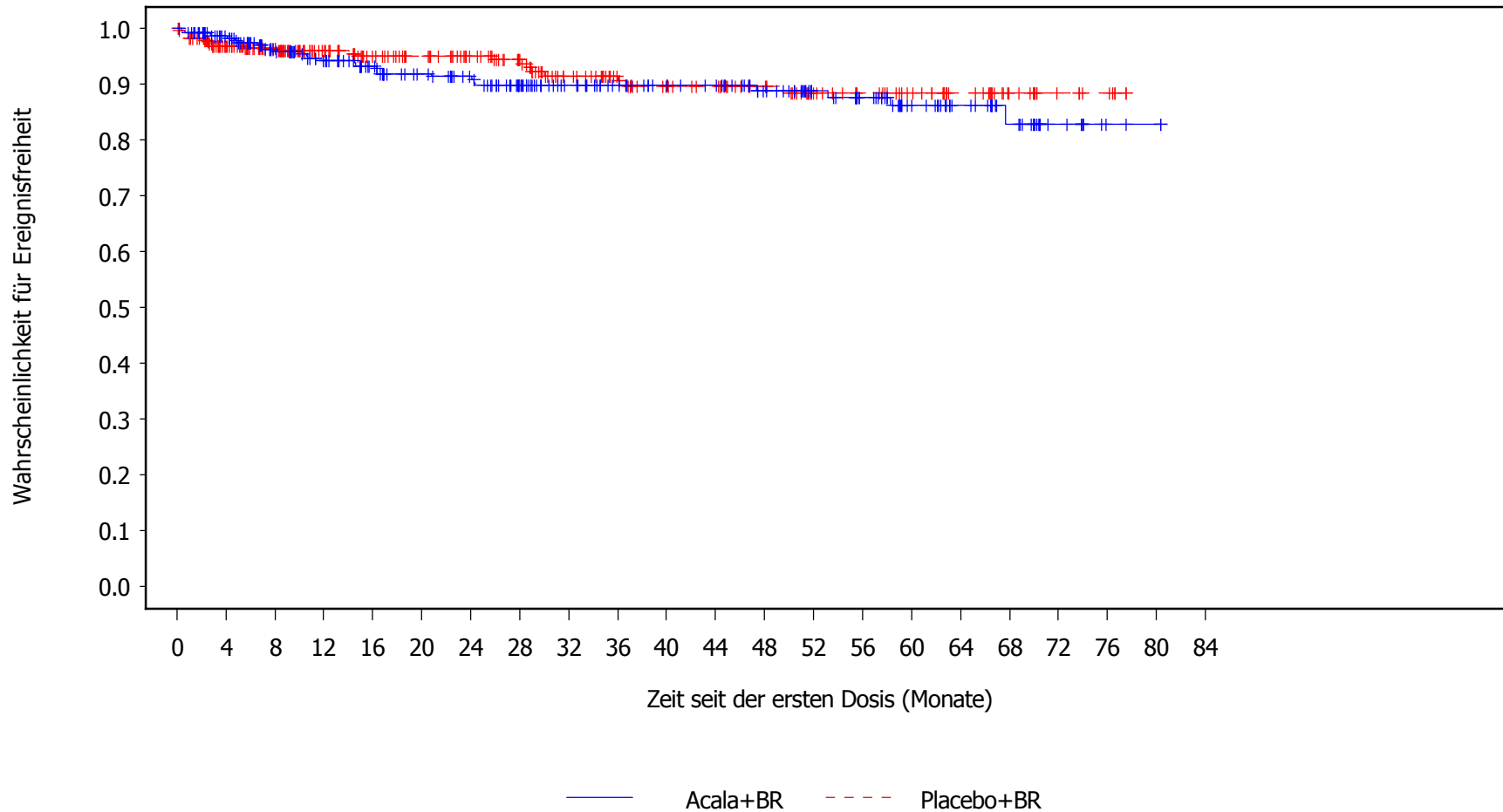
Anzahl an Patienten unter Risiko:

297	275	248	230	208	192	180	158	137	122	111	102	92	74	62	46	34	26	9	1	0	0	Acala+BR
297	267	237	202	182	169	153	134	114	97	90	85	77	61	53	46	32	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.146 ECHO: Kaplan-Meier plot of time to first occurrence of SUE PT: Pneumonie
 Safety Analysis Set, DC0 15FEB2024



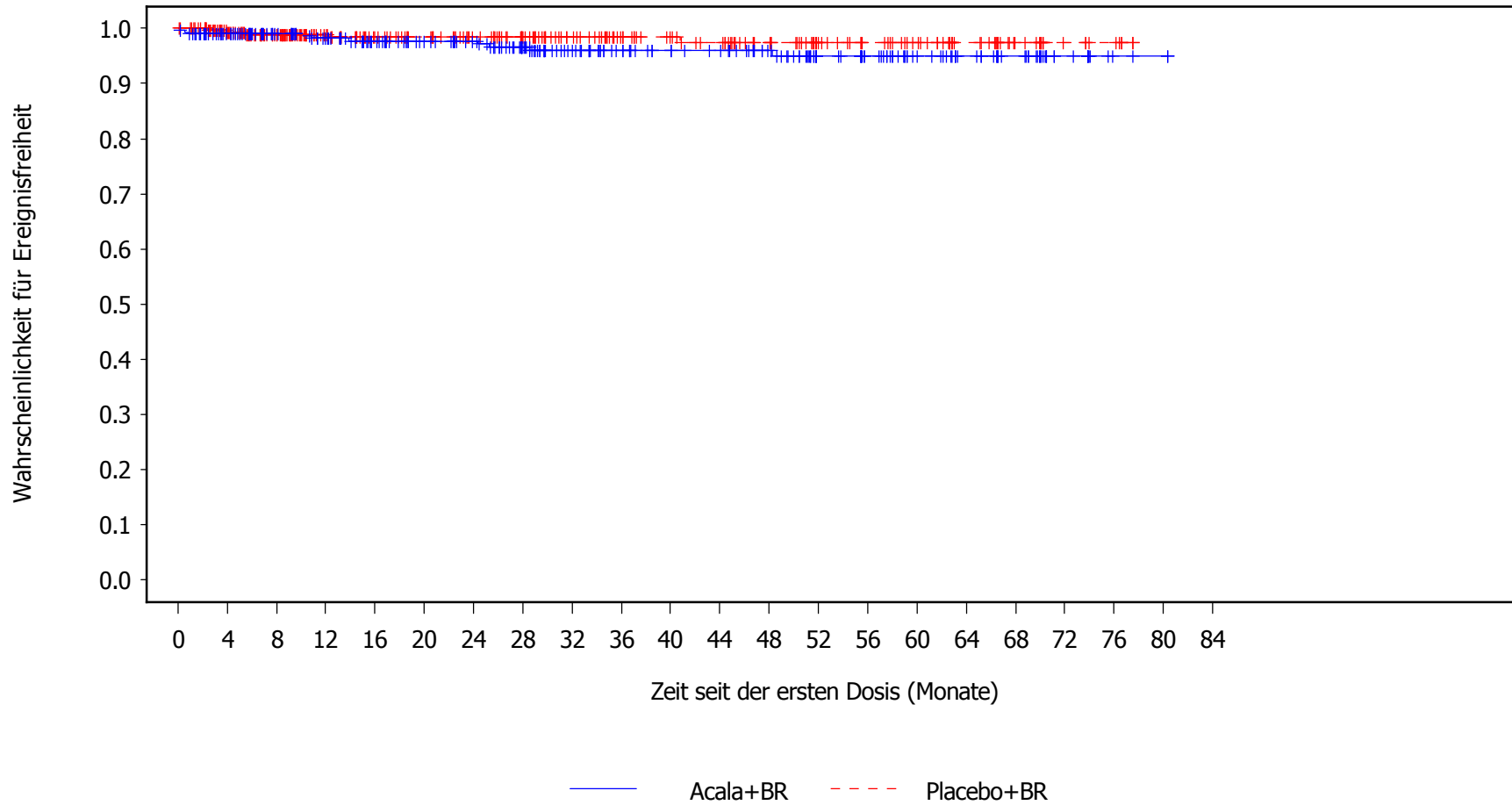
Anzahl an Patienten unter Risiko:

297	271	238	219	199	183	172	151	132	121	112	108	95	77	65	47	36	25	10	2	1	0	Acala+BR
297	260	231	198	178	166	152	136	114	101	90	86	76	59	51	43	30	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.147 ECH0: Kaplan-Meier plot of time to first occurrence of SUE SOC: Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen
 Safety Analysis Set, DC0 15FEB2024



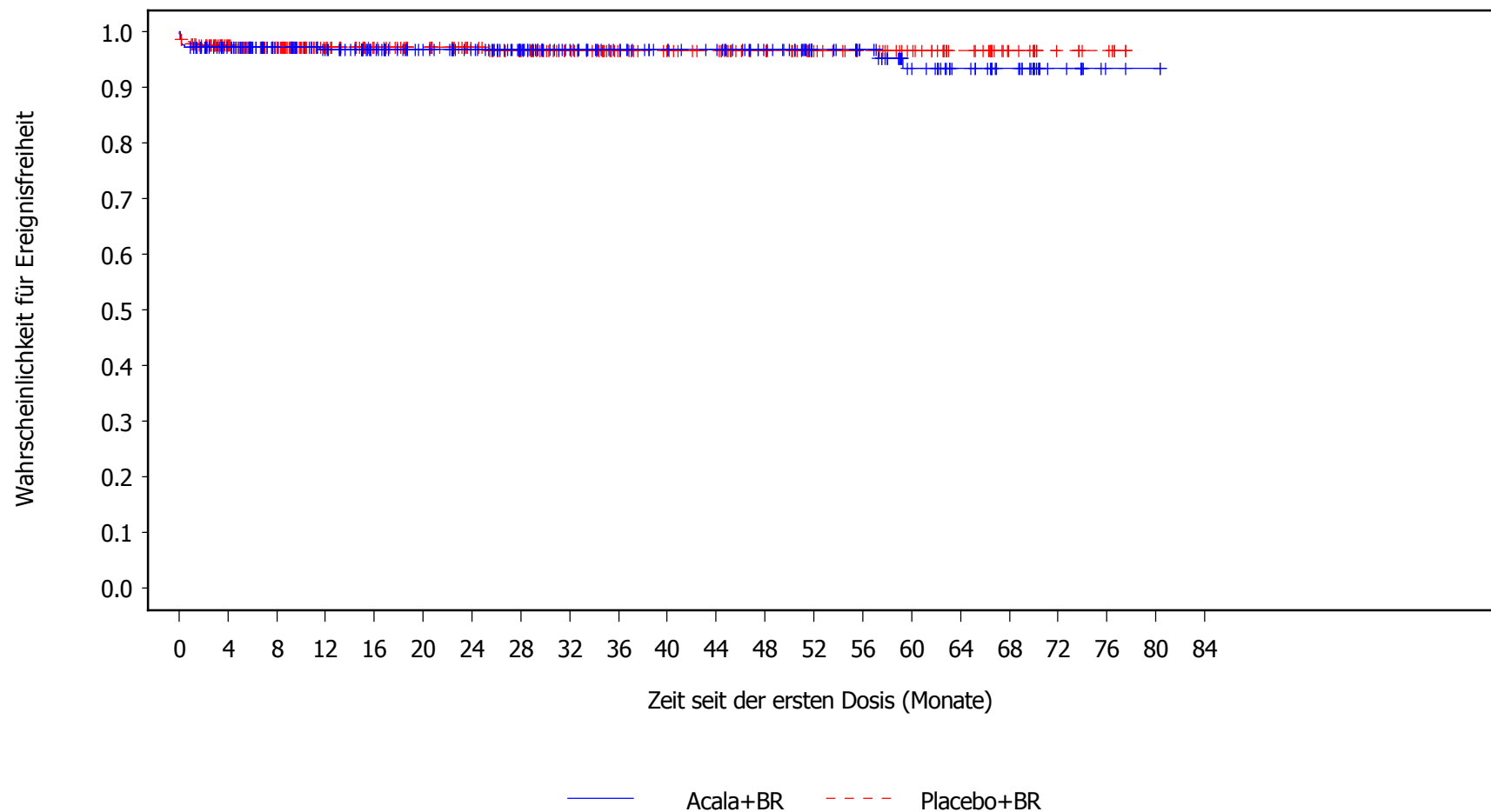
Anzahl an Patienten unter Risiko:

297	273	246	228	207	190	179	157	135	120	111	107	96	74	64	48	38	28	11	2	1	0	Acala+BR
297	266	236	202	182	170	156	141	123	108	99	93	81	65	56	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.148 ECHO: Kaplan-Meier plot of time to first occurrence of SUE SOC: Stoffwechsel- und Ernährungsstörungen
 Safety Analysis Set, DC0 15FEB2024



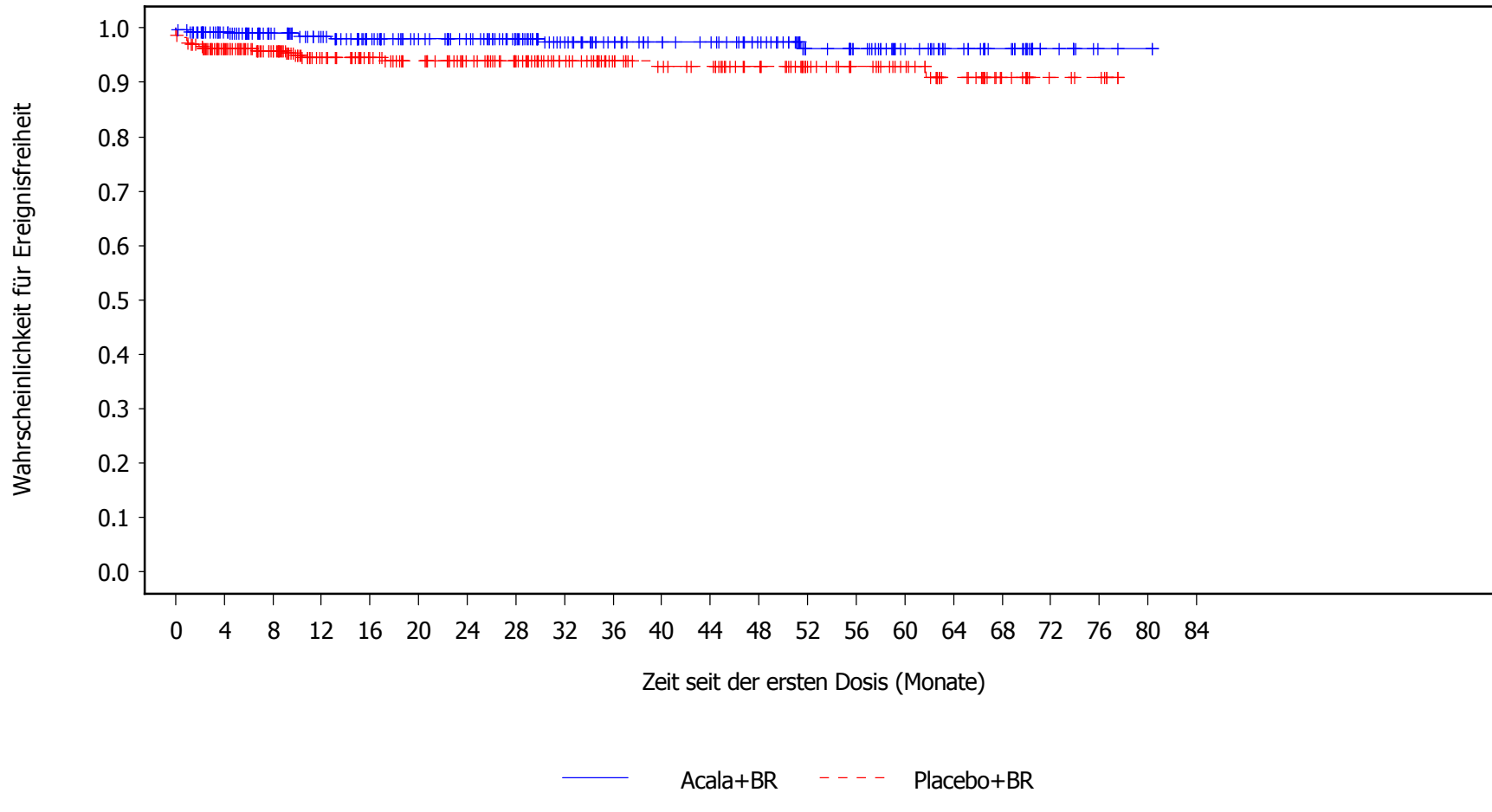
Anzahl an Patienten unter Risiko:

297	269	242	224	205	189	178	157	136	122	113	109	97	77	67	49	38	27	11	2	1	0	Acala+BR
297	263	236	202	184	172	158	142	123	108	99	94	82	65	56	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.149 ECHO: Kaplan-Meier plot of time to first occurrence of SUE SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen
 Safety Analysis Set, DCO 15FEB2024



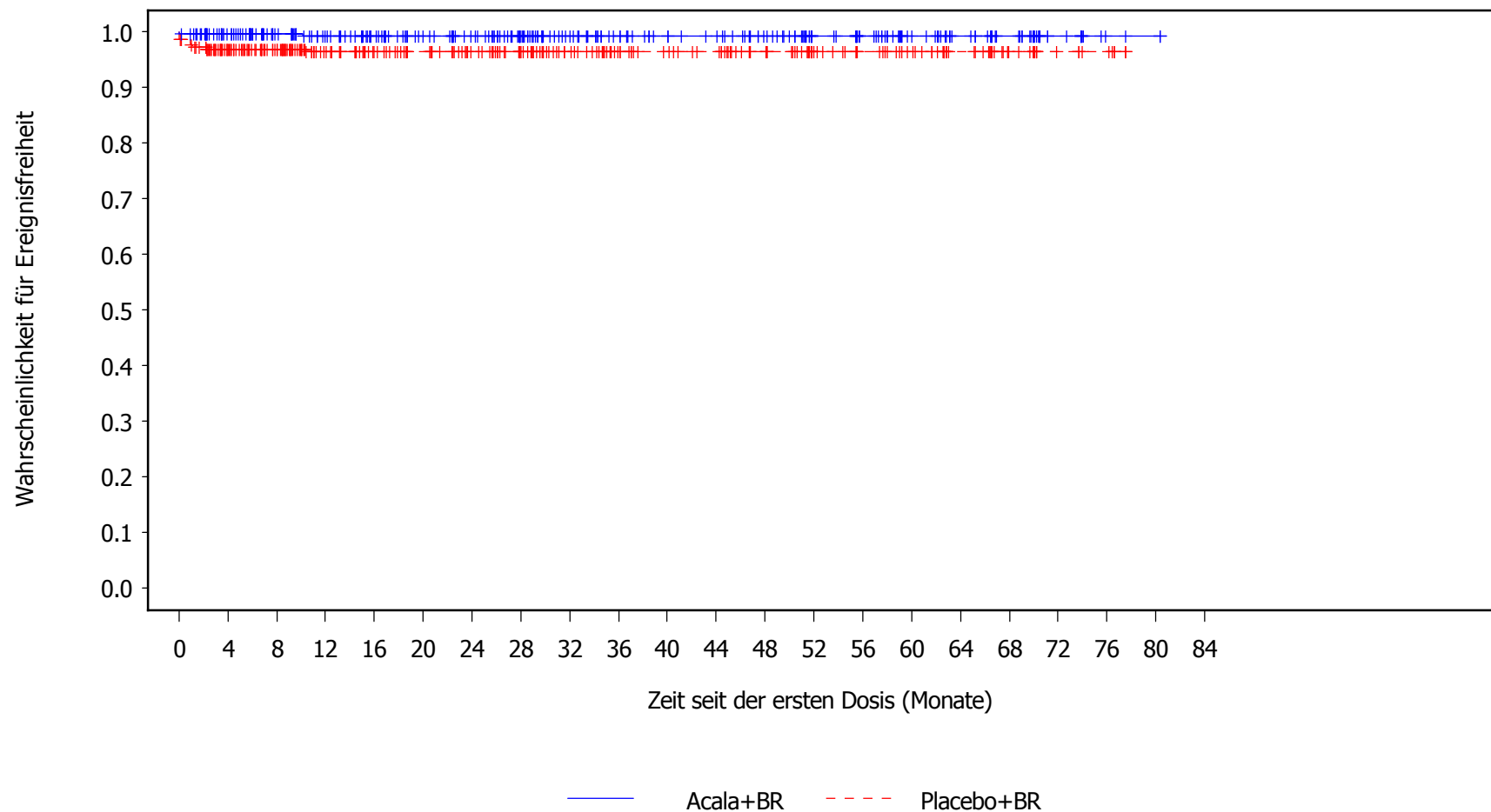
Anzahl an Patienten unter Risiko:

297	273	245	227	207	190	179	159	137	122	112	108	97	75	65	48	37	28	10	2	1	0	Acala+BR
297	260	231	198	181	168	154	139	120	105	96	92	80	64	55	47	31	17	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.150 ECH0: Kaplan-Meier plot of time to first occurrence of SUE PT: Reaktion im Zusammenhang mit einer Infusion
 Safety Analysis Set, DC0 15FEB2024



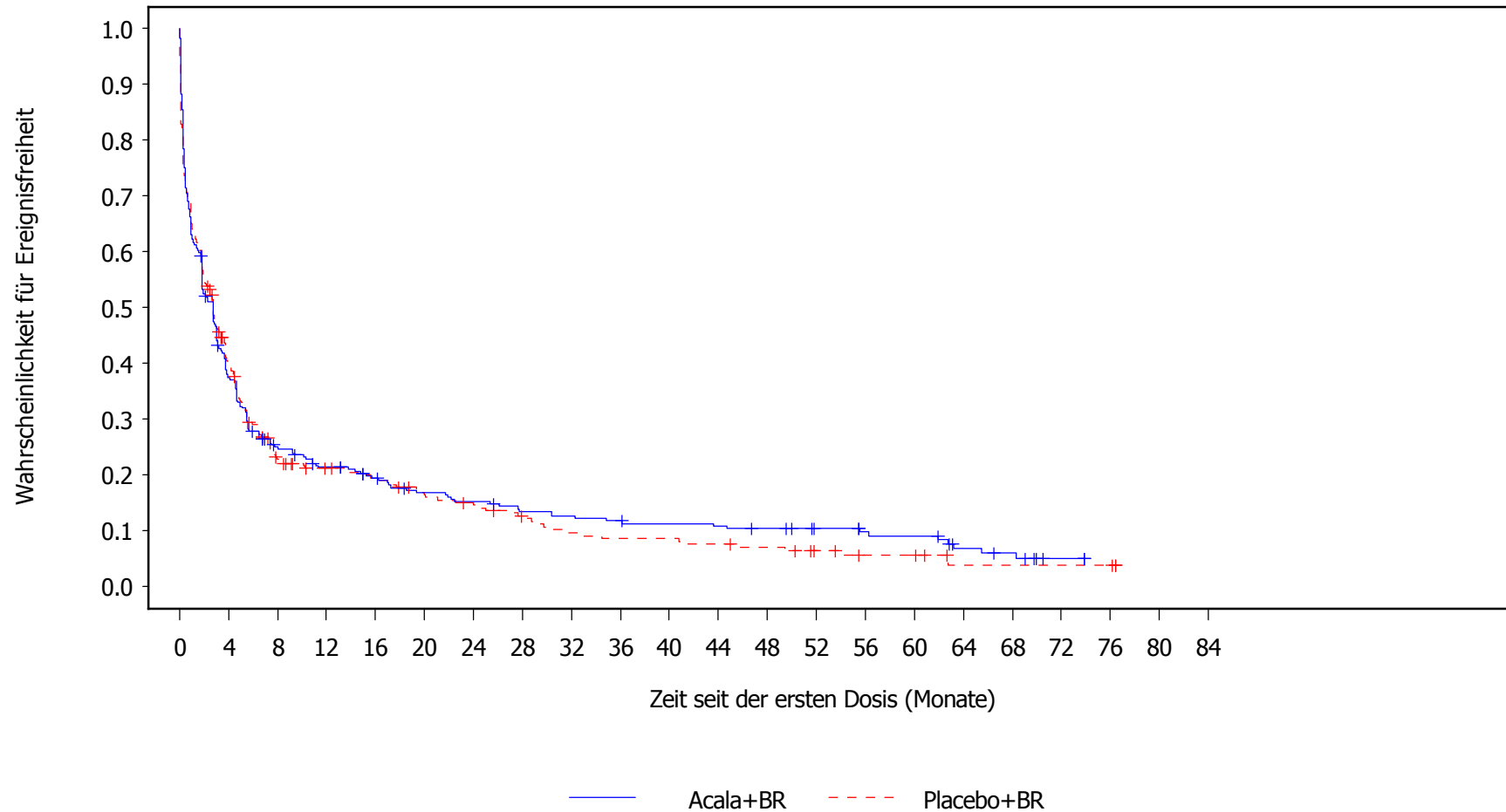
Anzahl an Patienten unter Risiko:

297	274	247	229	210	193	182	161	140	125	115	111	100	79	68	51	40	29	11	2	1	0	Acala+BR
297	261	233	199	182	170	156	140	121	106	98	93	81	64	55	47	32	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.151 ECH0: Kaplan-Meier plot of time to first occurrence of UE mit CTCAE Grad ≥ 3
 Safety Analysis Set, DCO 15FEB2024



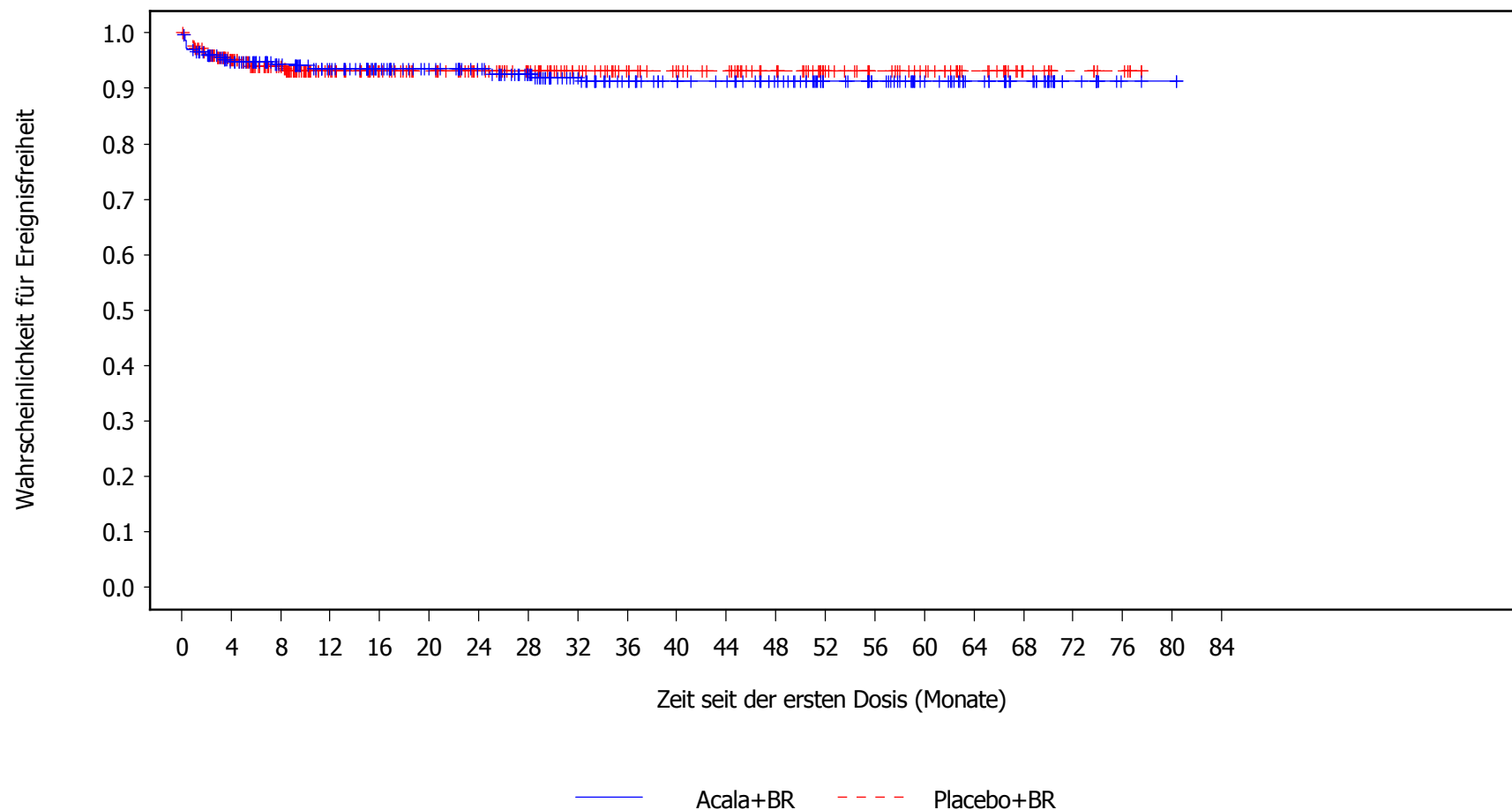
Anzahl an Patienten unter Risiko:

297	109	69	57	48	40	36	31	29	27	25	24	22	18	15	14	8	6	1	0	0	0	Acala+BR
297	113	60	50	44	36	31	25	19	17	17	15	13	9	6	6	2	2	2	2	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.152 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 SOC: Allgemeine Erkrankungen und Beschwerden am Verabreichungsort
 Safety Analysis Set, DCO 15FEB2024



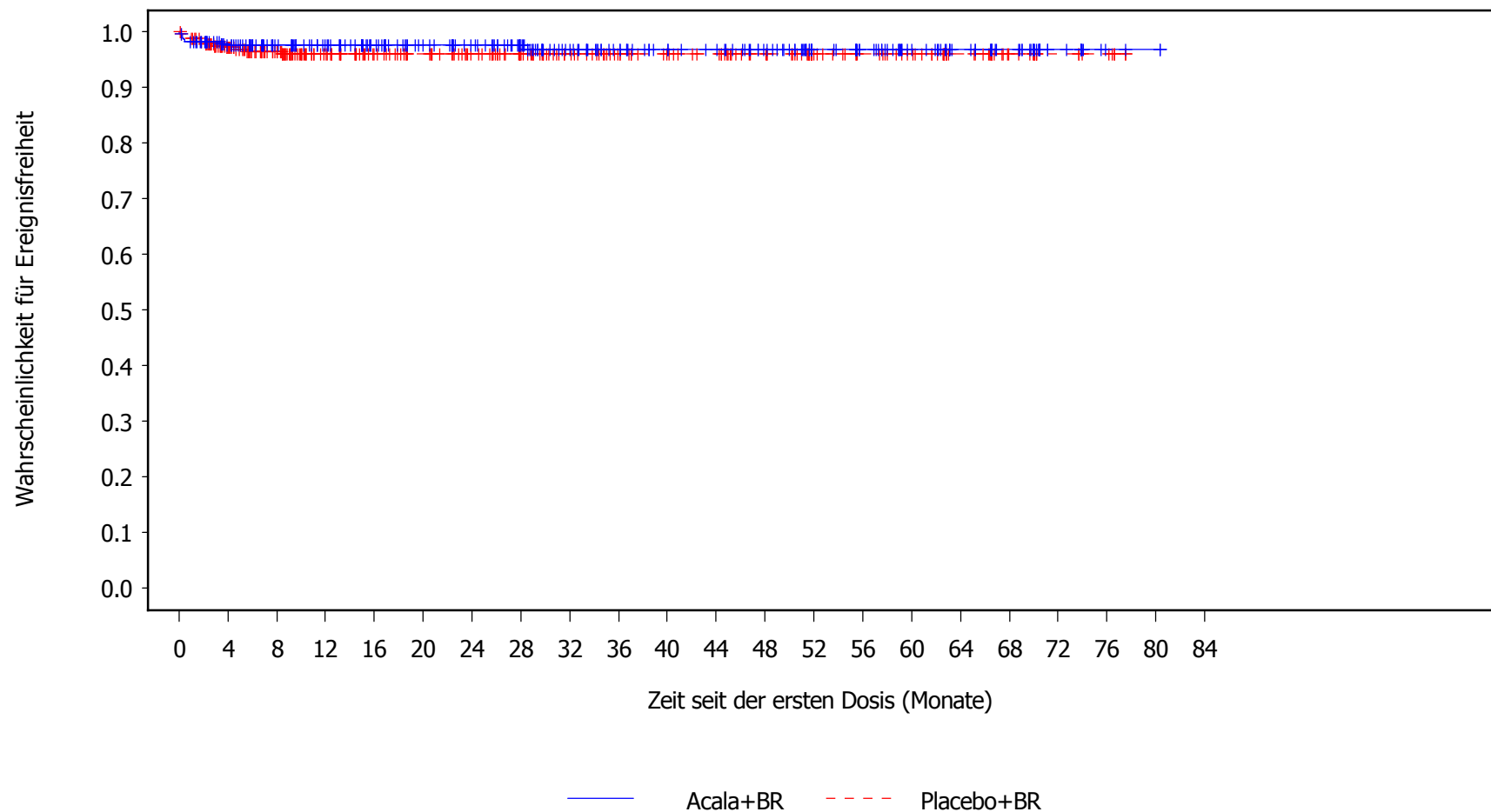
Anzahl an Patienten unter Risiko:

297	261	236	217	198	183	172	153	132	117	107	103	93	75	65	50	39	29	11	2	1	0	Acala+BR
297	255	225	190	172	160	146	131	113	101	93	88	76	59	50	43	28	15	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.153 ECH0: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 PT: Ermuedung
 Safety Analysis Set, DC0 15FEB2024



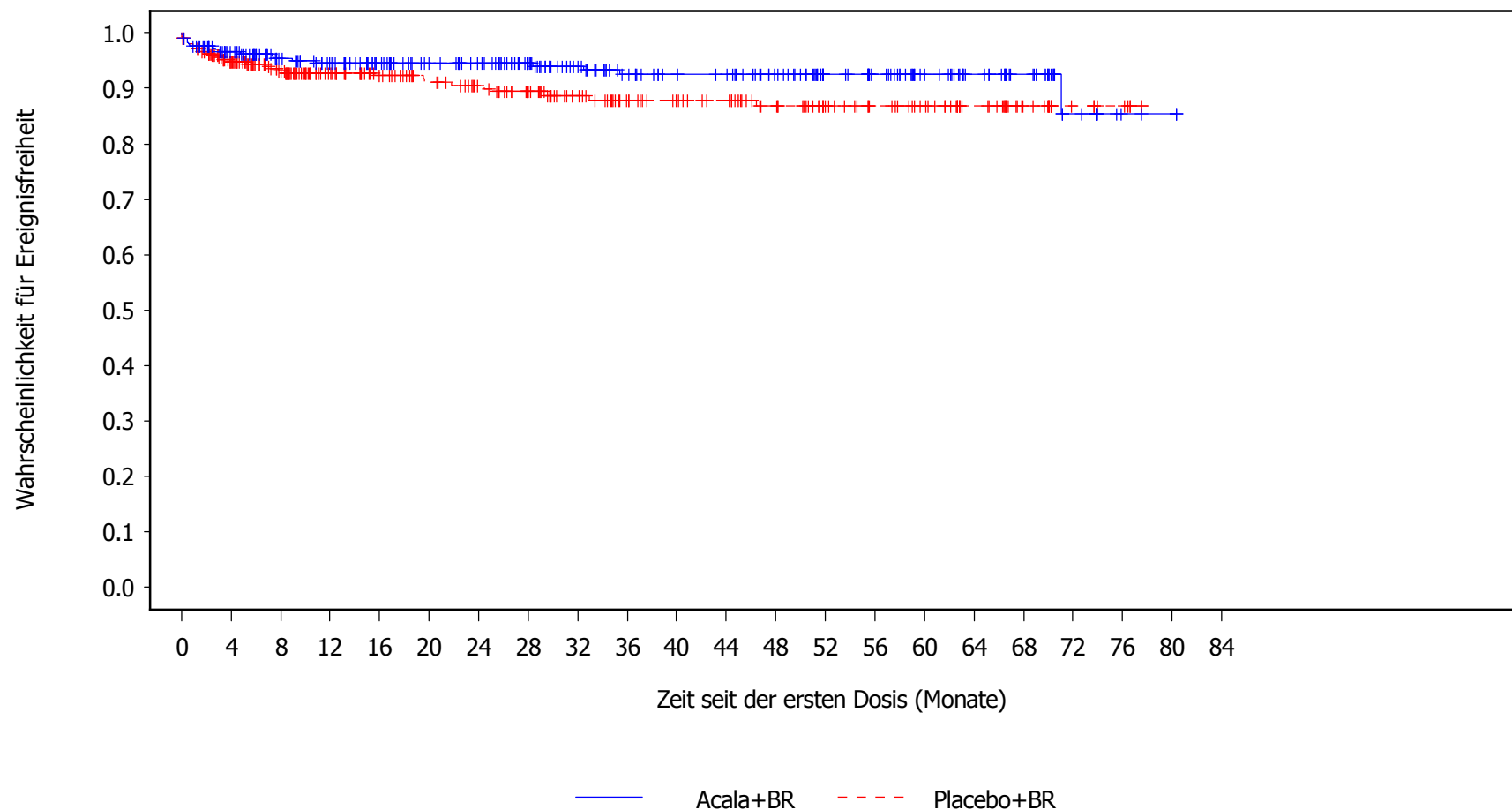
Anzahl an Patienten unter Risiko:

297	268	242	225	205	188	177	158	136	121	111	107	96	76	66	50	39	29	11	2	1	0	Acala+BR
297	260	230	196	177	165	151	135	117	104	96	91	79	62	53	46	31	17	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.154 ECH0: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 SOC: Erkrankungen der Atemwege, des Brustraums und Mediastinums
 Safety Analysis Set, DCO 15FEB2024



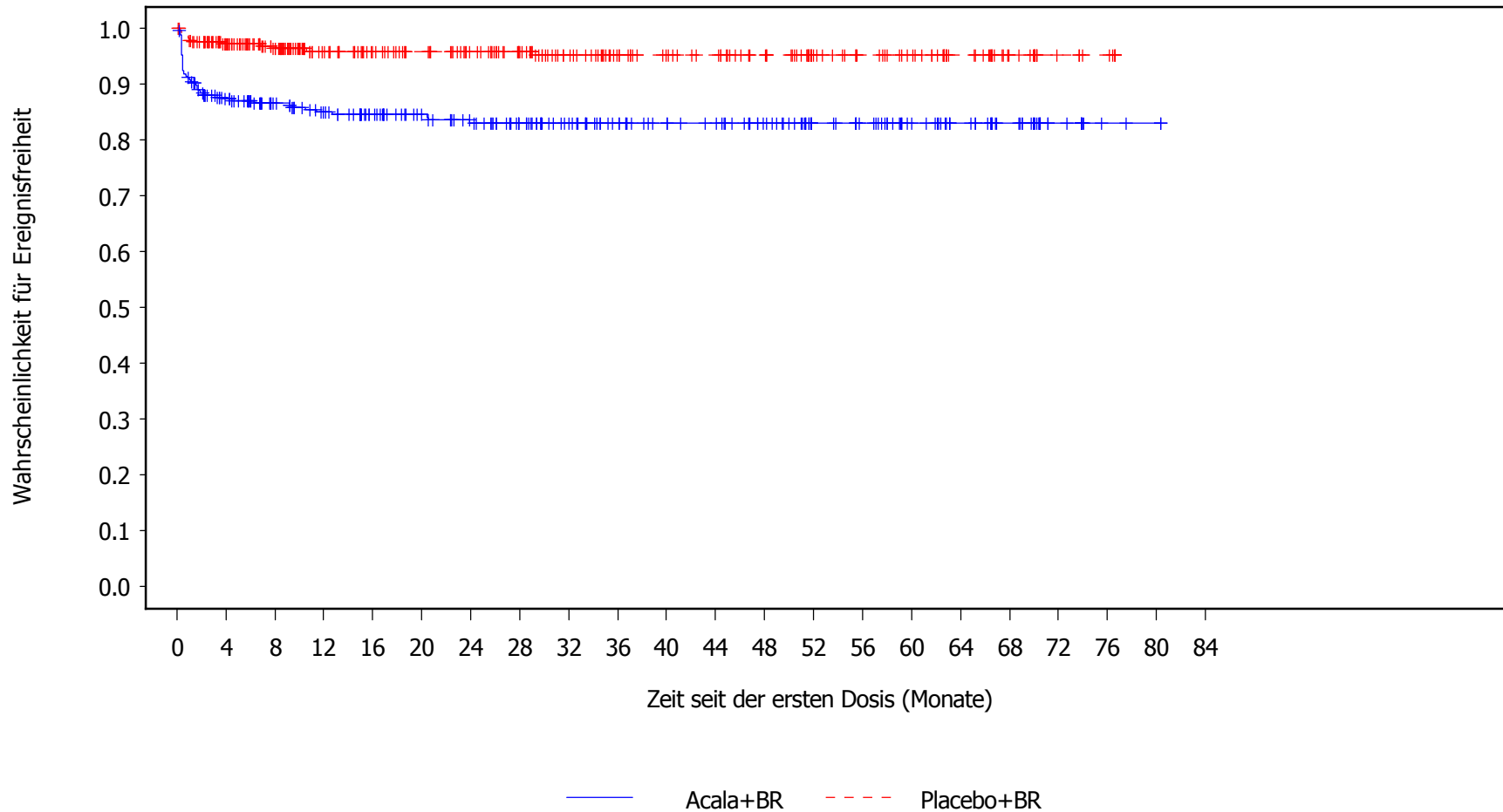
Anzahl an Patienten unter Risiko:

297	268	240	224	205	189	179	160	140	123	114	111	99	78	67	50	39	28	10	2	1	0	Acala+BR
297	258	227	193	175	161	150	135	117	103	94	89	76	62	53	46	32	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.155 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 SOC: Erkrankungen der Haut und des Unterhautgewebes
 Safety Analysis Set, DCO 15FEB2024



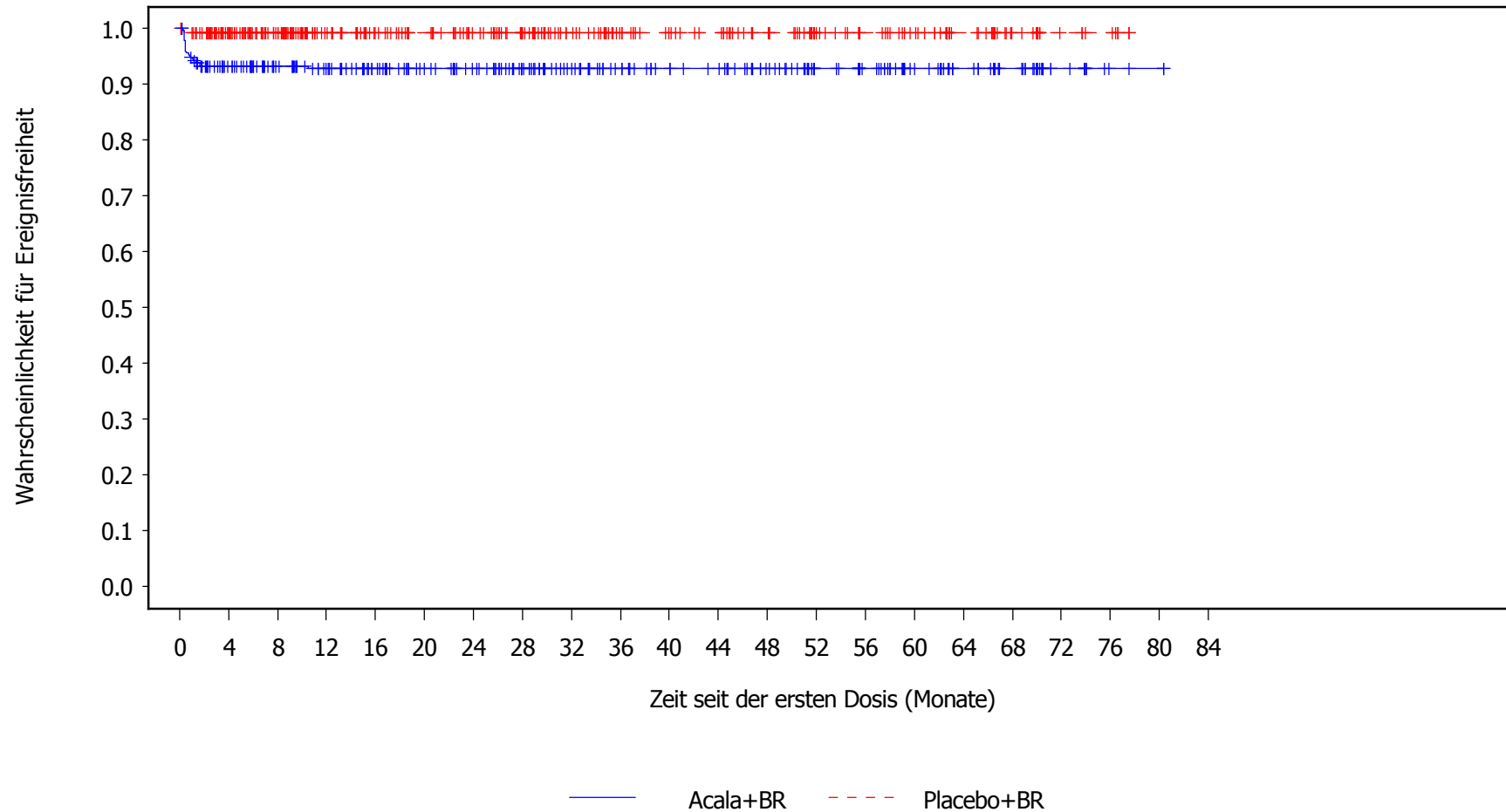
Anzahl an Patienten unter Risiko:

297	242	217	201	184	168	157	141	125	111	102	98	87	69	62	48	38	27	10	2	1	0	Acala+BR
297	261	231	196	179	167	154	138	119	104	95	90	80	63	54	47	32	18	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.156 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 PT: Ausschlag makulo-papuloes
 Safety Analysis Set, DCO 15FEB2024



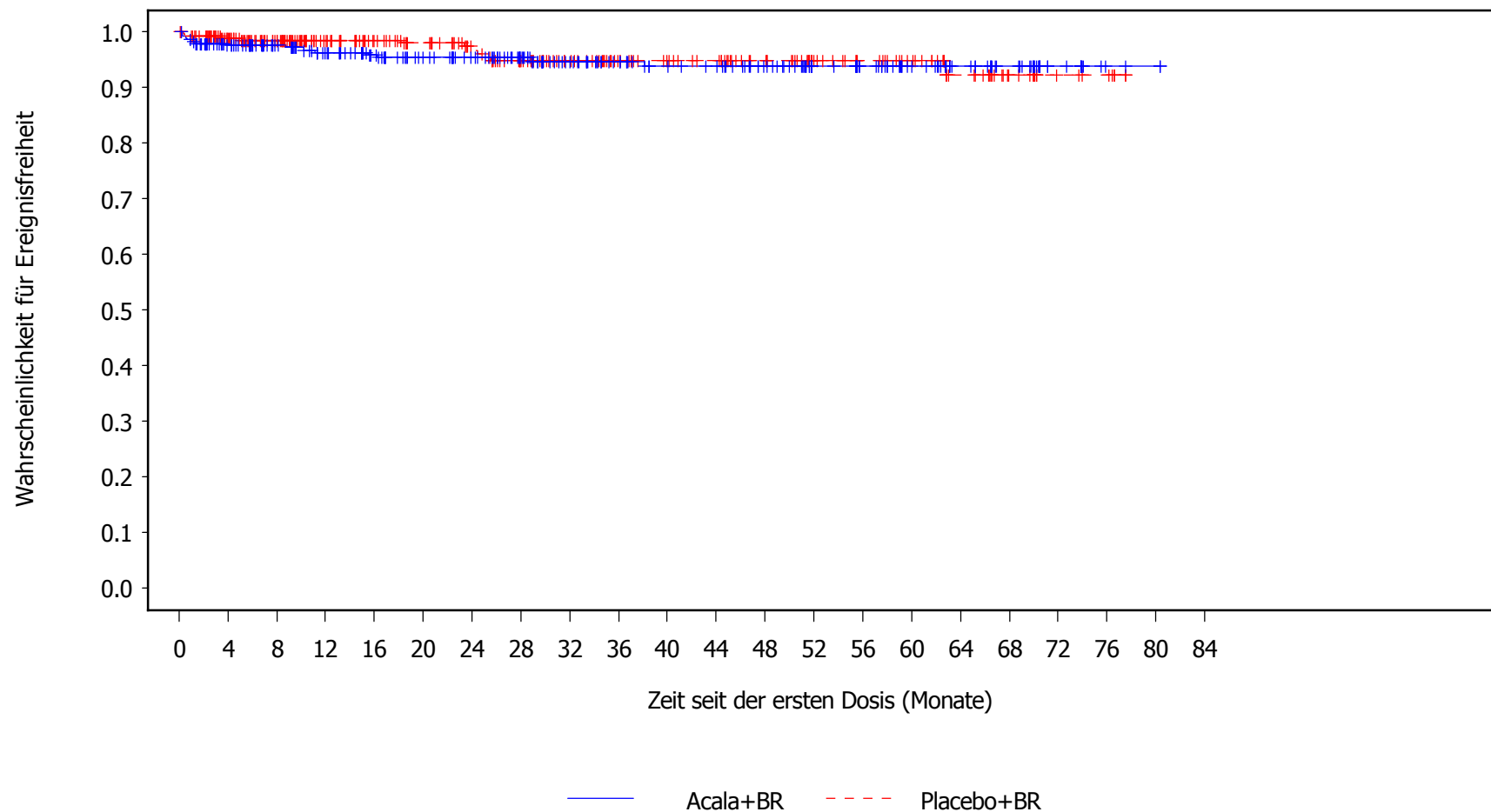
Anzahl an Patienten unter Risiko:

297	257	232	216	197	180	170	151	133	119	109	105	93	75	66	50	40	29	11	2	1	0	Acala+BR
297	265	236	201	183	171	157	141	122	107	98	93	82	65	56	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.157 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 SOC: Erkrankungen der Nieren und Harnwege
 Safety Analysis Set, DCO 15FEB2024



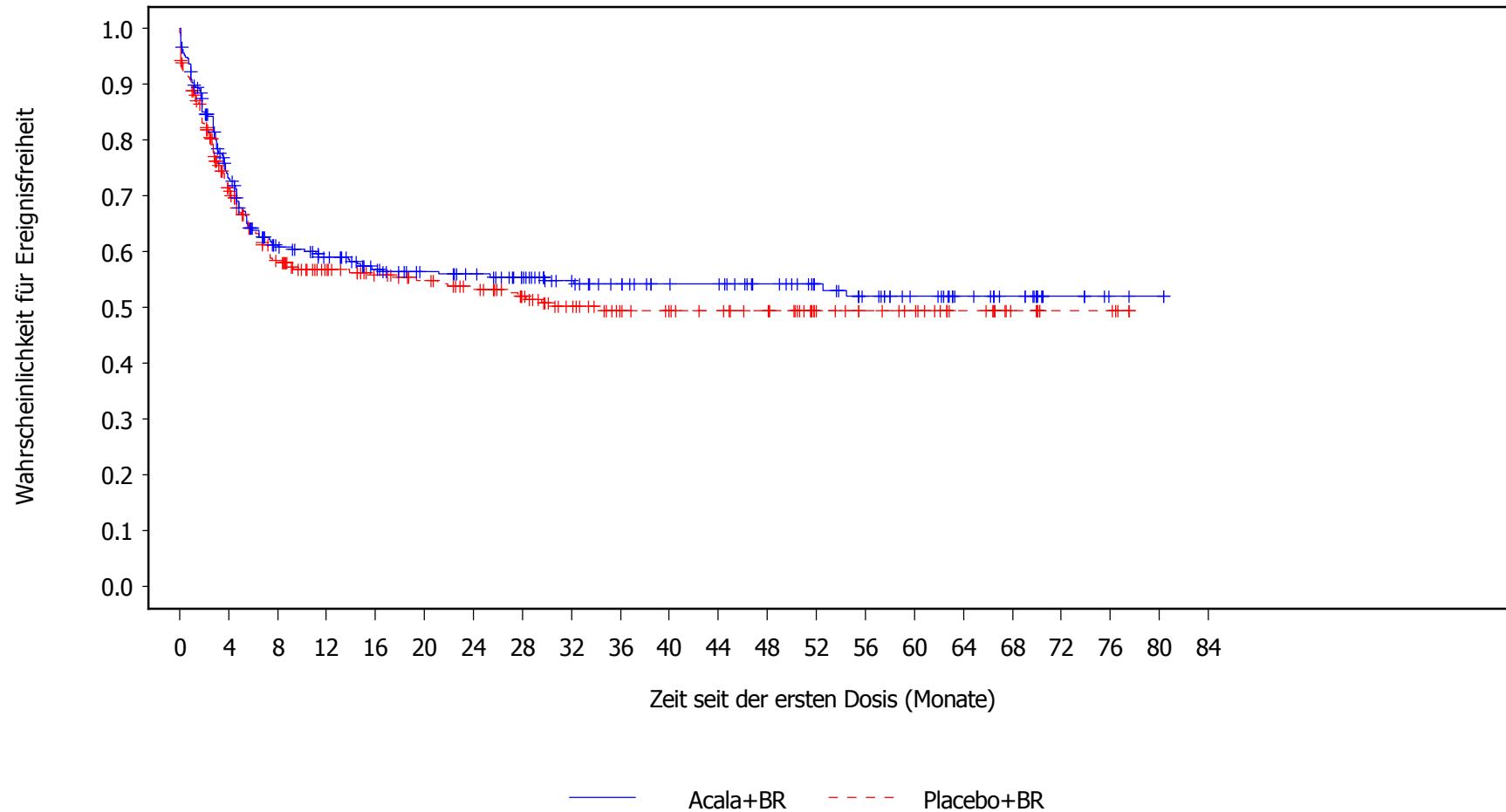
Anzahl an Patienten unter Risiko:

297	268	242	222	203	186	175	155	134	119	109	106	94	74	64	49	38	28	11	2	1	0	Acala+BR
297	267	237	203	184	171	156	139	121	106	97	92	80	63	54	46	30	18	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.158 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 SOC: Erkrankungen des Blutes und des Lymphsystems
 Safety Analysis Set, DCO 15FEB2024



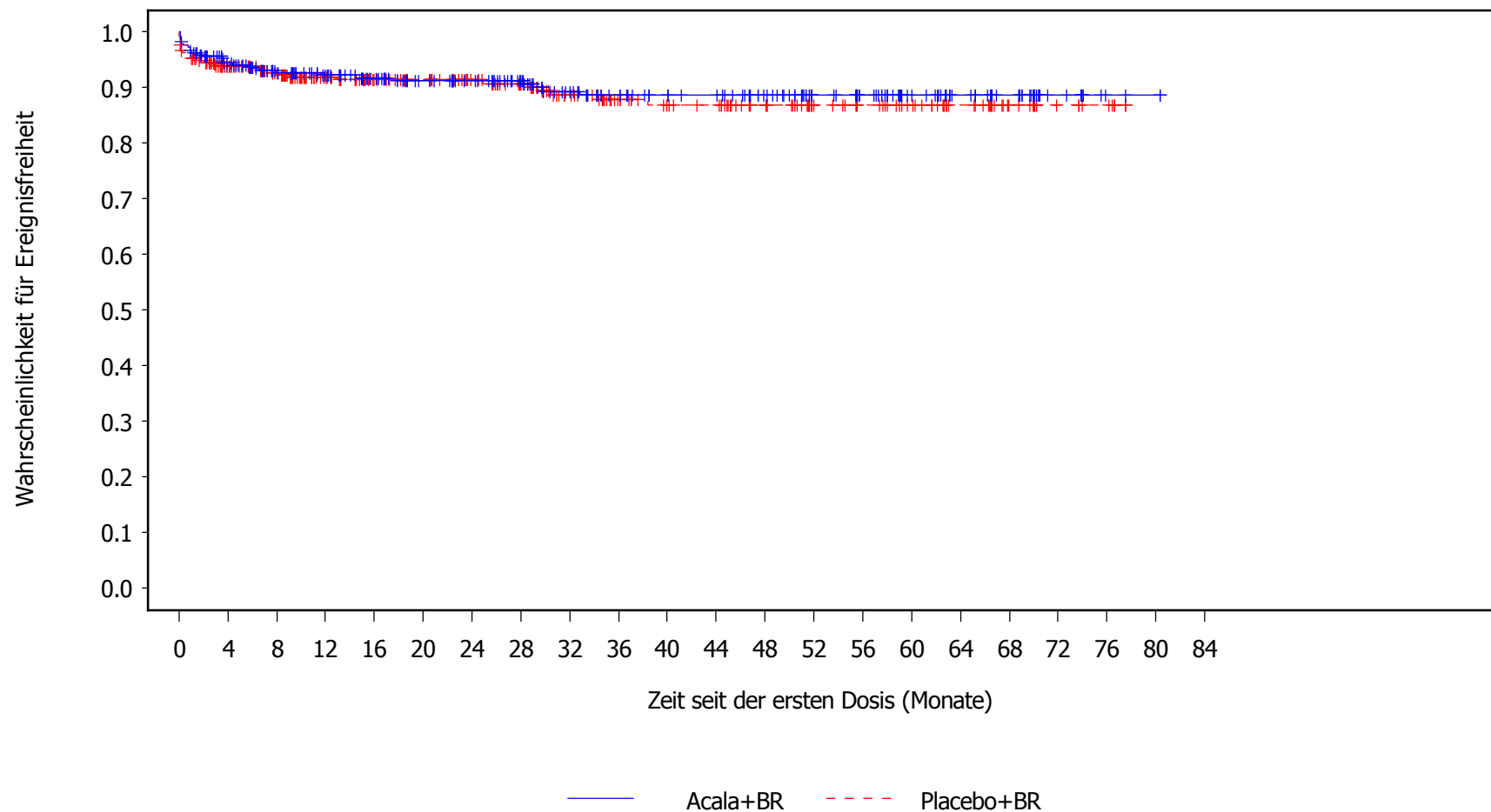
Anzahl an Patienten unter Risiko:

297	204	154	140	124	114	109	99	85	77	70	69	61	51	42	34	25	19	7	2	1	0	Acala+BR
297	193	147	126	114	107	98	85	72	61	57	54	50	36	31	28	19	10	4	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.159 ECH0: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 PT: Anaemie
 Safety Analysis Set, DCO 15FEB2024



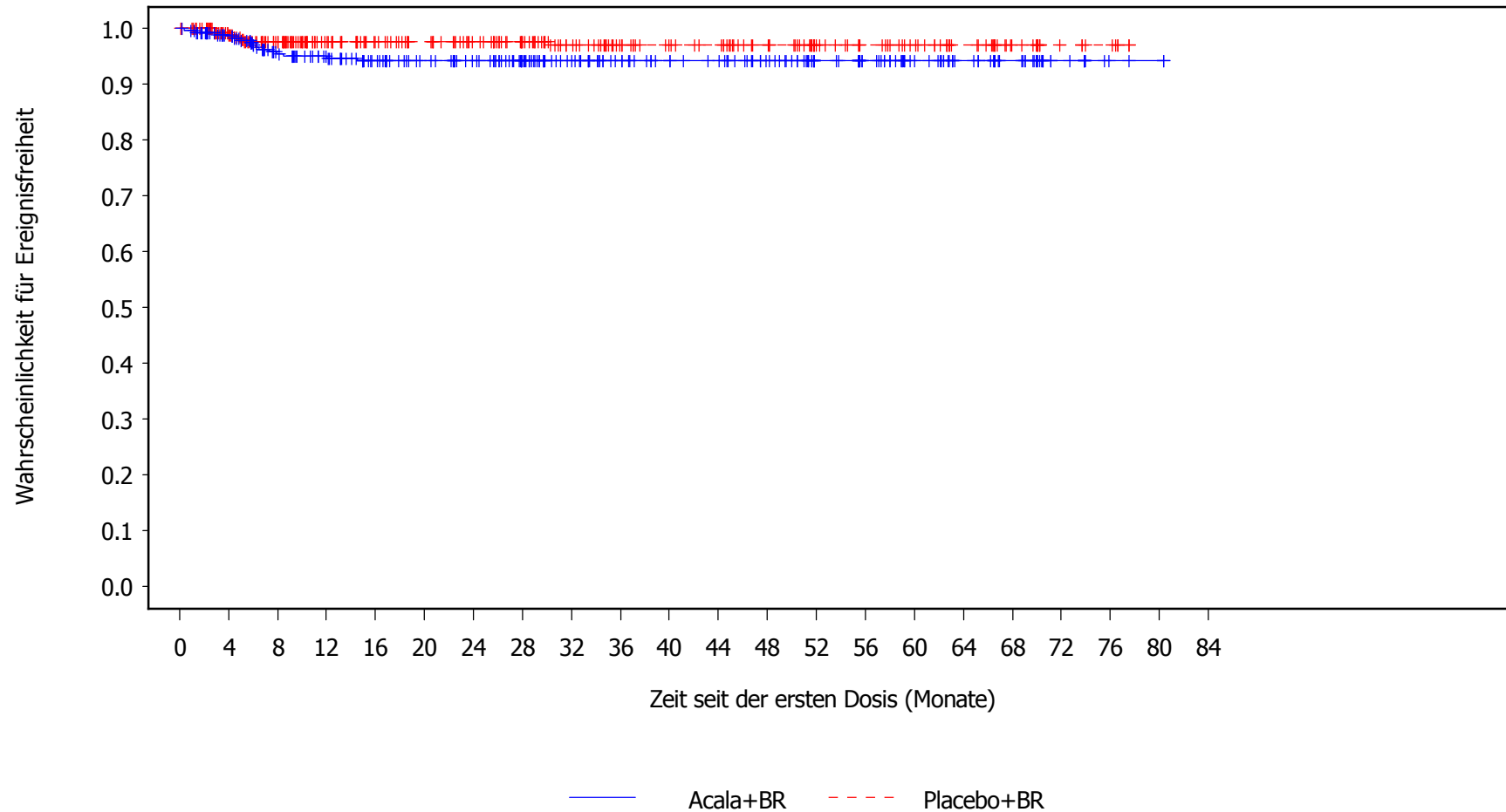
Anzahl an Patienten unter Risiko:

297	260	232	216	196	180	170	152	131	117	109	106	95	76	65	49	38	28	11	2	1	0	Acala+BR
297	254	230	197	178	166	152	137	116	100	91	88	76	60	53	45	32	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.160 ECH0: Kaplan-Meier plot of time to first occurrence of $G \geq 3$ PT: Febrile Neutropenie
 Safety Analysis Set, DCO 15FEB2024



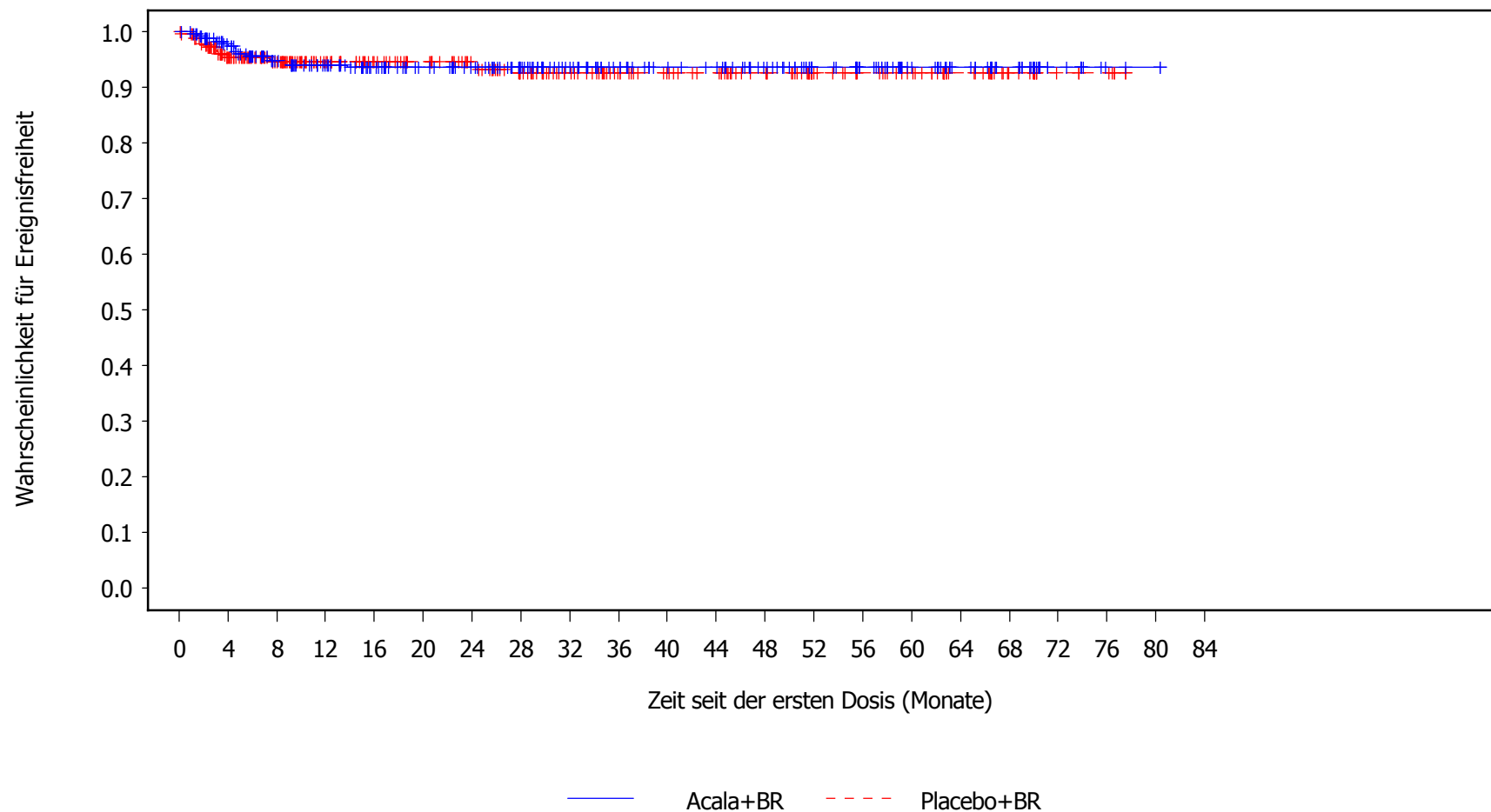
Anzahl an Patienten unter Risiko:

297	273	238	221	202	188	177	157	137	122	113	109	97	77	66	50	39	28	10	2	1	0	Acala+BR
297	266	234	200	183	171	157	141	121	106	97	93	81	64	55	47	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.161 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 PT: Leukopenie
 Safety Analysis Set, DC0 15FEB2024



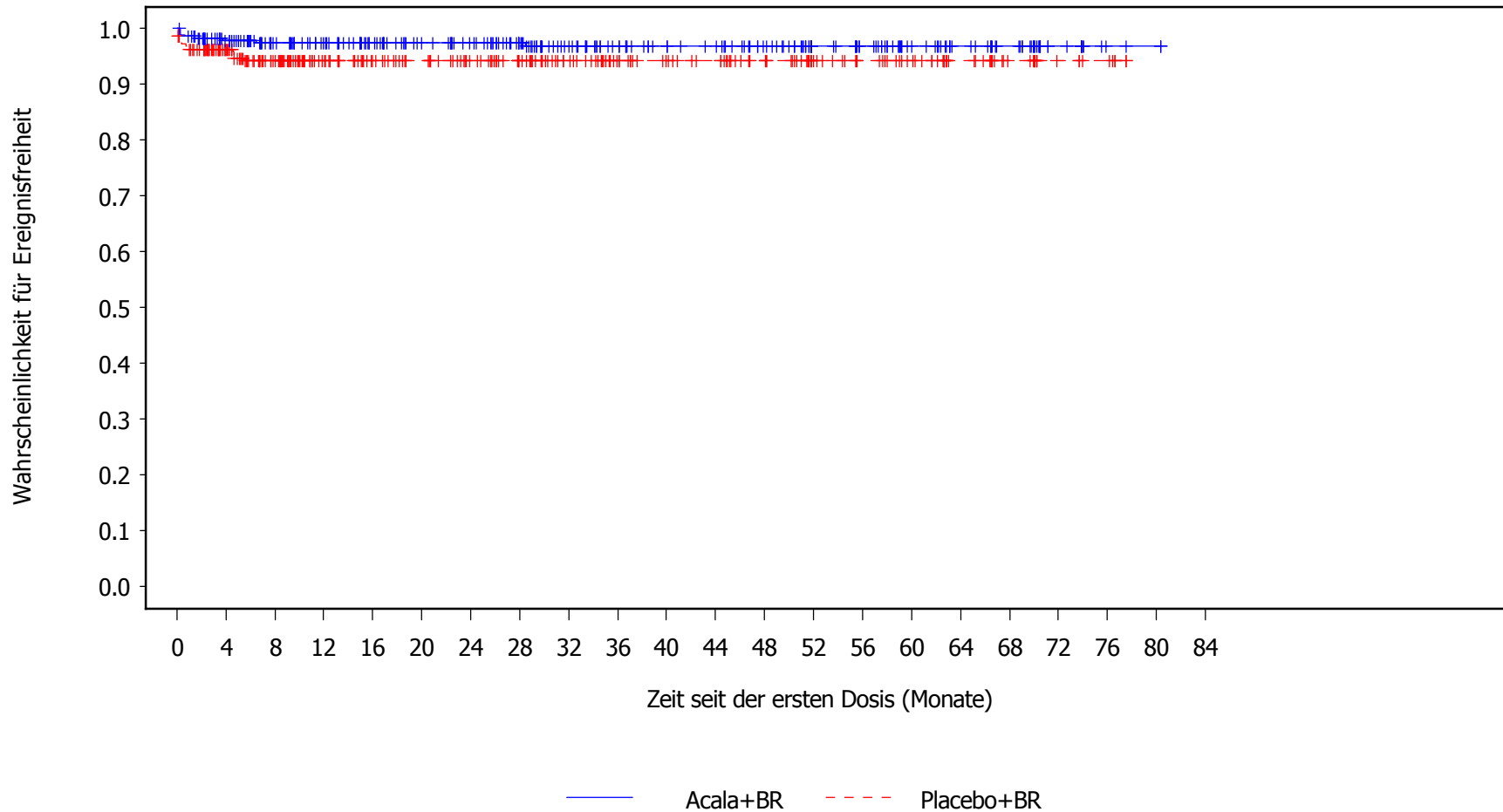
Anzahl an Patienten unter Risiko:

297	269	235	217	197	182	172	154	135	120	110	107	96	77	66	49	39	28	10	2	1	0	Acala+BR
297	255	224	193	176	164	149	132	116	102	94	89	78	61	53	46	32	18	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.162 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 PT: Lymphopenie
 Safety Analysis Set, DC0 15FEB2024



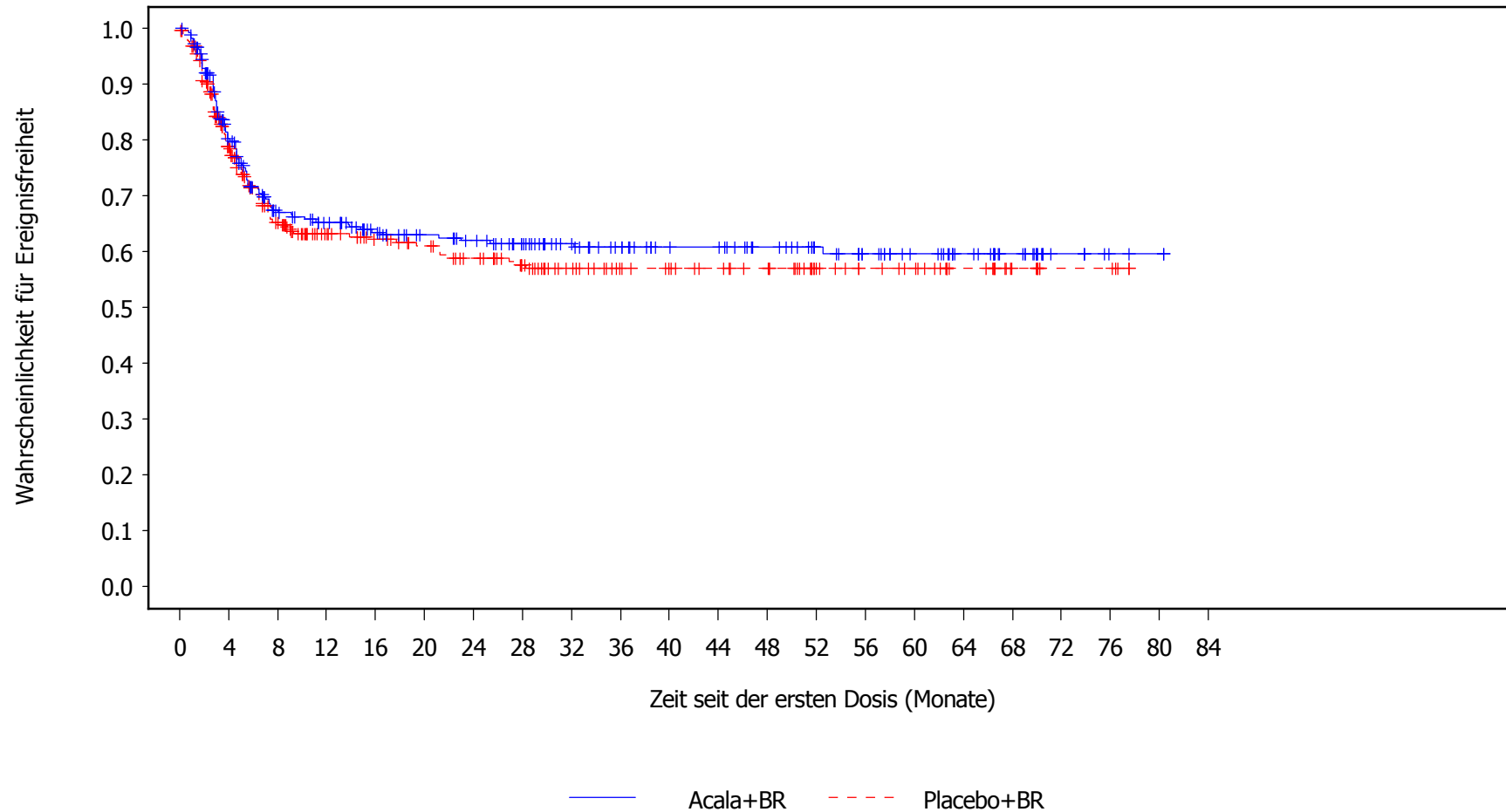
Anzahl an Patienten unter Risiko:

297	269	241	224	204	187	177	158	137	122	112	108	96	76	66	49	38	29	11	2	1	0	Acala+BR
297	256	223	192	174	163	150	135	118	103	94	89	78	62	53	45	30	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.163 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 PT: Neutropenie
 Safety Analysis Set, DC0 15FEB2024



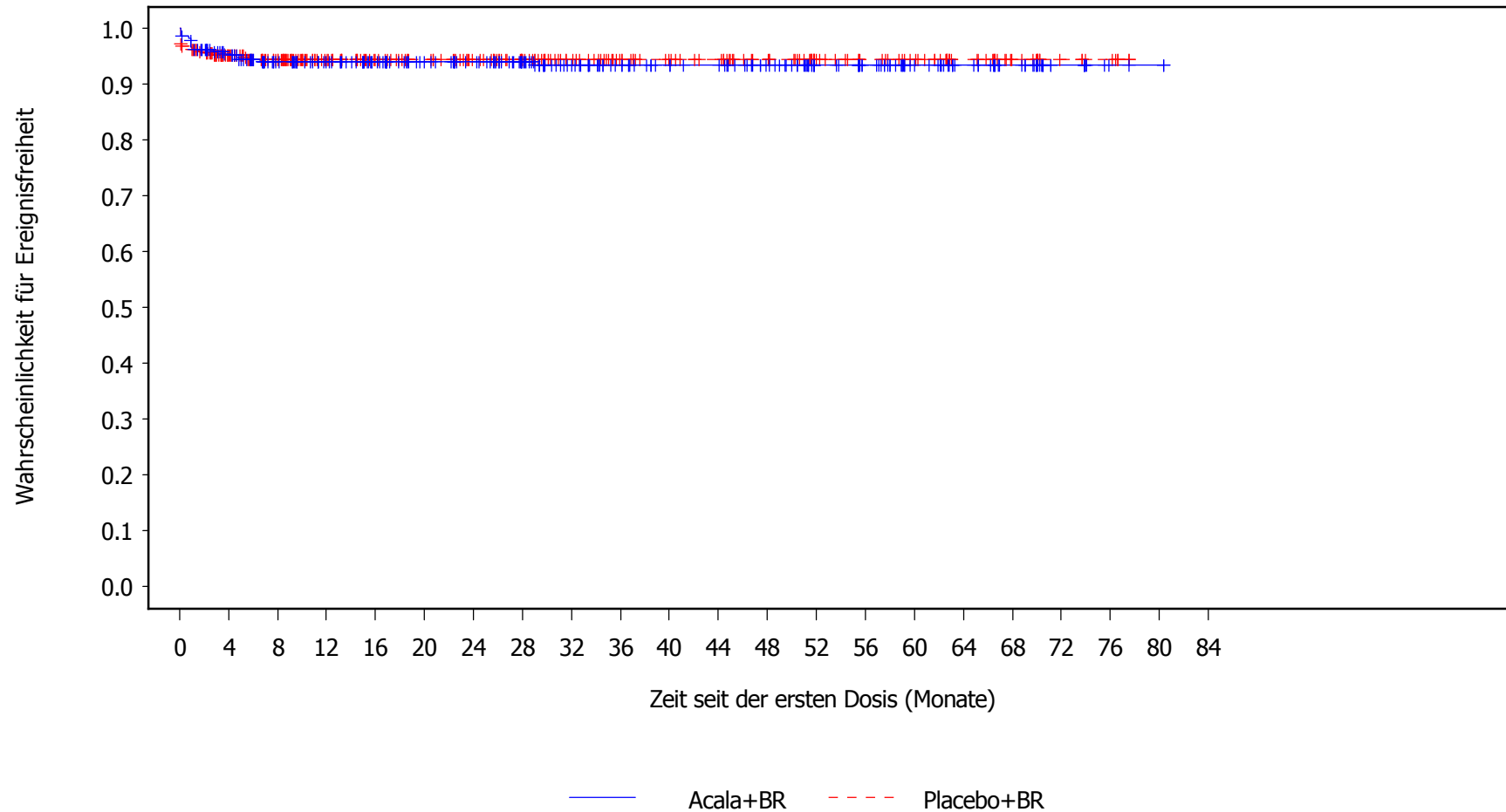
Anzahl an Patienten unter Risiko:

297	219	166	152	135	124	118	107	93	84	75	74	66	56	47	39	30	21	7	2	1	0	Acala+BR
297	210	158	131	119	112	102	89	76	66	62	58	54	40	34	31	20	10	4	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.164 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 PT: Thrombozytopenie
 Safety Analysis Set, DC0 15FEB2024



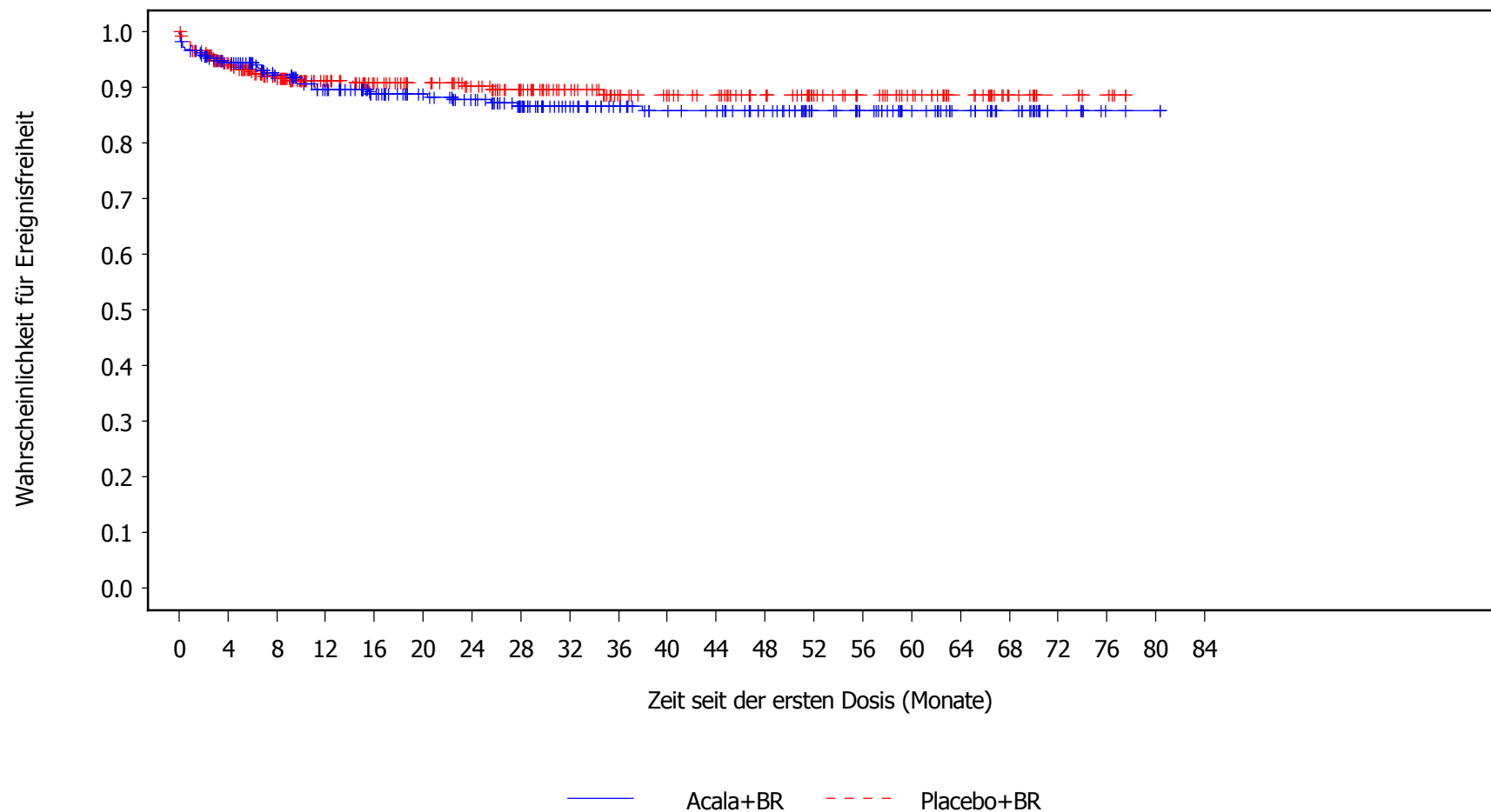
Anzahl an Patienten unter Risiko:

297	265	236	220	202	185	176	157	137	122	112	109	97	76	66	49	38	27	10	2	1	0	Acala+BR
297	256	230	197	178	166	153	137	119	105	96	91	80	63	54	47	32	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.165 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 SOC: Erkrankungen des Gastrointestinaltrakts
 Safety Analysis Set, DCO 15FEB2024



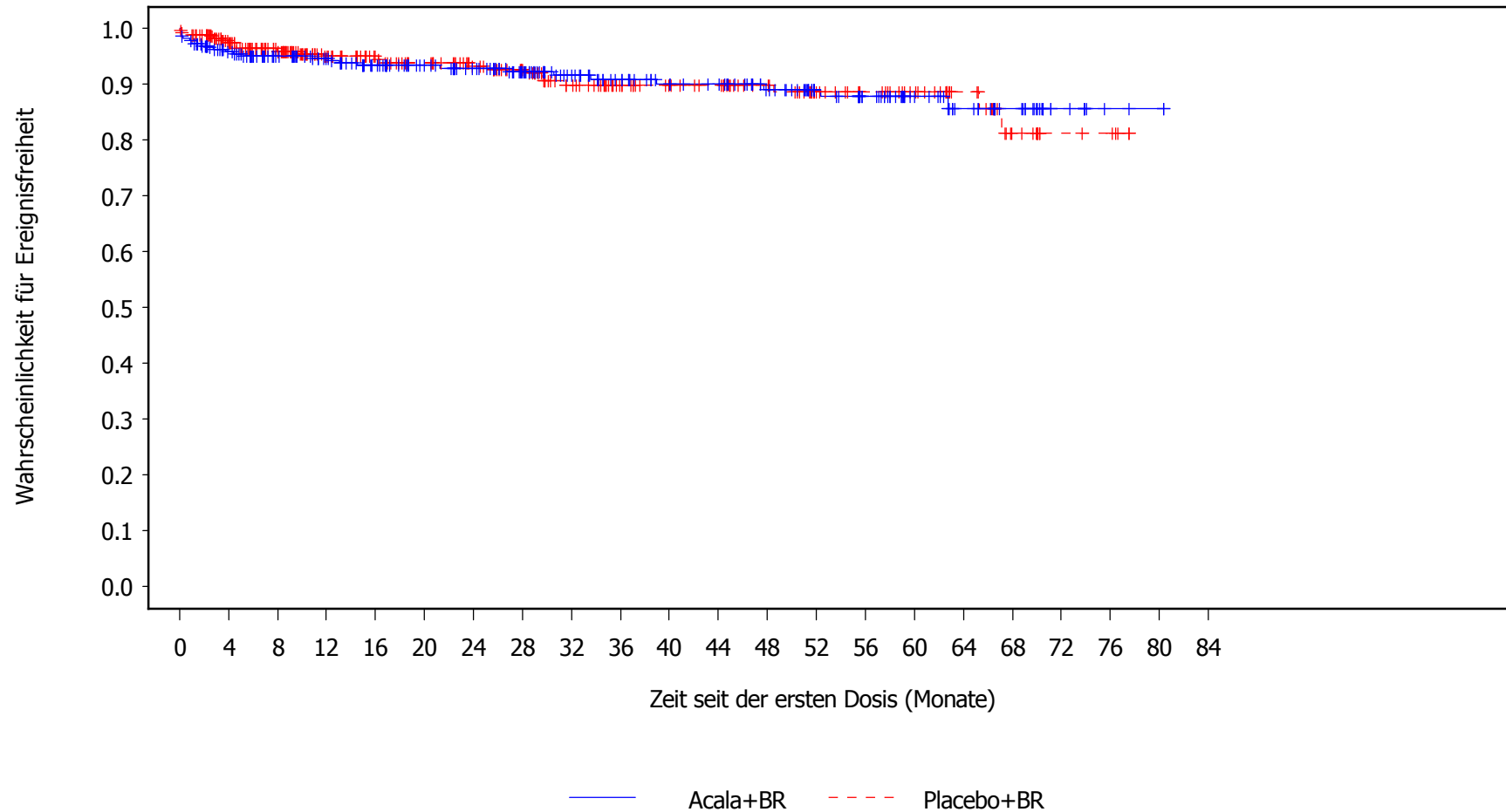
Anzahl an Patienten unter Risiko:

297	264	232	213	192	177	164	144	125	113	103	100	89	70	60	47	37	27	10	2	1	0	Acala+BR
297	256	222	190	173	161	148	131	113	98	91	86	75	61	52	44	29	15	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.166 ECH0: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 SOC: Erkrankungen des Nervensystems
 Safety Analysis Set, DCO 15FEB2024



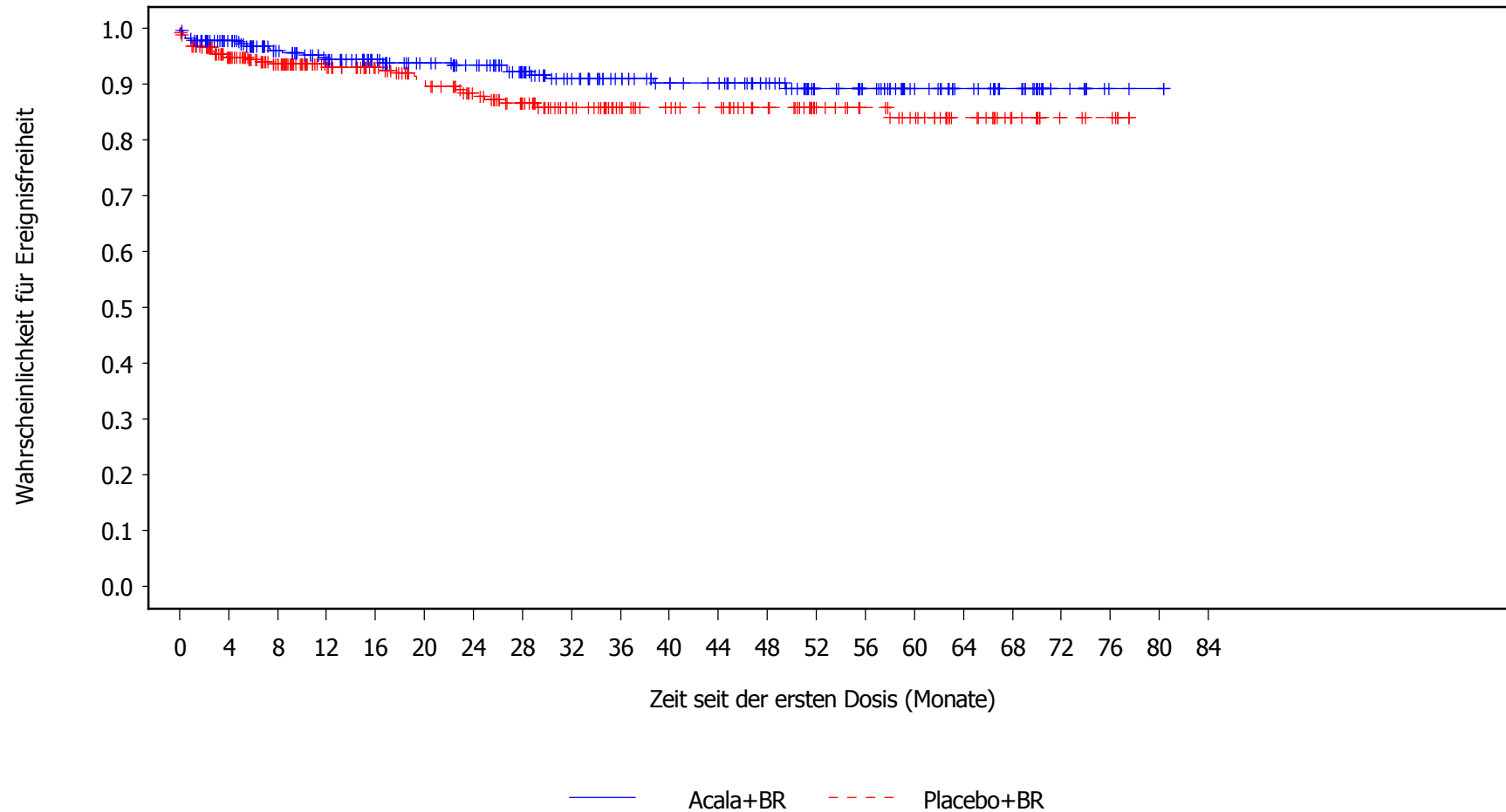
Anzahl an Patienten unter Risiko:

297	265	240	222	202	185	173	152	131	118	107	103	90	72	60	43	33	24	9	2	1	0	Acala+BR
297	262	232	196	179	165	150	135	116	101	92	88	78	62	53	45	31	15	5	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.167 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 SOC: Gefaesserkrankungen
 Safety Analysis Set, DCO 15FEB2024



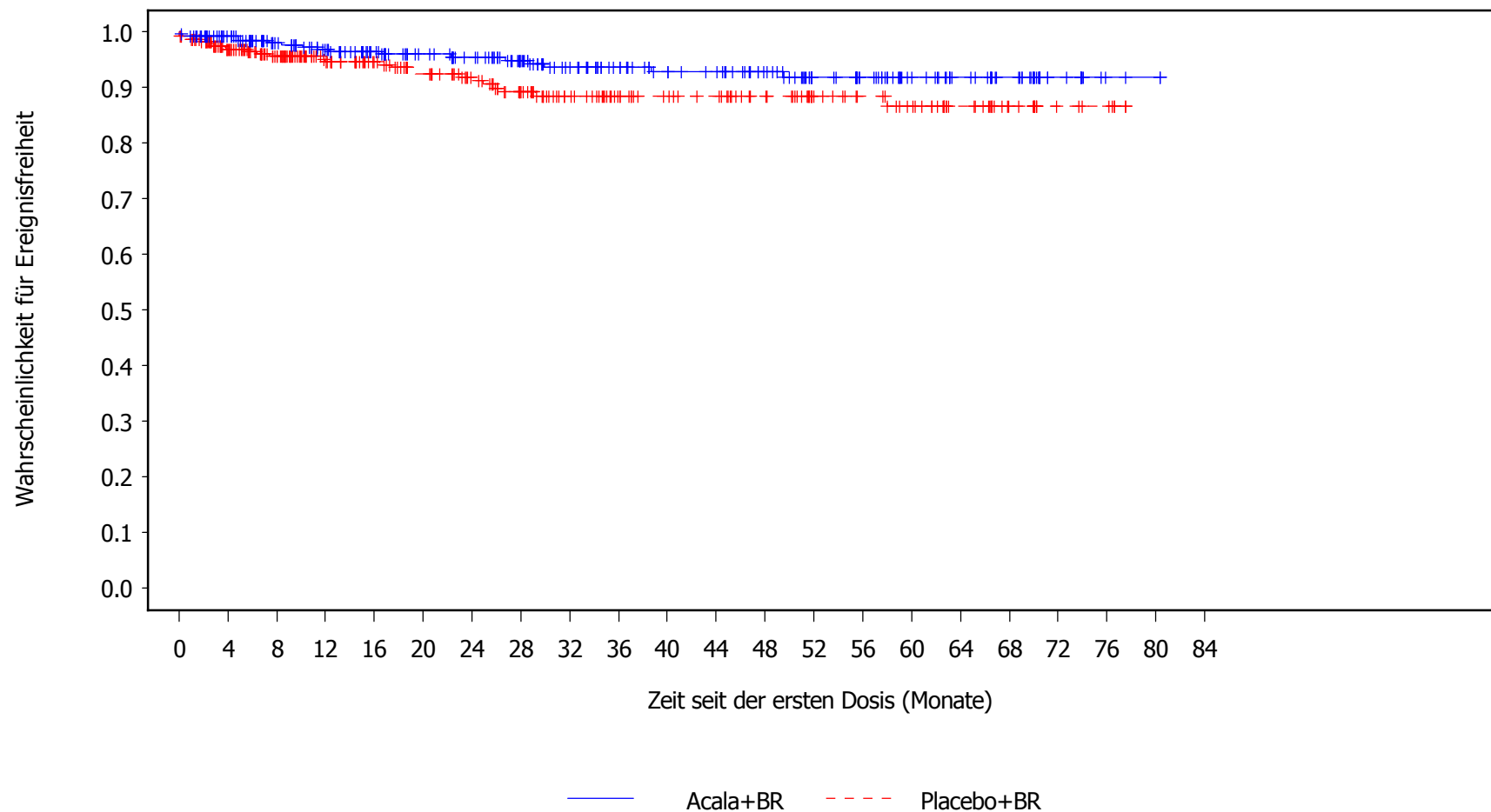
Anzahl an Patienten unter Risiko:

297	269	239	220	201	186	175	154	135	121	111	107	95	75	64	48	38	29	11	2	1	0	Acala+BR
297	254	224	193	176	160	144	126	107	93	85	81	72	56	49	42	28	17	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.168 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 PT: Hypertonie
 Safety Analysis Set, DC0 15FEB2024



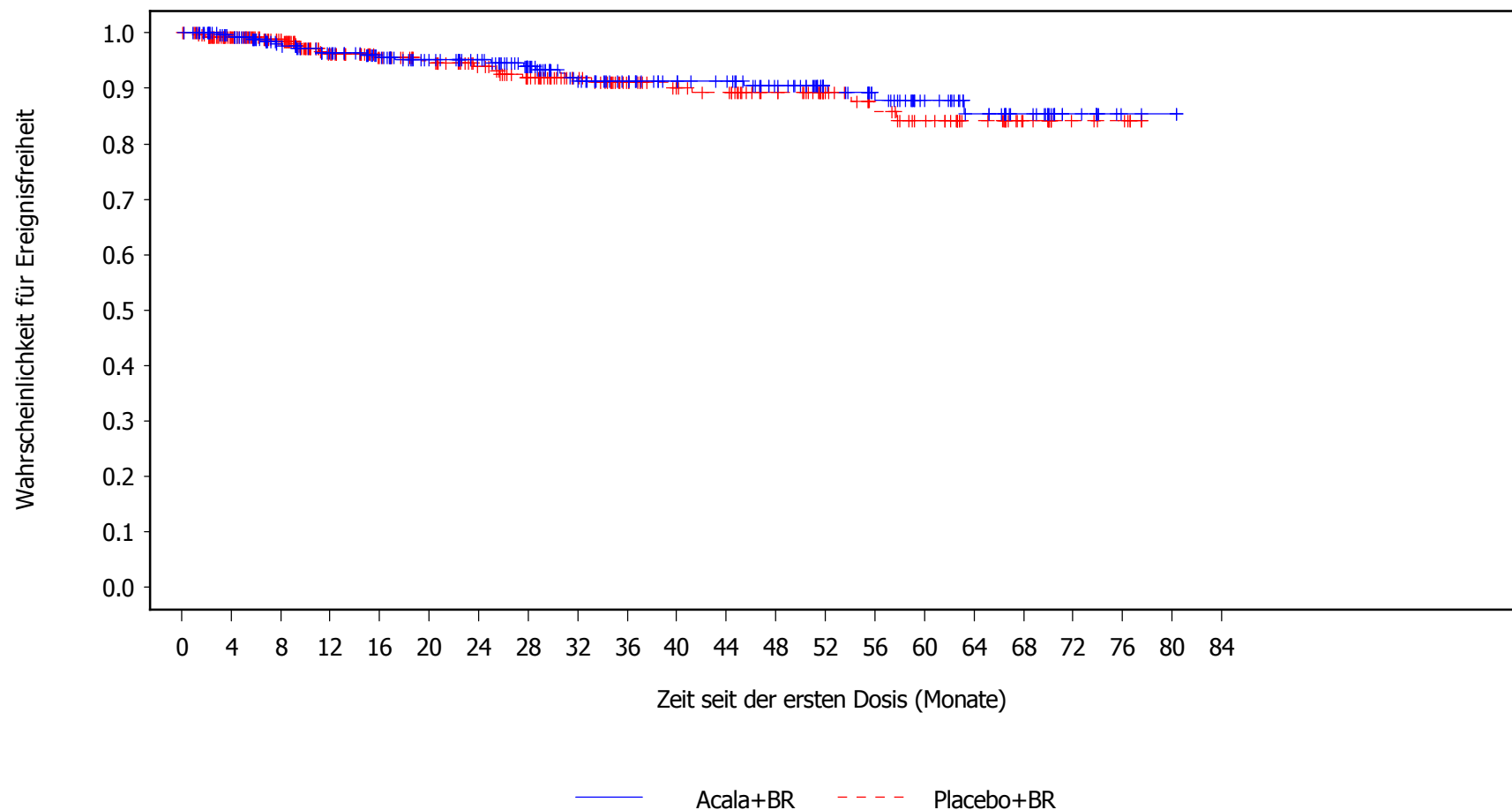
Anzahl an Patienten unter Risiko:

297	273	243	224	204	188	177	156	136	122	111	107	95	75	64	48	38	29	11	2	1	0	Acala+BR
297	259	229	196	178	162	147	128	109	95	87	83	73	57	50	43	29	17	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.169 ECH0: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 SOC: Gutartige, boesartige und nicht spezifizierte Neubildungen (einschl. Zysten und Polypen)
 Safety Analysis Set, DCO 15FEB2024



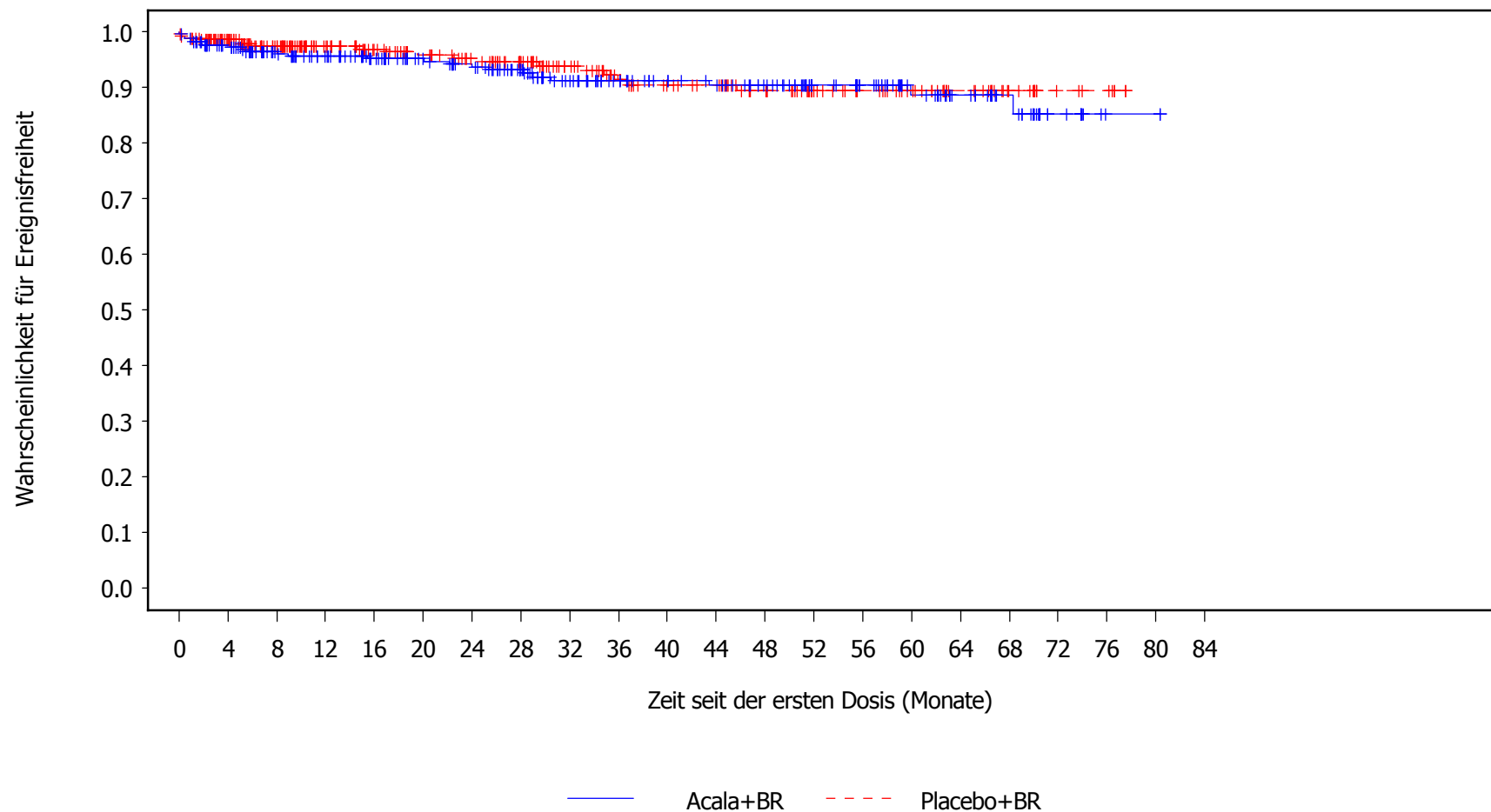
Anzahl an Patienten unter Risiko:

297	274	245	226	206	188	177	156	134	121	111	107	94	74	62	48	36	26	11	2	1	0	Acala+BR
297	266	236	197	177	165	151	135	117	102	92	88	76	60	50	42	29	17	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.170 ECH0: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 SOC: Herzerkrankungen
 Safety Analysis Set, DC0 15FEB2024



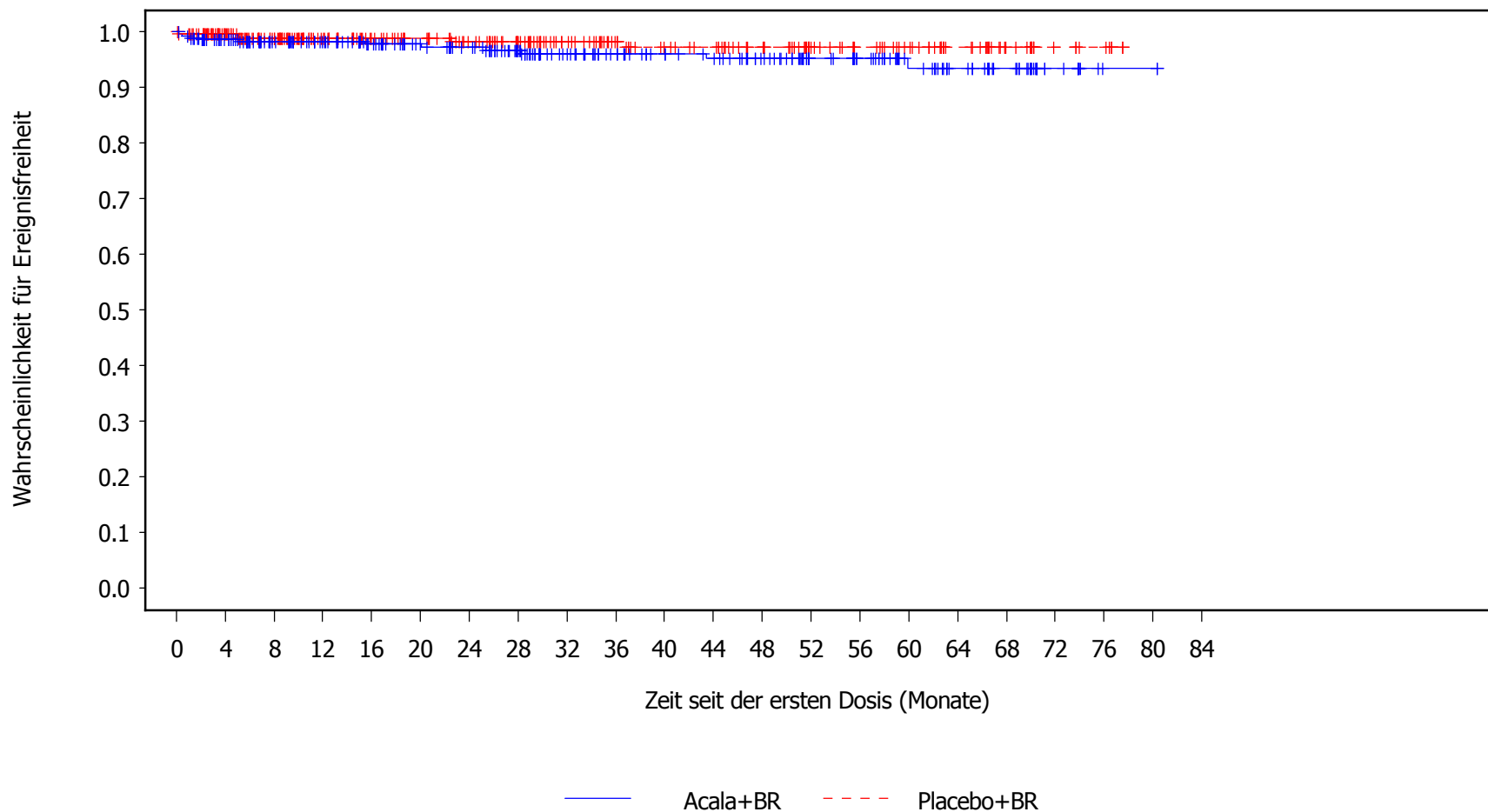
Anzahl an Patienten unter Risiko:

297	272	243	226	206	189	178	158	136	122	112	107	97	76	65	48	37	26	10	1	1	0	Acala+BR
297	265	234	201	182	168	156	140	120	104	94	90	79	62	53	45	31	18	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.171 ECH0: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 PT: Vorhofflimmern
 Safety Analysis Set, DC0 15FEB2024



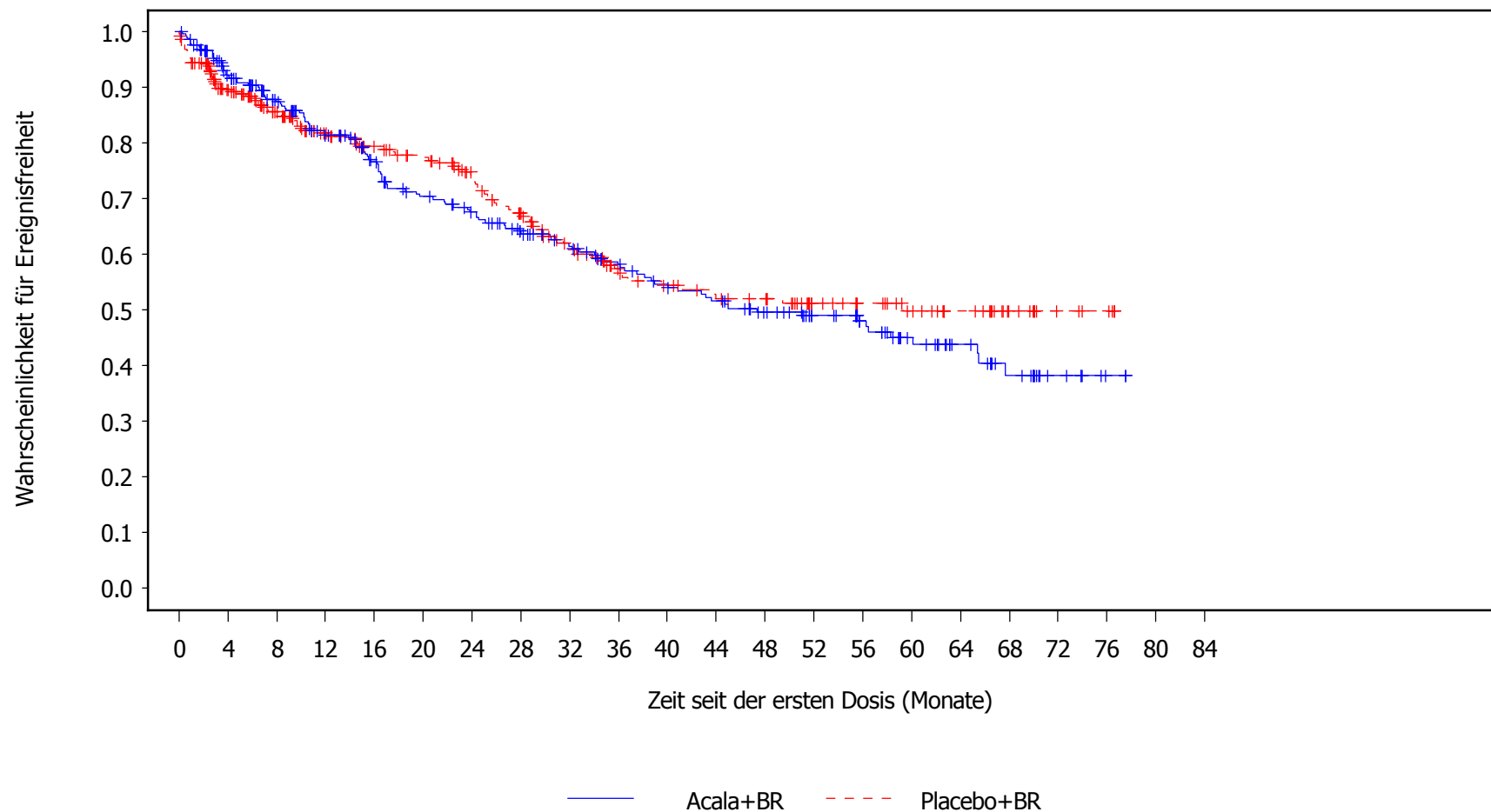
Anzahl an Patienten unter Risiko:

297	273	246	229	209	192	182	160	139	125	115	110	99	78	67	50	39	28	10	1	1	0	Acala+BR
297	266	236	202	183	171	157	141	122	107	97	93	82	65	56	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.172 ECH0: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 SOC: Infektionen und parasitäre Erkrankungen
 Safety Analysis Set, DC0 15FEB2024



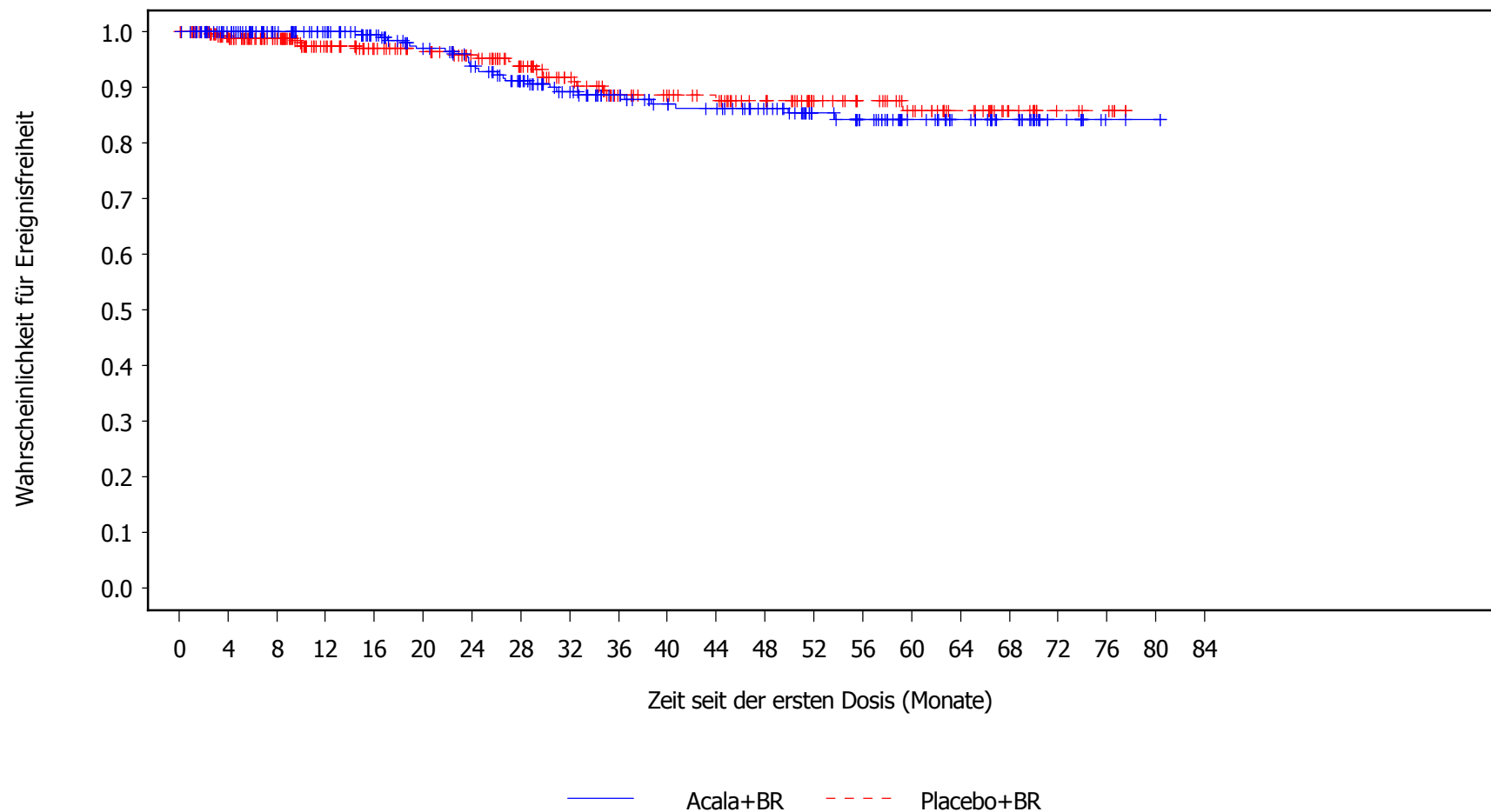
Anzahl an Patienten unter Risiko:

297	257	225	198	173	153	142	125	113	100	91	85	75	62	50	37	27	17	7	1	0	0	Acala+BR
297	243	210	179	162	151	132	116	97	79	72	66	63	47	41	34	25	14	6	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.173 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 PT: COVID-19
 Safety Analysis Set, DC0 15FEB2024



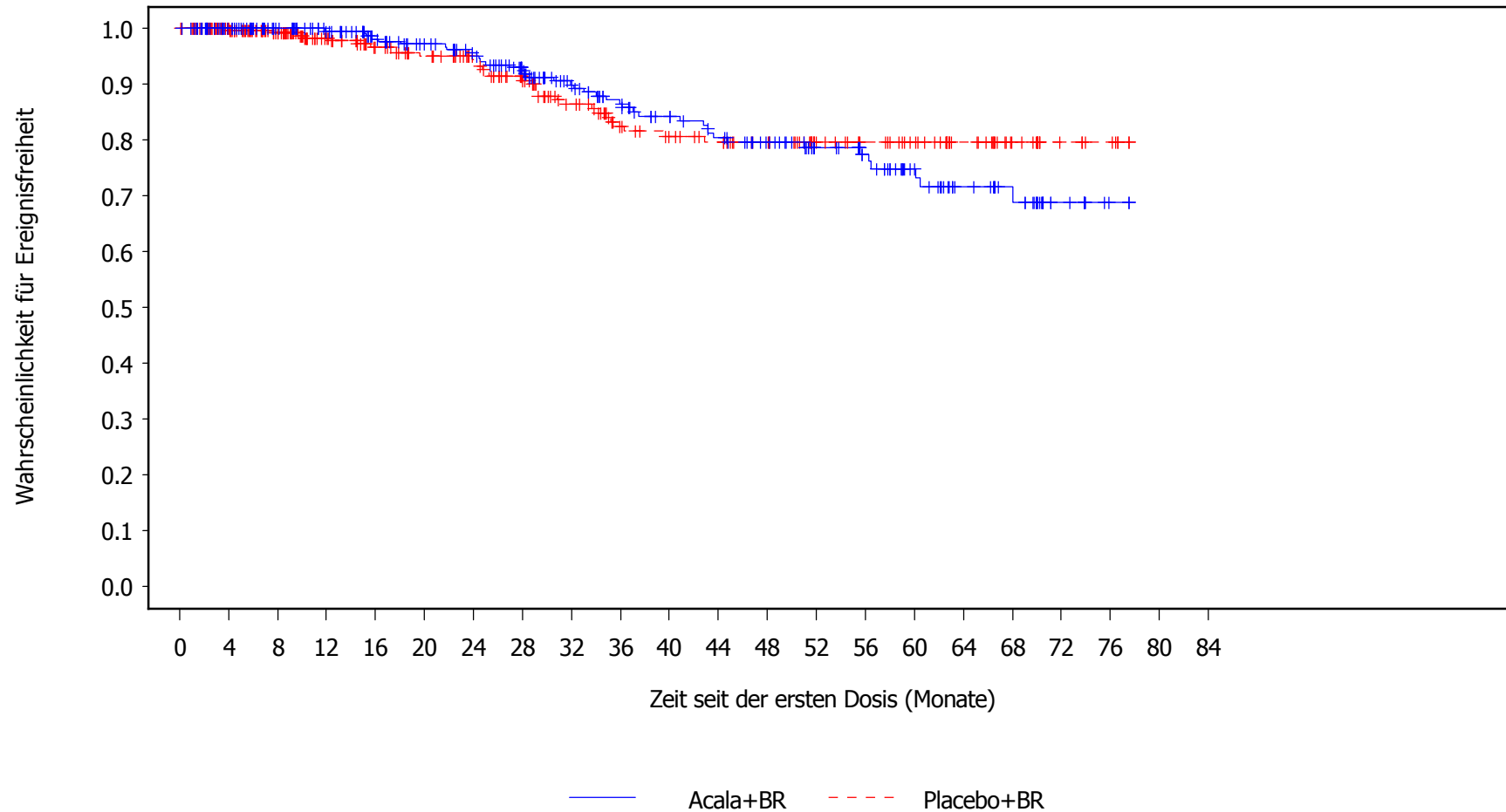
Anzahl an Patienten unter Risiko:

297	275	248	231	210	191	177	157	138	122	111	107	97	78	66	50	40	29	11	2	1	0	Acala+BR
297	267	238	202	183	171	158	140	120	102	95	89	78	62	54	45	32	18	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.174 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 PT: COVID-19-Lungenentzündung
 Safety Analysis Set, DCO 15FEB2024



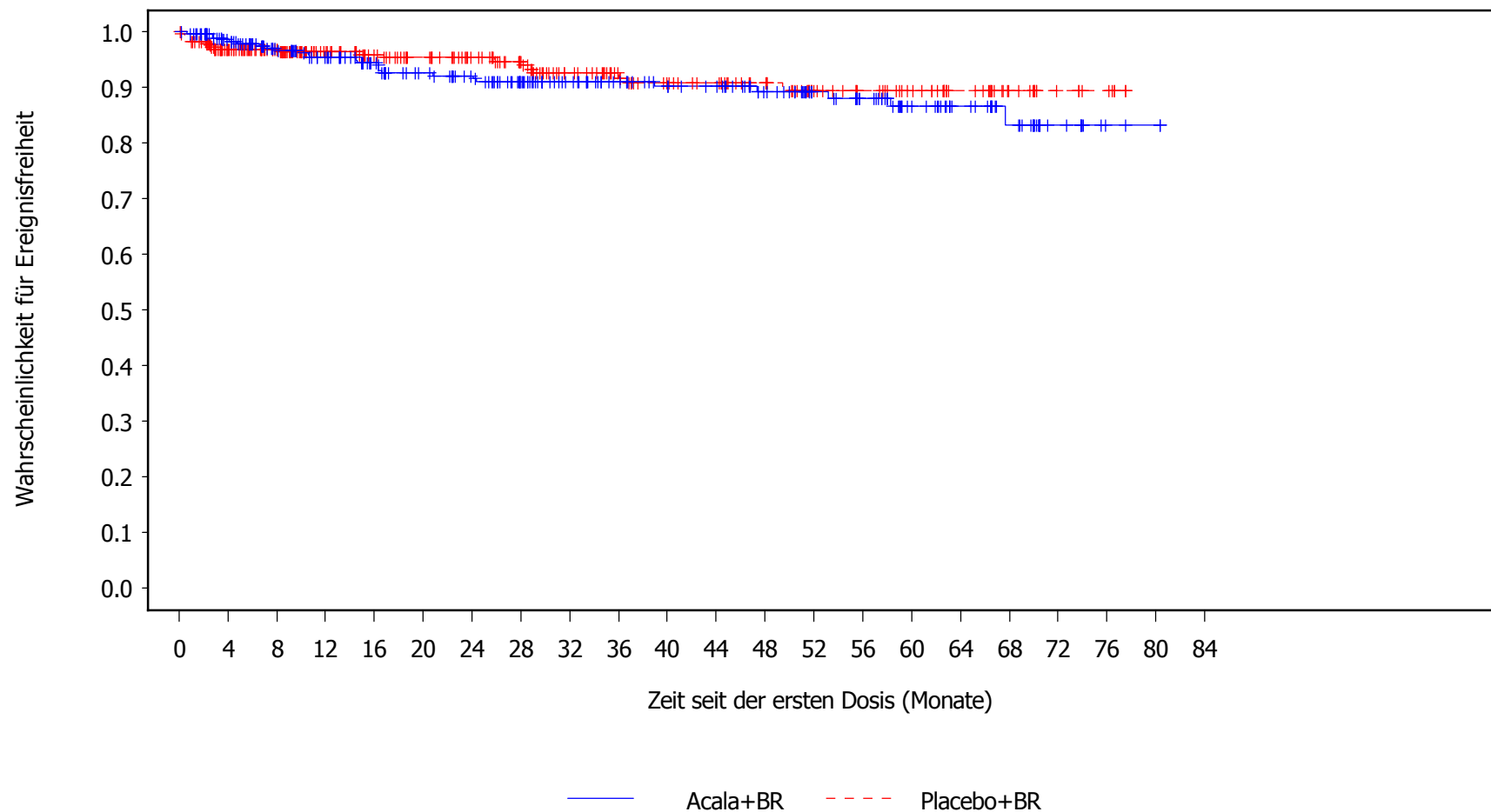
Anzahl an Patienten unter Risiko:

297	275	248	230	208	193	181	160	137	122	111	102	92	74	62	46	34	26	9	1	0	0	Acala+BR
297	267	237	202	182	169	153	135	115	97	90	85	77	61	53	46	32	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.175 ECH0: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 PT: Pneumonie
 Safety Analysis Set, DC0 15FEB2024



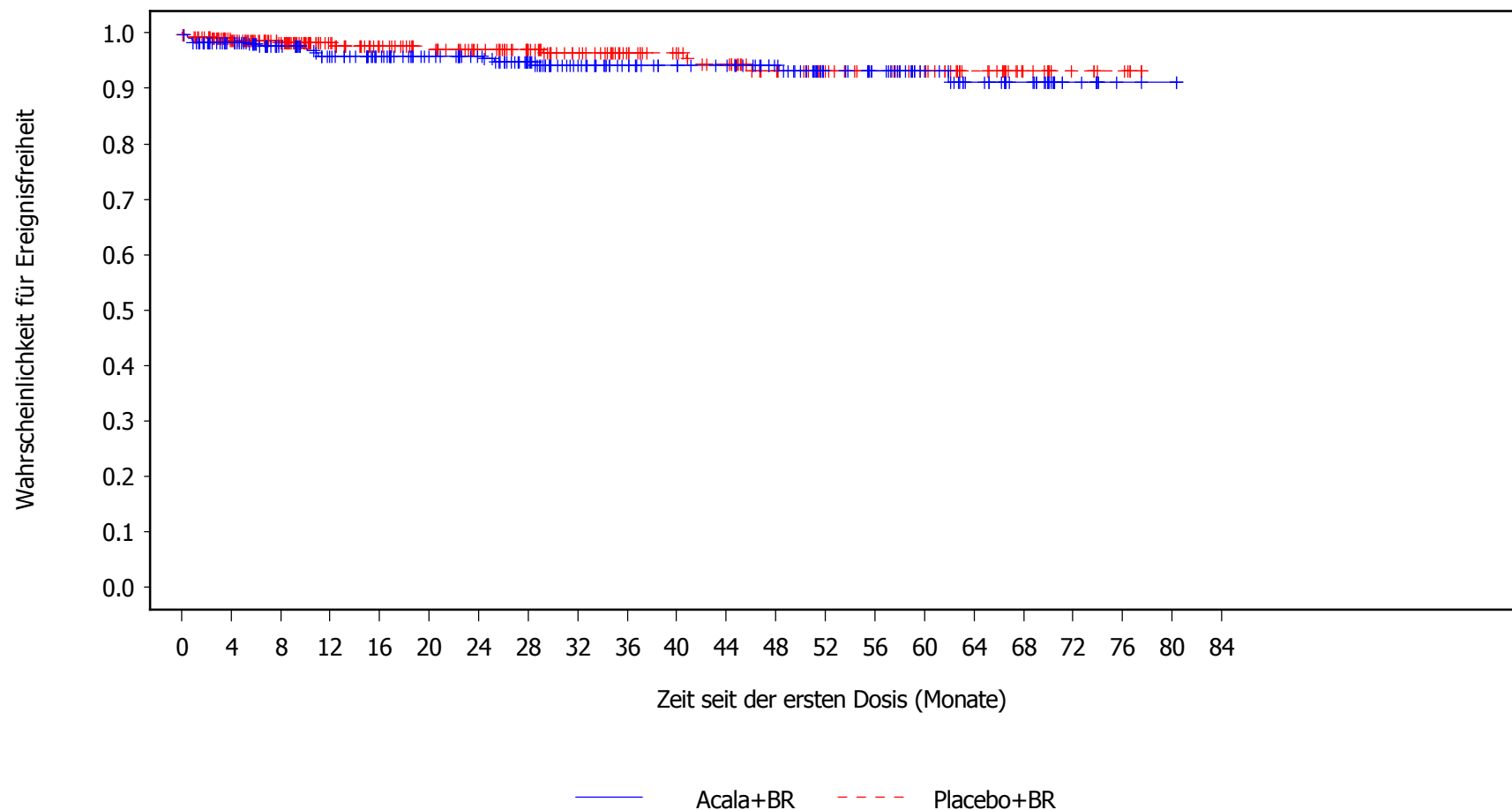
Anzahl an Patienten unter Risiko:

297	271	240	222	201	184	173	152	133	120	111	107	94	77	65	47	36	25	10	2	1	0	Acala+BR
297	260	232	198	179	166	152	136	115	102	91	86	76	59	51	43	29	17	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.176 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 SOC: Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen
 Safety Analysis Set, DC0 15FEB2024



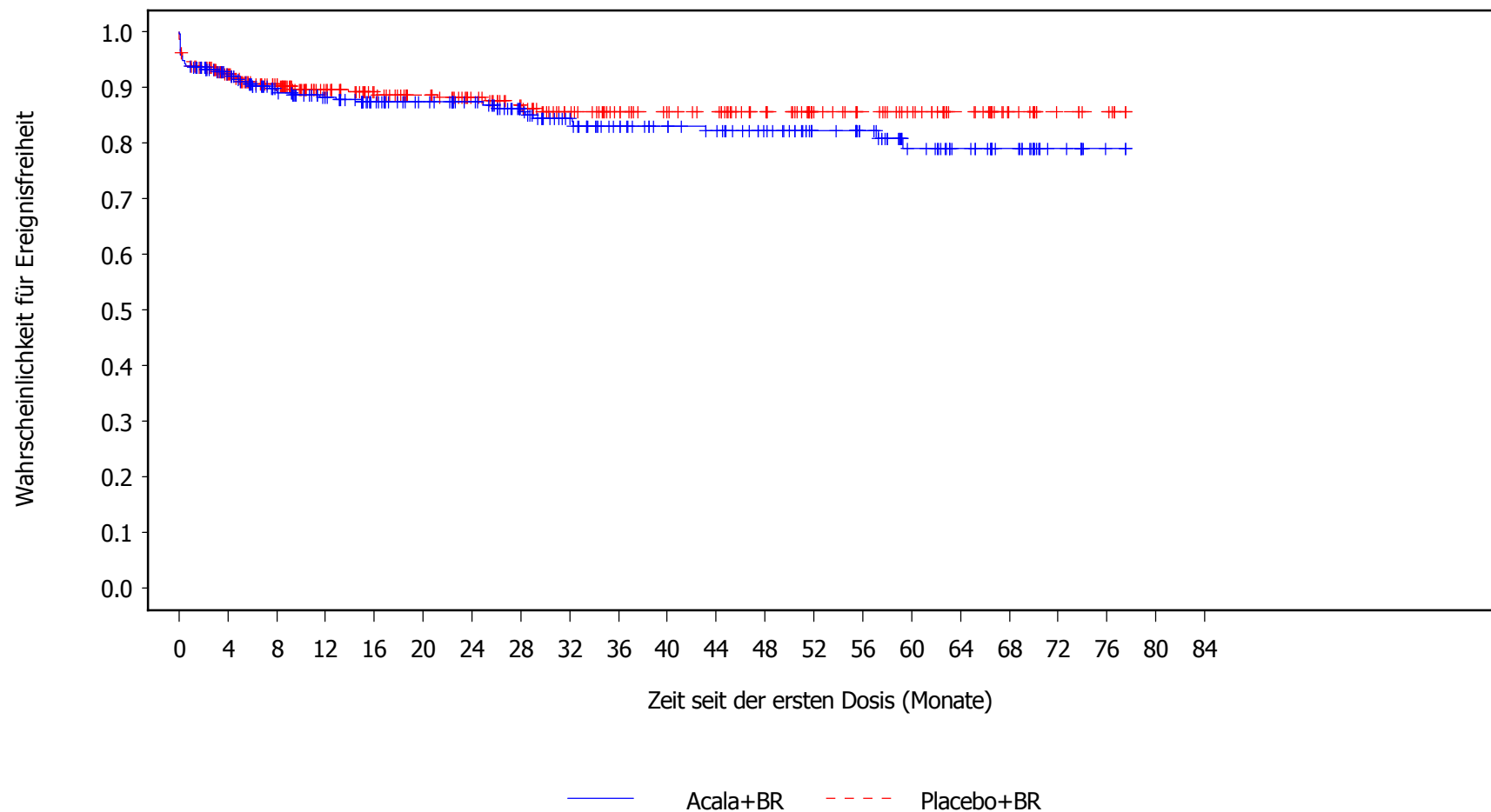
Anzahl an Patienten unter Risiko:

297	272	244	224	207	190	179	157	135	120	111	107	96	74	64	48	38	28	10	2	1	0	Acala+BR
297	264	234	199	180	167	153	138	121	106	97	90	77	62	53	45	31	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.177 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 SOC: Stoffwechsel- und Ernährungsstörungen
 Safety Analysis Set, DCO 15FEB2024



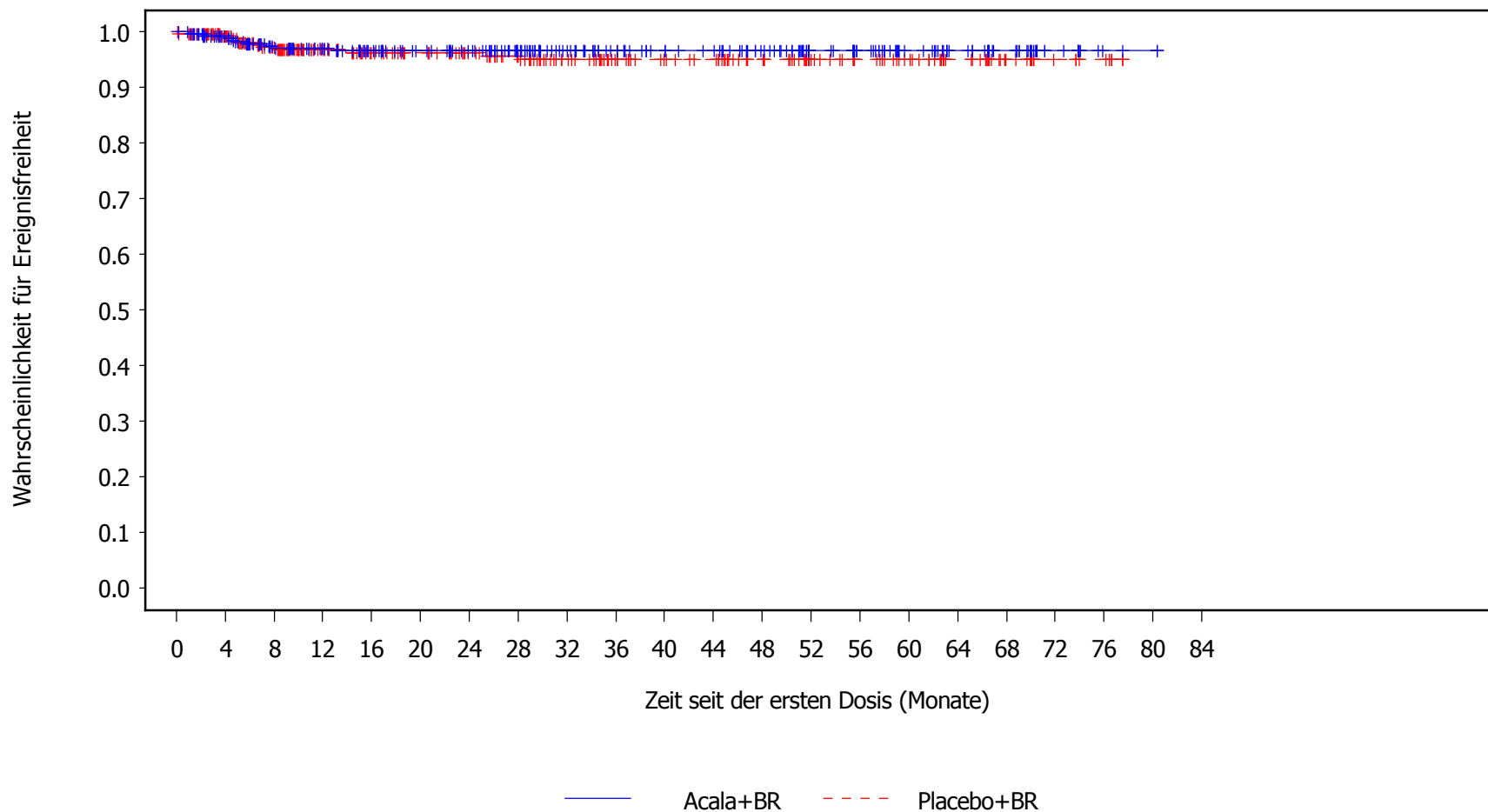
Anzahl an Patienten unter Risiko:

297	256	224	205	186	174	164	143	125	110	101	96	86	70	61	44	33	23	8	1	0	0	Acala+BR
297	251	224	190	173	160	146	133	115	103	94	90	78	61	53	45	31	17	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.178 ECHO: Kaplan-Meier plot of time to first occurrence of $G \geq 3$ PT: Hypokaliaemie
 Safety Analysis Set, DC0 15FEB2024



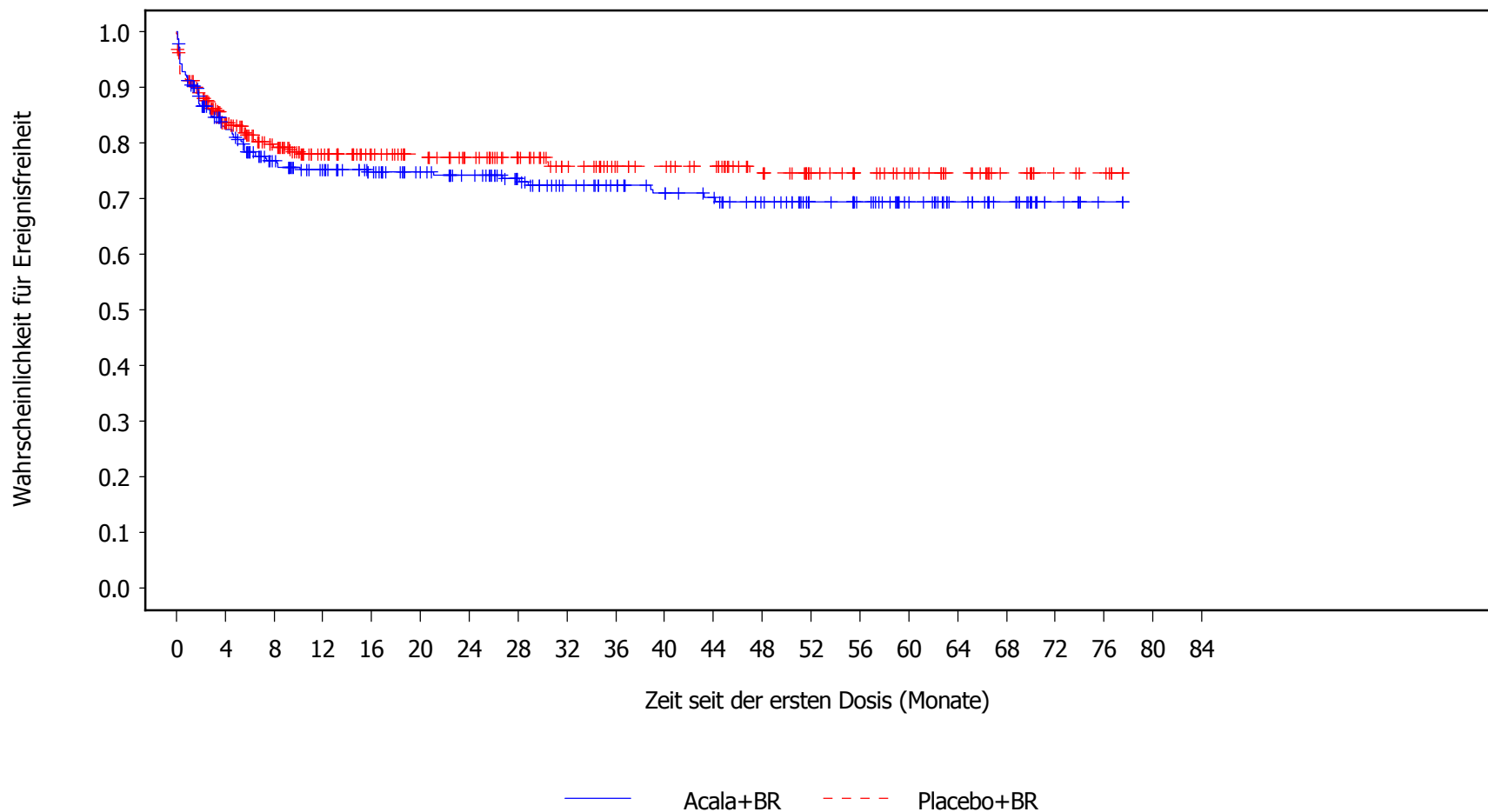
Anzahl an Patienten unter Risiko:

297	273	242	225	206	192	181	160	140	125	115	111	99	78	67	51	40	29	11	2	1	0	Acala+BR
297	265	233	197	178	166	153	139	121	107	98	94	82	65	56	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.179 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 SOC: Untersuchungen
 Safety Analysis Set, DC0 15FEB2024



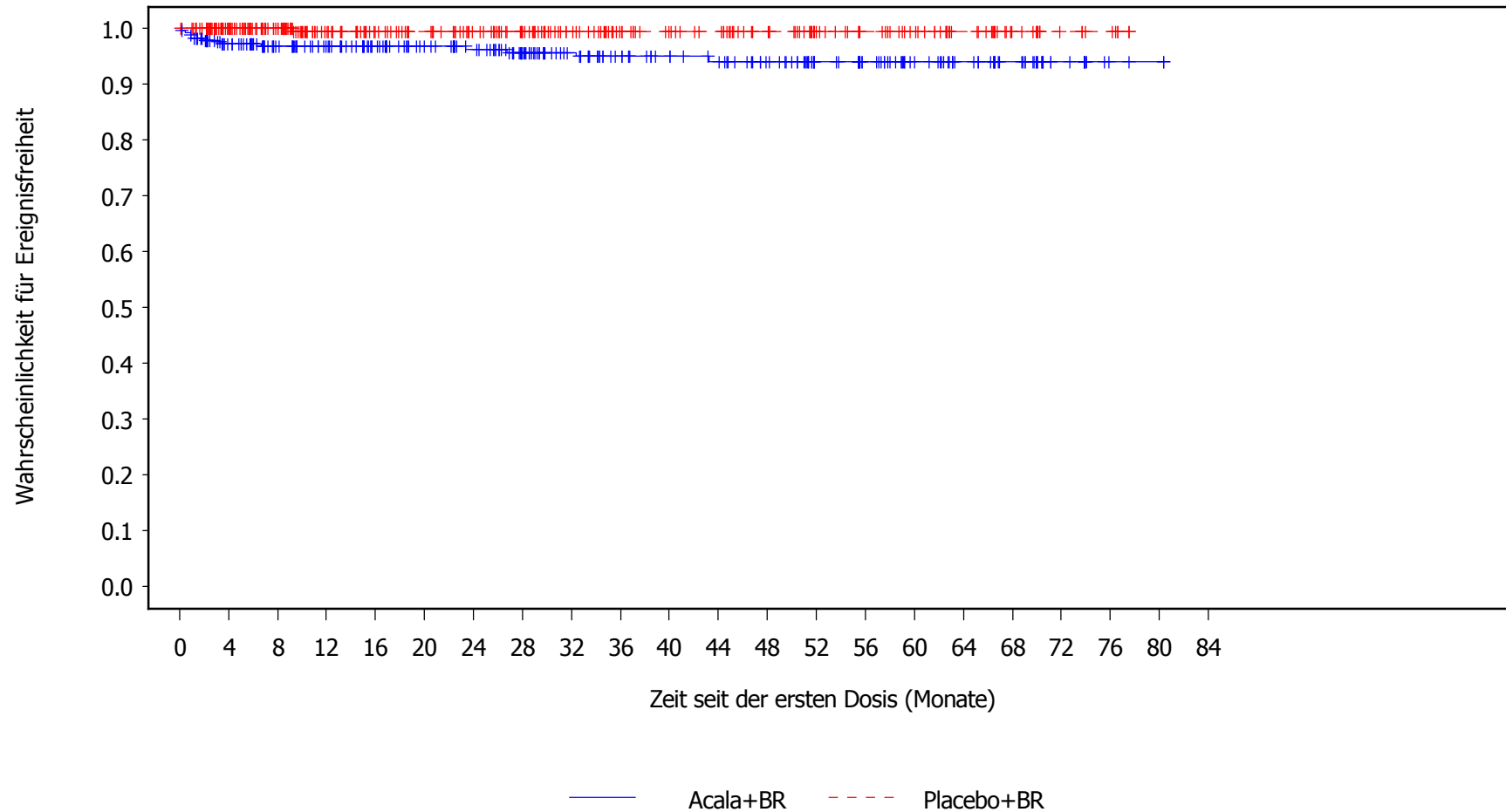
Anzahl an Patienten unter Risiko:

297	227	194	177	163	150	140	123	110	102	94	89	79	64	57	43	32	23	7	1	0	0	Acala+BR
297	224	188	161	144	132	122	108	93	83	79	74	61	48	41	35	25	15	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.180 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 PT: Alaninaminotransferase erhoeht
 Safety Analysis Set, DC0 15FEB2024



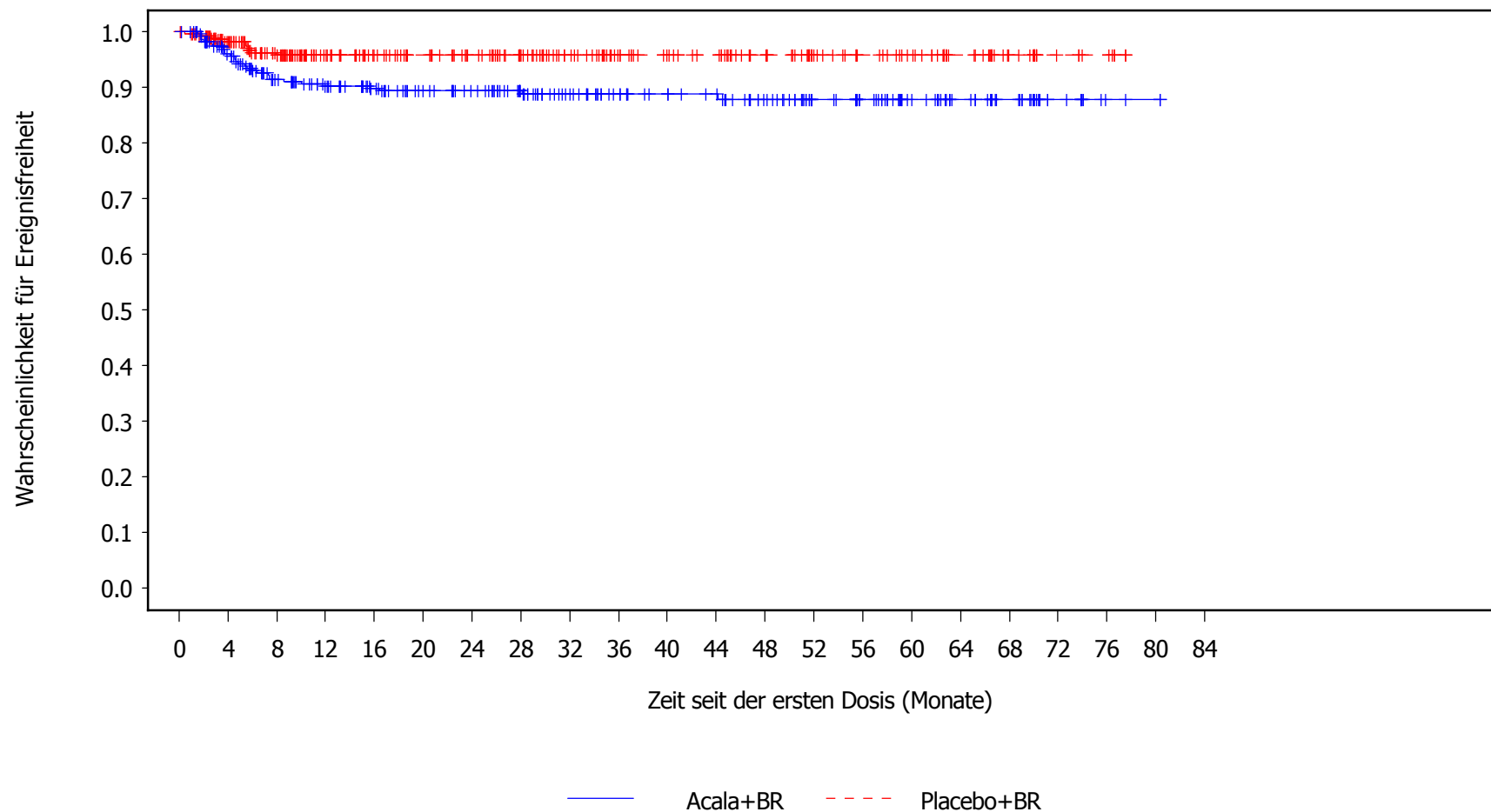
Anzahl an Patienten unter Risiko:

297	267	241	225	206	189	178	156	135	121	112	107	96	77	66	50	39	28	11	2	1	0	Acala+BR
297	267	238	203	184	172	158	142	123	108	99	94	82	65	56	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.181 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 PT: Leukozytenzahl erniedrigt
 Safety Analysis Set, DCO 15FEB2024



