

Anhang 4-G: Ergänzende Analysen zur Studie ARANOTE

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Anhang 4-G1: Zusätzliche Analysen zum Datenschnitt 07. Juni 2024

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 1.1
Observation time per endpoint in months
(full analysis set)

Final

		Darolutamide (N=446)	Placebo (N=223)	Total (N=669)
Time to Death [1]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	23.71 (7.79)	22.91 (8.39)	23.44 (8.00)
	Median	25.31	24.97	25.16
	Q1, Q3	20.76, 29.34	18.86, 29.50	19.51, 29.34
	Min, Max	0.03, 38.76	0.23, 37.02	0.03, 38.76
Time to symptomatic skeletal event [2]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	20.86 (8.70)	19.11 (8.57)	20.28 (8.69)
	Median	22.95	21.16	22.50
	Q1, Q3	14.45, 27.56	12.65, 25.76	14.13, 27.33
	Min, Max	0.03, 38.63	0.03, 35.05	0.03, 38.63
Worst Pain subscale score (BPI-SF Item 3)	n (missing)	445 (1)	223 (0)	668 (1)
	Mean (SD)	20.42 (8.72)	17.77 (8.92)	19.53 (8.87)
	Median	22.54	19.12	22.06
	Q1, Q3	13.70, 27.37	9.99, 25.00	12.02, 26.35
	Min, Max	0.03, 38.44	0.03, 34.86	0.03, 38.44
Pain interference score (BPI-SF Item 9 a-g)	n (missing)	444 (2)	223 (0)	667 (2)
	Mean (SD)	20.46 (8.67)	17.76 (8.94)	19.56 (8.85)
	Median	22.55	19.12	22.08
	Q1, Q3	13.72, 27.37	9.99, 25.00	12.02, 26.35
	Min, Max	0.03, 38.44	0.03, 34.86	0.03, 38.44
FACT-P total score	n (missing)	440 (6)	222 (1)	662 (7)
	Mean (SD)	20.87 (8.56)	18.13 (8.85)	19.95 (8.75)
	Median	22.80	19.32	22.34
	Q1, Q3	14.24, 27.56	11.17, 25.26	12.75, 26.81
	Min, Max	0.03, 38.63	0.03, 35.05	0.03, 38.63
Worst Pain subscale score (BPI-SF Item 3) - Time to (first) improvement of at least 2 points [2]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	15.60 (10.59)	14.41 (9.73)	15.20 (10.32)
	Median	15.98	13.90	14.42
	Q1, Q3	5.35, 24.87	5.45, 24.15	5.35, 24.70
	Min, Max	0.03, 38.44	0.03, 34.86	0.03, 38.44
Worst Pain subscale score (BPI-SF Item 3) - Time to (sustained) improvement of at least 2 points [2]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	16.48 (10.39)	15.29 (9.47)	16.08 (10.10)
	Median	19.10	14.75	16.52
	Q1, Q3	5.72, 25.13	6.24, 24.31	5.85, 24.80
	Min, Max	0.03, 38.44	0.03, 34.86	0.03, 38.44
Worst Pain subscale score (BPI-SF Item 3) - Time to (first) deterioration of at least 2 points [2]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	15.83 (10.00)	13.47 (9.54)	15.05 (9.90)
	Median	16.48	11.04	14.06
	Q1, Q3	5.65, 24.67	5.32, 22.40	5.45, 24.51
	Min, Max	0.03, 38.44	0.03, 34.86	0.03, 38.44

N=Number of participants; n=Number of participants with non-missing values; SD=Standard Deviation; Q1=25%-Quartile; Q3=75%-Quartile; Min=Minimum; Max=Maximum
BPI-SF=Brief Pain Inventory - Short Form; FACT-P=Functional Assessment of Cancer Therapy-Prostate; PSA=Prostate-specific antigen
Observation times for time-to-event endpoints: (Event/Censor date minus randomization date)/30.44 and for questionnaires and PSA undetectable rate: (Last assesment date minus randomization date)/30.44.
[1] Participants without death are censored at min(last known alive date or cutoff date).
[2] Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[3] Participants without event are censored at last assessment date or randomization date if there is no post-baseline assessment and died later than (24+1) weeks after randomization.
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[5] Participants without event are censored at last assessment date or randomization date if there is no follow-up available or end date of the first subsequent anticancer therapy (ACT) for prostate cancer. If first subsequent ACT is on-going participants are censored at cutoff date or last known alive date if they discontinued study or lost follow up.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 1.1
Observation time per endpoint in months
(full analysis set)

Final

		Darolutamide (N=446)	Placebo (N=223)	Total (N=669)
Worst Pain subscale score (BPI-SF Item 3) - Time to (sustained) deterioration of at least 2 points [2]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	17.72 (9.71)	15.67 (9.44)	17.04 (9.66)
	Median	21.45	14.75	18.40
	Q1, Q3	8.38, 25.59	6.31, 24.64	8.25, 25.00
	Min, Max	0.03, 38.44	0.03, 34.86	0.03, 38.44
Pain interference score (BPI-SF Item 9 a-g) - Time to (first) improvement of at least 2 points [2]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	17.35 (10.39)	15.34 (9.40)	16.68 (10.11)
	Median	21.60	14.75	18.53
	Q1, Q3	7.59, 25.76	6.54, 24.31	7.39, 25.00
	Min, Max	0.03, 38.44	0.03, 34.86	0.03, 38.44
Pain interference score (BPI-SF Item 9 a-g) - Time to (first) deterioration of at least 2 points [2]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	16.81 (9.78)	14.59 (9.51)	16.07 (9.74)
	Median	19.09	13.60	16.29
	Q1, Q3	8.21, 24.87	5.58, 23.46	7.62, 24.70
	Min, Max	0.03, 38.44	0.03, 34.86	0.03, 38.44
FACT-P total score - Time to improvement of at least 10 points [2]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	11.66 (9.64)	11.10 (9.35)	11.47 (9.54)
	Median	8.31	8.34	8.31
	Q1, Q3	2.86, 21.16	2.83, 17.41	2.86, 19.71
	Min, Max	0.03, 35.87	0.03, 33.08	0.03, 35.87
FACT-P total score - Time to deterioration of at least 10 points [2]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	13.96 (9.96)	11.66 (9.11)	13.19 (9.74)
	Median	11.24	8.54	11.01
	Q1, Q3	5.52, 23.06	2.92, 19.35	5.26, 22.54
	Min, Max	0.03, 38.63	0.03, 31.73	0.03, 38.63
FACT-P total score - Time to improvement of at least 23.4 points [2]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	17.14 (10.05)	15.43 (9.41)	16.57 (9.86)
	Median	19.56	15.14	17.38
	Q1, Q3	8.25, 25.56	6.04, 24.47	7.26, 25.00
	Min, Max	0.03, 35.87	0.03, 33.08	0.03, 35.87
FACT-P total score - Time to deterioration of at least 23.4 points [2]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	18.22 (9.56)	14.95 (9.41)	17.13 (9.63)
	Median	21.65	14.06	18.40
	Q1, Q3	9.26, 25.59	5.81, 23.23	8.48, 25.00
	Min, Max	0.03, 38.63	0.03, 35.05	0.03, 38.63
Radiological progression-free survival [3]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	19.71 (9.19)	15.86 (9.13)	18.43 (9.34)
	Median	22.31	14.22	21.88
	Q1, Q3	11.24, 27.37	8.31, 24.44	10.78, 25.56
	Min, Max	0.03, 36.17	0.03, 35.05	0.03, 36.17

N=Number of participants; n=Number of participants with non-missing values; SD=Standard Deviation; Q1=25%-Quartile; Q3=75%-Quartile; Min=Minimum; Max=Maximum
BPI-SF=Brief Pain Inventory - Short Form; FACT-P=Functional Assessment of Cancer Therapy-Prostate; PSA=Prostate-specific antigen
Observation times for time-to-event endpoints: (Event/Censor date minus randomization date)/30.44 and for questionnaires and PSA undetectable rate: (Last assesment date minus randomization date)/30.44.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 1.1
Observation time per endpoint in months
(full analysis set)

Final

		Darolutamide (N=446)	Placebo (N=223)	Total (N=669)
Time to castration-resistant prostate cancer [2]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	18.97 (9.59)	14.06 (8.82)	17.33 (9.62)
	Median	22.13	11.96	19.32
	Q1, Q3	10.94, 26.54	5.98, 22.11	8.31, 25.13
	Min, Max	0.03, 36.20	0.03, 35.22	0.03, 36.20
PSA undetectable rate	n (missing)	425 (21)	211 (12)	636 (33)
	Mean (SD)	20.31 (8.78)	17.92 (8.79)	19.52 (8.85)
	Median	22.50	19.28	22.08
	Q1, Q3	13.70, 27.46	11.04, 25.13	12.22, 26.00
	Min, Max	0.03, 38.63	0.03, 35.05	0.03, 38.63
Time to initiation of subsequent systemic anticancer therapy for prostate cancer [4]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	21.28 (8.28)	18.89 (8.77)	20.48 (8.52)
	Median	23.01	20.63	22.60
	Q1, Q3	14.55, 27.60	11.50, 25.76	13.80, 27.53
	Min, Max	0.03, 38.63	0.03, 35.05	0.03, 38.63
Time to first prostate cancer-related invasive procedure [2]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	21.51 (8.62)	20.25 (9.17)	21.09 (8.82)
	Median	23.67	22.70	23.19
	Q1, Q3	16.59, 27.63	14.59, 27.63	16.33, 27.63
	Min, Max	0.03, 38.63	0.03, 35.05	0.03, 38.63
Time to PSA progression [2]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	18.12 (9.77)	13.19 (8.82)	16.48 (9.74)
	Median	20.40	11.27	17.18
	Q1, Q3	8.54, 25.56	5.58, 20.53	7.13, 24.87
	Min, Max	0.03, 38.63	0.03, 35.05	0.03, 38.63
Progression-free survival 2 [5]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	21.08 (8.70)	19.48 (9.10)	20.54 (8.86)
	Median	23.19	22.11	22.90
	Q1, Q3	14.59, 27.56	11.66, 25.99	13.86, 27.53
	Min, Max	0.03, 38.70	0.03, 37.02	0.03, 38.70

N=Number of participants; n=Number of participants with non-missing values; SD=Standard Deviation; Q1=25%-Quartile; Q3=75%-Quartile; Min=Minimum; Max=Maximum
BPI-SF=Brief Pain Inventory - Short Form; FACT-P=Functional Assessment of Cancer Therapy-Prostate; PSA=Prostate-specific antigen
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[3] Participants without event are censored at last assessment date or randomization date if there is no post-baseline assessment and died later than (24+1) weeks after randomization.
[4] Participants without event are censored at last visit date or randomization date if there is no follow-up available.
[5] Participants without event are censored at last assessment date or randomization date if there is no follow-up available or end date of the first subsequent anticancer therapy (ACT) for prostate cancer. If first subsequent ACT is on-going participants are censored at cutoff date or last known alive date if they discontinued study or lost follow up.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 1.2
Overview Completion Rates
(full analysis set)

Final

Endpoint		Darolutamide (N=446)		Placebo (N=223)	
		Number of participants expected to complete	n (%)	Number of participants expected to complete	n (%)
FACT-P total score	Baseline / Day 1	443	440 (99.3)	223	222 (99.6)
	Visit 2 / Week 12	433	422 (97.5)	214	212 (99.1)
	Visit 3 / Week 24	417	411 (98.6)	201	198 (98.5)
	Visit 4 / Week 36	394	378 (95.9)	179	173 (96.6)
	Visit 5 / Week 48	361	348 (96.4)	159	152 (95.6)
	Visit 6 / Week 60	326	307 (94.2)	140	136 (97.1)
	Visit 7 / Week 72	310	302 (97.4)	117	114 (97.4)
	Visit 8 / Week 84	290	280 (96.6)	98	96 (98.0)
	Visit 9 / Week 96	270	256 (94.8)	91	82 (90.1)
	Visit 10 / Week 108	202	178 (88.1)	71	63 (88.7)
	Visit 11 / Week 120	126	116 (92.1)	40	34 (85.0)
	Visit 12 / Week 132	68	56 (82.4)	18	15 (83.3)
	Visit 13 / Week 144	20	18 (90.0)	4	2 (50.0)
	Visit 14 / Week 156	7	6 (85.7)	1	1 (100.0)
	Visit 15 / Week 168	1	1 (100.0)	0	0
	End of Treatment		109		105
	Active Follow-up Visit 1		38		27
	Active Follow-up Visit 2		20		17
	Active Follow-up Visit 3		15		14
	Active Follow-up Visit 4		9		6
	Active Follow-up Visit 5		7		4
Pain interference score (BPI-SF Item 9 a-g)	Baseline / Day 1	443	434 (98.0)	223	222 (99.6)
	Visit 2 / Week 12	433	419 (96.8)	214	212 (99.1)
	Visit 3 / Week 24	417	414 (99.3)	201	199 (99.0)
	Visit 4 / Week 36	394	381 (96.7)	179	175 (97.8)
	Visit 5 / Week 48	361	352 (97.5)	159	155 (97.5)
	Visit 6 / Week 60	326	313 (96.0)	140	138 (98.6)
	Visit 7 / Week 72	310	304 (98.1)	117	113 (96.6)
	Visit 8 / Week 84	290	282 (97.2)	98	96 (98.0)
	Visit 9 / Week 96	270	258 (95.6)	91	82 (90.1)
	Visit 10 / Week 108	202	181 (89.6)	71	63 (88.7)
	Visit 11 / Week 120	126	117 (92.9)	40	34 (85.0)
	Visit 12 / Week 132	68	57 (83.8)	18	15 (83.3)
	Visit 13 / Week 144	20	18 (90.0)	4	2 (50.0)
	Visit 14 / Week 156	7	6 (85.7)	1	1 (100.0)
	Visit 15 / Week 168	1	1 (100.0)	0	0
	End of Treatment		108		104
	Active Follow-up Visit 1		30		22
	Active Follow-up Visit 2		14		14
	Active Follow-up Visit 3		10		9
	Active Follow-up Visit 4		6		6
	Active Follow-up Visit 5		3		4

N=Number of participants; n=Number of participants with non missing value; BPI-SF=Brief Pain Inventory-Short Form; FACT-P=Functional Assessment of Cancer Therapy-Prostate
Participants are expected to complete if they are still alive and under treatment at the planned day of the respective visit (VISIT 2 /Week 12 = Day 85, VISIT 3 /Week 24 = Day 169, VISIT 4 /Week 36 = Day 253 ...).
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Table 1.2
Overview Completion Rates
(full analysis set)

Final

Endpoint	Darolutamide (N=446)		Placebo (N=223)		
	Number of participants expected to complete	n (%)	Number of participants expected to complete	n (%)	
Worst Pain subscale score (BPI-SF Item 3)	Baseline / Day 1	443	436 (98.4)	223	222 (99.6)
	Visit 2 / Week 12	433	420 (97.0)	214	213 (99.5)
	Visit 3 / Week 24	417	415 (99.5)	201	199 (99.0)
	Visit 4 / Week 36	394	383 (97.2)	179	176 (98.3)
	Visit 5 / Week 48	361	352 (97.5)	159	155 (97.5)
	Visit 6 / Week 60	326	313 (96.0)	140	138 (98.6)
	Visit 7 / Week 72	310	304 (98.1)	117	113 (96.6)
	Visit 8 / Week 84	290	282 (97.2)	98	96 (98.0)
	Visit 9 / Week 96	270	258 (95.6)	91	82 (90.1)
	Visit 10 / Week 108	202	181 (89.6)	71	63 (88.7)
	Visit 11 / Week 120	126	117 (92.9)	40	34 (85.0)
	Visit 12 / Week 132	68	57 (83.8)	18	15 (83.3)
	Visit 13 / Week 144	20	18 (90.0)	4	2 (50.0)
	Visit 14 / Week 156	7	6 (85.7)	1	1 (100.0)
	Visit 15 / Week 168	1	1 (100.0)	0	0
	End of Treatment		108		104
	Active Follow-up Visit 1		30		22
	Active Follow-up Visit 2		14		14
	Active Follow-up Visit 3		10		9
	Active Follow-up Visit 4		6		6
	Active Follow-up Visit 5		3		4

N=Number of participants; n=Number of participants with non missing value; BPI-SF=Brief Pain Inventory-Short Form; FACT-P=Functional Assessment of Cancer Therapy-Prostate
Participants are expected to complete if they are still alive and under treatment at the planned day of the respective visit (VISIT 2 /Week 12 = Day 85, VISIT 3 /Week 24 = Day 169, VISIT 4 /Week 36 = Day 253 ...).
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Study population

Table 2.1.1

Overall survival

(full analysis set)

Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	103 (23.1)	60 (26.9)
Number of censored participants, n (%)	343 (76.9)	163 (73.1)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	28.4 (24.4, 33.1)	24.3 (19.2, 33.8)
Median (95%-CI)	NE (NE, NE)	NE (32.8, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.813 (0.591, 1.118)	
p-value [4]	0.2014	

N=Number of participants; CI=Confidence Interval; NE=Not estimable
Participants without death are censored at last known alive date or cutoff date, whichever comes earlier or at randomization day if there is no contact after randomization.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Study population
Table 2.1.1.1.1
Overall survival - Subgroup analysis
(full analysis set)

Final

Subgroup Level	Darolutamide(N=446)				Placebo(N=223)				Unstratified Analysis			
	n/N[s]	(%)	Median	(95% CI)[1]	n/N[s]	(%)	Median	(95% CI)[1]	Hazard Ratio	(95% CI)[2]	p-value [3]	Interaction p-value[4]
Presence of visceral metastases assessed by central review (from IWRS)												
Yes	15/ 53	(28.3)	NE (28.4,	NE)	9/ 27	(33.3)	NE (18.7,	NE)	0.820	(0.359, 1.875)	0.6380	0.9861
No	88/ 393	(22.4)	NE (NE,	NE)	51/ 196	(26.0)	NE (32.8,	NE)	0.819	(0.580, 1.156)	0.2558	
Received prior local therapy (from IWRS)												
Yes	19/ 80	(23.8)	NE (33.1,	NE)	11/ 40	(27.5)	NE (25.3,	NE)	0.744	(0.353, 1.568)	0.4350	0.8778
No	84/ 366	(23.0)	NE (NE,	NE)	49/ 183	(26.8)	NE (32.8,	NE)	0.831	(0.584, 1.182)	0.3032	
Prior local radiotherapy and/or prostatectomy												
Yes	17/ 87	(19.5)	NE (33.1,	NE)	13/ 50	(26.0)	NE (NE,	NE)	0.704	(0.341, 1.452)	0.3389	0.6825
No	86/ 359	(24.0)	NE (NE,	NE)	47/ 173	(27.2)	33.8 (32.8,	NE)	0.845	(0.592, 1.206)	0.3519	
Age group												
<65 years	25/ 118	(21.2)	NE (33.1,	NE)	21/ 65	(32.3)	32.8 (27.9,	NE)	0.602	(0.337, 1.075)	0.0829	0.2804
65-74	47/ 193	(24.4)	NE (NE,	NE)	20/ 96	(20.8)	33.8 (33.8,	NE)	1.190	(0.704, 2.009)	0.5156	
75-84	23/ 117	(19.7)	NE (NE,	NE)	15/ 52	(28.8)	NE (NE,	NE)	0.628	(0.328, 1.204)	0.1575	
>=85 years	8/ 18	(44.4)	30.0 (15.4,	NE)	4/ 10	(40.0)	NE (2.4,	NE)	0.902	(0.270, 3.008)	0.8663	
Race												
White	66/ 251	(26.3)	NE (NE,	NE)	40/ 125	(32.0)	NE (32.8,	NE)	0.771	(0.521, 1.143)	0.1941	0.9610
Asian	26/ 144	(18.1)	NE (NE,	NE)	12/ 65	(18.5)	NE (NE,	NE)	0.971	(0.490, 1.925)	0.9330	
Black or African American	9/ 41	(22.0)	NE (NE,	NE)	6/ 24	(25.0)	NE (24.7,	NE)	0.862	(0.307, 2.425)	0.7784	
Other	2/ 10	(20.0)	NE (14.9,	NE)	2/ 9	(22.2)	NE (2.5,	NE)	0.859	(0.121, 6.103)	0.8791	
Geographical region												
Asia	25/ 141	(17.7)	NE (NE,	NE)	12/ 63	(19.0)	NE (27.9,	NE)	0.906	(0.455, 1.804)	0.7778	0.5492
Latin America	32/ 119	(26.9)	NE (30.5,	NE)	18/ 72	(25.0)	NE (NE,	NE)	1.032	(0.579, 1.839)	0.9149	
Europe and Rest of the world	46/ 186	(24.7)	NE (NE,	NE)	30/ 88	(34.1)	33.8 (32.8,	NE)	0.697	(0.440, 1.104)	0.1220	
Baseline PSA values by median												
< median of overall population	42/ 216	(19.4)	NE (NE,	NE)	26/ 111	(23.4)	NE (NE,	NE)	0.827	(0.507, 1.348)	0.4452	0.9138
>= median of overall population	60/ 220	(27.3)	NE (NE,	NE)	34/ 108	(31.5)	32.8 (32.8,	NE)	0.797	(0.523, 1.214)	0.2900	
ECOG PS at baseline												
=0	47/ 235	(20.0)	NE (NE,	NE)	21/ 98	(21.4)	NE (NE,	NE)	0.887	(0.530, 1.485)	0.6484	0.8760
>=1	56/ 211	(26.5)	NE (NE,	NE)	39/ 125	(31.2)	33.8 (32.8,	NE)	0.840	(0.558, 1.264)	0.4016	
Gleason score at initial diagnosis												
Gleason <8	27/ 122	(22.1)	NE (NE,	NE)	19/ 67	(28.4)	NE (33.8,	NE)	0.735	(0.408, 1.322)	0.3022	0.5976
Gleason >=8	74/ 311	(23.8)	NE (NE,	NE)	38/ 146	(26.0)	NE (32.8,	NE)	0.893	(0.604, 1.321)	0.5717	
Disease volume at baseline												
high	88/ 315	(27.9)	NE (NE,	NE)	52/ 157	(33.1)	33.8 (33.8,	NE)	0.801	(0.569, 1.129)	0.2039	0.7740
low	15/ 131	(11.5)	NE (NE,	NE)	8/ 66	(12.1)	NE (32.8,	NE)	0.902	(0.382, 2.130)	0.8140	
Renal function - eGFR at baseline												
Normal: eGFR >= 90 mL/min	47/ 219	(21.5)	NE (NE,	NE)	18/ 104	(17.3)	NE (32.8,	NE)	1.269	(0.736, 2.187)	0.3895	0.1450
Mild impairment: 60 <= eGFR < 90 mL/min	42/ 180	(23.3)	NE (NE,	NE)	30/ 91	(33.0)	NE (NE,	NE)	0.629	(0.393, 1.007)	0.0514	
Moderate impairment: 30 <= eGFR < 60 mL/min	13/ 46	(28.3)	NE (NE,	NE)	11/ 27	(40.7)	33.8 (19.7, 33.8)		0.689	(0.308, 1.543)	0.3624	

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable

AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;

IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Participants without death are censored at last known alive date or cutoff date, whichever comes earlier or at randomization day if there is no contact after randomization.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided P-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.1.1.1

Overall survival - Subgroup analysis

(full analysis set)

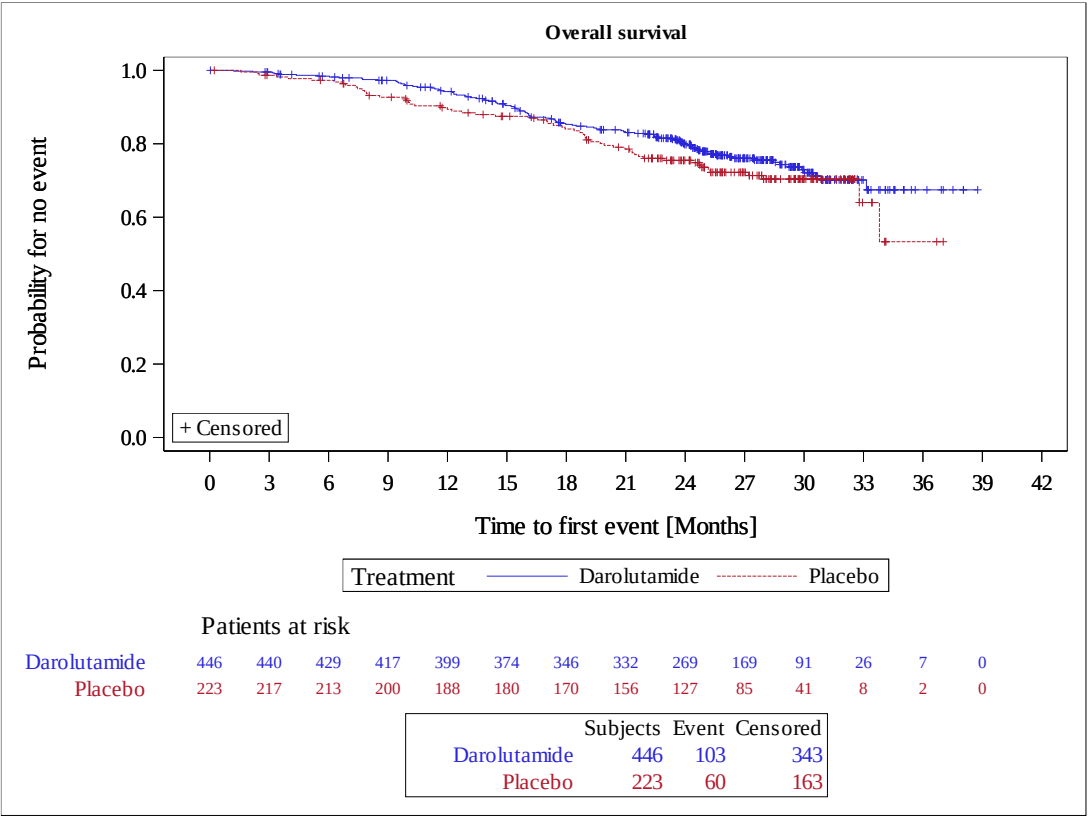
Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis		
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3]	Interaction p-Value[4]
Hepatic function at baseline									0.9029
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	90/ 387 (23.3)	NE (	NE, NE)	55/ 204 (27.0)	NE (32.8,	NE)	0.825 (0.589, 1.153)	0.2591	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	13/ 59 (22.0)	NE (	NE, NE)	5/ 19 (26.3)	NE (18.9,	NE)	0.760 (0.271, 2.135)	0.6018	
Age Group (Titan)									0.1759
<65	25/ 118 (21.2)	NE (33.1,	NE)	21/ 65 (32.3)	32.8 (27.9,	NE)	0.602 (0.337, 1.075)	0.0829	
>=65 and <75	47/ 193 (24.4)	NE (	NE, NE)	20/ 96 (20.8)	33.8 (33.8,	NE)	1.190 (0.704, 2.009)	0.5156	
>=75	31/ 135 (23.0)	NE (	NE, NE)	19/ 62 (30.6)	NE (	NE, NE)	0.677 (0.382, 1.199)	0.1785	
Geographic region (Titan)									0.5375
Europe and north america	42/ 145 (29.0)	NE (	NE, NE)	29/ 77 (37.7)	33.8 (32.8,	NE)	0.753 (0.469, 1.209)	0.2378	
ROTW	61/ 301 (20.3)	NE (	NE, NE)	31/ 146 (21.2)	NE (	NE, NE)	0.916 (0.594, 1.412)	0.6907	

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable
AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;
IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal
Participants without death are censored at last known alive date or cutoff date, whichever comes earlier or at randomization day if there is no contact after randomization.
[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.
[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

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Study population
Figure 2.1.1.2
Kaplan-Meier Plot of Overall survival
(full analysis set)

Final



Participants without death are censored at last known alive date or cutoff date, whichever comes earlier or at randomization day if there is no contact after randomization.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 2.1.2
Time to symptomatic skeletal event
(full analysis set)

Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	28 (6.3)	16 (7.2)
External beam radiation therapy to relieve skeletal symptoms, n (%)*	15 (53.6)	13 (81.3)
New symptomatic pathologic bone fracture, n (%)*	5 (17.9)	1 (6.3)
Tumor-related orthopedic surgical intervention, n (%)*	1 (3.6)	1 (6.3)
Spinal cord compression, n (%)*	7 (25.0)	1 (6.3)
Number of censored participants, n (%)	418 (93.7)	207 (92.8)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.826 (0.447, 1.528)	
p-value [4]	0.5416	

N=Number of participants; CI=Confidence Interval; NE=Not estimable
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
*Percentages are based on participants with events.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 2.1.2.1

Time to symptomatic skeletal event - Subgroup analysis

(full analysis set)

Final

Subgroup Level	Darolutamide (N=446)			Placebo (N=223)			Unstratified Analysis		
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3]	Interaction p-Value [4]
Presence of visceral metastases assessed by central review (from IWRS)									0.3094
Yes	1/ 53 (1.9)	NE (NE, NE)		2/ 27 (7.4)	NE (NE, NE)		0.251 (0.023, 2.767)	0.2220	
No	27/ 393 (6.9)	NE (NE, NE)		14/ 196 (7.1)	NE (NE, NE)		0.894 (0.468, 1.706)	0.7334	
Received prior local therapy (from IWRS)									0.5025
Yes	5/ 80 (6.3)	NE (NE, NE)		4/ 40 (10.0)	NE (NE, NE)		0.581 (0.156, 2.165)	0.4126	
No	23/ 366 (6.3)	NE (NE, NE)		12/ 183 (6.6)	NE (NE, NE)		0.904 (0.449, 1.817)	0.7759	
Prior local radiotherapy and/or prostatectomy									0.5245
Yes	4/ 87 (4.6)	NE (NE, NE)		4/ 50 (8.0)	NE (NE, NE)		0.551 (0.138, 2.204)	0.3923	
No	24/ 359 (6.7)	NE (NE, NE)		12/ 173 (6.9)	NE (NE, NE)		0.895 (0.447, 1.790)	0.7530	
Age group									0.4841
<65 years	11/ 118 (9.3)	NE (NE, NE)		9/ 65 (13.8)	NE (NE, NE)		0.577 (0.239, 1.395)	0.2162	
65-74	11/ 193 (5.7)	NE (NE, NE)		3/ 96 (3.1)	NE (NE, NE)		1.799 (0.502, 6.451)	0.3605	
75-84	5/ 117 (4.3)	NE (NE, NE)		4/ 52 (7.7)	NE (NE, NE)		0.528 (0.142, 1.968)	0.3334	
>=85 years	1/ 18 (5.6)	NE (27.7, NE)		0/ 10 (0.0)	NE (NE, NE)		NE (NE, NE)	NE	
Race									0.9750
White	15/ 251 (6.0)	NE (NE, NE)		9/ 125 (7.2)	NE (NE, NE)		0.772 (0.337, 1.766)	0.5387	
Asian	8/ 144 (5.6)	NE (NE, NE)		5/ 65 (7.7)	NE (NE, NE)		0.696 (0.228, 2.129)	0.5236	
Black or African American	4/ 41 (9.8)	NE (NE, NE)		2/ 24 (8.3)	NE (NE, NE)		1.071 (0.196, 5.848)	0.9372	
Other	1/ 10 (10.0)	NE (25.6, NE)		0/ 9 (0.0)	NE (NE, NE)		NE (NE, NE)	NE	
Geographical region									0.7564
Asia	7/ 141 (5.0)	NE (NE, NE)		5/ 63 (7.9)	NE (NE, NE)		0.601 (0.191, 1.894)	0.3796	
Latin America	11/ 119 (9.2)	NE (NE, NE)		6/ 72 (8.3)	NE (NE, NE)		1.073 (0.396, 2.902)	0.8903	
Europe and Rest of the world	10/ 186 (5.4)	NE (NE, NE)		5/ 88 (5.7)	NE (NE, NE)		0.849 (0.289, 2.491)	0.7653	
Baseline PSA values by median									0.0635
< median of overall population	19/ 216 (8.8)	NE (NE, NE)		7/ 111 (6.3)	NE (NE, NE)		1.312 (0.551, 3.126)	0.5381	
>= median of overall population	8/ 220 (3.6)	NE (NE, NE)		9/ 108 (8.3)	NE (NE, NE)		0.396 (0.153, 1.027)	0.0484	
ECOG PS at baseline									0.5330
=0	12/ 235 (5.1)	NE (NE, NE)		7/ 98 (7.1)	NE (NE, NE)		0.679 (0.267, 1.726)	0.4137	
>=1	16/ 211 (7.6)	NE (NE, NE)		9/ 125 (7.2)	NE (NE, NE)		0.991 (0.438, 2.244)	0.9830	
Gleason score at initial diagnosis									0.8047
Gleason <8	4/ 122 (3.3)	NE (NE, NE)		3/ 67 (4.5)	NE (NE, NE)		0.726 (0.163, 3.246)	0.6742	
Gleason >=8	23/ 311 (7.4)	NE (NE, NE)		12/ 146 (8.2)	NE (NE, NE)		0.846 (0.421, 1.702)	0.6391	
Disease volume at baseline									0.8999
high	24/ 315 (7.6)	NE (NE, NE)		14/ 157 (8.9)	NE (NE, NE)		0.805 (0.416, 1.557)	0.5181	
low	4/ 131 (3.1)	NE (NE, NE)		2/ 66 (3.0)	NE (NE, NE)		0.930 (0.170, 5.089)	0.9336	
Renal function - eGFR at baseline									0.9835
Normal: eGFR >= 90 mL/min	14/ 219 (6.4)	NE (NE, NE)		7/ 104 (6.7)	NE (NE, NE)		0.862 (0.348, 2.138)	0.7491	
Mild impairment: 60 <= eGFR < 90 mL/min	10/ 180 (5.6)	NE (NE, NE)		6/ 91 (6.6)	NE (NE, NE)		0.791 (0.287, 2.178)	0.6488	
Moderate impairment: 30 <= eGFR < 60 mL/min	4/ 46 (8.7)	NE (NE, NE)		3/ 27 (11.1)	NE (NE, NE)		0.832 (0.186, 3.719)	0.8092	

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable

AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;

IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Participants without event are censored at last assessment date or randomization date if there is no follow-up available.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Study population

Table 2.1.2.1

Time to symptomatic skeletal event - Subgroup analysis

(full analysis set)

Final

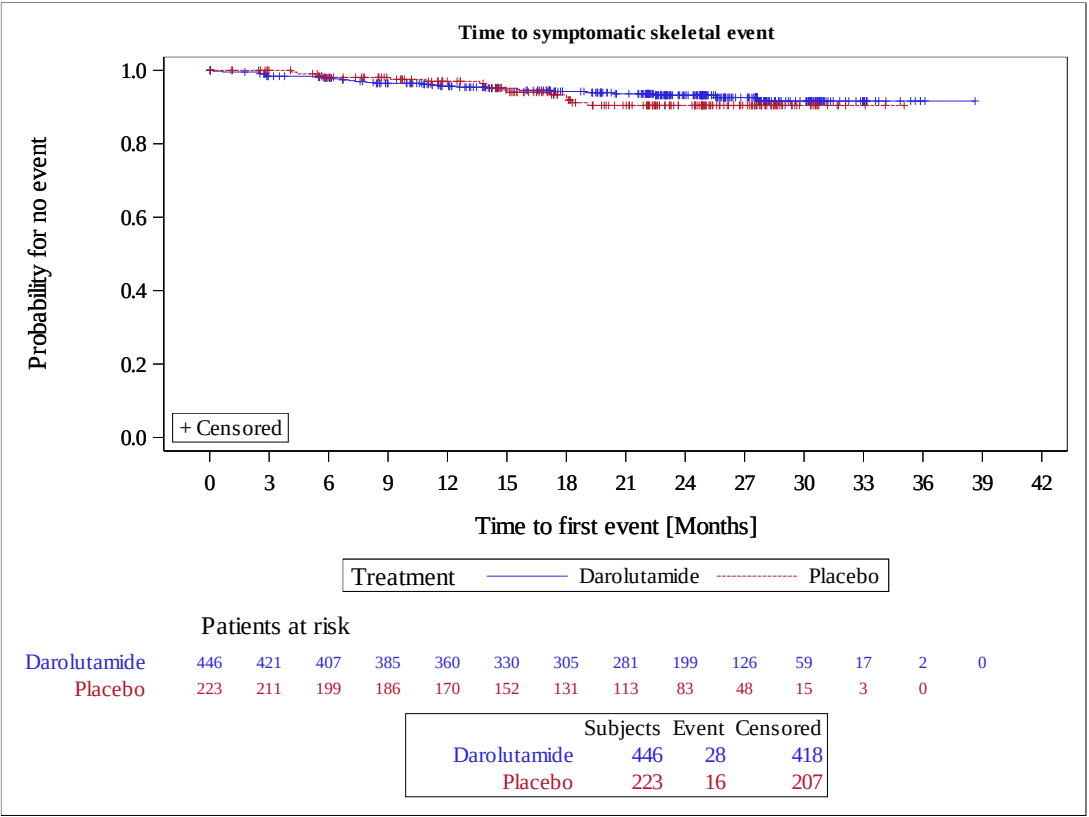
Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis	
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3] Interaction p-Value[4]
Hepatic function at baseline								0.7493
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	26/ 387 (6.7)	NE (	NE, NE)	15/ 204 (7.4)	NE (	NE, NE)	0.855 (0.453, 1.615)	0.6283
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	2/ 59 (3.4)	NE (	NE, NE)	1/ 19 (5.3)	NE (	NE, NE)	0.562 (0.051, 6.202)	0.6332
Age Group (Titan)								0.3354
<65	11/ 118 (9.3)	NE (	NE, NE)	9/ 65 (13.8)	NE (	NE, NE)	0.577 (0.239, 1.395)	0.2162
>=65 and <75	11/ 193 (5.7)	NE (	NE, NE)	3/ 96 (3.1)	NE (	NE, NE)	1.799 (0.502, 6.451)	0.3605
>=75	6/ 135 (4.4)	NE (	NE, NE)	4/ 62 (6.5)	NE (	NE, NE)	0.631 (0.178, 2.241)	0.4724
Geographic region (Titan)								0.6374
Europe and north america	5/ 145 (3.4)	NE (	NE, NE)	4/ 77 (5.2)	NE (	NE, NE)	0.638 (0.171, 2.379)	0.5002
ROTW	23/ 301 (7.6)	NE (	NE, NE)	12/ 146 (8.2)	NE (	NE, NE)	0.875 (0.435, 1.759)	0.7077

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable
AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;
IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.
[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 2.1.2.2
Kaplan-Meier Plot of Time to symptomatic skeletal event
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 2.1.3

Time to symptomatic skeletal event: External beam radiation therapy to relieve skeletal symptoms (full analysis set)

Final

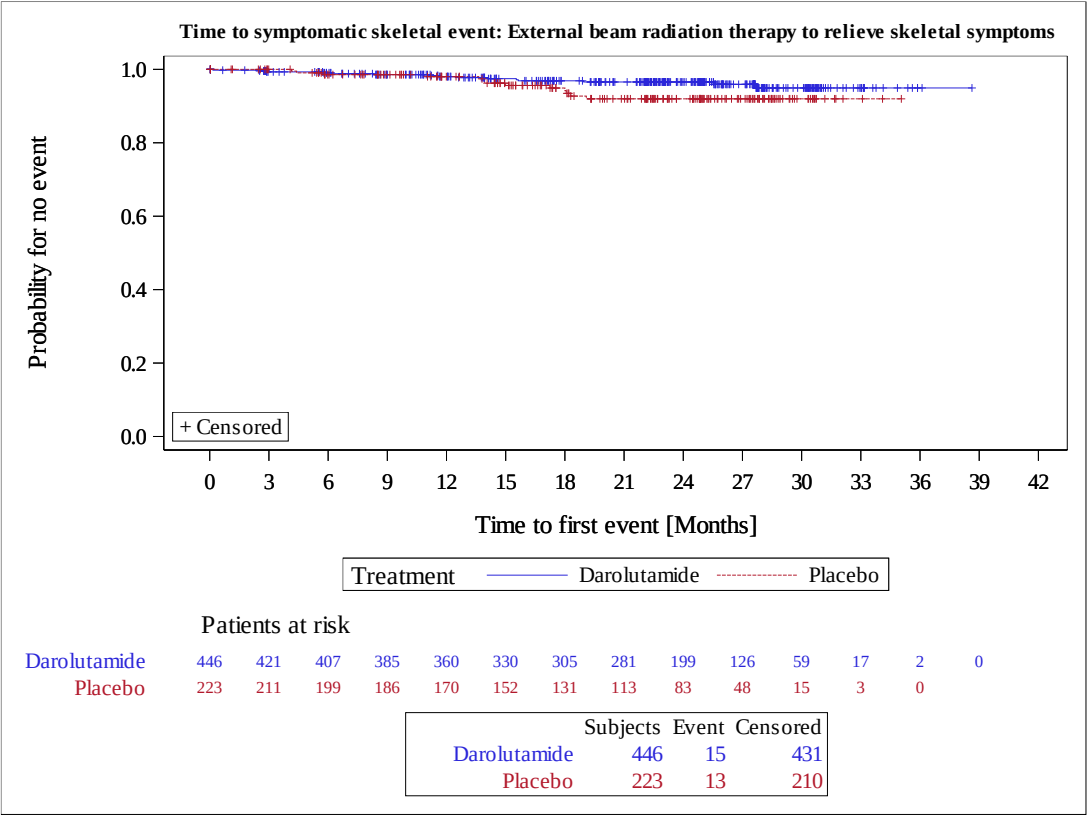
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	15 (3.4)	13 (5.8)
Number of censored participants, n (%)	431 (96.6)	210 (94.2)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.543 (0.258, 1.142)	
p-value [4]	0.1022	

N=Number of participants; CI=Confidence Interval; NE=Not estimable
Participants without event are censored at last assessment date or event date of other (first) single item, whichever comes earlier, or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.3.1
Kaplan-Meier Plot of Time to symptomatic skeletal event: External beam radiation therapy to relieve skeletal symptoms
(full analysis set)

Final



Participants without event are censored at last assessment date or event date of other (first) single item, whichever comes earlier, or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.4

Time to symptomatic skeletal event: New symptomatic pathologic bone fracture (full analysis set)

Final

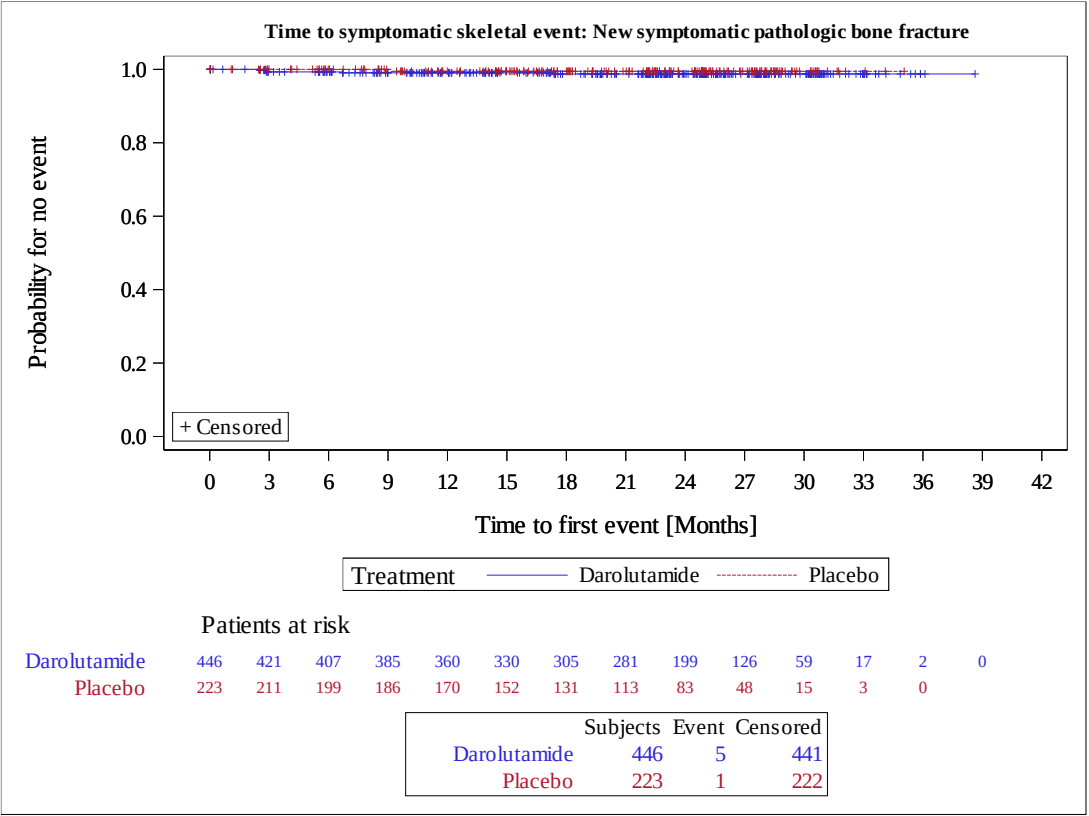
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	5 (1.1)	1 (0.4)
Number of censored participants, n (%)	441 (98.9)	222 (99.6)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	2.444 (0.285, 20.928)	
p-value [4]	0.3991	

N=Number of participants; CI=Confidence Interval; NE=Not estimable
Participants without event are censored at last assessment date or event date of other (first) single item, whichever comes earlier, or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

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BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.4.1
Kaplan-Meier Plot of Time to symptomatic skeletal event: New symptomatic pathologic bone fracture
(full analysis set)

Final



Participants without event are censored at last assessment date or event date of other (first) single item, whichever comes earlier, or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Table 2.1.5
Time to symptomatic skeletal event: Spinal cord compression
(full analysis set)

Final

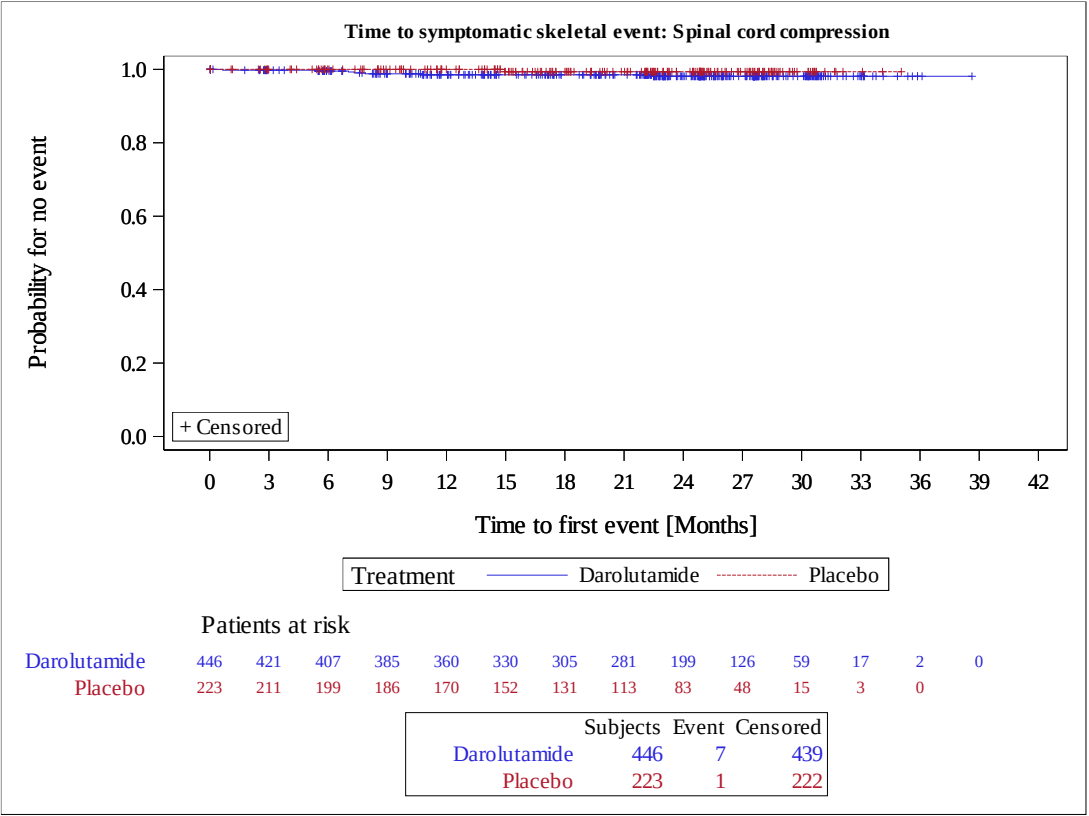
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	7 (1.6)	1 (0.4)
Number of censored participants, n (%)	439 (98.4)	222 (99.6)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	3.300 (0.406, 26.835)	
p-value [4]	0.2364	

N=Number of participants; CI=Confidence Interval; NE=Not estimable
Participants without event are censored at last assessment date or event date of other (first) single item, whichever comes earlier, or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 2.1.5.1
Kaplan-Meier Plot of Time to symptomatic skeletal event: Spinal cord compression
(full analysis set)

Final



Participants without event are censored at last assessment date or event date of other (first) single item, whichever comes earlier, or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Table 2.1.6

Time to symptomatic skeletal event: Tumor-related orthopedic surgical intervention

(full analysis set)

Final

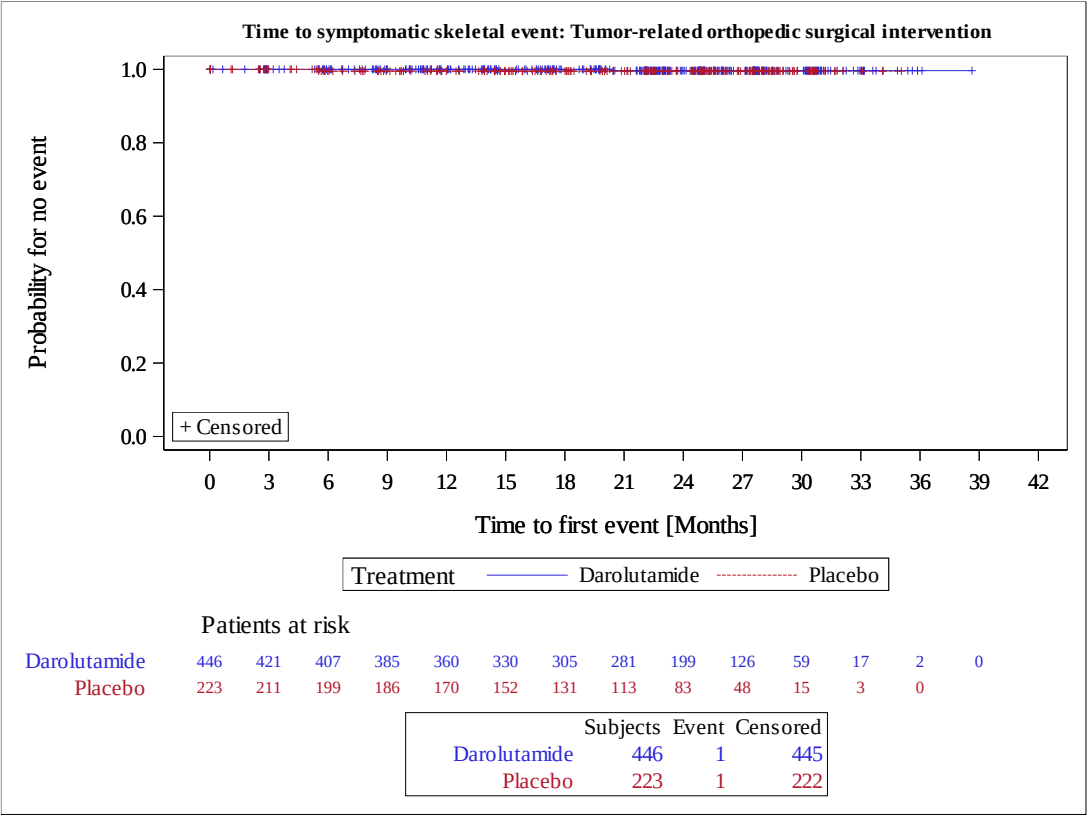
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	1 (0.2)	1 (0.4)
Number of censored participants, n (%)	445 (99.8)	222 (99.6)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.440 (0.027, 7.049)	
p-value [4]	0.5507	

N=Number of participants; CI=Confidence Interval; NE=Not estimable
Participants without event are censored at last assessment date or event date of other (first) single item, whichever comes earlier, or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Study population
Figure 2.1.6.1
Kaplan-Meier Plot of Time to symptomatic skeletal event: Tumor-related orthopedic surgical intervention
(full analysis set)

Final



Participants without event are censored at last assessment date or event date of other (first) single item, whichever comes earlier, or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Study population

Table 2.1.7

Worst Pain subscale score (BPI-SF Item 3) - Time to (first) improvement of at least 2 points

(full analysis set)

Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	124 (27.8)	50 (22.4)
Number of censored participants, n (%)	322 (72.2)	173 (77.6)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	8.1 (5.5, 16.6)	19.2 (8.1, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	1.218 (0.877, 1.692)	
p-value [4]	0.2369	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

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Table 2.1.7.1

Worst Pain subscale score (BPI-SF Item 3) - Time to (first) improvement of at least 2 points - Subgroup analysis

(full analysis set)

Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis	
	n/N[s]	(%)	Median (95% CI) [1]	n/N[s]	(%)	Median (95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3] Interaction p-Value[4]
Presence of visceral metastases assessed by central review (from IWRS)								0.5444
Yes	19/	53 (35.8)	NE (8.4, NE)	6/	27 (22.2)	NE (NE, NE)	1.611 (0.642, 4.043)	0.3022
No	105/	393 (26.7)	NE (NE, NE)	44/	196 (22.4)	NE (NE, NE)	1.184 (0.832, 1.684)	0.3450
Received prior local therapy (from IWRS)								0.5309
Yes	23/	80 (28.8)	NE (NE, NE)	7/	40 (17.5)	NE (NE, NE)	1.572 (0.673, 3.668)	0.2884
No	101/	366 (27.6)	NE (NE, NE)	43/	183 (23.5)	NE (NE, NE)	1.176 (0.823, 1.681)	0.3695
Prior local radiotherapy and/or prostatectomy								0.5313
Yes	20/	87 (23.0)	NE (NE, NE)	11/	50 (22.0)	NE (NE, NE)	0.983 (0.471, 2.054)	0.9643
No	104/	359 (29.0)	NE (NE, NE)	39/	173 (22.5)	NE (NE, NE)	1.292 (0.894, 1.866)	0.1697
Age group								0.4597
<65 years	42/	118 (35.6)	NE (24.7, NE)	13/	65 (20.0)	NE (NE, NE)	1.816 (0.975, 3.383)	0.0552
65-74	52/	193 (26.9)	NE (NE, NE)	25/	96 (26.0)	NE (NE, NE)	1.025 (0.636, 1.651)	0.9191
75-84	26/	117 (22.2)	NE (NE, NE)	12/	52 (23.1)	NE (NE, NE)	0.939 (0.474, 1.863)	0.8570
>=85 years	4/	18 (22.2)	NE (11.3, NE)	0/	10 (0.0)	NE (NE, NE)	NE (NE, NE)	NE
Race								0.6340
White	62/	251 (24.7)	NE (NE, NE)	20/	125 (16.0)	NE (NE, NE)	1.559 (0.942, 2.581)	0.0798
Asian	45/	144 (31.3)	NE (25.3, NE)	19/	65 (29.2)	NE (24.3, NE)	1.080 (0.632, 1.846)	0.7782
Black or African American	12/	41 (29.3)	NE (NE, NE)	8/	24 (33.3)	NE (14.2, NE)	0.801 (0.326, 1.968)	0.6269
Other	5/	10 (50.0)	7.9 (2.6, NE)	3/	9 (33.3)	NE (2.6, NE)	1.189 (0.283, 4.988)	0.8116
Geographical region								0.5541
Asia	44/	141 (31.2)	NE (25.3, NE)	19/	63 (30.2)	NE (24.3, NE)	1.048 (0.612, 1.794)	0.8634
Latin America	41/	119 (34.5)	NE (NE, NE)	20/	72 (27.8)	NE (NE, NE)	1.208 (0.708, 2.063)	0.4849
Europe and Rest of the world	39/	186 (21.0)	NE (NE, NE)	11/	88 (12.5)	NE (NE, NE)	1.693 (0.867, 3.307)	0.1173
Baseline PSA values by median								0.1756
< median of overall population	49/	216 (22.7)	NE (NE, NE)	26/	111 (23.4)	NE (NE, NE)	0.951 (0.591, 1.531)	0.8367
>= median of overall population	71/	220 (32.3)	NE (NE, NE)	23/	108 (21.3)	NE (NE, NE)	1.510 (0.943, 2.417)	0.0820
ECOG PS at baseline								0.1183
=0	59/	235 (25.1)	NE (NE, NE)	14/	98 (14.3)	NE (NE, NE)	1.829 (1.021, 3.277)	0.0385
>=1	65/	211 (30.8)	NE (NE, NE)	36/	125 (28.8)	NE (NE, NE)	1.041 (0.693, 1.564)	0.8451
Gleason score at initial diagnosis								0.2157
Gleason <8	25/	122 (20.5)	NE (NE, NE)	14/	67 (20.9)	NE (NE, NE)	0.899 (0.467, 1.730)	0.7495
Gleason >=8	96/	311 (30.9)	NE (NE, NE)	33/	146 (22.6)	NE (NE, NE)	1.439 (0.969, 2.137)	0.0685
Disease volume at baseline								0.9212
high	97/	315 (30.8)	NE (NE, NE)	39/	157 (24.8)	NE (NE, NE)	1.215 (0.838, 1.762)	0.3006
low	27/	131 (20.6)	NE (NE, NE)	11/	66 (16.7)	NE (NE, NE)	1.261 (0.625, 2.544)	0.5137
Renal function - eGFR at baseline								0.5910
Normal: eGFR >= 90 mL/min	66/	219 (30.1)	NE (NE, NE)	25/	104 (24.0)	NE (NE, NE)	1.218 (0.769, 1.930)	0.3979
Mild impairment: 60 <= eGFR < 90 mL/min	45/	180 (25.0)	NE (NE, NE)	21/	91 (23.1)	NE (NE, NE)	1.081 (0.644, 1.816)	0.7662
Moderate impairment: 30 <= eGFR < 60 mL/min	13/	46 (28.3)	NE (24.7, NE)	4/	27 (14.8)	NE (NE, NE)	2.020 (0.658, 6.197)	0.2080

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form

AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;

IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Participants without event are censored at last assessment date or randomization date if there is no follow-up available.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Study population

Table 2.1.7.1

Worst Pain subscale score (BPI-SF Item 3) - Time to (first) improvement of at least 2 points - Subgroup analysis

(full analysis set)

Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis		
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3]	Interaction p-Value[4]
Hepatic function at baseline									0.2788
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	112/ 387 (28.9)	NE (	NE, NE)	49/ 204 (24.0)	NE (	NE, NE)	1.203 (0.860, 1.683)	0.2775	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	12/ 59 (20.3)	NE (	NE, NE)	1/ 19 (5.3)	NE (	NE, NE)	3.743 (0.487, 28.793)	0.1714	
Age Group (Titan)									0.3484
<65	42/ 118 (35.6)	NE (	24.7, NE)	13/ 65 (20.0)	NE (	NE, NE)	1.816 (0.975, 3.383)	0.0552	
>=65 and <75	52/ 193 (26.9)	NE (	NE, NE)	25/ 96 (26.0)	NE (	NE, NE)	1.025 (0.636, 1.651)	0.9191	
>=75	30/ 135 (22.2)	NE (	NE, NE)	12/ 62 (19.4)	NE (	NE, NE)	1.127 (0.577, 2.203)	0.7254	
Geographic region (Titan)									0.4224
Europe and north america	29/ 145 (20.0)	NE (	NE, NE)	10/ 77 (13.0)	NE (	NE, NE)	1.579 (0.769, 3.242)	0.2066	
ROTW	95/ 301 (31.6)	NE (	NE, NE)	40/ 146 (27.4)	NE (	NE, NE)	1.122 (0.776, 1.624)	0.5380	

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form

AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;

IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Participants without event are censored at last assessment date or randomization date if there is no follow-up available.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

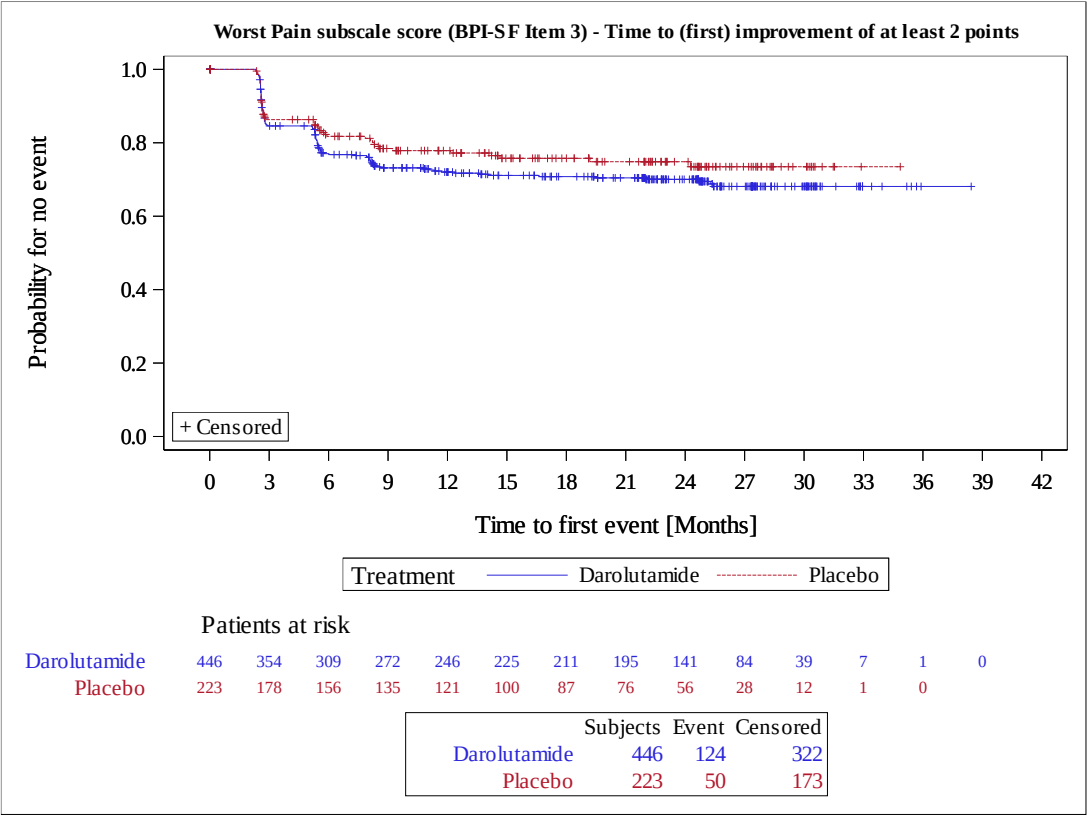
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Study population
Figure 2.1.7.2
Kaplan-Meier Plot of Worst Pain subscale score (BPI-SF Item 3) - Time to (first) improvement of at least 2 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

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Table 2.1.8

Worst Pain subscale score (BPI-SF Item 3) - Time to (sustained) improvement of at least 2 points

(full analysis set)

Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	94 (21.1)	33 (14.8)
Number of censored participants, n (%)	352 (78.9)	190 (85.2)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	27.8 (11.3, NE)	NE (27.7, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	1.394 (0.937, 2.073)	
p-value [4]	0.0984	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 2.1.8.1

Worst Pain subscale score (BPI-SF Item 3) - Time to (sustained) improvement of at least 2 points - Subgroup analysis (full analysis set)

Final

Subgroup Level	Darolutamide (N=446)			Placebo (N=223)			Unstratified Analysis		p-Value [3]	Interaction p-Value[4]
	n/N[s]	(%)	Median (95% CI) [1]	n/N[s]	(%)	Median (95% CI) [1]	Hazard Ratio (95% CI) [2]			
Presence of visceral metastases assessed by central review (from IWRS)										0.7869
Yes	13/	53 (24.5)	NE (NE, NE)	4/ 27 (14.8)	NE (NE, NE)		1.571 (0.512, 4.817)	0.4244		
No	81/ 393 (20.6)		NE (NE, NE)	29/ 196 (14.8)	NE (NE, NE)		1.372 (0.897, 2.097)	0.1413		
Received prior local therapy (from IWRS)										0.8000
Yes	17/ 80 (21.3)		NE (NE, NE)	5/ 40 (12.5)	NE (NE, NE)		1.608 (0.592, 4.368)	0.3444		
No	77/ 366 (21.0)		NE (NE, NE)	28/ 183 (15.3)	NE (NE, NE)		1.377 (0.893, 2.122)	0.1445		
Prior local radiotherapy and/or prostatectomy										0.0629
Yes	11/ 87 (12.6)		NE (NE, NE)	9/ 50 (18.0)	NE (27.7, NE)		0.652 (0.270, 1.575)	0.3375		
No	83/ 359 (23.1)		NE (NE, NE)	24/ 173 (13.9)	NE (NE, NE)		1.676 (1.064, 2.639)	0.0239		
Age group										0.7016
<65 years	29/ 118 (24.6)		NE (NE, NE)	8/ 65 (12.3)	NE (NE, NE)		2.032 (0.929, 4.447)	0.0686		
65-74	41/ 193 (21.2)		NE (NE, NE)	18/ 96 (18.8)	NE (NE, NE)		1.122 (0.644, 1.953)	0.6839		
75-84	21/ 117 (17.9)		NE (NE, NE)	7/ 52 (13.5)	NE (NE, NE)		1.319 (0.560, 3.103)	0.5234		
>=85 years	3/ 18 (16.7)		NE (11.3, NE)	0/ 10 (0.0)	NE (NE, NE)		NE (NE, NE)	NE		
Race										0.7428
White	49/ 251 (19.5)		NE (NE, NE)	15/ 125 (12.0)	NE (NE, NE)		1.601 (0.897, 2.855)	0.1059		
Asian	35/ 144 (24.3)		NE (NE, NE)	11/ 65 (16.9)	NE (NE, NE)		1.460 (0.741, 2.874)	0.2691		
Black or African American	7/ 41 (17.1)		NE (NE, NE)	4/ 24 (16.7)	NE (27.7, NE)		1.061 (0.307, 3.672)	0.9250		
Other	3/ 10 (30.0)		NE (2.6, NE)	3/ 9 (33.3)	NE (2.6, NE)		0.705 (0.142, 3.506)	0.6648		
Geographical region										0.7421
Asia	34/ 141 (24.1)		NE (NE, NE)	11/ 63 (17.5)	NE (NE, NE)		1.410 (0.715, 2.783)	0.3176		
Latin America	29/ 119 (24.4)		NE (NE, NE)	14/ 72 (19.4)	NE (27.7, NE)		1.212 (0.640, 2.297)	0.5527		
Europe and Rest of the world	31/ 186 (16.7)		NE (NE, NE)	8/ 88 (9.1)	NE (NE, NE)		1.809 (0.831, 3.939)	0.1285		
Baseline PSA values by median										0.0103
< median of overall population	36/ 216 (16.7)		NE (NE, NE)	21/ 111 (18.9)	NE (27.7, NE)		0.833 (0.486, 1.428)	0.5050		
>= median of overall population	55/ 220 (25.0)		NE (NE, NE)	11/ 108 (10.2)	NE (NE, NE)		2.520 (1.319, 4.814)	0.0036		
ECOG PS at baseline										0.6282
=0	43/ 235 (18.3)		NE (NE, NE)	11/ 98 (11.2)	NE (NE, NE)		1.642 (0.846, 3.185)	0.1374		
>=1	51/ 211 (24.2)		NE (NE, NE)	22/ 125 (17.6)	NE (NE, NE)		1.348 (0.817, 2.223)	0.2381		
Gleason score at initial diagnosis										0.1607
Gleason <8	17/ 122 (13.9)		NE (NE, NE)	10/ 67 (14.9)	NE (NE, NE)		0.866 (0.396, 1.892)	0.7173		
Gleason >=8	74/ 311 (23.8)		NE (NE, NE)	22/ 146 (15.1)	NE (NE, NE)		1.648 (1.024, 2.653)	0.0371		
Disease volume at baseline										0.5337
high	71/ 315 (22.5)		NE (NE, NE)	23/ 157 (14.6)	NE (NE, NE)		1.522 (0.951, 2.437)	0.0766		
low	23/ 131 (17.6)		NE (NE, NE)	10/ 66 (15.2)	NE (NE, NE)		1.130 (0.538, 2.377)	0.7455		
Renal function - eGFR at baseline										0.9731
Normal: eGFR >= 90 mL/min	51/ 219 (23.3)		NE (NE, NE)	16/ 104 (15.4)	NE (NE, NE)		1.467 (0.836, 2.572)	0.1770		
Mild impairment: 60 <= eGFR < 90 mL/min	34/ 180 (18.9)		NE (NE, NE)	13/ 91 (14.3)	NE (NE, NE)		1.301 (0.686, 2.467)	0.4180		
Moderate impairment: 30 <= eGFR < 60 mL/min	9/ 46 (19.6)		NE (NE, NE)	4/ 27 (14.8)	NE (NE, NE)		1.414 (0.435, 4.594)	0.5606		

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form

AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;

IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Participants without event are censored at last assessment date or randomization date if there is no follow-up available.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.8.1

Worst Pain subscale score (BPI-SF Item 3) - Time to (sustained) improvement of at least 2 points - Subgroup analysis (full analysis set)

Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis	
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3] Interaction p-Value[4]
Hepatic function at baseline								0.4479
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	84/ 387 (21.7)	NE (	NE, NE)	32/ 204 (15.7)	NE (	NE, NE)	1.367 (0.910, 2.055)	0.1293
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	10/ 59 (16.9)	NE (	NE, NE)	1/ 19 (5.3)	NE (	NE, NE)	3.067 (0.393, 23.957)	0.2584
Age Group (Titan)								0.4781
<65	29/ 118 (24.6)	NE (	NE, NE)	8/ 65 (12.3)	NE (	NE, NE)	2.032 (0.929, 4.447)	0.0696
>=65 and <75	41/ 193 (21.2)	NE (	NE, NE)	18/ 96 (18.8)	NE (	NE, NE)	1.122 (0.644, 1.953)	0.6839
>=75	24/ 135 (17.8)	NE (	NE, NE)	7/ 62 (11.3)	NE (	NE, NE)	1.565 (0.674, 3.633)	0.2913
Geographic region (Titan)								0.5285
Europe and north america	23/ 145 (15.9)	NE (	NE, NE)	7/ 77 (9.1)	NE (	NE, NE)	1.762 (0.755, 4.111)	0.1825
ROTW	71/ 301 (23.6)	NE (	NE, NE)	26/ 146 (17.8)	NE (	NE, NE)	1.287 (0.821, 2.017)	0.2680

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form

AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;

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[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

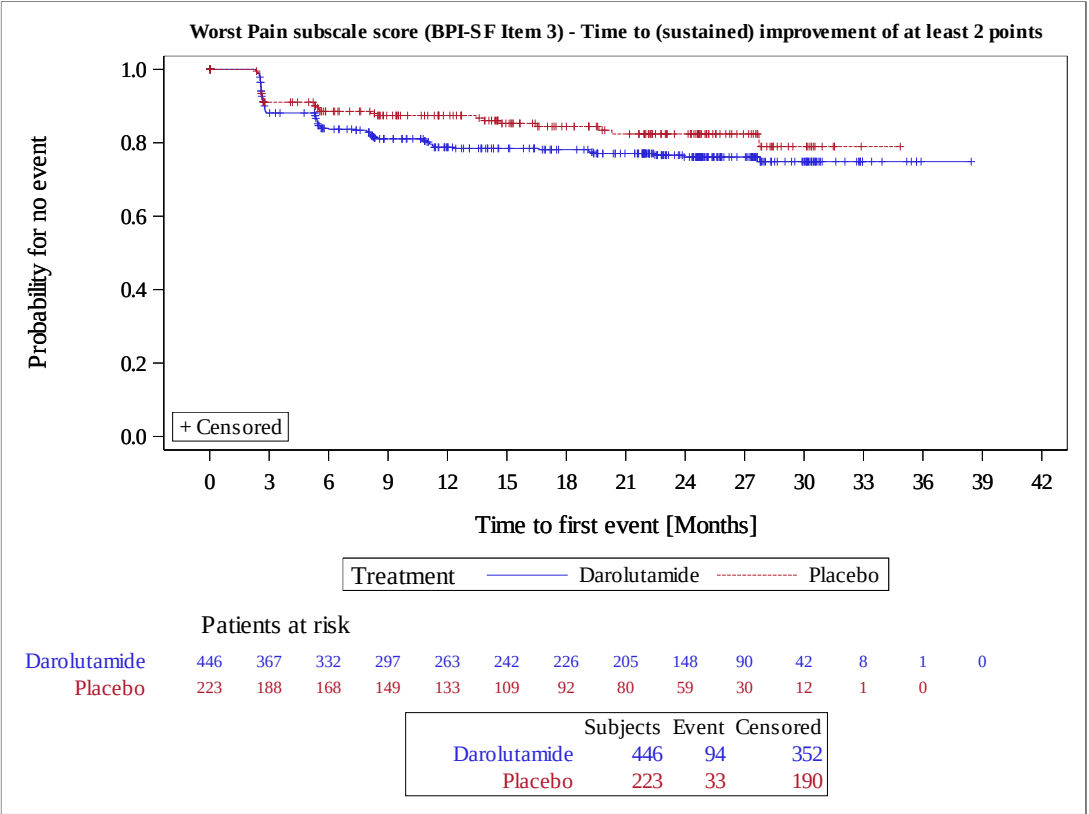
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.8.2
Kaplan-Meier Plot of Worst Pain subscale score (BPI-SF Item 3) - Time to (sustained) improvement of at least 2 points
(full analysis set)

Final

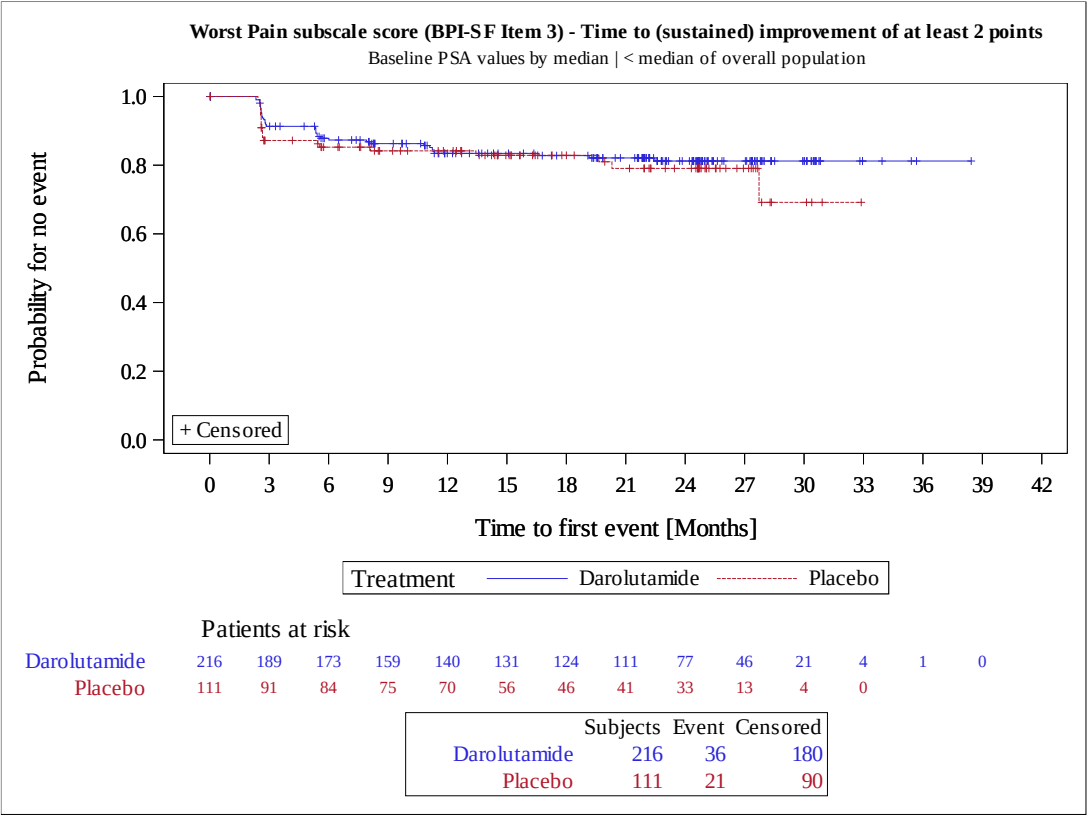


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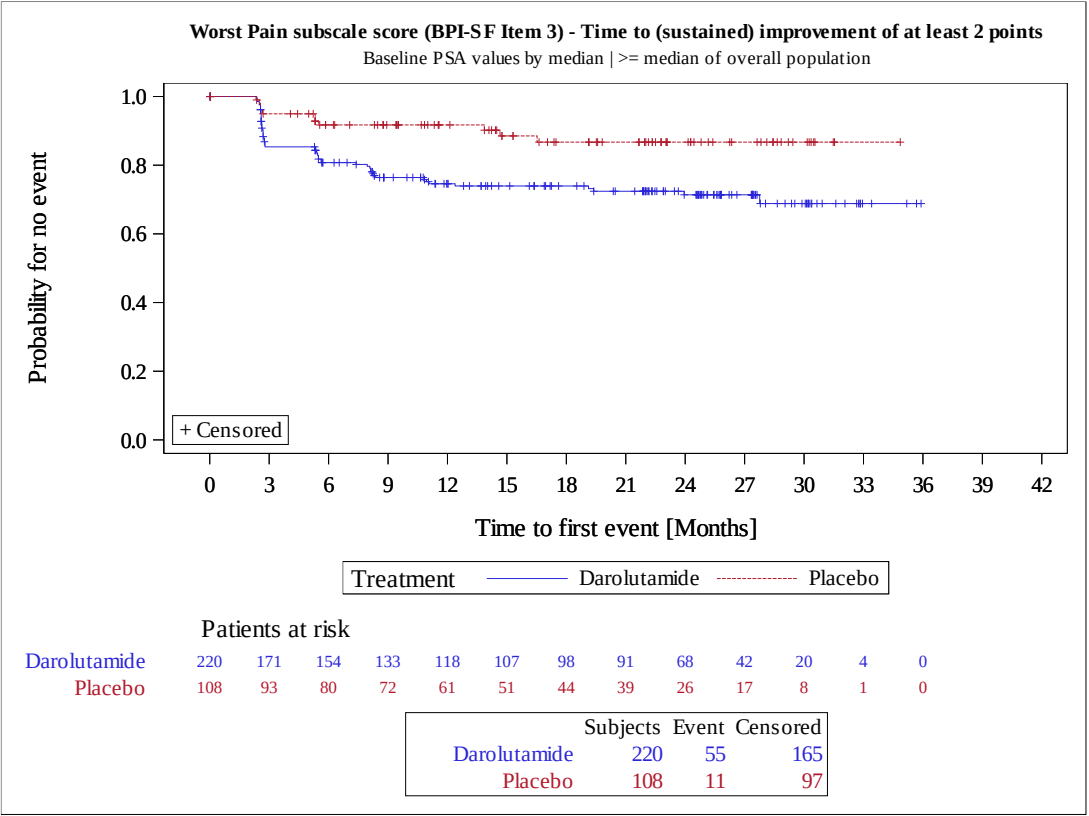


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Kaplan-Meier Plot of Worst Pain subscale score (BPI-SF Item 3) - Time to (sustained) improvement of at least 2 points
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Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 2.1.9

Worst Pain subscale score (BPI-SF Item 3) - Time to (first) deterioration of at least 2 points

(full analysis set)

Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	159 (35.7)	103 (46.2)
Number of censored participants, n (%)	287 (64.3)	120 (53.8)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	10.3 (8.1, 13.1)	5.6 (5.4, 8.1)
Median (95%-CI)	NE (NE, NE)	18.9 (12.4, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.678 (0.528, 0.870)	
p-value [4]	0.0021	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 2.1.9.1

Worst Pain subscale score (BPI-SF Item 3) - Time to (first) deterioration of at least 2 points - Subgroup analysis
(full analysis set)

Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis		
	n/N[s]	(%)	Median (95% CI) [1]	n/N[s]	(%)	Median (95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3]	Interaction p-Value[4]
Presence of visceral metastases assessed by central review (from IWRS)									0.3901
Yes	23/	53 (43.4)	16.6 (10.6, NE)	12/	27 (44.4)	11.0 (7.9, NE)	0.905 (0.450, 1.821)	0.7786	
No	136/ 393	(34.6)	NE (NE, NE)	91/ 196	(46.4)	19.2 (13.6, NE)	0.656 (0.503, 0.856)	0.0017	
Received prior local therapy (from IWRS)									0.0009
Yes	24/	80 (30.0)	NE (27.8, NE)	27/	40 (67.5)	6.3 (5.3, 11.0)	0.292 (0.167, 0.510)	<.0001	
No	135/ 366	(36.9)	NE (27.4, NE)	76/ 183	(41.5)	NE (15.7, NE)	0.836 (0.631, 1.108)	0.2110	
Prior local radiotherapy and/or prostatectomy									0.0474
Yes	28/	87 (32.2)	NE (21.7, NE)	29/	50 (58.0)	8.4 (5.5, NE)	0.440 (0.261, 0.743)	0.0015	
No	131/ 359	(36.5)	NE (27.8, NE)	74/ 173	(42.8)	21.9 (14.5, NE)	0.786 (0.591, 1.045)	0.0954	
Age group									0.2529
<65 years	40/	118 (33.9)	NE (22.6, NE)	28/	65 (43.1)	19.5 (10.9, NE)	0.681 (0.420, 1.106)	0.1169	
65-74	62/	193 (32.1)	NE (NE, NE)	45/	96 (46.9)	18.4 (10.8, NE)	0.601 (0.409, 0.883)	0.0085	
75-84	49/	117 (41.9)	NE (16.6, NE)	22/	52 (42.3)	NE (11.0, NE)	0.969 (0.586, 1.602)	0.9012	
>=85 years	8/	18 (44.4)	22.0 (10.8, NE)	8/	10 (80.0)	6.1 (2.5, 16.3)	0.294 (0.104, 0.830)	0.0142	
Race									0.8770
White	90/	251 (35.9)	NE (NE, NE)	63/	125 (50.4)	14.5 (10.7, NE)	0.636 (0.461, 0.879)	0.0054	
Asian	47/	144 (32.6)	NE (27.8, NE)	24/	65 (36.9)	NE (15.7, NE)	0.786 (0.481, 1.286)	0.3363	
Black or African American	19/	41 (46.3)	17.2 (8.2, NE)	13/	24 (54.2)	11.0 (5.5, NE)	0.777 (0.383, 1.574)	0.4808	
Other	3/	10 (30.0)	NE (5.4, NE)	3/	9 (33.3)	NE (2.7, NE)	0.817 (0.162, 4.105)	0.8055	
Geographical region									0.3561
Asia	45/	141 (31.9)	NE (27.8, NE)	22/	63 (34.9)	NE (16.6, NE)	0.836 (0.502, 1.393)	0.4908	
Latin America	52/	119 (43.7)	22.9 (14.1, NE)	36/	72 (50.0)	11.0 (8.2, NE)	0.792 (0.517, 1.212)	0.2793	
Europe and Rest of the world	62/	186 (33.3)	NE (NE, NE)	45/	88 (51.1)	14.5 (9.5, NE)	0.568 (0.387, 0.835)	0.0034	
Baseline PSA values by median									0.7075
< median of overall population	88/	216 (40.7)	NE (21.7, NE)	53/	111 (47.7)	19.2 (10.8, NE)	0.745 (0.530, 1.049)	0.0893	
>= median of overall population	69/	220 (31.4)	NE (NE, NE)	46/	108 (42.6)	19.5 (12.1, NE)	0.668 (0.460, 0.971)	0.0325	
ECOG PS at baseline									0.9806
=0	89/	235 (37.9)	NE (27.4, NE)	47/	98 (48.0)	18.9 (8.3, NE)	0.682 (0.479, 0.971)	0.0322	
>=1	70/	211 (33.2)	NE (NE, NE)	56/	125 (44.8)	18.4 (13.6, NE)	0.669 (0.470, 0.951)	0.0238	
Gleason score at initial diagnosis									0.7788
Gleason <8	49/	122 (40.2)	NE (17.0, NE)	33/	67 (49.3)	16.6 (6.3, NE)	0.754 (0.485, 1.174)	0.2080	
Gleason >=8	107/	311 (34.4)	NE (27.8, NE)	67/	146 (45.9)	18.9 (12.4, NE)	0.682 (0.502, 0.926)	0.0132	
Disease volume at baseline									0.3867
high	119/	315 (37.8)	NE (22.9, NE)	73/	157 (46.5)	18.4 (11.8, NE)	0.730 (0.546, 0.978)	0.0333	
low	40/	131 (30.5)	NE (NE, NE)	30/	66 (45.5)	NE (10.8, NE)	0.581 (0.361, 0.934)	0.0228	
Renal function - eGFR at baseline									0.9655
Normal: eGFR >= 90 mL/min	76/	219 (34.7)	NE (27.8, NE)	46/	104 (44.2)	19.5 (11.0, NE)	0.676 (0.469, 0.976)	0.0347	
Mild impairment: 60 <= eGFR < 90 mL/min	67/	180 (37.2)	NE (19.3, NE)	44/	91 (48.4)	18.9 (11.0, NE)	0.709 (0.484, 1.039)	0.0755	
Moderate impairment: 30 <= eGFR < 60 mL/min	15/	46 (32.6)	NE (17.9, NE)	12/	27 (44.4)	14.1 (5.4, NE)	0.668 (0.312, 1.429)	0.2926	

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 2.1.9.1
Worst Pain subscale score (BPI-SF Item 3) - Time to (first) deterioration of at least 2 points - Subgroup analysis
(full analysis set)

Final

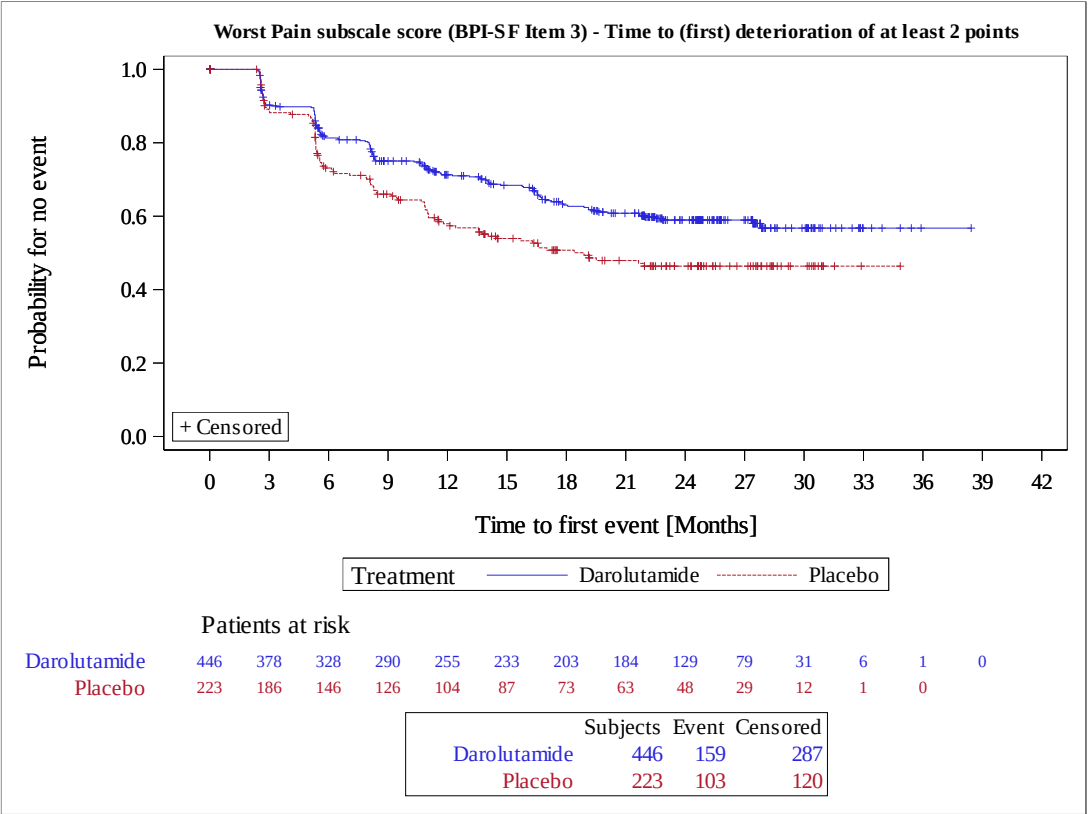
Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis		p-Value [3]	Interaction p-Value[4]
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio	(95% CI) [2]		
Hepatic function at baseline										0.4844
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	139/ 387 (35.9)	NE	(27.8, NE)	97/ 204 (47.5)	17.0	(11.8, NE)	0.672	(0.518, 0.871)	0.0024	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	20/ 59 (33.9)	NE	(19.1, NE)	6/ 19 (31.6)	NE	(5.7, NE)	0.914	(0.367, 2.276)	0.8461	
Age Group (Titan)										0.6256
<65	40/ 118 (33.9)	NE	(22.6, NE)	28/ 65 (43.1)	19.5	(10.9, NE)	0.681	(0.420, 1.106)	0.1169	
>=65 and <75	62/ 193 (32.1)	NE	(NE, NE)	45/ 96 (46.9)	18.4	(10.8, NE)	0.601	(0.409, 0.883)	0.0085	
>=75	57/ 135 (42.2)	27.4	(17.7, NE)	30/ 62 (48.4)	18.9	(10.8, NE)	0.807	(0.518, 1.256)	0.3392	
Geographic region (Titan)										0.1022
Europe and north america	41/ 145 (28.3)	NE	(NE, NE)	38/ 77 (49.4)	16.6	(10.8, NE)	0.507	(0.325, 0.789)	0.0021	
ROTW	118/ 301 (39.2)	NE	(21.7, NE)	65/ 146 (44.5)	18.9	(11.4, NE)	0.785	(0.580, 1.063)	0.1154	

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form
AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.9.2
Kaplan-Meier Plot of Worst Pain subscale score (BPI-SF Item 3) - Time to (first) deterioration of at least 2 points
(full analysis set)

Final

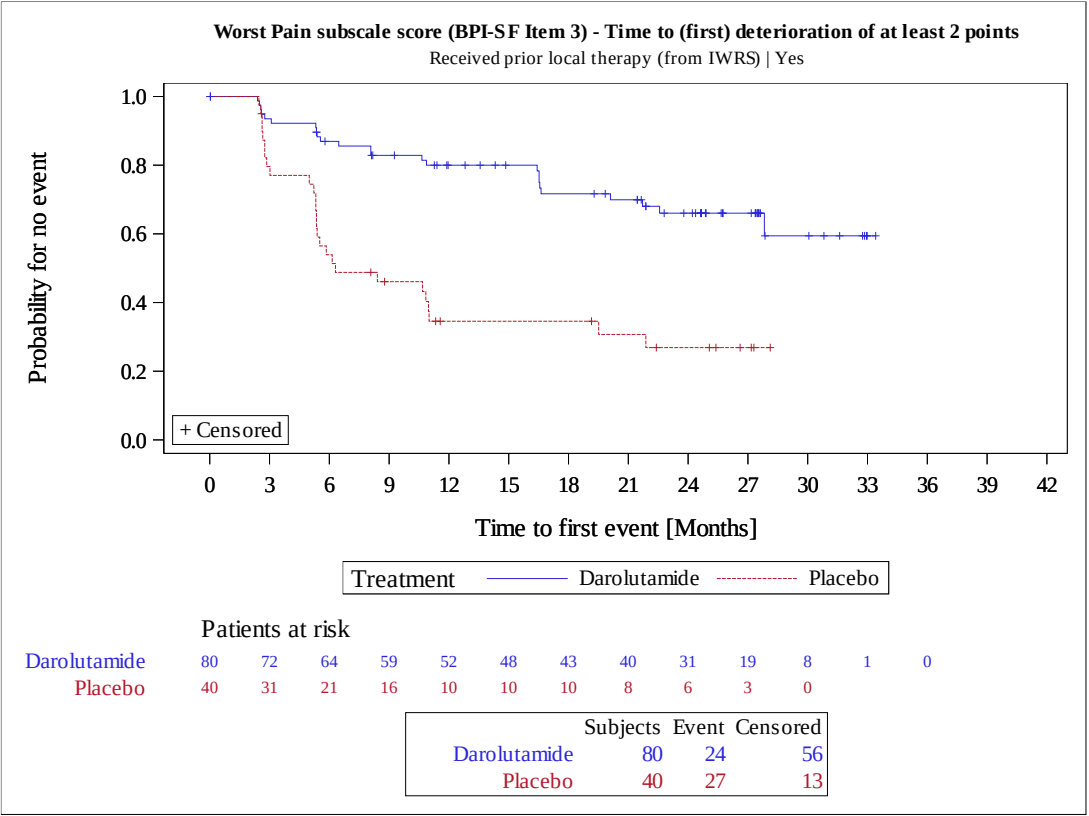


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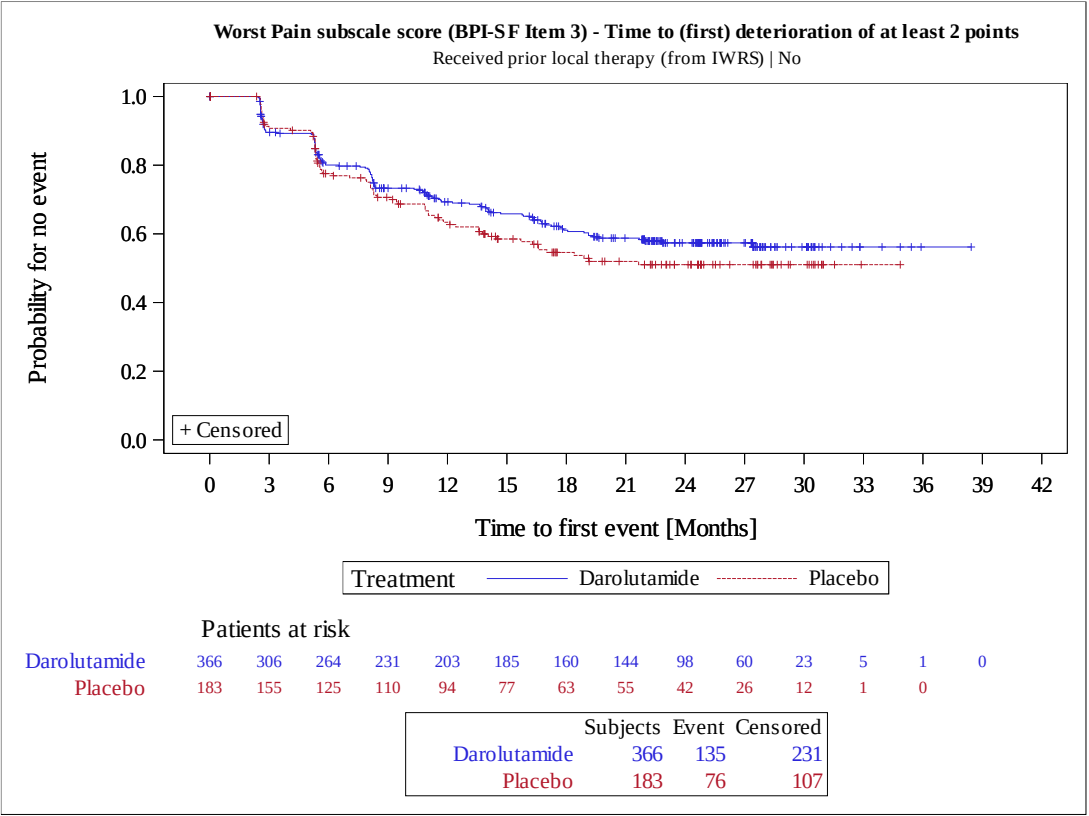


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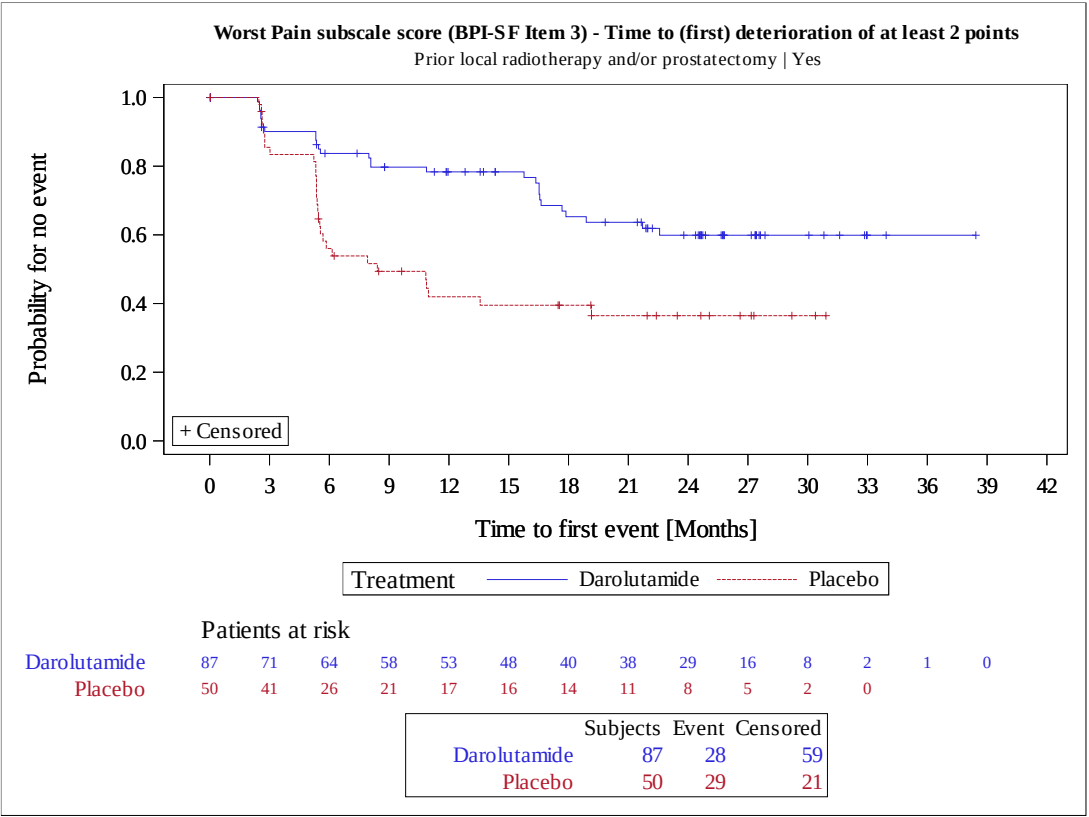


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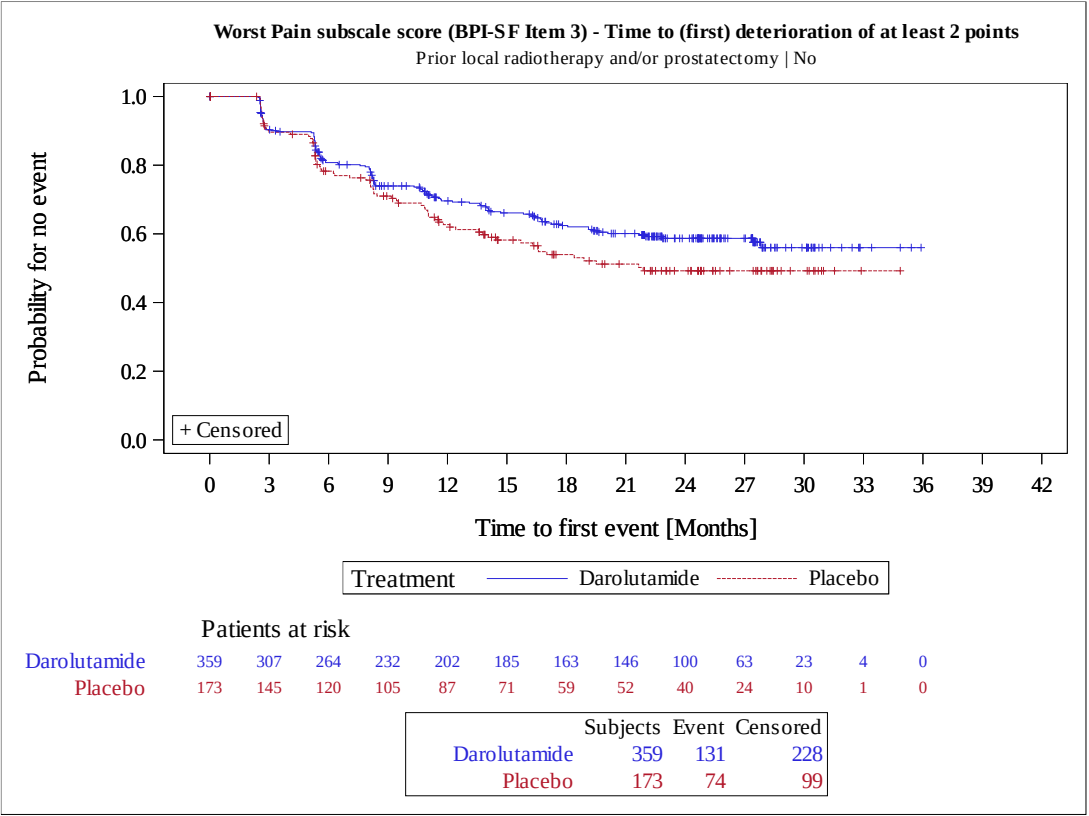


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Study population

Table 2.1.10

Worst Pain subscale score (BPI-SF Item 3) - Time to (sustained) deterioration of at least 2 points

(full analysis set)

Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	79 (17.7)	47 (21.1)
Number of censored participants, n (%)	367 (82.3)	176 (78.9)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	NE (22.1, NE)	18.9 (13.6, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.773 (0.538, 1.111)	
p-value [4]	0.1618	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Study population

Table 2.1.10.1

Worst Pain subscale score (BPI-SF Item 3) - Time to (sustained) deterioration of at least 2 points - Subgroup analysis

(full analysis set)

Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis	
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3] Interaction p-Value[4]
Presence of visceral metastases assessed by central review (from IWRS)								0.8944
Yes	11/ 53 (20.8)	NE (NE, NE)		7/ 27 (25.9)	29.9 (16.5, NE)		0.821 (0.318, 2.120)	0.6822
No	68/ 393 (17.3)	NE (NE, NE)		40/ 196 (20.4)	NE (NE, NE)		0.768 (0.519, 1.135)	0.1835
Received prior local therapy (from IWRS)								0.1025
Yes	10/ 80 (12.5)	NE (NE, NE)		10/ 40 (25.0)	NE (16.5, NE)		0.422 (0.175, 1.019)	0.0480
No	69/ 366 (18.9)	NE (NE, NE)		37/ 183 (20.2)	NE (NE, NE)		0.884 (0.593, 1.318)	0.5427
Prior local radiotherapy and/or prostatectomy								0.3044
Yes	15/ 87 (17.2)	NE (NE, NE)		14/ 50 (28.0)	NE (19.2, NE)		0.565 (0.272, 1.173)	0.1199
No	64/ 359 (17.8)	NE (NE, NE)		33/ 173 (19.1)	NE (NE, NE)		0.866 (0.569, 1.319)	0.5021
Age group								0.3791
<65 years	18/ 118 (15.3)	NE (NE, NE)		10/ 65 (15.4)	NE (NE, NE)		0.931 (0.429, 2.018)	0.8553
65-74	26/ 193 (13.5)	NE (NE, NE)		23/ 96 (24.0)	NE (29.9, NE)		0.522 (0.298, 0.915)	0.0207
75-84	29/ 117 (24.8)	NE (NE, NE)		11/ 52 (21.2)	NE (NE, NE)		1.075 (0.537, 2.152)	0.8388
>=85 years	6/ 18 (33.3)	25.0 (10.8, NE)		3/ 10 (30.0)	NE (2.5, NE)		0.961 (0.240, 3.850)	0.9552
Race								0.9795
White	48/ 251 (19.1)	NE (NE, NE)		26/ 125 (20.8)	NE (29.9, NE)		0.822 (0.509, 1.326)	0.4203
Asian	20/ 144 (13.9)	NE (NE, NE)		12/ 65 (18.5)	NE (NE, NE)		0.707 (0.345, 1.446)	0.3392
Black or African American	10/ 41 (24.4)	NE (NE, NE)		8/ 24 (33.3)	NE (11.0, NE)		0.710 (0.280, 1.800)	0.4675
Other	1/ 10 (10.0)	NE (5.4, NE)		1/ 9 (11.1)	NE (10.7, NE)		0.828 (0.052, 13.244)	0.8937
Geographical region								0.9808
Asia	20/ 141 (14.2)	NE (NE, NE)		11/ 63 (17.5)	NE (NE, NE)		0.778 (0.373, 1.624)	0.5020
Latin America	24/ 119 (20.2)	NE (NE, NE)		18/ 72 (25.0)	NE (29.9, NE)		0.767 (0.416, 1.415)	0.3943
Europe and Rest of the world	35/ 186 (18.8)	NE (NE, NE)		18/ 88 (20.5)	NE (NE, NE)		0.806 (0.456, 1.427)	0.4581
Baseline PSA values by median								0.9893
< median of overall population	44/ 216 (20.4)	NE (NE, NE)		26/ 111 (23.4)	NE (NE, NE)		0.794 (0.488, 1.290)	0.3496
>= median of overall population	33/ 220 (15.0)	NE (NE, NE)		19/ 108 (17.6)	NE (29.9, NE)		0.791 (0.449, 1.391)	0.4132
ECOG PS at baseline								0.6113
=0	46/ 235 (19.6)	NE (NE, NE)		21/ 98 (21.4)	NE (NE, NE)		0.849 (0.506, 1.422)	0.5324
>=1	33/ 211 (15.6)	NE (NE, NE)		26/ 125 (20.8)	NE (29.9, NE)		0.688 (0.411, 1.151)	0.1514
Gleason score at initial diagnosis								0.4573
Gleason <8	29/ 122 (23.8)	NE (NE, NE)		15/ 67 (22.4)	NE (NE, NE)		0.972 (0.521, 1.814)	0.9289
Gleason >=8	50/ 311 (16.1)	NE (NE, NE)		31/ 146 (21.2)	NE (29.9, NE)		0.721 (0.460, 1.129)	0.1507
Disease volume at baseline								0.7679
high	62/ 315 (19.7)	NE (NE, NE)		36/ 157 (22.9)	NE (29.9, NE)		0.799 (0.530, 1.205)	0.2818
low	17/ 131 (13.0)	NE (NE, NE)		11/ 66 (16.7)	NE (NE, NE)		0.683 (0.319, 1.461)	0.3229
Renal function - eGFR at baseline								0.5332
Normal: eGFR >= 90 mL/min	37/ 219 (16.9)	NE (NE, NE)		17/ 104 (16.3)	NE (NE, NE)		0.955 (0.538, 1.697)	0.8771
Mild impairment: 60 <= eGFR < 90 mL/min	32/ 180 (17.8)	NE (NE, NE)		24/ 91 (26.4)	NE (29.9, NE)		0.591 (0.347, 1.005)	0.0494
Moderate impairment: 30 <= eGFR < 60 mL/min	9/ 46 (19.6)	NE (27.4, NE)		6/ 27 (22.2)	NE (14.1, NE)		0.835 (0.297, 2.352)	0.7329

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form

AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;

IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Participants without event are censored at last assessment date or randomization date if there is no follow-up available.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 2.1.10.1
Worst Pain subscale score (BPI-SF Item 3) - Time to (sustained) deterioration of at least 2 points - Subgroup analysis
(full analysis set)

Final

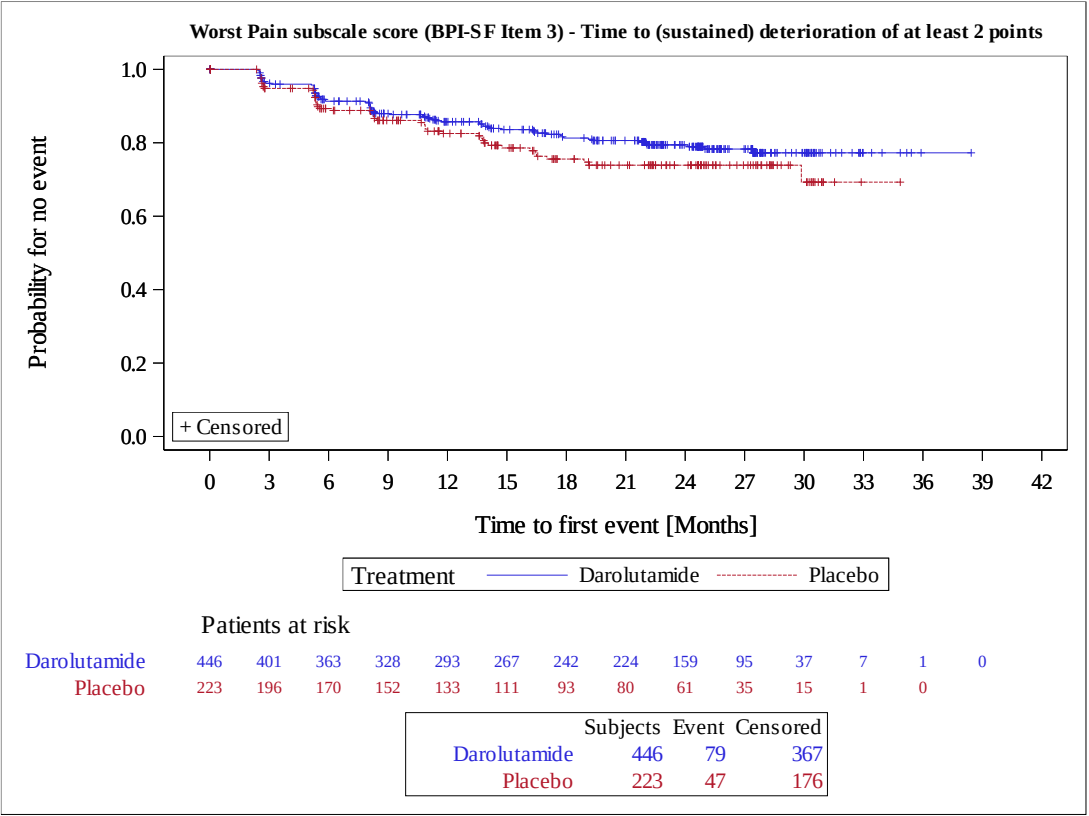
Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis	
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3] Interaction p-Value[4]
Hepatic function at baseline								0.4967
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	70/ 387 (18.1)	NE (	NE, NE)	45/ 204 (22.1)	NE (	NE, NE)	0.757 (0.520, 1.101)	0.1437
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	9/ 59 (15.3)	NE (	NE, NE)	2/ 19 (10.5)	NE (	NE, NE)	1.287 (0.278, 5.962)	0.7460
Age Group (Titan)								0.2241
<65	18/ 118 (15.3)	NE (	NE, NE)	10/ 65 (15.4)	NE (	NE, NE)	0.931 (0.429, 2.019)	0.8553
>=65 and <75	26/ 193 (13.5)	NE (	NE, NE)	23/ 96 (24.0)	NE (	29.9, NE)	0.522 (0.298, 0.915)	0.0207
>=75	35/ 135 (25.9)	NE (	NE, NE)	14/ 62 (22.6)	NE (	NE, NE)	1.039 (0.559, 1.933)	0.9021
Geographic region (Titan)								0.7839
Europe and north america	21/ 145 (14.5)	NE (	NE, NE)	14/ 77 (18.2)	NE (	NE, NE)	0.707 (0.358, 1.393)	0.3131
ROTW	58/ 301 (19.3)	NE (	NE, NE)	33/ 146 (22.6)	NE (	29.9, NE)	0.799 (0.521, 1.225)	0.3019

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form
AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;
IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.
[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.10.2
Kaplan-Meier Plot of Worst Pain subscale score (BPI-SF Item 3) - Time to (sustained) deterioration of at least 2 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 2.1.11
Pain interference score (BPI-SF Item 9 a-g) - Time to (first) improvement of at least 2 points
(full analysis set)

Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	82 (18.4)	33 (14.8)
Number of censored participants, n (%)	364 (81.6)	190 (85.2)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	NE (24.7, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	1.226 (0.818, 1.836)	
p-value [4]	0.3218	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.11.1

Pain interference score (BPI-SF Item 9 a-g) - Time to (first) improvement of at least 2 points - Subgroup analysis (full analysis set)

Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis		p-Value Interaction p-Value[4]
	n/N[s]	(%)	Median (95% CI) [1]	n/N[s]	(%)	Median (95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3]	
Presence of visceral metastases assessed by central review (from IWRS)									
Yes	14/	53 (26.4)	NE (NE, NE)	4/ 27 (14.8)	NE (NE, NE)	1.687 (0.555, 5.126)	0.3493	0.5373	0.4901
No	68/ 393 (17.3)	NE (NE, NE)	29/ 196 (14.8)	NE (NE, NE)	1.165 (0.754, 1.800)				
Received prior local therapy (from IWRS)									
Yes	12/ 80 (15.0)	NE (NE, NE)	5/ 40 (12.5)	NE (NE, NE)	1.143 (0.402, 3.247)	0.8016	0.8572	0.3058	0.5629
No	70/ 366 (19.1)	NE (NE, NE)	28/ 183 (15.3)	NE (NE, NE)	1.256 (0.810, 1.947)				
Prior local radiotherapy and/or prostatectomy									
Yes	16/ 87 (18.4)	NE (NE, NE)	6/ 50 (12.0)	NE (NE, NE)	1.587 (0.621, 4.056)	0.3288	0.5244	0.9171	0.4972
No	66/ 359 (18.4)	NE (NE, NE)	27/ 173 (15.6)	NE (NE, NE)	1.156 (0.739, 1.809)				
Age group									
<65 years	25/ 118 (21.2)	NE (NE, NE)	11/ 65 (16.9)	NE (NE, NE)	1.211 (0.595, 2.464)	0.5945	0.8229	0.7164	0.5453
65-74	41/ 193 (21.2)	NE (NE, NE)	15/ 96 (15.6)	NE (NE, NE)	1.380 (0.764, 2.494)	0.2819			
75-84	15/ 117 (12.8)	NE (NE, NE)	6/ 52 (11.5)	NE (NE, NE)	1.114 (0.432, 2.871)	0.8229	1.155 (0.275, 4.850)	0.8428	0.5453
>=85 years	1/ 18 (5.6)	NE (NE, NE)	1/ 10 (10.0)	NE (8.1, NE)	0.601 (0.038, 9.629)	0.7164			
Race									
White	41/ 251 (16.3)	NE (NE, NE)	12/ 125 (9.6)	NE (NE, NE)	1.760 (0.925, 3.349)	0.0802	0.8751	0.6969	0.8428
Asian	29/ 144 (20.1)	NE (NE, NE)	13/ 65 (20.0)	NE (NE, NE)	0.949 (0.493, 1.826)	0.8751			
Black or African American	7/ 41 (17.1)	NE (NE, NE)	5/ 24 (20.8)	NE (14.2, NE)	0.797 (0.253, 2.513)	0.6969	1.155 (0.275, 4.850)	0.8428	0.5453
Other	5/ 10 (50.0)	13.4 (2.6, NE)	3/ 9 (33.3)	NE (2.6, NE)					
Geographical region									
Asia	29/ 141 (20.6)	NE (NE, NE)	13/ 63 (20.6)	NE (NE, NE)	0.947 (0.492, 1.823)	0.8705	0.7133	0.2442	0.1146
Latin America	29/ 119 (24.4)	NE (NE, NE)	13/ 72 (18.1)	NE (NE, NE)	1.373 (0.713, 2.642)	0.3381			
Europe and Rest of the world	24/ 186 (12.9)	NE (NE, NE)	7/ 88 (8.0)	NE (NE, NE)	1.640 (0.706, 3.807)	0.2442	0.859 (0.472, 1.564)	0.6172	0.0748
Baseline PSA values by median									
< median of overall population	29/ 216 (13.4)	NE (NE, NE)	17/ 111 (15.3)	NE (NE, NE)	0.859 (0.472, 1.564)	0.6172	1.675 (0.942, 2.980)	0.1212	0.4491
>= median of overall population	51/ 220 (23.2)	NE (NE, NE)	15/ 108 (13.9)	NE (NE, NE)	1.675 (0.942, 2.980)	0.0748			
ECOG PS at baseline									
=0	28/ 235 (11.9)	NE (NE, NE)	11/ 98 (11.2)	NE (NE, NE)	1.041 (0.518, 2.092)	0.9100	1.473 (0.897, 2.418)	0.3989	0.5765
>=1	54/ 211 (25.6)	NE (NE, NE)	22/ 125 (17.6)	NE (NE, NE)	1.473 (0.897, 2.418)	0.1212			
Gleason score at initial diagnosis									
Gleason <8	20/ 122 (16.4)	NE (NE, NE)	9/ 67 (13.4)	NE (NE, NE)	1.155 (0.525, 2.537)	0.7198	1.237 (0.764, 2.004)	0.3836	0.8585
Gleason >=8	59/ 311 (19.0)	NE (NE, NE)	23/ 146 (15.8)	NE (NE, NE)	1.237 (0.764, 2.004)	0.3836			
Disease volume at baseline									
high	69/ 315 (21.9)	NE (NE, NE)	28/ 157 (17.8)	NE (NE, NE)	1.207 (0.778, 1.873)	0.3989	1.340 (0.477, 3.761)	0.5765	0.3980
low	13/ 131 (9.9)	NE (NE, NE)	5/ 66 (7.6)	NE (NE, NE)	1.340 (0.477, 3.761)	0.5765			
Renal function - eGFR at baseline									
Normal: eGFR >= 90 mL/min	41/ 219 (18.7)	NE (NE, NE)	19/ 104 (18.3)	NE (NE, NE)	0.962 (0.558, 1.657)	0.8888	1.444 (0.745, 2.796)	0.2713	0.2351
Mild impairment: 60 <= eGFR < 90 mL/min	33/ 180 (18.3)	NE (NE, NE)	12/ 91 (13.2)	NE (NE, NE)	1.444 (0.745, 2.796)	0.2713			
Moderate impairment: 30 <= eGFR < 60 mL/min	8/ 46 (17.4)	NE (NE, NE)	2/ 27 (7.4)	NE (NE, NE)	2.480 (0.526, 11.693)	0.2351			

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form

AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;

IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Participants without event are censored at last assessment date or randomization date if there is no follow-up available.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 2.1.11.1
Pain interference score (BPI-SF Item 9 a-g) - Time to (first) improvement of at least 2 points - Subgroup analysis
(full analysis set)

Final

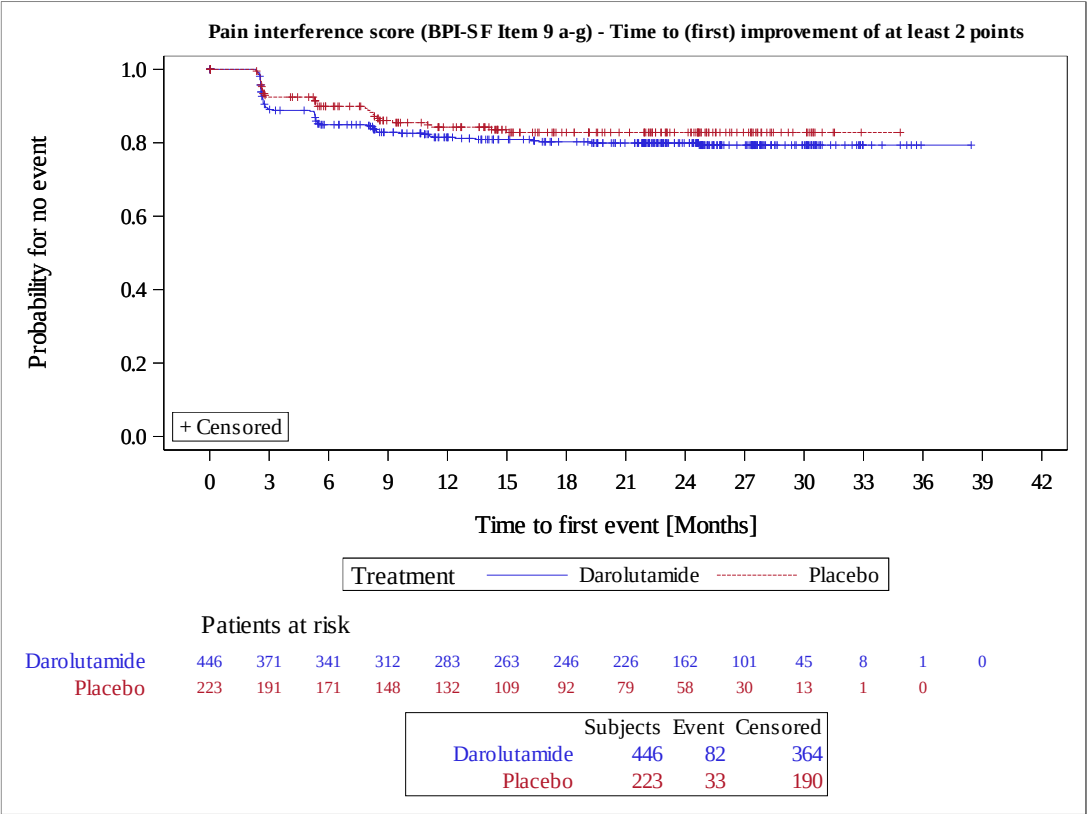
Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis	
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3] Interaction p-Value[4]
Hepatic function at baseline								0.3607
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	72/ 387 (18.6)	NE (	NE, NE)	32/ 204 (15.7)	NE (	NE, NE)	1.176 (0.775, 1.784)	0.4434
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	10/ 59 (16.9)	NE (	NE, NE)	1/ 19 (5.3)	NE (	NE, NE)	3.010 (0.385, 23.508)	0.2625
Age Group (Titan)								0.8741
<65	25/ 118 (21.2)	NE (	NE, NE)	11/ 65 (16.9)	NE (	NE, NE)	1.211 (0.595, 2.464)	0.5945
>=65 and <75	41/ 193 (21.2)	NE (	NE, NE)	15/ 96 (15.6)	NE (	NE, NE)	1.380 (0.764, 2.494)	0.2819
>=75	16/ 135 (11.9)	NE (	NE, NE)	7/ 62 (11.3)	NE (	NE, NE)	1.051 (0.432, 2.554)	0.9120
Geographic region (Titan)								0.1674
Europe and north america	20/ 145 (13.8)	NE (	NE, NE)	5/ 77 (6.5)	NE (	NE, NE)	2.252 (0.845, 5.999)	0.0943
ROTW	62/ 301 (20.6)	NE (	NE, NE)	28/ 146 (19.2)	NE (	NE, NE)	1.031 (0.659, 1.611)	0.8935

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form
AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;
IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.
[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.11.2
Kaplan-Meier Plot of Pain interference score (BPI-SF Item 9 a-g) - Time to (first) improvement of at least 2 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.12

Pain interference score (BPI-SF Item 9 a-g) - Time to (first) deterioration of at least 2 points (full analysis set)

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	132 (29.6)	91 (40.8)
Number of censored participants, n (%)	314 (70.4)	132 (59.2)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	14.8 (11.1, 19.1)	8.5 (6.3, 11.0)
Median (95%-CI)	NE (33.0, NE)	26.9 (16.6, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.637 (0.487, 0.833)	
p-value [4]	0.0009	

Final

N=Number of participants; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.12.1

Pain interference score (BPI-SF Item 9 a-g) - Time to (first) deterioration of at least 2 points - Subgroup analysis (full analysis set)

Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis		
	n/N[s]	(%)	Median (95% CI) [1]	n/N[s]	(%)	Median (95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3]	Interaction p-Value[4]
Presence of visceral metastases assessed by central review (from IWRS)									0.1779
Yes	18/	53 (34.0)	NE (17.2, NE)	8/	27 (29.6)	NE (8.4, NE)	1.094 (0.476, 2.518)	0.8313	
No	114/	393 (29.0)	NE (30.6, NE)	83/	196 (42.3)	26.9 (15.5, NE)	0.597 (0.449, 0.792)	0.0003	
Received prior local therapy (from IWRS)									0.0273
Yes	22/	80 (27.5)	NE (NE, NE)	22/	40 (55.0)	12.7 (6.3, NE)	0.363 (0.200, 0.660)	0.0005	
No	110/	366 (30.1)	33.0 (30.6, NE)	69/	183 (37.7)	NE (19.2, NE)	0.731 (0.541, 0.989)	0.0408	
Prior local radiotherapy and/or prostatectomy									0.1701
Yes	22/	87 (25.3)	NE (NE, NE)	24/	50 (48.0)	18.4 (10.8, NE)	0.465 (0.260, 0.831)	0.0080	
No	110/	359 (30.6)	33.0 (30.6, NE)	67/	173 (38.7)	NE (16.6, NE)	0.700 (0.517, 0.949)	0.0209	
Age group									0.1026
<65 years	33/	118 (28.0)	NE (NE, NE)	22/	65 (33.8)	NE (17.5, NE)	0.718 (0.418, 1.232)	0.2254	
65-74	50/	193 (25.9)	NE (NE, NE)	43/	96 (44.8)	26.9 (11.8, NE)	0.513 (0.341, 0.772)	0.0011	
75-84	45/	117 (38.5)	30.6 (22.1, NE)	20/	52 (38.5)	NE (16.2, NE)	0.930 (0.548, 1.580)	0.7891	
>=85 years	4/	18 (22.2)	NE (16.4, NE)	6/	10 (60.0)	8.5 (2.5, NE)	0.184 (0.045, 0.749)	0.0085	
Race									0.3125
White	74/	251 (29.5)	NE (33.0, NE)	55/	125 (44.0)	24.6 (13.8, NE)	0.576 (0.406, 0.818)	0.0018	
Asian	37/	144 (25.7)	NE (NE, NE)	21/	65 (32.3)	NE (17.5, NE)	0.734 (0.429, 1.254)	0.2548	
Black or African American	17/	41 (41.5)	27.8 (13.8, 27.8)	14/	24 (58.3)	11.0 (6.2, NE)	0.574 (0.280, 1.179)	0.1255	
Other	4/	10 (40.0)	22.9 (2.6, NE)	1/	9 (11.1)	NE (10.7, NE)	4.052 (0.449, 36.540)	0.1776	
Geographical region									0.7065
Asia	35/	141 (24.8)	NE (NE, NE)	21/	63 (33.3)	NE (17.5, NE)	0.694 (0.404, 1.193)	0.1839	
Latin America	46/	119 (38.7)	27.8 (19.6, NE)	34/	72 (47.2)	13.8 (10.9, NE)	0.719 (0.461, 1.121)	0.1425	
Europe and Rest of the world	51/	186 (27.4)	NE (33.0, NE)	36/	88 (40.9)	26.9 (16.2, NE)	0.567 (0.369, 0.870)	0.0085	
Baseline PSA values by median									0.2592
< median of overall population	76/	216 (35.2)	33.0 (25.2, NE)	46/	111 (41.4)	26.9 (16.2, NE)	0.747 (0.517, 1.079)	0.1179	
>= median of overall population	54/	220 (24.5)	NE (NE, NE)	42/	108 (38.9)	NE (13.8, NE)	0.556 (0.371, 0.832)	0.0037	
ECOG PS at baseline									0.2154
=0	74/	235 (31.5)	33.0 (30.6, NE)	37/	98 (37.8)	NE (16.2, NE)	0.760 (0.512, 1.129)	0.1724	
>=1	58/	211 (27.5)	NE (NE, NE)	54/	125 (43.2)	22.3 (14.1, NE)	0.545 (0.376, 0.790)	0.0011	
Gleason score at initial diagnosis									0.2808
Gleason <8	41/	122 (33.6)	NE (NE, NE)	27/	67 (40.3)	NE (12.7, NE)	0.785 (0.483, 1.276)	0.3266	
Gleason >=8	86/	311 (27.7)	NE (30.6, NE)	63/	146 (43.2)	26.9 (14.2, NE)	0.559 (0.403, 0.775)	0.0004	
Disease volume at baseline									0.9416
high	97/	315 (30.8)	33.0 (33.0, NE)	66/	157 (42.0)	22.3 (14.1, NE)	0.628 (0.459, 0.860)	0.0033	
low	35/	131 (26.7)	NE (30.6, NE)	25/	66 (37.9)	NE (16.2, NE)	0.650 (0.389, 1.088)	0.0982	
Renal function - eGFR at baseline									0.0356
Normal: eGFR >= 90 mL/min	63/	219 (28.8)	NE (30.6, NE)	28/	104 (26.9)	NE (NE, NE)	0.984 (0.631, 1.537)	0.9447	
Mild impairment: 60 <= eGFR < 90 mL/min	56/	180 (31.1)	NE (27.8, NE)	50/	91 (54.9)	14.2 (10.7, 22.3)	0.451 (0.307, 0.661)	<.0001	
Moderate impairment: 30 <= eGFR < 60 mL/min	12/	46 (26.1)	33.0 (23.0, NE)	12/	27 (44.4)	18.4 (11.8, NE)	0.506 (0.223, 1.148)	0.0951	

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form

AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;

IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Participants without event are censored at last assessment date or randomization date if there is no follow-up available.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 2.1.12.1

Pain interference score (BPI-SF Item 9 a-g) - Time to (first) deterioration of at least 2 points - Subgroup analysis (full analysis set)

Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis			p-Value [3]	Interaction p-Value[4]
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio	(95% CI) [2]			
Hepatic function at baseline											0.0640
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	115/ 387 (29.7)	NE	(30.6, NE)	88/ 204 (43.1)	22.3	(15.5, NE)	0.585	(0.443, 0.773)		0.0001	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	17/ 59 (28.8)	NE	(NE, NE)	3/ 19 (15.8)	NE	(NE, NE)	1.725	(0.505, 5.892)		0.3771	
Age Group (Titan)											0.3116
<65	33/ 118 (28.0)	NE	(NE, NE)	22/ 65 (33.8)	NE	(17.5, NE)	0.718	(0.418, 1.232)		0.2254	
>=65 and <75	50/ 193 (25.9)	NE	(NE, NE)	43/ 96 (44.8)	26.9	(11.8, NE)	0.513	(0.341, 0.772)		0.0011	
>=75	49/ 135 (36.3)	30.6	(22.9, NE)	26/ 62 (41.9)	22.3	(15.5, NE)	0.758	(0.470, 1.223)		0.2541	
Geographic region (Titan)											0.1170
Europe and north america	34/ 145 (23.4)	NE	(33.0, NE)	33/ 77 (42.9)	26.9	(14.2, NE)	0.468	(0.289, 0.759)		0.0016	
ROTW	98/ 301 (32.6)	NE	(25.2, NE)	58/ 146 (39.7)	NE	(14.1, NE)	0.728	(0.526, 1.008)		0.0544	

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; BPI-SF=Brief Pain Inventory - Short Form

AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;

IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Participants without event are censored at last assessment date or randomization date if there is no follow-up available.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

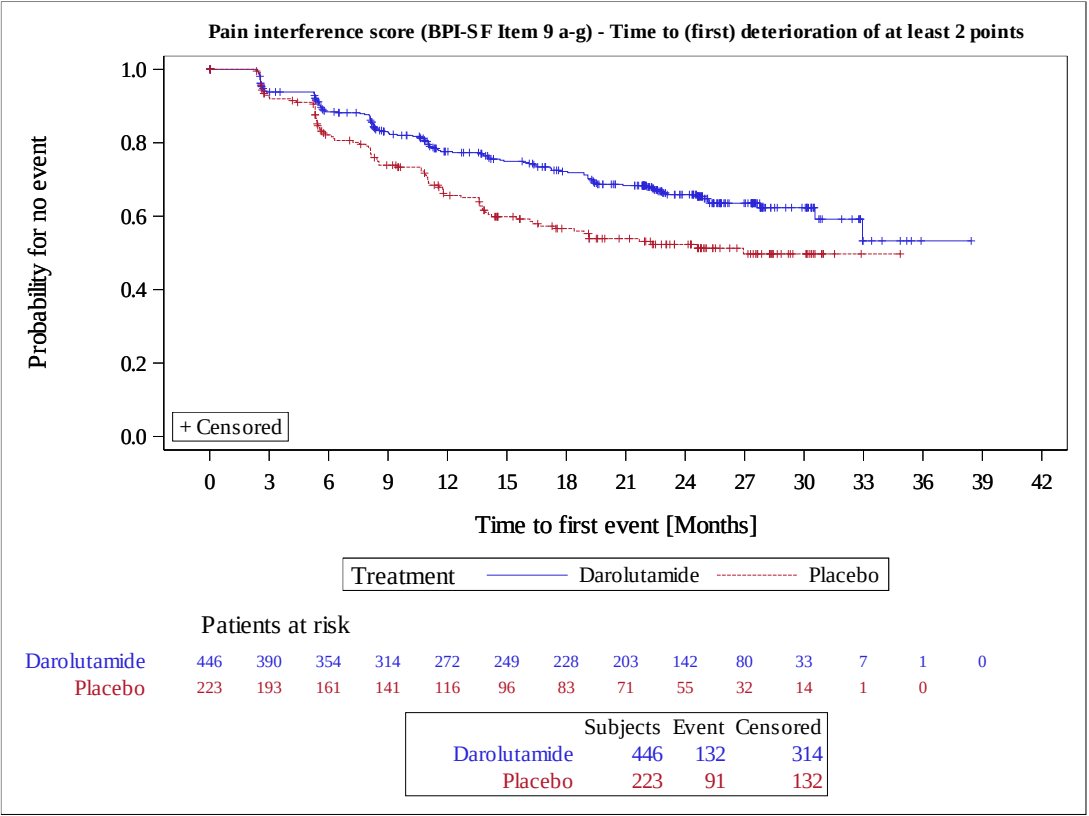
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Study population
Figure 2.1.12.2
Kaplan-Meier Plot of Pain interference score (BPI-SF Item 9 a-g) - Time to (first) deterioration of at least 2 points
(full analysis set)

Final

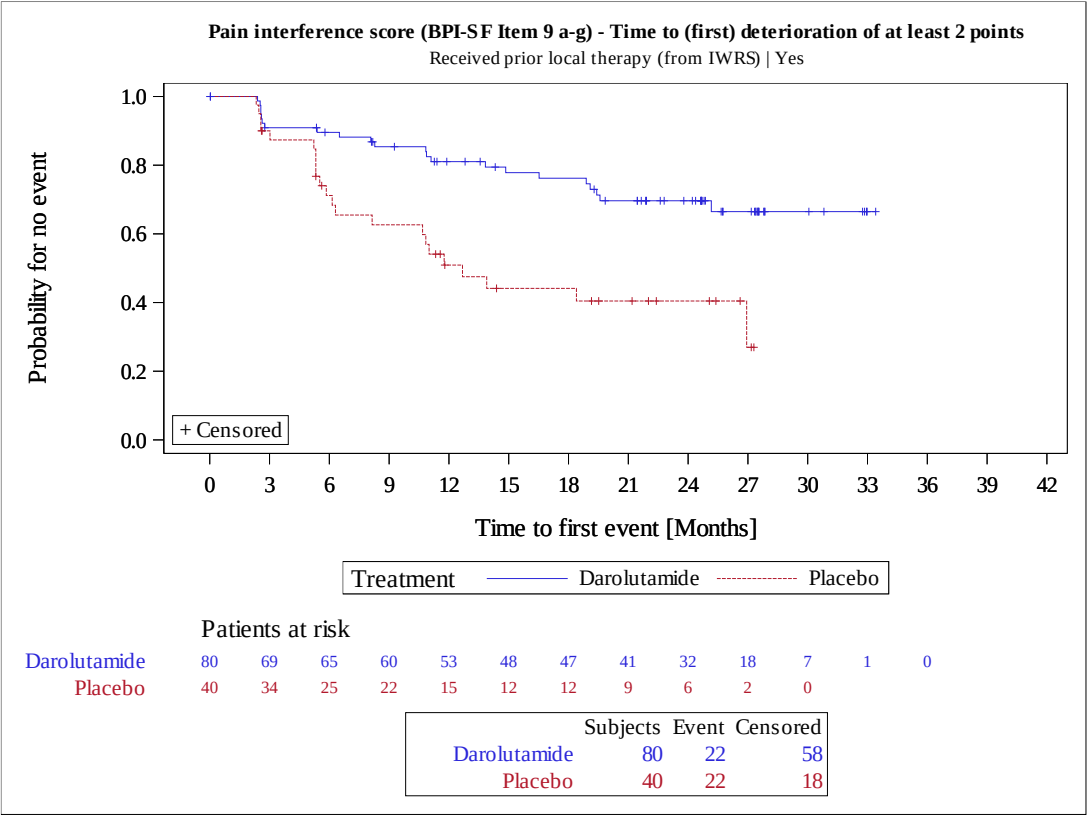


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Kaplan-Meier Plot of Pain interference score (BPI-SF Item 9 a-g) - Time to (first) deterioration of at least 2 points
(full analysis set)

Final

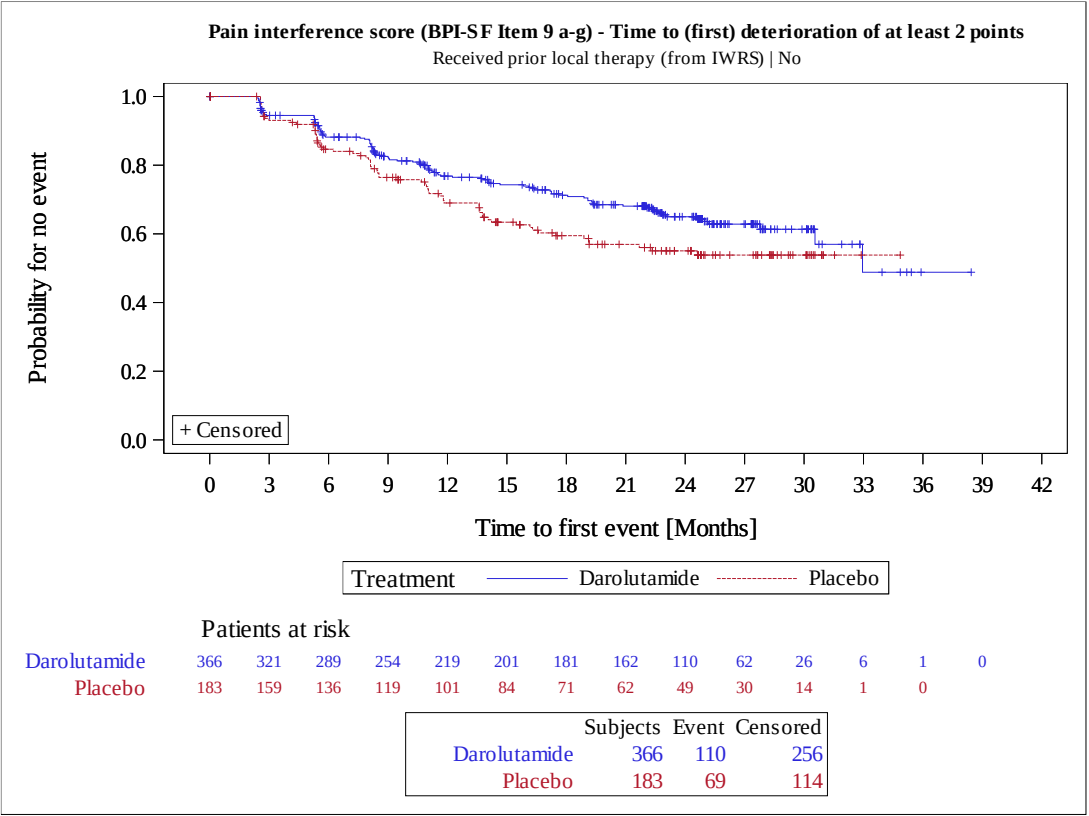


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Figure 2.1.12.2
Kaplan-Meier Plot of Pain interference score (BPI-SF Item 9 a-g) - Time to (first) deterioration of at least 2 points
(full analysis set)

Final

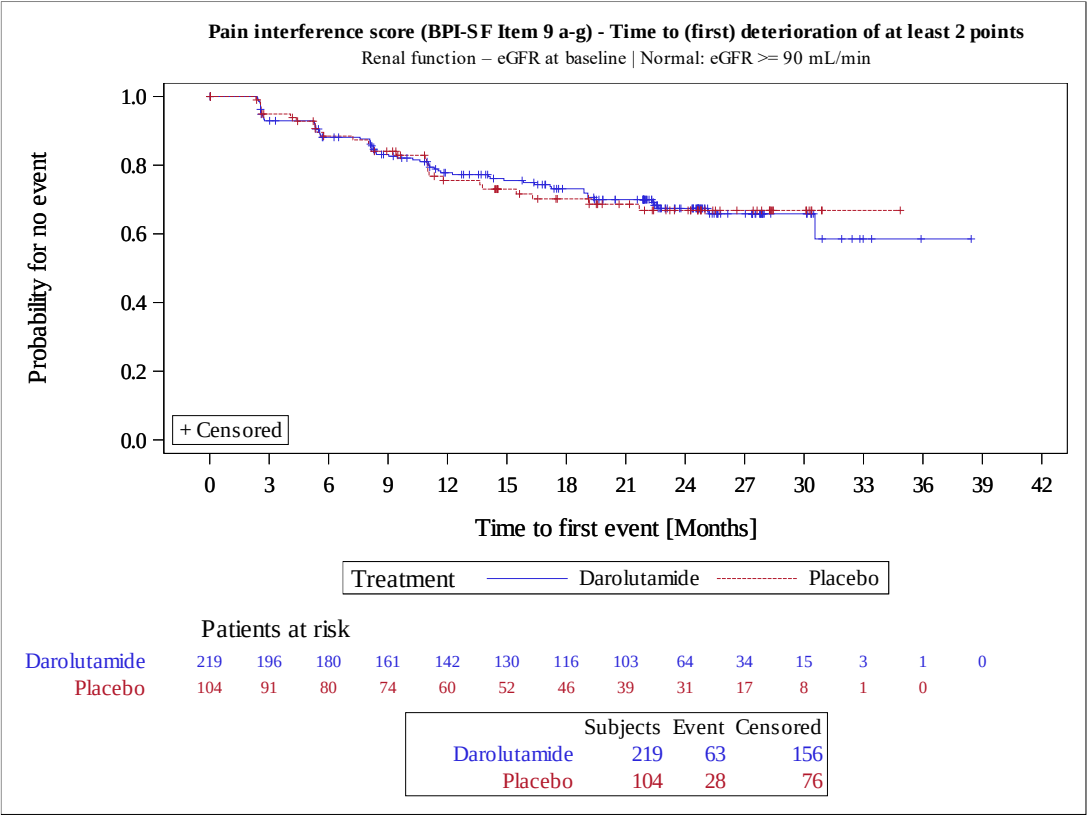


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

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Study population
Figure 2.1.12.2
Kaplan-Meier Plot of Pain interference score (BPI-SF Item 9 a-g) - Time to (first) deterioration of at least 2 points
(full analysis set)

Final

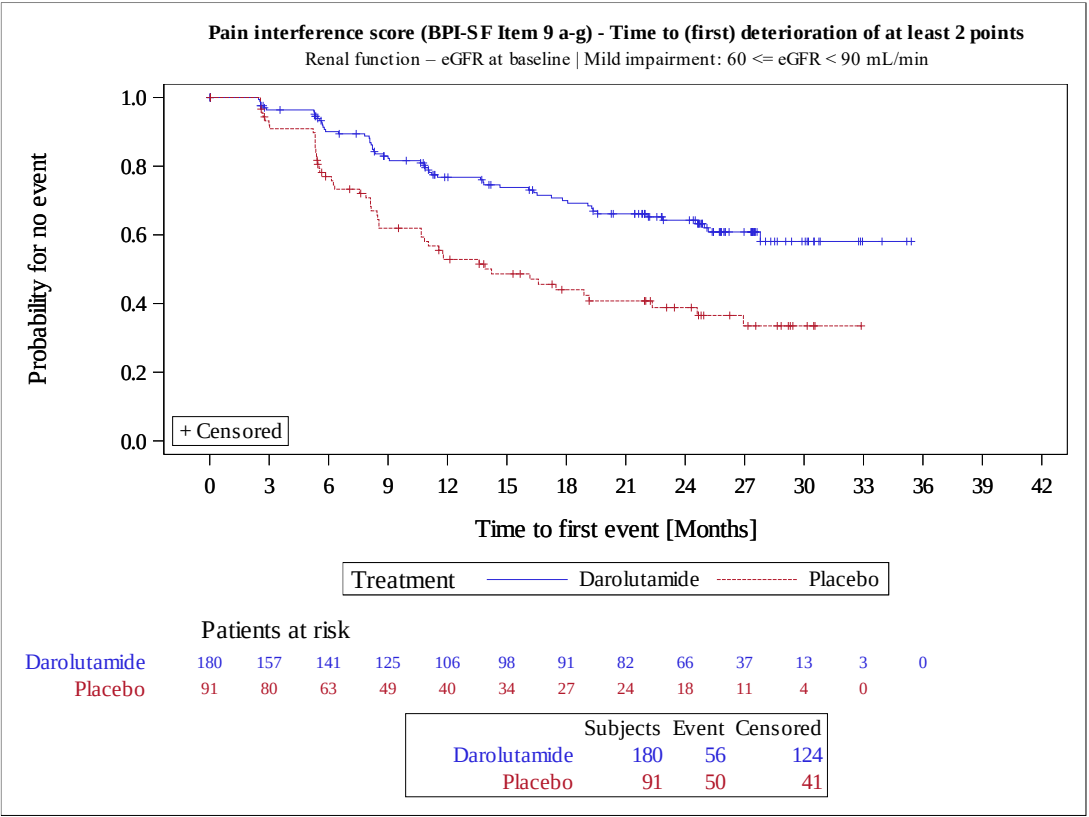


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 2.1.12.2
Kaplan-Meier Plot of Pain interference score (BPI-SF Item 9 a-g) - Time to (first) deterioration of at least 2 points
(full analysis set)

Final

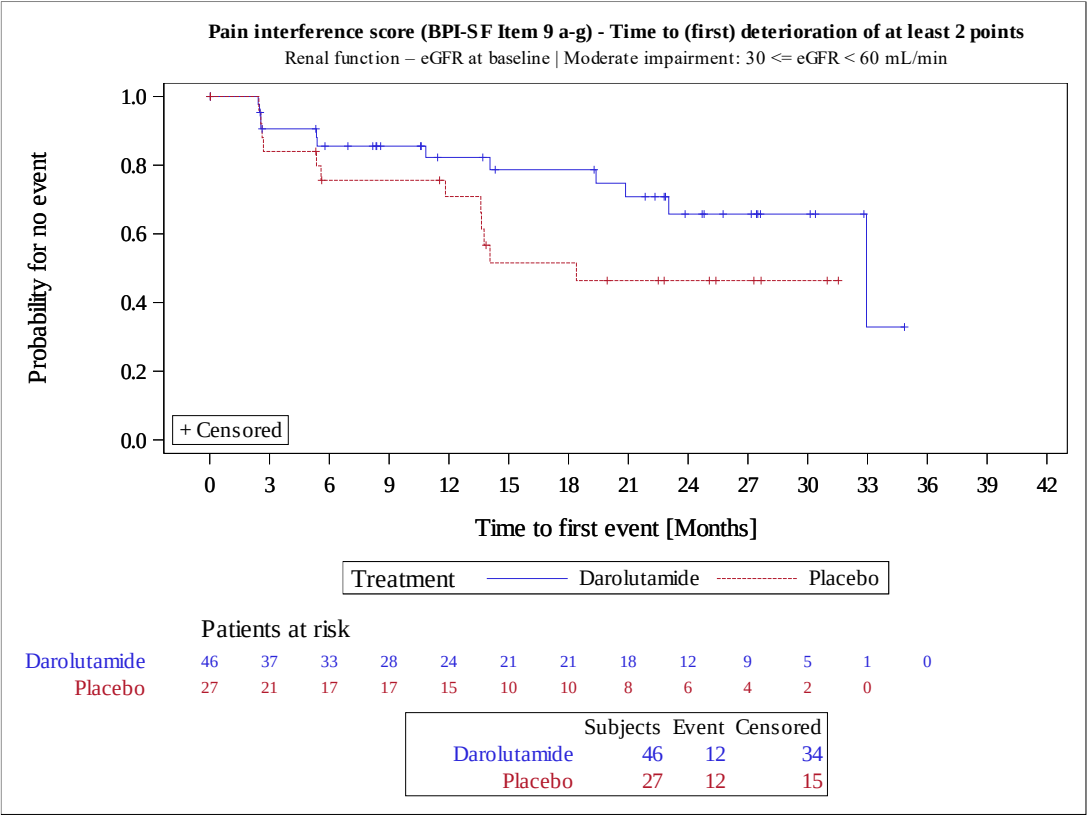


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Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 2.1.12.2
Kaplan-Meier Plot of Pain interference score (BPI-SF Item 9 a-g) - Time to (first) deterioration of at least 2 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 2.1.13

FACT-P total score - Time to deterioration of at least 10 points

(full analysis set)

Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	236 (52.9)	136 (61.0)
Number of censored participants, n (%)	210 (47.1)	87 (39.0)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	5.7 (5.5, 6.2)	5.3 (2.9, 5.6)
Median (95%-CI)	16.6 (12.5, 19.5)	11.5 (8.6, 14.0)
75%-ile (95%-CI)	NE (NE, NE)	28.3 (25.0, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.756 (0.612, 0.935)	
p-value [4]	0.0090	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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BAY 1841788 / 21140 - 07JUN2024											Final
Study population											
Table 2.1.13.1											
FACT-P total score - Time to deterioration of at least 10 points - Subgroup analysis											
(full analysis set)											
Subgroup Level	Darolutamide(N=446)				Placebo(N=223)				Unstratified Analysis		
	n/N[s]	(%)	Median	(95% CI) [1]	n/N[s]	(%)	Median	(95% CI) [1]	Hazard Ratio	(95% CI) [2]	p-Value [3] Interaction p-Value[4]
Presence of visceral metastases assessed by central review (from IWRS)											
Yes	27/	53	(50.9)	14.8 (11.2, NE)	16/	27	(59.3)	8.4 (5.6, 25.0)	0.682 (0.367, 1.270)		0.7672
No	209/	393	(53.2)	16.7 (11.7, 22.3)	120/	196	(61.2)	12.0 (9.3, 16.4)	0.766 (0.611, 0.959)		
Received prior local therapy (from IWRS)											
Yes	50/	80	(62.5)	11.5 (5.7, 16.9)	27/	40	(67.5)	10.9 (5.6, 16.8)	0.877 (0.548, 1.402)		0.5388
No	186/	366	(50.8)	17.2 (13.5, 24.1)	109/	183	(59.6)	12.2 (9.3, 16.4)	0.731 (0.577, 0.927)		
Prior local radiotherapy and/or prostatectomy											
Yes	55/	87	(63.2)	11.5 (6.2, 16.6)	29/	50	(58.0)	12.0 (6.3, 21.1)	1.145 (0.730, 1.796)		0.0389
No	181/	359	(50.4)	17.8 (13.5, 24.7)	107/	173	(61.8)	11.4 (8.3, 14.4)	0.676 (0.532, 0.859)		
Age group											
<65 years	62/	118	(52.5)	16.8 (11.4, 25.0)	38/	65	(58.5)	11.2 (6.3, 21.9)	0.697 (0.465, 1.046)		0.9154
65-74	100/	193	(51.8)	17.1 (11.5, 28.0)	59/	96	(61.5)	12.0 (8.3, 17.1)	0.760 (0.551, 1.049)		
75-84	63/	117	(53.8)	16.6 (10.8, 23.1)	31/	52	(59.6)	12.7 (8.3, 25.1)	0.855 (0.556, 1.315)		
>=85 years	11/	18	(61.1)	9.9 (5.5, NE)	8/	10	(80.0)	8.1 (2.7, 16.8)	0.624 (0.246, 1.585)		
Race											
White	134/	251	(53.4)	16.6 (11.2, 22.4)	81/	125	(64.8)	11.2 (7.4, 13.8)	0.719 (0.545, 0.948)		0.0810
Asian	76/	144	(52.8)	15.5 (11.4, 24.5)	32/	65	(49.2)	18.6 (11.2, NE)	1.070 (0.708, 1.617)		
Black or African American	20/	41	(48.8)	24.1 (16.6, NE)	18/	24	(75.0)	5.7 (2.8, 13.8)	0.381 (0.199, 0.727)		
Other	6/	10	(60.0)	17.1 (5.6, NE)	5/	9	(55.6)	16.6 (2.9, NE)	0.929 (0.279, 3.094)		
Geographical region											
Asia	73/	141	(51.8)	16.0 (11.5, 24.5)	31/	63	(49.2)	18.6 (9.3, NE)	1.026 (0.674, 1.562)		0.1043
Latin America	61/	119	(51.3)	19.5 (11.6, 28.0)	50/	72	(69.4)	8.4 (5.7, 13.8)	0.552 (0.379, 0.803)		
Europe and Rest of the world	102/	186	(54.8)	14.7 (11.0, 24.7)	55/	88	(62.5)	11.4 (7.8, 16.5)	0.788 (0.567, 1.094)		
Baseline PSA values by median											
< median of overall population	124/	216	(57.4)	12.5 (11.0, 19.4)	70/	111	(63.1)	12.0 (8.5, 17.1)	0.854 (0.637, 1.146)		0.1985
>= median of overall population	108/	220	(49.1)	17.2 (14.7, 28.1)	65/	108	(60.2)	11.0 (6.7, 13.8)	0.650 (0.478, 0.885)		
ECOG PS at baseline											
=0	129/	235	(54.9)	16.6 (11.4, 19.5)	59/	98	(60.2)	11.5 (8.3, 16.8)	0.856 (0.629, 1.165)		0.2810
>=1	107/	211	(50.7)	17.1 (11.6, 25.0)	77/	125	(61.6)	11.4 (8.1, 15.6)	0.672 (0.501, 0.901)		
Gleason score at initial diagnosis											
Gleason <8	65/	122	(53.3)	12.5 (8.0, NE)	42/	67	(62.7)	11.5 (6.3, 16.8)	0.849 (0.576, 1.252)		0.6411
Gleason >=8	167/	311	(53.7)	16.6 (11.7, 22.3)	90/	146	(61.6)	11.4 (8.3, 16.4)	0.743 (0.575, 0.961)		
Disease volume at baseline											
high	169/	315	(53.7)	16.3 (11.5, 19.5)	95/	157	(60.5)	11.2 (8.1, 13.8)	0.742 (0.577, 0.954)		0.8262
low	67/	131	(51.1)	18.3 (12.5, NE)	41/	66	(62.1)	13.8 (11.0, 24.8)	0.787 (0.533, 1.162)		
Renal function - eGFR at baseline											
Normal: eGFR >= 90 mL/min	115/	219	(52.5)	16.9 (13.8, 25.4)	55/	104	(52.9)	15.6 (11.2, 21.9)	0.851 (0.617, 1.174)		0.5806
Mild impairment: 60 <= eGFR < 90 mL/min	104/	180	(57.8)	11.7 (9.2, 19.3)	66/	91	(72.5)	8.5 (7.3, 11.4)	0.702 (0.515, 0.958)		
Moderate impairment: 30 <= eGFR < 60 mL/min	16/	46	(34.8)	NE (11.6, NE)	14/	27	(51.9)	23.4 (2.9, NE)	0.648 (0.316, 1.330)		

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;
IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.
[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
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Study population

Table 2.1.13.1

FACT-P total score - Time to deterioration of at least 10 points - Subgroup analysis (full analysis set)

Final

Subgroup Level	Darolutamide(N=446)		Placebo(N=223)		Unstratified Analysis		p-Value [3]	Interaction p-Value[4]	
	n/N[s] (%)	Median (95% CI) [1]	n/N[s] (%)	Median (95% CI) [1]	Hazard Ratio (95% CI) [2]				
Hepatic function at baseline									
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	206/ 387	(53.2) 16.8 (13.5, 19.7)	128/ 204	(62.7) 11.2 (8.5, 14.0)	0.724 (0.581, 0.904)	0.0039	0.2319		
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	30/ 59	(50.8) 11.7 (8.3, NE)	8/ 19	(42.1) 13.8 (5.4, NE)	1.146 (0.525, 2.504)	0.7306			
Age Group (Titan)									
<65	62/ 118	(52.5) 16.8 (11.4, 25.0)	38/ 65	(58.5) 11.2 (6.3, 21.9)	0.697 (0.465, 1.046)	0.0779	0.8988		
>=65 and <75	100/ 193	(51.8) 17.1 (11.5, 28.0)	59/ 96	(61.5) 12.0 (8.3, 17.1)	0.760 (0.551, 1.049)	0.0918			
>=75	74/ 135	(54.8) 16.3 (10.8, 22.3)	39/ 62	(62.9) 12.2 (7.8, 16.8)	0.805 (0.546, 1.188)	0.2706			
Geographic region (Titan)									
Europe and north america	74/ 145	(51.0) 16.8 (11.3, NE)	49/ 77	(63.6) 11.4 (7.8, 16.5)	0.677 (0.471, 0.972)	0.0317	0.4058		
ROTW	162/ 301	(53.8) 16.3 (11.6, 19.7)	87/ 146	(59.6) 11.5 (8.4, 16.6)	0.803 (0.618, 1.042)	0.0958			

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate; AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate; IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Participants without event are censored at last assessment date or randomization date if there is no follow-up available.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

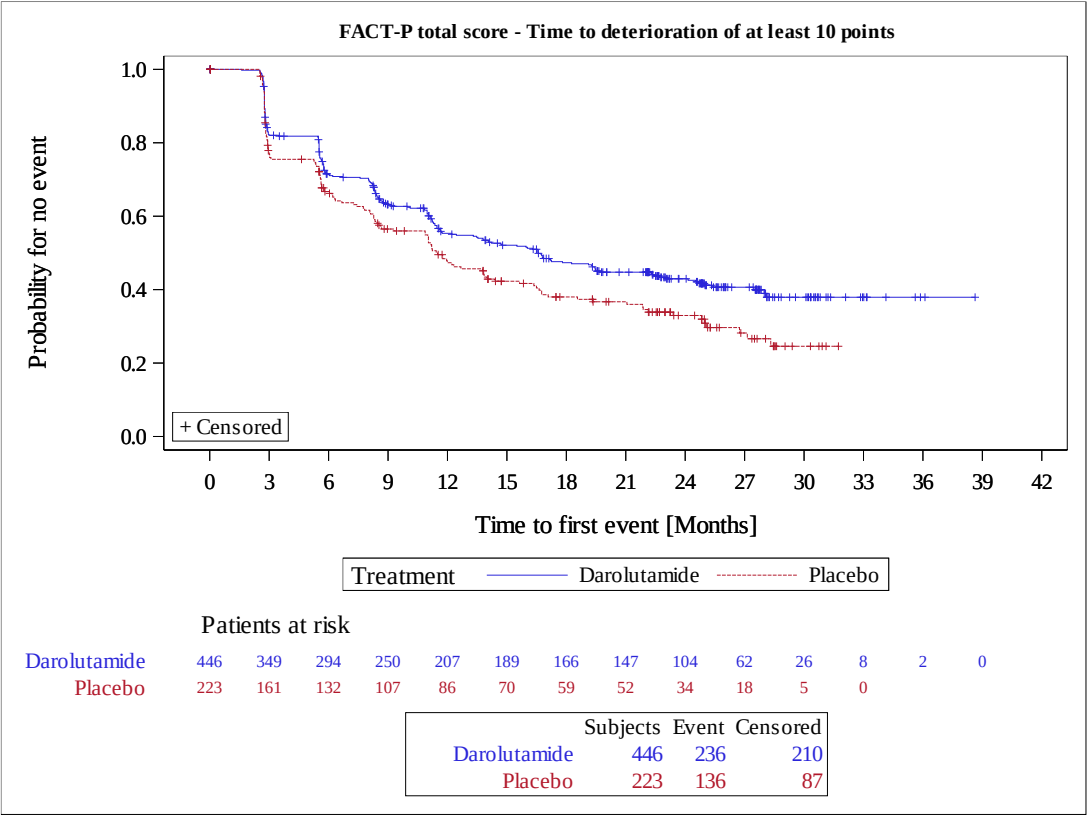
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.13.2
Kaplan-Meier Plot of FACT-P total score - Time to deterioration of at least 10 points
(full analysis set)

Final

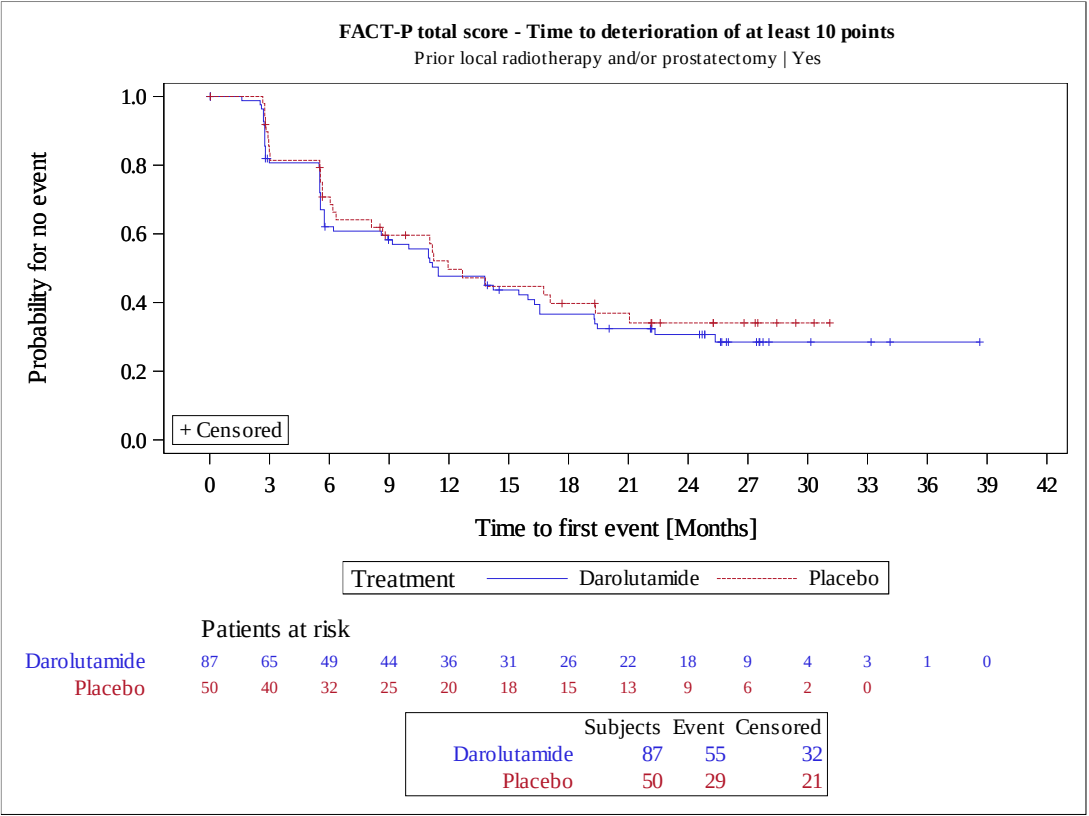


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Study population
Figure 2.1.13.2
Kaplan-Meier Plot of FACT-P total score - Time to deterioration of at least 10 points
(full analysis set)

Final

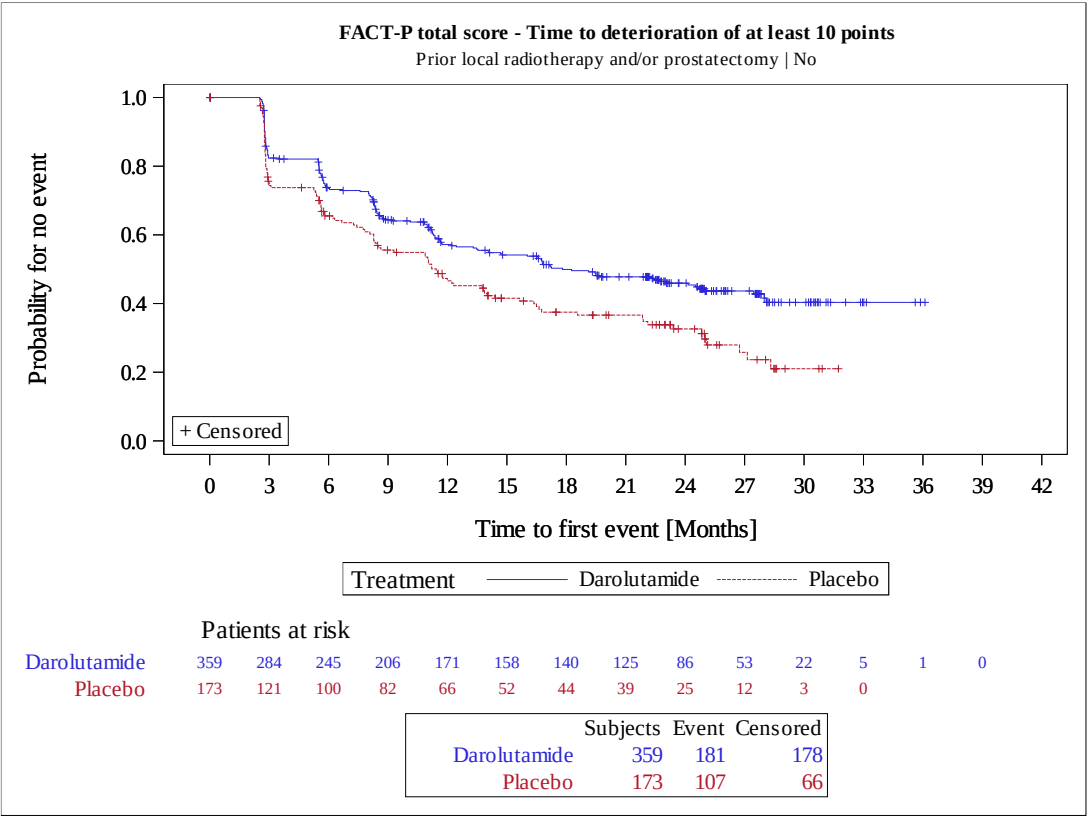


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 2.1.13.2
Kaplan-Meier Plot of FACT-P total score - Time to deterioration of at least 10 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 2.1.14

FACT-P Physical Well-Being score - Time to deterioration of at least 3 points

(full analysis set)

Final

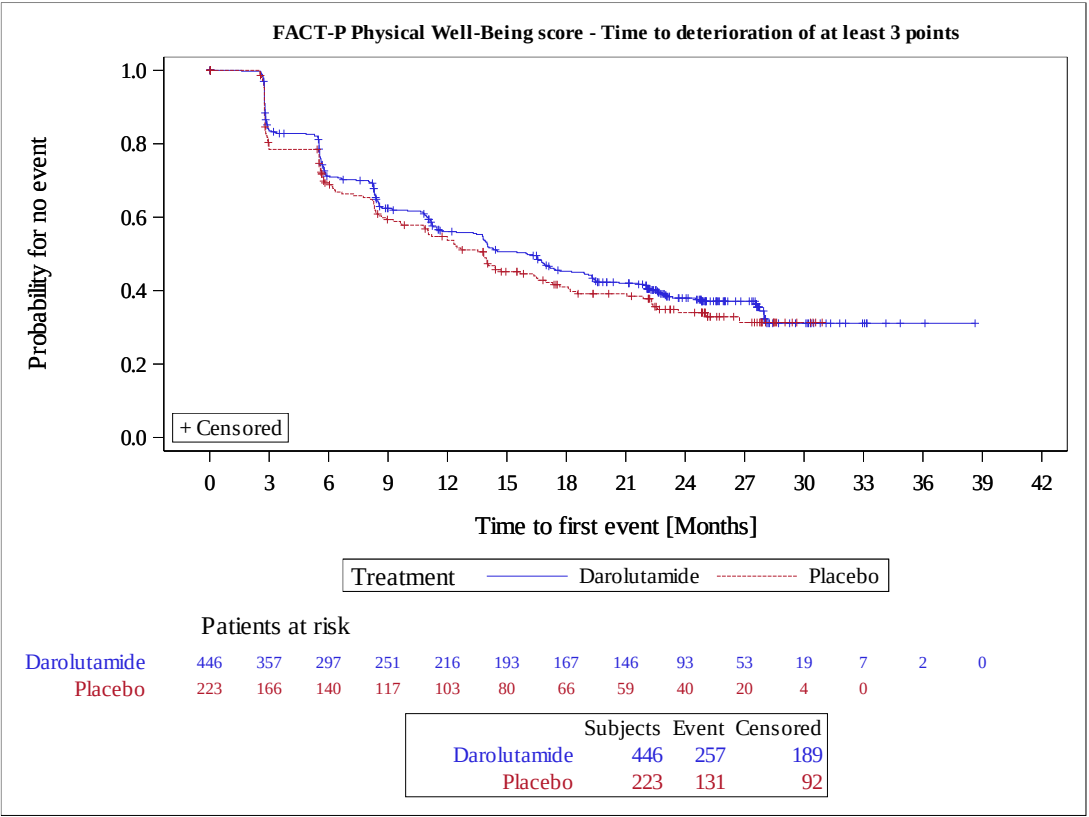
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	257 (57.6)	131 (58.7)
Number of censored participants, n (%)	189 (42.4)	92 (41.3)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	5.6 (5.5, 6.5)	5.5 (2.9, 6.0)
Median (95%-CI)	16.0 (13.8, 18.3)	13.8 (10.9, 16.6)
75%-ile (95%-CI)	NE (NE, NE)	NE (26.7, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.884 (0.716, 1.091)	
p-value [4]	0.2474	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Study population
Figure 2.1.14.1
Kaplan-Meier Plot of FACT-P Physical Well-Being score - Time to deterioration of at least 3 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 2.1.15
FACT-P Social/Family Well- Being score - Time to deterioration of at least 3 points
(full analysis set)

Final

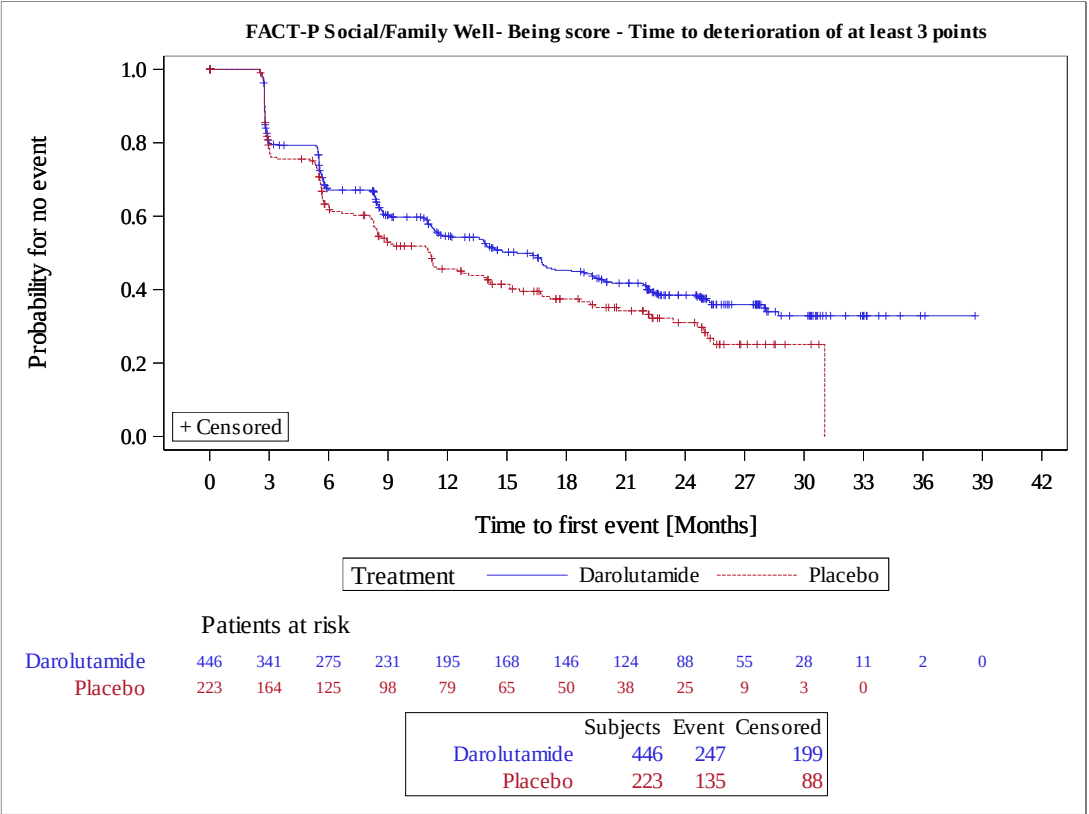
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	247 (55.4)	135 (60.5)
Number of censored participants, n (%)	199 (44.6)	88 (39.5)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	5.5 (5.4, 5.7)	5.3 (2.9, 5.6)
Median (95%-CI)	15.5 (11.6, 18.3)	11.1 (8.3, 14.0)
75%-ile (95%-CI)	NE (NE, NE)	31.0 (23.4, 31.0)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.804 (0.651, 0.993)	
p-value [4]	0.0401	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 2.1.15.1
Kaplan-Meier Plot of FACT-P Social/Family Well- Being score - Time to deterioration of at least 3 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 2.1.16

FACT-P Emotional Well-Being score - Time to deterioration of at least 3 points

(full analysis set)

Final

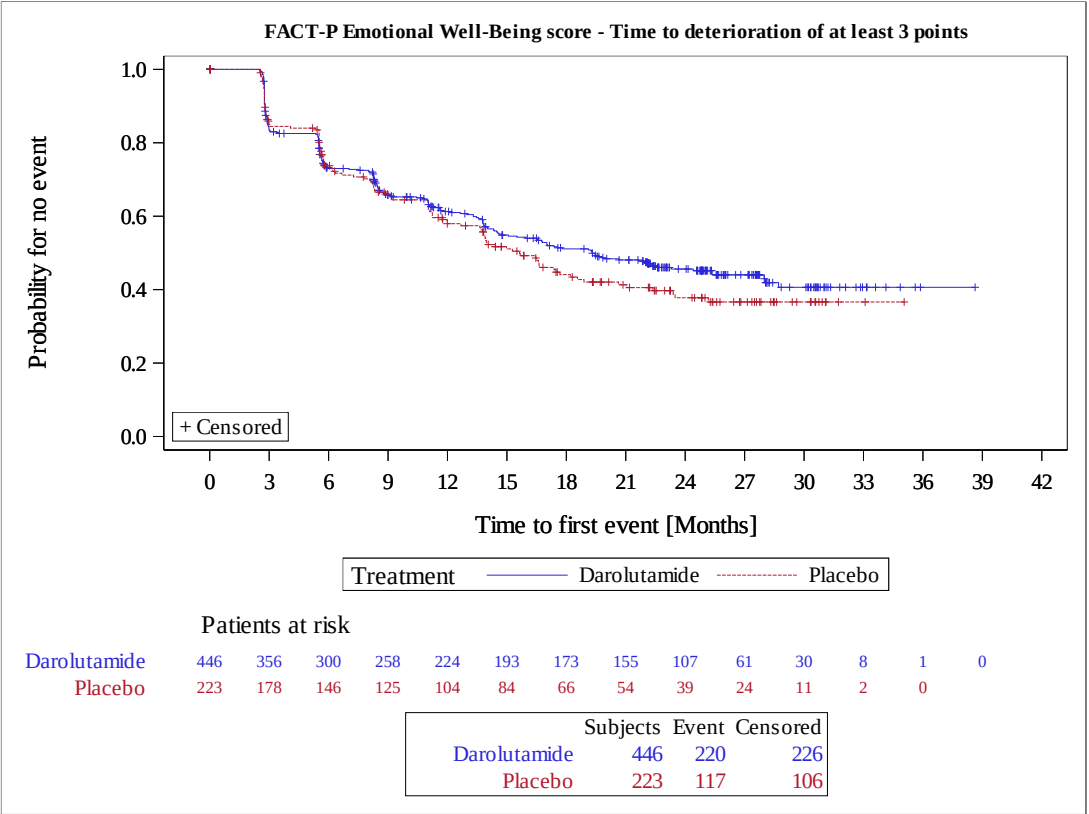
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	220 (49.3)	117 (52.5)
Number of censored participants, n (%)	226 (50.7)	106 (47.5)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	5.7 (5.5, 8.3)	5.7 (5.5, 8.1)
Median (95%-CI)	19.3 (14.8, 25.4)	15.6 (13.6, 18.6)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.982 (0.705, 1.105)	
p-value [4]	0.2715	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Study population
Figure 2.1.16.1
Kaplan-Meier Plot of FACT-P Emotional Well-Being score - Time to deterioration of at least 3 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Table 2.1.17

FACT-P Functional Well-Being score - Time to deterioration of at least 3 points

(full analysis set)

Final

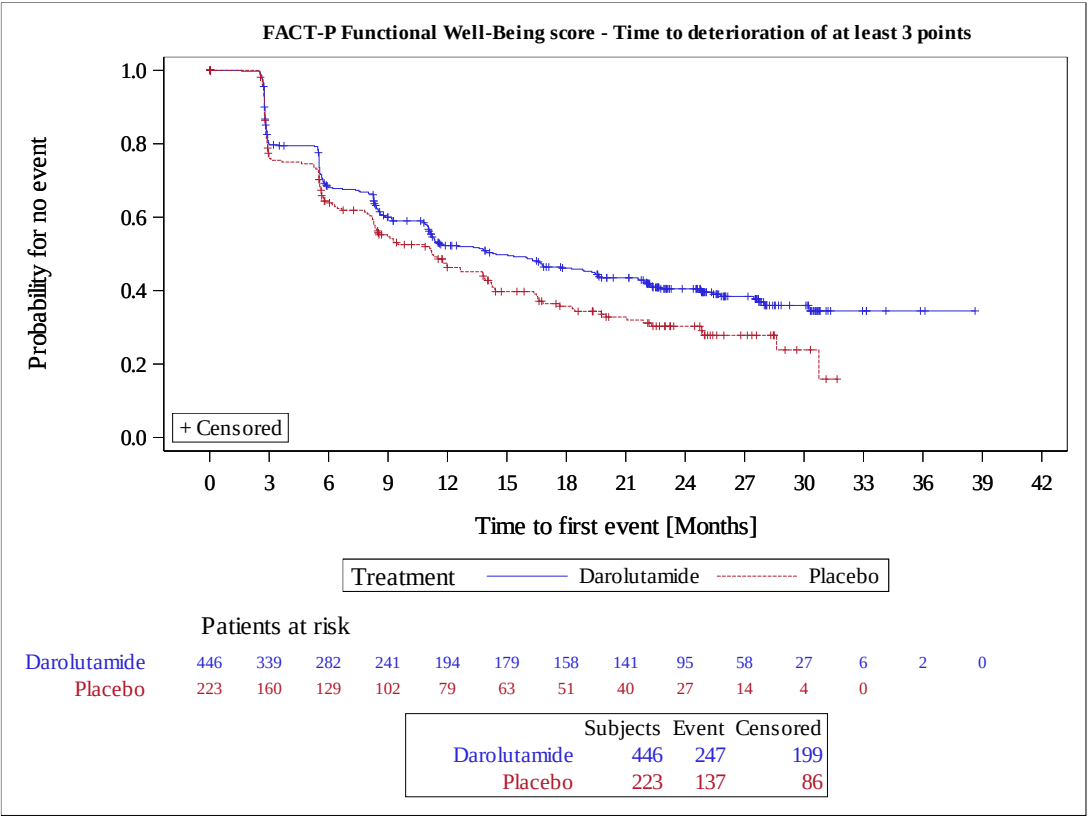
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	247 (55.4)	137 (61.4)
Number of censored participants, n (%)	199 (44.6)	86 (38.6)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	5.5 (5.5, 5.7)	4.6 (2.9, 5.6)
Median (95%-CI)	14.5 (11.2, 19.3)	11.2 (8.3, 13.9)
75%-ile (95%-CI)	NE (NE, NE)	28.6 (21.9, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.779 (0.631, 0.961)	
p-value [4]	0.0185	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate; Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Figure 2.1.17.1
Kaplan-Meier Plot of FACT-P Functional Well-Being score - Time to deterioration of at least 3 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 2.1.18
FACT-P Prostate cancer subscale score - Time to deterioration of at least 3 points
(full analysis set)

Final

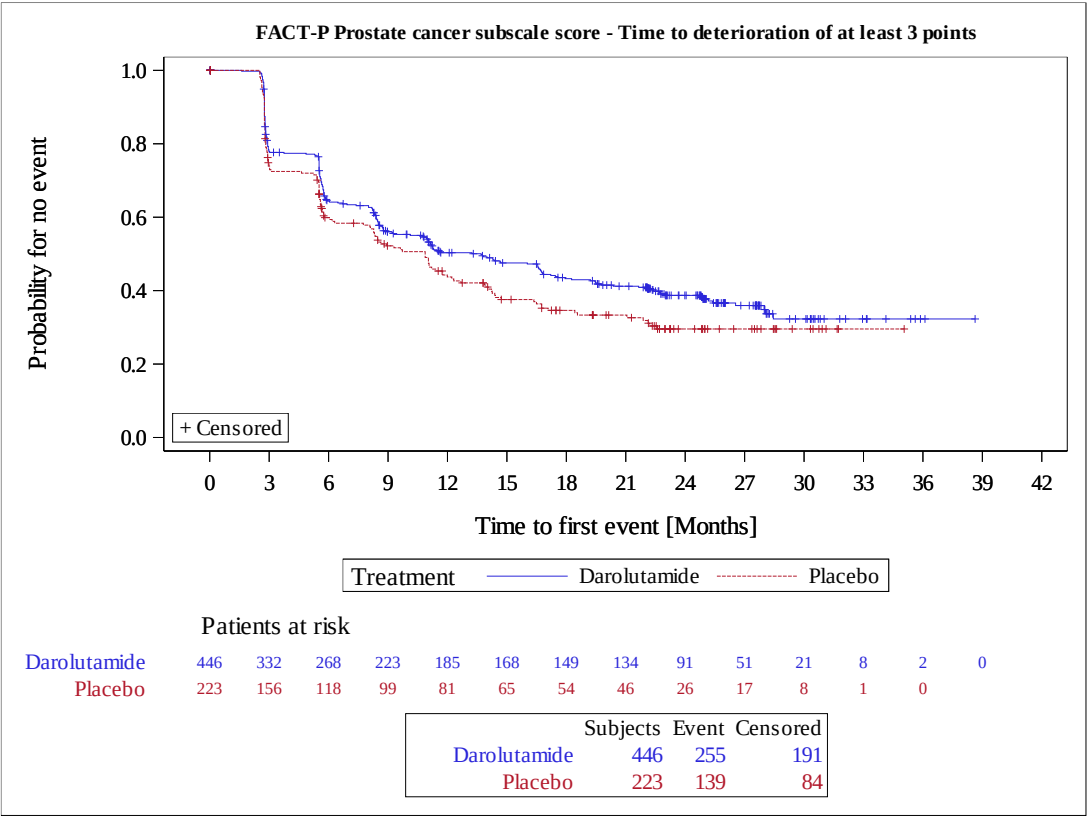
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	255 (57.2)	139 (62.3)
Number of censored participants, n (%)	191 (42.8)	84 (37.7)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	5.5 (3.0, 5.6)	3.0 (2.8, 5.5)
Median (95%-CI)	13.7 (10.7, 16.8)	10.9 (8.1, 12.2)
75%-ile (95%-CI)	NE (NE, NE)	NE (22.1, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.823 (0.669, 1.013)	
p-value [4]	0.0629	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Study population
Figure 2.1.18.1
Kaplan-Meier Plot of FACT-P Prostate cancer subscale score - Time to deterioration of at least 3 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Study population

Table 2.1.19

FACT-P total score - Time to improvement of at least 10 points

(full analysis set)

Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	245 (54.9)	110 (49.3)
Number of censored participants, n (%)	201 (45.1)	113 (50.7)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	2.9 (2.9, 3.2)	2.9 (2.8, 5.3)
Median (95%-CI)	10.9 (8.3, 14.1)	15.2 (10.6, 30.6)
75%-ile (95%-CI)	NE (NE, NE)	33.1 (30.6, 33.1)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	1.080 (0.862, 1.353)	
p-value [4]	0.4986	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate; Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Study population

Table 2.1.19.1

FACT-P total score - Time to improvement of at least 10 points - Subgroup analysis
(full analysis set)

Final

Subgroup Level	Darolutamide(N=446)				Placebo(N=223)				Unstratified Analysis		p-Value [3]	Interaction p-Value[4]		
	n/N[s]	(%)	Median	(95% CI)[1]	n/N[s]	(%)	Median	(95% CI)[1]	Hazard Ratio	(95% CI)[2]				
Presence of visceral metastases assessed by central review (from IWRS)														
Yes	37/ 208	53/ 393	(69.8)	6.2	(2.9, 11.2)	11/ 99	27/ 196	(40.7)	19.7	(2.8, NE)	1.739	(0.885, 3.419)	0.0992	0.1425
No			(52.9)	11.0	(8.5, 17.2)			(50.5)	14.3	(8.5, 33.1)	1.010	(0.795, 1.283)	0.9348	
Received prior local therapy (from IWRS)														
Yes	40/ 205	80/ 366	(50.0)	14.0	(8.3, NE)	14/ 96	40/ 183	(35.0)	NE	(16.6, NE)	1.484	(0.807, 2.728)	0.1936	0.2639
No			(56.0)	9.2	(8.3, 13.2)			(52.5)	11.1	(8.3, 18.9)	1.018	(0.799, 1.297)	0.8857	
Prior local radiotherapy and/or prostatectomy														
Yes	46/ 199	87/ 359	(52.9)	9.0	(5.7, NE)	21/ 89	50/ 173	(42.0)	19.4	(11.4, NE)	1.364	(0.814, 2.285)	0.2286	0.2891
No			(55.4)	11.0	(8.3, 16.6)			(51.4)	11.1	(8.3, 22.3)	1.007	(0.785, 1.294)	0.9531	
Age group														
<65 years	65/ 112	118/ 193	(55.1)	11.0	(5.9, 23.3)	30/ 49	65/ 96	(46.2)	11.1	(5.4, NE)	1.039	(0.674, 1.602)	0.8609	0.8577
65-74			(58.0)	8.6	(5.8, 11.5)			(51.0)	16.7	(8.3, 33.1)	1.192	(0.852, 1.669)	0.2973	
75-84	61/ 7	117/ 18	(52.1)	13.9	(6.2, NE)	26/ 5	52/ 10	(50.0)	12.8	(5.6, 30.6)	1.001	(0.632, 1.585)	0.9970	
>=85 years			(38.9)	NE	(2.8, NE)			(50.0)	11.4	(2.8, NE)	0.763	(0.240, 2.423)	0.6374	
Race														
White	131/ 74	251/ 144	(52.2)	11.0	(8.5, 23.3)	58/ 37	125/ 65	(46.4)	16.6	(10.6, NE)	1.084	(0.796, 1.478)	0.6025	0.0328
Asian			(51.4)	13.9	(8.5, NE)			(56.9)	11.1	(3.0, 19.7)	0.817	(0.549, 1.218)	0.3146	
Black or African American	31/ 11	41/ 24	(75.6)	5.5	(2.8, 8.3)	11/ 24		(45.8)	30.6	(2.9, NE)	2.243	(1.096, 4.590)	0.0195	
Other	9/ 4	10/ 9	(90.0)	2.9	(2.8, 5.7)			(44.4)	NE	(2.5, NE)	2.814	(0.848, 9.332)	0.0733	
Geographical region														
Asia	73/ 83	141/ 119	(51.8)	13.9	(8.3, NE)	37/ 35	63/ 72	(58.7)	8.9	(3.0, 18.9)	0.790	(0.530, 1.178)	0.2404	0.0312
Latin America			(69.7)	5.6	(5.4, 8.3)			(48.6)	11.3	(5.7, NE)	1.626	(1.092, 2.421)	0.0137	
Europe and Rest of the world	89/ 88	186/ 88	(47.8)	22.0	(11.0, NE)	38/ 38		(43.2)	16.7	(11.1, NE)	1.044	(0.713, 1.529)	0.8189	
Baseline PSA values by median														
< median of overall population	113/ 127	216/ 220	(52.3)	12.2	(8.5, 27.4)	54/ 53	111/ 108	(48.6)	16.6	(8.4, 33.1)	1.062	(0.766, 1.472)	0.7138	0.6504
>= median of overall population			(57.7)	8.5	(5.9, 11.6)			(49.1)	15.2	(8.3, 30.6)	1.173	(0.852, 1.617)	0.3216	
ECOG PS at baseline														
=0	123/ 122	235/ 211	(52.3)	11.0	(8.4, 27.4)	49/ 61	98/ 125	(50.0)	16.6	(11.0, 33.1)	1.049	(0.753, 1.460)	0.7734	0.7606
>=1			(57.8)	9.0	(5.8, 13.0)			(48.8)	11.7	(6.0, NE)	1.127	(0.829, 1.532)	0.4399	
Gleason score at initial diagnosis														
Gleason <8	63/ 173	122/ 311	(51.6)	16.8	(9.7, 27.5)	31/ 76	67/ 146	(46.3)	19.4	(5.6, NE)	1.014	(0.660, 1.559)	0.9489	0.8577
Gleason >=8			(55.6)	8.9	(5.9, 14.0)			(52.1)	12.8	(8.4, 19.7)	1.071	(0.818, 1.403)	0.6111	
Disease volume at baseline														
high	173/ 72	315/ 131	(54.9)	9.5	(8.3, 16.6)	78/ 32	157/ 66	(49.7)	12.8	(8.5, 22.3)	1.058	(0.809, 1.382)	0.6765	0.7963
low			(55.0)	11.5	(8.3, 27.4)			(48.5)	18.9	(6.0, 33.1)	1.126	(0.742, 1.708)	0.5728	
Renal function - eGFR at baseline														
Normal: eGFR >= 90 mL/min	129/ 88	219/ 180	(58.9)	9.0	(8.0, 13.2)	56/ 39	104/ 91	(53.8)	11.0	(5.7, 18.9)	0.988	(0.722, 1.353)	0.9403	0.6473
Mild impairment: 60 <= eGFR < 90 mL/min			(48.9)	16.8	(8.7, NE)			(42.9)	30.6	(11.7, 33.1)	1.148	(0.787, 1.674)	0.4690	
Moderate impairment: 30 <= eGFR < 60 mL/min	28/ 14	46/ 27	(60.9)	5.7	(2.8, 16.8)			(51.9)	11.4	(2.8, NE)	1.328	(0.698, 2.525)	0.3723	

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;

AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;

IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Participants without event are censored at last assessment date or randomization date if there is no follow-up available.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 2.1.19.1
FACT-P total score - Time to improvement of at least 10 points - Subgroup analysis
(full analysis set)

Final

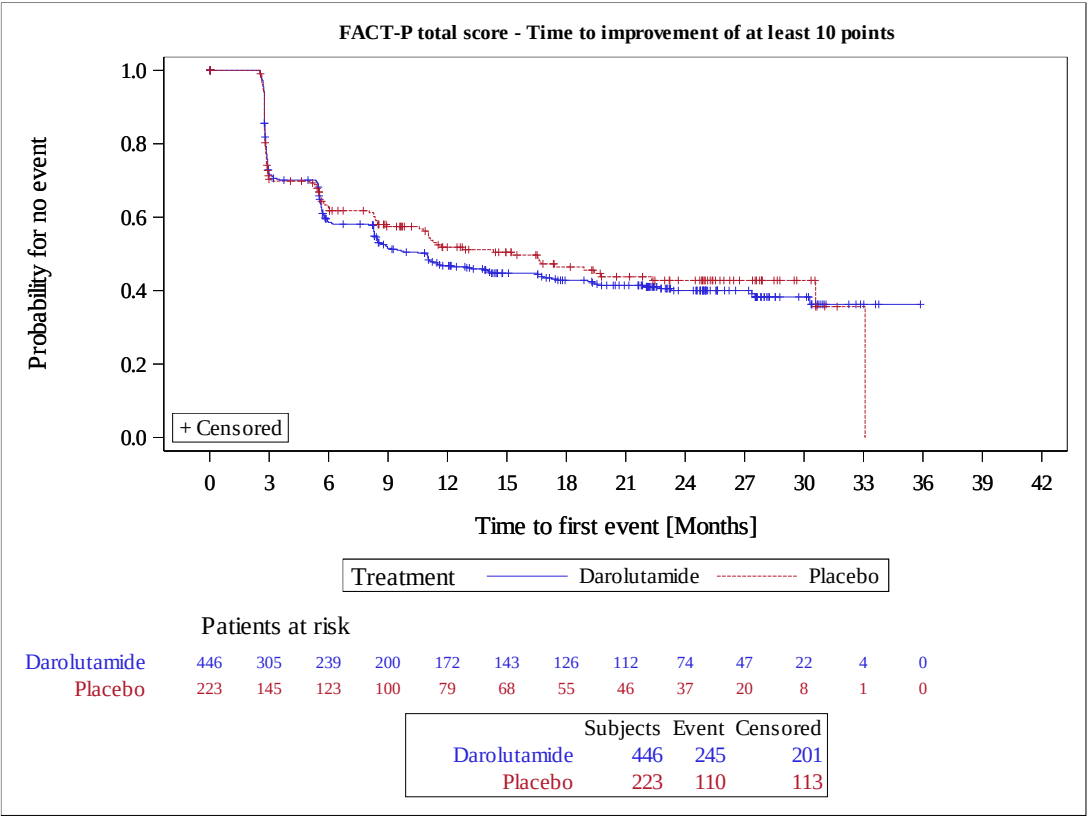
Subgroup Level	Darolutamide(N=446)		Placebo(N=223)		Unstratified Analysis		Hazard Ratio (95% CI) [2]	p-Value Interaction	
	n/N[s] (%)	Median (95% CI) [1]	n/N[s] (%)	Median (95% CI) [1]				[3]	p-Value[4]
Hepatic function at baseline									0.3836
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	216/ 387 (55.8)	10.9 (8.3, 14.0)	101/ 204 (49.5)	16.6 (10.8, 33.1)			1.114 (0.880, 1.411)	0.3624	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	29/ 59 (49.2)	11.0 (8.0, NE)	9/ 19 (47.4)	10.6 (3.0, NE)			0.753 (0.355, 1.599)	0.4512	
Age Group (Titan)									0.7610
<65	65/ 118 (55.1)	11.0 (5.9, 23.3)	30/ 65 (46.2)	11.1 (5.4, NE)			1.039 (0.674, 1.602)	0.8609	
>=65 and <75	112/ 193 (58.0)	8.6 (5.8, 11.5)	49/ 96 (51.0)	16.7 (8.3, 33.1)			1.192 (0.852, 1.669)	0.2973	
>=75	68/ 135 (50.4)	16.8 (8.3, NE)	31/ 62 (50.0)	12.8 (8.3, 30.6)			0.969 (0.633, 1.482)	0.8822	
Geographic region (Titan)									0.6869
Europe and north america	75/ 145 (51.7)	11.0 (8.3, NE)	35/ 77 (45.5)	16.6 (10.6, NE)			1.165 (0.780, 1.741)	0.4486	
ROTW	170/ 301 (56.5)	9.7 (8.3, 14.2)	75/ 146 (51.4)	11.3 (6.0, 30.6)			1.049 (0.798, 1.378)	0.7267	

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate; AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate; IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.
[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.19.2
Kaplan-Meier Plot of FACT-P total score - Time to improvement of at least 10 points
(full analysis set)

Final

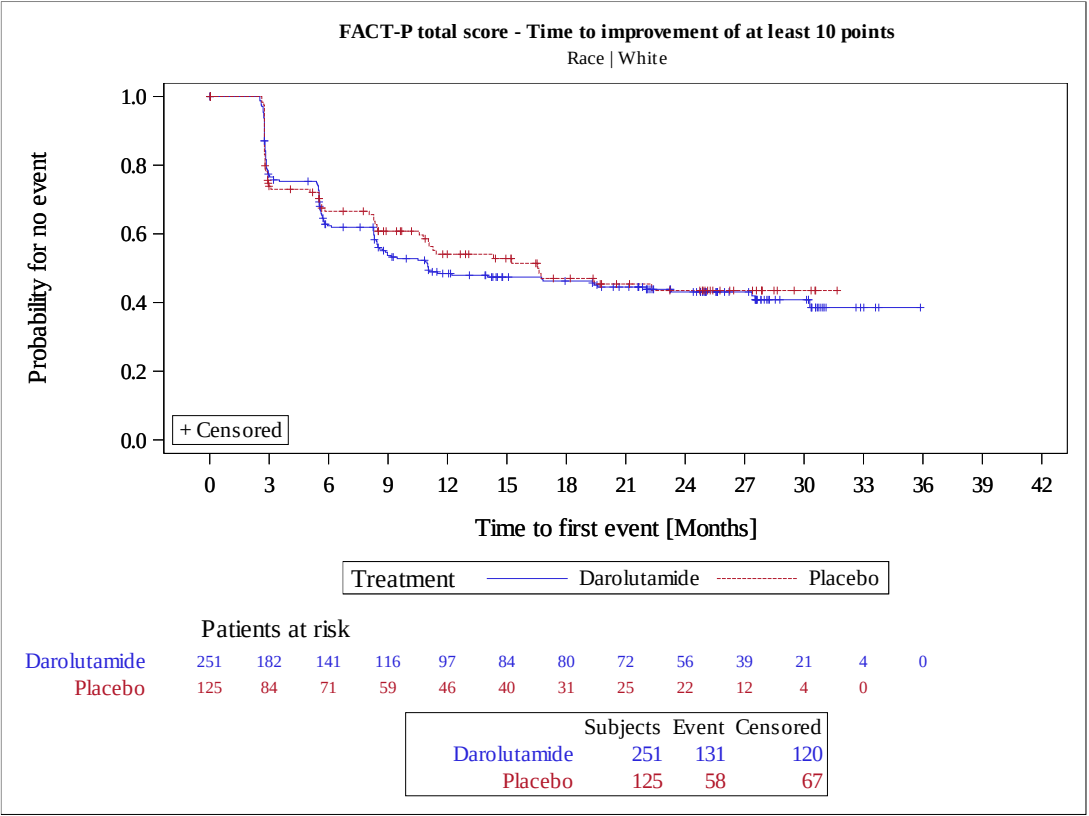


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.19.2
Kaplan-Meier Plot of FACT-P total score - Time to improvement of at least 10 points
(full analysis set)

Final

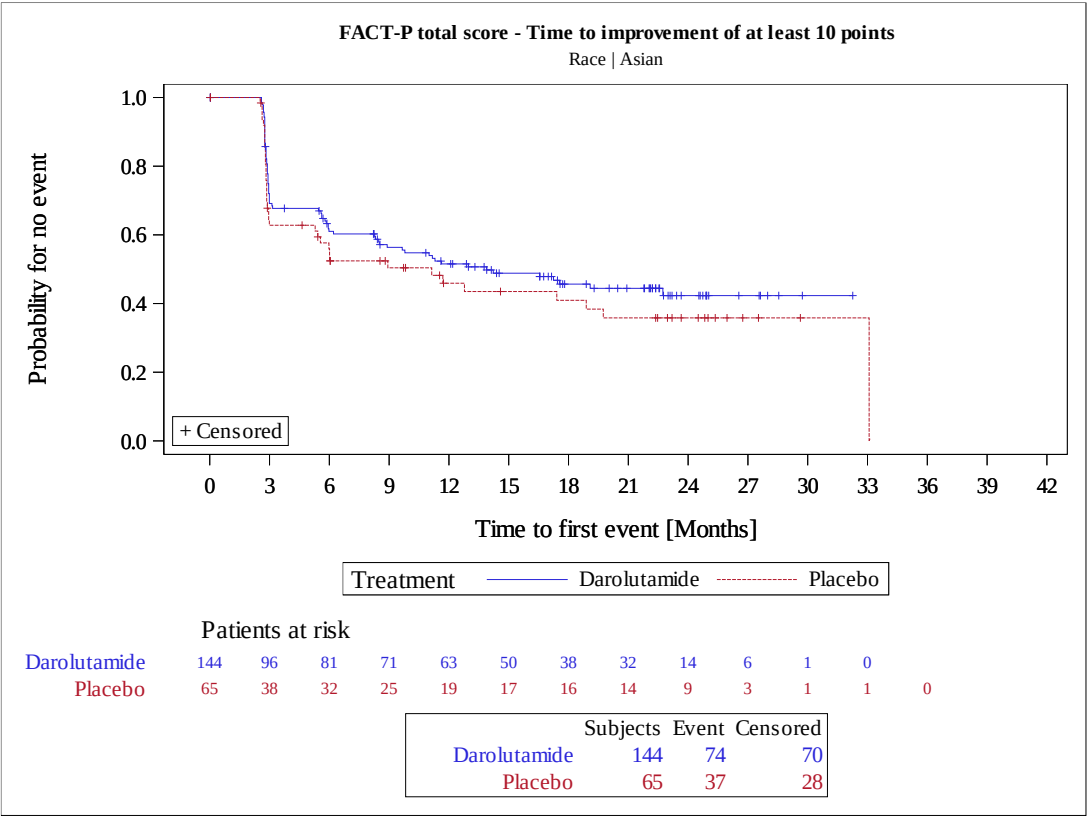


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.19.2
Kaplan-Meier Plot of FACT-P total score - Time to improvement of at least 10 points
(full analysis set)

Final

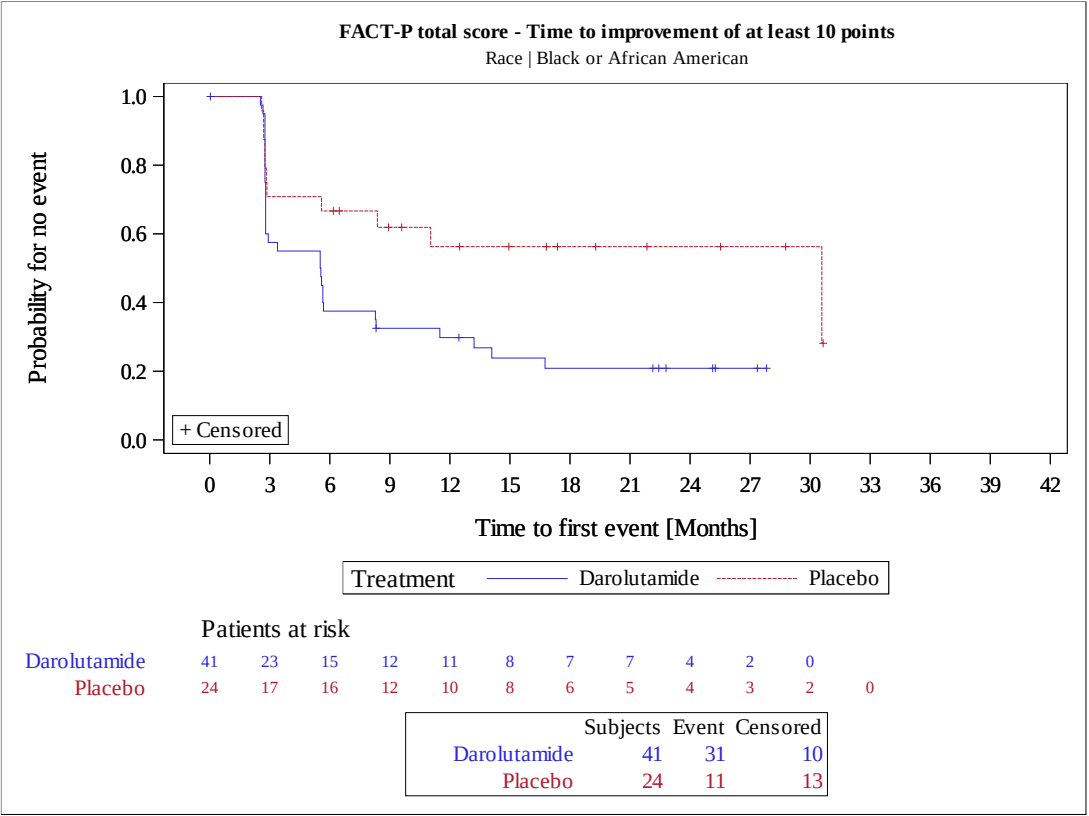


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.19.2
Kaplan-Meier Plot of FACT-P total score - Time to improvement of at least 10 points
(full analysis set)

Final

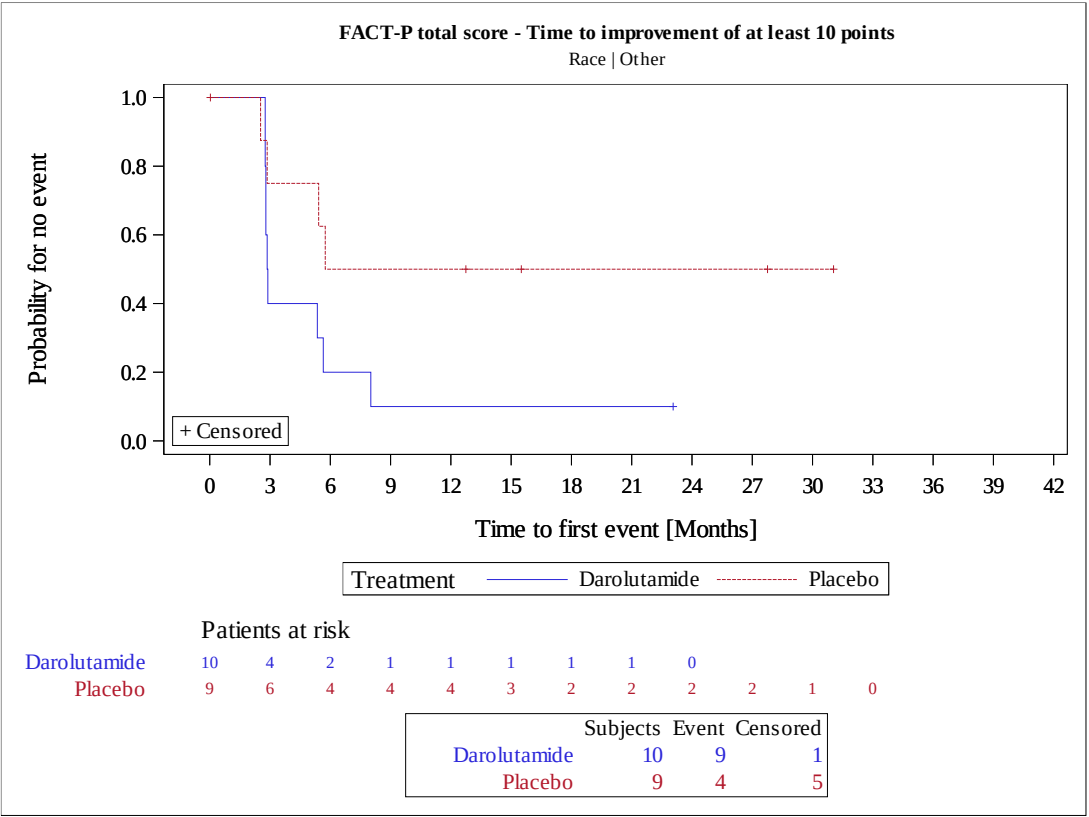


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.19.2
Kaplan-Meier Plot of FACT-P total score - Time to improvement of at least 10 points
(full analysis set)

Final

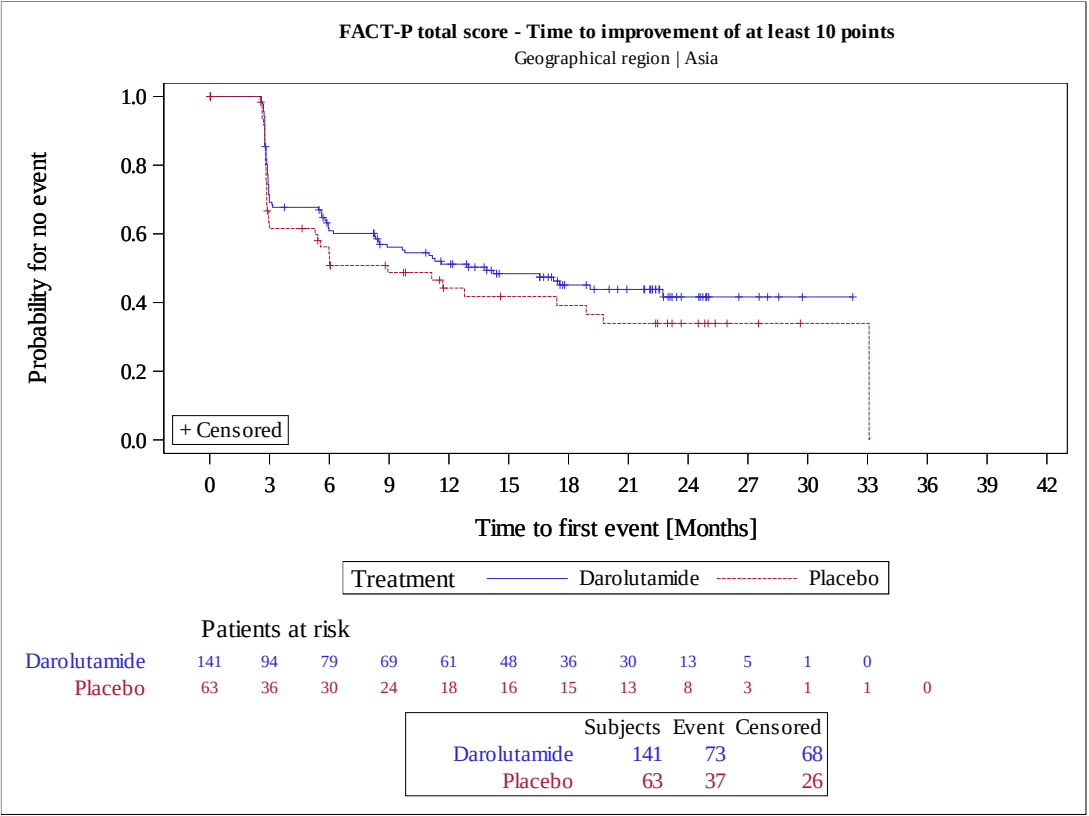


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.19.2
Kaplan-Meier Plot of FACT-P total score - Time to improvement of at least 10 points
(full analysis set)

Final

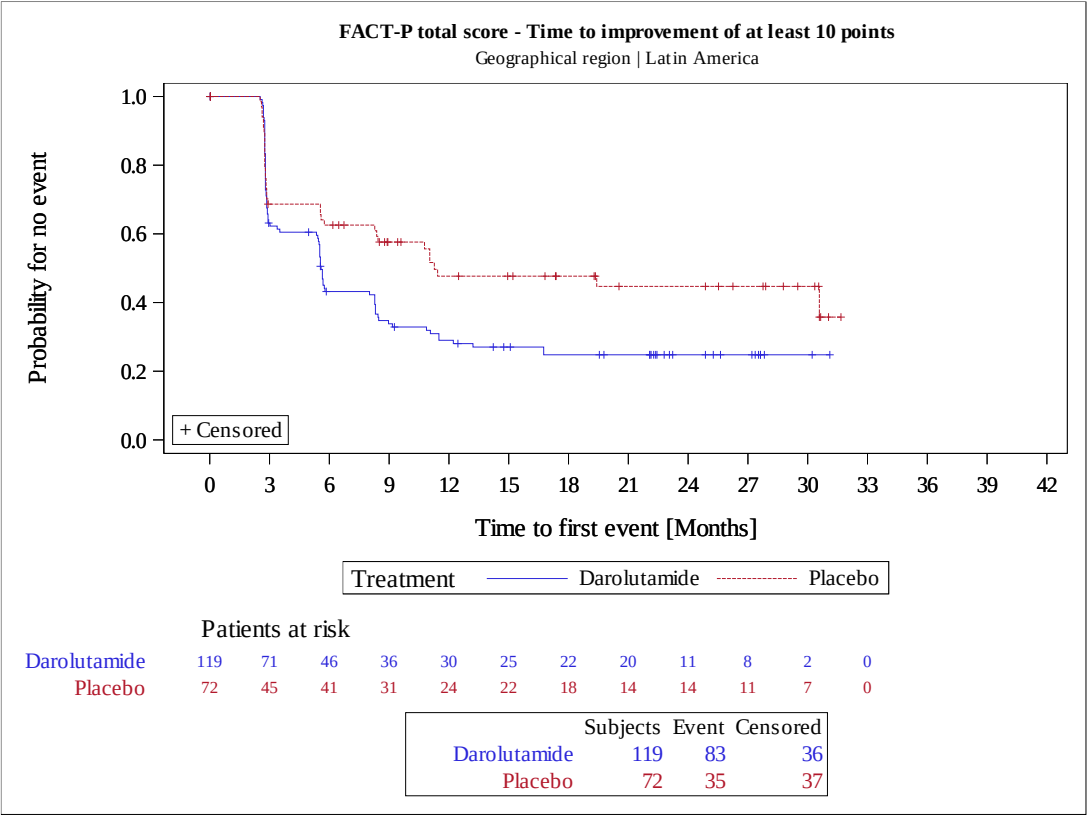


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.19.2
Kaplan-Meier Plot of FACT-P total score - Time to improvement of at least 10 points
(full analysis set)

Final

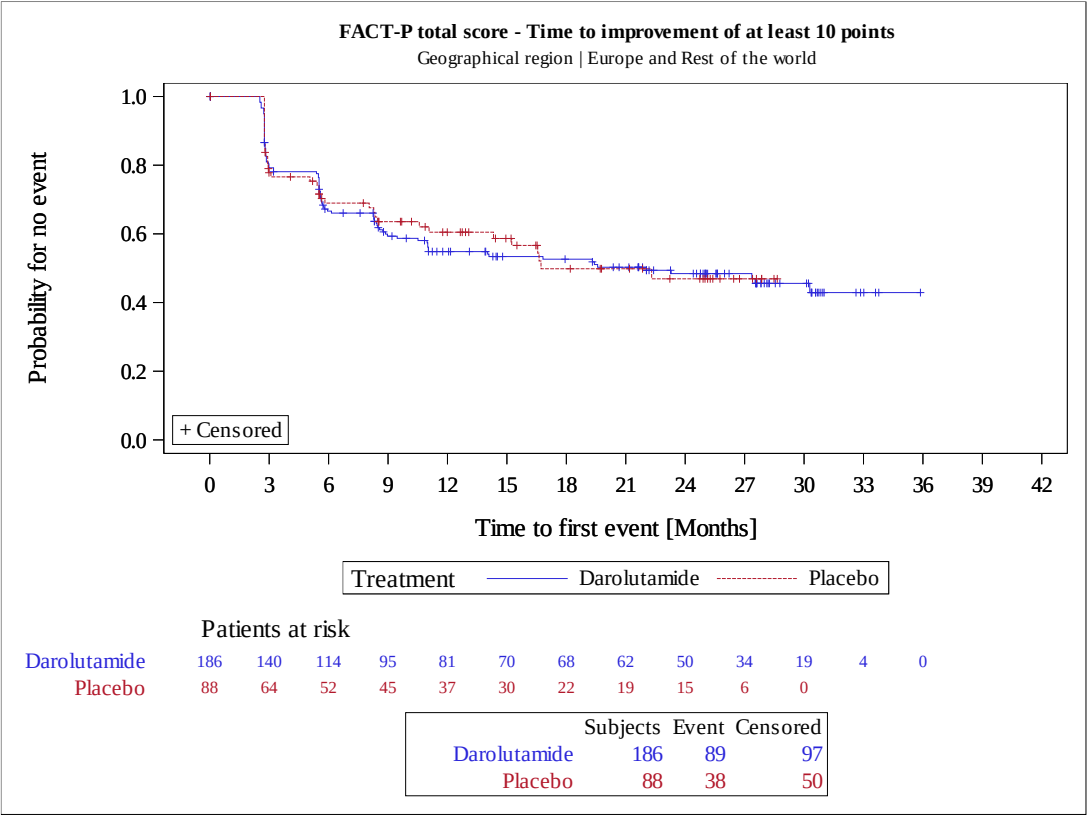


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.19.2
Kaplan-Meier Plot of FACT-P total score - Time to improvement of at least 10 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 2.1.20
FACT-P Physical Well-Being score - Time to improvement of at least 3 points
(full analysis set)

Final

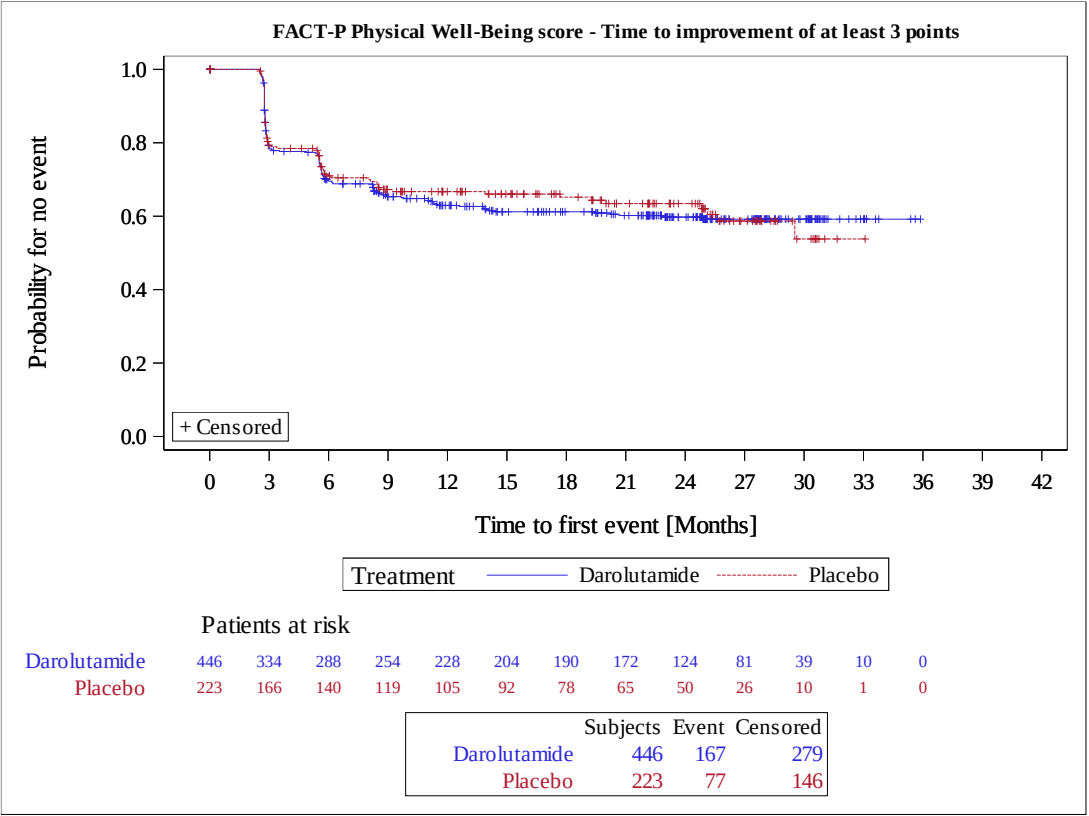
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	167 (37.4)	77 (34.5)
Number of censored participants, n (%)	279 (62.6)	146 (65.5)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	5.5 (3.0, 5.7)	5.6 (2.9, 8.4)
Median (95%-CI)	NE (NE, NE)	NE (25.6, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	1.047 (0.799, 1.373)	
p-value [4]	0.7332	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.20.1
Kaplan-Meier Plot of FACT-P Physical Well-Being score - Time to improvement of at least 3 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.21

FACT-P Social/Family Well- Being score - Time to improvement of at least 3 points

(full analysis set)

Final

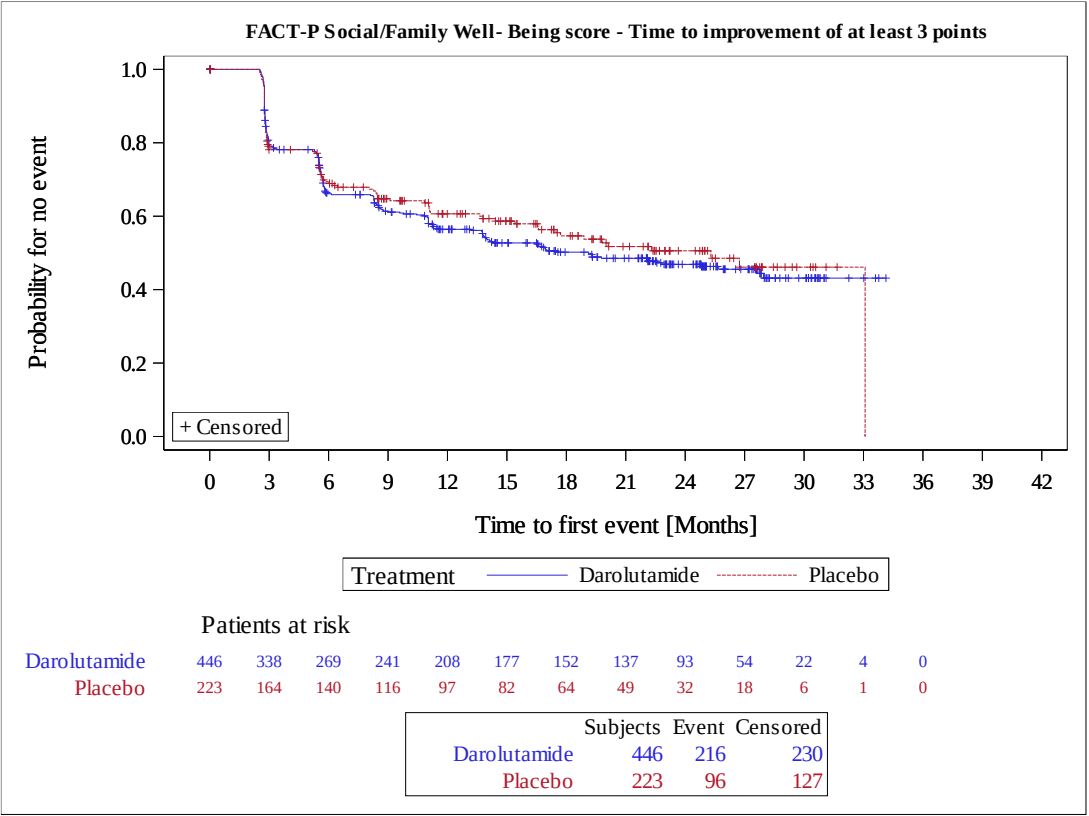
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	216 (48.4)	96 (43.0)
Number of censored participants, n (%)	230 (51.6)	127 (57.0)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	5.5 (3.0, 5.7)	5.5 (2.9, 6.0)
Median (95%-CI)	19.1 (13.8, 27.7)	25.3 (16.6, 33.1)
75%-ile (95%-CI)	NE (NE, NE)	33.1 (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	1.061 (0.833, 1.351)	
p-value [4]	0.6271	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.21.1
Kaplan-Meier Plot of FACT-P Social/Family Well- Being score - Time to improvement of at least 3 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.22

FACT-P Emotional Well-Being score - Time to improvement of at least 3 points

(full analysis set)

Final

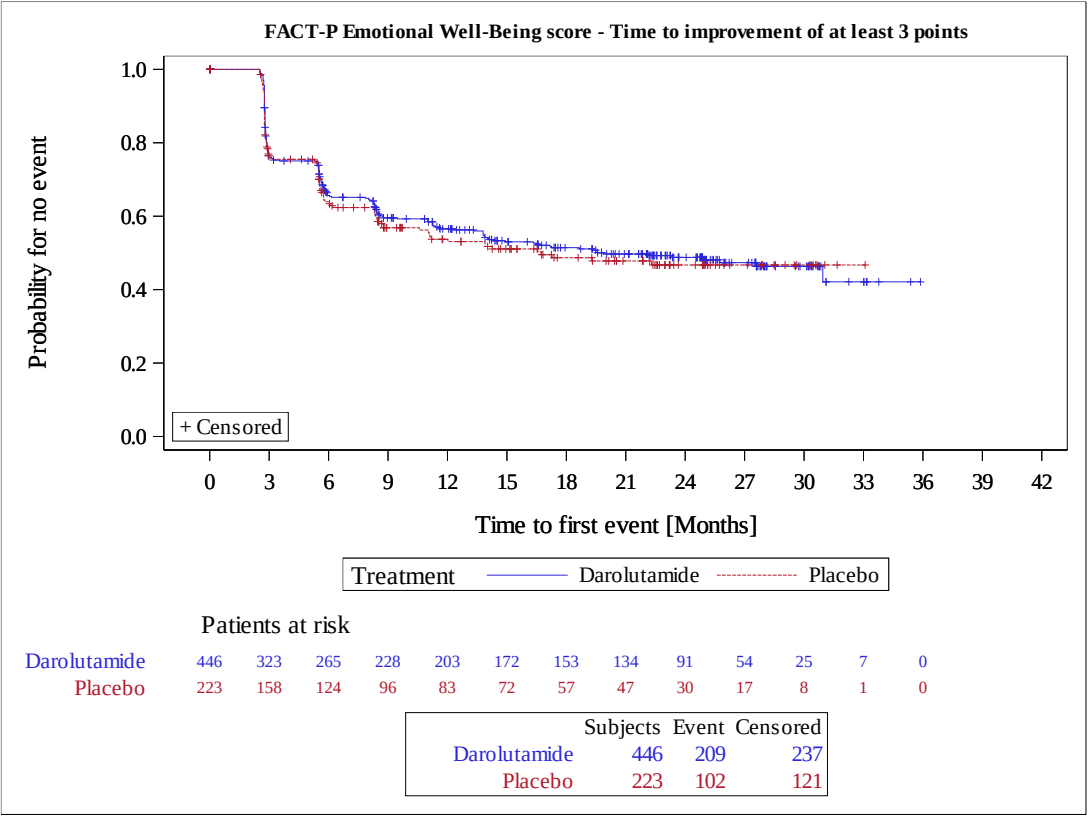
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	209 (46.9)	102 (45.7)
Number of censored participants, n (%)	237 (53.1)	121 (54.3)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	5.4 (2.9, 5.6)	5.4 (2.8, 5.6)
Median (95%-CI)	19.9 (13.8, NE)	16.7 (8.8, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.932 (0.734, 1.182)	
p-value [4]	0.5548	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.22.1
Kaplan-Meier Plot of FACT-P Emotional Well-Being score - Time to improvement of at least 3 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.23

FACT-P Functional Well-Being score - Time to improvement of at least 3 points

(full analysis set)

Final

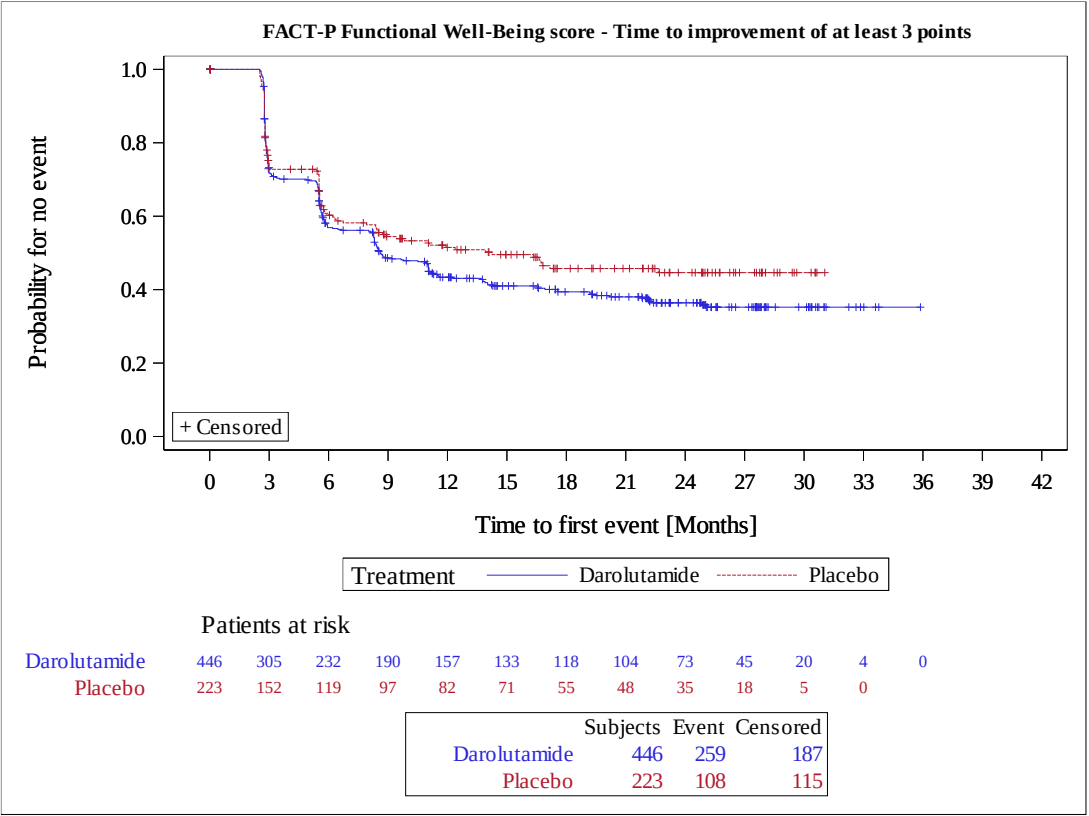
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	259 (58.1)	108 (48.4)
Number of censored participants, n (%)	187 (41.9)	115 (51.6)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	2.9 (2.8, 3.2)	3.0 (2.8, 5.5)
Median (95%-CI)	8.6 (8.3, 11.0)	14.3 (8.4, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	1.191 (0.951, 1.491)	
p-value [4]	0.1224	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate; Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.23.1
Kaplan-Meier Plot of FACT-P Functional Well-Being score - Time to improvement of at least 3 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 2.1.24
FACT-P Prostate cancer subscale score - Time to improvement of at least 3 points
(full analysis set)

Final

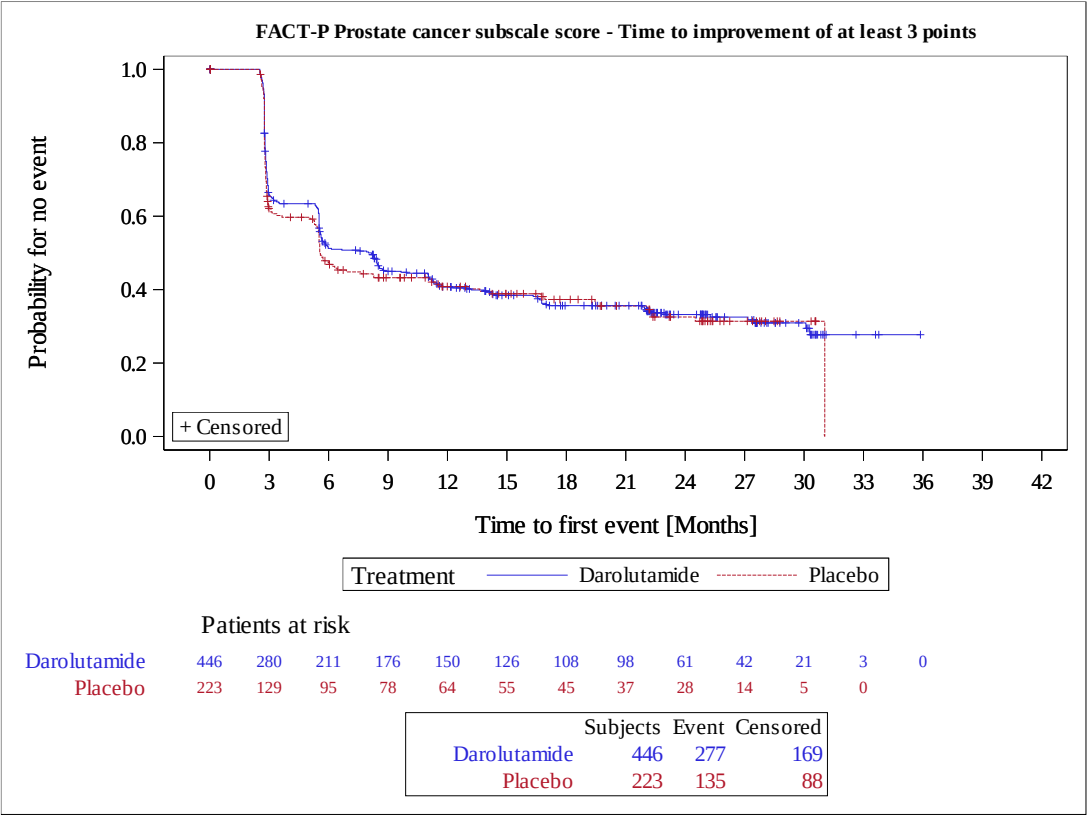
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	277 (62.1)	135 (60.5)
Number of censored participants, n (%)	169 (37.9)	88 (39.5)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	2.8 (2.8, 2.9)	2.8 (2.8, 2.9)
Median (95%-CI)	8.2 (5.6, 8.7)	5.6 (5.4, 8.3)
75%-ile (95%-CI)	NE (30.1, NE)	31.0 (24.5, 31.0)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.918 (0.747, 1.129)	
p-value [4]	0.4080	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.24.1
Kaplan-Meier Plot of FACT-P Prostate cancer subscale score - Time to improvement of at least 3 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.25

FACT-P total score - Time to deterioration of at least 23.4 points

(full analysis set)

Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	130 (29.1)	81 (36.3)
Number of censored participants, n (%)	316 (70.9)	142 (63.7)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	18.4 (15.1, 22.1)	11.2 (8.3, 13.8)
Median (95%-CI)	NE (33.8, NE)	NE (21.1, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.661 (0.500, 0.874)	
p-value [4]	0.0034	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.25.1

FACT-P total score - Time to deterioration of at least 23.4 points - Subgroup analysis (full analysis set)

Final

Subgroup Level	Darolutamide (N=446)			Placebo (N=223)			Unstratified Analysis		p-Value [3]	Interaction p-Value[4]
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio	(95% CI) [2]		
Presence of visceral metastases assessed by central review (from IWRS)										0.8334
Yes	13/ 53 (24.5)	NE (28.8,	NE)	8/ 27 (29.6)	NE (11.2,	NE)	0.719 (0.298,	1.736)	0.4606	
No	117/ 393 (29.8)	NE (33.8,	NE)	73/ 196 (37.2)	NE (19.3,	NE)	0.653 (0.487,	0.876)	0.0041	
Received prior local therapy (from IWRS)										0.9432
Yes	26/ 80 (32.5)	NE (30.3,	NE)	16/ 40 (40.0)	NE (16.5,	NE)	0.687 (0.366,	1.290)	0.2395	
No	104/ 366 (28.4)	NE (33.8,	NE)	65/ 183 (35.5)	NE (21.9,	NE)	0.656 (0.481,	0.895)	0.0072	
Prior local radiotherapy and/or prostatectomy										0.3168
Yes	29/ 87 (33.3)	NE (30.3,	NE)	18/ 50 (36.0)	NE (18.2,	NE)	0.874 (0.485,	1.574)	0.6523	
No	101/ 359 (28.1)	NE (33.8,	NE)	63/ 173 (36.4)	NE (17.0,	NE)	0.613 (0.447,	0.840)	0.0021	
Age group										0.2073
<65 years	35/ 118 (29.7)	NE (27.6,	NE)	24/ 65 (36.9)	NE (15.5,	NE)	0.654 (0.389,	1.102)	0.1078	
65-74	54/ 193 (28.0)	NE (28.8,	NE)	34/ 96 (35.4)	NE (18.7,	NE)	0.636 (0.413,	0.980)	0.0381	
75-84	36/ 117 (30.8)	NE (30.3,	NE)	16/ 52 (30.8)	NE (15.7,	NE)	0.901 (0.500,	1.625)	0.7288	
>=85 years	5/ 18 (27.8)	NE (17.9,	NE)	7/ 10 (70.0)	11.0 (2.7,	16.8)	0.169 (0.048,	0.597)	0.0018	
Race										0.0394
White	73/ 251 (29.1)	NE (33.8,	NE)	46/ 125 (36.8)	NE (16.8,	NE)	0.641 (0.442,	0.928)	0.0173	
Asian	45/ 144 (31.3)	NE (NE,	NE)	20/ 65 (30.8)	NE (21.9,	NE)	0.946 (0.559,	1.603)	0.8369	
Black or African American	8/ 41 (19.5)	NE (28.0,	NE)	13/ 24 (54.2)	13.9 (5.4,	NE)	0.248 (0.102,	0.604)	0.0009	
Other	4/ 10 (40.0)	23.1 (5.6,	NE)	2/ 9 (22.2)	NE (2.9,	NE)	1.478 (0.269,	8.139)	0.6513	
Geographical region										0.2596
Asia	43/ 141 (30.5)	NE (NE,	NE)	20/ 63 (31.7)	NE (21.1,	NE)	0.878 (0.517,	1.493)	0.6311	
Latin America	33/ 119 (27.7)	NE (28.0,	NE)	31/ 72 (43.1)	22.1 (13.6,	NE)	0.498 (0.305,	0.816)	0.0046	
Europe and Rest of the world	54/ 186 (29.0)	NE (33.8,	NE)	30/ 88 (34.1)	NE (16.8,	NE)	0.692 (0.441,	1.084)	0.1053	
Baseline PSA values by median										0.8839
< median of overall population	65/ 216 (30.1)	NE (28.8,	NE)	42/ 111 (37.8)	NE (18.2,	NE)	0.670 (0.454,	0.989)	0.0422	
>= median of overall population	63/ 220 (28.6)	33.8 (33.8,	NE)	39/ 108 (36.1)	NE (16.5,	NE)	0.633 (0.424,	0.945)	0.0237	
ECOG PS at baseline										0.9912
=0	70/ 235 (29.8)	33.8 (30.3,	NE)	36/ 98 (36.7)	NE (18.2,	NE)	0.661 (0.442,	0.988)	0.0420	
>=1	60/ 211 (28.4)	NE (NE,	NE)	45/ 125 (36.0)	NE (16.8,	NE)	0.673 (0.457,	0.992)	0.0434	
Gleason score at initial diagnosis										0.4954
Gleason <8	37/ 122 (30.3)	NE (30.3,	NE)	23/ 67 (34.3)	NE (19.3,	NE)	0.804 (0.477,	1.354)	0.4106	
Gleason >=8	92/ 311 (29.6)	33.8 (28.8,	NE)	56/ 146 (38.4)	NE (16.5,	NE)	0.630 (0.451,	0.880)	0.0061	
Disease volume at baseline										0.4677
high	96/ 315 (30.5)	NE (28.8,	NE)	56/ 157 (35.7)	NE (18.7,	NE)	0.707 (0.508,	0.984)	0.0383	
low	34/ 131 (26.0)	NE (33.8,	NE)	25/ 66 (37.9)	NE (15.5,	NE)	0.565 (0.336,	0.949)	0.0285	
Renal function - eGFR at baseline										0.0925
Normal: eGFR >= 90 mL/min	53/ 219 (24.2)	NE (NE,	NE)	33/ 104 (31.7)	NE (22.1,	NE)	0.615 (0.398,	0.950)	0.0268	
Mild impairment: 60 <= eGFR < 90 mL/min	68/ 180 (37.8)	30.3 (25.4,	NE)	34/ 91 (37.4)	NE (16.5,	NE)	0.836 (0.552,	1.265)	0.3943	
Moderate impairment: 30 <= eGFR < 60 mL/min	8/ 46 (17.4)	NE (NE,	NE)	13/ 27 (48.1)	23.4 (2.9,	NE)	0.326 (0.135,	0.787)	0.0083	

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;

AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;

IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Participants without event are censored at last assessment date or randomization date if there is no follow-up available.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 2.1.25.1
FACT-P total score - Time to deterioration of at least 23.4 points - Subgroup analysis
(full analysis set)

Final

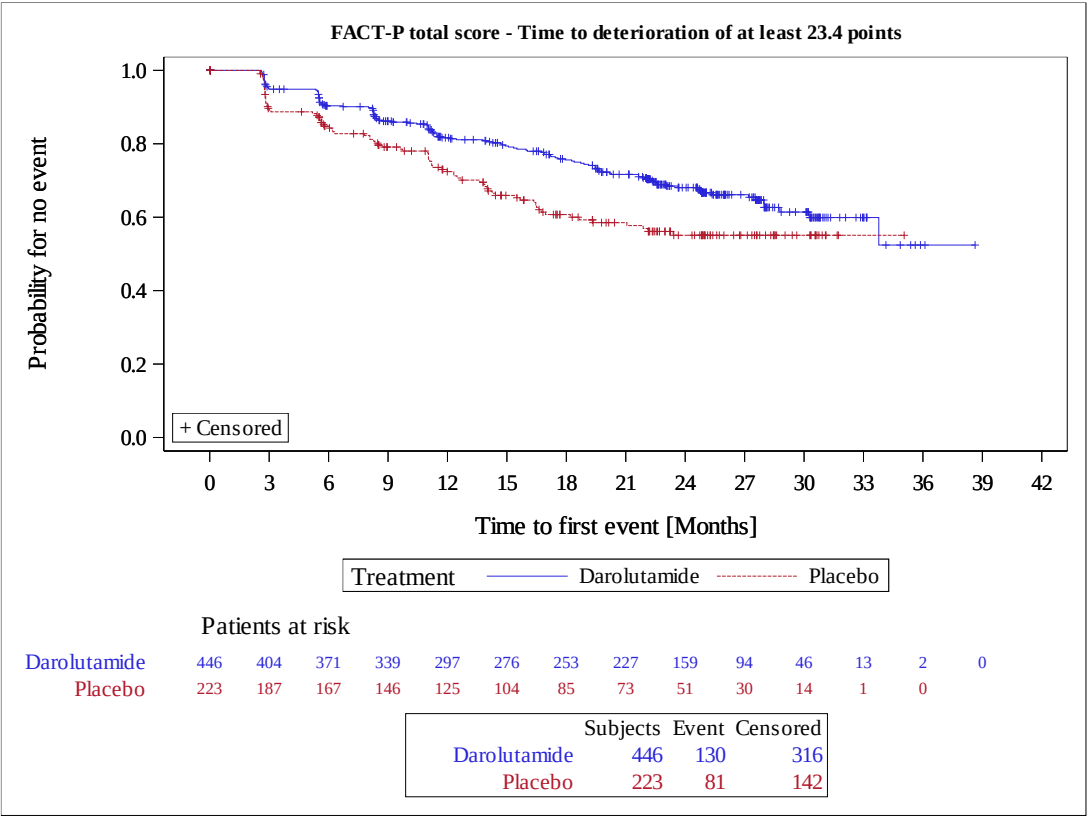
Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis		
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3]	Interaction p-Value[4]
Hepatic function at baseline									0.1773
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	116/ 387 (30.0)	NE (33.8,	NE)	78/ 204 (38.2)	NE (18.7,	NE)	0.625 (0.468, 0.834)	0.0012	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	14/ 59 (23.7)	NE (NE,	NE)	3/ 19 (15.8)	NE (15.5,	NE)	1.445 (0.415, 5.031)	0.5590	
Age Group (Titan)									0.9779
<65	35/ 118 (29.7)	NE (27.6,	NE)	24/ 65 (36.9)	NE (15.5,	NE)	0.654 (0.389, 1.102)	0.1078	
>=65 and <75	54/ 193 (28.0)	NE (28.8,	NE)	34/ 96 (35.4)	NE (18.7,	NE)	0.636 (0.413, 0.980)	0.0381	
>=75	41/ 135 (30.4)	NE (30.3,	NE)	23/ 62 (37.1)	NE (14.3,	NE)	0.693 (0.416, 1.156)	0.1563	
Geographic region (Titan)									0.9077
Europe and north america	41/ 145 (28.3)	NE (33.8,	NE)	27/ 77 (35.1)	NE (16.8,	NE)	0.651 (0.399, 1.062)	0.0825	
ROTW	89/ 301 (29.6)	NE (NE,	NE)	54/ 146 (37.0)	NE (19.3,	NE)	0.662 (0.472, 0.929)	0.0161	

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate; AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate; IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.
[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.25.2
Kaplan-Meier Plot of FACT-P total score - Time to deterioration of at least 23.4 points
(full analysis set)

Final

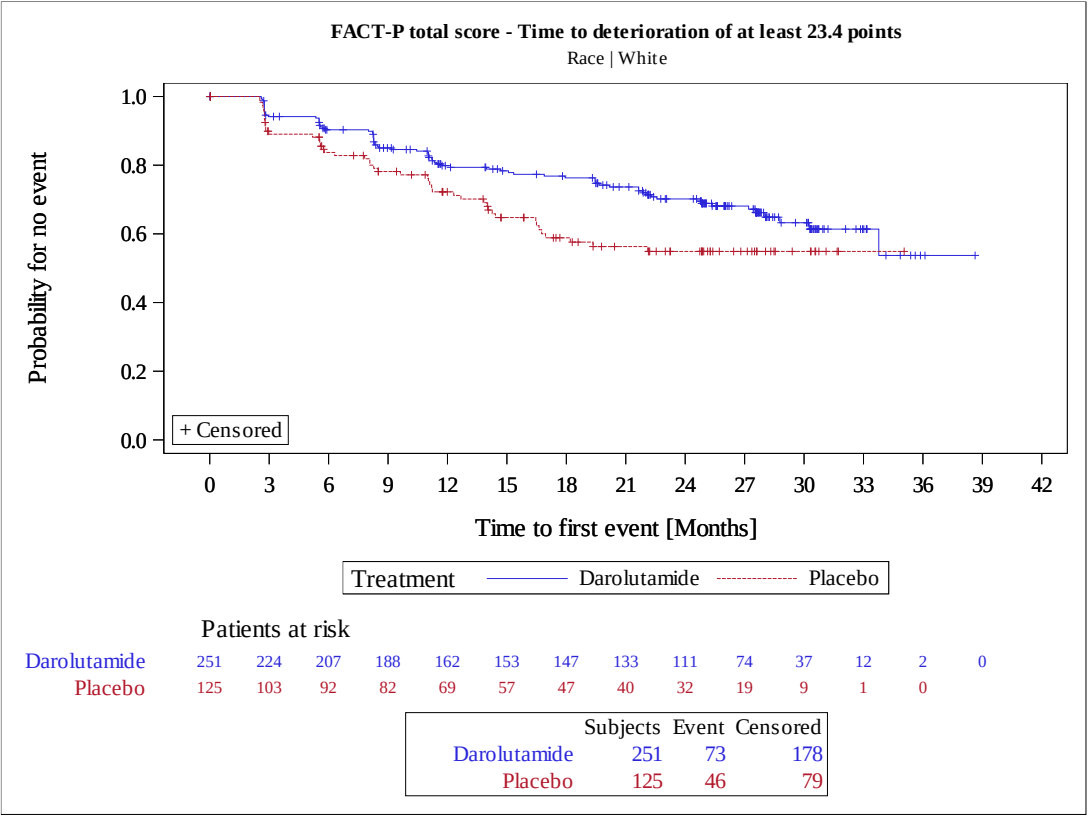


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.25.2
Kaplan-Meier Plot of FACT-P total score - Time to deterioration of at least 23.4 points
(full analysis set)

Final

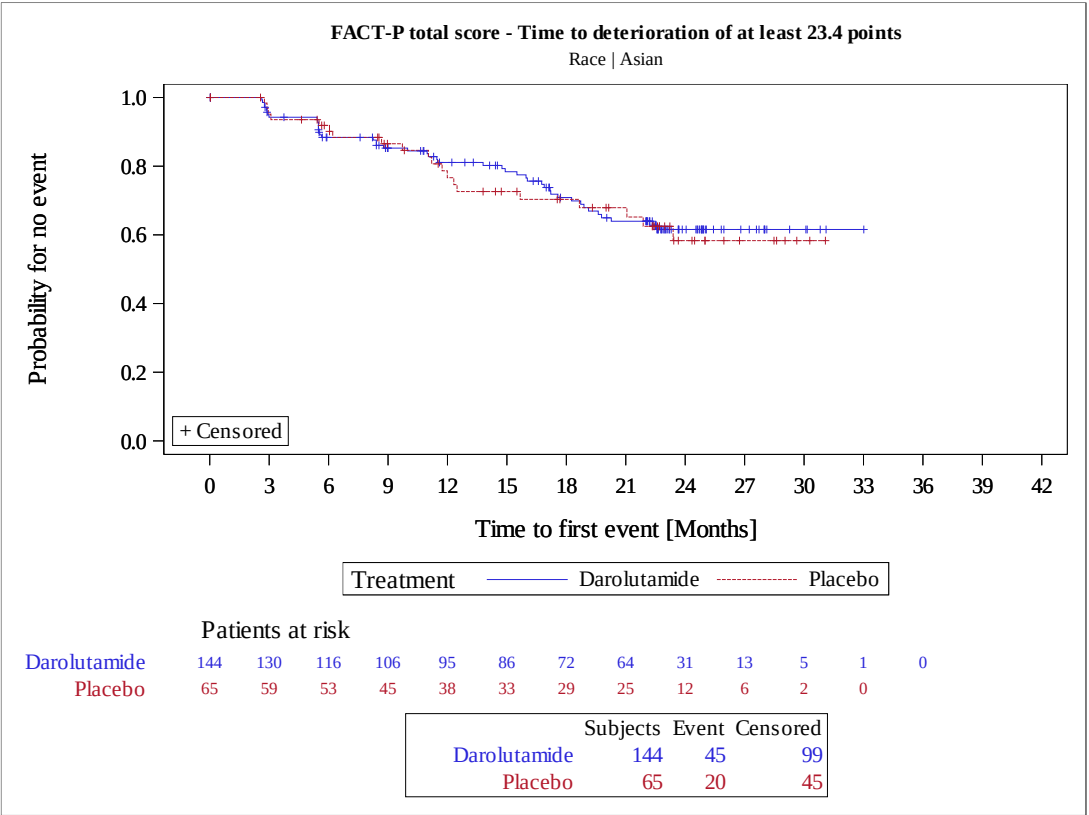


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.25.2
Kaplan-Meier Plot of FACT-P total score - Time to deterioration of at least 23.4 points
(full analysis set)

Final

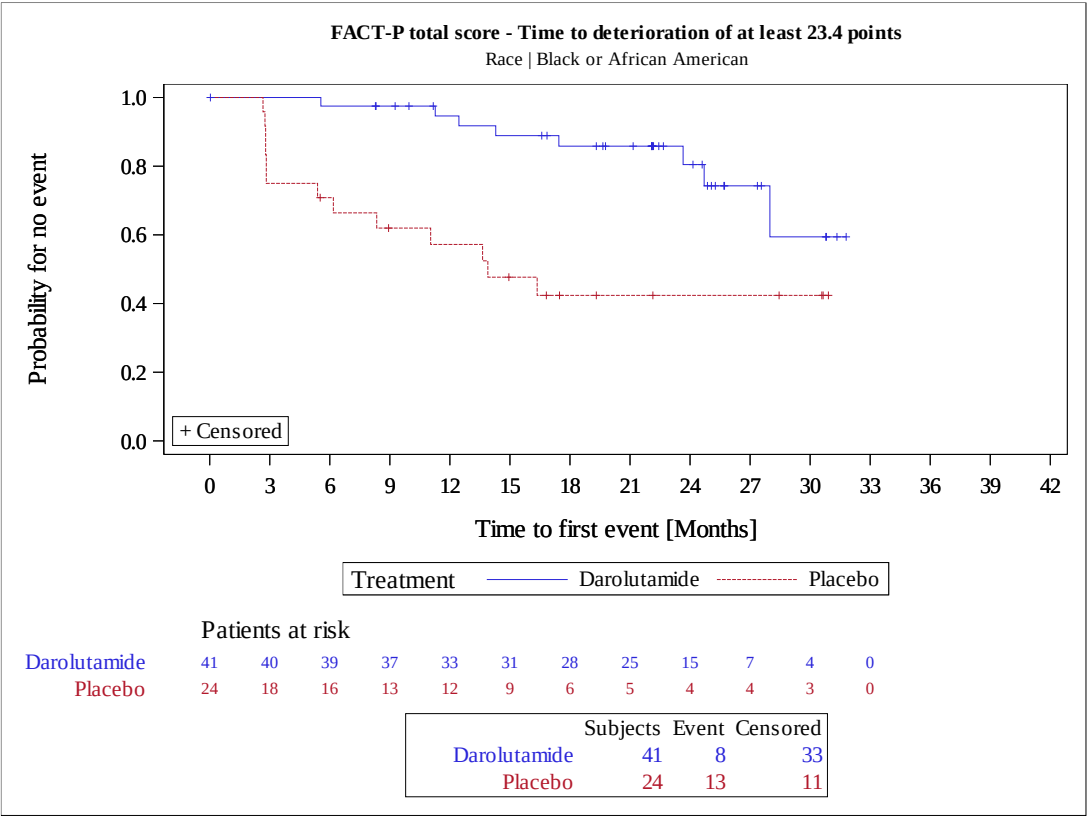


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.25.2
Kaplan-Meier Plot of FACT-P total score - Time to deterioration of at least 23.4 points
(full analysis set)

Final

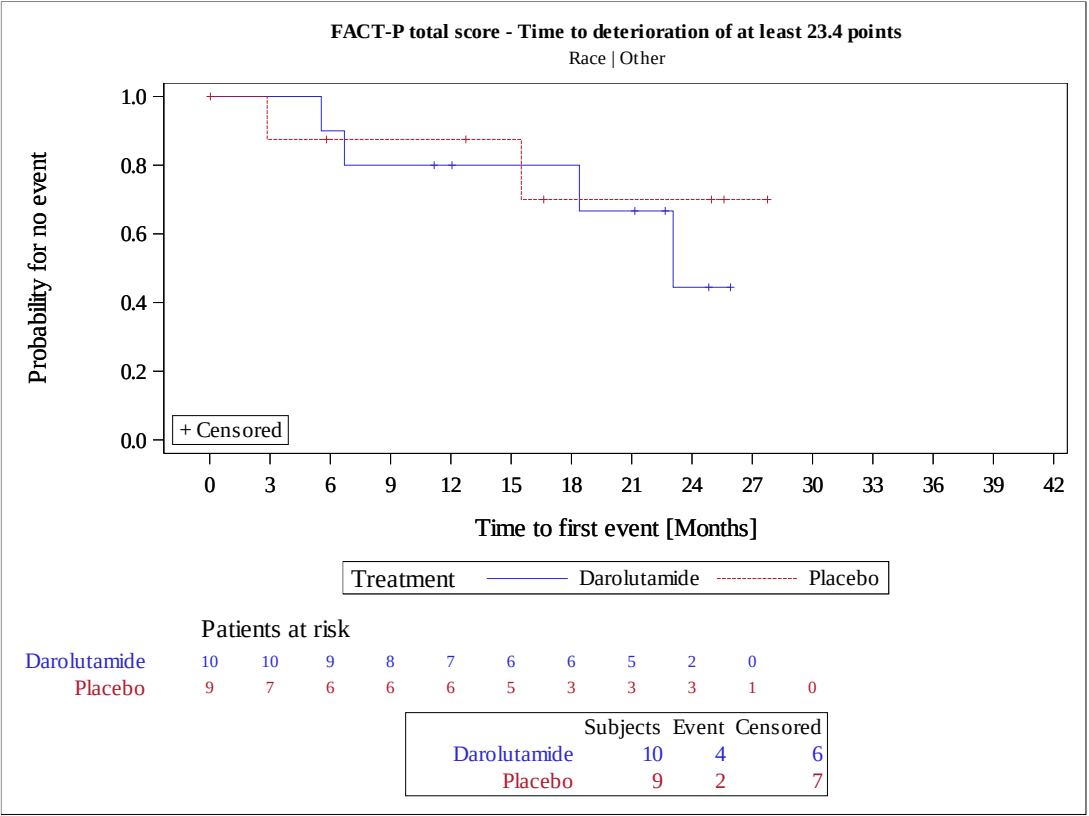


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.25.2
Kaplan-Meier Plot of FACT-P total score - Time to deterioration of at least 23.4 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.26

FACT-P Physical Well-Being score - Time to deterioration of at least 4.2 points

(full analysis set)

Final

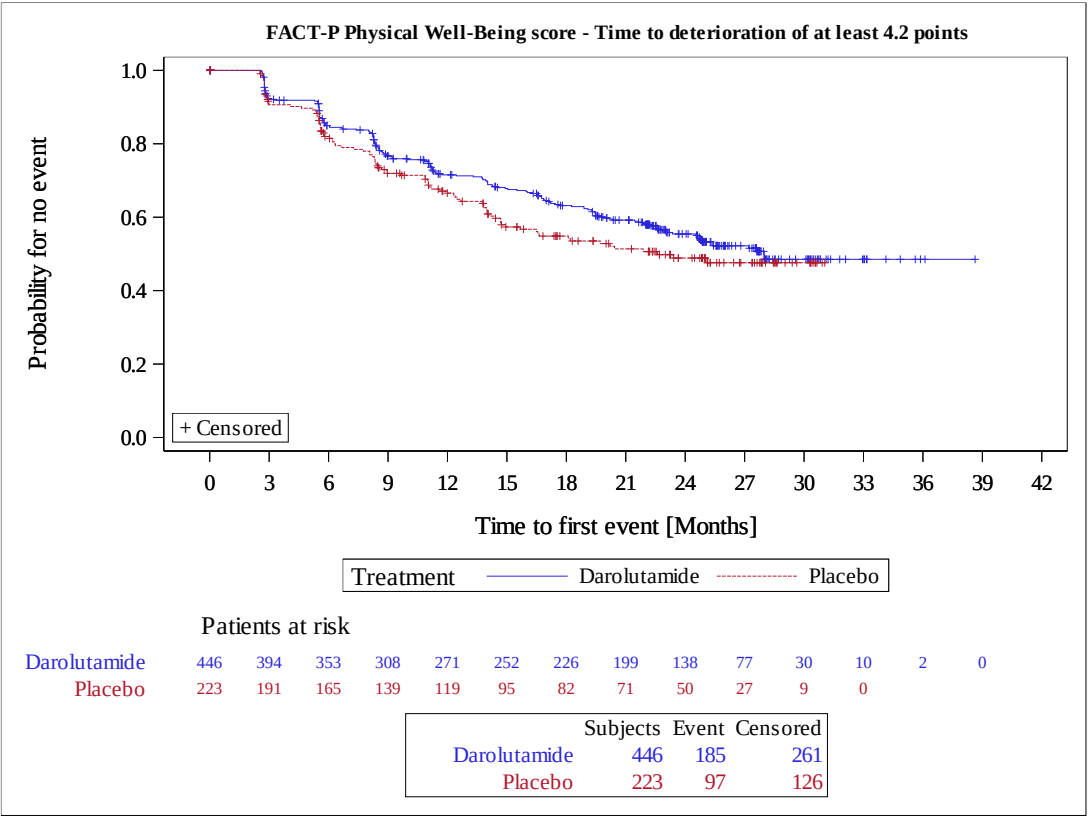
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	185 (41.5)	97 (43.5)
Number of censored participants, n (%)	261 (58.5)	126 (56.5)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	11.0 (8.5, 13.7)	8.3 (6.2, 11.0)
Median (95%-CI)	28.0 (24.5, NE)	22.6 (15.7, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.827 (0.646, 1.058)	
p-value [4]	0.1292	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.26.1
Kaplan-Meier Plot of FACT-P Physical Well-Being score - Time to deterioration of at least 4.2 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.27

FACT-P Social/Family Well- Being score - Time to deterioration of at least 4.2 points

(full analysis set)

Final

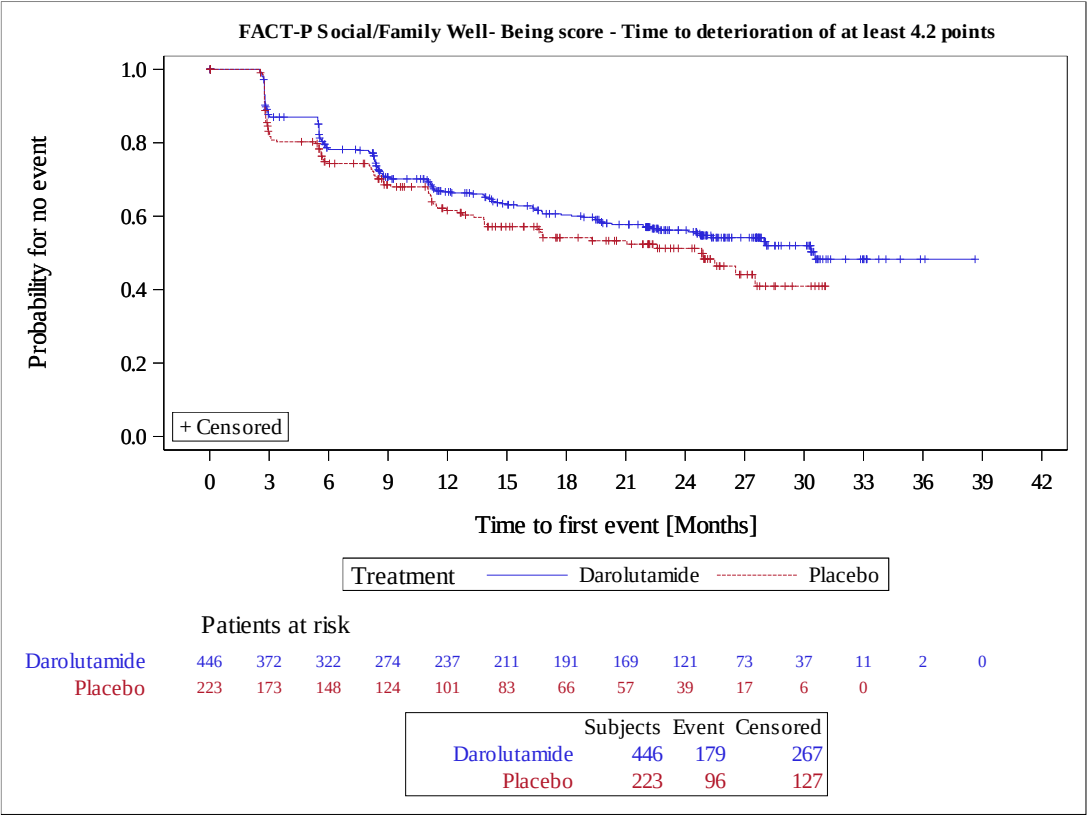
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	179 (40.1)	96 (43.0)
Number of censored participants, n (%)	267 (59.9)	127 (57.0)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	8.3 (5.8, 8.8)	5.8 (3.1, 8.8)
Median (95%-CI)	30.6 (24.6, NE)	24.8 (14.0, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.837 (0.652, 1.073)	
p-value [4]	0.1566	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.27.1
Kaplan-Meier Plot of FACT-P Social/Family Well- Being score - Time to deterioration of at least 4.2 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.28

FACT-P Emotional Well-Being score - Time to deterioration of at least 3.6 points

(full analysis set)

Final

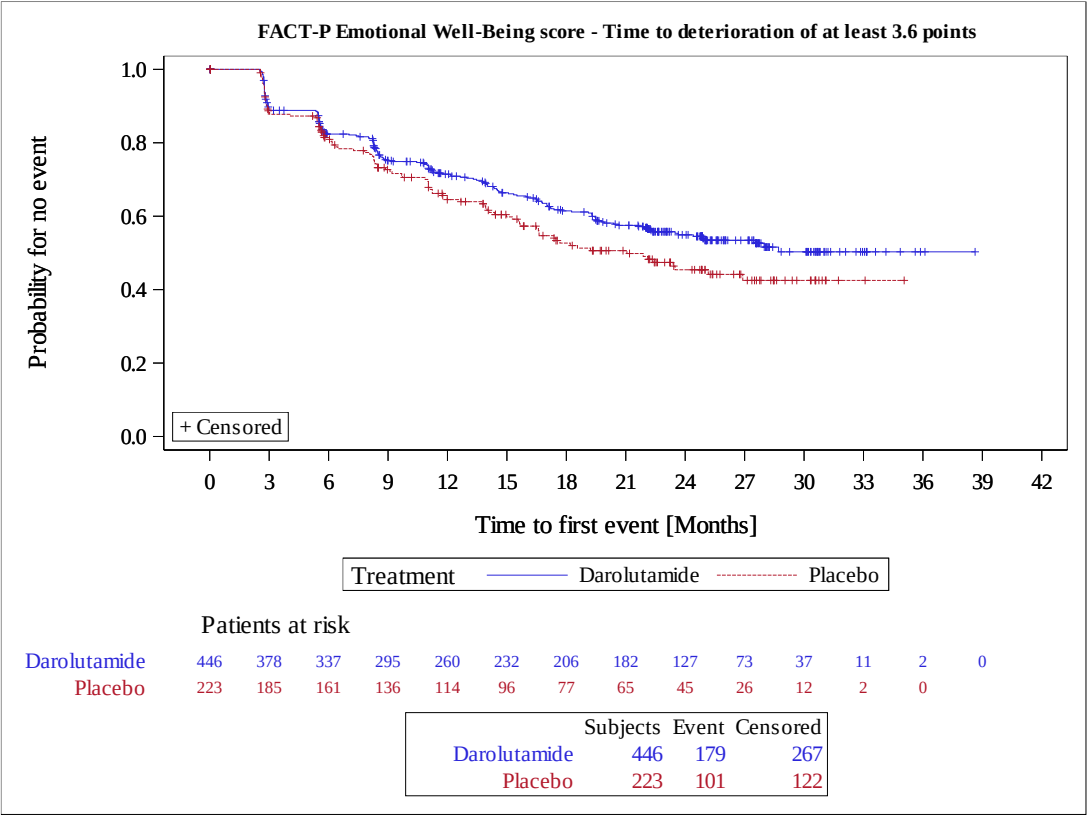
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	179 (40.1)	101 (45.3)
Number of censored participants, n (%)	267 (59.9)	122 (54.7)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	9.2 (8.3, 12.6)	8.3 (6.0, 11.0)
Median (95%-CI)	NE (23.7, NE)	21.1 (15.7, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.796 (0.623, 1.016)	
p-value [4]	0.0655	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.28.1
Kaplan-Meier Plot of FACT-P Emotional Well-Being score - Time to deterioration of at least 3.6 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 2.1.29
FACT-P Functional Well-Being score - Time to deterioration of at least 4.2 points
(full analysis set)

Final

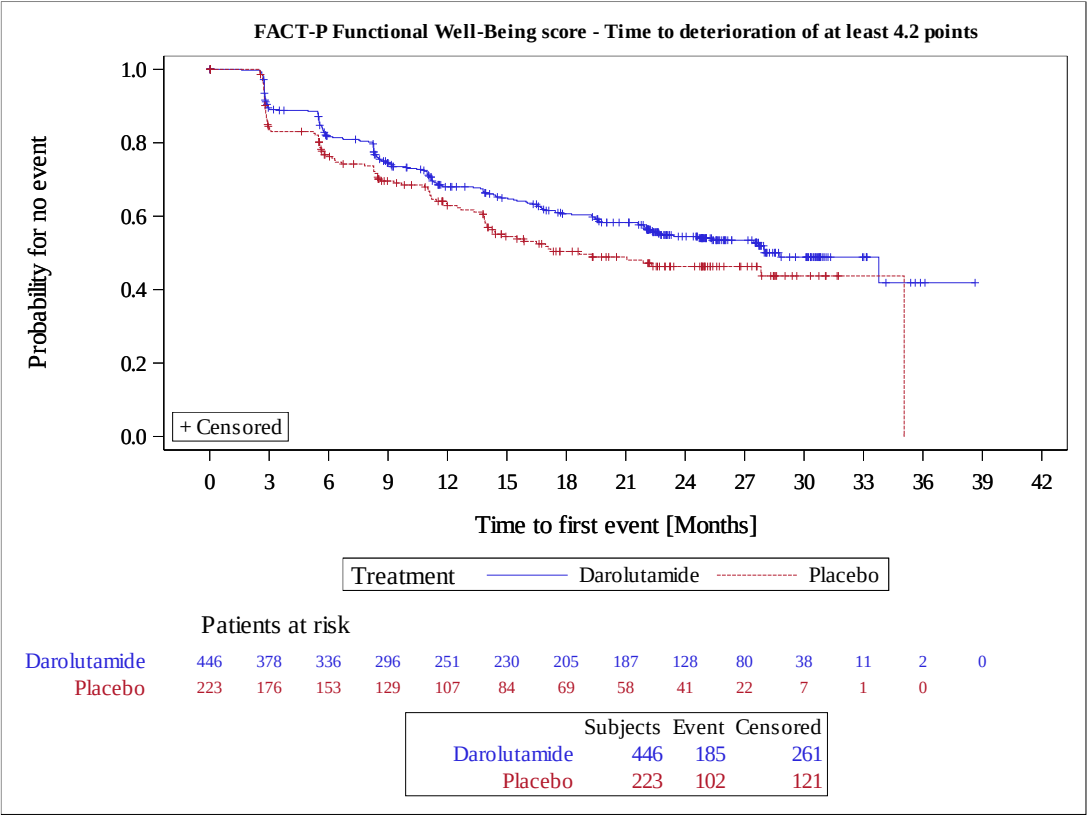
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	185 (41.5)	102 (45.7)
Number of censored participants, n (%)	261 (58.5)	121 (54.3)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	8.9 (8.3, 11.1)	6.3 (5.5, 9.3)
Median (95%-CI)	28.8 (22.7, NE)	18.7 (14.0, 35.1)
75%-ile (95%-CI)	NE (NE, NE)	35.1 (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.772 (0.606, 0.984)	
p-value [4]	0.0355	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.29.1
Kaplan-Meier Plot of FACT-P Functional Well-Being score - Time to deterioration of at least 4.2 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 2.1.30
FACT-P Prostate cancer subscale score - Time to deterioration of at least 7.2 points
(full analysis set)

Final

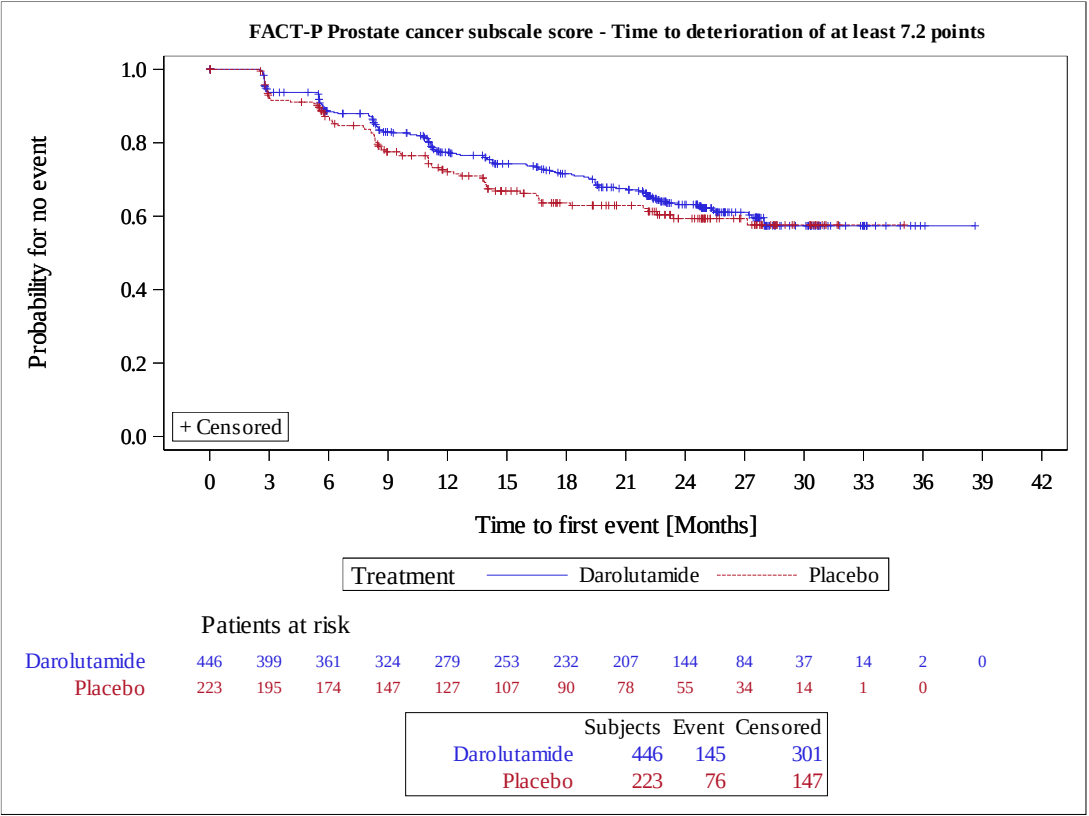
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	145 (32.5)	76 (34.1)
Number of censored participants, n (%)	301 (67.5)	147 (65.9)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	14.3 (11.2, 18.9)	11.0 (8.3, 13.9)
Median (95%-CI)	NE (NE, NE)	NE (27.1, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.855 (0.647, 1.130)	
p-value [4]	0.2691	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.30.1
Kaplan-Meier Plot of FACT-P Prostate cancer subscale score - Time to deterioration of at least 7.2 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.31

FACT-P total score - Time to improvement of at least 23.4 points

(full analysis set)

Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	104 (23.3)	40 (17.9)
Number of censored participants, n (%)	342 (76.7)	183 (82.1)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	20.1 (11.3, NE)	31.1 (17.0, NE)
Median (95%-CI)	NE (NE, NE)	NE (31.1, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (31.1, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	1.235 (0.857, 1.780)	
p-value [4]	0.2548	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 2.1.31.1

FACT-P total score - Time to improvement of at least 23.4 points - Subgroup analysis (full analysis set)

Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis	
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3] Interaction p-Value[4]
Presence of visceral metastases assessed by central review (from IWRS)								0.2290
Yes	19/ 53 (35.8)	NE (9.1,	NE)	4/ 27 (14.8)	NE (NE,	NE)	2.283 (0.776, 6.715)	0.1212
No	85/ 393 (21.6)	NE (NE,	NE)	36/ 196 (18.4)	31.1 (31.1,	NE)	1.121 (0.758, 1.655)	0.5661
Received prior local therapy (from IWRS)								0.1614
Yes	20/ 80 (25.0)	NE (NE,	NE)	4/ 40 (10.0)	NE (NE,	NE)	2.509 (0.857, 7.345)	0.0816
No	84/ 366 (23.0)	NE (NE,	NE)	36/ 183 (19.7)	NE (31.1,	NE)	1.102 (0.746, 1.629)	0.6237
Prior local radiotherapy and/or prostatectomy								0.7310
Yes	22/ 87 (25.3)	NE (NE,	NE)	9/ 50 (18.0)	31.1 (NE,	NE)	1.404 (0.646, 3.054)	0.3873
No	82/ 359 (22.8)	NE (NE,	NE)	31/ 173 (17.9)	NE (NE,	NE)	1.201 (0.794, 1.816)	0.3828
Age group								0.2399
<65 years	25/ 118 (21.2)	NE (NE,	NE)	16/ 65 (24.6)	31.1 (NE,	NE)	0.730 (0.389, 1.372)	0.3251
65-74	48/ 193 (24.9)	NE (NE,	NE)	16/ 96 (16.7)	NE (NE,	NE)	1.454 (0.826, 2.561)	0.1908
75-84	28/ 117 (23.9)	NE (NE,	NE)	6/ 52 (11.5)	NE (NE,	NE)	2.128 (0.881, 5.139)	0.0847
>=85 years	3/ 18 (16.7)	NE (NE,	NE)	2/ 10 (20.0)	NE (2.8,	NE)	0.908 (0.152, 5.445)	0.9156
Race								0.6412
White	45/ 251 (17.9)	NE (NE,	NE)	14/ 125 (11.2)	31.1 (31.1,	NE)	1.539 (0.844, 2.806)	0.1549
Asian	40/ 144 (27.8)	NE (NE,	NE)	18/ 65 (27.7)	NE (23.4,	NE)	0.951 (0.545, 1.660)	0.8616
Black or African American	14/ 41 (34.1)	NE (11.3,	NE)	5/ 24 (20.8)	NE (NE,	NE)	1.583 (0.570, 4.396)	0.3629
Other	5/ 10 (50.0)	17.2 (2.8,	NE)	3/ 9 (33.3)	NE (5.3,	NE)	1.163 (0.276, 4.909)	0.8370
Geographical region								0.3468
Asia	40/ 141 (28.4)	NE (NE,	NE)	18/ 63 (28.6)	NE (23.4,	NE)	0.939 (0.538, 1.638)	0.8244
Latin America	31/ 119 (26.1)	NE (NE,	NE)	10/ 72 (13.9)	NE (NE,	NE)	1.822 (0.893, 3.717)	0.0916
Europe and Rest of the world	33/ 186 (17.7)	NE (NE,	NE)	12/ 88 (13.6)	31.1 (NE,	NE)	1.227 (0.632, 2.380)	0.5441
Baseline PSA values by median								0.5972
< median of overall population	46/ 216 (21.3)	NE (NE,	NE)	20/ 111 (18.0)	31.1 (31.1,	NE)	1.155 (0.683, 1.953)	0.5898
>= median of overall population	55/ 220 (25.0)	NE (NE,	NE)	18/ 108 (16.7)	NE (NE,	NE)	1.419 (0.833, 2.417)	0.1931
ECOG PS at baseline								0.5424
=0	50/ 235 (21.3)	NE (NE,	NE)	18/ 98 (18.4)	31.1 (31.1,	NE)	1.115 (0.650, 1.912)	0.6912
>=1	54/ 211 (25.6)	NE (NE,	NE)	22/ 125 (17.6)	NE (NE,	NE)	1.397 (0.851, 2.294)	0.1820
Gleason score at initial diagnosis								0.6271
Gleason <8	23/ 122 (18.9)	NE (NE,	NE)	12/ 67 (17.9)	31.1 (NE,	NE)	0.997 (0.495, 2.006)	0.9930
Gleason >=8	76/ 311 (24.4)	NE (NE,	NE)	28/ 146 (19.2)	NE (NE,	NE)	1.234 (0.800, 1.904)	0.3386
Disease volume at baseline								0.9557
high	79/ 315 (25.1)	NE (NE,	NE)	30/ 157 (19.1)	NE (NE,	NE)	1.250 (0.821, 1.903)	0.2957
low	25/ 131 (19.1)	NE (NE,	NE)	10/ 66 (15.2)	31.1 (31.1,	NE)	1.191 (0.571, 2.483)	0.6402
Renal function - eGFR at baseline								0.1779
Normal: eGFR >= 90 mL/min	57/ 219 (26.0)	NE (NE,	NE)	24/ 104 (23.1)	31.1 (NE,	NE)	1.003 (0.622, 1.617)	0.9905
Mild impairment: 60 <= eGFR < 90 mL/min	34/ 180 (18.9)	NE (NE,	NE)	14/ 91 (15.4)	NE (NE,	NE)	1.195 (0.641, 2.228)	0.5739
Moderate impairment: 30 <= eGFR < 60 mL/min	13/ 46 (28.3)	NE (NE,	NE)	2/ 27 (7.4)	NE (NE,	NE)	4.421 (0.997, 19.595)	0.0312

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate; AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate; IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Participants without event are censored at last assessment date or randomization date if there is no follow-up available.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.31.1

FACT-P total score - Time to improvement of at least 23.4 points - Subgroup analysis (full analysis set)

Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis	
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3] Interaction p-Value[4]
Hepatic function at baseline								0.6086
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	94/ 387 (24.3)	NE (	NE, NE)	37/ 204 (18.1)	NE (31.1,	NE)	1.286 (0.879, 1.881)	0.1932
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	10/ 59 (16.9)	NE (	NE, NE)	3/ 19 (15.8)	NE (18.5,	NE)	0.884 (0.243, 3.214)	0.8512
Age Group (Titan)								0.1726
<65	25/ 118 (21.2)	NE (	NE, NE)	16/ 65 (24.6)	31.1 (	NE, NE)	0.730 (0.389, 1.372)	0.3251
>=65 and <75	48/ 193 (24.9)	NE (	NE, NE)	16/ 96 (16.7)	NE (	NE, NE)	1.454 (0.826, 2.561)	0.1908
>=75	31/ 135 (23.0)	NE (	NE, NE)	8/ 62 (12.9)	NE (	NE, NE)	1.812 (0.833, 3.943)	0.1266
Geographic region (Titan)								0.8280
Europe and north america	28/ 145 (19.3)	NE (	NE, NE)	11/ 77 (14.3)	31.1 (	NE, NE)	1.296 (0.644, 2.609)	0.4646
ROTW	76/ 301 (25.2)	NE (	NE, NE)	29/ 146 (19.9)	NE (	NE, NE)	1.197 (0.780, 1.836)	0.4082

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate; AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate; IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Participants without event are censored at last assessment date or randomization date if there is no follow-up available.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

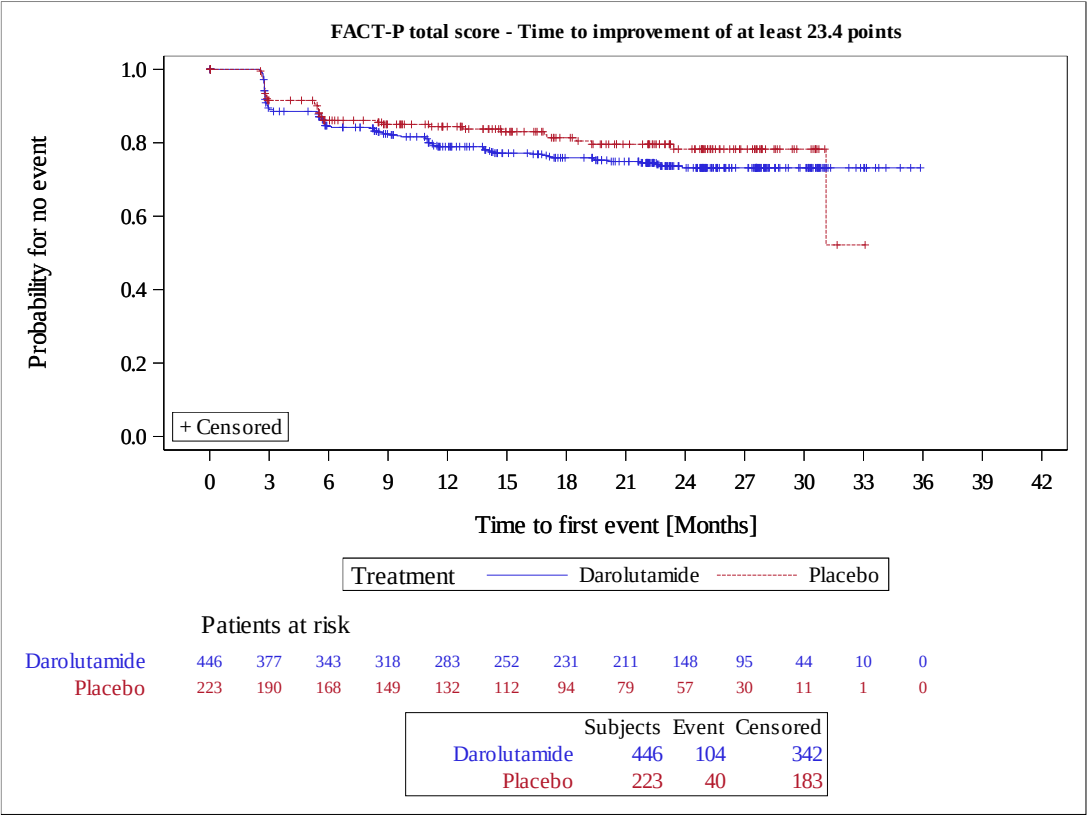
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.31.2
Kaplan-Meier Plot of FACT-P total score - Time to improvement of at least 23.4 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 2.1.32

FACT-P Physical Well-Being score - Time to improvement of at least 4.2 points

(full analysis set)

Final

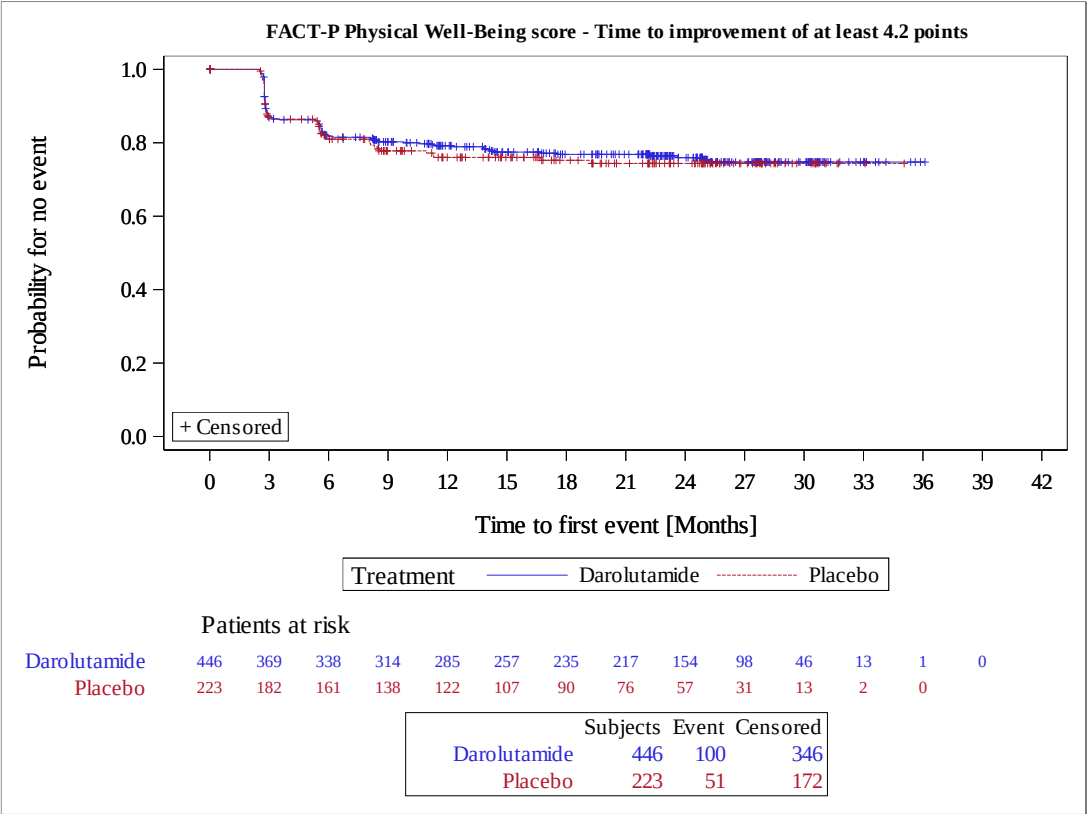
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	100 (22.4)	51 (22.9)
Number of censored participants, n (%)	346 (77.6)	172 (77.1)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	25.2 (12.2, NE)	19.3 (6.0, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.929 (0.663, 1.303)	
p-value [4]	0.6681	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 2.1.32.1
Kaplan-Meier Plot of FACT-P Physical Well-Being score - Time to improvement of at least 4.2 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 2.1.33
FACT-P Social/Family Well- Being score - Time to improvement of at least 4.2 points
(full analysis set)

Final

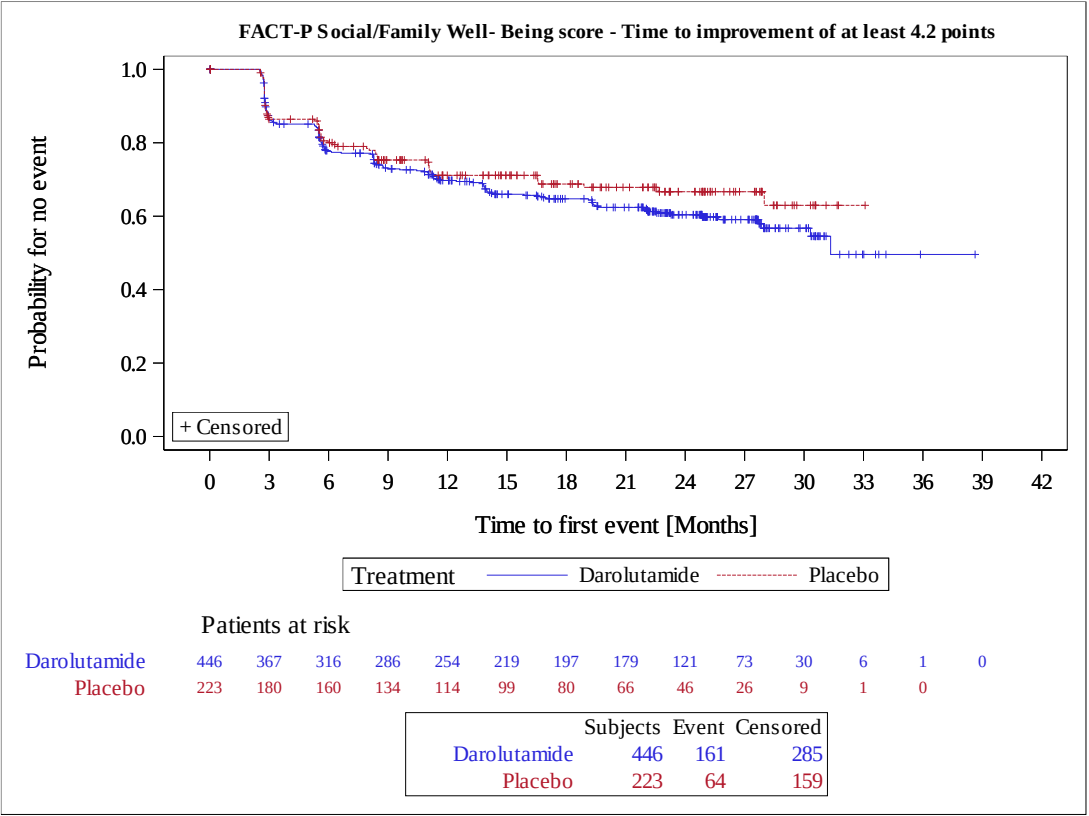
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	161 (36.1)	64 (28.7)
Number of censored participants, n (%)	285 (63.9)	159 (71.3)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	8.3 (5.7, 11.3)	11.0 (5.7, 16.6)
Median (95%-CI)	31.3 (30.3, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	1.183 (0.884, 1.584)	
p-value [4]	0.2547	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 2.1.33.1
Kaplan-Meier Plot of FACT-P Social/Family Well- Being score - Time to improvement of at least 4.2 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Table 2.1.34

FACT-P Emotional Well-Being score - Time to improvement of at least 3.6 points

(full analysis set)

Final

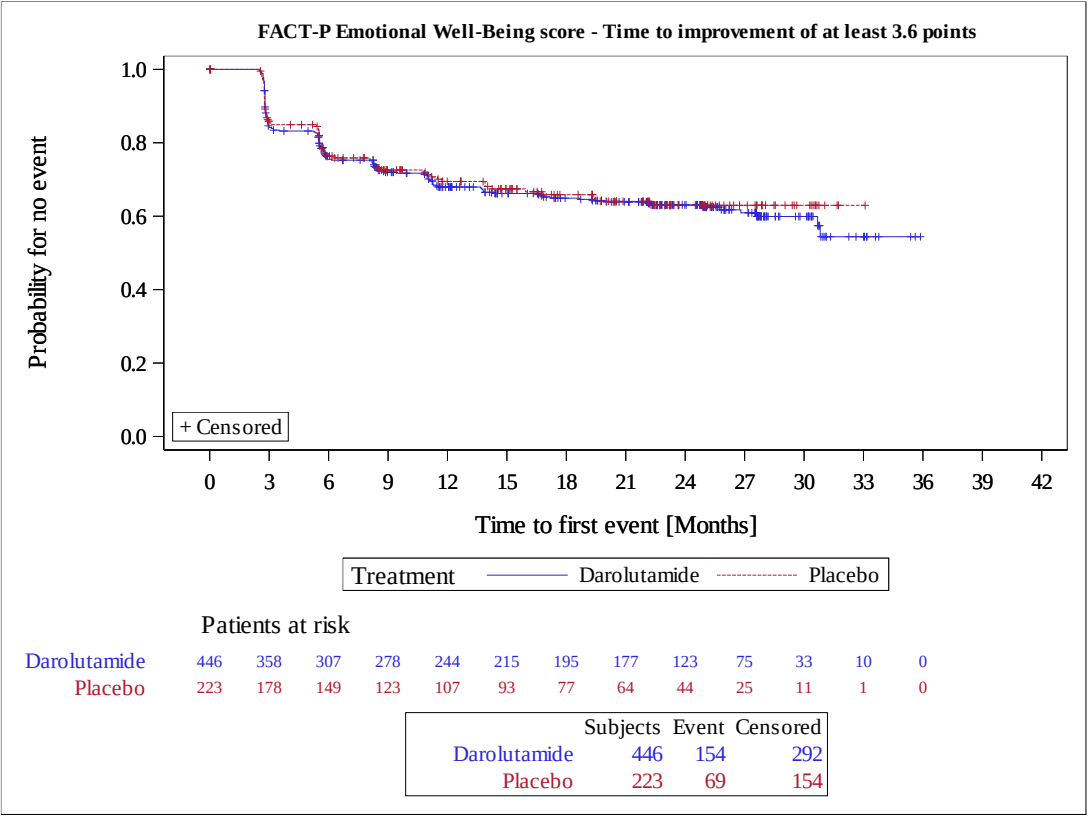
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	154 (34.5)	69 (30.9)
Number of censored participants, n (%)	292 (65.5)	154 (69.1)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	8.3 (5.6, 11.0)	8.1 (5.6, 13.9)
Median (95%-CI)	NE (30.7, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	1.033 (0.777, 1.373)	
p-value [4]	0.8198	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate;
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 2.1.34.1
Kaplan-Meier Plot of FACT-P Emotional Well-Being score - Time to improvement of at least 3.6 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Study population

Table 2.1.35

FACT-P Functional Well-Being score - Time to improvement of at least 4.2 points

(full analysis set)

Final

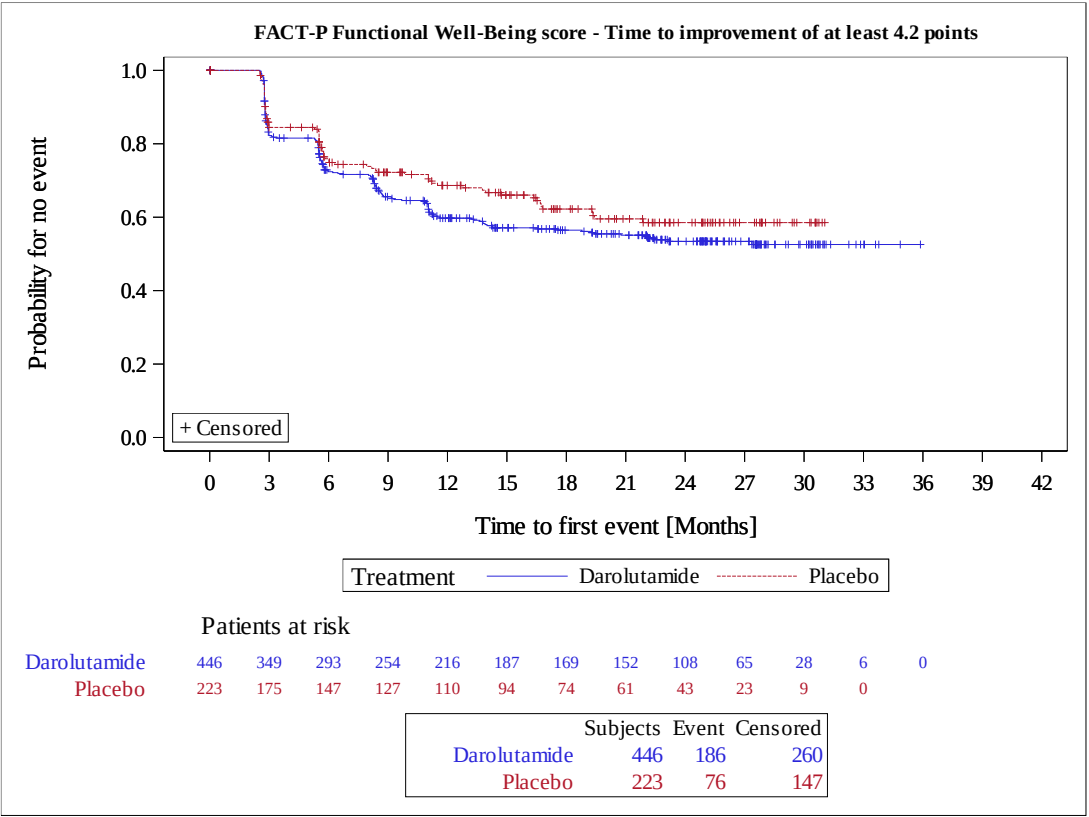
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	186 (41.7)	76 (34.1)
Number of censored participants, n (%)	260 (58.3)	147 (65.9)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	5.7 (5.5, 8.1)	6.0 (5.5, 11.5)
Median (95%-CI)	NE (22.1, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	1.199 (0.917, 1.567)	
p-value [4]	0.1806	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate; Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 2.1.35.1
Kaplan-Meier Plot of FACT-P Functional Well-Being score - Time to improvement of at least 4.2 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 2.1.36

FACT-P Prostate cancer subscale score - Time to improvement of at least 7.2 points

(full analysis set)

Final

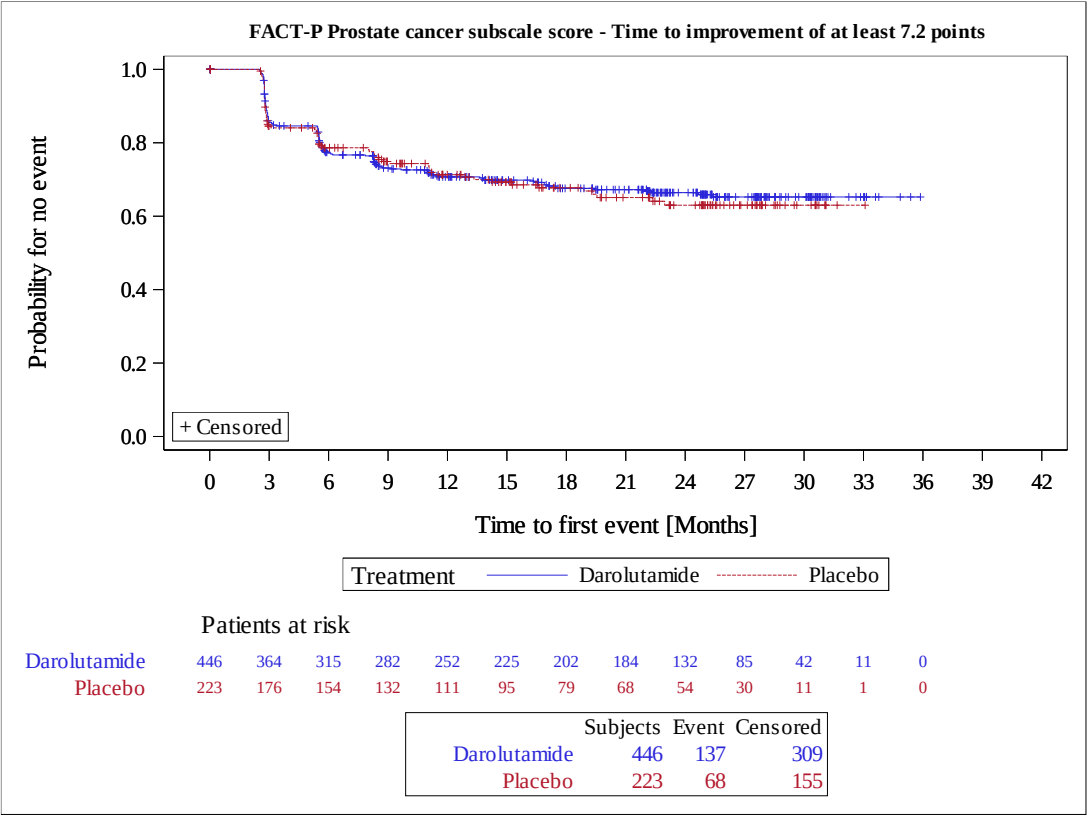
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	137 (30.7)	68 (30.5)
Number of censored participants, n (%)	309 (69.3)	155 (69.5)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	8.3 (5.7, 11.5)	8.7 (5.5, 15.2)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.935 (0.699, 1.251)	
p-value [4]	0.6485	

N=Number of participants; CI=Confidence Interval; NE=Not estimable; FACT-P=Functional Assessment of Cancer Therapy-Prostate; Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.36.1
Kaplan-Meier Plot of FACT-P Prostate cancer subscale score - Time to improvement of at least 7.2 points
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 2.1.37
Radiological progression-free survival
(full analysis set)

Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	128 (28.7)	94 (42.2)
Number of participants with radiological progression in soft tissue, n (%)*	66 (51.6)	43 (45.7)
Number of participants with radiological progression in bone, n (%)*	33 (25.8)	37 (39.4)
Number of participants who died, n (%)*	29 (22.7)	14 (14.9)
Number of censored participants, n (%)	318 (71.3)	129 (57.8)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	19.6 (15.9, 23.2)	11.2 (9.9, 13.7)
Median (95%-CI)	NE (NE, NE)	25.0 (19.0, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.541 (0.413, 0.707)	
p-value [4]	<.0001	

N=Number of participants; CI=Confidence Interval; NE=Not estimable
Participants without event are censored at last assessment date or randomization date if there is no post-baseline assessment and died later than (24+1) weeks after randomization.
*Percentages are based on participants with events.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.37.1

Radiological progression-free survival - Subgroup analysis
(full analysis set)

Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis		Hazard Ratio (95% CI) [2]	p-Value [3]	Interaction p-Value[4]
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]					
Presence of visceral metastases assessed by central review (from IWRS)											0.4826
Yes	21/ 53 (39.6)	NE (15.9, NE)		13/ 27 (48.1)	25.0 (10.0, NE)			0.706 (0.353, 1.412)		0.3226	
No	107/ 393 (27.2)	NE (NE, NE)		81/ 196 (41.3)	25.0 (19.0, NE)			0.515 (0.386, 0.689)		<.0001	
Received prior local therapy (from IWRS)											0.1796
Yes	19/ 80 (23.8)	NE (30.0, NE)		18/ 40 (45.0)	19.5 (12.4, NE)			0.339 (0.174, 0.662)		0.0009	
No	109/ 366 (29.8)	NE (NE, NE)		76/ 183 (41.5)	25.0 (18.8, NE)			0.588 (0.438, 0.789)		0.0003	
Prior local radiotherapy and/or prostatectomy											0.4089
Yes	21/ 87 (24.1)	NE (29.9, NE)		23/ 50 (46.0)	22.2 (13.7, NE)			0.423 (0.233, 0.768)		0.0035	
No	107/ 359 (29.8)	NE (NE, NE)		71/ 173 (41.0)	25.0 (18.4, NE)			0.571 (0.423, 0.772)		0.0002	
Age group											0.6179
<65 years	37/ 118 (31.4)	NE (26.8, NE)		32/ 65 (49.2)	14.2 (11.2, NE)			0.441 (0.274, 0.710)		0.0005	
65-74	53/ 193 (27.5)	NE (NE, NE)		35/ 96 (36.5)	NE (21.9, NE)			0.636 (0.415, 0.976)		0.0369	
75-84	29/ 117 (24.8)	NE (30.5, NE)		22/ 52 (42.3)	NE (14.1, NE)			0.476 (0.272, 0.831)		0.0074	
>=85 years	9/ 18 (50.0)	27.4 (13.9, NE)		5/ 10 (50.0)	19.2 (2.4, 22.9)			0.510 (0.157, 1.660)		0.2555	
Race											0.9183
White	76/ 251 (30.3)	NE (NE, NE)		55/ 125 (44.0)	22.2 (16.1, NE)			0.517 (0.364, 0.733)		0.0002	
Asian	38/ 144 (26.4)	NE (30.0, NE)		24/ 65 (36.9)	25.0 (18.4, NE)			0.588 (0.352, 0.982)		0.0401	
Black or African American	10/ 41 (24.4)	NE (NE, NE)		10/ 24 (41.7)	NE (13.8, NE)			0.511 (0.212, 1.232)		0.1267	
Other	4/ 10 (40.0)	NE (6.4, NE)		5/ 9 (55.6)	13.7 (2.5, NE)			0.686 (0.184, 2.564)		0.5732	
Geographical region											0.7709
Asia	37/ 141 (26.2)	NE (30.0, NE)		23/ 63 (36.5)	25.0 (18.4, NE)			0.597 (0.354, 1.007)		0.0506	
Latin America	35/ 119 (29.4)	NE (28.8, NE)		32/ 72 (44.4)	25.1 (16.1, NE)			0.559 (0.346, 0.905)		0.0162	
Europe and Rest of the world	56/ 186 (30.1)	NE (NE, NE)		39/ 88 (44.3)	22.6 (13.7, NE)			0.499 (0.330, 0.755)		0.0008	
Baseline PSA values by median											0.9837
< median of overall population	58/ 216 (26.9)	NE (30.5, NE)		44/ 111 (39.6)	26.0 (18.4, NE)			0.547 (0.369, 0.811)		0.0023	
>= median of overall population	67/ 220 (30.5)	NE (30.0, NE)		47/ 108 (43.5)	22.9 (16.6, NE)			0.550 (0.379, 0.799)		0.0015	
ECOG PS at baseline											0.9583
=0	61/ 235 (26.0)	NE (NE, NE)		37/ 98 (37.8)	NE (21.5, NE)			0.552 (0.367, 0.832)		0.0039	
>=1	67/ 211 (31.8)	NE (28.8, NE)		57/ 125 (45.6)	22.6 (14.2, NE)			0.557 (0.391, 0.795)		0.0011	
Gleason score at initial diagnosis											0.4624
Gleason <8	32/ 122 (26.2)	NE (29.9, NE)		30/ 67 (44.8)	22.9 (16.6, NE)			0.456 (0.276, 0.752)		0.0016	
Gleason >=8	91/ 311 (29.3)	NE (NE, NE)		60/ 146 (41.1)	25.1 (16.7, NE)			0.583 (0.420, 0.809)		0.0011	
Disease volume at baseline											0.0714
high	113/ 315 (35.9)	30.2 (28.8, NE)		75/ 157 (47.8)	19.2 (16.1, 26.0)			0.595 (0.444, 0.798)		0.0005	
low	15/ 131 (11.5)	NE (NE, NE)		19/ 66 (28.8)	NE (25.0, NE)			0.305 (0.154, 0.602)		0.0003	
Renal function - eGFR at baseline											0.6520
Normal: eGFR >= 90 mL/min	62/ 219 (28.3)	NE (29.9, NE)		40/ 104 (38.5)	25.0 (19.5, NE)			0.568 (0.381, 0.847)		0.0049	
Mild impairment: 60 <= eGFR < 90 mL/min	48/ 180 (26.7)	NE (NE, NE)		40/ 91 (44.0)	25.1 (13.9, NE)			0.492 (0.323, 0.749)		0.0007	
Moderate impairment: 30 <= eGFR < 60 mL/min	17/ 46 (37.0)	NE (16.7, NE)		13/ 27 (48.1)	21.9 (12.2, NE)			0.679 (0.329, 1.403)		0.2924	

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable

AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;

IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Participants without event are censored at last assessment date or randomization date if there is no post-baseline assessment and died later than (24+1) weeks after randomization.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.37.1

Radiological progression-free survival - Subgroup analysis

(full analysis set)

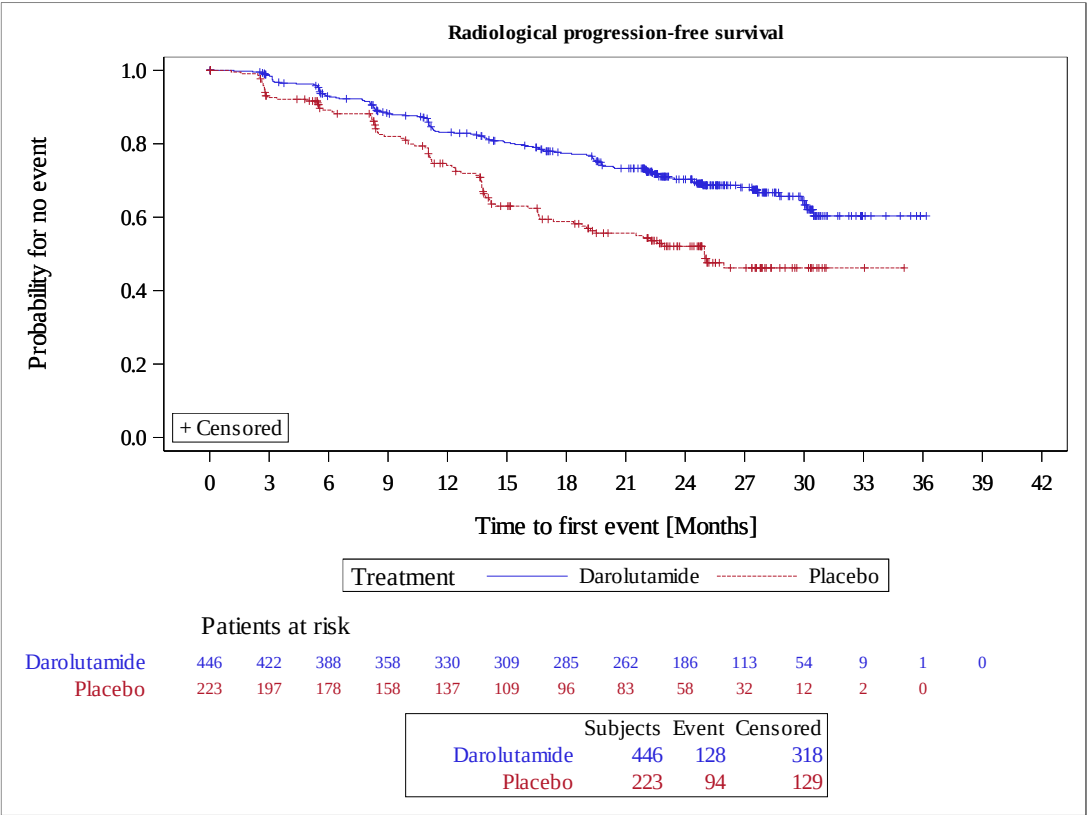
Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis		
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3]	Interaction p-Value[4]
Hepatic function at baseline									0.4862
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	117/ 387 (30.2)	NE (30.5,	NE)	87/ 204 (42.6)	25.0 (18.8,	NE)	0.558 (0.422, 0.738)	<.0001	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	11/ 59 (18.6)	NE (NE,	NE)	7/ 19 (36.8)	NE (12.2,	NE)	0.384 (0.149, 0.994)	0.0406	
Age Group (Titan)									0.5581
<65	37/ 118 (31.4)	NE (26.8,	NE)	32/ 65 (49.2)	14.2 (11.2,	NE)	0.441 (0.274, 0.710)	0.0005	
>=65 and <75	53/ 193 (27.5)	NE (NE,	NE)	35/ 96 (36.5)	NE (21.9,	NE)	0.636 (0.415, 0.976)	0.0369	
>=75	38/ 135 (28.1)	NE (30.2,	NE)	27/ 62 (43.5)	25.1 (16.1,	NE)	0.507 (0.308, 0.835)	0.0064	
Geographic region (Titan)									0.8237
Europe and north america	51/ 145 (35.2)	NE (30.2,	NE)	35/ 77 (45.5)	22.2 (13.6,	NE)	0.579 (0.375, 0.894)	0.0126	
ROTW	77/ 301 (25.6)	NE (NE,	NE)	59/ 146 (40.4)	26.0 (18.8,	NE)	0.524 (0.373, 0.737)	0.0002	

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable
AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;
IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal
Participants without event are censored at last assessment date or randomization date if there is no post-baseline assessment and died later than (24+1) weeks after randomization.
[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.
[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Study population
Figure 2.1.37.2
Kaplan-Meier Plot of Radiological progression-free survival
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no post-baseline assessment and died later than (24+1) weeks after randomization.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Study population
Table 2.1.38
Time to castration-resistant prostate cancer
(full analysis set)

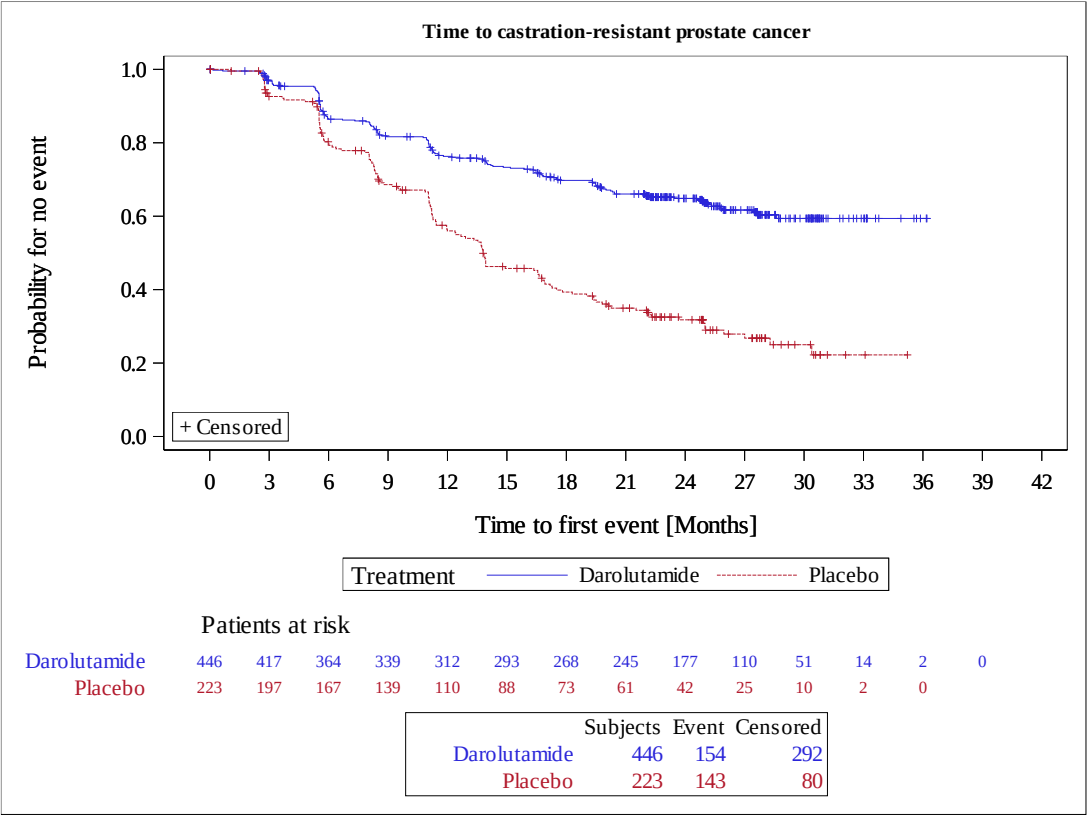
Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	154 (34.5)	143 (64.1)
PSA progression, n (%)*	85 (55.2)	91 (63.6)
Radiological progression by soft tissue and visceral lesions, n (%)*	39 (25.3)	29 (20.3)
Radiological progression by bone lesions, n (%)*	16 (10.4)	20 (14.0)
Symptomatic skeletal event, n (%)*	14 (9.1)	3 (2.1)
Number of censored participants, n (%)	292 (65.5)	80 (35.9)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	13.9 (11.1, 16.9)	8.1 (5.7, 8.6)
Median (95%-CI)	NE (NE, NE)	13.8 (12.0, 16.8)
75%-ile (95%-CI)	NE (NE, NE)	28.3 (24.9, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.404 (0.321, 0.508)	
p-value [4]	<.0001	

N=Number of participants; CI=Confidence Interval; NE=Not estimable
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
*Percentages are based on participants with events.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Study population
Figure 2.1.38.1
Kaplan-Meier Plot of Time to castration-resistant prostate cancer
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 2.1.39

Time to initiation of subsequent systemic anticancer therapy for prostate cancer

(full analysis set)

Final

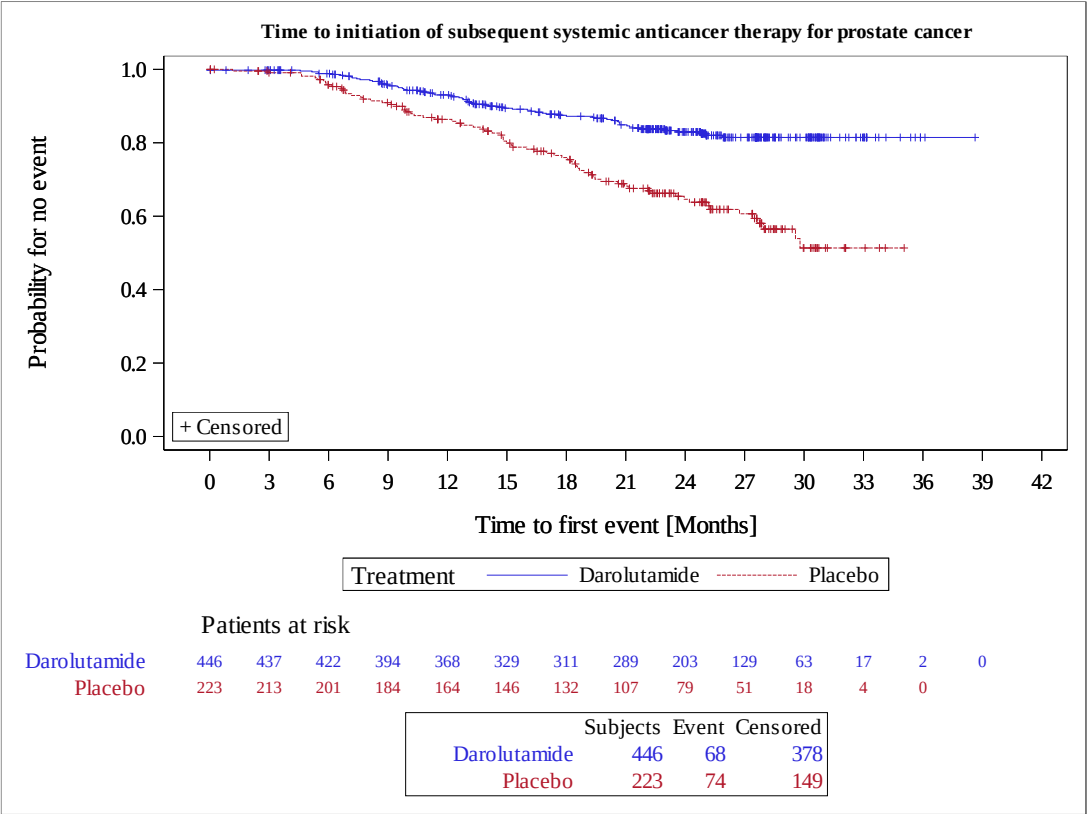
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	68 (15.2)	74 (33.2)
Number of censored participants, n (%)	378 (84.8)	149 (66.8)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	NE (NE, NE)	18.2 (14.8, 20.6)
Median (95%-CI)	NE (NE, NE)	NE (27.7, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.401 (0.288, 0.558)	
p-value [4]	<.0001	

N=Number of participants; CI=Confidence Interval; NE=Not estimable
Participants without event are censored at last visit date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 2.1.39.1
Kaplan-Meier Plot of Time to initiation of subsequent systemic anticancer therapy for prostate cancer
(full analysis set)

Final



Participants without event are censored at last visit date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 2.1.40

Time to first prostate cancer-related invasive procedure (full analysis set)

Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	22 (4.9)	15 (6.7)
Number of censored participants, n (%)	424 (95.1)	208 (93.3)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.689 (0.357, 1.328)	
p-value [4]	0.2633	

N=Number of participants; CI=Confidence Interval; NE=Not estimable
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
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Study population

Table 2.1.40.1

Time to first prostate cancer-related invasive procedure - Subgroup analysis

(full analysis set)

Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis	
	n/N[s]	(%)	Median (95% CI) [1]	n/N[s]	(%)	Median (95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3] Interaction p-Value[4]
Presence of visceral metastases assessed by central review (from IWRS)								0.7097
Yes	4/ 53	(7.5)	NE (NE, NE)	2/ 27	(7.4)	NE (NE, NE)	0.919 (0.168, 5.016)	0.9219
No	18/ 393	(4.6)	NE (NE, NE)	13/ 196	(6.6)	NE (NE, NE)	0.658 (0.322, 1.343)	0.2471
Received prior local therapy (from IWRS)								0.9148
Yes	5/ 80	(6.3)	NE (NE, NE)	3/ 40	(7.5)	NE (NE, NE)	0.736 (0.176, 3.081)	0.6733
No	17/ 366	(4.6)	NE (NE, NE)	12/ 183	(6.6)	NE (NE, NE)	0.685 (0.327, 1.434)	0.3130
Prior local radiotherapy and/or prostatectomy								0.0626
Yes	7/ 87	(8.0)	NE (NE, NE)	1/ 50	(2.0)	NE (NE, NE)	3.989 (0.491, 32.414)	0.1614
No	15/ 359	(4.2)	NE (NE, NE)	14/ 173	(8.1)	NE (NE, NE)	0.488 (0.235, 1.011)	0.0485
Age group								0.7564
<65 years	5/ 118	(4.2)	NE (NE, NE)	6/ 65	(9.2)	NE (NE, NE)	0.427 (0.130, 1.399)	0.1472
65-74	10/ 193	(5.2)	NE (NE, NE)	5/ 96	(5.2)	NE (NE, NE)	1.010 (0.345, 2.956)	0.9848
75-84	6/ 117	(5.1)	NE (NE, NE)	4/ 52	(7.7)	NE (NE, NE)	0.591 (0.167, 2.096)	0.4103
>=85 years	1/ 18	(5.6)	NE (NE, NE)	0/ 10	(0.0)	NE (NE, NE)	NE (NE, NE)	NE
Race								0.6414
White	8/ 251	(3.2)	NE (NE, NE)	7/ 125	(5.6)	NE (NE, NE)	0.537 (0.195, 1.481)	0.2221
Asian	11/ 144	(7.6)	NE (NE, NE)	4/ 65	(6.2)	NE (NE, NE)	1.210 (0.385, 3.800)	0.7436
Black or African American	3/ 41	(7.3)	NE (NE, NE)	4/ 24	(16.7)	NE (NE, NE)	0.397 (0.089, 1.775)	0.2103
Other	0/ 10	(0.0)	NE (NE, NE)	0/ 9	(0.0)	NE (NE, NE)	NE (NE, NE)	NE
Geographical region								0.5985
Asia	10/ 141	(7.1)	NE (NE, NE)	4/ 63	(6.3)	NE (NE, NE)	1.079 (0.338, 3.441)	0.8977
Latin America	4/ 119	(3.4)	NE (NE, NE)	5/ 72	(6.9)	NE (NE, NE)	0.463 (0.124, 1.725)	0.2397
Europe and Rest of the world	8/ 186	(4.3)	NE (NE, NE)	6/ 88	(6.8)	NE (NE, NE)	0.599 (0.208, 1.726)	0.3369
Baseline PSA values by median								0.0019
< median of overall population	5/ 216	(2.3)	NE (NE, NE)	12/ 111	(10.8)	NE (NE, NE)	0.206 (0.073, 0.586)	0.0010
>= median of overall population	17/ 220	(7.7)	NE (NE, NE)	3/ 108	(2.8)	NE (NE, NE)	2.648 (0.776, 9.036)	0.1058
ECOG PS at baseline								0.8586
=0	10/ 235	(4.3)	NE (NE, NE)	6/ 98	(6.1)	NE (NE, NE)	0.663 (0.241, 1.826)	0.4239
>=1	12/ 211	(5.7)	NE (NE, NE)	9/ 125	(7.2)	NE (NE, NE)	0.756 (0.319, 1.795)	0.5249
Gleason score at initial diagnosis								0.9778
Gleason <8	5/ 122	(4.1)	NE (NE, NE)	4/ 67	(6.0)	NE (NE, NE)	0.660 (0.177, 2.458)	0.5328
Gleason >=8	16/ 311	(5.1)	NE (NE, NE)	11/ 146	(7.5)	NE (NE, NE)	0.663 (0.308, 1.429)	0.2911
Disease volume at baseline								0.6365
high	19/ 315	(6.0)	NE (NE, NE)	12/ 157	(7.6)	NE (NE, NE)	0.745 (0.362, 1.535)	0.4237
low	3/ 131	(2.3)	NE (NE, NE)	3/ 66	(4.5)	NE (NE, NE)	0.492 (0.099, 2.439)	0.3755
Renal function - eGFR at baseline								0.3714
Normal: eGFR >= 90 mL/min	10/ 219	(4.6)	NE (NE, NE)	4/ 104	(3.8)	NE (NE, NE)	1.161 (0.364, 3.703)	0.8002
Mild impairment: 60 <= eGFR < 90 mL/min	8/ 180	(4.4)	NE (NE, NE)	9/ 91	(9.9)	NE (NE, NE)	0.416 (0.160, 1.078)	0.0623
Moderate impairment: 30 <= eGFR < 60 mL/min	3/ 46	(6.5)	NE (NE, NE)	2/ 27	(7.4)	NE (NE, NE)	0.943 (0.157, 5.650)	0.9489

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable

AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;

IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Participants without event are censored at last assessment date or randomization date if there is no follow-up available.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Study population

Table 2.1.40.1

Time to first prostate cancer-related invasive procedure - Subgroup analysis (full analysis set)

Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis	
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3] Interaction p-Value[4]
Hepatic function at baseline								0.1665
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	21/ 387 (5.4)	NE (	NE, NE)	13/ 204 (6.4)	NE (	NE, NE)	0.817 (0.409, 1.631)	0.5656
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 59 (1.7)	NE (	NE, NE)	2/ 19 (10.5)	NE (	NE, NE)	0.143 (0.013, 1.577)	0.0643
Age Group (Titan)								0.5582
<65	5/ 118 (4.2)	NE (	NE, NE)	6/ 65 (9.2)	NE (	NE, NE)	0.427 (0.130, 1.399)	0.1472
>=65 and <75	10/ 193 (5.2)	NE (	NE, NE)	5/ 96 (5.2)	NE (	NE, NE)	1.010 (0.345, 2.956)	0.9848
>=75	7/ 135 (5.2)	NE (	NE, NE)	4/ 62 (6.5)	NE (	NE, NE)	0.712 (0.208, 2.435)	0.5867
Geographic region (Titan)								0.8340
Europe and north america	6/ 145 (4.1)	NE (	NE, NE)	4/ 77 (5.2)	NE (	NE, NE)	0.779 (0.220, 2.763)	0.6989
ROTW	16/ 301 (5.3)	NE (	NE, NE)	11/ 146 (7.5)	NE (	NE, NE)	0.667 (0.309, 1.437)	0.2977

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable

AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;

IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Participants without event are censored at last assessment date or randomization date if there is no follow-up available.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

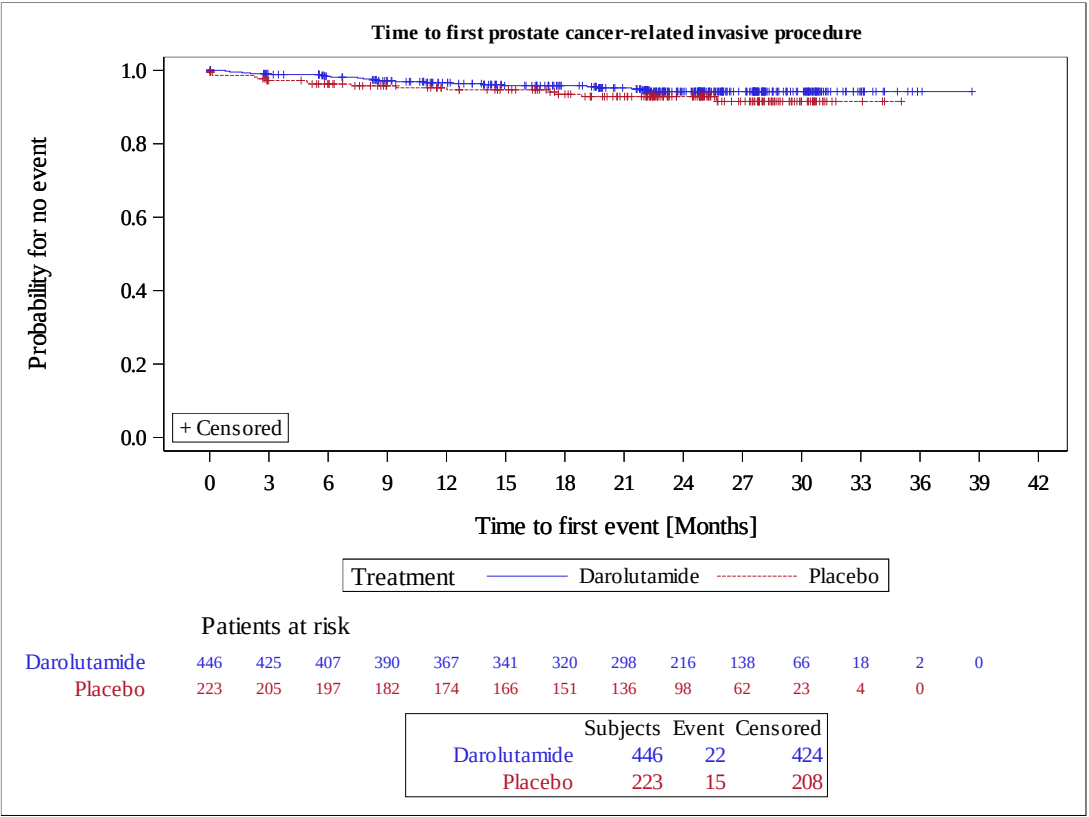
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.40.2
Kaplan-Meier Plot of Time to first prostate cancer-related invasive procedure
(full analysis set)

Final

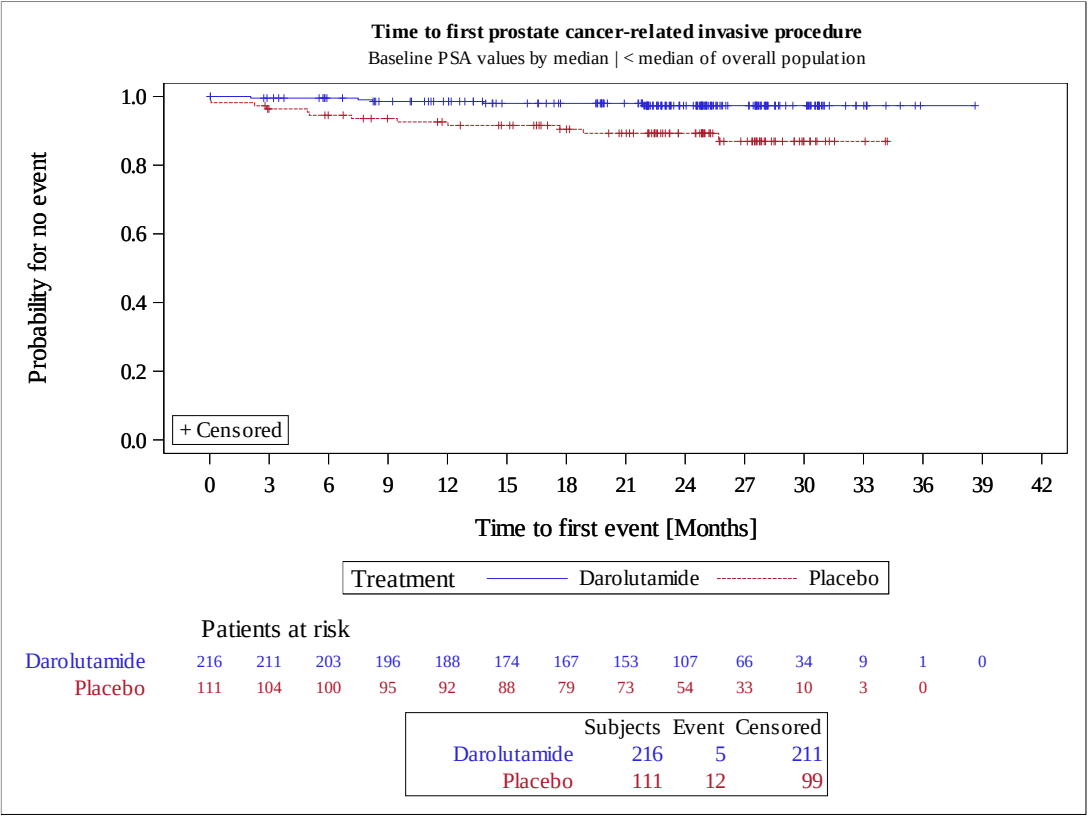


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.40.2
Kaplan-Meier Plot of Time to first prostate cancer-related invasive procedure
(full analysis set)

Final

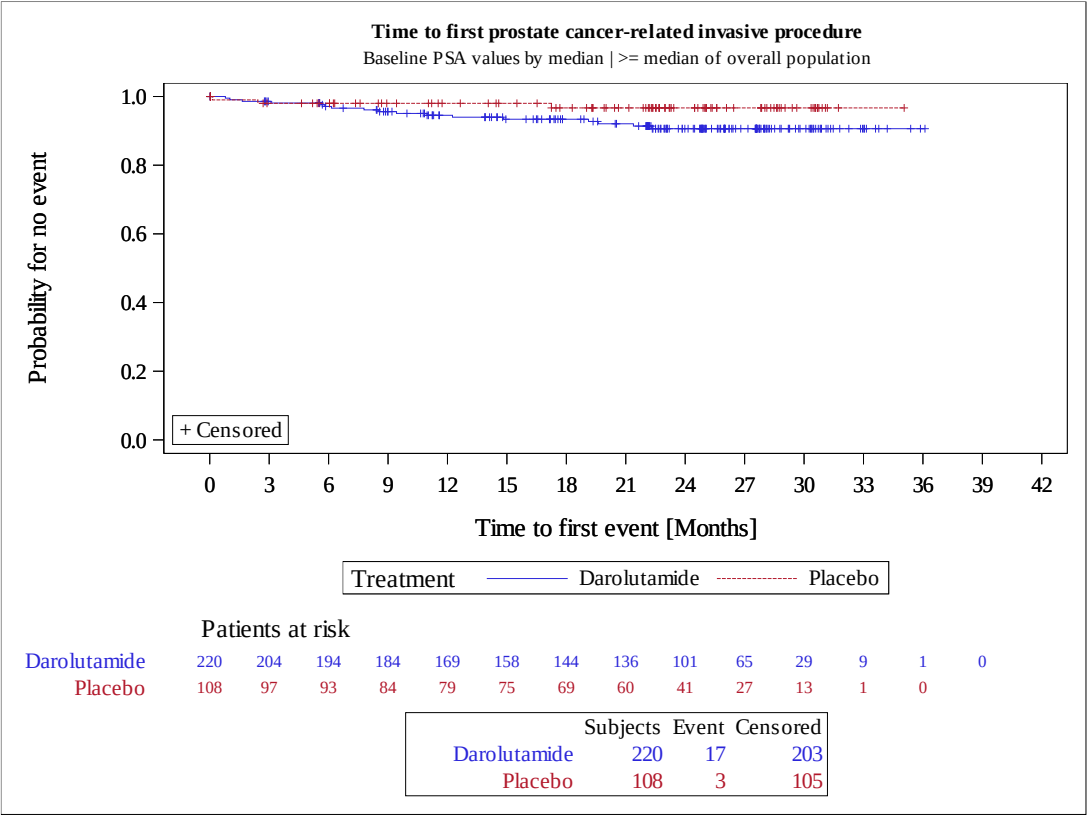


Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.40.2
Kaplan-Meier Plot of Time to first prostate cancer-related invasive procedure
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 2.1.41
Time to prostate-specific antigen progression
(full analysis set)

Final

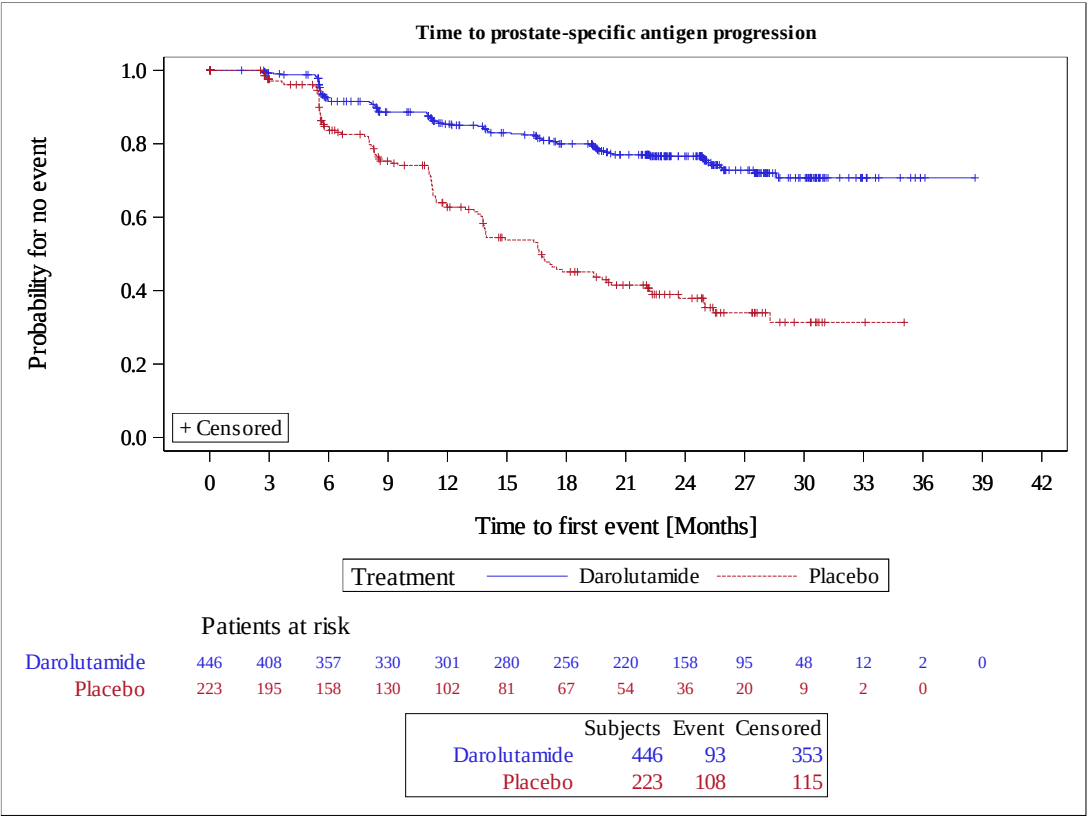
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	93 (20.9)	108 (48.4)
Number of censored participants, n (%)	353 (79.1)	115 (51.6)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	25.2 (19.3, NE)	9.2 (8.0, 11.2)
Median (95%-CI)	NE (NE, NE)	16.8 (13.8, 20.1)
75%-ile (95%-CI)	NE (NE, NE)	NE (28.3, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.306 (0.231, 0.405)	
p-value [4]	<.0001	

N=Number of participants; CI=Confidence Interval; NE=Not estimable
Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.41.1
Kaplan-Meier Plot of Time to prostate-specific antigen progression
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.1.42

Progression-free survival 2

(full analysis set)

Final

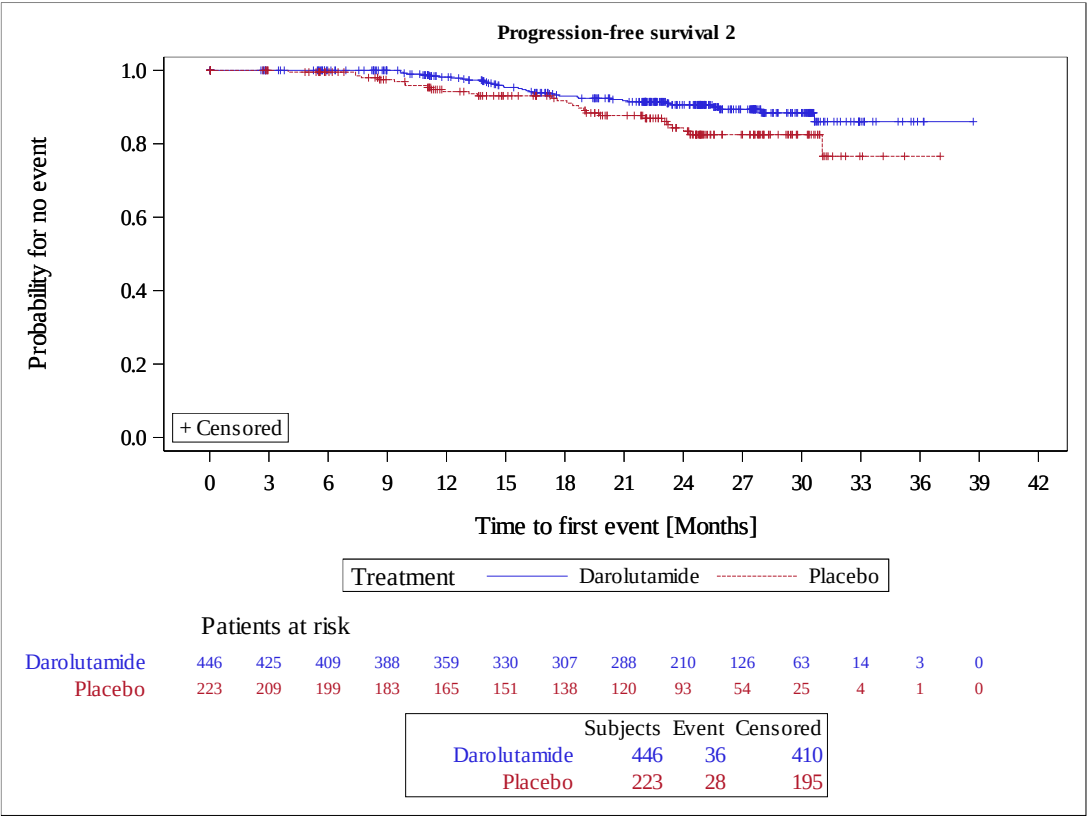
	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	36 (8.1)	28 (12.6)
Number of censored participants, n (%)	410 (91.9)	195 (87.4)
Kaplan-Meier estimates of Time to Event (Days) [1]		
25%-ile (95%-CI)	NE (NE, NE)	NE (31.0, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.590 (0.360, 0.968)	
p-value [4]	0.0346	

N=Number of participants; CI=Confidence Interval; NE=Not estimable
Participants without event are censored at last assessment date or randomization date if there is no follow-up available or end date of the first subsequent anticancer therapy (ACT) for prostate cancer. If first subsequent ACT is on-going participants are censored at cutoff date or last known alive date if they discontinued study or lost follow up.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.1.42.1
Kaplan-Meier Plot of Progression-free survival 2
(full analysis set)

Final



Participants without event are censored at last assessment date or randomization date if there is no follow-up available or end date of the first subsequent anticancer therapy (ACT) for prostate cancer. If first subsequent ACT is on-going participants are censored at cutoff date or last known alive date if they discontinued study or lost follow up.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 2.2.1
FACT-P total score: Descriptive statistics
(full analysis set)

Final

Visit	Darolutamide (N=446)				Placebo (N=223)			
	n	Value at Visit Mean (SD)	n	Change from Baseline Mean (SD)	n	Value at Visit Mean (SD)	n	Change from Baseline Mean (SD)
Baseline / Day 1	440	113.37 (21.13)			222	112.55 (22.41)		
Visit 2 / Week 12	422	117.28 (20.58)	422	3.41 (17.26)	212	115.27 (20.19)	212	1.00 (18.82)
Visit 3 / Week 24	411	116.96 (21.41)	411	2.60 (18.08)	198	115.73 (22.08)	198	1.81 (18.13)
Visit 4 / Week 36	378	117.17 (21.11)	378	1.55 (18.92)	173	116.51 (20.22)	173	1.45 (18.59)
Visit 5 / Week 48	348	117.47 (21.33)	348	1.28 (20.38)	152	115.51 (21.92)	152	0.59 (20.06)
Visit 6 / Week 60	307	118.20 (21.22)	307	1.95 (19.45)	136	113.93 (21.36)	136	-1.87 (21.36)
Visit 7 / Week 72	302	117.47 (21.49)	302	1.27 (19.75)	114	116.27 (22.90)	114	-0.86 (21.95)
Visit 8 / Week 84	280	118.69 (21.64)	280	2.40 (19.51)	96	117.99 (21.66)	96	-0.13 (21.50)
Visit 9 / Week 96	256	118.18 (21.61)	256	1.95 (19.01)	82	119.71 (20.99)	82	1.30 (20.29)
Visit 10 / Week 108	178	118.79 (21.21)	178	2.17 (18.29)	63	118.58 (21.24)	63	0.93 (21.31)
Visit 11 / Week 120	116	117.01 (21.36)	116	0.02 (18.75)	34	122.69 (20.47)	34	2.89 (23.87)
Visit 12 / Week 132	56	118.01 (20.94)	56	2.78 (17.22)	15	127.74 (16.69)	15	6.44 (14.63)
Visit 13 / Week 144	18	119.41 (19.17)	18	8.13 (16.82)	2	142.50 (3.54)	2	28.50 (21.92)
Visit 14 / Week 156	6	112.18 (25.80)	6	7.02 (19.52)	1	109.00 (NE)	1	13.00 (NE)
Visit 15 / Week 168	1	110.50 (NE)	1	25.50 (NE)	0			
End of Treatment	105	98.15 (26.54)	109	-14.57 (26.05)	105	98.07 (26.36)	105	-14.99 (19.28)
Active Follow-up Visit 1	27	105.96 (27.74)	38	-7.16 (20.63)	27	109.83 (20.34)	27	-7.67 (15.90)
Active Follow-up Visit 2	17	117.40 (28.72)	20	-3.08 (25.35)	17	106.93 (29.61)	17	-8.85 (19.82)
Active Follow-up Visit 3	14	112.68 (30.50)	15	-12.55 (18.44)	14	109.33 (29.83)	14	-13.52 (25.05)
Active Follow-up Visit 4	6	111.33 (27.26)	9	-10.70 (19.24)	6	123.86 (31.94)	6	-1.67 (12.96)
Active Follow-up Visit 5	4	119.57 (29.53)	7	0.98 (17.63)	4	132.08 (34.77)	4	-1.46 (16.79)

N=Number of participants; n=Number of participants with non missing values; SD=Standard Deviation; NE=Not estimable
FACT-P=Functional Assessment of Cancer Therapy-Prostate
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.2.2

Worst Pain subscale score (BPI-SF Item 3): Descriptive statistics
(full analysis set)

Final

Visit	Darolutamide (N=446)				Placebo (N=223)			
	n	Value at Visit Mean (SD)	n	Change from Baseline Mean (SD)	n	Value at Visit Mean (SD)	n	Change from Baseline Mean (SD)
Baseline / Day 1	436	2.31 (2.61)			222	2.21 (2.67)		
Visit 2 / Week 12	420	1.86 (2.32)	413	-0.40 (2.19)	213	2.10 (2.48)	212	-0.03 (2.25)
Visit 3 / Week 24	415	1.90 (2.50)	407	-0.30 (2.57)	199	2.23 (2.67)	198	0.18 (2.39)
Visit 4 / Week 36	383	1.87 (2.50)	374	-0.28 (2.66)	176	2.02 (2.61)	175	-0.01 (2.45)
Visit 5 / Week 48	352	1.80 (2.54)	343	-0.29 (2.69)	155	2.16 (2.72)	155	0.09 (2.83)
Visit 6 / Week 60	313	1.73 (2.39)	304	-0.31 (2.70)	138	2.39 (2.93)	138	0.26 (2.87)
Visit 7 / Week 72	304	1.77 (2.43)	296	-0.28 (2.67)	113	2.12 (2.64)	113	0.09 (2.90)
Visit 8 / Week 84	282	1.61 (2.47)	275	-0.36 (2.69)	96	1.62 (2.15)	96	-0.36 (2.47)
Visit 9 / Week 96	258	1.66 (2.55)	252	-0.32 (2.67)	82	1.61 (2.22)	82	-0.33 (2.39)
Visit 10 / Week 108	181	1.39 (2.31)	175	-0.37 (2.48)	63	1.83 (2.60)	63	-0.05 (3.16)
Visit 11 / Week 120	117	1.61 (2.42)	111	-0.03 (2.70)	34	1.49 (2.33)	34	-0.63 (1.68)
Visit 12 / Week 132	57	1.42 (2.36)	52	0.26 (2.36)	15	1.29 (2.47)	15	-1.05 (2.49)
Visit 13 / Week 144	18	1.27 (2.46)	18	0.09 (2.27)	2	0.00 (0.00)	2	-0.50 (0.71)
Visit 14 / Week 156	6	2.48 (3.84)	6	1.39 (2.33)	1	0.00 (NE)	1	0.00 (NE)
Visit 15 / Week 168	1	0.00 (NE)	1	0.00 (NE)	0			
End of Treatment	104	3.82 (3.38)	104	1.23 (3.20)	104	3.46 (3.23)	103	1.31 (2.82)
Active Follow-up Visit 1	22	2.92 (3.42)	29	0.41 (2.77)	22	2.27 (2.75)	22	1.26 (1.67)
Active Follow-up Visit 2	14	1.88 (3.21)	13	-0.52 (3.78)	14	2.91 (3.77)	14	1.74 (3.60)
Active Follow-up Visit 3	9	1.07 (2.11)	9	-0.43 (0.71)	9	2.81 (4.35)	9	1.25 (4.15)
Active Follow-up Visit 4	6	0.81 (1.72)	6	-0.45 (0.57)	6	2.33 (3.67)	6	0.63 (1.05)
Active Follow-up Visit 5	4	0.00 (0.00)	3	-0.33 (0.58)	4	1.75 (3.50)	4	0.38 (0.75)

N=Number of participants; n=Number of participants with non missing values; SD=Standard Deviation; NE=Not estimable

BPI-SF=Brief Pain Inventory - Short Form

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 2.2.3
Pain interference score (BPI-SF Item 9 a-g): Descriptive statistics
(full analysis set)

Final

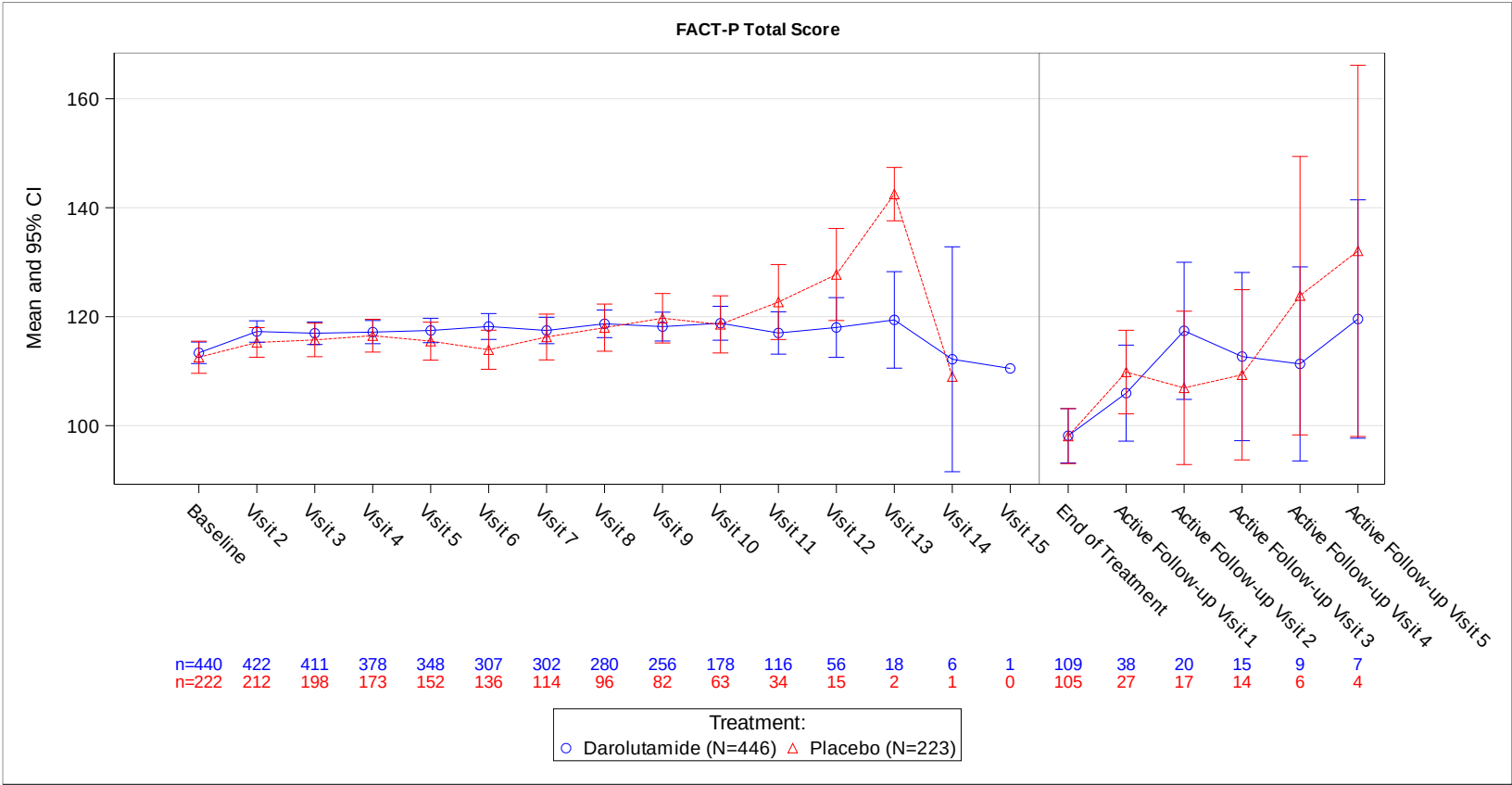
Visit	Darolutamide (N=446)				Placebo (N=223)			
	n	Value at Visit Mean (SD)	n	Change from Baseline Mean (SD)	n	Value at Visit Mean (SD)	n	Change from Baseline Mean (SD)
Baseline / Day 1	434	1.61 (2.21)			222	1.54 (2.05)		
Visit 2 / Week 12	419	1.26 (1.91)	412	-0.27 (1.74)	212	1.51 (2.13)	211	0.07 (1.74)
Visit 3 / Week 24	414	1.30 (1.99)	406	-0.19 (1.89)	199	1.59 (2.25)	198	0.19 (1.92)
Visit 4 / Week 36	381	1.38 (2.14)	371	-0.03 (2.13)	175	1.45 (2.23)	174	0.05 (2.15)
Visit 5 / Week 48	352	1.29 (2.13)	342	-0.04 (2.20)	155	1.77 (2.56)	155	0.40 (2.58)
Visit 6 / Week 60	313	1.20 (1.90)	303	-0.09 (2.09)	138	1.80 (2.40)	138	0.39 (2.48)
Visit 7 / Week 72	304	1.25 (2.03)	295	-0.04 (2.13)	113	1.71 (2.39)	113	0.34 (2.63)
Visit 8 / Week 84	282	1.10 (1.97)	274	-0.14 (2.20)	96	1.47 (2.17)	96	0.14 (2.35)
Visit 9 / Week 96	258	1.14 (2.00)	251	-0.13 (2.09)	82	1.35 (2.08)	82	0.00 (2.29)
Visit 10 / Week 108	181	0.98 (1.76)	174	-0.09 (1.97)	63	1.48 (2.27)	63	0.28 (2.78)
Visit 11 / Week 120	117	1.11 (1.87)	110	0.17 (2.32)	34	1.44 (2.53)	34	0.01 (2.97)
Visit 12 / Week 132	57	1.05 (2.00)	51	0.42 (1.90)	15	0.70 (1.66)	15	-0.42 (1.68)
Visit 13 / Week 144	18	0.92 (1.78)	18	0.42 (1.31)	2	0.06 (0.09)	2	0.06 (0.09)
Visit 14 / Week 156	6	1.82 (2.86)	6	1.12 (1.74)	1	0.00 (NE)	1	0.00 (NE)
Visit 15 / Week 168	1	0.00 (NE)	1	0.00 (NE)	0			
End of Treatment	104	3.16 (3.01)	104	1.26 (2.81)	104	2.66 (2.65)	103	1.23 (2.17)
Active Follow-up Visit 1	22	2.33 (2.82)	29	0.69 (2.82)	22	1.75 (2.59)	22	0.68 (2.18)
Active Follow-up Visit 2	14	1.88 (3.15)	13	0.66 (3.22)	14	2.29 (3.44)	14	1.13 (3.33)
Active Follow-up Visit 3	9	0.94 (1.80)	9	0.14 (0.45)	9	2.34 (3.75)	9	0.87 (3.89)
Active Follow-up Visit 4	6	1.07 (2.63)	6	0.19 (0.82)	6	1.91 (3.01)	6	0.30 (1.16)
Active Follow-up Visit 5	4	0.00 (0.00)	3	-0.21 (0.37)	4	1.39 (2.79)	4	0.27 (1.63)

N=Number of participants; n=Number of participants with non missing values; SD=Standard Deviation; NE=Not estimable
BPI-SF=Brief Pain Inventory - Short Form
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.3.1
FACT-P total score: Means with 95% CI
(full analysis set)

Final

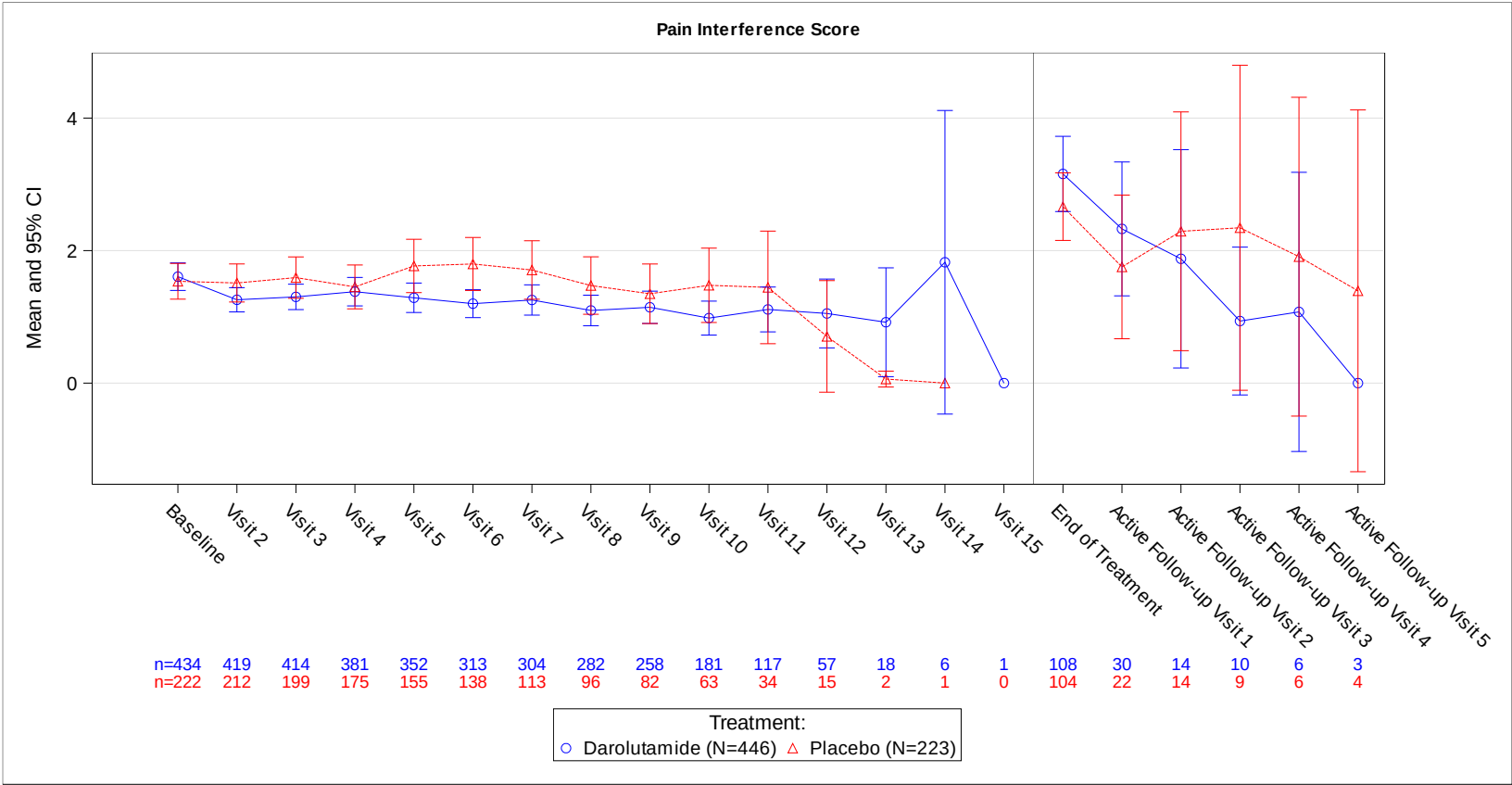


N=Number of participants; n=Number of participants with non missing values
FACT-P=Functional Assessment of Cancer Therapy-Prostate
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.3.2
Pain interference score (BPI-SF Item 9 a-g): Means with 95% CI
(full analysis set)

Final

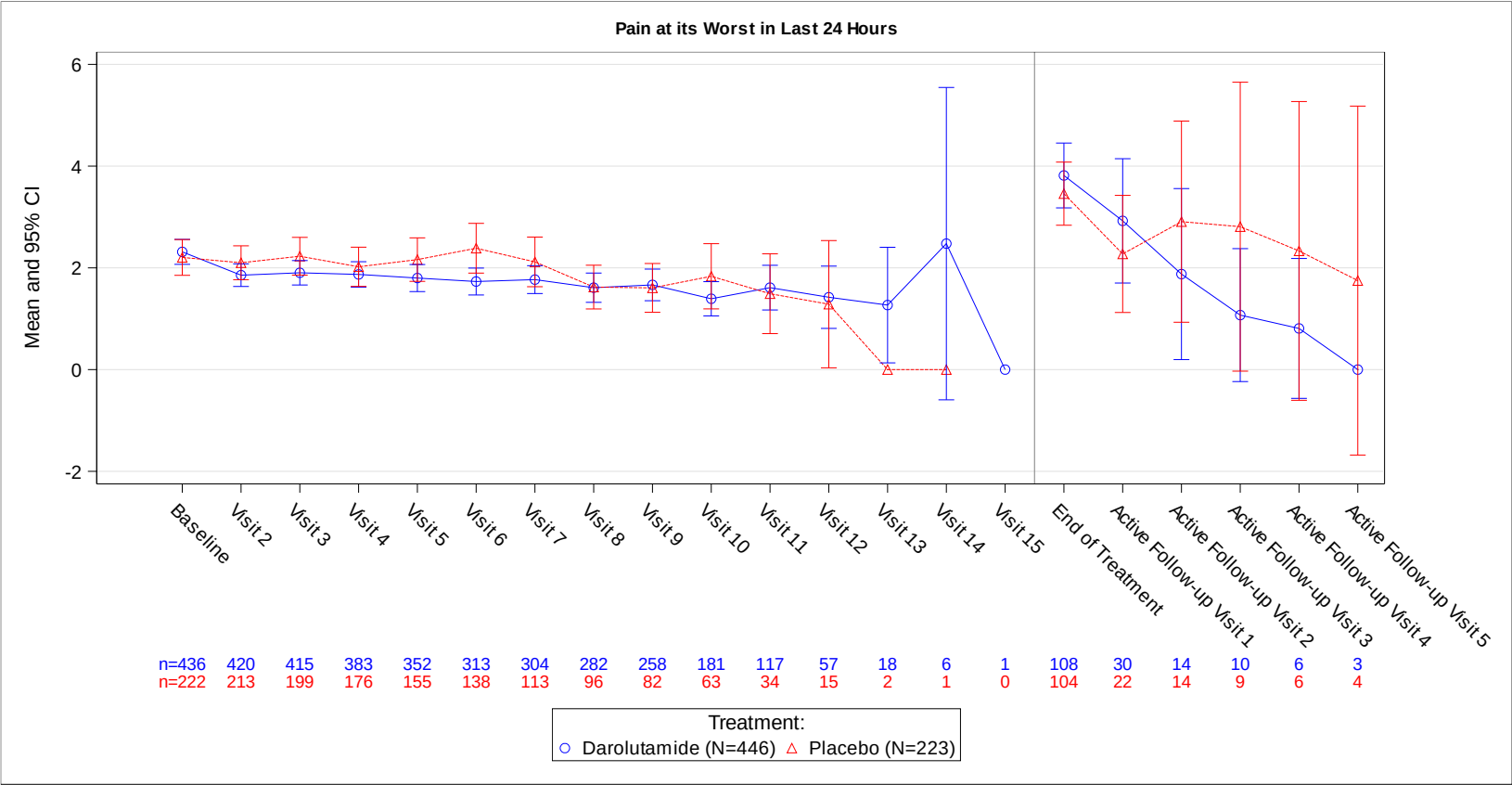


N=Number of participants; n=Number of participants with non missing values
BPI-SF=Brief Pain Inventory - Short Form
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 2.3.3
Worst Pain subscale score (BPI-SF Item 3): Means with 95% CI
(full analysis set)

Final



N=Number of participants; n=Number of participants with non missing values
BPI-SF=Brief Pain Inventory - Short Form
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 2.4.1
Prostate-specific antigen undetectable rates
(full analysis set)

Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with detectable PSA values >=0.2 ng/mL at baseline	425	211
Number of participants with undetectable PSA values <0.2 ng/mL at any timepoint, n (%)	266 (62.6)	39 (18.5)
Stratified Analysis		
Odds Ratio	7.384	
95% CI	4.886, 11.159	
p-value	<.0001	
Relative Risk	3.041	
95% CI	2.285, 4.047	
p-value	<.0001	
Risk Difference	44.281	
95% CI	37.381, 51.181	
p-value	<.0001	

N=Number of participants; n=Number of participants with undetectable PSA values; CI=Confidence Interval; NE=Not estimable; PSA=Prostate-specific antigen; OR=Odds Ratio; RR=Relative Risk; RD=Risk Difference
Percentages are based on participants who had a detectable PSA value at baseline.
OR, RR, RD were constructed using proc freq stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no). In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for OR, RR, RD were constructed using normal approximation (Wald). P-values for OR, RR, RD were calculated using Wald test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 2.4.1.1.1

Prostate-specific antigen undetectable rates - Subgroup analysis
(full analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=223) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Relative Risk	(95% CI)	p-Value	
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	30/ 50 (60.0)	2/ 23 (8.7)	15.750	(3.320, 74.716)	0.0005	0.2734
No	236/ 375 (62.9)	37/ 188 (19.7)	6.929	(4.570, 10.505)	<.0001	
Received prior local therapy (from IWRS)						
Yes	49/ 70 (70.0)	13/ 37 (35.1)	4.308	(1.847, 10.045)	0.0007	0.0168
No	217/ 355 (61.1)	26/ 174 (14.9)	8.951	(5.604, 14.296)	<.0001	
Prior local radiotherapy and/or prostatectomy						
Yes	51/ 76 (67.1)	19/ 44 (43.2)	2.684	(1.249, 5.767)	0.0114	<.0001
No	215/ 349 (61.6)	20/ 167 (12.0)	11.793	(7.050, 19.728)	<.0001	
Age group						
<65 years	69/ 112 (61.6)	13/ 63 (20.6)	6.172	(3.006, 12.670)	<.0001	0.4960
65-74	116/ 187 (62.0)	19/ 89 (21.3)	6.019	(3.347, 10.824)	<.0001	
75-84	70/ 108 (64.8)	6/ 49 (12.2)	13.202	(5.152, 33.831)	<.0001	
>=85 years	11/ 18 (61.1)	1/ 10 (10.0)	14.143	(1.457, 137.30)	0.0223	
Race						
White	157/ 241 (65.1)	22/ 117 (18.8)	8.071	(4.731, 13.768)	<.0001	0.9219
Asian	81/ 138 (58.7)	12/ 63 (19.0)	6.039	(2.956, 12.338)	<.0001	
Black or African American	22/ 37 (59.5)	4/ 22 (18.2)	6.600	(1.860, 23.424)	0.0035	
Other	6/ 9 (66.7)	1/ 9 (11.1)	16.000	(1.315, 194.62)	0.0296	
Geographical region						
Asia	79/ 136 (58.1)	11/ 61 (18.0)	6.300	(3.017, 13.155)	<.0001	0.4723
Latin America	74/ 111 (66.7)	10/ 68 (14.7)	11.600	(5.325, 25.268)	<.0001	
Europe and Rest of the world	113/ 178 (63.5)	18/ 82 (22.0)	6.181	(3.374, 11.324)	<.0001	
Baseline PSA values by median						
< median of overall population	155/ 205 (75.6)	28/ 103 (27.2)	8.304	(4.846, 14.228)	<.0001	0.0869
>= median of overall population	111/ 220 (50.5)	11/ 108 (10.2)	8.980	(4.562, 17.677)	<.0001	
ECOG PS at baseline						
=0	155/ 224 (69.2)	24/ 91 (26.4)	6.271	(3.634, 10.823)	<.0001	0.0910
>=1	111/ 201 (55.2)	15/ 120 (12.5)	8.633	(4.699, 15.861)	<.0001	
Gleason score at initial diagnosis						
Gleason <8	74/ 113 (65.5)	19/ 62 (30.6)	4.294	(2.209, 8.348)	<.0001	0.0130
Gleason >=8	183/ 299 (61.2)	19/ 139 (13.7)	9.964	(5.824, 17.045)	<.0001	
Disease volume at baseline						
high	166/ 304 (54.6)	23/ 148 (15.5)	6.537	(3.970, 10.765)	<.0001	0.7956
low	100/ 121 (82.6)	16/ 63 (25.4)	13.988	(6.694, 29.230)	<.0001	
Renal function - eGFR at baseline						
Normal; eGFR >= 90 mL/min	136/ 213 (63.8)	19/ 98 (19.4)	7.344	(4.138, 13.032)	<.0001	0.6776
Mild impairment: 60 <= eGFR < 90 mL/min	104/ 170 (61.2)	13/ 86 (15.1)	8.848	(4.547, 17.219)	<.0001	
Moderate impairment: 30 <= eGFR < 60 mL/min	26/ 41 (63.4)	6/ 26 (23.1)	5.778	(1.901, 17.564)	0.0020	

N=Number of participants; N[s]=Number of participants with detectable PSA values at baseline in subgroup; n=Number of participants with undetectable PSA values; CI=Confidence Interval; NE=Not estimable
 PSA=Prostate-specific antigen; OR=Odds Ratio; RR=Relative Risk; RD=Risk Difference
 AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate; IWRS=Interactive Web Response System; ULN=Upper limit of normal
 Percentages are based on participants who had a detectable PSA value at baseline.
 Relative risk was constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
 95% CI for Relative Risk was constructed using normal approximation (Wald). P-value for Relative Risk was calculated using Wald test.
 p-Value for interaction from a generalized linear model with treatment, subgroup and treatment by subgroup interaction as covariates with log-link.
 Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 2.4.1.1
Prostate-specific antigen undetectable rates - Subgroup analysis
(full analysis set)

Final

Subgroup Level	Darolutamide(N=446) n/N[s] (%)	Placebo (N=223) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Relative Risk	(95% CI)	p-Value	
Hepatic function at baseline						0.4116
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	229/ 367 (62.4)	37/ 193 (19.2)	6.996	(4.615, 10.606)	<.0001	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	37/ 58 (63.8)	2/ 18 (11.1)	14.095	(2.949, 67.377)	0.0009	
Age Group (Titan)						0.3022
<65	69/ 112 (61.6)	13/ 63 (20.6)	6.172	(3.006, 12.670)	<.0001	
>=65 and <75	116/ 187 (62.0)	19/ 89 (21.3)	6.019	(3.347, 10.824)	<.0001	
>=75	81/ 126 (64.3)	7/ 59 (11.9)	13.371	(5.607, 31.890)	<.0001	
Geographic region (Titan)						0.2556
Europe and north america	86/ 142 (60.6)	16/ 72 (22.2)	5.375	(2.807, 10.292)	<.0001	
ROTW	180/ 283 (63.6)	23/ 139 (16.5)	8.814	(5.300, 14.659)	<.0001	

N=Number of participants; N[s]=Number of participants with detectable PSA values at baseline in subgroup; n=Number of participants with undetectable PSA values; CI=Confidence Interval; NE=Not estimable
PSA=Prostate-specific antigen; OR=Odds Ratio; RR=Relative Risk; RD=Risk Difference
AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate; IWRS=Interactive Web Response System; ULN=Upper limit of normal
Percentages are based on participants who had a detectable PSA value at baseline.
Relative risk was constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Relative Risk was constructed using normal approximation (Wald). P-value for Relative Risk was calculated using Wald test.
p-Value for interaction from a generalized linear model with treatment, subgroup and treatment by subgroup interaction as covariates with log-link.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.1.1
Treatment duration and observation time for Safety in months
(safety analysis set)

Final

		Darolutamide (N=445)	Placebo (N=221)	Total (N=666)
Treatment Duration[1]	n (missing)	445 (0)	221 (0)	666 (0)
	Mean (SD)	21.32 (9.16)	17.74 (9.32)	20.13 (9.36)
	Median	24.21	17.35	22.82
	Q1, Q3	13.40, 28.15	9.86, 25.79	11.73, 27.60
	Min, Max	0.03, 38.80	0.23, 36.73	0.03, 38.80
Safety Observation Time[2]	n (missing)	445 (0)	221 (0)	666 (0)
	Mean (SD)	21.63 (8.88)	18.28 (9.09)	20.52 (9.08)
	Median	24.21	18.04	23.26
	Q1, Q3	13.99, 28.35	9.92, 26.48	12.65, 27.69
	Min, Max	0.03, 38.76	0.23, 36.70	0.03, 38.76

N=Number of participants; n=Number of participants with non-missing values; SD=Standard Deviation; Q1=25%-Quartile; Q3=75%-Quartile; Min=Minimum; Max=Maximum
[1] (day of last dose of study drug minus day of first dose of study drug + 1) / 30.44. Time off drug and dose interruptions are included.
[2] (min(day of last dose of study drug + 30, death date, last known alive date, cutoff date) minus day of first dose of study drug) / 30.44
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Study population

Table 3.1.2

Incidence of Adverse Events leading to discontinuation of study treatment (by SOC and PT)
(safety analysis set)

Final

System Organ Class (SOC) Preferred Term (PT)	Darolutamide (N=445)		Placebo (N=221)	
	n	(%)	n	(%)
Investigations	4	(0.9)	2	(0.9)
Alanine aminotransferase increased	2	(0.4)	1	(0.5)
Aspartate aminotransferase increased	2	(0.4)	1	(0.5)
Blood bilirubin increased	1	(0.2)	0	(0.0)
Blood creatinine increased	1	(0.2)	0	(0.0)
Blood sodium decreased	1	(0.2)	0	(0.0)
Eastern Cooperative Oncology Group performance status worsened	0	(0.0)	1	(0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	(0.9)	2	(0.9)
Bladder cancer recurrent	0	(0.0)	1	(0.5)
Diffuse large B-cell lymphoma	1	(0.2)	0	(0.0)
Lung carcinoma cell type unspecified stage IV	0	(0.0)	1	(0.5)
Malignant melanoma	1	(0.2)	0	(0.0)
Rectal cancer	1	(0.2)	0	(0.0)
Squamous cell carcinoma of lung	1	(0.2)	0	(0.0)
Cardiac disorders	2	(0.4)	3	(1.4)
Myocardial infarction	2	(0.4)	0	(0.0)
Acute myocardial infarction	0	(0.0)	1	(0.5)
Cardiac arrest	0	(0.0)	1	(0.5)
Cardiac failure congestive	0	(0.0)	1	(0.5)
Musculoskeletal and connective tissue disorders	2	(0.4)	3	(1.4)
Back pain	0	(0.0)	2	(0.9)
Bone pain	1	(0.2)	1	(0.5)
Pain in extremity	0	(0.0)	2	(0.9)
Neck pain	1	(0.2)	0	(0.0)
Infections and infestations	3	(0.7)	1	(0.5)
Herpes zoster meningitis	0	(0.0)	1	(0.5)
Pneumonia	1	(0.2)	0	(0.0)
Pulmonary sepsis	1	(0.2)	0	(0.0)
Septic shock	1	(0.2)	0	(0.0)
Gastrointestinal disorders	0	(0.0)	3	(1.4)
Gastrointestinal haemorrhage	0	(0.0)	2	(0.9)
Intestinal ischaemia	0	(0.0)	1	(0.5)
Injury, poisoning and procedural complications	3	(0.7)	0	(0.0)
Craniocerebral injury	2	(0.4)	0	(0.0)
Femur fracture	1	(0.2)	0	(0.0)
Renal and urinary disorders	1	(0.2)	2	(0.9)
Tubulointerstitial nephritis	0	(0.0)	1	(0.5)
Urinary retention	1	(0.2)	0	(0.0)
Urinary tract obstruction	0	(0.0)	1	(0.5)
Skin and subcutaneous tissue disorders	2	(0.4)	1	(0.5)
Rash	1	(0.2)	0	(0.0)
Rash papular	1	(0.2)	0	(0.0)
Skin ulcer	0	(0.0)	1	(0.5)
General disorders and administration site conditions	0	(0.0)	2	(0.9)
Death	0	(0.0)	1	(0.5)
Gait disturbance	0	(0.0)	1	(0.5)
Performance status decreased	0	(0.0)	1	(0.5)
Hepatobiliary disorders	2	(0.4)	0	(0.0)
Hyperbilirubinaemia	1	(0.2)	0	(0.0)

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, n: Number of participants with event

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Study population
Table 3.1.2
Incidence of Adverse Events leading to discontinuation of study treatment (by SOC and PT)
(safety analysis set)

Final

System Organ Class (SOC) Preferred Term (PT)	Darolutamide (N=445)		Placebo (N=221)	
	n	(%)	n	(%)
Liver injury	1	(0.2)	0	(0.0)
Nervous system disorders	1	(0.2)	1	(0.5)
Cerebral infarction	0	(0.0)	1	(0.5)
Paraparesis	1	(0.2)	0	(0.0)
Spinal cord compression	1	(0.2)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	1	(0.2)	1	(0.5)
Dyspnoea	1	(0.2)	0	(0.0)
Pulmonary embolism	0	(0.0)	1	(0.5)
Vascular disorders	2	(0.4)	0	(0.0)
Hypertension	1	(0.2)	0	(0.0)
Pelvic venous thrombosis	1	(0.2)	0	(0.0)
Superficial vein thrombosis	1	(0.2)	0	(0.0)
Thrombosis	1	(0.2)	0	(0.0)
Metabolism and nutrition disorders	0	(0.0)	1	(0.5)
Decreased appetite	0	(0.0)	1	(0.5)

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, n: Number of participants with event
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.1
Summary of Adverse Events
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	405 (91.0)	199 (90.0)
Number of censored patients, n (%)	40 (9.0)	22 (10.0)
Time to Event (Month)		
25%-ile (95% CI)	1.6 (1.2, 2.1)	1.7 (1.2, 2.3)
Median (95% CI)	3.7 (2.9, 5.0)	3.3 (2.8, 5.2)
75%-ile (95% CI)	8.3 (7.8, 10.8)	8.4 (7.0, 10.8)
Unstratified Analysis		
Hazard Ratio	0.988	
95% CI	0.834, 1.171	
p-value	0.8914	
Odds Ratio	1.119	
95% CI	0.648, 1.935	
p-value	0.6863	
Relative Risk	1.011	
95% CI	0.959, 1.065	
p-value	0.6913	
Risk Difference	0.966	
95% CI	-3.792, 5.724	
p-value	0.6907	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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 Study population
 Table 3.2.1.1
 Summary of Adverse Events - Subgroup analysis
 (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	49/ 54 (90.7)	24/ 26 (92.3)	1.145	(0.694, 1.888)	0.5928	0.5497
No	356/391 (91.0)	175/195 (89.7)	0.971	(0.810, 1.163)	0.7472	
Received prior local therapy (from IWRS)						
Yes	74/ 80 (92.5)	37/ 40 (92.5)	0.972	(0.654, 1.442)	0.8851	0.8565
No	331/365 (90.7)	162/181 (89.5)	0.996	(0.826, 1.203)	0.9704	
Prior local radiotherapy and/or prostatectomy						
Yes	78/ 87 (89.7)	45/ 50 (90.0)	1.088	(0.753, 1.571)	0.6519	0.5347
No	327/358 (91.3)	154/171 (90.1)	0.959	(0.792, 1.162)	0.6709	
Age group						
<65 years	106/117 (90.6)	54/ 64 (84.4)	0.978	(0.704, 1.359)	0.8960	0.1896
65-74	172/193 (89.1)	87/ 95 (91.6)	0.816	(0.630, 1.059)	0.1225	
75-84	111/117 (94.9)	48/ 52 (92.3)	1.334	(0.949, 1.874)	0.0945	
>=85 years	16/ 18 (88.9)	10/ 10 (100.0)	1.083	(0.470, 2.495)	0.8504	
Race						
White	218/249 (87.6)	108/124 (87.1)	1.002	(0.796, 1.263)	0.9836	0.6601
Asian	136/144 (94.4)	59/ 65 (90.8)	0.934	(0.687, 1.270)	0.6604	
Black or African American	42/ 42 (100.0)	23/ 23 (100.0)	1.208	(0.705, 2.069)	0.4841	
Other	9/ 10 (90.0)	9/ 9 (100.0)	0.599	(0.229, 1.566)	0.2871	
Geographical region						
Asia	133/141 (94.3)	57/ 63 (90.5)	0.925	(0.677, 1.263)	0.6203	0.6694
Latin America	117/120 (97.5)	68/ 70 (97.1)	1.129	(0.836, 1.526)	0.4237	
Europe and Rest of the world	155/184 (84.2)	74/ 88 (84.1)	0.966	(0.732, 1.274)	0.8055	
Baseline PSA values by median						
< median of overall population	195/215 (90.7)	102/110 (92.7)	0.906	(0.712, 1.152)	0.4157	0.3868
>= median of overall population	199/219 (90.9)	94/108 (87.0)	1.063	(0.831, 1.358)	0.6260	
ECOG PS at baseline						
=0	211/235 (89.8)	87/ 96 (90.6)	0.923	(0.719, 1.186)	0.5295	0.4386
>=1	194/210 (92.4)	112/125 (89.6)	1.050	(0.832, 1.326)	0.6752	
Gleason score at initial diagnosis						
Gleason <8	114/124 (91.9)	56/ 65 (86.2)	1.256	(0.912, 1.729)	0.1608	0.0751
Gleason >=8	278/308 (90.3)	135/146 (92.5)	0.880	(0.716, 1.081)	0.2195	
Disease volume at baseline						
high	292/314 (93.0)	143/156 (91.7)	1.000	(0.819, 1.222)	0.9988	0.8252
low	113/131 (86.3)	56/ 65 (86.2)	0.954	(0.692, 1.316)	0.7764	
Renal function - eGFR at baseline						
Normal: eGFR >= 90 mL/min	209/221 (94.6)	92/102 (90.2)	0.969	(0.758, 1.238)	0.7988	0.9229
Mild impairment: 60 <= eGFR < 90 mL/min	155/178 (87.1)	82/ 91 (90.1)	1.012	(0.774, 1.324)	0.9287	
Moderate impairment: 30 <= eGFR < 60 mL/min	40/ 45 (88.9)	24/ 27 (88.9)	0.893	(0.536, 1.488)	0.6622	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
 N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
 Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
 Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
 p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
 Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Study population
Table 3.2.1.1
Summary of Adverse Events - Subgroup analysis
(safety analysis set)

Final

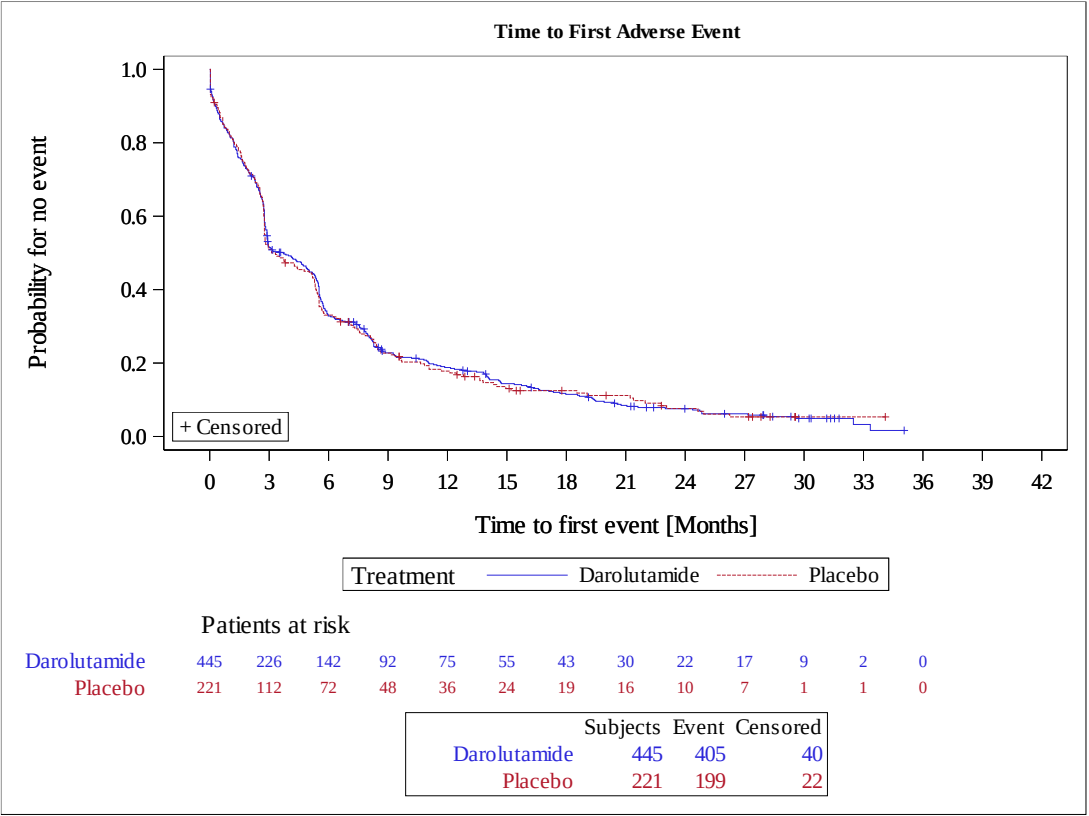
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.0785
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	351/387 (90.7)	183/202 (90.6)	0.936	(0.783, 1.120)	0.4662	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	54/ 58 (93.1)	16/ 19 (84.2)	1.726	(0.956, 3.117)	0.0653	
Age Group (Titan)						0.1116
<65	106/117 (90.6)	54/ 64 (84.4)	0.978	(0.704, 1.359)	0.8960	
>=65 and <75	172/193 (89.1)	87/ 95 (91.6)	0.816	(0.630, 1.059)	0.1225	
>=75	127/135 (94.1)	58/ 62 (93.5)	1.273	(0.931, 1.739)	0.1268	
Geographic region (Titan)						0.3358
Europe and north america	115/144 (79.9)	63/ 77 (81.8)	0.868	(0.638, 1.181)	0.3659	
ROTW	290/301 (96.3)	136/144 (94.4)	1.042	(0.850, 1.278)	0.6878	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.1.2
Kaplan-Meier Plot of Time to First Adverse Event
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.2
Summary of Adverse Events (disease-related AEs are excluded)
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	404 (90.8)	199 (90.0)
Number of censored patients, n (%)	41 (9.2)	22 (10.0)
Time to Event (Month)		
25%-ile (95% CI)	1.6 (1.2, 2.1)	1.7 (1.2, 2.3)
Median (95% CI)	3.7 (2.9, 5.0)	3.3 (2.8, 5.2)
75%-ile (95% CI)	8.3 (7.8, 10.8)	8.4 (7.0, 10.8)
Unstratified Analysis		
Hazard Ratio	0.986	
95% CI	0.832, 1.169	
p-value	0.8716	
Odds Ratio	1.089	
95% CI	0.632, 1.879	
p-value	0.7583	
Relative Risk	1.008	
95% CI	0.956, 1.063	
p-value	0.7613	
Risk Difference	0.741	
95% CI	-4.034, 5.516	
p-value	0.7609	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.2.1

Summary of Adverse Events (disease-related AEs are excluded) - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	49/ 54 (90.7)	24/ 26 (92.3)	1.145	(0.694, 1.888)	0.5928	0.5458
No	355/391 (90.8)	175/195 (89.7)	0.968	(0.808, 1.161)	0.7279	
Received prior local therapy (from IWRS)						
Yes	74/ 80 (92.5)	37/ 40 (92.5)	0.972	(0.654, 1.442)	0.8851	0.8687
No	330/365 (90.4)	162/181 (89.5)	0.994	(0.823, 1.199)	0.9477	
Prior local radiotherapy and/or prostatectomy						
Yes	78/ 87 (89.7)	45/ 50 (90.0)	1.088	(0.753, 1.571)	0.6519	0.5273
No	326/358 (91.1)	154/171 (90.1)	0.957	(0.790, 1.159)	0.6526	
Age group						
<65 years	106/117 (90.6)	54/ 64 (84.4)	0.978	(0.704, 1.359)	0.8960	0.1902
65-74	172/193 (89.1)	87/ 95 (91.6)	0.816	(0.630, 1.059)	0.1225	
75-84	111/117 (94.9)	48/ 52 (92.3)	1.334	(0.949, 1.874)	0.0945	
>=85 years	15/ 18 (83.3)	10/ 10 (100.0)	0.989	(0.425, 2.302)	0.9798	
Race						
White	218/249 (87.6)	108/124 (87.1)	1.002	(0.796, 1.263)	0.9836	0.6603
Asian	135/144 (93.8)	59/ 65 (90.8)	0.932	(0.685, 1.267)	0.6504	
Black or African American	42/ 42 (100.0)	23/ 23 (100.0)	1.208	(0.705, 2.069)	0.4841	
Other	9/ 10 (90.0)	9/ 9 (100.0)	0.599	(0.229, 1.566)	0.2871	
Geographical region						
Asia	132/141 (93.6)	57/ 63 (90.5)	0.923	(0.675, 1.261)	0.6103	0.6611
Latin America	117/120 (97.5)	68/ 70 (97.1)	1.129	(0.836, 1.526)	0.4237	
Europe and Rest of the world	155/184 (84.2)	74/ 88 (84.1)	0.966	(0.732, 1.274)	0.8055	
Baseline PSA values by median						
< median of overall population	195/215 (90.7)	102/110 (92.7)	0.906	(0.712, 1.152)	0.4157	0.4051
>= median of overall population	198/219 (90.4)	94/108 (87.0)	1.057	(0.827, 1.352)	0.6553	
ECOG PS at baseline						
=0	211/235 (89.8)	87/ 96 (90.6)	0.923	(0.719, 1.186)	0.5295	0.4575
>=1	193/210 (91.9)	112/125 (89.6)	1.046	(0.828, 1.320)	0.7053	
Gleason score at initial diagnosis						
Gleason <8	114/124 (91.9)	56/ 65 (86.2)	1.256	(0.912, 1.729)	0.1608	0.0728
Gleason >=8	277/308 (89.9)	135/146 (92.5)	0.877	(0.714, 1.078)	0.2101	
Disease volume at baseline						
high	291/314 (92.7)	143/156 (91.7)	0.997	(0.816, 1.218)	0.9762	0.8410
low	113/131 (86.3)	56/ 65 (86.2)	0.954	(0.692, 1.316)	0.7764	
Renal function - eGFR at baseline						
Normal: eGFR >= 90 mL/min	209/221 (94.6)	92/102 (90.2)	0.969	(0.758, 1.238)	0.7988	0.8898
Mild impairment: 60 <= eGFR < 90 mL/min	155/178 (87.1)	82/ 91 (90.1)	1.012	(0.774, 1.324)	0.9287	
Moderate impairment: 30 <= eGFR < 60 mL/min	39/ 45 (86.7)	24/ 27 (88.9)	0.872	(0.522, 1.456)	0.5963	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.2.1
Summary of Adverse Events (disease-related AEs are excluded) - Subgroup analysis
(safety analysis set)

Final

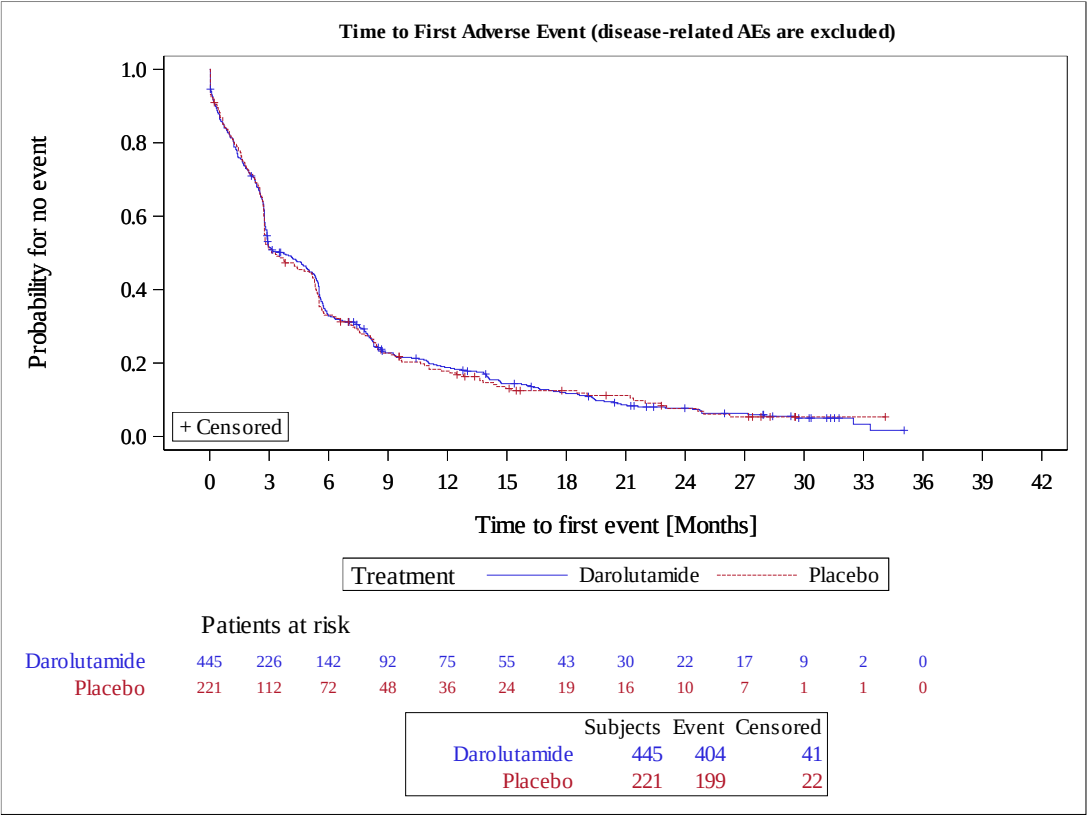
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.0782
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	350/387 (90.4)	183/202 (90.6)	0.934	(0.781, 1.117)	0.4517	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	54/ 58 (93.1)	16/ 19 (84.2)	1.726	(0.956, 3.117)	0.0653	
Age Group (Titan)						0.1222
<65	106/117 (90.6)	54/ 64 (84.4)	0.978	(0.704, 1.359)	0.8960	
>=65 and <75	172/193 (89.1)	87/ 95 (91.6)	0.816	(0.630, 1.059)	0.1225	
>=75	126/135 (93.3)	58/ 62 (93.5)	1.261	(0.922, 1.723)	0.1431	
Geographic region (Titan)						0.3462
Europe and north america	115/144 (79.9)	63/ 77 (81.8)	0.868	(0.638, 1.181)	0.3659	
ROTW	289/301 (96.0)	136/144 (94.4)	1.039	(0.847, 1.274)	0.7095	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.2.2
Kaplan-Meier Plot of Time to First Adverse Event (disease-related AEs are excluded)
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.3
Summary of Serious Adverse Events
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	105 (23.6)	52 (23.5)
Number of censored patients, n (%)	340 (76.4)	169 (76.5)
Time to Event (Month)		
25%-ile (95% CI)	22.4 (15.6, NE)	20.1 (12.2, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.897	
95% CI	0.643, 1.252	
p-value	0.5237	
Odds Ratio	1.004	
95% CI	0.686, 1.468	
p-value	0.9849	
Relative Risk	1.003	
95% CI	0.750, 1.341	
p-value	0.9849	
Risk Difference	0.066	
95% CI	-6.778, 6.910	
p-value	0.9849	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.3.1

Summary of Serious Adverse Events - Subgroup analysis

(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.8693
Yes	17/ 54 (31.5)	8/ 26 (30.8)	0.953	(0.411, 2.209)	0.9112	
No	88/391 (22.5)	44/195 (22.6)	0.887	(0.617, 1.275)	0.5166	
Received prior local therapy (from IWRS)						0.8242
Yes	21/ 80 (26.3)	11/ 40 (27.5)	0.793	(0.380, 1.656)	0.5364	
No	84/365 (23.0)	41/181 (22.7)	0.918	(0.632, 1.335)	0.6552	
Prior local radiotherapy and/or prostatectomy						0.9897
Yes	23/ 87 (26.4)	14/ 50 (28.0)	0.872	(0.448, 1.696)	0.6862	
No	82/358 (22.9)	38/171 (22.2)	0.915	(0.623, 1.345)	0.6523	
Age group						0.6008
<65 years	21/117 (17.9)	10/ 64 (15.6)	0.999	(0.470, 2.126)	0.9982	
65-74	44/193 (22.8)	26/ 95 (27.4)	0.752	(0.463, 1.222)	0.2478	
75-84	33/117 (28.2)	11/ 52 (21.2)	1.276	(0.645, 2.525)	0.4828	
>=85 years	7/ 18 (38.9)	5/ 10 (50.0)	0.551	(0.167, 1.820)	0.3182	
Race						0.5318
White	50/249 (20.1)	26/124 (21.0)	0.837	(0.521, 1.347)	0.4637	
Asian	44/144 (30.6)	16/ 65 (24.6)	1.152	(0.649, 2.042)	0.6286	
Black or African American	9/ 42 (21.4)	8/ 23 (34.8)	0.484	(0.187, 1.257)	0.1278	
Other	2/ 10 (20.0)	2/ 9 (22.2)	0.859	(0.121, 6.103)	0.8791	
Geographical region						0.6249
Asia	43/141 (30.5)	16/ 63 (25.4)	1.114	(0.627, 1.978)	0.7132	
Latin America	23/120 (19.2)	16/ 70 (22.9)	0.786	(0.415, 1.489)	0.4588	
Europe and Rest of the world	39/184 (21.2)	20/ 88 (22.7)	0.782	(0.456, 1.344)	0.3726	
Baseline PSA values by median						0.4229
< median of overall population	47/215 (21.9)	22/110 (20.0)	0.989	(0.596, 1.642)	0.9663	
>= median of overall population	53/219 (24.2)	30/108 (27.8)	0.770	(0.492, 1.206)	0.2520	
ECOG PS at baseline						0.6084
=0	50/235 (21.3)	21/ 96 (21.9)	0.818	(0.491, 1.363)	0.4398	
>=1	55/210 (26.2)	31/125 (24.8)	1.017	(0.654, 1.580)	0.9412	
Gleason score at initial diagnosis						0.1318
Gleason <8	25/124 (20.2)	18/ 65 (27.7)	0.650	(0.355, 1.193)	0.1613	
Gleason >=8	78/308 (25.3)	30/146 (20.5)	1.134	(0.744, 1.728)	0.5583	
Disease volume at baseline						0.1675
high	89/314 (28.3)	40/156 (25.6)	1.008	(0.694, 1.464)	0.9677	
low	16/131 (12.2)	12/ 65 (18.5)	0.564	(0.266, 1.194)	0.1292	
Renal function - eGFR at baseline						0.0238
Normal: eGFR >= 90 mL/min	51/221 (23.1)	12/102 (11.8)	1.798	(0.958, 3.374)	0.0637	
Mild impairment: 60 <= eGFR < 90 mL/min	38/178 (21.3)	26/ 91 (28.6)	0.667	(0.405, 1.100)	0.1101	
Moderate impairment: 30 <= eGFR < 60 mL/min	15/ 45 (33.3)	13/ 27 (48.1)	0.613	(0.292, 1.289)	0.1923	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.3.1
Summary of Serious Adverse Events - Subgroup analysis
(safety analysis set)

Final

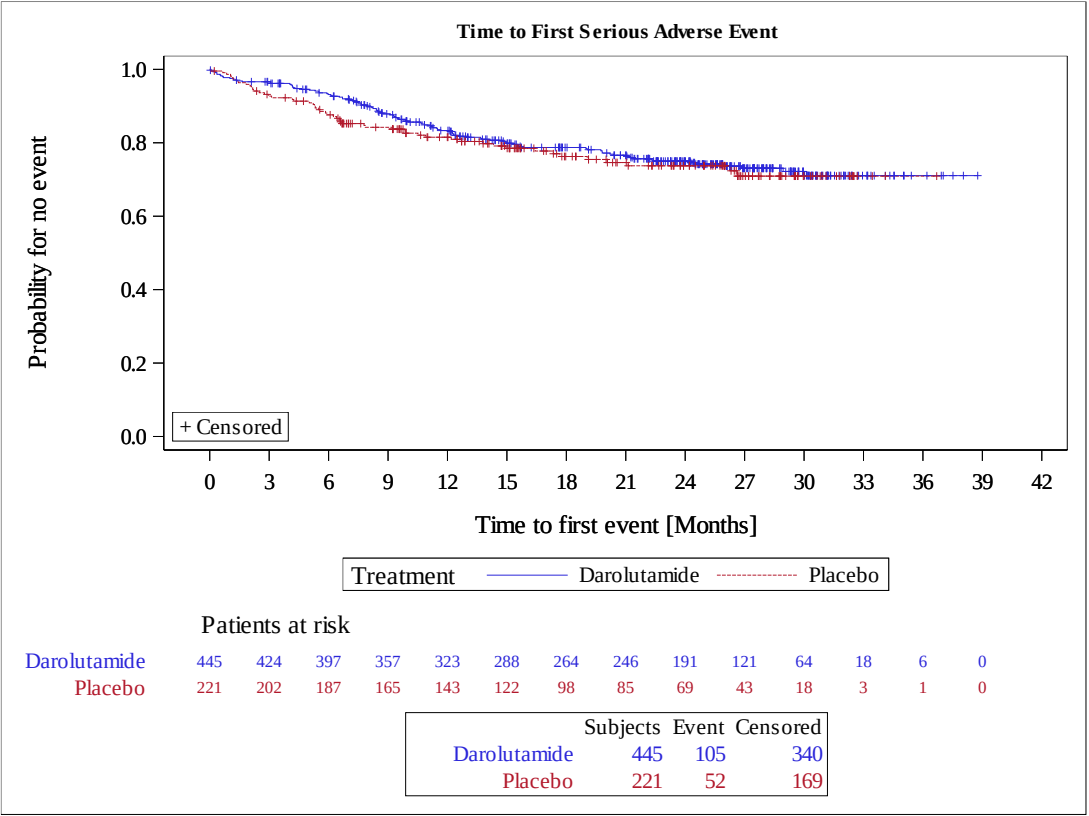
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.1592
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	98/387 (25.3)	47/202 (23.3)	0.973	(0.687, 1.378)	0.8766	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	7/ 58 (12.1)	5/ 19 (26.3)	0.420	(0.133, 1.324)	0.1265	
Age Group (Titan)						0.6296
<65	21/117 (17.9)	10/ 64 (15.6)	0.999	(0.470, 2.126)	0.9982	
>=65 and <75	44/193 (22.8)	26/ 95 (27.4)	0.752	(0.463, 1.222)	0.2478	
>=75	40/135 (29.6)	16/ 62 (25.8)	1.067	(0.597, 1.906)	0.8267	
Geographic region (Titan)						0.2194
Europe and north america	26/144 (18.1)	18/ 77 (23.4)	0.654	(0.358, 1.195)	0.1641	
ROTW	79/301 (26.2)	34/144 (23.6)	1.027	(0.687, 1.536)	0.8946	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.3.2
Kaplan-Meier Plot of Time to First Serious Adverse Event
(safety analysis set)

Final

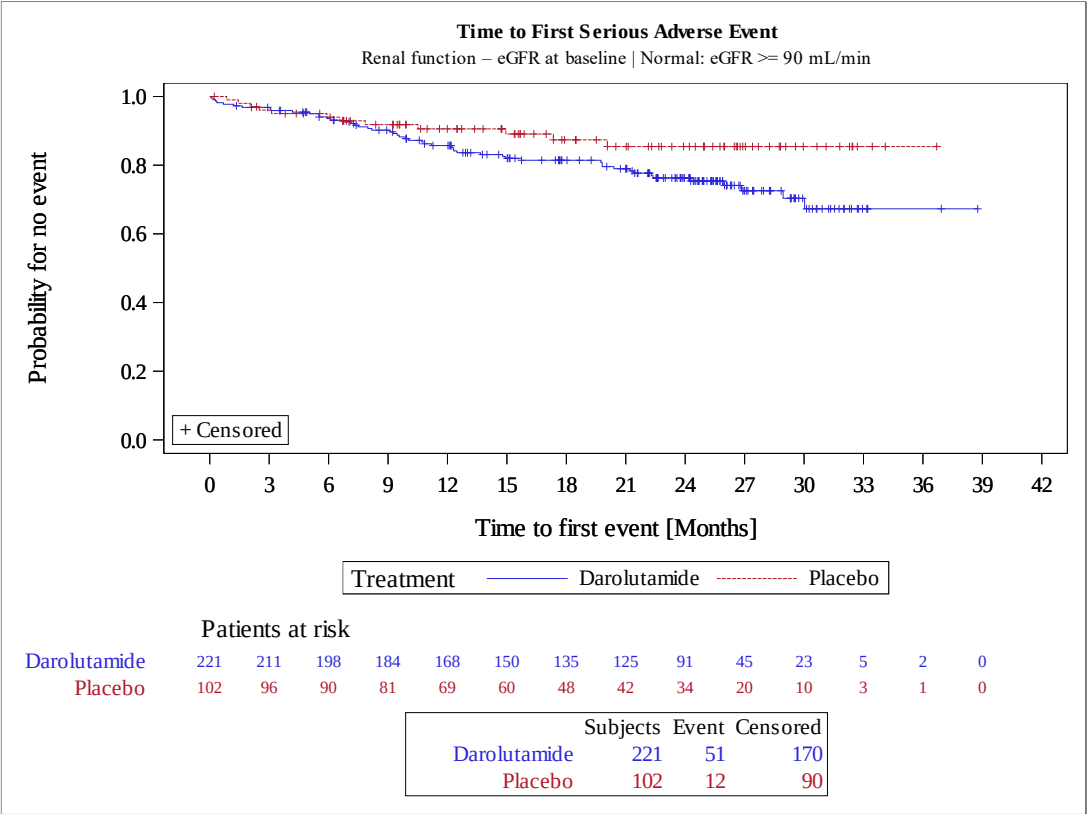


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.3.2
Kaplan-Meier Plot of Time to First Serious Adverse Event
(safety analysis set)

Final

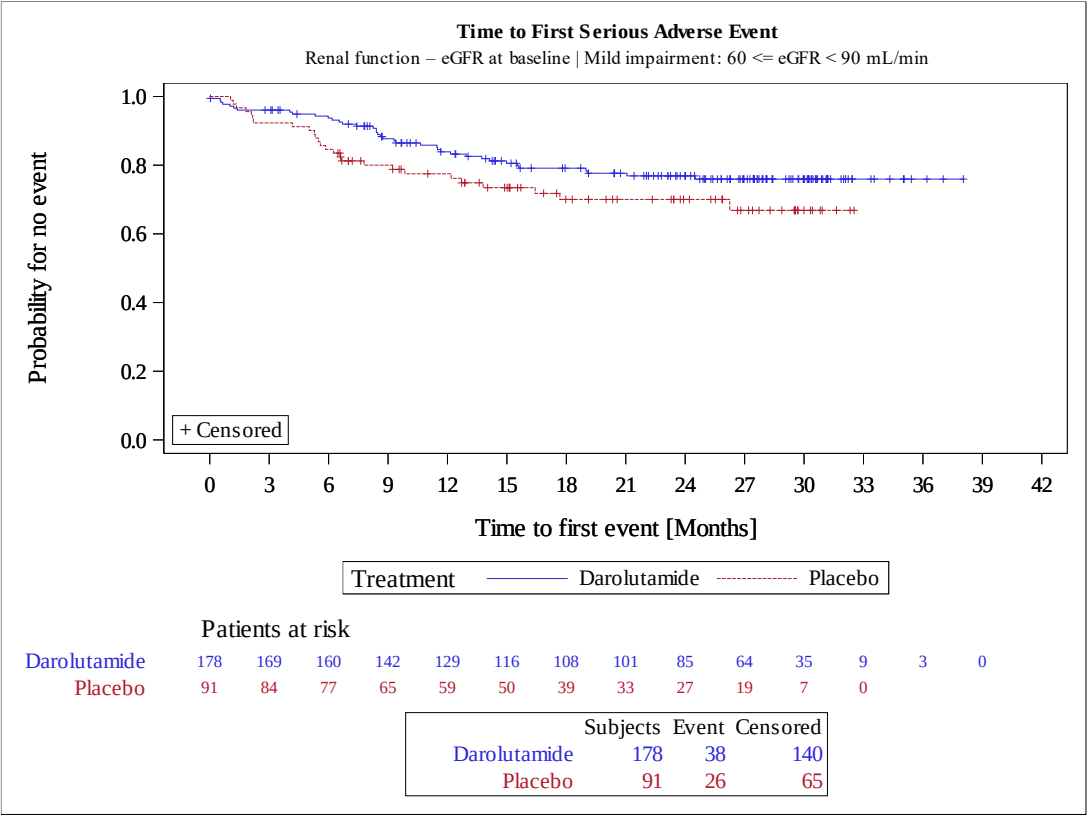


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.3.2
Kaplan-Meier Plot of Time to First Serious Adverse Event
(safety analysis set)

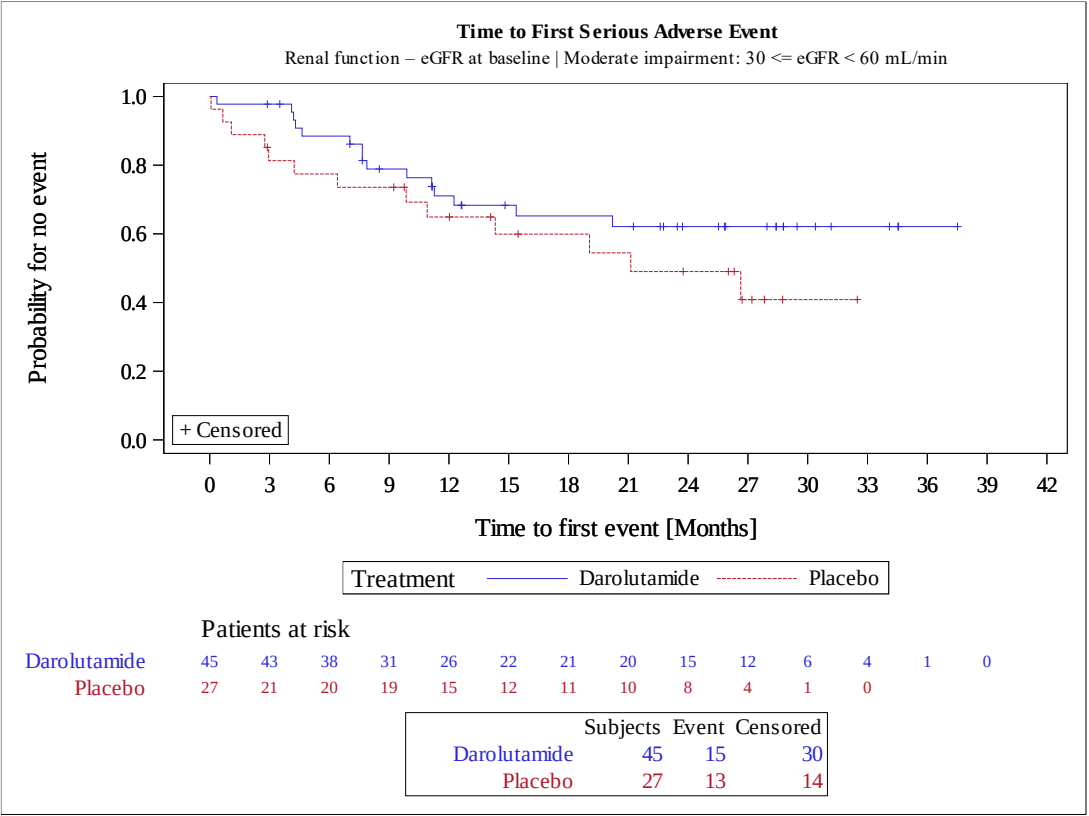
Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

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Study population
Figure 3.2.3.2
Kaplan-Meier Plot of Time to First Serious Adverse Event
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.4
Summary of Serious Adverse Events (disease-related AEs are excluded)
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	103 (23.1)	52 (23.5)
Number of censored patients, n (%)	342 (76.9)	169 (76.5)
Time to Event (Month)		
25%-ile (95% CI)	24.5 (15.7, NE)	20.1 (12.7, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.881	
95% CI	0.631, 1.230	
p-value	0.4564	
Odds Ratio	0.979	
95% CI	0.669, 1.433	
p-value	0.9122	
Relative Risk	0.984	
95% CI	0.735, 1.317	
p-value	0.9121	
Risk Difference	-0.383	
95% CI	-7.212, 6.445	
p-value	0.9124	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.4.1

Summary of Serious Adverse Events (disease-related AEs are excluded) - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.8316
Yes	17/ 54 (31.5)	8/ 26 (30.8)	0.953	(0.411, 2.209)	0.9112	
No	86/391 (22.0)	44/195 (22.6)	0.867	(0.603, 1.248)	0.4431	
Received prior local therapy (from IWRS)						0.8671
Yes	21/ 80 (26.3)	11/ 40 (27.5)	0.793	(0.380, 1.656)	0.5364	
No	82/365 (22.5)	41/181 (22.7)	0.898	(0.617, 1.306)	0.5720	
Prior local radiotherapy and/or prostatectomy						0.9608
Yes	23/ 87 (26.4)	14/ 50 (28.0)	0.872	(0.448, 1.696)	0.6862	
No	80/358 (22.3)	38/171 (22.2)	0.894	(0.607, 1.316)	0.5693	
Age group						0.5761
<65 years	21/117 (17.9)	10/ 64 (15.6)	0.998	(0.469, 2.124)	0.9961	
65-74	44/193 (22.8)	26/ 95 (27.4)	0.752	(0.463, 1.222)	0.2478	
75-84	32/117 (27.4)	11/ 52 (21.2)	1.237	(0.623, 2.454)	0.5423	
>=85 years	6/ 18 (33.3)	5/ 10 (50.0)	0.459	(0.132, 1.599)	0.2066	
Race						0.4705
White	50/249 (20.1)	26/124 (21.0)	0.837	(0.521, 1.347)	0.4637	
Asian	43/144 (29.9)	16/ 65 (24.6)	1.126	(0.634, 2.000)	0.6855	
Black or African American	8/ 42 (19.0)	8/ 23 (34.8)	0.435	(0.163, 1.160)	0.0868	
Other	2/ 10 (20.0)	2/ 9 (22.2)	0.859	(0.121, 6.103)	0.8791	
Geographical region						0.6323
Asia	42/141 (29.8)	16/ 63 (25.4)	1.088	(0.612, 1.937)	0.7733	
Latin America	22/120 (18.3)	16/ 70 (22.9)	0.753	(0.395, 1.435)	0.3870	
Europe and Rest of the world	39/184 (21.2)	20/ 88 (22.7)	0.782	(0.456, 1.344)	0.3726	
Baseline PSA values by median						0.3615
< median of overall population	47/215 (21.9)	22/110 (20.0)	0.990	(0.597, 1.644)	0.9705	
>= median of overall population	51/219 (23.3)	30/108 (27.8)	0.742	(0.472, 1.165)	0.1934	
ECOG PS at baseline						0.6874
=0	50/235 (21.3)	21/ 96 (21.9)	0.818	(0.491, 1.363)	0.4398	
>=1	53/210 (25.2)	31/125 (24.8)	0.980	(0.629, 1.527)	0.9294	
Gleason score at initial diagnosis						0.1512
Gleason <8	25/124 (20.2)	18/ 65 (27.7)	0.650	(0.355, 1.193)	0.1613	
Gleason >=8	76/308 (24.7)	30/146 (20.5)	1.105	(0.724, 1.687)	0.6435	
Disease volume at baseline						0.1866
high	87/314 (27.7)	40/156 (25.6)	0.985	(0.677, 1.433)	0.9368	
low	16/131 (12.2)	12/ 65 (18.5)	0.563	(0.266, 1.192)	0.1284	
Renal function - eGFR at baseline						0.0236
Normal: eGFR >= 90 mL/min	50/221 (22.6)	12/102 (11.8)	1.763	(0.938, 3.312)	0.0741	
Mild impairment: 60 <= eGFR < 90 mL/min	38/178 (21.3)	26/ 91 (28.6)	0.668	(0.405, 1.100)	0.1106	
Moderate impairment: 30 <= eGFR < 60 mL/min	14/ 45 (31.1)	13/ 27 (48.1)	0.572	(0.269, 1.217)	0.1414	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.4.1

Summary of Serious Adverse Events (disease-related AEs are excluded) - Subgroup analysis (safety analysis set)

Final

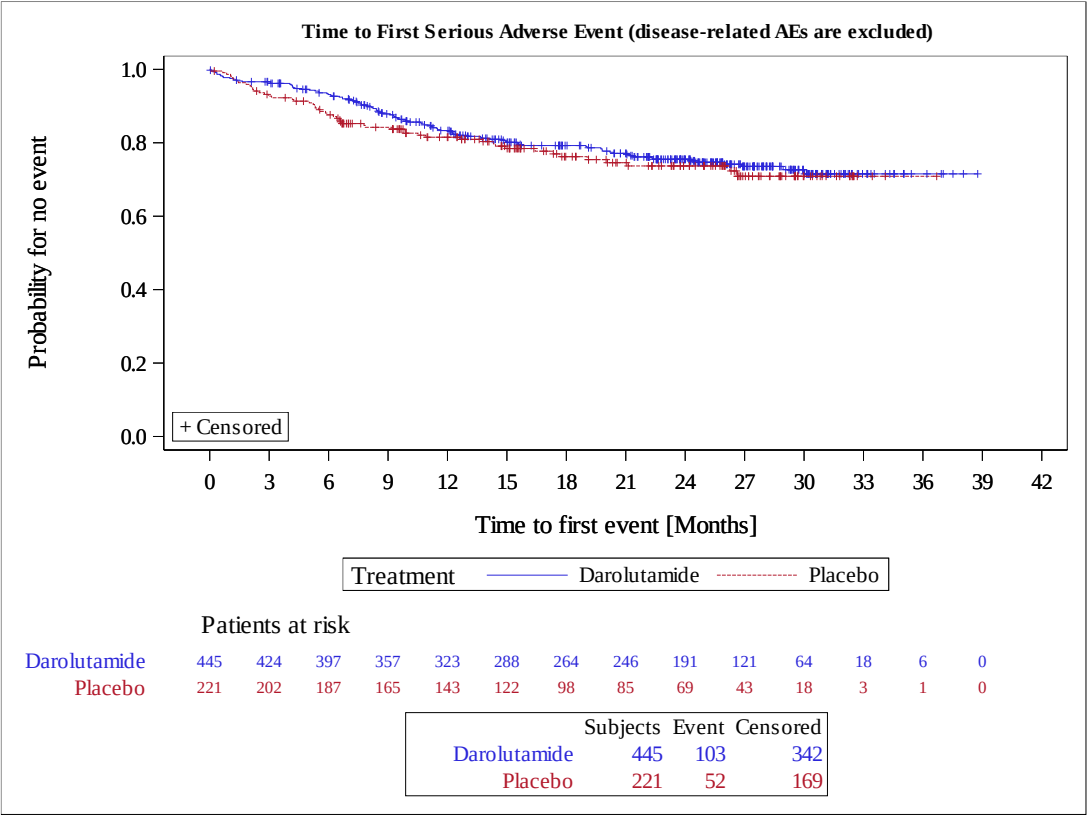
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.1692
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	96/387 (24.8)	47/202 (23.3)	0.953	(0.672, 1.352)	0.7900	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	7/ 58 (12.1)	5/ 19 (26.3)	0.420	(0.133, 1.324)	0.1265	
Age Group (Titan)						0.6967
<65	21/117 (17.9)	10/ 64 (15.6)	0.998	(0.469, 2.124)	0.9961	
>=65 and <75	44/193 (22.8)	26/ 95 (27.4)	0.752	(0.463, 1.222)	0.2478	
>=75	38/135 (28.1)	16/ 62 (25.8)	1.013	(0.565, 1.818)	0.9652	
Geographic region (Titan)						0.2457
Europe and north america	26/144 (18.1)	18/ 77 (23.4)	0.654	(0.358, 1.195)	0.1641	
ROTW	77/301 (25.6)	34/144 (23.6)	1.003	(0.670, 1.502)	0.9886	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Study population
Figure 3.2.4.2
Kaplan-Meier Plot of Time to First Serious Adverse Event (disease-related AEs are excluded)
(safety analysis set)

Final

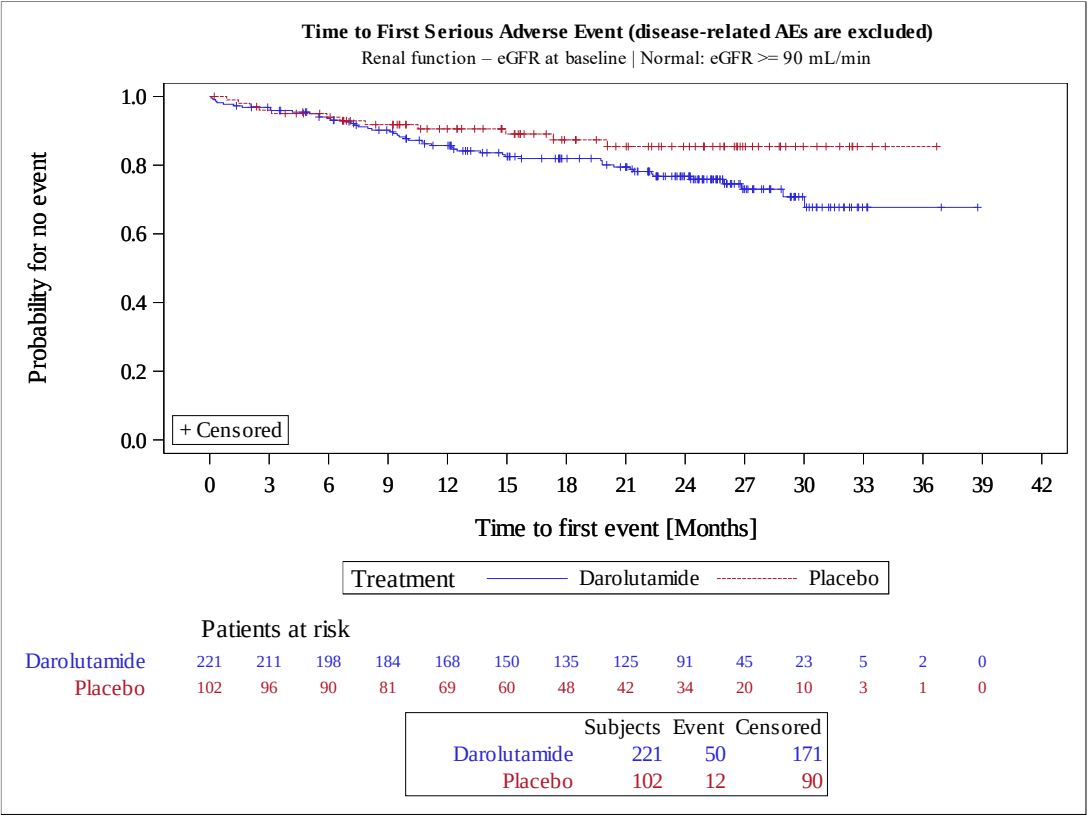


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Study population
Figure 3.2.4.2
Kaplan-Meier Plot of Time to First Serious Adverse Event (disease-related AEs are excluded)
(safety analysis set)

Final



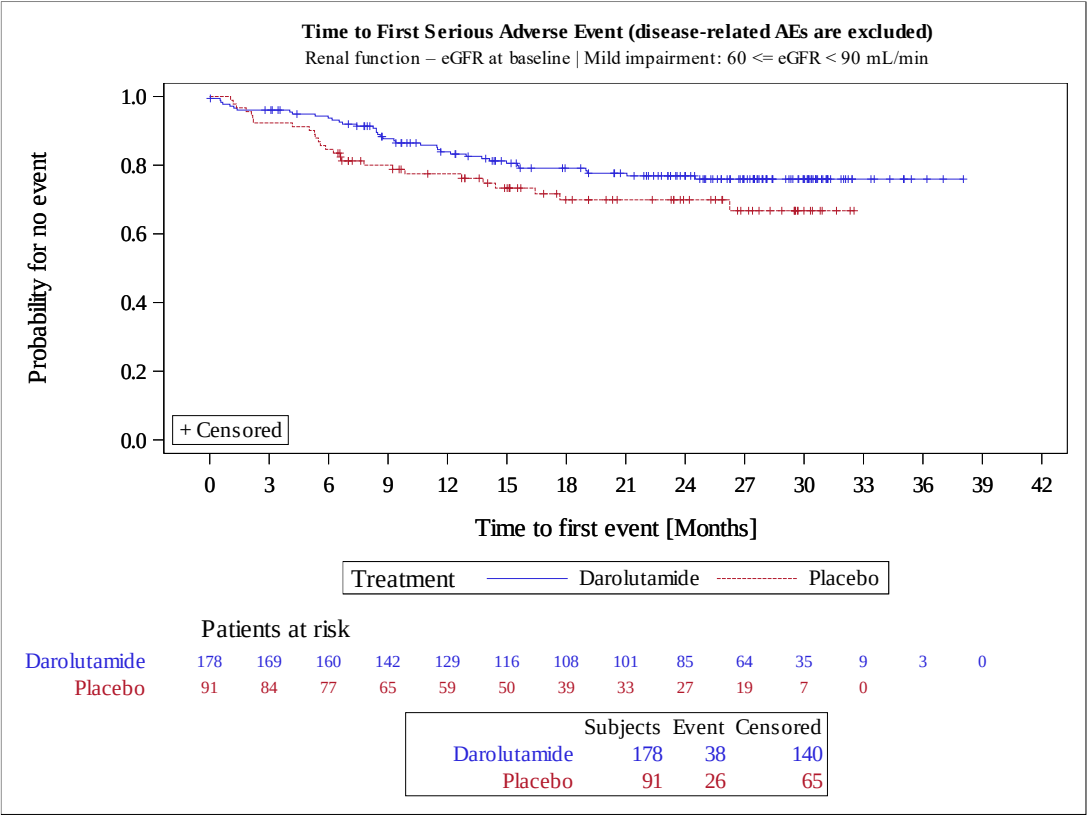
Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).

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Study population
Figure 3.2.4.2
Kaplan-Meier Plot of Time to First Serious Adverse Event (disease-related AEs are excluded)
(safety analysis set)

Final

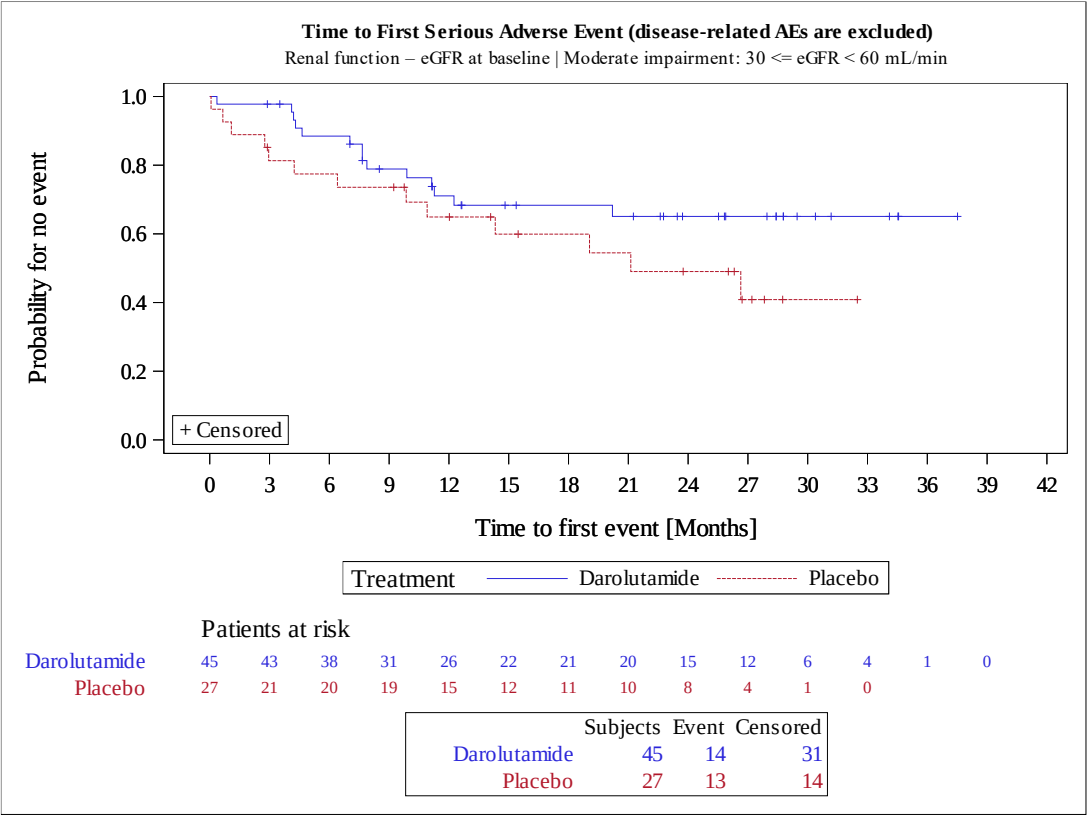


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Study population
Figure 3.2.4.2
Kaplan-Meier Plot of Time to First Serious Adverse Event (disease-related AEs are excluded)
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha≤0.05).
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Study population
Table 3.2.5
Summary of Adverse Events of CTCAE Grade >=3
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	158 (35.5)	79 (35.7)
Number of censored patients, n (%)	287 (64.5)	142 (64.3)
Time to Event (Month)		
25%-ile (95% CI)	12.3 (10.2, 15.4)	11.2 (7.7, 15.0)
Median (95% CI)	NE (NE, NE)	NE (26.6, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.901	
95% CI	0.687, 1.181	
p-value	0.4486	
Odds Ratio	0.990	
95% CI	0.707, 1.386	
p-value	0.9512	
Relative Risk	0.993	
95% CI	0.800, 1.234	
p-value	0.9512	
Risk Difference	-0.241	
95% CI	-7.967, 7.485	
p-value	0.9513	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population

Table 3.2.5.1

Summary of Adverse Events of CTCAE Grade ≥3 - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.9910
Yes	21/ 54 (38.9)	11/ 26 (42.3)	0.888	(0.428, 1.843)	0.7497	
No	137/391 (35.0)	68/195 (34.9)	0.901	(0.674, 1.206)	0.4846	
Received prior local therapy (from IWRS)						0.8304
Yes	27/ 80 (33.8)	14/ 40 (35.0)	0.823	(0.428, 1.583)	0.5595	
No	131/365 (35.9)	65/181 (35.9)	0.916	(0.680, 1.233)	0.5628	
Prior local radiotherapy and/or prostatectomy						0.6764
Yes	30/ 87 (34.5)	17/ 50 (34.0)	1.002	(0.552, 1.818)	0.9955	
No	128/358 (35.8)	62/171 (36.3)	0.872	(0.644, 1.182)	0.3772	
Age group						0.9518
<65 years	40/117 (34.2)	19/ 64 (29.7)	1.001	(0.579, 1.730)	0.9982	
65-74	62/193 (32.1)	33/ 95 (34.7)	0.857	(0.561, 1.308)	0.4727	
75-84	47/117 (40.2)	21/ 52 (40.4)	0.935	(0.559, 1.566)	0.7995	
≥85 years	9/ 18 (50.0)	6/ 10 (60.0)	0.627	(0.215, 1.822)	0.3867	
Race						0.9203
White	76/249 (30.5)	41/124 (33.1)	0.821	(0.561, 1.201)	0.3079	
Asian	59/144 (41.0)	25/ 65 (38.5)	1.001	(0.627, 1.600)	0.9958	
Black or African American	21/ 42 (50.0)	11/ 23 (47.8)	0.953	(0.458, 1.984)	0.8982	
Other	2/ 10 (20.0)	2/ 9 (22.2)	0.859	(0.121, 6.103)	0.8791	
Geographical region						0.7859
Asia	58/141 (41.1)	25/ 63 (39.7)	0.974	(0.609, 1.558)	0.9144	
Latin America	48/120 (40.0)	28/ 70 (40.0)	0.977	(0.613, 1.559)	0.9232	
Europe and Rest of the world	52/184 (28.3)	26/ 88 (29.5)	0.804	(0.501, 1.290)	0.3645	
Baseline PSA values by median						0.5492
< median of overall population	69/215 (32.1)	33/110 (30.0)	0.993	(0.655, 1.504)	0.9722	
≥ median of overall population	83/219 (37.9)	44/108 (40.7)	0.835	(0.579, 1.204)	0.3337	
ECOG PS at baseline						0.6997
=0	80/235 (34.0)	33/ 96 (34.4)	0.860	(0.573, 1.290)	0.4641	
≥1	78/210 (37.1)	46/125 (36.8)	0.966	(0.671, 1.392)	0.8540	
Gleason score at initial diagnosis						0.4806
Gleason <8	38/124 (30.6)	23/ 65 (35.4)	0.778	(0.463, 1.307)	0.3412	
Gleason ≥8	115/308 (37.3)	52/146 (35.6)	0.974	(0.702, 1.351)	0.8740	
Disease volume at baseline						0.8519
high	119/314 (37.9)	61/156 (39.1)	0.889	(0.653, 1.211)	0.4546	
low	39/131 (29.8)	18/ 65 (27.7)	0.945	(0.540, 1.654)	0.8429	
Renal function - eGFR at baseline						0.0154
Normal: eGFR ≥ 90 mL/min	82/221 (37.1)	24/102 (23.5)	1.486	(0.942, 2.342)	0.0859	
Mild impairment: 60 ≤ eGFR < 90 mL/min	54/178 (30.3)	38/ 91 (41.8)	0.632	(0.417, 0.958)	0.0292	
Moderate impairment: 30 ≤ eGFR < 60 mL/min	21/ 45 (46.7)	17/ 27 (63.0)	0.698	(0.367, 1.328)	0.2705	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Study population
Table 3.2.5.1
Summary of Adverse Events of CTCAE Grade >=3 - Subgroup analysis
(safety analysis set)

Final

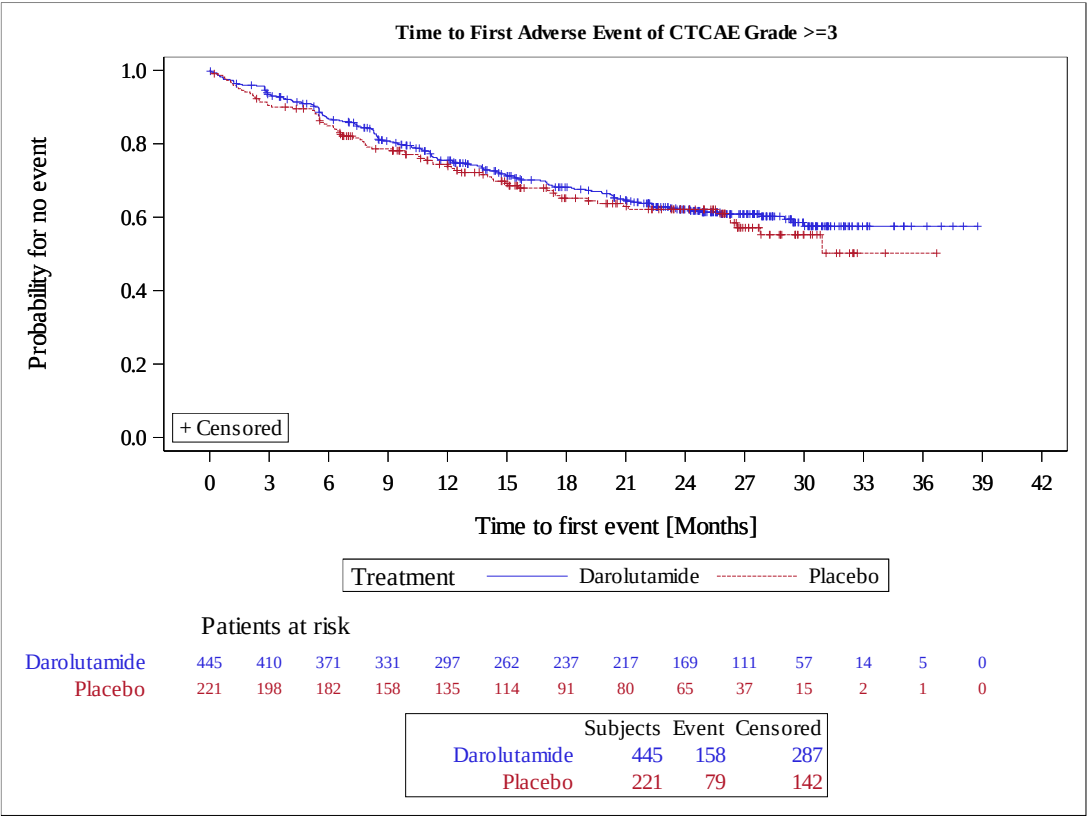
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.3620
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	143/387 (37.0)	72/202 (35.6)	0.943	(0.710, 1.252)	0.6833	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	15/ 58 (25.9)	7/ 19 (36.8)	0.616	(0.251, 1.512)	0.2856	
Age Group (Titan)						0.9273
<65	40/117 (34.2)	19/ 64 (29.7)	1.001	(0.579, 1.730)	0.9982	
>=65 and <75	62/193 (32.1)	33/ 95 (34.7)	0.857	(0.561, 1.308)	0.4727	
>=75	56/135 (41.5)	27/ 62 (43.5)	0.874	(0.551, 1.385)	0.5653	
Geographic region (Titan)						0.2659
Europe and north america	38/144 (26.4)	24/ 77 (31.2)	0.721	(0.431, 1.205)	0.2093	
ROTW	120/301 (39.9)	55/144 (38.2)	0.990	(0.719, 1.362)	0.9485	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.5.2
Kaplan-Meier Plot of Time to First Adverse Event of CTCAE Grade ≥ 3
(safety analysis set)

Final

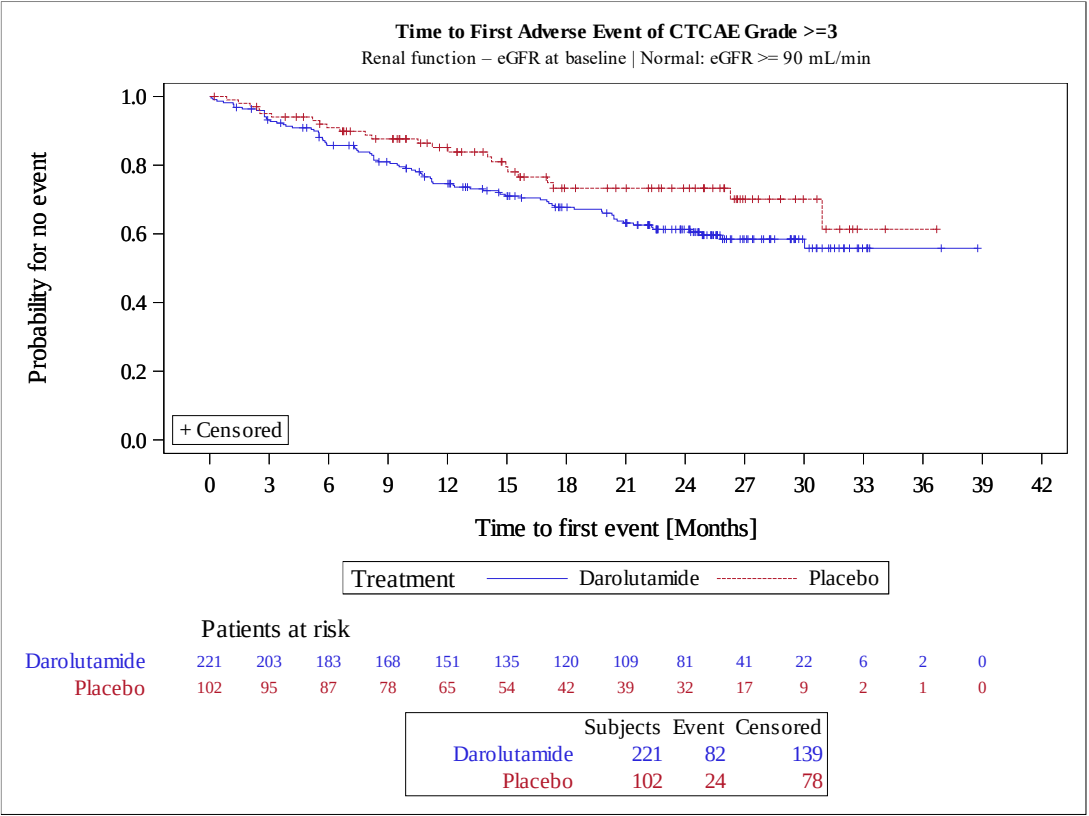


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.5.2
Kaplan-Meier Plot of Time to First Adverse Event of CTCAE Grade ≥ 3
(safety analysis set)

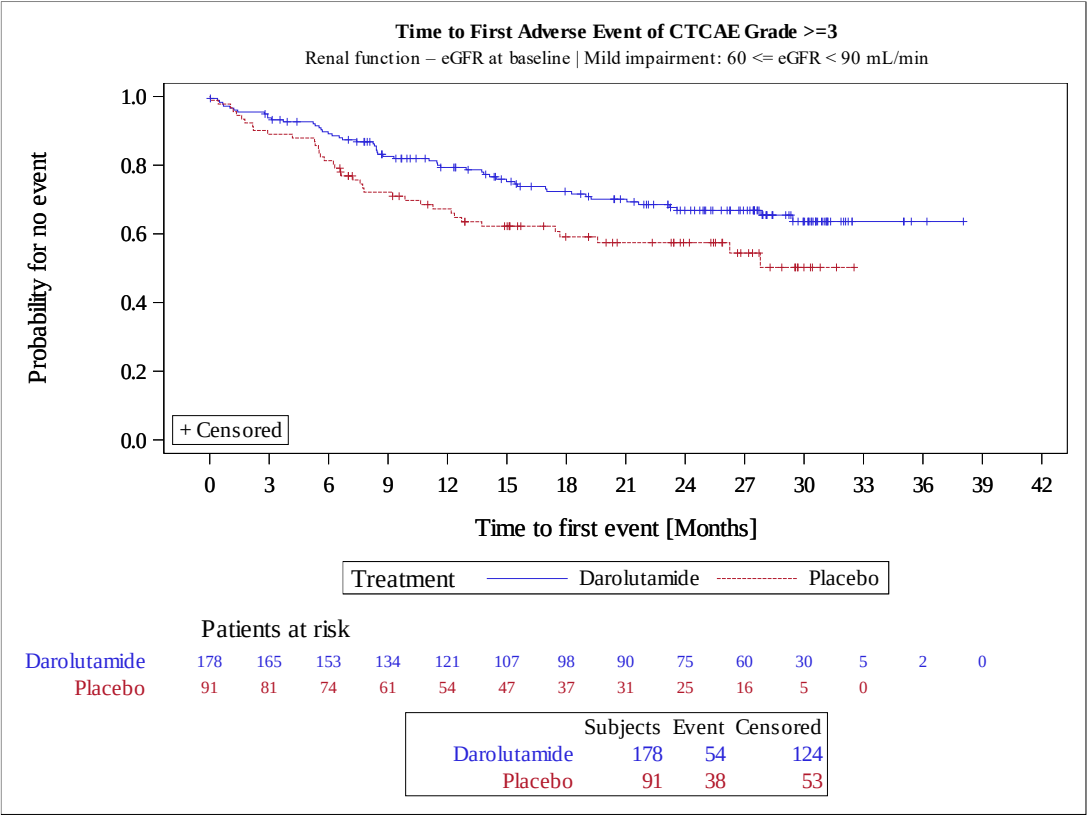
Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.5.2
Kaplan-Meier Plot of Time to First Adverse Event of CTCAE Grade ≥ 3
(safety analysis set)

Final

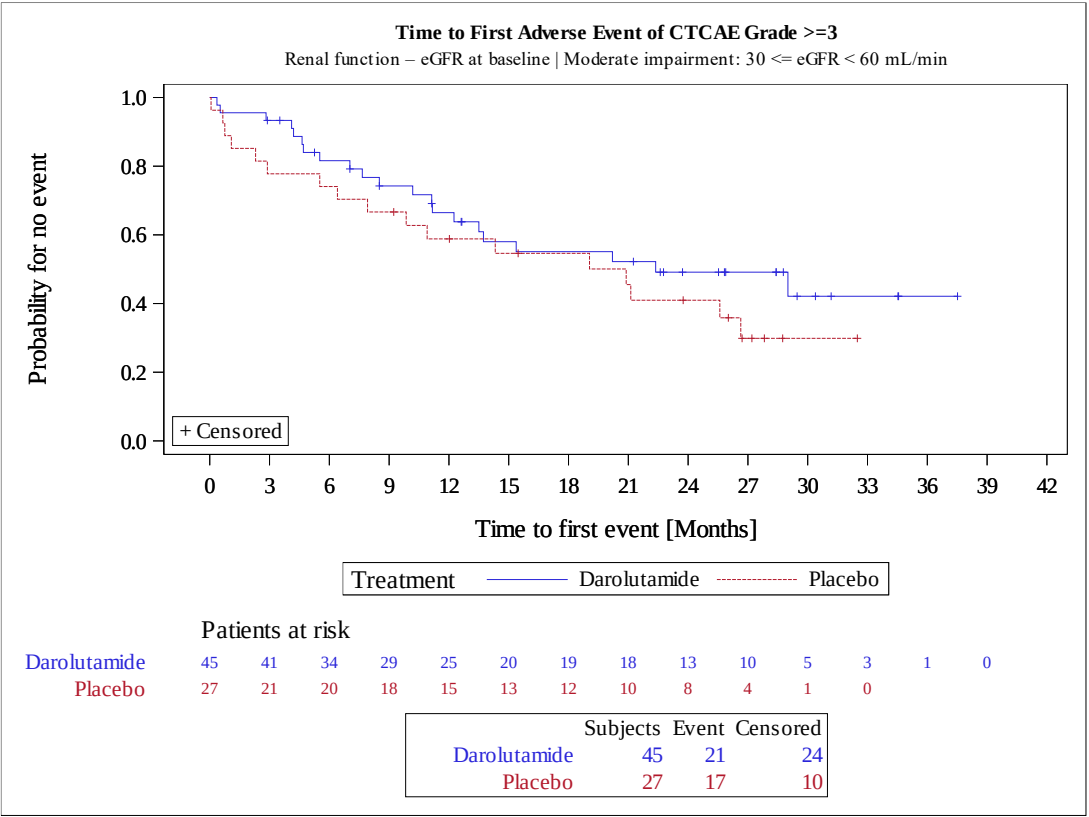


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.5.2
Kaplan-Meier Plot of Time to First Adverse Event of CTCAE Grade ≥ 3
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.6
Summary of Adverse Events of CTCAE Grade >=3 (disease-related AEs are excluded)
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	157 (35.3)	79 (35.7)
Number of censored patients, n (%)	288 (64.7)	142 (64.3)
Time to Event (Month)		
25%-ile (95% CI)	12.3 (10.2, 15.5)	11.2 (7.7, 15.0)
Median (95% CI)	NE (NE, NE)	NE (26.6, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.896	
95% CI	0.683, 1.174	
p-value	0.4238	
Odds Ratio	0.980	
95% CI	0.700, 1.372	
p-value	0.9058	
Relative Risk	0.987	
95% CI	0.794, 1.226	
p-value	0.9057	
Risk Difference	-0.466	
95% CI	-8.188, 7.257	
p-value	0.9059	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.6.1

Summary of Adverse Events of CTCAE Grade ≥3 (disease-related AEs are excluded) - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.9957
Yes	21/ 54 (38.9)	11/ 26 (42.3)	0.888	(0.428, 1.843)	0.7497	
No	136/391 (34.8)	68/195 (34.9)	0.895	(0.669, 1.198)	0.4567	
Received prior local therapy (from IWRS)						0.8448
Yes	27/ 80 (33.8)	14/ 40 (35.0)	0.823	(0.428, 1.583)	0.5595	
No	130/365 (35.6)	65/181 (35.9)	0.910	(0.675, 1.225)	0.5326	
Prior local radiotherapy and/or prostatectomy						0.6610
Yes	30/ 87 (34.5)	17/ 50 (34.0)	1.002	(0.552, 1.818)	0.9955	
No	127/358 (35.5)	62/171 (36.3)	0.866	(0.639, 1.174)	0.3531	
Age group						0.9049
<65 years	40/117 (34.2)	19/ 64 (29.7)	1.000	(0.578, 1.729)	0.9993	
65-74	62/193 (32.1)	33/ 95 (34.7)	0.857	(0.561, 1.308)	0.4727	
75-84	47/117 (40.2)	21/ 52 (40.4)	0.935	(0.559, 1.566)	0.7995	
≥85 years	8/ 18 (44.4)	6/ 10 (60.0)	0.540	(0.180, 1.622)	0.2649	
Race						0.9350
White	76/249 (30.5)	41/124 (33.1)	0.821	(0.561, 1.201)	0.3079	
Asian	58/144 (40.3)	25/ 65 (38.5)	0.985	(0.616, 1.575)	0.9491	
Black or African American	21/ 42 (50.0)	11/ 23 (47.8)	0.955	(0.459, 1.988)	0.9025	
Other	2/ 10 (20.0)	2/ 9 (22.2)	0.859	(0.121, 6.103)	0.8791	
Geographical region						0.8000
Asia	57/141 (40.4)	25/ 63 (39.7)	0.958	(0.598, 1.534)	0.8597	
Latin America	48/120 (40.0)	28/ 70 (40.0)	0.978	(0.613, 1.559)	0.9249	
Europe and Rest of the world	52/184 (28.3)	26/ 88 (29.5)	0.804	(0.501, 1.290)	0.3645	
Baseline PSA values by median						0.5204
< median of overall population	69/215 (32.1)	33/110 (30.0)	0.993	(0.655, 1.504)	0.9732	
≥ median of overall population	82/219 (37.4)	44/108 (40.7)	0.826	(0.572, 1.191)	0.3048	
ECOG PS at baseline						0.7331
=0	80/235 (34.0)	33/ 96 (34.4)	0.860	(0.573, 1.290)	0.4641	
≥1	77/210 (36.7)	46/125 (36.8)	0.955	(0.662, 1.376)	0.8045	
Gleason score at initial diagnosis						0.4986
Gleason <8	38/124 (30.6)	23/ 65 (35.4)	0.778	(0.463, 1.307)	0.3412	
Gleason ≥8	114/308 (37.0)	52/146 (35.6)	0.965	(0.695, 1.340)	0.8343	
Disease volume at baseline						0.8299
high	118/314 (37.6)	61/156 (39.1)	0.882	(0.647, 1.201)	0.4245	
low	39/131 (29.8)	18/ 65 (27.7)	0.945	(0.540, 1.653)	0.8416	
Renal function - eGFR at baseline						0.0140
Normal: eGFR ≥ 90 mL/min	82/221 (37.1)	24/102 (23.5)	1.486	(0.942, 2.342)	0.0859	
Mild impairment: 60 ≤ eGFR < 90 mL/min	54/178 (30.3)	38/ 91 (41.8)	0.632	(0.417, 0.958)	0.0292	
Moderate impairment: 30 ≤ eGFR < 60 mL/min	20/ 45 (44.4)	17/ 27 (63.0)	0.662	(0.346, 1.268)	0.2103	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.6.1
Summary of Adverse Events of CTCAE Grade >=3 (disease-related AEs are excluded) - Subgroup analysis
(safety analysis set)

Final

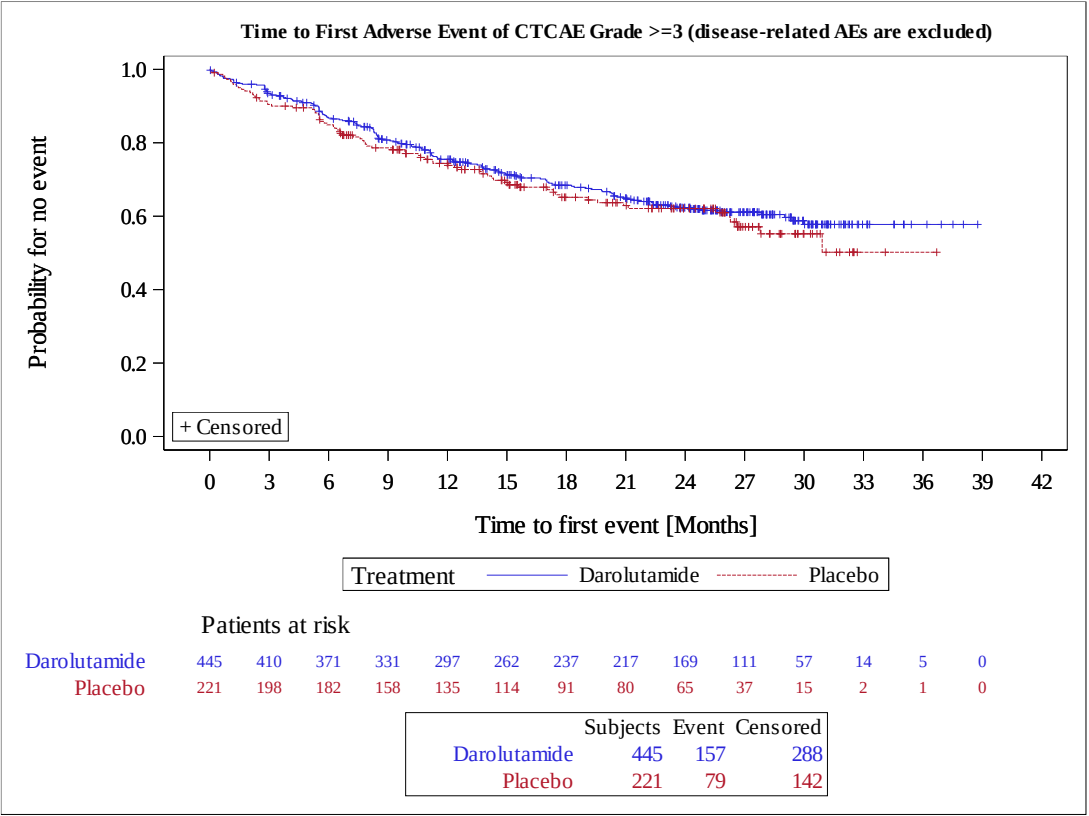
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.3693
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	142/387 (36.7)	72/202 (35.6)	0.937	(0.705, 1.244)	0.6509	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	15/ 58 (25.9)	7/ 19 (36.8)	0.616	(0.251, 1.512)	0.2856	
Age Group (Titan)						0.9193
<65	40/117 (34.2)	19/ 64 (29.7)	1.000	(0.578, 1.729)	0.9993	
>=65 and <75	62/193 (32.1)	33/ 95 (34.7)	0.857	(0.561, 1.308)	0.4727	
>=75	55/135 (40.7)	27/ 62 (43.5)	0.858	(0.541, 1.361)	0.5146	
Geographic region (Titan)						0.2773
Europe and north america	38/144 (26.4)	24/ 77 (31.2)	0.721	(0.431, 1.205)	0.2093	
ROTW	119/301 (39.5)	55/144 (38.2)	0.982	(0.713, 1.352)	0.9108	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.6.2
Kaplan-Meier Plot of Time to First Adverse Event of CTCAE Grade ≥ 3 (disease-related AEs are excluded)
(safety analysis set)

Final

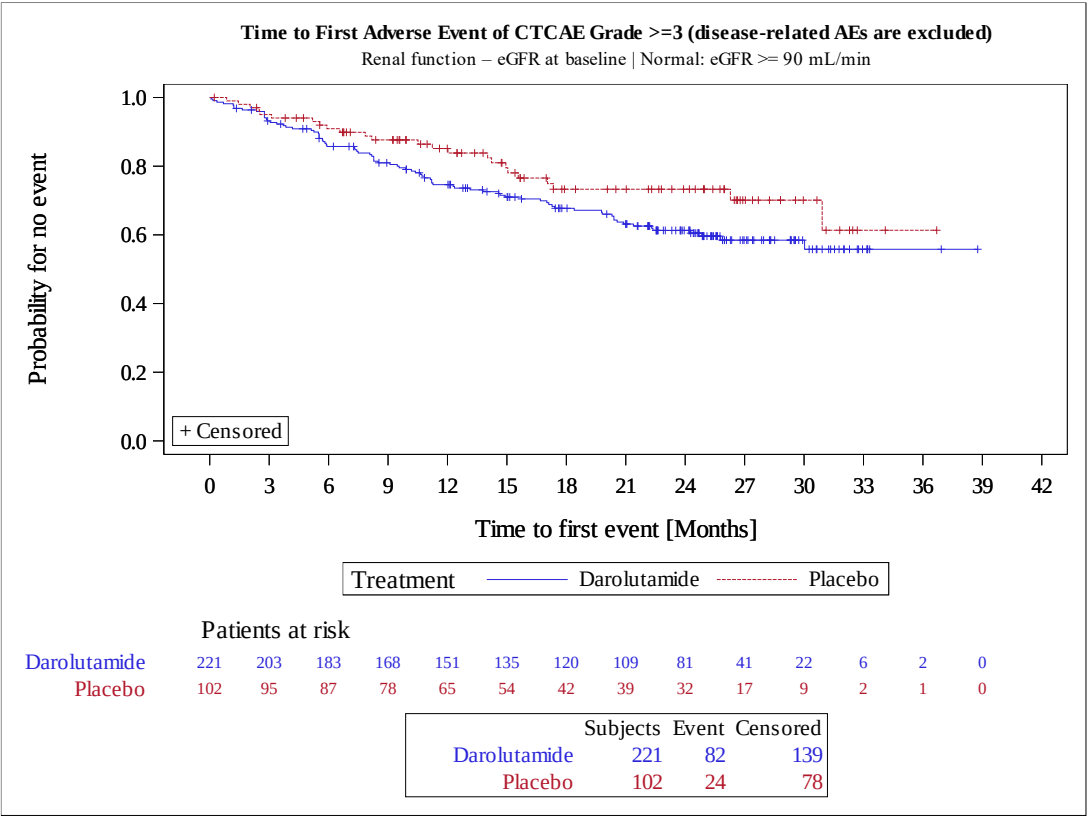


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.6.2
Kaplan-Meier Plot of Time to First Adverse Event of CTCAE Grade ≥ 3 (disease-related AEs are excluded)
(safety analysis set)

Final

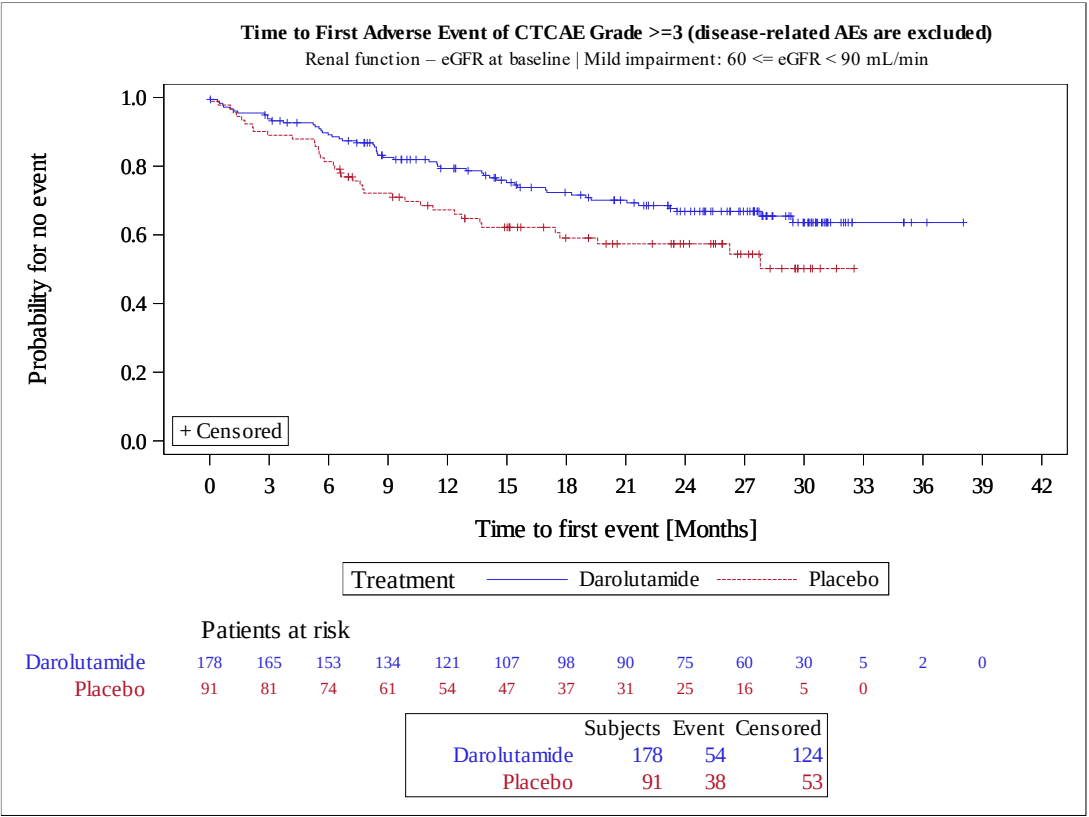


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.6.2
Kaplan-Meier Plot of Time to First Adverse Event of CTCAE Grade ≥ 3 (disease-related AEs are excluded)
(safety analysis set)

Final

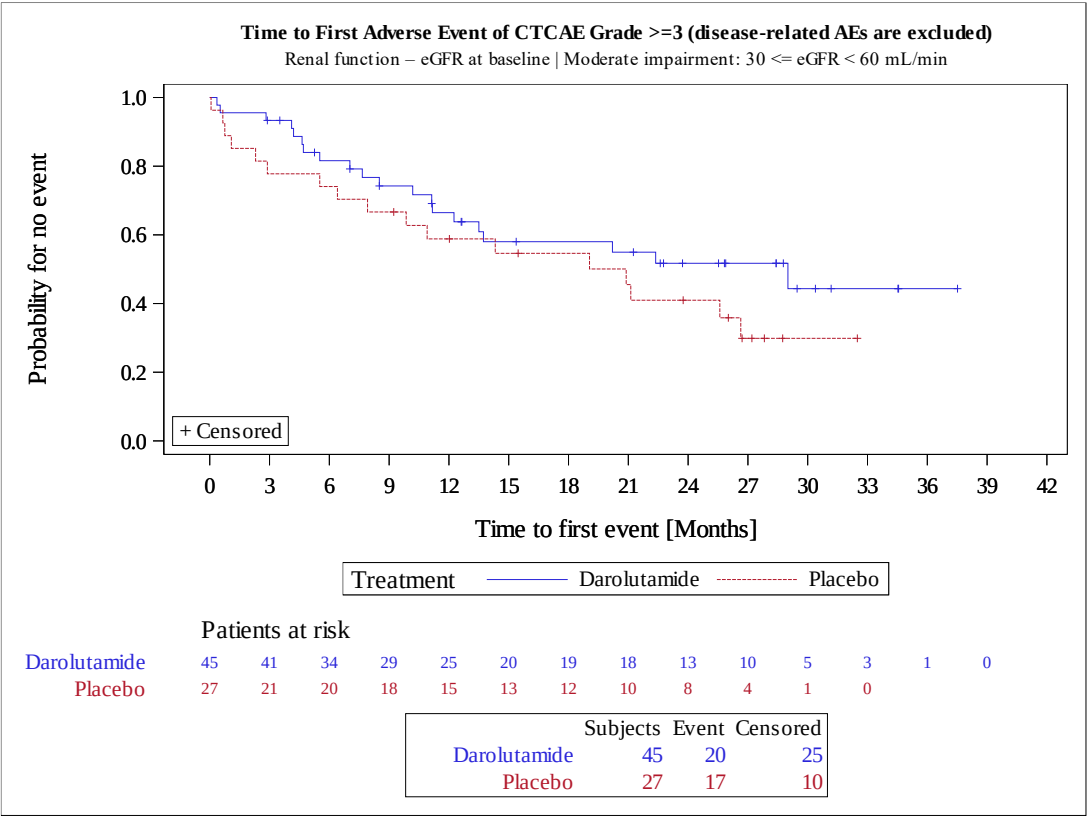


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.6.2
Kaplan-Meier Plot of Time to First Adverse Event of CTCAE Grade ≥ 3 (disease-related AEs are excluded)
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.7
Summary of Adverse Events of CTCAE Grade <3
(safety analysis set)

Final

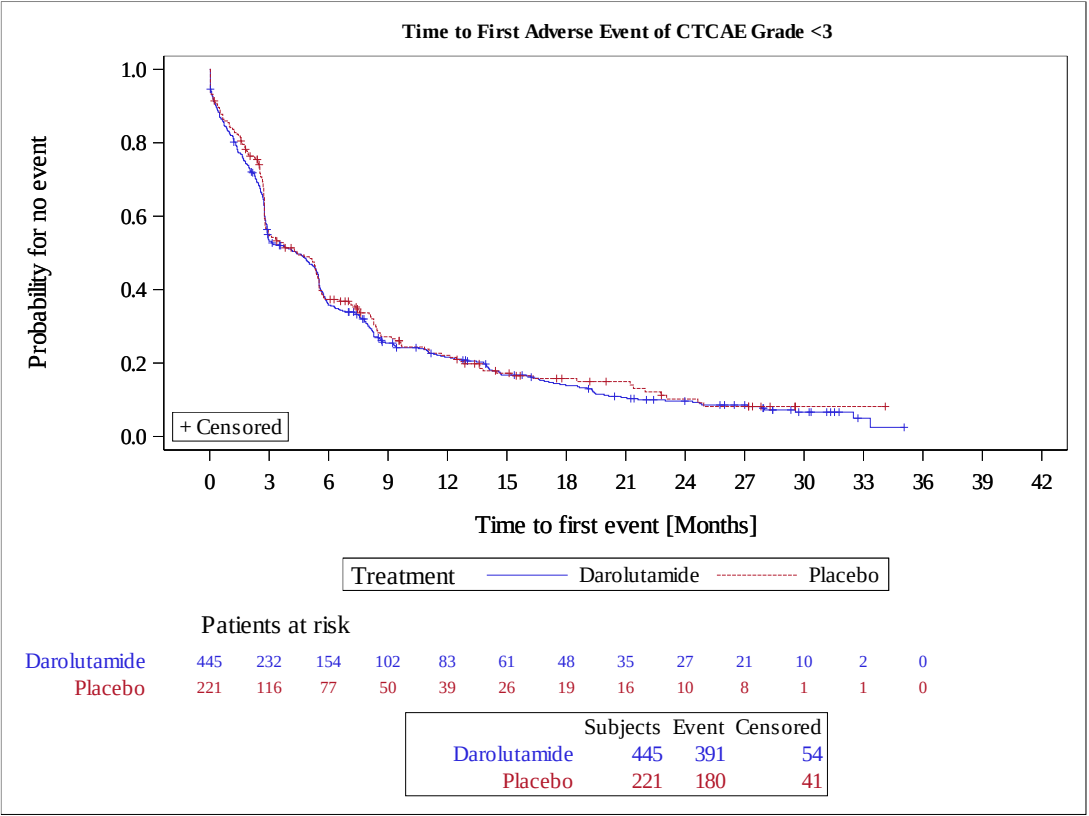
	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	391 (87.9)	180 (81.4)
Number of censored patients, n (%)	54 (12.1)	41 (18.6)
Time to Event (Month)		
25%-ile (95% CI)	1.7 (1.3, 2.3)	2.4 (1.6, 2.7)
Median (95% CI)	4.4 (3.0, 5.4)	4.4 (2.8, 5.5)
75%-ile (95% CI)	9.3 (8.2, 12.7)	9.7 (8.3, 13.6)
Unstratified Analysis		
Hazard Ratio	1.049	
95% CI	0.879, 1.252	
p-value	0.5902	
Odds Ratio	1.649	
95% CI	1.059, 2.568	
p-value	0.0268	
Relative Risk	1.079	
95% CI	1.004, 1.159	
p-value	0.0384	
Risk Difference	6.417	
95% CI	0.462, 12.373	
p-value	0.0347	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population
Figure 3.2.7.1
Kaplan-Meier Plot of Time to First Adverse Event of CTCAE Grade <3
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.8
Summary of Adverse Events leading to discontinuation of study treatment
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	27 (6.1)	20 (9.0)
Number of censored patients, n (%)	418 (93.9)	201 (91.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.577	
95% CI	0.323, 1.030	
p-value	0.0597	
Odds Ratio	0.649	
95% CI	0.355, 1.185	
p-value	0.1597	
Relative Risk	0.670	
95% CI	0.385, 1.168	
p-value	0.1582	
Risk Difference	-2.982	
95% CI	-7.367, 1.402	
p-value	0.1825	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.8.1

Summary of Adverse Events leading to discontinuation of study treatment - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.4338
Yes	2/ 54 (3.7)	3/ 26 (11.5)	0.295	(0.049, 1.768)	0.1556	
No	25/391 (6.4)	17/195 (8.7)	0.617	(0.333, 1.146)	0.1228	
Received prior local therapy (from IWRS)						0.0878
Yes	2/ 80 (2.5)	5/ 40 (12.5)	0.138	(0.026, 0.723)	0.0065	
No	25/365 (6.8)	15/181 (8.3)	0.732	(0.385, 1.389)	0.3373	
Prior local radiotherapy and/or prostatectomy						0.7525
Yes	7/ 87 (8.0)	7/ 50 (14.0)	0.471	(0.164, 1.351)	0.1518	
No	20/358 (5.6)	13/171 (7.6)	0.642	(0.319, 1.293)	0.2112	
Age group						0.7702
<65 years	6/117 (5.1)	3/ 64 (4.7)	0.811	(0.201, 3.268)	0.7678	
65-74	11/193 (5.7)	10/ 95 (10.5)	0.493	(0.209, 1.163)	0.0993	
75-84	8/117 (6.8)	4/ 52 (7.7)	0.816	(0.245, 2.714)	0.7398	
>=85 years	2/ 18 (11.1)	3/ 10 (30.0)	0.282	(0.046, 1.716)	0.1437	
Race						0.2005
White	11/249 (4.4)	14/124 (11.3)	0.321	(0.145, 0.710)	0.0031	
Asian	12/144 (8.3)	4/ 65 (6.2)	1.241	(0.400, 3.851)	0.7075	
Black or African American	3/ 42 (7.1)	1/ 23 (4.3)	1.234	(0.128, 11.882)	0.8555	
Other	1/ 10 (10.0)	1/ 9 (11.1)	0.894	(0.056, 14.297)	0.9371	
Geographical region						0.1144
Asia	12/141 (8.5)	4/ 63 (6.3)	1.233	(0.397, 3.824)	0.7166	
Latin America	7/120 (5.8)	5/ 70 (7.1)	0.744	(0.236, 2.348)	0.6124	
Europe and Rest of the world	8/184 (4.3)	11/ 88 (12.5)	0.282	(0.113, 0.706)	0.0039	
Baseline PSA values by median						0.7548
< median of overall population	11/215 (5.1)	10/110 (9.1)	0.490	(0.208, 1.156)	0.0965	
>= median of overall population	14/219 (6.4)	10/108 (9.3)	0.584	(0.259, 1.317)	0.1896	
ECOG PS at baseline						0.4998
=0	8/235 (3.4)	6/ 96 (6.3)	0.437	(0.151, 1.264)	0.1160	
>=1	19/210 (9.0)	14/125 (11.2)	0.728	(0.364, 1.452)	0.3651	
Gleason score at initial diagnosis						0.0242
Gleason <8	6/124 (4.8)	11/ 65 (16.9)	0.252	(0.093, 0.683)	0.0034	
Gleason >=8	21/308 (6.8)	8/146 (5.5)	1.088	(0.481, 2.459)	0.8399	
Disease volume at baseline						0.0976
high	23/314 (7.3)	13/156 (8.3)	0.765	(0.387, 1.513)	0.4405	
low	4/131 (3.1)	7/ 65 (10.8)	0.237	(0.069, 0.812)	0.0128	
Renal function - eGFR at baseline						0.5544
Normal: eGFR >= 90 mL/min	14/221 (6.3)	6/102 (5.9)	0.909	(0.349, 2.369)	0.8447	
Mild impairment: 60 <= eGFR < 90 mL/min	7/178 (3.9)	7/ 91 (7.7)	0.463	(0.162, 1.323)	0.1407	
Moderate impairment: 30 <= eGFR < 60 mL/min	6/ 45 (13.3)	6/ 27 (22.2)	0.563	(0.181, 1.747)	0.3135	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.8.1
Summary of Adverse Events leading to discontinuation of study treatment - Subgroup analysis
(safety analysis set)

Final

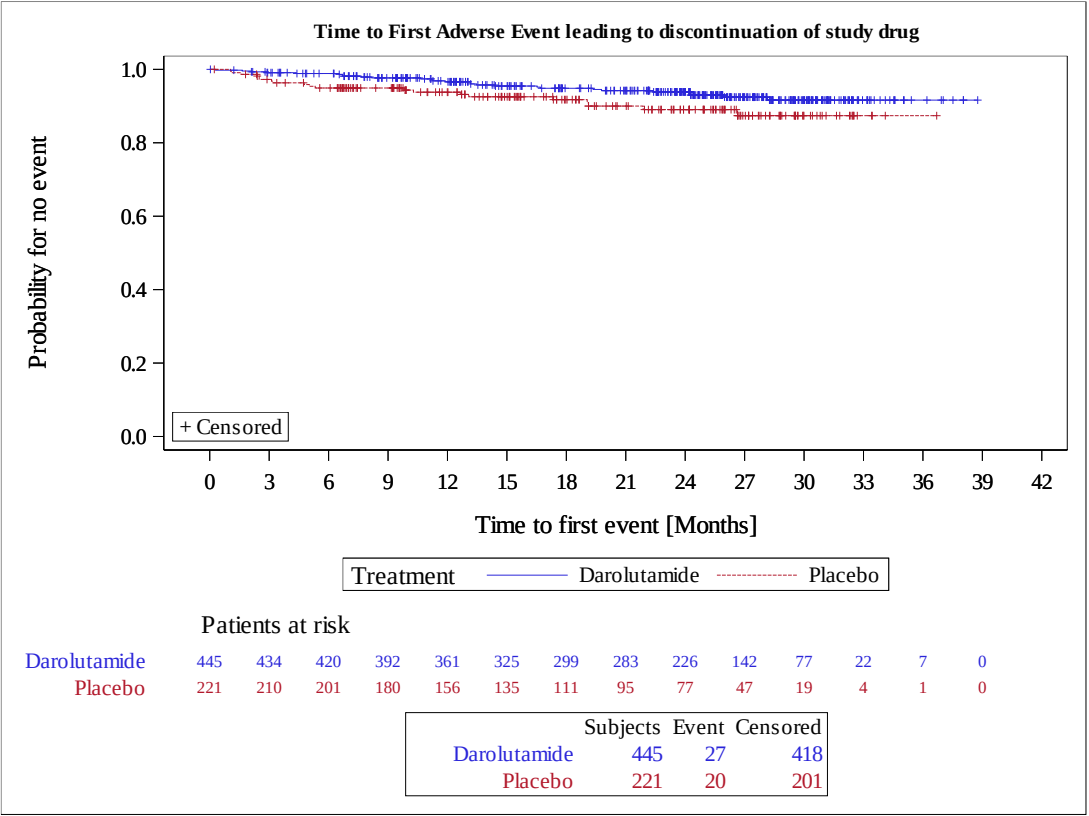
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.5752
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	23/387 (5.9)	17/202 (8.4)	0.593	(0.316, 1.111)	0.0992	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	4/ 58 (6.9)	3/ 19 (15.8)	0.392	(0.088, 1.752)	0.2037	
Age Group (Titan)						0.7940
<65	6/117 (5.1)	3/ 64 (4.7)	0.811	(0.201, 3.268)	0.7678	
>=65 and <75	11/193 (5.7)	10/ 95 (10.5)	0.493	(0.209, 1.163)	0.0993	
>=75	10/135 (7.4)	7/ 62 (11.3)	0.589	(0.224, 1.551)	0.2787	
Geographic region (Titan)						0.0274
Europe and north america	5/144 (3.5)	10/ 77 (13.0)	0.222	(0.076, 0.653)	0.0028	
ROTW	22/301 (7.3)	10/144 (6.9)	0.935	(0.443, 1.977)	0.8611	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.8.2
Kaplan-Meier Plot of Time to First Adverse Event leading to discontinuation of study treatment
(safety analysis set)

Final

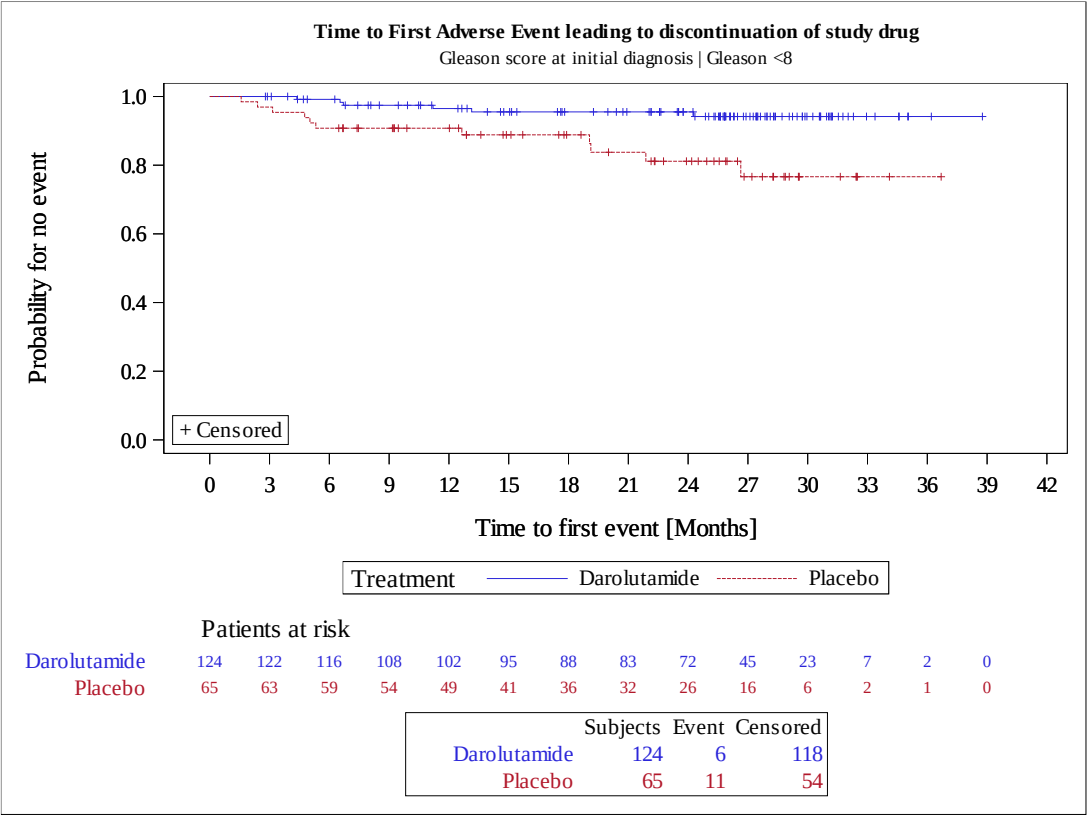


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.8.2
Kaplan-Meier Plot of Time to First Adverse Event leading to discontinuation of study treatment
(safety analysis set)

Final

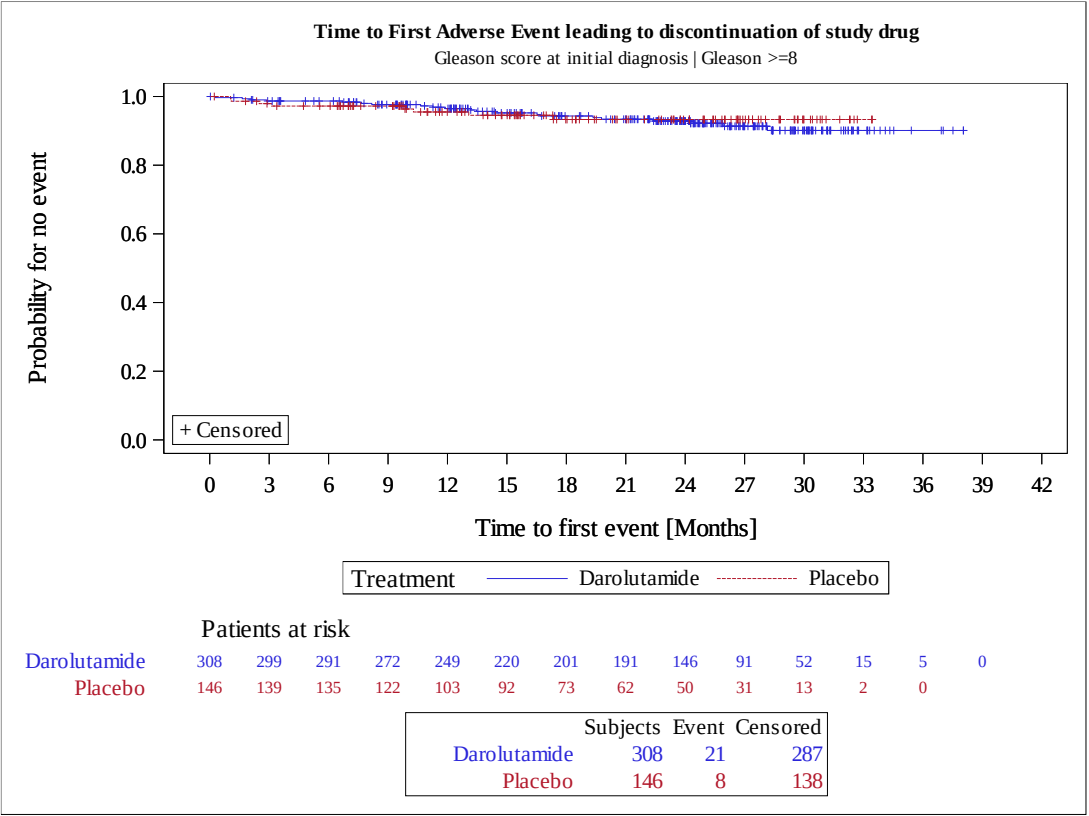


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.8.2
Kaplan-Meier Plot of Time to First Adverse Event leading to discontinuation of study treatment
(safety analysis set)

Final

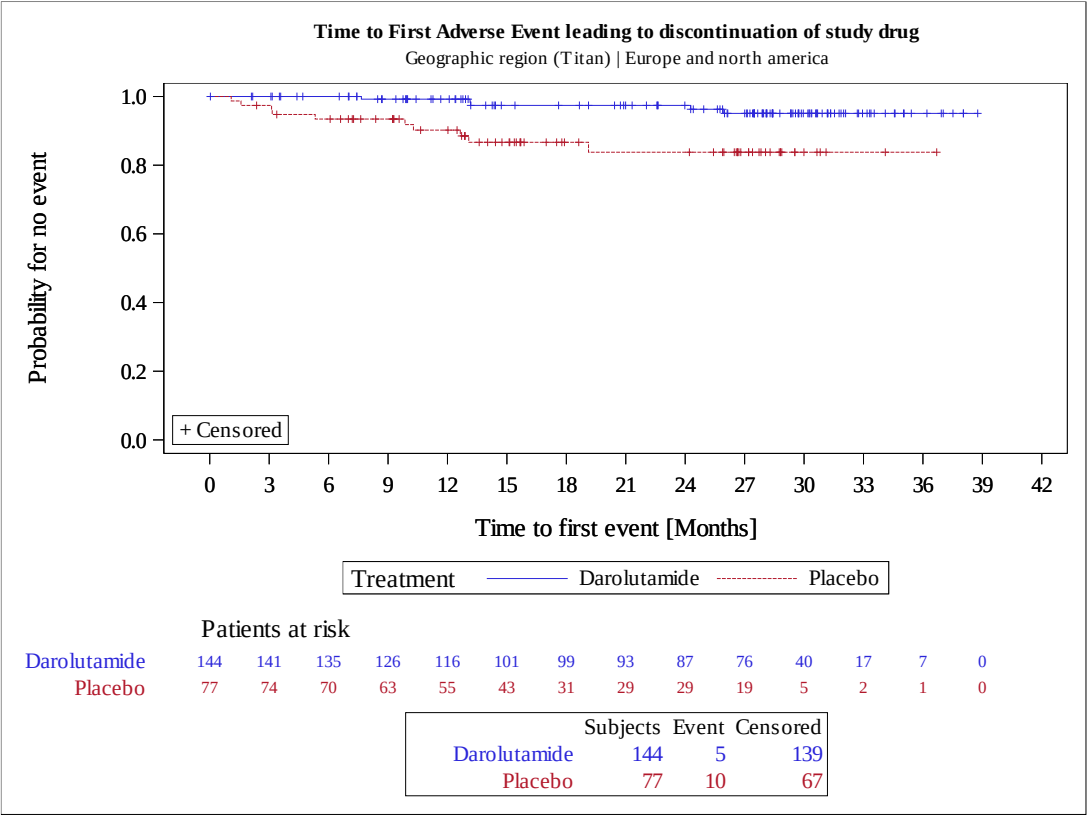


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.8.2
Kaplan-Meier Plot of Time to First Adverse Event leading to discontinuation of study treatment
(safety analysis set)

Final

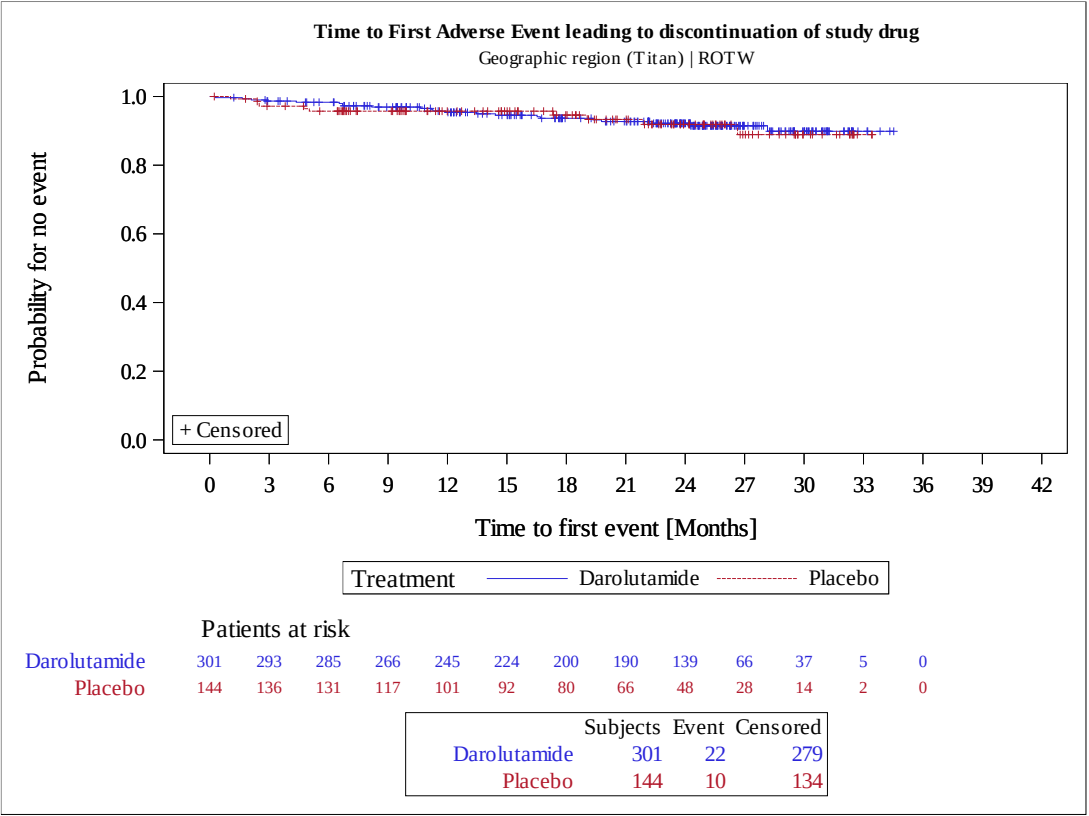


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.8.2
Kaplan-Meier Plot of Time to First Adverse Event leading to discontinuation of study treatment
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.1
Summary of Adverse Events of Special Interest - Bone fractures excluding pathological fractures
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	18 (4.0)	5 (2.3)
Number of censored patients, n (%)	427 (96.0)	216 (97.7)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.471	
95% CI	0.545, 3.972	
p-value	0.4428	
Odds Ratio	1.821	
95% CI	0.667, 4.971	
p-value	0.2420	
Relative Risk	1.788	
95% CI	0.673, 4.752	
p-value	0.2441	
Risk Difference	1.783	
95% CI	-0.900, 4.465	
p-value	0.1927	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.9.1.1.1

Summary of Adverse Events of Special Interest - Bone fractures excluding pathological fractures - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.9918
Yes	1/ 54 (1.9)	0/ 26 (0.0)	NE	(NE, NE)	NE	
No	17/391 (4.3)	5/195 (2.6)	1.379	(0.507, 3.751)	0.5268	
Received prior local therapy (from IWRS)						0.9892
Yes	5/ 80 (6.3)	0/ 40 (0.0)	NE	(NE, NE)	NE	
No	13/365 (3.6)	5/181 (2.8)	1.075	(0.383, 3.021)	0.8903	
Prior local radiotherapy and/or prostatectomy						0.9871
Yes	4/ 87 (4.6)	0/ 50 (0.0)	NE	(NE, NE)	NE	
No	14/358 (3.9)	5/171 (2.9)	1.039	(0.373, 2.892)	0.9414	
Age group						0.9690
<65 years	5/117 (4.3)	2/ 64 (3.1)	1.090	(0.210, 5.664)	0.9184	
65-74	4/193 (2.1)	1/ 95 (1.1)	1.732	(0.193, 15.535)	0.6194	
75-84	9/117 (7.7)	2/ 52 (3.8)	1.606	(0.346, 7.448)	0.5415	
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)	NE	(NE, NE)	NE	
Race						0.9978
White	12/249 (4.8)	3/124 (2.4)	1.491	(0.418, 5.322)	0.5353	
Asian	6/144 (4.2)	2/ 65 (3.1)	1.180	(0.237, 5.864)	0.8393	
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)	NE	(NE, NE)	NE	
Other	0/ 10 (0.0)	0/ 9 (0.0)	NE	(NE, NE)	NE	
Geographical region						0.9147
Asia	6/141 (4.3)	2/ 63 (3.2)	1.177	(0.237, 5.844)	0.8420	
Latin America	5/120 (4.2)	0/ 70 (0.0)	NE	(NE, NE)	NE	
Europe and Rest of the world	7/184 (3.8)	3/ 88 (3.4)	0.786	(0.199, 3.111)	0.7311	
Baseline PSA values by median						0.1198
< median of overall population	13/215 (6.0)	2/110 (1.8)	2.952	(0.666, 13.088)	0.1350	
>= median of overall population	4/219 (1.8)	3/108 (2.8)	0.510	(0.114, 2.288)	0.3706	
ECOG PS at baseline						0.5392
=0	10/235 (4.3)	3/ 96 (3.1)	1.060	(0.290, 3.867)	0.9299	
>=1	8/210 (3.8)	2/125 (1.6)	2.125	(0.451, 10.016)	0.3295	
Gleason score at initial diagnosis						0.6983
Gleason <8	5/124 (4.0)	1/ 65 (1.5)	2.294	(0.267, 19.678)	0.4361	
Gleason >=8	13/308 (4.2)	4/146 (2.7)	1.301	(0.423, 4.000)	0.6446	
Disease volume at baseline						0.6452
high	9/314 (2.9)	2/156 (1.3)	1.903	(0.411, 8.817)	0.4028	
low	9/131 (6.9)	3/ 65 (4.6)	1.191	(0.321, 4.422)	0.7938	
Renal function - eGFR at baseline						0.9999
Normal: eGFR >= 90 mL/min	6/221 (2.7)	5/102 (4.9)	0.455	(0.139, 1.495)	0.1837	
Mild impairment: 60 <= eGFR < 90 mL/min	12/178 (6.7)	0/ 91 (0.0)	NE	(NE, NE)	NE	
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)	NE	(NE, NE)	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.1.1
Summary of Adverse Events of Special Interest - Bone fractures excluding pathological fractures - Subgroup analysis
(safety analysis set)

Final

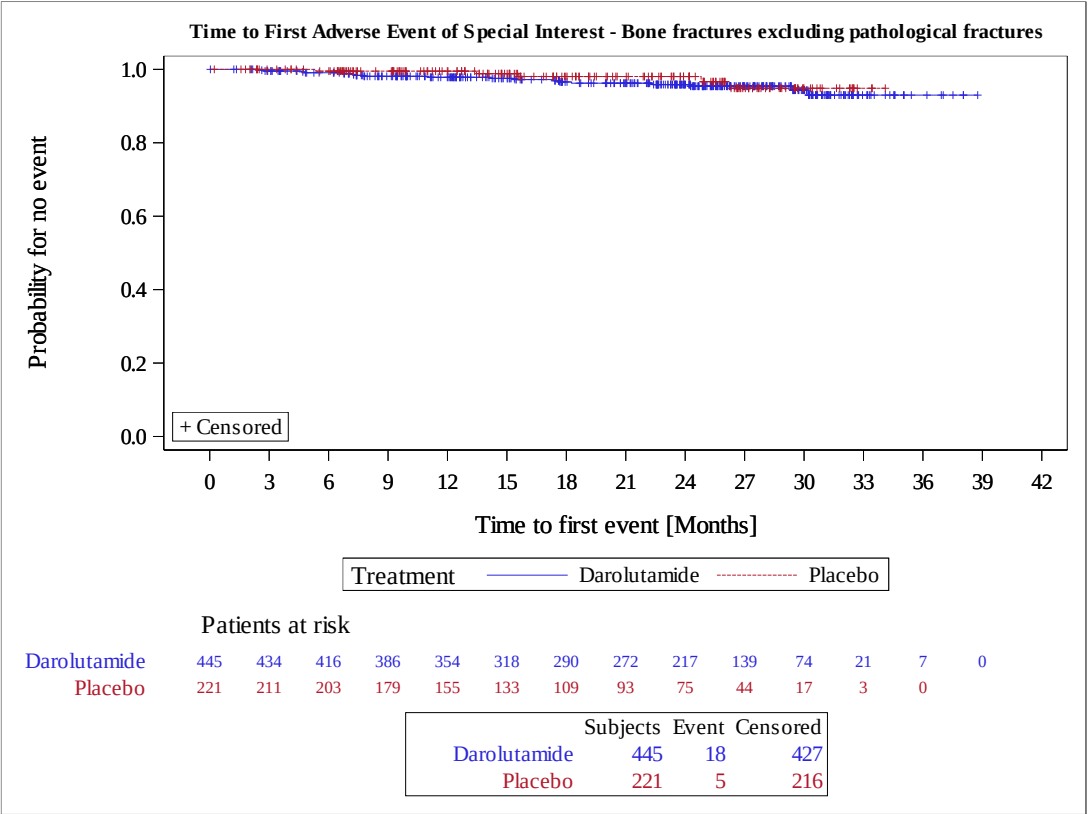
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.0310
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	17/387 (4.4)	3/202 (1.5)	2.431	(0.711, 8.315)	0.1436	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 58 (1.7)	2/ 19 (10.5)	0.133	(0.012, 1.473)	0.0529	
Age Group (Titan)						0.8752
<65	5/117 (4.3)	2/ 64 (3.1)	1.090	(0.210, 5.664)	0.9184	
>=65 and <75	4/193 (2.1)	1/ 95 (1.1)	1.732	(0.193, 15.535)	0.6194	
>=75	9/135 (6.7)	2/ 62 (3.2)	1.642	(0.354, 7.620)	0.5226	
Geographic region (Titan)						0.0240
Europe and north america	2/144 (1.4)	3/ 77 (3.9)	0.276	(0.046, 1.660)	0.1326	
ROTW	16/301 (5.3)	2/144 (1.4)	3.464	(0.796, 15.067)	0.0775	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.9.1.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Bone fractures excluding pathological fractures
(safety analysis set)

Final

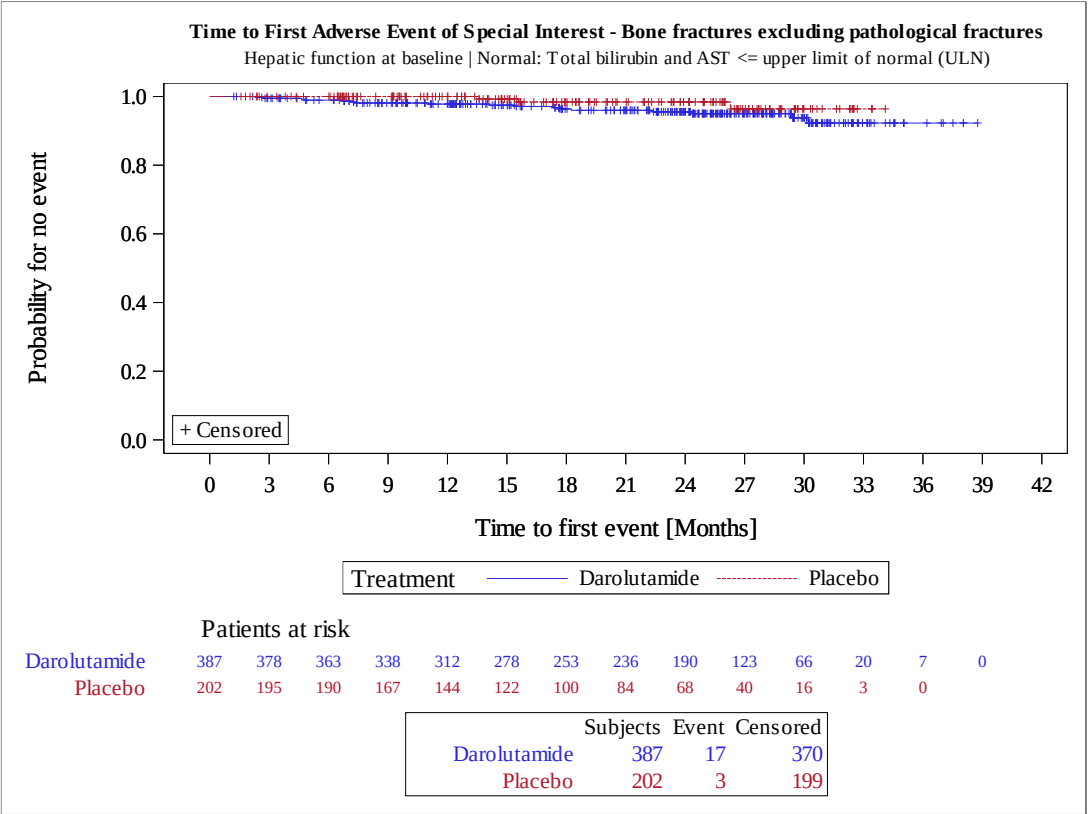


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.9.1.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Bone fractures excluding pathological fractures
(safety analysis set)