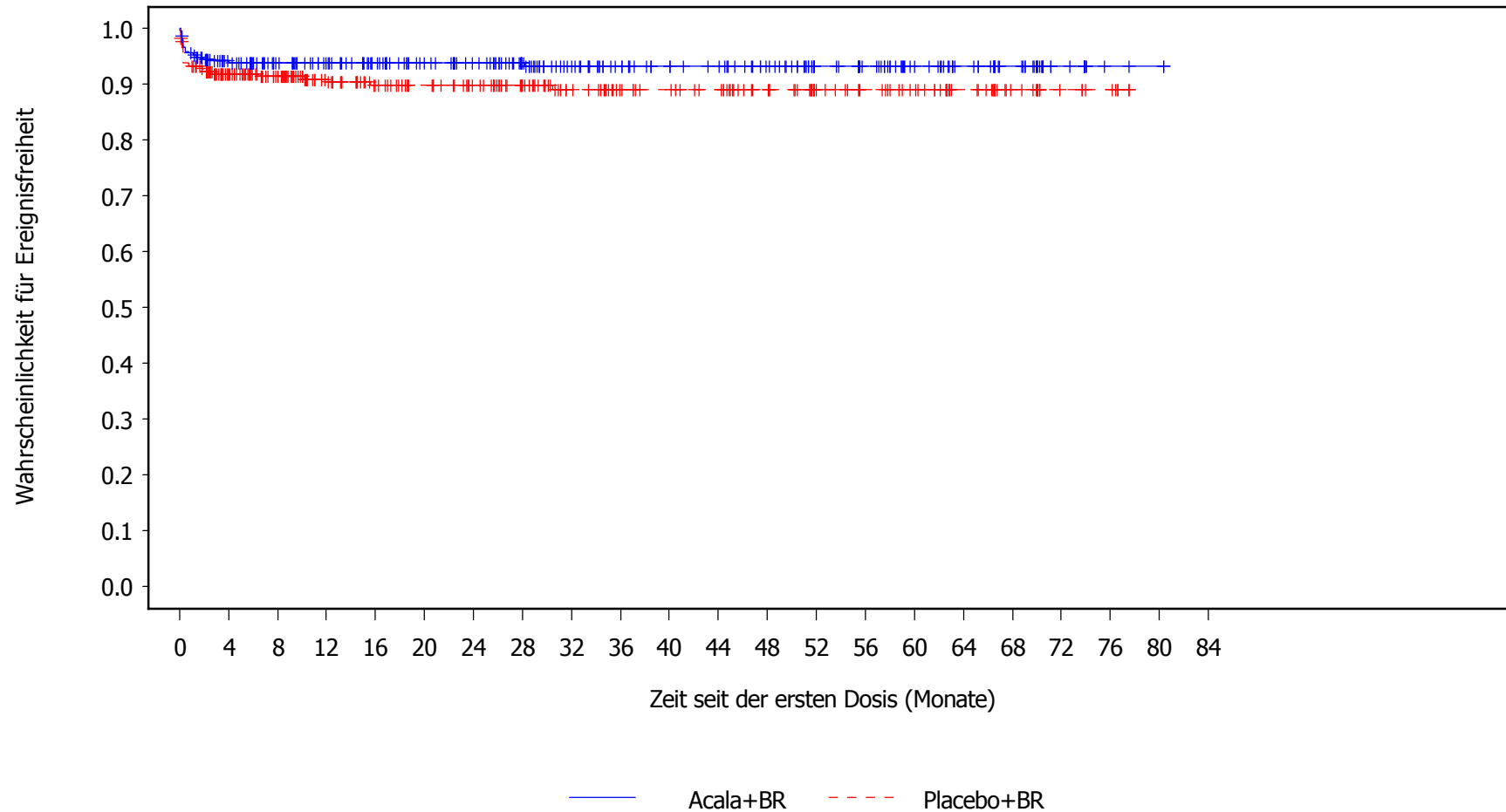
Anzahl an Patienten unter Risiko:

297	264	228	210	192	176	166	148	131	118	111	107	95	76	66	49	38	27	10	2	1	0	Acala+BR
297	263	229	195	176	164	152	136	119	104	95	90	78	63	54	47	32	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.182 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 PT: Lymphozytenzahl erniedrigt
 Safety Analysis Set, DC0 15FEB2024



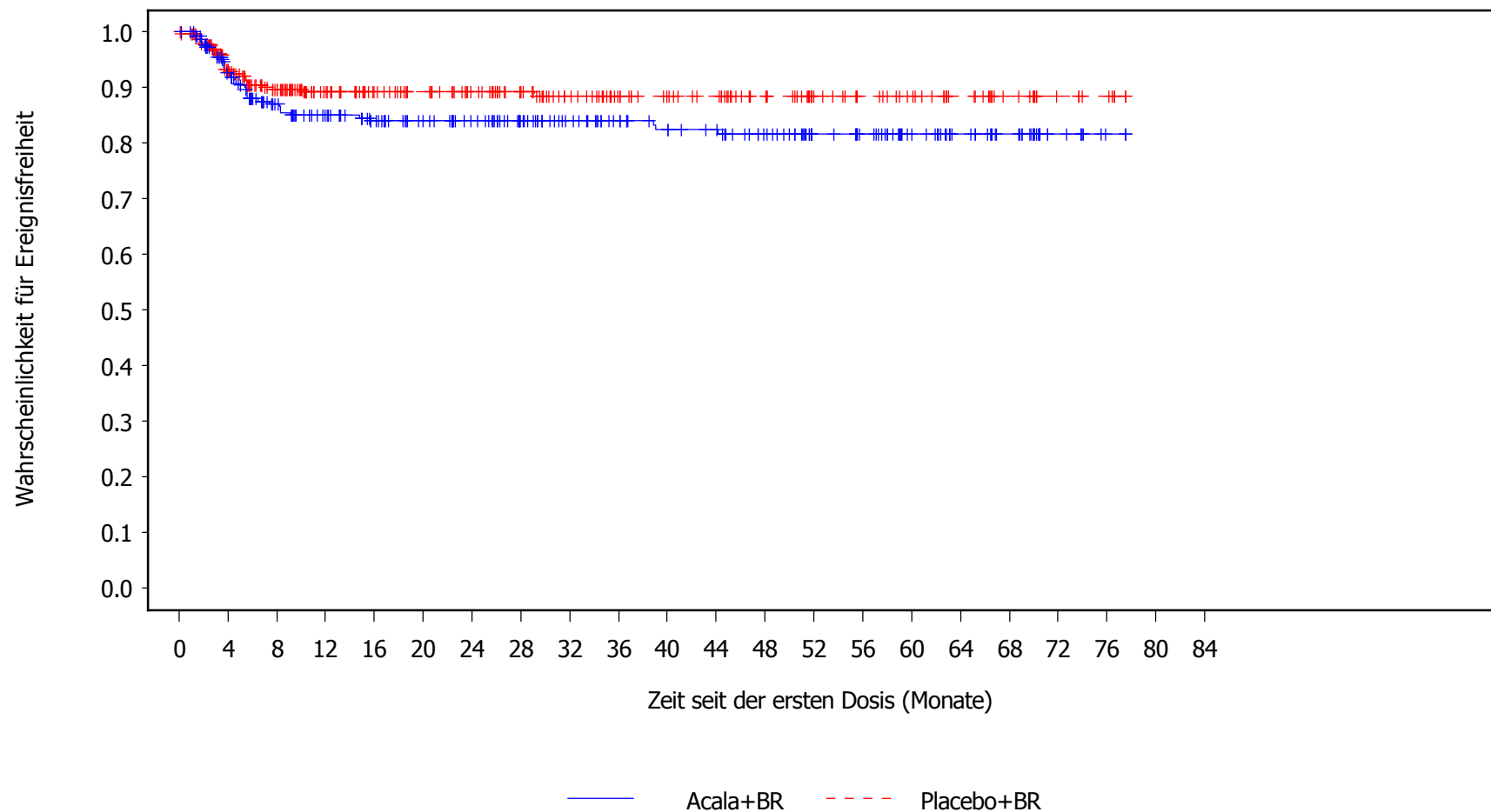
Anzahl an Patienten unter Risiko:

297	258	234	218	200	184	173	153	134	119	110	106	95	76	67	50	39	28	10	2	1	0	Acala+BR
297	244	216	186	167	155	144	128	110	98	93	88	76	62	54	47	32	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.183 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 PT: Neutrophilenzahl erniedrigt
 Safety Analysis Set, DCO 15FEB2024



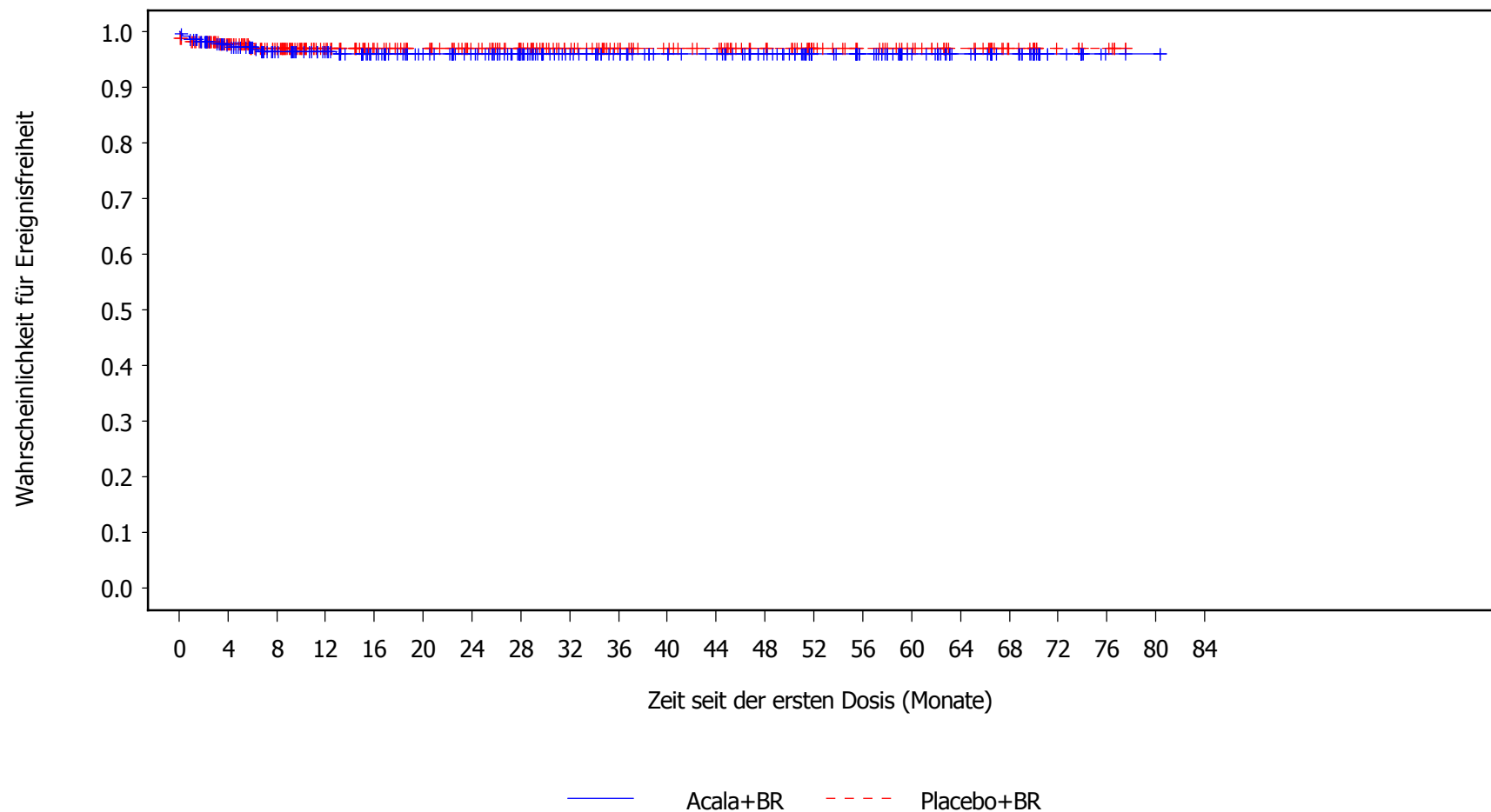
Anzahl an Patienten unter Risiko:

297	255	218	198	181	168	157	140	125	114	106	102	91	72	63	47	36	26	8	1	0	0	Acala+BR
297	250	215	182	163	152	139	124	108	95	87	82	70	54	46	40	28	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.184 ECHO: Kaplan-Meier plot of time to first occurrence of G $\geq$ 3 PT: Thrombozytenzahl vermindert
 Safety Analysis Set, DCO 15FEB2024



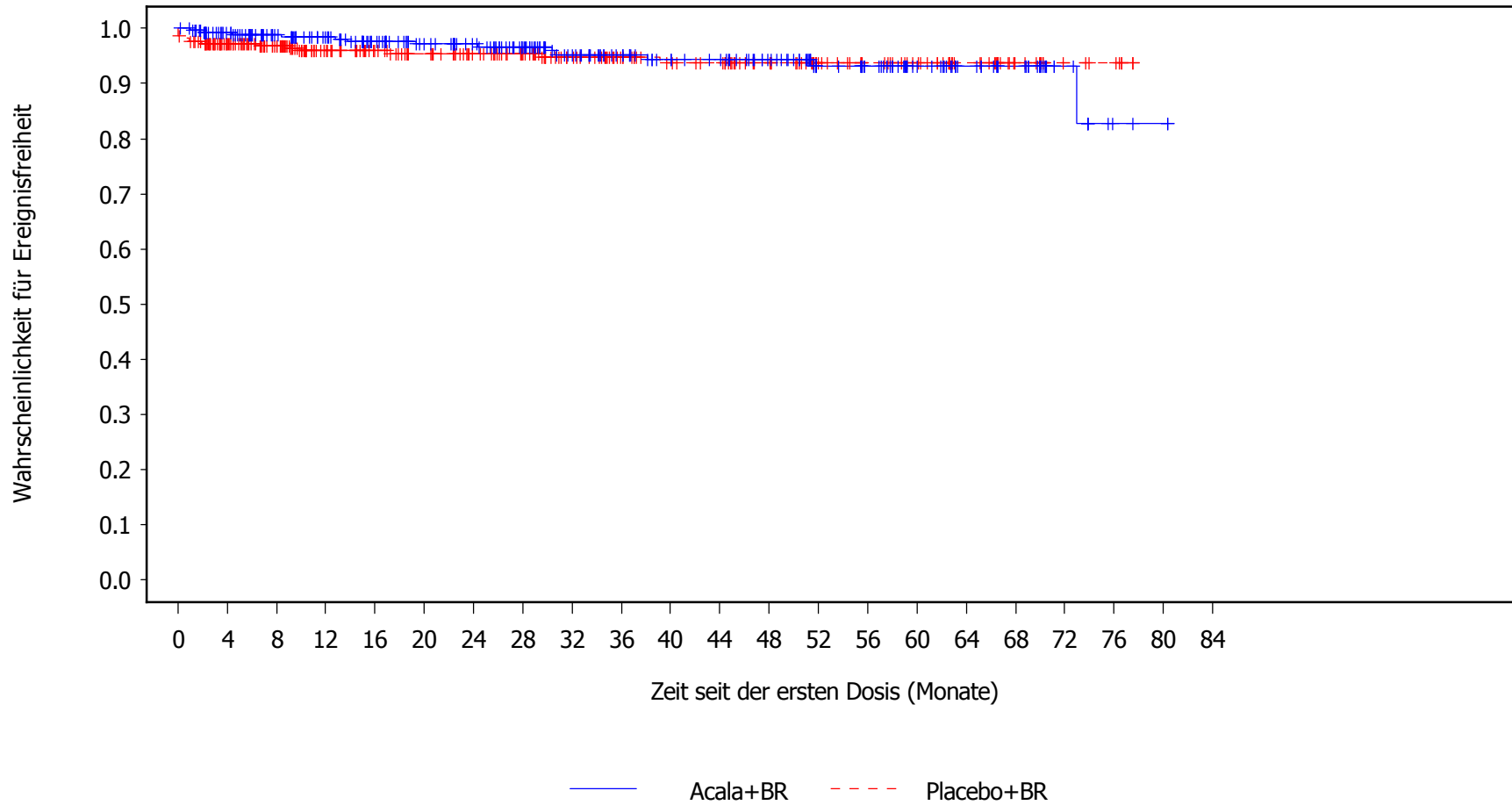
Anzahl an Patienten unter Risiko:

297	269	242	226	207	190	179	158	138	125	115	111	99	78	67	50	39	29	11	2	1	0	Acala+BR
297	262	233	198	179	167	153	137	119	105	97	92	80	63	54	46	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.185 ECHO: Kaplan-Meier plot of time to first occurrence of $G \geq 3$ SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen
 Safety Analysis Set, DCO 15FEB2024



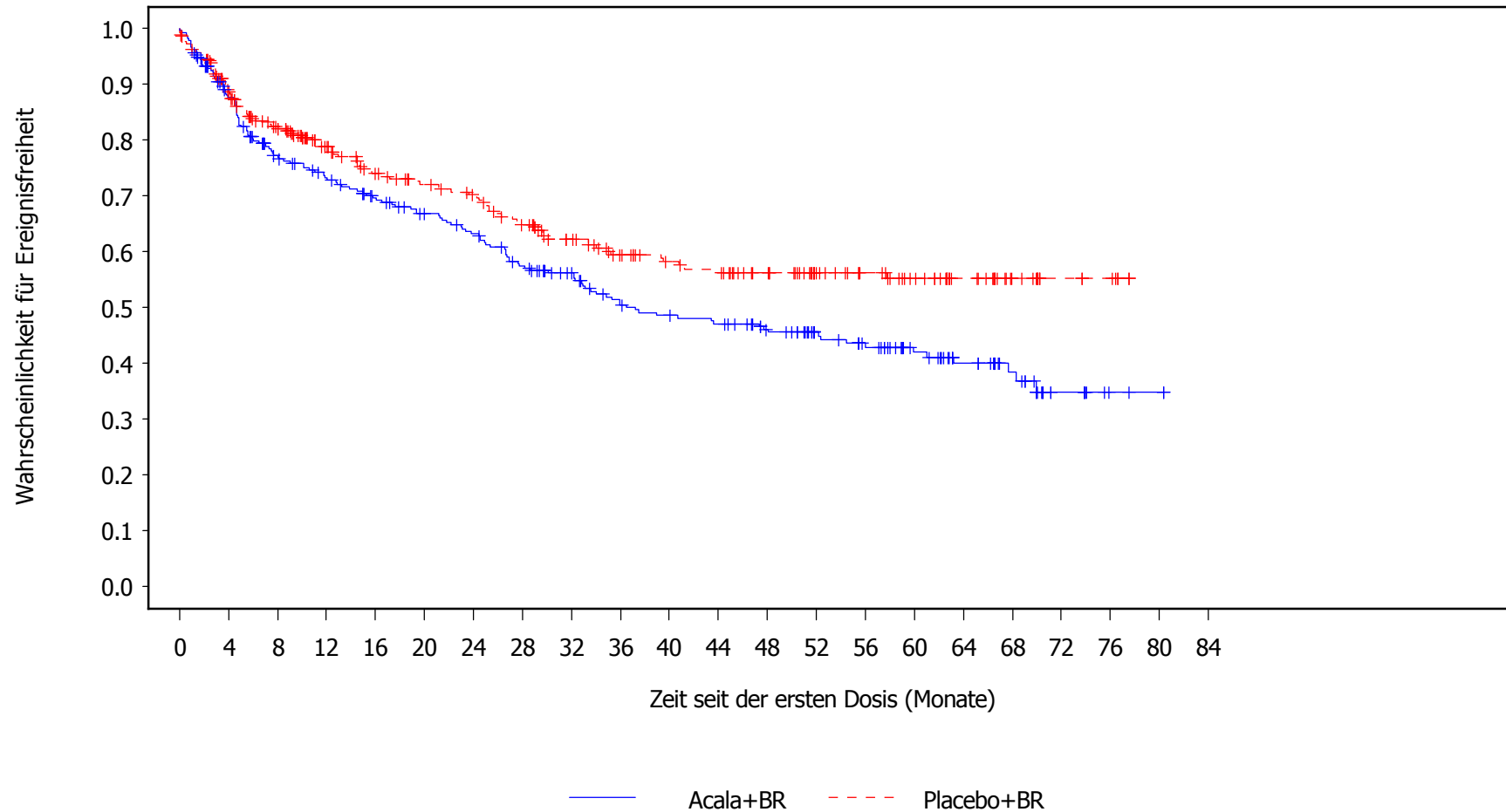
Anzahl an Patienten unter Risiko:

297	274	246	228	206	188	177	157	135	120	109	105	93	71	63	46	35	27	10	2	1	0	Acala+BR
297	261	232	198	180	167	153	138	119	104	95	91	79	63	54	46	31	17	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.186 ECHO: Kaplan-Meier plot of time to first occurrence of Therapieabbruch aufgrund von UE
 Safety Analysis Set, DC0 15FEB2024



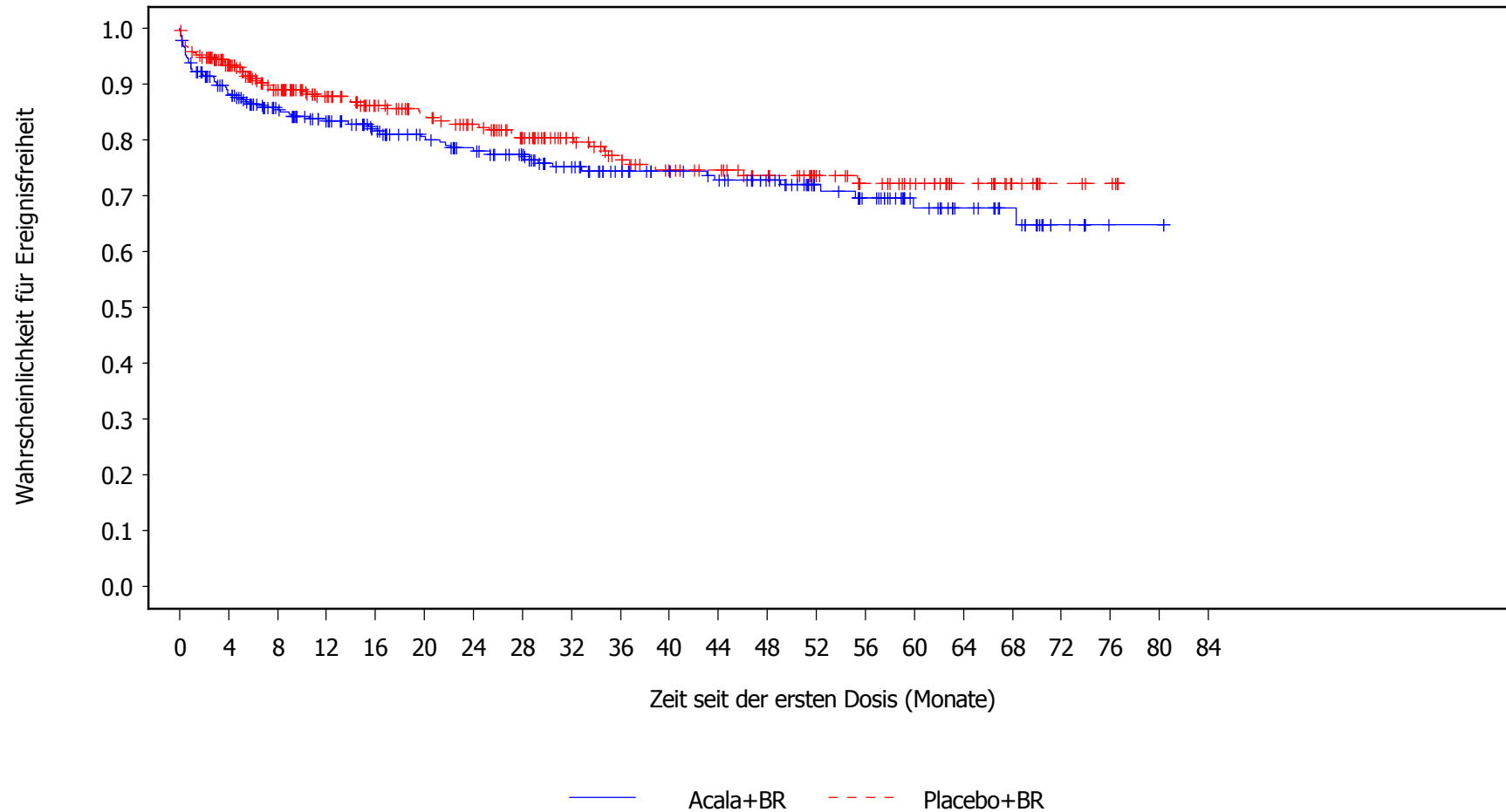
Anzahl an Patienten unter Risiko:

297	249	209	193	177	164	154	137	123	106	101	97	86	71	60	47	35	24	9	2	1	0	Acala+BR
297	250	217	185	165	154	146	131	115	101	92	88	78	62	53	44	30	17	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.187 ECHO: Kaplan-Meier plot of time to first occurrence of EKI GT: Kardiale Ereignisse
 Safety Analysis Set, DCO 15FEB2024



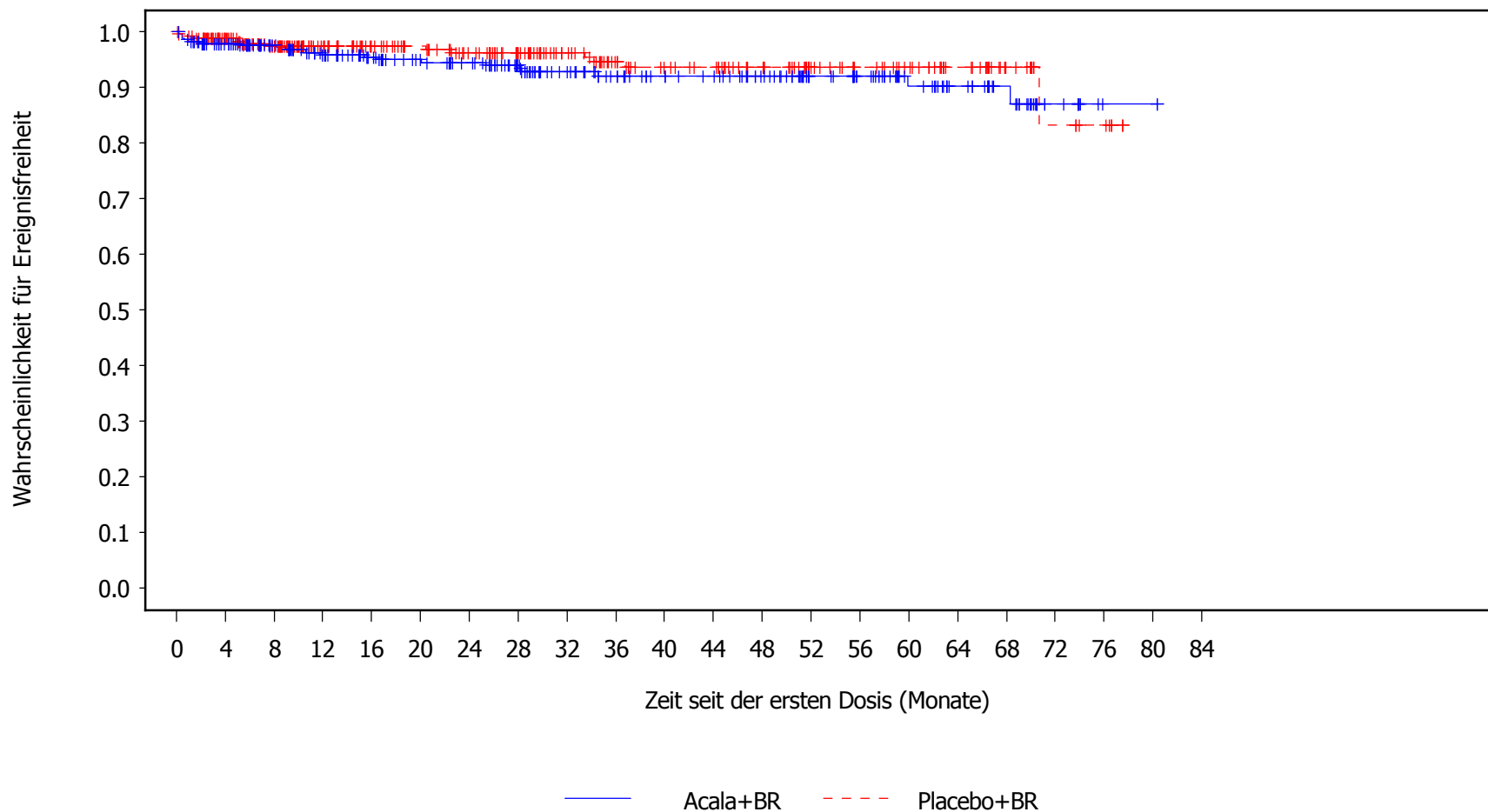
Anzahl an Patienten unter Risiko:

297	249	218	198	177	162	149	136	118	105	97	91	82	63	53	38	29	22	8	1	1	0	Acala+BR
297	253	216	187	166	152	140	122	104	91	82	78	70	55	46	39	26	16	6	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.188 ECHO: Kaplan-Meier plot of time to first occurrence of EKI GT: Vorhofflimmern
 Safety Analysis Set, DC0 15FEB2024



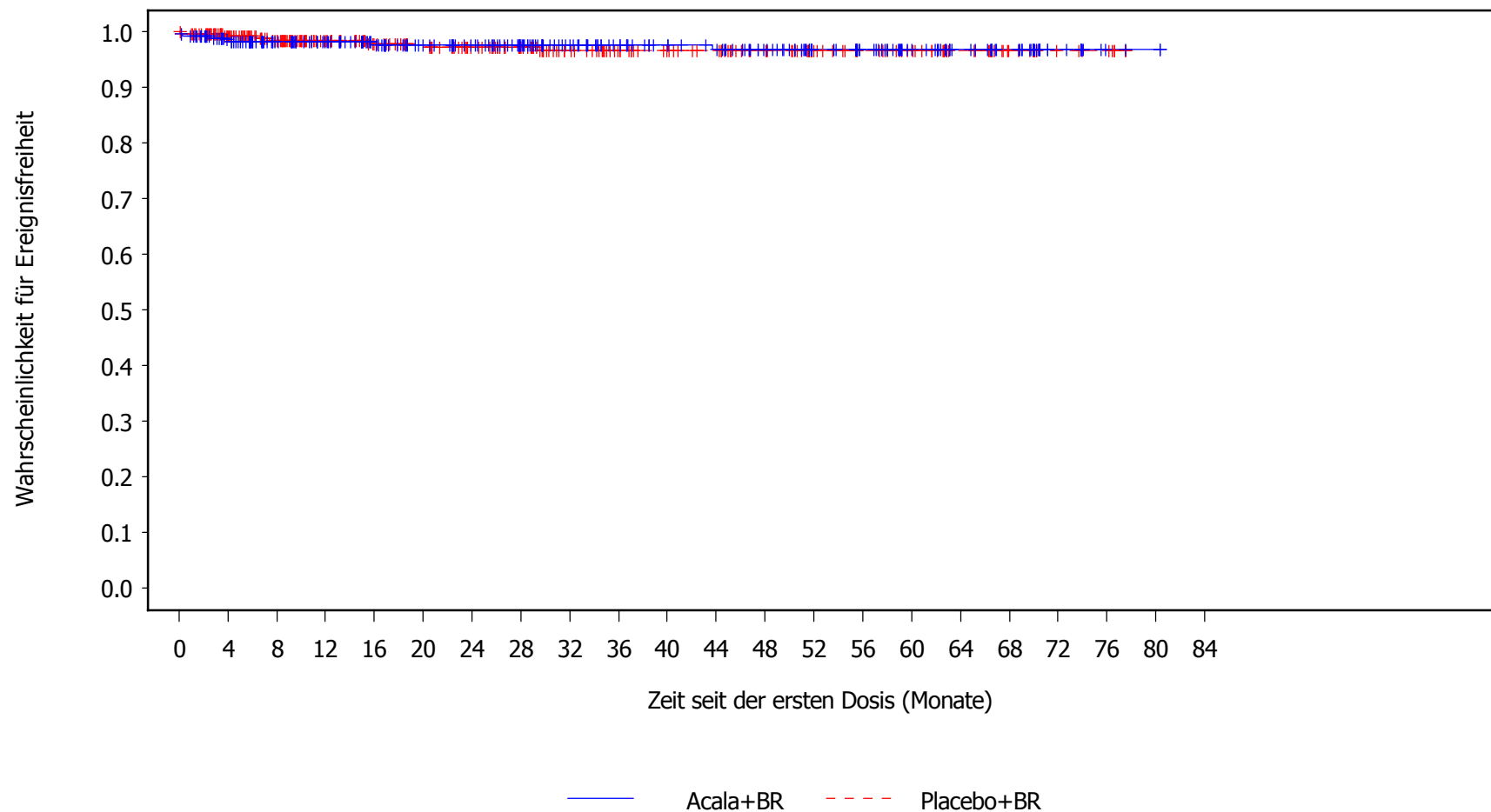
Anzahl an Patienten unter Risiko:

297	273	246	225	205	190	180	158	137	123	113	109	98	78	67	50	39	28	10	1	1	0	Acala+BR
297	266	235	202	183	171	157	141	122	105	95	91	80	63	54	47	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.189 ECHO: Kaplan-Meier plot of time to first occurrence of EKI GT: Ventrikuläre Tachyarrhythmie
 Safety Analysis Set, DCO 15FEB2024



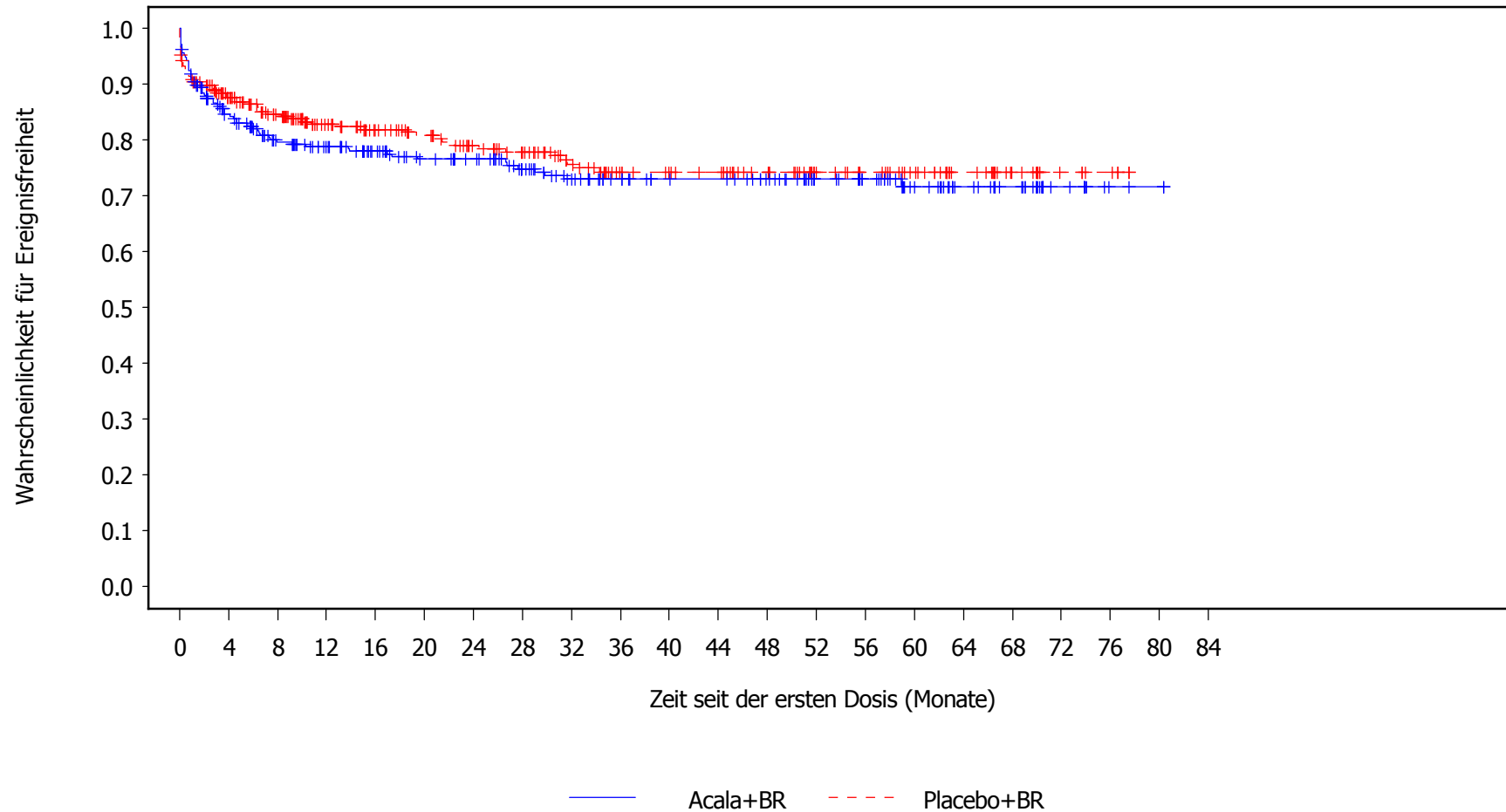
Anzahl an Patienten unter Risiko:

297	272	244	227	207	189	178	159	139	124	114	109	97	77	66	49	38	29	11	2	1	0	Acala+BR
297	266	236	201	181	168	154	138	118	105	96	91	80	63	54	46	31	18	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.190 ECHO: Kaplan-Meier plot of time to first occurrence of EKI GT: Anämie
 Safety Analysis Set, DC0 15FEB2024



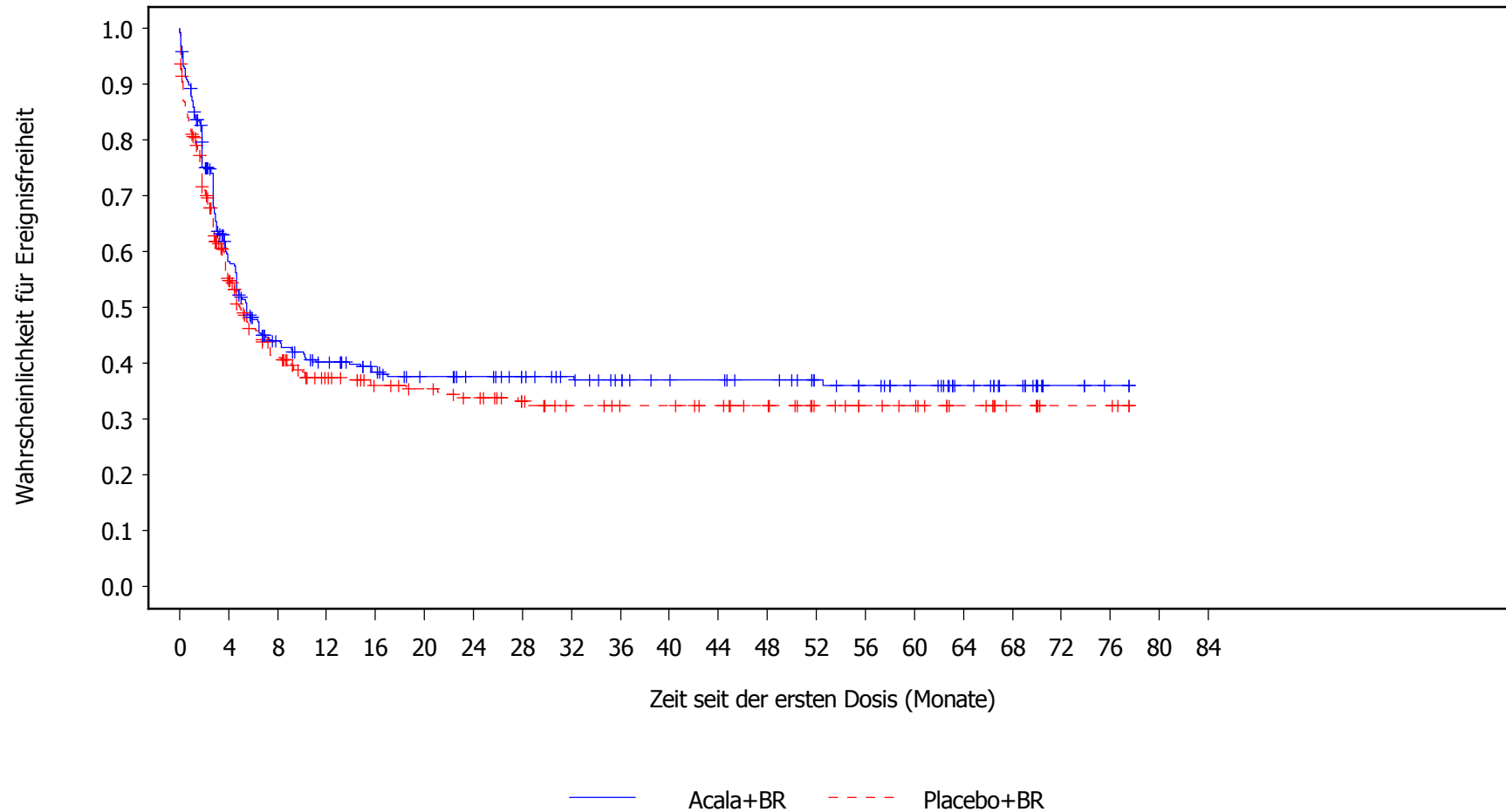
Anzahl an Patienten unter Risiko:

297	234	202	187	168	153	145	126	112	101	94	93	86	70	61	45	34	27	11	2	1	0	Acala+BR
297	238	209	178	160	147	132	122	104	90	85	82	72	57	50	42	29	17	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.191 ECH0: Kaplan-Meier plot of time to first occurrence of EKI GT: Leukopenie
 Safety Analysis Set, DCO 15FEB2024



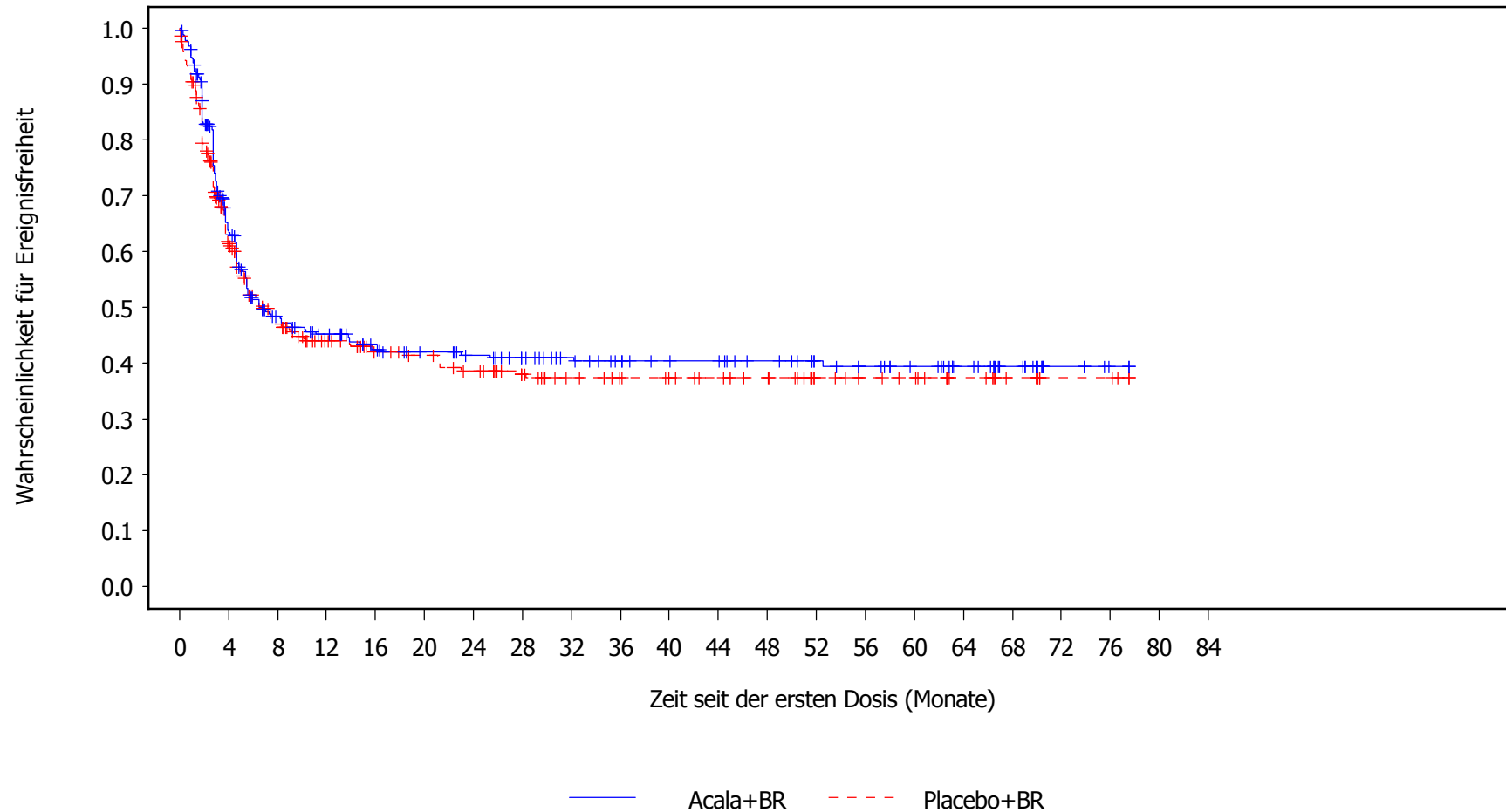
Anzahl an Patienten unter Risiko:

297	158	110	96	84	76	72	66	61	55	51	50	47	40	36	31	22	16	4	1	0	0	Acala+BR
297	148	100	80	69	65	59	50	44	41	41	38	34	27	23	21	14	9	3	3	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.192 ECHO: Kaplan-Meier plot of time to first occurrence of EKI GT: Neutropenie
 Safety Analysis Set, DCO 15FEB2024



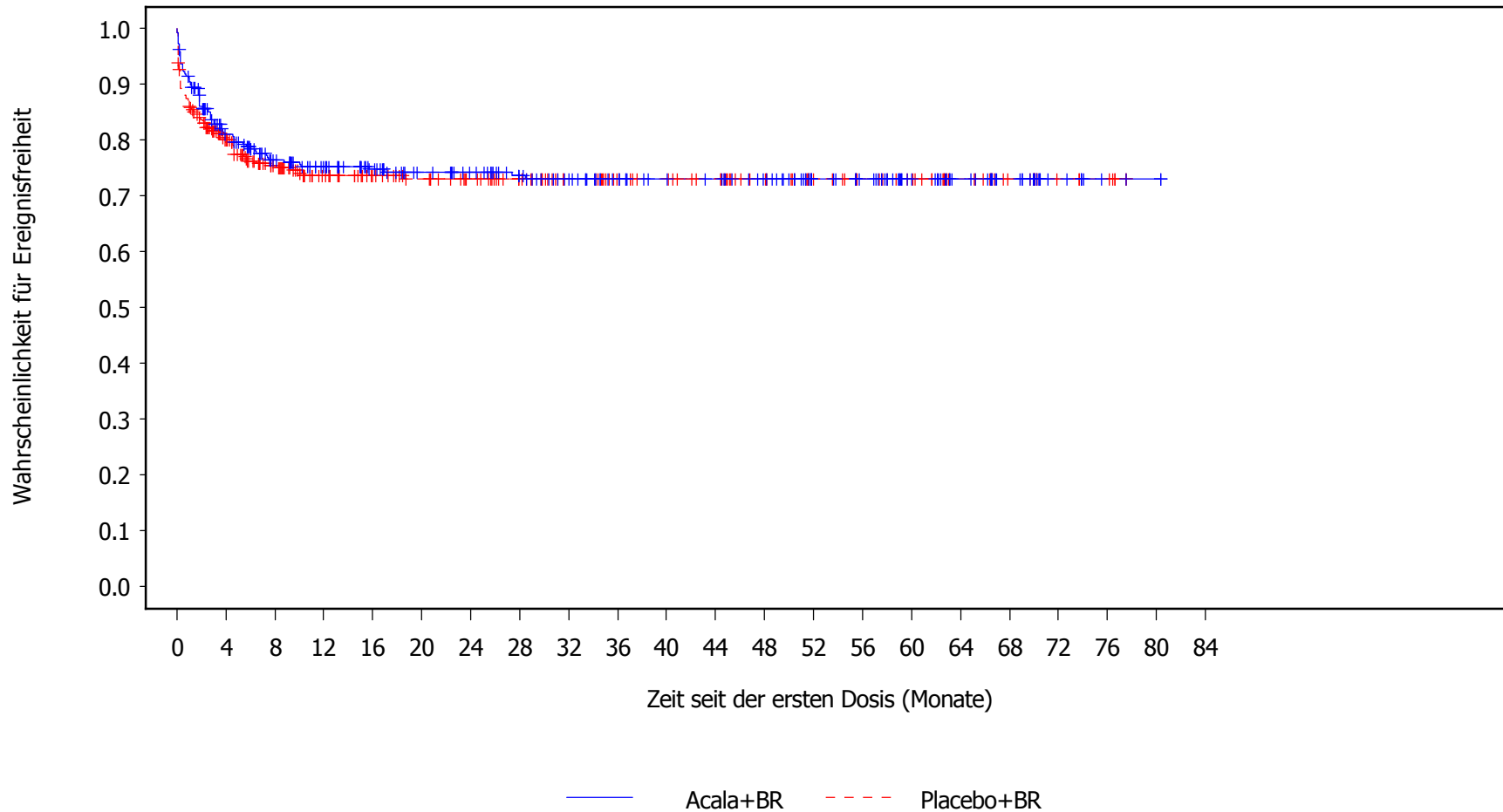
Anzahl an Patienten unter Risiko:

297	174	120	107	93	86	81	74	67	61	57	56	51	44	39	34	25	17	5	1	0	0	Acala+BR
297	166	115	94	81	77	69	59	51	47	44	41	37	27	23	21	14	9	3	3	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.193 ECHO: Kaplan-Meier plot of time to first occurrence of EKI GT: Andere Leukopenie
 Safety Analysis Set, DC0 15FEB2024



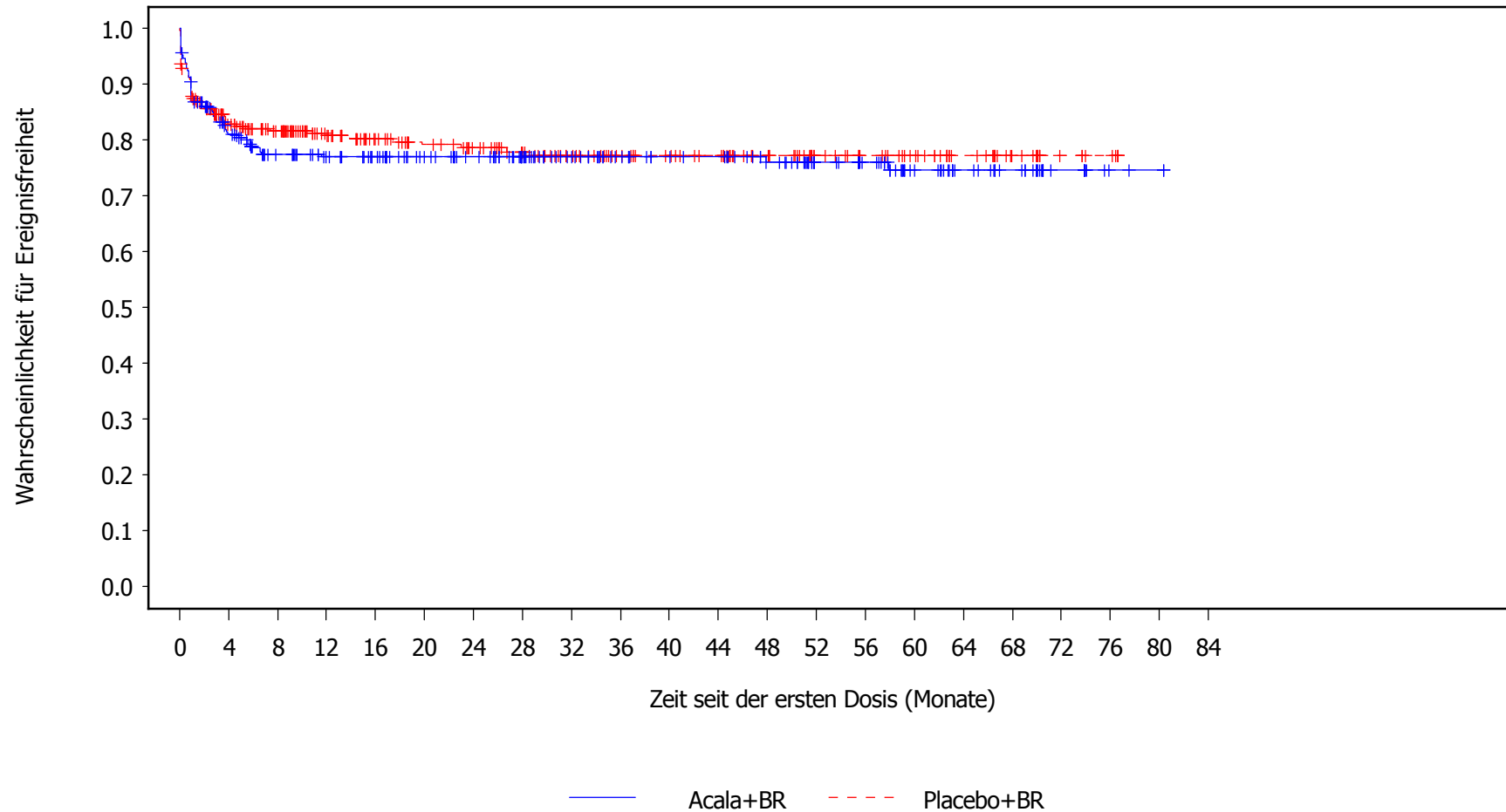
Anzahl an Patienten unter Risiko:

297	221	190	173	157	143	135	121	111	99	92	90	83	65	58	41	31	22	8	2	1	0	Acala+BR
297	214	176	152	137	127	118	106	92	83	79	74	64	53	46	41	28	17	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.194 ECHO: Kaplan-Meier plot of time to first occurrence of EKI GT: Thrombozytopenie
 Safety Analysis Set, DCO 15FEB2024



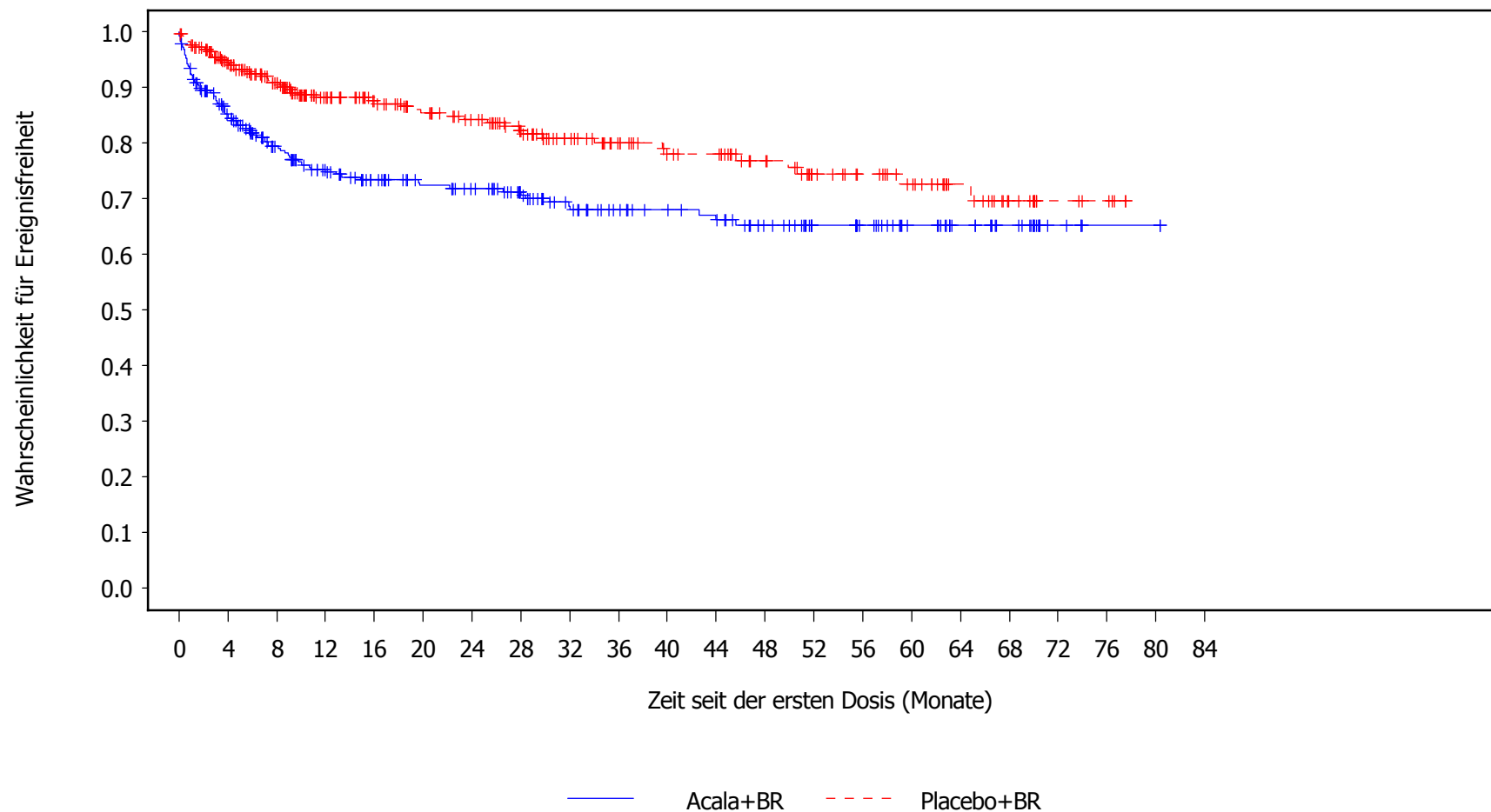
Anzahl an Patienten unter Risiko:

297	226	198	185	174	158	150	134	119	106	99	97	87	69	60	42	32	25	10	2	1	0	Acala+BR
297	224	201	172	152	139	130	117	103	92	86	81	70	55	48	41	28	17	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.195 ECHO: Kaplan-Meier plot of time to first occurrence of EKI GT: Blutung
 Safety Analysis Set, DCO 15FEB2024



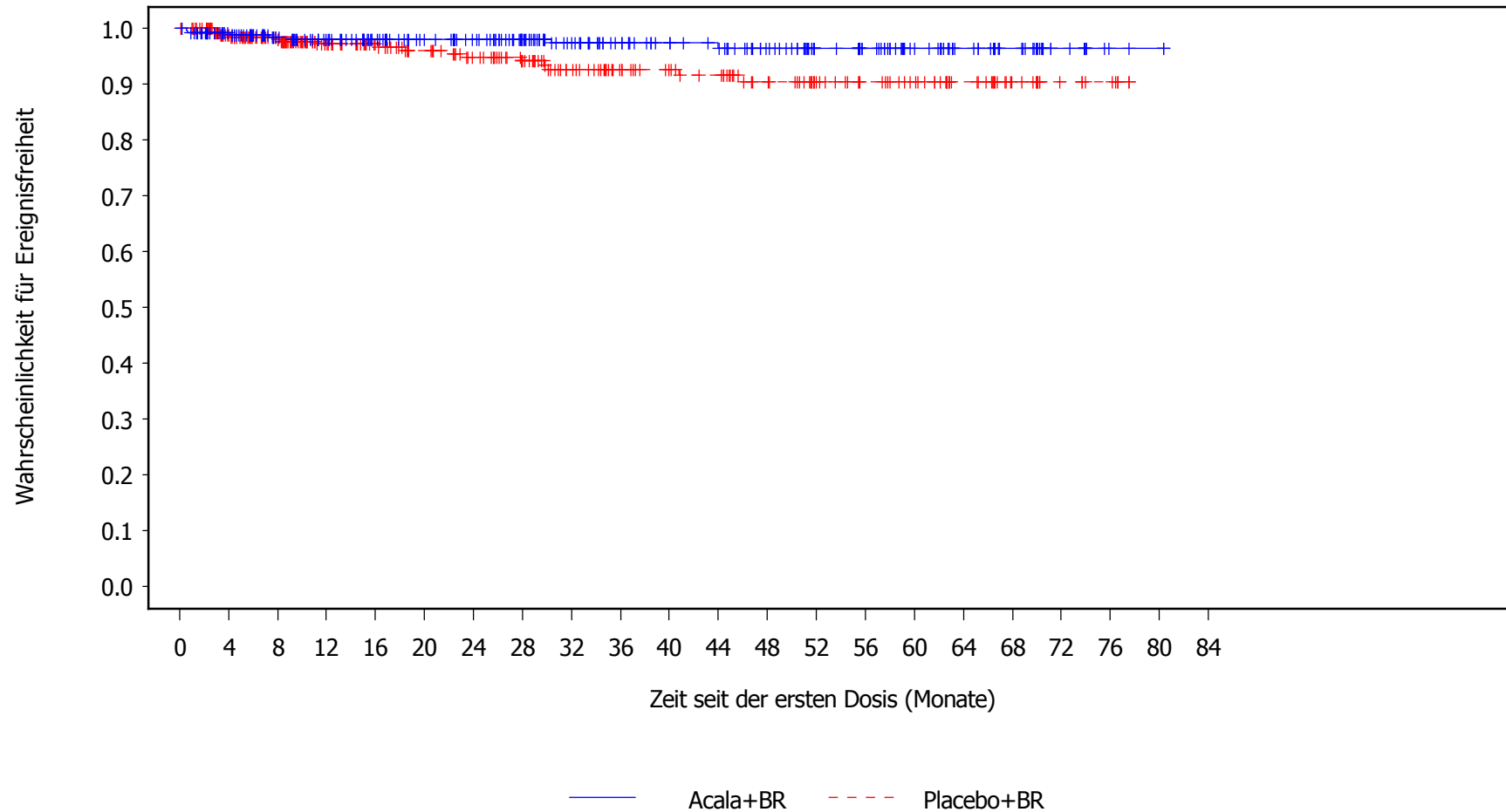
Anzahl an Patienten unter Risiko:

297	234	194	169	152	139	132	115	98	86	80	76	65	52	45	35	26	19	5	1	1	0	Acala+BR
297	254	220	181	164	149	137	119	101	89	79	77	65	52	46	39	25	15	6	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.196 ECH0: Kaplan-Meier plot of time to first occurrence of EKI GT: Schwere Blutung
 Safety Analysis Set, DC0 15FEB2024



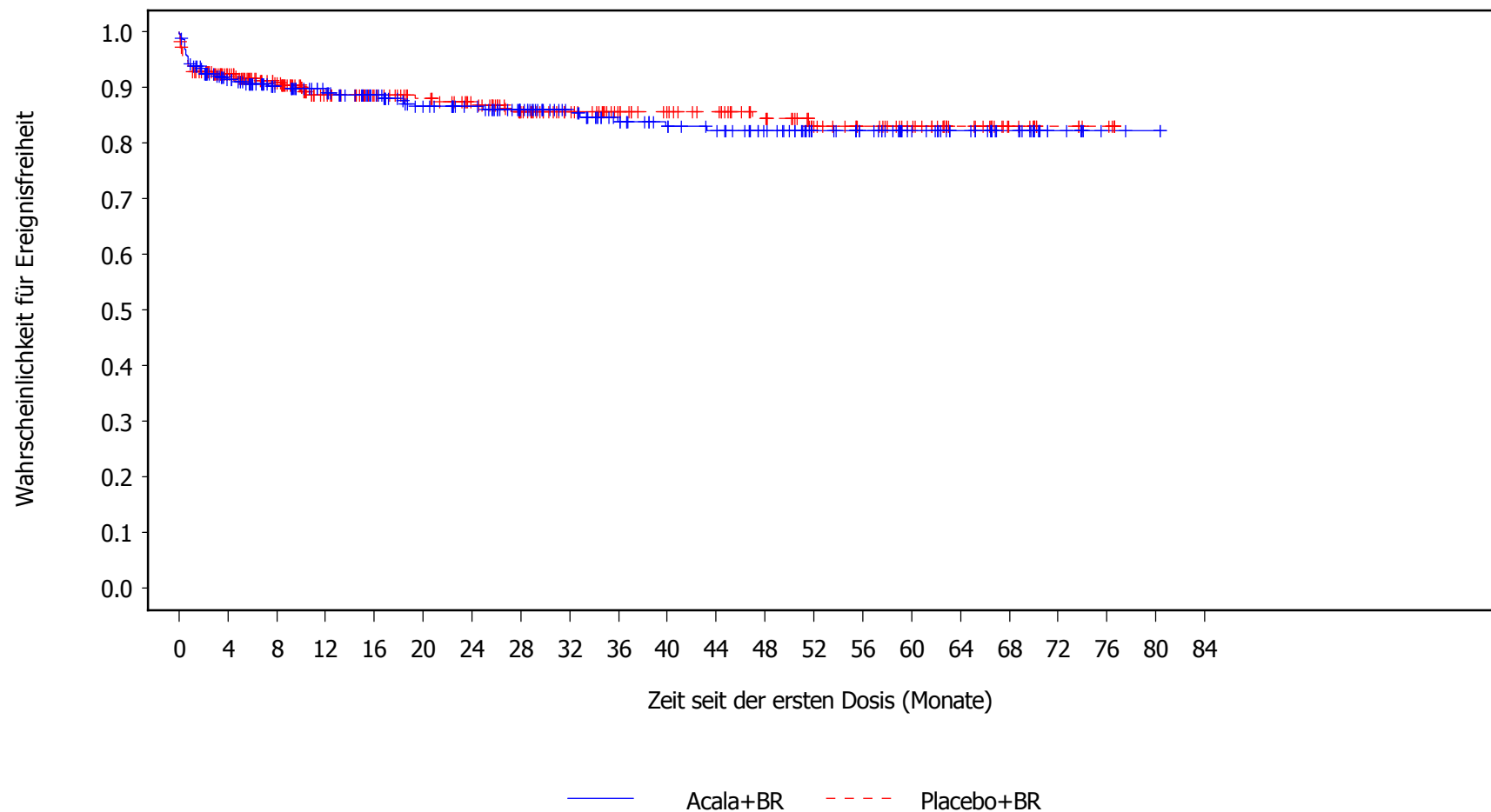
Anzahl an Patienten unter Risiko:

297	273	244	226	206	190	180	159	138	123	113	108	96	76	66	50	39	28	11	2	1	0	Acala+BR
297	266	236	199	180	166	152	136	115	101	93	88	75	62	53	46	31	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.197 ECH0: Kaplan-Meier plot of time to first occurrence of EKI GT: Hepatotoxizität
 Safety Analysis Set, DCO 15FEB2024



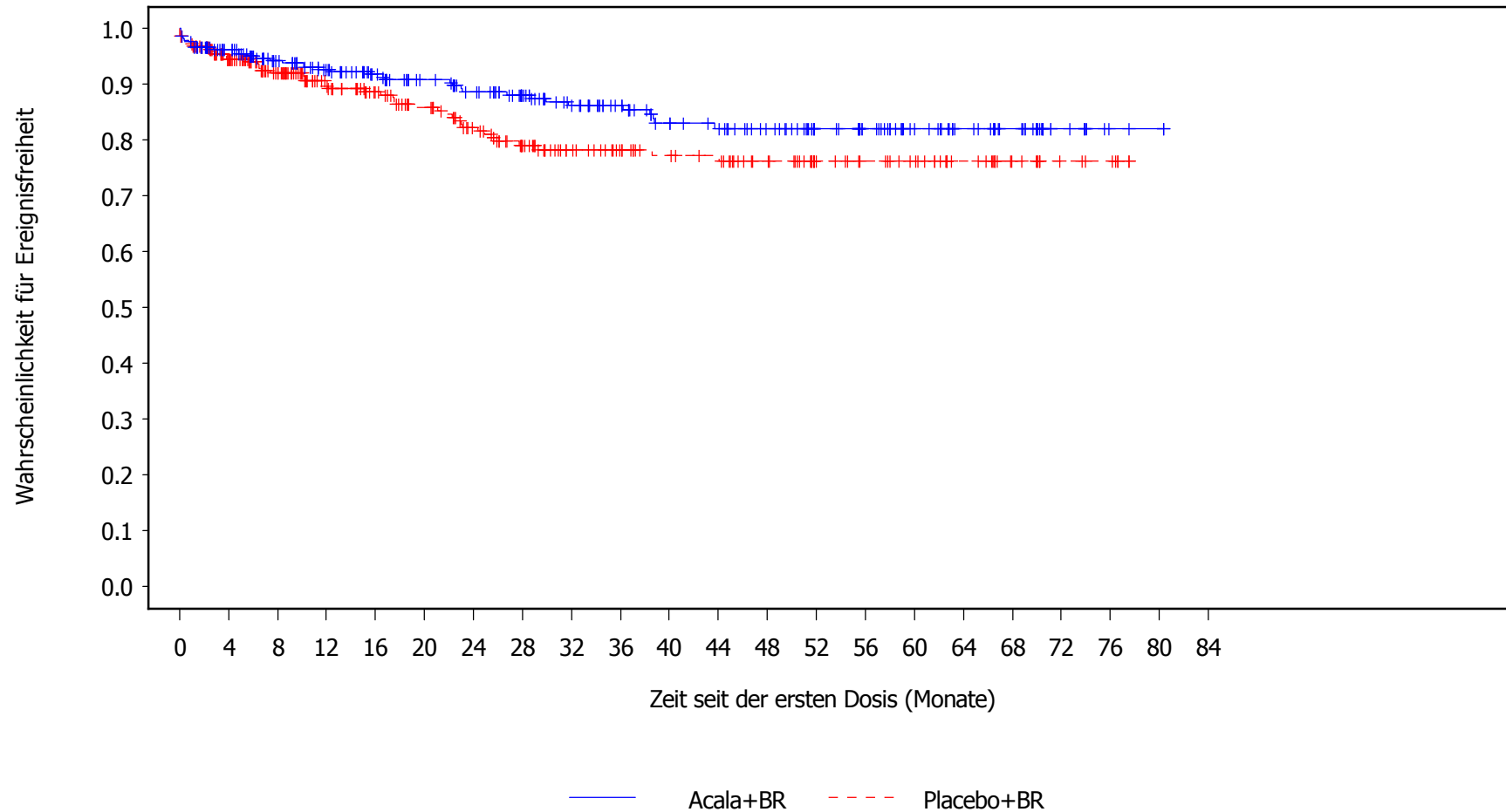
Anzahl an Patienten unter Risiko:

297	250	223	208	188	169	160	142	126	111	101	96	86	69	60	46	37	26	10	2	1	0	Acala+BR
297	248	219	185	167	156	143	125	109	96	88	83	72	57	49	41	27	15	7	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.198 ECH0: Kaplan-Meier plot of time to first occurrence of EKI GT: Hypertonie
 Safety Analysis Set, DCO 15FEB2024



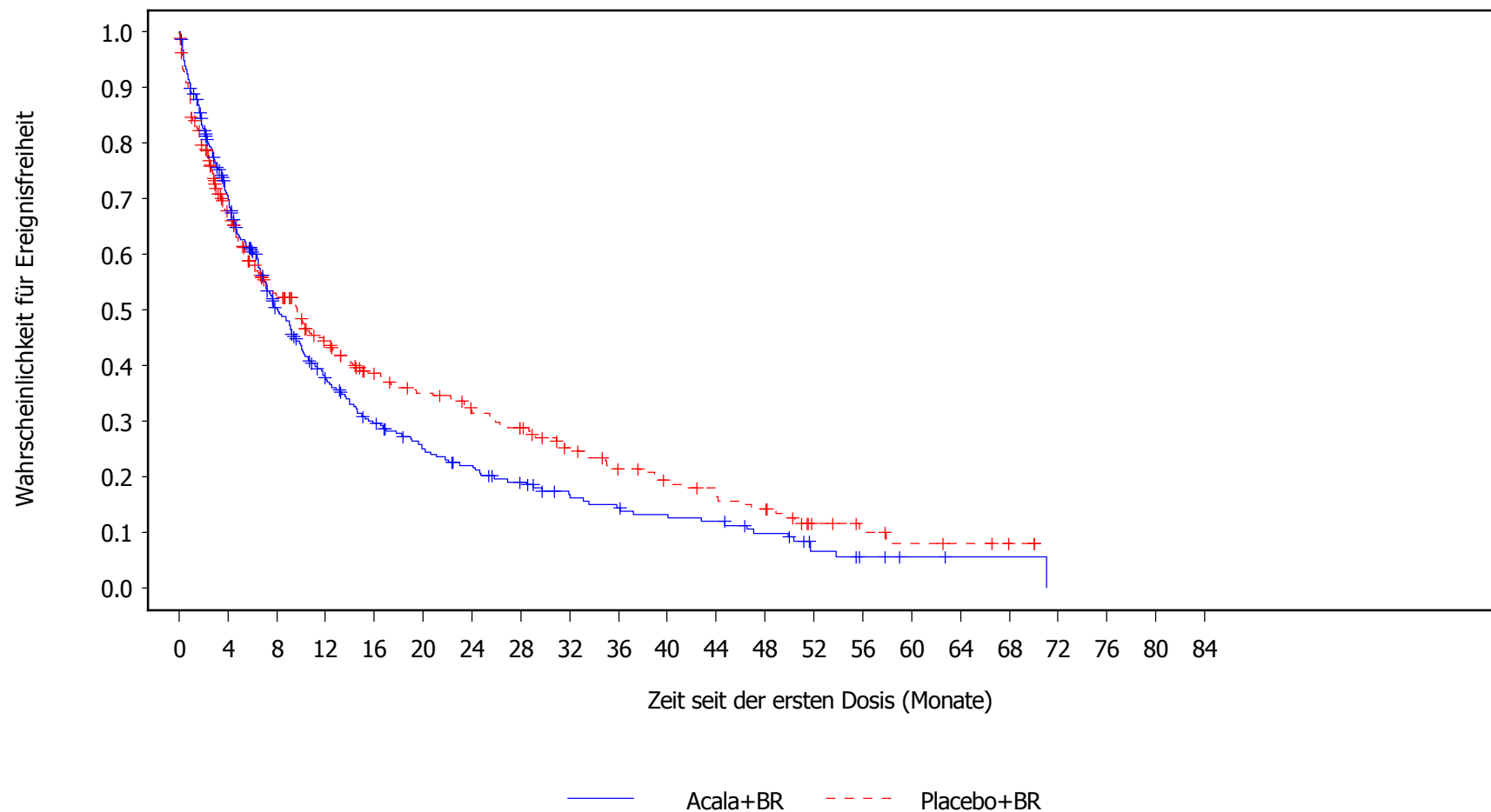
Anzahl an Patienten unter Risiko:

297	265	234	214	193	177	164	146	129	115	101	96	86	70	59	45	35	26	9	2	1	0	Acala+BR
297	253	221	188	167	150	131	112	94	84	76	73	62	47	41	36	25	15	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.199 ECHO: Kaplan-Meier plot of time to first occurrence of EKI GT: Infektionen
 Safety Analysis Set, DC0 15FEB2024



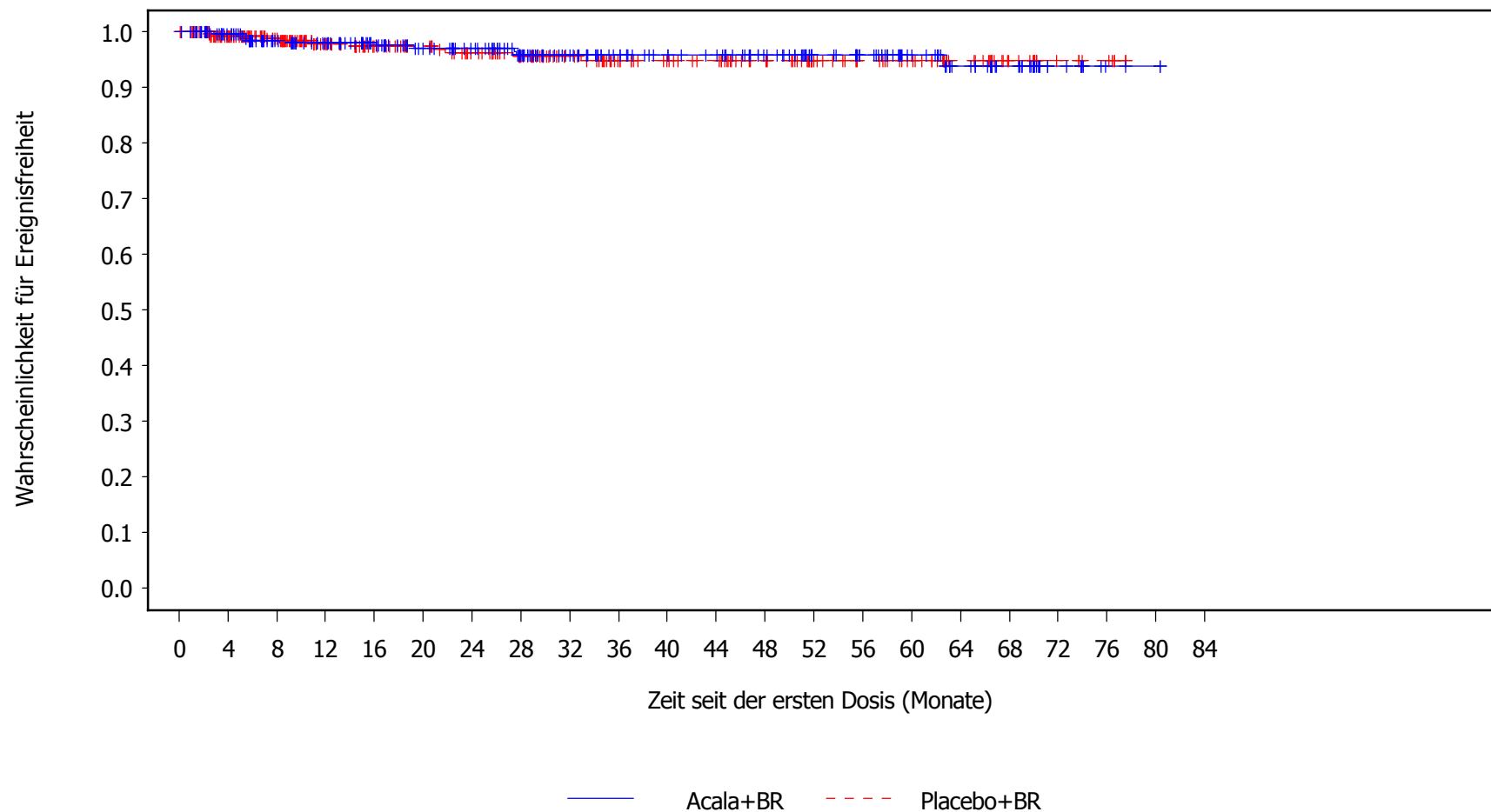
Anzahl an Patienten unter Risiko:

297	196	127	89	67	53	45	36	28	24	21	19	14	7	4	2	1	1	0	0	0	0	Acala+BR
297	184	131	101	79	69	59	52	41	32	27	22	19	9	6	4	3	1	0	0	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.200 ECHO: Kaplan-Meier plot of time to first occurrence of EKI GT: Interstitielle Lungenerkrankung/Pneumonitis
 Safety Analysis Set, DC0 15FEB2024



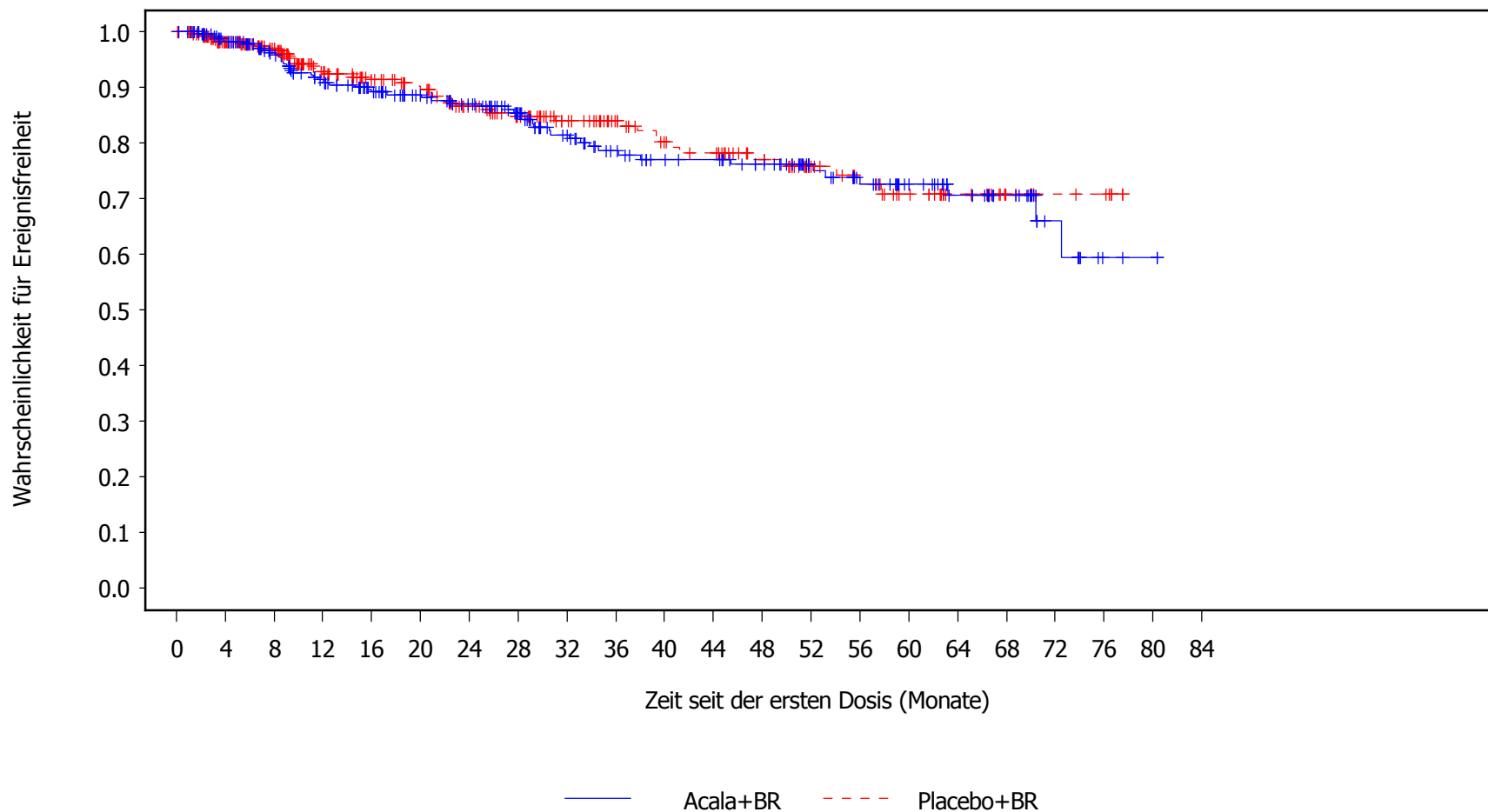
Anzahl an Patienten unter Risiko:

297	275	245	229	209	190	179	157	138	124	115	111	99	79	68	51	39	28	11	2	1	0	Acala+BR
297	266	236	201	181	169	155	139	120	106	98	93	81	64	55	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.201 ECHO: Kaplan-Meier plot of time to first occurrence of EKI GT: Zweiter Primärtumor
 Safety Analysis Set, DCO 15FEB2024



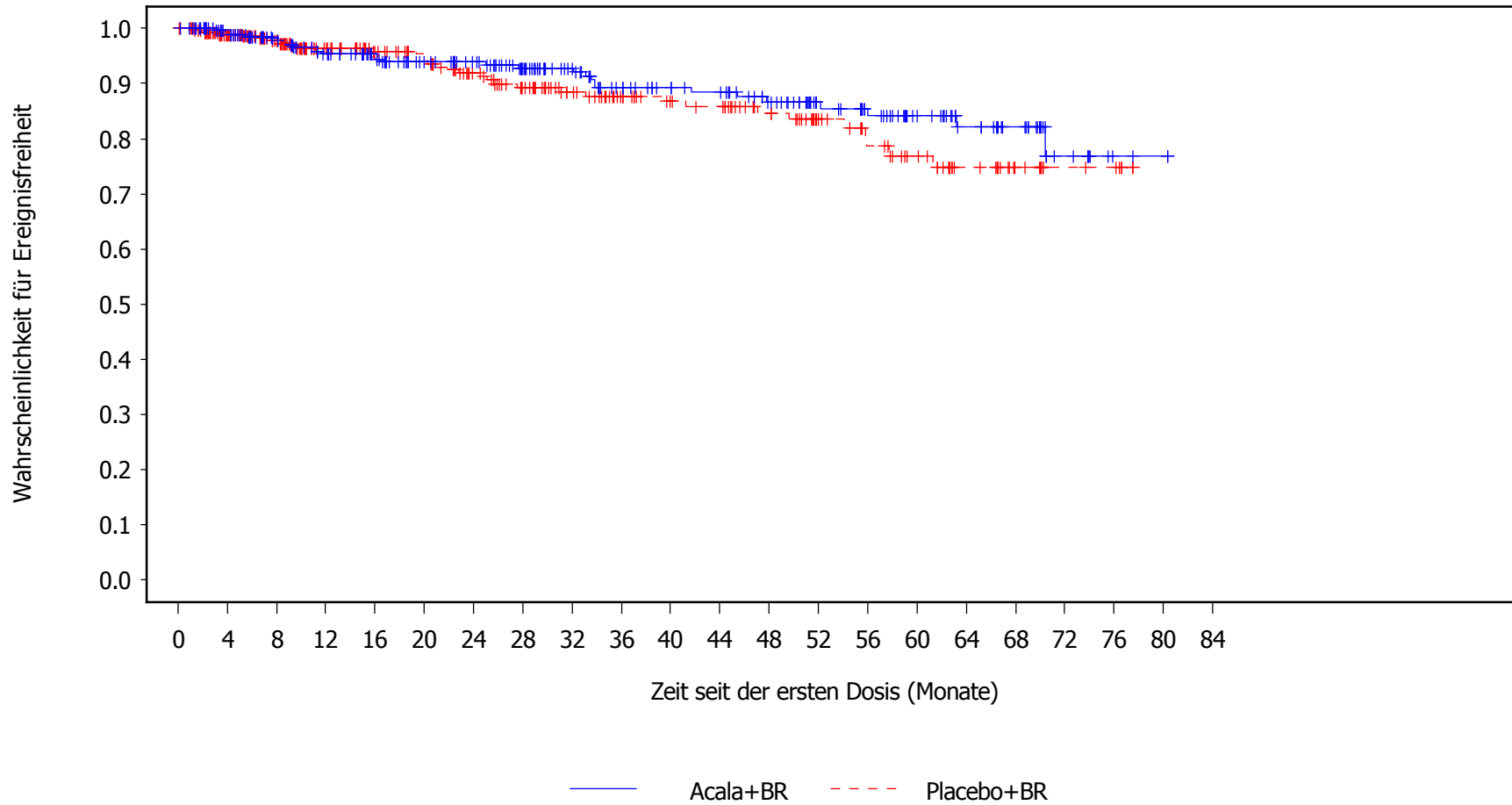
Anzahl an Patienten unter Risiko:

297	272	241	216	193	175	162	140	118	103	94	92	84	67	57	46	35	25	10	2	1	0	Acala+BR
297	263	231	191	171	158	140	125	107	94	82	78	66	51	42	34	23	14	6	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.202 ECHO: Kaplan-Meier plot of time to first occurrence of EKI GT: Zweiter Primärtumor - ausgenommen
 nicht-melanotischer Hautkrebs
 Safety Analysis Set, DCO 15FEB2024



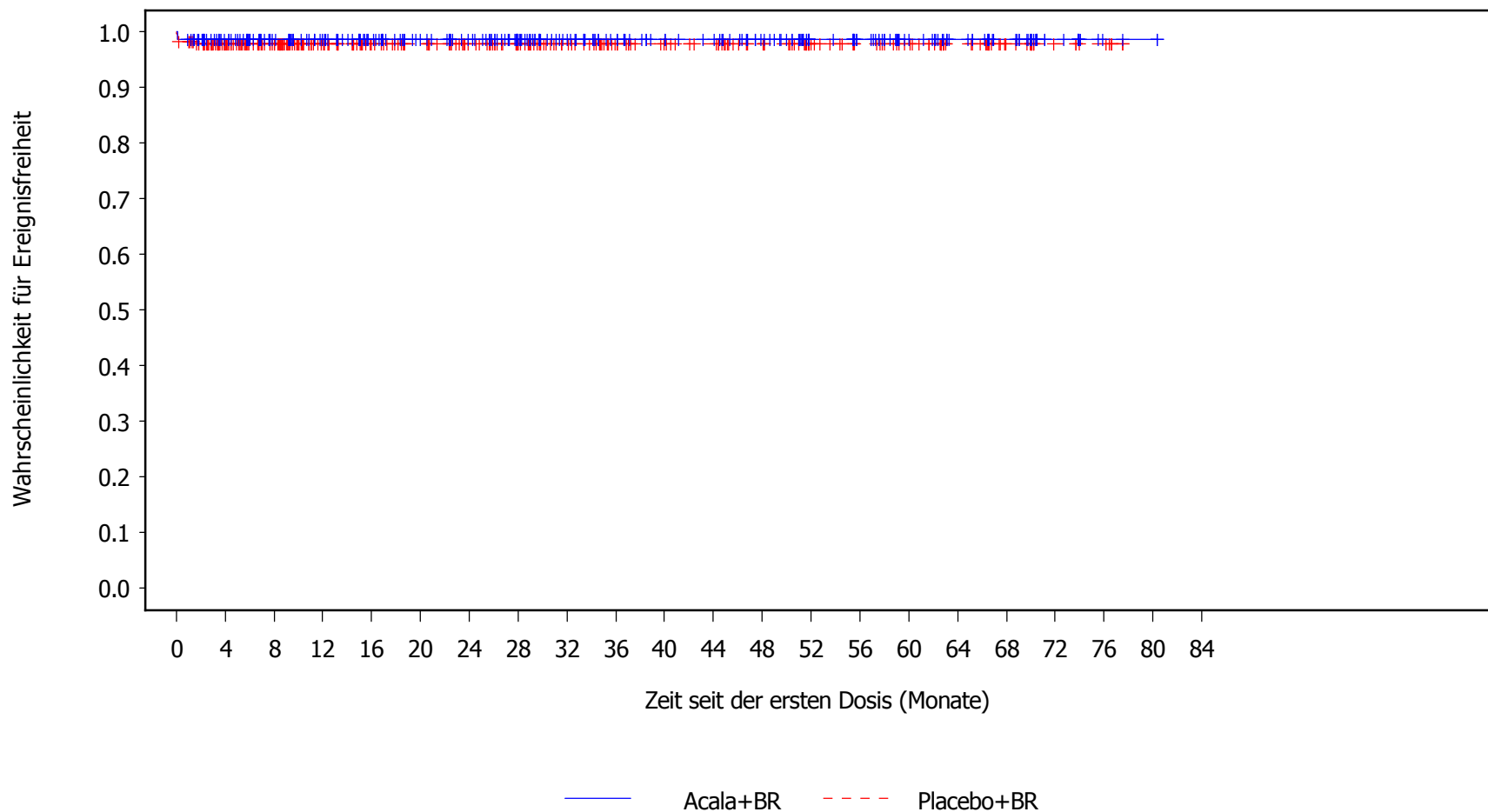
Anzahl an Patienten unter Risiko:

297	274	246	225	205	187	176	155	136	119	111	107	95	76	63	50	38	28	11	2	1	0	Acala+BR
297	265	233	199	179	167	148	131	113	99	89	86	74	57	47	39	25	15	6	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.203 ECHO: Kaplan-Meier plot of time to first occurrence of EKI GT: Tumorlysesyndrom
 Safety Analysis Set, DC0 15FEB2024



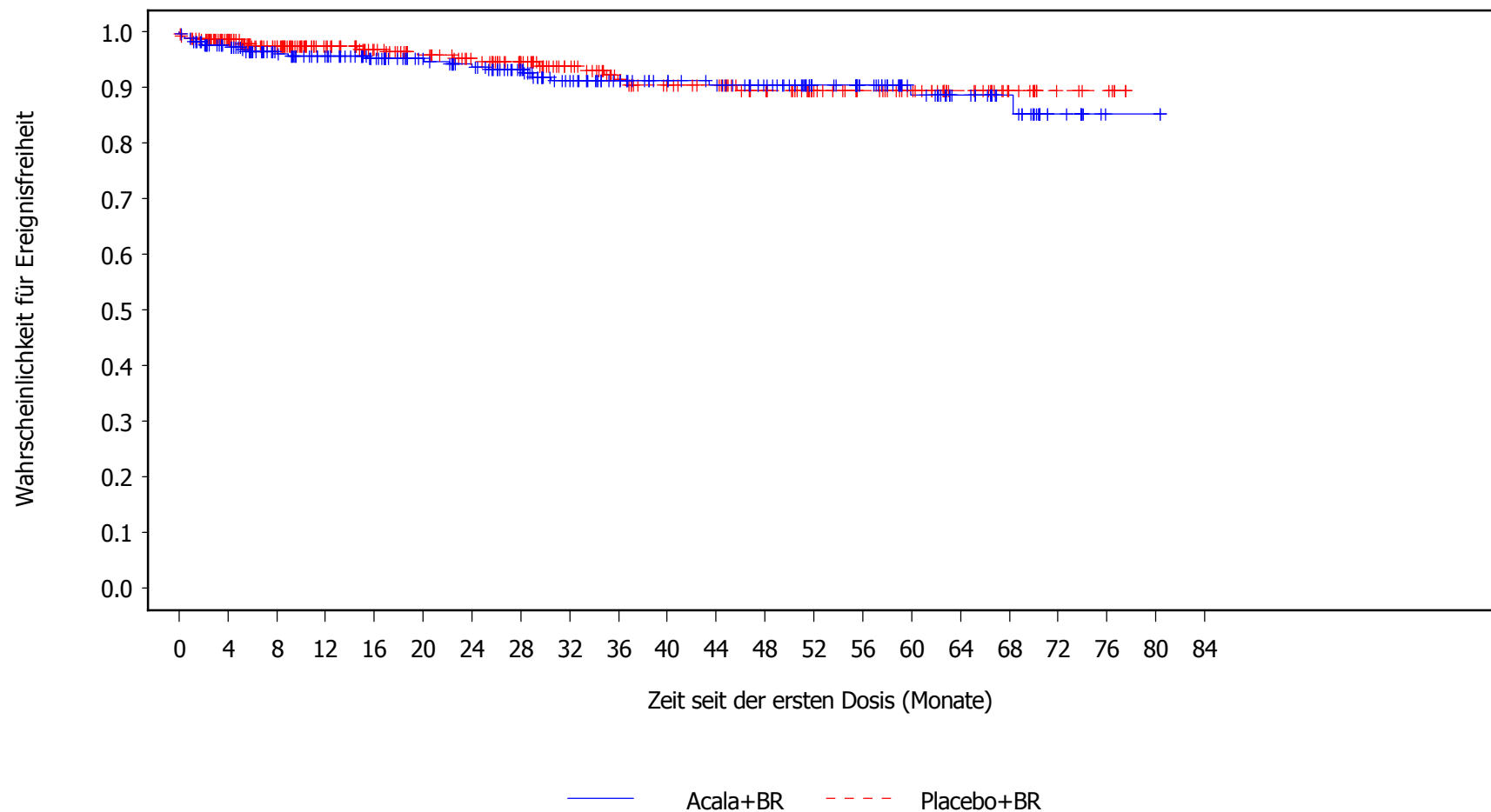
Anzahl an Patienten unter Risiko:

297	272	246	229	209	192	181	160	140	125	115	111	99	78	68	51	40	29	11	2	1	0	Acala+BR
297	263	236	203	184	172	158	142	123	108	99	94	82	65	56	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.204 ECHO: Kaplan-Meier plot of time to first occurrence of EKI G $\geq$ 3 GT: Kardiale Ereignisse
 Safety Analysis Set, DCO 15FEB2024



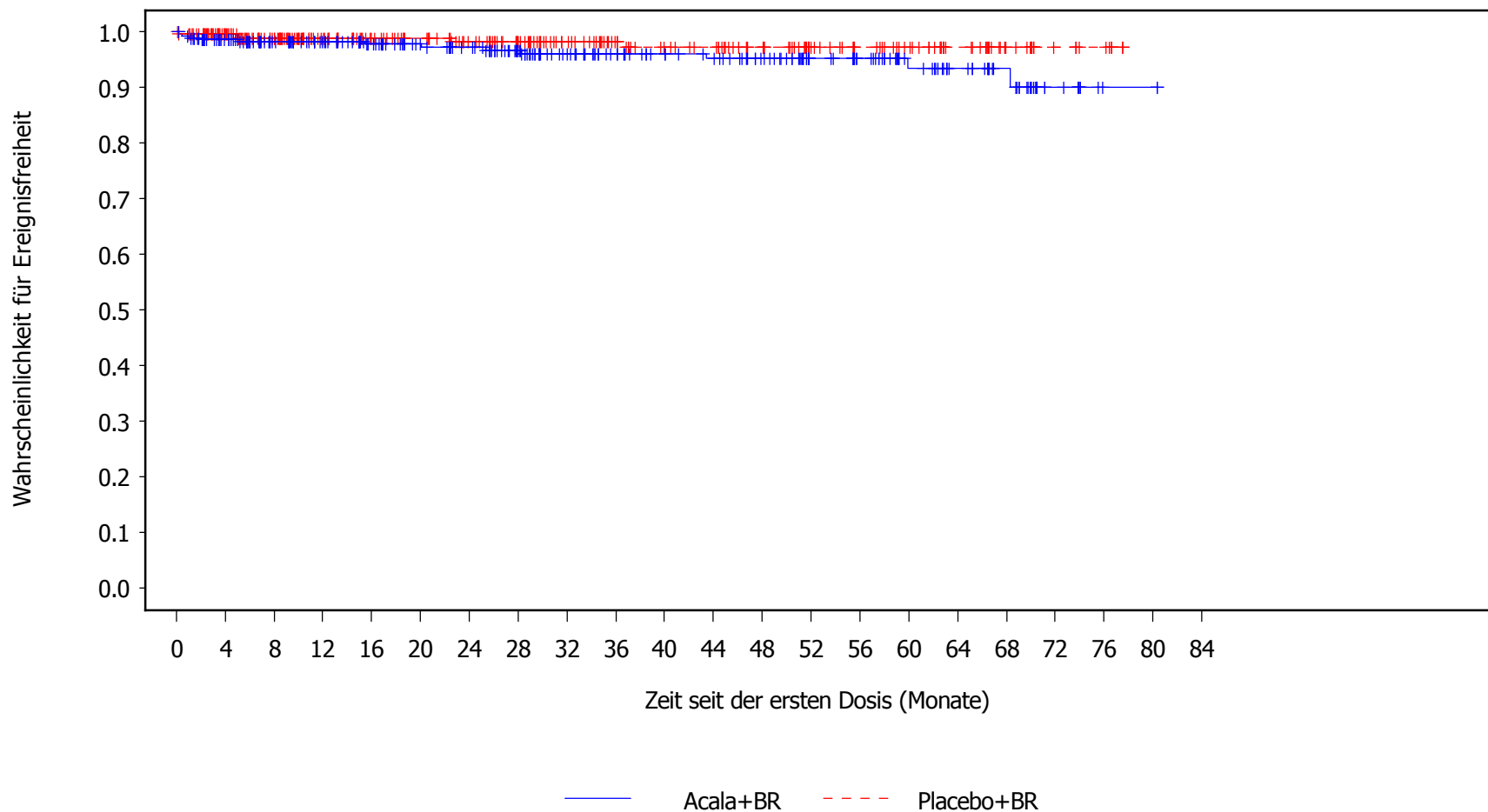
Anzahl an Patienten unter Risiko:

297	272	243	226	206	189	178	158	136	122	112	107	97	76	65	48	37	26	10	1	1	0	Acala+BR
297	265	234	201	182	168	156	140	120	104	94	90	79	62	53	45	31	18	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.205 ECHO: Kaplan-Meier plot of time to first occurrence of EKI G $\geq$ 3 GT: Vorhofflimmern
 Safety Analysis Set, DC0 15FEB2024



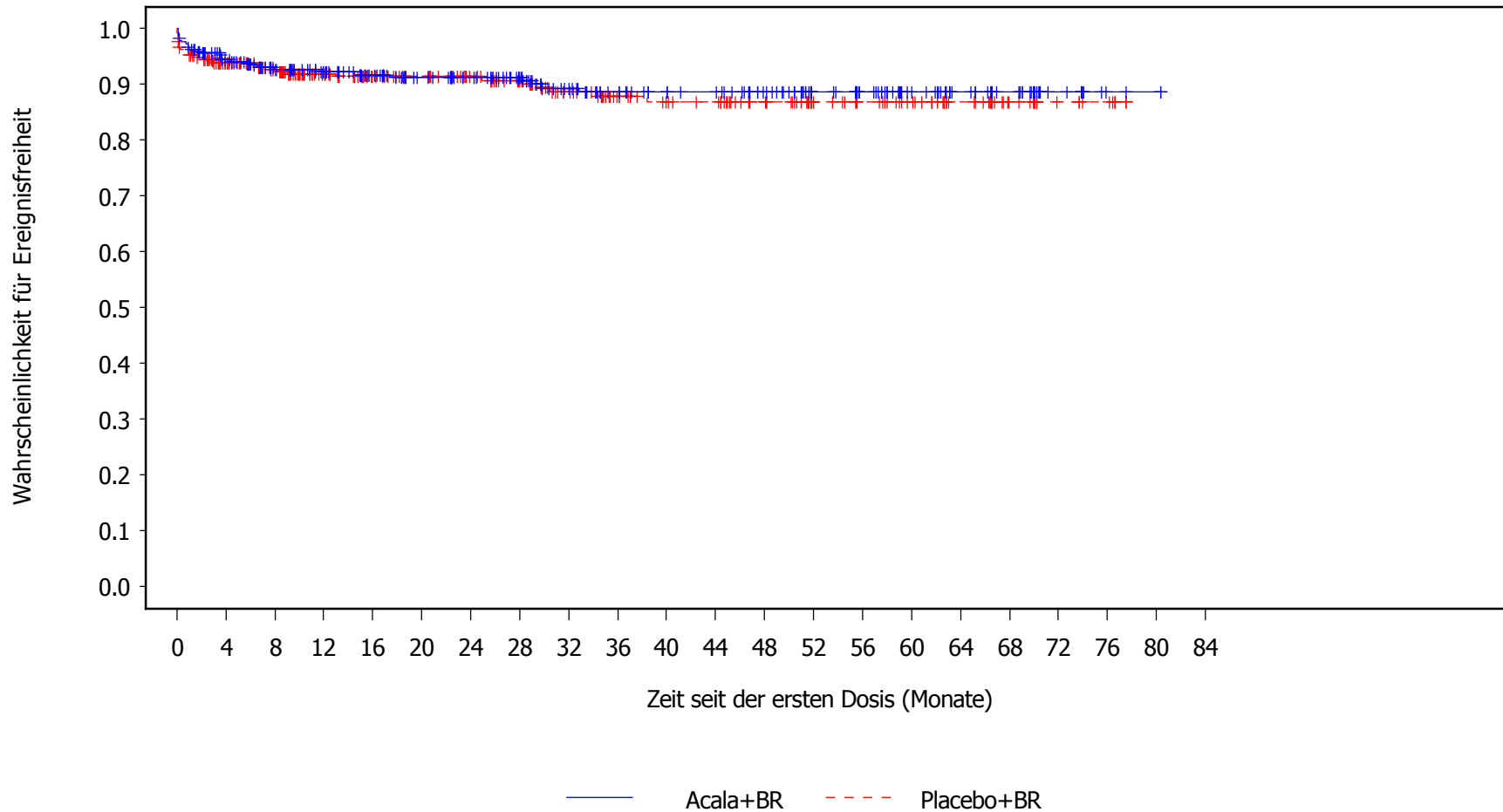
Anzahl an Patienten unter Risiko:

297	273	246	229	209	192	182	160	139	125	115	110	99	78	67	50	39	28	10	1	1	0	Acala+BR
297	266	236	202	183	171	157	141	122	107	97	93	82	65	56	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.206 ECHO: Kaplan-Meier plot of time to first occurrence of EKI G $\geq$ 3 GT: Anämie
 Safety Analysis Set, DC0 15FEB2024



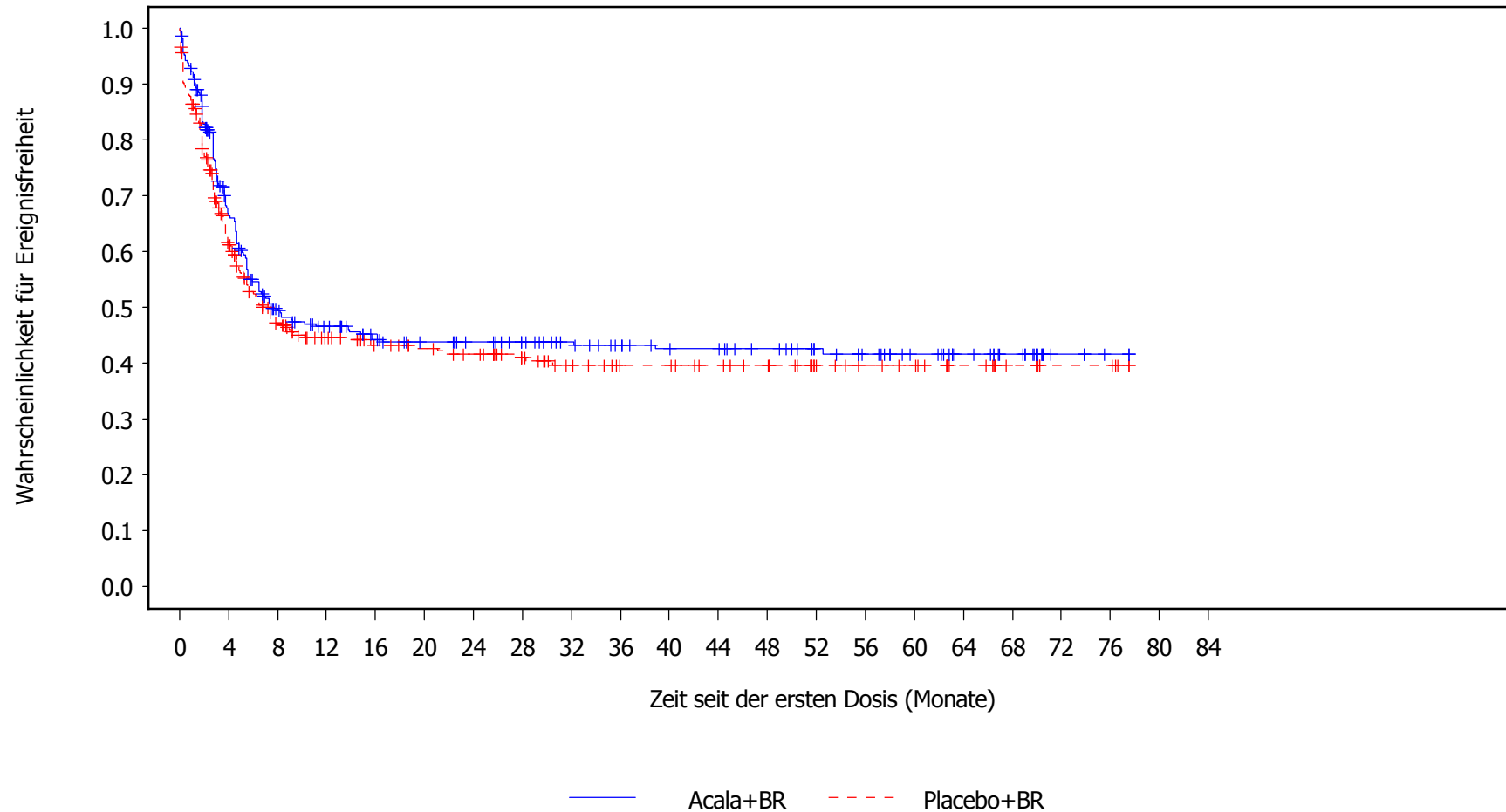
Anzahl an Patienten unter Risiko:

297	260	232	216	196	180	170	152	131	117	109	106	95	76	65	49	38	28	11	2	1	0	Acala+BR
297	254	230	197	178	166	152	137	116	100	91	88	76	60	53	45	32	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.207 ECH0: Kaplan-Meier plot of time to first occurrence of EKI G $\geq$ 3 GT: Leukopenie
 Safety Analysis Set, DC0 15FEB2024



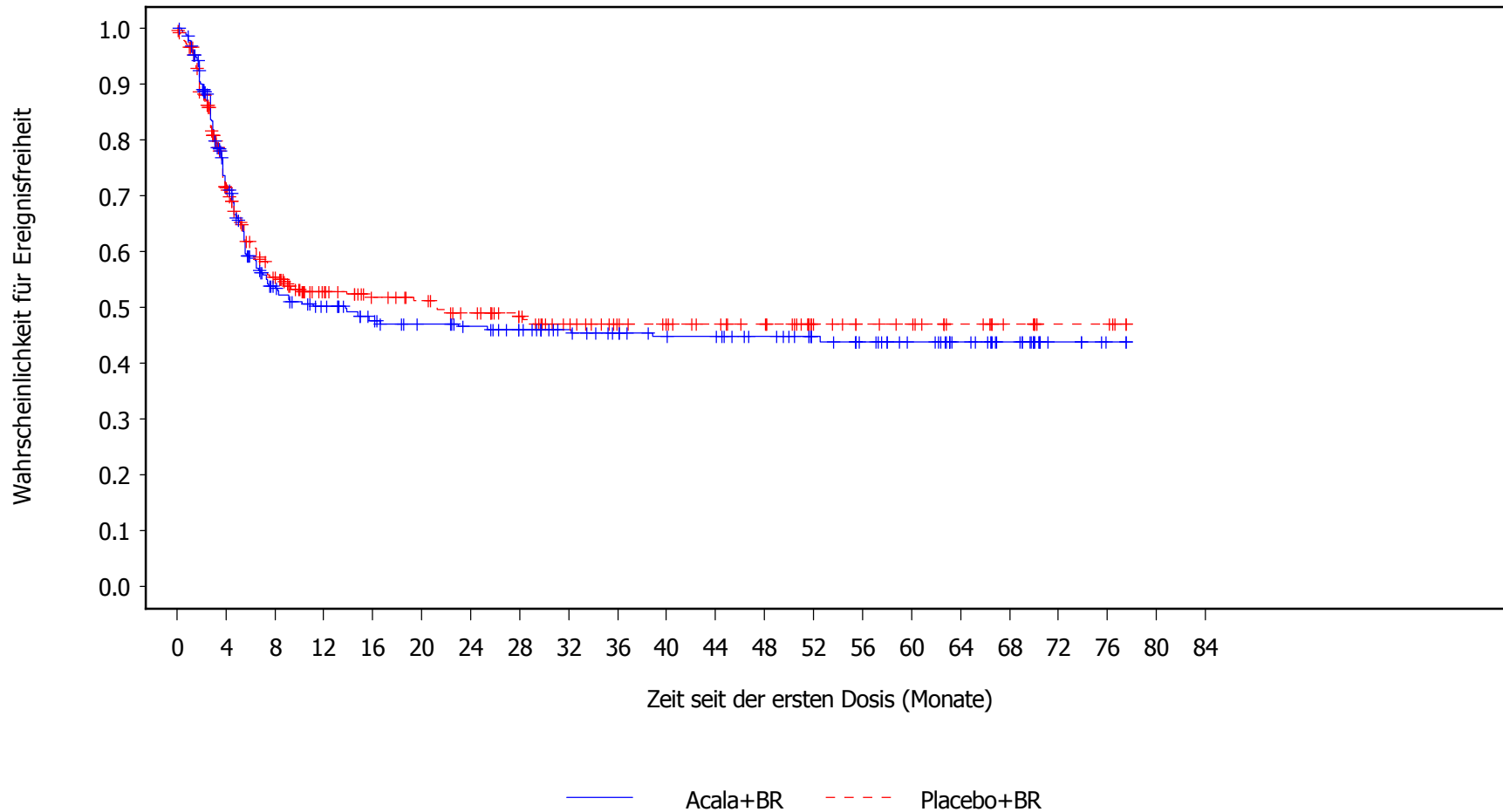
Anzahl an Patienten unter Risiko:

297	183	126	111	98	91	87	81	72	66	61	60	55	47	40	33	24	18	4	1	0	0	Acala+BR
297	166	116	97	86	81	76	65	56	50	50	46	42	31	26	24	16	10	4	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.208 ECHO: Kaplan-Meier plot of time to first occurrence of EKI $G \geq 3$ GT: Neutropenie
 Safety Analysis Set, DC0 15FEB2024



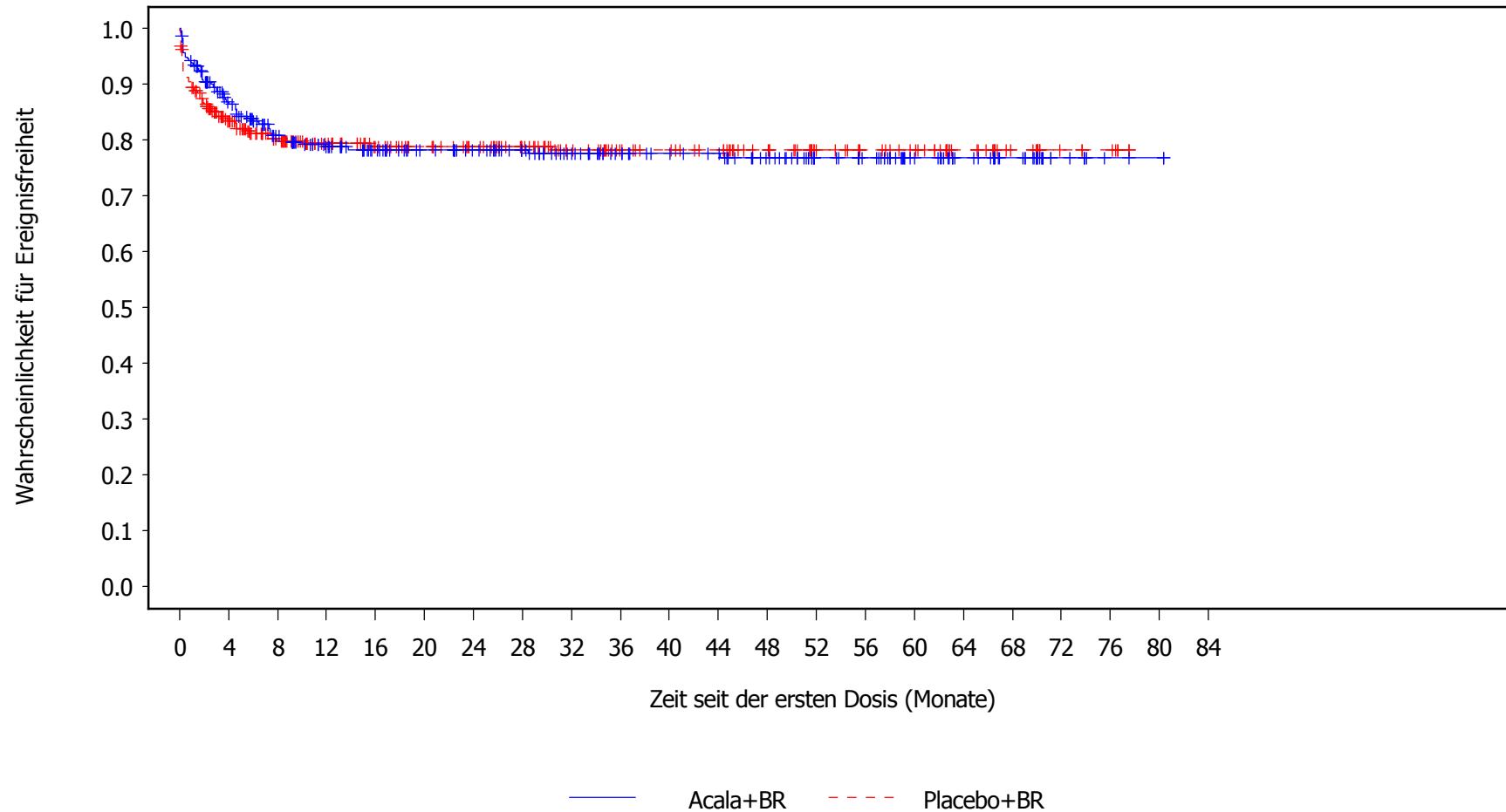
Anzahl an Patienten unter Risiko:

297	198	135	119	105	98	93	86	77	71	66	65	59	50	43	36	27	19	5	1	0	0	Acala+BR
297	193	137	111	99	94	85	74	64	56	52	48	44	31	26	24	16	10	4	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.209 ECHO: Kaplan-Meier plot of time to first occurrence of EKI $G \geq 3$ GT: Andere Leukopenie
 Safety Analysis Set, DCO 15FEB2024



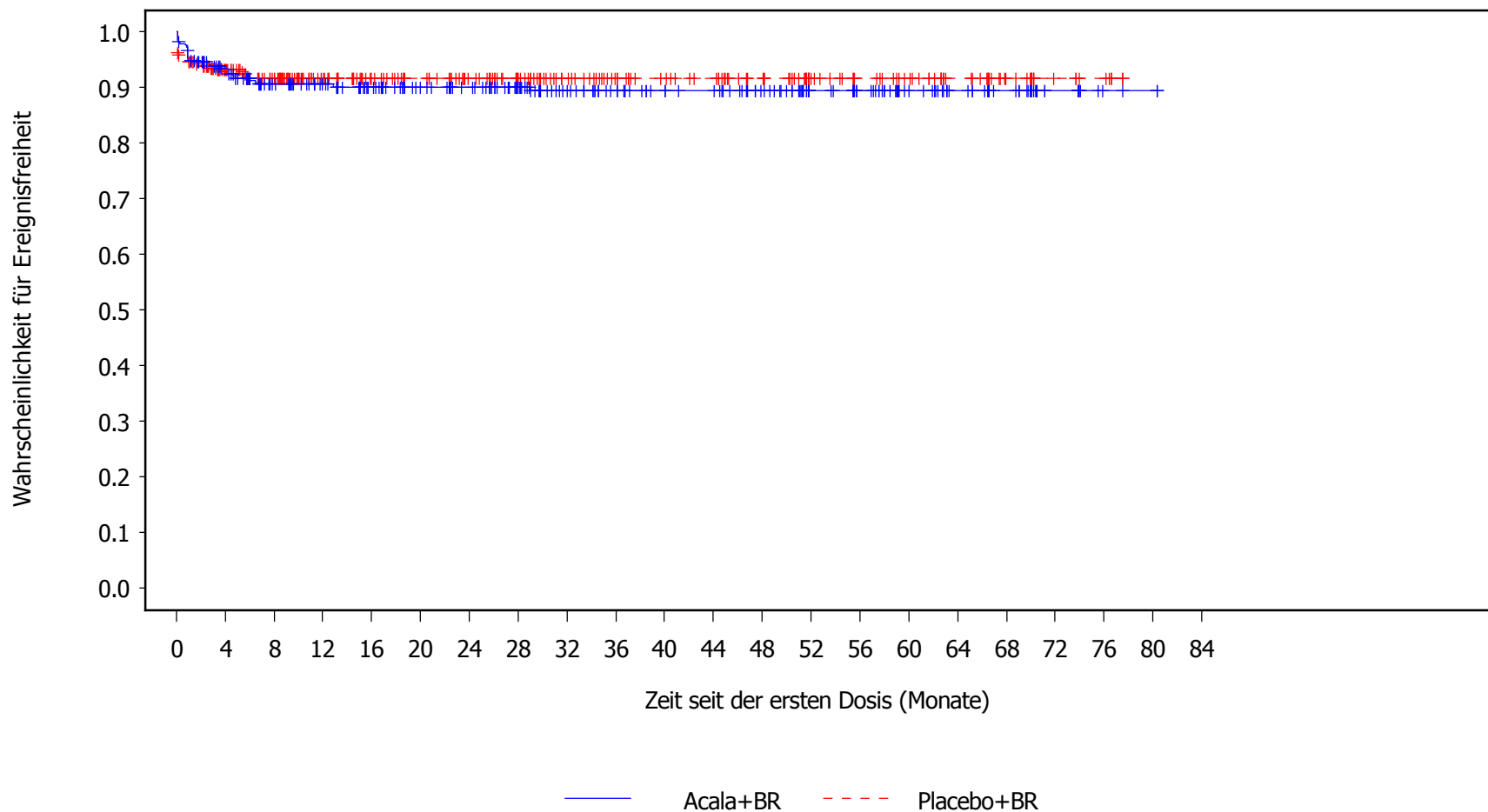
Anzahl an Patienten unter Risiko:

297	238	202	183	167	154	146	133	119	106	99	96	86	68	60	43	33	24	8	2	1	0	Acala+BR
297	223	188	164	148	137	128	113	97	86	82	77	67	54	47	42	28	17	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.210 ECHO: Kaplan-Meier plot of time to first occurrence of EKI G $\geq$ 3 GT: Thrombozytopenie
 Safety Analysis Set, DCO 15FEB2024



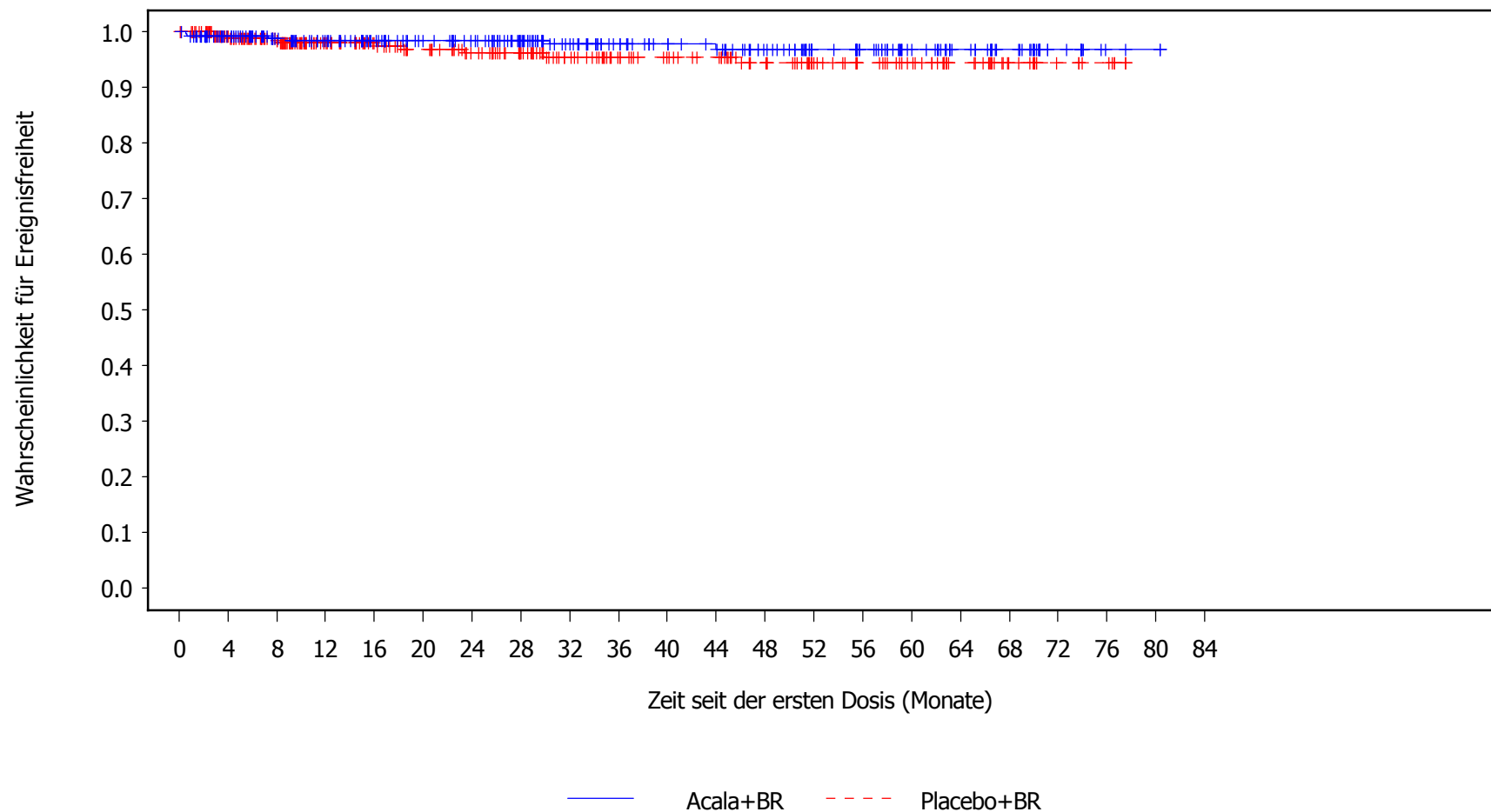
Anzahl an Patienten unter Risiko:

297	259	230	215	198	181	172	153	134	121	111	108	96	75	65	48	37	27	10	2	1	0	Acala+BR
297	251	225	192	173	161	148	132	115	102	94	89	78	61	52	45	32	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.211 ECHO: Kaplan-Meier plot of time to first occurrence of EKI G $\geq$ 3 GT: Blutung
 Safety Analysis Set, DC0 15FEB2024



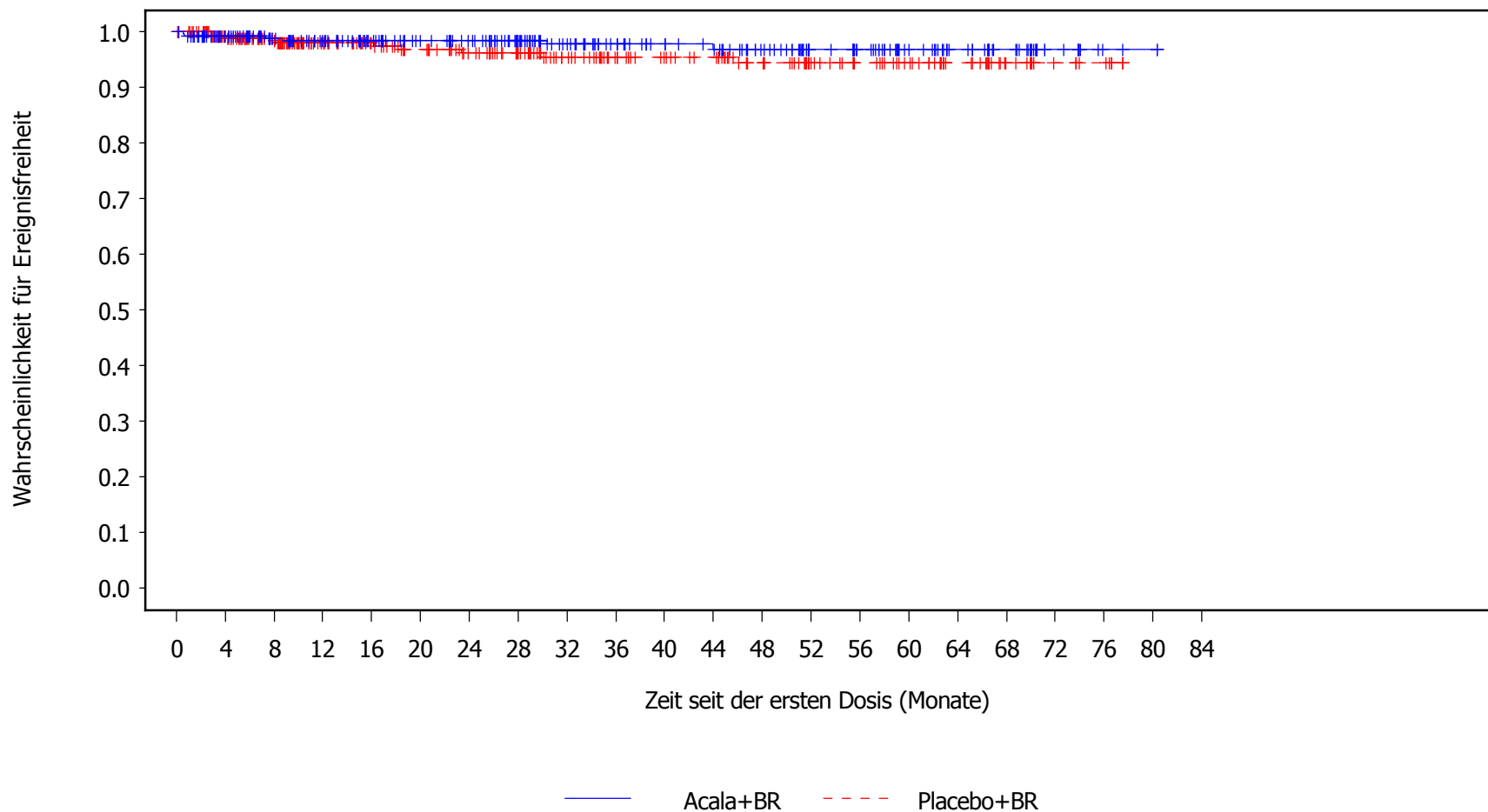
Anzahl an Patienten unter Risiko:

297	273	245	227	207	191	181	160	139	124	114	109	97	77	67	50	39	28	11	2	1	0	Acala+BR
297	266	236	200	181	167	153	138	118	104	96	91	78	63	54	46	31	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.212 ECH0: Kaplan-Meier plot of time to first occurrence of EKI G $\geq$ 3 GT: Schwere Blutung
 Safety Analysis Set, DC0 15FEB2024



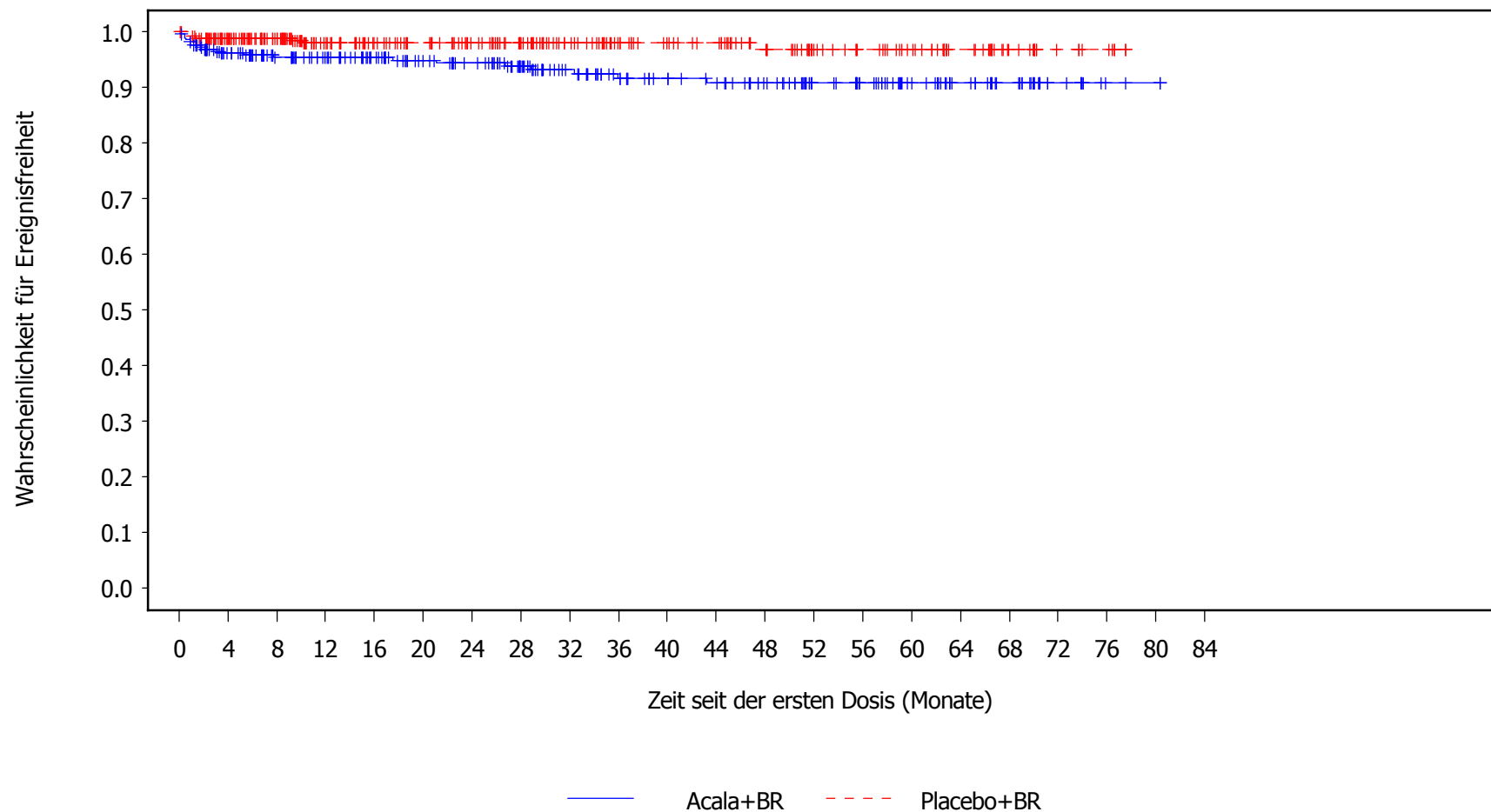
Anzahl an Patienten unter Risiko:

297	273	245	227	207	191	181	160	139	124	114	109	97	77	67	50	39	28	11	2	1	0	Acala+BR
297	266	236	200	181	167	153	138	118	104	96	91	78	63	54	46	31	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.213 ECH0: Kaplan-Meier plot of time to first occurrence of EKI G $\geq$ 3 GT: Hepatotoxizität
 Safety Analysis Set, DC0 15FEB2024



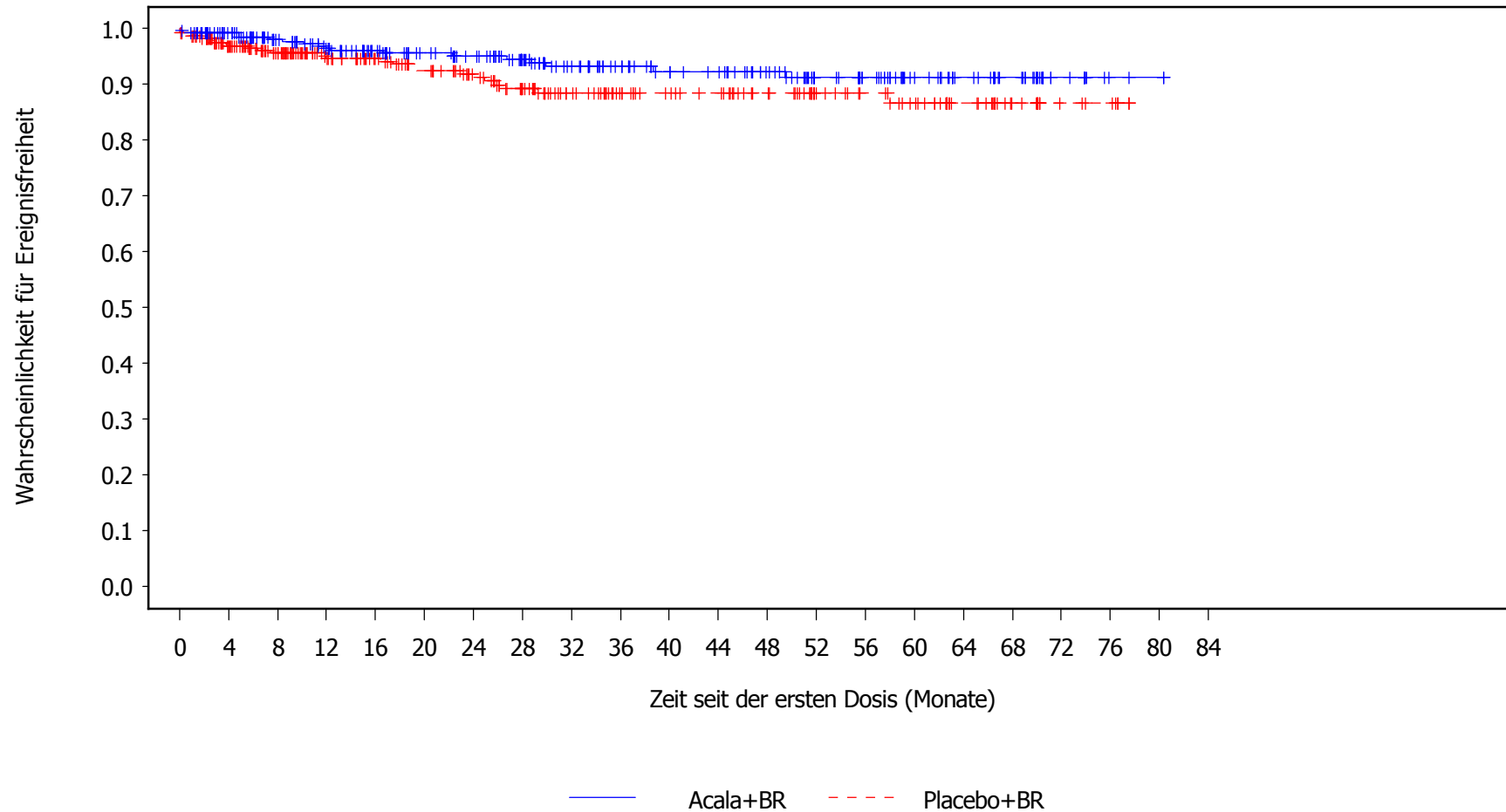
Anzahl an Patienten unter Risiko:

297	264	237	222	204	186	175	154	134	119	110	105	95	77	66	50	39	28	11	2	1	0	Acala+BR
297	266	237	201	182	170	156	140	121	106	97	92	79	63	55	47	32	18	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.214 ECH0: Kaplan-Meier plot of time to first occurrence of EKI G $\geq$ 3 GT: Hypertonie
 Safety Analysis Set, DC0 15FEB2024



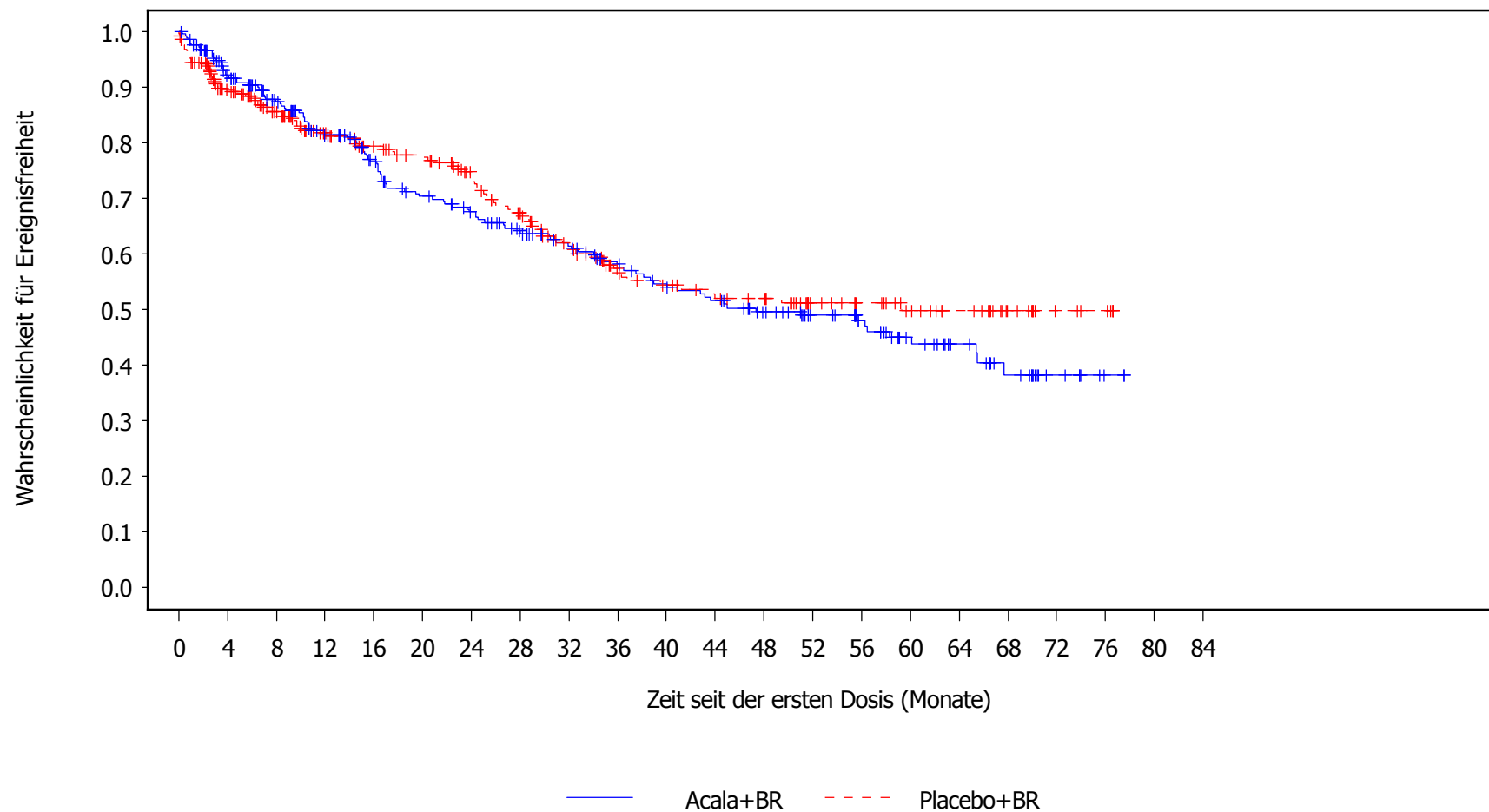
Anzahl an Patienten unter Risiko:

297	273	243	223	203	187	176	156	136	122	111	107	95	75	64	48	38	29	11	2	1	0	Acala+BR
297	259	229	196	178	162	147	128	109	95	87	83	73	57	50	43	29	17	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.215 ECHO: Kaplan-Meier plot of time to first occurrence of EKI G $\geq$ 3 GT: Infektionen
 Safety Analysis Set, DC0 15FEB2024



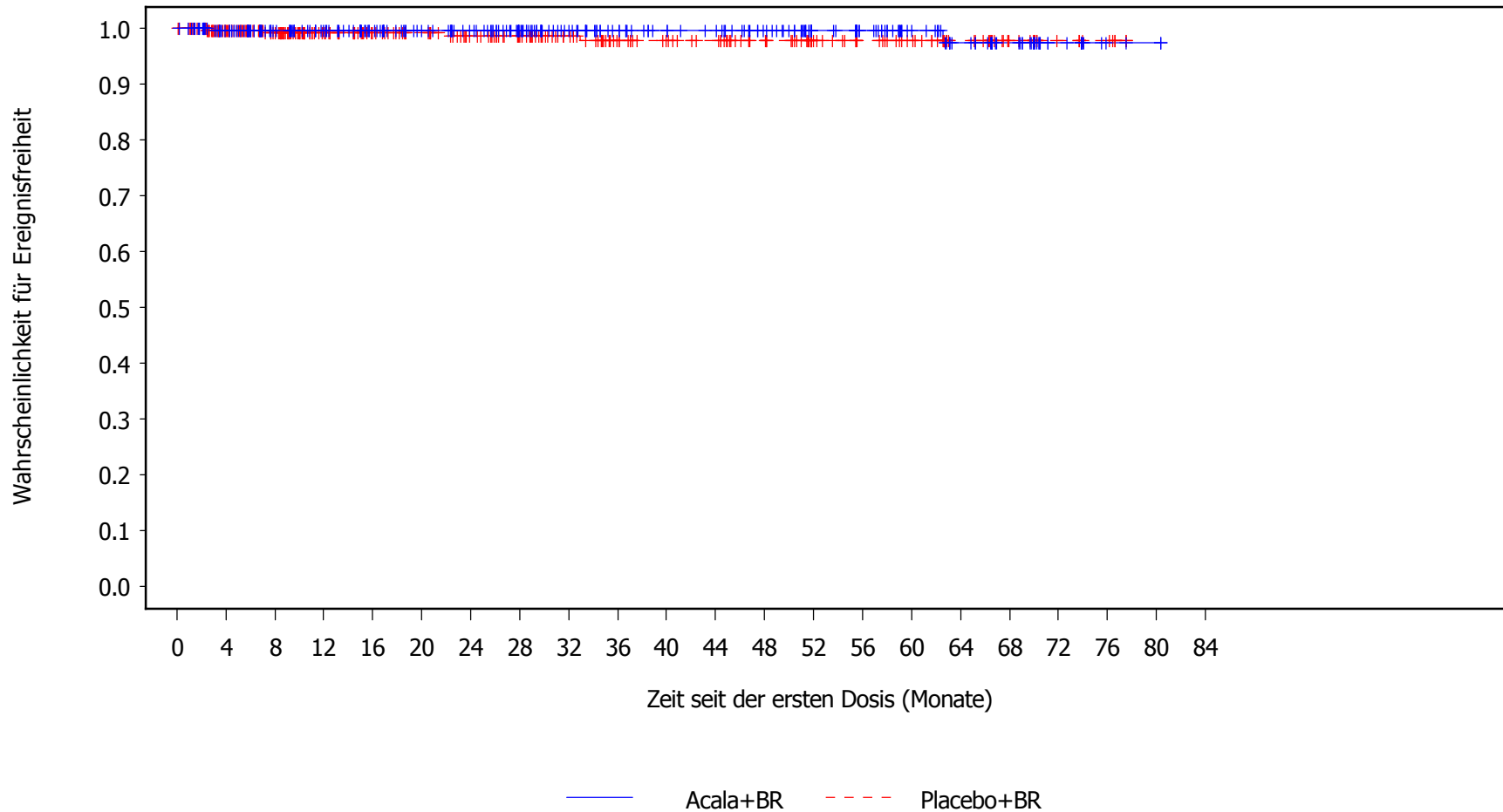
Anzahl an Patienten unter Risiko:

297	257	225	198	173	153	142	125	113	100	91	85	75	62	50	37	27	17	7	1	0	0	Acala+BR
297	243	210	179	162	151	132	116	97	79	72	66	63	47	41	34	25	14	6	4	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.216 ECHO: Kaplan-Meier plot of time to first occurrence of EKI G $\geq$ 3 GT: Interstitielle Lungenerkrankung/Pneumonitis
 Safety Analysis Set, DCO 15FEB2024



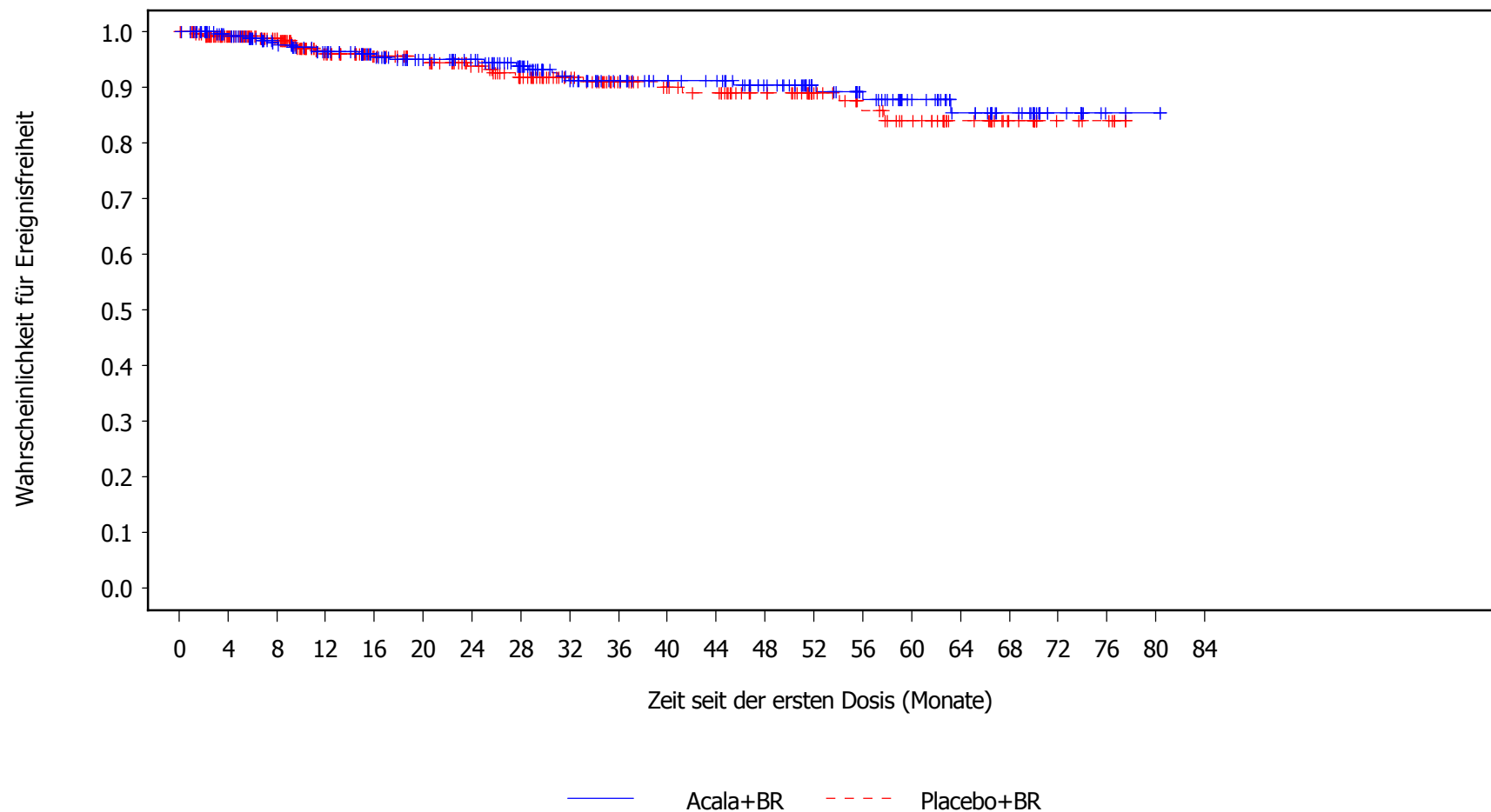
Anzahl an Patienten unter Risiko:

297	275	248	231	211	194	183	162	141	126	116	112	100	79	68	51	39	28	11	2	1	0	Acala+BR
297	267	237	203	184	172	158	142	123	108	99	94	82	65	56	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.217 ECHO: Kaplan-Meier plot of time to first occurrence of EKI G $\geq$ 3 GT: Zweiter Primärtumor
 Safety Analysis Set, DCO 15FEB2024



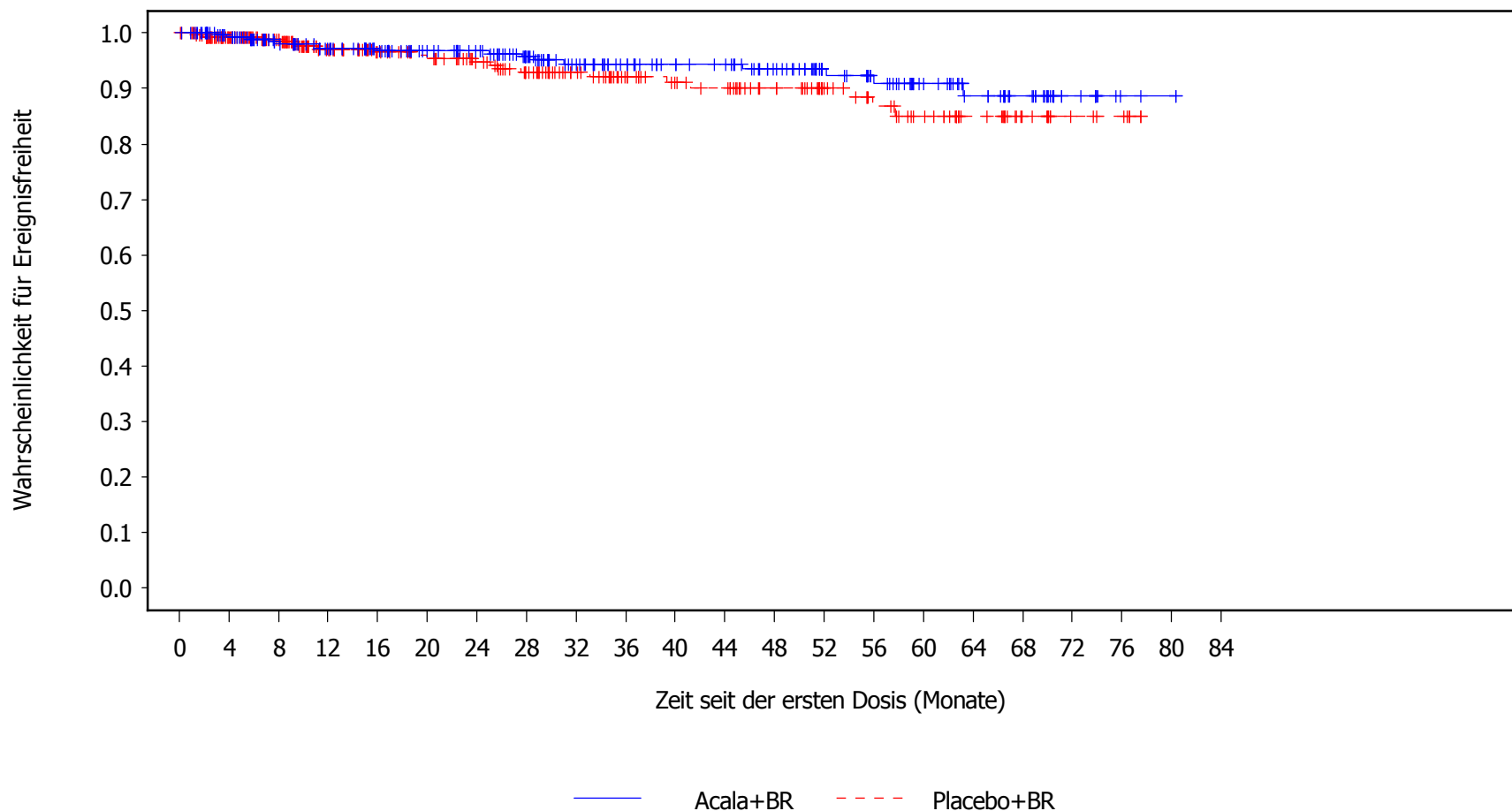
Anzahl an Patienten unter Risiko:

297	274	245	226	206	188	177	156	134	121	111	107	94	74	62	48	36	26	11	2	1	0	Acala+BR
297	266	236	197	177	165	151	135	117	102	92	88	76	60	50	42	29	17	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.218 ECHO: Kaplan-Meier plot of time to first occurrence of EKI G $\geq$ 3 GT: Zweiter Primärtumor - ausgenommen nicht-melanotischer Hautkrebs
 Safety Analysis Set, DCO 15FEB2024



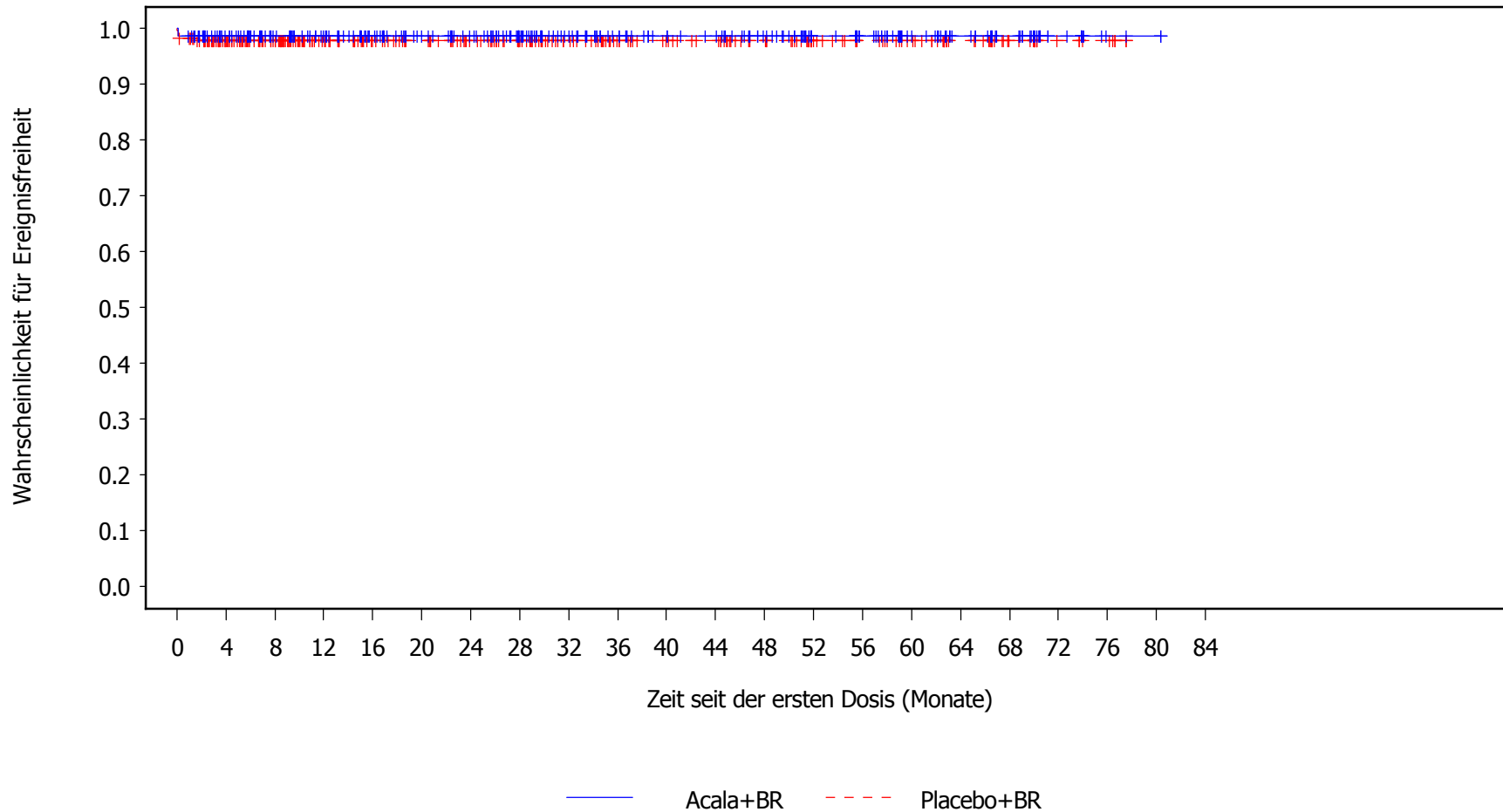
Anzahl an Patienten unter Risiko:

297	274	246	228	209	192	181	160	139	125	115	111	98	77	64	50	38	28	11	2	1	0	Acala+BR
297	266	236	199	179	167	152	136	118	103	93	89	77	61	51	43	29	17	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.219 ECHO: Kaplan-Meier plot of time to first occurrence of EKI $G \geq 3$ GT: Tumorlysesyndrom
 Safety Analysis Set, DC0 15FEB2024



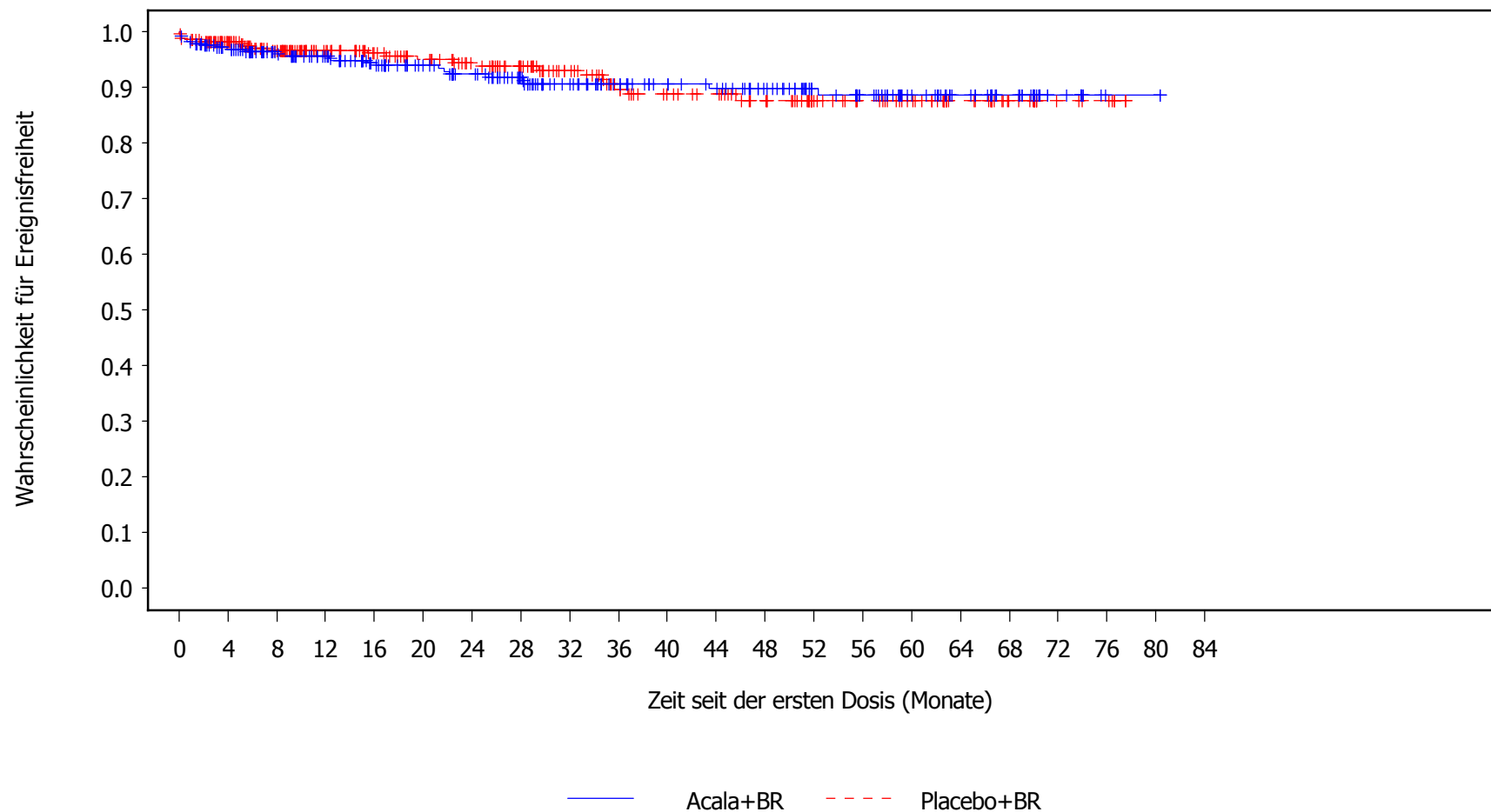
Anzahl an Patienten unter Risiko:

297	272	246	229	209	192	181	160	140	125	115	111	99	78	68	51	40	29	11	2	1	0	Acala+BR
297	263	236	203	184	172	158	142	123	108	99	94	82	65	56	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.220 ECH0: Kaplan-Meier plot of time to first occurrence of SEKI GT: Kardiale Ereignisse
 Safety Analysis Set, DC0 15FEB2024



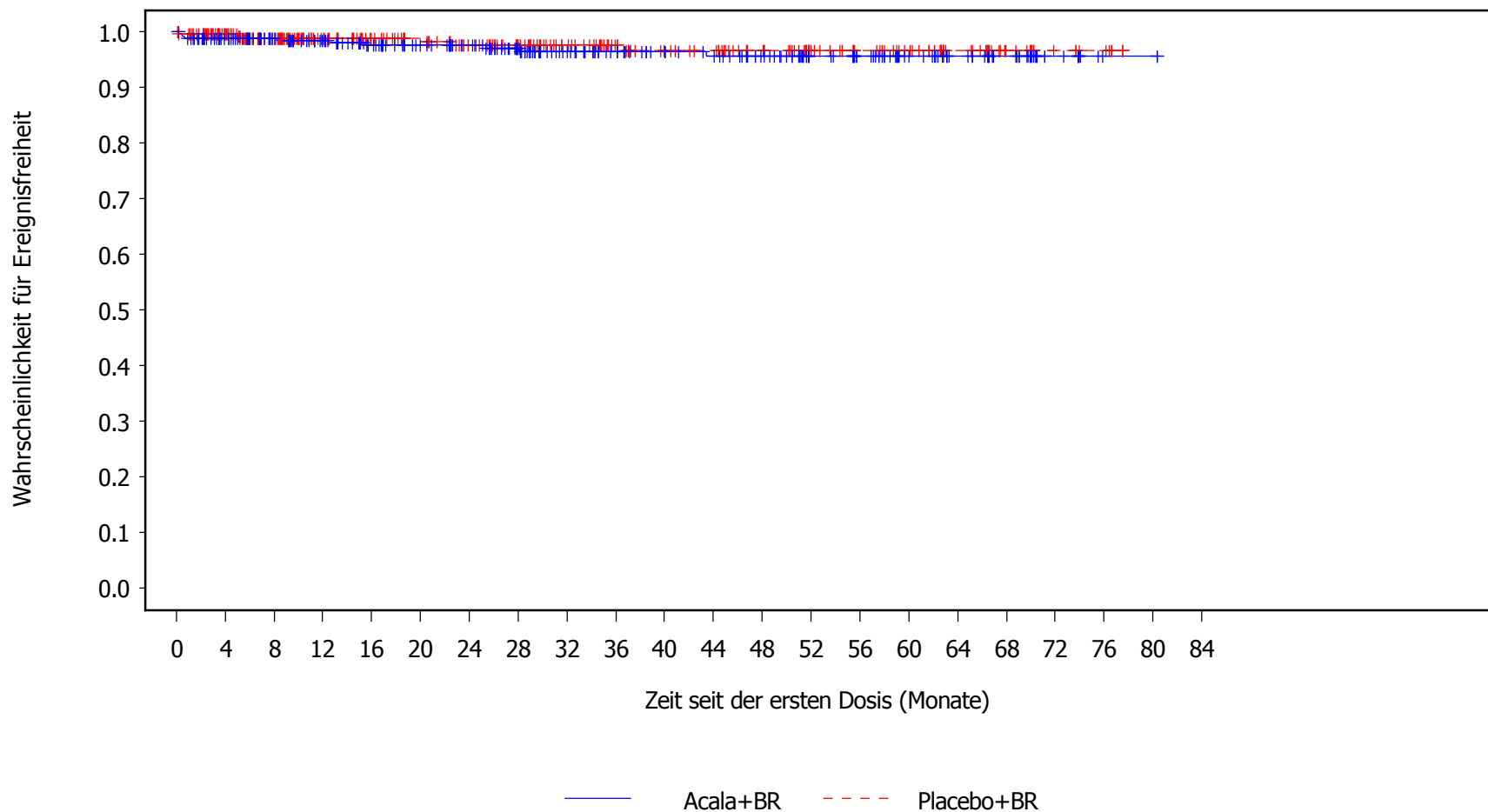
Anzahl an Patienten unter Risiko:

297	272	244	226	204	187	175	155	135	121	111	106	95	75	64	47	36	26	10	1	1	0	Acala+BR
297	264	233	199	180	166	153	137	118	101	92	88	78	61	52	44	30	18	7	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.221 ECH0: Kaplan-Meier plot of time to first occurrence of SEKI GT: Vorhofflimmern
 Safety Analysis Set, DC0 15FEB2024



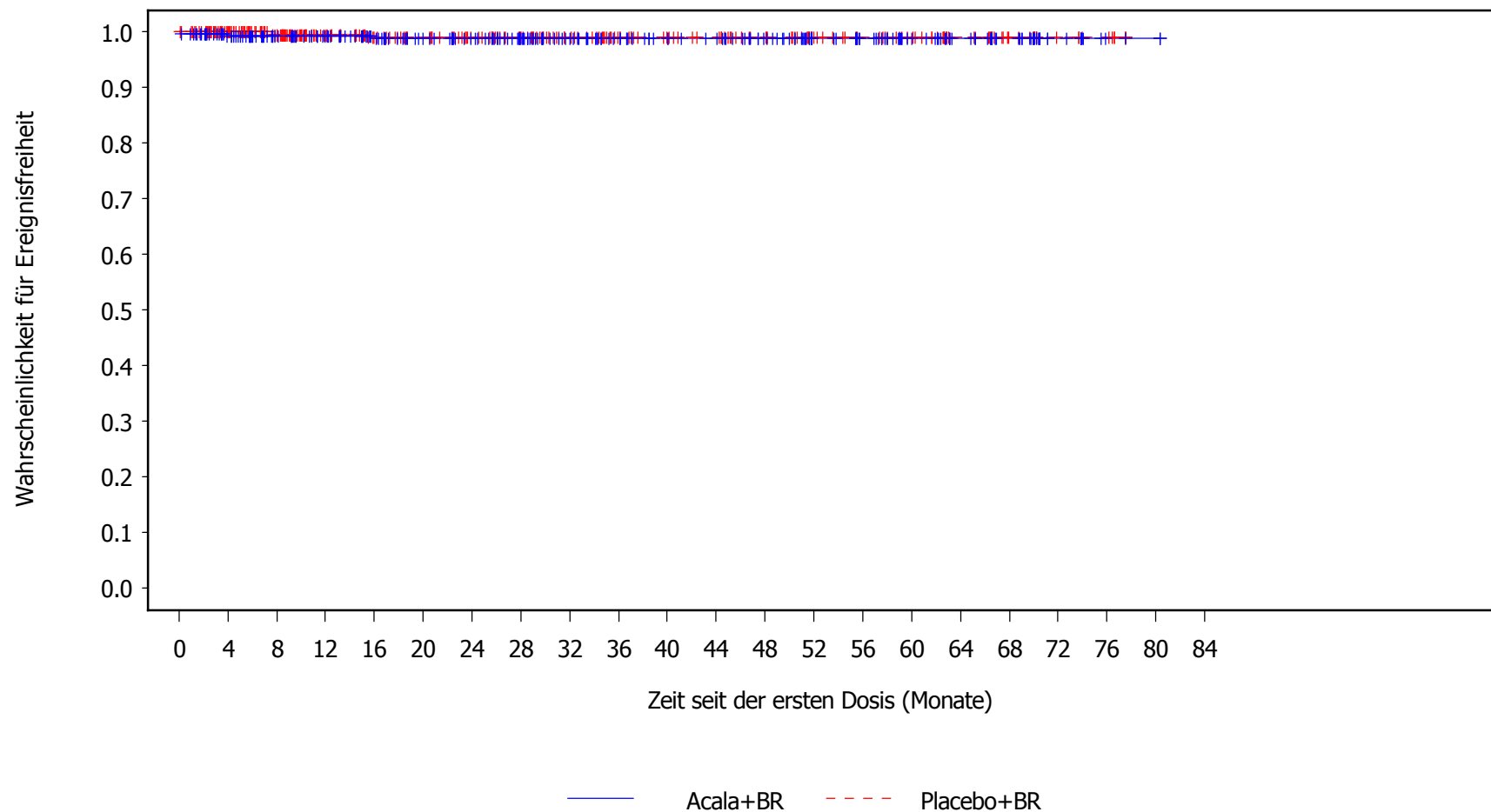
Anzahl an Patienten unter Risiko:

297	274	247	229	208	192	182	160	138	124	114	109	98	78	67	50	39	28	10	1	1	0	Acala+BR
297	266	237	202	183	171	157	141	122	107	97	93	82	65	56	48	33	19	8	5	0	0	Placebo+BR

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Figure 3.3.1.222 ECHO: Kaplan-Meier plot of time to first occurrence of SEKI GT: Ventrikuläre Tachyarrhythmie
 Safety Analysis Set, DC0 15FEB2024



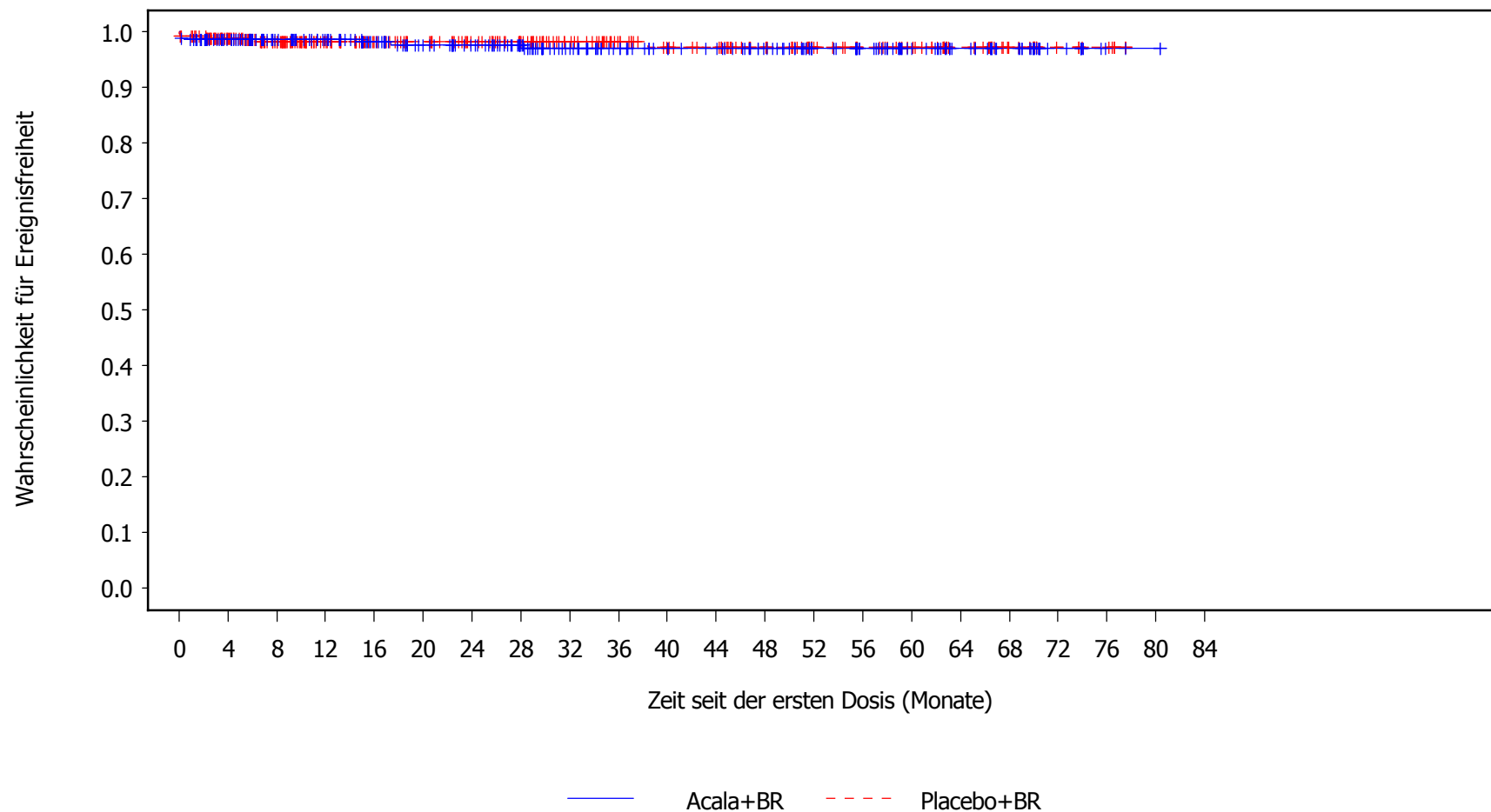
Anzahl an Patienten unter Risiko:

297	274	247	230	210	192	181	161	141	126	116	112	100	79	68	51	40	29	11	2	1	0	Acala+BR
297	267	237	202	182	170	156	140	121	106	97	92	81	64	55	47	32	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Figure 3.3.1.223 ECHO: Kaplan-Meier plot of time to first occurrence of SEKI GT: Anämie
 Safety Analysis Set, DC0 15FEB2024



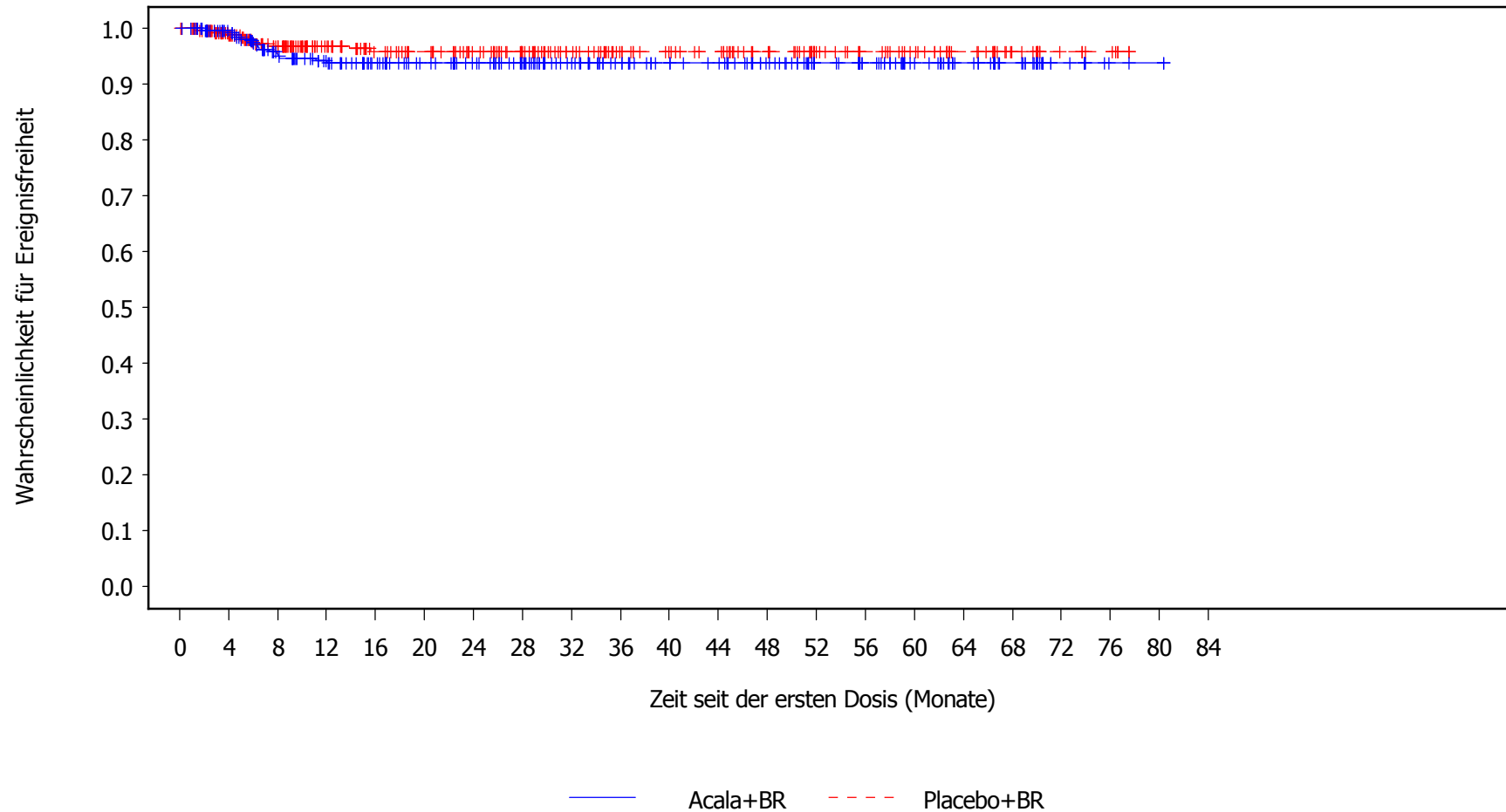
Anzahl an Patienten unter Risiko:

297	271	244	227	207	190	179	159	138	123	113	109	98	78	67	50	39	28	11	2	1	0	Acala+BR
297	266	236	202	183	171	157	141	122	107	97	93	81	64	56	48	33	19	8	5	0	0	Placebo+BR

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Figure 3.3.1.224 ECHO: Kaplan-Meier plot of time to first occurrence of SEKI GT: Leukopenie
 Safety Analysis Set, DC0 15FEB2024



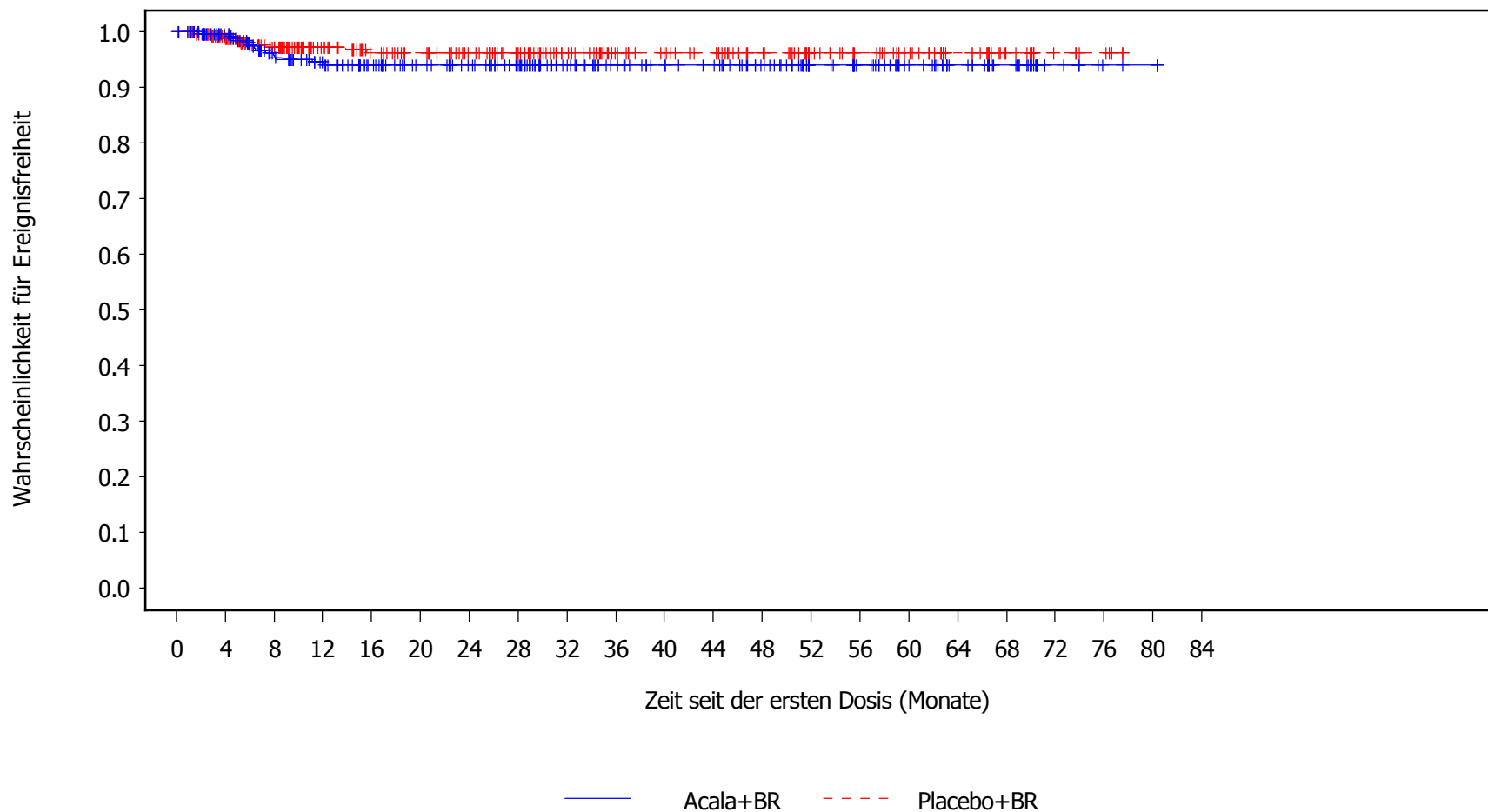
Anzahl an Patienten unter Risiko:

297	274	237	218	198	184	173	158	138	123	113	109	97	77	66	50	39	28	10	2	1	0	Acala+BR
297	265	233	199	178	168	154	138	120	105	97	92	80	63	54	46	32	19	8	5	0	0	Placebo+BR

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Figure 3.3.1.225 ECHO: Kaplan-Meier plot of time to first occurrence of SEKI GT: Neutropenie
 Safety Analysis Set, DC0 15FEB2024



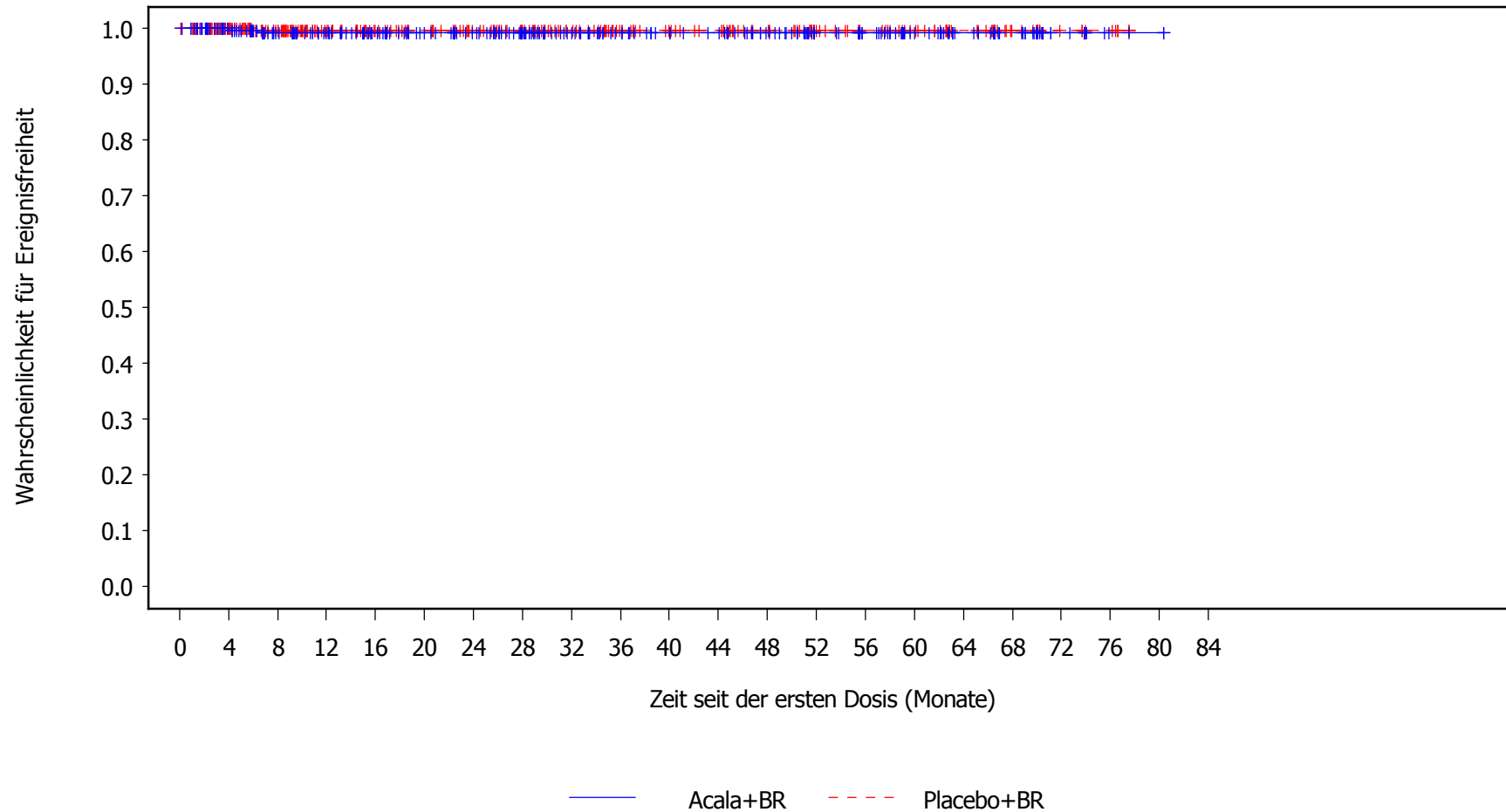
Anzahl an Patienten unter Risiko:

297	274	237	218	198	184	173	158	138	123	113	109	97	77	66	50	39	28	10	2	1	0	Acala+BR
297	265	233	199	178	168	154	138	120	105	97	92	80	63	54	46	32	19	8	5	0	0	Placebo+BR

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Figure 3.3.1.226 ECHO: Kaplan-Meier plot of time to first occurrence of SEKI GT: Andere Leukopenie
 Safety Analysis Set, DC0 15FEB2024



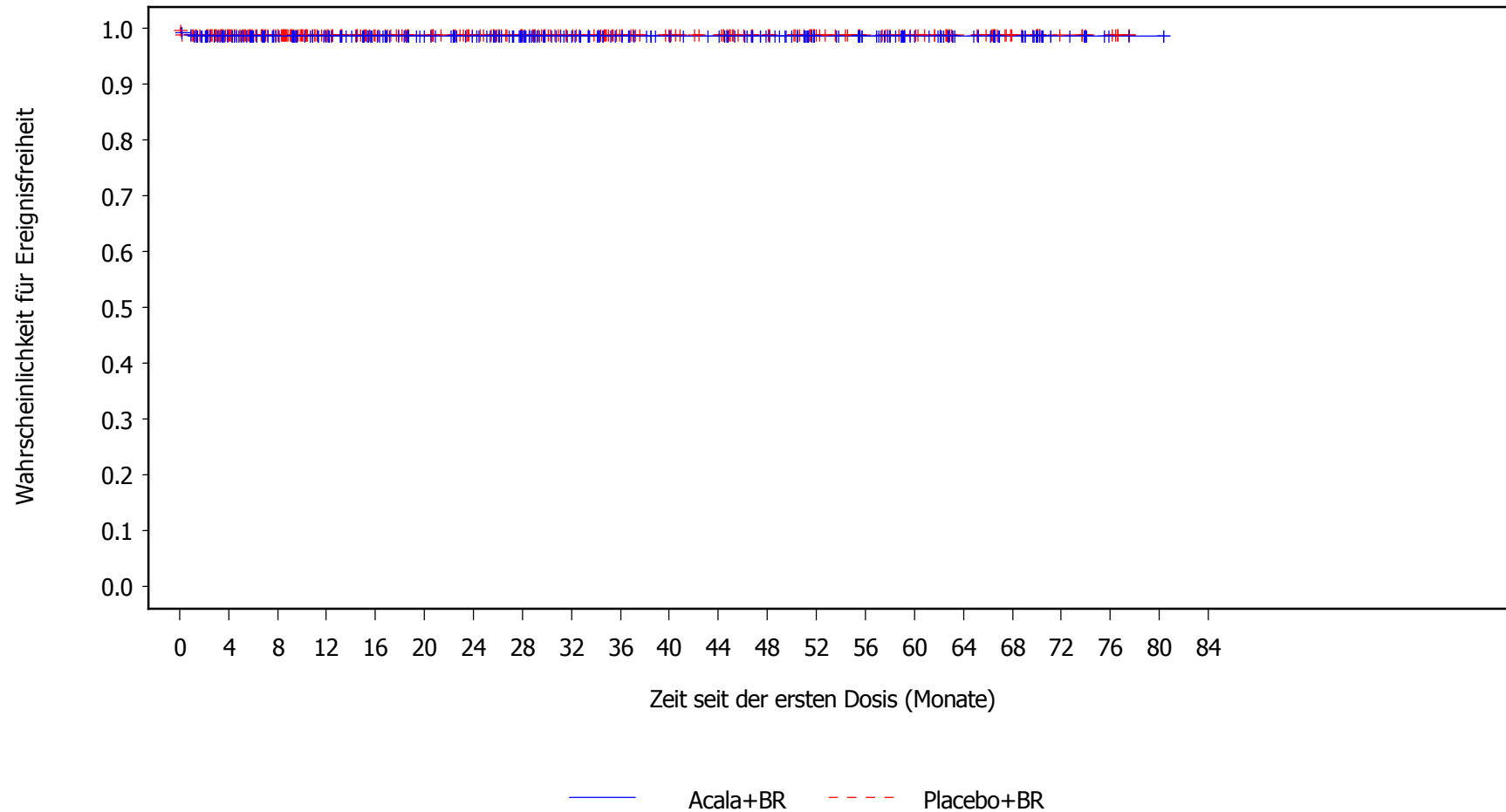
Anzahl an Patienten unter Risiko:

297	275	247	230	210	193	182	162	141	126	116	112	100	79	68	51	40	29	11	2	1	0	Acala+BR
297	267	238	203	184	172	158	142	123	108	99	94	82	65	56	48	33	19	8	5	0	0	Placebo+BR

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Figure 3.3.1.227 ECHO: Kaplan-Meier plot of time to first occurrence of SEKI GT: Thrombozytopenie
 Safety Analysis Set, DC0 15FEB2024



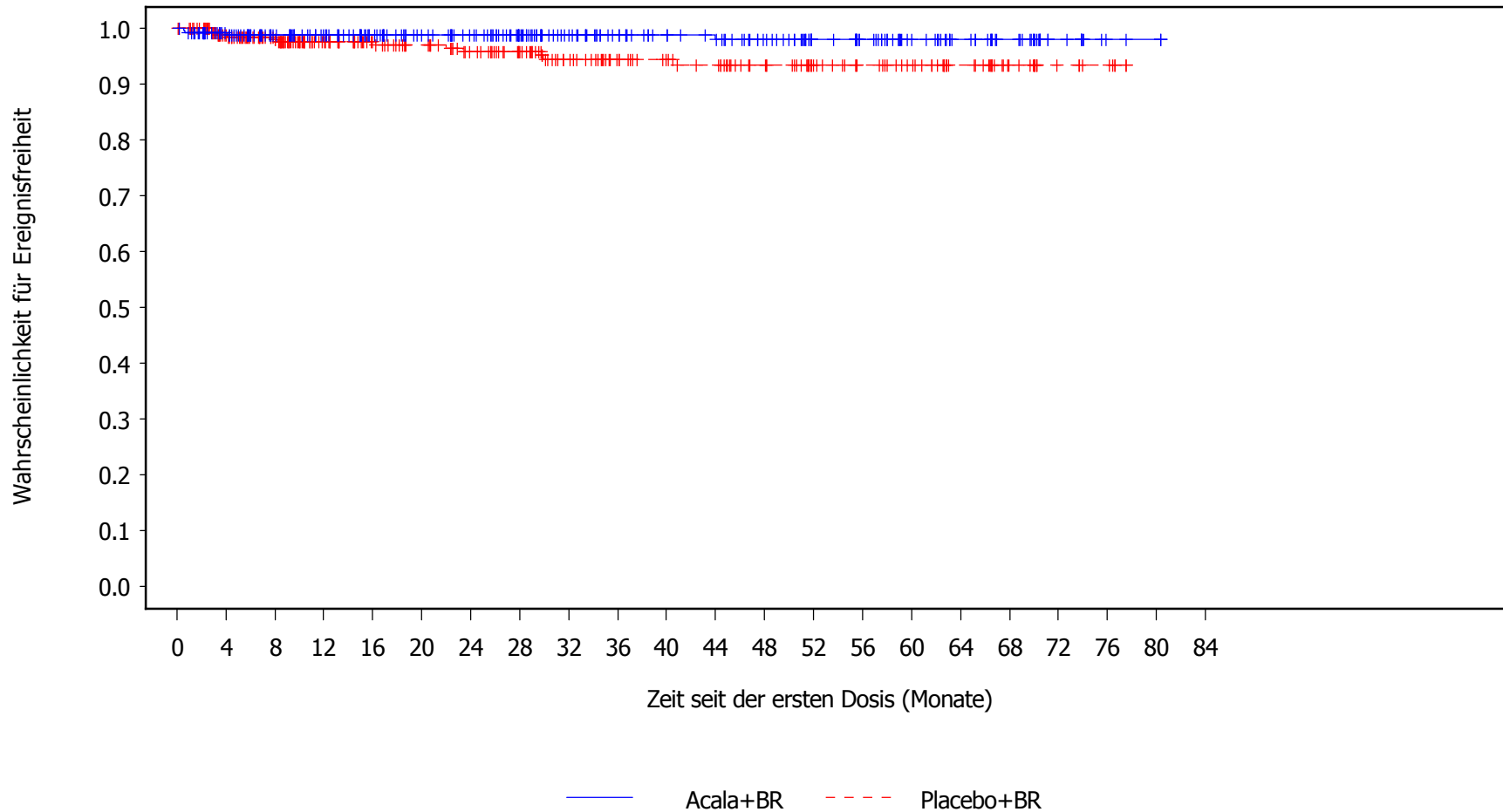
Anzahl an Patienten unter Risiko:

297	272	245	228	208	191	180	161	141	126	116	112	100	79	68	51	40	29	11	2	1	0	Acala+BR
297	267	238	203	184	172	158	142	123	108	99	94	82	65	56	48	33	19	8	5	0	0	Placebo+BR

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Figure 3.3.1.228 ECH0: Kaplan-Meier plot of time to first occurrence of SEKI GT: Blutung
 Safety Analysis Set, DCO 15FEB2024



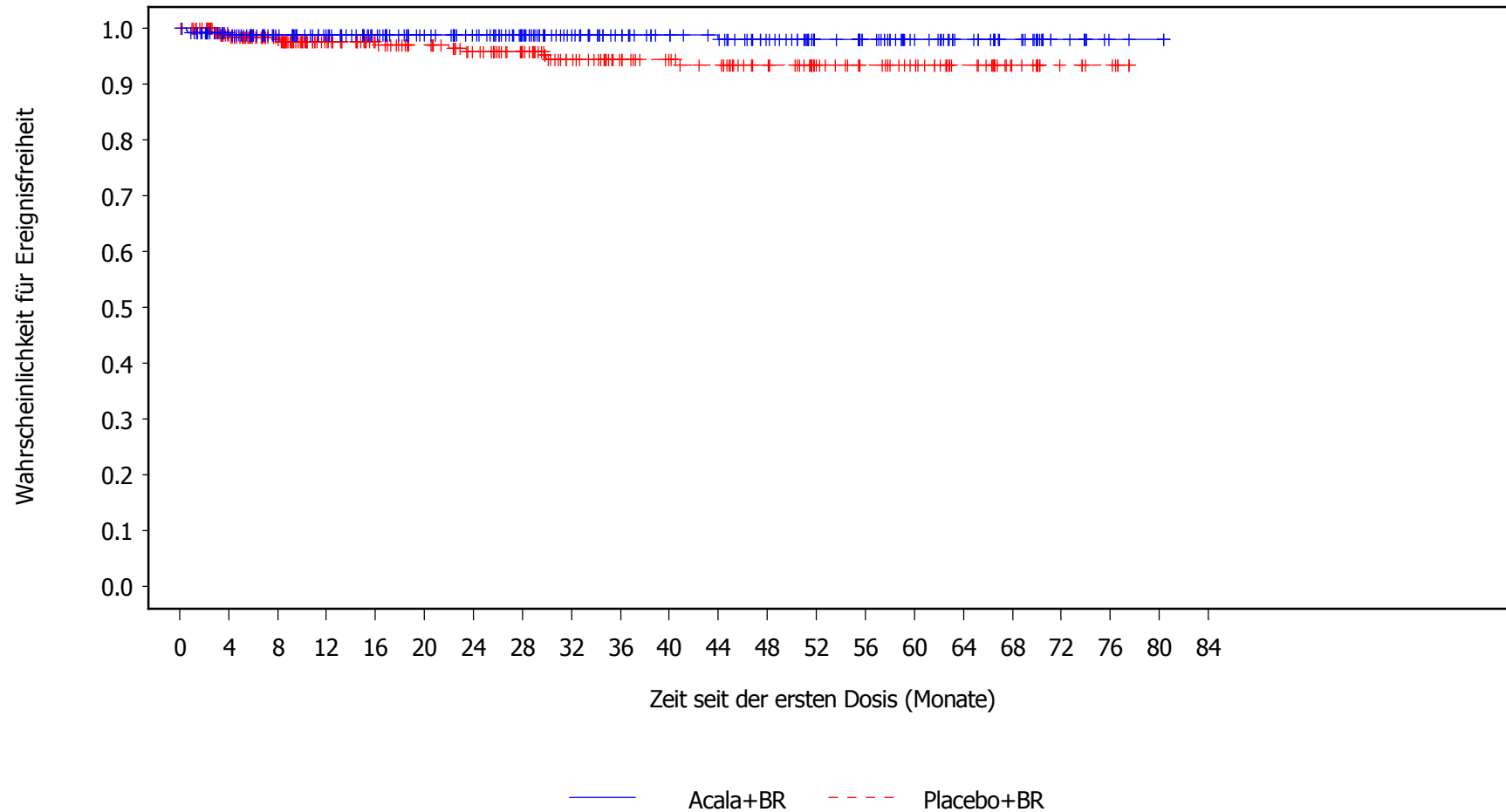
Anzahl an Patienten unter Risiko:

297	273	245	228	208	191	180	159	138	123	113	108	96	76	66	50	39	28	11	2	1	0	Acala+BR
297	266	236	200	181	168	154	139	118	104	96	91	79	64	55	48	33	19	8	5	0	0	Placebo+BR

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Figure 3.3.1.229 ECHO: Kaplan-Meier plot of time to first occurrence of SEKI GT: Schwere Blutung
 Safety Analysis Set, DC0 15FEB2024



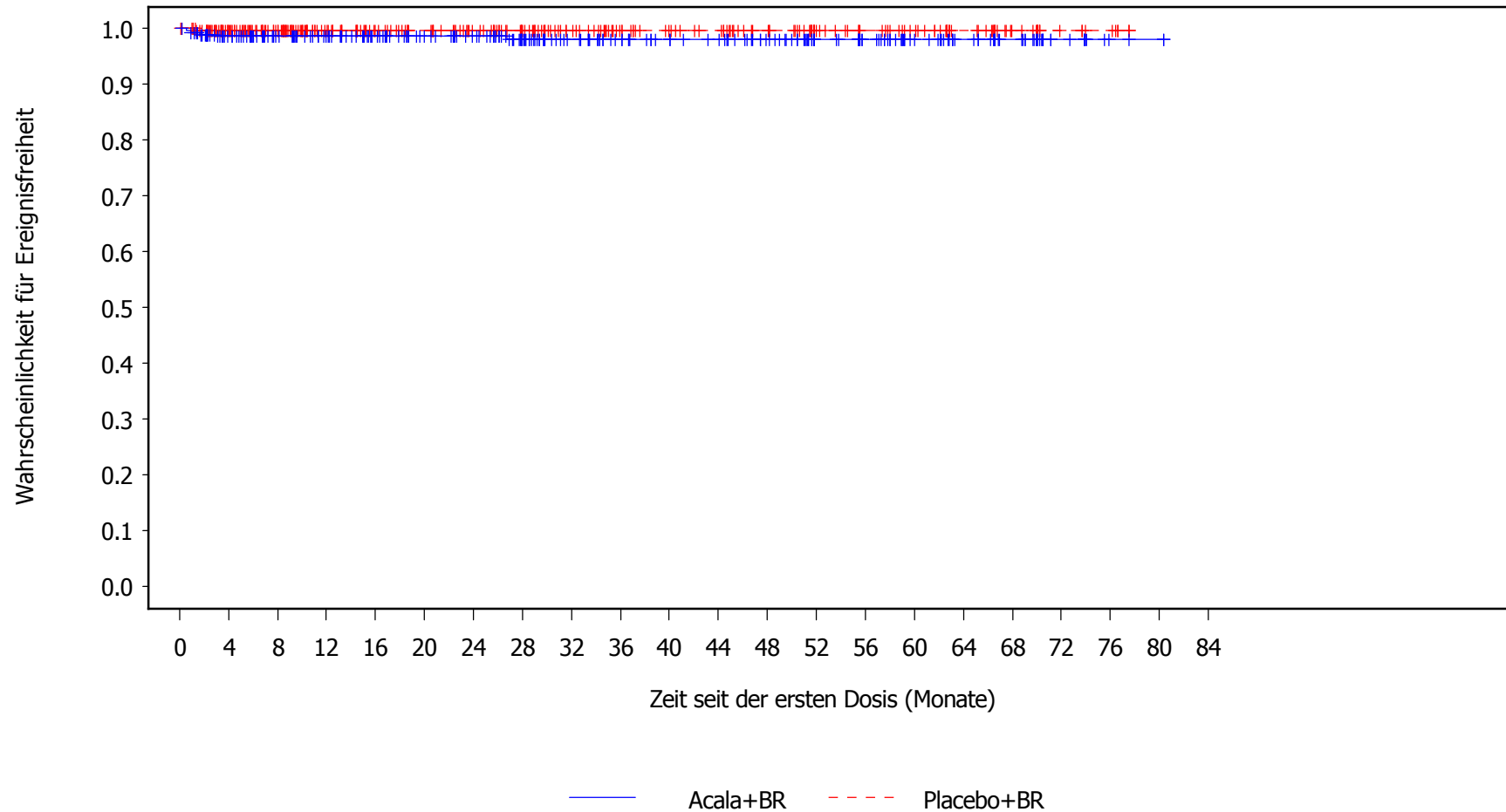
Anzahl an Patienten unter Risiko:

297	273	245	228	208	191	180	159	138	123	113	108	96	76	66	50	39	28	11	2	1	0	Acala+BR
297	266	236	200	181	168	154	139	118	104	96	91	79	64	55	48	33	19	8	5	0	0	Placebo+BR

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Figure 3.3.1.230 ECHO: Kaplan-Meier plot of time to first occurrence of SEKI GT: Hepatotoxizität
 Safety Analysis Set, DCO 15FEB2024



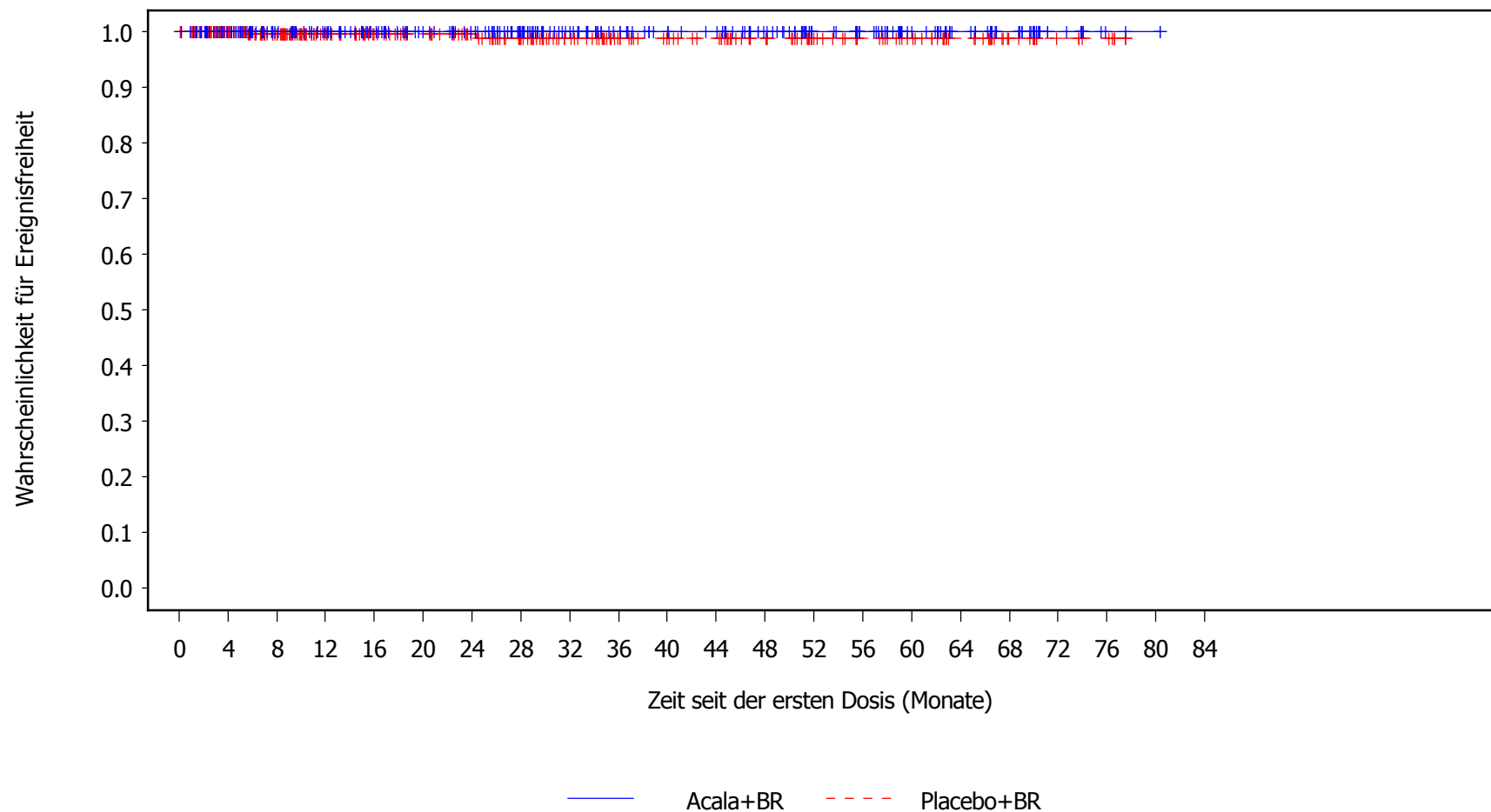
Anzahl an Patienten unter Risiko:

297	271	245	228	208	191	180	158	137	124	115	111	99	79	68	51	40	29	11	2	1	0	Acala+BR
297	267	238	203	184	172	158	142	123	108	99	94	82	65	56	48	33	19	8	5	0	0	Placebo+BR

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Figure 3.3.1.231 ECHO: Kaplan-Meier plot of time to first occurrence of SEKI GT: Hypertonie
 Safety Analysis Set, DCO 15FEB2024



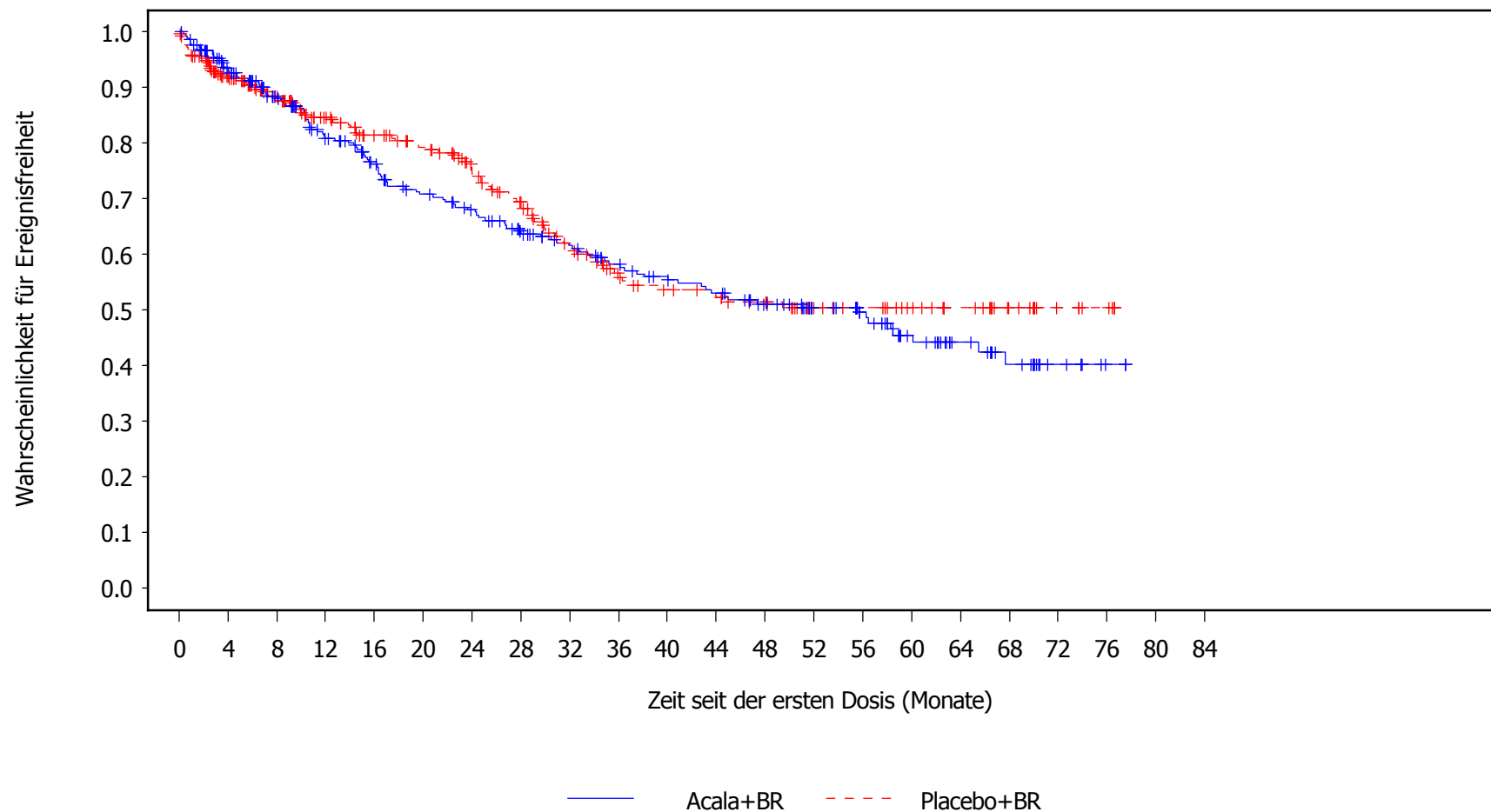
Anzahl an Patienten unter Risiko:

297	275	248	231	211	194	183	162	141	126	116	112	100	79	68	51	40	29	11	2	1	0	Acala+BR
297	267	238	203	184	172	158	141	122	107	98	93	81	64	55	47	33	19	8	5	0	0	Placebo+BR

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Figure 3.3.1.232 ECHO: Kaplan-Meier plot of time to first occurrence of SEKI GT: Infektionen
 Safety Analysis Set, DC0 15FEB2024



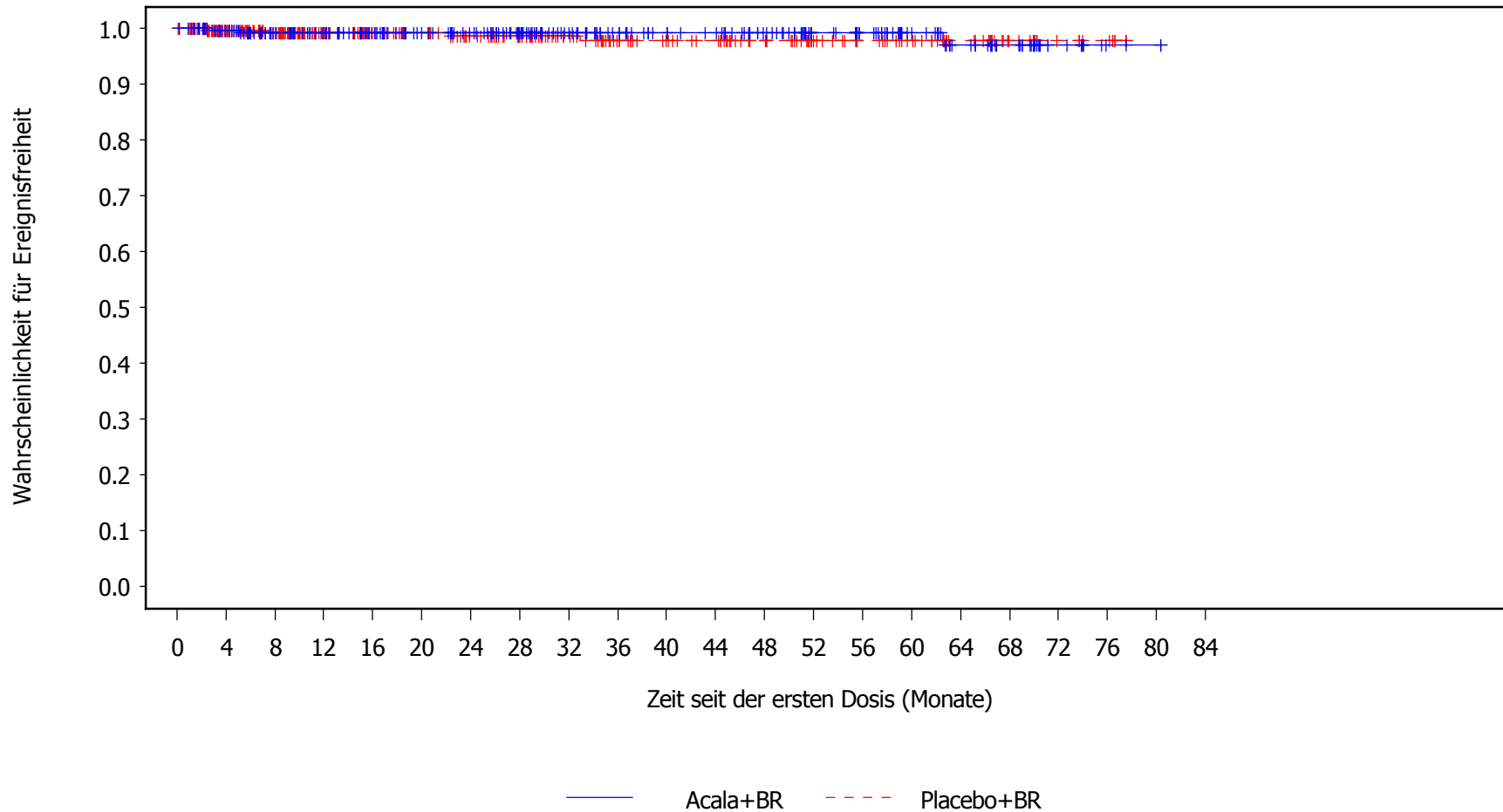
Anzahl an Patienten unter Risiko:

297	259	226	196	173	155	144	126	114	103	95	89	79	65	53	37	26	17	7	1	0	0	Acala+BR
297	250	216	186	167	155	135	118	96	79	71	67	62	46	39	33	25	16	7	4	0	0	Placebo+BR

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Figure 3.3.1.233 ECHO: Kaplan-Meier plot of time to first occurrence of SEKI GT: Interstitielle Lungenerkrankung/Pneumonitis
 Safety Analysis Set, DCO 15FEB2024



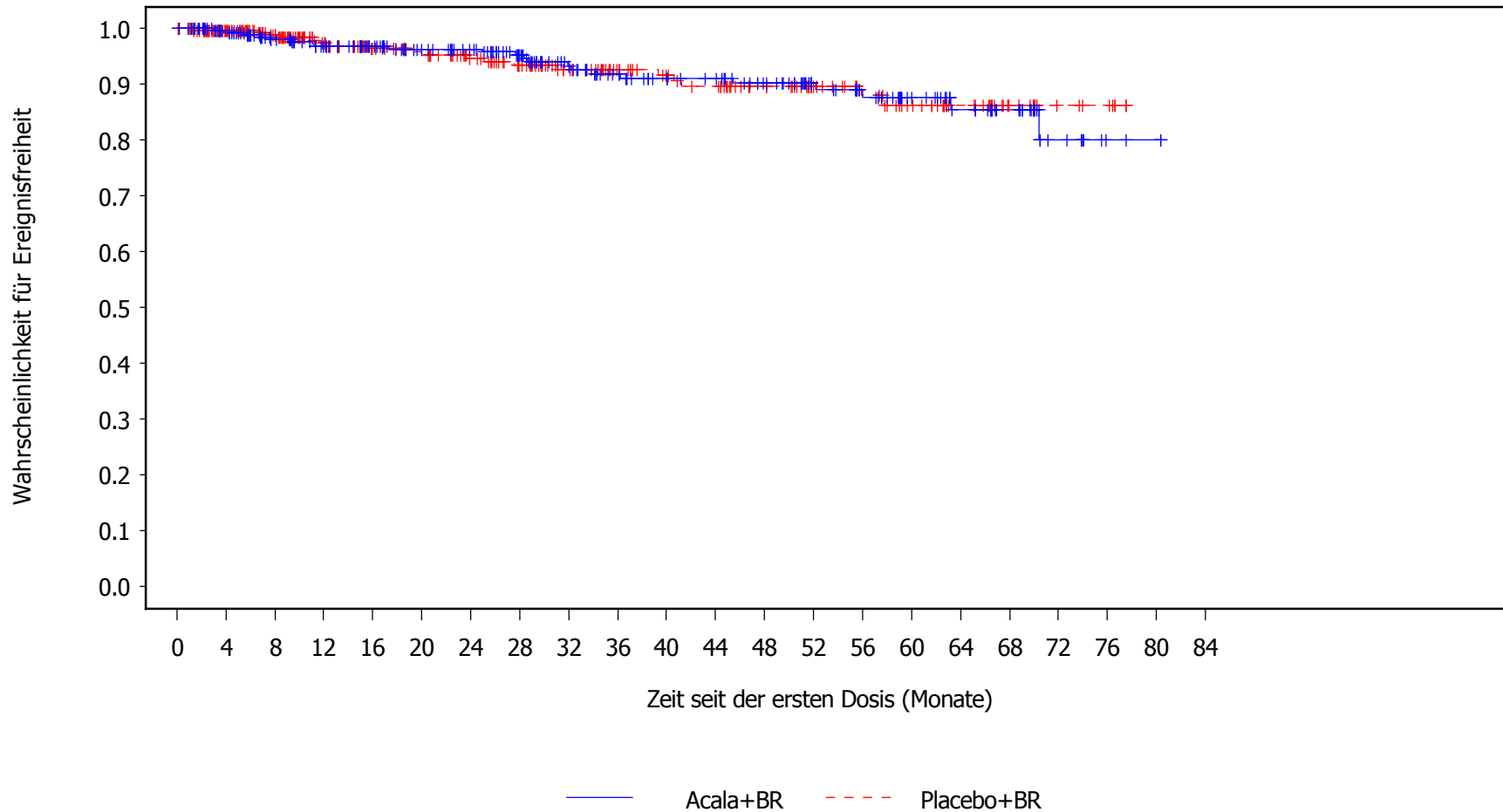
Anzahl an Patienten unter Risiko:

297	275	247	230	210	193	182	161	140	126	116	112	100	79	68	51	39	28	11	2	1	0	Acala+BR
297	267	237	203	184	172	158	142	123	108	99	94	82	65	56	48	33	19	8	5	0	0	Placebo+BR

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Figure 3.3.1.234 ECH0: Kaplan-Meier plot of time to first occurrence of SEKI GT: Zweiter Primärtumor
 Safety Analysis Set, DC0 15FEB2024



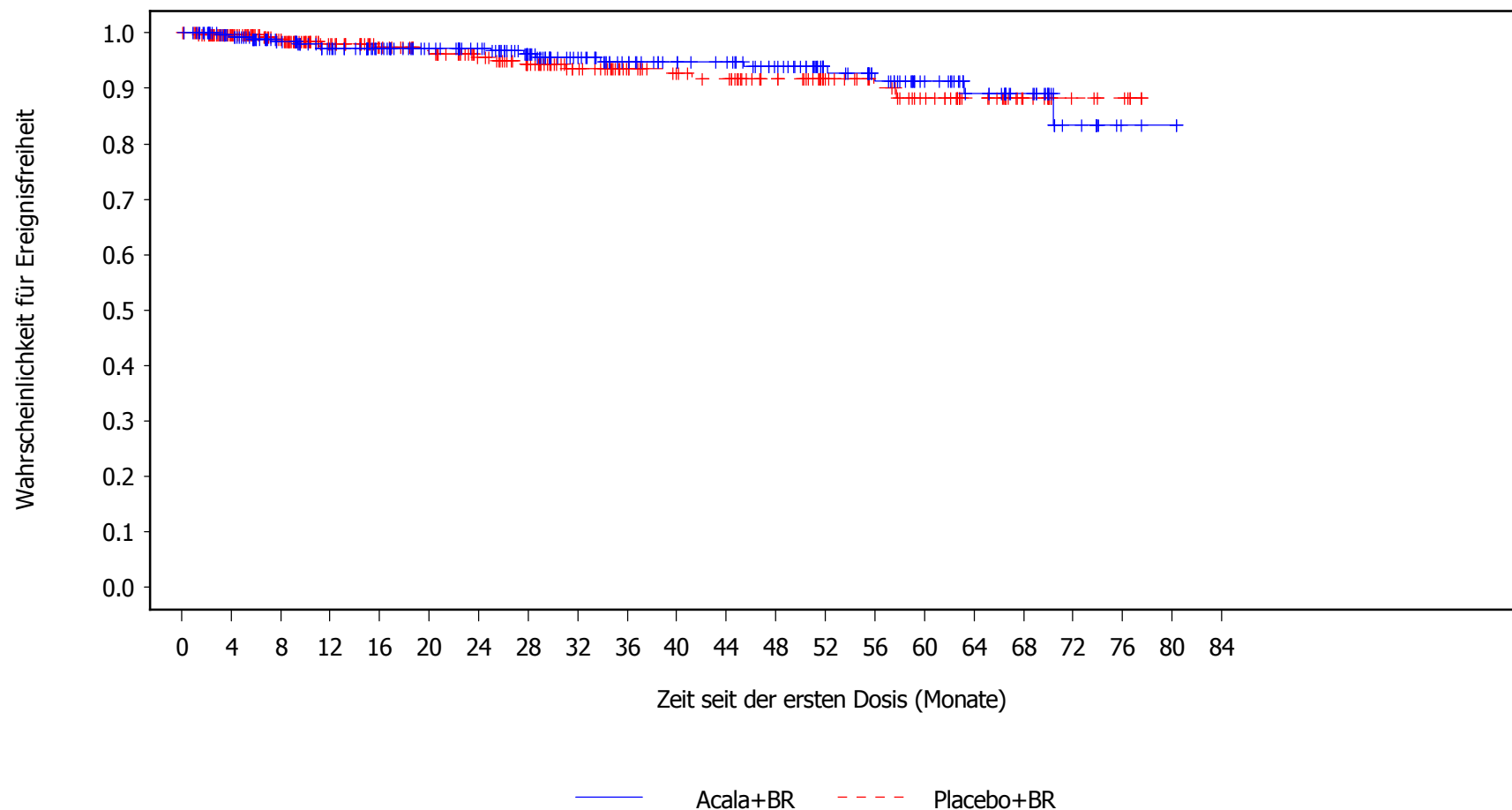
Anzahl an Patienten unter Risiko:

297	274	245	226	208	190	179	157	135	120	110	106	95	75	63	49	38	28	11	2	1	0	Acala+BR
297	267	236	201	181	169	154	138	119	105	95	90	78	63	53	44	30	17	7	5	0	0	Placebo+BR

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Figure 3.3.1.235 ECHO: Kaplan-Meier plot of time to first occurrence of SEKI GT: Zweiter Primärtumor - ausgenommen nicht-melanotischer Hautkrebs
 Safety Analysis Set, DC0 15FEB2024



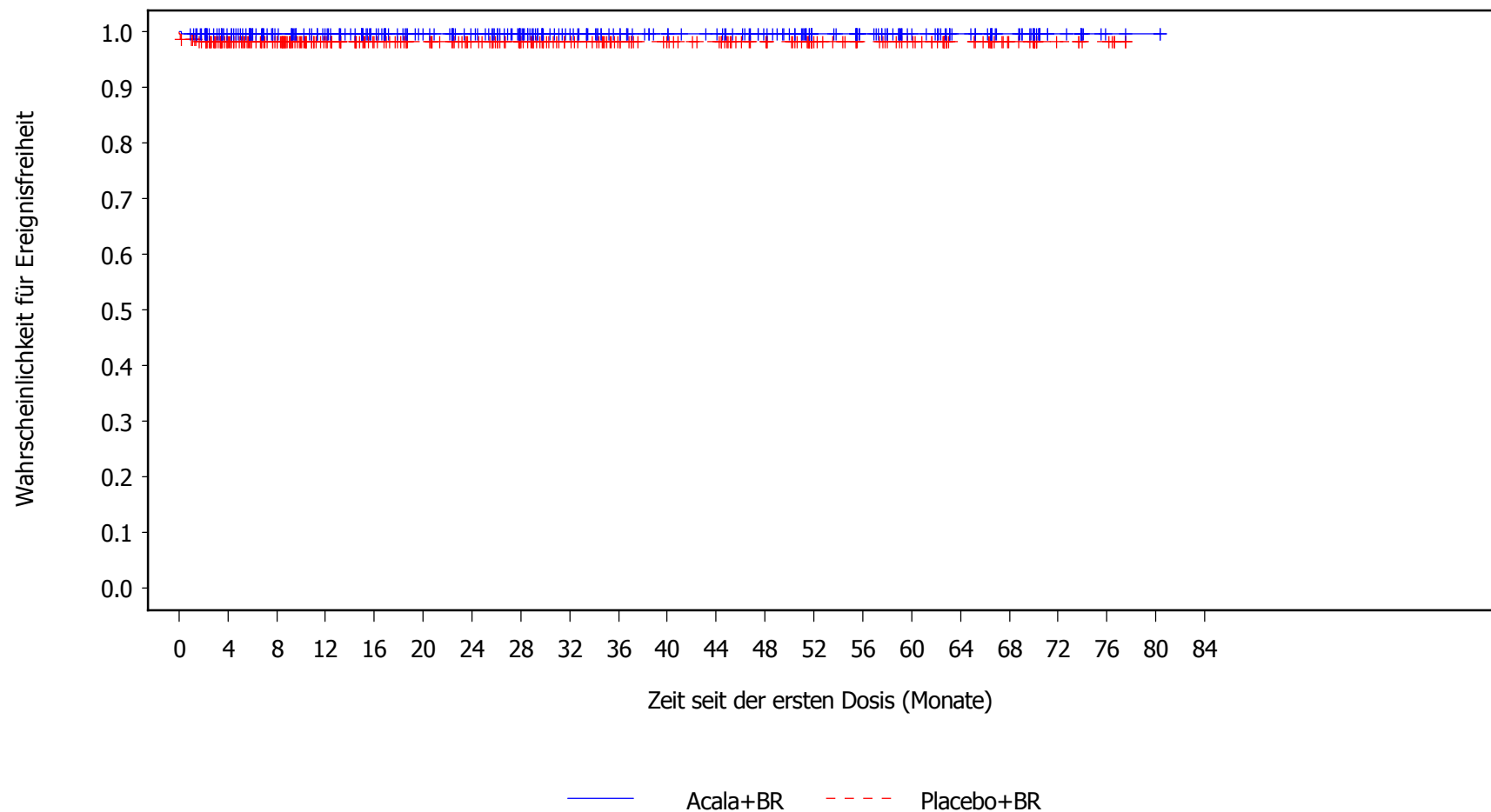
Anzahl an Patienten unter Risiko:

297	274	246	227	209	192	181	159	139	124	115	111	99	78	65	50	38	28	11	2	1	0	Acala+BR
297	267	236	202	182	170	155	139	120	106	96	92	80	64	54	45	31	18	7	5	0	0	Placebo+BR

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Figure 3.3.1.236 ECHO: Kaplan-Meier plot of time to first occurrence of SEKI GT: Tumorlysesyndrom
 Safety Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

297	275	248	231	211	194	183	162	141	126	116	112	100	79	68	51	40	29	11	2	1	0	Acala+BR
297	264	237	203	184	172	158	142	123	108	99	94	82	65	56	48	33	19	8	5	0	0	Placebo+BR

Nutzenbewertung nach AMNOG

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Table 4.1.1.1.1 ECHO: Summary of subgroup analysis of Gesamtüberleben
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	15 (18,3)	NE [NE; NE]	83	26 (31,3)	NE [NE; NE]	0,52	[0,27; 0,97]	0,0402*
Westeuropa	46	15 (32,6)	NE [NE; NE]	46	20 (43,5)	NE [NE; NE]	0,73	[0,36; 1,41]	0,3442
Andere	171	67 (39,2)	72,1 [49,0; NE]	170	60 (35,3)	NE [NE; NE]	1,09	[0,77; 1,54]	0,6387
Interaktion p-Wert									0,1087
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	26 (26,3)	NE [NE; NE]	101	21 (20,8)	NE [NE; NE]	1,22	[0,69; 2,19]	0,4936
Intermediäres Risiko [4-5]	128	35 (27,3)	NE [NE; NE]	125	48 (38,4)	NE [NE; NE]	0,69	[0,44; 1,06]	0,0879
Hohes Risiko [6-11]	72	36 (50,0)	51,7 [32,2; NE]	73	37 (50,7)	55,4 [20,8; NE]	0,89	[0,56; 1,41]	0,6097
Interaktion p-Wert									0,2860
Geschlecht [eCRF]									
Männlich	214	80 (37,4)	NE [NE; NE]	209	76 (36,4)	NE [NE; NE]	1,01	[0,74; 1,38]	0,9484
Weiblich	85	17 (20,0)	NE [NE; NE]	90	30 (33,3)	NE [NE; NE]	0,53	[0,29; 0,95]	0,0321*
Interaktion p-Wert									0,0559
Altersgruppe I [eCRF]									
< 70 Jahre	123	36 (29,3)	NE [NE; NE]	117	35 (29,9)	NE [NE; NE]	0,94	[0,59; 1,50]	0,7893
>= 70 Jahre	176	61 (34,7)	NE [NE; NE]	182	71 (39,0)	NE [NE; NE]	0,84	[0,60; 1,19]	0,3272
Interaktion p-Wert									0,7156
Altersgruppe II [eCRF]									
< 75 Jahre	215	64 (29,8)	NE [NE; NE]	222	72 (32,4)	NE [NE; NE]	0,87	[0,62; 1,22]	0,4139
>= 75 Jahre	84	33 (39,3)	67,0 [52,0; NE]	77	34 (44,2)	60,2 [30,7; NE]	0,85	[0,52; 1,37]	0,4994
Interaktion p-Wert									0,9337
Abstammung [eCRF]									
Weiß	233	76 (32,6)	NE [NE; NE]	235	89 (37,9)	NE [NE; NE]	0,81	[0,60; 1,11]	0,1880

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.1.1 ECHO: Summary of subgroup analysis of Gesamtüberleben
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	18 (34,6)	NE [NE; NE]	53	13 (24,5)	NE [NE; NE]	1,45	[0,71; 3,02]	0,3051
Interaktion p-Wert									0,1431
ECOG-PS [eCRF]									
0	156	37 (23,7)	NE [NE; NE]	140	44 (31,4)	NE [NE; NE]	0,70	[0,45; 1,09]	0,1115
1	129	56 (43,4)	67,0 [44,6; NE]	132	47 (35,6)	73,8 [60,2; NE]	1,22	[0,83; 1,81]	0,3102
>=2	12	4 (33,3)	36,8 [3,6; NE]	25	14 (56,0)	31,6 [12,2; NE]	0,67	[0,19; 1,86]	0,4574
Interaktion p-Wert									0,1437
Bulky Disease I [eCRF]									
< 5 cm	187	55 (29,4)	NE [NE; NE]	186	50 (26,9)	NE [NE; NE]	1,08	[0,73; 1,58]	0,7009
>= 5 cm	112	42 (37,5)	NE [NE; NE]	113	56 (49,6)	53,5 [35,6;73,8]	0,68	[0,45; 1,01]	0,0541
Interaktion p-Wert									0,0984
Bulky Disease II [eCRF]									
< 10 cm	279	88 (31,5)	NE [NE; NE]	278	92 (33,1)	NE [NE; NE]	0,91	[0,68; 1,22]	0,5253
>= 10 cm	20	9 (45,0)	67,0 [29,4; NE]	21	14 (66,7)	26,9 [16,7; NE]	0,62	[0,26; 1,41]	0,2558
Interaktion p-Wert									0,3911
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	17 (35,4)	NE [NE; NE]	36	8 (22,2)	NE [NE; NE]	1,56	[0,70; 3,83]	0,2854
Stadium IV	251	80 (31,9)	NE [NE; NE]	263	98 (37,3)	NE [NE; NE]	0,81	[0,60; 1,09]	0,1647
Interaktion p-Wert									0,1385
MCL-Typ [eCRF]									
Klassische Variante	197	60 (30,5)	NE [NE; NE]	205	64 (31,2)	NE [NE; NE]	0,92	[0,64; 1,30]	0,6287
Blastoide und pleomorphische Variante	39	21 (53,8)	35,6 [19,9; NE]	33	21 (63,6)	40,6 [15,4;60,2]	0,88	[0,48; 1,62]	0,6836
Andere	0	0	NE	8	1 (12,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,9131

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.1.1 ECHO: Summary of subgroup analysis of Gesamtüberleben
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	28 (25,7)	NE [NE; NE]	103	23 (22,3)	NE [NE; NE]	1,19	[0,68; 2,08]	0,5428
>= 30%	128	52 (40,6)	NE [NE; NE]	127	59 (46,5)	55,4 [36,0; NE]	0,83	[0,57; 1,21]	0,3359
Interaktion p-Wert									0,2967
Ki-67 (%) II [eCRF]									
< 50%	180	50 (27,8)	NE [NE; NE]	164	46 (28,0)	NE [NE; NE]	1,02	[0,68; 1,52]	0,9324
>= 50%	57	30 (52,6)	45,3 [27,2; NE]	66	36 (54,5)	32,8 [20,8; NE]	0,87	[0,53; 1,42]	0,5797
Interaktion p-Wert									0,6307
Knochenmarksbeteiligung [eCRF]									
Ja	178	54 (30,3)	NE [NE; NE]	180	68 (37,8)	NE [NE; NE]	0,76	[0,53; 1,09]	0,1391
Nein	50	16 (32,0)	NE [NE; NE]	45	15 (33,3)	NE [NE; NE]	0,93	[0,46; 1,90]	0,8431
Interaktion p-Wert									0,6241
Extranodale Erkrankung [eCRF]									
Ja	264	87 (33,0)	NE [NE; NE]	277	102 (36,8)	NE [NE; NE]	0,85	[0,64; 1,13]	0,2737
Nein	35	10 (28,6)	NE [NE; NE]	22	4 (18,2)	NE [NE; NE]	1,56	[0,52; 5,68]	0,4401
Interaktion p-Wert									0,3061
Gastrointestinale Erkrankung [eCRF]									
Ja	74	29 (39,2)	NE [NE; NE]	75	32 (42,7)	73,8 [39,1; NE]	0,87	[0,53; 1,45]	0,6032
Nein	225	68 (30,2)	NE [NE; NE]	224	74 (33,0)	NE [NE; NE]	0,87	[0,63; 1,21]	0,4087
Interaktion p-Wert									0,9858
LDH > ULN [eCRF]									
Ja	52	26 (50,0)	51,7 [20,9; NE]	54	33 (61,1)	25,2 [19,1;55,4]	0,65	[0,39; 1,09]	0,1044
Nein	245	71 (29,0)	NE [NE; NE]	241	70 (29,0)	NE [NE; NE]	0,98	[0,70; 1,36]	0,9039
Interaktion p-Wert									0,1940

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.5.1 ECHO: Summary of subgroup analysis of Gesamtüberleben - Sensitivitätsanalyse: Zensierung von Todesfällen durch COVID-19
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]	
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Geographic Region [IXRS]										
Nordamerika	82	12 (14,6)	NE [NE; NE]	83	20 (24,1)	NE [NE; NE]	0,55	[0,26; 1,10]	0,0932	
Westeuropa	46	10 (21,7)	NE [NE; NE]	46	14 (30,4)	NE [NE; NE]	0,70	[0,30; 1,56]	0,3777	
Andere	171	42 (24,6)	NE [NE; NE]	170	46 (27,1)	NE [NE; NE]	0,88	[0,58; 1,34]	0,5628	
Interaktion p-Wert									0,5049	
Vereinfachter MIPI-Score [IXRS]										
Geringes Risiko [0-3]	99	13 (13,1)	NE [NE; NE]	101	13 (12,9)	NE [NE; NE]	0,99	[0,45; 2,15]	0,9699	
Intermediäres Risiko [4-5]	128	18 (14,1)	NE [NE; NE]	125	33 (26,4)	NE [NE; NE]	0,51	[0,28; 0,90]	0,0199*	
Hohes Risiko [6-11]	72	33 (45,8)	64,6 [34,6; NE]	73	34 (46,6)	60,2 [23,1; NE]	0,89	[0,55; 1,44]	0,6302	
Interaktion p-Wert									0,2616	
Geschlecht [eCRF]										
Männlich	214	54 (25,2)	NE [NE; NE]	209	60 (28,7)	NE [NE; NE]	0,86	[0,60; 1,24]	0,4263	
Weiblich	85	10 (11,8)	NE [NE; NE]	90	20 (22,2)	NE [NE; NE]	0,47	[0,21; 0,98]	0,0451*	
Interaktion p-Wert									0,1536	
Altersgruppe I [eCRF]										
< 70 Jahre	123	21 (17,1)	NE [NE; NE]	117	26 (22,2)	NE [NE; NE]	0,73	[0,41; 1,30]	0,2841	
>= 70 Jahre	176	43 (24,4)	NE [NE; NE]	182	54 (29,7)	NE [NE; NE]	0,79	[0,52; 1,17]	0,2397	
Interaktion p-Wert									0,8369	
Altersgruppe II [eCRF]										
< 75 Jahre	215	40 (18,6)	NE [NE; NE]	222	55 (24,8)	NE [NE; NE]	0,71	[0,47; 1,07]	0,0983	
>= 75 Jahre	84	24 (28,6)	NE [NE; NE]	77	25 (32,5)	NE [NE; NE]	0,84	[0,48; 1,48]	0,5515	
Interaktion p-Wert									0,6283	
Abstammung [eCRF]										

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.5.1 ECHO: Summary of subgroup analysis of Gesamtüberleben - Sensitivitätsanalyse: Zensierung von Todesfällen durch COVID-19
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Weiß	233	49 (21,0)	NE [NE; NE]	235	69 (29,4)	NE [NE; NE]	0,68	[0,47; 0,98]	0,0369*
Nicht-weiß	52	12 (23,1)	NE [NE; NE]	53	9 (17,0)	NE [NE; NE]	1,38	[0,59; 3,39]	0,4602
Interaktion p-Wert									0,1354
ECOG-PS [eCRF]									
0	156	20 (12,8)	NE [NE; NE]	140	30 (21,4)	NE [NE; NE]	0,56	[0,31; 0,98]	0,0421*
1	129	41 (31,8)	NE [NE; NE]	132	36 (27,3)	NE [NE; NE]	1,16	[0,74; 1,82]	0,5176
>=2	12	3 (25,0)	NE [NE; NE]	25	13 (52,0)	33,0 [12,2; NE]	0,52	[0,12; 1,62]	0,2796
Interaktion p-Wert									0,0998
Bulky Disease I [eCRF]									
< 5 cm	187	34 (18,2)	NE [NE; NE]	186	37 (19,9)	NE [NE; NE]	0,90	[0,56; 1,43]	0,6506
>= 5 cm	112	30 (26,8)	NE [NE; NE]	113	43 (38,1)	73,8 [50,2; NE]	0,63	[0,39; 1,01]	0,0537
Interaktion p-Wert									0,3011
Bulky Disease II [eCRF]									
< 10 cm	279	56 (20,1)	NE [NE; NE]	278	70 (25,2)	NE [NE; NE]	0,76	[0,53; 1,08]	0,1266
>= 10 cm	20	8 (40,0)	67,0 [29,4; NE]	21	10 (47,6)	37,4 [22,8; NE]	0,78	[0,30; 1,97]	0,5945
Interaktion p-Wert									0,9665
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	7 (14,6)	NE [NE; NE]	36	5 (13,9)	NE [NE; NE]	1,02	[0,33; 3,44]	0,9740
Stadium IV	251	57 (22,7)	NE [NE; NE]	263	75 (28,5)	NE [NE; NE]	0,76	[0,54; 1,07]	0,1130
Interaktion p-Wert									0,6260
MCL-Typ [eCRF]									
Klassische Variante	197	39 (19,8)	NE [NE; NE]	205	45 (22,0)	NE [NE; NE]	0,85	[0,55; 1,31]	0,4622
Blastoide und pleomorphische Variante	39	14 (35,9)	60,2 [19,9; NE]	33	16 (48,5)	53,4 [15,4; NE]	0,75	[0,36; 1,54]	0,4314
Andere	0	0	NE	8	1 (12,5)	NE [NE; NE]	NC	[NC]	NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.5.1 ECHO: Summary of subgroup analysis of Gesamtüberleben - Sensitivitätsanalyse: Zensierung von Todesfällen durch COVID-19
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Interaktion p-Wert									0,7657
Ki-67 (%) I [eCRF]									
< 30%	109	17 (15,6)	NE [NE; NE]	103	17 (16,5)	NE [NE; NE]	0,97	[0,49; 1,91]	0,9288
>= 30%	128	38 (29,7)	NE [NE; NE]	127	44 (34,6)	NE [NE; NE]	0,82	[0,53; 1,26]	0,3629
Interaktion p-Wert									0,6761
Ki-67 (%) II [eCRF]									
< 50%	180	32 (17,8)	NE [NE; NE]	164	32 (19,5)	NE [NE; NE]	0,93	[0,57; 1,53]	0,7833
>= 50%	57	23 (40,4)	67,0 [36,2; NE]	66	29 (43,9)	67,6 [25,8; NE]	0,83	[0,48; 1,43]	0,5045
Interaktion p-Wert									0,7543
Knochenmarksbeteiligung [eCRF]									
Ja	178	39 (21,9)	NE [NE; NE]	180	56 (31,1)	NE [NE; NE]	0,67	[0,44; 1,01]	0,0561
Nein	50	8 (16,0)	NE [NE; NE]	45	9 (20,0)	NE [NE; NE]	0,77	[0,29; 2,02]	0,5963
Interaktion p-Wert									0,7945
Extranodale Erkrankung [eCRF]									
Ja	264	60 (22,7)	NE [NE; NE]	277	78 (28,2)	NE [NE; NE]	0,77	[0,55; 1,08]	0,1271
Nein	35	4 (11,4)	NE [NE; NE]	22	2 (9,1)	NE [NE; NE]	1,23	[0,24; 8,90]	0,8064
Interaktion p-Wert									0,5862
Gastrointestinale Erkrankung [eCRF]									
Ja	74	23 (31,1)	NE [NE; NE]	75	21 (28,0)	73,8 [55,4; NE]	1,06	[0,58; 1,92]	0,8584
Nein	225	41 (18,2)	NE [NE; NE]	224	59 (26,3)	NE [NE; NE]	0,66	[0,44; 0,98]	0,0389*
Interaktion p-Wert									0,1959
LDH > ULN [eCRF]									
Ja	52	23 (44,2)	67,0 [20,9; NE]	54	27 (50,0)	30,5 [19,3; NE]	0,72	[0,41; 1,25]	0,2438

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.5.1 ECHO: Summary of subgroup analysis of Gesamtüberleben - Sensitivitätsanalyse: Zensierung von Todesfällen durch COVID-19
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]		2-seitigen p-Wert [b]
	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]			
	n			n					
Nein	245	41 (16,7)	NE [NE; NE]	241	50 (20,7)	NE [NE; NE]	0,79	[0,52; 1,19]	0,2653
Interaktion p-Wert									0,7849

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.2.1 ECHO: Summary of subgroup analysis of Progressionsfreies Überleben (IRC)
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	19 (23,2)	NE [NE; NE]	83	35 (42,2)	64,1 [33,2; NE]	0,48	[0,27; 0,83]	0,0084*
Westeuropa	46	14 (30,4)	66,4 [42,0; NE]	46	24 (52,2)	27,8 [22,1; NE]	0,53	[0,27; 1,005]	0,0517
Andere	171	77 (45,0)	49,0 [35,2;70,2]	170	78 (45,9)	49,6 [35,6;61,6]	0,90	[0,65; 1,23]	0,4960
Interaktion p-Wert									0,0906
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	24 (24,2)	NE [NE; NE]	101	39 (38,6)	68,9 [39,6; NE]	0,60	[0,36; 0,996]	0,0480*
Intermediäres Risiko [4-5]	128	46 (35,9)	66,7 [49,2; NE]	125	52 (41,6)	56,6 [33,3; NE]	0,75	[0,50; 1,12]	0,1615
Hohes Risiko [6-11]	72	40 (55,6)	34,6 [22,2;55,1]	73	46 (63,0)	19,4 [9,2;49,6]	0,76	[0,50; 1,16]	0,2043
Interaktion p-Wert									0,7485
Geschlecht [eCRF]									
Männlich	214	93 (43,5)	55,1 [35,2;66,7]	209	94 (45,0)	56,6 [36,0;67,8]	0,91	[0,68; 1,21]	0,5193
Weiblich	85	17 (20,0)	NE [NE; NE]	90	43 (47,8)	38,7 [29,9; NE]	0,34	[0,19; 0,59]	<0,0001*
Interaktion p-Wert									0,0015*
Altersgruppe I [eCRF]									
< 70 Jahre	123	42 (34,1)	66,4 [55,3; NE]	117	57 (48,7)	56,6 [32,1;66,3]	0,64	[0,43; 0,96]	0,0294*
>= 70 Jahre	176	68 (38,6)	66,2 [42,0; NE]	182	80 (44,0)	46,8 [33,2; NE]	0,78	[0,57; 1,08]	0,1384
Interaktion p-Wert									0,4545
Altersgruppe II [eCRF]									
< 75 Jahre	215	74 (34,4)	66,7 [55,3; NE]	222	96 (43,2)	56,6 [39,6;67,8]	0,71	[0,52; 0,96]	0,0270*
>= 75 Jahre	84	36 (42,9)	42,0 [27,6; NE]	77	41 (53,2)	30,7 [19,4; NE]	0,73	[0,47; 1,15]	0,1721
Interaktion p-Wert									0,9163
Abstammung [eCRF]									
Weiß	233	89 (38,2)	66,4 [49,5; NE]	235	113 (48,1)	44,2 [32,6;60,8]	0,70	[0,53; 0,92]	0,0107*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.2.1 ECHO: Summary of subgroup analysis of Progressionsfreies Überleben (IRC)
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	19 (36,5)	NE [NE; NE]	53	20 (37,7)	67,8 [34,9; NE]	1,00	[0,53; 1,89]	0,9878
Interaktion p-Wert									0,2984
ECOG-PS [eCRF]									
0	156	42 (26,9)	70,2 [66,4; NE]	140	60 (42,9)	60,8 [36,1; NE]	0,57	[0,38; 0,84]	0,0048*
1	129	63 (48,8)	42,0 [33,4;60,2]	132	60 (45,5)	49,6 [31,6; NE]	1,02	[0,71; 1,45]	0,9293
>=2	12	5 (41,7)	29,4 [2,0; NE]	25	17 (68,0)	22,1 [5,5;32,6]	0,54	[0,18; 1,36]	0,1969
Interaktion p-Wert									0,0763
Bulky Disease I [eCRF]									
< 5 cm	187	62 (33,2)	66,4 [66,2; NE]	186	68 (36,6)	66,3 [50,1; NE]	0,88	[0,62; 1,24]	0,4611
>= 5 cm	112	48 (42,9)	49,0 [34,8; NE]	113	69 (61,1)	27,7 [16,6;36,1]	0,55	[0,38; 0,79]	0,0013*
Interaktion p-Wert									0,0682
Bulky Disease II [eCRF]									
< 10 cm	279	99 (35,5)	66,4 [55,3; NE]	278	122 (43,9)	50,1 [38,7;66,3]	0,74	[0,57; 0,96]	0,0260*
>= 10 cm	20	11 (55,0)	44,8 [11,0; NE]	21	15 (71,4)	19,4 [9,5;34,9]	0,54	[0,24; 1,18]	0,1216
Interaktion p-Wert									0,4576
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	16 (33,3)	NE [NE; NE]	36	12 (33,3)	61,6 [36,0; NE]	0,95	[0,45; 2,06]	0,8981
Stadium IV	251	94 (37,5)	66,4 [53,7; NE]	263	125 (47,5)	44,2 [33,2;60,8]	0,71	[0,54; 0,92]	0,0104*
Interaktion p-Wert									0,4592
MCL-Typ [eCRF]									
Klassische Variante	197	70 (35,5)	66,7 [55,1; NE]	205	92 (44,9)	50,1 [38,7;64,1]	0,74	[0,54; 1,01]	0,0544
Blastoide und pleomorphische Variante	39	22 (56,4)	33,4 [12,2;49,5]	33	20 (60,6)	16,7 [8,3;32,8]	0,67	[0,37; 1,24]	0,2044
Andere	0	0	NE	8	3 (37,5)	33,2 [11,7; NE]	NC	[NC]	NC
Interaktion p-Wert									0,7922

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.2.1 ECHO: Summary of subgroup analysis of Progressionsfreies Überleben (IRC)
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Ki-67 (%) I [eCRF]											
< 30%	109	32 (29,4)	70,2 [66,4; NE]		103	40 (38,8)	66,3 [44,2; NE]		0,74	[0,46; 1,18]	0,2099
>= 30%	128	57 (44,5)	45,3 [33,5; NE]		127	70 (55,1)	32,6 [20,7;49,7]		0,68	[0,48; 0,97]	0,0316*
Interaktion p-Wert											0,7715
Ki-67 (%) II [eCRF]											
< 50%	180	58 (32,2)	70,2 [66,4; NE]		164	68 (41,5)	60,8 [40,2; NE]		0,75	[0,52; 1,06]	0,1019
>= 50%	57	31 (54,4)	36,2 [24,3;55,1]		66	42 (63,6)	19,3 [11,3;32,1]		0,67	[0,42; 1,07]	0,0933
Interaktion p-Wert											0,7263
Knochenmarksbeteiligung [eCRF]											
Ja	178	62 (34,8)	66,7 [55,3; NE]		180	85 (47,2)	50,1 [32,8;66,3]		0,67	[0,48; 0,93]	0,0158*
Nein	50	16 (32,0)	NE [NE; NE]		45	19 (42,2)	49,7 [35,6; NE]		0,70	[0,35; 1,36]	0,2887
Interaktion p-Wert											0,9138
Extranodale Erkrankung [eCRF]											
Ja	264	100 (37,9)	66,4 [53,7; NE]		277	131 (47,3)	46,8 [33,2;61,6]		0,73	[0,56; 0,94]	0,0156*
Nein	35	10 (28,6)	NE [NE; NE]		22	6 (27,3)	NE [NE; NE]		0,93	[0,35; 2,74]	0,8923
Interaktion p-Wert											0,6373
Gastrointestinale Erkrankung [eCRF]											
Ja	74	30 (40,5)	66,4 [29,2; NE]		75	40 (53,3)	33,2 [22,1;44,2]		0,65	[0,40; 1,04]	0,0700
Nein	225	80 (35,6)	66,7 [53,7; NE]		224	97 (43,3)	60,8 [39,6;67,8]		0,75	[0,56; 1,01]	0,0599
Interaktion p-Wert											0,5939
LDH > ULN [eCRF]											
Ja	52	33 (63,5)	27,9 [11,0;53,7]		54	37 (68,5)	11,3 [8,2;21,9]		0,74	[0,46; 1,19]	0,2142
Nein	245	77 (31,4)	70,2 [66,7; NE]		241	98 (40,7)	60,8 [43,5; NE]		0,71	[0,53; 0,96]	0,0250*
Interaktion p-Wert											0,8827

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.6.1 ECHO: Summary of subgroup analysis of Progressionsfreies Überleben – Sensitivitätsanalyse: Zensierung von Todesfällen durch COVID-19 (IRC)
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]	
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Geographic Region [IXRS]										
Nordamerika	82	17 (20,7)	NE [NE; NE]	83	31 (37,3)	67,8 [39,6; NE]	0,49	[0,26; 0,87]	0,0146*	
Westeuropa	46	10 (21,7)	66,4 [66,4; NE]	46	19 (41,3)	NE [NE; NE]	0,48	[0,22; 1,02]	0,0558	
Andere	171	56 (32,7)	NE [NE; NE]	170	67 (39,4)	56,6 [44,3; NE]	0,76	[0,53; 1,08]	0,1267	
Interaktion p-Wert									0,3263	
Vereinfachter MIPI-Score [IXRS]										
Geringes Risiko [0-3]	99	12 (12,1)	NE [NE; NE]	101	31 (30,7)	68,9 [60,8; NE]	0,38	[0,19; 0,72]	0,0027*	
Intermediäres Risiko [4-5]	128	33 (25,8)	NE [NE; NE]	125	42 (33,6)	64,1 [44,3; NE]	0,67	[0,42; 1,06]	0,0861	
Hohes Risiko [6-11]	72	38 (52,8)	36,0 [22,2;55,3]	73	44 (60,3)	21,9 [10,1;49,7]	0,76	[0,49; 1,17]	0,2100	
Interaktion p-Wert									0,2113	
Geschlecht [eCRF]										
Männlich	214	71 (33,2)	66,4 [55,3; NE]	209	83 (39,7)	64,1 [46,8;68,9]	0,79	[0,57; 1,08]	0,1378	
Weiblich	85	12 (14,1)	NE [NE; NE]	90	34 (37,8)	61,6 [37,1; NE]	0,31	[0,15; 0,58]	0,0002*	
Interaktion p-Wert									0,0085*	
Altersgruppe I [eCRF]										
< 70 Jahre	123	29 (23,6)	NE [NE; NE]	117	49 (41,9)	61,6 [44,3;68,9]	0,52	[0,32; 0,82]	0,0045*	
>= 70 Jahre	176	54 (30,7)	NE [NE; NE]	182	68 (37,4)	60,8 [43,5; NE]	0,73	[0,51; 1,05]	0,0878	
Interaktion p-Wert									0,2458	
Altersgruppe II [eCRF]										
< 75 Jahre	215	55 (25,6)	NE [NE; NE]	222	83 (37,4)	64,1 [50,1; NE]	0,61	[0,44; 0,86]	0,0047*	
>= 75 Jahre	84	28 (33,3)	NE [NE; NE]	77	34 (44,2)	44,2 [24,5; NE]	0,68	[0,41; 1,13]	0,1360	
Interaktion p-Wert									0,7302	
Abstammung [eCRF]										

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.6.1 ECHO: Summary of subgroup analysis of Progressionsfreies Überleben – Sensitivitätsanalyse: Zensierung von Todesfällen durch COVID-19 (IRC)
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]		
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]					
Weiß	233	67 (28,8)	NE	[	NE;	NE]	235	98 (41,7)	60,8	[39,8;68,9]	0,61	[0,44; 0,83]	0,0016*
Nicht-weiß	52	14 (26,9)	NE	[	NE;	NE]	53	16 (30,2)	67,8	[49,7; NE]	0,92	[0,44; 1,88]	0,8151
Interaktion p-Wert													0,3053
ECOG-PS [eCRF]													
0	156	29 (18,6)	NE	[	NE;	NE]	140	47 (33,6)	67,8	[60,8; NE]	0,50	[0,31; 0,80]	0,0033*
1	129	50 (38,8)	60,2	[42,0;	NE]		132	54 (40,9)	61,6	[38,7; NE]	0,90	[0,61; 1,32]	0,5770
>=2	12	4 (33,3)	29,4	[2,0;	NE]		25	16 (64,0)	22,1	[5,5;49,7]	0,44	[0,13; 1,22]	0,1196
Interaktion p-Wert													0,1231
Bulky Disease I [eCRF]													
< 5 cm	187	45 (24,1)	66,7	[66,4;	NE]		186	56 (30,1)	67,8	[61,6; NE]	0,77	[0,52; 1,14]	0,1942
>= 5 cm	112	38 (33,9)	NE	[	NE;	NE]	113	61 (54,0)	32,6	[19,4;49,6]	0,50	[0,33; 0,75]	0,0007*
Interaktion p-Wert													0,1340
Bulky Disease II [eCRF]													
< 10 cm	279	73 (26,2)	NE	[	NE;	NE]	278	103 (37,1)	64,1	[50,1; NE]	0,65	[0,48; 0,87]	0,0042*
>= 10 cm	20	10 (50,0)	55,1	[11,0;	NE]		21	14 (66,7)	22,1	[9,5;34,9]	0,55	[0,24; 1,24]	0,1495
Interaktion p-Wert													0,7207
Ann Arbor-Stadium für Lymphome [eCRF]													
Stadium I-III	48	9 (18,8)	NE	[	NE;	NE]	36	9 (25,0)	61,6	[61,6; NE]	0,71	[0,28; 1,83]	0,4777
Stadium IV	251	74 (29,5)	NE	[	NE;	NE]	263	108 (41,1)	60,8	[44,2;68,9]	0,65	[0,48; 0,87]	0,0034*
Interaktion p-Wert													0,8363
MCL-Typ [eCRF]													
Klassische Variante	197	55 (27,9)	NE	[	NE;	NE]	205	76 (37,1)	61,6	[49,7; NE]	0,70	[0,49; 0,99]	0,0445*
Blastoide und pleomorphische Variante	39	15 (38,5)	60,2	[12,2;	NE]		33	18 (54,5)	16,8	[8,3;49,6]	0,52	[0,26; 1,03]	0,0605
Andere	0	0	NE				8	3 (37,5)	33,2	[11,7; NE]	NC	[NC]	NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.6.1 ECHO: Summary of subgroup analysis of Progressionsfreies Überleben – Sensitivitätsanalyse: Zensierung von Todesfällen durch COVID-19 (IRC)
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Interaktion p-Wert									0,4387
Ki-67 (%) I [eCRF]									
< 30%	109	24 (22,0)	NE [NE; NE]	103	35 (34,0)	66,3 [60,8; NE]	0,64	[0,37; 1,06]	0,0854
>= 30%	128	44 (34,4)	NE [NE; NE]	127	60 (47,2)	49,7 [25,8;61,6]	0,62	[0,42; 0,92]	0,0161*
Interaktion p-Wert									0,9444
Ki-67 (%) II [eCRF]									
< 50%	180	43 (23,9)	NE [NE; NE]	164	57 (34,8)	66,3 [60,8; NE]	0,66	[0,44; 0,98]	0,0386*
>= 50%	57	25 (43,9)	49,5 [33,4; NE]	66	38 (57,6)	19,4 [13,6;38,7]	0,62	[0,37; 1,02]	0,0584
Interaktion p-Wert									0,8373
Knochenmarksbeteiligung [eCRF]									
Ja	178	49 (27,5)	NE [NE; NE]	180	77 (42,8)	60,8 [43,5;68,9]	0,59	[0,41; 0,84]	0,0031*
Nein	50	12 (24,0)	NE [NE; NE]	45	13 (28,9)	NE [NE; NE]	0,77	[0,35; 1,70]	0,5142
Interaktion p-Wert									0,5376
Extranodale Erkrankung [eCRF]									
Ja	264	77 (29,2)	NE [NE; NE]	277	113 (40,8)	60,8 [44,3;68,9]	0,65	[0,49; 0,87]	0,0033*
Nein	35	6 (17,1)	NE [NE; NE]	22	4 (18,2)	NE [NE; NE]	0,84	[0,24; 3,28]	0,7876
Interaktion p-Wert									0,6979
Gastrointestinale Erkrankung [eCRF]									
Ja	74	25 (33,8)	66,4 [66,4; NE]	75	30 (40,0)	44,2 [27,7; NE]	0,72	[0,42; 1,23]	0,2337
Nein	225	58 (25,8)	NE [NE; NE]	224	87 (38,8)	61,6 [49,7;68,9]	0,61	[0,44; 0,85]	0,0032*
Interaktion p-Wert									0,5912
LDH > ULN [eCRF]									
Ja	52	31 (59,6)	27,9 [11,0;55,3]	54	34 (63,0)	11,3 [8,2;60,8]	0,77	[0,47; 1,26]	0,2955

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.6.1 ECHO: Summary of subgroup analysis of Progressionsfreies Überleben – Sensitivitätsanalyse: Zensierung von Todesfällen durch COVID-19 (IRC)
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]		2-seitiger p-Wert [b]
	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]			
	n			n					
Nein	245	52 (21,2)	NE [NE; NE]	241	81 (33,6)	66,3 [56,6; NE]	0,58	[0,41; 0,82]	0,0021*
Interaktion p-Wert									0,3621

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are ≥10 patients in each subgroup level, ≥10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.3.1 ECHO: Summary of subgroup analysis of Zeit bis zum Ansprechen CR, PR (IRC)
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	75 (91,5)	2,8 [2,8; 2,8]	83	71 (85,5)	2,8 [2,8; 2,9]	1,06	[0,76; 1,47]	0,7305
Westeuropa	46	41 (89,1)	2,7 [2,7; 2,8]	46	41 (89,1)	2,8 [2,7; 2,9]	1,42	[0,92; 2,19]	0,1159
Andere	171	156 (91,2)	2,8 [2,8; 2,8]	170	151 (88,8)	2,8 [2,8; 2,8]	1,10	[0,88; 1,37]	0,4263
Interaktion p-Wert									0,5287
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	95 (96,0)	2,8 [2,8; 2,9]	101	94 (93,1)	2,8 [2,8; 2,8]	1,06	[0,79; 1,41]	0,7005
Intermediäres Risiko [4-5]	128	118 (92,2)	2,8 [2,7; 2,8]	125	118 (94,4)	2,8 [2,8; 2,9]	1,13	[0,88; 1,46]	0,3454
Hohes Risiko [6-11]	72	59 (81,9)	2,8 [2,8; 2,8]	73	51 (69,9)	2,8 [2,8; 2,8]	1,21	[0,83; 1,77]	0,3123
Interaktion p-Wert									0,8461
Geschlecht [eCRF]									
Männlich	214	196 (91,6)	2,8 [NE; NE]	209	181 (86,6)	2,8 [2,8; 2,8]	1,07	[0,88; 1,31]	0,5059
Weiblich	85	76 (89,4)	2,8 [2,8; 2,8]	90	82 (91,1)	2,8 [2,8; 2,9]	1,22	[0,89; 1,67]	0,2162
Interaktion p-Wert									0,4969
Altersgruppe I [eCRF]									
< 70 Jahre	123	114 (92,7)	2,8 [2,8; 2,8]	117	104 (88,9)	2,8 [2,8; 2,8]	1,11	[0,85; 1,45]	0,4364
>= 70 Jahre	176	158 (89,8)	2,8 [2,8; 2,8]	182	159 (87,4)	2,8 [2,8; 2,8]	1,13	[0,90; 1,40]	0,2906
Interaktion p-Wert									0,9397
Altersgruppe II [eCRF]									
< 75 Jahre	215	197 (91,6)	2,8 [2,8; 2,8]	222	193 (86,9)	2,8 [2,8; 2,8]	1,06	[0,87; 1,30]	0,5431
>= 75 Jahre	84	75 (89,3)	2,8 [2,7; 2,8]	77	70 (90,9)	2,8 [2,8; 2,8]	1,30	[0,94; 1,81]	0,1130
Interaktion p-Wert									0,2991
Abstammung [eCRF]									
Weiß	233	209 (89,7)	2,8 [2,8; 2,8]	235	204 (86,8)	2,8 [2,8; 2,8]	1,15	[0,94; 1,39]	0,1672

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.3.1 ECHO: Summary of subgroup analysis of Zeit bis zum Ansprechen CR, PR (IRC)
 Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	51 (98,1)	2,8 [2,7; 2,8]	53	50 (94,3)	2,8 [2,7; 2,8]	1,03	[0,69; 1,52]	0,8865
Interaktion p-Wert									0,6289
ECOG-PS [eCRF]									
0	156	148 (94,9)	2,8 [2,8; 2,8]	140	133 (95,0)	2,8 [2,8; 2,8]	1,10	[0,87; 1,39]	0,4267
1	129	116 (89,9)	2,8 [2,8; 2,8]	132	113 (85,6)	2,8 [2,8; 2,9]	1,12	[0,87; 1,46]	0,3825
>=2	12	8 (66,7)	3,0 [2,7; 3,2]	25	17 (68,0)	2,8 [2,8; 2,9]	1,07	[0,44; 2,42]	0,8671
Interaktion p-Wert									0,9909
Bulky Disease I [eCRF]									
< 5 cm	187	170 (90,9)	2,8 [2,8; 2,8]	186	163 (87,6)	2,8 [2,8; 2,8]	1,11	[0,90; 1,38]	0,3238
>= 5 cm	112	102 (91,1)	2,8 [2,8; 2,8]	113	100 (88,5)	2,8 [2,8; 2,9]	1,12	[0,85; 1,48]	0,4157
Interaktion p-Wert									0,9716
Bulky Disease II [eCRF]									
< 10 cm	279	253 (90,7)	2,8 [2,8; 2,8]	278	244 (87,8)	2,8 [NE; NE]	1,10	[0,93; 1,32]	0,2688
>= 10 cm	20	19 (95,0)	2,8 [2,7; 2,9]	21	19 (90,5)	2,9 [2,7; 3,0]	1,33	[0,70; 2,53]	0,3807
Interaktion p-Wert									0,5818
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	46 (95,8)	2,8 [2,7; 2,8]	36	33 (91,7)	2,8 [2,7; 2,8]	1,17	[0,75; 1,85]	0,4892
Stadium IV	251	226 (90,0)	2,8 [2,8; 2,8]	263	230 (87,5)	2,8 [2,8; 2,8]	1,10	[0,92; 1,32]	0,3080
Interaktion p-Wert									0,8023
MCL-Typ [eCRF]									
Klassische Variante	197	183 (92,9)	2,8 [2,8; 2,8]	205	188 (91,7)	2,8 [2,8; 2,8]	1,13	[0,92; 1,38]	0,2508
Blastoide und pleomorphische Variante	39	32 (82,1)	2,8 [2,7; 2,8]	33	24 (72,7)	2,8 [2,8; 3,0]	1,40	[0,82; 2,40]	0,2141
Andere	0	0	NE	8	7 (87,5)	2,8 [2,5; 5,6]	NC	[NC]	NC
Interaktion p-Wert									0,4576

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.3.1 ECHO: Summary of subgroup analysis of Zeit bis zum Ansprechen CR, PR (IRC)
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	100 (91,7)	2,8 [2,8; 2,9]	103	99 (96,1)	2,8 [2,8; 2,8]	1,02	[0,77; 1,35]	0,9026
>= 30%	128	116 (90,6)	2,8 [2,8; 2,8]	127	109 (85,8)	2,8 [2,8; 2,8]	1,38	[1,06; 1,80]	0,0164*
Interaktion p-Wert									0,1175
Ki-67 (%) II [eCRF]									
< 50%	180	166 (92,2)	2,8 [2,8; 2,8]	164	155 (94,5)	2,8 [2,8; 2,8]	1,14	[0,91; 1,42]	0,2468
>= 50%	57	50 (87,7)	2,8 [2,8; 2,8]	66	53 (80,3)	2,8 [2,8; 2,9]	1,33	[0,90; 1,96]	0,1507
Interaktion p-Wert									0,4963
Knochenmarksbeteiligung [eCRF]									
Ja	178	162 (91,0)	2,8 [2,8; 2,8]	180	159 (88,3)	2,8 [2,8; 2,8]	1,06	[0,85; 1,32]	0,5963
Nein	50	46 (92,0)	2,8 [2,7; 2,8]	45	43 (95,6)	2,8 [2,7; 2,8]	1,28	[0,84; 1,95]	0,2421
Interaktion p-Wert									0,4298
Extranodale Erkrankung [eCRF]									
Ja	264	239 (90,5)	2,8 [NE; NE]	277	243 (87,7)	2,8 [2,8; 2,8]	1,09	[0,91; 1,30]	0,3551
Nein	35	33 (94,3)	2,8 [2,7; 2,8]	22	20 (90,9)	2,8 [2,7; 2,8]	1,38	[0,80; 2,45]	0,2527
Interaktion p-Wert									0,4227
Gastrointestinale Erkrankung [eCRF]									
Ja	74	68 (91,9)	2,8 [2,8; 2,8]	75	65 (86,7)	2,8 [2,8; 2,9]	1,53	[1,09; 2,16]	0,0153*
Nein	225	204 (90,7)	2,8 [2,8; 2,8]	224	198 (88,4)	2,8 [NE; NE]	1,00	[0,82; 1,22]	0,9767
Interaktion p-Wert									0,0364*
LDH > ULN [eCRF]									
Ja	52	44 (84,6)	2,8 [2,8; 2,8]	54	38 (70,4)	2,8 [2,7; 2,8]	1,05	[0,68; 1,63]	0,8195
Nein	245	228 (93,1)	2,8 [2,8; 2,8]	241	223 (92,5)	2,8 [2,8; 2,8]	1,13	[0,94; 1,36]	0,1921
Interaktion p-Wert									0,7635

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.4.1 ECHO: Summary of subgroup analysis of Dauer des Ansprechens (IRC)
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	75	17 (22,7)	NE [NE; NE]	71	30 (42,3)	65,2 [34,5; NE]	0,49	[0,27; 0,88]	0,0173*
Westeuropa	41	14 (34,1)	63,5 [39,4; NE]	41	20 (48,8)	30,6 [23,0; NE]	0,62	[0,31; 1,22]	0,1643
Andere	156	68 (43,6)	52,5 [33,5; NE]	151	67 (44,4)	47,3 [37,6; NE]	0,90	[0,64; 1,26]	0,5284
Interaktion p-Wert									0,1885
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	95	24 (25,3)	NE [NE; NE]	94	37 (39,4)	66,1 [36,9; NE]	0,64	[0,38; 1,06]	0,0830
Intermediäres Risiko [4-5]	118	44 (37,3)	67,4 [46,5; NE]	118	49 (41,5)	58,0 [33,0; NE]	0,75	[0,49; 1,12]	0,1579
Hohes Risiko [6-11]	59	31 (52,5)	38,4 [26,7;63,5]	51	31 (60,8)	44,1 [12,7;47,3]	0,80	[0,49; 1,33]	0,3933
Interaktion p-Wert									0,8096
Geschlecht [eCRF]									
Männlich	196	84 (42,9)	57,2 [34,1;67,4]	181	78 (43,1)	58,0 [41,5;68,2]	0,97	[0,71; 1,32]	0,8563
Weiblich	76	15 (19,7)	NE [NE; NE]	82	39 (47,6)	41,5 [28,6; NE]	0,32	[0,17; 0,57]	<0,0001*
Interaktion p-Wert									0,0007*
Altersgruppe I [eCRF]									
< 70 Jahre	114	39 (34,2)	63,5 [52,5; NE]	104	48 (46,2)	57,9 [33,0;66,1]	0,70	[0,46; 1,07]	0,0965
>= 70 Jahre	158	60 (38,0)	67,4 [42,4; NE]	159	69 (43,4)	46,7 [33,4; NE]	0,78	[0,55; 1,10]	0,1535
Interaktion p-Wert									0,7047
Altersgruppe II [eCRF]									
< 75 Jahre	197	67 (34,0)	63,5 [57,2; NE]	193	81 (42,0)	58,0 [44,1;68,2]	0,75	[0,54; 1,03]	0,0755
>= 75 Jahre	75	32 (42,7)	52,5 [25,5; NE]	70	36 (51,4)	30,0 [19,4; NE]	0,72	[0,45; 1,16]	0,1781
Interaktion p-Wert									0,9072
Abstammung [eCRF]									
Weiß	209	78 (37,3)	63,5 [52,5; NE]	204	94 (46,1)	53,8 [33,4;66,1]	0,72	[0,53; 0,97]	0,0298*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.4.1 ECHO: Summary of subgroup analysis of Dauer des Ansprechens (IRC)
 Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	51	19 (37,3)	NE [NE; NE]	50	20 (40,0)	65,2 [32,2; NE]	0,98	[0,52; 1,84]	0,9482
Interaktion p-Wert									0,3819
ECOG-PS [eCRF]									
0	148	40 (27,0)	NE [NE; NE]	133	55 (41,4)	60,8 [36,8; NE]	0,59	[0,39; 0,88]	0,0099*
1	116	56 (48,3)	42,4 [31,1;63,5]	113	51 (45,1)	53,8 [30,3; NE]	1,02	[0,70; 1,50]	0,9061
>=2	8	3 (37,5)	34,1 [12,4; NE]	17	11 (64,7)	24,9 [5,8; NE]	0,48	[0,11; 1,52]	0,2240
Interaktion p-Wert									0,1075
Bulky Disease I [eCRF]									
< 5 cm	170	57 (33,5)	67,4 [63,5; NE]	163	57 (35,0)	65,2 [57,9; NE]	0,95	[0,66; 1,37]	0,7901
>= 5 cm	102	42 (41,2)	52,5 [33,1; NE]	100	60 (60,0)	29,1 [19,1;36,9]	0,53	[0,35; 0,78]	0,0013*
Interaktion p-Wert									0,0309*
Bulky Disease II [eCRF]									
< 10 cm	253	89 (35,2)	67,4 [57,2; NE]	244	104 (42,6)	58,0 [41,5;66,1]	0,76	[0,57; 1,01]	0,0612
>= 10 cm	19	10 (52,6)	42,1 [13,9; NE]	19	13 (68,4)	19,1 [8,3;32,2]	0,55	[0,23; 1,25]	0,1499
Interaktion p-Wert									0,4522
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	46	18 (39,1)	NE [NE; NE]	33	10 (30,3)	NE [NE; NE]	1,22	[0,58; 2,76]	0,6038
Stadium IV	226	81 (35,8)	63,5 [52,5; NE]	230	107 (46,5)	46,9 [33,4;65,2]	0,70	[0,52; 0,93]	0,0142*
Interaktion p-Wert									0,1748
MCL-Typ [eCRF]									
Klassische Variante	183	64 (35,0)	67,4 [52,5; NE]	188	84 (44,7)	53,8 [36,9;65,2]	0,72	[0,52; 0,999]	0,0493*
Blastoide und pleomorphische Variante	32	20 (62,5)	32,0 [17,2;57,2]	24	14 (58,3)	29,5 [8,4; NE]	0,84	[0,43; 1,69]	0,6118
Andere	0	0	NE	7	3 (42,9)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,7037

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.1.1.4.1 ECHO: Summary of subgroup analysis of Dauer des Ansprechens (IRC)
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	100	28 (28,0)	67,4 [63,5; NE]	99	37 (37,4)	65,2 [41,5; NE]	0,70	[0,42; 1,13]	0,1464
>= 30%	116	54 (46,6)	46,2 [32,0; NE]	109	58 (53,2)	31,2 [24,7;53,8]	0,74	[0,51; 1,07]	0,1105
Interaktion p-Wert									0,8503
Ki-67 (%) II [eCRF]									
< 50%	166	54 (32,5)	67,4 [63,5; NE]	155	62 (40,0)	58,0 [41,5; NE]	0,74	[0,52; 1,07]	0,1122
>= 50%	50	28 (56,0)	34,1 [21,3;52,5]	53	33 (62,3)	23,0 [11,3;53,8]	0,73	[0,44; 1,21]	0,2228
Interaktion p-Wert									0,9546
Knochenmarksbeteiligung [eCRF]									
Ja	162	53 (32,7)	67,4 [63,5; NE]	159	72 (45,3)	58,0 [36,9;66,1]	0,67	[0,47; 0,95]	0,0263*
Nein	46	17 (37,0)	NE [NE; NE]	43	17 (39,5)	46,3 [31,2; NE]	0,77	[0,39; 1,52]	0,4526
Interaktion p-Wert									0,7159
Extranodale Erkrankung [eCRF]									
Ja	239	88 (36,8)	63,5 [52,5; NE]	243	112 (46,1)	47,3 [36,8;65,2]	0,73	[0,55; 0,96]	0,0260*
Nein	33	11 (33,3)	NE [NE; NE]	20	5 (25,0)	NE [NE; NE]	1,25	[0,46; 3,97]	0,6730
Interaktion p-Wert									0,3204
Gastrointestinale Erkrankung [eCRF]									
Ja	68	25 (36,8)	63,5 [29,1; NE]	65	35 (53,8)	30,3 [20,5;46,3]	0,58	[0,34; 0,97]	0,0370*
Nein	204	74 (36,3)	63,5 [52,5; NE]	198	82 (41,4)	58,0 [46,7; NE]	0,81	[0,59; 1,11]	0,1935
Interaktion p-Wert									0,2760
LDH > ULN [eCRF]									
Ja	44	27 (61,4)	39,4 [17,2;52,5]	38	25 (65,8)	17,9 [8,4;65,2]	0,86	[0,50; 1,49]	0,5836
Nein	228	72 (31,6)	NE [NE; NE]	223	90 (40,4)	58,0 [41,5; NE]	0,71	[0,52; 0,97]	0,0293*
Interaktion p-Wert									0,5498

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

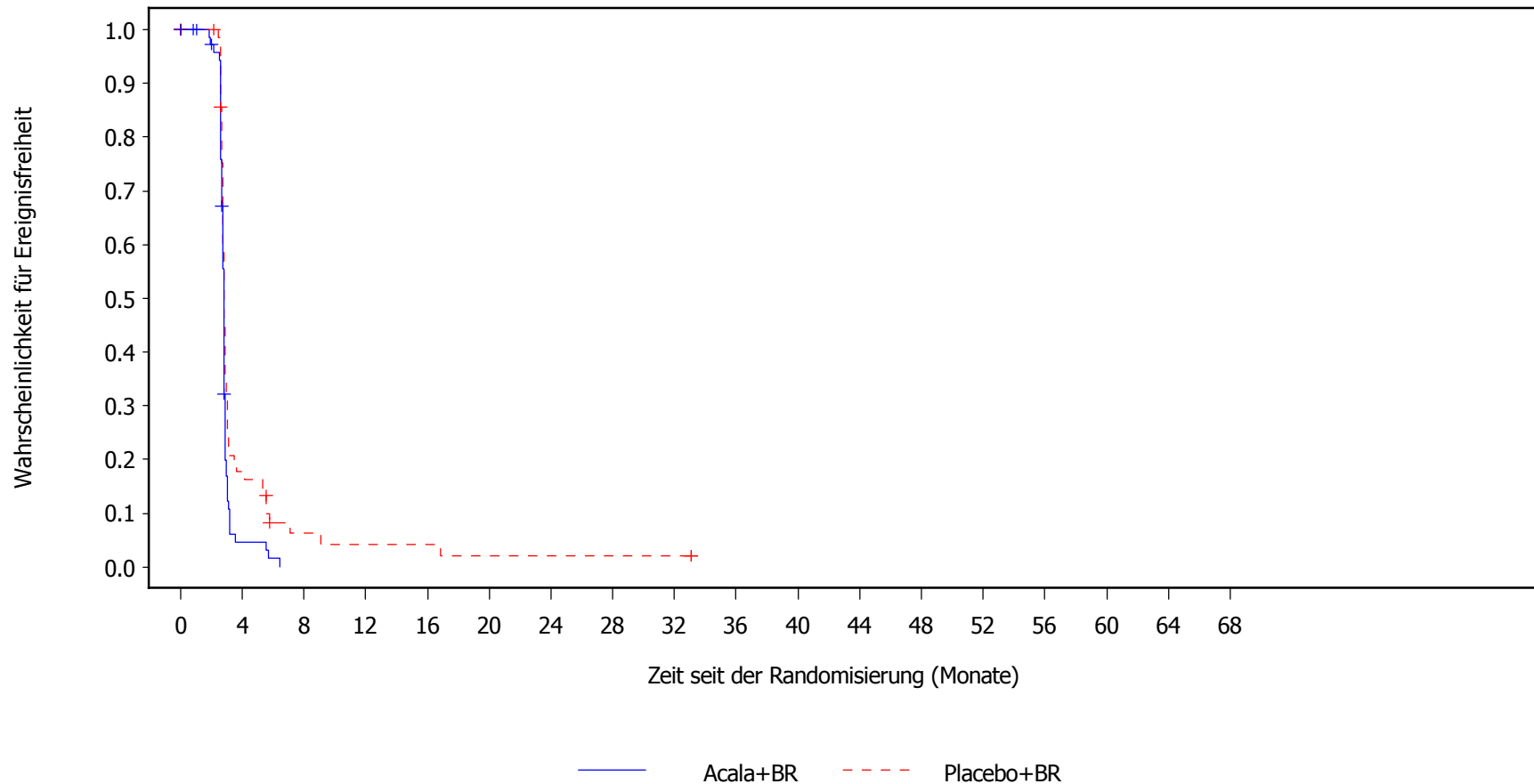
Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.1.2.3.1 ECHO: Subgroup Analysis: Kaplan-Meier plot of Zeit bis zum Ansprechen CR, PR (IRC) for Gastrointestinale
 Erkrankung [eCRF] = Ja
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

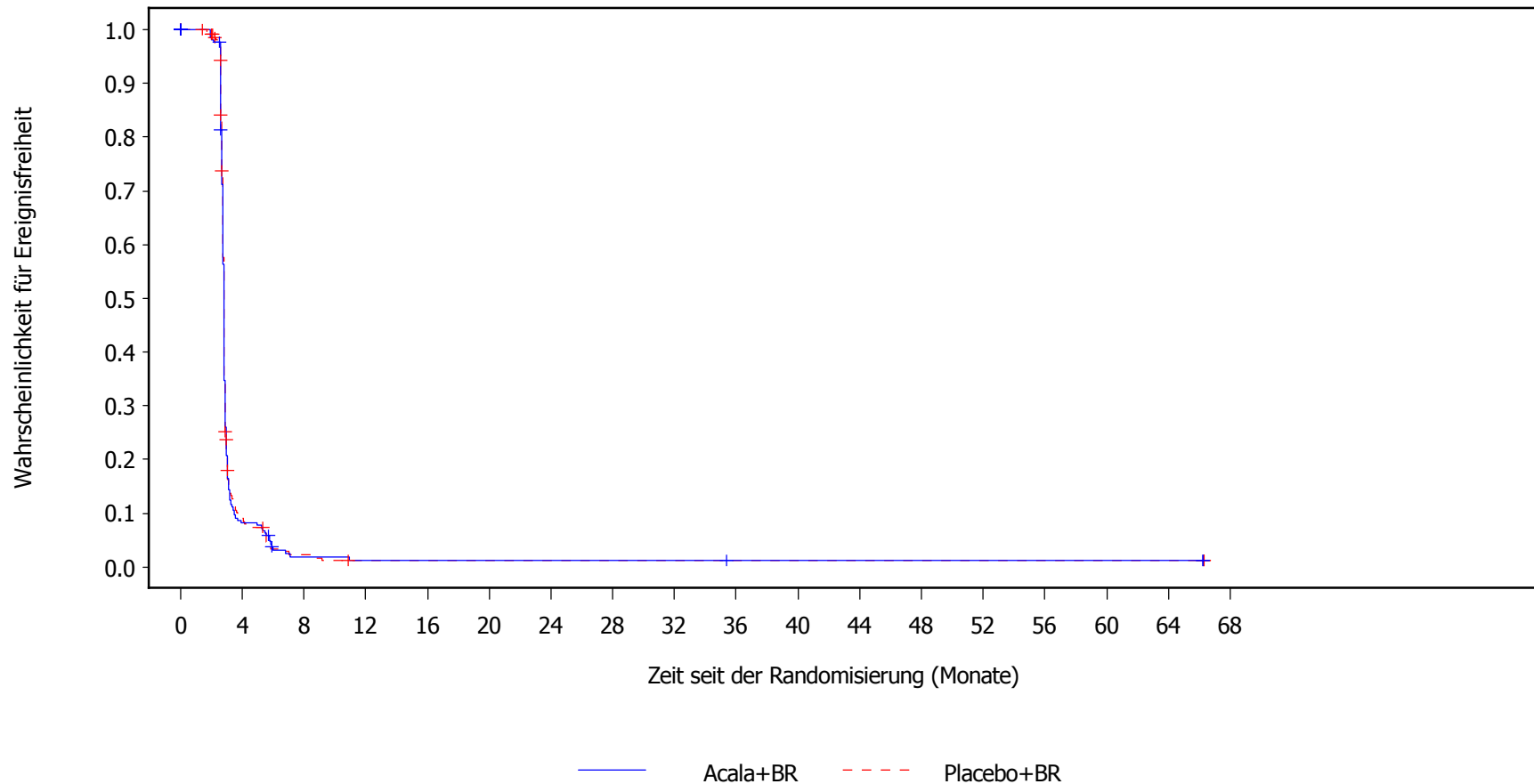
74	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Acala+BR
75	12	3	2	2	1	1	1	1	0	0	0	0	0	0	0	0	0	Placebo+BR

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

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Figure 4.1.2.3.2 ECHO: Subgroup Analysis: Kaplan-Meier plot of Zeit bis zum Ansprechen CR, PR (IRC) for Gastrointestinale Erkrankung [eCRF] = Nein
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

225	17	3	2	2	2	2	2	2	1	1	1	1	1	1	1	1	0	Acala+BR
224	17	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	Placebo+BR

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

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Table 4.2.1.1.1 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Allgemeine Lebensqualität/Gesundheitsszustand
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	43 (52,4)	6,7 [3,9;28,6]	83	27 (32,5)	NE [NE; NE]	1,61	[0,9996; 2,63]	0,0502
Westeuropa	46	22 (47,8)	10,4 [3,8; NE]	46	21 (45,7)	6,7 [3,7; NE]	0,98	[0,54; 1,80]	0,9518
Andere	171	81 (47,4)	21,2 [10,3;50,7]	170	69 (40,6)	21,2 [10,5;39,6]	1,07	[0,78; 1,48]	0,6762
Interaktion p-Wert									0,3131
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	55 (55,6)	13,8 [6,7;24,9]	101	42 (41,6)	28,6 [10,5; NE]	1,21	[0,81; 1,82]	0,3510
Intermediäres Risiko [4-5]	128	62 (48,4)	13,8 [4,0;36,0]	125	52 (41,6)	18,0 [7,1; NE]	1,14	[0,79; 1,66]	0,4760
Hohes Risiko [6-11]	72	29 (40,3)	24,9 [7,7;39,7]	73	23 (31,5)	39,6 [6,7; NE]	1,17	[0,68; 2,04]	0,5759
Interaktion p-Wert									0,9794
Geschlecht [eCRF]									
Männlich	214	102 (47,7)	13,9 [6,7;21,3]	209	82 (39,2)	21,2 [10,5;35,9]	1,18	[0,88; 1,58]	0,2705
Weiblich	85	44 (51,8)	10,4 [6,5;36,0]	90	35 (38,9)	32,3 [6,5; NE]	1,16	[0,75; 1,82]	0,5114
Interaktion p-Wert									0,9568
Altersgruppe I [eCRF]									
< 70 Jahre	123	57 (46,3)	21,2 [10,2; NE]	117	46 (39,3)	21,1 [10,0;39,6]	0,95	[0,65; 1,41]	0,8069
>= 70 Jahre	176	89 (50,6)	10,0 [4,0;21,2]	182	71 (39,0)	28,6 [10,2; NE]	1,36	[0,999; 1,87]	0,0508
Interaktion p-Wert									0,1602
Altersgruppe II [eCRF]									
< 75 Jahre	215	102 (47,4)	17,6 [10,2;28,6]	222	82 (36,9)	28,7 [14,0; NE]	1,17	[0,88; 1,57]	0,2856
>= 75 Jahre	84	44 (52,4)	6,7 [3,9;32,3]	77	35 (45,5)	10,5 [6,5;35,9]	1,17	[0,75; 1,83]	0,4879
Interaktion p-Wert									0,9966

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.1 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Allgemeine Lebensqualität/Gesundheitszustand
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Abstammung [eCRF]									
Weiß	233	107 (45,9)	17,6 [10,0;36,0]	235	94 (40,0)	18,0 [10,0;35,9]	1,01	[0,77; 1,34]	0,9282
Nicht-weiß	52	30 (57,7)	10,0 [3,7;21,2]	53	20 (37,7)	39,7 [13,9; NE]	1,90	[1,09; 3,40]	0,0246*
Interaktion p-Wert									0,0490*
ECOG-PS [eCRF]									
0	156	87 (55,8)	10,2 [6,5;17,8]	140	57 (40,7)	21,2 [10,2; NE]	1,32	[0,95; 1,86]	0,0974
1	129	58 (45,0)	21,2 [10,0;39,7]	132	53 (40,2)	17,5 [7,1; NE]	1,03	[0,71; 1,50]	0,8662
>=2	12	1 (8,3)	NE [NE; NE]	25	7 (28,0)	39,6 [6,5; NE]	0,24	[0,01; 1,36]	0,1177
Interaktion p-Wert									0,1326
Bulky Disease I [eCRF]									
< 5 cm	187	95 (50,8)	10,4 [6,6;21,2]	186	71 (38,2)	29,0 [10,5; NE]	1,29	[0,95; 1,76]	0,0998
>= 5 cm	112	51 (45,5)	17,8 [6,7;50,7]	113	46 (40,7)	18,0 [6,5; NE]	0,99	[0,66; 1,48]	0,9670
Interaktion p-Wert									0,3028
Bulky Disease II [eCRF]									
< 10 cm	279	137 (49,1)	13,8 [6,8;21,2]	278	111 (39,9)	21,2 [10,5;35,9]	1,18	[0,92; 1,52]	0,1978
>= 10 cm	20	9 (45,0)	64,7 [3,7; NE]	21	6 (28,6)	NE [NE; NE]	1,16	[0,42; 3,47]	0,7774
Interaktion p-Wert									0,9771
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	28 (58,3)	4,5 [3,7;17,7]	36	14 (38,9)	17,5 [3,6; NE]	1,57	[0,84; 3,07]	0,1596
Stadium IV	251	118 (47,0)	17,6 [10,2;28,6]	263	103 (39,2)	21,2 [13,8;35,9]	1,11	[0,85; 1,44]	0,4588
Interaktion p-Wert									0,3156
MCL-Typ [eCRF]									
Klassische Variante	197	101 (51,3)	13,9 [6,7;21,3]	205	85 (41,5)	21,2 [10,5;39,6]	1,17	[0,88; 1,57]	0,2831

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.1 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Allgemeine Lebensqualität/Gesundheitsszustand
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]		2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Blastoide und pleomorphische Variante	39	15 (38,5)	24,9 [6,6; NE]		33	8 (24,2)	28,6 [10,3; NE]		1,51	[0,65; 3,74]	0,3423
Andere	0	0	NE		8	5 (62,5)	4,0 [1,9; NE]		NC	[NC]	NC
Interaktion p-Wert											0,5835
Ki-67 (%) I [eCRF]											
< 30%	109	52 (47,7)	13,8 [4,5;36,0]		103	41 (39,8)	32,3 [10,5; NE]		1,27	[0,85; 1,93]	0,2436
>= 30%	128	59 (46,1)	21,1 [10,2;35,9]		127	51 (40,2)	18,0 [6,9; NE]		1,05	[0,72; 1,54]	0,7831
Interaktion p-Wert											0,5029
Ki-67 (%) II [eCRF]											
< 50%	180	88 (48,9)	13,8 [6,7;24,9]		164	67 (40,9)	32,3 [14,0; NE]		1,25	[0,91; 1,72]	0,1666
>= 50%	57	23 (40,4)	24,9 [6,8; NE]		66	25 (37,9)	10,3 [6,7; NE]		0,88	[0,50; 1,56]	0,6729
Interaktion p-Wert											0,2976
Knochenmarksbeteiligung [eCRF]											
Ja	178	87 (48,9)	17,5 [7,1;28,6]		180	67 (37,2)	32,3 [10,2; NE]		1,22	[0,89; 1,68]	0,2184
Nein	50	27 (54,0)	4,1 [3,7; NE]		45	24 (53,3)	10,5 [3,7;29,0]		1,11	[0,64; 1,94]	0,7037
Interaktion p-Wert											0,7751
Extranodale Erkrankung [eCRF]											
Ja	264	124 (47,0)	17,7 [10,2;28,6]		277	107 (38,6)	28,6 [13,8;39,6]		1,13	[0,87; 1,46]	0,3645
Nein	35	22 (62,9)	4,1 [3,0;10,3]		22	10 (45,5)	10,2 [2,1; NE]		1,40	[0,68; 3,08]	0,3725
Interaktion p-Wert											0,5918
Gastrointestinale Erkrankung [eCRF]											
Ja	74	35 (47,3)	13,8 [3,8;36,0]		75	29 (38,7)	18,0 [7,0; NE]		1,21	[0,74; 2,00]	0,4405
Nein	225	111 (49,3)	13,9 [7,1;25,0]		224	88 (39,3)	28,6 [10,5;39,7]		1,16	[0,88; 1,54]	0,2976
Interaktion p-Wert											0,8759

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.1 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Allgemeine Lebensqualität/Gesundheitsszustand
 Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b] [95%-KI] [b]		2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
LDH > ULN [eCRF]									
Ja	52	20 (38,5)	24,9 [3,8; NE]	54	14 (25,9)	39,7 [10,3; NE]	1,51	[0,77; 3,04]	0,2366
Nein	245	126 (51,4)	13,8 [6,8;21,2]	241	103 (42,7)	21,2 [10,2;35,9]	1,11	[0,86; 1,45]	0,4203
Interaktion p-Wert									0,4159

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.2 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Körper
 Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	34 (41,5)	21,1 [10,1; NE]	83	35 (42,2)	17,5 [3,7;43,5]	0,74	[0,46; 1,19]	0,2102
Westeuropa	46	23 (50,0)	10,2 [3,7;39,6]	46	24 (52,2)	6,6 [2,0;33,0]	0,83	[0,47; 1,48]	0,5328
Andere	171	90 (52,6)	17,5 [6,5;28,6]	170	79 (46,5)	13,9 [6,5;32,3]	1,03	[0,76; 1,40]	0,8403
Interaktion p-Wert									0,4743
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	48 (48,5)	25,2 [10,3;58,3]	101	58 (57,4)	6,5 [3,7;10,4]	0,61	[0,42; 0,90]	0,0116*
Intermediäres Risiko [4-5]	128	70 (54,7)	10,3 [4,1;17,6]	125	55 (44,0)	24,6 [3,8;47,1]	1,23	[0,86; 1,76]	0,2506
Hohes Risiko [6-11]	72	29 (40,3)	17,5 [6,5; NE]	73	25 (34,2)	32,2 [3,9; NE]	1,01	[0,59; 1,73]	0,9794
Interaktion p-Wert									0,0285*
Geschlecht [eCRF]									
Männlich	214	99 (46,3)	17,5 [10,3;32,2]	209	90 (43,1)	17,6 [6,6;32,7]	0,98	[0,74; 1,30]	0,8848
Weiblich	85	48 (56,5)	10,2 [4,1;35,7]	90	48 (53,3)	3,9 [3,7;17,5]	0,78	[0,52; 1,17]	0,2284
Interaktion p-Wert									0,3689
Altersgruppe I [eCRF]									
< 70 Jahre	123	59 (48,0)	17,7 [10,1;58,3]	117	57 (48,7)	6,5 [3,9;32,3]	0,79	[0,55; 1,14]	0,2019
>= 70 Jahre	176	88 (50,0)	13,8 [6,5;21,1]	182	81 (44,5)	17,6 [6,4;32,3]	1,02	[0,75; 1,38]	0,9059
Interaktion p-Wert									0,2893
Altersgruppe II [eCRF]									
< 75 Jahre	215	101 (47,0)	17,8 [11,1;35,7]	222	101 (45,5)	13,9 [6,5;32,2]	0,87	[0,66; 1,14]	0,3042
>= 75 Jahre	84	46 (54,8)	6,4 [3,9;17,6]	77	37 (48,1)	10,1 [3,7;43,5]	1,04	[0,68; 1,61]	0,8545
Interaktion p-Wert									0,4790
Abstammung [eCRF]									
Weiß	233	116 (49,8)	16,9 [10,1;25,2]	235	110 (46,8)	10,4 [6,4;21,0]	0,86	[0,66; 1,12]	0,2692