Final

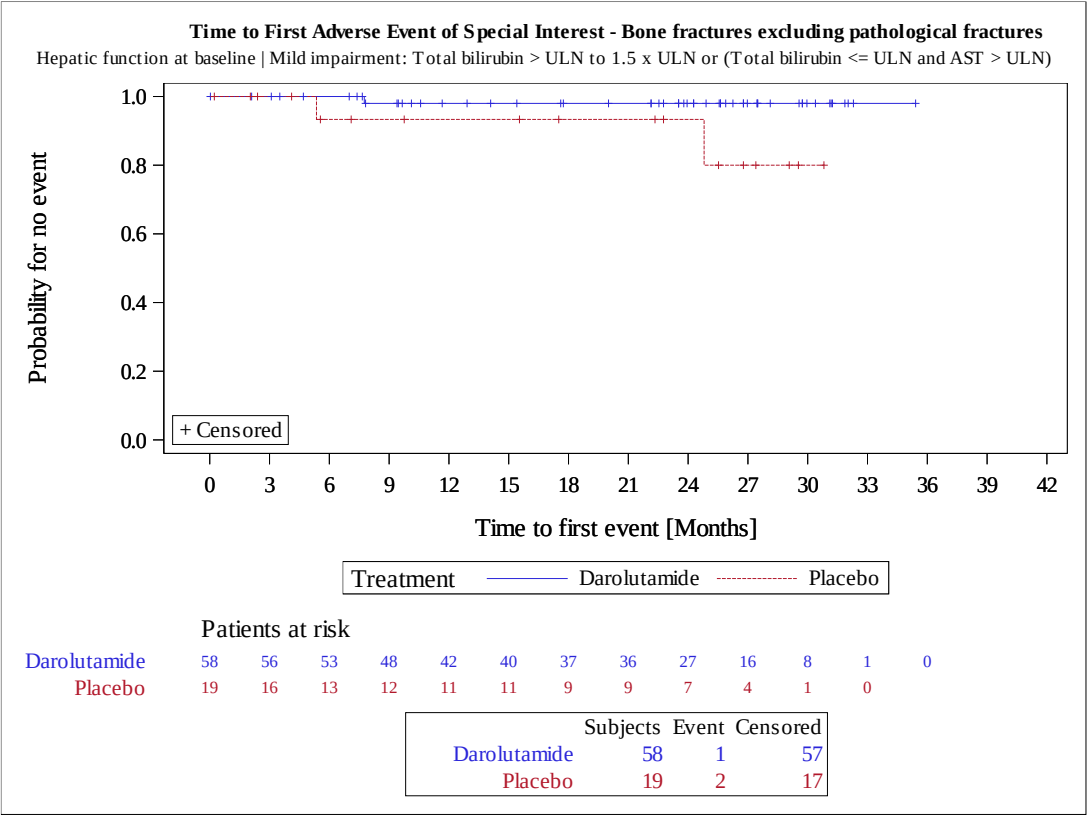


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.9.1.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Bone fractures excluding pathological fractures
(safety analysis set)

Final

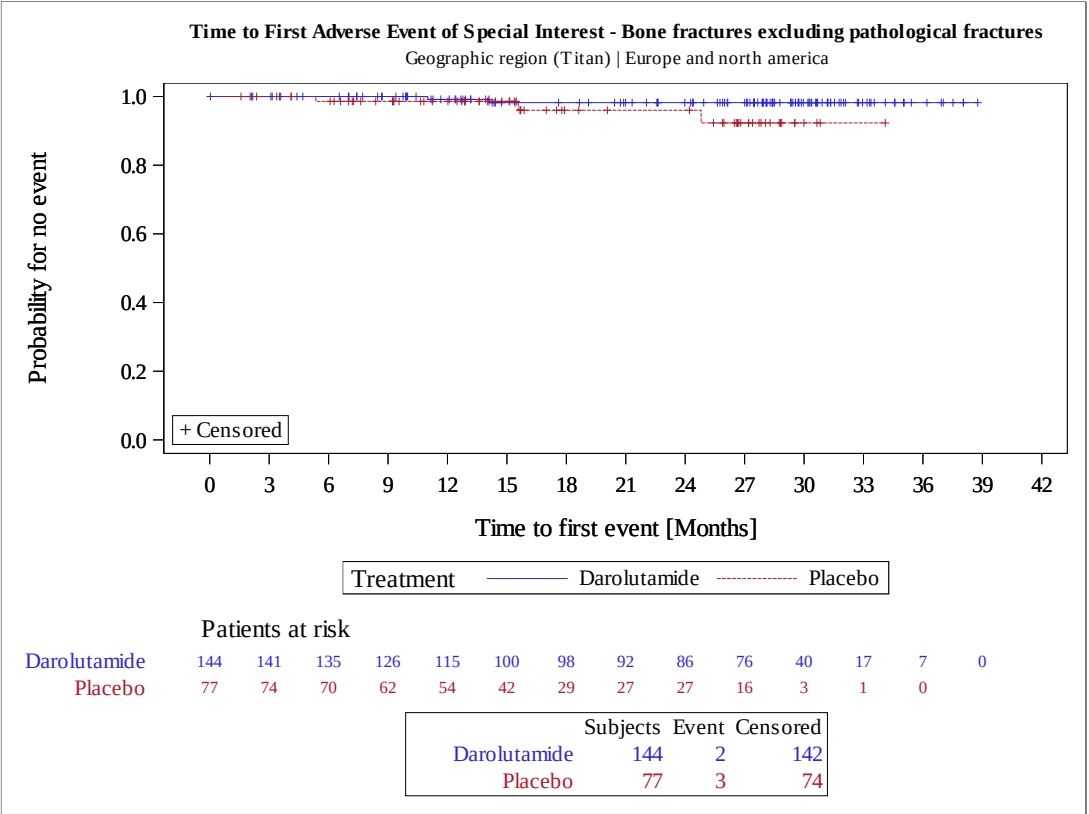


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.9.1.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Bone fractures excluding pathological fractures
(safety analysis set)

Final

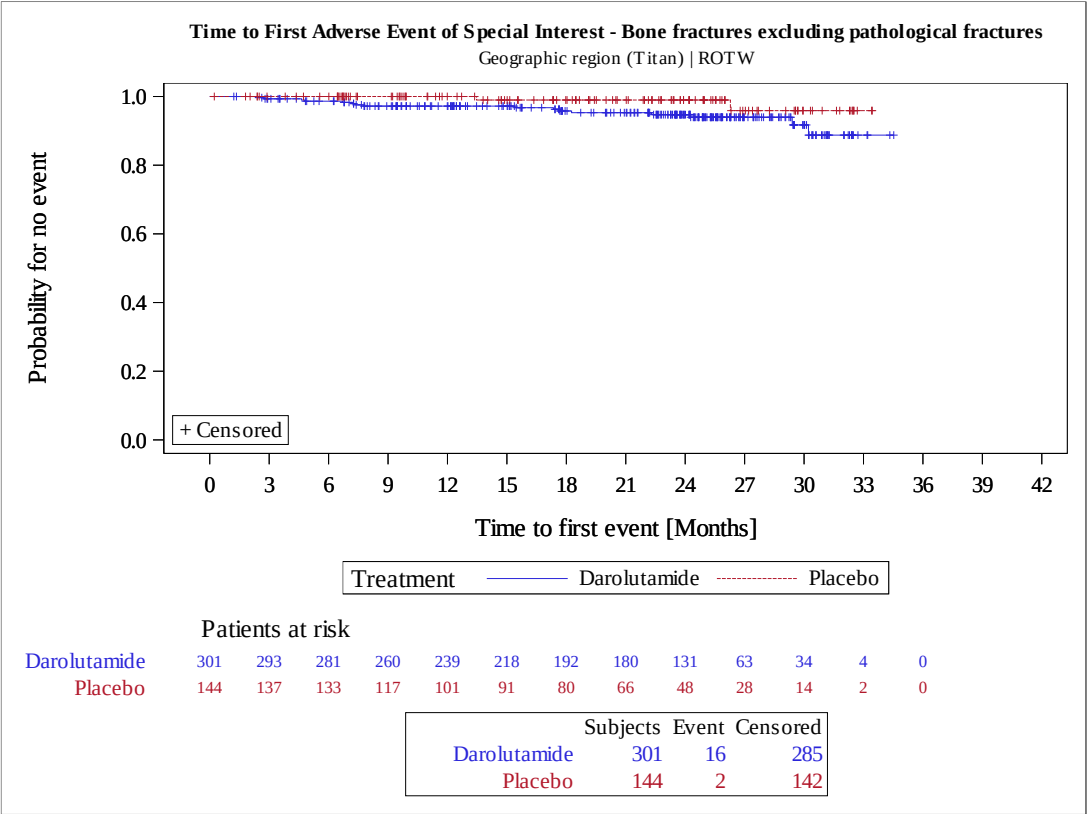


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.9.1.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Bone fractures excluding pathological fractures
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.2
Summary of Adverse Events of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	40 (9.0)	21 (9.5)
Number of censored patients, n (%)	405 (91.0)	200 (90.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.823	
95% CI	0.485, 1.396	
p-value	0.4683	
Odds Ratio	0.941	
95% CI	0.540, 1.638	
p-value	0.8288	
Relative Risk	0.946	
95% CI	0.572, 1.564	
p-value	0.8286	
Risk Difference	-0.513	
95% CI	-5.205, 4.178	
p-value	0.8301	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.9.2.1

Summary of Adverse Events of Special Interest - Diabetes mellitus and hyperglycemia - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	7/ 54 (13.0)	3/ 26 (11.5)	1.069	(0.276, 4.135)	0.9233	0.6618
No	33/391 (8.4)	18/195 (9.2)	0.781	(0.439, 1.389)	0.3986	
Received prior local therapy (from IWRS)						
Yes	6/ 80 (7.5)	5/ 40 (12.5)	0.473	(0.143, 1.561)	0.2089	0.3405
No	34/365 (9.3)	16/181 (8.8)	0.933	(0.515, 1.692)	0.8201	
Prior local radiotherapy and/or prostatectomy						
Yes	4/ 87 (4.6)	6/ 50 (12.0)	0.328	(0.092, 1.167)	0.0703	0.1329
No	36/358 (10.1)	15/171 (8.8)	0.992	(0.543, 1.813)	0.9784	
Age group						
<65 years	15/117 (12.8)	3/ 64 (4.7)	2.308	(0.667, 7.984)	0.1740	0.0483
65-74	13/193 (6.7)	15/ 95 (15.8)	0.374	(0.177, 0.787)	0.0070	
75-84	9/117 (7.7)	2/ 52 (3.8)	1.795	(0.388, 8.314)	0.4478	
>=85 years	3/ 18 (16.7)	1/ 10 (10.0)	1.374	(0.143, 13.232)	0.7825	
Race						
White	20/249 (8.0)	7/124 (5.6)	1.244	(0.525, 2.948)	0.6197	0.3598
Asian	11/144 (7.6)	10/ 65 (15.4)	0.411	(0.174, 0.971)	0.0362	
Black or African American	9/ 42 (21.4)	4/ 23 (17.4)	1.086	(0.334, 3.529)	0.8905	
Other	0/ 10 (0.0)	0/ 9 (0.0)	NE	(NE, NE)	NE	
Geographical region						
Asia	11/141 (7.8)	10/ 63 (15.9)	0.408	(0.173, 0.965)	0.0348	0.1305
Latin America	21/120 (17.5)	8/ 70 (11.4)	1.430	(0.632, 3.236)	0.3875	
Europe and Rest of the world	8/184 (4.3)	3/ 88 (3.4)	1.079	(0.285, 4.088)	0.9107	
Baseline PSA values by median						
< median of overall population	15/215 (7.0)	11/110 (10.0)	0.587	(0.269, 1.280)	0.1750	0.1434
>= median of overall population	24/219 (11.0)	8/108 (7.4)	1.351	(0.607, 3.010)	0.4594	
ECOG PS at baseline						
=0	27/235 (11.5)	9/ 96 (9.4)	1.112	(0.522, 2.366)	0.7834	0.2319
>=1	13/210 (6.2)	12/125 (9.6)	0.549	(0.250, 1.204)	0.1286	
Gleason score at initial diagnosis						
Gleason <8	14/124 (11.3)	9/ 65 (13.8)	0.747	(0.323, 1.728)	0.4925	0.5450
Gleason >=8	26/308 (8.4)	11/146 (7.5)	0.994	(0.491, 2.013)	0.9858	
Disease volume at baseline						
high	25/314 (8.0)	14/156 (9.0)	0.782	(0.406, 1.506)	0.4605	0.8218
low	15/131 (11.5)	7/ 65 (10.8)	0.899	(0.366, 2.212)	0.8169	
Renal function - eGFR at baseline						
Normal: eGFR >= 90 mL/min	23/221 (10.4)	12/102 (11.8)	0.741	(0.369, 1.491)	0.3995	0.7478
Mild impairment: 60 <= eGFR < 90 mL/min	14/178 (7.9)	6/ 91 (6.6)	1.040	(0.399, 2.713)	0.9351	
Moderate impairment: 30 <= eGFR < 60 mL/min	3/ 45 (6.7)	3/ 27 (11.1)	0.606	(0.122, 3.004)	0.5357	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.2.1
Summary of Adverse Events of Special Interest - Diabetes mellitus and hyperglycemia - Subgroup analysis
(safety analysis set)

Final

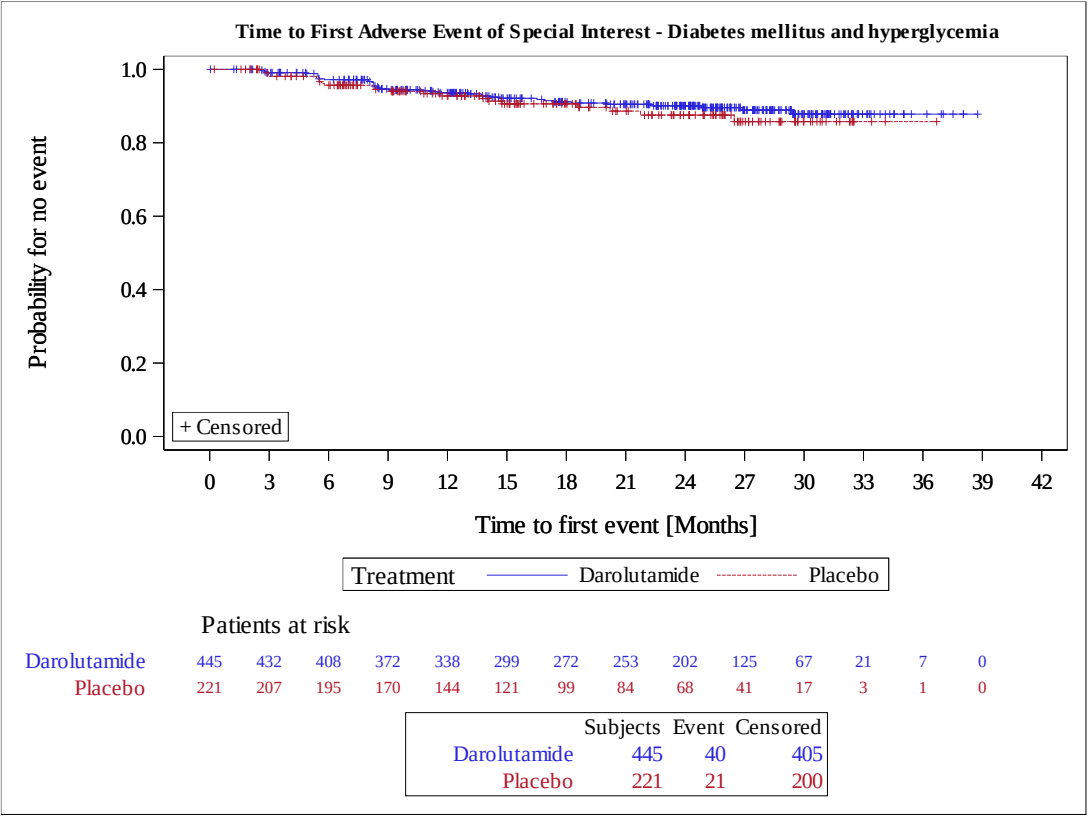
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.5773
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	36/387 (9.3)	19/202 (9.4)	0.861	(0.494, 1.503)	0.5990	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	4/ 58 (6.9)	2/ 19 (10.5)	0.493	(0.090, 2.695)	0.4011	
Age Group (Titan)						0.0205
<65	15/117 (12.8)	3/ 64 (4.7)	2.308	(0.667, 7.984)	0.1740	
>=65 and <75	13/193 (6.7)	15/ 95 (15.8)	0.374	(0.177, 0.787)	0.0070	
>=75	12/135 (8.9)	3/ 62 (4.8)	1.647	(0.465, 5.839)	0.4349	
Geographic region (Titan)						0.8772
Europe and north america	5/144 (3.5)	3/ 77 (3.9)	0.722	(0.171, 3.044)	0.6560	
ROTW	35/301 (11.6)	18/144 (12.5)	0.831	(0.470, 1.467)	0.5214	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.9.2.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final

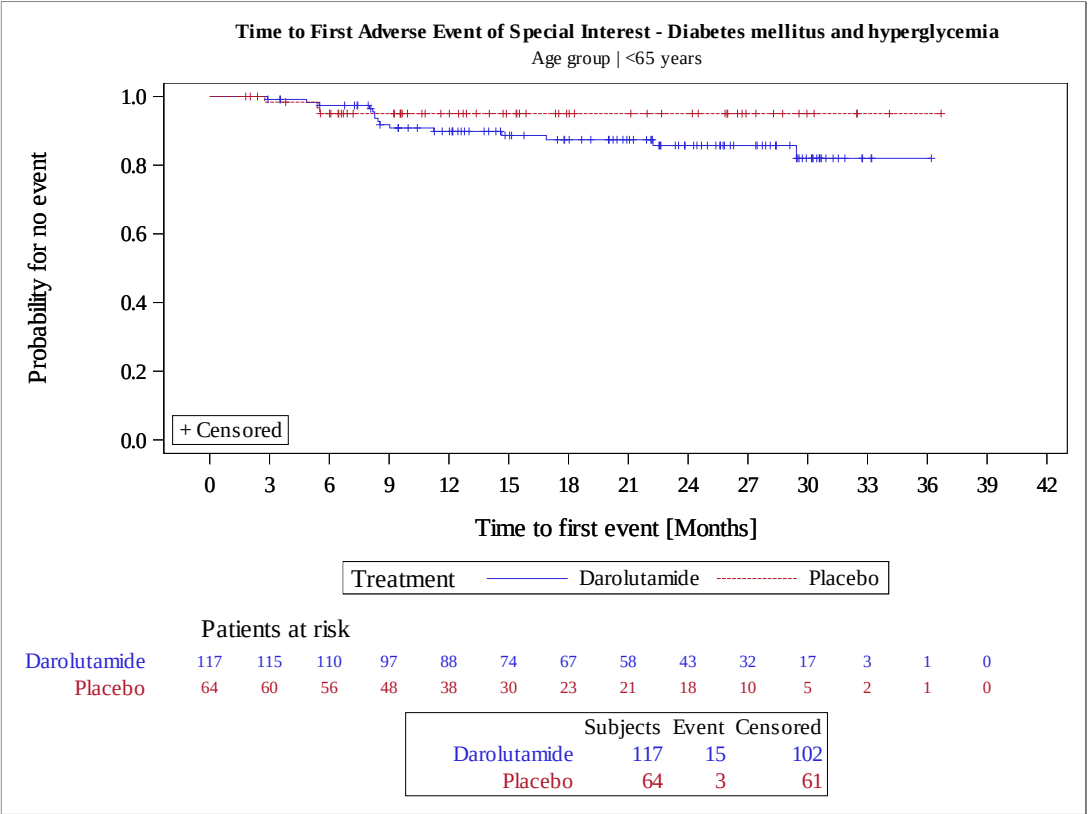


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.9.2.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final

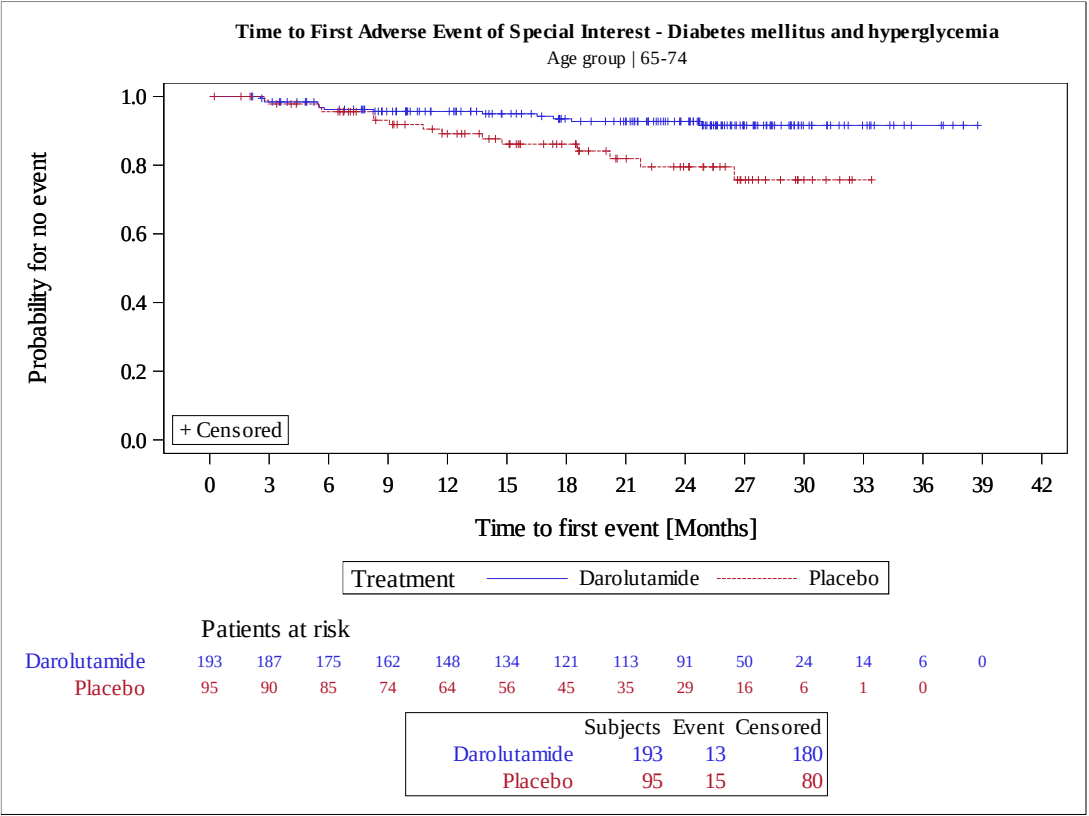


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.9.2.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final

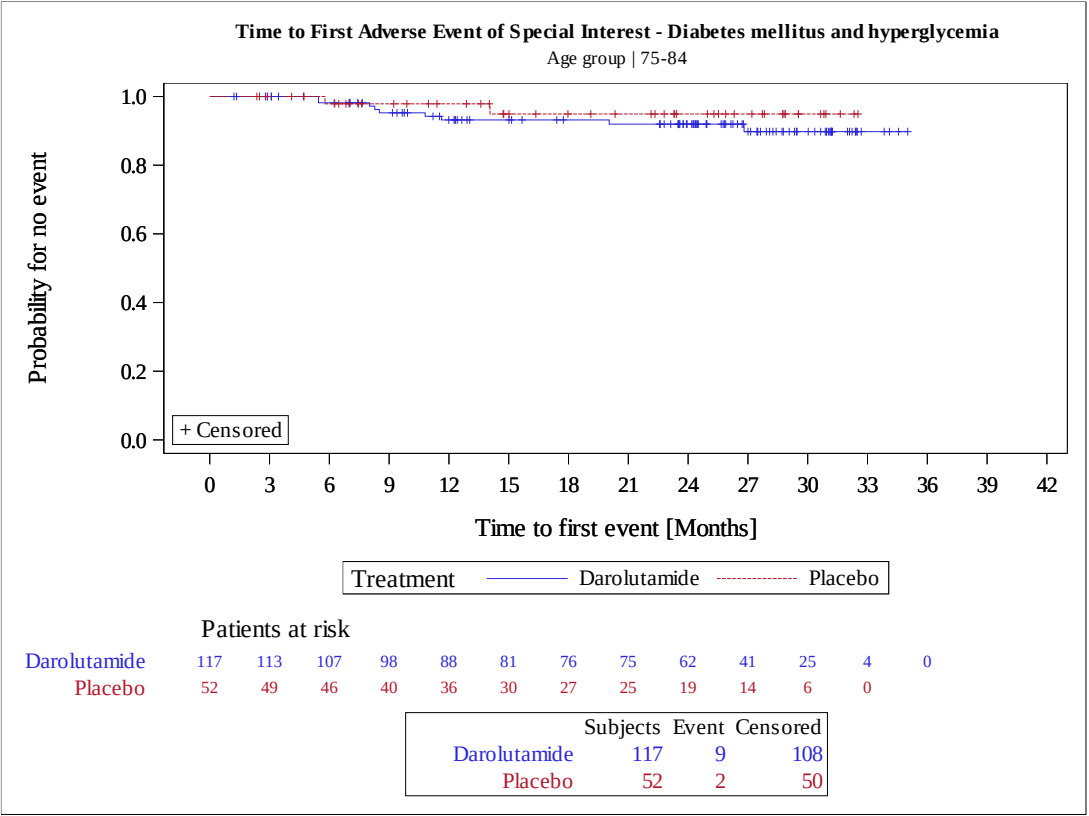


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.9.2.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

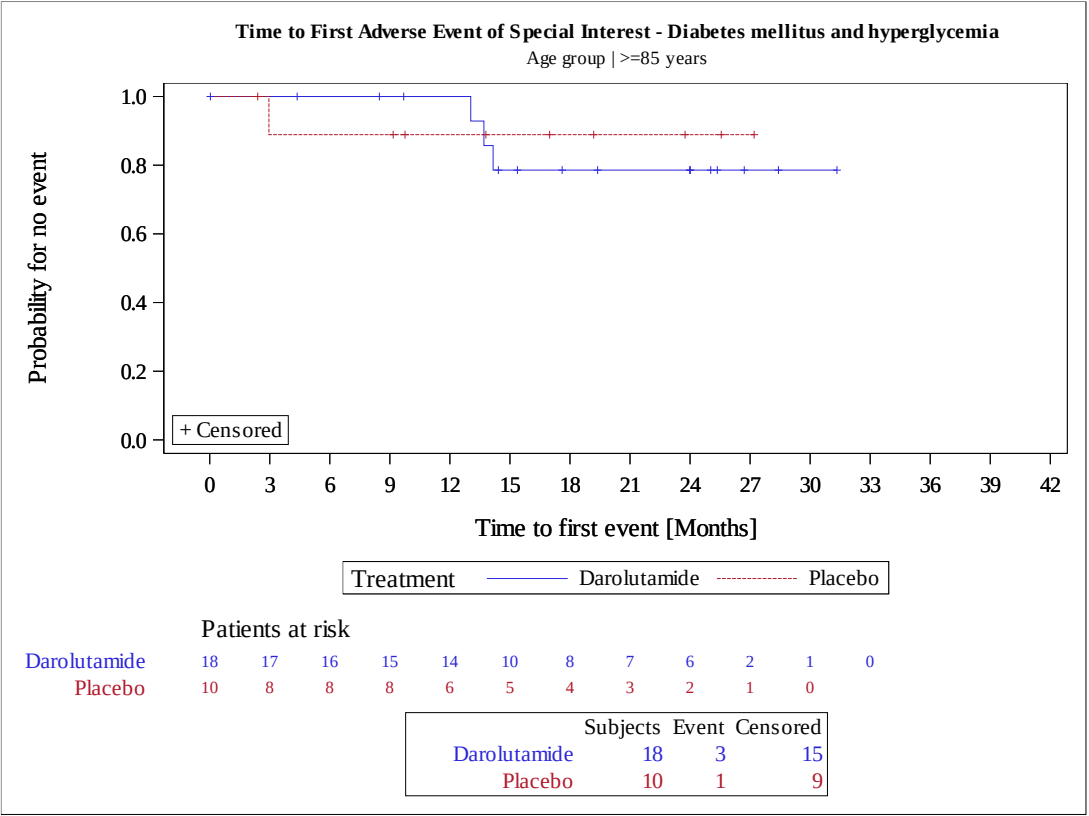
Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

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Study population
Figure 3.2.9.2.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final

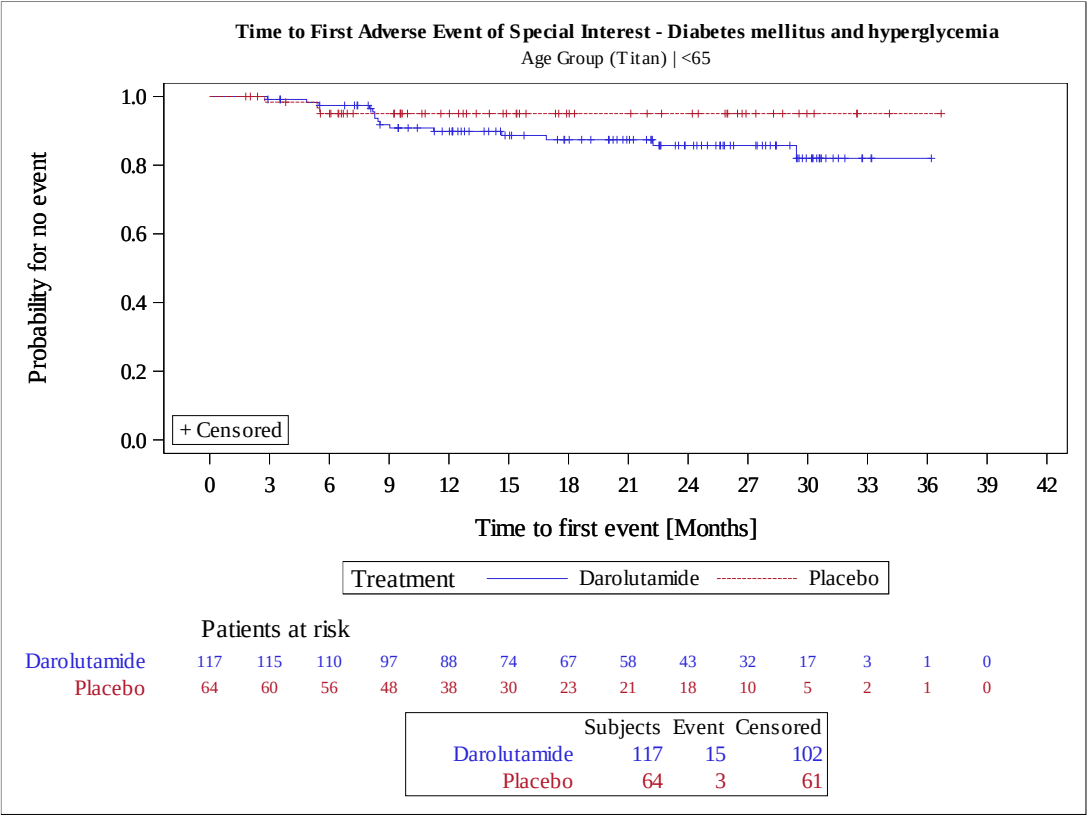


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.9.2.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final

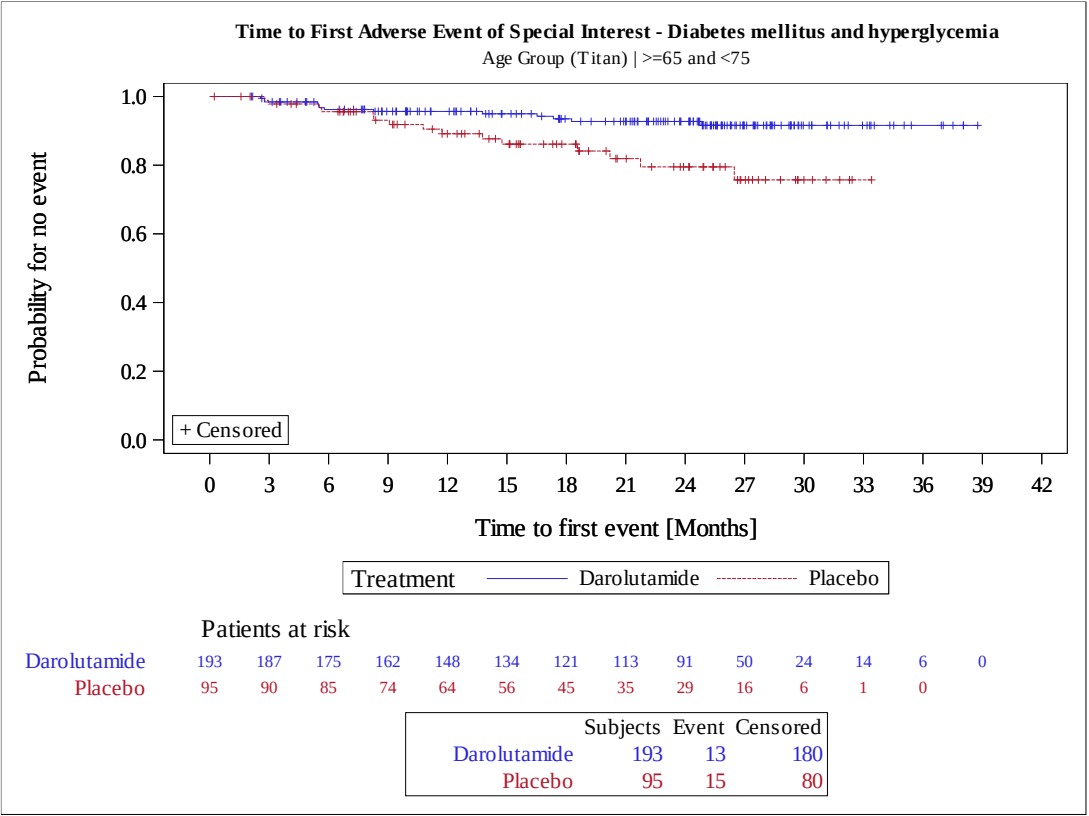


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.9.2.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final

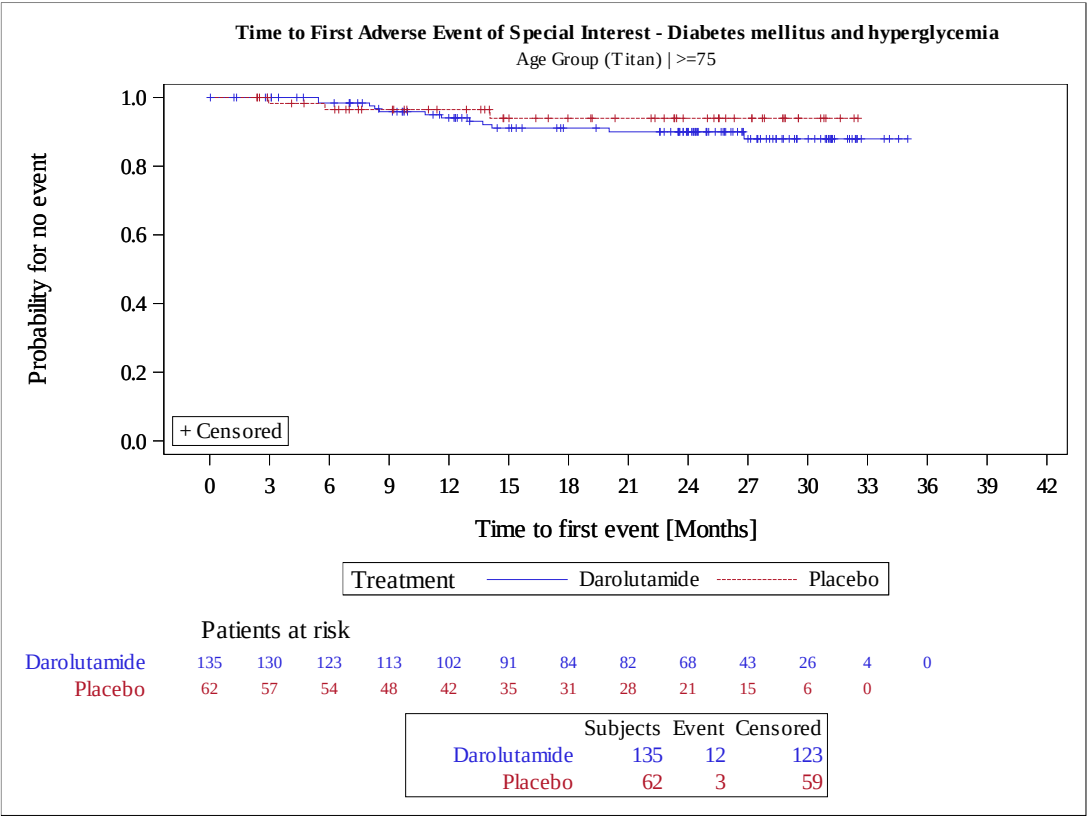


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.9.2.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.3
Summary of Adverse Events of Special Interest - Fall
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	6 (1.3)	2 (0.9)
Number of censored patients, n (%)	439 (98.7)	219 (99.1)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.350	
95% CI	0.272, 6.703	
p-value	0.7123	
Odds Ratio	1.497	
95% CI	0.300, 7.476	
p-value	0.6232	
Relative Risk	1.490	
95% CI	0.303, 7.322	
p-value	0.6236	
Risk Difference	0.443	
95% CI	-1.202, 2.089	
p-value	0.5974	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.9.3.1

Summary of Adverse Events of Special Interest - Fall - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	1/ 54 (1.9)	1/ 26 (3.8)			
No	5/391 (1.3)	1/195 (0.5)			
Received prior local therapy (from IWRS)					
Yes	3/ 80 (3.8)	2/ 40 (5.0)			
No	3/365 (0.8)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	1/ 87 (1.1)	2/ 50 (4.0)			
No	5/358 (1.4)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	1/193 (0.5)	0/ 95 (0.0)			
75-84	4/117 (3.4)	2/ 52 (3.8)			
>=85 years	1/ 18 (5.6)	0/ 10 (0.0)			
Race					
White	5/249 (2.0)	2/124 (1.6)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	1/ 42 (2.4)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	3/120 (2.5)	1/ 70 (1.4)			
Europe and Rest of the world	3/184 (1.6)	1/ 88 (1.1)			
Baseline PSA values by median					
< median of overall population	4/215 (1.9)	2/110 (1.8)			
>= median of overall population	2/219 (0.9)	0/108 (0.0)			
ECOG PS at baseline					
=0	6/235 (2.6)	1/ 96 (1.0)			
>=1	0/210 (0.0)	1/125 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	3/124 (2.4)	1/ 65 (1.5)			
Gleason >=8	3/308 (1.0)	1/146 (0.7)			
Disease volume at baseline					
high	4/314 (1.3)	2/156 (1.3)			
low	2/131 (1.5)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	2/221 (0.9)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	4/178 (2.2)	2/ 91 (2.2)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.9.3.1

Summary of Adverse Events of Special Interest - Fall - Subgroup analysis (safety analysis set)

Final

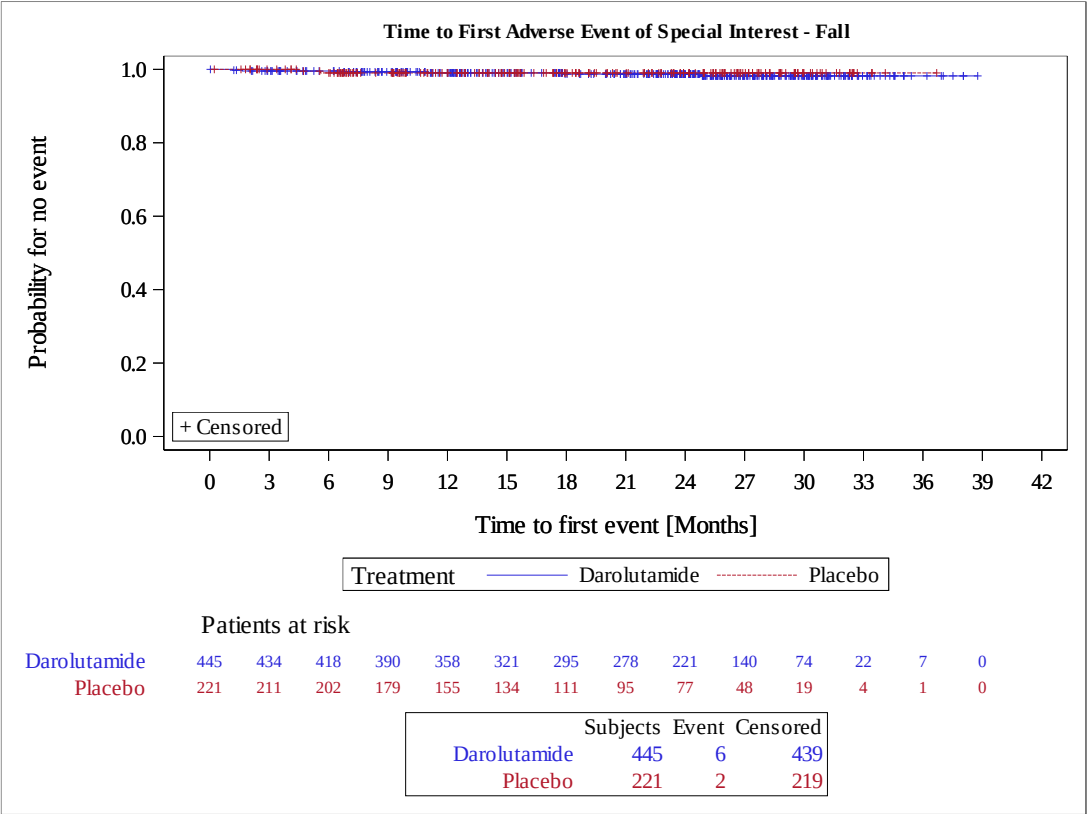
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	6/387 (1.6)	2/202 (1.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	1/193 (0.5)	0/ 95 (0.0)			
>=75	5/135 (3.7)	2/ 62 (3.2)			
Geographic region (Titan)					
Europe and north america	1/144 (0.7)	0/ 77 (0.0)			
ROTW	5/301 (1.7)	2/144 (1.4)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.9.3.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Fall
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.4
Summary of Adverse Events of Special Interest - Fatigue/ asthenic conditions
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	41 (9.2)	28 (12.7)
Number of censored patients, n (%)	404 (90.8)	193 (87.3)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (27.8, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.635	
95% CI	0.392, 1.028	
p-value	0.0625	
Odds Ratio	0.700	
95% CI	0.420, 1.165	
p-value	0.1698	
Relative Risk	0.727	
95% CI	0.462, 1.143	
p-value	0.1678	
Risk Difference	-3.456	
95% CI	-8.599, 1.687	
p-value	0.1878	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.9.4.1

Summary of Adverse Events of Special Interest - Fatigue/ asthenic conditions - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	3/ 54 (5.6)	4/ 26 (15.4)	0.328	(0.073, 1.469)	0.1252	0.3203
No	38/391 (9.7)	24/195 (12.3)	0.683	(0.409, 1.140)	0.1424	
Received prior local therapy (from IWRS)						
Yes	6/ 80 (7.5)	10/ 40 (25.0)	0.235	(0.084, 0.657)	0.0027	0.0228
No	35/365 (9.6)	18/181 (9.9)	0.865	(0.490, 1.529)	0.6174	
Prior local radiotherapy and/or prostatectomy						
Yes	5/ 87 (5.7)	7/ 50 (14.0)	0.353	(0.111, 1.119)	0.0645	0.3001
No	36/358 (10.1)	21/171 (12.3)	0.715	(0.417, 1.227)	0.2213	
Age group						
<65 years	4/117 (3.4)	8/ 64 (12.5)	0.242	(0.073, 0.806)	0.0122	0.3655
65-74	19/193 (9.8)	13/ 95 (13.7)	0.637	(0.314, 1.291)	0.2069	
75-84	14/117 (12.0)	7/ 52 (13.5)	0.781	(0.314, 1.943)	0.5947	
>=85 years	4/ 18 (22.2)	0/ 10 (0.0)	NE	(NE, NE)	NE	
Race						
White	26/249 (10.4)	16/124 (12.9)	0.662	(0.354, 1.239)	0.1940	0.9974
Asian	11/144 (7.6)	8/ 65 (12.3)	0.585	(0.235, 1.457)	0.2439	
Black or African American	4/ 42 (9.5)	3/ 23 (13.0)	0.685	(0.153, 3.064)	0.6182	
Other	0/ 10 (0.0)	1/ 9 (11.1)	NE	(NE, NE)	NE	
Geographical region						
Asia	10/141 (7.1)	7/ 63 (11.1)	0.600	(0.228, 1.577)	0.2948	0.9863
Latin America	9/120 (7.5)	8/ 70 (11.4)	0.580	(0.224, 1.507)	0.2581	
Europe and Rest of the world	22/184 (12.0)	13/ 88 (14.8)	0.657	(0.329, 1.311)	0.2295	
Baseline PSA values by median						
< median of overall population	28/215 (13.0)	16/110 (14.5)	0.789	(0.426, 1.460)	0.4488	0.2256
>= median of overall population	12/219 (5.5)	12/108 (11.1)	0.426	(0.191, 0.952)	0.0321	
ECOG PS at baseline						
=0	24/235 (10.2)	13/ 96 (13.5)	0.655	(0.333, 1.290)	0.2179	0.8660
>=1	17/210 (8.1)	15/125 (12.0)	0.608	(0.303, 1.218)	0.1561	
Gleason score at initial diagnosis						
Gleason <8	9/124 (7.3)	7/ 65 (10.8)	0.596	(0.222, 1.606)	0.3012	0.6944
Gleason >=8	32/308 (10.4)	18/146 (12.3)	0.747	(0.418, 1.332)	0.3207	
Disease volume at baseline						
high	32/314 (10.2)	17/156 (10.9)	0.843	(0.467, 1.519)	0.5685	0.0824
low	9/131 (6.9)	11/ 65 (16.9)	0.335	(0.138, 0.813)	0.0111	
Renal function - eGFR at baseline						
Normal: eGFR >= 90 mL/min	23/221 (10.4)	10/102 (9.8)	0.934	(0.444, 1.965)	0.8577	0.1548
Mild impairment: 60 <= eGFR < 90 mL/min	15/178 (8.4)	11/ 91 (12.1)	0.618	(0.283, 1.349)	0.2227	
Moderate impairment: 30 <= eGFR < 60 mL/min	2/ 45 (4.4)	6/ 27 (22.2)	0.147	(0.028, 0.767)	0.0096	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.9.4.1

Summary of Adverse Events of Special Interest - Fatigue/ asthenic conditions - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.8823
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	36/387 (9.3)	26/202 (12.9)	0.625	(0.376, 1.036)	0.0660	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	5/ 58 (8.6)	2/ 19 (10.5)	0.733	(0.142, 3.782)	0.7101	
Age Group (Titan)						0.1028
<65	4/117 (3.4)	8/ 64 (12.5)	0.242	(0.073, 0.806)	0.0122	
>=65 and <75	19/193 (9.8)	13/ 95 (13.7)	0.637	(0.314, 1.291)	0.2069	
>=75	18/135 (13.3)	7/ 62 (11.3)	1.073	(0.447, 2.575)	0.8751	
Geographic region (Titan)						0.6586
Europe and north america	14/144 (9.7)	8/ 77 (10.4)	0.725	(0.302, 1.742)	0.4701	
ROTW	27/301 (9.0)	20/144 (13.9)	0.601	(0.337, 1.072)	0.0811	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

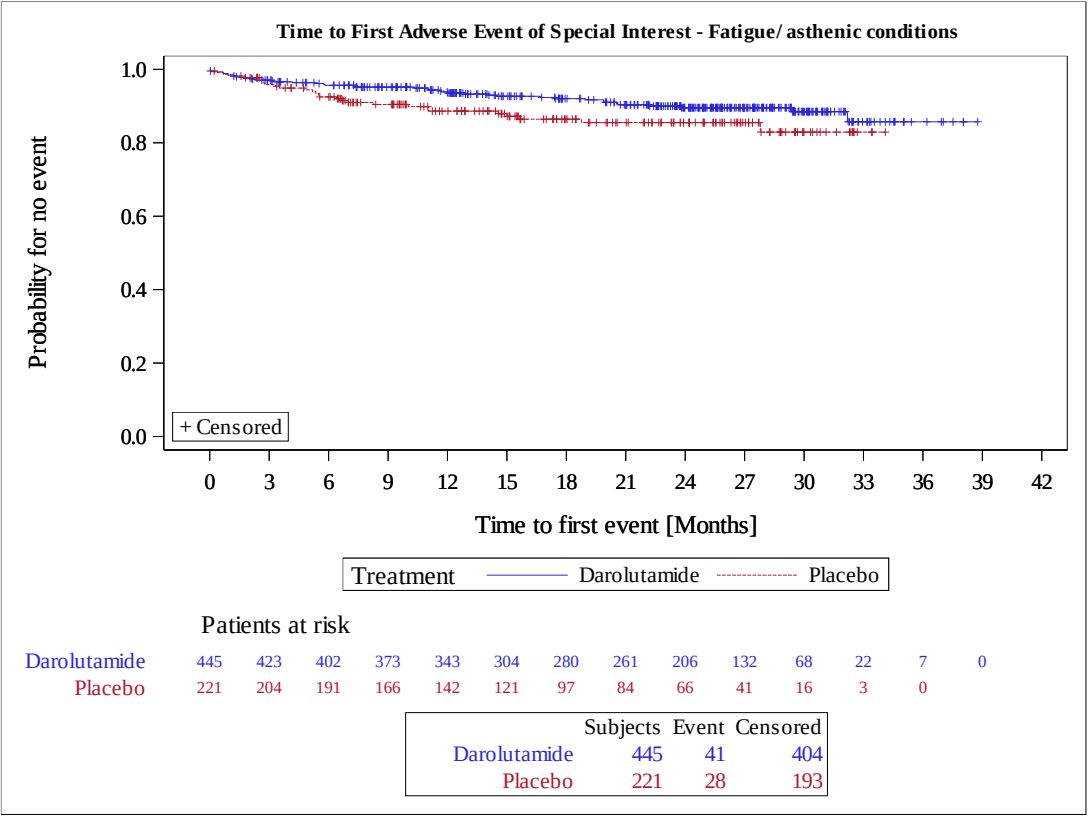
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.9.4.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Fatigue/ asthenic conditions
(safety analysis set)

Final

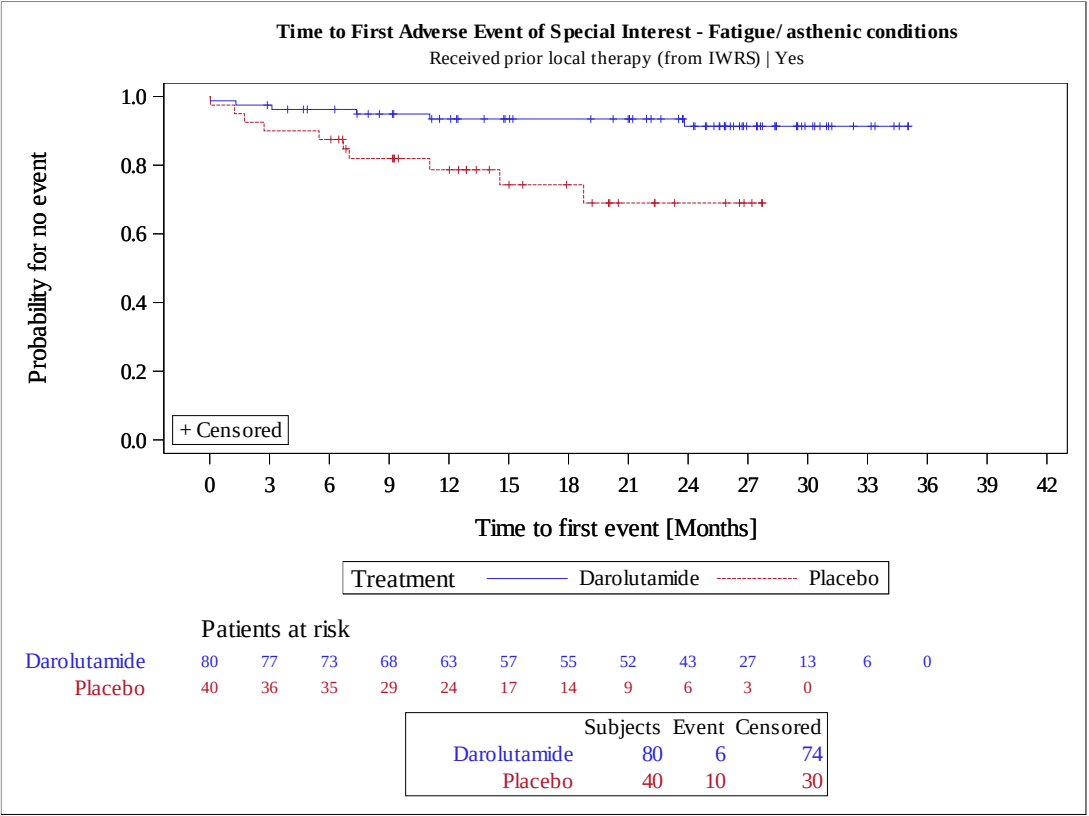


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.9.4.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Fatigue/ asthenic conditions
(safety analysis set)

Final

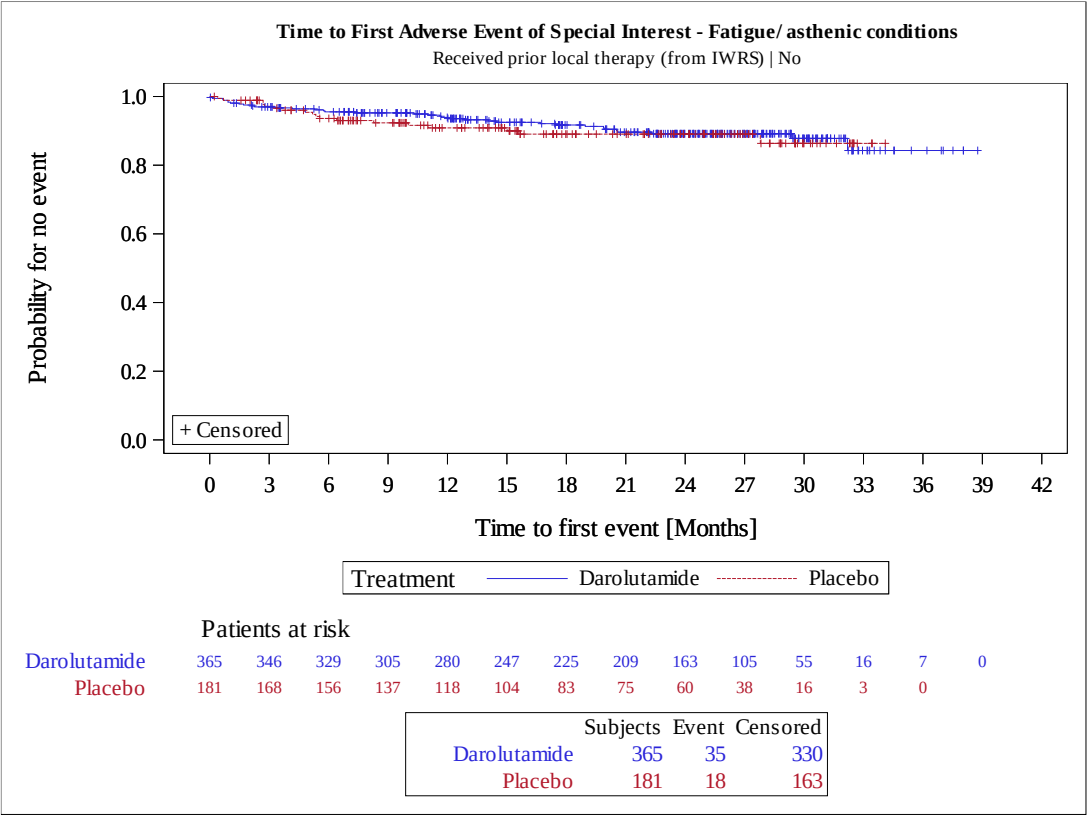


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.9.4.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Fatigue/ asthenic conditions
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.5
Summary of Adverse Events of Special Interest - Weight decreased
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	14 (3.1)	6 (2.7)
Number of censored patients, n (%)	431 (96.9)	215 (97.3)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.994	
95% CI	0.381, 2.590	
p-value	0.9898	
Odds Ratio	1.164	
95% CI	0.441, 3.071	
p-value	0.7591	
Relative Risk	1.159	
95% CI	0.451, 2.974	
p-value	0.7593	
Risk Difference	0.431	
95% CI	-2.256, 3.118	
p-value	0.7532	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.9.5.1

Summary of Adverse Events of Special Interest - Weight decreased - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.9872
Yes	0/ 54 (0.0)	1/ 26 (3.8)	NE	(NE, NE)	NE	
No	14/391 (3.6)	5/195 (2.6)	1.182	(0.425, 3.288)	0.7483	
Received prior local therapy (from IWRS)						0.9893
Yes	3/ 80 (3.8)	0/ 40 (0.0)	NE	(NE, NE)	NE	
No	11/365 (3.0)	6/181 (3.3)	0.797	(0.295, 2.158)	0.6551	
Prior local radiotherapy and/or prostatectomy						0.9881
Yes	2/ 87 (2.3)	0/ 50 (0.0)	NE	(NE, NE)	NE	
No	12/358 (3.4)	6/171 (3.5)	0.807	(0.302, 2.153)	0.6672	
Age group						0.9952
<65 years	2/117 (1.7)	1/ 64 (1.6)	0.943	(0.085, 10.430)	0.9615	
65-74	7/193 (3.6)	3/ 95 (3.2)	1.012	(0.261, 3.924)	0.9858	
75-84	4/117 (3.4)	2/ 52 (3.8)	0.771	(0.141, 4.212)	0.7632	
>=85 years	1/ 18 (5.6)	0/ 10 (0.0)	NE	(NE, NE)	NE	
Race						0.6293
White	7/249 (2.8)	1/124 (0.8)	2.790	(0.343, 22.731)	0.3166	
Asian	6/144 (4.2)	4/ 65 (6.2)	0.608	(0.171, 2.157)	0.4368	
Black or African American	1/ 42 (2.4)	1/ 23 (4.3)	0.500	(0.031, 7.994)	0.6171	
Other	0/ 10 (0.0)	0/ 9 (0.0)	NE	(NE, NE)	NE	
Geographical region						0.5553
Asia	6/141 (4.3)	4/ 63 (6.3)	0.604	(0.170, 2.144)	0.4311	
Latin America	2/120 (1.7)	1/ 70 (1.4)	0.989	(0.090, 10.917)	0.9926	
Europe and Rest of the world	6/184 (3.3)	1/ 88 (1.1)	2.336	(0.280, 19.483)	0.4193	
Baseline PSA values by median						0.3263
< median of overall population	10/215 (4.7)	3/110 (2.7)	1.492	(0.410, 5.427)	0.5407	
>= median of overall population	4/219 (1.8)	3/108 (2.8)	0.538	(0.120, 2.420)	0.4122	
ECOG PS at baseline						0.1427
=0	9/235 (3.8)	1/ 96 (1.0)	3.043	(0.385, 24.043)	0.2668	
>=1	5/210 (2.4)	5/125 (4.0)	0.536	(0.155, 1.855)	0.3173	
Gleason score at initial diagnosis						0.9966
Gleason <8	2/124 (1.6)	1/ 65 (1.5)	0.917	(0.083, 10.132)	0.9439	
Gleason >=8	11/308 (3.6)	5/146 (3.4)	0.906	(0.314, 2.611)	0.8548	
Disease volume at baseline						0.9923
high	13/314 (4.1)	6/156 (3.8)	0.927	(0.352, 2.441)	0.8774	
low	1/131 (0.8)	0/ 65 (0.0)	NE	(NE, NE)	NE	
Renal function - eGFR at baseline						0.5388
Normal: eGFR >= 90 mL/min	9/221 (4.1)	2/102 (2.0)	1.757	(0.379, 8.145)	0.4652	
Mild impairment: 60 <= eGFR < 90 mL/min	4/178 (2.2)	3/ 91 (3.3)	0.609	(0.136, 2.722)	0.5117	
Moderate impairment: 30 <= eGFR < 60 mL/min	1/ 45 (2.2)	1/ 27 (3.7)	0.504	(0.031, 8.141)	0.6226	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.9.5.1

Summary of Adverse Events of Special Interest - Weight decreased - Subgroup analysis (safety analysis set)

Final

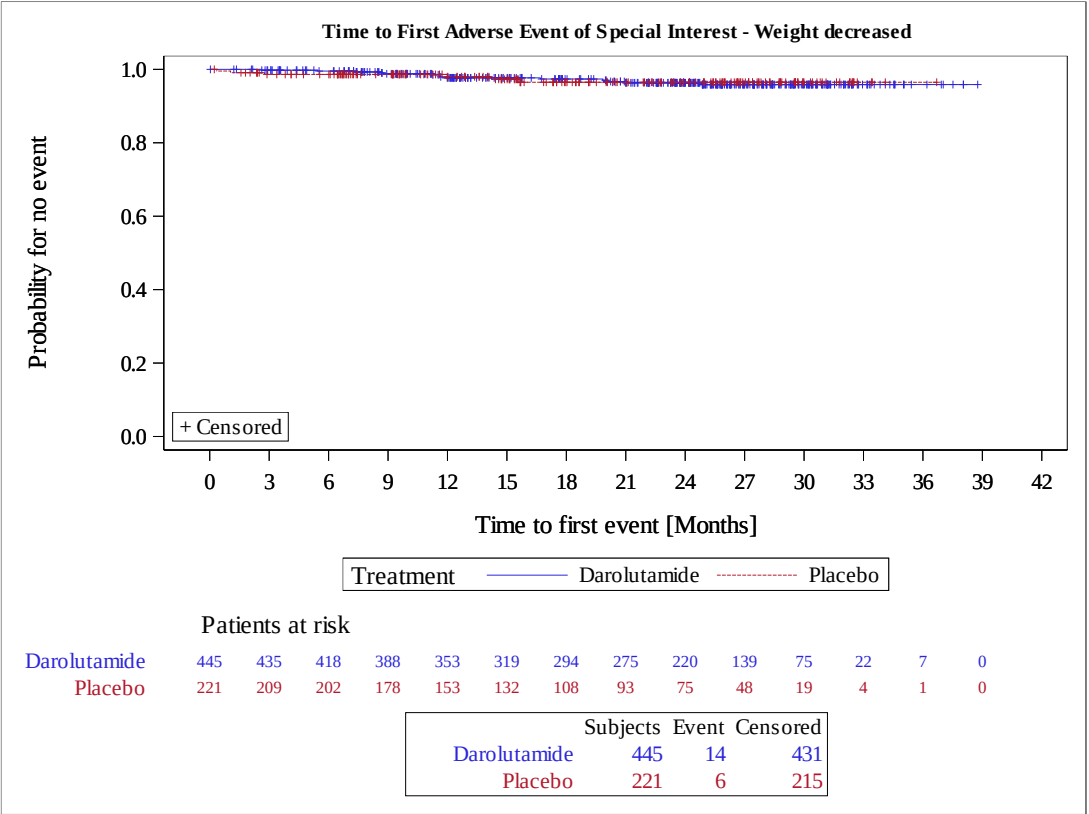
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.3461
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	13/387 (3.4)	5/202 (2.5)	1.150	(0.409, 3.231)	0.7910	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 58 (1.7)	1/ 19 (5.3)	0.293	(0.018, 4.701)	0.3568	
Age Group (Titan)						0.9911
<65	2/117 (1.7)	1/ 64 (1.6)	0.943	(0.085, 10.430)	0.9615	
>=65 and <75	7/193 (3.6)	3/ 95 (3.2)	1.012	(0.261, 3.924)	0.9858	
>=75	5/135 (3.7)	2/ 62 (3.2)	0.971	(0.188, 5.011)	0.9720	
Geographic region (Titan)						0.2587
Europe and north america	6/144 (4.2)	1/ 77 (1.3)	2.646	(0.317, 22.056)	0.3497	
ROTW	8/301 (2.7)	5/144 (3.5)	0.669	(0.219, 2.049)	0.4790	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.9.5.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Weight decreased
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.6
Summary of Adverse Events of Special Interest - Rash
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	19 (4.3)	8 (3.6)
Number of censored patients, n (%)	426 (95.7)	213 (96.4)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.092	
95% CI	0.477, 2.497	
p-value	0.8348	
Odds Ratio	1.188	
95% CI	0.511, 2.757	
p-value	0.6892	
Relative Risk	1.179	
95% CI	0.525, 2.652	
p-value	0.6896	
Risk Difference	0.650	
95% CI	-2.447, 3.747	
p-value	0.6809	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.9.6.1

Summary of Adverse Events of Special Interest - Rash - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.9901
Yes	2/ 54 (3.7)	0/ 26 (0.0)	NE	(NE, NE)	NE	
No	17/391 (4.3)	8/195 (4.1)	0.976	(0.420, 2.264)	0.9542	
Received prior local therapy (from IWRS)						0.6188
Yes	4/ 80 (5.0)	1/ 40 (2.5)	1.905	(0.212, 17.097)	0.5580	
No	15/365 (4.1)	7/181 (3.9)	0.984	(0.401, 2.415)	0.9716	
Prior local radiotherapy and/or prostatectomy						0.5512
Yes	6/ 87 (6.9)	2/ 50 (4.0)	1.618	(0.325, 8.045)	0.5527	
No	13/358 (3.6)	6/171 (3.5)	0.956	(0.363, 2.518)	0.9280	
Age group						0.8644
<65 years	1/117 (0.9)	1/ 64 (1.6)	0.528	(0.033, 8.440)	0.6459	
65-74	8/193 (4.1)	3/ 95 (3.2)	1.232	(0.326, 4.648)	0.7580	
75-84	9/117 (7.7)	3/ 52 (5.8)	1.295	(0.350, 4.785)	0.6977	
>=85 years	1/ 18 (5.6)	1/ 10 (10.0)	0.448	(0.028, 7.296)	0.5629	
Race						0.8227
White	7/249 (2.8)	4/124 (3.2)	0.843	(0.247, 2.881)	0.7852	
Asian	11/144 (7.6)	3/ 65 (4.6)	1.610	(0.449, 5.774)	0.4604	
Black or African American	1/ 42 (2.4)	1/ 23 (4.3)	0.454	(0.028, 7.258)	0.5664	
Other	0/ 10 (0.0)	0/ 9 (0.0)	NE	(NE, NE)	NE	
Geographical region						0.5779
Asia	11/141 (7.8)	3/ 63 (4.8)	1.598	(0.446, 5.730)	0.4676	
Latin America	4/120 (3.3)	2/ 70 (2.9)	1.086	(0.199, 5.934)	0.9245	
Europe and Rest of the world	4/184 (2.2)	3/ 88 (3.4)	0.586	(0.130, 2.632)	0.4802	
Baseline PSA values by median						0.5821
< median of overall population	12/215 (5.6)	6/110 (5.5)	0.952	(0.357, 2.541)	0.9230	
>= median of overall population	7/219 (3.2)	2/108 (1.9)	1.583	(0.328, 7.630)	0.5635	
ECOG PS at baseline						0.6453
=0	13/235 (5.5)	4/ 96 (4.2)	1.247	(0.406, 3.830)	0.6995	
>=1	6/210 (2.9)	4/125 (3.2)	0.821	(0.231, 2.914)	0.7603	
Gleason score at initial diagnosis						0.6731
Gleason <8	3/124 (2.4)	2/ 65 (3.1)	0.720	(0.120, 4.312)	0.7176	
Gleason >=8	15/308 (4.9)	6/146 (4.1)	1.112	(0.431, 2.870)	0.8258	
Disease volume at baseline						0.6740
high	11/314 (3.5)	4/156 (2.6)	1.293	(0.411, 4.064)	0.6593	
low	8/131 (6.1)	4/ 65 (6.2)	0.894	(0.269, 2.979)	0.8556	
Renal function - eGFR at baseline						0.7540
Normal: eGFR >= 90 mL/min	13/221 (5.9)	4/102 (3.9)	1.373	(0.447, 4.216)	0.5775	
Mild impairment: 60 <= eGFR < 90 mL/min	6/178 (3.4)	4/ 91 (4.4)	0.706	(0.199, 2.512)	0.5894	
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)	NE	(NE, NE)	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.6.1
Summary of Adverse Events of Special Interest - Rash - Subgroup analysis
(safety analysis set)

Final

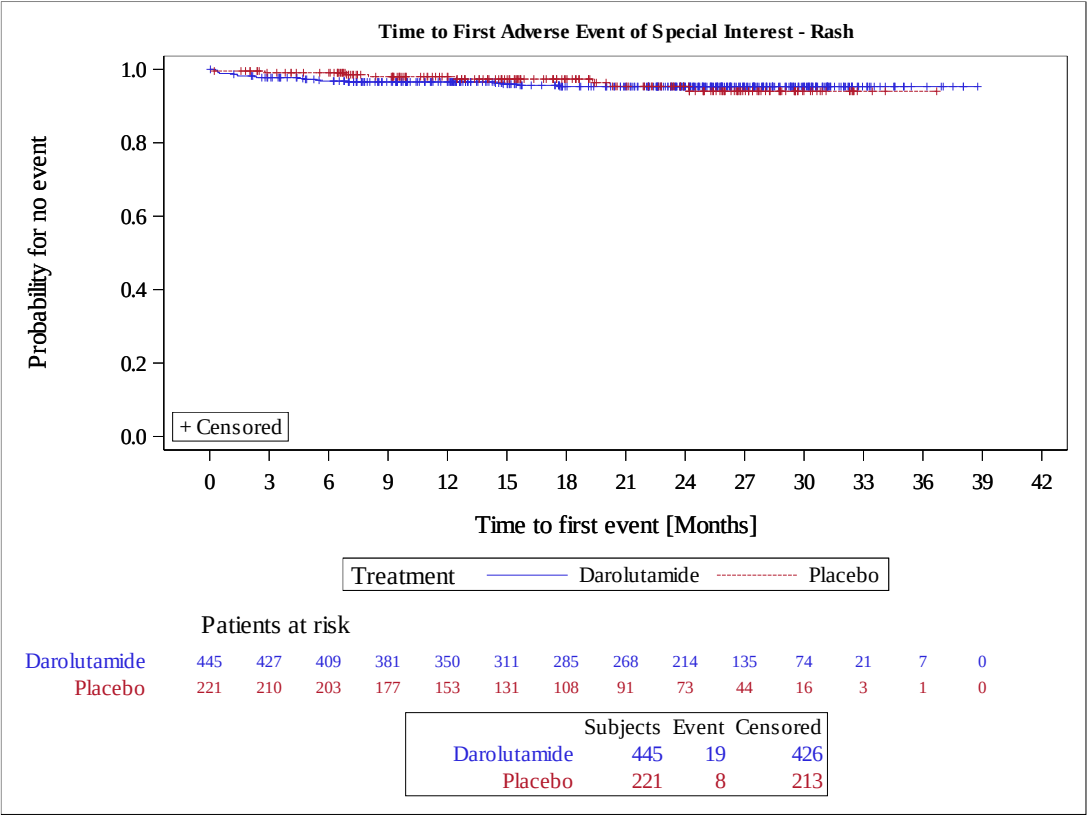
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.8504
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	16/387 (4.1)	7/202 (3.5)	1.107	(0.455, 2.694)	0.8226	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	3/ 58 (5.2)	1/ 19 (5.3)	0.877	(0.091, 8.442)	0.9096	
Age Group (Titan)						0.8173
<65	1/117 (0.9)	1/ 64 (1.6)	0.528	(0.033, 8.440)	0.6459	
>=65 and <75	8/193 (4.1)	3/ 95 (3.2)	1.232	(0.326, 4.648)	0.7580	
>=75	10/135 (7.4)	4/ 62 (6.5)	1.103	(0.346, 3.519)	0.8687	
Geographic region (Titan)						0.9850
Europe and north america	0/144 (0.0)	2/ 77 (2.6)	NE	(NE, NE)	NE	
ROTW	19/301 (6.3)	6/144 (4.2)	1.432	(0.572, 3.588)	0.4409	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.9.6.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Rash
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.7
Summary of Adverse Events of Special Interest - Seizure
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	445 (100.0)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.9.7.1

Summary of Adverse Events of Special Interest - Seizure - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.7.1
Summary of Adverse Events of Special Interest - Seizure - Subgroup analysis
(safety analysis set)

Final

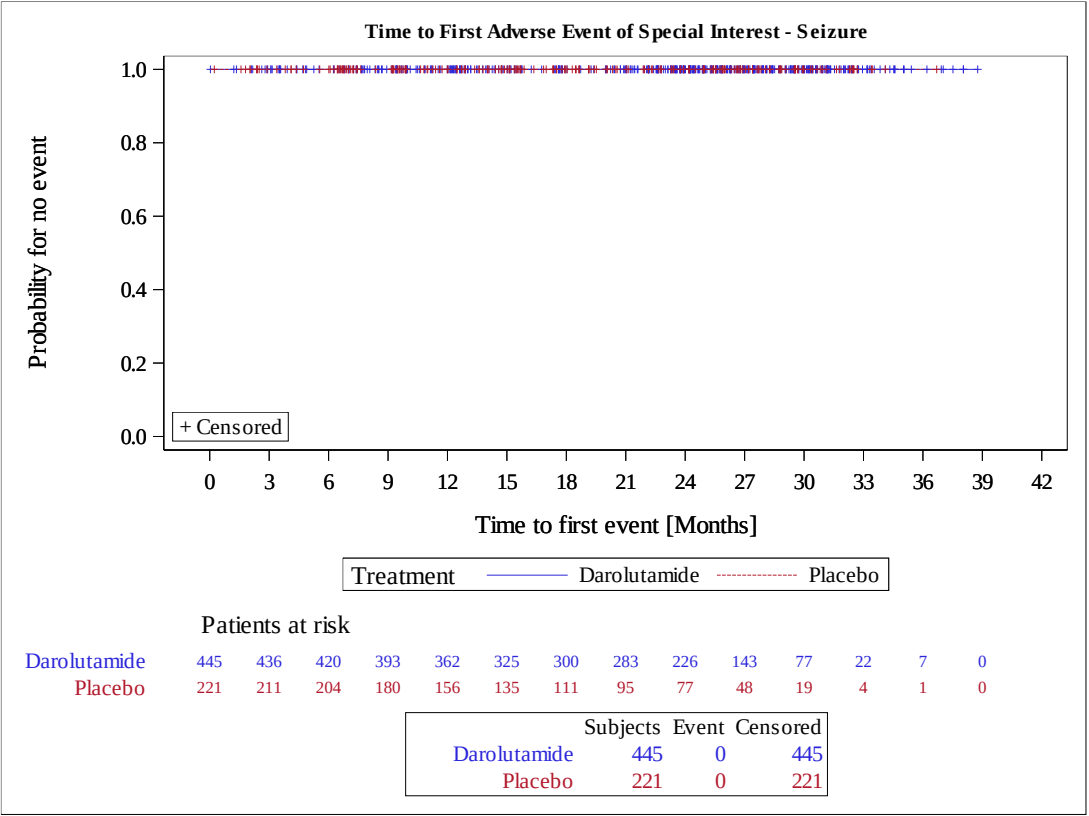
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.9.7.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Seizure
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.8
Summary of Adverse Events of Special Interest - Hypertension
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	42 (9.4)	21 (9.5)
Number of censored patients, n (%)	403 (90.6)	200 (90.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (33.3, NE)	NE (30.9, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.855	
95% CI	0.505, 1.446	
p-value	0.5576	
Odds Ratio	0.993	
95% CI	0.572, 1.721	
p-value	0.9788	
Relative Risk	0.993	
95% CI	0.603, 1.635	
p-value	0.9788	
Risk Difference	-0.064	
95% CI	-4.789, 4.661	
p-value	0.9788	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.9.8.1

Summary of Adverse Events of Special Interest - Hypertension - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.5801
Yes	6/ 54 (11.1)	2/ 26 (7.7)	1.318	(0.266, 6.537)	0.7342	
No	36/391 (9.2)	19/195 (9.7)	0.808	(0.462, 1.411)	0.4519	
Received prior local therapy (from IWRS)						0.9337
Yes	8/ 80 (10.0)	4/ 40 (10.0)	0.895	(0.268, 2.993)	0.8570	
No	34/365 (9.3)	17/181 (9.4)	0.859	(0.479, 1.540)	0.6101	
Prior local radiotherapy and/or prostatectomy						0.7131
Yes	10/ 87 (11.5)	5/ 50 (10.0)	1.083	(0.370, 3.172)	0.8847	
No	32/358 (8.9)	16/171 (9.4)	0.800	(0.438, 1.461)	0.4663	
Age group						0.6926
<65 years	13/117 (11.1)	4/ 64 (6.3)	1.508	(0.490, 4.636)	0.4702	
65-74	17/193 (8.8)	11/ 95 (11.6)	0.660	(0.308, 1.416)	0.2824	
75-84	10/117 (8.5)	5/ 52 (9.6)	0.748	(0.254, 2.203)	0.5972	
>=85 years	2/ 18 (11.1)	1/ 10 (10.0)	0.970	(0.087, 10.821)	0.9806	
Race						0.7912
White	19/249 (7.6)	8/124 (6.5)	0.988	(0.430, 2.270)	0.9775	
Asian	14/144 (9.7)	5/ 65 (7.7)	1.189	(0.428, 3.303)	0.7396	
Black or African American	9/ 42 (21.4)	7/ 23 (30.4)	0.642	(0.237, 1.738)	0.3782	
Other	0/ 10 (0.0)	1/ 9 (11.1)	NE	(NE, NE)	NE	
Geographical region						0.7704
Asia	14/141 (9.9)	5/ 63 (7.9)	1.178	(0.424, 3.271)	0.7536	
Latin America	14/120 (11.7)	10/ 70 (14.3)	0.733	(0.325, 1.655)	0.4531	
Europe and Rest of the world	14/184 (7.6)	6/ 88 (6.8)	0.893	(0.339, 2.350)	0.8182	
Baseline PSA values by median						0.8015
< median of overall population	18/215 (8.4)	10/110 (9.1)	0.788	(0.363, 1.713)	0.5473	
>= median of overall population	24/219 (11.0)	11/108 (10.2)	0.934	(0.456, 1.912)	0.8519	
ECOG PS at baseline						0.6979
=0	26/235 (11.1)	12/ 96 (12.5)	0.756	(0.381, 1.501)	0.4221	
>=1	16/210 (7.6)	9/125 (7.2)	0.945	(0.416, 2.144)	0.8924	
Gleason score at initial diagnosis						0.9897
Gleason <8	11/124 (8.9)	6/ 65 (9.2)	0.840	(0.310, 2.278)	0.7311	
Gleason >=8	30/308 (9.7)	15/146 (10.3)	0.825	(0.443, 1.538)	0.5446	
Disease volume at baseline						0.8322
high	27/314 (8.6)	13/156 (8.3)	0.914	(0.471, 1.775)	0.7907	
low	15/131 (11.5)	8/ 65 (12.3)	0.787	(0.333, 1.861)	0.5849	
Renal function - eGFR at baseline						0.7484
Normal: eGFR >= 90 mL/min	24/221 (10.9)	9/102 (8.8)	1.099	(0.510, 2.366)	0.8100	
Mild impairment: 60 <= eGFR < 90 mL/min	14/178 (7.9)	8/ 91 (8.8)	0.787	(0.330, 1.879)	0.5886	
Moderate impairment: 30 <= eGFR < 60 mL/min	4/ 45 (8.9)	3/ 27 (11.1)	0.553	(0.112, 2.742)	0.4619	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.8.1
Summary of Adverse Events of Special Interest - Hypertension - Subgroup analysis
(safety analysis set)

Final

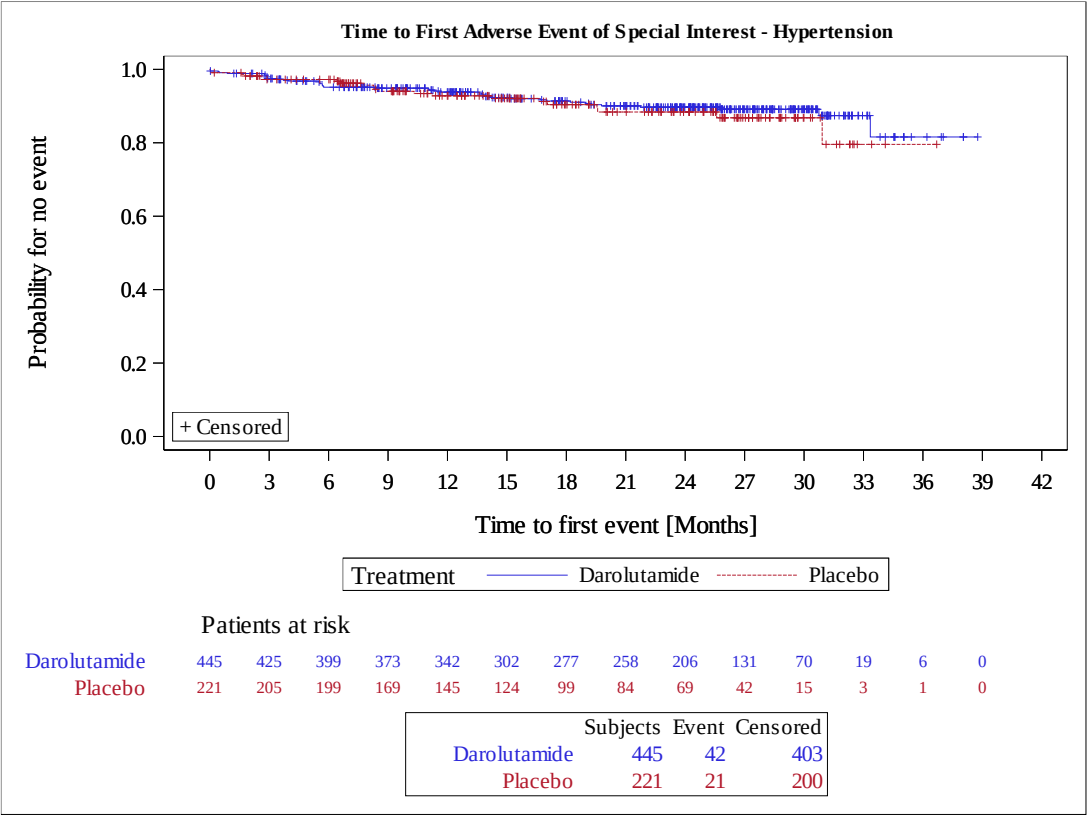
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.9681
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	36/387 (9.3)	19/202 (9.4)	0.843	(0.482, 1.475)	0.5492	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	6/ 58 (10.3)	2/ 19 (10.5)	0.833	(0.168, 4.129)	0.8226	
Age Group (Titan)						0.4875
<65	13/117 (11.1)	4/ 64 (6.3)	1.508	(0.490, 4.636)	0.4702	
>=65 and <75	17/193 (8.8)	11/ 95 (11.6)	0.660	(0.308, 1.416)	0.2824	
>=75	12/135 (8.9)	6/ 62 (9.7)	0.778	(0.290, 2.087)	0.6174	
Geographic region (Titan)						0.9628
Europe and north america	10/144 (6.9)	5/ 77 (6.5)	0.810	(0.272, 2.408)	0.7036	
ROTW	32/301 (10.6)	16/144 (11.1)	0.859	(0.471, 1.566)	0.6190	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.9.8.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Hypertension
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.9
Summary of Adverse Events of Special Interest - Vasodilatation and flushing
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	41 (9.2)	16 (7.2)
Number of censored patients, n (%)	404 (90.8)	205 (92.8)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.234	
95% CI	0.692, 2.200	
p-value	0.4744	
Odds Ratio	1.300	
95% CI	0.712, 2.373	
p-value	0.3924	
Relative Risk	1.273	
95% CI	0.731, 2.216	
p-value	0.3944	
Risk Difference	1.974	
95% CI	-2.373, 6.320	
p-value	0.3735	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.9.9.1

Summary of Adverse Events of Special Interest - Vasodilatation and flushing - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.9850
Yes	6/ 54 (11.1)	0/ 26 (0.0)	NE	(NE, NE)	NE	
No	35/391 (9.0)	16/195 (8.2)	1.052	(0.582, 1.901)	0.8667	
Received prior local therapy (from IWRS)						0.0563
Yes	6/ 80 (7.5)	6/ 40 (15.0)	0.476	(0.153, 1.478)	0.1886	
No	35/365 (9.6)	10/181 (5.5)	1.697	(0.840, 3.427)	0.1358	
Prior local radiotherapy and/or prostatectomy						0.8444
Yes	7/ 87 (8.0)	3/ 50 (6.0)	1.401	(0.362, 5.417)	0.6238	
No	34/358 (9.5)	13/171 (7.6)	1.186	(0.626, 2.249)	0.5996	
Age group						0.2232
<65 years	13/117 (11.1)	2/ 64 (3.1)	3.396	(0.765, 15.067)	0.0873	
65-74	17/193 (8.8)	12/ 95 (12.6)	0.663	(0.317, 1.390)	0.2733	
75-84	9/117 (7.7)	2/ 52 (3.8)	1.999	(0.432, 9.252)	0.3659	
>=85 years	2/ 18 (11.1)	0/ 10 (0.0)	NE	(NE, NE)	NE	
Race						0.6247
White	30/249 (12.0)	8/124 (6.5)	1.852	(0.849, 4.042)	0.1153	
Asian	2/144 (1.4)	1/ 65 (1.5)	0.863	(0.078, 9.524)	0.9044	
Black or African American	9/ 42 (21.4)	6/ 23 (26.1)	0.747	(0.265, 2.105)	0.5795	
Other	0/ 10 (0.0)	1/ 9 (11.1)	NE	(NE, NE)	NE	
Geographical region						0.9292
Asia	2/141 (1.4)	1/ 63 (1.6)	0.853	(0.077, 9.408)	0.8964	
Latin America	18/120 (15.0)	8/ 70 (11.4)	1.251	(0.544, 2.878)	0.5977	
Europe and Rest of the world	21/184 (11.4)	7/ 88 (8.0)	1.440	(0.612, 3.390)	0.4001	
Baseline PSA values by median						0.0815
< median of overall population	14/215 (6.5)	10/110 (9.1)	0.675	(0.300, 1.521)	0.3397	
>= median of overall population	24/219 (11.0)	6/108 (5.6)	1.973	(0.806, 4.828)	0.1291	
ECOG PS at baseline						0.2995
=0	32/235 (13.6)	9/ 96 (9.4)	1.421	(0.678, 2.977)	0.3491	
>=1	9/210 (4.3)	7/125 (5.6)	0.731	(0.272, 1.966)	0.5331	
Gleason score at initial diagnosis						0.3468
Gleason <8	15/124 (12.1)	4/ 65 (6.2)	1.996	(0.662, 6.014)	0.2100	
Gleason >=8	25/308 (8.1)	11/146 (7.5)	1.039	(0.511, 2.112)	0.9157	
Disease volume at baseline						0.8595
high	29/314 (9.2)	11/156 (7.1)	1.276	(0.637, 2.555)	0.4901	
low	12/131 (9.2)	5/ 65 (7.7)	1.148	(0.404, 3.263)	0.7948	
Renal function - eGFR at baseline						0.3316
Normal: eGFR >= 90 mL/min	22/221 (10.0)	11/102 (10.8)	0.855	(0.414, 1.764)	0.6707	
Mild impairment: 60 <= eGFR < 90 mL/min	15/178 (8.4)	3/ 91 (3.3)	2.577	(0.746, 8.904)	0.1200	
Moderate impairment: 30 <= eGFR < 60 mL/min	3/ 45 (6.7)	2/ 27 (7.4)	0.914	(0.153, 5.473)	0.9216	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.9.9.1

Summary of Adverse Events of Special Interest - Vasodilatation and flushing - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.9824
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	37/387 (9.6)	15/202 (7.4)	1.248	(0.685, 2.276)	0.4677	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	4/ 58 (6.9)	1/ 19 (5.3)	1.206	(0.135, 10.805)	0.8666	
Age Group (Titan)						0.0814
<65	13/117 (11.1)	2/ 64 (3.1)	3.396	(0.765, 15.067)	0.0873	
>=65 and <75	17/193 (8.8)	12/ 95 (12.6)	0.663	(0.317, 1.390)	0.2733	
>=75	11/135 (8.1)	2/ 62 (3.2)	2.566	(0.569, 11.579)	0.2029	
Geographic region (Titan)						0.4896
Europe and north america	13/144 (9.0)	4/ 77 (5.2)	1.735	(0.565, 5.327)	0.3291	
ROTW	28/301 (9.3)	12/144 (8.3)	1.068	(0.543, 2.100)	0.8494	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

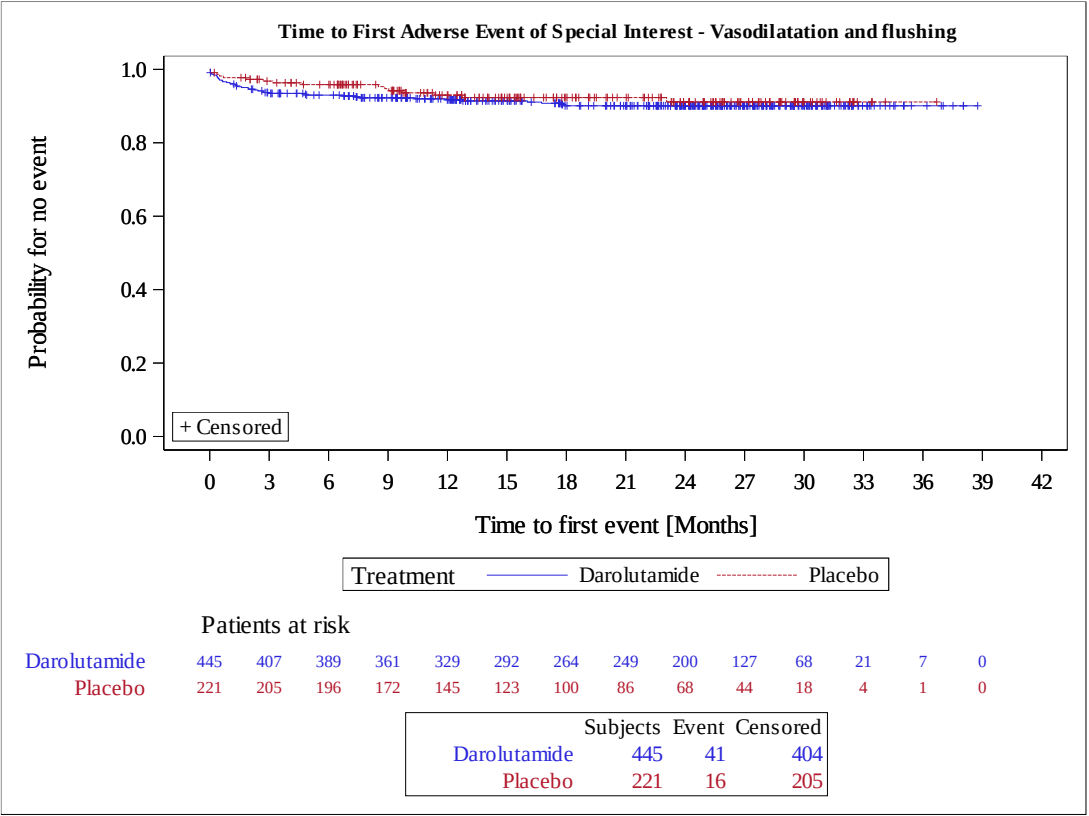
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.9.9.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Vasodilatation and flushing
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.9.10
Summary of Adverse Events of Special Interest - Mental impairment disorders
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	7 (1.6)	1 (0.5)
Number of censored patients, n (%)	438 (98.4)	220 (99.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	3.098	
95% CI	0.381, 25.202	
p-value	0.2651	
Odds Ratio	3.516	
95% CI	0.430, 28.756	
p-value	0.2409	
Relative Risk	3.476	
95% CI	0.430, 28.080	
p-value	0.2424	
Risk Difference	1.121	
95% CI	-0.335, 2.576	
p-value	0.1314	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population

Table 3.2.9.10.1

Summary of Adverse Events of Special Interest - Mental impairment disorders - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	1/ 54 (1.9)	1/ 26 (3.8)			
No	6/391 (1.5)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	3/ 80 (3.8)	1/ 40 (2.5)			
No	4/365 (1.1)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	3/ 87 (3.4)	1/ 50 (2.0)			
No	4/358 (1.1)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	4/193 (2.1)	1/ 95 (1.1)			
75-84	3/117 (2.6)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	5/249 (2.0)	1/124 (0.8)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	2/ 42 (4.8)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	3/120 (2.5)	0/ 70 (0.0)			
Europe and Rest of the world	4/184 (2.2)	1/ 88 (1.1)			
Baseline PSA values by median					
< median of overall population	3/215 (1.4)	1/110 (0.9)			
>= median of overall population	3/219 (1.4)	0/108 (0.0)			
ECOG PS at baseline					
=0	5/235 (2.1)	1/ 96 (1.0)			
>=1	2/210 (1.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	5/124 (4.0)	0/ 65 (0.0)			
Gleason >=8	2/308 (0.6)	1/146 (0.7)			
Disease volume at baseline					
high	3/314 (1.0)	1/156 (0.6)			
low	4/131 (3.1)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	5/221 (2.3)	1/102 (1.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	2/178 (1.1)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Study population

Table 3.2.9.10.1

Summary of Adverse Events of Special Interest - Mental impairment disorders - Subgroup analysis (safety analysis set)

Final

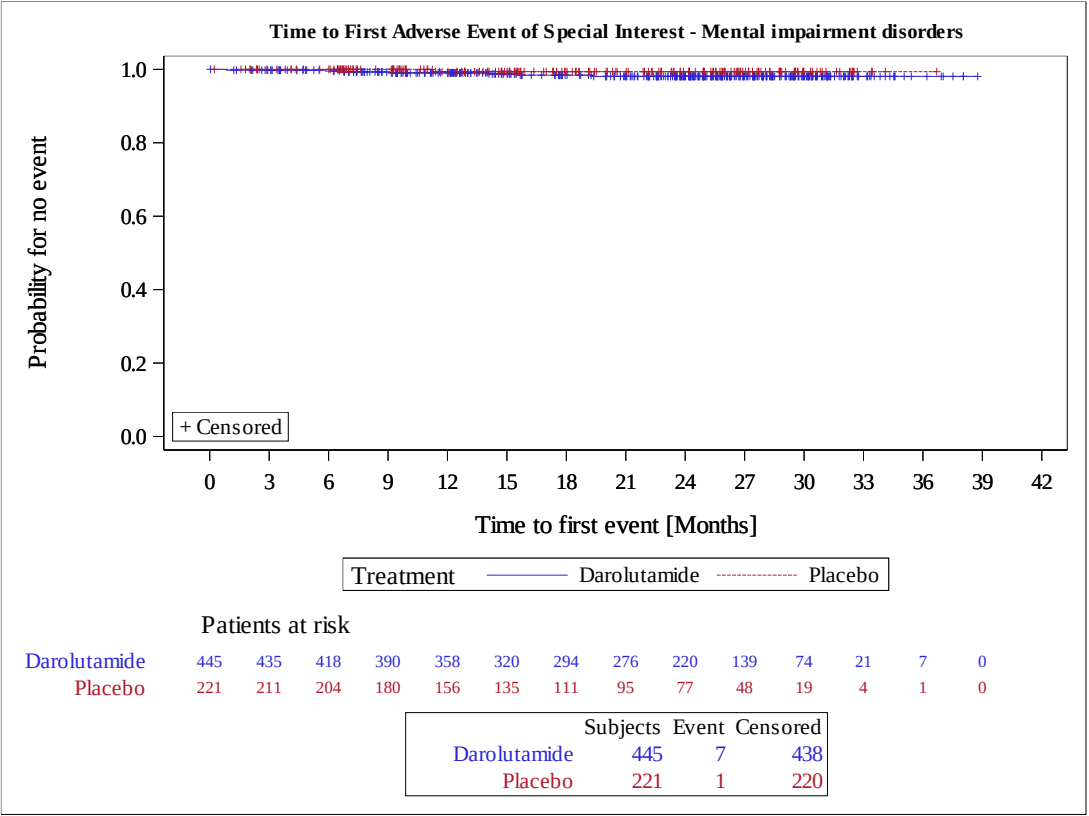
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction
			Hazard Ratio	(95% CI)	p-Value
p-Value					
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	7/387 (1.8)	1/202 (0.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	4/193 (2.1)	1/ 95 (1.1)			
>=75	3/135 (2.2)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	3/144 (2.1)	0/ 77 (0.0)			
ROTW	4/301 (1.3)	1/144 (0.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.9.10.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Mental impairment disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Study population
Table 3.2.9.11
Summary of Adverse Events of Special Interest - Depressed mood disorders
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	2 (0.4)	2 (0.9)
Number of censored patients, n (%)	443 (99.6)	219 (99.1)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.439	
95% CI	0.062, 3.125	
p-value	0.3981	
Odds Ratio	0.494	
95% CI	0.069, 3.533	
p-value	0.4826	
Relative Risk	0.497	
95% CI	0.070, 3.502	
p-value	0.4825	
Risk Difference	-0.456	
95% CI	-1.850, 0.939	
p-value	0.5220	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

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Study population

Table 3.2.9.11.1

Summary of Adverse Events of Special Interest - Depressed mood disorders - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	2/391 (0.5)	2/195 (1.0)			
Received prior local therapy (from IWRS)					
Yes	1/ 80 (1.3)	0/ 40 (0.0)			
No	1/365 (0.3)	2/181 (1.1)			
Prior local radiotherapy and/or prostatectomy					
Yes	1/ 87 (1.1)	1/ 50 (2.0)			
No	1/358 (0.3)	1/171 (0.6)			
Age group					
<65 years	1/117 (0.9)	0/ 64 (0.0)			
65-74	1/193 (0.5)	1/ 95 (1.1)			
75-84	0/117 (0.0)	1/ 52 (1.9)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	1/249 (0.4)	2/124 (1.6)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	1/ 42 (2.4)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	2/120 (1.7)	1/ 70 (1.4)			
Europe and Rest of the world	0/184 (0.0)	1/ 88 (1.1)			
Baseline PSA values by median					
< median of overall population	2/215 (0.9)	2/110 (1.8)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	2/ 96 (2.1)			
>=1	2/210 (1.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	1/ 65 (1.5)			
Gleason >=8	2/308 (0.6)	1/146 (0.7)			
Disease volume at baseline					
high	1/314 (0.3)	0/156 (0.0)			
low	1/131 (0.8)	2/ 65 (3.1)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	2/178 (1.1)	1/ 91 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	1/ 27 (3.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.9.11.1

Summary of Adverse Events of Special Interest - Depressed mood disorders - Subgroup analysis (safety analysis set)

Final

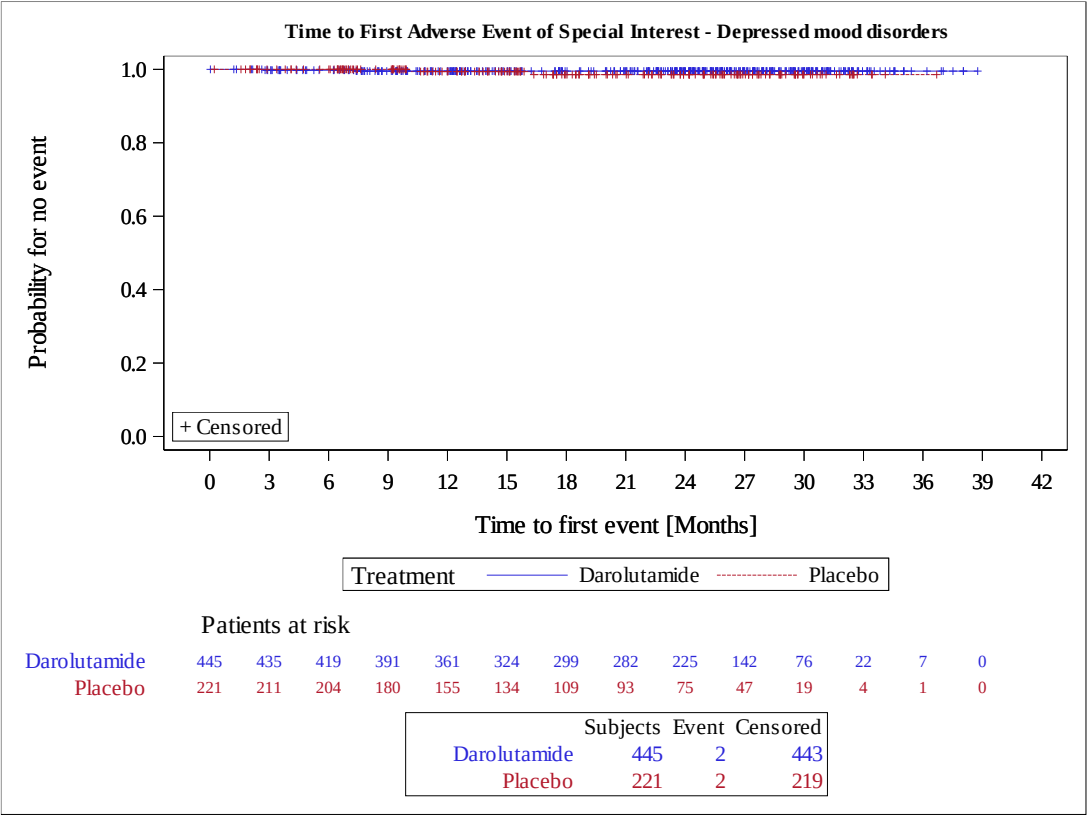
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	1/387 (0.3)	2/202 (1.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 58 (1.7)	0/ 19 (0.0)			
Age Group (Titan)					
<65	1/117 (0.9)	0/ 64 (0.0)			
>=65 and <75	1/193 (0.5)	1/ 95 (1.1)			
>=75	0/135 (0.0)	1/ 62 (1.6)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	1/ 77 (1.3)			
ROTW	2/301 (0.7)	1/144 (0.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.9.11.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Depressed mood disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.12
Summary of Adverse Events of Special Interest - Breast disorders/gynecomastia
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	6 (1.3)	2 (0.9)
Number of censored patients, n (%)	439 (98.7)	219 (99.1)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.303	
95% CI	0.263, 6.464	
p-value	0.7451	
Odds Ratio	1.497	
95% CI	0.300, 7.476	
p-value	0.6232	
Relative Risk	1.490	
95% CI	0.303, 7.322	
p-value	0.6236	
Risk Difference	0.443	
95% CI	-1.202, 2.089	
p-value	0.5974	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.9.12.1

Summary of Adverse Events of Special Interest - Breast disorders/gynecomastia - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	1/ 54 (1.9)	0/ 26 (0.0)			
No	5/391 (1.3)	2/195 (1.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	6/365 (1.6)	2/181 (1.1)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	6/358 (1.7)	2/171 (1.2)			
Age group					
<65 years	3/117 (2.6)	0/ 64 (0.0)			
65-74	3/193 (1.6)	2/ 95 (2.1)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	5/249 (2.0)	2/124 (1.6)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	1/ 42 (2.4)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	3/120 (2.5)	2/ 70 (2.9)			
Europe and Rest of the world	3/184 (1.6)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	5/215 (2.3)	1/110 (0.9)			
>= median of overall population	1/219 (0.5)	1/108 (0.9)			
ECOG PS at baseline					
=0	3/235 (1.3)	1/ 96 (1.0)			
>=1	3/210 (1.4)	1/125 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	1/124 (0.8)	0/ 65 (0.0)			
Gleason >=8	4/308 (1.3)	2/146 (1.4)			
Disease volume at baseline					
high	4/314 (1.3)	0/156 (0.0)			
low	2/131 (1.5)	2/ 65 (3.1)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	2/221 (0.9)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	4/178 (2.2)	1/ 91 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	1/ 27 (3.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.9.12.1

Summary of Adverse Events of Special Interest - Breast disorders/gynecomastia - Subgroup analysis (safety analysis set)

Final

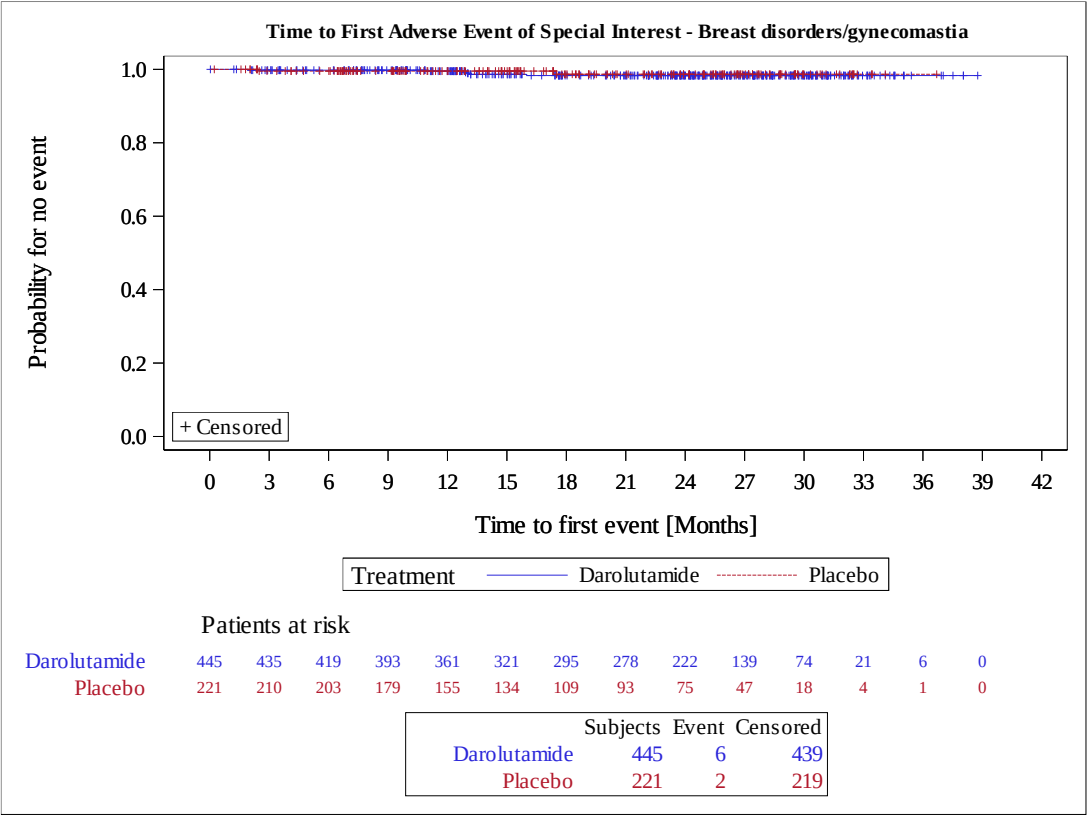
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI) p-Value	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	6/387 (1.6)	2/202 (1.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	3/117 (2.6)	0/ 64 (0.0)			
>=65 and <75	3/193 (1.6)	2/ 95 (2.1)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	3/144 (2.1)	0/ 77 (0.0)			
ROTW	3/301 (1.0)	2/144 (1.4)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.9.12.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Breast disorders/gynecomastia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.13
Summary of Adverse Events of Special Interest - Cardiac disorders
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	55 (12.4)	20 (9.0)
Number of censored patients, n (%)	390 (87.6)	201 (91.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.193	
95% CI	0.715, 1.992	
p-value	0.4991	
Odds Ratio	1.417	
95% CI	0.826, 2.430	
p-value	0.2050	
Relative Risk	1.366	
95% CI	0.840, 2.220	
p-value	0.2085	
Risk Difference	3.310	
95% CI	-1.554, 8.174	
p-value	0.1823	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.9.13.1

Summary of Adverse Events of Special Interest - Cardiac disorders - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.5573
Yes	8/ 54 (14.8)	2/ 26 (7.7)	1.702	(0.361, 8.017)	0.4962	
No	47/391 (12.0)	18/195 (9.2)	1.117	(0.648, 1.925)	0.6906	
Received prior local therapy (from IWRS)						0.8601
Yes	8/ 80 (10.0)	3/ 40 (7.5)	1.108	(0.289, 4.255)	0.8805	
No	47/365 (12.9)	17/181 (9.4)	1.214	(0.697, 2.115)	0.4924	
Prior local radiotherapy and/or prostatectomy						0.4492
Yes	10/ 87 (11.5)	6/ 50 (12.0)	0.847	(0.306, 2.343)	0.7484	
No	45/358 (12.6)	14/171 (8.2)	1.339	(0.734, 2.440)	0.3391	
Age group						0.5958
<65 years	9/117 (7.7)	1/ 64 (1.6)	3.961	(0.501, 31.343)	0.1589	
65-74	21/193 (10.9)	9/ 95 (9.5)	1.074	(0.492, 2.347)	0.8574	
75-84	24/117 (20.5)	9/ 52 (17.3)	1.013	(0.470, 2.182)	0.9734	
>=85 years	1/ 18 (5.6)	1/ 10 (10.0)	0.348	(0.022, 5.570)	0.4348	
Race						0.9059
White	31/249 (12.4)	12/124 (9.7)	1.030	(0.528, 2.010)	0.9306	
Asian	18/144 (12.5)	5/ 65 (7.7)	1.517	(0.563, 4.088)	0.4058	
Black or African American	4/ 42 (9.5)	2/ 23 (8.7)	0.982	(0.180, 5.368)	0.9832	
Other	2/ 10 (20.0)	1/ 9 (11.1)	1.795	(0.162, 19.837)	0.6284	
Geographical region						0.6577
Asia	18/141 (12.8)	5/ 63 (7.9)	1.510	(0.561, 4.069)	0.4109	
Latin America	16/120 (13.3)	6/ 70 (8.6)	1.416	(0.554, 3.620)	0.4649	
Europe and Rest of the world	21/184 (11.4)	9/ 88 (10.2)	0.862	(0.393, 1.894)	0.7119	
Baseline PSA values by median						0.4775
< median of overall population	31/215 (14.4)	10/110 (9.1)	1.401	(0.686, 2.859)	0.3519	
>= median of overall population	23/219 (10.5)	10/108 (9.3)	0.993	(0.472, 2.088)	0.9844	
ECOG PS at baseline						0.2514
=0	31/235 (13.2)	12/ 96 (12.5)	0.880	(0.451, 1.715)	0.7066	
>=1	24/210 (11.4)	8/125 (6.4)	1.646	(0.739, 3.666)	0.2170	
Gleason score at initial diagnosis						0.9521
Gleason <8	13/124 (10.5)	5/ 65 (7.7)	1.211	(0.431, 3.399)	0.7164	
Gleason >=8	42/308 (13.6)	14/146 (9.6)	1.262	(0.689, 2.313)	0.4500	
Disease volume at baseline						0.1670
high	32/314 (10.2)	15/156 (9.6)	0.927	(0.501, 1.712)	0.8078	
low	23/131 (17.6)	5/ 65 (7.7)	1.994	(0.757, 5.252)	0.1543	
Renal function - eGFR at baseline						0.3703
Normal: eGFR >= 90 mL/min	27/221 (12.2)	6/102 (5.9)	1.846	(0.762, 4.474)	0.1678	
Mild impairment: 60 <= eGFR < 90 mL/min	21/178 (11.8)	11/ 91 (12.1)	0.810	(0.389, 1.684)	0.5713	
Moderate impairment: 30 <= eGFR < 60 mL/min	7/ 45 (15.6)	3/ 27 (11.1)	1.365	(0.353, 5.281)	0.6509	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.13.1
Summary of Adverse Events of Special Interest - Cardiac disorders - Subgroup analysis
(safety analysis set)

Final

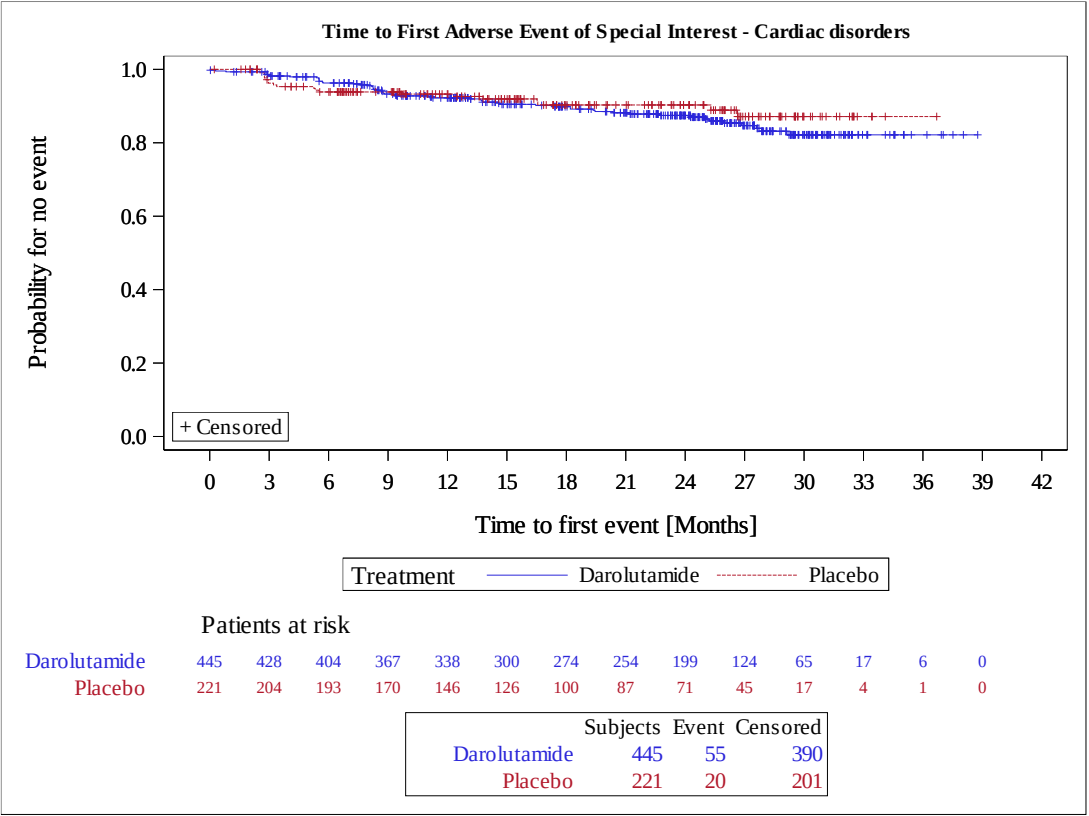
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.9775
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	44/387 (11.4)	20/202 (9.9)	0.996	(0.586, 1.691)	0.9874	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	11/ 58 (19.0)	0/ 19 (0.0)	NE	(NE, NE)	NE	
Age Group (Titan)						0.4509
<65	9/117 (7.7)	1/ 64 (1.6)	3.961	(0.501, 31.343)	0.1589	
>=65 and <75	21/193 (10.9)	9/ 95 (9.5)	1.074	(0.492, 2.347)	0.8574	
>=75	25/135 (18.5)	10/ 62 (16.1)	0.980	(0.470, 2.042)	0.9567	
Geographic region (Titan)						0.2124
Europe and north america	14/144 (9.7)	8/ 77 (10.4)	0.729	(0.304, 1.749)	0.4777	
ROTW	41/301 (13.6)	12/144 (8.3)	1.498	(0.787, 2.851)	0.2149	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.9.13.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Cardiac disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.14
Summary of Adverse Events of Special Interest - Cerebral ischaemia
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	1 (0.2)	3 (1.4)
Number of censored patients, n (%)	444 (99.8)	218 (98.6)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.152	
95% CI	0.016, 1.458	
p-value	0.0592	
Odds Ratio	0.164	
95% CI	0.017, 1.583	
p-value	0.1179	
Relative Risk	0.166	
95% CI	0.017, 1.582	
p-value	0.1184	
Risk Difference	-1.133	
95% CI	-2.721, 0.455	
p-value	0.1620	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.9.14.1

Summary of Adverse Events of Special Interest - Cerebral ischaemia - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	1/ 26 (3.8)			
No	1/391 (0.3)	2/195 (1.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	1/365 (0.3)	3/181 (1.7)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	1/358 (0.3)	3/171 (1.8)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	3/ 95 (3.2)			
75-84	1/117 (0.9)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	1/249 (0.4)	3/124 (2.4)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	1/120 (0.8)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	3/ 88 (3.4)			
Baseline PSA values by median					
< median of overall population	1/215 (0.5)	1/110 (0.9)			
>= median of overall population	0/219 (0.0)	2/108 (1.9)			
ECOG PS at baseline					
=0	1/235 (0.4)	2/ 96 (2.1)			
>=1	0/210 (0.0)	1/125 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	1/ 65 (1.5)			
Gleason >=8	1/308 (0.3)	2/146 (1.4)			
Disease volume at baseline					
high	0/314 (0.0)	3/156 (1.9)			
low	1/131 (0.8)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	1/221 (0.5)	1/102 (1.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	1/ 91 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	1/ 27 (3.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.14.1
Summary of Adverse Events of Special Interest - Cerebral ischaemia - Subgroup analysis
(safety analysis set)

Final

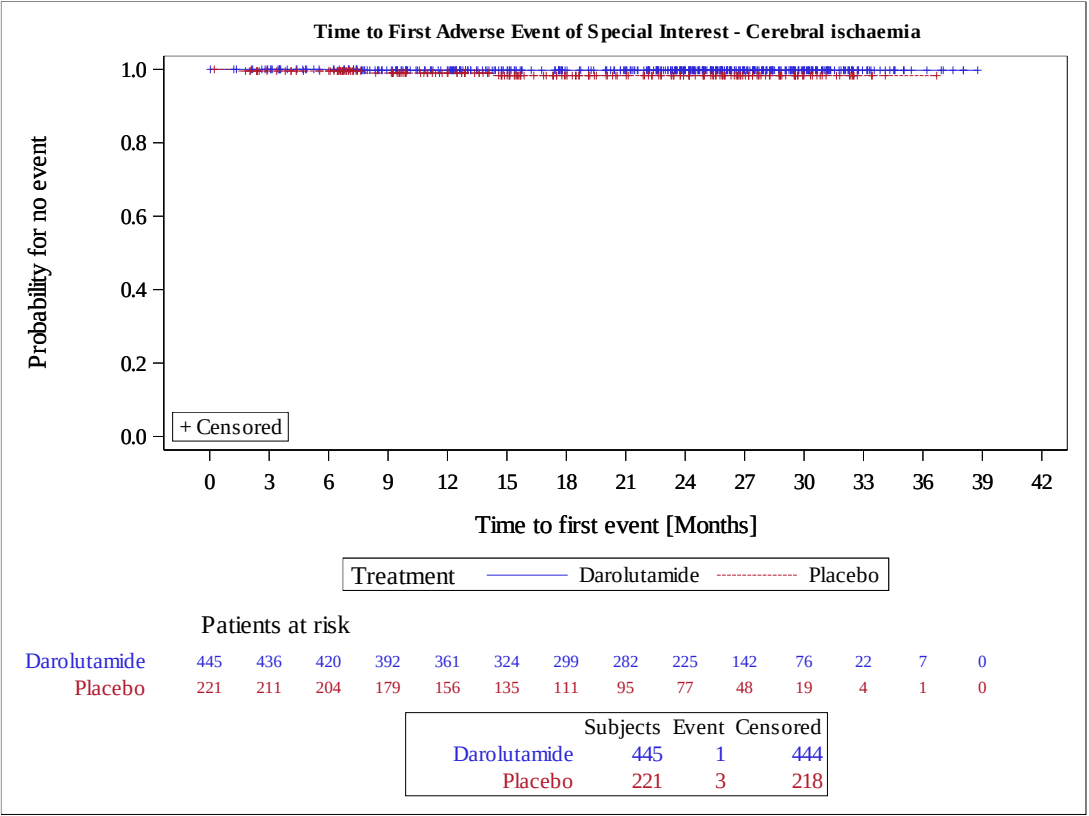
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI) p-Value	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	3/202 (1.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 58 (1.7)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	3/ 95 (3.2)			
>=75	1/135 (0.7)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	3/ 77 (3.9)			
ROTW	1/301 (0.3)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.9.14.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Cerebral ischaemia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.15
Summary of Adverse Events of Special Interest - Cerebral and intracranial hemorrhage
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	2 (0.4)	1 (0.5)
Number of censored patients, n (%)	443 (99.6)	220 (99.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.831	
95% CI	0.075, 9.212	
p-value	0.8801	
Odds Ratio	0.993	
95% CI	0.090, 11.013	
p-value	0.9956	
Relative Risk	0.993	
95% CI	0.091, 10.895	
p-value	0.9956	
Risk Difference	-0.003	
95% CI	-1.084, 1.078	
p-value	0.9956	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.9.15.1

Summary of Adverse Events of Special Interest - Cerebral and intracranial hemorrhage - Subgroup analysis (safety analysis set)

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	2/391 (0.5)	1/195 (0.5)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	2/365 (0.5)	1/181 (0.6)			
Prior local radiotherapy and/or prostatectomy					
Yes	2/ 87 (2.3)	0/ 50 (0.0)			
No	0/358 (0.0)	1/171 (0.6)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	1/117 (0.9)	0/ 52 (0.0)			
>=85 years	1/ 18 (5.6)	1/ 10 (10.0)			
Race					
White	1/249 (0.4)	0/124 (0.0)			
Asian	1/144 (0.7)	1/ 65 (1.5)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	1/141 (0.7)	1/ 63 (1.6)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	1/184 (0.5)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	2/215 (0.9)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	1/108 (0.9)			
ECOG PS at baseline					
=0	2/235 (0.9)	0/ 96 (0.0)			
>=1	0/210 (0.0)	1/125 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	1/ 65 (1.5)			
Gleason >=8	2/308 (0.6)	0/146 (0.0)			
Disease volume at baseline					
high	1/314 (0.3)	0/156 (0.0)			
low	1/131 (0.8)	1/ 65 (1.5)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	2/178 (1.1)	1/ 91 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.9.15.1

Summary of Adverse Events of Special Interest - Cerebral and intracranial hemorrhage - Subgroup analysis (safety analysis set)

Final

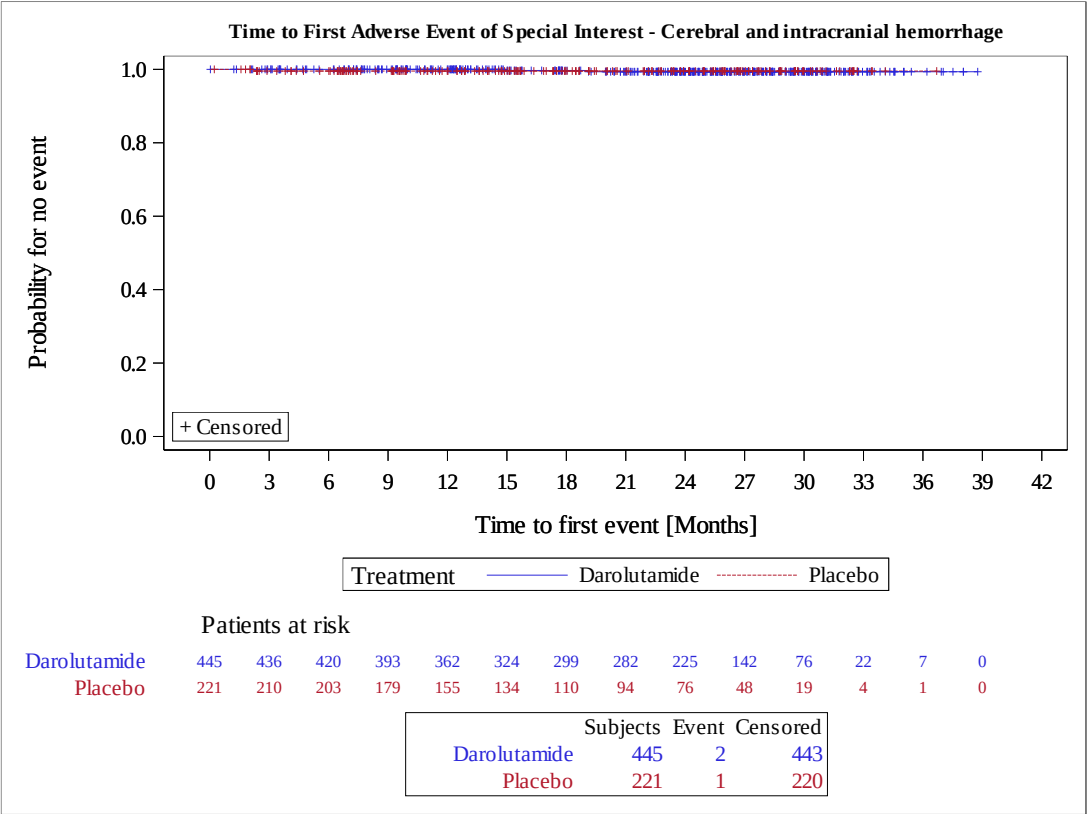
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	1/387 (0.3)	1/202 (0.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 58 (1.7)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	2/135 (1.5)	1/ 62 (1.6)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	2/301 (0.7)	1/144 (0.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.9.15.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Cerebral and intracranial hemorrhage
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.16
Summary of Adverse Events of Special Interest - Interstitial lung disease
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	1 (0.2)	1 (0.5)
Number of censored patients, n (%)	444 (99.8)	220 (99.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.381	
95% CI	0.024, 6.119	
p-value	0.4789	
Odds Ratio	0.495	
95% CI	0.031, 7.959	
p-value	0.6201	
Relative Risk	0.497	
95% CI	0.031, 7.903	
p-value	0.6201	
Risk Difference	-0.228	
95% CI	-1.216, 0.760	
p-value	0.6514	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.9.16.1

Summary of Adverse Events of Special Interest - Interstitial lung disease - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	1/391 (0.3)	1/195 (0.5)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	1/365 (0.3)	1/181 (0.6)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	1/358 (0.3)	1/171 (0.6)			
Age group					
<65 years	1/117 (0.9)	0/ 64 (0.0)			
65-74	0/193 (0.0)	1/ 95 (1.1)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	1/249 (0.4)	1/124 (0.8)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	1/120 (0.8)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	1/ 88 (1.1)			
Baseline PSA values by median					
< median of overall population	1/215 (0.5)	1/110 (0.9)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	1/235 (0.4)	0/ 96 (0.0)			
>=1	0/210 (0.0)	1/125 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	1/308 (0.3)	1/146 (0.7)			
Disease volume at baseline					
high	1/314 (0.3)	1/156 (0.6)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	1/178 (0.6)	1/ 91 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.9.16.1
Summary of Adverse Events of Special Interest - Interstitial lung disease - Subgroup analysis
(safety analysis set)

Final

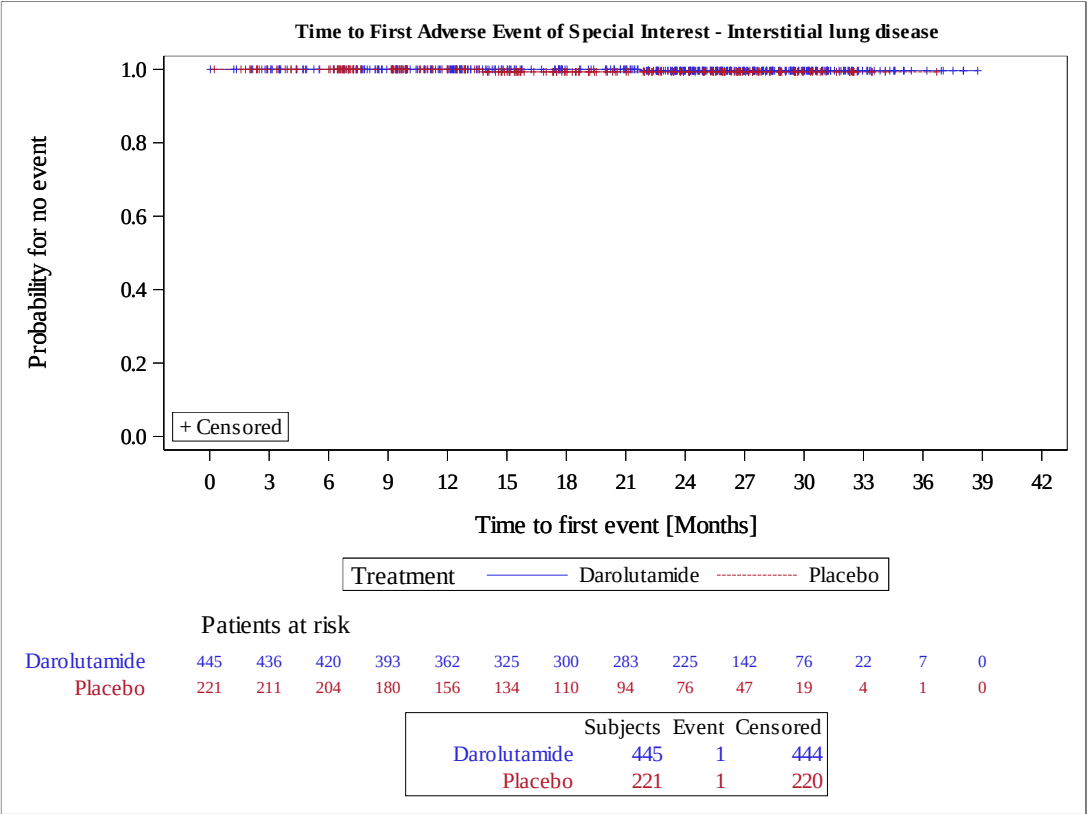
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	1/387 (0.3)	1/202 (0.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	1/117 (0.9)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	1/ 95 (1.1)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	1/ 77 (1.3)			
ROTW	1/301 (0.3)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.9.16.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Interstitial lung disease
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.1
Summary of Serious Adverse Events of Special Interest - Bone fractures excluding pathological fractures
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	6 (1.3)	0 (0.0)
Number of censored patients, n (%)	439 (98.7)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	6.552	
95% CI	0.367, 116.828	
p-value	0.2010	
Relative Risk	6.471	
95% CI	0.366, 114.347	
p-value	0.2025	
Risk Difference	1.348	
95% CI	0.277, 2.420	
p-value	0.0137	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.1.1

Summary of Serious Adverse Events of Special Interest - Bone fractures excluding pathological fractures - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	1/ 54 (1.9)	0/ 26 (0.0)			
No	5/391 (1.3)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	2/ 80 (2.5)	0/ 40 (0.0)			
No	4/365 (1.1)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	6/358 (1.7)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	1/193 (0.5)	0/ 95 (0.0)			
75-84	5/117 (4.3)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	4/249 (1.6)	0/124 (0.0)			
Asian	2/144 (1.4)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	2/141 (1.4)	0/ 63 (0.0)			
Latin America	2/120 (1.7)	0/ 70 (0.0)			
Europe and Rest of the world	2/184 (1.1)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	5/215 (2.3)	0/110 (0.0)			
>= median of overall population	1/219 (0.5)	0/108 (0.0)			
ECOG PS at baseline					
=0	3/235 (1.3)	0/ 96 (0.0)			
>=1	3/210 (1.4)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	3/124 (2.4)	0/ 65 (0.0)			
Gleason >=8	3/308 (1.0)	0/146 (0.0)			
Disease volume at baseline					
high	4/314 (1.3)	0/156 (0.0)			
low	2/131 (1.5)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	1/221 (0.5)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	5/178 (2.8)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.1.1

Summary of Serious Adverse Events of Special Interest - Bone fractures excluding pathological fractures - Subgroup analysis (safety analysis set)

Final

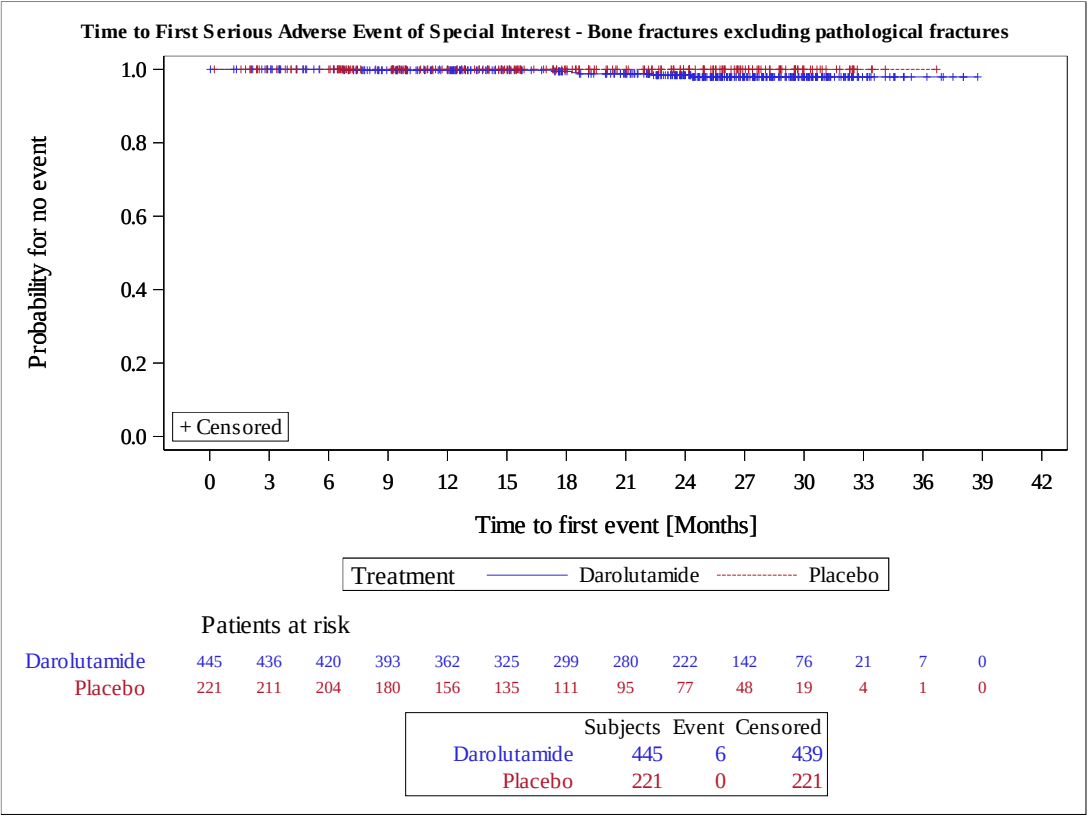
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	6/387 (1.6)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	1/193 (0.5)	0/ 95 (0.0)			
>=75	5/135 (3.7)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	6/301 (2.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.10.1.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Bone fractures excluding pathological fractures
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.2
Summary of Serious Adverse Events of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	1 (0.2)	0 (0.0)
Number of censored patients, n (%)	444 (99.8)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	1.495	
95% CI	0.061, 36.846	
p-value	0.8057	
Relative Risk	1.493	
95% CI	0.061, 36.508	
p-value	0.8058	
Risk Difference	0.225	
95% CI	-0.215, 0.665	
p-value	0.3168	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.2.1

Summary of Serious Adverse Events of Special Interest - Diabetes mellitus and hyperglycemia - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	1/391 (0.3)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	1/365 (0.3)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	1/358 (0.3)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	1/117 (0.9)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	1/144 (0.7)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	1/141 (0.7)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	1/215 (0.5)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	1/210 (0.5)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	1/308 (0.3)	0/146 (0.0)			
Disease volume at baseline					
high	1/314 (0.3)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	1/221 (0.5)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.2.1

Summary of Serious Adverse Events of Special Interest - Diabetes mellitus and hyperglycemia - Subgroup analysis (safety analysis set)

Final

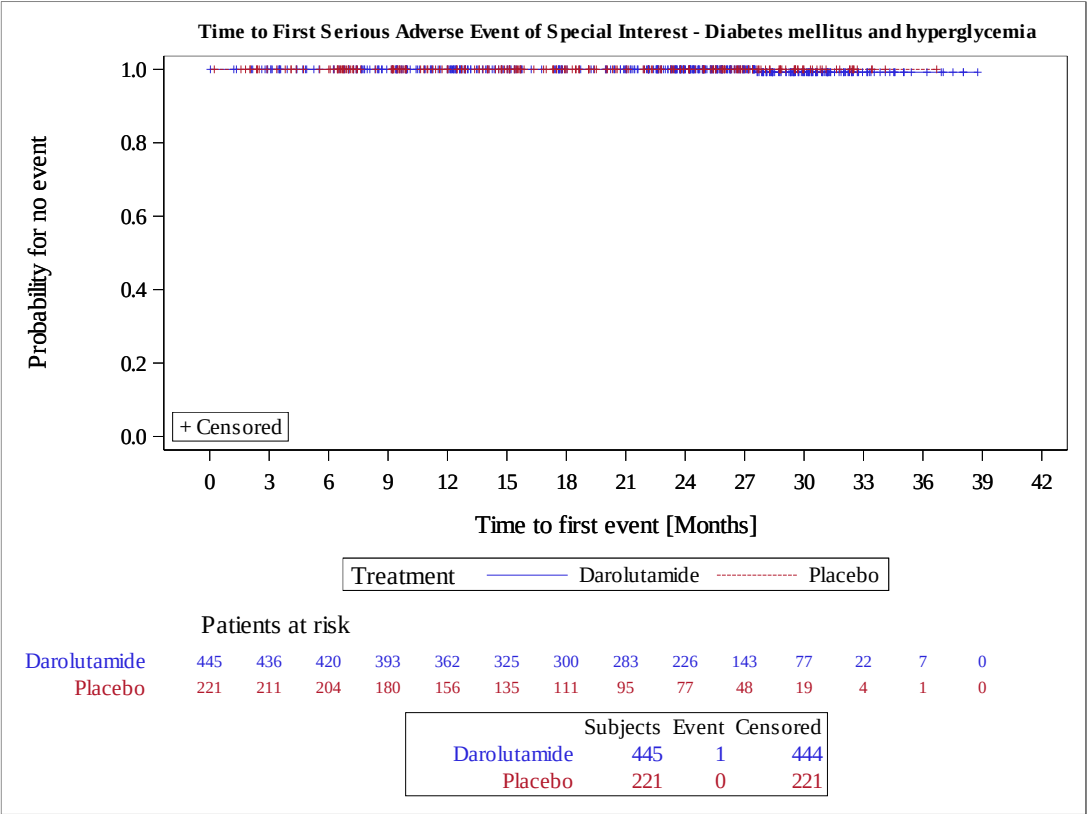
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction
			Hazard Ratio	(95% CI)	p-Value
p-Value					
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	1/387 (0.3)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	1/135 (0.7)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	1/301 (0.3)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.10.2.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.3
Summary of Serious Adverse Events of Special Interest - Fall
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	1 (0.5)
Number of censored patients, n (%)	445 (100.0)	220 (99.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	0.165	
95% CI	0.007, 4.066	
p-value	0.2704	
Relative Risk	0.166	
95% CI	0.007, 4.056	
p-value	0.2707	
Risk Difference	-0.452	
95% CI	-1.337, 0.432	
p-value	0.3162	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.3.1

Summary of Serious Adverse Events of Special Interest - Fall - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	1/ 26 (3.8)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	1/ 40 (2.5)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	1/ 50 (2.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	1/ 52 (1.9)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	1/124 (0.8)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	1/ 88 (1.1)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	1/110 (0.9)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	1/ 96 (1.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	1/ 65 (1.5)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	1/156 (0.6)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	1/ 91 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.3.1
Summary of Serious Adverse Events of Special Interest - Fall - Subgroup analysis
(safety analysis set)

Final

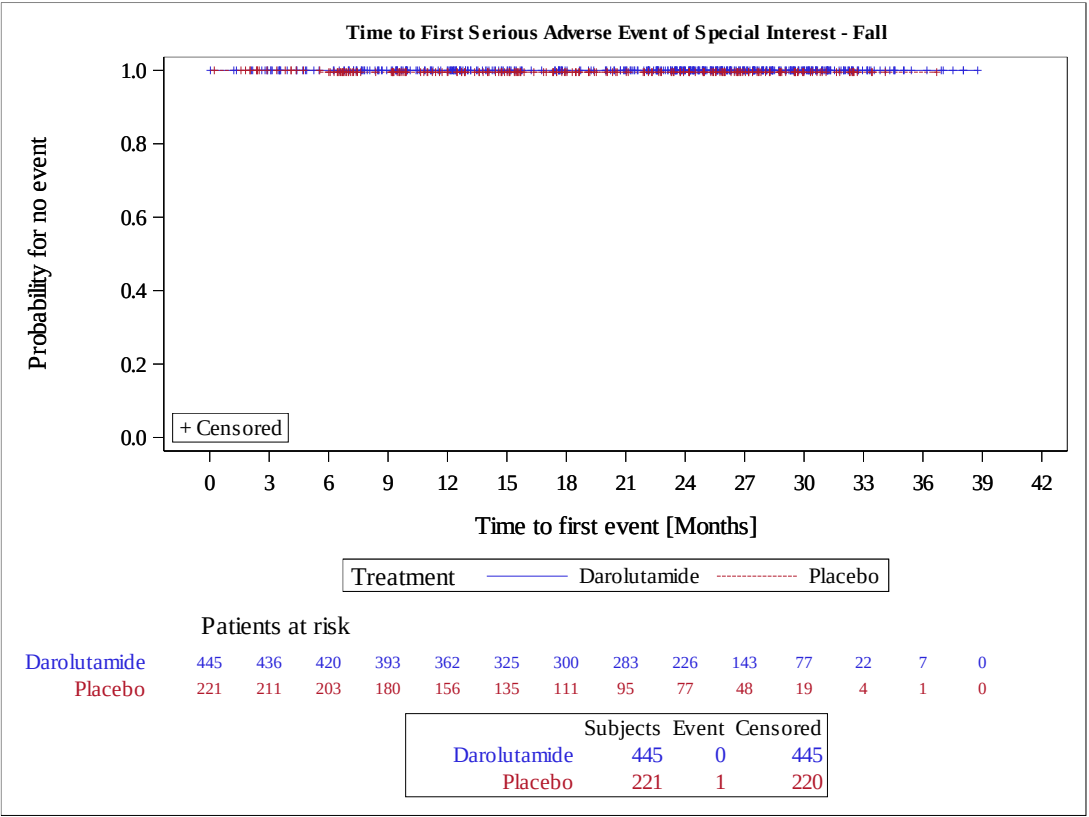
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	1/202 (0.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	1/ 62 (1.6)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	1/144 (0.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.10.3.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Fall
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.4
Summary of Serious Adverse Events of Special Interest - Fatigue/ asthenic conditions
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	445 (100.0)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.4.1

Summary of Serious Adverse Events of Special Interest - Fatigue/ asthenic conditions - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.4.1

Summary of Serious Adverse Events of Special Interest - Fatigue/ asthenic conditions - Subgroup analysis (safety analysis set)

Final

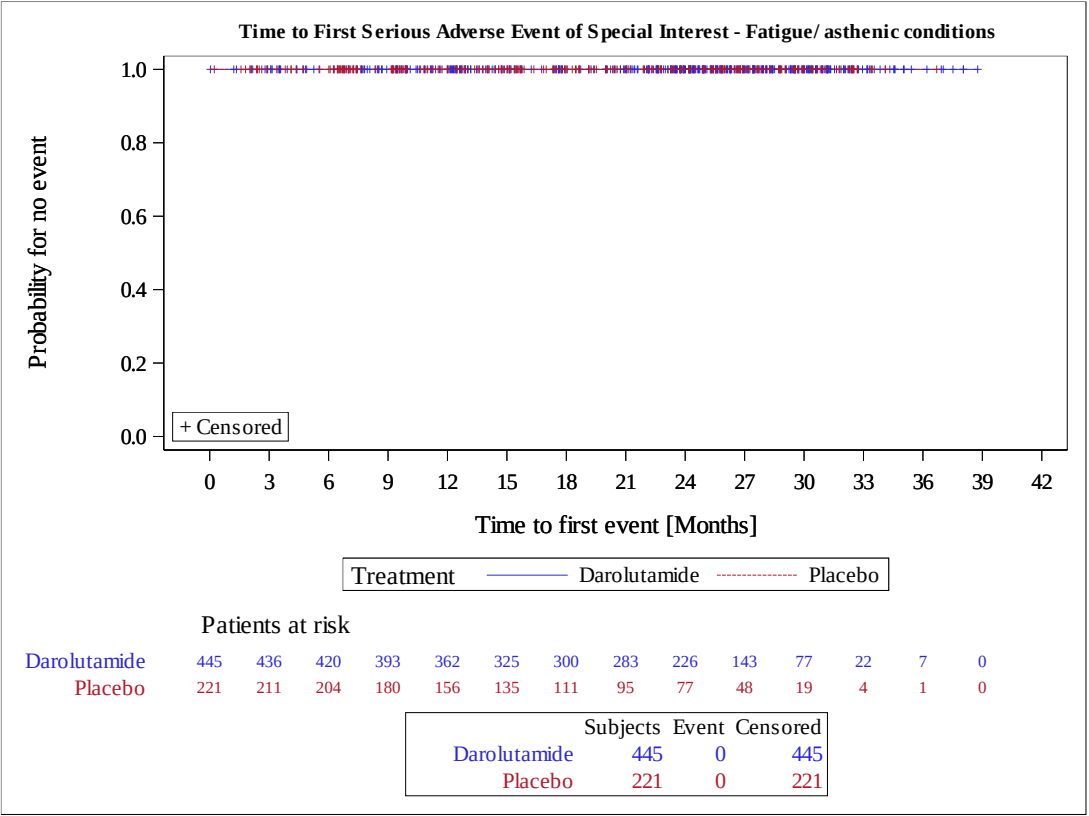
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.10.4.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Fatigue/ asthenic conditions
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.5
Summary of Serious Adverse Events of Special Interest - Weight decreased
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	445 (100.0)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.5.1

Summary of Serious Adverse Events of Special Interest - Weight decreased - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.5.1
Summary of Serious Adverse Events of Special Interest - Weight decreased - Subgroup analysis
(safety analysis set)

Final

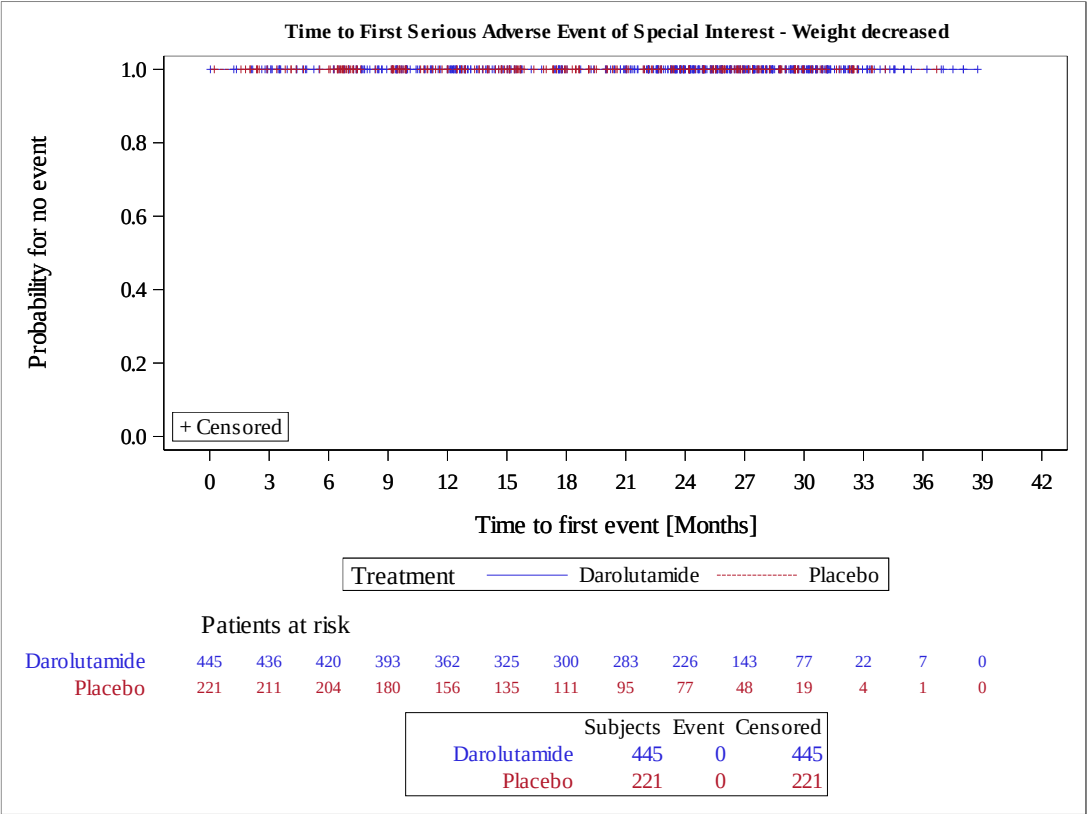
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.10.5.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Weight decreased
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.6
Summary of Serious Adverse Events of Special Interest - Rash
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	445 (100.0)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.6.1

Summary of Serious Adverse Events of Special Interest - Rash - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.6.1

Summary of Serious Adverse Events of Special Interest - Rash - Subgroup analysis (safety analysis set)

Final

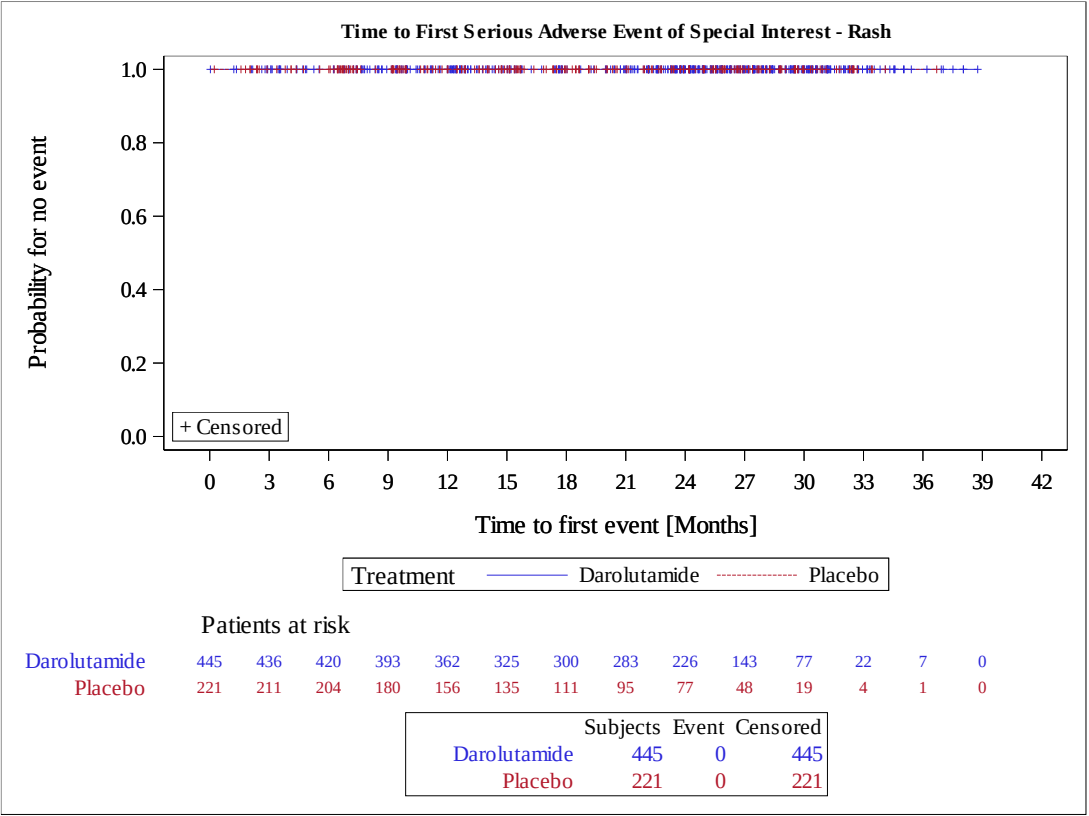
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.10.6.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Rash
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.7
Summary of Serious Adverse Events of Special Interest - Seizure
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	445 (100.0)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.7.1

Summary of Serious Adverse Events of Special Interest - Seizure - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.7.1
Summary of Serious Adverse Events of Special Interest - Seizure - Subgroup analysis
(safety analysis set)

Final

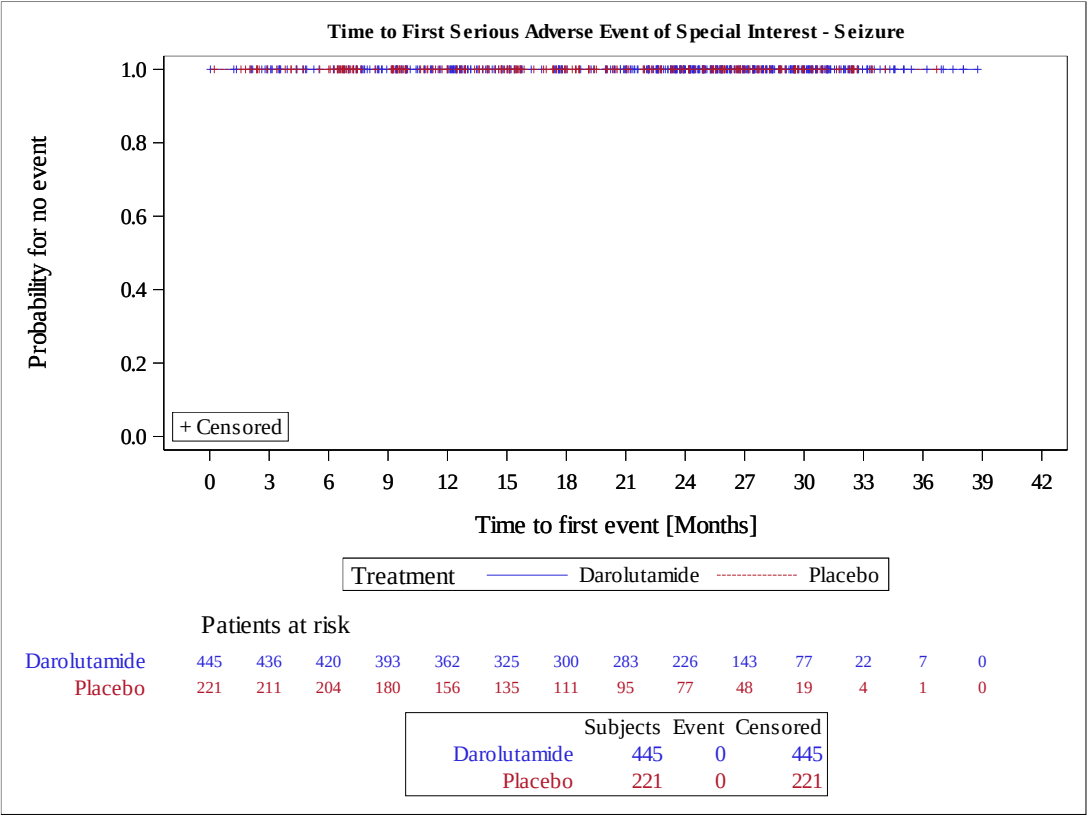
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI) p-Value	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.10.7.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Seizure
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.8
Summary of Serious Adverse Events of Special Interest - Hypertension
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	445 (100.0)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.8.1

Summary of Serious Adverse Events of Special Interest - Hypertension - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.8.1

Summary of Serious Adverse Events of Special Interest - Hypertension - Subgroup analysis (safety analysis set)

Final

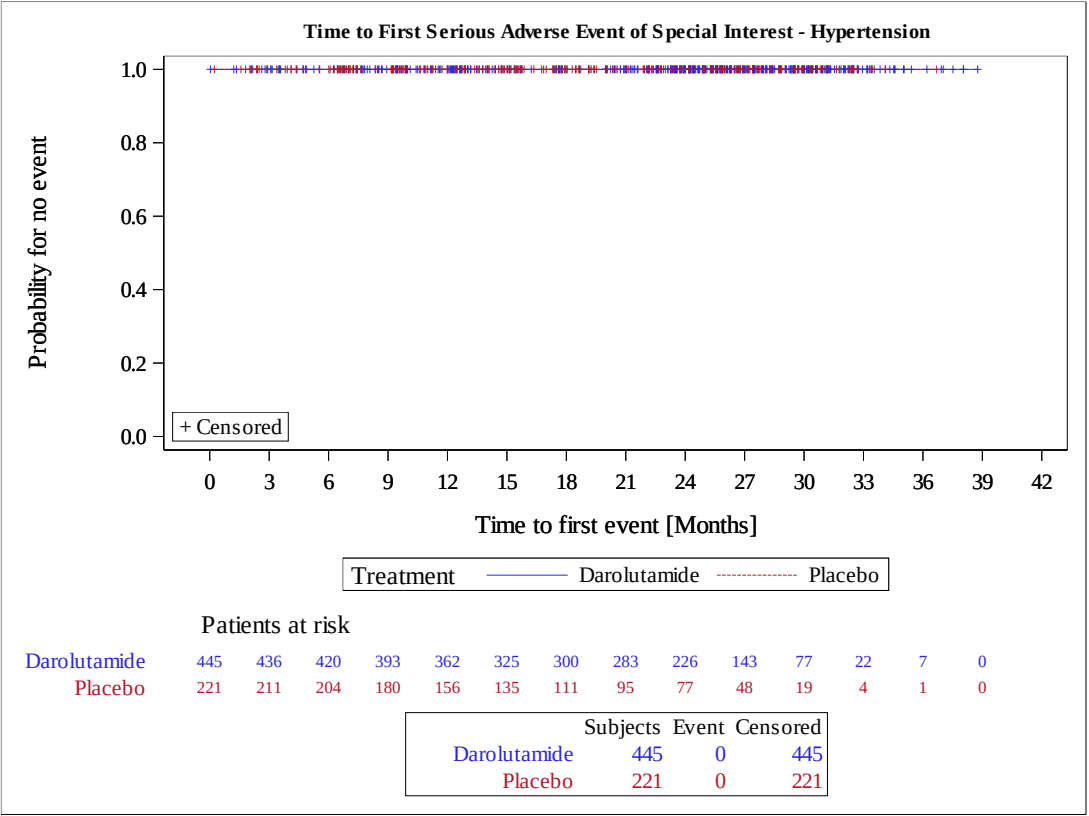
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI) p-Value	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.10.8.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Hypertension
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.9
Summary of Serious Adverse Events of Special Interest - Vasodilatation and flushing
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	445 (100.0)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.10.9.1

Summary of Serious Adverse Events of Special Interest - Vasodilatation and flushing - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.9.1

Summary of Serious Adverse Events of Special Interest - Vasodilatation and flushing - Subgroup analysis (safety analysis set)

Final

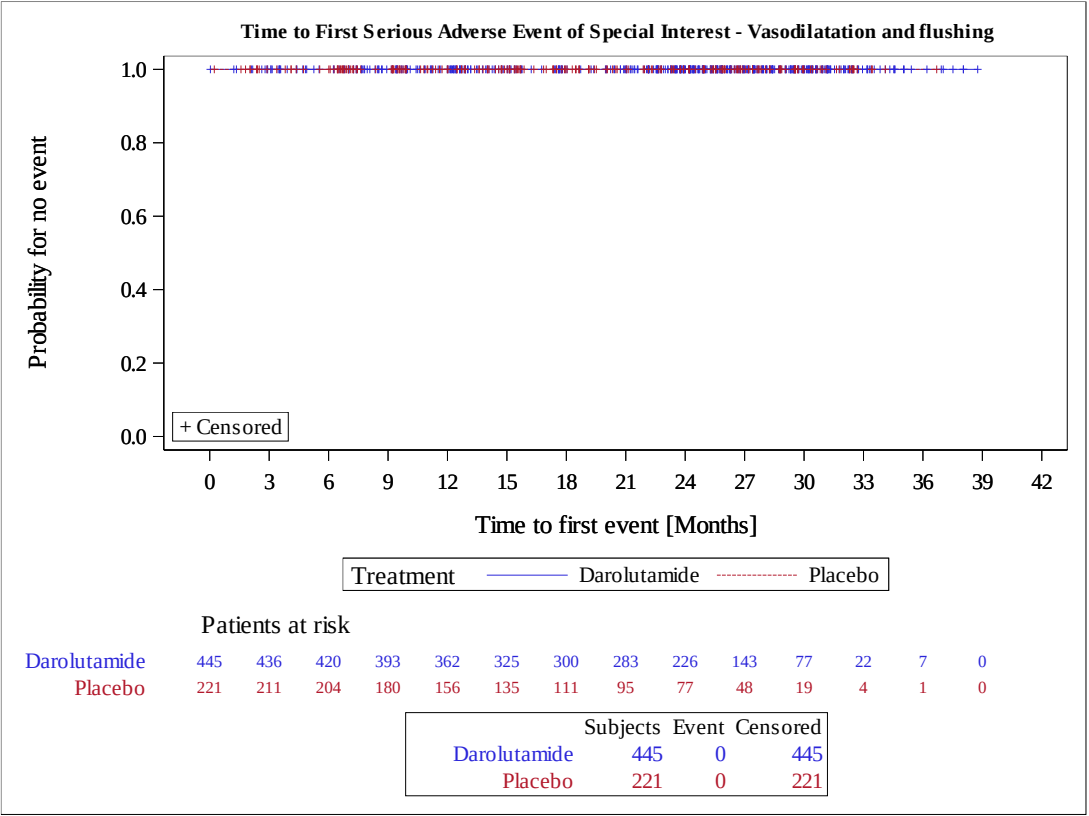
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction
			Hazard Ratio	(95% CI)	p-Value
p-Value					
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.10.9.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Vasodilatation and flushing
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.10
Summary of Serious Adverse Events of Special Interest - Mental impairment disorders
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	445 (100.0)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.10.1

Summary of Serious Adverse Events of Special Interest - Mental impairment disorders - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.10.1
Summary of Serious Adverse Events of Special Interest - Mental impairment disorders - Subgroup analysis
(safety analysis set)

Final

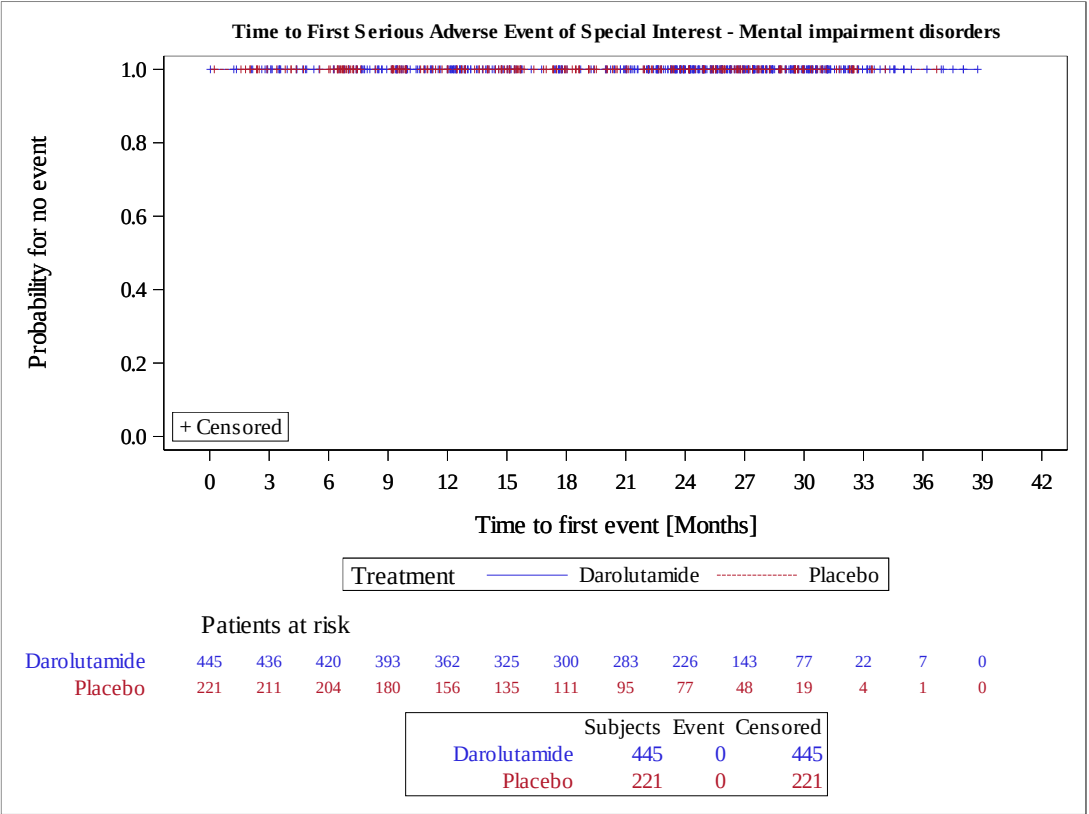
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.10.10.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Mental impairment disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.11
Summary of Serious Adverse Events of Special Interest - Depressed mood disorders
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	445 (100.0)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Final

Study population

Table 3.2.10.11.1

Summary of Serious Adverse Events of Special Interest - Depressed mood disorders - Subgroup analysis (safety analysis set)

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.11.1
Summary of Serious Adverse Events of Special Interest - Depressed mood disorders - Subgroup analysis
(safety analysis set)

Final

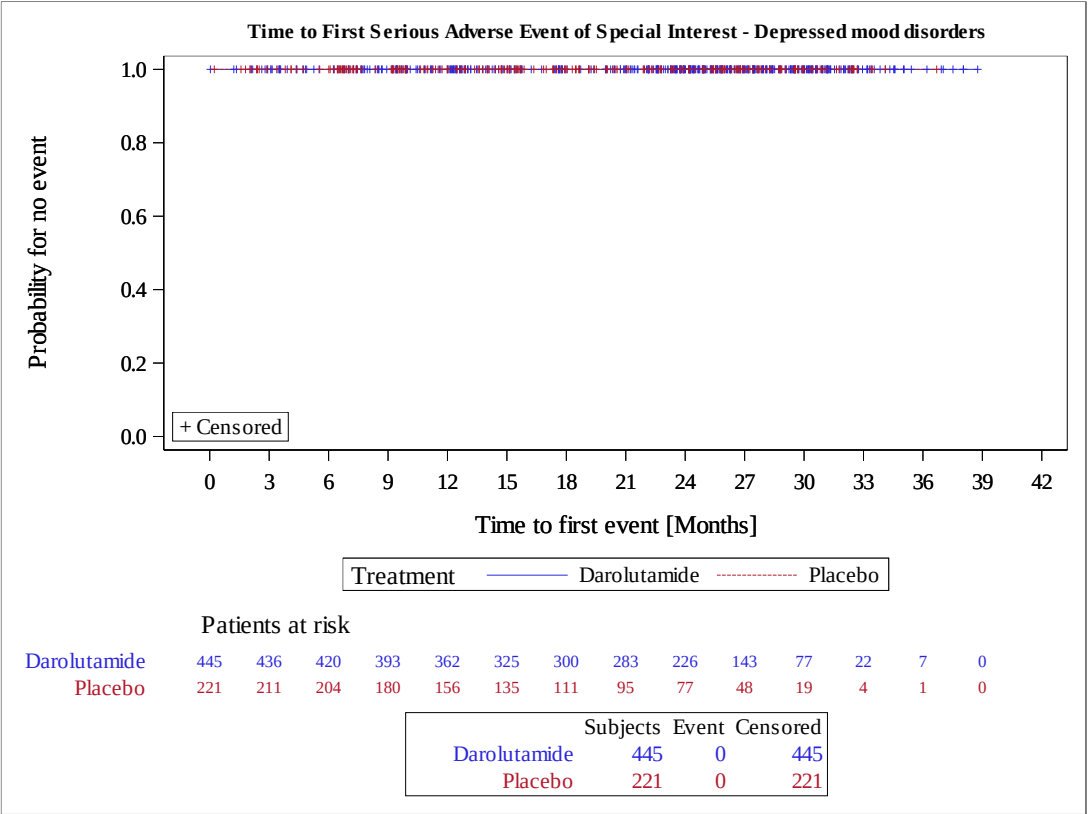
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.10.11.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Depressed mood disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.12
Summary of Serious Adverse Events of Special Interest - Breast disorders/gynecomastia
(safety analysis set)

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	445 (100.0)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.12.1

Summary of Serious Adverse Events of Special Interest - Breast disorders/gynecomastia - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.12.1
Summary of Serious Adverse Events of Special Interest - Breast disorders/gynecomastia - Subgroup analysis
(safety analysis set)

Final

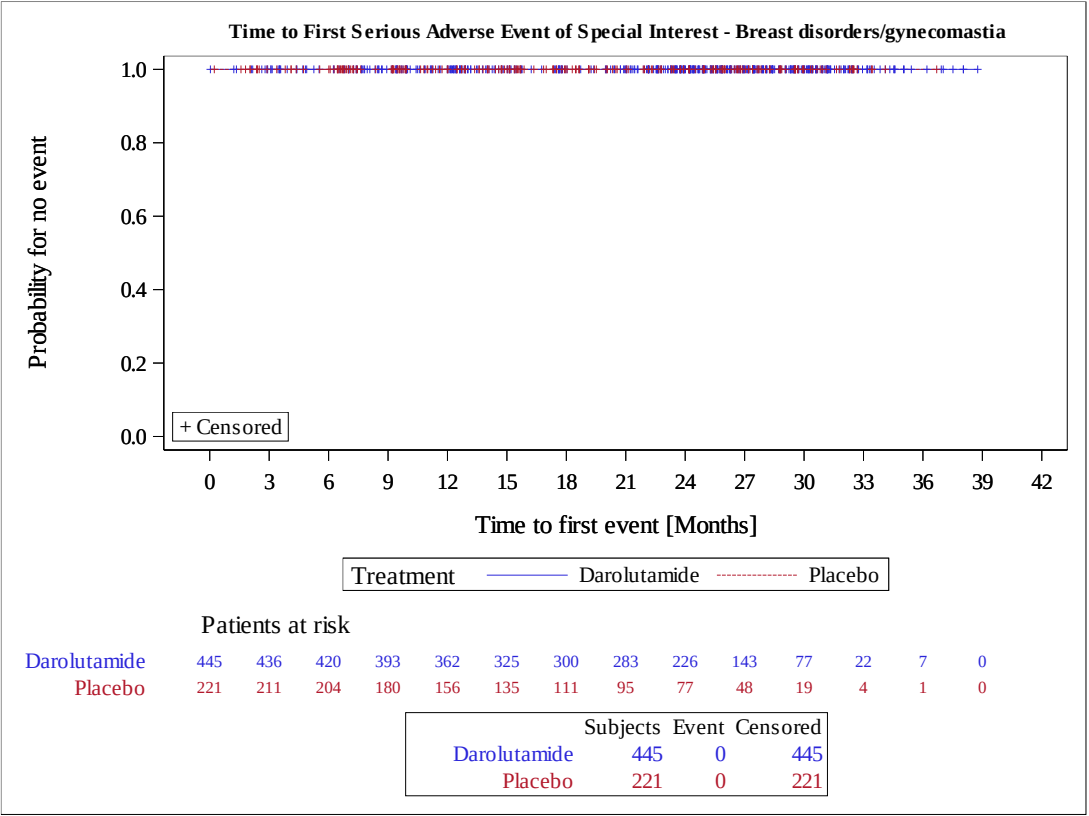
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.10.12.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Breast disorders/gynecomastia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.13
Summary of Serious Adverse Events of Special Interest - Cardiac disorders
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	15 (3.4)	7 (3.2)
Number of censored patients, n (%)	430 (96.6)	214 (96.8)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.939	
95% CI	0.382, 2.305	
p-value	0.8903	
Odds Ratio	1.066	
95% CI	0.428, 2.655	
p-value	0.8900	
Relative Risk	1.064	
95% CI	0.440, 2.572	
p-value	0.8901	
Risk Difference	0.203	
95% CI	-2.650, 3.057	
p-value	0.8889	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.13.1

Summary of Serious Adverse Events of Special Interest - Cardiac disorders - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	3/ 54 (5.6)	1/ 26 (3.8)	1.214	(0.126, 11.676)	0.8662	0.7424
No	12/391 (3.1)	6/195 (3.1)	0.870	(0.326, 2.323)	0.7806	
Received prior local therapy (from IWRS)						
Yes	4/ 80 (5.0)	2/ 40 (5.0)	0.871	(0.158, 4.814)	0.8745	0.8910
No	11/365 (3.0)	5/181 (2.8)	0.964	(0.335, 2.777)	0.9460	
Prior local radiotherapy and/or prostatectomy						
Yes	5/ 87 (5.7)	4/ 50 (8.0)	0.650	(0.174, 2.433)	0.5191	0.4209
No	10/358 (2.8)	3/171 (1.8)	1.385	(0.381, 5.041)	0.6193	
Age group						
<65 years	1/117 (0.9)	0/ 64 (0.0)	NE	(NE, NE)	NE	0.9990
65-74	7/193 (3.6)	4/ 95 (4.2)	0.786	(0.230, 2.690)	0.7009	
75-84	7/117 (6.0)	3/ 52 (5.8)	0.938	(0.242, 3.631)	0.9260	
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)	NE	(NE, NE)	NE	
Race						
White	8/249 (3.2)	4/124 (3.2)	0.804	(0.241, 2.685)	0.7229	0.8490
Asian	6/144 (4.2)	1/ 65 (1.5)	2.590	(0.312, 21.514)	0.3604	
Black or African American	0/ 42 (0.0)	1/ 23 (4.3)	NE	(NE, NE)	NE	
Other	1/ 10 (10.0)	1/ 9 (11.1)	0.887	(0.055, 14.184)	0.9327	
Geographical region						
Asia	6/141 (4.3)	1/ 63 (1.6)				0.9264
Latin America	3/120 (2.5)	3/ 70 (4.3)				
Europe and Rest of the world	6/184 (3.3)	3/ 88 (3.4)				
Baseline PSA values by median						
< median of overall population	8/215 (3.7)	4/110 (3.6)	0.924	(0.278, 3.071)	0.8967	0.9871
>= median of overall population	7/219 (3.2)	3/108 (2.8)	0.989	(0.255, 3.834)	0.9871	
ECOG PS at baseline						
=0	9/235 (3.8)	3/ 96 (3.1)	1.077	(0.291, 3.985)	0.9115	0.7607
>=1	6/210 (2.9)	4/125 (3.2)	0.820	(0.231, 2.909)	0.7580	
Gleason score at initial diagnosis						
Gleason <8	3/124 (2.4)	3/ 65 (4.6)	0.480	(0.097, 2.384)	0.3589	0.2088
Gleason >=8	12/308 (3.9)	3/146 (2.1)	1.684	(0.475, 5.974)	0.4148	
Disease volume at baseline						
high	11/314 (3.5)	5/156 (3.2)	0.977	(0.339, 2.816)	0.9662	0.9077
low	4/131 (3.1)	2/ 65 (3.1)	0.817	(0.149, 4.483)	0.8158	
Renal function - eGFR at baseline						
Normal: eGFR >= 90 mL/min	9/221 (4.1)	1/102 (1.0)	3.596	(0.455, 28.416)	0.1944	0.1512
Mild impairment: 60 <= eGFR < 90 mL/min	5/178 (2.8)	3/ 91 (3.3)	0.783	(0.187, 3.285)	0.7375	
Moderate impairment: 30 <= eGFR < 60 mL/min	1/ 45 (2.2)	3/ 27 (11.1)	0.174	(0.018, 1.675)	0.0868	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.13.1
Summary of Serious Adverse Events of Special Interest - Cardiac disorders - Subgroup analysis
(safety analysis set)

Final

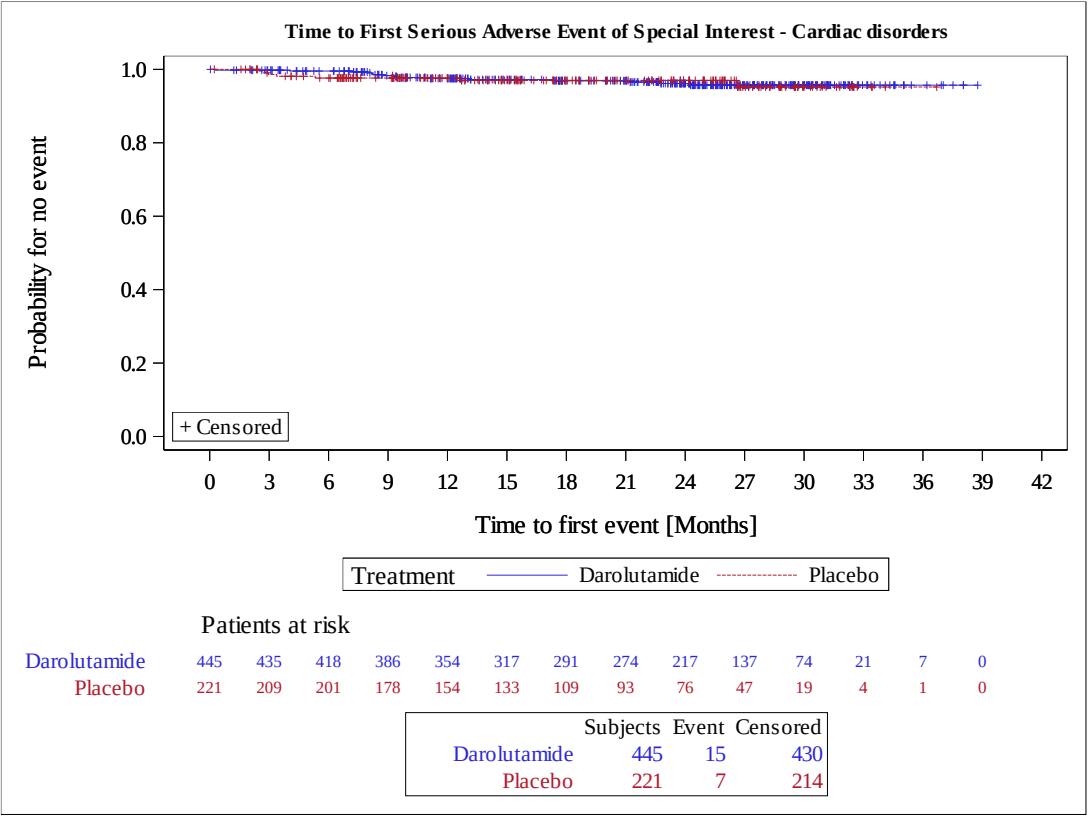
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.9880
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	12/387 (3.1)	7/202 (3.5)	0.792	(0.311, 2.016)	0.6242	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	3/ 58 (5.2)	0/ 19 (0.0)	NE	(NE, NE)	NE	
Age Group (Titan)						0.9826
<65	1/117 (0.9)	0/ 64 (0.0)	NE	(NE, NE)	NE	
>=65 and <75	7/193 (3.6)	4/ 95 (4.2)	0.786	(0.230, 2.690)	0.7009	
>=75	7/135 (5.2)	3/ 62 (4.8)	0.970	(0.250, 3.755)	0.9649	
Geographic region (Titan)						0.4823
Europe and north america	4/144 (2.8)	3/ 77 (3.9)	0.600	(0.133, 2.698)	0.5008	
ROTW	11/301 (3.7)	4/144 (2.8)	1.195	(0.380, 3.756)	0.7596	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.10.13.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Cardiac disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.14
Summary of Serious Adverse Events of Special Interest - Cerebral ischaemia
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	1 (0.2)	3 (1.4)
Number of censored patients, n (%)	444 (99.8)	218 (98.6)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.152	
95% CI	0.016, 1.458	
p-value	0.0592	
Odds Ratio	0.164	
95% CI	0.017, 1.583	
p-value	0.1179	
Relative Risk	0.166	
95% CI	0.017, 1.582	
p-value	0.1184	
Risk Difference	-1.133	
95% CI	-2.721, 0.455	
p-value	0.1620	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.14.1

Summary of Serious Adverse Events of Special Interest - Cerebral ischaemia - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	1/ 26 (3.8)			
No	1/391 (0.3)	2/195 (1.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	1/365 (0.3)	3/181 (1.7)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	1/358 (0.3)	3/171 (1.8)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	3/ 95 (3.2)			
75-84	1/117 (0.9)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	1/249 (0.4)	3/124 (2.4)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	1/120 (0.8)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	3/ 88 (3.4)			
Baseline PSA values by median					
< median of overall population	1/215 (0.5)	1/110 (0.9)			
>= median of overall population	0/219 (0.0)	2/108 (1.9)			
ECOG PS at baseline					
=0	1/235 (0.4)	2/ 96 (2.1)			
>=1	0/210 (0.0)	1/125 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	1/ 65 (1.5)			
Gleason >=8	1/308 (0.3)	2/146 (1.4)			
Disease volume at baseline					
high	0/314 (0.0)	3/156 (1.9)			
low	1/131 (0.8)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	1/221 (0.5)	1/102 (1.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	1/ 91 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	1/ 27 (3.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.14.1
Summary of Serious Adverse Events of Special Interest - Cerebral ischaemia - Subgroup analysis
(safety analysis set)

Final

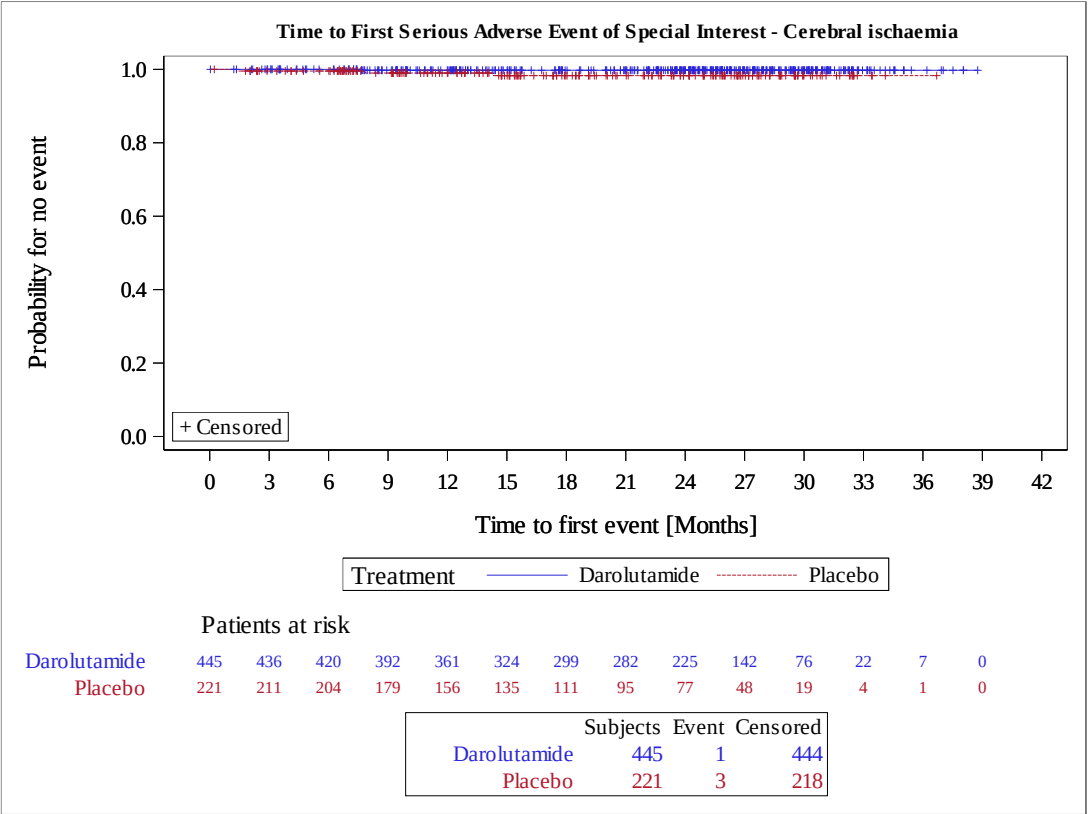
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI) p-Value	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	3/202 (1.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 58 (1.7)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	3/ 95 (3.2)			
>=75	1/135 (0.7)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	3/ 77 (3.9)			
ROTW	1/301 (0.3)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.10.14.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Cerebral ischaemia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.15
Summary of Serious Adverse Events of Special Interest - Cerebral and intracranial hemorrhage
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	2 (0.4)	1 (0.5)
Number of censored patients, n (%)	443 (99.6)	220 (99.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.831	
95% CI	0.075, 9.212	
p-value	0.8801	
Odds Ratio	0.993	
95% CI	0.090, 11.013	
p-value	0.9956	
Relative Risk	0.993	
95% CI	0.091, 10.895	
p-value	0.9956	
Risk Difference	-0.003	
95% CI	-1.084, 1.078	
p-value	0.9956	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.15.1

Summary of Serious Adverse Events of Special Interest - Cerebral and intracranial hemorrhage - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis			Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value	p-Value
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	0/ 54 (0.0)	0/ 26 (0.0)				
No	2/391 (0.5)	1/195 (0.5)				
Received prior local therapy (from IWRS)						
Yes	0/ 80 (0.0)	0/ 40 (0.0)				
No	2/365 (0.5)	1/181 (0.6)				
Prior local radiotherapy and/or prostatectomy						
Yes	2/ 87 (2.3)	0/ 50 (0.0)				
No	0/358 (0.0)	1/171 (0.6)				
Age group						
<65 years	0/117 (0.0)	0/ 64 (0.0)				
65-74	0/193 (0.0)	0/ 95 (0.0)				
75-84	1/117 (0.9)	0/ 52 (0.0)				
>=85 years	1/ 18 (5.6)	1/ 10 (10.0)				
Race						
White	1/249 (0.4)	0/124 (0.0)				
Asian	1/144 (0.7)	1/ 65 (1.5)				
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)				
Other	0/ 10 (0.0)	0/ 9 (0.0)				
Geographical region						
Asia	1/141 (0.7)	1/ 63 (1.6)				
Latin America	0/120 (0.0)	0/ 70 (0.0)				
Europe and Rest of the world	1/184 (0.5)	0/ 88 (0.0)				
Baseline PSA values by median						
< median of overall population	2/215 (0.9)	0/110 (0.0)				
>= median of overall population	0/219 (0.0)	1/108 (0.9)				
ECOG PS at baseline						
=0	2/235 (0.9)	0/ 96 (0.0)				
>=1	0/210 (0.0)	1/125 (0.8)				
Gleason score at initial diagnosis						
Gleason <8	0/124 (0.0)	1/ 65 (1.5)				
Gleason >=8	2/308 (0.6)	0/146 (0.0)				
Disease volume at baseline						
high	1/314 (0.3)	0/156 (0.0)				
low	1/131 (0.8)	1/ 65 (1.5)				
Renal function - eGFR at baseline						
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)				
Mild impairment: 60 <= eGFR < 90 mL/min	2/178 (1.1)	1/ 91 (1.1)				
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)				

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.10.15.1

Summary of Serious Adverse Events of Special Interest - Cerebral and intracranial hemorrhage - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	1/387 (0.3)	1/202 (0.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 58 (1.7)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	2/135 (1.5)	1/ 62 (1.6)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	2/301 (0.7)	1/144 (0.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

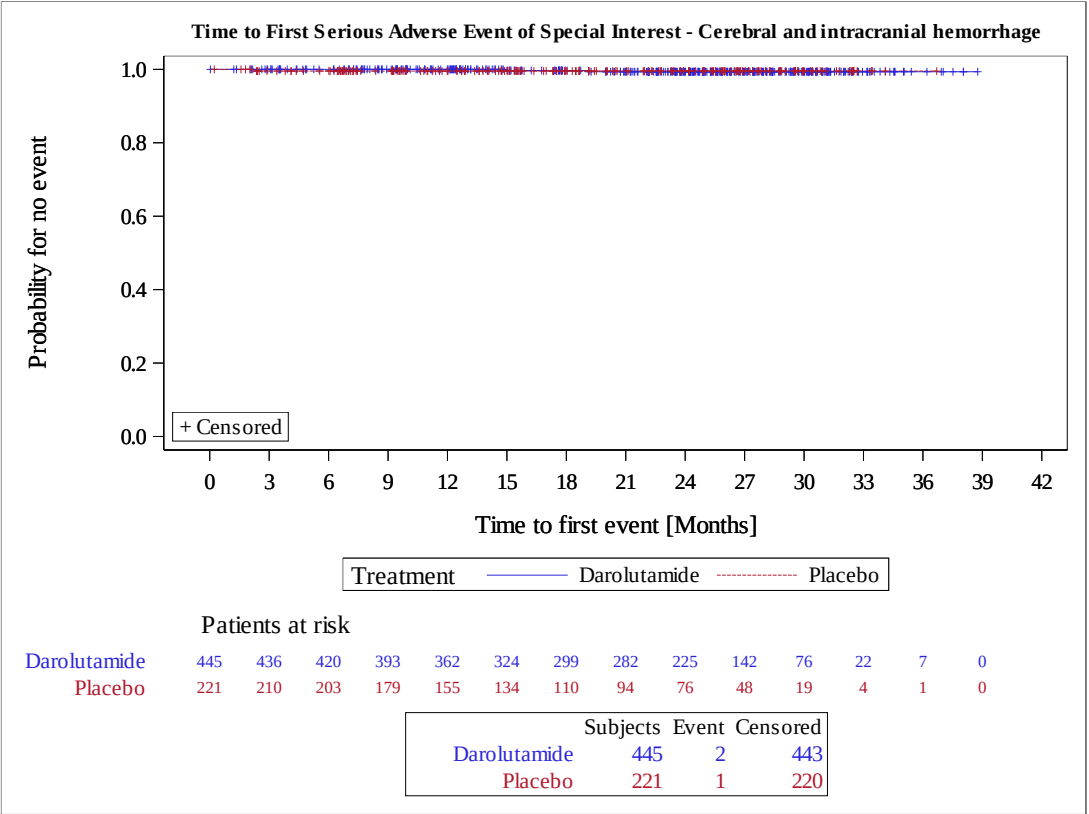
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.10.15.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Cerebral and intracranial hemorrhage
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.10.16
Summary of Serious Adverse Events of Special Interest - Interstitial lung disease
(safety analysis set)

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	445 (100.0)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.10.16.1

Summary of Serious Adverse Events of Special Interest - Interstitial lung disease - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.10.16.1
Summary of Serious Adverse Events of Special Interest - Interstitial lung disease - Subgroup analysis
(safety analysis set)

Final

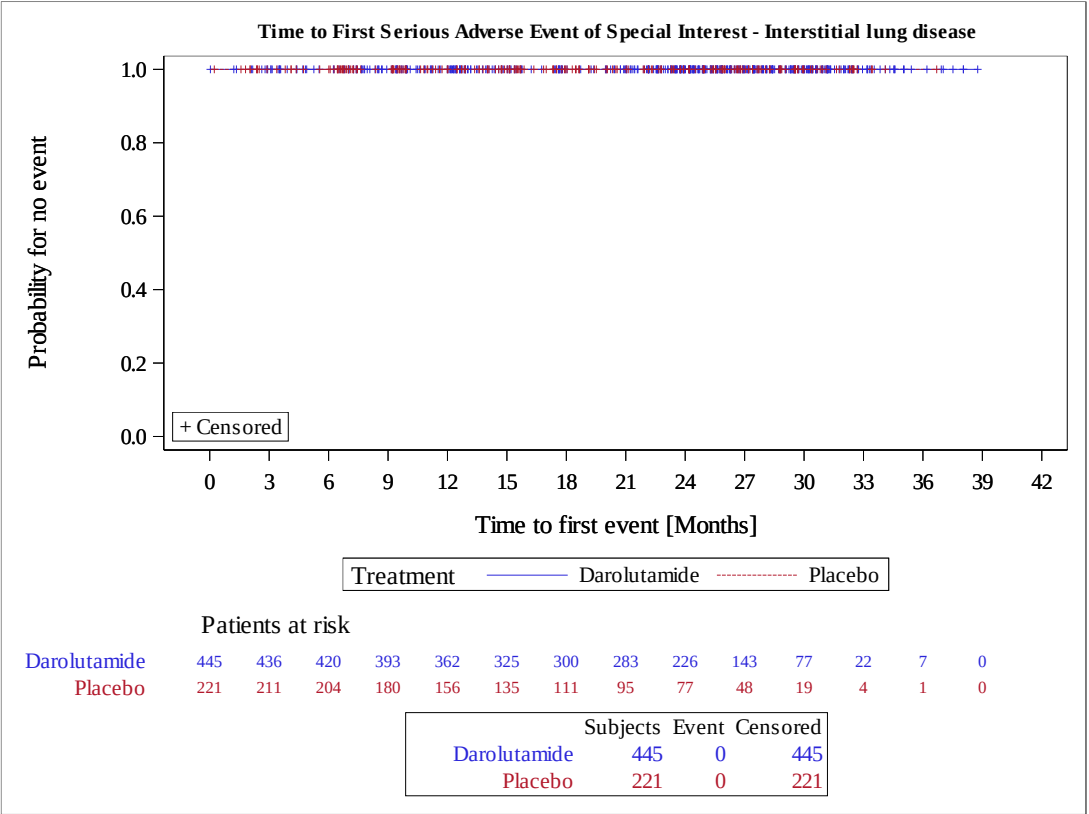
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Figure 3.2.10.16.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Interstitial lung disease
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.11.1
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Bone fractures excluding pathological fractures
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	7 (1.6)	1 (0.5)
Number of censored patients, n (%)	438 (98.4)	220 (99.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	2.749	
95% CI	0.338, 22.365	
p-value	0.3241	
Odds Ratio	3.516	
95% CI	0.430, 28.756	
p-value	0.2409	
Relative Risk	3.476	
95% CI	0.430, 28.080	
p-value	0.2424	
Risk Difference	1.121	
95% CI	-0.335, 2.576	
p-value	0.1314	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population

Table 3.2.11.1.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥3 - Bone fractures excluding pathological fractures - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	1/ 54 (1.9)	0/ 26 (0.0)			
No	6/391 (1.5)	1/195 (0.5)			
Received prior local therapy (from IWRS)					
Yes	2/ 80 (2.5)	0/ 40 (0.0)			
No	5/365 (1.4)	1/181 (0.6)			
Prior local radiotherapy and/or prostatectomy					
Yes	1/ 87 (1.1)	0/ 50 (0.0)			
No	6/358 (1.7)	1/171 (0.6)			
Age group					
<65 years	1/117 (0.9)	0/ 64 (0.0)			
65-74	1/193 (0.5)	0/ 95 (0.0)			
75-84	5/117 (4.3)	1/ 52 (1.9)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	5/249 (2.0)	0/124 (0.0)			
Asian	2/144 (1.4)	1/ 65 (1.5)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	2/141 (1.4)	1/ 63 (1.6)			
Latin America	3/120 (2.5)	0/ 70 (0.0)			
Europe and Rest of the world	2/184 (1.1)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	6/215 (2.8)	0/110 (0.0)			
>= median of overall population	1/219 (0.5)	1/108 (0.9)			
ECOG PS at baseline					
=0	3/235 (1.3)	1/ 96 (1.0)			
>=1	4/210 (1.9)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	3/124 (2.4)	0/ 65 (0.0)			
Gleason >=8	4/308 (1.3)	1/146 (0.7)			
Disease volume at baseline					
high	5/314 (1.6)	0/156 (0.0)			
low	2/131 (1.5)	1/ 65 (1.5)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	2/221 (0.9)	1/102 (1.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	5/178 (2.8)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Study population

Table 3.2.11.1.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Bone fractures excluding pathological fractures - Subgroup analysis (safety analysis set)

Final

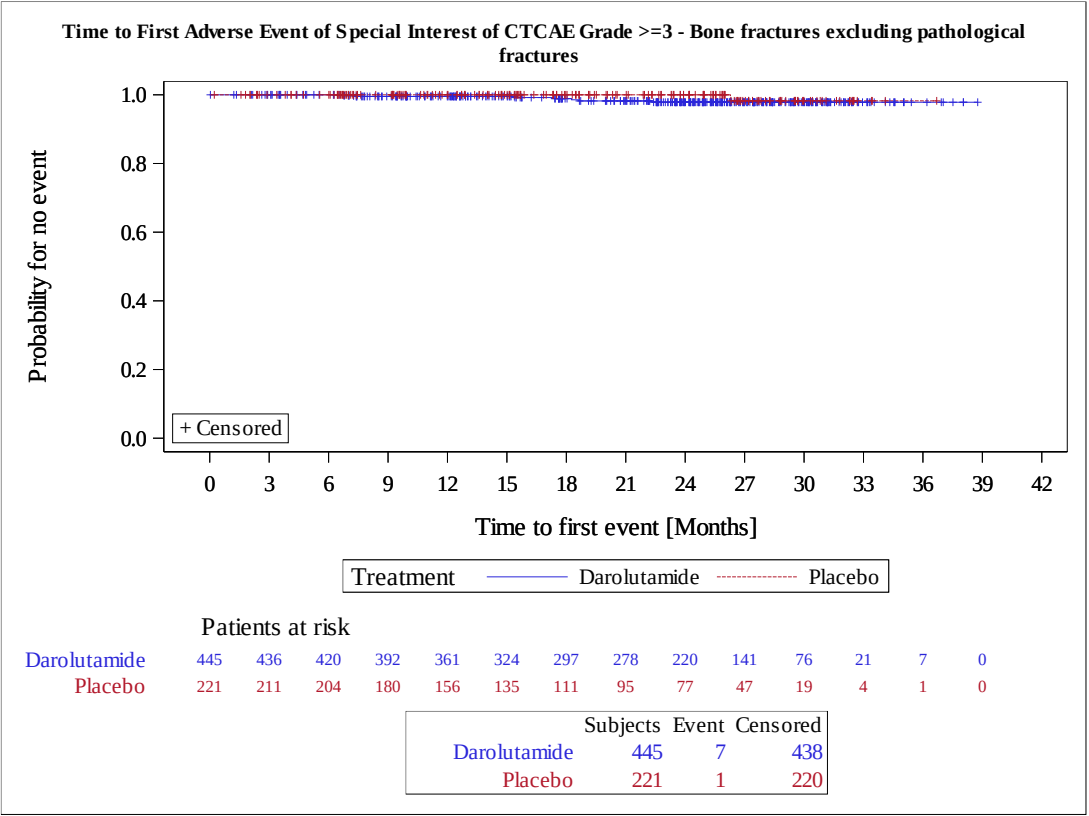
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	7/387 (1.8)	1/202 (0.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	1/117 (0.9)	0/ 64 (0.0)			
>=65 and <75	1/193 (0.5)	0/ 95 (0.0)			
>=75	5/135 (3.7)	1/ 62 (1.6)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	7/301 (2.3)	1/144 (0.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.11.1.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Bone fractures excluding pathological fractures
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.11.2
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	2 (0.4)	0 (0.0)
Number of censored patients, n (%)	443 (99.6)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	2.497	
95% CI	0.119, 52.238	
p-value	0.5553	
Relative Risk	2.489	
95% CI	0.120, 51.619	
p-value	0.5556	
Risk Difference	0.449	
95% CI	-0.172, 1.071	
p-value	0.1564	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Final

Study population

Table 3.2.11.2.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥ 3 - Diabetes mellitus and hyperglycemia - Subgroup analysis (safety analysis set)

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	2/391 (0.5)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	2/365 (0.5)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	2/358 (0.6)	0/171 (0.0)			
Age group					
<65 years	1/117 (0.9)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	1/117 (0.9)	0/ 52 (0.0)			
≥ 85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	1/249 (0.4)	0/124 (0.0)			
Asian	1/144 (0.7)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	1/141 (0.7)	0/ 63 (0.0)			
Latin America	1/120 (0.8)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	2/215 (0.9)	0/110 (0.0)			
$\geq$ median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	1/235 (0.4)	0/ 96 (0.0)			
≥ 1	1/210 (0.5)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	1/124 (0.8)	0/ 65 (0.0)			
Gleason ≥ 8	1/308 (0.3)	0/146 (0.0)			
Disease volume at baseline					
high	1/314 (0.3)	0/156 (0.0)			
low	1/131 (0.8)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR ≥ 90 mL/min	1/221 (0.5)	0/102 (0.0)			
Mild impairment: $60 \leq$ eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: $30 \leq$ eGFR < 60 mL/min	1/ 45 (2.2)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.11.2.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Diabetes mellitus and hyperglycemia - Subgroup analysis (safety analysis set)

Final

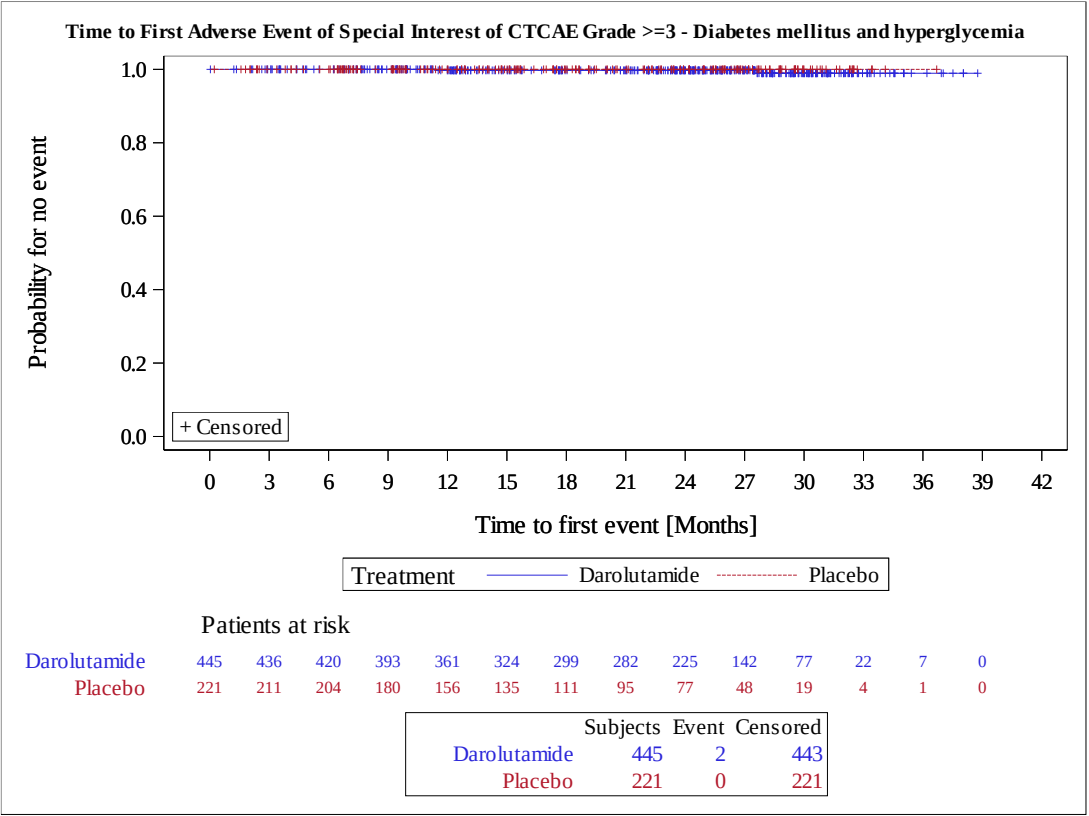
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	2/387 (0.5)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	1/117 (0.9)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	1/135 (0.7)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	2/301 (0.7)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.11.2.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade ≥ 3 - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.11.3
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Fall
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	1 (0.5)
Number of censored patients, n (%)	445 (100.0)	220 (99.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	0.165	
95% CI	0.007, 4.066	
p-value	0.2704	
Relative Risk	0.166	
95% CI	0.007, 4.056	
p-value	0.2707	
Risk Difference	-0.452	
95% CI	-1.337, 0.432	
p-value	0.3162	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.11.3.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Fall - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	1/ 26 (3.8)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	1/ 40 (2.5)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	1/ 50 (2.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	1/ 52 (1.9)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	1/124 (0.8)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	1/ 88 (1.1)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	1/110 (0.9)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	1/ 96 (1.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	1/ 65 (1.5)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	1/156 (0.6)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	1/ 91 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.11.3.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Fall - Subgroup analysis (safety analysis set)

Final

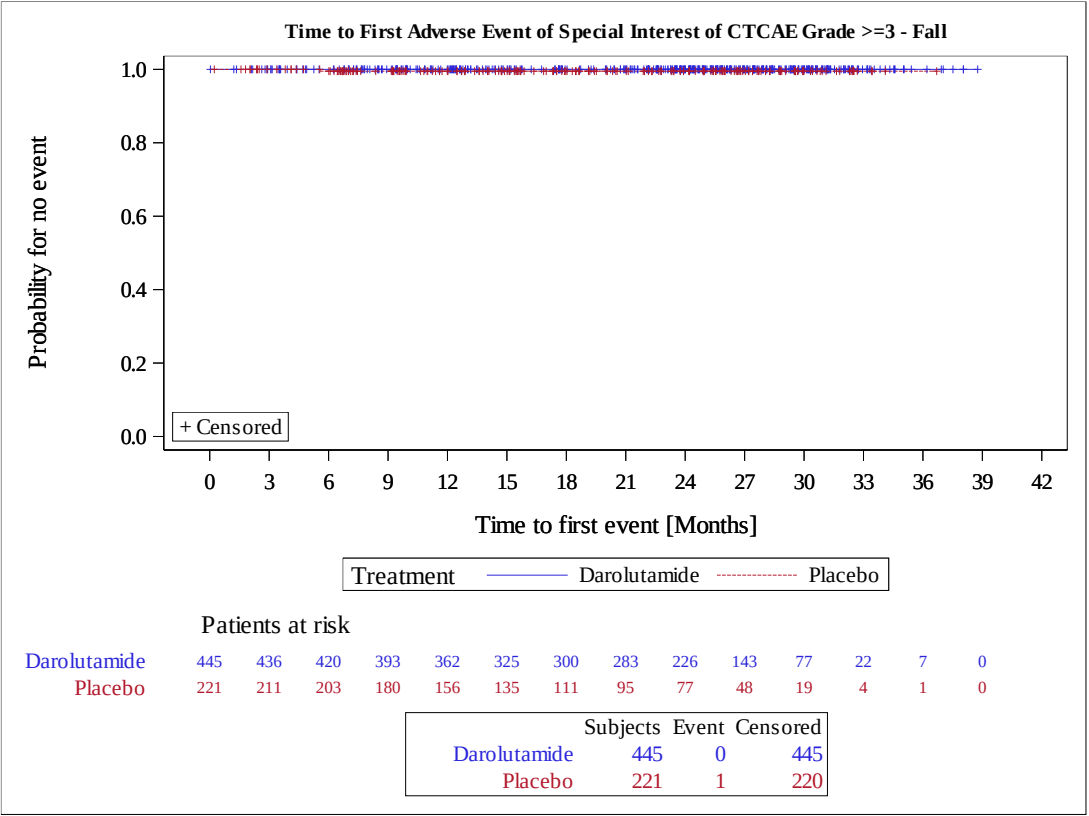
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	1/202 (0.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	1/ 62 (1.6)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	1/144 (0.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.11.3.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Fall
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.11.4
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Fatigue/ asthenic conditions
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	1 (0.5)
Number of censored patients, n (%)	445 (100.0)	220 (99.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	0.165	
95% CI	0.007, 4.066	
p-value	0.2704	
Relative Risk	0.166	
95% CI	0.007, 4.056	
p-value	0.2707	
Risk Difference	-0.452	
95% CI	-1.337, 0.432	
p-value	0.3162	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.11.4.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥3 - Fatigue/ asthenic conditions - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	1/195 (0.5)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	1/181 (0.6)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	1/171 (0.6)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	1/ 95 (1.1)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	1/ 65 (1.5)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	1/ 63 (1.6)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	1/108 (0.9)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	1/125 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	1/146 (0.7)			
Disease volume at baseline					
high	0/314 (0.0)	1/156 (0.6)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	1/ 91 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.11.4.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Fatigue/ asthenic conditions - Subgroup analysis (safety analysis set)

Final

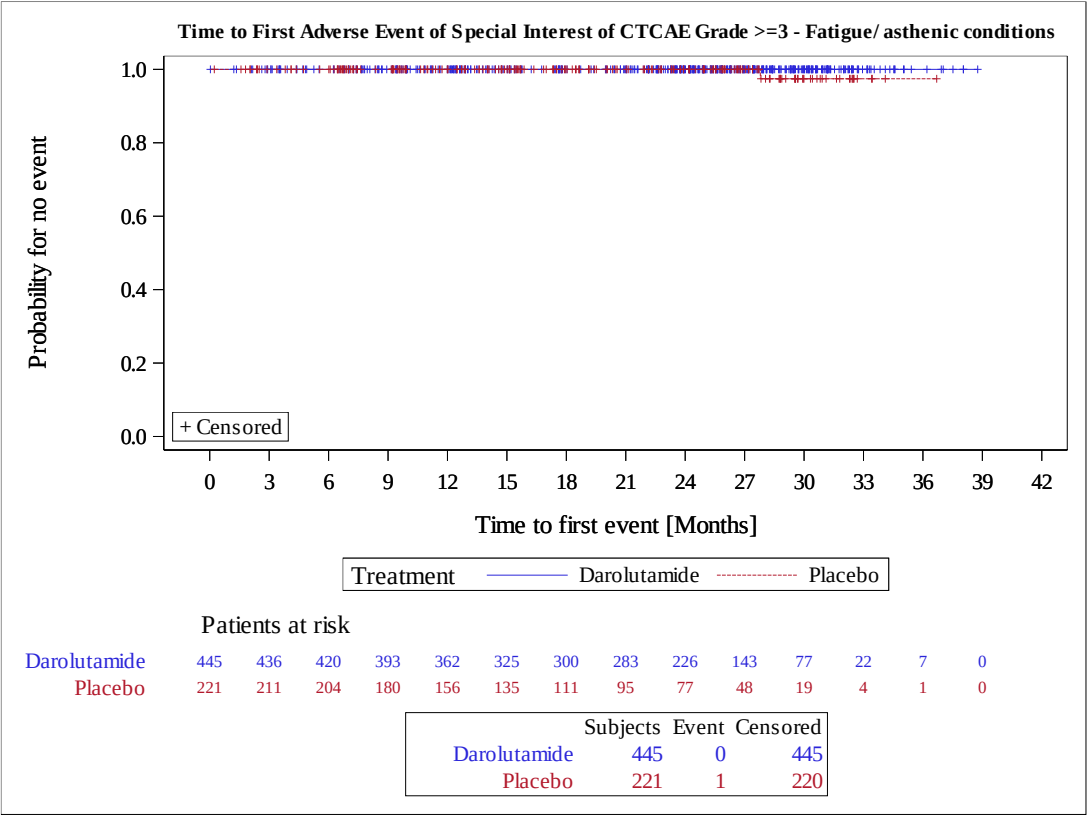
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	1/202 (0.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	1/ 95 (1.1)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	1/144 (0.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.11.4.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Fatigue/ asthenic conditions
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.11.5
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Weight decreased
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	2 (0.9)
Number of censored patients, n (%)	445 (100.0)	219 (99.1)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	0.099	
95% CI	0.005, 2.061	
p-value	0.1353	
Relative Risk	0.100	
95% CI	0.005, 2.065	
p-value	0.1359	
Risk Difference	-0.905	
95% CI	-2.154, 0.344	
p-value	0.1554	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.11.5.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥3 - Weight decreased - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	2/195 (1.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	2/181 (1.1)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	2/171 (1.2)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	1/ 95 (1.1)			
75-84	0/117 (0.0)	1/ 52 (1.9)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	1/124 (0.8)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	1/ 23 (4.3)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	1/ 70 (1.4)			
Europe and Rest of the world	0/184 (0.0)	1/ 88 (1.1)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	1/110 (0.9)			
>= median of overall population	0/219 (0.0)	1/108 (0.9)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	2/125 (1.6)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	2/146 (1.4)			
Disease volume at baseline					
high	0/314 (0.0)	2/156 (1.3)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	2/ 91 (2.2)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.11.5.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Weight decreased - Subgroup analysis (safety analysis set)

Final

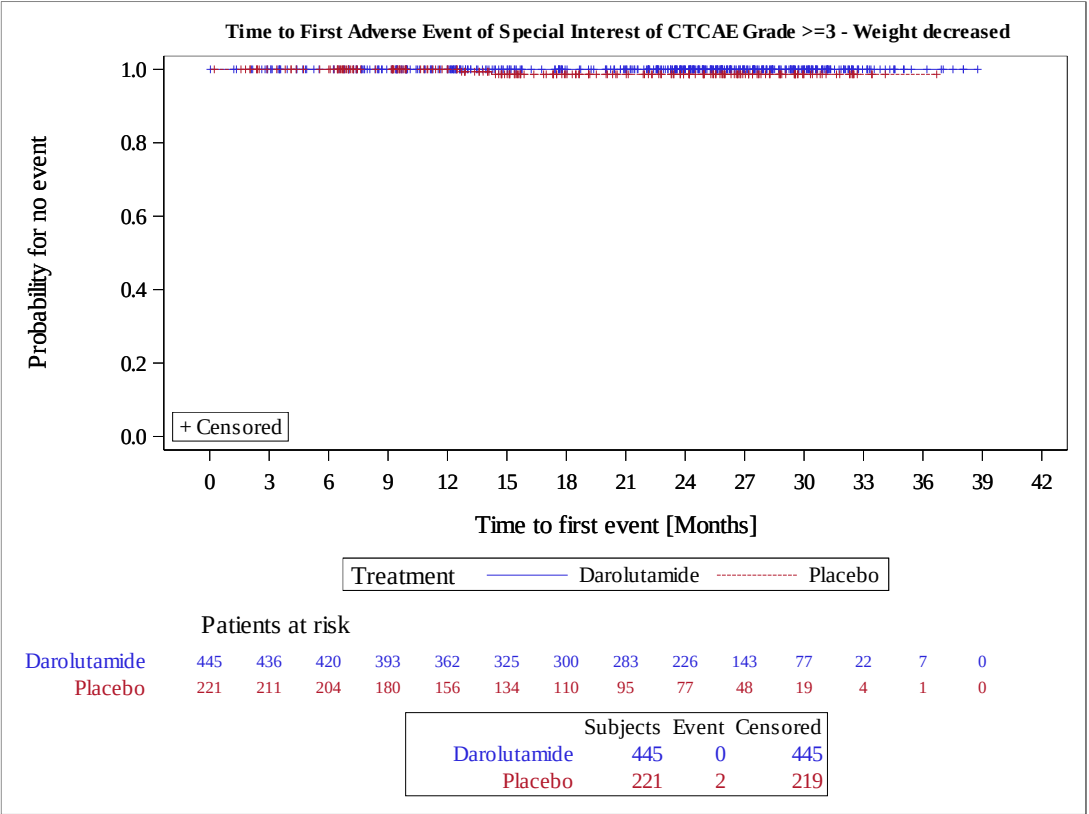
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	2/202 (1.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	1/ 95 (1.1)			
>=75	0/135 (0.0)	1/ 62 (1.6)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	1/ 77 (1.3)			
ROTW	0/301 (0.0)	1/144 (0.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.11.5.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade ≥ 3 - Weight decreased
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.11.6
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Rash
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	4 (0.9)	0 (0.0)
Number of censored patients, n (%)	441 (99.1)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	4.515	
95% CI	0.242, 84.240	
p-value	0.3126	
Relative Risk	4.480	
95% CI	0.242, 82.838	
p-value	0.3137	
Risk Difference	0.899	
95% CI	0.022, 1.776	
p-value	0.0445	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population

Table 3.2.11.6.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Rash - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	4/391 (1.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	4/365 (1.1)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	4/358 (1.1)	0/171 (0.0)			
Age group					
<65 years	1/117 (0.9)	0/ 64 (0.0)			
65-74	1/193 (0.5)	0/ 95 (0.0)			
75-84	2/117 (1.7)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	3/249 (1.2)	0/124 (0.0)			
Asian	1/144 (0.7)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	1/141 (0.7)	0/ 63 (0.0)			
Latin America	2/120 (1.7)	0/ 70 (0.0)			
Europe and Rest of the world	1/184 (0.5)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	3/215 (1.4)	0/110 (0.0)			
>= median of overall population	1/219 (0.5)	0/108 (0.0)			
ECOG PS at baseline					
=0	2/235 (0.9)	0/ 96 (0.0)			
>=1	2/210 (1.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	3/308 (1.0)	0/146 (0.0)			
Disease volume at baseline					
high	3/314 (1.0)	0/156 (0.0)			
low	1/131 (0.8)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	2/221 (0.9)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	2/178 (1.1)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.11.6.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Rash - Subgroup analysis (safety analysis set)

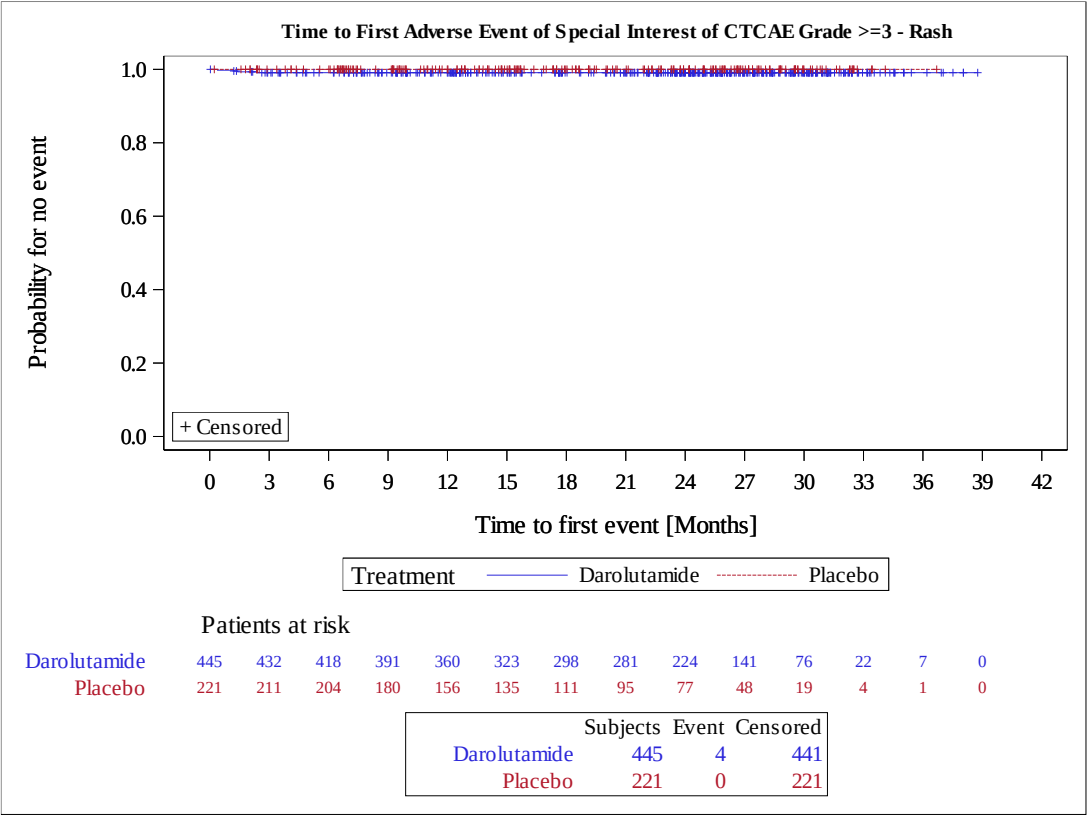
Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	2/387 (0.5)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	2/ 58 (3.4)	0/ 19 (0.0)			
Age Group (Titan)					
<65	1/117 (0.9)	0/ 64 (0.0)			
>=65 and <75	1/193 (0.5)	0/ 95 (0.0)			
>=75	2/135 (1.5)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	4/301 (1.3)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Study population
Figure 3.2.11.6.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Rash
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.11.7
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Seizure
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	445 (100.0)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.11.7.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥3 - Seizure - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Study population

Table 3.2.11.7.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Seizure - Subgroup analysis (safety analysis set)

Final

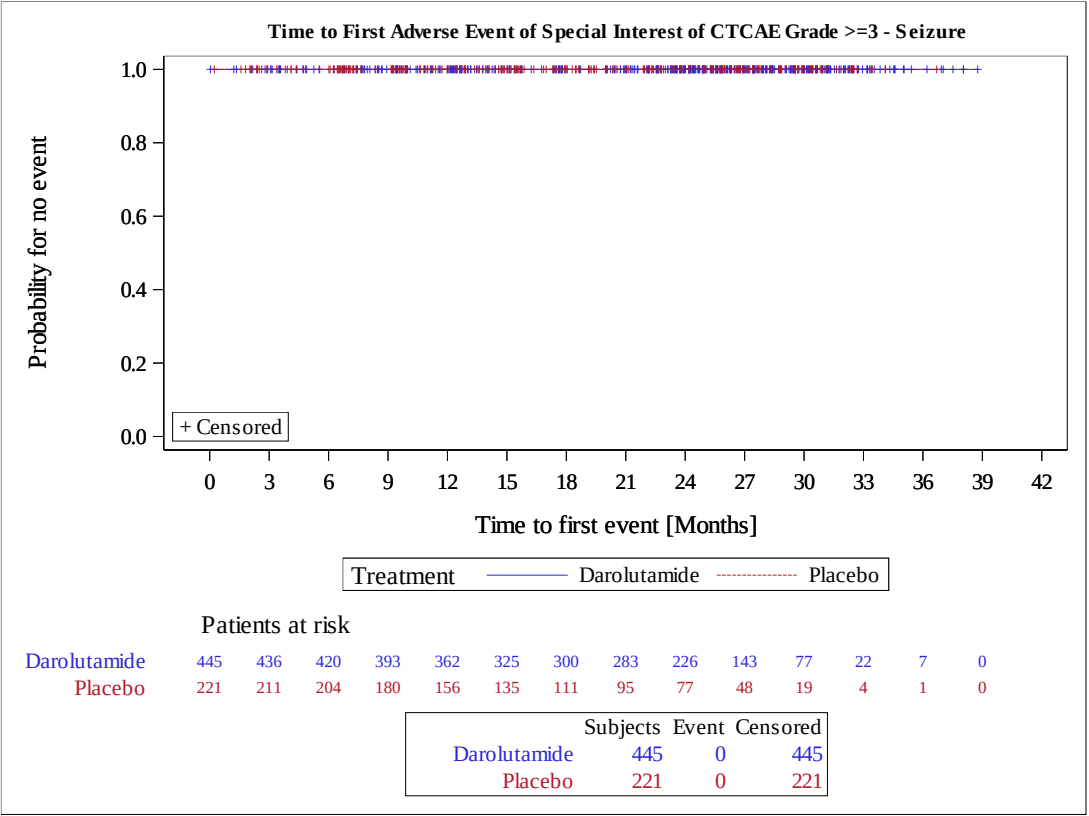
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.11.7.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Seizure
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.11.8
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Hypertension
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	21 (4.7)	9 (4.1)
Number of censored patients, n (%)	424 (95.3)	212 (95.9)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (30.9, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.007	
95% CI	0.460, 2.204	
p-value	0.9854	
Odds Ratio	1.167	
95% CI	0.525, 2.591	
p-value	0.7050	
Relative Risk	1.159	
95% CI	0.540, 2.488	
p-value	0.7054	
Risk Difference	0.647	
95% CI	-2.620, 3.913	
p-value	0.6980	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.11.8.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Hypertension - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.8961
Yes	2/ 54 (3.7)	1/ 26 (3.8)	0.820	(0.074, 9.045)	0.8709	
No	19/391 (4.9)	8/195 (4.1)	1.024	(0.447, 2.346)	0.9541	
Received prior local therapy (from IWRS)						0.6399
Yes	4/ 80 (5.0)	1/ 40 (2.5)	1.694	(0.187, 15.370)	0.6356	
No	17/365 (4.7)	8/181 (4.4)	0.934	(0.403, 2.167)	0.8736	
Prior local radiotherapy and/or prostatectomy						0.3271
Yes	5/ 87 (5.7)	1/ 50 (2.0)	2.774	(0.324, 23.791)	0.3307	
No	16/358 (4.5)	8/171 (4.7)	0.809	(0.345, 1.894)	0.6241	
Age group						0.6485
<65 years	6/117 (5.1)	1/ 64 (1.6)	2.732	(0.328, 22.754)	0.3324	
65-74	10/193 (5.2)	5/ 95 (5.3)	0.895	(0.305, 2.624)	0.8399	
75-84	4/117 (3.4)	3/ 52 (5.8)	0.513	(0.114, 2.305)	0.3754	
>=85 years	1/ 18 (5.6)	0/ 10 (0.0)	NE	(NE, NE)	NE	
Race						0.9993
White	8/249 (3.2)	3/124 (2.4)	1.215	(0.322, 4.589)	0.7733	
Asian	7/144 (4.9)	3/ 65 (4.6)	0.950	(0.245, 3.679)	0.9409	
Black or African American	6/ 42 (14.3)	3/ 23 (13.0)	1.130	(0.280, 4.558)	0.8634	
Other	0/ 10 (0.0)	0/ 9 (0.0)	NE	(NE, NE)	NE	
Geographical region						0.8227
Asia	7/141 (5.0)	3/ 63 (4.8)	0.942	(0.243, 3.646)	0.9305	
Latin America	10/120 (8.3)	4/ 70 (5.7)	1.410	(0.440, 4.515)	0.5605	
Europe and Rest of the world	4/184 (2.2)	2/ 88 (2.3)	0.887	(0.162, 4.853)	0.8900	
Baseline PSA values by median						0.6133
< median of overall population	7/215 (3.3)	4/110 (3.6)	0.826	(0.242, 2.822)	0.7595	
>= median of overall population	14/219 (6.4)	5/108 (4.6)	1.150	(0.413, 3.205)	0.7892	
ECOG PS at baseline						0.5313
=0	14/235 (6.0)	4/ 96 (4.2)	1.253	(0.412, 3.816)	0.6901	
>=1	7/210 (3.3)	5/125 (4.0)	0.722	(0.228, 2.289)	0.5787	
Gleason score at initial diagnosis						0.9325
Gleason <8	6/124 (4.8)	3/ 65 (4.6)	0.901	(0.224, 3.614)	0.8826	
Gleason >=8	14/308 (4.5)	6/146 (4.1)	1.001	(0.384, 2.609)	0.9980	
Disease volume at baseline						0.9080
high	11/314 (3.5)	5/156 (3.2)	0.948	(0.328, 2.739)	0.9213	
low	10/131 (7.6)	4/ 65 (6.2)	1.078	(0.337, 3.446)	0.8990	
Renal function - eGFR at baseline						0.8462
Normal: eGFR >= 90 mL/min	12/221 (5.4)	4/102 (3.9)	1.243	(0.400, 3.856)	0.7064	
Mild impairment: 60 <= eGFR < 90 mL/min	8/178 (4.5)	4/ 91 (4.4)	0.896	(0.269, 2.984)	0.8583	
Moderate impairment: 30 <= eGFR < 60 mL/min	1/ 45 (2.2)	1/ 27 (3.7)	0.569	(0.036, 9.111)	0.6864	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.11.8.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Hypertension - Subgroup analysis (safety analysis set)

Final

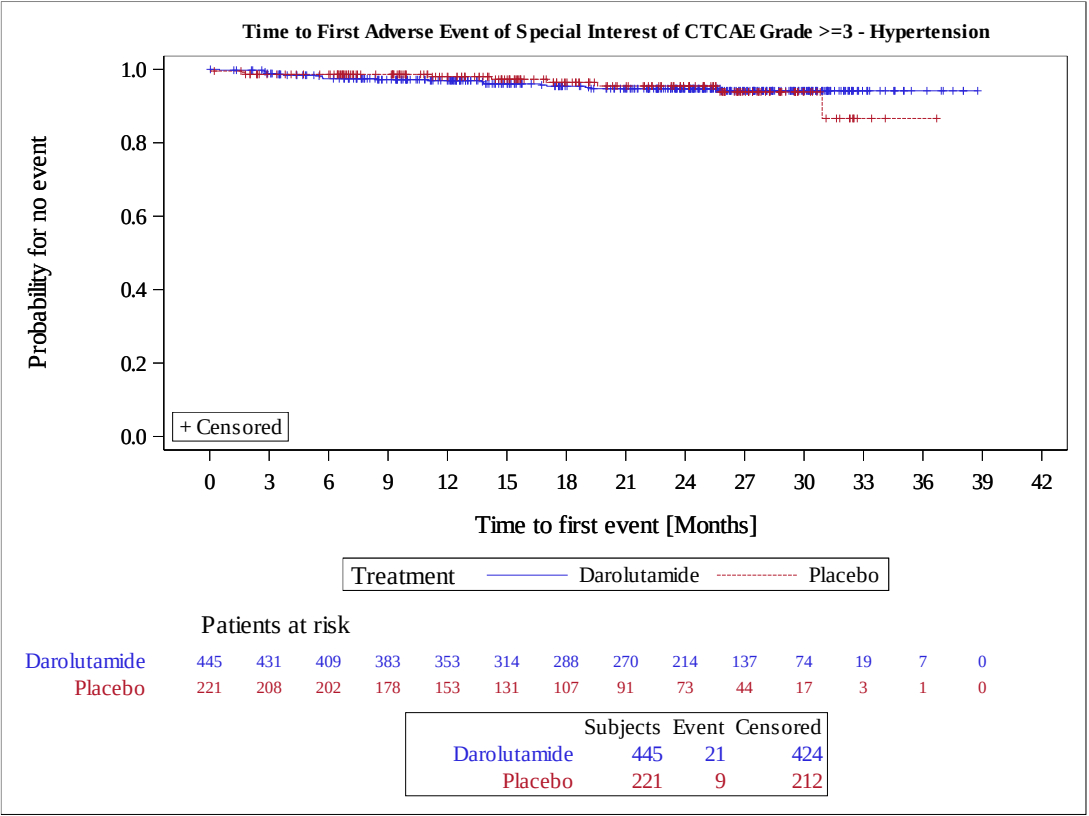
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.3475
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	20/387 (5.2)	8/202 (4.0)	1.127	(0.495, 2.564)	0.7760	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 58 (1.7)	1/ 19 (5.3)	0.293	(0.018, 4.701)	0.3568	
Age Group (Titan)						0.5394
<65	6/117 (5.1)	1/ 64 (1.6)	2.732	(0.328, 22.754)	0.3324	
>=65 and <75	10/193 (5.2)	5/ 95 (5.3)	0.895	(0.305, 2.624)	0.8399	
>=75	5/135 (3.7)	3/ 62 (4.8)	0.661	(0.157, 2.783)	0.5700	
Geographic region (Titan)						0.5727
Europe and north america	3/144 (2.1)	2/ 77 (2.6)	0.767	(0.128, 4.596)	0.7708	
ROTW	18/301 (6.0)	7/144 (4.9)	1.102	(0.460, 2.641)	0.8274	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.11.8.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Hypertension
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.11.9
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Vasodilatation and flushing
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	445 (100.0)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.11.9.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥3 - Vasodilatation and flushing - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.11.9.1
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Vasodilatation and flushing - Subgroup analysis
(safety analysis set)

Final

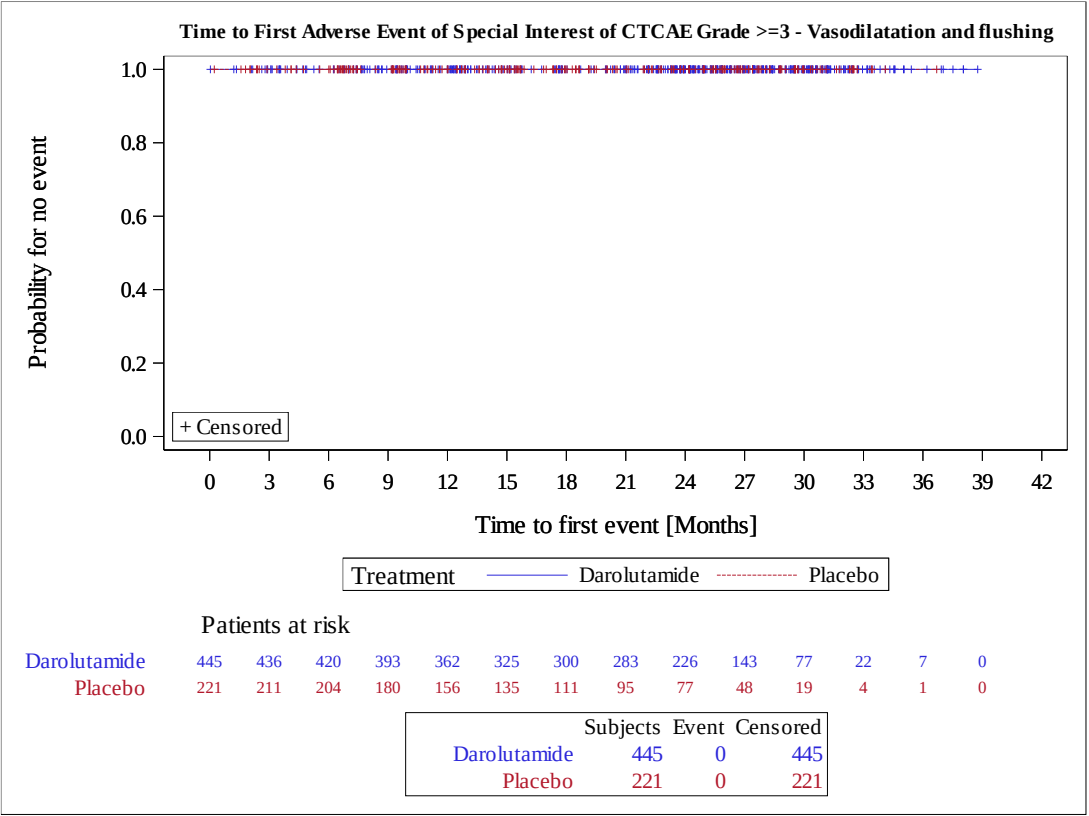
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.11.9.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Vasodilatation and flushing
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.11.10
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Mental impairment disorders
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	445 (100.0)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.11.10.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥3 - Mental impairment disorders - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.11.10.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Mental impairment disorders - Subgroup analysis (safety analysis set)

Final

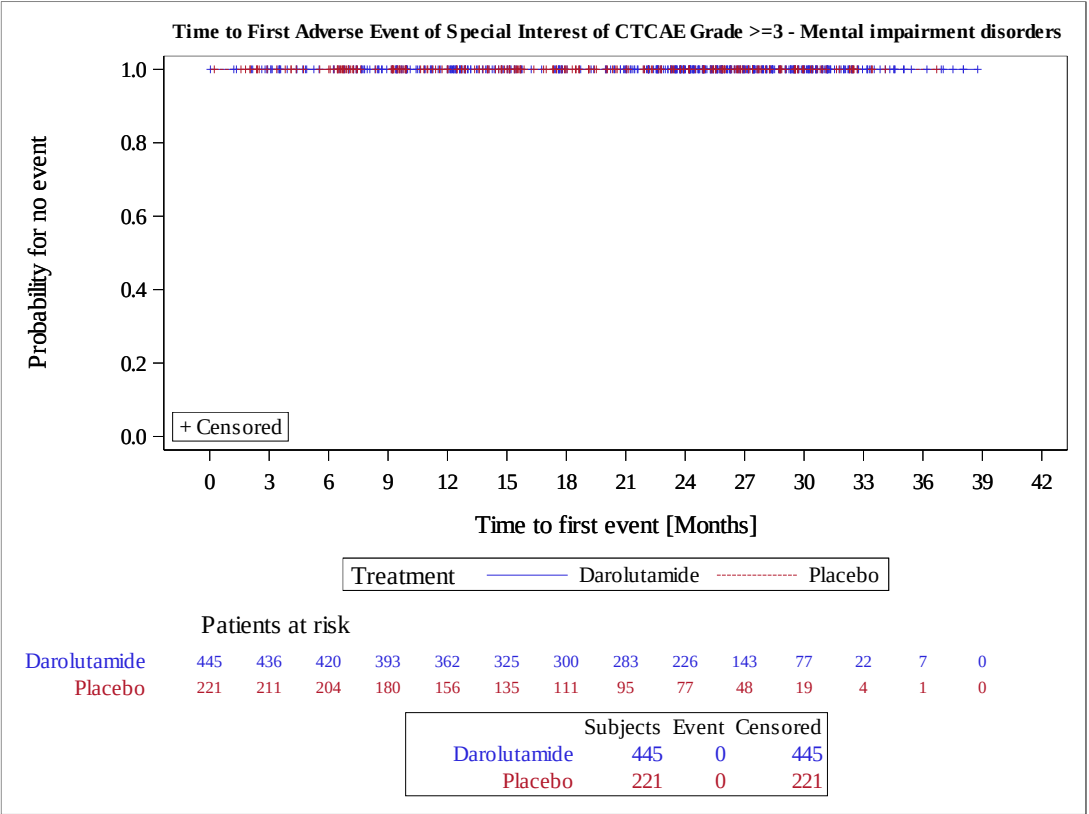
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI) p-Value	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.11.10.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Mental impairment disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.11.11
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Depressed mood disorders
(safety analysis set)

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	445 (100.0)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

1841788 / 21140 - 07JUN2024

Study population

Table 3.2.11.11.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Depressed mood disorders - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.11.11.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Depressed mood disorders - Subgroup analysis (safety analysis set)

Final

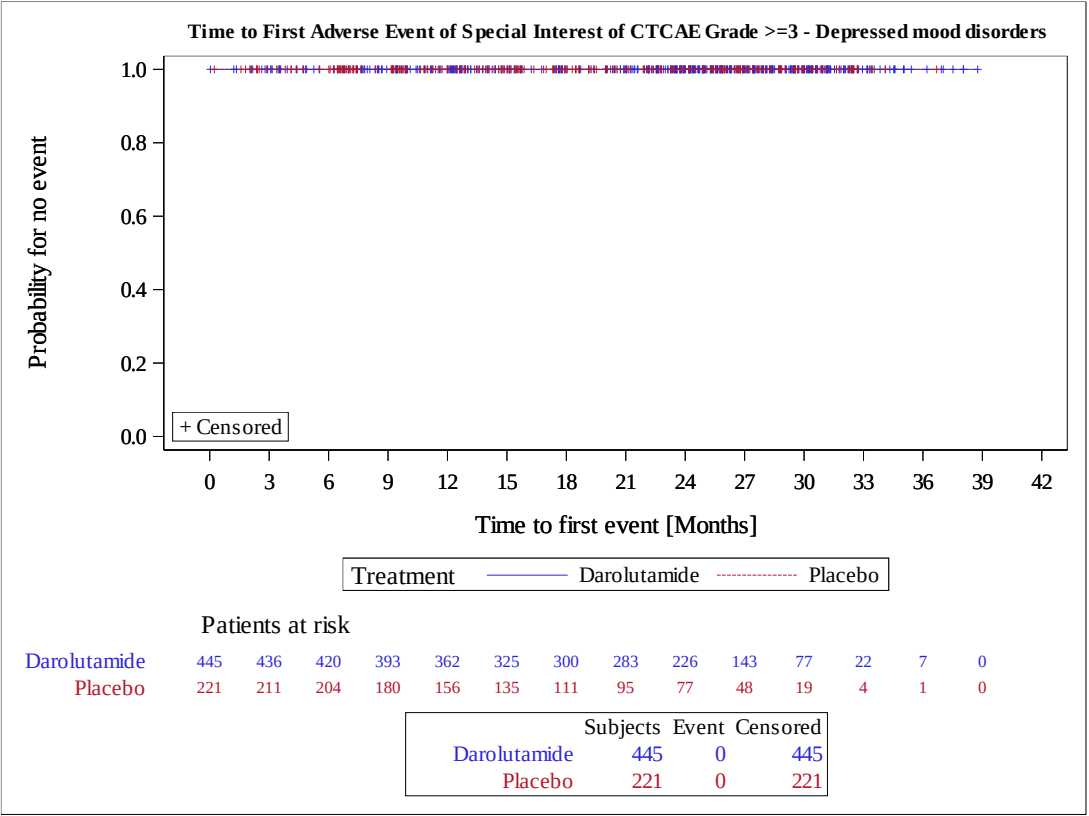
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.11.11.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Depressed mood disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.11.12
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Breast disorders/gynecomastia
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	445 (100.0)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.11.12.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥3 - Breast disorders/gynecomastia - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	
Presence of visceral metastases assessed by central review (from IWSR)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWSR)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
≥85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
≥ median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
≥1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason ≥8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR ≥ 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 ≤ eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 ≤ eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.11.12.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Breast disorders/gynecomastia - Subgroup analysis (safety analysis set)

Final

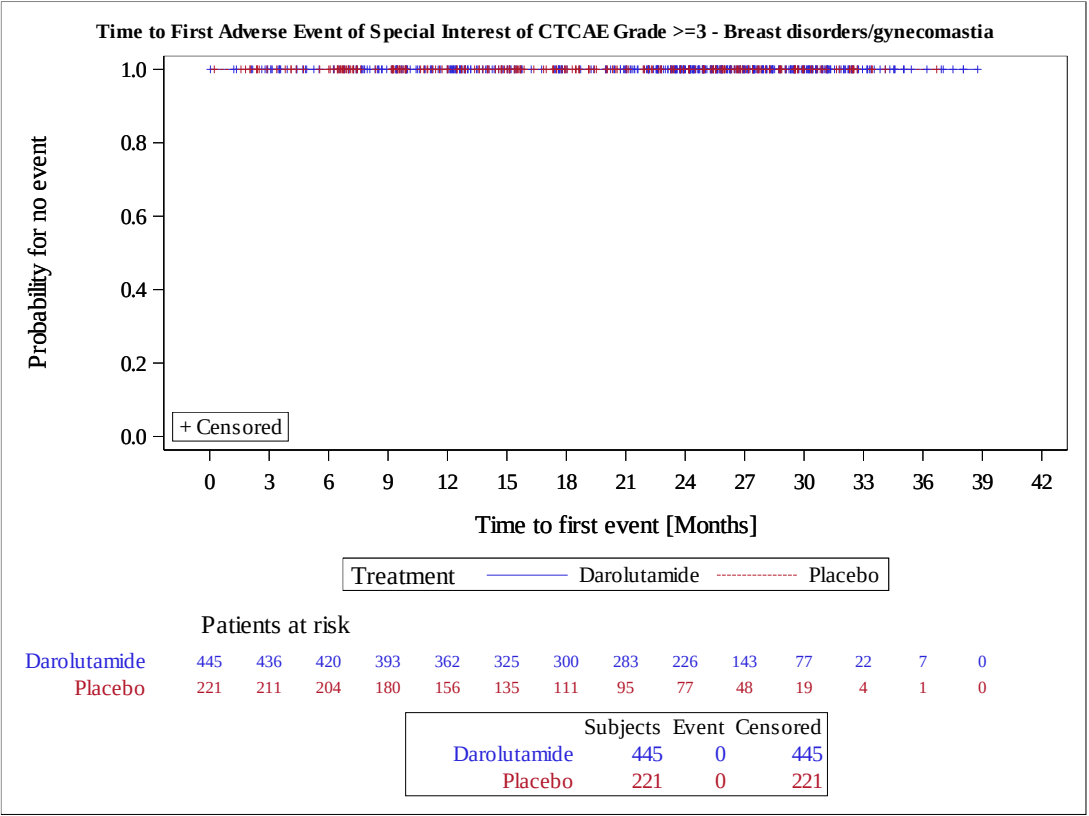
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.11.12.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Breast disorders/gynecomastia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.11.13
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Cardiac disorders
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	11 (2.5)	5 (2.3)
Number of censored patients, n (%)	434 (97.5)	216 (97.7)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.945	
95% CI	0.328, 2.724	
p-value	0.9166	
Odds Ratio	1.095	
95% CI	0.376, 3.191	
p-value	0.8680	
Relative Risk	1.093	
95% CI	0.384, 3.106	
p-value	0.8681	
Risk Difference	0.209	
95% CI	-2.225, 2.644	
p-value	0.8661	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.11.13.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Cardiac disorders - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	3/ 54 (5.6)	1/ 26 (3.8)	1.201	(0.125, 11.551)	0.8737	0.7557
No	8/391 (2.0)	4/195 (2.1)	0.865	(0.260, 2.880)	0.8129	
Received prior local therapy (from IWRS)						
Yes	3/ 80 (3.8)	1/ 40 (2.5)	1.235	(0.126, 12.077)	0.8556	0.7847
No	8/365 (2.2)	4/181 (2.2)	0.866	(0.260, 2.880)	0.8142	
Prior local radiotherapy and/or prostatectomy						
Yes	6/ 87 (6.9)	2/ 50 (4.0)				
No	5/358 (1.4)	3/171 (1.8)				
Age group						
<65 years	1/117 (0.9)	0/ 64 (0.0)				
65-74	4/193 (2.1)	3/ 95 (3.2)				
75-84	5/117 (4.3)	2/ 52 (3.8)				
>=85 years	1/ 18 (5.6)	0/ 10 (0.0)				
Race						
White	3/249 (1.2)	3/124 (2.4)				
Asian	6/144 (4.2)	1/ 65 (1.5)				
Black or African American	1/ 42 (2.4)	0/ 23 (0.0)				
Other	1/ 10 (10.0)	1/ 9 (11.1)				
Geographical region						
Asia	6/141 (4.3)	1/ 63 (1.6)				
Latin America	2/120 (1.7)	2/ 70 (2.9)				
Europe and Rest of the world	3/184 (1.6)	2/ 88 (2.3)				
Baseline PSA values by median						
< median of overall population	5/215 (2.3)	3/110 (2.7)				
>= median of overall population	6/219 (2.7)	2/108 (1.9)				
ECOG PS at baseline						
=0	7/235 (3.0)	1/ 96 (1.0)				
>=1	4/210 (1.9)	4/125 (3.2)				
Gleason score at initial diagnosis						
Gleason <8	2/124 (1.6)	2/ 65 (3.1)	0.468	(0.066, 3.334)	0.4377	0.2652
Gleason >=8	9/308 (2.9)	2/146 (1.4)	1.861	(0.401, 8.627)	0.4200	
Disease volume at baseline						
high	9/314 (2.9)	4/156 (2.6)	0.990	(0.304, 3.218)	0.9863	0.9196
low	2/131 (1.5)	1/ 65 (1.5)	0.765	(0.069, 8.487)	0.8266	
Renal function - eGFR at baseline						
Normal: eGFR >= 90 mL/min	6/221 (2.7)	1/102 (1.0)				
Mild impairment: 60 <= eGFR < 90 mL/min	4/178 (2.2)	3/ 91 (3.3)				
Moderate impairment: 30 <= eGFR < 60 mL/min	1/ 45 (2.2)	1/ 27 (3.7)				

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.11.13.1
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Cardiac disorders - Subgroup analysis
(safety analysis set)

Final

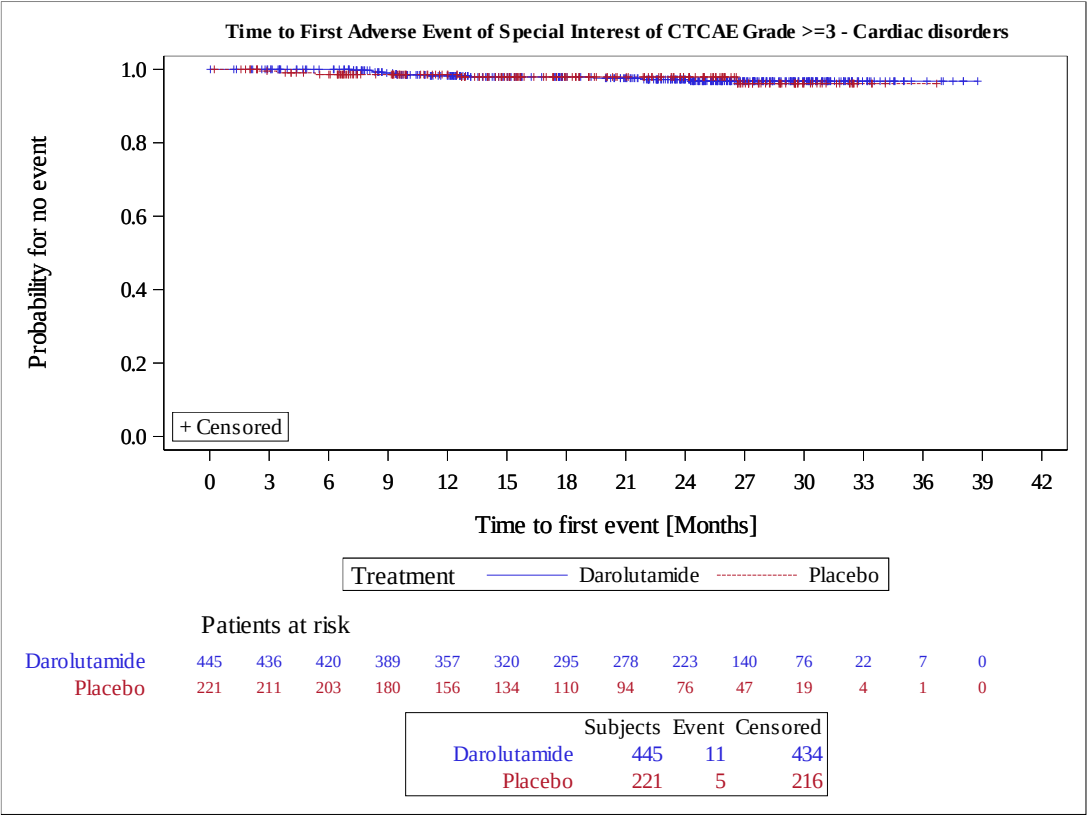
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.9899
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	9/387 (2.3)	5/202 (2.5)	0.805	(0.269, 2.409)	0.6978	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	2/ 58 (3.4)	0/ 19 (0.0)	NE	(NE, NE)	NE	
Age Group (Titan)						
<65	1/117 (0.9)	0/ 64 (0.0)				
>=65 and <75	4/193 (2.1)	3/ 95 (3.2)				
>=75	6/135 (4.4)	2/ 62 (3.2)				
Geographic region (Titan)						0.1792
Europe and north america	1/144 (0.7)	2/ 77 (2.6)	0.257	(0.023, 2.833)	0.2312	
ROTW	10/301 (3.3)	3/144 (2.1)	1.389	(0.382, 5.050)	0.6164	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.11.13.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade ≥ 3 - Cardiac disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.11.14
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Cerebral ischaemia
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	3 (1.4)
Number of censored patients, n (%)	445 (100.0)	218 (98.6)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	0.070	
95% CI	0.004, 1.362	
p-value	0.0791	
Relative Risk	0.071	
95% CI	0.004, 1.371	
p-value	0.0799	
Risk Difference	-1.357	
95% CI	-2.883, 0.168	
p-value	0.0812	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.2.11.14.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Cerebral ischaemia - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	1/ 26 (3.8)			
No	0/391 (0.0)	2/195 (1.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	3/181 (1.7)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	3/171 (1.8)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	3/ 95 (3.2)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	3/124 (2.4)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	3/ 88 (3.4)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	1/110 (0.9)			
>= median of overall population	0/219 (0.0)	2/108 (1.9)			
ECOG PS at baseline					
=0	0/235 (0.0)	2/ 96 (2.1)			
>=1	0/210 (0.0)	1/125 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	1/ 65 (1.5)			
Gleason >=8	0/308 (0.0)	2/146 (1.4)			
Disease volume at baseline					
high	0/314 (0.0)	3/156 (1.9)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	1/102 (1.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	1/ 91 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	1/ 27 (3.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.11.14.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Cerebral ischaemia - Subgroup analysis (safety analysis set)

Final

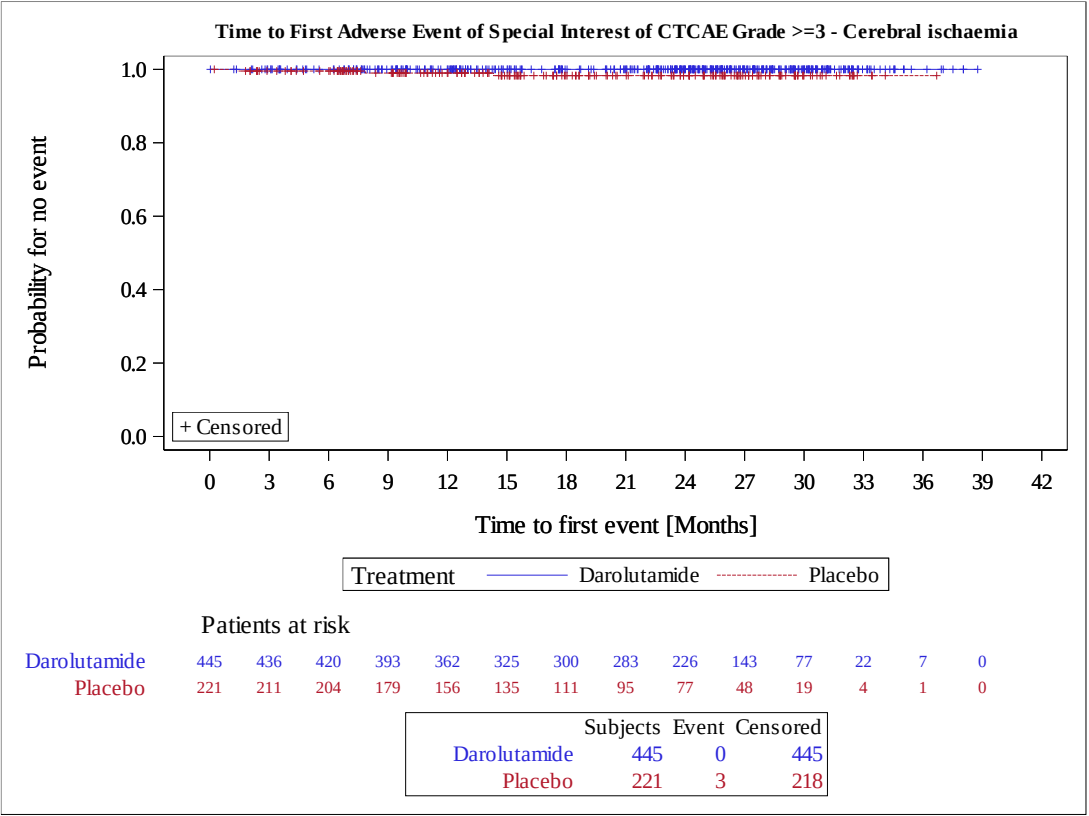
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI) p-Value	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	3/202 (1.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	3/ 95 (3.2)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	3/ 77 (3.9)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.11.14.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade ≥ 3 - Cerebral ischaemia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.11.15
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Cerebral and intracranial hemorrhage
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	2 (0.4)	1 (0.5)
Number of censored patients, n (%)	443 (99.6)	220 (99.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.831	
95% CI	0.075, 9.212	
p-value	0.8801	
Odds Ratio	0.993	
95% CI	0.090, 11.013	
p-value	0.9956	
Relative Risk	0.993	
95% CI	0.091, 10.895	
p-value	0.9956	
Risk Difference	-0.003	
95% CI	-1.084, 1.078	
p-value	0.9956	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.11.15.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥3 - Cerebral and intracranial hemorrhage - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	2/391 (0.5)	1/195 (0.5)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	2/365 (0.5)	1/181 (0.6)			
Prior local radiotherapy and/or prostatectomy					
Yes	2/ 87 (2.3)	0/ 50 (0.0)			
No	0/358 (0.0)	1/171 (0.6)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	1/117 (0.9)	0/ 52 (0.0)			
>=85 years	1/ 18 (5.6)	1/ 10 (10.0)			
Race					
White	1/249 (0.4)	0/124 (0.0)			
Asian	1/144 (0.7)	1/ 65 (1.5)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	1/141 (0.7)	1/ 63 (1.6)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	1/184 (0.5)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	2/215 (0.9)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	1/108 (0.9)			
ECOG PS at baseline					
=0	2/235 (0.9)	0/ 96 (0.0)			
>=1	0/210 (0.0)	1/125 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	1/ 65 (1.5)			
Gleason >=8	2/308 (0.6)	0/146 (0.0)			
Disease volume at baseline					
high	1/314 (0.3)	0/156 (0.0)			
low	1/131 (0.8)	1/ 65 (1.5)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	2/178 (1.1)	1/ 91 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.11.15.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Cerebral and intracranial hemorrhage - Subgroup analysis (safety analysis set)

Final

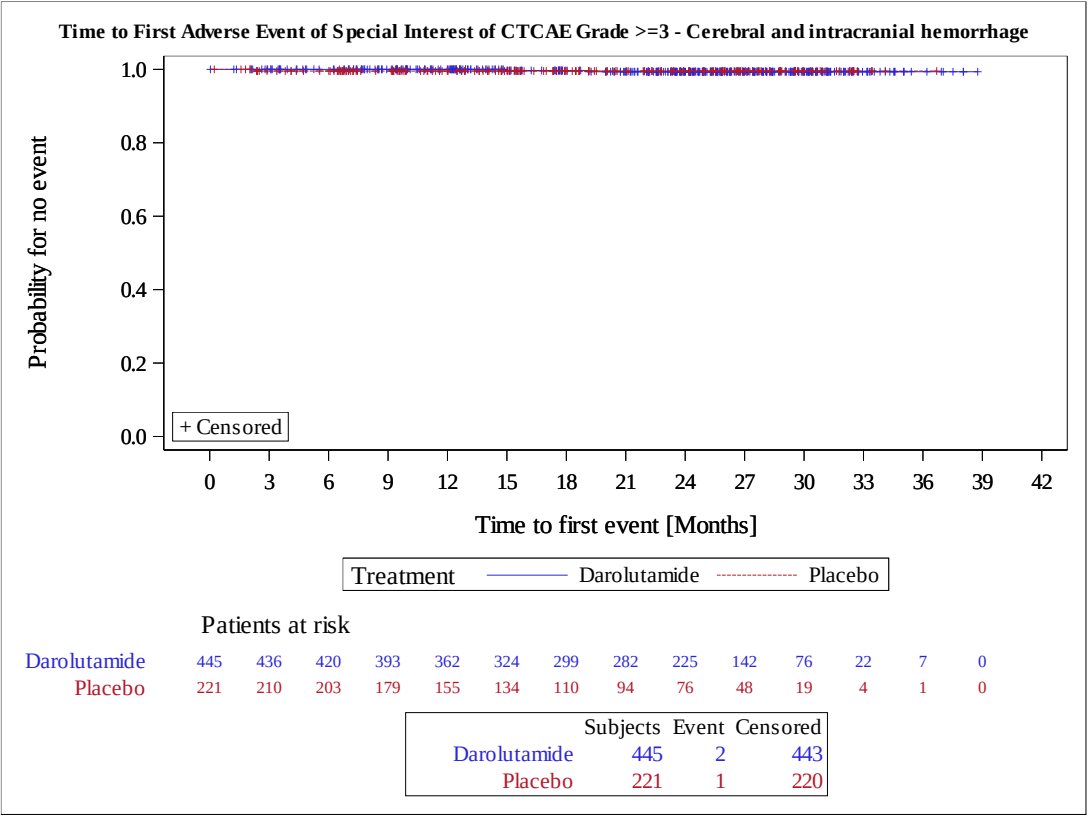
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	1/387 (0.3)	1/202 (0.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 58 (1.7)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	2/135 (1.5)	1/ 62 (1.6)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	2/301 (0.7)	1/144 (0.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.2.11.15.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Cerebral and intracranial hemorrhage
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.2.11.16
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Interstitial lung disease
(safety analysis set)

Final

	Darolutamide (N=445)	Placebo (N=221)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	445 (100.0)	221 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.11.16.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥3 - Interstitial lung disease - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=445)	Placebo (N=221)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/391 (0.0)	0/195 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 80 (0.0)	0/ 40 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 87 (0.0)	0/ 50 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/117 (0.0)	0/ 52 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/249 (0.0)	0/124 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/184 (0.0)	0/ 88 (0.0)			
Baseline PSA values by median					
< median of overall population	0/215 (0.0)	0/110 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/210 (0.0)	0/125 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/124 (0.0)	0/ 65 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/314 (0.0)	0/156 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/178 (0.0)	0/ 91 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Table 3.2.11.16.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Interstitial lung disease - Subgroup analysis (safety analysis set)

Final

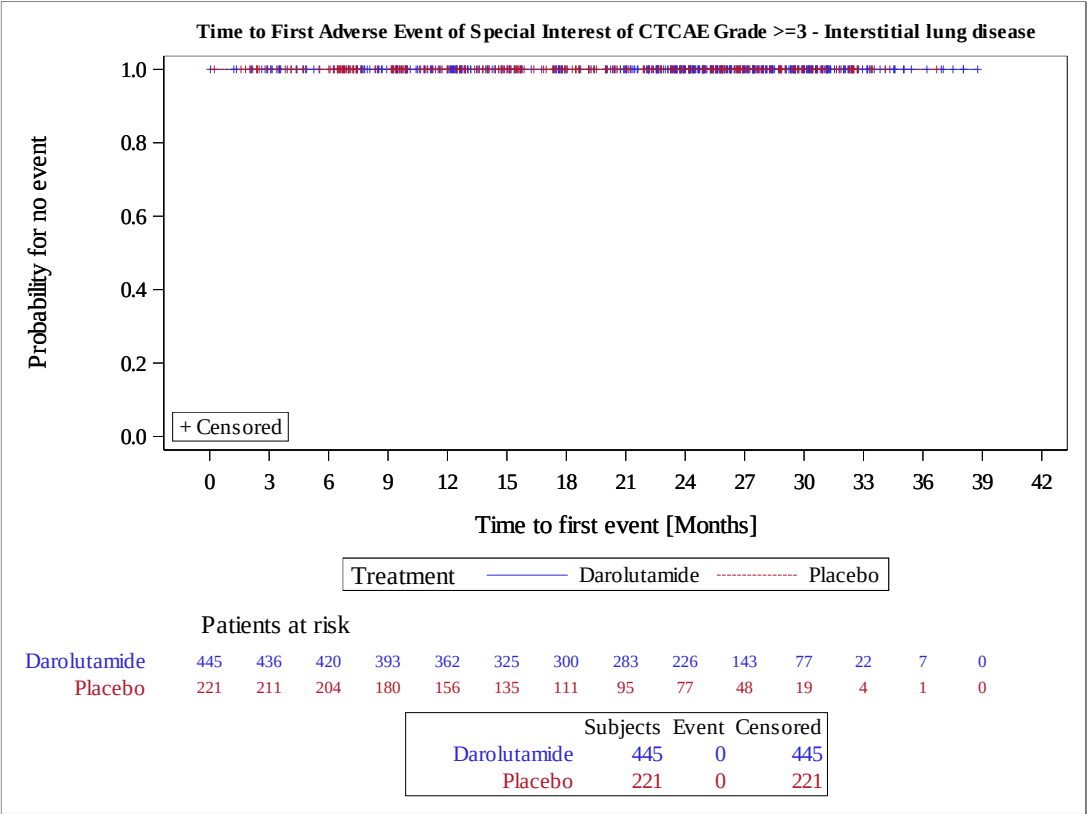
Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/202 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 58 (0.0)	0/ 19 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/135 (0.0)	0/ 62 (0.0)			
Geographic region (Titan)					
Europe and north america	0/144 (0.0)	0/ 77 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Figure 3.2.11.16.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Interstitial lung disease
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Blood and lymphatic system disorders	Number of subjects with events, n (%)	105 (23.6)	43 (19.5)
	Number of censored subjects, n (%)	340 (76.4)	178 (80.5)
	Time to Event (Month)		
	25%-ile (95%-CI)	22.2 (17.1, NE)	27.9 (16.5, NE)
	Median (95%-CI)	NE (35.2, NE)	NE (31.0, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.092	
	95% CI	0.765, 1.558	
	p-value	0.6276	
	Odds Ratio	1.278	
	95% CI	0.858, 1.904	
	p-value	0.2271	
	Relative Risk	1.213	
	95% CI	0.884, 1.664	
	p-value	0.2318	
	Risk Difference	4.138	
	95% CI	-2.404, 10.681	
	p-value	0.2150	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Blood and lymphatic system disorders - PT:Anaemia	Number of subjects with events, n (%)	91 (20.4)	39 (17.6)
	Number of censored subjects, n (%)	354 (79.6)	182 (82.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	35.2 (21.2, NE)	28.4 (17.0, NE)
	Median (95%-CI)	NE (35.2, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.035	
	95% CI	0.710, 1.507	
	p-value	0.8585	
	Odds Ratio	1.200	
	95% CI	0.792, 1.818	
	p-value	0.3906	
	Relative Risk	1.159	
	95% CI	0.826, 1.626	
	p-value	0.3937	
	Risk Difference	2.802	
	95% CI	-3.467, 9.072	
	p-value	0.3810	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Blood and lymphatic system disorders - PT:Leukopenia*	Number of subjects with events, n (%)	7 (1.6)	3 (1.4)
	Number of censored subjects, n (%)	438 (98.4)	218 (98.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.013	
	95% CI	0.261, 3.929	
	p-value	0.9853	
	Odds Ratio	1.161	
	95% CI	0.297, 4.535	
	p-value	0.8296	
	Relative Risk	1.159	
	95% CI	0.303, 4.438	
	p-value	0.8297	
	Risk Difference	0.216	
	95% CI	-1.699, 2.130	
	p-value	0.8253	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Blood and lymphatic system disorders - PT:Neutropenia*	Number of subjects with events, n (%) 6 (1.3)	4 (1.8)
	Number of censored subjects, n (%) 439 (98.7)	217 (98.2)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	0.610 0.171, 2.170 0.4406
	Odds Ratio 95% CI p-value	0.741 0.207, 2.655 0.6458
	Relative Risk 95% CI p-value	0.745 0.212, 2.613 0.6456
	Risk Difference 95% CI p-value	-0.462 -2.520, 1.597 0.6603

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Blood and lymphatic system disorders - PT:Thrombocytopenia	Number of subjects with events, n (%)	10 (2.2)	3 (1.4)
	Number of censored subjects, n (%)	435 (97.8)	218 (98.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.438	
	95% CI	0.395, 5.241	
	p-value	0.5793	
	Odds Ratio	1.670	
	95% CI	0.455, 6.132	
	p-value	0.4393	
	Relative Risk	1.655	
	95% CI	0.460, 5.954	
	p-value	0.4402	
	Risk Difference	0.890	
	95% CI	-1.165, 2.945	
	p-value	0.3962	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Cardiac disorders	Number of subjects with events, n (%)	59 (13.3)	20 (9.0)
	Number of censored subjects, n (%)	386 (86.7)	201 (91.0)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.294	
	95% CI	0.779, 2.151	
	p-value	0.3175	
	Odds Ratio	1.536	
	95% CI	0.900, 2.623	
	p-value	0.1158	
	Relative Risk	1.465	
	95% CI	0.906, 2.370	
	p-value	0.1195	
	Risk Difference	4.209	
	95% CI	-0.714, 9.132	
	p-value	0.0938	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Ear and labyrinth disorders*		
Number of subjects with events, n (%)	6 (1.3)	1 (0.5)
Number of censored subjects, n (%)	439 (98.7)	220 (99.5)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	2.406	
95% CI	0.289, 20.046	
p-value	0.4023	
Odds Ratio	3.007	
95% CI	0.360, 25.130	
p-value	0.3095	
Relative Risk	2.980	
95% CI	0.361, 24.599	
p-value	0.3107	
Risk Difference	0.896	
95% CI	-0.494, 2.286	
p-value	0.2064	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Eye disorders	Number of subjects with events, n (%)	16 (3.6)	5 (2.3)
	Number of censored subjects, n (%)	429 (96.4)	216 (97.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.420	
	95% CI	0.519, 3.881	
	p-value	0.4924	
	Odds Ratio	1.611	
	95% CI	0.582, 4.457	
	p-value	0.3582	
	Relative Risk	1.589	
	95% CI	0.590, 4.282	
	p-value	0.3596	
	Risk Difference	1.333	
	95% CI	-1.281, 3.948	
	p-value	0.3176	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Gastrointestinal disorders	Number of subjects with events, n (%)	106 (23.8)	49 (22.2)
	Number of censored subjects, n (%)	339 (76.2)	172 (77.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	22.2 (15.2, NE)	19.2 (13.4, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.962	
	95% CI	0.686, 1.351	
	p-value	0.8256	
	Odds Ratio	1.098	
	95% CI	0.747, 1.613	
	p-value	0.6356	
	Relative Risk	1.074	
	95% CI	0.798, 1.447	
	p-value	0.6369	
	Risk Difference	1.648	
	95% CI	-5.109, 8.405	
	p-value	0.6326	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Gastrointestinal disorders - PT:Abdominal pain upper*	Number of subjects with events, n (%) 7 (1.6)	1 (0.5)
	Number of censored subjects, n (%) 438 (98.4)	220 (99.5)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	3.310 0.407, 26.904 0.2348
	Odds Ratio 95% CI p-value	3.516 0.430, 28.756 0.2409
	Relative Risk 95% CI p-value	3.476 0.430, 28.080 0.2424
	Risk Difference 95% CI p-value	1.121 -0.335, 2.576 0.1314

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Gastrointestinal disorders - PT:Abdominal pain*		
Number of subjects with events, n (%)	8 (1.8)	5 (2.3)
Number of censored subjects, n (%)	437 (98.2)	216 (97.7)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.649	
95% CI	0.212, 1.989	
p-value	0.4458	
Odds Ratio	0.791	
95% CI	0.256, 2.446	
p-value	0.6838	
Relative Risk	0.795	
95% CI	0.263, 2.401	
p-value	0.6836	
Risk Difference	-0.465	
95% CI	-2.782, 1.852	
p-value	0.6942	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Gastrointestinal disorders - PT:Constipation	Number of subjects with events, n (%)	42 (9.4)	16 (7.2)
	Number of censored subjects, n (%)	403 (90.6)	205 (92.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.182	
	95% CI	0.664, 2.103	
	p-value	0.5698	
	Odds Ratio	1.335	
	95% CI	0.733, 2.433	
	p-value	0.3448	
	Relative Risk	1.304	
	95% CI	0.750, 2.266	
	p-value	0.3471	
	Risk Difference	2.198	
	95% CI	-2.166, 6.563	
	p-value	0.3236	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Gastrointestinal disorders - PT:Diarrhoea	Number of subjects with events, n (%)	15 (3.4)	7 (3.2)
	Number of censored subjects, n (%)	430 (96.6)	214 (96.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.929	
	95% CI	0.378, 2.283	
	p-value	0.8723	
	Odds Ratio	1.066	
	95% CI	0.428, 2.655	
	p-value	0.8900	
	Relative Risk	1.064	
	95% CI	0.440, 2.572	
	p-value	0.8901	
	Risk Difference	0.203	
	95% CI	-2.650, 3.057	
	p-value	0.8889	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Gastrointestinal disorders - PT:Dyspepsia*		
Number of subjects with events, n (%)	5 (1.1)	3 (1.4)
Number of censored subjects, n (%)	440 (98.9)	218 (98.6)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.792	
95% CI	0.189, 3.314	
p-value	0.7487	
Odds Ratio	0.826	
95% CI	0.196, 3.487	
p-value	0.7945	
Relative Risk	0.828	
95% CI	0.200, 3.432	
p-value	0.7944	
Risk Difference	-0.234	
95% CI	-2.047, 1.579	
p-value	0.8004	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Gastrointestinal disorders - PT:Nausea	Number of subjects with events, n (%)	11 (2.5)	5 (2.3)
	Number of censored subjects, n (%)	434 (97.5)	216 (97.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.975	
	95% CI	0.338, 2.810	
	p-value	0.9622	
	Odds Ratio	1.095	
	95% CI	0.376, 3.191	
	p-value	0.8680	
	Relative Risk	1.093	
	95% CI	0.384, 3.106	
	p-value	0.8681	
	Risk Difference	0.209	
	95% CI	-2.225, 2.644	
	p-value	0.8661	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Gastrointestinal disorders - PT:Vomiting*	Number of subjects with events, n (%) 5 (1.1)	3 (1.4)
	Number of censored subjects, n (%) 440 (98.9)	218 (98.6)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	0.714 0.170, 2.995 0.6432
	Odds Ratio 95% CI p-value	0.826 0.196, 3.487 0.7945
	Relative Risk 95% CI p-value	0.828 0.200, 3.432 0.7944
	Risk Difference 95% CI p-value	-0.234 -2.047, 1.579 0.8004

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: General disorders and administration site conditions	Number of subjects with events, n (%)	106 (23.8)	52 (23.5)
	Number of censored subjects, n (%)	339 (76.2)	169 (76.5)
	Time to Event (Month)		
	25%-ile (95%-CI)	23.9 (19.2, 32.2)	18.4 (10.9, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.881	
	95% CI	0.631, 1.228	
	p-value	0.4536	
	Odds Ratio	1.016	
	95% CI	0.695, 1.486	
	p-value	0.9338	
	Relative Risk	1.012	
	95% CI	0.758, 1.353	
	p-value	0.9338	
	Risk Difference	0.291	
	95% CI	-6.561, 7.142	
	p-value	0.9337	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: General disorders and administration site conditions - PT:Asthenia	Number of subjects with events, n (%)	15 (3.4)	9 (4.1)
	Number of censored subjects, n (%)	430 (96.6)	212 (95.9)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.705	
	95% CI	0.308, 1.615	
	p-value	0.4065	
	Odds Ratio	0.822	
	95% CI	0.354, 1.908	
	p-value	0.6478	
	Relative Risk	0.828	
	95% CI	0.368, 1.862	
	p-value	0.6475	
	Risk Difference	-0.702	
	95% CI	-3.800, 2.397	
	p-value	0.6572	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: General disorders and administration site conditions - PT:Fatigue	Number of subjects with events, n (%)	25 (5.6)	18 (8.1)
	Number of censored subjects, n (%)	420 (94.4)	203 (91.9)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.618	
	95% CI	0.337, 1.135	
	p-value	0.1172	
	Odds Ratio	0.671	
	95% CI	0.358, 1.259	
	p-value	0.2140	
	Relative Risk	0.690	
	95% CI	0.385, 1.237	
	p-value	0.2126	
	Risk Difference	-2.527	
	95% CI	-6.720, 1.666	
	p-value	0.2376	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: General disorders and administration site conditions - PT:Influenza like illness*	Number of subjects with events, n (%)	5 (1.1)	3 (1.4)
	Number of censored subjects, n (%)	440 (98.9)	218 (98.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.726	
	95% CI	0.173, 3.048	
	p-value	0.6609	
	Odds Ratio	0.826	
	95% CI	0.196, 3.487	
	p-value	0.7945	
	Relative Risk	0.828	
	95% CI	0.200, 3.432	
	p-value	0.7944	
	Risk Difference	-0.234	
	95% CI	-2.047, 1.579	
	p-value	0.8004	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: General disorders and administration site conditions - PT:Oedema peripheral	Number of subjects with events, n (%)	19 (4.3)	7 (3.2)
	Number of censored subjects, n (%)	426 (95.7)	214 (96.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.211	
	95% CI	0.508, 2.885	
	p-value	0.6651	
	Odds Ratio	1.364	
	95% CI	0.564, 3.294	
	p-value	0.4908	
	Relative Risk	1.348	
	95% CI	0.575, 3.158	
	p-value	0.4918	
	Risk Difference	1.102	
	95% CI	-1.874, 4.079	
	p-value	0.4680	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: General disorders and administration site conditions - PT:Pain	Number of subjects with events, n (%)	12 (2.7)	5 (2.3)
	Number of censored subjects, n (%)	433 (97.3)	216 (97.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.049	
	95% CI	0.369, 2.984	
	p-value	0.9273	
	Odds Ratio	1.197	
	95% CI	0.416, 3.442	
	p-value	0.7383	
	Relative Risk	1.192	
	95% CI	0.425, 3.341	
	p-value	0.7385	
	Risk Difference	0.434	
	95% CI	-2.037, 2.906	
	p-value	0.7306	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: General disorders and administration site conditions - PT:Pyrexia	Number of subjects with events, n (%)	20 (4.5)	7 (3.2)
	Number of censored subjects, n (%)	425 (95.5)	214 (96.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.198	
	95% CI	0.506, 2.841	
	p-value	0.6806	
	Odds Ratio	1.439	
	95% CI	0.599, 3.456	
	p-value	0.4159	
	Relative Risk	1.419	
	95% CI	0.609, 3.305	
	p-value	0.4173	
	Risk Difference	1.327	
	95% CI	-1.679, 4.333	
	p-value	0.3869	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Hepatobiliary disorders		
Number of subjects with events, n (%)	25 (5.6)	1 (0.5)
Number of censored subjects, n (%)	420 (94.4)	220 (99.5)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	11.040	
95% CI	1.495, 81.529	
p-value	0.0031	
Odds Ratio	13.095	
95% CI	1.763, 97.288	
p-value	0.0119	
Relative Risk	12.416	
95% CI	1.693, 91.033	
p-value	0.0132	
Risk Difference	5.165	
95% CI	2.850, 7.481	
p-value	<.0001	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Infections and infestations	Number of subjects with events, n (%)	152 (34.2)	57 (25.8)
	Number of censored subjects, n (%)	293 (65.8)	164 (74.2)
	Time to Event (Month)		
	25%-ile (95%-CI)	13.8 (10.6, 17.3)	15.2 (8.5, NE)
	Median (95%-CI)	35.4 (30.3, NE)	NE (32.1, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.165	
	95% CI	0.859, 1.581	
	p-value	0.3260	
	Odds Ratio	1.493	
	95% CI	1.042, 2.138	
	p-value	0.0290	
	Relative Risk	1.324	
	95% CI	1.023, 1.714	
	p-value	0.0330	
	Risk Difference	8.365	
	95% CI	1.107, 15.624	
	p-value	0.0239	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Infections and infestations - PT:Bronchitis*		
Number of subjects with events, n (%)	3 (0.7)	1 (0.5)
Number of censored subjects, n (%)	442 (99.3)	220 (99.5)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.299	
95% CI	0.135, 12.517	
p-value	0.8206	
Odds Ratio	1.493	
95% CI	0.154, 14.438	
p-value	0.7291	
Relative Risk	1.490	
95% CI	0.156, 14.241	
p-value	0.7292	
Risk Difference	0.222	
95% CI	-0.945, 1.388	
p-value	0.7096	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Infections and infestations - PT:COVID-19	Number of subjects with events, n (%)	32 (7.2)	15 (6.8)
	Number of censored subjects, n (%)	413 (92.8)	206 (93.2)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.954	
	95% CI	0.516, 1.762	
	p-value	0.8808	
	Odds Ratio	1.064	
	95% CI	0.564, 2.009	
	p-value	0.8481	
	Relative Risk	1.059	
	95% CI	0.586, 1.915	
	p-value	0.8482	
	Risk Difference	0.404	
	95% CI	-3.690, 4.497	
	p-value	0.8467	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Infections and infestations - PT:Herpes zoster*	Number of subjects with events, n (%) 7 (1.6)	1 (0.5)
	Number of censored subjects, n (%) 438 (98.4)	220 (99.5)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	3.047 0.374, 24.804 0.2732
	Odds Ratio 95% CI p-value	3.516 0.430, 28.756 0.2409
	Relative Risk 95% CI p-value	3.476 0.430, 28.080 0.2424
	Risk Difference 95% CI p-value	1.121 -0.335, 2.576 0.1314

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Infections and infestations - PT:Influenza*		
Number of subjects with events, n (%)	6 (1.3)	1 (0.5)
Number of censored subjects, n (%)	439 (98.7)	220 (99.5)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	2.644	
95% CI	0.317, 22.024	
p-value	0.3500	
Odds Ratio	3.007	
95% CI	0.360, 25.130	
p-value	0.3095	
Relative Risk	2.980	
95% CI	0.361, 24.599	
p-value	0.3107	
Risk Difference	0.896	
95% CI	-0.494, 2.286	
p-value	0.2064	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Infections and infestations - PT:Pneumonia	Number of subjects with events, n (%)	16 (3.6)	2 (0.9)
	Number of censored subjects, n (%)	429 (96.4)	219 (99.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	3.294	
	95% CI	0.756, 14.345	
	p-value	0.0923	
	Odds Ratio	4.084	
	95% CI	0.931, 17.922	
	p-value	0.0622	
	Relative Risk	3.973	
	95% CI	0.922, 17.127	
	p-value	0.0642	
	Risk Difference	2.691	
	95% CI	0.557, 4.824	
	p-value	0.0134	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Infections and infestations - PT:Upper respiratory tract infection	Number of subjects with events, n (%)	12 (2.7)	2 (0.9)
	Number of censored subjects, n (%)	433 (97.3)	219 (99.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	2.522	
	95% CI	0.564, 11.279	
	p-value	0.2100	
	Odds Ratio	3.035	
	95% CI	0.673, 13.679	
	p-value	0.1485	
	Relative Risk	2.980	
	95% CI	0.673, 13.198	
	p-value	0.1505	
	Risk Difference	1.792	
	95% CI	-0.164, 3.747	
	p-value	0.0725	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Infections and infestations - PT:Urinary tract infection	Number of subjects with events, n (%)	52 (11.7)	17 (7.7)
	Number of censored subjects, n (%)	393 (88.3)	204 (92.3)
	Time to Event (Month)		
	25%-ile (95%-CI)	35.4 (35.4, NE)	NE (NE, NE)
	Median (95%-CI)	NE (35.4, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.312	
	95% CI	0.757, 2.274	
	p-value	0.3308	
	Odds Ratio	1.588	
	95% CI	0.895, 2.816	
	p-value	0.1138	
	Relative Risk	1.519	
	95% CI	0.900, 2.564	
	p-value	0.1173	
	Risk Difference	3.993	
	95% CI	-0.617, 8.603	
	p-value	0.0896	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Injury, poisoning and procedural complications	Number of subjects with events, n (%)	34 (7.6)	18 (8.1)
	Number of censored subjects, n (%)	411 (92.4)	203 (91.9)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.792	
	95% CI	0.446, 1.404	
	p-value	0.4235	
	Odds Ratio	0.933	
	95% CI	0.514, 1.692	
	p-value	0.8193	
	Relative Risk	0.938	
	95% CI	0.542, 1.623	
	p-value	0.8192	
	Risk Difference	-0.504	
	95% CI	-4.874, 3.866	
	p-value	0.8210	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Injury, poisoning and procedural complications - PT:Contusion*	Number of subjects with events, n (%) 1 (0.2)	1 (0.5)
	Number of censored subjects, n (%) 444 (99.8)	220 (99.5)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	0.414 0.026, 6.702 0.5220
	Odds Ratio 95% CI p-value	0.495 0.031, 7.959 0.6201
	Relative Risk 95% CI p-value	0.497 0.031, 7.903 0.6201
	Risk Difference 95% CI p-value	-0.228 -1.216, 0.760 0.6514

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Injury, poisoning and procedural complications - PT:Fall*	Number of subjects with events, n (%) 5 (1.1)	2 (0.9)
	Number of censored subjects, n (%) 440 (98.9)	219 (99.1)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	1.106 0.214, 5.713 0.9044
	Odds Ratio 95% CI p-value	1.244 0.239, 6.465 0.7949
	Relative Risk 95% CI p-value	1.242 0.243, 6.349 0.7950
	Risk Difference 95% CI p-value	0.219 -1.368, 1.805 0.7871

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Injury, poisoning and procedural complications - PT:Rib fracture*	Number of subjects with events, n (%)	6 (1.3)	3 (1.4)
	Number of censored subjects, n (%)	439 (98.7)	218 (98.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.877	
	95% CI	0.219, 3.516	
	p-value	0.8530	
	Odds Ratio	0.993	
	95% CI	0.246, 4.009	
	p-value	0.9923	
	Relative Risk	0.993	
	95% CI	0.251, 3.934	
	p-value	0.9923	
	Risk Difference	-0.009	
	95% CI	-1.873, 1.855	
	p-value	0.9923	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Investigations	Number of subjects with events, n (%)	149 (33.5)	73 (33.0)
	Number of censored subjects, n (%)	296 (66.5)	148 (67.0)
	Time to Event (Month)		
	25%-ile (95%-CI)	11.1 (8.4, 14.4)	9.0 (6.2, 14.8)
	Median (95%-CI)	NE (NE, NE)	NE (24.9, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.891	
	95% CI	0.673, 1.180	
	p-value	0.4206	
	Odds Ratio	1.021	
	95% CI	0.725, 1.437	
	p-value	0.9074	
	Relative Risk	1.014	
	95% CI	0.806, 1.274	
	p-value	0.9075	
	Risk Difference	0.451	
	95% CI	-7.143, 8.046	
	p-value	0.9072	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Investigations - PT:Alanine aminotransferase increased	Number of subjects with events, n (%)	40 (9.0)	18 (8.1)
	Number of censored subjects, n (%)	405 (91.0)	203 (91.9)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.024	
	95% CI	0.587, 1.787	
	p-value	0.9340	
	Odds Ratio	1.114	
	95% CI	0.623, 1.992	
	p-value	0.7162	
	Relative Risk	1.104	
	95% CI	0.648, 1.879	
	p-value	0.7166	
	Risk Difference	0.844	
	95% CI	-3.636, 5.324	
	p-value	0.7119	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Investigations - PT:Aspartate aminotransferase increased	Number of subjects with events, n (%)	43 (9.7)	17 (7.7)
	Number of censored subjects, n (%)	402 (90.3)	204 (92.3)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.120	
	95% CI	0.638, 1.966	
	p-value	0.6916	
	Odds Ratio	1.284	
	95% CI	0.714, 2.307	
	p-value	0.4039	
	Relative Risk	1.256	
	95% CI	0.734, 2.151	
	p-value	0.4059	
	Risk Difference	1.971	
	95% CI	-2.488, 6.429	
	p-value	0.3863	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Investigations - PT:Blood alkaline phosphatase increased	Number of subjects with events, n (%)	30 (6.7)	13 (5.9)
	Number of censored subjects, n (%)	415 (93.3)	208 (94.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.974	
	95% CI	0.507, 1.869	
	p-value	0.9364	
	Odds Ratio	1.157	
	95% CI	0.591, 2.264	
	p-value	0.6712	
	Relative Risk	1.146	
	95% CI	0.610, 2.153	
	p-value	0.6717	
	Risk Difference	0.859	
	95% CI	-3.020, 4.739	
	p-value	0.6642	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Investigations - PT:Blood bilirubin increased	Number of subjects with events, n (%)	19 (4.3)	2 (0.9)
	Number of censored subjects, n (%)	426 (95.7)	219 (99.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	4.128	
	95% CI	0.961, 17.738	
	p-value	0.0385	
	Odds Ratio	4.884	
	95% CI	1.127, 21.158	
	p-value	0.0340	
	Relative Risk	4.718	
	95% CI	1.109, 20.074	
	p-value	0.0357	
	Risk Difference	3.365	
	95% CI	1.109, 5.620	
	p-value	0.0035	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Investigations - PT:Blood creatinine increased	Number of subjects with events, n (%)	21 (4.7)	15 (6.8)
	Number of censored subjects, n (%)	424 (95.3)	206 (93.2)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.593	
	95% CI	0.305, 1.153	
	p-value	0.1192	
	Odds Ratio	0.680	
	95% CI	0.344, 1.347	
	p-value	0.2689	
	Relative Risk	0.695	
	95% CI	0.366, 1.322	
	p-value	0.2677	
	Risk Difference	-2.068	
	95% CI	-5.926, 1.789	
	p-value	0.2933	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Investigations - PT:Blood lactate dehydrogenase increased	Number of subjects with events, n (%)	11 (2.5)	2 (0.9)
	Number of censored subjects, n (%)	434 (97.5)	219 (99.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	2.348	
	95% CI	0.520, 10.609	
	p-value	0.2526	
	Odds Ratio	2.775	
	95% CI	0.610, 12.631	
	p-value	0.1867	
	Relative Risk	2.731	
	95% CI	0.611, 12.217	
	p-value	0.1886	
	Risk Difference	1.567	
	95% CI	-0.341, 3.475	
	p-value	0.1075	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Investigations - PT:Platelet count decreased		
Number of subjects with events, n (%)	10 (2.2)	2 (0.9)
Number of censored subjects, n (%)	435 (97.8)	219 (99.1)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	2.200	
95% CI	0.481, 10.052	
p-value	0.2967	
Odds Ratio	2.517	
95% CI	0.547, 11.588	
p-value	0.2360	
Relative Risk	2.483	
95% CI	0.549, 11.236	
p-value	0.2377	
Risk Difference	1.342	
95% CI	-0.517, 3.201	
p-value	0.1570	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Investigations - PT:Weight decreased	Number of subjects with events, n (%)	14 (3.1)	6 (2.7)
	Number of censored subjects, n (%)	431 (96.9)	215 (97.3)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.994	
	95% CI	0.381, 2.590	
	p-value	0.9898	
	Odds Ratio	1.164	
	95% CI	0.441, 3.071	
	p-value	0.7591	
	Relative Risk	1.159	
	95% CI	0.451, 2.974	
	p-value	0.7593	
	Risk Difference	0.431	
	95% CI	-2.256, 3.118	
	p-value	0.7532	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Investigations - PT:Weight increased	Number of subjects with events, n (%)	33 (7.4)	17 (7.7)
	Number of censored subjects, n (%)	412 (92.6)	204 (92.3)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.880	
	95% CI	0.490, 1.581	
	p-value	0.6688	
	Odds Ratio	0.961	
	95% CI	0.523, 1.767	
	p-value	0.8985	
	Relative Risk	0.964	
	95% CI	0.549, 1.692	
	p-value	0.8985	
	Risk Difference	-0.277	
	95% CI	-4.551, 3.998	
	p-value	0.8991	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Metabolism and nutrition disorders	Number of subjects with events, n (%)	107 (24.0)	46 (20.8)
	Number of censored subjects, n (%)	338 (76.0)	175 (79.2)
	Time to Event (Month)		
	25%-ile (95%-CI)	21.6 (14.8, 32.2)	26.5 (13.8, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.015	
	95% CI	0.718, 1.435	
	p-value	0.9314	
	Odds Ratio	1.204	
	95% CI	0.815, 1.780	
	p-value	0.3511	
	Relative Risk	1.155	
	95% CI	0.851, 1.568	
	p-value	0.3548	
	Risk Difference	3.230	
	95% CI	-3.434, 9.895	
	p-value	0.3421	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Metabolism and nutrition disorders - PT:Decreased appetite	Number of subjects with events, n (%)	14 (3.1)	9 (4.1)
	Number of censored subjects, n (%)	431 (96.9)	212 (95.9)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.682	
	95% CI	0.295, 1.578	
	p-value	0.3684	
	Odds Ratio	0.765	
	95% CI	0.326, 1.796	
	p-value	0.5387	
	Relative Risk	0.773	
	95% CI	0.340, 1.757	
	p-value	0.5382	
	Risk Difference	-0.926	
	95% CI	-3.996, 2.143	
	p-value	0.5542	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Metabolism and nutrition disorders - PT:Hypercholesterolaemia*	Number of subjects with events, n (%) 7 (1.6)	3 (1.4)
	Number of censored subjects, n (%) 438 (98.4)	218 (98.6)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (33.3, NE) NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	0.976 0.251, 3.795 0.9723
	Odds Ratio 95% CI p-value	1.161 0.297, 4.535 0.8296
	Relative Risk 95% CI p-value	1.159 0.303, 4.438 0.8297
	Risk Difference 95% CI p-value	0.216 -1.699, 2.130 0.8253

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Metabolism and nutrition disorders - PT:Hyperglycaemia		
Number of subjects with events, n (%)	27 (6.1)	8 (3.6)
Number of censored subjects, n (%)	418 (93.9)	213 (96.4)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.483	
95% CI	0.673, 3.267	
p-value	0.3246	
Odds Ratio	1.720	
95% CI	0.768, 3.851	
p-value	0.1874	
Relative Risk	1.676	
95% CI	0.774, 3.628	
p-value	0.1899	
Risk Difference	2.448	
95% CI	-0.867, 5.762	
p-value	0.1478	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Metabolism and nutrition disorders - PT:Hyperkalaemia*	Number of subjects with events, n (%) 8 (1.8)	8 (3.6)
	Number of censored subjects, n (%) 437 (98.2)	213 (96.4)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	0.420 0.157, 1.121 0.0739
	Odds Ratio 95% CI p-value	0.487 0.180, 1.316 0.1563
	Relative Risk 95% CI p-value	0.497 0.189, 1.306 0.1558
	Risk Difference 95% CI p-value	-1.822 -4.577, 0.933 0.1948

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Metabolism and nutrition disorders - PT:Hyperlipidaemia		
Number of subjects with events, n (%)	11 (2.5)	1 (0.5)
Number of censored subjects, n (%)	434 (97.5)	220 (99.5)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	5.178	
95% CI	0.668, 40.113	
p-value	0.0788	
Odds Ratio	5.576	
95% CI	0.715, 43.467	
p-value	0.1010	
Relative Risk	5.463	
95% CI	0.710, 42.045	
p-value	0.1029	
Risk Difference	2.019	
95% CI	0.327, 3.712	
p-value	0.0193	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Metabolism and nutrition disorders - PT:Hypertriglyceridaemia*	Number of subjects with events, n (%) 6 (1.3)	2 (0.9)
	Number of censored subjects, n (%) 439 (98.7)	219 (99.1)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	1.330 0.268, 6.600 0.7259
	Odds Ratio 95% CI p-value	1.497 0.300, 7.476 0.6232
	Relative Risk 95% CI p-value	1.490 0.303, 7.322 0.6236
	Risk Difference 95% CI p-value	0.443 -1.202, 2.089 0.5974

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Metabolism and nutrition disorders - PT:Hypocalcaemia*	Number of subjects with events, n (%) 6 (1.3)	4 (1.8)
	Number of censored subjects, n (%) 439 (98.7)	217 (98.2)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	0.628 0.177, 2.232 0.4687
	Odds Ratio 95% CI p-value	0.741 0.207, 2.655 0.6458
	Relative Risk 95% CI p-value	0.745 0.212, 2.613 0.6456
	Risk Difference 95% CI p-value	-0.462 -2.520, 1.597 0.6603

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Metabolism and nutrition disorders - PT:Hyponatraemia	Number of subjects with events, n (%)	11 (2.5)	6 (2.7)
	Number of censored subjects, n (%)	434 (97.5)	215 (97.3)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.800	
	95% CI	0.295, 2.165	
	p-value	0.6592	
	Odds Ratio	0.908	
	95% CI	0.331, 2.489	
	p-value	0.8515	
	Relative Risk	0.910	
	95% CI	0.341, 2.430	
	p-value	0.8515	
	Risk Difference	-0.243	
	95% CI	-2.826, 2.340	
	p-value	0.8537	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Musculoskeletal and connective tissue disorders	Number of subjects with events, n (%)	180 (40.4)	90 (40.7)
	Number of censored subjects, n (%)	265 (59.6)	131 (59.3)
	Time to Event (Month)		
	25%-ile (95%-CI)	8.4 (7.5, 11.2)	8.3 (5.6, 10.7)
	Median (95%-CI)	NE (26.2, NE)	NE (16.5, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.904	
	95% CI	0.702, 1.165	
	p-value	0.4354	
	Odds Ratio	0.989	
	95% CI	0.712, 1.373	
	p-value	0.9458	
	Relative Risk	0.993	
	95% CI	0.817, 1.207	
	p-value	0.9458	
	Risk Difference	-0.275	
	95% CI	-8.196, 7.647	
	p-value	0.9458	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Musculoskeletal and connective tissue disorders - PT:Arthralgia	Number of subjects with events, n (%)	55 (12.4)	25 (11.3)
	Number of censored subjects, n (%)	390 (87.6)	196 (88.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.977	
	95% CI	0.608, 1.569	
	p-value	0.9231	
	Odds Ratio	1.106	
	95% CI	0.669, 1.828	
	p-value	0.6955	
	Relative Risk	1.093	
	95% CI	0.701, 1.704	
	p-value	0.6962	
	Risk Difference	1.047	
	95% CI	-4.129, 6.223	
	p-value	0.6917	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Musculoskeletal and connective tissue disorders - PT:Back pain	Number of subjects with events, n (%)	43 (9.7)	23 (10.4)
	Number of censored subjects, n (%)	402 (90.3)	198 (89.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (28.0, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.814	
	95% CI	0.490, 1.351	
	p-value	0.4247	
	Odds Ratio	0.921	
	95% CI	0.540, 1.571	
	p-value	0.7622	
	Relative Risk	0.928	
	95% CI	0.575, 1.500	
	p-value	0.7619	
	Risk Difference	-0.744	
	95% CI	-5.617, 4.128	
	p-value	0.7646	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Musculoskeletal and connective tissue disorders - PT:Bone pain	Number of subjects with events, n (%)	33 (7.4)	27 (12.2)
	Number of censored subjects, n (%)	412 (92.6)	194 (87.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.540	
	95% CI	0.324, 0.899	
	p-value	0.0160	
	Odds Ratio	0.576	
	95% CI	0.337, 0.984	
	p-value	0.0435	
	Relative Risk	0.607	
	95% CI	0.375, 0.983	
	p-value	0.0425	
	Risk Difference	-4.801	
	95% CI	-9.758, 0.155	
	p-value	0.0576	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Musculoskeletal and connective tissue disorders - PT:Groin pain*	Number of subjects with events, n (%) 2 (0.4)	3 (1.4)
	Number of censored subjects, n (%) 443 (99.6)	218 (98.6)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	0.280 0.047, 1.687 0.1381
	Odds Ratio 95% CI p-value	0.328 0.054, 1.978 0.2240
	Relative Risk 95% CI p-value	0.331 0.056, 1.967 0.2240
	Risk Difference 95% CI p-value	-0.908 -2.555, 0.739 0.2800

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Musculoskeletal and connective tissue disorders - PT:Muscle spasms*		
Number of subjects with events, n (%)	1 (0.2)	3 (1.4)
Number of censored subjects, n (%)	444 (99.8)	218 (98.6)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.153	
95% CI	0.016, 1.475	
p-value	0.0613	
Odds Ratio	0.164	
95% CI	0.017, 1.583	
p-value	0.1179	
Relative Risk	0.166	
95% CI	0.017, 1.582	
p-value	0.1184	
Risk Difference	-1.133	
95% CI	-2.721, 0.455	
p-value	0.1620	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Musculoskeletal and connective tissue disorders - PT:Muscular weakness*	Number of subjects with events, n (%)	5 (1.1)	6 (2.7)
	Number of censored subjects, n (%)	440 (98.9)	215 (97.3)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.385	
	95% CI	0.117, 1.262	
	p-value	0.1016	
	Odds Ratio	0.407	
	95% CI	0.123, 1.349	
	p-value	0.1416	
	Relative Risk	0.414	
	95% CI	0.128, 1.341	
	p-value	0.1414	
	Risk Difference	-1.591	
	95% CI	-3.947, 0.765	
	p-value	0.1855	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)		Placebo (N=221)	
SOC: Musculoskeletal and connective tissue disorders - PT:Musculoskeletal chest pain*	Number of subjects with events, n (%)	4 (0.9)		2 (0.9)	
	Number of censored subjects, n (%)	441 (99.1)		219 (99.1)	
	Time to Event (Month)				
	25%-ile (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	Median (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	75%-ile (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	Unstratified Analysis				
	Hazard Ratio	0.866			
	95% CI	0.158, 4.737			
	p-value	0.8678			
	Odds Ratio	0.993			
	95% CI	0.181, 5.464			
	p-value	0.9937			
	Relative Risk	0.993			
	95% CI	0.183, 5.381			
	p-value	0.9937			
	Risk Difference	-0.006			
	95% CI	-1.532, 1.520			
	p-value	0.9937			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Musculoskeletal and connective tissue disorders - PT:Musculoskeletal pain*	Number of subjects with events, n (%)	5 (1.1)	4 (1.8)
	Number of censored subjects, n (%)	440 (98.9)	217 (98.2)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.534	
	95% CI	0.143, 1.998	
	p-value	0.3439	
	Odds Ratio	0.616	
	95% CI	0.164, 2.319	
	p-value	0.4742	
	Relative Risk	0.621	
	95% CI	0.168, 2.289	
	p-value	0.4739	
	Risk Difference	-0.686	
	95% CI	-2.698, 1.326	
	p-value	0.5037	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Musculoskeletal and connective tissue disorders - PT:Myalgia*	Number of subjects with events, n (%) 7 (1.6)	2 (0.9)
	Number of censored subjects, n (%) 438 (98.4)	219 (99.1)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	1.431 0.296, 6.909 0.6536
	Odds Ratio 95% CI p-value	1.750 0.361, 8.495 0.4875
	Relative Risk 95% CI p-value	1.738 0.364, 8.298 0.4882
	Risk Difference 95% CI p-value	0.668 -1.034, 2.370 0.4416

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Musculoskeletal and connective tissue disorders - PT:Neck pain*	Number of subjects with events, n (%)	8 (1.8)	2 (0.9)
	Number of censored subjects, n (%)	437 (98.2)	219 (99.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.697	
	95% CI	0.360, 8.009	
	p-value	0.4993	
	Odds Ratio	2.005	
	95% CI	0.422, 9.520	
	p-value	0.3816	
	Relative Risk	1.987	
	95% CI	0.425, 9.276	
	p-value	0.3827	
	Risk Difference	0.893	
	95% CI	-0.863, 2.649	
	p-value	0.3190	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Musculoskeletal and connective tissue disorders - PT:Pain in extremity	Number of subjects with events, n (%)	38 (8.5)	20 (9.0)
	Number of censored subjects, n (%)	407 (91.5)	201 (91.0)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.850	
	95% CI	0.495, 1.463	
	p-value	0.5577	
	Odds Ratio	0.938	
	95% CI	0.532, 1.655	
	p-value	0.8259	
	Relative Risk	0.944	
	95% CI	0.563, 1.582	
	p-value	0.8257	
	Risk Difference	-0.510	
	95% CI	-5.098, 4.077	
	p-value	0.8274	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Musculoskeletal and connective tissue disorders - PT:Pathological fracture*	Number of subjects with events, n (%)	5 (1.1)	3 (1.4)
	Number of censored subjects, n (%)	440 (98.9)	218 (98.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.733	
	95% CI	0.175, 3.074	
	p-value	0.6695	
	Odds Ratio	0.826	
	95% CI	0.196, 3.487	
	p-value	0.7945	
	Relative Risk	0.828	
	95% CI	0.200, 3.432	
	p-value	0.7944	
	Risk Difference	-0.234	
	95% CI	-2.047, 1.579	
	p-value	0.8004	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Musculoskeletal and connective tissue disorders - PT:Spinal pain*	Number of subjects with events, n (%) 7 (1.6)	4 (1.8)
	Number of censored subjects, n (%) 438 (98.4)	217 (98.2)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	0.781 0.228, 2.671 0.6928
	Odds Ratio 95% CI p-value	0.867 0.251, 2.994 0.8214
	Relative Risk 95% CI p-value	0.869 0.257, 2.937 0.8214
	Risk Difference 95% CI p-value	-0.237 -2.341, 1.867 0.8253

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Number of subjects with events, n (%)	18 (4.0)	7 (3.2)
	Number of censored subjects, n (%)	427 (96.0)	214 (96.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.095	
	95% CI	0.457, 2.625	
	p-value	0.8394	
	Odds Ratio	1.289	
	95% CI	0.530, 3.133	
	p-value	0.5757	
	Relative Risk	1.277	
	95% CI	0.541, 3.012	
	p-value	0.5764	
	Risk Difference	0.878	
	95% CI	-2.069, 3.824	
	p-value	0.5594	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Nervous system disorders	Number of subjects with events, n (%)	60 (13.5)	34 (15.4)
	Number of censored subjects, n (%)	385 (86.5)	187 (84.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (22.8, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.781	
	95% CI	0.512, 1.191	
	p-value	0.2496	
	Odds Ratio	0.857	
	95% CI	0.544, 1.352	
	p-value	0.5072	
	Relative Risk	0.876	
	95% CI	0.594, 1.293	
	p-value	0.5058	
	Risk Difference	-1.901	
	95% CI	-7.620, 3.817	
	p-value	0.5146	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Nervous system disorders - PT:Dizziness*	Number of subjects with events, n (%) 9 (2.0)	4 (1.8)
	Number of censored subjects, n (%) 436 (98.0)	217 (98.2)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	0.897 0.275, 2.924 0.8573
	Odds Ratio 95% CI p-value	1.120 0.341, 3.677 0.8520
	Relative Risk 95% CI p-value	1.117 0.348, 3.588 0.8521
	Risk Difference 95% CI p-value	0.213 -1.978, 2.403 0.8492

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Nervous system disorders - PT:Headache	Number of subjects with events, n (%)	18 (4.0)	14 (6.3)
	Number of censored subjects, n (%)	427 (96.0)	207 (93.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.576	
	95% CI	0.286, 1.159	
	p-value	0.1174	
	Odds Ratio	0.623	
	95% CI	0.304, 1.278	
	p-value	0.1968	
	Relative Risk	0.639	
	95% CI	0.324, 1.260	
	p-value	0.1957	
	Risk Difference	-2.290	
	95% CI	-5.986, 1.407	
	p-value	0.2247	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Nervous system disorders - PT:Paraesthesia*	Number of subjects with events, n (%) 2 (0.4)	3 (1.4)
	Number of censored subjects, n (%) 443 (99.6)	218 (98.6)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	0.304 0.051, 1.818 0.1664
	Odds Ratio 95% CI p-value	0.328 0.054, 1.978 0.2240
	Relative Risk 95% CI p-value	0.331 0.056, 1.967 0.2240
	Risk Difference 95% CI p-value	-0.908 -2.555, 0.739 0.2800

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Psychiatric disorders	Number of subjects with events, n (%)	39 (8.8)
		14 (6.3)
	Number of censored subjects, n (%)	406 (91.2)
		207 (93.7)
	Time to Event (Month)	
	25%-ile (95%-CI)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)
	Unstratified Analysis	
	Hazard Ratio	1.268
	95% CI	0.688, 2.337
	p-value	0.4456
	Odds Ratio	1.420
	95% CI	0.754, 2.675
	p-value	0.2774
	Relative Risk	1.383
	95% CI	0.768, 2.493
	p-value	0.2801
	Risk Difference	2.429
	95% CI	-1.720, 6.578
	p-value	0.2512

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Psychiatric disorders - PT:Insomnia	Number of subjects with events, n (%)	28 (6.3)	6 (2.7)
	Number of censored subjects, n (%)	417 (93.7)	215 (97.3)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	2.157	
	95% CI	0.893, 5.214	
	p-value	0.0800	
	Odds Ratio	2.406	
	95% CI	0.981, 5.900	
	p-value	0.0550	
	Relative Risk	2.318	
	95% CI	0.974, 5.514	
	p-value	0.0574	
	Risk Difference	3.577	
	95% CI	0.466, 6.689	
	p-value	0.0242	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Renal and urinary disorders	Number of subjects with events, n (%)	98 (22.0)	39 (17.6)
	Number of censored subjects, n (%)	347 (78.0)	182 (82.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	24.8 (16.7, NE)	NE (17.1, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.140	
	95% CI	0.787, 1.653	
	p-value	0.4879	
	Odds Ratio	1.318	
	95% CI	0.873, 1.990	
	p-value	0.1892	
	Relative Risk	1.248	
	95% CI	0.893, 1.743	
	p-value	0.1939	
	Risk Difference	4.375	
	95% CI	-1.956, 10.707	
	p-value	0.1756	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Renal and urinary disorders - PT:Dysuria	Number of subjects with events, n (%)	14 (3.1)	7 (3.2)
	Number of censored subjects, n (%)	431 (96.9)	214 (96.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.927	
	95% CI	0.374, 2.298	
	p-value	0.8701	
	Odds Ratio	0.993	
	95% CI	0.395, 2.497	
	p-value	0.9882	
	Relative Risk	0.993	
	95% CI	0.407, 2.426	
	p-value	0.9882	
	Risk Difference	-0.021	
	95% CI	-2.843, 2.800	
	p-value	0.9882	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Renal and urinary disorders - PT:Haematuria		
Number of subjects with events, n (%)	22 (4.9)	10 (4.5)
Number of censored subjects, n (%)	423 (95.1)	211 (95.5)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.940	
95% CI	0.445, 1.987	
p-value	0.8712	
Odds Ratio	1.097	
95% CI	0.510, 2.360	
p-value	0.8119	
Relative Risk	1.093	
95% CI	0.527, 2.267	
p-value	0.8121	
Risk Difference	0.419	
95% CI	-2.982, 3.820	
p-value	0.8092	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Renal and urinary disorders - PT:Hydronephrosis*	Number of subjects with events, n (%) 3 (0.7)	3 (1.4)
	Number of censored subjects, n (%) 442 (99.3)	218 (98.6)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	0.460 0.093, 2.281 0.3297
	Odds Ratio 95% CI p-value	0.493 0.099, 2.464 0.3891
	Relative Risk 95% CI p-value	0.497 0.101, 2.441 0.3889
	Risk Difference 95% CI p-value	-0.683 -2.388, 1.021 0.4321

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Renal and urinary disorders - PT:Nocturia*	Number of subjects with events, n (%)	5 (1.1)	3 (1.4)
	Number of censored subjects, n (%)	440 (98.9)	218 (98.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.798	
	95% CI	0.191, 3.341	
	p-value	0.7571	
	Odds Ratio	0.826	
	95% CI	0.196, 3.487	
	p-value	0.7945	
	Relative Risk	0.828	
	95% CI	0.200, 3.432	
	p-value	0.7944	
	Risk Difference	-0.234	
	95% CI	-2.047, 1.579	
	p-value	0.8004	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Renal and urinary disorders - PT:Pollakiuria	Number of subjects with events, n (%)	11 (2.5)	2 (0.9)
	Number of censored subjects, n (%)	434 (97.5)	219 (99.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	2.585	
	95% CI	0.573, 11.666	
	p-value	0.1998	
	Odds Ratio	2.775	
	95% CI	0.610, 12.631	
	p-value	0.1867	
	Relative Risk	2.731	
	95% CI	0.611, 12.217	
	p-value	0.1886	
	Risk Difference	1.567	
	95% CI	-0.341, 3.475	
	p-value	0.1075	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Renal and urinary disorders - PT:Urinary retention*	Number of subjects with events, n (%) 8 (1.8)	6 (2.7)
	Number of censored subjects, n (%) 437 (98.2)	215 (97.3)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	0.597 0.207, 1.723 0.3348
	Odds Ratio 95% CI p-value	0.656 0.225, 1.914 0.4404
	Relative Risk 95% CI p-value	0.662 0.233, 1.885 0.4399
	Risk Difference 95% CI p-value	-0.917 -3.390, 1.556 0.4673

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Reproductive system and breast disorders	Number of subjects with events, n (%)	31 (7.0)	13 (5.9)
	Number of censored subjects, n (%)	414 (93.0)	208 (94.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.060	
	95% CI	0.554, 2.028	
	p-value	0.8594	
	Odds Ratio	1.198	
	95% CI	0.614, 2.338	
	p-value	0.5963	
	Relative Risk	1.184	
	95% CI	0.632, 2.217	
	p-value	0.5972	
	Risk Difference	1.084	
	95% CI	-2.817, 4.985	
	p-value	0.5860	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Reproductive system and breast disorders - PT:Erectile dysfunction*	Number of subjects with events, n (%)	5 (1.1)	3 (1.4)
	Number of censored subjects, n (%)	440 (98.9)	218 (98.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.789	
	95% CI	0.189, 3.305	
	p-value	0.7455	
	Odds Ratio	0.826	
	95% CI	0.196, 3.487	
	p-value	0.7945	
	Relative Risk	0.828	
	95% CI	0.200, 3.432	
	p-value	0.7944	
	Risk Difference	-0.234	
	95% CI	-2.047, 1.579	
	p-value	0.8004	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Reproductive system and breast disorders - PT: Pelvic pain*	Number of subjects with events, n (%)	8 (1.8)	5 (2.3)
	Number of censored subjects, n (%)	437 (98.2)	216 (97.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.677	
	95% CI	0.221, 2.073	
	p-value	0.4917	
	Odds Ratio	0.791	
	95% CI	0.256, 2.446	
	p-value	0.6838	
	Relative Risk	0.795	
	95% CI	0.263, 2.401	
	p-value	0.6836	
	Risk Difference	-0.465	
	95% CI	-2.782, 1.852	
	p-value	0.6942	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Respiratory, thoracic and mediastinal disorders	Number of subjects with events, n (%)	58 (13.0)	18 (8.1)
	Number of censored subjects, n (%)	387 (87.0)	203 (91.9)
	Time to Event (Month)		
	25%-ile (95%-CI)	37.8 (30.8, NE)	NE (NE, NE)
	Median (95%-CI)	37.8 (37.8, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (37.8, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.409	
	95% CI	0.829, 2.396	
	p-value	0.2032	
	Odds Ratio	1.690	
	95% CI	0.970, 2.945	
	p-value	0.0640	
	Relative Risk	1.600	
	95% CI	0.967, 2.648	
	p-value	0.0673	
	Risk Difference	4.889	
	95% CI	0.115, 9.663	
	p-value	0.0447	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Respiratory, thoracic and mediastinal disorders - PT:Cough	Number of subjects with events, n (%)	21 (4.7)	7 (3.2)
	Number of censored subjects, n (%)	424 (95.3)	214 (96.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.309	
	95% CI	0.556, 3.086	
	p-value	0.5364	
	Odds Ratio	1.514	
	95% CI	0.634, 3.618	
	p-value	0.3506	
	Relative Risk	1.490	
	95% CI	0.643, 3.451	
	p-value	0.3523	
	Risk Difference	1.552	
	95% CI	-1.484, 4.587	
	p-value	0.3164	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Respiratory, thoracic and mediastinal disorders - PT:Dyspnoea*		
Number of subjects with events, n (%)	7 (1.6)	4 (1.8)
Number of censored subjects, n (%)	438 (98.4)	217 (98.2)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.757	
95% CI	0.221, 2.592	
p-value	0.6566	
Odds Ratio	0.867	
95% CI	0.251, 2.994	
p-value	0.8214	
Relative Risk	0.869	
95% CI	0.257, 2.937	
p-value	0.8214	
Risk Difference	-0.237	
95% CI	-2.341, 1.867	
p-value	0.8253	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Respiratory, thoracic and mediastinal disorders - PT:Epistaxis*	Number of subjects with events, n (%) 2 (0.4)	1 (0.5)
	Number of censored subjects, n (%) 443 (99.6)	220 (99.5)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	0.901 0.081, 9.973 0.9326
	Odds Ratio 95% CI p-value	0.993 0.090, 11.013 0.9956
	Relative Risk 95% CI p-value	0.993 0.091, 10.895 0.9956
	Risk Difference 95% CI p-value	-0.003 -1.084, 1.078 0.9956

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Skin and subcutaneous tissue disorders	Number of subjects with events, n (%)	42 (9.4)	19 (8.6)
	Number of censored subjects, n (%)	403 (90.6)	202 (91.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.017	
	95% CI	0.591, 1.750	
	p-value	0.9501	
	Odds Ratio	1.108	
	95% CI	0.628, 1.955	
	p-value	0.7232	
	Relative Risk	1.098	
	95% CI	0.654, 1.842	
	p-value	0.7237	
	Risk Difference	0.841	
	95% CI	-3.746, 5.428	
	p-value	0.7193	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Skin and subcutaneous tissue disorders - PT:Pruritus*	Number of subjects with events, n (%) 8 (1.8)	5 (2.3)
	Number of censored subjects, n (%) 437 (98.2)	216 (97.7)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	0.703 0.229, 2.154 0.5350
	Odds Ratio 95% CI p-value	0.791 0.256, 2.446 0.6838
	Relative Risk 95% CI p-value	0.795 0.263, 2.401 0.6836
	Risk Difference 95% CI p-value	-0.465 -2.782, 1.852 0.6942

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Skin and subcutaneous tissue disorders - PT:Rash	Number of subjects with events, n (%)	11 (2.5)	5 (2.3)
	Number of censored subjects, n (%)	434 (97.5)	216 (97.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.986	
	95% CI	0.342, 2.844	
	p-value	0.9794	
	Odds Ratio	1.095	
	95% CI	0.376, 3.191	
	p-value	0.8680	
	Relative Risk	1.093	
	95% CI	0.384, 3.106	
	p-value	0.8681	
	Risk Difference	0.209	
	95% CI	-2.225, 2.644	
	p-value	0.8661	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Vascular disorders	Number of subjects with events, n (%)	89 (20.0)	34 (15.4)
	Number of censored subjects, n (%)	356 (80.0)	187 (84.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	33.3 (17.8, NE)	NE (19.6, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.242	
	95% CI	0.836, 1.844	
	p-value	0.2822	
	Odds Ratio	1.375	
	95% CI	0.892, 2.120	
	p-value	0.1494	
	Relative Risk	1.300	
	95% CI	0.906, 1.865	
	p-value	0.1540	
	Risk Difference	4.615	
	95% CI	-1.421, 10.652	
	p-value	0.1340	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Vascular disorders - PT:Hot flush	Number of subjects with events, n (%)	41 (9.2)	16 (7.2)
	Number of censored subjects, n (%)	404 (90.8)	205 (92.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.234	
	95% CI	0.692, 2.200	
	p-value	0.4744	
	Odds Ratio	1.300	
	95% CI	0.712, 2.373	
	p-value	0.3924	
	Relative Risk	1.273	
	95% CI	0.731, 2.216	
	p-value	0.3944	
	Risk Difference	1.974	
	95% CI	-2.373, 6.320	
	p-value	0.3735	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Vascular disorders - PT:Hypertension	Number of subjects with events, n (%)	38 (8.5)	19 (8.6)
	Number of censored subjects, n (%)	407 (91.5)	202 (91.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (33.3, NE)	NE (30.9, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.857	
	95% CI	0.493, 1.489	
	p-value	0.5840	
	Odds Ratio	0.993	
	95% CI	0.558, 1.766	
	p-value	0.9799	
	Relative Risk	0.993	
	95% CI	0.587, 1.682	
	p-value	0.9799	
	Risk Difference	-0.058	
	95% CI	-4.575, 4.459	
	p-value	0.9799	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1.1								
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm) - Subgroup analysis (safety analysis set)								
System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Subgroup Level	Darolutamide(N=445) n/N[s] (%)	Placebo(N=221) n/N[s] (%)	Unstratified Analysis			Interaction	
				Hazard Ratio	(95% CI)	p-Value	p-Value	
SOC: Hepatobiliary disorders	Presence of visceral metastases assessed by central review (from IWRS)						0.9923	
	Yes	3/ 54 (5.6)	0/ 26 (0.0)	NE	(NE, NE)	NE		
	No	22/391 (5.6)	1/195 (0.5)	9.615	(1.296, 71.343)	0.0066		
	Received prior local therapy (from IWRS)						0.9901	
	Yes	6/ 80 (7.5)	0/ 40 (0.0)	NE	(NE, NE)	NE		
	No	19/365 (5.2)	1/181 (0.6)	8.511	(1.139, 63.575)	0.0121		
	Prior local radiotherapy and/or prostatectomy						0.9889	
	Yes	4/ 87 (4.6)	0/ 50 (0.0)	NE	(NE, NE)	NE		
	No	21/358 (5.9)	1/171 (0.6)	8.856	(1.191, 65.832)	0.0099		
	Age group						1.0000	
	<65 years	7/117 (6.0)	0/ 64 (0.0)	NE	(NE, NE)	NE		
	65-74	13/193 (6.7)	0/ 95 (0.0)	NE	(NE, NE)	NE		
	75-84	5/117 (4.3)	0/ 52 (0.0)	NE	(NE, NE)	NE		
	>=85 years	0/ 18 (0.0)	1/ 10 (10.0)	NE	(NE, NE)	NE		
	Race						1.0000	
	White	8/249 (3.2)	0/124 (0.0)	NE	(NE, NE)	NE		
	Asian	17/144 (11.8)	1/ 65 (1.5)	7.441	(0.990, 55.913)	0.0218		
	Black or African American	0/ 42 (0.0)	0/ 23 (0.0)	NE	(NE, NE)	NE		
	Other	0/ 10 (0.0)	0/ 9 (0.0)	NE	(NE, NE)	NE		
	Geographical region						1.0000	
	Asia	17/141 (12.1)	1/ 63 (1.6)	7.408	(0.986, 55.660)	0.0221		
	Latin America	1/120 (0.8)	0/ 70 (0.0)	NE	(NE, NE)	NE		
	Europe and Rest of the world	7/184 (3.8)	0/ 88 (0.0)	NE	(NE, NE)	NE		
	Baseline PSA values by median						0.9892	
	< median of overall population	10/215 (4.7)	0/110 (0.0)	NE	(NE, NE)	NE		
	>= median of overall population	15/219 (6.8)	1/108 (0.9)	6.813	(0.900, 51.596)	0.0311		
	ECOG PS at baseline						0.9894	
	=0	15/235 (6.4)	0/ 96 (0.0)	NE	(NE, NE)	NE		
	>=1	10/210 (4.8)	1/125 (0.8)	5.584	(0.714, 43.637)	0.0645		
	Gleason score at initial diagnosis						0.9866	
	Gleason <8	6/124 (4.8)	1/ 65 (1.5)	2.922	(0.351, 24.290)	0.2981		
	Gleason >=8	18/308 (5.8)	0/146 (0.0)	NE	(NE, NE)	NE		
	Disease volume at baseline						0.9864	
	high	21/314 (6.7)	0/156 (0.0)	NE	(NE, NE)	NE		
	low	4/131 (3.1)	1/ 65 (1.5)	1.540	(0.171, 13.855)	0.6978		
	Renal function - eGFR at baseline						0.9999	
	Normal: eGFR >= 90 mL/min	13/221 (5.9)	0/102 (0.0)	NE	(NE, NE)	NE		
	Mild impairment: 60 <= eGFR < 90 mL/min	9/178 (5.1)	1/ 91 (1.1)	4.412	(0.559, 34.837)	0.1234		
	Moderate impairment: 30 <= eGFR < 60 mL/min	3/ 45 (6.7)	0/ 27 (0.0)	NE	(NE, NE)	NE		

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Subgroup analysis was done for SOC / PTs with significant overall treatment effect (significant log-rank test).
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.3.1.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm) - Subgroup analysis
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Subgroup Level	Darolutamide(N=445) n/N[s] (%)	Placebo(N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
				Hazard Ratio	(95% CI)	p-Value	
SOC: Hepatobiliary disorders	Hepatic function at baseline						0.9898
	Normal: Total bilirubin and AST <= upper limit of normal (ULN)	21/387 (5.4)	1/202 (0.5)	9.613	(1.293, 71.490)	0.0067	
	Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	4/ 58 (6.9)	0/ 19 (0.0)	NE	(NE, NE)	NE	
	Age Group (Titan)						0.9998
	<65	7/117 (6.0)	0/ 64 (0.0)	NE	(NE, NE)	NE	
	>=65 and <75	13/193 (6.7)	0/ 95 (0.0)	NE	(NE, NE)	NE	
	>=75	5/135 (3.7)	1/ 62 (1.6)	2.073	(0.242, 17.782)	0.4968	
	Geographic region (Titan)						0.9912
	Europe and north america	7/144 (4.9)	0/ 77 (0.0)	NE	(NE, NE)	NE	
	ROTW	18/301 (6.0)	1/144 (0.7)	8.001	(1.068, 59.933)	0.0160	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.3.1.1

Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm) - Subgroup analysis (safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Subgroup Level	Darolutamide (N=445) n/N[s] (%)	Placebo (N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
				Hazard Ratio	(95% CI)	p-Value	
SOC: Investigations - PT:Blood bilirubin increased	Presence of visceral metastases assessed by central review (from IWRS)						0.9923
	Yes	3/ 54 (5.6)	0/ 26 (0.0)	NE	(NE, NE)	NE	
	No	16/391 (4.1)	2/195 (1.0)	3.461	(0.795, 15.066)	0.0779	
	Received prior local therapy (from IWRS)						0.9902
	Yes	4/ 80 (5.0)	0/ 40 (0.0)	NE	(NE, NE)	NE	
	No	15/365 (4.1)	2/181 (1.1)	3.319	(0.759, 14.521)	0.0908	
	Prior local radiotherapy and/or prostatectomy						0.9889
	Yes	3/ 87 (3.4)	0/ 50 (0.0)	NE	(NE, NE)	NE	
	No	16/358 (4.5)	2/171 (1.2)	3.230	(0.742, 14.061)	0.0982	
	Age group						
	<65 years	6/117 (5.1)	0/ 64 (0.0)				
	65-74	7/193 (3.6)	1/ 95 (1.1)				
	75-84	6/117 (5.1)	1/ 52 (1.9)				
	>=85 years	0/ 18 (0.0)	0/ 10 (0.0)				
	Race						
	White	8/249 (3.2)	1/124 (0.8)				
	Asian	6/144 (4.2)	1/ 65 (1.5)				
	Black or African American	4/ 42 (9.5)	0/ 23 (0.0)				
	Other	1/ 10 (10.0)	0/ 9 (0.0)				
	Geographical region						0.9186
	Asia	6/141 (4.3)	1/ 63 (1.6)	2.468	(0.297, 20.514)	0.3873	
	Latin America	9/120 (7.5)	1/ 70 (1.4)	4.793	(0.607, 37.845)	0.1003	
	Europe and Rest of the world	4/184 (2.2)	0/ 88 (0.0)	NE	(NE, NE)	NE	
	Baseline PSA values by median						0.9891
	< median of overall population	9/215 (4.2)	0/110 (0.0)	NE	(NE, NE)	NE	
	>= median of overall population	9/219 (4.1)	2/108 (1.9)	1.909	(0.412, 8.849)	0.4005	
	ECOG PS at baseline						0.9896
	=0	11/235 (4.7)	0/ 96 (0.0)	NE	(NE, NE)	NE	
	>=1	8/210 (3.8)	2/125 (1.6)	2.025	(0.429, 9.555)	0.3631	
	Gleason score at initial diagnosis						0.9916
	Gleason <8	5/124 (4.0)	0/ 65 (0.0)	NE	(NE, NE)	NE	
	Gleason >=8	14/308 (4.5)	2/146 (1.4)	2.927	(0.664, 12.892)	0.1366	
	Disease volume at baseline						0.7004
	high	12/314 (3.8)	1/156 (0.6)	5.225	(0.679, 40.221)	0.0760	
	low	7/131 (5.3)	1/ 65 (1.5)	2.941	(0.361, 23.957)	0.2903	
	Renal function - eGFR at baseline						0.9999
	Normal: eGFR >= 90 mL/min	12/221 (5.4)	0/102 (0.0)	NE	(NE, NE)	NE	
	Mild impairment: 60 <= eGFR < 90 mL/min	5/178 (2.8)	2/ 91 (2.2)	1.090	(0.211, 5.643)	0.9182	
	Moderate impairment: 30 <= eGFR < 60 mL/min	2/ 45 (4.4)	0/ 27 (0.0)	NE	(NE, NE)	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Subgroup analysis was done for SOC / PTs with significant overall treatment effect (significant log-rank test).

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.3.1.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm) - Subgroup analysis
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Subgroup Level	Darolutamide(N=445) n/N[s] (%)	Placebo(N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
				Hazard Ratio	(95% CI)	p-Value	
SOC: Investigations - PT:Blood bilirubin increased	Hepatic function at baseline						0.3215
	Normal: Total bilirubin and AST <= upper limit of normal (ULN)	14/387 (3.6)	1/202 (0.5)	6.479	(0.851, 49.311)	0.0377	
	Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	5/ 58 (8.6)	1/ 19 (5.3)	1.444	(0.169, 12.364)	0.7356	
	Age Group (Titan)						
	<65	6/117 (5.1)	0/ 64 (0.0)				
	>=65 and <75	7/193 (3.6)	1/ 95 (1.1)				
	>=75	6/135 (4.4)	1/ 62 (1.6)				
	Geographic region (Titan)						0.9918
	Europe and north america	4/144 (2.8)	0/ 77 (0.0)	NE	(NE, NE)	NE	
	ROTW	15/301 (5.0)	2/144 (1.4)	3.251	(0.743, 14.218)	0.0973	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
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Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024

Study population

Table 3.3.1.1.1

Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm) - Subgroup analysis (safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Subgroup Level	Darolutamide(N=445) n/N[s] (%)	Placebo(N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
				Hazard Ratio	(95% CI)	p-Value	
SOC: Musculoskeletal and connective tissue disorders - PT:Bone pain	Presence of visceral metastases assessed by central review (from IWRS)						0.3462
	Yes	5/ 54 (9.3)	2/ 26 (7.7)	1.148	(0.222, 5.942)	0.8688	
	No	28/391 (7.2)	25/195 (12.8)	0.495	(0.288, 0.849)	0.0092	
	Received prior local therapy (from IWRS)						0.5637
	Yes	7/ 80 (8.8)	4/ 40 (10.0)	0.773	(0.224, 2.666)	0.6825	
	No	26/365 (7.1)	23/181 (12.7)	0.502	(0.286, 0.881)	0.0143	
	Prior local radiotherapy and/or prostatectomy						0.9865
	Yes	6/ 87 (6.9)	6/ 50 (12.0)	0.532	(0.171, 1.658)	0.2685	
	No	27/358 (7.5)	21/171 (12.3)	0.539	(0.304, 0.954)	0.0312	
	Age group						0.3429
	<65 years	11/117 (9.4)	5/ 64 (7.8)	1.061	(0.368, 3.060)	0.9123	
	65-74	11/193 (5.7)	15/ 95 (15.8)	0.314	(0.144, 0.686)	0.0021	
	75-84	10/117 (8.5)	6/ 52 (11.5)	0.665	(0.241, 1.832)	0.4266	
	>=85 years	1/ 18 (5.6)	1/ 10 (10.0)	0.564	(0.035, 9.023)	0.6812	
	Race						0.9590
	White	20/249 (8.0)	17/124 (13.7)	0.504	(0.263, 0.964)	0.0347	
	Asian	6/144 (4.2)	4/ 65 (6.2)	0.632	(0.178, 2.241)	0.4735	
	Black or African American	7/ 42 (16.7)	5/ 23 (21.7)	0.714	(0.226, 2.253)	0.5641	
	Other	0/ 10 (0.0)	1/ 9 (11.1)	NE	(NE, NE)	NE	
	Geographical region						0.9809
	Asia	5/141 (3.5)	4/ 63 (6.3)	0.523	(0.140, 1.948)	0.3256	
	Latin America	17/120 (14.2)	15/ 70 (21.4)	0.598	(0.298, 1.199)	0.1431	
	Europe and Rest of the world	11/184 (6.0)	8/ 88 (9.1)	0.579	(0.232, 1.443)	0.2352	
	Baseline PSA values by median						0.8224
	< median of overall population	14/215 (6.5)	13/110 (11.8)	0.493	(0.232, 1.051)	0.0613	
	>= median of overall population	17/219 (7.8)	13/108 (12.0)	0.566	(0.274, 1.166)	0.1178	
	ECOG PS at baseline						0.3111
	=0	21/235 (8.9)	11/ 96 (11.5)	0.695	(0.335, 1.444)	0.3270	
	>=1	12/210 (5.7)	16/125 (12.8)	0.409	(0.194, 0.866)	0.0157	
	Gleason score at initial diagnosis						0.4859
	Gleason <8	8/124 (6.5)	9/ 65 (13.8)	0.417	(0.161, 1.084)	0.0638	
	Gleason >=8	24/308 (7.8)	16/146 (11.0)	0.652	(0.346, 1.228)	0.1821	
	Disease volume at baseline						0.9931
	high	28/314 (8.9)	23/156 (14.7)	0.542	(0.312, 0.941)	0.0271	
	low	5/131 (3.8)	4/ 65 (6.2)	0.539	(0.144, 2.015)	0.3510	
	Renal function - eGFR at baseline						0.4385
	Normal: eGFR >= 90 mL/min	20/221 (9.0)	13/102 (12.7)	0.627	(0.312, 1.263)	0.1876	
	Mild impairment: 60 <= eGFR < 90 mL/min	12/178 (6.7)	10/ 91 (11.0)	0.543	(0.234, 1.259)	0.1487	
	Moderate impairment: 30 <= eGFR < 60 mL/min	1/ 45 (2.2)	4/ 27 (14.8)	0.134	(0.015, 1.200)	0.0347	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.3.1.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm) - Subgroup analysis (safety analysis set)

Final

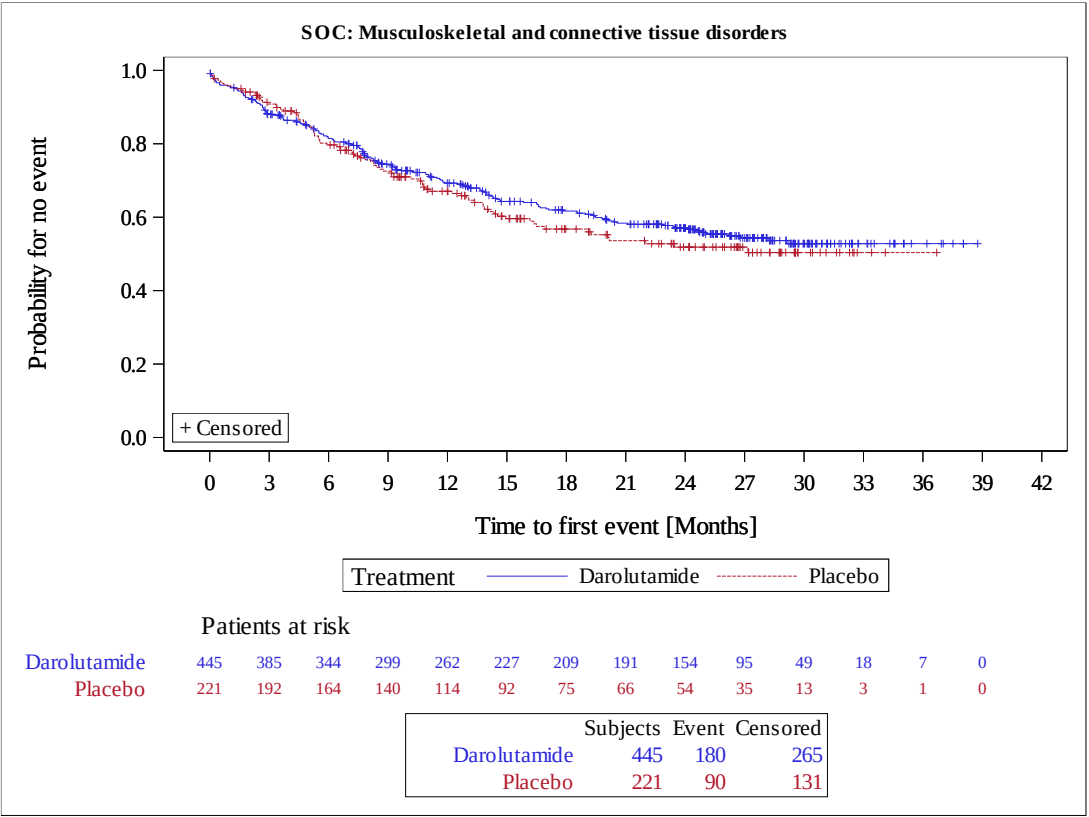
System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Subgroup Level	Darolutamide(N=445) n/N[s] (%)	Placebo(N=221) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
				Hazard Ratio	(95% CI)	p-Value	
SOC: Musculoskeletal and connective tissue disorders - PT:Bone pain	Hepatic function at baseline						0.5557
	Normal: Total bilirubin and AST <= upper limit of normal (ULN)	29/387 (7.5)	24/202 (11.9)	0.559	(0.325, 0.962)	0.0331	
	Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	4/ 58 (6.9)	3/ 19 (15.8)	0.357	(0.080, 1.600)	0.1589	
	Age Group (Titan)						0.1901
	<65	11/117 (9.4)	5/ 64 (7.8)	1.061	(0.368, 3.060)	0.9123	
	>=65 and <75	11/193 (5.7)	15/ 95 (15.8)	0.314	(0.144, 0.686)	0.0021	
	>=75	11/135 (8.1)	7/ 62 (11.3)	0.651	(0.252, 1.684)	0.3728	
	Geographic region (Titan)						0.8223
	Europe and north america	9/144 (6.3)	7/ 77 (9.1)	0.594	(0.220, 1.602)	0.2982	
	ROTW	24/301 (8.0)	20/144 (13.9)	0.523	(0.289, 0.947)	0.0293	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.3.1.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

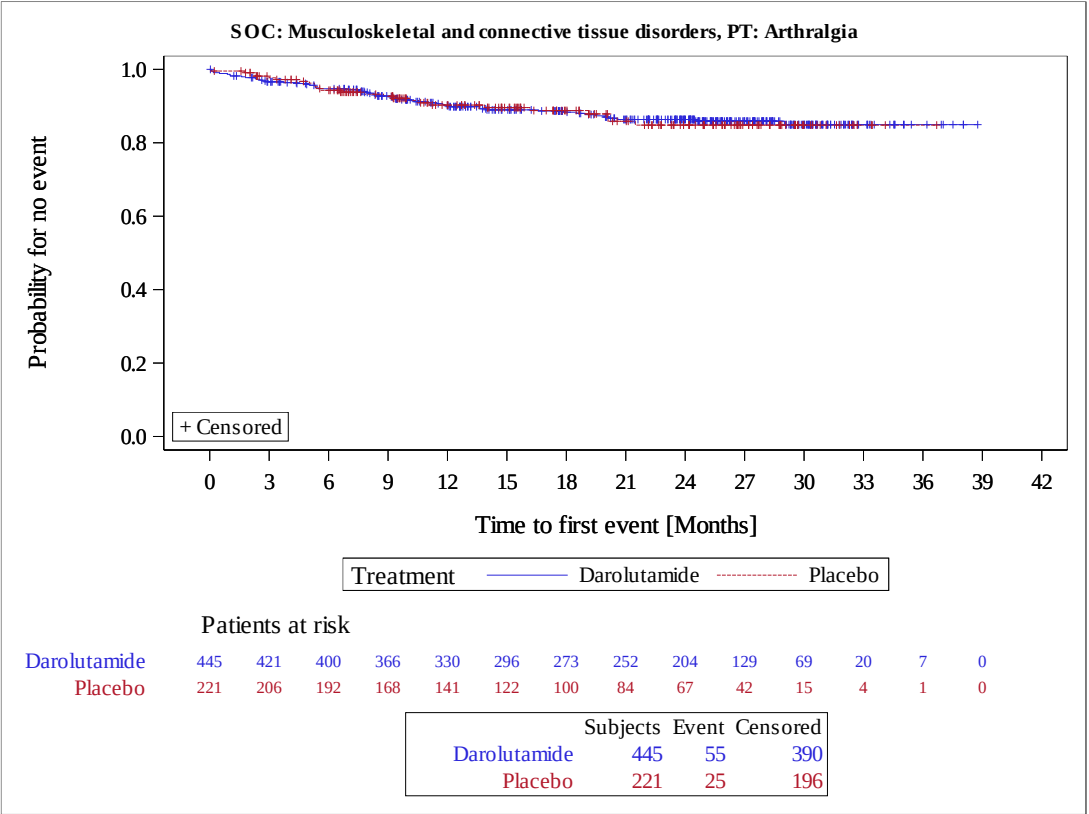


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC/PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
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Figure 3.3.1.2
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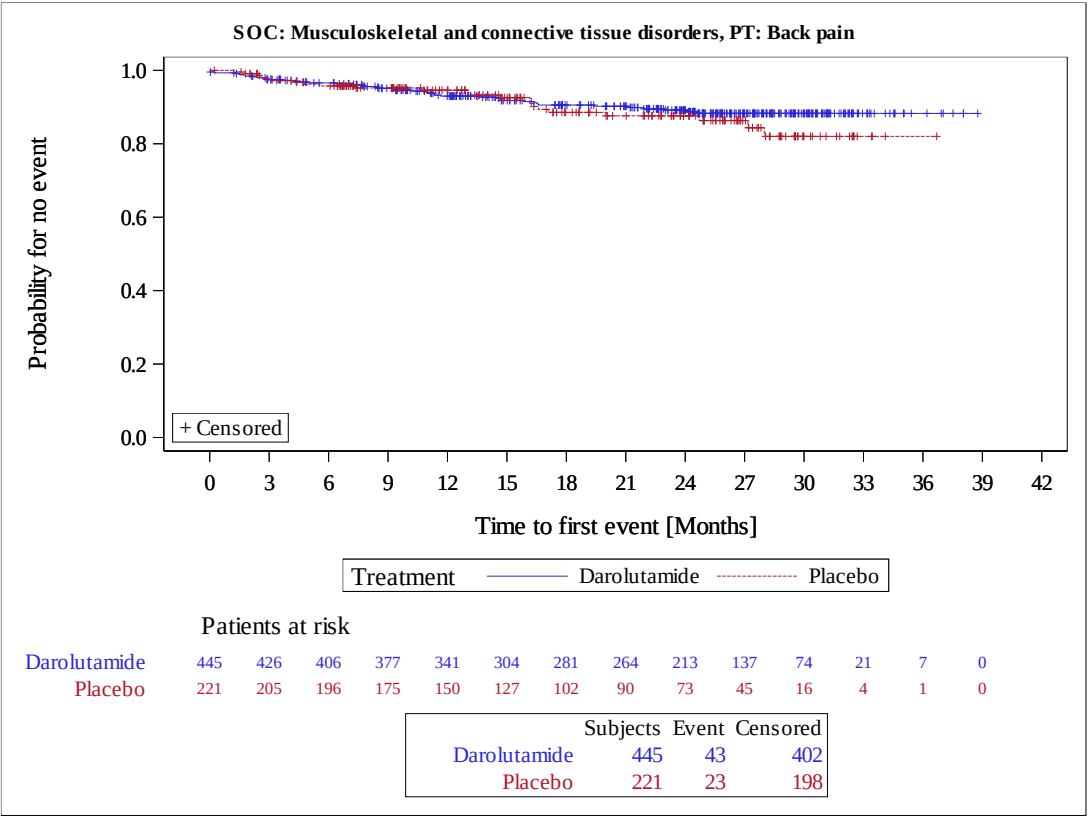


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.3.1.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

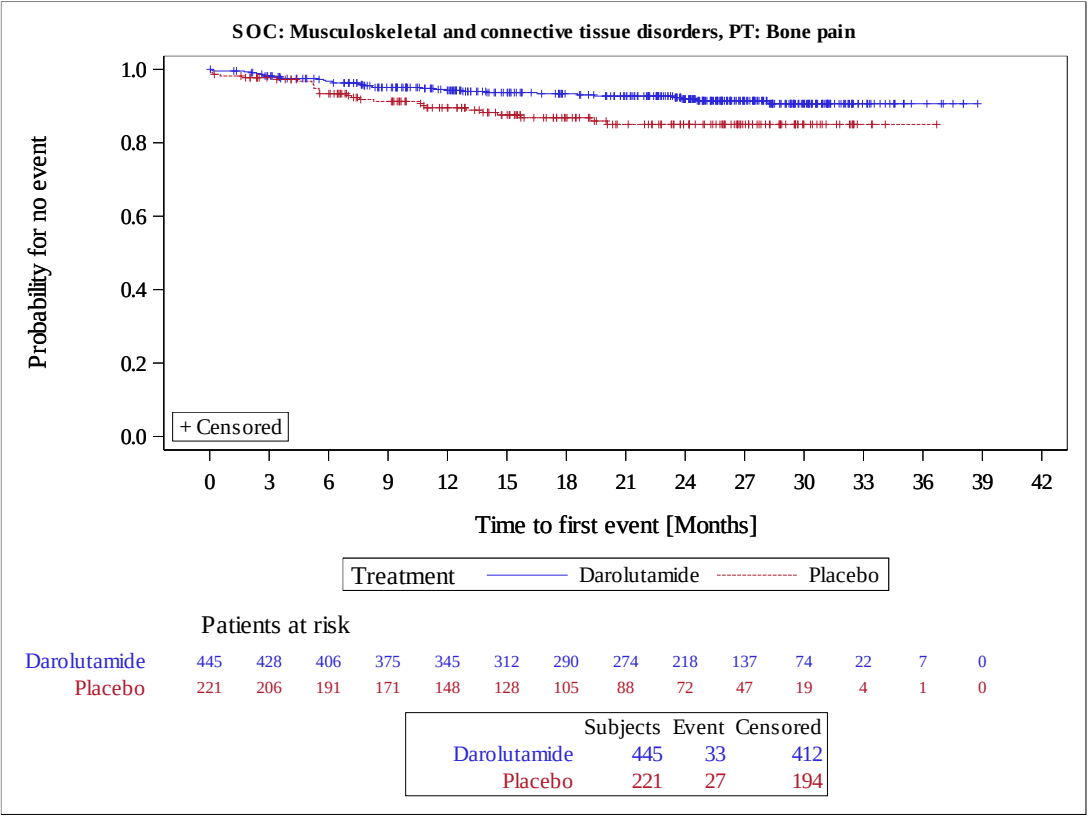


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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Figure 3.3.1.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

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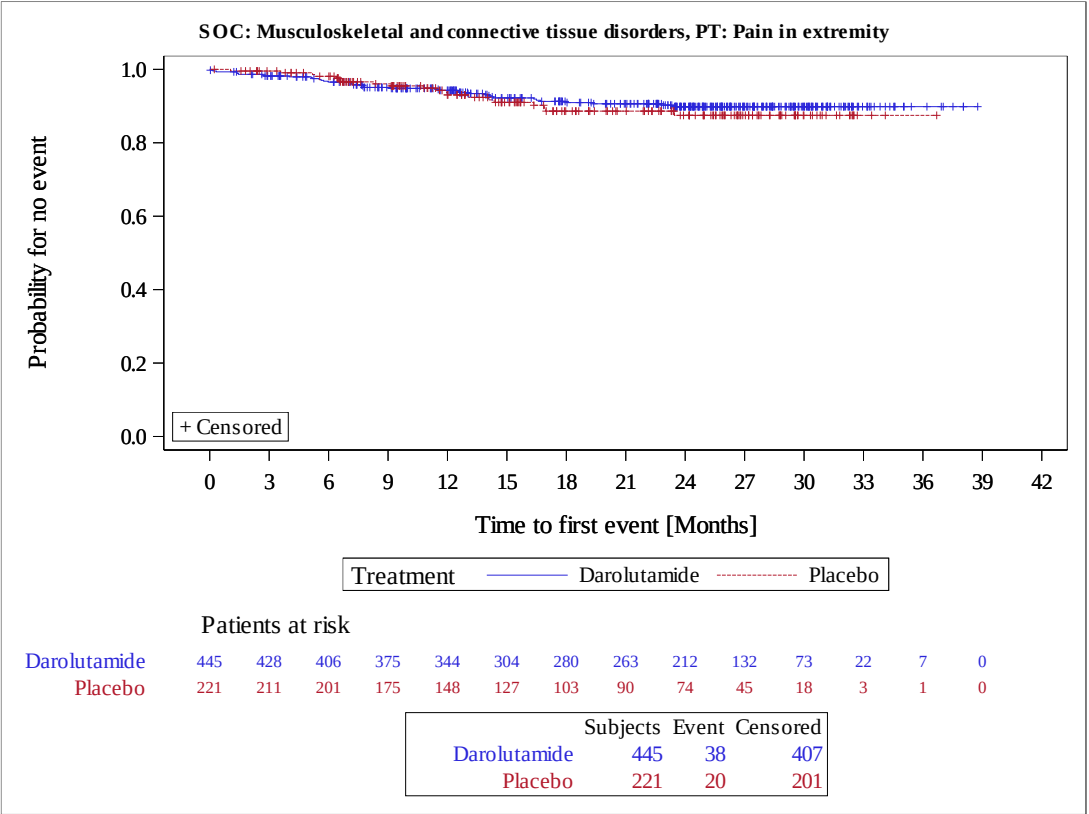


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Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.3.1.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

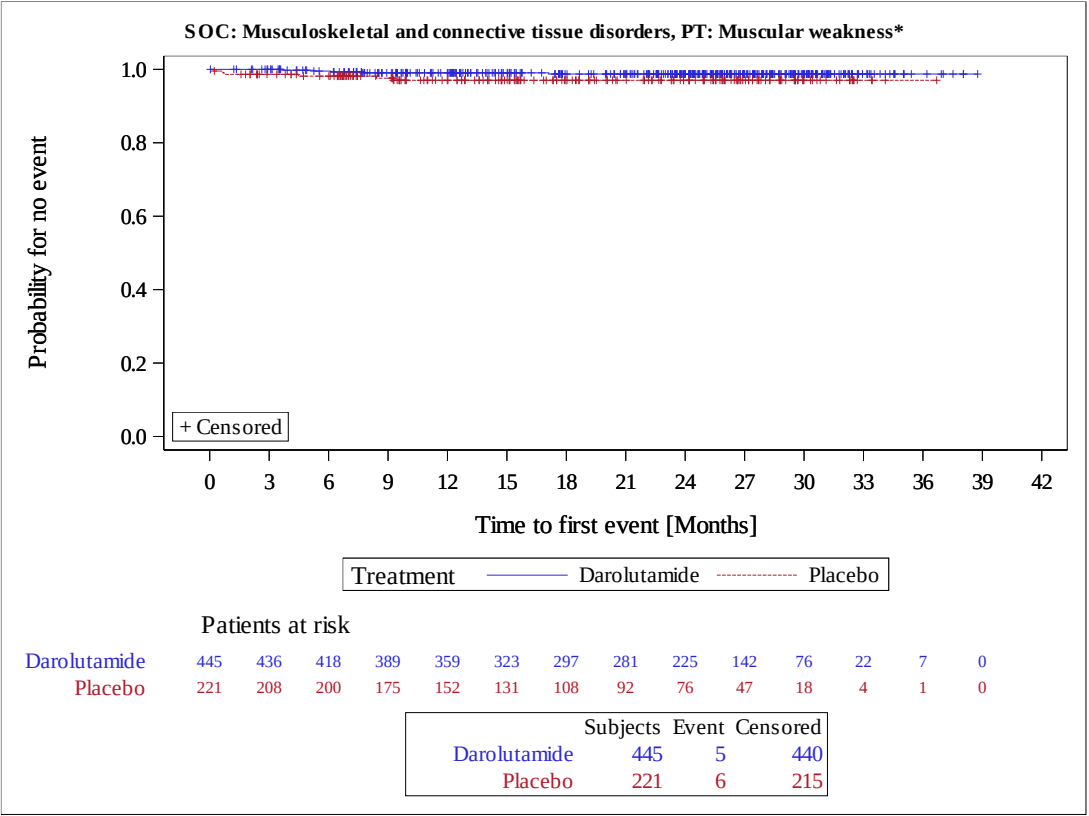


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BAY 1841788 / 21140 - 07JUN2024
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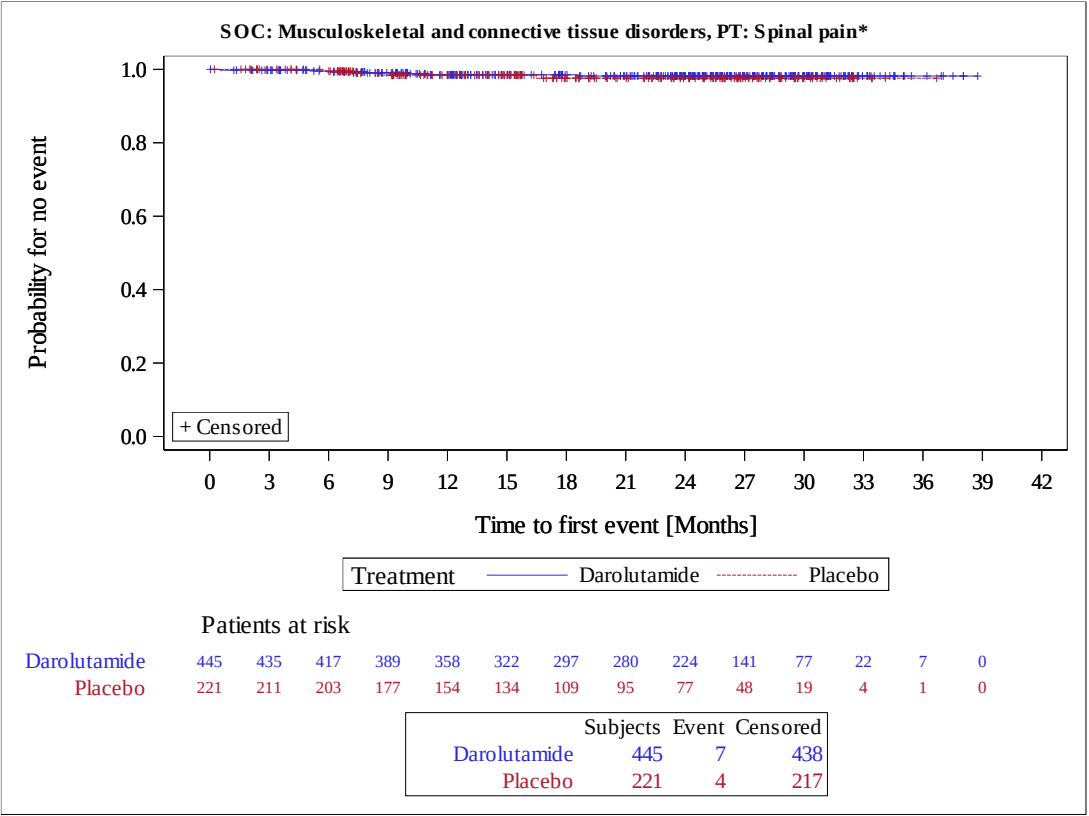


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BAY 1841788 / 21140 - 07JUN2024
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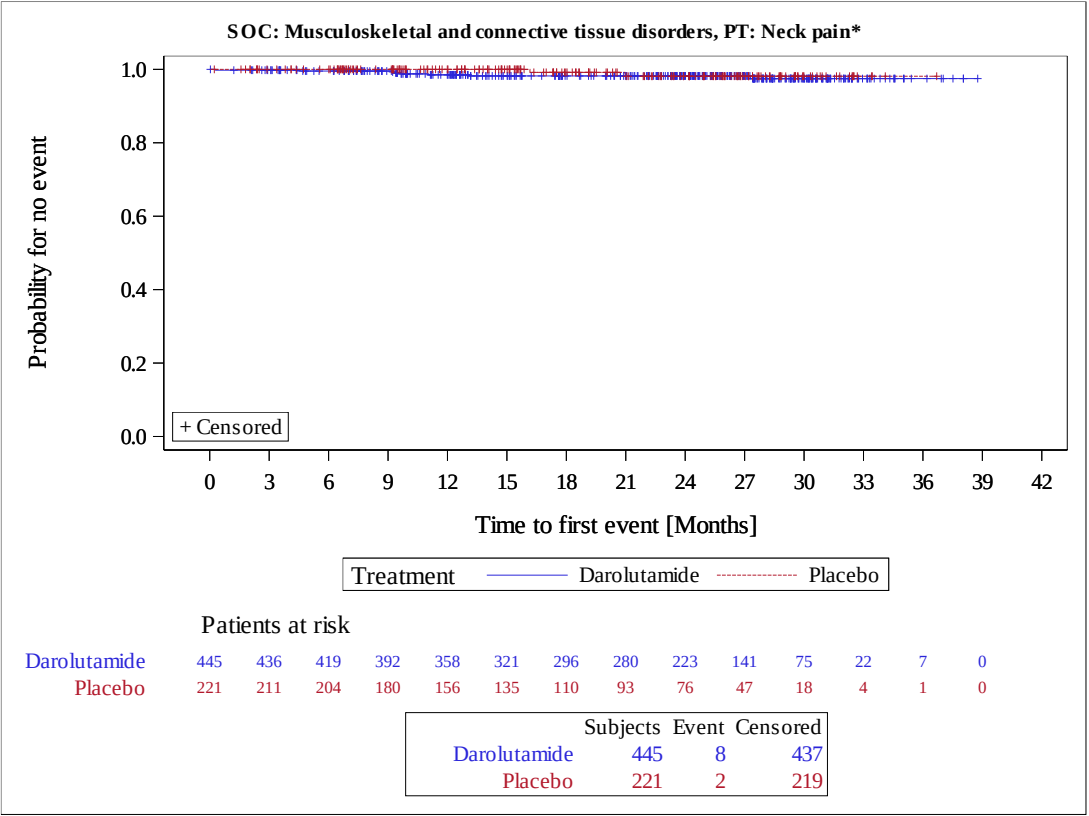


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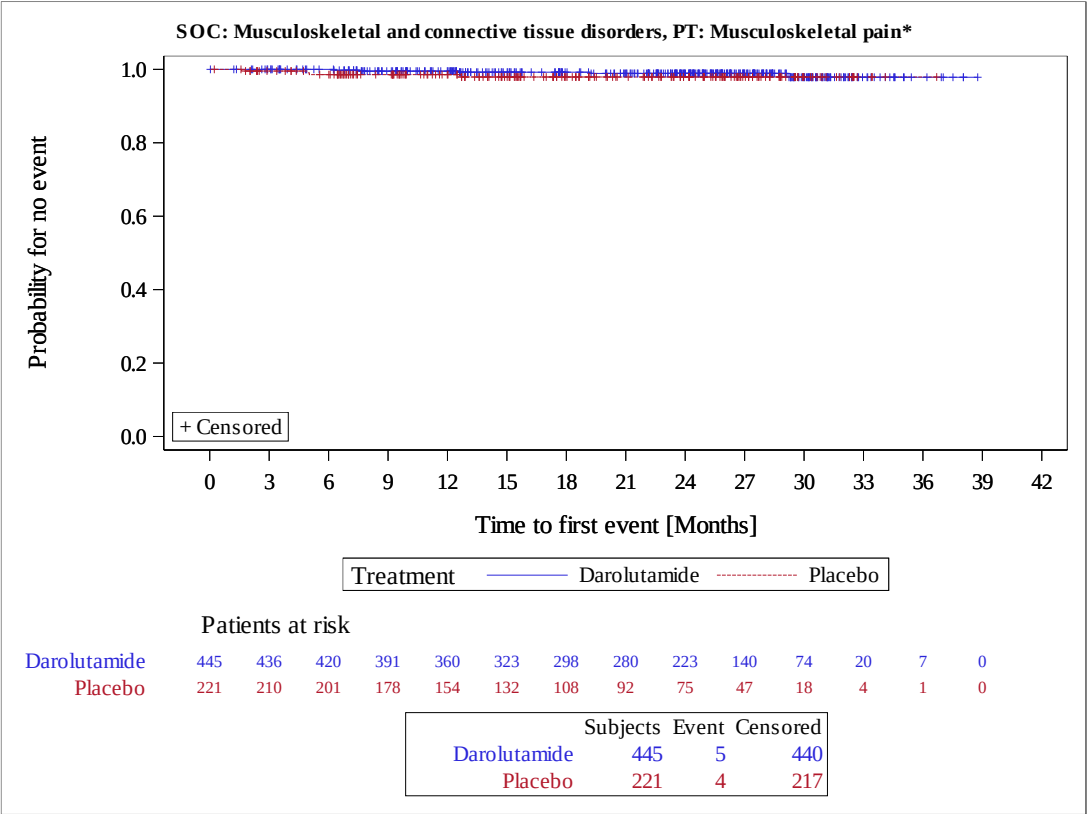


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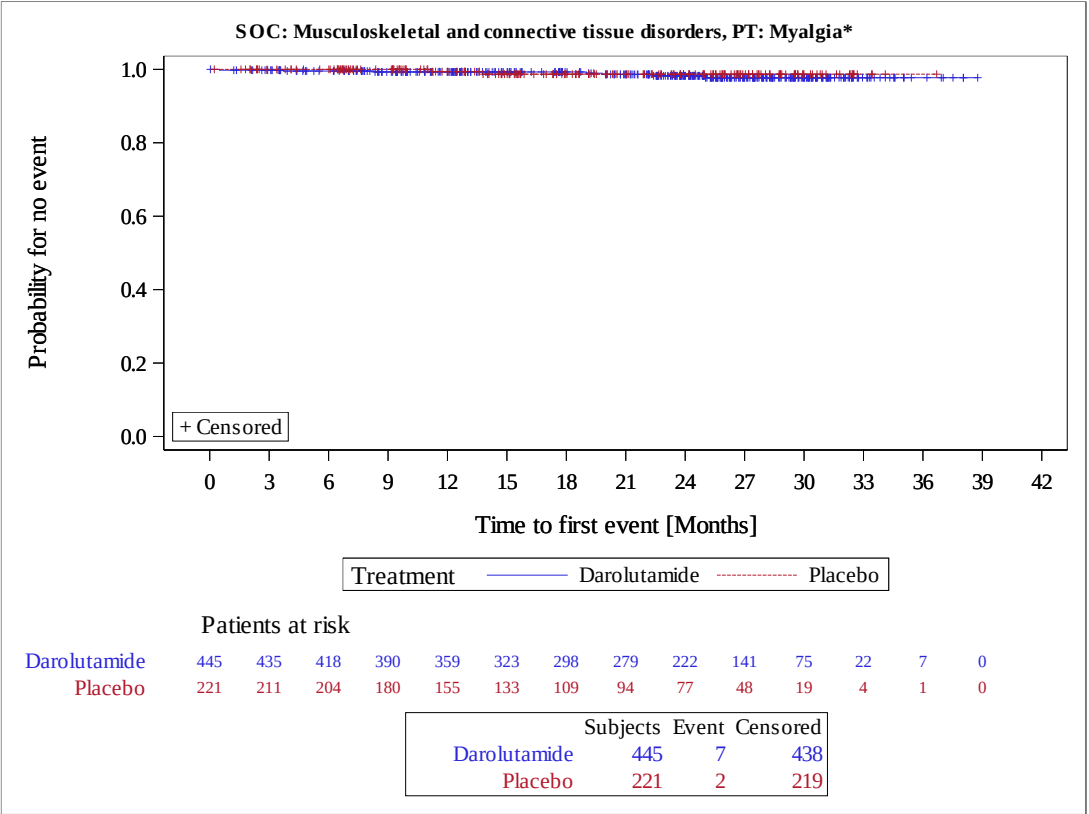


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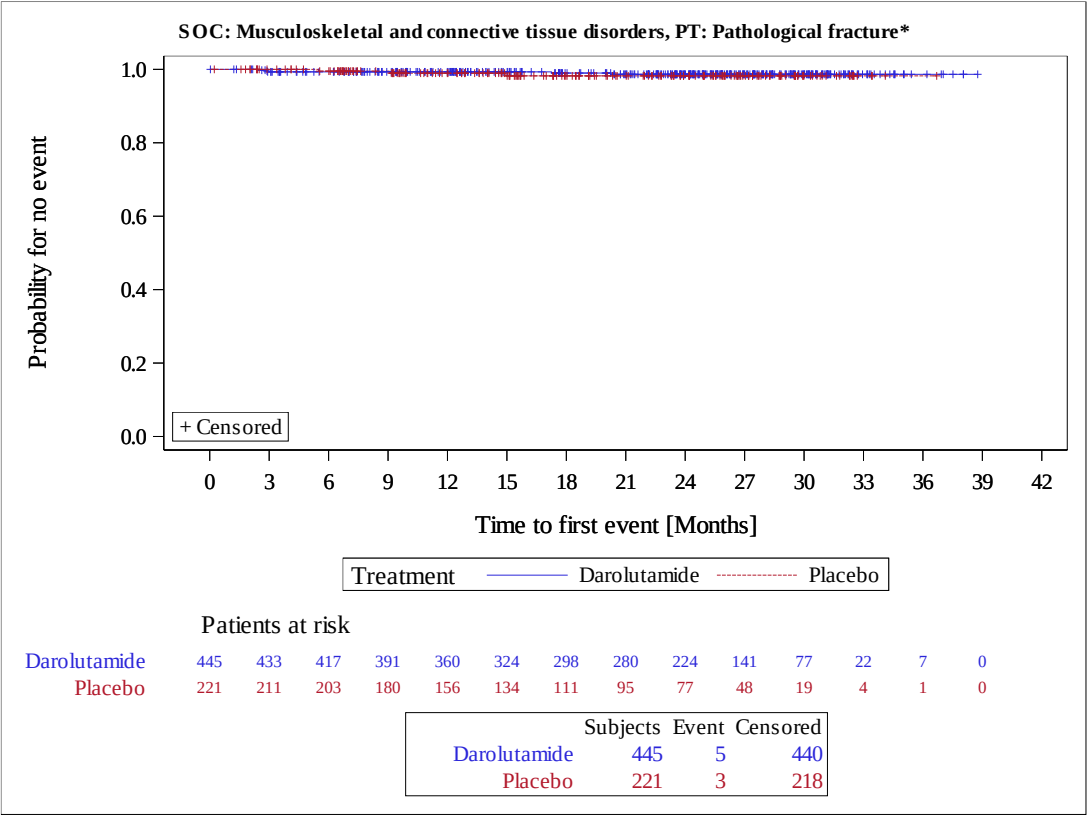


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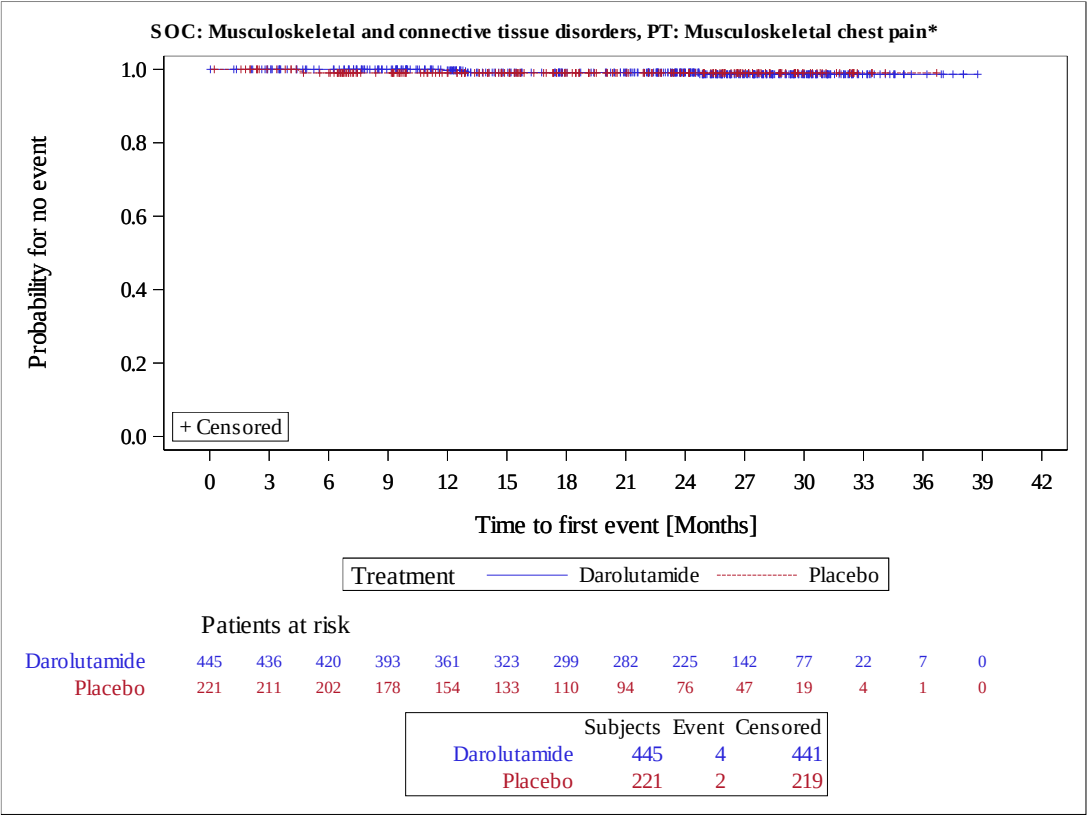


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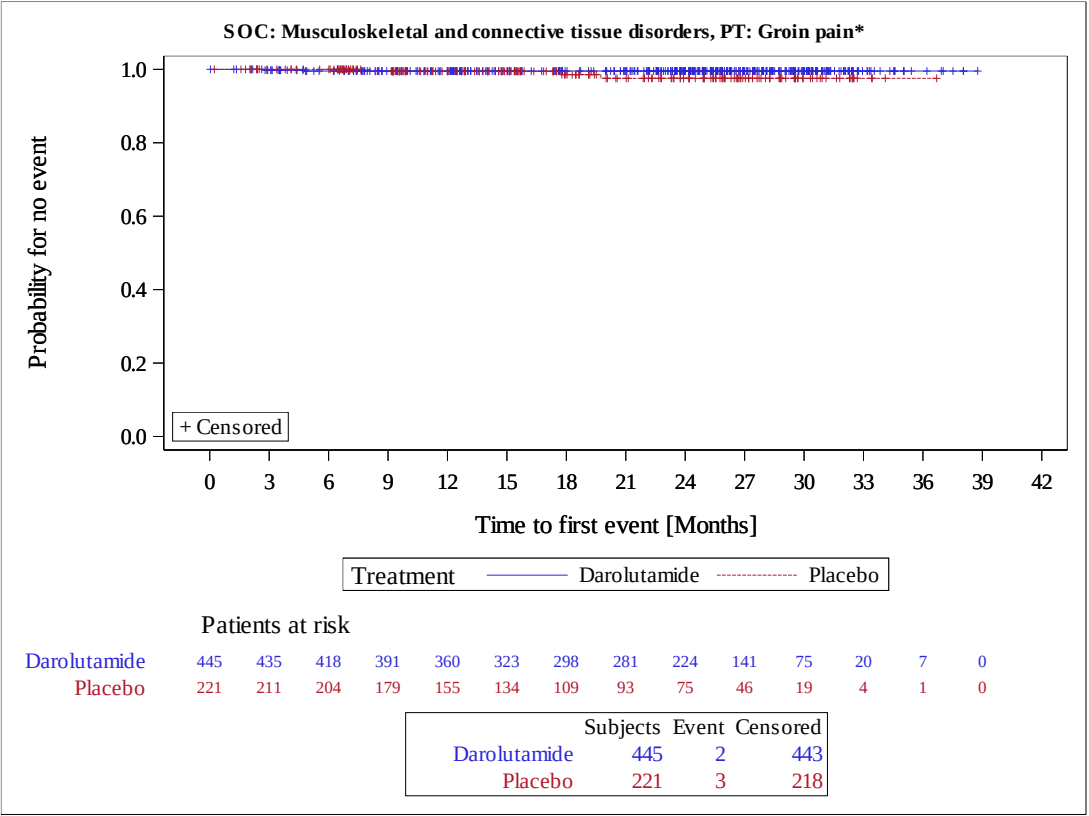


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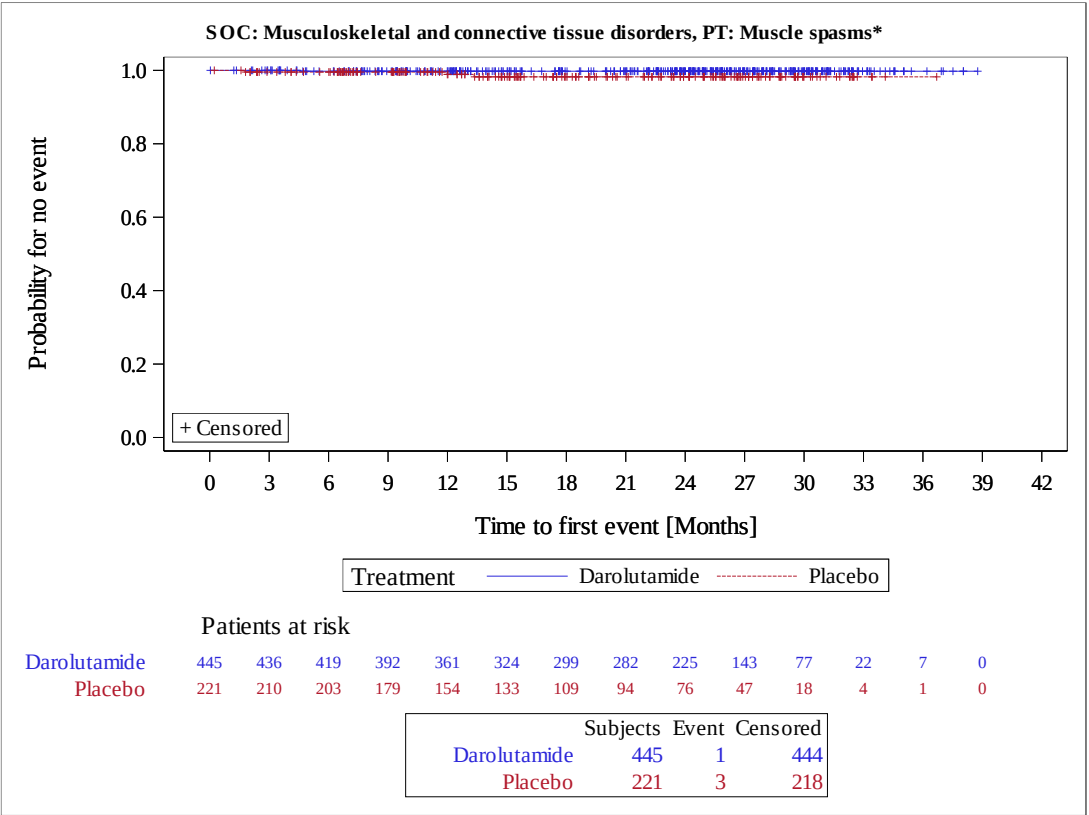


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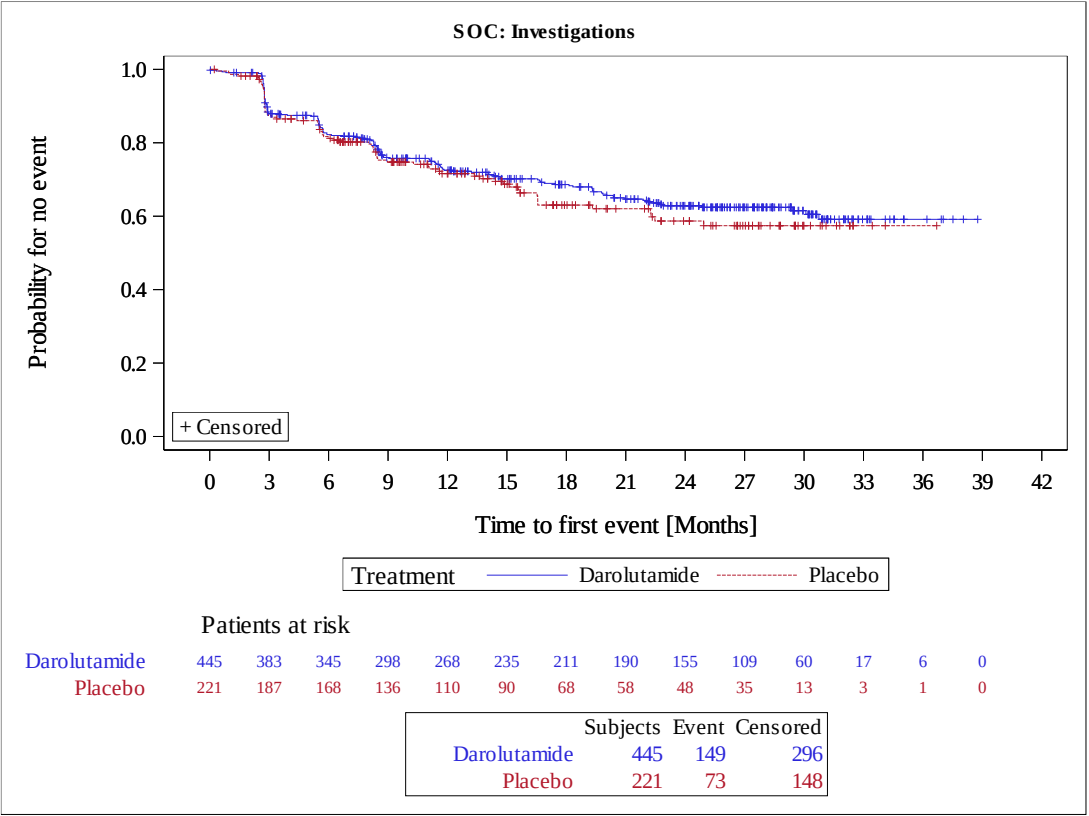


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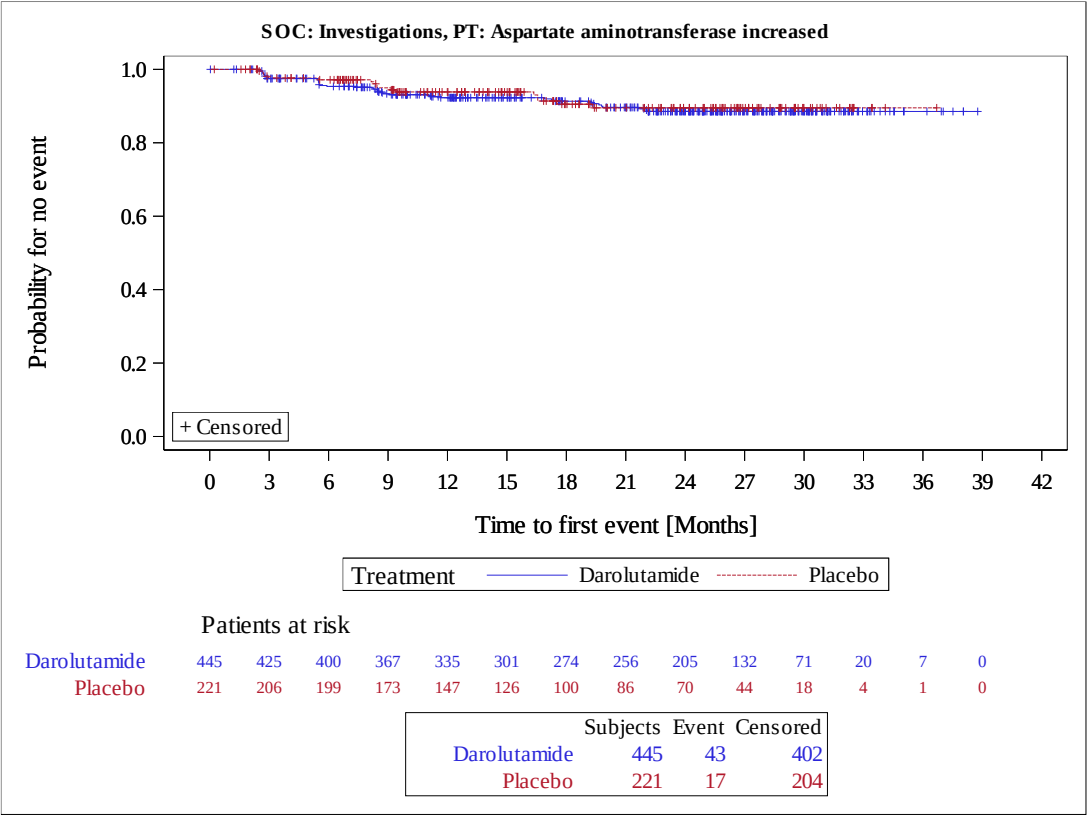


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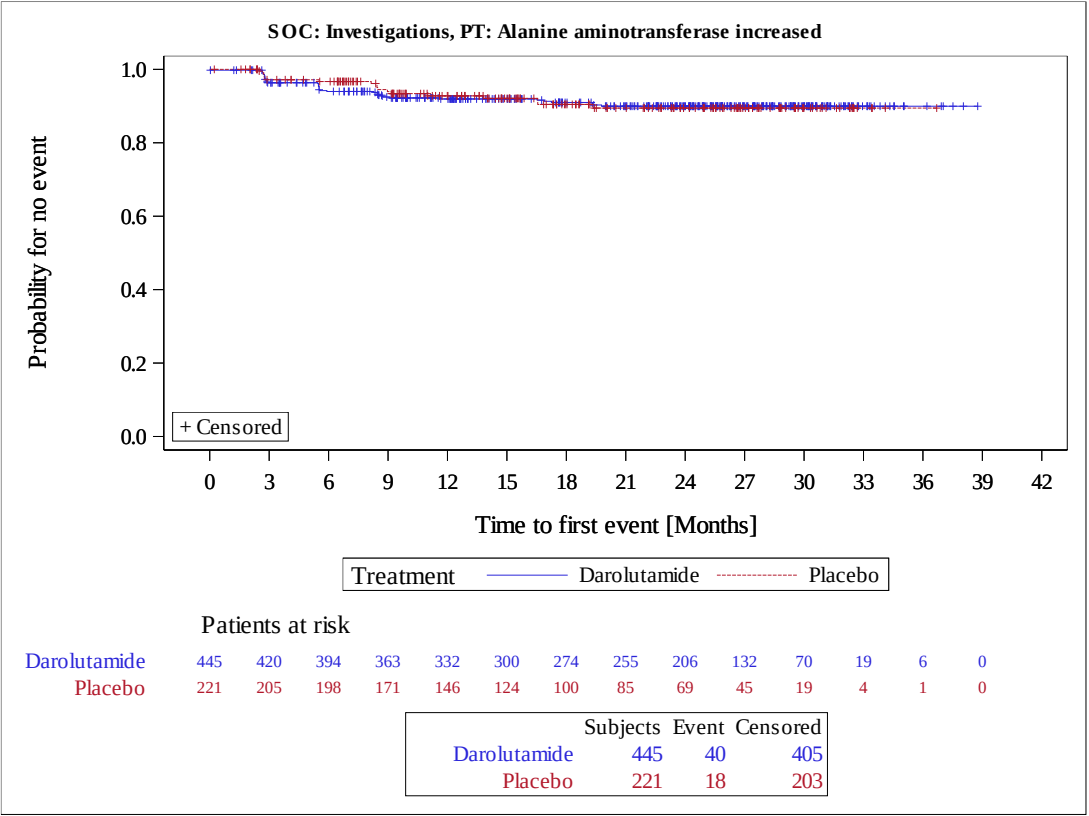


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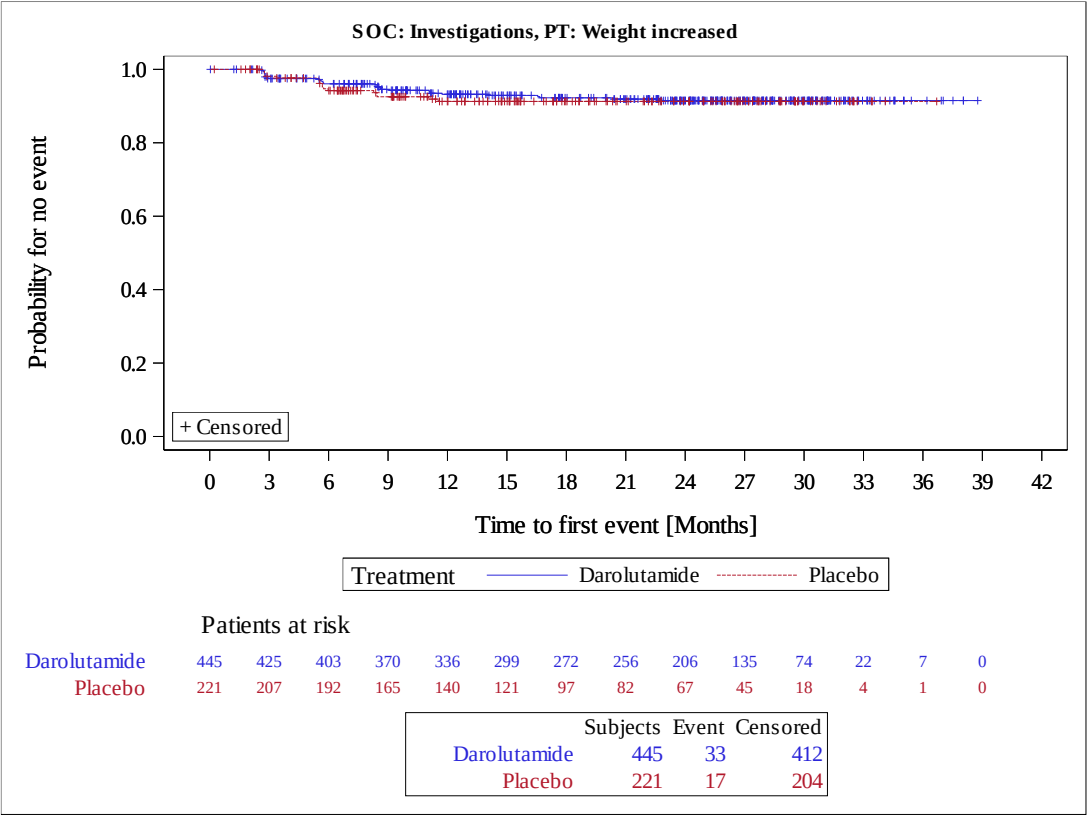


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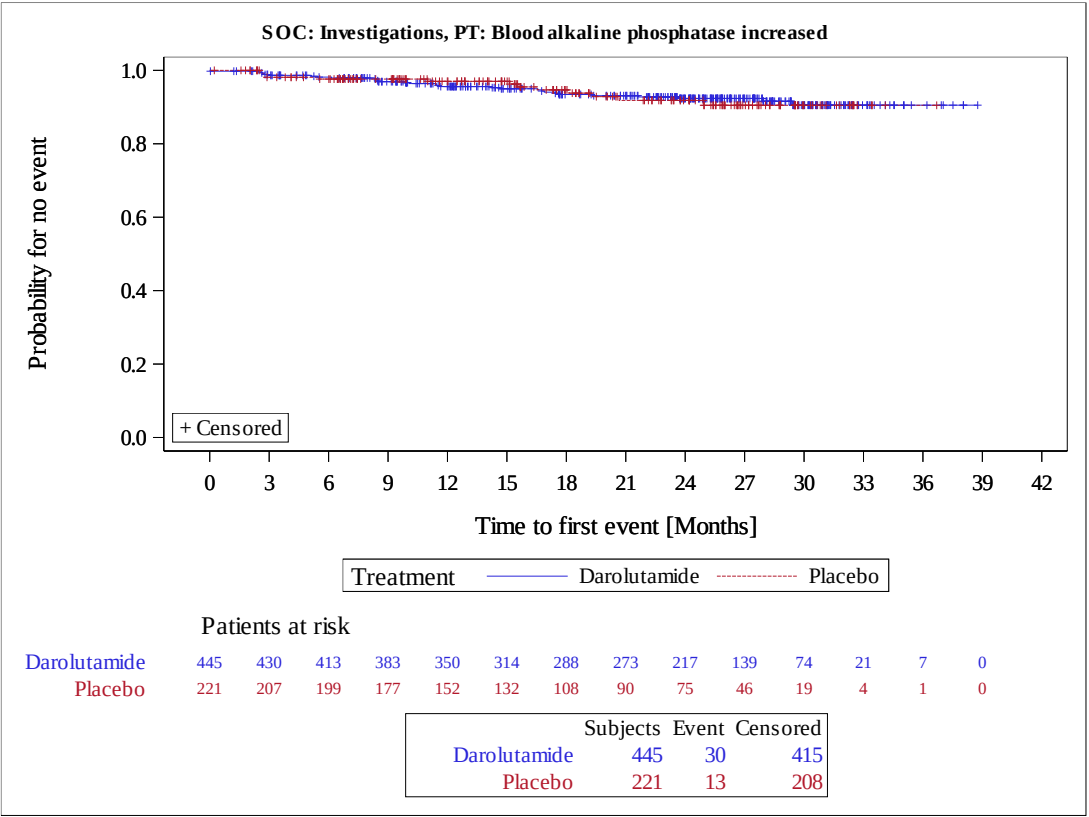


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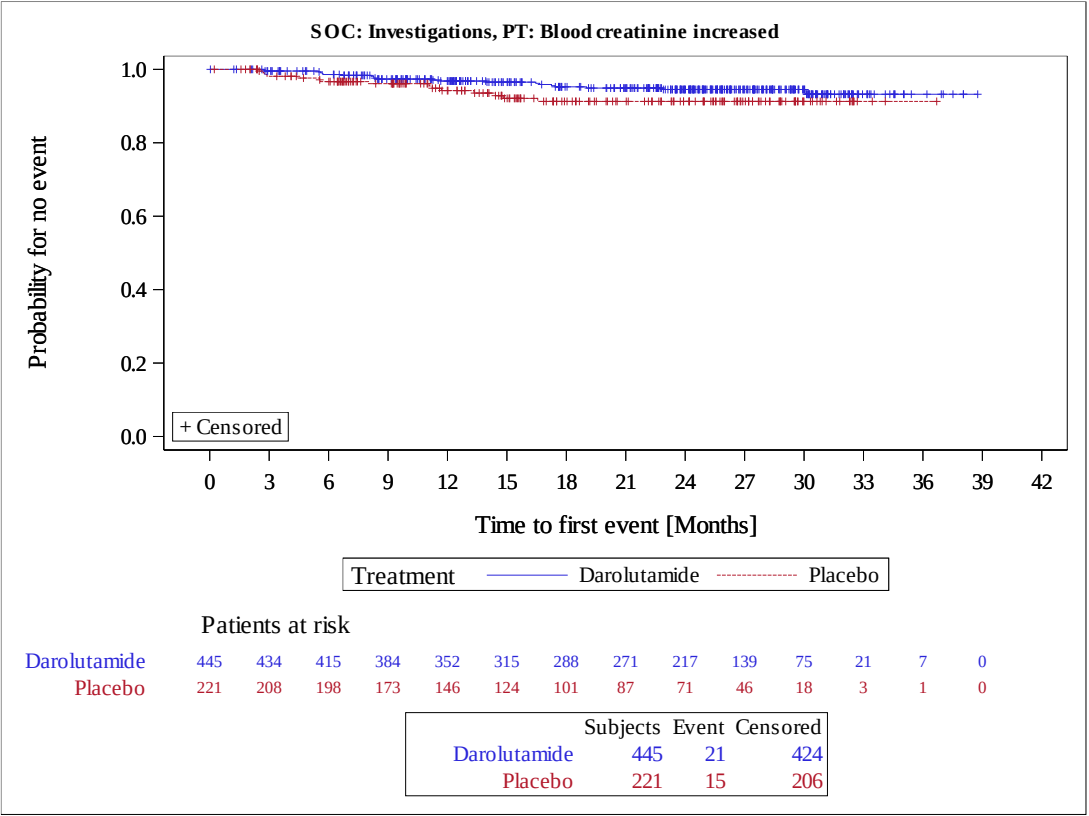


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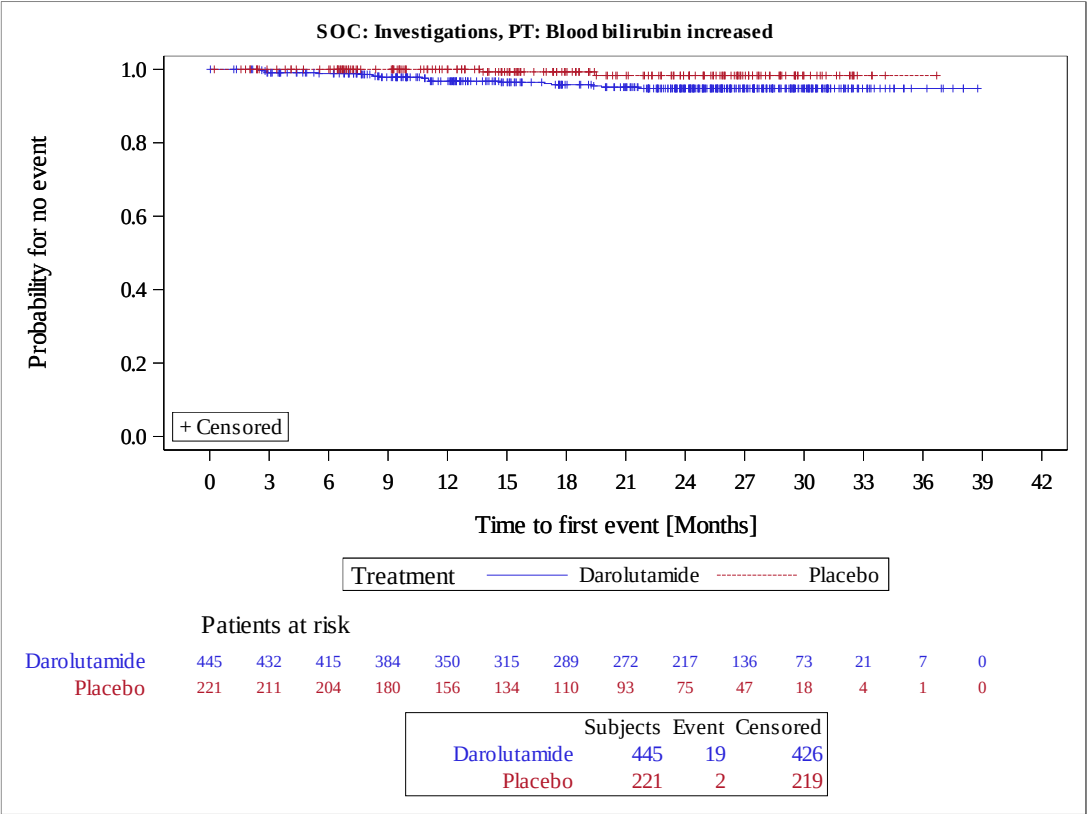


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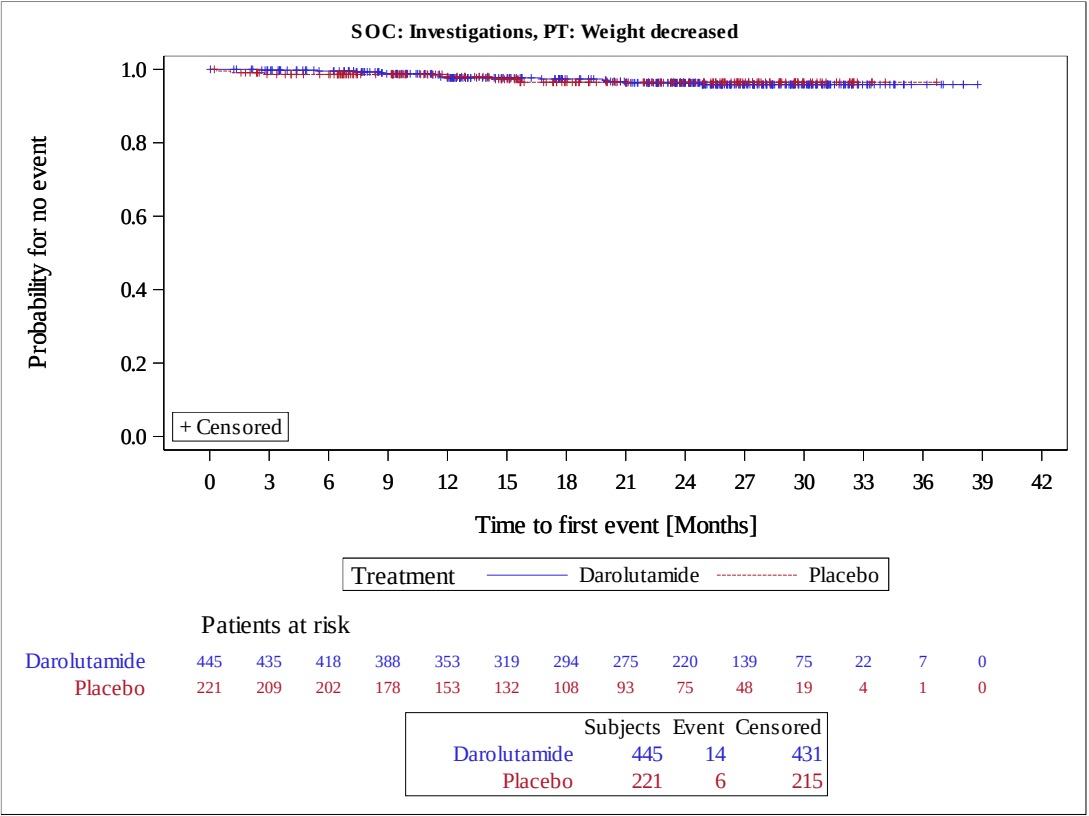


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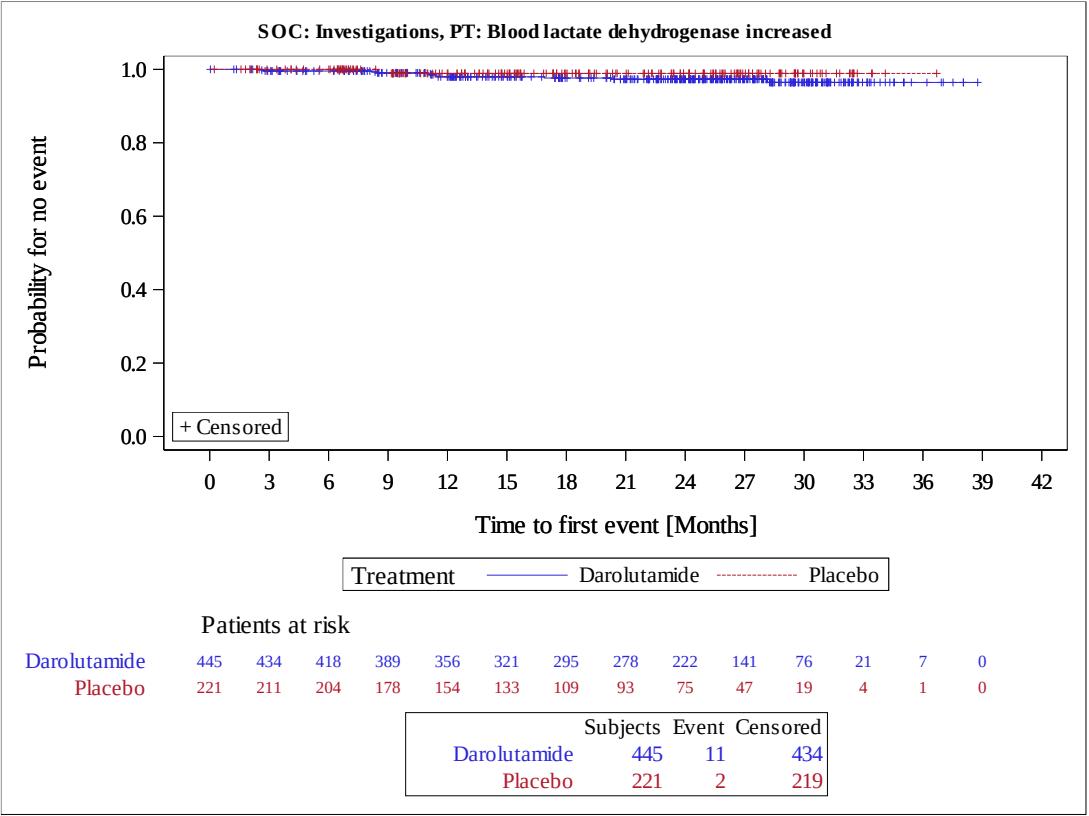


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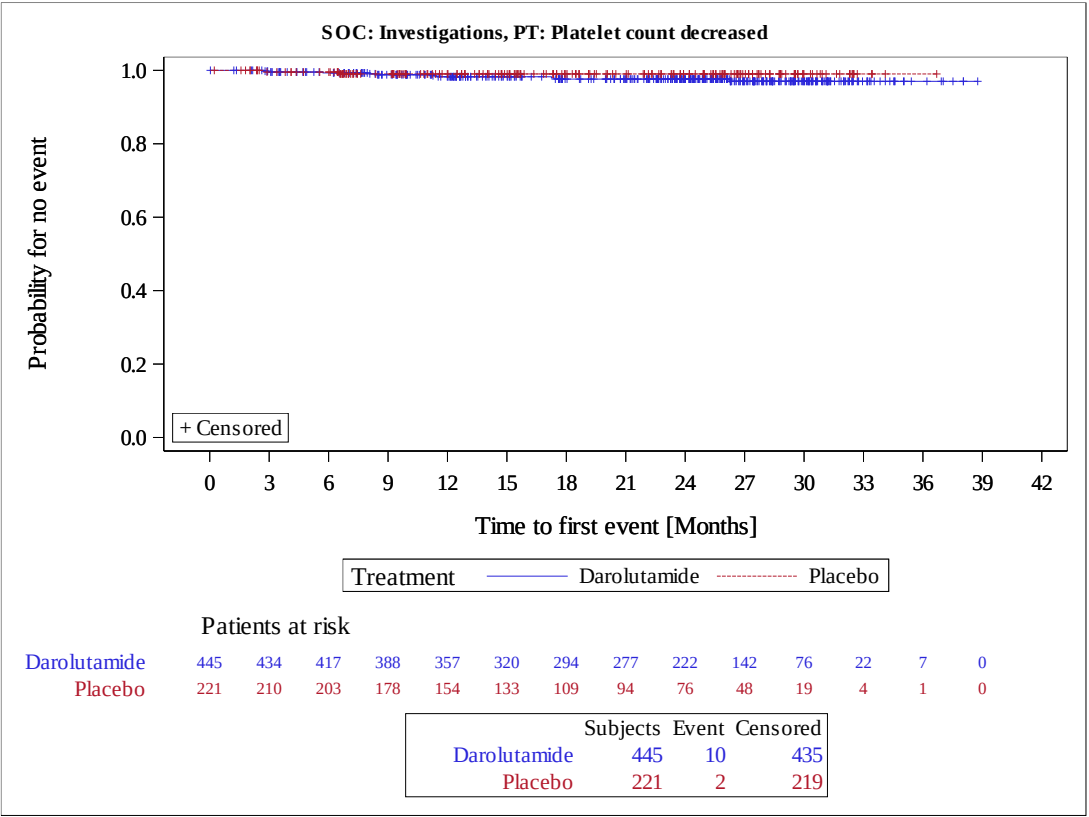


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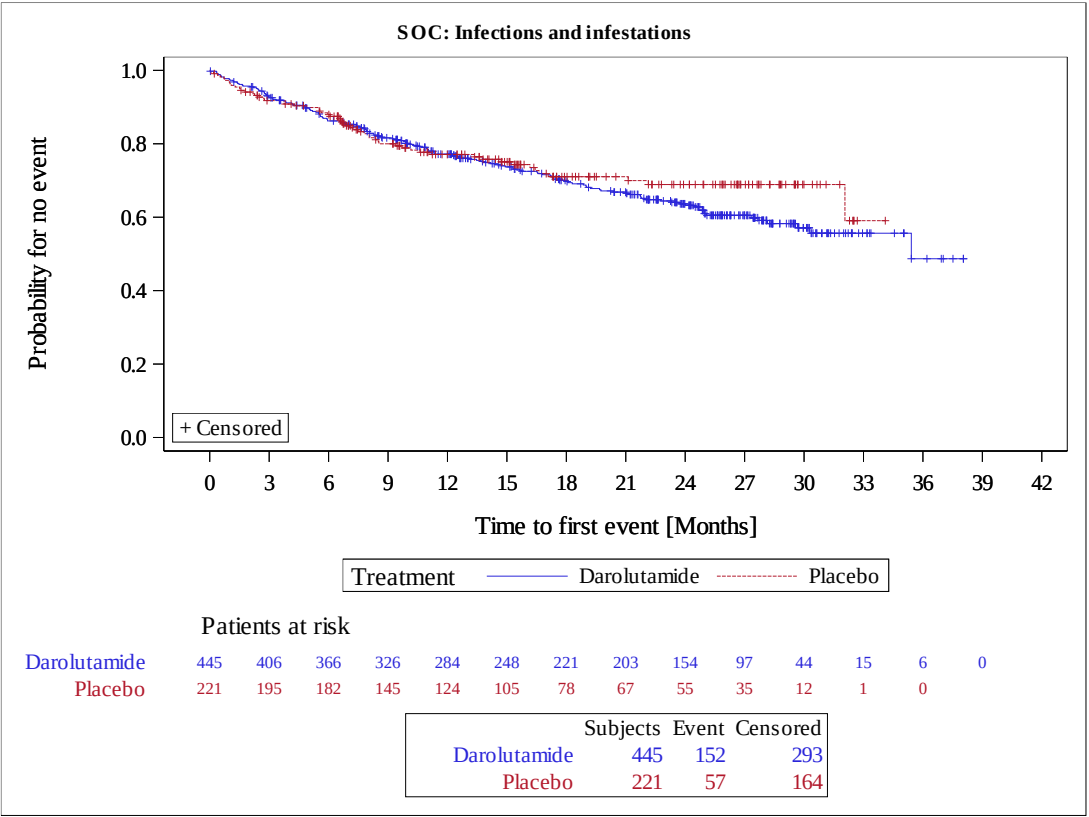


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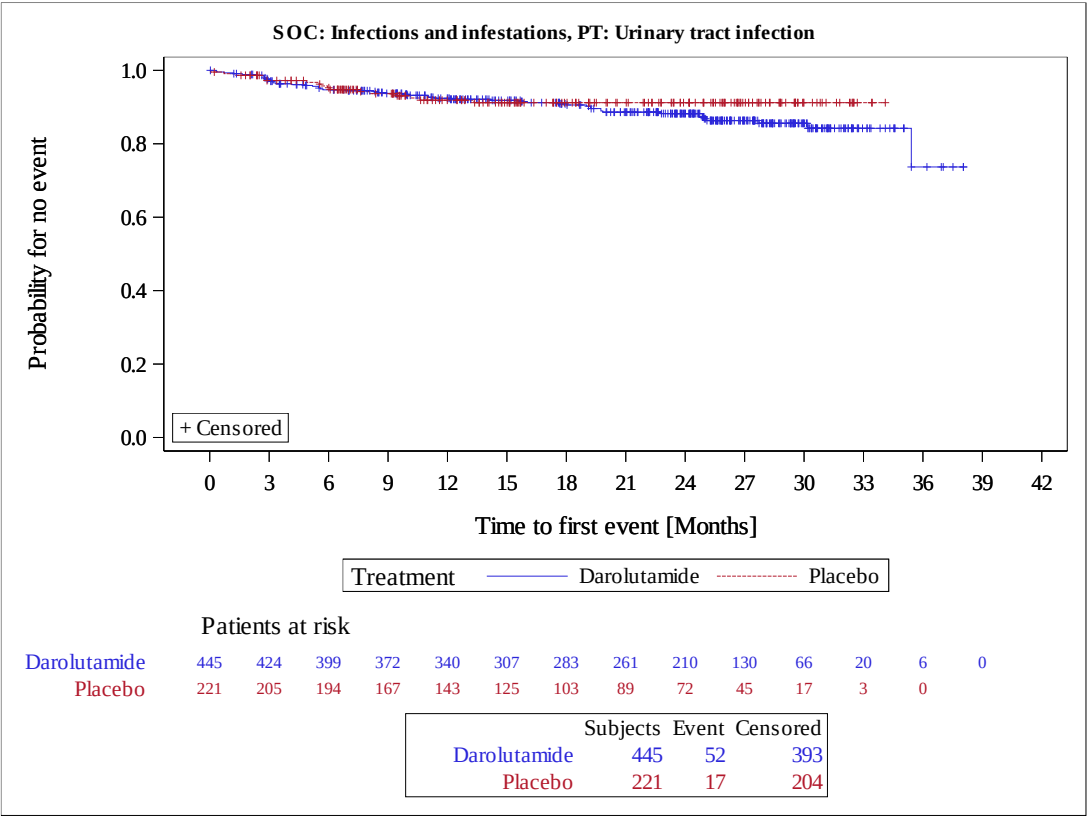


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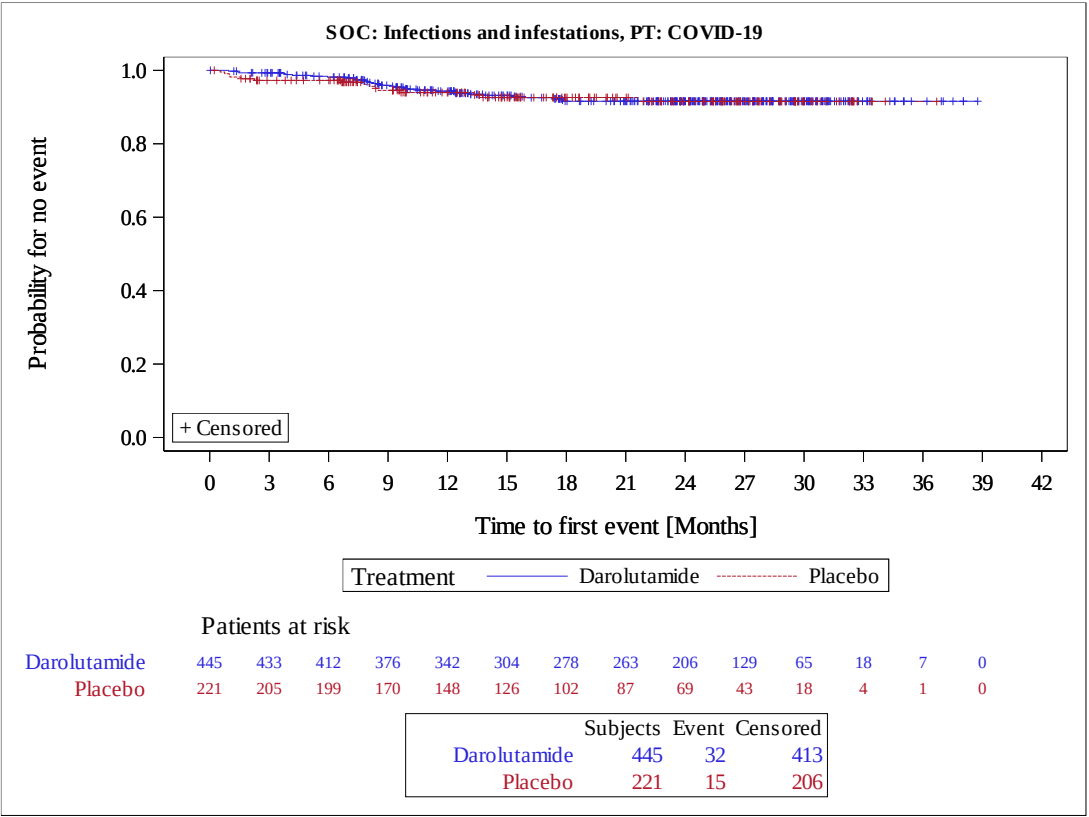


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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.3.1.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

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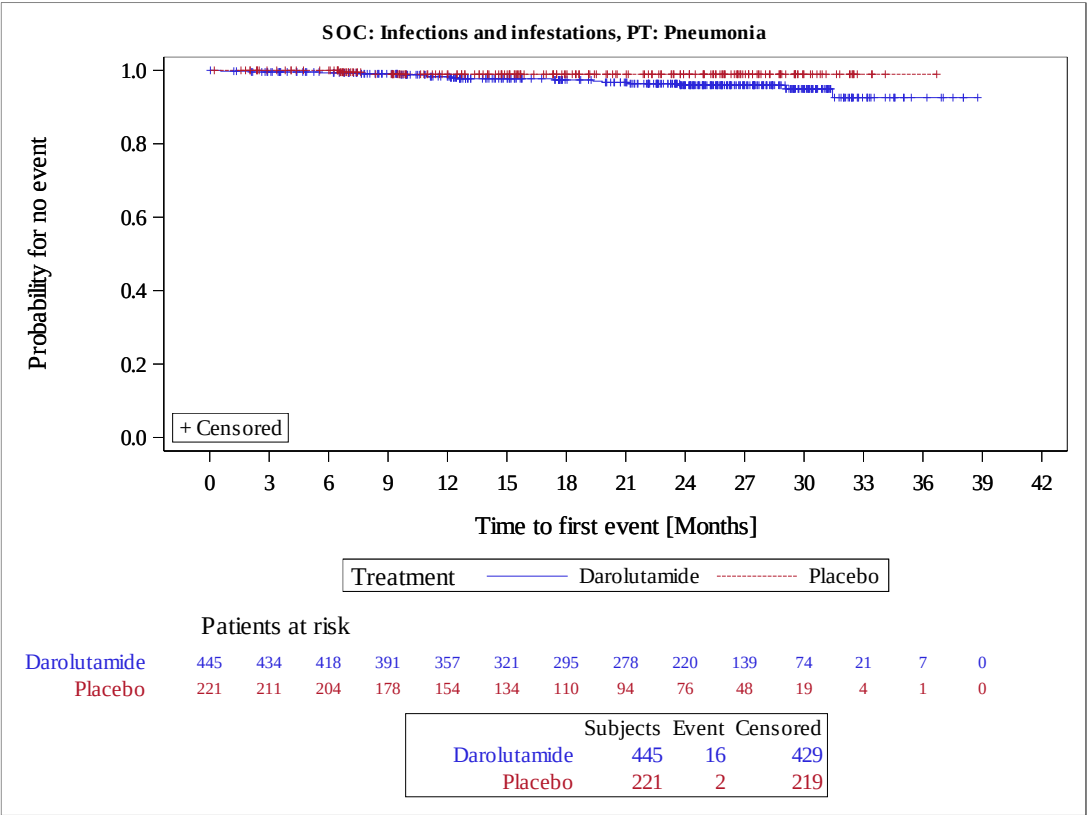


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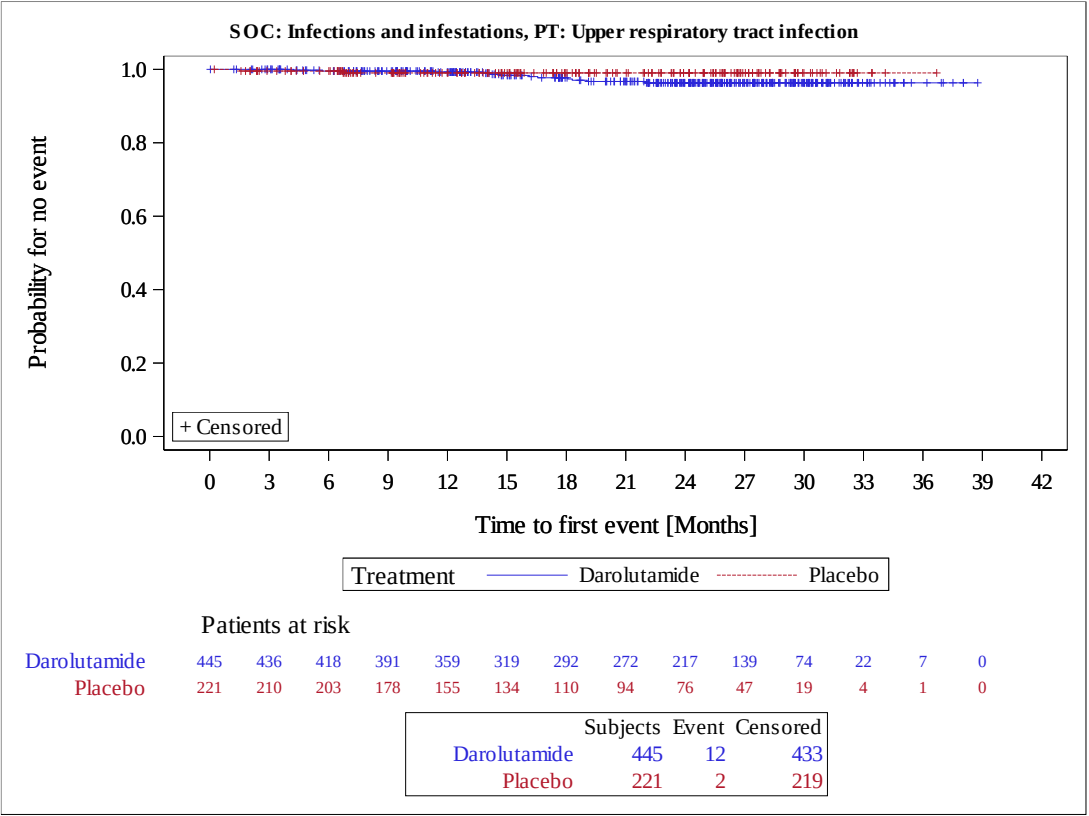


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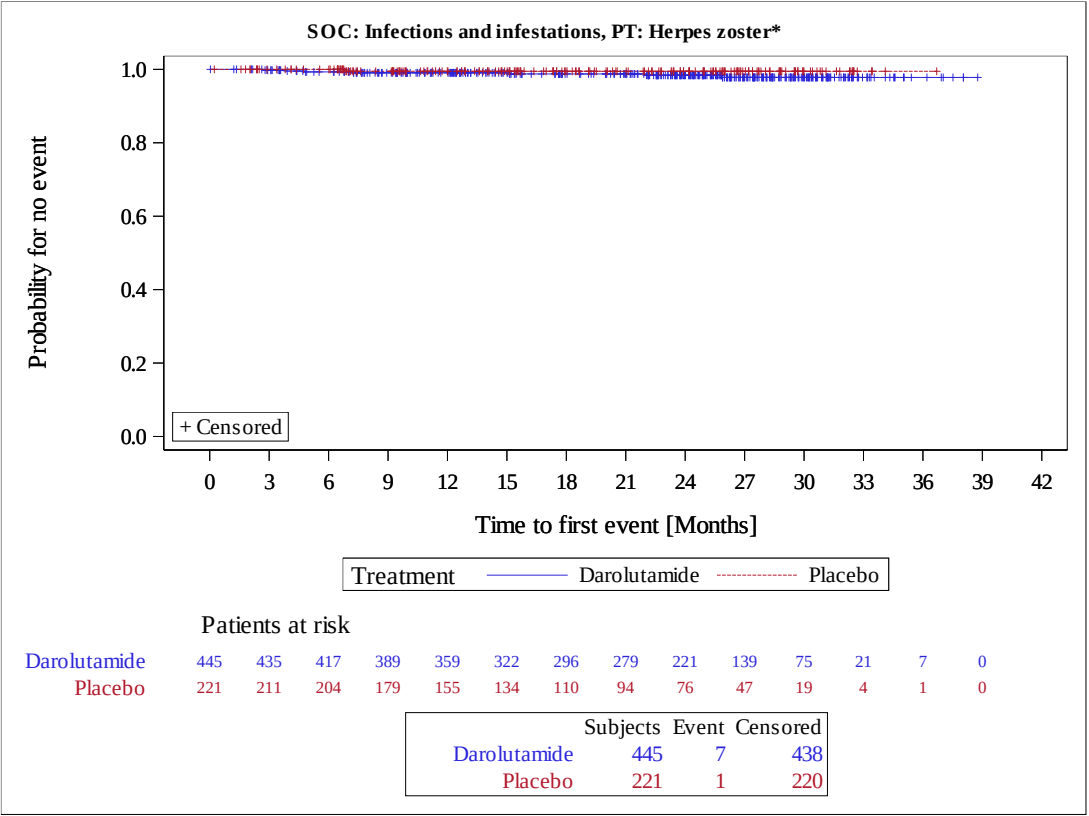


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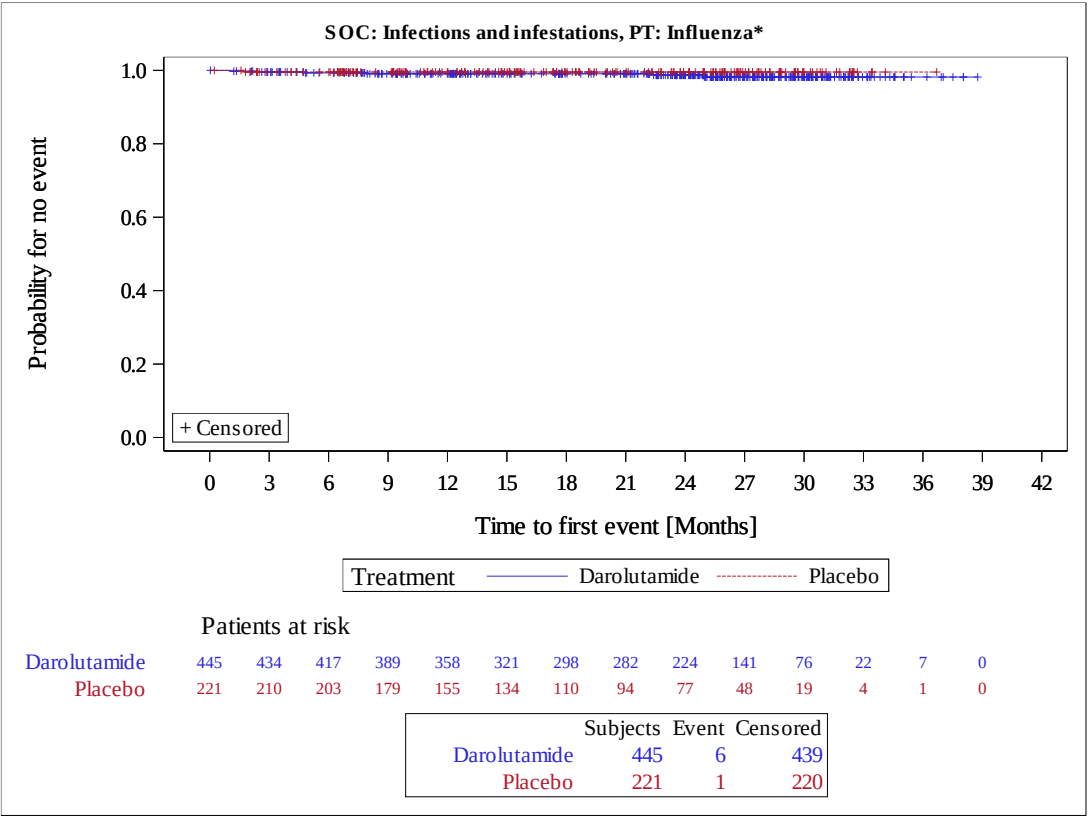


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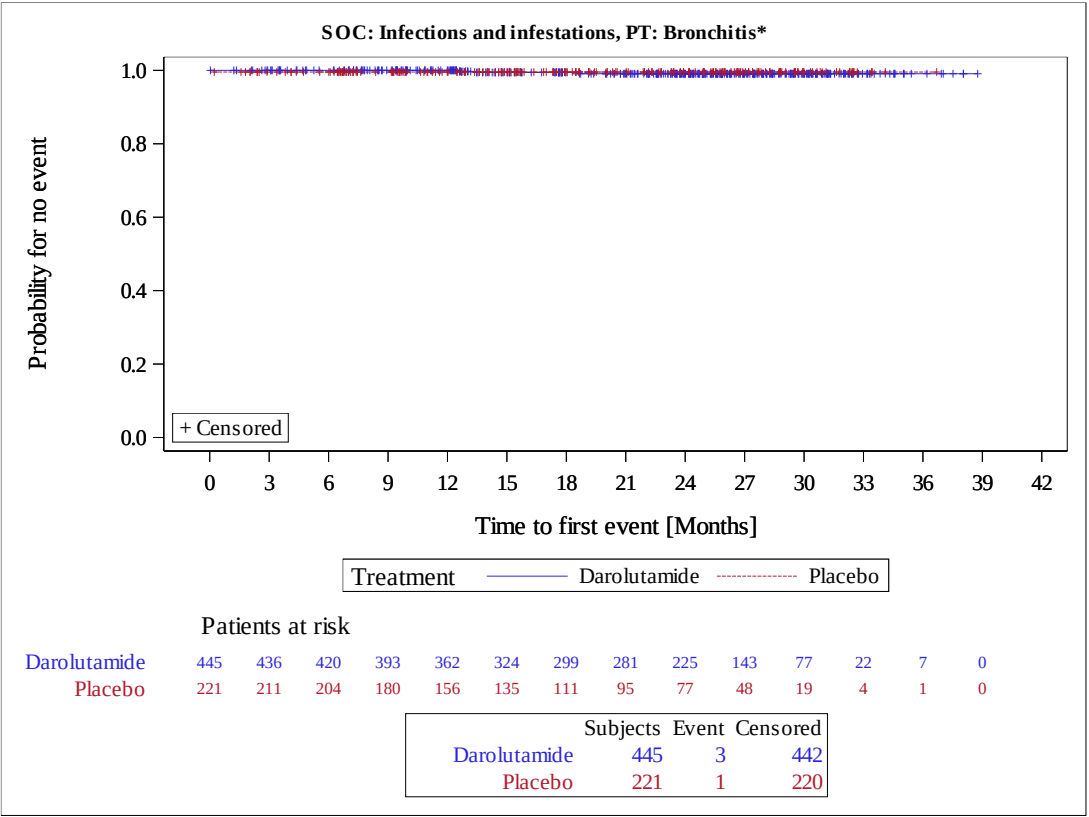


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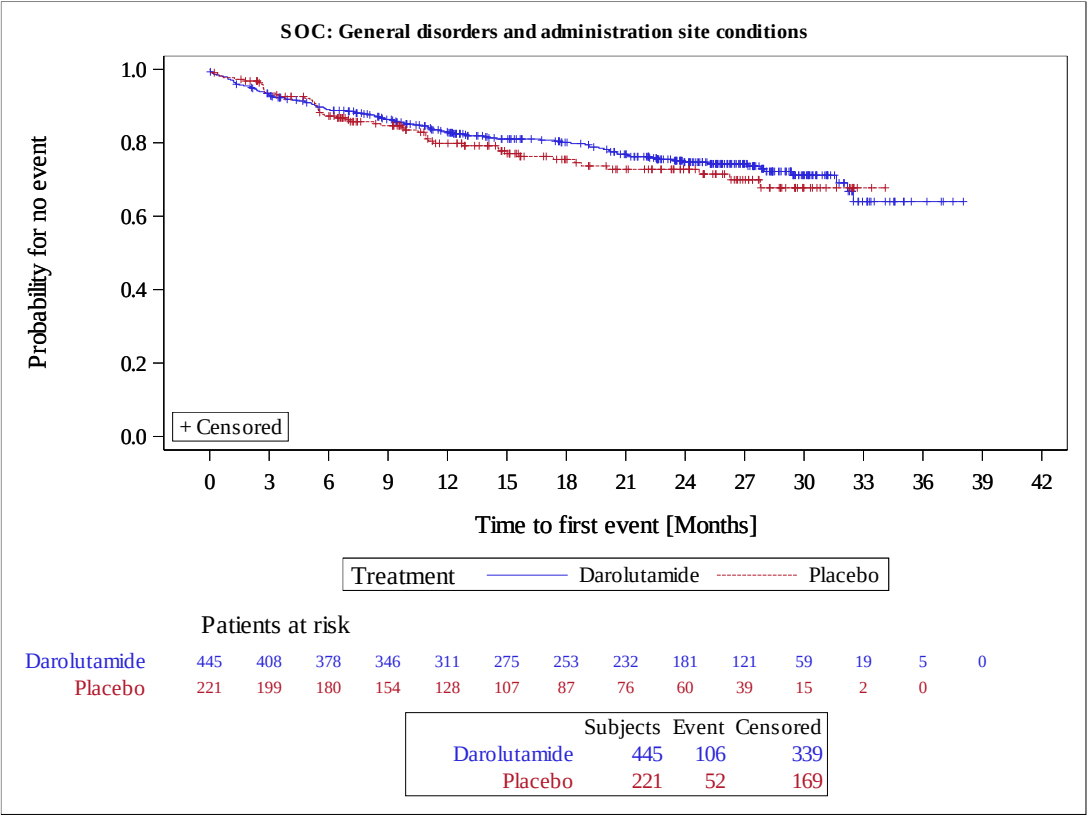


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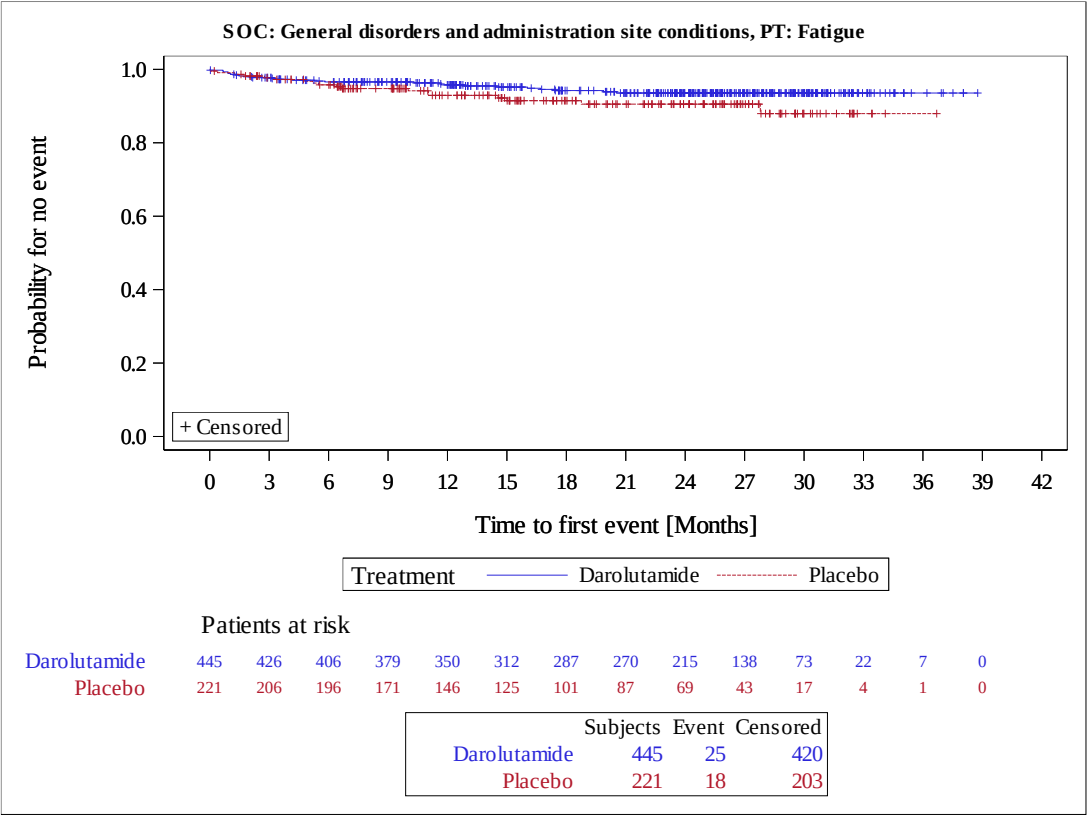


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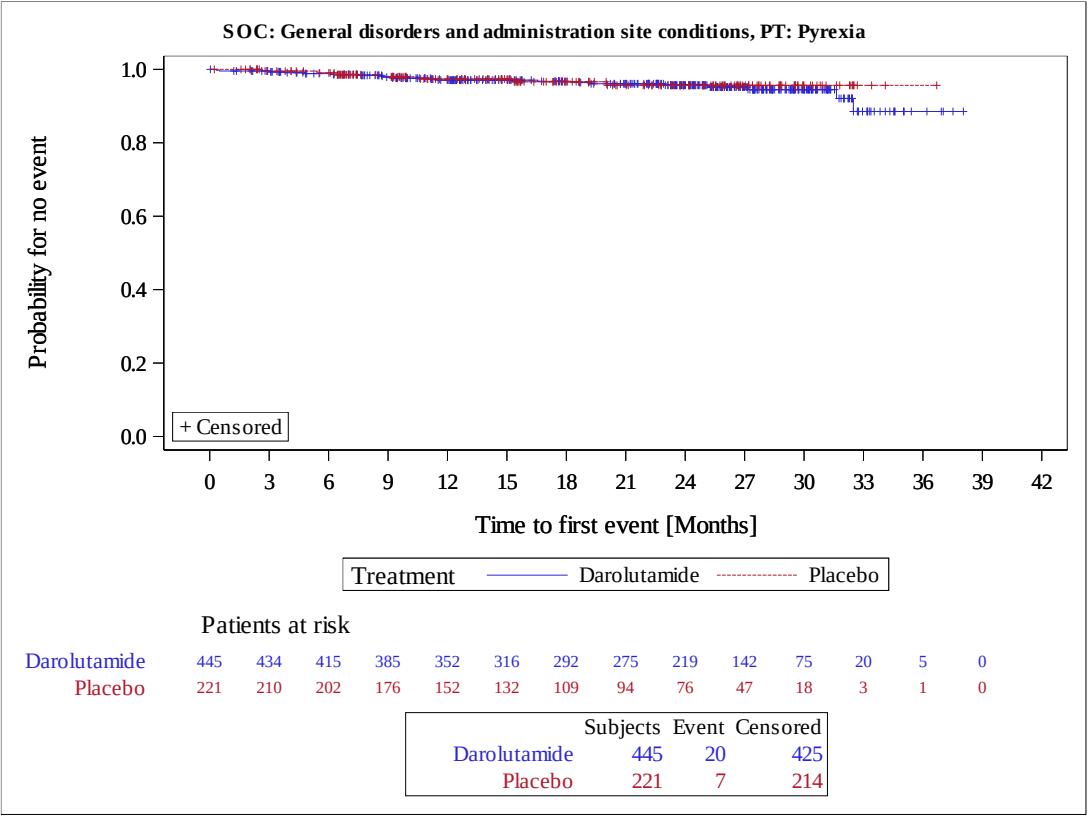


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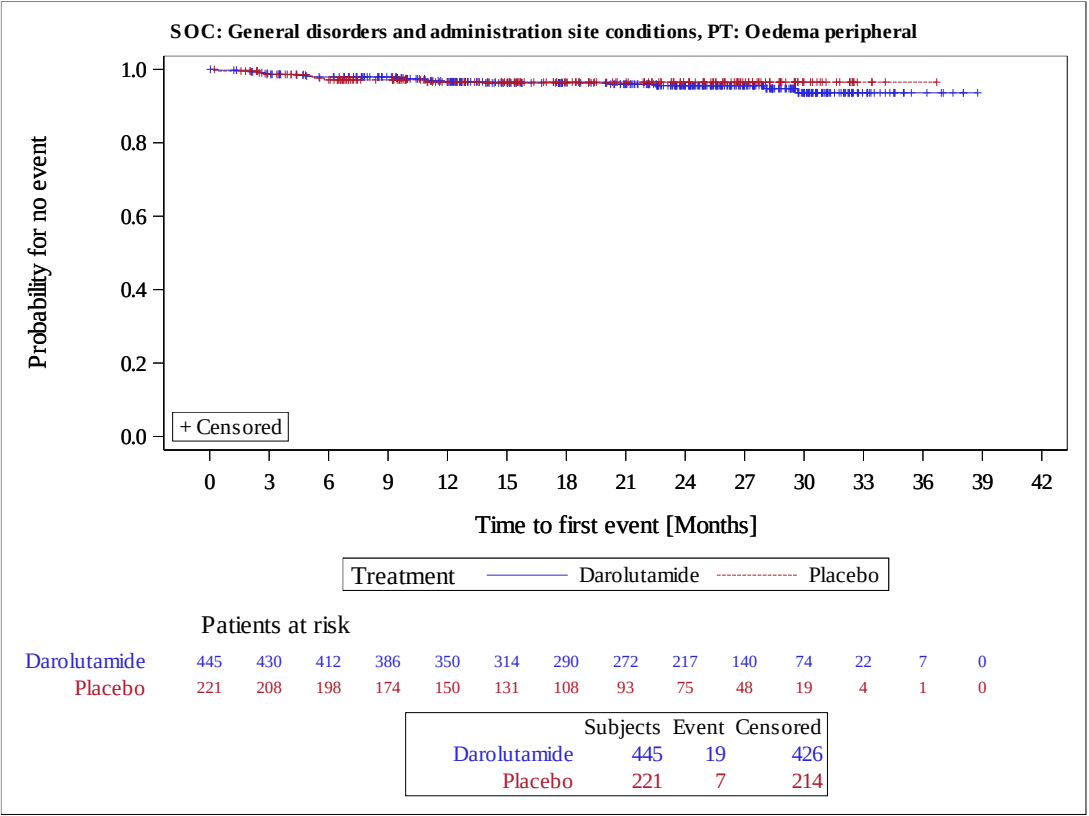


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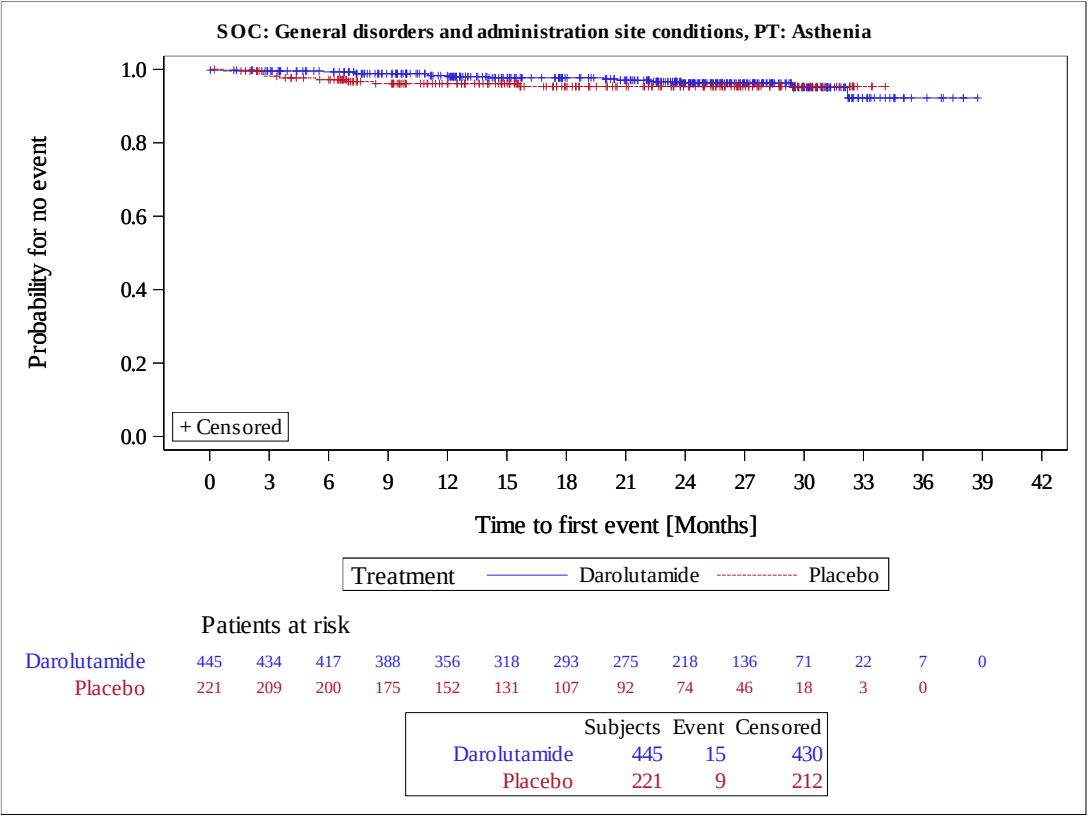


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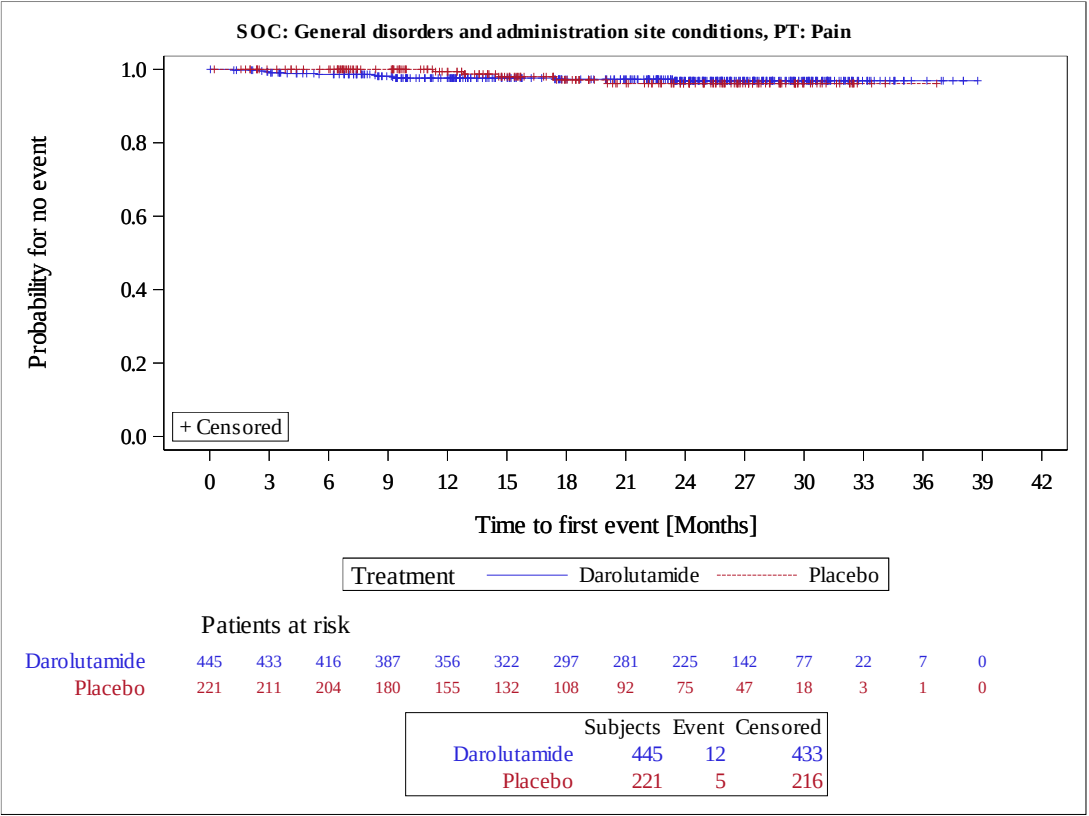


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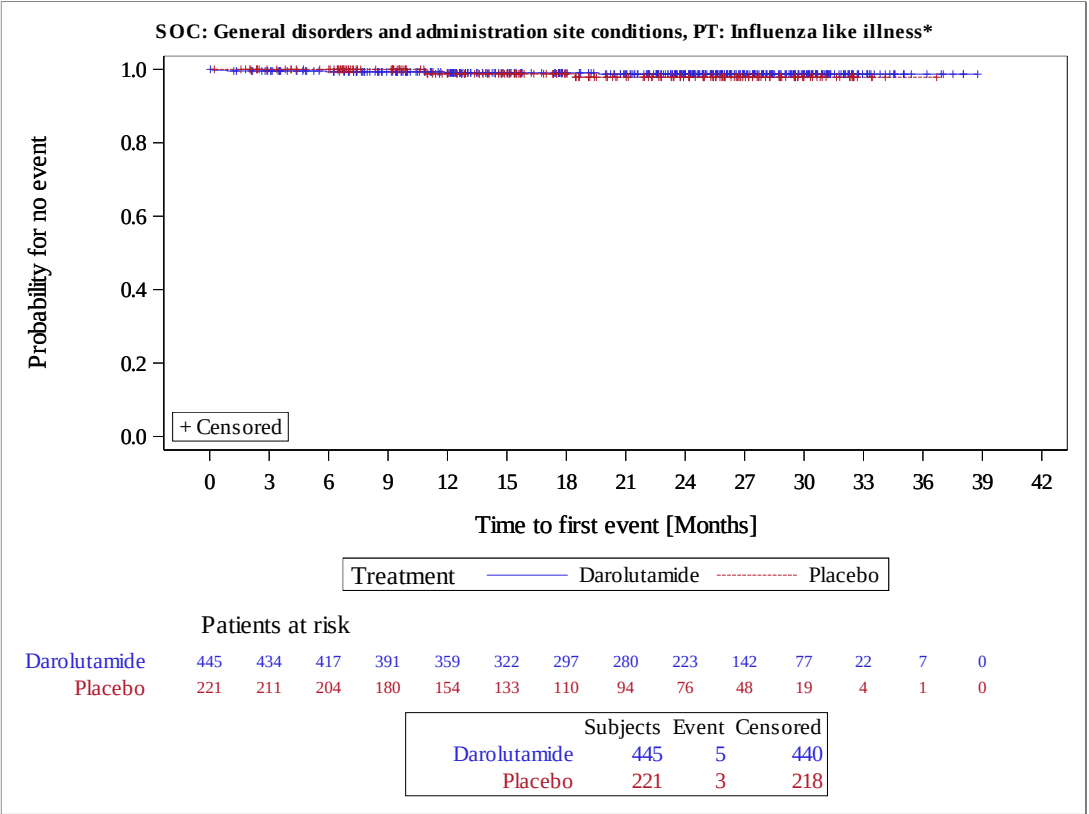


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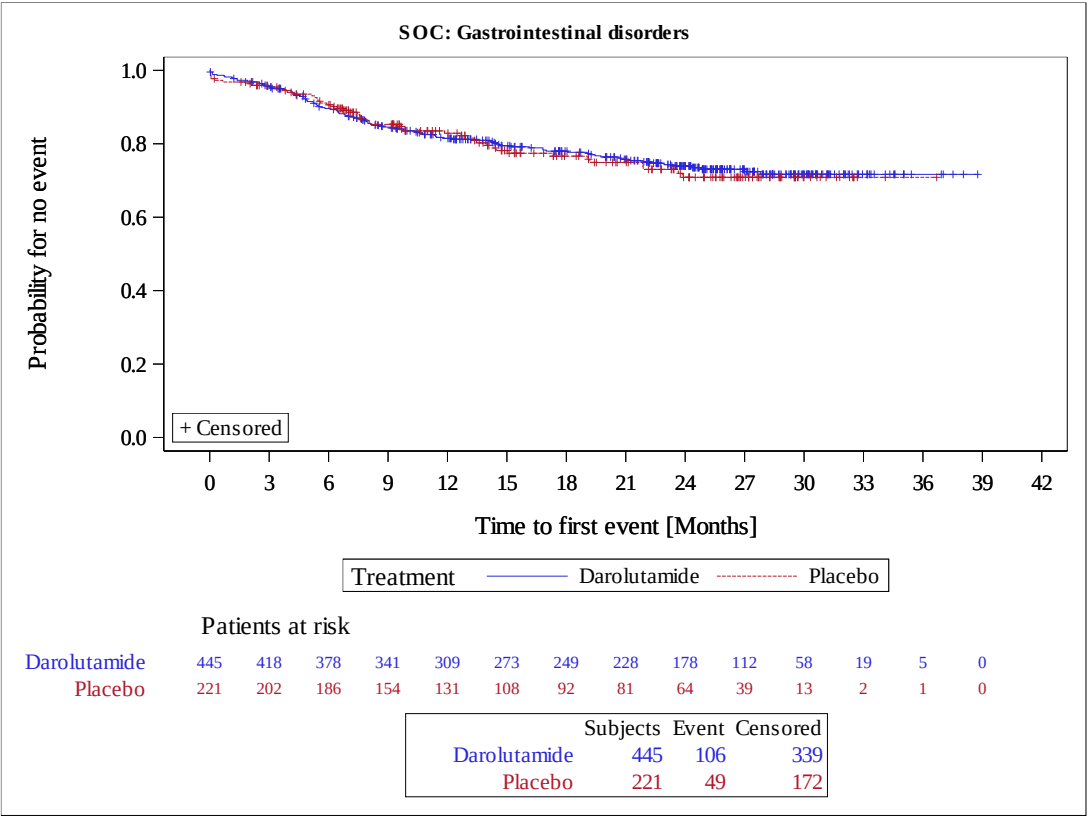


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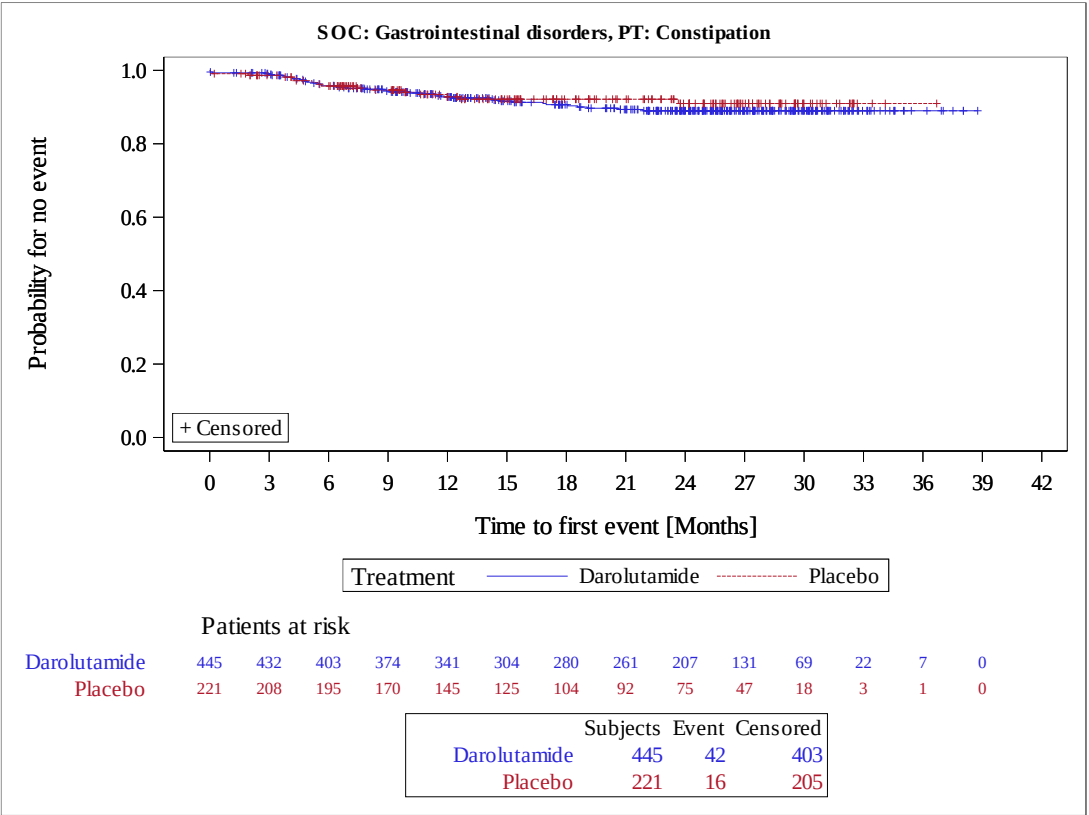


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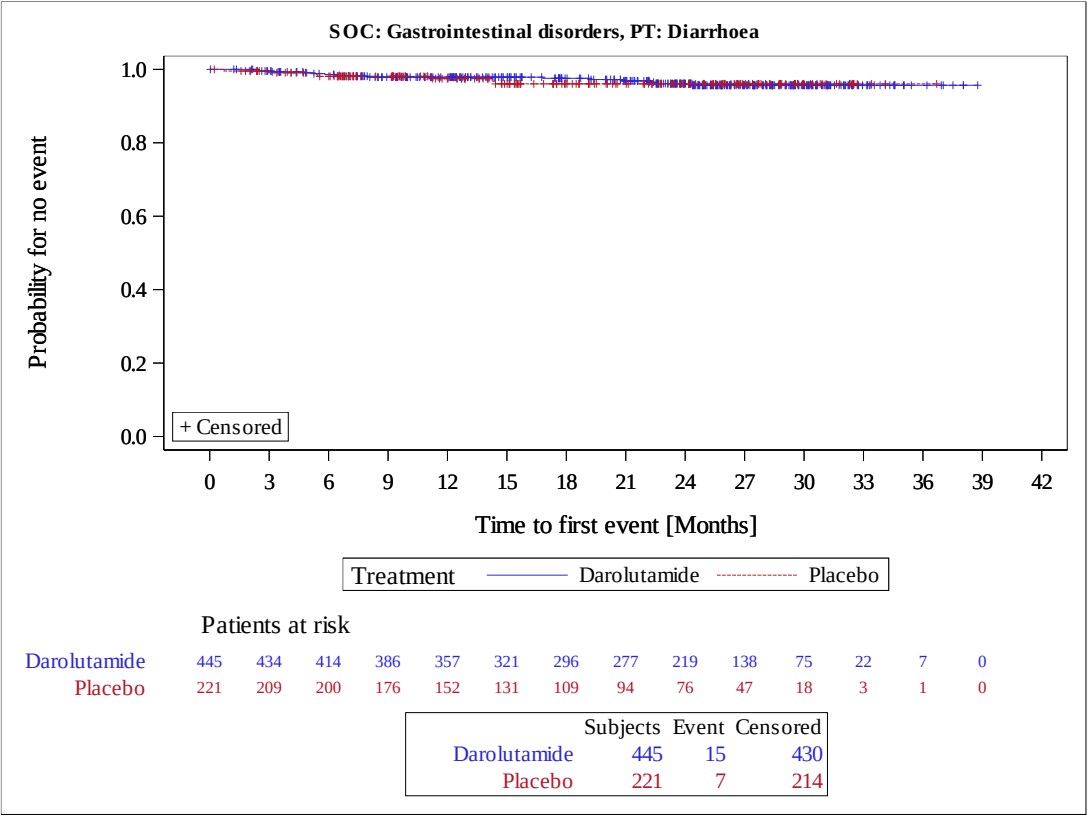


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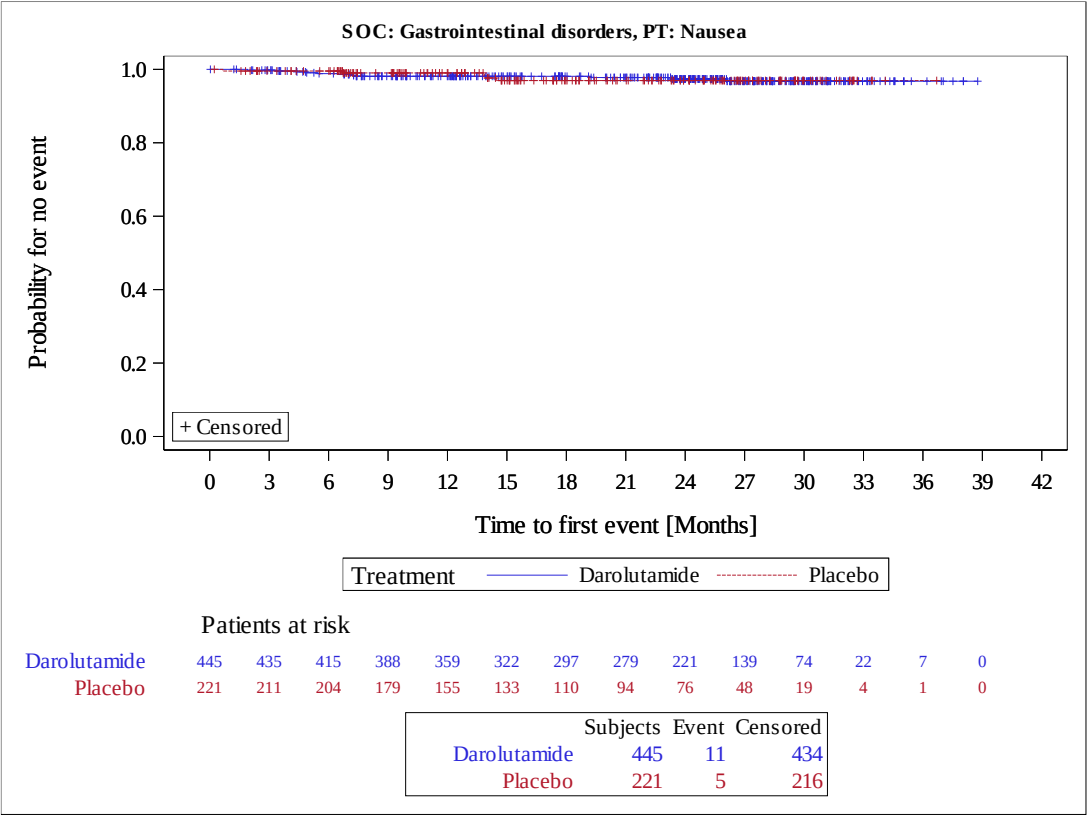


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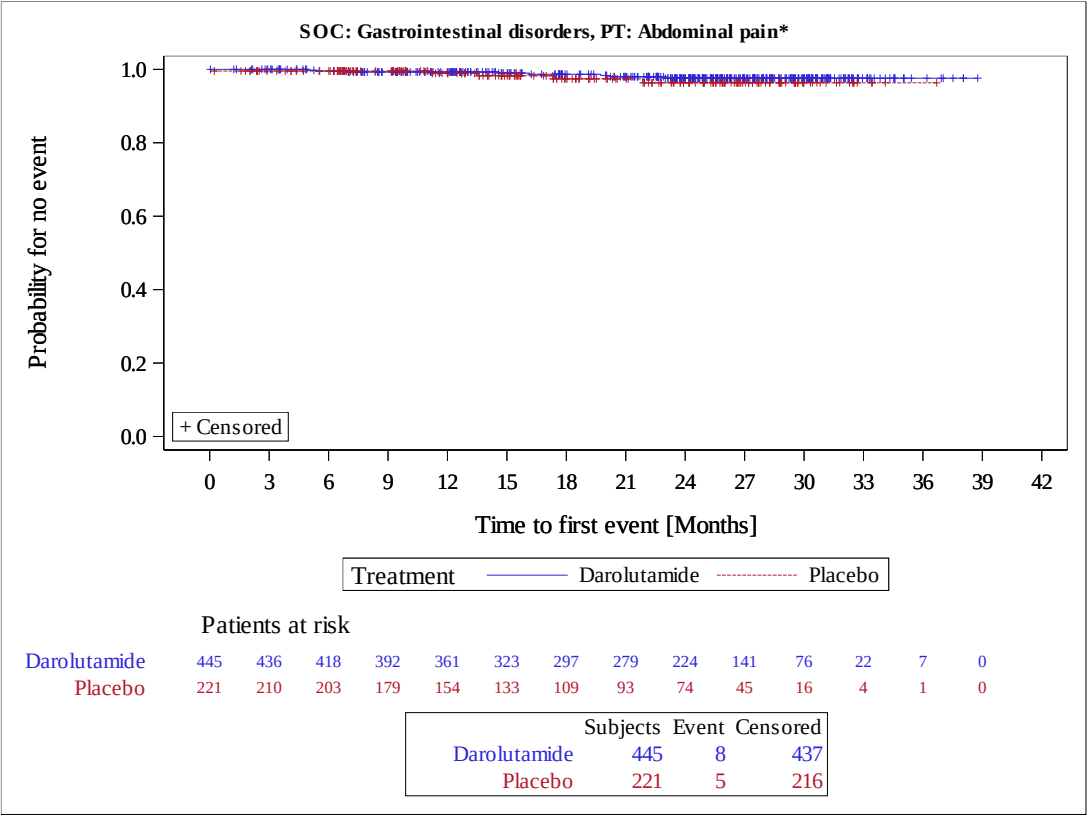


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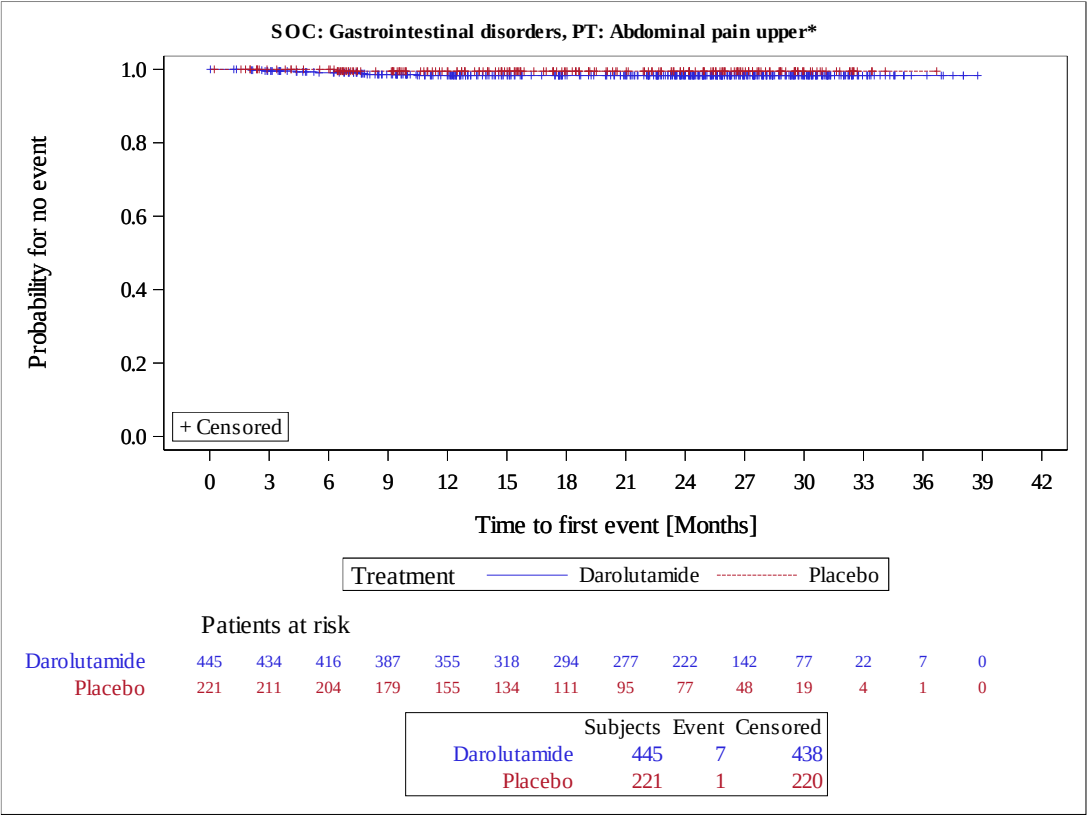


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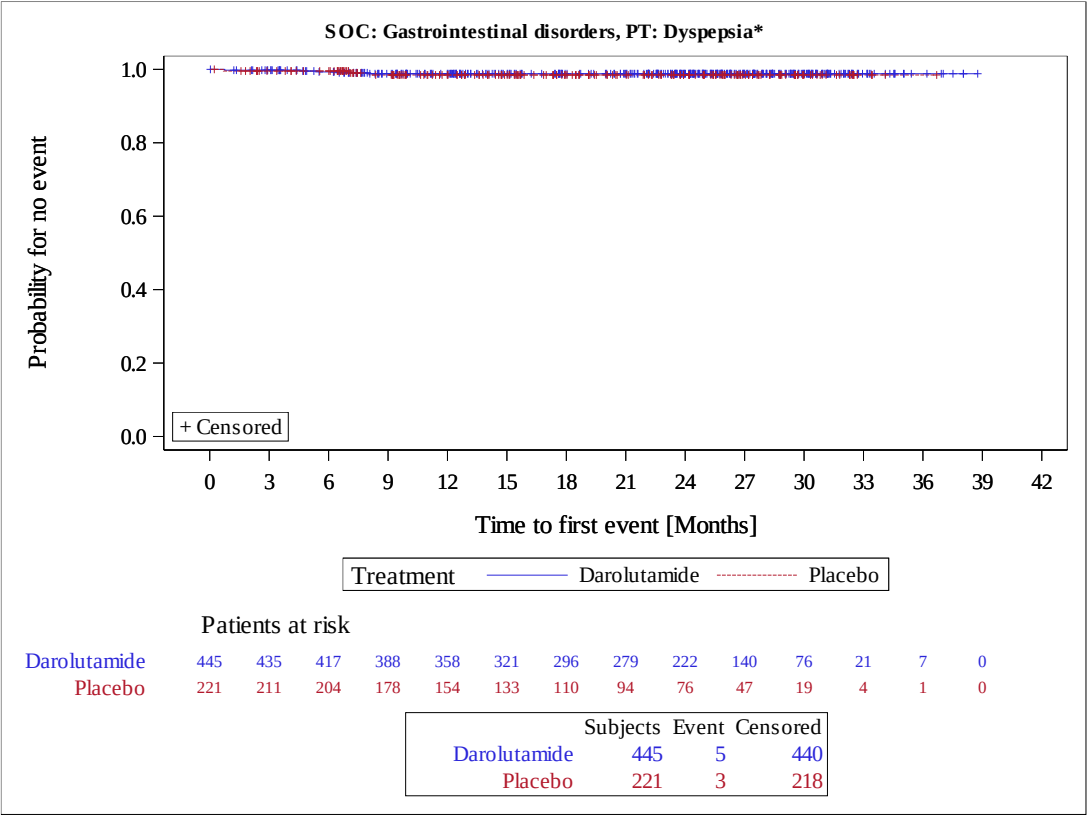


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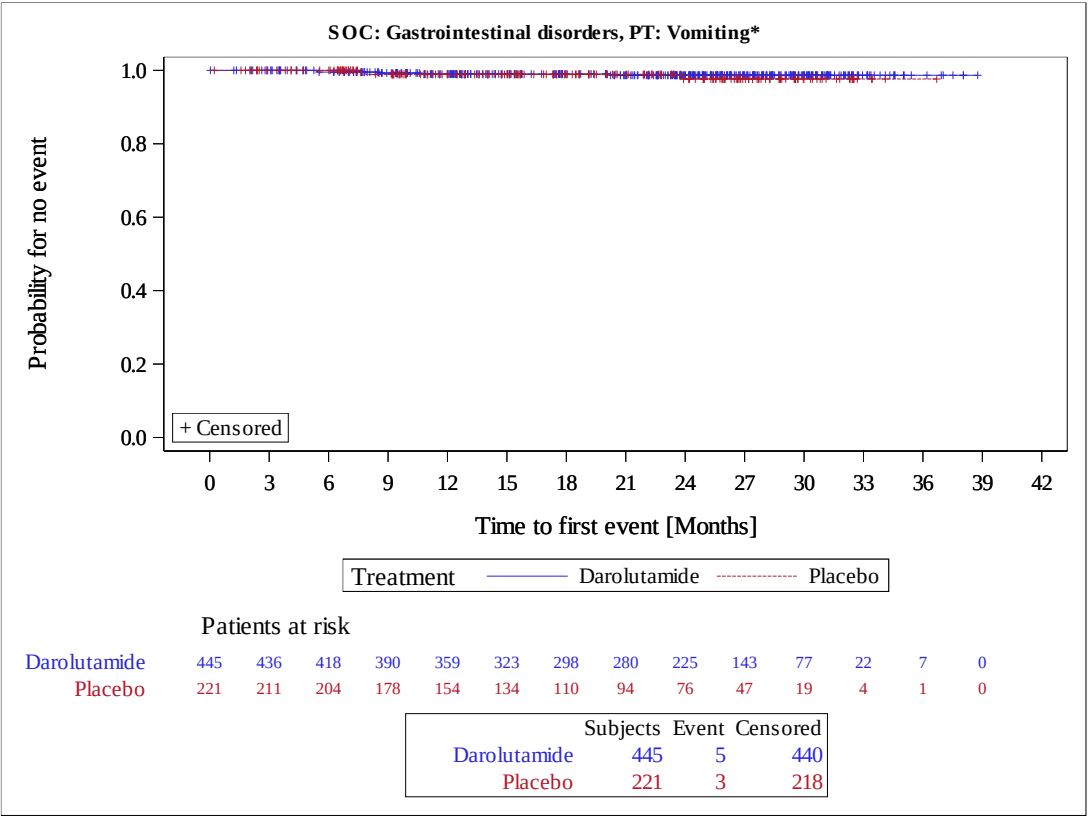


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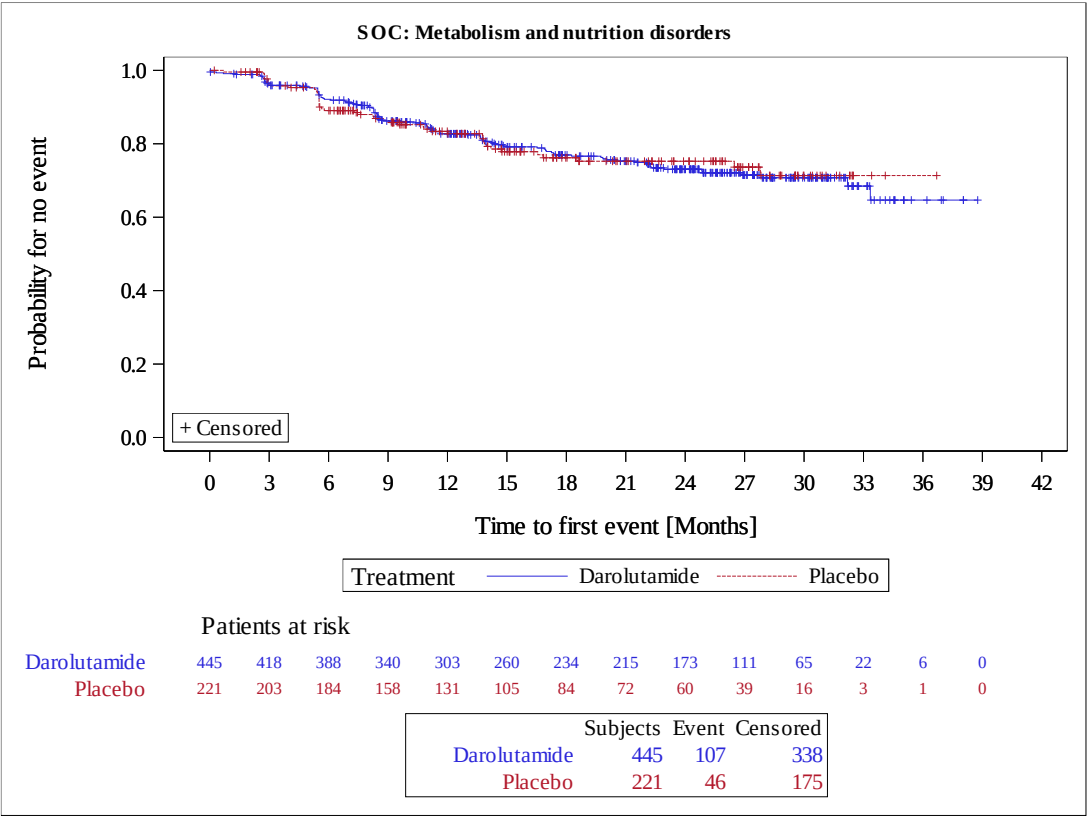


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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.3.1.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

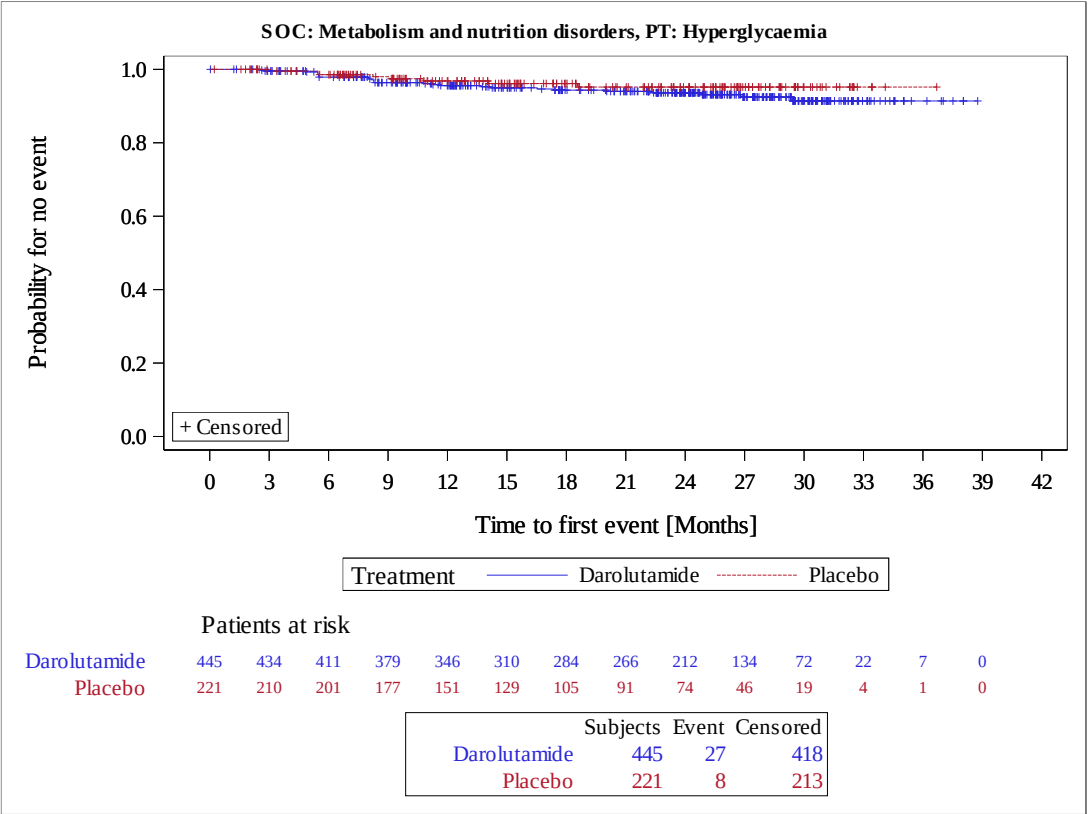


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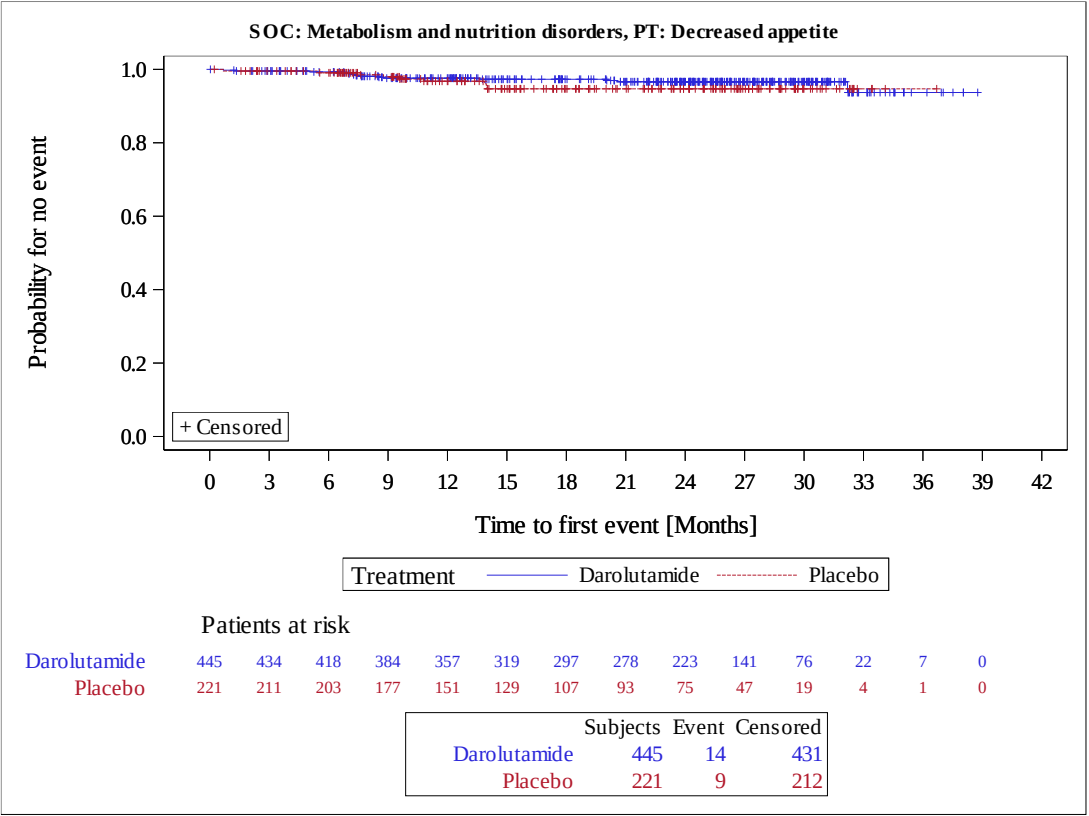


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BAY 1841788 / 21140 - 07JUN2024
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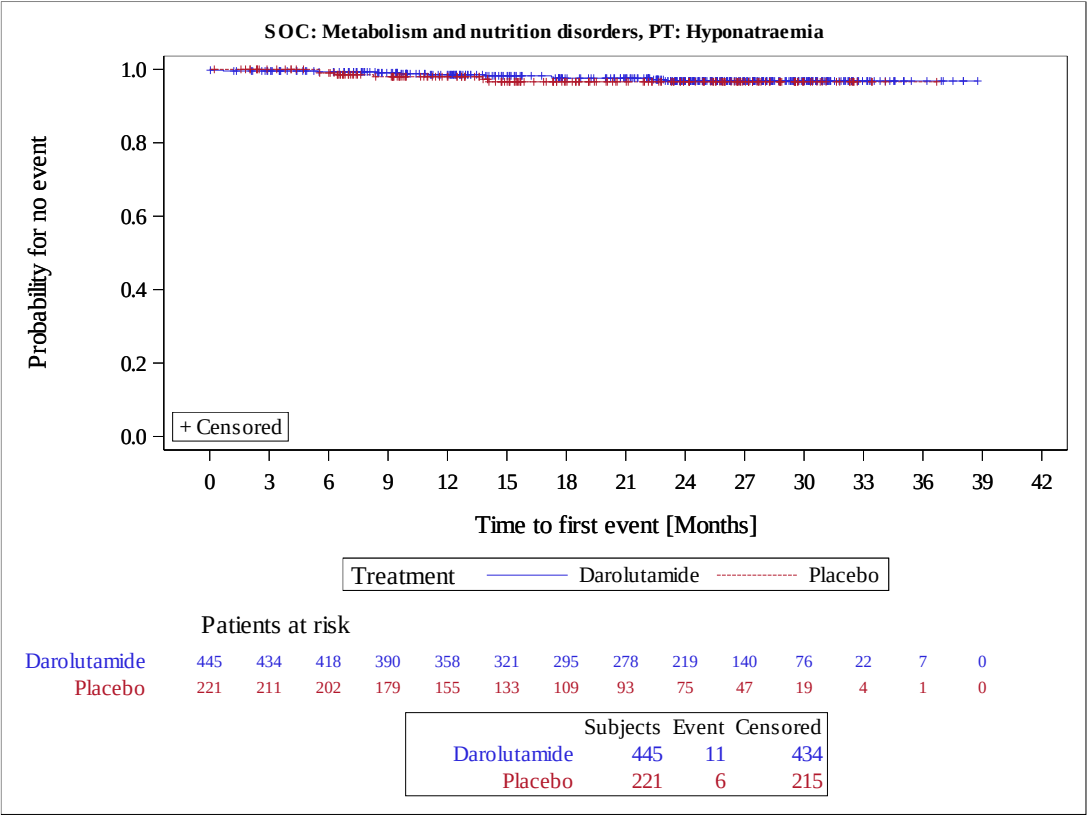


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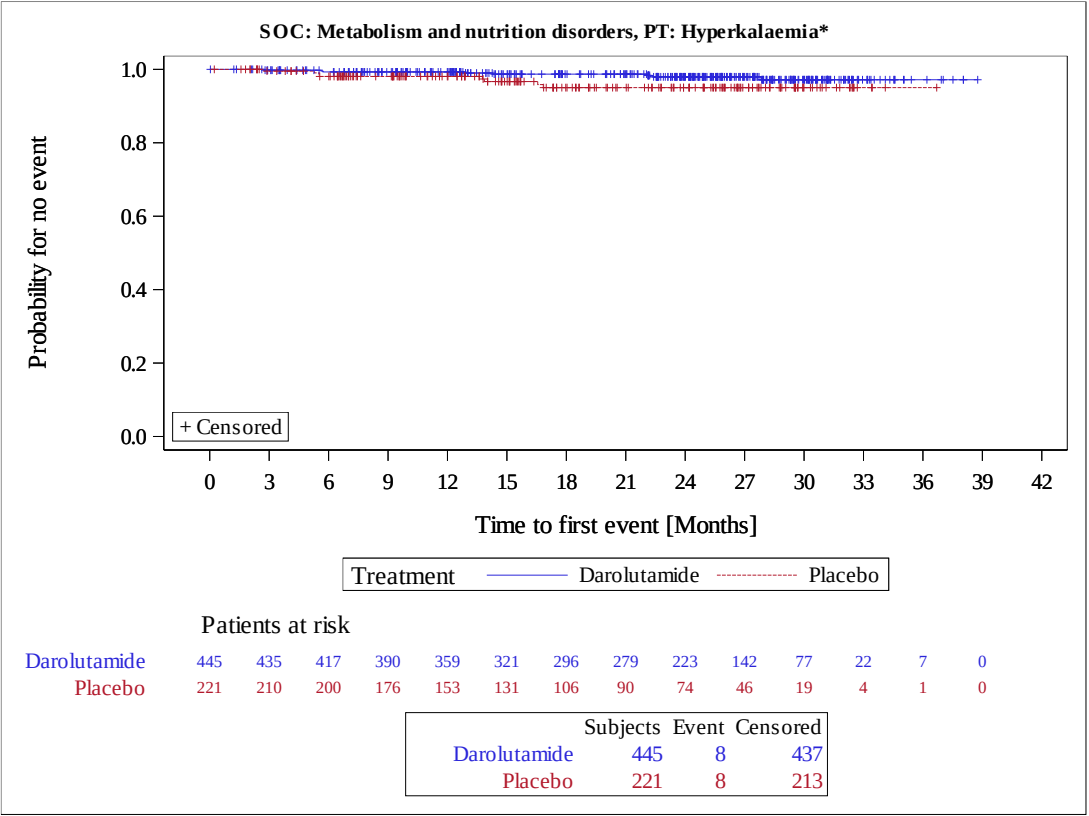


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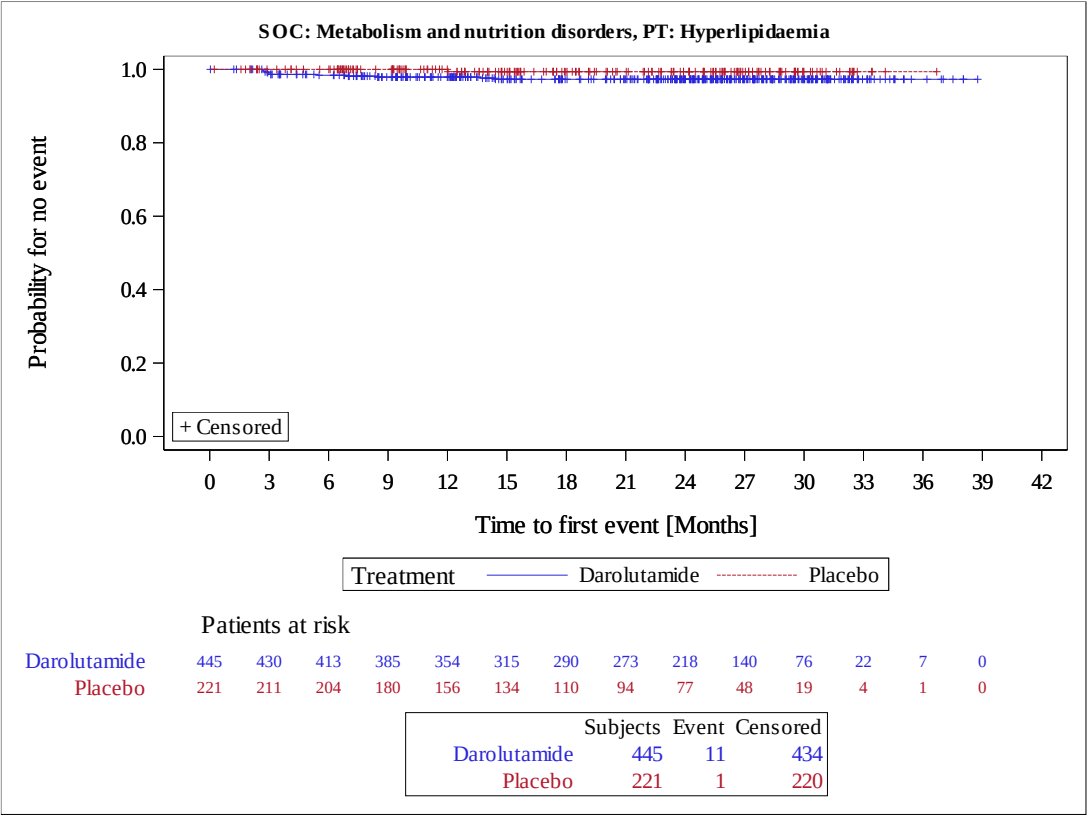


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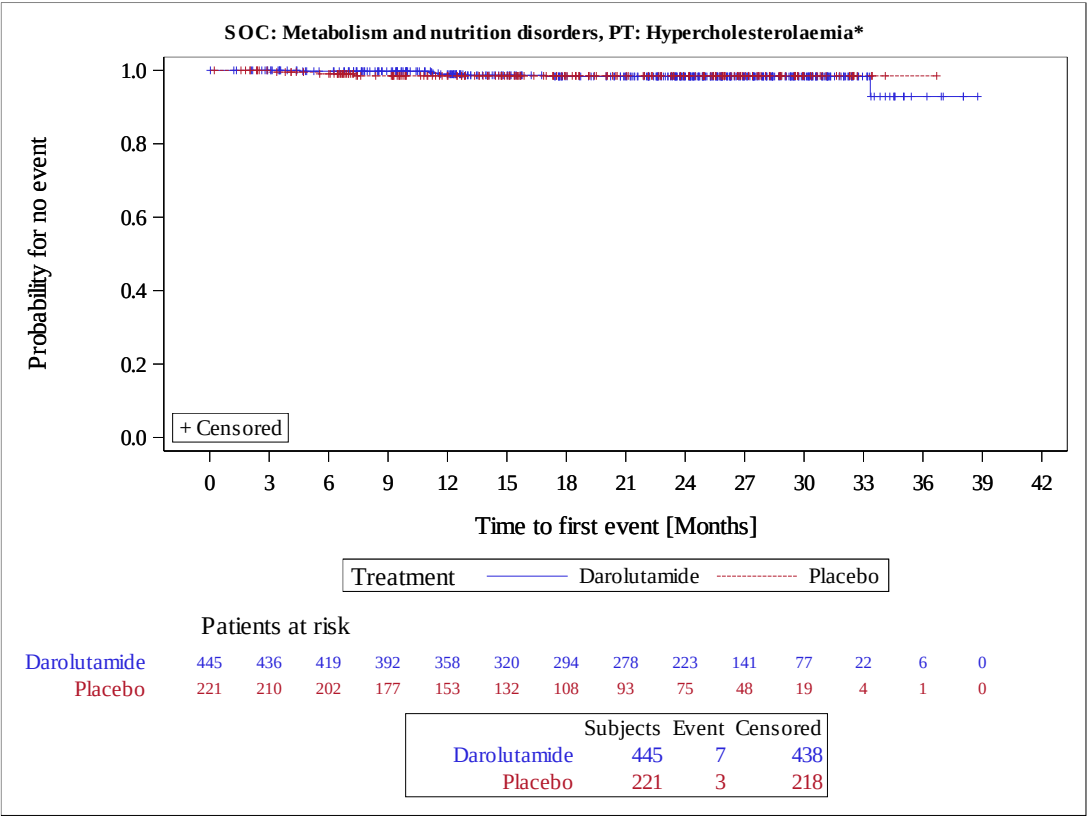


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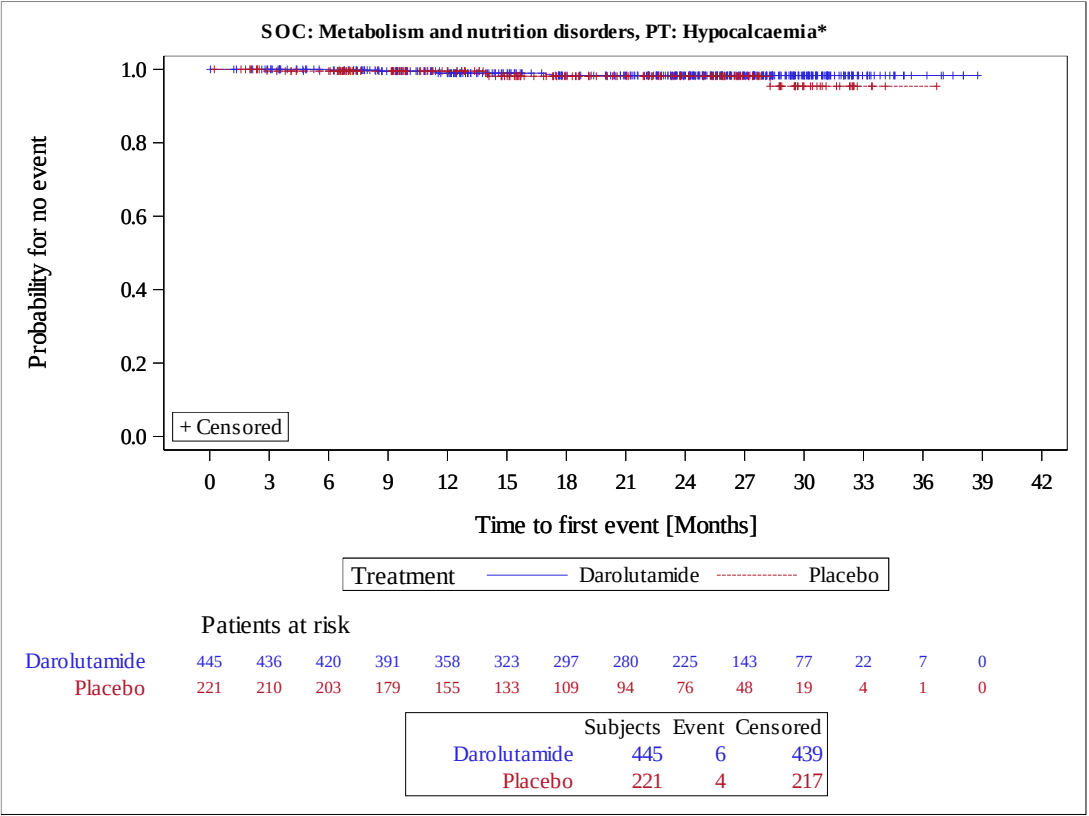


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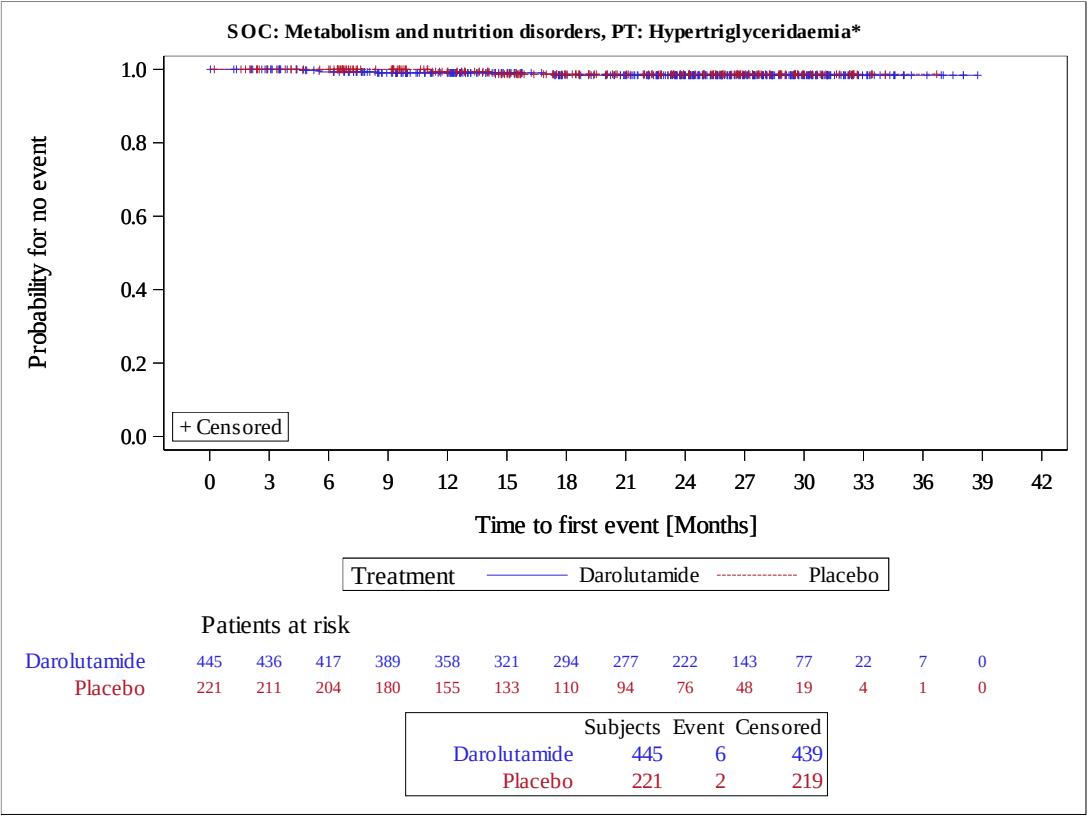


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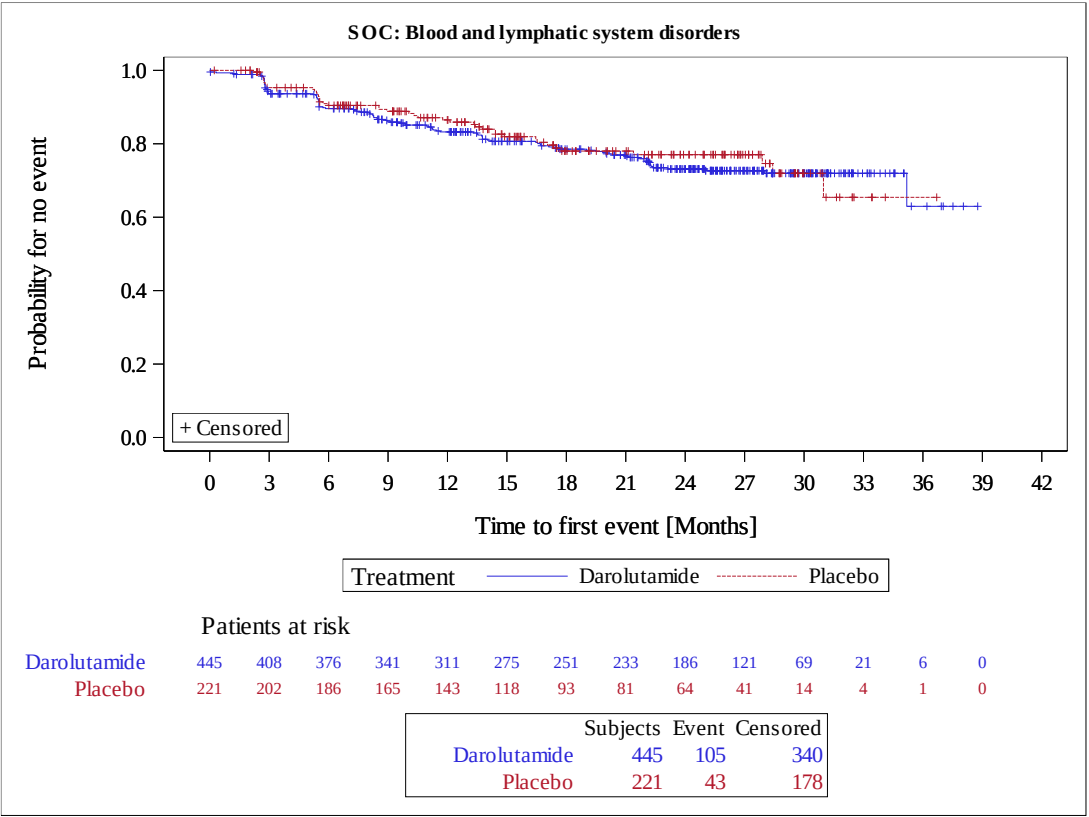


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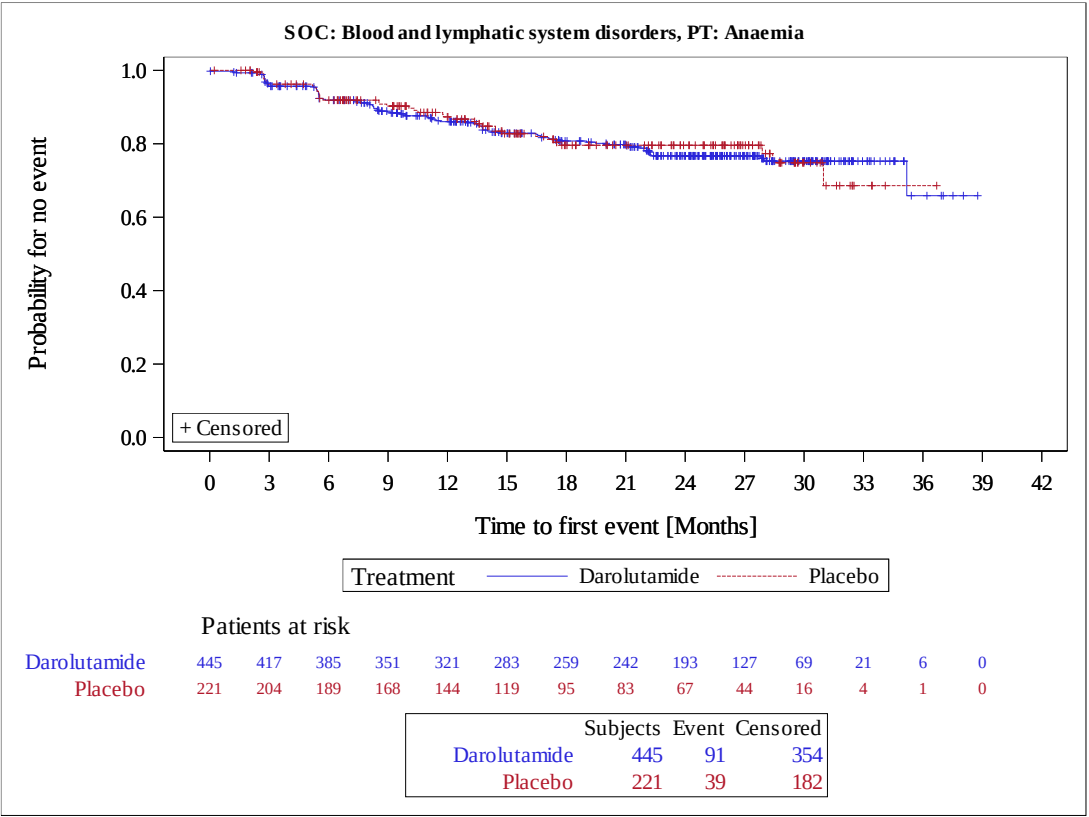


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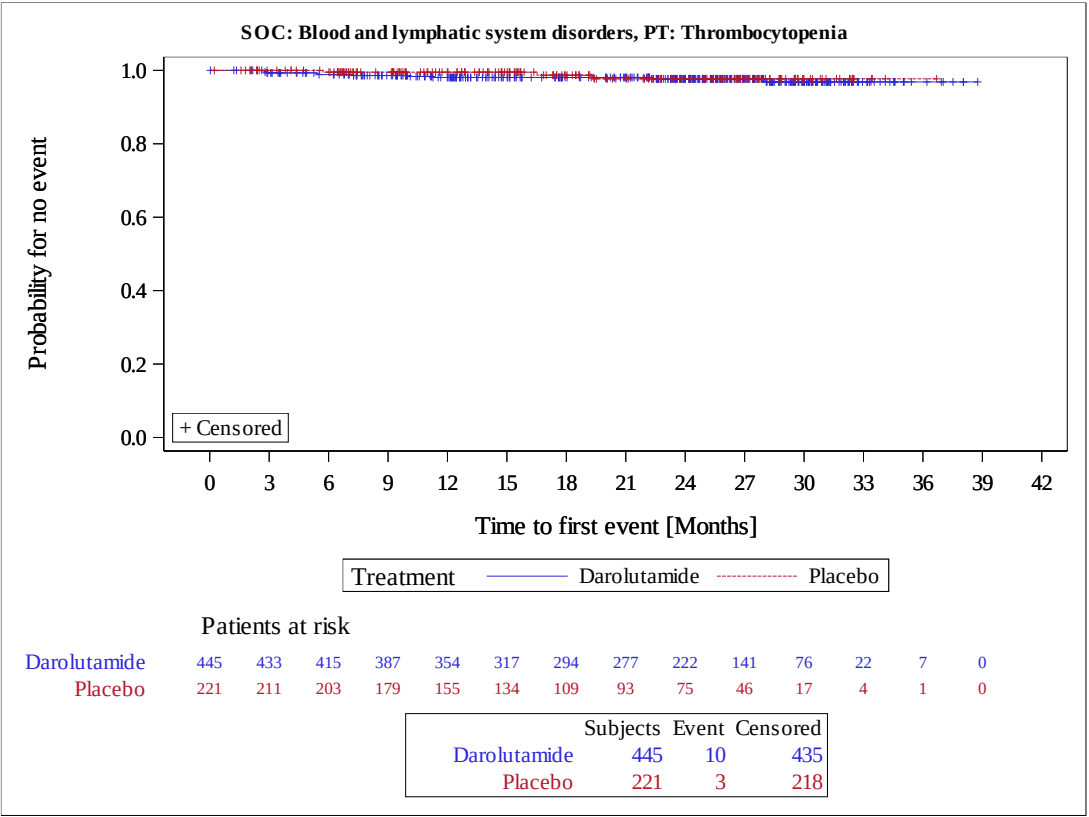