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.2 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Körper
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Nicht-weiß	52	24 (46,2)	17,7 [3,8; NE]		53	22 (41,5)	32,7 [3,7; NE]		1,19	[0,67; 2,14]	0,5533
Interaktion p-Wert											0,3198
ECOG-PS [eCRF]											
0	156	82 (52,6)	13,8 [7,1;25,2]		140	64 (45,7)	17,5 [6,4;32,7]		1,04	[0,75; 1,45]	0,7932
1	129	62 (48,1)	17,5 [6,4;33,4]		132	65 (49,2)	6,6 [3,8;24,6]		0,81	[0,57; 1,15]	0,2395
>=2	12	3 (25,0)	28,6 [4,1; NE]		25	9 (36,0)	39,6 [2,0; NE]		0,50	[0,11; 1,67]	0,2690
Interaktion p-Wert											0,3666
Bulky Disease I [eCRF]											
< 5 cm	187	98 (52,4)	11,1 [6,4;17,8]		186	84 (45,2)	17,5 [6,5;32,3]		1,09	[0,81; 1,46]	0,5805
>= 5 cm	112	49 (43,8)	25,2 [13,9;47,0]		113	54 (47,8)	6,6 [3,7;24,9]		0,68	[0,46; 1,01]	0,0545
Interaktion p-Wert											0,0617
Bulky Disease II [eCRF]											
< 10 cm	279	136 (48,7)	16,9 [10,1;28,6]		278	129 (46,4)	13,9 [6,4;24,6]		0,91	[0,72; 1,16]	0,4561
>= 10 cm	20	11 (55,0)	17,6 [3,8;50,7]		21	9 (42,9)	17,5 [2,1; NE]		0,96	[0,40; 2,37]	0,9187
Interaktion p-Wert											0,9216
Ann Arbor-Stadium für Lymphome [eCRF]											
Stadium I-III	48	29 (60,4)	13,8 [3,8;28,6]		36	21 (58,3)	4,4 [2,0;21,2]		0,80	[0,46; 1,43]	0,4477
Stadium IV	251	118 (47,0)	17,5 [10,2;33,4]		263	117 (44,5)	17,5 [6,5;32,2]		0,92	[0,71; 1,19]	0,5190
Interaktion p-Wert											0,6692
MCL-Typ [eCRF]											
Klassische Variante	197	96 (48,7)	17,6 [10,2;33,4]		205	100 (48,8)	13,8 [6,4;24,9]		0,88	[0,66; 1,16]	0,3568
Blastoide und pleomorphische Variante	39	18 (46,2)	13,8 [3,9;32,2]		33	11 (33,3)	17,5 [3,7; NE]		1,15	[0,55; 2,51]	0,7182
Andere	0	0	NE		8	3 (37,5)	NE [NE; NE]		NC	[NC]	NC
Interaktion p-Wert											0,5067

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.2 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Körper
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	56 (51,4)	13,9 [6,4;35,7]	103	55 (53,4)	6,6 [3,7;21,2]	0,83	[0,57; 1,21]	0,3313
>= 30%	128	64 (50,0)	17,5 [6,5;28,6]	127	61 (48,0)	13,9 [3,9;33,0]	0,95	[0,67; 1,35]	0,7822
Interaktion p-Wert									0,6038
Ki-67 (%) II [eCRF]									
< 50%	180	89 (49,4)	17,6 [10,2;32,5]	164	85 (51,8)	6,6 [3,7;24,6]	0,83	[0,62; 1,12]	0,2283
>= 50%	57	31 (54,4)	6,5 [3,8;17,6]	66	31 (47,0)	13,8 [3,9;21,2]	1,13	[0,69; 1,87]	0,6255
Interaktion p-Wert									0,2996
Knochenmarksbeteiligung [eCRF]									
Ja	178	85 (47,8)	17,5 [7,1;43,5]	180	77 (42,8)	21,0 [7,0;39,6]	1,02	[0,75; 1,40]	0,8766
Nein	50	28 (56,0)	13,8 [4,1;32,2]	45	24 (53,3)	3,9 [2,0;32,3]	0,79	[0,46; 1,37]	0,3910
Interaktion p-Wert									0,4097
Extranodale Erkrankung [eCRF]									
Ja	264	126 (47,7)	17,5 [10,2;32,5]	277	125 (45,1)	13,9 [6,5;32,2]	0,90	[0,71; 1,16]	0,4254
Nein	35	21 (60,0)	10,3 [3,0;17,8]	22	13 (59,1)	4,0 [2,0;32,3]	0,89	[0,45; 1,82]	0,7394
Interaktion p-Wert									0,9632
Gastrointestinale Erkrankung [eCRF]									
Ja	74	35 (47,3)	11,1 [6,4;36,0]	75	38 (50,7)	13,9 [3,7;33,0]	0,81	[0,51; 1,28]	0,3551
Nein	225	112 (49,8)	17,5 [10,2;28,6]	224	100 (44,6)	13,9 [4,4;32,3]	0,96	[0,73; 1,25]	0,7465
Interaktion p-Wert									0,5262
LDH > ULN [eCRF]									
Ja	52	22 (42,3)	10,2 [3,8; NE]	54	18 (33,3)	17,5 [3,7; NE]	1,05	[0,57; 1,99]	0,8695
Nein	245	125 (51,0)	17,5 [10,2;28,6]	241	119 (49,4)	13,9 [6,4;24,6]	0,90	[0,70; 1,16]	0,4039
Interaktion p-Wert									0,6417

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.3 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Rolle Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	44 (53,7)	7,6 [3,9;21,3]	83	46 (55,4)	3,9 [2,1; 6,8]	0,71	[0,47; 1,08]	0,1062
Westeuropa	46	25 (54,3)	6,8 [2,8;32,2]	46	22 (47,8)	10,3 [6,5;44,4]	1,23	[0,69; 2,20]	0,4816
Andere	171	92 (53,8)	17,5 [6,8;28,6]	170	79 (46,5)	17,5 [6,5;32,7]	1,05	[0,78; 1,42]	0,7410
Interaktion p-Wert									0,2132
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	57 (57,6)	10,2 [3,9;32,2]	101	56 (55,4)	6,6 [3,8;17,8]	0,89	[0,61; 1,29]	0,5315
Intermediäres Risiko [4-5]	128	73 (57,0)	13,9 [6,5;21,3]	125	60 (48,0)	10,3 [6,5;24,9]	1,12	[0,80; 1,58]	0,5114
Hohes Risiko [6-11]	72	31 (43,1)	10,2 [3,8; NE]	73	31 (42,5)	6,7 [2,1;32,6]	0,84	[0,51; 1,38]	0,4826
Interaktion p-Wert									0,5359
Geschlecht [eCRF]									
Männlich	214	107 (50,0)	13,9 [6,8;21,5]	209	104 (49,8)	10,1 [6,5;17,6]	0,91	[0,69; 1,19]	0,4769
Weiblich	85	54 (63,5)	7,1 [3,7;21,3]	90	43 (47,8)	10,2 [3,7;46,9]	1,13	[0,76; 1,69]	0,5602
Interaktion p-Wert									0,3782
Altersgruppe I [eCRF]									
< 70 Jahre	123	73 (59,3)	10,1 [3,9;21,3]	117	58 (49,6)	11,0 [4,0;32,5]	1,08	[0,77; 1,53]	0,6656
>= 70 Jahre	176	88 (50,0)	13,9 [7,4;28,6]	182	89 (48,9)	10,1 [6,5;17,7]	0,89	[0,67; 1,20]	0,4612
Interaktion p-Wert									0,4192
Altersgruppe II [eCRF]									
< 75 Jahre	215	116 (54,0)	10,9 [6,8;21,3]	222	109 (49,1)	10,2 [6,4;21,2]	1,00	[0,77; 1,30]	0,9785
>= 75 Jahre	84	45 (53,6)	13,9 [3,7;32,4]	77	38 (49,4)	10,1 [3,7;28,6]	0,89	[0,58; 1,38]	0,6107
Interaktion p-Wert									0,6730
Abstammung [eCRF]									
Weiß	233	127 (54,5)	10,9 [6,7;21,3]	235	117 (49,8)	6,7 [4,1;17,5]	0,93	[0,72; 1,19]	0,5482

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.3 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Rolle Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	26 (50,0)	17,5 [6,5; NE]	53	25 (47,2)	13,9 [6,5; NE]	1,10	[0,64; 1,92]	0,7263
Interaktion p-Wert									0,5700
ECOG-PS [eCRF]									
0	156	92 (59,0)	10,2 [6,5;17,6]	140	70 (50,0)	10,3 [6,5;28,6]	1,09	[0,80; 1,49]	0,5990
1	129	66 (51,2)	15,5 [6,5;32,2]	132	66 (50,0)	6,5 [4,0;32,2]	0,92	[0,65; 1,29]	0,6233
>=2	12	3 (25,0)	NE [NE; NE]	25	11 (44,0)	6,7 [1,9; NE]	0,33	[0,07; 1,05]	0,0620
Interaktion p-Wert									0,1419
Bulky Disease I [eCRF]									
< 5 cm	187	102 (54,5)	10,3 [6,5;21,3]	186	94 (50,5)	6,8 [4,3;17,7]	0,96	[0,73; 1,28]	0,8033
>= 5 cm	112	59 (52,7)	13,9 [6,5;24,9]	113	53 (46,9)	10,2 [6,5;32,7]	0,98	[0,68; 1,42]	0,9130
Interaktion p-Wert									0,9499
Bulky Disease II [eCRF]									
< 10 cm	279	146 (52,3)	13,9 [7,4;21,3]	278	138 (49,6)	6,8 [6,5;17,5]	0,93	[0,74; 1,18]	0,5578
>= 10 cm	20	15 (75,0)	6,5 [2,1;24,9]	21	9 (42,9)	32,7 [1,9; NE]	1,57	[0,70; 3,74]	0,2781
Interaktion p-Wert									0,2284
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	29 (60,4)	4,1 [3,6;21,3]	36	20 (55,6)	6,4 [2,0;28,6]	0,90	[0,51; 1,61]	0,7079
Stadium IV	251	132 (52,6)	13,9 [7,1;21,3]	263	127 (48,3)	10,2 [6,5;17,8]	0,97	[0,76; 1,24]	0,8051
Interaktion p-Wert									0,8040
MCL-Typ [eCRF]									
Klassische Variante	197	108 (54,8)	13,8 [6,5;21,3]	205	108 (52,7)	10,1 [6,4;17,8]	0,94	[0,72; 1,23]	0,6414
Blastoide und pleomorphische Variante	39	23 (59,0)	3,9 [3,7;10,3]	33	10 (30,3)	13,8 [4,0; NE]	1,94	[0,95; 4,27]	0,0697
Andere	0	0	NE	8	5 (62,5)	4,0 [1,9; NE]	NC	[NC]	NC
Interaktion p-Wert									0,0628

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.3 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Rolle Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	63 (57,8)	10,2 [3,8;17,6]	103	55 (53,4)	6,5 [3,7;28,6]	1,04	[0,72; 1,50]	0,8295
>= 30%	128	69 (53,9)	10,1 [4,0;21,3]	127	64 (50,4)	6,7 [6,2;17,7]	1,02	[0,73; 1,44]	0,9116
Interaktion p-Wert									0,9356
Ki-67 (%) II [eCRF]									
< 50%	180	101 (56,1)	10,2 [6,5;17,5]	164	91 (55,5)	6,7 [4,0;17,7]	0,99	[0,75; 1,32]	0,9617
>= 50%	57	31 (54,4)	6,5 [3,7;21,3]	66	28 (42,4)	6,5 [3,9; NE]	1,16	[0,69; 1,94]	0,5743
Interaktion p-Wert									0,6071
Knochenmarksbeteiligung [eCRF]									
Ja	178	99 (55,6)	10,2 [6,5;21,3]	180	83 (46,1)	17,6 [6,5;32,6]	1,13	[0,85; 1,52]	0,4019
Nein	50	29 (58,0)	3,9 [3,7;17,6]	45	25 (55,6)	3,9 [2,0;28,6]	0,92	[0,54; 1,59]	0,7764
Interaktion p-Wert									0,5162
Extranodale Erkrankung [eCRF]									
Ja	264	139 (52,7)	13,9 [7,4;21,3]	277	133 (48,0)	10,2 [6,5;21,2]	0,97	[0,77; 1,23]	0,8164
Nein	35	22 (62,9)	3,9 [1,9;17,6]	22	14 (63,6)	2,9 [1,9;13,8]	0,77	[0,40; 1,54]	0,4525
Interaktion p-Wert									0,5264
Gastrointestinale Erkrankung [eCRF]									
Ja	74	40 (54,1)	6,8 [3,7;21,3]	75	43 (57,3)	6,6 [3,9;24,9]	0,92	[0,60; 1,42]	0,7182
Nein	225	121 (53,8)	13,9 [7,4;21,5]	224	104 (46,4)	10,2 [6,5;28,6]	0,99	[0,76; 1,29]	0,9630
Interaktion p-Wert									0,7764
LDH > ULN [eCRF]									
Ja	52	24 (46,2)	6,5 [3,6; NE]	54	20 (37,0)	6,5 [3,7; NE]	1,23	[0,68; 2,25]	0,4928
Nein	245	137 (55,9)	13,9 [7,6;21,3]	241	127 (52,7)	10,1 [6,5;17,6]	0,92	[0,72; 1,17]	0,4993
Interaktion p-Wert									0,3732

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.4 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala:
Emotionalität
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]	
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Geographic Region [IXRS]										
Nordamerika	82	21 (25,6)	NE [NE; NE]	83	33 (39,8)	21,2 [4,0;32,2]	0,43	[0,25; 0,74]	0,0024*	
Westeuropa	46	15 (32,6)	35,9 [13,8; NE]	46	15 (32,6)	52,4 [10,3; NE]	0,80	[0,39; 1,65]	0,5394	
Andere	171	59 (34,5)	58,0 [28,7; NE]	170	48 (28,2)	NE [NE; NE]	1,06	[0,73; 1,56]	0,7552	
Interaktion p-Wert									0,0292*	
Vereinfachter MIPI-Score [IXRS]										
Geringes Risiko [0-3]	99	32 (32,3)	NE [NE; NE]	101	33 (32,7)	69,0 [21,3; NE]	0,78	[0,48; 1,26]	0,3078	
Intermediäres Risiko [4-5]	128	44 (34,4)	39,6 [25,0; NE]	125	39 (31,2)	NE [NE; NE]	0,91	[0,59; 1,40]	0,6632	
Hohes Risiko [6-11]	72	19 (26,4)	32,6 [21,2; NE]	73	24 (32,9)	21,2 [13,9; NE]	0,66	[0,36; 1,20]	0,1700	
Interaktion p-Wert									0,6840	
Geschlecht [eCRF]										
Männlich	214	67 (31,3)	39,6 [28,7; NE]	209	62 (29,7)	69,0 [24,9; NE]	0,92	[0,65; 1,30]	0,6439	
Weiblich	85	28 (32,9)	58,0 [32,5; NE]	90	34 (37,8)	29,0 [10,2; NE]	0,59	[0,35; 0,97]	0,0376*	
Interaktion p-Wert									0,1478	
Altersgruppe I [eCRF]										
< 70 Jahre	123	38 (30,9)	NE [NE; NE]	117	39 (33,3)	NE [NE; NE]	0,67	[0,43; 1,05]	0,0787	
>= 70 Jahre	176	57 (32,4)	35,9 [24,9; NE]	182	57 (31,3)	52,4 [21,2; NE]	0,91	[0,63; 1,31]	0,6124	
Interaktion p-Wert									0,2981	
Altersgruppe II [eCRF]										
< 75 Jahre	215	65 (30,2)	58,0 [32,6; NE]	222	75 (33,8)	39,6 [18,4; NE]	0,70	[0,50; 0,97]	0,0318*	
>= 75 Jahre	84	30 (35,7)	32,4 [13,9; NE]	77	21 (27,3)	52,4 [21,2; NE]	1,18	[0,68; 2,09]	0,5572	
Interaktion p-Wert									0,1076	
Abstammung [eCRF]										

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.4 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala:
Emotionalität
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]		2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Weiß	233	76 (32,6)	50,6 [32,3; NE]		235	75 (31,9)	39,6 [21,2; NE]		0,79	[0,57; 1,09]	0,1517
Nicht-weiß	52	13 (25,0)	NE [NE; NE]		53	19 (35,8)	69,0 [14,0; NE]		0,62	[0,30; 1,25]	0,1850
Interaktion p-Wert											0,5445
ECOG-PS [eCRF]											
0	156	48 (30,8)	NE [NE; NE]		140	45 (32,1)	NE [NE; NE]		0,73	[0,48; 1,09]	0,1255
1	129	43 (33,3)	36,2 [21,2; NE]		132	47 (35,6)	32,2 [18,4; NE]		0,82	[0,54; 1,25]	0,3613
>=2	12	4 (33,3)	58,0 [6,5; NE]		25	4 (16,0)	NE [NE; NE]		1,73	[0,41; 7,35]	0,4434
Interaktion p-Wert											0,5002
Bulky Disease I [eCRF]											
< 5 cm	187	61 (32,6)	58,0 [28,7; NE]		186	65 (34,9)	35,9 [17,5; NE]		0,74	[0,52; 1,04]	0,0846
>= 5 cm	112	34 (30,4)	NE [NE; NE]		113	31 (27,4)	52,4 [21,2; NE]		0,94	[0,57; 1,53]	0,7873
Interaktion p-Wert											0,4312
Bulky Disease II [eCRF]											
< 10 cm	279	87 (31,2)	58,0 [32,5; NE]		278	91 (32,7)	52,4 [21,3; NE]		0,76	[0,57; 1,03]	0,0726
>= 10 cm	20	8 (40,0)	NE [NE; NE]		21	5 (23,8)	NE [NE; NE]		1,54	[0,51; 5,10]	0,4443
Interaktion p-Wert											0,2280
Ann Arbor-Stadium für Lymphome [eCRF]											
Stadium I-III	48	18 (37,5)	35,9 [24,9; NE]		36	13 (36,1)	NE [NE; NE]		0,67	[0,33; 1,40]	0,2764
Stadium IV	251	77 (30,7)	58,0 [32,6; NE]		263	83 (31,6)	52,4 [24,9; NE]		0,82	[0,60; 1,11]	0,1992
Interaktion p-Wert											0,6180
MCL-Typ [eCRF]											
Klassische Variante	197	61 (31,0)	58,0 [32,5; NE]		205	71 (34,6)	39,6 [21,2; NE]		0,75	[0,53; 1,05]	0,0942
Blastoide und pleomorphische Variante	39	13 (33,3)	32,6 [10,4; NE]		33	7 (21,2)	21,2 [14,0; NE]		1,17	[0,48; 3,12]	0,7370
Andere	0	0	NE		8	4 (50,0)	29,0 [1,9; NE]		NC	[NC]	NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.4 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala:
Emotionalität
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Interaktion p-Wert									0,3637
Ki-67 (%) I [eCRF]									
< 30%	109	40 (36,7)	50,6 [21,2; NE]	103	34 (33,0)	69,0 [18,4; NE]	1,00	[0,63; 1,58]	0,9906
>= 30%	128	30 (23,4)	NE [NE; NE]	127	41 (32,3)	52,4 [17,5; NE]	0,56	[0,35; 0,89]	0,0151*
Interaktion p-Wert									0,0837
Ki-67 (%) II [eCRF]									
< 50%	180	53 (29,4)	NE [NE; NE]	164	58 (35,4)	39,6 [18,4; NE]	0,71	[0,49; 1,04]	0,0774
>= 50%	57	17 (29,8)	32,6 [24,9; NE]	66	17 (25,8)	52,4 [14,0; NE]	0,87	[0,44; 1,73]	0,6969
Interaktion p-Wert									0,6070
Knochenmarksbeteiligung [eCRF]									
Ja	178	53 (29,8)	NE [NE; NE]	180	59 (32,8)	39,6 [21,3; NE]	0,76	[0,52; 1,10]	0,1397
Nein	50	19 (38,0)	32,5 [17,5; NE]	45	17 (37,8)	21,2 [6,5; NE]	0,78	[0,41; 1,52]	0,4678
Interaktion p-Wert									0,9250
Extranodale Erkrankung [eCRF]									
Ja	264	81 (30,7)	58,0 [32,4; NE]	277	86 (31,0)	52,4 [24,9; NE]	0,83	[0,61; 1,12]	0,2193
Nein	35	14 (40,0)	35,9 [24,9; NE]	22	10 (45,5)	6,5 [2,1; NE]	0,49	[0,22; 1,13]	0,0918
Interaktion p-Wert									0,2383
Gastrointestinale Erkrankung [eCRF]									
Ja	74	22 (29,7)	NE [NE; NE]	75	26 (34,7)	21,3 [14,0; NE]	0,69	[0,39; 1,22]	0,2063
Nein	225	73 (32,4)	39,6 [32,1; NE]	224	70 (31,3)	69,0 [29,0; NE]	0,84	[0,60; 1,17]	0,2966
Interaktion p-Wert									0,5685
LDH > ULN [eCRF]									
Ja	52	12 (23,1)	NE [NE; NE]	54	11 (20,4)	NE [NE; NE]	0,95	[0,42; 2,19]	0,9069

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.4 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala:
 Emotionalität
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]		2-seitiger p-Wert [b]
	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]		Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]				
	n				n						
Nein	245	83 (33,9)	58,0 [32,5; NE]		241	84 (34,9)	52,4 [21,3; NE]		0,78	[0,58; 1,06]	0,1170
Interaktion p-Wert											0,6626

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.

Note: An interaction model is only used when there are ≥ 10 patients in each subgroup level, ≥ 10 events in at least one subgroup level and > 0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value < 0.05 . HR < 1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.5 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala:
 Kognition
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	36 (43,9)	17,5 [6,9;28,7]	83	39 (47,0)	13,9 [3,8;32,2]	0,83	[0,52; 1,31]	0,4180
Westeuropa	46	20 (43,5)	17,5 [10,3;43,3]	46	18 (39,1)	14,3 [10,1; NE]	0,98	[0,52; 1,86]	0,9398
Andere	171	90 (52,6)	13,9 [10,2;24,9]	170	90 (52,9)	13,8 [9,5;21,0]	0,89	[0,66; 1,19]	0,4207
Interaktion p-Wert									0,9183
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	52 (52,5)	21,2 [10,2;28,7]	101	50 (49,5)	17,5 [11,0;21,7]	0,93	[0,63; 1,38]	0,7279
Intermediäres Risiko [4-5]	128	66 (51,6)	13,9 [7,6;21,3]	125	63 (50,4)	10,3 [6,5;28,4]	0,94	[0,67; 1,33]	0,7341
Hohes Risiko [6-11]	72	28 (38,9)	21,3 [7,0; NE]	73	34 (46,6)	6,7 [3,8;24,9]	0,70	[0,42; 1,15]	0,1623
Interaktion p-Wert									0,5956
Geschlecht [eCRF]									
Männlich	214	100 (46,7)	14,3 [10,3;25,0]	209	101 (48,3)	13,9 [10,2;18,4]	0,90	[0,69; 1,19]	0,4747
Weiblich	85	46 (54,1)	21,2 [7,1;29,3]	90	46 (51,1)	13,8 [6,5;28,6]	0,84	[0,55; 1,26]	0,3888
Interaktion p-Wert									0,7539
Altersgruppe I [eCRF]									
< 70 Jahre	123	61 (49,6)	21,0 [10,3;28,6]	117	55 (47,0)	17,4 [10,2;24,9]	0,86	[0,60; 1,25]	0,4330
>= 70 Jahre	176	85 (48,3)	14,0 [7,6;25,0]	182	92 (50,5)	13,8 [6,6;21,0]	0,90	[0,67; 1,21]	0,4948
Interaktion p-Wert									0,8567
Altersgruppe II [eCRF]									
< 75 Jahre	215	101 (47,0)	21,2 [13,8;28,6]	222	104 (46,8)	17,4 [10,3;21,2]	0,90	[0,68; 1,19]	0,4559
>= 75 Jahre	84	45 (53,6)	10,3 [6,4;21,2]	77	43 (55,8)	6,6 [3,7;14,0]	0,81	[0,53; 1,23]	0,3234
Interaktion p-Wert									0,6755
Abstammung [eCRF]									

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.5 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala:
Kognition
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
weiß	233	108 (46,4)	21,0 [13,8;28,6]		235	119 (50,6)	13,8 [10,1;17,4]		0,75	[0,58; 0,97]	0,0310*
Nicht-weiß	52	32 (61,5)	10,2 [3,8;21,2]		53	23 (43,4)	43,3 [6,5; NE]		1,66	[0,98; 2,88]	0,0617
Interaktion p-Wert											0,0087*
ECOG-PS [eCRF]											
0	156	80 (51,3)	14,3 [10,2;28,7]		140	64 (45,7)	14,2 [10,2;28,6]		1,04	[0,75; 1,45]	0,8253
1	129	63 (48,8)	14,0 [10,0;25,0]		132	71 (53,8)	13,8 [4,1;18,4]		0,82	[0,58; 1,15]	0,2509
>=2	12	3 (25,0)	NE [NE; NE]		25	12 (48,0)	13,8 [1,9; NE]		0,32	[0,07; 1,01]	0,0531
Interaktion p-Wert											0,1329
Bulky Disease I [eCRF]											
< 5 cm	187	89 (47,6)	17,5 [10,4;28,6]		186	97 (52,2)	11,0 [6,5;17,5]		0,78	[0,58; 1,04]	0,0911
>= 5 cm	112	57 (50,9)	13,9 [7,1;28,8]		113	50 (44,2)	18,4 [10,2;25,1]		1,09	[0,74; 1,60]	0,6633
Interaktion p-Wert											0,1717
Bulky Disease II [eCRF]											
< 10 cm	279	134 (48,0)	17,5 [10,8;25,0]		278	138 (49,6)	13,9 [10,2;17,7]		0,87	[0,68; 1,10]	0,2340
>= 10 cm	20	12 (60,0)	10,3 [3,7; NE]		21	9 (42,9)	11,3 [3,7;28,8]		1,13	[0,48; 2,78]	0,7779
Interaktion p-Wert											0,5556
Ann Arbor-Stadium für Lymphome [eCRF]											
Stadium I-III	48	27 (56,3)	13,8 [3,9;35,8]		36	17 (47,2)	21,2 [3,8; NE]		1,15	[0,63; 2,16]	0,6435
Stadium IV	251	119 (47,4)	14,3 [10,4;25,0]		263	130 (49,4)	13,9 [10,2;17,7]		0,84	[0,66; 1,08]	0,1740
Interaktion p-Wert											0,3428
MCL-Typ [eCRF]											
Klassische Variante	197	92 (46,7)	13,9 [10,2;28,6]		205	102 (49,8)	14,3 [10,2;21,7]		0,88	[0,66; 1,17]	0,3842
Blastoide und pleomorphische Variante	39	18 (46,2)	21,0 [6,5;43,3]		33	15 (45,5)	6,4 [2,1; NE]		0,64	[0,32; 1,29]	0,2050
Andere	0	0	NE		8	5 (62,5)	6,7 [1,8; NE]		NC	[NC]	NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.5 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala:
Kognition
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Interaktion p-Wert									0,3957
Ki-67 (%) I [eCRF]									
< 30%	109	56 (51,4)	13,8 [6,5;24,9]	103	50 (48,5)	21,2 [10,3;32,2]	1,20	[0,82; 1,77]	0,3416
>= 30%	128	57 (44,5)	21,0 [10,3;43,3]	127	65 (51,2)	11,0 [6,4;14,3]	0,74	[0,51; 1,05]	0,0934
Interaktion p-Wert									0,0667
Ki-67 (%) II [eCRF]									
< 50%	180	86 (47,8)	17,5 [10,2;28,6]	164	87 (53,0)	14,3 [10,2;25,0]	0,93	[0,69; 1,26]	0,6383
>= 50%	57	27 (47,4)	17,5 [3,8;29,3]	66	28 (42,4)	13,8 [3,9; NE]	0,92	[0,54; 1,56]	0,7504
Interaktion p-Wert									0,9632
Knochenmarksbeteiligung [eCRF]									
Ja	178	81 (45,5)	17,5 [10,4;25,8]	180	82 (45,6)	17,5 [10,3;28,4]	0,90	[0,66; 1,23]	0,5147
Nein	50	28 (56,0)	13,8 [3,9;29,3]	45	25 (55,6)	11,3 [6,5;21,7]	1,00	[0,58; 1,72]	0,9945
Interaktion p-Wert									0,7515
Extranodale Erkrankung [eCRF]									
Ja	264	126 (47,7)	14,0 [10,3;25,0]	277	137 (49,5)	13,9 [10,2;17,7]	0,86	[0,68; 1,10]	0,2332
Nein	35	20 (57,1)	17,5 [4,5;43,3]	22	10 (45,5)	21,2 [3,7; NE]	1,09	[0,52; 2,44]	0,8166
Interaktion p-Wert									0,5566
Gastrointestinale Erkrankung [eCRF]									
Ja	74	37 (50,0)	10,2 [3,8;32,2]	75	40 (53,3)	14,3 [10,1;21,7]	0,98	[0,62; 1,54]	0,9349
Nein	225	109 (48,4)	21,2 [13,8;25,8]	224	107 (47,8)	13,9 [6,7;21,2]	0,86	[0,65; 1,12]	0,2546
Interaktion p-Wert									0,6080
LDH > ULN [eCRF]									
Ja	52	23 (44,2)	13,7 [3,8;21,3]	54	22 (40,7)	11,3 [2,6;58,0]	0,88	[0,49; 1,58]	0,6579

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.5 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala:
 Kognition
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	2-seitigen p-Wert [b]
	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]				
	n			n						
Nein	245	123 (50,2)	17,5 [10,4;28,6]	241	123 (51,0)	13,9 [10,2;21,2]	0,89	[0,70; 1,15]	0,3788	
Interaktion p-Wert									0,9515	

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are ≥ 10 patients in each subgroup level, ≥ 10 events in at least one subgroup level and > 0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value < 0.05 . HR < 1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.6 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Sozial
 Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	37 (45,1)	7,1 [3,8;58,2]	83	37 (44,6)	6,5 [3,7;35,9]	0,91	[0,58; 1,44]	0,6947
Westeuropa	46	28 (60,9)	4,0 [3,5;17,5]	46	18 (39,1)	25,1 [6,5; NE]	1,76	[0,98; 3,25]	0,0569
Andere	171	96 (56,1)	17,5 [6,5;21,3]	170	82 (48,2)	10,2 [3,9;21,2]	1,07	[0,80; 1,44]	0,6561
Interaktion p-Wert									0,2046
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	59 (59,6)	6,8 [3,7;17,5]	101	49 (48,5)	13,8 [3,7;29,0]	1,19	[0,82; 1,74]	0,3657
Intermediäres Risiko [4-5]	128	73 (57,0)	14,6 [6,5;21,3]	125	58 (46,4)	10,2 [4,0;35,9]	1,16	[0,82; 1,64]	0,3948
Hohes Risiko [6-11]	72	29 (40,3)	14,2 [3,8; NE]	73	30 (41,1)	10,2 [3,7; NE]	0,89	[0,53; 1,48]	0,6420
Interaktion p-Wert									0,6231
Geschlecht [eCRF]									
Männlich	214	107 (50,0)	14,0 [6,5;21,3]	209	91 (43,5)	13,9 [6,6;32,5]	1,13	[0,85; 1,49]	0,4013
Weiblich	85	54 (63,5)	6,8 [3,8;17,5]	90	46 (51,1)	6,9 [3,7;28,6]	1,06	[0,72; 1,58]	0,7588
Interaktion p-Wert									0,8138
Altersgruppe I [eCRF]									
< 70 Jahre	123	73 (59,3)	6,5 [3,8;17,4]	117	47 (40,2)	28,6 [3,8; NE]	1,51	[1,05; 2,19]	0,0257*
>= 70 Jahre	176	88 (50,0)	17,5 [6,5;24,9]	182	90 (49,5)	10,1 [3,9;17,5]	0,90	[0,67; 1,21]	0,4977
Interaktion p-Wert									0,0311*
Altersgruppe II [eCRF]									
< 75 Jahre	215	115 (53,5)	10,2 [6,5;17,5]	222	100 (45,0)	13,8 [3,9;28,8]	1,12	[0,86; 1,46]	0,4133
>= 75 Jahre	84	46 (54,8)	10,2 [3,7;29,0]	77	37 (48,1)	10,2 [3,8;39,8]	1,07	[0,70; 1,67]	0,7437
Interaktion p-Wert									0,8789
Abstammung [eCRF]									
Weiß	233	123 (52,8)	14,0 [6,5;21,3]	235	108 (46,0)	10,2 [4,0;17,5]	1,03	[0,80; 1,34]	0,8165

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.6 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Sozial
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	31 (59,6)	7,0 [3,7;17,5]	53	25 (47,2)	28,8 [3,7; NE]	1,39	[0,82; 2,38]	0,2167
Interaktion p-Wert									0,3148
ECOG-PS [eCRF]									
0	156	87 (55,8)	14,2 [6,5;24,9]	140	63 (45,0)	17,5 [6,4;32,6]	1,14	[0,82; 1,58]	0,4323
1	129	71 (55,0)	6,7 [3,8;17,5]	132	60 (45,5)	13,8 [3,8;32,3]	1,24	[0,88; 1,76]	0,2160
>=2	12	3 (25,0)	NE [NE; NE]	25	14 (56,0)	6,6 [1,9;13,8]	0,32	[0,07; 0,99]	0,0487*
Interaktion p-Wert									0,0765
Bulky Disease I [eCRF]									
< 5 cm	187	102 (54,5)	10,2 [4,5;21,2]	186	86 (46,2)	10,2 [3,8;21,2]	1,05	[0,79; 1,41]	0,7191
>= 5 cm	112	59 (52,7)	14,6 [6,5;21,3]	113	51 (45,1)	14,0 [6,5;35,9]	1,20	[0,82; 1,75]	0,3485
Interaktion p-Wert									0,5995
Bulky Disease II [eCRF]									
< 10 cm	279	148 (53,0)	13,9 [6,5;17,5]	278	131 (47,1)	10,2 [6,4;17,5]	1,06	[0,83; 1,34]	0,6493
>= 10 cm	20	13 (65,0)	7,0 [2,0;50,7]	21	6 (28,6)	NE [NE; NE]	2,27	[0,90; 6,47]	0,0842
Interaktion p-Wert									0,1193
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	29 (60,4)	6,5 [3,7;17,6]	36	17 (47,2)	10,3 [2,1; NE]	1,21	[0,67; 2,24]	0,5377
Stadium IV	251	132 (52,6)	14,0 [6,5;21,3]	263	120 (45,6)	10,3 [6,4;28,6]	1,08	[0,85; 1,39]	0,5272
Interaktion p-Wert									0,7450
MCL-Typ [eCRF]									
Klassische Variante	197	110 (55,8)	6,8 [4,5;17,5]	205	97 (47,3)	10,3 [6,5;28,6]	1,20	[0,92; 1,59]	0,1813
Blastoide und pleomorphische Variante	39	21 (53,8)	6,5 [3,7;21,3]	33	15 (45,5)	4,0 [2,3; NE]	1,03	[0,53; 2,04]	0,9288
Andere	0	0	NE	8	5 (62,5)	21,2 [1,9; NE]	NC	[NC]	NC
Interaktion p-Wert									0,6712

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.6 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Sozial
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	64 (58,7)	6,5 [3,9;14,6]	103	43 (41,7)	29,0 [10,1; NE]	1,65	[1,13; 2,45]	0,0100*
>= 30%	128	61 (47,7)	17,5 [6,5;50,7]	127	64 (50,4)	6,6 [3,7;17,5]	0,86	[0,60; 1,22]	0,3860
Interaktion p-Wert									0,0133*
Ki-67 (%) II [eCRF]									
< 50%	180	95 (52,8)	14,0 [6,5;21,3]	164	76 (46,3)	17,5 [3,9;32,5]	1,22	[0,90; 1,65]	0,2018
>= 50%	57	30 (52,6)	6,4 [3,7;24,9]	66	31 (47,0)	6,6 [3,7;21,2]	1,03	[0,62; 1,70]	0,9107
Interaktion p-Wert									0,5759
Knochenmarksbeteiligung [eCRF]									
Ja	178	94 (52,8)	14,2 [6,5;24,9]	180	77 (42,8)	25,1 [6,5;39,8]	1,19	[0,88; 1,61]	0,2553
Nein	50	26 (52,0)	6,5 [3,7;25,3]	45	25 (55,6)	6,6 [3,7;10,3]	0,94	[0,54; 1,63]	0,8156
Interaktion p-Wert									0,4530
Extranodale Erkrankung [eCRF]									
Ja	264	138 (52,3)	14,0 [6,5;21,2]	277	123 (44,4)	13,8 [6,5;29,0]	1,11	[0,87; 1,41]	0,4109
Nein	35	23 (65,7)	4,5 [2,1;17,6]	22	14 (63,6)	6,9 [1,9;17,5]	0,91	[0,47; 1,81]	0,7806
Interaktion p-Wert									0,5883
Gastrointestinale Erkrankung [eCRF]									
Ja	74	38 (51,4)	6,8 [3,8;28,7]	75	40 (53,3)	6,6 [3,7;28,8]	0,93	[0,59; 1,45]	0,7362
Nein	225	123 (54,7)	13,9 [6,5;17,6]	224	97 (43,3)	13,8 [6,5;32,6]	1,18	[0,91; 1,55]	0,2140
Interaktion p-Wert									0,3544
LDH > ULN [eCRF]									
Ja	52	22 (42,3)	6,5 [3,5; NE]	54	22 (40,7)	3,7 [2,1; NE]	0,98	[0,54; 1,77]	0,9387
Nein	245	139 (56,7)	13,9 [6,5;17,5]	241	114 (47,3)	13,8 [6,6;28,6]	1,13	[0,88; 1,45]	0,3236
Interaktion p-Wert									0,6515

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.7 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Fatigue
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	53 (64,6)	3,7 [2,0; 4,6]	83	42 (50,6)	3,8 [2,0;17,6]	1,24	[0,83; 1,87]	0,2914
Westeuropa	46	29 (63,0)	4,0 [2,1;13,9]	46	26 (56,5)	3,9 [2,0;21,2]	1,07	[0,63; 1,83]	0,7909
Andere	171	108 (63,2)	4,2 [3,7;10,1]	170	93 (54,7)	6,5 [3,7;13,9]	1,15	[0,88; 1,53]	0,3079
Interaktion p-Wert									0,9086
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	69 (69,7)	3,8 [2,0; 6,6]	101	64 (63,4)	3,8 [2,1; 6,6]	0,99	[0,70; 1,39]	0,9317
Intermediäres Risiko [4-5]	128	82 (64,1)	3,7 [2,0; 6,5]	125	68 (54,4)	6,4 [3,7;18,0]	1,37	[0,99; 1,89]	0,0565
Hohes Risiko [6-11]	72	39 (54,2)	6,5 [3,7;14,8]	73	29 (39,7)	17,7 [3,7; NE]	1,15	[0,71; 1,88]	0,5659
Interaktion p-Wert									0,3918
Geschlecht [eCRF]									
Männlich	214	132 (61,7)	3,8 [3,0; 6,5]	209	116 (55,5)	4,0 [3,7;10,4]	1,11	[0,87; 1,43]	0,4099
Weiblich	85	58 (68,2)	4,1 [2,1; 7,1]	90	45 (50,0)	6,5 [3,7;32,2]	1,31	[0,89; 1,94]	0,1746
Interaktion p-Wert									0,4870
Altersgruppe I [eCRF]									
< 70 Jahre	123	80 (65,0)	3,9 [3,7;10,2]	117	65 (55,6)	6,4 [3,7;13,8]	1,10	[0,79; 1,53]	0,5802
>= 70 Jahre	176	110 (62,5)	3,8 [2,2; 6,5]	182	96 (52,7)	3,9 [3,7;14,0]	1,22	[0,93; 1,60]	0,1595
Interaktion p-Wert									0,6333
Altersgruppe II [eCRF]									
< 75 Jahre	215	136 (63,3)	4,3 [3,7; 6,8]	222	117 (52,7)	6,5 [3,9;13,9]	1,19	[0,93; 1,52]	0,1769
>= 75 Jahre	84	54 (64,3)	2,8 [2,0; 4,6]	77	44 (57,1)	3,7 [1,9;10,4]	1,10	[0,74; 1,64]	0,6474
Interaktion p-Wert									0,7470
Abstammung [eCRF]									
Weiß	233	145 (62,2)	4,2 [3,7; 6,8]	235	123 (52,3)	4,1 [3,7;10,5]	1,13	[0,89; 1,44]	0,3156

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.7 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Fatigue
 Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	38 (73,1)	2,5 [1,9; 6,5]	53	32 (60,4)	3,9 [3,7;13,9]	1,42	[0,89; 2,28]	0,1452
Interaktion p-Wert									0,4013
ECOG-PS [eCRF]									
0	156	111 (71,2)	3,7 [2,0; 4,6]	140	80 (57,1)	3,9 [3,7; 6,5]	1,35	[1,01; 1,80]	0,0413*
1	129	75 (58,1)	4,1 [3,7;14,8]	132	72 (54,5)	6,5 [3,7;17,4]	0,97	[0,70; 1,34]	0,8575
>=2	12	4 (33,3)	13,9 [2,0; NE]	25	9 (36,0)	18,0 [2,0; NE]	0,73	[0,20; 2,24]	0,5942
Interaktion p-Wert									0,2453
Bulky Disease I [eCRF]									
< 5 cm	187	123 (65,8)	3,7 [2,2; 6,5]	186	103 (55,4)	3,9 [3,7;10,1]	1,19	[0,91; 1,55]	0,1978
>= 5 cm	112	67 (59,8)	4,6 [3,7;10,1]	113	58 (51,3)	6,4 [3,9;17,4]	1,13	[0,79; 1,61]	0,5020
Interaktion p-Wert									0,8185
Bulky Disease II [eCRF]									
< 10 cm	279	174 (62,4)	4,0 [3,7; 6,5]	278	153 (55,0)	4,0 [3,7; 7,0]	1,11	[0,89; 1,38]	0,3457
>= 10 cm	20	16 (80,0)	2,1 [1,9; 6,5]	21	8 (38,1)	NE [NE; NE]	2,34	[1,03; 5,77]	0,0428*
Interaktion p-Wert									0,0870
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	34 (70,8)	2,0 [1,9; 4,6]	36	24 (66,7)	3,7 [1,9; 6,4]	1,01	[0,60; 1,71]	0,9857
Stadium IV	251	156 (62,2)	4,1 [3,7; 6,8]	263	137 (52,1)	6,5 [3,9;13,9]	1,18	[0,94; 1,48]	0,1631
Interaktion p-Wert									0,5884
MCL-Typ [eCRF]									
Klassische Variante	197	125 (63,5)	3,8 [2,2; 6,5]	205	118 (57,6)	3,9 [3,7; 6,6]	1,11	[0,87; 1,43]	0,3990
Blastoide und pleomorphische Variante	39	24 (61,5)	6,4 [1,9;10,4]	33	13 (39,4)	17,4 [2,1; NE]	1,66	[0,86; 3,37]	0,1312
Andere	0	0	NE	8	3 (37,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,2688

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.7 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Fatigue
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	72 (66,1)	3,7 [2,1; 4,6]	103	65 (63,1)	3,7 [2,4; 6,4]	1,10	[0,79; 1,54]	0,5830
>= 30%	128	78 (60,9)	4,3 [2,0;10,2]	127	66 (52,0)	6,5 [3,7;18,0]	1,23	[0,89; 1,71]	0,2173
Interaktion p-Wert									0,6397
Ki-67 (%) II [eCRF]									
< 50%	180	116 (64,4)	3,8 [2,1; 6,5]	164	100 (61,0)	3,8 [3,7; 6,5]	1,11	[0,85; 1,46]	0,4251
>= 50%	57	34 (59,6)	3,9 [2,0;10,4]	66	31 (47,0)	7,0 [3,7;39,9]	1,31	[0,80; 2,14]	0,2761
Interaktion p-Wert									0,5684
Knochenmarksbeteiligung [eCRF]									
Ja	178	112 (62,9)	4,0 [3,7; 6,8]	180	89 (49,4)	6,6 [3,9;21,2]	1,33	[1,01; 1,76]	0,0446*
Nein	50	35 (70,0)	2,0 [1,9; 4,1]	45	32 (71,1)	2,0 [1,9; 3,7]	0,90	[0,56; 1,46]	0,6696
Interaktion p-Wert									0,1708
Extranodale Erkrankung [eCRF]									
Ja	264	162 (61,4)	4,1 [3,7; 6,8]	277	146 (52,7)	6,4 [3,8;10,5]	1,13	[0,91; 1,42]	0,2724
Nein	35	28 (80,0)	1,9 [1,9; 4,1]	22	15 (68,2)	2,0 [1,9; 6,4]	1,21	[0,66; 2,33]	0,5467
Interaktion p-Wert									0,8455
Gastrointestinale Erkrankung [eCRF]									
Ja	74	44 (59,5)	3,8 [2,0;15,5]	75	46 (61,3)	4,1 [3,7;14,0]	1,06	[0,70; 1,61]	0,7723
Nein	225	146 (64,9)	4,0 [3,7; 6,5]	224	115 (51,3)	4,7 [3,7;13,8]	1,21	[0,95; 1,54]	0,1321
Interaktion p-Wert									0,6066
LDH > ULN [eCRF]									
Ja	52	28 (53,8)	3,7 [2,0; 6,5]	54	17 (31,5)	18,4 [3,9; NE]	1,94	[1,07; 3,61]	0,0284*
Nein	245	162 (66,1)	4,0 [3,7; 6,5]	241	144 (59,8)	3,9 [3,7; 6,5]	1,06	[0,85; 1,33]	0,6171
Interaktion p-Wert									0,0618

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.8 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Übelkeit und Erbrechen
 Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)					Placebo+BR (N=299)					Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]					
Geographic Region [IXRS]													
Nordamerika	82	30 (36,6)	39,9 [10,3; NE]			83	23 (27,7)	43,3 [32,2; NE]			1,16	[0,68; 2,02]	0,5920
Westeuropa	46	17 (37,0)	32,4 [4,0; NE]			46	16 (34,8)	54,4 [3,8; NE]			1,01	[0,51; 2,02]	0,9725
Andere	171	63 (36,8)	69,2 [28,6; NE]			170	66 (38,8)	32,5 [14,9; NE]			0,86	[0,61; 1,22]	0,3980
Interaktion p-Wert													0,6500
Vereinfachter MIPI-Score [IXRS]													
Geringes Risiko [0-3]	99	40 (40,4)	NE [NE; NE]			101	40 (39,6)	32,7 [14,9;58,3]			0,88	[0,57; 1,37]	0,5827
Intermediäres Risiko [4-5]	128	47 (36,7)	58,0 [32,2; NE]			125	43 (34,4)	54,4 [25,0; NE]			1,01	[0,66; 1,52]	0,9804
Hohes Risiko [6-11]	72	23 (31,9)	50,8 [24,9; NE]			73	22 (30,1)	32,2 [6,6; NE]			0,96	[0,53; 1,73]	0,8879
Interaktion p-Wert													0,9161
Geschlecht [eCRF]													
Männlich	214	70 (32,7)	58,0 [36,2; NE]			209	64 (30,6)	54,4 [32,7; NE]			1,02	[0,72; 1,43]	0,9304
Weiblich	85	40 (47,1)	24,9 [6,5; NE]			90	41 (45,6)	13,9 [3,7;39,4]			0,83	[0,54; 1,29]	0,4066
Interaktion p-Wert													0,4781
Altersgruppe I [eCRF]													
< 70 Jahre	123	59 (48,0)	28,6 [6,5; NE]			117	43 (36,8)	32,7 [17,5; NE]			1,20	[0,81; 1,78]	0,3673
>= 70 Jahre	176	51 (29,0)	NE [NE; NE]			182	62 (34,1)	54,4 [25,0; NE]			0,77	[0,53; 1,11]	0,1562
Interaktion p-Wert													0,1033
Altersgruppe II [eCRF]													
< 75 Jahre	215	88 (40,9)	39,7 [17,6; NE]			222	75 (33,8)	46,9 [32,2; NE]			1,13	[0,83; 1,54]	0,4266
>= 75 Jahre	84	22 (26,2)	NE [NE; NE]			77	30 (39,0)	25,0 [6,6; NE]			0,56	[0,32; 0,97]	0,0373*
Interaktion p-Wert													0,0275*
Abstammung [eCRF]													
Weiß	233	86 (36,9)	58,0 [32,2; NE]			235	81 (34,5)	39,4 [25,0; NE]			0,94	[0,70; 1,28]	0,7069

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.8 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Übelkeit und Erbrechen
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	17 (32,7)	NE [NE; NE]	53	20 (37,7)	NE [NE; NE]	0,89	[0,46; 1,70]	0,7202
Interaktion p-Wert									0,8698
ECOG-PS [eCRF]									
0	156	53 (34,0)	NE [NE; NE]	140	47 (33,6)	58,3 [32,7; NE]	0,91	[0,61; 1,35]	0,6337
1	129	52 (40,3)	39,7 [6,9; NE]	132	51 (38,6)	25,9 [13,8;54,4]	0,98	[0,66; 1,44]	0,9101
>=2	12	5 (41,7)	24,9 [2,0; NE]	25	7 (28,0)	NE [NE; NE]	1,30	[0,38; 4,09]	0,6630
Interaktion p-Wert									0,8450
Bulky Disease I [eCRF]									
< 5 cm	187	76 (40,6)	39,7 [17,4; NE]	186	61 (32,8)	54,4 [32,3; NE]	1,24	[0,89; 1,74]	0,2089
>= 5 cm	112	34 (30,4)	NE [NE; NE]	113	44 (38,9)	25,0 [6,5; NE]	0,60	[0,38; 0,94]	0,0253*
Interaktion p-Wert									0,0110*
Bulky Disease II [eCRF]									
< 10 cm	279	104 (37,3)	50,8 [32,2; NE]	278	97 (34,9)	46,9 [25,9; NE]	1,00	[0,76; 1,32]	0,9943
>= 10 cm	20	6 (30,0)	NE [NE; NE]	21	8 (38,1)	32,7 [3,7; NE]	0,48	[0,16; 1,38]	0,1708
Interaktion p-Wert									0,1856
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	20 (41,7)	28,6 [4,1; NE]	36	15 (41,7)	58,3 [3,7; NE]	0,82	[0,42; 1,64]	0,5714
Stadium IV	251	90 (35,9)	50,8 [32,4; NE]	263	90 (34,2)	39,4 [28,4; NE]	0,96	[0,72; 1,29]	0,8083
Interaktion p-Wert									0,6721
MCL-Typ [eCRF]									
Klassische Variante	197	74 (37,6)	50,8 [24,9; NE]	205	75 (36,6)	35,9 [25,9; NE]	0,96	[0,69; 1,32]	0,7974
Blastoide und pleomorphische Variante	39	12 (30,8)	NE [NE; NE]	33	9 (27,3)	39,4 [3,7; NE]	0,90	[0,38; 2,21]	0,8140
Andere	0	0	NE	8	4 (50,0)	13,9 [1,9; NE]	NC	[NC]	NC
Interaktion p-Wert									0,8952

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.8 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Übelkeit und Erbrechen
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Ki-67 (%) I [eCRF]											
< 30%	109	45 (41,3)	36,2 [14,0; NE]		103	33 (32,0)	58,3 [32,3; NE]		1,34	[0,86; 2,11]	0,2014
>= 30%	128	44 (34,4)	69,2 [32,2; NE]		127	54 (42,5)	14,9 [6,5;54,4]		0,71	[0,47; 1,06]	0,0908
Interaktion p-Wert											0,0376*
Ki-67 (%) II [eCRF]											
< 50%	180	70 (38,9)	39,7 [24,9; NE]		164	64 (39,0)	43,3 [21,2; NE]		0,98	[0,70; 1,38]	0,9177
>= 50%	57	19 (33,3)	NE [NE; NE]		66	23 (34,8)	14,9 [6,4; NE]		0,83	[0,45; 1,53]	0,5592
Interaktion p-Wert											0,6460
Knochenmarksbeteiligung [eCRF]											
Ja	178	67 (37,6)	50,8 [32,2; NE]		180	58 (32,2)	54,4 [32,3; NE]		1,07	[0,75; 1,52]	0,7083
Nein	50	21 (42,0)	28,6 [3,9; NE]		45	19 (42,2)	14,9 [3,8; NE]		0,99	[0,53; 1,86]	0,9733
Interaktion p-Wert											0,8311
Extranodale Erkrankung [eCRF]											
Ja	264	95 (36,0)	50,8 [32,4; NE]		277	95 (34,3)	43,3 [28,4; NE]		0,97	[0,73; 1,29]	0,8147
Nein	35	15 (42,9)	28,6 [3,7; NE]		22	10 (45,5)	6,4 [2,0; NE]		0,70	[0,32; 1,61]	0,3927
Interaktion p-Wert											0,4645
Gastrointestinale Erkrankung [eCRF]											
Ja	74	25 (33,8)	58,0 [36,2; NE]		75	24 (32,0)	39,4 [25,0; NE]		0,99	[0,56; 1,74]	0,9759
Nein	225	85 (37,8)	47,1 [25,0; NE]		224	81 (36,2)	35,9 [17,5; NE]		0,94	[0,69; 1,27]	0,6697
Interaktion p-Wert											0,8594
LDH > ULN [eCRF]											
Ja	52	14 (26,9)	NE [NE; NE]		54	18 (33,3)	13,8 [3,7; NE]		0,66	[0,32; 1,33]	0,2484
Nein	245	96 (39,2)	50,8 [32,2; NE]		241	86 (35,7)	43,3 [32,2; NE]		1,02	[0,76; 1,36]	0,9187
Interaktion p-Wert											0,2697

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.9 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Schmerzen
 Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	40 (48,8)	14,2 [6,6;33,4]	83	32 (38,6)	21,2 [7,5;39,7]	1,17	[0,74; 1,87]	0,5102
Westeuropa	46	22 (47,8)	10,4 [6,5;32,4]	46	17 (37,0)	47,1 [10,3; NE]	1,39	[0,74; 2,66]	0,3015
Andere	171	95 (55,6)	13,9 [6,8;18,0]	170	70 (41,2)	21,4 [13,9;43,3]	1,45	[1,07; 1,99]	0,0168*
Interaktion p-Wert									0,7444
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	60 (60,6)	10,2 [3,9;17,6]	101	43 (42,6)	28,8 [14,3;46,8]	1,58	[1,07; 2,35]	0,0216*
Intermediäres Risiko [4-5]	128	63 (49,2)	13,9 [10,2;21,3]	125	53 (42,4)	21,3 [10,3;40,0]	1,19	[0,83; 1,72]	0,3516
Hohes Risiko [6-11]	72	34 (47,2)	21,2 [6,5;32,2]	73	23 (31,5)	21,3 [13,8; NE]	1,41	[0,84; 2,42]	0,1988
Interaktion p-Wert									0,5821
Geschlecht [eCRF]									
Männlich	214	103 (48,1)	17,5 [10,3;24,9]	209	79 (37,8)	28,6 [21,2;39,8]	1,37	[1,03; 1,85]	0,0327*
Weiblich	85	54 (63,5)	10,2 [6,5;17,5]	90	40 (44,4)	13,8 [6,5;47,1]	1,33	[0,89; 2,01]	0,1689
Interaktion p-Wert									0,8996
Altersgruppe I [eCRF]									
< 70 Jahre	123	71 (57,7)	10,3 [3,9;17,6]	117	43 (36,8)	35,9 [21,2;47,1]	1,71	[1,18; 2,52]	0,0048*
>= 70 Jahre	176	86 (48,9)	17,5 [10,3;21,3]	182	76 (41,8)	21,2 [13,8;28,6]	1,17	[0,86; 1,60]	0,3186
Interaktion p-Wert									0,1262
Altersgruppe II [eCRF]									
< 75 Jahre	215	120 (55,8)	13,8 [10,0;17,6]	222	82 (36,9)	35,9 [21,2;46,9]	1,62	[1,22; 2,15]	0,0007*
>= 75 Jahre	84	37 (44,0)	17,5 [6,5;43,1]	77	37 (48,1)	13,8 [10,2;21,3]	0,86	[0,54; 1,35]	0,5049
Interaktion p-Wert									0,0202*
Abstammung [eCRF]									
Weiß	233	128 (54,9)	13,8 [10,0;17,5]	235	96 (40,9)	21,3 [13,8;39,7]	1,34	[1,03; 1,74]	0,0311*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.9 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Schmerzen
 Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Nicht-weiß	52	23 (44,2)	28,6 [7,1; NE]		53	19 (35,8)	28,8 [21,2; NE]		1,49	[0,81; 2,77]	0,1943
Interaktion p-Wert											0,7412
ECOG-PS [eCRF]											
0	156	86 (55,1)	14,2 [10,2;21,2]		140	52 (37,1)	28,6 [21,2;51,2]		1,56	[1,11; 2,22]	0,0097*
1	129	64 (49,6)	13,9 [6,5;28,7]		132	57 (43,2)	21,2 [10,2;39,7]		1,20	[0,84; 1,72]	0,3163
>=2	12	7 (58,3)	3,9 [1,9;21,3]		25	10 (40,0)	6,6 [2,0; NE]		1,58	[0,57; 4,12]	0,3599
Interaktion p-Wert											0,5553
Bulky Disease I [eCRF]											
< 5 cm	187	106 (56,7)	10,8 [7,1;17,5]		186	73 (39,2)	21,4 [13,9;40,0]		1,55	[1,16; 2,10]	0,0035*
>= 5 cm	112	51 (45,5)	17,6 [6,5;43,6]		113	46 (40,7)	28,6 [13,8;39,8]		1,09	[0,73; 1,63]	0,6743
Interaktion p-Wert											0,1628
Bulky Disease II [eCRF]											
< 10 cm	279	151 (54,1)	13,8 [7,1;17,5]		278	112 (40,3)	21,4 [17,5;36,1]		1,44	[1,13; 1,84]	0,0034*
>= 10 cm	20	6 (30,0)	NE [NE; NE]		21	7 (33,3)	47,1 [6,5; NE]		0,63	[0,20; 1,89]	0,3998
Interaktion p-Wert											0,1460
Ann Arbor-Stadium für Lymphome [eCRF]											
Stadium I-III	48	30 (62,5)	14,0 [3,7;21,3]		36	13 (36,1)	35,9 [6,5; NE]		1,96	[1,05; 3,89]	0,0355*
Stadium IV	251	127 (50,6)	13,9 [10,2;21,2]		263	106 (40,3)	21,3 [14,3;36,1]		1,28	[0,99; 1,66]	0,0605
Interaktion p-Wert											0,2232
MCL-Typ [eCRF]											
Klassische Variante	197	100 (50,8)	13,9 [10,2;21,2]		205	89 (43,4)	21,3 [14,3;36,1]		1,25	[0,94; 1,67]	0,1218
Blastoide und pleomorphische Variante	39	21 (53,8)	10,2 [3,8;28,7]		33	9 (27,3)	13,8 [6,5; NE]		1,53	[0,72; 3,53]	0,2741
Andere	0	0	NE		8	1 (12,5)	NE [NE; NE]		NC	[NC]	NC
Interaktion p-Wert											0,6338

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.9 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Schmerzen
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	59 (54,1)	10,0 [4,0;14,0]	103	47 (45,6)	21,4 [17,5;39,7]	1,61	[1,10; 2,37]	0,0152*
>= 30%	128	67 (52,3)	17,5 [10,2;21,3]	127	52 (40,9)	21,3 [6,9;47,1]	1,23	[0,86; 1,77]	0,2633
Interaktion p-Wert									0,3210
Ki-67 (%) II [eCRF]									
< 50%	180	99 (55,0)	10,4 [6,5;17,5]	164	80 (48,8)	21,3 [14,3;32,3]	1,39	[1,04; 1,87]	0,0283*
>= 50%	57	27 (47,4)	17,6 [6,4;47,1]	66	19 (28,8)	52,4 [6,9; NE]	1,41	[0,79; 2,57]	0,2490
Interaktion p-Wert									0,9679
Knochenmarksbeteiligung [eCRF]									
Ja	178	91 (51,1)	17,5 [10,3;24,9]	180	70 (38,9)	28,6 [21,2;40,0]	1,30	[0,96; 1,79]	0,0929
Nein	50	27 (54,0)	17,5 [4,1;36,1]	45	21 (46,7)	13,8 [6,6; NE]	1,31	[0,74; 2,35]	0,3465
Interaktion p-Wert									0,9833
Extranodale Erkrankung [eCRF]									
Ja	264	135 (51,1)	13,9 [10,2;21,2]	277	109 (39,4)	24,8 [17,5;39,8]	1,35	[1,05; 1,73]	0,0207*
Nein	35	22 (62,9)	10,3 [3,7;36,1]	22	10 (45,5)	21,3 [2,0; NE]	1,39	[0,67; 3,07]	0,3806
Interaktion p-Wert									0,9378
Gastrointestinale Erkrankung [eCRF]									
Ja	74	32 (43,2)	13,9 [6,5; NE]	75	31 (41,3)	28,6 [10,3;40,0]	1,21	[0,74; 2,00]	0,4403
Nein	225	125 (55,6)	13,9 [10,2;17,6]	224	88 (39,3)	21,3 [14,3;43,3]	1,41	[1,07; 1,85]	0,0135*
Interaktion p-Wert									0,6110
LDH > ULN [eCRF]									
Ja	52	22 (42,3)	21,2 [3,9;43,6]	54	14 (25,9)	21,3 [3,9; NE]	1,48	[0,76; 2,96]	0,2486
Nein	245	135 (55,1)	13,9 [10,2;17,6]	241	104 (43,2)	24,8 [17,5;36,1]	1,35	[1,05; 1,75]	0,0197*
Interaktion p-Wert									0,8115

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.10 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Dyspnoe
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	34 (41,5)	21,2 [17,5;32,4]	83	19 (22,9)	58,2 [24,6; NE]	1,66	[0,96; 2,96]	0,0717
Westeuropa	46	15 (32,6)	32,4 [6,8; NE]	46	15 (32,6)	25,4 [10,2; NE]	0,98	[0,48; 2,03]	0,9631
Andere	171	73 (42,7)	32,3 [21,2;47,2]	170	65 (38,2)	28,4 [18,6;43,3]	0,98	[0,70; 1,37]	0,8965
Interaktion p-Wert									0,2607
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	46 (46,5)	25,8 [17,5;47,2]	101	40 (39,6)	24,9 [10,3;43,3]	0,97	[0,64; 1,50]	0,9058
Intermediäres Risiko [4-5]	128	54 (42,2)	24,9 [17,5;46,9]	125	41 (32,8)	58,2 [18,0; NE]	1,26	[0,84; 1,90]	0,2682
Hohes Risiko [6-11]	72	22 (30,6)	32,6 [25,1; NE]	73	18 (24,7)	32,2 [21,0; NE]	1,07	[0,58; 2,02]	0,8237
Interaktion p-Wert									0,6939
Geschlecht [eCRF]									
Männlich	214	81 (37,9)	32,3 [24,9;50,7]	209	70 (33,5)	28,6 [21,0;58,2]	1,03	[0,75; 1,42]	0,8438
Weiblich	85	41 (48,2)	21,2 [13,9;42,3]	90	29 (32,2)	32,3 [17,5; NE]	1,30	[0,81; 2,11]	0,2780
Interaktion p-Wert									0,4315
Altersgruppe I [eCRF]									
< 70 Jahre	123	53 (43,1)	25,8 [17,5;61,7]	117	40 (34,2)	24,9 [17,5; NE]	1,05	[0,70; 1,59]	0,8178
>= 70 Jahre	176	69 (39,2)	28,8 [21,2;36,4]	182	59 (32,4)	32,3 [21,0; NE]	1,15	[0,81; 1,63]	0,4258
Interaktion p-Wert									0,7354
Altersgruppe II [eCRF]									
< 75 Jahre	215	90 (41,9)	28,6 [17,7;47,2]	222	70 (31,5)	32,6 [22,3; NE]	1,24	[0,91; 1,70]	0,1776
>= 75 Jahre	84	32 (38,1)	32,2 [17,5;46,9]	77	29 (37,7)	32,2 [10,3; NE]	0,80	[0,48; 1,33]	0,3866
Interaktion p-Wert									0,1493
Abstammung [eCRF]									
Weiß	233	98 (42,1)	28,8 [21,2;36,4]	235	73 (31,1)	28,6 [18,6; NE]	1,18	[0,87; 1,60]	0,2950

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.10 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Dyspnoe
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Nicht-weiß	52	20 (38,5)	47,2 [13,9; NE]		53	23 (43,4)	28,6 [10,3; NE]		0,91	[0,50; 1,66]	0,7645
Interaktion p-Wert											0,4598
ECOG-PS [eCRF]											
0	156	69 (44,2)	32,3 [21,2;46,9]		140	47 (33,6)	32,3 [21,6; NE]		1,18	[0,82; 1,72]	0,3828
1	129	50 (38,8)	24,9 [13,8; NE]		132	45 (34,1)	28,6 [17,5; NE]		1,09	[0,73; 1,64]	0,6747
>=2	12	3 (25,0)	32,2 [2,0; NE]		25	7 (28,0)	24,9 [17,5; NE]		0,59	[0,13; 2,13]	0,4339
Interaktion p-Wert											0,6073
Bulky Disease I [eCRF]											
< 5 cm	187	80 (42,8)	25,1 [17,6;36,0]		186	62 (33,3)	32,2 [21,6; NE]		1,20	[0,86; 1,68]	0,2763
>= 5 cm	112	42 (37,5)	36,4 [17,7; NE]		113	37 (32,7)	24,9 [14,0; NE]		0,97	[0,62; 1,51]	0,8802
Interaktion p-Wert											0,4407
Bulky Disease II [eCRF]											
< 10 cm	279	115 (41,2)	28,6 [21,2;39,6]		278	95 (34,2)	28,6 [21,2;47,5]		1,09	[0,83; 1,43]	0,5303
>= 10 cm	20	7 (35,0)	36,4 [10,1; NE]		21	4 (19,0)	NE [NE; NE]		1,55	[0,47; 5,93]	0,4758
Interaktion p-Wert											0,5780
Ann Arbor-Stadium für Lymphome [eCRF]											
Stadium I-III	48	23 (47,9)	21,3 [6,7;47,2]		36	18 (50,0)	10,3 [3,7;32,3]		0,79	[0,43; 1,48]	0,4498
Stadium IV	251	99 (39,4)	32,2 [21,2;42,3]		263	81 (30,8)	32,6 [24,6; NE]		1,16	[0,87; 1,56]	0,3206
Interaktion p-Wert											0,2692
MCL-Typ [eCRF]											
Klassische Variante	197	79 (40,1)	32,2 [21,2;61,7]		205	68 (33,2)	32,3 [24,9;58,2]		1,14	[0,82; 1,58]	0,4333
Blastoide und pleomorphische Variante	39	14 (35,9)	24,8 [4,2; NE]		33	8 (24,2)	28,6 [13,8; NE]		1,42	[0,61; 3,56]	0,4232
Andere	0	0	NE		8	2 (25,0)	NE [NE; NE]		NC	[NC]	NC
Interaktion p-Wert											0,6383

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.10 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Dyspnoe
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	47 (43,1)	21,2 [10,2;50,7]	103	42 (40,8)	24,9 [17,5;43,4]	1,13	[0,74; 1,71]	0,5759
>= 30%	128	51 (39,8)	28,6 [17,5;39,6]	127	42 (33,1)	28,6 [17,5; NE]	1,08	[0,72; 1,63]	0,7275
Interaktion p-Wert									0,8770
Ki-67 (%) II [eCRF]									
< 50%	180	76 (42,2)	24,9 [15,5;50,7]	164	72 (43,9)	22,3 [17,5;32,2]	0,94	[0,68; 1,30]	0,7180
>= 50%	57	22 (38,6)	32,3 [13,9;39,6]	66	12 (18,2)	NE [NE; NE]	2,01	[1,01; 4,20]	0,0458*
Interaktion p-Wert									0,0503
Knochenmarksbeteiligung [eCRF]									
Ja	178	75 (42,1)	28,6 [21,2;36,4]	180	44 (24,4)	58,2 [32,2; NE]	1,66	[1,15; 2,43]	0,0064*
Nein	50	25 (50,0)	6,7 [3,7; NE]	45	23 (51,1)	6,7 [3,7;25,4]	1,01	[0,57; 1,80]	0,9598
Interaktion p-Wert									0,1537
Extranodale Erkrankung [eCRF]									
Ja	264	102 (38,6)	32,2 [24,9;46,9]	277	87 (31,4)	32,6 [24,6; NE]	1,11	[0,83; 1,48]	0,4844
Nein	35	20 (57,1)	10,2 [3,7;39,6]	22	12 (54,5)	6,7 [2,0;32,3]	0,82	[0,40; 1,72]	0,5824
Interaktion p-Wert									0,4433
Gastrointestinale Erkrankung [eCRF]									
Ja	74	31 (41,9)	21,2 [6,8; NE]	75	23 (30,7)	NE [NE; NE]	1,41	[0,82; 2,44]	0,2124
Nein	225	91 (40,4)	28,8 [21,3;39,6]	224	76 (33,9)	28,6 [21,0;47,5]	1,03	[0,76; 1,40]	0,8650
Interaktion p-Wert									0,3179
LDH > ULN [eCRF]									
Ja	52	19 (36,5)	17,5 [6,5; NE]	54	13 (24,1)	28,6 [13,8; NE]	1,57	[0,78; 3,24]	0,2099
Nein	245	103 (42,0)	32,3 [24,8;42,3]	241	86 (35,7)	28,6 [21,0;47,5]	1,04	[0,78; 1,38]	0,8033
Interaktion p-Wert									0,2874

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.11 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Schlaflosigkeit
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Geographic Region [IXRS]											
Nordamerika	82	27 (32,9)	36,0 [17,5; NE]		83	31 (37,3)	29,0 [6,7; NE]		0,72	[0,43; 1,21]	0,2184
Westeuropa	46	15 (32,6)	58,0 [10,4; NE]		46	17 (37,0)	17,6 [10,3; NE]		0,79	[0,39; 1,59]	0,5152
Andere	171	84 (49,1)	21,3 [13,8;36,2]		170	55 (32,4)	65,9 [28,6; NE]		1,58	[1,13; 2,23]	0,0074*
Interaktion p-Wert											0,0223*
Vereinfachter MIPI-Score [IXRS]											
Geringes Risiko [0-3]	99	45 (45,5)	28,8 [17,5;54,6]		101	41 (40,6)	21,3 [10,6; NE]		0,94	[0,62; 1,45]	0,7900
Intermediäres Risiko [4-5]	128	65 (50,8)	14,0 [6,5;28,6]		125	44 (35,2)	36,4 [17,6; NE]		1,64	[1,12; 2,42]	0,0109*
Hohes Risiko [6-11]	72	16 (22,2)	NE [NE; NE]		73	18 (24,7)	NE [NE; NE]		0,77	[0,39; 1,51]	0,4464
Interaktion p-Wert											0,0659
Geschlecht [eCRF]											
Männlich	214	85 (39,7)	28,5 [17,5;54,6]		209	73 (34,9)	36,4 [17,6;69,0]		1,12	[0,82; 1,53]	0,4892
Weiblich	85	41 (48,2)	28,8 [10,3;43,5]		90	30 (33,3)	29,0 [17,6; NE]		1,31	[0,82; 2,11]	0,2655
Interaktion p-Wert											0,5882
Altersgruppe I [eCRF]											
< 70 Jahre	123	57 (46,3)	28,6 [13,8;58,0]		117	38 (32,5)	65,9 [21,2; NE]		1,27	[0,85; 1,93]	0,2455
>= 70 Jahre	176	69 (39,2)	32,6 [17,5;50,7]		182	65 (35,7)	28,6 [17,6; NE]		1,11	[0,79; 1,56]	0,5485
Interaktion p-Wert											0,6110
Altersgruppe II [eCRF]											
< 75 Jahre	215	93 (43,3)	28,6 [17,5;54,6]		222	73 (32,9)	65,9 [21,2; NE]		1,29	[0,95; 1,76]	0,1010
>= 75 Jahre	84	33 (39,3)	28,7 [10,4;43,5]		77	30 (39,0)	28,6 [10,2; NE]		0,89	[0,54; 1,46]	0,6384
Interaktion p-Wert											0,2088
Abstammung [eCRF]											
Weiß	233	97 (41,6)	32,6 [17,6;50,7]		235	81 (34,5)	29,0 [17,6; NE]		1,09	[0,81; 1,46]	0,5870

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.11 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Schlaflosigkeit
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Nicht-weiß	52	26 (50,0)	28,5 [6,5;54,6]		53	17 (32,1)	69,0 [28,6; NE]		1,92	[1,05; 3,60]	0,0347*
Interaktion p-Wert											0,0978
ECOG-PS [eCRF]											
0	156	67 (42,9)	32,6 [21,2;50,7]		140	55 (39,3)	28,6 [13,9; NE]		0,98	[0,69; 1,41]	0,9229
1	129	53 (41,1)	28,6 [13,8;58,0]		132	43 (32,6)	43,3 [17,6; NE]		1,35	[0,91; 2,03]	0,1398
>=2	12	6 (50,0)	13,9 [2,0; NE]		25	5 (20,0)	NE [NE; NE]		2,03	[0,60; 7,11]	0,2466
Interaktion p-Wert											0,3266
Bulky Disease I [eCRF]											
< 5 cm	187	78 (41,7)	28,6 [14,0;43,5]		186	66 (35,5)	36,4 [17,6; NE]		1,14	[0,82; 1,58]	0,4376
>= 5 cm	112	48 (42,9)	36,2 [14,0;54,6]		113	37 (32,7)	32,2 [14,0; NE]		1,23	[0,80; 1,90]	0,3414
Interaktion p-Wert											0,7776
Bulky Disease II [eCRF]											
< 10 cm	279	116 (41,6)	28,7 [17,5;43,5]		278	96 (34,5)	36,4 [21,2;69,0]		1,17	[0,89; 1,54]	0,2523
>= 10 cm	20	10 (50,0)	21,2 [6,5; NE]		21	7 (33,3)	21,2 [3,7; NE]		1,17	[0,45; 3,22]	0,7511
Interaktion p-Wert											0,9968
Ann Arbor-Stadium für Lymphome [eCRF]											
Stadium I-III	48	24 (50,0)	14,0 [6,5; NE]		36	14 (38,9)	28,6 [10,6; NE]		1,27	[0,66; 2,51]	0,4798
Stadium IV	251	102 (40,6)	32,6 [21,1;50,7]		263	89 (33,8)	36,4 [21,2;69,0]		1,15	[0,86; 1,53]	0,3442
Interaktion p-Wert											0,7877
MCL-Typ [eCRF]											
Klassische Variante	197	85 (43,1)	28,7 [10,4;50,7]		205	71 (34,6)	43,3 [21,2; NE]		1,27	[0,93; 1,75]	0,1327
Blastoide und pleomorphische Variante	39	13 (33,3)	32,6 [21,1; NE]		33	8 (24,2)	21,2 [13,8; NE]		0,98	[0,41; 2,48]	0,9633
Andere	0	0	NE		8	5 (62,5)	29,0 [1,9; NE]		NC	[NC]	NC
Interaktion p-Wert											0,5874

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.11 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Schlaflosigkeit
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]											
< 30%	109	47 (43,1)	17,5 [10,1;58,0]	103	36 (35,0)	43,3 [17,6; NE]	1,41	[0,91; 2,19]	0,1217		
>= 30%	128	54 (42,2)	28,7 [10,4;65,5]	127	45 (35,4)	28,6 [13,9; NE]	1,14	[0,77; 1,70]	0,5239		
Interaktion p-Wert										0,4775	
Ki-67 (%) II [eCRF]											
< 50%	180	77 (42,8)	28,6 [10,4;58,0]	164	58 (35,4)	43,3 [21,3; NE]	1,36	[0,97; 1,92]	0,0753		
>= 50%	57	24 (42,1)	28,7 [6,6; NE]	66	23 (34,8)	17,6 [6,5; NE]	0,99	[0,56; 1,76]	0,9708		
Interaktion p-Wert										0,3500	
Knochenmarksbeteiligung [eCRF]											
Ja	178	80 (44,9)	28,6 [10,3;43,5]	180	62 (34,4)	29,0 [17,6; NE]	1,29	[0,92; 1,80]	0,1374		
Nein	50	17 (34,0)	NE [NE; NE]	45	18 (40,0)	21,2 [10,2; NE]	0,83	[0,42; 1,61]	0,5753		
Interaktion p-Wert										0,2441	
Extranodale Erkrankung [eCRF]											
Ja	264	110 (41,7)	28,7 [17,6;43,5]	277	94 (33,9)	42,9 [21,2;69,0]	1,18	[0,90; 1,56]	0,2319		
Nein	35	16 (45,7)	28,8 [6,5; NE]	22	9 (40,9)	21,3 [10,2; NE]	1,05	[0,47; 2,48]	0,9071		
Interaktion p-Wert										0,7875	
Gastrointestinale Erkrankung [eCRF]											
Ja	74	29 (39,2)	36,0 [10,0; NE]	75	24 (32,0)	NE [NE; NE]	1,16	[0,68; 2,02]	0,5827		
Nein	225	97 (43,1)	28,6 [17,6;39,4]	224	79 (35,3)	36,4 [21,2;69,0]	1,17	[0,87; 1,59]	0,2910		
Interaktion p-Wert										0,9784	
LDH > ULN [eCRF]											
Ja	52	17 (32,7)	25,1 [6,5; NE]	54	13 (24,1)	NE [NE; NE]	1,17	[0,57; 2,46]	0,6676		
Nein	245	109 (44,5)	28,8 [17,5;43,5]	241	90 (37,3)	32,2 [21,2;69,0]	1,16	[0,88; 1,54]	0,2982		
Interaktion p-Wert										0,9804	

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.12 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Appetitverlust
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	32 (39,0)	29,0 [6,5; NE]	83	25 (30,1)	32,2 [6,5; NE]	1,09	[0,65; 1,86]	0,7380
Westeuropa	46	14 (30,4)	NE [NE; NE]	46	17 (37,0)	17,7 [6,6; NE]	0,70	[0,34; 1,42]	0,3184
Andere	171	83 (48,5)	17,5 [10,0;54,4]	170	63 (37,1)	39,9 [17,5; NE]	1,27	[0,92; 1,77]	0,1488
Interaktion p-Wert									0,3162
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	45 (45,5)	32,4 [6,7; NE]	101	40 (39,6)	35,9 [14,0; NE]	1,00	[0,65; 1,54]	0,9996
Intermediäres Risiko [4-5]	128	57 (44,5)	18,0 [7,6;61,3]	125	47 (37,6)	39,9 [13,8; NE]	1,15	[0,78; 1,69]	0,4866
Hohes Risiko [6-11]	72	27 (37,5)	17,5 [6,5; NE]	73	18 (24,7)	39,6 [17,7; NE]	1,37	[0,76; 2,53]	0,2987
Interaktion p-Wert									0,6970
Geschlecht [eCRF]									
Männlich	214	88 (41,1)	24,9 [7,6; NE]	209	71 (34,0)	39,9 [17,7; NE]	1,19	[0,87; 1,63]	0,2838
Weiblich	85	41 (48,2)	24,9 [10,0;61,3]	90	34 (37,8)	32,2 [6,9; NE]	1,00	[0,64; 1,59]	0,9973
Interaktion p-Wert									0,5470
Altersgruppe I [eCRF]									
< 70 Jahre	123	58 (47,2)	29,0 [6,5;61,7]	117	41 (35,0)	35,9 [17,5; NE]	1,23	[0,83; 1,85]	0,3042
>= 70 Jahre	176	71 (40,3)	24,9 [10,1; NE]	182	64 (35,2)	39,6 [14,0; NE]	1,06	[0,75; 1,48]	0,7507
Interaktion p-Wert									0,5641
Altersgruppe II [eCRF]									
< 75 Jahre	215	87 (40,5)	35,7 [17,6; NE]	222	82 (36,9)	35,9 [17,5;58,3]	0,97	[0,71; 1,31]	0,8174
>= 75 Jahre	84	42 (50,0)	10,1 [6,5;17,5]	77	23 (29,9)	54,1 [17,6; NE]	1,72	[1,04; 2,90]	0,0331*
Interaktion p-Wert									0,0528
Abstammung [eCRF]									
Weiß	233	94 (40,3)	29,0 [13,9; NE]	235	79 (33,6)	35,9 [18,4;54,1]	1,03	[0,77; 1,40]	0,8311

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.12 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Appetitverlust
 Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Nicht-weiß	52	30 (57,7)	10,0 [3,7;35,7]		53	23 (43,4)	NE [NE; NE]		1,61	[0,94; 2,81]	0,0837
Interaktion p-Wert											0,1596
ECOG-PS [eCRF]											
0	156	69 (44,2)	28,6 [6,7; NE]		140	51 (36,4)	39,9 [17,7; NE]		1,10	[0,77; 1,59]	0,6043
1	129	56 (43,4)	17,6 [10,0; NE]		132	49 (37,1)	32,2 [13,8; NE]		1,11	[0,75; 1,63]	0,6073
>=2	12	4 (33,3)	24,9 [2,0; NE]		25	5 (20,0)	39,6 [6,9; NE]		1,50	[0,37; 5,69]	0,5500
Interaktion p-Wert											0,9049
Bulky Disease I [eCRF]											
< 5 cm	187	84 (44,9)	17,5 [6,7;54,4]		186	67 (36,0)	39,6 [17,7; NE]		1,16	[0,84; 1,61]	0,3587
>= 5 cm	112	45 (40,2)	35,7 [10,2; NE]		113	38 (33,6)	32,5 [14,9; NE]		1,07	[0,70; 1,66]	0,7585
Interaktion p-Wert											0,7647
Bulky Disease II [eCRF]											
< 10 cm	279	115 (41,2)	28,6 [13,8; NE]		278	98 (35,3)	39,6 [18,4; NE]		1,07	[0,82; 1,41]	0,5995
>= 10 cm	20	14 (70,0)	6,5 [2,1;24,9]		21	7 (33,3)	NE [NE; NE]		1,89	[0,78; 4,98]	0,1597
Interaktion p-Wert											0,2350
Ann Arbor-Stadium für Lymphome [eCRF]											
Stadium I-III	48	22 (45,8)	17,5 [6,5; NE]		36	16 (44,4)	35,9 [3,7; NE]		0,86	[0,45; 1,66]	0,6467
Stadium IV	251	107 (42,6)	25,8 [10,2;61,3]		263	89 (33,8)	39,6 [18,4; NE]		1,18	[0,89; 1,56]	0,2594
Interaktion p-Wert											0,3862
MCL-Typ [eCRF]											
Klassische Variante	197	83 (42,1)	29,0 [10,1;61,7]		205	77 (37,6)	35,9 [17,5;58,3]		1,05	[0,77; 1,44]	0,7485
Blastoide und pleomorphische Variante	39	17 (43,6)	17,5 [3,8; NE]		33	12 (36,4)	17,4 [3,7; NE]		0,99	[0,47; 2,12]	0,9742
Andere	0	0	NE		8	4 (50,0)	29,0 [1,8; NE]		NC	[NC]	NC
Interaktion p-Wert											0,8780

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.12 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Appetitverlust
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]			
	n			n					
Ki-67 (%) I [eCRF]									
< 30%	109	47 (43,1)	24,9 [6,8;61,7]	103	38 (36,9)	58,3 [13,8; NE]	1,24	[0,81; 1,92]	0,3142
>= 30%	128	55 (43,0)	28,6 [6,5; NE]	127	54 (42,5)	17,5 [6,9;39,9]	0,87	[0,60; 1,28]	0,4877
Interaktion p-Wert									0,2256
Ki-67 (%) II [eCRF]									
< 50%	180	77 (42,8)	24,9 [10,2;61,3]	164	72 (43,9)	29,0 [13,8;58,3]	0,96	[0,70; 1,33]	0,8090
>= 50%	57	25 (43,9)	10,0 [3,8; NE]	66	20 (30,3)	39,9 [6,9; NE]	1,30	[0,72; 2,37]	0,3816
Interaktion p-Wert									0,3771
Knochenmarksbeteiligung [eCRF]									
Ja	178	71 (39,9)	47,5 [13,8; NE]	180	53 (29,4)	47,5 [32,3; NE]	1,29	[0,90; 1,85]	0,1610
Nein	50	24 (48,0)	13,8 [6,5; NE]	45	22 (48,9)	7,1 [3,7; NE]	0,85	[0,48; 1,53]	0,5865
Interaktion p-Wert									0,2332
Extranodale Erkrankung [eCRF]									
Ja	264	112 (42,4)	28,6 [10,2;61,3]	277	92 (33,2)	39,9 [32,2; NE]	1,21	[0,92; 1,59]	0,1823
Nein	35	17 (48,6)	17,5 [4,5; NE]	22	13 (59,1)	3,7 [1,9;17,5]	0,52	[0,25; 1,09]	0,0814
Interaktion p-Wert									0,0365*
Gastrointestinale Erkrankung [eCRF]									
Ja	74	33 (44,6)	10,2 [6,5; NE]	75	27 (36,0)	39,9 [10,3; NE]	1,28	[0,77; 2,15]	0,3396
Nein	225	96 (42,7)	28,6 [13,8;61,3]	224	78 (34,8)	39,6 [29,0; NE]	1,08	[0,80; 1,46]	0,6045
Interaktion p-Wert									0,5756
LDH > ULN [eCRF]									
Ja	52	21 (40,4)	6,5 [3,7; NE]	54	13 (24,1)	NE [NE; NE]	1,74	[0,88; 3,56]	0,1125
Nein	245	108 (44,1)	25,8 [13,8;61,3]	241	92 (38,2)	35,9 [17,7;58,3]	1,04	[0,79; 1,38]	0,7798
Interaktion p-Wert									0,1737

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.13 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Verstopfung
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	30 (36,6)	32,3 [10,3; NE]	83	30 (36,1)	13,8 [3,8; NE]	0,77	[0,46; 1,28]	0,3058
Westeuropa	46	15 (32,6)	43,3 [10,2; NE]	46	21 (45,7)	10,6 [3,8;58,1]	0,56	[0,28; 1,08]	0,0830
Andere	171	67 (39,2)	35,7 [17,5; NE]	170	57 (33,5)	65,4 [17,5; NE]	1,04	[0,73; 1,48]	0,8279
Interaktion p-Wert									0,2286
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	43 (43,4)	29,0 [10,3; NE]	101	36 (35,6)	NE [NE; NE]	1,00	[0,64; 1,56]	0,9881
Intermediäres Risiko [4-5]	128	50 (39,1)	35,7 [10,3; NE]	125	45 (36,0)	58,1 [10,2; NE]	0,99	[0,66; 1,48]	0,9588
Hohes Risiko [6-11]	72	19 (26,4)	NE [NE; NE]	73	27 (37,0)	17,5 [3,8; NE]	0,53	[0,29; 0,94]	0,0305*
Interaktion p-Wert									0,1635
Geschlecht [eCRF]									
Männlich	214	75 (35,0)	54,5 [17,5; NE]	209	71 (34,0)	58,1 [17,5; NE]	0,92	[0,66; 1,27]	0,6095
Weiblich	85	37 (43,5)	28,5 [13,9;61,9]	90	37 (41,1)	10,6 [3,7; NE]	0,77	[0,48; 1,21]	0,2537
Interaktion p-Wert									0,5252
Altersgruppe I [eCRF]									
< 70 Jahre	123	47 (38,2)	43,3 [17,5; NE]	117	35 (29,9)	65,4 [17,5; NE]	1,05	[0,68; 1,64]	0,8314
>= 70 Jahre	176	65 (36,9)	32,3 [13,9; NE]	182	73 (40,1)	17,5 [6,9; NE]	0,79	[0,56; 1,10]	0,1596
Interaktion p-Wert									0,3054
Altersgruppe II [eCRF]									
< 75 Jahre	215	74 (34,4)	50,6 [28,6; NE]	222	78 (35,1)	36,0 [17,5; NE]	0,78	[0,57; 1,08]	0,1316
>= 75 Jahre	84	38 (45,2)	10,3 [6,4;61,9]	77	30 (39,0)	13,8 [6,9; NE]	1,12	[0,69; 1,82]	0,6450
Interaktion p-Wert									0,2222
Abstammung [eCRF]									
Weiß	233	85 (36,5)	50,6 [21,5; NE]	235	90 (38,3)	21,2 [10,2;65,4]	0,75	[0,56; 1,01]	0,0587

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.13 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Verstopfung
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Nicht-weiß	52	22 (42,3)	28,5 [10,0; NE]		53	14 (26,4)	NE [NE; NE]		1,70	[0,88; 3,41]	0,1148
Interaktion p-Wert											0,0268*
ECOG-PS [eCRF]											
0	156	56 (35,9)	61,9 [29,0; NE]		140	51 (36,4)	36,0 [10,6; NE]		0,82	[0,56; 1,20]	0,3043
1	129	52 (40,3)	28,5 [13,9;43,3]		132	48 (36,4)	25,0 [10,1; NE]		0,96	[0,65; 1,43]	0,8470
>=2	12	4 (33,3)	6,5 [1,8; NE]		25	9 (36,0)	6,9 [1,9; NE]		0,85	[0,23; 2,61]	0,7810
Interaktion p-Wert											0,8450
Bulky Disease I [eCRF]											
< 5 cm	187	73 (39,0)	32,3 [13,8; NE]		186	70 (37,6)	28,6 [10,2; NE]		0,85	[0,61; 1,18]	0,3299
>= 5 cm	112	39 (34,8)	50,6 [25,2; NE]		113	38 (33,6)	36,0 [10,2; NE]		0,90	[0,58; 1,42]	0,6590
Interaktion p-Wert											0,8250
Bulky Disease II [eCRF]											
< 10 cm	279	106 (38,0)	32,3 [21,2; NE]		278	102 (36,7)	28,6 [13,8; NE]		0,88	[0,67; 1,15]	0,3503
>= 10 cm	20	6 (30,0)	54,5 [14,1; NE]		21	6 (28,6)	NE [NE; NE]		0,77	[0,24; 2,46]	0,6491
Interaktion p-Wert											0,8222
Ann Arbor-Stadium für Lymphome [eCRF]											
Stadium I-III	48	20 (41,7)	NE [NE; NE]		36	13 (36,1)	NE [NE; NE]		1,06	[0,53; 2,19]	0,8685
Stadium IV	251	92 (36,7)	35,7 [24,9;61,9]		263	95 (36,1)	28,6 [13,7; NE]		0,84	[0,63; 1,12]	0,2358
Interaktion p-Wert											0,5440
MCL-Typ [eCRF]											
Klassische Variante	197	72 (36,5)	43,3 [24,9; NE]		205	81 (39,5)	28,6 [10,2; NE]		0,79	[0,58; 1,09]	0,1544
Blastoide und pleomorphische Variante	39	14 (35,9)	21,5 [6,5; NE]		33	8 (24,2)	NE [NE; NE]		1,41	[0,60; 3,53]	0,4343
Andere	0	0	NE		8	2 (25,0)	NE [NE; NE]		NC	[NC]	NC
Interaktion p-Wert											0,2177

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.13 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Verstopfung
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]		2-seitiger p-Wert [b]
	Anzahl (%) der Patienten mit		Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit		Mediane Zeit [95%-KI] (Monate) [a]					
	n	Ereignis		n	Ereignis						
Ki-67 (%) I [eCRF]											
< 30%	109	40 (36,7)	35,7 [28,5; NE]	103	41 (39,8)	17,5 [6,5; NE]	0,84	[0,54; 1,30]	0,4241		
>= 30%	128	47 (36,7)	54,5 [13,9; NE]	127	46 (36,2)	36,0 [10,1; NE]	0,87	[0,58; 1,32]	0,5204		
Interaktion p-Wert									0,8844		
Ki-67 (%) II [eCRF]											
< 50%	180	65 (36,1)	43,3 [28,5; NE]	164	69 (42,1)	21,2 [10,2; NE]	0,78	[0,55; 1,09]	0,1460		
>= 50%	57	22 (38,6)	14,1 [10,0; NE]	66	18 (27,3)	58,1 [6,9; NE]	1,18	[0,63; 2,22]	0,6040		
Interaktion p-Wert									0,2491		
Knochenmarksbeteiligung [eCRF]											
Ja	178	68 (38,2)	28,6 [13,9; NE]	180	69 (38,3)	28,6 [10,1; NE]	0,85	[0,60; 1,18]	0,3260		
Nein	50	18 (36,0)	NE [NE; NE]	45	18 (40,0)	13,8 [3,9; NE]	0,82	[0,42; 1,58]	0,5481		
Interaktion p-Wert									0,9310		
Extranodale Erkrankung [eCRF]											
Ja	264	96 (36,4)	35,7 [24,9; NE]	277	99 (35,7)	36,0 [13,8; NE]	0,85	[0,64; 1,13]	0,2647		
Nein	35	16 (45,7)	10,0 [3,8; NE]	22	9 (40,9)	21,2 [3,7; NE]	0,97	[0,44; 2,30]	0,9488		
Interaktion p-Wert									0,7615		
Gastrointestinale Erkrankung [eCRF]											
Ja	74	27 (36,5)	50,6 [10,1; NE]	75	21 (28,0)	NE [NE; NE]	1,19	[0,67; 2,12]	0,5572		
Nein	225	85 (37,8)	32,3 [21,2; NE]	224	87 (38,8)	21,2 [10,2;65,4]	0,79	[0,59; 1,07]	0,1296		
Interaktion p-Wert									0,2200		
LDH > ULN [eCRF]											
Ja	52	13 (25,0)	NE [NE; NE]	54	17 (31,5)	7,3 [6,4; NE]	0,60	[0,28; 1,22]	0,1589		
Nein	245	99 (40,4)	32,3 [21,2;61,9]	241	91 (37,8)	36,0 [13,8; NE]	0,91	[0,69; 1,22]	0,5315		
Interaktion p-Wert									0,2809		

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.14 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Diarrhö
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	36 (43,9)	13,9 [6,6;39,7]	83	27 (32,5)	47,1 [6,9; NE]	1,37	[0,84; 2,28]	0,2129
Westeuropa	46	13 (28,3)	NE [NE; NE]	46	13 (28,3)	NE [NE; NE]	0,88	[0,40; 1,91]	0,7412
Andere	171	70 (40,9)	35,9 [14,3; NE]	170	45 (26,5)	NE [NE; NE]	1,50	[1,04; 2,20]	0,0309*
Interaktion p-Wert									0,4699
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	46 (46,5)	24,9 [13,8;50,5]	101	32 (31,7)	47,1 [28,6; NE]	1,30	[0,83; 2,06]	0,2505
Intermediäres Risiko [4-5]	128	51 (39,8)	24,9 [10,0; NE]	125	36 (28,8)	NE [NE; NE]	1,43	[0,93; 2,20]	0,1000
Hohes Risiko [6-11]	72	22 (30,6)	35,9 [10,2; NE]	73	17 (23,3)	47,0 [28,5; NE]	1,29	[0,69; 2,46]	0,4292
Interaktion p-Wert									0,9460
Geschlecht [eCRF]									
Männlich	214	85 (39,7)	24,9 [10,2; NE]	209	61 (29,2)	47,1 [28,6; NE]	1,39	[1,01; 1,94]	0,0465*
Weiblich	85	34 (40,0)	35,9 [21,2; NE]	90	24 (26,7)	NE [NE; NE]	1,27	[0,76; 2,17]	0,3617
Interaktion p-Wert									0,7758
Altersgruppe I [eCRF]									
< 70 Jahre	123	52 (42,3)	24,9 [10,2; NE]	117	30 (25,6)	NE [NE; NE]	1,51	[0,97; 2,39]	0,0678
>= 70 Jahre	176	67 (38,1)	35,9 [10,2; NE]	182	55 (30,2)	47,1 [28,6; NE]	1,27	[0,89; 1,81]	0,1929
Interaktion p-Wert									0,5462
Altersgruppe II [eCRF]									
< 75 Jahre	215	86 (40,0)	28,6 [14,3; NE]	222	61 (27,5)	NE [NE; NE]	1,40	[1,01; 1,95]	0,0449*
>= 75 Jahre	84	33 (39,3)	39,6 [10,0; NE]	77	24 (31,2)	39,8 [14,0; NE]	1,24	[0,73; 2,12]	0,4234
Interaktion p-Wert									0,7062
Abstammung [eCRF]									
Weiß	233	91 (39,1)	35,9 [13,8; NE]	235	70 (29,8)	47,1 [32,3; NE]	1,21	[0,89; 1,66]	0,2248

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.14 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Diarrhö
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)					Placebo+BR (N=299)					Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]					
Nicht-weiß	52	20 (38,5)	50,5 [17,5; NE]			53	12 (22,6)	NE [NE; NE]			1,90	[0,94; 4,01]	0,0730
Interaktion p-Wert													0,2534
ECOG-PS [eCRF]													
0	156	66 (42,3)	25,5 [13,9; NE]			140	43 (30,7)	39,8 [28,6; NE]			1,26	[0,86; 1,86]	0,2428
1	129	51 (39,5)	24,8 [10,0; NE]			132	35 (26,5)	47,2 [39,6; NE]			1,59	[1,04; 2,46]	0,0339*
>=2	12	2 (16,7)	NE [NE; NE]			25	7 (28,0)	28,5 [10,2; NE]			0,53	[0,08; 2,20]	0,4055
Interaktion p-Wert													0,3253
Bulky Disease I [eCRF]													
< 5 cm	187	74 (39,6)	35,9 [10,3; NE]			186	55 (29,6)	47,2 [32,3; NE]			1,29	[0,91; 1,84]	0,1515
>= 5 cm	112	45 (40,2)	25,5 [10,2; NE]			113	30 (26,5)	47,1 [28,5; NE]			1,47	[0,93; 2,36]	0,0985
Interaktion p-Wert													0,6552
Bulky Disease II [eCRF]													
< 10 cm	279	109 (39,1)	35,9 [13,9; NE]			278	78 (28,1)	47,2 [39,6; NE]			1,36	[1,02; 1,82]	0,0372*
>= 10 cm	20	10 (50,0)	21,2 [3,7; NE]			21	7 (33,3)	28,5 [4,1; NE]			1,27	[0,49; 3,48]	0,6314
Interaktion p-Wert													0,8890
Ann Arbor-Stadium für Lymphome [eCRF]													
Stadium I-III	48	22 (45,8)	39,4 [6,5; NE]			36	11 (30,6)	NE [NE; NE]			1,32	[0,65; 2,83]	0,4492
Stadium IV	251	97 (38,6)	25,5 [14,3; NE]			263	74 (28,1)	47,2 [39,6; NE]			1,35	[0,997; 1,83]	0,0527
Interaktion p-Wert													0,9575
MCL-Typ [eCRF]													
Klassische Variante	197	79 (40,1)	35,9 [17,5; NE]			205	58 (28,3)	47,2 [39,6; NE]			1,43	[1,02; 2,01]	0,0393*
Blastoide und pleomorphische Variante	39	17 (43,6)	10,2 [3,8; NE]			33	11 (33,3)	28,5 [6,9; NE]			1,29	[0,61; 2,83]	0,5140
Andere	0	0	NE			8	2 (25,0)	NE [NE; NE]			NC	[NC]	NC
Interaktion p-Wert													0,8088

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.14 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Diarrhö
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	44 (40,4)	24,8 [6,9; NE]	103	30 (29,1)	NE [NE; NE]	1,51	[0,95; 2,42]	0,0798
>= 30%	128	52 (40,6)	28,6 [10,2;50,5]	127	36 (28,3)	47,1 [28,5; NE]	1,46	[0,96; 2,24]	0,0808
Interaktion p-Wert									0,9121
Ki-67 (%) II [eCRF]									
< 50%	180	74 (41,1)	24,9 [10,2; NE]	164	51 (31,1)	47,2 [32,3; NE]	1,45	[1,01; 2,07]	0,0413*
>= 50%	57	22 (38,6)	28,6 [10,0; NE]	66	15 (22,7)	NE [NE; NE]	1,60	[0,84; 3,15]	0,1562
Interaktion p-Wert									0,7884
Knochenmarksbeteiligung [eCRF]									
Ja	178	69 (38,8)	28,6 [13,8; NE]	180	57 (31,7)	47,0 [28,6; NE]	1,17	[0,83; 1,67]	0,3765
Nein	50	20 (40,0)	39,7 [6,5; NE]	45	12 (26,7)	NE [NE; NE]	1,49	[0,74; 3,14]	0,2677
Interaktion p-Wert									0,5506
Extranodale Erkrankung [eCRF]									
Ja	264	101 (38,3)	28,6 [17,5; NE]	277	78 (28,2)	47,2 [39,6; NE]	1,32	[0,98; 1,78]	0,0633
Nein	35	18 (51,4)	10,0 [3,8; NE]	22	7 (31,8)	21,2 [6,7; NE]	1,45	[0,63; 3,74]	0,3895
Interaktion p-Wert									0,8386
Gastrointestinale Erkrankung [eCRF]									
Ja	74	27 (36,5)	24,9 [10,1; NE]	75	17 (22,7)	NE [NE; NE]	1,70	[0,94; 3,18]	0,0820
Nein	225	92 (40,9)	35,9 [13,9;50,5]	224	68 (30,4)	39,8 [28,6; NE]	1,26	[0,92; 1,73]	0,1424
Interaktion p-Wert									0,3911
LDH > ULN [eCRF]									
Ja	52	15 (28,8)	39,7 [10,1; NE]	54	10 (18,5)	NE [NE; NE]	1,65	[0,75; 3,79]	0,2164
Nein	245	104 (42,4)	25,5 [13,9;50,5]	241	74 (30,7)	47,1 [32,6; NE]	1,32	[0,98; 1,79]	0,0654
Interaktion p-Wert									0,6111

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.15 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Finanzielle Schwierigkeiten
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)					Placebo+BR (N=299)					Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]					
Geographic Region [IXRS]													
Nordamerika	82	16 (19,5)	NE	[	NE; NE]	83	17 (20,5)	69,0	[69,0; NE]	0,79	[0,39; 1,57]	0,4956	
Westeuropa	46	12 (26,1)	NE	[	NE; NE]	46	8 (17,4)	NE	[NE; NE]	1,48	[0,61; 3,78]	0,3837	
Andere	171	53 (31,0)	NE	[	NE; NE]	170	53 (31,2)	62,0	[28,8; NE]	0,87	[0,59; 1,27]	0,4597	
Interaktion p-Wert												0,4959	
Vereinfachter MIPI-Score [IXRS]													
Geringes Risiko [0-3]	99	26 (26,3)	NE	[	NE; NE]	101	23 (22,8)	69,0	[62,0; NE]	0,96	[0,55; 1,70]	0,8900	
Intermediäres Risiko [4-5]	128	38 (29,7)	NE	[	NE; NE]	125	33 (26,4)	NE	[NE; NE]	1,09	[0,68; 1,74]	0,7259	
Hohes Risiko [6-11]	72	17 (23,6)	51,7	[17,5; NE]		73	22 (30,1)	NE	[NE; NE]	0,60	[0,32; 1,14]	0,1179	
Interaktion p-Wert												0,3314	
Geschlecht [eCRF]													
Männlich	214	58 (27,1)	NE	[	NE; NE]	209	47 (22,5)	69,0	[62,0; NE]	1,17	[0,80; 1,72]	0,4245	
Weiblich	85	23 (27,1)	NE	[	NE; NE]	90	31 (34,4)	NE	[NE; NE]	0,54	[0,31; 0,92]	0,0229*	
Interaktion p-Wert												0,0206*	
Altersgruppe I [eCRF]													
< 70 Jahre	123	40 (32,5)	NE	[	NE; NE]	117	31 (26,5)	62,0	[30,0; NE]	1,03	[0,65; 1,66]	0,8981	
>= 70 Jahre	176	41 (23,3)	NE	[	NE; NE]	182	47 (25,8)	69,0	[43,3; NE]	0,81	[0,53; 1,24]	0,3376	
Interaktion p-Wert												0,4626	
Altersgruppe II [eCRF]													
< 75 Jahre	215	57 (26,5)	NE	[	NE; NE]	222	59 (26,6)	69,0	[62,0; NE]	0,85	[0,59; 1,23]	0,3899	
>= 75 Jahre	84	24 (28,6)	51,7	[32,4; NE]		77	19 (24,7)	NE	[NE; NE]	1,09	[0,60; 2,01]	0,7820	
Interaktion p-Wert												0,4947	
Abstammung [eCRF]													

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.15 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Finanzielle Schwierigkeiten
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Weiß	233	67 (28,8)	NE [NE; NE]	235	61 (26,0)	NE [NE; NE]	0,96	[0,68; 1,36]	0,8130
Nicht-weiß	52	11 (21,2)	50,7 [47,1; NE]	53	16 (30,2)	69,0 [17,7; NE]	0,65	[0,29; 1,38]	0,2610
Interaktion p-Wert									0,3562
ECOG-PS [eCRF]									
0	156	35 (22,4)	NE [NE; NE]	140	27 (19,3)	NE [NE; NE]	1,03	[0,63; 1,72]	0,9054
1	129	43 (33,3)	50,7 [25,2; NE]	132	42 (31,8)	69,0 [21,3; NE]	0,93	[0,61; 1,42]	0,7338
>=2	12	3 (25,0)	NE [NE; NE]	25	9 (36,0)	NE [NE; NE]	0,62	[0,14; 2,11]	0,4672
Interaktion p-Wert									0,7681
Bulky Disease I [eCRF]									
< 5 cm	187	55 (29,4)	NE [NE; NE]	186	49 (26,3)	69,0 [62,0; NE]	0,97	[0,66; 1,43]	0,8681
>= 5 cm	112	26 (23,2)	NE [NE; NE]	113	29 (25,7)	NE [NE; NE]	0,81	[0,47; 1,37]	0,4295
Interaktion p-Wert									0,5883
Bulky Disease II [eCRF]									
< 10 cm	279	75 (26,9)	NE [NE; NE]	278	75 (27,0)	69,0 [62,0; NE]	0,87	[0,63; 1,20]	0,4073
>= 10 cm	20	6 (30,0)	NE [NE; NE]	21	3 (14,3)	35,6 [11,3; NE]	1,84	[0,49; 8,75]	0,3741
Interaktion p-Wert									0,2896
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	16 (33,3)	NE [NE; NE]	36	8 (22,2)	62,0 [28,6; NE]	1,37	[0,60; 3,38]	0,4616
Stadium IV	251	65 (25,9)	NE [NE; NE]	263	70 (26,6)	69,0 [69,0; NE]	0,85	[0,60; 1,19]	0,3420
Interaktion p-Wert									0,2973
MCL-Typ [eCRF]									
Klassische Variante	197	54 (27,4)	NE [NE; NE]	205	58 (28,3)	69,0 [62,0; NE]	0,88	[0,60; 1,27]	0,4825
Blastoide und pleomorphische Variante	39	11 (28,2)	NE [NE; NE]	33	6 (18,2)	43,3 [35,6; NE]	1,45	[0,55; 4,20]	0,4615
Andere	0	0	NE	8	0	NE [NE; NE]	NC	[NC]	NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.15 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Finanzielle Schwierigkeiten
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Interaktion p-Wert									0,3475
Ki-67 (%) I [eCRF]									
< 30%	109	31 (28,4)	NE [NE; NE]	103	28 (27,2)	62,0 [30,0; NE]	1,04	[0,63; 1,75]	0,8696
>= 30%	128	33 (25,8)	NE [NE; NE]	127	33 (26,0)	NE [NE; NE]	0,89	[0,55; 1,45]	0,6507
Interaktion p-Wert									0,6666
Ki-67 (%) II [eCRF]									
< 50%	180	51 (28,3)	NE [NE; NE]	164	43 (26,2)	69,0 [62,0; NE]	1,08	[0,72; 1,62]	0,7235
>= 50%	57	13 (22,8)	NE [NE; NE]	66	18 (27,3)	43,3 [14,0; NE]	0,68	[0,33; 1,39]	0,2913
Interaktion p-Wert									0,2750
Knochenmarksbeteiligung [eCRF]									
Ja	178	46 (25,8)	NE [NE; NE]	180	43 (23,9)	69,0 [69,0; NE]	0,98	[0,64; 1,48]	0,9097
Nein	50	15 (30,0)	NE [NE; NE]	45	14 (31,1)	62,0 [11,3; NE]	0,92	[0,44; 1,93]	0,8203
Interaktion p-Wert									0,8878
Extranodale Erkrankung [eCRF]									
Ja	264	67 (25,4)	NE [NE; NE]	277	75 (27,1)	69,0 [62,0; NE]	0,81	[0,58; 1,13]	0,2186
Nein	35	14 (40,0)	NE [NE; NE]	22	3 (13,6)	NE [NE; NE]	2,87	[0,94; 12,44]	0,0666
Interaktion p-Wert									0,0338*
Gastrointestinale Erkrankung [eCRF]									
Ja	74	17 (23,0)	NE [NE; NE]	75	23 (30,7)	NE [NE; NE]	0,70	[0,37; 1,30]	0,2563
Nein	225	64 (28,4)	NE [NE; NE]	224	55 (24,6)	69,0 [62,0; NE]	1,00	[0,70; 1,43]	0,9842
Interaktion p-Wert									0,3310
LDH > ULN [eCRF]									
Ja	52	11 (21,2)	NE [NE; NE]	54	14 (25,9)	NE [NE; NE]	0,68	[0,30; 1,50]	0,3421

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.1.15 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Finanzielle Schwierigkeiten
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	2-seitiger p-Wert [b]
	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]				
	n			n						
Nein	245	70 (28,6)	NE [NE; NE]	241	64 (26,6)	69,0 [62,0; NE]	0,95	[0,68; 1,34]	0,7676	
Interaktion p-Wert									0,4503	

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.

Note: An interaction model is only used when there are ≥ 10 patients in each subgroup level, ≥ 10 events in at least one subgroup level and > 0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value < 0.05 . HR < 1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.1 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Gesamtscore
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	12 (14,6)	NE [NE; NE]	83	14 (16,9)	69,0 [NE; NE]	0,67	[0,31; 1,46]	0,3131
Westeuropa	46	6 (13,0)	NE [NE; NE]	46	9 (19,6)	65,0 [28,6; NE]	0,59	[0,20; 1,63]	0,3061
Andere	171	38 (22,2)	NE [NE; NE]	170	23 (13,5)	NE [NE; NE]	1,50	[0,90; 2,55]	0,1213
Interaktion p-Wert									0,1118
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	17 (17,2)	NE [NE; NE]	101	16 (15,8)	69,0 [NE; NE]	0,93	[0,47; 1,86]	0,8393
Intermediäres Risiko [4-5]	128	24 (18,8)	NE [NE; NE]	125	22 (17,6)	65,0 [65,0; NE]	0,93	[0,52; 1,67]	0,8063
Hohes Risiko [6-11]	72	15 (20,8)	54,3 [29,5; NE]	73	8 (11,0)	NE [NE; NE]	1,68	[0,73; 4,18]	0,2262
Interaktion p-Wert									0,4766
Geschlecht [eCRF]									
Männlich	214	41 (19,2)	NE [NE; NE]	209	30 (14,4)	69,0 [65,0; NE]	1,25	[0,79; 2,02]	0,3455
Weiblich	85	15 (17,6)	NE [NE; NE]	90	16 (17,8)	NE [NE; NE]	0,72	[0,35; 1,47]	0,3624
Interaktion p-Wert									0,2005
Altersgruppe I [eCRF]									
< 70 Jahre	123	21 (17,1)	NE [NE; NE]	117	16 (13,7)	NE [NE; NE]	0,99	[0,52; 1,93]	0,9835
>= 70 Jahre	176	35 (19,9)	NE [NE; NE]	182	30 (16,5)	69,0 [65,0; NE]	1,13	[0,69; 1,85]	0,6324
Interaktion p-Wert									0,7618
Altersgruppe II [eCRF]									
< 75 Jahre	215	37 (17,2)	NE [NE; NE]	222	31 (14,0)	69,0 [65,0; NE]	1,05	[0,65; 1,71]	0,8322
>= 75 Jahre	84	19 (22,6)	NE [NE; NE]	77	15 (19,5)	NE [NE; NE]	1,06	[0,54; 2,12]	0,8749
Interaktion p-Wert									0,9948
Abstammung [eCRF]									
Weiß	233	39 (16,7)	NE [NE; NE]	235	35 (14,9)	NE [NE; NE]	0,93	[0,59; 1,48]	0,7583

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.1 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Gesamtscore
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	15 (28,8)	NE [NE; NE]	53	10 (18,9)	69,0 [NE; NE]	1,71	[0,78; 3,93]	0,1848
Interaktion p-Wert									0,1940
ECOG-PS [eCRF]									
0	156	27 (17,3)	NE [NE; NE]	140	24 (17,1)	NE [NE; NE]	0,84	[0,49; 1,47]	0,5426
1	129	28 (21,7)	NE [NE; NE]	132	20 (15,2)	69,0 [69,0; NE]	1,35	[0,76; 2,43]	0,3016
>=2	12	1 (8,3)	NE [NE; NE]	25	2 (8,0)	NE [NE; NE]	0,75	[0,03; 7,93]	0,8145
Interaktion p-Wert									0,4888
Bulky Disease I [eCRF]									
< 5 cm	187	39 (20,9)	NE [NE; NE]	186	31 (16,7)	69,0 [65,0; NE]	1,18	[0,74; 1,90]	0,4921
>= 5 cm	112	17 (15,2)	NE [NE; NE]	113	15 (13,3)	NE [NE; NE]	0,87	[0,43; 1,76]	0,6869
Interaktion p-Wert									0,4732
Bulky Disease II [eCRF]									
< 10 cm	279	54 (19,4)	NE [NE; NE]	278	43 (15,5)	69,0 [65,0; NE]	1,12	[0,75; 1,68]	0,5828
>= 10 cm	20	2 (10,0)	NE [NE; NE]	21	3 (14,3)	NE [NE; NE]	0,42	[0,06; 2,54]	0,3371
Interaktion p-Wert									0,2902
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	11 (22,9)	NE [NE; NE]	36	9 (25,0)	58,0 [21,2; NE]	0,72	[0,30; 1,79]	0,4699
Stadium IV	251	45 (17,9)	NE [NE; NE]	263	37 (14,1)	69,0 [65,0; NE]	1,13	[0,73; 1,75]	0,5933
Interaktion p-Wert									0,3769
MCL-Typ [eCRF]									
Klassische Variante	197	38 (19,3)	NE [NE; NE]	205	30 (14,6)	69,0 [NE; NE]	1,23	[0,76; 2,01]	0,3905
Blastoide und pleomorphische Variante	39	5 (12,8)	NE [NE; NE]	33	4 (12,1)	NE [NE; NE]	0,70	[0,18; 2,82]	0,5920
Andere	0	0	NE	8	4 (50,0)	6,4 [1,9; NE]	NC	[NC]	NC
Interaktion p-Wert									0,4288

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.1 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Gesamtscore
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	21 (19,3)	NE [NE; NE]	103	17 (16,5)	69,0 [69,0; NE]	1,19	[0,63; 2,28]	0,5966
>= 30%	128	24 (18,8)	NE [NE; NE]	127	18 (14,2)	65,0 [NE; NE]	1,14	[0,62; 2,14]	0,6679
Interaktion p-Wert									0,9316
Ki-67 (%) II [eCRF]									
< 50%	180	35 (19,4)	NE [NE; NE]	164	26 (15,9)	69,0 [69,0; NE]	1,23	[0,74; 2,07]	0,4169
>= 50%	57	10 (17,5)	NE [NE; NE]	66	9 (13,6)	65,0 [28,6; NE]	0,97	[0,39; 2,45]	0,9506
Interaktion p-Wert									0,6525
Knochenmarksbeteiligung [eCRF]									
Ja	178	31 (17,4)	NE [NE; NE]	180	28 (15,6)	69,0 [65,0; NE]	0,94	[0,56; 1,58]	0,8248
Nein	50	9 (18,0)	NE [NE; NE]	45	8 (17,8)	NE [NE; NE]	1,08	[0,41; 2,89]	0,8708
Interaktion p-Wert									0,8040
Extranodale Erkrankung [eCRF]									
Ja	264	49 (18,6)	NE [NE; NE]	277	39 (14,1)	69,0 [65,0; NE]	1,17	[0,77; 1,78]	0,4760
Nein	35	7 (20,0)	NE [NE; NE]	22	7 (31,8)	58,0 [6,5; NE]	0,47	[0,16; 1,37]	0,1627
Interaktion p-Wert									0,1187
Gastrointestinale Erkrankung [eCRF]									
Ja	74	14 (18,9)	NE [NE; NE]	75	11 (14,7)	65,0 [51,2; NE]	1,36	[0,62; 3,07]	0,4429
Nein	225	42 (18,7)	NE [NE; NE]	224	35 (15,6)	69,0 [69,0; NE]	0,98	[0,62; 1,54]	0,9186
Interaktion p-Wert									0,4733
LDH > ULN [eCRF]									
Ja	52	11 (21,2)	NE [NE; NE]	54	6 (11,1)	NE [NE; NE]	1,71	[0,65; 4,96]	0,2818
Nein	245	45 (18,4)	NE [NE; NE]	241	40 (16,6)	69,0 [65,0; NE]	0,96	[0,63; 1,48]	0,8528
Interaktion p-Wert									0,2895

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.2 ECH0: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Physisches Wohlbefinden (PWB)
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)					Placebo+BR (N=299)					Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]				
Geographic Region [IXRS]													
Nordamerika	82	26 (31,7)	54,3	[17,5;	NE]	83	29 (34,9)	39,8	[17,4;	NE]	0,86	[0,50; 1,47]	0,5800
Westeuropa	46	16 (34,8)	39,6	[10,4;	NE]	46	17 (37,0)	21,3	[3,8;	NE]	0,86	[0,43; 1,70]	0,6568
Andere	171	58 (33,9)	65,5	[58,0;	NE]	170	60 (35,3)	46,9	[21,2;	NE]	0,86	[0,60; 1,23]	0,4066
Interaktion p-Wert													1,0000
Vereinfachter MIPI-Score [IXRS]													
Geringes Risiko [0-3]	99	31 (31,3)	NE	[NE;	NE]	101	44 (43,6)	24,9	[14,9;69,0]		0,64	[0,40; 1,01]	0,0560
Intermediäres Risiko [4-5]	128	44 (34,4)	58,0	[32,5;	NE]	125	43 (34,4)	NE	[NE;	NE]	0,93	[0,61; 1,42]	0,7470
Hohes Risiko [6-11]	72	25 (34,7)	54,3	[13,7;	NE]	73	19 (26,0)	NE	[NE;	NE]	1,18	[0,65; 2,18]	0,5763
Interaktion p-Wert													0,2393
Geschlecht [eCRF]													
Männlich	214	64 (29,9)	NE	[NE;	NE]	209	67 (32,1)	69,0	[35,9;	NE]	0,89	[0,63; 1,25]	0,4975
Weiblich	85	36 (42,4)	39,6	[10,0;	NE]	90	39 (43,3)	28,6	[6,5;46,9]		0,80	[0,50; 1,26]	0,3285
Interaktion p-Wert													0,7118
Altersgruppe I [eCRF]													
< 70 Jahre	123	44 (35,8)	65,3	[32,5;	NE]	117	42 (35,9)	46,9	[14,9;	NE]	0,84	[0,55; 1,29]	0,4269
>= 70 Jahre	176	56 (31,8)	65,5	[36,0;	NE]	182	64 (35,2)	39,9	[21,2;	NE]	0,87	[0,60; 1,24]	0,4404
Interaktion p-Wert													0,9148
Altersgruppe II [eCRF]													
< 75 Jahre	215	68 (31,6)	65,5	[58,0;	NE]	222	77 (34,7)	46,9	[28,6;	NE]	0,80	[0,58; 1,11]	0,1795
>= 75 Jahre	84	32 (38,1)	36,0	[10,4;	NE]	77	29 (37,7)	35,9	[10,3;	NE]	1,01	[0,61; 1,69]	0,9695
Interaktion p-Wert													0,4483
Abstammung [eCRF]													

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.2 ECH0: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Physisches Wohlbefinden (PWB)
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]		2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Weiß	233	78 (33,5)	65,3 [39,6; NE]		235	83 (35,3)	39,9 [21,3; NE]		0,85	[0,62; 1,16]	0,3052
Nicht-weiß	52	16 (30,8)	65,5 [65,5; NE]		53	21 (39,6)	69,0 [13,9; NE]		0,76	[0,39; 1,45]	0,4026
Interaktion p-Wert											0,7555
ECOG-PS [eCRF]											
0	156	52 (33,3)	NE [NE; NE]		140	53 (37,9)	39,9 [21,2; NE]		0,77	[0,52; 1,13]	0,1802
1	129	46 (35,7)	65,3 [28,6; NE]		132	48 (36,4)	35,9 [17,5; NE]		0,96	[0,64; 1,45]	0,8626
>=2	12	2 (16,7)	NE [NE; NE]		25	5 (20,0)	NE [NE; NE]		0,64	[0,09; 2,99]	0,5854
Interaktion p-Wert											0,6847
Bulky Disease I [eCRF]											
< 5 cm	187	66 (35,3)	58,0 [32,5; NE]		186	71 (38,2)	46,9 [21,2; NE]		0,85	[0,61; 1,19]	0,3411
>= 5 cm	112	34 (30,4)	NE [NE; NE]		113	35 (31,0)	39,8 [17,5; NE]		0,88	[0,54; 1,41]	0,5810
Interaktion p-Wert											0,9186
Bulky Disease II [eCRF]											
< 10 cm	279	95 (34,1)	65,3 [39,6; NE]		278	100 (36,0)	46,9 [24,9; NE]		0,88	[0,66; 1,16]	0,3624
>= 10 cm	20	5 (25,0)	NE [NE; NE]		21	6 (28,6)	32,1 [14,9; NE]		0,62	[0,18; 2,08]	0,4370
Interaktion p-Wert											0,5852
Ann Arbor-Stadium für Lymphome [eCRF]											
Stadium I-III	48	17 (35,4)	NE [NE; NE]		36	17 (47,2)	21,2 [3,7;55,6]		0,54	[0,27; 1,06]	0,0712
Stadium IV	251	83 (33,1)	65,3 [39,6; NE]		263	89 (33,8)	50,7 [32,1; NE]		0,92	[0,68; 1,24]	0,5794
Interaktion p-Wert											0,1526
MCL-Typ [eCRF]											
Klassische Variante	197	68 (34,5)	65,3 [36,0; NE]		205	73 (35,6)	55,6 [35,9; NE]		0,95	[0,68; 1,33]	0,7726
Blastoide und pleomorphische Variante	39	13 (33,3)	NE [NE; NE]		33	10 (30,3)	21,2 [3,7; NE]		0,81	[0,35; 1,90]	0,6169
Andere	0	0	NE		8	5 (62,5)	6,4 [1,9; NE]		NC	[NC]	NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.2 ECH0: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Physisches Wohlbefinden (PWB)
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]		2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Interaktion p-Wert											0,7202
Ki-67 (%) I [eCRF]											
< 30%	109	41 (37,6)	58,0 [14,0; NE]		103	36 (35,0)	55,6 [24,9; NE]		1,13	[0,72; 1,78]	0,5895
>= 30%	128	34 (26,6)	NE [NE; NE]		127	45 (35,4)	39,9 [13,9; NE]		0,66	[0,42; 1,03]	0,0684
Interaktion p-Wert											0,0959
Ki-67 (%) II [eCRF]											
< 50%	180	58 (32,2)	65,3 [36,0; NE]		164	58 (35,4)	69,0 [35,9; NE]		0,91	[0,63; 1,31]	0,5971
>= 50%	57	17 (29,8)	65,5 [32,3; NE]		66	23 (34,8)	21,2 [13,9; NE]		0,74	[0,39; 1,39]	0,3513
Interaktion p-Wert											0,5905
Knochenmarksbeteiligung [eCRF]											
Ja	178	59 (33,1)	65,3 [54,3; NE]		180	58 (32,2)	69,0 [35,9; NE]		1,00	[0,69; 1,44]	0,9984
Nein	50	18 (36,0)	39,7 [4,5; NE]		45	24 (53,3)	14,9 [3,7;46,9]		0,59	[0,32; 1,09]	0,0911
Interaktion p-Wert											0,1472
Extranodale Erkrankung [eCRF]											
Ja	264	86 (32,6)	65,5 [54,3; NE]		277	95 (34,3)	50,7 [32,1; NE]		0,87	[0,65; 1,17]	0,3684
Nein	35	14 (40,0)	39,7 [4,1; NE]		22	11 (50,0)	6,6 [2,0; NE]		0,61	[0,28; 1,37]	0,2233
Interaktion p-Wert											0,4007
Gastrointestinale Erkrankung [eCRF]											
Ja	74	23 (31,1)	NE [NE; NE]		75	29 (38,7)	35,9 [13,9; NE]		0,76	[0,43; 1,30]	0,3136
Nein	225	77 (34,2)	65,3 [39,6; NE]		224	77 (34,4)	55,6 [21,3; NE]		0,90	[0,65; 1,23]	0,4958
Interaktion p-Wert											0,5972
LDH > ULN [eCRF]											
Ja	52	18 (34,6)	32,3 [4,6; NE]		54	13 (24,1)	NE [NE; NE]		1,37	[0,67; 2,85]	0,3881

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.2 ECH0: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Physisches Wohlbefinden (PWB)
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]		2-seitigen p-Wert [b]
	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]		Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]				
	n				n						
Nein	245	82 (33,5)	65,5	[54,3; NE]	241	92 (38,2)	46,9	[21,3; NE]	0,80	[0,59; 1,07]	0,1327
Interaktion p-Wert											0,1676

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are ≥ 10 patients in each subgroup level, ≥ 10 events in at least one subgroup level and > 0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value < 0.05 . HR < 1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.3 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Soziales Wohlbefinden (SWB)
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	27 (32,9)	32,3 [17,5; NE]	83	26 (31,3)	28,6 [17,4; NE]	0,83	[0,48; 1,43]	0,5028
Westeuropa	46	12 (26,1)	NE [NE; NE]	46	17 (37,0)	32,5 [10,2; NE]	0,58	[0,27; 1,22]	0,1505
Andere	171	86 (50,3)	21,3 [13,8;32,2]	170	69 (40,6)	24,9 [10,3;32,3]	1,08	[0,79; 1,49]	0,6369
Interaktion p-Wert									0,2798
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	41 (41,4)	32,5 [21,3; NE]	101	38 (37,6)	28,5 [14,0;46,9]	0,86	[0,55; 1,34]	0,5091
Intermediäres Risiko [4-5]	128	52 (40,6)	28,6 [17,5;54,3]	125	50 (40,0)	17,4 [10,2;65,0]	0,86	[0,58; 1,27]	0,4566
Hohes Risiko [6-11]	72	32 (44,4)	13,9 [6,5;32,2]	73	24 (32,9)	28,6 [6,5;43,2]	1,29	[0,76; 2,22]	0,3383
Interaktion p-Wert									0,4183
Geschlecht [eCRF]									
Männlich	214	87 (40,7)	24,9 [17,5;39,6]	209	79 (37,8)	17,6 [13,9;32,5]	0,98	[0,72; 1,33]	0,8880
Weiblich	85	38 (44,7)	28,6 [17,5;54,3]	90	33 (36,7)	28,6 [10,2; NE]	0,86	[0,54; 1,38]	0,5337
Interaktion p-Wert									0,6559
Altersgruppe I [eCRF]									
< 70 Jahre	123	52 (42,3)	39,6 [21,1;58,0]	117	39 (33,3)	30,0 [17,4; NE]	0,93	[0,61; 1,42]	0,7324
>= 70 Jahre	176	73 (41,5)	24,9 [13,9;28,6]	182	73 (40,1)	17,6 [10,3;32,5]	0,98	[0,71; 1,35]	0,8918
Interaktion p-Wert									0,8522
Altersgruppe II [eCRF]									
< 75 Jahre	215	88 (40,9)	28,6 [21,1;50,6]	222	80 (36,0)	28,6 [14,0;47,2]	0,93	[0,69; 1,26]	0,6333
>= 75 Jahre	84	37 (44,0)	17,6 [10,2;32,3]	77	32 (41,6)	17,5 [10,2;28,6]	0,96	[0,60; 1,55]	0,8649
Interaktion p-Wert									0,9092
Abstammung [eCRF]									
Weiß	233	92 (39,5)	32,2 [21,3;50,6]	235	86 (36,6)	28,5 [17,4;32,5]	0,89	[0,66; 1,20]	0,4415

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.3 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Soziales Wohlbefinden (SWB)
 Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	27 (51,9)	17,6	[10,1;24,9]	53	26 (49,1)	10,2	[6,5; NE]	0,92	[0,54; 1,58]	0,7593
Interaktion p-Wert											0,9197
ECOG-PS [eCRF]											
0	156	62 (39,7)	28,6	[17,7;58,0]	140	51 (36,4)	29,0	[17,4;47,2]	0,94	[0,65; 1,36]	0,7302
1	129	58 (45,0)	24,9	[13,8;32,5]	132	53 (40,2)	17,6	[10,2;30,0]	0,97	[0,67; 1,41]	0,8826
>=2	12	5 (41,7)	14,0	[1,9; NE]	25	8 (32,0)	NE	[NE; NE]	0,97	[0,29; 2,92]	0,9616
Interaktion p-Wert											0,9899
Bulky Disease I [eCRF]											
< 5 cm	187	86 (46,0)	21,3	[17,5;32,3]	186	72 (38,7)	28,6	[14,0;46,9]	1,09	[0,80; 1,49]	0,5895
>= 5 cm	112	39 (34,8)	32,5	[17,5; NE]	113	40 (35,4)	17,6	[10,3; NE]	0,71	[0,46; 1,11]	0,1340
Interaktion p-Wert											0,1242
Bulky Disease II [eCRF]											
< 10 cm	279	119 (42,7)	25,8	[17,6;36,1]	278	106 (38,1)	24,9	[14,0;32,5]	0,96	[0,74; 1,24]	0,7382
>= 10 cm	20	6 (30,0)	NE	[NE; NE]	21	6 (28,6)	28,5	[6,5; NE]	0,73	[0,23; 2,34]	0,5894
Interaktion p-Wert											0,6521
Ann Arbor-Stadium für Lymphome [eCRF]											
Stadium I-III	48	23 (47,9)	24,9	[10,2;43,4]	36	12 (33,3)	NE	[NE; NE]	1,12	[0,57; 2,33]	0,7479
Stadium IV	251	102 (40,6)	28,5	[17,5;42,3]	263	100 (38,0)	28,3	[13,9;32,3]	0,91	[0,69; 1,21]	0,5282
Interaktion p-Wert											0,5938
MCL-Typ [eCRF]											
Klassische Variante	197	80 (40,6)	28,6	[17,5;50,6]	205	79 (38,5)	28,5	[13,9;46,9]	0,95	[0,70; 1,30]	0,7586
Blastoide und pleomorphische Variante	39	13 (33,3)	32,2	[13,8; NE]	33	10 (30,3)	13,8	[10,2; NE]	0,72	[0,32; 1,69]	0,4439
Andere	0	0	NE		8	4 (50,0)	29,0	[1,8; NE]	NC	[NC]	NC
Interaktion p-Wert											0,5406

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine und Rituximab.

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Table 4.2.1.2.3 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Soziales Wohlbefinden (SWB)
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	Anzahl (%) der Patienten mit		Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit		Mediane Zeit [95%-KI] (Monate) [a]			
	n	Ereignis		n	Ereignis				
Ki-67 (%) I [eCRF]									
< 30%	109	45 (41,3)	28,6 [17,5;50,6]	103	41 (39,8)	29,0 [14,0;47,2]	1,04	[0,68; 1,59]	0,8687
>= 30%	128	51 (39,8)	24,9 [13,8; NE]	127	48 (37,8)	17,6 [10,5; NE]	0,87	[0,58; 1,29]	0,4816
Interaktion p-Wert									0,5474
Ki-67 (%) II [eCRF]									
< 50%	180	73 (40,6)	28,6 [17,5;50,6]	164	68 (41,5)	28,6 [14,0;46,9]	0,95	[0,68; 1,32]	0,7464
>= 50%	57	23 (40,4)	24,9 [10,0; NE]	66	21 (31,8)	28,5 [10,2; NE]	0,94	[0,52; 1,71]	0,8359
Interaktion p-Wert									0,9814
Knochenmarksbeteiligung [eCRF]									
Ja	178	72 (40,4)	28,6 [17,7;47,0]	180	72 (40,0)	24,9 [13,8;32,3]	0,83	[0,60; 1,15]	0,2542
Nein	50	20 (40,0)	36,1 [6,9; NE]	45	14 (31,1)	28,5 [10,3; NE]	1,37	[0,69; 2,76]	0,3676
Interaktion p-Wert									0,1905
Extranodale Erkrankung [eCRF]									
Ja	264	105 (39,8)	28,6 [17,8;47,0]	277	103 (37,2)	28,5 [17,4;43,2]	0,91	[0,70; 1,20]	0,5225
Nein	35	20 (57,1)	17,6 [6,7;36,1]	22	9 (40,9)	14,0 [3,7; NE]	1,02	[0,48; 2,36]	0,9615
Interaktion p-Wert									0,7978
Gastrointestinale Erkrankung [eCRF]									
Ja	74	31 (41,9)	17,5 [13,8; NE]	75	29 (38,7)	17,6 [10,2; NE]	1,23	[0,74; 2,05]	0,4275
Nein	225	94 (41,8)	28,6 [21,3;42,3]	224	83 (37,1)	28,3 [17,4;32,3]	0,87	[0,64; 1,17]	0,3387
Interaktion p-Wert									0,2429
LDH > ULN [eCRF]									
Ja	52	21 (40,4)	17,6 [4,9; NE]	54	18 (33,3)	17,6 [6,5;28,6]	0,85	[0,45; 1,61]	0,6117
Nein	245	104 (42,4)	28,6 [21,1;42,3]	241	93 (38,6)	28,6 [14,0;46,9]	0,95	[0,72; 1,26]	0,7143
Interaktion p-Wert									0,7515

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.4 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Funktionales Wohlbefinden (FWB)
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]	
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Geographic Region [IXRS]										
Nordamerika	82	36 (43,9)	24,9 [7,1;36,2]	83	27 (32,5)	47,0 [14,0; NE]	1,21	[0,74; 2,02]	0,4433	
Westeuropa	46	19 (41,3)	25,3 [4,0; NE]	46	19 (41,3)	13,9 [7,0; NE]	0,89	[0,47; 1,69]	0,7095	
Andere	171	78 (45,6)	28,6 [10,2;58,0]	170	64 (37,6)	32,3 [17,5;58,0]	1,18	[0,85; 1,65]	0,3192	
Interaktion p-Wert									0,7007	
Vereinfachter MIPI-Score [IXRS]										
Geringes Risiko [0-3]	99	47 (47,5)	21,2 [6,7; NE]	101	38 (37,6)	24,9 [14,0;58,1]	1,09	[0,71; 1,68]	0,7021	
Intermediäres Risiko [4-5]	128	58 (45,3)	28,6 [10,2;58,0]	125	48 (38,4)	28,7 [15,0;47,4]	1,17	[0,80; 1,72]	0,4213	
Hohes Risiko [6-11]	72	28 (38,9)	17,6 [4,6; NE]	73	24 (32,9)	28,6 [10,2;47,2]	1,16	[0,67; 2,02]	0,5862	
Interaktion p-Wert									0,9655	
Geschlecht [eCRF]										
Männlich	214	93 (43,5)	21,2 [10,2;47,2]	209	72 (34,4)	39,9 [17,6;58,1]	1,33	[0,98; 1,81]	0,0704	
Weiblich	85	40 (47,1)	28,6 [10,0;64,7]	90	38 (42,2)	17,7 [6,5;32,3]	0,80	[0,51; 1,26]	0,3338	
Interaktion p-Wert									0,0689	
Altersgruppe I [eCRF]										
< 70 Jahre	123	55 (44,7)	35,9 [17,5; NE]	117	43 (36,8)	47,0 [17,5;47,4]	0,99	[0,66; 1,49]	0,9628	
>= 70 Jahre	176	78 (44,3)	14,2 [7,1;39,6]	182	67 (36,8)	21,6 [13,9;47,2]	1,27	[0,91; 1,76]	0,1546	
Interaktion p-Wert									0,3516	
Altersgruppe II [eCRF]										
< 75 Jahre	215	94 (43,7)	28,6 [10,3;47,2]	222	83 (37,4)	28,7 [17,5;47,1]	1,06	[0,79; 1,42]	0,7191	
>= 75 Jahre	84	39 (46,4)	13,8 [6,5;36,2]	77	27 (35,1)	21,3 [10,1; NE]	1,40	[0,86; 2,31]	0,1773	
Interaktion p-Wert									0,3349	
Abstammung [eCRF]										

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.4 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Funktionales Wohlbefinden (FWB)
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
weiß	233	101 (43,3)	25,3 [10,3;47,2]	235	88 (37,4)	21,6 [17,5;47,0]	1,05	[0,79; 1,41]	0,7225
Nicht-weiß	52	26 (50,0)	17,5 [3,8; NE]	53	21 (39,6)	28,7 [13,8; NE]	1,43	[0,81; 2,56]	0,2226
Interaktion p-Wert									0,3516
ECOG-PS [eCRF]									
0	156	73 (46,8)	25,3 [10,2;54,4]	140	52 (37,1)	32,1 [17,6;58,1]	1,23	[0,86; 1,76]	0,2604
1	129	56 (43,4)	21,2 [6,5;39,6]	132	49 (37,1)	21,3 [13,8;47,1]	1,11	[0,76; 1,64]	0,5916
>=2	12	4 (33,3)	43,3 [3,9; NE]	25	9 (36,0)	21,3 [3,7; NE]	0,67	[0,18; 2,07]	0,5014
Interaktion p-Wert									0,6095
Bulky Disease I [eCRF]									
< 5 cm	187	85 (45,5)	21,2 [7,1;36,2]	186	68 (36,6)	32,3 [17,6;58,0]	1,28	[0,93; 1,76]	0,1325
>= 5 cm	112	48 (42,9)	28,6 [10,3;64,7]	113	42 (37,2)	21,2 [10,2;47,1]	0,94	[0,62; 1,43]	0,7715
Interaktion p-Wert									0,2530
Bulky Disease II [eCRF]									
< 10 cm	279	125 (44,8)	21,2 [10,2;36,2]	278	105 (37,8)	24,9 [17,5;47,0]	1,14	[0,88; 1,48]	0,3295
>= 10 cm	20	8 (40,0)	64,7 [3,9; NE]	21	5 (23,8)	NE [NE; NE]	1,27	[0,42; 4,20]	0,6758
Interaktion p-Wert									0,8535
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	29 (60,4)	6,5 [3,7;17,5]	36	13 (36,1)	24,9 [3,7; NE]	1,64	[0,87; 3,26]	0,1287
Stadium IV	251	104 (41,4)	35,9 [17,5;47,2]	263	97 (36,9)	28,7 [17,6;47,1]	1,04	[0,79; 1,38]	0,7756
Interaktion p-Wert									0,2037
MCL-Typ [eCRF]									
Klassische Variante	197	92 (46,7)	17,5 [10,2;36,2]	205	76 (37,1)	32,3 [17,6;47,4]	1,28	[0,94; 1,74]	0,1130
Blastoide und pleomorphische Variante	39	14 (35,9)	28,7 [3,8; NE]	33	10 (30,3)	13,9 [4,1; NE]	0,94	[0,42; 2,18]	0,8768
Andere	0	0	NE	8	4 (50,0)	15,8 [3,5; NE]	NC	[NC]	NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.4 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Funktionales Wohlbefinden (FWB)
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Interaktion p-Wert									0,4876
Ki-67 (%) I [eCRF]									
< 30%	109	51 (46,8)	13,9 [6,5;54,4]	103	42 (40,8)	28,6 [17,5;47,2]	1,28	[0,85; 1,93]	0,2411
>= 30%	128	49 (38,3)	39,6 [17,5; NE]	127	49 (38,6)	21,3 [13,9;47,4]	0,91	[0,61; 1,36]	0,6423
Interaktion p-Wert									0,2448
Ki-67 (%) II [eCRF]									
< 50%	180	78 (43,3)	28,6 [10,2;58,0]	164	66 (40,2)	24,9 [17,5;47,2]	1,13	[0,81; 1,57]	0,4723
>= 50%	57	22 (38,6)	39,6 [4,1; NE]	66	25 (37,9)	21,3 [10,1;39,9]	0,91	[0,51; 1,63]	0,7603
Interaktion p-Wert									0,5339
Knochenmarksbeteiligung [eCRF]									
Ja	178	78 (43,8)	25,8 [10,3;47,2]	180	66 (36,7)	28,6 [17,6;47,2]	1,12	[0,81; 1,56]	0,4970
Nein	50	24 (48,0)	6,5 [3,7; NE]	45	16 (35,6)	28,7 [10,4; NE]	1,62	[0,87; 3,11]	0,1319
Interaktion p-Wert									0,3104
Extranodale Erkrankung [eCRF]									
Ja	264	113 (42,8)	28,6 [14,2;47,2]	277	101 (36,5)	28,7 [17,6;47,1]	1,10	[0,84; 1,44]	0,5017
Nein	35	20 (57,1)	6,5 [3,7;28,6]	22	9 (40,9)	17,5 [3,6; NE]	1,28	[0,60; 2,96]	0,5329
Interaktion p-Wert									0,7139
Gastrointestinale Erkrankung [eCRF]									
Ja	74	31 (41,9)	21,2 [6,5; NE]	75	33 (44,0)	28,6 [13,8;39,9]	1,04	[0,63; 1,70]	0,8863
Nein	225	102 (45,3)	25,8 [10,2;45,3]	224	77 (34,4)	47,0 [17,5;58,0]	1,18	[0,88; 1,60]	0,2641
Interaktion p-Wert									0,6500
LDH > ULN [eCRF]									
Ja	52	22 (42,3)	10,3 [3,7; NE]	54	21 (38,9)	15,0 [6,4;28,6]	1,07	[0,59; 1,96]	0,8226

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.4 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Funktionales Wohlbefinden (FWB)
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	2-seitigen p-Wert [b]
	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]				
	n			n						
Nein	245	111 (45,3)	25,8 [13,9;45,3]	241	88 (36,5)	32,3 [17,7;58,0]	1,17	[0,88; 1,55]	0,2815	
Interaktion p-Wert									0,7999	

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are ≥ 10 patients in each subgroup level, ≥ 10 events in at least one subgroup level and > 0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value < 0.05 . HR < 1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.5 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Emotionales Wohlbefinden (EMB)
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]	
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Geographic Region [IXRS]										
Nordamerika	82	16 (19,5)	NE [NE; NE]	83	17 (20,5)	NE [NE; NE]	0,75	[0,38; 1,49]	0,4128	
Westeuropa	46	11 (23,9)	NE [NE; NE]	46	11 (23,9)	32,4 [24,9; NE]	0,93	[0,40; 2,18]	0,8668	
Andere	171	54 (31,6)	54,3 [35,9; NE]	170	39 (22,9)	NE [NE; NE]	1,29	[0,86; 1,96]	0,2227	
Interaktion p-Wert									0,3830	
Vereinfachter MIPI-Score [IXRS]										
Geringes Risiko [0-3]	99	27 (27,3)	58,3 [46,7; NE]	101	22 (21,8)	NE [NE; NE]	1,05	[0,60; 1,87]	0,8582	
Intermediäres Risiko [4-5]	128	35 (27,3)	NE [NE; NE]	125	31 (24,8)	NE [NE; NE]	1,06	[0,65; 1,72]	0,8265	
Hohes Risiko [6-11]	72	19 (26,4)	50,8 [29,5; NE]	73	14 (19,2)	NE [NE; NE]	1,19	[0,60; 2,42]	0,6176	
Interaktion p-Wert									0,9540	
Geschlecht [eCRF]										
Männlich	214	54 (25,2)	58,3 [46,7; NE]	209	42 (20,1)	NE [NE; NE]	1,18	[0,79; 1,78]	0,4096	
Weiblich	85	27 (31,8)	54,3 [28,6; NE]	90	25 (27,8)	NE [NE; NE]	0,90	[0,52; 1,56]	0,7058	
Interaktion p-Wert									0,4278	
Altersgruppe I [eCRF]										
< 70 Jahre	123	35 (28,5)	58,3 [43,8; NE]	117	27 (23,1)	NE [NE; NE]	1,00	[0,61; 1,67]	0,9854	
>= 70 Jahre	176	46 (26,1)	54,4 [39,9; NE]	182	40 (22,0)	NE [NE; NE]	1,14	[0,75; 1,75]	0,5386	
Interaktion p-Wert									0,7028	
Altersgruppe II [eCRF]										
< 75 Jahre	215	58 (27,0)	58,3 [46,7; NE]	222	56 (25,2)	NE [NE; NE]	0,92	[0,64; 1,33]	0,6519	
>= 75 Jahre	84	23 (27,4)	54,4 [32,3; NE]	77	11 (14,3)	NE [NE; NE]	1,92	[0,96; 4,09]	0,0672	
Interaktion p-Wert									0,0679	
Abstammung [eCRF]										

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.5 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Emotionales Wohlbefinden (EMB)
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)					Placebo+BR (N=299)					2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	
Weiß	233	63 (27,0)	58,3 [46,7; NE]			235	53 (22,6)	NE [NE; NE]	1,04	[0,72; 1,50]	0,8434
Nicht-weiß	52	15 (28,8)	47,1 [39,9; NE]			53	12 (22,6)	61,6 [61,6; NE]	1,39	[0,65; 3,04]	0,3913
Interaktion p-Wert											0,4933
ECOG-PS [eCRF]											
0	156	39 (25,0)	58,3 [47,2; NE]			140	27 (19,3)	NE [NE; NE]	1,15	[0,71; 1,89]	0,5825
1	129	39 (30,2)	47,1 [35,9; NE]			132	36 (27,3)	61,6 [24,9; NE]	1,02	[0,64; 1,60]	0,9476
>=2	12	3 (25,0)	NE [NE; NE]			25	4 (16,0)	NE [NE; NE]	1,57	[0,31; 7,15]	0,5599
Interaktion p-Wert											0,8353
Bulky Disease I [eCRF]											
< 5 cm	187	51 (27,3)	54,4 [39,9; NE]			186	45 (24,2)	NE [NE; NE]	1,07	[0,72; 1,61]	0,7318
>= 5 cm	112	30 (26,8)	NE [NE; NE]			113	22 (19,5)	NE [NE; NE]	1,11	[0,64; 1,94]	0,7210
Interaktion p-Wert											0,9307
Bulky Disease II [eCRF]											
< 10 cm	279	76 (27,2)	54,4 [46,7; NE]			278	64 (23,0)	NE [NE; NE]	1,07	[0,77; 1,50]	0,6723
>= 10 cm	20	5 (25,0)	NE [NE; NE]			21	3 (14,3)	NE [NE; NE]	1,28	[0,31; 6,26]	0,7347
Interaktion p-Wert											0,8156
Ann Arbor-Stadium für Lymphome [eCRF]											
Stadium I-III	48	14 (29,2)	46,7 [25,0; NE]			36	9 (25,0)	NE [NE; NE]	0,90	[0,40; 2,17]	0,8119
Stadium IV	251	67 (26,7)	58,3 [47,1; NE]			263	58 (22,1)	NE [NE; NE]	1,11	[0,78; 1,58]	0,5610
Interaktion p-Wert											0,6581
MCL-Typ [eCRF]											
Klassische Variante	197	56 (28,4)	50,8 [39,8; NE]			205	44 (21,5)	NE [NE; NE]	1,25	[0,84; 1,86]	0,2729
Blastoide und pleomorphische Variante	39	10 (25,6)	NE [NE; NE]			33	7 (21,2)	32,1 [10,3; NE]	0,96	[0,37; 2,66]	0,9419
Andere	0	0	NE			8	2 (25,0)	NE [NE; NE]	NC	[NC]	NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.5 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Emotionales Wohlbefinden (EMB)
Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Interaktion p-Wert									0,6332
Ki-67 (%) I [eCRF]									
< 30%	109	31 (28,4)	54,3 [39,6; NE]	103	17 (16,5)	NE [NE; NE]	1,81	[1,02; 3,35]	0,0437*
>= 30%	128	30 (23,4)	NE [NE; NE]	127	34 (26,8)	NE [NE; NE]	0,76	[0,46; 1,25]	0,2810
Interaktion p-Wert									0,0258*
Ki-67 (%) II [eCRF]									
< 50%	180	49 (27,2)	58,3 [43,8; NE]	164	33 (20,1)	NE [NE; NE]	1,41	[0,91; 2,21]	0,1256
>= 50%	57	12 (21,1)	NE [NE; NE]	66	18 (27,3)	32,1 [14,0; NE]	0,57	[0,27; 1,17]	0,1278
Interaktion p-Wert									0,0361*
Knochenmarksbeteiligung [eCRF]									
Ja	178	46 (25,8)	NE [NE; NE]	180	38 (21,1)	NE [NE; NE]	1,08	[0,70; 1,67]	0,7237
Nein	50	13 (26,0)	35,9 [25,0; NE]	45	12 (26,7)	NE [NE; NE]	1,02	[0,46; 2,28]	0,9559
Interaktion p-Wert									0,9039
Extranodale Erkrankung [eCRF]									
Ja	264	69 (26,1)	NE [NE; NE]	277	60 (21,7)	NE [NE; NE]	1,09	[0,77; 1,55]	0,6155
Nein	35	12 (34,3)	46,7 [21,2; NE]	22	7 (31,8)	NE [NE; NE]	0,87	[0,35; 2,33]	0,7667
Interaktion p-Wert									0,6522
Gastrointestinale Erkrankung [eCRF]									
Ja	74	16 (21,6)	NE [NE; NE]	75	16 (21,3)	NE [NE; NE]	1,00	[0,49; 2,01]	0,9911
Nein	225	65 (28,9)	54,3 [43,8; NE]	224	51 (22,8)	NE [NE; NE]	1,10	[0,76; 1,59]	0,6066
Interaktion p-Wert									0,8025
LDH > ULN [eCRF]									
Ja	52	13 (25,0)	NE [NE; NE]	54	12 (22,2)	NE [NE; NE]	0,96	[0,43; 2,13]	0,9138

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.5 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Emotionales Wohlbefinden (EMB)
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b] [95%-KI] [b]		2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nein	245	68 (27,8)	58,3 [47,1; NE]	241	55 (22,8)	NE [NE; NE]	1,10	[0,77; 1,57]	0,6114
Interaktion p-Wert									0,7584

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are ≥10 patients in each subgroup level, ≥10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.6 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Lym-Subscala (LYMS)
 Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	7 (8,5)	NE [NE; NE]	83	15 (18,1)	NE [NE; NE]	0,36	[0,14; 0,87]	0,0217*
Westeuropa	46	7 (15,2)	NE [NE; NE]	46	9 (19,6)	NE [NE; NE]	0,73	[0,26; 1,96]	0,5319
Andere	171	42 (24,6)	NE [NE; NE]	170	28 (16,5)	NE [NE; NE]	1,37	[0,85; 2,23]	0,1958
Interaktion p-Wert									0,0262*
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	17 (17,2)	NE [NE; NE]	101	20 (19,8)	62,0 [51,6; NE]	0,73	[0,38; 1,39]	0,3350
Intermediäres Risiko [4-5]	128	27 (21,1)	NE [NE; NE]	125	22 (17,6)	NE [NE; NE]	1,11	[0,64; 1,98]	0,7046
Hohes Risiko [6-11]	72	12 (16,7)	NE [NE; NE]	73	10 (13,7)	NE [NE; NE]	1,03	[0,45; 2,45]	0,9392
Interaktion p-Wert									0,6052
Geschlecht [eCRF]									
Männlich	214	36 (16,8)	NE [NE; NE]	209	32 (15,3)	NE [NE; NE]	0,99	[0,62; 1,61]	0,9819
Weiblich	85	20 (23,5)	65,5 [54,3; NE]	90	20 (22,2)	NE [NE; NE]	0,87	[0,47; 1,63]	0,6637
Interaktion p-Wert									0,7403
Altersgruppe I [eCRF]									
< 70 Jahre	123	23 (18,7)	NE [NE; NE]	117	18 (15,4)	NE [NE; NE]	1,00	[0,54; 1,88]	0,9942
>= 70 Jahre	176	33 (18,8)	NE [NE; NE]	182	34 (18,7)	NE [NE; NE]	0,93	[0,57; 1,50]	0,7543
Interaktion p-Wert									0,8432
Altersgruppe II [eCRF]									
< 75 Jahre	215	40 (18,6)	NE [NE; NE]	222	34 (15,3)	NE [NE; NE]	1,06	[0,67; 1,68]	0,8135
>= 75 Jahre	84	16 (19,0)	NE [NE; NE]	77	18 (23,4)	NE [NE; NE]	0,74	[0,37; 1,45]	0,3721
Interaktion p-Wert									0,3833
Abstammung [eCRF]									
Weiß	233	39 (16,7)	NE [NE; NE]	235	40 (17,0)	NE [NE; NE]	0,84	[0,54; 1,30]	0,4317

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.6 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Lym-Subscala (LYMS)
 Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Nicht-weiß	52	16 (30,8)	65,5 [65,5; NE]		53	11 (20,8)	NE [NE; NE]		1,55	[0,73; 3,44]	0,2574
Interaktion p-Wert											0,1693
ECOG-PS [eCRF]											
0	156	23 (14,7)	NE [NE; NE]		140	24 (17,1)	NE [NE; NE]		0,76	[0,43; 1,36]	0,3586
1	129	32 (24,8)	65,5 [54,3; NE]		132	25 (18,9)	NE [NE; NE]		1,15	[0,68; 1,96]	0,5930
>=2	12	1 (8,3)	NE [NE; NE]		25	3 (12,0)	NE [NE; NE]		0,62	[0,03; 4,84]	0,6647
Interaktion p-Wert											0,5404
Bulky Disease I [eCRF]											
< 5 cm	187	41 (21,9)	NE [NE; NE]		186	38 (20,4)	NE [NE; NE]		0,98	[0,63; 1,52]	0,9113
>= 5 cm	112	15 (13,4)	NE [NE; NE]		113	14 (12,4)	NE [NE; NE]		0,90	[0,43; 1,90]	0,7873
Interaktion p-Wert											0,8624
Bulky Disease II [eCRF]											
< 10 cm	279	54 (19,4)	NE [NE; NE]		278	49 (17,6)	NE [NE; NE]		0,99	[0,67; 1,46]	0,9560
>= 10 cm	20	2 (10,0)	NE [NE; NE]		21	3 (14,3)	NE [NE; NE]		0,45	[0,06; 2,74]	0,3807
Interaktion p-Wert											0,3983
Ann Arbor-Stadium für Lymphome [eCRF]											
Stadium I-III	48	14 (29,2)	NE [NE; NE]		36	8 (22,2)	62,0 [28,6; NE]		1,12	[0,48; 2,80]	0,8019
Stadium IV	251	42 (16,7)	NE [NE; NE]		263	44 (16,7)	NE [NE; NE]		0,89	[0,58; 1,35]	0,5750
Interaktion p-Wert											0,6362
MCL-Typ [eCRF]											
Klassische Variante	197	35 (17,8)	NE [NE; NE]		205	39 (19,0)	NE [NE; NE]		0,83	[0,52; 1,31]	0,4308
Blastoide und pleomorphische Variante	39	8 (20,5)	NE [NE; NE]		33	4 (12,1)	NE [NE; NE]		1,50	[0,47; 5,62]	0,5008
Andere	0	0	NE		8	2 (25,0)	NE [NE; NE]		NC	[NC]	NC
Interaktion p-Wert											0,3597

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.2.6 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - FACT-Lym Lym-Subscala (LYMS)
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	24 (22,0)	NE [NE; NE]	103	23 (22,3)	NE [NE; NE]	0,97	[0,55; 1,73]	0,9272
>= 30%	128	22 (17,2)	NE [NE; NE]	127	19 (15,0)	NE [NE; NE]	1,06	[0,57; 1,99]	0,8435
Interaktion p-Wert									0,8362
Ki-67 (%) II [eCRF]									
< 50%	180	37 (20,6)	NE [NE; NE]	164	34 (20,7)	NE [NE; NE]	0,99	[0,62; 1,58]	0,9679
>= 50%	57	9 (15,8)	65,5 [65,5; NE]	66	8 (12,1)	NE [NE; NE]	1,10	[0,42; 2,93]	0,8472
Interaktion p-Wert									0,8487
Knochenmarksbeteiligung [eCRF]									
Ja	178	27 (15,2)	NE [NE; NE]	180	29 (16,1)	NE [NE; NE]	0,81	[0,47; 1,37]	0,4232
Nein	50	11 (22,0)	NE [NE; NE]	45	11 (24,4)	62,0 [21,2; NE]	0,93	[0,40; 2,16]	0,8556
Interaktion p-Wert									0,7864
Extranodale Erkrankung [eCRF]									
Ja	264	46 (17,4)	NE [NE; NE]	277	48 (17,3)	NE [NE; NE]	0,88	[0,59; 1,33]	0,5525
Nein	35	10 (28,6)	NE [NE; NE]	22	4 (18,2)	NE [NE; NE]	1,42	[0,47; 5,17]	0,5461
Interaktion p-Wert									0,4407
Gastrointestinale Erkrankung [eCRF]									
Ja	74	11 (14,9)	NE [NE; NE]	75	15 (20,0)	NE [NE; NE]	0,72	[0,32; 1,56]	0,4062
Nein	225	45 (20,0)	NE [NE; NE]	224	37 (16,5)	NE [NE; NE]	1,03	[0,67; 1,60]	0,8880
Interaktion p-Wert									0,4278
LDH > ULN [eCRF]									
Ja	52	7 (13,5)	NE [NE; NE]	54	4 (7,4)	NE [NE; NE]	1,60	[0,48; 6,12]	0,4430
Nein	245	49 (20,0)	NE [NE; NE]	241	47 (19,5)	NE [NE; NE]	0,91	[0,61; 1,36]	0,6297
Interaktion p-Wert									0,3784

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.3.1 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EQ-5D-5L Visuelle Analogskala
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)			Placebo+BR (N=299)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	30 (36,6)	36,0 [7,6; NE]	83	18 (21,7)	76,4 [44,5; NE]	1,74	[0,97; 3,23]	0,0619
Westeuropa	46	13 (28,3)	NE [NE; NE]	46	14 (30,4)	32,4 [7,1; NE]	0,81	[0,38; 1,73]	0,5831
Andere	171	68 (39,8)	50,7 [24,9;69,2]	170	56 (32,9)	47,0 [28,6; NE]	1,12	[0,79; 1,60]	0,5292
Interaktion p-Wert									0,2546
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	37 (37,4)	50,7 [25,0; NE]	101	29 (28,7)	62,0 [28,5; NE]	1,24	[0,76; 2,04]	0,3932
Intermediäres Risiko [4-5]	128	50 (39,1)	36,0 [17,8; NE]	125	46 (36,8)	35,9 [18,0; NE]	1,01	[0,67; 1,51]	0,9708
Hohes Risiko [6-11]	72	24 (33,3)	28,6 [10,2; NE]	73	13 (17,8)	NE [NE; NE]	1,72	[0,89; 3,48]	0,1078
Interaktion p-Wert									0,3937
Geschlecht [eCRF]									
Männlich	214	75 (35,0)	NE [NE; NE]	209	60 (28,7)	47,0 [32,6; NE]	1,22	[0,87; 1,72]	0,2533
Weiblich	85	36 (42,4)	35,8 [21,2;69,2]	90	28 (31,1)	NE [NE; NE]	1,12	[0,69; 1,85]	0,6492
Interaktion p-Wert									0,7847
Altersgruppe I [eCRF]									
< 70 Jahre	123	47 (38,2)	NE [NE; NE]	117	36 (30,8)	47,2 [28,5; NE]	1,12	[0,72; 1,73]	0,6215
>= 70 Jahre	176	64 (36,4)	35,8 [21,2;69,2]	182	52 (28,6)	44,5 [35,9; NE]	1,24	[0,86; 1,80]	0,2487
Interaktion p-Wert									0,7133
Altersgruppe II [eCRF]									
< 75 Jahre	215	83 (38,6)	50,7 [25,1; NE]	222	62 (27,9)	47,2 [36,0; NE]	1,24	[0,90; 1,73]	0,1933
>= 75 Jahre	84	28 (33,3)	61,3 [10,2; NE]	77	26 (33,8)	32,4 [14,0; NE]	1,05	[0,61; 1,82]	0,8491
Interaktion p-Wert									0,6086
Abstammung [eCRF]									
Weiß	233	82 (35,2)	50,7 [25,2; NE]	235	70 (29,8)	47,0 [32,4; NE]	1,07	[0,78; 1,48]	0,6717

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.2.1.3.1 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EQ-5D-5L Visuelle Analogskala
 Full Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=299)					Placebo+BR (N=299)					Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]					
Nicht-weiß	52	24 (46,2)	21,2 [6,5; NE]			53	16 (30,2)	NE [NE; NE]			1,65	[0,88; 3,17]	0,1168
Interaktion p-Wert													0,2303
ECOG-PS [eCRF]													
0	156	60 (38,5)	50,7 [21,2; NE]			140	46 (32,9)	44,5 [25,1; NE]			1,10	[0,75; 1,62]	0,6349
1	129	48 (37,2)	39,7 [21,2; NE]			132	39 (29,5)	47,0 [32,4; NE]			1,18	[0,78; 1,81]	0,4353
>=2	12	3 (25,0)	NE [NE; NE]			25	3 (12,0)	NE [NE; NE]			2,27	[0,42; 12,32]	0,3230
Interaktion p-Wert													0,6891
Bulky Disease I [eCRF]													
< 5 cm	187	75 (40,1)	28,6 [21,2; NE]			186	59 (31,7)	62,0 [36,0; NE]			1,26	[0,90; 1,79]	0,1787
>= 5 cm	112	36 (32,1)	61,3 [25,0; NE]			113	29 (25,7)	35,9 [28,5; NE]			1,07	[0,66; 1,76]	0,7867
Interaktion p-Wert													0,5852
Bulky Disease II [eCRF]													
< 10 cm	279	103 (36,9)	39,7 [25,0; NE]			278	82 (29,5)	47,2 [36,0; NE]			1,21	[0,90; 1,62]	0,2078
>= 10 cm	20	8 (40,0)	61,3 [7,0; NE]			21	6 (28,6)	NE [NE; NE]			0,97	[0,34; 2,96]	0,9619
Interaktion p-Wert													0,7061
Ann Arbor-Stadium für Lymphome [eCRF]													
Stadium I-III	48	17 (35,4)	NE [NE; NE]			36	12 (33,3)	28,6 [10,2; NE]			0,89	[0,43; 1,91]	0,7561
Stadium IV	251	94 (37,5)	39,7 [21,2; NE]			263	76 (28,9)	47,2 [36,0; NE]			1,25	[0,92; 1,70]	0,1482
Interaktion p-Wert													0,4073
MCL-Typ [eCRF]													
Klassische Variante	197	74 (37,6)	50,7 [25,1; NE]			205	61 (29,8)	62,0 [39,9; NE]			1,25	[0,89; 1,77]	0,1919
Blastoide und pleomorphische Variante	39	12 (30,8)	39,7 [3,8; NE]			33	8 (24,2)	NE [NE; NE]			1,02	[0,42; 2,60]	0,9707
Andere	0	0	NE			8	4 (50,0)	7,1 [3,5; NE]			NC	[NC]	NC
Interaktion p-Wert													0,6708

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
 [b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

Acala = Acalabrutinib; BR = Bendamustine und Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/ttesubpr.sas gttsubprcaa 11APR2025:08:52 khcs324

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Table 4.2.1.3.1 ECHO: Summary of subgroup analysis of Zeit bis zur ersten Verschlechterung - EQ-5D-5L Visuelle Analogskala
Full Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=299)				Placebo+BR (N=299)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Ki-67 (%) I [eCRF]											
< 30%	109	42 (38,5)	35,8 [14,0; NE]		103	34 (33,0)	62,0 [28,6; NE]		1,24	[0,79; 1,96]	0,3487
>= 30%	128	41 (32,0)	61,3 [28,6; NE]		127	39 (30,7)	39,9 [28,5; NE]		0,88	[0,57; 1,37]	0,5687
Interaktion p-Wert											0,2852
Ki-67 (%) II [eCRF]											
< 50%	180	64 (35,6)	57,8 [25,0; NE]		164	50 (30,5)	62,0 [35,9; NE]		1,17	[0,81; 1,70]	0,4100
>= 50%	57	19 (33,3)	69,2 [7,0; NE]		66	23 (34,8)	28,5 [10,2; 39,9]		0,75	[0,40; 1,39]	0,3615
Interaktion p-Wert											0,2271
Knochenmarksbeteiligung [eCRF]											
Ja	178	72 (40,4)	36,0 [18,7; NE]		180	47 (26,1)	76,4 [43,3; NE]		1,51	[1,04; 2,19]	0,0283*
Nein	50	17 (34,0)	35,8 [17,5; NE]		45	17 (37,8)	28,5 [10,3; NE]		0,87	[0,44; 1,72]	0,6927
Interaktion p-Wert											0,1651
Extranodale Erkrankung [eCRF]											
Ja	264	98 (37,1)	50,7 [21,2; NE]		277	79 (28,5)	62,0 [36,0; NE]		1,26	[0,94; 1,71]	0,1204
Nein	35	13 (37,1)	35,8 [21,2; NE]		22	9 (40,9)	14,0 [6,5; NE]		0,66	[0,28; 1,60]	0,3456
Interaktion p-Wert											0,1658
Gastrointestinale Erkrankung [eCRF]											
Ja	74	25 (33,8)	NE [NE; NE]		75	20 (26,7)	39,9 [35,9; NE]		1,30	[0,72; 2,37]	0,3829
Nein	225	86 (38,2)	50,7 [25,0; NE]		224	68 (30,4)	47,2 [32,4; NE]		1,16	[0,84; 1,59]	0,3751
Interaktion p-Wert											0,7317
LDH > ULN [eCRF]											
Ja	52	19 (36,5)	24,9 [3,7; NE]		54	15 (27,8)	28,5 [6,4; NE]		1,27	[0,64; 2,53]	0,4941
Nein	245	92 (37,6)	50,7 [25,2; NE]		241	73 (30,3)	47,2 [36,0; NE]		1,17	[0,86; 1,59]	0,3298
Interaktion p-Wert											0,8280

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.
[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

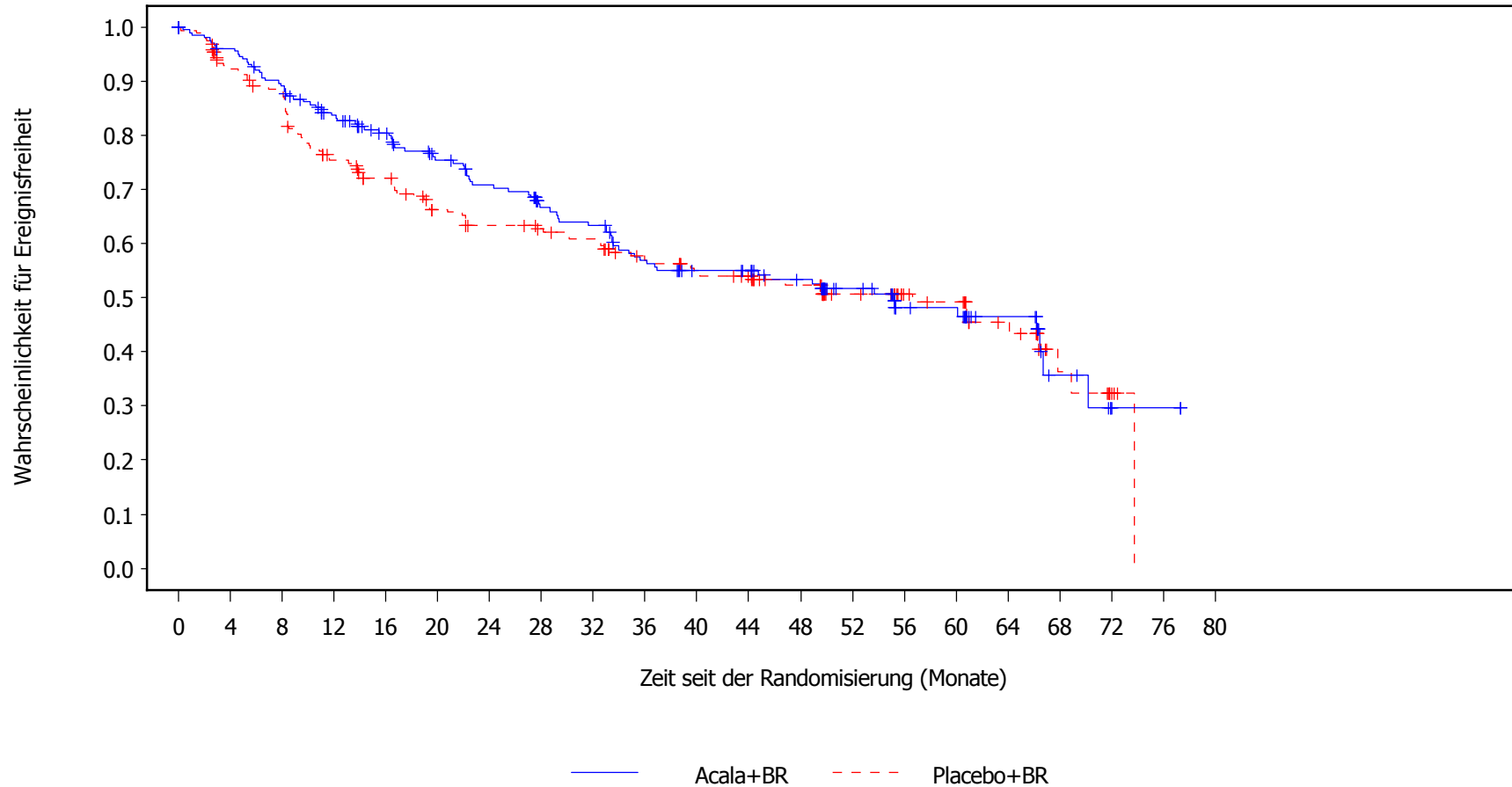
Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

root/cdar/d822/acely308/ar/echo_payer_germany/tlf/prod/program/ttesubpr.sas gttsubprcaa 11APR2025:08:52 khcs324

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Figure 4.1.2.2.1 ECHO: Subgroup Analysis: Kaplan-Meier plot of Progressionsfreies Überleben (IRC) for Geschlecht [eCRF] = Männlich
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

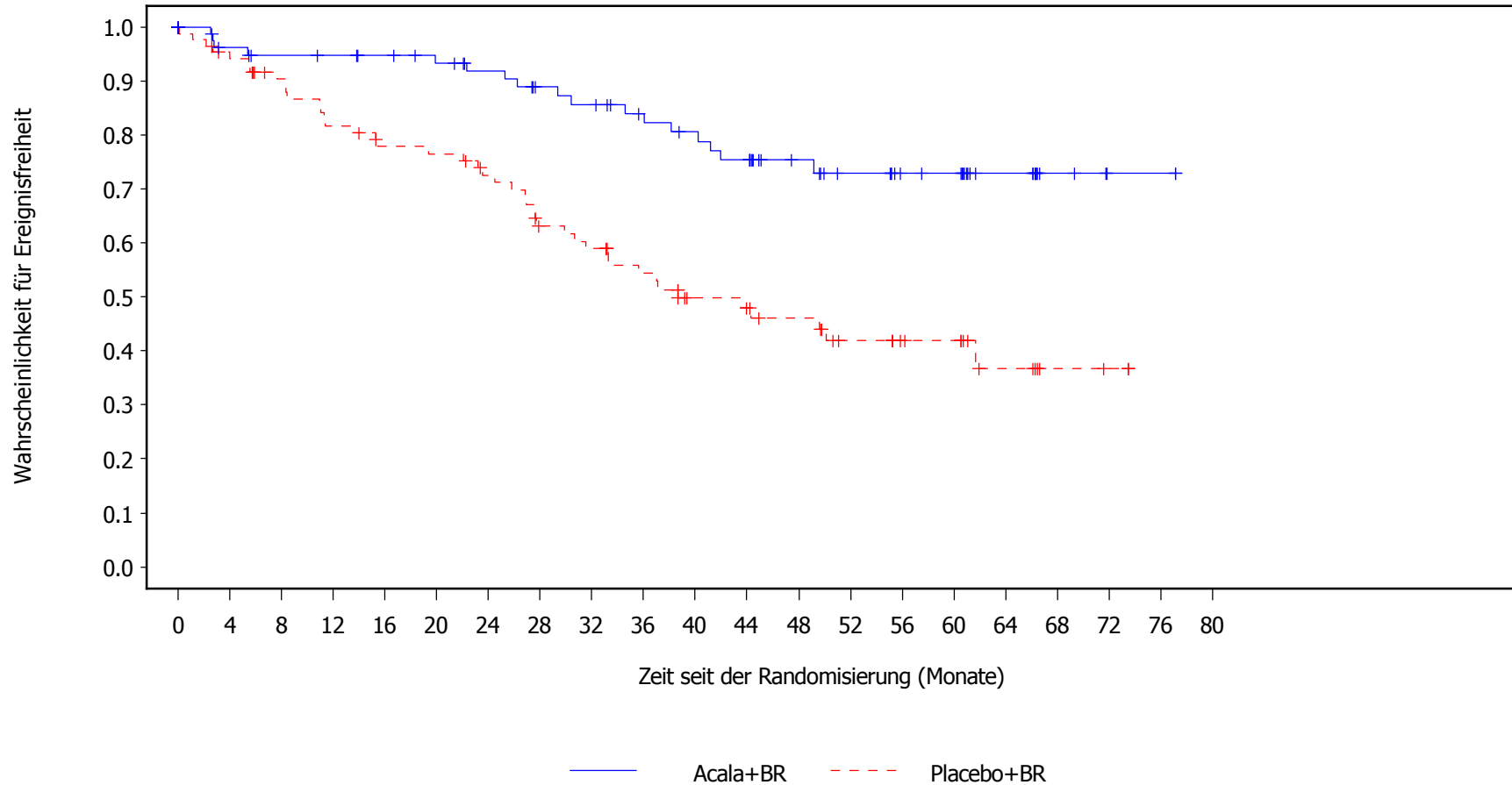
214	196	181	162	147	132	121	105	100	87	79	77	66	49	33	32	21	7	1	1	0	Acala+BR
209	177	168	139	128	112	105	101	97	82	75	71	61	47	35	32	21	9	3	0	0	Placebo+BR

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

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Figure 4.1.2.2.2 ECHO: Subgroup Analysis: Kaplan-Meier plot of Progressionsfreies Überleben (IRC) for Geschlecht [eCRF] = Weiblich
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

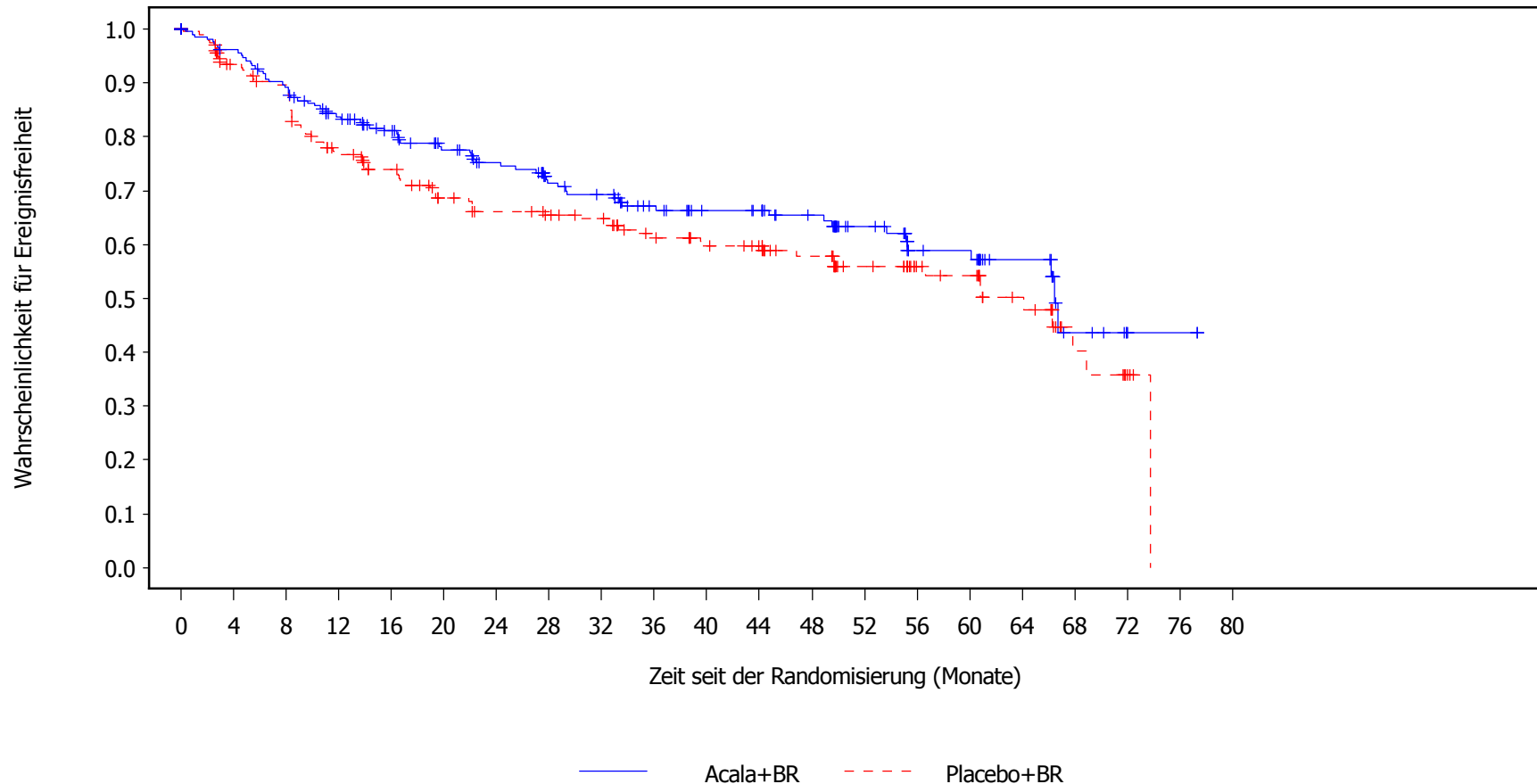
85	74	71	70	68	65	61	56	54	49	46	43	32	27	22	21	13	4	1	1	0	Acala+BR
90	80	72	65	60	59	54	45	42	36	28	26	23	17	13	12	6	2	1	0	0	Placebo+BR

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

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Figure 4.1.2.6.1 ECHO: Subgroup Analysis: Kaplan-Meier plot of Progressionsfreies Überleben – Sensitivitätsanalyse: Zensierung von Todesfällen durch COVID-19 (IRC) for Geschlecht [eCRF] = Männlich
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

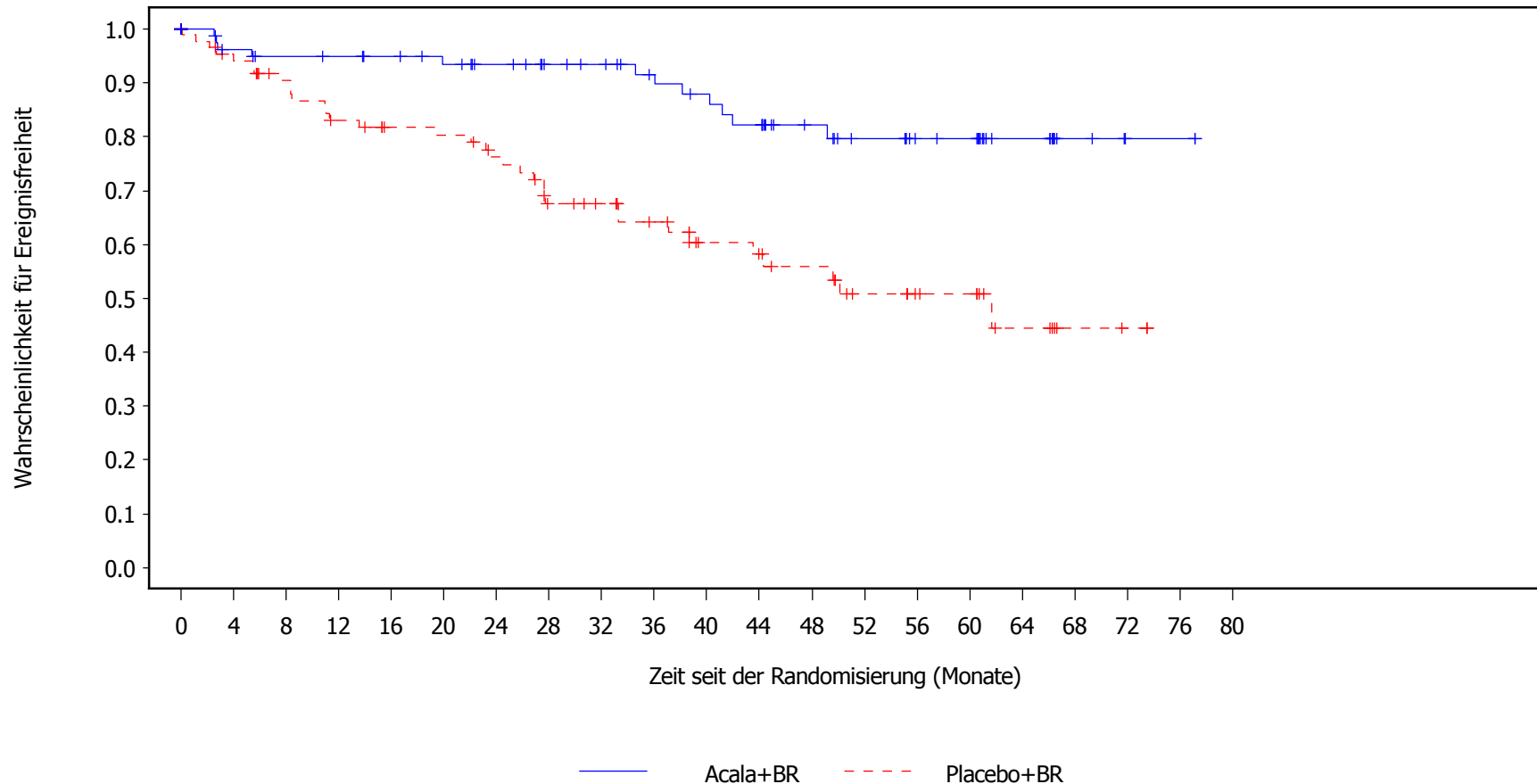
214	196	181	162	147	132	121	105	100	87	79	77	66	49	33	32	21	7	1	1	0	Acala+BR
209	177	168	139	128	112	105	101	97	82	75	71	61	47	35	32	21	9	3	0	0	Placebo+BR

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

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Figure 4.1.2.6.2 ECHO: Subgroup Analysis: Kaplan-Meier plot of Progressionsfreies Überleben – Sensitivitätsanalyse: Zensierung von Todesfällen durch COVID-19 (IRC) for Geschlecht [eCRF] = Weiblich
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

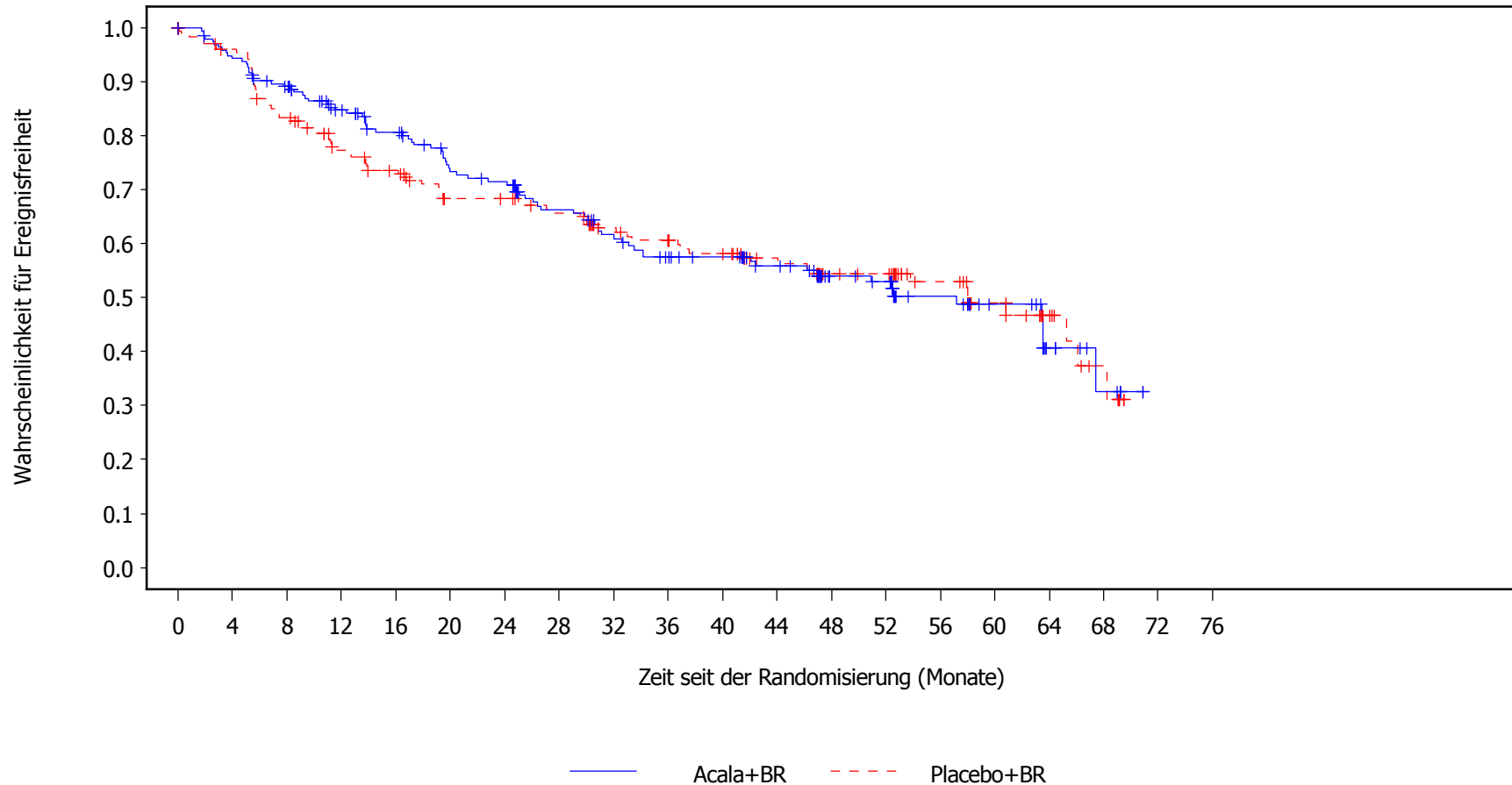
85	74	71	70	68	65	61	56	54	49	46	43	32	27	22	21	13	4	1	1	0	Acala+BR
90	80	72	65	60	59	54	45	42	36	28	26	23	17	13	12	6	2	1	0	0	Placebo+BR

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

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Figure 4.1.2.4.1 ECH0: Subgroup Analysis: Kaplan-Meier plot of Dauer des Ansprechens (IRC) for Geschlecht [eCRF] = Männlich
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

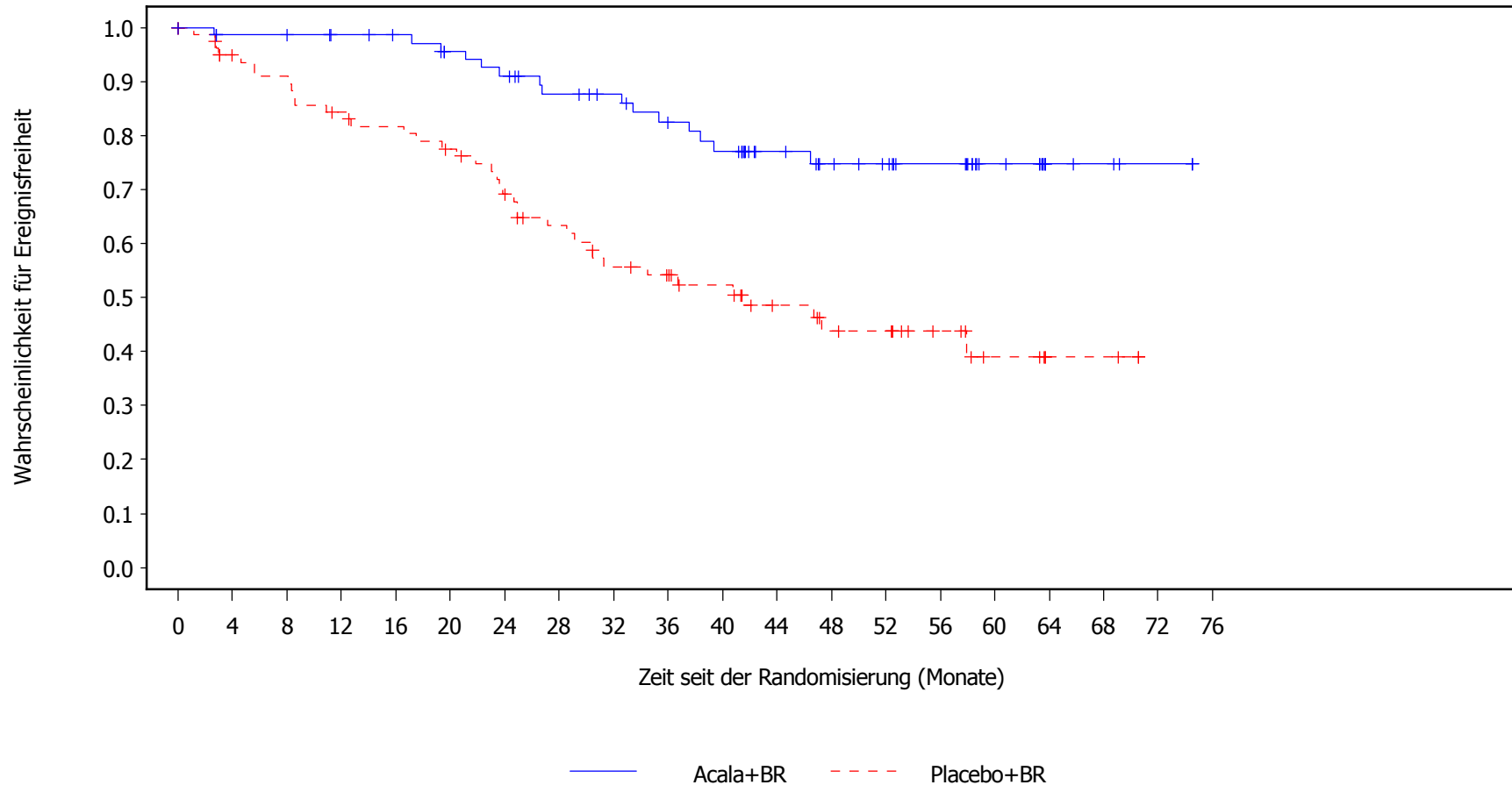
196	183	169	150	137	120	116	100	90	81	77	67	49	46	32	21	10	4	0	0	Acala+BR
181	167	144	126	117	103	102	95	84	79	73	61	46	44	31	21	13	6	0	0	Placebo+BR

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

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Figure 4.1.2.4.2 ECH0: Subgroup Analysis: Kaplan-Meier plot of Dauer des Ansprechens (IRC) for Geschlecht [eCRF] = Weiblich
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

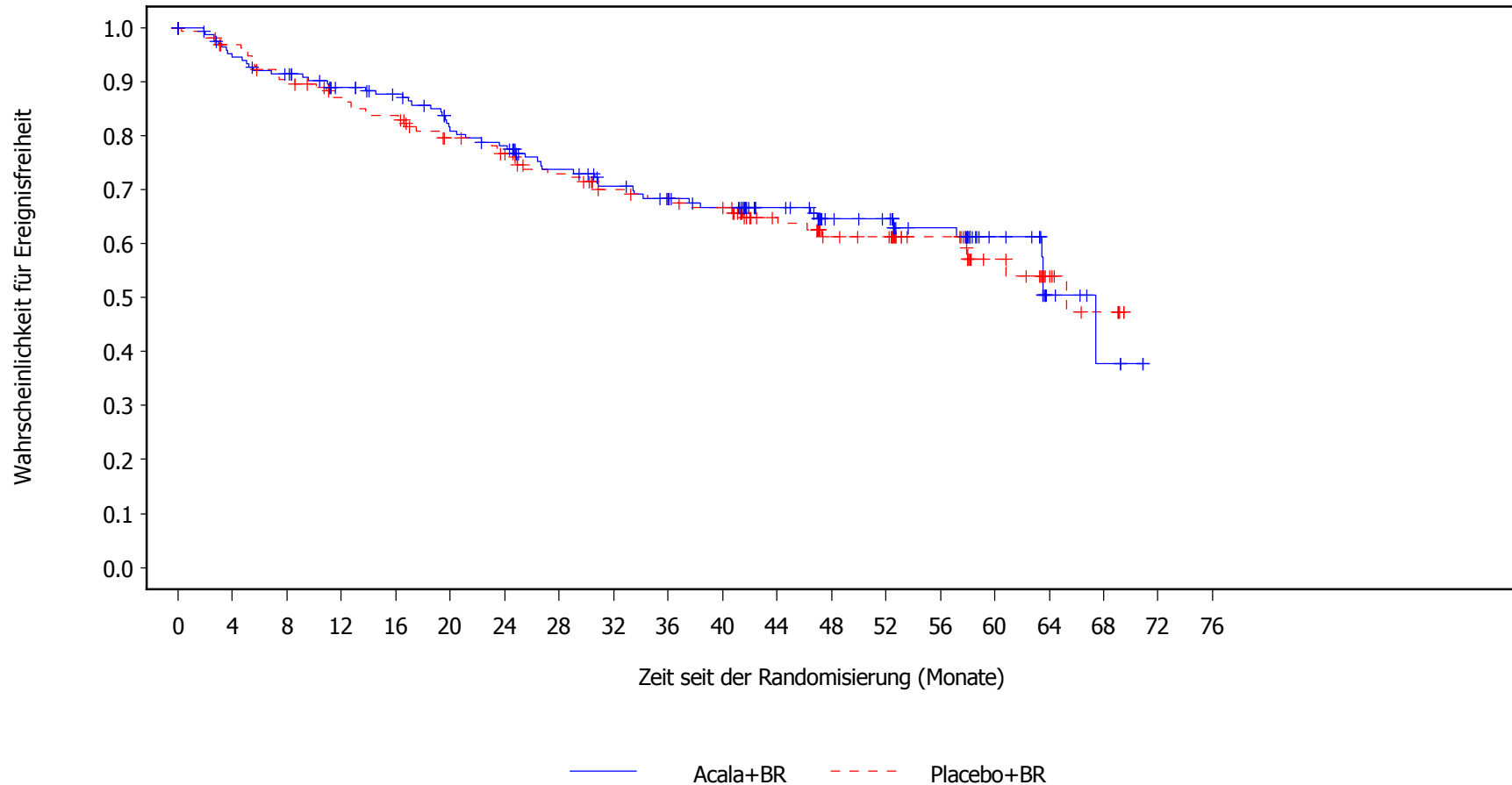
76	72	72	69	67	62	59	54	51	46	43	33	28	25	21	13	4	3	1	0	Acala+BR
82	72	69	63	60	56	49	42	36	33	29	22	18	17	11	6	2	2	0	0	Placebo+BR

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

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Figure 4.1.2.4.3 ECHO: Subgroup Analysis: Kaplan-Meier plot of Dauer des Ansprechens (IRC) for Bulky Disease I [eCRF] = < 5 cm
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

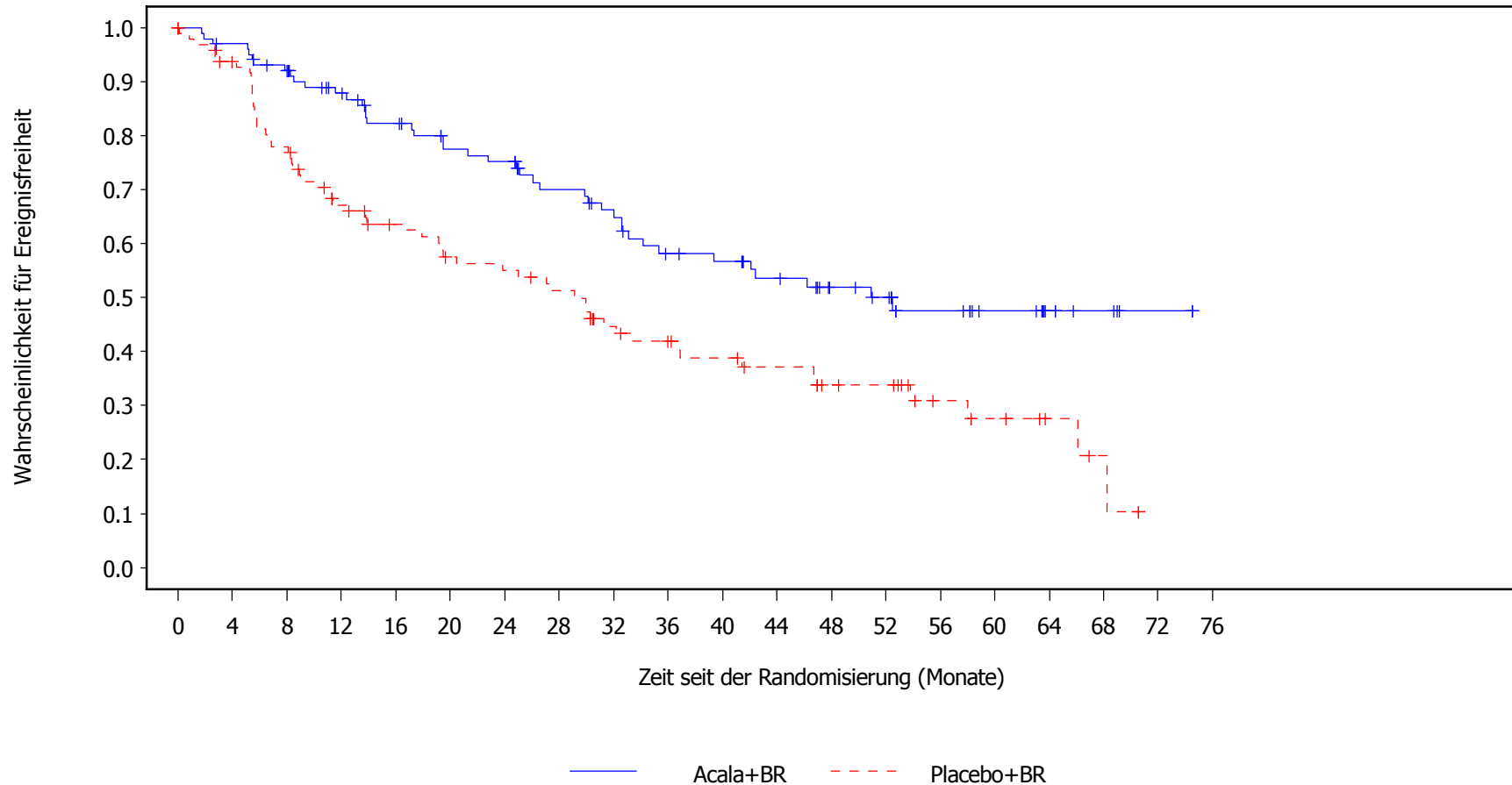
170	157	150	138	131	117	112	99	91	85	80	66	50	47	36	22	7	3	0	0	Acala+BR
163	150	139	130	125	113	107	97	88	84	77	61	47	45	33	20	11	6	0	0	Placebo+BR

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

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Figure 4.1.2.4.4 ECH0: Subgroup Analysis: Kaplan-Meier plot of Dauer des Ansprechens (IRC) for Bulky Disease I [eCRF] = >= 5 cm
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

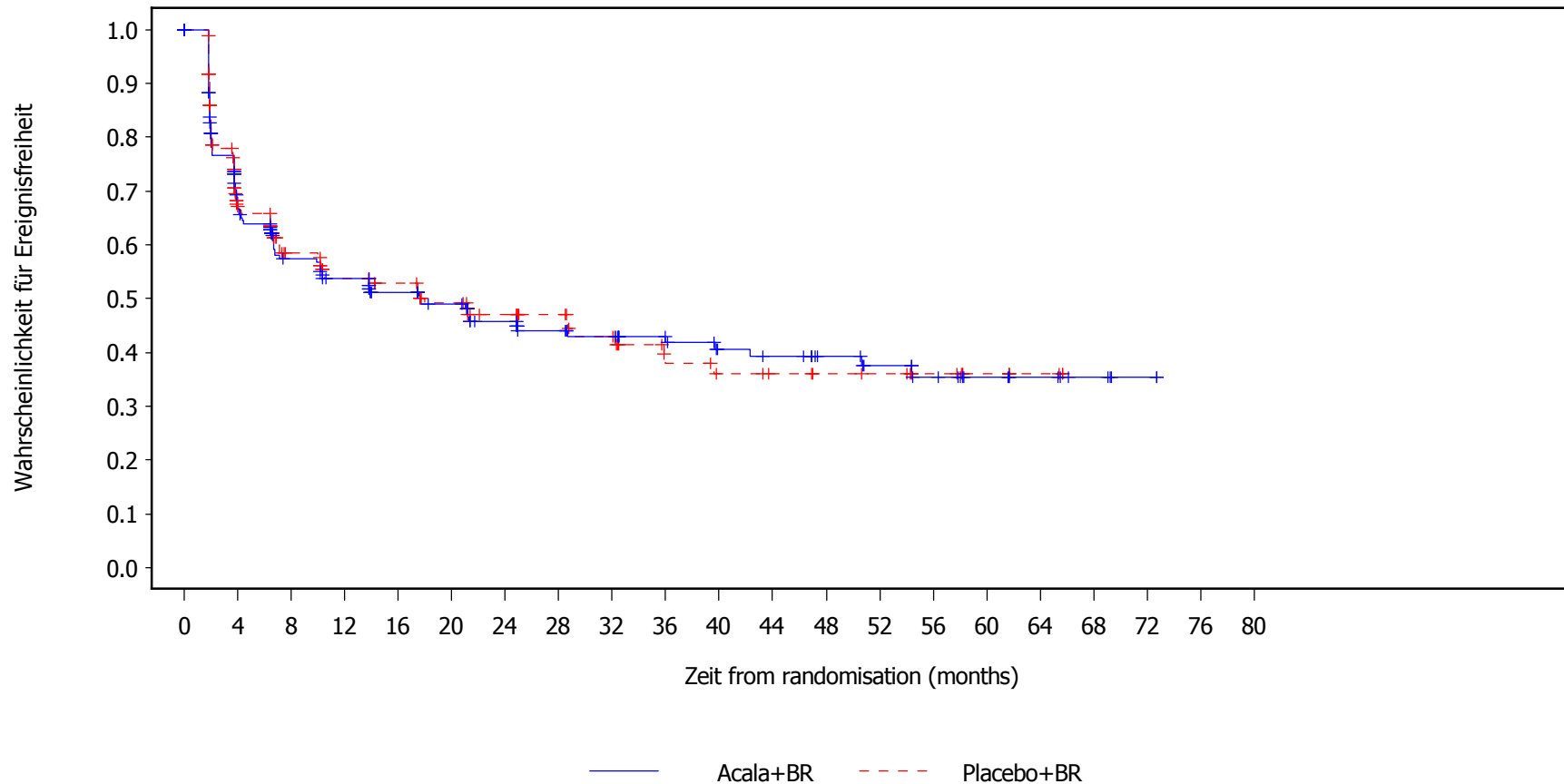
102	98	91	81	73	65	63	55	50	42	40	34	27	24	17	12	7	4	1	0	Acala+BR
100	89	74	59	52	46	44	40	32	28	25	22	17	16	9	7	4	2	0	0	Placebo+BR

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

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Figure 4.2.2.1.1 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Allgemeine Lebensqualität/Gesundheitszustand for Abstammung [eCRF]=Weiß
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

233	124	95	85	73	64	54	47	43	37	31	29	23	19	15	10	7	4	1	0	0	Acala+BR
235	111	77	65	59	51	41	37	31	21	18	16	14	13	9	5	2	0	0	0	0	Placebo+BR

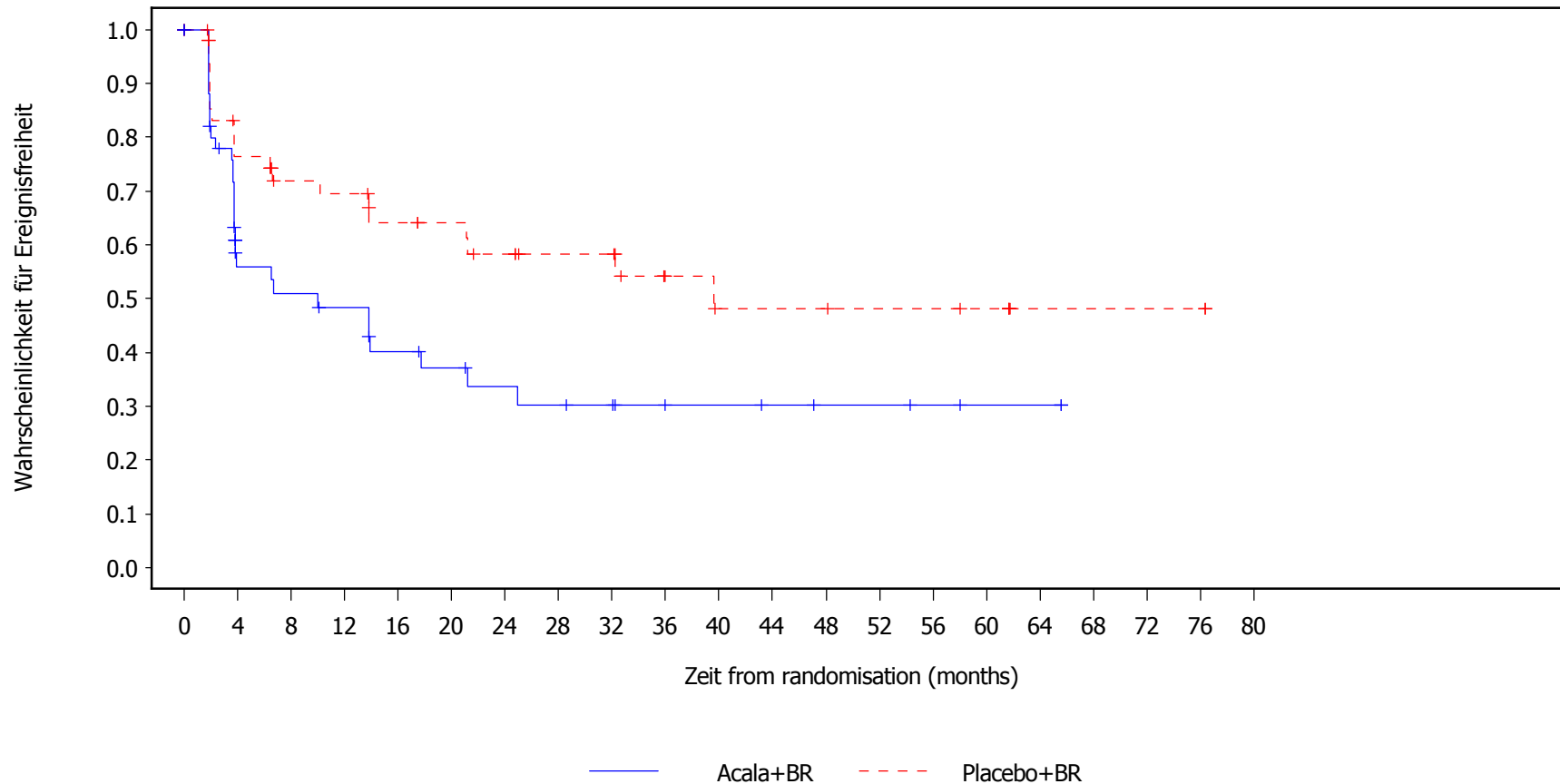
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.2 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Allgemeine Lebensqualität/Gesundheitsszustand for Abstammung [eCRF]=Nicht-weiß
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

52	22	20	18	14	12	10	9	8	5	5	4	3	3	2	1	1	0	0	0	0	Acala+BR
53	35	29	28	24	22	19	16	16	9	7	7	7	6	6	5	1	1	1	1	0	Placebo+BR

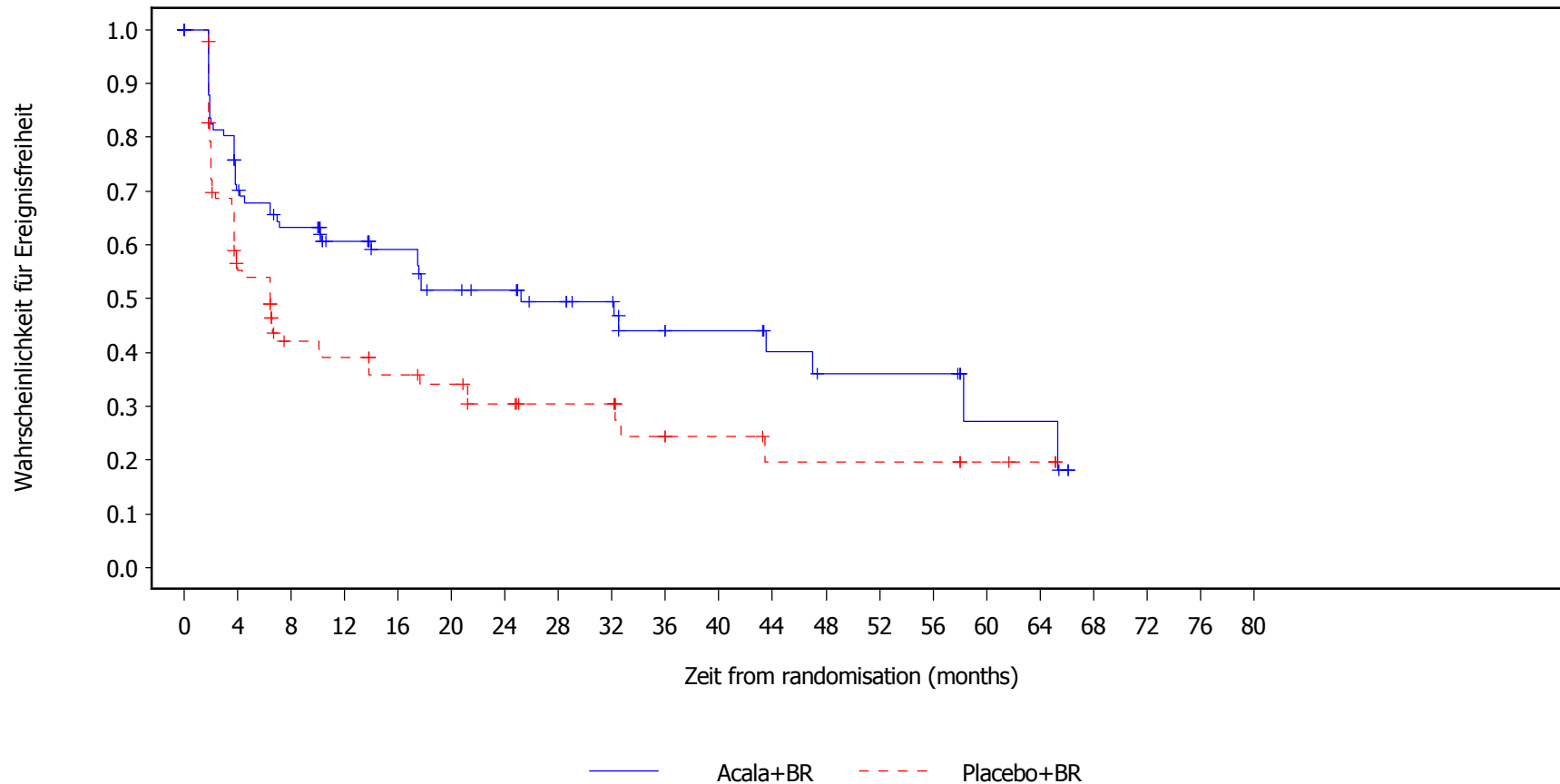
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.3 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Körper for Vereinfachter MIPI-Score [IXRS]=Geringes Risiko [0-3]
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

99	62	54	45	39	32	30	23	20	13	13	10	8	8	8	3	3	0	0	0	0	Acala+BR
101	44	28	26	22	20	16	13	13	6	6	4	4	4	4	2	1	0	0	0	0	Placebo+BR

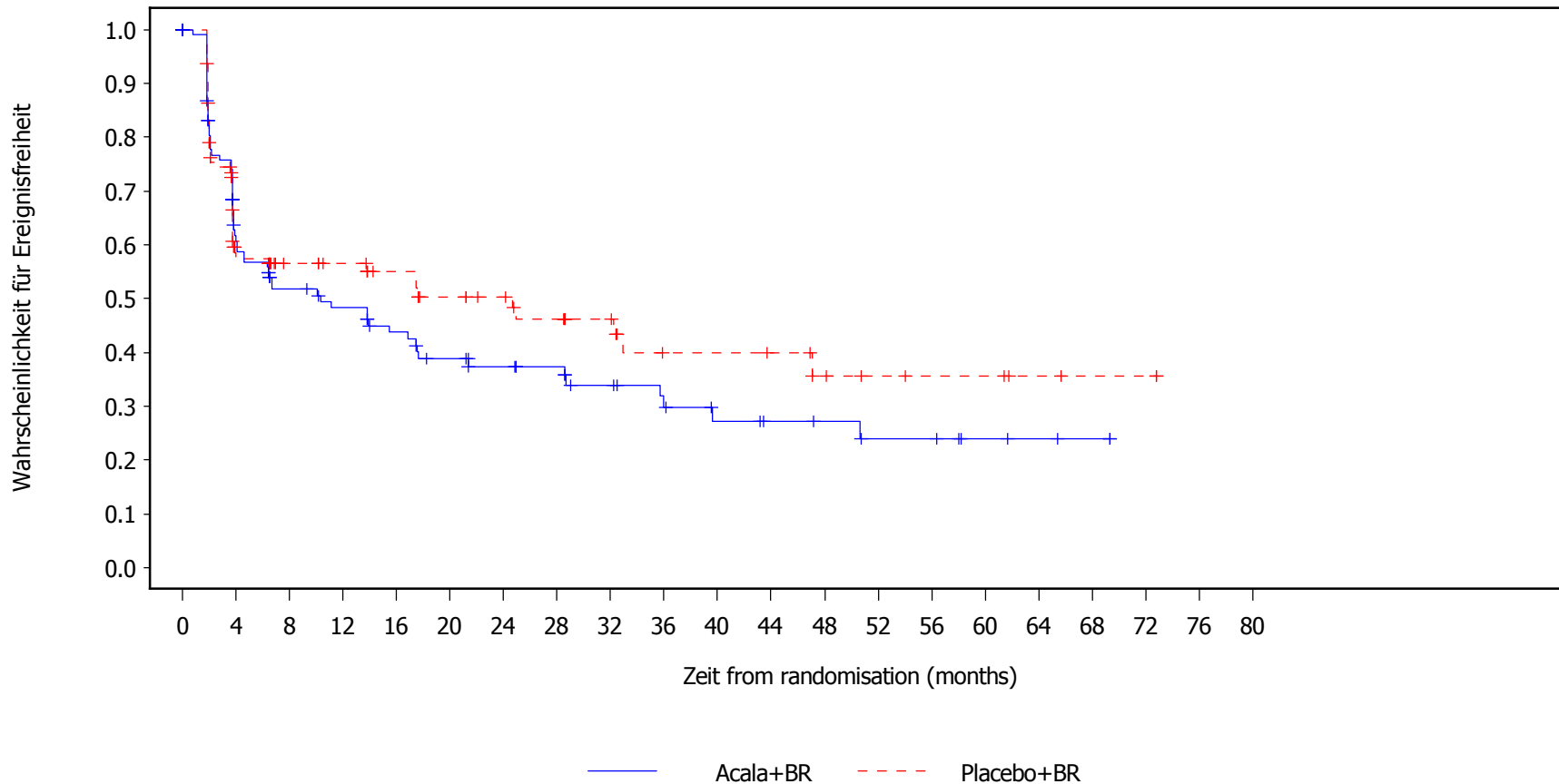
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.4 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Körper for Vereinfachter MIPI-Score [IXRS]=Intermediäres Risiko [4-5]
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

128	62	48	43	36	30	26	23	18	15	11	9	8	6	6	3	2	1	0	0	0	Acala+BR
125	56	44	41	35	29	26	22	17	11	11	10	7	5	4	4	2	1	1	0	0	Placebo+BR

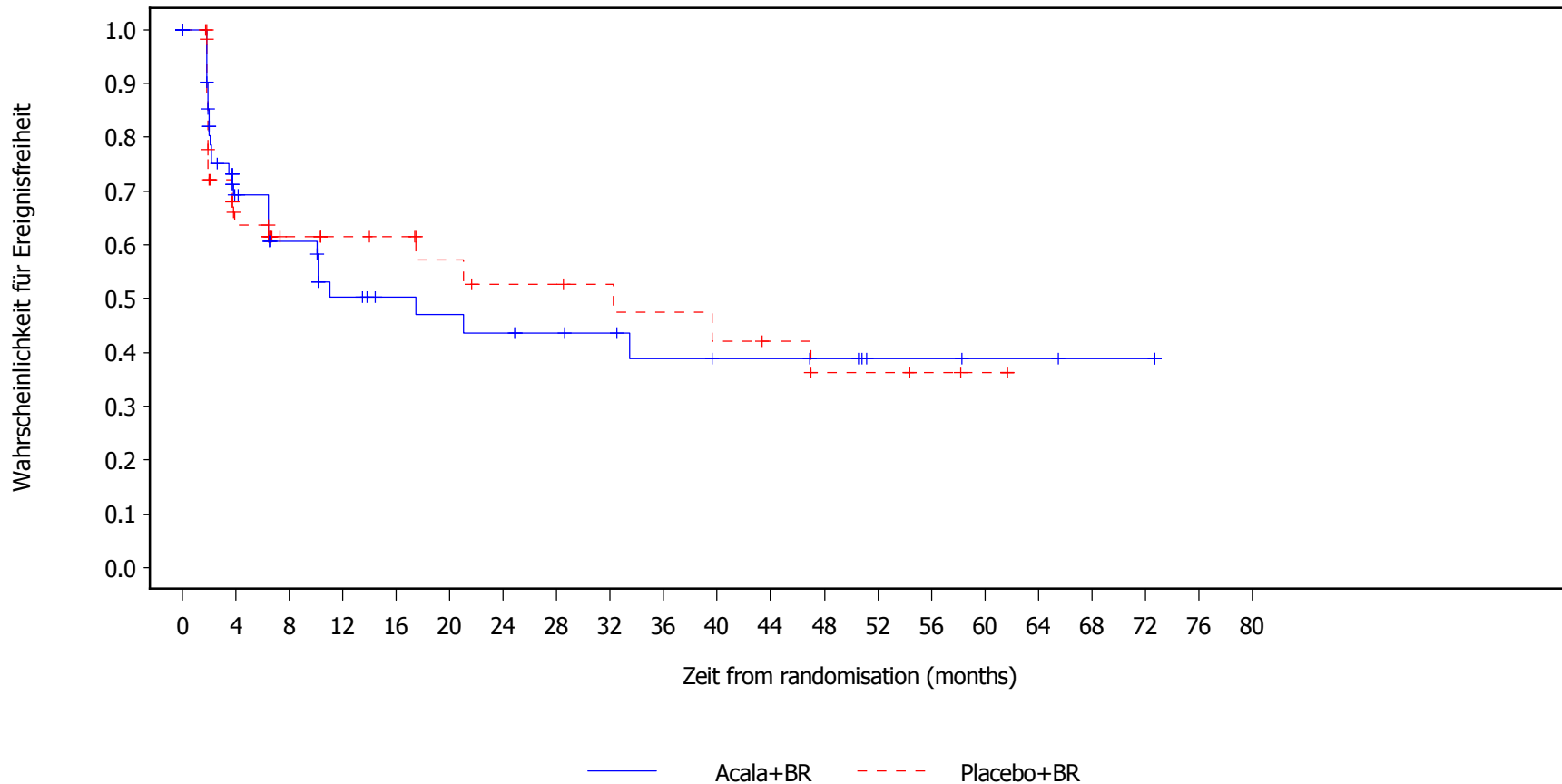
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.5 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Körper for Vereinfachter MIPI-Score [IXRS]=Hohes Risiko [6-11]
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

72	33	25	18	15	14	13	11	10	8	7	7	6	3	3	2	2	1	1	0	0	Acala+BR
73	29	20	17	16	13	11	11	10	9	8	7	5	5	3	2	0	0	0	0	0	Placebo+BR

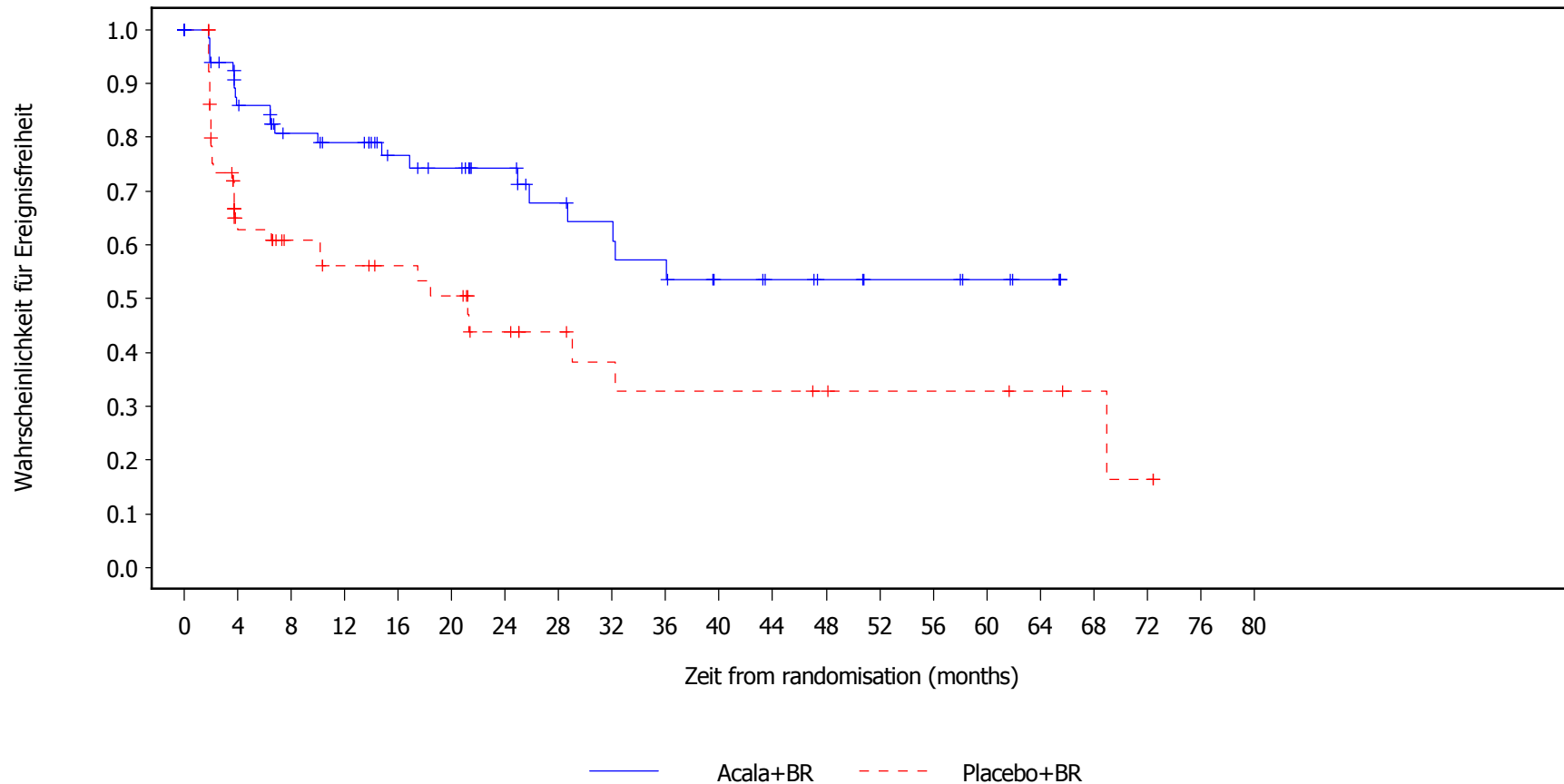
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

Nutzenbewertung nach AMNOG

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Figure 4.2.2.1.6 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Emotionalität
 for Geographic Region [IXRS]=Nordamerika
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

82	53	44	41	33	30	25	20	18	16	12	10	8	6	6	4	2	0	0	0	0	Acala+BR
83	33	25	22	20	18	12	9	7	6	6	6	5	4	4	4	3	2	1	0	0	Placebo+BR

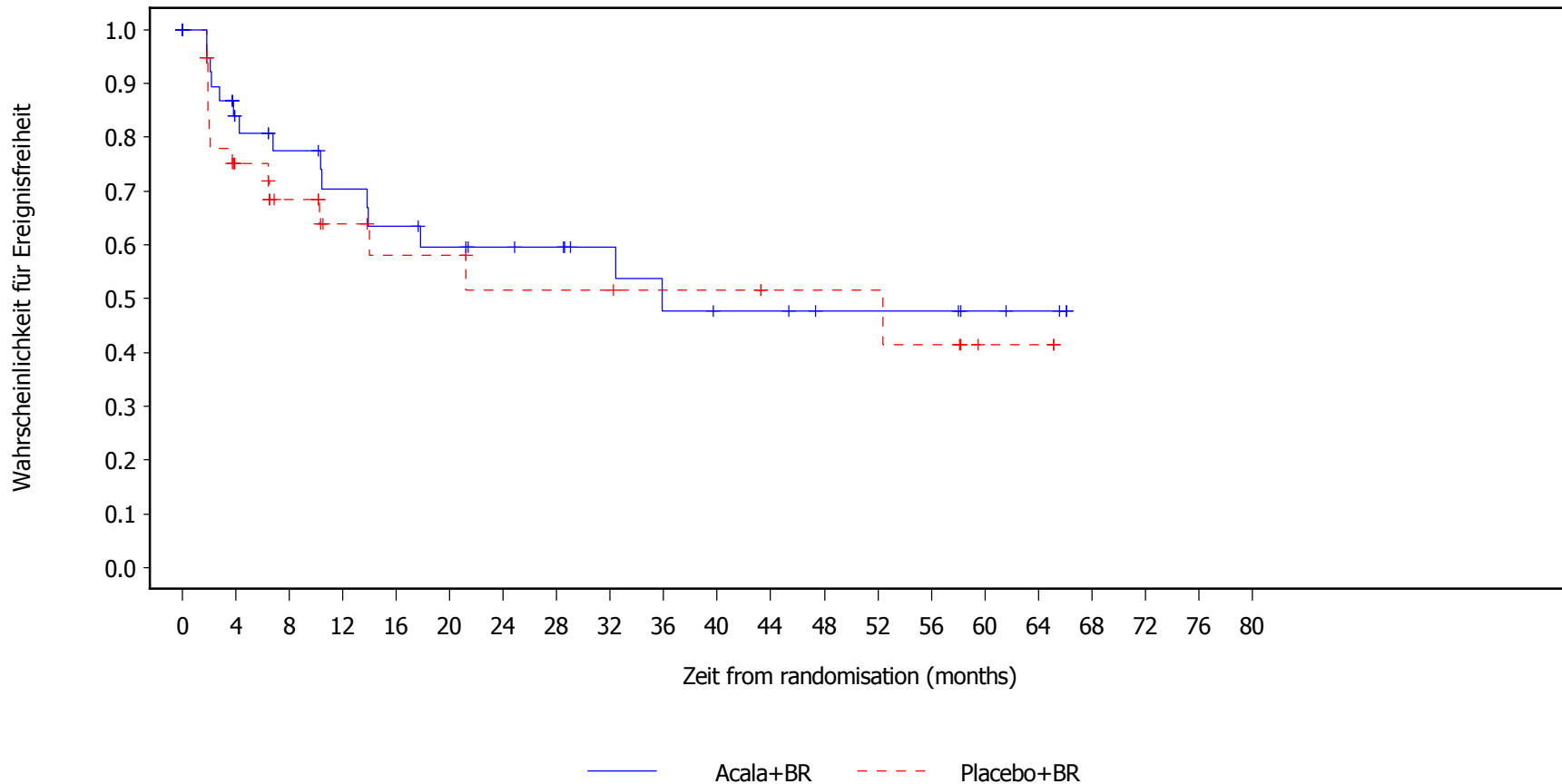
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.7 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Emotionalität
 for Geographic Region [IXRS]=Westeuropa
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

46	27	23	20	18	16	14	13	10	8	7	7	5	5	5	3	2	0	0	0	0	Acala+BR
46	23	17	12	10	10	8	8	8	7	7	5	5	5	4	1	1	0	0	0	0	Placebo+BR

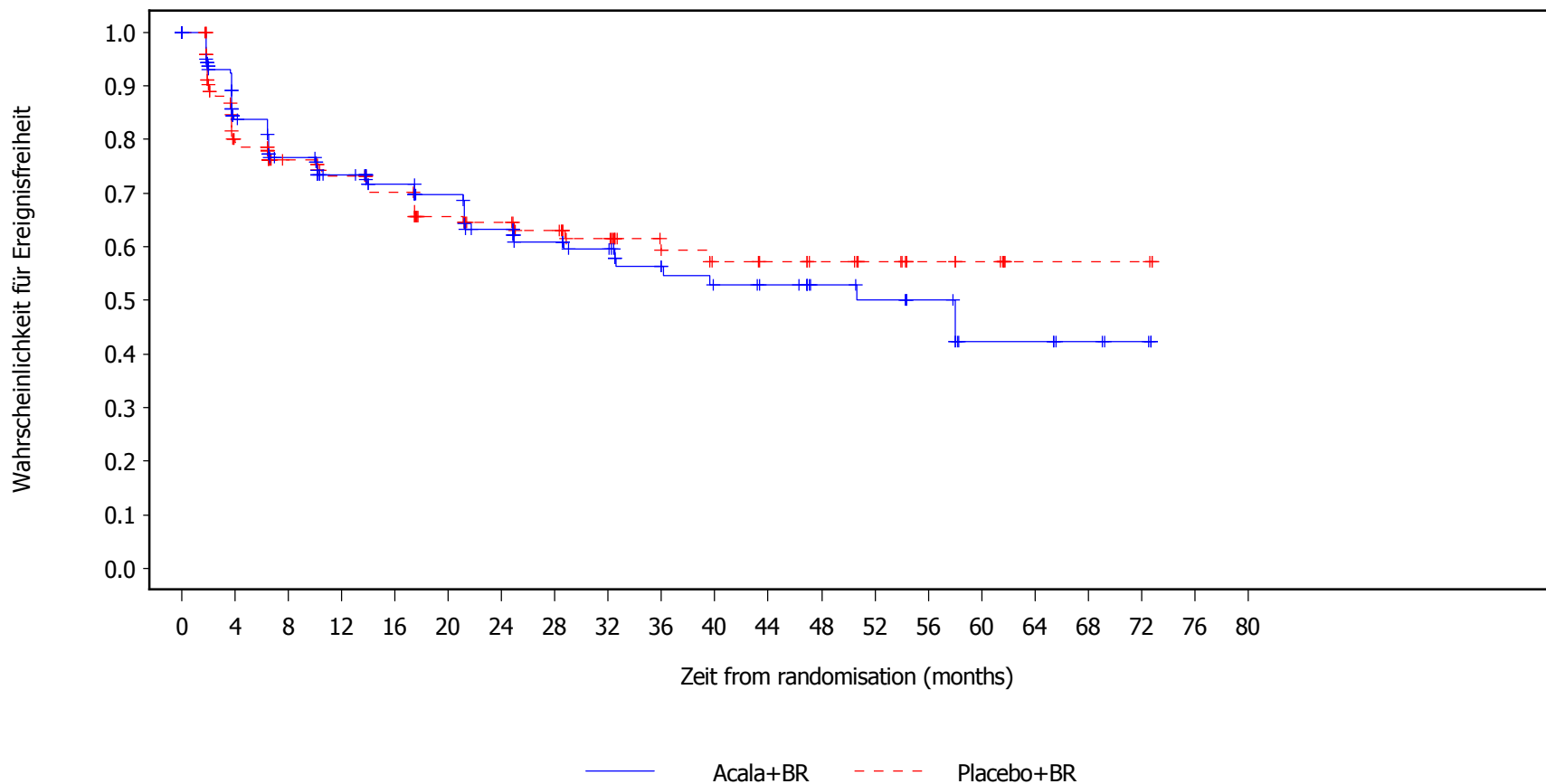
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.8 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Emotionalität
 for Geographic Region [IXRS]=Andere
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

171	119	102	88	75	66	56	48	42	32	29	27	20	18	14	7	7	4	2	0	0	Acala+BR
170	105	82	73	65	54	48	44	37	27	24	22	19	15	10	8	2	2	2	0	0	Placebo+BR

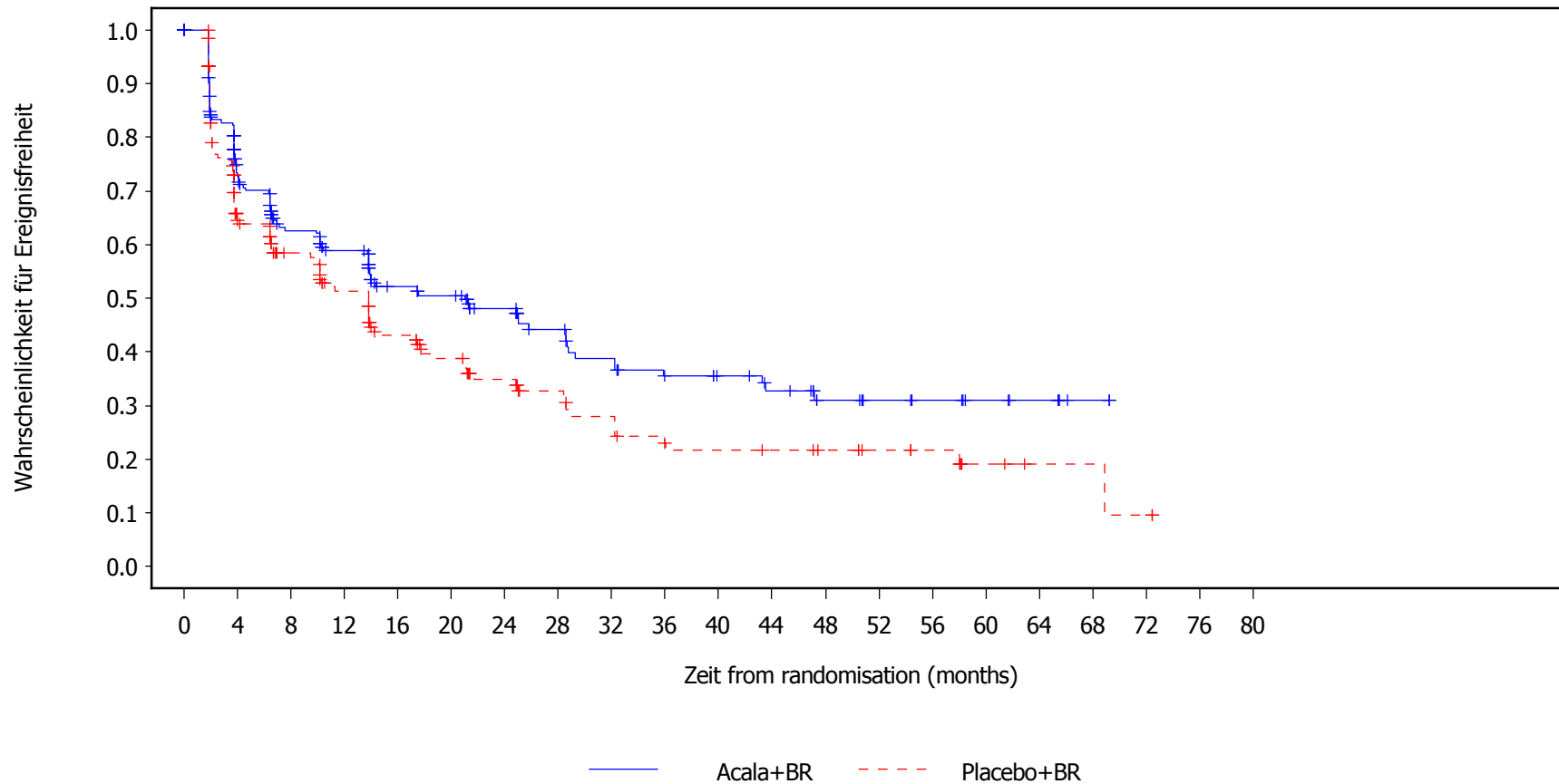
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.9 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Kognition for Abstammung [eCRF]=Weiß
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

233	134	105	92	69	65	54	43	36	30	27	23	16	13	11	8	6	1	0	0	0	Acala+BR
235	109	86	70	53	43	34	28	23	17	16	15	13	10	8	4	2	2	1	0	0	Placebo+BR

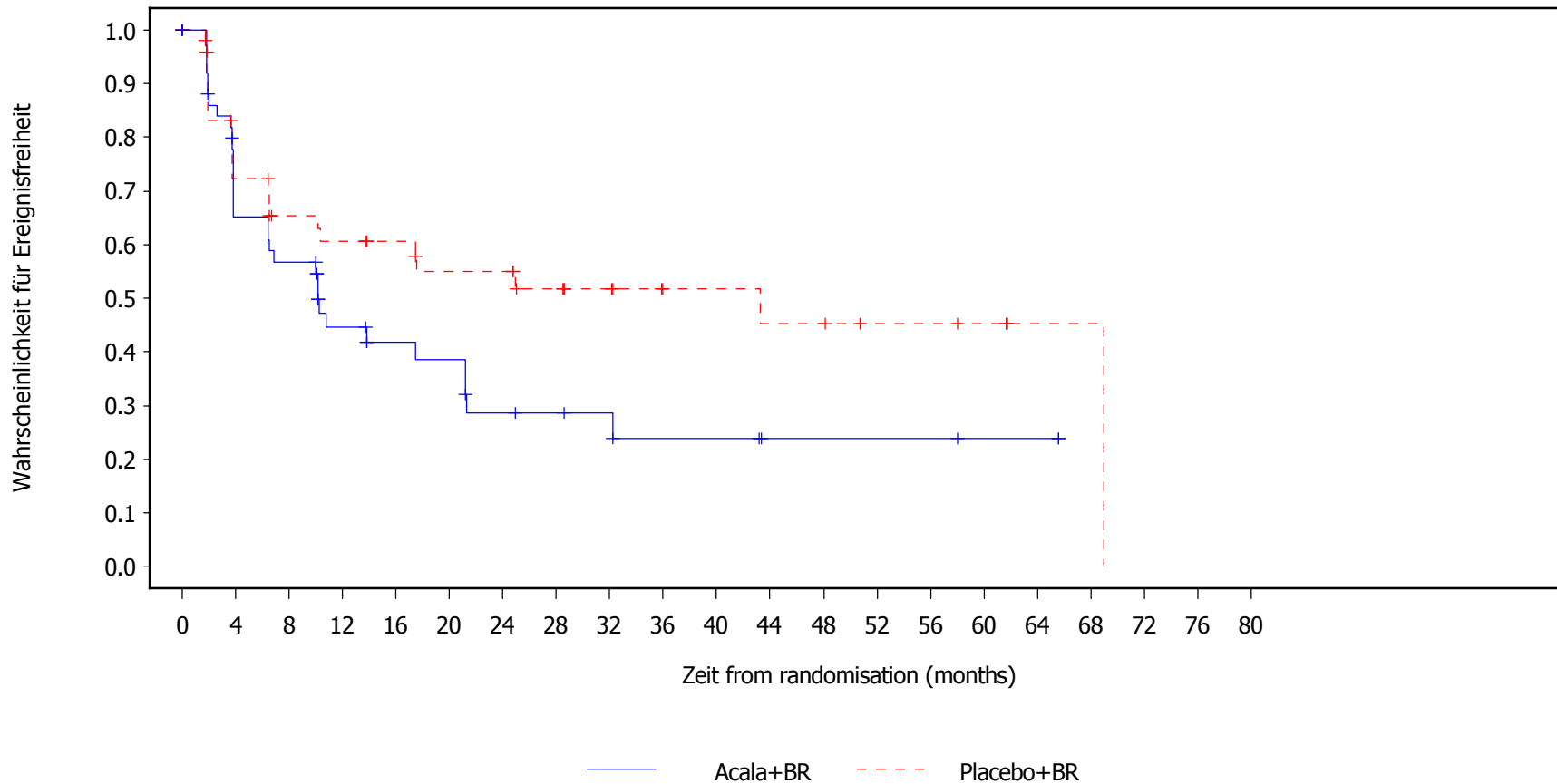
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.10 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Kognition for Abstammung [eCRF]=Nicht-weiß
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

52	31	27	17	13	12	8	7	6	4	4	2	2	2	2	1	1	0	0	0	0	Acala+BR
53	33	27	25	22	19	19	15	12	8	8	7	7	5	5	4	1	1	0	0	0	Placebo+BR

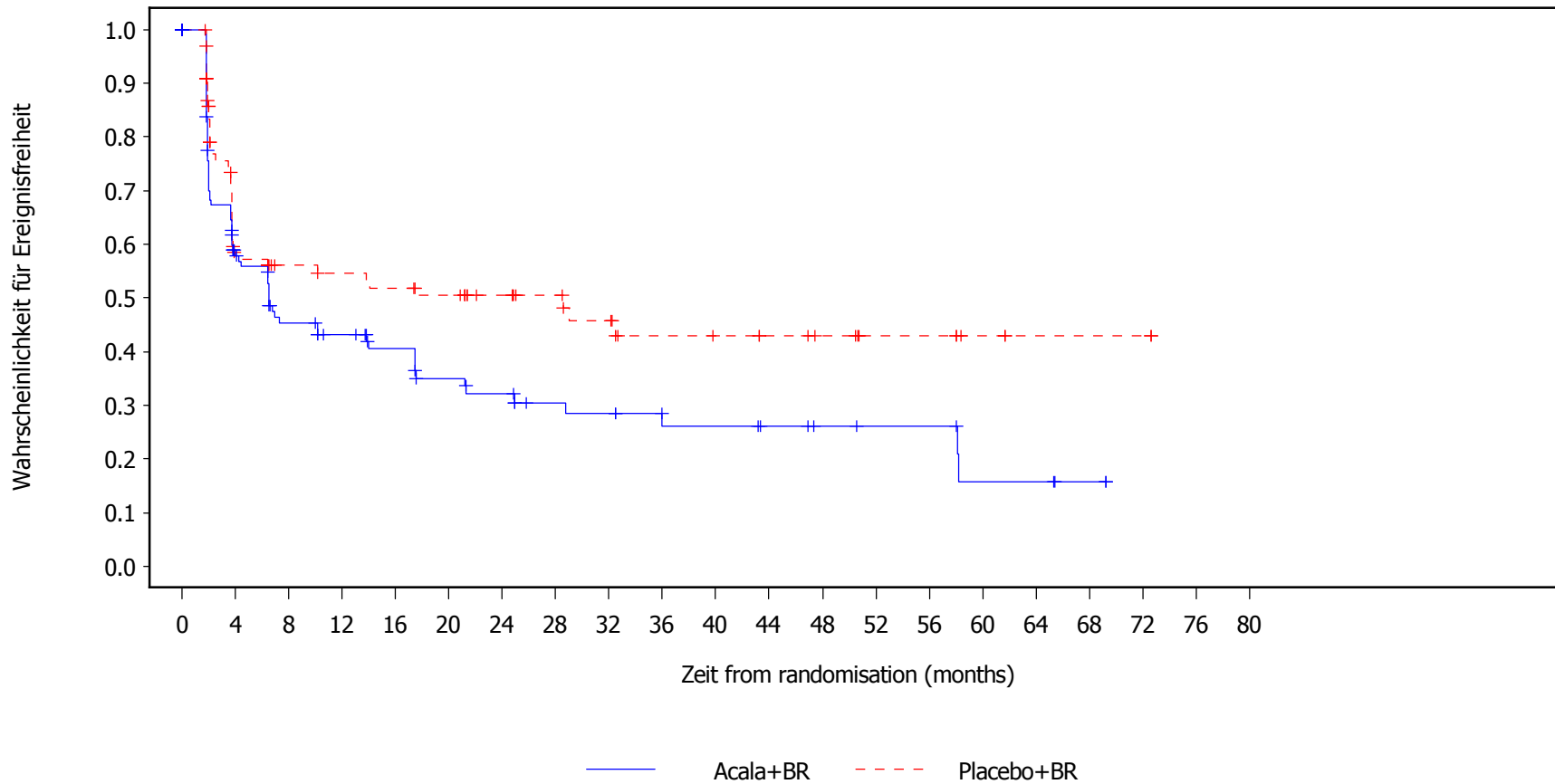
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.11 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Sozial for Altersgruppe I [eCRF]<= 70 Jahre Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

123	58	42	36	30	24	21	16	15	11	11	9	7	6	6	3	3	1	0	0	0	Acala+BR
117	49	41	39	37	34	27	23	19	14	13	11	9	6	6	3	1	1	1	0	0	Placebo+BR

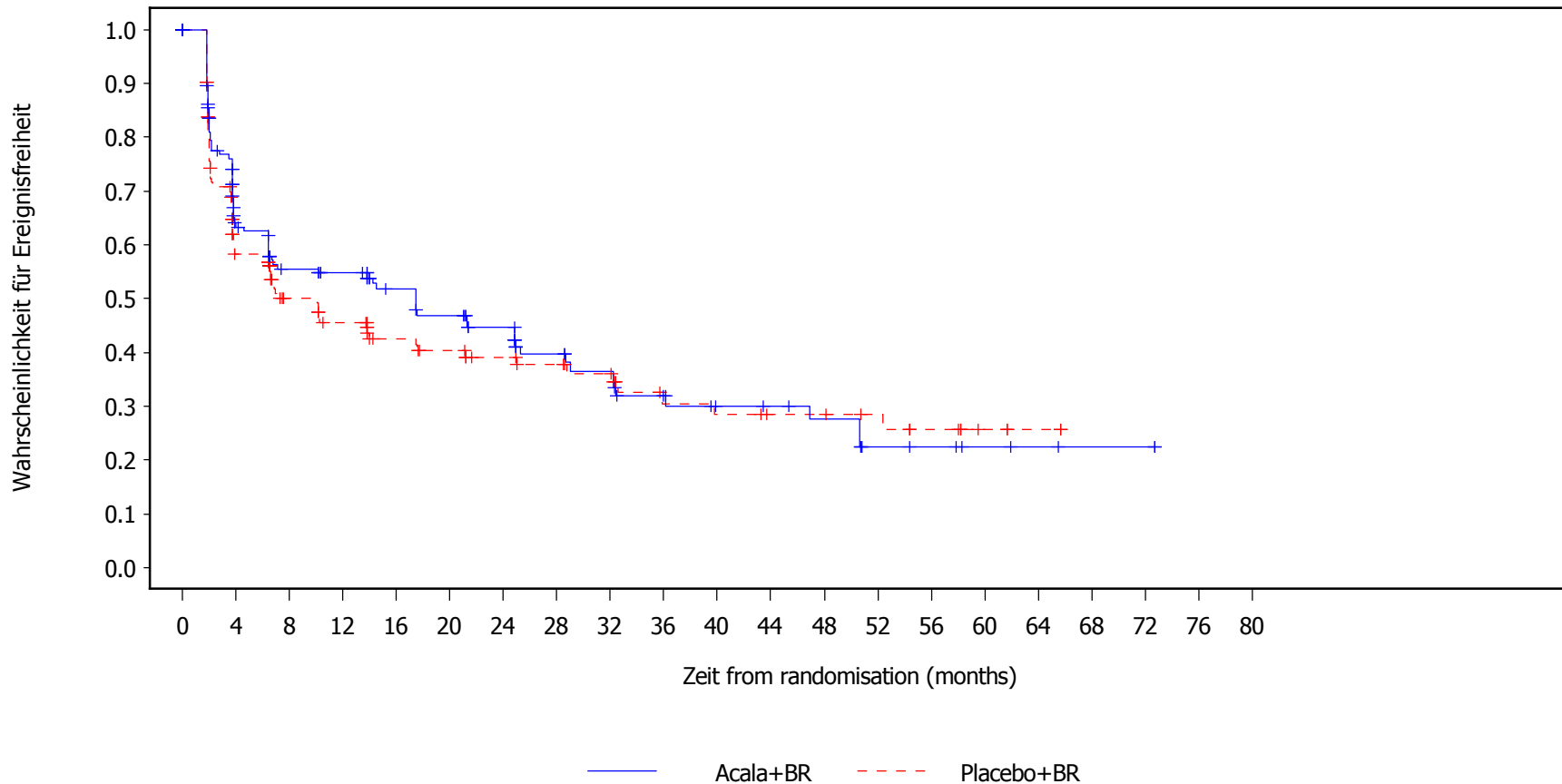
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

Nutzenbewertung nach AMNOG

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Figure 4.2.2.1.12 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Sozial for Altersgruppe I [eCRF]>= 70 Jahre
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

176	85	68	63	52	46	39	28	24	18	14	13	11	6	5	3	2	1	1	0	0	Acala+BR
182	79	56	48	38	34	29	26	23	15	14	12	12	10	7	3	1	0	0	0	0	Placebo+BR

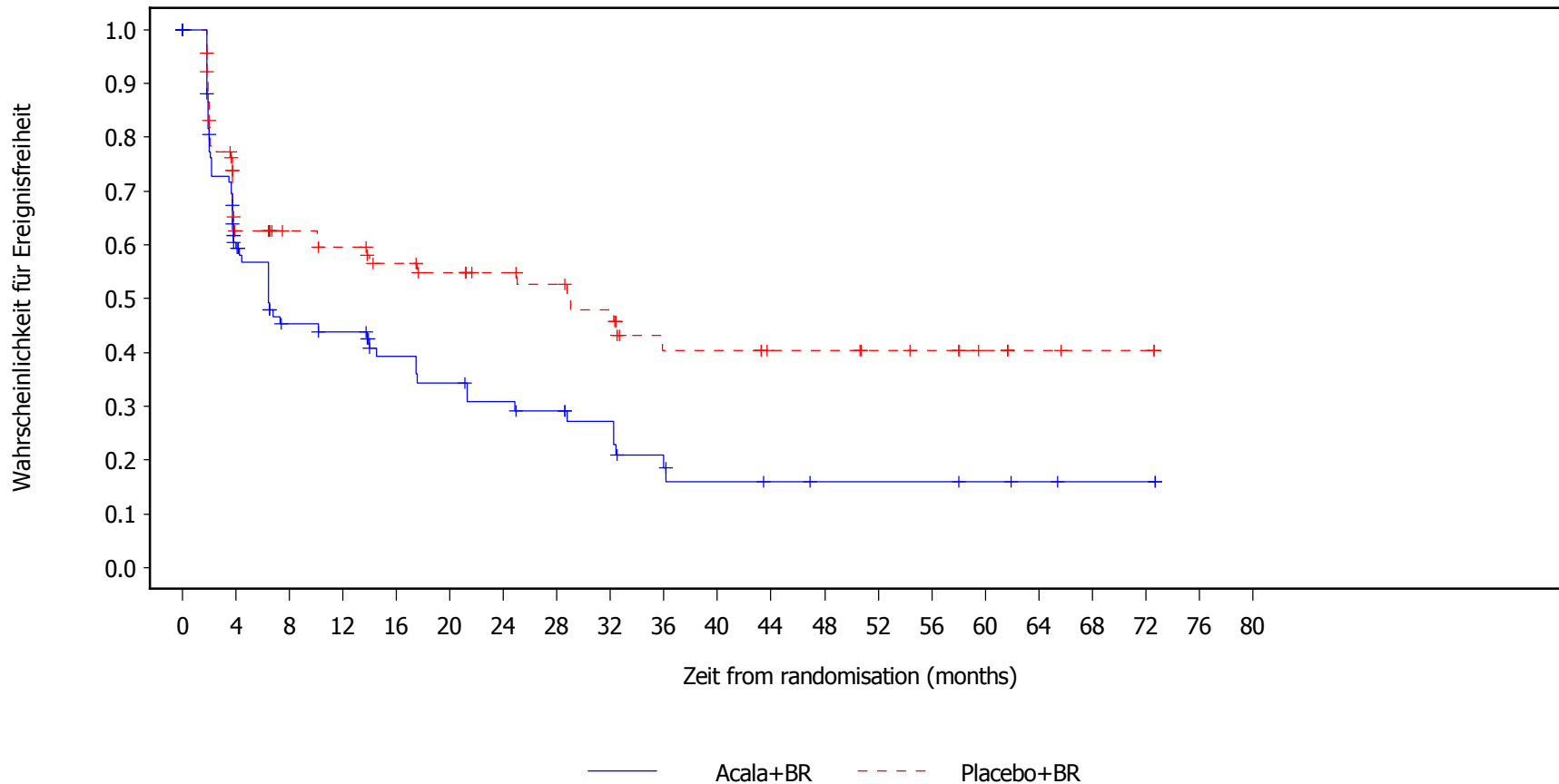
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.13 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Sozial for
 Ki-67 (%) I [eCRF]<= 30%
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

109	49	33	31	24	21	18	16	13	8	6	5	4	4	4	3	2	1	1	0	0	Acala+BR
103	49	42	39	34	31	26	24	21	14	14	11	11	9	8	5	2	1	1	0	0	Placebo+BR

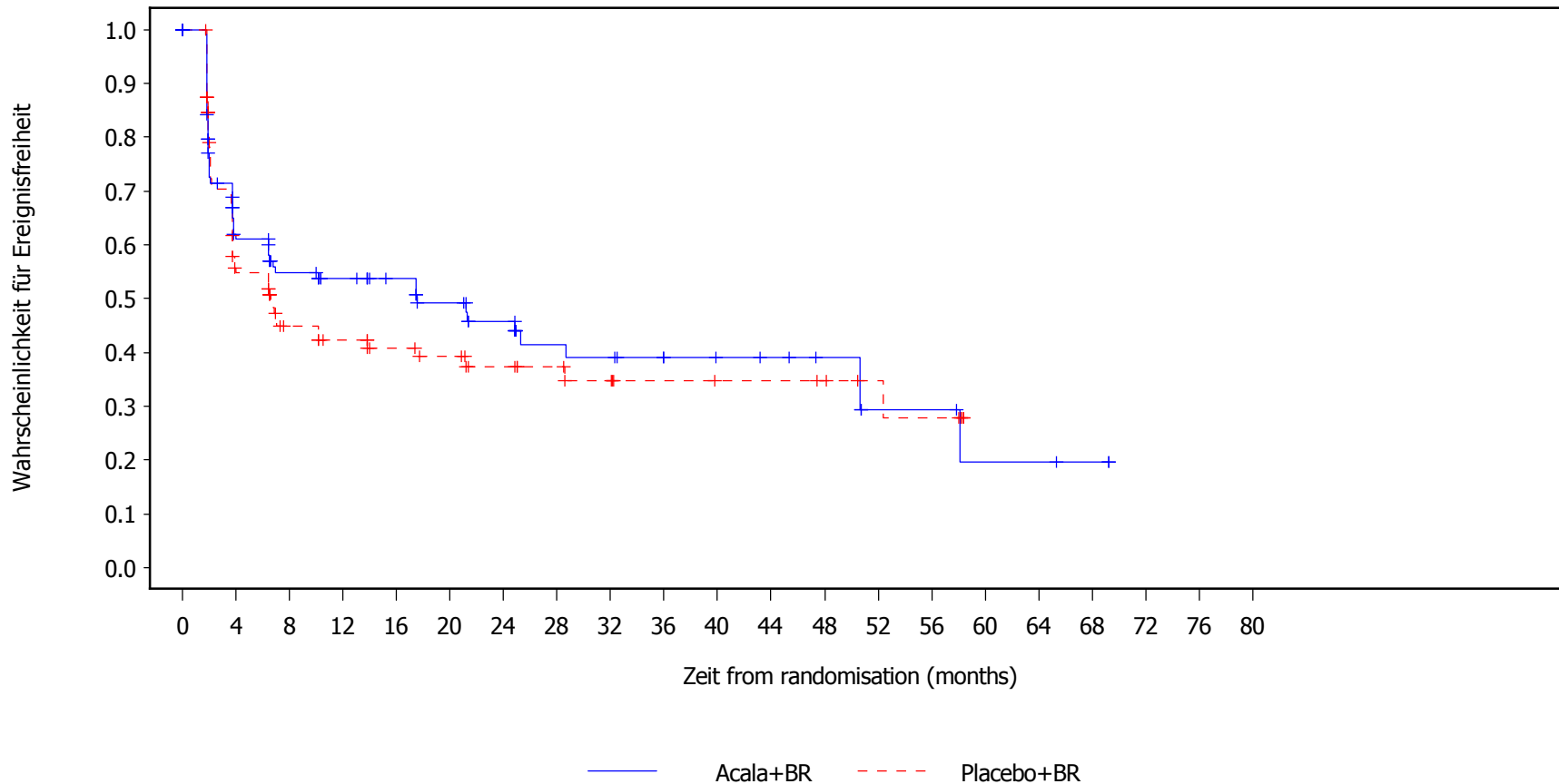
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.14 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Funktionsskala: Sozial for
 Ki-67 (%) I [eCRF]>= 30%
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

128	62	50	43	37	31	25	17	16	12	11	10	8	4	4	2	2	1	0	0	0	Acala+BR
127	55	36	31	26	23	18	15	12	9	8	8	7	5	4	0	0	0	0	0	0	Placebo+BR

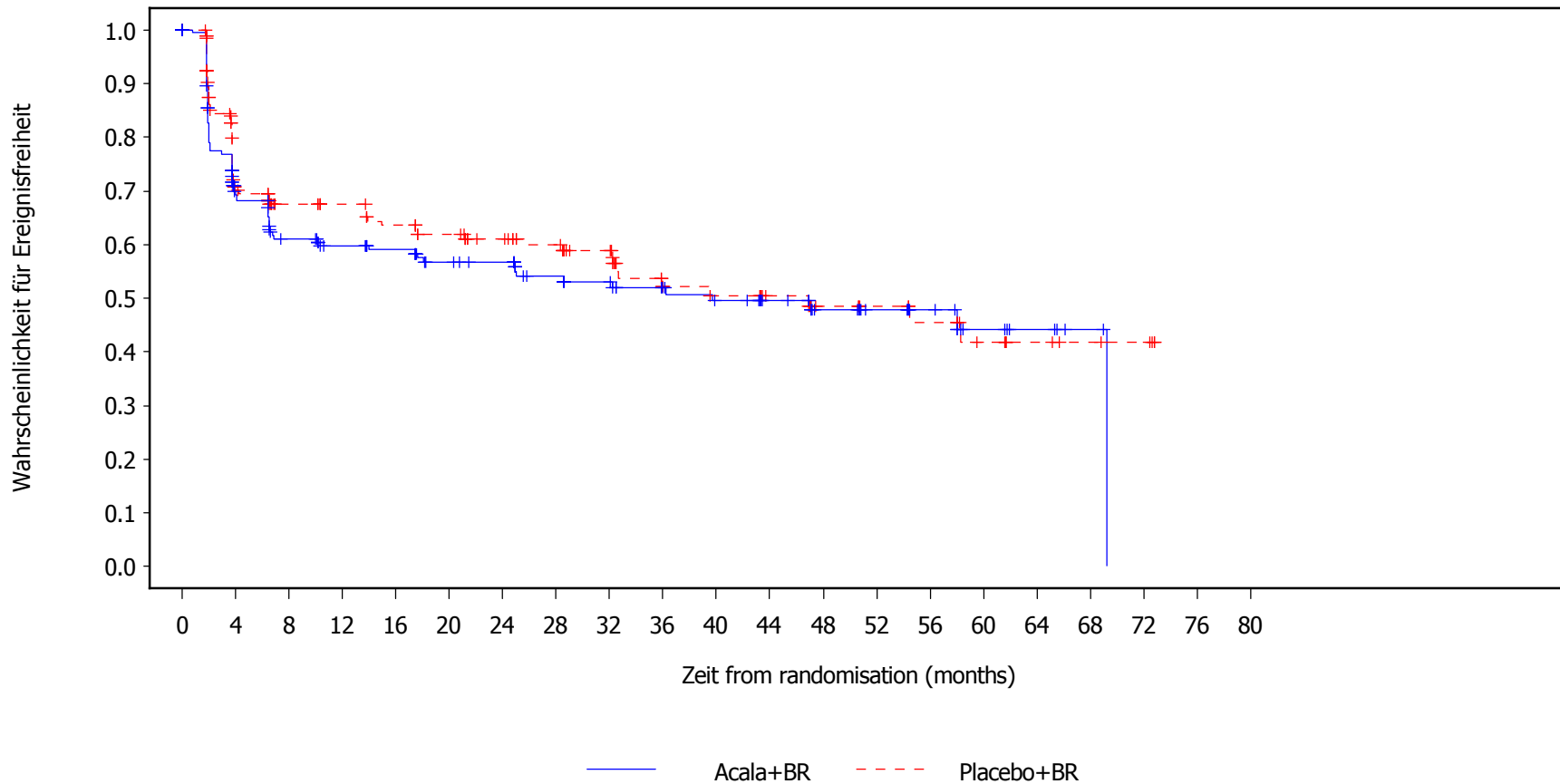
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.15 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Übelkeit und Erbrechen for Altersgruppe II [eCRF]<= 75 Jahre
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

215	120	100	90	83	72	69	56	50	43	39	33	25	20	15	8	5	2	0	0	0	Acala+BR
222	113	92	87	79	73	64	57	49	33	31	26	21	18	15	10	6	4	3	0	0	Placebo+BR

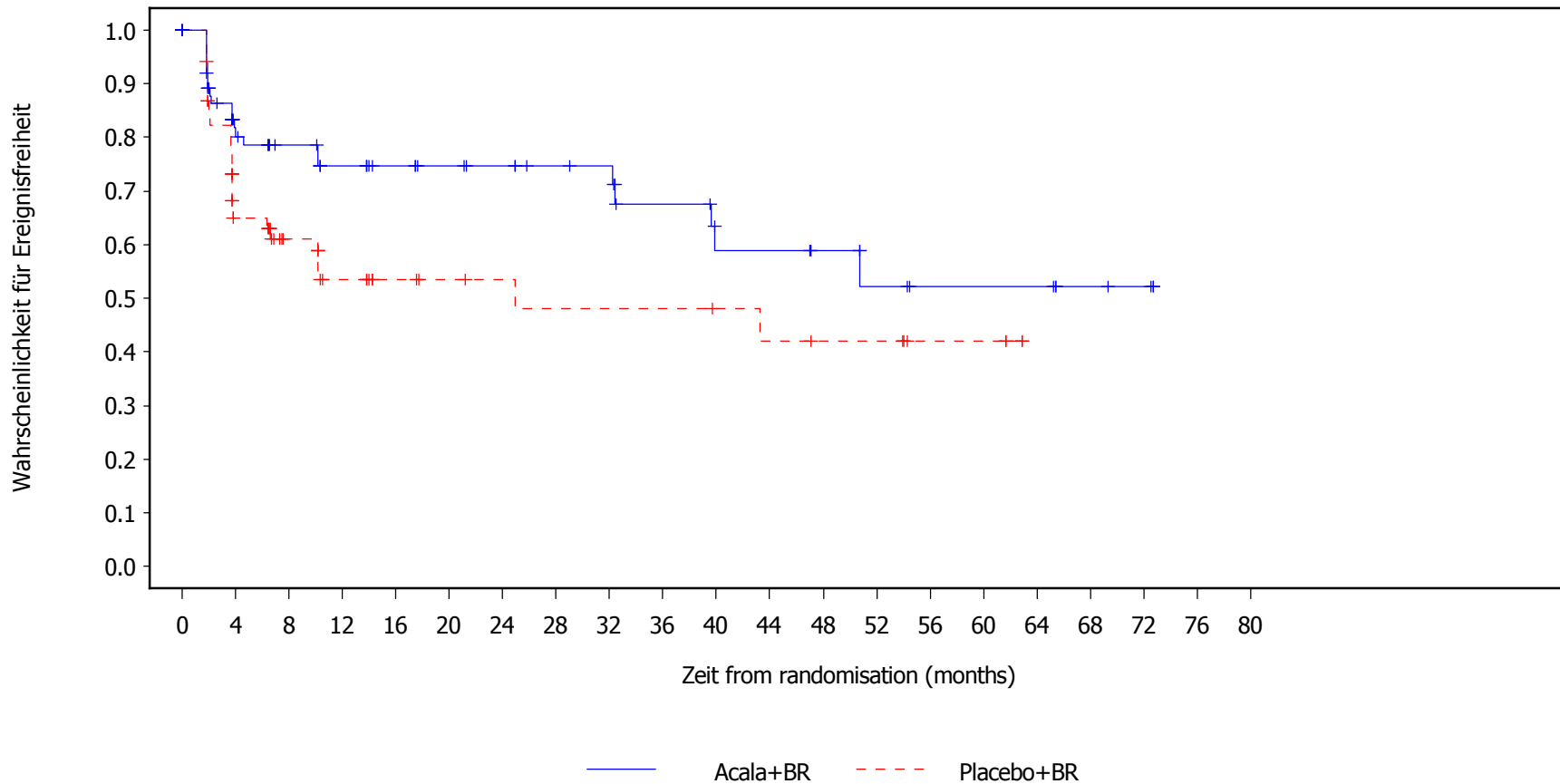
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.16 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Übelkeit und Erbrechen for Altersgruppe II [eCRF]>= 75 Jahre
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

84	50	42	36	31	28	26	23	22	17	13	13	11	8	6	6	6	3	2	0	0	Acala+BR
77	37	26	18	13	11	10	9	9	9	8	7	6	6	3	3	0	0	0	0	0	Placebo+BR

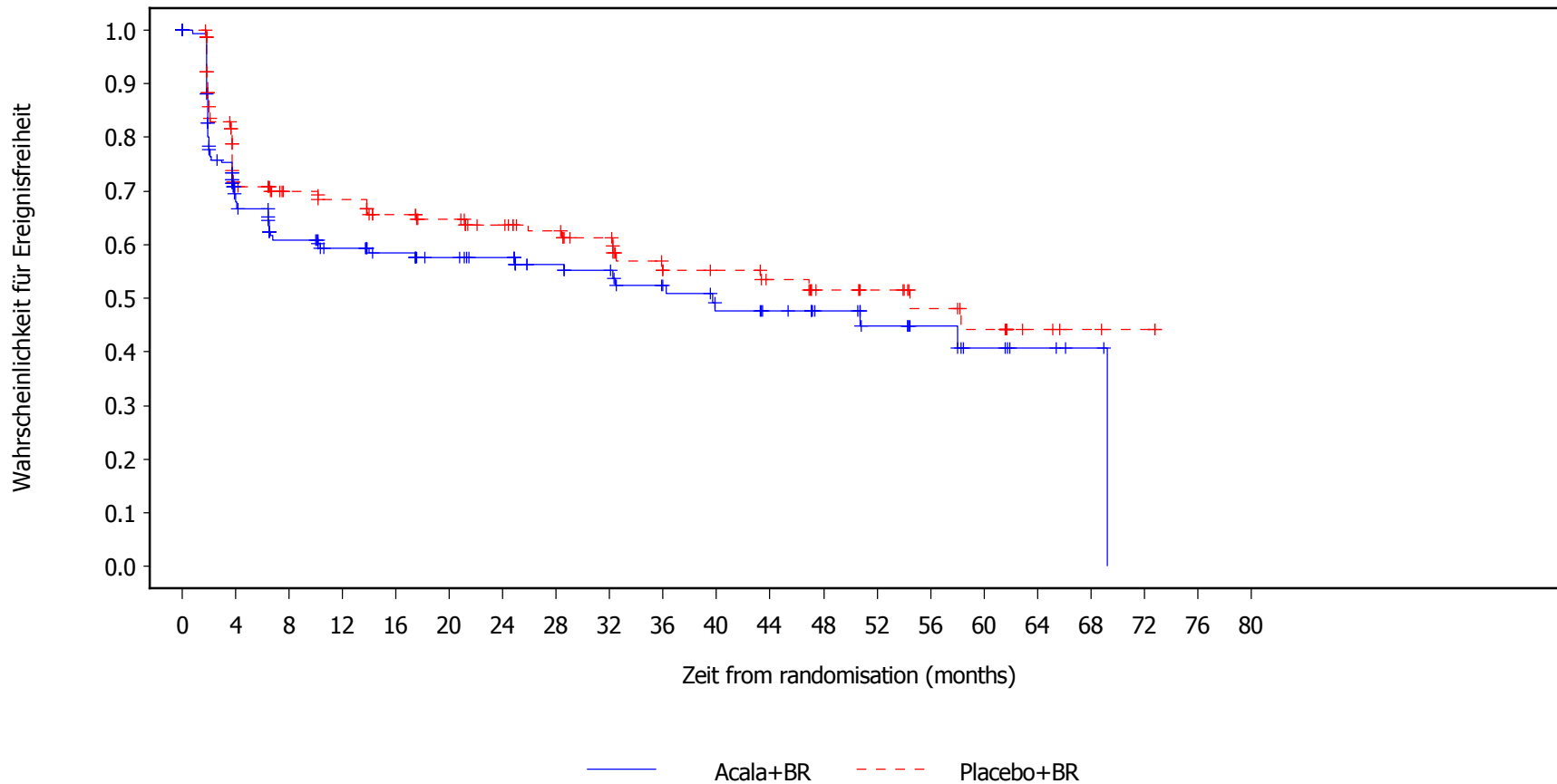
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.17 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Übelkeit und Erbrechen for Bulky Disease I [eCRF]<= 5 cm
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

187	99	81	73	65	58	54	44	41	34	29	26	20	15	11	7	4	2	0	0	0	Acala+BR
186	95	83	79	70	65	57	51	45	33	32	28	22	19	14	11	4	2	1	0	0	Placebo+BR

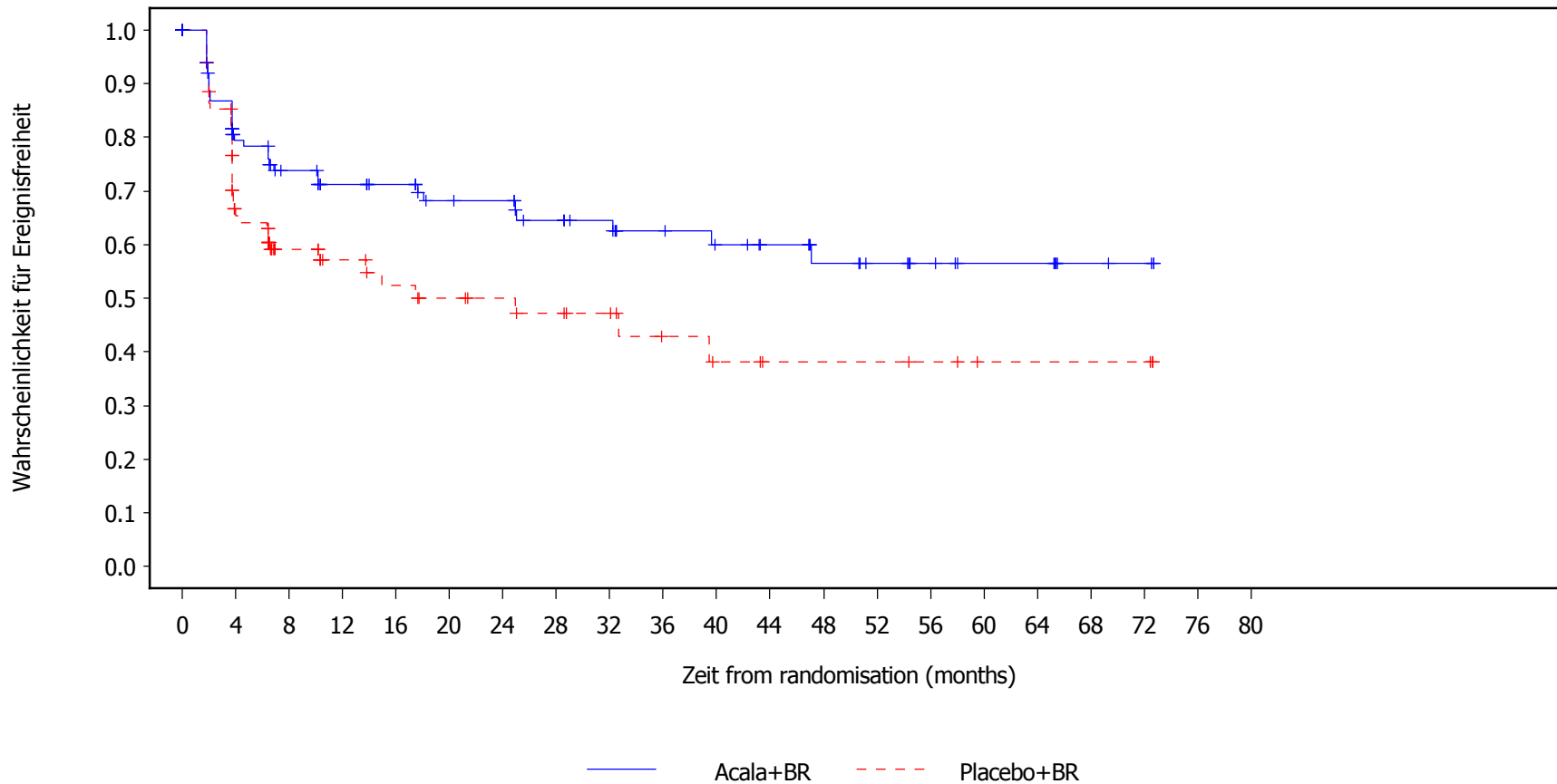
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.18 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Übelkeit und Erbrechen for Bulky Disease I [eCRF]>= 5 cm
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

112	71	61	53	49	42	41	35	31	26	23	20	16	13	10	7	7	3	2	0	0	Acala+BR
113	55	35	26	22	19	17	15	13	9	7	5	5	5	4	2	2	2	2	0	0	Placebo+BR

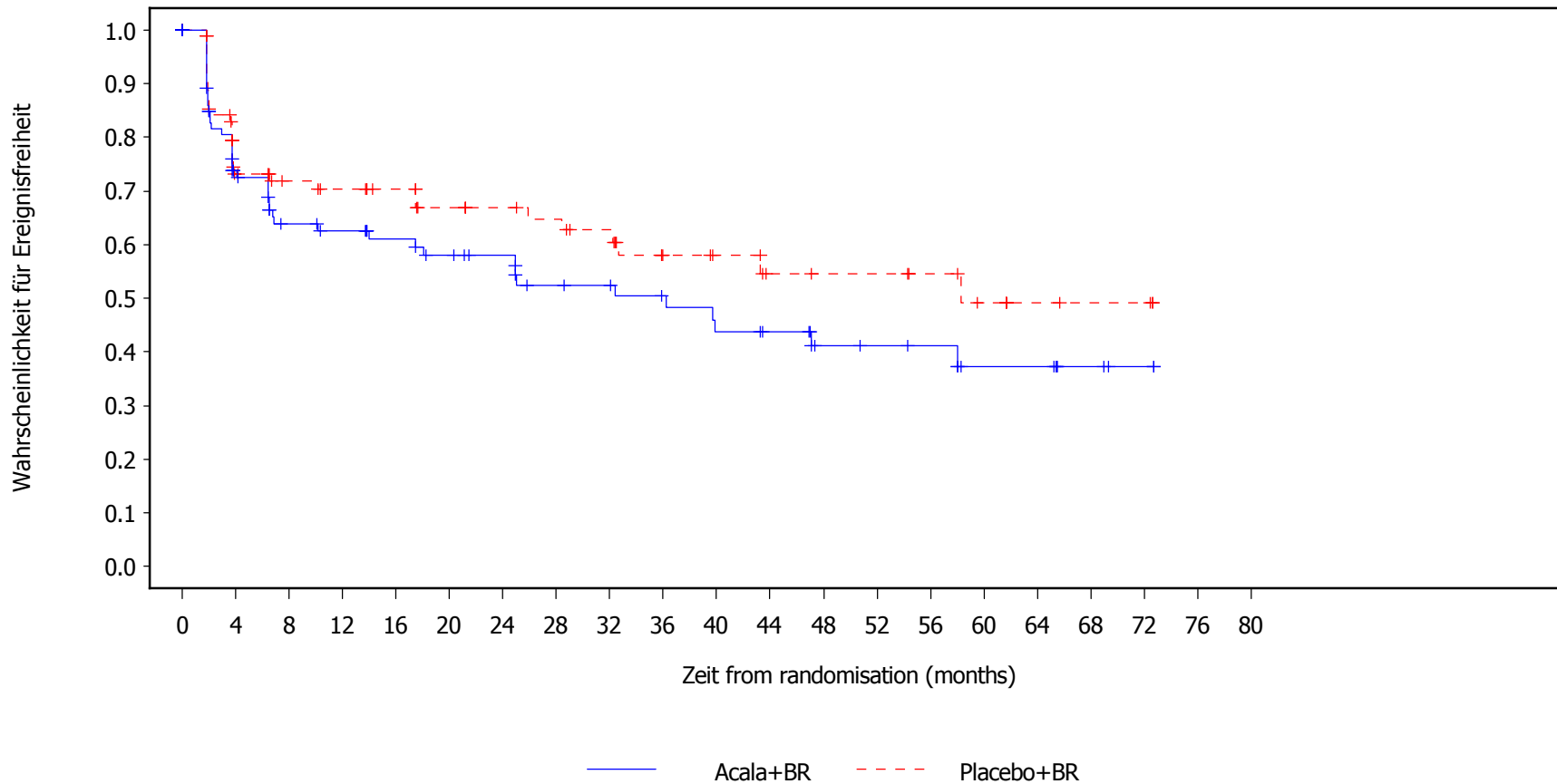
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.19 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Übelkeit und Erbrechen for
 Ki-67 (%) I [eCRF]<= 30%
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

109	62	49	46	40	36	33	27	26	23	20	18	13	12	11	7	7	3	1	0	0	Acala+BR
103	57	50	47	43	37	33	31	28	20	18	14	13	13	11	8	3	2	2	0	0	Placebo+BR

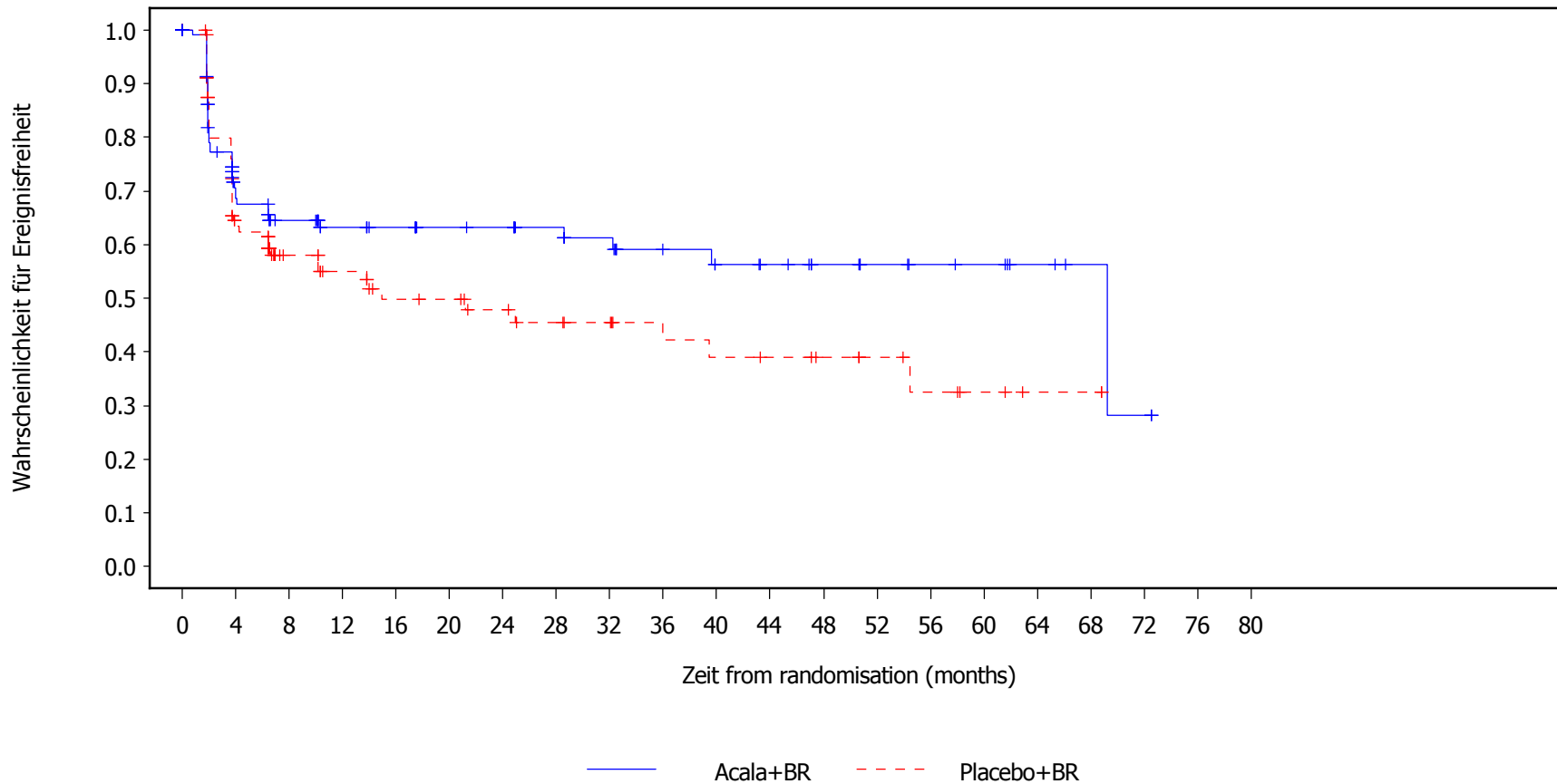
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.20 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Übelkeit und Erbrechen for
 Ki-67 (%) I [eCRF]>= 30%
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

128	68	57	48	44	38	37	32	28	22	19	17	13	10	8	7	4	2	1	0	0	Acala+BR
127	63	41	34	27	26	22	19	17	13	12	11	9	7	5	3	1	1	0	0	0	Placebo+BR

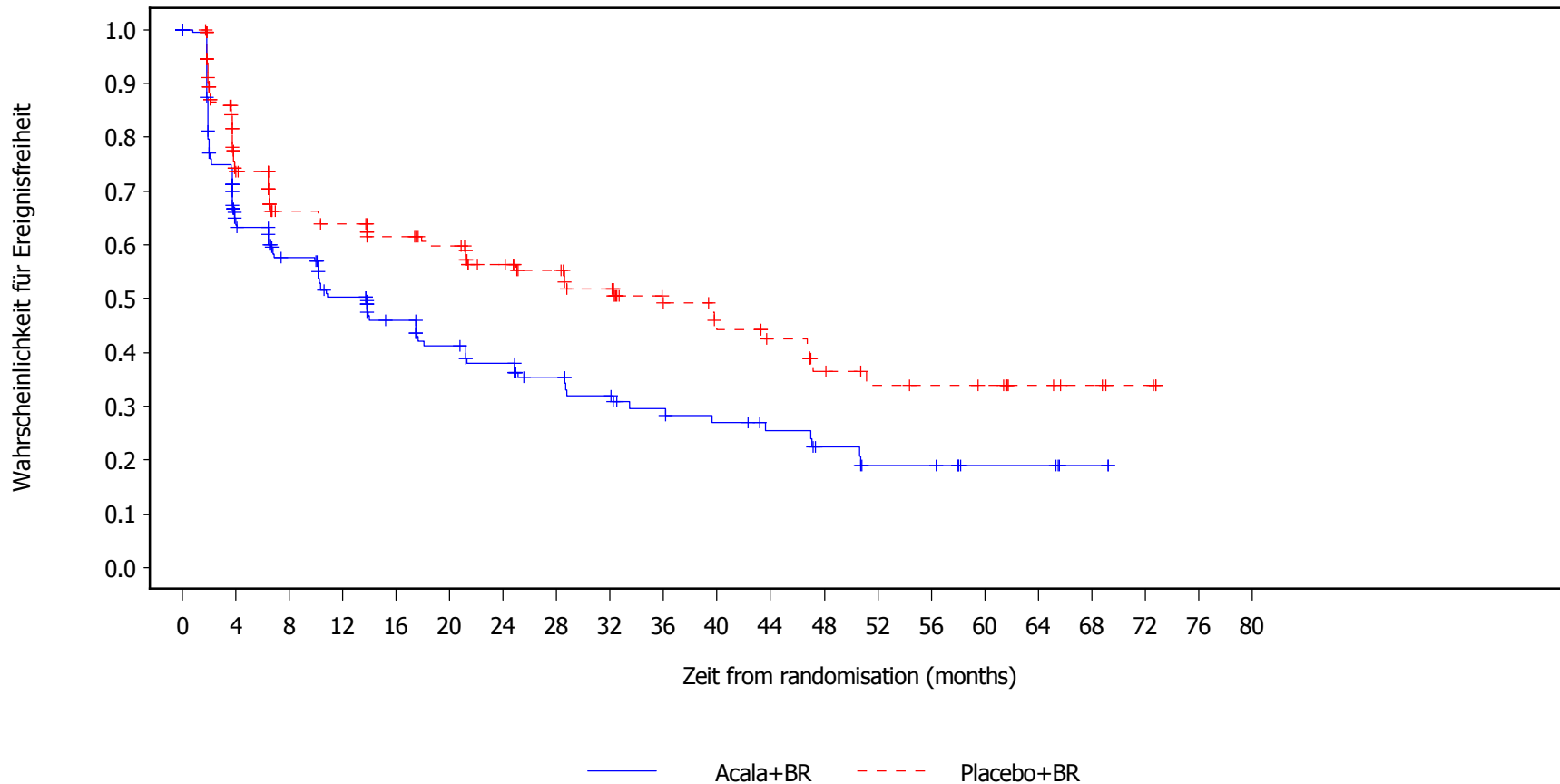
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.21 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Schmerzen for Altersgruppe II
 [eCRF]<= 75 Jahre
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

215	107	90	75	61	52	46	35	28	23	20	17	13	9	9	4	4	1	0	0	0	Acala+BR
222	116	88	84	76	71	58	51	44	32	27	23	16	13	12	11	6	4	2	0	0	Placebo+BR

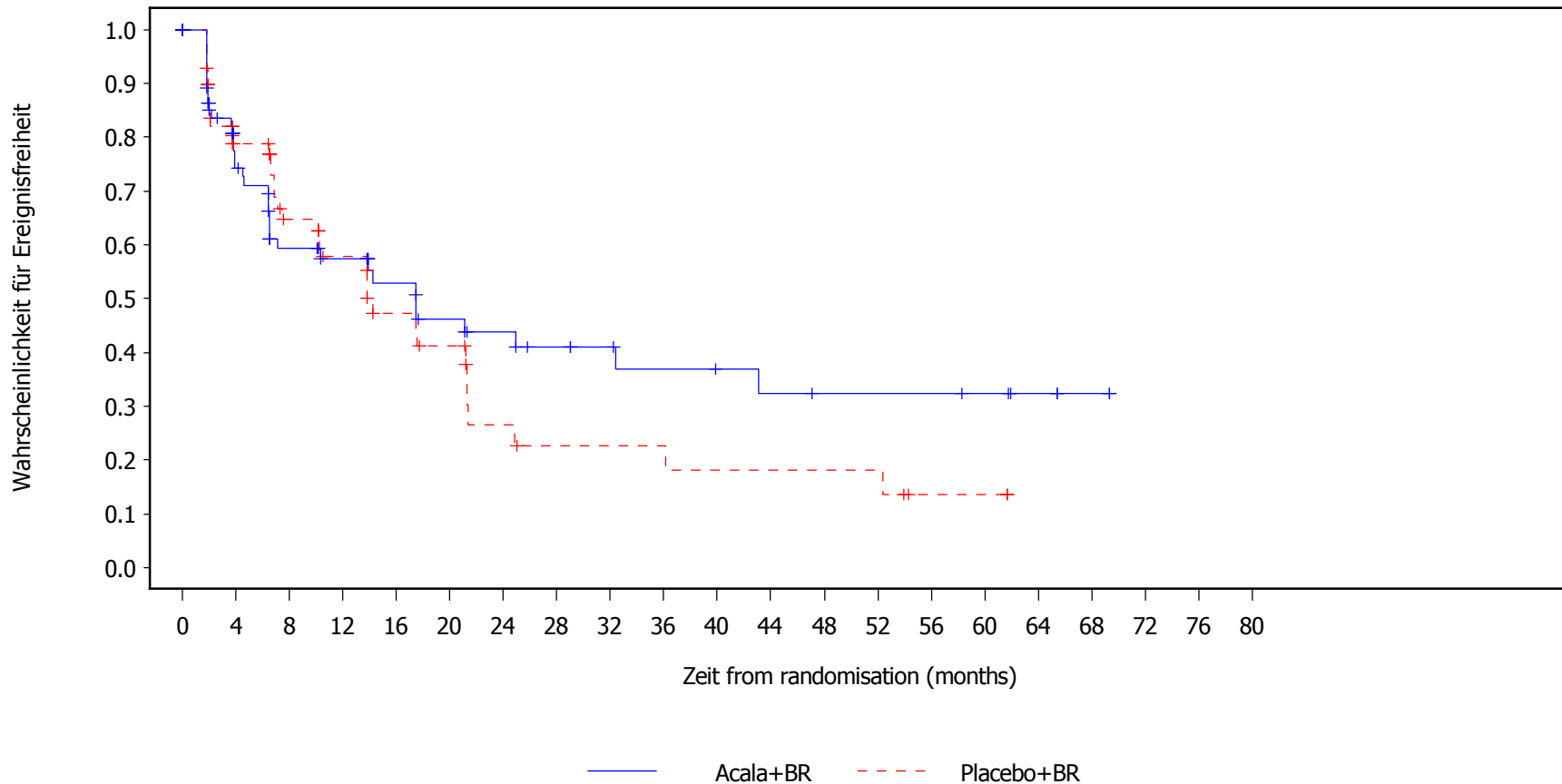
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.22 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Schmerzen for Altersgruppe II
 [eCRF]>= 75 Jahre
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

84	47	33	29	24	19	16	13	11	9	8	7	6	6	6	5	3	1	0	0	0	0	Acala+BR
77	45	30	23	16	13	7	5	5	5	4	4	4	4	1	1	0	0	0	0	0	0	Placebo+BR

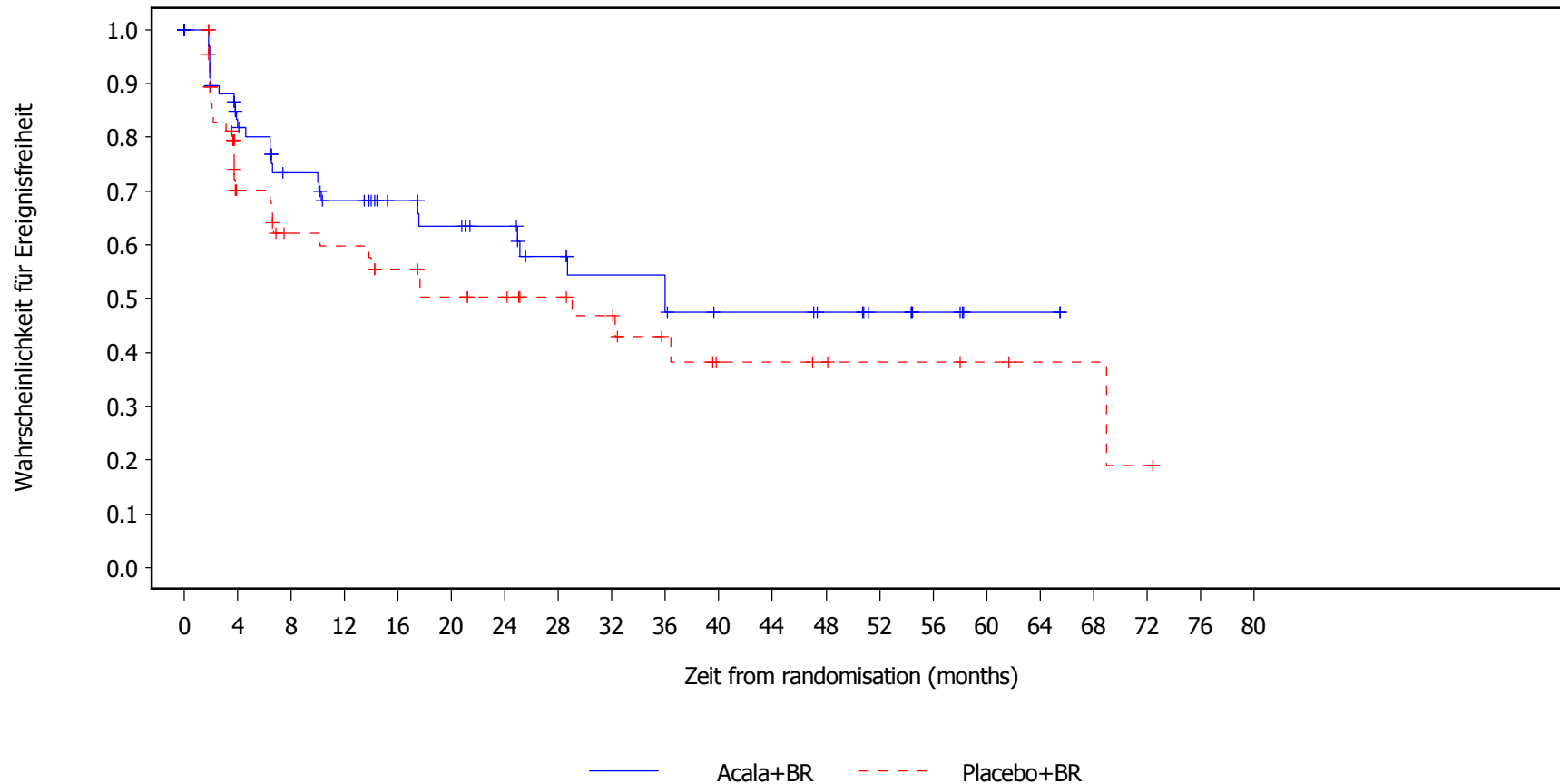
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.23 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Schlaflosigkeit for Geographic Region [IXRS]=Nordamerika
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

82	51	42	37	30	27	24	19	16	15	12	12	10	7	4	1	1	0	0	0	0	Acala+BR
83	35	28	27	23	20	18	15	13	9	6	6	5	4	4	3	2	2	1	0	0	Placebo+BR

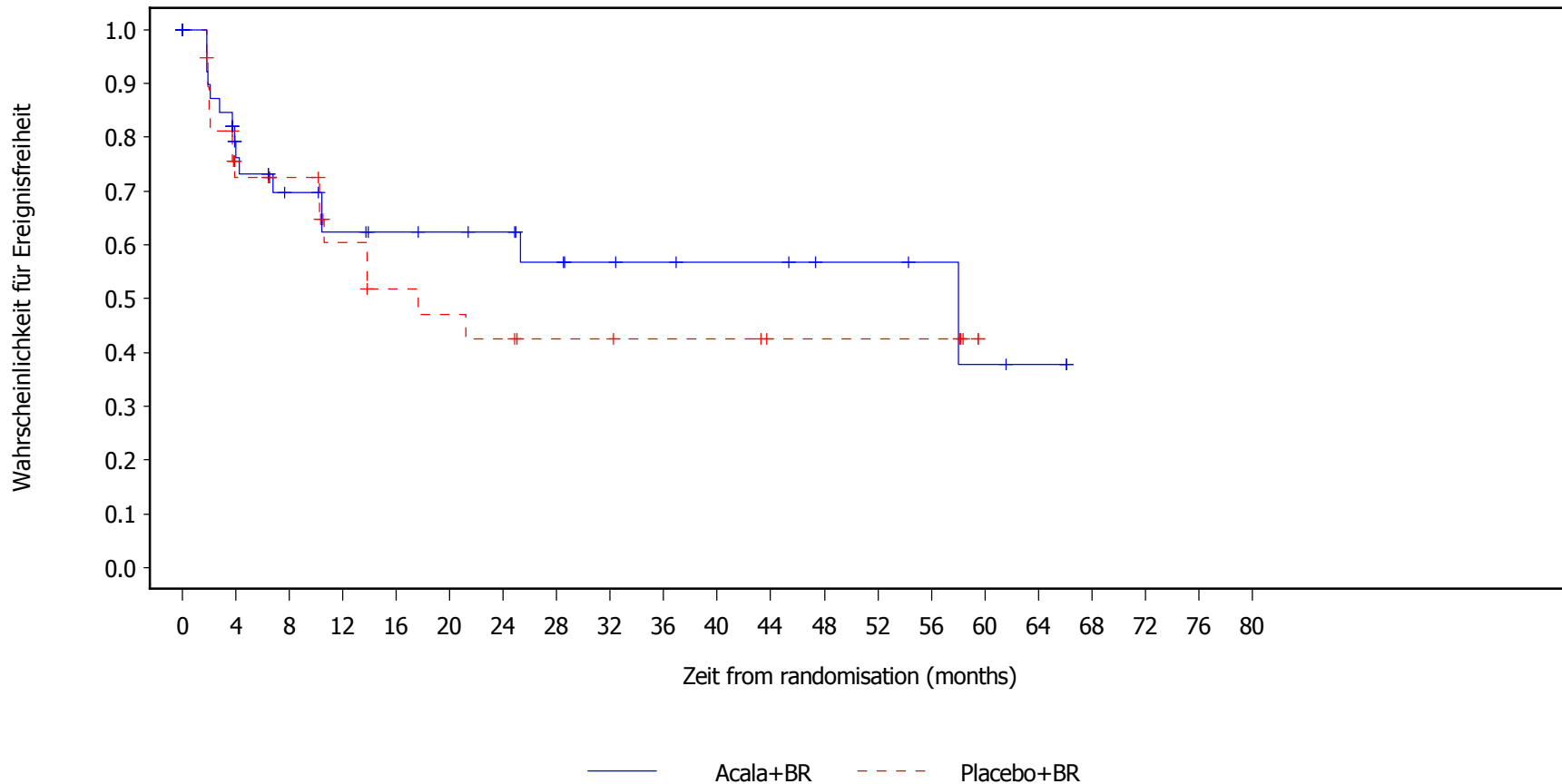
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.24 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Schlaflosigkeit for Geographic Region [IXRS]=Westeuropa
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