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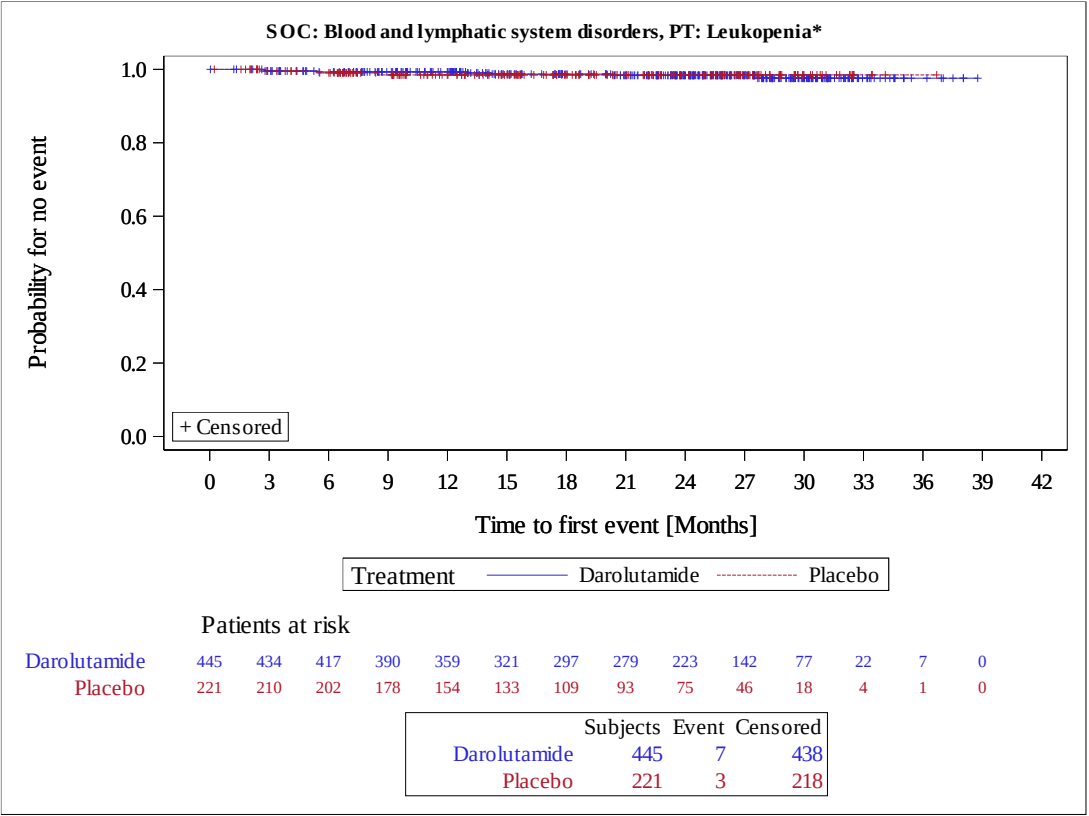


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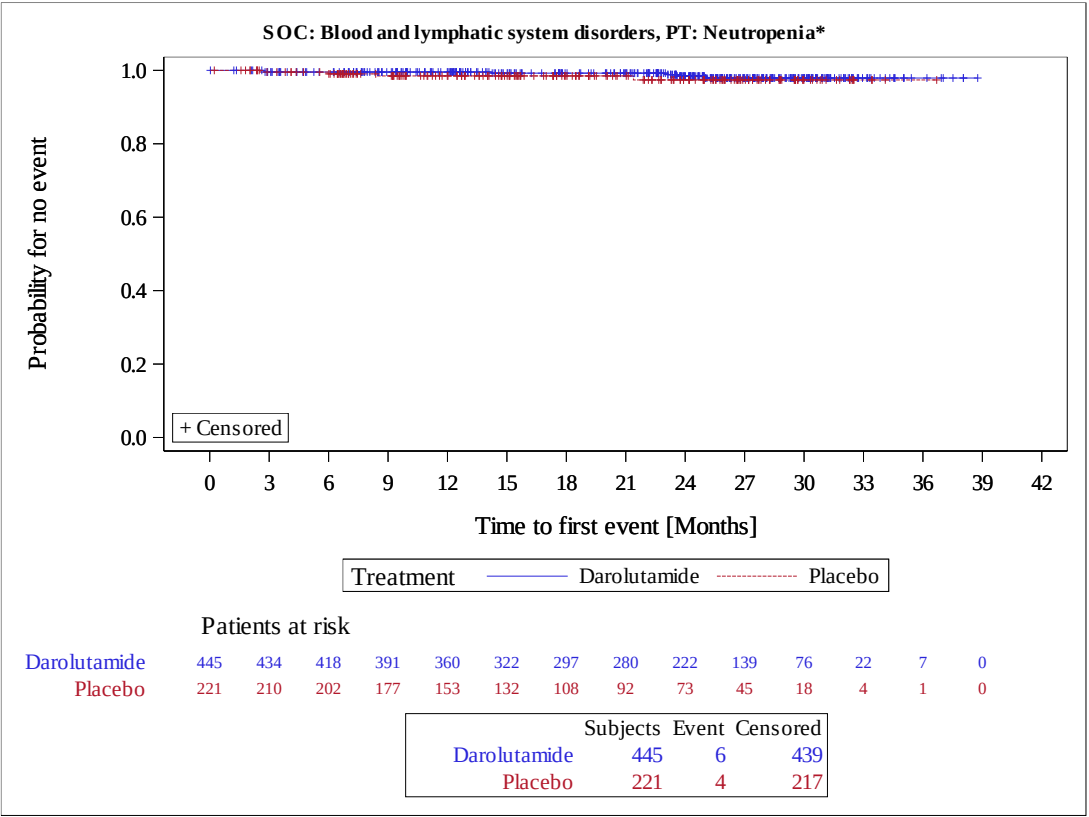


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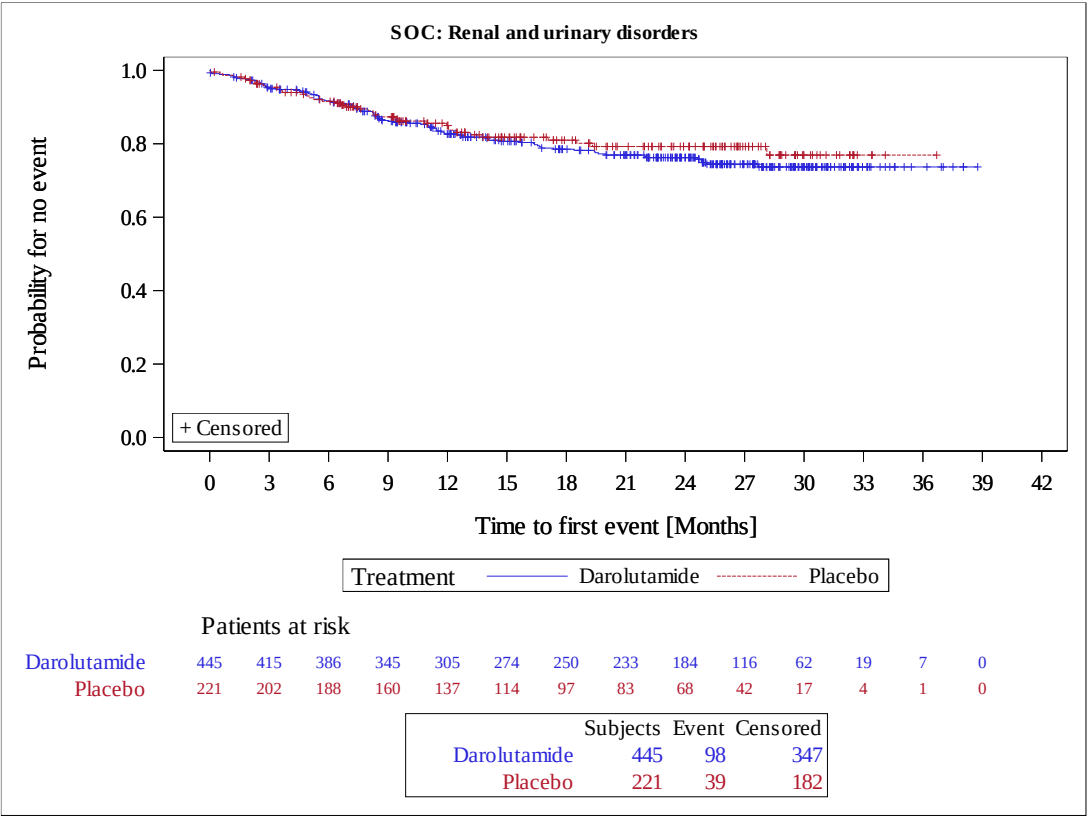


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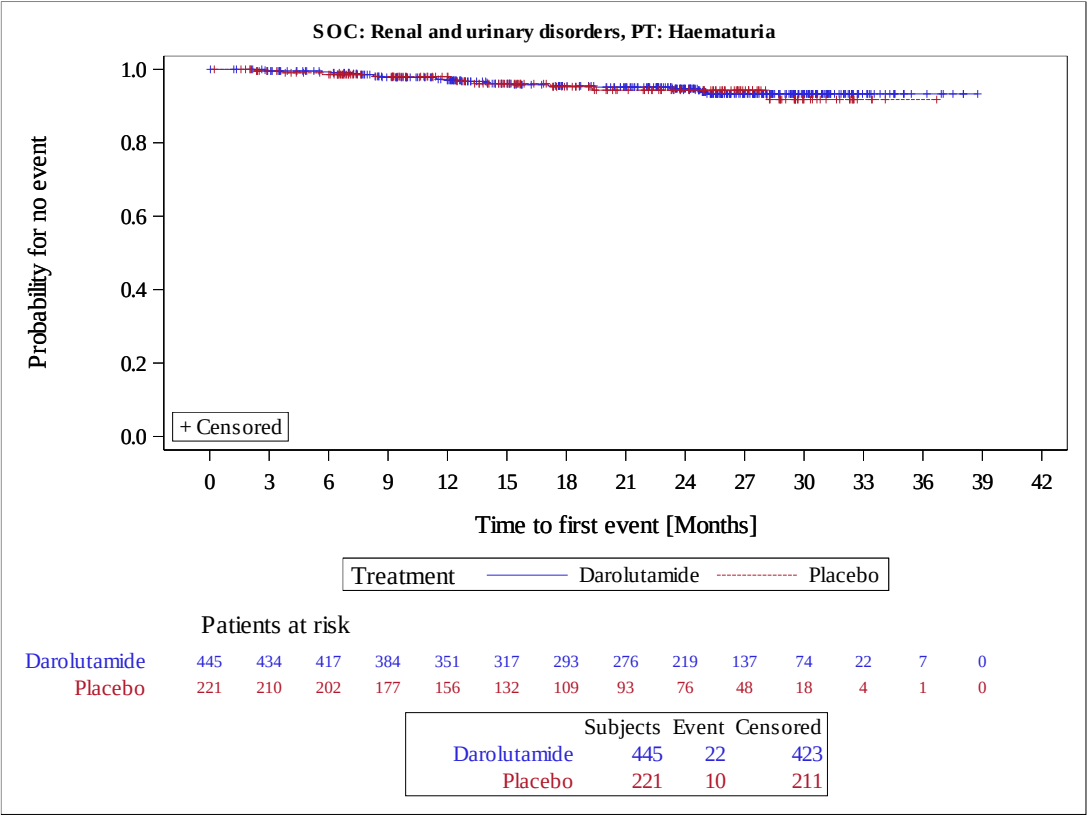


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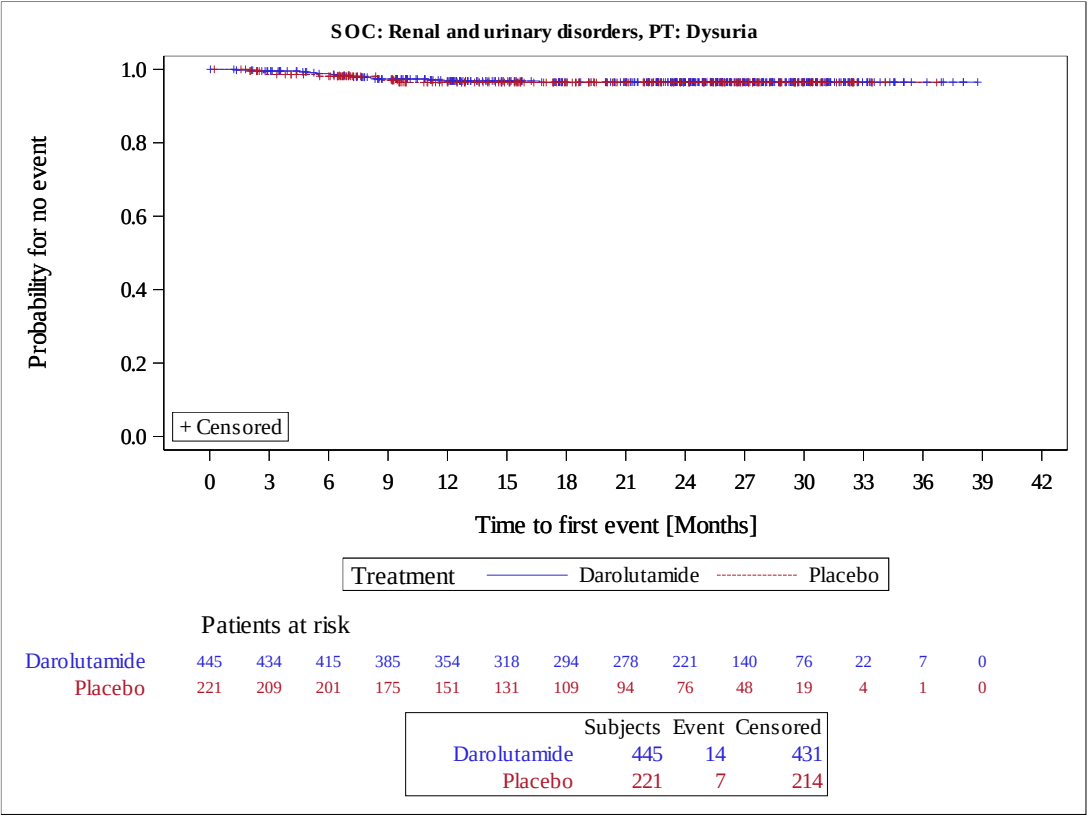


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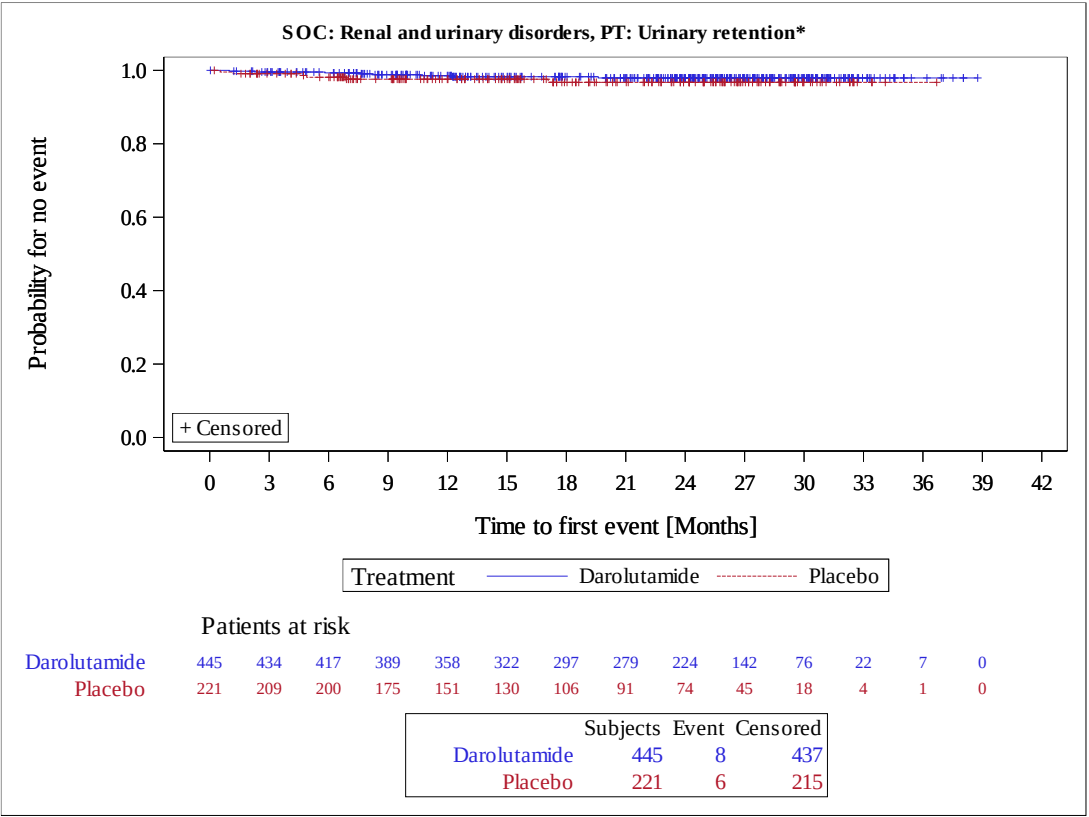


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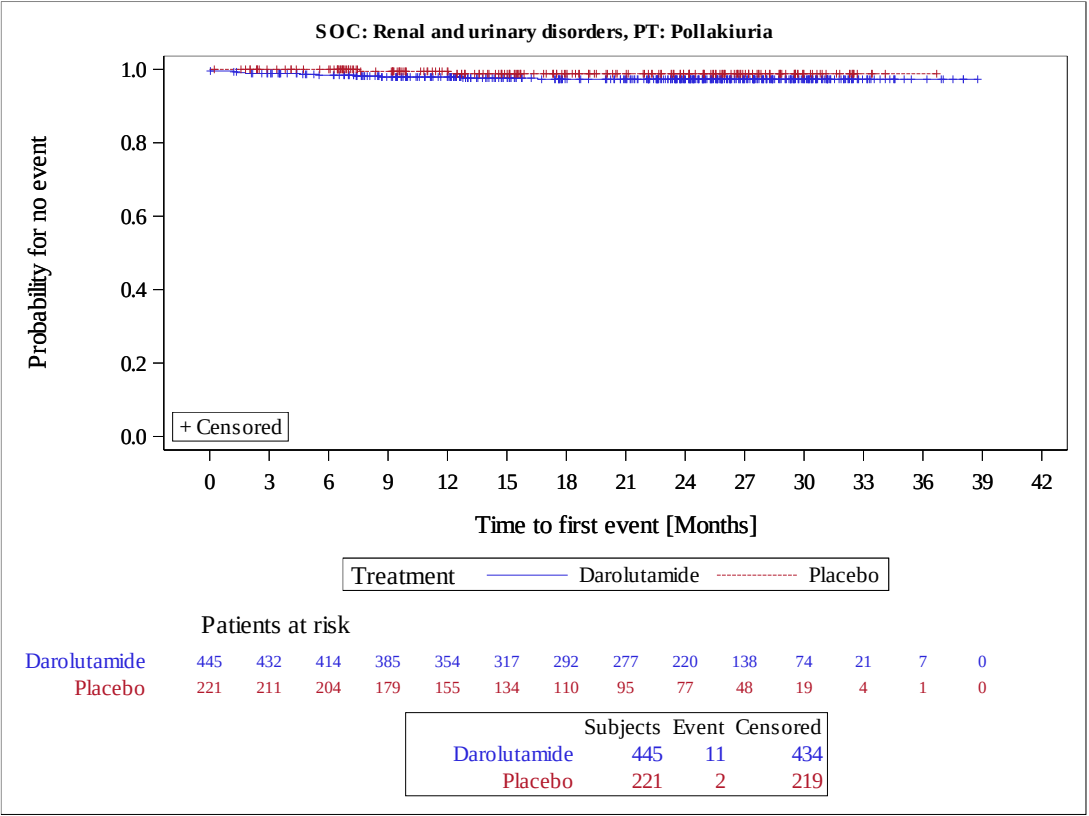


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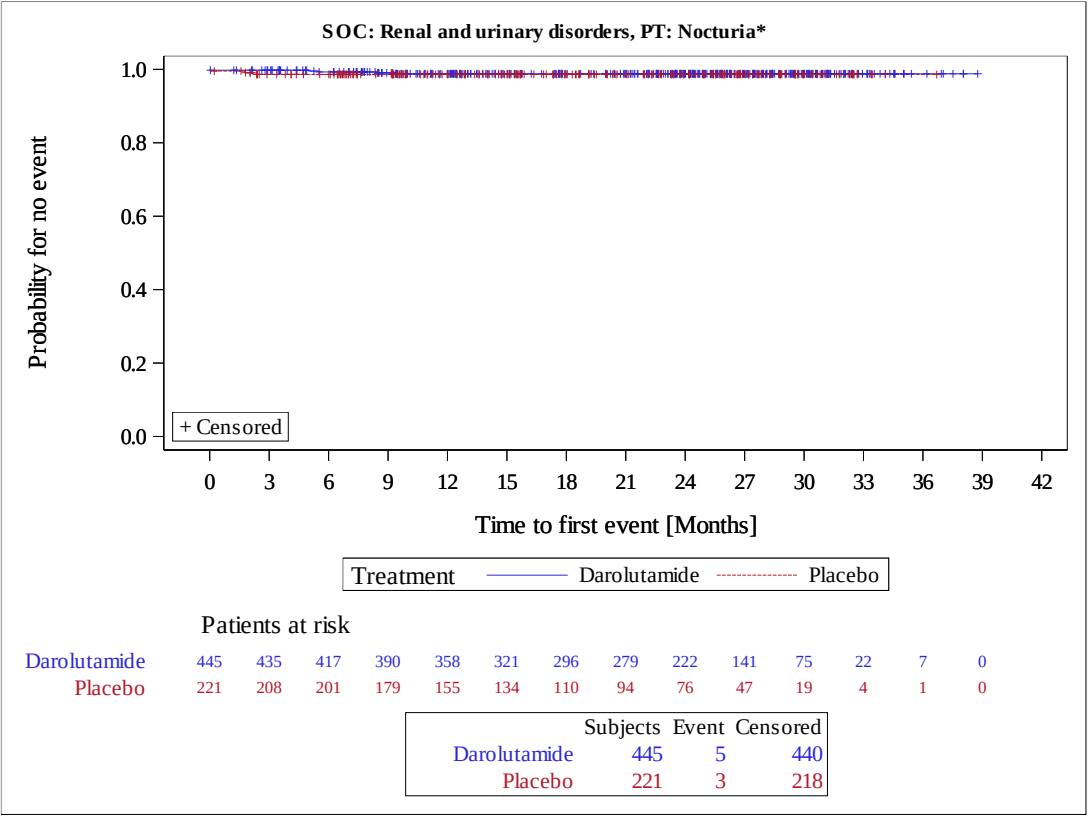


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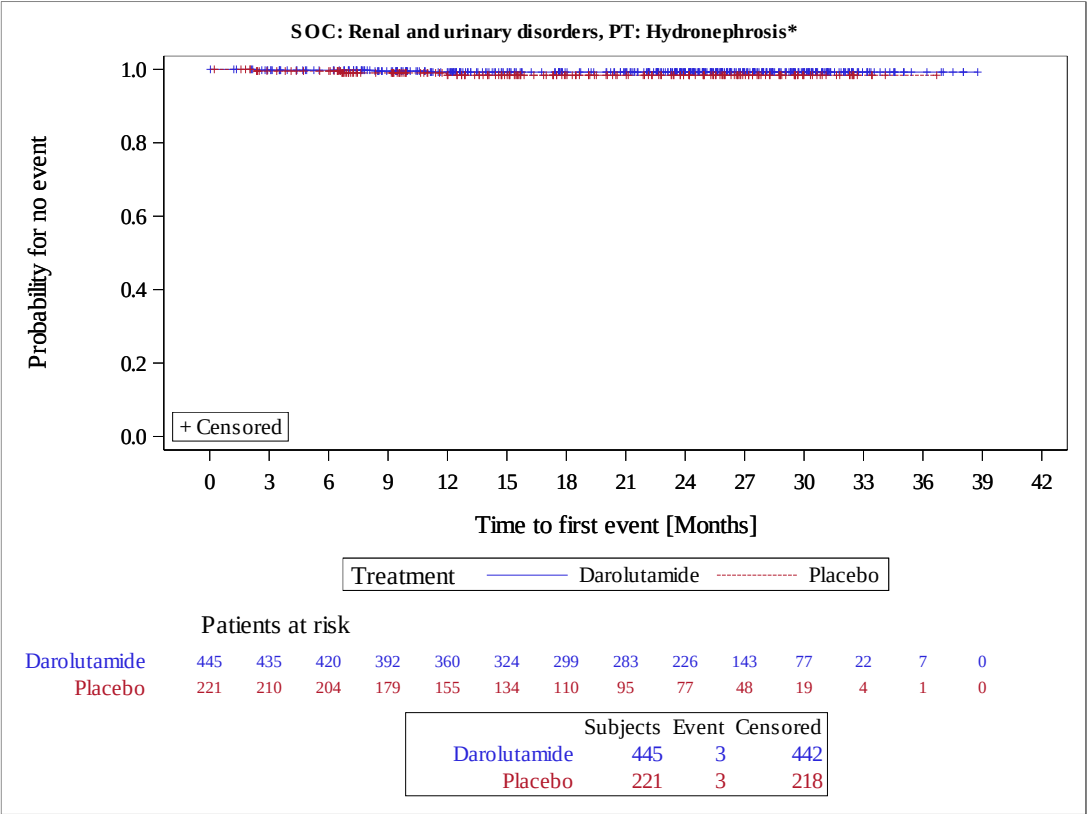


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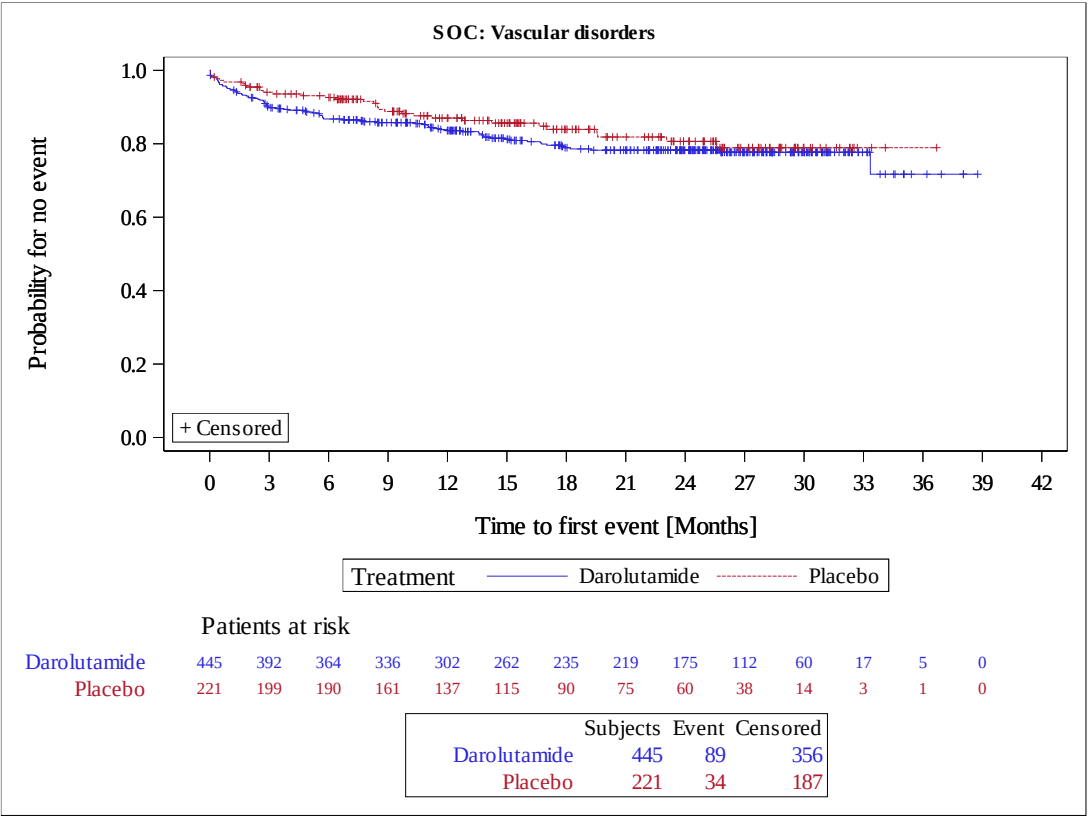


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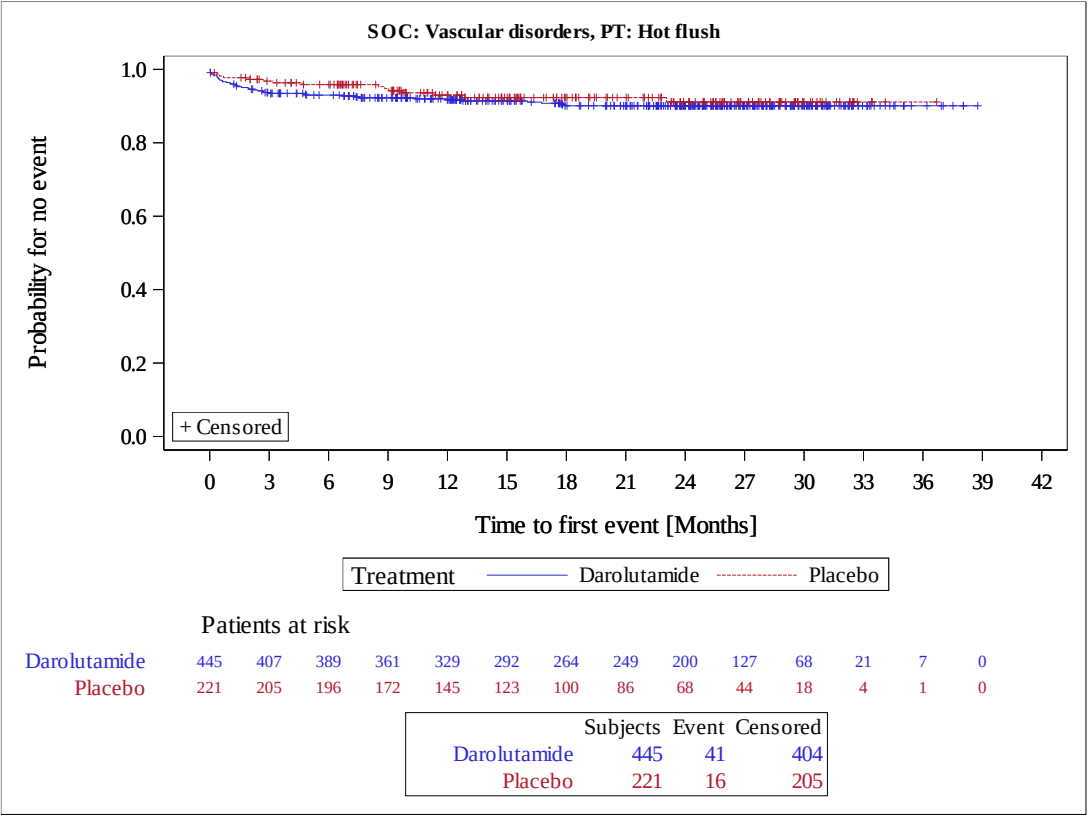


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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.3.1.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

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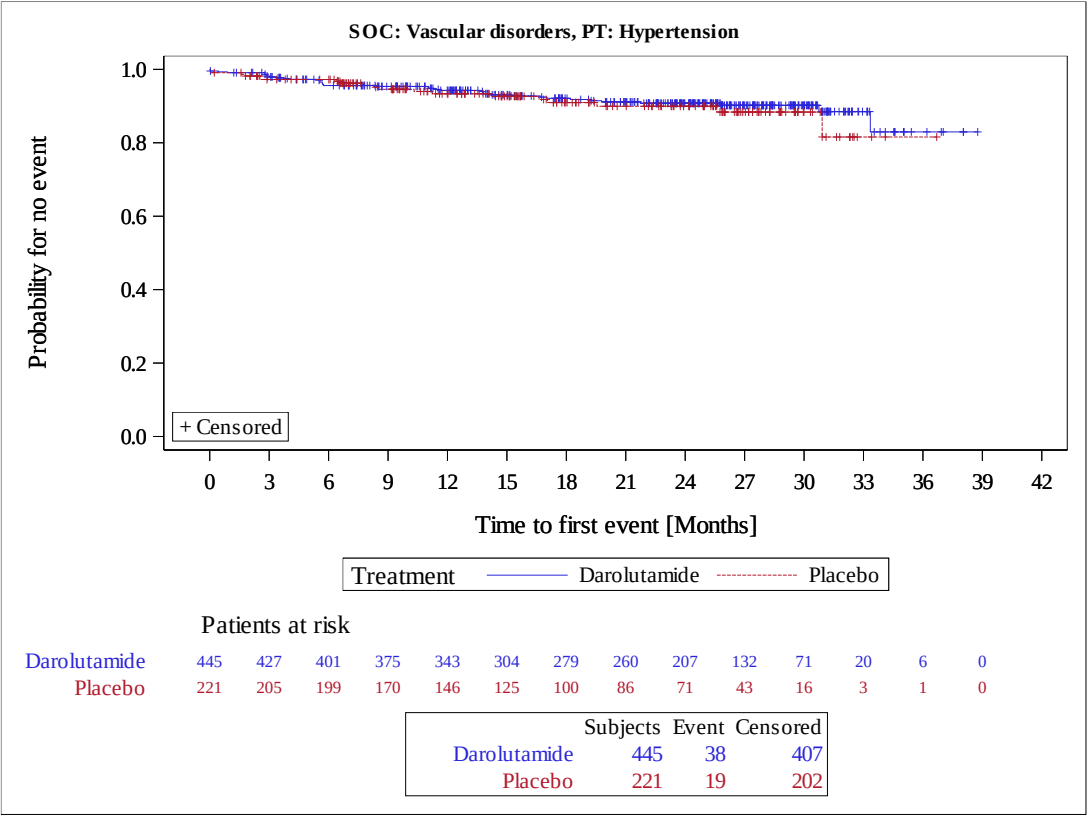


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BAY 1841788 / 21140 - 07JUN2024
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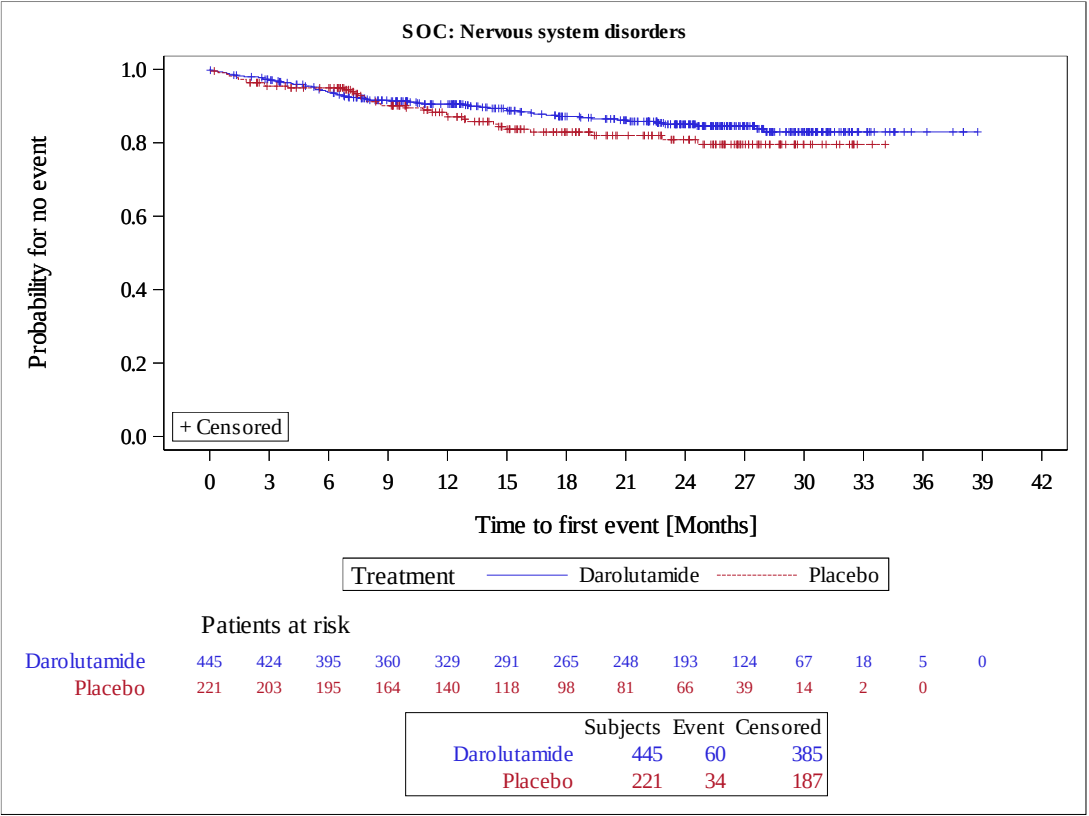


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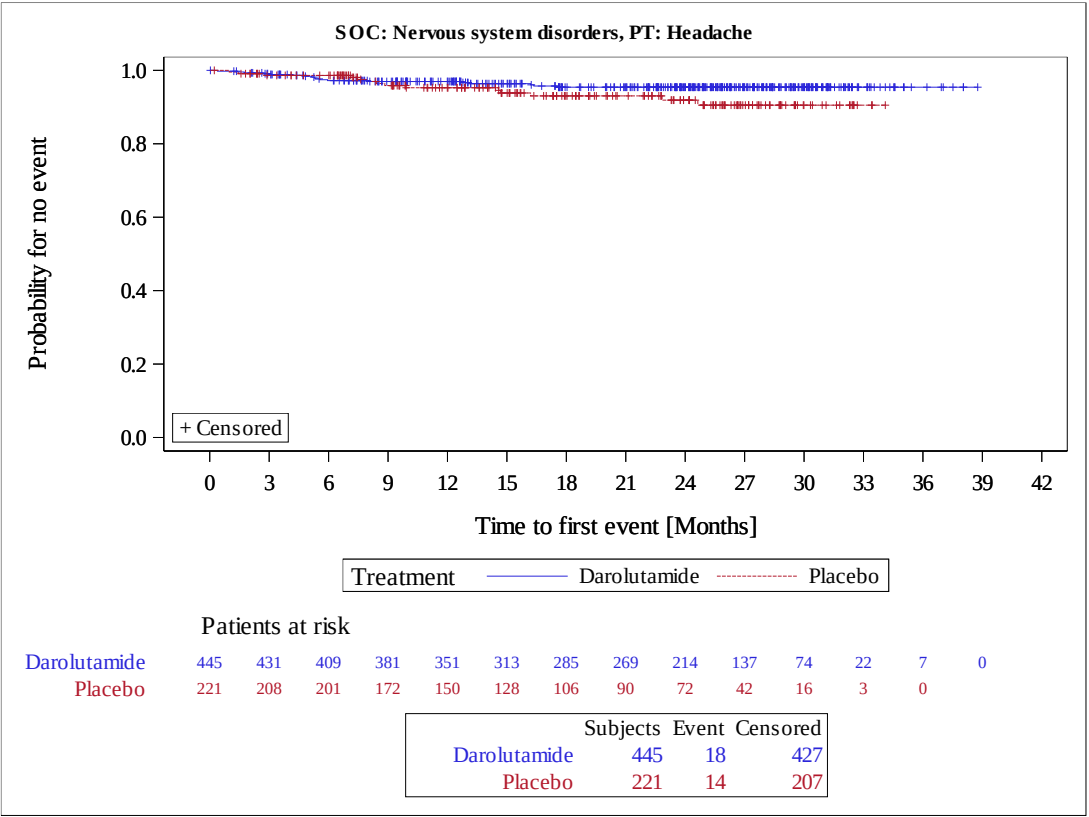


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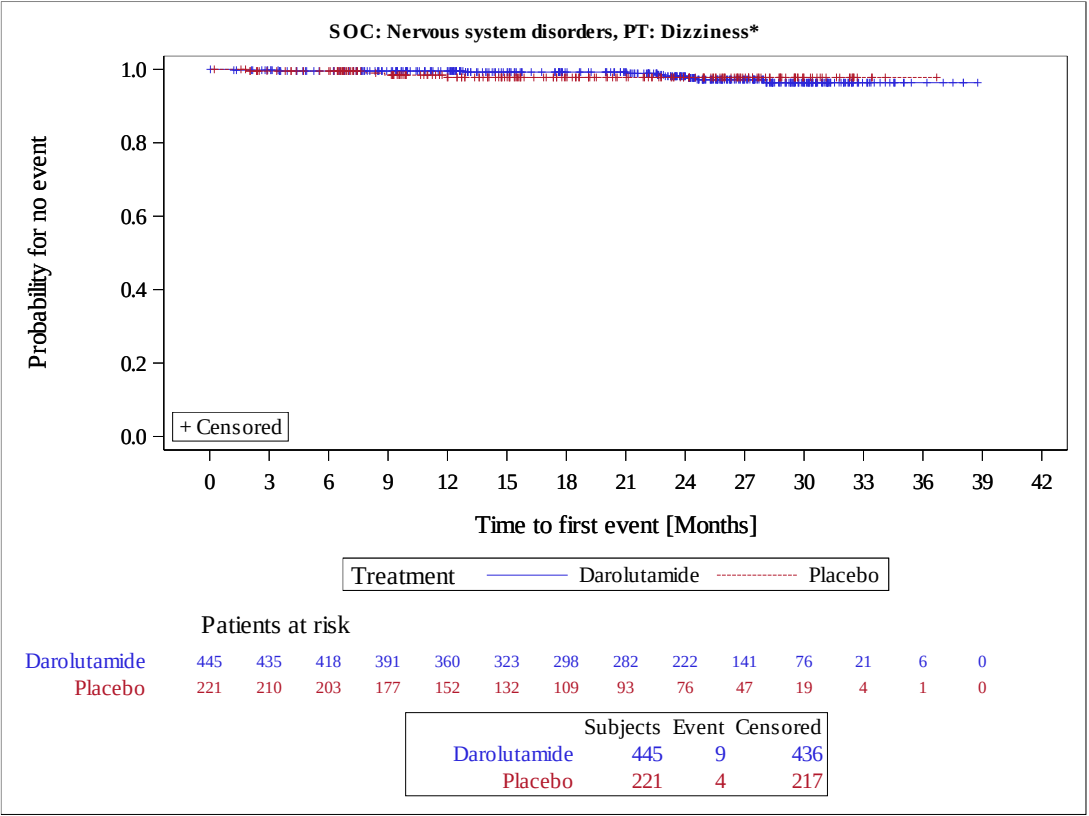


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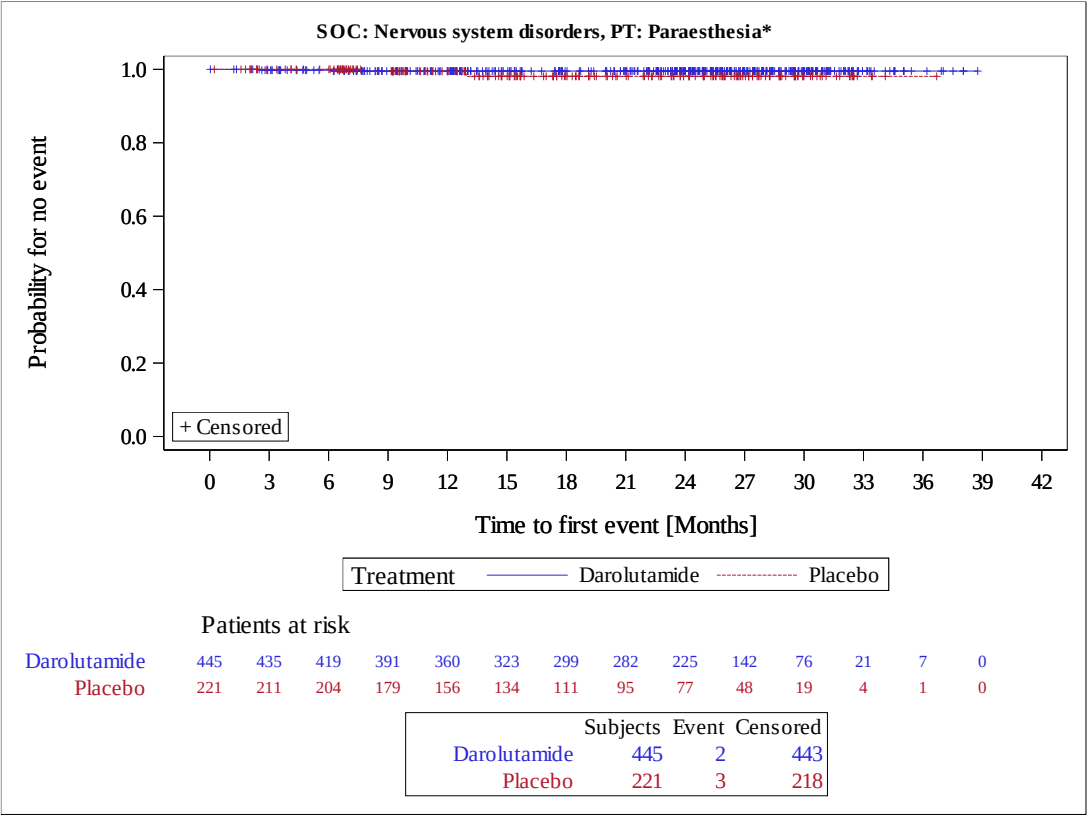


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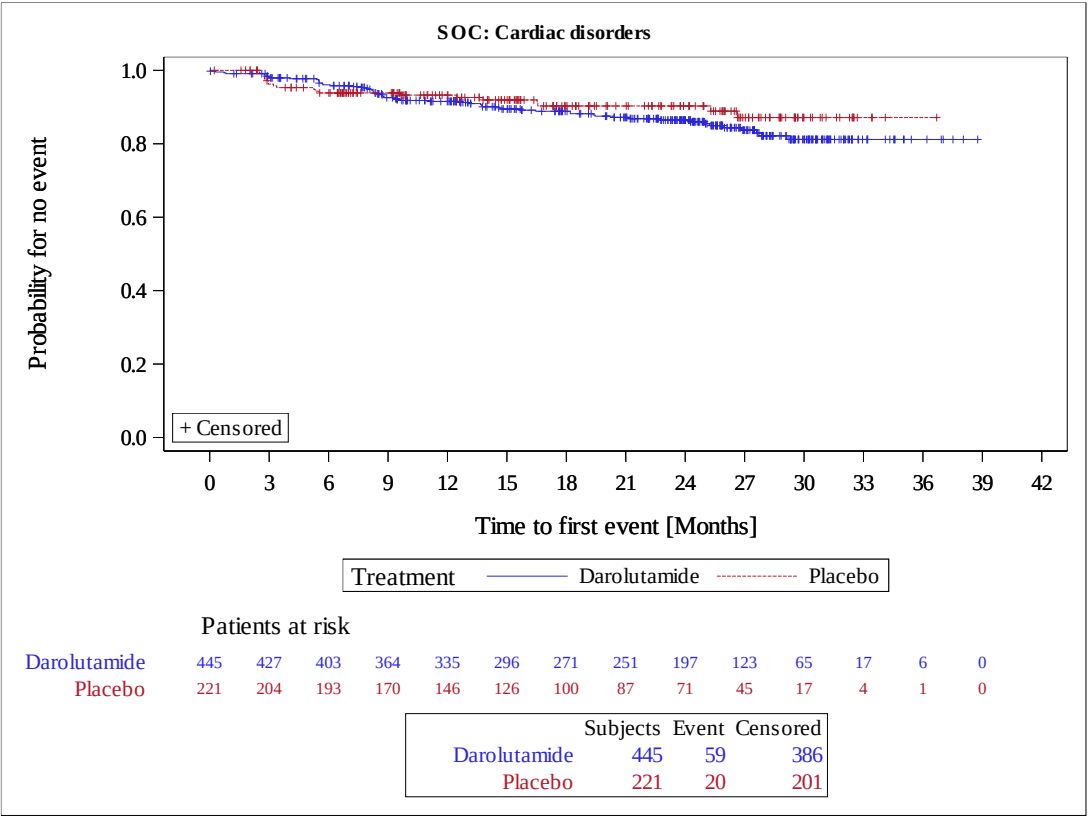


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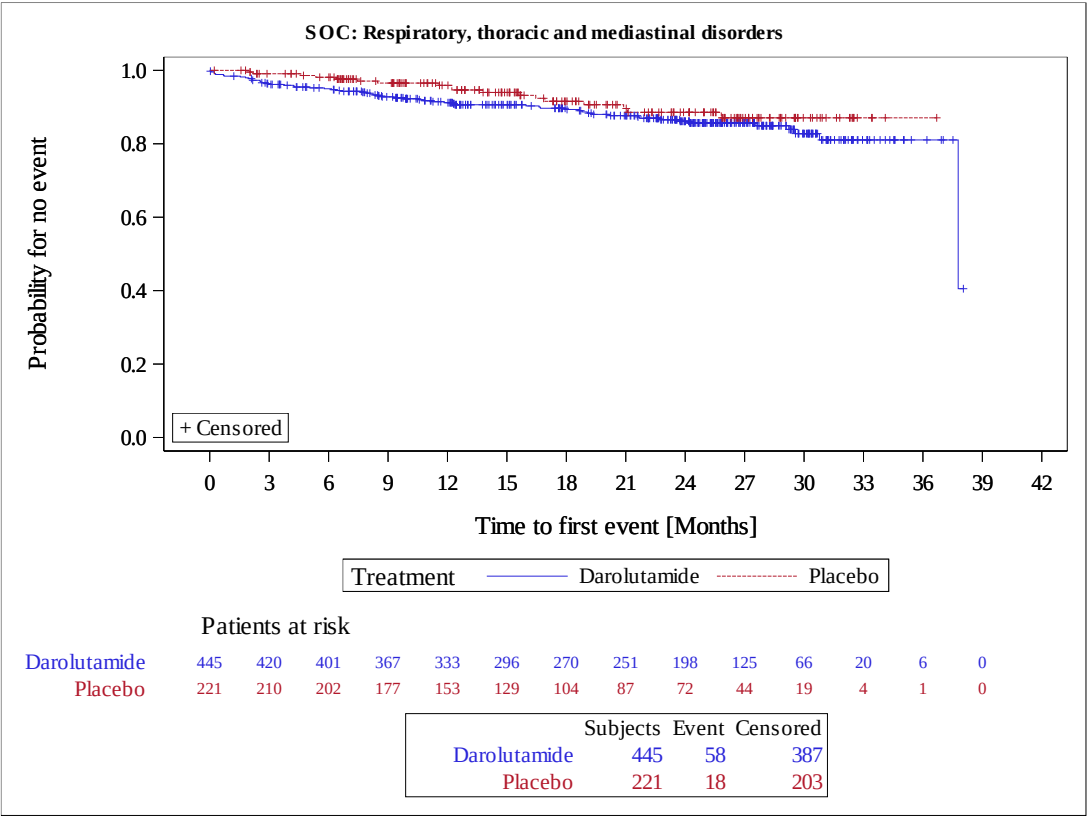


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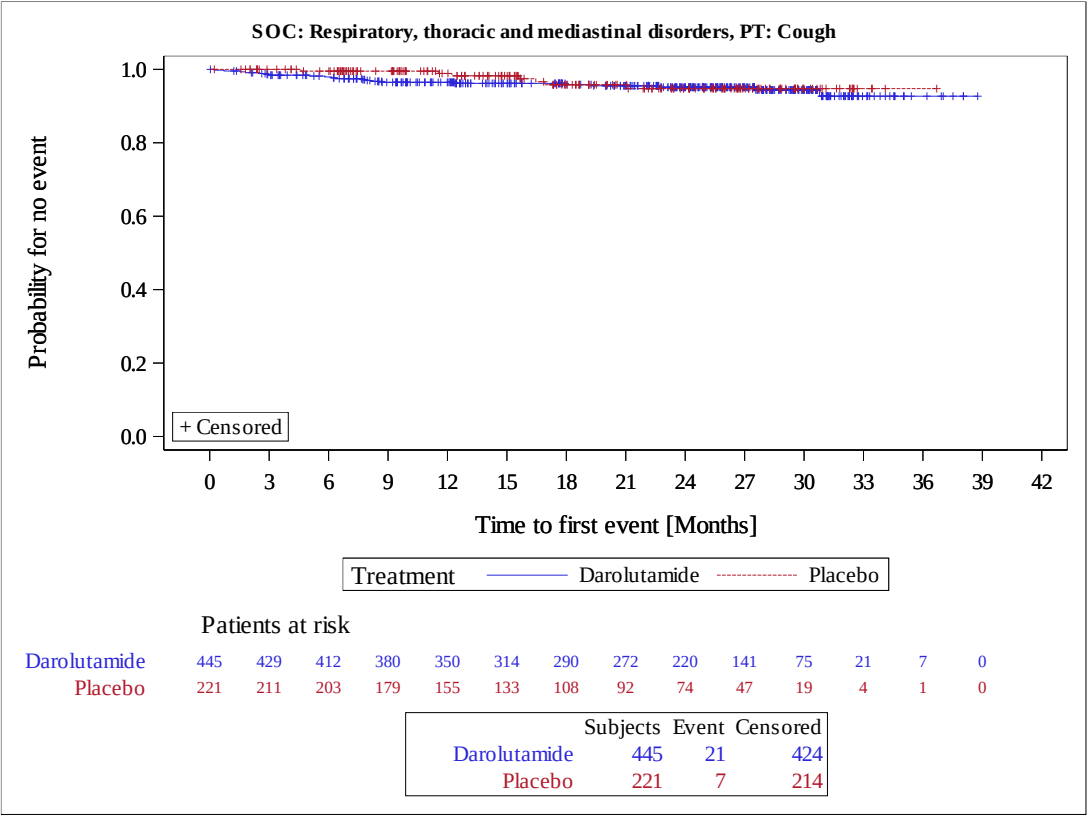


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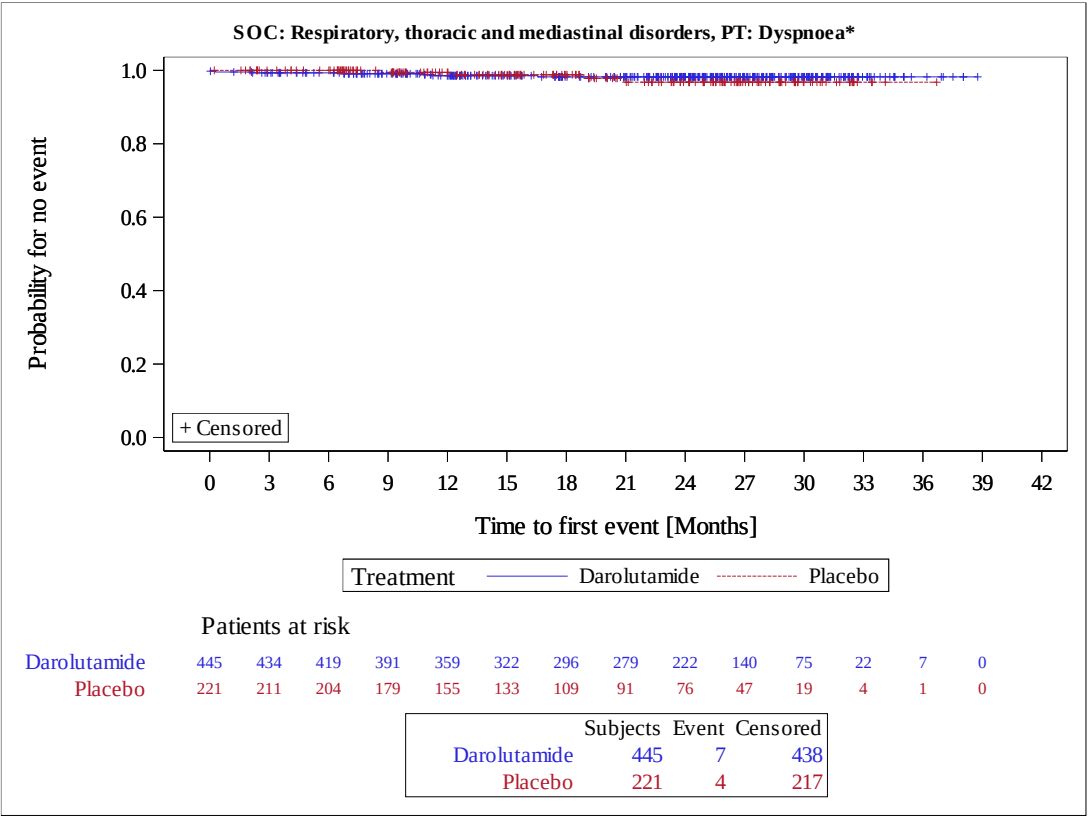


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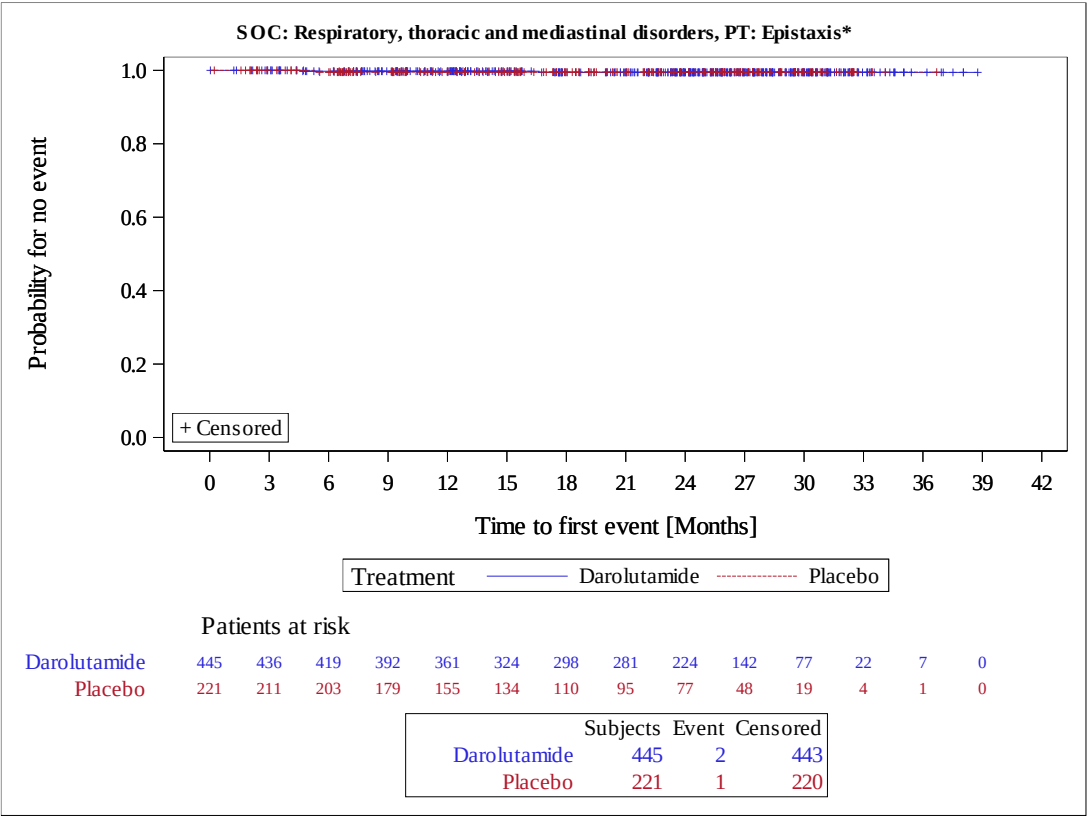


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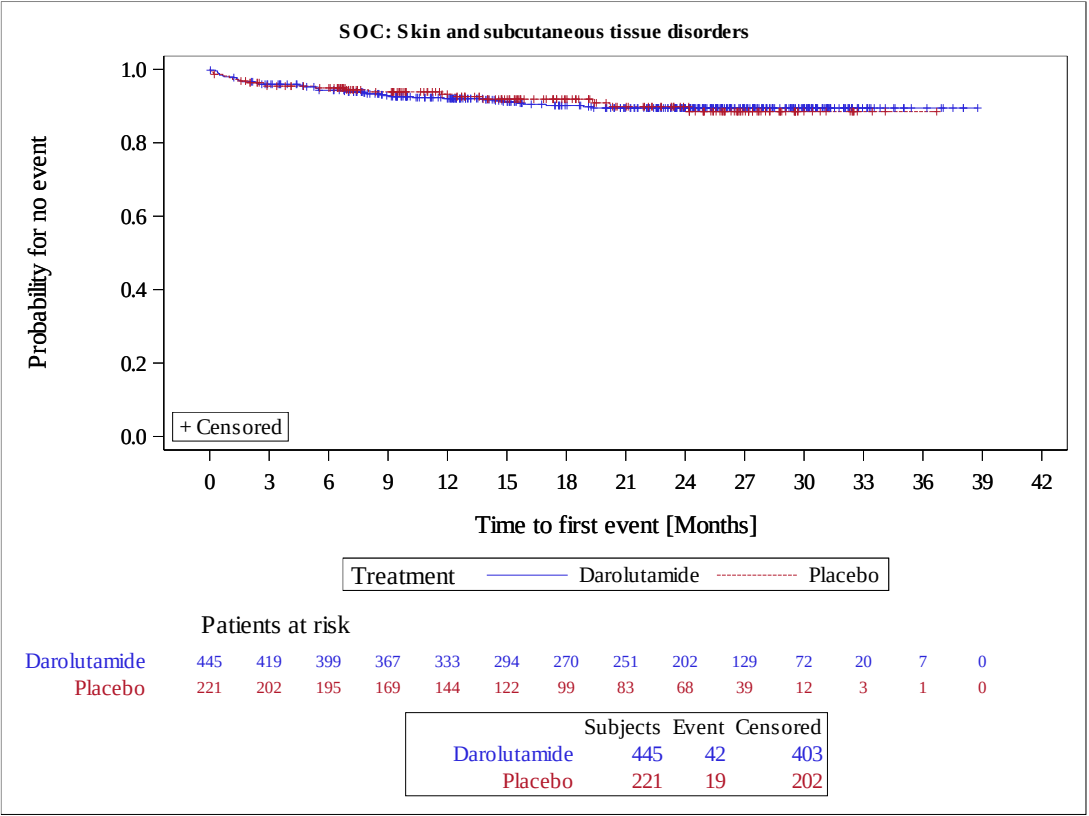


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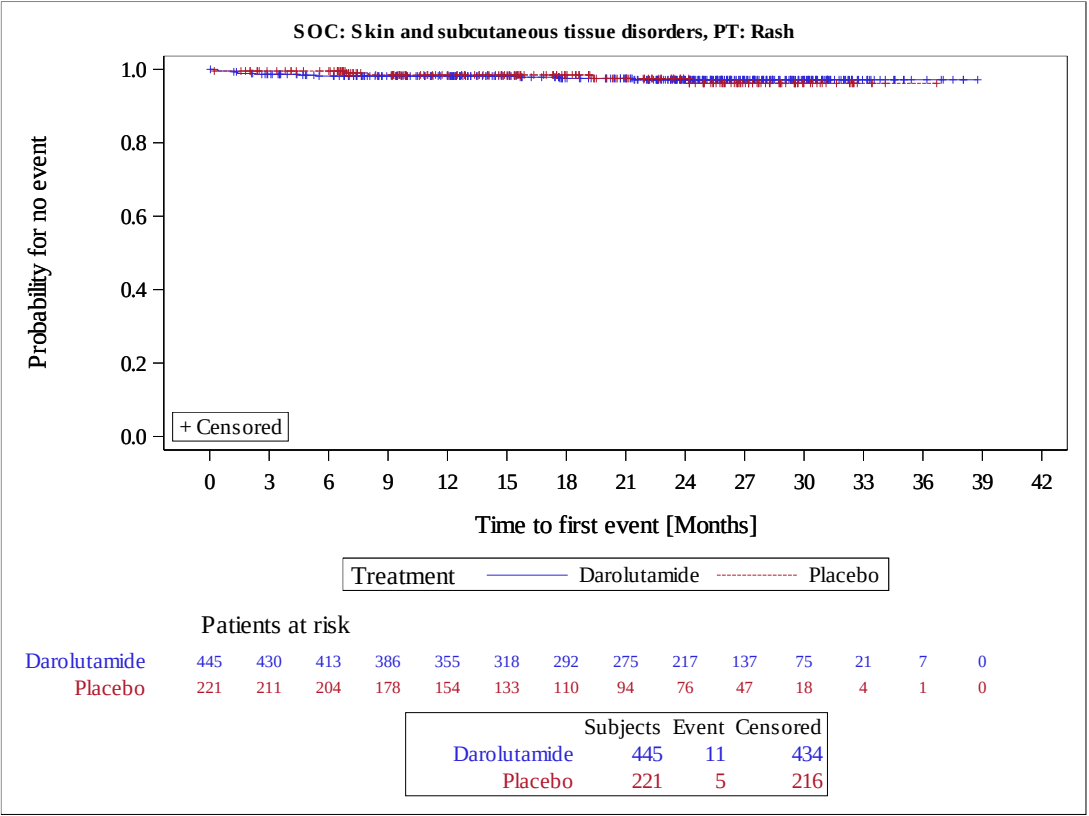


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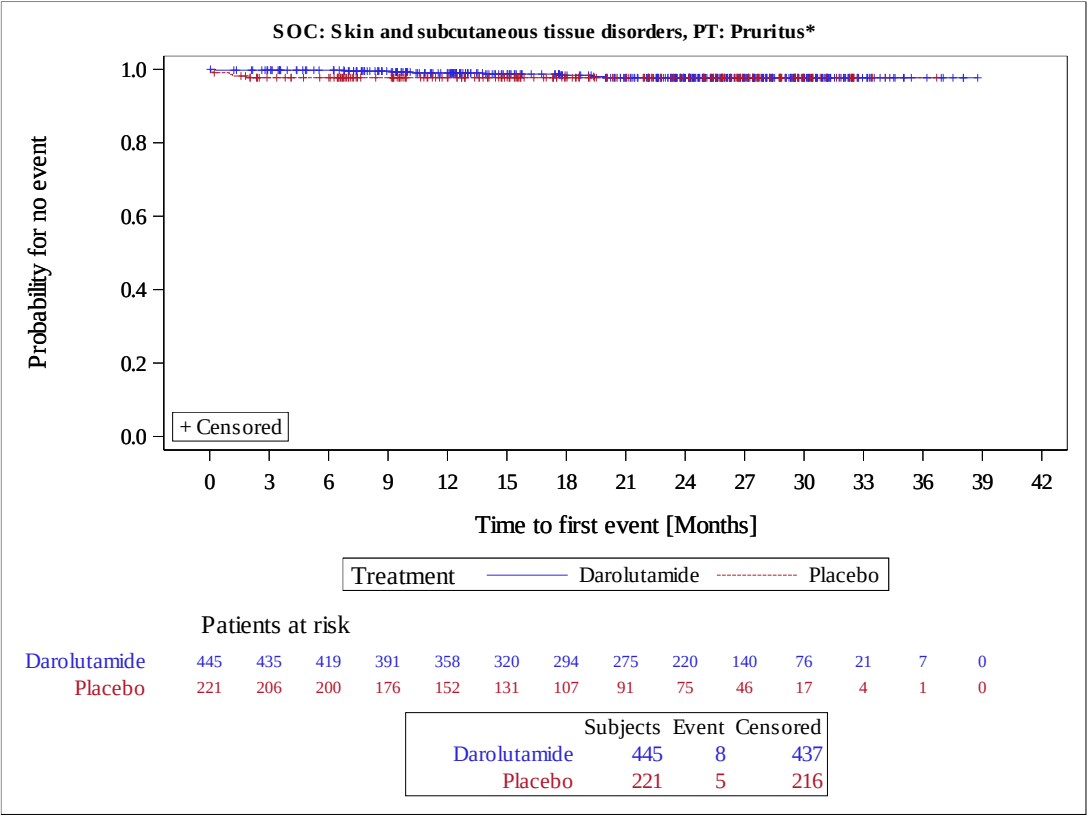


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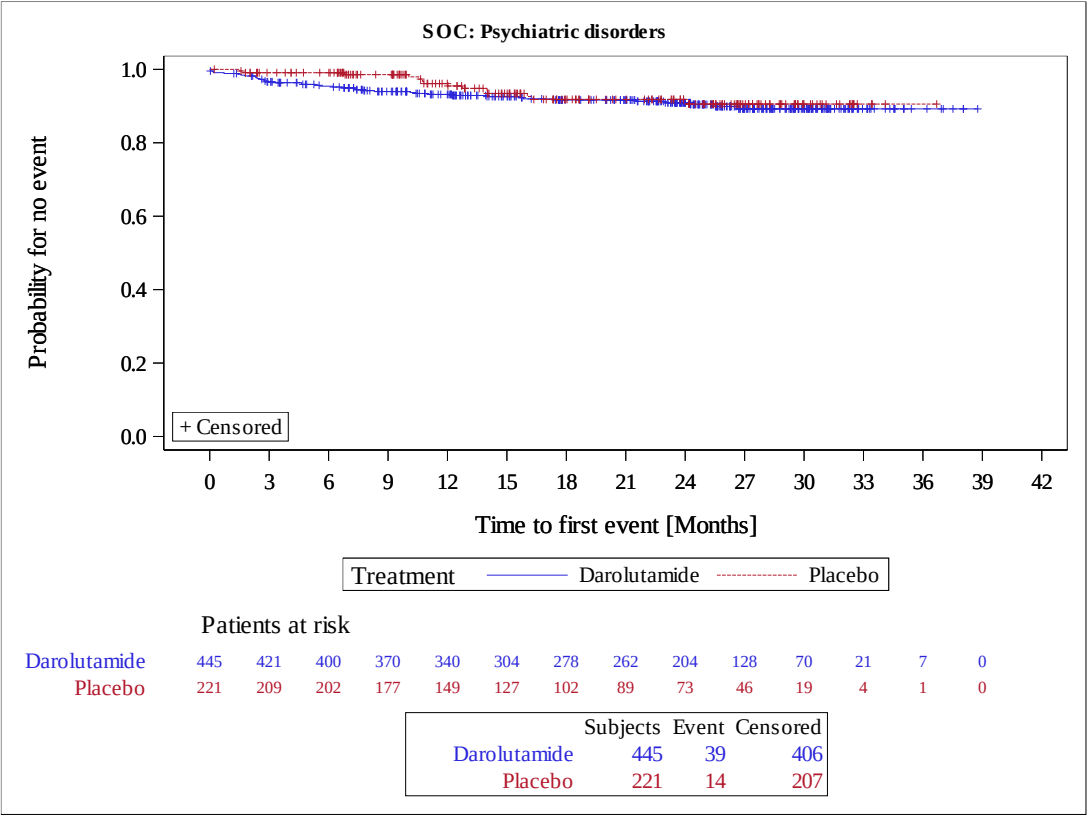


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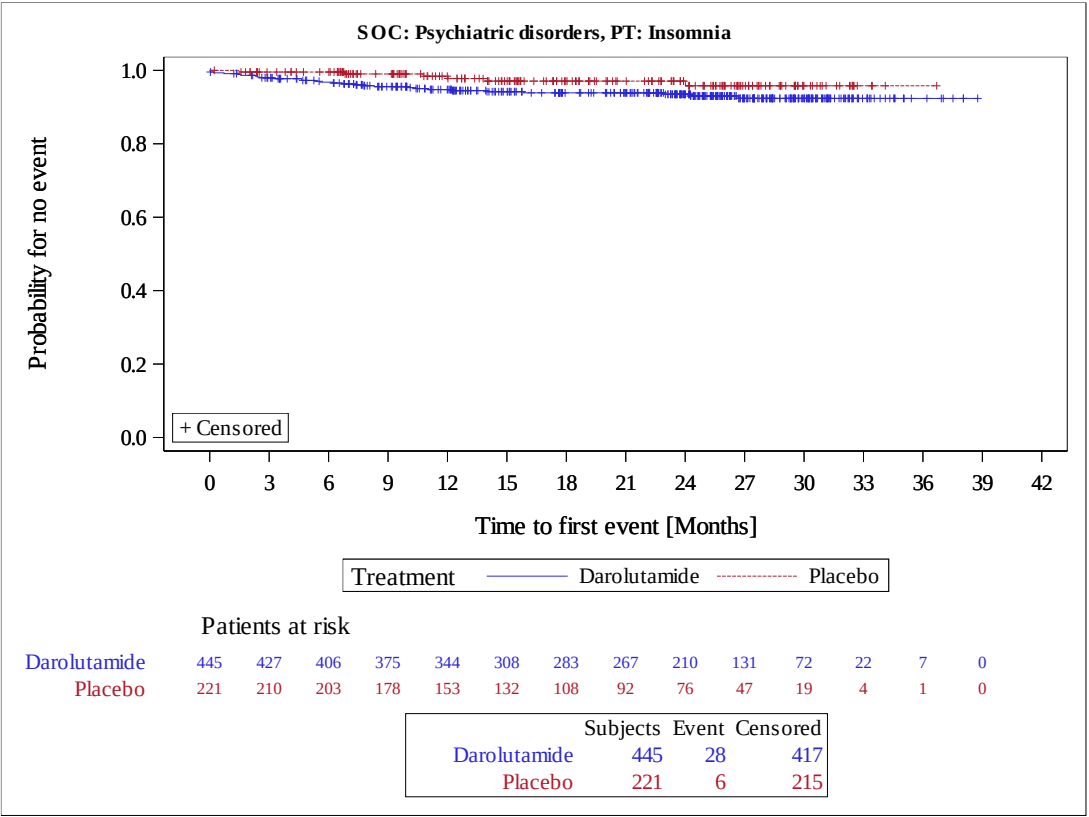


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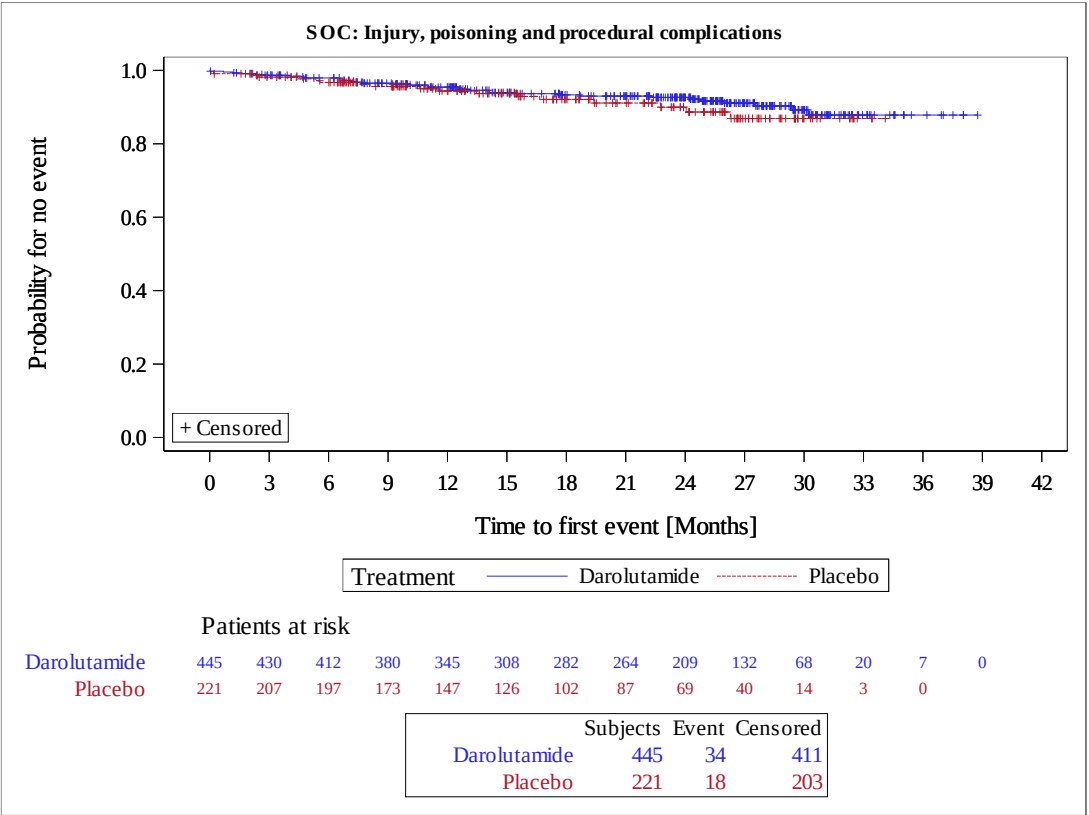


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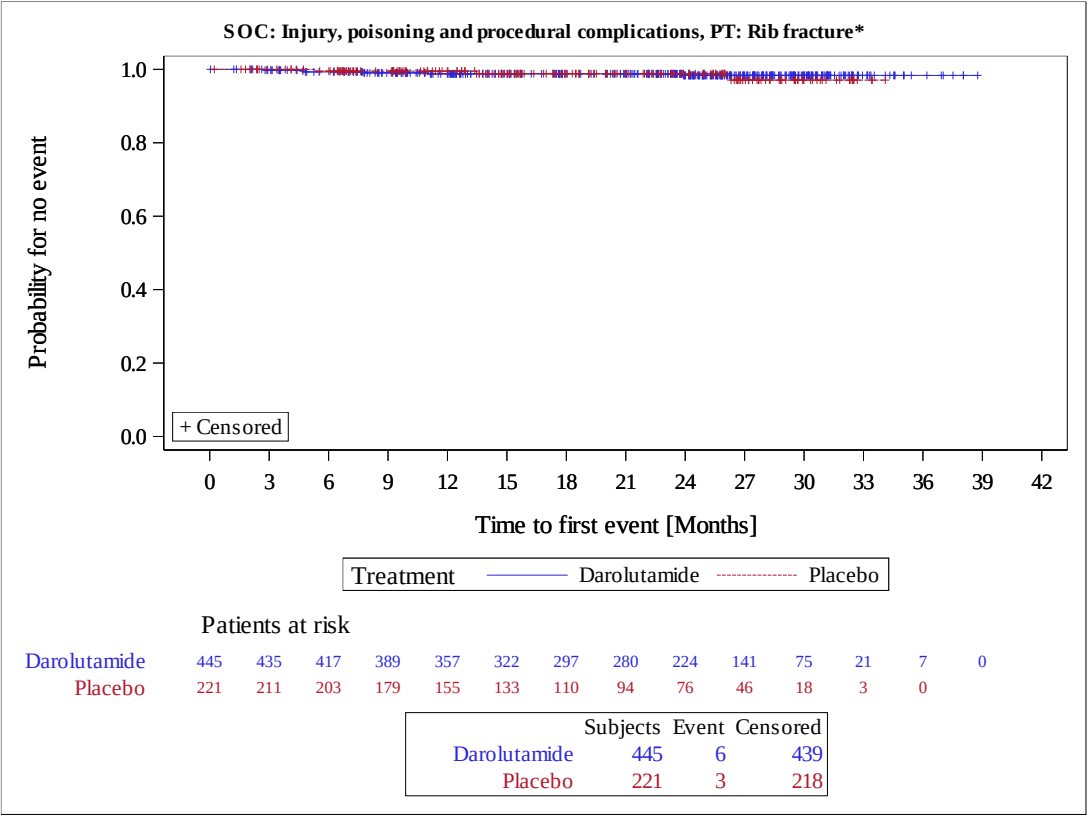


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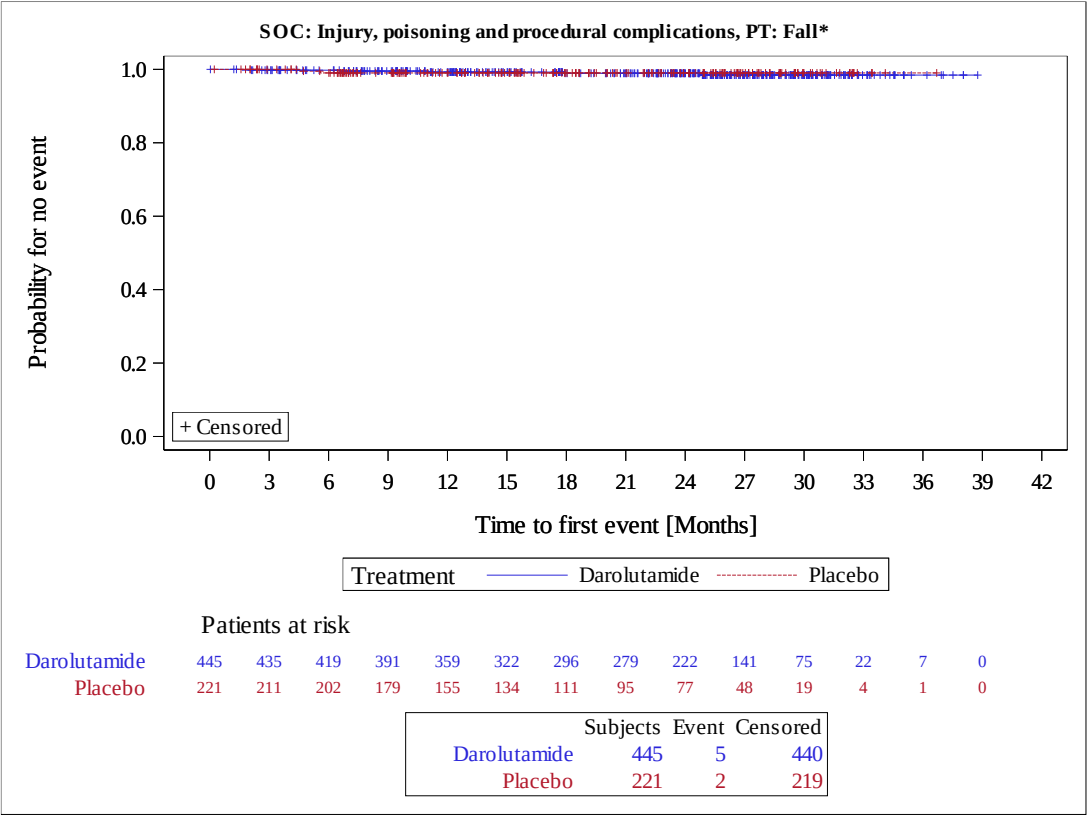


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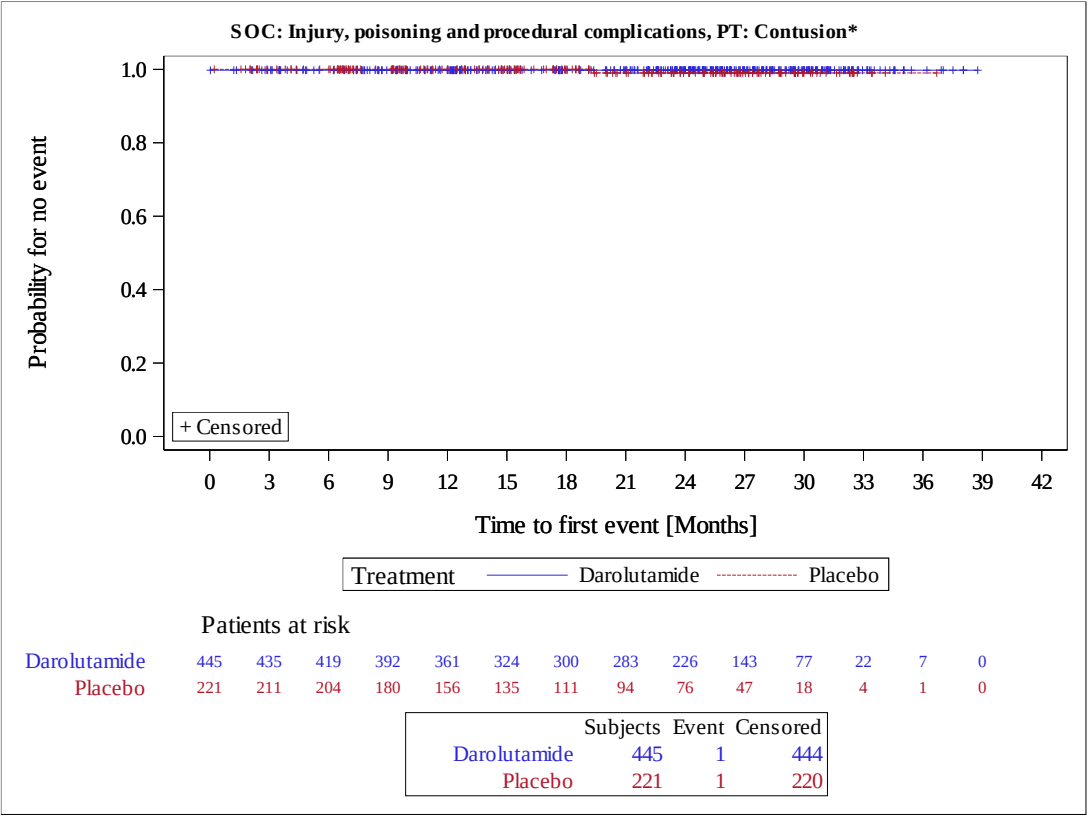


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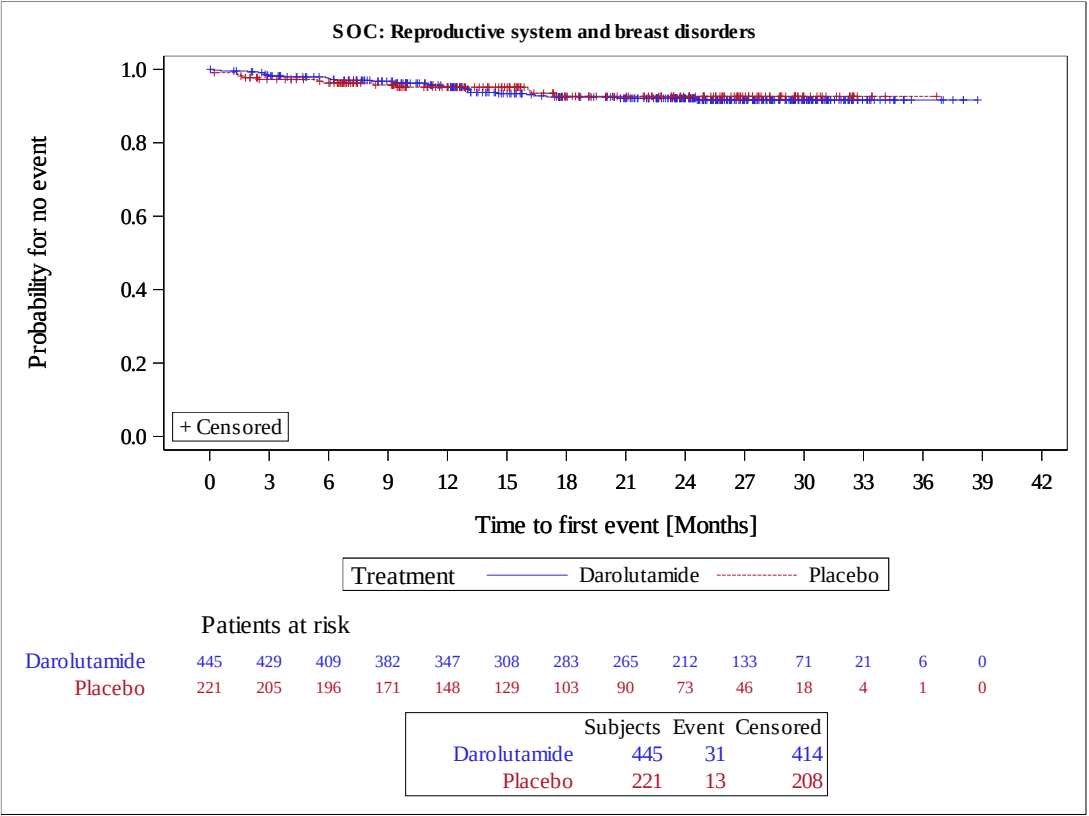


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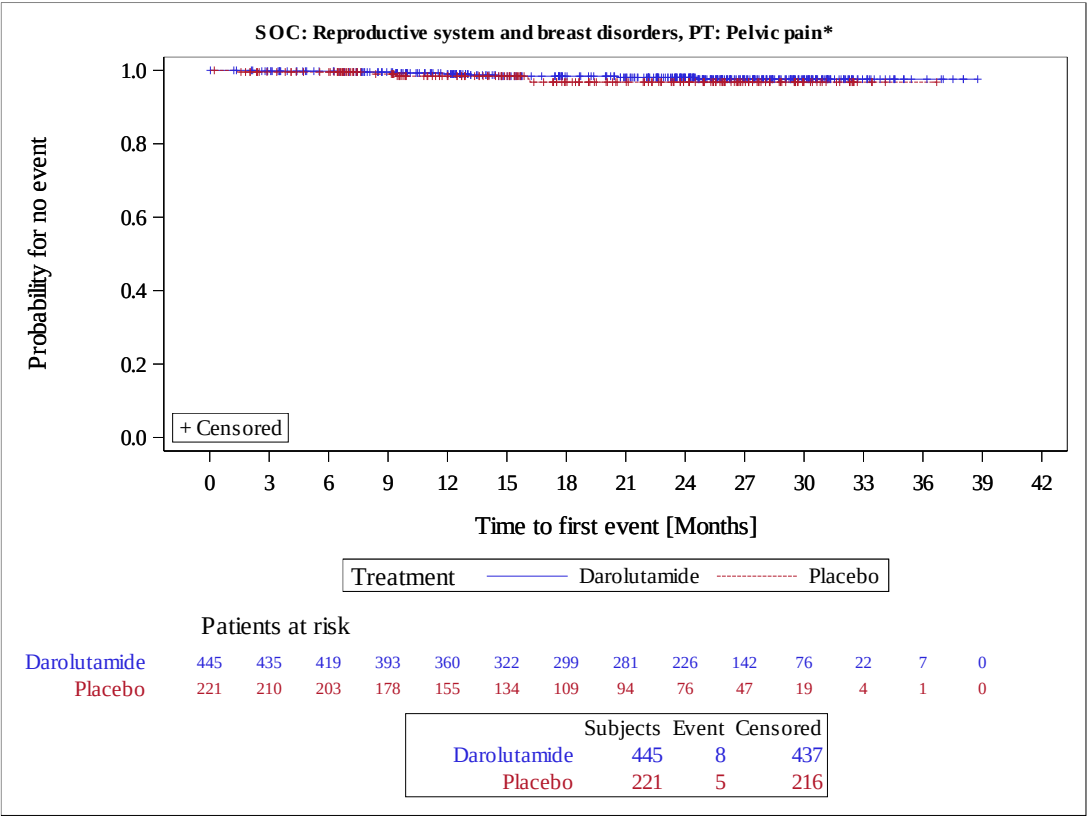


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Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.3.1.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

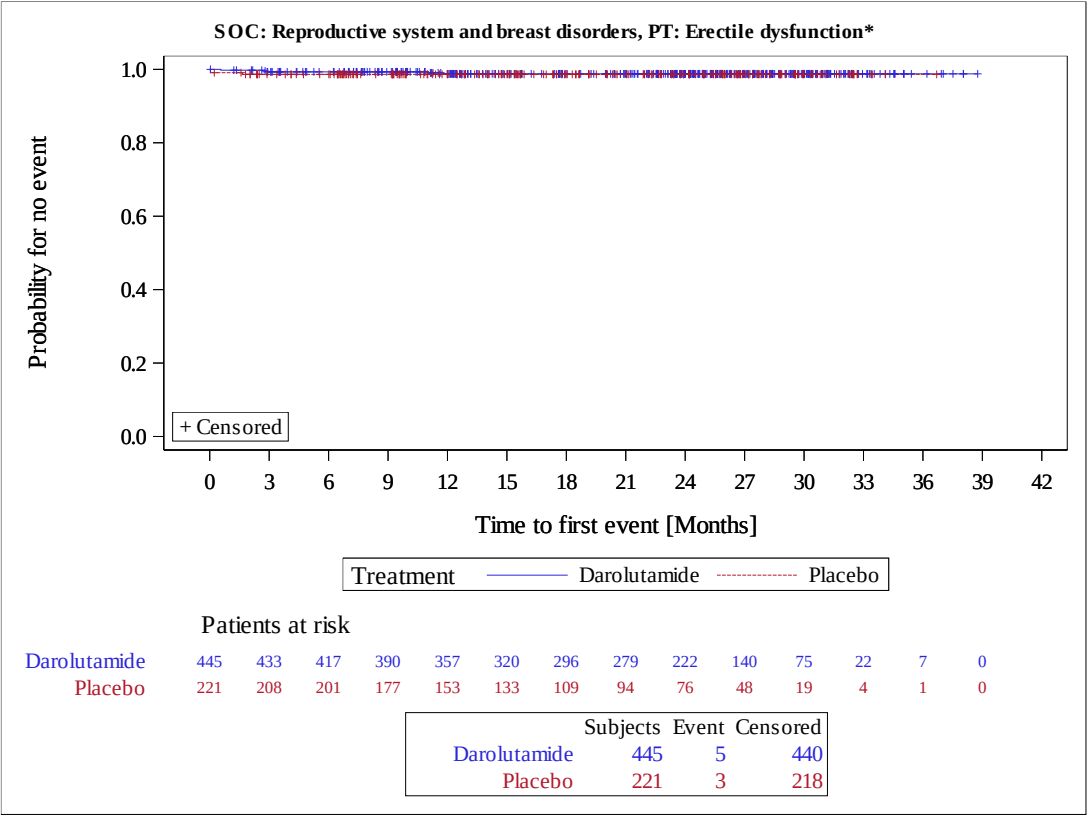


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
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Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

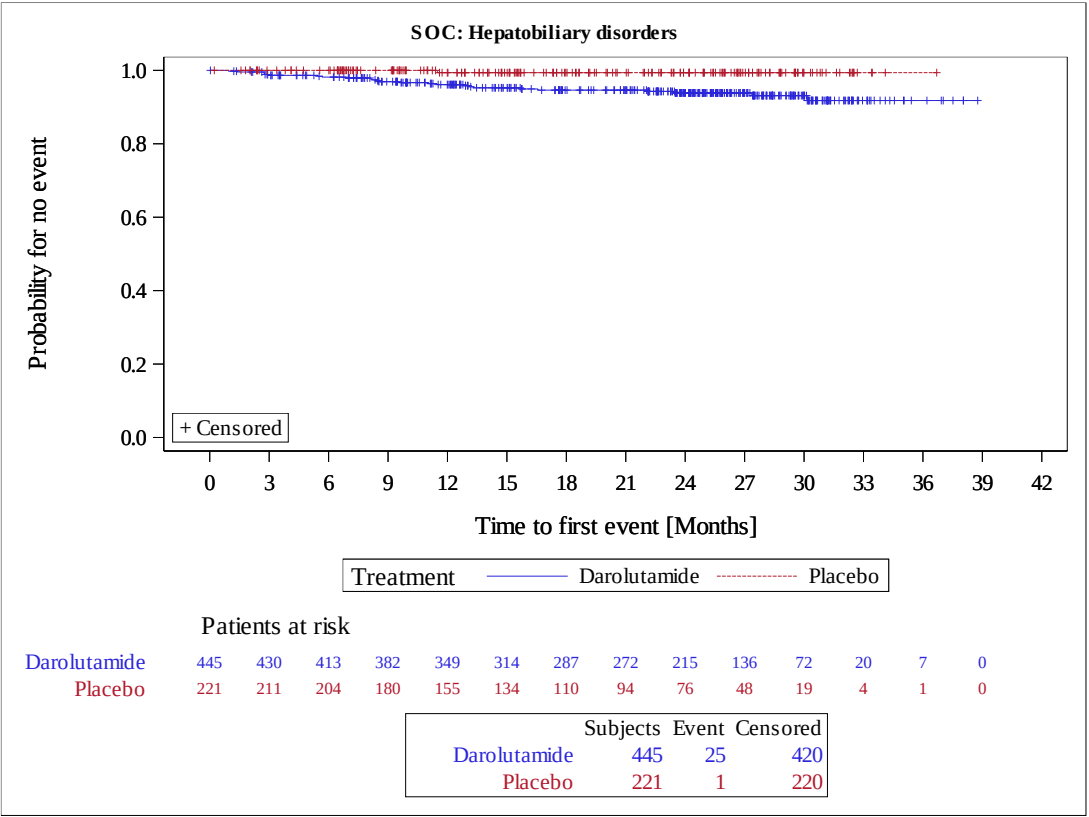


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(safety analysis set)

Final

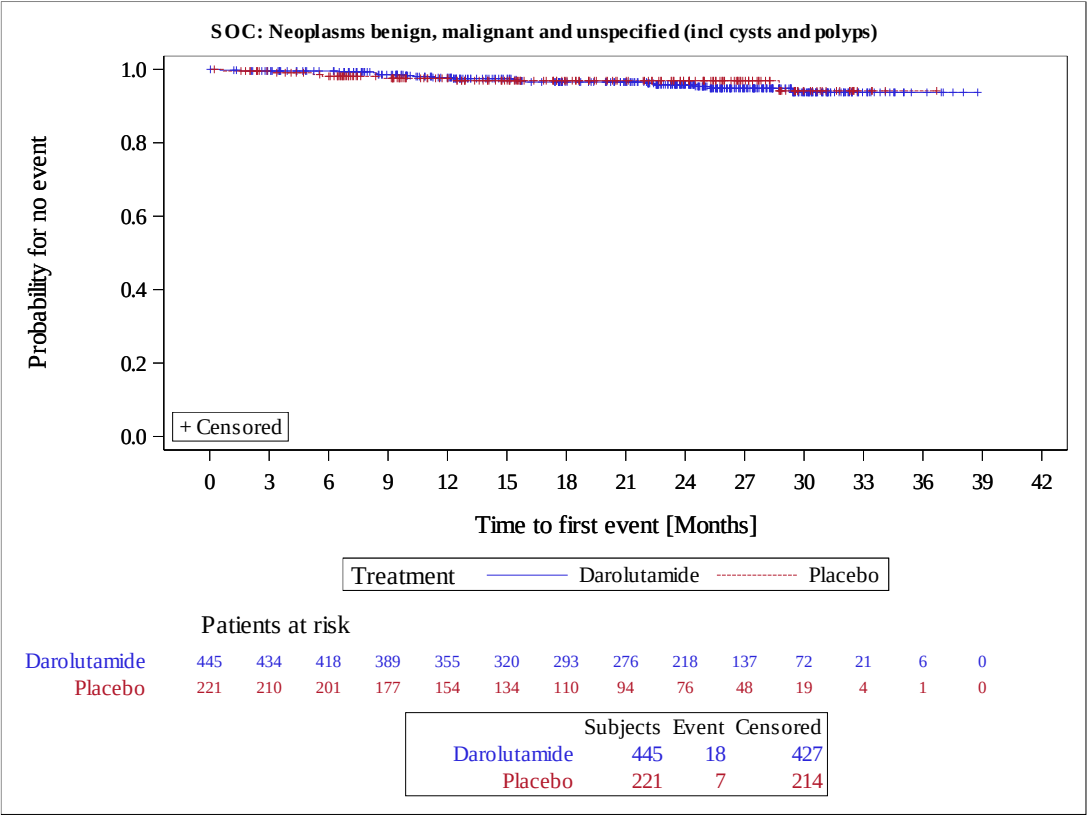


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
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(safety analysis set)

Final

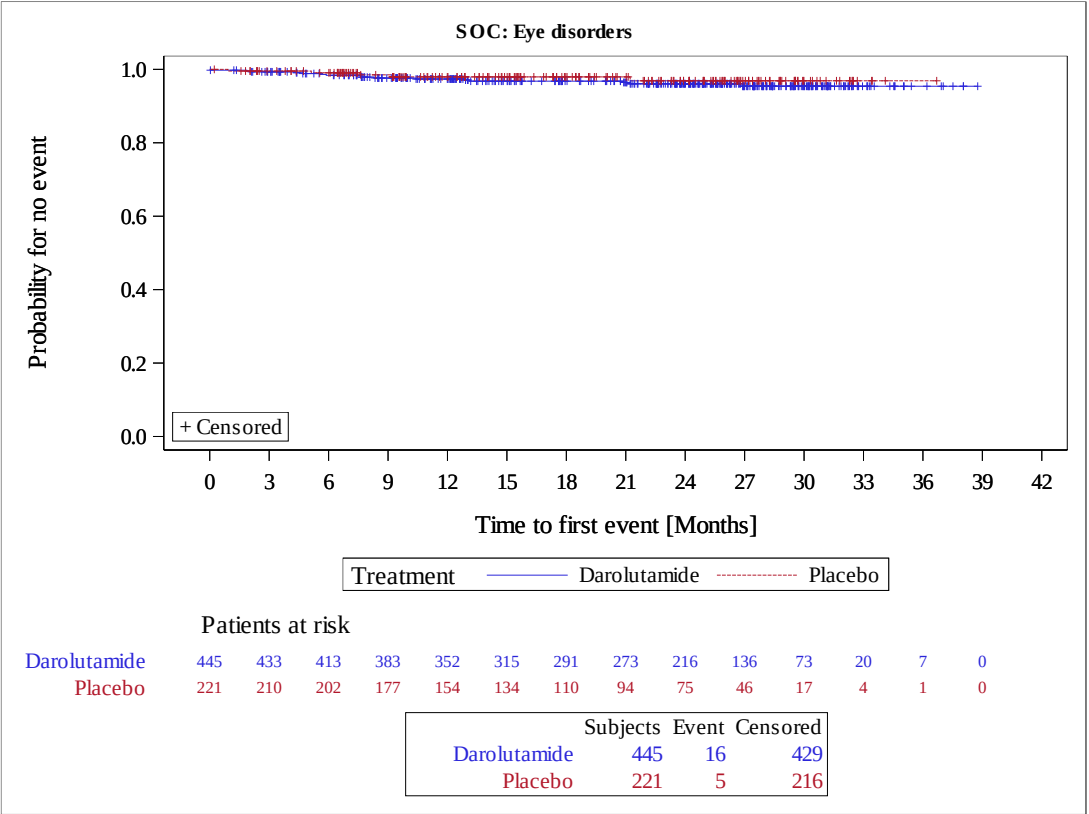


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
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Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

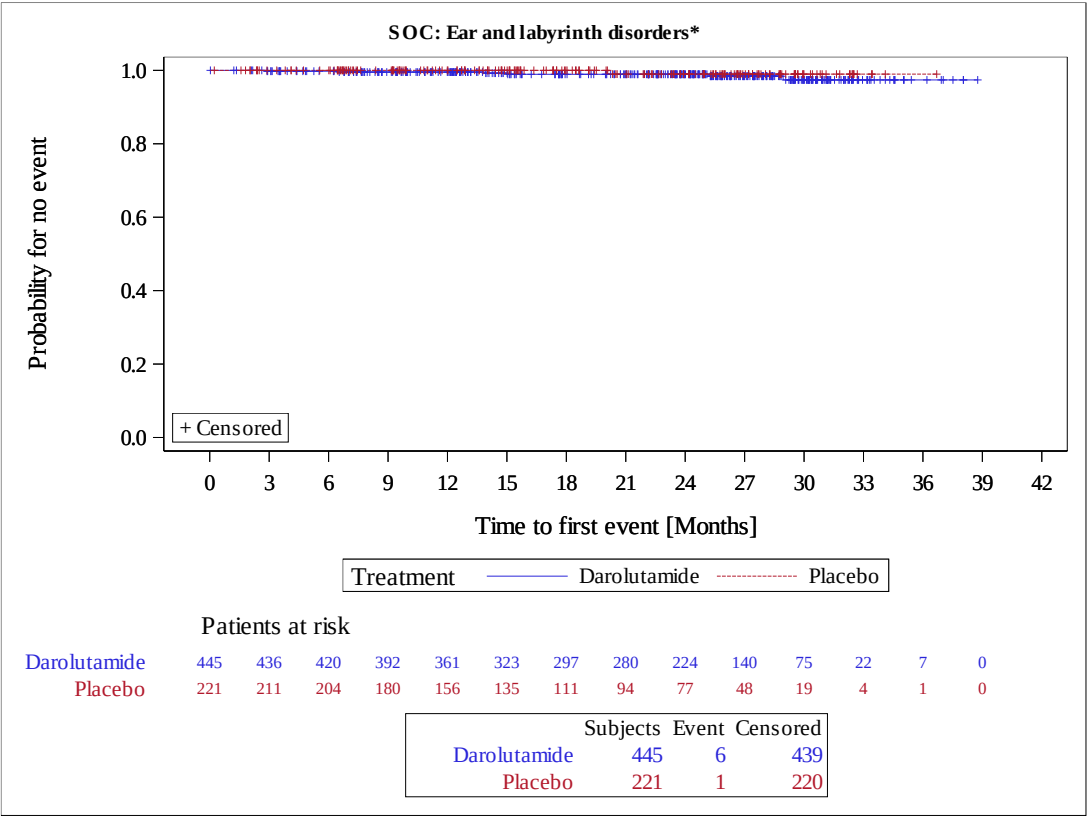


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
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Figure 3.3.1.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

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Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
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Table 3.3.2
Summary of Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Cardiac disorders	Number of subjects with events, n (%)	16 (3.6)	7 (3.2)
	Number of censored subjects, n (%)	429 (96.4)	214 (96.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.007	
	95% CI	0.414, 2.451	
	p-value	0.9873	
	Odds Ratio	1.140	
	95% CI	0.462, 2.813	
	p-value	0.7759	
	Relative Risk	1.135	
	95% CI	0.474, 2.719	
	p-value	0.7761	
	Risk Difference	0.428	
	95% CI	-2.457, 3.313	
	p-value	0.7712	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.2
Summary of Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)		Placebo (N=221)	
SOC: Infections and infestations	Number of subjects with events, n (%)	33 (7.4)		10 (4.5)	
	Number of censored subjects, n (%)	412 (92.6)		211 (95.5)	
	Time to Event (Month)				
	25%-ile (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	Median (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	75%-ile (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	Unstratified Analysis				
	Hazard Ratio	1.416			
	95% CI	0.697, 2.878			
	p-value	0.3333			
	Odds Ratio	1.690			
	95% CI	0.817, 3.495			
	p-value	0.1570			
	Relative Risk	1.639			
	95% CI	0.823, 3.264			
	p-value	0.1599			
	Risk Difference	2.891			
	95% CI	-0.775, 6.556			
	p-value	0.1222			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.2
Summary of Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Injury, poisoning and procedural complications*		
Number of subjects with events, n (%)	9 (2.0)	3 (1.4)
Number of censored subjects, n (%)	436 (98.0)	218 (98.6)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.265	
95% CI	0.342, 4.684	
p-value	0.7245	
Odds Ratio	1.500	
95% CI	0.402, 5.597	
p-value	0.5461	
Relative Risk	1.490	
95% CI	0.407, 5.449	
p-value	0.5467	
Risk Difference	0.665	
95% CI	-1.345, 2.675	
p-value	0.5166	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Table 3.3.2
Summary of Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Musculoskeletal and connective tissue disorders	Number of subjects with events, n (%)	11 (2.5)	6 (2.7)
	Number of censored subjects, n (%)	434 (97.5)	215 (97.3)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.846	
	95% CI	0.312, 2.289	
	p-value	0.7411	
	Odds Ratio	0.908	
	95% CI	0.331, 2.489	
	p-value	0.8515	
	Relative Risk	0.910	
	95% CI	0.341, 2.430	
	p-value	0.8515	
	Risk Difference	-0.243	
	95% CI	-2.826, 2.340	
	p-value	0.8537	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.2
Summary of Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Number of subjects with events, n (%)	11 (2.5)	5 (2.3)
	Number of censored subjects, n (%)	434 (97.5)	216 (97.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.970	
	95% CI	0.337, 2.794	
	p-value	0.9552	
	Odds Ratio	1.095	
	95% CI	0.376, 3.191	
	p-value	0.8680	
	Relative Risk	1.093	
	95% CI	0.384, 3.106	
	p-value	0.8681	
	Risk Difference	0.209	
	95% CI	-2.225, 2.644	
	p-value	0.8661	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
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Table 3.3.2
Summary of Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Nervous system disorders	Number of subjects with events, n (%)	13 (2.9)	5 (2.3)
	Number of censored subjects, n (%)	432 (97.1)	216 (97.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.121	
	95% CI	0.399, 3.149	
	p-value	0.8287	
	Odds Ratio	1.300	
	95% CI	0.458, 3.694	
	p-value	0.6224	
	Relative Risk	1.291	
	95% CI	0.466, 3.576	
	p-value	0.6229	
	Risk Difference	0.659	
	95% CI	-1.849, 3.167	
	p-value	0.6067	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
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Summary of Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Renal and urinary disorders	Number of subjects with events, n (%)	15 (3.4)	8 (3.6)
	Number of censored subjects, n (%)	430 (96.6)	213 (96.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.827	
	95% CI	0.350, 1.953	
	p-value	0.6650	
	Odds Ratio	0.929	
	95% CI	0.388, 2.225	
	p-value	0.8683	
	Relative Risk	0.931	
	95% CI	0.401, 2.163	
	p-value	0.8683	
	Risk Difference	-0.249	
	95% CI	-3.228, 2.730	
	p-value	0.8698	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
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Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.2
Summary of Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Respiratory, thoracic and mediastinal disorders*		
Number of subjects with events, n (%)	6 (1.3)	6 (2.7)
Number of censored subjects, n (%)	439 (98.7)	215 (97.3)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.422	
95% CI	0.135, 1.312	
p-value	0.1240	
Odds Ratio	0.490	
95% CI	0.156, 1.536	
p-value	0.2210	
Relative Risk	0.497	
95% CI	0.162, 1.522	
p-value	0.2207	
Risk Difference	-1.367	
95% CI	-3.762, 1.029	
p-value	0.2635	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.3.2.1
Summary of Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) - Subgroup analysis (safety analysis set)

Final

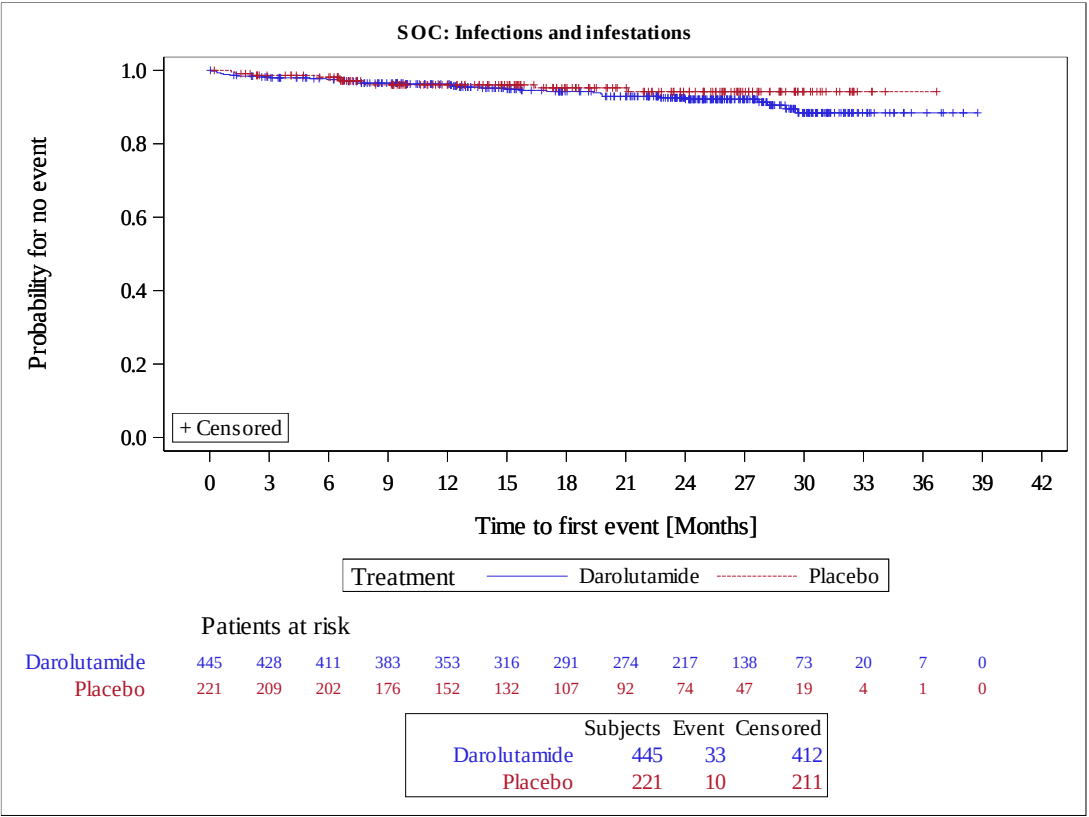
!!! There are no Observations for this Report !!!

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Subgroup analysis was done for SOC's / PTs with significant overall treatment effect (significant log-rank test).
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.3.2.2
Kaplan-Meier Plot of Time to First Frequent Serious Adverse Event by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

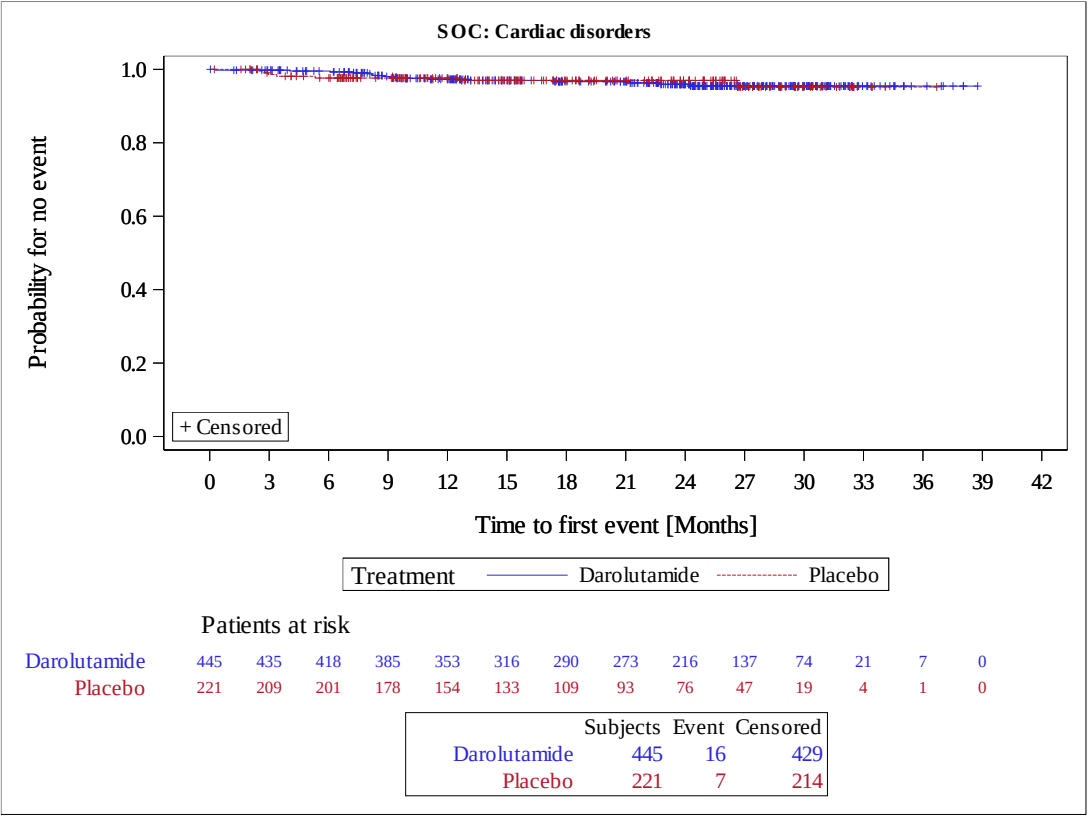


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC/ PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.3.2.2
Kaplan-Meier Plot of Time to First Frequent Serious Adverse Event by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

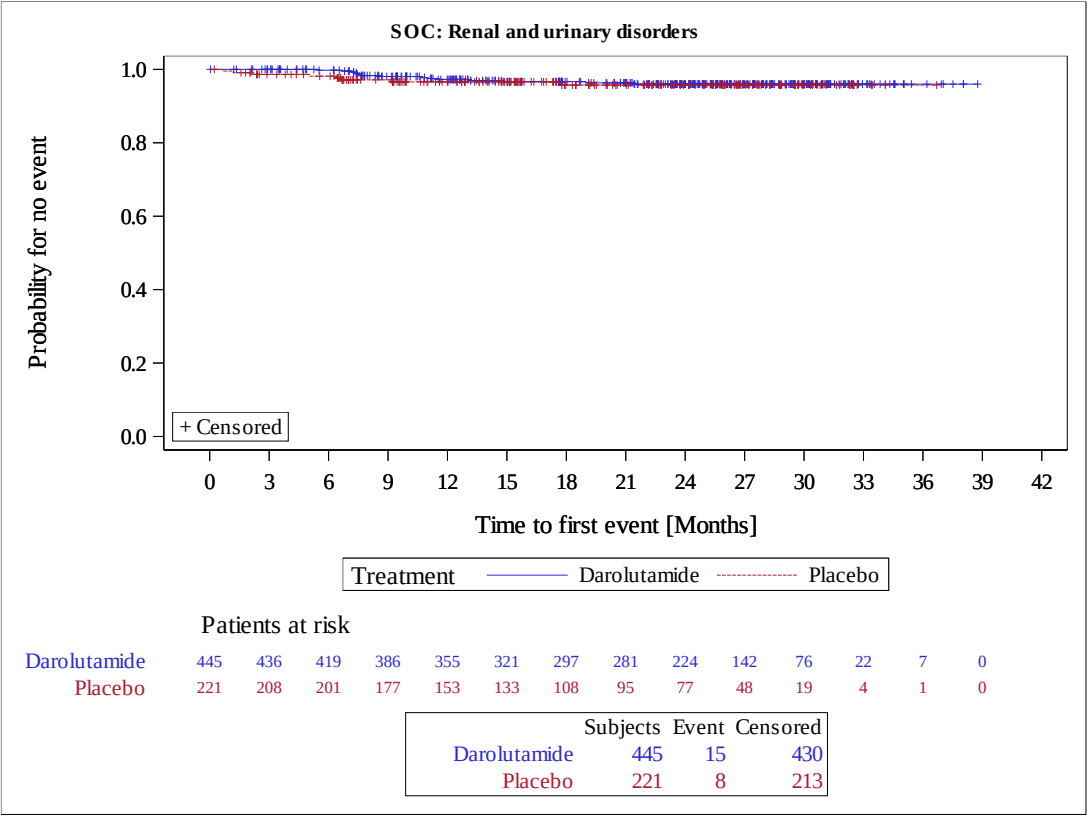


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC/PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.3.2.2
Kaplan-Meier Plot of Time to First Frequent Serious Adverse Event by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

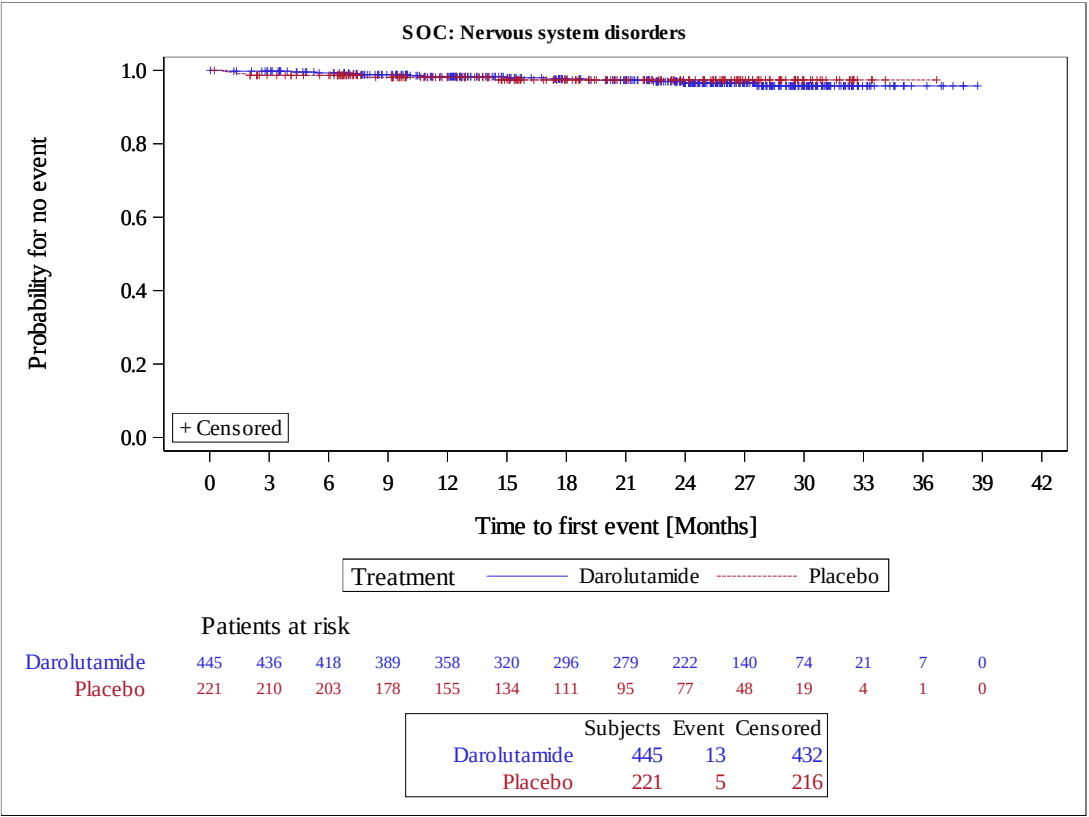


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC/PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.3.2.2
Kaplan-Meier Plot of Time to First Frequent Serious Adverse Event by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

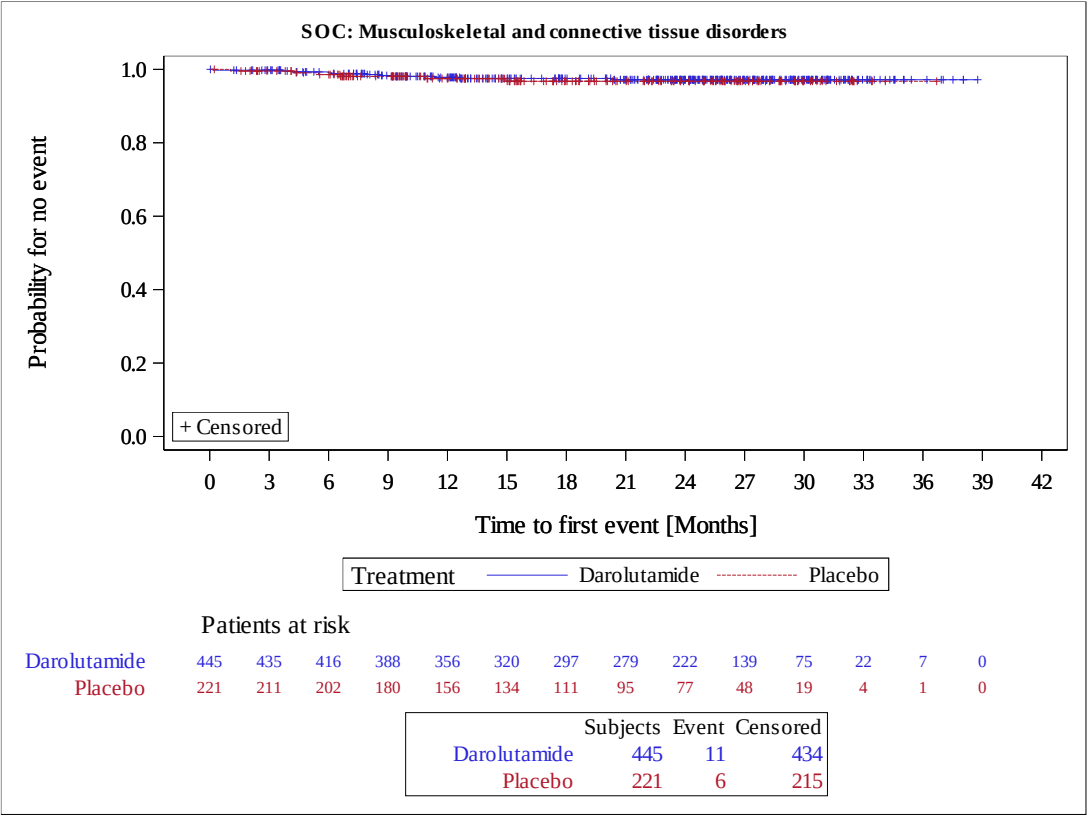


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC/PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.3.2.2
Kaplan-Meier Plot of Time to First Frequent Serious Adverse Event by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

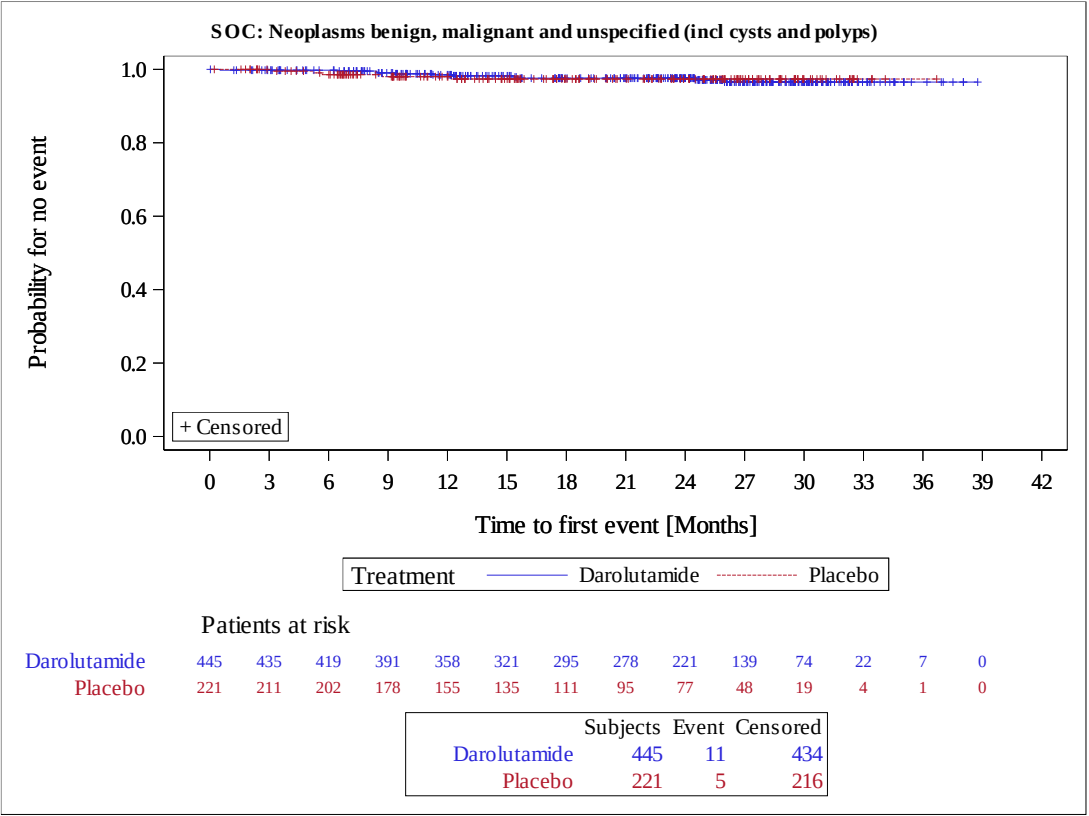


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC/PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.3.2.2
Kaplan-Meier Plot of Time to First Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

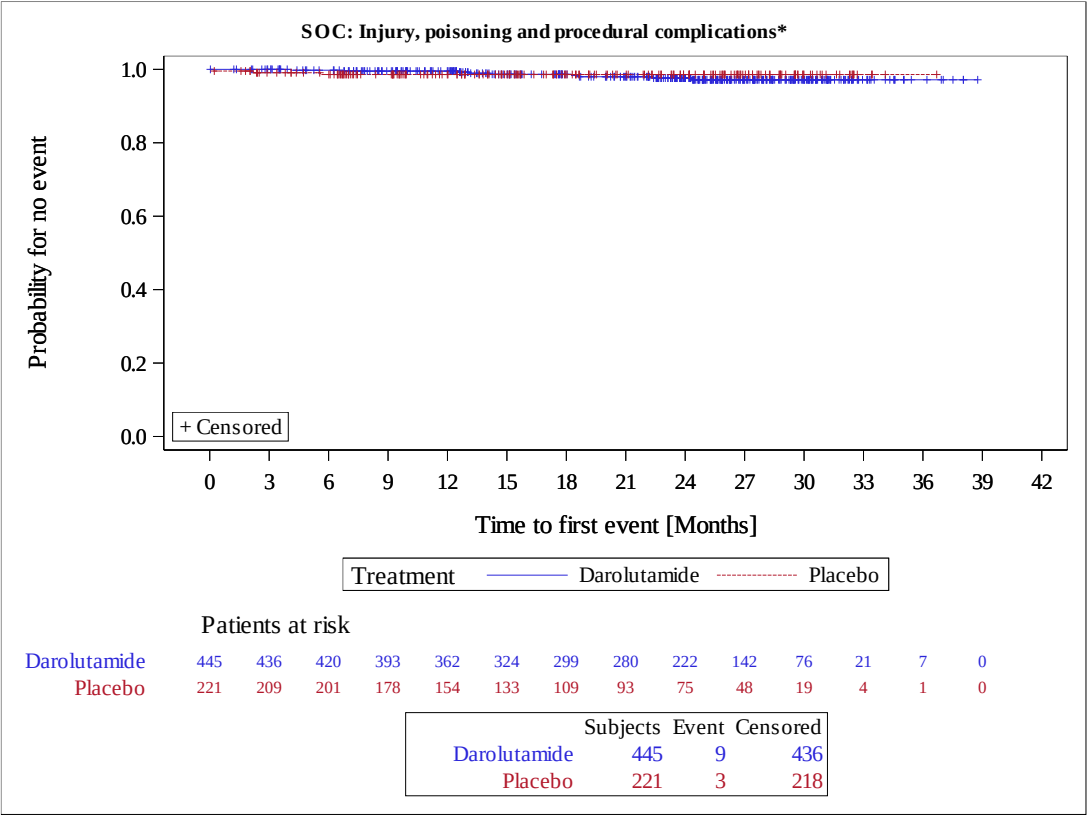


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC/ PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.3.2.2
Kaplan-Meier Plot of Time to First Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

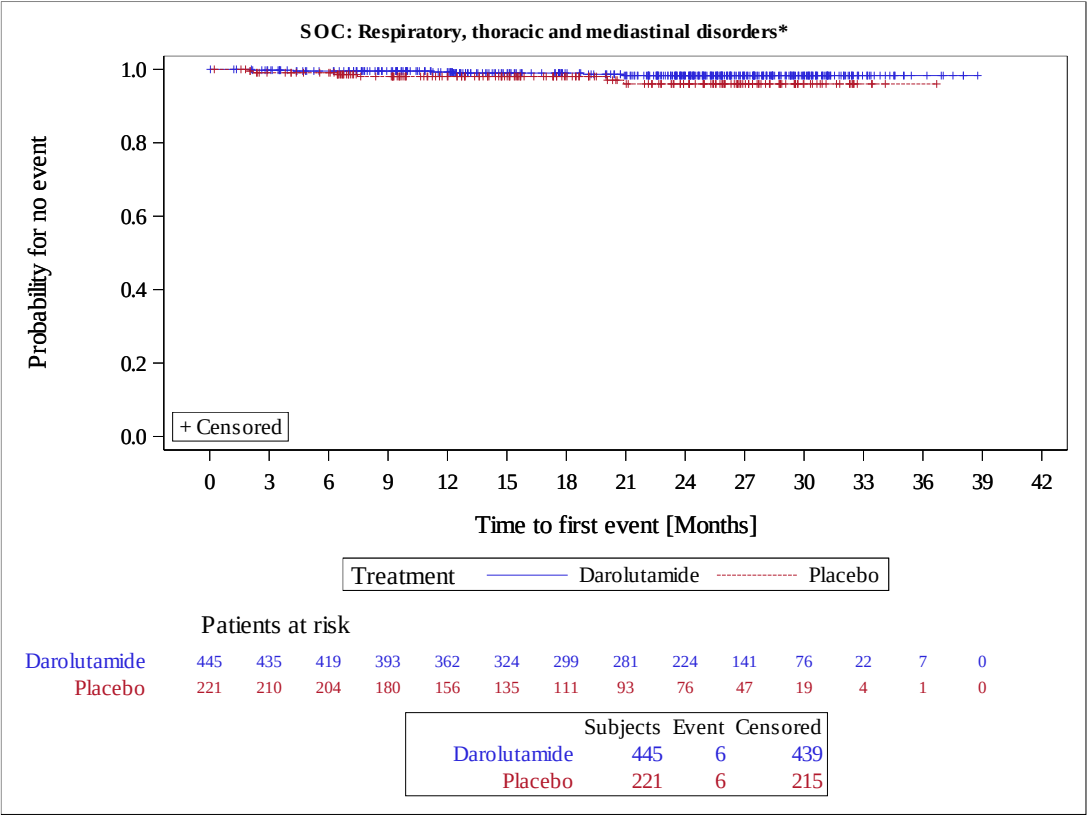


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC/ PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.3.2.2
Kaplan-Meier Plot of Time to First Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC/ PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Blood and lymphatic system disorders	Number of subjects with events, n (%)	17 (3.8)	10 (4.5)
	Number of censored subjects, n (%)	428 (96.2)	211 (95.5)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.733	
	95% CI	0.335, 1.603	
	p-value	0.4347	
	Odds Ratio	0.838	
	95% CI	0.377, 1.862	
	p-value	0.6645	
	Relative Risk	0.844	
	95% CI	0.393, 1.813	
	p-value	0.6642	
	Risk Difference	-0.705	
	95% CI	-3.973, 2.564	
	p-value	0.6726	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Blood and lymphatic system disorders - PT:Anaemia	Number of subjects with events, n (%)	14 (3.1)	8 (3.6)
	Number of censored subjects, n (%)	431 (96.9)	213 (96.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.760	
	95% CI	0.318, 1.814	
	p-value	0.5351	
	Odds Ratio	0.865	
	95% CI	0.357, 2.093	
	p-value	0.7475	
	Relative Risk	0.869	
	95% CI	0.370, 2.041	
	p-value	0.7473	
	Risk Difference	-0.474	
	95% CI	-3.423, 2.475	
	p-value	0.7528	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Cardiac disorders	Number of subjects with events, n (%)	12 (2.7)	5 (2.3)
	Number of censored subjects, n (%)	433 (97.3)	216 (97.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.053	
	95% CI	0.371, 2.993	
	p-value	0.9218	
	Odds Ratio	1.197	
	95% CI	0.416, 3.442	
	p-value	0.7383	
	Relative Risk	1.192	
	95% CI	0.425, 3.341	
	p-value	0.7385	
	Risk Difference	0.434	
	95% CI	-2.037, 2.906	
	p-value	0.7306	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Gastrointestinal disorders*		
Number of subjects with events, n (%)	5 (1.1)	9 (4.1)
Number of censored subjects, n (%)	440 (98.9)	212 (95.9)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.241	
95% CI	0.080, 0.720	
p-value	0.0057	
Odds Ratio	0.268	
95% CI	0.089, 0.809	
p-value	0.0194	
Relative Risk	0.276	
95% CI	0.094, 0.813	
p-value	0.0196	
Risk Difference	-2.949	
95% CI	-5.733, -0.165	
p-value	0.0379	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: General disorders and administration site conditions	Number of subjects with events, n (%)	11 (2.5)	9 (4.1)
	Number of censored subjects, n (%)	434 (97.5)	212 (95.9)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.485	
	95% CI	0.200, 1.175	
	p-value	0.1017	
	Odds Ratio	0.597	
	95% CI	0.244, 1.463	
	p-value	0.2593	
	Relative Risk	0.607	
	95% CI	0.255, 1.443	
	p-value	0.2585	
	Risk Difference	-1.600	
	95% CI	-4.579, 1.378	
	p-value	0.2923	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
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Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)		Placebo (N=221)	
SOC: Infections and infestations	Number of subjects with events, n (%)	31 (7.0)		8 (3.6)	
	Number of censored subjects, n (%)	414 (93.0)		213 (96.4)	
	Time to Event (Month)				
	25%-ile (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	Median (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	75%-ile (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	Unstratified Analysis				
	Hazard Ratio	1.672			
	95% CI	0.768, 3.643			
	p-value	0.1906			
	Odds Ratio	1.994			
	95% CI	0.901, 4.413			
	p-value	0.0888			
	Relative Risk	1.924			
	95% CI	0.900, 4.116			
	p-value	0.0915			
	Risk Difference	3.346			
	95% CI	-0.068, 6.761			
	p-value	0.0548			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
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95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Injury, poisoning and procedural complications*		
Number of subjects with events, n (%)	9 (2.0)	5 (2.3)
Number of censored subjects, n (%)	436 (98.0)	216 (97.7)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.764	
95% CI	0.256, 2.285	
p-value	0.6293	
Odds Ratio	0.892	
95% CI	0.295, 2.693	
p-value	0.8390	
Relative Risk	0.894	
95% CI	0.303, 2.636	
p-value	0.8389	
Risk Difference	-0.240	
95% CI	-2.597, 2.117	
p-value	0.8418	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Investigations	Number of subjects with events, n (%)	23 (5.2)	8 (3.6)
	Number of censored subjects, n (%)	422 (94.8)	213 (96.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.225	
	95% CI	0.547, 2.741	
	p-value	0.6212	
	Odds Ratio	1.451	
	95% CI	0.638, 3.299	
	p-value	0.3742	
	Relative Risk	1.428	
	95% CI	0.649, 3.140	
	p-value	0.3758	
	Risk Difference	1.549	
	95% CI	-1.660, 4.757	
	p-value	0.3442	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Investigations - PT:Aspartate aminotransferase increased	Number of subjects with events, n (%)	10 (2.2)	1 (0.5)
	Number of censored subjects, n (%)	435 (97.8)	220 (99.5)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	4.102	
	95% CI	0.524, 32.081	
	p-value	0.1446	
	Odds Ratio	5.057	
	95% CI	0.643, 39.761	
	p-value	0.1234	
	Relative Risk	4.966	
	95% CI	0.640, 38.550	
	p-value	0.1253	
	Risk Difference	1.795	
	95% CI	0.158, 3.432	
	p-value	0.0316	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Investigations - PT:Weight increased*		
Number of subjects with events, n (%)	4 (0.9)	1 (0.5)
Number of censored subjects, n (%)	441 (99.1)	220 (99.5)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.634	
95% CI	0.182, 14.680	
p-value	0.6578	
Odds Ratio	1.995	
95% CI	0.222, 17.960	
p-value	0.5377	
Relative Risk	1.987	
95% CI	0.223, 17.668	
p-value	0.5382	
Risk Difference	0.446	
95% CI	-0.799, 1.692	
p-value	0.4825	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Metabolism and nutrition disorders	Number of subjects with events, n (%)	11 (2.5)	5 (2.3)
	Number of censored subjects, n (%)	434 (97.5)	216 (97.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.961	
	95% CI	0.333, 2.770	
	p-value	0.9412	
	Odds Ratio	1.095	
	95% CI	0.376, 3.191	
	p-value	0.8680	
	Relative Risk	1.093	
	95% CI	0.384, 3.106	
	p-value	0.8681	
	Risk Difference	0.209	
	95% CI	-2.225, 2.644	
	p-value	0.8661	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Musculoskeletal and connective tissue disorders	Number of subjects with events, n (%)	28 (6.3)	12 (5.4)
	Number of censored subjects, n (%)	417 (93.7)	209 (94.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.030	
	95% CI	0.523, 2.027	
	p-value	0.9324	
	Odds Ratio	1.169	
	95% CI	0.583, 2.346	
	p-value	0.6595	
	Relative Risk	1.159	
	95% CI	0.601, 2.235	
	p-value	0.6600	
	Risk Difference	0.862	
	95% CI	-2.881, 4.606	
	p-value	0.6517	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Musculoskeletal and connective tissue disorders - PT:Back pain*	Number of subjects with events, n (%)	5 (1.1)	2 (0.9)
	Number of censored subjects, n (%)	440 (98.9)	219 (99.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.087	
	95% CI	0.210, 5.614	
	p-value	0.9211	
	Odds Ratio	1.244	
	95% CI	0.239, 6.465	
	p-value	0.7949	
	Relative Risk	1.242	
	95% CI	0.243, 6.349	
	p-value	0.7950	
	Risk Difference	0.219	
	95% CI	-1.368, 1.805	
	p-value	0.7871	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Number of subjects with events, n (%)	10 (2.2)	3 (1.4)
	Number of censored subjects, n (%)	435 (97.8)	218 (98.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.442	
	95% CI	0.396, 5.248	
	p-value	0.5764	
	Odds Ratio	1.670	
	95% CI	0.455, 6.132	
	p-value	0.4393	
	Relative Risk	1.655	
	95% CI	0.460, 5.954	
	p-value	0.4402	
	Risk Difference	0.890	
	95% CI	-1.165, 2.945	
	p-value	0.3962	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Nervous system disorders	Number of subjects with events, n (%)	12 (2.7)	10 (4.5)
	Number of censored subjects, n (%)	433 (97.3)	211 (95.5)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.519	
	95% CI	0.224, 1.203	
	p-value	0.1196	
	Odds Ratio	0.585	
	95% CI	0.249, 1.375	
	p-value	0.2188	
	Relative Risk	0.596	
	95% CI	0.262, 1.358	
	p-value	0.2180	
	Risk Difference	-1.828	
	95% CI	-4.955, 1.298	
	p-value	0.2517	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)	Placebo (N=221)
SOC: Renal and urinary disorders	Number of subjects with events, n (%)	20 (4.5)	8 (3.6)
	Number of censored subjects, n (%)	425 (95.5)	213 (96.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.102	
	95% CI	0.485, 2.504	
	p-value	0.8161	
	Odds Ratio	1.253	
	95% CI	0.543, 2.891	
	p-value	0.5972	
	Relative Risk	1.242	
	95% CI	0.556, 2.774	
	p-value	0.5978	
	Risk Difference	0.874	
	95% CI	-2.251, 4.000	
	p-value	0.5835	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Renal and urinary disorders - PT:Urinary retention*		
Number of subjects with events, n (%)	2 (0.4)	1 (0.5)
Number of censored subjects, n (%)	443 (99.6)	220 (99.5)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.946	
95% CI	0.086, 10.439	
p-value	0.9643	
Odds Ratio	0.993	
95% CI	0.090, 11.013	
p-value	0.9956	
Relative Risk	0.993	
95% CI	0.091, 10.895	
p-value	0.9956	
Risk Difference	-0.003	
95% CI	-1.084, 1.078	
p-value	0.9956	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Respiratory, thoracic and mediastinal disorders*		
Number of subjects with events, n (%)	5 (1.1)	6 (2.7)
Number of censored subjects, n (%)	440 (98.9)	215 (97.3)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.343	
95% CI	0.104, 1.128	
p-value	0.0649	
Odds Ratio	0.407	
95% CI	0.123, 1.349	
p-value	0.1416	
Relative Risk	0.414	
95% CI	0.128, 1.341	
p-value	0.1414	
Risk Difference	-1.591	
95% CI	-3.947, 0.765	
p-value	0.1855	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0		Darolutamide (N=445)		Placebo (N=221)	
SOC: Vascular disorders	Number of subjects with events, n (%)	25 (5.6)		10 (4.5)	
	Number of censored subjects, n (%)	420 (94.4)		211 (95.5)	
	Time to Event (Month)				
	25%-ile (95%-CI)	NE (NE, NE)		NE (30.9, NE)	
	Median (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	75%-ile (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	Unstratified Analysis				
	Hazard Ratio	1.109			
	95% CI	0.532, 2.313			
	p-value	0.7818			
	Odds Ratio	1.256			
	95% CI	0.592, 2.664			
	p-value	0.5524			
	Relative Risk	1.242			
	95% CI	0.607, 2.539			
	p-value	0.5533			
	Risk Difference	1.093			
	95% CI	-2.383, 4.570			
	p-value	0.5377			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 25.0	Darolutamide (N=445)	Placebo (N=221)
SOC: Vascular disorders - PT:Hypertension		
Number of subjects with events, n (%)	19 (4.3)	8 (3.6)
Number of censored subjects, n (%)	426 (95.7)	213 (96.4)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (30.9, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.035	
95% CI	0.452, 2.369	
p-value	0.9345	
Odds Ratio	1.188	
95% CI	0.511, 2.757	
p-value	0.6892	
Relative Risk	1.179	
95% CI	0.525, 2.652	
p-value	0.6896	
Risk Difference	0.650	
95% CI	-2.447, 3.747	
p-value	0.6809	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.3.1

Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) - Subgroup analysis (safety analysis set)

Final

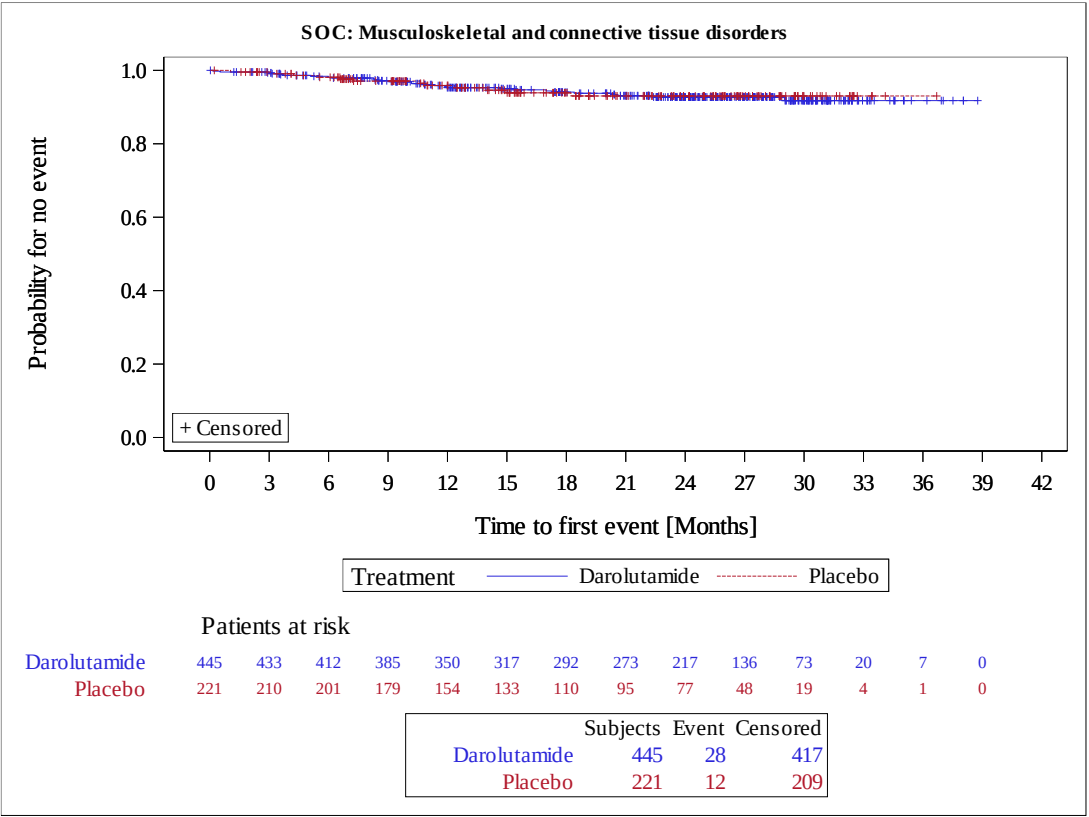
!!! There are no Observations for this Report !!!

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Subgroup analysis was done for SOC / PTs with significant overall treatment effect (significant log-rank test).
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Figure 3.3.3.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

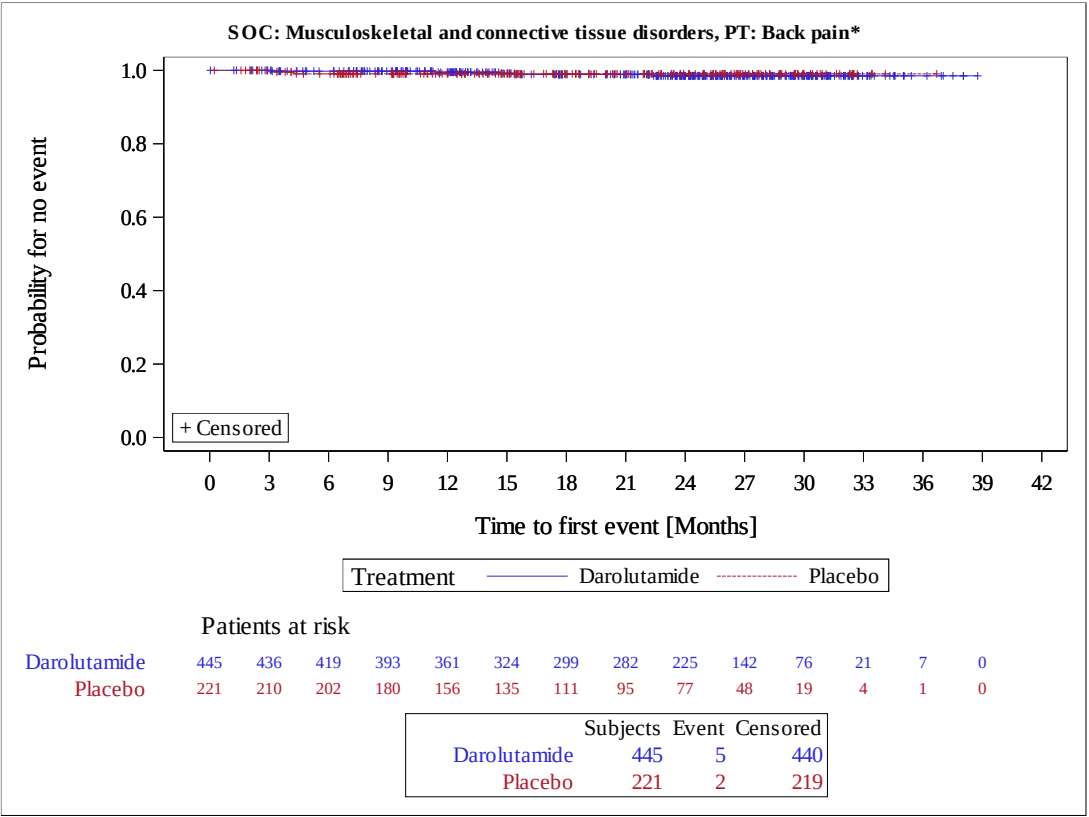


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC/PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

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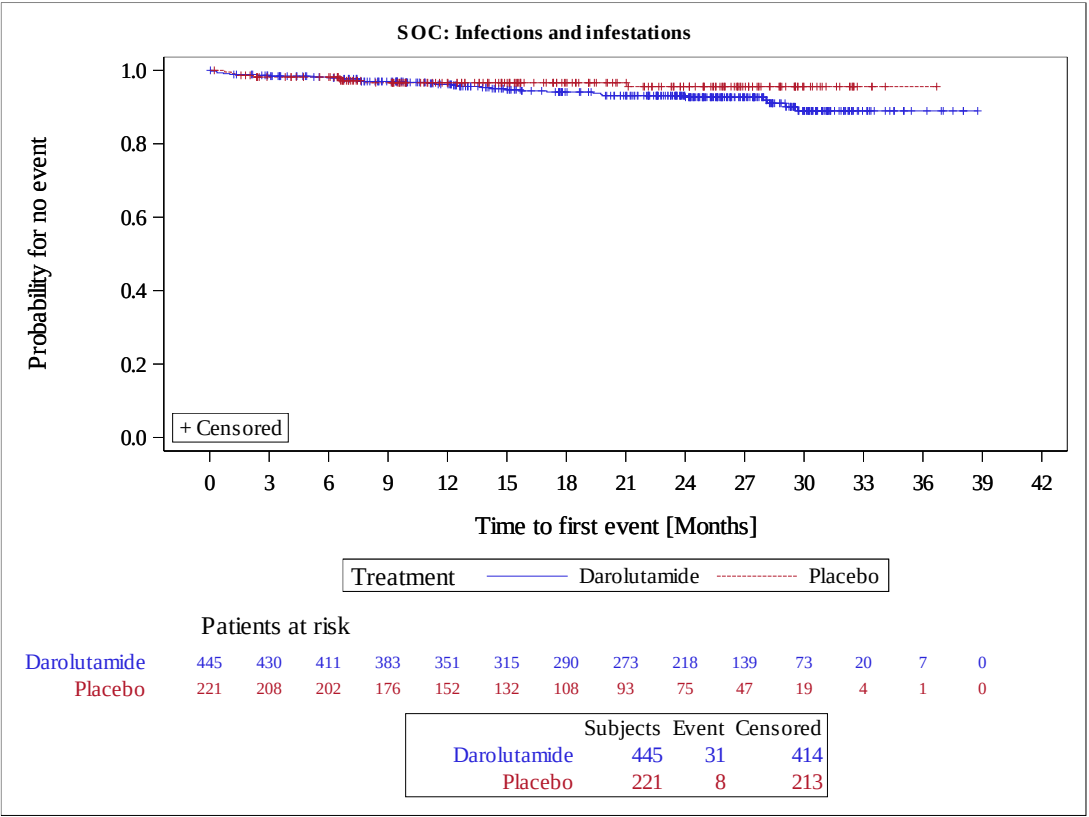


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Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

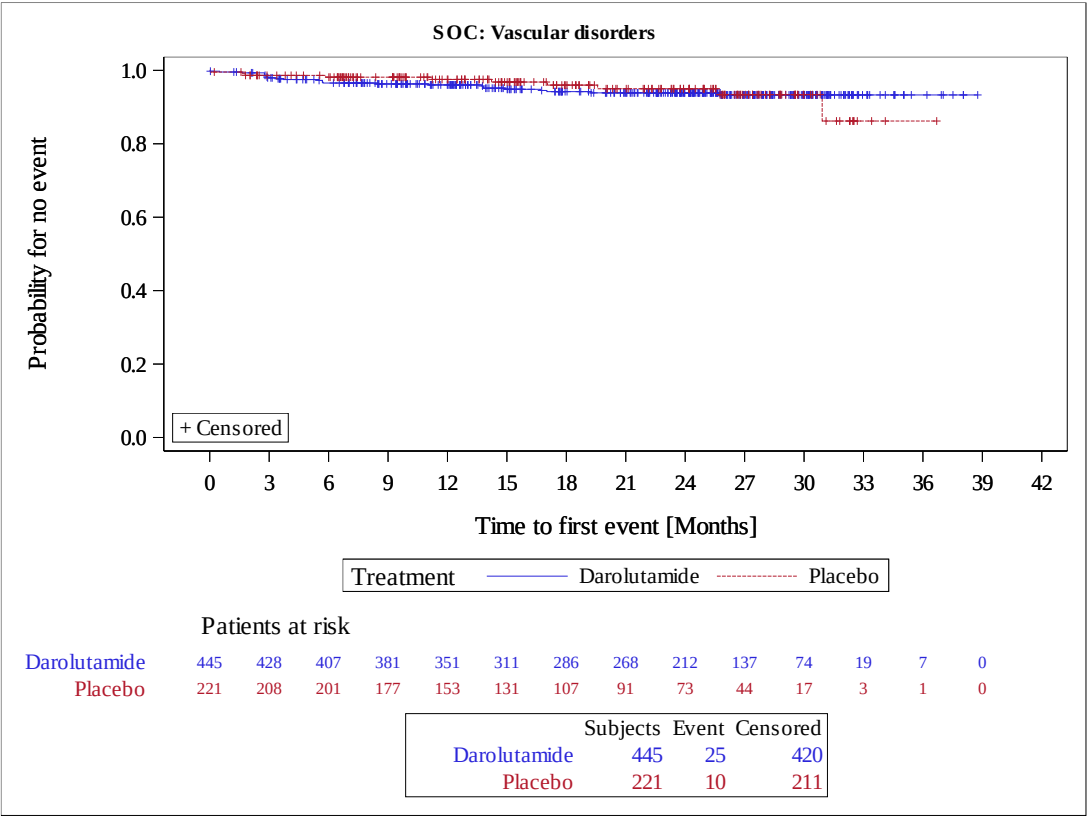


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Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

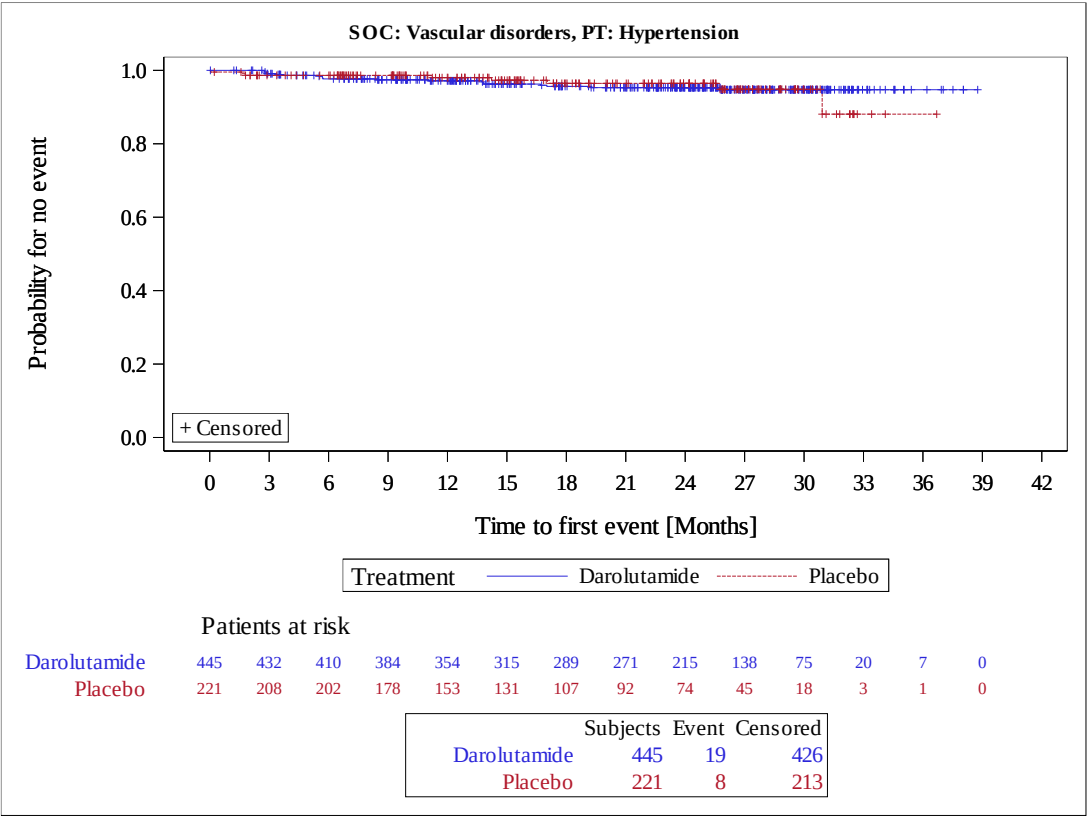


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
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Study population
Figure 3.3.3.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) (safety analysis set)

Final

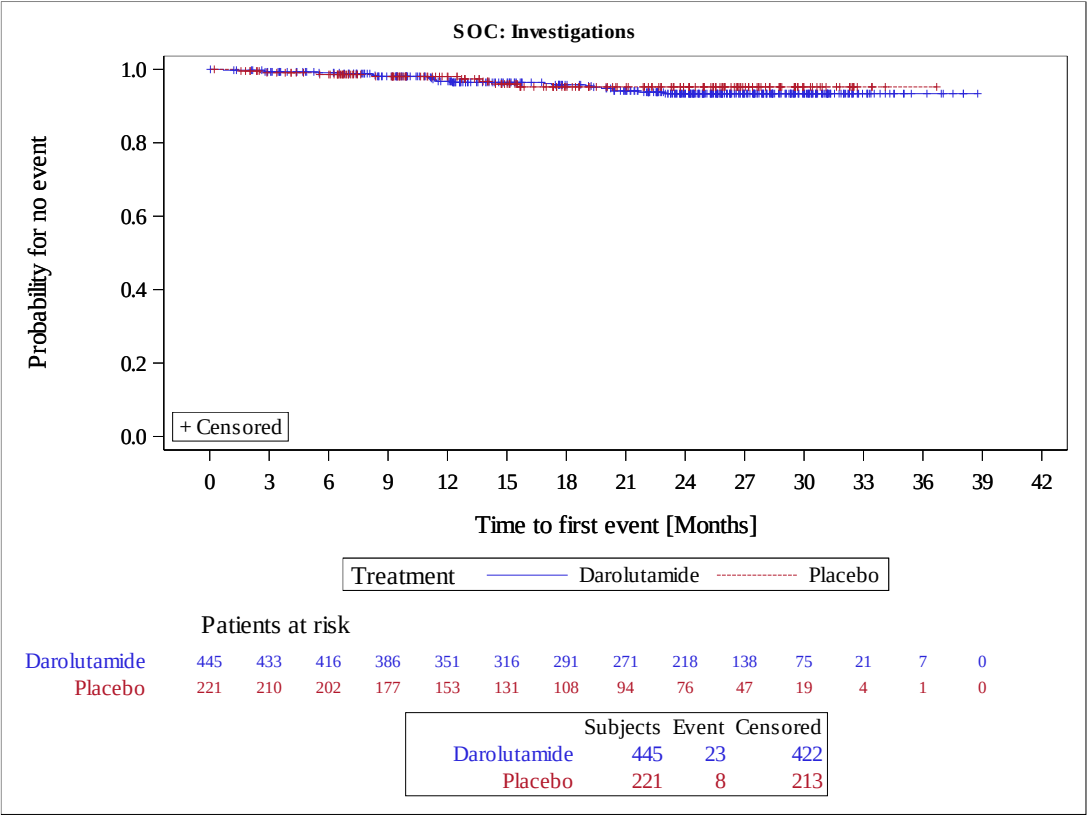


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Study population
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Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

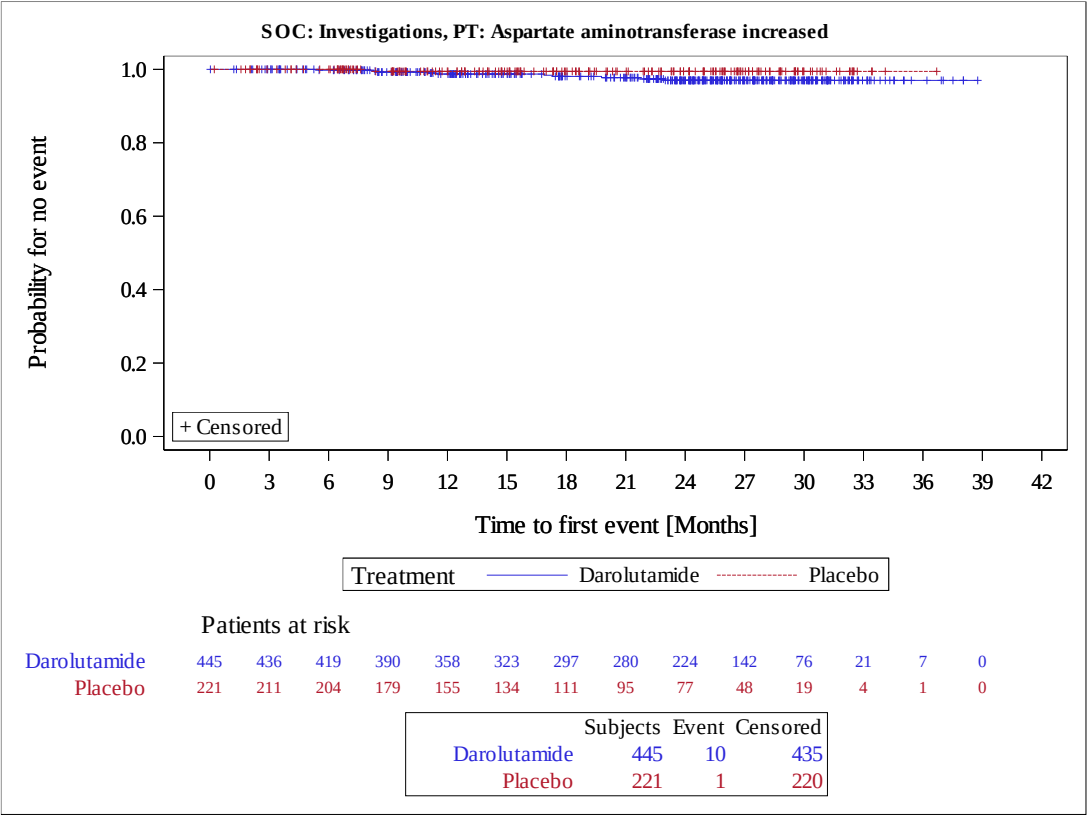


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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
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Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

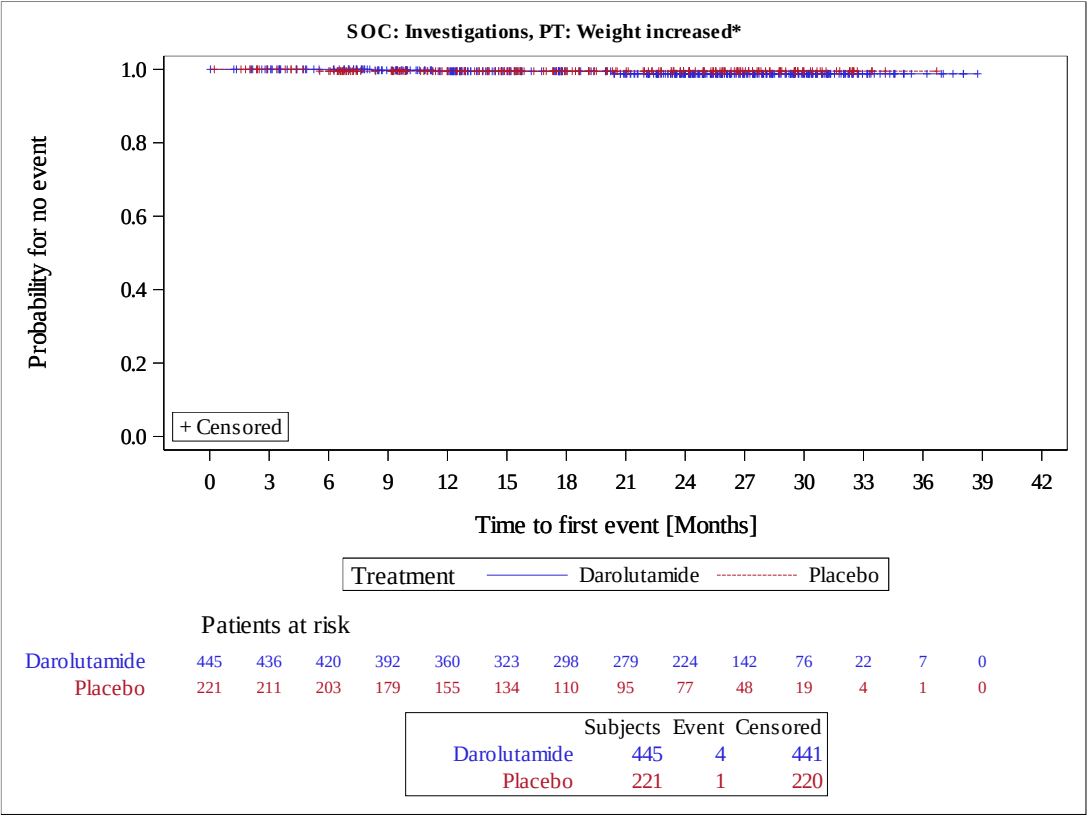
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Study population

Figure 3.3.3.2

Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) (safety analysis set)

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Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Subgroup analysis was done for SOC/ PTs with significant overall treatment effect (significant log-rank test).

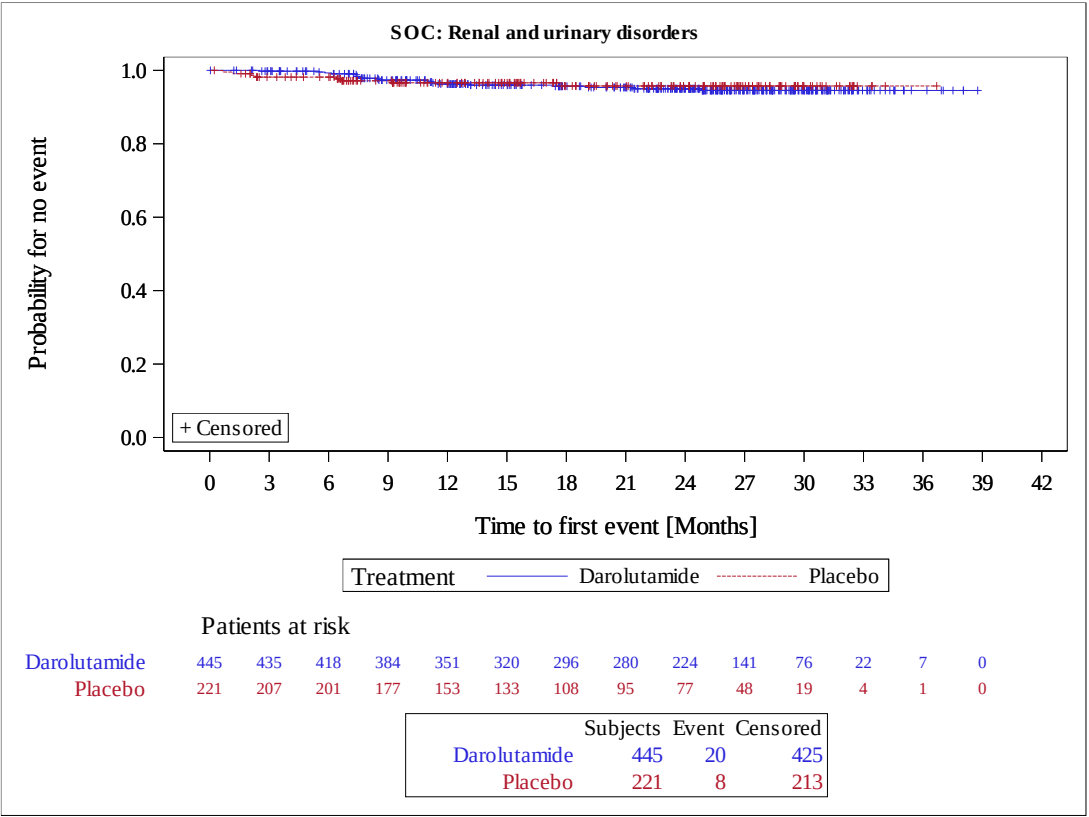
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
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Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) (safety analysis set)

Final

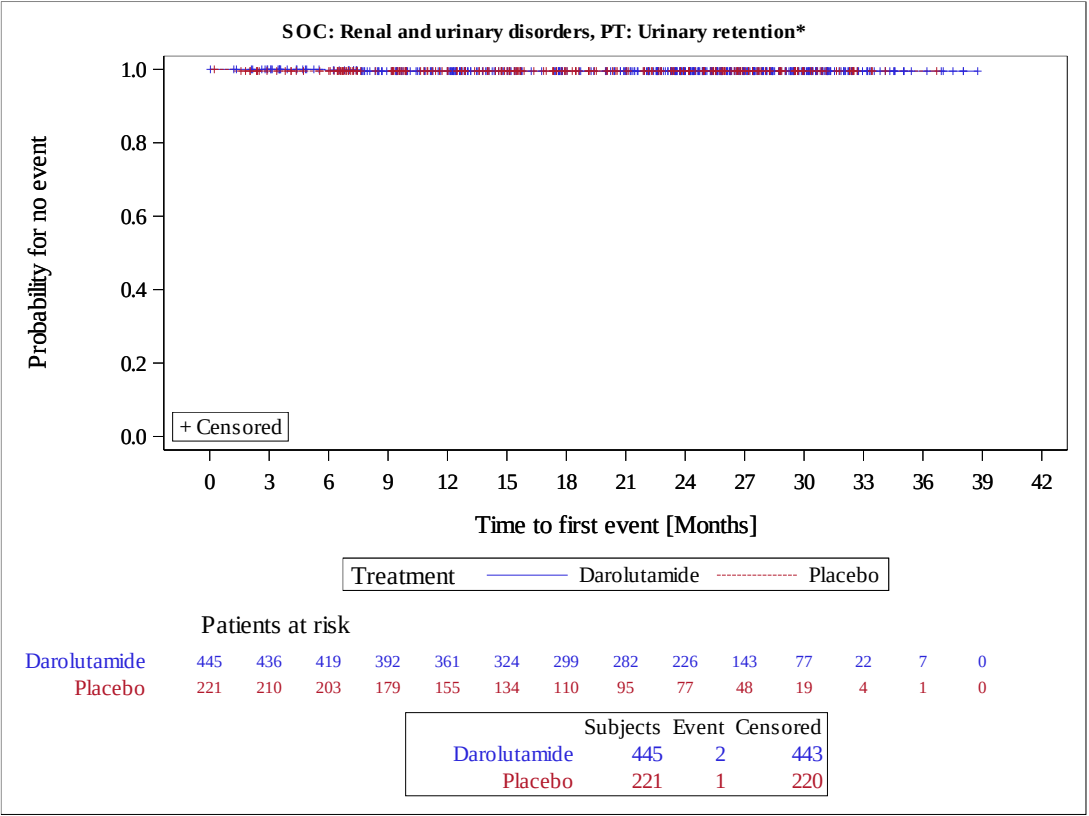


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Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

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Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
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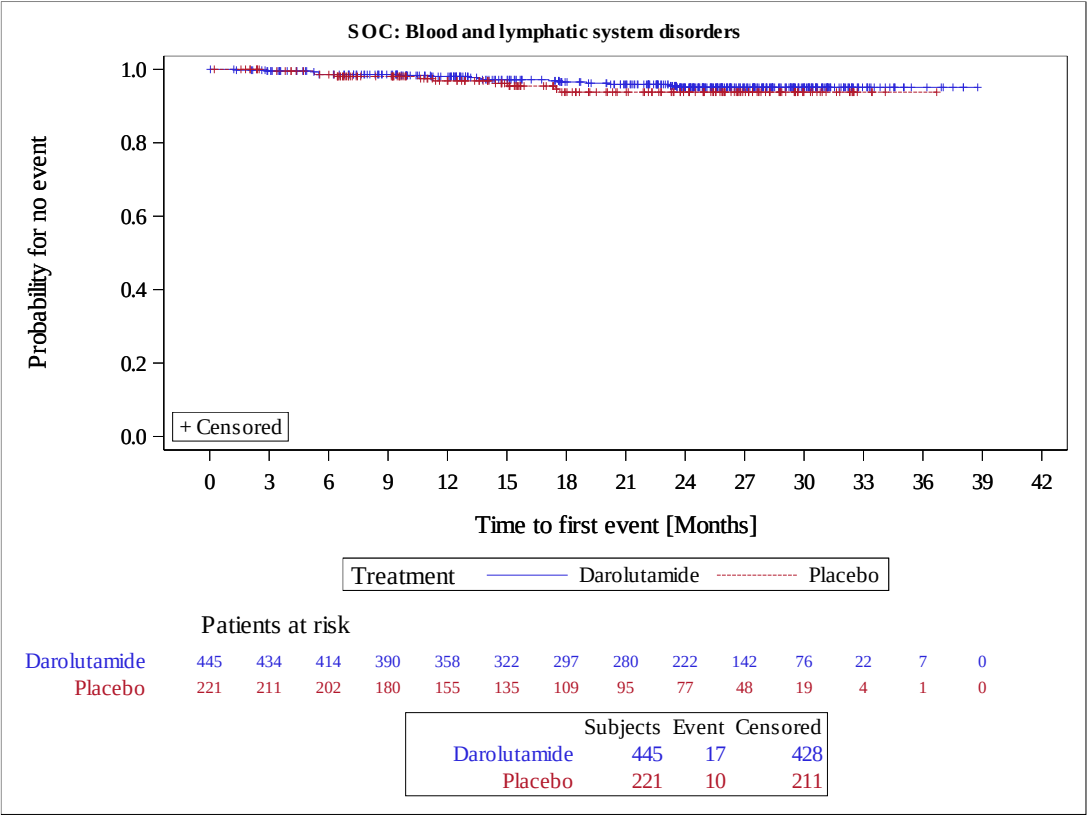
BAY 1841788 / 21140 - 07JUN2024

Study population

Figure 3.3.3.2

Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) (safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Subgroup analysis was done for SOC/ PTs with significant overall treatment effect (significant log-rank test).

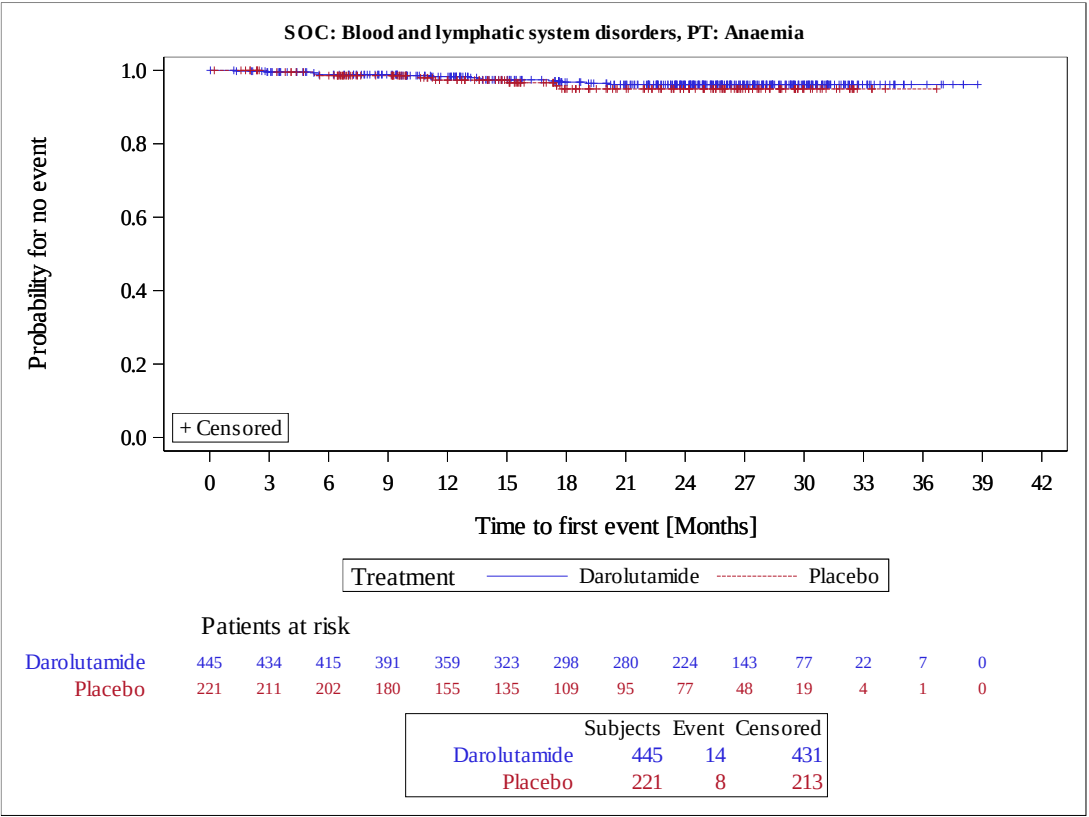
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).

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Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) (safety analysis set)

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Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
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Subgroup analysis was done for SOC/PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

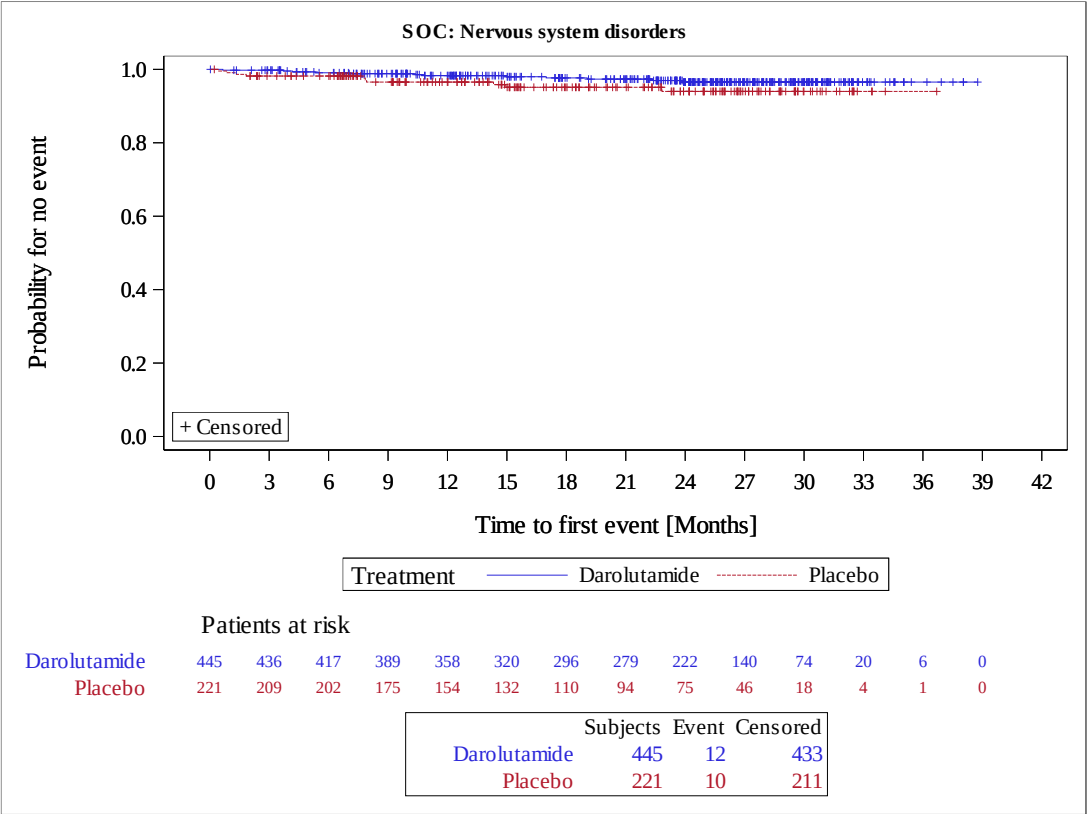
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Figure 3.3.3.2

Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) (safety analysis set)

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Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

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Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Subgroup analysis was done for SOC/PTs with significant overall treatment effect (significant log-rank test).

Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

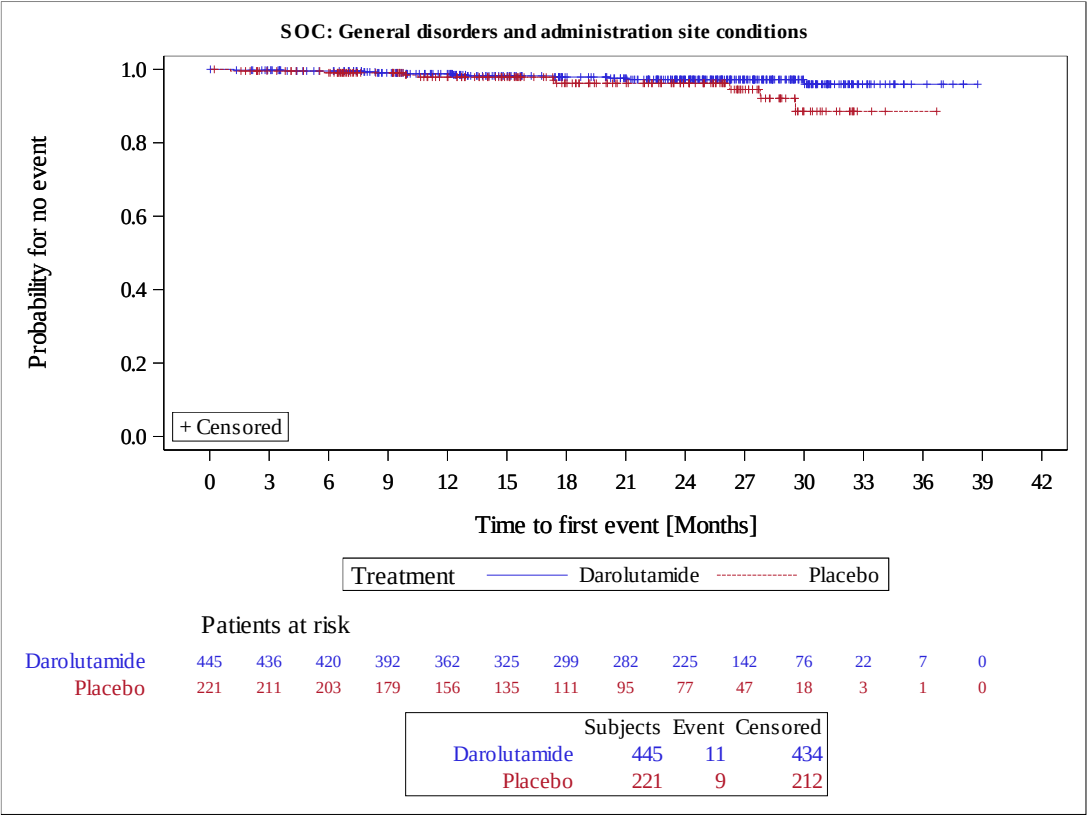
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Study population

Figure 3.3.3.2

Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) (safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Subgroup analysis was done for SOC/PTs with significant overall treatment effect (significant log-rank test).

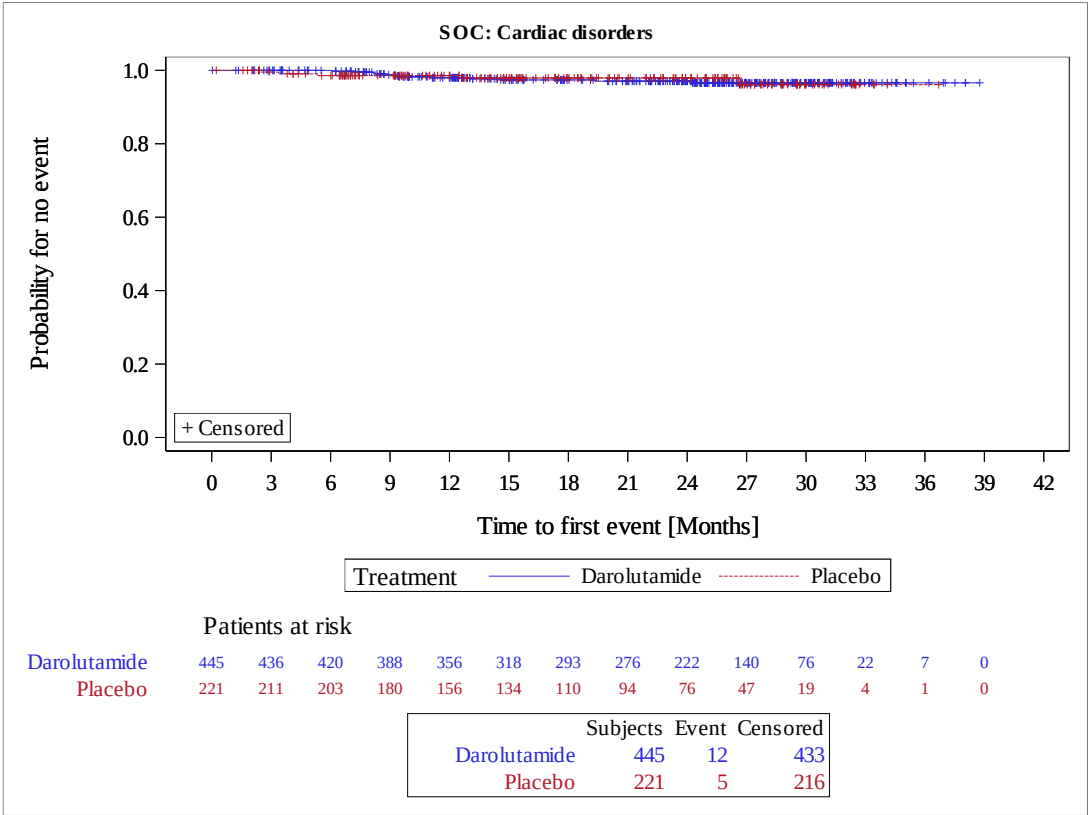
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.3.3.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

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Subgroup analysis was done for SOC/PTs with significant overall treatment effect (significant log-rank test).

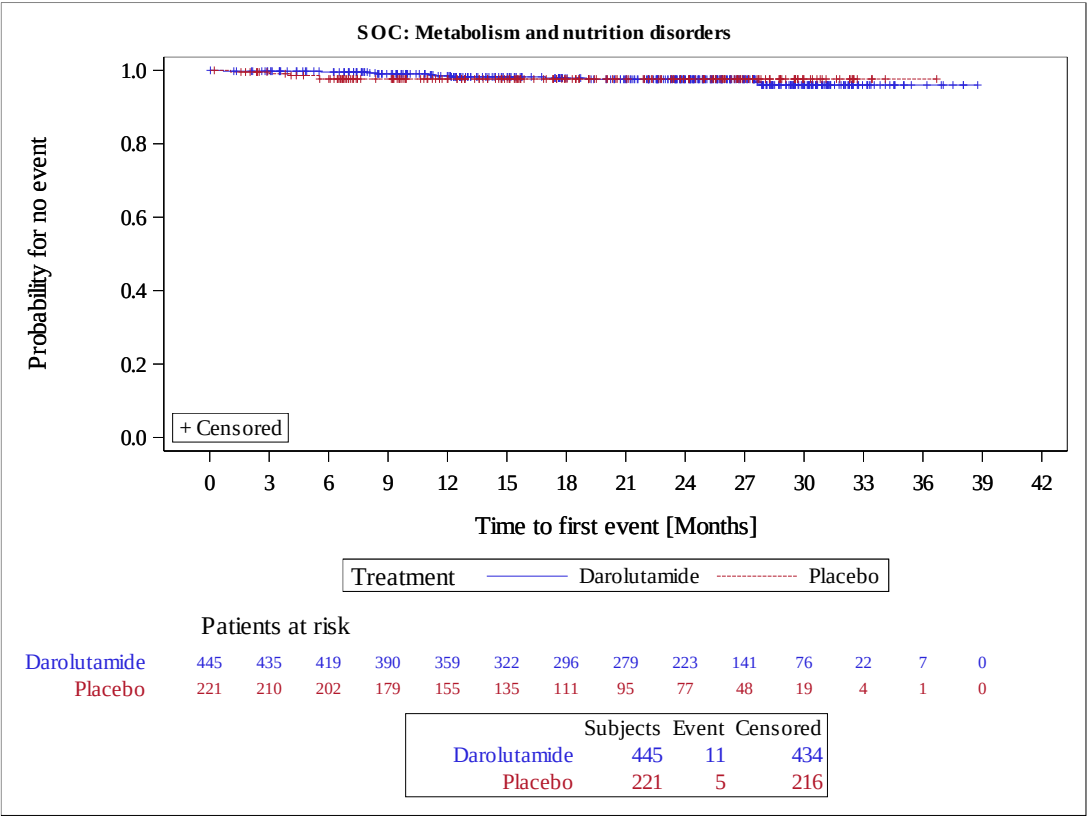
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.3.3.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) (safety analysis set)

Final

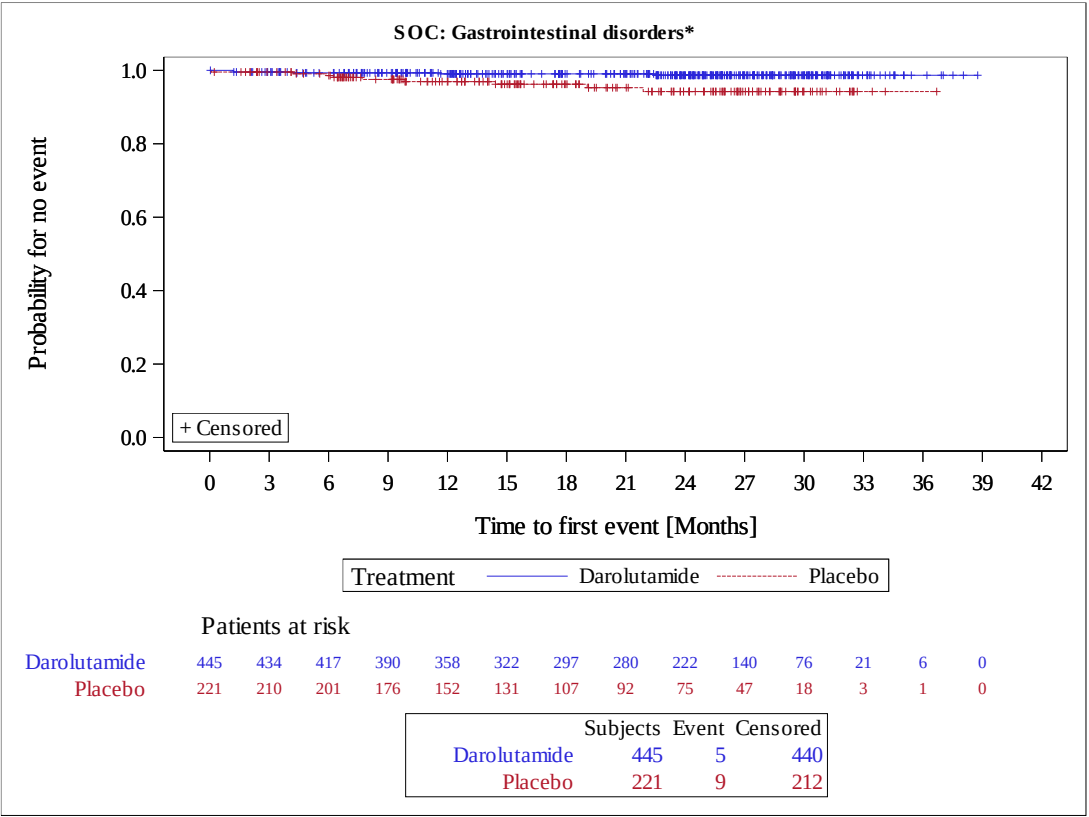


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
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Subgroup analysis was done for SOC/PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 07JUN2024
Study population
Figure 3.3.3.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC/PTs with significant overall treatment effect (significant log-rank test).
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Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

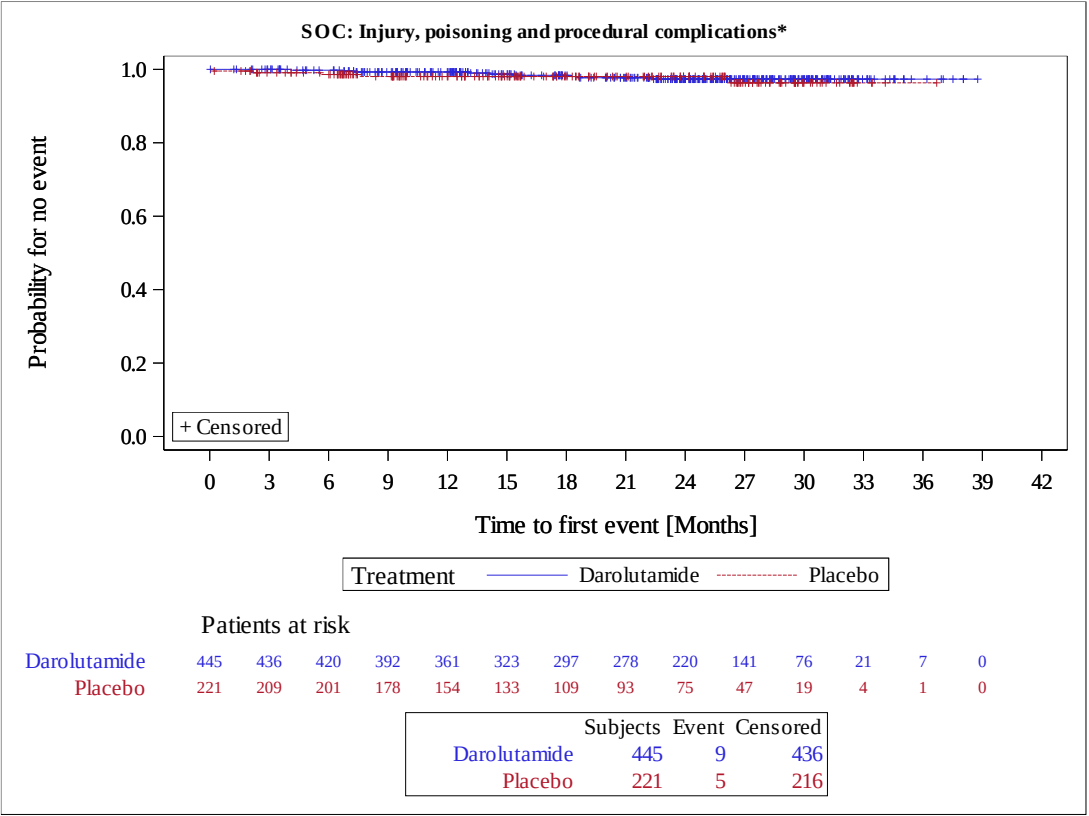
BAY 1841788 / 21140 - 07JUN2024

Study population

Figure 3.3.3.2

Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) (safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Subgroup analysis was done for SOC/ PTs with significant overall treatment effect (significant log-rank test).

Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

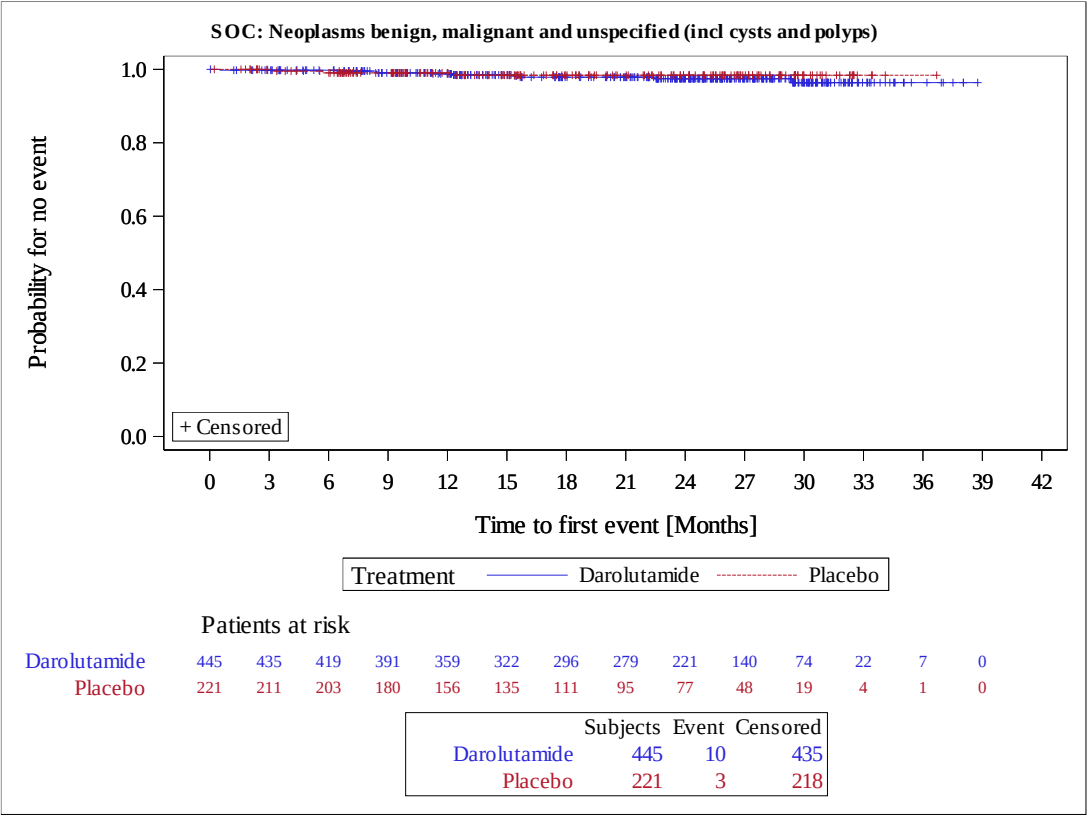
BAY 1841788 / 21140 - 07JUN2024

Study population

Figure 3.3.3.2

Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade ≥ 3 by SOC and PT (incidence in either arm $\geq 5\%$ or both incidence $\geq 1\%$ and ≥ 10 participants affected in either arm) (safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Subgroup analysis was done for SOC/PTs with significant overall treatment effect (significant log-rank test).

Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

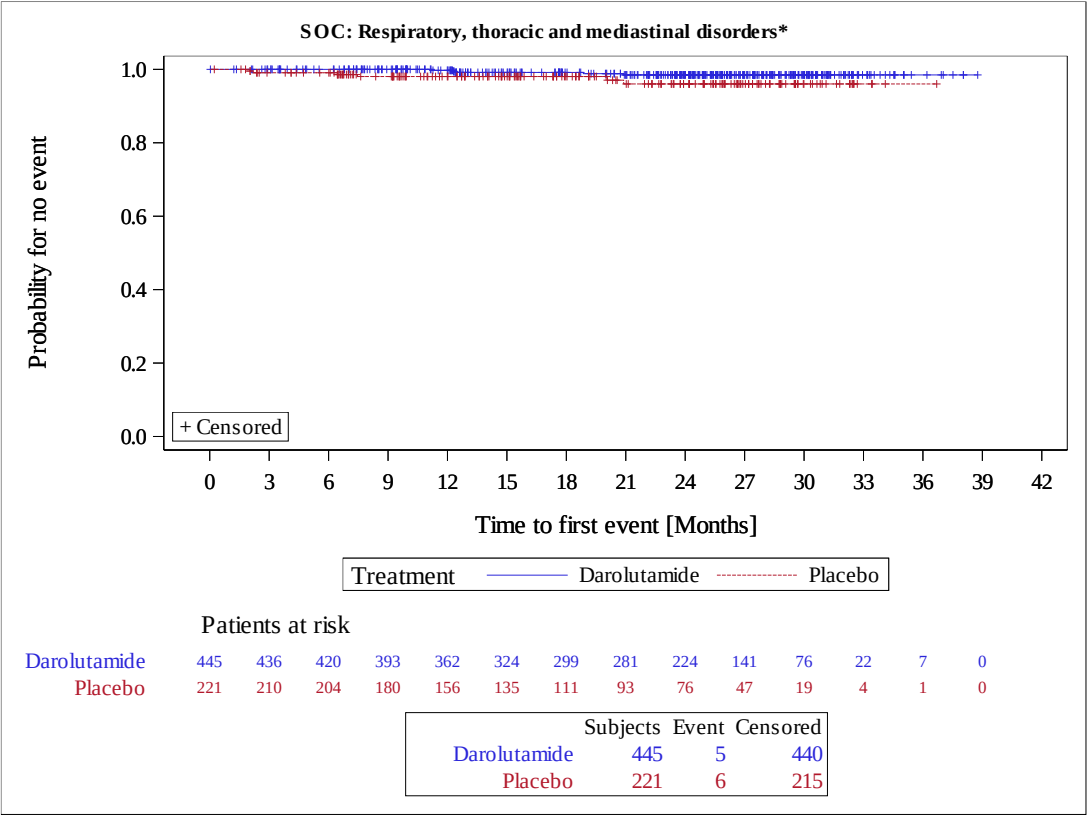
BAY 1841788 / 21140 - 07JUN2024

Study population

Figure 3.3.3.2

Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) (safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

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Subgroup analysis was done for SOC/ PTs with significant overall treatment effect (significant log-rank test).

Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).

Bayer CONFIDENTIAL database cut-off date: 07JUN2024 date of table generation: 13FEB2025

Anhang 4-G2: Analysen zum Datenschnitt 10. Januar 2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 1.1
Observation time per endpoint in months
(full analysis set)

Final

		Darolutamide (N=446)	Placebo (N=223)	Total (N=669)
Time to Death [1]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	27.95 (10.43)	26.55 (10.80)	27.49 (10.57)
	Median	31.41	30.45	31.34
	Q1, Q3	20.76, 35.91	18.92, 34.76	19.71, 35.41
	Min, Max	0.03, 45.89	0.23, 43.82	0.03, 45.89
Time to Death - crossover correction by IPE method [2]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	27.95 (10.43)	26.32 (10.63)	27.41 (10.52)
	Median	31.41	30.16	30.95
	Q1, Q3	20.76, 35.91	18.92, 34.13	19.71, 35.41
	Min, Max	0.03, 45.89	0.23, 42.97	0.03, 45.89
Time to Death - crossover correction by RPSFT method [3]	n (missing)	446 (0)	223 (0)	669 (0)
	Mean (SD)	27.95 (10.43)	22.84 (8.12)	26.25 (10.01)
	Median	31.41	25.26	28.94
	Q1, Q3	20.76, 35.91	18.92, 28.94	19.71, 33.48
	Min, Max	0.03, 45.89	0.23, 34.86	0.03, 45.89

N=Number of participants; n=Number of participants with non-missing values; SD=Standard Deviation; Q1=25%-Quartile; Q3=75%-Quartile; Min=Minimum; Max=Maximum
Observation times for time-to-event endpoints: (Event/Censor date minus randomization date)/30.44
[1] Participants without death are censored at min(last known alive date or cutoff date).
[2] Time to event or censoring is adjusted by iterative parameter estimation (IPE) method.
[3] Time to event or censoring is adjusted by rank preserving structural failure time (RPSFT) method. As a result, the status of 11 subjects in the placebo arm changed from an event to censoring.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 2.1.1

Overall survival

(full analysis set)

Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	115 (25.8)	70 (31.4)
Number of censored participants, n (%)	331 (74.2)	153 (68.6)
Kaplan-Meier estimates of Time to Event (Month) [1]		
25%-ile (95%-CI)	29.2 (24.6, 38.8)	24.3 (19.7, 32.2)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.776 (0.577, 1.045)	
p-value [4]	0.0945	

N=Number of participants; CI=Confidence Interval; NE=Not estimable
Participants without death are censored at last known alive date or cutoff date, whichever comes earlier or at randomization day if there is no contact after randomization.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025										Final
Study population										
Table 2.1.1.1.1										
Overall survival - Subgroup analysis										
(full analysis set)										
Subgroup Level	Darolutamide(N=446)				Placebo(N=223)				Unstratified Analysis	
	n/N[s] (%)	Median	(95% CI)	[1]	n/N[s] (%)	Median	(95% CI)	[1]	Hazard Ratio (95% CI) [2]	p-Value [3] Interaction p-Value[4]
Presence of visceral metastases assessed by central review (from IWRS)										0.9529
Yes	16/ 53 (30.2)	NE (38.8,	NE		10/ 27 (37.0)	NE (21.6,	NE		0.781 (0.354, 1.723)	0.5398
No	99/ 393 (25.2)	NE (NE,	NE		60/ 196 (30.6)	NE (NE,	NE		0.777 (0.564, 1.071)	0.1229
Received prior local therapy (from IWRS)										0.8838
Yes	20/ 80 (25.0)	NE (NE,	NE		11/ 40 (27.5)	NE (NE,	NE		0.812 (0.389, 1.695)	0.5782
No	95/ 366 (26.0)	NE (NE,	NE		59/ 183 (32.2)	NE (38.5,	NE		0.773 (0.559, 1.070)	0.1192
Prior local radiotherapy and/or prostatectomy										0.9710
Yes	20/ 87 (23.0)	NE (NE,	NE		14/ 50 (28.0)	NE (NE,	NE		0.772 (0.389, 1.530)	0.4563
No	95/ 359 (26.5)	NE (NE,	NE		56/ 173 (32.4)	NE (38.5,	NE		0.774 (0.556, 1.077)	0.1278
Age group										0.7010
<65 years	29/ 118 (24.6)	NE (NE,	NE		23/ 65 (35.4)	NE (32.8,	NE		0.638 (0.369, 1.104)	0.1055
65-74	51/ 193 (26.4)	NE (NE,	NE		27/ 96 (28.1)	NE (38.5,	NE		0.951 (0.597, 1.517)	0.8347
75-84	27/ 117 (23.1)	NE (NE,	NE		16/ 52 (30.8)	NE (NE,	NE		0.681 (0.367, 1.265)	0.2209
>=85 years	8/ 18 (44.4)	30.9 (19.0,	NE		4/ 10 (40.0)	NE (17.0,	NE		0.890 (0.267, 2.969)	0.8496
Race										0.9838
White	75/ 251 (29.9)	NE (NE,	NE		43/ 125 (34.4)	NE (NE,	NE		0.807 (0.555, 1.175)	0.2628
Asian	27/ 144 (18.8)	NE (NE,	NE		17/ 65 (26.2)	38.5 (32.7,	NE		0.694 (0.378, 1.273)	0.2348
Black or African American	11/ 41 (26.8)	NE (NE,	NE		8/ 24 (33.3)	NE (25.8,	NE		0.767 (0.308, 1.907)	0.5668
Other	2/ 10 (20.0)	NE (NE,	NE		2/ 9 (22.2)	NE (NE,	NE		0.859 (0.121, 6.103)	0.8791
Geographical region										0.6180
Asia	26/ 141 (18.4)	NE (NE,	NE		17/ 63 (27.0)	38.5 (32.7,	NE		0.652 (0.354, 1.202)	0.1674
Latin America	38/ 119 (31.9)	NE (37.5,	NE		23/ 72 (31.9)	NE (NE,	NE		0.960 (0.572, 1.611)	0.8766
Europe and Rest of the world	51/ 186 (27.4)	NE (NE,	NE		30/ 88 (34.1)	NE (NE,	NE		0.757 (0.482, 1.189)	0.2253
Baseline PSA values by median										0.8732
< median of overall population	50/ 216 (23.1)	NE (NE,	NE		31/ 111 (27.9)	NE (38.5,	NE		0.802 (0.512, 1.255)	0.3331
>= median of overall population	64/ 220 (29.1)	NE (NE,	NE		38/ 108 (35.2)	NE (32.8,	NE		0.770 (0.515, 1.150)	0.2005
ECOG PS at baseline										0.6137
=0	54/ 235 (23.0)	NE (NE,	NE		24/ 98 (24.5)	NE (NE,	NE		0.889 (0.550, 1.439)	0.6329
>=1	61/ 211 (28.9)	NE (NE,	NE		46/ 125 (36.8)	38.5 (32.8,	NE		0.762 (0.520, 1.117)	0.1623
Gleason score at initial diagnosis										0.6728
Gleason <8	29/ 122 (23.8)	NE (NE,	NE		21/ 67 (31.3)	NE (NE,	NE		0.708 (0.404, 1.242)	0.2263
Gleason >=8	82/ 311 (26.4)	NE (NE,	NE		46/ 146 (31.5)	NE (38.5,	NE		0.814 (0.568, 1.169)	0.2641
Disease volume at baseline										0.6828
high	98/ 315 (31.1)	NE (NE,	NE		61/ 157 (38.9)	NE (33.5,	NE		0.756 (0.549, 1.041)	0.0856
low	17/ 131 (13.0)	NE (NE,	NE		9/ 66 (13.6)	NE (NE,	NE		0.911 (0.406, 2.045)	0.8221
Renal function - eGFR at baseline										0.5169
Normal: eGFR >= 90 mL/min	53/ 219 (24.2)	NE (NE,	NE		26/ 104 (25.0)	NE (38.5,	NE		0.966 (0.604, 1.545)	0.8874
Mild impairment: 60 <= eGFR < 90 mL/min	47/ 180 (26.1)	NE (NE,	NE		32/ 91 (35.2)	NE (NE,	NE		0.666 (0.425, 1.045)	0.0752
Moderate impairment: 30 <= eGFR < 60 mL/min	14/ 46 (30.4)	NE (NE,	NE		11/ 27 (40.7)	NE (19.7,	NE		0.767 (0.348, 1.691)	0.5097

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable
AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;
IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal
Participants without death are censored at last known alive date or cutoff date, whichever comes earlier or at randomization day if there is no contact after randomization.
[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided P-value from the log-rank test.
[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 2.1.1.1.1

Overall survival - Subgroup analysis

(full analysis set)

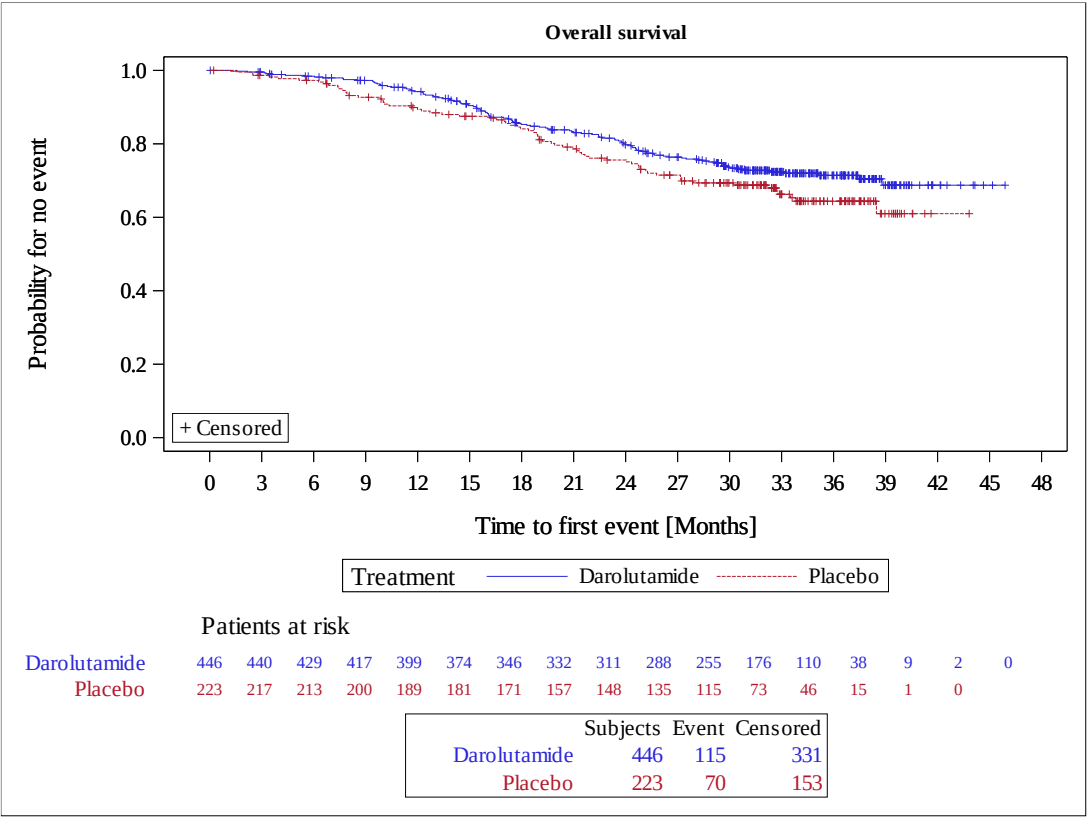
Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis		
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3]	Interaction p-Value[4]
Hepatic function at baseline									0.8895
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	101/ 386 (26.2)	NE (	NE, NE)	65/ 203 (32.0)	NE (	NE, NE)	0.779 (0.571, 1.064)	0.1160	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	14/ 60 (23.3)	NE (	NE, NE)	5/ 20 (25.0)	NE (	NE, NE)	0.839 (0.302, 2.329)	0.7353	
Age Group (Titan)									0.5228
<65	29/ 118 (24.6)	NE (	NE, NE)	23/ 65 (35.4)	NE (	32.8, NE)	0.638 (0.369, 1.104)	0.1055	
>=65 and <75	51/ 193 (26.4)	NE (	NE, NE)	27/ 96 (28.1)	NE (	38.5, NE)	0.951 (0.597, 1.517)	0.8347	
>=75	35/ 135 (25.9)	NE (	NE, NE)	20/ 62 (32.3)	NE (	NE, NE)	0.716 (0.413, 1.241)	0.2318	
Geographic region (Titan)									0.8493
Europe and north america	44/ 145 (30.3)	NE (	NE, NE)	29/ 77 (37.7)	NE (	33.8, NE)	0.782 (0.489, 1.250)	0.3020	
ROTW	71/ 301 (23.6)	NE (	NE, NE)	41/ 146 (28.1)	NE (	38.5, NE)	0.805 (0.548, 1.182)	0.2676	

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable
AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;
IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal
Participants without death are censored at last known alive date or cutoff date, whichever comes earlier or at randomization day if there is no contact after randomization.
[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.
[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 2.1.1.2
Kaplan-Meier Plot of Overall survival
(full analysis set)

Final



Participants without death are censored at last known alive date or cutoff date, whichever comes earlier or at randomization day if there is no contact after randomization.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 2.1.2

Overall survival - crossover correction by Iterative Parametric Estimation (IPE) method

(full analysis set)

Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	115 (25.8)	70 (31.4)
Number of censored participants, n (%)	331 (74.2)	153 (68.6)
Kaplan-Meier estimates of Time to Event (Month) [1]		
25%-ile (95%-CI)	29.2 (24.6, 38.8)	24.3 (19.7, 32.1)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.769 (0.571, 1.036)	
p-value [4]	0.0829	

N=Number of participants; CI=Confidence Interval; NE=Not estimable
Time to event or censoring is adjusted by iterative parameter estimation (IPE) method.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 2.1.2.1

Overall survival - crossover correction by Iterative Parametric Estimation (IPE) method - Subgroup analysis

(full analysis set)

Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis	
	n/N[s]	(%)	Median (95% CI) [1]	n/N[s]	(%)	Median (95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3] Interaction p-Value[4]
Presence of visceral metastases assessed by central review (from IWRS)								
Yes	16/	53 (30.2)	NE (38.8, NE)	10/	27 (37.0)	NE (21.6, NE)	0.764 (0.346, 1.689)	0.5050
No	99/	393 (25.2)	NE (NE, NE)	60/	196 (30.6)	NE (38.5, NE)	0.772 (0.560, 1.064)	0.1123
Received prior local therapy (from IWRS)								
Yes	20/	80 (25.0)	NE (NE, NE)	11/	40 (27.5)	NE (NE, NE)	0.810 (0.388, 1.691)	0.5734
No	95/	366 (26.0)	NE (NE, NE)	59/	183 (32.2)	NE (38.5, NE)	0.767 (0.554, 1.061)	0.1078
Prior local radiotherapy and/or prostatectomy								
Yes	20/	87 (23.0)	NE (NE, NE)	14/	50 (28.0)	NE (NE, NE)	0.752 (0.378, 1.496)	0.4156
No	95/	359 (26.5)	NE (NE, NE)	56/	173 (32.4)	NE (38.5, NE)	0.770 (0.553, 1.071)	0.1196
Age group								
<65 years	29/	118 (24.6)	NE (NE, NE)	23/	65 (35.4)	NE (32.8, NE)	0.635 (0.367, 1.098)	0.1014
65-74	51/	193 (26.4)	NE (NE, NE)	27/	96 (28.1)	NE (38.5, NE)	0.946 (0.593, 1.508)	0.8155
75-84	27/	117 (23.1)	NE (NE, NE)	16/	52 (30.8)	NE (NE, NE)	0.680 (0.366, 1.263)	0.2191
>=85 years	8/	18 (44.4)	30.9 (19.0, NE)	4/	10 (40.0)	NE (17.0, NE)	0.863 (0.258, 2.883)	0.8102
Race								
White	75/	251 (29.9)	NE (NE, NE)	43/	125 (34.4)	NE (NE, NE)	0.802 (0.551, 1.168)	0.2487
Asian	27/	144 (18.8)	NE (NE, NE)	17/	65 (26.2)	38.5 (32.7, NE)	0.685 (0.373, 1.258)	0.2198
Black or African American	11/	41 (26.8)	NE (NE, NE)	8/	24 (33.3)	NE (25.5, NE)	0.767 (0.308, 1.907)	0.5668
Other	2/	10 (20.0)	NE (NE, NE)	2/	9 (22.2)	NE (NE, NE)	0.859 (0.121, 6.103)	0.8791
Geographical region								
Asia	26/	141 (18.4)	NE (NE, NE)	17/	63 (27.0)	38.5 (32.7, NE)	0.643 (0.349, 1.187)	0.1547
Latin America	38/	119 (31.9)	NE (37.5, NE)	23/	72 (31.9)	NE (NE, NE)	0.952 (0.567, 1.598)	0.8528
Europe and Rest of the world	51/	186 (27.4)	NE (NE, NE)	30/	88 (34.1)	NE (NE, NE)	0.754 (0.480, 1.185)	0.2194
Baseline PSA values by median								
< median of overall population	50/	216 (23.1)	NE (NE, NE)	31/	111 (27.9)	NE (38.5, NE)	0.794 (0.507, 1.242)	0.3109
>= median of overall population	64/	220 (29.1)	NE (NE, NE)	38/	108 (35.2)	NE (32.8, NE)	0.767 (0.514, 1.147)	0.1951
ECOG PS at baseline								
=0	54/	235 (23.0)	NE (NE, NE)	24/	98 (24.5)	NE (NE, NE)	0.881 (0.545, 1.426)	0.6060
>=1	61/	211 (28.9)	NE (NE, NE)	46/	125 (36.8)	38.5 (32.8, NE)	0.758 (0.517, 1.112)	0.1550
Gleason score at initial diagnosis								
Gleason <8	29/	122 (23.8)	NE (NE, NE)	21/	67 (31.3)	NE (NE, NE)	0.706 (0.402, 1.237)	0.2212
Gleason >=8	82/	311 (26.4)	NE (NE, NE)	46/	146 (31.5)	NE (38.5, NE)	0.808 (0.563, 1.160)	0.2469
Disease volume at baseline								
high	98/	315 (31.1)	NE (NE, NE)	61/	157 (38.9)	NE (33.5, NE)	0.751 (0.546, 1.035)	0.0788
low	17/	131 (13.0)	NE (NE, NE)	9/	66 (13.6)	NE (NE, NE)	0.902 (0.402, 2.024)	0.8023
Renal function - eGFR at baseline								
Normal: eGFR >= 90 mL/min	53/	219 (24.2)	NE (NE, NE)	26/	104 (25.0)	NE (38.5, NE)	0.960 (0.600, 1.535)	0.8649
Mild impairment: 60 <= eGFR < 90 mL/min	47/	180 (26.1)	NE (NE, NE)	32/	91 (35.2)	NE (NE, NE)	0.662 (0.422, 1.039)	0.0708
Moderate impairment: 30 <= eGFR < 60 mL/min	14/	46 (30.4)	NE (NE, NE)	11/	27 (40.7)	NE (19.7, NE)	0.767 (0.348, 1.691)	0.5097

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable

AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;

IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Time to event or censoring is adjusted by iterative parameter estimation (IPE) method.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Study population
Table 2.1.2.1
Overall survival - crossover correction by Iterative Parametric Estimation (IPE) method - Subgroup analysis
(full analysis set)

Final

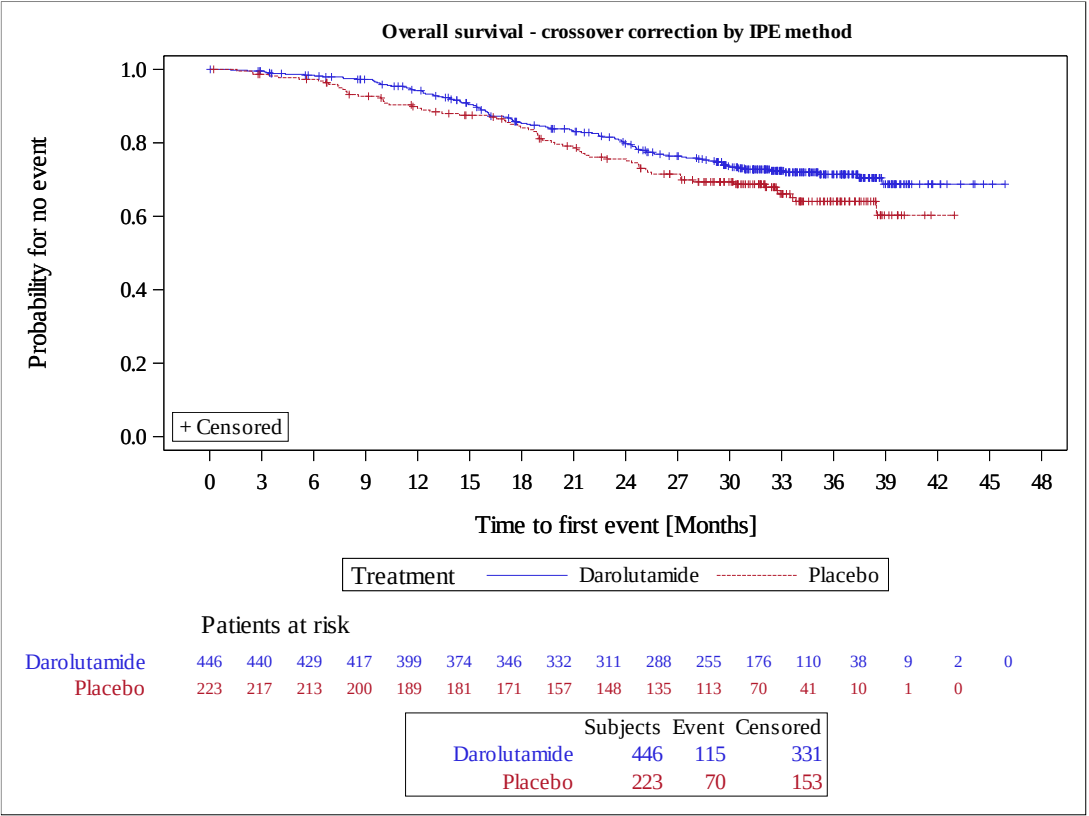
Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis	
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3] Interaction p-Value[4]
Hepatic function at baseline								0.8931
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	101/ 386 (26.2)	NE (	NE, NE)	65/ 203 (32.0)	NE (38.5,	NE)	0.773 (0.566, 1.056)	0.1048
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	14/ 60 (23.3)	NE (	NE, NE)	5/ 20 (25.0)	NE (	NE, NE)	0.835 (0.301, 2.318)	0.7282
Age Group (Titan)								0.5223
<65	29/ 118 (24.6)	NE (	NE, NE)	23/ 65 (35.4)	NE (32.8,	NE)	0.635 (0.367, 1.098)	0.1014
>=65 and <75	51/ 193 (26.4)	NE (	NE, NE)	27/ 96 (28.1)	NE (38.5,	NE)	0.946 (0.593, 1.508)	0.8155
>=75	35/ 135 (25.9)	NE (	NE, NE)	20/ 62 (32.3)	NE (	NE, NE)	0.714 (0.412, 1.238)	0.2286
Geographic region (Titan)								0.8602
Europe and north america	44/ 145 (30.3)	NE (	NE, NE)	29/ 77 (37.7)	NE (33.8,	NE)	0.779 (0.487, 1.246)	0.2958
ROTW	71/ 301 (23.6)	NE (	NE, NE)	41/ 146 (28.1)	NE (38.5,	NE)	0.794 (0.540, 1.166)	0.2375

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable
AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;
IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal
Time to event or censoring is adjusted by iterative parameter estimation (IPE) method.
[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.
[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Study population
Figure 2.1.2.2
Kaplan-Meier Plot of Overall survival - crossover correction by Iterative Parametric Estimation (IPE) method
(full analysis set)

Final



Time to event or censoring is adjusted by iterative parameter estimation (IPE) method.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Table 2.1.3

Overall survival - crossover correction by Rank-Preserving Structural Failure Time (RPSFT) method (full analysis set)

Final

	Darolutamide (N=446)	Placebo (N=223)
Number of participants with events, n (%)	115 (25.8)	59 (26.5)
Number of censored participants, n (%)	331 (74.2)	164 (73.5)
Kaplan-Meier estimates of Time to Event (Month) [1]		
25%-ile (95%-CI)	29.2 (24.6, 38.8)	24.7 (19.7, 33.8)
Median (95%-CI)	NE (NE, NE)	33.8 (32.8, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (33.8, NE)
Stratified Analysis [2]		
Hazard Ratio (95% CI) [3]	0.802 (0.583, 1.104)	
p-value [4]	0.1758	

N=Number of participants; CI=Confidence Interval; NE=Not estimable
Time to event or censoring is adjusted by rank preserving structural failure time (RPSFT) method. As a result, the status of 11 subjects in the placebo arm changed from an event to censoring.
[1] Based on the Brookmeyer and Crowley Method. [2] Stratified by visceral metastases (present vs. absent) and prior local therapy (yes vs. no).
[3] Estimated by cox regression model assuming proportional hazards. [4] 2-sided p-value from the log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population

Table 2.1.3.1

Overall survival - crossover correction by Rank-Preserving Structural Failure Time (RPSFT) method - Subgroup analysis
(full analysis set)

Final

Subgroup Level	Darolutamide(N=446)					Placebo(N=223)					Unstratified Analysis		p-Value [3]	Interaction p-Value[4]			
	n/N[s]		(%)	Median (95% CI) [1]		n/N[s]		(%)	Median (95% CI) [1]		Hazard Ratio	(95% CI) [2]					
Presence of visceral metastases assessed by central review (from IWRS)																	
Yes	16/	53	(30.2)	NE	(38.8,	NE)	9/	27	(33.3)	NE	(21.6,	NE)	0.797	(0.348,	1.824)	0.5905	0.8984
No	99/	393	(25.2)	NE	(NE,	NE)	50/	196	(25.5)	33.8	(32.8,	NE)	0.806	(0.570,	1.139)	0.2214	
Received prior local therapy (from IWRS)																	
Yes	20/	80	(25.0)	NE	(NE,	NE)	11/	40	(27.5)	NE	(NE,	NE)	0.686	(0.324,	1.452)	0.3222	0.7355
No	95/	366	(26.0)	NE	(NE,	NE)	48/	183	(26.2)	33.8	(32.8,	NE)	0.832	(0.585,	1.184)	0.3075	
Prior local radiotherapy and/or prostatectomy																	
Yes	20/	87	(23.0)	NE	(NE,	NE)	13/	50	(26.0)	NE	(NE,	NE)	0.671	(0.325,	1.385)	0.2775	0.7625
No	95/	359	(26.5)	NE	(NE,	NE)	46/	173	(26.6)	33.8	(32.8,	NE)	0.837	(0.586,	1.195)	0.3261	
Age group																	
<65 years	29/	118	(24.6)	NE	(NE,	NE)	20/	65	(30.8)	32.8	(32.8,	NE)	0.588	(0.326,	1.059)	0.0738	0.4172
65-74	51/	193	(26.4)	NE	(NE,	NE)	20/	96	(20.8)	33.8	(33.8,	NE)	1.147	(0.681,	1.933)	0.6059	
75-84	27/	117	(23.1)	NE	(NE,	NE)	15/	52	(28.8)	NE	(NE,	NE)	0.658	(0.347,	1.247)	0.1967	
>=85 years	8/	18	(44.4)	30.9	(19.0,	NE)	4/	10	(40.0)	NE	(17.0,	NE)	0.775	(0.228,	2.636)	0.6819	
Race																	
White	75/	251	(29.9)	NE	(NE,	NE)	40/	125	(32.0)	33.8	(32.8,	NE)	0.754	(0.510,	1.116)	0.1573	0.9556
Asian	27/	144	(18.8)	NE	(NE,	NE)	11/	65	(16.9)	NE	(NE,	NE)	0.939	(0.462,	1.908)	0.8624	
Black or African American	11/	41	(26.8)	NE	(NE,	NE)	6/	24	(25.0)	NE	(NE,	NE)	0.928	(0.341,	2.520)	0.8826	
Other	2/	10	(20.0)	NE	(NE,	NE)	2/	9	(22.2)	NE	(NE,	NE)	0.859	(0.121,	6.103)	0.8791	
Geographical region																	
Asia	26/	141	(18.4)	NE	(NE,	NE)	11/	63	(17.5)	NE	(NE,	NE)	0.875	(0.429,	1.788)	0.7148	0.4668
Latin America	38/	119	(31.9)	NE	(37.5,	NE)	18/	72	(25.0)	NE	(NE,	NE)	1.023	(0.579,	1.808)	0.9365	
Europe and Rest of the world	51/	186	(27.4)	NE	(NE,	NE)	30/	88	(34.1)	33.8	(32.8,	NE)	0.675	(0.426,	1.070)	0.0928	
Baseline PSA values by median																	
< median of overall population	50/	216	(23.1)	NE	(NE,	NE)	25/	111	(22.5)	NE	(NE,	NE)	0.851	(0.522,	1.387)	0.5165	0.6639
>= median of overall population	64/	220	(29.1)	NE	(NE,	NE)	34/	108	(31.5)	32.8	(32.8,	NE)	0.765	(0.502,	1.167)	0.2126	
ECOG PS at baseline																	
=0	54/	235	(23.0)	NE	(NE,	NE)	20/	98	(20.4)	NE	(NE,	NE)	0.900	(0.534,	1.516)	0.6913	0.6320
>=1	61/	211	(28.9)	NE	(NE,	NE)	39/	125	(31.2)	32.8	(32.8,	NE)	0.803	(0.534,	1.207)	0.2900	
Gleason score at initial diagnosis																	
Gleason <8	29/	122	(23.8)	NE	(NE,	NE)	19/	67	(28.4)	33.8	(33.8,	NE)	0.685	(0.381,	1.231)	0.2029	0.4584
Gleason >=8	82/	311	(26.4)	NE	(NE,	NE)	37/	146	(25.3)	32.8	(32.8,	NE)	0.889	(0.599,	1.318)	0.5580	
Disease volume at baseline																	
high	98/	315	(31.1)	NE	(NE,	NE)	51/	157	(32.5)	33.8	(33.8,	NE)	0.788	(0.559,	1.111)	0.1727	0.8301
low	17/	131	(13.0)	NE	(NE,	NE)	8/	66	(12.1)	NE	(32.8,	NE)	0.849	(0.358,	2.010)	0.7089	
Renal function - eGFR at baseline																	
Normal: eGFR >= 90 mL/min	53/	219	(24.2)	NE	(NE,	NE)	18/	104	(17.3)	NE	(32.8,	NE)	1.179	(0.687,	2.024)	0.5497	0.1811
Mild impairment: 60 <= eGFR < 90 mL/min	47/	180	(26.1)	NE	(NE,	NE)	29/	91	(31.9)	NE	(NE,	NE)	0.650	(0.405,	1.044)	0.0724	
Moderate impairment: 30 <= eGFR < 60 mL/min	14/	46	(30.4)	NE	(NE,	NE)	11/	27	(40.7)	33.8	(19.7,	33.8)	0.693	(0.311,	1.544)	0.3675	

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable

AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;

IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal

Time to event or censoring is adjusted by rank preserving structural failure time (RPSFT) method. As a result, the status of 11 subjects in the placebo arm changed from an event to censoring.

[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.