46	25	20	17	15	14	13	10	8	7	6	6	4	4	3	2	1	0	0	0	0	Acala+BR
46	23	20	14	11	10	9	7	7	6	6	4	4	4	4	0	0	0	0	0	0	Placebo+BR

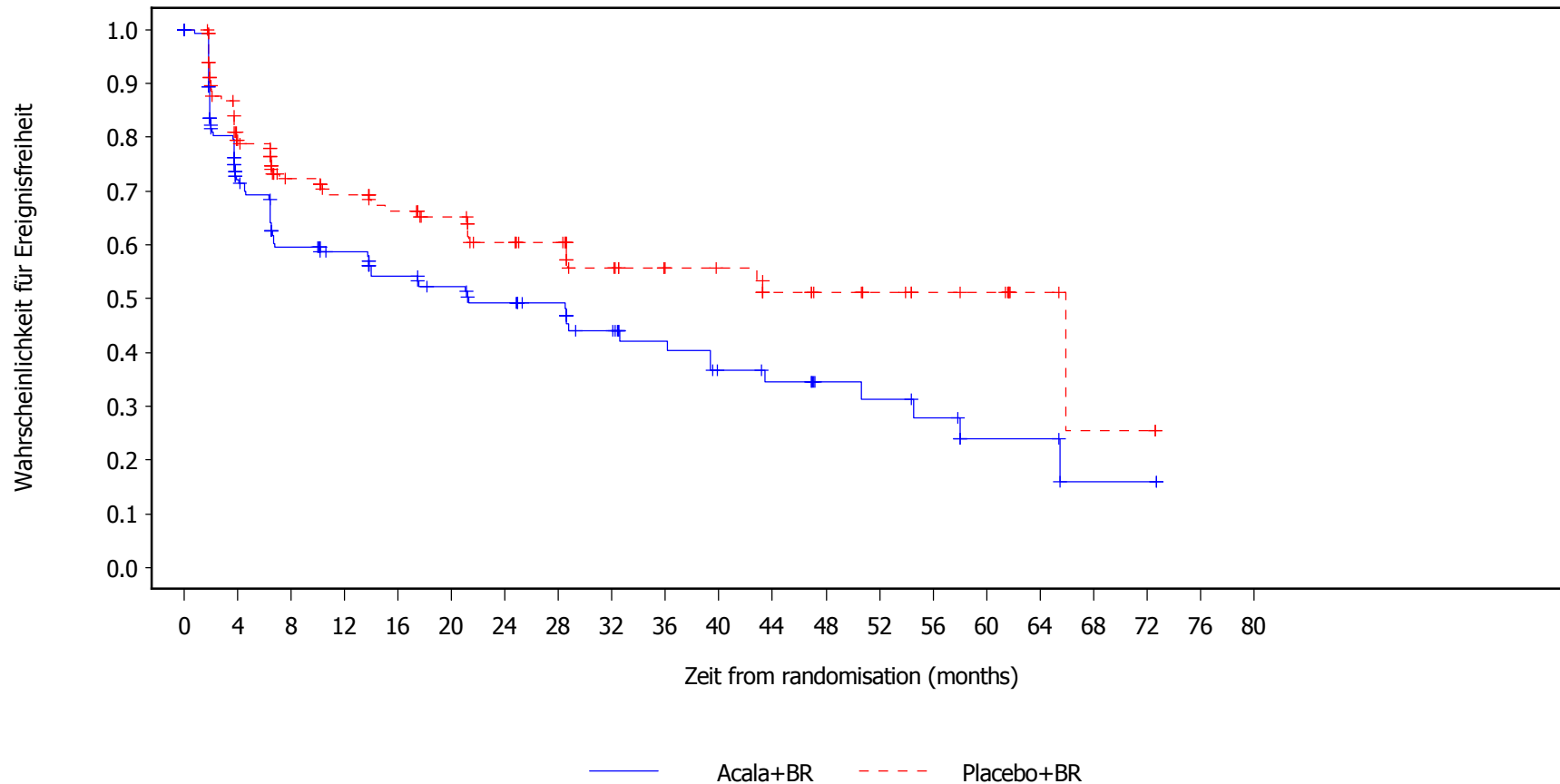
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.25 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Schlaflosigkeit for Geographic
 Region [IXRS]=Andere
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

171	100	77	69	58	53	48	40	30	23	18	16	11	10	8	4	4	1	1	0	0	Acala+BR
170	105	80	71	63	57	48	44	33	26	25	19	16	13	10	9	3	1	1	0	0	Placebo+BR

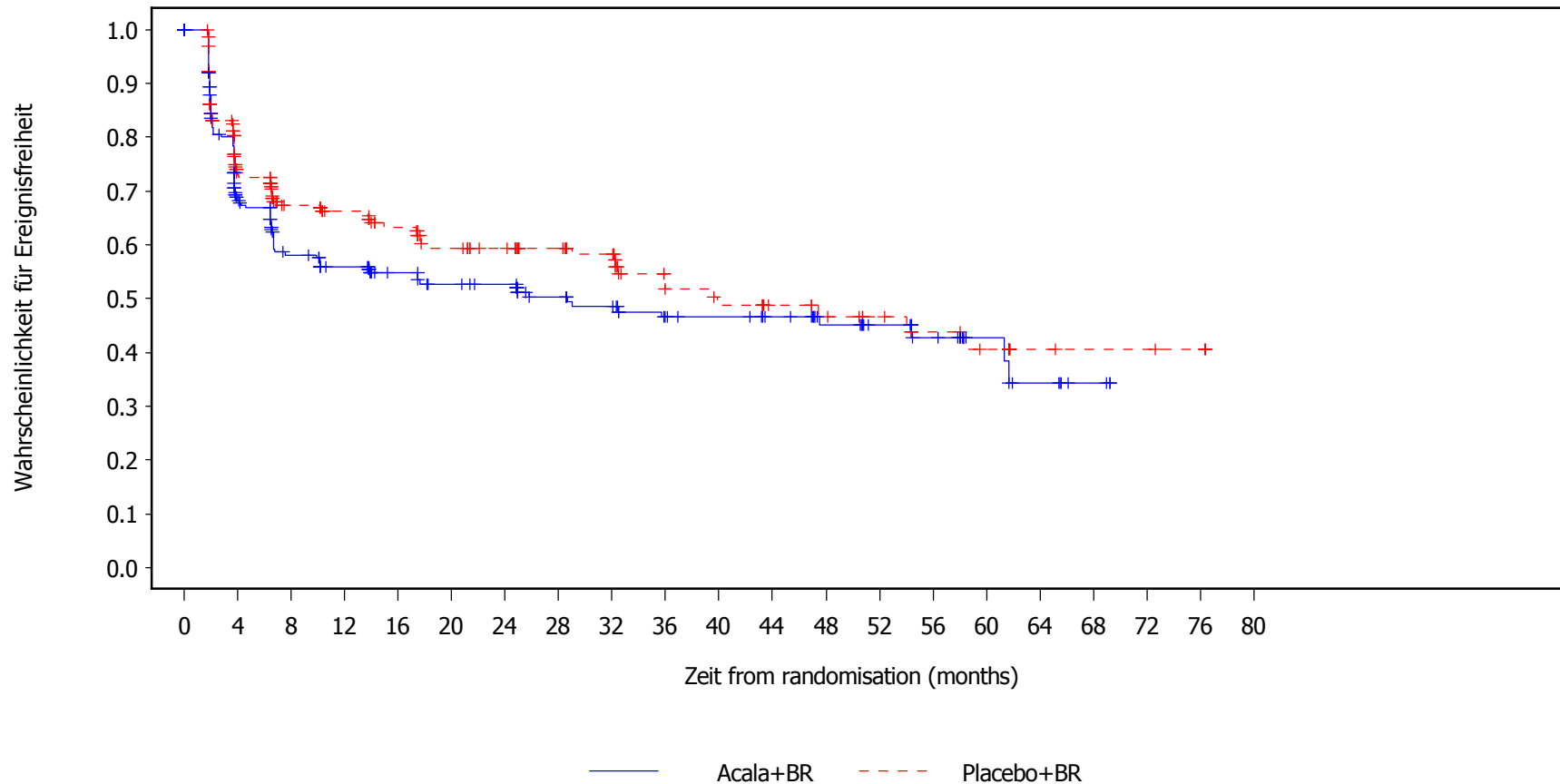
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.26 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Appetitverlust for Extranodale Erkrankung [eCRF]=Ja
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

264	142	111	98	81	74	71	58	53	44	42	38	30	24	18	10	6	2	0	0	0	Acala+BR
277	144	111	97	85	73	66	58	52	35	32	25	22	18	14	11	4	3	3	2	0	Placebo+BR

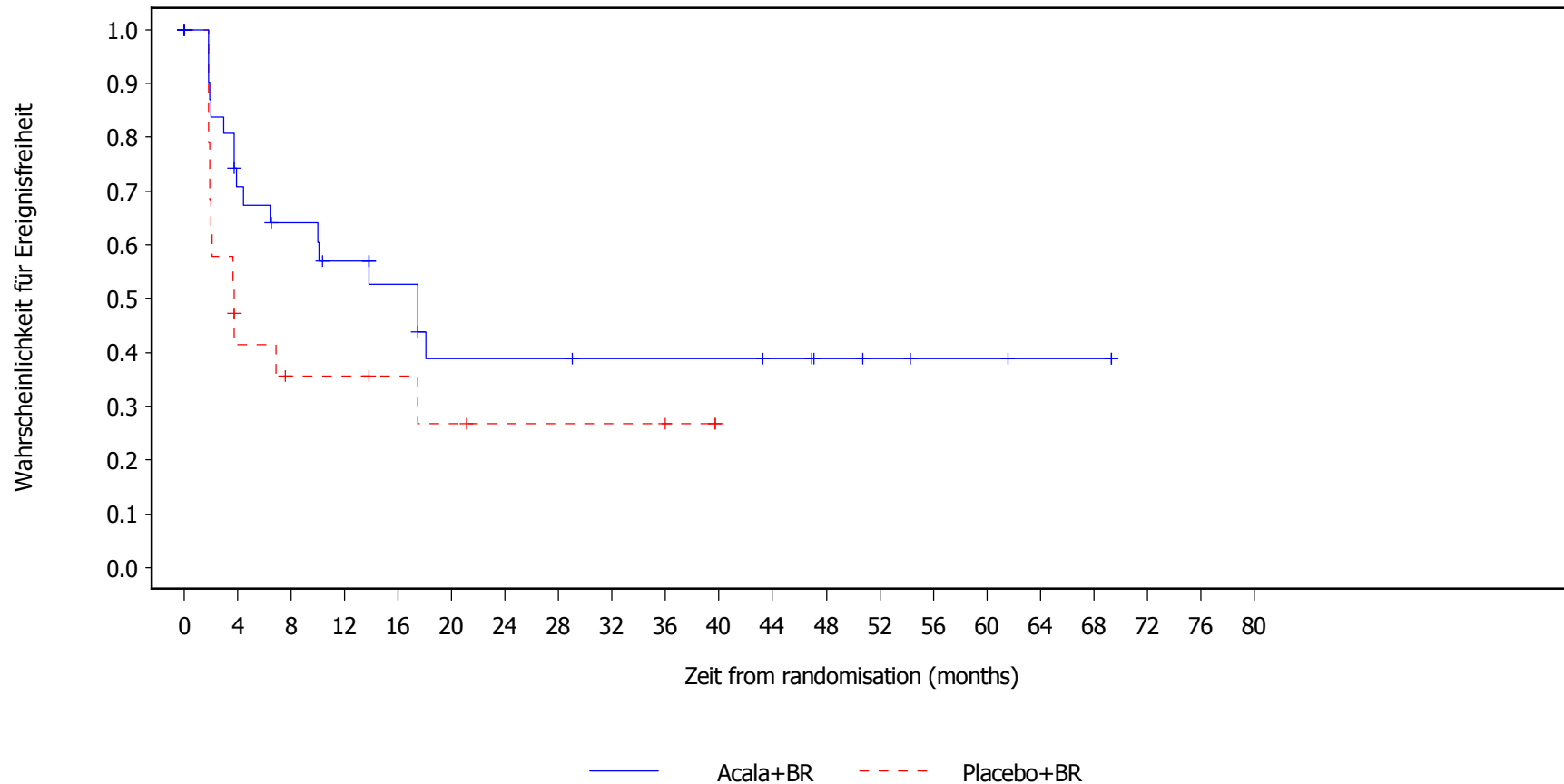
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.27 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Appetitverlust for Extranodale
 Erkrankung [eCRF]=Nein
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

35	21	18	15	12	8	8	8	7	7	7	6	4	3	2	2	1	1	0	0	0	Acala+BR
22	7	5	5	4	3	2	2	2	1	0	0	0	0	0	0	0	0	0	0	0	Placebo+BR

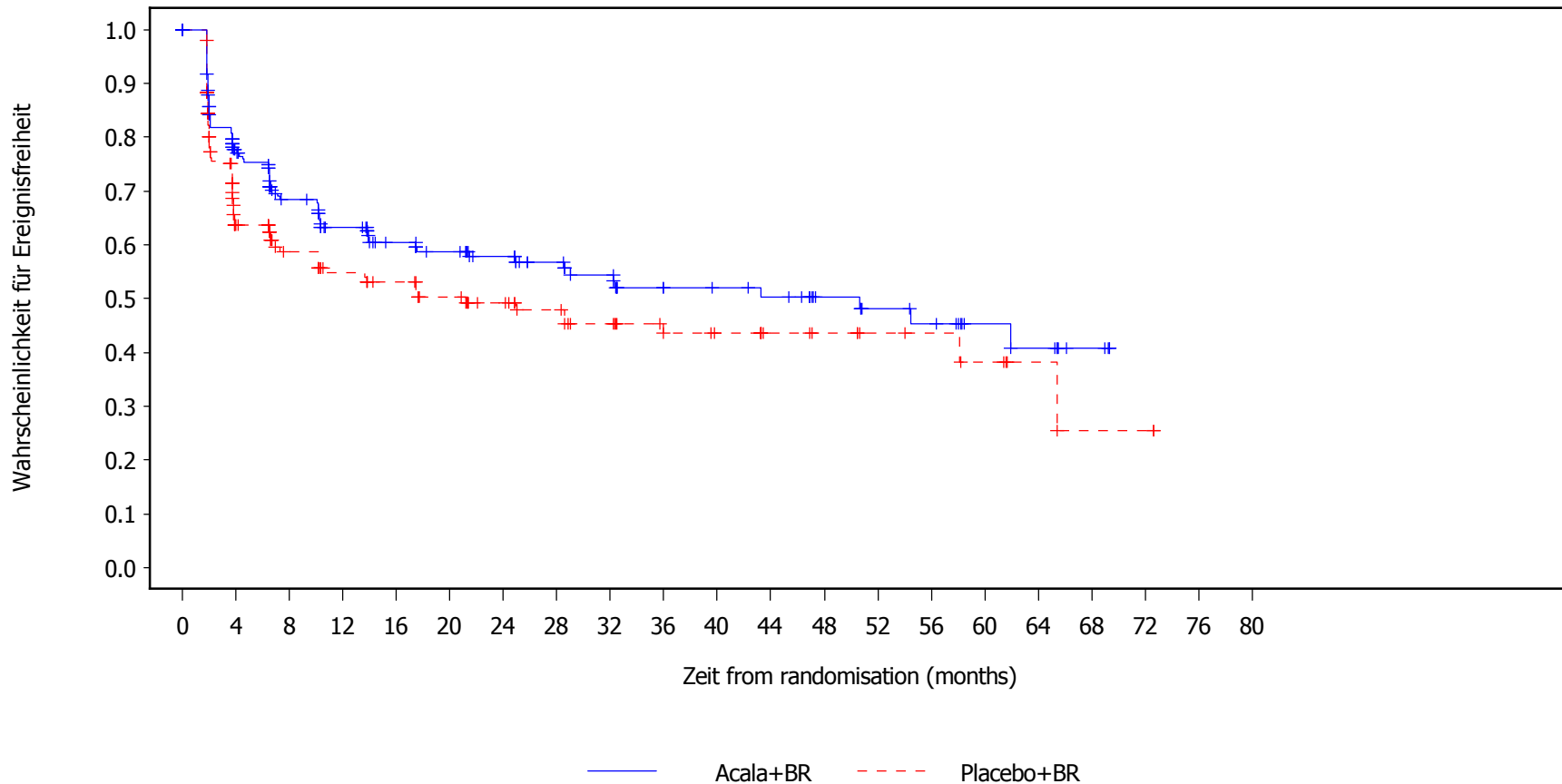
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.28 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Verstopfung for Abstammung [eCRF]=Weiß
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

233	141	110	93	77	69	61	52	45	34	33	31	22	18	16	10	8	3	0	0	0	Acala+BR
235	100	77	65	58	50	43	37	31	25	22	14	12	9	8	6	3	1	1	0	0	Placebo+BR

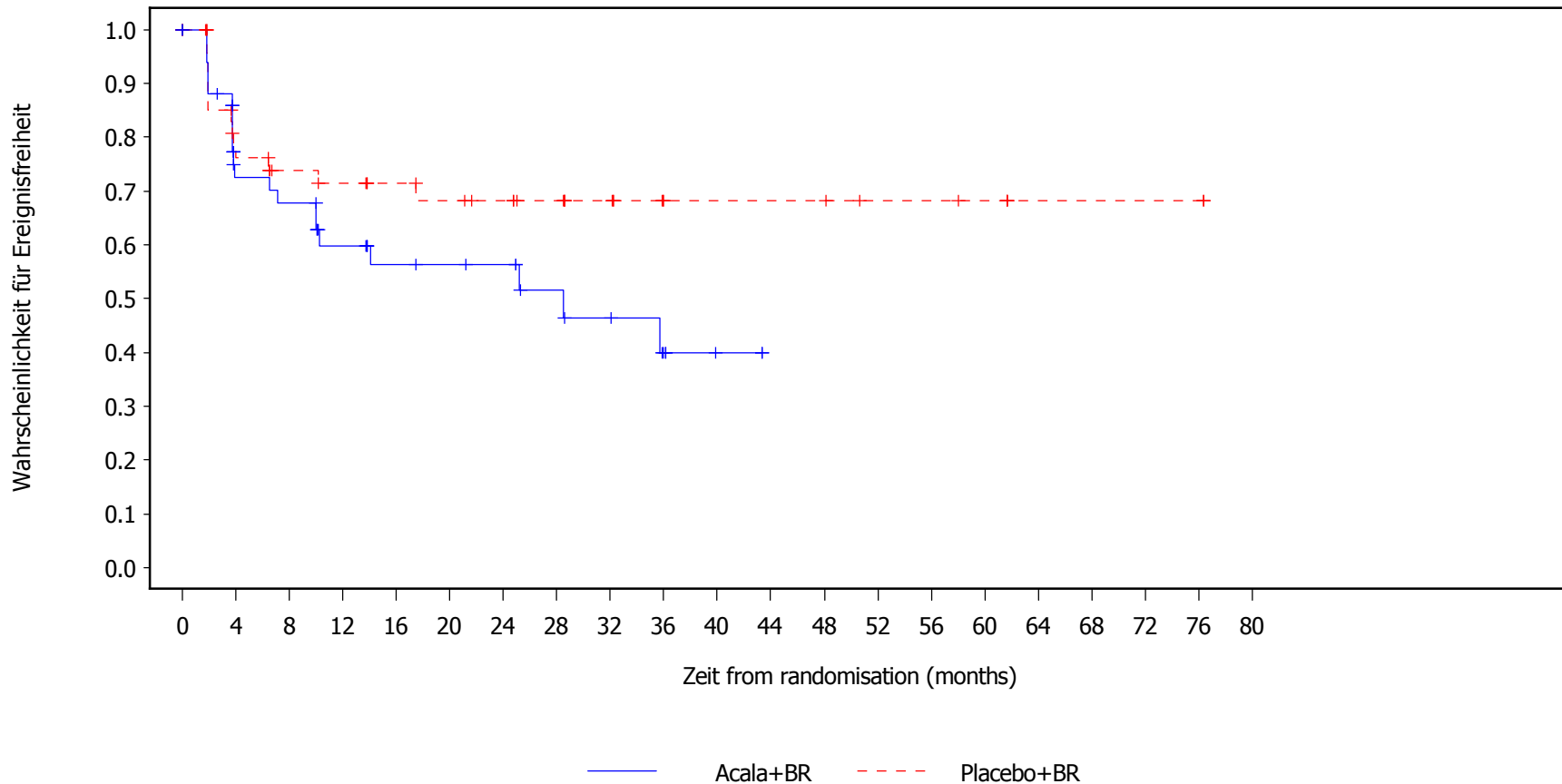
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.29 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Verstopfung for Abstammung [eCRF]=Nicht-weiß
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

52	30	28	21	16	15	14	10	8	4	1	0	0	0	0	0	0	0	0	0	Acala+BR	
53	34	29	27	24	22	20	17	13	7	7	7	7	5	5	4	1	1	1	1	0	Placebo+BR

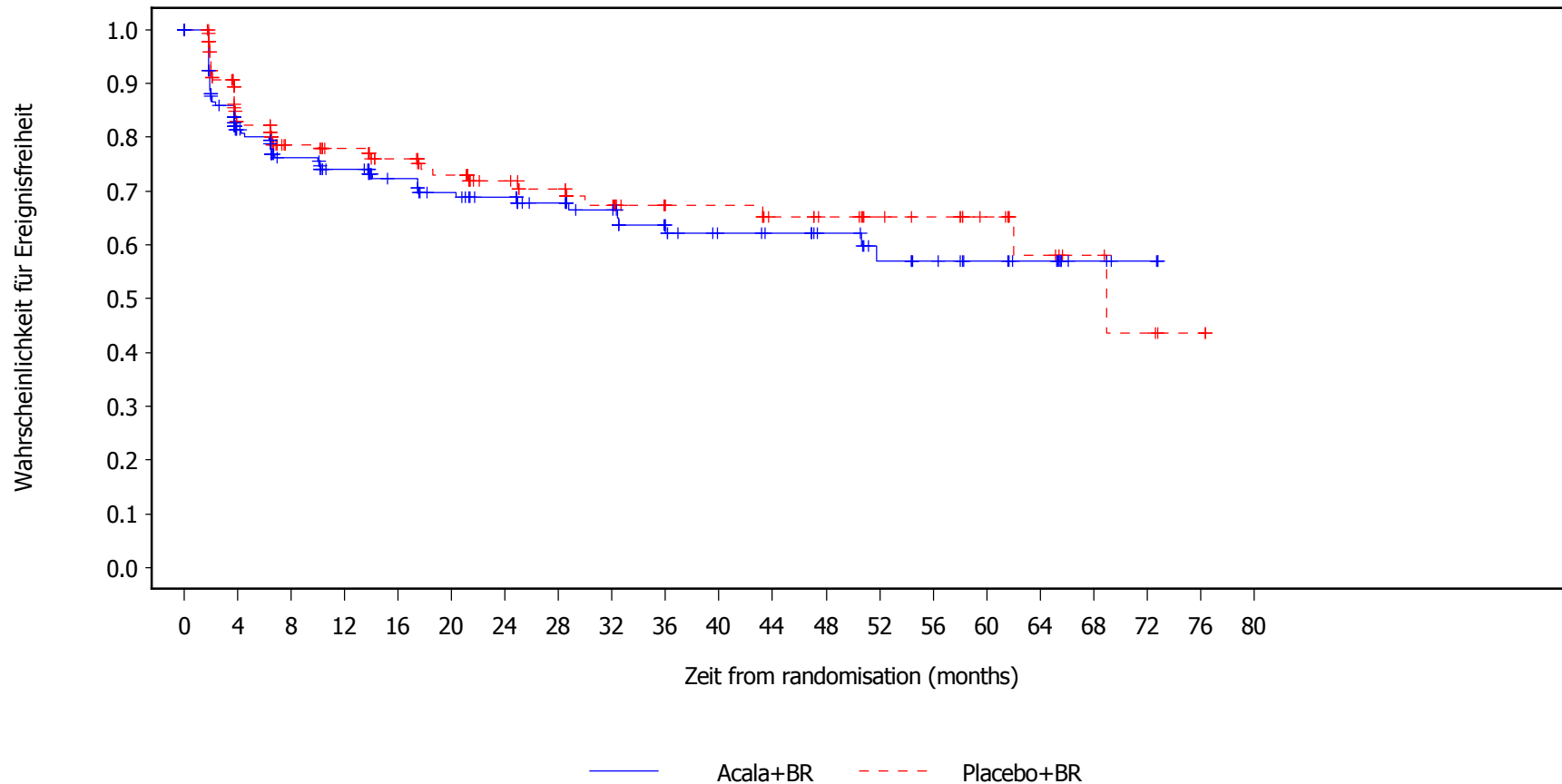
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.30 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Finanzielle Schwierigkeiten for
 Geschlecht [eCRF]=Männlich
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

214	129	109	98	83	75	69	57	50	40	34	32	27	21	18	14	11	4	2	0	0	Acala+BR
209	124	99	91	78	70	56	50	42	32	32	27	24	20	18	13	8	5	3	1	0	Placebo+BR

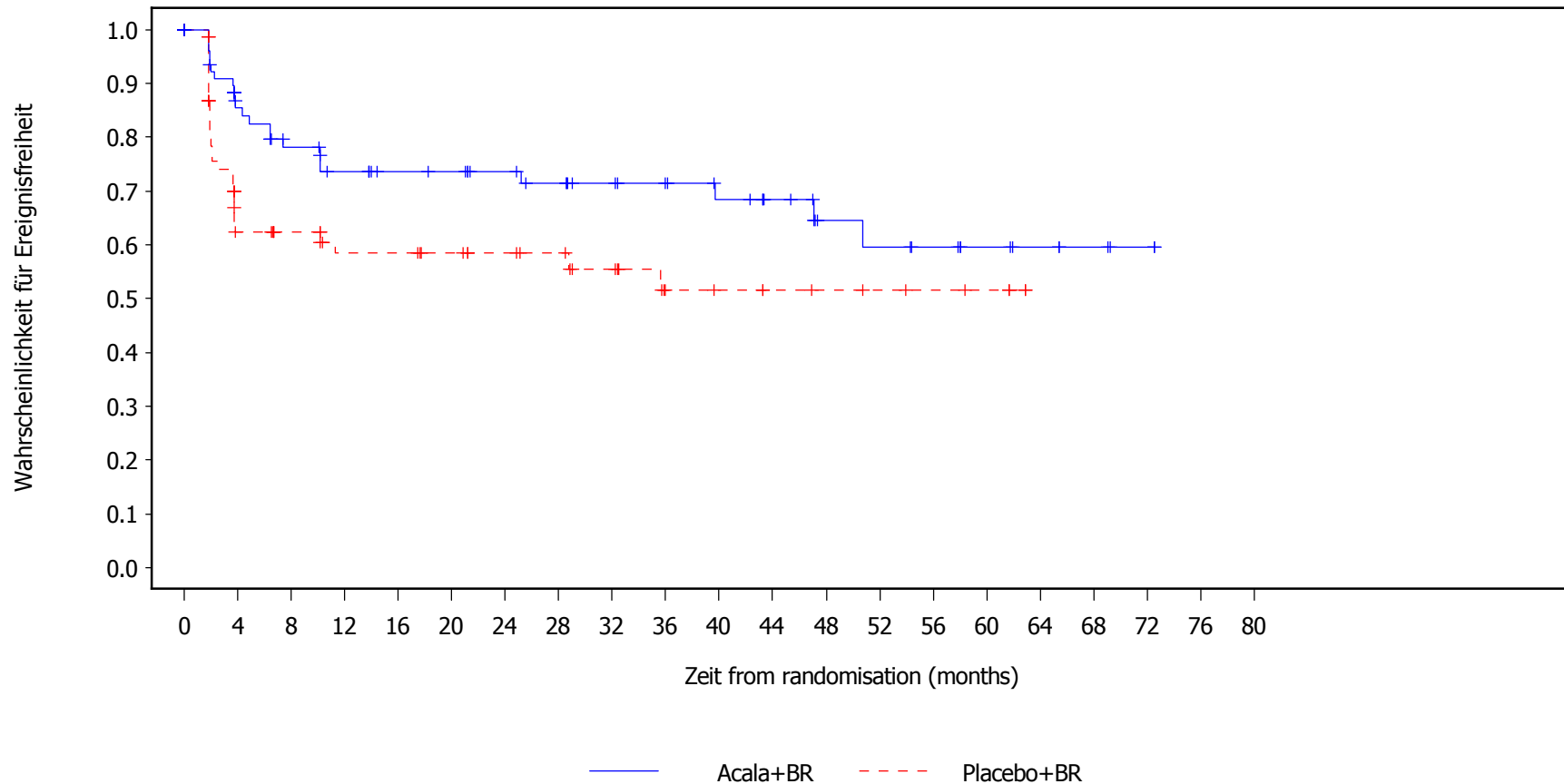
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.31 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Finanzielle Schwierigkeiten for
 Geschlecht [eCRF]=Weiblich
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

85	60	52	46	41	40	36	33	29	26	23	19	13	12	10	7	5	3	1	0	0	Acala+BR
90	40	35	29	29	26	23	21	17	10	9	7	6	5	4	3	0	0	0	0	0	Placebo+BR

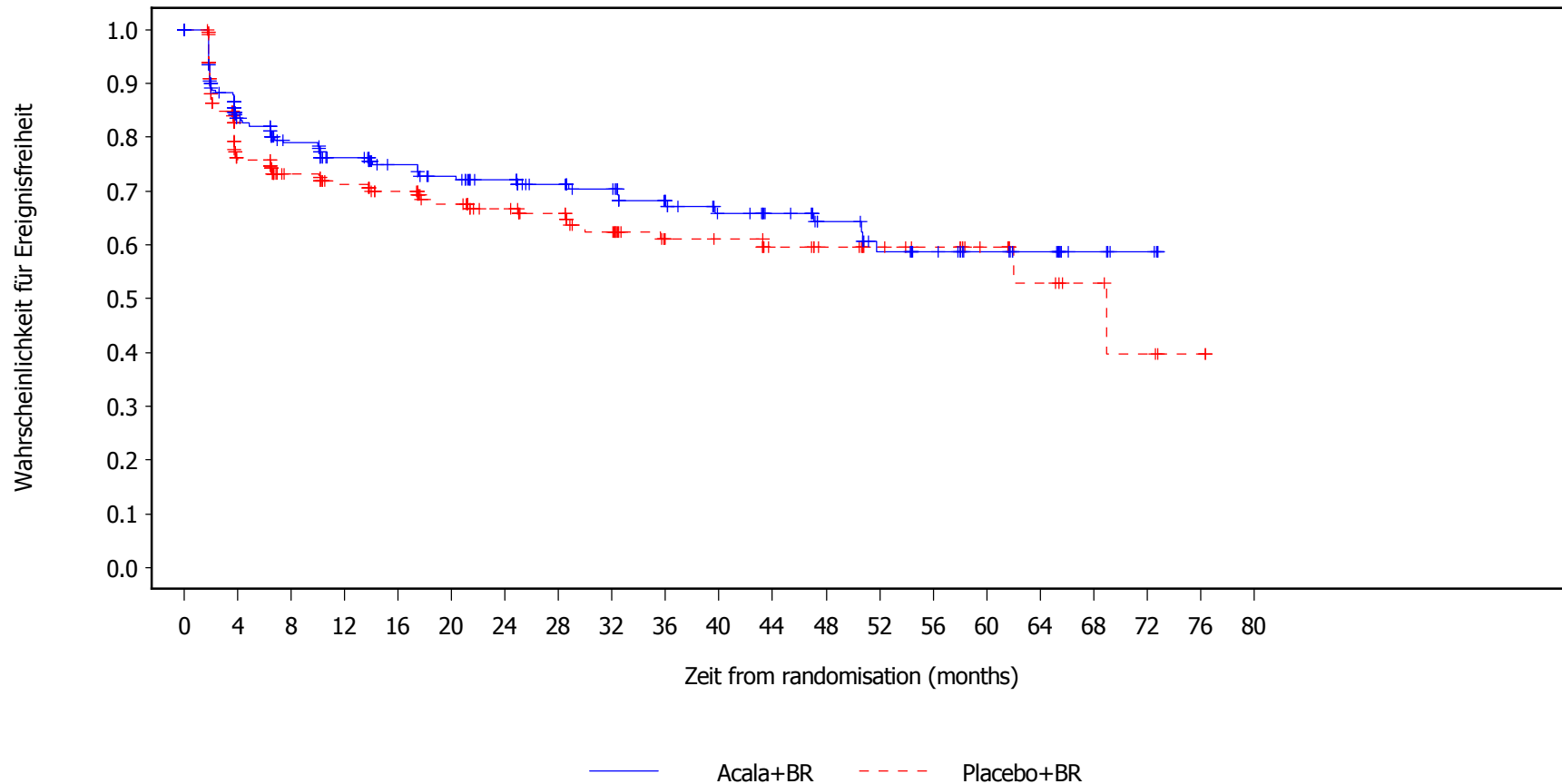
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.32 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Finanzielle Schwierigkeiten for Extranodale Erkrankung [eCRF]=Ja
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

264	167	144	128	110	103	94	81	72	59	51	45	37	30	25	19	15	6	3	0	0	Acala+BR
277	151	123	109	97	86	72	65	54	40	39	32	28	23	20	14	8	5	3	1	0	Placebo+BR

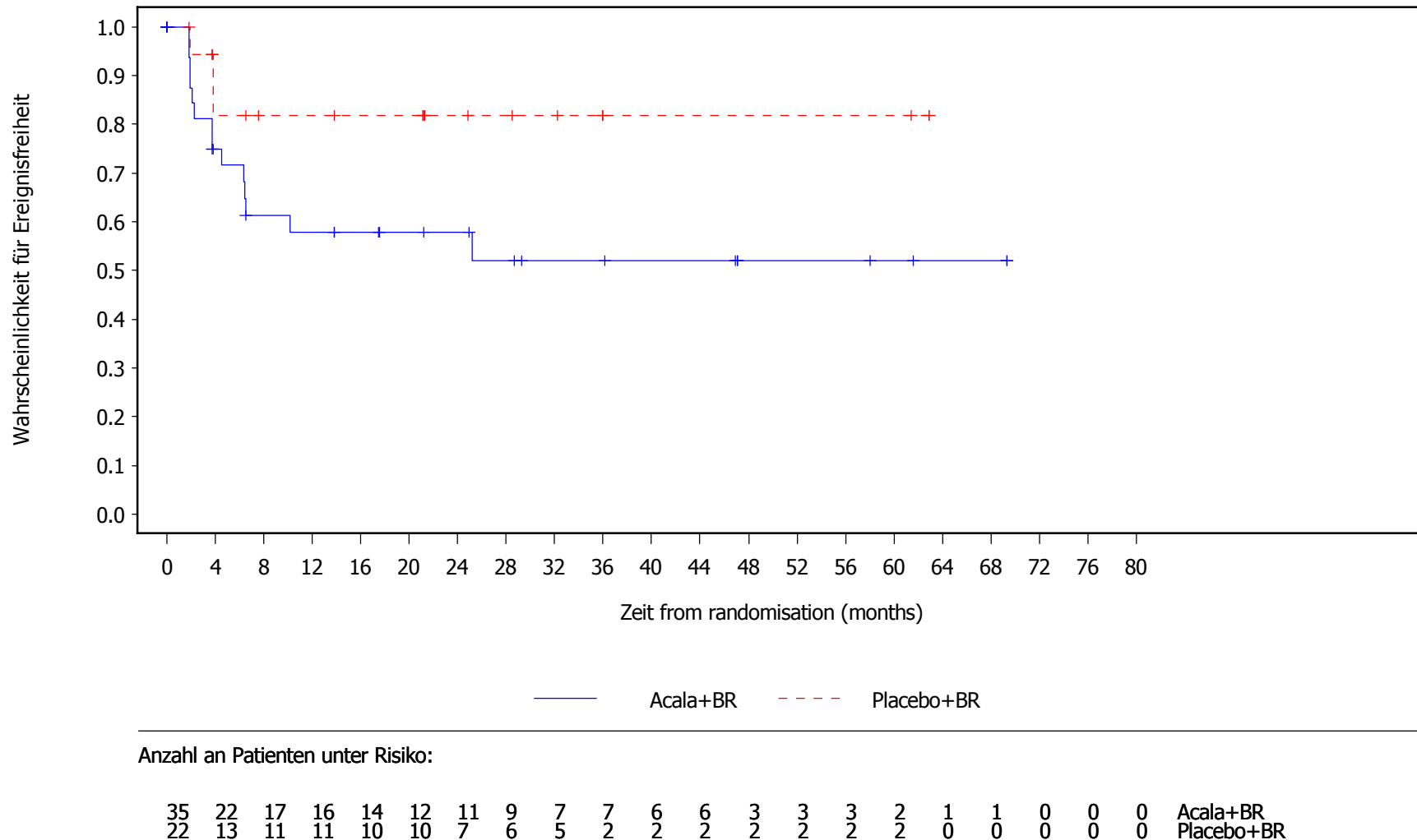
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.1.33 ECHO): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - EORTC QLQ-C30 Finanzielle Schwierigkeiten for Extranodale Erkrankung [eCRF]=Nein
 Full Analysis Set, DCO 15FEB2024



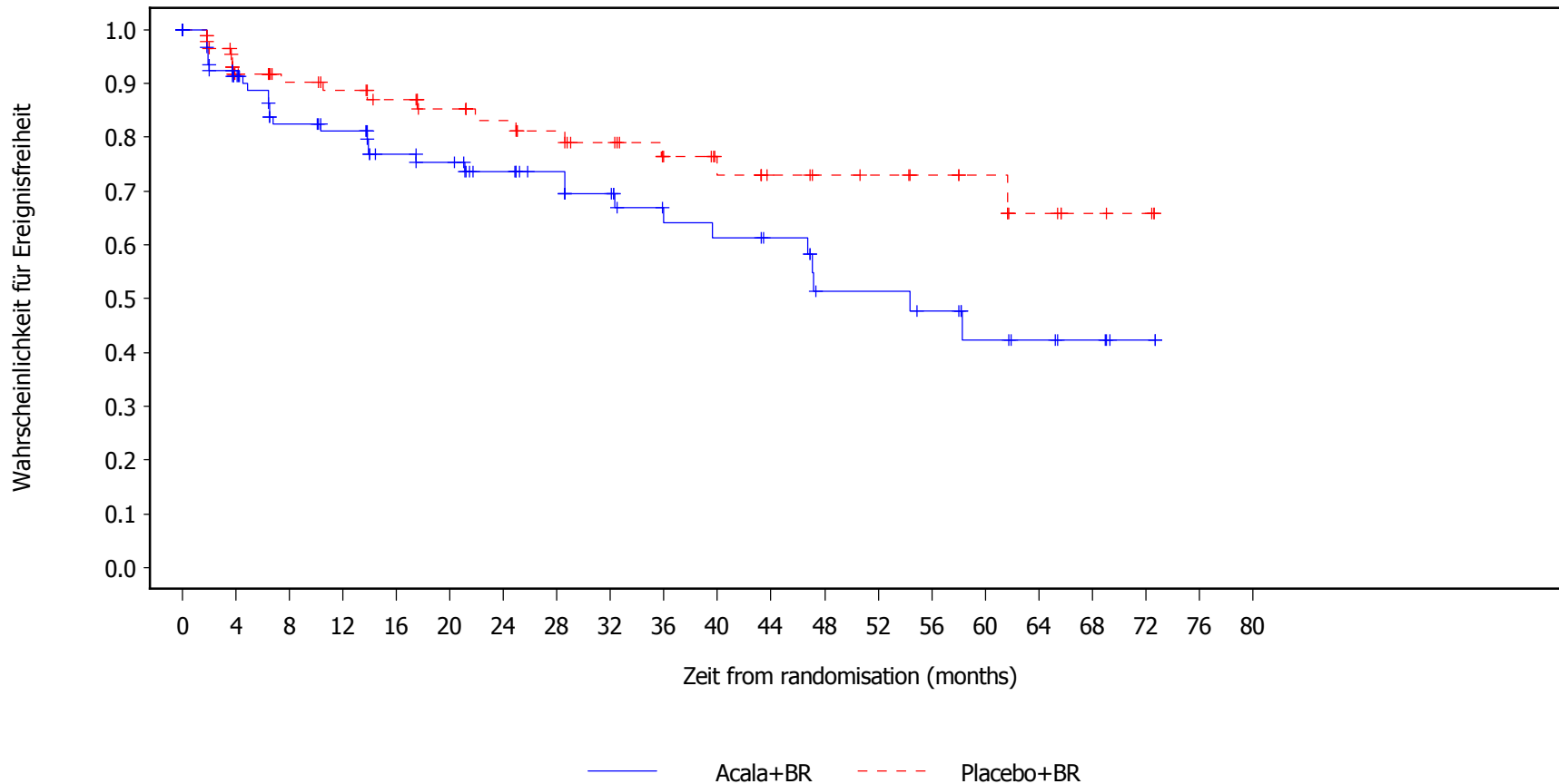
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

Nutzenbewertung nach AMNOG

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Figure 4.2.2.2.1 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - FACT-Lym Emotionales Wohlbefinden (EMB) for
 Ki-67 (%) I [eCRF]<= 30%
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

109	77	64	60	50	47	40	35	30	23	22	20	14	14	12	8	6	4	1	0	0	Acala+BR
103	70	59	56	52	47	41	37	33	26	22	17	15	14	12	10	6	3	2	0	0	Placebo+BR

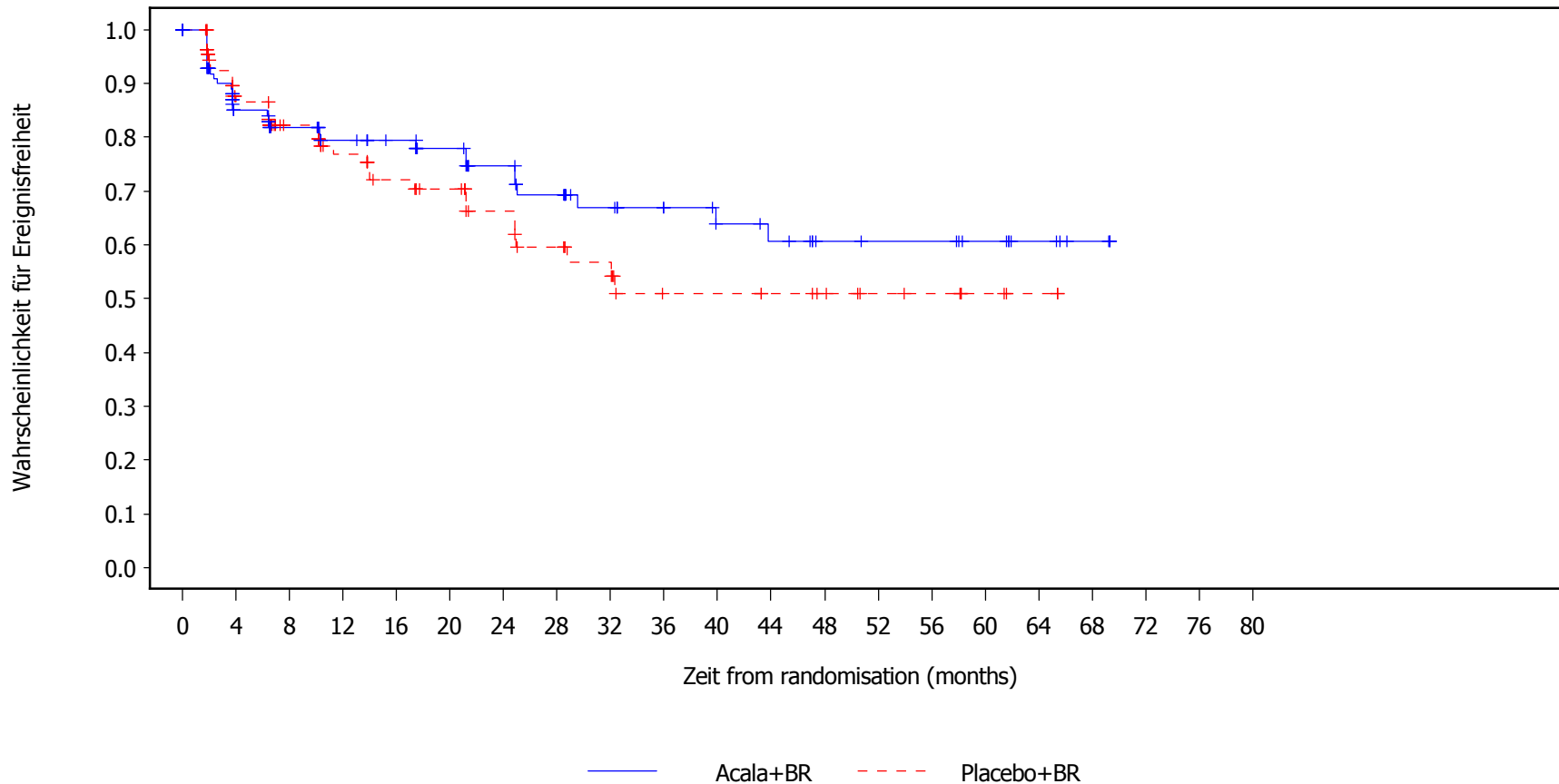
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

Nutzenbewertung nach AMNOG

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Figure 4.2.2.2.2 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - FACT-Lym Emotionales Wohlbefinden (EMB) for
 Ki-67 (%) I [eCRF]>= 30%
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

128	80	71	63	57	50	43	37	29	23	20	18	13	12	12	9	5	2	0	0	0	Acala+BR
127	84	64	52	43	38	30	25	21	14	14	12	10	7	6	3	1	0	0	0	0	Placebo+BR

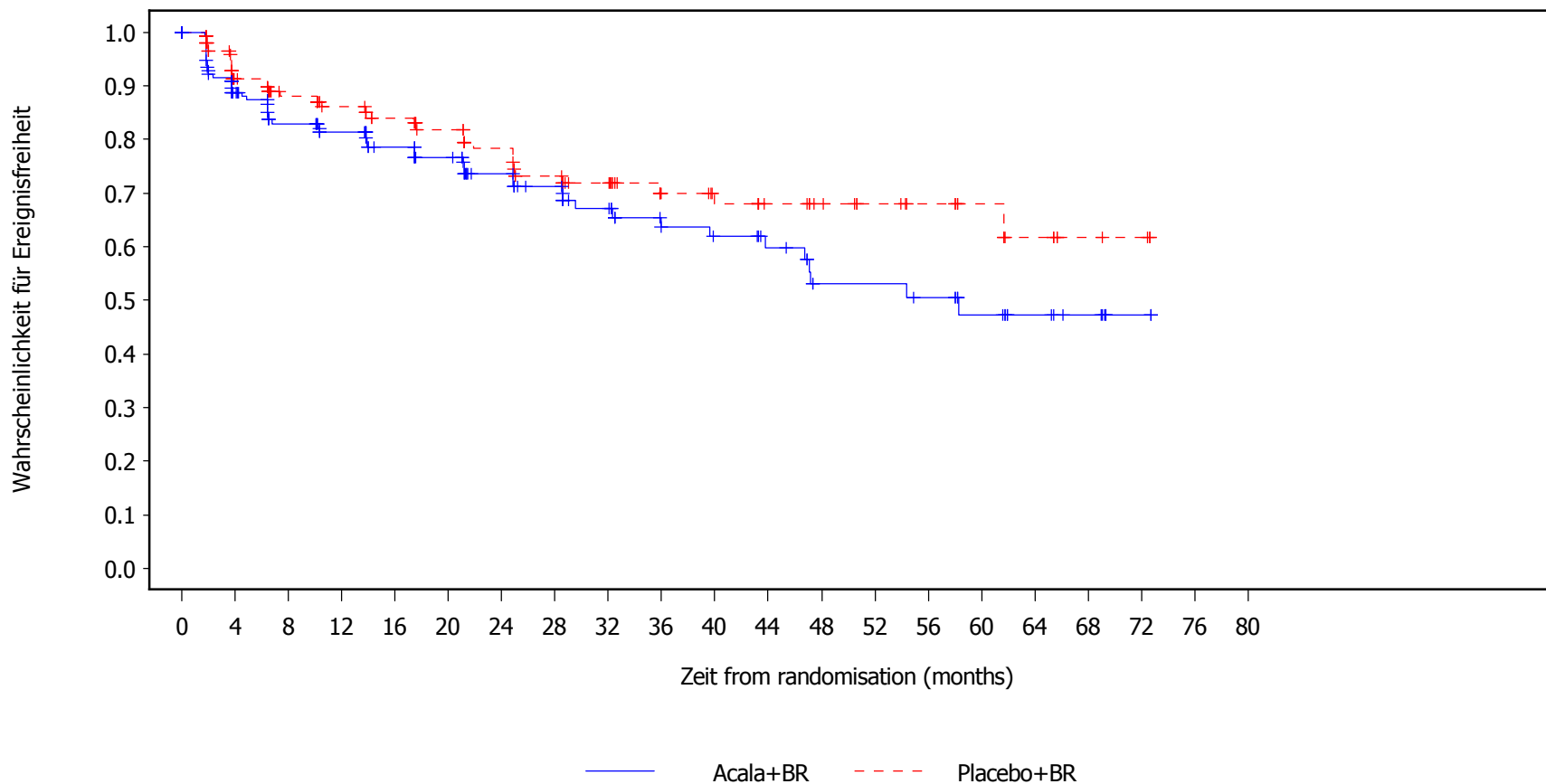
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.2.3 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - FACT-Lym Emotionales Wohlbefinden (EMB) for
 Ki-67 (%) II [eCRF]<= 50%
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

180	125	108	98	85	77	63	55	45	35	33	29	21	21	19	14	9	6	1	0	0	Acala+BR
164	116	98	87	79	72	62	54	47	36	32	26	22	18	15	11	7	3	2	0	0	Placebo+BR

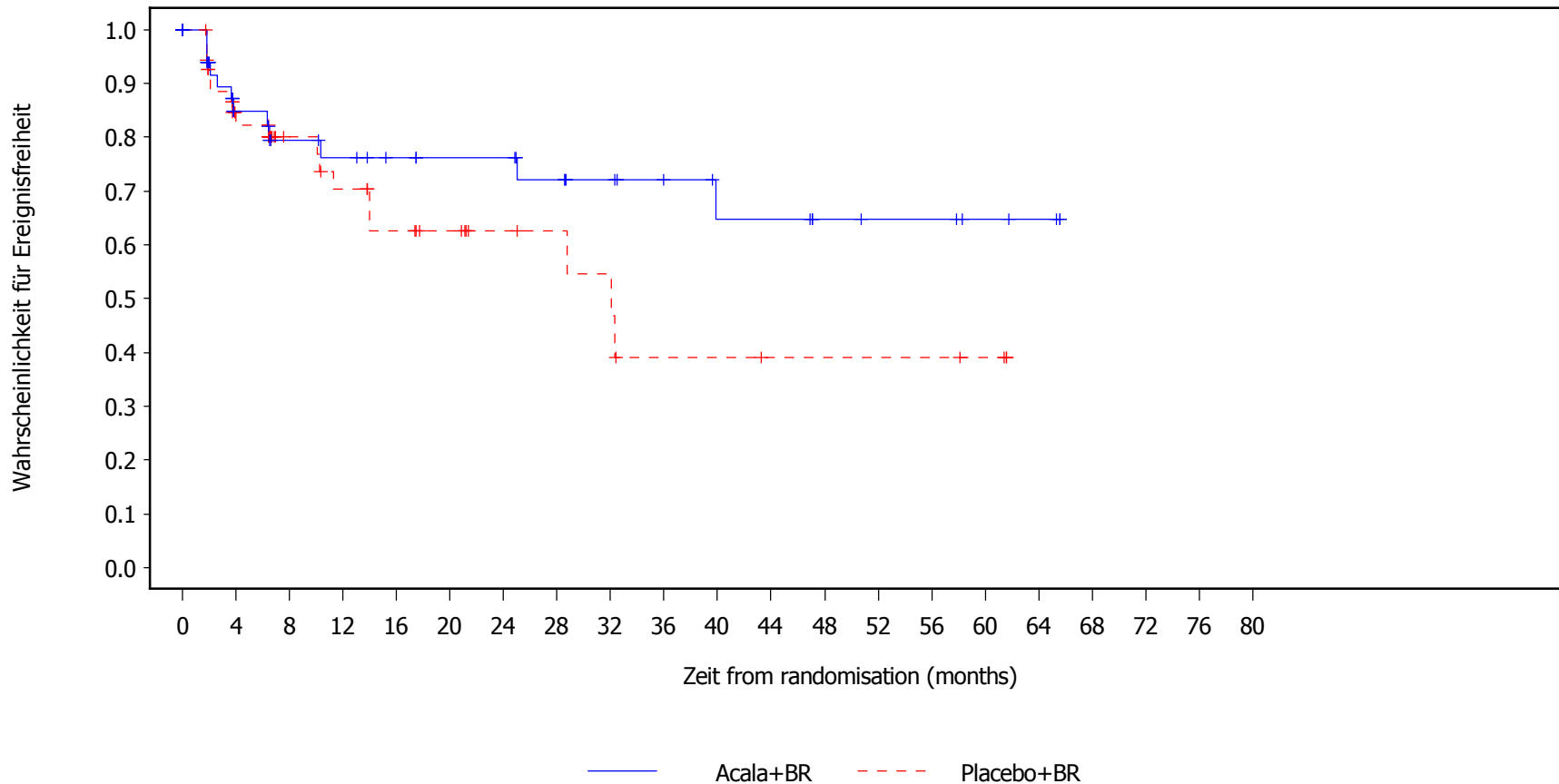
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.2.4 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - FACT-Lym Emotionales Wohlbefinden (EMB) for
 Ki-67 (%) II [eCRF]>= 50%
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

57	32	27	25	22	20	20	17	14	11	9	9	6	5	5	3	2	0	0	0	0	Acala+BR
66	38	25	21	16	13	9	8	7	4	4	3	3	3	3	2	0	0	0	0	0	Placebo+BR

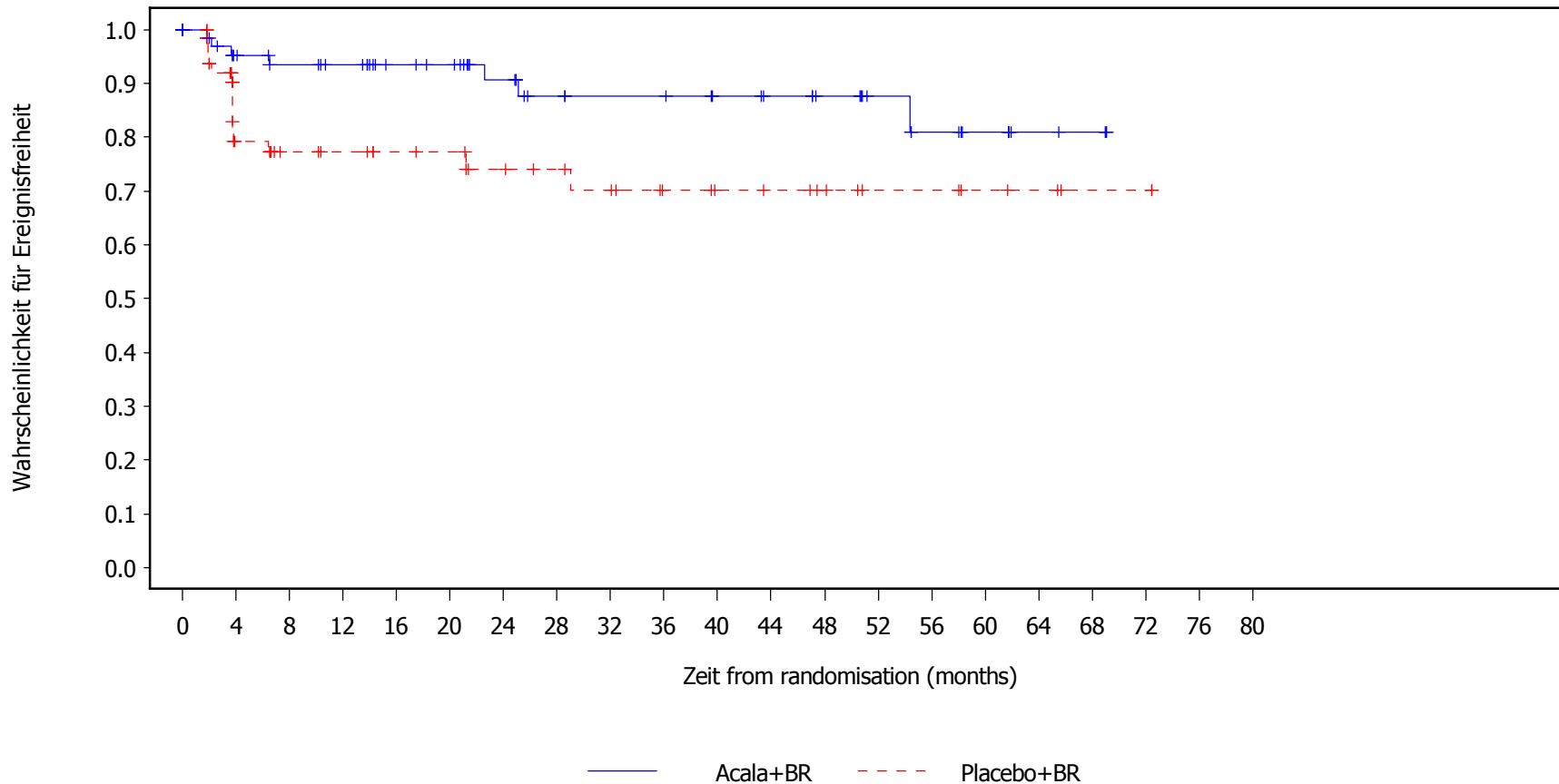
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.2.5 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - FACT-Lym Lym-Subscala (LYMS) for Geographic Region [IXRS]=Nordamerika
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

82	56	52	49	42	40	33	27	25	25	22	20	17	13	10	7	3	2	0	0	0	Acala+BR
83	40	32	30	27	26	22	20	18	14	12	11	9	6	6	4	3	1	1	0	0	Placebo+BR

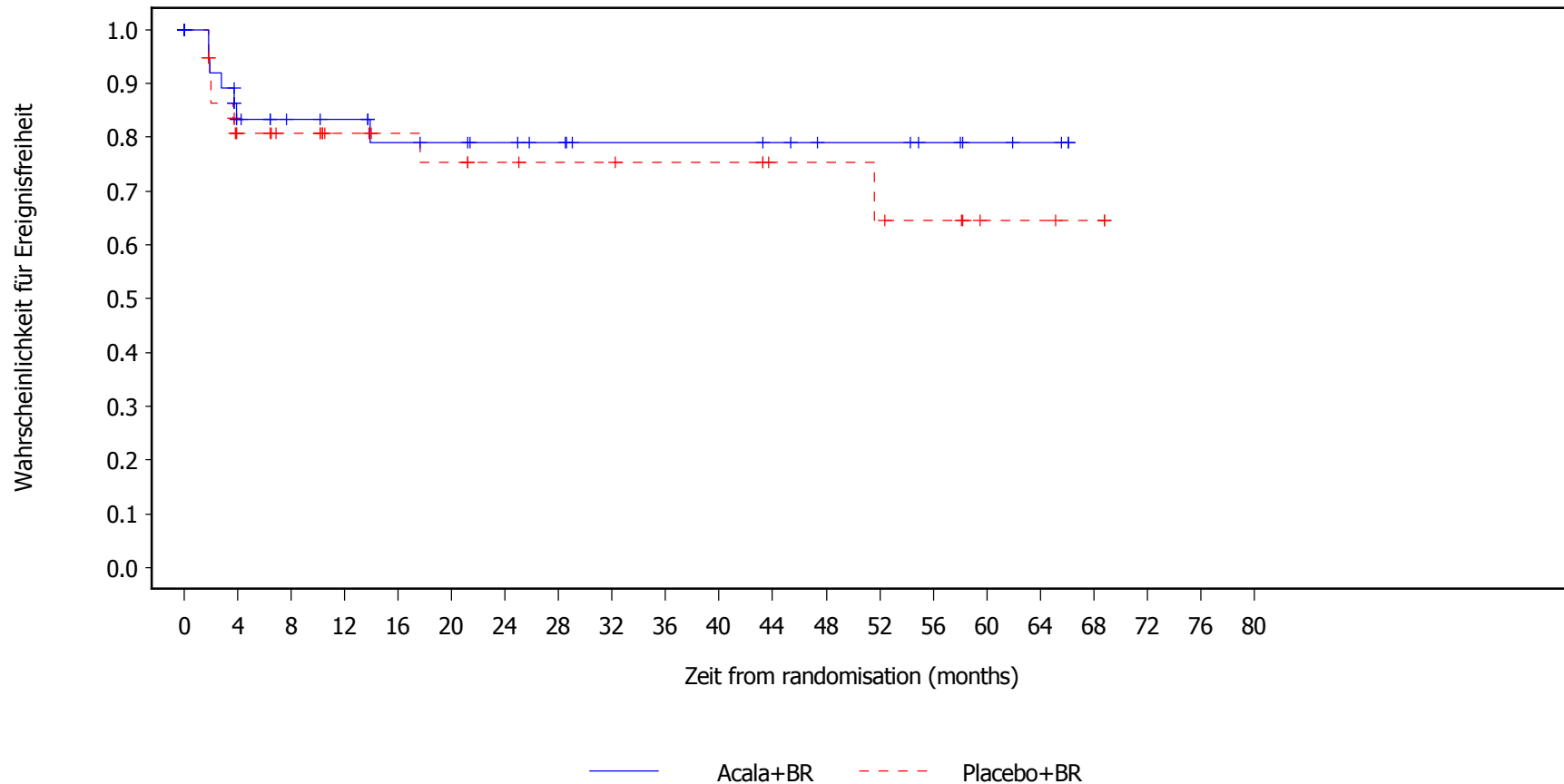
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.2.6 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - FACT-Lym Lym-Subscala (LYMS) for Geographic Region [IXRS]=Westeuropa
 Full Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

46	26	22	21	18	17	15	13	10	10	10	9	7	7	5	3	2	0	0	0	0	Acala+BR
46	25	22	17	15	14	12	11	11	10	10	7	7	6	5	2	2	1	0	0	0	Placebo+BR

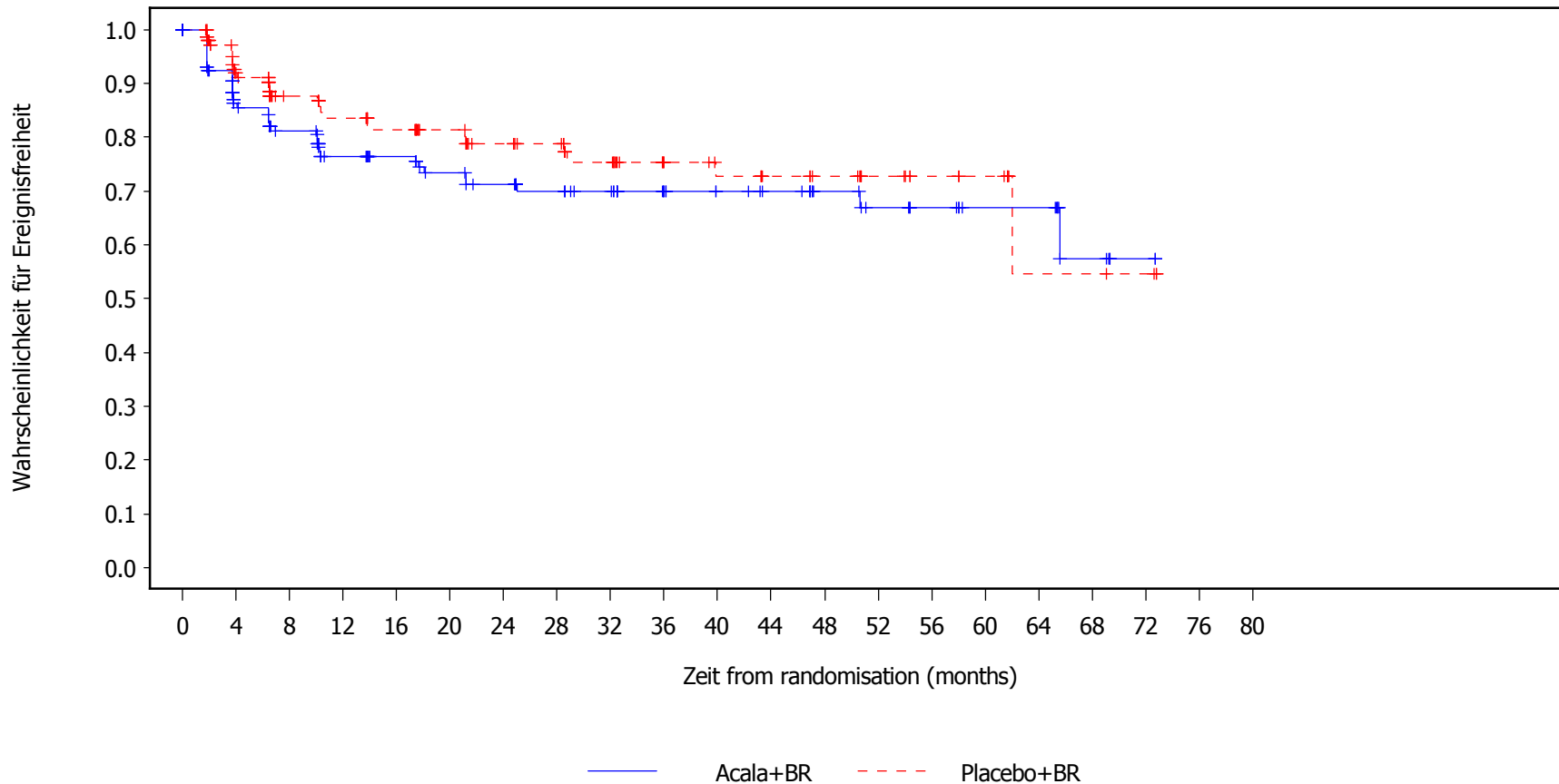
Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.2.2.2.7 ECH0): Kaplan-Meier plot of Zeit bis zur ersten Verschlechterung - FACT-Lym Lym-Subscala (LYMS) for Geographic
 Region [IXRS]=Andere
 Full Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

171	121	107	89	79	70	65	56	51	39	35	32	24	20	16	12	12	5	1	0	0	Acala+BR
170	118	90	81	73	64	56	52	43	31	28	24	21	16	12	10	3	3	2	0	0	Placebo+BR

Kaplan-Meier plot is presented only if the interaction term in unstratified Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.1 ECHO: Summary of subgroup analysis of time to first UE
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	Anzahl (%) der Patienten mit		Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit		Mediane Zeit [95%-KI] (Monate) [a]			
	n	Ereignis		n	Ereignis				
Geographic Region [IXRS]									
Nordamerika	82	82 (100)	0,1 [0,0; 0,1]	81	81 (100)	0,0 [NE; NE]	0,71	[0,52; 0,96]	0,0271*
Westeuropa	44	43 (97,7)	0,1 [0,1; 0,3]	46	46 (100)	0,1 [0,0; 0,4]	0,83	[0,54; 1,26]	0,3762
Andere	171	171 (100)	0,1 [0,1; 0,1]	170	167 (98,2)	0,1 [0,1; 0,2]	1,11	[0,90; 1,38]	0,3230
Interaktion p-Wert									0,0484*
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	98 (99,0)	0,1 [0,1; 0,1]	101	99 (98,0)	0,1 [0,1; 0,2]	1,07	[0,80; 1,41]	0,6592
Intermediäres Risiko [4-5]	126	126 (100)	0,1 [0,1; 0,1]	124	123 (99,2)	0,1 [0,1; 0,1]	0,94	[0,73; 1,21]	0,6367
Hohes Risiko [6-11]	72	72 (100)	0,1 [0,0; 0,1]	72	72 (100)	0,0 [NE; NE]	0,88	[0,63; 1,22]	0,4451
Interaktion p-Wert									0,6638
Geschlecht [eCRF]									
Männlich	212	211 (99,5)	0,1 [0,1; 0,1]	208	205 (98,6)	0,1 [0,1; 0,1]	0,95	[0,79; 1,16]	0,6283
Weiblich	85	85 (100)	0,1 [0,1; 0,1]	89	89 (100)	0,1 [0,0; 0,1]	1,06	[0,79; 1,43]	0,6897
Interaktion p-Wert									0,5499
Altersgruppe I [eCRF]									
< 70 Jahre	122	121 (99,2)	0,1 [0,1; 0,1]	117	115 (98,3)	0,1 [0,1; 0,1]	1,06	[0,82; 1,37]	0,6560
>= 70 Jahre	175	175 (100)	0,1 [0,1; 0,1]	180	179 (99,4)	0,1 [0,0; 0,1]	0,92	[0,75; 1,13]	0,4326
Interaktion p-Wert									0,4002
Altersgruppe II [eCRF]									
< 75 Jahre	214	213 (99,5)	0,1 [0,1; 0,1]	221	218 (98,6)	0,1 [0,1; 0,1]	1,04	[0,86; 1,26]	0,6510
>= 75 Jahre	83	83 (100)	0,1 [0,1; 0,2]	76	76 (100)	0,0 [0,0; 0,1]	0,78	[0,57; 1,06]	0,1127
Interaktion p-Wert									0,1116
Abstammung [eCRF]									
Weiß	232	231 (99,6)	0,1 [0,1; 0,1]	233	230 (98,7)	0,1 [0,1; 0,1]	1,00	[0,84; 1,21]	0,9588

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.1 ECHO: Summary of subgroup analysis of time to first UE
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)				Placebo+BR (N=297)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Nicht-weiß	52	52 (100)	0,1 [0,0; 0,1]		53	53 (100)	0,1 [0,0; 0,1]		0,95	[0,65; 1,40]	0,8017
Interaktion p-Wert											0,8033
ECOG-PS [eCRF]											
0	156	155 (99,4)	0,1 [0,1; 0,1]		140	139 (99,3)	0,1 [0,1; 0,1]		1,00	[0,80; 1,26]	0,9914
1	129	129 (100)	0,1 [0,1; 0,1]		132	130 (98,5)	0,1 [0,0; 0,1]		0,94	[0,74; 1,21]	0,6449
>=2	12	12 (100)	0,1 [0,0; 0,9]		25	25 (100)	0,0 [0,0; 0,7]		1,00	[0,49; 1,95]	NC
Interaktion p-Wert											0,9402
Bulky Disease I [eCRF]											
< 5 cm	185	184 (99,5)	0,1 [0,1; 0,1]		185	183 (98,9)	0,1 [0,0; 0,1]		0,98	[0,80; 1,20]	0,8338
>= 5 cm	112	112 (100)	0,1 [0,1; 0,1]		112	111 (99,1)	0,1 [0,1; 0,2]		0,98	[0,75; 1,27]	0,8637
Interaktion p-Wert											0,9949
Bulky Disease II [eCRF]											
< 10 cm	277	276 (99,6)	0,1 [0,1; 0,1]		276	273 (98,9)	0,1 [NE; NE]		0,96	[0,81; 1,14]	0,6583
>= 10 cm	20	20 (100)	0,1 [0,0; 0,3]		21	21 (100)	0,1 [0,0; 0,5]		1,21	[0,65; 2,25]	0,5357
Interaktion p-Wert											0,4751
Ann Arbor-Stadium für Lymphome [eCRF]											
Stadium I-III	48	48 (100)	0,1 [0,1; 0,2]		36	36 (100)	0,1 [0,0; 0,3]		1,07	[0,69; 1,66]	0,7646
Stadium IV	249	248 (99,6)	0,1 [0,1; 0,1]		261	258 (98,9)	0,1 [NE; NE]		0,97	[0,81; 1,15]	0,7213
Interaktion p-Wert											0,6813
MCL-Typ [eCRF]											
Klassische Variante	195	194 (99,5)	0,1 [0,1; 0,1]		205	204 (99,5)	0,1 [0,1; 0,1]		0,99	[0,81; 1,20]	0,9137
Blastoide und pleomorphische Variante	39	39 (100)	0,1 [0,1; 0,1]		32	31 (96,9)	0,0 [0,0; 0,2]		0,97	[0,61; 1,57]	0,9077
Andere	0	0	NE		8	8 (100)	0,1 [0,0; 1,1]		NC	[NC]	NC
Interaktion p-Wert											0,9477

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.1 ECHO: Summary of subgroup analysis of time to first UE
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	108 (99,1)	0,1 [0,1; 0,1]	103	103 (100)	0,1 [0,1; 0,1]	0,94	[0,72; 1,24]	0,6814
>= 30%	126	126 (100)	0,1 [0,1; 0,1]	126	124 (98,4)	0,1 [0,0; 0,1]	1,00	[0,78; 1,29]	0,9703
Interaktion p-Wert									0,7434
Ki-67 (%) II [eCRF]									
< 50%	179	178 (99,4)	0,1 [0,1; 0,1]	164	162 (98,8)	0,1 [0,1; 0,1]	0,98	[0,79; 1,21]	0,8219
>= 50%	56	56 (100)	0,1 [0,1; 0,1]	65	65 (100)	0,1 [0,0; 0,1]	1,00	[0,69; 1,42]	0,9824
Interaktion p-Wert									0,9233
Knochenmarksbeteiligung [eCRF]									
Ja	178	177 (99,4)	0,1 [0,1; 0,1]	180	179 (99,4)	0,0 [0,0; 0,1]	0,90	[0,73; 1,11]	0,3409
Nein	50	50 (100)	0,1 [0,0; 0,1]	45	44 (97,8)	0,1 [0,0; 0,3]	1,15	[0,77; 1,73]	0,5022
Interaktion p-Wert									0,3016
Extranodale Erkrankung [eCRF]									
Ja	262	261 (99,6)	0,1 [0,1; 0,1]	275	272 (98,9)	0,1 [0,0; 0,1]	0,96	[0,81; 1,14]	0,6798
Nein	35	35 (100)	0,1 [0,0; 0,1]	22	22 (100)	0,1 [0,1; 0,6]	1,15	[0,68; 1,99]	0,6022
Interaktion p-Wert									0,5337
Gastrointestinale Erkrankung [eCRF]									
Ja	74	73 (98,6)	0,1 [0,1; 0,1]	74	74 (100)	0,1 [0,0; 0,3]	0,93	[0,67; 1,29]	0,6760
Nein	223	223 (100)	0,1 [0,1; 0,1]	223	220 (98,7)	0,1 [NE; NE]	0,99	[0,82; 1,20]	0,9459
Interaktion p-Wert									0,7425
LDH > ULN [eCRF]									
Ja	52	52 (100)	0,1 [0,0; 0,1]	54	54 (100)	0,0 [0,0; 0,1]	0,86	[0,59; 1,26]	0,4410
Nein	245	244 (99,6)	0,1 [0,1; 0,1]	241	238 (98,8)	0,1 [0,1; 0,1]	1,01	[0,84; 1,21]	0,9236
Interaktion p-Wert									0,4603

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.2 ECHO: Summary of subgroup analysis of time to first SOC: Erkrankungen der Haut und des Unterhautgewebes
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	70 (85,4)	1,3 [0,8; 2,0]	81	48 (59,3)	6,5 [2,8;29,3]	2,02	[1,40; 2,93]	0,0002*
Westeuropa	44	26 (59,1)	4,7 [1,6; NE]	46	20 (43,5)	34,0 [6,6; NE]	1,56	[0,87; 2,82]	0,1340
Andere	171	94 (55,0)	8,2 [5,2;24,9]	170	72 (42,4)	44,5 [15,7; NE]	1,45	[1,07; 1,98]	0,0171*
Interaktion p-Wert									0,3926
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	64 (64,6)	6,6 [2,6;11,1]	101	51 (50,5)	10,6 [5,4; NE]	1,39	[0,97; 2,02]	0,0765
Intermediäres Risiko [4-5]	126	84 (66,7)	3,2 [1,7; 5,5]	124	59 (47,6)	29,4 [10,2; NE]	1,75	[1,26; 2,45]	0,0009*
Hohes Risiko [6-11]	72	42 (58,3)	2,8 [1,5; 7,3]	72	30 (41,7)	44,5 [5,6; NE]	1,67	[1,05; 2,69]	0,0312*
Interaktion p-Wert									0,6515
Geschlecht [eCRF]									
Männlich	212	124 (58,5)	5,2 [2,6; 9,4]	208	98 (47,1)	24,4 [10,2; NE]	1,41	[1,08; 1,84]	0,0103*
Weiblich	85	66 (77,6)	2,5 [1,0; 5,2]	89	42 (47,2)	29,4 [6,6; NE]	2,12	[1,44; 3,14]	0,0001*
Interaktion p-Wert									0,0888
Altersgruppe I [eCRF]									
< 70 Jahre	122	73 (59,8)	3,8 [1,6;11,1]	117	43 (36,8)	NE [NE; NE]	2,13	[1,47; 3,12]	<0,0001*
>= 70 Jahre	175	117 (66,9)	4,2 [1,9; 6,1]	180	97 (53,9)	12,5 [5,4;29,4]	1,36	[1,04; 1,78]	0,0256*
Interaktion p-Wert									0,0559
Altersgruppe II [eCRF]									
< 75 Jahre	214	135 (63,1)	3,7 [2,1; 6,1]	221	103 (46,6)	29,4 [8,0; NE]	1,63	[1,26; 2,11]	0,0002*
>= 75 Jahre	83	55 (66,3)	4,7 [1,6;10,1]	76	37 (48,7)	15,3 [6,5; NE]	1,50	[0,99; 2,29]	0,0544
Interaktion p-Wert									0,7344
Abstammung [eCRF]									
Weiß	232	145 (62,5)	4,6 [2,0; 7,0]	233	103 (44,2)	43,2 [15,5; NE]	1,66	[1,29; 2,14]	<0,0001*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.2 ECHO: Summary of subgroup analysis of time to first SOC: Erkrankungen der Haut und des Unterhautgewebes
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	35 (67,3)	3,7 [1,5; 9,0]	53	29 (54,7)	7,7 [4,5;40,0]	1,42	[0,87; 2,33]	0,1651
Interaktion p-Wert									0,5748
ECOG-PS [eCRF]									
0	156	114 (73,1)	2,9 [1,4; 4,7]	140	70 (50,0)	23,0 [6,6; NE]	1,87	[1,39; 2,52]	<0,0001*
1	129	73 (56,6)	5,8 [2,5;24,9]	132	61 (46,2)	26,5 [6,8; NE]	1,34	[0,96; 1,89]	0,0880
>=2	12	3 (25,0)	NE [NE; NE]	25	9 (36,0)	44,5 [12,5; NE]	0,68	[0,15; 2,27]	0,5455
Interaktion p-Wert									0,1423
Bulky Disease I [eCRF]									
< 5 cm	185	120 (64,9)	3,2 [1,9; 6,1]	185	88 (47,6)	40,0 [7,6; NE]	1,66	[1,26; 2,19]	0,0003*
>= 5 cm	112	70 (62,5)	5,5 [1,9; 8,3]	112	52 (46,4)	29,3 [7,4; NE]	1,50	[1,05; 2,16]	0,0256*
Interaktion p-Wert									0,6662
Bulky Disease II [eCRF]									
< 10 cm	277	176 (63,5)	4,6 [2,3; 6,5]	276	131 (47,5)	29,3 [10,2; NE]	1,57	[1,25; 1,97]	<0,0001*
>= 10 cm	20	14 (70,0)	2,0 [0,5; 7,3]	21	9 (42,9)	NE [NE; NE]	2,14	[0,94; 5,14]	0,0704
Interaktion p-Wert									0,4764
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	31 (64,6)	5,2 [1,6;19,3]	36	15 (41,7)	NE [NE; NE]	1,87	[1,02; 3,55]	0,0414*
Stadium IV	249	159 (63,9)	3,7 [1,9; 6,1]	261	125 (47,9)	26,5 [8,1;52,5]	1,57	[1,25; 1,99]	0,0001*
Interaktion p-Wert									0,6113
MCL-Typ [eCRF]									
Klassische Variante	195	124 (63,6)	4,7 [2,8; 8,1]	205	98 (47,8)	29,3 [12,2; NE]	1,60	[1,23; 2,09]	0,0005*
Blastoide und pleomorphische Variante	39	25 (64,1)	1,5 [0,7;51,1]	32	12 (37,5)	NE [NE; NE]	1,90	[0,98; 3,93]	0,0591
Andere	0	0	NE	8	2 (25,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,6380

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.2 ECHO: Summary of subgroup analysis of time to first SOC: Erkrankungen der Haut und des Unterhautgewebes
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)				Placebo+BR (N=297)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	Anzahl (%) der Patienten mit		Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit		Mediane Zeit [95%-KI] (Monate) [a]					
	n	Ereignis		n	Ereignis						
Ki-67 (%) I [eCRF]											
< 30%	109	63 (57,8)	5,2 [2,0;19,3]	103	54 (52,4)	24,4 [5,6; NE]	1,28	[0,89; 1,85]		0,1840	
>= 30%	126	82 (65,1)	3,6 [1,5; 8,3]	126	55 (43,7)	29,3 [10,6; NE]	1,73	[1,23; 2,45]		0,0015*	
Interaktion p-Wert											0,2357
Ki-67 (%) II [eCRF]											
< 50%	179	107 (59,8)	5,2 [2,3; 9,0]	164	87 (53,0)	21,2 [6,9;44,5]	1,30	[0,98; 1,73]		0,0652	
>= 50%	56	38 (67,9)	2,6 [0,8;13,6]	65	22 (33,8)	NE [NE; NE]	2,38	[1,42; 4,08]		0,0010*	
Interaktion p-Wert											0,0464*
Knochenmarksbeteiligung [eCRF]											
Ja	178	126 (70,8)	1,9 [1,6; 4,6]	180	96 (53,3)	10,2 [4,6;34,0]	1,64	[1,26; 2,14]		0,0002*	
Nein	50	33 (66,0)	5,2 [1,3;11,7]	45	22 (48,9)	24,4 [6,5; NE]	1,57	[0,92; 2,72]		0,0996	
Interaktion p-Wert											0,8795
Extranodale Erkrankung [eCRF]											
Ja	262	167 (63,7)	4,6 [2,0; 6,5]	275	131 (47,6)	26,5 [8,1;52,5]	1,58	[1,25; 1,98]		<0,0001*	
Nein	35	23 (65,7)	3,8 [1,2;24,9]	22	9 (40,9)	NE [NE; NE]	1,97	[0,94; 4,50]		0,0713	
Interaktion p-Wert											0,5771
Gastrointestinale Erkrankung [eCRF]											
Ja	74	45 (60,8)	5,5 [1,6; 8,0]	74	39 (52,7)	15,5 [5,4;40,0]	1,35	[0,88; 2,08]		0,1695	
Nein	223	145 (65,0)	3,7 [2,1; 6,1]	223	101 (45,3)	43,2 [8,0; NE]	1,69	[1,32; 2,19]		<0,0001*	
Interaktion p-Wert											0,3728
LDH > ULN [eCRF]											
Ja	52	28 (53,8)	6,1 [1,3; NE]	54	24 (44,4)	7,9 [2,9; NE]	1,28	[0,74; 2,23]		0,3686	
Nein	245	162 (66,1)	3,8 [2,1; 5,8]	241	115 (47,7)	34,0 [12,2; NE]	1,67	[1,32; 2,13]		<0,0001*	
Interaktion p-Wert											0,3831

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.3 ECHO: Summary of subgroup analysis of time to first PT: Ausschlag makulo-papuloes
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	24 (29,3)	NE [NE; NE]	81	10 (12,3)	NE [NE; NE]	2,65	[1,30; 5,80]	0,0066*
Westeuropa	44	4 (9,1)	NE [NE; NE]	46	1 (2,2)	NE [NE; NE]	4,28	[0,63; 83,72]	0,1437
Andere	171	19 (11,1)	NE [NE; NE]	170	8 (4,7)	NE [NE; NE]	2,38	[1,08; 5,77]	0,0312*
Interaktion p-Wert									0,8764
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	10 (10,1)	NE [NE; NE]	101	4 (4,0)	NE [NE; NE]	2,61	[0,87; 9,50]	0,0880
Intermediäres Risiko [4-5]	126	28 (22,2)	NE [NE; NE]	124	11 (8,9)	NE [NE; NE]	2,70	[1,38; 5,66]	0,0032*
Hohes Risiko [6-11]	72	9 (12,5)	NE [NE; NE]	72	4 (5,6)	NE [NE; NE]	2,23	[0,73; 8,24]	0,1644
Interaktion p-Wert									0,9639
Geschlecht [eCRF]									
Männlich	212	29 (13,7)	NE [NE; NE]	208	14 (6,7)	NE [NE; NE]	2,11	[1,14; 4,12]	0,0175*
Weiblich	85	18 (21,2)	NE [NE; NE]	89	5 (5,6)	NE [NE; NE]	3,90	[1,55; 11,81]	0,0029*
Interaktion p-Wert									0,2978
Altersgruppe I [eCRF]									
< 70 Jahre	122	17 (13,9)	NE [NE; NE]	117	7 (6,0)	NE [NE; NE]	2,41	[1,04; 6,23]	0,0402*
>= 70 Jahre	175	30 (17,1)	NE [NE; NE]	180	12 (6,7)	NE [NE; NE]	2,68	[1,41; 5,44]	0,0023*
Interaktion p-Wert									0,8501
Altersgruppe II [eCRF]									
< 75 Jahre	214	33 (15,4)	NE [NE; NE]	221	13 (5,9)	NE [NE; NE]	2,71	[1,46; 5,34]	0,0013*
>= 75 Jahre	83	14 (16,9)	NE [NE; NE]	76	6 (7,9)	NE [NE; NE]	2,24	[0,90; 6,32]	0,0851
Interaktion p-Wert									0,7466
Abstammung [eCRF]									
Weiß	232	40 (17,2)	NE [NE; NE]	233	14 (6,0)	NE [NE; NE]	2,98	[1,66; 5,67]	0,0002*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.3 ECHO: Summary of subgroup analysis of time to first PT: Ausschlag makulo-papuloes
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	5 (9,6)	NE [NE; NE]	53	3 (5,7)	NE [NE; NE]	1,76	[0,43; 8,60]	0,4292
Interaktion p-Wert									0,5168
ECOG-PS [eCRF]									
0	156	26 (16,7)	NE [NE; NE]	140	10 (7,1)	NE [NE; NE]	2,46	[1,22; 5,34]	0,0109*
1	129	20 (15,5)	NE [NE; NE]	132	9 (6,8)	NE [NE; NE]	2,38	[1,11; 5,49]	0,0246*
>=2	12	1 (8,3)	NE [NE; NE]	25	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,9527
Bulky Disease I [eCRF]									
< 5 cm	185	27 (14,6)	NE [NE; NE]	185	15 (8,1)	NE [NE; NE]	1,87	[1,01; 3,59]	0,0477*
>= 5 cm	112	20 (17,9)	NE [NE; NE]	112	4 (3,6)	NE [NE; NE]	5,21	[1,97; 17,91]	0,0005*
Interaktion p-Wert									0,0894
Bulky Disease II [eCRF]									
< 10 cm	277	44 (15,9)	NE [NE; NE]	276	18 (6,5)	NE [NE; NE]	2,53	[1,49; 4,49]	0,0005*
>= 10 cm	20	3 (15,0)	NE [NE; NE]	21	1 (4,8)	NE [NE; NE]	3,21	[0,41; 64,88]	0,2761
Interaktion p-Wert									0,8390
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	4 (8,3)	NE [NE; NE]	36	2 (5,6)	NE [NE; NE]	1,51	[0,29; 10,87]	0,6293
Stadium IV	249	43 (17,3)	NE [NE; NE]	261	17 (6,5)	NE [NE; NE]	2,78	[1,62; 5,01]	0,0002*
Interaktion p-Wert									0,5157
MCL-Typ [eCRF]									
Klassische Variante	195	37 (19,0)	NE [NE; NE]	205	14 (6,8)	NE [NE; NE]	2,96	[1,64; 5,67]	0,0002*
Blastoide und pleomorphische Variante	39	4 (10,3)	NE [NE; NE]	32	2 (6,3)	NE [NE; NE]	1,54	[0,30; 11,09]	0,6126
Andere	0	0	NE	8	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,4909

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.3 ECHO: Summary of subgroup analysis of time to first PT: Ausschlag makulo-papuloes
Safety Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	17 (15,6)	NE [NE; NE]	103	8 (7,8)	NE [NE; NE]	2,14	[0,95; 5,23]	0,0669
>= 30%	126	20 (15,9)	NE [NE; NE]	126	5 (4,0)	NE [NE; NE]	4,10	[1,66; 12,33]	0,0015*
Interaktion p-Wert									0,3161
Ki-67 (%) II [eCRF]									
< 50%	179	27 (15,1)	NE [NE; NE]	164	12 (7,3)	NE [NE; NE]	2,18	[1,13; 4,46]	0,0196*
>= 50%	56	10 (17,9)	NE [NE; NE]	65	1 (1,5)	NE [NE; NE]	11,78	[2,26; 216,31]	0,0015*
Interaktion p-Wert									0,0712
Knochenmarksbeteiligung [eCRF]									
Ja	178	36 (20,2)	NE [NE; NE]	180	13 (7,2)	NE [NE; NE]	2,99	[1,63; 5,85]	0,0003*
Nein	50	7 (14,0)	NE [NE; NE]	45	4 (8,9)	NE [NE; NE]	1,61	[0,49; 6,14]	0,4404
Interaktion p-Wert									0,3886
Extranodale Erkrankung [eCRF]									
Ja	262	44 (16,8)	NE [NE; NE]	275	18 (6,5)	NE [NE; NE]	2,68	[1,58; 4,76]	0,0002*
Nein	35	3 (8,6)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	1,91	[0,24; 38,58]	0,5569
Interaktion p-Wert									0,7808
Gastrointestinale Erkrankung [eCRF]									
Ja	74	11 (14,9)	NE [NE; NE]	74	4 (5,4)	NE [NE; NE]	2,91	[0,99; 10,50]	0,0511
Nein	223	36 (16,1)	NE [NE; NE]	223	15 (6,7)	NE [NE; NE]	2,48	[1,38; 4,66]	0,0020*
Interaktion p-Wert									0,8052
LDH > ULN [eCRF]									
Ja	52	6 (11,5)	NE [NE; NE]	54	3 (5,6)	NE [NE; NE]	1,99	[0,53; 9,44]	0,3159
Nein	245	41 (16,7)	NE [NE; NE]	241	15 (6,2)	NE [NE; NE]	2,84	[1,61; 5,30]	0,0002*
Interaktion p-Wert									0,6495

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.4 ECHO: Summary of subgroup analysis of time to first PT: Haematurie
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	4 (4,9)	NE [NE; NE]	81	1 (1,2)	NE [NE; NE]	NC	[NC]	NC
Westeuropa	44	1 (2,3)	NE [NE; NE]	46	0	NE [NE; NE]	NC	[NC]	NC
Andere	171	7 (4,1)	NE [NE; NE]	170	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	4 (4,0)	NE [NE; NE]	101	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
Intermediäres Risiko [4-5]	126	5 (4,0)	NE [NE; NE]	124	1 (0,8)	NE [NE; NE]	NC	[NC]	NC
Hohes Risiko [6-11]	72	3 (4,2)	NE [NE; NE]	72	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht [eCRF]									
Männlich	212	10 (4,7)	NE [NE; NE]	208	1 (0,5)	NE [NE; NE]	9,55	[1,83;175,20]	0,0043*
Weiblich	85	2 (2,4)	NE [NE; NE]	89	1 (1,1)	NE [NE; NE]	1,83	[0,17; 39,37]	0,6136
Interaktion p-Wert									0,3145
Altersgruppe I [eCRF]									
< 70 Jahre	122	4 (3,3)	NE [NE; NE]	117	1 (0,9)	NE [NE; NE]	NC	[NC]	NC
>= 70 Jahre	175	8 (4,6)	NE [NE; NE]	180	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Altersgruppe II [eCRF]									
< 75 Jahre	214	7 (3,3)	NE [NE; NE]	221	1 (0,5)	NE [NE; NE]	NC	[NC]	NC
>= 75 Jahre	83	5 (6,0)	NE [NE; NE]	76	1 (1,3)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Abstammung [eCRF]									
Weiß	232	10 (4,3)	NE [NE; NE]	233	1 (0,4)	NE [NE; NE]	9,43	[1,80;173,02]	0,0046*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.4 ECHO: Summary of subgroup analysis of time to first PT: Haematurie
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	2 (3,8)	NE [NE; NE]	53	1 (1,9)	NE [NE; NE]	2,09	[0,20; 44,90]	0,5354
Interaktion p-Wert									0,3569
ECOG-PS [eCRF]									
0	156	10 (6,4)	NE [NE; NE]	140	1 (0,7)	NE [NE; NE]	8,91	[1,71;163,49]	0,0060*
1	129	2 (1,6)	NE [NE; NE]	132	1 (0,8)	NE [NE; NE]	1,96	[0,19; 42,14]	0,5719
>=2	12	0	NE [NE; NE]	25	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,3548
Bulky Disease I [eCRF]									
< 5 cm	185	6 (3,2)	NE [NE; NE]	185	2 (1,1)	NE [NE; NE]	NC	[NC]	NC
>= 5 cm	112	6 (5,4)	NE [NE; NE]	112	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Bulky Disease II [eCRF]									
< 10 cm	277	11 (4,0)	NE [NE; NE]	276	2 (0,7)	NE [NE; NE]	5,25	[1,41; 33,91]	0,0111*
>= 10 cm	20	1 (5,0)	NE [NE; NE]	21	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	3 (6,3)	NE [NE; NE]	36	0	NE [NE; NE]	NC	[NC]	NC
Stadium IV	249	9 (3,6)	NE [NE; NE]	261	2 (0,8)	NE [NE; NE]	4,38	[1,13; 28,76]	0,0314*
Interaktion p-Wert									NC
MCL-Typ [eCRF]									
Klassische Variante	195	11 (5,6)	NE [NE; NE]	205	1 (0,5)	NE [NE; NE]	11,45	[2,23;209,17]	0,0014*
Blastoide und pleomorphische Variante	39	0	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Andere	0	0	NE	8	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.4 ECHO: Summary of subgroup analysis of time to first PT: Haematurie
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b] [95%-KI] [b]		2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	6 (5,5)	NE [NE; NE]	103	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
>= 30%	126	5 (4,0)	NE [NE; NE]	126	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ki-67 (%) II [eCRF]									
< 50%	179	10 (5,6)	NE [NE; NE]	164	1 (0,6)	NE [NE; NE]	9,40	[1,80;172,42]	0,0047*
>= 50%	56	1 (1,8)	NE [NE; NE]	65	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Knochenmarksbeteiligung [eCRF]									
Ja	178	6 (3,4)	NE [NE; NE]	180	0	NE [NE; NE]	NC	[NC]	NC
Nein	50	3 (6,0)	NE [NE; NE]	45	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Extranodale Erkrankung [eCRF]									
Ja	262	10 (3,8)	NE [NE; NE]	275	2 (0,7)	NE [NE; NE]	4,96	[1,31; 32,25]	0,0165*
Nein	35	2 (5,7)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Gastrointestinale Erkrankung [eCRF]									
Ja	74	3 (4,1)	NE [NE; NE]	74	1 (1,4)	NE [NE; NE]	2,75	[0,35; 55,65]	0,3505
Nein	223	9 (4,0)	NE [NE; NE]	223	1 (0,4)	NE [NE; NE]	8,57	[1,61;158,03]	0,0083*
Interaktion p-Wert									0,4725
LDH > ULN [eCRF]									
Ja	52	1 (1,9)	NE [NE; NE]	54	0	NE [NE; NE]	NC	[NC]	NC
Nein	245	11 (4,5)	NE [NE; NE]	241	2 (0,8)	NE [NE; NE]	5,22	[1,40; 33,73]	0,0115*
Interaktion p-Wert									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.5 ECHO: Summary of subgroup analysis of time to first PT: Diarrhoe
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	49 (59,8)	8,0 [2,8;43,2]	81	39 (48,1)	30,2 [4,3; NE]	1,29	[0,85; 1,98]	0,2293
Westeuropa	44	13 (29,5)	NE [NE; NE]	46	11 (23,9)	NE [NE; NE]	1,12	[0,50; 2,56]	0,7778
Andere	171	49 (28,7)	NE [NE; NE]	170	33 (19,4)	NE [NE; NE]	1,48	[0,96; 2,33]	0,0767
Interaktion p-Wert									0,8110
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	39 (39,4)	66,2 [29,2; NE]	101	29 (28,7)	NE [NE; NE]	1,39	[0,86; 2,27]	0,1729
Intermediäres Risiko [4-5]	126	44 (34,9)	NE [NE; NE]	124	38 (30,6)	NE [NE; NE]	1,12	[0,73; 1,74]	0,6008
Hohes Risiko [6-11]	72	28 (38,9)	39,5 [18,8;62,0]	72	16 (22,2)	NE [NE; NE]	1,73	[0,95; 3,27]	0,0743
Interaktion p-Wert									0,5119
Geschlecht [eCRF]									
Männlich	212	69 (32,5)	66,2 [61,1; NE]	208	61 (29,3)	NE [NE; NE]	1,07	[0,76; 1,52]	0,6871
Weiblich	85	42 (49,4)	19,9 [10,0; NE]	89	22 (24,7)	NE [NE; NE]	2,15	[1,30; 3,67]	0,0027*
Interaktion p-Wert									0,0260*
Altersgruppe I [eCRF]									
< 70 Jahre	122	43 (35,2)	NE [NE; NE]	117	32 (27,4)	NE [NE; NE]	1,27	[0,81; 2,02]	0,3054
>= 70 Jahre	175	68 (38,9)	61,1 [39,5; NE]	180	51 (28,3)	NE [NE; NE]	1,38	[0,96; 2,00]	0,0780
Interaktion p-Wert									0,7721
Altersgruppe II [eCRF]									
< 75 Jahre	214	78 (36,4)	NE [NE; NE]	221	59 (26,7)	NE [NE; NE]	1,38	[0,99; 1,94]	0,0612
>= 75 Jahre	83	33 (39,8)	60,5 [39,5; NE]	76	24 (31,6)	NE [NE; NE]	1,21	[0,72; 2,06]	0,4811
Interaktion p-Wert									0,6770
Abstammung [eCRF]									
Weiß	232	87 (37,5)	NE [NE; NE]	233	66 (28,3)	NE [NE; NE]	1,32	[0,96; 1,83]	0,0836

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.5 ECHO: Summary of subgroup analysis of time to first PT: Diarrhoe
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Subgruppen	Acala+BR (N=297)				Placebo+BR (N=297)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Nicht-weiß	52	16 (30,8)	66,2 [24,9; NE]		53	13 (24,5)	NE [NE; NE]		1,26	[0,61; 2,67]	0,5290
Interaktion p-Wert											0,9088
ECOG-PS [eCRF]											
0	156	69 (44,2)	60,5 [21,2; NE]		140	43 (30,7)	NE [NE; NE]		1,50	[1,03; 2,21]	0,0352*
1	129	39 (30,2)	NE [NE; NE]		132	34 (25,8)	NE [NE; NE]		1,13	[0,71; 1,80]	0,6051
>=2	12	3 (25,0)	NE [NE; NE]		25	6 (24,0)	NE [NE; NE]		1,07	[0,23; 4,07]	0,9200
Interaktion p-Wert											0,6199
Bulky Disease I [eCRF]											
< 5 cm	185	77 (41,6)	62,0 [19,9; NE]		185	55 (29,7)	NE [NE; NE]		1,47	[1,04; 2,09]	0,0270*
>= 5 cm	112	34 (30,4)	NE [NE; NE]		112	28 (25,0)	NE [NE; NE]		1,11	[0,67; 1,84]	0,6837
Interaktion p-Wert											0,3620
Bulky Disease II [eCRF]											
< 10 cm	277	103 (37,2)	NE [NE; NE]		276	76 (27,5)	NE [NE; NE]		1,37	[1,02; 1,84]	0,0377*
>= 10 cm	20	8 (40,0)	60,5 [8,0; NE]		21	7 (33,3)	NE [NE; NE]		0,99	[0,36; 2,83]	0,9860
Interaktion p-Wert											0,5530
Ann Arbor-Stadium für Lymphome [eCRF]											
Stadium I-III	48	13 (27,1)	66,2 [66,2; NE]		36	4 (11,1)	NE [NE; NE]		2,55	[0,90; 9,06]	0,0791
Stadium IV	249	98 (39,4)	62,0 [43,2; NE]		261	79 (30,3)	NE [NE; NE]		1,30	[0,96; 1,75]	0,0850
Interaktion p-Wert											0,2306
MCL-Typ [eCRF]											
Klassische Variante	195	75 (38,5)	NE [NE; NE]		205	59 (28,8)	NE [NE; NE]		1,37	[0,97; 1,93]	0,0706
Blastoide und pleomorphische Variante	39	11 (28,2)	NE [NE; NE]		32	7 (21,9)	NE [NE; NE]		1,09	[0,43; 2,96]	0,8625
Andere	0	0	NE		8	4 (50,0)	NE [NE; NE]		NC	[NC]	NC
Interaktion p-Wert											0,6572

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.5 ECHO: Summary of subgroup analysis of time to first PT: Diarrhoe
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	39 (35,8)	NE [NE; NE]	103	30 (29,1)	NE [NE; NE]	1,33	[0,83; 2,16]	0,2373
>= 30%	126	45 (35,7)	62,0 [36,5; NE]	126	33 (26,2)	NE [NE; NE]	1,29	[0,82; 2,03]	0,2705
Interaktion p-Wert									0,9181
Ki-67 (%) II [eCRF]									
< 50%	179	66 (36,9)	66,2 [60,5; NE]	164	49 (29,9)	NE [NE; NE]	1,29	[0,89; 1,87]	0,1801
>= 50%	56	18 (32,1)	NE [NE; NE]	65	14 (21,5)	NE [NE; NE]	1,37	[0,69; 2,81]	0,3709
Interaktion p-Wert									0,8699
Knochenmarksbeteiligung [eCRF]									
Ja	178	77 (43,3)	60,5 [21,2; NE]	180	57 (31,7)	NE [NE; NE]	1,40	[0,99; 1,97]	0,0547
Nein	50	13 (26,0)	NE [NE; NE]	45	9 (20,0)	NE [NE; NE]	1,30	[0,56; 3,14]	0,5482
Interaktion p-Wert									0,8728
Extranodale Erkrankung [eCRF]									
Ja	262	101 (38,5)	62,0 [43,2; NE]	275	80 (29,1)	NE [NE; NE]	1,33	[0,99; 1,78]	0,0581
Nein	35	10 (28,6)	66,2 [66,2; NE]	22	3 (13,6)	NE [NE; NE]	2,18	[0,67; 9,73]	0,2077
Interaktion p-Wert									0,4445
Gastrointestinale Erkrankung [eCRF]									
Ja	74	25 (33,8)	NE [NE; NE]	74	29 (39,2)	36,3 [25,7; NE]	0,80	[0,47; 1,37]	0,4234
Nein	223	86 (38,6)	66,2 [43,3; NE]	223	54 (24,2)	NE [NE; NE]	1,62	[1,16; 2,29]	0,0047*
Interaktion p-Wert									0,0296*
LDH > ULN [eCRF]									
Ja	52	17 (32,7)	NE [NE; NE]	54	12 (22,2)	NE [NE; NE]	1,37	[0,66; 2,95]	0,3955
Nein	245	94 (38,4)	66,2 [60,5; NE]	241	70 (29,0)	NE [NE; NE]	1,34	[0,98; 1,83]	0,0635
Interaktion p-Wert									0,9478

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.6 ECH0: Summary of subgroup analysis of time to first PT: Erbrechen
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	29 (35,4)	NE [NE; NE]	81	21 (25,9)	NE [NE; NE]	1,48	[0,85; 2,62]	0,1694
Westeuropa	44	11 (25,0)	NE [NE; NE]	46	3 (6,5)	NE [NE; NE]	4,22	[1,32; 18,67]	0,0138*
Andere	171	36 (21,1)	NE [NE; NE]	170	17 (10,0)	NE [NE; NE]	2,28	[1,30; 4,15]	0,0037*
Interaktion p-Wert									0,2485
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	34 (34,3)	NE [NE; NE]	101	15 (14,9)	NE [NE; NE]	2,62	[1,46; 4,96]	0,0011*
Intermediäres Risiko [4-5]	126	32 (25,4)	NE [NE; NE]	124	14 (11,3)	NE [NE; NE]	2,51	[1,37; 4,86]	0,0026*
Hohes Risiko [6-11]	72	10 (13,9)	NE [NE; NE]	72	12 (16,7)	NE [NE; NE]	0,81	[0,34; 1,87]	0,6146
Interaktion p-Wert									0,0557
Geschlecht [eCRF]									
Männlich	212	40 (18,9)	NE [NE; NE]	208	23 (11,1)	NE [NE; NE]	1,79	[1,08; 3,04]	0,0232*
Weiblich	85	36 (42,4)	NE [NE; NE]	89	18 (20,2)	NE [NE; NE]	2,50	[1,44; 4,51]	0,0010*
Interaktion p-Wert									0,3893
Altersgruppe I [eCRF]									
< 70 Jahre	122	34 (27,9)	NE [NE; NE]	117	12 (10,3)	NE [NE; NE]	3,02	[1,61; 6,08]	0,0004*
>= 70 Jahre	175	42 (24,0)	NE [NE; NE]	180	29 (16,1)	NE [NE; NE]	1,59	[0,995; 2,58]	0,0524
Interaktion p-Wert									0,1144
Altersgruppe II [eCRF]									
< 75 Jahre	214	61 (28,5)	NE [NE; NE]	221	25 (11,3)	NE [NE; NE]	2,82	[1,80; 4,58]	<0,0001*
>= 75 Jahre	83	15 (18,1)	NE [NE; NE]	76	16 (21,1)	NE [NE; NE]	0,86	[0,42; 1,74]	0,6643
Interaktion p-Wert									0,0056*
Abstammung [eCRF]									
Weiß	232	56 (24,1)	NE [NE; NE]	233	34 (14,6)	NE [NE; NE]	1,76	[1,15; 2,72]	0,0083*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.6 ECH0: Summary of subgroup analysis of time to first PT: Erbrechen
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	16 (30,8)	NE [NE; NE]	53	6 (11,3)	NE [NE; NE]	3,26	[1,34; 9,09]	0,0084*
Interaktion p-Wert									0,2273
ECOG-PS [eCRF]									
0	156	47 (30,1)	NE [NE; NE]	140	24 (17,1)	NE [NE; NE]	1,97	[1,22; 3,27]	0,0056*
1	129	29 (22,5)	NE [NE; NE]	132	16 (12,1)	NE [NE; NE]	1,97	[1,09; 3,72]	0,0254*
>=2	12	0	NE [NE; NE]	25	1 (4,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,9933
Bulky Disease I [eCRF]									
< 5 cm	185	58 (31,4)	NE [NE; NE]	185	26 (14,1)	NE [NE; NE]	2,55	[1,62; 4,11]	<0,0001*
>= 5 cm	112	18 (16,1)	NE [NE; NE]	112	15 (13,4)	NE [NE; NE]	1,20	[0,60; 2,41]	0,6027
Interaktion p-Wert									0,0756
Bulky Disease II [eCRF]									
< 10 cm	277	75 (27,1)	NE [NE; NE]	276	38 (13,8)	NE [NE; NE]	2,16	[1,47; 3,23]	<0,0001*
>= 10 cm	20	1 (5,0)	NE [NE; NE]	21	3 (14,3)	NE [NE; NE]	0,32	[0,02; 2,48]	0,2843
Interaktion p-Wert									0,0727
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	13 (27,1)	NE [NE; NE]	36	2 (5,6)	NE [NE; NE]	5,54	[1,53; 35,41]	0,0067*
Stadium IV	249	63 (25,3)	NE [NE; NE]	261	39 (14,9)	NE [NE; NE]	1,83	[1,23; 2,74]	0,0027*
Interaktion p-Wert									0,1159
MCL-Typ [eCRF]									
Klassische Variante	195	49 (25,1)	NE [NE; NE]	205	26 (12,7)	NE [NE; NE]	2,16	[1,35; 3,52]	0,0011*
Blastoide und pleomorphische Variante	39	9 (23,1)	NE [NE; NE]	32	4 (12,5)	NE [NE; NE]	1,91	[0,62; 7,07]	0,2633
Andere	0	0	NE	8	1 (12,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,8544

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.6 ECH0: Summary of subgroup analysis of time to first PT: Erbrechen
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	28 (25,7)	NE [NE; NE]	103	14 (13,6)	NE [NE; NE]	2,13	[1,14; 4,17]	0,0169*
>= 30%	126	34 (27,0)	NE [NE; NE]	126	19 (15,1)	NE [NE; NE]	1,92	[1,11; 3,43]	0,0199*
Interaktion p-Wert									0,8068
Ki-67 (%) II [eCRF]									
< 50%	179	50 (27,9)	NE [NE; NE]	164	25 (15,2)	NE [NE; NE]	2,06	[1,29; 3,38]	0,0023*
>= 50%	56	12 (21,4)	NE [NE; NE]	65	8 (12,3)	NE [NE; NE]	1,80	[0,74; 4,58]	0,1940
Interaktion p-Wert									0,7911
Knochenmarksbeteiligung [eCRF]									
Ja	178	48 (27,0)	NE [NE; NE]	180	25 (13,9)	NE [NE; NE]	2,11	[1,31; 3,47]	0,0018*
Nein	50	14 (28,0)	NE [NE; NE]	45	6 (13,3)	NE [NE; NE]	2,38	[0,96; 6,73]	0,0627
Interaktion p-Wert									0,8223
Extranodale Erkrankung [eCRF]									
Ja	262	64 (24,4)	NE [NE; NE]	275	39 (14,2)	NE [NE; NE]	1,85	[1,25; 2,78]	0,0020*
Nein	35	12 (34,3)	NE [NE; NE]	22	2 (9,1)	NE [NE; NE]	4,44	[1,21; 28,53]	0,0222*
Interaktion p-Wert									0,2288
Gastrointestinale Erkrankung [eCRF]									
Ja	74	15 (20,3)	NE [NE; NE]	74	16 (21,6)	NE [NE; NE]	0,97	[0,47; 1,97]	0,9332
Nein	223	61 (27,4)	NE [NE; NE]	223	25 (11,2)	NE [NE; NE]	2,69	[1,71; 4,36]	<0,0001*
Interaktion p-Wert									0,0179*
LDH > ULN [eCRF]									
Ja	52	5 (9,6)	NE [NE; NE]	54	8 (14,8)	NE [NE; NE]	0,60	[0,18; 1,79]	0,3605
Nein	245	71 (29,0)	NE [NE; NE]	241	32 (13,3)	NE [NE; NE]	2,45	[1,63; 3,77]	<0,0001*
Interaktion p-Wert									0,0185*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.7 ECHO: Summary of subgroup analysis of time to first SOC: Erkrankungen des Immunsystems
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	9 (11,0)	NE [NE; NE]	81	3 (3,7)	NE [NE; NE]	2,85	[0,85; 12,85]	0,0920
Westeuropa	44	4 (9,1)	NE [NE; NE]	46	1 (2,2)	NE [NE; NE]	3,95	[0,58; 77,28]	0,1691
Andere	171	15 (8,8)	NE [NE; NE]	170	10 (5,9)	NE [NE; NE]	1,44	[0,65; 3,32]	0,3655
Interaktion p-Wert									0,5141
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	7 (7,1)	NE [NE; NE]	101	7 (6,9)	NE [NE; NE]	1,00	[0,34; 2,91]	0,9958
Intermediäres Risiko [4-5]	126	15 (11,9)	NE [NE; NE]	124	3 (2,4)	NE [NE; NE]	4,79	[1,58; 20,69]	0,0041*
Hohes Risiko [6-11]	72	6 (8,3)	NE [NE; NE]	72	4 (5,6)	NE [NE; NE]	1,37	[0,39; 5,34]	0,6262
Interaktion p-Wert									0,1181
Geschlecht [eCRF]									
Männlich	212	15 (7,1)	NE [NE; NE]	208	10 (4,8)	NE [NE; NE]	1,39	[0,63; 3,20]	0,4144
Weiblich	85	13 (15,3)	NE [NE; NE]	89	4 (4,5)	NE [NE; NE]	3,41	[1,20; 12,09]	0,0197*
Interaktion p-Wert									0,1917
Altersgruppe I [eCRF]									
< 70 Jahre	122	11 (9,0)	NE [NE; NE]	117	7 (6,0)	NE [NE; NE]	1,46	[0,57; 3,96]	0,4305
>= 70 Jahre	175	17 (9,7)	NE [NE; NE]	180	7 (3,9)	NE [NE; NE]	2,40	[1,03; 6,20]	0,0413*
Interaktion p-Wert									0,4511
Altersgruppe II [eCRF]									
< 75 Jahre	214	22 (10,3)	NE [NE; NE]	221	12 (5,4)	NE [NE; NE]	1,82	[0,92; 3,80]	0,0877
>= 75 Jahre	83	6 (7,2)	NE [NE; NE]	76	2 (2,6)	NE [NE; NE]	2,63	[0,61; 17,99]	0,2047
Interaktion p-Wert									0,6722
Abstammung [eCRF]									
Weiß	232	22 (9,5)	NE [NE; NE]	233	9 (3,9)	NE [NE; NE]	2,36	[1,12; 5,40]	0,0230*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.7 ECHO: Summary of subgroup analysis of time to first SOC: Erkrankungen des Immunsystems
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	6 (11,5)	NE [NE; NE]	53	4 (7,5)	NE [NE; NE]	1,55	[0,44; 6,08]	0,4905
Interaktion p-Wert									0,5838
ECOG-PS [eCRF]									
0	156	15 (9,6)	NE [NE; NE]	140	7 (5,0)	NE [NE; NE]	1,87	[0,79; 4,90]	0,1581
1	129	13 (10,1)	NE [NE; NE]	132	6 (4,5)	NE [NE; NE]	2,19	[0,87; 6,24]	0,0988
>=2	12	0	NE [NE; NE]	25	1 (4,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,8137
Bulky Disease I [eCRF]									
< 5 cm	185	16 (8,6)	NE [NE; NE]	185	9 (4,9)	NE [NE; NE]	1,80	[0,81; 4,24]	0,1517
>= 5 cm	112	12 (10,7)	NE [NE; NE]	112	5 (4,5)	NE [NE; NE]	2,12	[0,78; 6,65]	0,1429
Interaktion p-Wert									0,8081
Bulky Disease II [eCRF]									
< 10 cm	277	26 (9,4)	NE [NE; NE]	276	14 (5,1)	NE [NE; NE]	1,79	[0,95; 3,51]	0,0737
>= 10 cm	20	2 (10,0)	NE [NE; NE]	21	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	2 (4,2)	NE [NE; NE]	36	1 (2,8)	NE [NE; NE]	1,52	[0,15; 32,69]	0,7273
Stadium IV	249	26 (10,4)	NE [NE; NE]	261	13 (5,0)	NE [NE; NE]	2,00	[1,05; 4,03]	0,0350*
Interaktion p-Wert									0,8300
MCL-Typ [eCRF]									
Klassische Variante	195	19 (9,7)	NE [NE; NE]	205	8 (3,9)	NE [NE; NE]	2,48	[1,12; 6,01]	0,0240*
Blastoide und pleomorphische Variante	39	3 (7,7)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	2,02	[0,26; 40,84]	0,5218
Andere	0	0	NE	8	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,8698

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.7 ECHO: Summary of subgroup analysis of time to first SOC: Erkrankungen des Immunsystems
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	7 (6,4)	NE [NE; NE]	103	5 (4,9)	NE [NE; NE]	1,36	[0,43; 4,59]	0,5979
>= 30%	126	12 (9,5)	NE [NE; NE]	126	5 (4,0)	NE [NE; NE]	2,22	[0,82; 7,00]	0,1167
Interaktion p-Wert									0,5330
Ki-67 (%) II [eCRF]									
< 50%	179	14 (7,8)	NE [NE; NE]	164	9 (5,5)	NE [NE; NE]	1,45	[0,64; 3,48]	0,3810
>= 50%	56	5 (8,9)	NE [NE; NE]	65	1 (1,5)	NE [NE; NE]	5,05	[0,81; 96,82]	0,0859
Interaktion p-Wert									0,2456
Knochenmarksbeteiligung [eCRF]									
Ja	178	20 (11,2)	NE [NE; NE]	180	10 (5,6)	NE [NE; NE]	1,97	[0,94; 4,39]	0,0716
Nein	50	2 (4,0)	NE [NE; NE]	45	2 (4,4)	NE [NE; NE]	0,85	[0,10; 7,06]	0,8681
Interaktion p-Wert									0,4354
Extranodale Erkrankung [eCRF]									
Ja	262	27 (10,3)	NE [NE; NE]	275	13 (4,7)	NE [NE; NE]	2,10	[1,11; 4,21]	0,0230*
Nein	35	1 (2,9)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	0,62	[0,02; 15,55]	0,7326
Interaktion p-Wert									0,4101
Gastrointestinale Erkrankung [eCRF]									
Ja	74	5 (6,8)	NE [NE; NE]	74	2 (2,7)	NE [NE; NE]	2,36	[0,51; 16,50]	0,2805
Nein	223	23 (10,3)	NE [NE; NE]	223	12 (5,4)	NE [NE; NE]	1,85	[0,94; 3,85]	0,0753
Interaktion p-Wert									0,7874
LDH > ULN [eCRF]									
Ja	52	8 (15,4)	NE [NE; NE]	54	2 (3,7)	NE [NE; NE]	3,81	[0,96; 25,27]	0,0588
Nein	245	20 (8,2)	NE [NE; NE]	241	12 (5,0)	NE [NE; NE]	1,59	[0,79; 3,36]	0,1958
Interaktion p-Wert									0,2916

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.8 ECHO: Summary of subgroup analysis of time to first PT: Hypogammaglobulinaemie
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	2 (2,4)	NE [NE; NE]	81	0	NE [NE; NE]	NC	[NC]	NC
Westeuropa	44	2 (4,5)	NE [NE; NE]	46	0	NE [NE; NE]	NC	[NC]	NC
Andere	171	6 (3,5)	NE [NE; NE]	170	2 (1,2)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	2 (2,0)	NE [NE; NE]	101	2 (2,0)	NE [NE; NE]	NC	[NC]	NC
Intermediäres Risiko [4-5]	126	3 (2,4)	NE [NE; NE]	124	0	NE [NE; NE]	NC	[NC]	NC
Hohes Risiko [6-11]	72	5 (6,9)	NE [NE; NE]	72	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht [eCRF]									
Männlich	212	6 (2,8)	NE [NE; NE]	208	1 (0,5)	NE [NE; NE]	NC	[NC]	NC
Weiblich	85	4 (4,7)	NE [NE; NE]	89	1 (1,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Altersgruppe I [eCRF]									
< 70 Jahre	122	4 (3,3)	NE [NE; NE]	117	2 (1,7)	NE [NE; NE]	NC	[NC]	NC
>= 70 Jahre	175	6 (3,4)	NE [NE; NE]	180	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Altersgruppe II [eCRF]									
< 75 Jahre	214	9 (4,2)	NE [NE; NE]	221	2 (0,9)	NE [NE; NE]	4,38	[1,13; 28,71]	0,0315*
>= 75 Jahre	83	1 (1,2)	NE [NE; NE]	76	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Abstammung [eCRF]									
Weiß	232	6 (2,6)	NE [NE; NE]	233	2 (0,9)	NE [NE; NE]	NC	[NC]	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% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.8 ECHO: Summary of subgroup analysis of time to first PT: Hypogammaglobulinaemie
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	4 (7,7)	NE [NE; NE]	53	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ECOG-PS [eCRF]									
0	156	5 (3,2)	NE [NE; NE]	140	2 (1,4)	NE [NE; NE]	NC	[NC]	NC
1	129	5 (3,9)	NE [NE; NE]	132	0	NE [NE; NE]	NC	[NC]	NC
>=2	12	0	NE [NE; NE]	25	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Bulky Disease I [eCRF]									
< 5 cm	185	5 (2,7)	NE [NE; NE]	185	1 (0,5)	NE [NE; NE]	NC	[NC]	NC
>= 5 cm	112	5 (4,5)	NE [NE; NE]	112	1 (0,9)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Bulky Disease II [eCRF]									
< 10 cm	277	9 (3,2)	NE [NE; NE]	276	2 (0,7)	NE [NE; NE]	4,20	[1,08; 27,53]	0,0372*
>= 10 cm	20	1 (5,0)	NE [NE; NE]	21	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	0	NE [NE; NE]	36	0	NE [NE; NE]	NC	[NC]	NC
Stadium IV	249	10 (4,0)	NE [NE; NE]	261	2 (0,8)	NE [NE; NE]	4,94	[1,30; 32,15]	0,0167*
Interaktion p-Wert									NC
MCL-Typ [eCRF]									
Klassische Variante	195	6 (3,1)	NE [NE; NE]	205	2 (1,0)	NE [NE; NE]	NC	[NC]	NC
Blastoide und pleomorphische Variante	39	2 (5,1)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Andere	0	0	NE	8	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.8 ECHO: Summary of subgroup analysis of time to first PT: Hypogammaglobulinaemie
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b] [95%-KI] [b]		2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	2 (1,8)	NE [NE; NE]	103	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
>= 30%	126	5 (4,0)	NE [NE; NE]	126	1 (0,8)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ki-67 (%) II [eCRF]									
< 50%	179	5 (2,8)	NE [NE; NE]	164	2 (1,2)	NE [NE; NE]	NC	[NC]	NC
>= 50%	56	2 (3,6)	NE [NE; NE]	65	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Knochenmarksbeteiligung [eCRF]									
Ja	178	8 (4,5)	NE [NE; NE]	180	2 (1,1)	NE [NE; NE]	3,79	[0,95; 25,09]	0,0602
Nein	50	0	NE [NE; NE]	45	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Extranodale Erkrankung [eCRF]									
Ja	262	10 (3,8)	NE [NE; NE]	275	1 (0,4)	NE [NE; NE]	9,96	[1,91;182,68]	0,0035*
Nein	35	0	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Gastrointestinale Erkrankung [eCRF]									
Ja	74	4 (5,4)	NE [NE; NE]	74	0	NE [NE; NE]	NC	[NC]	NC
Nein	223	6 (2,7)	NE [NE; NE]	223	2 (0,9)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
LDH > ULN [eCRF]									
Ja	52	4 (7,7)	NE [NE; NE]	54	0	NE [NE; NE]	NC	[NC]	NC
Nein	245	6 (2,4)	NE [NE; NE]	241	2 (0,8)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.9 ECHO: Summary of subgroup analysis of time to first SOC: Erkrankungen des Nervensystems
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	69 (84,1)	0,5 [0,2; 1,4]	81	57 (70,4)	3,6 [1,8;14,2]	1,83	[1,29; 2,61]	0,0008*
Westeuropa	44	20 (45,5)	47,7 [17,4; NE]	46	10 (21,7)	NE [NE; NE]	2,24	[1,07; 5,00]	0,0312*
Andere	171	65 (38,0)	68,0 [55,0; NE]	170	57 (33,5)	65,3 [39,2; NE]	1,21	[0,85; 1,74]	0,2837
Interaktion p-Wert									0,1682
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	54 (54,5)	6,1 [1,6; NE]	101	47 (46,5)	29,7 [17,6; NE]	1,35	[0,91; 2,01]	0,1299
Intermediäres Risiko [4-5]	126	66 (52,4)	25,3 [6,9;63,1]	124	53 (42,7)	63,9 [25,0; NE]	1,42	[0,99; 2,04]	0,0576
Hohes Risiko [6-11]	72	34 (47,2)	12,6 [6,1; NE]	72	24 (33,3)	NE [NE; NE]	1,58	[0,94; 2,70]	0,0812
Interaktion p-Wert									0,8914
Geschlecht [eCRF]									
Männlich	212	95 (44,8)	55,0 [21,2; NE]	208	88 (42,3)	38,3 [27,1;65,3]	1,15	[0,86; 1,54]	0,3507
Weiblich	85	59 (69,4)	1,7 [0,5;10,9]	89	36 (40,4)	NE [NE; NE]	2,31	[1,54; 3,53]	<0,0001*
Interaktion p-Wert									0,0062*
Altersgruppe I [eCRF]									
< 70 Jahre	122	62 (50,8)	25,3 [2,8; NE]	117	47 (40,2)	65,3 [27,1; NE]	1,45	[0,99; 2,12]	0,0558
>= 70 Jahre	175	92 (52,6)	21,2 [6,9;49,8]	180	77 (42,8)	32,2 [18,4; NE]	1,41	[1,05; 1,92]	0,0247*
Interaktion p-Wert									0,9290
Altersgruppe II [eCRF]									
< 75 Jahre	214	107 (50,0)	33,1 [5,1; NE]	221	95 (43,0)	39,2 [25,0; NE]	1,33	[1,01; 1,75]	0,0447*
>= 75 Jahre	83	47 (56,6)	12,6 [3,5;55,0]	76	29 (38,2)	58,4 [24,8; NE]	1,72	[1,09; 2,77]	0,0194*
Interaktion p-Wert									0,3404
Abstammung [eCRF]									
Weiß	232	125 (53,9)	11,5 [4,5;38,9]	233	101 (43,3)	34,3 [25,0;65,3]	1,47	[1,13; 1,91]	0,0039*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.9 ECHO: Summary of subgroup analysis of time to first SOC: Erkrankungen des Nervensystems
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	17 (32,7)	NE [NE; NE]	53	19 (35,8)	NE [NE; NE]	0,91	[0,47; 1,76]	0,7860
Interaktion p-Wert									0,1857
ECOG-PS [eCRF]									
0	156	93 (59,6)	10,9 [2,1;34,4]	140	66 (47,1)	34,3 [20,9;65,3]	1,49	[1,09; 2,05]	0,0124*
1	129	57 (44,2)	NE [NE; NE]	132	49 (37,1)	NE [NE; NE]	1,35	[0,92; 1,98]	0,1224
>=2	12	4 (33,3)	NE [NE; NE]	25	9 (36,0)	16,6 [3,7; NE]	0,96	[0,26; 2,95]	0,9449
Interaktion p-Wert									0,7415
Bulky Disease I [eCRF]									
< 5 cm	185	102 (55,1)	11,5 [4,5;38,9]	185	87 (47,0)	32,2 [20,9;65,3]	1,39	[1,04; 1,85]	0,0243*
>= 5 cm	112	52 (46,4)	55,0 [6,1; NE]	112	37 (33,0)	NE [NE; NE]	1,53	[1,01; 2,35]	0,0463*
Interaktion p-Wert									0,7086
Bulky Disease II [eCRF]									
< 10 cm	277	146 (52,7)	13,4 [5,1;47,7]	276	117 (42,4)	38,3 [27,1; NE]	1,46	[1,15; 1,87]	0,0021*
>= 10 cm	20	8 (40,0)	63,1 [9,3; NE]	21	7 (33,3)	NE [NE; NE]	1,02	[0,37; 2,91]	0,9695
Interaktion p-Wert									0,5013
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	21 (43,8)	NE [NE; NE]	36	11 (30,6)	NE [NE; NE]	1,70	[0,83; 3,65]	0,1462
Stadium IV	249	133 (53,4)	13,4 [6,1;38,9]	261	113 (43,3)	38,3 [25,0;65,3]	1,41	[1,10; 1,82]	0,0067*
Interaktion p-Wert									0,6403
MCL-Typ [eCRF]									
Klassische Variante	195	104 (53,3)	17,4 [3,7;63,1]	205	97 (47,3)	28,6 [20,9;63,9]	1,30	[0,98; 1,71]	0,0645
Blastoide und pleomorphische Variante	39	17 (43,6)	33,1 [4,5; NE]	32	6 (18,8)	NE [NE; NE]	2,49	[1,03; 6,90]	0,0415*
Andere	0	0	NE	8	4 (50,0)	65,3 [2,8; NE]	NC	[NC]	NC
Interaktion p-Wert									0,1719

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.9 ECH0: Summary of subgroup analysis of time to first SOC: Erkrankungen des Nervensystems
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	55 (50,5)	38,9 [3,5; NE]	103	50 (48,5)	34,3 [17,6; NE]	1,22	[0,83; 1,80]	0,3059
>= 30%	126	58 (46,0)	47,7 [8,3; NE]	126	44 (34,9)	NE [NE; NE]	1,43	[0,97; 2,12]	0,0741
Interaktion p-Wert									0,5788
Ki-67 (%) II [eCRF]									
< 50%	179	86 (48,0)	47,7 [9,3;68,0]	164	81 (49,4)	29,7 [15,6; NE]	1,07	[0,79; 1,45]	0,6651
>= 50%	56	27 (48,2)	17,4 [1,0; NE]	65	13 (20,0)	NE [NE; NE]	2,94	[1,55; 5,89]	0,0009*
Interaktion p-Wert									0,0050*
Knochenmarksbeteiligung [eCRF]									
Ja	178	105 (59,0)	8,1 [3,0;25,3]	180	85 (47,2)	28,6 [17,2;63,9]	1,46	[1,10; 1,95]	0,0088*
Nein	50	27 (54,0)	11,5 [0,7; NE]	45	17 (37,8)	32,2 [24,8; NE]	1,90	[1,05; 3,56]	0,0352*
Interaktion p-Wert									0,4420
Extranodale Erkrankung [eCRF]									
Ja	262	136 (51,9)	17,4 [6,9;47,7]	275	118 (42,9)	38,3 [25,0;65,3]	1,38	[1,08; 1,76]	0,0110*
Nein	35	18 (51,4)	34,4 [0,7; NE]	22	6 (27,3)	NE [NE; NE]	2,41	[1,01; 6,64]	0,0475*
Interaktion p-Wert									0,2346
Gastrointestinale Erkrankung [eCRF]									
Ja	74	37 (50,0)	25,3 [2,8; NE]	74	32 (43,2)	29,7 [20,9; NE]	1,30	[0,81; 2,10]	0,2714
Nein	223	117 (52,5)	21,2 [6,7;55,0]	223	92 (41,3)	58,4 [27,2; NE]	1,47	[1,12; 1,93]	0,0058*
Interaktion p-Wert									0,6741
LDH > ULN [eCRF]									
Ja	52	21 (40,4)	NE [NE; NE]	54	15 (27,8)	63,9 [38,3; NE]	1,53	[0,79; 3,02]	0,2056
Nein	245	133 (54,3)	12,6 [4,5;47,7]	241	107 (44,4)	34,3 [25,0; NE]	1,43	[1,11; 1,85]	0,0057*
Interaktion p-Wert									0,8539

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.10 ECHO: Summary of subgroup analysis of time to first PT: Kopfschmerzen
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	39 (47,6)	NE [NE; NE]	81	24 (29,6)	NE [NE; NE]	2,06	[1,25; 3,48]	0,0045*
Westeuropa	44	8 (18,2)	NE [NE; NE]	46	3 (6,5)	NE [NE; NE]	3,02	[0,87; 13,77]	0,0826
Andere	171	43 (25,1)	NE [NE; NE]	170	15 (8,8)	NE [NE; NE]	3,13	[1,78; 5,83]	<0,0001*
Interaktion p-Wert									0,5489
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	39 (39,4)	NE [NE; NE]	101	17 (16,8)	NE [NE; NE]	2,79	[1,61; 5,06]	0,0002*
Intermediäres Risiko [4-5]	126	37 (29,4)	NE [NE; NE]	124	20 (16,1)	NE [NE; NE]	2,06	[1,21; 3,62]	0,0075*
Hohes Risiko [6-11]	72	14 (19,4)	NE [NE; NE]	72	5 (6,9)	NE [NE; NE]	3,03	[1,16; 9,38]	0,0228*
Interaktion p-Wert									0,6856
Geschlecht [eCRF]									
Männlich	212	50 (23,6)	NE [NE; NE]	208	27 (13,0)	NE [NE; NE]	1,98	[1,25; 3,21]	0,0033*
Weiblich	85	40 (47,1)	NE [NE; NE]	89	15 (16,9)	NE [NE; NE]	3,57	[2,02; 6,67]	<0,0001*
Interaktion p-Wert									0,1240
Altersgruppe I [eCRF]									
< 70 Jahre	122	44 (36,1)	NE [NE; NE]	117	16 (13,7)	NE [NE; NE]	3,12	[1,80; 5,70]	<0,0001*
>= 70 Jahre	175	46 (26,3)	NE [NE; NE]	180	26 (14,4)	NE [NE; NE]	2,02	[1,26; 3,31]	0,0033*
Interaktion p-Wert									0,2527
Altersgruppe II [eCRF]									
< 75 Jahre	214	67 (31,3)	NE [NE; NE]	221	31 (14,0)	NE [NE; NE]	2,56	[1,69; 3,96]	<0,0001*
>= 75 Jahre	83	23 (27,7)	NE [NE; NE]	76	11 (14,5)	NE [NE; NE]	2,15	[1,07; 4,59]	0,0304*
Interaktion p-Wert									0,6888
Abstammung [eCRF]									
Weiß	232	76 (32,8)	NE [NE; NE]	233	35 (15,0)	NE [NE; NE]	2,54	[1,72; 3,83]	<0,0001*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.10 ECHO: Summary of subgroup analysis of time to first PT: Kopfschmerzen
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	9 (17,3)	NE [NE; NE]	53	5 (9,4)	NE [NE; NE]	1,91	[0,66; 6,22]	0,2347
Interaktion p-Wert									0,6365
ECOG-PS [eCRF]									
0	156	51 (32,7)	NE [NE; NE]	140	20 (14,3)	NE [NE; NE]	2,65	[1,61; 4,55]	<0,0001*
1	129	37 (28,7)	NE [NE; NE]	132	19 (14,4)	NE [NE; NE]	2,27	[1,32; 4,02]	0,0028*
>=2	12	2 (16,7)	NE [NE; NE]	25	3 (12,0)	NE [NE; NE]	1,42	[0,19; 8,56]	0,7052
Interaktion p-Wert									0,7707
Bulky Disease I [eCRF]									
< 5 cm	185	61 (33,0)	NE [NE; NE]	185	29 (15,7)	NE [NE; NE]	2,43	[1,58; 3,83]	<0,0001*
>= 5 cm	112	29 (25,9)	NE [NE; NE]	112	13 (11,6)	NE [NE; NE]	2,48	[1,32; 4,94]	0,0045*
Interaktion p-Wert									0,9575
Bulky Disease II [eCRF]									
< 10 cm	277	90 (32,5)	NE [NE; NE]	276	39 (14,1)	NE [NE; NE]	2,65	[1,84; 3,91]	<0,0001*
>= 10 cm	20	0	NE [NE; NE]	21	3 (14,3)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	14 (29,2)	NE [NE; NE]	36	3 (8,3)	NE [NE; NE]	4,04	[1,32; 17,54]	0,0126*
Stadium IV	249	76 (30,5)	NE [NE; NE]	261	39 (14,9)	NE [NE; NE]	2,32	[1,59; 3,45]	<0,0001*
Interaktion p-Wert									0,3836
MCL-Typ [eCRF]									
Klassische Variante	195	63 (32,3)	NE [NE; NE]	205	35 (17,1)	NE [NE; NE]	2,20	[1,46; 3,35]	0,0001*
Blastoide und pleomorphische Variante	39	10 (25,6)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	8,90	[1,70;163,24]	0,0061*
Andere	0	0	NE	8	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,1215

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.10 ECHO: Summary of subgroup analysis of time to first PT: Kopfschmerzen
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	35 (32,1)	NE [NE; NE]	103	17 (16,5)	NE [NE; NE]	2,30	[1,31; 4,20]	0,0035*
>= 30%	126	31 (24,6)	NE [NE; NE]	126	17 (13,5)	NE [NE; NE]	1,96	[1,10; 3,61]	0,0229*
Interaktion p-Wert									0,7013
Ki-67 (%) II [eCRF]									
< 50%	179	50 (27,9)	NE [NE; NE]	164	31 (18,9)	NE [NE; NE]	1,65	[1,06; 2,61]	0,0263*
>= 50%	56	16 (28,6)	NE [NE; NE]	65	3 (4,6)	NE [NE; NE]	7,05	[2,35; 30,30]	0,0002*
Interaktion p-Wert									0,0156*
Knochenmarksbeteiligung [eCRF]									
Ja	178	54 (30,3)	NE [NE; NE]	180	27 (15,0)	NE [NE; NE]	2,30	[1,46; 3,71]	0,0003*
Nein	50	16 (32,0)	NE [NE; NE]	45	5 (11,1)	NE [NE; NE]	3,50	[1,37; 10,70]	0,0078*
Interaktion p-Wert									0,4472
Extranodale Erkrankung [eCRF]									
Ja	262	77 (29,4)	NE [NE; NE]	275	40 (14,5)	NE [NE; NE]	2,28	[1,57; 3,38]	<0,0001*
Nein	35	13 (37,1)	NE [NE; NE]	22	2 (9,1)	NE [NE; NE]	4,95	[1,37; 31,69]	0,0121*
Interaktion p-Wert									0,2851
Gastrointestinale Erkrankung [eCRF]									
Ja	74	22 (29,7)	NE [NE; NE]	74	13 (17,6)	NE [NE; NE]	1,89	[0,97; 3,86]	0,0635
Nein	223	68 (30,5)	NE [NE; NE]	223	29 (13,0)	NE [NE; NE]	2,69	[1,76; 4,21]	<0,0001*
Interaktion p-Wert									0,3986
LDH > ULN [eCRF]									
Ja	52	7 (13,5)	NE [NE; NE]	54	1 (1,9)	NE [NE; NE]	7,47	[1,33;139,60]	0,0195*
Nein	245	83 (33,9)	NE [NE; NE]	241	40 (16,6)	NE [NE; NE]	2,38	[1,64; 3,50]	<0,0001*
Interaktion p-Wert									0,2320

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.11 ECHO: Summary of subgroup analysis of time to first PT: Sinusitis
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	14 (17,1)	NE [NE; NE]	81	3 (3,7)	NE [NE; NE]	4,24	[1,38; 18,41]	0,0096*
Westeuropa	44	2 (4,5)	NE [NE; NE]	46	0	NE [NE; NE]	NC	[NC]	NC
Andere	171	3 (1,8)	NE [NE; NE]	170	3 (1,8)	NE [NE; NE]	0,95	[0,18; 5,12]	0,9479
Interaktion p-Wert									0,1453
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	7 (7,1)	NE [NE; NE]	101	2 (2,0)	NE [NE; NE]	3,36	[0,81; 22,53]	0,0980
Intermediäres Risiko [4-5]	126	9 (7,1)	NE [NE; NE]	124	2 (1,6)	NE [NE; NE]	4,01	[1,03; 26,33]	0,0441*
Hohes Risiko [6-11]	72	3 (4,2)	NE [NE; NE]	72	2 (2,8)	NE [NE; NE]	1,41	[0,23; 10,71]	0,7042
Interaktion p-Wert									0,6696
Geschlecht [eCRF]									
Männlich	212	10 (4,7)	NE [NE; NE]	208	6 (2,9)	NE [NE; NE]	1,52	[0,56; 4,46]	0,4143
Weiblich	85	9 (10,6)	NE [NE; NE]	89	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Altersgruppe I [eCRF]									
< 70 Jahre	122	9 (7,4)	NE [NE; NE]	117	4 (3,4)	NE [NE; NE]	1,97	[0,64; 7,27]	0,2428
>= 70 Jahre	175	10 (5,7)	NE [NE; NE]	180	2 (1,1)	NE [NE; NE]	4,82	[1,27; 31,38]	0,0186*
Interaktion p-Wert									0,3499
Altersgruppe II [eCRF]									
< 75 Jahre	214	18 (8,4)	NE [NE; NE]	221	5 (2,3)	NE [NE; NE]	3,47	[1,39; 10,52]	0,0068*
>= 75 Jahre	83	1 (1,2)	NE [NE; NE]	76	1 (1,3)	NE [NE; NE]	0,82	[0,03; 20,59]	0,8849
Interaktion p-Wert									0,3479
Abstammung [eCRF]									
Weiß	232	17 (7,3)	NE [NE; NE]	233	6 (2,6)	NE [NE; NE]	2,59	[1,08; 7,19]	0,0328*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.11 ECHO: Summary of subgroup analysis of time to first PT: Sinusitis
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	0	NE [NE; NE]	53	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ECOG-PS [eCRF]									
0	156	13 (8,3)	NE [NE; NE]	140	3 (2,1)	NE [NE; NE]	3,63	[1,17; 15,82]	0,0241*
1	129	6 (4,7)	NE [NE; NE]	132	3 (2,3)	NE [NE; NE]	1,98	[0,52; 9,39]	0,3193
>=2	12	0	NE [NE; NE]	25	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,5266
Bulky Disease I [eCRF]									
< 5 cm	185	11 (5,9)	NE [NE; NE]	185	3 (1,6)	NE [NE; NE]	3,70	[1,16; 16,38]	0,0262*
>= 5 cm	112	8 (7,1)	NE [NE; NE]	112	3 (2,7)	NE [NE; NE]	2,06	[0,60; 9,44]	0,2626
Interaktion p-Wert									0,5348
Bulky Disease II [eCRF]									
< 10 cm	277	17 (6,1)	NE [NE; NE]	276	5 (1,8)	NE [NE; NE]	3,16	[1,25; 9,62]	0,0137*
>= 10 cm	20	2 (10,0)	NE [NE; NE]	21	1 (4,8)	NE [NE; NE]	1,71	[0,16; 36,86]	0,6532
Interaktion p-Wert									0,6532
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	1 (2,1)	NE [NE; NE]	36	0	NE [NE; NE]	NC	[NC]	NC
Stadium IV	249	18 (7,2)	NE [NE; NE]	261	6 (2,3)	NE [NE; NE]	2,98	[1,25; 8,21]	0,0129*
Interaktion p-Wert									NC
MCL-Typ [eCRF]									
Klassische Variante	195	14 (7,2)	NE [NE; NE]	205	4 (2,0)	NE [NE; NE]	3,58	[1,29; 12,65]	0,0133*
Blastoide und pleomorphische Variante	39	2 (5,1)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	1,15	[0,11; 24,69]	0,9104
Andere	0	0	NE	8	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,4238

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.11 ECHO: Summary of subgroup analysis of time to first PT: Sinusitis
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	6 (5,5)	NE [NE; NE]	103	2 (1,9)	NE [NE; NE]	2,99	[0,69; 20,39]	0,1496
>= 30%	126	8 (6,3)	NE [NE; NE]	126	2 (1,6)	NE [NE; NE]	3,48	[0,87; 23,05]	0,0801
Interaktion p-Wert									0,8936
Ki-67 (%) II [eCRF]									
< 50%	179	12 (6,7)	NE [NE; NE]	164	3 (1,8)	NE [NE; NE]	3,84	[1,22; 16,86]	0,0199*
>= 50%	56	2 (3,6)	NE [NE; NE]	65	1 (1,5)	NE [NE; NE]	1,67	[0,16; 35,85]	0,6701
Interaktion p-Wert									0,5590
Knochenmarksbeteiligung [eCRF]									
Ja	178	16 (9,0)	NE [NE; NE]	180	4 (2,2)	NE [NE; NE]	3,86	[1,41; 13,47]	0,0070*
Nein	50	1 (2,0)	NE [NE; NE]	45	1 (2,2)	NE [NE; NE]	0,73	[0,03; 18,49]	0,8253
Interaktion p-Wert									0,2903
Extranodale Erkrankung [eCRF]									
Ja	262	18 (6,9)	NE [NE; NE]	275	6 (2,2)	NE [NE; NE]	2,98	[1,25; 8,22]	0,0128*
Nein	35	1 (2,9)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Gastrointestinale Erkrankung [eCRF]									
Ja	74	3 (4,1)	NE [NE; NE]	74	1 (1,4)	NE [NE; NE]	2,71	[0,35; 54,75]	0,3562
Nein	223	16 (7,2)	NE [NE; NE]	223	5 (2,2)	NE [NE; NE]	2,99	[1,17; 9,13]	0,0211*
Interaktion p-Wert									0,9386
LDH > ULN [eCRF]									
Ja	52	2 (3,8)	NE [NE; NE]	54	1 (1,9)	NE [NE; NE]	1,66	[0,16; 35,77]	0,6706
Nein	245	17 (6,9)	NE [NE; NE]	241	5 (2,1)	NE [NE; NE]	3,17	[1,25; 9,64]	0,0135*
Interaktion p-Wert									0,6370

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.12 ECHO: Summary of subgroup analysis of time to first PT: Rueckenschmerzen
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	20 (24,4)	NE [NE; NE]	81	11 (13,6)	NE [NE; NE]	1,81	[0,88; 3,92]	0,1049
Westeuropa	44	4 (9,1)	NE [NE; NE]	46	7 (15,2)	NE [NE; NE]	0,51	[0,13; 1,69]	0,2726
Andere	171	24 (14,0)	NE [NE; NE]	170	10 (5,9)	NE [NE; NE]	2,47	[1,21; 5,41]	0,0119*
Interaktion p-Wert									0,0849
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	11 (11,1)	NE [NE; NE]	101	11 (10,9)	NE [NE; NE]	1,00	[0,43; 2,33]	0,9989
Intermediäres Risiko [4-5]	126	26 (20,6)	NE [NE; NE]	124	12 (9,7)	NE [NE; NE]	2,20	[1,14; 4,52]	0,0190*
Hohes Risiko [6-11]	72	11 (15,3)	NE [NE; NE]	72	5 (6,9)	NE [NE; NE]	2,10	[0,76; 6,68]	0,1529
Interaktion p-Wert									0,3234
Geschlecht [eCRF]									
Männlich	212	23 (10,8)	NE [NE; NE]	208	21 (10,1)	NE [NE; NE]	1,04	[0,57; 1,89]	0,9046
Weiblich	85	25 (29,4)	NE [NE; NE]	89	7 (7,9)	NE [NE; NE]	4,03	[1,84; 10,10]	0,0003*
Interaktion p-Wert									0,0068*
Altersgruppe I [eCRF]									
< 70 Jahre	122	16 (13,1)	NE [NE; NE]	117	13 (11,1)	NE [NE; NE]	1,14	[0,55; 2,42]	0,7215
>= 70 Jahre	175	32 (18,3)	NE [NE; NE]	180	15 (8,3)	NE [NE; NE]	2,24	[1,24; 4,26]	0,0074*
Interaktion p-Wert									0,1661
Altersgruppe II [eCRF]									
< 75 Jahre	214	31 (14,5)	NE [NE; NE]	221	21 (9,5)	NE [NE; NE]	1,51	[0,87; 2,65]	0,1442
>= 75 Jahre	83	17 (20,5)	NE [NE; NE]	76	7 (9,2)	NE [NE; NE]	2,26	[0,98; 5,85]	0,0575
Interaktion p-Wert									0,4380
Abstammung [eCRF]									
Weiß	232	41 (17,7)	NE [NE; NE]	233	24 (10,3)	NE [NE; NE]	1,71	[1,04; 2,88]	0,0329*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.12 ECHO: Summary of subgroup analysis of time to first PT: Rueckenschmerzen
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	4 (7,7)	NE [NE; NE]	53	4 (7,5)	NE [NE; NE]	1,05	[0,25; 4,44]	0,9445
Interaktion p-Wert									0,5166
ECOG-PS [eCRF]									
0	156	33 (21,2)	NE [NE; NE]	140	16 (11,4)	NE [NE; NE]	1,91	[1,07; 3,56]	0,0284*
1	129	14 (10,9)	NE [NE; NE]	132	10 (7,6)	NE [NE; NE]	1,42	[0,64; 3,30]	0,3915
>=2	12	1 (8,3)	NE [NE; NE]	25	2 (8,0)	NE [NE; NE]	0,92	[0,04; 9,58]	0,9434
Interaktion p-Wert									0,7409
Bulky Disease I [eCRF]									
< 5 cm	185	29 (15,7)	NE [NE; NE]	185	16 (8,6)	NE [NE; NE]	1,87	[1,03; 3,53]	0,0391*
>= 5 cm	112	19 (17,0)	NE [NE; NE]	112	12 (10,7)	NE [NE; NE]	1,48	[0,72; 3,13]	0,2864
Interaktion p-Wert									0,6206
Bulky Disease II [eCRF]									
< 10 cm	277	45 (16,2)	NE [NE; NE]	276	24 (8,7)	NE [NE; NE]	1,88	[1,16; 3,14]	0,0104*
>= 10 cm	20	3 (15,0)	NE [NE; NE]	21	4 (19,0)	NE [NE; NE]	0,68	[0,13; 3,08]	0,6091
Interaktion p-Wert									0,2029
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	7 (14,6)	NE [NE; NE]	36	3 (8,3)	NE [NE; NE]	1,78	[0,50; 8,28]	0,3861
Stadium IV	249	41 (16,5)	NE [NE; NE]	261	25 (9,6)	NE [NE; NE]	1,71	[1,05; 2,85]	0,0313*
Interaktion p-Wert									0,9553
MCL-Typ [eCRF]									
Klassische Variante	195	35 (17,9)	NE [NE; NE]	205	20 (9,8)	NE [NE; NE]	1,89	[1,10; 3,33]	0,0207*
Blastoide und pleomorphische Variante	39	6 (15,4)	NE [NE; NE]	32	4 (12,5)	NE [NE; NE]	1,05	[0,30; 4,10]	0,9425
Andere	0	0	NE	8	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,4112

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.12 ECHO: Summary of subgroup analysis of time to first PT: Rueckenschmerzen
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	16 (14,7)	NE [NE; NE]	103	6 (5,8)	NE [NE; NE]	2,83	[1,16; 7,89]	0,0209*
>= 30%	126	19 (15,1)	NE [NE; NE]	126	17 (13,5)	NE [NE; NE]	1,03	[0,53; 2,00]	0,9330
Interaktion p-Wert									0,0749
Ki-67 (%) II [eCRF]									
< 50%	179	24 (13,4)	NE [NE; NE]	164	17 (10,4)	NE [NE; NE]	1,37	[0,74; 2,59]	0,3186
>= 50%	56	11 (19,6)	NE [NE; NE]	65	6 (9,2)	NE [NE; NE]	1,92	[0,73; 5,57]	0,1896
Interaktion p-Wert									0,5713
Knochenmarksbeteiligung [eCRF]									
Ja	178	32 (18,0)	NE [NE; NE]	180	21 (11,7)	NE [NE; NE]	1,51	[0,88; 2,66]	0,1351
Nein	50	10 (20,0)	NE [NE; NE]	45	3 (6,7)	NE [NE; NE]	3,18	[0,97; 14,19]	0,0559
Interaktion p-Wert									0,2801
Extranodale Erkrankung [eCRF]									
Ja	262	41 (15,6)	NE [NE; NE]	275	25 (9,1)	NE [NE; NE]	1,71	[1,05; 2,85]	0,0314*
Nein	35	7 (20,0)	NE [NE; NE]	22	3 (13,6)	NE [NE; NE]	1,53	[0,43; 7,11]	0,5259
Interaktion p-Wert									0,8811
Gastrointestinale Erkrankung [eCRF]									
Ja	74	11 (14,9)	NE [NE; NE]	74	8 (10,8)	NE [NE; NE]	1,33	[0,54; 3,44]	0,5366
Nein	223	37 (16,6)	NE [NE; NE]	223	20 (9,0)	NE [NE; NE]	1,86	[1,09; 3,27]	0,0219*
Interaktion p-Wert									0,5367
LDH > ULN [eCRF]									
Ja	52	10 (19,2)	NE [NE; NE]	54	3 (5,6)	NE [NE; NE]	3,18	[0,97; 14,16]	0,0563
Nein	245	38 (15,5)	NE [NE; NE]	241	25 (10,4)	NE [NE; NE]	1,51	[0,92; 2,54]	0,1031
Interaktion p-Wert									0,2740

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.13 ECHO: Summary of subgroup analysis of time to first PT: Hypokalzaemie
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	5 (6,1)	NE [NE; NE]	81	1 (1,2)	NE [NE; NE]	4,75	[0,77; 90,99]	0,0997
Westeuropa	44	0	NE [NE; NE]	46	0	NE [NE; NE]	NC	[NC]	NC
Andere	171	10 (5,8)	NE [NE; NE]	170	4 (2,4)	NE [NE; NE]	2,43	[0,81; 8,85]	0,1150
Interaktion p-Wert									0,5756
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	6 (6,1)	NE [NE; NE]	101	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
Intermediäres Risiko [4-5]	126	4 (3,2)	NE [NE; NE]	124	4 (3,2)	NE [NE; NE]	NC	[NC]	NC
Hohes Risiko [6-11]	72	5 (6,9)	NE [NE; NE]	72	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht [eCRF]									
Männlich	212	12 (5,7)	NE [NE; NE]	208	3 (1,4)	NE [NE; NE]	3,79	[1,20; 16,64]	0,0212*
Weiblich	85	3 (3,5)	NE [NE; NE]	89	2 (2,2)	NE [NE; NE]	1,47	[0,24; 11,14]	0,6712
Interaktion p-Wert									0,4012
Altersgruppe I [eCRF]									
< 70 Jahre	122	6 (4,9)	NE [NE; NE]	117	3 (2,6)	NE [NE; NE]	1,85	[0,49; 8,76]	0,3719
>= 70 Jahre	175	9 (5,1)	NE [NE; NE]	180	2 (1,1)	NE [NE; NE]	4,42	[1,14; 28,99]	0,0303*
Interaktion p-Wert									0,4030
Altersgruppe II [eCRF]									
< 75 Jahre	214	11 (5,1)	NE [NE; NE]	221	3 (1,4)	NE [NE; NE]	3,64	[1,14; 16,10]	0,0284*
>= 75 Jahre	83	4 (4,8)	NE [NE; NE]	76	2 (2,6)	NE [NE; NE]	1,71	[0,33; 12,37]	0,5234
Interaktion p-Wert									0,4925
Abstammung [eCRF]									
Weiß	232	8 (3,4)	NE [NE; NE]	233	2 (0,9)	NE [NE; NE]	3,80	[0,95; 25,17]	0,0596

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.13 ECHO: Summary of subgroup analysis of time to first PT: Hypokalzaemie
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	7 (13,5)	NE [NE; NE]	53	3 (5,7)	NE [NE; NE]	2,52	[0,70; 11,70]	0,1607
Interaktion p-Wert									0,6944
ECOG-PS [eCRF]									
0	156	5 (3,2)	NE [NE; NE]	140	2 (1,4)	NE [NE; NE]	2,13	[0,46; 14,88]	0,3444
1	129	9 (7,0)	NE [NE; NE]	132	2 (1,5)	NE [NE; NE]	4,58	[1,18; 30,05]	0,0262*
>=2	12	1 (8,3)	NE [NE; NE]	25	1 (4,0)	NE [NE; NE]	1,95	[0,08; 49,23]	0,6403
Interaktion p-Wert									0,7533
Bulky Disease I [eCRF]									
< 5 cm	185	8 (4,3)	NE [NE; NE]	185	4 (2,2)	NE [NE; NE]	2,00	[0,63; 7,50]	0,2428
>= 5 cm	112	7 (6,3)	NE [NE; NE]	112	1 (0,9)	NE [NE; NE]	6,19	[1,10;115,84]	0,0371*
Interaktion p-Wert									0,3287
Bulky Disease II [eCRF]									
< 10 cm	277	12 (4,3)	NE [NE; NE]	276	5 (1,8)	NE [NE; NE]	2,29	[0,85; 7,20]	0,1035
>= 10 cm	20	3 (15,0)	NE [NE; NE]	21	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	1 (2,1)	NE [NE; NE]	36	0	NE [NE; NE]	NC	[NC]	NC
Stadium IV	249	14 (5,6)	NE [NE; NE]	261	5 (1,9)	NE [NE; NE]	2,84	[1,09; 8,79]	0,0326*
Interaktion p-Wert									NC
MCL-Typ [eCRF]									
Klassische Variante	195	10 (5,1)	NE [NE; NE]	205	3 (1,5)	NE [NE; NE]	3,42	[1,04; 15,24]	0,0416*
Blastoide und pleomorphische Variante	39	2 (5,1)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Andere	0	0	NE	8	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.13 ECHO: Summary of subgroup analysis of time to first PT: Hypokalzaemie
 Safety Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	4 (3,7)	NE [NE; NE]	103	0	NE [NE; NE]	NC	[NC]	NC
>= 30%	126	9 (7,1)	NE [NE; NE]	126	3 (2,4)	NE [NE; NE]	2,64	[0,79; 11,92]	0,1199
Interaktion p-Wert									NC
Ki-67 (%) II [eCRF]									
< 50%	179	8 (4,5)	NE [NE; NE]	164	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
>= 50%	56	5 (8,9)	NE [NE; NE]	65	2 (3,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Knochenmarksbeteiligung [eCRF]									
Ja	178	8 (4,5)	NE [NE; NE]	180	0	NE [NE; NE]	NC	[NC]	NC
Nein	50	0	NE [NE; NE]	45	1 (2,2)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Extranodale Erkrankung [eCRF]									
Ja	262	14 (5,3)	NE [NE; NE]	275	5 (1,8)	NE [NE; NE]	2,85	[1,09; 8,82]	0,0321*
Nein	35	1 (2,9)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Gastrointestinale Erkrankung [eCRF]									
Ja	74	3 (4,1)	NE [NE; NE]	74	1 (1,4)	NE [NE; NE]	2,91	[0,37; 58,77]	0,3209
Nein	223	12 (5,4)	NE [NE; NE]	223	4 (1,8)	NE [NE; NE]	2,86	[0,997; 10,24]	0,0508
Interaktion p-Wert									0,9901
LDH > ULN [eCRF]									
Ja	52	2 (3,8)	NE [NE; NE]	54	1 (1,9)	NE [NE; NE]	1,89	[0,18; 40,65]	0,5932
Nein	245	13 (5,3)	NE [NE; NE]	241	4 (1,7)	NE [NE; NE]	3,10	[1,10; 10,99]	0,0322*
Interaktion p-Wert									0,7205

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.14 ECH0: Summary of subgroup analysis of time to first PT: Gewicht erhoeht
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	2 (2,4)	NE [NE; NE]	81	7 (8,6)	NE [NE; NE]	0,26	[0,04; 1,07]	0,0626
Westeuropa	44	0	NE [NE; NE]	46	2 (4,3)	NE [NE; NE]	NC	[NC]	NC
Andere	171	5 (2,9)	NE [NE; NE]	170	7 (4,1)	NE [NE; NE]	0,69	[0,20; 2,16]	0,5234
Interaktion p-Wert									0,3088
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	2 (2,0)	NE [NE; NE]	101	4 (4,0)	NE [NE; NE]	0,49	[0,07; 2,53]	0,4016
Intermediäres Risiko [4-5]	126	3 (2,4)	NE [NE; NE]	124	10 (8,1)	NE [NE; NE]	0,27	[0,06; 0,89]	0,0309*
Hohes Risiko [6-11]	72	2 (2,8)	NE [NE; NE]	72	2 (2,8)	NE [NE; NE]	0,93	[0,11; 7,71]	0,9385
Interaktion p-Wert									0,5772
Geschlecht [eCRF]									
Männlich	212	6 (2,8)	NE [NE; NE]	208	13 (6,3)	NE [NE; NE]	0,43	[0,15; 1,09]	0,0750
Weiblich	85	1 (1,2)	NE [NE; NE]	89	3 (3,4)	NE [NE; NE]	0,32	[0,02; 2,51]	0,2902
Interaktion p-Wert									0,8154
Altersgruppe I [eCRF]									
< 70 Jahre	122	2 (1,6)	NE [NE; NE]	117	8 (6,8)	NE [NE; NE]	0,22	[0,03; 0,90]	0,0335*
>= 70 Jahre	175	5 (2,9)	NE [NE; NE]	180	8 (4,4)	NE [NE; NE]	0,61	[0,18; 1,82]	0,3752
Interaktion p-Wert									0,2929
Altersgruppe II [eCRF]									
< 75 Jahre	214	7 (3,3)	NE [NE; NE]	221	14 (6,3)	NE [NE; NE]	0,49	[0,18; 1,17]	0,1087
>= 75 Jahre	83	0	NE [NE; NE]	76	2 (2,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Abstammung [eCRF]									
Weiß	232	3 (1,3)	NE [NE; NE]	233	12 (5,2)	NE [NE; NE]	0,23	[0,05; 0,74]	0,0117*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.14 ECH0: Summary of subgroup analysis of time to first PT: Gewicht erhoeht
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	4 (7,7)	NE [NE; NE]	53	3 (5,7)	NE [NE; NE]	1,38	[0,31; 7,02]	0,6690
Interaktion p-Wert									0,0688
ECOG-PS [eCRF]									
0	156	2 (1,3)	NE [NE; NE]	140	6 (4,3)	NE [NE; NE]	0,28	[0,04; 1,21]	0,0897
1	129	5 (3,9)	NE [NE; NE]	132	10 (7,6)	NE [NE; NE]	0,50	[0,15; 1,40]	0,1876
>=2	12	0	NE [NE; NE]	25	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,5495
Bulky Disease I [eCRF]									
< 5 cm	185	2 (1,1)	NE [NE; NE]	185	11 (5,9)	NE [NE; NE]	0,18	[0,03; 0,65]	0,0073*
>= 5 cm	112	5 (4,5)	NE [NE; NE]	112	5 (4,5)	NE [NE; NE]	0,90	[0,25; 3,25]	0,8723
Interaktion p-Wert									0,0837
Bulky Disease II [eCRF]									
< 10 cm	277	6 (2,2)	NE [NE; NE]	276	13 (4,7)	NE [NE; NE]	0,43	[0,15; 1,10]	0,0783
>= 10 cm	20	1 (5,0)	NE [NE; NE]	21	3 (14,3)	NE [NE; NE]	0,32	[0,02; 2,51]	0,2895
Interaktion p-Wert									0,8083
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	0	NE [NE; NE]	36	1 (2,8)	NE [NE; NE]	NC	[NC]	NC
Stadium IV	249	7 (2,8)	NE [NE; NE]	261	15 (5,7)	NE [NE; NE]	0,46	[0,18; 1,09]	0,0791
Interaktion p-Wert									NC
MCL-Typ [eCRF]									
Klassische Variante	195	6 (3,1)	NE [NE; NE]	205	9 (4,4)	NE [NE; NE]	0,68	[0,23; 1,88]	0,4565
Blastoide und pleomorphische Variante	39	0	NE [NE; NE]	32	3 (9,4)	NE [NE; NE]	NC	[NC]	NC
Andere	0	0	NE	8	1 (12,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									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% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.14 ECH0: Summary of subgroup analysis of time to first PT: Gewicht erhoeht
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	6 (5,5)	NE [NE; NE]	103	4 (3,9)	NE [NE; NE]	1,46	[0,42; 5,72]	0,5523
>= 30%	126	1 (0,8)	NE [NE; NE]	126	6 (4,8)	NE [NE; NE]	0,15	[0,01; 0,89]	0,0352*
Interaktion p-Wert									0,0432*
Ki-67 (%) II [eCRF]									
< 50%	179	7 (3,9)	NE [NE; NE]	164	7 (4,3)	NE [NE; NE]	0,92	[0,32; 2,70]	0,8838
>= 50%	56	0	NE [NE; NE]	65	3 (4,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Knochenmarksbeteiligung [eCRF]									
Ja	178	4 (2,2)	NE [NE; NE]	180	13 (7,2)	NE [NE; NE]	0,29	[0,08; 0,82]	0,0183*
Nein	50	0	NE [NE; NE]	45	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Extranodale Erkrankung [eCRF]									
Ja	262	7 (2,7)	NE [NE; NE]	275	15 (5,5)	NE [NE; NE]	0,46	[0,18; 1,09]	0,0802
Nein	35	0	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Gastrointestinale Erkrankung [eCRF]									
Ja	74	1 (1,4)	NE [NE; NE]	74	3 (4,1)	NE [NE; NE]	0,33	[0,02; 2,54]	0,2951
Nein	223	6 (2,7)	NE [NE; NE]	223	13 (5,8)	NE [NE; NE]	0,43	[0,15; 1,09]	0,0752
Interaktion p-Wert									0,8221
LDH > ULN [eCRF]									
Ja	52	1 (1,9)	NE [NE; NE]	54	4 (7,4)	NE [NE; NE]	0,22	[0,01; 1,48]	0,1254
Nein	245	6 (2,4)	NE [NE; NE]	241	12 (5,0)	NE [NE; NE]	0,47	[0,16; 1,22]	0,1218
Interaktion p-Wert									0,5102

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.15 ECHO: Summary of subgroup analysis of time to first PT: Kontusion
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	15 (18,3)	NE [NE; NE]	81	10 (12,3)	NE [NE; NE]	1,41	[0,64; 3,25]	0,3929
Westeuropa	44	1 (2,3)	NE [NE; NE]	46	1 (2,2)	NE [NE; NE]	0,94	[0,04; 23,69]	0,9635
Andere	171	17 (9,9)	NE [NE; NE]	170	5 (2,9)	NE [NE; NE]	3,39	[1,34; 10,30]	0,0088*
Interaktion p-Wert									0,3405
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	9 (9,1)	NE [NE; NE]	101	3 (3,0)	NE [NE; NE]	3,00	[0,90; 13,54]	0,0761
Intermediäres Risiko [4-5]	126	16 (12,7)	NE [NE; NE]	124	8 (6,5)	NE [NE; NE]	1,92	[0,84; 4,74]	0,1212
Hohes Risiko [6-11]	72	8 (11,1)	NE [NE; NE]	72	5 (6,9)	NE [NE; NE]	1,50	[0,50; 4,97]	0,4700
Interaktion p-Wert									0,7221
Geschlecht [eCRF]									
Männlich	212	25 (11,8)	NE [NE; NE]	208	10 (4,8)	NE [NE; NE]	2,44	[1,21; 5,34]	0,0120*
Weiblich	85	8 (9,4)	NE [NE; NE]	89	6 (6,7)	NE [NE; NE]	1,28	[0,44; 3,87]	0,6512
Interaktion p-Wert									0,3248
Altersgruppe I [eCRF]									
< 70 Jahre	122	7 (5,7)	NE [NE; NE]	117	4 (3,4)	NE [NE; NE]	1,61	[0,49; 6,14]	0,4402
>= 70 Jahre	175	26 (14,9)	NE [NE; NE]	180	12 (6,7)	NE [NE; NE]	2,19	[1,13; 4,50]	0,0199*
Interaktion p-Wert									0,6708
Altersgruppe II [eCRF]									
< 75 Jahre	214	18 (8,4)	NE [NE; NE]	221	12 (5,4)	NE [NE; NE]	1,48	[0,72; 3,15]	0,2907
>= 75 Jahre	83	15 (18,1)	NE [NE; NE]	76	4 (5,3)	NE [NE; NE]	3,49	[1,27; 12,23]	0,0143*
Interaktion p-Wert									0,1892
Abstammung [eCRF]									
Weiß	232	29 (12,5)	NE [NE; NE]	233	14 (6,0)	NE [NE; NE]	2,02	[1,09; 3,94]	0,0258*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.15 ECHO: Summary of subgroup analysis of time to first PT: Kontusion
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	3 (5,8)	NE [NE; NE]	53	1 (1,9)	NE [NE; NE]	3,12	[0,40; 63,04]	0,2886
Interaktion p-Wert									0,7092
ECOG-PS [eCRF]									
0	156	19 (12,2)	NE [NE; NE]	140	7 (5,0)	NE [NE; NE]	2,40	[1,05; 6,15]	0,0364*
1	129	13 (10,1)	NE [NE; NE]	132	7 (5,3)	NE [NE; NE]	1,89	[0,77; 5,02]	0,1656
>=2	12	1 (8,3)	NE [NE; NE]	25	2 (8,0)	NE [NE; NE]	0,93	[0,04; 9,69]	0,9511
Interaktion p-Wert									0,7381
Bulky Disease I [eCRF]									
< 5 cm	185	16 (8,6)	NE [NE; NE]	185	11 (5,9)	NE [NE; NE]	1,45	[0,68; 3,21]	0,3381
>= 5 cm	112	17 (15,2)	NE [NE; NE]	112	5 (4,5)	NE [NE; NE]	3,15	[1,24; 9,58]	0,0142*
Interaktion p-Wert									0,2185
Bulky Disease II [eCRF]									
< 10 cm	277	29 (10,5)	NE [NE; NE]	276	15 (5,4)	NE [NE; NE]	1,87	[1,02; 3,59]	0,0426*
>= 10 cm	20	4 (20,0)	NE [NE; NE]	21	1 (4,8)	NE [NE; NE]	3,98	[0,59; 77,88]	0,1666
Interaktion p-Wert									0,4920
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	8 (16,7)	NE [NE; NE]	36	0	NE [NE; NE]	NC	[NC]	NC
Stadium IV	249	25 (10,0)	NE [NE; NE]	261	16 (6,1)	NE [NE; NE]	1,57	[0,85; 3,00]	0,1529
Interaktion p-Wert									NC
MCL-Typ [eCRF]									
Klassische Variante	195	24 (12,3)	NE [NE; NE]	205	13 (6,3)	NE [NE; NE]	1,92	[0,99; 3,88]	0,0529
Blastoide und pleomorphische Variante	39	5 (12,8)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	3,65	[0,59; 70,01]	0,1795
Andere	0	0	NE	8	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,5528

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.15 ECHO: Summary of subgroup analysis of time to first PT: Kontusion
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	13 (11,9)	NE [NE; NE]	103	8 (7,8)	NE [NE; NE]	1,62	[0,68; 4,09]	0,2779
>= 30%	126	15 (11,9)	NE [NE; NE]	126	4 (3,2)	NE [NE; NE]	3,60	[1,31; 12,64]	0,0118*
Interaktion p-Wert									0,2572
Ki-67 (%) II [eCRF]									
< 50%	179	17 (9,5)	NE [NE; NE]	164	12 (7,3)	NE [NE; NE]	1,33	[0,64; 2,86]	0,4432
>= 50%	56	11 (19,6)	NE [NE; NE]	65	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Knochenmarksbeteiligung [eCRF]									
Ja	178	23 (12,9)	NE [NE; NE]	180	13 (7,2)	NE [NE; NE]	1,73	[0,89; 3,52]	0,1058
Nein	50	8 (16,0)	NE [NE; NE]	45	1 (2,2)	NE [NE; NE]	7,35	[1,35;136,37]	0,0178*
Interaktion p-Wert									0,1378
Extranodale Erkrankung [eCRF]									
Ja	262	29 (11,1)	NE [NE; NE]	275	16 (5,8)	NE [NE; NE]	1,84	[1,01; 3,47]	0,0451*
Nein	35	4 (11,4)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Gastrointestinale Erkrankung [eCRF]									
Ja	74	9 (12,2)	NE [NE; NE]	74	3 (4,1)	NE [NE; NE]	3,06	[0,91; 13,79]	0,0711
Nein	223	24 (10,8)	NE [NE; NE]	223	13 (5,8)	NE [NE; NE]	1,77	[0,91; 3,57]	0,0917
Interaktion p-Wert									0,4525
LDH > ULN [eCRF]									
Ja	52	6 (11,5)	NE [NE; NE]	54	2 (3,7)	NE [NE; NE]	2,79	[0,64; 19,05]	0,1778
Nein	245	27 (11,0)	NE [NE; NE]	241	13 (5,4)	NE [NE; NE]	2,02	[1,06; 4,05]	0,0313*
Interaktion p-Wert									0,7100

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.16 ECHO: Summary of subgroup analysis of time to first PT: Reaktion im Zusammenhang mit einer Infusion
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	17 (20,7)	NE [NE; NE]	81	33 (40,7)	NE [NE; NE]	0,44	[0,24; 0,79]	0,0051*
Westeuropa	44	7 (15,9)	NE [NE; NE]	46	7 (15,2)	NE [NE; NE]	1,01	[0,35; 2,96]	0,9778
Andere	171	19 (11,1)	NE [NE; NE]	170	25 (14,7)	NE [NE; NE]	0,72	[0,39; 1,30]	0,2799
Interaktion p-Wert									0,3071
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	7 (7,1)	NE [NE; NE]	101	18 (17,8)	NE [NE; NE]	0,37	[0,14; 0,84]	0,0169*
Intermediäres Risiko [4-5]	126	17 (13,5)	NE [NE; NE]	124	18 (14,5)	NE [NE; NE]	0,91	[0,47; 1,77]	0,7826
Hohes Risiko [6-11]	72	19 (26,4)	NE [NE; NE]	72	29 (40,3)	NE [NE; NE]	0,57	[0,31; 1,01]	0,0521
Interaktion p-Wert									0,2395
Geschlecht [eCRF]									
Männlich	212	33 (15,6)	NE [NE; NE]	208	45 (21,6)	NE [NE; NE]	0,68	[0,43; 1,07]	0,0952
Weiblich	85	10 (11,8)	NE [NE; NE]	89	20 (22,5)	NE [NE; NE]	0,47	[0,21; 0,98]	0,0448*
Interaktion p-Wert									0,4021
Altersgruppe I [eCRF]									
< 70 Jahre	122	14 (11,5)	NE [NE; NE]	117	23 (19,7)	NE [NE; NE]	0,55	[0,28; 1,06]	0,0736
>= 70 Jahre	175	29 (16,6)	NE [NE; NE]	180	42 (23,3)	NE [NE; NE]	0,66	[0,41; 1,06]	0,0829
Interaktion p-Wert									0,6625
Altersgruppe II [eCRF]									
< 75 Jahre	214	26 (12,1)	NE [NE; NE]	221	48 (21,7)	NE [NE; NE]	0,52	[0,32; 0,83]	0,0060*
>= 75 Jahre	83	17 (20,5)	NE [NE; NE]	76	17 (22,4)	NE [NE; NE]	0,87	[0,44; 1,71]	0,6767
Interaktion p-Wert									0,2253
Abstammung [eCRF]									
Weiß	232	34 (14,7)	NE [NE; NE]	233	54 (23,2)	NE [NE; NE]	0,59	[0,38; 0,90]	0,0137*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.16 ECHO: Summary of subgroup analysis of time to first PT: Reaktion im Zusammenhang mit einer Infusion
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	7 (13,5)	NE [NE; NE]	53	7 (13,2)	NE [NE; NE]	1,01	[0,35; 2,95]	0,9853
Interaktion p-Wert									0,3499
ECOG-PS [eCRF]									
0	156	23 (14,7)	NE [NE; NE]	140	23 (16,4)	NE [NE; NE]	0,87	[0,49; 1,56]	0,6350
1	129	20 (15,5)	NE [NE; NE]	132	33 (25,0)	NE [NE; NE]	0,58	[0,32; 0,99]	0,0473*
>=2	12	0	NE [NE; NE]	25	9 (36,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,3111
Bulky Disease I [eCRF]									
< 5 cm	185	30 (16,2)	NE [NE; NE]	185	45 (24,3)	NE [NE; NE]	0,63	[0,39; 0,99]	0,0447*
>= 5 cm	112	13 (11,6)	NE [NE; NE]	112	20 (17,9)	NE [NE; NE]	0,60	[0,29; 1,20]	0,1512
Interaktion p-Wert									0,9310
Bulky Disease II [eCRF]									
< 10 cm	277	40 (14,4)	NE [NE; NE]	276	60 (21,7)	NE [NE; NE]	0,63	[0,42; 0,93]	0,0202*
>= 10 cm	20	3 (15,0)	72,9 [72,9; NE]	21	5 (23,8)	NE [NE; NE]	0,53	[0,11; 2,18]	0,3833
Interaktion p-Wert									0,8354
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	4 (8,3)	NE [NE; NE]	36	3 (8,3)	NE [NE; NE]	0,97	[0,21; 4,91]	0,9651
Stadium IV	249	39 (15,7)	NE [NE; NE]	261	62 (23,8)	NE [NE; NE]	0,61	[0,41; 0,91]	0,0159*
Interaktion p-Wert									0,5645
MCL-Typ [eCRF]									
Klassische Variante	195	27 (13,8)	NE [NE; NE]	205	40 (19,5)	NE [NE; NE]	0,68	[0,41; 1,09]	0,1118
Blastoide und pleomorphische Variante	39	9 (23,1)	NE [NE; NE]	32	11 (34,4)	NE [NE; NE]	0,58	[0,23; 1,40]	0,2211
Andere	0	0	NE	8	1 (12,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,7610

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.1.16 ECHO: Summary of subgroup analysis of time to first PT: Reaktion im Zusammenhang mit einer Infusion
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]			
	n			n					
Ki-67 (%) I [eCRF]									
< 30%	109	13 (11,9)	NE [NE; NE]	103	15 (14,6)	NE [NE; NE]	0,81	[0,38; 1,71]	0,5773
>= 30%	126	20 (15,9)	NE [NE; NE]	126	27 (21,4)	NE [NE; NE]	0,67	[0,37; 1,20]	0,1794
Interaktion p-Wert									0,7029
Ki-67 (%) II [eCRF]									
< 50%	179	22 (12,3)	NE [NE; NE]	164	28 (17,1)	NE [NE; NE]	0,69	[0,39; 1,21]	0,1930
>= 50%	56	11 (19,6)	NE [NE; NE]	65	14 (21,5)	NE [NE; NE]	0,83	[0,37; 1,83]	0,6473
Interaktion p-Wert									0,7078
Knochenmarksbeteiligung [eCRF]									
Ja	178	32 (18,0)	NE [NE; NE]	180	55 (30,6)	NE [NE; NE]	0,53	[0,34; 0,82]	0,0041*
Nein	50	5 (10,0)	NE [NE; NE]	45	5 (11,1)	NE [NE; NE]	0,87	[0,24; 3,13]	0,8260
Interaktion p-Wert									0,4694
Extranodale Erkrankung [eCRF]									
Ja	262	39 (14,9)	NE [NE; NE]	275	63 (22,9)	NE [NE; NE]	0,61	[0,40; 0,90]	0,0129*
Nein	35	4 (11,4)	NE [NE; NE]	22	2 (9,1)	NE [NE; NE]	1,22	[0,24; 8,79]	0,8170
Interaktion p-Wert									0,4203
Gastrointestinale Erkrankung [eCRF]									
Ja	74	10 (13,5)	NE [NE; NE]	74	14 (18,9)	NE [NE; NE]	0,68	[0,29; 1,52]	0,3454
Nein	223	33 (14,8)	NE [NE; NE]	223	51 (22,9)	NE [NE; NE]	0,60	[0,39; 0,93]	0,0214*
Interaktion p-Wert									0,7998
LDH > ULN [eCRF]									
Ja	52	12 (23,1)	NE [NE; NE]	54	17 (31,5)	NE [NE; NE]	0,68	[0,32; 1,42]	0,3104
Nein	245	31 (12,7)	NE [NE; NE]	241	46 (19,1)	NE [NE; NE]	0,62	[0,39; 0,98]	0,0396*
Interaktion p-Wert									0,8328

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.2.1 ECHO: Summary of subgroup analysis of time to first SUE
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	50 (61,0)	26,7 [10,8;47,6]	81	53 (65,4)	23,5 [7,6;30,9]	0,87	[0,59; 1,28]	0,4790
Westeuropa	44	34 (77,3)	12,0 [7,3;28,4]	46	29 (63,0)	19,4 [7,5;34,7]	1,23	[0,75; 2,02]	0,4201
Andere	171	121 (70,8)	14,6 [9,4;18,5]	170	102 (60,0)	24,0 [15,1;27,6]	1,25	[0,96; 1,62]	0,1022
Interaktion p-Wert									0,3033
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	60 (60,6)	29,6 [20,8;43,2]	101	66 (65,3)	25,2 [19,4;30,4]	0,84	[0,59; 1,19]	0,3356
Intermediäres Risiko [4-5]	126	92 (73,0)	11,1 [8,1;18,5]	124	73 (58,9)	23,7 [14,6;29,1]	1,35	[0,997; 1,85]	0,0525
Hohes Risiko [6-11]	72	53 (73,6)	6,6 [2,8;11,2]	72	45 (62,5)	7,9 [4,1;23,5]	1,25	[0,84; 1,86]	0,2761
Interaktion p-Wert									0,1175
Geschlecht [eCRF]									
Männlich	212	147 (69,3)	15,4 [10,8;20,3]	208	127 (61,1)	22,0 [14,6;27,6]	1,14	[0,90; 1,45]	0,2646
Weiblich	85	58 (68,2)	15,7 [8,1;28,0]	89	57 (64,0)	24,3 [14,5;28,8]	1,08	[0,75; 1,56]	0,6895
Interaktion p-Wert									0,7860
Altersgruppe I [eCRF]									
< 70 Jahre	122	80 (65,6)	23,7 [15,5;32,2]	117	71 (60,7)	24,4 [17,7;28,9]	1,02	[0,74; 1,40]	0,9141
>= 70 Jahre	175	125 (71,4)	11,1 [7,8;16,4]	180	113 (62,8)	17,8 [10,3;25,2]	1,22	[0,95; 1,58]	0,1217
Interaktion p-Wert									0,3800
Altersgruppe II [eCRF]									
< 75 Jahre	214	149 (69,6)	16,7 [11,3;23,7]	221	132 (59,7)	24,4 [19,5;28,9]	1,19	[0,94; 1,50]	0,1486
>= 75 Jahre	83	56 (67,5)	11,1 [7,3;21,2]	76	52 (68,4)	14,5 [6,2;21,8]	0,95	[0,65; 1,38]	0,7726
Interaktion p-Wert									0,3145
Abstammung [eCRF]									
Weiß	232	164 (70,7)	16,2 [10,7;22,2]	233	147 (63,1)	19,5 [14,5;24,4]	1,08	[0,86; 1,35]	0,4962

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.2.1 ECHO: Summary of subgroup analysis of time to first SUE
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Subgruppen	Acala+BR (N=297)				Placebo+BR (N=297)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Nicht-weiß	52	32 (61,5)	15,7 [9,4;32,2]		53	29 (54,7)	27,6 [24,0;33,6]		1,40	[0,85; 2,34]	0,1840
Interaktion p-Wert											0,3480
ECOG-PS [eCRF]											
0	156	105 (67,3)	20,3 [11,3;30,4]		140	86 (61,4)	23,7 [16,2;29,5]		1,11	[0,83; 1,48]	0,4775
1	129	92 (71,3)	12,8 [7,3;17,3]		132	83 (62,9)	23,5 [10,0;27,6]		1,22	[0,90; 1,64]	0,1956
>=2	12	8 (66,7)	4,4 [0,1; NE]		25	15 (60,0)	7,9 [1,1; NE]		0,97	[0,39; 2,24]	0,9484
Interaktion p-Wert											0,8397
Bulky Disease I [eCRF]											
< 5 cm	185	129 (69,7)	15,7 [11,1;22,2]		185	115 (62,2)	24,4 [19,4;28,6]		1,19	[0,93; 1,53]	0,1696
>= 5 cm	112	76 (67,9)	15,0 [7,8;30,4]		112	69 (61,6)	14,5 [9,2;23,5]		1,00	[0,72; 1,39]	0,9774
Interaktion p-Wert											0,4156
Bulky Disease II [eCRF]											
< 10 cm	277	190 (68,6)	15,5 [11,1;22,2]		276	169 (61,2)	23,7 [17,2;27,3]		1,15	[0,94; 1,42]	0,1852
>= 10 cm	20	15 (75,0)	10,2 [0,9;33,5]		21	15 (71,4)	5,3 [0,2;33,6]		0,78	[0,38; 1,62]	0,5050
Interaktion p-Wert											0,3139
Ann Arbor-Stadium für Lymphome [eCRF]											
Stadium I-III	48	35 (72,9)	15,7 [7,1;22,4]		36	22 (61,1)	24,4 [17,1;28,9]		1,39	[0,82; 2,40]	0,2236
Stadium IV	249	170 (68,3)	15,5 [10,9;22,2]		261	162 (62,1)	20,0 [14,0;27,0]		1,09	[0,88; 1,35]	0,4501
Interaktion p-Wert											0,4010
MCL-Typ [eCRF]											
Klassische Variante	195	137 (70,3)	15,5 [10,8;22,4]		205	129 (62,9)	22,0 [16,2;27,3]		1,11	[0,87; 1,41]	0,3918
Blastoide und pleomorphische Variante	39	28 (71,8)	10,3 [3,1;20,3]		32	23 (71,9)	6,2 [1,0;27,6]		0,86	[0,49; 1,50]	0,5836
Andere	0	0	NE		8	5 (62,5)	27,0 [0,3; NE]		NC	[NC]	NC
Interaktion p-Wert											0,3992

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.2.1 ECHO: Summary of subgroup analysis of time to first SUE
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	Anzahl (%) der Patienten mit		Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit		Mediane Zeit [95%-KI] (Monate) [a]			
	n	Ereignis		n	Ereignis				
Ki-67 (%) I [eCRF]									
< 30%	109	78 (71,6)	16,4 [10,3;28,4]	103	64 (62,1)	24,0 [19,4;30,9]	1,24	[0,89; 1,73]	0,2055
>= 30%	126	88 (69,8)	11,1 [8,1;19,4]	126	79 (62,7)	17,7 [9,7;25,2]	1,13	[0,83; 1,53]	0,4380
Interaktion p-Wert									0,6843
Ki-67 (%) II [eCRF]									
< 50%	179	128 (71,5)	15,7 [11,1;25,2]	164	103 (62,8)	24,3 [19,9;28,9]	1,24	[0,96; 1,61]	0,1032
>= 50%	56	38 (67,9)	8,7 [5,5;16,7]	65	40 (61,5)	8,0 [5,0;28,2]	1,03	[0,66; 1,60]	0,9117
Interaktion p-Wert									0,4685
Knochenmarksbeteiligung [eCRF]									
Ja	178	125 (70,2)	15,0 [10,3;22,2]	180	113 (62,8)	19,4 [9,8;28,8]	1,13	[0,87; 1,45]	0,3636
Nein	50	36 (72,0)	12,4 [7,3;23,7]	45	24 (53,3)	24,4 [16,2;40,6]	1,44	[0,86; 2,44]	0,1643
Interaktion p-Wert									0,4020
Extranodale Erkrankung [eCRF]									
Ja	262	180 (68,7)	15,3 [10,8;20,8]	275	169 (61,5)	21,8 [15,1;27,3]	1,13	[0,92; 1,40]	0,2382
Nein	35	25 (71,4)	19,4 [7,3;31,9]	22	15 (68,2)	24,0 [16,2;27,2]	1,06	[0,56; 2,05]	0,8645
Interaktion p-Wert									0,8376
Gastrointestinale Erkrankung [eCRF]									
Ja	74	47 (63,5)	25,3 [7,9;42,8]	74	41 (55,4)	28,1 [16,6;36,1]	1,14	[0,75; 1,74]	0,5338
Nein	223	158 (70,9)	15,3 [10,8;19,4]	223	143 (64,1)	19,5 [14,5;24,4]	1,12	[0,89; 1,41]	0,3249
Interaktion p-Wert									0,9361
LDH > ULN [eCRF]									
Ja	52	35 (67,3)	8,3 [5,7;26,8]	54	36 (66,7)	9,7 [4,7;23,5]	0,79	[0,50; 1,27]	0,3335
Nein	245	170 (69,4)	16,4 [11,3;22,2]	241	146 (60,6)	24,4 [19,5;28,8]	1,21	[0,97; 1,51]	0,0946
Interaktion p-Wert									0,1121

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.2.2 ECHO: Summary of subgroup analysis of time to first SUE SOC: Erkrankungen der Haut und des Unterhautgewebes
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	3 (3,7)	NE [NE; NE]	81	0	NE [NE; NE]	NC	[NC]	NC
Westeuropa	44	2 (4,5)	NE [NE; NE]	46	1 (2,2)	NE [NE; NE]	1,91	[0,18; 41,18]	0,5861
Andere	171	8 (4,7)	NE [NE; NE]	170	2 (1,2)	NE [NE; NE]	3,95	[0,99; 26,19]	0,0518
Interaktion p-Wert									0,6253
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	6 (6,1)	NE [NE; NE]	101	0	NE [NE; NE]	NC	[NC]	NC
Intermediäres Risiko [4-5]	126	6 (4,8)	NE [NE; NE]	124	1 (0,8)	NE [NE; NE]	NC	[NC]	NC
Hohes Risiko [6-11]	72	1 (1,4)	NE [NE; NE]	72	2 (2,8)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht [eCRF]									
Männlich	212	8 (3,8)	NE [NE; NE]	208	3 (1,4)	NE [NE; NE]	2,54	[0,74; 11,62]	0,1446
Weiblich	85	5 (5,9)	NE [NE; NE]	89	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Altersgruppe I [eCRF]									
< 70 Jahre	122	8 (6,6)	NE [NE; NE]	117	0	NE [NE; NE]	NC	[NC]	NC
>= 70 Jahre	175	5 (2,9)	NE [NE; NE]	180	3 (1,7)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Altersgruppe II [eCRF]									
< 75 Jahre	214	11 (5,1)	NE [NE; NE]	221	2 (0,9)	NE [NE; NE]	5,58	[1,50; 36,09]	0,0082*
>= 75 Jahre	83	2 (2,4)	NE [NE; NE]	76	1 (1,3)	NE [NE; NE]	1,80	[0,17; 38,68]	0,6227
Interaktion p-Wert									0,4493
Abstammung [eCRF]									
Weiß	232	9 (3,9)	NE [NE; NE]	233	3 (1,3)	NE [NE; NE]	2,95	[0,88; 13,31]	0,0812

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.2.2 ECHO: Summary of subgroup analysis of time to first SUE SOC: Erkrankungen der Haut und des Unterhautgewebes
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	3 (5,8)	NE [NE; NE]	53	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ECOG-PS [eCRF]									
0	156	3 (1,9)	NE [NE; NE]	140	2 (1,4)	NE [NE; NE]	1,30	[0,22; 9,90]	0,7696
1	129	10 (7,8)	NE [NE; NE]	132	1 (0,8)	NE [NE; NE]	10,45	[2,00;191,76]	0,0028*
>=2	12	0	NE [NE; NE]	25	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,1199
Bulky Disease I [eCRF]									
< 5 cm	185	7 (3,8)	NE [NE; NE]	185	1 (0,5)	NE [NE; NE]	NC	[NC]	NC
>= 5 cm	112	6 (5,4)	NE [NE; NE]	112	2 (1,8)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Bulky Disease II [eCRF]									
< 10 cm	277	13 (4,7)	NE [NE; NE]	276	2 (0,7)	NE [NE; NE]	6,38	[1,76; 40,78]	0,0030*
>= 10 cm	20	0	NE [NE; NE]	21	1 (4,8)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	5 (10,4)	NE [NE; NE]	36	0	NE [NE; NE]	NC	[NC]	NC
Stadium IV	249	8 (3,2)	NE [NE; NE]	261	3 (1,1)	NE [NE; NE]	2,74	[0,79; 12,50]	0,1145
Interaktion p-Wert									NC
MCL-Typ [eCRF]									
Klassische Variante	195	9 (4,6)	NE [NE; NE]	205	1 (0,5)	NE [NE; NE]	9,34	[1,75;172,19]	0,0057*
Blastoide und pleomorphische Variante	39	0	NE [NE; NE]	32	2 (6,3)	NE [NE; NE]	NC	[NC]	NC
Andere	0	0	NE	8	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.2.2 ECHO: Summary of subgroup analysis of time to first SUE SOC: Erkrankungen der Haut und des Unterhautgewebes
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	6 (5,5)	NE [NE; NE]	103	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
>= 30%	126	6 (4,8)	NE [NE; NE]	126	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ki-67 (%) II [eCRF]									
< 50%	179	9 (5,0)	NE [NE; NE]	164	1 (0,6)	NE [NE; NE]	8,47	[1,59;156,19]	0,0087*
>= 50%	56	3 (5,4)	NE [NE; NE]	65	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Knochenmarksbeteiligung [eCRF]									
Ja	178	6 (3,4)	NE [NE; NE]	180	3 (1,7)	NE [NE; NE]	NC	[NC]	NC
Nein	50	4 (8,0)	NE [NE; NE]	45	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Extranodale Erkrankung [eCRF]									
Ja	262	10 (3,8)	NE [NE; NE]	275	3 (1,1)	NE [NE; NE]	3,42	[1,05; 15,27]	0,0414*
Nein	35	3 (8,6)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Gastrointestinale Erkrankung [eCRF]									
Ja	74	5 (6,8)	NE [NE; NE]	74	0	NE [NE; NE]	NC	[NC]	NC
Nein	223	8 (3,6)	NE [NE; NE]	223	3 (1,3)	NE [NE; NE]	2,63	[0,76; 12,01]	0,1304
Interaktion p-Wert									NC
LDH > ULN [eCRF]									
Ja	52	1 (1,9)	NE [NE; NE]	54	1 (1,9)	NE [NE; NE]	0,95	[0,04; 23,98]	0,9705
Nein	245	12 (4,9)	NE [NE; NE]	241	2 (0,8)	NE [NE; NE]	5,89	[1,61; 37,86]	0,0054*
Interaktion p-Wert									0,2675

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.2.3 ECHO: Summary of subgroup analysis of time to first SUE SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen
 Safety Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]	
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Geographic Region [IXRS]										
Nordamerika	82	1 (1,2)	NE [NE; NE]	81	4 (4,9)	NE [NE; NE]	0,23	[0,01; 1,53]	0,1348	
Westeuropa	44	3 (6,8)	NE [NE; NE]	46	4 (8,7)	NE [NE; NE]	0,70	[0,14; 3,18]	0,6398	
Andere	171	3 (1,8)	NE [NE; NE]	170	10 (5,9)	NE [NE; NE]	0,29	[0,06; 0,94]	0,0392*	
Interaktion p-Wert									0,5981	
Vereinfachter MIPI-Score [IXRS]										
Geringes Risiko [0-3]	99	1 (1,0)	NE [NE; NE]	101	5 (5,0)	NE [NE; NE]	0,19	[0,01; 1,19]	0,0790	
Intermediäres Risiko [4-5]	126	3 (2,4)	NE [NE; NE]	124	5 (4,0)	NE [NE; NE]	0,56	[0,11; 2,27]	0,4162	
Hohes Risiko [6-11]	72	3 (4,2)	NE [NE; NE]	72	8 (11,1)	NE [NE; NE]	0,35	[0,08; 1,20]	0,0978	
Interaktion p-Wert									0,6956	
Geschlecht [eCRF]										
Männlich	212	2 (0,9)	NE [NE; NE]	208	15 (7,2)	NE [NE; NE]	0,12	[0,02; 0,44]	0,0004*	
Weiblich	85	5 (5,9)	NE [NE; NE]	89	3 (3,4)	NE [NE; NE]	1,65	[0,40; 8,05]	0,4857	
Interaktion p-Wert									0,0075*	
Altersgruppe I [eCRF]										
< 70 Jahre	122	2 (1,6)	NE [NE; NE]	117	5 (4,3)	NE [NE; NE]	0,36	[0,05; 1,67]	0,1983	
>= 70 Jahre	175	5 (2,9)	NE [NE; NE]	180	13 (7,2)	NE [NE; NE]	0,37	[0,12; 0,99]	0,0473*	
Interaktion p-Wert									0,9738	
Altersgruppe II [eCRF]										
< 75 Jahre	214	5 (2,3)	NE [NE; NE]	221	14 (6,3)	NE [NE; NE]	0,35	[0,11; 0,91]	0,0314*	
>= 75 Jahre	83	2 (2,4)	NE [NE; NE]	76	4 (5,3)	NE [NE; NE]	0,42	[0,06; 2,16]	0,3010	
Interaktion p-Wert									0,8554	
Abstammung [eCRF]										

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.2.3 ECHO: Summary of subgroup analysis of time to first SUE SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Weiß	232	7 (3,0)	NE [NE; NE]	233	14 (6,0)	NE [NE; NE]	0,47	[0,18; 1,13]	0,0926
Nicht-weiß	52	0	NE [NE; NE]	53	2 (3,8)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ECOG-PS [eCRF]									
0	156	5 (3,2)	NE [NE; NE]	140	4 (2,9)	NE [NE; NE]	1,07	[0,28; 4,34]	0,9159
1	129	1 (0,8)	NE [NE; NE]	132	12 (9,1)	NE [NE; NE]	0,08	[0,00; 0,41]	0,0008*
>=2	12	1 (8,3)	NE [NE; NE]	25	2 (8,0)	NE [NE; NE]	0,94	[0,04; 9,86]	0,9608
Interaktion p-Wert									0,0438*
Bulky Disease I [eCRF]									
< 5 cm	185	6 (3,2)	NE [NE; NE]	185	10 (5,4)	NE [NE; NE]	0,59	[0,20; 1,60]	0,3038
>= 5 cm	112	1 (0,9)	NE [NE; NE]	112	8 (7,1)	NE [NE; NE]	0,11	[0,01; 0,59]	0,0070*
Interaktion p-Wert									0,1043
Bulky Disease II [eCRF]									
< 10 cm	277	7 (2,5)	NE [NE; NE]	276	16 (5,8)	NE [NE; NE]	0,41	[0,16; 0,97]	0,0412*
>= 10 cm	20	0	NE [NE; NE]	21	2 (9,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	1 (2,1)	NE [NE; NE]	36	2 (5,6)	NE [NE; NE]	0,35	[0,02; 3,67]	0,3753
Stadium IV	249	6 (2,4)	NE [NE; NE]	261	16 (6,1)	NE [NE; NE]	0,37	[0,13; 0,90]	0,0281*
Interaktion p-Wert									0,9663
MCL-Typ [eCRF]									
Klassische Variante	195	4 (2,1)	NE [NE; NE]	205	12 (5,9)	NE [NE; NE]	0,33	[0,09; 0,95]	0,0391*
Blastoide und pleomorphische Variante	39	1 (2,6)	NE [NE; NE]	32	4 (12,5)	NE [NE; NE]	0,17	[0,01; 1,14]	0,0687
Andere	0	0	NE	8	0	NE [NE; NE]	NC	[NC]	NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.2.3 ECHO: Summary of subgroup analysis of time to first SUE SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Interaktion p-Wert									0,5772
Ki-67 (%) I [eCRF]									
< 30%	109	1 (0,9)	NE [NE; NE]	103	3 (2,9)	NE [NE; NE]	0,32	[0,02; 2,50]	0,2882
>= 30%	126	4 (3,2)	NE [NE; NE]	126	9 (7,1)	NE [NE; NE]	0,40	[0,11; 1,24]	0,1139
Interaktion p-Wert									0,8596
Ki-67 (%) II [eCRF]									
< 50%	179	4 (2,2)	NE [NE; NE]	164	10 (6,1)	NE [NE; NE]	0,37	[0,10; 1,10]	0,0734
>= 50%	56	1 (1,8)	NE [NE; NE]	65	2 (3,1)	NE [NE; NE]	0,50	[0,02; 5,22]	0,5594
Interaktion p-Wert									0,8225
Knochenmarksbeteiligung [eCRF]									
Ja	178	6 (3,4)	NE [NE; NE]	180	11 (6,1)	NE [NE; NE]	0,52	[0,18; 1,37]	0,1903
Nein	50	1 (2,0)	NE [NE; NE]	45	3 (6,7)	NE [NE; NE]	0,28	[0,01; 2,16]	0,2270
Interaktion p-Wert									0,6012
Extranodale Erkrankung [eCRF]									
Ja	262	6 (2,3)	NE [NE; NE]	275	16 (5,8)	NE [NE; NE]	0,37	[0,13; 0,91]	0,0291*
Nein	35	1 (2,9)	NE [NE; NE]	22	2 (9,1)	NE [NE; NE]	0,28	[0,01; 2,96]	0,2848
Interaktion p-Wert									0,8330
Gastrointestinale Erkrankung [eCRF]									
Ja	74	3 (4,1)	NE [NE; NE]	74	4 (5,4)	NE [NE; NE]	0,72	[0,14; 3,26]	0,6624
Nein	223	4 (1,8)	NE [NE; NE]	223	14 (6,3)	NE [NE; NE]	0,27	[0,08; 0,75]	0,0104*
Interaktion p-Wert									0,3027
LDH > ULN [eCRF]									
Ja	52	1 (1,9)	NE [NE; NE]	54	5 (9,3)	NE [NE; NE]	0,19	[0,01; 1,15]	0,0733

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.2.3 ECHO: Summary of subgroup analysis of time to first SUE SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]		2-seitiger p-Wert [b]
	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]			
	n			n					
Nein	245	6 (2,4)	NE [NE; NE]	241	13 (5,4)	NE [NE; NE]	0,43	[0,15; 1,09]	0,0771
Interaktion p-Wert									0,4582

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.

Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.2.4 ECHO: Summary of subgroup analysis of time to first SUE PT: Reaktion im Zusammenhang mit einer Infusion
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	0	NE [NE; NE]	81	4 (4,9)	NE [NE; NE]	NC	[NC]	NC
Westeuropa	44	1 (2,3)	NE [NE; NE]	46	2 (4,3)	NE [NE; NE]	NC	[NC]	NC
Andere	171	1 (0,6)	NE [NE; NE]	170	4 (2,4)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	0	NE [NE; NE]	101	3 (3,0)	NE [NE; NE]	NC	[NC]	NC
Intermediäres Risiko [4-5]	126	1 (0,8)	NE [NE; NE]	124	1 (0,8)	NE [NE; NE]	NC	[NC]	NC
Hohes Risiko [6-11]	72	1 (1,4)	NE [NE; NE]	72	6 (8,3)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht [eCRF]									
Männlich	212	0	NE [NE; NE]	208	9 (4,3)	NE [NE; NE]	NC	[NC]	NC
Weiblich	85	2 (2,4)	NE [NE; NE]	89	1 (1,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Altersgruppe I [eCRF]									
< 70 Jahre	122	0	NE [NE; NE]	117	3 (2,6)	NE [NE; NE]	NC	[NC]	NC
>= 70 Jahre	175	2 (1,1)	NE [NE; NE]	180	7 (3,9)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Altersgruppe II [eCRF]									
< 75 Jahre	214	1 (0,5)	NE [NE; NE]	221	8 (3,6)	NE [NE; NE]	NC	[NC]	NC
>= 75 Jahre	83	1 (1,2)	NE [NE; NE]	76	2 (2,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Abstammung [eCRF]									
Weiß	232	2 (0,9)	NE [NE; NE]	233	8 (3,4)	NE [NE; NE]	0,24	[0,04; 0,97]	0,0446*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.2.4 ECHO: Summary of subgroup analysis of time to first SUE PT: Reaktion im Zusammenhang mit einer Infusion
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	0	NE [NE; NE]	53	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ECOG-PS [eCRF]									
0	156	2 (1,3)	NE [NE; NE]	140	2 (1,4)	NE [NE; NE]	NC	[NC]	NC
1	129	0	NE [NE; NE]	132	7 (5,3)	NE [NE; NE]	NC	[NC]	NC
>=2	12	0	NE [NE; NE]	25	1 (4,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Bulky Disease I [eCRF]									
< 5 cm	185	2 (1,1)	NE [NE; NE]	185	5 (2,7)	NE [NE; NE]	NC	[NC]	NC
>= 5 cm	112	0	NE [NE; NE]	112	5 (4,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Bulky Disease II [eCRF]									
< 10 cm	277	2 (0,7)	NE [NE; NE]	276	8 (2,9)	NE [NE; NE]	0,24	[0,04; 0,96]	0,0436*
>= 10 cm	20	0	NE [NE; NE]	21	2 (9,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	0	NE [NE; NE]	36	0	NE [NE; NE]	NC	[NC]	NC
Stadium IV	249	2 (0,8)	NE [NE; NE]	261	10 (3,8)	NE [NE; NE]	0,20	[0,03; 0,77]	0,0169*
Interaktion p-Wert									NC
MCL-Typ [eCRF]									
Klassische Variante	195	1 (0,5)	NE [NE; NE]	205	5 (2,4)	NE [NE; NE]	NC	[NC]	NC
Blastoide und pleomorphische Variante	39	1 (2,6)	NE [NE; NE]	32	3 (9,4)	NE [NE; NE]	NC	[NC]	NC
Andere	0	0	NE	8	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									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% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.2.4 ECHO: Summary of subgroup analysis of time to first SUE PT: Reaktion im Zusammenhang mit einer Infusion
 Safety Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b] [95%-KI] [b]		2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	0	NE [NE; NE]	103	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
>= 30%	126	1 (0,8)	NE [NE; NE]	126	4 (3,2)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ki-67 (%) II [eCRF]									
< 50%	179	0	NE [NE; NE]	164	4 (2,4)	NE [NE; NE]	NC	[NC]	NC
>= 50%	56	1 (1,8)	NE [NE; NE]	65	1 (1,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Knochenmarksbeteiligung [eCRF]									
Ja	178	2 (1,1)	NE [NE; NE]	180	8 (4,4)	NE [NE; NE]	0,24	[0,04; 0,97]	0,0453*
Nein	50	0	NE [NE; NE]	45	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Extranodale Erkrankung [eCRF]									
Ja	262	2 (0,8)	NE [NE; NE]	275	10 (3,6)	NE [NE; NE]	0,20	[0,03; 0,77]	0,0171*
Nein	35	0	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Gastrointestinale Erkrankung [eCRF]									
Ja	74	1 (1,4)	NE [NE; NE]	74	1 (1,4)	NE [NE; NE]	0,99	[0,04; 24,99]	0,9939
Nein	223	1 (0,4)	NE [NE; NE]	223	9 (4,0)	NE [NE; NE]	0,11	[0,01; 0,57]	0,0057*
Interaktion p-Wert									0,2096
LDH > ULN [eCRF]									
Ja	52	0	NE [NE; NE]	54	4 (7,4)	NE [NE; NE]	NC	[NC]	NC
Nein	245	2 (0,8)	NE [NE; NE]	241	6 (2,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.3.1 ECHO: Summary of subgroup analysis of time to first Therapieabbruch aufgrund von UE
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)				Placebo+BR (N=297)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Geographic Region [IXRS]											
Nordamerika	82	39 (47,6)	56,0 [26,9; NE]		81	32 (39,5)	57,8 [28,9; NE]		1,11	[0,70; 1,79]	0,6502
Westeuropa	44	25 (56,8)	37,5 [10,2; NE]		46	16 (34,8)	NE [NE; NE]		1,53	[0,83; 2,93]	0,1769
Andere	171	86 (50,3)	34,8 [27,7;47,4]		170	57 (33,5)	NE [NE; NE]		1,50	[1,07; 2,10]	0,0172*
Interaktion p-Wert											0,5681
Vereinfachter MIPI-Score [IXRS]											
Geringes Risiko [0-3]	99	47 (47,5)	47,4 [26,9; NE]		101	31 (30,7)	NE [NE; NE]		1,59	[1,02; 2,53]	0,0420*
Intermediäres Risiko [4-5]	126	58 (46,0)	56,0 [33,0;70,0]		124	51 (41,1)	NE [NE; NE]		1,05	[0,72; 1,53]	0,8056
Hohes Risiko [6-11]	72	45 (62,5)	24,6 [10,1;33,6]		72	23 (31,9)	NE [NE; NE]		1,80	[1,10; 3,03]	0,0185*
Interaktion p-Wert											0,1719
Geschlecht [eCRF]											
Männlich	212	109 (51,4)	35,3 [26,9;52,2]		208	74 (35,6)	NE [NE; NE]		1,40	[1,05; 1,89]	0,0240*
Weiblich	85	41 (48,2)	56,0 [26,7; NE]		89	31 (34,8)	NE [NE; NE]		1,33	[0,83; 2,13]	0,2327
Interaktion p-Wert											0,8470
Altersgruppe I [eCRF]											
< 70 Jahre	122	55 (45,1)	56,0 [28,2; NE]		117	40 (34,2)	NE [NE; NE]		1,23	[0,82; 1,85]	0,3227
>= 70 Jahre	175	95 (54,3)	33,1 [25,3;47,4]		180	65 (36,1)	NE [NE; NE]		1,50	[1,10; 2,06]	0,0110*
Interaktion p-Wert											0,4451
Altersgruppe II [eCRF]											
< 75 Jahre	214	103 (48,1)	47,4 [33,0;63,2]		221	75 (33,9)	NE [NE; NE]		1,36	[1,01; 1,84]	0,0410*
>= 75 Jahre	83	47 (56,6)	28,6 [12,9;43,6]		76	30 (39,5)	57,8 [16,4; NE]		1,40	[0,89; 2,24]	0,1441
Interaktion p-Wert											0,9154
Abstammung [eCRF]											
Weiß	232	118 (50,9)	39,0 [30,1;59,9]		233	83 (35,6)	NE [NE; NE]		1,35	[1,02; 1,79]	0,0367*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.3.1 ECHO: Summary of subgroup analysis of time to first Therapieabbruch aufgrund von UE
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)				Placebo+BR (N=297)				Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]		n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]				
Nicht-weiß	52	27 (51,9)	28,2 [13,2; NE]		53	16 (30,2)	NE [NE; NE]		2,02	[1,10; 3,82]	0,0234*
Interaktion p-Wert											0,2396
ECOG-PS [eCRF]											
0	156	74 (47,4)	56,0 [35,3; NE]		140	50 (35,7)	NE [NE; NE]		1,24	[0,87; 1,79]	0,2368
1	129	71 (55,0)	26,9 [21,3;47,4]		132	47 (35,6)	NE [NE; NE]		1,66	[1,15; 2,41]	0,0065*
>=2	12	5 (41,7)	36,5 [7,1; NE]		25	8 (32,0)	29,9 [10,7; NE]		1,05	[0,32; 3,15]	0,9344
Interaktion p-Wert											0,4699
Bulky Disease I [eCRF]											
< 5 cm	185	97 (52,4)	36,5 [26,5;61,0]		185	64 (34,6)	NE [NE; NE]		1,56	[1,14; 2,14]	0,0055*
>= 5 cm	112	53 (47,3)	35,9 [30,1; NE]		112	41 (36,6)	57,8 [34,1; NE]		1,12	[0,75; 1,69]	0,5811
Interaktion p-Wert											0,2144
Bulky Disease II [eCRF]											
< 10 cm	277	141 (50,9)	37,3 [30,1;56,0]		276	96 (34,8)	NE [NE; NE]		1,42	[1,10; 1,85]	0,0075*
>= 10 cm	20	9 (45,0)	34,1 [17,3; NE]		21	9 (42,9)	34,1 [14,5; NE]		0,97	[0,38; 2,48]	0,9450
Interaktion p-Wert											0,4347
Ann Arbor-Stadium für Lymphome [eCRF]											
Stadium I-III	48	22 (45,8)	39,0 [26,5; NE]		36	16 (44,4)	28,9 [21,2; NE]		0,96	[0,51; 1,87]	0,9095
Stadium IV	249	128 (51,4)	35,9 [27,8;56,0]		261	89 (34,1)	NE [NE; NE]		1,47	[1,12; 1,93]	0,0049*
Interaktion p-Wert											0,2407
MCL-Typ [eCRF]											
Klassische Variante	195	99 (50,8)	39,0 [30,1;61,0]		205	70 (34,1)	NE [NE; NE]		1,52	[1,12; 2,07]	0,0071*
Blastoide und pleomorphische Variante	39	17 (43,6)	34,1 [12,0; NE]		32	14 (43,8)	27,6 [7,1; NE]		0,78	[0,39; 1,61]	0,4997
Andere	0	0	NE		8	3 (37,5)	NE [NE; NE]		NC	[NC]	NC
Interaktion p-Wert											0,0966

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.3.1 ECHO: Summary of subgroup analysis of time to first Therapieabbruch aufgrund von UE
Safety Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	60 (55,0)	32,2 [23,9;61,0]	103	37 (35,9)	NE [NE; NE]	1,75	[1,17; 2,66]	0,0064*
>= 30%	126	58 (46,0)	37,3 [27,8; NE]	126	45 (35,7)	NE [NE; NE]	1,13	[0,77; 1,68]	0,5252
Interaktion p-Wert									0,1314
Ki-67 (%) II [eCRF]									
< 50%	179	97 (54,2)	32,9 [25,3;61,0]	164	57 (34,8)	NE [NE; NE]	1,70	[1,23; 2,38]	0,0012*
>= 50%	56	21 (37,5)	NE [NE; NE]	65	25 (38,5)	43,5 [14,7; NE]	0,73	[0,41; 1,31]	0,2962
Interaktion p-Wert									0,0131*
Knochenmarksbeteiligung [eCRF]									
Ja	178	90 (50,6)	40,7 [27,7;61,0]	180	60 (33,3)	NE [NE; NE]	1,49	[1,08; 2,08]	0,0152*
Nein	50	25 (50,0)	37,5 [26,7;70,0]	45	22 (48,9)	39,5 [17,1; NE]	0,96	[0,54; 1,72]	0,8936
Interaktion p-Wert									0,1929
Extranodale Erkrankung [eCRF]									
Ja	262	132 (50,4)	36,5 [28,6;56,0]	275	94 (34,2)	NE [NE; NE]	1,44	[1,10; 1,88]	0,0069*
Nein	35	18 (51,4)	39,0 [21,2; NE]	22	11 (50,0)	27,2 [14,7; NE]	0,97	[0,46; 2,12]	0,9344
Interaktion p-Wert									0,3396
Gastrointestinale Erkrankung [eCRF]									
Ja	74	34 (45,9)	54,5 [26,9; NE]	74	27 (36,5)	57,8 [29,9; NE]	1,23	[0,74; 2,05]	0,4227
Nein	223	116 (52,0)	35,3 [27,7;52,3]	223	78 (35,0)	NE [NE; NE]	1,43	[1,08; 1,92]	0,0129*
Interaktion p-Wert									0,6032
LDH > ULN [eCRF]									
Ja	52	35 (67,3)	13,2 [6,1;26,7]	54	19 (35,2)	43,5 [16,4; NE]	1,73	[0,999; 3,08]	0,0503
Nein	245	115 (46,9)	47,7 [33,6;68,3]	241	86 (35,7)	NE [NE; NE]	1,29	[0,98; 1,71]	0,0745
Interaktion p-Wert									0,3540

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.4.1 ECHO: Summary of subgroup analysis of time to first UE mit CTCAE Grad >=3
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	70 (85,4)	2,8 [1,1; 4,6]	81	71 (87,7)	2,9 [1,0; 4,9]	0,99	[0,71; 1,38]	0,9541
Westeuropa	44	42 (95,5)	1,5 [0,4; 3,0]	46	39 (84,8)	2,8 [1,0; 4,4]	1,40	[0,90; 2,17]	0,1341
Andere	171	152 (88,9)	2,8 [1,9; 3,7]	170	152 (89,4)	2,8 [1,9; 3,3]	0,85	[0,68; 1,07]	0,1694
Interaktion p-Wert									0,1423
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	85 (85,9)	3,4 [2,8; 4,6]	101	86 (85,1)	3,1 [1,9; 4,6]	0,90	[0,66; 1,21]	0,4839
Intermediäres Risiko [4-5]	126	114 (90,5)	2,8 [1,8; 3,9]	124	112 (90,3)	3,2 [2,1; 4,2]	0,98	[0,76; 1,28]	0,8904
Hohes Risiko [6-11]	72	65 (90,3)	0,9 [0,3; 1,2]	72	64 (88,9)	1,3 [0,4; 2,6]	1,02	[0,72; 1,44]	0,9090
Interaktion p-Wert									0,8453
Geschlecht [eCRF]									
Männlich	212	184 (86,8)	2,8 [1,9; 3,7]	208	180 (86,5)	2,8 [1,9; 3,7]	0,96	[0,78; 1,18]	0,6885
Weiblich	85	80 (94,1)	1,9 [0,9; 3,0]	89	82 (92,1)	2,8 [1,2; 3,7]	0,96	[0,70; 1,31]	0,7934
Interaktion p-Wert									0,9964
Altersgruppe I [eCRF]									
< 70 Jahre	122	108 (88,5)	3,0 [1,9; 3,7]	117	100 (85,5)	3,0 [1,9; 4,1]	0,90	[0,68; 1,18]	0,4440
>= 70 Jahre	175	156 (89,1)	1,9 [1,5; 3,0]	180	162 (90,0)	2,7 [1,9; 3,3]	1,01	[0,81; 1,26]	0,9407
Interaktion p-Wert									0,5197
Altersgruppe II [eCRF]									
< 75 Jahre	214	189 (88,3)	2,8 [1,9; 3,7]	221	191 (86,4)	2,8 [1,9; 3,7]	0,94	[0,77; 1,15]	0,5531
>= 75 Jahre	83	75 (90,4)	1,9 [1,2; 3,0]	76	71 (93,4)	2,5 [1,0; 4,6]	1,00	[0,72; 1,39]	0,9977
Interaktion p-Wert									0,7523
Abstammung [eCRF]									
Weiß	232	205 (88,4)	2,8 [1,9; 3,7]	233	203 (87,1)	3,1 [2,6; 4,1]	0,98	[0,80; 1,19]	0,8184

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.4.1 ECHO: Summary of subgroup analysis of time to first UE mit CTCAE Grad >=3
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	48 (92,3)	1,9 [0,9; 3,0]	53	49 (92,5)	1,8 [0,6; 3,1]	0,96	[0,65; 1,44]	0,8534
Interaktion p-Wert									0,9483
ECOG-PS [eCRF]									
0	156	139 (89,1)	2,8 [1,9; 3,7]	140	122 (87,1)	3,7 [2,6; 4,6]	1,01	[0,79; 1,29]	0,9558
1	129	114 (88,4)	1,9 [1,0; 3,1]	132	117 (88,6)	2,3 [1,1; 3,1]	0,95	[0,73; 1,23]	0,6895
>=2	12	11 (91,7)	0,7 [0,1; 4,6]	25	23 (92,0)	1,2 [0,2; 3,3]	0,90	[0,42; 1,80]	0,7622
Interaktion p-Wert									0,9209
Bulky Disease I [eCRF]									
< 5 cm	185	167 (90,3)	2,8 [1,9; 3,4]	185	167 (90,3)	2,8 [1,9; 3,3]	0,92	[0,74; 1,14]	0,4412
>= 5 cm	112	97 (86,6)	1,9 [0,9; 3,3]	112	95 (84,8)	2,8 [1,8; 4,4]	1,03	[0,77; 1,36]	0,8550
Interaktion p-Wert									0,5406
Bulky Disease II [eCRF]									
< 10 cm	277	247 (89,2)	2,8 [1,9; 3,1]	276	243 (88,0)	2,8 [2,0; 3,7]	0,98	[0,82; 1,17]	0,7906
>= 10 cm	20	17 (85,0)	2,3 [0,3; 5,1]	21	19 (90,5)	0,7 [0,1; 3,7]	0,71	[0,37; 1,38]	0,3149
Interaktion p-Wert									0,3671
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	43 (89,6)	3,1 [1,8; 5,5]	36	31 (86,1)	3,6 [1,3; 8,0]	1,00	[0,63; 1,60]	0,9945
Stadium IV	249	221 (88,8)	2,7 [1,8; 3,0]	261	231 (88,5)	2,8 [1,9; 3,3]	0,96	[0,79; 1,15]	0,6261
Interaktion p-Wert									0,8511
MCL-Typ [eCRF]									
Klassische Variante	195	173 (88,7)	2,8 [1,9; 3,1]	205	184 (89,8)	2,8 [1,9; 3,7]	0,94	[0,76; 1,16]	0,5519
Blastoide und pleomorphische Variante	39	36 (92,3)	2,7 [0,3; 3,8]	32	27 (84,4)	2,5 [0,3; 5,1]	1,15	[0,70; 1,91]	0,5889
Andere	0	0	NE	8	8 (100)	1,4 [0,3; 2,8]	NC	[NC]	NC
Interaktion p-Wert									0,4661

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.4.1 ECHO: Summary of subgroup analysis of time to first UE mit CTCAE Grad >=3
Safety Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	96 (88,1)	1,9 [1,2; 3,7]	103	91 (88,3)	3,7 [1,4; 4,6]	1,08	[0,81; 1,43]	0,6202
>= 30%	126	115 (91,3)	2,8 [1,8; 3,1]	126	108 (85,7)	2,8 [1,9; 3,7]	1,00	[0,77; 1,31]	0,9729
Interaktion p-Wert									0,7316
Ki-67 (%) II [eCRF]									
< 50%	179	160 (89,4)	2,3 [1,8; 3,3]	164	144 (87,8)	3,2 [1,9; 4,4]	1,05	[0,83; 1,31]	0,7009
>= 50%	56	51 (91,1)	1,9 [0,7; 3,1]	65	55 (84,6)	2,0 [1,0; 2,8]	1,04	[0,71; 1,52]	0,8508
Interaktion p-Wert									0,9732
Knochenmarksbeteiligung [eCRF]									
Ja	178	158 (88,8)	1,9 [1,1; 3,0]	180	157 (87,2)	2,8 [1,9; 3,7]	1,04	[0,83; 1,30]	0,7296
Nein	50	45 (90,0)	3,1 [1,9; 4,6]	45	40 (88,9)	2,8 [0,7; 3,9]	0,81	[0,53; 1,25]	0,3369
Interaktion p-Wert									0,3112
Extranodale Erkrankung [eCRF]									
Ja	262	232 (88,5)	2,7 [1,8; 3,0]	275	242 (88,0)	2,8 [1,9; 3,7]	0,96	[0,80; 1,15]	0,6695
Nein	35	32 (91,4)	3,1 [1,8; 4,6]	22	20 (90,9)	2,8 [0,3; 6,7]	0,92	[0,53; 1,63]	0,7571
Interaktion p-Wert									0,8697
Gastrointestinale Erkrankung [eCRF]									
Ja	74	65 (87,8)	1,9 [0,8; 3,1]	74	67 (90,5)	3,1 [1,4; 5,0]	1,02	[0,73; 1,44]	0,8927
Nein	223	199 (89,2)	2,8 [1,9; 3,4]	223	195 (87,4)	2,8 [1,9; 3,7]	0,94	[0,77; 1,14]	0,5165
Interaktion p-Wert									0,6586
LDH > ULN [eCRF]									
Ja	52	48 (92,3)	0,9 [0,3; 2,8]	54	47 (87,0)	0,6 [0,3; 2,0]	0,93	[0,62; 1,40]	0,7290
Nein	245	216 (88,2)	2,8 [1,9; 3,7]	241	213 (88,4)	3,0 [2,6; 3,7]	0,96	[0,80; 1,17]	0,7106
Interaktion p-Wert									0,8766

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.4.2 ECHO: Summary of subgroup analysis of time to first G $\geq$ 3 SOC: Erkrankungen der Haut und des Unterhautgewebes
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	16 (19,5)	NE [NE; NE]	81	4 (4,9)	NE [NE; NE]	4,32	[1,58; 15,08]	0,0032*
Westeuropa	44	7 (15,9)	NE [NE; NE]	46	1 (2,2)	NE [NE; NE]	7,49	[1,33;139,98]	0,0193*
Andere	171	24 (14,0)	NE [NE; NE]	170	7 (4,1)	NE [NE; NE]	3,47	[1,58; 8,73]	0,0015*
Interaktion p-Wert									0,7707
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	15 (15,2)	NE [NE; NE]	101	4 (4,0)	NE [NE; NE]	3,91	[1,42; 13,72]	0,0071*
Intermediäres Risiko [4-5]	126	21 (16,7)	NE [NE; NE]	124	3 (2,4)	NE [NE; NE]	7,37	[2,54; 31,20]	<0,0001*
Hohes Risiko [6-11]	72	11 (15,3)	NE [NE; NE]	72	5 (6,9)	NE [NE; NE]	2,22	[0,81; 7,05]	0,1242
Interaktion p-Wert									0,3274
Geschlecht [eCRF]									
Männlich	212	31 (14,6)	NE [NE; NE]	208	8 (3,8)	NE [NE; NE]	3,95	[1,91; 9,23]	0,0001*
Weiblich	85	16 (18,8)	NE [NE; NE]	89	4 (4,5)	NE [NE; NE]	4,36	[1,60; 15,22]	0,0030*
Interaktion p-Wert									0,8852
Altersgruppe I [eCRF]									
< 70 Jahre	122	11 (9,0)	NE [NE; NE]	117	5 (4,3)	NE [NE; NE]	2,15	[0,78; 6,82]	0,1408
>= 70 Jahre	175	36 (20,6)	NE [NE; NE]	180	7 (3,9)	NE [NE; NE]	5,59	[2,64; 13,70]	<0,0001*
Interaktion p-Wert									0,1675
Altersgruppe II [eCRF]									
< 75 Jahre	214	28 (13,1)	NE [NE; NE]	221	10 (4,5)	NE [NE; NE]	2,97	[1,49; 6,43]	0,0016*
>= 75 Jahre	83	19 (22,9)	NE [NE; NE]	76	2 (2,6)	NE [NE; NE]	9,32	[2,71; 58,49]	<0,0001*
Interaktion p-Wert									0,1340
Abstammung [eCRF]									
Weiß	232	40 (17,2)	NE [NE; NE]	233	9 (3,9)	NE [NE; NE]	4,67	[2,38; 10,27]	<0,0001*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are ≥ 10 patients in each subgroup level, ≥ 10 events in at least one subgroup level and > 0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value < 0.05 . HR < 1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.4.2 ECHO: Summary of subgroup analysis of time to first G_{≥3} SOC: Erkrankungen der Haut und des Unterhautgewebes
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	6 (11,5)	NE [NE; NE]	53	2 (3,8)	NE [NE; NE]	3,16	[0,73; 21,55]	0,1290
Interaktion p-Wert									0,6697
ECOG-PS [eCRF]									
0	156	21 (13,5)	NE [NE; NE]	140	7 (5,0)	NE [NE; NE]	2,79	[1,24; 7,08]	0,0118*
1	129	24 (18,6)	NE [NE; NE]	132	4 (3,0)	NE [NE; NE]	6,53	[2,53; 22,24]	<0,0001*
≥2	12	2 (16,7)	NE [NE; NE]	25	1 (4,0)	NE [NE; NE]	4,15	[0,40; 89,19]	0,2270
Interaktion p-Wert									0,4588
Bulky Disease I [eCRF]									
< 5 cm	185	26 (14,1)	NE [NE; NE]	185	7 (3,8)	NE [NE; NE]	3,87	[1,77; 9,66]	0,0004*
≥ 5 cm	112	21 (18,8)	NE [NE; NE]	112	5 (4,5)	NE [NE; NE]	4,36	[1,78; 13,05]	0,0008*
Interaktion p-Wert									0,8551
Bulky Disease II [eCRF]									
< 10 cm	277	42 (15,2)	NE [NE; NE]	276	10 (3,6)	NE [NE; NE]	4,36	[2,28; 9,19]	<0,0001*
≥ 10 cm	20	5 (25,0)	NE [NE; NE]	21	2 (9,5)	NE [NE; NE]	2,70	[0,58; 18,83]	0,2106
Interaktion p-Wert									0,6073
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	8 (16,7)	NE [NE; NE]	36	1 (2,8)	NE [NE; NE]	6,31	[1,16; 117,11]	0,0308*
Stadium IV	249	39 (15,7)	NE [NE; NE]	261	11 (4,2)	NE [NE; NE]	3,87	[2,05; 7,93]	<0,0001*
Interaktion p-Wert									0,6432
MCL-Typ [eCRF]									
Klassische Variante	195	30 (15,4)	NE [NE; NE]	205	9 (4,4)	NE [NE; NE]	3,65	[1,81; 8,17]	0,0002*
Blastoide und pleomorphische Variante	39	5 (12,8)	NE [NE; NE]	32	2 (6,3)	NE [NE; NE]	1,95	[0,42; 13,63]	0,4049
Andere	0	0	NE	8	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,5101

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are ≥10 patients in each subgroup level, ≥10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.4.2 ECHO: Summary of subgroup analysis of time to first G $\geq$ 3 SOC: Erkrankungen der Haut und des Unterhautgewebes
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]			
	n			n					
Ki-67 (%) I [eCRF]									
< 30%	109	19 (17,4)	NE [NE; NE]	103	3 (2,9)	NE [NE; NE]	6,47	[2,20; 27,53]	0,0003*
>= 30%	126	17 (13,5)	NE [NE; NE]	126	6 (4,8)	NE [NE; NE]	2,90	[1,20; 8,04]	0,0166*
Interaktion p-Wert									0,2935
Ki-67 (%) II [eCRF]									
< 50%	179	27 (15,1)	NE [NE; NE]	164	7 (4,3)	NE [NE; NE]	3,76	[1,73; 9,38]	0,0005*
>= 50%	56	9 (16,1)	NE [NE; NE]	65	2 (3,1)	NE [NE; NE]	5,33	[1,37; 35,01]	0,0136*
Interaktion p-Wert									0,6892
Knochenmarksbeteiligung [eCRF]									
Ja	178	28 (15,7)	NE [NE; NE]	180	9 (5,0)	NE [NE; NE]	3,31	[1,62; 7,43]	0,0007*
Nein	50	10 (20,0)	NE [NE; NE]	45	3 (6,7)	NE [NE; NE]	3,14	[0,96; 13,98]	0,0592
Interaktion p-Wert									0,9447
Extranodale Erkrankung [eCRF]									
Ja	262	42 (16,0)	NE [NE; NE]	275	11 (4,0)	NE [NE; NE]	4,18	[2,23; 8,53]	<0,0001*
Nein	35	5 (14,3)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	3,29	[0,53; 62,99]	0,2212
Interaktion p-Wert									0,8387
Gastrointestinale Erkrankung [eCRF]									
Ja	74	16 (21,6)	NE [NE; NE]	74	2 (2,7)	NE [NE; NE]	8,93	[2,54; 56,52]	0,0002*
Nein	223	31 (13,9)	NE [NE; NE]	223	10 (4,5)	NE [NE; NE]	3,15	[1,60; 6,77]	0,0007*
Interaktion p-Wert									0,1774
LDH > ULN [eCRF]									
Ja	52	8 (15,4)	NE [NE; NE]	54	5 (9,3)	NE [NE; NE]	1,62	[0,54; 5,35]	0,3936
Nein	245	39 (15,9)	NE [NE; NE]	241	7 (2,9)	NE [NE; NE]	5,78	[2,75; 14,12]	<0,0001*
Interaktion p-Wert									0,0751

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are ≥ 10 patients in each subgroup level, ≥ 10 events in at least one subgroup level and > 0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value < 0.05 . HR < 1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.4.3 ECHO: Summary of subgroup analysis of time to first G_{≥3} PT: Ausschlag makulo-papuloes
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	10 (12,2)	NE [NE; NE]	81	0	NE [NE; NE]	NC	[NC]	NC
Westeuropa	44	3 (6,8)	NE [NE; NE]	46	0	NE [NE; NE]	NC	[NC]	NC
Andere	171	8 (4,7)	NE [NE; NE]	170	2 (1,2)	NE [NE; NE]	3,94	[0,99; 26,11]	0,0524
Interaktion p-Wert									NC
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	4 (4,0)	NE [NE; NE]	101	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
Intermediäres Risiko [4-5]	126	12 (9,5)	NE [NE; NE]	124	0	NE [NE; NE]	NC	[NC]	NC
Hohes Risiko [6-11]	72	5 (6,9)	NE [NE; NE]	72	1 (1,4)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht [eCRF]									
Männlich	212	14 (6,6)	NE [NE; NE]	208	2 (1,0)	NE [NE; NE]	7,01	[1,96; 44,64]	0,0014*
Weiblich	85	7 (8,2)	NE [NE; NE]	89	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Altersgruppe I [eCRF]									
< 70 Jahre	122	5 (4,1)	NE [NE; NE]	117	0	NE [NE; NE]	NC	[NC]	NC
≥ 70 Jahre	175	16 (9,1)	NE [NE; NE]	180	2 (1,1)	NE [NE; NE]	8,36	[2,38; 52,87]	0,0003*
Interaktion p-Wert									NC
Altersgruppe II [eCRF]									
< 75 Jahre	214	11 (5,1)	NE [NE; NE]	221	1 (0,5)	NE [NE; NE]	11,43	[2,22;208,90]	0,0014*
≥ 75 Jahre	83	10 (12,0)	NE [NE; NE]	76	1 (1,3)	NE [NE; NE]	9,61	[1,84;176,31]	0,0042*
Interaktion p-Wert									0,9066
Abstammung [eCRF]									
Weiß	232	19 (8,2)	NE [NE; NE]	233	2 (0,9)	NE [NE; NE]	9,73	[2,83; 61,05]	<0,0001*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are ≥10 patients in each subgroup level, ≥10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.4.3 ECHO: Summary of subgroup analysis of time to first G_{≥3} PT: Ausschlag makulo-papuloes
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	2 (3,8)	NE [NE; NE]	53	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ECOG-PS [eCRF]									
0	156	10 (6,4)	NE [NE; NE]	140	2 (1,4)	NE [NE; NE]	4,55	[1,20; 29,61]	0,0240*
1	129	10 (7,8)	NE [NE; NE]	132	0	NE [NE; NE]	NC	[NC]	NC
≥2	12	1 (8,3)	NE [NE; NE]	25	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Bulky Disease I [eCRF]									
< 5 cm	185	11 (5,9)	NE [NE; NE]	185	1 (0,5)	NE [NE; NE]	11,20	[2,18;204,60]	0,0016*
≥ 5 cm	112	10 (8,9)	NE [NE; NE]	112	1 (0,9)	NE [NE; NE]	10,18	[1,95;186,81]	0,0032*
Interaktion p-Wert									0,9488
Bulky Disease II [eCRF]									
< 10 cm	277	20 (7,2)	NE [NE; NE]	276	2 (0,7)	NE [NE; NE]	10,15	[2,96; 63,53]	<0,0001*
≥ 10 cm	20	1 (5,0)	NE [NE; NE]	21	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	3 (6,3)	NE [NE; NE]	36	0	NE [NE; NE]	NC	[NC]	NC
Stadium IV	249	18 (7,2)	NE [NE; NE]	261	2 (0,8)	NE [NE; NE]	9,65	[2,78; 60,68]	<0,0001*
Interaktion p-Wert									NC
MCL-Typ [eCRF]									
Klassische Variante	195	17 (8,7)	NE [NE; NE]	205	1 (0,5)	NE [NE; NE]	18,40	[3,78;331,76]	<0,0001*
Blastoide und pleomorphische Variante	39	2 (5,1)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	1,58	[0,15; 33,96]	0,7030
Andere	0	0	NE	8	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,1437

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are ≥10 patients in each subgroup level, ≥10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.4.3 ECHO: Summary of subgroup analysis of time to first G $\geq$ 3 PT: Ausschlag makulo-papuloes
Safety Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	8 (7,3)	NE [NE; NE]	103	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
$\geq$ 30%	126	8 (6,3)	NE [NE; NE]	126	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ki-67 (%) II [eCRF]									
< 50%	179	11 (6,1)	NE [NE; NE]	164	1 (0,6)	NE [NE; NE]	10,36	[2,02;189,35]	0,0025*
$\geq$ 50%	56	5 (8,9)	NE [NE; NE]	65	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Knochenmarksbeteiligung [eCRF]									
Ja	178	16 (9,0)	NE [NE; NE]	180	1 (0,6)	NE [NE; NE]	16,68	[3,41;301,28]	<0,0001*
Nein	50	4 (8,0)	NE [NE; NE]	45	1 (2,2)	NE [NE; NE]	3,66	[0,54; 71,45]	0,1967
Interaktion p-Wert									0,3312
Extranodale Erkrankung [eCRF]									
Ja	262	19 (7,3)	NE [NE; NE]	275	2 (0,7)	NE [NE; NE]	10,14	[2,95; 63,66]	<0,0001*
Nein	35	2 (5,7)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Gastrointestinale Erkrankung [eCRF]									
Ja	74	7 (9,5)	NE [NE; NE]	74	1 (1,4)	NE [NE; NE]	7,23	[1,29;135,17]	0,0218*
Nein	223	14 (6,3)	NE [NE; NE]	223	1 (0,4)	NE [NE; NE]	14,18	[2,85;256,94]	0,0002*
Interaktion p-Wert									0,6528
LDH > ULN [eCRF]									
Ja	52	3 (5,8)	NE [NE; NE]	54	0	NE [NE; NE]	NC	[NC]	NC
Nein	245	18 (7,3)	NE [NE; NE]	241	2 (0,8)	NE [NE; NE]	9,08	[2,62; 57,11]	0,0001*
Interaktion p-Wert									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are ≥ 10 patients in each subgroup level, ≥ 10 events in at least one subgroup level and > 0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value < 0.05 . HR < 1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.4.4 ECHO: Summary of subgroup analysis of time to first G $\geq$ 3 PT: Alaninaminotransferase erhoeht
Safety Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	4 (4,9)	NE [NE; NE]	81	0	NE [NE; NE]	NC	[NC]	NC
Westeuropa	44	2 (4,5)	NE [NE; NE]	46	0	NE [NE; NE]	NC	[NC]	NC
Andere	171	7 (4,1)	NE [NE; NE]	170	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	4 (4,0)	NE [NE; NE]	101	0	NE [NE; NE]	NC	[NC]	NC
Intermediäres Risiko [4-5]	126	7 (5,6)	NE [NE; NE]	124	1 (0,8)	NE [NE; NE]	NC	[NC]	NC
Hohes Risiko [6-11]	72	2 (2,8)	NE [NE; NE]	72	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht [eCRF]									
Männlich	212	10 (4,7)	NE [NE; NE]	208	1 (0,5)	NE [NE; NE]	9,45	[1,81;173,32]	0,0046*
Weiblich	85	3 (3,5)	NE [NE; NE]	89	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Altersgruppe I [eCRF]									
< 70 Jahre	122	3 (2,5)	NE [NE; NE]	117	1 (0,9)	NE [NE; NE]	NC	[NC]	NC
>= 70 Jahre	175	10 (5,7)	NE [NE; NE]	180	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Altersgruppe II [eCRF]									
< 75 Jahre	214	10 (4,7)	NE [NE; NE]	221	1 (0,5)	NE [NE; NE]	9,82	[1,88;180,21]	0,0038*
>= 75 Jahre	83	3 (3,6)	NE [NE; NE]	76	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Abstammung [eCRF]									
Weiß	232	9 (3,9)	NE [NE; NE]	233	1 (0,4)	NE [NE; NE]	8,47	[1,59;156,09]	0,0087*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are ≥ 10 patients in each subgroup level, ≥ 10 events in at least one subgroup level and > 0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value < 0.05 . HR < 1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.4.4 ECHO: Summary of subgroup analysis of time to first G $\geq$ 3 PT: Alaninaminotransferase erhoeht
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	3 (5,8)	NE [NE; NE]	53	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ECOG-PS [eCRF]									
0	156	5 (3,2)	NE [NE; NE]	140	0	NE [NE; NE]	NC	[NC]	NC
1	129	8 (6,2)	NE [NE; NE]	132	1 (0,8)	NE [NE; NE]	NC	[NC]	NC
$\geq$ 2	12	0	NE [NE; NE]	25	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Bulky Disease I [eCRF]									
< 5 cm	185	6 (3,2)	NE [NE; NE]	185	0	NE [NE; NE]	NC	[NC]	NC
$\geq$ 5 cm	112	7 (6,3)	NE [NE; NE]	112	1 (0,9)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Bulky Disease II [eCRF]									
< 10 cm	277	12 (4,3)	NE [NE; NE]	276	1 (0,4)	NE [NE; NE]	11,54	[2,27;210,18]	0,0012*
$\geq$ 10 cm	20	1 (5,0)	NE [NE; NE]	21	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	2 (4,2)	NE [NE; NE]	36	0	NE [NE; NE]	NC	[NC]	NC
Stadium IV	249	11 (4,4)	NE [NE; NE]	261	1 (0,4)	NE [NE; NE]	11,17	[2,17;204,15]	0,0016*
Interaktion p-Wert									NC
MCL-Typ [eCRF]									
Klassische Variante	195	8 (4,1)	NE [NE; NE]	205	1 (0,5)	NE [NE; NE]	NC	[NC]	NC
Blastoide und pleomorphische Variante	39	2 (5,1)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Andere	0	0	NE	8	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									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% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are $\geq$ 10 patients in each subgroup level, $\geq$ 10 events in at least one subgroup level and $>$ 0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value $<$ 0.05. HR $<$ 1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.4.4 ECHO: Summary of subgroup analysis of time to first G $\geq$ 3 PT: Alaninaminotransferase erhoeht
Safety Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	5 (4,6)	NE [NE; NE]	103	0	NE [NE; NE]	NC	[NC]	NC
$\geq$ 30%	126	5 (4,0)	NE [NE; NE]	126	1 (0,8)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ki-67 (%) II [eCRF]									
< 50%	179	6 (3,4)	NE [NE; NE]	164	0	NE [NE; NE]	NC	[NC]	NC
$\geq$ 50%	56	4 (7,1)	NE [NE; NE]	65	1 (1,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Knochenmarksbeteiligung [eCRF]									
Ja	178	7 (3,9)	NE [NE; NE]	180	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Nein	50	3 (6,0)	NE [NE; NE]	45	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Extranodale Erkrankung [eCRF]									
Ja	262	11 (4,2)	NE [NE; NE]	275	1 (0,4)	NE [NE; NE]	11,21	[2,18;204,88]	0,0016*
Nein	35	2 (5,7)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Gastrointestinale Erkrankung [eCRF]									
Ja	74	1 (1,4)	NE [NE; NE]	74	0	NE [NE; NE]	NC	[NC]	NC
Nein	223	12 (5,4)	NE [NE; NE]	223	1 (0,4)	NE [NE; NE]	11,62	[2,29;211,55]	0,0011*
Interaktion p-Wert									NC
LDH > ULN [eCRF]									
Ja	52	3 (5,8)	NE [NE; NE]	54	0	NE [NE; NE]	NC	[NC]	NC
Nein	245	10 (4,1)	NE [NE; NE]	241	1 (0,4)	NE [NE; NE]	9,72	[1,86;178,32]	0,0040*
Interaktion p-Wert									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are ≥ 10 patients in each subgroup level, ≥ 10 events in at least one subgroup level and > 0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value < 0.05 . HR < 1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.4.5 ECHO: Summary of subgroup analysis of time to first G_{≥3} PT: Leukozytenzahl erniedrigt
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	5 (6,1)	NE [NE; NE]	81	3 (3,7)	NE [NE; NE]	1,59	[0,39; 7,77]	0,5165
Westeuropa	44	3 (6,8)	NE [NE; NE]	46	1 (2,2)	NE [NE; NE]	3,08	[0,39; 62,28]	0,2940
Andere	171	22 (12,9)	NE [NE; NE]	170	7 (4,1)	NE [NE; NE]	3,09	[1,39; 7,83]	0,0049*
Interaktion p-Wert									0,7384
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	13 (13,1)	NE [NE; NE]	101	4 (4,0)	NE [NE; NE]	3,29	[1,17; 11,70]	0,0234*
Intermediäres Risiko [4-5]	126	13 (10,3)	NE [NE; NE]	124	4 (3,2)	NE [NE; NE]	3,21	[1,14; 11,41]	0,0267*
Hohes Risiko [6-11]	72	4 (5,6)	NE [NE; NE]	72	3 (4,2)	NE [NE; NE]	1,23	[0,27; 6,25]	0,7847
Interaktion p-Wert									0,5445
Geschlecht [eCRF]									
Männlich	212	21 (9,9)	NE [NE; NE]	208	7 (3,4)	NE [NE; NE]	2,94	[1,31; 7,45]	0,0080*
Weiblich	85	9 (10,6)	NE [NE; NE]	89	4 (4,5)	NE [NE; NE]	2,24	[0,73; 8,26]	0,1633
Interaktion p-Wert									0,7158
Altersgruppe I [eCRF]									
< 70 Jahre	122	16 (13,1)	NE [NE; NE]	117	5 (4,3)	NE [NE; NE]	3,03	[1,19; 9,26]	0,0194*
≥ 70 Jahre	175	14 (8,0)	NE [NE; NE]	180	6 (3,3)	NE [NE; NE]	2,36	[0,94; 6,65]	0,0666
Interaktion p-Wert									0,7218
Altersgruppe II [eCRF]									
< 75 Jahre	214	24 (11,2)	NE [NE; NE]	221	11 (5,0)	NE [NE; NE]	2,19	[1,10; 4,66]	0,0250*
≥ 75 Jahre	83	6 (7,2)	NE [NE; NE]	76	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Abstammung [eCRF]									
Weiß	232	10 (4,3)	NE [NE; NE]	233	5 (2,1)	NE [NE; NE]	1,93	[0,69; 6,21]	0,2150

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are ≥10 patients in each subgroup level, ≥10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.4.5 ECHO: Summary of subgroup analysis of time to first G $\geq$ 3 PT: Leukozytenzahl erniedrigt
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	19 (36,5)	NE [NE; NE]	53	6 (11,3)	NE [NE; NE]	3,52	[1,49; 9,66]	0,0035*
Interaktion p-Wert									0,4093
ECOG-PS [eCRF]									
0	156	15 (9,6)	NE [NE; NE]	140	4 (2,9)	NE [NE; NE]	3,38	[1,23; 11,86]	0,0170*
1	129	14 (10,9)	NE [NE; NE]	132	7 (5,3)	NE [NE; NE]	1,99	[0,83; 5,24]	0,1268
$\geq$ 2	12	1 (8,3)	NE [NE; NE]	25	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,4605
Bulky Disease I [eCRF]									
< 5 cm	185	25 (13,5)	NE [NE; NE]	185	9 (4,9)	NE [NE; NE]	2,81	[1,36; 6,37]	0,0046*
$\geq$ 5 cm	112	5 (4,5)	NE [NE; NE]	112	2 (1,8)	NE [NE; NE]	2,34	[0,51; 16,36]	0,2853
Interaktion p-Wert									0,8446
Bulky Disease II [eCRF]									
< 10 cm	277	28 (10,1)	NE [NE; NE]	276	11 (4,0)	NE [NE; NE]	2,50	[1,28; 5,25]	0,0066*
$\geq$ 10 cm	20	2 (10,0)	NE [NE; NE]	21	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	7 (14,6)	NE [NE; NE]	36	0	NE [NE; NE]	NC	[NC]	NC
Stadium IV	249	23 (9,2)	NE [NE; NE]	261	11 (4,2)	NE [NE; NE]	2,15	[1,07; 4,59]	0,0303*
Interaktion p-Wert									NC
MCL-Typ [eCRF]									
Klassische Variante	195	18 (9,2)	NE [NE; NE]	205	7 (3,4)	NE [NE; NE]	2,66	[1,16; 6,85]	0,0201*
Blastoide und pleomorphische Variante	39	5 (12,8)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Andere	0	0	NE	8	1 (12,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are $\geq$ 10 patients in each subgroup level, $\geq$ 10 events in at least one subgroup level and $>$ 0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value $<$ 0.05. HR $<$ 1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.4.5 ECHO: Summary of subgroup analysis of time to first G $\geq$ 3 PT: Leukozytenzahl erniedrigt
Safety Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	11 (10,1)	NE [NE; NE]	103	4 (3,9)	NE [NE; NE]	2,84	[0,97; 10,24]	0,0571
$\geq$ 30%	126	16 (12,7)	NE [NE; NE]	126	2 (1,6)	NE [NE; NE]	7,78	[2,21; 49,18]	0,0005*
Interaktion p-Wert									0,2752
Ki-67 (%) II [eCRF]									
< 50%	179	21 (11,7)	NE [NE; NE]	164	5 (3,0)	NE [NE; NE]	4,10	[1,67; 12,29]	0,0014*
$\geq$ 50%	56	6 (10,7)	NE [NE; NE]	65	1 (1,5)	NE [NE; NE]	6,46	[1,10; 121,95]	0,0373*
Interaktion p-Wert									0,6937
Knochenmarksbeteiligung [eCRF]									
Ja	178	12 (6,7)	NE [NE; NE]	180	5 (2,8)	NE [NE; NE]	2,36	[0,88; 7,43]	0,0907
Nein	50	4 (8,0)	NE [NE; NE]	45	1 (2,2)	NE [NE; NE]	3,61	[0,53; 70,62]	0,2012
Interaktion p-Wert									0,7253
Extranodale Erkrankung [eCRF]									
Ja	262	25 (9,5)	NE [NE; NE]	275	11 (4,0)	NE [NE; NE]	2,35	[1,19; 4,97]	0,0138*
Nein	35	5 (14,3)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Gastrointestinale Erkrankung [eCRF]									
Ja	74	5 (6,8)	NE [NE; NE]	74	3 (4,1)	NE [NE; NE]	1,70	[0,42; 8,27]	0,4617
Nein	223	25 (11,2)	NE [NE; NE]	223	8 (3,6)	NE [NE; NE]	3,04	[1,43; 7,20]	0,0032*
Interaktion p-Wert									0,4925
LDH > ULN [eCRF]									
Ja	52	5 (9,6)	NE [NE; NE]	54	4 (7,4)	NE [NE; NE]	1,10	[0,29; 4,43]	0,8898
Nein	245	25 (10,2)	NE [NE; NE]	241	7 (2,9)	NE [NE; NE]	3,55	[1,62; 8,89]	0,0011*
Interaktion p-Wert									0,1458

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are ≥ 10 patients in each subgroup level, ≥ 10 events in at least one subgroup level and > 0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value < 0.05 . HR < 1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.5.1 ECHO: Summary of subgroup analysis of time to first EKI GT: Blutung
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	30 (36,6)	NE [NE; NE]	81	27 (33,3)	64,9 [39,8; NE]	1,12	[0,66; 1,89]	0,6724
Westeuropa	44	10 (22,7)	NE [NE; NE]	46	6 (13,0)	NE [NE; NE]	1,76	[0,65; 5,16]	0,2669
Andere	171	44 (25,7)	NE [NE; NE]	170	18 (10,6)	NE [NE; NE]	2,66	[1,56; 4,72]	0,0002*
Interaktion p-Wert									0,0764
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	25 (25,3)	NE [NE; NE]	101	20 (19,8)	NE [NE; NE]	1,34	[0,75; 2,44]	0,3282
Intermediäres Risiko [4-5]	126	42 (33,3)	NE [NE; NE]	124	18 (14,5)	NE [NE; NE]	2,52	[1,47; 4,48]	0,0006*
Hohes Risiko [6-11]	72	17 (23,6)	NE [NE; NE]	72	13 (18,1)	NE [NE; NE]	1,31	[0,64; 2,75]	0,4598
Interaktion p-Wert									0,2093
Geschlecht [eCRF]									
Männlich	212	57 (26,9)	NE [NE; NE]	208	37 (17,8)	NE [NE; NE]	1,65	[1,10; 2,52]	0,0160*
Weiblich	85	27 (31,8)	NE [NE; NE]	89	14 (15,7)	NE [NE; NE]	1,99	[1,06; 3,91]	0,0314*
Interaktion p-Wert									0,6307
Altersgruppe I [eCRF]									
< 70 Jahre	122	30 (24,6)	NE [NE; NE]	117	18 (15,4)	NE [NE; NE]	1,70	[0,96; 3,11]	0,0706
>= 70 Jahre	175	54 (30,9)	NE [NE; NE]	180	33 (18,3)	NE [NE; NE]	1,79	[1,16; 2,78]	0,0076*
Interaktion p-Wert									0,8942
Altersgruppe II [eCRF]									
< 75 Jahre	214	54 (25,2)	NE [NE; NE]	221	38 (17,2)	NE [NE; NE]	1,53	[1,01; 2,33]	0,0436*
>= 75 Jahre	83	30 (36,1)	45,6 [28,4; NE]	76	13 (17,1)	NE [NE; NE]	2,34	[1,25; 4,65]	0,0074*
Interaktion p-Wert									0,2711
Abstammung [eCRF]									
Weiß	232	67 (28,9)	NE [NE; NE]	233	46 (19,7)	NE [NE; NE]	1,53	[1,06; 2,24]	0,0243*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.5.1 ECHO: Summary of subgroup analysis of time to first EKI GT: Blutung
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Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	13 (25,0)	NE [NE; NE]	53	4 (7,5)	NE [NE; NE]	3,81	[1,35; 13,52]	0,0105*
Interaktion p-Wert									0,1111
ECOG-PS [eCRF]									
0	156	52 (33,3)	NE [NE; NE]	140	24 (17,1)	NE [NE; NE]	2,20	[1,38; 3,64]	0,0009*
1	129	30 (23,3)	NE [NE; NE]	132	24 (18,2)	NE [NE; NE]	1,30	[0,76; 2,24]	0,3413
>=2	12	2 (16,7)	NE [NE; NE]	25	3 (12,0)	NE [NE; NE]	1,33	[0,17; 8,00]	0,7597
Interaktion p-Wert									0,3377
Bulky Disease I [eCRF]									
< 5 cm	185	49 (26,5)	NE [NE; NE]	185	36 (19,5)	NE [NE; NE]	1,49	[0,97; 2,30]	0,0695
>= 5 cm	112	35 (31,3)	NE [NE; NE]	112	15 (13,4)	NE [NE; NE]	2,35	[1,31; 4,43]	0,0038*
Interaktion p-Wert									0,2214
Bulky Disease II [eCRF]									
< 10 cm	277	77 (27,8)	NE [NE; NE]	276	49 (17,8)	NE [NE; NE]	1,66	[1,17; 2,39]	0,0048*
>= 10 cm	20	7 (35,0)	NE [NE; NE]	21	2 (9,5)	NE [NE; NE]	3,83	[0,93; 25,73]	0,0647
Interaktion p-Wert									0,2802
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	18 (37,5)	NE [NE; NE]	36	3 (8,3)	NE [NE; NE]	5,55	[1,88; 23,69]	0,0010*
Stadium IV	249	66 (26,5)	NE [NE; NE]	261	48 (18,4)	NE [NE; NE]	1,49	[1,03; 2,17]	0,0335*
Interaktion p-Wert									0,0237*
MCL-Typ [eCRF]									
Klassische Variante	195	59 (30,3)	NE [NE; NE]	205	35 (17,1)	NE [NE; NE]	1,94	[1,29; 2,98]	0,0015*
Blastoide und pleomorphische Variante	39	12 (30,8)	NE [NE; NE]	32	3 (9,4)	NE [NE; NE]	3,22	[1,02; 14,15]	0,0454*
Andere	0	0	NE	8	3 (37,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,4393

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.5.1 ECHO: Summary of subgroup analysis of time to first EKI GT: Blutung
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	31 (28,4)	NE [NE; NE]	103	23 (22,3)	NE [NE; NE]	1,44	[0,84; 2,50]	0,1801
>= 30%	126	36 (28,6)	NE [NE; NE]	126	17 (13,5)	NE [NE; NE]	2,25	[1,28; 4,11]	0,0043*
Interaktion p-Wert									0,2685
Ki-67 (%) II [eCRF]									
< 50%	179	48 (26,8)	NE [NE; NE]	164	37 (22,6)	NE [NE; NE]	1,32	[0,86; 2,04]	0,2054
>= 50%	56	19 (33,9)	NE [NE; NE]	65	3 (4,6)	NE [NE; NE]	7,97	[2,71; 33,91]	<0,0001*
Interaktion p-Wert									0,0016*
Knochenmarksbeteiligung [eCRF]									
Ja	178	52 (29,2)	NE [NE; NE]	180	33 (18,3)	NE [NE; NE]	1,69	[1,10; 2,64]	0,0170*
Nein	50	18 (36,0)	NE [NE; NE]	45	6 (13,3)	NE [NE; NE]	3,18	[1,33; 8,78]	0,0081*
Interaktion p-Wert									0,2097
Extranodale Erkrankung [eCRF]									
Ja	262	71 (27,1)	NE [NE; NE]	275	48 (17,5)	NE [NE; NE]	1,62	[1,13; 2,36]	0,0087*
Nein	35	13 (37,1)	NE [NE; NE]	22	3 (13,6)	NE [NE; NE]	3,33	[1,07; 14,51]	0,0365*
Interaktion p-Wert									0,2546
Gastrointestinale Erkrankung [eCRF]									
Ja	74	19 (25,7)	NE [NE; NE]	74	11 (14,9)	NE [NE; NE]	1,91	[0,92; 4,16]	0,0806
Nein	223	65 (29,1)	NE [NE; NE]	223	40 (17,9)	NE [NE; NE]	1,70	[1,15; 2,54]	0,0074*
Interaktion p-Wert									0,7817
LDH > ULN [eCRF]									
Ja	52	10 (19,2)	NE [NE; NE]	54	7 (13,0)	64,9 [64,9; NE]	1,45	[0,56; 4,00]	0,4450
Nein	245	74 (30,2)	NE [NE; NE]	241	43 (17,8)	NE [NE; NE]	1,83	[1,26; 2,69]	0,0013*
Interaktion p-Wert									0,6630

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.5.2 ECHO: Summary of subgroup analysis of time to first EKI GT: Schwere Blutung
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	1 (1,2)	NE [NE; NE]	81	5 (6,2)	NE [NE; NE]	0,17	[0,01; 1,05]	0,0573
Westeuropa	44	1 (2,3)	NE [NE; NE]	46	3 (6,5)	NE [NE; NE]	0,28	[0,01; 2,21]	0,2360
Andere	171	5 (2,9)	NE [NE; NE]	170	8 (4,7)	NE [NE; NE]	0,59	[0,18; 1,78]	0,3532
Interaktion p-Wert									0,5239
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	2 (2,0)	NE [NE; NE]	101	10 (9,9)	NE [NE; NE]	0,19	[0,03; 0,71]	0,0117*
Intermediäres Risiko [4-5]	126	2 (1,6)	NE [NE; NE]	124	1 (0,8)	NE [NE; NE]	1,76	[0,17; 37,93]	0,6346
Hohes Risiko [6-11]	72	3 (4,2)	NE [NE; NE]	72	5 (6,9)	NE [NE; NE]	0,54	[0,11; 2,18]	0,3833
Interaktion p-Wert									0,2383
Geschlecht [eCRF]									
Männlich	212	5 (2,4)	NE [NE; NE]	208	12 (5,8)	NE [NE; NE]	0,38	[0,12; 1,01]	0,0536
Weiblich	85	2 (2,4)	NE [NE; NE]	89	4 (4,5)	NE [NE; NE]	0,45	[0,06; 2,32]	0,3441
Interaktion p-Wert									0,8573
Altersgruppe I [eCRF]									
< 70 Jahre	122	1 (0,8)	NE [NE; NE]	117	9 (7,7)	NE [NE; NE]	0,09	[0,01; 0,50]	0,0031*
>= 70 Jahre	175	6 (3,4)	NE [NE; NE]	180	7 (3,9)	NE [NE; NE]	0,81	[0,26; 2,44]	0,7066
Interaktion p-Wert									0,0385*
Altersgruppe II [eCRF]									
< 75 Jahre	214	3 (1,4)	NE [NE; NE]	221	14 (6,3)	NE [NE; NE]	0,20	[0,05; 0,61]	0,0035*
>= 75 Jahre	83	4 (4,8)	NE [NE; NE]	76	2 (2,6)	NE [NE; NE]	1,64	[0,32; 11,83]	0,5590
Interaktion p-Wert									0,0393*
Abstammung [eCRF]									
Weiß	232	6 (2,6)	NE [NE; NE]	233	15 (6,4)	NE [NE; NE]	0,36	[0,13; 0,88]	0,0246*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.5.2 ECHO: Summary of subgroup analysis of time to first EKI GT: Schwere Blutung
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	1 (1,9)	NE [NE; NE]	53	1 (1,9)	NE [NE; NE]	1,04	[0,04; 26,19]	0,9798
Interaktion p-Wert									0,4835
ECOG-PS [eCRF]									
0	156	3 (1,9)	NE [NE; NE]	140	7 (5,0)	NE [NE; NE]	0,34	[0,07; 1,24]	0,1050
1	129	4 (3,1)	NE [NE; NE]	132	9 (6,8)	NE [NE; NE]	0,43	[0,12; 1,32]	0,1438
>=2	12	0	NE [NE; NE]	25	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,8087
Bulky Disease I [eCRF]									
< 5 cm	185	2 (1,1)	NE [NE; NE]	185	11 (5,9)	NE [NE; NE]	0,17	[0,03; 0,65]	0,0072*
>= 5 cm	112	5 (4,5)	NE [NE; NE]	112	5 (4,5)	NE [NE; NE]	0,80	[0,22; 2,90]	0,7299
Interaktion p-Wert									0,1085
Bulky Disease II [eCRF]									
< 10 cm	277	5 (1,8)	NE [NE; NE]	276	16 (5,8)	NE [NE; NE]	0,28	[0,09; 0,72]	0,0072*
>= 10 cm	20	2 (10,0)	NE [NE; NE]	21	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	2 (4,2)	NE [NE; NE]	36	3 (8,3)	NE [NE; NE]	0,46	[0,06; 2,79]	0,3920
Stadium IV	249	5 (2,0)	NE [NE; NE]	261	13 (5,0)	NE [NE; NE]	0,36	[0,12; 0,96]	0,0418*
Interaktion p-Wert									0,8203
MCL-Typ [eCRF]									
Klassische Variante	195	7 (3,6)	NE [NE; NE]	205	11 (5,4)	NE [NE; NE]	0,63	[0,23; 1,60]	0,3360
Blastoide und pleomorphische Variante	39	0	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	NC	[NC]	NC
Andere	0	0	NE	8	1 (12,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.5.2 ECH0: Summary of subgroup analysis of time to first EKI GT: Schwere Blutung
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	4 (3,7)	NE [NE; NE]	103	5 (4,9)	NE [NE; NE]	NC	[NC]	NC
>= 30%	126	1 (0,8)	NE [NE; NE]	126	7 (5,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ki-67 (%) II [eCRF]									
< 50%	179	5 (2,8)	NE [NE; NE]	164	12 (7,3)	NE [NE; NE]	0,38	[0,12; 1,04]	0,0592
>= 50%	56	0	NE [NE; NE]	65	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Knochenmarksbeteiligung [eCRF]									
Ja	178	6 (3,4)	NE [NE; NE]	180	8 (4,4)	NE [NE; NE]	0,69	[0,23; 1,99]	0,4898
Nein	50	1 (2,0)	NE [NE; NE]	45	4 (8,9)	NE [NE; NE]	0,20	[0,01; 1,36]	0,1039
Interaktion p-Wert									0,2879
Extranodale Erkrankung [eCRF]									
Ja	262	6 (2,3)	NE [NE; NE]	275	13 (4,7)	NE [NE; NE]	0,44	[0,15; 1,12]	0,0852
Nein	35	1 (2,9)	NE [NE; NE]	22	3 (13,6)	NE [NE; NE]	0,18	[0,01; 1,42]	0,1051
Interaktion p-Wert									0,4596
Gastrointestinale Erkrankung [eCRF]									
Ja	74	1 (1,4)	NE [NE; NE]	74	3 (4,1)	NE [NE; NE]	0,30	[0,02; 2,38]	0,2667
Nein	223	6 (2,7)	NE [NE; NE]	223	13 (5,8)	NE [NE; NE]	0,42	[0,15; 1,05]	0,0645
Interaktion p-Wert									0,8009
LDH > ULN [eCRF]									
Ja	52	1 (1,9)	NE [NE; NE]	54	1 (1,9)	NE [NE; NE]	0,83	[0,03; 20,97]	0,8951
Nein	245	6 (2,4)	NE [NE; NE]	241	14 (5,8)	NE [NE; NE]	0,39	[0,14; 0,97]	0,0433*
Interaktion p-Wert									0,6168

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.6.1 ECHO: Summary of subgroup analysis of time to first EKI G>=3 GT: Hepatotoxizität
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	5 (6,1)	NE [NE; NE]	81	0	NE [NE; NE]	NC	[NC]	NC
Westeuropa	44	2 (4,5)	NE [NE; NE]	46	1 (2,2)	NE [NE; NE]	1,90	[0,18; 40,81]	0,5910
Andere	171	13 (7,6)	NE [NE; NE]	170	5 (2,9)	NE [NE; NE]	2,55	[0,96; 7,95]	0,0601
Interaktion p-Wert									0,8261
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	9 (9,1)	NE [NE; NE]	101	1 (1,0)	NE [NE; NE]	9,21	[1,73;169,79]	0,0060*
Intermediäres Risiko [4-5]	126	9 (7,1)	NE [NE; NE]	124	2 (1,6)	NE [NE; NE]	4,14	[1,07; 27,19]	0,0391*
Hohes Risiko [6-11]	72	2 (2,8)	NE [NE; NE]	72	3 (4,2)	NE [NE; NE]	0,63	[0,08; 3,82]	0,6134
Interaktion p-Wert									0,1004
Geschlecht [eCRF]									
Männlich	212	14 (6,6)	NE [NE; NE]	208	4 (1,9)	NE [NE; NE]	3,33	[1,19; 11,74]	0,0202*
Weiblich	85	6 (7,1)	NE [NE; NE]	89	2 (2,2)	NE [NE; NE]	2,97	[0,68; 20,25]	0,1526
Interaktion p-Wert									0,9080
Altersgruppe I [eCRF]									
< 70 Jahre	122	6 (4,9)	NE [NE; NE]	117	4 (3,4)	NE [NE; NE]	1,37	[0,39; 5,37]	0,6198
>= 70 Jahre	175	14 (8,0)	NE [NE; NE]	180	2 (1,1)	NE [NE; NE]	6,97	[1,95; 44,39]	0,0015*
Interaktion p-Wert									0,0906
Altersgruppe II [eCRF]									
< 75 Jahre	214	15 (7,0)	NE [NE; NE]	221	6 (2,7)	NE [NE; NE]	2,44	[0,99; 6,83]	0,0528
>= 75 Jahre	83	5 (6,0)	NE [NE; NE]	76	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Abstammung [eCRF]									
Weiß	232	13 (5,6)	NE [NE; NE]	233	4 (1,7)	NE [NE; NE]	3,08	[1,09; 10,95]	0,0330*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.6.1 ECHO: Summary of subgroup analysis of time to first EKI G>=3 GT: Hepatotoxizität
 Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	6 (11,5)	NE [NE; NE]	53	2 (3,8)	NE [NE; NE]	3,22	[0,74; 21,98]	0,1224
Interaktion p-Wert									0,9649
ECOG-PS [eCRF]									
0	156	9 (5,8)	NE [NE; NE]	140	1 (0,7)	NE [NE; NE]	7,75	[1,46;142,99]	0,0126*
1	129	11 (8,5)	NE [NE; NE]	132	5 (3,8)	NE [NE; NE]	2,24	[0,82; 7,12]	0,1193
>=2	12	0	NE [NE; NE]	25	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,2536
Bulky Disease I [eCRF]									
< 5 cm	185	10 (5,4)	NE [NE; NE]	185	3 (1,6)	NE [NE; NE]	3,36	[1,03; 15,00]	0,0444*
>= 5 cm	112	10 (8,9)	NE [NE; NE]	112	3 (2,7)	NE [NE; NE]	2,93	[0,90; 13,10]	0,0772
Interaktion p-Wert									0,8833
Bulky Disease II [eCRF]									
< 10 cm	277	18 (6,5)	NE [NE; NE]	276	6 (2,2)	NE [NE; NE]	2,88	[1,21; 7,96]	0,0159*
>= 10 cm	20	2 (10,0)	NE [NE; NE]	21	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	7 (14,6)	NE [NE; NE]	36	0	NE [NE; NE]	NC	[NC]	NC
Stadium IV	249	13 (5,2)	NE [NE; NE]	261	6 (2,3)	NE [NE; NE]	2,20	[0,87; 6,27]	0,0968
Interaktion p-Wert									NC
MCL-Typ [eCRF]									
Klassische Variante	195	13 (6,7)	NE [NE; NE]	205	6 (2,9)	NE [NE; NE]	2,26	[0,89; 6,44]	0,0858
Blastoide und pleomorphische Variante	39	2 (5,1)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Andere	0	0	NE	8	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									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% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.6.1 ECHO: Summary of subgroup analysis of time to first EKI G>=3 GT: Hepatotoxizität
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	7 (6,4)	NE [NE; NE]	103	3 (2,9)	NE [NE; NE]	2,32	[0,65; 10,77]	0,2024
>= 30%	126	9 (7,1)	NE [NE; NE]	126	3 (2,4)	NE [NE; NE]	2,71	[0,81; 12,23]	0,1097
Interaktion p-Wert									0,8714
Ki-67 (%) II [eCRF]									
< 50%	179	11 (6,1)	NE [NE; NE]	164	4 (2,4)	NE [NE; NE]	2,59	[0,89; 9,36]	0,0834
>= 50%	56	5 (8,9)	NE [NE; NE]	65	2 (3,1)	NE [NE; NE]	2,39	[0,51; 16,74]	0,2739
Interaktion p-Wert									0,9378
Knochenmarksbeteiligung [eCRF]									
Ja	178	8 (4,5)	NE [NE; NE]	180	3 (1,7)	NE [NE; NE]	2,58	[0,75; 11,80]	0,1379
Nein	50	8 (16,0)	NE [NE; NE]	45	1 (2,2)	NE [NE; NE]	6,65	[1,22;123,40]	0,0258*
Interaktion p-Wert									0,4313
Extranodale Erkrankung [eCRF]									
Ja	262	14 (5,3)	NE [NE; NE]	275	6 (2,2)	NE [NE; NE]	2,38	[0,95; 6,72]	0,0631
Nein	35	6 (17,1)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Gastrointestinale Erkrankung [eCRF]									
Ja	74	2 (2,7)	NE [NE; NE]	74	2 (2,7)	NE [NE; NE]	0,93	[0,11; 7,76]	0,9435
Nein	223	18 (8,1)	NE [NE; NE]	223	4 (1,8)	NE [NE; NE]	4,38	[1,63; 15,15]	0,0024*
Interaktion p-Wert									0,1826
LDH > ULN [eCRF]									
Ja	52	4 (7,7)	NE [NE; NE]	54	1 (1,9)	NE [NE; NE]	3,60	[0,53; 70,38]	0,2026
Nein	245	16 (6,5)	NE [NE; NE]	241	5 (2,1)	NE [NE; NE]	3,09	[1,21; 9,44]	0,0173*
Interaktion p-Wert									0,8999

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.7.1 ECHO: Summary of subgroup analysis of time to first SEKI GT: Blutung
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	0	NE [NE; NE]	81	3 (3,7)	NE [NE; NE]	NC	[NC]	NC
Westeuropa	44	0	NE [NE; NE]	46	3 (6,5)	NE [NE; NE]	NC	[NC]	NC
Andere	171	4 (2,3)	NE [NE; NE]	170	6 (3,5)	NE [NE; NE]	0,64	[0,16; 2,24]	0,4861
Interaktion p-Wert									NC
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	2 (2,0)	NE [NE; NE]	101	9 (8,9)	NE [NE; NE]	0,21	[0,03; 0,83]	0,0243*
Intermediäres Risiko [4-5]	126	1 (0,8)	NE [NE; NE]	124	0	NE [NE; NE]	NC	[NC]	NC
Hohes Risiko [6-11]	72	1 (1,4)	NE [NE; NE]	72	3 (4,2)	NE [NE; NE]	0,30	[0,01; 2,36]	0,2638
Interaktion p-Wert									0,8064
Geschlecht [eCRF]									
Männlich	212	3 (1,4)	NE [NE; NE]	208	8 (3,8)	NE [NE; NE]	0,35	[0,08; 1,21]	0,0983
Weiblich	85	1 (1,2)	NE [NE; NE]	89	4 (4,5)	NE [NE; NE]	0,23	[0,01; 1,56]	0,1404
Interaktion p-Wert									0,7474
Altersgruppe I [eCRF]									
< 70 Jahre	122	1 (0,8)	NE [NE; NE]	117	6 (5,1)	NE [NE; NE]	NC	[NC]	NC
>= 70 Jahre	175	3 (1,7)	NE [NE; NE]	180	6 (3,3)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Altersgruppe II [eCRF]									
< 75 Jahre	214	2 (0,9)	NE [NE; NE]	221	11 (5,0)	NE [NE; NE]	0,17	[0,03; 0,64]	0,0069*
>= 75 Jahre	83	2 (2,4)	NE [NE; NE]	76	1 (1,3)	NE [NE; NE]	1,72	[0,16; 36,94]	0,6508
Interaktion p-Wert									0,0966
Abstammung [eCRF]									
Weiß	232	3 (1,3)	NE [NE; NE]	233	11 (4,7)	NE [NE; NE]	0,25	[0,06; 0,81]	0,0189*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CLs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.7.1 ECHO: Summary of subgroup analysis of time to first SEKI GT: Blutung
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	1 (1,9)	NE [NE; NE]	53	1 (1,9)	NE [NE; NE]	1,03	[0,04; 26,07]	0,9824
Interaktion p-Wert									0,3748
ECOG-PS [eCRF]									
0	156	2 (1,3)	NE [NE; NE]	140	5 (3,6)	NE [NE; NE]	NC	[NC]	NC
1	129	2 (1,6)	NE [NE; NE]	132	7 (5,3)	NE [NE; NE]	NC	[NC]	NC
>=2	12	0	NE [NE; NE]	25	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Bulky Disease I [eCRF]									
< 5 cm	185	2 (1,1)	NE [NE; NE]	185	7 (3,8)	NE [NE; NE]	NC	[NC]	NC
>= 5 cm	112	2 (1,8)	NE [NE; NE]	112	5 (4,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Bulky Disease II [eCRF]									
< 10 cm	277	4 (1,4)	NE [NE; NE]	276	12 (4,3)	NE [NE; NE]	0,31	[0,09; 0,89]	0,0287*
>= 10 cm	20	0	NE [NE; NE]	21	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	2 (4,2)	NE [NE; NE]	36	3 (8,3)	NE [NE; NE]	0,47	[0,06; 2,85]	0,4035
Stadium IV	249	2 (0,8)	NE [NE; NE]	261	9 (3,4)	NE [NE; NE]	0,22	[0,03; 0,84]	0,0250*
Interaktion p-Wert									0,5159
MCL-Typ [eCRF]									
Klassische Variante	195	4 (2,1)	NE [NE; NE]	205	8 (3,9)	NE [NE; NE]	0,51	[0,14; 1,61]	0,2530
Blastoide und pleomorphische Variante	39	0	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	NC	[NC]	NC
Andere	0	0	NE	8	1 (12,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									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% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.7.1 ECHO: Summary of subgroup analysis of time to first SEKI GT: Blutung
 Safety Analysis Set, DCO 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b] [95%-KI] [b]		2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Ki-67 (%) I [eCRF]									
< 30%	109	3 (2,8)	NE [NE; NE]	103	3 (2,9)	NE [NE; NE]	NC	[NC]	NC
>= 30%	126	1 (0,8)	NE [NE; NE]	126	6 (4,8)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ki-67 (%) II [eCRF]									
< 50%	179	4 (2,2)	NE [NE; NE]	164	9 (5,5)	NE [NE; NE]	0,42	[0,11; 1,28]	0,1289
>= 50%	56	0	NE [NE; NE]	65	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Knochenmarksbeteiligung [eCRF]									
Ja	178	3 (1,7)	NE [NE; NE]	180	5 (2,8)	NE [NE; NE]	NC	[NC]	NC
Nein	50	1 (2,0)	NE [NE; NE]	45	4 (8,9)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Extranodale Erkrankung [eCRF]									
Ja	262	3 (1,1)	NE [NE; NE]	275	9 (3,3)	NE [NE; NE]	0,33	[0,07; 1,10]	0,0711
Nein	35	1 (2,9)	NE [NE; NE]	22	3 (13,6)	NE [NE; NE]	0,19	[0,01; 1,46]	0,1114
Interaktion p-Wert									0,6673
Gastrointestinale Erkrankung [eCRF]									
Ja	74	0	NE [NE; NE]	74	3 (4,1)	NE [NE; NE]	NC	[NC]	NC
Nein	223	4 (1,8)	NE [NE; NE]	223	9 (4,0)	NE [NE; NE]	0,42	[0,11; 1,28]	0,1273
Interaktion p-Wert									NC
LDH > ULN [eCRF]									
Ja	52	0	NE [NE; NE]	54	1 (1,9)	NE [NE; NE]	NC	[NC]	NC
Nein	245	4 (1,6)	NE [NE; NE]	241	10 (4,1)	NE [NE; NE]	0,38	[0,10; 1,13]	0,0828
Interaktion p-Wert									NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
 Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.7.2 ECHO: Summary of subgroup analysis of time to first SEKI GT: Schwere Blutung
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Geographic Region [IXRS]									
Nordamerika	82	0	NE [NE; NE]	81	3 (3,7)	NE [NE; NE]	NC	[NC]	NC
Westeuropa	44	0	NE [NE; NE]	46	3 (6,5)	NE [NE; NE]	NC	[NC]	NC
Andere	171	4 (2,3)	NE [NE; NE]	170	6 (3,5)	NE [NE; NE]	0,64	[0,16; 2,24]	0,4861
Interaktion p-Wert									NC
Vereinfachter MIPI-Score [IXRS]									
Geringes Risiko [0-3]	99	2 (2,0)	NE [NE; NE]	101	9 (8,9)	NE [NE; NE]	0,21	[0,03; 0,83]	0,0243*
Intermediäres Risiko [4-5]	126	1 (0,8)	NE [NE; NE]	124	0	NE [NE; NE]	NC	[NC]	NC
Hohes Risiko [6-11]	72	1 (1,4)	NE [NE; NE]	72	3 (4,2)	NE [NE; NE]	0,30	[0,01; 2,36]	0,2638
Interaktion p-Wert									0,8064
Geschlecht [eCRF]									
Männlich	212	3 (1,4)	NE [NE; NE]	208	8 (3,8)	NE [NE; NE]	0,35	[0,08; 1,21]	0,0983
Weiblich	85	1 (1,2)	NE [NE; NE]	89	4 (4,5)	NE [NE; NE]	0,23	[0,01; 1,56]	0,1404
Interaktion p-Wert									0,7474
Altersgruppe I [eCRF]									
< 70 Jahre	122	1 (0,8)	NE [NE; NE]	117	6 (5,1)	NE [NE; NE]	NC	[NC]	NC
>= 70 Jahre	175	3 (1,7)	NE [NE; NE]	180	6 (3,3)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Altersgruppe II [eCRF]									
< 75 Jahre	214	2 (0,9)	NE [NE; NE]	221	11 (5,0)	NE [NE; NE]	0,17	[0,03; 0,64]	0,0069*
>= 75 Jahre	83	2 (2,4)	NE [NE; NE]	76	1 (1,3)	NE [NE; NE]	1,72	[0,16; 36,94]	0,6508
Interaktion p-Wert									0,0966
Abstammung [eCRF]									
Weiß	232	3 (1,3)	NE [NE; NE]	233	11 (4,7)	NE [NE; NE]	0,25	[0,06; 0,81]	0,0189*

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.7.2 ECHO: Summary of subgroup analysis of time to first SEKI GT: Schwere Blutung
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]			
Nicht-weiß	52	1 (1,9)	NE [NE; NE]	53	1 (1,9)	NE [NE; NE]	1,03	[0,04; 26,07]	0,9824
Interaktion p-Wert									0,3748
ECOG-PS [eCRF]									
0	156	2 (1,3)	NE [NE; NE]	140	5 (3,6)	NE [NE; NE]	NC	[NC]	NC
1	129	2 (1,6)	NE [NE; NE]	132	7 (5,3)	NE [NE; NE]	NC	[NC]	NC
>=2	12	0	NE [NE; NE]	25	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Bulky Disease I [eCRF]									
< 5 cm	185	2 (1,1)	NE [NE; NE]	185	7 (3,8)	NE [NE; NE]	NC	[NC]	NC
>= 5 cm	112	2 (1,8)	NE [NE; NE]	112	5 (4,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Bulky Disease II [eCRF]									
< 10 cm	277	4 (1,4)	NE [NE; NE]	276	12 (4,3)	NE [NE; NE]	0,31	[0,09; 0,89]	0,0287*
>= 10 cm	20	0	NE [NE; NE]	21	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Ann Arbor-Stadium für Lymphome [eCRF]									
Stadium I-III	48	2 (4,2)	NE [NE; NE]	36	3 (8,3)	NE [NE; NE]	0,47	[0,06; 2,85]	0,4035
Stadium IV	249	2 (0,8)	NE [NE; NE]	261	9 (3,4)	NE [NE; NE]	0,22	[0,03; 0,84]	0,0250*
Interaktion p-Wert									0,5159
MCL-Typ [eCRF]									
Klassische Variante	195	4 (2,1)	NE [NE; NE]	205	8 (3,9)	NE [NE; NE]	0,51	[0,14; 1,61]	0,2530
Blastoide und pleomorphische Variante	39	0	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	NC	[NC]	NC
Andere	0	0	NE	8	1 (12,5)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									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% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Table 4.3.1.7.2 ECHO: Summary of subgroup analysis of time to first SEKI GT: Schwere Blutung
Safety Analysis Set, DC0 15FEB2024

Subgruppen	Acala+BR (N=297)			Placebo+BR (N=297)			Hazard Ratio [b]		[95%-KI] [b]	2-seitiger p-Wert [b]
	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]	Anzahl (%) der Patienten mit Ereignis		Mediane Zeit [95%-KI] (Monate) [a]				
	n			n						
Ki-67 (%) I [eCRF]										
< 30%	109	3 (2,8)	NE [NE; NE]	103	3 (2,9)	NE [NE; NE]	NC	[NC]		NC
>= 30%	126	1 (0,8)	NE [NE; NE]	126	6 (4,8)	NE [NE; NE]	NC	[NC]		NC
Interaktion p-Wert										NC
Ki-67 (%) II [eCRF]										
< 50%	179	4 (2,2)	NE [NE; NE]	164	9 (5,5)	NE [NE; NE]	0,42	[0,11; 1,28]		0,1289
>= 50%	56	0	NE [NE; NE]	65	0	NE [NE; NE]	NC	[NC]		NC
Interaktion p-Wert										NC
Knochenmarksbeteiligung [eCRF]										
Ja	178	3 (1,7)	NE [NE; NE]	180	5 (2,8)	NE [NE; NE]	NC	[NC]		NC
Nein	50	1 (2,0)	NE [NE; NE]	45	4 (8,9)	NE [NE; NE]	NC	[NC]		NC
Interaktion p-Wert										NC
Extranodale Erkrankung [eCRF]										
Ja	262	3 (1,1)	NE [NE; NE]	275	9 (3,3)	NE [NE; NE]	0,33	[0,07; 1,10]		0,0711
Nein	35	1 (2,9)	NE [NE; NE]	22	3 (13,6)	NE [NE; NE]	0,19	[0,01; 1,46]		0,1114
Interaktion p-Wert										0,6673
Gastrointestinale Erkrankung [eCRF]										
Ja	74	0	NE [NE; NE]	74	3 (4,1)	NE [NE; NE]	NC	[NC]		NC
Nein	223	4 (1,8)	NE [NE; NE]	223	9 (4,0)	NE [NE; NE]	0,42	[0,11; 1,28]		0,1273
Interaktion p-Wert										NC
LDH > ULN [eCRF]										
Ja	52	0	NE [NE; NE]	54	1 (1,9)	NE [NE; NE]	NC	[NC]		NC
Nein	245	4 (1,6)	NE [NE; NE]	241	10 (4,1)	NE [NE; NE]	0,38	[0,10; 1,13]		0,0828
Interaktion p-Wert										NC

[a] Median time to event based on the Kaplan Meier estimate. NE = not estimable as median (or 95% CIs) not reached.

[b] HR, 95% CIs and p-values are estimated using an unstratified Cox PH model with treatment, subgroup and treatment by subgroup interaction. The CIs are calculated using a profile likelihood approach. Efron method for handling ties.
Note: An interaction model is only used when there are >=10 patients in each subgroup level, >=10 events in at least one subgroup level and >0 events in each treatment arm within a subgroup level. A subgroup level is removed from the analysis if insufficient data. If only one subgroup level then the model will include only treatment as a covariate.

* Interaction p-value <0.05. HR <1 favours acalabrutinib. NC = not calculable.