[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Study population

Table 2.1.3.1

Overall survival - crossover correction by Rank-Preserving Structural Failure Time (RPSFT) method - Subgroup analysis (full analysis set)

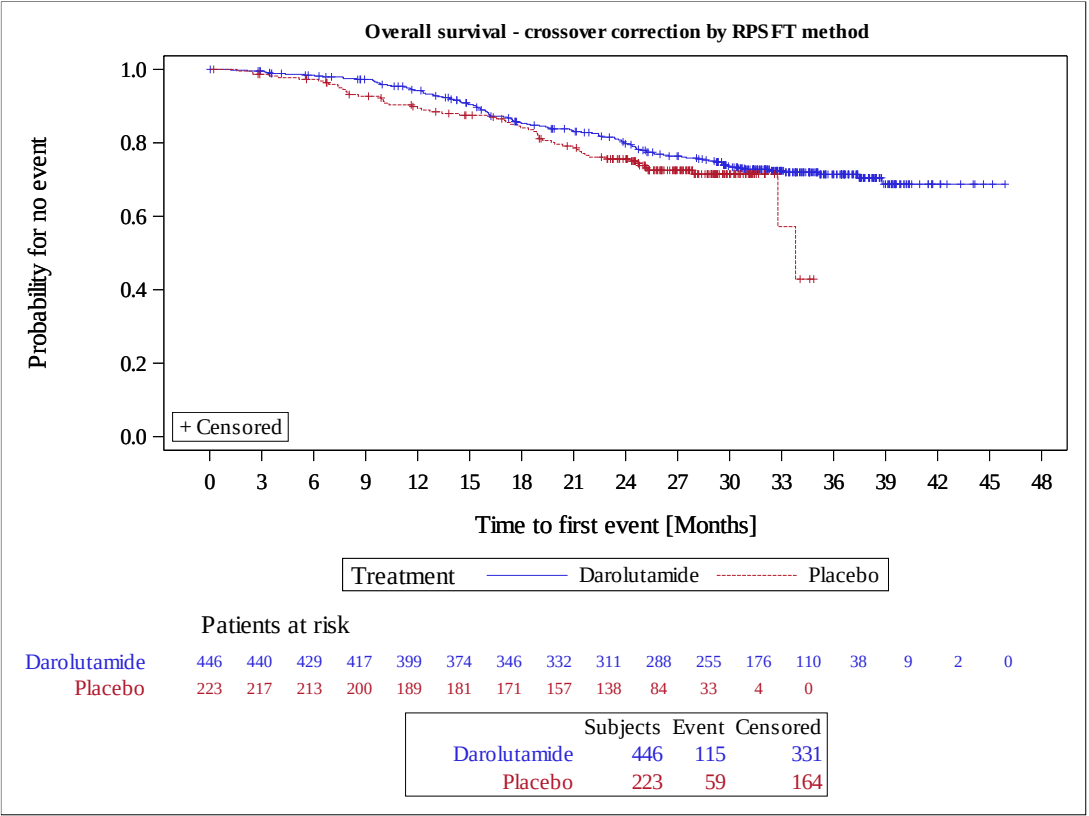
Final

Subgroup Level	Darolutamide(N=446)			Placebo(N=223)			Unstratified Analysis	
	n/N[s] (%)	Median	(95% CI) [1]	n/N[s] (%)	Median	(95% CI) [1]	Hazard Ratio (95% CI) [2]	p-Value [3] Interaction p-Value[4]
Hepatic function at baseline								0.8046
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	101/ 386 (26.2)	NE (	NE, NE)	54/ 203 (26.6)	33.8 (32.8,	NE)	0.811 (0.579, 1.135)	0.2213
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	14/ 60 (23.3)	NE (	NE, NE)	5/ 20 (25.0)	NE (	NE, NE)	0.773 (0.277, 2.158)	0.6225
Age Group (Titan)								0.2522
<65	29/ 118 (24.6)	NE (	NE, NE)	20/ 65 (30.8)	32.8 (32.8,	NE)	0.588 (0.326, 1.059)	0.0738
>=65 and <75	51/ 193 (26.4)	NE (	NE, NE)	20/ 96 (20.8)	33.8 (33.8,	NE)	1.147 (0.681, 1.933)	0.6059
>=75	35/ 135 (25.9)	NE (	NE, NE)	19/ 62 (30.6)	NE (	NE, NE)	0.674 (0.383, 1.189)	0.1707
Geographic region (Titan)								0.3272
Europe and north america	44/ 145 (30.3)	NE (	NE, NE)	29/ 77 (37.7)	33.8 (32.8,	NE)	0.716 (0.444, 1.154)	0.1679
ROTW	71/ 301 (23.6)	NE (	NE, NE)	30/ 146 (20.5)	NE (	NE, NE)	0.910 (0.590, 1.404)	0.6701

N=Number of participants; N[s]=Number of participants in subgroup; CI=Confidence Interval; NE=Not estimable
AST=Aspartate aminotransferase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eGFR=Estimated glomerular filtration rate;
IWRS=Interactive Web Response System; PSA=Prostate-specific antigen; ULN=Upper limit of normal
Time to event or censoring is adjusted by rank preserving structural failure time (RPSFT) method. As a result, the status of 11 subjects in the placebo arm changed from an event to censoring.
[1] Based on the Brookmeyer and Crowley Method. [2] Estimated by cox regression model assuming proportional hazards. [3] 2-sided p-value from the log-rank test.
[4] P-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Study population
Figure 2.1.3.2
Kaplan-Meier Plot of Overall survival - crossover correction by Rank-Preserving Structural Failure Time (RPSFT) method
(full analysis set)

Final



Time to event or censoring is adjusted by rank preserving structural failure time (RPSFT) method. As a result, the status of 11 subjects in the placebo arm changed from an event to censoring.
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Study population
Table 3.1.1
Treatment duration and observation time for Safety in months
(safety analysis set)

Final

		Darolutamide (N=446)	Placebo (N=220)	Total (N=666)
Treatment Duration[1]	n (missing)	446 (0)	220 (0)	666 (0)
	Mean (SD)	25.04 (12.05)	19.52 (11.52)	23.22 (12.15)
	Median	30.01	17.21	25.41
	Q1, Q3	13.40, 35.02	9.77, 30.26	11.73, 33.77
	Min, Max	0.03, 45.93	0.23, 43.10	0.03, 45.93
Safety Observation Time[2]	n (missing)	446 (0)	220 (0)	666 (0)
	Mean (SD)	25.37 (11.74)	20.15 (11.32)	23.65 (11.85)
	Median	30.08	18.00	26.36
	Q1, Q3	13.99, 34.99	10.27, 30.88	12.65, 33.90
	Min, Max	0.03, 45.89	0.23, 43.82	0.03, 45.89

After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N=Number of participants; n=Number of participants with non-missing values; SD=Standard Deviation; Q1=25%-Quartile; Q3=75%-Quartile; Min=Minimum; Max=Maximum
[1] (day of last dose of study drug minus day of first dose of study drug + 1) / 30.44. Time off drug and dose interruptions are included.
[2] (min(day of last dose of study drug + 30, death date, last known alive date, cutoff date) minus day of first dose of study drug) / 30.44
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Table 3.1.2

Incidence of Adverse Events leading to discontinuation of study treatment (by SOC and PT)
(safety analysis set)

Final

System Organ Class (SOC) Preferred Term (PT)	Darolutamide (N=446)	Placebo (N=220)
	n (%)	n (%)
Cardiac disorders	2 (0.4)	4 (1.8)
Myocardial infarction	2 (0.4)	1 (0.5)
Acute myocardial infarction	0 (0.0)	1 (0.5)
Cardiac arrest	0 (0.0)	1 (0.5)
Cardiac failure congestive	0 (0.0)	1 (0.5)
Investigations	4 (0.9)	2 (0.9)
Alanine aminotransferase increased	2 (0.4)	1 (0.5)
Aspartate aminotransferase increased	2 (0.4)	1 (0.5)
Blood bilirubin increased	1 (0.2)	0 (0.0)
Blood creatinine increased	1 (0.2)	0 (0.0)
Blood sodium decreased	1 (0.2)	0 (0.0)
Eastern Cooperative Oncology Group performance status worsened	0 (0.0)	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (0.9)	2 (0.9)
Bladder cancer recurrent	0 (0.0)	1 (0.5)
Diffuse large B-cell lymphoma	1 (0.2)	0 (0.0)
Lung carcinoma cell type unspecified stage IV	0 (0.0)	1 (0.5)
Malignant melanoma	1 (0.2)	0 (0.0)
Rectal cancer	1 (0.2)	0 (0.0)
Squamous cell carcinoma of lung	1 (0.2)	0 (0.0)
Infections and infestations	3 (0.7)	2 (0.9)
Herpes zoster meningitis	0 (0.0)	1 (0.5)
Liver abscess	0 (0.0)	1 (0.5)
Pneumonia	1 (0.2)	0 (0.0)
Pulmonary sepsis	1 (0.2)	0 (0.0)
Septic shock	1 (0.2)	0 (0.0)
Musculoskeletal and connective tissue disorders	2 (0.4)	3 (1.4)
Back pain	0 (0.0)	2 (0.9)
Bone pain	1 (0.2)	1 (0.5)
Pain in extremity	0 (0.0)	2 (0.9)
Neck pain	1 (0.2)	0 (0.0)
Injury, poisoning and procedural complications	3 (0.7)	1 (0.5)
Craniocerebral injury	2 (0.4)	0 (0.0)
Fall	0 (0.0)	1 (0.5)
Femur fracture	1 (0.2)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	3 (1.4)
Gastrointestinal haemorrhage	0 (0.0)	2 (0.9)
Intestinal ischaemia	0 (0.0)	1 (0.5)
Renal and urinary disorders	1 (0.2)	2 (0.9)
Tubulointerstitial nephritis	0 (0.0)	1 (0.5)
Urinary retention	1 (0.2)	0 (0.0)
Urinary tract obstruction	0 (0.0)	1 (0.5)
Skin and subcutaneous tissue disorders	2 (0.4)	1 (0.5)
Rash	1 (0.2)	0 (0.0)
Rash papular	1 (0.2)	0 (0.0)
Skin ulcer	0 (0.0)	1 (0.5)
General disorders and administration site conditions	0 (0.0)	2 (0.9)
Death	0 (0.0)	1 (0.5)
Gait disturbance	0 (0.0)	1 (0.5)
Performance status decreased	0 (0.0)	1 (0.5)

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, n: Number of participants with event

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Table 3.1.2

Incidence of Adverse Events leading to discontinuation of study treatment (by SOC and PT)
(safety analysis set)

System Organ Class (SOC) Preferred Term (PT)	Darolutamide (N=446)		Placebo (N=220)	
	n	(%)	n	(%)
Hepatobiliary disorders	2	(0.4)	0	(0.0)
Hyperbilirubinaemia	1	(0.2)	0	(0.0)
Liver injury	1	(0.2)	0	(0.0)
Nervous system disorders	1	(0.2)	1	(0.5)
Cerebral infarction	0	(0.0)	1	(0.5)
Paraparesis	1	(0.2)	0	(0.0)
Spinal cord compression	1	(0.2)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	1	(0.2)	1	(0.5)
Dyspnoea	1	(0.2)	0	(0.0)
Pulmonary embolism	0	(0.0)	1	(0.5)
Vascular disorders	2	(0.4)	0	(0.0)
Hypertension	1	(0.2)	0	(0.0)
Pelvic venous thrombosis	1	(0.2)	0	(0.0)
Superficial vein thrombosis	1	(0.2)	0	(0.0)
Thrombosis	1	(0.2)	0	(0.0)
Endocrine disorders	1	(0.2)	0	(0.0)
Pituitary-dependent Cushing's syndrome	1	(0.2)	0	(0.0)
Metabolism and nutrition disorders	0	(0.0)	1	(0.5)
Decreased appetite	0	(0.0)	1	(0.5)

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, n: Number of participants with event
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Study population
Table 3.2.1
Summary of Adverse Events
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	407 (91.3)	199 (90.5)
Number of censored patients, n (%)	39 (8.7)	21 (9.5)
Time to Event (Month)		
25%-ile (95% CI)	1.6 (1.3, 2.3)	1.6 (1.2, 2.4)
Median (95% CI)	3.7 (2.9, 4.9)	3.3 (2.8, 5.2)
75%-ile (95% CI)	8.3 (7.7, 10.5)	8.4 (7.0, 10.8)
Unstratified Analysis		
Hazard Ratio	0.987	
95% CI	0.833, 1.170	
p-value	0.8806	
Odds Ratio	1.101	
95% CI	0.631, 1.922	
p-value	0.7342	
Relative Risk	1.009	
95% CI	0.958, 1.062	
p-value	0.7380	
Risk Difference	0.801	
95% CI	-3.884, 5.486	
p-value	0.7375	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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 Table 3.2.1.1
 Summary of Adverse Events - Subgroup analysis
 (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.5549
Yes	49/ 54 (90.7)	24/ 26 (92.3)	1.145	(0.694, 1.888)	0.5928	
No	358/392 (91.3)	175/194 (90.2)	0.970	(0.809, 1.162)	0.7396	
Received prior local therapy (from IWRS)						0.9930
Yes	76/ 81 (93.8)	36/ 39 (92.3)	0.986	(0.662, 1.468)	0.9453	
No	331/365 (90.7)	163/181 (90.1)	0.989	(0.819, 1.193)	0.9038	
Prior local radiotherapy and/or prostatectomy						0.4956
Yes	79/ 88 (89.8)	44/ 49 (89.8)	1.104	(0.763, 1.598)	0.5975	
No	328/358 (91.6)	155/171 (90.6)	0.957	(0.790, 1.158)	0.6490	
Age group						0.1561
<65 years	106/117 (90.6)	55/ 64 (85.9)	0.960	(0.693, 1.331)	0.8082	
65-74	173/193 (89.6)	87/ 95 (91.6)	0.815	(0.629, 1.057)	0.1198	
75-84	112/118 (94.9)	47/ 51 (92.2)	1.367	(0.970, 1.926)	0.0712	
>=85 years	16/ 18 (88.9)	10/ 10 (100.0)	1.083	(0.470, 2.495)	0.8504	
Race						0.6511
White	220/250 (88.0)	108/123 (87.8)	1.005	(0.799, 1.266)	0.9629	
Asian	136/144 (94.4)	59/ 65 (90.8)	0.932	(0.686, 1.267)	0.6510	
Black or African American	42/ 42 (100.0)	23/ 23 (100.0)	1.208	(0.705, 2.069)	0.4841	
Other	9/ 10 (90.0)	9/ 9 (100.0)	0.599	(0.229, 1.566)	0.2871	
Geographical region						0.6143
Asia	133/141 (94.3)	57/ 63 (90.5)	0.923	(0.676, 1.261)	0.6109	
Latin America	117/120 (97.5)	68/ 70 (97.1)	1.142	(0.845, 1.542)	0.3821	
Europe and Rest of the world	157/185 (84.9)	74/ 87 (85.1)	0.965	(0.731, 1.272)	0.7986	
Baseline PSA values by median						0.3308
< median of overall population	196/216 (90.7)	102/109 (93.6)	0.894	(0.703, 1.136)	0.3555	
>= median of overall population	200/219 (91.3)	94/108 (87.0)	1.069	(0.837, 1.367)	0.5901	
ECOG PS at baseline						0.4583
=0	212/235 (90.2)	87/ 96 (90.6)	0.925	(0.720, 1.187)	0.5360	
>=1	195/211 (92.4)	112/124 (90.3)	1.051	(0.833, 1.326)	0.6729	
Gleason score at initial diagnosis						0.0823
Gleason <8	116/125 (92.8)	56/ 64 (87.5)	1.240	(0.900, 1.708)	0.1847	
Gleason >=8	278/308 (90.3)	135/146 (92.5)	0.888	(0.722, 1.090)	0.2522	
Disease volume at baseline						0.7409
high	293/315 (93.0)	142/155 (91.6)	1.007	(0.824, 1.230)	0.9459	
low	114/131 (87.0)	57/ 65 (87.7)	0.937	(0.681, 1.289)	0.6875	
Renal function - eGFR at baseline						0.9457
Normal: eGFR >= 90 mL/min	209/221 (94.6)	92/102 (90.2)	0.967	(0.757, 1.236)	0.7887	
Mild impairment: 60 <= eGFR < 90 mL/min	157/179 (87.7)	82/ 90 (91.1)	1.010	(0.773, 1.320)	0.9399	
Moderate impairment: 30 <= eGFR < 60 mL/min	40/ 45 (88.9)	24/ 27 (88.9)	0.925	(0.557, 1.538)	0.7633	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
 After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
 N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
 Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
 Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
 p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
 Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Table 3.2.1.1
Summary of Adverse Events - Subgroup analysis
(safety analysis set)

Final

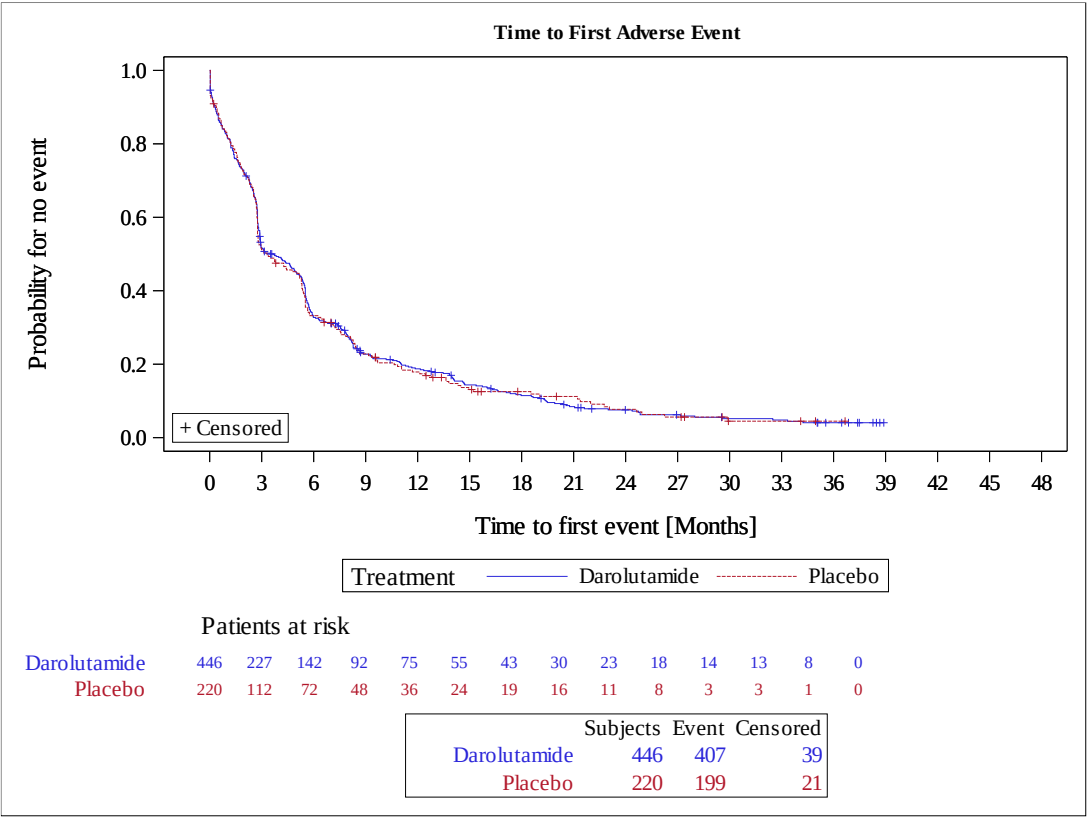
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.1017
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	352/387 (91.0)	182/200 (91.0)	0.937	(0.783, 1.121)	0.4760	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	55/ 59 (93.2)	17/ 20 (85.0)	1.621	(0.912, 2.882)	0.0945	
Age Group (Titan)						0.0928
<65	106/117 (90.6)	55/ 64 (85.9)	0.960	(0.693, 1.331)	0.8082	
>=65 and <75	173/193 (89.6)	87/ 95 (91.6)	0.815	(0.629, 1.057)	0.1198	
>=75	128/136 (94.1)	57/ 61 (93.4)	1.299	(0.949, 1.779)	0.0997	
Geographic region (Titan)						0.3432
Europe and north america	117/145 (80.7)	63/ 76 (82.9)	0.869	(0.640, 1.182)	0.3689	
ROTW	290/301 (96.3)	136/144 (94.4)	1.042	(0.850, 1.277)	0.6889	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Figure 3.2.1.2
Kaplan-Meier Plot of Time to First Adverse Event
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Table 3.2.2
Summary of Adverse Events (disease-related AEs are excluded)
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	406 (91.0)	199 (90.5)
Number of censored patients, n (%)	40 (9.0)	21 (9.5)
Time to Event (Month)		
25%-ile (95% CI)	1.6 (1.3, 2.3)	1.6 (1.2, 2.4)
Median (95% CI)	3.7 (2.9, 4.9)	3.3 (2.8, 5.2)
75%-ile (95% CI)	8.3 (7.7, 10.5)	8.4 (7.0, 10.8)
Unstratified Analysis		
Hazard Ratio	0.985	
95% CI	0.831, 1.167	
p-value	0.8609	
Odds Ratio	1.071	
95% CI	0.615, 1.865	
p-value	0.8082	
Relative Risk	1.006	
95% CI	0.956, 1.060	
p-value	0.8102	
Risk Difference	0.577	
95% CI	-4.125, 5.279	
p-value	0.8100	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.2.2.1

Summary of Adverse Events (disease-related AEs are excluded) - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.5509
Yes	49/ 54 (90.7)	24/ 26 (92.3)	1.145	(0.694, 1.888)	0.5928	
No	357/392 (91.1)	175/194 (90.2)	0.968	(0.807, 1.160)	0.7204	
Received prior local therapy (from IWRS)						0.9948
Yes	76/ 81 (93.8)	36/ 39 (92.3)	0.986	(0.662, 1.468)	0.9453	
No	330/365 (90.4)	163/181 (90.1)	0.986	(0.817, 1.189)	0.8811	
Prior local radiotherapy and/or prostatectomy						0.4886
Yes	79/ 88 (89.8)	44/ 49 (89.8)	1.104	(0.763, 1.598)	0.5975	
No	327/358 (91.3)	155/171 (90.6)	0.954	(0.788, 1.155)	0.6309	
Age group						0.1567
<65 years	106/117 (90.6)	55/ 64 (85.9)	0.960	(0.693, 1.331)	0.8082	
65-74	173/193 (89.6)	87/ 95 (91.6)	0.815	(0.629, 1.057)	0.1198	
75-84	112/118 (94.9)	47/ 51 (92.2)	1.367	(0.970, 1.926)	0.0712	
>=85 years	15/ 18 (83.3)	10/ 10 (100.0)	0.989	(0.425, 2.302)	0.9798	
Race						0.6504
White	220/250 (88.0)	108/123 (87.8)	1.005	(0.799, 1.266)	0.9629	
Asian	135/144 (93.8)	59/ 65 (90.8)	0.930	(0.684, 1.265)	0.6411	
Black or African American	42/ 42 (100.0)	23/ 23 (100.0)	1.208	(0.705, 2.069)	0.4841	
Other	9/ 10 (90.0)	9/ 9 (100.0)	0.599	(0.229, 1.566)	0.2871	
Geographical region						0.6052
Asia	132/141 (93.6)	57/ 63 (90.5)	0.921	(0.674, 1.258)	0.6010	
Latin America	117/120 (97.5)	68/ 70 (97.1)	1.142	(0.845, 1.542)	0.3821	
Europe and Rest of the world	157/185 (84.9)	74/ 87 (85.1)	0.965	(0.731, 1.272)	0.7986	
Baseline PSA values by median						0.3473
< median of overall population	196/216 (90.7)	102/109 (93.6)	0.894	(0.703, 1.136)	0.3555	
>= median of overall population	199/219 (90.9)	94/108 (87.0)	1.064	(0.832, 1.360)	0.6185	
ECOG PS at baseline						0.4776
=0	212/235 (90.2)	87/ 96 (90.6)	0.925	(0.720, 1.187)	0.5360	
>=1	194/211 (91.9)	112/124 (90.3)	1.046	(0.829, 1.320)	0.7029	
Gleason score at initial diagnosis						0.0799
Gleason <8	116/125 (92.8)	56/ 64 (87.5)	1.240	(0.900, 1.708)	0.1847	
Gleason >=8	277/308 (89.9)	135/146 (92.5)	0.885	(0.720, 1.088)	0.2418	
Disease volume at baseline						0.7562
high	292/315 (92.7)	142/155 (91.6)	1.004	(0.821, 1.227)	0.9708	
low	114/131 (87.0)	57/ 65 (87.7)	0.937	(0.681, 1.289)	0.6875	
Renal function - eGFR at baseline						0.9202
Normal: eGFR >= 90 mL/min	209/221 (94.6)	92/102 (90.2)	0.967	(0.757, 1.236)	0.7887	
Mild impairment: 60 <= eGFR < 90 mL/min	157/179 (87.7)	82/ 90 (91.1)	1.010	(0.773, 1.320)	0.9399	
Moderate impairment: 30 <= eGFR < 60 mL/min	39/ 45 (86.7)	24/ 27 (88.9)	0.904	(0.542, 1.506)	0.6950	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Table 3.2.2.1

Summary of Adverse Events (disease-related AEs are excluded) - Subgroup analysis (safety analysis set)

Final

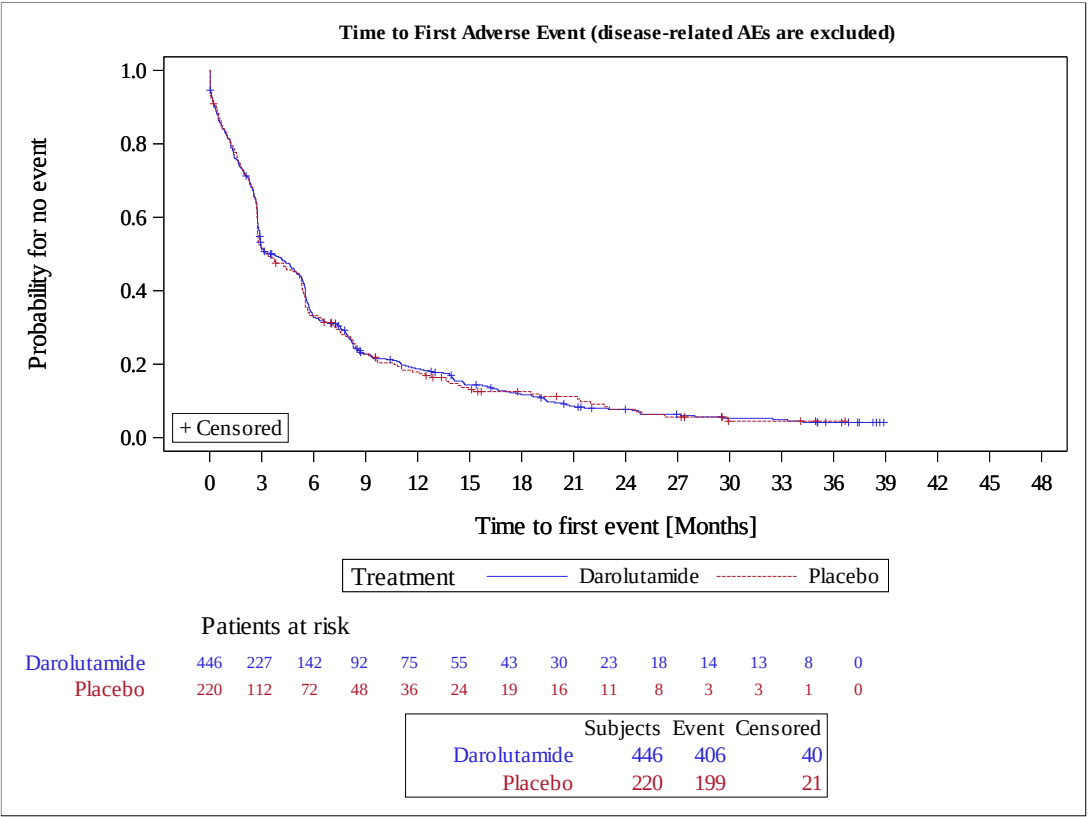
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Hepatic function at baseline						0.1013
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	351/387 (90.7)	182/200 (91.0)	0.935	(0.782, 1.119)	0.4613	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	55/ 59 (93.2)	17/ 20 (85.0)	1.621	(0.912, 2.882)	0.0945	
Age Group (Titan)						0.1025
<65	106/117 (90.6)	55/ 64 (85.9)	0.960	(0.693, 1.331)	0.8082	
>=65 and <75	173/193 (89.6)	87/ 95 (91.6)	0.815	(0.629, 1.057)	0.1198	
>=75	127/136 (93.4)	57/ 61 (93.4)	1.287	(0.939, 1.763)	0.1133	
Geographic region (Titan)						0.3538
Europe and north america	117/145 (80.7)	63/ 76 (82.9)	0.869	(0.640, 1.182)	0.3689	
ROTW	289/301 (96.0)	136/144 (94.4)	1.039	(0.847, 1.274)	0.7106	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.2.2
Kaplan-Meier Plot of Time to First Adverse Event (disease-related AEs are excluded)
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.3
Summary of Serious Adverse Events
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	113 (25.3)	56 (25.5)
Number of censored patients, n (%)	333 (74.7)	164 (74.5)
Time to Event (Month)		
25%-ile (95% CI)	23.2 (15.7, 35.4)	20.1 (12.7, NE)
Median (95% CI)	NE (NE, NE)	NE (38.7, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.861	
95% CI	0.625, 1.188	
p-value	0.3621	
Odds Ratio	0.994	
95% CI	0.686, 1.440	
p-value	0.9737	
Relative Risk	0.995	
95% CI	0.755, 1.313	
p-value	0.9737	
Risk Difference	-0.118	
95% CI	-7.149, 6.912	
p-value	0.9737	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.3.1

Summary of Serious Adverse Events - Subgroup analysis

(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.9808
Yes	18/ 54 (33.3)	9/ 26 (34.6)	0.869	(0.390, 1.937)	0.7307	
No	95/392 (24.2)	47/194 (24.2)	0.861	(0.606, 1.223)	0.4023	
Received prior local therapy (from IWRS)						0.7942
Yes	22/ 81 (27.2)	11/ 39 (28.2)	0.775	(0.373, 1.609)	0.4928	
No	91/365 (24.9)	45/181 (24.9)	0.880	(0.615, 1.258)	0.4830	
Prior local radiotherapy and/or prostatectomy						0.8589
Yes	25/ 88 (28.4)	14/ 49 (28.6)	0.883	(0.458, 1.702)	0.7107	
No	88/358 (24.6)	42/171 (24.6)	0.860	(0.595, 1.244)	0.4232	
Age group						0.6717
<65 years	21/117 (17.9)	11/ 64 (17.2)	0.885	(0.425, 1.841)	0.7430	
65-74	48/193 (24.9)	28/ 95 (29.5)	0.731	(0.458, 1.167)	0.1877	
75-84	36/118 (30.5)	12/ 51 (23.5)	1.210	(0.630, 2.327)	0.5662	
>=85 years	8/ 18 (44.4)	5/ 10 (50.0)	0.592	(0.185, 1.900)	0.3707	
Race						0.4022
White	55/250 (22.0)	27/123 (22.0)	0.834	(0.525, 1.325)	0.4409	
Asian	46/144 (31.9)	17/ 65 (26.2)	1.117	(0.640, 1.950)	0.6973	
Black or African American	10/ 42 (23.8)	10/ 23 (43.5)	0.461	(0.191, 1.114)	0.0779	
Other	2/ 10 (20.0)	2/ 9 (22.2)	0.859	(0.121, 6.103)	0.8791	
Geographical region						0.6239
Asia	45/141 (31.9)	17/ 63 (27.0)	1.082	(0.619, 1.892)	0.7824	
Latin America	26/120 (21.7)	18/ 70 (25.7)	0.788	(0.431, 1.442)	0.4390	
Europe and Rest of the world	42/185 (22.7)	21/ 87 (24.1)	0.749	(0.442, 1.268)	0.2804	
Baseline PSA values by median						0.3456
< median of overall population	53/216 (24.5)	24/109 (22.0)	0.963	(0.594, 1.561)	0.8779	
>= median of overall population	55/219 (25.1)	32/108 (29.6)	0.736	(0.476, 1.139)	0.1676	
ECOG PS at baseline						0.9531
=0	56/235 (23.8)	22/ 96 (22.9)	0.854	(0.521, 1.399)	0.5299	
>=1	57/211 (27.0)	34/124 (27.4)	0.913	(0.596, 1.398)	0.6761	
Gleason score at initial diagnosis						0.1217
Gleason <8	27/125 (21.6)	19/ 64 (29.7)	0.622	(0.345, 1.121)	0.1108	
Gleason >=8	84/308 (27.3)	33/146 (22.6)	1.074	(0.717, 1.607)	0.7302	
Disease volume at baseline						0.4394
high	93/315 (29.5)	44/155 (28.4)	0.922	(0.643, 1.320)	0.6564	
low	20/131 (15.3)	12/ 65 (18.5)	0.668	(0.326, 1.371)	0.2685	
Renal function - eGFR at baseline						0.0358
Normal: eGFR >= 90 mL/min	56/221 (25.3)	15/102 (14.7)	1.523	(0.861, 2.695)	0.1451	
Mild impairment: 60 <= eGFR < 90 mL/min	41/179 (22.9)	27/ 90 (30.0)	0.657	(0.404, 1.070)	0.0893	
Moderate impairment: 30 <= eGFR < 60 mL/min	15/ 45 (33.3)	13/ 27 (48.1)	0.613	(0.292, 1.289)	0.1923	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population

Table 3.2.3.1

Summary of Serious Adverse Events - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		p-Value	Interaction p-Value
			Hazard Ratio	(95% CI)		
Hepatic function at baseline						0.2770
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	105/387 (27.1)	51/200 (25.5)	0.918	(0.656, 1.284)	0.6183	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	8/ 59 (13.6)	5/ 20 (25.0)	0.505	(0.165, 1.544)	0.2217	
Age Group (Titan)						0.6260
<65	21/117 (17.9)	11/ 64 (17.2)	0.885	(0.425, 1.841)	0.7430	
>=65 and <75	48/193 (24.9)	28/ 95 (29.5)	0.731	(0.458, 1.167)	0.1877	
>=75	44/136 (32.4)	17/ 61 (27.9)	1.048	(0.598, 1.835)	0.8683	
Geographic region (Titan)						0.1719
Europe and north america	26/145 (17.9)	18/ 76 (23.7)	0.634	(0.347, 1.159)	0.1355	
ROTW	87/301 (28.9)	38/144 (26.4)	0.987	(0.674, 1.445)	0.9446	

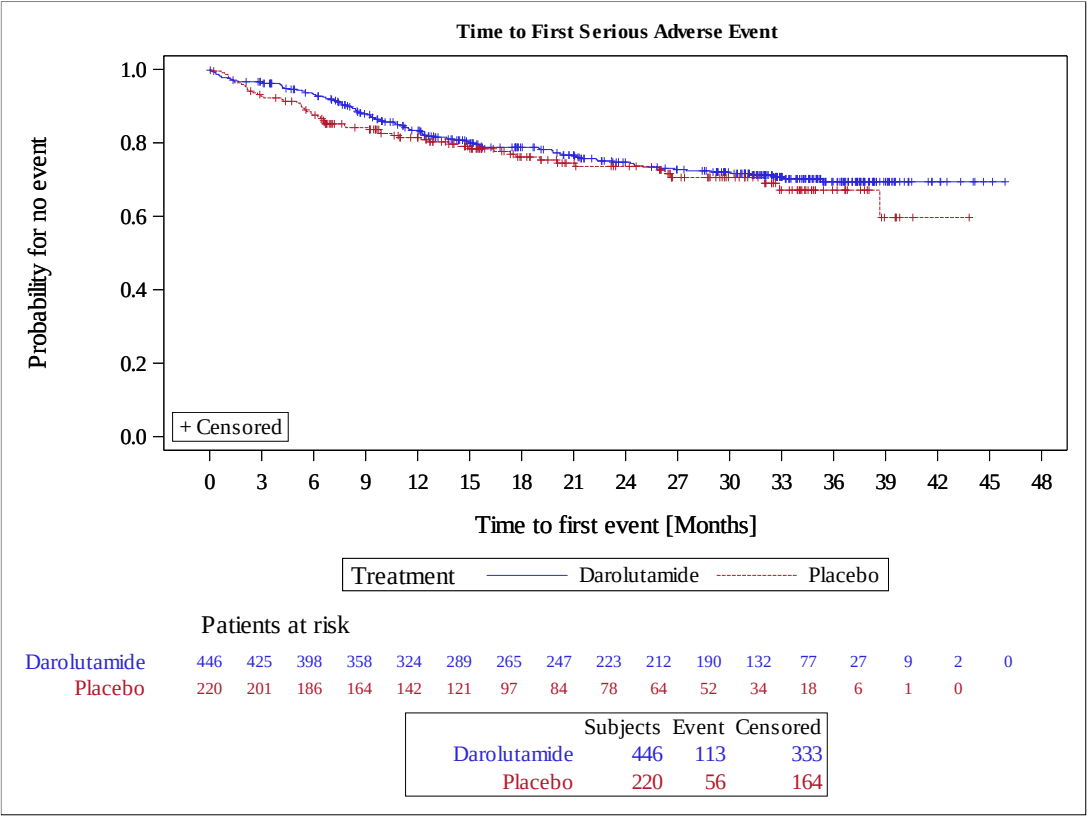
Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Study population
Figure 3.2.3.2
Kaplan-Meier Plot of Time to First Serious Adverse Event
(safety analysis set)

Final

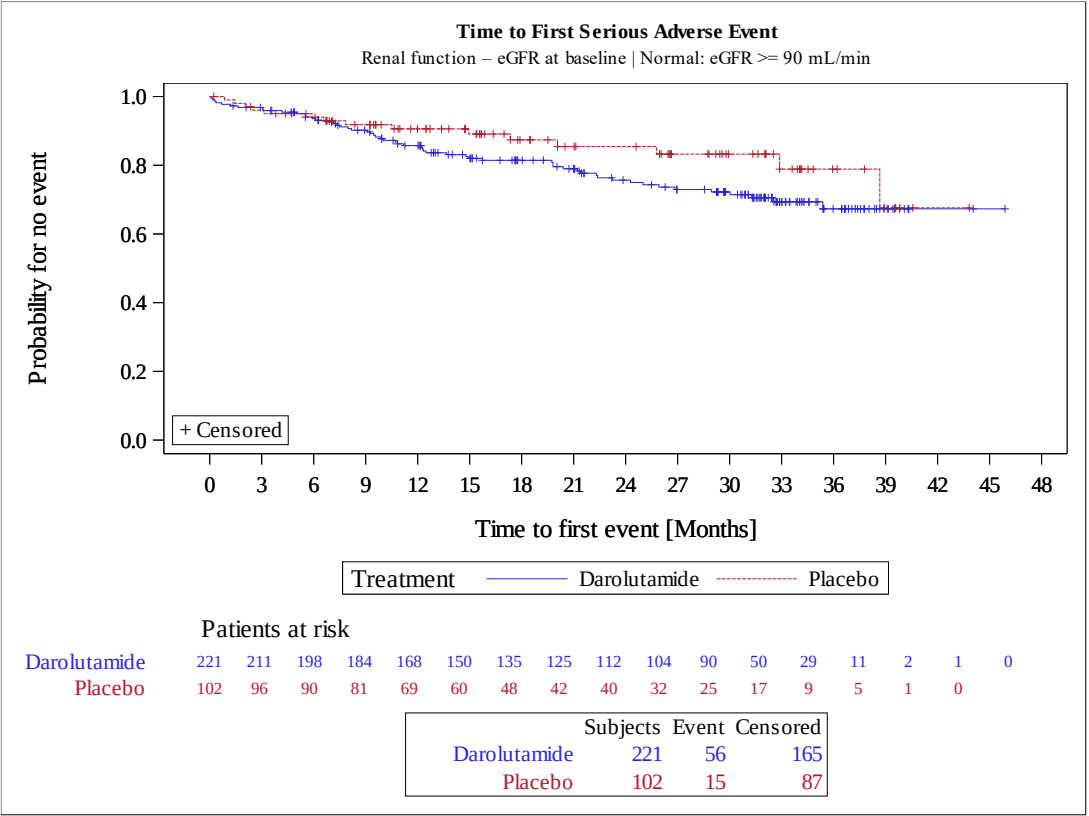


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.3.2
Kaplan-Meier Plot of Time to First Serious Adverse Event
(safety analysis set)

Final

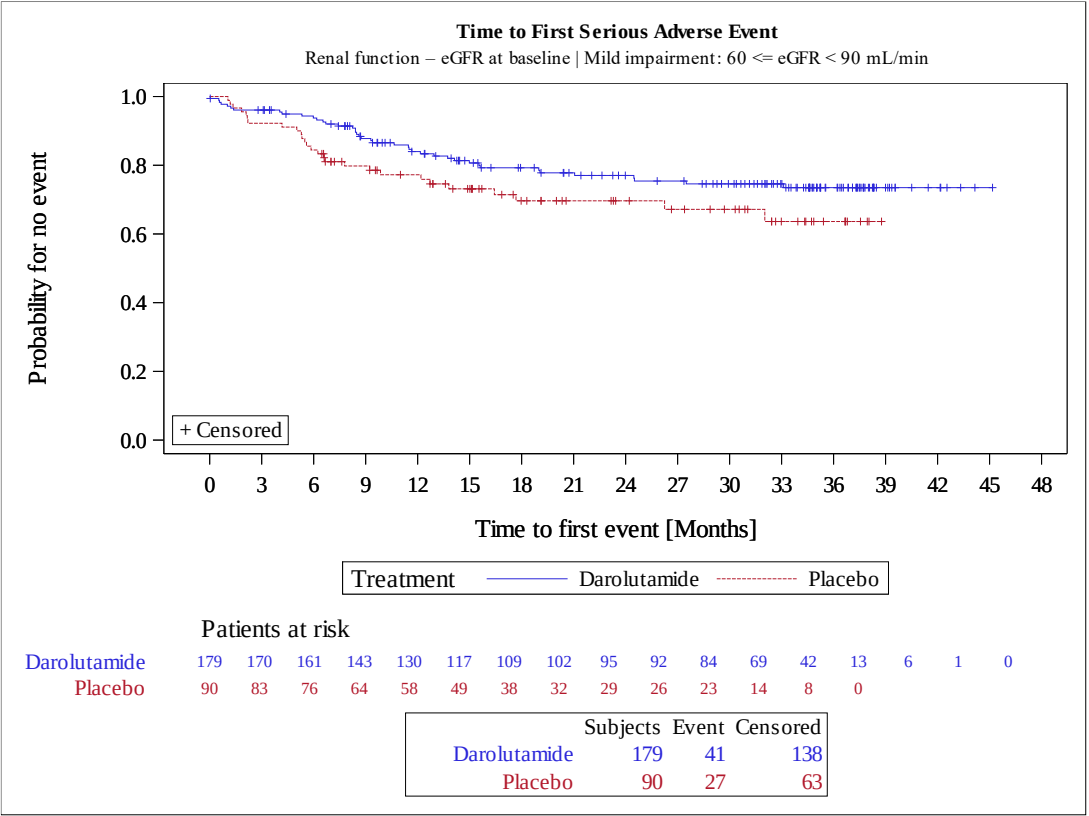


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.3.2
Kaplan-Meier Plot of Time to First Serious Adverse Event
(safety analysis set)

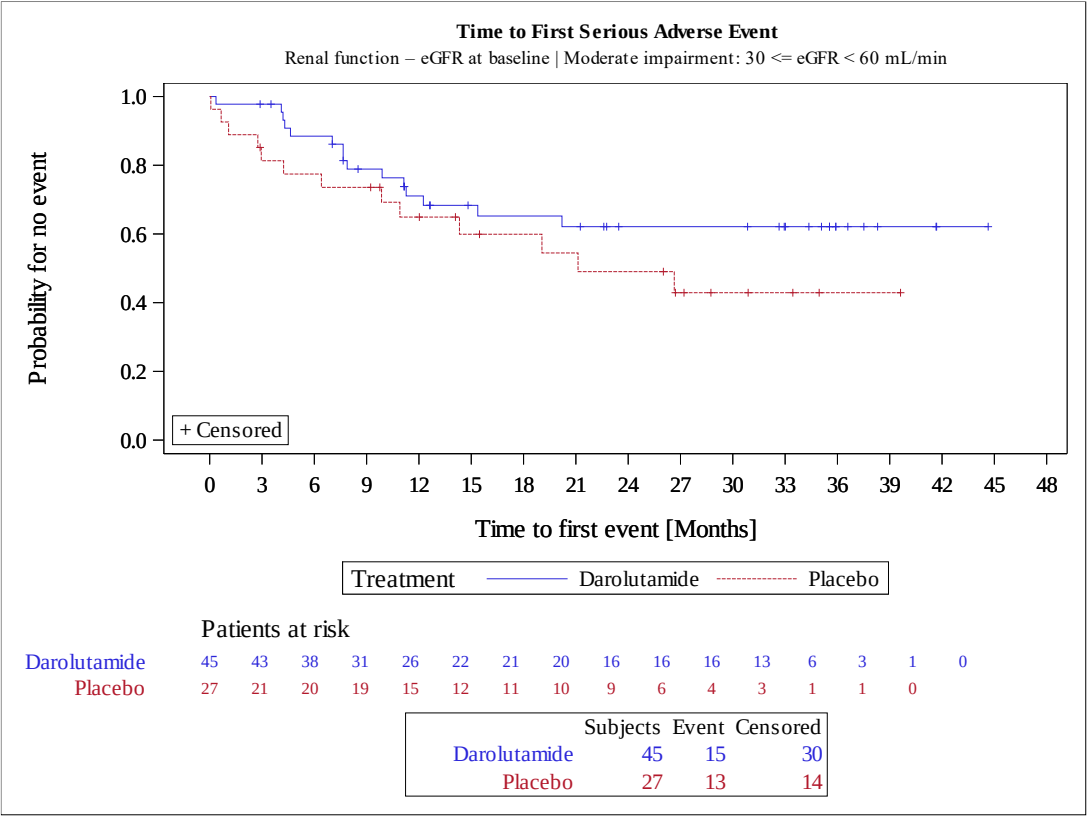
Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha≤0.05).
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Study population
Figure 3.2.3.2
Kaplan-Meier Plot of Time to First Serious Adverse Event
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha≤0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.4
Summary of Serious Adverse Events (disease-related AEs are excluded)
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	111 (24.9)	56 (25.5)
Number of censored patients, n (%)	335 (75.1)	164 (74.5)
Time to Event (Month)		
25%-ile (95% CI)	24.3 (19.1, 35.4)	20.1 (13.8, NE)
Median (95% CI)	NE (NE, NE)	NE (38.7, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.846	
95% CI	0.613, 1.168	
p-value	0.3095	
Odds Ratio	0.970	
95% CI	0.669, 1.407	
p-value	0.8739	
Relative Risk	0.978	
95% CI	0.741, 1.291	
p-value	0.8738	
Risk Difference	-0.567	
95% CI	-7.583, 6.450	
p-value	0.8742	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.4.1

Summary of Serious Adverse Events (disease-related AEs are excluded) - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	18/ 54 (33.3)	9/ 26 (34.6)	0.869	(0.390, 1.937)	0.7307	0.9437
No	93/392 (23.7)	47/194 (24.2)	0.843	(0.593, 1.198)	0.3406	
Received prior local therapy (from IWRS)						
Yes	22/ 81 (27.2)	11/ 39 (28.2)	0.775	(0.373, 1.609)	0.4928	0.8338
No	89/365 (24.4)	45/181 (24.9)	0.861	(0.601, 1.233)	0.4136	
Prior local radiotherapy and/or prostatectomy						
Yes	25/ 88 (28.4)	14/ 49 (28.6)	0.883	(0.458, 1.702)	0.7107	0.8126
No	86/358 (24.0)	42/171 (24.6)	0.841	(0.581, 1.218)	0.3585	
Age group						
<65 years	21/117 (17.9)	11/ 64 (17.2)	0.884	(0.425, 1.839)	0.7410	0.6722
65-74	48/193 (24.9)	28/ 95 (29.5)	0.731	(0.458, 1.167)	0.1877	
75-84	35/118 (29.7)	12/ 51 (23.5)	1.176	(0.610, 2.266)	0.6274	
>=85 years	7/ 18 (38.9)	5/ 10 (50.0)	0.502	(0.150, 1.680)	0.2512	
Race						
White	55/250 (22.0)	27/123 (22.0)	0.834	(0.525, 1.325)	0.4409	0.3441
Asian	45/144 (31.3)	17/ 65 (26.2)	1.093	(0.625, 1.911)	0.7558	
Black or African American	9/ 42 (21.4)	10/ 23 (43.5)	0.419	(0.169, 1.038)	0.0527	
Other	2/ 10 (20.0)	2/ 9 (22.2)	0.859	(0.121, 6.103)	0.8791	
Geographical region						
Asia	44/141 (31.2)	17/ 63 (27.0)	1.058	(0.604, 1.853)	0.8433	0.6371
Latin America	25/120 (20.8)	18/ 70 (25.7)	0.759	(0.413, 1.395)	0.3729	
Europe and Rest of the world	42/185 (22.7)	21/ 87 (24.1)	0.749	(0.442, 1.268)	0.2804	
Baseline PSA values by median						
< median of overall population	53/216 (24.5)	24/109 (22.0)	0.964	(0.594, 1.563)	0.8818	0.2912
>= median of overall population	53/219 (24.2)	32/108 (29.6)	0.710	(0.457, 1.102)	0.1249	
ECOG PS at baseline						
=0	56/235 (23.8)	22/ 96 (22.9)	0.854	(0.521, 1.399)	0.5299	0.9601
>=1	55/211 (26.1)	34/124 (27.4)	0.881	(0.574, 1.353)	0.5616	
Gleason score at initial diagnosis						
Gleason <8	27/125 (21.6)	19/ 64 (29.7)	0.622	(0.345, 1.121)	0.1108	0.1392
Gleason >=8	82/308 (26.6)	33/146 (22.6)	1.047	(0.698, 1.570)	0.8229	
Disease volume at baseline						
high	91/315 (28.9)	44/155 (28.4)	0.901	(0.628, 1.293)	0.5725	0.4749
low	20/131 (15.3)	12/ 65 (18.5)	0.668	(0.325, 1.369)	0.2673	
Renal function - eGFR at baseline						
Normal: eGFR >= 90 mL/min	55/221 (24.9)	15/102 (14.7)	1.495	(0.844, 2.648)	0.1649	0.0350
Mild impairment: 60 <= eGFR < 90 mL/min	41/179 (22.9)	27/ 90 (30.0)	0.658	(0.404, 1.071)	0.0897	
Moderate impairment: 30 <= eGFR < 60 mL/min	14/ 45 (31.1)	13/ 27 (48.1)	0.572	(0.269, 1.217)	0.1414	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population

Table 3.2.4.1

Summary of Serious Adverse Events (disease-related AEs are excluded) - Subgroup analysis (safety analysis set)

Final

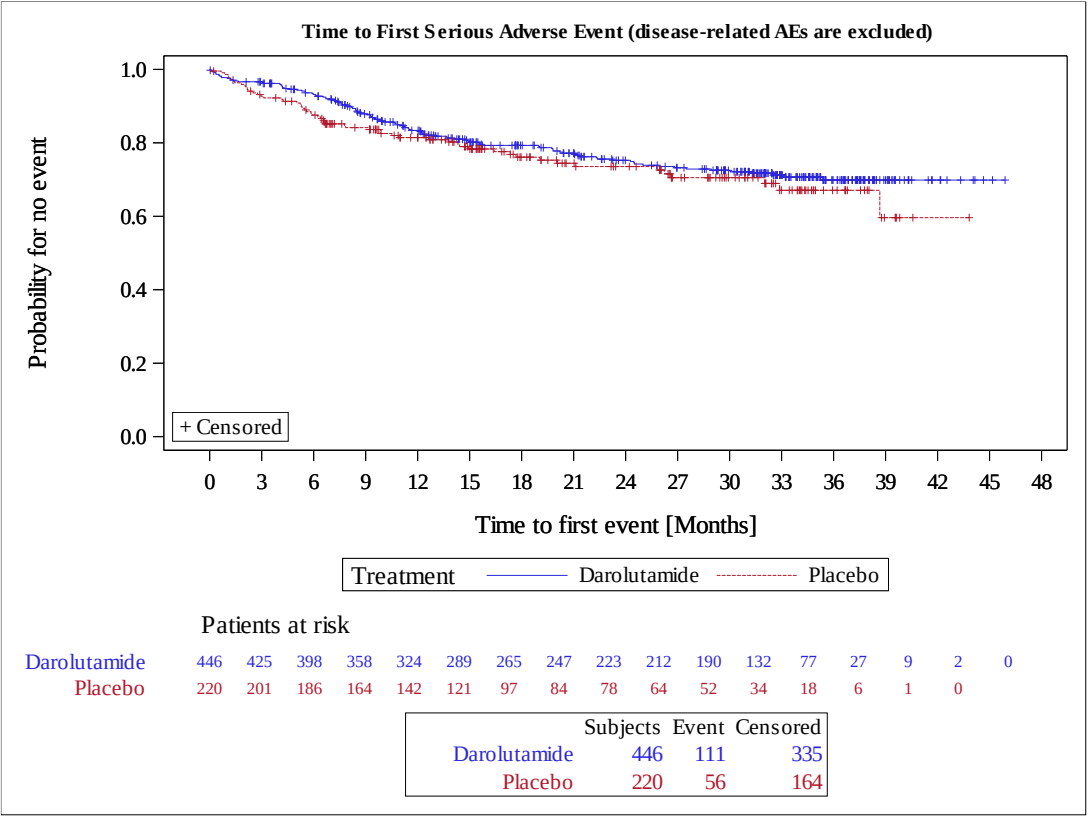
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					0.2911
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	103/387 (26.6)	51/200 (25.5)	0.901	(0.643, 1.262)	0.5437
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	8/ 59 (13.6)	5/ 20 (25.0)	0.505	(0.165, 1.544)	0.2217
Age Group (Titan)					0.7019
<65	21/117 (17.9)	11/ 64 (17.2)	0.884	(0.425, 1.839)	0.7410
>=65 and <75	48/193 (24.9)	28/ 95 (29.5)	0.731	(0.458, 1.167)	0.1877
>=75	42/136 (30.9)	17/ 61 (27.9)	1.000	(0.569, 1.758)	0.9997
Geographic region (Titan)					0.1918
Europe and north america	26/145 (17.9)	18/ 76 (23.7)	0.634	(0.347, 1.159)	0.1355
ROTW	85/301 (28.2)	38/144 (26.4)	0.964	(0.658, 1.414)	0.8539

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.4.2
Kaplan-Meier Plot of Time to First Serious Adverse Event (disease-related AEs are excluded)
(safety analysis set)

Final

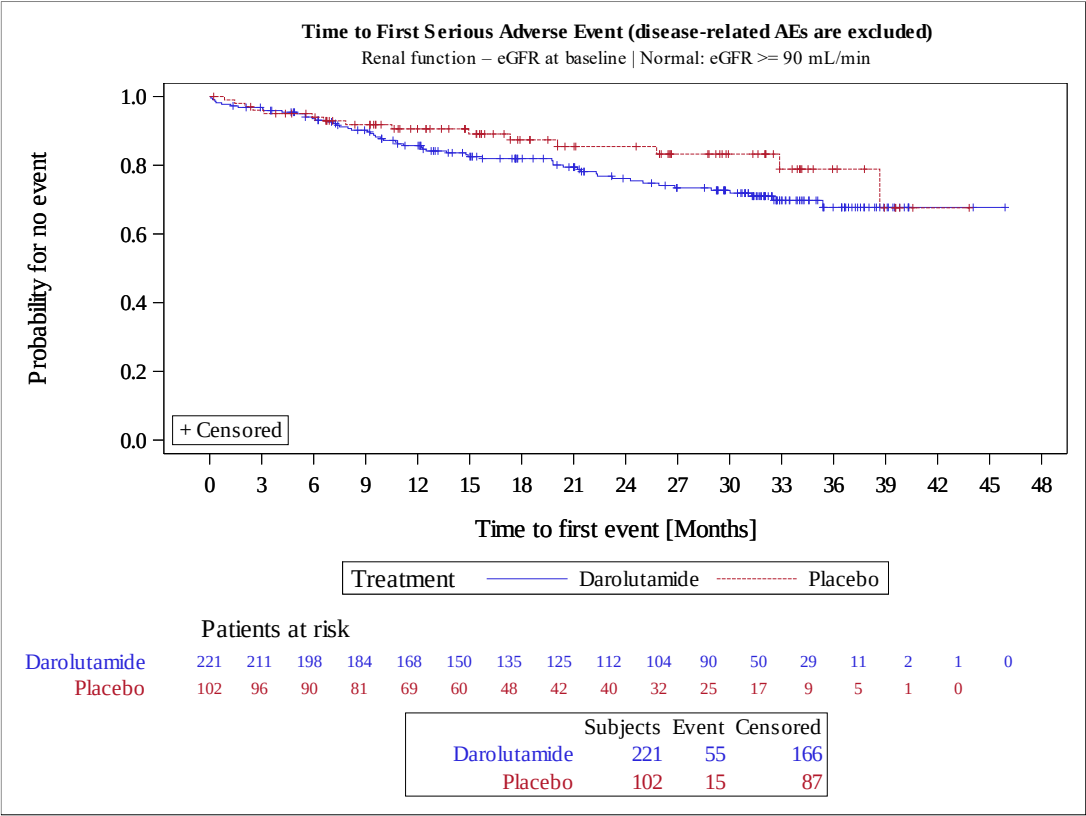


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.4.2
Kaplan-Meier Plot of Time to First Serious Adverse Event (disease-related AEs are excluded)
(safety analysis set)

Final

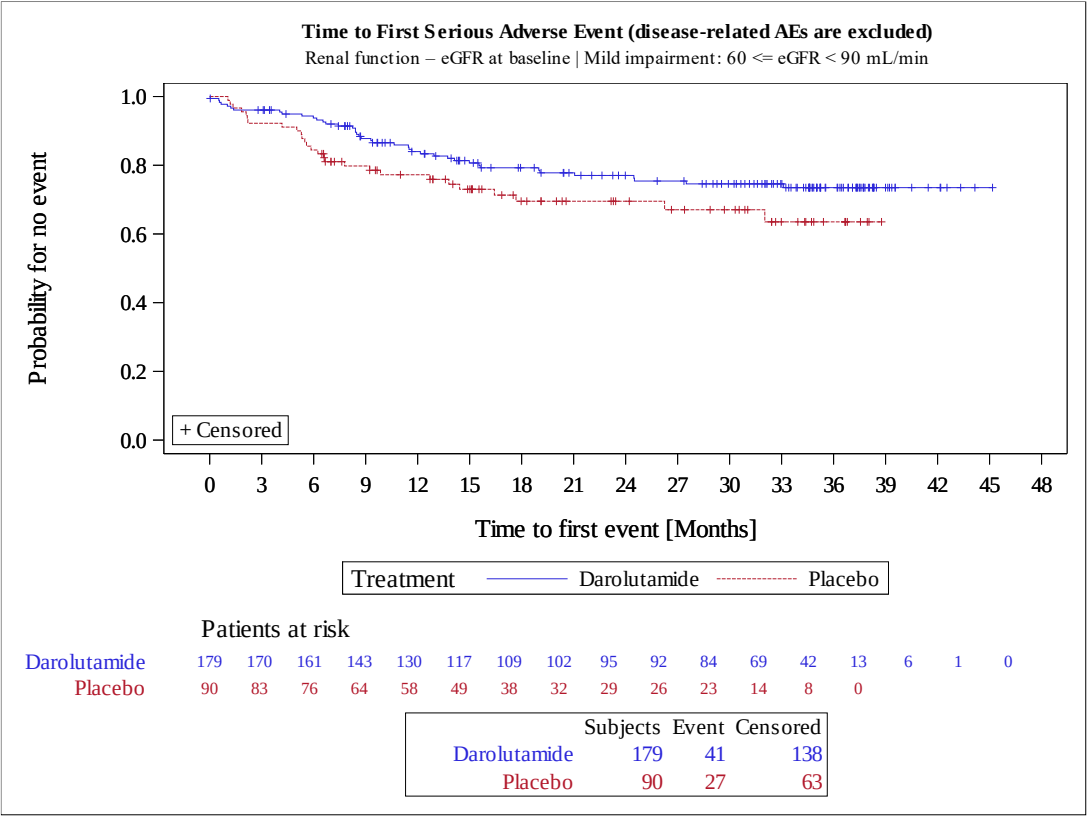


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.4.2
Kaplan-Meier Plot of Time to First Serious Adverse Event (disease-related AEs are excluded)
(safety analysis set)

Final

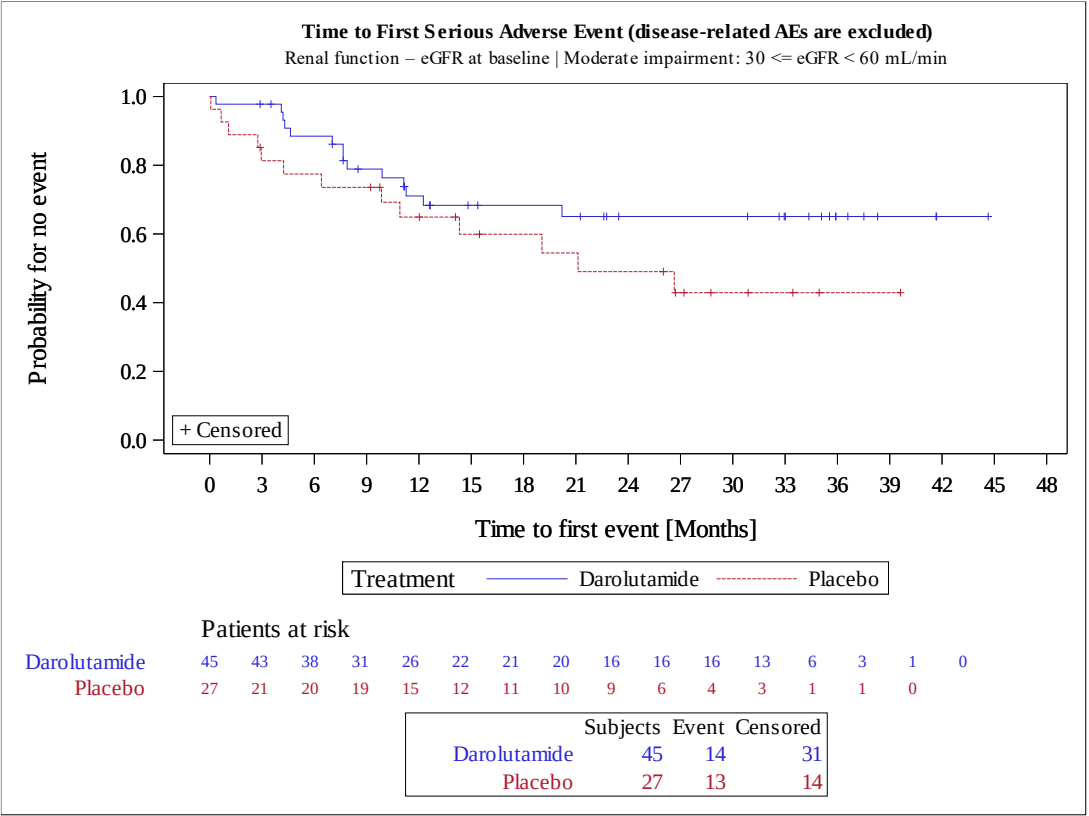


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.4.2
Kaplan-Meier Plot of Time to First Serious Adverse Event (disease-related AEs are excluded)
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.5
Summary of Adverse Events of CTCAE Grade >=3
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	166 (37.2)	84 (38.2)
Number of censored patients, n (%)	280 (62.8)	136 (61.8)
Time to Event (Month)		
25%-ile (95% CI)	12.4 (10.4, 15.5)	11.2 (7.8, 14.9)
Median (95% CI)	NE (NE, NE)	34.5 (26.6, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (38.7, NE)
Unstratified Analysis		
Hazard Ratio	0.858	
95% CI	0.659, 1.116	
p-value	0.2522	
Odds Ratio	0.960	
95% CI	0.688, 1.339	
p-value	0.8094	
Relative Risk	0.975	
95% CI	0.793, 1.199	
p-value	0.8090	
Risk Difference	-0.962	
95% CI	-8.794, 6.870	
p-value	0.8097	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population

Table 3.2.5.1

Summary of Adverse Events of CTCAE Grade ≥3 - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	21/ 54 (38.9)	12/ 26 (46.2)	0.816	(0.401, 1.659)	0.5730	0.8353
No	145/392 (37.0)	72/194 (37.1)	0.867	(0.653, 1.151)	0.3240	
Received prior local therapy (from IWRS)						
Yes	29/ 81 (35.8)	14/ 39 (35.9)	0.818	(0.429, 1.560)	0.5412	0.9172
No	137/365 (37.5)	70/181 (38.7)	0.866	(0.649, 1.156)	0.3282	
Prior local radiotherapy and/or prostatectomy						
Yes	33/ 88 (37.5)	17/ 49 (34.7)	1.020	(0.567, 1.835)	0.9465	0.4816
No	133/358 (37.2)	67/171 (39.2)	0.816	(0.608, 1.095)	0.1742	
Age group						
<65 years	40/117 (34.2)	20/ 64 (31.3)	0.937	(0.547, 1.606)	0.8134	0.9935
65-74	67/193 (34.7)	36/ 95 (37.9)	0.810	(0.539, 1.216)	0.3083	
75-84	48/118 (40.7)	22/ 51 (43.1)	0.881	(0.531, 1.459)	0.6212	
≥85 years	11/ 18 (61.1)	6/ 10 (60.0)	0.683	(0.240, 1.938)	0.4708	
Race						
White	81/250 (32.4)	43/123 (35.0)	0.793	(0.547, 1.149)	0.2191	0.9168
Asian	61/144 (42.4)	26/ 65 (40.0)	0.975	(0.615, 1.546)	0.9152	
Black or African American	22/ 42 (52.4)	13/ 23 (56.5)	0.791	(0.398, 1.571)	0.5017	
Other	2/ 10 (20.0)	2/ 9 (22.2)	0.859	(0.121, 6.103)	0.8791	
Geographical region						
Asia	60/141 (42.6)	26/ 63 (41.3)	0.949	(0.598, 1.506)	0.8238	0.8072
Latin America	51/120 (42.5)	31/ 70 (44.3)	0.918	(0.587, 1.435)	0.7061	
Europe and Rest of the world	55/185 (29.7)	27/ 87 (31.0)	0.778	(0.489, 1.236)	0.2857	
Baseline PSA values by median						
< median of overall population	72/216 (33.3)	35/109 (32.1)	0.942	(0.628, 1.411)	0.7706	0.6097
≥ median of overall population	88/219 (40.2)	47/108 (43.5)	0.803	(0.563, 1.146)	0.2256	
ECOG PS at baseline						
=0	85/235 (36.2)	35/ 96 (36.5)	0.843	(0.568, 1.251)	0.3955	0.8772
≥1	81/211 (38.4)	49/124 (39.5)	0.896	(0.628, 1.280)	0.5466	
Gleason score at initial diagnosis						
Gleason <8	40/125 (32.0)	24/ 64 (37.5)	0.740	(0.445, 1.229)	0.2420	0.4216
Gleason ≥8	121/308 (39.3)	55/146 (37.7)	0.943	(0.685, 1.298)	0.7197	
Disease volume at baseline						
high	124/315 (39.4)	64/155 (41.3)	0.854	(0.631, 1.156)	0.3063	0.9065
low	42/131 (32.1)	20/ 65 (30.8)	0.873	(0.511, 1.489)	0.6172	
Renal function - eGFR at baseline						
Normal: eGFR ≥ 90 mL/min	86/221 (38.9)	29/102 (28.4)	1.239	(0.812, 1.888)	0.3186	0.0593
Mild impairment: 60 ≤ eGFR < 90 mL/min	58/179 (32.4)	38/ 90 (42.2)	0.650	(0.431, 0.980)	0.0382	
Moderate impairment: 30 ≤ eGFR < 60 mL/min	21/ 45 (46.7)	17/ 27 (63.0)	0.699	(0.368, 1.328)	0.2713	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.5.1

Summary of Adverse Events of CTCAE Grade ≥3 - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		p-Value	Interaction p-Value
			Hazard Ratio	(95% CI)		
Hepatic function at baseline						0.5434
Normal: Total bilirubin and AST ≤ upper limit of normal (ULN)	150/387 (38.8)	77/200 (38.5)	0.886	(0.672, 1.167)	0.3879	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin ≤ ULN and AST > ULN)	16/ 59 (27.1)	7/ 20 (35.0)	0.675	(0.277, 1.641)	0.3827	
Age Group (Titan)						0.9603
<65	40/117 (34.2)	20/ 64 (31.3)	0.937	(0.547, 1.606)	0.8134	
≥65 and <75	67/193 (34.7)	36/ 95 (37.9)	0.810	(0.539, 1.216)	0.3083	
≥75	59/136 (43.4)	28/ 61 (45.9)	0.857	(0.546, 1.345)	0.5020	
Geographic region (Titan)						0.2461
Europe and north america	38/145 (26.2)	24/ 76 (31.6)	0.700	(0.419, 1.171)	0.1719	
ROTW	128/301 (42.5)	60/144 (41.7)	0.937	(0.689, 1.273)	0.6759	

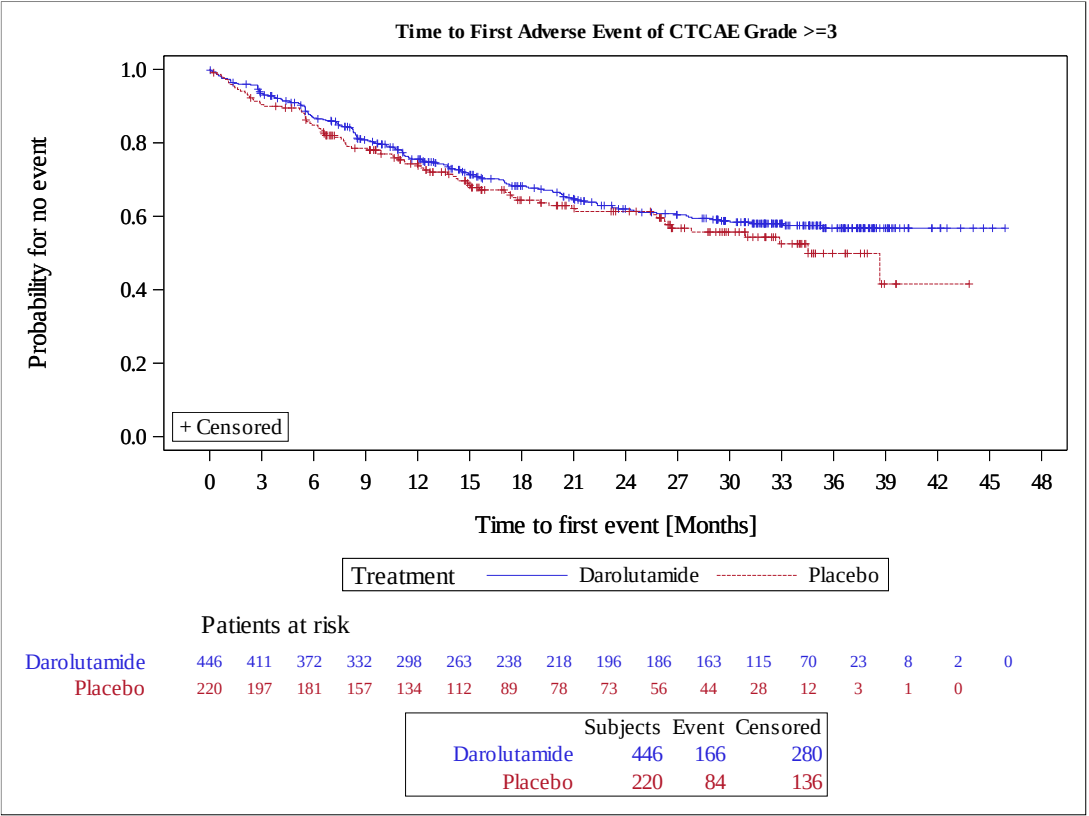
Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.5.2
Kaplan-Meier Plot of Time to First Adverse Event of CTCAE Grade ≥ 3
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.6
Summary of Adverse Events of CTCAE Grade >=3 (disease-related AEs are excluded)
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	165 (37.0)	84 (38.2)
Number of censored patients, n (%)	281 (63.0)	136 (61.8)
Time to Event (Month)		
25%-ile (95% CI)	12.4 (10.4, 15.7)	11.2 (7.8, 14.9)
Median (95% CI)	NE (NE, NE)	34.5 (26.6, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (38.7, NE)
Unstratified Analysis		
Hazard Ratio	0.853	
95% CI	0.655, 1.110	
p-value	0.2355	
Odds Ratio	0.951	
95% CI	0.681, 1.326	
p-value	0.7660	
Relative Risk	0.969	
95% CI	0.788, 1.192	
p-value	0.7653	
Risk Difference	-1.186	
95% CI	-9.015, 6.643	
p-value	0.7665	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.6.1

Summary of Adverse Events of CTCAE Grade ≥3 (disease-related AEs are excluded) - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	21/ 54 (38.9)	12/ 26 (46.2)	0.816	(0.401, 1.659)	0.5730	0.8479
No	144/392 (36.7)	72/194 (37.1)	0.862	(0.649, 1.144)	0.3027	
Received prior local therapy (from IWRS)						
Yes	29/ 81 (35.8)	14/ 39 (35.9)	0.818	(0.429, 1.560)	0.5412	0.9313
No	136/365 (37.3)	70/181 (38.7)	0.860	(0.644, 1.148)	0.3065	
Prior local radiotherapy and/or prostatectomy						
Yes	33/ 88 (37.5)	17/ 49 (34.7)	1.020	(0.567, 1.835)	0.9465	0.4688
No	132/358 (36.9)	67/171 (39.2)	0.810	(0.603, 1.088)	0.1602	
Age group						
<65 years	40/117 (34.2)	20/ 64 (31.3)	0.936	(0.546, 1.605)	0.8109	0.9912
65-74	67/193 (34.7)	36/ 95 (37.9)	0.810	(0.539, 1.216)	0.3083	
75-84	48/118 (40.7)	22/ 51 (43.1)	0.881	(0.531, 1.459)	0.6212	
≥85 years	10/ 18 (55.6)	6/ 10 (60.0)	0.596	(0.204, 1.739)	0.3387	
Race						
White	81/250 (32.4)	43/123 (35.0)	0.793	(0.547, 1.149)	0.2191	0.9343
Asian	60/144 (41.7)	26/ 65 (40.0)	0.960	(0.605, 1.523)	0.8621	
Black or African American	22/ 42 (52.4)	13/ 23 (56.5)	0.792	(0.399, 1.574)	0.5052	
Other	2/ 10 (20.0)	2/ 9 (22.2)	0.859	(0.121, 6.103)	0.8791	
Geographical region						
Asia	59/141 (41.8)	26/ 63 (41.3)	0.934	(0.588, 1.484)	0.7719	0.8242
Latin America	51/120 (42.5)	31/ 70 (44.3)	0.918	(0.587, 1.436)	0.7077	
Europe and Rest of the world	55/185 (29.7)	27/ 87 (31.0)	0.778	(0.489, 1.236)	0.2857	
Baseline PSA values by median						
< median of overall population	72/216 (33.3)	35/109 (32.1)	0.942	(0.628, 1.412)	0.7715	0.5803
≥ median of overall population	87/219 (39.7)	47/108 (43.5)	0.795	(0.557, 1.134)	0.2041	
ECOG PS at baseline						
=0	85/235 (36.2)	35/ 96 (36.5)	0.843	(0.568, 1.251)	0.3955	0.9121
≥1	80/211 (37.9)	49/124 (39.5)	0.886	(0.620, 1.266)	0.5060	
Gleason score at initial diagnosis						
Gleason <8	40/125 (32.0)	24/ 64 (37.5)	0.740	(0.445, 1.229)	0.2420	0.4380
Gleason ≥8	120/308 (39.0)	55/146 (37.7)	0.935	(0.679, 1.288)	0.6825	
Disease volume at baseline						
high	123/315 (39.0)	64/155 (41.3)	0.847	(0.626, 1.147)	0.2831	0.8842
low	42/131 (32.1)	20/ 65 (30.8)	0.872	(0.511, 1.489)	0.6160	
Renal function - eGFR at baseline						
Normal: eGFR ≥ 90 mL/min	86/221 (38.9)	29/102 (28.4)	1.239	(0.812, 1.888)	0.3186	0.0540
Mild impairment: 60 ≤ eGFR < 90 mL/min	58/179 (32.4)	38/ 90 (42.2)	0.650	(0.431, 0.980)	0.0383	
Moderate impairment: 30 ≤ eGFR < 60 mL/min	20/ 45 (44.4)	17/ 27 (63.0)	0.663	(0.347, 1.268)	0.2110	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.6.1

Summary of Adverse Events of CTCAE Grade ≥ 3 (disease-related AEs are excluded) - Subgroup analysis (safety analysis set)

Final

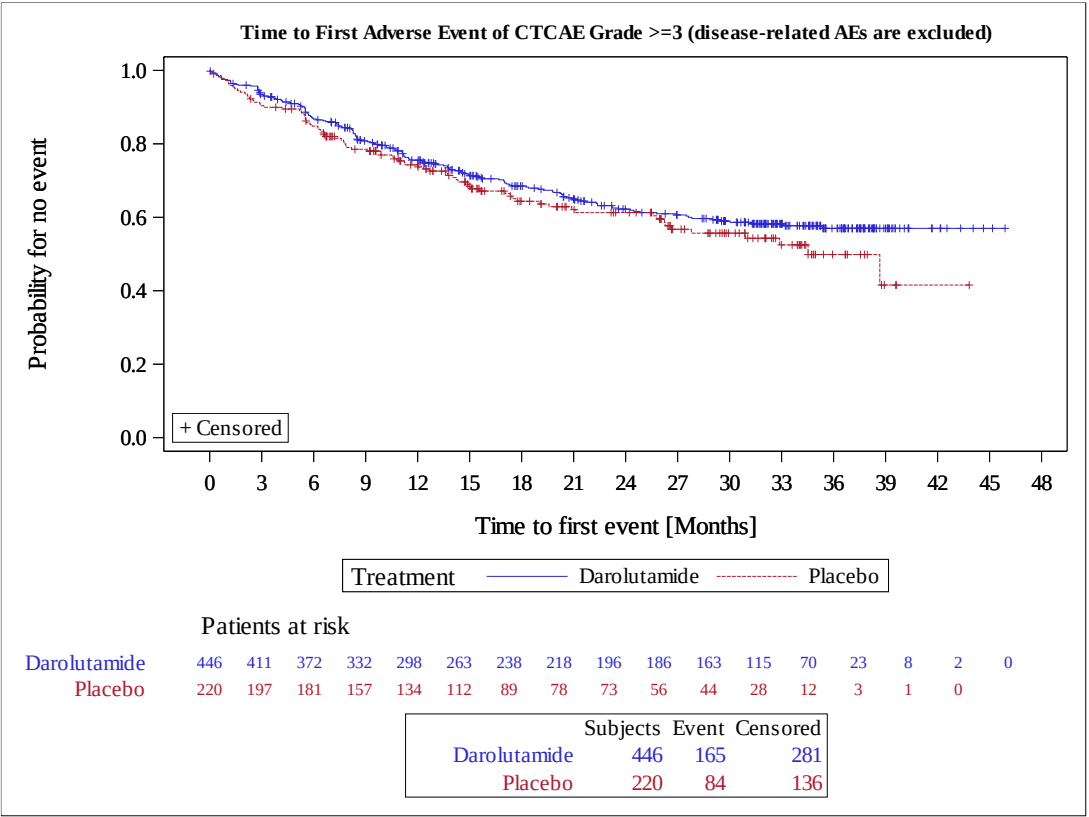
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		p-Value	Interaction p-Value
			Hazard Ratio	(95% CI)		
Hepatic function at baseline						0.5519
Normal: Total bilirubin and AST $\leq$ upper limit of normal (ULN)	149/387 (38.5)	77/200 (38.5)	0.880	(0.668, 1.160)	0.3642	
Mild impairment: Total bilirubin $>$ ULN to 1.5 x ULN or (Total bilirubin $\leq$ ULN and AST $>$ ULN)	16/ 59 (27.1)	7/ 20 (35.0)	0.675	(0.277, 1.641)	0.3827	
Age Group (Titan)						0.9594
<65	40/117 (34.2)	20/ 64 (31.3)	0.936	(0.546, 1.605)	0.8109	
≥ 65 and < 75	67/193 (34.7)	36/ 95 (37.9)	0.810	(0.539, 1.216)	0.3083	
≥ 75	58/136 (42.6)	28/ 61 (45.9)	0.842	(0.536, 1.324)	0.4563	
Geographic region (Titan)						0.2562
Europe and north america	38/145 (26.2)	24/ 76 (31.6)	0.700	(0.419, 1.171)	0.1719	
ROTW	127/301 (42.2)	60/144 (41.7)	0.930	(0.684, 1.264)	0.6423	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population
Figure 3.2.6.2
Kaplan-Meier Plot of Time to First Adverse Event of CTCAE Grade >=3 (disease-related AEs are excluded)
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.7
Summary of Adverse Events of CTCAE Grade <3
(safety analysis set)

Final

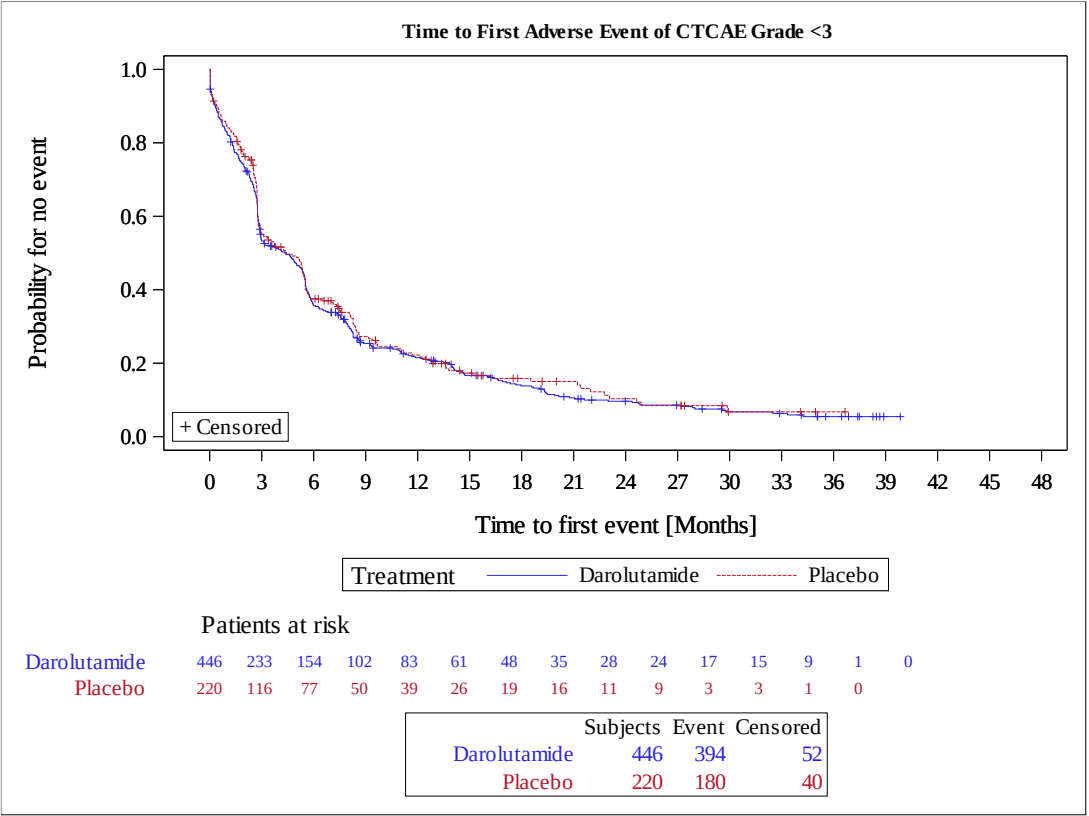
	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	394 (88.3)	180 (81.8)
Number of censored patients, n (%)	52 (11.7)	40 (18.2)
Time to Event (Month)		
25%-ile (95% CI)	1.8 (1.4, 2.3)	2.4 (1.6, 2.7)
Median (95% CI)	4.4 (3.0, 5.4)	4.4 (3.0, 5.5)
75%-ile (95% CI)	9.3 (8.1, 12.4)	9.7 (8.3, 13.6)
Unstratified Analysis		
Hazard Ratio	1.049	
95% CI	0.879, 1.251	
p-value	0.5913	
Odds Ratio	1.684	
95% CI	1.075, 2.636	
p-value	0.0227	
Relative Risk	1.080	
95% CI	1.006, 1.159	
p-value	0.0338	
Risk Difference	6.523	
95% CI	0.620, 12.426	
p-value	0.0303	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.7.1
Kaplan-Meier Plot of Time to First Adverse Event of CTCAE Grade <3
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.8
Summary of Adverse Events leading to discontinuation of study treatment
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	28 (6.3)	23 (10.5)
Number of censored patients, n (%)	418 (93.7)	197 (89.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.496	
95% CI	0.285, 0.864	
p-value	0.0115	
Odds Ratio	0.574	
95% CI	0.322, 1.022	
p-value	0.0591	
Relative Risk	0.601	
95% CI	0.354, 1.018	
p-value	0.0581	
Risk Difference	-4.177	
95% CI	-8.804, 0.451	
p-value	0.0769	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population

Table 3.2.8.1

Summary of Adverse Events leading to discontinuation of study treatment - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	2/ 54 (3.7)	3/ 26 (11.5)	0.295	(0.049, 1.768)	0.1556	0.5155
No	26/392 (6.6)	20/194 (10.3)	0.519	(0.289, 0.932)	0.0256	
Received prior local therapy (from IWRS)						
Yes	3/ 81 (3.7)	5/ 39 (12.8)	0.174	(0.040, 0.747)	0.0085	0.2016
No	25/365 (6.8)	18/181 (9.9)	0.591	(0.322, 1.085)	0.0860	
Prior local radiotherapy and/or prostatectomy						
Yes	8/ 88 (9.1)	7/ 49 (14.3)	0.505	(0.182, 1.402)	0.1817	0.8584
No	20/358 (5.6)	16/171 (9.4)	0.501	(0.259, 0.969)	0.0365	
Age group						
<65 years	6/117 (5.1)	3/ 64 (4.7)	0.793	(0.196, 3.203)	0.7445	0.7054
65-74	12/193 (6.2)	11/ 95 (11.6)	0.464	(0.204, 1.055)	0.0605	
75-84	8/118 (6.8)	5/ 51 (9.8)	0.620	(0.202, 1.899)	0.3983	
>=85 years	2/ 18 (11.1)	4/ 10 (40.0)	0.197	(0.035, 1.090)	0.0393	
Race						
White	12/250 (4.8)	14/123 (11.4)	0.332	(0.153, 0.723)	0.0036	0.4977
Asian	12/144 (8.3)	6/ 65 (9.2)	0.781	(0.292, 2.088)	0.6207	
Black or African American	3/ 42 (7.1)	2/ 23 (8.7)	0.607	(0.101, 3.639)	0.5811	
Other	1/ 10 (10.0)	1/ 9 (11.1)	0.894	(0.056, 14.297)	0.9371	
Geographical region						
Asia	12/141 (8.5)	6/ 63 (9.5)	0.777	(0.291, 2.078)	0.6145	0.2981
Latin America	7/120 (5.8)	6/ 70 (8.6)	0.565	(0.189, 1.687)	0.2999	
Europe and Rest of the world	9/185 (4.9)	11/ 87 (12.6)	0.297	(0.122, 0.722)	0.0045	
Baseline PSA values by median						
< median of overall population	12/216 (5.6)	11/109 (10.1)	0.455	(0.200, 1.036)	0.0545	0.9281
>= median of overall population	14/219 (6.4)	12/108 (11.1)	0.471	(0.217, 1.021)	0.0510	
ECOG PS at baseline						
=0	9/235 (3.8)	6/ 96 (6.3)	0.488	(0.173, 1.375)	0.1655	0.8940
>=1	19/211 (9.0)	17/124 (13.7)	0.557	(0.289, 1.075)	0.0769	
Gleason score at initial diagnosis						
Gleason <8	6/125 (4.8)	13/ 64 (20.3)	0.197	(0.075, 0.521)	0.0003	0.0109
Gleason >=8	22/308 (7.1)	9/146 (6.2)	0.981	(0.451, 2.136)	0.9621	
Disease volume at baseline						
high	24/315 (7.6)	15/155 (9.7)	0.662	(0.347, 1.265)	0.2091	0.0787
low	4/131 (3.1)	8/ 65 (12.3)	0.195	(0.058, 0.653)	0.0032	
Renal function - eGFR at baseline						
Normal: eGFR >= 90 mL/min	14/221 (6.3)	7/102 (6.9)	0.756	(0.304, 1.877)	0.5448	0.5424
Mild impairment: 60 <= eGFR < 90 mL/min	8/179 (4.5)	9/ 90 (10.0)	0.364	(0.139, 0.952)	0.0319	
Moderate impairment: 30 <= eGFR < 60 mL/min	6/ 45 (13.3)	6/ 27 (22.2)	0.564	(0.182, 1.752)	0.3157	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.8.1

Summary of Adverse Events leading to discontinuation of study treatment - Subgroup analysis
(safety analysis set)

Final

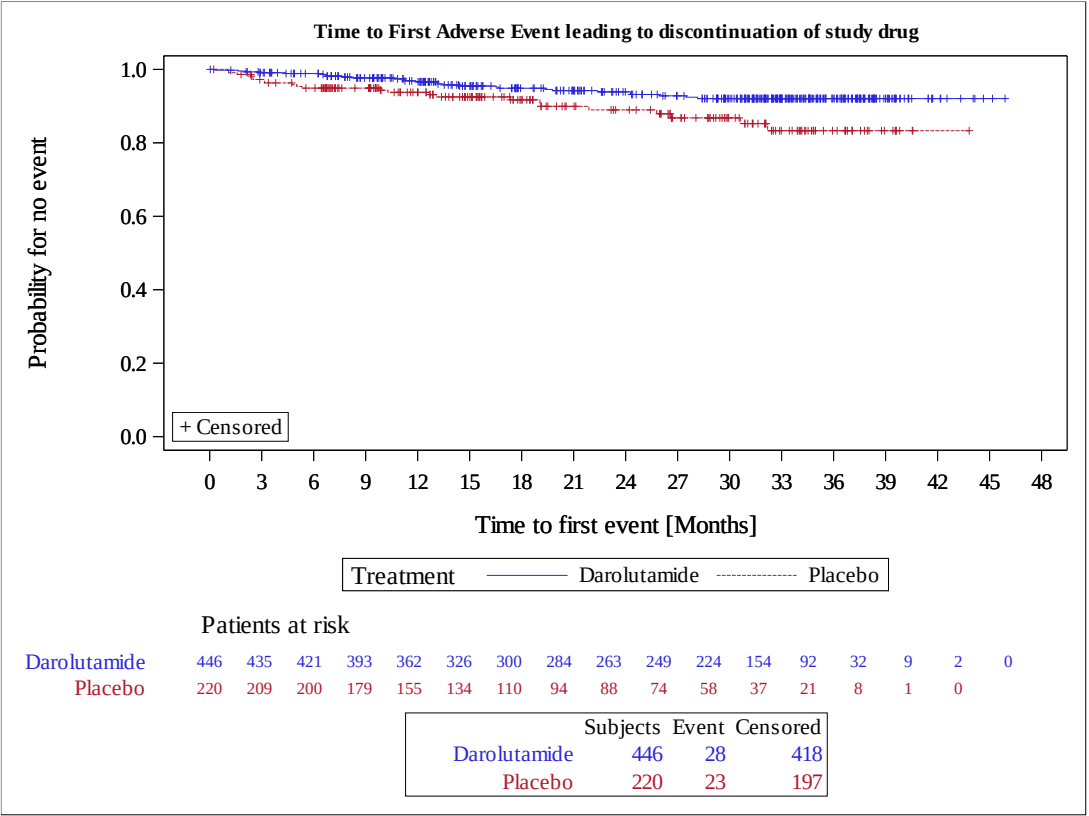
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		p-Value	Interaction p-Value
			Hazard Ratio	(95% CI)		
Hepatic function at baseline						0.7296
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	24/387 (6.2)	20/200 (10.0)	0.497	(0.274, 0.902)	0.0191	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	4/ 59 (6.8)	3/ 20 (15.0)	0.410	(0.092, 1.831)	0.2272	
Age Group (Titan)						0.7117
<65	6/117 (5.1)	3/ 64 (4.7)	0.793	(0.196, 3.203)	0.7445	
>=65 and <75	12/193 (6.2)	11/ 95 (11.6)	0.464	(0.204, 1.055)	0.0605	
>=75	10/136 (7.4)	9/ 61 (14.8)	0.427	(0.173, 1.055)	0.0575	
Geographic region (Titan)						0.0464
Europe and north america	5/145 (3.4)	10/ 76 (13.2)	0.215	(0.073, 0.632)	0.0022	
ROTW	23/301 (7.6)	13/144 (9.0)	0.721	(0.365, 1.425)	0.3443	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.8.2
Kaplan-Meier Plot of Time to First Adverse Event leading to discontinuation of study treatment
(safety analysis set)

Final

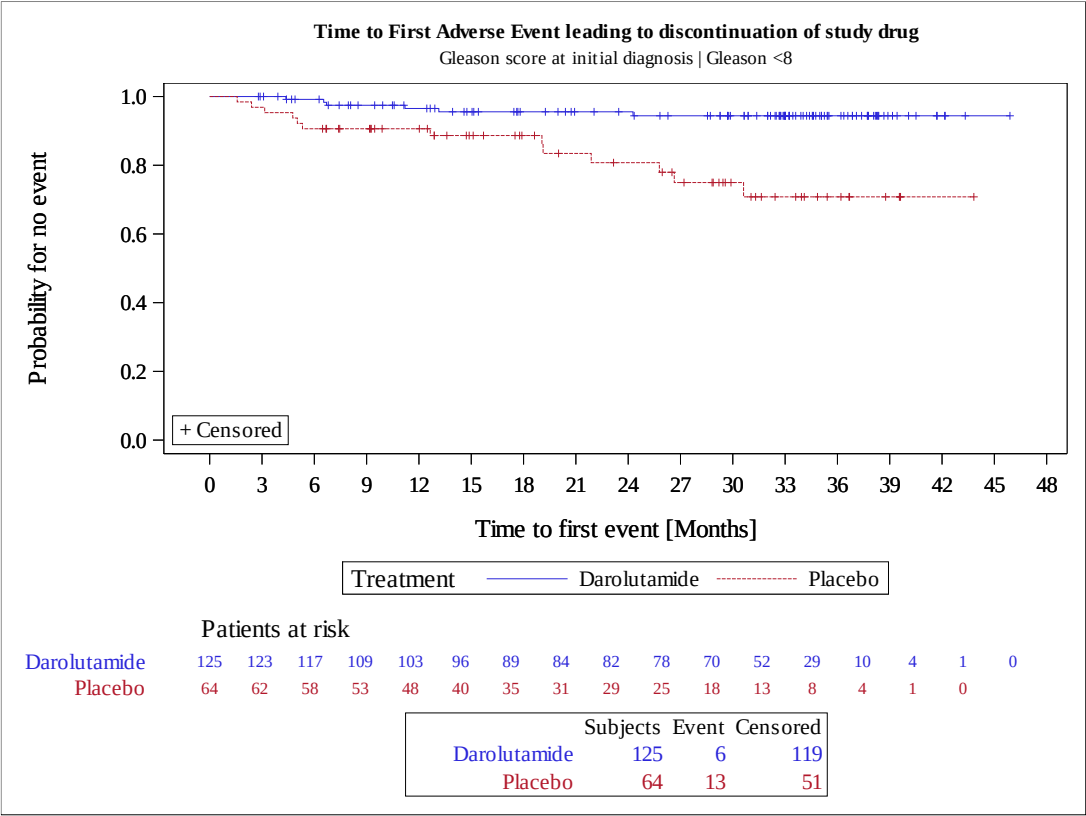


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.8.2
Kaplan-Meier Plot of Time to First Adverse Event leading to discontinuation of study treatment
(safety analysis set)

Final

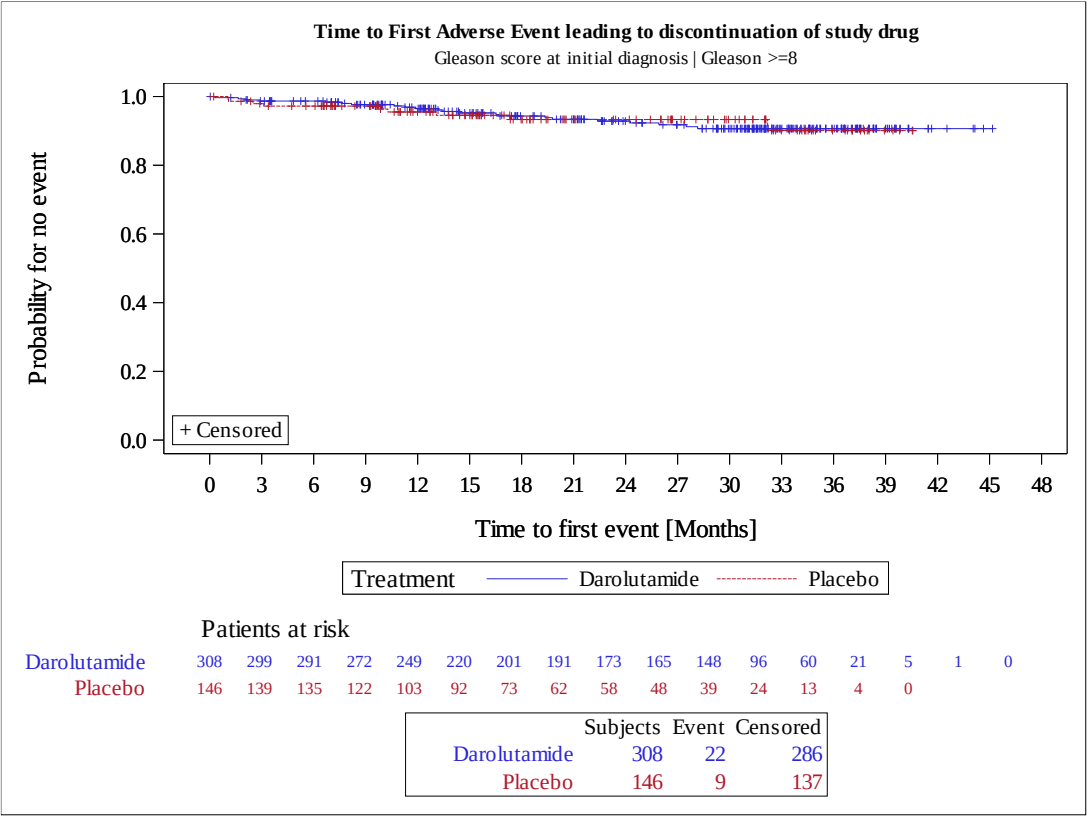


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.8.2
Kaplan-Meier Plot of Time to First Adverse Event leading to discontinuation of study treatment
(safety analysis set)

Final

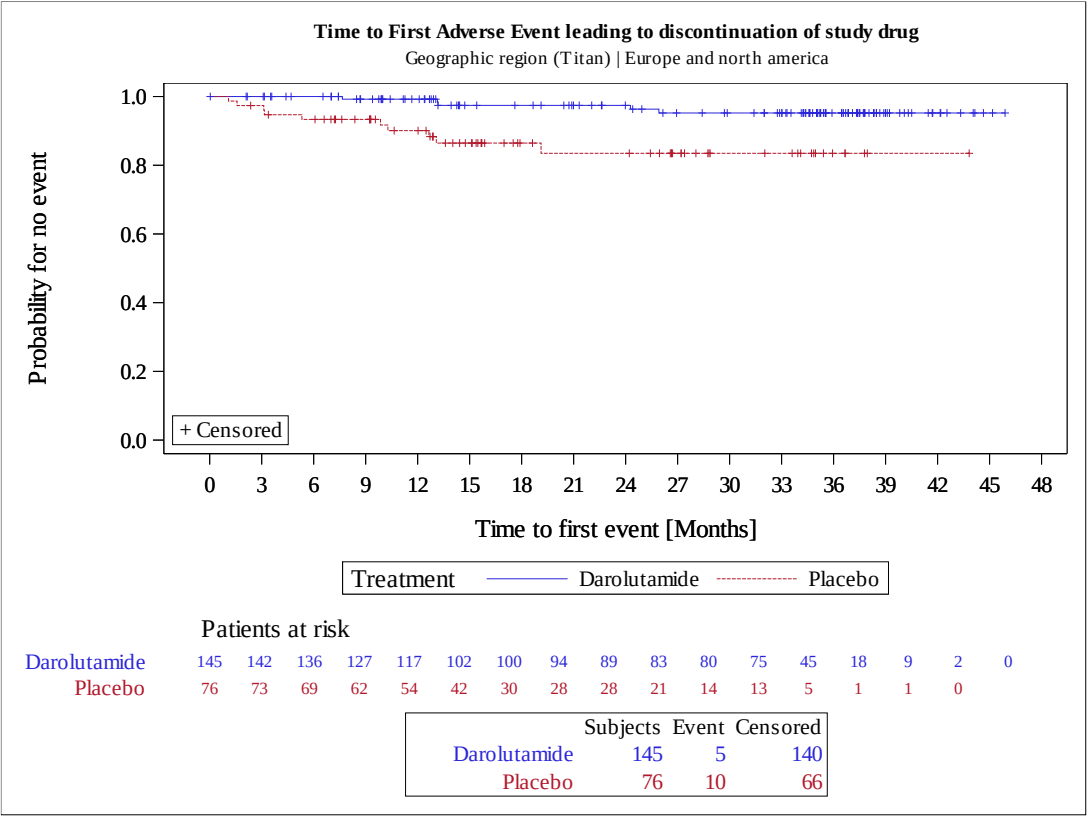


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.8.2
Kaplan-Meier Plot of Time to First Adverse Event leading to discontinuation of study treatment
(safety analysis set)

Final

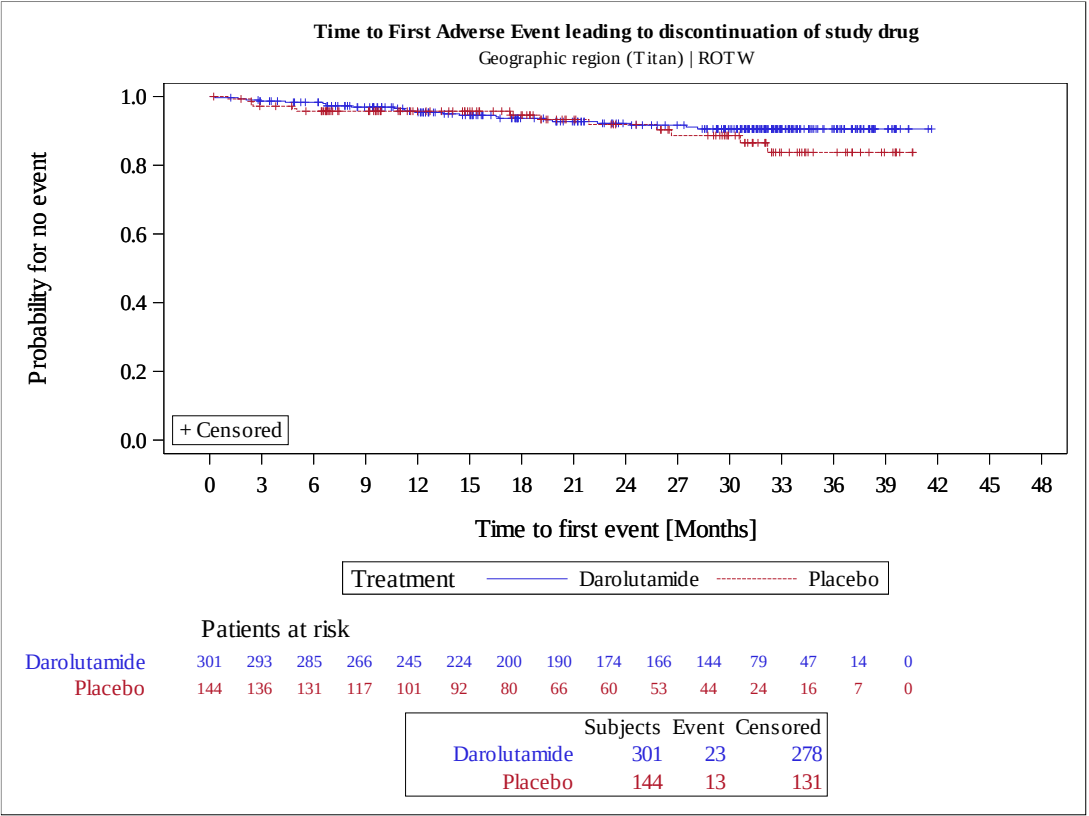


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.8.2
Kaplan-Meier Plot of Time to First Adverse Event leading to discontinuation of study treatment
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.9.1
Summary of Adverse Events of Special Interest - Bone fractures excluding pathological fractures
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	19 (4.3)	6 (2.7)
Number of censored patients, n (%)	427 (95.7)	214 (97.3)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.245	
95% CI	0.496, 3.127	
p-value	0.6402	
Odds Ratio	1.587	
95% CI	0.625, 4.032	
p-value	0.3316	
Relative Risk	1.562	
95% CI	0.633, 3.856	
p-value	0.3333	
Risk Difference	1.533	
95% CI	-1.321, 4.387	
p-value	0.2925	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.1.1

Summary of Adverse Events of Special Interest - Bone fractures excluding pathological fractures - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.9915
Yes	1/ 54 (1.9)	0/ 26 (0.0)	NE	(NE, NE)	NE	
No	18/392 (4.6)	6/194 (3.1)	1.171	(0.463, 2.962)	0.7383	
Received prior local therapy (from IWRS)						0.9889
Yes	5/ 81 (6.2)	0/ 39 (0.0)	NE	(NE, NE)	NE	
No	14/365 (3.8)	6/181 (3.3)	0.925	(0.355, 2.413)	0.8736	
Prior local radiotherapy and/or prostatectomy						0.9866
Yes	5/ 88 (5.7)	0/ 49 (0.0)	NE	(NE, NE)	NE	
No	14/358 (3.9)	6/171 (3.5)	0.849	(0.325, 2.216)	0.7377	
Age group						0.8201
<65 years	5/117 (4.3)	3/ 64 (4.7)	0.685	(0.162, 2.901)	0.6054	
65-74	4/193 (2.1)	1/ 95 (1.1)	1.734	(0.193, 15.558)	0.6183	
75-84	9/118 (7.6)	2/ 51 (3.9)	1.546	(0.333, 7.171)	0.5748	
>=85 years	1/ 18 (5.6)	0/ 10 (0.0)	NE	(NE, NE)	NE	
Race						0.9956
White	13/250 (5.2)	3/123 (2.4)	1.534	(0.434, 5.426)	0.5033	
Asian	6/144 (4.2)	2/ 65 (3.1)	1.245	(0.251, 6.171)	0.7880	
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)	NE	(NE, NE)	NE	
Other	0/ 10 (0.0)	1/ 9 (11.1)	NE	(NE, NE)	NE	
Geographical region						0.8338
Asia	6/141 (4.3)	2/ 63 (3.2)	1.239	(0.250, 6.138)	0.7930	
Latin America	5/120 (4.2)	0/ 70 (0.0)	NE	(NE, NE)	NE	
Europe and Rest of the world	8/185 (4.3)	4/ 87 (4.6)	0.619	(0.183, 2.092)	0.4362	
Baseline PSA values by median						0.1892
< median of overall population	14/216 (6.5)	3/109 (2.8)	1.984	(0.569, 6.921)	0.2731	
>= median of overall population	4/219 (1.8)	3/108 (2.8)	0.503	(0.112, 2.259)	0.3608	
ECOG PS at baseline						0.7635
=0	10/235 (4.3)	3/ 96 (3.1)	1.074	(0.295, 3.918)	0.9135	
>=1	9/211 (4.3)	3/124 (2.4)	1.451	(0.391, 5.385)	0.5758	
Gleason score at initial diagnosis						0.4650
Gleason <8	6/125 (4.8)	1/ 64 (1.6)	2.492	(0.298, 20.822)	0.3831	
Gleason >=8	13/308 (4.2)	5/146 (3.4)	1.007	(0.358, 2.835)	0.9892	
Disease volume at baseline						0.8591
high	10/315 (3.2)	3/155 (1.9)	1.320	(0.362, 4.810)	0.6731	
low	9/131 (6.9)	3/ 65 (4.6)	1.164	(0.313, 4.329)	0.8203	
Renal function - eGFR at baseline						0.9999
Normal: eGFR >= 90 mL/min	7/221 (3.2)	6/102 (5.9)	0.415	(0.139, 1.239)	0.1039	
Mild impairment: 60 <= eGFR < 90 mL/min	12/179 (6.7)	0/ 90 (0.0)	NE	(NE, NE)	NE	
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)	NE	(NE, NE)	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.1.1

Summary of Adverse Events of Special Interest - Bone fractures excluding pathological fractures - Subgroup analysis

(safety analysis set)

Final

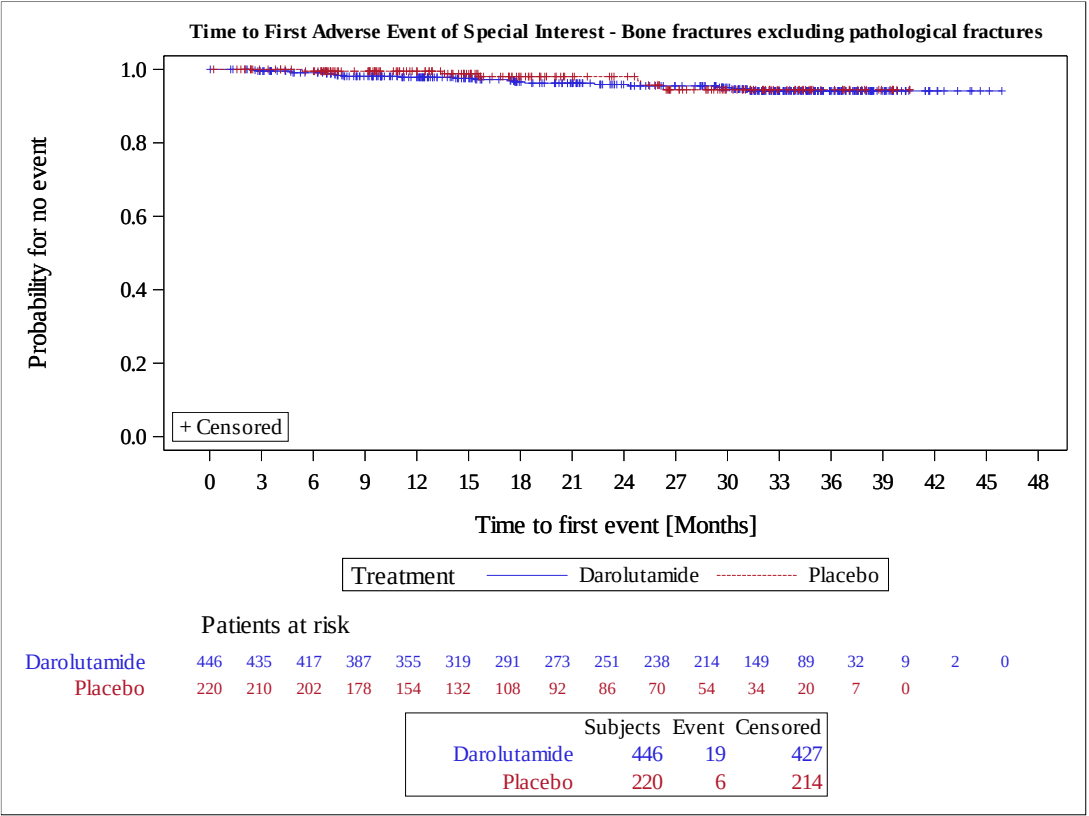
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Hepatic function at baseline						0.0093
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	18/387 (4.7)	3/200 (1.5)	2.471	(0.726, 8.413)	0.1345	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 59 (1.7)	3/ 20 (15.0)	0.087	(0.009, 0.835)	0.0074	
Age Group (Titan)						0.5707
<65	5/117 (4.3)	3/ 64 (4.7)	0.685	(0.162, 2.901)	0.6054	
>=65 and <75	4/193 (2.1)	1/ 95 (1.1)	1.734	(0.193, 15.558)	0.6183	
>=75	10/136 (7.4)	2/ 61 (3.3)	1.734	(0.379, 7.938)	0.4725	
Geographic region (Titan)						0.0394
Europe and north america	2/145 (1.4)	3/ 76 (3.9)	0.265	(0.044, 1.599)	0.1202	
ROTW	17/301 (5.6)	3/144 (2.1)	2.310	(0.676, 7.891)	0.1691	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.9.1.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Bone fractures excluding pathological fractures
(safety analysis set)

Final

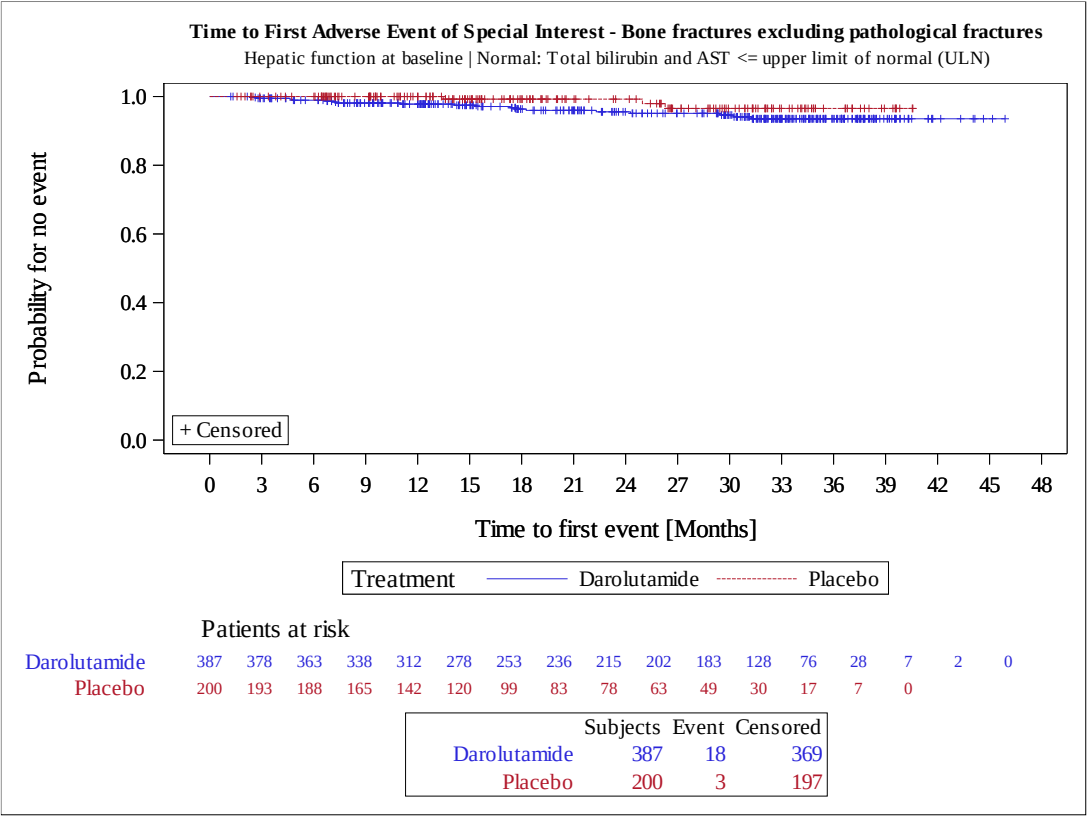


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population
Figure 3.2.9.1.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Bone fractures excluding pathological fractures
(safety analysis set)

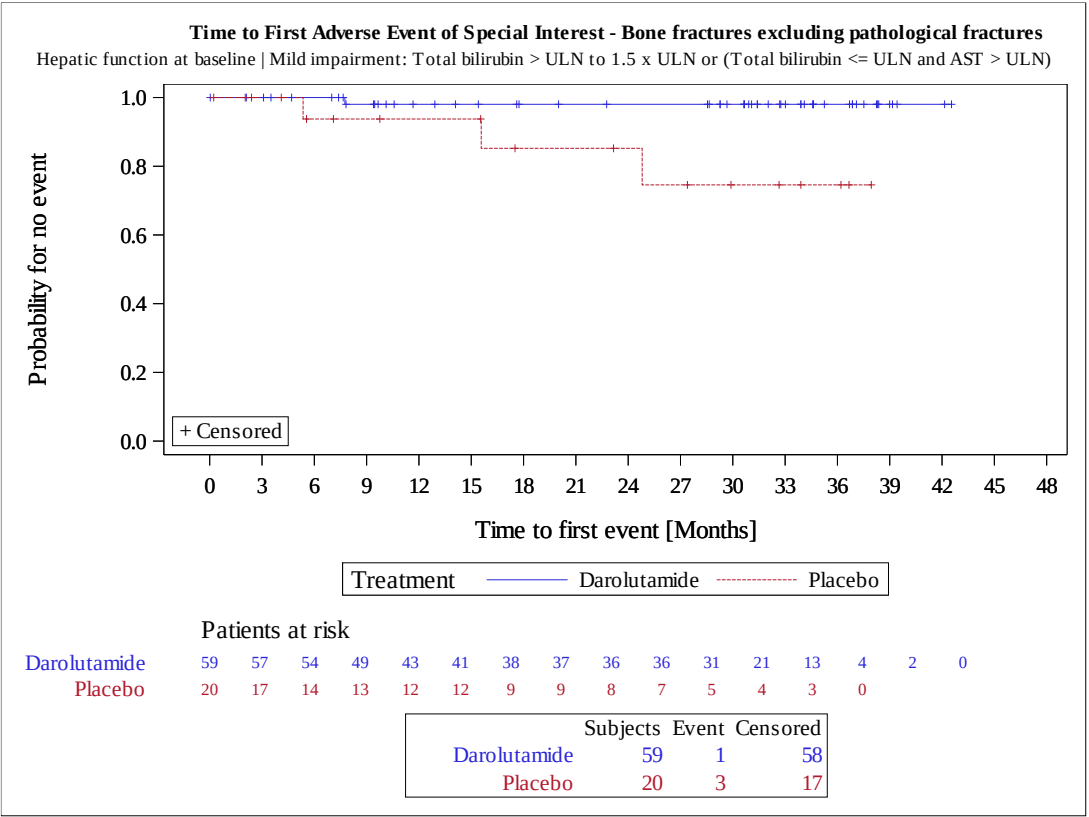
Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population
Figure 3.2.9.1.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Bone fractures excluding pathological fractures
(safety analysis set)

Final

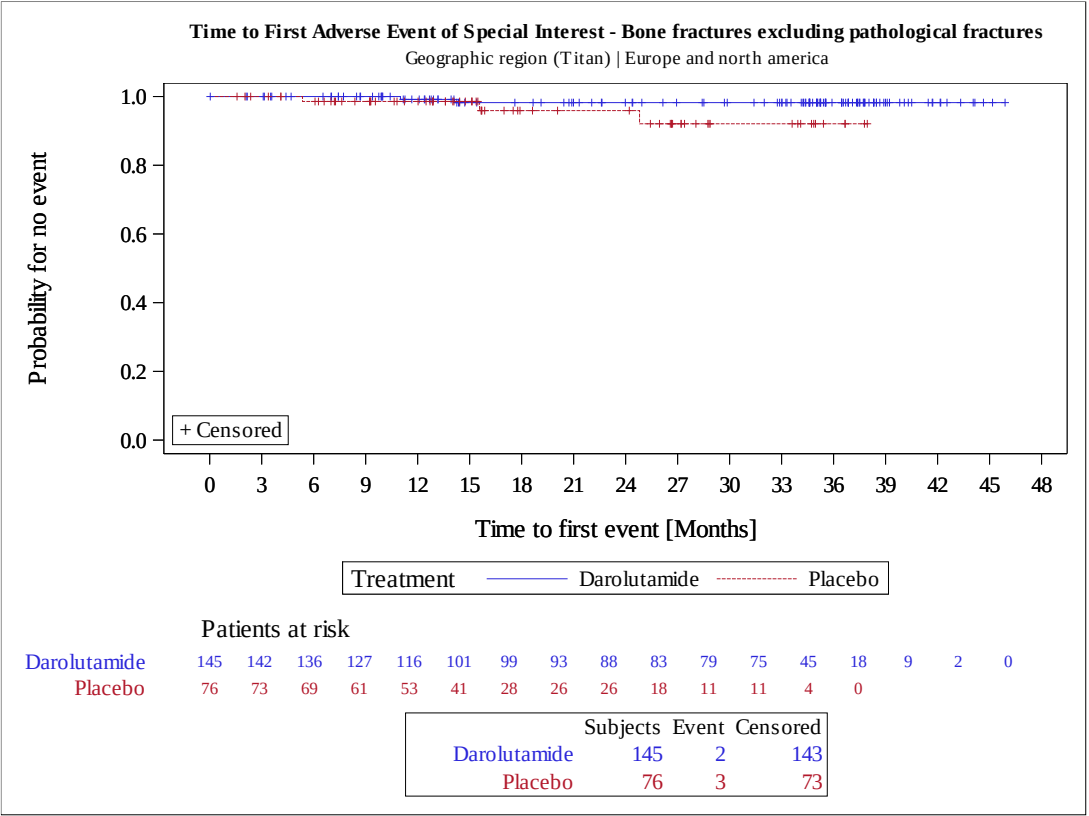


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population
Figure 3.2.9.1.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Bone fractures excluding pathological fractures
(safety analysis set)

Final

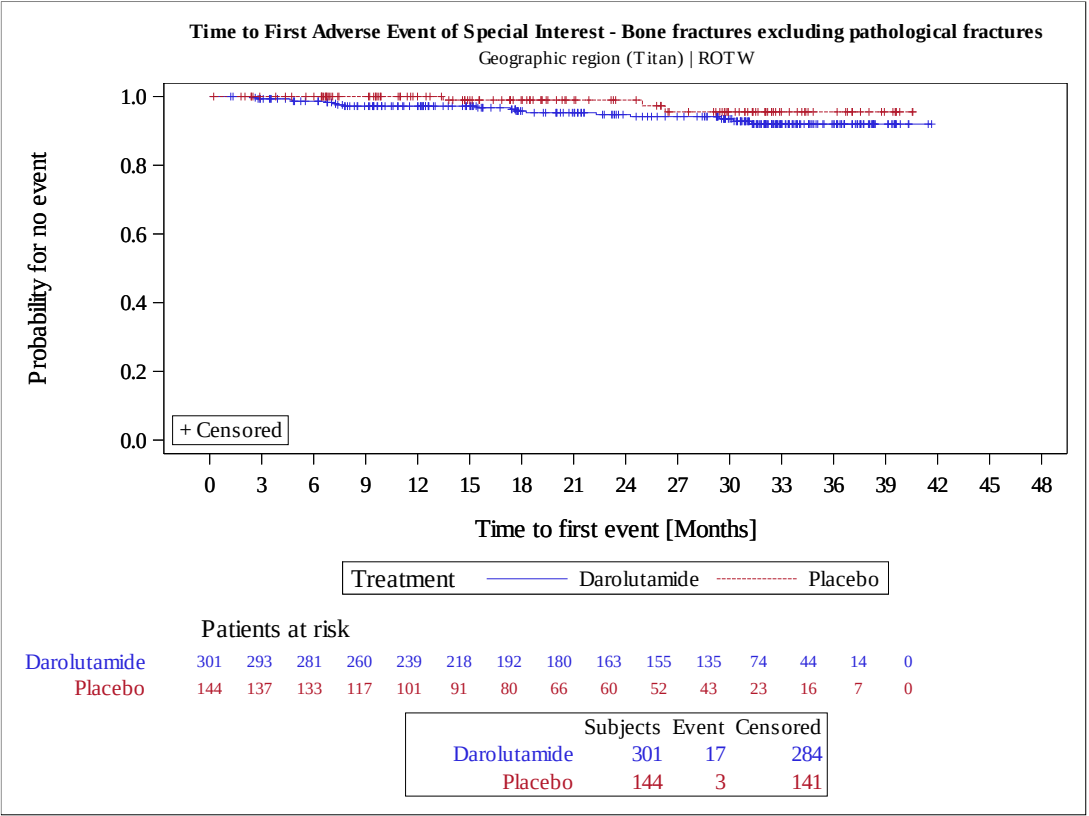


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.9.1.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Bone fractures excluding pathological fractures
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.9.2
Summary of Adverse Events of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	42 (9.4)	22 (10.0)
Number of censored patients, n (%)	404 (90.6)	198 (90.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.795	
95% CI	0.474, 1.333	
p-value	0.3825	
Odds Ratio	0.936	
95% CI	0.544, 1.611	
p-value	0.8103	
Relative Risk	0.942	
95% CI	0.577, 1.537	
p-value	0.8101	
Risk Difference	-0.583	
95% CI	-5.385, 4.219	
p-value	0.8119	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.2.1

Summary of Adverse Events of Special Interest - Diabetes mellitus and hyperglycemia - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	7/ 54 (13.0)	3/ 26 (11.5)	1.069	(0.276, 4.135)	0.9233	0.6842
No	35/392 (8.9)	19/194 (9.8)	0.755	(0.431, 1.322)	0.3234	
Received prior local therapy (from IWRS)						
Yes	7/ 81 (8.6)	5/ 39 (12.8)	0.487	(0.152, 1.558)	0.2161	0.4278
No	35/365 (9.6)	17/181 (9.4)	0.884	(0.495, 1.580)	0.6777	
Prior local radiotherapy and/or prostatectomy						
Yes	5/ 88 (5.7)	6/ 49 (12.2)	0.374	(0.113, 1.237)	0.0942	0.2069
No	37/358 (10.3)	16/171 (9.4)	0.935	(0.520, 1.683)	0.8226	
Age group						
<65 years	16/117 (13.7)	3/ 64 (4.7)	2.367	(0.687, 8.152)	0.1592	0.0620
65-74	14/193 (7.3)	15/ 95 (15.8)	0.393	(0.189, 0.816)	0.0093	
75-84	9/118 (7.6)	2/ 51 (3.9)	1.716	(0.370, 7.954)	0.4843	
>=85 years	3/ 18 (16.7)	2/ 10 (20.0)	0.668	(0.111, 4.007)	0.6569	
Race						
White	20/250 (8.0)	7/123 (5.7)	1.219	(0.514, 2.890)	0.6525	0.3411
Asian	12/144 (8.3)	11/ 65 (16.9)	0.401	(0.176, 0.911)	0.0240	
Black or African American	9/ 42 (21.4)	4/ 23 (17.4)	1.086	(0.334, 3.529)	0.8905	
Other	1/ 10 (10.0)	0/ 9 (0.0)	NE	(NE, NE)	NE	
Geographical region						
Asia	12/141 (8.5)	11/ 63 (17.5)	0.398	(0.175, 0.905)	0.0229	0.0989
Latin America	22/120 (18.3)	8/ 70 (11.4)	1.458	(0.649, 3.277)	0.3570	
Europe and Rest of the world	8/185 (4.3)	3/ 87 (3.4)	1.046	(0.276, 3.966)	0.9465	
Baseline PSA values by median						
< median of overall population	15/216 (6.9)	11/109 (10.1)	0.575	(0.264, 1.255)	0.1592	0.1560
>= median of overall population	25/219 (11.4)	9/108 (8.3)	1.218	(0.568, 2.614)	0.6116	
ECOG PS at baseline						
=0	28/235 (11.9)	9/ 96 (9.4)	1.141	(0.538, 2.420)	0.7313	0.1710
>=1	14/211 (6.6)	13/124 (10.5)	0.501	(0.235, 1.071)	0.0690	
Gleason score at initial diagnosis						
Gleason <8	14/125 (11.2)	10/ 64 (15.6)	0.636	(0.282, 1.436)	0.2712	0.3140
Gleason >=8	28/308 (9.1)	11/146 (7.5)	1.036	(0.515, 2.085)	0.9201	
Disease volume at baseline						
high	26/315 (8.3)	14/155 (9.0)	0.790	(0.412, 1.515)	0.4774	0.9501
low	16/131 (12.2)	8/ 65 (12.3)	0.811	(0.346, 1.903)	0.6294	
Renal function - eGFR at baseline						
Normal: eGFR >= 90 mL/min	24/221 (10.9)	12/102 (11.8)	0.761	(0.380, 1.524)	0.4394	0.8335
Mild impairment: 60 <= eGFR < 90 mL/min	15/179 (8.4)	7/ 90 (7.8)	0.887	(0.360, 2.186)	0.7943	
Moderate impairment: 30 <= eGFR < 60 mL/min	3/ 45 (6.7)	3/ 27 (11.1)	0.606	(0.122, 3.004)	0.5357	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.2.1

Summary of Adverse Events of Special Interest - Diabetes mellitus and hyperglycemia - Subgroup analysis (safety analysis set)

Final

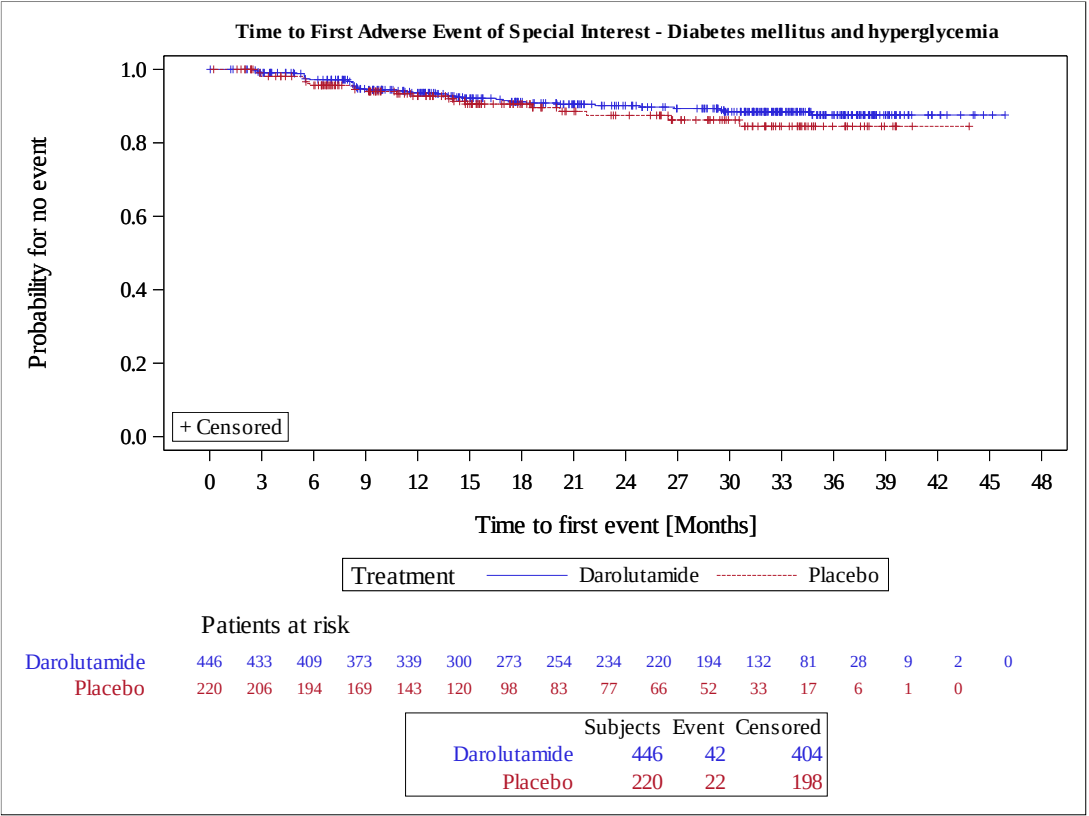
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		p-Value	Interaction p-Value
			Hazard Ratio	(95% CI)		
Hepatic function at baseline						0.6263
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	38/387 (9.8)	20/200 (10.0)	0.826	(0.480, 1.423)	0.4906	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	4/ 59 (6.8)	2/ 20 (10.0)	0.525	(0.096, 2.867)	0.4455	
Age Group (Titan)						0.0328
<65	16/117 (13.7)	3/ 64 (4.7)	2.367	(0.687, 8.152)	0.1592	
>=65 and <75	14/193 (7.3)	15/ 95 (15.8)	0.393	(0.189, 0.816)	0.0093	
>=75	12/136 (8.8)	4/ 61 (6.6)	1.163	(0.374, 3.611)	0.7940	
Geographic region (Titan)						0.8438
Europe and north america	5/145 (3.4)	3/ 76 (3.9)	0.698	(0.165, 2.946)	0.6229	
ROTW	37/301 (12.3)	19/144 (13.2)	0.808	(0.464, 1.406)	0.4500	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.9.2.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final

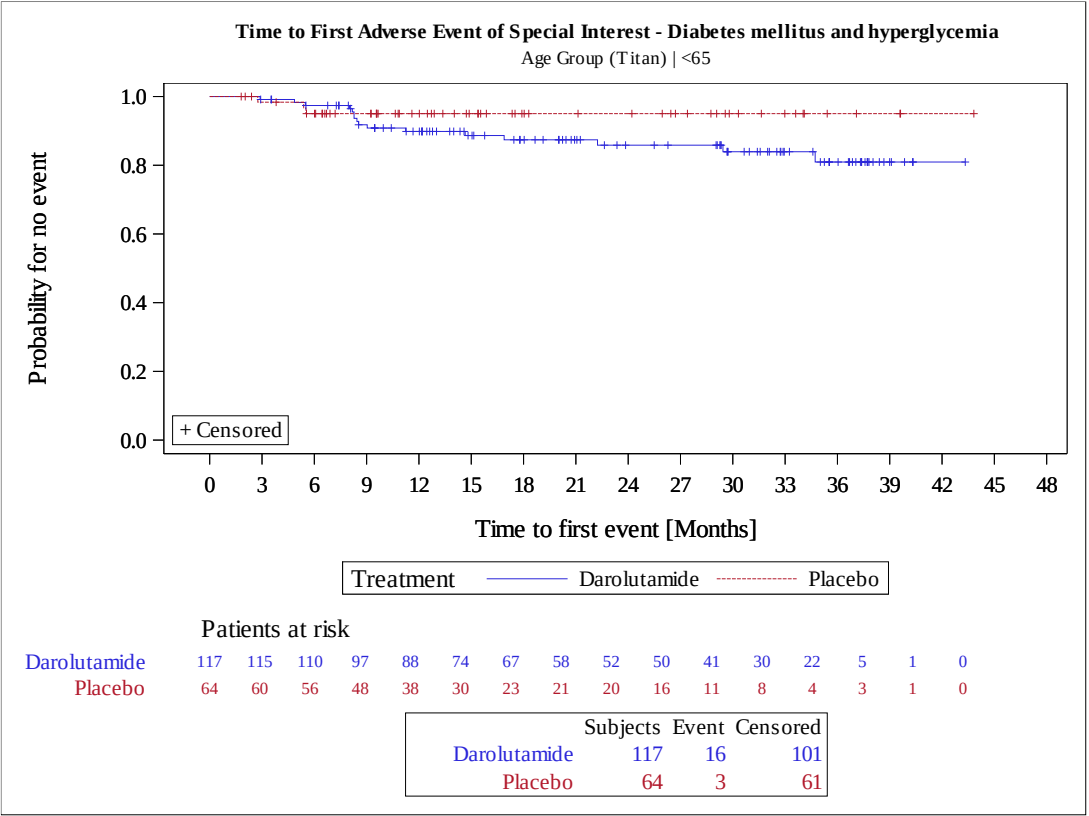


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.9.2.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final

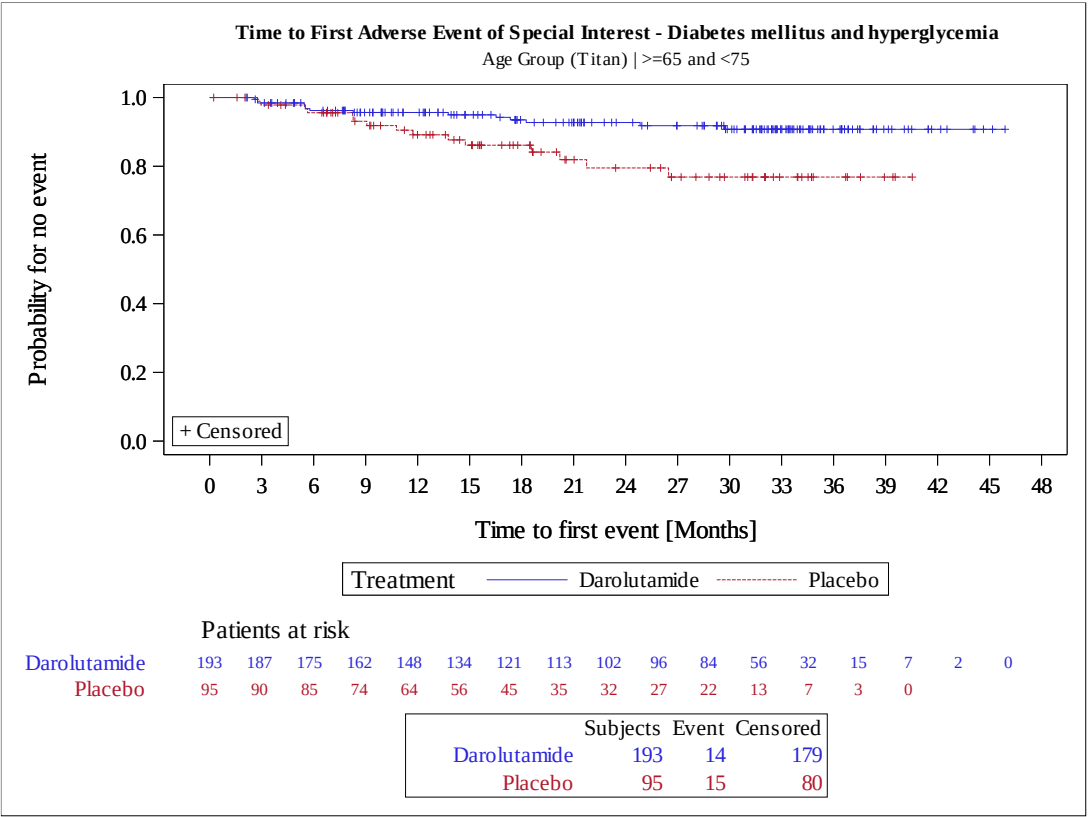


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.9.2.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final

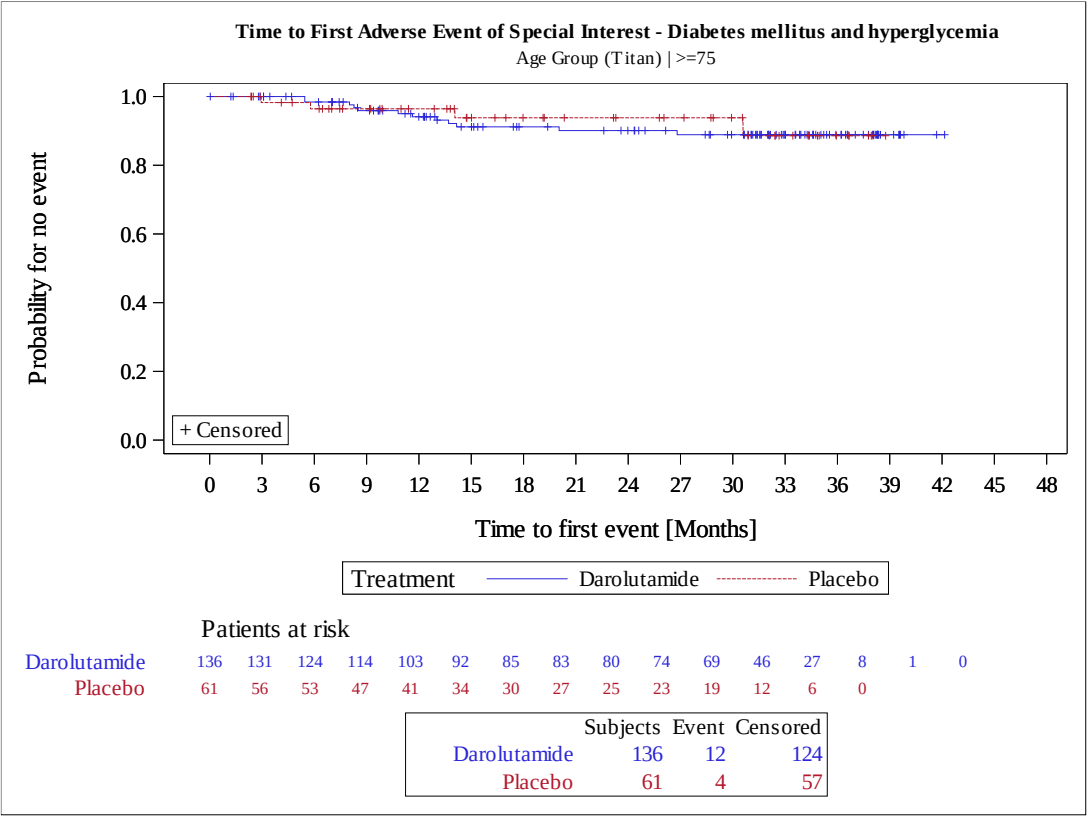


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.9.2.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.9.3
Summary of Adverse Events of Special Interest - Fall
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	6 (1.3)	3 (1.4)
Number of censored patients, n (%)	440 (98.7)	217 (98.6)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.843	
95% CI	0.210, 3.389	
p-value	0.8093	
Odds Ratio	0.986	
95% CI	0.244, 3.982	
p-value	0.9846	
Relative Risk	0.987	
95% CI	0.249, 3.908	
p-value	0.9846	
Risk Difference	-0.018	
95% CI	-1.887, 1.850	
p-value	0.9846	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.3.1

Summary of Adverse Events of Special Interest - Fall - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	1/ 54 (1.9)	1/ 26 (3.8)				
No	5/392 (1.3)	2/194 (1.0)				
Received prior local therapy (from IWRS)						
Yes	3/ 81 (3.7)	2/ 39 (5.1)				
No	3/365 (0.8)	1/181 (0.6)				
Prior local radiotherapy and/or prostatectomy						
Yes	1/ 88 (1.1)	2/ 49 (4.1)				
No	5/358 (1.4)	1/171 (0.6)				
Age group						
<65 years	0/117 (0.0)	0/ 64 (0.0)				
65-74	1/193 (0.5)	1/ 95 (1.1)				
75-84	4/118 (3.4)	2/ 51 (3.9)				
>=85 years	1/ 18 (5.6)	0/ 10 (0.0)				
Race						
White	5/250 (2.0)	2/123 (1.6)				
Asian	0/144 (0.0)	1/ 65 (1.5)				
Black or African American	1/ 42 (2.4)	0/ 23 (0.0)				
Other	0/ 10 (0.0)	0/ 9 (0.0)				
Geographical region						
Asia	0/141 (0.0)	1/ 63 (1.6)				
Latin America	3/120 (2.5)	1/ 70 (1.4)				
Europe and Rest of the world	3/185 (1.6)	1/ 87 (1.1)				
Baseline PSA values by median						
< median of overall population	4/216 (1.9)	2/109 (1.8)				
>= median of overall population	2/219 (0.9)	1/108 (0.9)				
ECOG PS at baseline						
=0	6/235 (2.6)	1/ 96 (1.0)				
>=1	0/211 (0.0)	2/124 (1.6)				
Gleason score at initial diagnosis						
Gleason <8	3/125 (2.4)	1/ 64 (1.6)				
Gleason >=8	3/308 (1.0)	2/146 (1.4)				
Disease volume at baseline						
high	4/315 (1.3)	3/155 (1.9)				
low	2/131 (1.5)	0/ 65 (0.0)				
Renal function - eGFR at baseline						
Normal: eGFR >= 90 mL/min	2/221 (0.9)	0/102 (0.0)				
Mild impairment: 60 <= eGFR < 90 mL/min	4/179 (2.2)	3/ 90 (3.3)				
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)				

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.9.3.1

Summary of Adverse Events of Special Interest - Fall - Subgroup analysis (safety analysis set)

Final

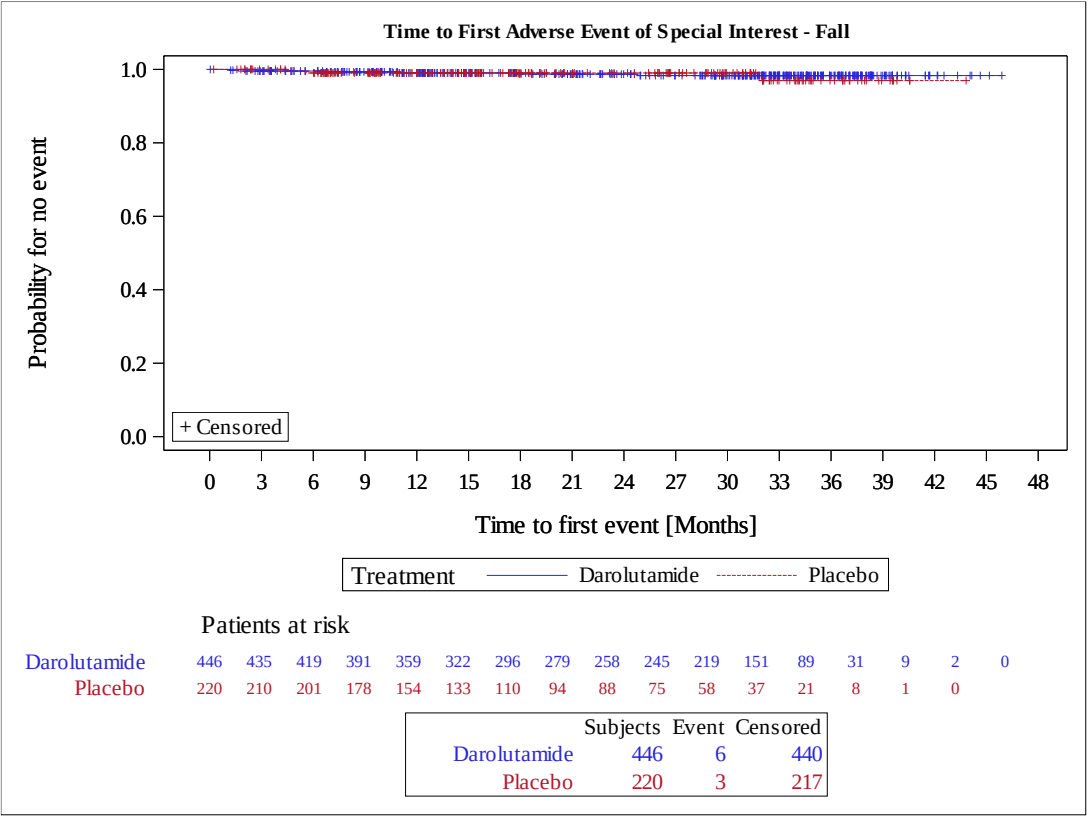
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	6/387 (1.6)	3/200 (1.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	1/193 (0.5)	1/ 95 (1.1)			
>=75	5/136 (3.7)	2/ 61 (3.3)			
Geographic region (Titan)					
Europe and north america	1/145 (0.7)	0/ 76 (0.0)			
ROTW	5/301 (1.7)	3/144 (2.1)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.9.3.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Fall
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.9.4
Summary of Adverse Events of Special Interest - Fatigue/ asthenic conditions
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	42 (9.4)	30 (13.6)
Number of censored patients, n (%)	404 (90.6)	190 (86.4)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (31.4, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.589	
95% CI	0.368, 0.942	
p-value	0.0256	
Odds Ratio	0.658	
95% CI	0.400, 1.085	
p-value	0.1009	
Relative Risk	0.691	
95% CI	0.445, 1.072	
p-value	0.0990	
Risk Difference	-4.219	
95% CI	-9.502, 1.064	
p-value	0.1175	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.9.4.1

Summary of Adverse Events of Special Interest - Fatigue/ asthenic conditions - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.3527
Yes	3/ 54 (5.6)	4/ 26 (15.4)	0.328	(0.073, 1.469)	0.1252	
No	39/392 (9.9)	26/194 (13.4)	0.626	(0.380, 1.031)	0.0635	
Received prior local therapy (from IWRS)						0.0444
Yes	7/ 81 (8.6)	10/ 39 (25.6)	0.249	(0.093, 0.666)	0.0028	
No	35/365 (9.6)	20/181 (11.0)	0.760	(0.438, 1.318)	0.3270	
Prior local radiotherapy and/or prostatectomy						0.4875
Yes	6/ 88 (6.8)	7/ 49 (14.3)	0.401	(0.134, 1.200)	0.0909	
No	36/358 (10.1)	23/171 (13.5)	0.638	(0.377, 1.079)	0.0908	
Age group						0.4111
<65 years	4/117 (3.4)	8/ 64 (12.5)	0.243	(0.073, 0.810)	0.0125	
65-74	19/193 (9.8)	14/ 95 (14.7)	0.583	(0.292, 1.165)	0.1224	
75-84	15/118 (12.7)	8/ 51 (15.7)	0.697	(0.295, 1.650)	0.4098	
>=85 years	4/ 18 (22.2)	0/ 10 (0.0)	NE	(NE, NE)	NE	
Race						0.9902
White	26/250 (10.4)	17/123 (13.8)	0.603	(0.326, 1.116)	0.1038	
Asian	12/144 (8.3)	8/ 65 (12.3)	0.624	(0.254, 1.531)	0.2981	
Black or African American	4/ 42 (9.5)	4/ 23 (17.4)	0.512	(0.128, 2.048)	0.3346	
Other	0/ 10 (0.0)	1/ 9 (11.1)	NE	(NE, NE)	NE	
Geographical region						0.9214
Asia	11/141 (7.8)	7/ 63 (11.1)	0.643	(0.248, 1.665)	0.3592	
Latin America	9/120 (7.5)	9/ 70 (12.9)	0.511	(0.203, 1.290)	0.1480	
Europe and Rest of the world	22/185 (11.9)	14/ 87 (16.1)	0.584	(0.297, 1.149)	0.1154	
Baseline PSA values by median						0.1921
< median of overall population	29/216 (13.4)	17/109 (15.6)	0.741	(0.406, 1.351)	0.3261	
>= median of overall population	12/219 (5.5)	13/108 (12.0)	0.379	(0.172, 0.836)	0.0125	
ECOG PS at baseline						0.7013
=0	24/235 (10.2)	13/ 96 (13.5)	0.656	(0.333, 1.290)	0.2185	
>=1	18/211 (8.5)	17/124 (13.7)	0.519	(0.266, 1.013)	0.0503	
Gleason score at initial diagnosis						0.8991
Gleason <8	10/125 (8.0)	7/ 64 (10.9)	0.631	(0.239, 1.663)	0.3476	
Gleason >=8	32/308 (10.4)	20/146 (13.7)	0.660	(0.377, 1.157)	0.1439	
Disease volume at baseline						0.1678
high	32/315 (10.2)	19/155 (12.3)	0.728	(0.412, 1.286)	0.2722	
low	10/131 (7.6)	11/ 65 (16.9)	0.364	(0.154, 0.863)	0.0169	
Renal function - eGFR at baseline						0.1198
Normal: eGFR >= 90 mL/min	24/221 (10.9)	10/102 (9.8)	0.954	(0.456, 1.997)	0.9012	
Mild impairment: 60 <= eGFR < 90 mL/min	15/179 (8.4)	13/ 90 (14.4)	0.489	(0.232, 1.034)	0.0559	
Moderate impairment: 30 <= eGFR < 60 mL/min	2/ 45 (4.4)	6/ 27 (22.2)	0.170	(0.034, 0.850)	0.0146	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.4.1

Summary of Adverse Events of Special Interest - Fatigue/ asthenic conditions - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.7699
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	37/387 (9.6)	28/200 (14.0)	0.573	(0.350, 0.938)	0.0250	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	5/ 59 (8.5)	2/ 20 (10.0)	0.769	(0.149, 3.967)	0.7535	
Age Group (Titan)						0.1223
<65	4/117 (3.4)	8/ 64 (12.5)	0.243	(0.073, 0.810)	0.0125	
>=65 and <75	19/193 (9.8)	14/ 95 (14.7)	0.583	(0.292, 1.165)	0.1224	
>=75	19/136 (14.0)	8/ 61 (13.1)	0.946	(0.413, 2.167)	0.8955	
Geographic region (Titan)						0.8131
Europe and north america	14/145 (9.7)	9/ 76 (11.8)	0.606	(0.259, 1.414)	0.2418	
ROTW	28/301 (9.3)	21/144 (14.6)	0.574	(0.326, 1.012)	0.0519	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

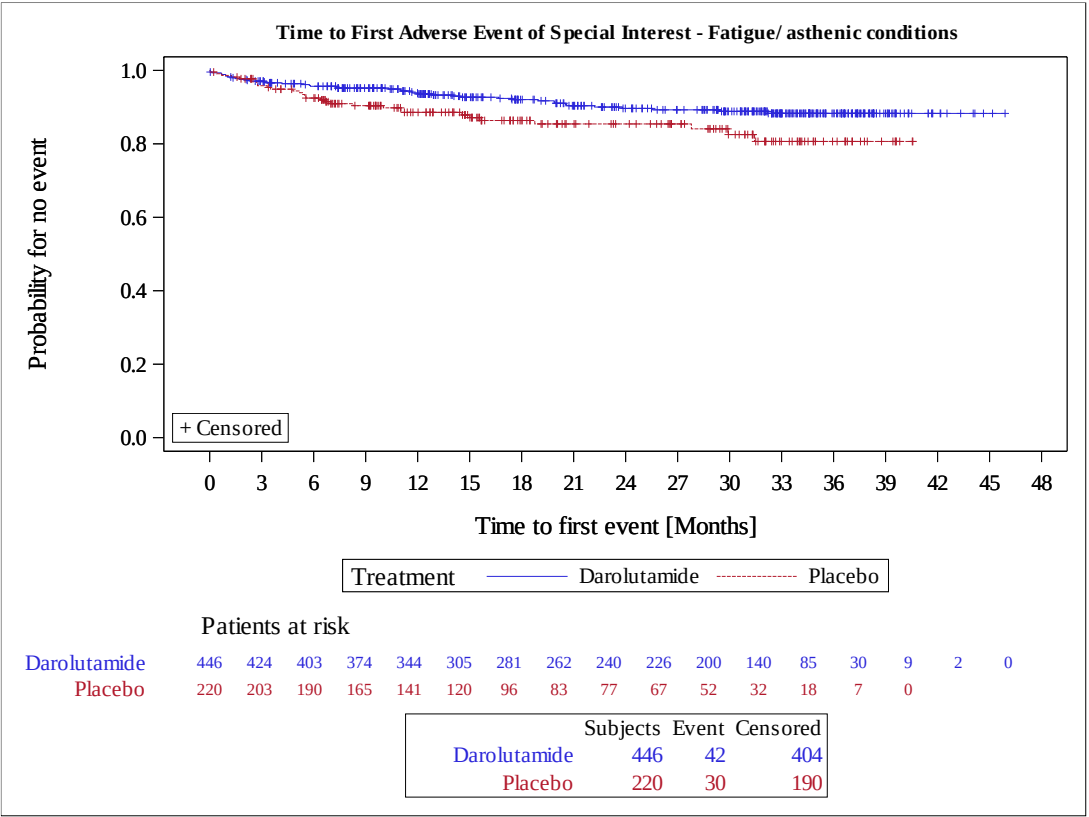
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.9.4.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Fatigue/ asthenic conditions
(safety analysis set)

Final

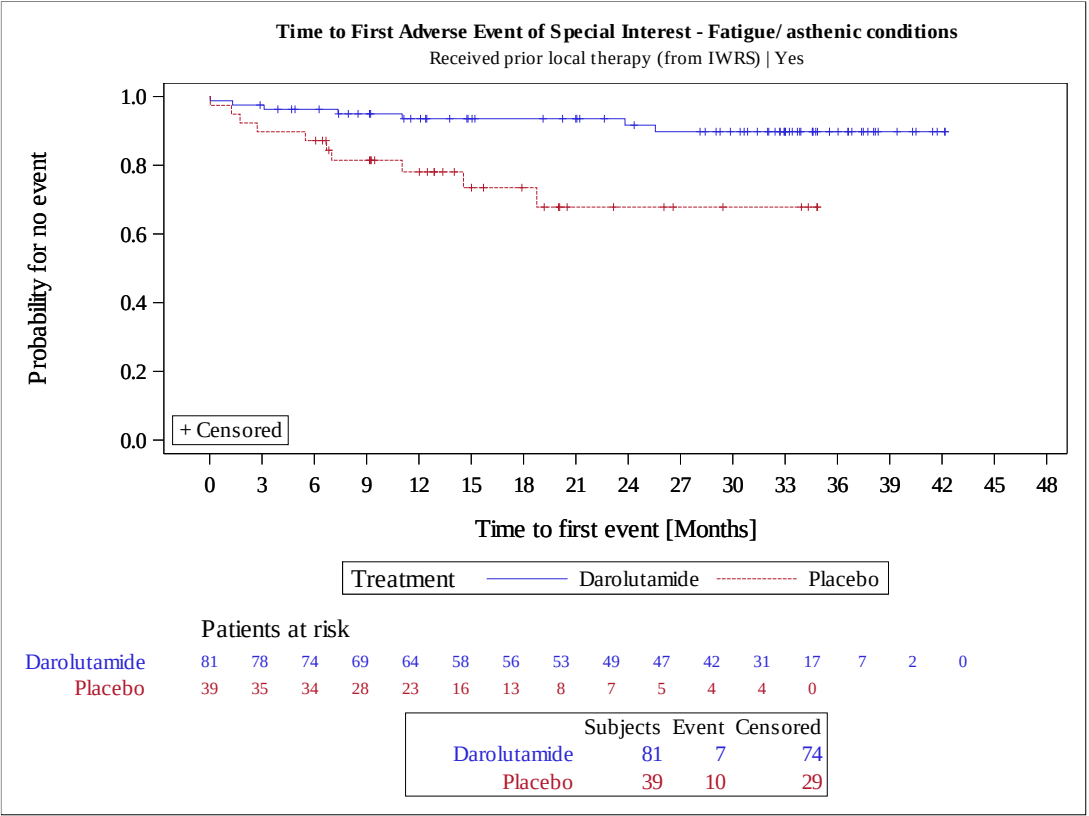


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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.9.4.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Fatigue/ asthenic conditions
(safety analysis set)

Final

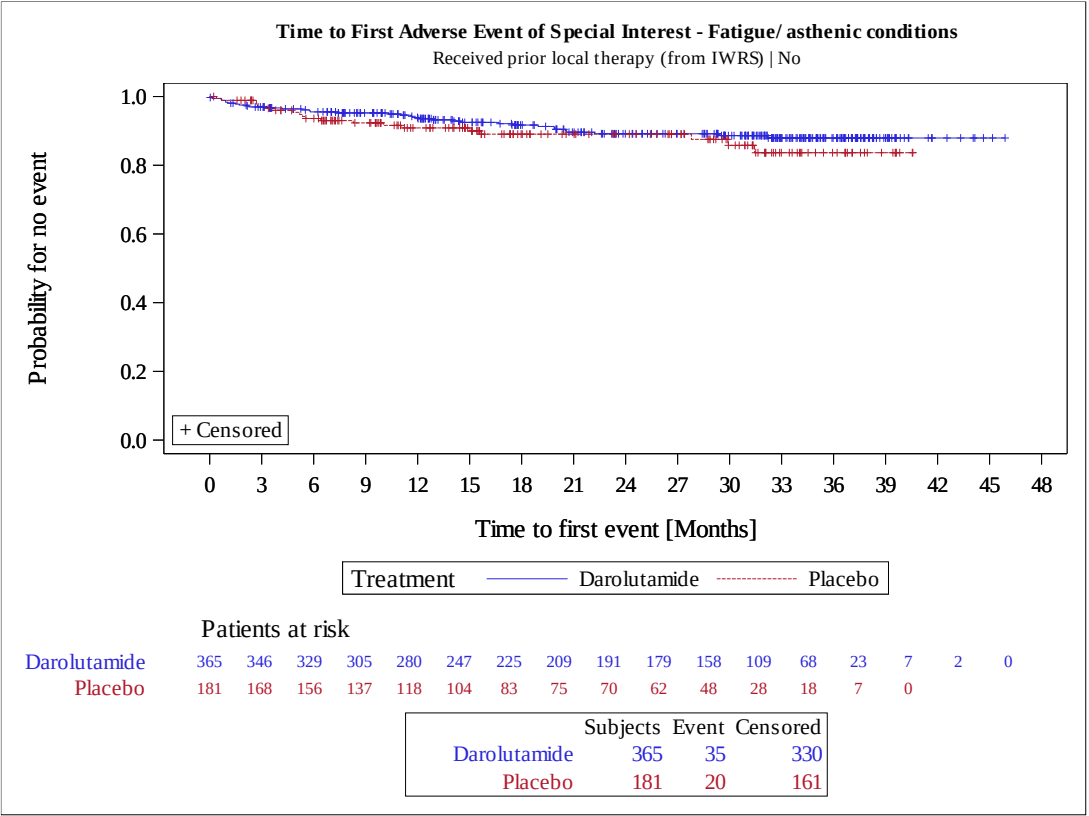


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.9.4.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Fatigue/ asthenic conditions
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.9.5
Summary of Adverse Events of Special Interest - Weight decreased
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	14 (3.1)	6 (2.7)
Number of censored patients, n (%)	432 (96.9)	214 (97.3)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.982	
95% CI	0.377, 2.559	
p-value	0.9702	
Odds Ratio	1.156	
95% CI	0.438, 3.050	
p-value	0.7698	
Relative Risk	1.151	
95% CI	0.448, 2.954	
p-value	0.7700	
Risk Difference	0.412	
95% CI	-2.281, 3.105	
p-value	0.7644	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.9.5.1

Summary of Adverse Events of Special Interest - Weight decreased - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.9871
Yes	0/ 54 (0.0)	1/ 26 (3.8)	NE	(NE, NE)	NE	
No	14/392 (3.6)	5/194 (2.6)	1.167	(0.419, 3.247)	0.7671	
Received prior local therapy (from IWRS)						0.9895
Yes	3/ 81 (3.7)	0/ 39 (0.0)	NE	(NE, NE)	NE	
No	11/365 (3.0)	6/181 (3.3)	0.797	(0.295, 2.158)	0.6551	
Prior local radiotherapy and/or prostatectomy						0.9883
Yes	2/ 88 (2.3)	0/ 49 (0.0)	NE	(NE, NE)	NE	
No	12/358 (3.4)	6/171 (3.5)	0.807	(0.302, 2.153)	0.6672	
Age group						0.9933
<65 years	2/117 (1.7)	1/ 64 (1.6)	0.943	(0.085, 10.430)	0.9615	
65-74	7/193 (3.6)	3/ 95 (3.2)	1.012	(0.261, 3.924)	0.9858	
75-84	4/118 (3.4)	2/ 51 (3.9)	0.741	(0.135, 4.047)	0.7279	
>=85 years	1/ 18 (5.6)	0/ 10 (0.0)	NE	(NE, NE)	NE	
Race						0.6373
White	7/250 (2.8)	1/123 (0.8)	2.741	(0.336, 22.330)	0.3259	
Asian	6/144 (4.2)	4/ 65 (6.2)	0.613	(0.173, 2.173)	0.4439	
Black or African American	1/ 42 (2.4)	1/ 23 (4.3)	0.500	(0.031, 7.994)	0.6171	
Other	0/ 10 (0.0)	0/ 9 (0.0)	NE	(NE, NE)	NE	
Geographical region						0.5681
Asia	6/141 (4.3)	4/ 63 (6.3)	0.609	(0.172, 2.158)	0.4375	
Latin America	2/120 (1.7)	1/ 70 (1.4)	0.989	(0.090, 10.917)	0.9926	
Europe and Rest of the world	6/185 (3.2)	1/ 87 (1.1)	2.280	(0.273, 19.020)	0.4336	
Baseline PSA values by median						0.3406
< median of overall population	10/216 (4.6)	3/109 (2.8)	1.465	(0.403, 5.329)	0.5596	
>= median of overall population	4/219 (1.8)	3/108 (2.8)	0.542	(0.121, 2.434)	0.4170	
ECOG PS at baseline						0.1381
=0	9/235 (3.8)	1/ 96 (1.0)	3.043	(0.385, 24.043)	0.2668	
>=1	5/211 (2.4)	5/124 (4.0)	0.523	(0.151, 1.809)	0.2973	
Gleason score at initial diagnosis						0.9897
Gleason <8	2/125 (1.6)	1/ 64 (1.6)	0.888	(0.080, 9.808)	0.9227	
Gleason >=8	11/308 (3.6)	5/146 (3.4)	0.900	(0.312, 2.596)	0.8460	
Disease volume at baseline						0.9923
high	13/315 (4.1)	6/155 (3.9)	0.912	(0.346, 2.403)	0.8518	
low	1/131 (0.8)	0/ 65 (0.0)	NE	(NE, NE)	NE	
Renal function - eGFR at baseline						0.5312
Normal: eGFR >= 90 mL/min	9/221 (4.1)	2/102 (2.0)	1.744	(0.376, 8.086)	0.4714	
Mild impairment: 60 <= eGFR < 90 mL/min	4/179 (2.2)	3/ 90 (3.3)	0.596	(0.133, 2.664)	0.4932	
Moderate impairment: 30 <= eGFR < 60 mL/min	1/ 45 (2.2)	1/ 27 (3.7)	0.504	(0.031, 8.141)	0.6226	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.9.5.1
Summary of Adverse Events of Special Interest - Weight decreased - Subgroup analysis
(safety analysis set)

Final

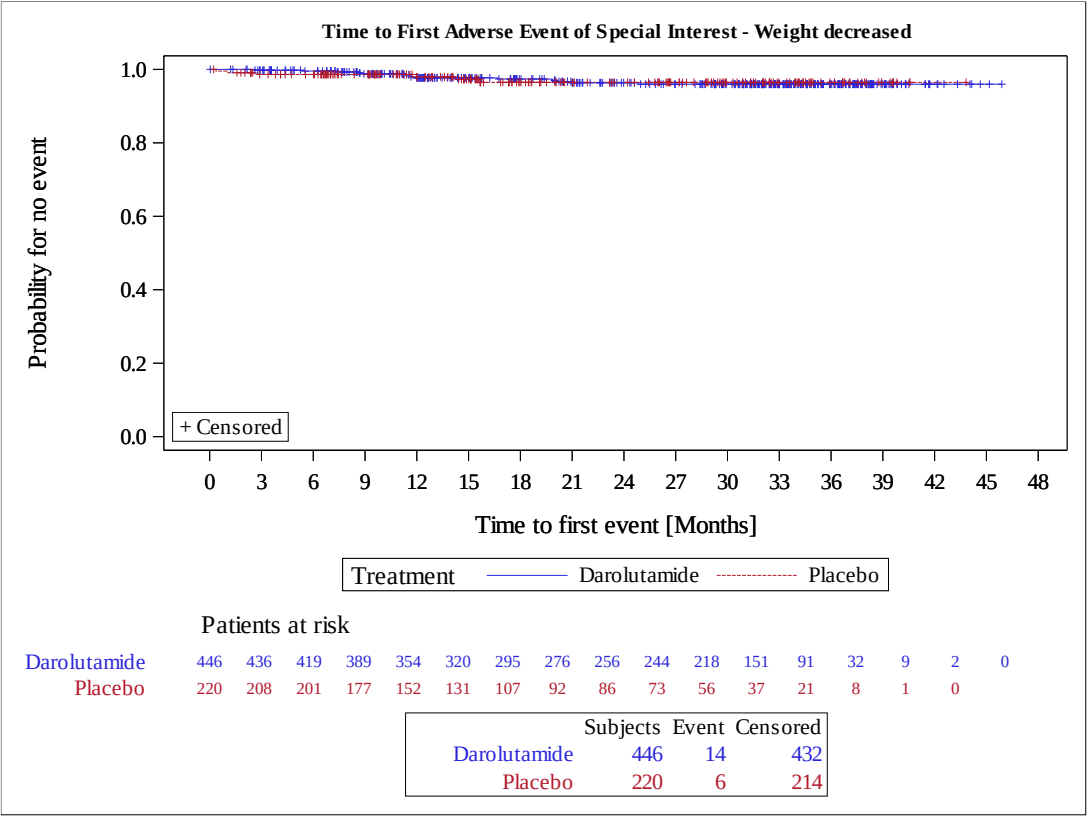
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.3671
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	13/387 (3.4)	5/200 (2.5)	1.131	(0.402, 3.178)	0.8159	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 59 (1.7)	1/ 20 (5.0)	0.308	(0.019, 4.925)	0.3777	
Age Group (Titan)						0.9909
<65	2/117 (1.7)	1/ 64 (1.6)	0.943	(0.085, 10.430)	0.9615	
>=65 and <75	7/193 (3.6)	3/ 95 (3.2)	1.012	(0.261, 3.924)	0.9858	
>=75	5/136 (3.7)	2/ 61 (3.3)	0.936	(0.181, 4.834)	0.9372	
Geographic region (Titan)						0.2668
Europe and north america	6/145 (4.1)	1/ 76 (1.3)	2.570	(0.308, 21.431)	0.3655	
ROTW	8/301 (2.7)	5/144 (3.5)	0.666	(0.217, 2.038)	0.4731	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population
Figure 3.2.9.5.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Weight decreased
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Study population
Table 3.2.9.6
Summary of Adverse Events of Special Interest - Rash
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	21 (4.7)	8 (3.6)
Number of censored patients, n (%)	425 (95.3)	212 (96.4)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.159	
95% CI	0.512, 2.624	
p-value	0.7225	
Odds Ratio	1.309	
95% CI	0.570, 3.005	
p-value	0.5248	
Relative Risk	1.295	
95% CI	0.583, 2.876	
p-value	0.5257	
Risk Difference	1.072	
95% CI	-2.087, 4.232	
p-value	0.5060	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population

Table 3.2.9.6.1

Summary of Adverse Events of Special Interest - Rash - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.9899
Yes	2/ 54 (3.7)	0/ 26 (0.0)	NE	(NE, NE)	NE	
No	19/392 (4.8)	8/194 (4.1)	1.042	(0.454, 2.387)	0.9228	
Received prior local therapy (from IWRS)						0.7305
Yes	4/ 81 (4.9)	1/ 39 (2.6)	1.823	(0.203, 16.365)	0.5862	
No	17/365 (4.7)	7/181 (3.9)	1.076	(0.445, 2.602)	0.8703	
Prior local radiotherapy and/or prostatectomy						0.6710
Yes	6/ 88 (6.8)	2/ 49 (4.1)	1.579	(0.318, 7.845)	0.5727	
No	15/358 (4.2)	6/171 (3.5)	1.051	(0.406, 2.719)	0.9174	
Age group						0.8236
<65 years	1/117 (0.9)	1/ 64 (1.6)	0.528	(0.033, 8.440)	0.6459	
65-74	9/193 (4.7)	3/ 95 (3.2)	1.324	(0.357, 4.911)	0.6732	
75-84	10/118 (8.5)	3/ 51 (5.9)	1.359	(0.374, 4.946)	0.6398	
>=85 years	1/ 18 (5.6)	1/ 10 (10.0)	0.448	(0.028, 7.296)	0.5629	
Race						0.8019
White	8/250 (3.2)	4/123 (3.3)	0.885	(0.264, 2.963)	0.8428	
Asian	12/144 (8.3)	3/ 65 (4.6)	1.749	(0.493, 6.198)	0.3806	
Black or African American	1/ 42 (2.4)	1/ 23 (4.3)	0.418	(0.026, 6.694)	0.5250	
Other	0/ 10 (0.0)	0/ 9 (0.0)	NE	(NE, NE)	NE	
Geographical region						0.5992
Asia	12/141 (8.5)	3/ 63 (4.8)	1.738	(0.490, 6.160)	0.3859	
Latin America	4/120 (3.3)	2/ 70 (2.9)	1.064	(0.194, 5.827)	0.9427	
Europe and Rest of the world	5/185 (2.7)	3/ 87 (3.4)	0.638	(0.149, 2.729)	0.5410	
Baseline PSA values by median						0.3944
< median of overall population	12/216 (5.6)	6/109 (5.5)	0.937	(0.351, 2.499)	0.8959	
>= median of overall population	9/219 (4.1)	2/108 (1.9)	1.886	(0.405, 8.771)	0.4109	
ECOG PS at baseline						0.6951
=0	14/235 (6.0)	4/ 96 (4.2)	1.300	(0.426, 3.962)	0.6437	
>=1	7/211 (3.3)	4/124 (3.2)	0.920	(0.269, 3.150)	0.8945	
Gleason score at initial diagnosis						0.5688
Gleason <8	3/125 (2.4)	2/ 64 (3.1)	0.699	(0.117, 4.188)	0.6933	
Gleason >=8	17/308 (5.5)	6/146 (4.1)	1.209	(0.475, 3.076)	0.6893	
Disease volume at baseline						0.6856
high	12/315 (3.8)	4/155 (2.6)	1.370	(0.441, 4.253)	0.5844	
low	9/131 (6.9)	4/ 65 (6.2)	0.951	(0.291, 3.110)	0.9337	
Renal function - eGFR at baseline						0.8855
Normal: eGFR >= 90 mL/min	13/221 (5.9)	4/102 (3.9)	1.374	(0.448, 4.218)	0.5767	
Mild impairment: 60 <= eGFR < 90 mL/min	8/179 (4.5)	4/ 90 (4.4)	0.833	(0.248, 2.800)	0.7678	
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)	NE	(NE, NE)	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population

Table 3.2.9.6.1

Summary of Adverse Events of Special Interest - Rash - Subgroup analysis
(safety analysis set)

Final

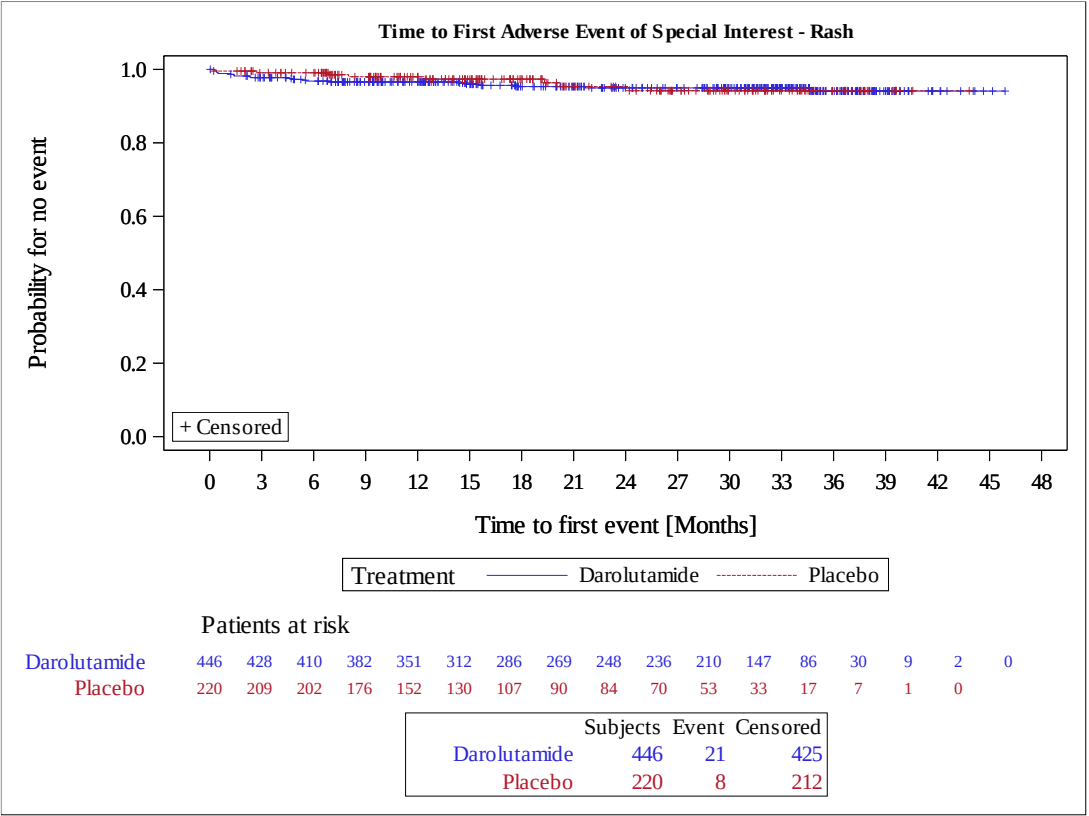
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Hepatic function at baseline						0.9455
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	17/387 (4.4)	7/200 (3.5)	1.127	(0.466, 2.726)	0.7914	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	4/ 59 (6.8)	1/ 20 (5.0)	1.191	(0.133, 10.666)	0.8758	
Age Group (Titan)						0.7681
<65	1/117 (0.9)	1/ 64 (1.6)	0.528	(0.033, 8.440)	0.6459	
>=65 and <75	9/193 (4.7)	3/ 95 (3.2)	1.324	(0.357, 4.911)	0.6732	
>=75	11/136 (8.1)	4/ 61 (6.6)	1.154	(0.367, 3.629)	0.8065	
Geographic region (Titan)						0.9842
Europe and north america	0/145 (0.0)	2/ 76 (2.6)	NE	(NE, NE)	NE	
ROTW	21/301 (7.0)	6/144 (4.2)	1.544	(0.622, 3.830)	0.3446	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Figure 3.2.9.6.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Rash
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population
Table 3.2.9.7
Summary of Adverse Events of Special Interest - Seizure
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	446 (100.0)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Table 3.2.9.7.1

Summary of Adverse Events of Special Interest - Seizure - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/211 (0.0)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/315 (0.0)	0/155 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population

Table 3.2.9.7.1

Summary of Adverse Events of Special Interest - Seizure - Subgroup analysis (safety analysis set)

Final

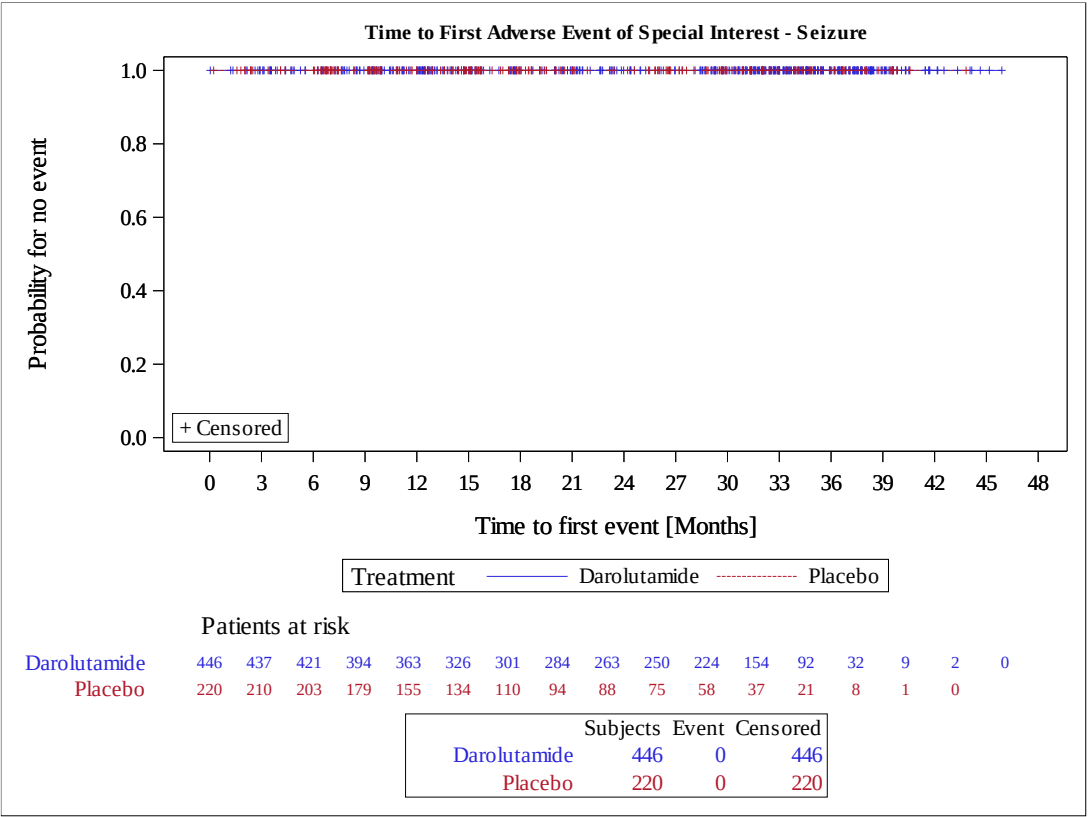
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Figure 3.2.9.7.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Seizure
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Study population
Table 3.2.9.8
Summary of Adverse Events of Special Interest - Hypertension
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	48 (10.8)	22 (10.0)
Number of censored patients, n (%)	398 (89.2)	198 (90.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.877	
95% CI	0.528, 1.458	
p-value	0.6132	
Odds Ratio	1.085	
95% CI	0.637, 1.849	
p-value	0.7629	
Relative Risk	1.076	
95% CI	0.667, 1.736	
p-value	0.7633	
Risk Difference	0.762	
95% CI	-4.135, 5.660	
p-value	0.7603	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.2.9.8.1

Summary of Adverse Events of Special Interest - Hypertension - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.6298
Yes	6/ 54 (11.1)	2/ 26 (7.7)	1.318	(0.266, 6.537)	0.7342	
No	42/392 (10.7)	20/194 (10.3)	0.833	(0.487, 1.424)	0.5038	
Received prior local therapy (from IWRS)						0.8920
Yes	9/ 81 (11.1)	4/ 39 (10.3)	0.897	(0.272, 2.955)	0.8585	
No	39/365 (10.7)	18/181 (9.9)	0.887	(0.506, 1.554)	0.6746	
Prior local radiotherapy and/or prostatectomy						0.8892
Yes	10/ 88 (11.4)	5/ 49 (10.2)	1.039	(0.355, 3.045)	0.9440	
No	38/358 (10.6)	17/171 (9.9)	0.838	(0.471, 1.490)	0.5456	
Age group						0.8442
<65 years	13/117 (11.1)	4/ 64 (6.3)	1.496	(0.486, 4.602)	0.4789	
65-74	22/193 (11.4)	12/ 95 (12.6)	0.742	(0.366, 1.505)	0.4062	
75-84	11/118 (9.3)	5/ 51 (9.8)	0.770	(0.265, 2.235)	0.6297	
>=85 years	2/ 18 (11.1)	1/ 10 (10.0)	0.970	(0.087, 10.821)	0.9806	
Race						0.5206
White	22/250 (8.8)	8/123 (6.5)	1.063	(0.470, 2.406)	0.8827	
Asian	17/144 (11.8)	5/ 65 (7.7)	1.345	(0.494, 3.657)	0.5602	
Black or African American	9/ 42 (21.4)	8/ 23 (34.8)	0.513	(0.197, 1.335)	0.1626	
Other	0/ 10 (0.0)	1/ 9 (11.1)	NE	(NE, NE)	NE	
Geographical region						0.4865
Asia	17/141 (12.1)	5/ 63 (7.9)	1.335	(0.491, 3.630)	0.5701	
Latin America	14/120 (11.7)	11/ 70 (15.7)	0.630	(0.285, 1.389)	0.2474	
Europe and Rest of the world	17/185 (9.2)	6/ 87 (6.9)	0.989	(0.385, 2.539)	0.9815	
Baseline PSA values by median						0.5467
< median of overall population	20/216 (9.3)	11/109 (10.1)	0.741	(0.353, 1.553)	0.4251	
>= median of overall population	28/219 (12.8)	11/108 (10.2)	1.042	(0.517, 2.101)	0.9068	
ECOG PS at baseline						0.5446
=0	29/235 (12.3)	13/ 96 (13.5)	0.748	(0.388, 1.443)	0.3850	
>=1	19/211 (9.0)	9/124 (7.3)	1.042	(0.469, 2.314)	0.9193	
Gleason score at initial diagnosis						0.7823
Gleason <8	14/125 (11.2)	6/ 64 (9.4)	0.948	(0.361, 2.486)	0.9132	
Gleason >=8	33/308 (10.7)	16/146 (11.0)	0.823	(0.452, 1.501)	0.5252	
Disease volume at baseline						0.9745
high	30/315 (9.5)	14/155 (9.0)	0.877	(0.463, 1.662)	0.6875	
low	18/131 (13.7)	8/ 65 (12.3)	0.857	(0.370, 1.984)	0.7189	
Renal function - eGFR at baseline						0.9770
Normal: eGFR >= 90 mL/min	25/221 (11.3)	10/102 (9.8)	0.975	(0.467, 2.036)	0.9466	
Mild impairment: 60 <= eGFR < 90 mL/min	18/179 (10.1)	8/ 90 (8.9)	0.912	(0.395, 2.108)	0.8293	
Moderate impairment: 30 <= eGFR < 60 mL/min	5/ 45 (11.1)	3/ 27 (11.1)	0.608	(0.130, 2.852)	0.5245	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population

Table 3.2.9.8.1

Summary of Adverse Events of Special Interest - Hypertension - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		p-Value	Interaction p-Value
			Hazard Ratio	(95% CI)		
Hepatic function at baseline						0.8254
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	41/387 (10.6)	20/200 (10.0)	0.854	(0.498, 1.464)	0.5658	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	7/ 59 (11.9)	2/ 20 (10.0)	1.015	(0.211, 4.891)	0.9847	
Age Group (Titan)						0.6631
<65	13/117 (11.1)	4/ 64 (6.3)	1.496	(0.486, 4.602)	0.4789	
>=65 and <75	22/193 (11.4)	12/ 95 (12.6)	0.742	(0.366, 1.505)	0.4062	
>=75	13/136 (9.6)	6/ 61 (9.8)	0.797	(0.301, 2.113)	0.6476	
Geographic region (Titan)						0.9269
Europe and north america	12/145 (8.3)	5/ 76 (6.6)	0.873	(0.301, 2.528)	0.8019	
ROTW	36/301 (12.0)	17/144 (11.8)	0.883	(0.495, 1.574)	0.6717	

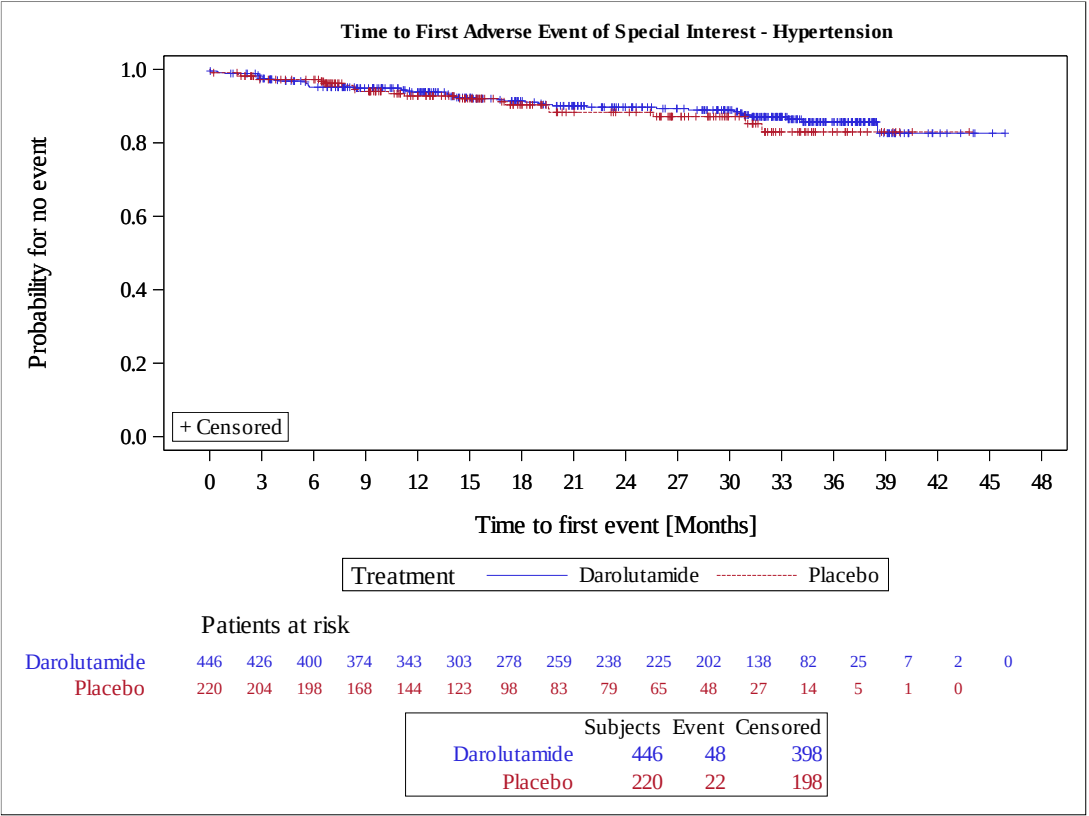
Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Figure 3.2.9.8.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Hypertension
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Study population
Table 3.2.9.9
Summary of Adverse Events of Special Interest - Vasodilatation and flushing
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	41 (9.2)	16 (7.3)
Number of censored patients, n (%)	405 (90.8)	204 (92.7)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.225	
95% CI	0.687, 2.183	
p-value	0.4910	
Odds Ratio	1.291	
95% CI	0.707, 2.356	
p-value	0.4058	
Relative Risk	1.264	
95% CI	0.726, 2.201	
p-value	0.4078	
Risk Difference	1.920	
95% CI	-2.435, 6.275	
p-value	0.3875	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.2.9.9.1

Summary of Adverse Events of Special Interest - Vasodilatation and flushing - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.9850
Yes	6/ 54 (11.1)	0/ 26 (0.0)	NE	(NE, NE)	NE	
No	35/392 (8.9)	16/194 (8.2)	1.042	(0.577, 1.884)	0.8900	
Received prior local therapy (from IWRS)						0.0485
Yes	6/ 81 (7.4)	6/ 39 (15.4)	0.456	(0.147, 1.415)	0.1629	
No	35/365 (9.6)	10/181 (5.5)	1.697	(0.840, 3.427)	0.1357	
Prior local radiotherapy and/or prostatectomy						0.8804
Yes	7/ 88 (8.0)	3/ 49 (6.1)	1.353	(0.350, 5.233)	0.6603	
No	34/358 (9.5)	13/171 (7.6)	1.186	(0.626, 2.249)	0.5998	
Age group						0.2284
<65 years	13/117 (11.1)	2/ 64 (3.1)	3.401	(0.766, 15.088)	0.0869	
65-74	17/193 (8.8)	12/ 95 (12.6)	0.662	(0.316, 1.387)	0.2706	
75-84	9/118 (7.6)	2/ 51 (3.9)	1.942	(0.419, 8.987)	0.3871	
>=85 years	2/ 18 (11.1)	0/ 10 (0.0)	NE	(NE, NE)	NE	
Race						0.6353
White	30/250 (12.0)	8/123 (6.5)	1.827	(0.837, 3.987)	0.1240	
Asian	2/144 (1.4)	1/ 65 (1.5)	0.863	(0.078, 9.524)	0.9044	
Black or African American	9/ 42 (21.4)	6/ 23 (26.1)	0.747	(0.265, 2.105)	0.5795	
Other	0/ 10 (0.0)	1/ 9 (11.1)	NE	(NE, NE)	NE	
Geographical region						0.9363
Asia	2/141 (1.4)	1/ 63 (1.6)	0.853	(0.077, 9.408)	0.8964	
Latin America	18/120 (15.0)	8/ 70 (11.4)	1.251	(0.544, 2.878)	0.5977	
Europe and Rest of the world	21/185 (11.4)	7/ 87 (8.0)	1.412	(0.600, 3.324)	0.4263	
Baseline PSA values by median						0.0768
< median of overall population	14/216 (6.5)	10/109 (9.2)	0.664	(0.295, 1.497)	0.3203	
>= median of overall population	24/219 (11.0)	6/108 (5.6)	1.976	(0.807, 4.834)	0.1283	
ECOG PS at baseline						0.2888
=0	32/235 (13.6)	9/ 96 (9.4)	1.421	(0.678, 2.977)	0.3491	
>=1	9/211 (4.3)	7/124 (5.6)	0.720	(0.268, 1.937)	0.5137	
Gleason score at initial diagnosis						0.3672
Gleason <8	15/125 (12.0)	4/ 64 (6.3)	1.944	(0.645, 5.859)	0.2284	
Gleason >=8	25/308 (8.1)	11/146 (7.5)	1.038	(0.511, 2.112)	0.9163	
Disease volume at baseline						0.8727
high	29/315 (9.2)	11/155 (7.1)	1.262	(0.630, 2.527)	0.5104	
low	12/131 (9.2)	5/ 65 (7.7)	1.147	(0.404, 3.258)	0.7972	
Renal function - eGFR at baseline						0.3453
Normal: eGFR >= 90 mL/min	22/221 (10.0)	11/102 (10.8)	0.855	(0.414, 1.765)	0.6718	
Mild impairment: 60 <= eGFR < 90 mL/min	15/179 (8.4)	3/ 90 (3.3)	2.530	(0.732, 8.743)	0.1279	
Moderate impairment: 30 <= eGFR < 60 mL/min	3/ 45 (6.7)	2/ 27 (7.4)	0.914	(0.153, 5.473)	0.9216	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.9.1

Summary of Adverse Events of Special Interest - Vasodilatation and flushing - Subgroup analysis (safety analysis set)

Final

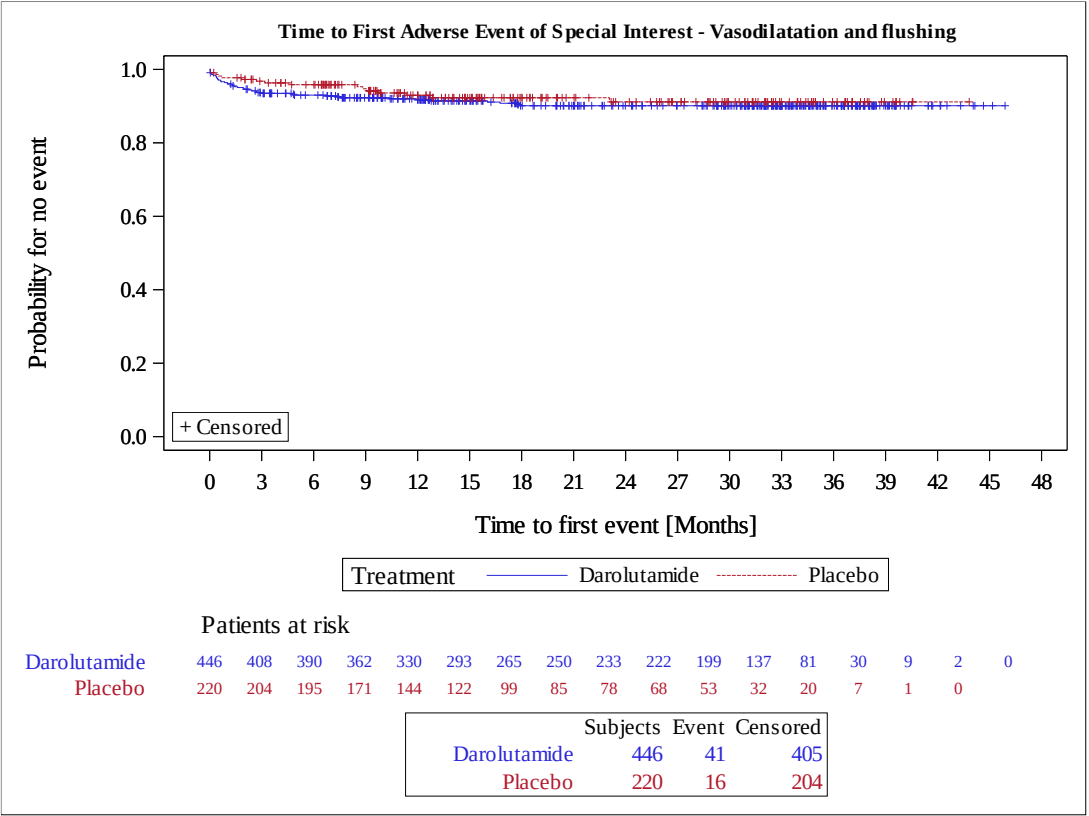
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					0.9778
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	37/387 (9.6)	15/200 (7.5)	1.233	(0.677, 2.249)	0.4923
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	4/ 59 (6.8)	1/ 20 (5.0)	1.258	(0.140, 11.266)	0.8370
Age Group (Titan)					0.0841
<65	13/117 (11.1)	2/ 64 (3.1)	3.401	(0.766, 15.088)	0.0869
>=65 and <75	17/193 (8.8)	12/ 95 (12.6)	0.662	(0.316, 1.387)	0.2706
>=75	11/136 (8.1)	2/ 61 (3.3)	2.504	(0.555, 11.298)	0.2157
Geographic region (Titan)					0.5118
Europe and north america	13/145 (9.0)	4/ 76 (5.3)	1.697	(0.553, 5.210)	0.3496
ROTW	28/301 (9.3)	12/144 (8.3)	1.068	(0.543, 2.101)	0.8489

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.9.9.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Vasodilatation and flushing
(safety analysis set)

Final

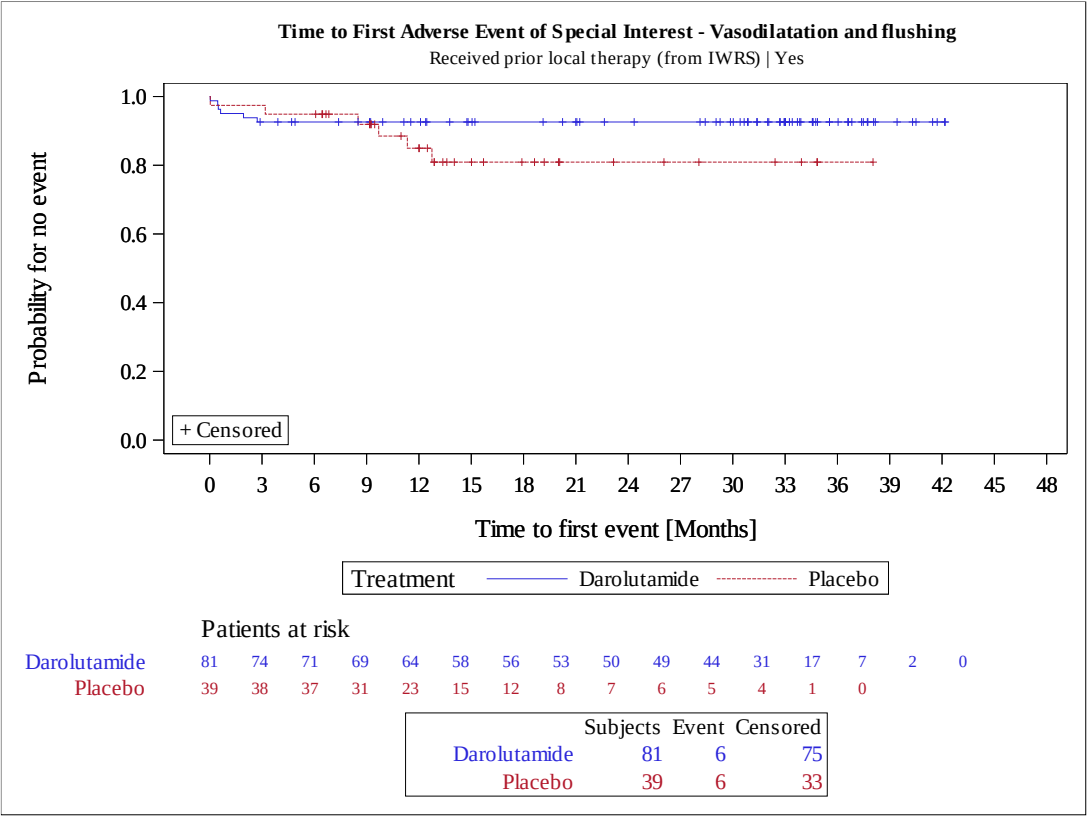


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.9.9.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Vasodilatation and flushing
(safety analysis set)

Final

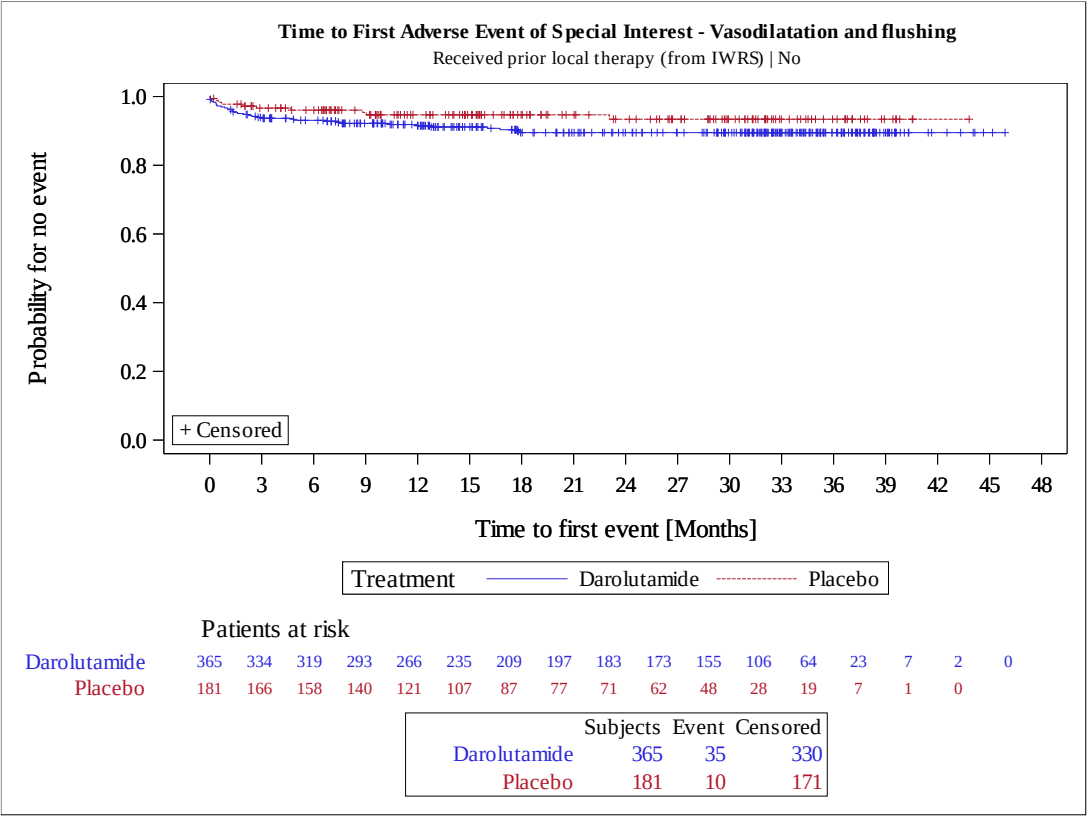


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.9.9.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Vasodilatation and flushing
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.9.10
Summary of Adverse Events of Special Interest - Mental impairment disorders
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	7 (1.6)	1 (0.5)
Number of censored patients, n (%)	439 (98.4)	219 (99.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	3.070	
95% CI	0.377, 24.977	
p-value	0.2694	
Odds Ratio	3.492	
95% CI	0.427, 28.561	
p-value	0.2435	
Relative Risk	3.453	
95% CI	0.427, 27.890	
p-value	0.2450	
Risk Difference	1.115	
95% CI	-0.341, 2.571	
p-value	0.1335	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.10.1

Summary of Adverse Events of Special Interest - Mental impairment disorders - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	1/ 54 (1.9)	1/ 26 (3.8)				
No	6/392 (1.5)	0/194 (0.0)				
Received prior local therapy (from IWRS)						
Yes	3/ 81 (3.7)	1/ 39 (2.6)				
No	4/365 (1.1)	0/181 (0.0)				
Prior local radiotherapy and/or prostatectomy						
Yes	3/ 88 (3.4)	1/ 49 (2.0)				
No	4/358 (1.1)	0/171 (0.0)				
Age group						
<65 years	0/117 (0.0)	0/ 64 (0.0)				
65-74	4/193 (2.1)	1/ 95 (1.1)				
75-84	3/118 (2.5)	0/ 51 (0.0)				
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)				
Race						
White	5/250 (2.0)	1/123 (0.8)				
Asian	0/144 (0.0)	0/ 65 (0.0)				
Black or African American	2/ 42 (4.8)	0/ 23 (0.0)				
Other	0/ 10 (0.0)	0/ 9 (0.0)				
Geographical region						
Asia	0/141 (0.0)	0/ 63 (0.0)				
Latin America	3/120 (2.5)	0/ 70 (0.0)				
Europe and Rest of the world	4/185 (2.2)	1/ 87 (1.1)				
Baseline PSA values by median						
< median of overall population	3/216 (1.4)	1/109 (0.9)				
>= median of overall population	3/219 (1.4)	0/108 (0.0)				
ECOG PS at baseline						
=0	5/235 (2.1)	1/ 96 (1.0)				
>=1	2/211 (0.9)	0/124 (0.0)				
Gleason score at initial diagnosis						
Gleason <8	5/125 (4.0)	0/ 64 (0.0)				
Gleason >=8	2/308 (0.6)	1/146 (0.7)				
Disease volume at baseline						
high	3/315 (1.0)	1/155 (0.6)				
low	4/131 (3.1)	0/ 65 (0.0)				
Renal function - eGFR at baseline						
Normal: eGFR >= 90 mL/min	5/221 (2.3)	1/102 (1.0)				
Mild impairment: 60 <= eGFR < 90 mL/min	2/179 (1.1)	0/ 90 (0.0)				
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)				

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.10.1

Summary of Adverse Events of Special Interest - Mental impairment disorders - Subgroup analysis (safety analysis set)

Final

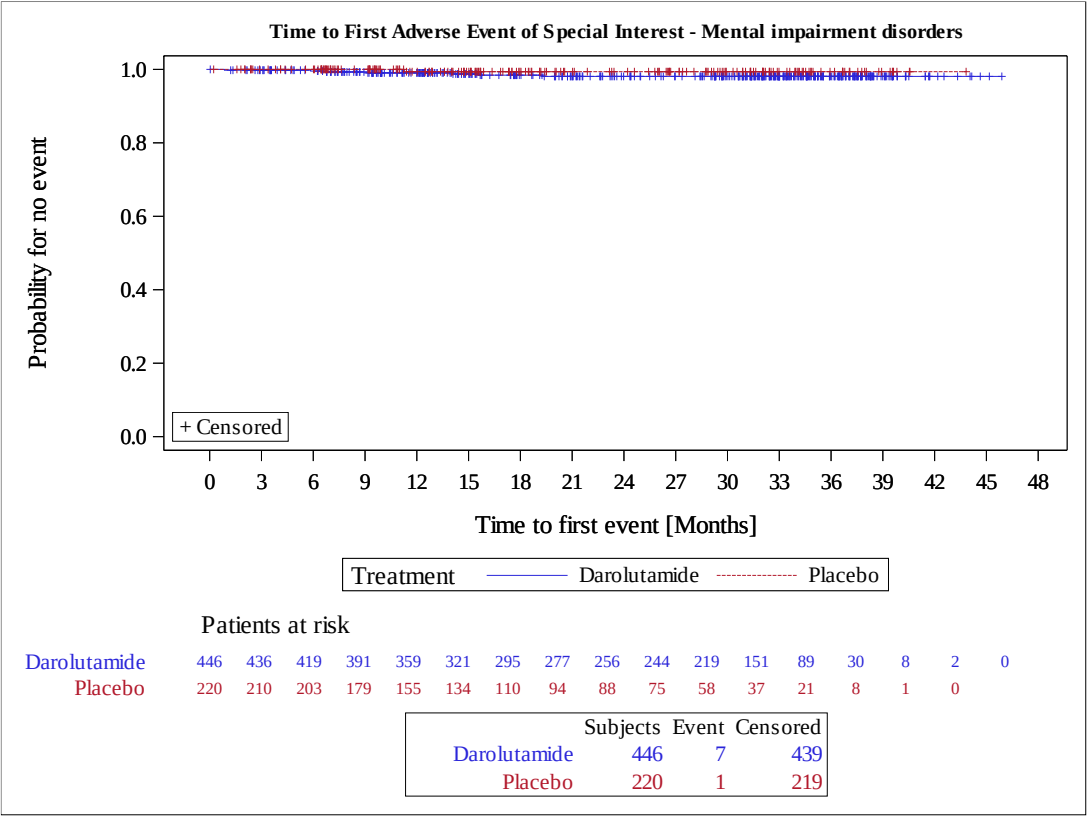
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	6/387 (1.6)	1/200 (0.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 59 (1.7)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	4/193 (2.1)	1/ 95 (1.1)			
>=75	3/136 (2.2)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	3/145 (2.1)	0/ 76 (0.0)			
ROTW	4/301 (1.3)	1/144 (0.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.9.10.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Mental impairment disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.9.11
Summary of Adverse Events of Special Interest - Depressed mood disorders
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	2 (0.4)	2 (0.9)
Number of censored patients, n (%)	444 (99.6)	218 (99.1)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.436	
95% CI	0.061, 3.102	
p-value	0.3938	
Odds Ratio	0.491	
95% CI	0.069, 3.509	
p-value	0.4784	
Relative Risk	0.493	
95% CI	0.070, 3.479	
p-value	0.4783	
Risk Difference	-0.461	
95% CI	-1.860, 0.938	
p-value	0.5187	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.11.1

Summary of Adverse Events of Special Interest - Depressed mood disorders - Subgroup analysis

(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	2/392 (0.5)	2/194 (1.0)			
Received prior local therapy (from IWRS)					
Yes	1/ 81 (1.2)	0/ 39 (0.0)			
No	1/365 (0.3)	2/181 (1.1)			
Prior local radiotherapy and/or prostatectomy					
Yes	1/ 88 (1.1)	1/ 49 (2.0)			
No	1/358 (0.3)	1/171 (0.6)			
Age group					
<65 years	1/117 (0.9)	0/ 64 (0.0)			
65-74	1/193 (0.5)	1/ 95 (1.1)			
75-84	0/118 (0.0)	1/ 51 (2.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	1/250 (0.4)	2/123 (1.6)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	1/ 42 (2.4)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	2/120 (1.7)	1/ 70 (1.4)			
Europe and Rest of the world	0/185 (0.0)	1/ 87 (1.1)			
Baseline PSA values by median					
< median of overall population	2/216 (0.9)	2/109 (1.8)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	2/ 96 (2.1)			
>=1	2/211 (0.9)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	1/ 64 (1.6)			
Gleason >=8	2/308 (0.6)	1/146 (0.7)			
Disease volume at baseline					
high	1/315 (0.3)	0/155 (0.0)			
low	1/131 (0.8)	2/ 65 (3.1)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	2/179 (1.1)	1/ 90 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	1/ 27 (3.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.11.1

Summary of Adverse Events of Special Interest - Depressed mood disorders - Subgroup analysis (safety analysis set)

Final

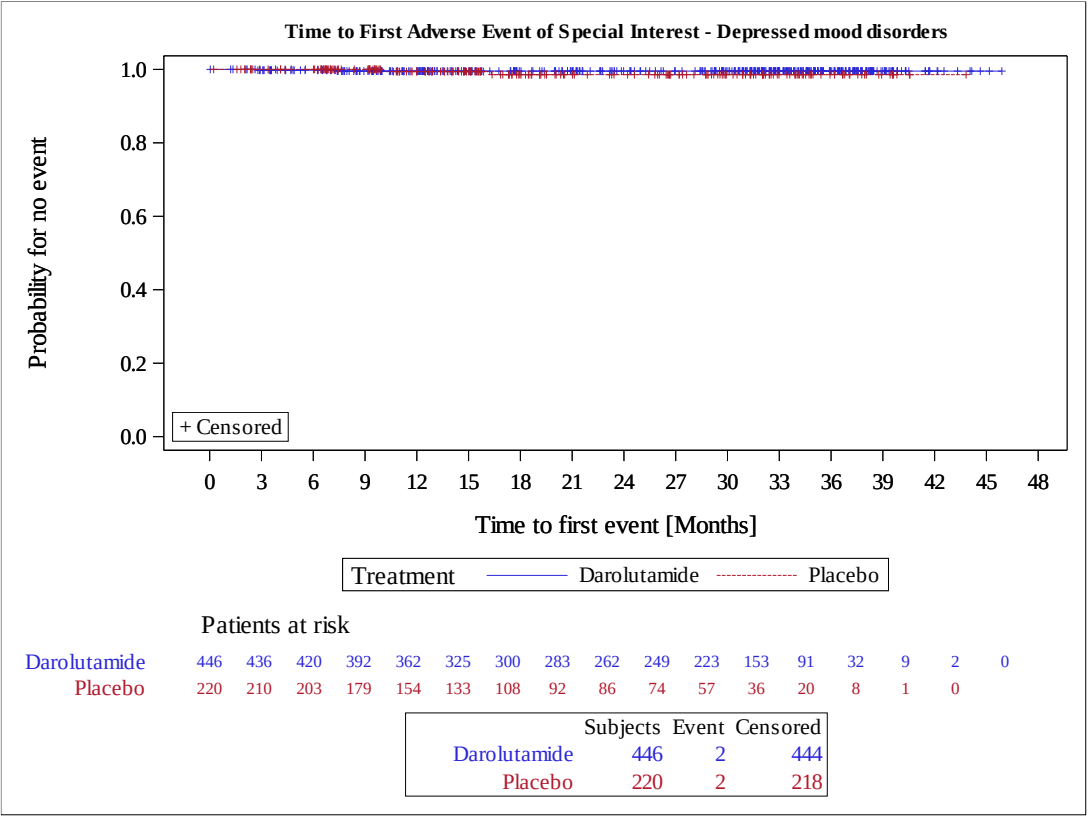
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	1/387 (0.3)	2/200 (1.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 59 (1.7)	0/ 20 (0.0)			
Age Group (Titan)					
<65	1/117 (0.9)	0/ 64 (0.0)			
>=65 and <75	1/193 (0.5)	1/ 95 (1.1)			
>=75	0/136 (0.0)	1/ 61 (1.6)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	1/ 76 (1.3)			
ROTW	2/301 (0.7)	1/144 (0.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.9.11.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Depressed mood disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.9.12
Summary of Adverse Events of Special Interest - Breast disorders/gynecomastia
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	7 (1.6)	2 (0.9)
Number of censored patients, n (%)	439 (98.4)	218 (99.1)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.463	
95% CI	0.303, 7.053	
p-value	0.6335	
Odds Ratio	1.738	
95% CI	0.358, 8.437	
p-value	0.4929	
Relative Risk	1.726	
95% CI	0.362, 8.242	
p-value	0.4935	
Risk Difference	0.660	
95% CI	-1.044, 2.364	
p-value	0.4475	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.12.1

Summary of Adverse Events of Special Interest - Breast disorders/gynecomastia - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	1/ 54 (1.9)	0/ 26 (0.0)			
No	6/392 (1.5)	2/194 (1.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	7/365 (1.9)	2/181 (1.1)			
Prior local radiotherapy and/or prostatectomy					
Yes	1/ 88 (1.1)	0/ 49 (0.0)			
No	6/358 (1.7)	2/171 (1.2)			
Age group					
<65 years	3/117 (2.6)	0/ 64 (0.0)			
65-74	3/193 (1.6)	2/ 95 (2.1)			
75-84	1/118 (0.8)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	6/250 (2.4)	2/123 (1.6)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	1/ 42 (2.4)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	3/120 (2.5)	2/ 70 (2.9)			
Europe and Rest of the world	4/185 (2.2)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	5/216 (2.3)	1/109 (0.9)			
>= median of overall population	2/219 (0.9)	1/108 (0.9)			
ECOG PS at baseline					
=0	4/235 (1.7)	1/ 96 (1.0)			
>=1	3/211 (1.4)	1/124 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	2/125 (1.6)	0/ 64 (0.0)			
Gleason >=8	4/308 (1.3)	2/146 (1.4)			
Disease volume at baseline					
high	4/315 (1.3)	0/155 (0.0)			
low	3/131 (2.3)	2/ 65 (3.1)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	2/221 (0.9)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	4/179 (2.2)	1/ 90 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	1/ 45 (2.2)	1/ 27 (3.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population

Table 3.2.9.12.1

Summary of Adverse Events of Special Interest - Breast disorders/gynecomastia - Subgroup analysis (safety analysis set)

Final

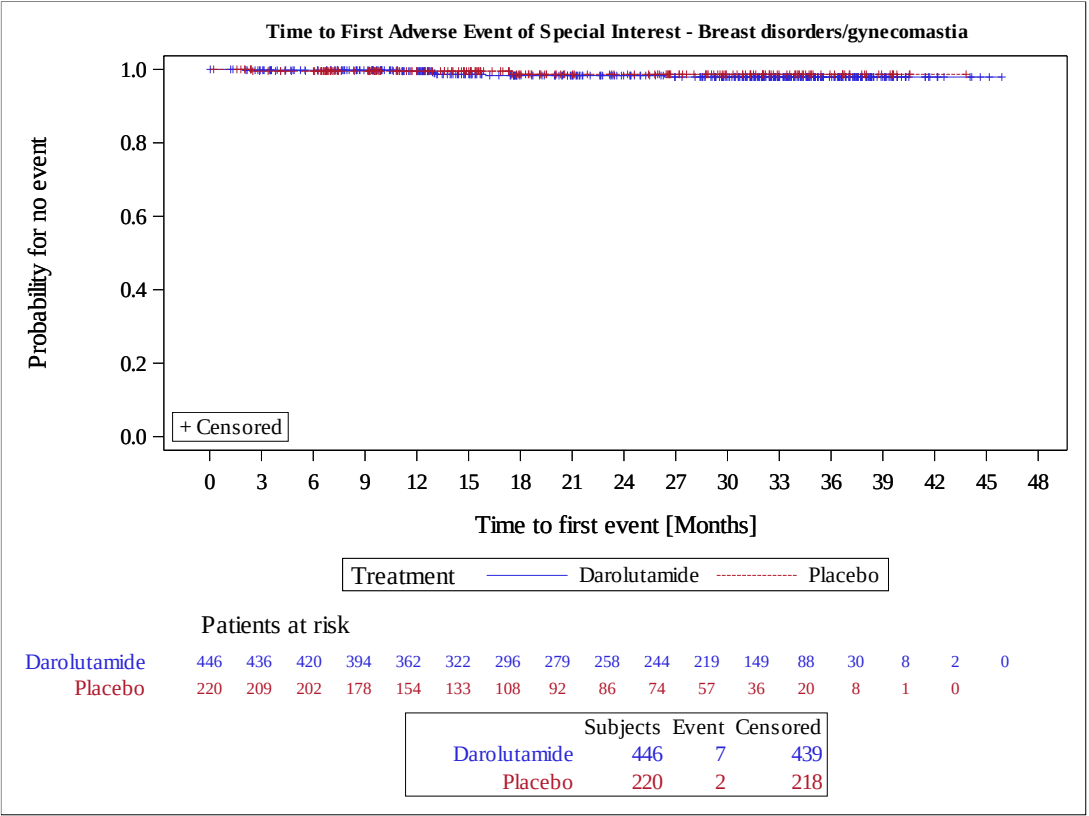
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction
			Hazard Ratio	(95% CI)	p-Value
p-Value					
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	7/387 (1.8)	2/200 (1.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	3/117 (2.6)	0/ 64 (0.0)			
>=65 and <75	3/193 (1.6)	2/ 95 (2.1)			
>=75	1/136 (0.7)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	4/145 (2.8)	0/ 76 (0.0)			
ROTW	3/301 (1.0)	2/144 (1.4)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.9.12.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Breast disorders/gynecomastia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.9.13
Summary of Adverse Events of Special Interest - Cardiac disorders
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	59 (13.2)	21 (9.5)
Number of censored patients, n (%)	387 (86.8)	199 (90.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.172	
95% CI	0.711, 1.930	
p-value	0.5334	
Odds Ratio	1.445	
95% CI	0.853, 2.446	
p-value	0.1709	
Relative Risk	1.386	
95% CI	0.865, 2.220	
p-value	0.1746	
Risk Difference	3.683	
95% CI	-1.313, 8.680	
p-value	0.1485	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.13.1

Summary of Adverse Events of Special Interest - Cardiac disorders - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	9/ 54 (16.7)	2/ 26 (7.7)	1.908	(0.412, 8.833)	0.4005	0.4881
No	50/392 (12.8)	19/194 (9.8)	1.085	(0.639, 1.844)	0.7618	
Received prior local therapy (from IWRS)						
Yes	9/ 81 (11.1)	3/ 39 (7.7)	1.143	(0.304, 4.296)	0.8431	0.9184
No	50/365 (13.7)	18/181 (9.9)	1.191	(0.694, 2.042)	0.5251	
Prior local radiotherapy and/or prostatectomy						
Yes	10/ 88 (11.4)	6/ 49 (12.2)	0.816	(0.295, 2.257)	0.6945	0.4001
No	49/358 (13.7)	15/171 (8.8)	1.312	(0.735, 2.342)	0.3565	
Age group						
<65 years	9/117 (7.7)	1/ 64 (1.6)	3.961	(0.501, 31.343)	0.1589	0.5792
65-74	23/193 (11.9)	9/ 95 (9.5)	1.122	(0.518, 2.428)	0.7702	
75-84	26/118 (22.0)	10/ 51 (19.6)	0.933	(0.449, 1.936)	0.8516	
>=85 years	1/ 18 (5.6)	1/ 10 (10.0)	0.348	(0.022, 5.570)	0.4348	
Race						
White	34/250 (13.6)	12/123 (9.8)	1.081	(0.558, 2.094)	0.8171	0.7481
Asian	19/144 (13.2)	5/ 65 (7.7)	1.557	(0.581, 4.176)	0.3742	
Black or African American	4/ 42 (9.5)	3/ 23 (13.0)	0.636	(0.142, 2.846)	0.5501	
Other	2/ 10 (20.0)	1/ 9 (11.1)	1.795	(0.162, 19.837)	0.6284	
Geographical region						
Asia	19/141 (13.5)	5/ 63 (7.9)	1.547	(0.577, 4.148)	0.3814	0.7882
Latin America	16/120 (13.3)	7/ 70 (10.0)	1.186	(0.488, 2.885)	0.7059	
Europe and Rest of the world	24/185 (13.0)	9/ 87 (10.3)	0.925	(0.427, 2.003)	0.8429	
Baseline PSA values by median						
< median of overall population	33/216 (15.3)	11/109 (10.1)	1.280	(0.646, 2.536)	0.4785	0.6667
>= median of overall population	25/219 (11.4)	10/108 (9.3)	1.051	(0.504, 2.192)	0.8934	
ECOG PS at baseline						
=0	35/235 (14.9)	12/ 96 (12.5)	0.974	(0.505, 1.880)	0.9386	0.5234
>=1	24/211 (11.4)	9/124 (7.3)	1.385	(0.643, 2.985)	0.4031	
Gleason score at initial diagnosis						
Gleason <8	14/125 (11.2)	6/ 64 (9.4)	1.004	(0.385, 2.620)	0.9938	0.6826
Gleason >=8	45/308 (14.6)	14/146 (9.6)	1.316	(0.722, 2.401)	0.3683	
Disease volume at baseline						
high	34/315 (10.8)	16/155 (10.3)	0.888	(0.490, 1.611)	0.6960	0.1155
low	25/131 (19.1)	5/ 65 (7.7)	2.075	(0.792, 5.434)	0.1286	
Renal function - eGFR at baseline						
Normal: eGFR >= 90 mL/min	29/221 (13.1)	7/102 (6.9)	1.642	(0.719, 3.753)	0.2346	0.4954
Mild impairment: 60 <= eGFR < 90 mL/min	23/179 (12.8)	11/ 90 (12.2)	0.839	(0.407, 1.727)	0.6328	
Moderate impairment: 30 <= eGFR < 60 mL/min	7/ 45 (15.6)	3/ 27 (11.1)	1.380	(0.357, 5.339)	0.6395	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.9.13.1
Summary of Adverse Events of Special Interest - Cardiac disorders - Subgroup analysis
(safety analysis set)

Final

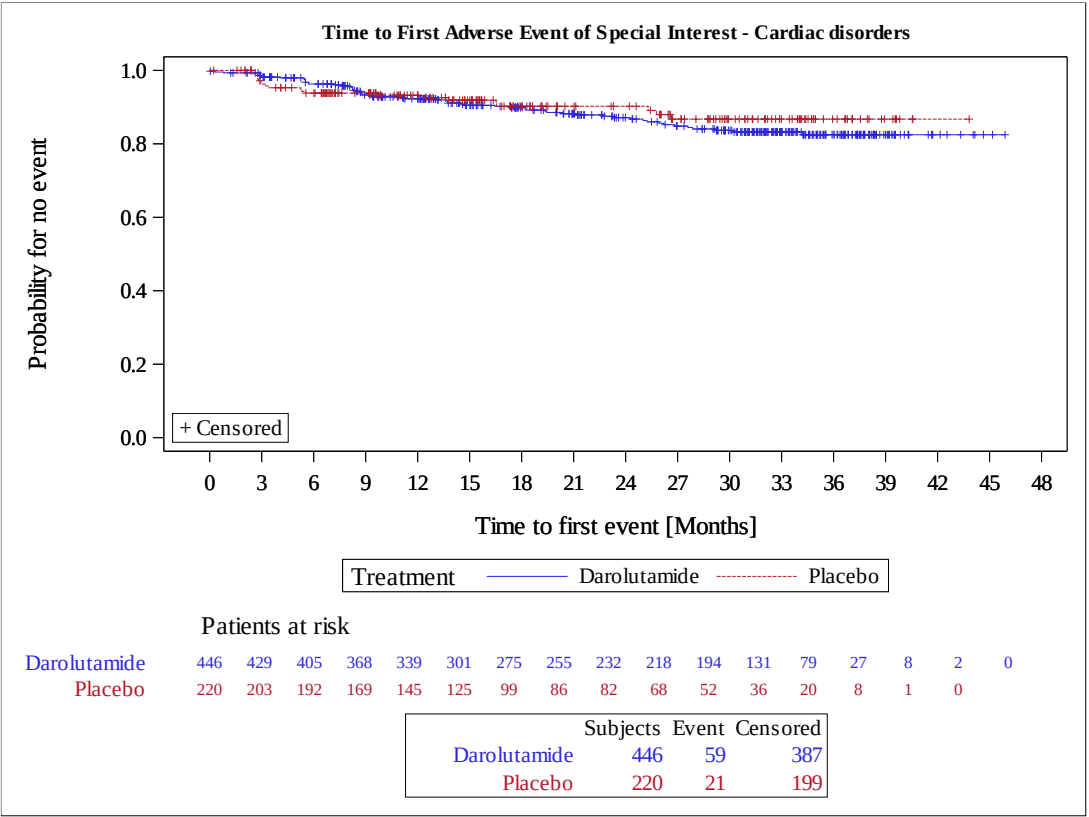
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Hepatic function at baseline						0.9843
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	47/387 (12.1)	21/200 (10.5)	0.967	(0.577, 1.621)	0.8993	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	12/ 59 (20.3)	0/ 20 (0.0)	NE	(NE, NE)	NE	
Age Group (Titan)						0.4343
<65	9/117 (7.7)	1/ 64 (1.6)	3.961	(0.501, 31.343)	0.1589	
>=65 and <75	23/193 (11.9)	9/ 95 (9.5)	1.122	(0.518, 2.428)	0.7702	
>=75	27/136 (19.9)	11/ 61 (18.0)	0.908	(0.450, 1.834)	0.7886	
Geographic region (Titan)						0.3295
Europe and north america	16/145 (11.0)	8/ 76 (10.5)	0.772	(0.328, 1.820)	0.5535	
ROTW	43/301 (14.3)	13/144 (9.0)	1.401	(0.753, 2.607)	0.2841	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population
Figure 3.2.9.13.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Cardiac disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.9.14
Summary of Adverse Events of Special Interest - Cerebral ischaemia
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	3 (0.7)	3 (1.4)
Number of censored patients, n (%)	443 (99.3)	217 (98.6)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.374	
95% CI	0.075, 1.882	
p-value	0.2155	
Odds Ratio	0.490	
95% CI	0.098, 2.447	
p-value	0.3845	
Relative Risk	0.493	
95% CI	0.100, 2.424	
p-value	0.3843	
Risk Difference	-0.691	
95% CI	-2.401, 1.019	
p-value	0.4284	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population

Table 3.2.9.14.1

Summary of Adverse Events of Special Interest - Cerebral ischaemia - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	1/ 26 (3.8)			
No	3/392 (0.8)	2/194 (1.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	3/365 (0.8)	3/181 (1.7)			
Prior local radiotherapy and/or prostatectomy					
Yes	1/ 88 (1.1)	0/ 49 (0.0)			
No	2/358 (0.6)	3/171 (1.8)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	3/ 95 (3.2)			
75-84	3/118 (2.5)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	2/250 (0.8)	3/123 (2.4)			
Asian	1/144 (0.7)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	1/141 (0.7)	0/ 63 (0.0)			
Latin America	1/120 (0.8)	0/ 70 (0.0)			
Europe and Rest of the world	1/185 (0.5)	3/ 87 (3.4)			
Baseline PSA values by median					
< median of overall population	3/216 (1.4)	1/109 (0.9)			
>= median of overall population	0/219 (0.0)	2/108 (1.9)			
ECOG PS at baseline					
=0	2/235 (0.9)	2/ 96 (2.1)			
>=1	1/211 (0.5)	1/124 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	1/ 64 (1.6)			
Gleason >=8	3/308 (1.0)	2/146 (1.4)			
Disease volume at baseline					
high	1/315 (0.3)	3/155 (1.9)			
low	2/131 (1.5)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	2/221 (0.9)	1/102 (1.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	1/179 (0.6)	1/ 90 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	1/ 27 (3.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.14.1

Summary of Adverse Events of Special Interest - Cerebral ischaemia - Subgroup analysis (safety analysis set)

Final

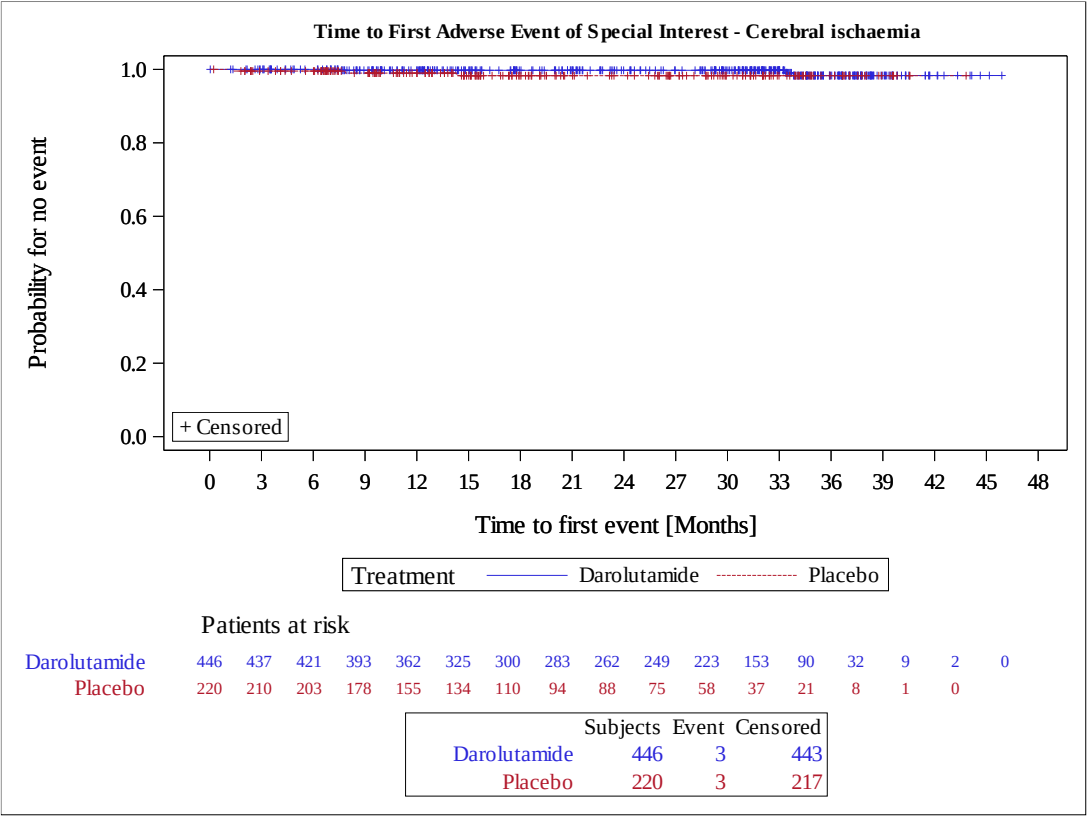
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	1/387 (0.3)	3/200 (1.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	2/ 59 (3.4)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	3/ 95 (3.2)			
>=75	3/136 (2.2)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	3/ 76 (3.9)			
ROTW	3/301 (1.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.9.14.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Cerebral ischaemia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.9.15
Summary of Adverse Events of Special Interest - Cerebral and intracranial hemorrhage
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	2 (0.4)	1 (0.5)
Number of censored patients, n (%)	444 (99.6)	219 (99.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.823	
95% CI	0.074, 9.122	
p-value	0.8736	
Odds Ratio	0.986	
95% CI	0.089, 10.939	
p-value	0.9912	
Relative Risk	0.987	
95% CI	0.090, 10.821	
p-value	0.9912	
Risk Difference	-0.006	
95% CI	-1.090, 1.078	
p-value	0.9912	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.15.1

Summary of Adverse Events of Special Interest - Cerebral and intracranial hemorrhage - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	2/392 (0.5)	1/194 (0.5)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	2/365 (0.5)	1/181 (0.6)			
Prior local radiotherapy and/or prostatectomy					
Yes	2/ 88 (2.3)	0/ 49 (0.0)			
No	0/358 (0.0)	1/171 (0.6)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	1/118 (0.8)	0/ 51 (0.0)			
>=85 years	1/ 18 (5.6)	1/ 10 (10.0)			
Race					
White	1/250 (0.4)	0/123 (0.0)			
Asian	1/144 (0.7)	1/ 65 (1.5)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	1/141 (0.7)	1/ 63 (1.6)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	1/185 (0.5)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	2/216 (0.9)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	1/108 (0.9)			
ECOG PS at baseline					
=0	2/235 (0.9)	0/ 96 (0.0)			
>=1	0/211 (0.0)	1/124 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	1/ 64 (1.6)			
Gleason >=8	2/308 (0.6)	0/146 (0.0)			
Disease volume at baseline					
high	1/315 (0.3)	0/155 (0.0)			
low	1/131 (0.8)	1/ 65 (1.5)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	2/179 (1.1)	1/ 90 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.15.1

Summary of Adverse Events of Special Interest - Cerebral and intracranial hemorrhage - Subgroup analysis (safety analysis set)

Final

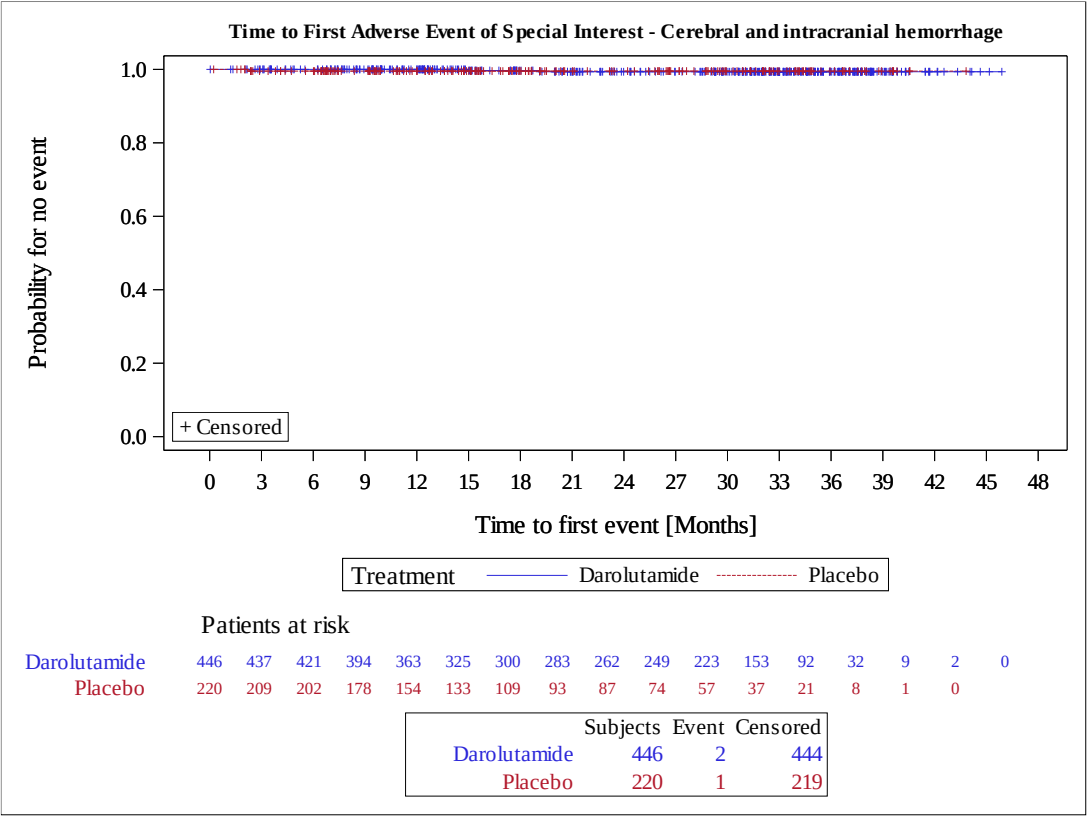
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	1/387 (0.3)	1/200 (0.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 59 (1.7)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	2/136 (1.5)	1/ 61 (1.6)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	2/301 (0.7)	1/144 (0.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.9.15.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Cerebral and intracranial hemorrhage
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.9.16
Summary of Adverse Events of Special Interest - Interstitial lung disease
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	1 (0.2)	1 (0.5)
Number of censored patients, n (%)	445 (99.8)	219 (99.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.376	
95% CI	0.023, 6.046	
p-value	0.4729	
Odds Ratio	0.492	
95% CI	0.031, 7.905	
p-value	0.6167	
Relative Risk	0.493	
95% CI	0.031, 7.849	
p-value	0.6167	
Risk Difference	-0.230	
95% CI	-1.222, 0.761	
p-value	0.6488	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.16.1

Summary of Adverse Events of Special Interest - Interstitial lung disease - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	1/392 (0.3)	1/194 (0.5)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	1/365 (0.3)	1/181 (0.6)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	1/358 (0.3)	1/171 (0.6)			
Age group					
<65 years	1/117 (0.9)	0/ 64 (0.0)			
65-74	0/193 (0.0)	1/ 95 (1.1)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	1/250 (0.4)	1/123 (0.8)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	1/120 (0.8)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	1/ 87 (1.1)			
Baseline PSA values by median					
< median of overall population	1/216 (0.5)	1/109 (0.9)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	1/235 (0.4)	0/ 96 (0.0)			
>=1	0/211 (0.0)	1/124 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	1/308 (0.3)	1/146 (0.7)			
Disease volume at baseline					
high	1/315 (0.3)	1/155 (0.6)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	1/179 (0.6)	1/ 90 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.9.16.1

Summary of Adverse Events of Special Interest - Interstitial lung disease - Subgroup analysis (safety analysis set)

Final

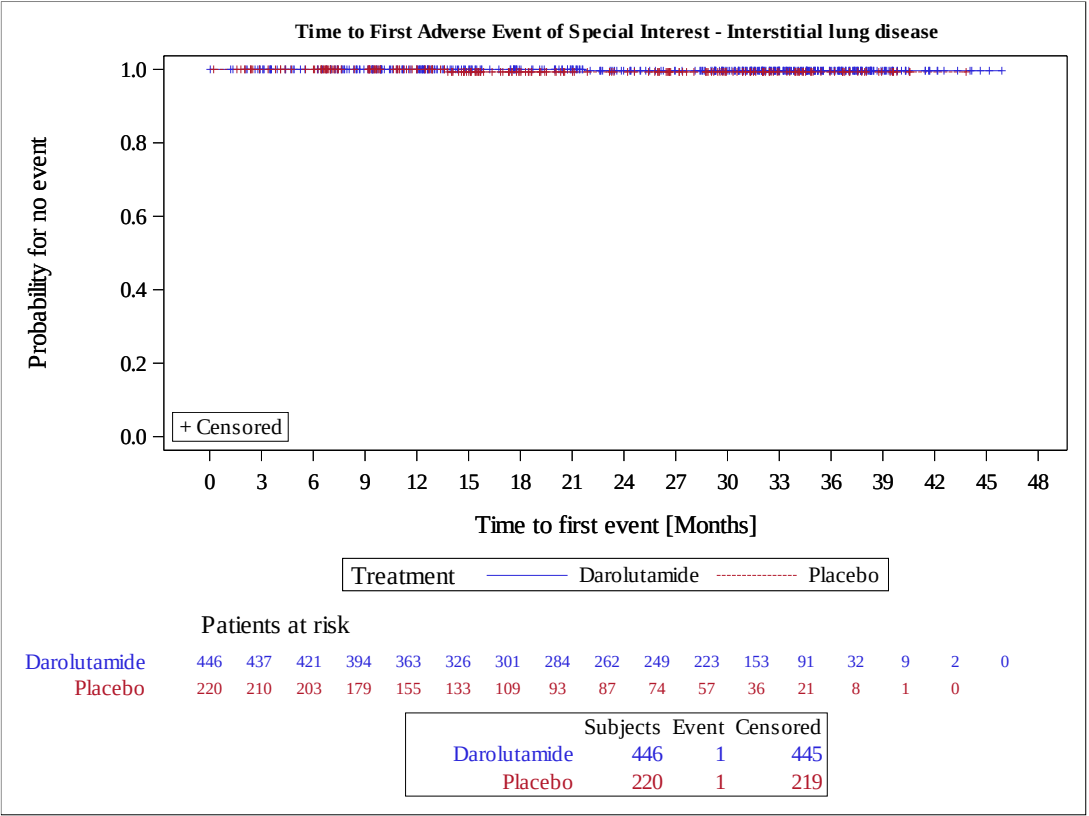
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	1/387 (0.3)	1/200 (0.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	1/117 (0.9)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	1/ 95 (1.1)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	1/ 76 (1.3)			
ROTW	1/301 (0.3)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.9.16.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest - Interstitial lung disease
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.10.1
Summary of Serious Adverse Events of Special Interest - Bone fractures excluding pathological fractures
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	7 (1.6)	0 (0.0)
Number of censored patients, n (%)	439 (98.4)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	7.526	
95% CI	0.428, 132.368	
p-value	0.1677	
Relative Risk	7.416	
95% CI	0.425, 129.260	
p-value	0.1694	
Risk Difference	1.570	
95% CI	0.416, 2.723	
p-value	0.0077	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.1.1

Summary of Serious Adverse Events of Special Interest - Bone fractures excluding pathological fractures - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	1/ 54 (1.9)	0/ 26 (0.0)			
No	6/392 (1.5)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	2/ 81 (2.5)	0/ 39 (0.0)			
No	5/365 (1.4)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	1/ 88 (1.1)	0/ 49 (0.0)			
No	6/358 (1.7)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	1/193 (0.5)	0/ 95 (0.0)			
75-84	5/118 (4.2)	0/ 51 (0.0)			
>=85 years	1/ 18 (5.6)	0/ 10 (0.0)			
Race					
White	5/250 (2.0)	0/123 (0.0)			
Asian	2/144 (1.4)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	2/141 (1.4)	0/ 63 (0.0)			
Latin America	2/120 (1.7)	0/ 70 (0.0)			
Europe and Rest of the world	3/185 (1.6)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	6/216 (2.8)	0/109 (0.0)			
>= median of overall population	1/219 (0.5)	0/108 (0.0)			
ECOG PS at baseline					
=0	3/235 (1.3)	0/ 96 (0.0)			
>=1	4/211 (1.9)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	4/125 (3.2)	0/ 64 (0.0)			
Gleason >=8	3/308 (1.0)	0/146 (0.0)			
Disease volume at baseline					
high	5/315 (1.6)	0/155 (0.0)			
low	2/131 (1.5)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	2/221 (0.9)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	5/179 (2.8)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.1.1

Summary of Serious Adverse Events of Special Interest - Bone fractures excluding pathological fractures - Subgroup analysis (safety analysis set)

Final

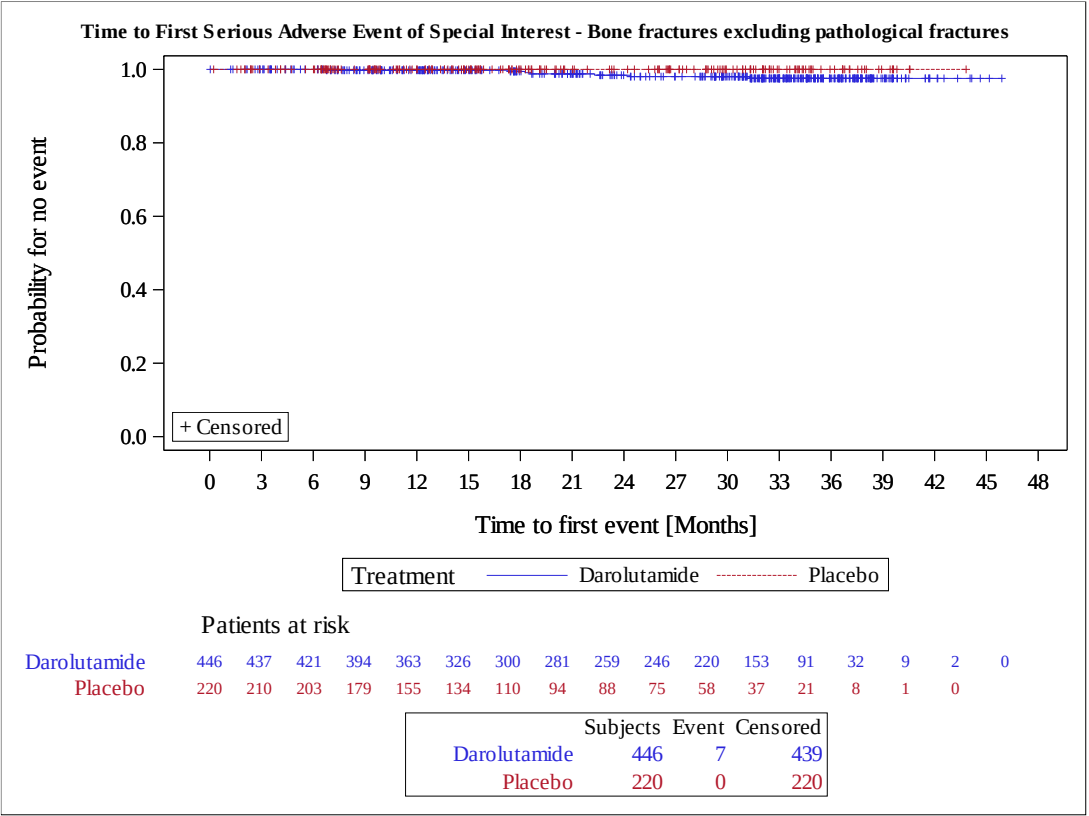
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI) p-Value	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	7/387 (1.8)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	1/193 (0.5)	0/ 95 (0.0)			
>=75	6/136 (4.4)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	7/301 (2.3)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.10.1.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Bone fractures excluding pathological fractures
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.10.2
Summary of Serious Adverse Events of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	1 (0.2)	0 (0.0)
Number of censored patients, n (%)	445 (99.8)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	1.485	
95% CI	0.060, 36.598	
p-value	0.8090	
Relative Risk	1.483	
95% CI	0.061, 36.262	
p-value	0.8090	
Risk Difference	0.224	
95% CI	-0.215, 0.663	
p-value	0.3168	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.2.1

Summary of Serious Adverse Events of Special Interest - Diabetes mellitus and hyperglycemia - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	1/392 (0.3)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	1/365 (0.3)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	1/358 (0.3)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	1/118 (0.8)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	1/144 (0.7)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	1/141 (0.7)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	1/216 (0.5)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	1/211 (0.5)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	1/308 (0.3)	0/146 (0.0)			
Disease volume at baseline					
high	1/315 (0.3)	0/155 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	1/221 (0.5)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.10.2.1

Summary of Serious Adverse Events of Special Interest - Diabetes mellitus and hyperglycemia - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	1/387 (0.3)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	1/136 (0.7)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	1/301 (0.3)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

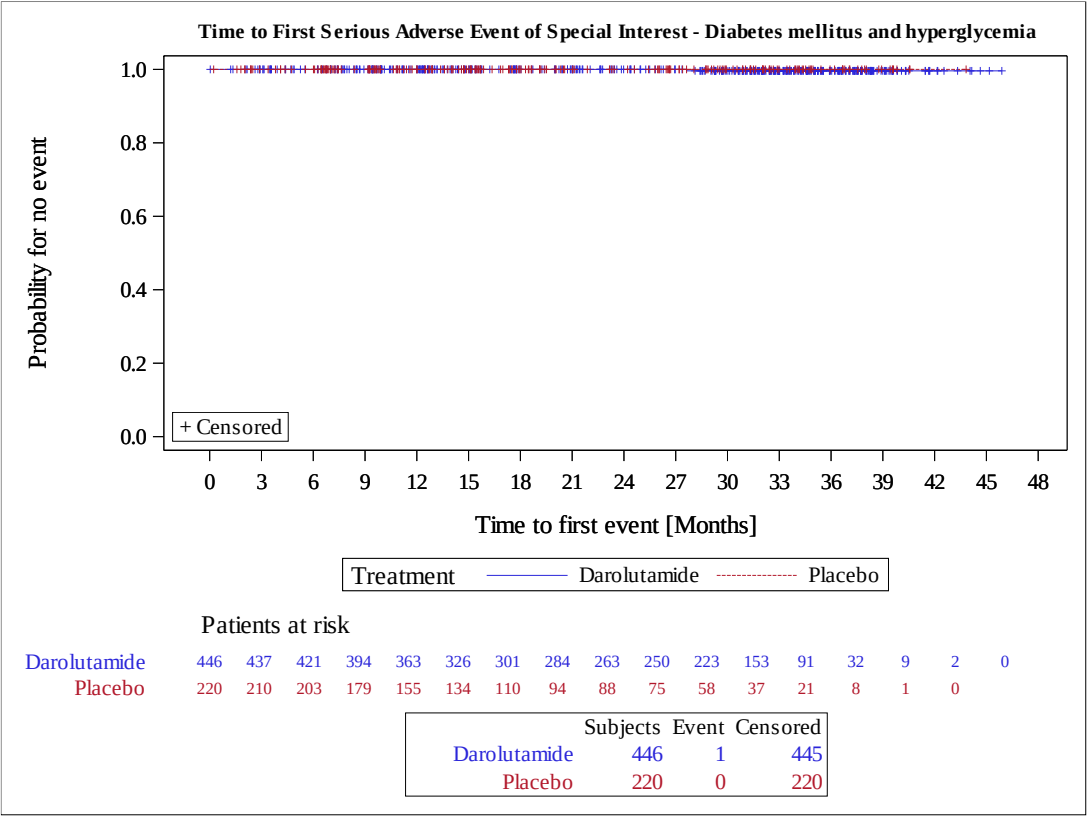
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.10.2.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.10.3
Summary of Serious Adverse Events of Special Interest - Fall
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	2 (0.9)
Number of censored patients, n (%)	446 (100.0)	218 (99.1)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	0.098	
95% CI	0.005, 2.047	
p-value	0.1341	
Relative Risk	0.099	
95% CI	0.005, 2.051	
p-value	0.1347	
Risk Difference	-0.909	
95% CI	-2.163, 0.345	
p-value	0.1554	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.10.3.1

Summary of Serious Adverse Events of Special Interest - Fall - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	1/ 26 (3.8)			
No	0/392 (0.0)	1/194 (0.5)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	1/ 39 (2.6)			
No	0/365 (0.0)	1/181 (0.6)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	1/ 49 (2.0)			
No	0/358 (0.0)	1/171 (0.6)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	1/ 95 (1.1)			
75-84	0/118 (0.0)	1/ 51 (2.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	1/123 (0.8)			
Asian	0/144 (0.0)	1/ 65 (1.5)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	1/ 63 (1.6)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	1/ 87 (1.1)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	1/109 (0.9)			
>= median of overall population	0/219 (0.0)	1/108 (0.9)			
ECOG PS at baseline					
=0	0/235 (0.0)	1/ 96 (1.0)			
>=1	0/211 (0.0)	1/124 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	1/ 64 (1.6)			
Gleason >=8	0/308 (0.0)	1/146 (0.7)			
Disease volume at baseline					
high	0/315 (0.0)	2/155 (1.3)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	2/ 90 (2.2)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.3.1

Summary of Serious Adverse Events of Special Interest - Fall - Subgroup analysis (safety analysis set)

Final

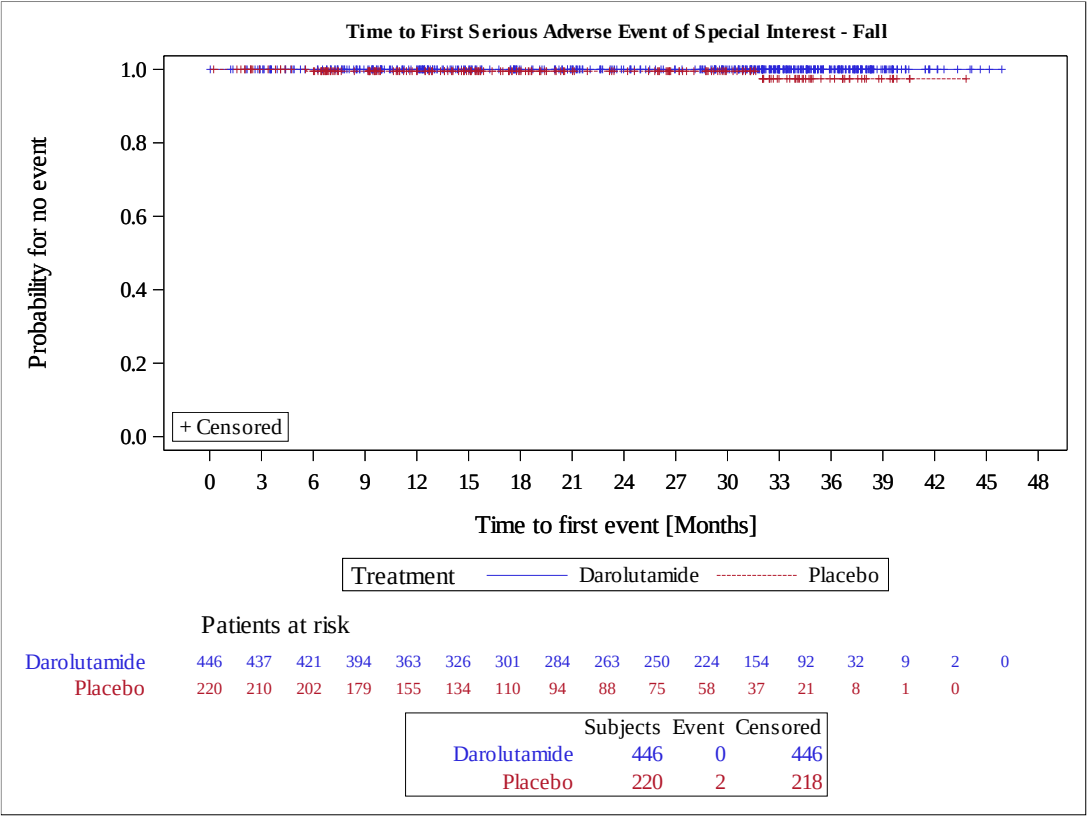
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	2/200 (1.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	1/ 95 (1.1)			
>=75	0/136 (0.0)	1/ 61 (1.6)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	2/144 (1.4)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.10.3.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Fall
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.10.4
Summary of Serious Adverse Events of Special Interest - Fatigue/ asthenic conditions
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	446 (100.0)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.4.1

Summary of Serious Adverse Events of Special Interest - Fatigue/ asthenic conditions - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/211 (0.0)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/315 (0.0)	0/155 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.4.1

Summary of Serious Adverse Events of Special Interest - Fatigue/ asthenic conditions - Subgroup analysis (safety analysis set)

Final

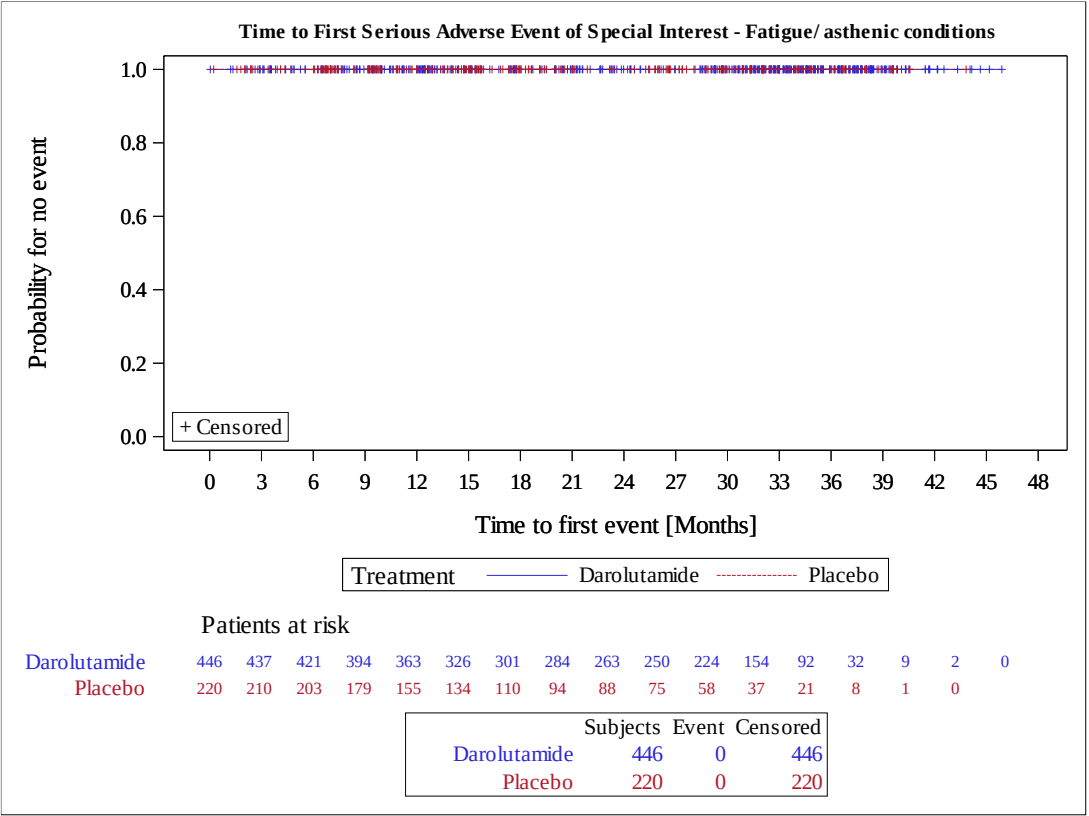
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.10.4.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Fatigue/ asthenic conditions
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.10.5
Summary of Serious Adverse Events of Special Interest - Weight decreased
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	446 (100.0)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.5.1

Summary of Serious Adverse Events of Special Interest - Weight decreased - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/211 (0.0)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/315 (0.0)	0/155 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.5.1

Summary of Serious Adverse Events of Special Interest - Weight decreased - Subgroup analysis (safety analysis set)

Final

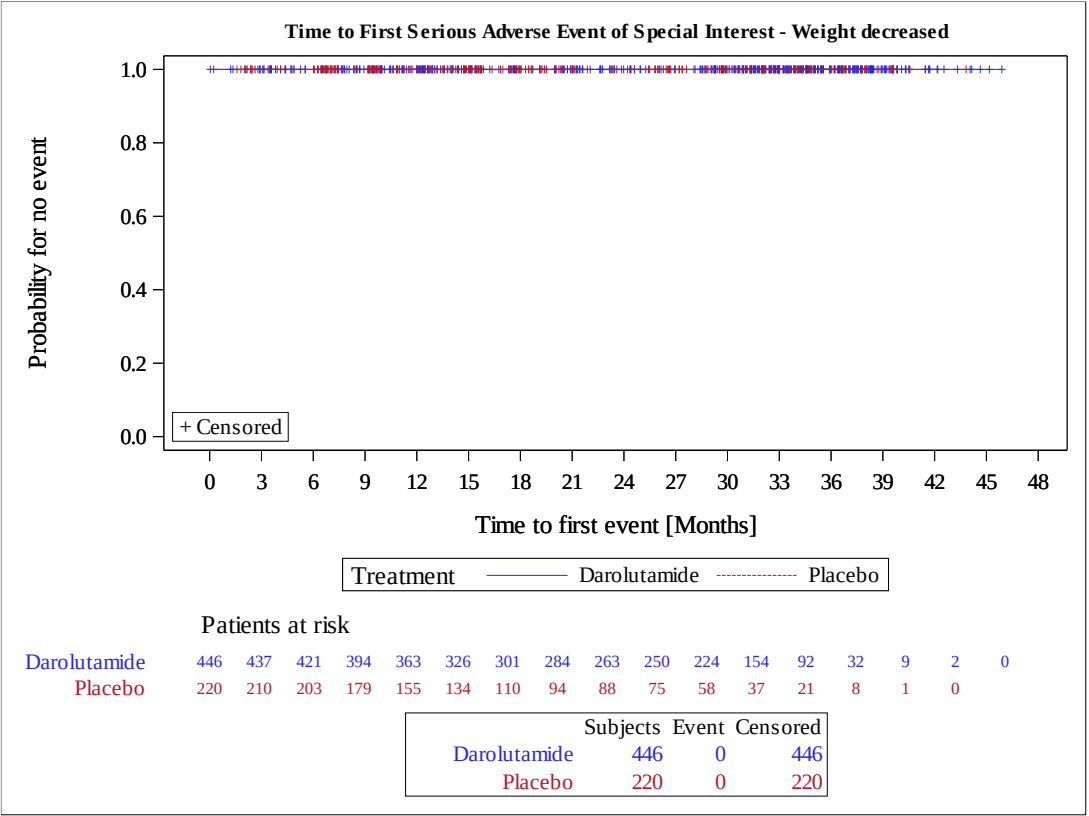
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.10.5.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Weight decreased
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.10.6
Summary of Serious Adverse Events of Special Interest - Rash
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	446 (100.0)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.6.1

Summary of Serious Adverse Events of Special Interest - Rash - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/211 (0.0)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/315 (0.0)	0/155 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.6.1

Summary of Serious Adverse Events of Special Interest - Rash - Subgroup analysis

(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

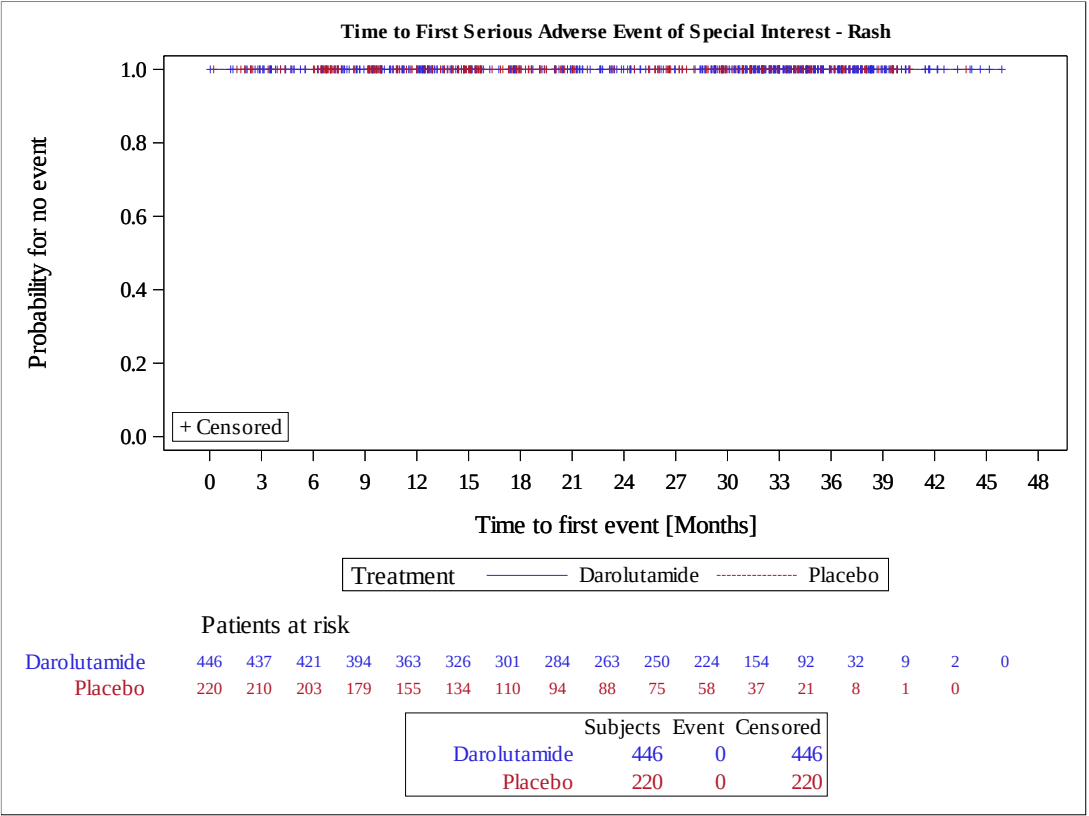
Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.10.6.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Rash
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.10.7
Summary of Serious Adverse Events of Special Interest - Seizure
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	446 (100.0)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.7.1

Summary of Serious Adverse Events of Special Interest - Seizure - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/211 (0.0)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/315 (0.0)	0/155 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.7.1

Summary of Serious Adverse Events of Special Interest - Seizure - Subgroup analysis (safety analysis set)

Final

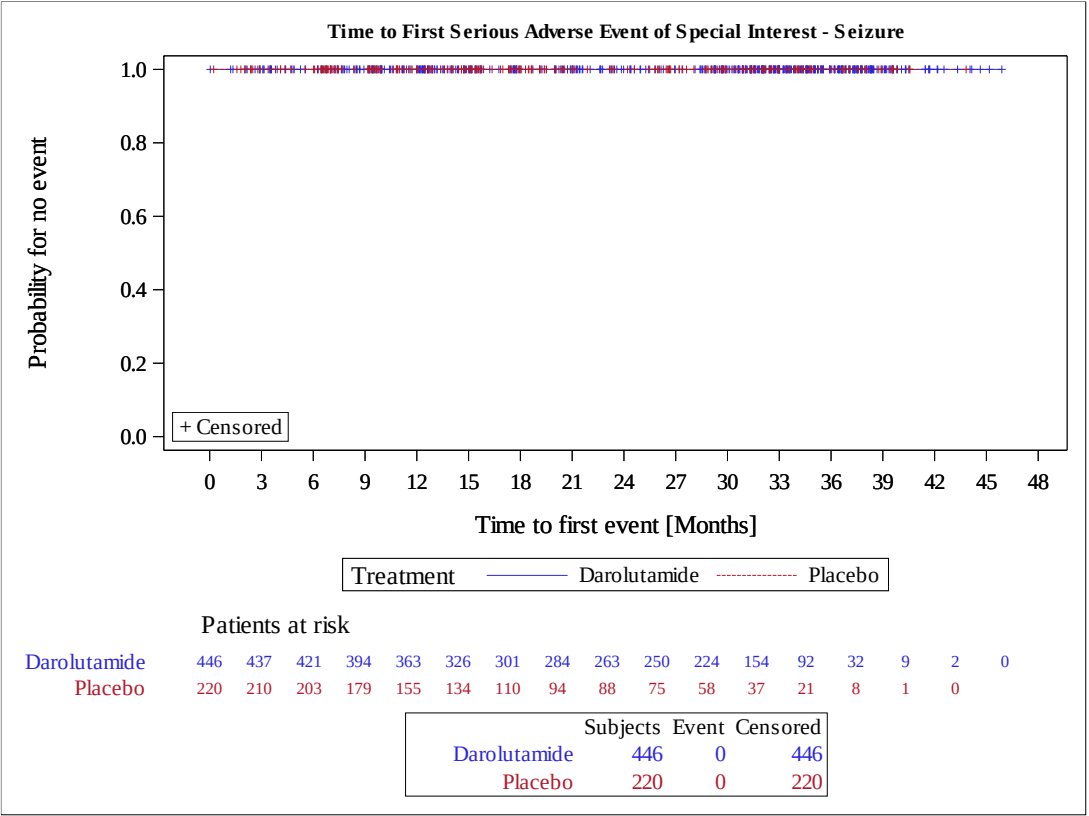
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI) p-Value	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.10.7.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Seizure
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.10.8
Summary of Serious Adverse Events of Special Interest - Hypertension
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	446 (100.0)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.8.1

Summary of Serious Adverse Events of Special Interest - Hypertension - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/211 (0.0)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/315 (0.0)	0/155 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.8.1

Summary of Serious Adverse Events of Special Interest - Hypertension - Subgroup analysis

(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI) p-Value	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

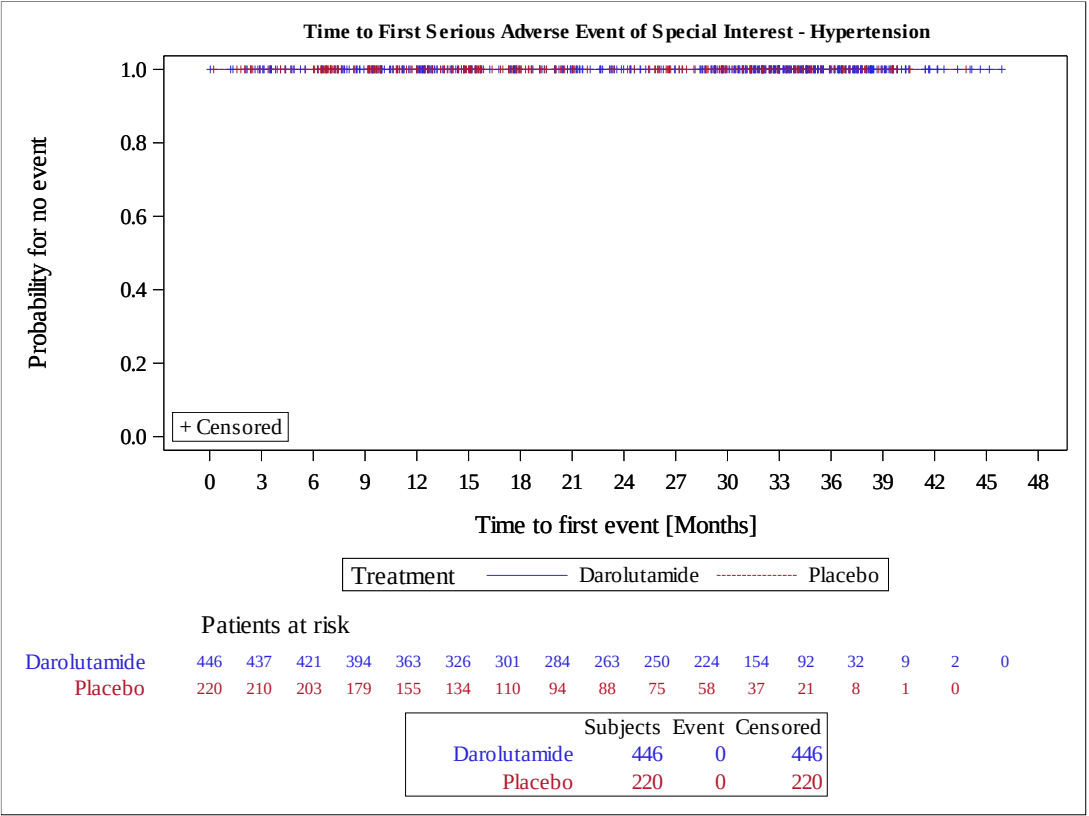
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.10.8.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Hypertension
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.10.9
Summary of Serious Adverse Events of Special Interest - Vasodilatation and flushing
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	446 (100.0)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.9.1

Summary of Serious Adverse Events of Special Interest - Vasodilatation and flushing - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/211 (0.0)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/315 (0.0)	0/155 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.9.1

Summary of Serious Adverse Events of Special Interest - Vasodilatation and flushing - Subgroup analysis (safety analysis set)

Final

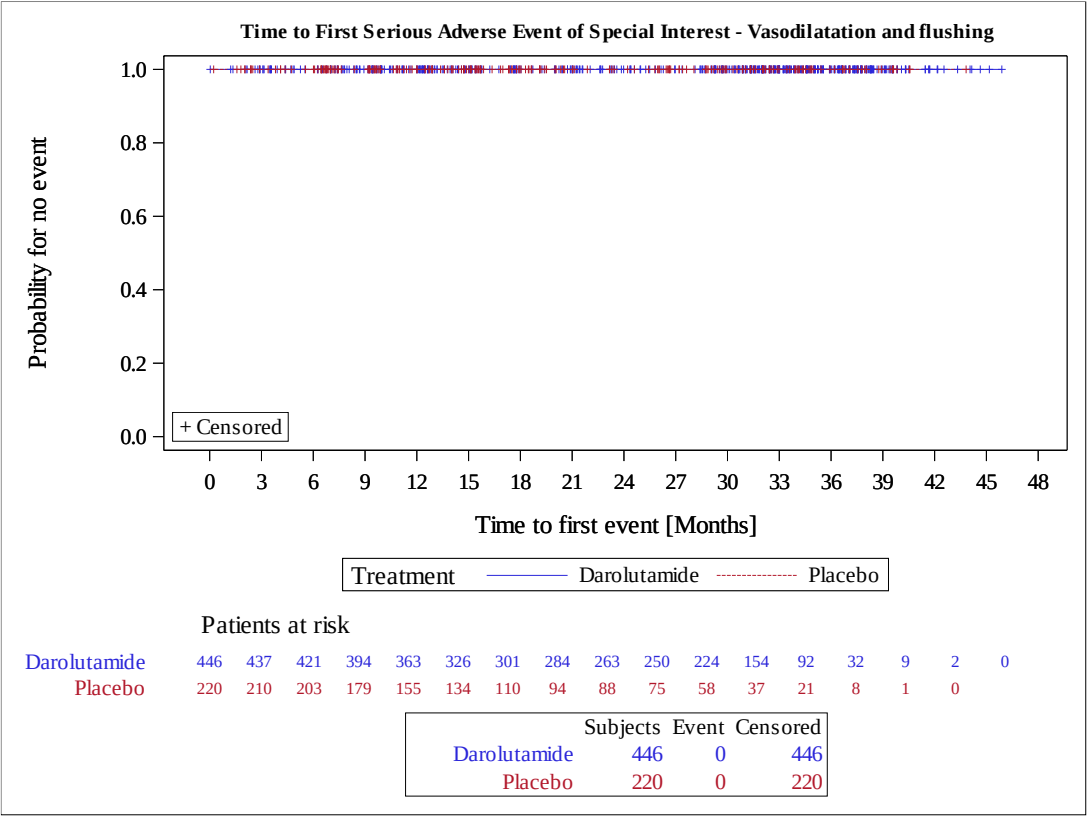
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.10.9.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Vasodilatation and flushing
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.10.10
Summary of Serious Adverse Events of Special Interest - Mental impairment disorders
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	446 (100.0)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.10.1

Summary of Serious Adverse Events of Special Interest - Mental impairment disorders - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value	
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	0/ 54 (0.0)	0/ 26 (0.0)				
No	0/392 (0.0)	0/194 (0.0)				
Received prior local therapy (from IWRS)						
Yes	0/ 81 (0.0)	0/ 39 (0.0)				
No	0/365 (0.0)	0/181 (0.0)				
Prior local radiotherapy and/or prostatectomy						
Yes	0/ 88 (0.0)	0/ 49 (0.0)				
No	0/358 (0.0)	0/171 (0.0)				
Age group						
<65 years	0/117 (0.0)	0/ 64 (0.0)				
65-74	0/193 (0.0)	0/ 95 (0.0)				
75-84	0/118 (0.0)	0/ 51 (0.0)				
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)				
Race						
White	0/250 (0.0)	0/123 (0.0)				
Asian	0/144 (0.0)	0/ 65 (0.0)				
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)				
Other	0/ 10 (0.0)	0/ 9 (0.0)				
Geographical region						
Asia	0/141 (0.0)	0/ 63 (0.0)				
Latin America	0/120 (0.0)	0/ 70 (0.0)				
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)				
Baseline PSA values by median						
< median of overall population	0/216 (0.0)	0/109 (0.0)				
>= median of overall population	0/219 (0.0)	0/108 (0.0)				
ECOG PS at baseline						
=0	0/235 (0.0)	0/ 96 (0.0)				
>=1	0/211 (0.0)	0/124 (0.0)				
Gleason score at initial diagnosis						
Gleason <8	0/125 (0.0)	0/ 64 (0.0)				
Gleason >=8	0/308 (0.0)	0/146 (0.0)				
Disease volume at baseline						
high	0/315 (0.0)	0/155 (0.0)				
low	0/131 (0.0)	0/ 65 (0.0)				
Renal function - eGFR at baseline						
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)				
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)				
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)				

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.10.1

Summary of Serious Adverse Events of Special Interest - Mental impairment disorders - Subgroup analysis (safety analysis set)

Final

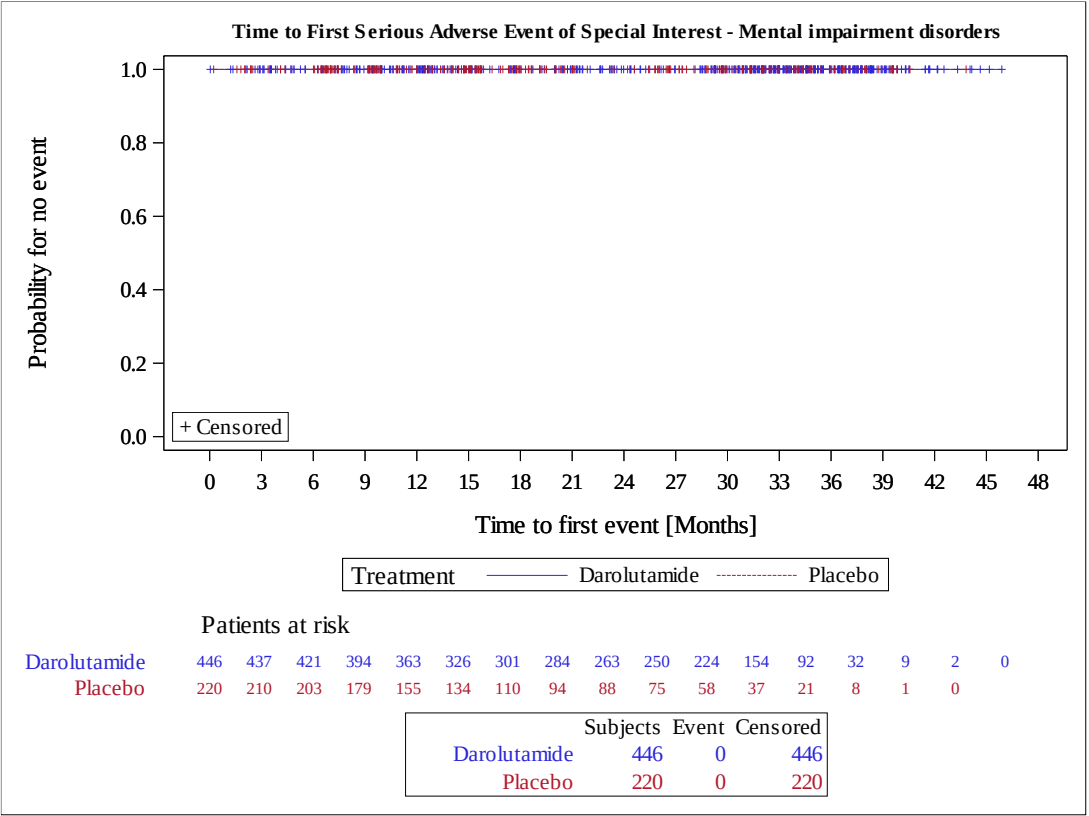
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Hepatic function at baseline						
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/200 (0.0)				
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)				
Age Group (Titan)						
<65	0/117 (0.0)	0/ 64 (0.0)				
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)				
>=75	0/136 (0.0)	0/ 61 (0.0)				
Geographic region (Titan)						
Europe and north america	0/145 (0.0)	0/ 76 (0.0)				
ROTW	0/301 (0.0)	0/144 (0.0)				

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.10.10.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Mental impairment disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.10.11
Summary of Serious Adverse Events of Special Interest - Depressed mood disorders
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	446 (100.0)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.11.1

Summary of Serious Adverse Events of Special Interest - Depressed mood disorders - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/211 (0.0)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/315 (0.0)	0/155 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.11.1

Summary of Serious Adverse Events of Special Interest - Depressed mood disorders - Subgroup analysis (safety analysis set)

Final

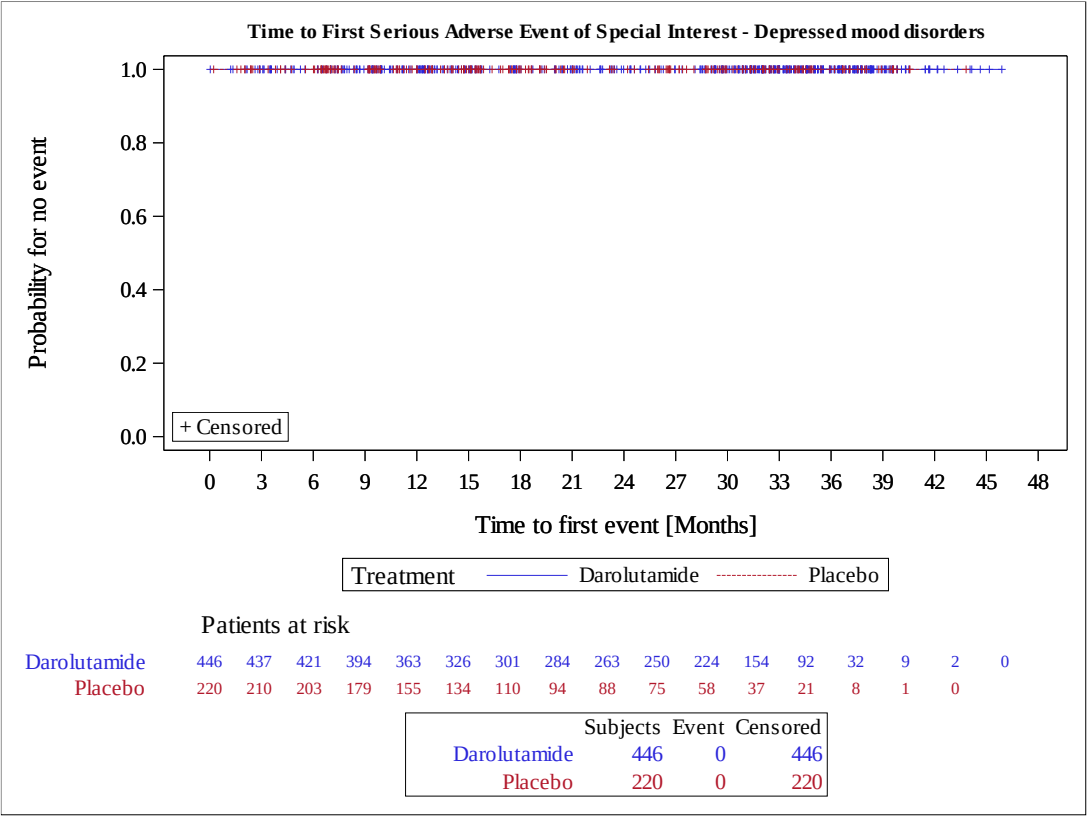
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.10.11.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Depressed mood disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.10.12
Summary of Serious Adverse Events of Special Interest - Breast disorders/gynecomastia
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	446 (100.0)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.12.1

Summary of Serious Adverse Events of Special Interest - Breast disorders/gynecomastia - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/211 (0.0)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/315 (0.0)	0/155 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.12.1

Summary of Serious Adverse Events of Special Interest - Breast disorders/gynecomastia - Subgroup analysis (safety analysis set)

Final

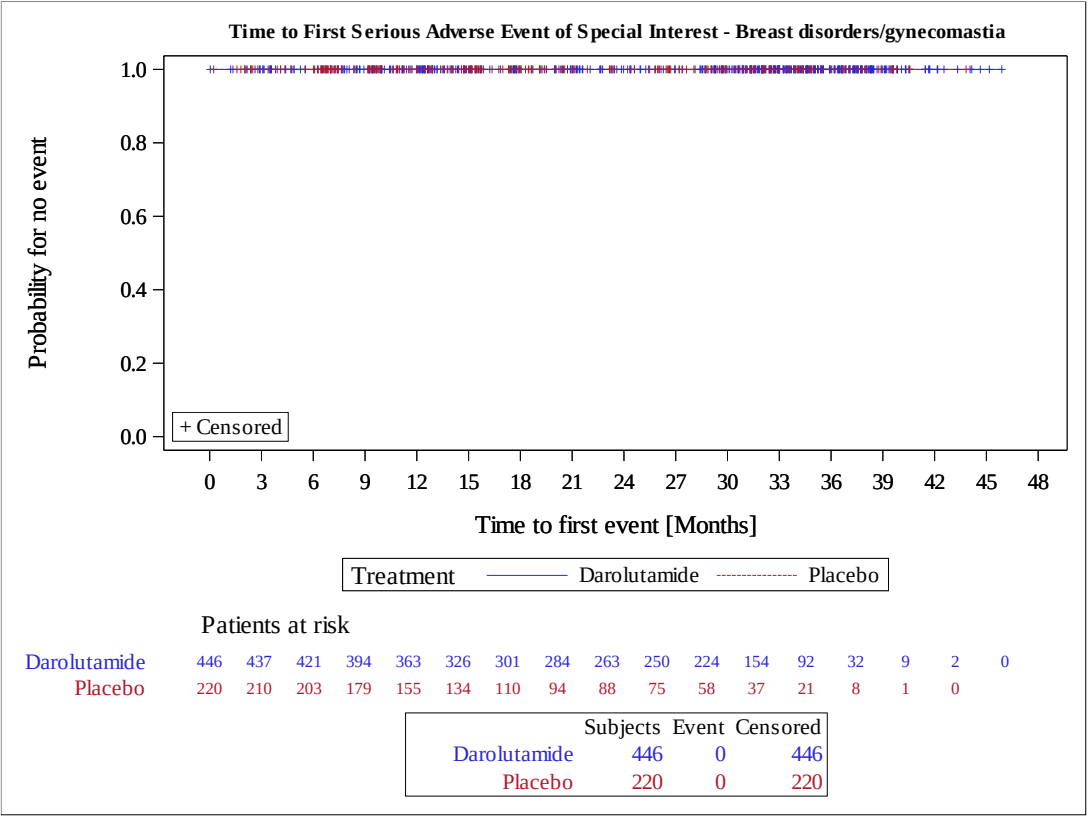
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.10.12.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Breast disorders/gynecomastia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.10.13
Summary of Serious Adverse Events of Special Interest - Cardiac disorders
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	15 (3.4)	8 (3.6)
Number of censored patients, n (%)	431 (96.6)	212 (96.4)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.800	
95% CI	0.339, 1.891	
p-value	0.6108	
Odds Ratio	0.922	
95% CI	0.385, 2.209	
p-value	0.8560	
Relative Risk	0.925	
95% CI	0.398, 2.148	
p-value	0.8559	
Risk Difference	-0.273	
95% CI	-3.259, 2.713	
p-value	0.8577	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.13.1

Summary of Serious Adverse Events of Special Interest - Cardiac disorders - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	3/ 54 (5.6)	1/ 26 (3.8)	1.214	(0.126, 11.676)	0.8662	0.6517
No	12/392 (3.1)	7/194 (3.6)	0.724	(0.284, 1.844)	0.4967	
Received prior local therapy (from IWRS)						
Yes	4/ 81 (4.9)	2/ 39 (5.1)	0.814	(0.146, 4.526)	0.8138	0.9870
No	11/365 (3.0)	6/181 (3.3)	0.794	(0.293, 2.149)	0.6485	
Prior local radiotherapy and/or prostatectomy						
Yes	5/ 88 (5.7)	4/ 49 (8.2)	0.630	(0.168, 2.358)	0.4888	0.5808
No	10/358 (2.8)	4/171 (2.3)	1.019	(0.319, 3.257)	0.9741	
Age group						
<65 years	1/117 (0.9)	0/ 64 (0.0)	NE	(NE, NE)	NE	0.9983
65-74	7/193 (3.6)	4/ 95 (4.2)	0.767	(0.224, 2.626)	0.6716	
75-84	7/118 (5.9)	4/ 51 (7.8)	0.671	(0.196, 2.293)	0.5215	
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)	NE	(NE, NE)	NE	
Race						
White	8/250 (3.2)	4/123 (3.3)	0.780	(0.233, 2.606)	0.6858	0.8393
Asian	6/144 (4.2)	1/ 65 (1.5)	2.590	(0.312, 21.514)	0.3604	
Black or African American	0/ 42 (0.0)	2/ 23 (8.7)	NE	(NE, NE)	NE	
Other	1/ 10 (10.0)	1/ 9 (11.1)	0.887	(0.055, 14.184)	0.9327	
Geographical region						
Asia	6/141 (4.3)	1/ 63 (1.6)				0.7048
Latin America	3/120 (2.5)	4/ 70 (5.7)				
Europe and Rest of the world	6/185 (3.2)	3/ 87 (3.4)				
Baseline PSA values by median						
< median of overall population	8/216 (3.7)	5/109 (4.6)	0.701	(0.228, 2.148)	0.5314	0.9921
>= median of overall population	7/219 (3.2)	3/108 (2.8)	0.993	(0.256, 3.849)	0.9921	
ECOG PS at baseline						
=0	9/235 (3.8)	3/ 96 (3.1)	1.079	(0.292, 3.993)	0.9092	0.5497
>=1	6/211 (2.8)	5/124 (4.0)	0.611	(0.186, 2.009)	0.4122	
Gleason score at initial diagnosis						
Gleason <8	3/125 (2.4)	4/ 64 (6.3)	0.332	(0.074, 1.492)	0.1310	0.1061
Gleason >=8	12/308 (3.9)	3/146 (2.1)	1.678	(0.473, 5.954)	0.4181	
Disease volume at baseline						
high	11/315 (3.5)	6/155 (3.9)	0.793	(0.293, 2.147)	0.6473	0.9429
low	4/131 (3.1)	2/ 65 (3.1)	0.792	(0.144, 4.358)	0.7887	
Renal function - eGFR at baseline						
Normal: eGFR >= 90 mL/min	9/221 (4.1)	2/102 (2.0)	1.771	(0.382, 8.209)	0.4592	0.2520
Mild impairment: 60 <= eGFR < 90 mL/min	5/179 (2.8)	3/ 90 (3.3)	0.766	(0.183, 3.217)	0.7155	
Moderate impairment: 30 <= eGFR < 60 mL/min	1/ 45 (2.2)	3/ 27 (11.1)	0.178	(0.018, 1.710)	0.0913	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.10.13.1
Summary of Serious Adverse Events of Special Interest - Cardiac disorders - Subgroup analysis
(safety analysis set)

Final

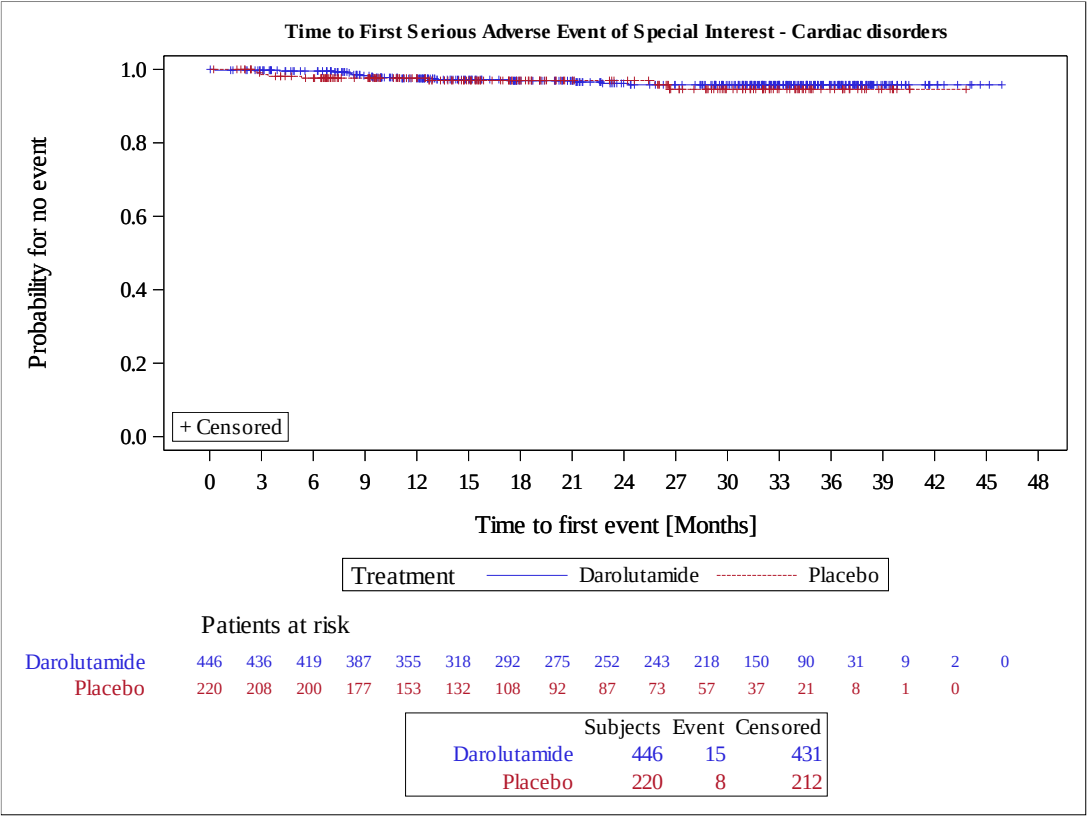
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Hepatic function at baseline						0.9873
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	12/387 (3.1)	8/200 (4.0)	0.670	(0.273, 1.645)	0.3795	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	3/ 59 (5.1)	0/ 20 (0.0)	NE	(NE, NE)	NE	
Age Group (Titan)						0.9897
<65	1/117 (0.9)	0/ 64 (0.0)	NE	(NE, NE)	NE	
>=65 and <75	7/193 (3.6)	4/ 95 (4.2)	0.767	(0.224, 2.626)	0.6716	
>=75	7/136 (5.1)	4/ 61 (6.6)	0.695	(0.203, 2.377)	0.5596	
Geographic region (Titan)						0.6202
Europe and north america	4/145 (2.8)	3/ 76 (3.9)	0.582	(0.129, 2.620)	0.4754	
ROTW	11/301 (3.7)	5/144 (3.5)	0.928	(0.322, 2.674)	0.8901	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.10.13.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Cardiac disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.10.14
Summary of Serious Adverse Events of Special Interest - Cerebral ischaemia
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	3 (0.7)	3 (1.4)
Number of censored patients, n (%)	443 (99.3)	217 (98.6)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.374	
95% CI	0.075, 1.882	
p-value	0.2155	
Odds Ratio	0.490	
95% CI	0.098, 2.447	
p-value	0.3845	
Relative Risk	0.493	
95% CI	0.100, 2.424	
p-value	0.3843	
Risk Difference	-0.691	
95% CI	-2.401, 1.019	
p-value	0.4284	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.14.1

Summary of Serious Adverse Events of Special Interest - Cerebral ischaemia - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	1/ 26 (3.8)			
No	3/392 (0.8)	2/194 (1.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	3/365 (0.8)	3/181 (1.7)			
Prior local radiotherapy and/or prostatectomy					
Yes	1/ 88 (1.1)	0/ 49 (0.0)			
No	2/358 (0.6)	3/171 (1.8)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	3/ 95 (3.2)			
75-84	3/118 (2.5)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	2/250 (0.8)	3/123 (2.4)			
Asian	1/144 (0.7)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	1/141 (0.7)	0/ 63 (0.0)			
Latin America	1/120 (0.8)	0/ 70 (0.0)			
Europe and Rest of the world	1/185 (0.5)	3/ 87 (3.4)			
Baseline PSA values by median					
< median of overall population	3/216 (1.4)	1/109 (0.9)			
>= median of overall population	0/219 (0.0)	2/108 (1.9)			
ECOG PS at baseline					
=0	2/235 (0.9)	2/ 96 (2.1)			
>=1	1/211 (0.5)	1/124 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	1/ 64 (1.6)			
Gleason >=8	3/308 (1.0)	2/146 (1.4)			
Disease volume at baseline					
high	1/315 (0.3)	3/155 (1.9)			
low	2/131 (1.5)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	2/221 (0.9)	1/102 (1.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	1/179 (0.6)	1/ 90 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	1/ 27 (3.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.14.1

Summary of Serious Adverse Events of Special Interest - Cerebral ischaemia - Subgroup analysis (safety analysis set)

Final

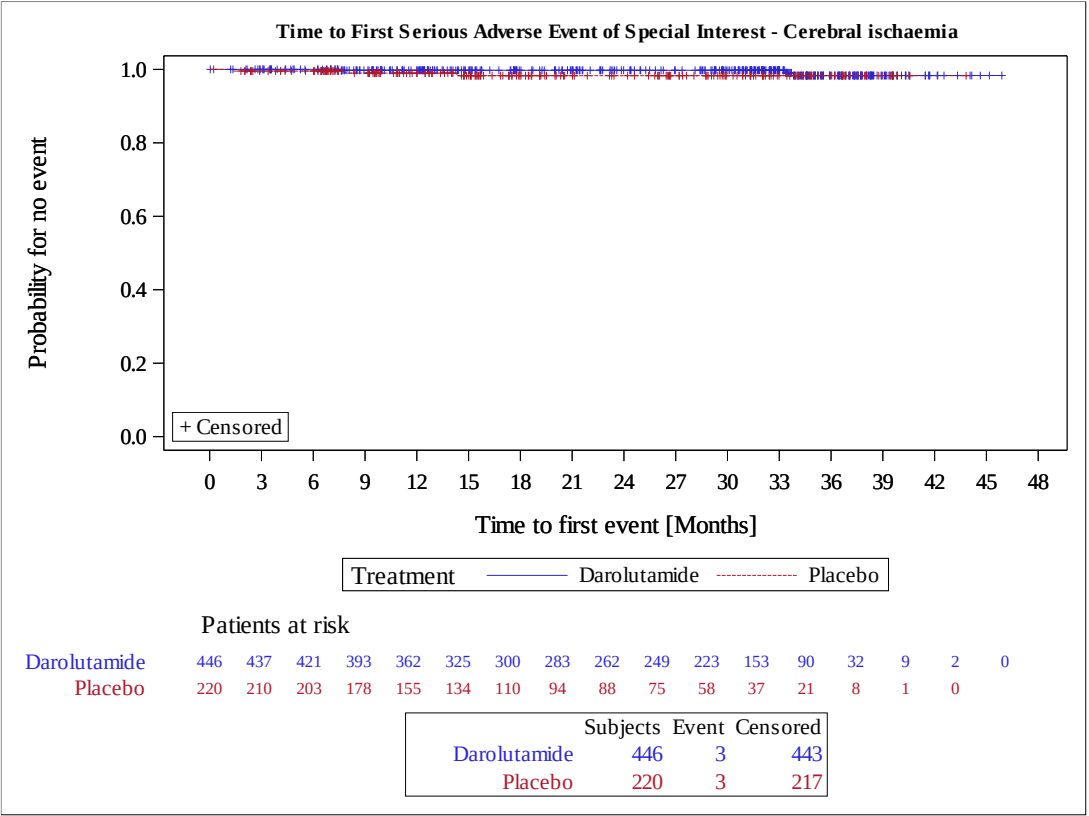
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI) p-Value	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	1/387 (0.3)	3/200 (1.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	2/ 59 (3.4)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	3/ 95 (3.2)			
>=75	3/136 (2.2)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	3/ 76 (3.9)			
ROTW	3/301 (1.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.10.14.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Cerebral ischaemia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.10.15
Summary of Serious Adverse Events of Special Interest - Cerebral and intracranial hemorrhage
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	2 (0.4)	1 (0.5)
Number of censored patients, n (%)	444 (99.6)	219 (99.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.823	
95% CI	0.074, 9.122	
p-value	0.8736	
Odds Ratio	0.986	
95% CI	0.089, 10.939	
p-value	0.9912	
Relative Risk	0.987	
95% CI	0.090, 10.821	
p-value	0.9912	
Risk Difference	-0.006	
95% CI	-1.090, 1.078	
p-value	0.9912	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.15.1

Summary of Serious Adverse Events of Special Interest - Cerebral and intracranial hemorrhage - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	2/392 (0.5)	1/194 (0.5)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	2/365 (0.5)	1/181 (0.6)			
Prior local radiotherapy and/or prostatectomy					
Yes	2/ 88 (2.3)	0/ 49 (0.0)			
No	0/358 (0.0)	1/171 (0.6)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	1/118 (0.8)	0/ 51 (0.0)			
>=85 years	1/ 18 (5.6)	1/ 10 (10.0)			
Race					
White	1/250 (0.4)	0/123 (0.0)			
Asian	1/144 (0.7)	1/ 65 (1.5)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	1/141 (0.7)	1/ 63 (1.6)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	1/185 (0.5)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	2/216 (0.9)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	1/108 (0.9)			
ECOG PS at baseline					
=0	2/235 (0.9)	0/ 96 (0.0)			
>=1	0/211 (0.0)	1/124 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	1/ 64 (1.6)			
Gleason >=8	2/308 (0.6)	0/146 (0.0)			
Disease volume at baseline					
high	1/315 (0.3)	0/155 (0.0)			
low	1/131 (0.8)	1/ 65 (1.5)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	2/179 (1.1)	1/ 90 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.15.1

Summary of Serious Adverse Events of Special Interest - Cerebral and intracranial hemorrhage - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	1/387 (0.3)	1/200 (0.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 59 (1.7)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	2/136 (1.5)	1/ 61 (1.6)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	2/301 (0.7)	1/144 (0.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

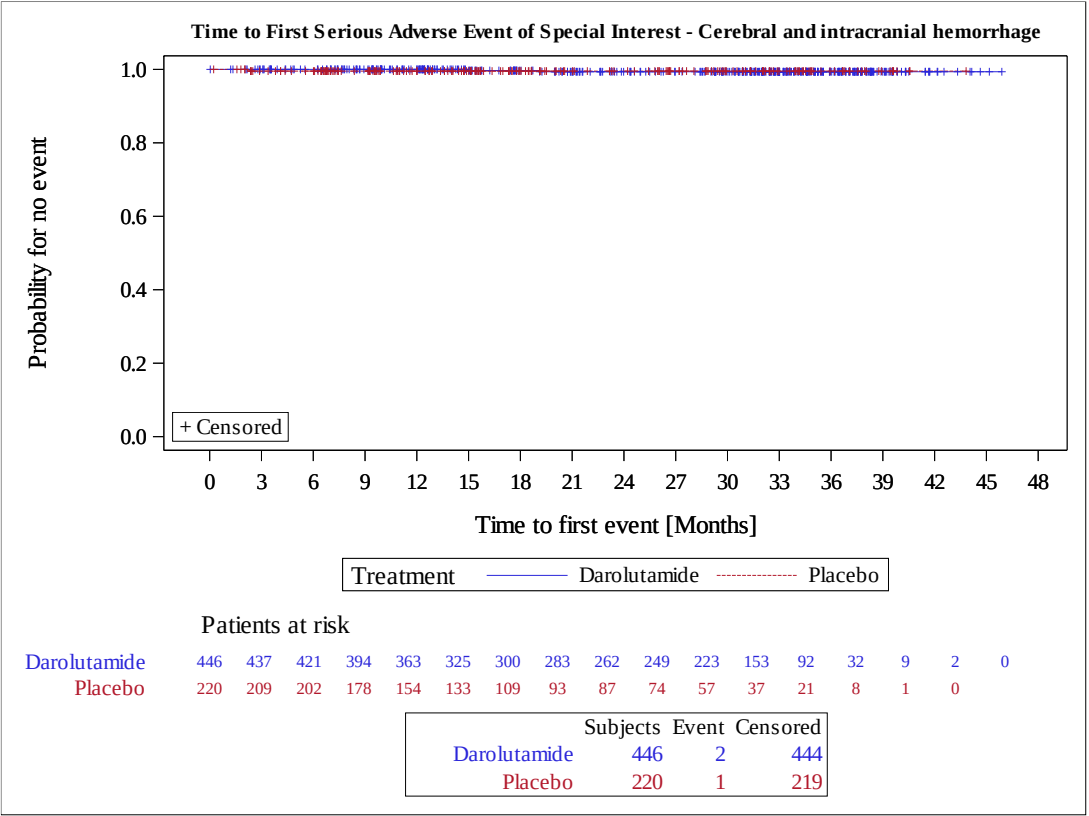
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.10.15.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Cerebral and intracranial hemorrhage
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.10.16
Summary of Serious Adverse Events of Special Interest - Interstitial lung disease
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	446 (100.0)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.10.16.1

Summary of Serious Adverse Events of Special Interest - Interstitial lung disease - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/211 (0.0)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/315 (0.0)	0/155 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.10.16.1

Summary of Serious Adverse Events of Special Interest - Interstitial lung disease - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

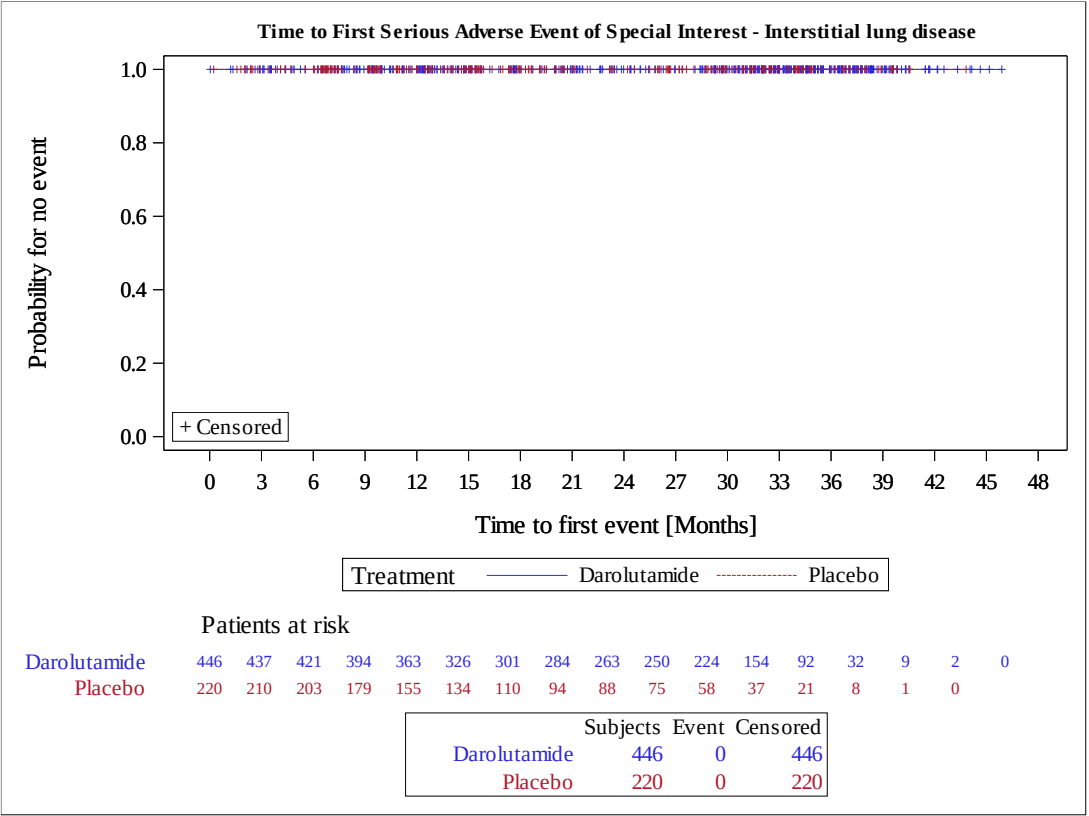
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.10.16.2
Kaplan-Meier Plot of Time to First Serious Adverse Event of Special Interest - Interstitial lung disease
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.11.1
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Bone fractures excluding pathological fractures
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	8 (1.8)	1 (0.5)
Number of censored patients, n (%)	438 (98.2)	219 (99.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	2.965	
95% CI	0.370, 23.757	
p-value	0.2826	
Odds Ratio	4.000	
95% CI	0.497, 32.184	
p-value	0.1926	
Relative Risk	3.946	
95% CI	0.497, 31.353	
p-value	0.1942	
Risk Difference	1.339	
95% CI	-0.180, 2.858	
p-value	0.0840	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.11.1.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥3 - Bone fractures excluding pathological fractures - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	1/ 54 (1.9)	0/ 26 (0.0)			
No	7/392 (1.8)	1/194 (0.5)			
Received prior local therapy (from IWRS)					
Yes	2/ 81 (2.5)	0/ 39 (0.0)			
No	6/365 (1.6)	1/181 (0.6)			
Prior local radiotherapy and/or prostatectomy					
Yes	2/ 88 (2.3)	0/ 49 (0.0)			
No	6/358 (1.7)	1/171 (0.6)			
Age group					
<65 years	1/117 (0.9)	0/ 64 (0.0)			
65-74	1/193 (0.5)	0/ 95 (0.0)			
75-84	5/118 (4.2)	1/ 51 (2.0)			
>=85 years	1/ 18 (5.6)	0/ 10 (0.0)			
Race					
White	6/250 (2.4)	0/123 (0.0)			
Asian	2/144 (1.4)	1/ 65 (1.5)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	2/141 (1.4)	1/ 63 (1.6)			
Latin America	3/120 (2.5)	0/ 70 (0.0)			
Europe and Rest of the world	3/185 (1.6)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	7/216 (3.2)	0/109 (0.0)			
>= median of overall population	1/219 (0.5)	1/108 (0.9)			
ECOG PS at baseline					
=0	3/235 (1.3)	1/ 96 (1.0)			
>=1	5/211 (2.4)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	4/125 (3.2)	0/ 64 (0.0)			
Gleason >=8	4/308 (1.3)	1/146 (0.7)			
Disease volume at baseline					
high	6/315 (1.9)	0/155 (0.0)			
low	2/131 (1.5)	1/ 65 (1.5)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	3/221 (1.4)	1/102 (1.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	5/179 (2.8)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.1.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Bone fractures excluding pathological fractures - Subgroup analysis (safety analysis set)

Final

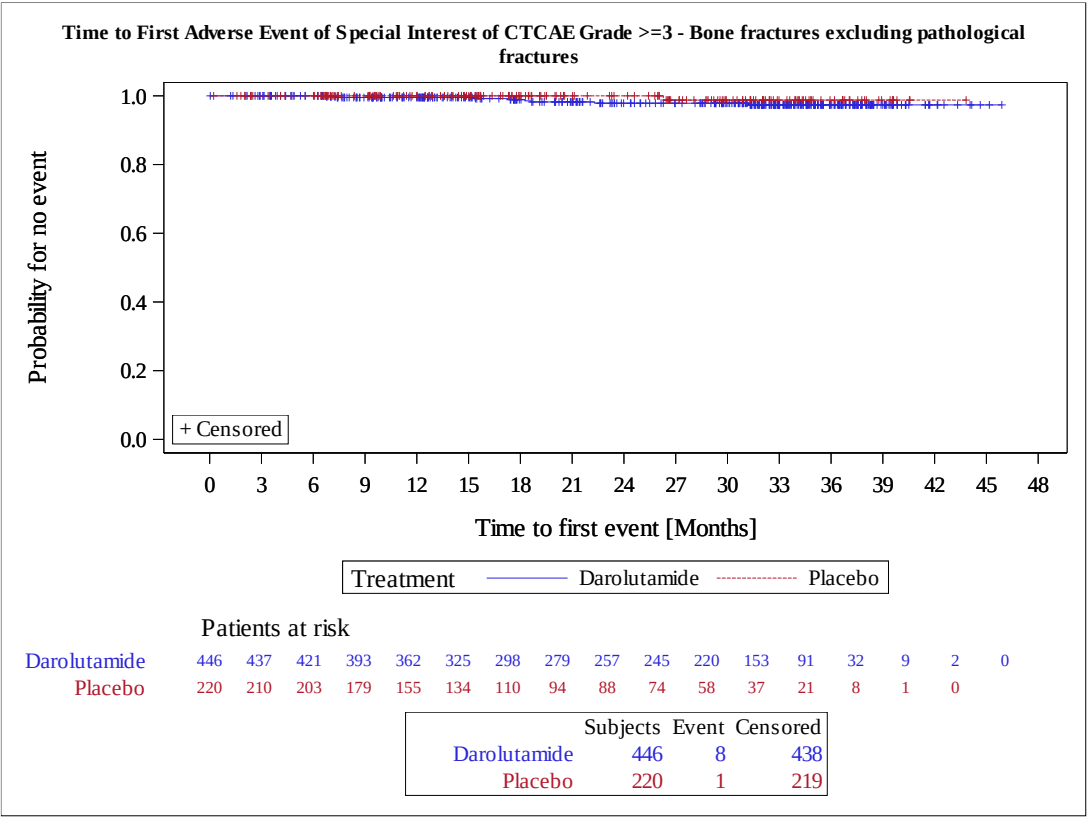
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	8/387 (2.1)	1/200 (0.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	1/117 (0.9)	0/ 64 (0.0)			
>=65 and <75	1/193 (0.5)	0/ 95 (0.0)			
>=75	6/136 (4.4)	1/ 61 (1.6)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	8/301 (2.7)	1/144 (0.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.11.1.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Bone fractures excluding pathological fractures
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.11.2
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	3 (0.7)	0 (0.0)
Number of censored patients, n (%)	443 (99.3)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	3.480	
95% CI	0.179, 67.674	
p-value	0.4101	
Relative Risk	3.461	
95% CI	0.180, 66.707	
p-value	0.4108	
Risk Difference	0.673	
95% CI	-0.086, 1.431	
p-value	0.0822	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.2.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥ 3 - Diabetes mellitus and hyperglycemia - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	3/392 (0.8)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	3/365 (0.8)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	3/358 (0.8)	0/171 (0.0)			
Age group					
<65 years	2/117 (1.7)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	1/118 (0.8)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	1/250 (0.4)	0/123 (0.0)			
Asian	1/144 (0.7)	0/ 65 (0.0)			
Black or African American	1/ 42 (2.4)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	1/141 (0.7)	0/ 63 (0.0)			
Latin America	2/120 (1.7)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	2/216 (0.9)	0/109 (0.0)			
>= median of overall population	1/219 (0.5)	0/108 (0.0)			
ECOG PS at baseline					
=0	2/235 (0.9)	0/ 96 (0.0)			
>=1	1/211 (0.5)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	1/125 (0.8)	0/ 64 (0.0)			
Gleason >=8	2/308 (0.6)	0/146 (0.0)			
Disease volume at baseline					
high	2/315 (0.6)	0/155 (0.0)			
low	1/131 (0.8)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	2/221 (0.9)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	1/ 45 (2.2)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.2.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Diabetes mellitus and hyperglycemia - Subgroup analysis (safety analysis set)

Final

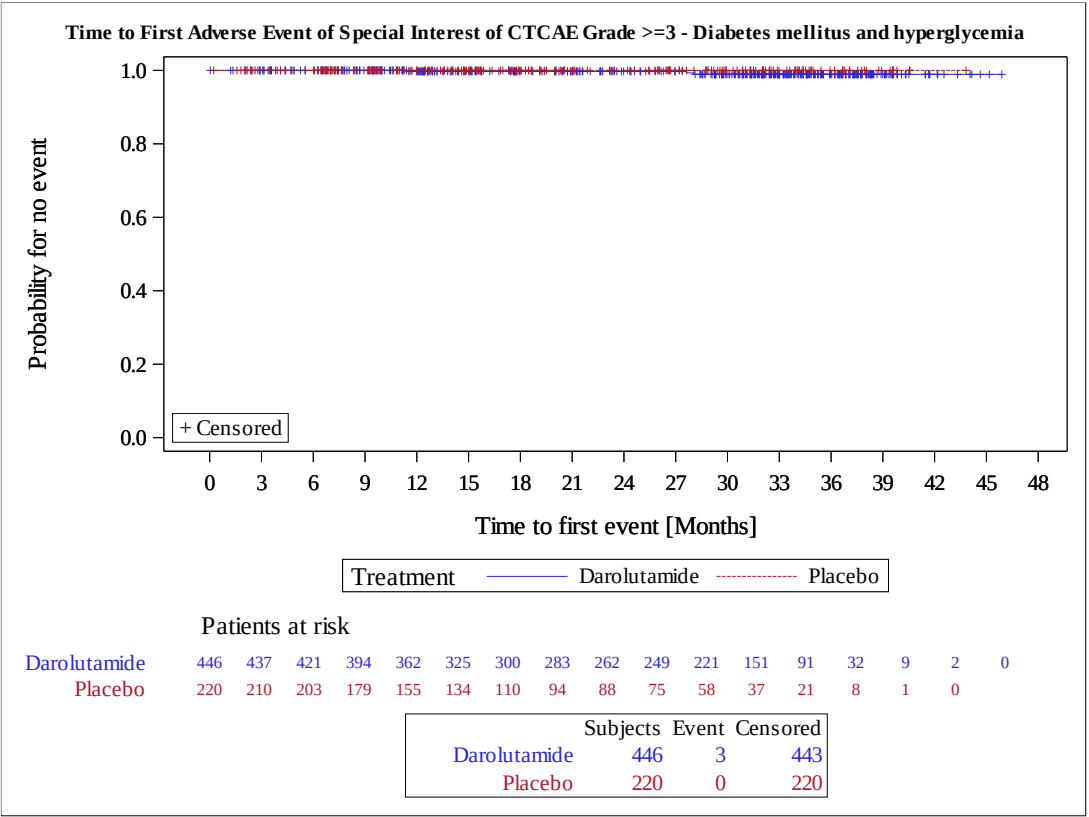
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	3/387 (0.8)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	2/117 (1.7)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	1/136 (0.7)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	3/301 (1.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.11.2.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade ≥ 3 - Diabetes mellitus and hyperglycemia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.11.3
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Fall
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	2 (0.9)
Number of censored patients, n (%)	446 (100.0)	218 (99.1)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	0.098	
95% CI	0.005, 2.047	
p-value	0.1341	
Relative Risk	0.099	
95% CI	0.005, 2.051	
p-value	0.1347	
Risk Difference	-0.909	
95% CI	-2.163, 0.345	
p-value	0.1554	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population

Table 3.2.11.3.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Fall - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	1/ 26 (3.8)			
No	0/392 (0.0)	1/194 (0.5)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	1/ 39 (2.6)			
No	0/365 (0.0)	1/181 (0.6)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	1/ 49 (2.0)			
No	0/358 (0.0)	1/171 (0.6)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	1/ 95 (1.1)			
75-84	0/118 (0.0)	1/ 51 (2.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	1/123 (0.8)			
Asian	0/144 (0.0)	1/ 65 (1.5)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	1/ 63 (1.6)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	1/ 87 (1.1)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	1/109 (0.9)			
>= median of overall population	0/219 (0.0)	1/108 (0.9)			
ECOG PS at baseline					
=0	0/235 (0.0)	1/ 96 (1.0)			
>=1	0/211 (0.0)	1/124 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	1/ 64 (1.6)			
Gleason >=8	0/308 (0.0)	1/146 (0.7)			
Disease volume at baseline					
high	0/315 (0.0)	2/155 (1.3)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	2/ 90 (2.2)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.3.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Fall - Subgroup analysis (safety analysis set)

Final

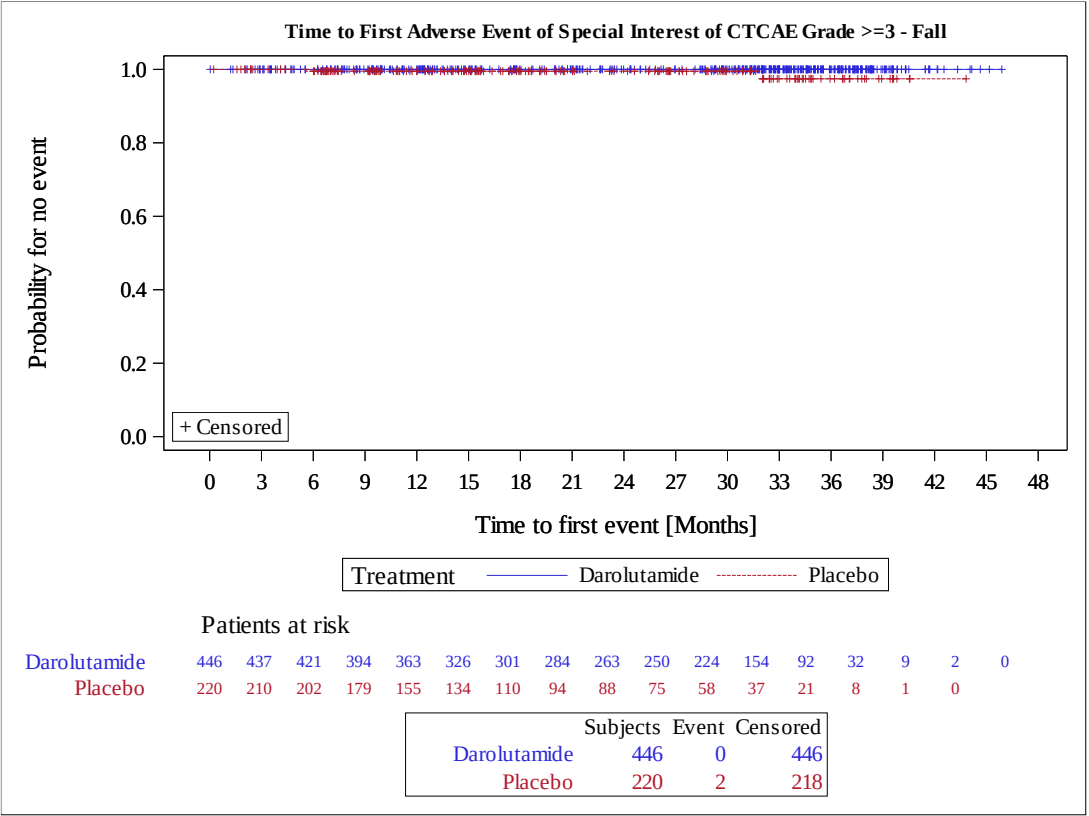
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	2/200 (1.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	1/ 95 (1.1)			
>=75	0/136 (0.0)	1/ 61 (1.6)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	2/144 (1.4)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.11.3.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Fall
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.11.4
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Fatigue/ asthenic conditions
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	1 (0.5)
Number of censored patients, n (%)	446 (100.0)	219 (99.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	0.164	
95% CI	0.007, 4.039	
p-value	0.2686	
Relative Risk	0.165	
95% CI	0.007, 4.029	
p-value	0.2689	
Risk Difference	-0.455	
95% CI	-1.343, 0.434	
p-value	0.3162	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population

Table 3.2.11.4.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥3 - Fatigue/ asthenic conditions - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	1/194 (0.5)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	1/181 (0.6)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	1/171 (0.6)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	1/ 95 (1.1)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	0/144 (0.0)	1/ 65 (1.5)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	1/ 63 (1.6)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	1/108 (0.9)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/211 (0.0)	1/124 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	0/308 (0.0)	1/146 (0.7)			
Disease volume at baseline					
high	0/315 (0.0)	1/155 (0.6)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	1/ 90 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population

Table 3.2.11.4.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Fatigue/ asthenic conditions - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI) p-Value	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	1/200 (0.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	1/ 95 (1.1)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	1/144 (0.7)			

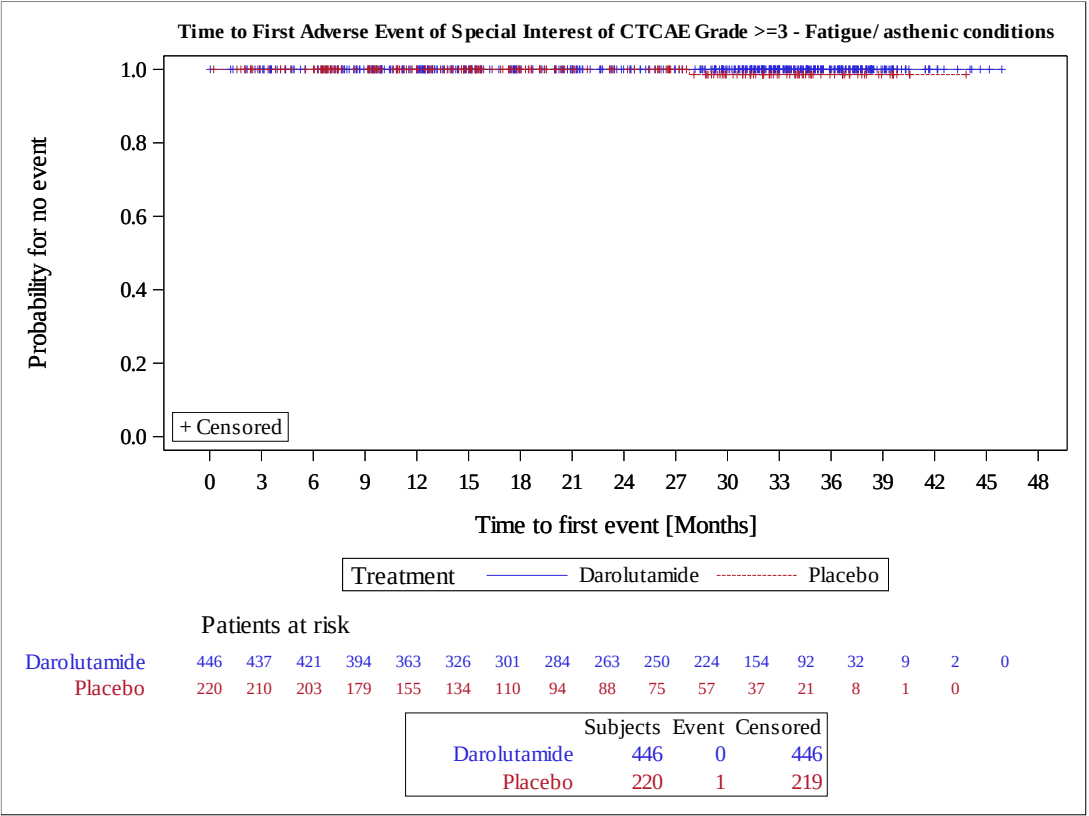
Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.11.4.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade ≥ 3 - Fatigue/ asthenic conditions
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.11.5
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Weight decreased
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	2 (0.9)
Number of censored patients, n (%)	446 (100.0)	218 (99.1)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	0.098	
95% CI	0.005, 2.047	
p-value	0.1341	
Relative Risk	0.099	
95% CI	0.005, 2.051	
p-value	0.1347	
Risk Difference	-0.909	
95% CI	-2.163, 0.345	
p-value	0.1554	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.5.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥ 3 - Weight decreased - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	2/194 (1.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	2/181 (1.1)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	2/171 (1.2)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	1/ 95 (1.1)			
75-84	0/118 (0.0)	1/ 51 (2.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	1/123 (0.8)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	1/ 23 (4.3)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	1/ 70 (1.4)			
Europe and Rest of the world	0/185 (0.0)	1/ 87 (1.1)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	1/109 (0.9)			
>= median of overall population	0/219 (0.0)	1/108 (0.9)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/211 (0.0)	2/124 (1.6)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	0/308 (0.0)	2/146 (1.4)			
Disease volume at baseline					
high	0/315 (0.0)	2/155 (1.3)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	2/ 90 (2.2)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.5.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Weight decreased - Subgroup analysis (safety analysis set)

Final

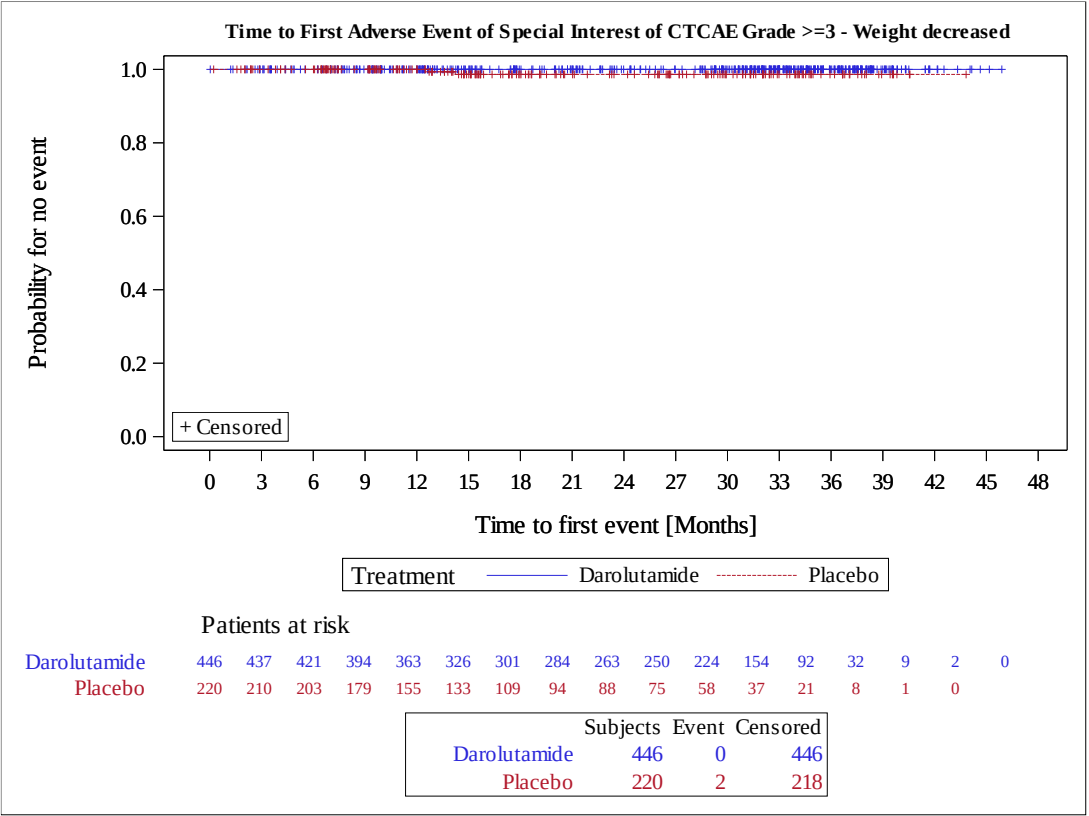
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	2/200 (1.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	1/ 95 (1.1)			
>=75	0/136 (0.0)	1/ 61 (1.6)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	1/ 76 (1.3)			
ROTW	0/301 (0.0)	1/144 (0.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.11.5.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Weight decreased
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.11.6
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Rash
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	4 (0.9)	0 (0.0)
Number of censored patients, n (%)	442 (99.1)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	4.485	
95% CI	0.240, 83.671	
p-value	0.3148	
Relative Risk	4.450	
95% CI	0.241, 82.279	
p-value	0.3159	
Risk Difference	0.897	
95% CI	0.022, 1.772	
p-value	0.0445	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.6.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥3 - Rash - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	4/392 (1.0)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	4/365 (1.1)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	4/358 (1.1)	0/171 (0.0)			
Age group					
<65 years	1/117 (0.9)	0/ 64 (0.0)			
65-74	1/193 (0.5)	0/ 95 (0.0)			
75-84	2/118 (1.7)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	3/250 (1.2)	0/123 (0.0)			
Asian	1/144 (0.7)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	1/141 (0.7)	0/ 63 (0.0)			
Latin America	2/120 (1.7)	0/ 70 (0.0)			
Europe and Rest of the world	1/185 (0.5)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	3/216 (1.4)	0/109 (0.0)			
>= median of overall population	1/219 (0.5)	0/108 (0.0)			
ECOG PS at baseline					
=0	2/235 (0.9)	0/ 96 (0.0)			
>=1	2/211 (0.9)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	3/308 (1.0)	0/146 (0.0)			
Disease volume at baseline					
high	3/315 (1.0)	0/155 (0.0)			
low	1/131 (0.8)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	2/221 (0.9)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	2/179 (1.1)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.6.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Rash - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI) p-Value	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	2/387 (0.5)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	2/ 59 (3.4)	0/ 20 (0.0)			
Age Group (Titan)					
<65	1/117 (0.9)	0/ 64 (0.0)			
>=65 and <75	1/193 (0.5)	0/ 95 (0.0)			
>=75	2/136 (1.5)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	4/301 (1.3)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

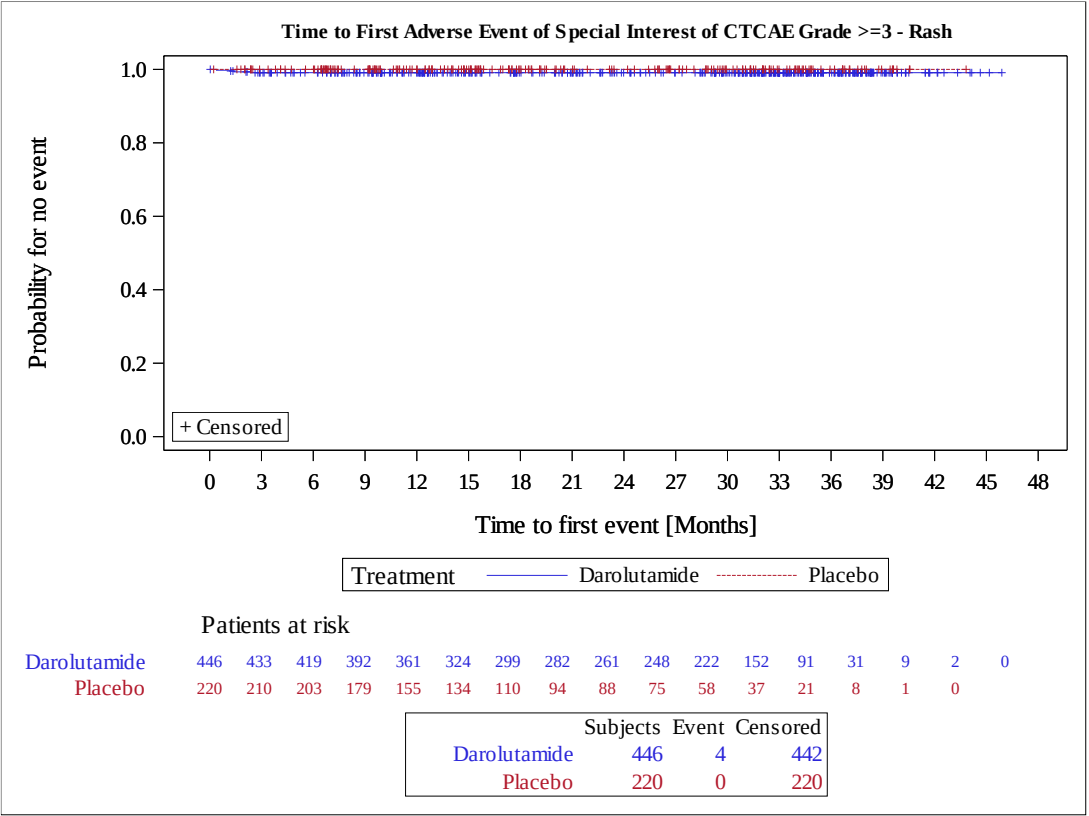
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.11.6.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Rash
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.11.7
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Seizure
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	446 (100.0)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.7.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥ 3 - Seizure - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/211 (0.0)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/315 (0.0)	0/155 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Final

Study population

Table 3.2.11.7.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Seizure - Subgroup analysis (safety analysis set)

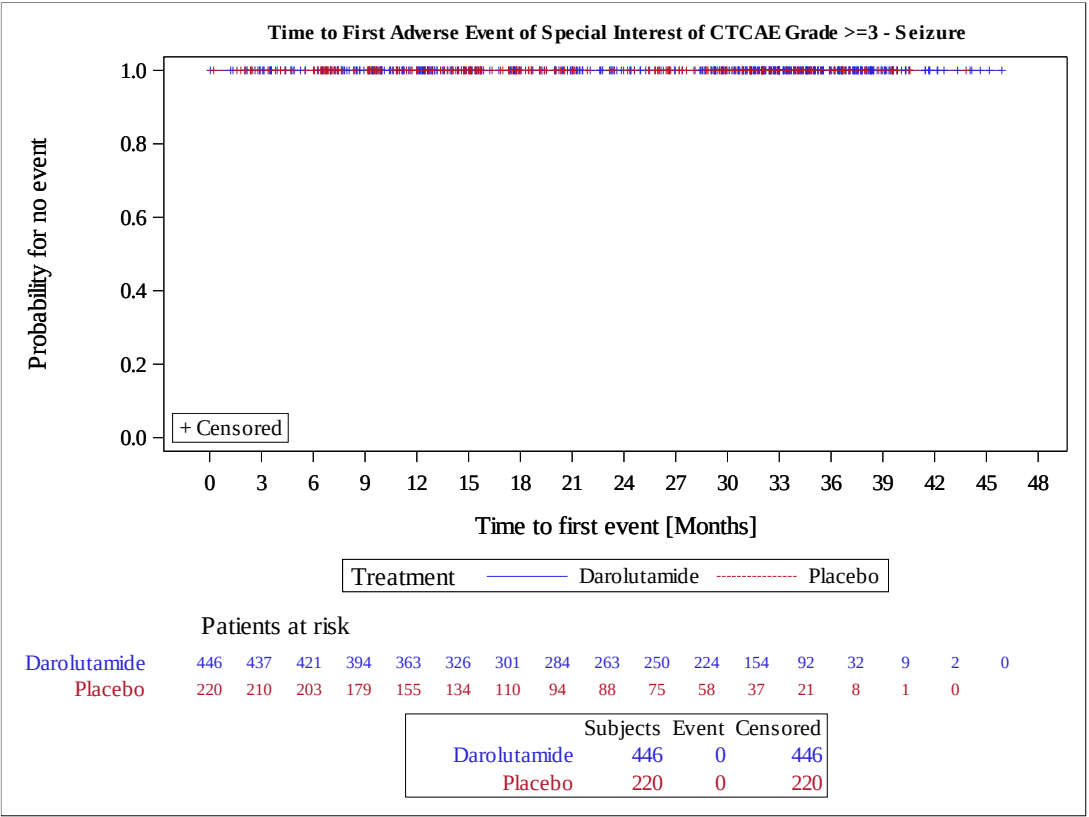
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.2.11.7.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Seizure
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.2.11.8
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Hypertension
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	22 (4.9)	9 (4.1)
Number of censored patients, n (%)	424 (95.1)	211 (95.9)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.032	
95% CI	0.474, 2.247	
p-value	0.9354	
Odds Ratio	1.216	
95% CI	0.550, 2.688	
p-value	0.6281	
Relative Risk	1.206	
95% CI	0.565, 2.575	
p-value	0.6287	
Risk Difference	0.842	
95% CI	-2.458, 4.142	
p-value	0.6171	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population

Table 3.2.11.8.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Hypertension - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						0.8632
Yes	2/ 54 (3.7)	1/ 26 (3.8)	0.820	(0.074, 9.045)	0.8709	
No	20/392 (5.1)	8/194 (4.1)	1.054	(0.463, 2.400)	0.9002	
Received prior local therapy (from IWRS)						0.7079
Yes	4/ 81 (4.9)	1/ 39 (2.6)	1.608	(0.177, 14.619)	0.6702	
No	18/365 (4.9)	8/181 (4.4)	0.974	(0.423, 2.243)	0.9505	
Prior local radiotherapy and/or prostatectomy						0.3650
Yes	5/ 88 (5.7)	1/ 49 (2.0)	2.673	(0.312, 22.930)	0.3501	
No	17/358 (4.7)	8/171 (4.7)	0.843	(0.363, 1.959)	0.6910	
Age group						0.6492
<65 years	6/117 (5.1)	1/ 64 (1.6)	2.674	(0.321, 22.306)	0.3439	
65-74	11/193 (5.7)	5/ 95 (5.3)	0.964	(0.334, 2.782)	0.9466	
75-84	4/118 (3.4)	3/ 51 (5.9)	0.503	(0.112, 2.259)	0.3612	
>=85 years	1/ 18 (5.6)	0/ 10 (0.0)	NE	(NE, NE)	NE	
Race						0.9941
White	9/250 (3.6)	3/123 (2.4)	1.285	(0.346, 4.770)	0.7069	
Asian	7/144 (4.9)	3/ 65 (4.6)	0.950	(0.245, 3.679)	0.9409	
Black or African American	6/ 42 (14.3)	3/ 23 (13.0)	0.950	(0.237, 3.809)	0.9419	
Other	0/ 10 (0.0)	0/ 9 (0.0)	NE	(NE, NE)	NE	
Geographical region						0.9159
Asia	7/141 (5.0)	3/ 63 (4.8)	0.942	(0.243, 3.646)	0.9305	
Latin America	10/120 (8.3)	4/ 70 (5.7)	1.289	(0.404, 4.116)	0.6672	
Europe and Rest of the world	5/185 (2.7)	2/ 87 (2.3)	0.985	(0.189, 5.138)	0.9856	
Baseline PSA values by median						0.5229
< median of overall population	7/216 (3.2)	4/109 (3.7)	0.812	(0.237, 2.775)	0.7389	
>= median of overall population	15/219 (6.8)	5/108 (4.6)	1.224	(0.443, 3.379)	0.6961	
ECOG PS at baseline						0.6101
=0	14/235 (6.0)	4/ 96 (4.2)	1.257	(0.413, 3.828)	0.6859	
>=1	8/211 (3.8)	5/124 (4.0)	0.784	(0.255, 2.412)	0.6702	
Gleason score at initial diagnosis						0.8446
Gleason <8	6/125 (4.8)	3/ 64 (4.7)	0.859	(0.214, 3.456)	0.8308	
Gleason >=8	15/308 (4.9)	6/146 (4.1)	1.047	(0.406, 2.704)	0.9233	
Disease volume at baseline						0.8116
high	11/315 (3.5)	5/155 (3.2)	0.943	(0.327, 2.722)	0.9135	
low	11/131 (8.4)	4/ 65 (6.2)	1.146	(0.364, 3.613)	0.8155	
Renal function - eGFR at baseline						0.8784
Normal: eGFR >= 90 mL/min	12/221 (5.4)	4/102 (3.9)	1.211	(0.390, 3.762)	0.7406	
Mild impairment: 60 <= eGFR < 90 mL/min	9/179 (5.0)	4/ 90 (4.4)	0.954	(0.293, 3.110)	0.9381	
Moderate impairment: 30 <= eGFR < 60 mL/min	1/ 45 (2.2)	1/ 27 (3.7)	0.578	(0.036, 9.246)	0.6947	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population

Table 3.2.11.8.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Hypertension - Subgroup analysis (safety analysis set)

Final

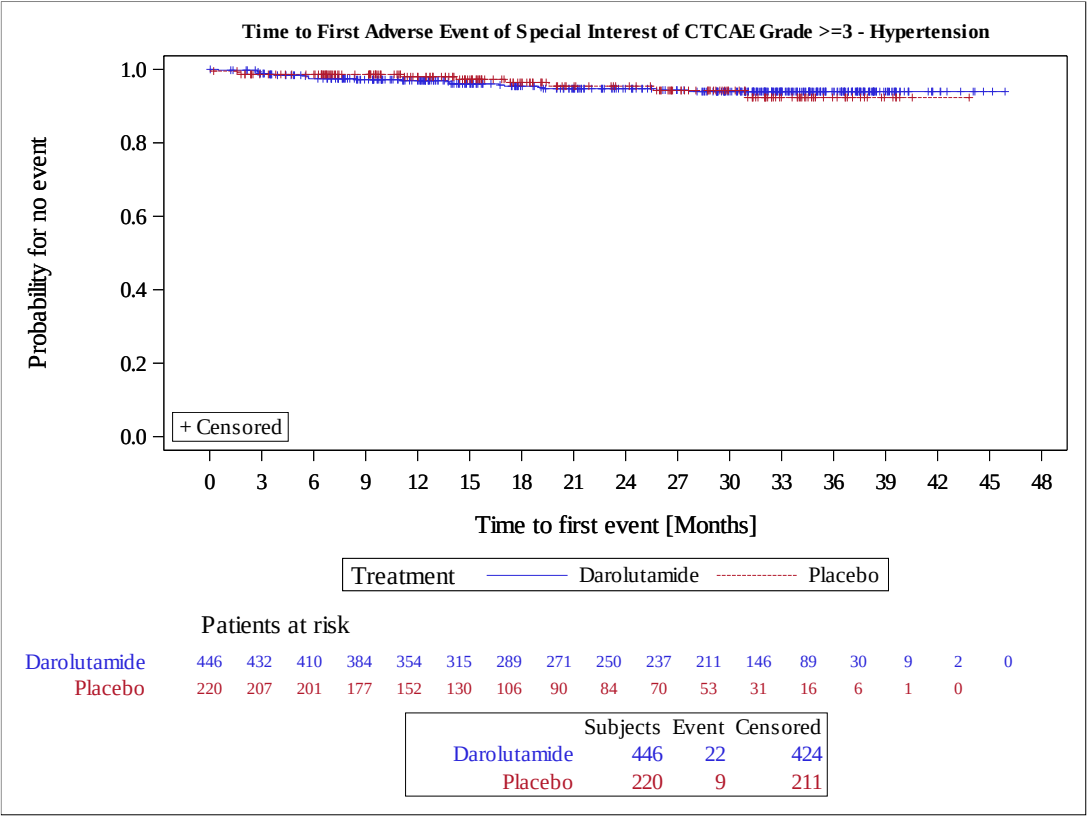
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		p-Value	Interaction p-Value
			Hazard Ratio	(95% CI)		
Hepatic function at baseline						0.3510
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	21/387 (5.4)	8/200 (4.0)	1.152	(0.509, 2.608)	0.7345	
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 59 (1.7)	1/ 20 (5.0)	0.308	(0.019, 4.925)	0.3777	
Age Group (Titan)						0.5537
<65	6/117 (5.1)	1/ 64 (1.6)	2.674	(0.321, 22.306)	0.3439	
>=65 and <75	11/193 (5.7)	5/ 95 (5.3)	0.964	(0.334, 2.782)	0.9466	
>=75	5/136 (3.7)	3/ 61 (4.9)	0.654	(0.156, 2.745)	0.5585	
Geographic region (Titan)						0.5417
Europe and north america	3/145 (2.1)	2/ 76 (2.6)	0.750	(0.125, 4.493)	0.7517	
ROTW	19/301 (6.3)	7/144 (4.9)	1.136	(0.477, 2.707)	0.7725	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Figure 3.2.11.8.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade ≥ 3 - Hypertension
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Study population
Table 3.2.11.9
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Vasodilatation and flushing
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	446 (100.0)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.2.11.9.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥3 - Vasodilatation and flushing - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/211 (0.0)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/315 (0.0)	0/155 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population

Table 3.2.11.9.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Vasodilatation and flushing - Subgroup analysis (safety analysis set)

Final

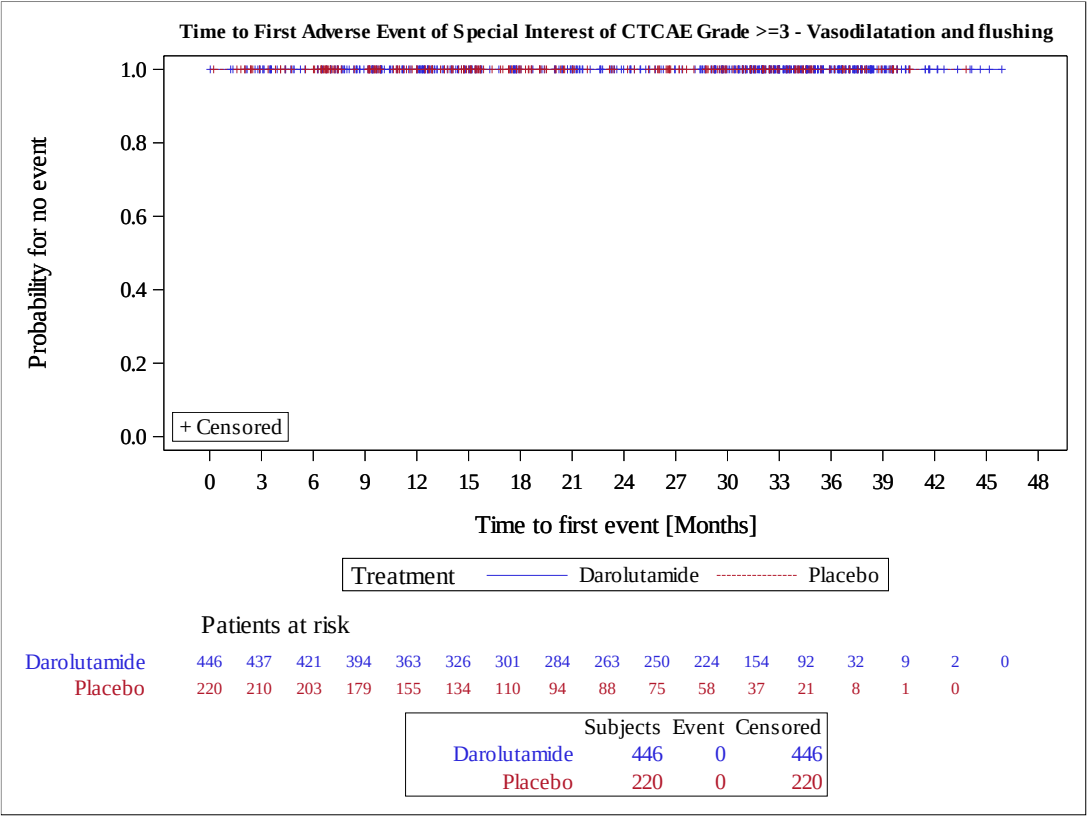
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population
Figure 3.2.11.9.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade ≥ 3 - Vasodilatation and flushing
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population
Table 3.2.11.10
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Mental impairment disorders
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	446 (100.0)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.10.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥3 - Mental impairment disorders - Subgroup analysis
(safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/211 (0.0)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/315 (0.0)	0/155 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.10.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Mental impairment disorders - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

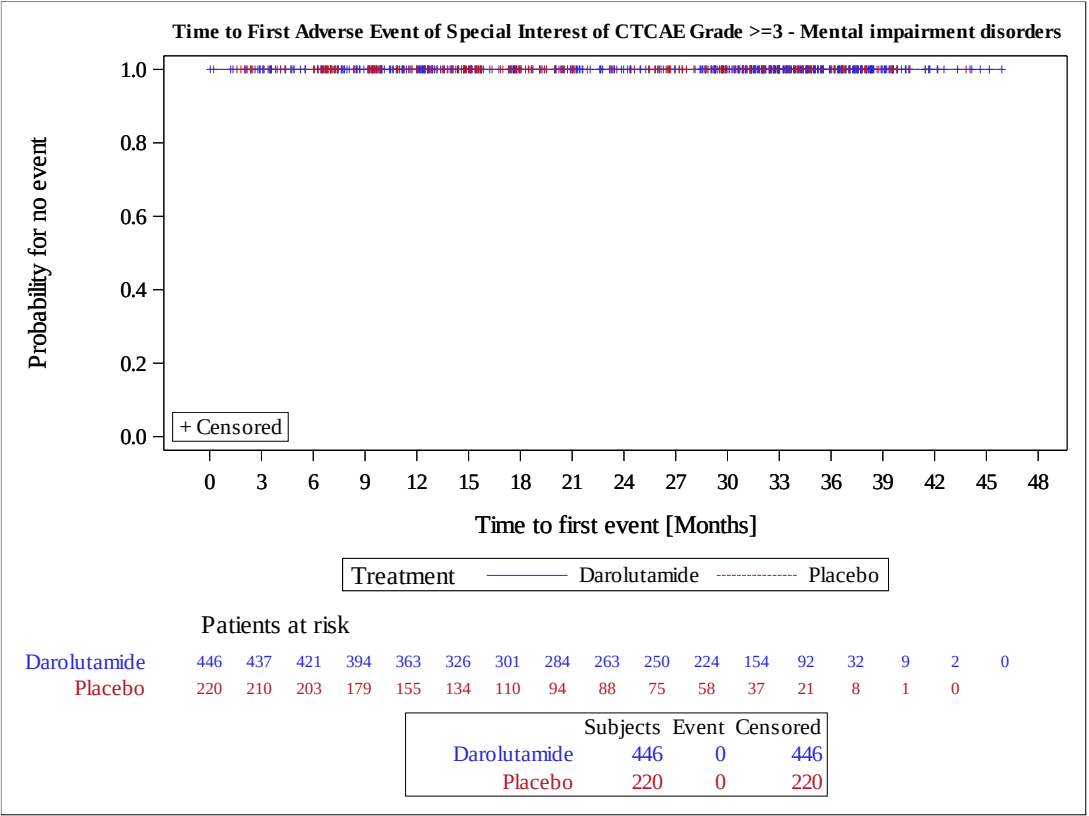
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.11.10.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade ≥ 3 - Mental impairment disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.11.11
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Depressed mood disorders
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	446 (100.0)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.11.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥3 - Depressed mood disorders - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/211 (0.0)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/315 (0.0)	0/155 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.11.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Depressed mood disorders - Subgroup analysis (safety analysis set)

Final

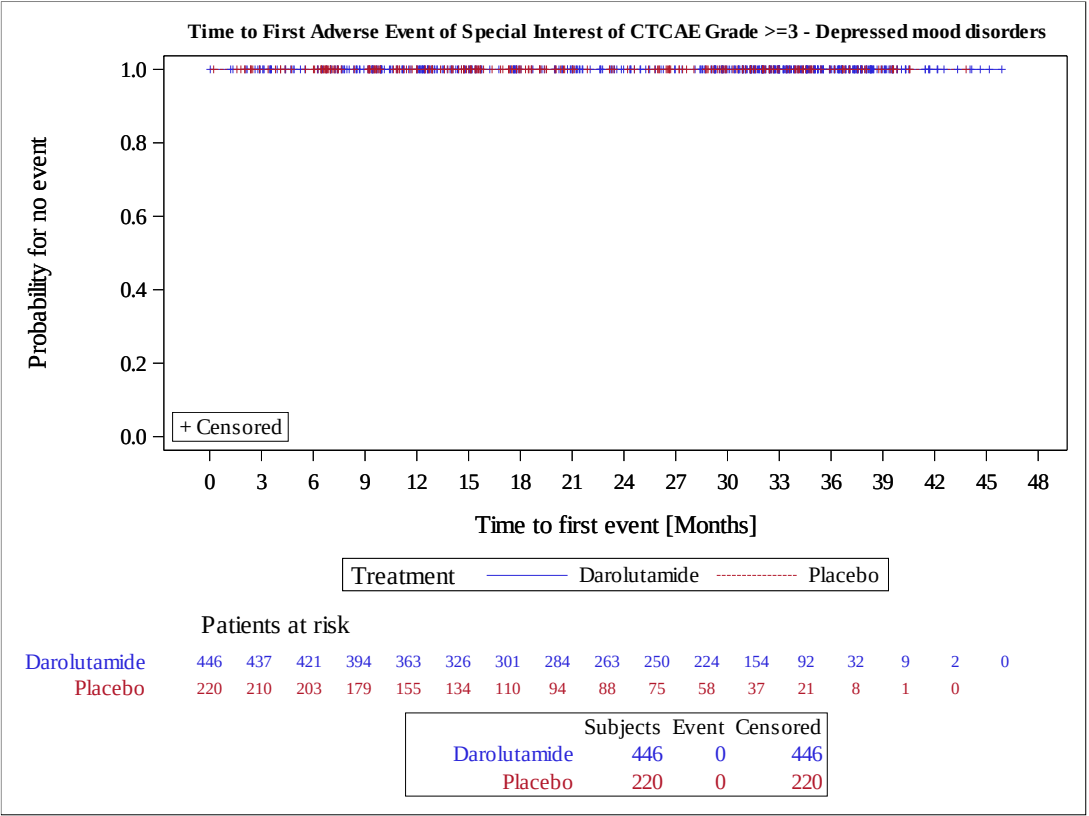
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.11.11.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Depressed mood disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.11.12
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Breast disorders/gynecomastia
(safety analysis set)

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	446 (100.0)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.12.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥3 - Breast disorders/gynecomastia - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
>=1	0/211 (0.0)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason >=8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/315 (0.0)	0/155 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.12.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Breast disorders/gynecomastia - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.

p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.

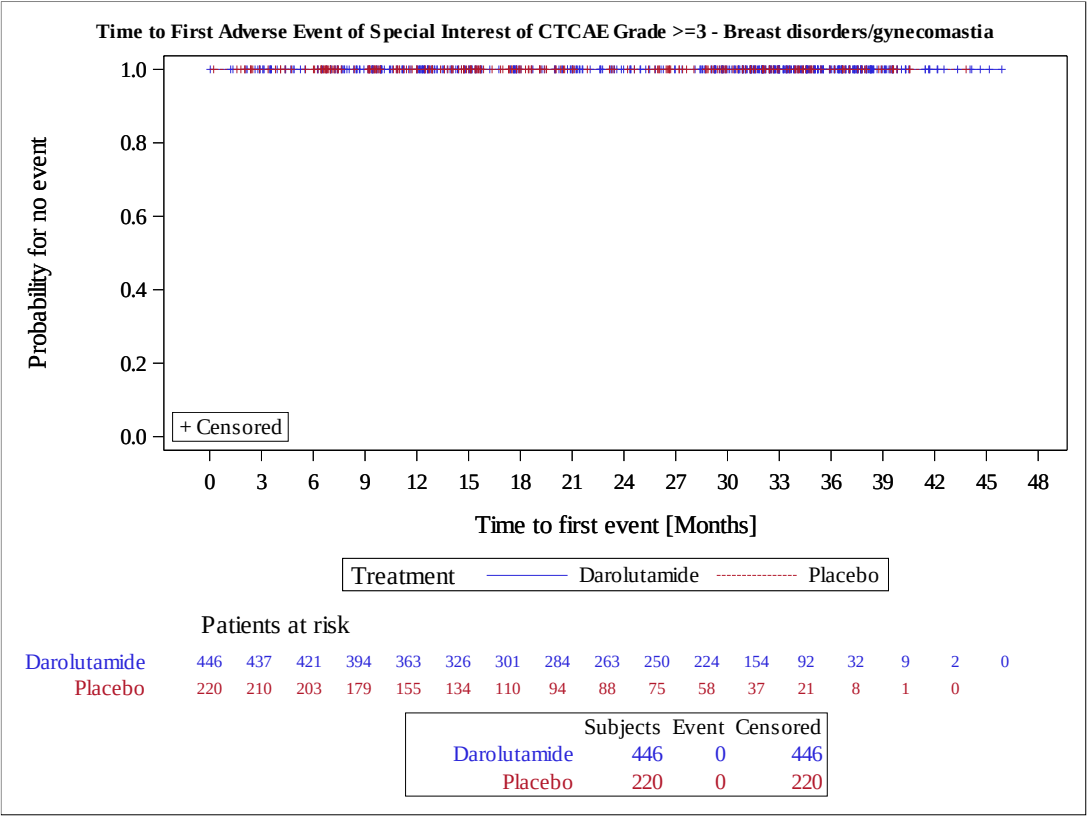
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.

Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.11.12.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade ≥ 3 - Breast disorders/gynecomastia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.11.13
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Cardiac disorders
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	11 (2.5)	6 (2.7)
Number of censored patients, n (%)	435 (97.5)	214 (97.3)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.763	
95% CI	0.282, 2.068	
p-value	0.5940	
Odds Ratio	0.902	
95% CI	0.329, 2.472	
p-value	0.8409	
Relative Risk	0.904	
95% CI	0.339, 2.413	
p-value	0.8409	
Risk Difference	-0.261	
95% CI	-2.850, 2.328	
p-value	0.8434	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.13.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Cardiac disorders - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Hazard Ratio	Unstratified Analysis (95% CI)	p-Value	Interaction p-Value
Presence of visceral metastases assessed by central review (from IWRS)						
Yes	3/ 54 (5.6)	1/ 26 (3.8)	1.201	(0.125, 11.551)	0.8737	0.6301
No	8/392 (2.0)	5/194 (2.6)	0.666	(0.217, 2.045)	0.4752	
Received prior local therapy (from IWRS)						
Yes	3/ 81 (3.7)	1/ 39 (2.6)	1.140	(0.115, 11.251)	0.9107	0.6913
No	8/365 (2.2)	5/181 (2.8)	0.683	(0.223, 2.090)	0.5012	
Prior local radiotherapy and/or prostatectomy						
Yes	6/ 88 (6.8)	2/ 49 (4.1)				
No	5/358 (1.4)	4/171 (2.3)				
Age group						
<65 years	1/117 (0.9)	0/ 64 (0.0)				
65-74	4/193 (2.1)	3/ 95 (3.2)				
75-84	5/118 (4.2)	3/ 51 (5.9)				
>=85 years	1/ 18 (5.6)	0/ 10 (0.0)				
Race						
White	3/250 (1.2)	3/123 (2.4)				
Asian	6/144 (4.2)	1/ 65 (1.5)				
Black or African American	1/ 42 (2.4)	1/ 23 (4.3)				
Other	1/ 10 (10.0)	1/ 9 (11.1)				
Geographical region						
Asia	6/141 (4.3)	1/ 63 (1.6)				
Latin America	2/120 (1.7)	3/ 70 (4.3)				
Europe and Rest of the world	3/185 (1.6)	2/ 87 (2.3)				
Baseline PSA values by median						
< median of overall population	5/216 (2.3)	4/109 (3.7)				
>= median of overall population	6/219 (2.7)	2/108 (1.9)				
ECOG PS at baseline						
=0	7/235 (3.0)	1/ 96 (1.0)				
>=1	4/211 (1.9)	5/124 (4.0)				
Gleason score at initial diagnosis						
Gleason <8	2/125 (1.6)	3/ 64 (4.7)	0.283	(0.047, 1.704)	0.1418	0.1256
Gleason >=8	9/308 (2.9)	2/146 (1.4)	1.857	(0.401, 8.609)	0.4217	
Disease volume at baseline						
high	9/315 (2.9)	5/155 (3.2)	0.767	(0.257, 2.293)	0.6342	0.9440
low	2/131 (1.5)	1/ 65 (1.5)	0.720	(0.065, 8.024)	0.7884	
Renal function - eGFR at baseline						
Normal: eGFR >= 90 mL/min	6/221 (2.7)	2/102 (2.0)				
Mild impairment: 60 <= eGFR < 90 mL/min	4/179 (2.2)	3/ 90 (3.3)				
Moderate impairment: 30 <= eGFR < 60 mL/min	1/ 45 (2.2)	1/ 27 (3.7)				

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.13.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Cardiac disorders - Subgroup analysis (safety analysis set)

Final

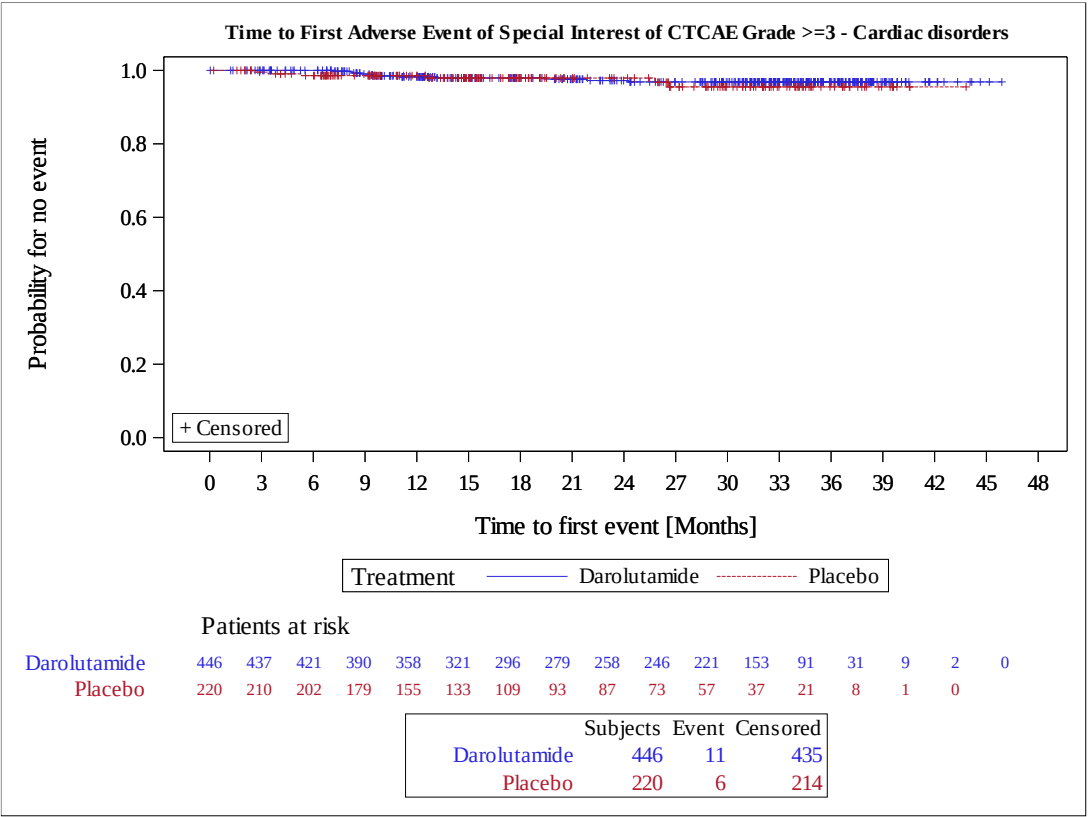
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					0.9892
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	9/387 (2.3)	6/200 (3.0)	0.645	(0.229, 1.820)	0.4042
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	2/ 59 (3.4)	0/ 20 (0.0)	NE	(NE, NE)	NE
Age Group (Titan)					
<65	1/117 (0.9)	0/ 64 (0.0)			
>=65 and <75	4/193 (2.1)	3/ 95 (3.2)			
>=75	6/136 (4.4)	3/ 61 (4.9)			
Geographic region (Titan)					0.2441
Europe and north america	1/145 (0.7)	2/ 76 (2.6)	0.251	(0.023, 2.771)	0.2225
ROTW	10/301 (3.3)	4/144 (2.8)	1.010	(0.316, 3.224)	0.9868

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.11.13.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade ≥ 3 - Cardiac disorders
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.11.14
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Cerebral ischaemia
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	2 (0.4)	3 (1.4)
Number of censored patients, n (%)	444 (99.6)	217 (98.6)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.238	
95% CI	0.039, 1.451	
p-value	0.0920	
Odds Ratio	0.326	
95% CI	0.054, 1.964	
p-value	0.2212	
Relative Risk	0.329	
95% CI	0.055, 1.954	
p-value	0.2212	
Risk Difference	-0.915	
95% CI	-2.568, 0.738	
p-value	0.2779	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.14.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥ 3 - Cerebral ischaemia - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	1/ 26 (3.8)			
No	2/392 (0.5)	2/194 (1.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	2/365 (0.5)	3/181 (1.7)			
Prior local radiotherapy and/or prostatectomy					
Yes	1/ 88 (1.1)	0/ 49 (0.0)			
No	1/358 (0.3)	3/171 (1.8)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	3/ 95 (3.2)			
75-84	2/118 (1.7)	0/ 51 (0.0)			
>=85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	1/250 (0.4)	3/123 (2.4)			
Asian	1/144 (0.7)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	1/141 (0.7)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	1/185 (0.5)	3/ 87 (3.4)			
Baseline PSA values by median					
< median of overall population	2/216 (0.9)	1/109 (0.9)			
>= median of overall population	0/219 (0.0)	2/108 (1.9)			
ECOG PS at baseline					
=0	1/235 (0.4)	2/ 96 (2.1)			
>=1	1/211 (0.5)	1/124 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	1/ 64 (1.6)			
Gleason >=8	2/308 (0.6)	2/146 (1.4)			
Disease volume at baseline					
high	1/315 (0.3)	3/155 (1.9)			
low	1/131 (0.8)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	1/221 (0.5)	1/102 (1.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	1/179 (0.6)	1/ 90 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	1/ 27 (3.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.14.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Cerebral ischaemia - Subgroup analysis (safety analysis set)

Final

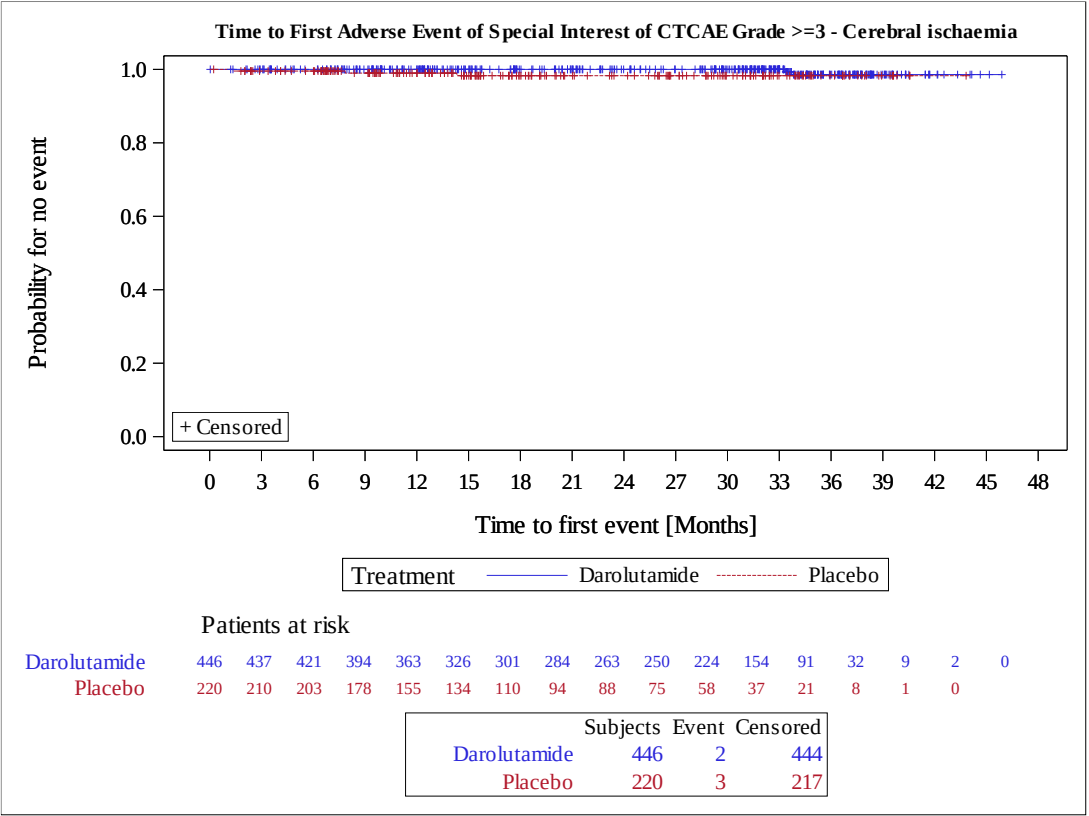
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	1/387 (0.3)	3/200 (1.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 59 (1.7)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	3/ 95 (3.2)			
>=75	2/136 (1.5)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	3/ 76 (3.9)			
ROTW	2/301 (0.7)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.2.11.14.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Cerebral ischaemia
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.2.11.15
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Cerebral and intracranial hemorrhage
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	2 (0.4)	1 (0.5)
Number of censored patients, n (%)	444 (99.6)	219 (99.5)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.823	
95% CI	0.074, 9.122	
p-value	0.8736	
Odds Ratio	0.986	
95% CI	0.089, 10.939	
p-value	0.9912	
Relative Risk	0.987	
95% CI	0.090, 10.821	
p-value	0.9912	
Risk Difference	-0.006	
95% CI	-1.090, 1.078	
p-value	0.9912	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.15.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥ 3 - Cerebral and intracranial hemorrhage - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446)	Placebo (N=220)	Unstratified Analysis		Interaction
	n/N[s] (%)	n/N[s] (%)	Hazard Ratio	(95% CI)	p-Value
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	2/392 (0.5)	1/194 (0.5)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	2/365 (0.5)	1/181 (0.6)			
Prior local radiotherapy and/or prostatectomy					
Yes	2/ 88 (2.3)	0/ 49 (0.0)			
No	0/358 (0.0)	1/171 (0.6)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	1/118 (0.8)	0/ 51 (0.0)			
>=85 years	1/ 18 (5.6)	1/ 10 (10.0)			
Race					
White	1/250 (0.4)	0/123 (0.0)			
Asian	1/144 (0.7)	1/ 65 (1.5)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	1/141 (0.7)	1/ 63 (1.6)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	1/185 (0.5)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	2/216 (0.9)	0/109 (0.0)			
>= median of overall population	0/219 (0.0)	1/108 (0.9)			
ECOG PS at baseline					
=0	2/235 (0.9)	0/ 96 (0.0)			
>=1	0/211 (0.0)	1/124 (0.8)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	1/ 64 (1.6)			
Gleason >=8	2/308 (0.6)	0/146 (0.0)			
Disease volume at baseline					
high	1/315 (0.3)	0/155 (0.0)			
low	1/131 (0.8)	1/ 65 (1.5)			
Renal function - eGFR at baseline					
Normal: eGFR >= 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: 60 <= eGFR < 90 mL/min	2/179 (1.1)	1/ 90 (1.1)			
Moderate impairment: 30 <= eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.2.11.15.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Cerebral and intracranial hemorrhage - Subgroup analysis (safety analysis set)

Final

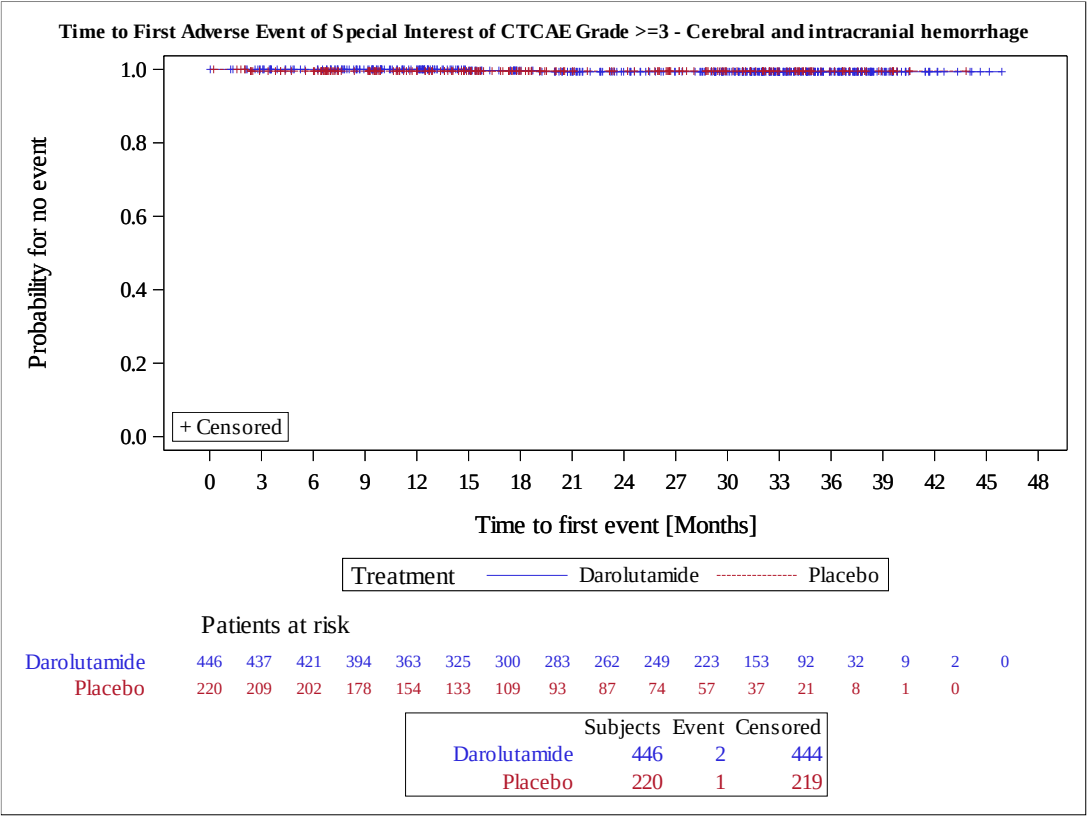
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	1/387 (0.3)	1/200 (0.5)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	1/ 59 (1.7)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	2/136 (1.5)	1/ 61 (1.6)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	2/301 (0.7)	1/144 (0.7)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population
Figure 3.2.11.15.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade >=3 - Cerebral and intracranial hemorrhage
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Study population
Table 3.2.11.16
Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Interstitial lung disease
(safety analysis set)

Final

	Darolutamide (N=446)	Placebo (N=220)
Number of patients with events, n (%)	0 (0.0)	0 (0.0)
Number of censored patients, n (%)	446 (100.0)	220 (100.0)
Time to Event (Month)		
25%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95% CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Odds Ratio	NE	
95% CI	NE, NE	
p-value	NE	
Relative Risk	NE	
95% CI	NE, NE	
p-value	NE	
Risk Difference	NE	
95% CI	NE, NE	
p-value	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, CI: Confidence Interval, NE: Not estimable
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population

Table 3.2.11.16.1

Summary of Adverse Events of Special Interest of CTCAE Grade ≥ 3 - Interstitial lung disease - Subgroup analysis (safety analysis set)

Final

Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	
Presence of visceral metastases assessed by central review (from IWRS)					
Yes	0/ 54 (0.0)	0/ 26 (0.0)			
No	0/392 (0.0)	0/194 (0.0)			
Received prior local therapy (from IWRS)					
Yes	0/ 81 (0.0)	0/ 39 (0.0)			
No	0/365 (0.0)	0/181 (0.0)			
Prior local radiotherapy and/or prostatectomy					
Yes	0/ 88 (0.0)	0/ 49 (0.0)			
No	0/358 (0.0)	0/171 (0.0)			
Age group					
<65 years	0/117 (0.0)	0/ 64 (0.0)			
65-74	0/193 (0.0)	0/ 95 (0.0)			
75-84	0/118 (0.0)	0/ 51 (0.0)			
≥ 85 years	0/ 18 (0.0)	0/ 10 (0.0)			
Race					
White	0/250 (0.0)	0/123 (0.0)			
Asian	0/144 (0.0)	0/ 65 (0.0)			
Black or African American	0/ 42 (0.0)	0/ 23 (0.0)			
Other	0/ 10 (0.0)	0/ 9 (0.0)			
Geographical region					
Asia	0/141 (0.0)	0/ 63 (0.0)			
Latin America	0/120 (0.0)	0/ 70 (0.0)			
Europe and Rest of the world	0/185 (0.0)	0/ 87 (0.0)			
Baseline PSA values by median					
< median of overall population	0/216 (0.0)	0/109 (0.0)			
$\geq$ median of overall population	0/219 (0.0)	0/108 (0.0)			
ECOG PS at baseline					
=0	0/235 (0.0)	0/ 96 (0.0)			
≥ 1	0/211 (0.0)	0/124 (0.0)			
Gleason score at initial diagnosis					
Gleason <8	0/125 (0.0)	0/ 64 (0.0)			
Gleason ≥ 8	0/308 (0.0)	0/146 (0.0)			
Disease volume at baseline					
high	0/315 (0.0)	0/155 (0.0)			
low	0/131 (0.0)	0/ 65 (0.0)			
Renal function - eGFR at baseline					
Normal: eGFR ≥ 90 mL/min	0/221 (0.0)	0/102 (0.0)			
Mild impairment: $60 \leq$ eGFR < 90 mL/min	0/179 (0.0)	0/ 90 (0.0)			
Moderate impairment: $30 \leq$ eGFR < 60 mL/min	0/ 45 (0.0)	0/ 27 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Study population

Table 3.2.11.16.1

Summary of Adverse Events of Special Interest of CTCAE Grade >=3 - Interstitial lung disease - Subgroup analysis (safety analysis set)

Final

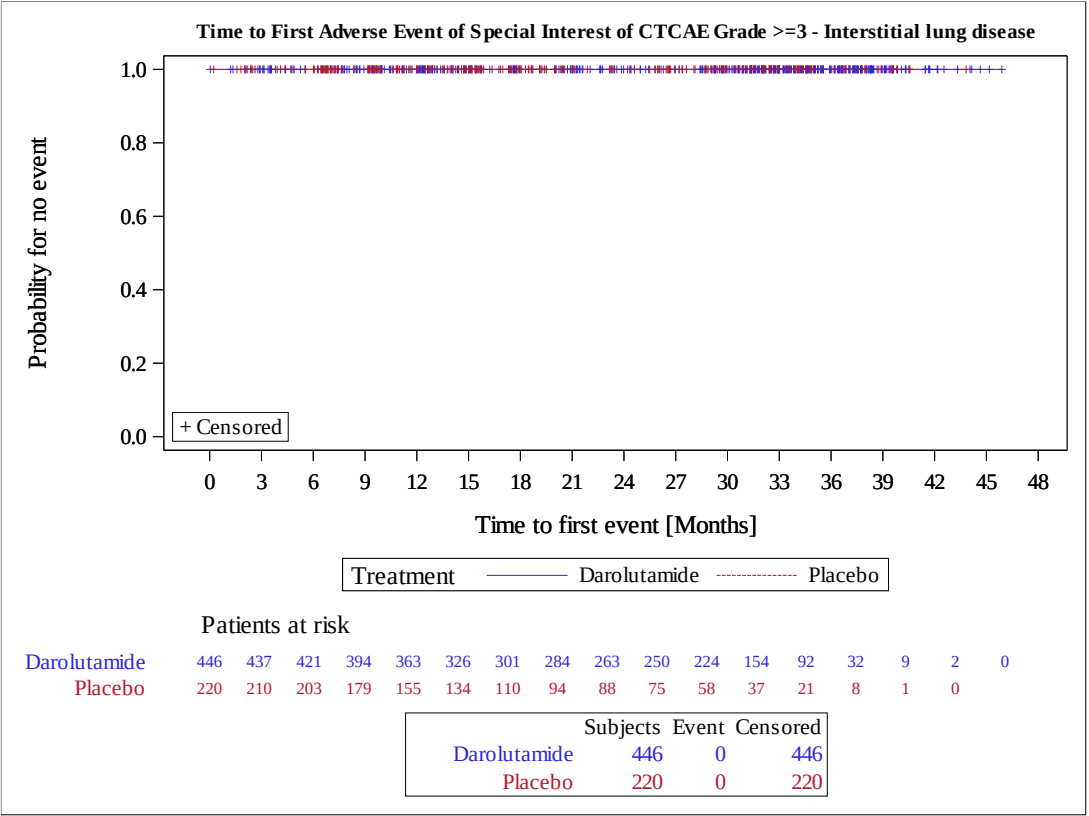
Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis		Interaction p-Value
			Hazard Ratio	(95% CI)	p-Value
Hepatic function at baseline					
Normal: Total bilirubin and AST <= upper limit of normal (ULN)	0/387 (0.0)	0/200 (0.0)			
Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	0/ 59 (0.0)	0/ 20 (0.0)			
Age Group (Titan)					
<65	0/117 (0.0)	0/ 64 (0.0)			
>=65 and <75	0/193 (0.0)	0/ 95 (0.0)			
>=75	0/136 (0.0)	0/ 61 (0.0)			
Geographic region (Titan)					
Europe and north america	0/145 (0.0)	0/ 76 (0.0)			
ROTW	0/301 (0.0)	0/144 (0.0)			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Figure 3.2.11.16.2
Kaplan-Meier Plot of Time to First Adverse Event of Special Interest of CTCAE Grade ≥ 3 - Interstitial lung disease
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant ($\alpha \leq 0.05$).
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Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Blood and lymphatic system disorders	Number of subjects with events, n (%)	109 (24.4)	44 (20.0)
	Number of censored subjects, n (%)	337 (75.6)	176 (80.0)
	Time to Event (Month)		
	25%-ile (95%-CI)	22.2 (17.4, 35.2)	28.4 (16.5, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.082	
	95% CI	0.762, 1.538	
	p-value	0.6580	
	Odds Ratio	1.294	
	95% CI	0.872, 1.920	
	p-value	0.2009	
	Relative Risk	1.222	
	95% CI	0.896, 1.667	
	p-value	0.2059	
	Risk Difference	4.439	
	95% CI	-2.182, 11.061	
	p-value	0.1888	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Blood and lymphatic system disorders - PT:Anaemia	Number of subjects with events, n (%)	96 (21.5)	40 (18.2)
	Number of censored subjects, n (%)	350 (78.5)	180 (81.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	30.4 (21.2, NE)	31.0 (17.4, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.034	
	95% CI	0.714, 1.497	
	p-value	0.8570	
	Odds Ratio	1.234	
	95% CI	0.819, 1.860	
	p-value	0.3147	
	Relative Risk	1.184	
	95% CI	0.850, 1.649	
	p-value	0.3185	
	Risk Difference	3.343	
	95% CI	-3.023, 9.709	
	p-value	0.3034	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Blood and lymphatic system disorders - PT:Leukopenia*	Number of subjects with events, n (%) 8 (1.8)	3 (1.4)
	Number of censored subjects, n (%) 438 (98.2)	217 (98.6)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	1.115 0.295, 4.219 0.8727
	Odds Ratio 95% CI p-value	1.321 0.347, 5.030 0.6830
	Relative Risk 95% CI p-value	1.315 0.352, 4.910 0.6833
	Risk Difference 95% CI p-value	0.430 -1.536, 2.396 0.6681

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Blood and lymphatic system disorders - PT:Neutropenia*	Number of subjects with events, n (%)	6 (1.3)	4 (1.8)
	Number of censored subjects, n (%)	440 (98.7)	216 (98.2)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.603	
	95% CI	0.169, 2.146	
	p-value	0.4299	
	Odds Ratio	0.736	
	95% CI	0.206, 2.637	
	p-value	0.6382	
	Relative Risk	0.740	
	95% CI	0.211, 2.595	
	p-value	0.6380	
	Risk Difference	-0.473	
	95% CI	-2.537, 1.591	
	p-value	0.6534	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Blood and lymphatic system disorders - PT:Thrombocytopenia	Number of subjects with events, n (%)	12 (2.7)	3 (1.4)
	Number of censored subjects, n (%)	434 (97.3)	217 (98.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.630	
	95% CI	0.458, 5.800	
	p-value	0.4463	
	Odds Ratio	2.000	
	95% CI	0.559, 7.162	
	p-value	0.2869	
	Relative Risk	1.973	
	95% CI	0.563, 6.920	
	p-value	0.2885	
	Risk Difference	1.327	
	95% CI	-0.819, 3.473	
	p-value	0.2255	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Cardiac disorders	Number of subjects with events, n (%)	63 (14.1)	21 (9.5)
	Number of censored subjects, n (%)	383 (85.9)	199 (90.5)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.268	
	95% CI	0.773, 2.080	
	p-value	0.3456	
	Odds Ratio	1.559	
	95% CI	0.924, 2.629	
	p-value	0.0960	
	Relative Risk	1.480	
	95% CI	0.928, 2.360	
	p-value	0.0998	
	Risk Difference	4.580	
	95% CI	-0.472, 9.632	
	p-value	0.0756	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Ear and labyrinth disorders*		
Number of subjects with events, n (%)	6 (1.3)	1 (0.5)
Number of censored subjects, n (%)	440 (98.7)	219 (99.5)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	2.336	
95% CI	0.280, 19.491	
p-value	0.4195	
Odds Ratio	2.986	
95% CI	0.357, 24.960	
p-value	0.3125	
Relative Risk	2.960	
95% CI	0.359, 24.432	
p-value	0.3137	
Risk Difference	0.891	
95% CI	-0.500, 2.281	
p-value	0.2092	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Eye disorders	Number of subjects with events, n (%)	19 (4.3)	5 (2.3)
	Number of censored subjects, n (%)	427 (95.7)	215 (97.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.596	
	95% CI	0.594, 4.285	
	p-value	0.3494	
	Odds Ratio	1.913	
	95% CI	0.705, 5.194	
	p-value	0.2029	
	Relative Risk	1.874	
	95% CI	0.709, 4.954	
	p-value	0.2051	
	Risk Difference	1.987	
	95% CI	-0.731, 4.706	
	p-value	0.1519	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Gastrointestinal disorders	Number of subjects with events, n (%)	114 (25.6)	50 (22.7)
	Number of censored subjects, n (%)	332 (74.4)	170 (77.3)
	Time to Event (Month)		
	25%-ile (95%-CI)	21.9 (16.1, 33.3)	19.2 (13.5, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.984	
	95% CI	0.705, 1.373	
	p-value	0.9254	
	Odds Ratio	1.167	
	95% CI	0.798, 1.708	
	p-value	0.4250	
	Relative Risk	1.125	
	95% CI	0.841, 1.504	
	p-value	0.4282	
	Risk Difference	2.833	
	95% CI	-4.026, 9.693	
	p-value	0.4182	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Gastrointestinal disorders - PT:Abdominal pain upper*	Number of subjects with events, n (%)	7 (1.6)	1 (0.5)
	Number of censored subjects, n (%)	439 (98.4)	219 (99.5)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	3.288	
	95% CI	0.405, 26.720	
	p-value	0.2378	
	Odds Ratio	3.492	
	95% CI	0.427, 28.561	
	p-value	0.2435	
	Relative Risk	3.453	
	95% CI	0.427, 27.890	
	p-value	0.2450	
	Risk Difference	1.115	
	95% CI	-0.341, 2.571	
	p-value	0.1335	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Gastrointestinal disorders - PT:Abdominal pain*		
Number of subjects with events, n (%)	8 (1.8)	5 (2.3)
Number of censored subjects, n (%)	438 (98.2)	215 (97.7)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.643	
95% CI	0.210, 1.971	
p-value	0.4362	
Odds Ratio	0.785	
95% CI	0.254, 2.429	
p-value	0.6750	
Relative Risk	0.789	
95% CI	0.261, 2.384	
p-value	0.6748	
Risk Difference	-0.479	
95% CI	-2.802, 1.844	
p-value	0.6861	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Gastrointestinal disorders - PT:Constipation	Number of subjects with events, n (%)	48 (10.8)	16 (7.3)
	Number of censored subjects, n (%)	398 (89.2)	204 (92.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.301	
	95% CI	0.738, 2.293	
	p-value	0.3609	
	Odds Ratio	1.538	
	95% CI	0.852, 2.775	
	p-value	0.1532	
	Relative Risk	1.480	
	95% CI	0.860, 2.545	
	p-value	0.1566	
	Risk Difference	3.490	
	95% CI	-0.988, 7.967	
	p-value	0.1266	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Gastrointestinal disorders - PT:Diarrhoea	Number of subjects with events, n (%)	17 (3.8)	8 (3.6)
	Number of censored subjects, n (%)	429 (96.2)	212 (96.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.866	
	95% CI	0.372, 2.015	
	p-value	0.7386	
	Odds Ratio	1.050	
	95% CI	0.446, 2.472	
	p-value	0.9109	
	Relative Risk	1.048	
	95% CI	0.460, 2.391	
	p-value	0.9109	
	Risk Difference	0.175	
	95% CI	-2.870, 3.221	
	p-value	0.9102	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Gastrointestinal disorders - PT:Dyspepsia*		
Number of subjects with events, n (%)	5 (1.1)	3 (1.4)
Number of censored subjects, n (%)	441 (98.9)	217 (98.6)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.786	
95% CI	0.188, 3.289	
p-value	0.7410	
Odds Ratio	0.820	
95% CI	0.194, 3.463	
p-value	0.7873	
Relative Risk	0.822	
95% CI	0.198, 3.409	
p-value	0.7872	
Risk Difference	-0.243	
95% CI	-2.060, 1.575	
p-value	0.7937	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Gastrointestinal disorders - PT:Nausea		
Number of subjects with events, n (%)	12 (2.7)	5 (2.3)
Number of censored subjects, n (%)	434 (97.3)	215 (97.7)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.022	
95% CI	0.359, 2.909	
p-value	0.9675	
Odds Ratio	1.189	
95% CI	0.414, 3.418	
p-value	0.7481	
Relative Risk	1.184	
95% CI	0.422, 3.318	
p-value	0.7483	
Risk Difference	0.418	
95% CI	-2.059, 2.894	
p-value	0.7409	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Gastrointestinal disorders - PT:Vomiting*		
Number of subjects with events, n (%)	6 (1.3)	3 (1.4)
Number of censored subjects, n (%)	440 (98.7)	217 (98.6)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.803	
95% CI	0.199, 3.230	
p-value	0.7566	
Odds Ratio	0.986	
95% CI	0.244, 3.982	
p-value	0.9846	
Relative Risk	0.987	
95% CI	0.249, 3.908	
p-value	0.9846	
Risk Difference	-0.018	
95% CI	-1.887, 1.850	
p-value	0.9846	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: General disorders and administration site conditions	Number of subjects with events, n (%)	110 (24.7)	56 (25.5)
	Number of censored subjects, n (%)	336 (75.3)	164 (74.5)
	Time to Event (Month)		
	25%-ile (95%-CI)	23.9 (19.2, 32.5)	18.4 (11.0, 31.2)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.821	
	95% CI	0.595, 1.135	
	p-value	0.2315	
	Odds Ratio	0.959	
	95% CI	0.661, 1.391	
	p-value	0.8244	
	Relative Risk	0.969	
	95% CI	0.734, 1.280	
	p-value	0.8241	
	Risk Difference	-0.791	
	95% CI	-7.801, 6.219	
	p-value	0.8250	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: General disorders and administration site conditions - PT:Asthenia	Number of subjects with events, n (%)	16 (3.6)	11 (5.0)
	Number of censored subjects, n (%)	430 (96.4)	209 (95.0)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.578	
	95% CI	0.267, 1.250	
	p-value	0.1589	
	Odds Ratio	0.707	
	95% CI	0.322, 1.550	
	p-value	0.3868	
	Relative Risk	0.717	
	95% CI	0.339, 1.520	
	p-value	0.3859	
	Risk Difference	-1.413	
	95% CI	-4.770, 1.945	
	p-value	0.4096	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

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95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: General disorders and administration site conditions - PT:Fatigue	Number of subjects with events, n (%)	25 (5.6)	18 (8.2)
	Number of censored subjects, n (%)	421 (94.4)	202 (91.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.613	
	95% CI	0.334, 1.125	
	p-value	0.1104	
	Odds Ratio	0.666	
	95% CI	0.355, 1.250	
	p-value	0.2057	
	Relative Risk	0.685	
	95% CI	0.382, 1.228	
	p-value	0.2043	
	Risk Difference	-2.576	
	95% CI	-6.781, 1.628	
	p-value	0.2297	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: General disorders and administration site conditions - PT:Influenza like illness*	Number of subjects with events, n (%)	5 (1.1)	3 (1.4)
	Number of censored subjects, n (%)	441 (98.9)	217 (98.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.720	
	95% CI	0.172, 3.021	
	p-value	0.6518	
	Odds Ratio	0.820	
	95% CI	0.194, 3.463	
	p-value	0.7873	
	Relative Risk	0.822	
	95% CI	0.198, 3.409	
	p-value	0.7872	
	Risk Difference	-0.243	
	95% CI	-2.060, 1.575	
	p-value	0.7937	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: General disorders and administration site conditions - PT:Oedema peripheral	Number of subjects with events, n (%)	20 (4.5)	8 (3.6)
	Number of censored subjects, n (%)	426 (95.5)	212 (96.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.068	
	95% CI	0.469, 2.431	
	p-value	0.8757	
	Odds Ratio	1.244	
	95% CI	0.539, 2.871	
	p-value	0.6087	
	Relative Risk	1.233	
	95% CI	0.552, 2.755	
	p-value	0.6093	
	Risk Difference	0.848	
	95% CI	-2.284, 3.980	
	p-value	0.5956	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: General disorders and administration site conditions - PT:Pain	Number of subjects with events, n (%)	12 (2.7)	5 (2.3)
	Number of censored subjects, n (%)	434 (97.3)	215 (97.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.041	
	95% CI	0.366, 2.959	
	p-value	0.9398	
	Odds Ratio	1.189	
	95% CI	0.414, 3.418	
	p-value	0.7481	
	Relative Risk	1.184	
	95% CI	0.422, 3.318	
	p-value	0.7483	
	Risk Difference	0.418	
	95% CI	-2.059, 2.894	
	p-value	0.7409	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: General disorders and administration site conditions - PT:Pyrexia	Number of subjects with events, n (%)	21 (4.7)	8 (3.6)
	Number of censored subjects, n (%)	425 (95.3)	212 (96.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.050	
	95% CI	0.463, 2.378	
	p-value	0.9066	
	Odds Ratio	1.309	
	95% CI	0.570, 3.005	
	p-value	0.5248	
	Relative Risk	1.295	
	95% CI	0.583, 2.876	
	p-value	0.5257	
	Risk Difference	1.072	
	95% CI	-2.087, 4.232	
	p-value	0.5060	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
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Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Hepatobiliary disorders		
Number of subjects with events, n (%)	26 (5.8)	1 (0.5)
Number of censored subjects, n (%)	420 (94.2)	219 (99.5)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	11.364	
95% CI	1.541, 83.798	
p-value	0.0026	
Odds Ratio	13.557	
95% CI	1.827, 100.573	
p-value	0.0108	
Relative Risk	12.825	
95% CI	1.752, 93.894	
p-value	0.0120	
Risk Difference	5.375	
95% CI	3.026, 7.724	
p-value	<.0001	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Infections and infestations	Number of subjects with events, n (%)	160 (35.9)	62 (28.2)
	Number of censored subjects, n (%)	286 (64.1)	158 (71.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	13.7 (10.6, 17.3)	14.7 (8.5, 26.1)
	Median (95%-CI)	NE (35.4, NE)	38.7 (33.4, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (38.7, NE)
	Unstratified Analysis		
	Hazard Ratio	1.098	
	95% CI	0.819, 1.474	
	p-value	0.5314	
	Odds Ratio	1.426	
	95% CI	1.003, 2.027	
	p-value	0.0481	
	Relative Risk	1.273	
	95% CI	0.997, 1.626	
	p-value	0.0533	
	Risk Difference	7.693	
	95% CI	0.266, 15.119	
	p-value	0.0423	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Infections and infestations - PT:Bronchitis*		
Number of subjects with events, n (%)	6 (1.3)	1 (0.5)
Number of censored subjects, n (%)	440 (98.7)	219 (99.5)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	2.141	
95% CI	0.256, 17.927	
p-value	0.4721	
Odds Ratio	2.986	
95% CI	0.357, 24.960	
p-value	0.3125	
Relative Risk	2.960	
95% CI	0.359, 24.432	
p-value	0.3137	
Risk Difference	0.891	
95% CI	-0.500, 2.281	
p-value	0.2092	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Infections and infestations - PT:COVID-19		
Number of subjects with events, n (%)	32 (7.2)	15 (6.8)
Number of censored subjects, n (%)	414 (92.8)	205 (93.2)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.946	
95% CI	0.512, 1.747	
p-value	0.8590	
Odds Ratio	1.056	
95% CI	0.559, 1.995	
p-value	0.8658	
Relative Risk	1.052	
95% CI	0.582, 1.902	
p-value	0.8659	
Risk Difference	0.357	
95% CI	-3.746, 4.459	
p-value	0.8647	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Infections and infestations - PT:Herpes zoster*		
Number of subjects with events, n (%)	8 (1.8)	1 (0.5)
Number of censored subjects, n (%)	438 (98.2)	219 (99.5)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	3.342	
95% CI	0.417, 26.778	
p-value	0.2276	
Odds Ratio	4.000	
95% CI	0.497, 32.184	
p-value	0.1926	
Relative Risk	3.946	
95% CI	0.497, 31.353	
p-value	0.1942	
Risk Difference	1.339	
95% CI	-0.180, 2.858	
p-value	0.0840	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Infections and infestations - PT:Influenza*		
Number of subjects with events, n (%)	7 (1.6)	2 (0.9)
Number of censored subjects, n (%)	439 (98.4)	218 (99.1)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.391	
95% CI	0.287, 6.744	
p-value	0.6807	
Odds Ratio	1.738	
95% CI	0.358, 8.437	
p-value	0.4929	
Relative Risk	1.726	
95% CI	0.362, 8.242	
p-value	0.4935	
Risk Difference	0.660	
95% CI	-1.044, 2.364	
p-value	0.4475	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Infections and infestations - PT:Pneumonia	Number of subjects with events, n (%)	16 (3.6)	2 (0.9)
	Number of censored subjects, n (%)	430 (96.4)	218 (99.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	3.218	
	95% CI	0.738, 14.024	
	p-value	0.0998	
	Odds Ratio	4.056	
	95% CI	0.924, 17.799	
	p-value	0.0635	
	Relative Risk	3.946	
	95% CI	0.915, 17.010	
	p-value	0.0656	
	Risk Difference	2.678	
	95% CI	0.545, 4.812	
	p-value	0.0139	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Infections and infestations - PT:Upper respiratory tract infection	Number of subjects with events, n (%)	15 (3.4)	2 (0.9)
	Number of censored subjects, n (%)	431 (96.6)	218 (99.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	2.976	
	95% CI	0.680, 13.037	
	p-value	0.1285	
	Odds Ratio	3.794	
	95% CI	0.860, 16.738	
	p-value	0.0783	
	Relative Risk	3.700	
	95% CI	0.854, 16.035	
	p-value	0.0804	
	Risk Difference	2.454	
	95% CI	0.363, 4.545	
	p-value	0.0214	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Infections and infestations - PT:Urinary tract infection	Number of subjects with events, n (%)	52 (11.7)	19 (8.6)
	Number of censored subjects, n (%)	394 (88.3)	201 (91.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.160	
	95% CI	0.685, 1.965	
	p-value	0.5803	
	Odds Ratio	1.396	
	95% CI	0.804, 2.425	
	p-value	0.2362	
	Relative Risk	1.350	
	95% CI	0.819, 2.226	
	p-value	0.2394	
	Risk Difference	3.023	
	95% CI	-1.736, 7.782	
	p-value	0.2132	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Injury, poisoning and procedural complications	Number of subjects with events, n (%)	36 (8.1)	20 (9.1)
	Number of censored subjects, n (%)	410 (91.9)	200 (90.9)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.720	
	95% CI	0.416, 1.248	
	p-value	0.2400	
	Odds Ratio	0.878	
	95% CI	0.495, 1.556	
	p-value	0.6560	
	Relative Risk	0.888	
	95% CI	0.527, 1.497	
	p-value	0.6554	
	Risk Difference	-1.019	
	95% CI	-5.582, 3.544	
	p-value	0.6616	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Injury, poisoning and procedural complications - PT:Contusion*	Number of subjects with events, n (%) 1 (0.2)	1 (0.5)
	Number of censored subjects, n (%) 445 (99.8)	219 (99.5)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	0.410 0.025, 6.639 0.5171
	Odds Ratio 95% CI p-value	0.492 0.031, 7.905 0.6167
	Relative Risk 95% CI p-value	0.493 0.031, 7.849 0.6167
	Risk Difference 95% CI p-value	-0.230 -1.222, 0.761 0.6488

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Injury, poisoning and procedural complications - PT:Fall*		
Number of subjects with events, n (%)	5 (1.1)	3 (1.4)
Number of censored subjects, n (%)	441 (98.9)	217 (98.6)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.685	
95% CI	0.163, 2.885	
p-value	0.6040	
Odds Ratio	0.820	
95% CI	0.194, 3.463	
p-value	0.7873	
Relative Risk	0.822	
95% CI	0.198, 3.409	
p-value	0.7872	
Risk Difference	-0.243	
95% CI	-2.060, 1.575	
p-value	0.7937	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Injury, poisoning and procedural complications - PT:Rib fracture*		
Number of subjects with events, n (%)	6 (1.3)	4 (1.8)
Number of censored subjects, n (%)	440 (98.7)	216 (98.2)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.628	
95% CI	0.177, 2.236	
p-value	0.4693	
Odds Ratio	0.736	
95% CI	0.206, 2.637	
p-value	0.6382	
Relative Risk	0.740	
95% CI	0.211, 2.595	
p-value	0.6380	
Risk Difference	-0.473	
95% CI	-2.537, 1.591	
p-value	0.6534	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Investigations	Number of subjects with events, n (%)	155 (34.8)	73 (33.2)
	Number of censored subjects, n (%)	291 (65.2)	147 (66.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	11.1 (8.3, 14.7)	10.3 (8.0, 15.6)
	Median (95%-CI)	NE (NE, NE)	NE (24.9, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.916	
	95% CI	0.693, 1.211	
	p-value	0.5365	
	Odds Ratio	1.073	
	95% CI	0.762, 1.509	
	p-value	0.6877	
	Relative Risk	1.047	
	95% CI	0.835, 1.314	
	p-value	0.6889	
	Risk Difference	1.572	
	95% CI	-6.060, 9.203	
	p-value	0.6865	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Investigations - PT:Alanine aminotransferase increased	Number of subjects with events, n (%)	42 (9.4)	19 (8.6)
	Number of censored subjects, n (%)	404 (90.6)	201 (91.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.986	
	95% CI	0.573, 1.697	
	p-value	0.9584	
	Odds Ratio	1.100	
	95% CI	0.623, 1.940	
	p-value	0.7426	
	Relative Risk	1.090	
	95% CI	0.650, 1.829	
	p-value	0.7430	
	Risk Difference	0.781	
	95% CI	-3.816, 5.377	
	p-value	0.7392	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

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Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Investigations - PT:Aspartate aminotransferase increased	Number of subjects with events, n (%)	47 (10.5)	17 (7.7)
	Number of censored subjects, n (%)	399 (89.5)	203 (92.3)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.186	
	95% CI	0.680, 2.068	
	p-value	0.5472	
	Odds Ratio	1.407	
	95% CI	0.788, 2.512	
	p-value	0.2488	
	Relative Risk	1.364	
	95% CI	0.802, 2.319	
	p-value	0.2519	
	Risk Difference	2.811	
	95% CI	-1.725, 7.346	
	p-value	0.2245	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

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Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Investigations - PT:Blood alkaline phosphatase increased	Number of subjects with events, n (%)	32 (7.2)	15 (6.8)
	Number of censored subjects, n (%)	414 (92.8)	205 (93.2)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.862	
	95% CI	0.466, 1.595	
	p-value	0.6355	
	Odds Ratio	1.056	
	95% CI	0.559, 1.995	
	p-value	0.8658	
	Relative Risk	1.052	
	95% CI	0.582, 1.902	
	p-value	0.8659	
	Risk Difference	0.357	
	95% CI	-3.746, 4.459	
	p-value	0.8647	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Investigations - PT:Blood bilirubin increased		
Number of subjects with events, n (%)	20 (4.5)	3 (1.4)
Number of censored subjects, n (%)	426 (95.5)	217 (98.6)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	2.781	
95% CI	0.825, 9.374	
p-value	0.0849	
Odds Ratio	3.396	
95% CI	0.998, 11.554	
p-value	0.0504	
Relative Risk	3.288	
95% CI	0.988, 10.948	
p-value	0.0524	
Risk Difference	3.121	
95% CI	0.663, 5.578	
p-value	0.0128	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

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Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Investigations - PT:Blood creatinine increased	Number of subjects with events, n (%)	23 (5.2)	15 (6.8)
	Number of censored subjects, n (%)	423 (94.8)	205 (93.2)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.635	
	95% CI	0.331, 1.219	
	p-value	0.1686	
	Odds Ratio	0.743	
	95% CI	0.380, 1.454	
	p-value	0.3862	
	Relative Risk	0.756	
	95% CI	0.403, 1.420	
	p-value	0.3851	
	Risk Difference	-1.661	
	95% CI	-5.574, 2.251	
	p-value	0.4053	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

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Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Investigations - PT:Blood lactate dehydrogenase increased		
Number of subjects with events, n (%)	11 (2.5)	2 (0.9)
Number of censored subjects, n (%)	435 (97.5)	218 (99.1)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	2.313	
95% CI	0.512, 10.452	
p-value	0.2619	
Odds Ratio	2.756	
95% CI	0.606, 12.545	
p-value	0.1897	
Relative Risk	2.713	
95% CI	0.607, 12.134	
p-value	0.1916	
Risk Difference	1.557	
95% CI	-0.352, 3.466	
p-value	0.1099	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Investigations - PT:Platelet count decreased	Number of subjects with events, n (%)	10 (2.2)	2 (0.9)
	Number of censored subjects, n (%)	436 (97.8)	218 (99.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	2.168	
	95% CI	0.474, 9.910	
	p-value	0.3063	
	Odds Ratio	2.500	
	95% CI	0.543, 11.509	
	p-value	0.2395	
	Relative Risk	2.466	
	95% CI	0.545, 11.160	
	p-value	0.2412	
	Risk Difference	1.333	
	95% CI	-0.527, 3.193	
	p-value	0.1602	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

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Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Investigations - PT:Weight decreased	Number of subjects with events, n (%)	14 (3.1)	6 (2.7)
	Number of censored subjects, n (%)	432 (96.9)	214 (97.3)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.982	
	95% CI	0.377, 2.559	
	p-value	0.9702	
	Odds Ratio	1.156	
	95% CI	0.438, 3.050	
	p-value	0.7698	
	Relative Risk	1.151	
	95% CI	0.448, 2.954	
	p-value	0.7700	
	Risk Difference	0.412	
	95% CI	-2.281, 3.105	
	p-value	0.7644	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Investigations - PT:Weight increased	Number of subjects with events, n (%)	34 (7.6)	17 (7.7)
	Number of censored subjects, n (%)	412 (92.4)	203 (92.3)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.894	
	95% CI	0.499, 1.601	
	p-value	0.7048	
	Odds Ratio	0.985	
	95% CI	0.538, 1.806	
	p-value	0.9622	
	Relative Risk	0.987	
	95% CI	0.564, 1.726	
	p-value	0.9621	
	Risk Difference	-0.104	
	95% CI	-4.407, 4.199	
	p-value	0.9622	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Metabolism and nutrition disorders	Number of subjects with events, n (%)	112 (25.1)	47 (21.4)
	Number of censored subjects, n (%)	334 (74.9)	173 (78.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	21.6 (16.5, 30.6)	26.5 (13.8, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.016	
	95% CI	0.722, 1.430	
	p-value	0.9265	
	Odds Ratio	1.234	
	95% CI	0.838, 1.818	
	p-value	0.2863	
	Relative Risk	1.175	
	95% CI	0.871, 1.587	
	p-value	0.2908	
	Risk Difference	3.748	
	95% CI	-2.999, 10.496	
	p-value	0.2762	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Metabolism and nutrition disorders - PT:Decreased appetite	Number of subjects with events, n (%)	15 (3.4)	9 (4.1)
	Number of censored subjects, n (%)	431 (96.6)	211 (95.9)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.706	
	95% CI	0.308, 1.618	
	p-value	0.4088	
	Odds Ratio	0.816	
	95% CI	0.351, 1.895	
	p-value	0.6361	
	Relative Risk	0.822	
	95% CI	0.366, 1.849	
	p-value	0.6357	
	Risk Difference	-0.728	
	95% CI	-3.834, 2.379	
	p-value	0.6462	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Metabolism and nutrition disorders - PT:Hypercholesterolaemia*		
Number of subjects with events, n (%)	9 (2.0)	2 (0.9)
Number of censored subjects, n (%)	437 (98.0)	218 (99.1)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.748	
95% CI	0.376, 8.134	
p-value	0.4708	
Odds Ratio	2.245	
95% CI	0.481, 10.479	
p-value	0.3036	
Relative Risk	2.220	
95% CI	0.484, 10.186	
p-value	0.3050	
Risk Difference	1.109	
95% CI	-0.701, 2.919	
p-value	0.2299	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Metabolism and nutrition disorders - PT:Hyperglycaemia	Number of subjects with events, n (%)	27 (6.1)	9 (4.1)
	Number of censored subjects, n (%)	419 (93.9)	211 (95.9)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.284	
	95% CI	0.603, 2.735	
	p-value	0.5153	
	Odds Ratio	1.511	
	95% CI	0.698, 3.270	
	p-value	0.2951	
	Relative Risk	1.480	
	95% CI	0.708, 3.092	
	p-value	0.2972	
	Risk Difference	1.963	
	95% CI	-1.465, 5.391	
	p-value	0.2617	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Metabolism and nutrition disorders - PT:Hyperkalaemia*		
Number of subjects with events, n (%)	8 (1.8)	8 (3.6)
Number of censored subjects, n (%)	438 (98.2)	212 (96.4)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.413	
95% CI	0.154, 1.104	
p-value	0.0687	
Odds Ratio	0.484	
95% CI	0.179, 1.307	
p-value	0.1523	
Relative Risk	0.493	
95% CI	0.188, 1.297	
p-value	0.1519	
Risk Difference	-1.843	
95% CI	-4.606, 0.921	
p-value	0.1912	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Metabolism and nutrition disorders - PT:Hyperlipidaemia		
Number of subjects with events, n (%)	12 (2.7)	2 (0.9)
Number of censored subjects, n (%)	434 (97.3)	218 (99.1)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	2.725	
95% CI	0.609, 12.187	
p-value	0.1716	
Odds Ratio	3.014	
95% CI	0.669, 13.585	
p-value	0.1510	
Relative Risk	2.960	
95% CI	0.668, 13.109	
p-value	0.1530	
Risk Difference	1.781	
95% CI	-0.175, 3.738	
p-value	0.0743	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Metabolism and nutrition disorders - PT:Hypertriglyceridaemia*		
Number of subjects with events, n (%)	8 (1.8)	2 (0.9)
Number of censored subjects, n (%)	438 (98.2)	218 (99.1)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.621	
95% CI	0.343, 7.668	
p-value	0.5385	
Odds Ratio	1.991	
95% CI	0.419, 9.455	
p-value	0.3864	
Relative Risk	1.973	
95% CI	0.423, 9.213	
p-value	0.3874	
Risk Difference	0.885	
95% CI	-0.873, 2.643	
p-value	0.3240	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Metabolism and nutrition disorders - PT:Hypocalcaemia*		
Number of subjects with events, n (%)	6 (1.3)	5 (2.3)
Number of censored subjects, n (%)	440 (98.7)	215 (97.7)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.472	
95% CI	0.143, 1.554	
p-value	0.2064	
Odds Ratio	0.586	
95% CI	0.177, 1.943	
p-value	0.3825	
Relative Risk	0.592	
95% CI	0.183, 1.918	
p-value	0.3821	
Risk Difference	-0.927	
95% CI	-3.168, 1.313	
p-value	0.4173	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Metabolism and nutrition disorders - PT:Hypokalaemia		
Number of subjects with events, n (%)	10 (2.2)	4 (1.8)
Number of censored subjects, n (%)	436 (97.8)	216 (98.2)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.005	
95% CI	0.314, 3.219	
p-value	0.9939	
Odds Ratio	1.239	
95% CI	0.384, 3.994	
p-value	0.7203	
Relative Risk	1.233	
95% CI	0.391, 3.888	
p-value	0.7205	
Risk Difference	0.424	
95% CI	-1.813, 2.661	
p-value	0.7103	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
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Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Metabolism and nutrition disorders - PT:Hyponatraemia		
Number of subjects with events, n (%)	11 (2.5)	6 (2.7)
Number of censored subjects, n (%)	435 (97.5)	214 (97.3)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.792	
95% CI	0.293, 2.146	
p-value	0.6463	
Odds Ratio	0.902	
95% CI	0.329, 2.472	
p-value	0.8409	
Relative Risk	0.904	
95% CI	0.339, 2.413	
p-value	0.8409	
Risk Difference	-0.261	
95% CI	-2.850, 2.328	
p-value	0.8434	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Musculoskeletal and connective tissue disorders	Number of subjects with events, n (%)	187 (41.9)	92 (41.8)
	Number of censored subjects, n (%)	259 (58.1)	128 (58.2)
	Time to Event (Month)		
	25%-ile (95%-CI)	8.4 (7.6, 11.5)	8.3 (5.6, 10.8)
	Median (95%-CI)	NE (25.0, NE)	31.4 (16.9, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.899	
	95% CI	0.700, 1.155	
	p-value	0.4046	
	Odds Ratio	1.005	
	95% CI	0.724, 1.394	
	p-value	0.9784	
	Relative Risk	1.003	
	95% CI	0.829, 1.213	
	p-value	0.9784	
	Risk Difference	0.110	
	95% CI	-7.856, 8.076	
	p-value	0.9784	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Musculoskeletal and connective tissue disorders - PT:Arthralgia	Number of subjects with events, n (%)	57 (12.8)	26 (11.8)
	Number of censored subjects, n (%)	389 (87.2)	194 (88.2)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (32.7, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.946	
	95% CI	0.594, 1.506	
	p-value	0.8141	
	Odds Ratio	1.093	
	95% CI	0.667, 1.793	
	p-value	0.7237	
	Relative Risk	1.081	
	95% CI	0.700, 1.670	
	p-value	0.7243	
	Risk Difference	0.962	
	95% CI	-4.310, 6.234	
	p-value	0.7206	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Musculoskeletal and connective tissue disorders - PT:Back pain	Number of subjects with events, n (%)	46 (10.3)	23 (10.5)
	Number of censored subjects, n (%)	400 (89.7)	197 (89.5)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.852	
	95% CI	0.516, 1.408	
	p-value	0.5319	
	Odds Ratio	0.985	
	95% CI	0.580, 1.671	
	p-value	0.9553	
	Relative Risk	0.987	
	95% CI	0.614, 1.584	
	p-value	0.9553	
	Risk Difference	-0.141	
	95% CI	-5.072, 4.790	
	p-value	0.9554	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Musculoskeletal and connective tissue disorders - PT:Bone pain	Number of subjects with events, n (%)	33 (7.4)	28 (12.7)
	Number of censored subjects, n (%)	413 (92.6)	192 (87.3)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.510	
	95% CI	0.308, 0.846	
	p-value	0.0078	
	Odds Ratio	0.548	
	95% CI	0.322, 0.933	
	p-value	0.0266	
	Relative Risk	0.581	
	95% CI	0.361, 0.937	
	p-value	0.0258	
	Risk Difference	-5.328	
	95% CI	-10.358, -0.299	
	p-value	0.0379	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Musculoskeletal and connective tissue disorders - PT:Groin pain*	Number of subjects with events, n (%) 2 (0.4)	3 (1.4)
	Number of censored subjects, n (%) 444 (99.6)	217 (98.6)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	0.278 0.046, 1.671 0.1348
	Odds Ratio 95% CI p-value	0.326 0.054, 1.964 0.2212
	Relative Risk 95% CI p-value	0.329 0.055, 1.954 0.2212
	Risk Difference 95% CI p-value	-0.915 -2.568, 0.738 0.2779

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Musculoskeletal and connective tissue disorders - PT:Muscle spasms*	Number of subjects with events, n (%)	1 (0.2)	3 (1.4)
	Number of censored subjects, n (%)	445 (99.8)	217 (98.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.152	
	95% CI	0.016, 1.463	
	p-value	0.0599	
	Odds Ratio	0.163	
	95% CI	0.017, 1.572	
	p-value	0.1166	
	Relative Risk	0.164	
	95% CI	0.017, 1.572	
	p-value	0.1170	
	Risk Difference	-1.139	
	95% CI	-2.734, 0.455	
	p-value	0.1612	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Musculoskeletal and connective tissue disorders - PT:Muscular weakness*		
Number of subjects with events, n (%)	6 (1.3)	6 (2.7)
Number of censored subjects, n (%)	440 (98.7)	214 (97.3)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.439	
95% CI	0.141, 1.367	
p-value	0.1443	
Odds Ratio	0.486	
95% CI	0.155, 1.526	
p-value	0.2166	
Relative Risk	0.493	
95% CI	0.161, 1.512	
p-value	0.2162	
Risk Difference	-1.382	
95% CI	-3.785, 1.021	
p-value	0.2597	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)		Placebo (N=220)	
SOC: Musculoskeletal and connective tissue disorders - PT:Musculoskeletal chest pain*	Number of subjects with events, n (%)	4 (0.9)		2 (0.9)	
	Number of censored subjects, n (%)	442 (99.1)		218 (99.1)	
	Time to Event (Month)				
	25%-ile (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	Median (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	75%-ile (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	Unstratified Analysis				
	Hazard Ratio	0.852			
	95% CI	0.156, 4.666			
	p-value	0.8537			
	Odds Ratio	0.986			
	95% CI	0.179, 5.427			
	p-value	0.9875			
	Relative Risk	0.987			
	95% CI	0.182, 5.345			
	p-value	0.9875			
	Risk Difference	-0.012			
	95% CI	-1.541, 1.517			
	p-value	0.9875			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Musculoskeletal and connective tissue disorders - PT:Musculoskeletal pain*	Number of subjects with events, n (%)	5 (1.1)	4 (1.8)
	Number of censored subjects, n (%)	441 (98.9)	216 (98.2)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.525	
	95% CI	0.140, 1.966	
	p-value	0.3308	
	Odds Ratio	0.612	
	95% CI	0.163, 2.303	
	p-value	0.4679	
	Relative Risk	0.617	
	95% CI	0.167, 2.273	
	p-value	0.4676	
	Risk Difference	-0.697	
	95% CI	-2.715, 1.321	
	p-value	0.4983	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Musculoskeletal and connective tissue disorders - PT:Myalgia*	Number of subjects with events, n (%) 7 (1.6)	2 (0.9)
	Number of censored subjects, n (%) 439 (98.4)	218 (99.1)
	Time to Event (Month) 25%-ile (95%-CI) Median (95%-CI) 75%-ile (95%-CI)	NE (NE, NE) NE (NE, NE) NE (NE, NE)
	Unstratified Analysis Hazard Ratio 95% CI p-value	1.410 0.292, 6.807 0.6676
	Odds Ratio 95% CI p-value	1.738 0.358, 8.437 0.4929
	Relative Risk 95% CI p-value	1.726 0.362, 8.242 0.4935
	Risk Difference 95% CI p-value	0.660 -1.044, 2.364 0.4475

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Musculoskeletal and connective tissue disorders - PT:Neck pain*	Number of subjects with events, n (%)	8 (1.8)	2 (0.9)
	Number of censored subjects, n (%)	438 (98.2)	218 (99.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.670	
	95% CI	0.354, 7.886	
	p-value	0.5129	
	Odds Ratio	1.991	
	95% CI	0.419, 9.455	
	p-value	0.3864	
	Relative Risk	1.973	
	95% CI	0.423, 9.213	
	p-value	0.3874	
	Risk Difference	0.885	
	95% CI	-0.873, 2.643	
	p-value	0.3240	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Musculoskeletal and connective tissue disorders - PT:Pain in extremity	Number of subjects with events, n (%)	42 (9.4)	21 (9.5)
	Number of censored subjects, n (%)	404 (90.6)	199 (90.5)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.869	
	95% CI	0.514, 1.470	
	p-value	0.6010	
	Odds Ratio	0.985	
	95% CI	0.568, 1.709	
	p-value	0.9575	
	Relative Risk	0.987	
	95% CI	0.599, 1.624	
	p-value	0.9575	
	Risk Difference	-0.128	
	95% CI	-4.864, 4.607	
	p-value	0.9576	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Musculoskeletal and connective tissue disorders - PT:Pathological fracture*	Number of subjects with events, n (%)	5 (1.1)	3 (1.4)
	Number of censored subjects, n (%)	441 (98.9)	217 (98.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.726	
	95% CI	0.173, 3.047	
	p-value	0.6605	
	Odds Ratio	0.820	
	95% CI	0.194, 3.463	
	p-value	0.7873	
	Relative Risk	0.822	
	95% CI	0.198, 3.409	
	p-value	0.7872	
	Risk Difference	-0.243	
	95% CI	-2.060, 1.575	
	p-value	0.7937	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
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Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
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Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Musculoskeletal and connective tissue disorders - PT:Spinal pain*	Number of subjects with events, n (%)	9 (2.0)	4 (1.8)
	Number of censored subjects, n (%)	437 (98.0)	216 (98.2)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.957	
	95% CI	0.294, 3.115	
	p-value	0.9427	
	Odds Ratio	1.112	
	95% CI	0.339, 3.652	
	p-value	0.8609	
	Relative Risk	1.110	
	95% CI	0.346, 3.564	
	p-value	0.8610	
	Risk Difference	0.200	
	95% CI	-1.996, 2.395	
	p-value	0.8585	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Number of subjects with events, n (%)	20 (4.5)	7 (3.2)
	Number of censored subjects, n (%)	426 (95.5)	213 (96.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.161	
	95% CI	0.489, 2.752	
	p-value	0.7351	
	Odds Ratio	1.429	
	95% CI	0.595, 3.431	
	p-value	0.4250	
	Relative Risk	1.409	
	95% CI	0.605, 3.282	
	p-value	0.4263	
	Risk Difference	1.302	
	95% CI	-1.709, 4.314	
	p-value	0.3966	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Nervous system disorders	Number of subjects with events, n (%)	67 (15.0)	35 (15.9)
	Number of censored subjects, n (%)	379 (85.0)	185 (84.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (37.9, NE)	NE (22.8, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.804	
	95% CI	0.533, 1.213	
	p-value	0.2974	
	Odds Ratio	0.934	
	95% CI	0.599, 1.458	
	p-value	0.7651	
	Relative Risk	0.944	
	95% CI	0.649, 1.375	
	p-value	0.7647	
	Risk Difference	-0.887	
	95% CI	-6.748, 4.975	
	p-value	0.7669	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Nervous system disorders - PT:Dizziness*	Number of subjects with events, n (%)	11 (2.5)	4 (1.8)
	Number of censored subjects, n (%)	435 (97.5)	216 (98.2)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.019	
	95% CI	0.323, 3.219	
	p-value	0.9741	
	Odds Ratio	1.366	
	95% CI	0.430, 4.338	
	p-value	0.5973	
	Relative Risk	1.357	
	95% CI	0.437, 4.212	
	p-value	0.5978	
	Risk Difference	0.648	
	95% CI	-1.630, 2.926	
	p-value	0.5770	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Nervous system disorders - PT:Headache		
Number of subjects with events, n (%)	20 (4.5)	14 (6.4)
Number of censored subjects, n (%)	426 (95.5)	206 (93.6)
Time to Event (Month)		
25%-ile (95%-CI)	NE (43.5, NE)	NE (NE, NE)
Median (95%-CI)	NE (43.5, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.591	
95% CI	0.296, 1.181	
p-value	0.1324	
Odds Ratio	0.691	
95% CI	0.342, 1.395	
p-value	0.3024	
Relative Risk	0.705	
95% CI	0.363, 1.368	
p-value	0.3012	
Risk Difference	-1.879	
95% CI	-5.633, 1.875	
p-value	0.3265	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Nervous system disorders - PT:Paraesthesia*		
Number of subjects with events, n (%)	3 (0.7)	4 (1.8)
Number of censored subjects, n (%)	443 (99.3)	216 (98.2)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.286	
95% CI	0.063, 1.297	
p-value	0.0844	
Odds Ratio	0.366	
95% CI	0.081, 1.648	
p-value	0.1904	
Relative Risk	0.370	
95% CI	0.084, 1.639	
p-value	0.1903	
Risk Difference	-1.146	
95% CI	-3.067, 0.776	
p-value	0.2426	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
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Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
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Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Psychiatric disorders	Number of subjects with events, n (%)	41 (9.2)	14 (6.4)
	Number of censored subjects, n (%)	405 (90.8)	206 (93.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.297	
	95% CI	0.706, 2.382	
	p-value	0.4000	
	Odds Ratio	1.490	
	95% CI	0.794, 2.795	
	p-value	0.2147	
	Relative Risk	1.445	
	95% CI	0.805, 2.593	
	p-value	0.2177	
	Risk Difference	2.829	
	95% CI	-1.365, 7.024	
	p-value	0.1862	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

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* SOC/PT is included in analysis due to indirect comparison versus TITAN.

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95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Psychiatric disorders - PT:Insomnia	Number of subjects with events, n (%)	29 (6.5)	6 (2.7)
	Number of censored subjects, n (%)	417 (93.5)	214 (97.3)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	2.183	
	95% CI	0.905, 5.263	
	p-value	0.0746	
	Odds Ratio	2.480	
	95% CI	1.014, 6.066	
	p-value	0.0465	
	Relative Risk	2.384	
	95% CI	1.005, 5.657	
	p-value	0.0487	
	Risk Difference	3.775	
	95% CI	0.634, 6.916	
	p-value	0.0185	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

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95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Renal and urinary disorders	Number of subjects with events, n (%)	100 (22.4)	40 (18.2)
	Number of censored subjects, n (%)	346 (77.6)	180 (81.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	24.8 (16.8, NE)	NE (18.5, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.114	
	95% CI	0.772, 1.608	
	p-value	0.5642	
	Odds Ratio	1.301	
	95% CI	0.864, 1.957	
	p-value	0.2074	
	Relative Risk	1.233	
	95% CI	0.887, 1.714	
	p-value	0.2121	
	Risk Difference	4.240	
	95% CI	-2.160, 10.639	
	p-value	0.1941	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Renal and urinary disorders - PT:Dysuria	Number of subjects with events, n (%)	14 (3.1)	7 (3.2)
	Number of censored subjects, n (%)	432 (96.9)	213 (96.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.920	
	95% CI	0.371, 2.280	
	p-value	0.8566	
	Odds Ratio	0.986	
	95% CI	0.392, 2.479	
	p-value	0.9763	
	Relative Risk	0.987	
	95% CI	0.404, 2.409	
	p-value	0.9763	
	Risk Difference	-0.043	
	95% CI	-2.871, 2.785	
	p-value	0.9763	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Renal and urinary disorders - PT:Haematuria		
Number of subjects with events, n (%)	22 (4.9)	10 (4.5)
Number of censored subjects, n (%)	424 (95.1)	210 (95.5)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.925	
95% CI	0.437, 1.955	
p-value	0.8374	
Odds Ratio	1.090	
95% CI	0.507, 2.343	
p-value	0.8261	
Relative Risk	1.085	
95% CI	0.523, 2.252	
p-value	0.8262	
Risk Difference	0.387	
95% CI	-3.021, 3.795	
p-value	0.8238	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Renal and urinary disorders - PT:Hydronephrosis*		
Number of subjects with events, n (%)	3 (0.7)	3 (1.4)
Number of censored subjects, n (%)	443 (99.3)	217 (98.6)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.456	
95% CI	0.092, 2.263	
p-value	0.3246	
Odds Ratio	0.490	
95% CI	0.098, 2.447	
p-value	0.3845	
Relative Risk	0.493	
95% CI	0.100, 2.424	
p-value	0.3843	
Risk Difference	-0.691	
95% CI	-2.401, 1.019	
p-value	0.4284	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Renal and urinary disorders - PT:Nocturia*		
Number of subjects with events, n (%)	6 (1.3)	3 (1.4)
Number of censored subjects, n (%)	440 (98.7)	217 (98.6)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.916	
95% CI	0.229, 3.671	
p-value	0.9016	
Odds Ratio	0.986	
95% CI	0.244, 3.982	
p-value	0.9846	
Relative Risk	0.987	
95% CI	0.249, 3.908	
p-value	0.9846	
Risk Difference	-0.018	
95% CI	-1.887, 1.850	
p-value	0.9846	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Renal and urinary disorders - PT:Pollakiuria		
Number of subjects with events, n (%)	11 (2.5)	2 (0.9)
Number of censored subjects, n (%)	435 (97.5)	218 (99.1)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	2.564	
95% CI	0.568, 11.575	
p-value	0.2039	
Odds Ratio	2.756	
95% CI	0.606, 12.545	
p-value	0.1897	
Relative Risk	2.713	
95% CI	0.607, 12.134	
p-value	0.1916	
Risk Difference	1.557	
95% CI	-0.352, 3.466	
p-value	0.1099	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Renal and urinary disorders - PT:Urinary retention*		
Number of subjects with events, n (%)	8 (1.8)	6 (2.7)
Number of censored subjects, n (%)	438 (98.2)	214 (97.3)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.592	
95% CI	0.205, 1.709	
p-value	0.3273	
Odds Ratio	0.651	
95% CI	0.223, 1.901	
p-value	0.4329	
Relative Risk	0.658	
95% CI	0.231, 1.872	
p-value	0.4324	
Risk Difference	-0.934	
95% CI	-3.413, 1.546	
p-value	0.4606	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Reproductive system and breast disorders	Number of subjects with events, n (%)	33 (7.4)	13 (5.9)
	Number of censored subjects, n (%)	413 (92.6)	207 (94.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.109	
	95% CI	0.583, 2.109	
	p-value	0.7522	
	Odds Ratio	1.272	
	95% CI	0.656, 2.469	
	p-value	0.4766	
	Relative Risk	1.252	
	95% CI	0.673, 2.330	
	p-value	0.4780	
	Risk Difference	1.490	
	95% CI	-2.461, 5.441	
	p-value	0.4598	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Reproductive system and breast disorders - PT:Erectile dysfunction*	Number of subjects with events, n (%)	6 (1.3)	3 (1.4)
	Number of censored subjects, n (%)	440 (98.7)	217 (98.6)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.946	
	95% CI	0.236, 3.783	
	p-value	0.9377	
	Odds Ratio	0.986	
	95% CI	0.244, 3.982	
	p-value	0.9846	
	Relative Risk	0.987	
	95% CI	0.249, 3.908	
	p-value	0.9846	
	Risk Difference	-0.018	
	95% CI	-1.887, 1.850	
	p-value	0.9846	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Reproductive system and breast disorders - PT: Pelvic pain*		
Number of subjects with events, n (%)	9 (2.0)	5 (2.3)
Number of censored subjects, n (%)	437 (98.0)	215 (97.7)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.742	
95% CI	0.248, 2.218	
p-value	0.5917	
Odds Ratio	0.886	
95% CI	0.293, 2.675	
p-value	0.8294	
Relative Risk	0.888	
95% CI	0.301, 2.618	
p-value	0.8293	
Risk Difference	-0.255	
95% CI	-2.617, 2.108	
p-value	0.8326	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Respiratory, thoracic and mediastinal disorders	Number of subjects with events, n (%)	62 (13.9)	20 (9.1)
	Number of censored subjects, n (%)	384 (86.1)	200 (90.9)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (37.8, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.326	
	95% CI	0.800, 2.198	
	p-value	0.2728	
	Odds Ratio	1.615	
	95% CI	0.948, 2.749	
	p-value	0.0777	
	Relative Risk	1.529	
	95% CI	0.949, 2.465	
	p-value	0.0813	
	Risk Difference	4.810	
	95% CI	-0.163, 9.784	
	p-value	0.0580	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Respiratory, thoracic and mediastinal disorders - PT:Cough	Number of subjects with events, n (%)	22 (4.9)	8 (3.6)
	Number of censored subjects, n (%)	424 (95.1)	212 (96.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.143	
	95% CI	0.507, 2.576	
	p-value	0.7470	
	Odds Ratio	1.375	
	95% CI	0.602, 3.140	
	p-value	0.4498	
	Relative Risk	1.357	
	95% CI	0.614, 2.998	
	p-value	0.4510	
	Risk Difference	1.296	
	95% CI	-1.891, 4.483	
	p-value	0.4253	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Respiratory, thoracic and mediastinal disorders - PT:Dyspnoea*		
Number of subjects with events, n (%)	7 (1.6)	4 (1.8)
Number of censored subjects, n (%)	439 (98.4)	216 (98.2)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.750	
95% CI	0.219, 2.570	
p-value	0.6466	
Odds Ratio	0.861	
95% CI	0.249, 2.973	
p-value	0.8130	
Relative Risk	0.863	
95% CI	0.255, 2.918	
p-value	0.8129	
Risk Difference	-0.249	
95% CI	-2.358, 1.860	
p-value	0.8172	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Respiratory, thoracic and mediastinal disorders - PT:Epistaxis*		
Number of subjects with events, n (%)	2 (0.4)	1 (0.5)
Number of censored subjects, n (%)	444 (99.6)	219 (99.5)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.894	
95% CI	0.081, 9.889	
p-value	0.9270	
Odds Ratio	0.986	
95% CI	0.089, 10.939	
p-value	0.9912	
Relative Risk	0.987	
95% CI	0.090, 10.821	
p-value	0.9912	
Risk Difference	-0.006	
95% CI	-1.090, 1.078	
p-value	0.9912	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Skin and subcutaneous tissue disorders	Number of subjects with events, n (%)	46 (10.3)	20 (9.1)
	Number of censored subjects, n (%)	400 (89.7)	200 (90.9)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.009	
	95% CI	0.596, 1.709	
	p-value	0.9727	
	Odds Ratio	1.150	
	95% CI	0.662, 1.997	
	p-value	0.6195	
	Relative Risk	1.135	
	95% CI	0.688, 1.870	
	p-value	0.6204	
	Risk Difference	1.223	
	95% CI	-3.510, 5.956	
	p-value	0.6125	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Skin and subcutaneous tissue disorders - PT:Pruritus*	Number of subjects with events, n (%)	10 (2.2)	5 (2.3)
	Number of censored subjects, n (%)	436 (97.8)	215 (97.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (41.4, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.785	
	95% CI	0.265, 2.327	
	p-value	0.6611	
	Odds Ratio	0.986	
	95% CI	0.333, 2.921	
	p-value	0.9800	
	Relative Risk	0.987	
	95% CI	0.341, 2.851	
	p-value	0.9800	
	Risk Difference	-0.031	
	95% CI	-2.432, 2.371	
	p-value	0.9801	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Skin and subcutaneous tissue disorders - PT:Rash	Number of subjects with events, n (%)	12 (2.7)	5 (2.3)
	Number of censored subjects, n (%)	434 (97.3)	215 (97.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.050	
	95% CI	0.369, 2.989	
	p-value	0.9258	
	Odds Ratio	1.189	
	95% CI	0.414, 3.418	
	p-value	0.7481	
	Relative Risk	1.184	
	95% CI	0.422, 3.318	
	p-value	0.7483	
	Risk Difference	0.418	
	95% CI	-2.059, 2.894	
	p-value	0.7409	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Vascular disorders		
Number of subjects with events, n (%)	99 (22.2)	34 (15.5)
Number of censored subjects, n (%)	347 (77.8)	186 (84.5)
Time to Event (Month)		
25%-ile (95%-CI)	33.3 (17.9, NE)	NE (23.1, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.315	
95% CI	0.890, 1.944	
p-value	0.1677	
Odds Ratio	1.561	
95% CI	1.017, 2.395	
p-value	0.0417	
Relative Risk	1.436	
95% CI	1.008, 2.048	
p-value	0.0453	
Risk Difference	6.743	
95% CI	0.604, 12.882	
p-value	0.0313	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

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Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Vascular disorders - PT:Hot flush	Number of subjects with events, n (%)	41 (9.2)	16 (7.3)
	Number of censored subjects, n (%)	405 (90.8)	204 (92.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.225	
	95% CI	0.687, 2.183	
	p-value	0.4910	
	Odds Ratio	1.291	
	95% CI	0.707, 2.356	
	p-value	0.4058	
	Relative Risk	1.264	
	95% CI	0.726, 2.201	
	p-value	0.4078	
	Risk Difference	1.920	
	95% CI	-2.435, 6.275	
	p-value	0.3875	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

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95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

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Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Vascular disorders - PT:Hypertension	Number of subjects with events, n (%)	44 (9.9)	20 (9.1)
	Number of censored subjects, n (%)	402 (90.1)	200 (90.9)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.886	
	95% CI	0.521, 1.508	
	p-value	0.6552	
	Odds Ratio	1.095	
	95% CI	0.628, 1.907	
	p-value	0.7498	
	Relative Risk	1.085	
	95% CI	0.656, 1.795	
	p-value	0.7502	
	Risk Difference	0.775	
	95% CI	-3.925, 5.475	
	p-value	0.7467	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.1.1

Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm) - Subgroup analysis (safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Subgroup Level	Darolutamide (N=446) n/N[s] (%)	Placebo (N=220) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
				Hazard Ratio	(95% CI)	p-Value	
SOC: Hepatobiliary disorders	Presence of visceral metastases assessed by central review (from IWRS)						0.9923
	Yes	3/ 54 (5.6)	0/ 26 (0.0)	NE	(NE, NE)	NE	
	No	23/392 (5.9)	1/194 (0.5)	9.961	(1.345, 73.749)	0.0055	
	Received prior local therapy (from IWRS)						0.9901
	Yes	7/ 81 (8.6)	0/ 39 (0.0)	NE	(NE, NE)	NE	
	No	19/365 (5.2)	1/181 (0.6)	8.472	(1.134, 63.287)	0.0124	
	Prior local radiotherapy and/or prostatectomy						0.9886
	Yes	5/ 88 (5.7)	0/ 49 (0.0)	NE	(NE, NE)	NE	
	No	21/358 (5.9)	1/171 (0.6)	8.815	(1.186, 65.537)	0.0101	
	Age group						1.0000
	<65 years	7/117 (6.0)	0/ 64 (0.0)	NE	(NE, NE)	NE	
	65-74	13/193 (6.7)	0/ 95 (0.0)	NE	(NE, NE)	NE	
	75-84	6/118 (5.1)	0/ 51 (0.0)	NE	(NE, NE)	NE	
	>=85 years	0/ 18 (0.0)	1/ 10 (10.0)	NE	(NE, NE)	NE	
	Race						1.0000
	White	8/250 (3.2)	0/123 (0.0)	NE	(NE, NE)	NE	
	Asian	18/144 (12.5)	1/ 65 (1.5)	7.804	(1.042, 58.469)	0.0178	
	Black or African American	0/ 42 (0.0)	0/ 23 (0.0)	NE	(NE, NE)	NE	
	Other	0/ 10 (0.0)	0/ 9 (0.0)	NE	(NE, NE)	NE	
	Geographical region						0.9999
	Asia	18/141 (12.8)	1/ 63 (1.6)	7.761	(1.036, 58.140)	0.0182	
	Latin America	1/120 (0.8)	0/ 70 (0.0)	NE	(NE, NE)	NE	
	Europe and Rest of the world	7/185 (3.8)	0/ 87 (0.0)	NE	(NE, NE)	NE	
	Baseline PSA values by median						0.9889
	< median of overall population	11/216 (5.1)	0/109 (0.0)	NE	(NE, NE)	NE	
	>= median of overall population	15/219 (6.8)	1/108 (0.9)	6.815	(0.900, 51.614)	0.0311	
	ECOG PS at baseline						0.9892
	=0	15/235 (6.4)	0/ 96 (0.0)	NE	(NE, NE)	NE	
	>=1	11/211 (5.2)	1/124 (0.8)	6.052	(0.781, 46.897)	0.0494	
	Gleason score at initial diagnosis						0.9864
	Gleason <8	7/125 (5.6)	1/ 64 (1.6)	3.271	(0.402, 26.603)	0.2403	
	Gleason >=8	18/308 (5.8)	0/146 (0.0)	NE	(NE, NE)	NE	
	Disease volume at baseline						0.9862
	high	21/315 (6.7)	0/155 (0.0)	NE	(NE, NE)	NE	
	low	5/131 (3.8)	1/ 65 (1.5)	1.897	(0.220, 16.344)	0.5533	
	Renal function - eGFR at baseline						0.9999
	Normal: eGFR >= 90 mL/min	14/221 (6.3)	0/102 (0.0)	NE	(NE, NE)	NE	
	Mild impairment: 60 <= eGFR < 90 mL/min	9/179 (5.0)	1/ 90 (1.1)	4.327	(0.548, 34.162)	0.1293	
	Moderate impairment: 30 <= eGFR < 60 mL/min	3/ 45 (6.7)	0/ 27 (0.0)	NE	(NE, NE)	NE	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Subgroup analysis was done for SOC/ PTs with significant overall treatment effect (significant log-rank test). Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.1.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm) - Subgroup analysis (safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Subgroup Level	Darolutamide(N=446) n/N[s] (%)	Placebo(N=220) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
				Hazard Ratio	(95% CI)	p-Value	
SOC: Hepatobiliary disorders	Hepatic function at baseline						
	Normal: Total bilirubin and AST <= upper limit of normal (ULN)	22/387 (5.7)	1/200 (0.5)	9.945	(1.340, 73.786)	0.0056	0.9893
	Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	4/ 59 (6.8)	0/ 20 (0.0)	NE	(NE, NE)	NE	
	Age Group (Titan)						
	<65	7/117 (6.0)	0/ 64 (0.0)	NE	(NE, NE)	NE	0.9998
	>=65 and <75	13/193 (6.7)	0/ 95 (0.0)	NE	(NE, NE)	NE	
	>=75	6/136 (4.4)	1/ 61 (1.6)	2.407	(0.289, 20.025)	0.4016	
	Geographic region (Titan)						
	Europe and north america	7/145 (4.8)	0/ 76 (0.0)	NE	(NE, NE)	NE	0.9912
	ROTW	19/301 (6.3)	1/144 (0.7)	8.236	(1.102, 61.532)	0.0140	

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025

Study population

Table 3.3.1.1

Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm) - Subgroup analysis (safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Subgroup Level	Darolutamide(N=446) n/N[s] (%)	Placebo(N=220) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
				Hazard Ratio	(95% CI)	p-Value	
SOC: Musculoskeletal and connective tissue disorders - PT: Bone pain	Presence of visceral metastases assessed by central review (from IWRS)						0.3247
	Yes	5/ 54 (9.3)	2/ 26 (7.7)	1.077	(0.209, 5.555)	0.9293	
	No	28/392 (7.1)	26/194 (13.4)	0.467	(0.273, 0.797)	0.0043	
	Received prior local therapy (from IWRS)						0.5647
	Yes	7/ 81 (8.6)	4/ 39 (10.3)	0.741	(0.215, 2.557)	0.6340	
	No	26/365 (7.1)	24/181 (13.3)	0.475	(0.272, 0.828)	0.0072	
	Prior local radiotherapy and/or prostatectomy						0.9676
	Yes	6/ 88 (6.8)	6/ 49 (12.2)	0.516	(0.166, 1.606)	0.2448	
	No	27/358 (7.5)	22/171 (12.9)	0.507	(0.288, 0.891)	0.0161	
	Age group						0.3744
	<65 years	11/117 (9.4)	5/ 64 (7.8)	1.063	(0.369, 3.064)	0.9102	
	65-74	11/193 (5.7)	15/ 95 (15.8)	0.314	(0.144, 0.686)	0.0021	
	75-84	10/118 (8.5)	7/ 51 (13.7)	0.538	(0.204, 1.416)	0.2022	
	>=85 years	1/ 18 (5.6)	1/ 10 (10.0)	0.564	(0.035, 9.023)	0.6812	
	Race						0.9862
	White	20/250 (8.0)	17/123 (13.8)	0.493	(0.258, 0.944)	0.0294	
	Asian	6/144 (4.2)	4/ 65 (6.2)	0.638	(0.180, 2.260)	0.4822	
	Black or African American	7/ 42 (16.7)	6/ 23 (26.1)	0.594	(0.199, 1.770)	0.3444	
	Other	0/ 10 (0.0)	1/ 9 (11.1)	NE	(NE, NE)	NE	
	Geographical region						0.9958
	Asia	5/141 (3.5)	4/ 63 (6.3)	0.528	(0.142, 1.967)	0.3331	
	Latin America	17/120 (14.2)	16/ 70 (22.9)	0.545	(0.275, 1.079)	0.0770	
	Europe and Rest of the world	11/185 (5.9)	8/ 87 (9.2)	0.563	(0.225, 1.404)	0.2118	
	Baseline PSA values by median						0.8945
	< median of overall population	14/216 (6.5)	13/109 (11.9)	0.484	(0.227, 1.030)	0.0542	
	>= median of overall population	17/219 (7.8)	14/108 (13.0)	0.515	(0.253, 1.047)	0.0621	
	ECOG PS at baseline						0.2385
	=0	21/235 (8.9)	11/ 96 (11.5)	0.695	(0.335, 1.443)	0.3264	
	>=1	12/211 (5.7)	17/124 (13.7)	0.369	(0.176, 0.774)	0.0060	
	Gleason score at initial diagnosis						0.5133
	Gleason <8	8/125 (6.4)	9/ 64 (14.1)	0.404	(0.156, 1.050)	0.0542	
	Gleason >=8	24/308 (7.8)	17/146 (11.6)	0.603	(0.324, 1.125)	0.1082	
	Disease volume at baseline						0.9392
	high	28/315 (8.9)	24/155 (15.5)	0.506	(0.293, 0.874)	0.0128	
	low	5/131 (3.8)	4/ 65 (6.2)	0.534	(0.143, 1.999)	0.3444	
	Renal function - eGFR at baseline						0.4304
	Normal: eGFR >= 90 mL/min	20/221 (9.0)	13/102 (12.7)	0.629	(0.313, 1.266)	0.1898	
	Mild impairment: 60 <= eGFR < 90 mL/min	12/179 (6.7)	11/ 90 (12.2)	0.468	(0.206, 1.065)	0.0640	
	Moderate impairment: 30 <= eGFR < 60 mL/min	1/ 45 (2.2)	4/ 27 (14.8)	0.134	(0.015, 1.200)	0.0347	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable. Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier. Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test. p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates. Subgroup analysis was done for SOC/ PTs with significant overall treatment effect (significant log-rank test). Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels. Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.1.1
Summary of Frequent Adverse Events by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm) - Subgroup analysis (safety analysis set)

Final

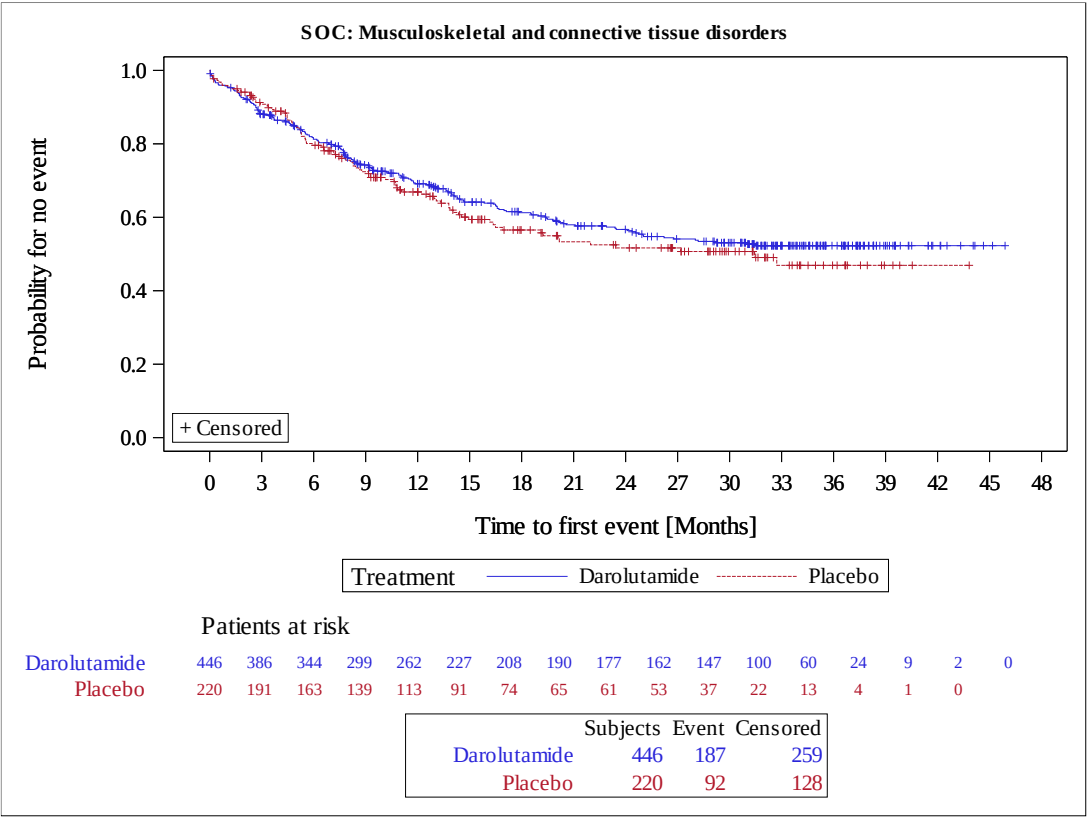
System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Subgroup Level	Darolutamide(N=446) n/N[s] (%)	Placebo(N=220) n/N[s] (%)	Unstratified Analysis			Interaction p-Value
				Hazard Ratio	(95% CI)	p-Value	
SOC: Musculoskeletal and connective tissue disorders - PT:Bone pain	Hepatic function at baseline						0.6459
	Normal: Total bilirubin and AST <= upper limit of normal (ULN)	29/387 (7.5)	25/200 (12.5)	0.523	(0.306, 0.895)	0.0161	
	Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin <= ULN and AST > ULN)	4/ 59 (6.8)	3/ 20 (15.0)	0.376	(0.084, 1.683)	0.1823	
	Age Group (Titan)						0.2100
	<65	11/117 (9.4)	5/ 64 (7.8)	1.063	(0.369, 3.064)	0.9102	
	>=65 and <75	11/193 (5.7)	15/ 95 (15.8)	0.314	(0.144, 0.686)	0.0021	
	>=75	11/136 (8.1)	8/ 61 (13.1)	0.543	(0.218, 1.355)	0.1839	
	Geographic region (Titan)						0.7890
	Europe and north america	9/145 (6.2)	7/ 76 (9.2)	0.577	(0.214, 1.556)	0.2715	
	ROTW	24/301 (8.0)	21/144 (14.6)	0.490	(0.273, 0.881)	0.0149	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.3.1.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

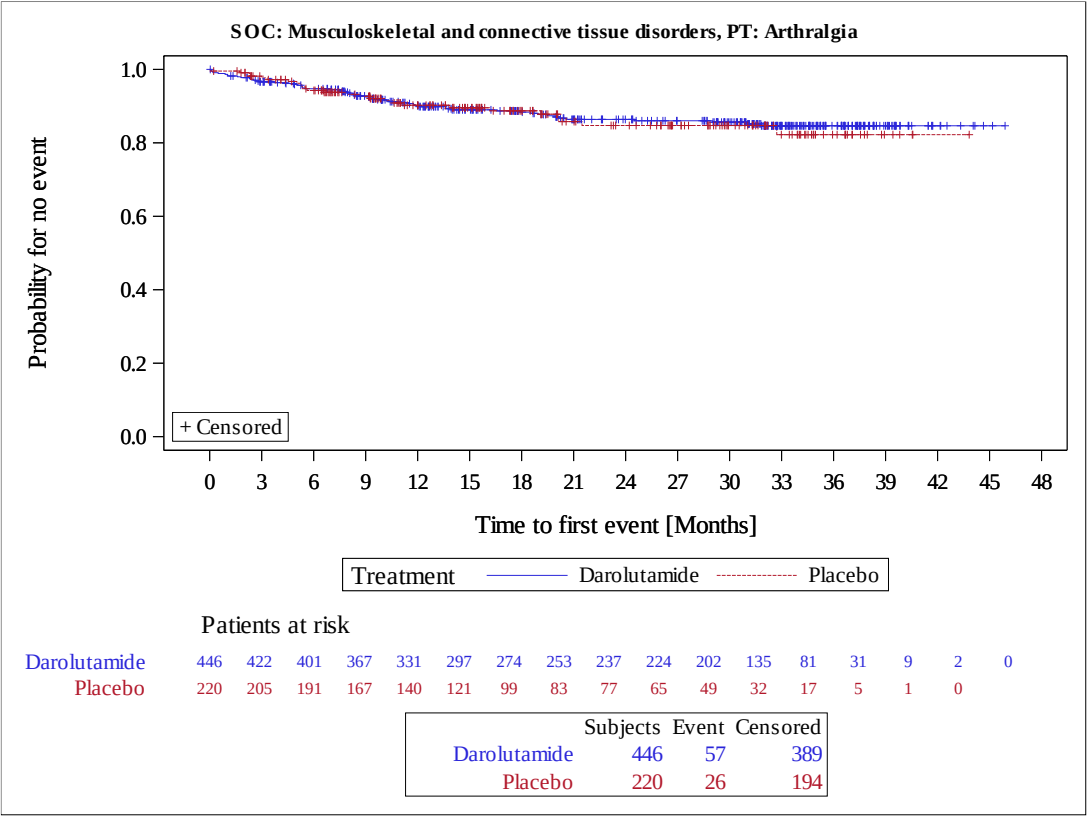


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Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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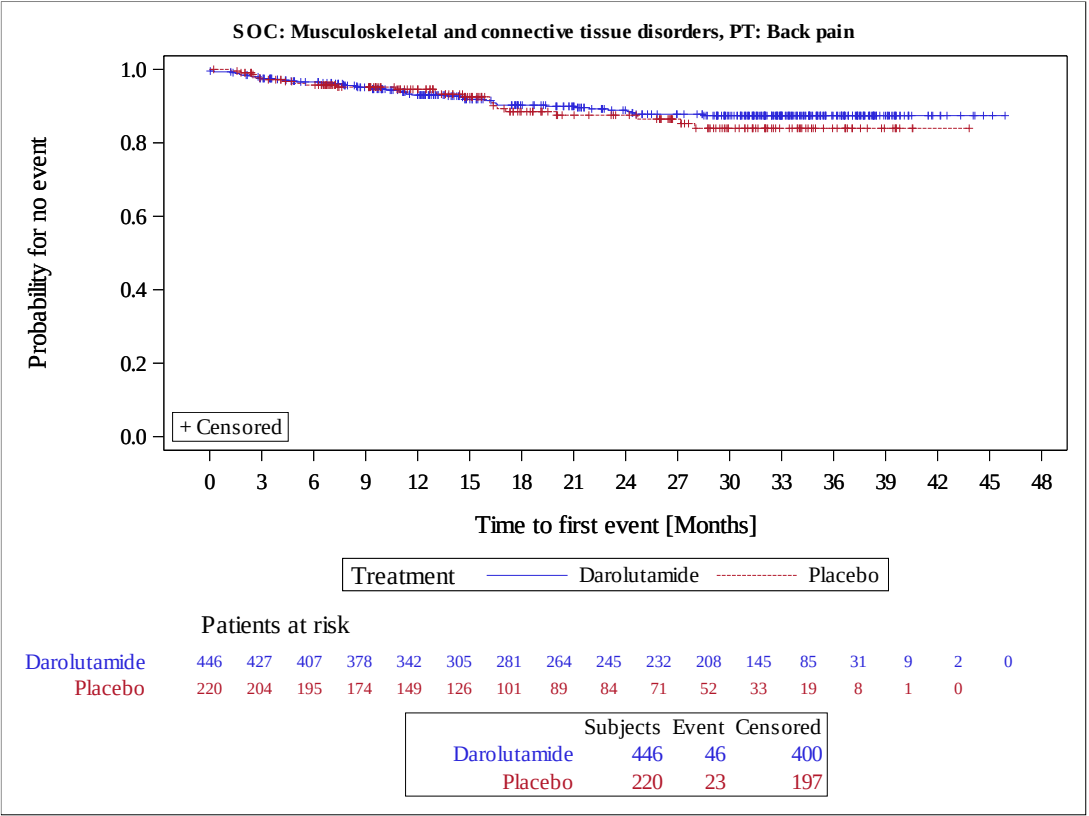


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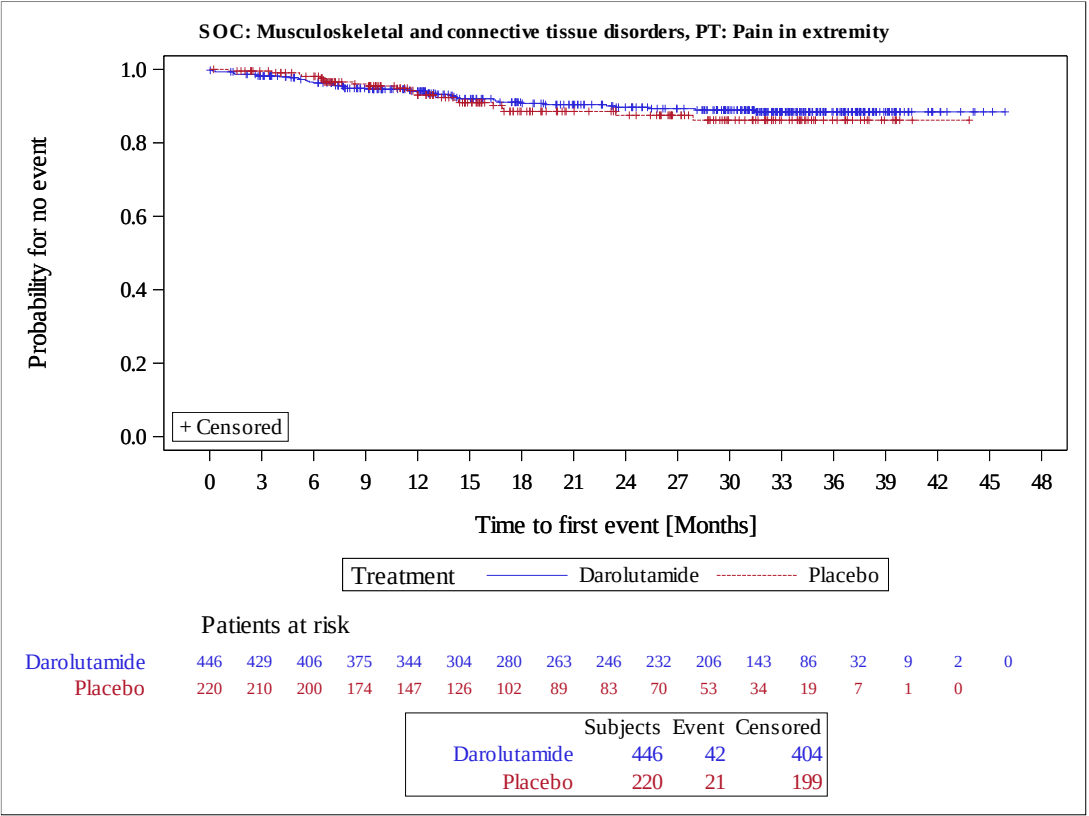


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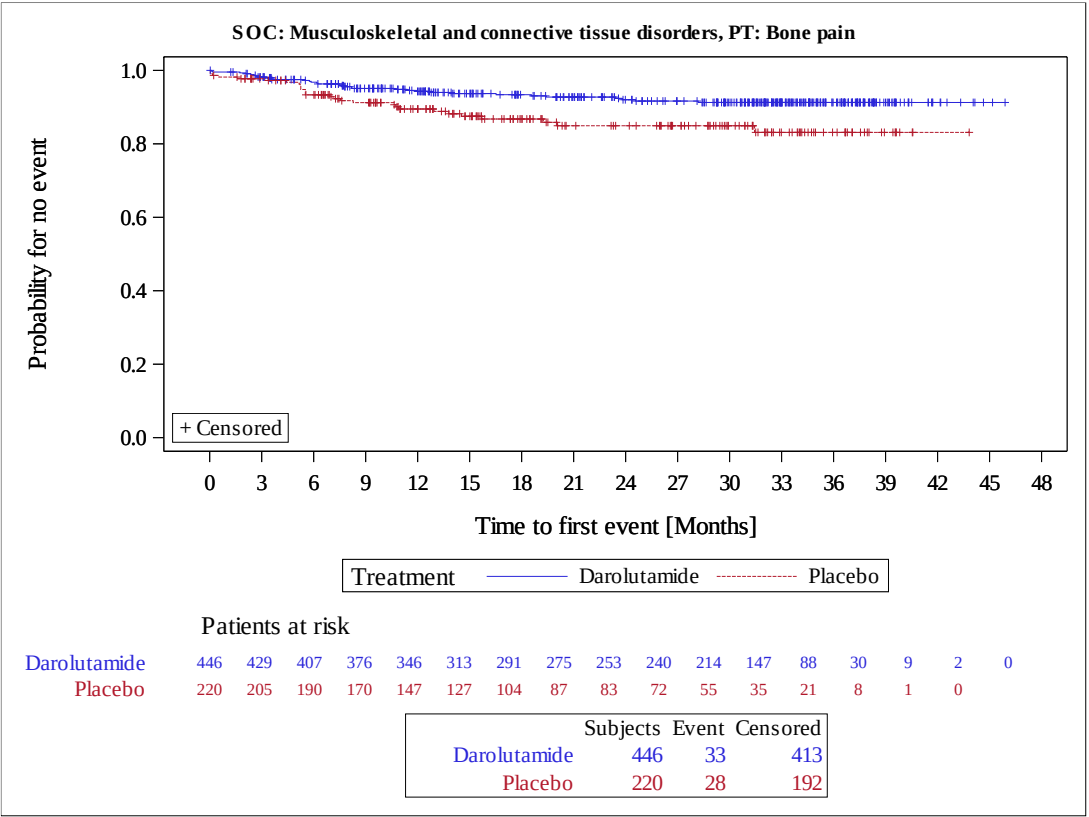


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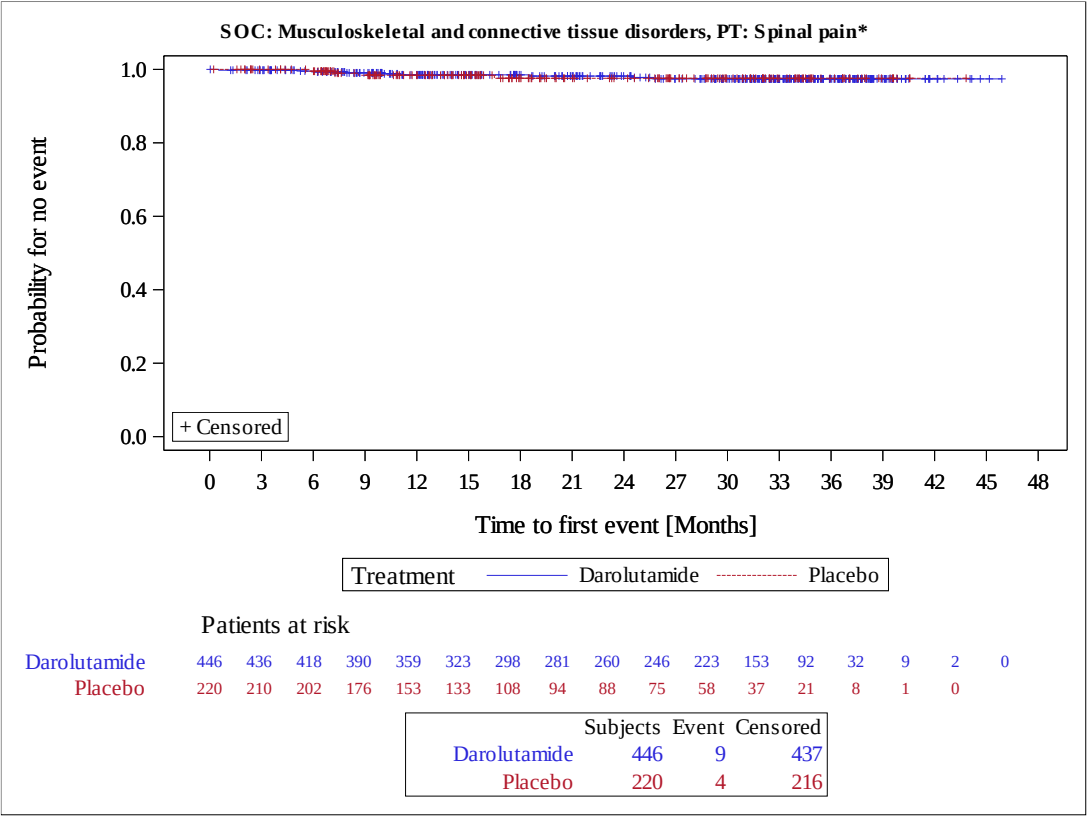


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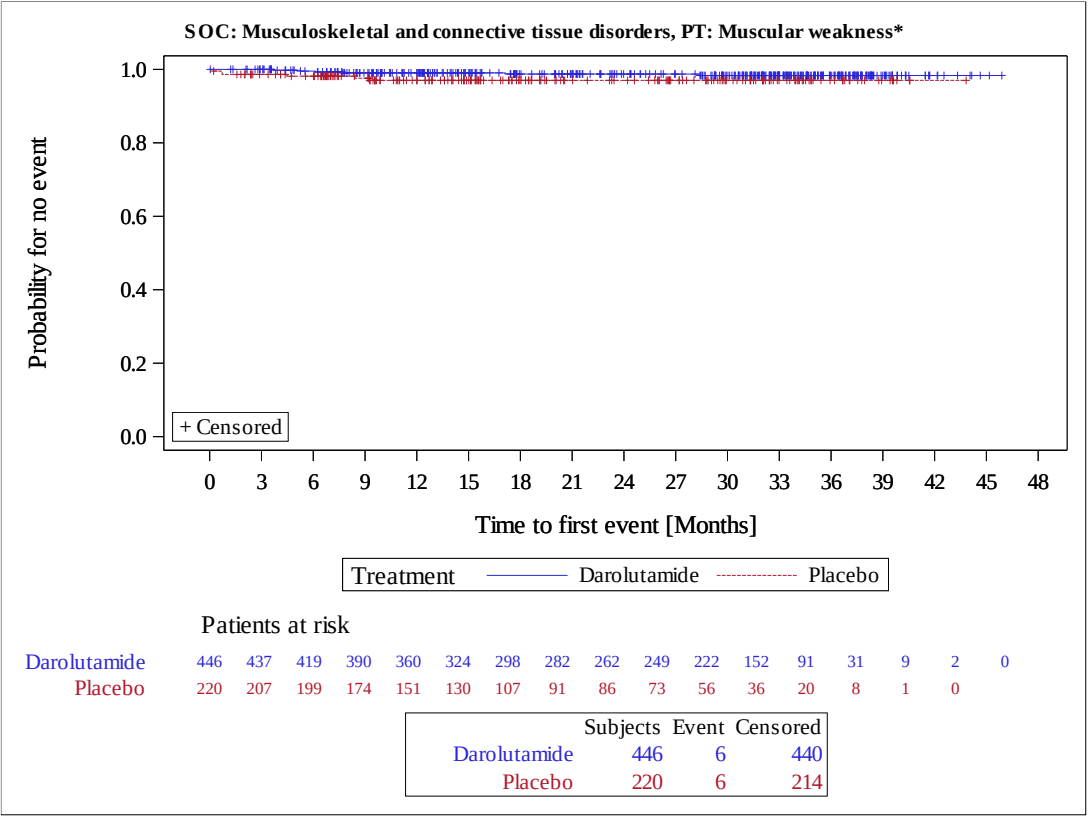


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BAY 1841788 / 21140 - 10JAN2025
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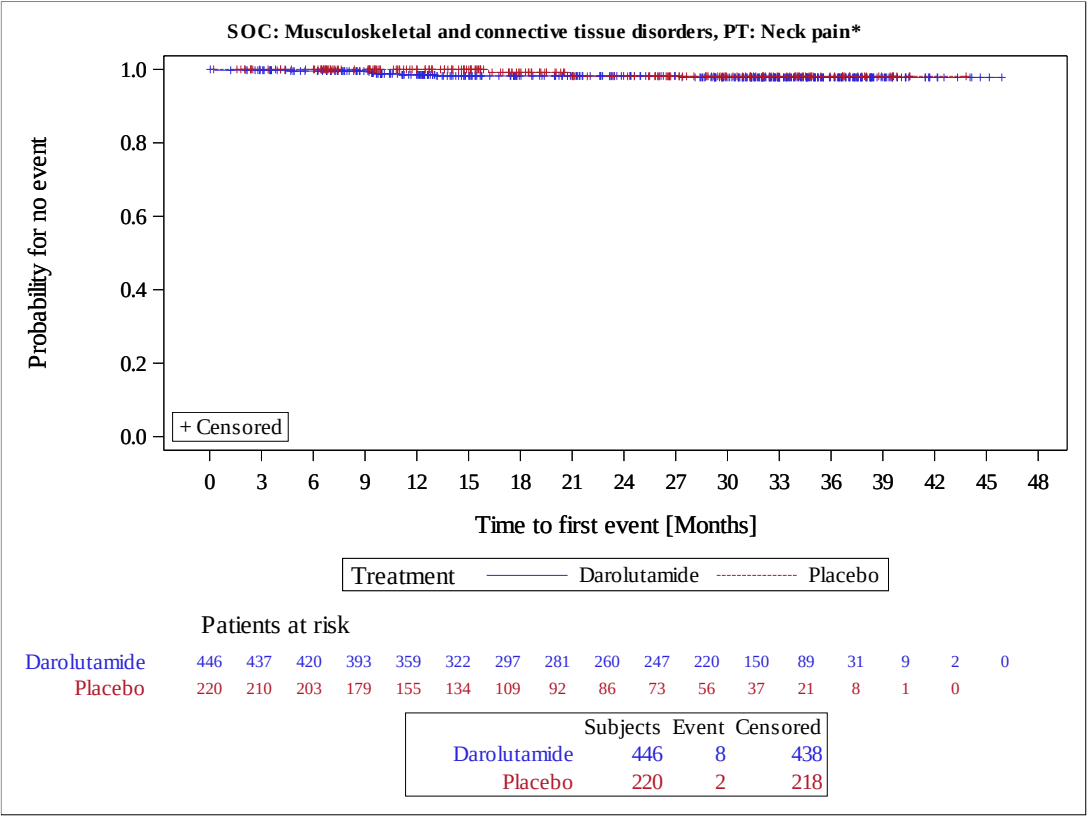


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(safety analysis set)

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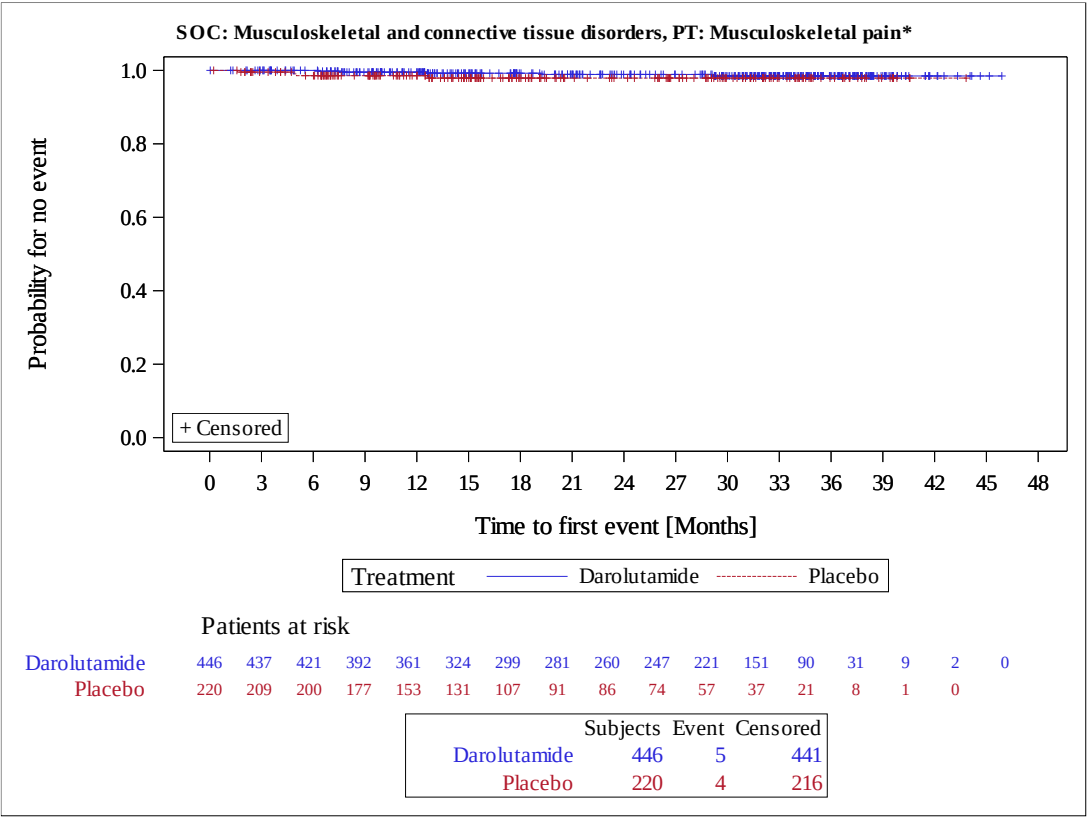


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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.3.1.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

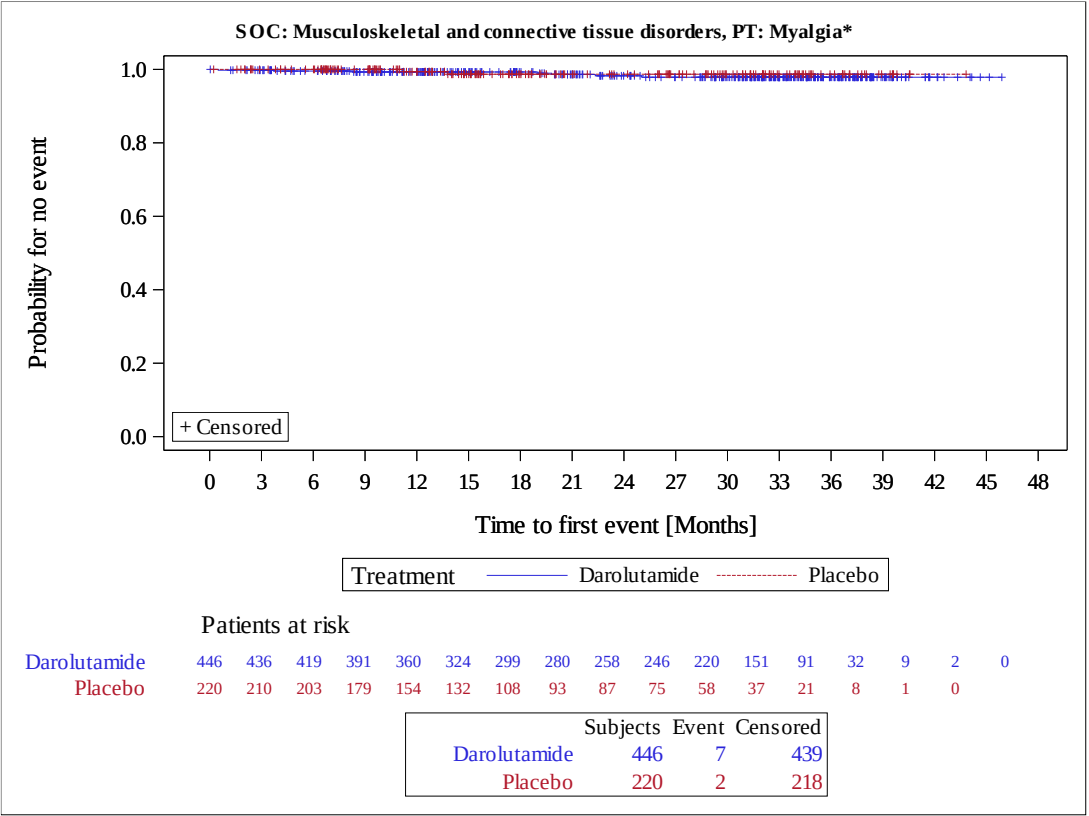


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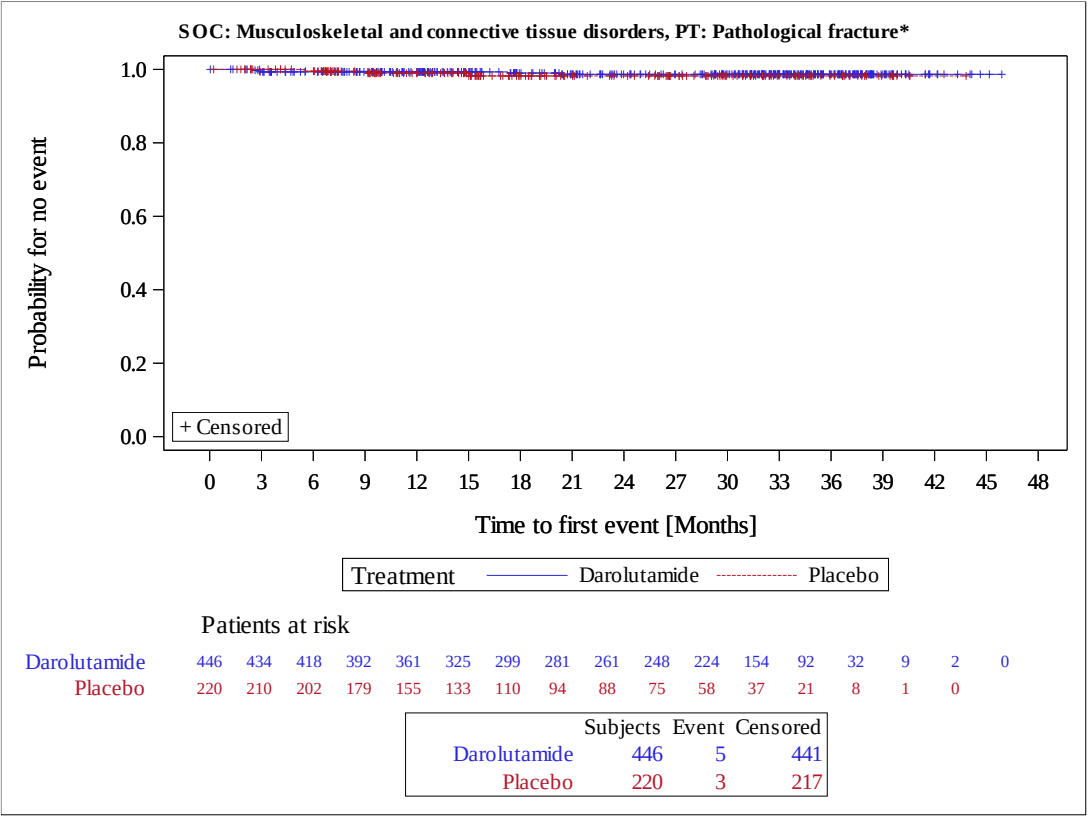


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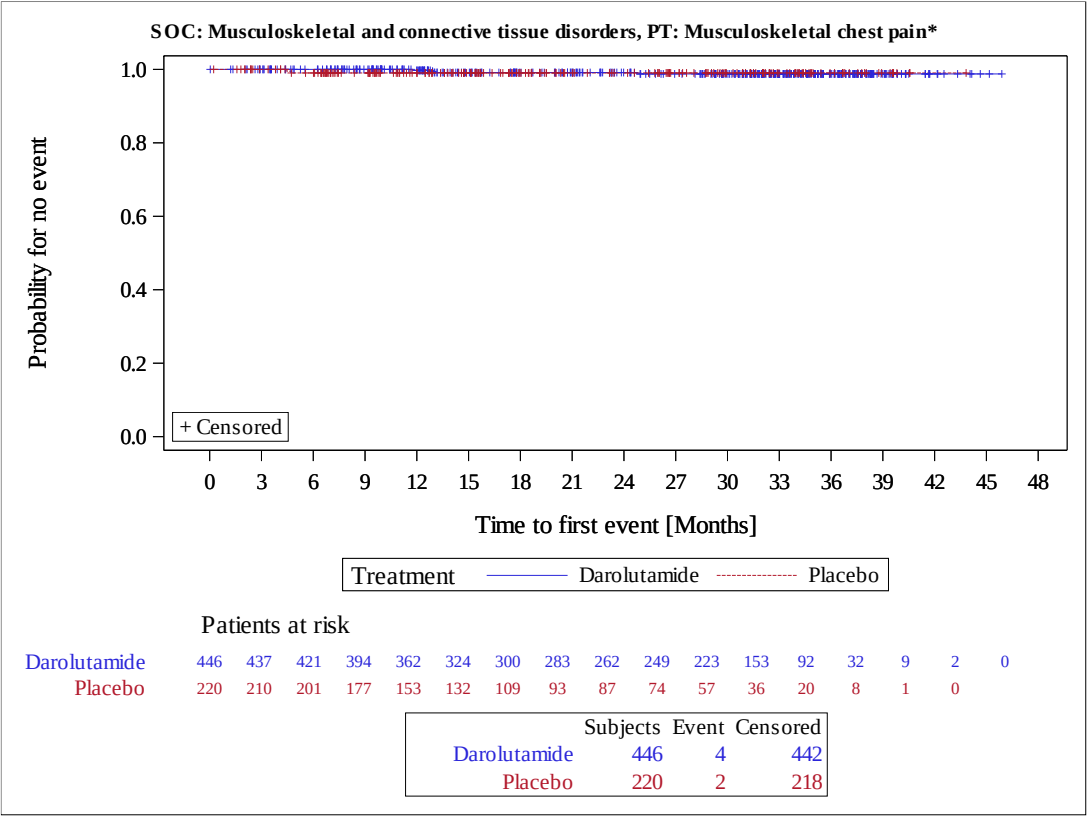


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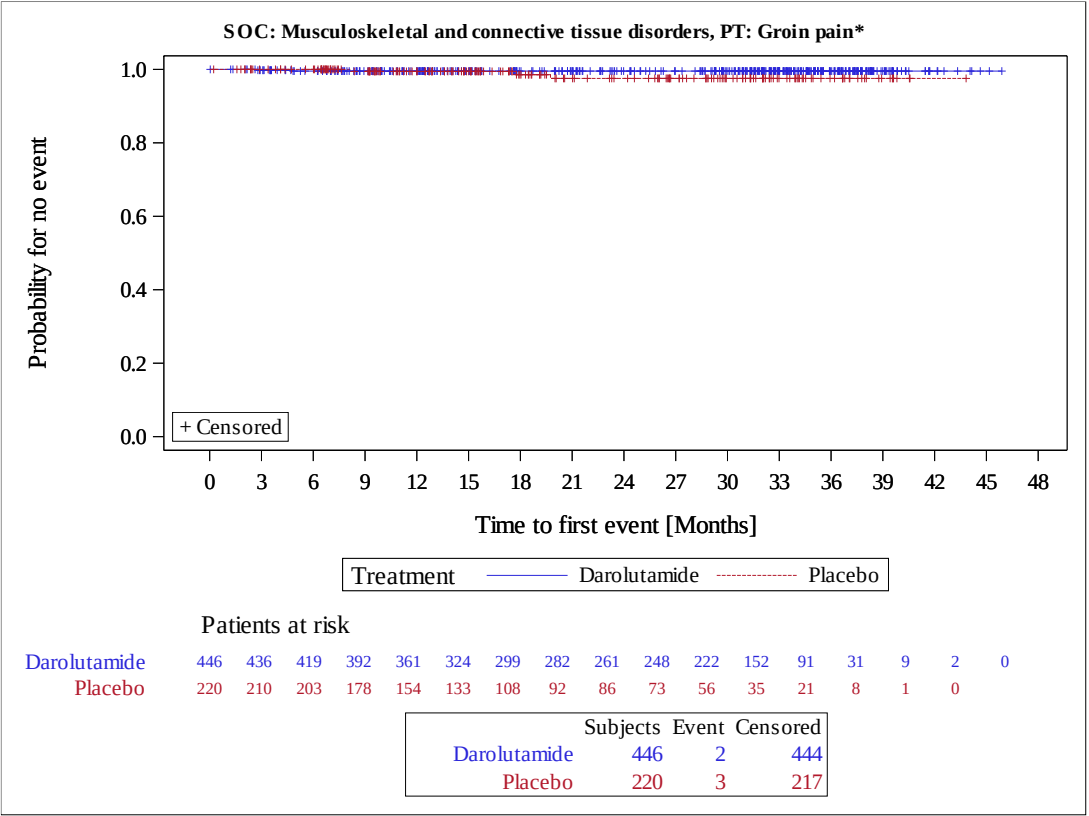


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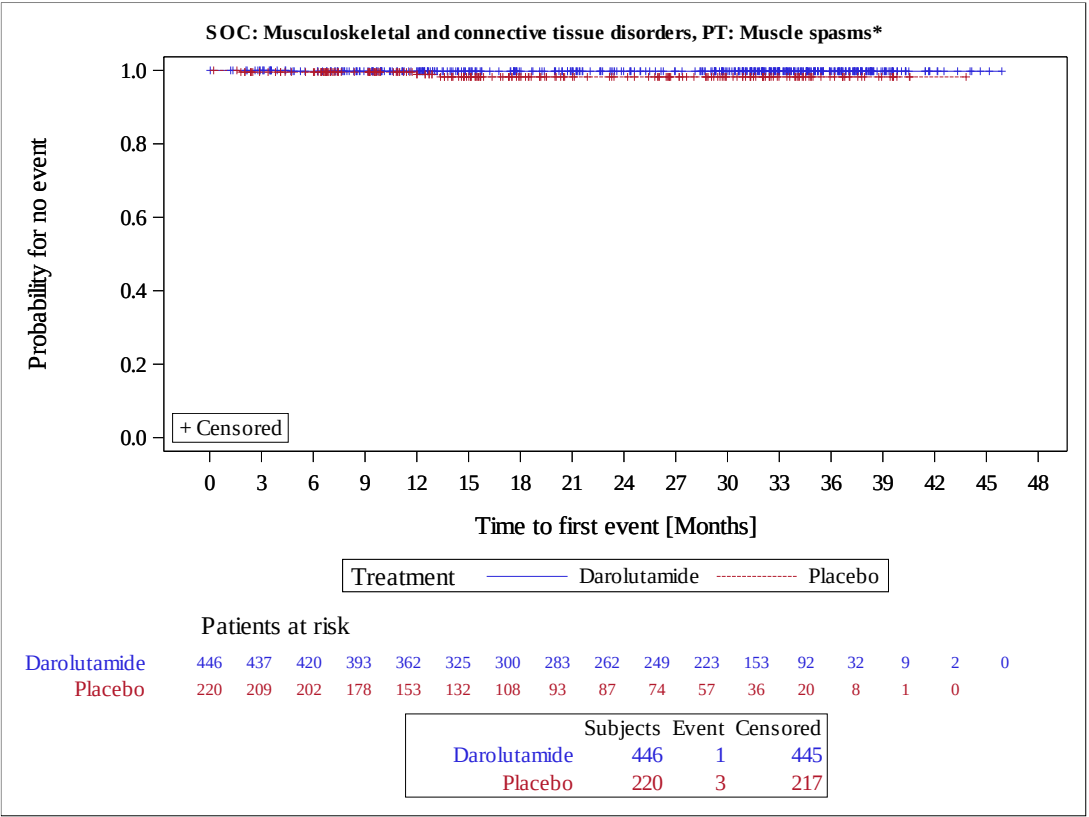


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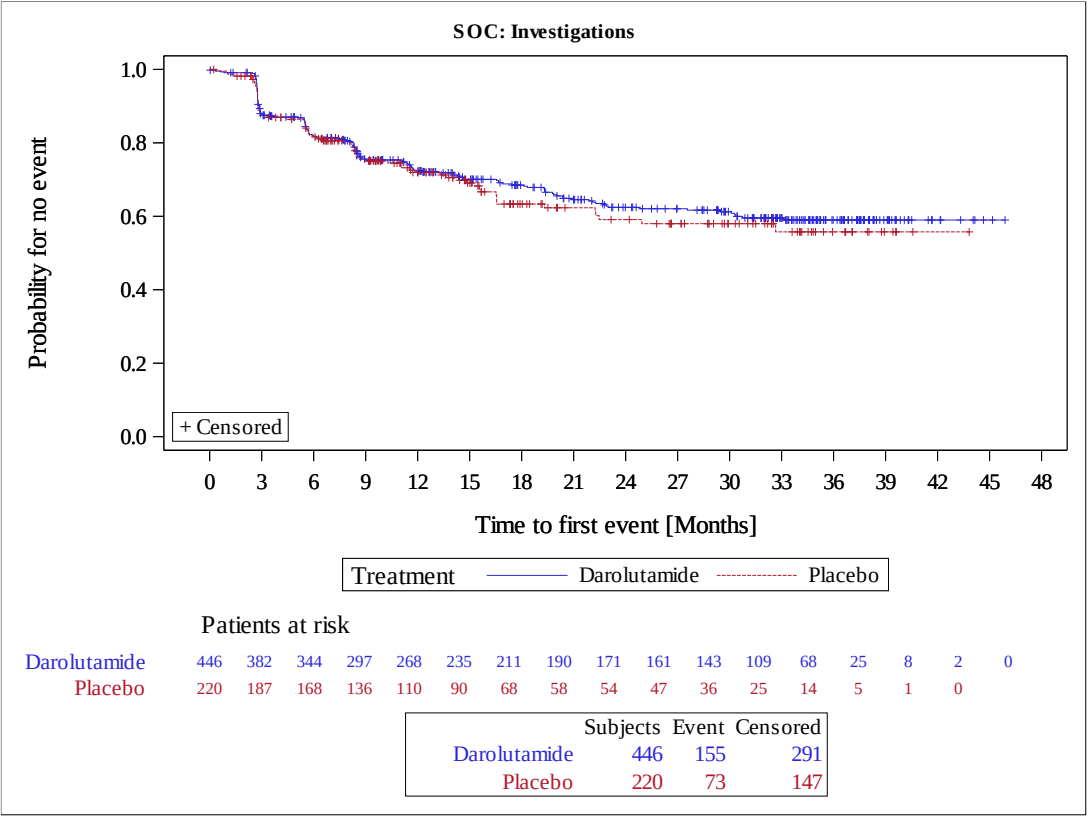


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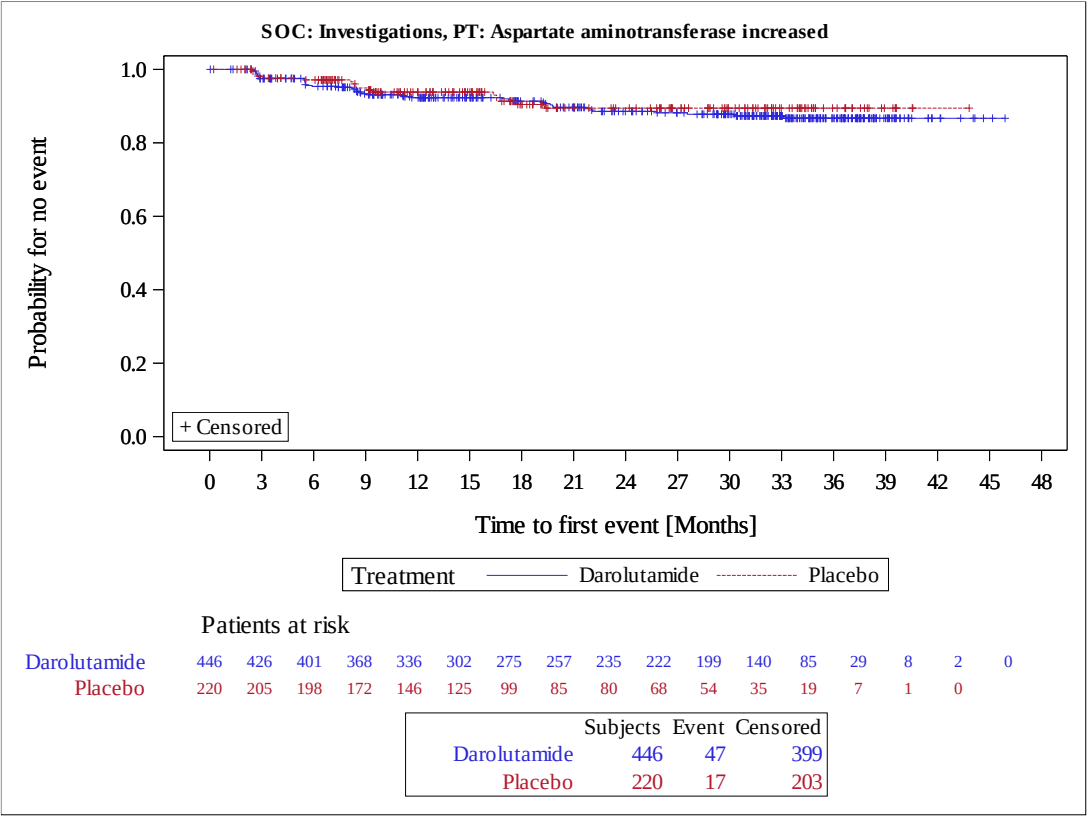


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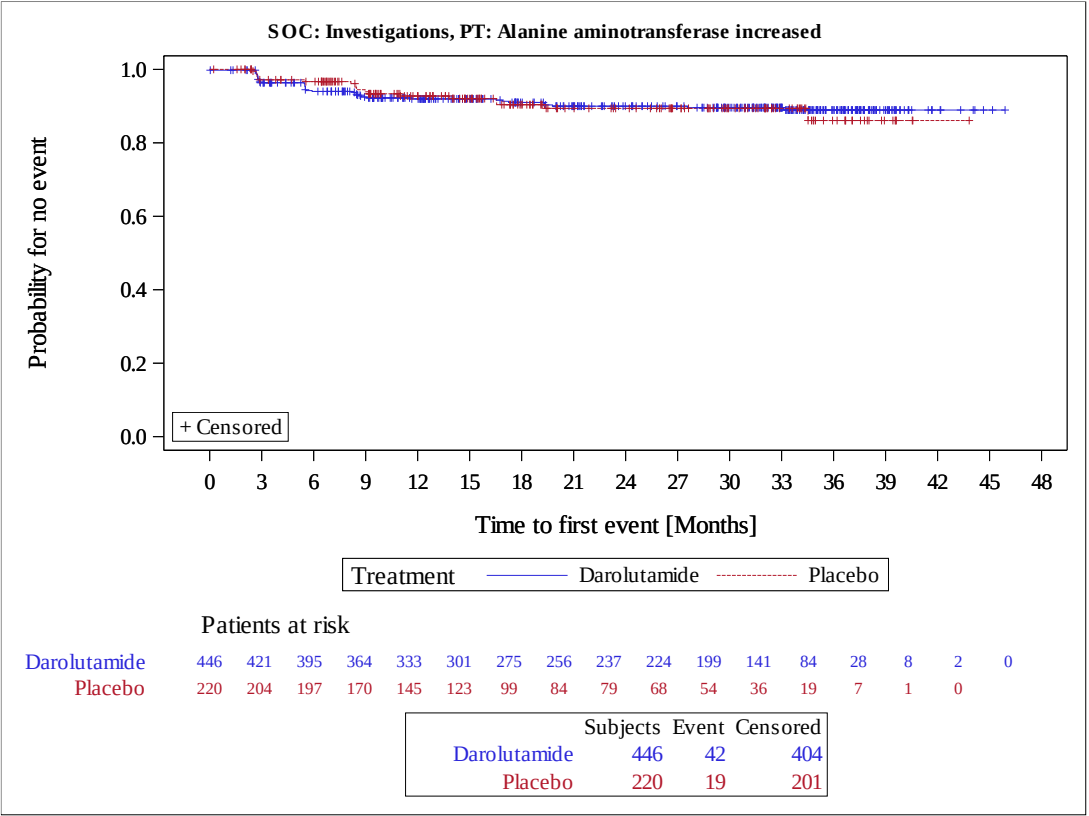


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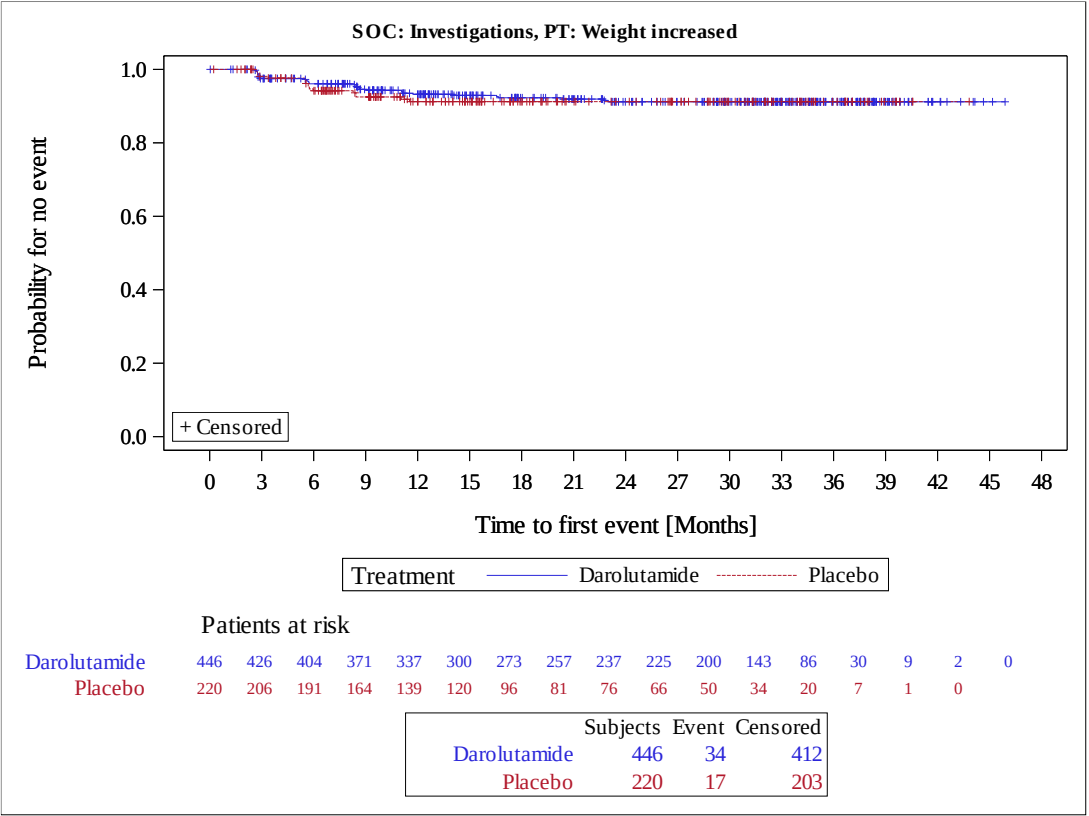


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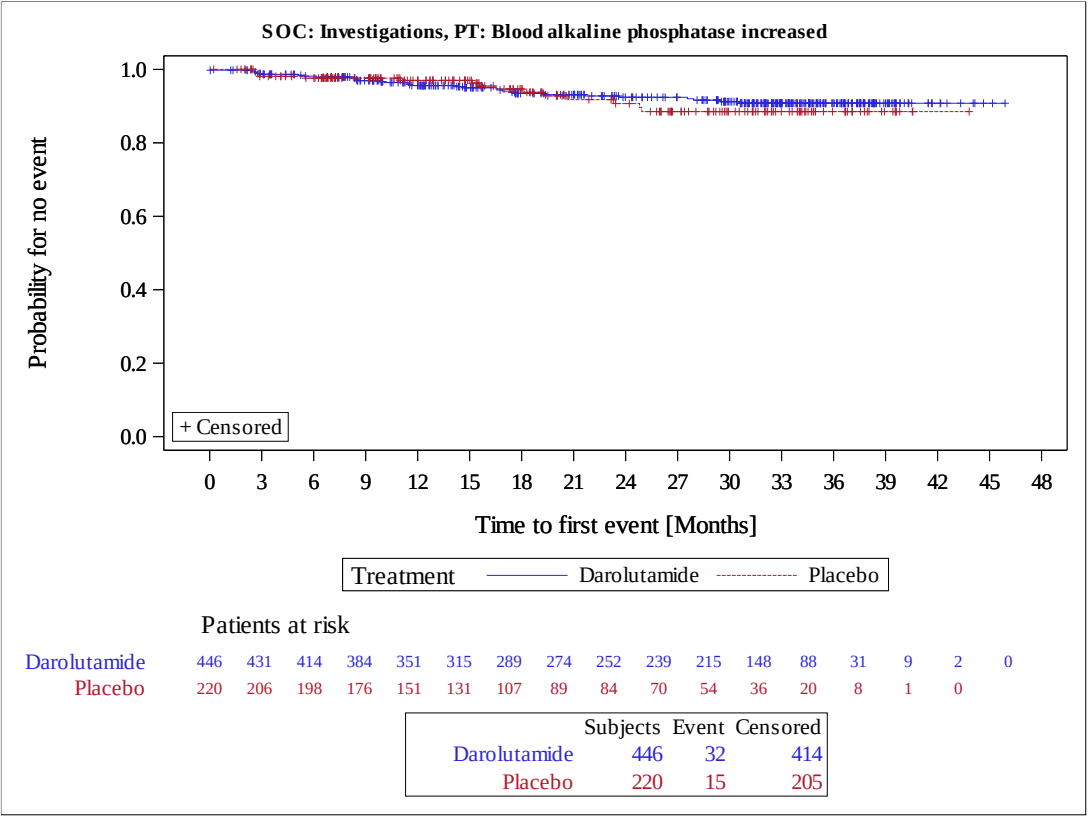


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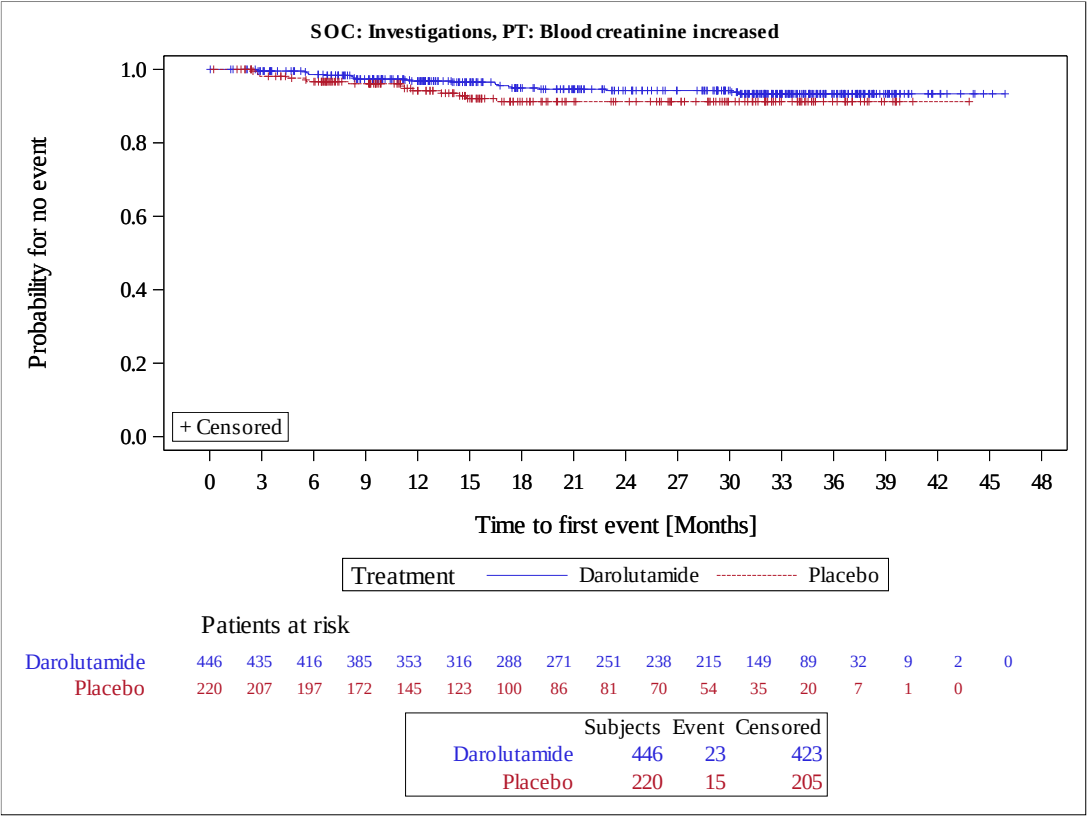


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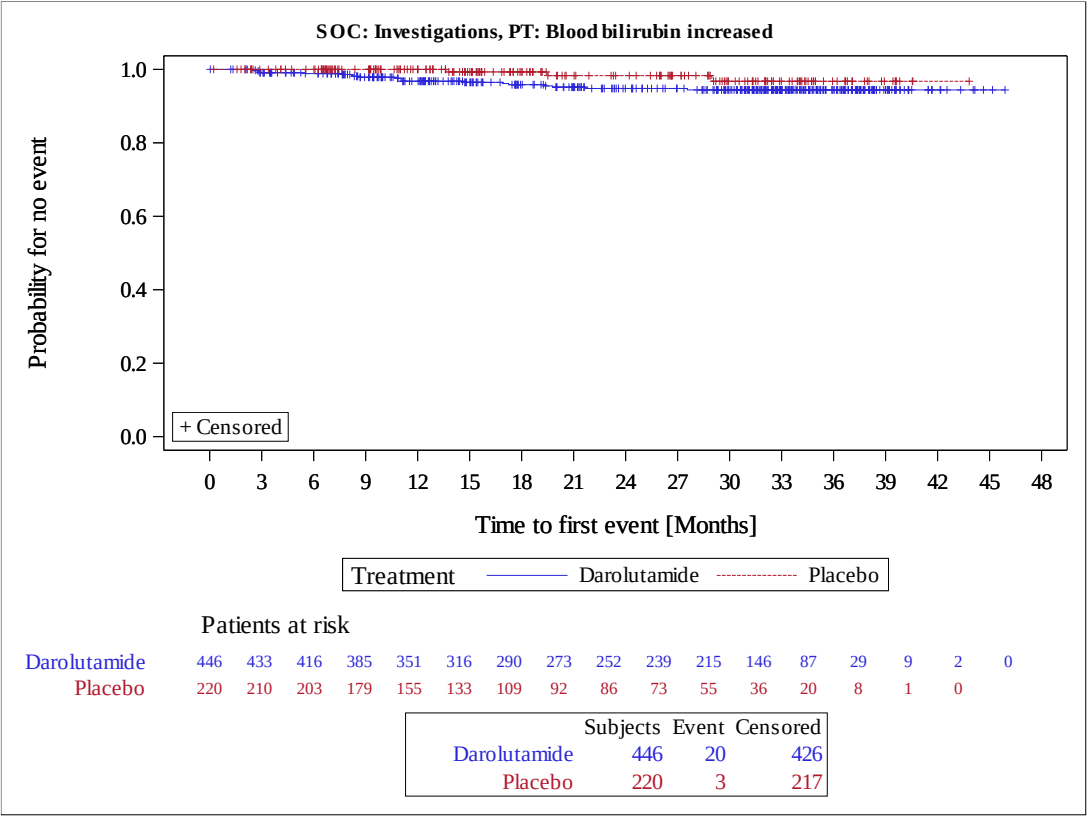


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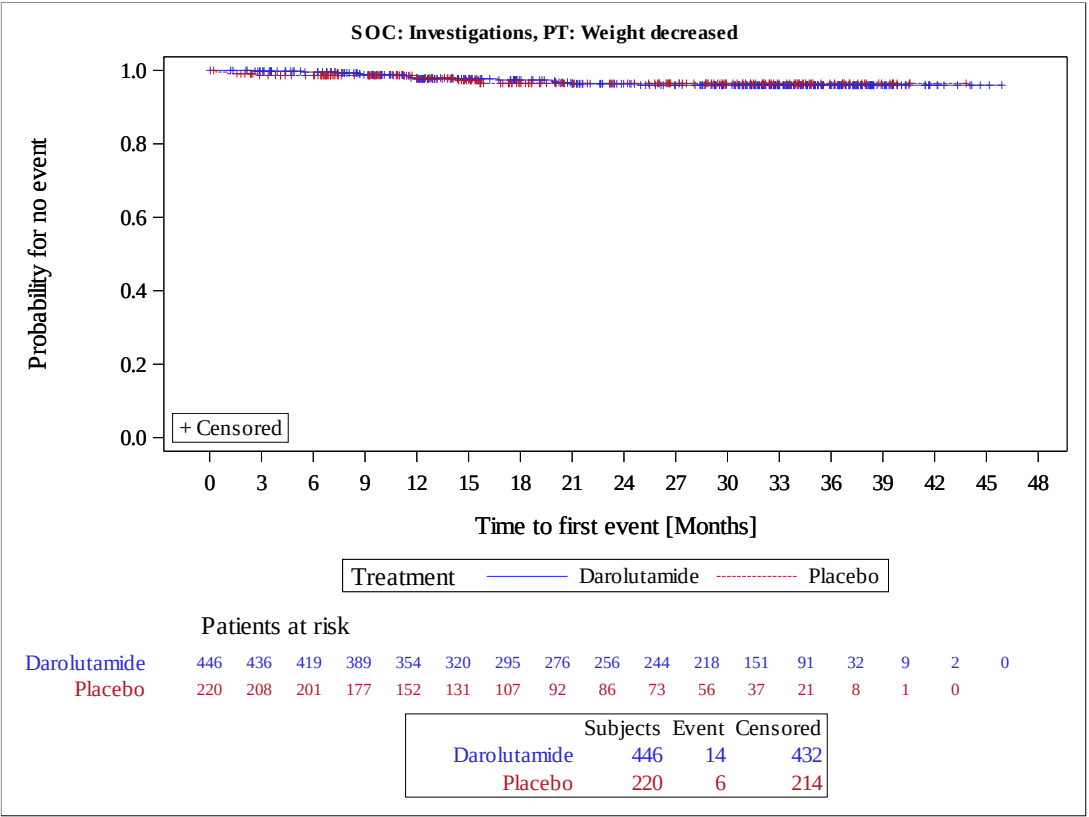