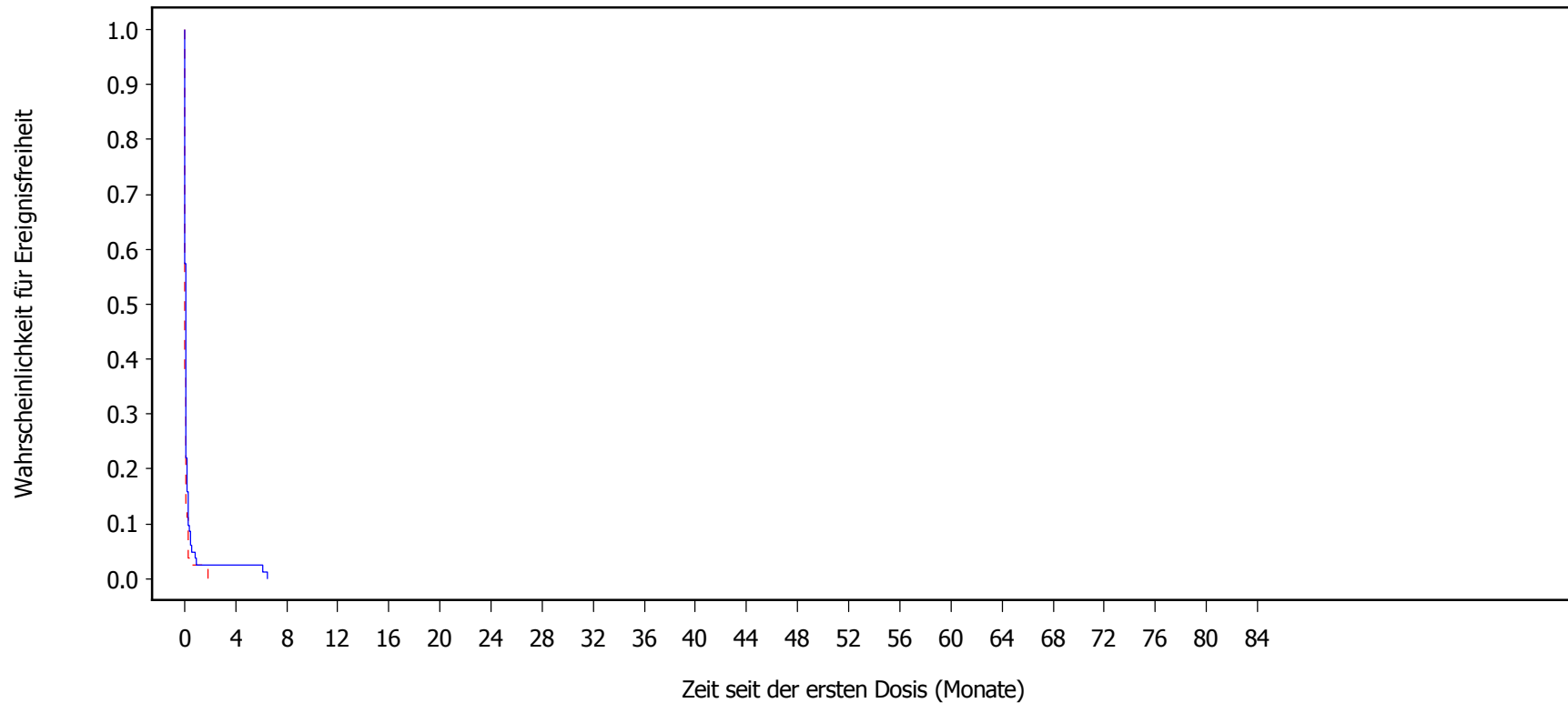
All AEs are coded using MedDRA version 26.1. Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.1 ECHO: Subgroup Analysis: Kaplan-Meier plot of UE for Geographic Region [IXRS]=Nordamerika
 Safety Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

82	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Acala+BR
81	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Placebo+BR

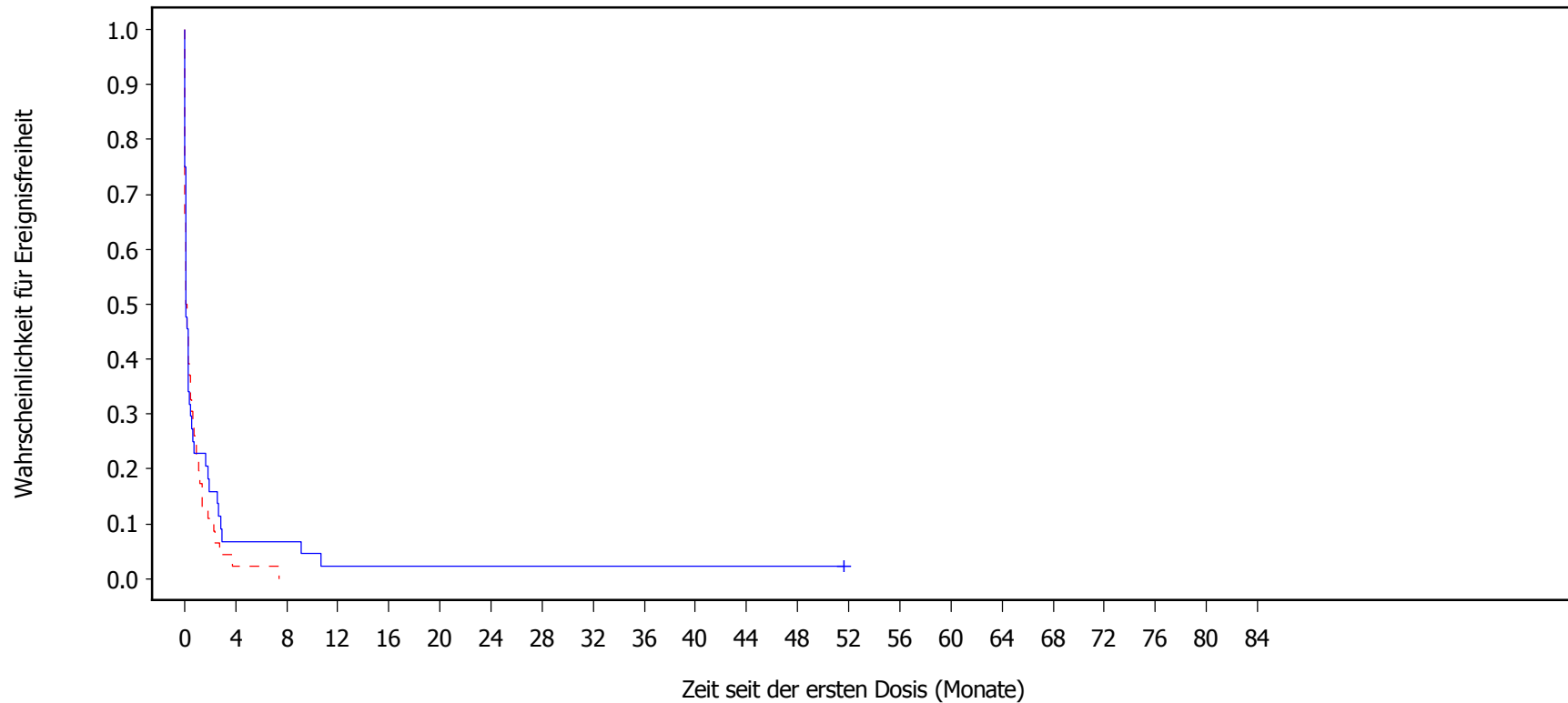
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.2 ECH0: Subgroup Analysis: Kaplan-Meier plot of UE for Geographic Region [IXRS]=Westeuropa
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

44	3	3	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	Acala+BR
46	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Placebo+BR

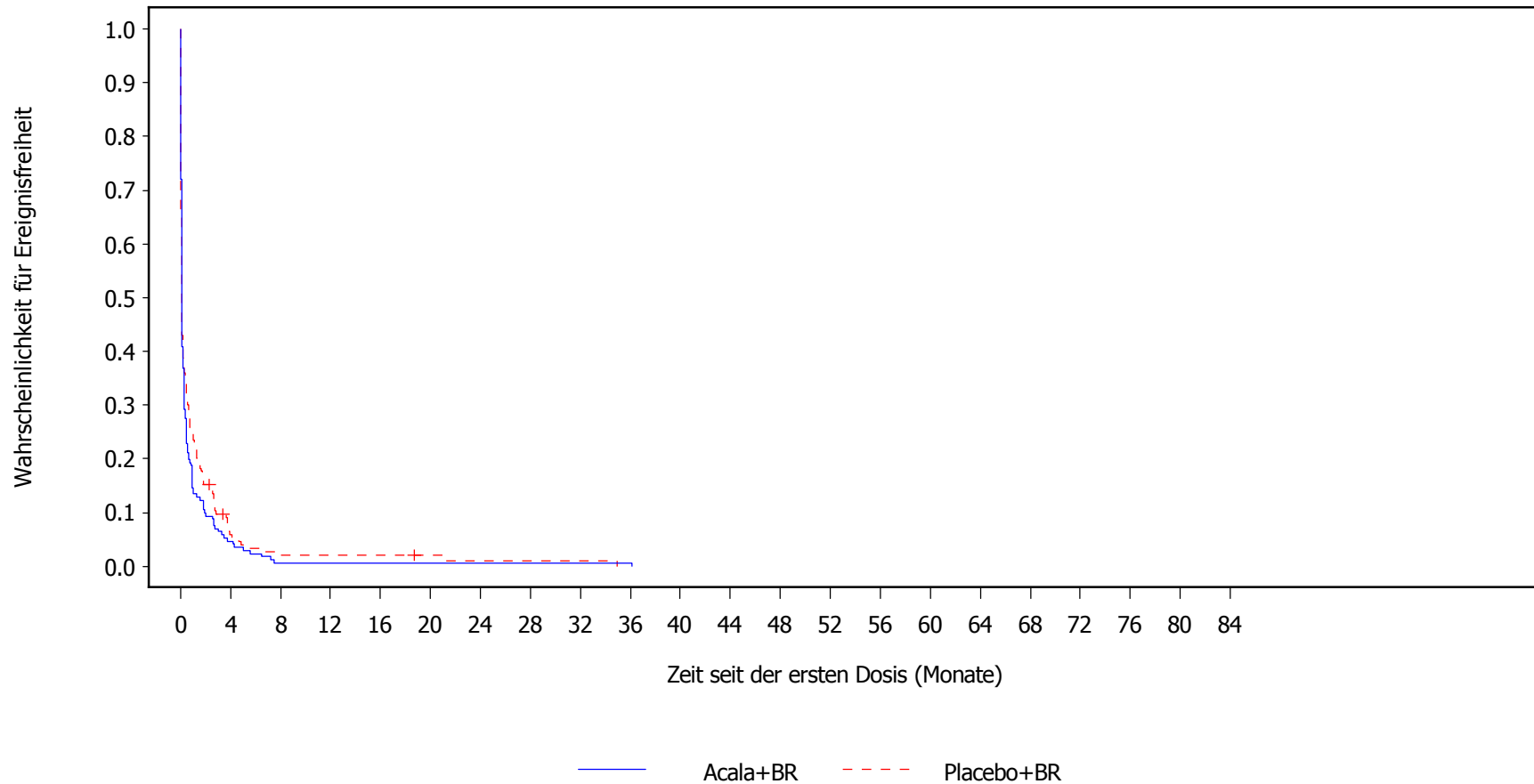
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.3 ECHO: Subgroup Analysis: Kaplan-Meier plot of UE for Geographic Region [IXRS]=Andere
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

171	8	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	Acala+BR
170	9	3	3	3	2	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	Placebo+BR

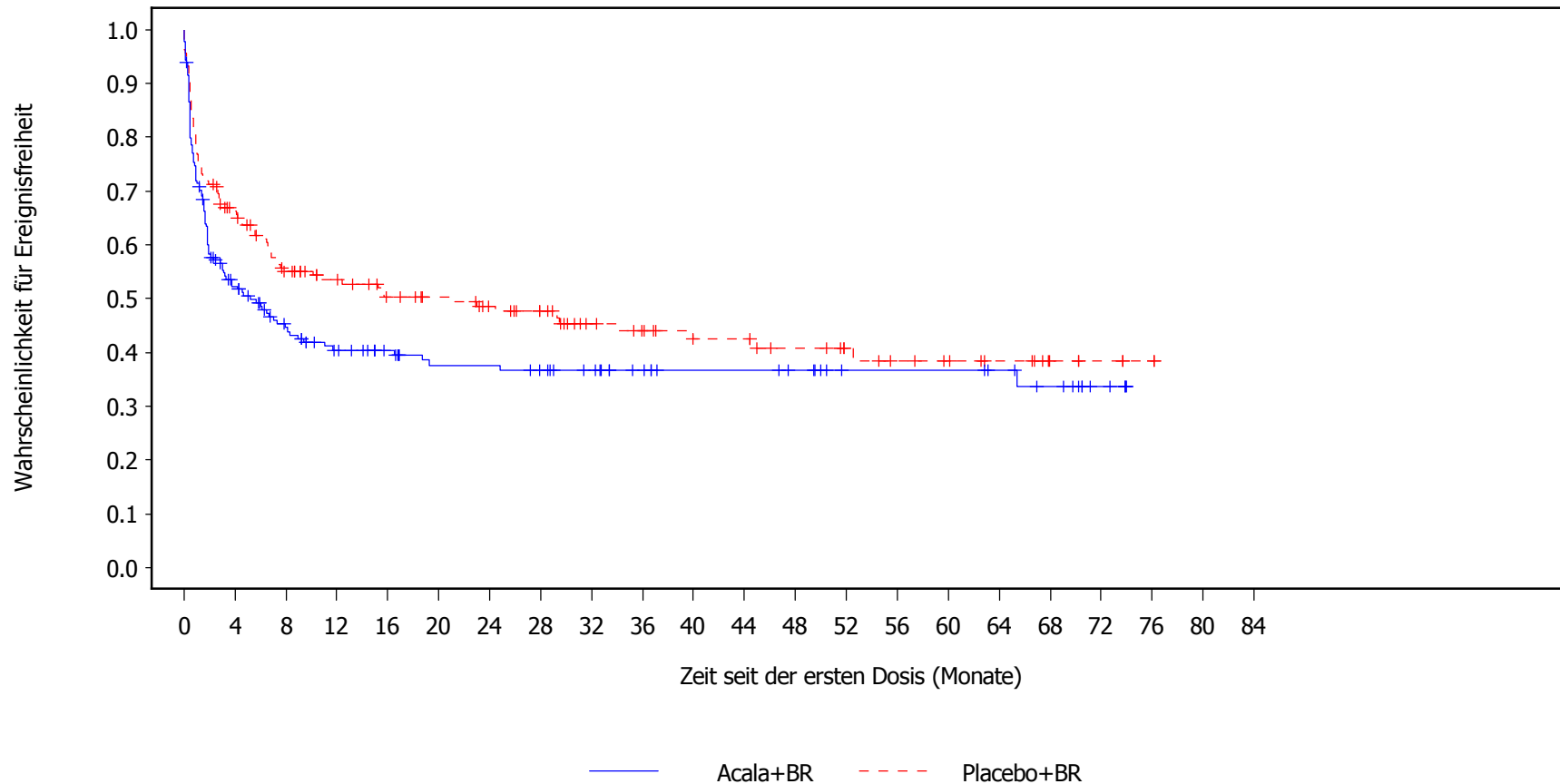
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.4 ECHO: Subgroup Analysis: Kaplan-Meier plot of SOC: Erkrankungen der Haut und des Unterhautgewebes for Ki-67 (%)
 II [eCRF]<= 50%
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

179	86	66	54	46	39	39	36	32	26	22	22	20	15	15	15	13	10	4	0	0	0	Acala+BR
164	103	80	70	61	57	51	45	35	31	26	26	22	18	15	13	10	5	3	1	0	0	Placebo+BR

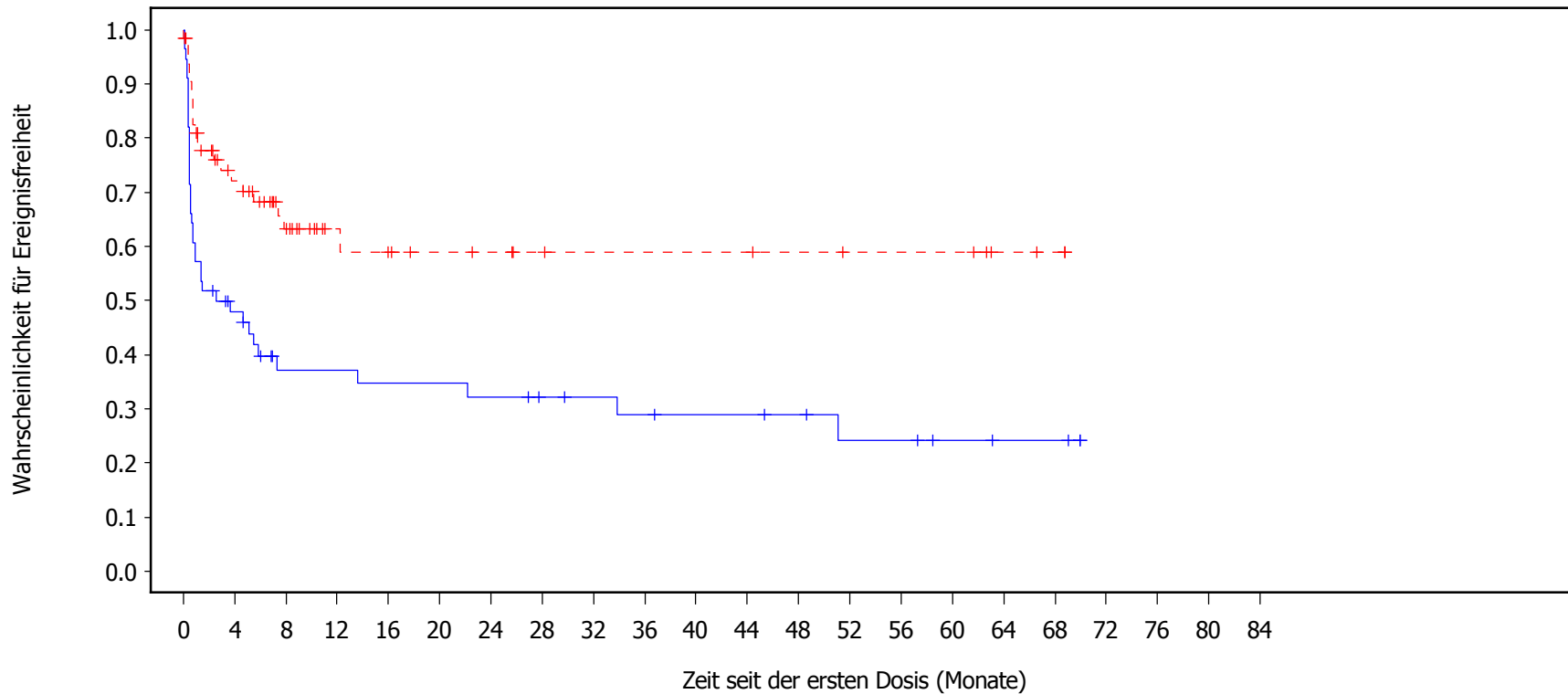
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.5 ECHO: Subgroup Analysis: Kaplan-Meier plot of SOC: Erkrankungen der Haut und des Unterhautgewebes for Ki-67 (%)
 II [eCRF]>= 50%
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

56	24	15	15	14	14	13	11	10	9	8	8	7	5	5	3	2	2	0	0	0	0	Acala+BR
65	38	25	15	14	11	10	8	7	7	7	6	5	5	5	2	1	0	0	0	0	0	Placebo+BR

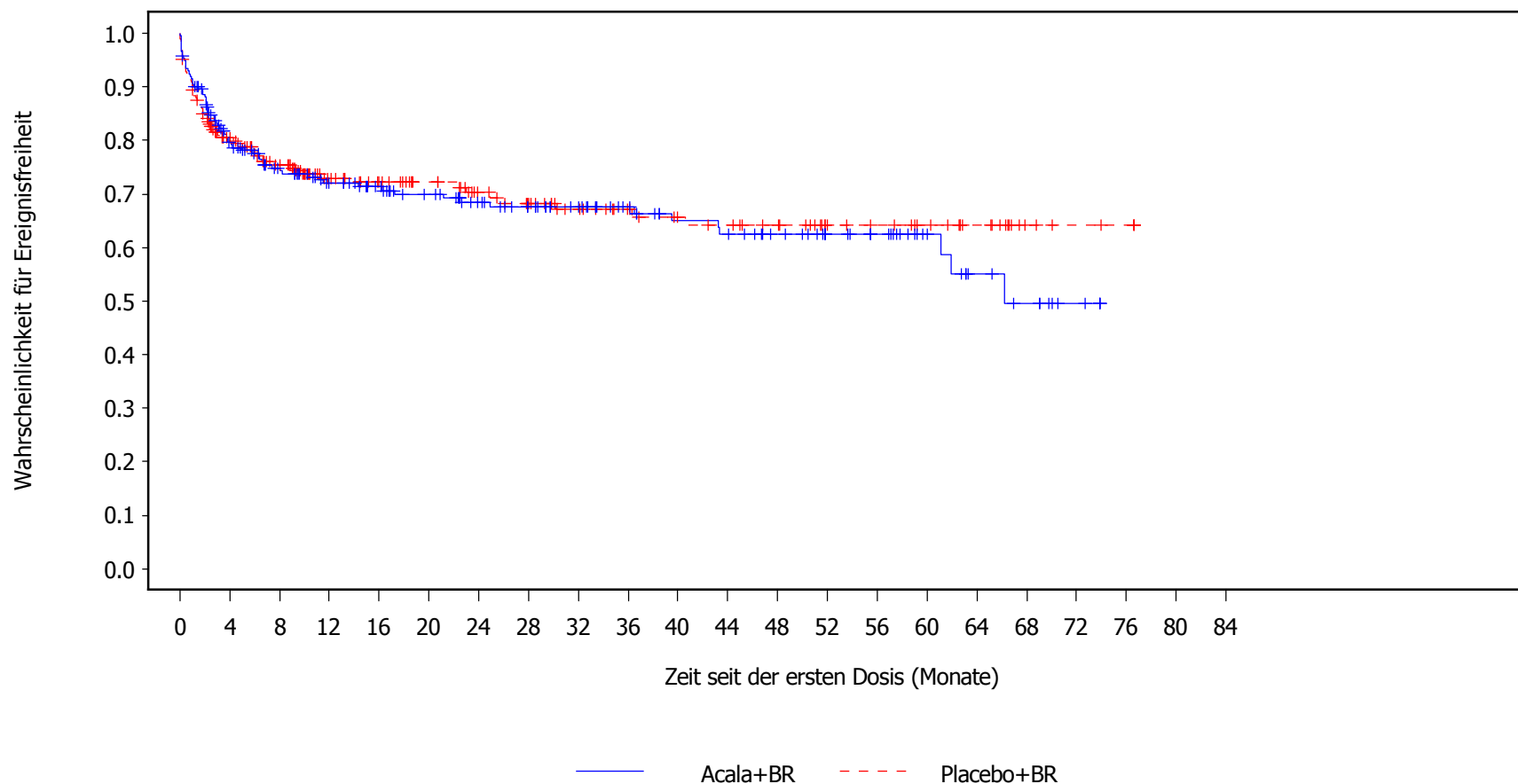
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.6 ECHO: Subgroup Analysis: Kaplan-Meier plot of PT: Diarrhoe for Geschlecht [eCRF]=Männlich
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

212	155	133	117	106	96	84	75	67	57	49	47	41	32	27	17	11	8	3	0	0	0	Acala+BR
208	151	129	102	92	82	71	64	54	47	42	40	36	27	24	20	14	5	3	2	0	0	Placebo+BR

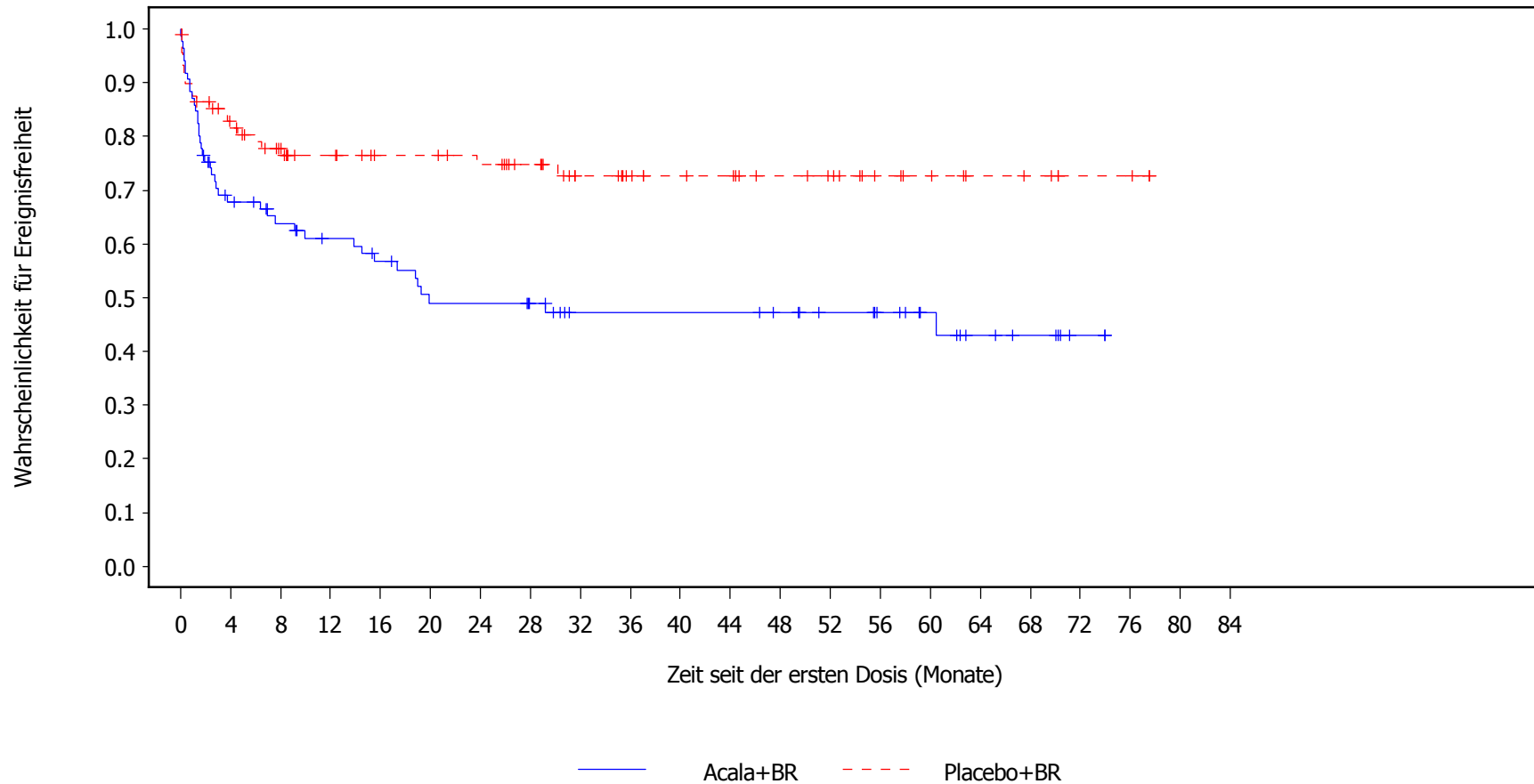
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.7 ECHO: Subgroup Analysis: Kaplan-Meier plot of PT: Diarrhoe for Geschlecht [eCRF]=Weiblich
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

85	54	47	42	38	32	32	29	23	23	23	23	21	18	15	11	7	5	1	0	0	0	Acala+BR
89	68	58	51	46	46	43	38	30	26	23	22	18	16	11	9	6	5	2	2	0	0	Placebo+BR

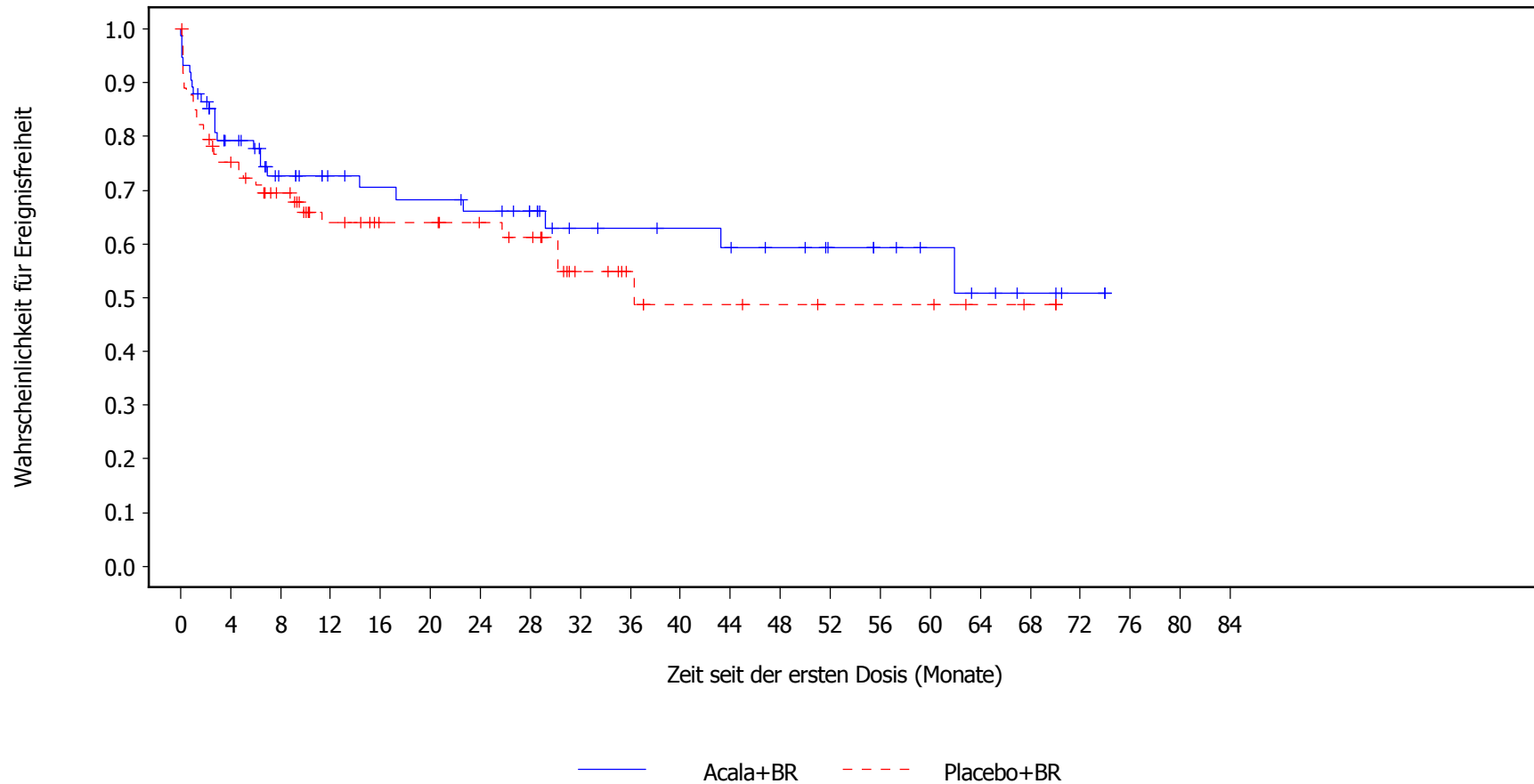
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.8 ECHO: Subgroup Analysis: Kaplan-Meier plot of PT: Diarrhoe for Gastrointestinale Erkrankung [eCRF]=Ja
 Safety Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

74	52	40	34	32	31	29	25	19	18	17	16	14	11	9	7	5	3	1	0	0	0	Acala+BR
74	53	43	32	27	27	24	22	13	9	6	6	5	4	4	4	2	1	0	0	0	0	Placebo+BR

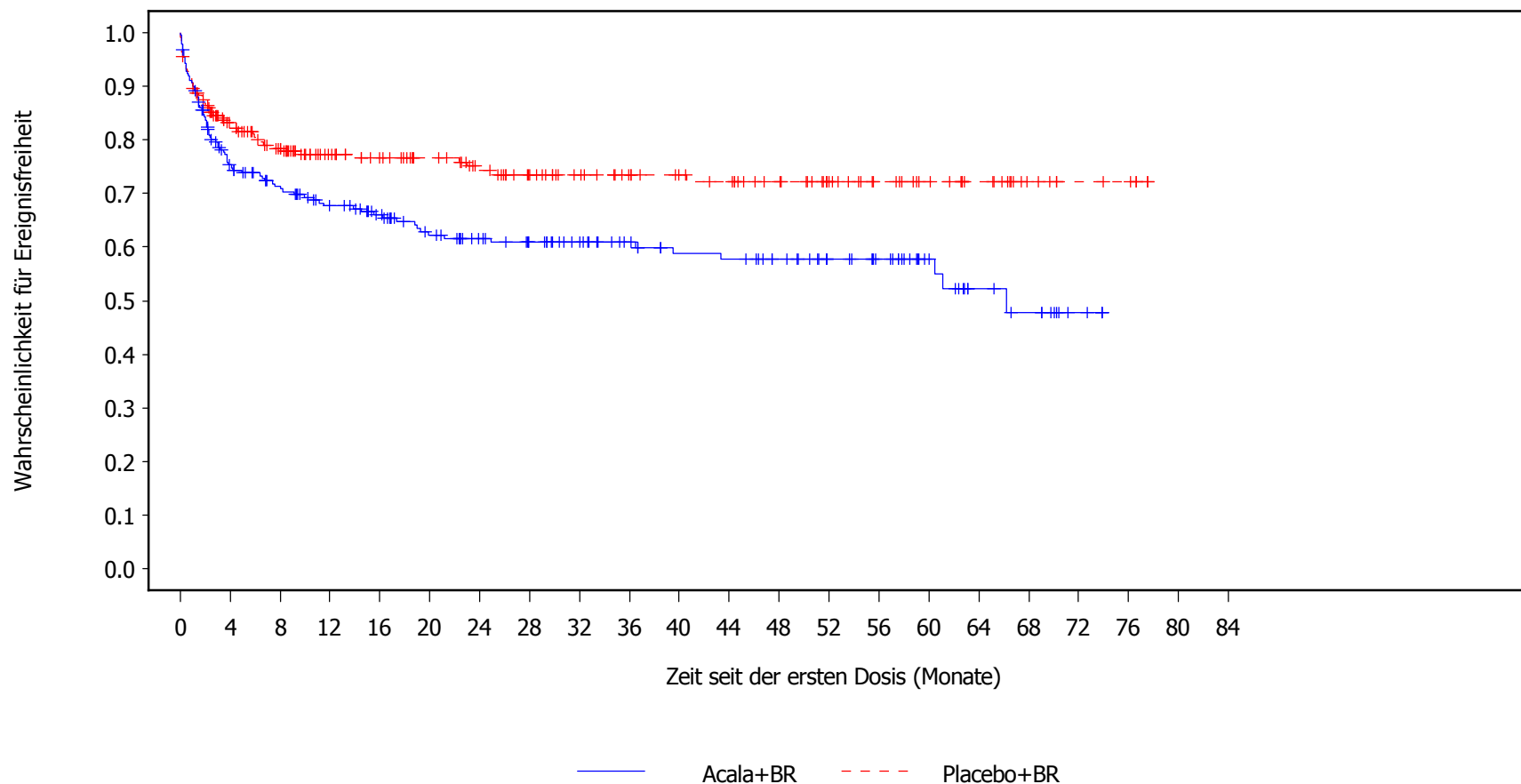
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.9 ECHO: Subgroup Analysis: Kaplan-Meier plot of PT: Diarrhoe for Gastrointestinale Erkrankung [eCRF]=Nein
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

223	157	140	125	112	97	87	79	71	62	55	54	48	39	33	21	13	10	3	0	0	0	Acala+BR
223	166	144	121	111	101	90	80	71	64	59	56	49	39	31	25	18	9	5	4	0	0	Placebo+BR

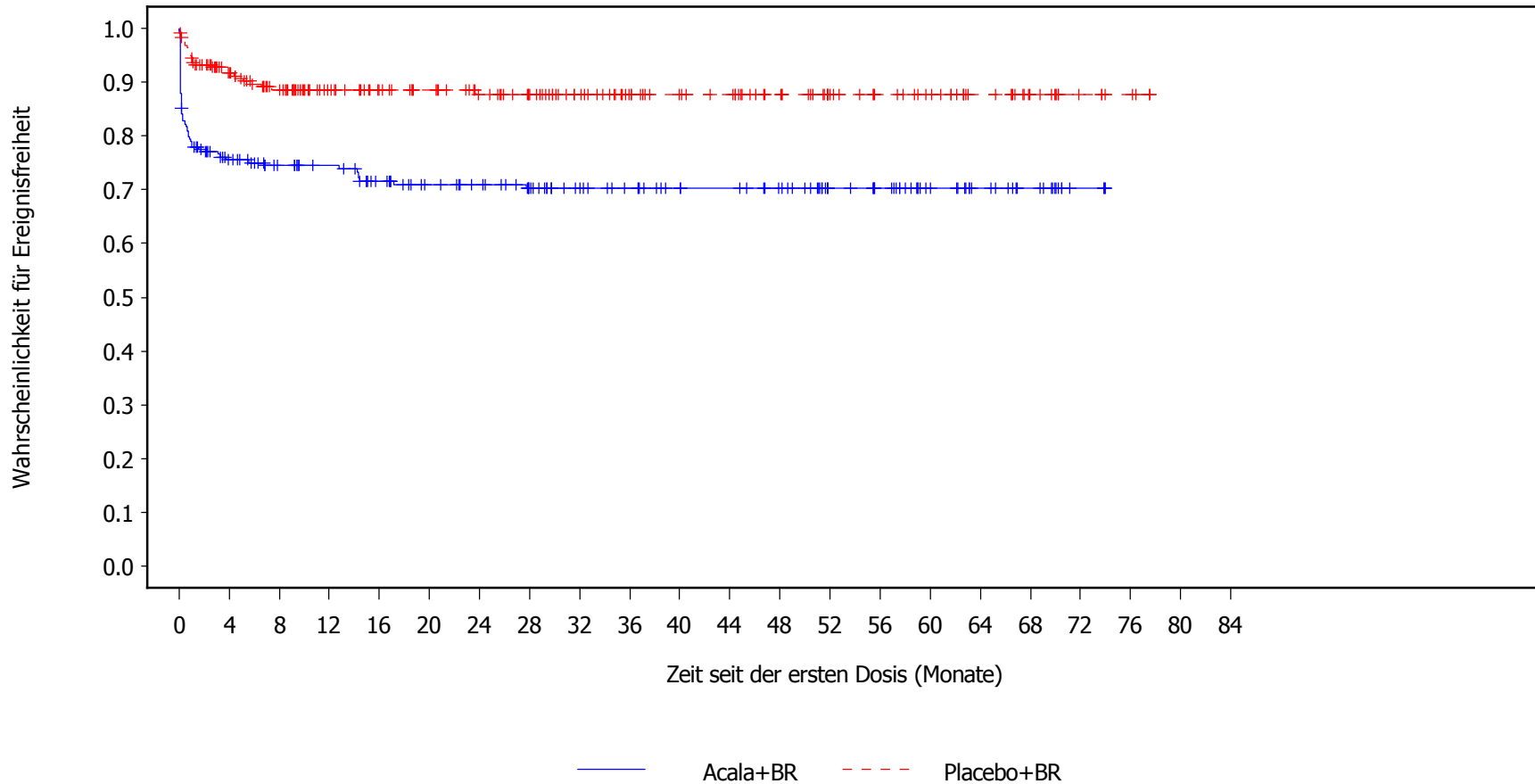
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.10 ECHO: Subgroup Analysis: Kaplan-Meier plot of PT: Erbrechen for Altersgruppe II [eCRF]<= 75 Jahre
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

214	149	135	129	116	105	100	90	79	73	66	64	59	45	39	26	19	13	3	0	0	0	Acala+BR
221	183	162	140	129	121	111	102	89	77	70	67	57	45	38	33	23	14	6	3	0	0	Placebo+BR

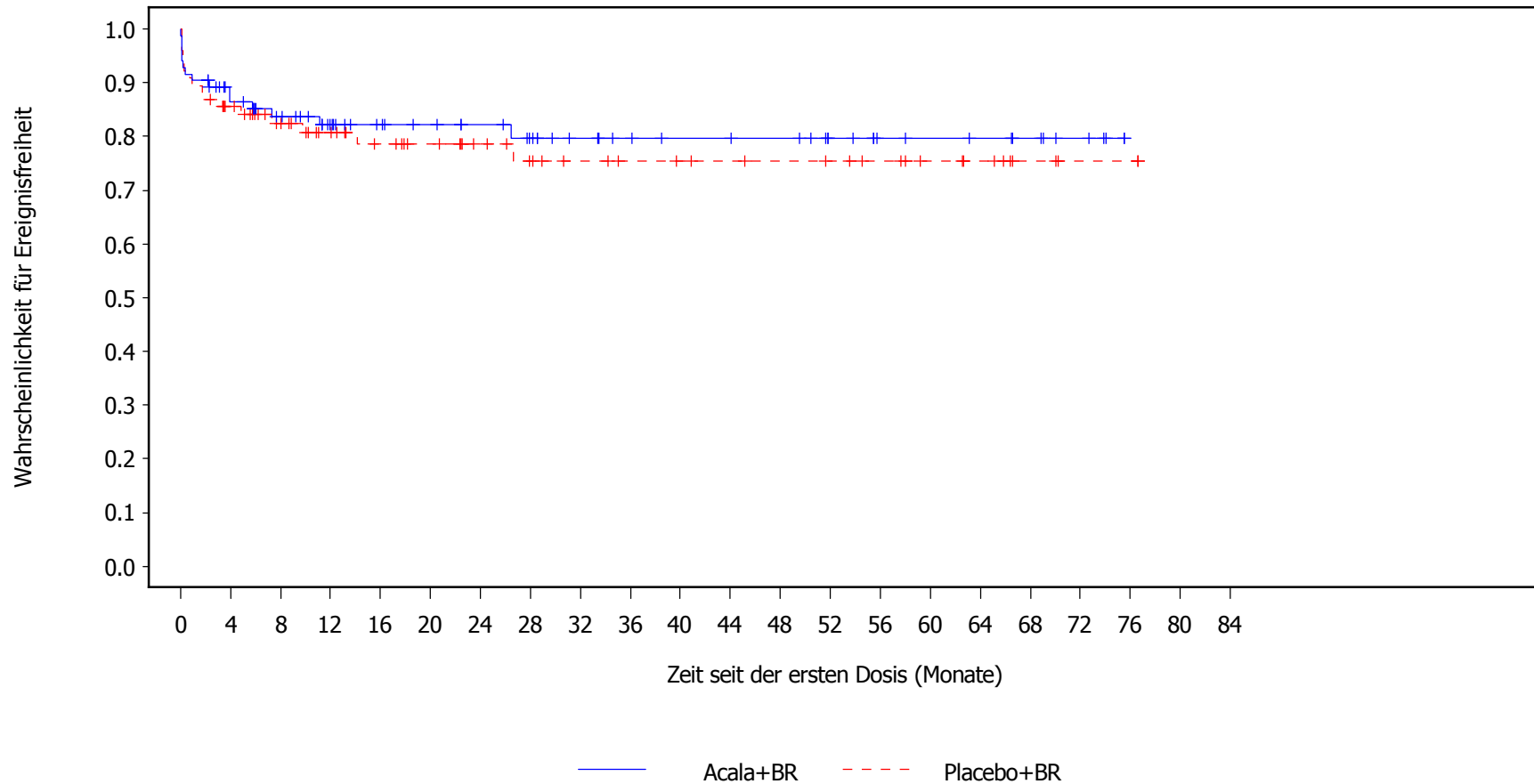
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.11 ECHO: Subgroup Analysis: Kaplan-Meier plot of PT: Erbrechen for Altersgruppe II [eCRF]>= 75 Jahre
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

83	65	57	47	41	38	35	31	26	23	21	21	20	15	11	10	9	7	4	0	0	0	Acala+BR
76	60	50	42	36	32	27	23	20	18	17	16	15	14	12	9	7	3	1	1	0	0	Placebo+BR

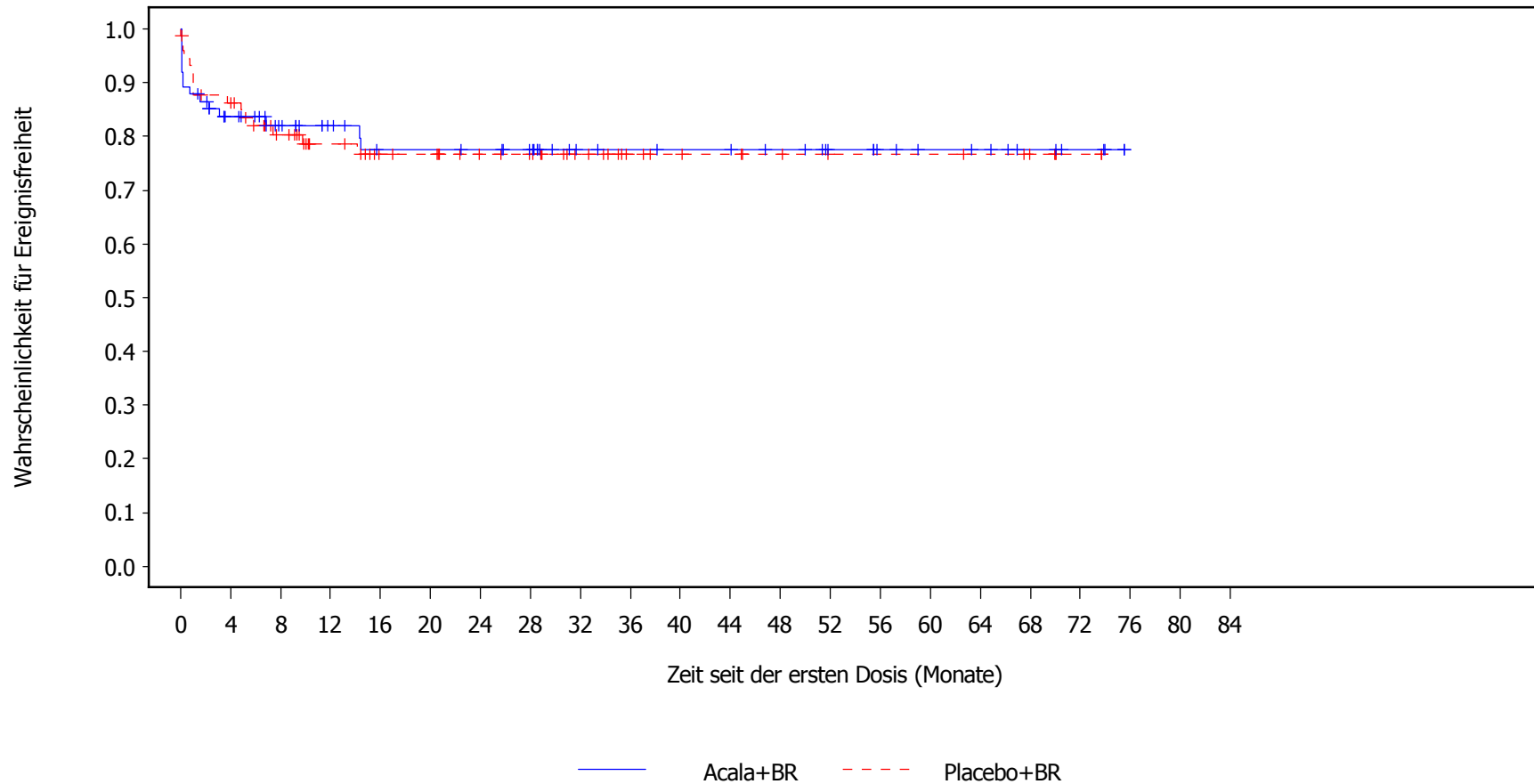
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.12 ECHO: Subgroup Analysis: Kaplan-Meier plot of PT: Erbrechen for Gastrointestinale Erkrankung [eCRF]=Ja
 Safety Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

74	55	46	39	34	34	33	30	22	21	20	20	18	14	11	9	8	5	3	0	0	0	Acala+BR
74	62	50	41	34	33	28	26	20	14	12	11	9	7	7	7	6	4	1	0	0	0	Placebo+BR

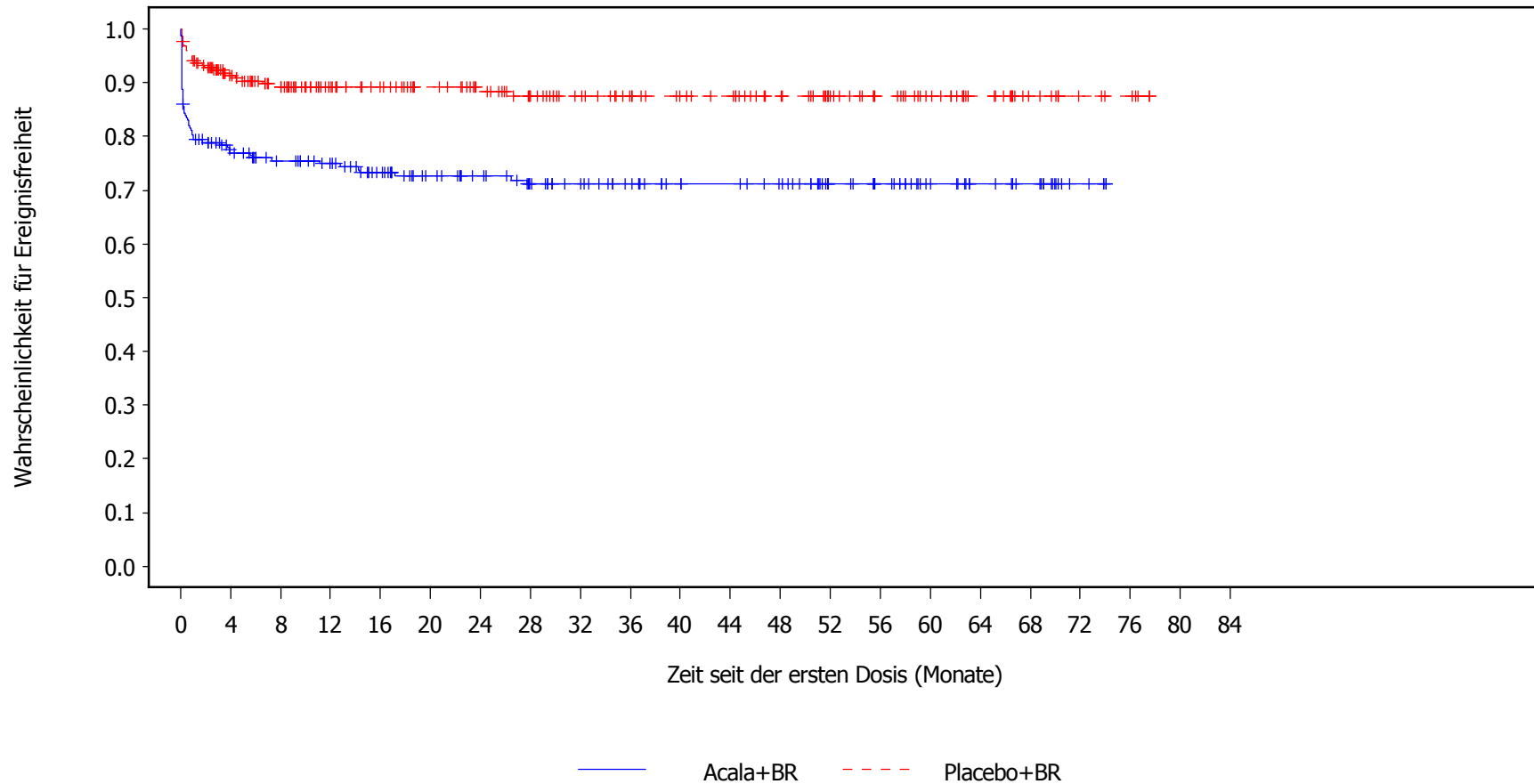
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.13 ECHO: Subgroup Analysis: Kaplan-Meier plot of PT: Erbrechen for Gastrointestinale Erkrankung [eCRF]=Nein
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

223	159	146	137	123	109	102	91	83	75	67	65	61	46	39	27	20	15	4	0	0	0	Acala+BR
223	181	162	141	131	120	110	99	89	81	75	72	63	52	43	35	24	13	6	4	0	0	Placebo+BR

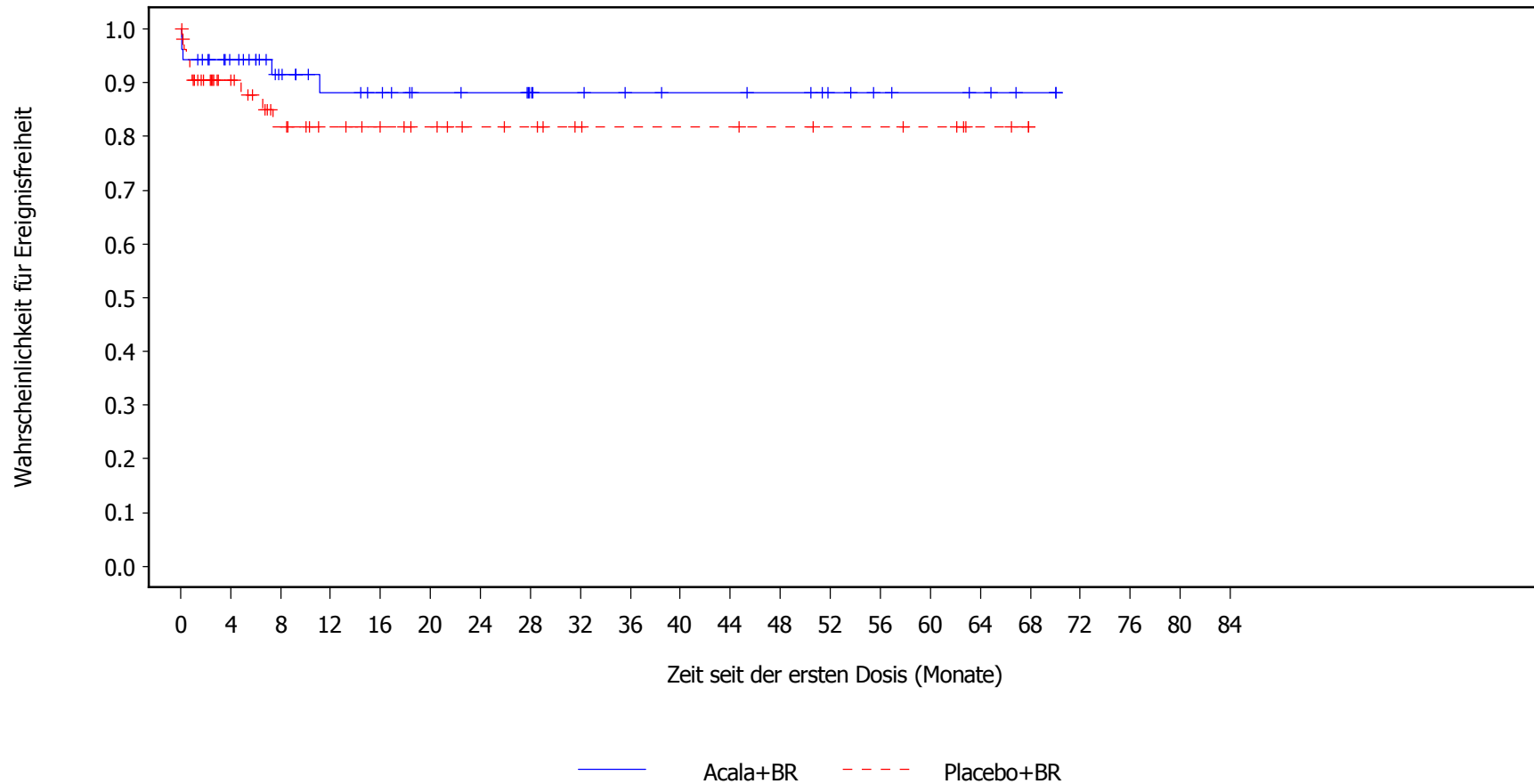
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.14 ECHO: Subgroup Analysis: Kaplan-Meier plot of PT: Erbrechen for LDH > ULN [eCRF]=Ja
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Anzahl an Patienten unter Risiko:

52	42	32	26	24	20	19	16	14	12	11	11	10	7	5	4	3	1	0	0	0	0	Acala+BR
54	36	26	21	19	16	13	12	9	8	8	8	7	6	6	5	2	0	0	0	0	0	Placebo+BR

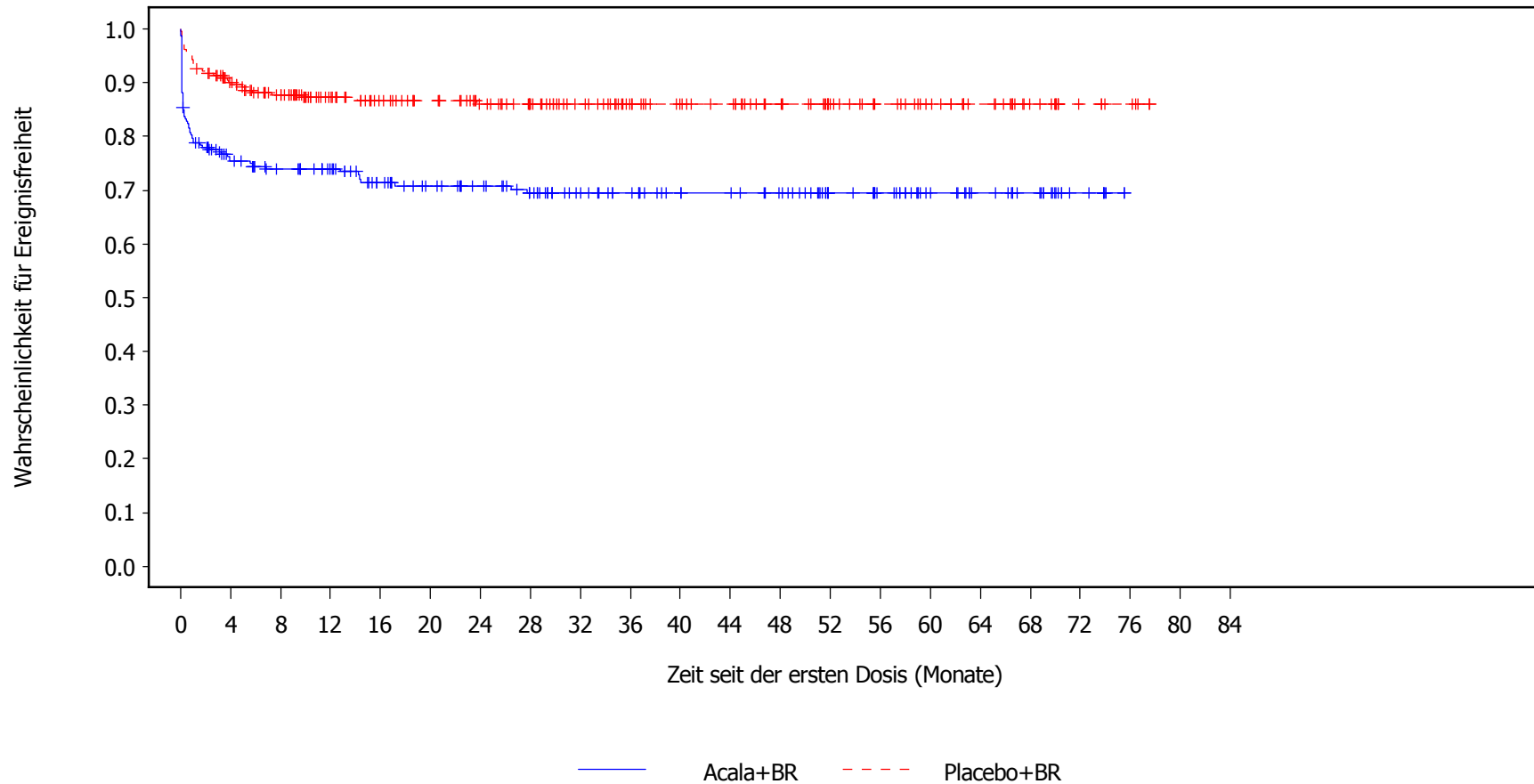
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.15 ECHO: Subgroup Analysis: Kaplan-Meier plot of PT: Erbrechen for LDH > ULN [eCRF]=Nein
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

245	172	160	150	133	123	116	105	91	84	76	74	69	53	45	32	25	19	7	0	0	0	Acala+BR
241	205	185	160	145	136	124	113	100	87	79	75	65	53	44	37	28	17	7	4	0	0	Placebo+BR

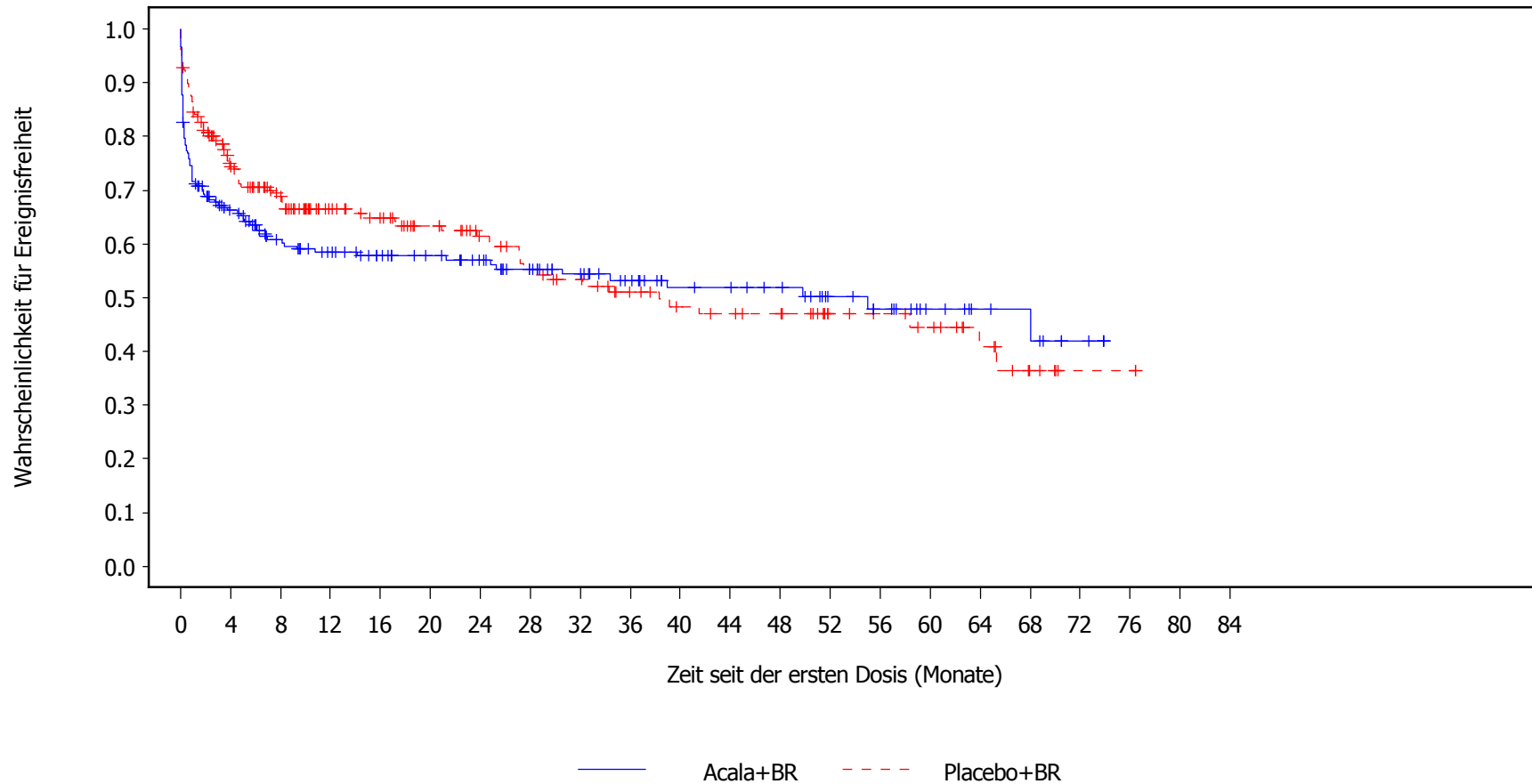
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.16 ECHO: Subgroup Analysis: Kaplan-Meier plot of SOC: Erkrankungen des Nervensystems for Geschlecht [eCRF]=Männlich
 Safety Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

212	127	105	94	85	78	71	61	53	45	36	35	32	24	20	13	9	8	3	0	0	0	Acala+BR
208	139	116	92	84	72	62	54	49	41	36	34	32	22	20	17	11	5	1	1	0	0	Placebo+BR

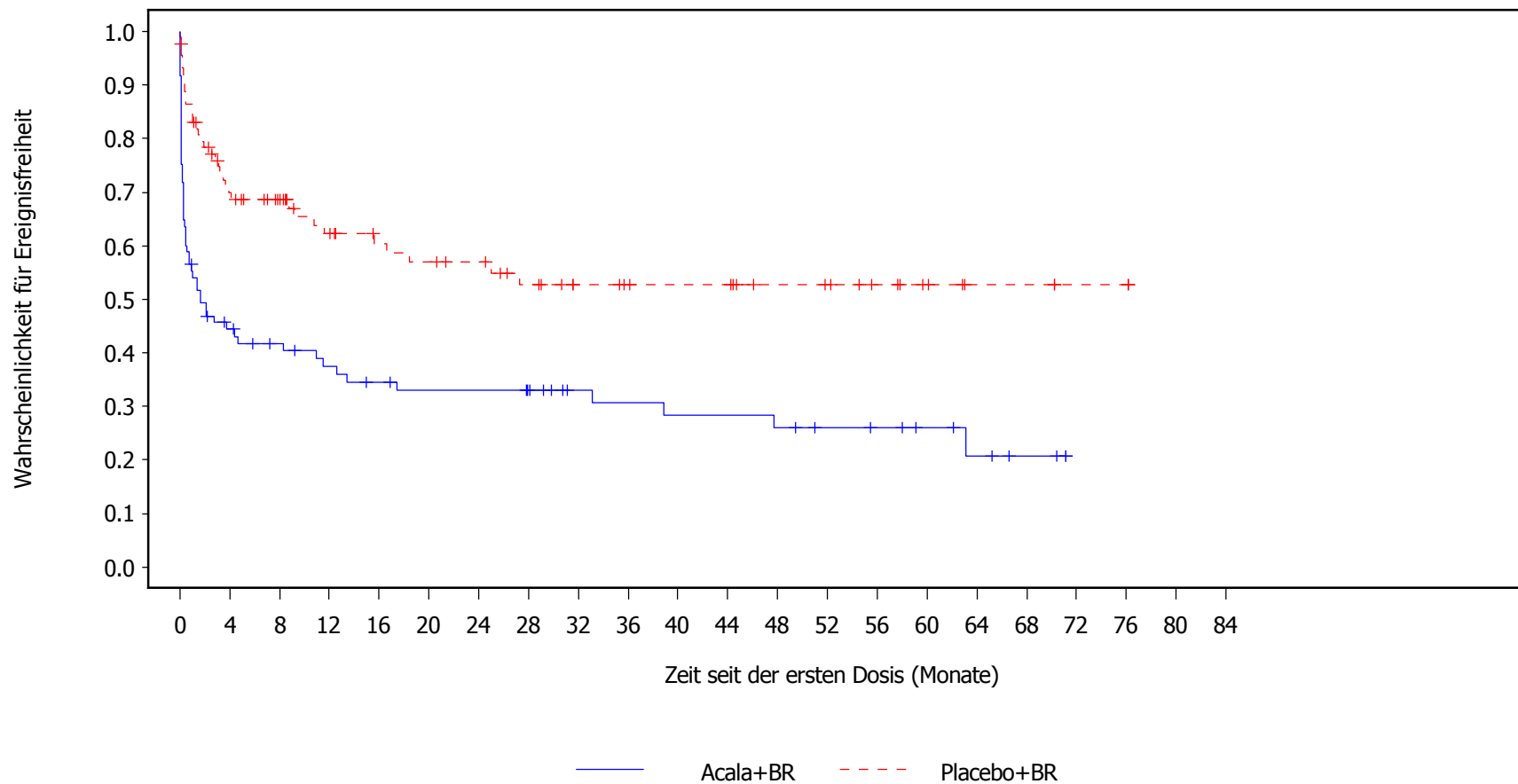
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.17 ECHO: Subgroup Analysis: Kaplan-Meier plot of SOC: Erkrankungen des Nervensystems for Geschlecht [eCRF]=Weiblich
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

85	35	30	26	23	21	21	19	14	13	12	12	11	9	8	6	4	2	0	0	0	0	Acala+BR
89	57	49	39	34	32	30	25	20	18	17	17	13	12	9	6	3	3	1	1	0	0	Placebo+BR

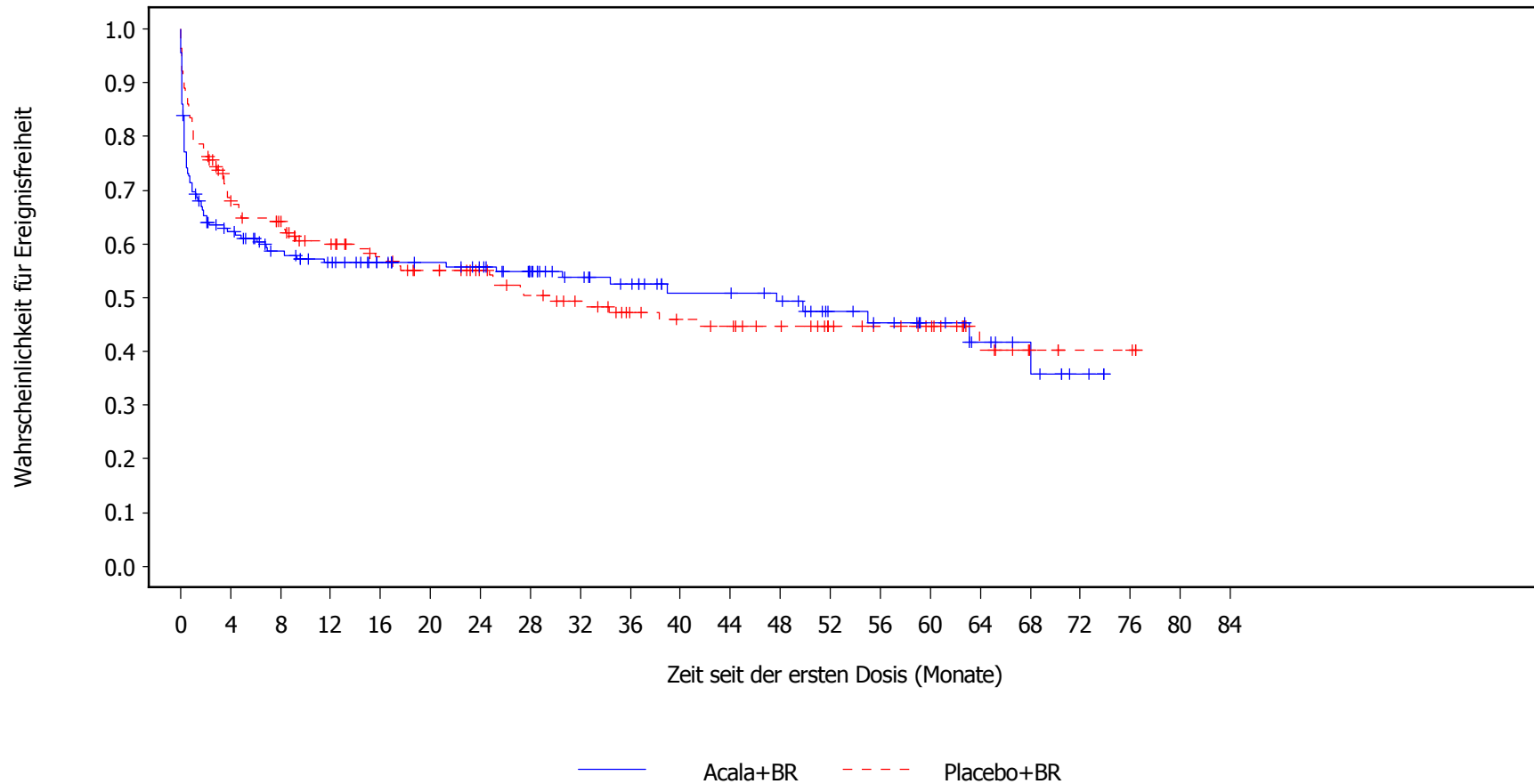
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.18 ECH0: Subgroup Analysis: Kaplan-Meier plot of SOC: Erkrankungen des Nervensystems for Ki-67 (%) II [eCRF]<= 50%
 Safety Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

179	105	91	83	74	68	64	55	46	41	33	33	30	22	19	15	10	7	2	0	0	0	Acala+BR
164	106	95	82	73	66	59	52	47	39	36	34	30	23	20	17	9	4	2	2	0	0	Placebo+BR

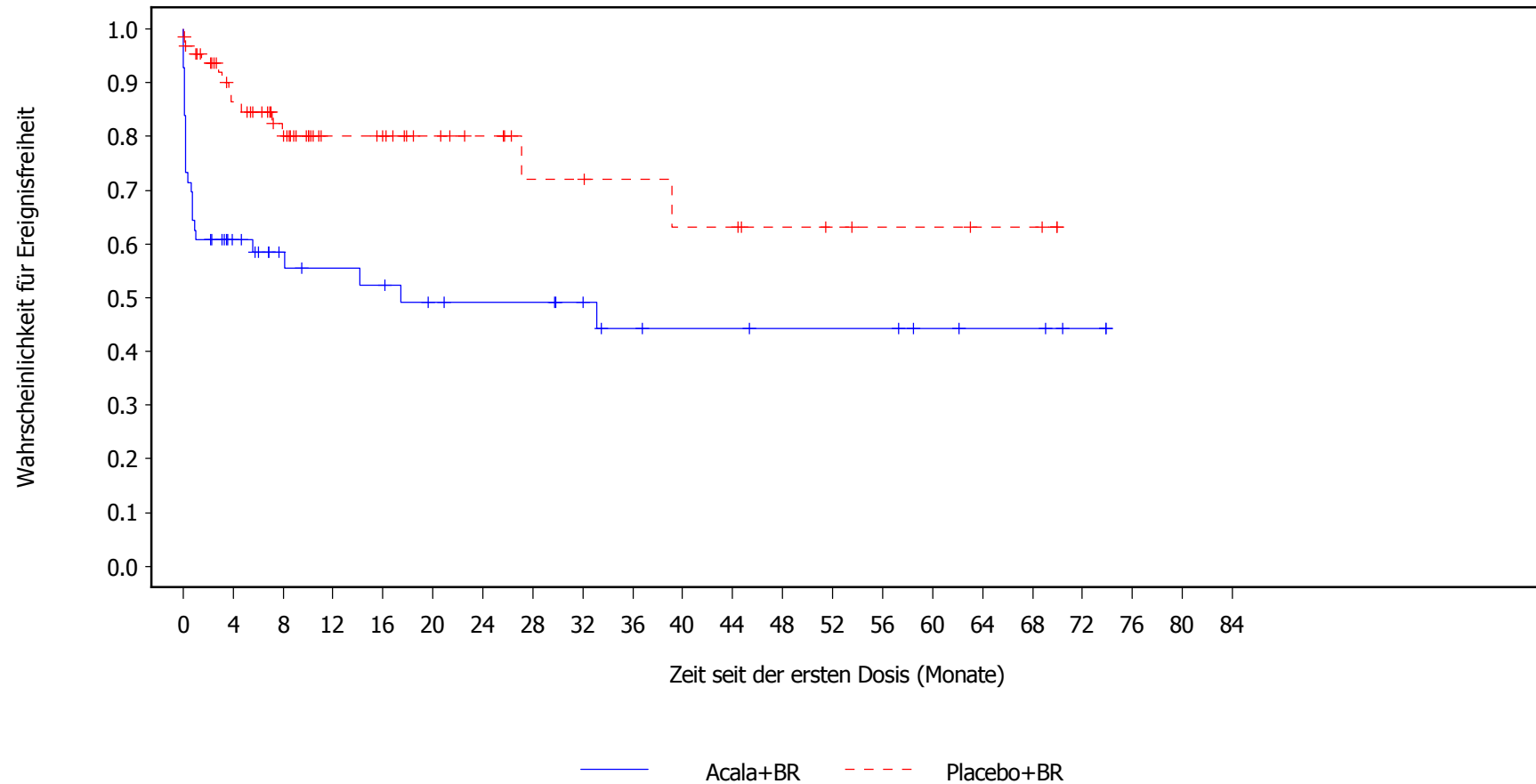
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.19 ECHO: Subgroup Analysis: Kaplan-Meier plot of SOC: Erkrankungen des Nervensystems for Ki-67 (%) II [eCRF]>= 50%
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

56	27	20	18	17	14	13	13	11	8	7	7	6	6	6	4	3	3	1	0	0	0	Acala+BR
65	47	36	23	22	16	13	9	9	8	7	7	5	4	3	3	2	2	0	0	0	0	Placebo+BR

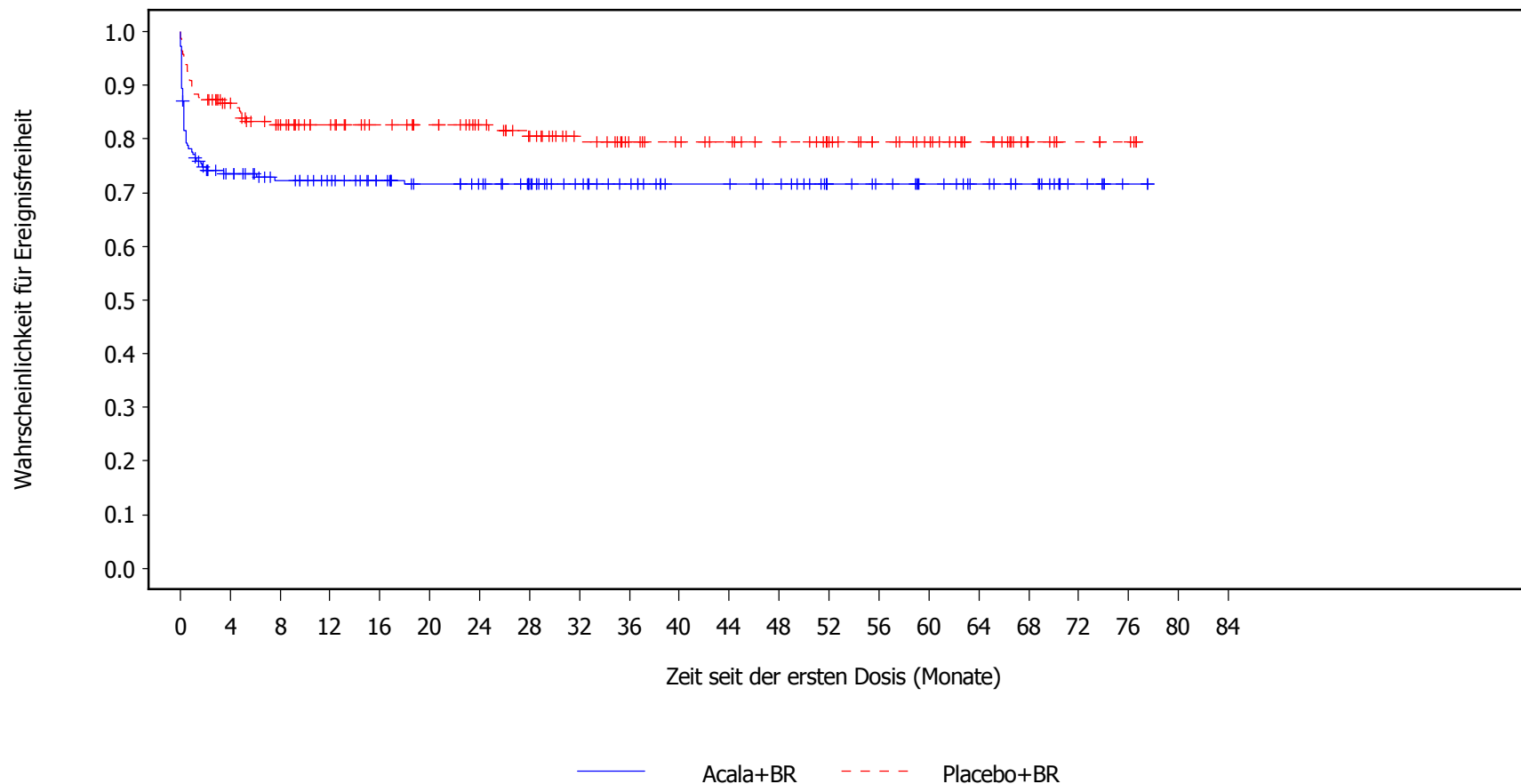
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.20 ECHO: Subgroup Analysis: Kaplan-Meier plot of PT: Kopfschmerzen for Ki-67 (%) II [eCRF]<= 50%
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

179	122	111	104	95	86	82	72	62	56	48	48	45	34	31	26	21	16	6	1	0	0	Acala+BR
164	133	118	107	99	94	86	78	68	59	55	52	48	40	33	28	19	9	5	3	0	0	Placebo+BR

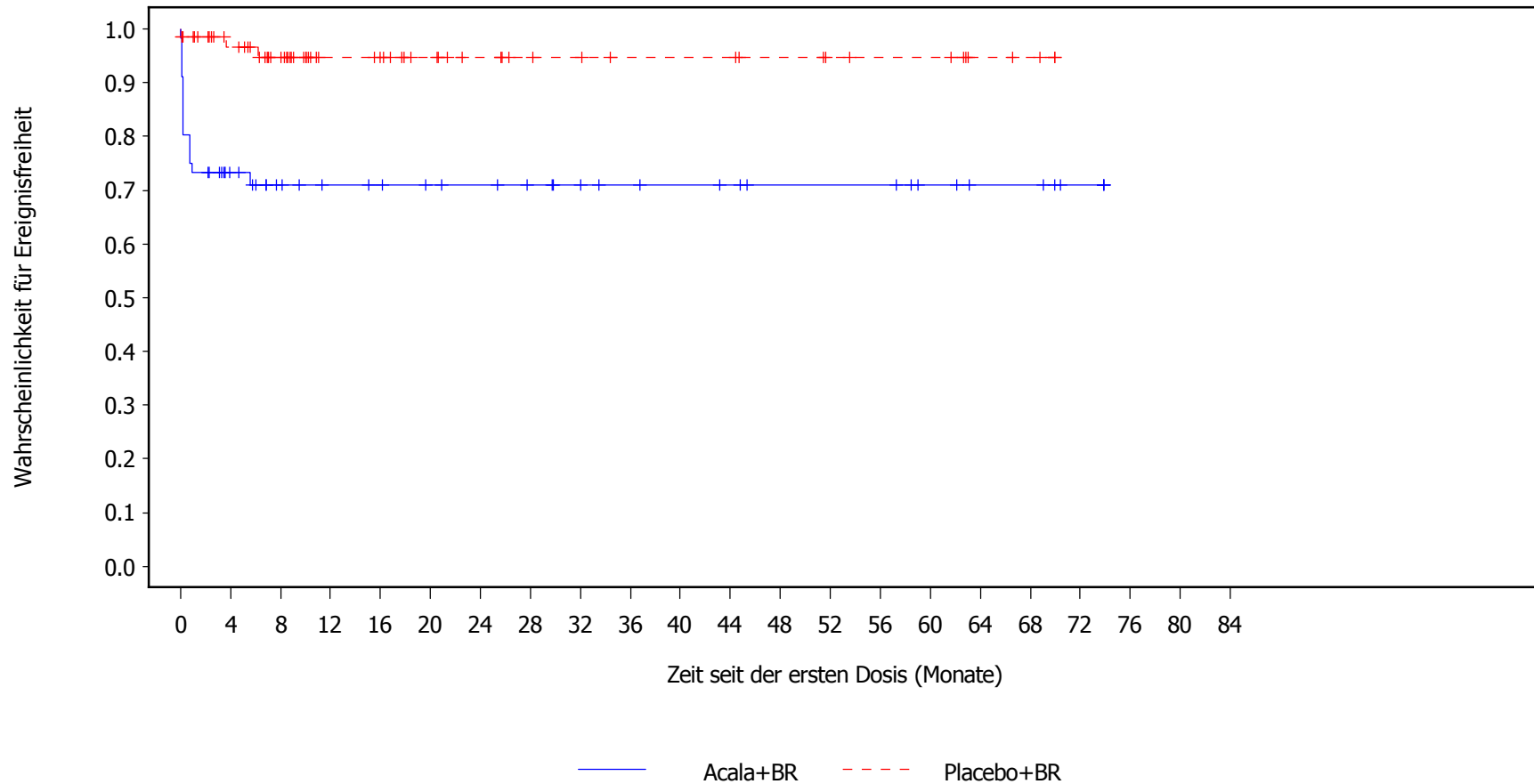
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.21 ECH0: Subgroup Analysis: Kaplan-Meier plot of PT: Kopfschmerzen for Ki-67 (%) II [eCRF]>= 50%
 Safety Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

56	34	27	24	23	21	20	18	16	14	13	12	10	10	10	7	5	5	2	0	0	0	Acala+BR
65	53	43	29	28	22	18	15	14	12	12	12	10	8	7	7	3	2	0	0	0	0	Placebo+BR

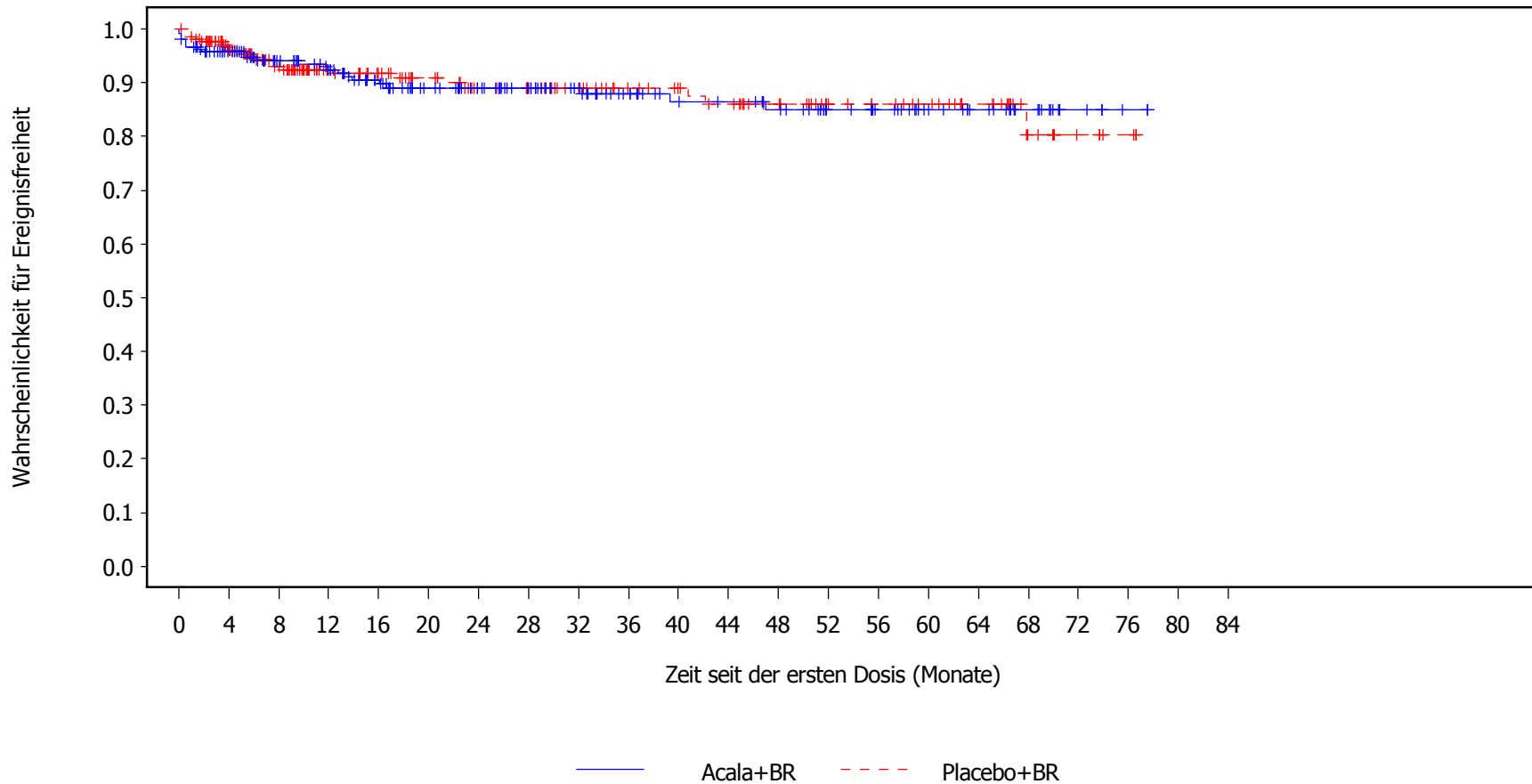
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.22 ECHO: Subgroup Analysis: Kaplan-Meier plot of PT: Rueckenschmerzen for Geschlecht [eCRF]=Männlich
 Safety Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

212	187	164	150	133	116	106	94	83	70	61	59	55	43	36	27	22	15	6	1	0	0	Acala+BR
208	178	154	127	115	103	91	85	74	65	61	57	50	40	36	32	24	12	5	2	0	0	Placebo+BR

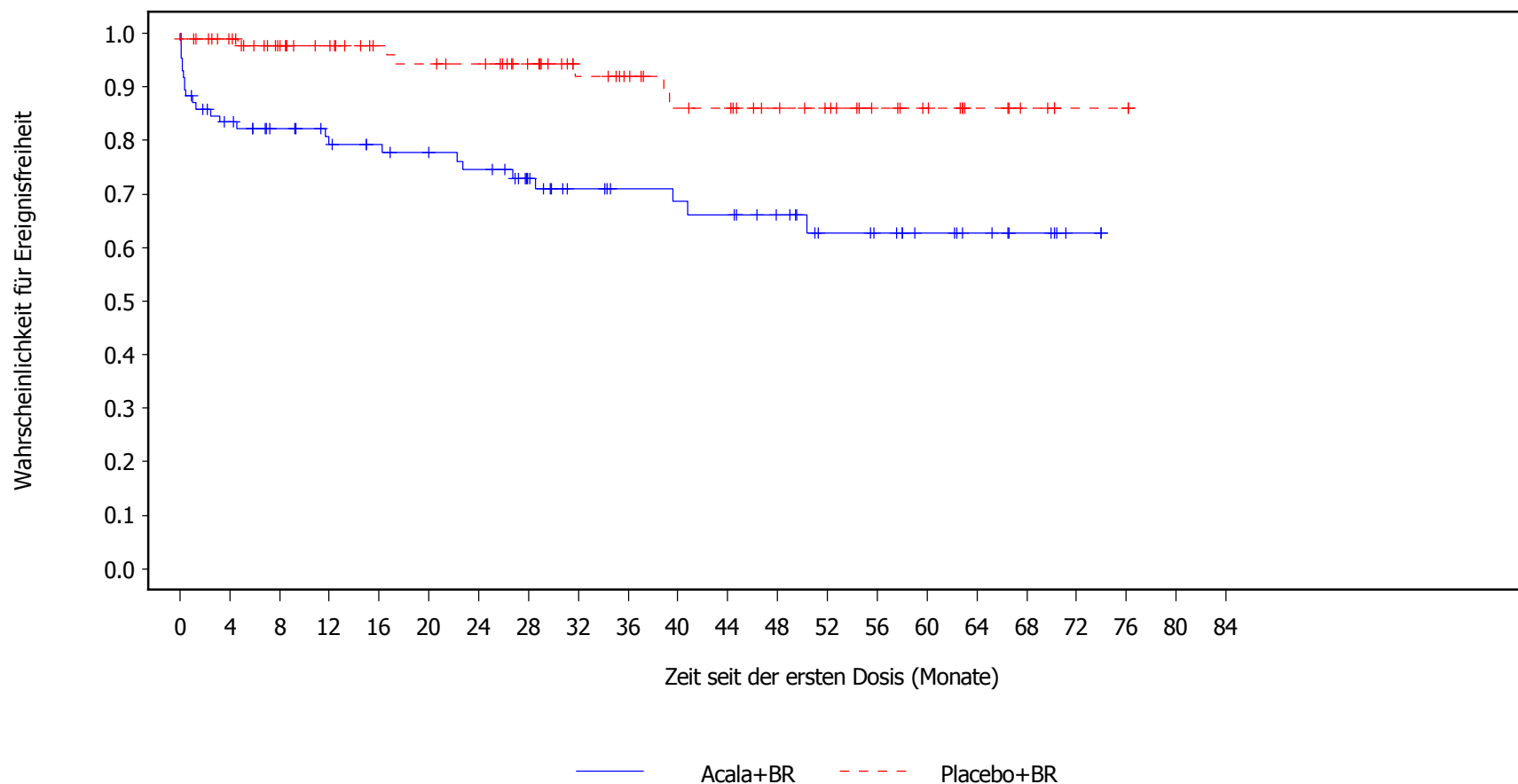
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.23 ECH0: Subgroup Analysis: Kaplan-Meier plot of PT: Rueckenschmerzen for Geschlecht [eCRF]=Weiblich
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

85	67	60	55	52	49	47	39	32	29	28	27	23	17	15	11	8	5	1	0	0	0	Acala+BR
89	81	71	65	58	56	54	47	38	34	29	28	23	20	15	12	7	4	1	1	0	0	Placebo+BR

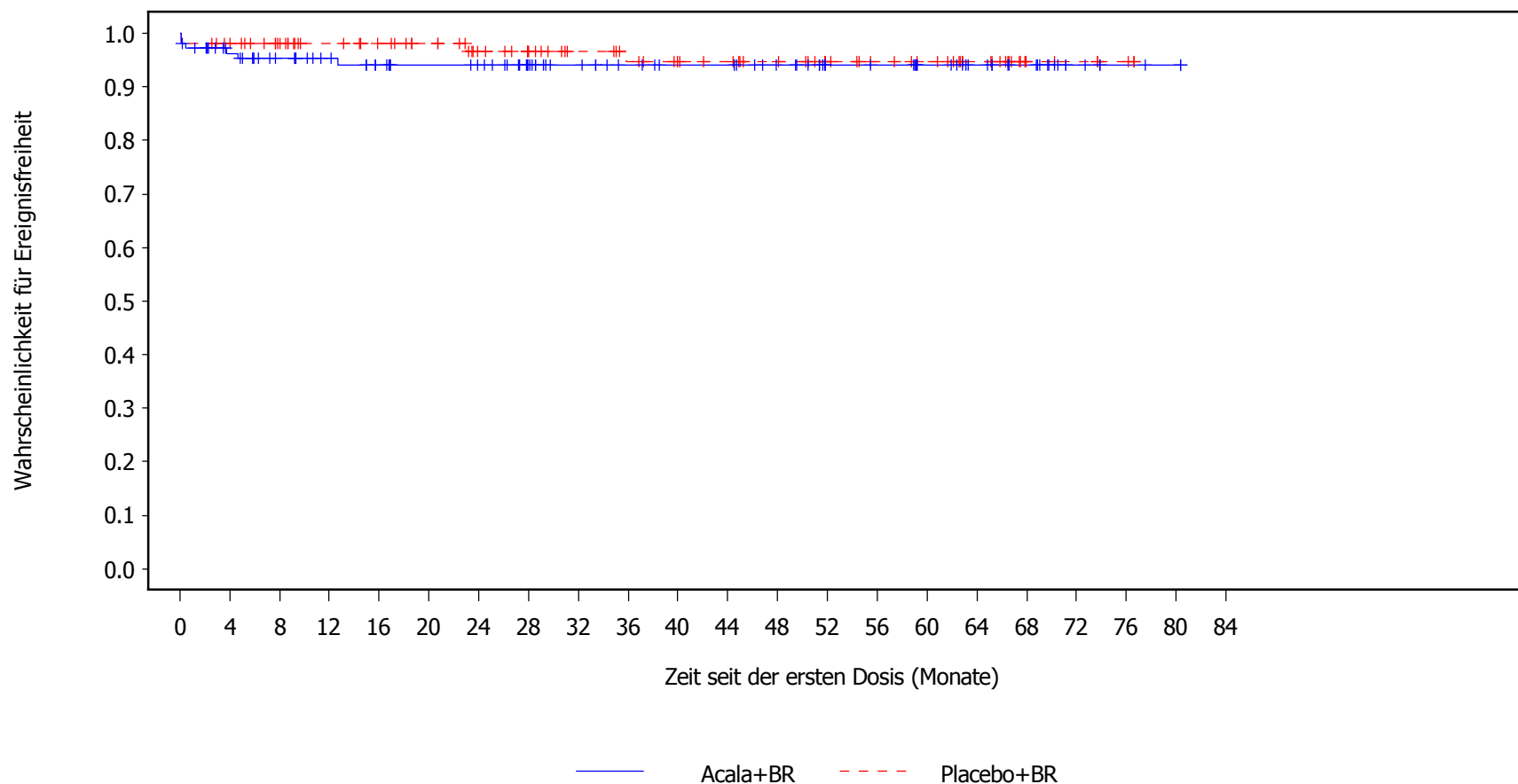
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.24 ECH0: Subgroup Analysis: Kaplan-Meier plot of PT: Gewicht erhoeht for Ki-67 (%) I [eCRF]<= 30%
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

109	97	88	82	76	71	69	59	52	47	44	44	39	30	29	24	19	14	5	2	1	0	Acala+BR
103	98	90	82	78	73	64	58	51	47	43	41	37	30	26	23	16	5	4	2	0	0	Placebo+BR

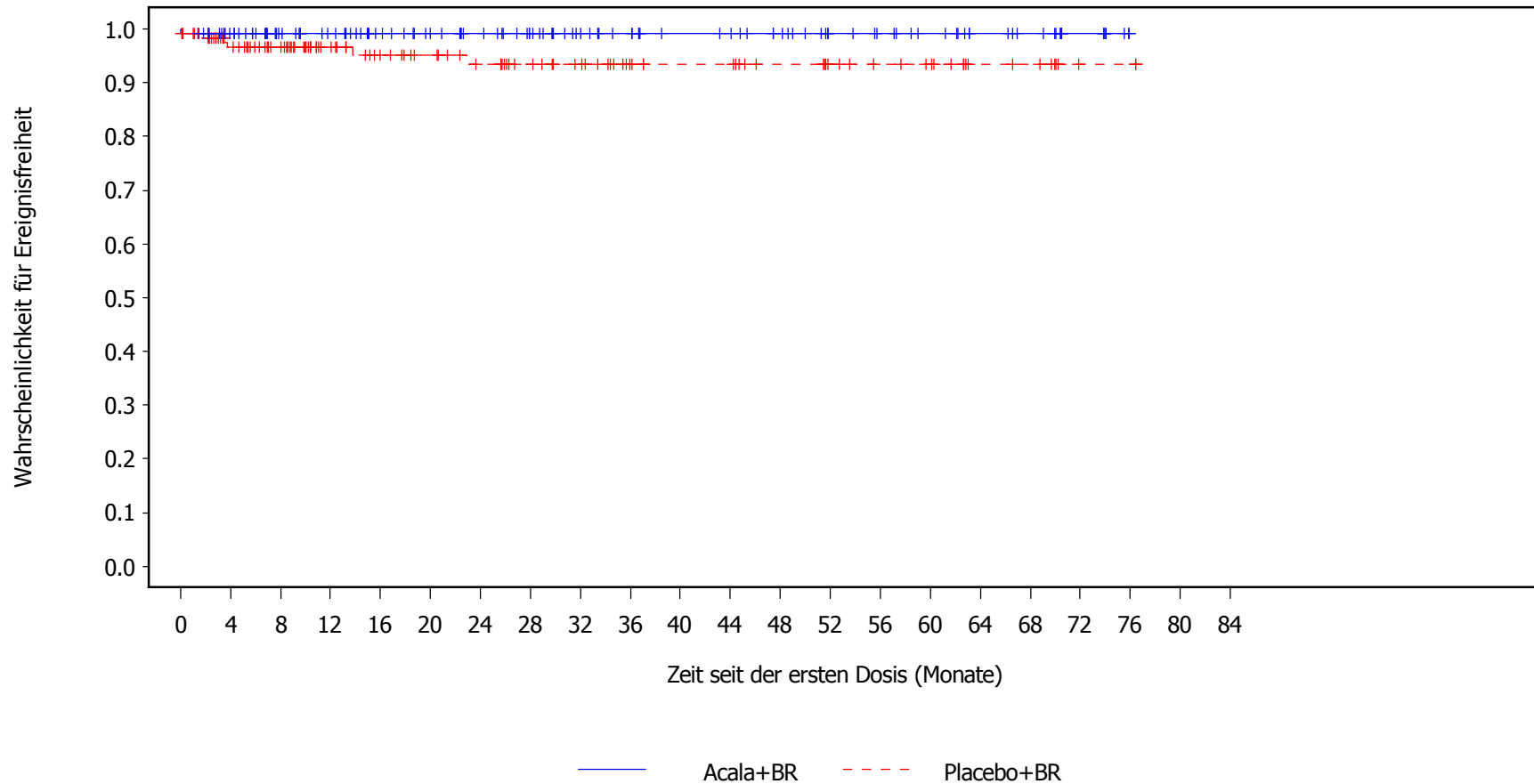
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.1.25 ECHO: Subgroup Analysis: Kaplan-Meier plot of PT: Gewicht erhoeht for Ki-67 (%) I [eCRF]>= 30%
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

126	115	101	94	83	76	71	63	54	49	43	42	37	29	26	22	16	13	6	0	0	0	Acala+BR
126	107	95	76	66	60	54	47	42	33	30	30	25	20	17	15	8	7	1	1	0	0	Placebo+BR

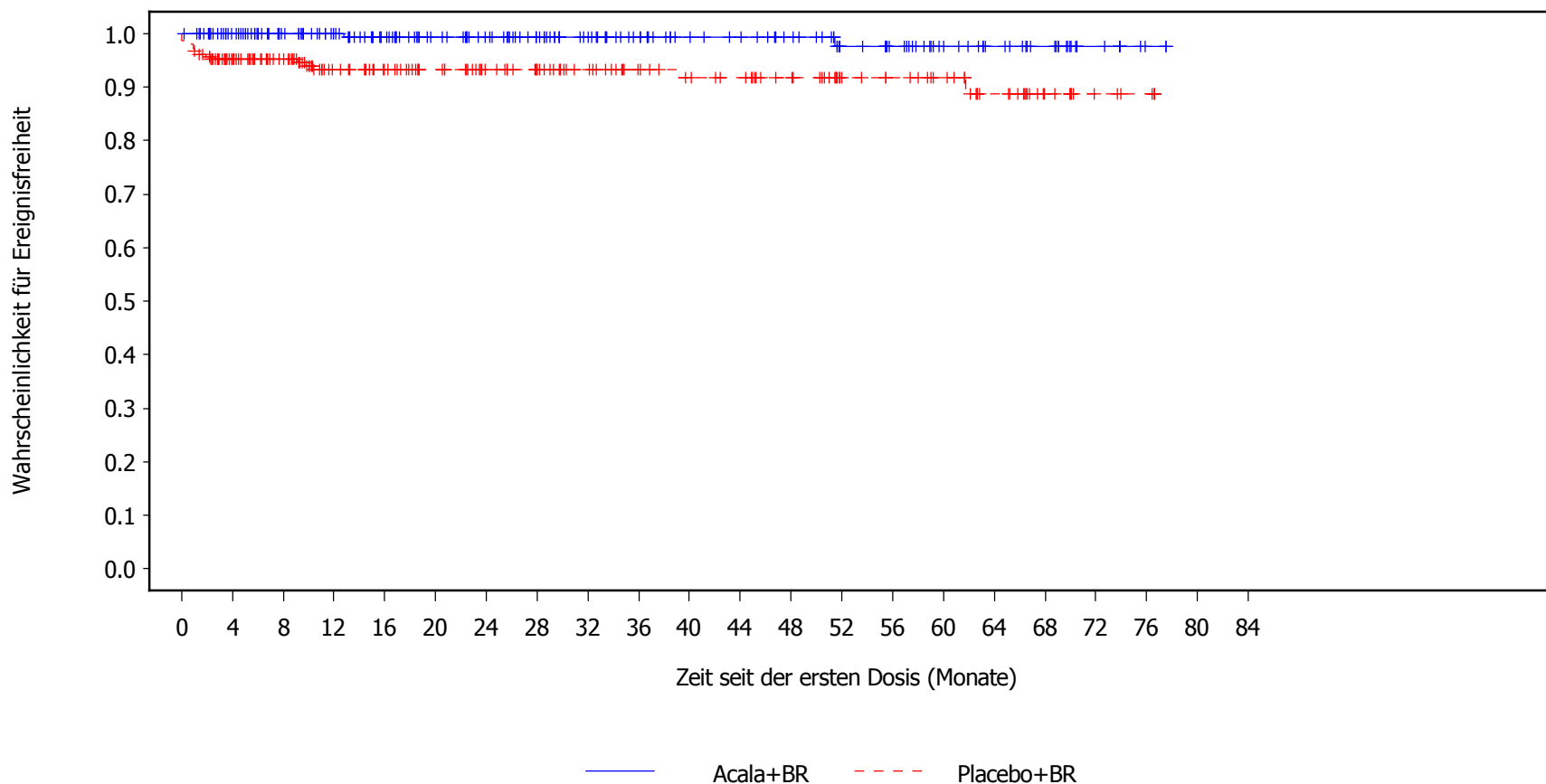
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.2.1 ECHO: Subgroup Analysis: Kaplan-Meier plot of SUE SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen for Geschlecht [eCRF]=Männlich
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

212	195	175	161	145	130	120	107	95	83	73	70	64	50	43	32	25	19	8	1	0	0	Acala+BR
208	178	159	133	123	111	99	91	80	70	65	62	55	43	39	34	23	12	5	3	0	0	Placebo+BR

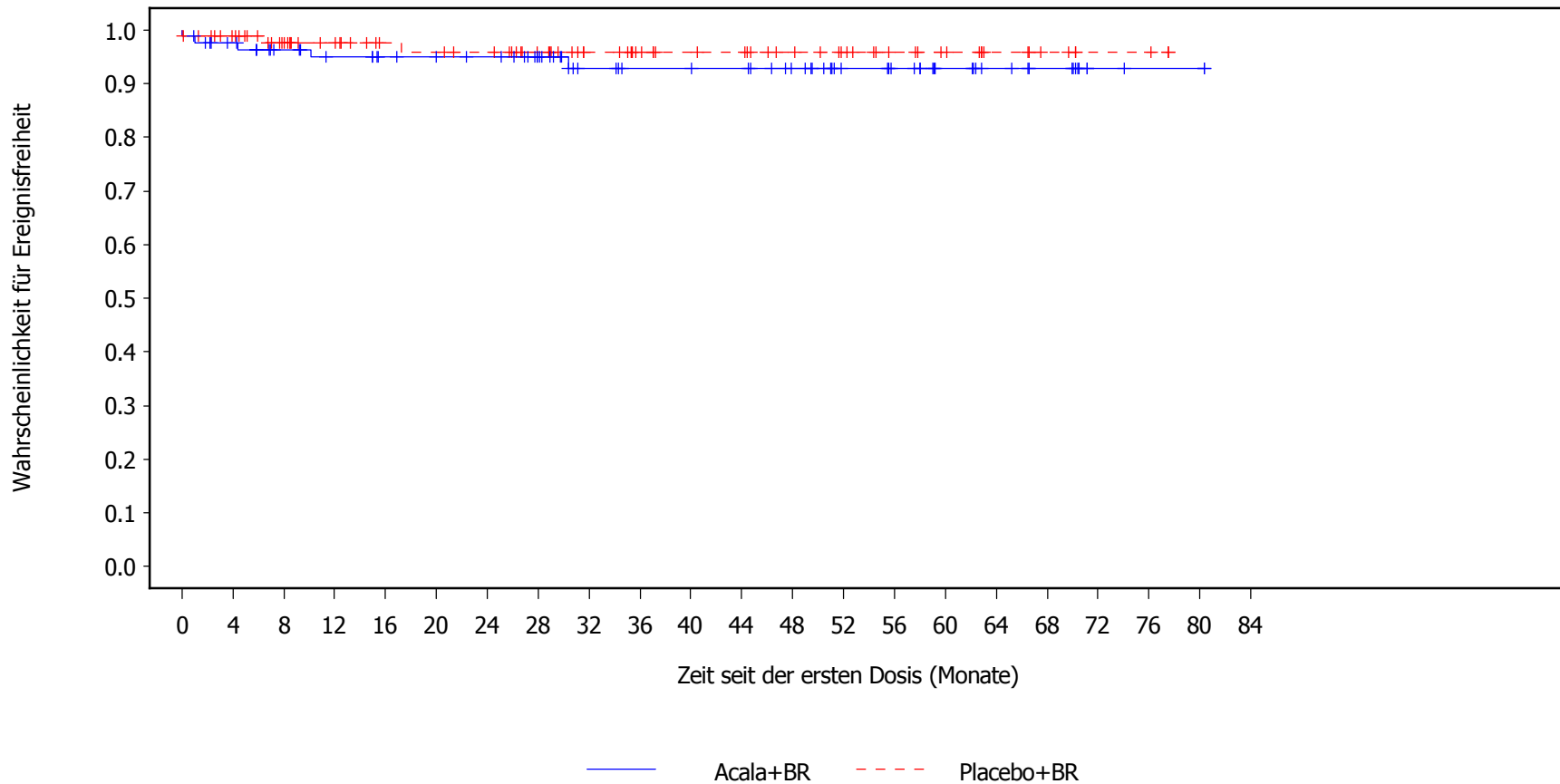
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.2.2 ECHO: Subgroup Analysis: Kaplan-Meier plot of SUE SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen for Geschlecht [eCRF]=Weiblich
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

85	78	70	66	62	60	59	52	42	39	39	38	33	25	22	16	12	9	2	1	1	0	Acala+BR
89	82	72	65	58	57	55	48	40	35	31	30	25	21	16	13	8	5	2	2	0	0	Placebo+BR

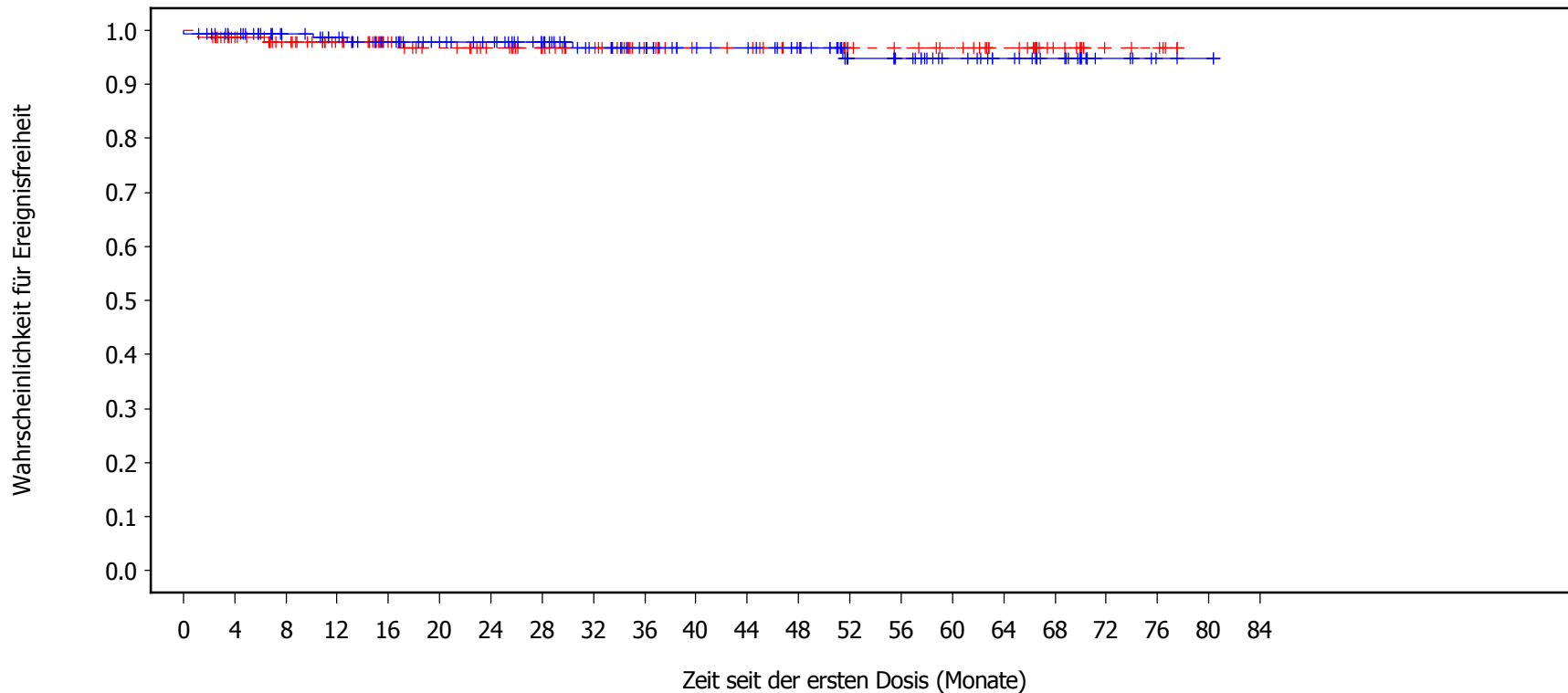
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.2.3 ECHO: Subgroup Analysis: Kaplan-Meier plot of SUE SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen for ECOG-PS [eCRF]=0
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

156	148	136	130	119	111	107	96	84	77	69	67	60	45	41	32	26	19	6	2	1	0	Acala+BR
140	129	117	105	95	87	81	74	66	55	50	49	44	36	34	31	24	13	5	4	0	0	Placebo+BR

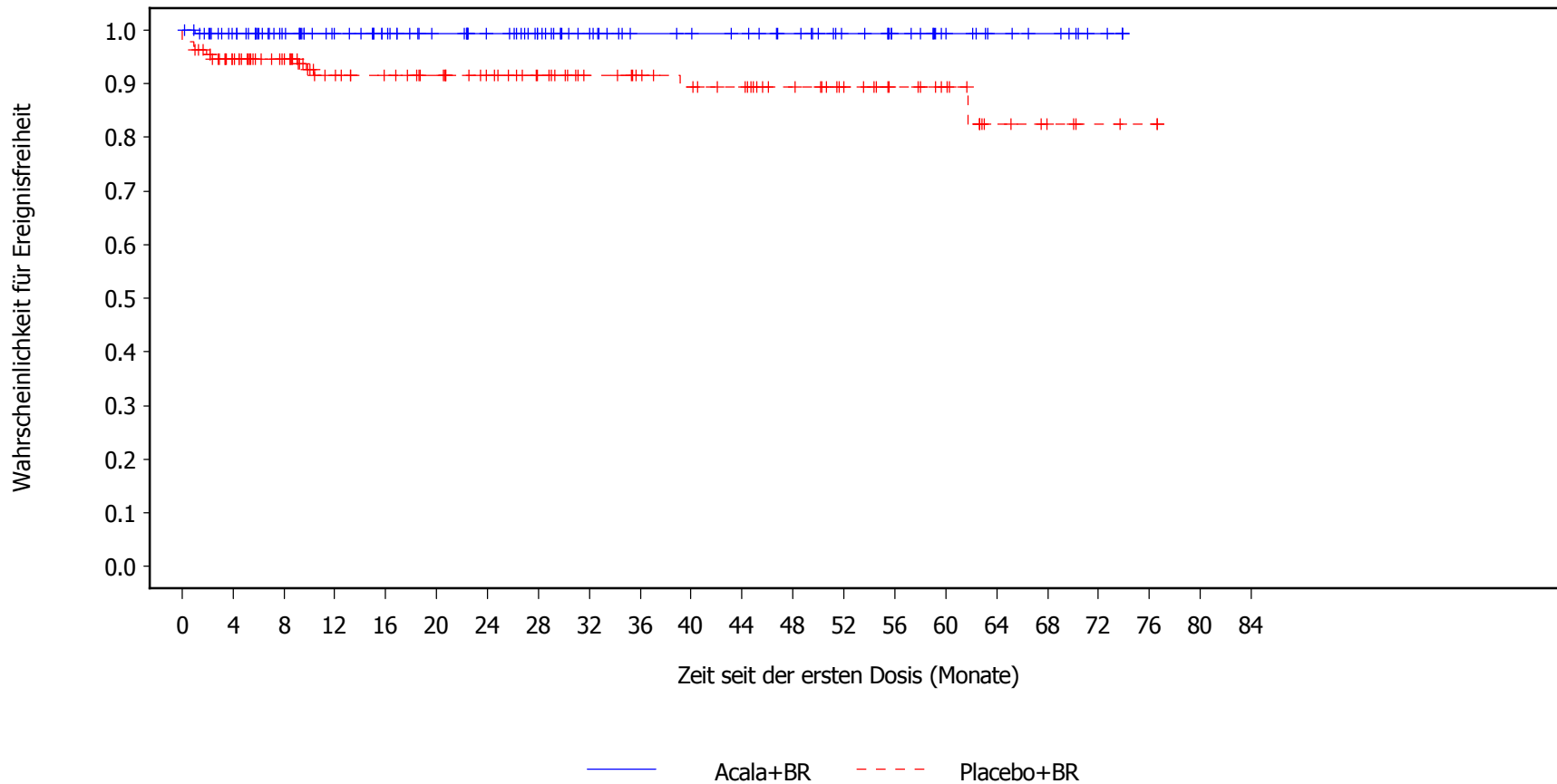
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.2.4 ECHO: Subgroup Analysis: Kaplan-Meier plot of SUE SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen for ECOG-PS [eCRF]=1
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

129	117	102	91	83	75	68	59	50	42	41	39	35	28	22	14	10	8	3	0	0	0	Acala+BR
132	112	98	81	76	71	64	57	49	45	42	39	32	26	20	16	7	4	2	1	0	0	Placebo+BR

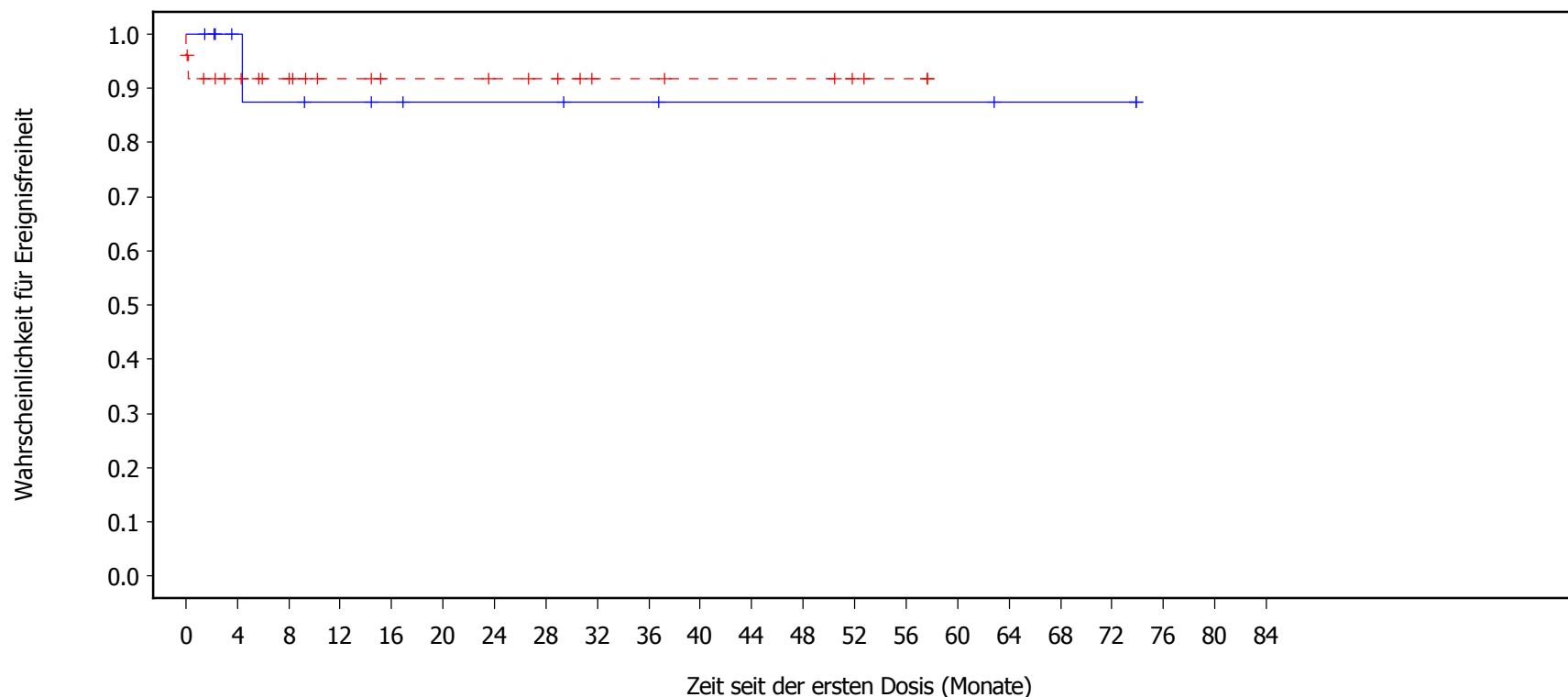
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.2.5 ECH0: Subgroup Analysis: Kaplan-Meier plot of SUE SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen for ECOG-PS [eCRF]>=2
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

12	8	7	6	5	4	4	4	3	3	2	2	2	2	2	1	1	1	0	0	0	Acala+BR
25	19	16	12	10	10	9	8	5	5	4	4	4	2	1	0	0	0	0	0	0	Placebo+BR

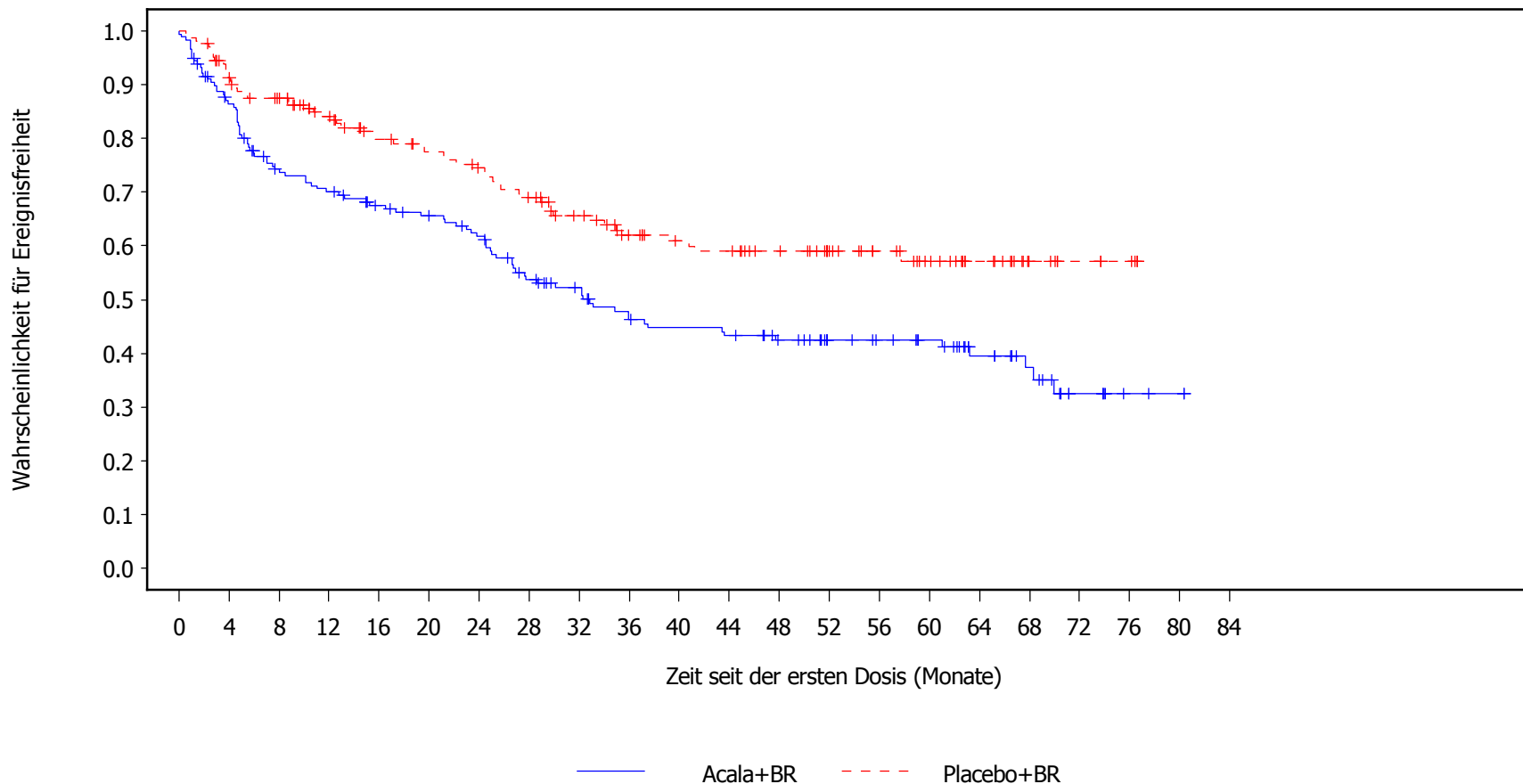
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.3.1 ECHO: Subgroup Analysis: Kaplan-Meier plot of Therapieabbruch aufgrund von UE for Ki-67 (%) II [eCRF]<= 50%
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

179	150	124	117	107	101	94	79	71	61	58	56	50	41	38	34	24	17	7	2	1	0	Acala+BR
164	146	135	120	107	101	95	87	76	65	59	57	51	42	35	28	19	9	5	3	0	0	Placebo+BR

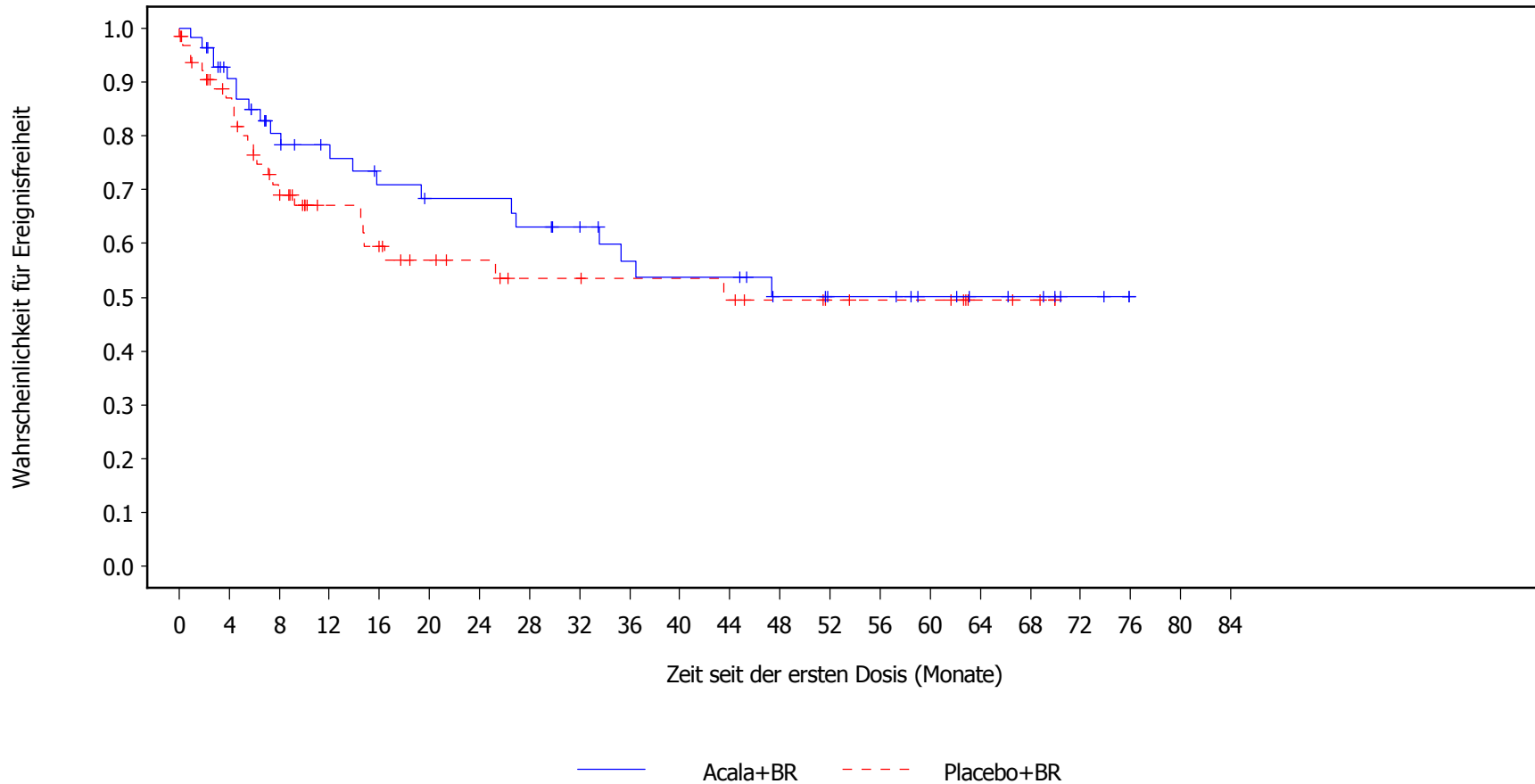
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.3.2 ECHO: Subgroup Analysis: Kaplan-Meier plot of Therapieabbruch aufgrund von UE for Ki-67 (%) II [eCRF]>= 50%
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

56	46	36	32	28	26	26	24	22	18	17	17	13	11	11	8	6	5	2	0	0	0	Acala+BR
65	50	37	27	24	19	17	14	14	13	13	12	10	8	7	7	3	2	0	0	0	0	Placebo+BR

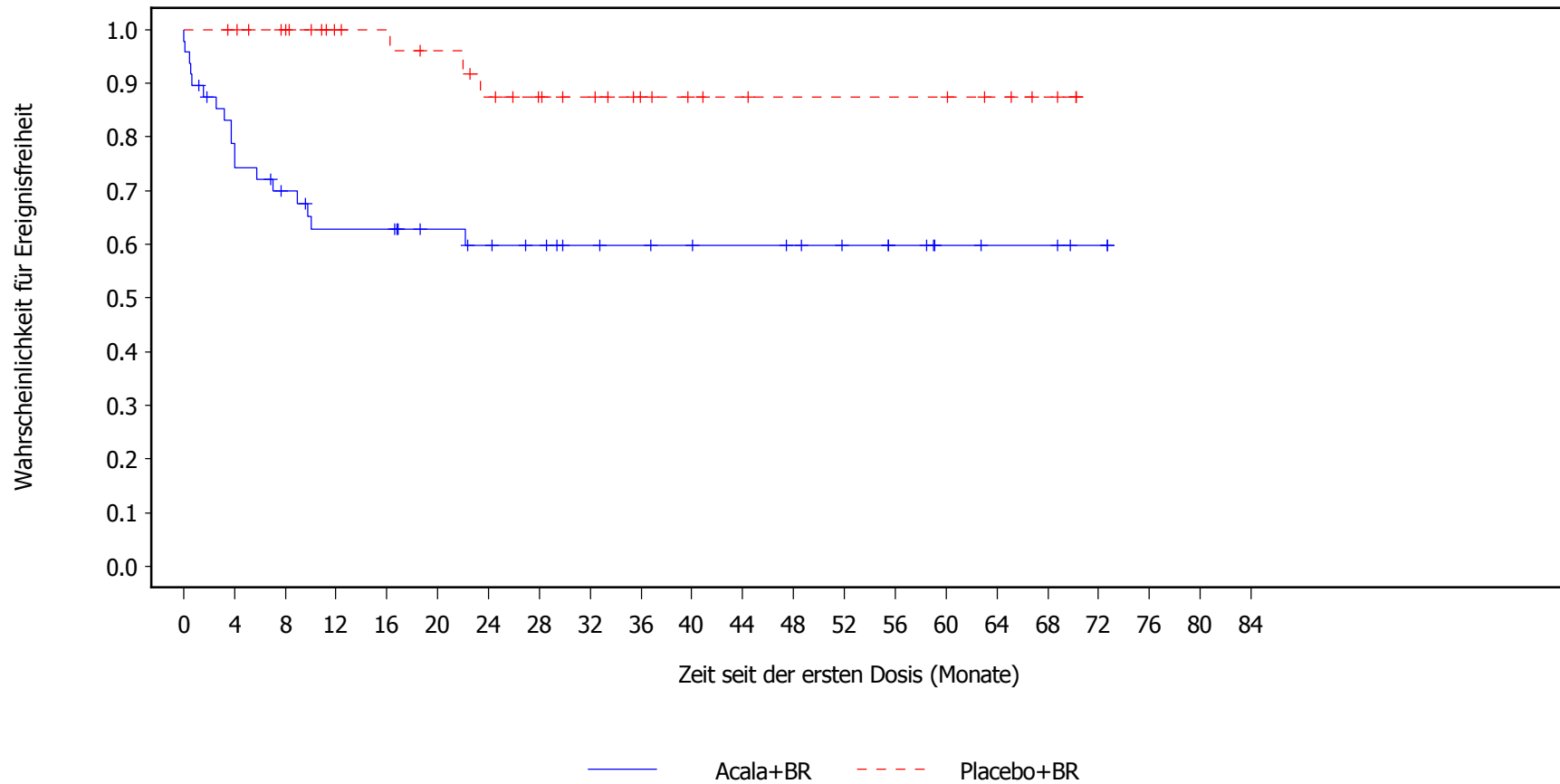
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.5.1 ECHO: Subgroup Analysis: Kaplan-Meier plot of EKI GT: Blutung for Ann Arbor-Stadium für Lymphome [eCRF]=Stadium I-III
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

48	36	30	26	26	22	20	18	15	14	13	12	11	9	7	4	3	3	1	0	0	0	Acala+BR
36	35	32	26	25	23	20	17	15	11	9	8	7	7	7	7	5	3	0	0	0	0	Placebo+BR

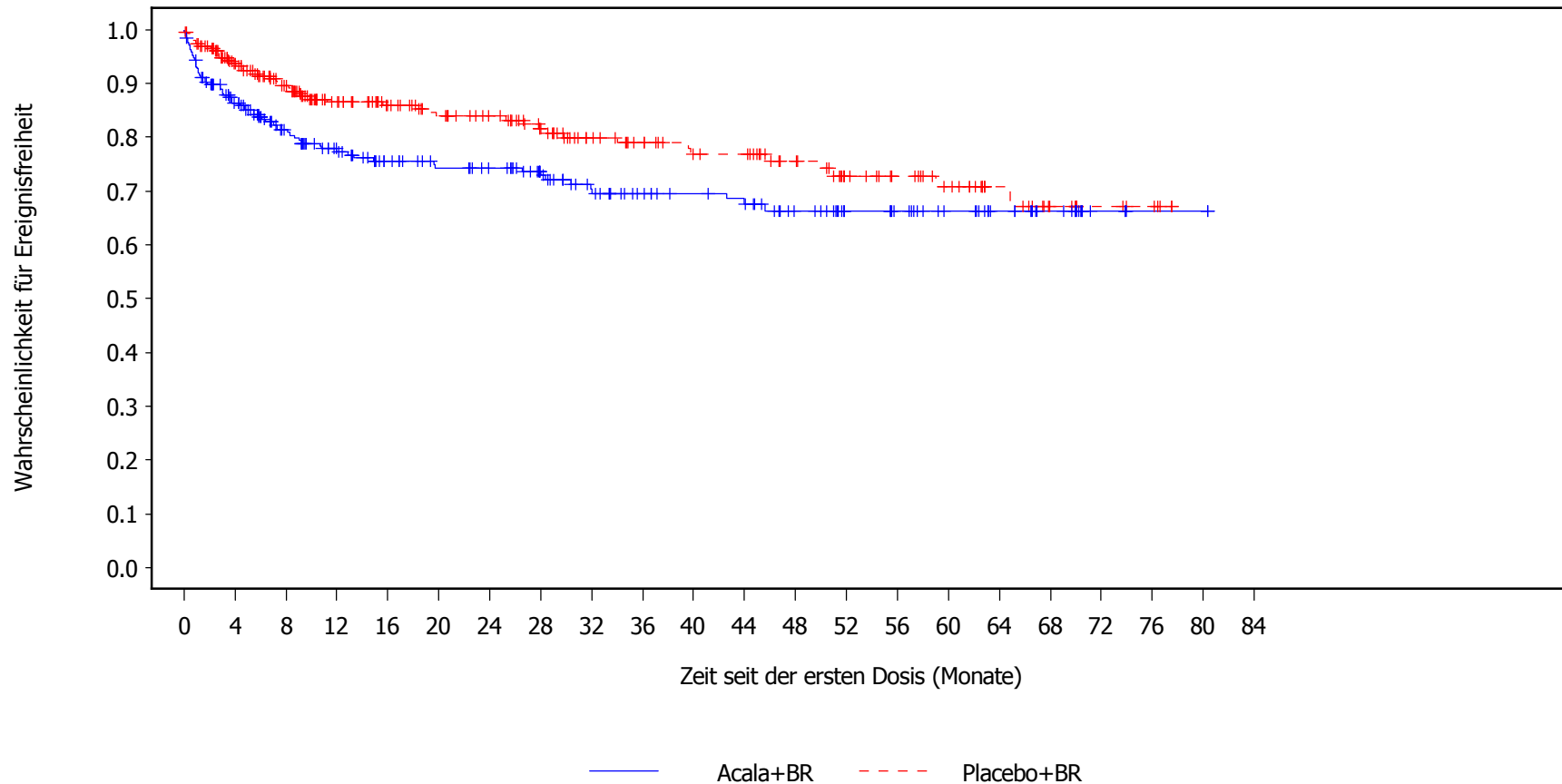
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.5.2 ECHO: Subgroup Analysis: Kaplan-Meier plot of EKI GT: Blutung for Ann Arbor-Stadium für Lymphome [eCRF]=Stadium
 IV
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Anzahl an Patienten unter Risiko:

249	198	164	143	126	117	112	97	83	72	67	64	54	43	38	31	23	16	4	1	1	0	Acala+BR
261	219	188	155	139	126	117	102	86	78	70	69	58	45	39	32	20	12	6	4	0	0	Placebo+BR

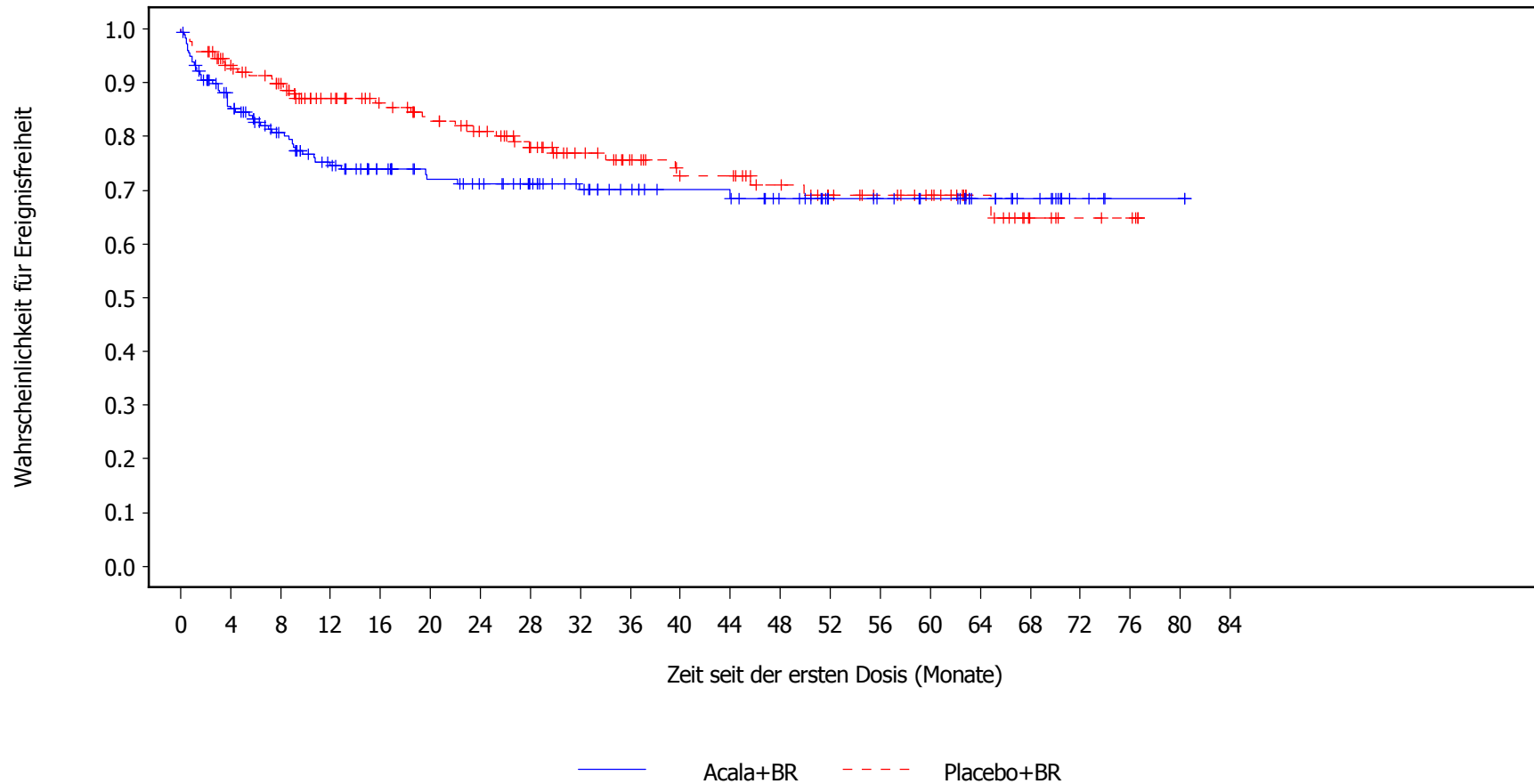
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.5.3 ECHO: Subgroup Analysis: Kaplan-Meier plot of EKI GT: Blutung for Ki-67 (%) II [eCRF]<= 50%
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Anzahl an Patienten unter Risiko:

179	143	122	105	92	83	78	68	59	51	46	45	39	30	28	25	18	13	4	1	1	0	Acala+BR
164	145	132	114	103	94	86	74	63	55	47	47	40	33	29	25	16	7	4	3	0	0	Placebo+BR

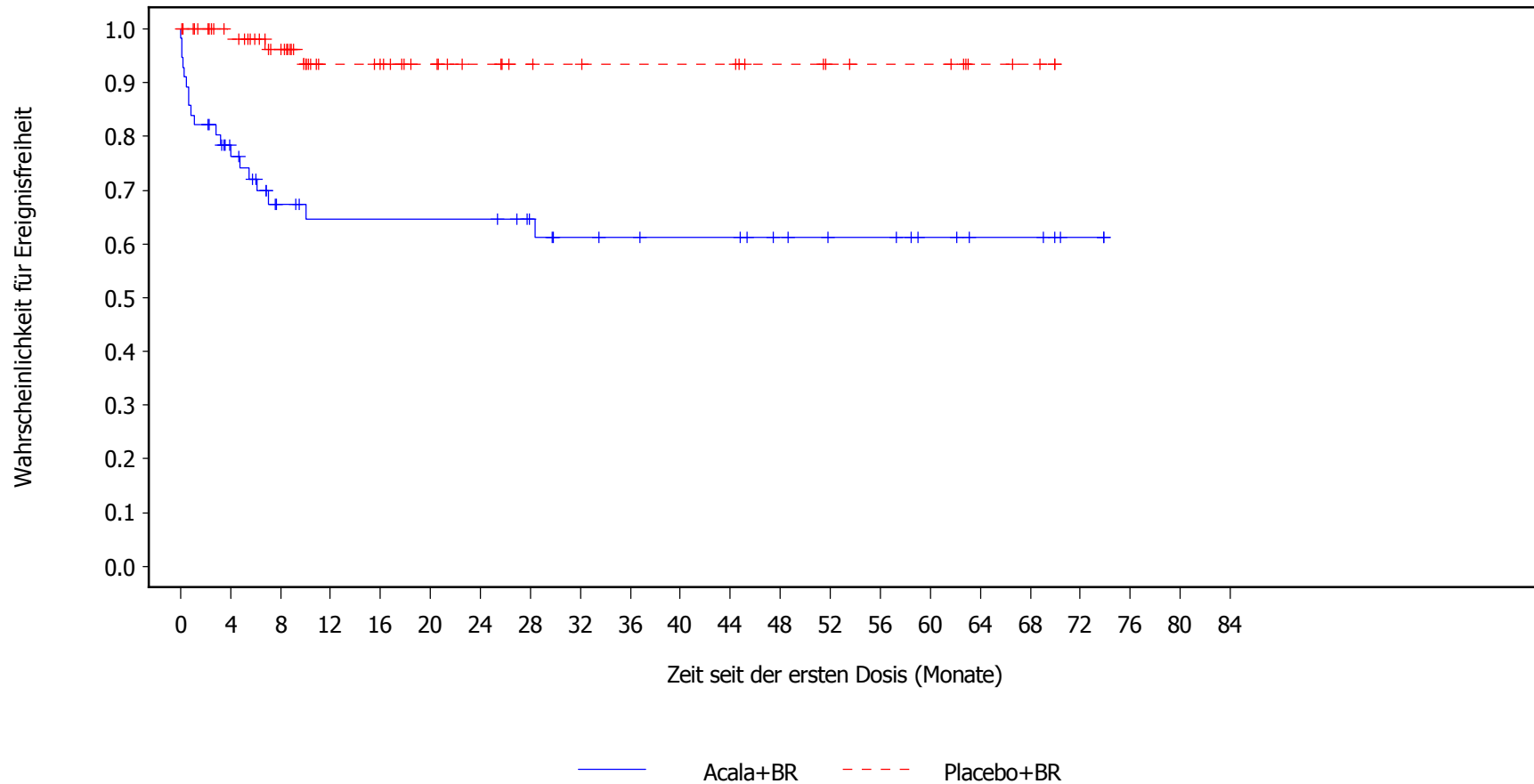
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.5.4 ECHO: Subgroup Analysis: Kaplan-Meier plot of EKI GT: Blutung for Ki-67 (%) II [eCRF]>= 50%
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Anzahl an Patienten unter Risiko:

56	38	26	23	23	23	23	19	16	15	14	14	11	9	9	6	4	4	1	0	0	0	Acala+BR
65	54	44	29	28	22	18	15	14	13	13	13	10	8	7	7	3	2	0	0	0	0	Placebo+BR

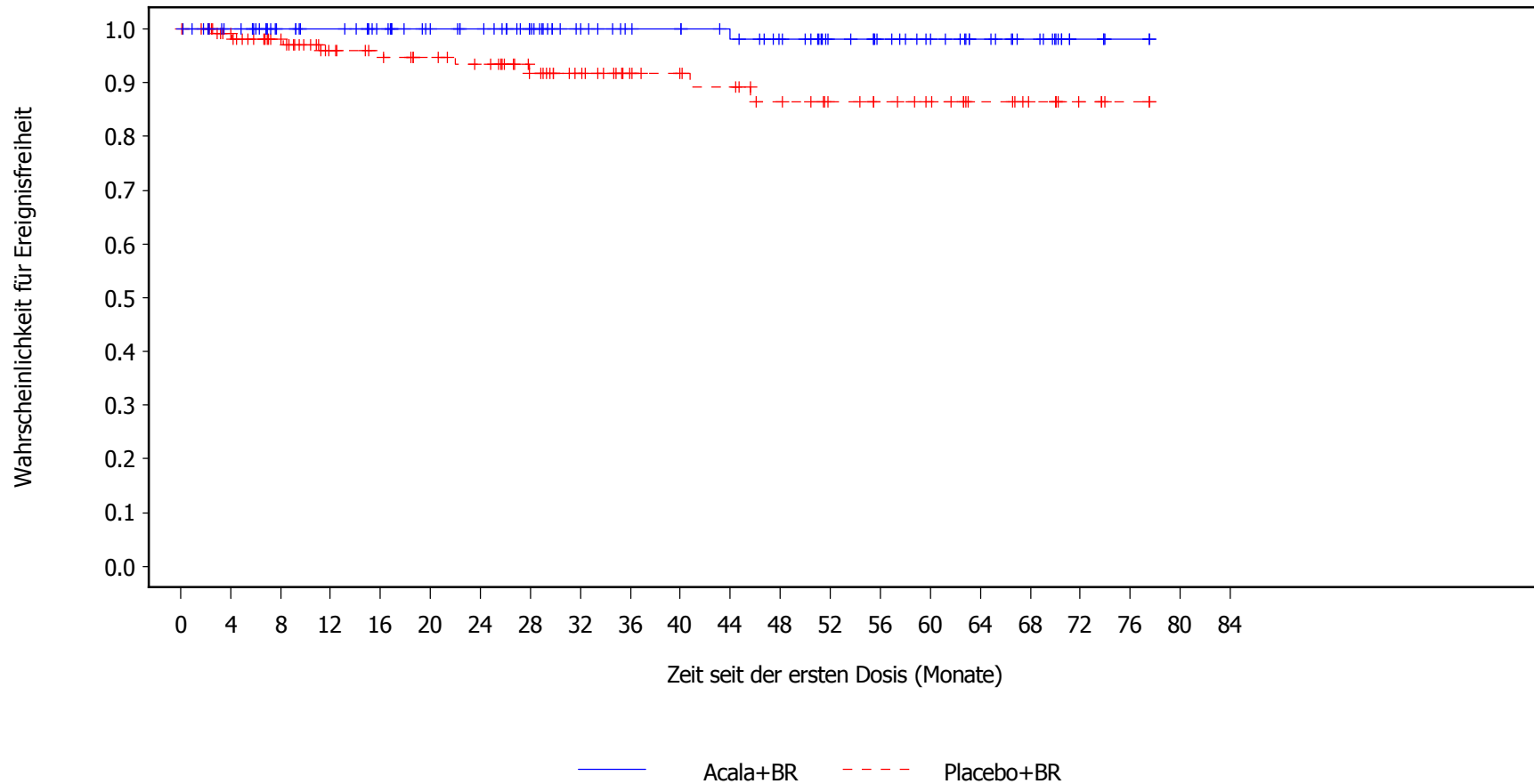
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.5.5 ECHO: Subgroup Analysis: Kaplan-Meier plot of EKI GT: Schwere Blutung for Altersgruppe I [eCRF]<= 70 Jahre
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

122	115	103	99	92	83	80	71	61	55	54	50	45	36	31	25	19	14	4	1	0	0	Acala+BR
117	107	95	80	76	71	67	57	49	40	37	35	30	25	22	19	13	9	4	1	0	0	Placebo+BR

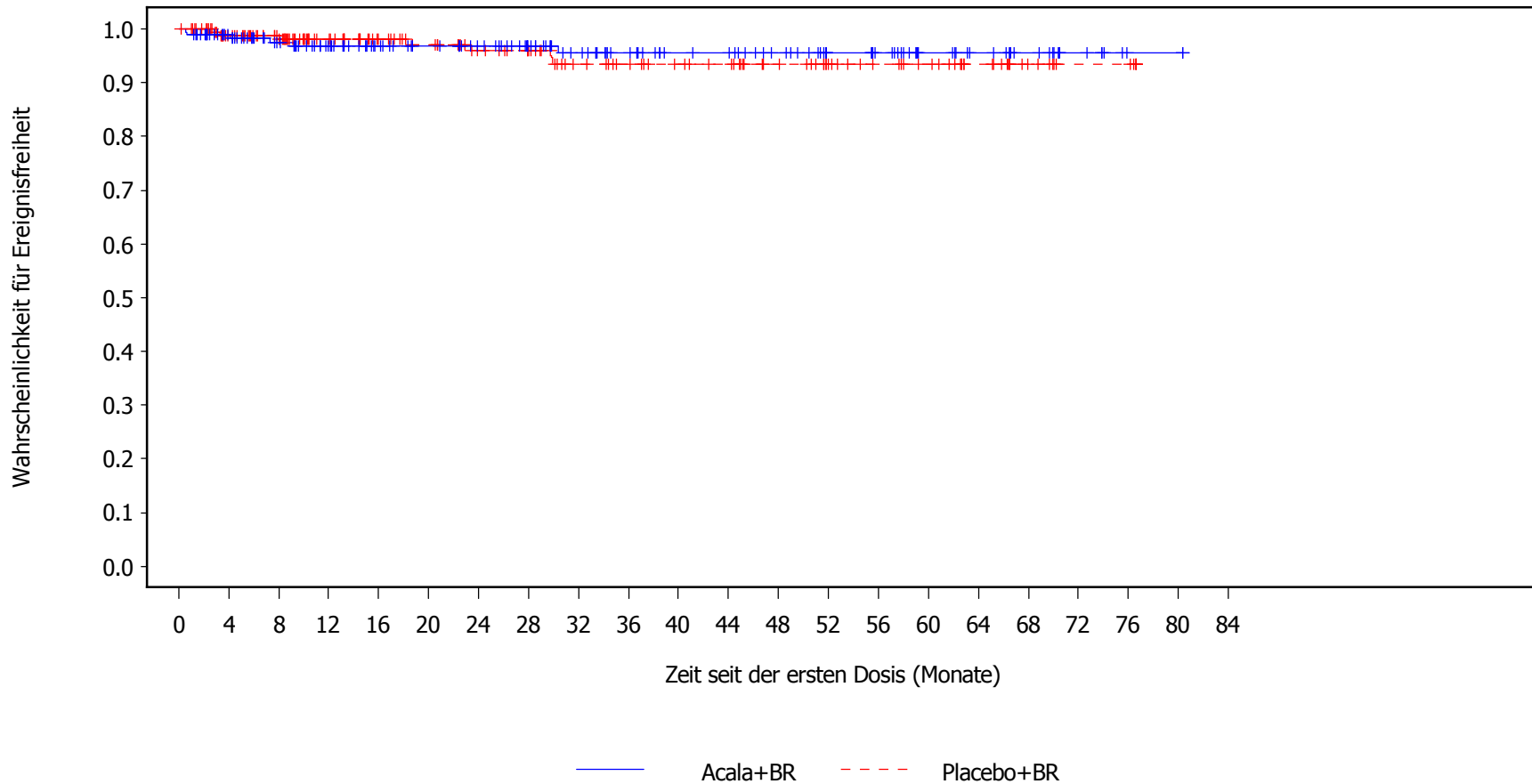
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.5.6 ECH0: Subgroup Analysis: Kaplan-Meier plot of EKI GT: Schwere Blutung for Altersgruppe I [eCRF]>= 70 Jahre
 Safety Analysis Set, DCO 15FEB2024



Anzahl an Patienten unter Risiko:

175	158	141	127	114	107	100	88	77	68	59	58	51	40	35	25	20	14	7	1	1	0	Acala+BR
180	159	141	119	104	95	85	79	66	61	56	53	45	37	31	27	18	9	4	4	0	0	Placebo+BR

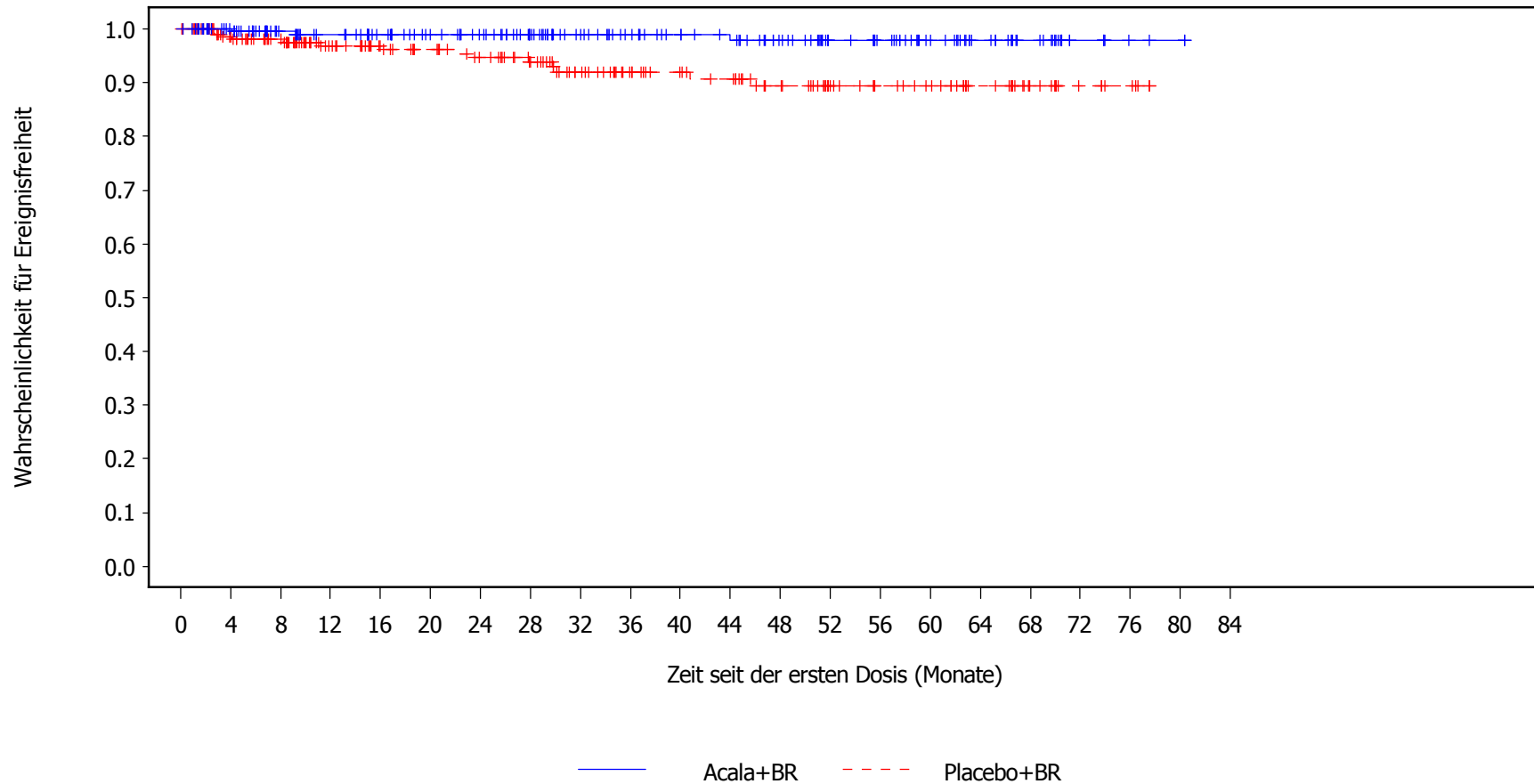
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.5.7 ECH0: Subgroup Analysis: Kaplan-Meier plot of EKI GT: Schwere Blutung for Altersgruppe II [eCRF]<= 75 Jahre
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Anzahl an Patienten unter Risiko:

214	199	178	169	157	145	138	123	108	98	90	85	75	60	53	40	30	21	7	2	1	0	Acala+BR
221	197	180	153	140	131	122	111	94	82	75	71	60	48	41	37	25	15	7	4	0	0	Placebo+BR

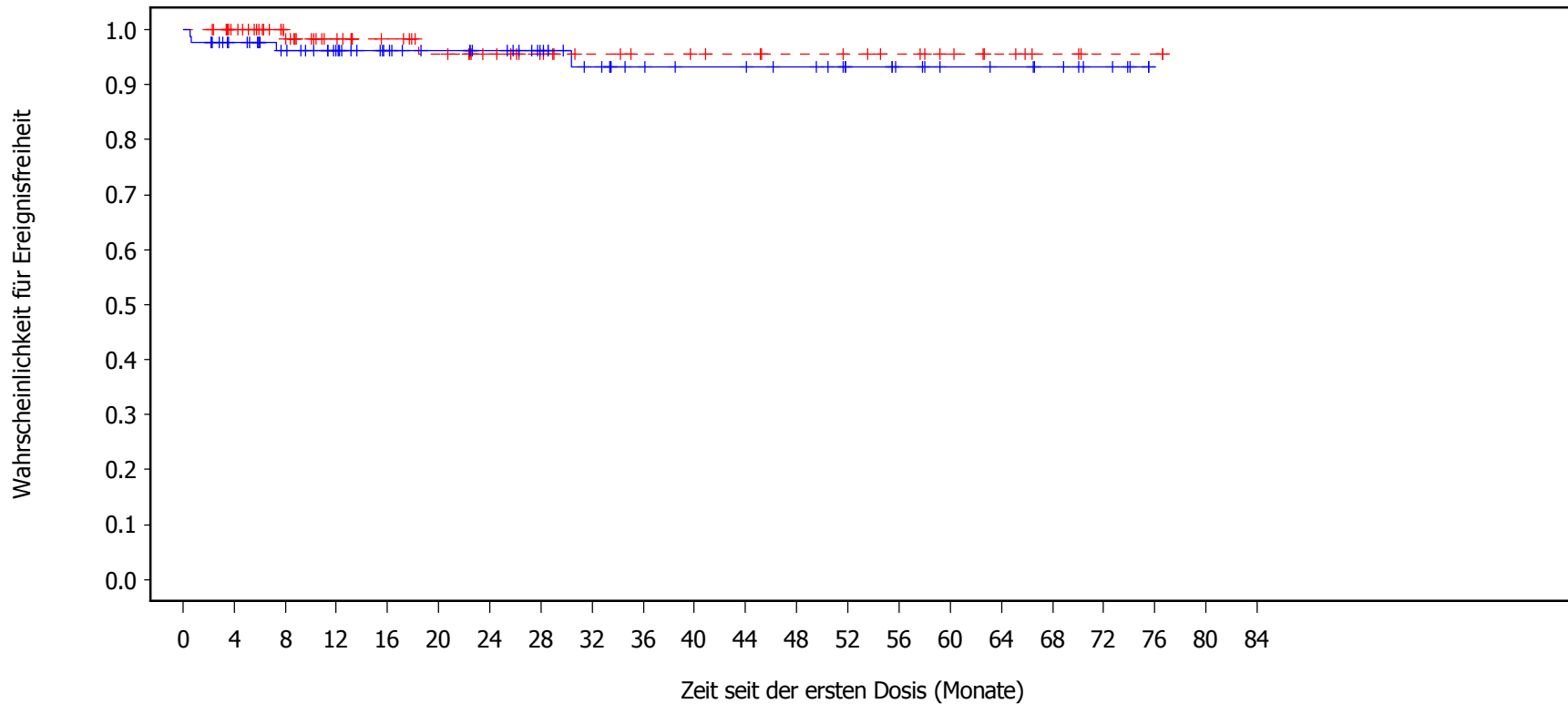
Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.

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Figure 4.3.2.5.8 ECHO: Subgroup Analysis: Kaplan-Meier plot of EKI GT: Schwere Blutung for Altersgruppe II [eCRF]>= 75 Jahre
 Safety Analysis Set, DC0 15FEB2024



Anzahl an Patienten unter Risiko:

83	74	66	57	49	45	42	36	30	25	23	23	21	16	13	10	9	7	4	0	0	0	Acala+BR
76	69	56	46	40	35	30	25	21	19	18	17	15	14	12	9	6	3	1	1	0	0	Placebo+BR

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

Acala = Acalabrutinib; BR = Bendamustine and Rituximab.