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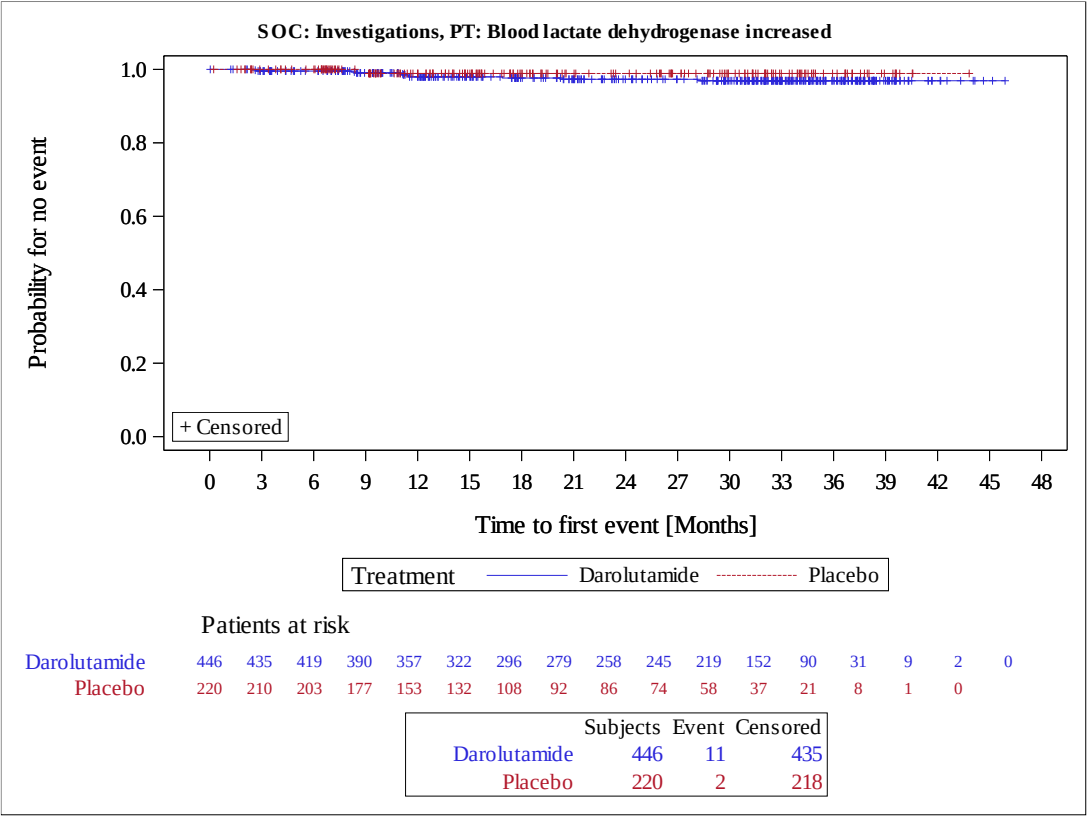


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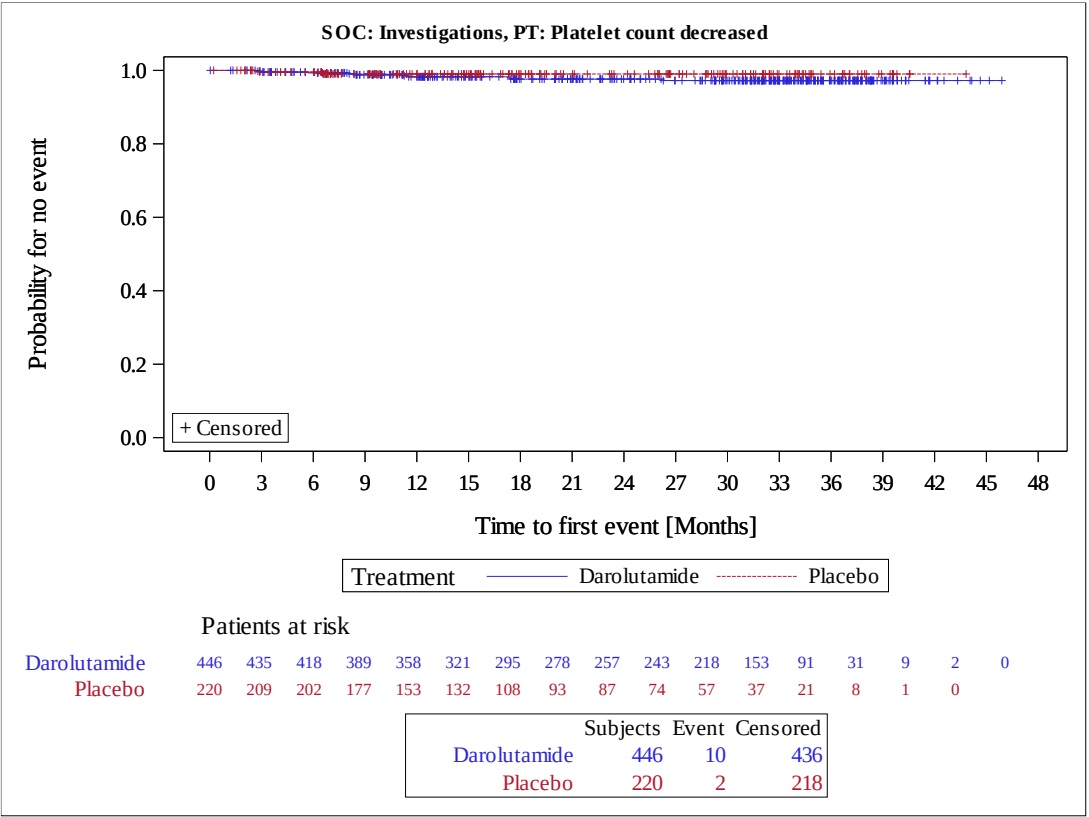


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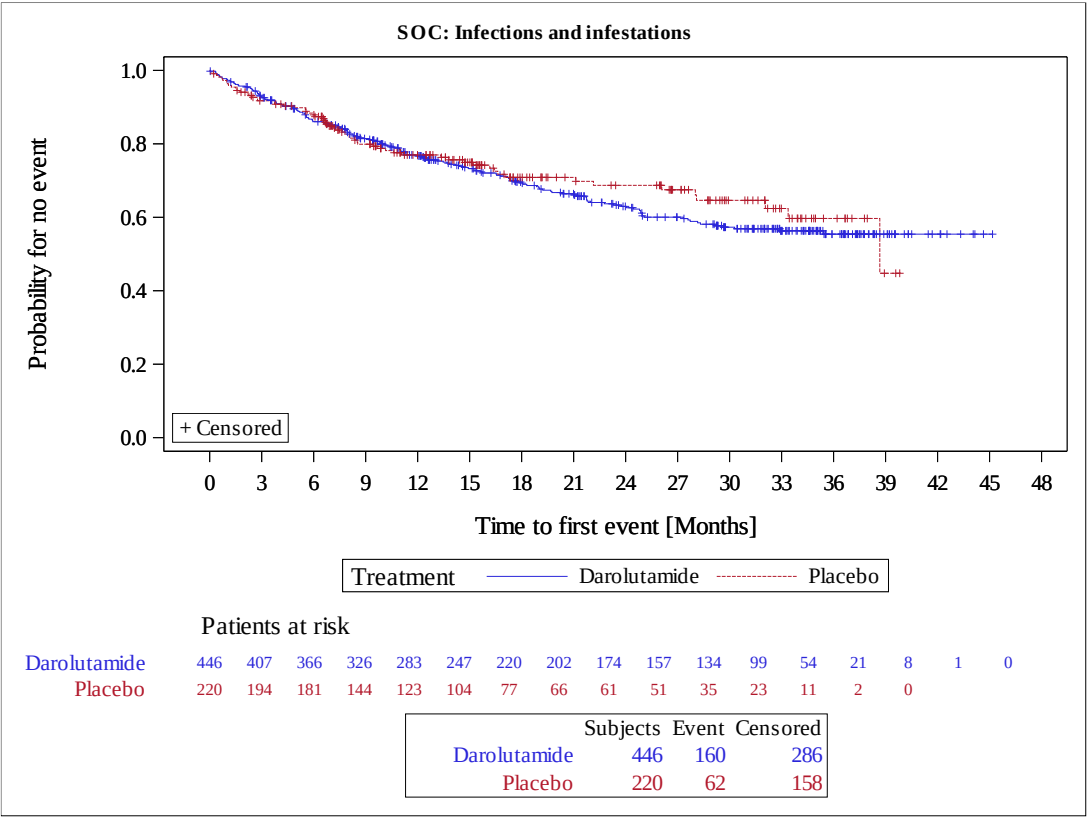


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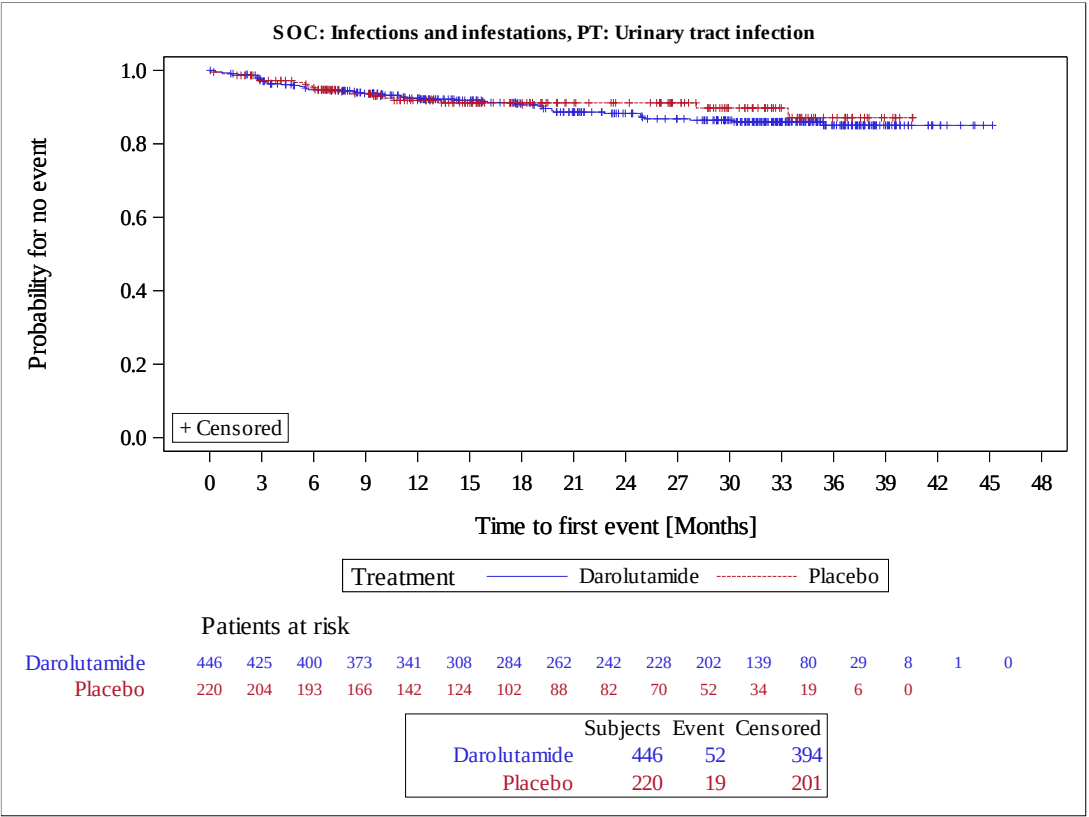


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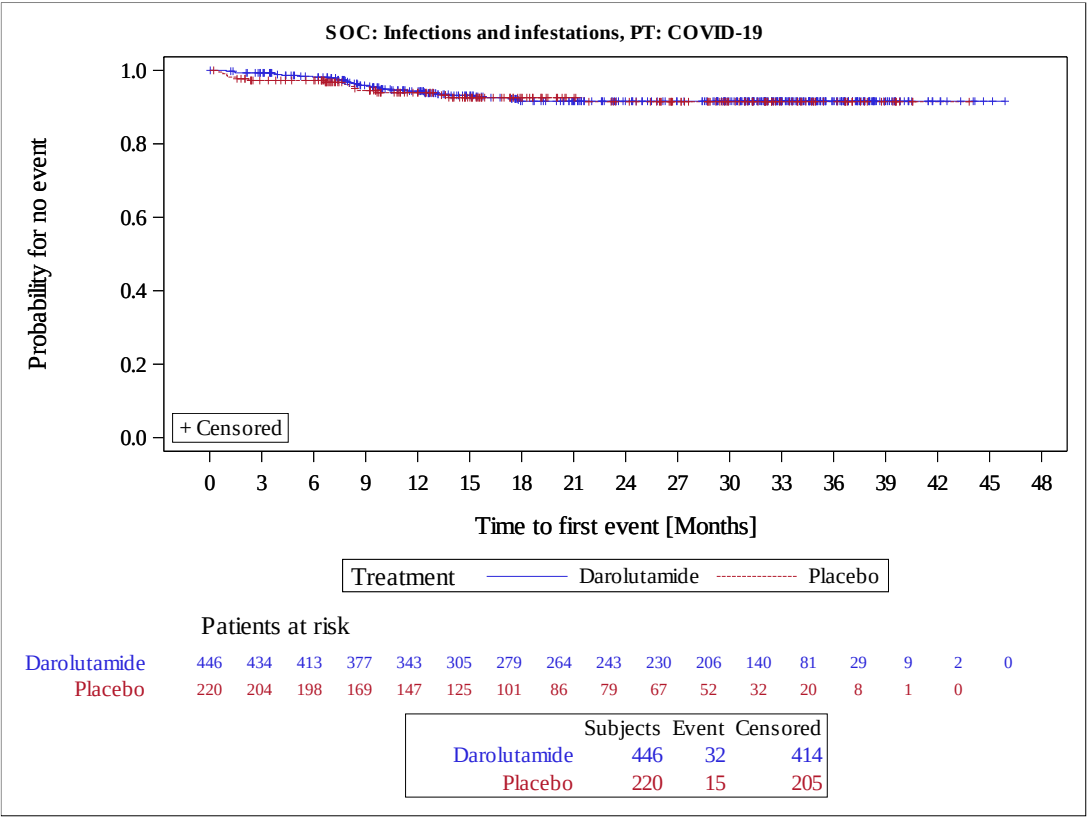


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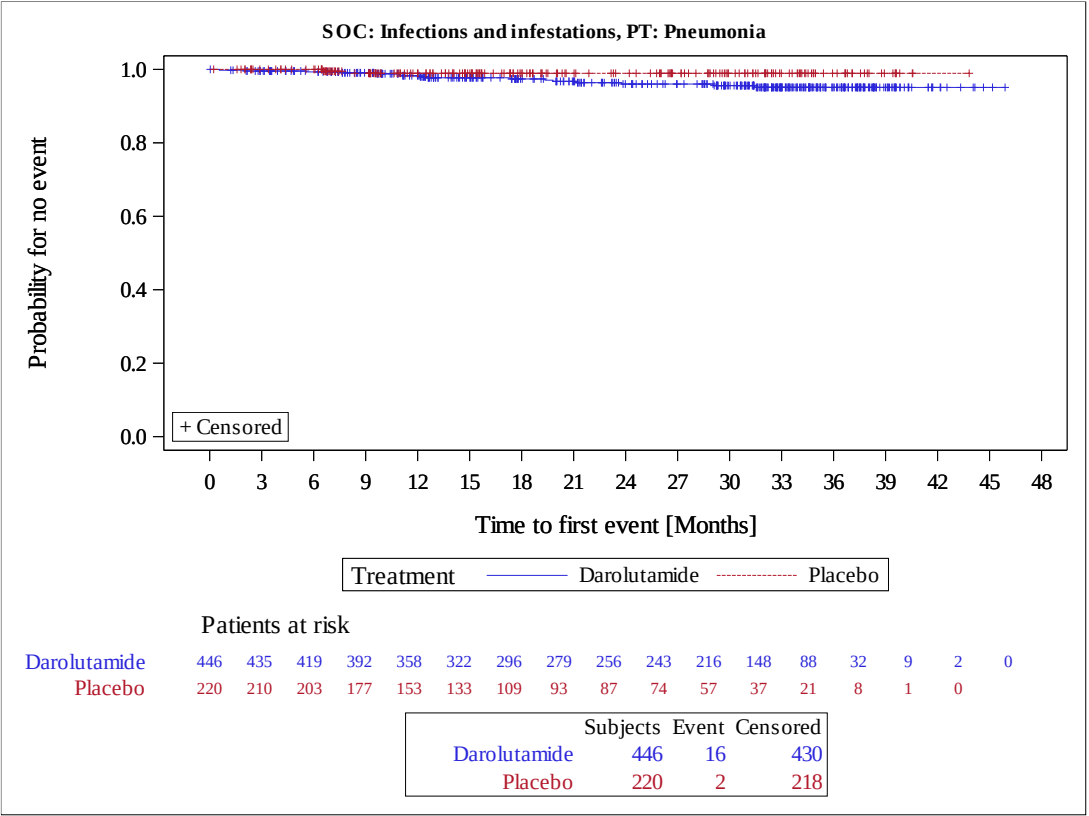


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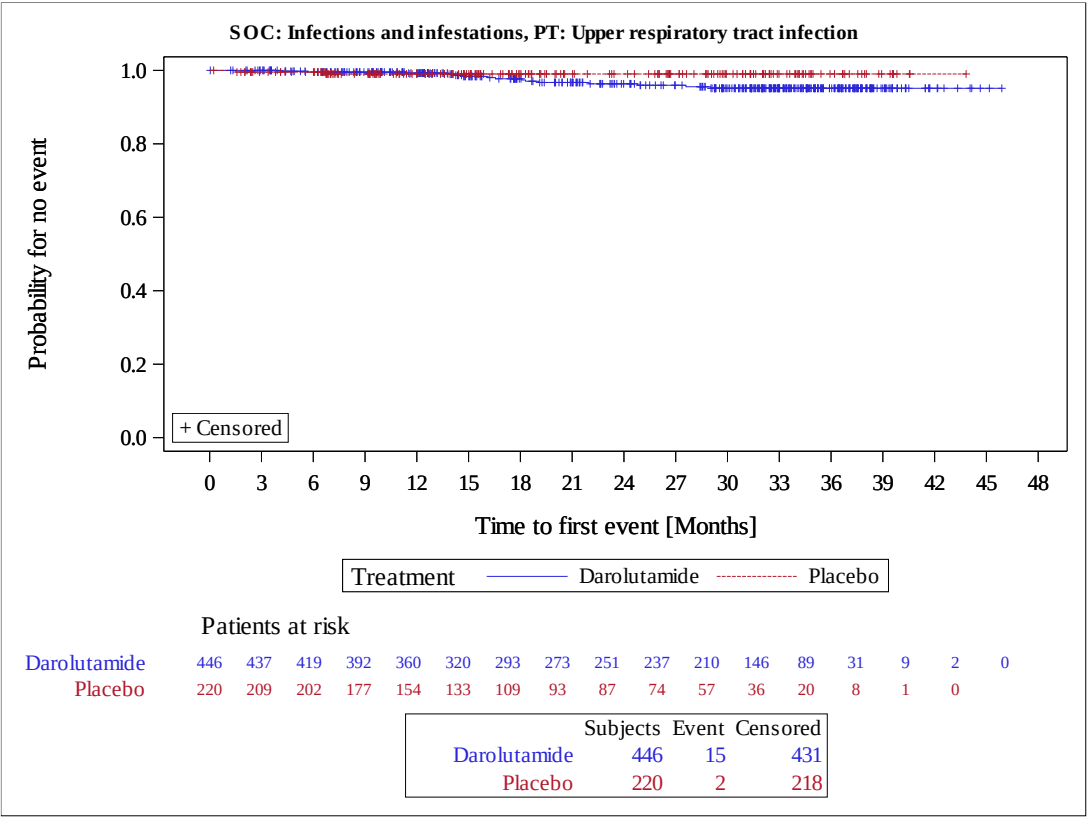


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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.3.1.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

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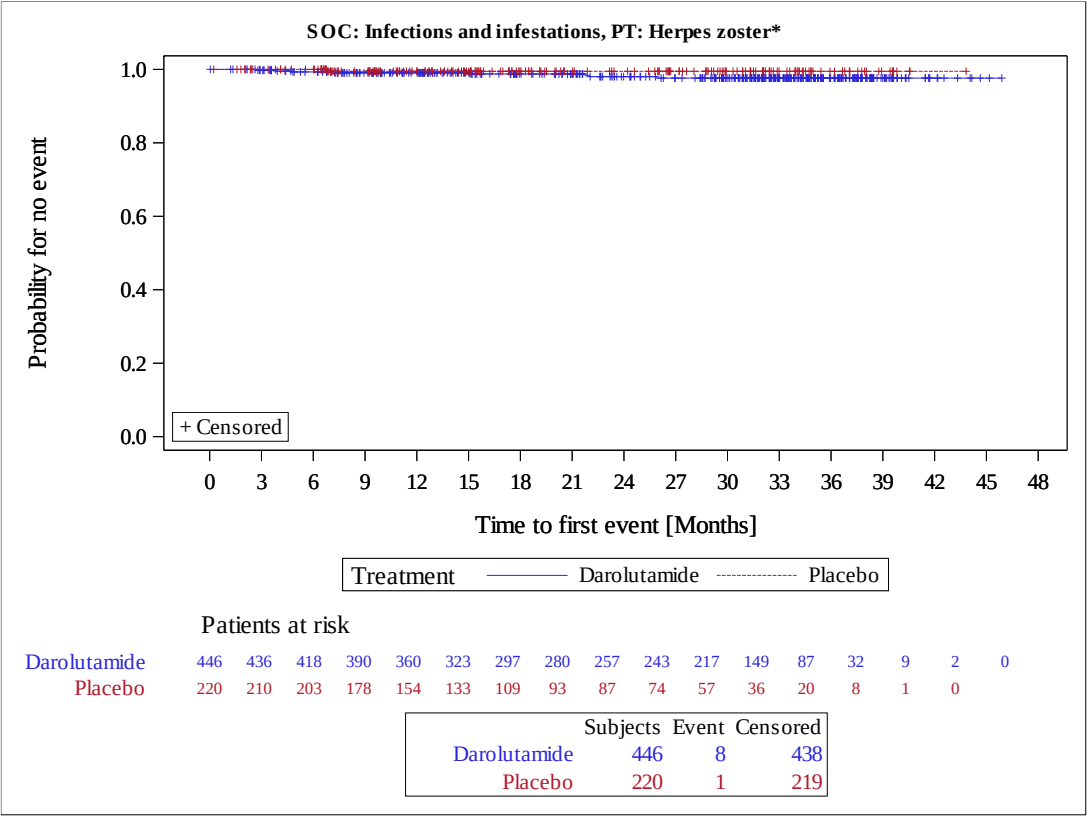


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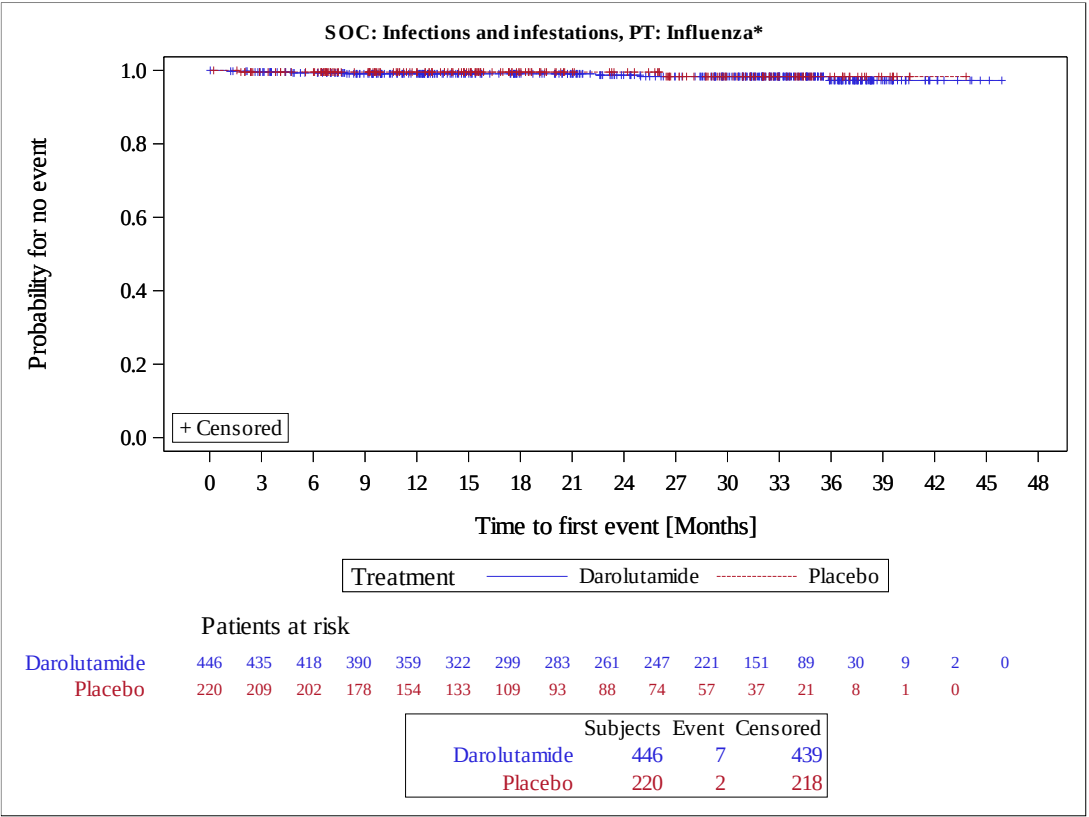


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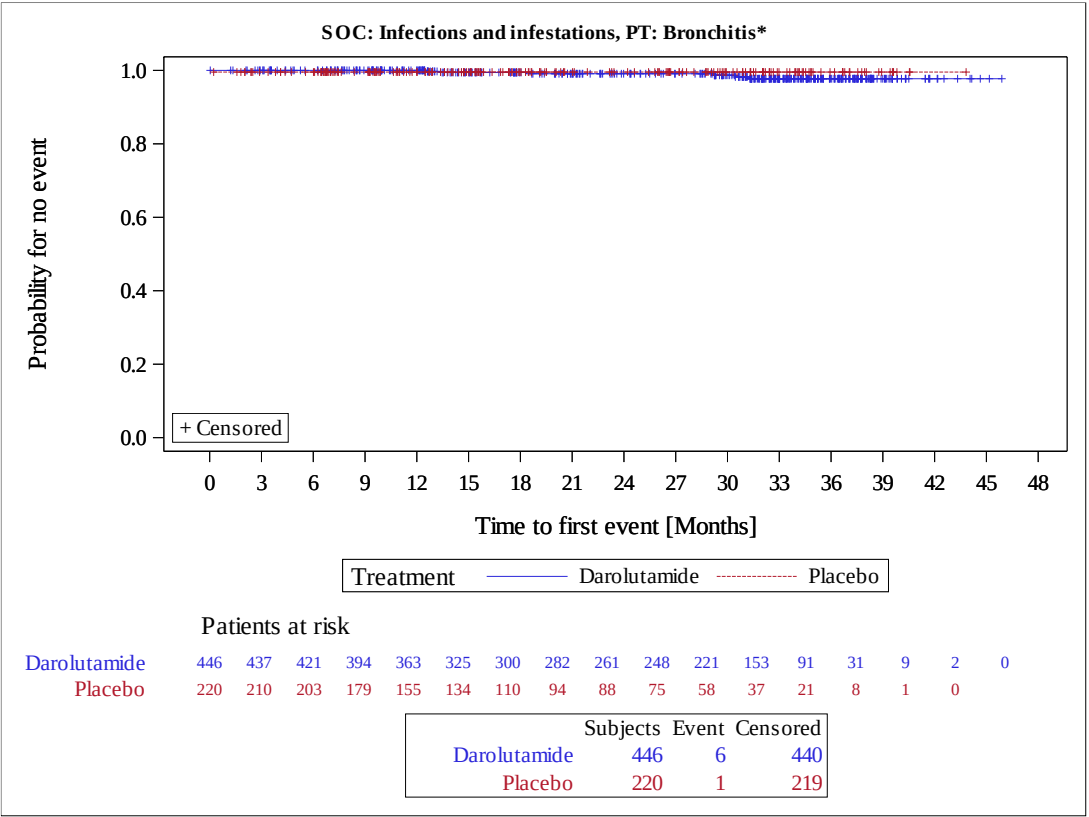


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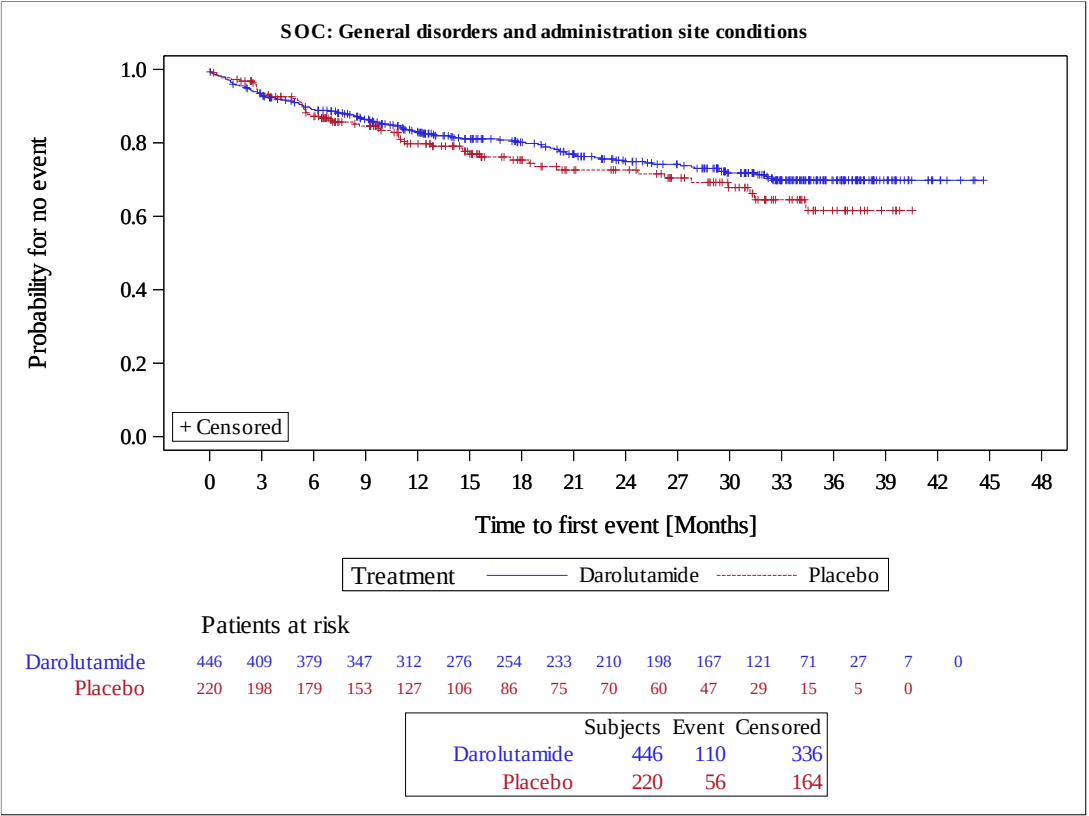


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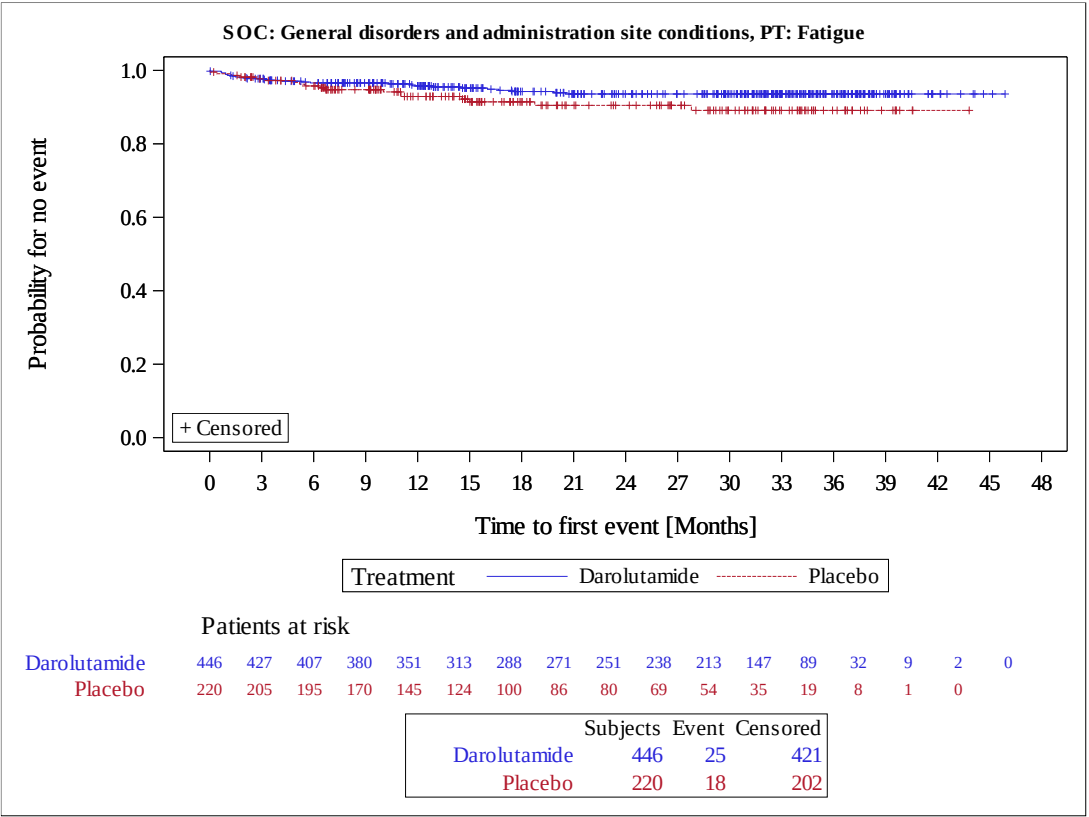


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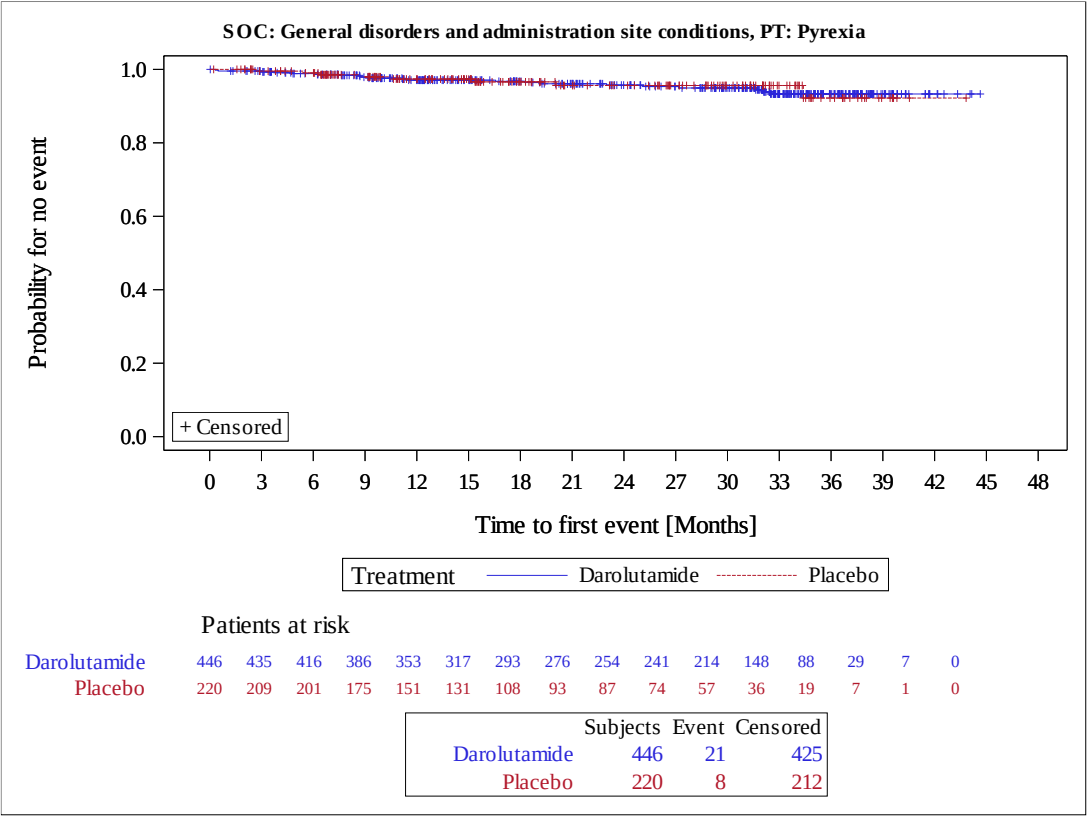


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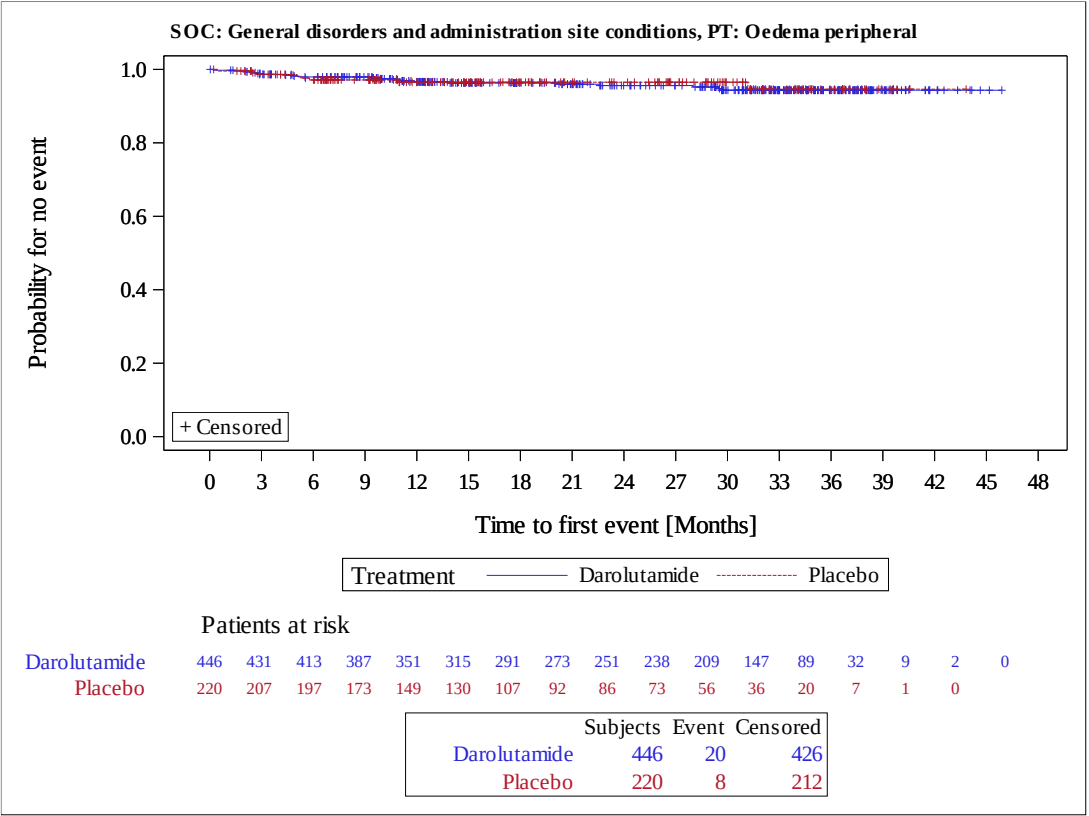


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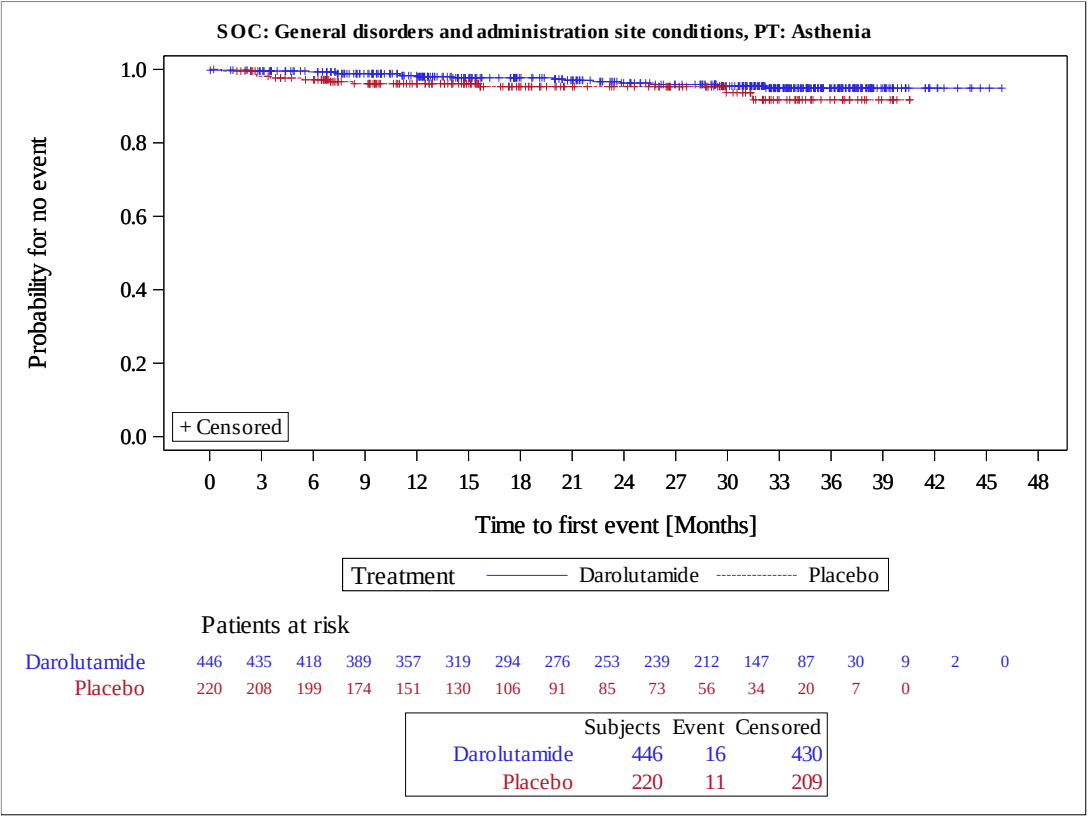


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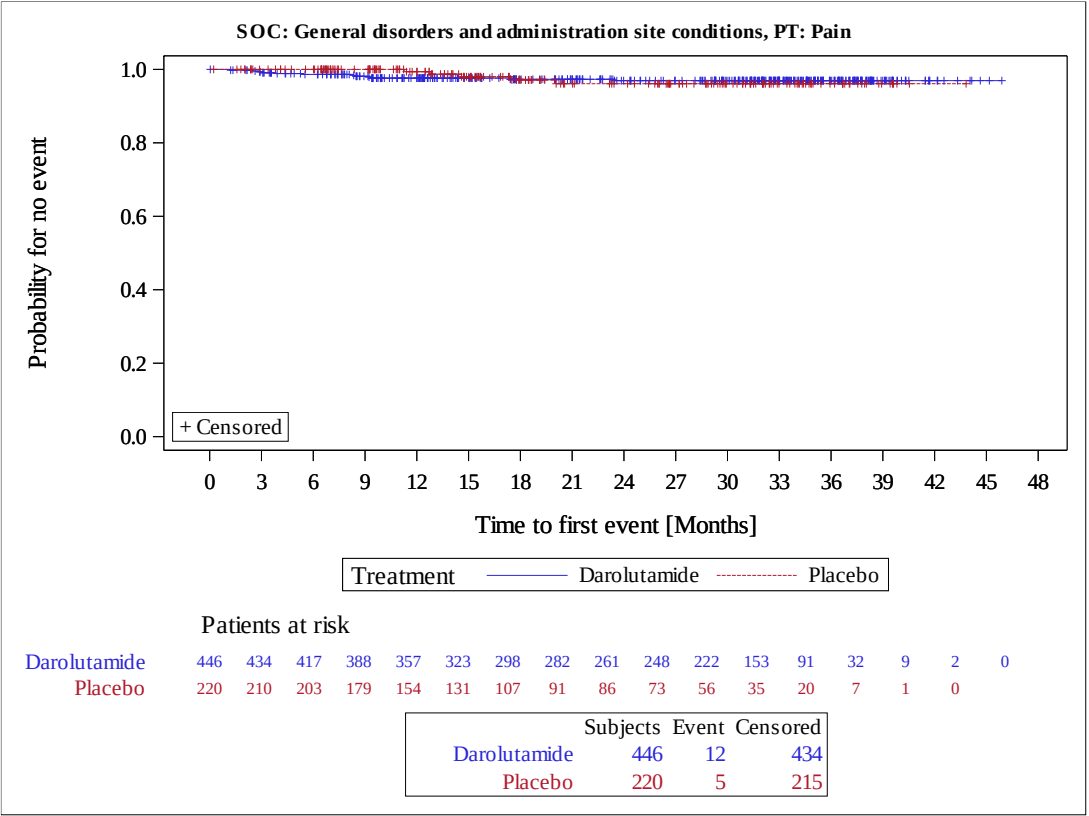


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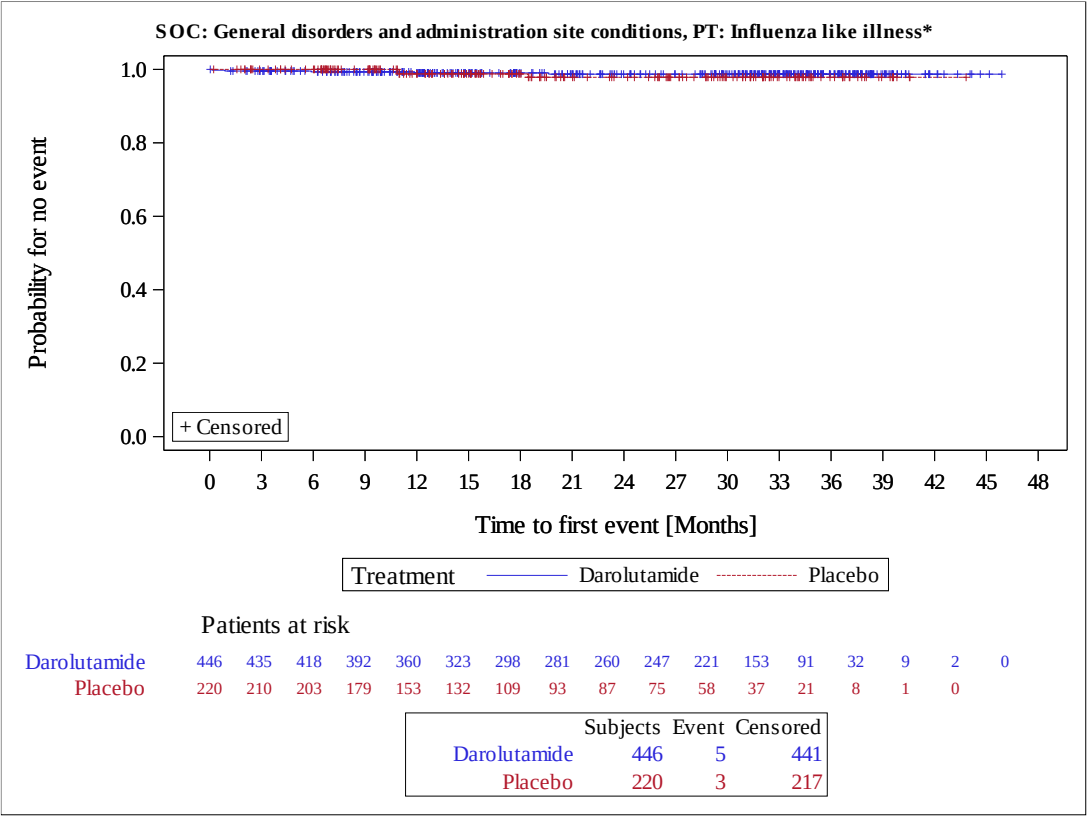


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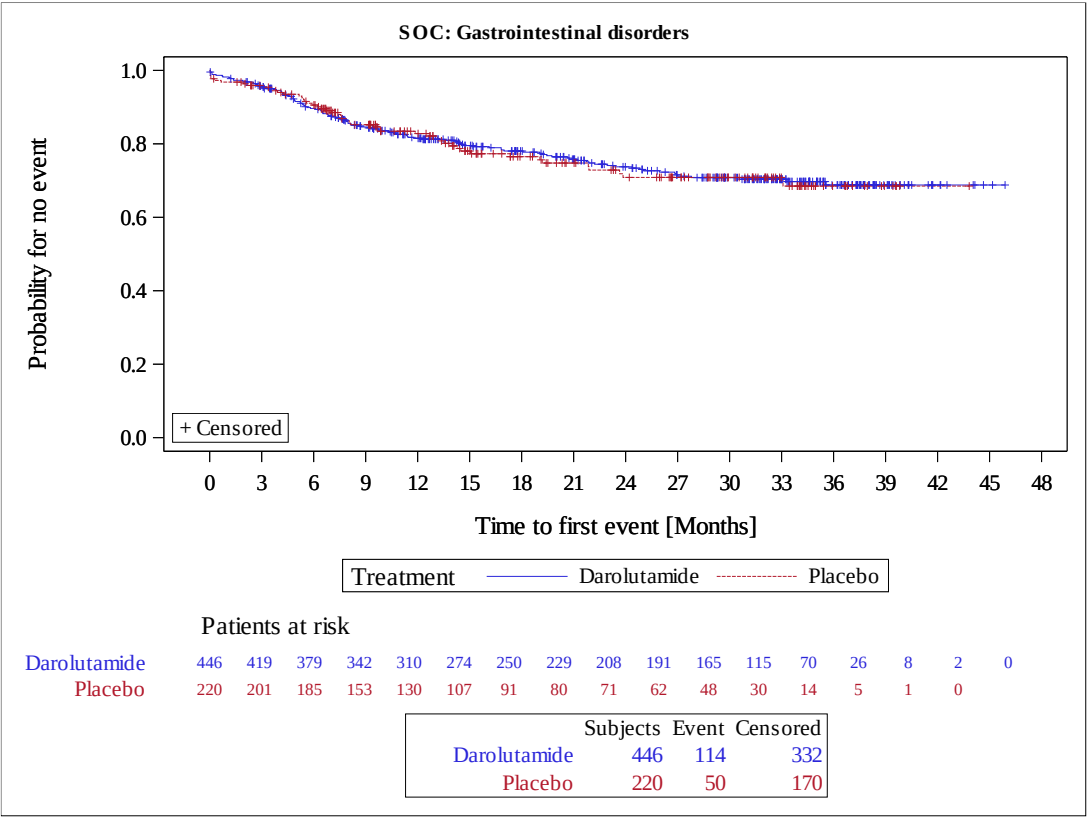


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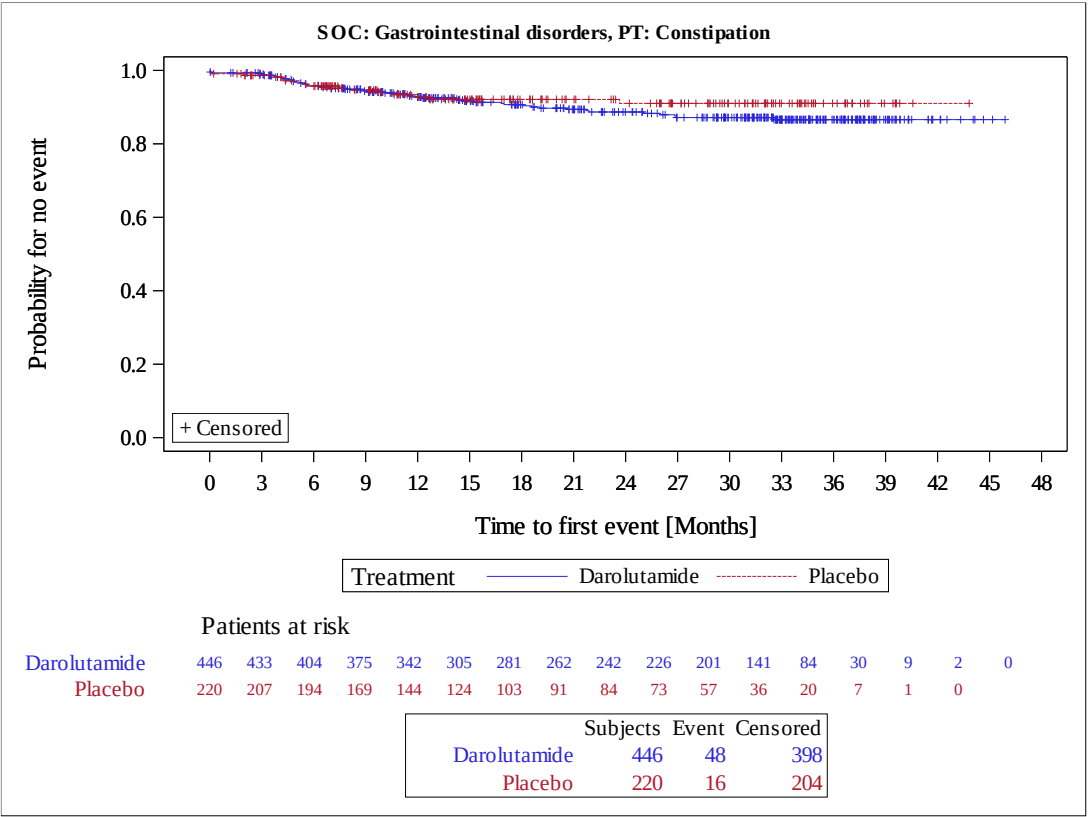


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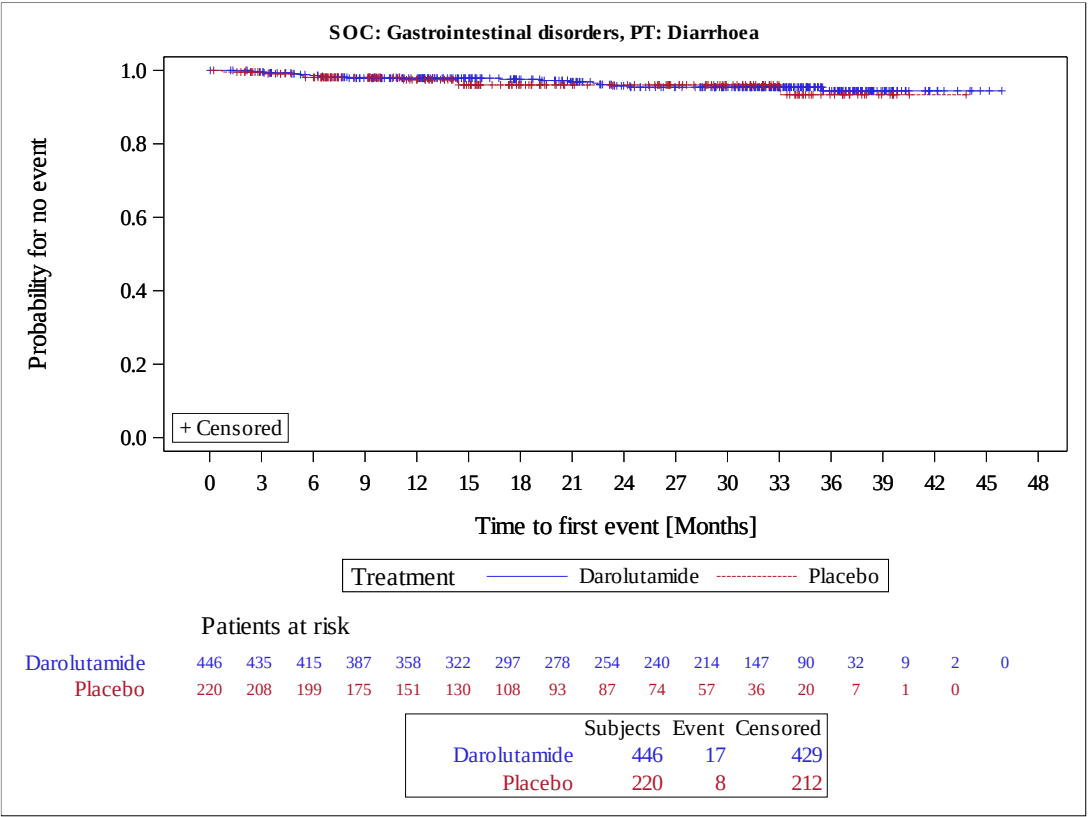


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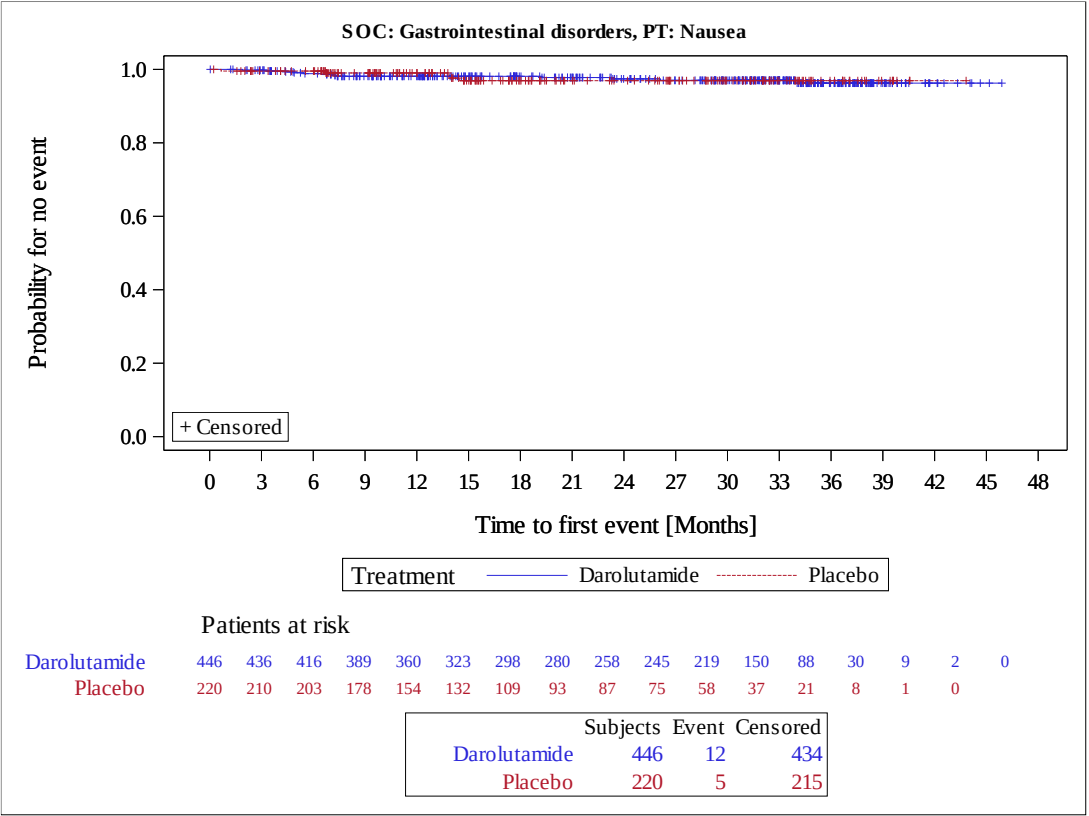


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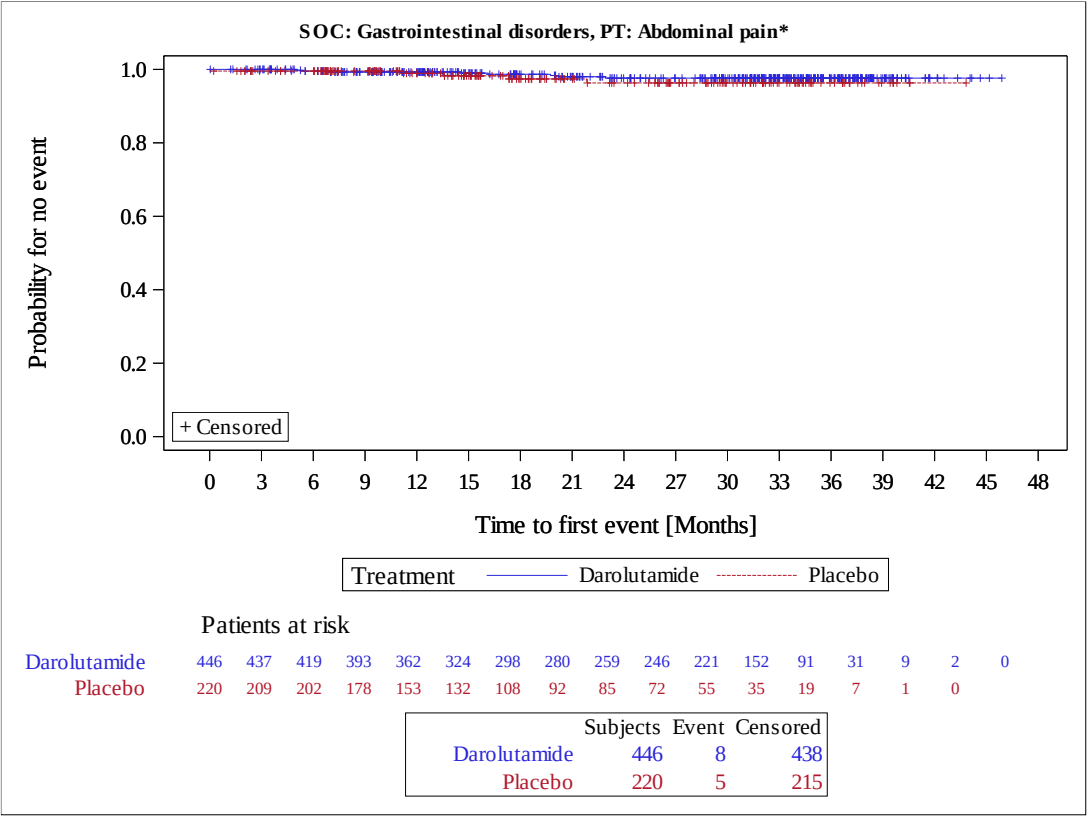


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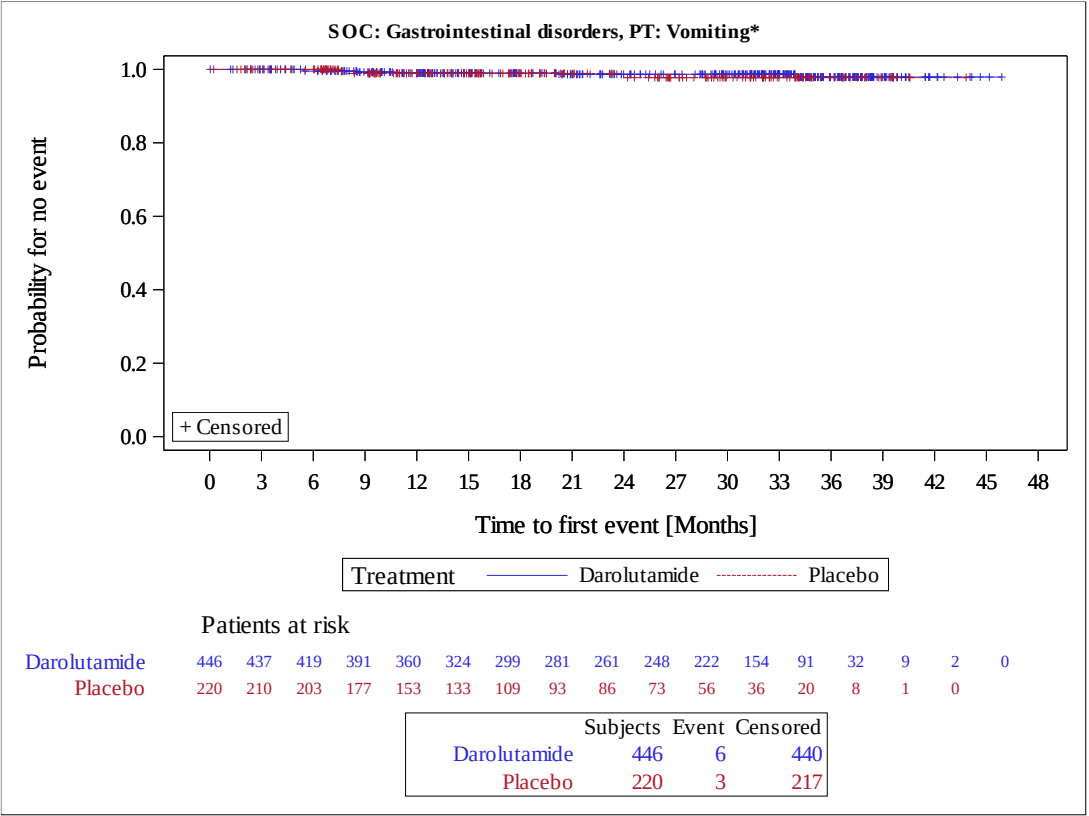


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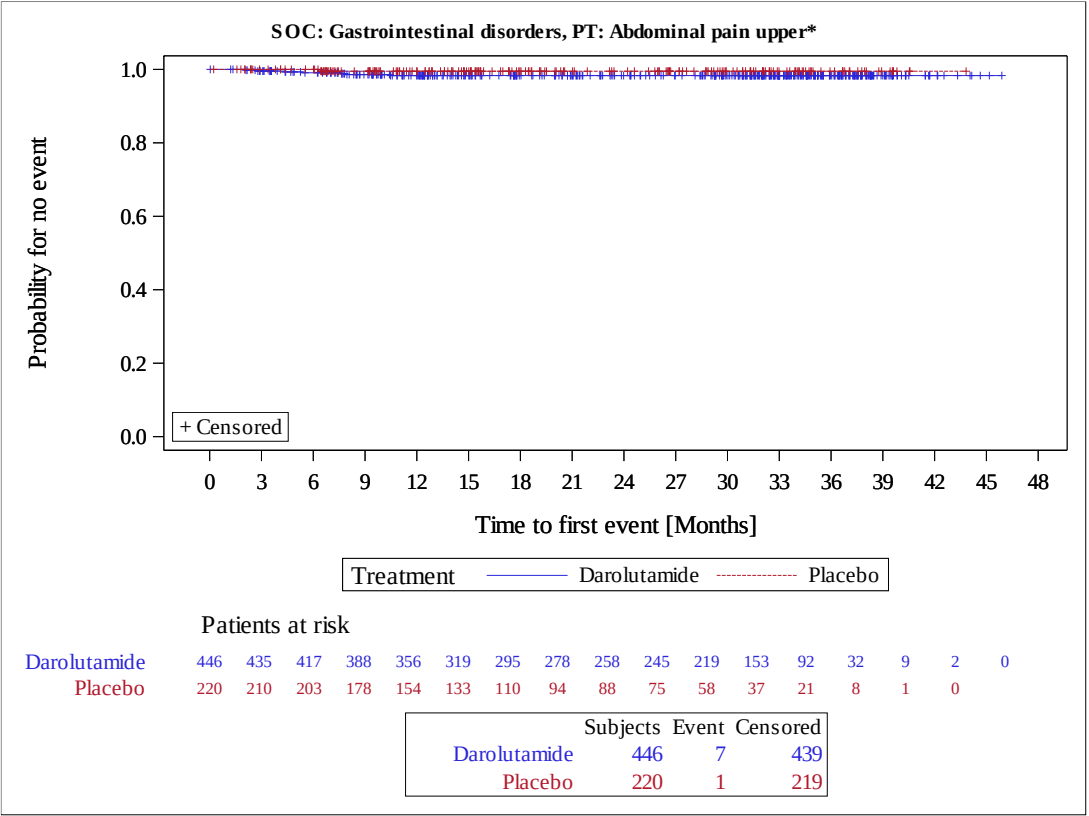


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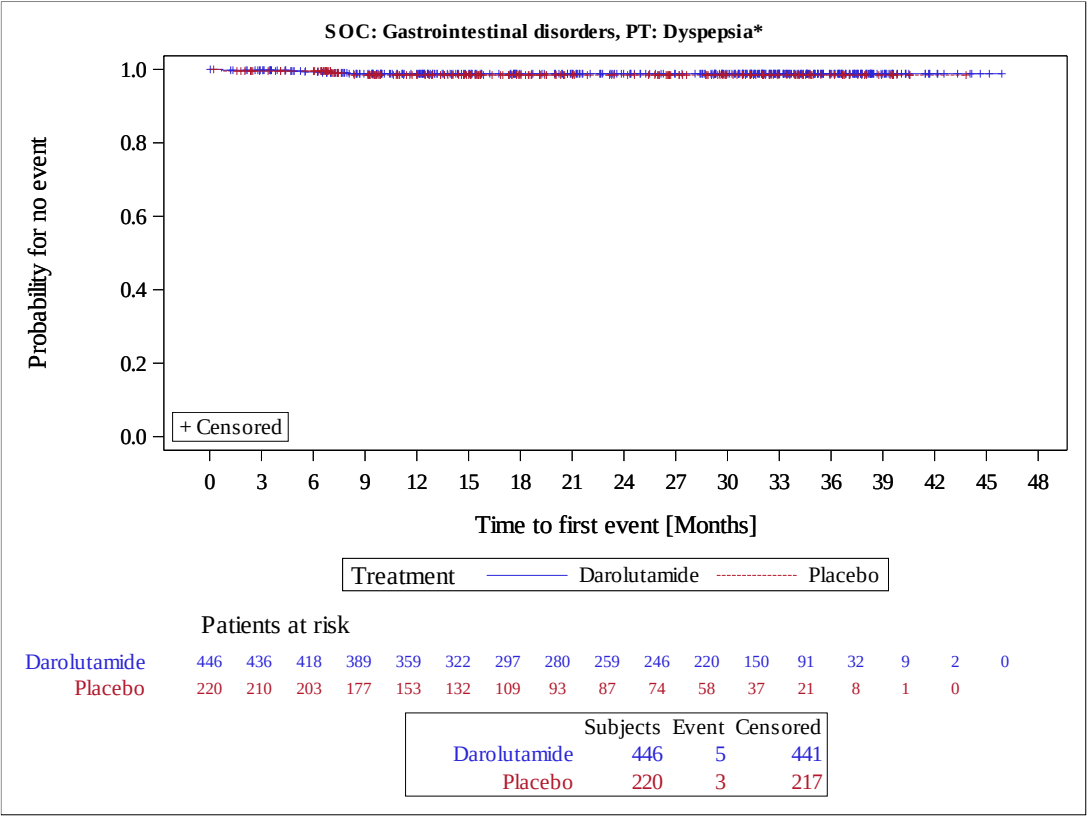


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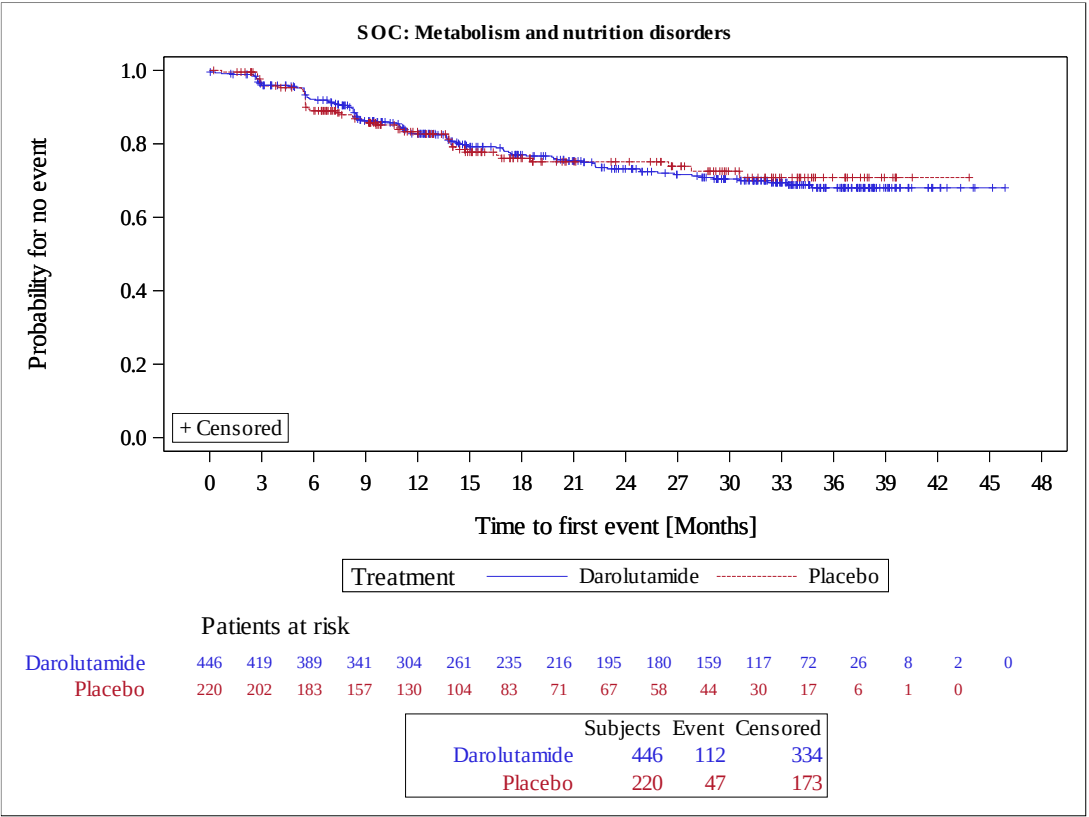


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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.3.1.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

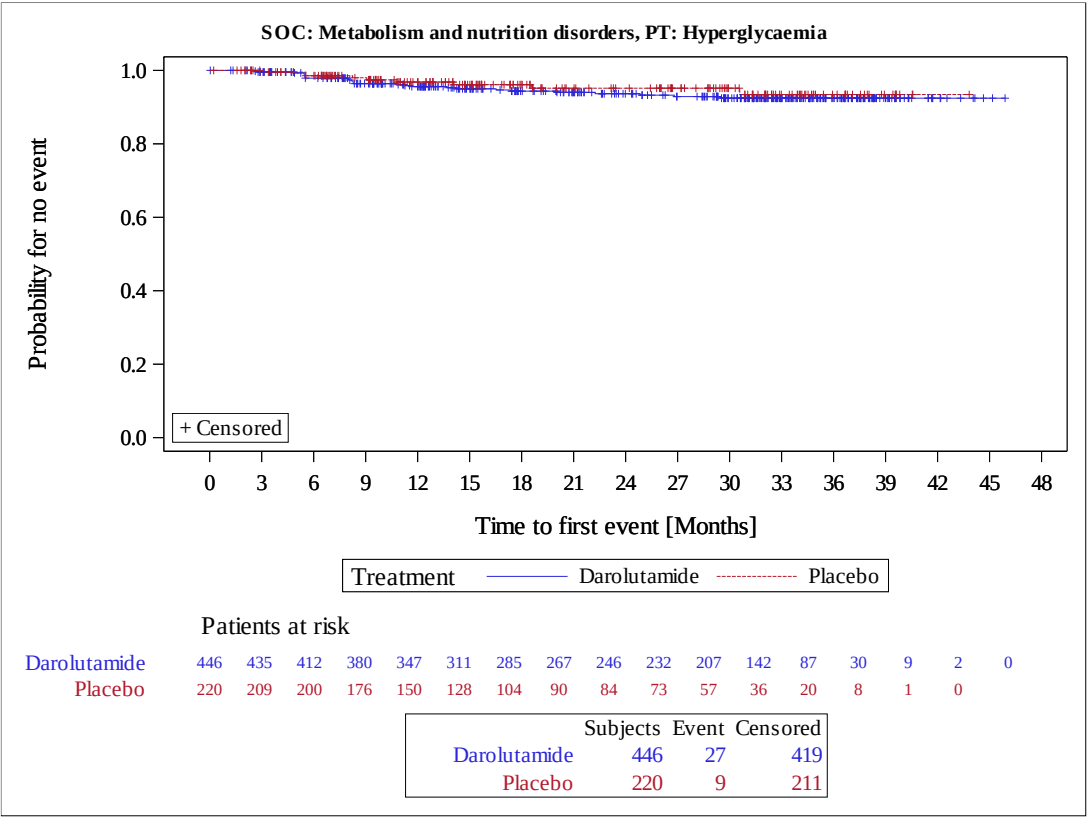


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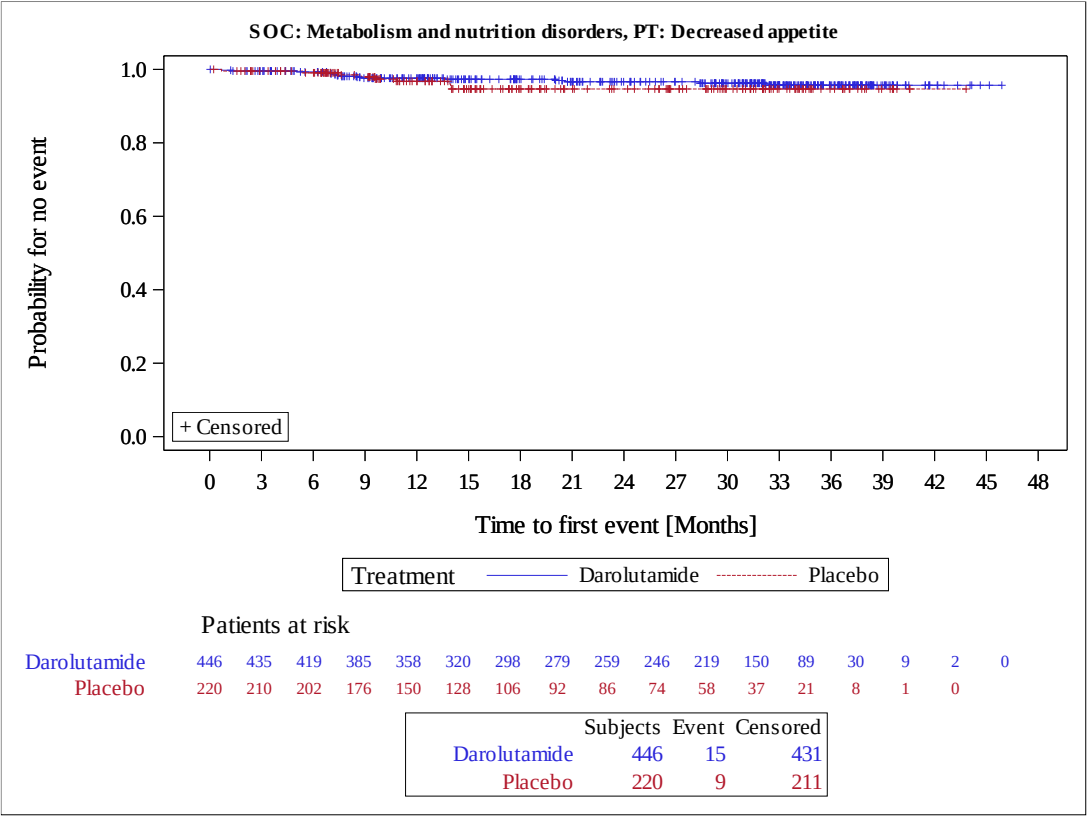


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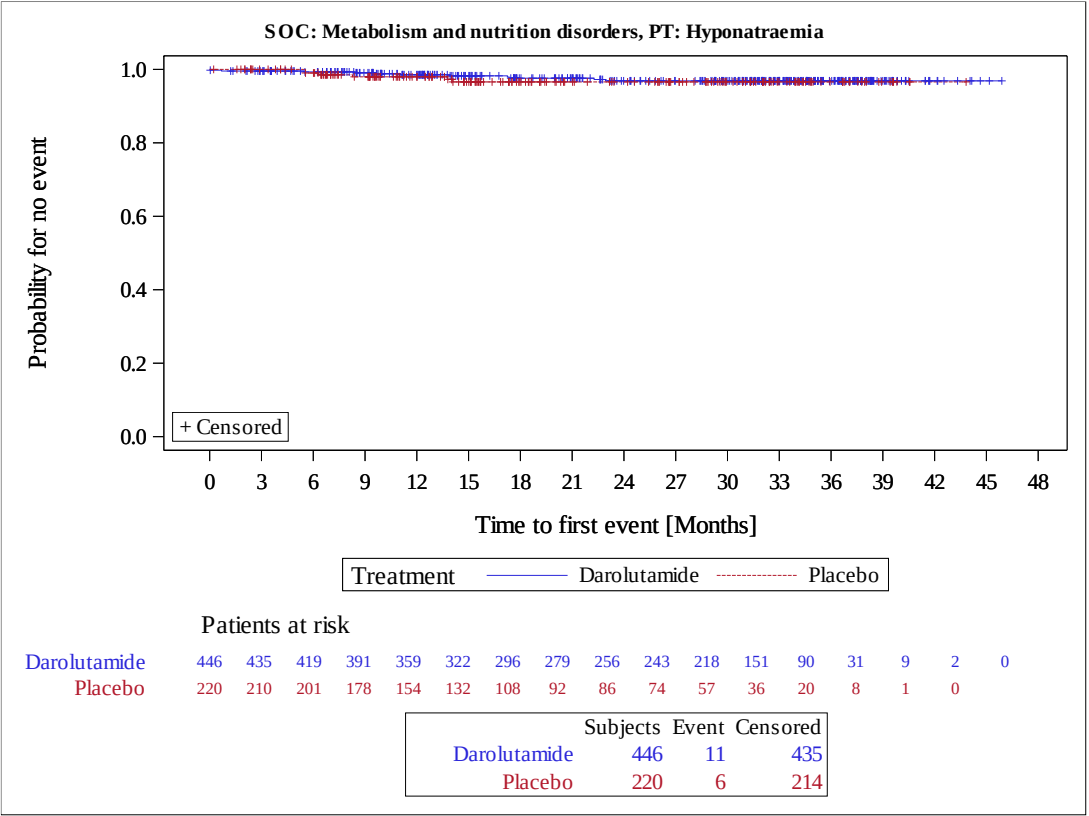


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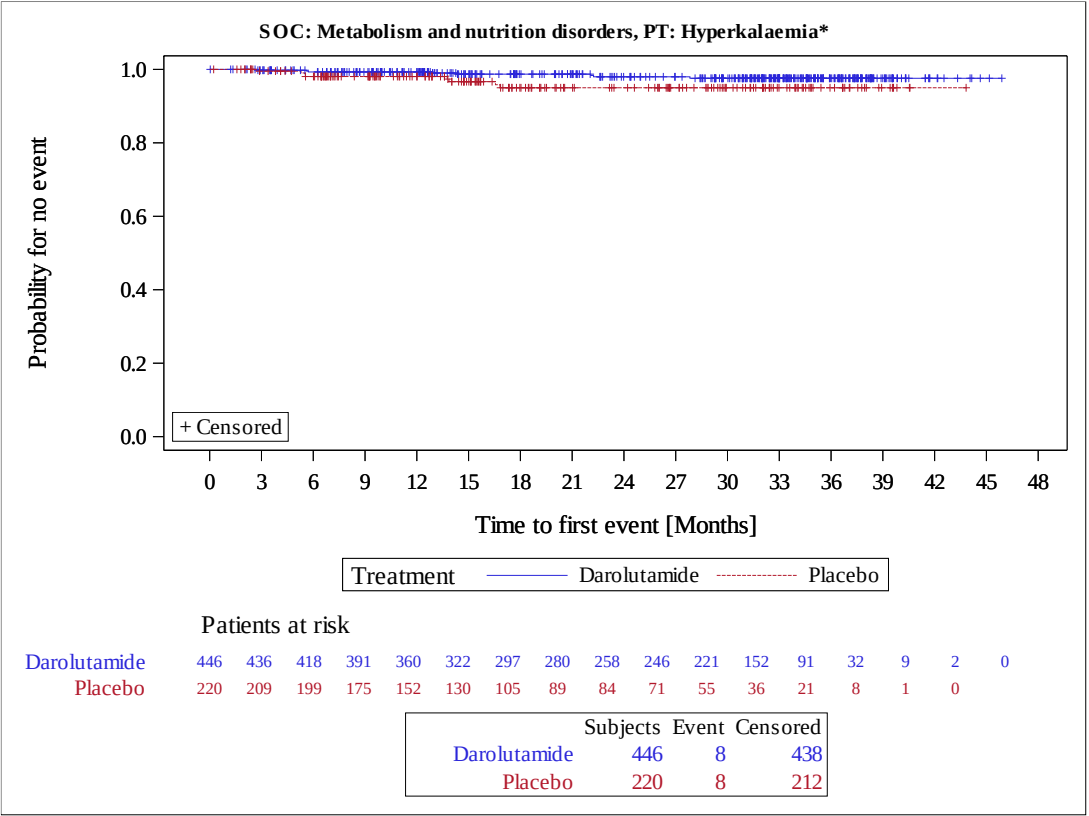


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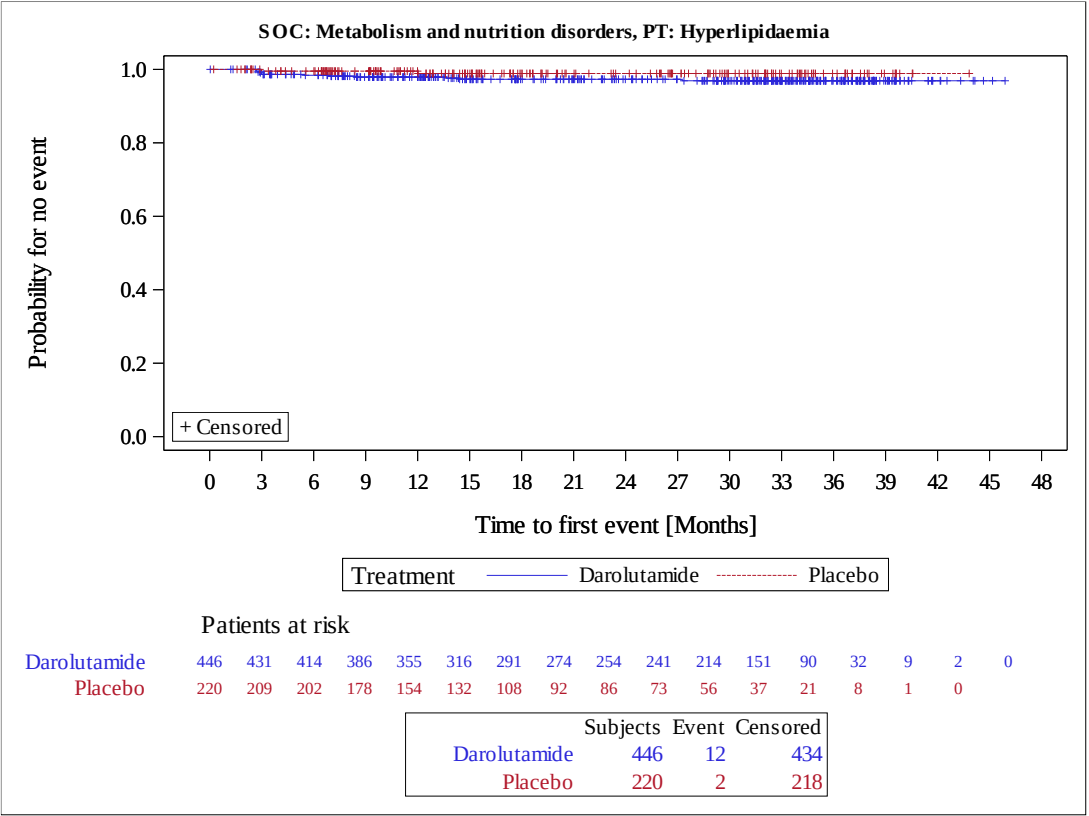


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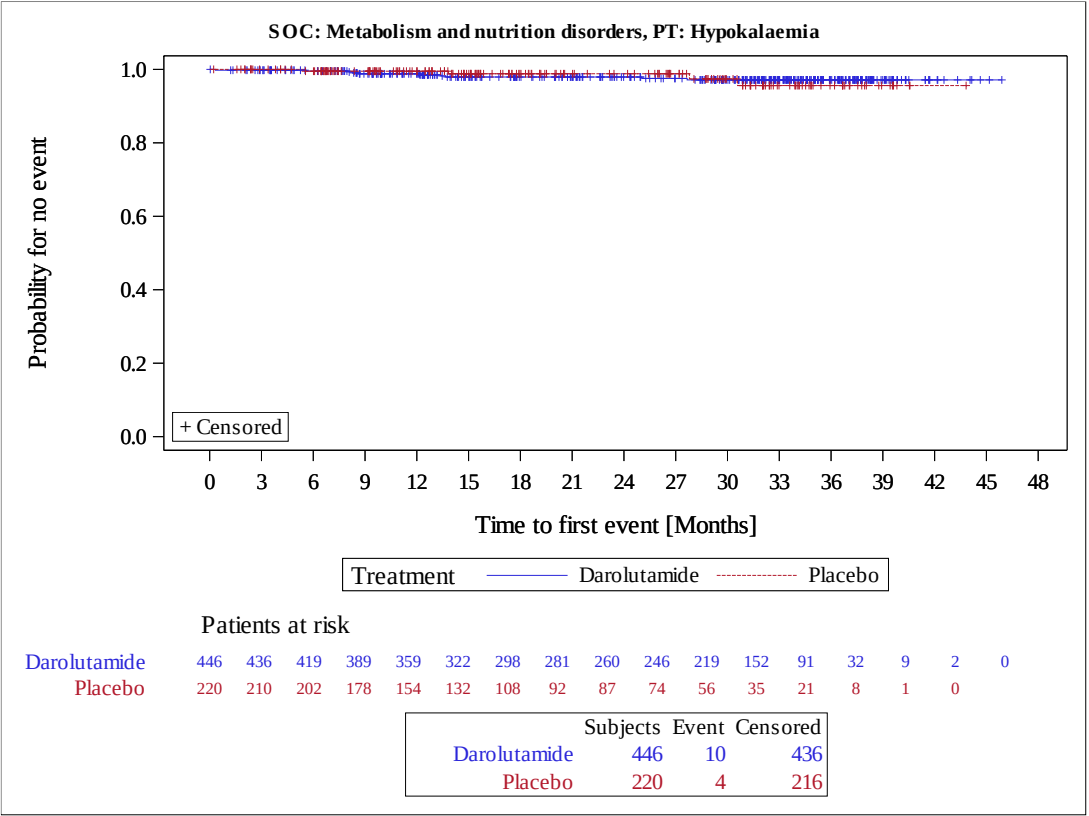


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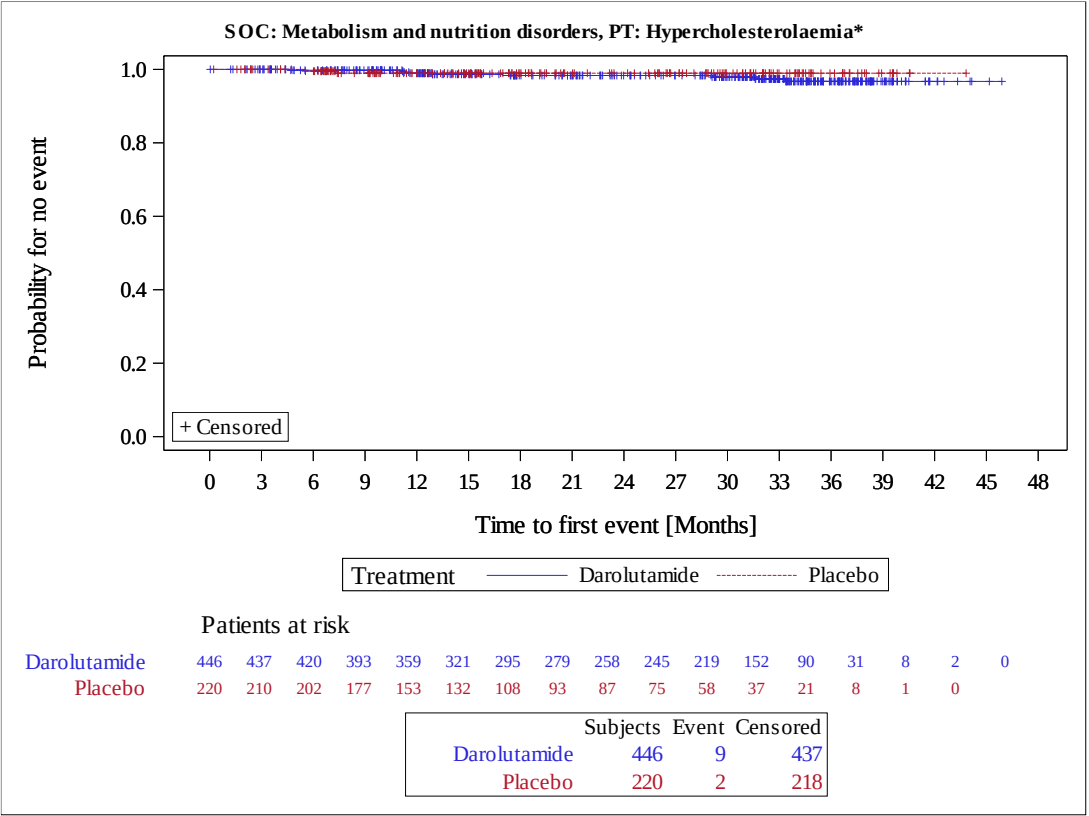


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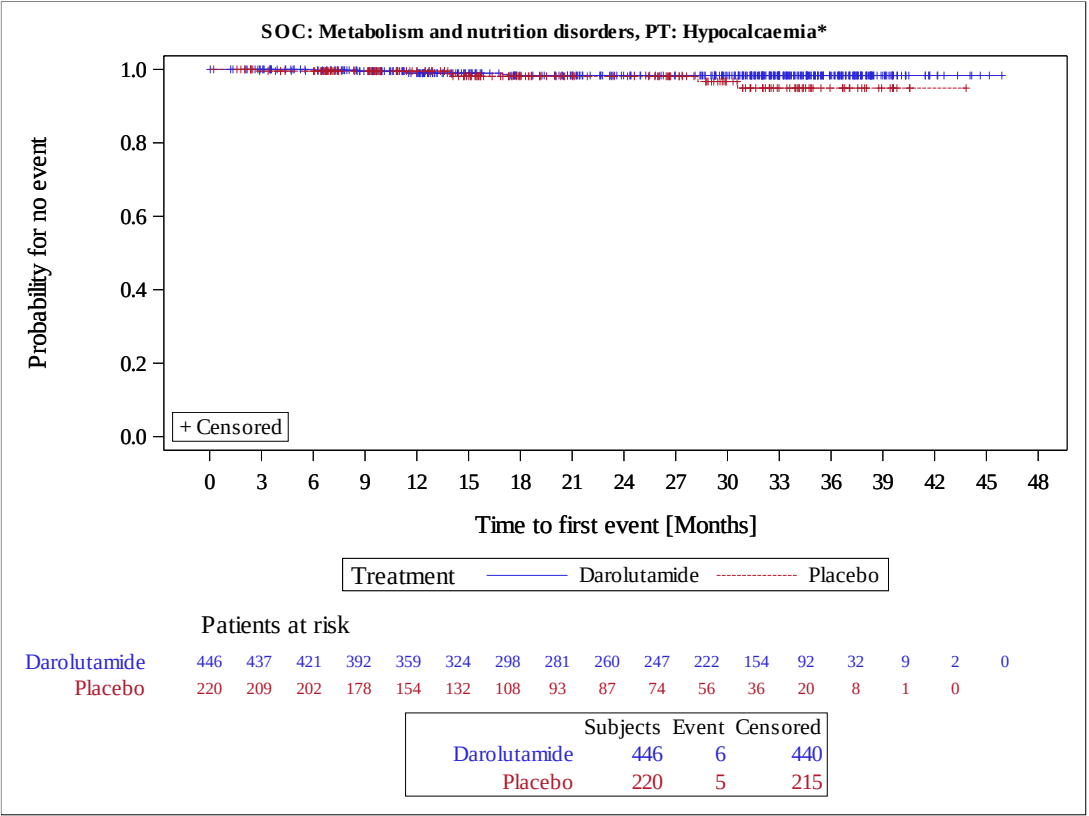


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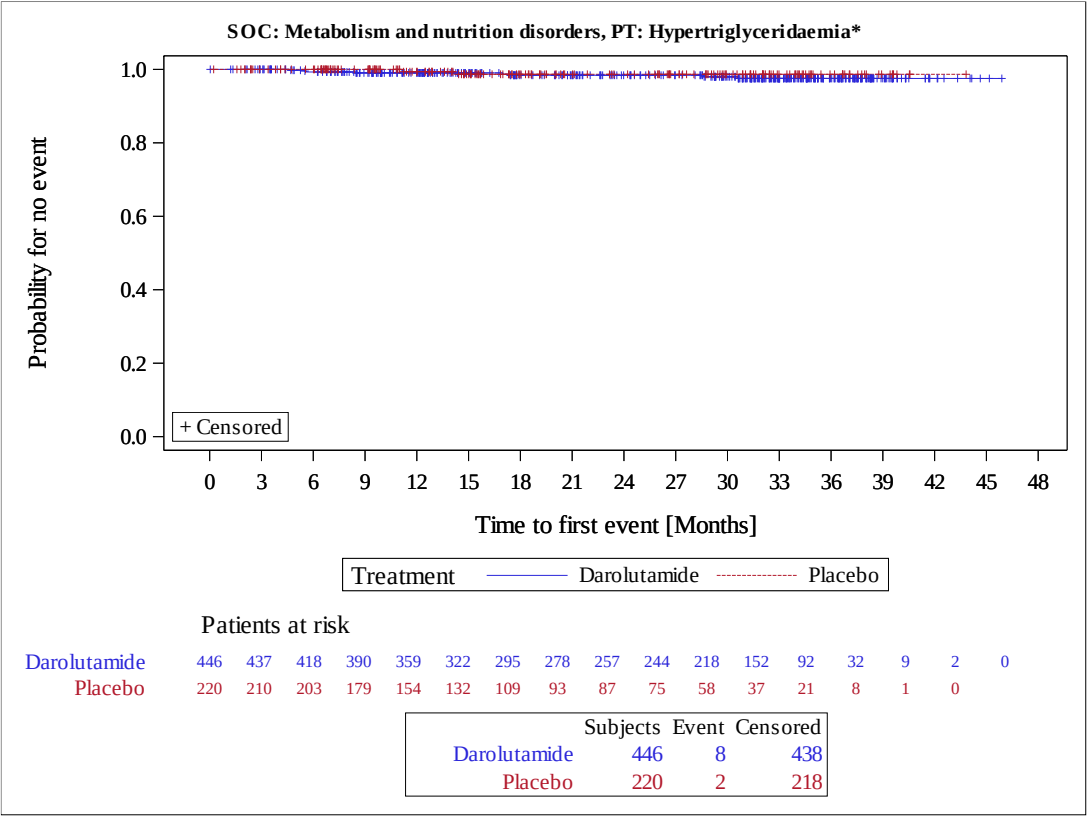


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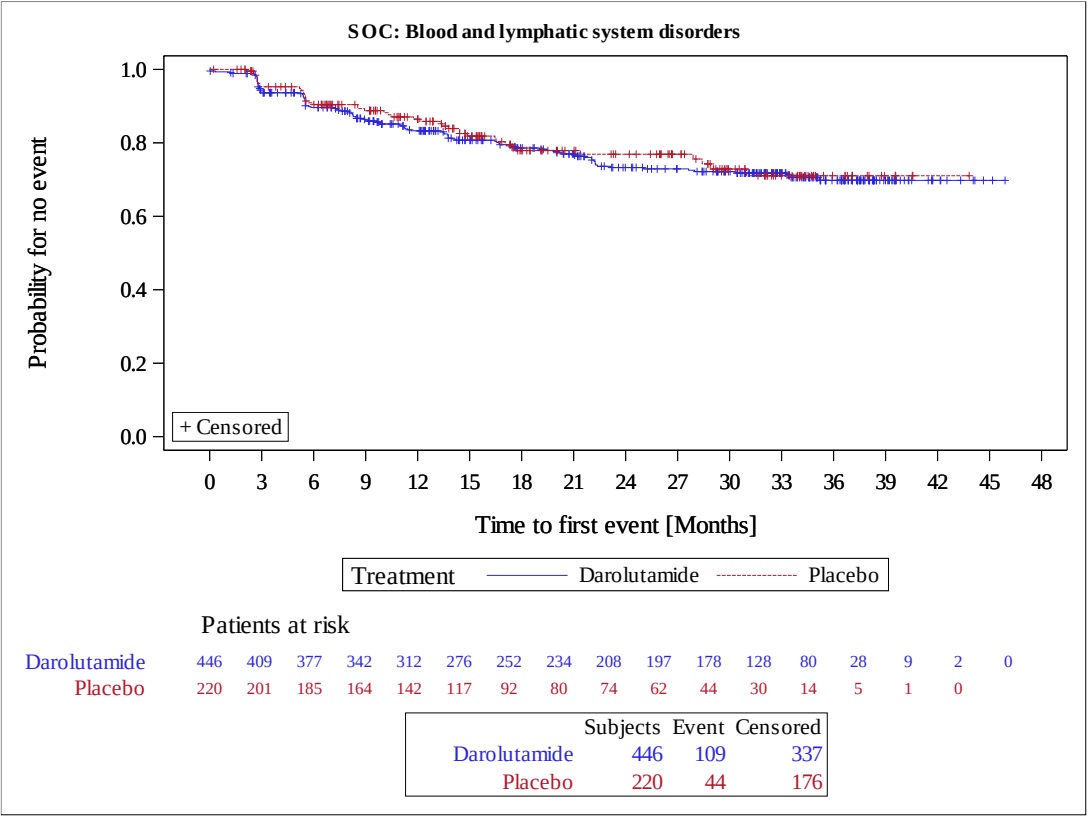


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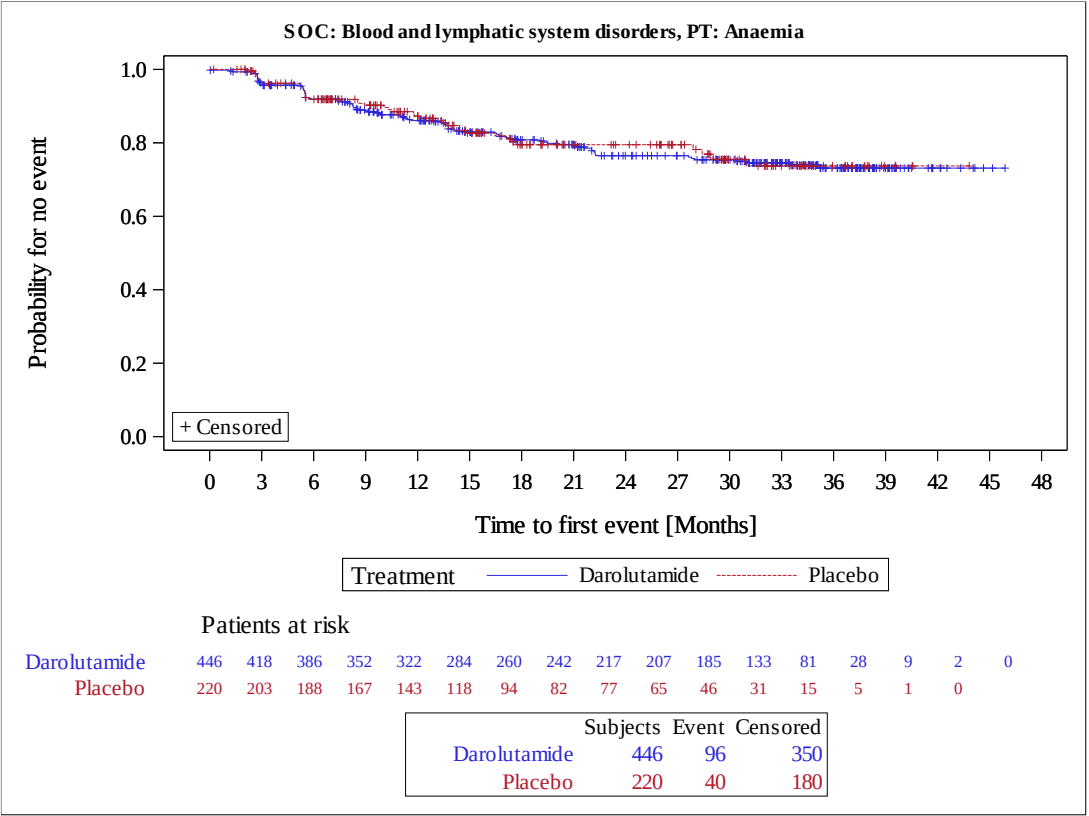


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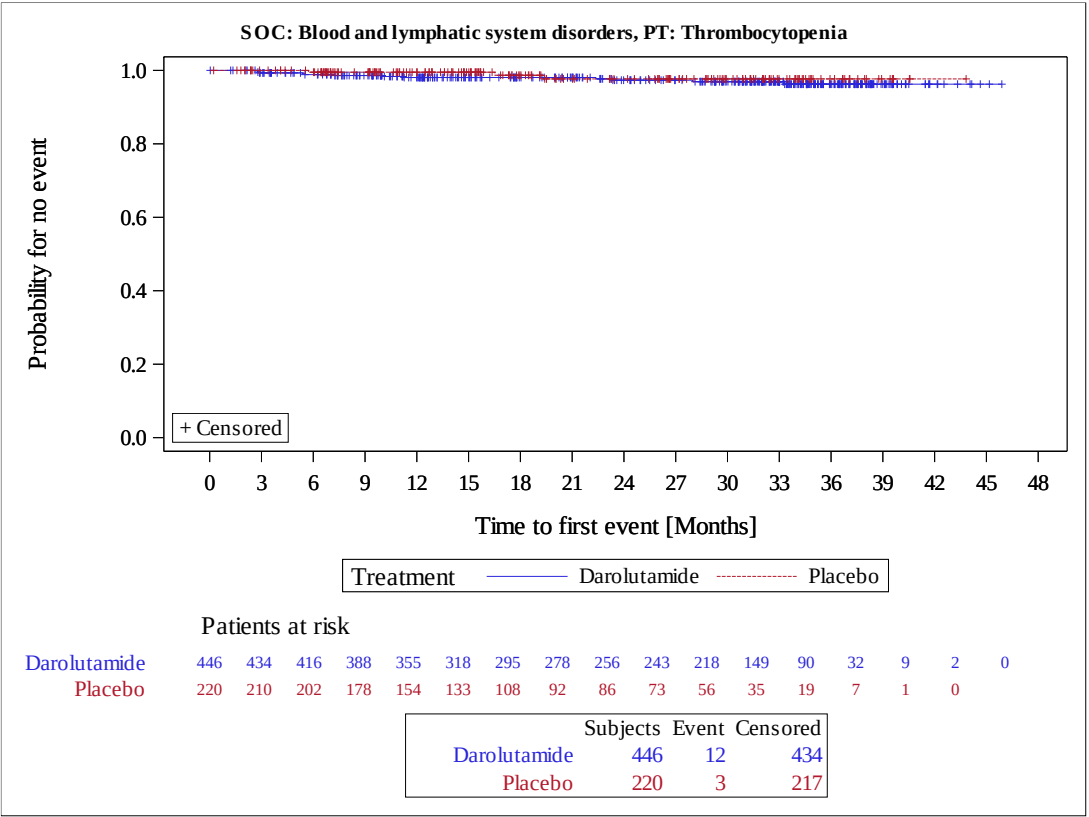


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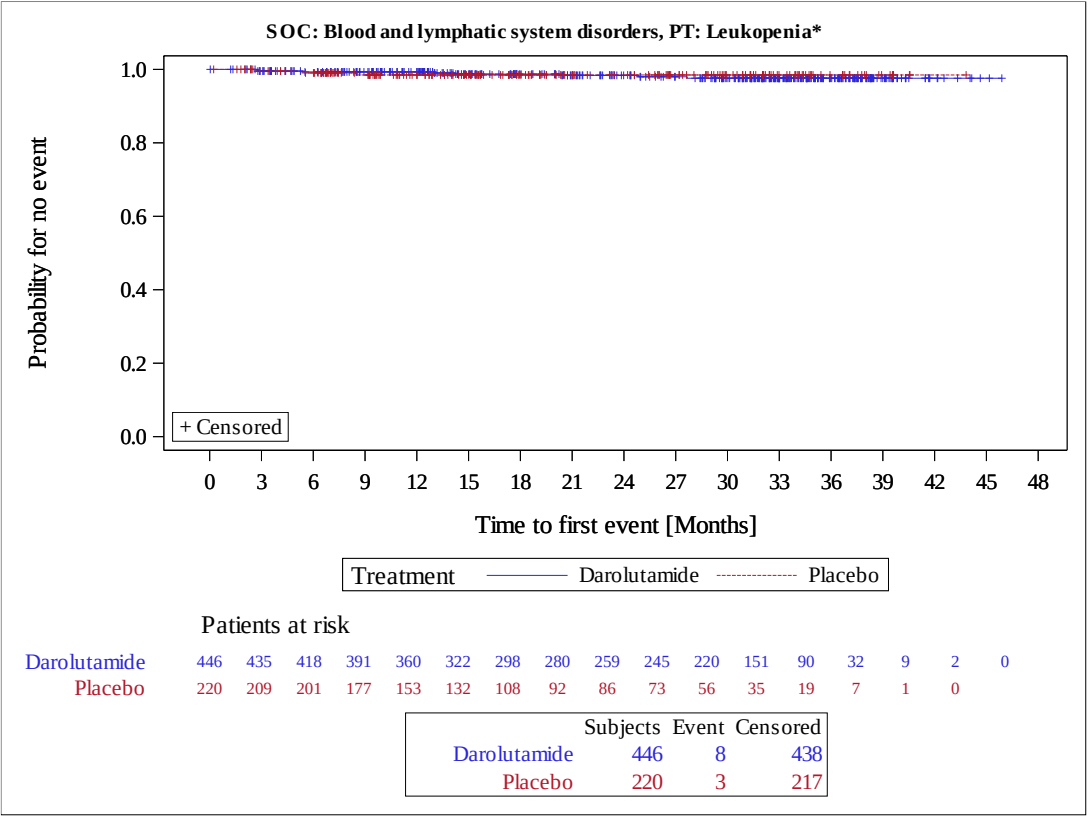


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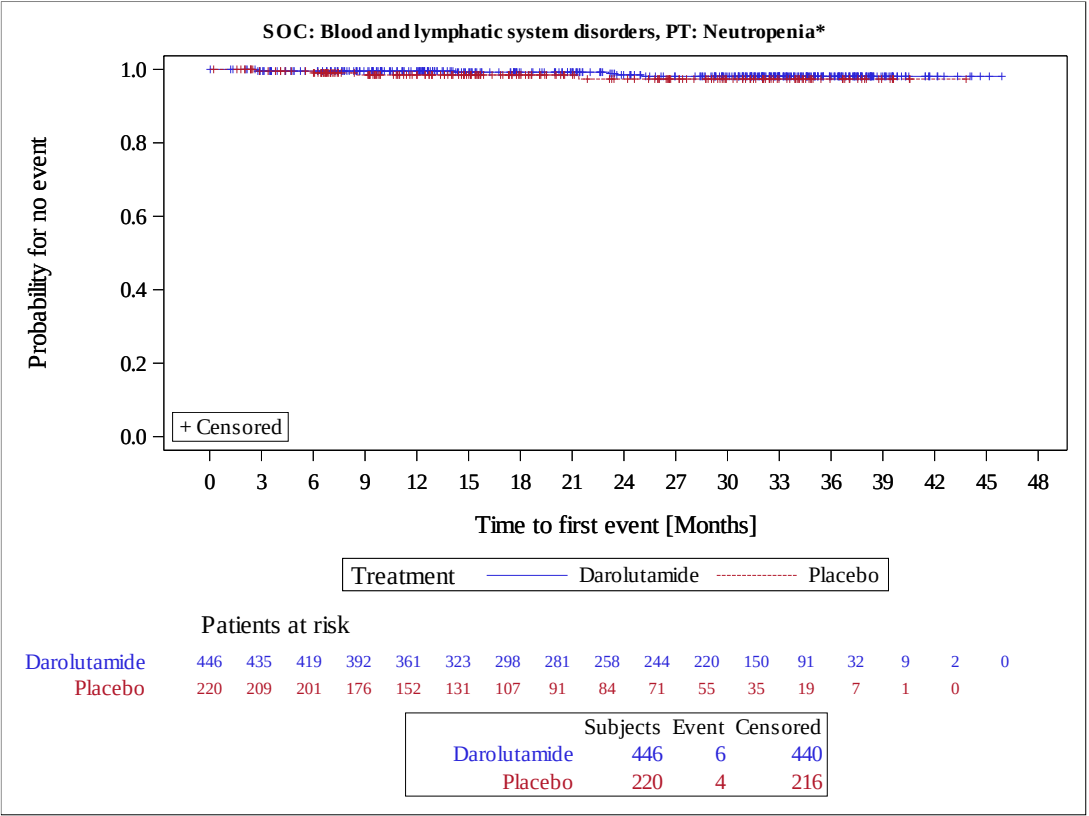


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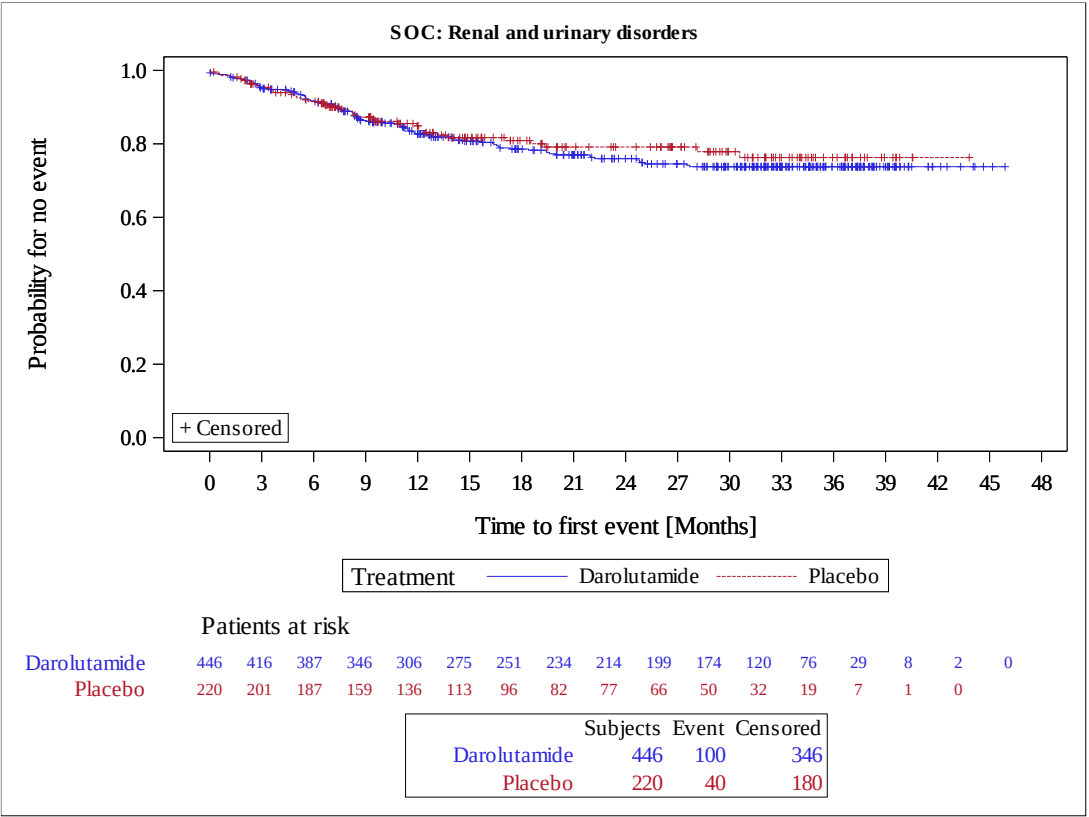


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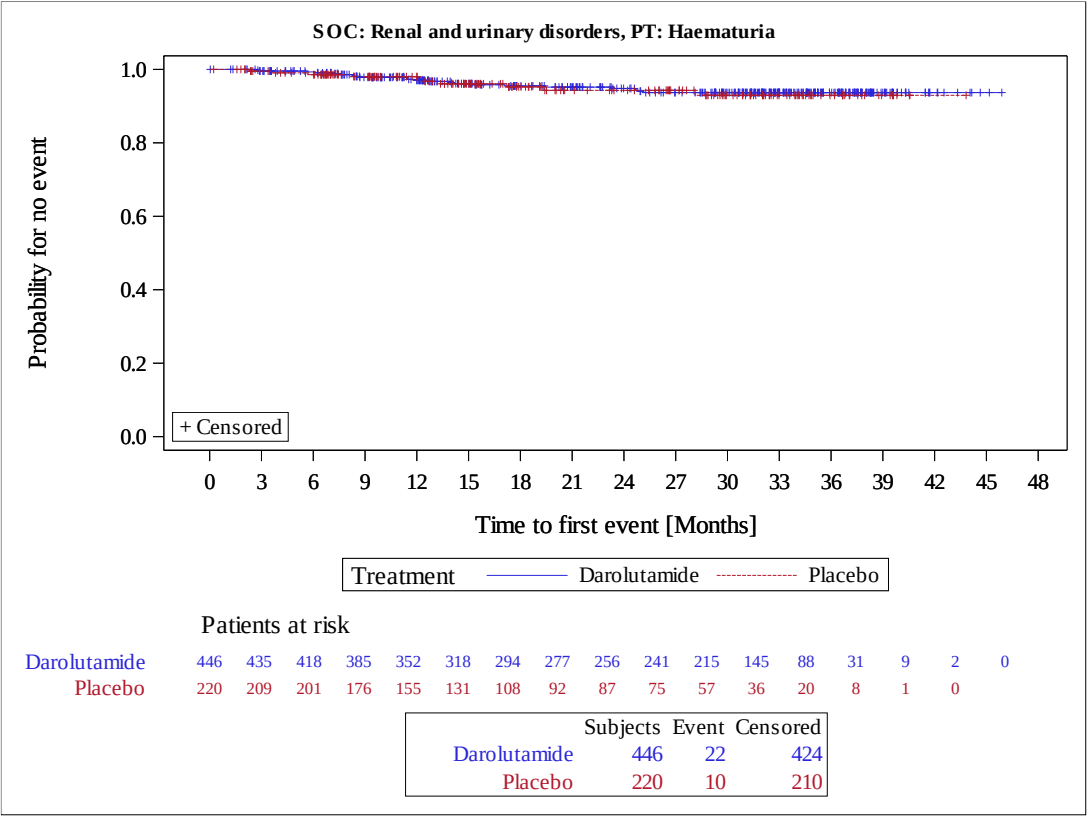


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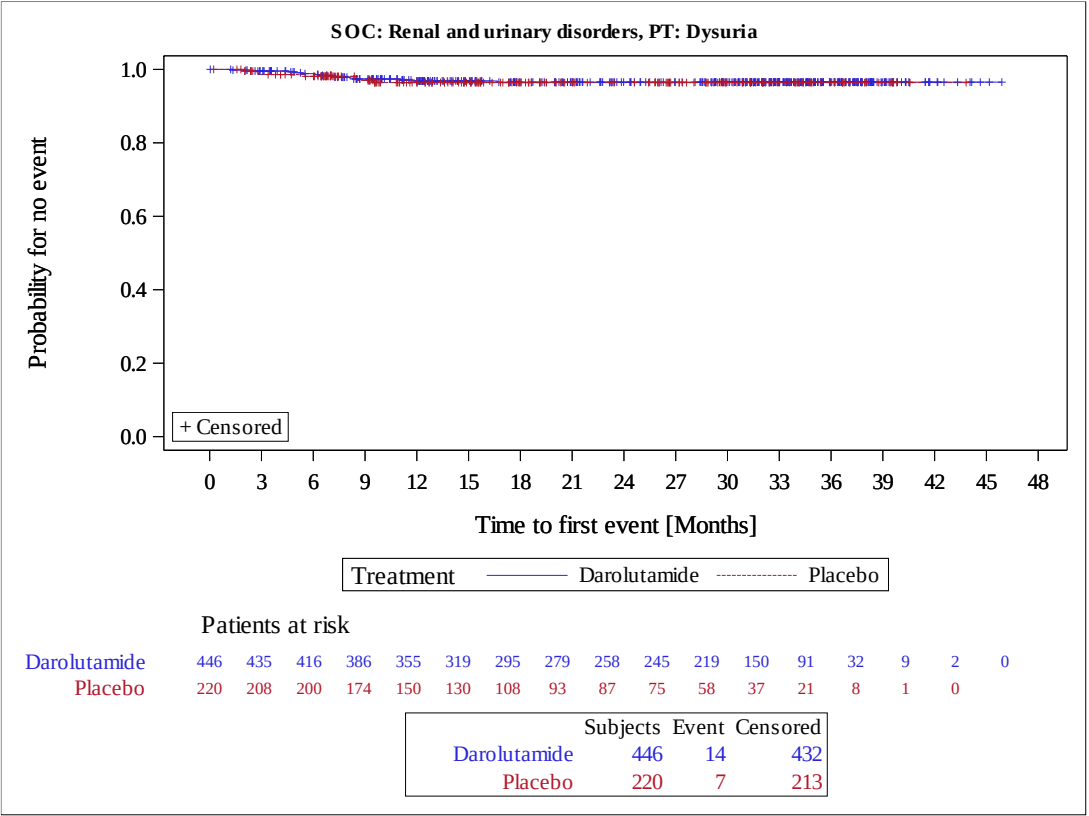


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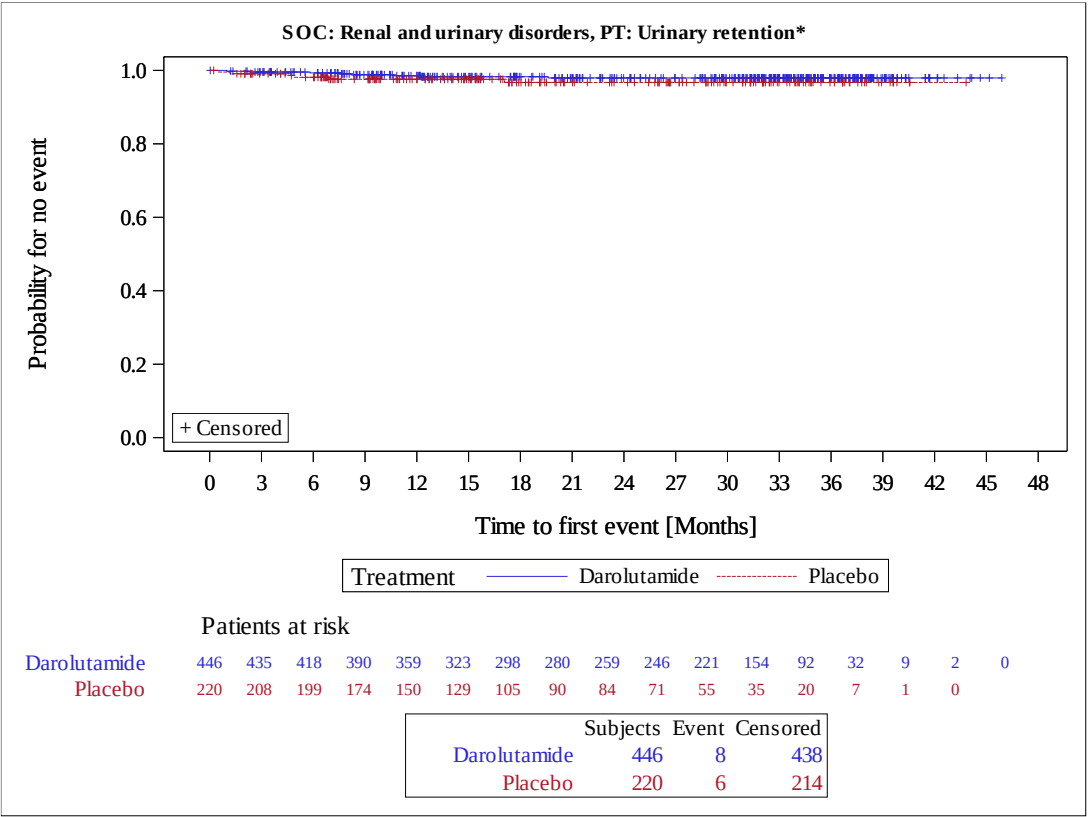


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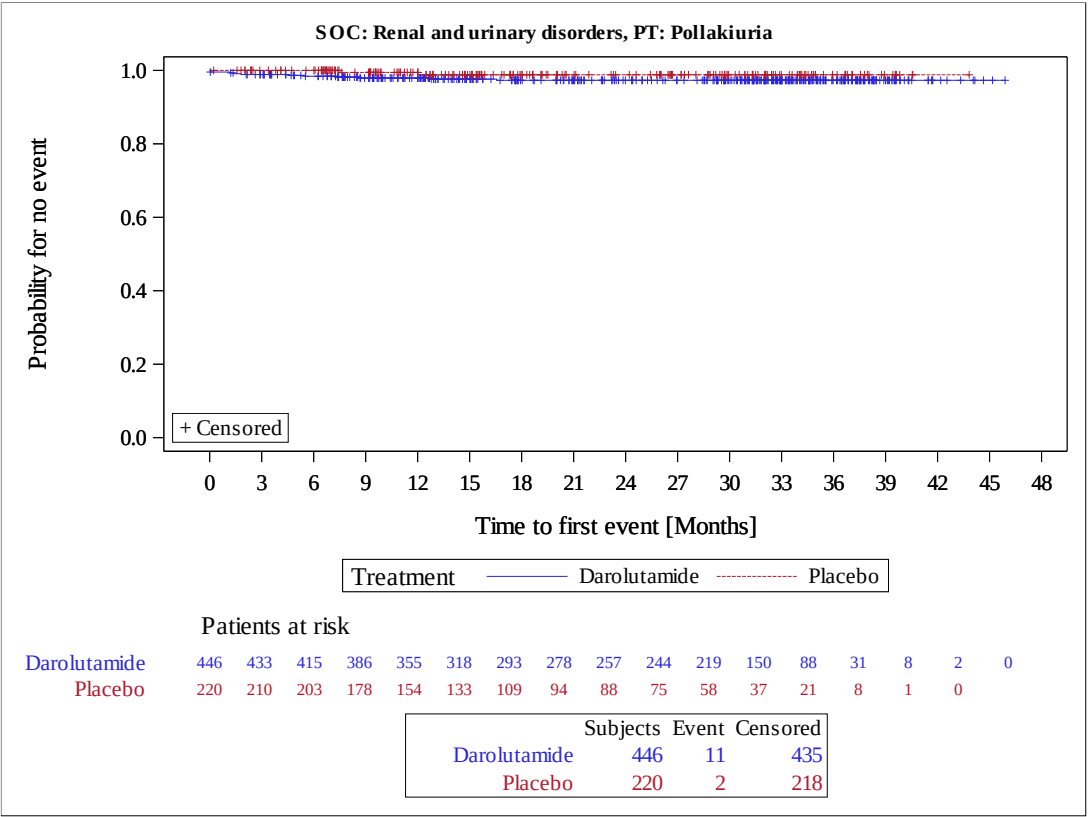


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BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.3.1.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

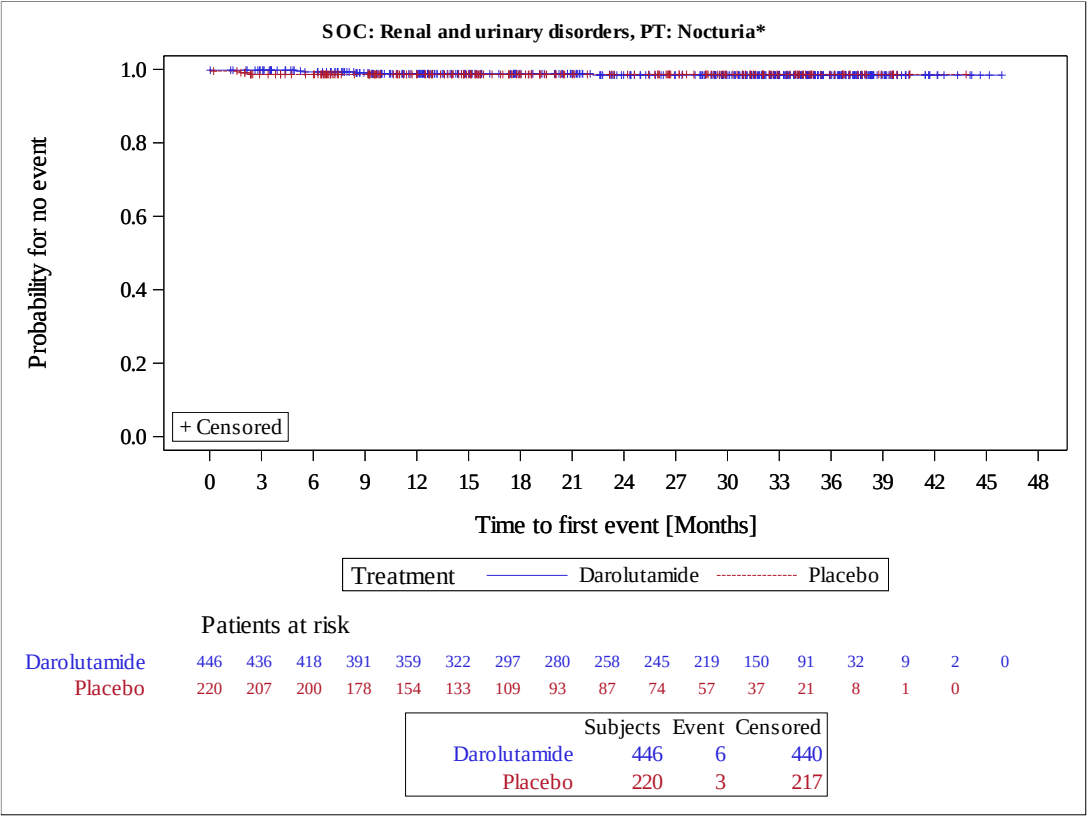


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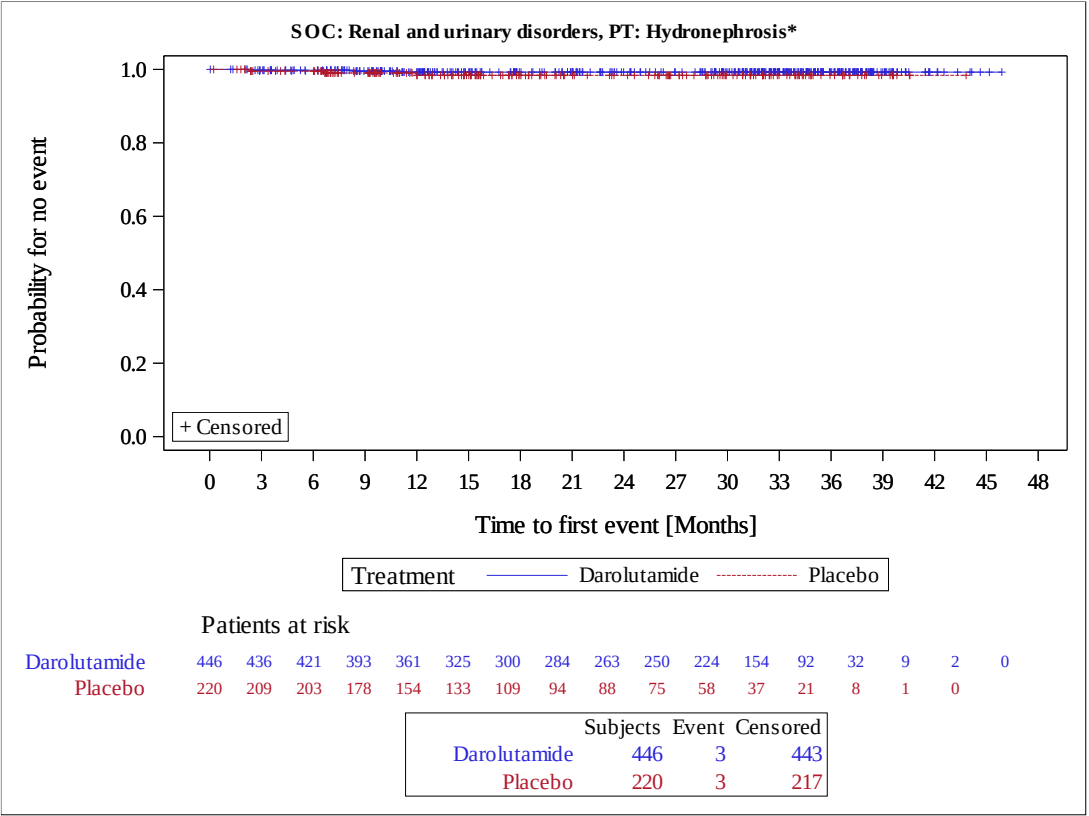


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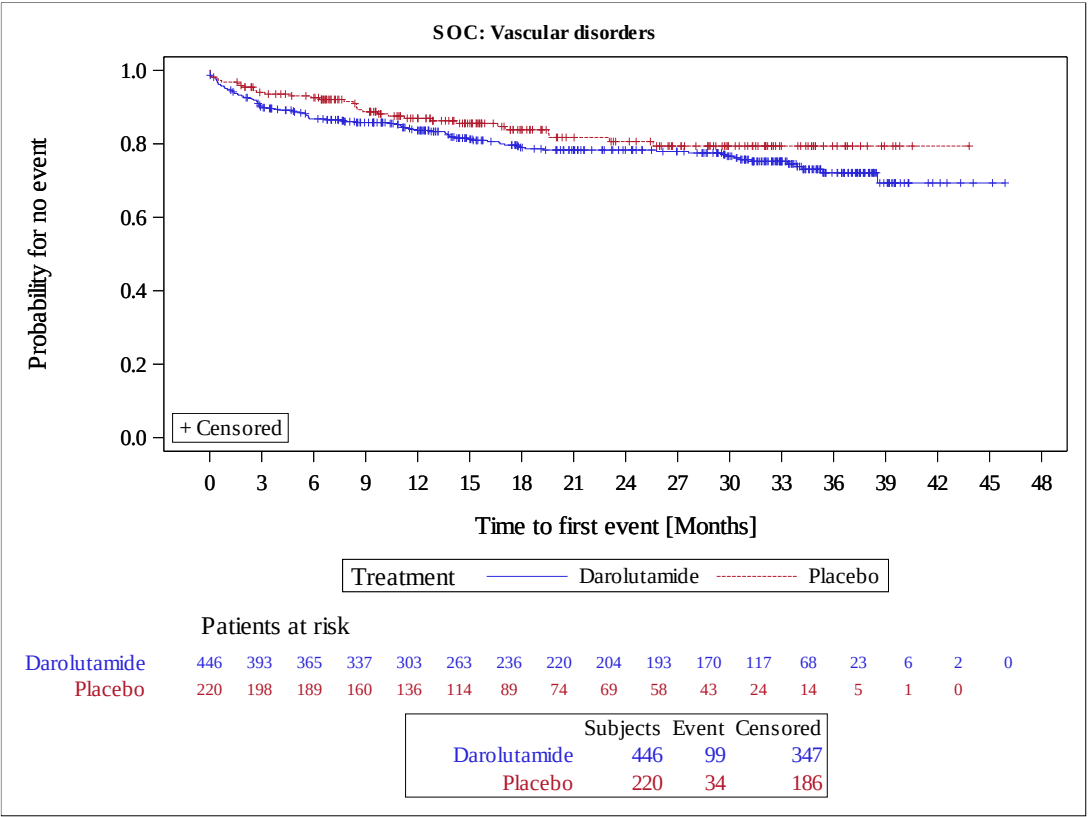


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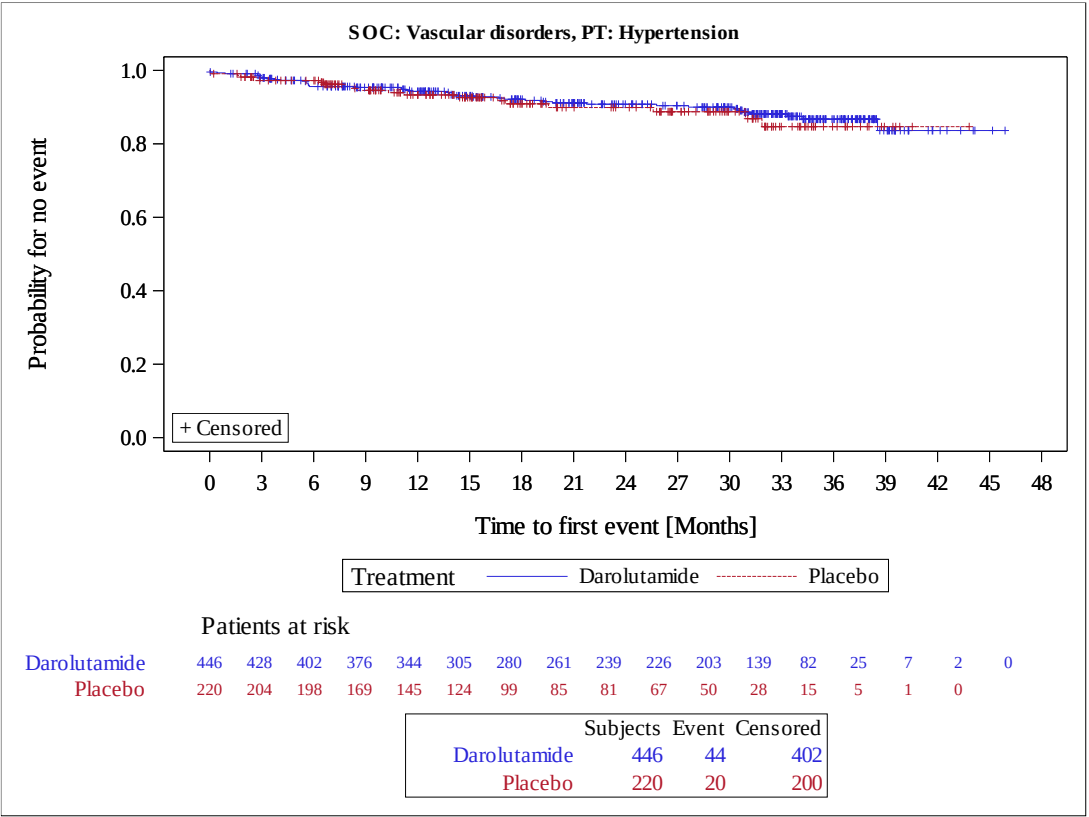


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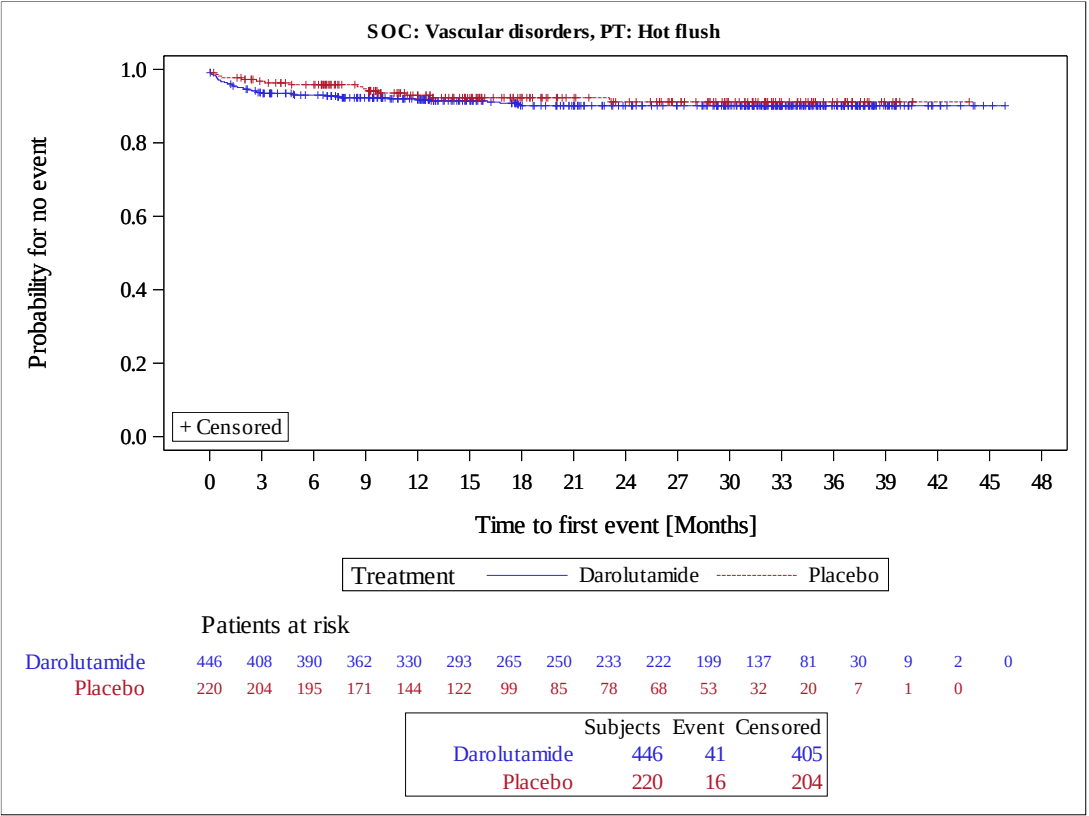


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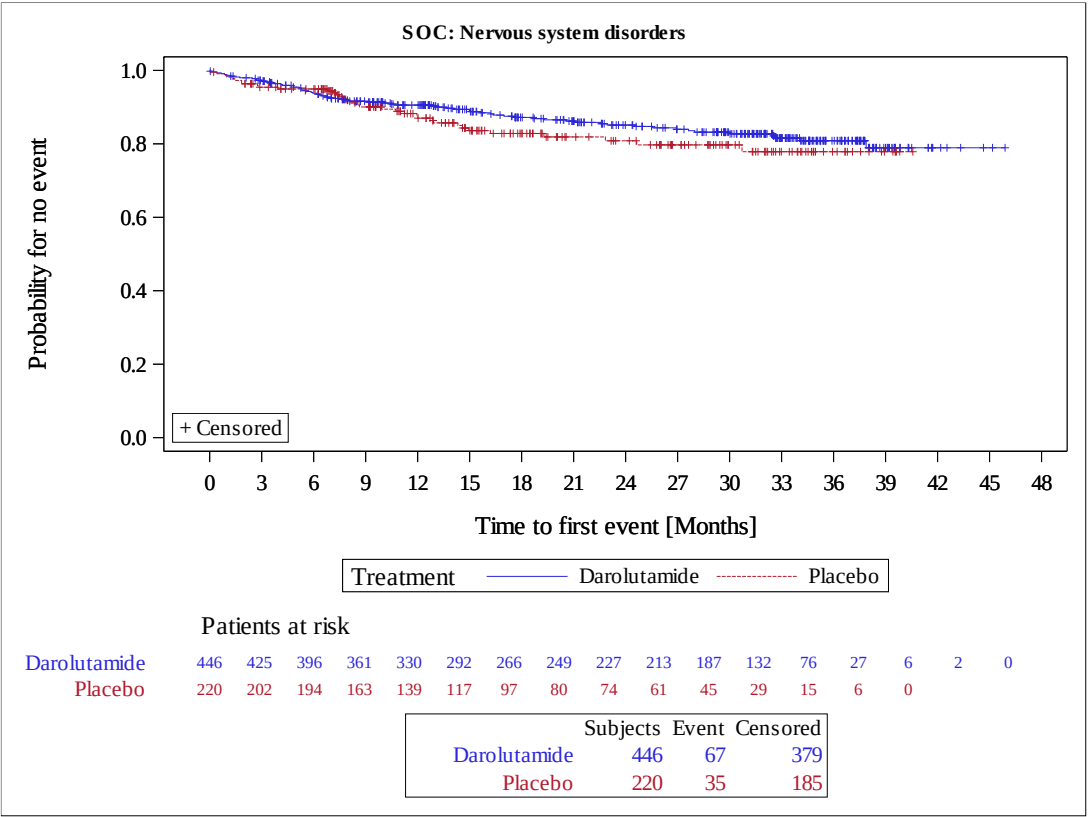


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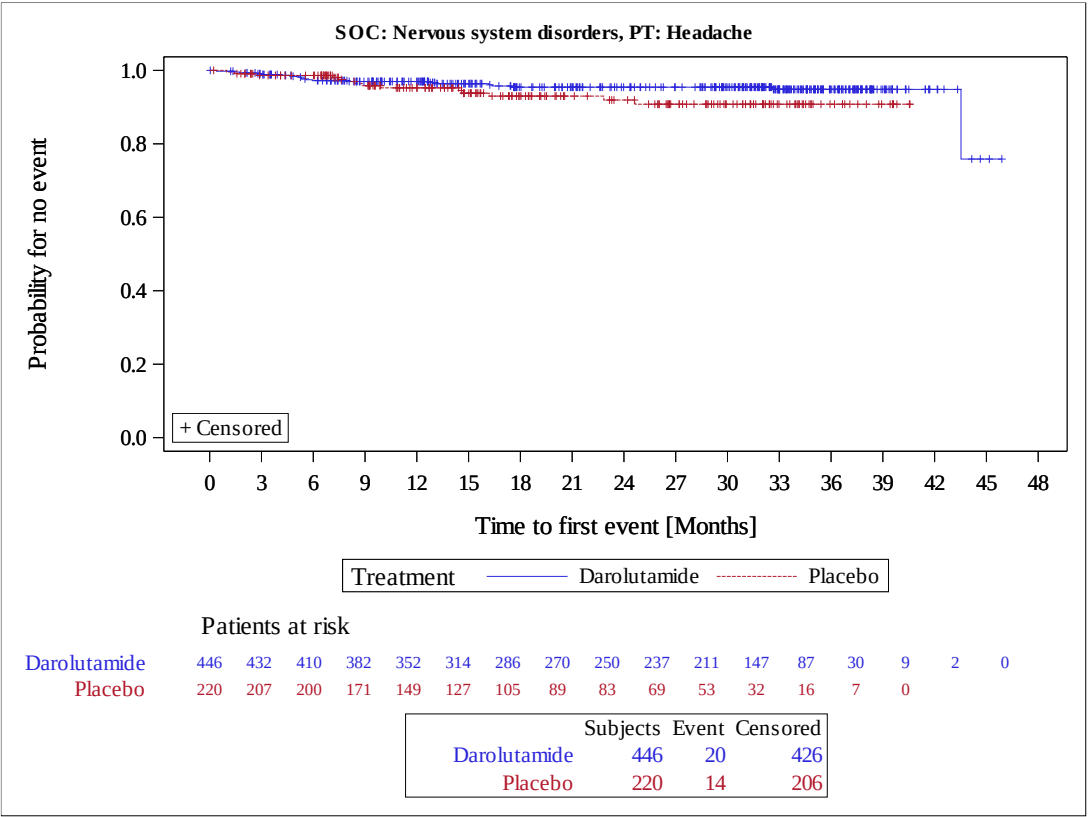


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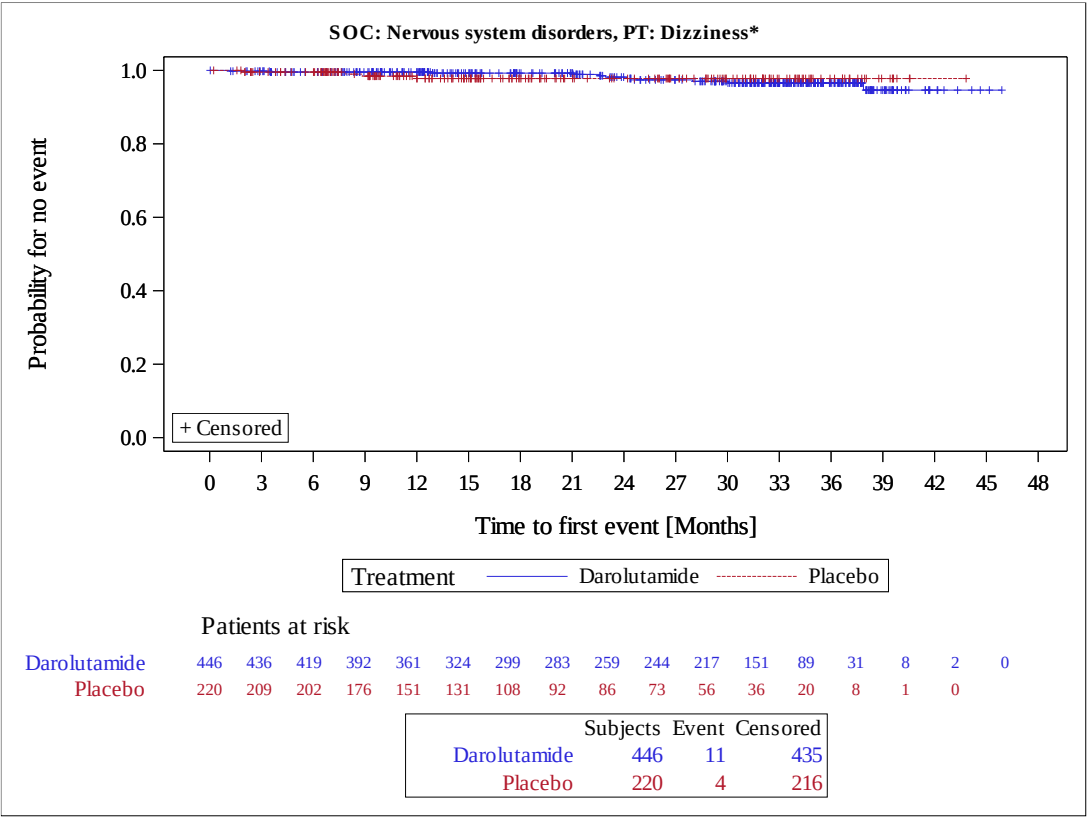


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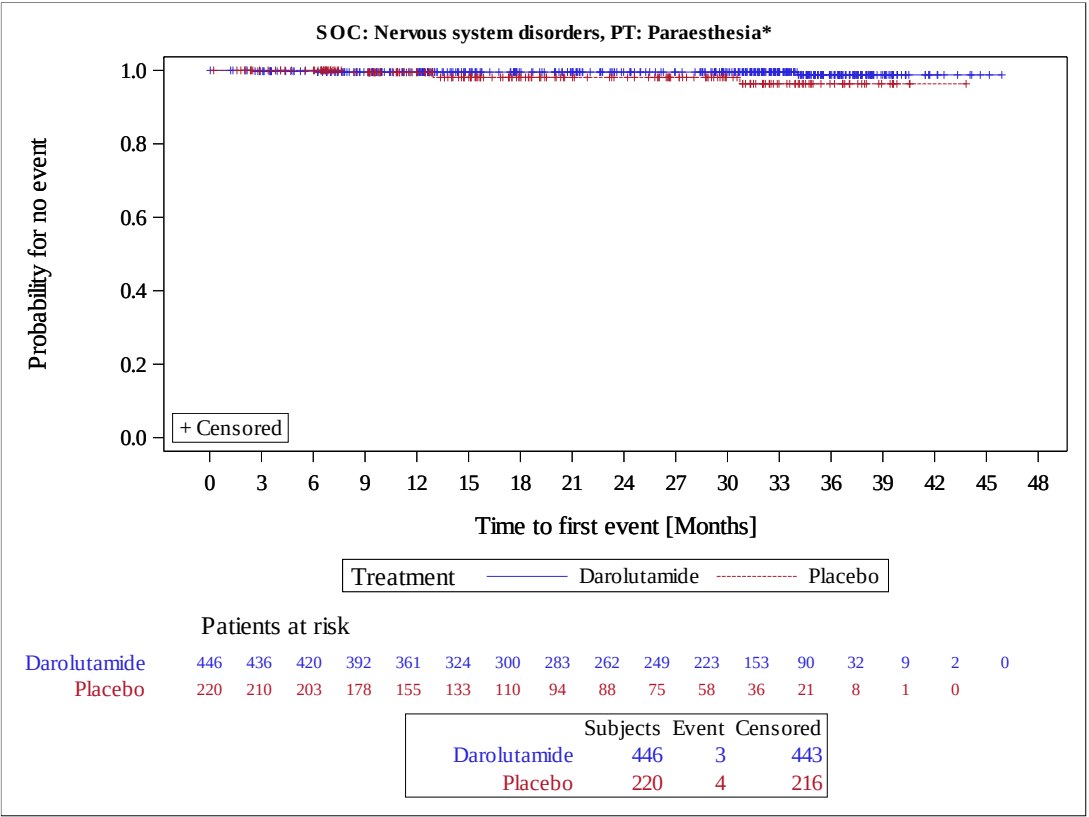


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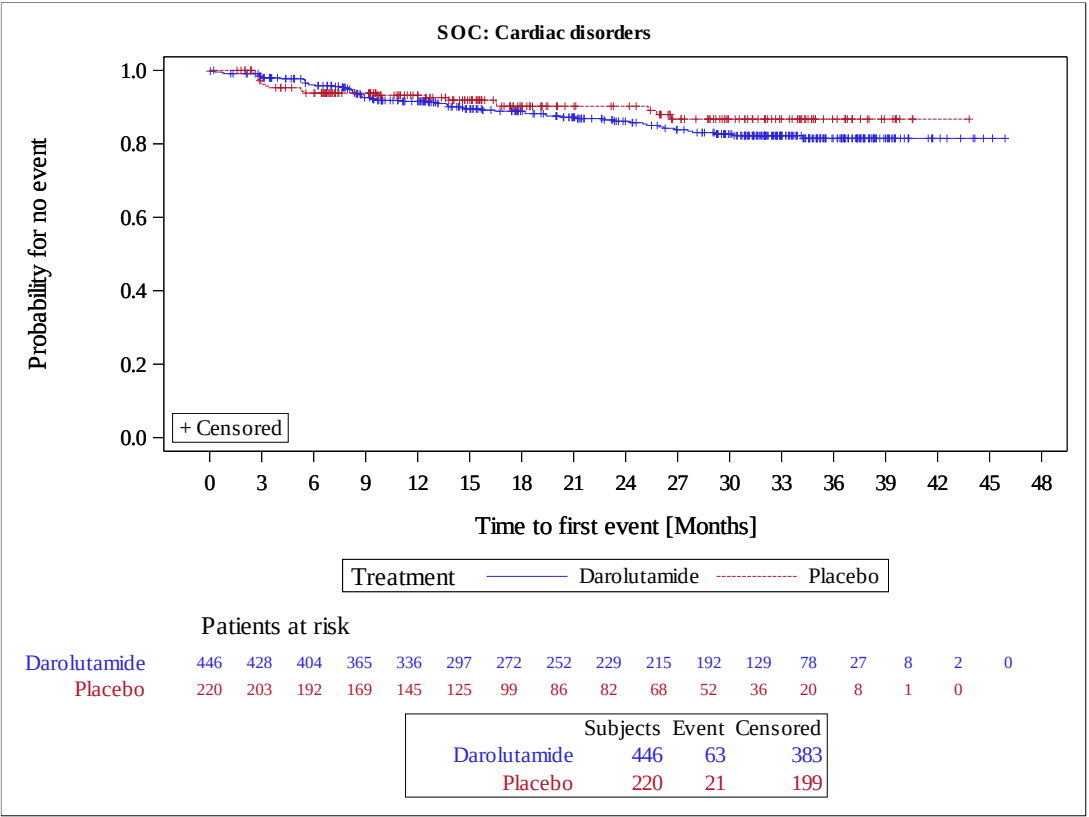


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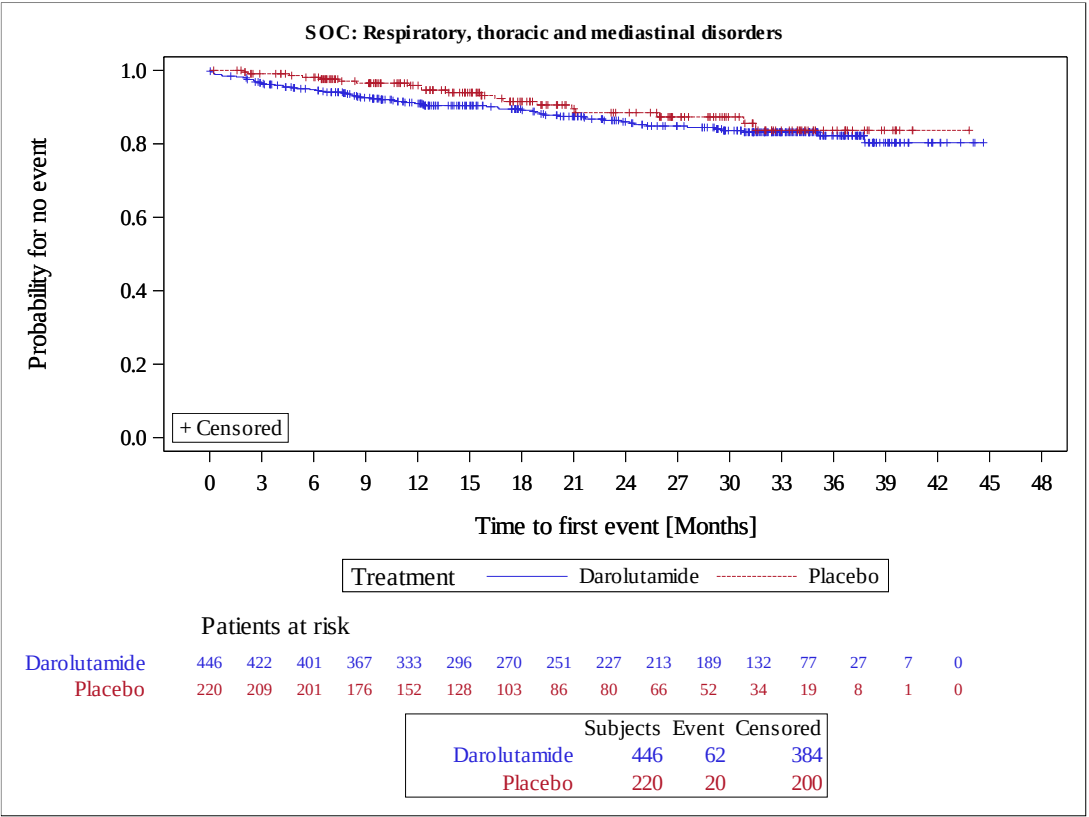


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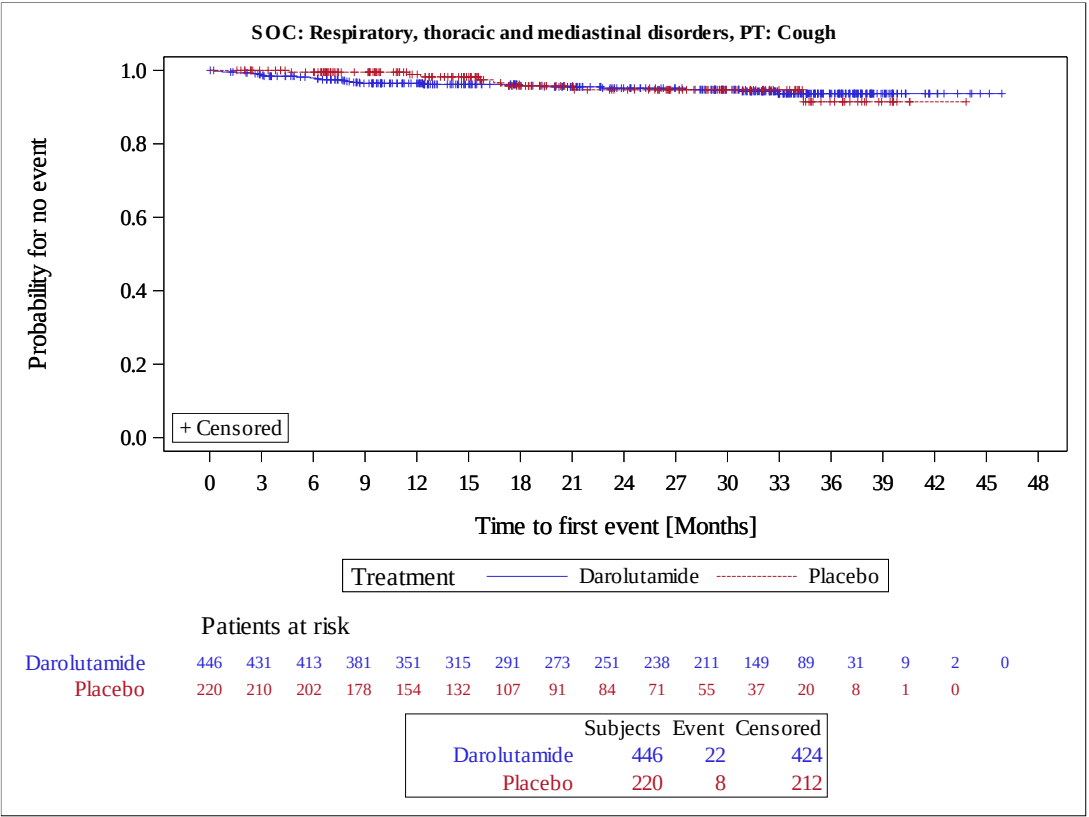


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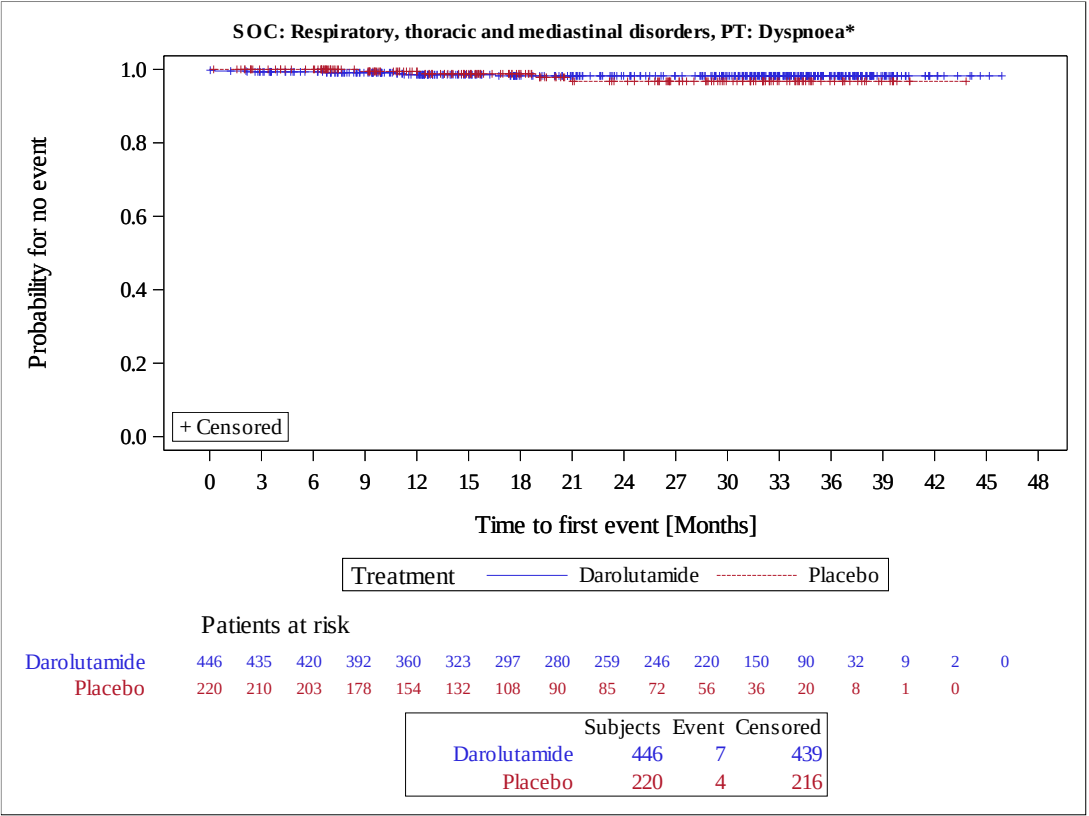


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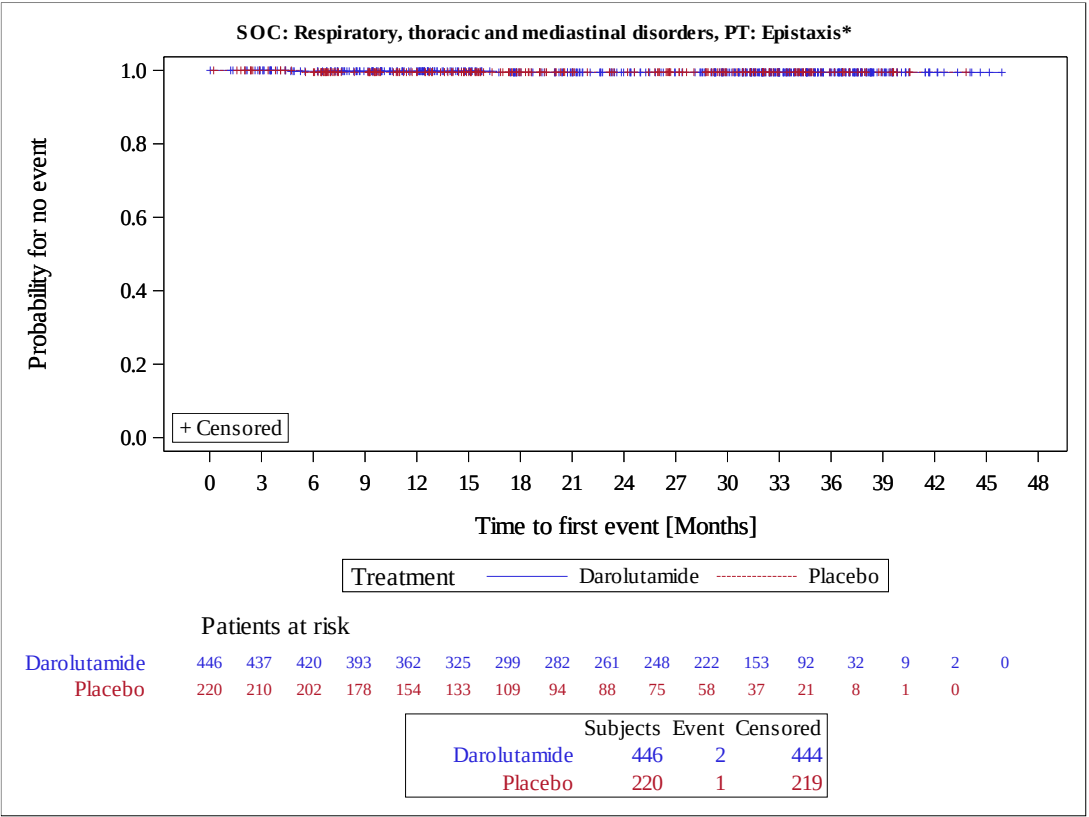


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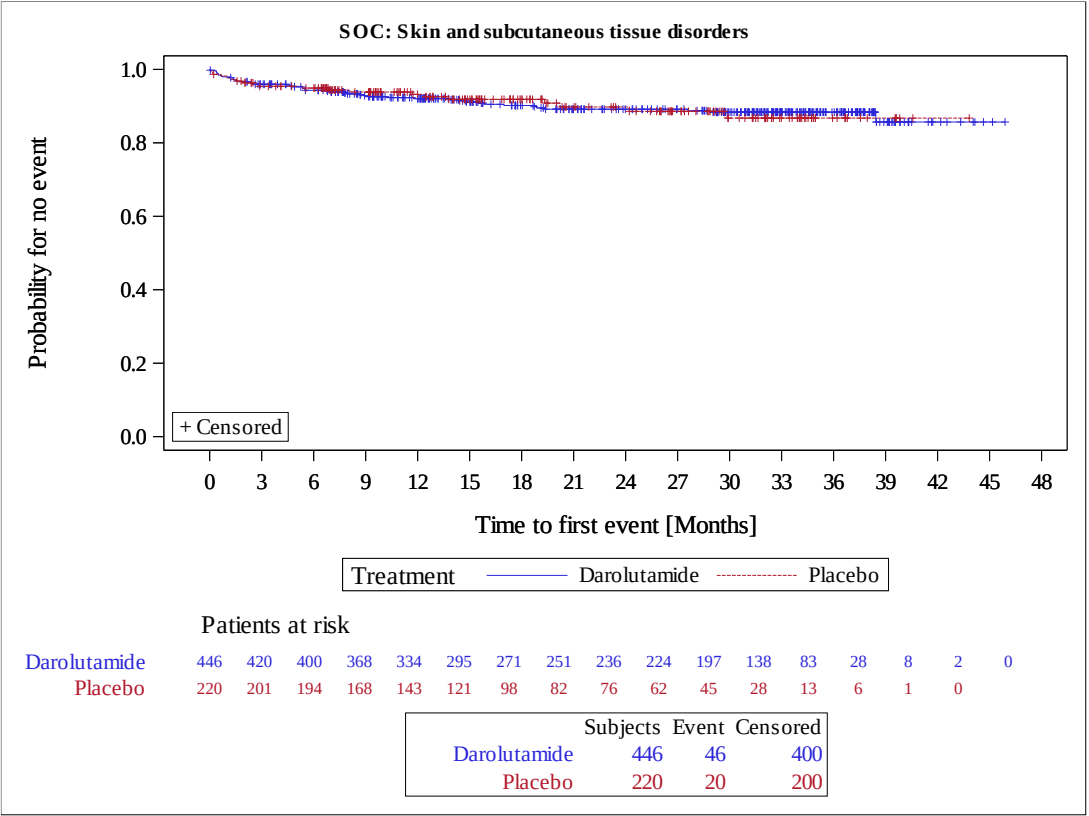


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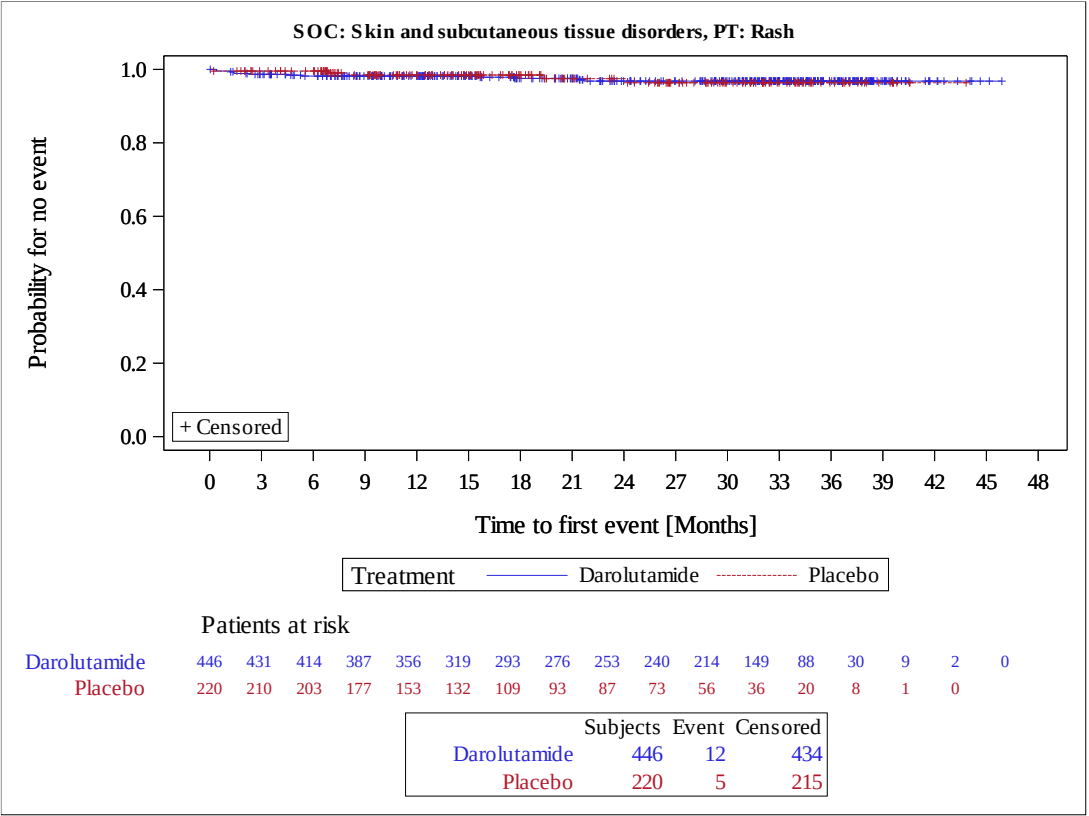


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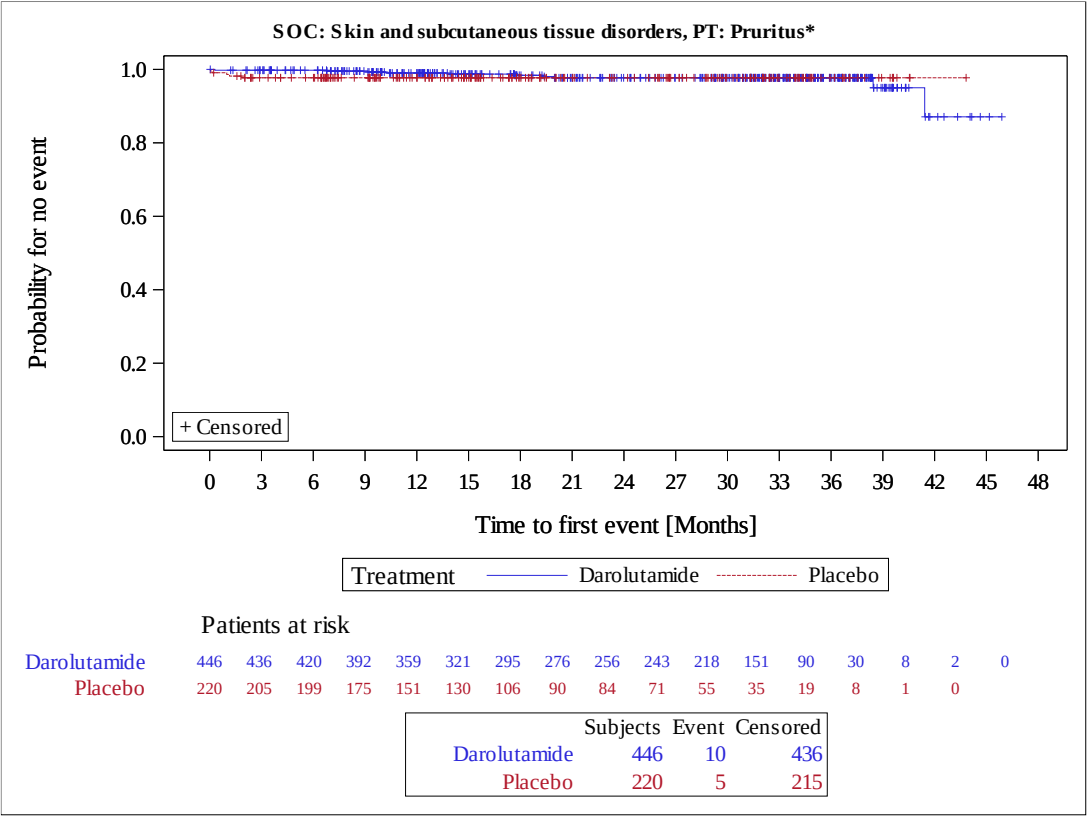


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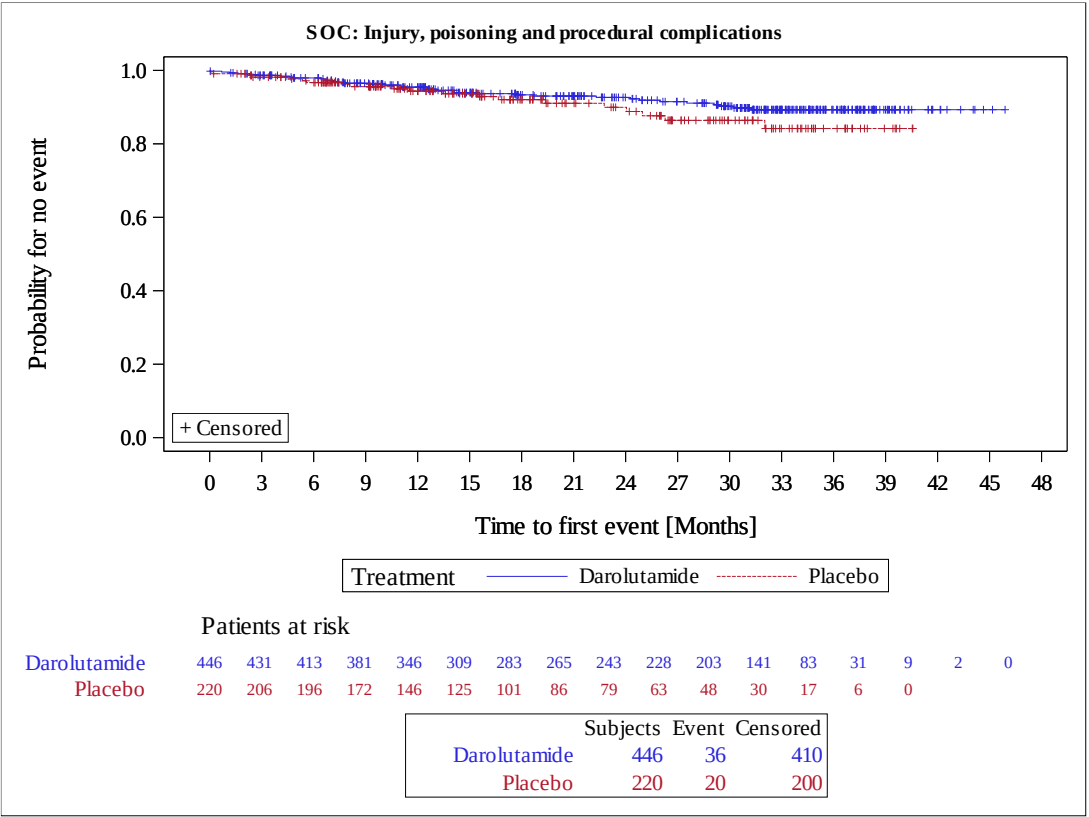


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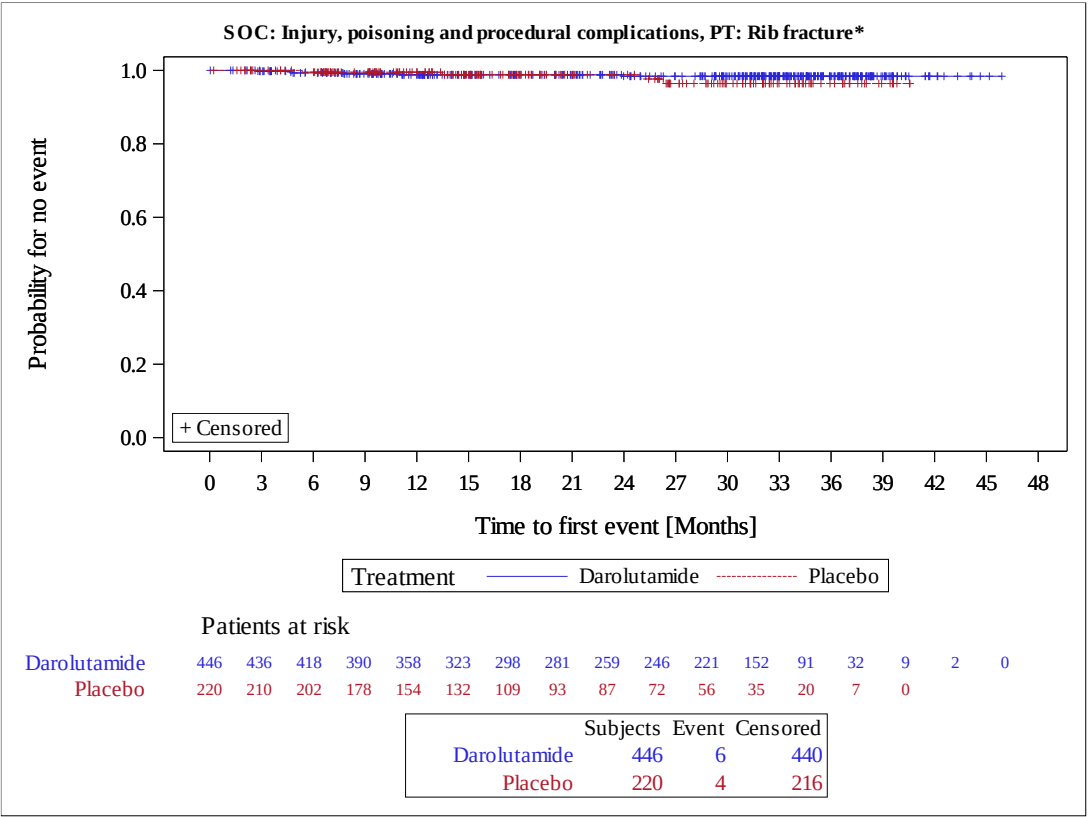


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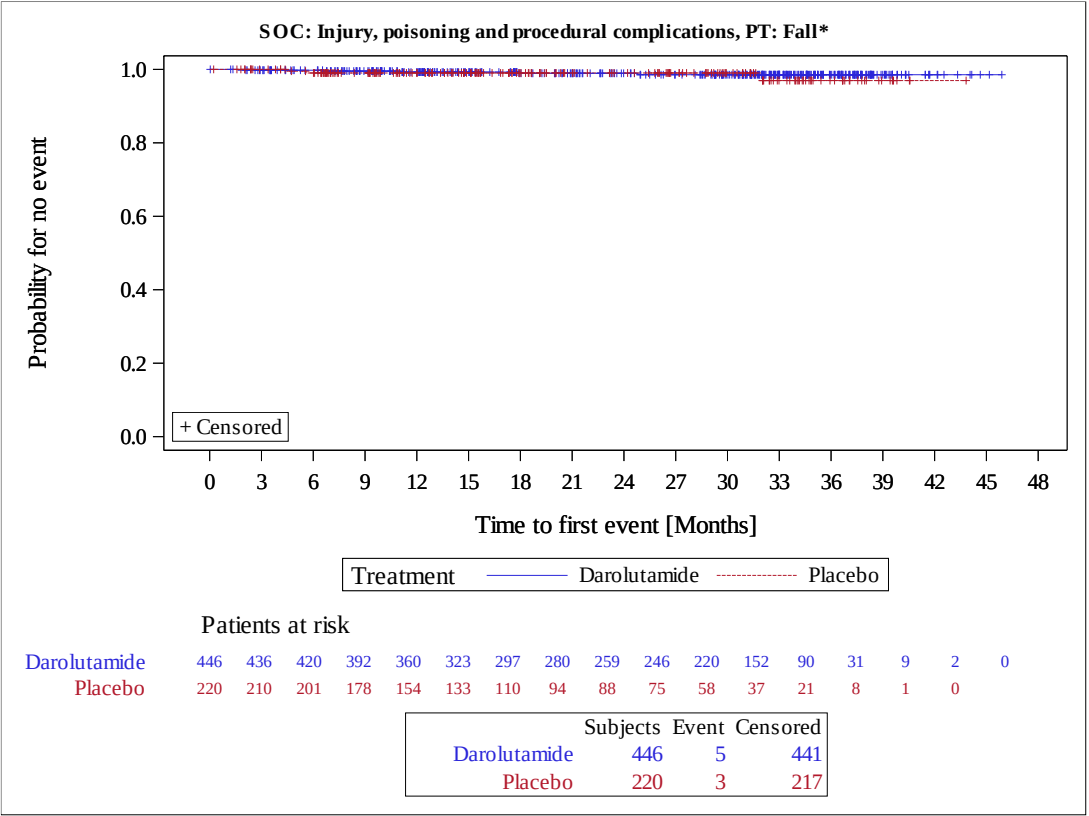


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
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Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
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Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.3.1.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

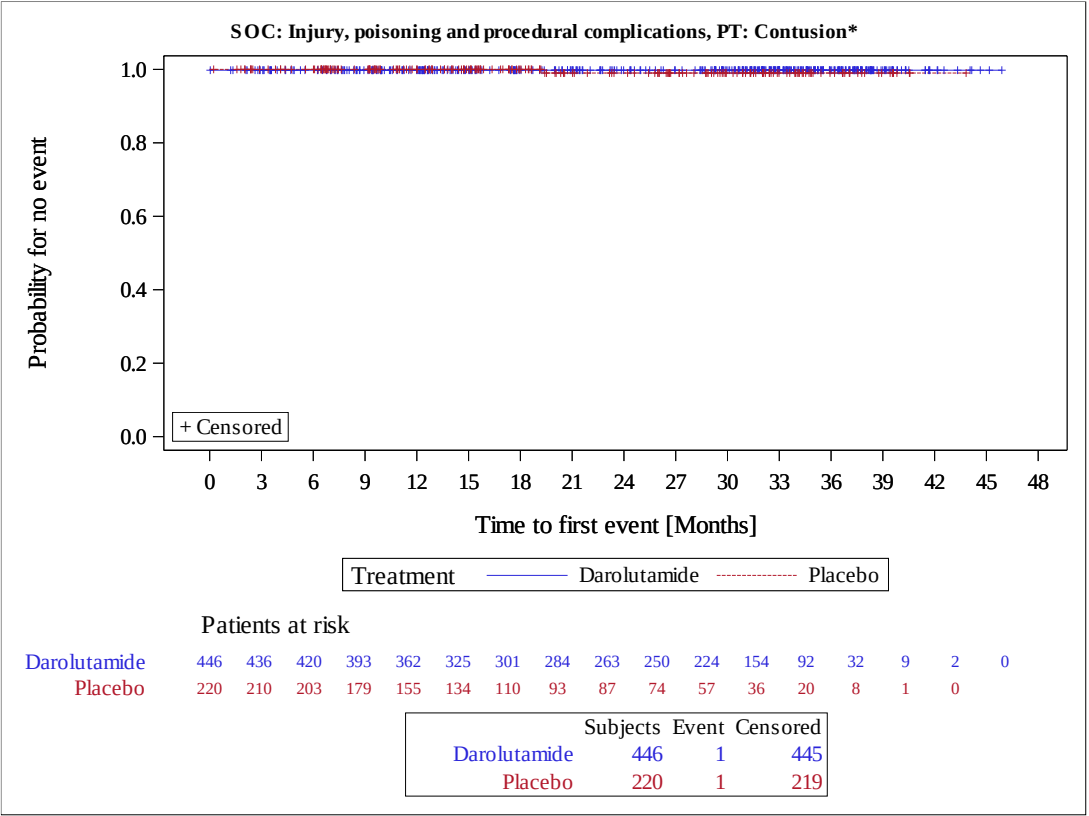


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Study population
Figure 3.3.1.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

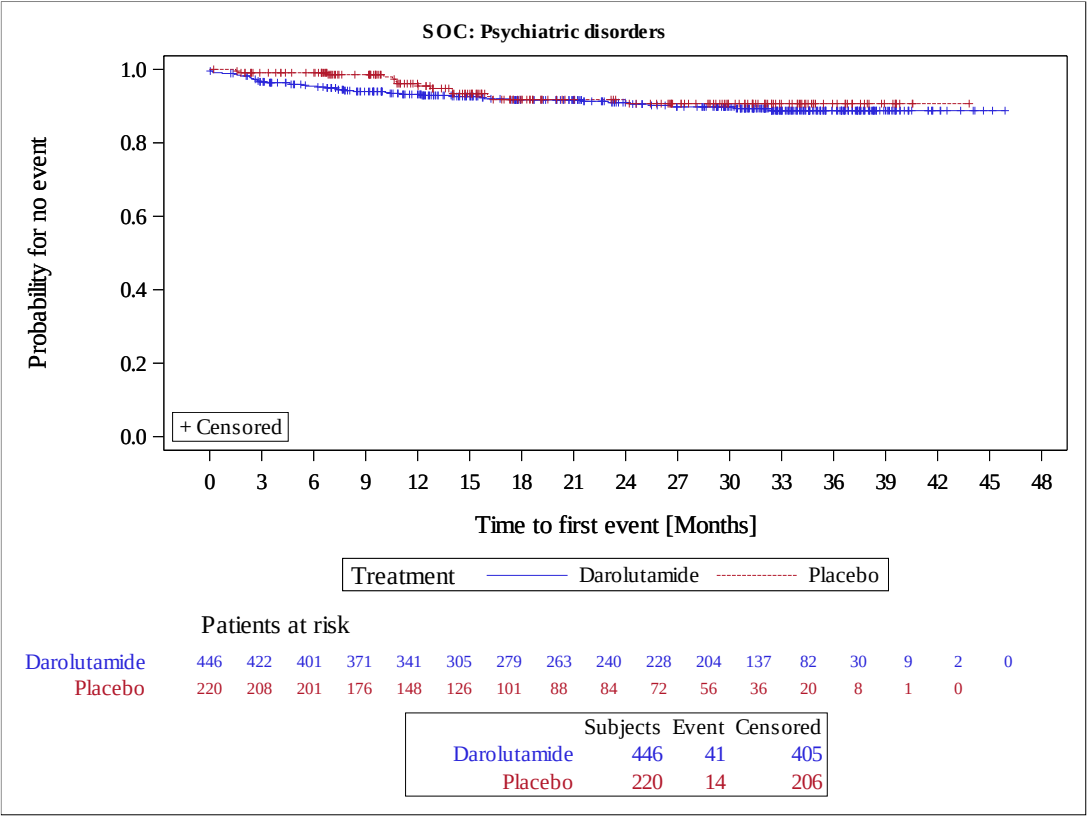


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(safety analysis set)

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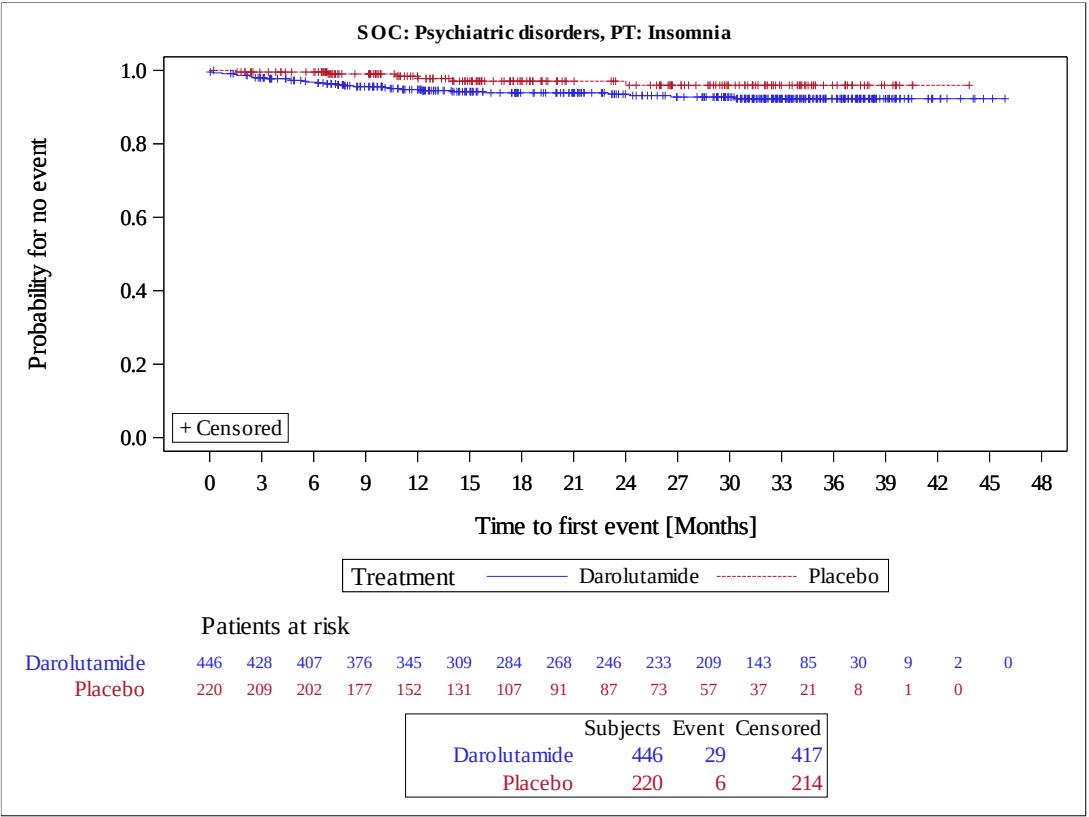


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Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

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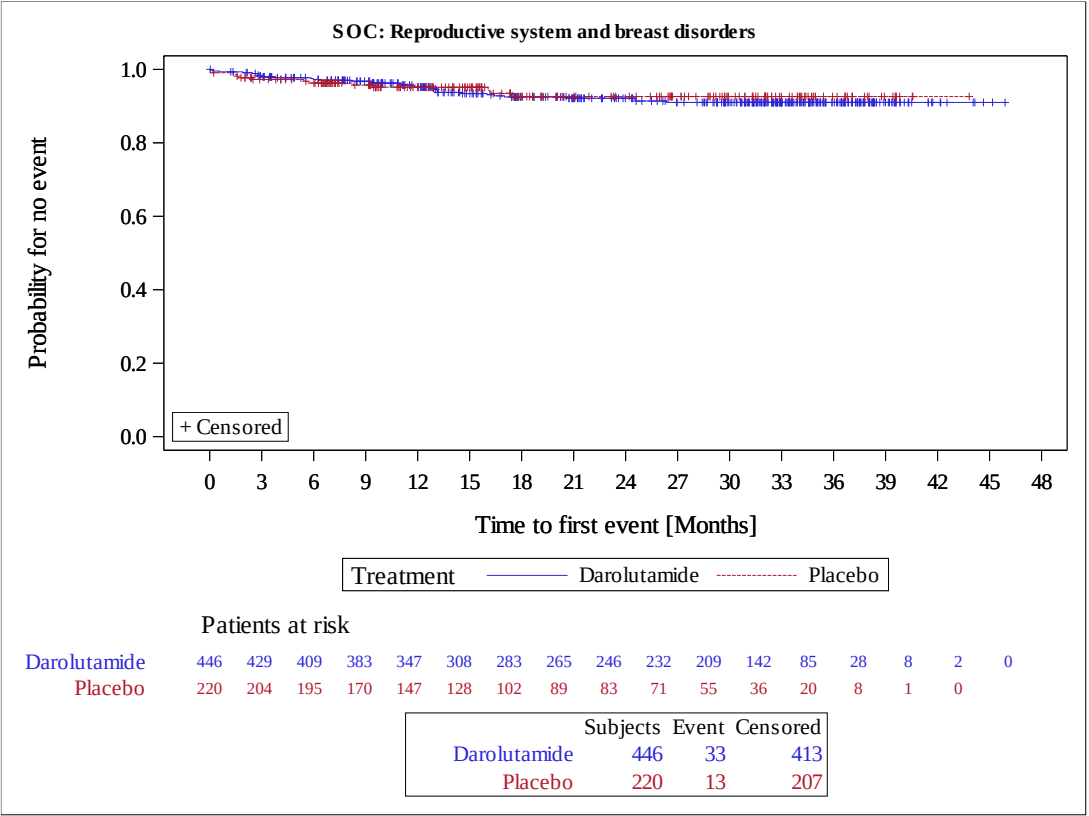


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(safety analysis set)

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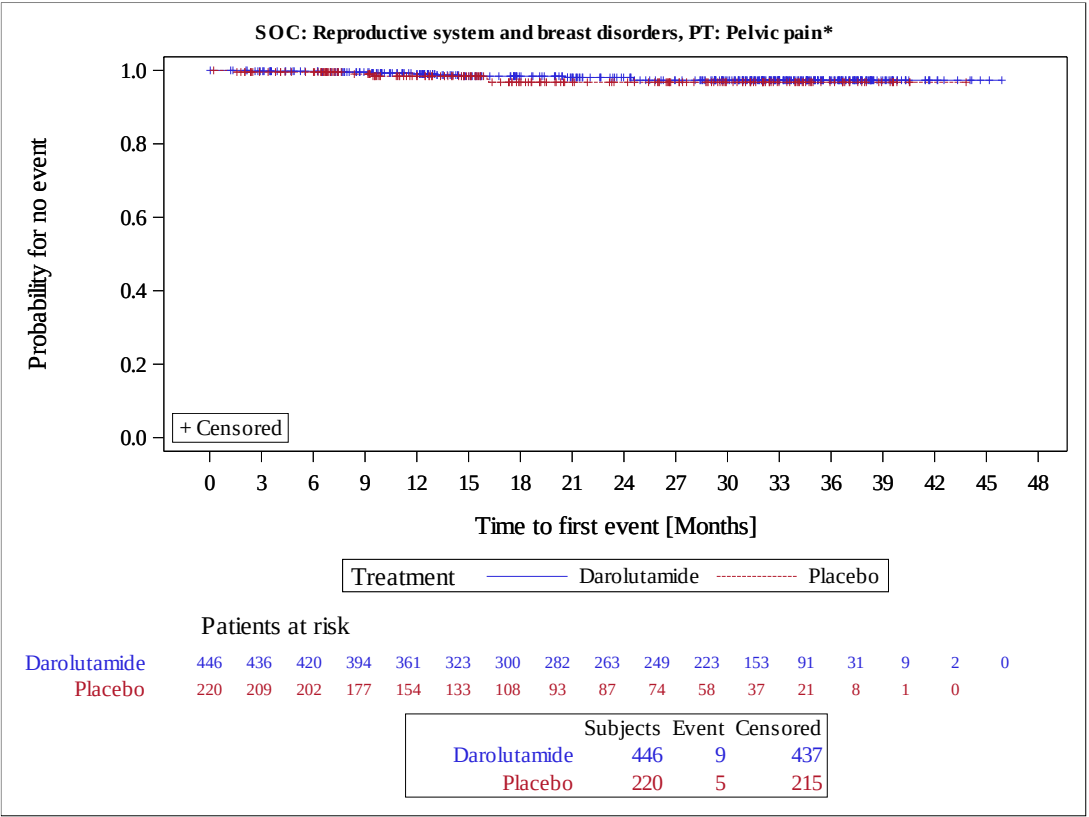


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(safety analysis set)

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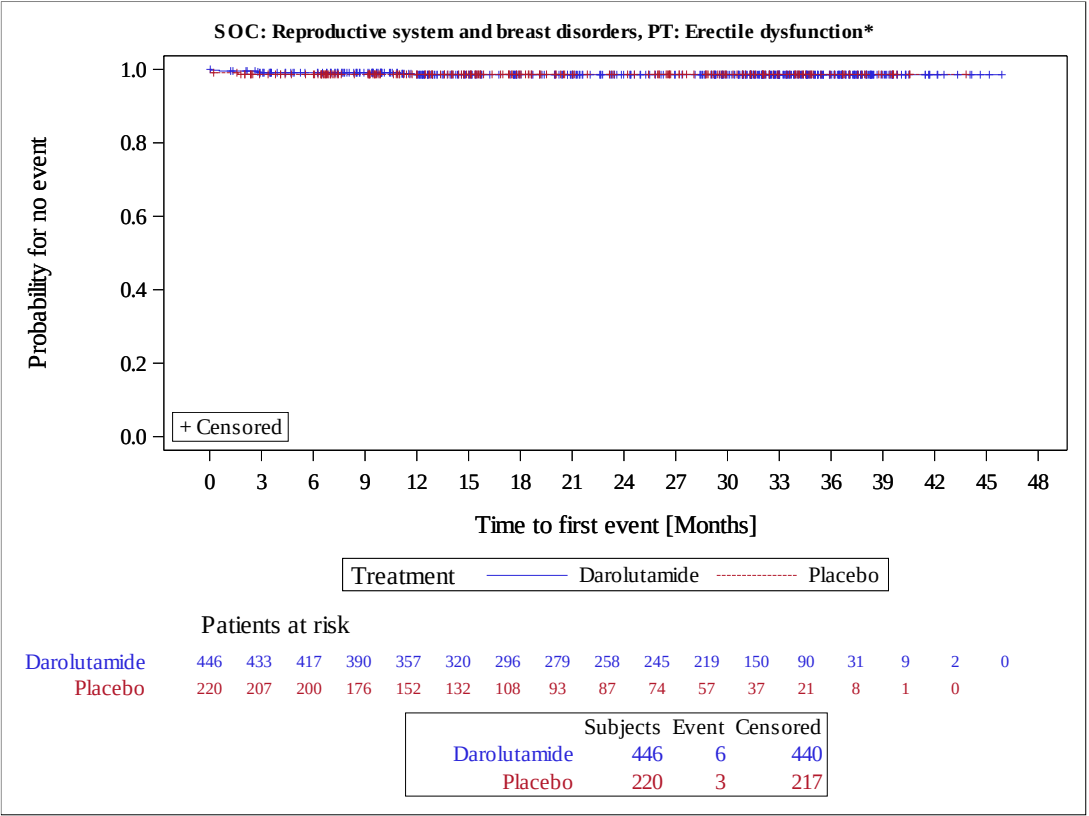


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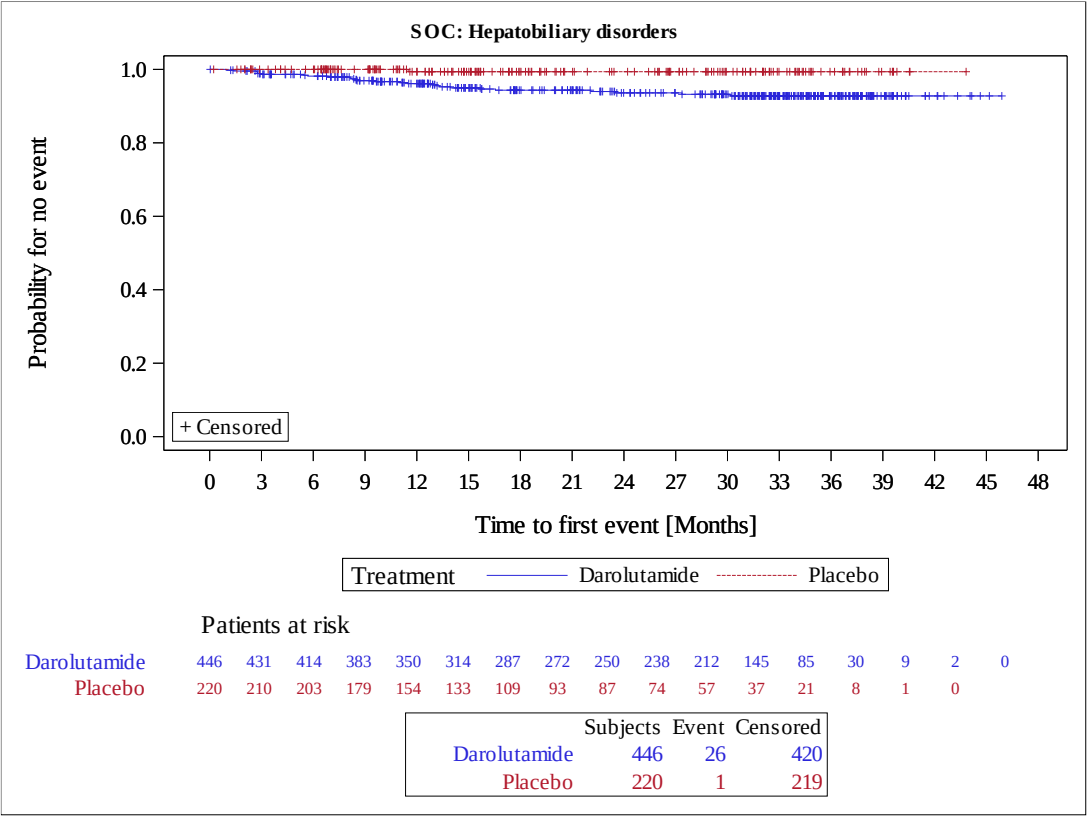


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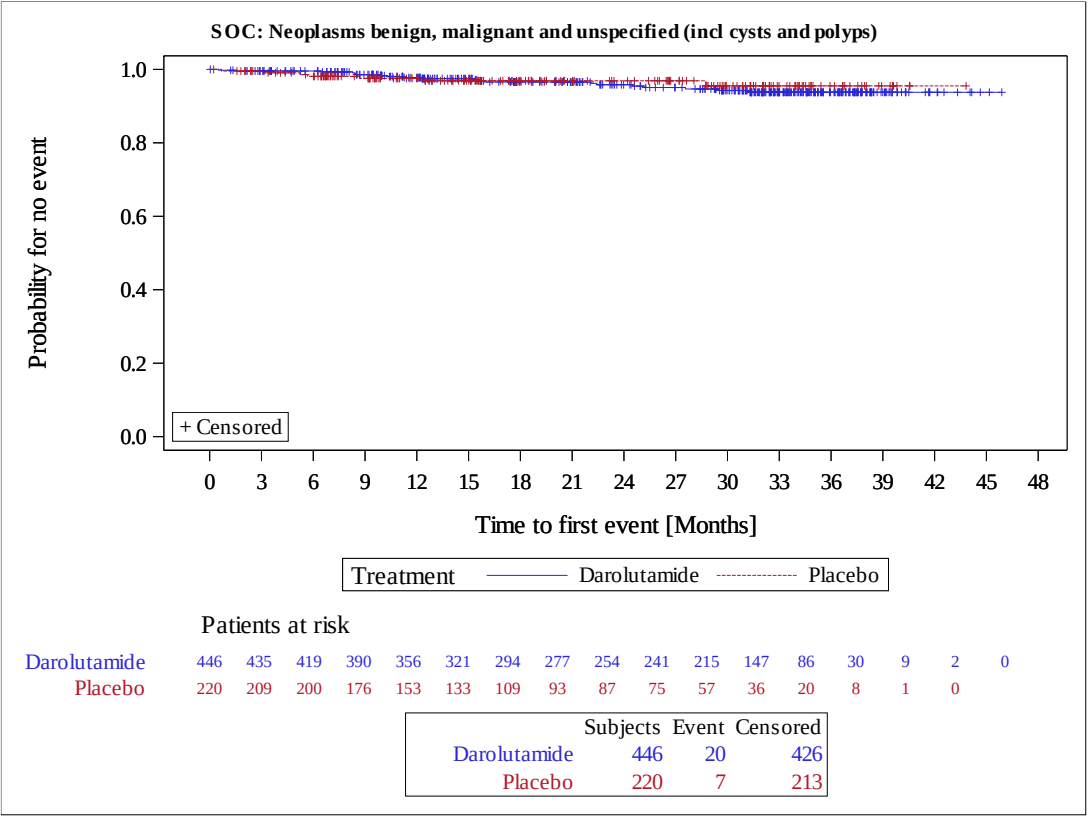


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(safety analysis set)

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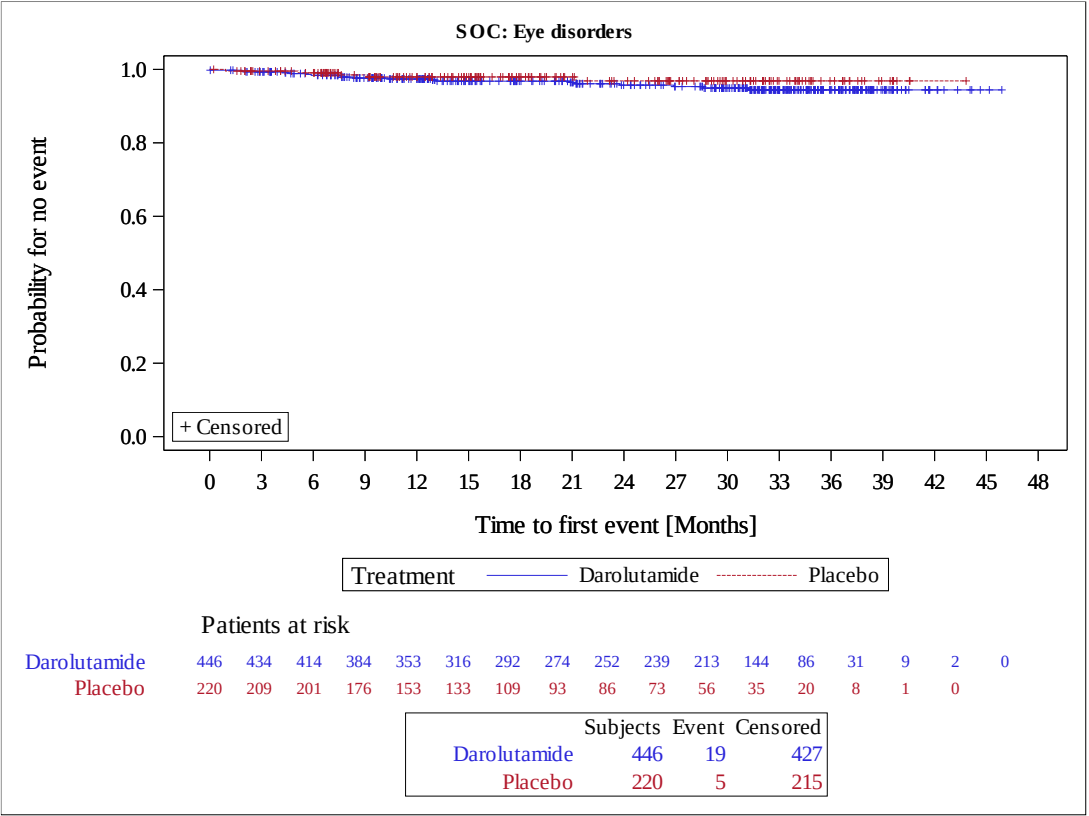


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Study population
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(safety analysis set)

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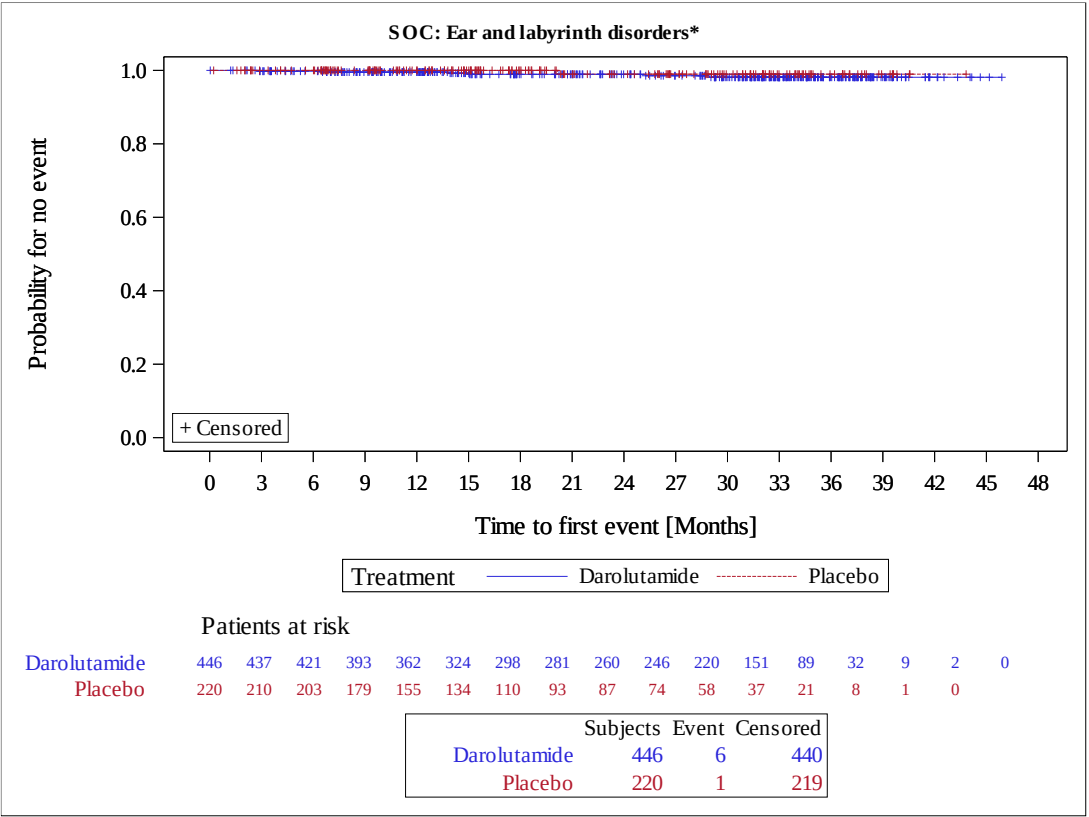


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Kaplan-Meier Plot of Time to First Frequent Adverse Event by SOC and PT (incidence in either arm >= 10% or both incidence >=1% and >=10 participants affected in either arm)
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.3.2
Summary of Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Cardiac disorders	Number of subjects with events, n (%)	16 (3.6)	8 (3.6)
	Number of censored subjects, n (%)	430 (96.4)	212 (96.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.859	
	95% CI	0.367, 2.011	
	p-value	0.7267	
	Odds Ratio	0.986	
	95% CI	0.415, 2.341	
	p-value	0.9746	
	Relative Risk	0.987	
	95% CI	0.429, 2.270	
	p-value	0.9746	
	Risk Difference	-0.049	
	95% CI	-3.065, 2.967	
	p-value	0.9746	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Study population
Table 3.3.2
Summary of Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)		Placebo (N=220)	
SOC: Infections and infestations	Number of subjects with events, n (%)	34 (7.6)		12 (5.5)	
	Number of censored subjects, n (%)	412 (92.4)		208 (94.5)	
	Time to Event (Month)				
	25%-ile (95%-CI)	NE (NE, NE)		NE (38.7, NE)	
	Median (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	75%-ile (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	Unstratified Analysis				
	Hazard Ratio	1.168			
	95% CI	0.603, 2.260			
	p-value	0.6454			
	Odds Ratio	1.430			
	95% CI	0.725, 2.820			
	p-value	0.3014			
	Relative Risk	1.398			
	95% CI	0.738, 2.645			
	p-value	0.3038			
	Risk Difference	2.169			
	95% CI	-1.713, 6.051			
	p-value	0.2735			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
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Table 3.3.2
Summary of Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Injury, poisoning and procedural complications*	Number of subjects with events, n (%)	10 (2.2)	4 (1.8)
	Number of censored subjects, n (%)	436 (97.8)	216 (98.2)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.980	
	95% CI	0.306, 3.141	
	p-value	0.9734	
	Odds Ratio	1.239	
	95% CI	0.384, 3.994	
	p-value	0.7203	
	Relative Risk	1.233	
	95% CI	0.391, 3.888	
	p-value	0.7205	
	Risk Difference	0.424	
	95% CI	-1.813, 2.661	
	p-value	0.7103	

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Summary of Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Musculoskeletal and connective tissue disorders	Number of subjects with events, n (%)	13 (2.9)	7 (3.2)
	Number of censored subjects, n (%)	433 (97.1)	213 (96.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.793	
	95% CI	0.315, 1.996	
	p-value	0.6220	
	Odds Ratio	0.914	
	95% CI	0.359, 2.323	
	p-value	0.8494	
	Relative Risk	0.916	
	95% CI	0.371, 2.263	
	p-value	0.8494	
	Risk Difference	-0.267	
	95% CI	-3.063, 2.529	
	p-value	0.8515	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

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Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Number of subjects with events, n (%)	11 (2.5)	5 (2.3)
	Number of censored subjects, n (%)	435 (97.5)	215 (97.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.955	
	95% CI	0.332, 2.753	
	p-value	0.9334	
	Odds Ratio	1.087	
	95% CI	0.373, 3.169	
	p-value	0.8780	
	Relative Risk	1.085	
	95% CI	0.382, 3.085	
	p-value	0.8781	
	Risk Difference	0.194	
	95% CI	-2.246, 2.633	
	p-value	0.8764	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.2
Summary of Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Nervous system disorders	Number of subjects with events, n (%)	15 (3.4)	5 (2.3)
	Number of censored subjects, n (%)	431 (96.6)	215 (97.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.220	
	95% CI	0.442, 3.369	
	p-value	0.7008	
	Odds Ratio	1.497	
	95% CI	0.537, 4.172	
	p-value	0.4409	
	Relative Risk	1.480	
	95% CI	0.545, 4.019	
	p-value	0.4420	
	Risk Difference	1.091	
	95% CI	-1.494, 3.675	
	p-value	0.4082	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.2
Summary of Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Renal and urinary disorders	Number of subjects with events, n (%)	15 (3.4)	8 (3.6)
	Number of censored subjects, n (%)	431 (96.6)	212 (96.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.820	
	95% CI	0.348, 1.937	
	p-value	0.6510	
	Odds Ratio	0.922	
	95% CI	0.385, 2.209	
	p-value	0.8560	
	Relative Risk	0.925	
	95% CI	0.398, 2.148	
	p-value	0.8559	
	Risk Difference	-0.273	
	95% CI	-3.259, 2.713	
	p-value	0.8577	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.2
Summary of Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Respiratory, thoracic and mediastinal disorders*		
Number of subjects with events, n (%)	7 (1.6)	6 (2.7)
Number of censored subjects, n (%)	439 (98.4)	214 (97.3)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.479	
95% CI	0.160, 1.431	
p-value	0.1778	
Odds Ratio	0.569	
95% CI	0.189, 1.713	
p-value	0.3158	
Relative Risk	0.575	
95% CI	0.196, 1.692	
p-value	0.3153	
Risk Difference	-1.158	
95% CI	-3.600, 1.284	
p-value	0.3528	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Table 3.3.2.1
Summary of Frequent Serious Adverse Evenst by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) - Subgroup analysis (safety analysis set)

Final

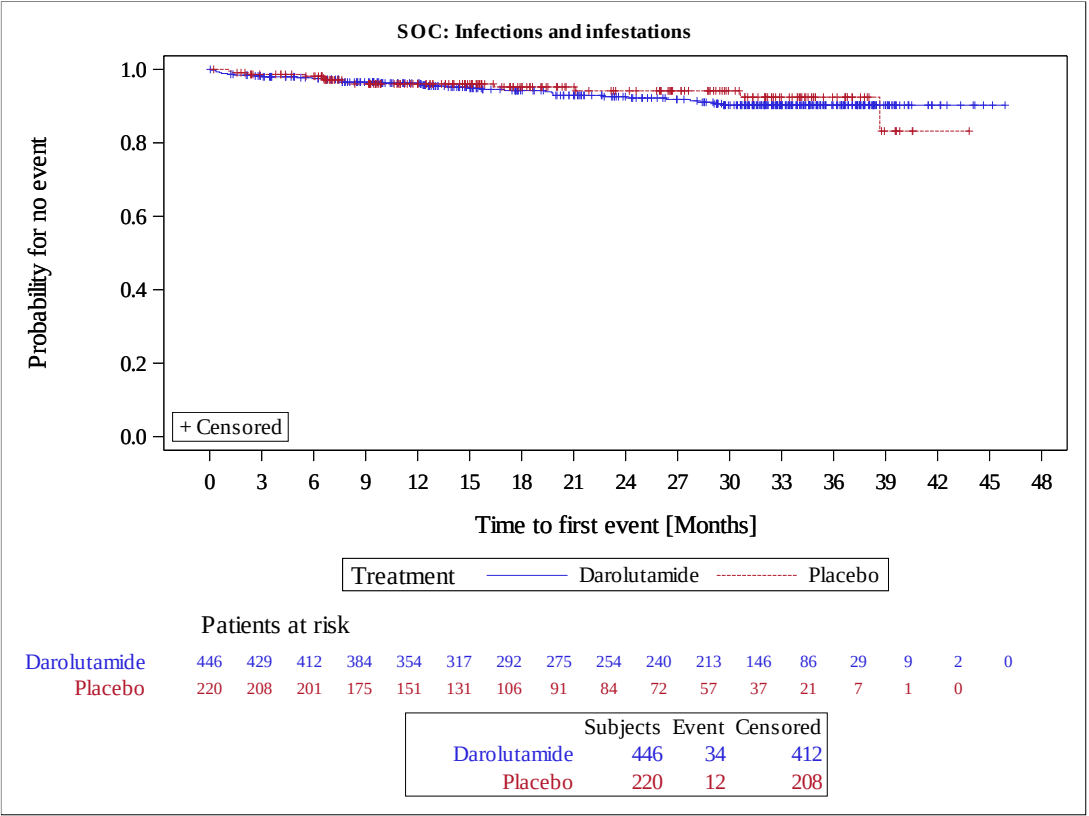
!!! There are no Observations for this Report !!!

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Subgroup analysis was done for SOC's / PTs with significant overall treatment effect (significant log-rank test).
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.3.2.2
Kaplan-Meier Plot of Time to First Frequent Serious Adverse Event by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

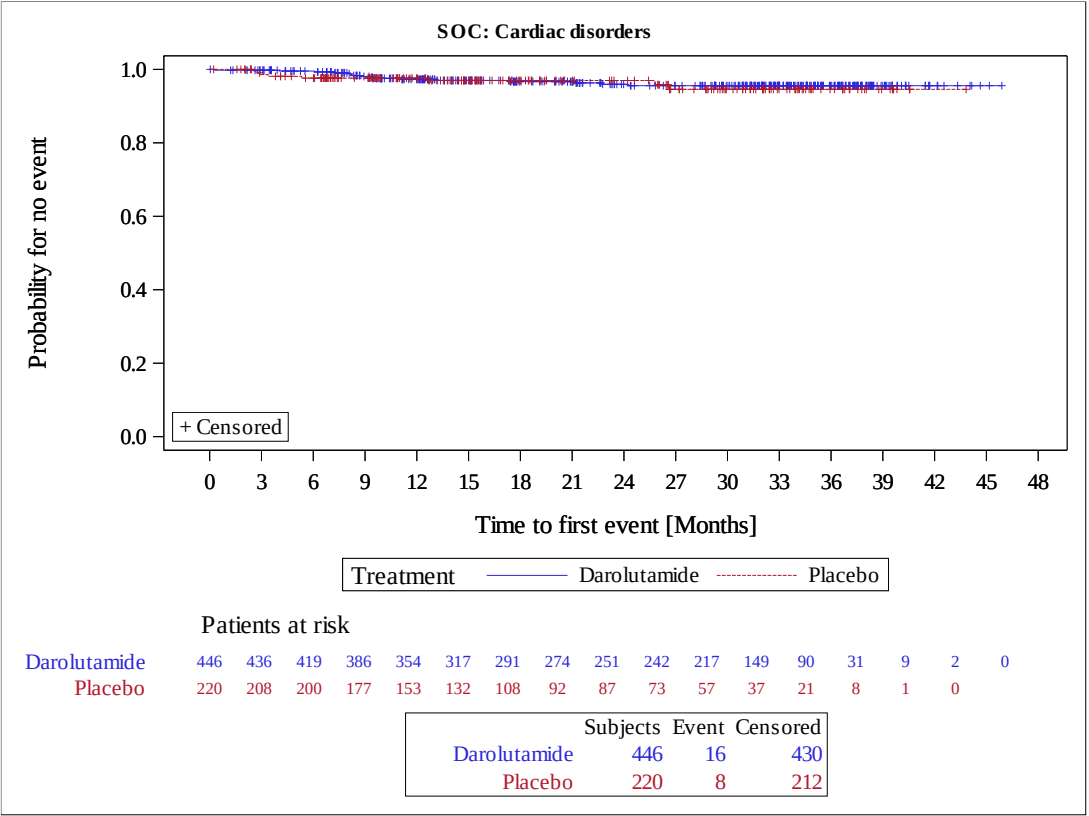


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC / PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.3.2.2
Kaplan-Meier Plot of Time to First Frequent Serious Adverse Event by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) (safety analysis set)

Final

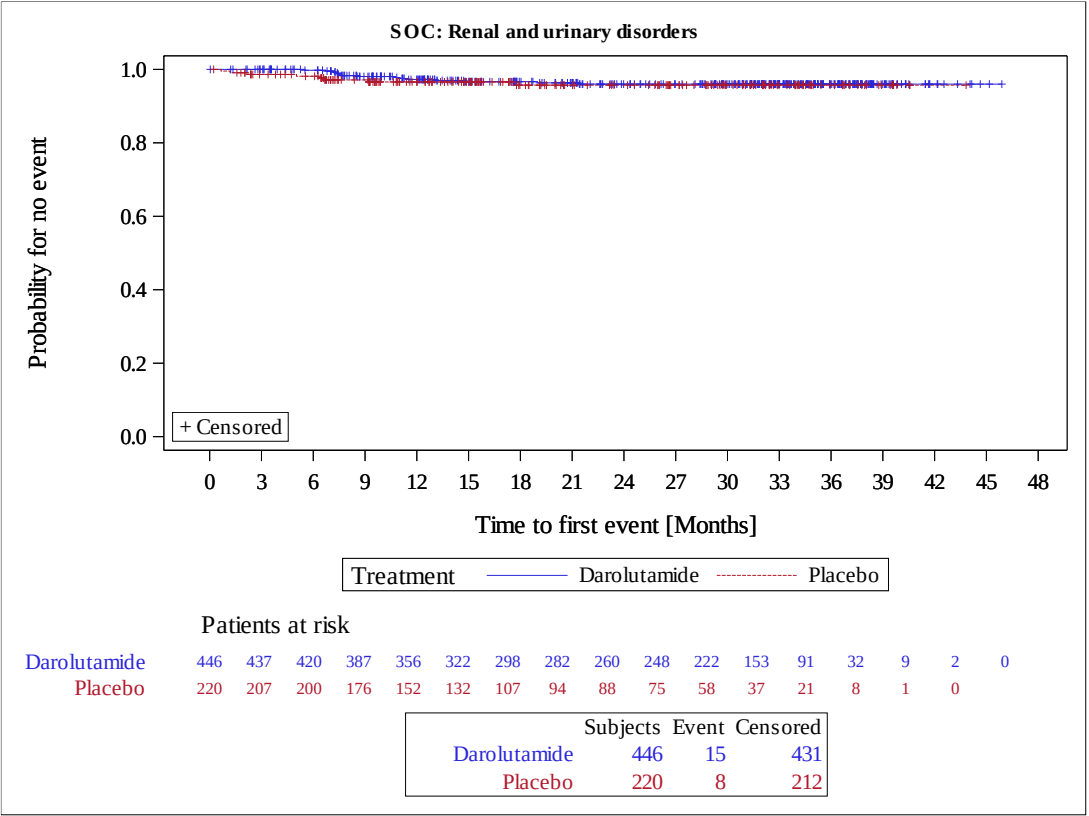


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC/PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.3.2.2
Kaplan-Meier Plot of Time to First Frequent Serious Adverse Event by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) (safety analysis set)

Final

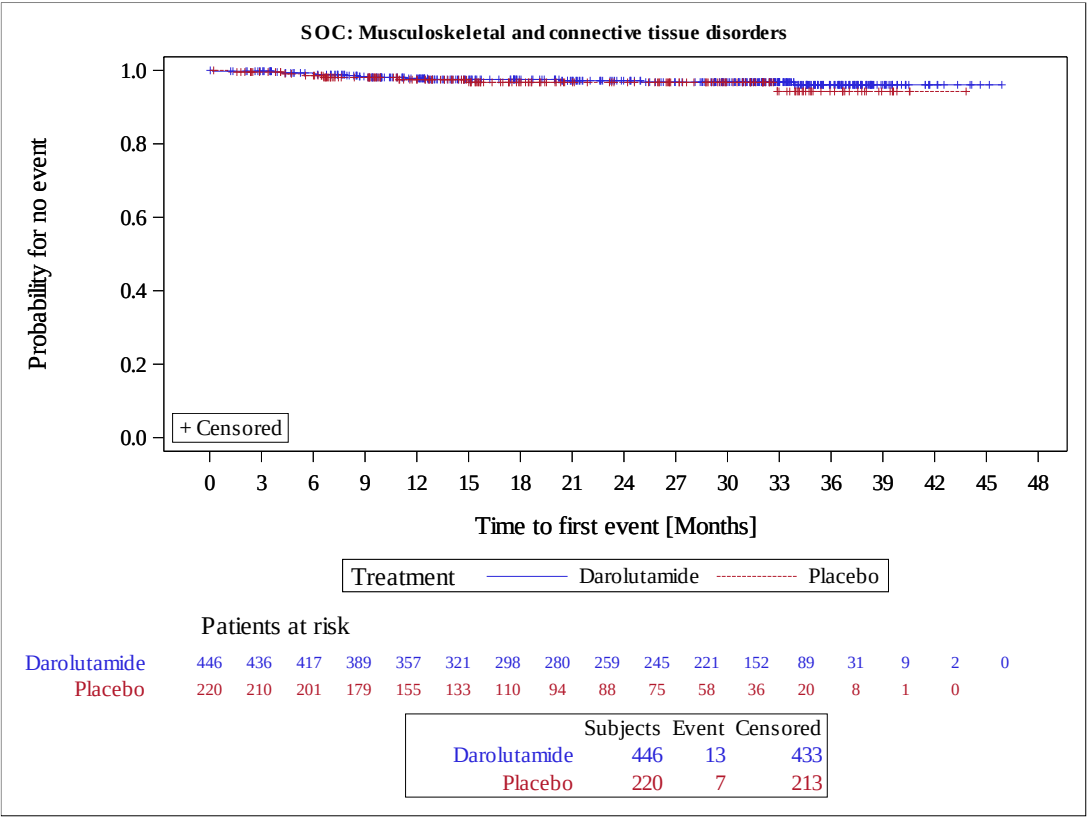


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC/PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.3.2.2
Kaplan-Meier Plot of Time to First Frequent Serious Adverse Event by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

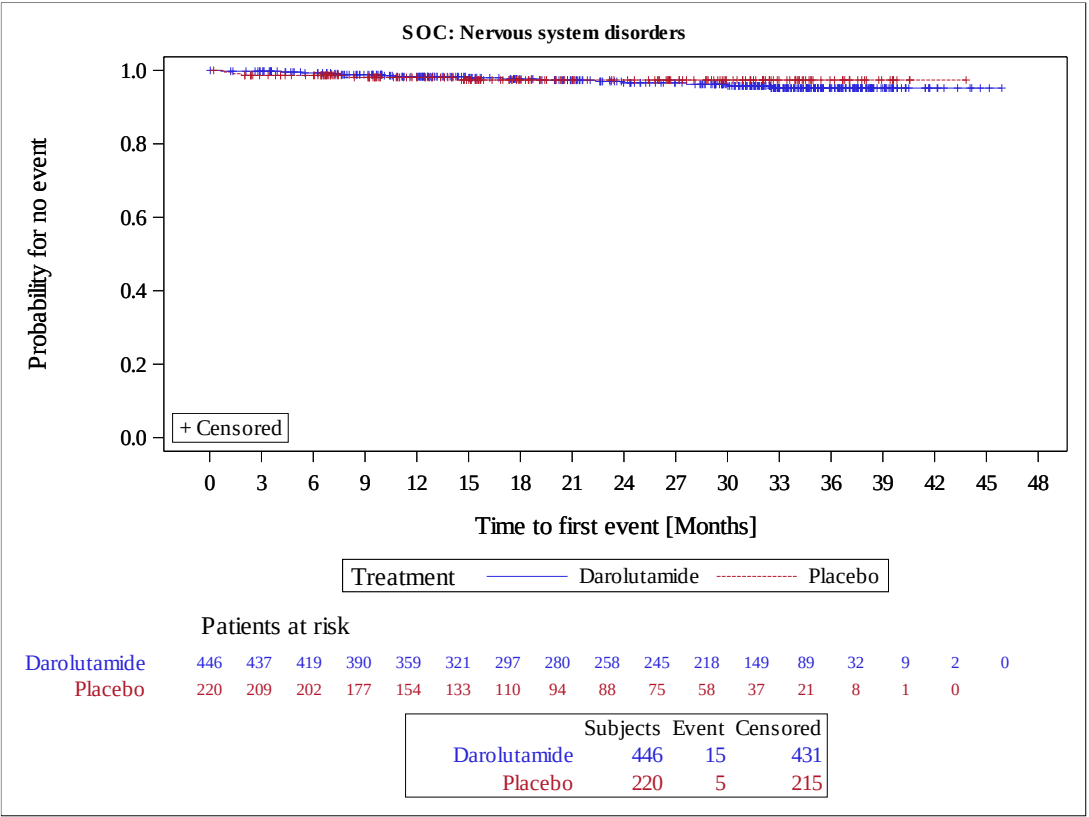


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC / PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.3.2.2
Kaplan-Meier Plot of Time to First Frequent Serious Adverse Event by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

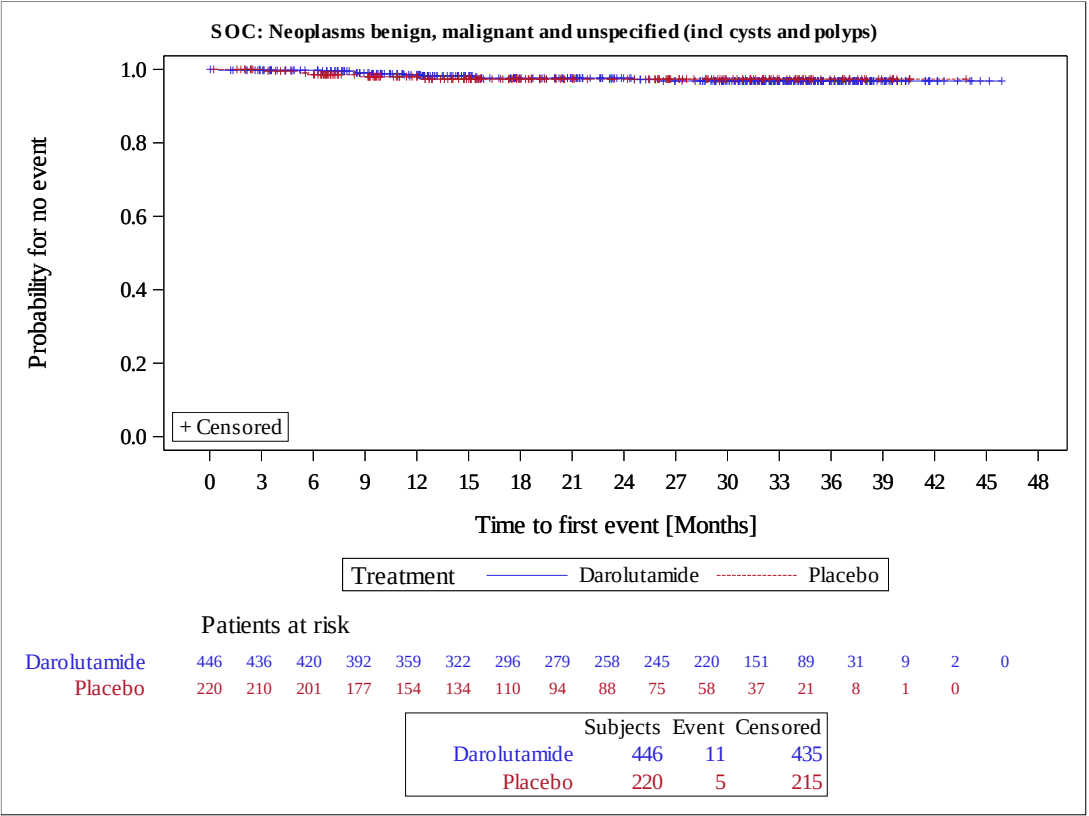


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC/PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.3.2.2
Kaplan-Meier Plot of Time to First Frequent Serious Adverse Event by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

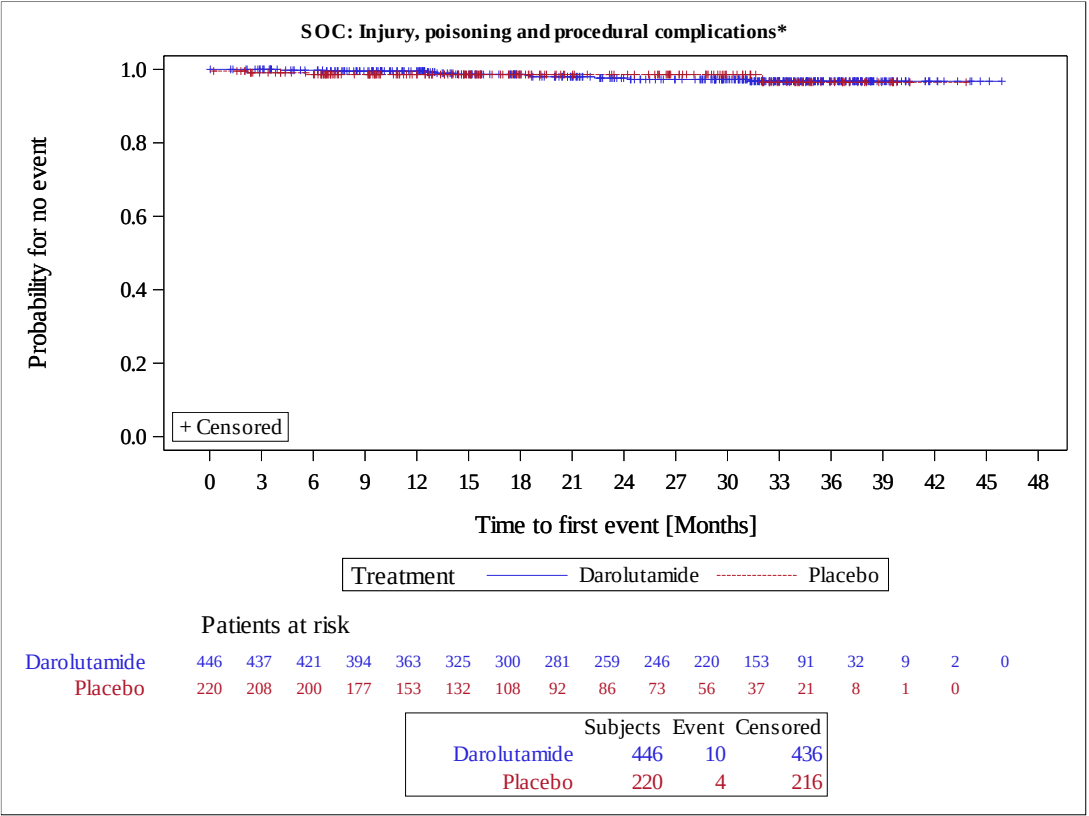


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC / PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Figure 3.3.2.2
Kaplan-Meier Plot of Time to First Frequent Serious Adverse Event by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) (safety analysis set)

Final

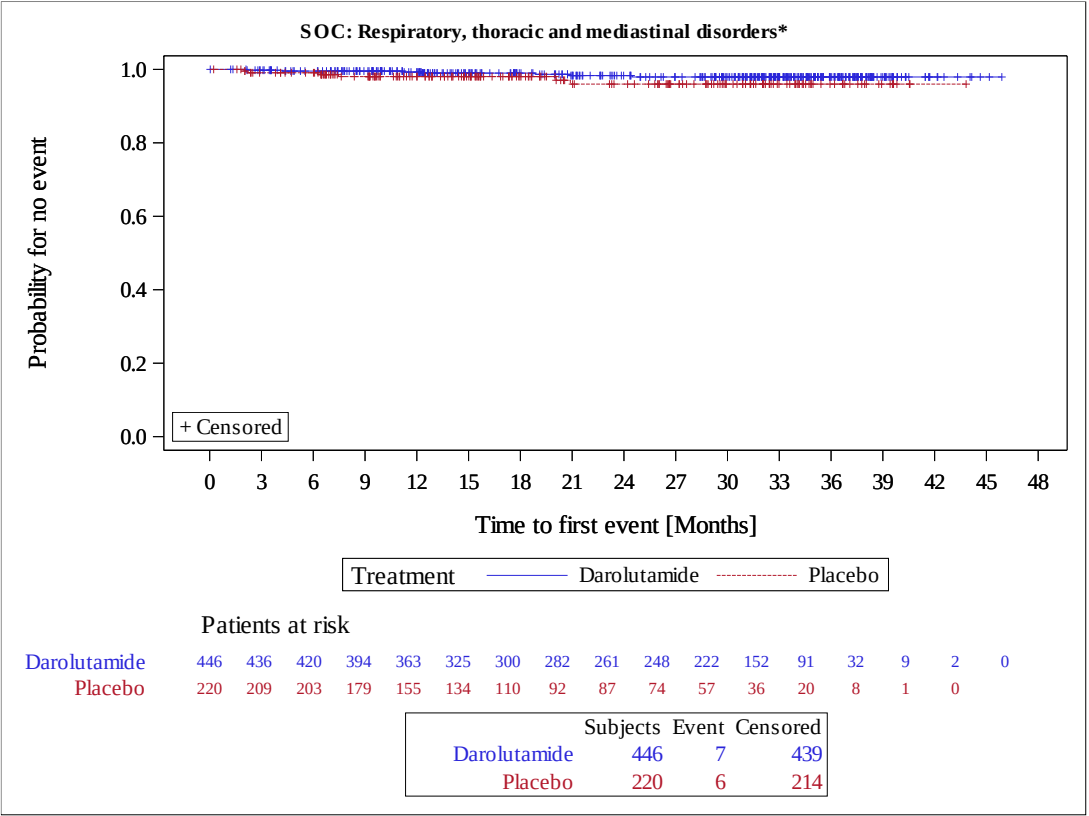


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC / PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Study population
Figure 3.3.2.2
Kaplan-Meier Plot of Time to First Frequent Serious Adverse Event by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC / PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Blood and lymphatic system disorders	Number of subjects with events, n (%)	20 (4.5)	10 (4.5)
	Number of censored subjects, n (%)	426 (95.5)	210 (95.5)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.820	
	95% CI	0.383, 1.757	
	p-value	0.6095	
	Odds Ratio	0.986	
	95% CI	0.453, 2.144	
	p-value	0.9715	
	Relative Risk	0.987	
	95% CI	0.470, 2.071	
	p-value	0.9714	
	Risk Difference	-0.061	
	95% CI	-3.418, 3.295	
	p-value	0.9715	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

Bayer CONFIDENTIAL database cut-off date: 10JAN2025 date of table generation: 25APR2025

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Blood and lymphatic system disorders - PT:Anaemia	Number of subjects with events, n (%)	16 (3.6)	8 (3.6)
	Number of censored subjects, n (%)	430 (96.4)	212 (96.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.834	
	95% CI	0.356, 1.954	
	p-value	0.6762	
	Odds Ratio	0.986	
	95% CI	0.415, 2.341	
	p-value	0.9746	
	Relative Risk	0.987	
	95% CI	0.429, 2.270	
	p-value	0.9746	
	Risk Difference	-0.049	
	95% CI	-3.065, 2.967	
	p-value	0.9746	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Cardiac disorders	Number of subjects with events, n (%)	12 (2.7)	6 (2.7)
	Number of censored subjects, n (%)	434 (97.3)	214 (97.3)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.852	
	95% CI	0.319, 2.274	
	p-value	0.7488	
	Odds Ratio	0.986	
	95% CI	0.365, 2.664	
	p-value	0.9781	
	Relative Risk	0.987	
	95% CI	0.375, 2.594	
	p-value	0.9781	
	Risk Difference	-0.037	
	95% CI	-2.661, 2.588	
	p-value	0.9781	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

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Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Gastrointestinal disorders*		
Number of subjects with events, n (%)	6 (1.3)	9 (4.1)
Number of censored subjects, n (%)	440 (98.7)	211 (95.9)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.281	
95% CI	0.100, 0.792	
p-value	0.0104	
Odds Ratio	0.320	
95% CI	0.112, 0.910	
p-value	0.0326	
Relative Risk	0.329	
95% CI	0.119, 0.912	
p-value	0.0326	
Risk Difference	-2.746	
95% CI	-5.573, 0.082	
p-value	0.0570	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: General disorders and administration site conditions	Number of subjects with events, n (%)	11 (2.5)	9 (4.1)
	Number of censored subjects, n (%)	435 (97.5)	211 (95.9)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.475	
	95% CI	0.196, 1.151	
	p-value	0.0921	
	Odds Ratio	0.593	
	95% CI	0.242, 1.453	
	p-value	0.2529	
	Relative Risk	0.603	
	95% CI	0.254, 1.433	
	p-value	0.2521	
	Risk Difference	-1.625	
	95% CI	-4.612, 1.363	
	p-value	0.2865	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)		Placebo (N=220)	
SOC: Infections and infestations	Number of subjects with events, n (%)	32 (7.2)		10 (4.5)	
	Number of censored subjects, n (%)	414 (92.8)		210 (95.5)	
	Time to Event (Month)				
	25%-ile (95%-CI)	NE (NE, NE)		NE (38.7, NE)	
	Median (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	75%-ile (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	Unstratified Analysis				
	Hazard Ratio	1.323			
	95% CI	0.649, 2.698			
	p-value	0.4394			
	Odds Ratio	1.623			
	95% CI	0.783, 3.366			
	p-value	0.1929			
	Relative Risk	1.578			
	95% CI	0.791, 3.152			
	p-value	0.1957			
	Risk Difference	2.629			
	95% CI	-1.019, 6.278			
	p-value	0.1578			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Injury, poisoning and procedural complications*	Number of subjects with events, n (%)	10 (2.2)	6 (2.7)
	Number of censored subjects, n (%)	436 (97.8)	214 (97.3)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.657	
	95% CI	0.238, 1.817	
	p-value	0.4154	
	Odds Ratio	0.818	
	95% CI	0.293, 2.281	
	p-value	0.7010	
	Relative Risk	0.822	
	95% CI	0.303, 2.233	
	p-value	0.7008	
	Risk Difference	-0.485	
	95% CI	-3.039, 2.068	
	p-value	0.7096	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
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Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Investigations	Number of subjects with events, n (%)	26 (5.8)	10 (4.5)
	Number of censored subjects, n (%)	420 (94.2)	210 (95.5)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.035	
	95% CI	0.498, 2.152	
	p-value	0.9261	
	Odds Ratio	1.300	
	95% CI	0.615, 2.746	
	p-value	0.4917	
	Relative Risk	1.283	
	95% CI	0.630, 2.612	
	p-value	0.4929	
	Risk Difference	1.284	
	95% CI	-2.224, 4.792	
	p-value	0.4731	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Investigations - PT:Aspartate aminotransferase increased	Number of subjects with events, n (%)	10 (2.2)	2 (0.9)
	Number of censored subjects, n (%)	436 (97.8)	218 (99.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.950	
	95% CI	0.426, 8.929	
	p-value	0.3811	
	Odds Ratio	2.500	
	95% CI	0.543, 11.509	
	p-value	0.2395	
	Relative Risk	2.466	
	95% CI	0.545, 11.160	
	p-value	0.2412	
	Risk Difference	1.333	
	95% CI	-0.527, 3.193	
	p-value	0.1602	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

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Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

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Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Investigations - PT:Weight increased*		
Number of subjects with events, n (%)	4 (0.9)	2 (0.9)
Number of censored subjects, n (%)	442 (99.1)	218 (99.1)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.807	
95% CI	0.147, 4.425	
p-value	0.8048	
Odds Ratio	0.986	
95% CI	0.179, 5.427	
p-value	0.9875	
Relative Risk	0.987	
95% CI	0.182, 5.345	
p-value	0.9875	
Risk Difference	-0.012	
95% CI	-1.541, 1.517	
p-value	0.9875	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
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Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Metabolism and nutrition disorders	Number of subjects with events, n (%)	13 (2.9)	5 (2.3)
	Number of censored subjects, n (%)	433 (97.1)	215 (97.7)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.065	
	95% CI	0.378, 2.999	
	p-value	0.9057	
	Odds Ratio	1.291	
	95% CI	0.454, 3.668	
	p-value	0.6317	
	Relative Risk	1.283	
	95% CI	0.463, 3.552	
	p-value	0.6321	
	Risk Difference	0.642	
	95% CI	-1.871, 3.155	
	p-value	0.6165	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

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Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

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Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Musculoskeletal and connective tissue disorders	Number of subjects with events, n (%)	31 (7.0)	13 (5.9)
	Number of censored subjects, n (%)	415 (93.0)	207 (94.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.001	
	95% CI	0.523, 1.917	
	p-value	0.9983	
	Odds Ratio	1.189	
	95% CI	0.609, 2.322	
	p-value	0.6112	
	Relative Risk	1.176	
	95% CI	0.628, 2.202	
	p-value	0.6119	
	Risk Difference	1.042	
	95% CI	-2.867, 4.950	
	p-value	0.6015	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Musculoskeletal and connective tissue disorders - PT:Back pain*	Number of subjects with events, n (%)	5 (1.1)	2 (0.9)
	Number of censored subjects, n (%)	441 (98.9)	218 (99.1)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.078	
	95% CI	0.209, 5.572	
	p-value	0.9282	
	Odds Ratio	1.236	
	95% CI	0.238, 6.421	
	p-value	0.8012	
	Relative Risk	1.233	
	95% CI	0.241, 6.306	
	p-value	0.8012	
	Risk Difference	0.212	
	95% CI	-1.378, 1.802	
	p-value	0.7938	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)		Placebo (N=220)	
SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Number of subjects with events, n (%)	10 (2.2)		3 (1.4)	
	Number of censored subjects, n (%)	436 (97.8)		217 (98.6)	
	Time to Event (Month)				
	25%-ile (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	Median (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	75%-ile (95%-CI)	NE (NE, NE)		NE (NE, NE)	
	Unstratified Analysis				
	Hazard Ratio	1.417			
	95% CI	0.389, 5.160			
	p-value	0.5952			
	Odds Ratio	1.659			
	95% CI	0.452, 6.090			
	p-value	0.4455			
	Relative Risk	1.644			
	95% CI	0.457, 5.914			
	p-value	0.4464			
	Risk Difference	0.879			
	95% CI	-1.180, 2.937			
	p-value	0.4028			

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Nervous system disorders	Number of subjects with events, n (%)	15 (3.4)	10 (4.5)
	Number of censored subjects, n (%)	431 (96.6)	210 (95.5)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.609	
	95% CI	0.273, 1.361	
	p-value	0.2222	
	Odds Ratio	0.731	
	95% CI	0.323, 1.654	
	p-value	0.4519	
	Relative Risk	0.740	
	95% CI	0.338, 1.620	
	p-value	0.4512	
	Risk Difference	-1.182	
	95% CI	-4.403, 2.039	
	p-value	0.4719	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Renal and urinary disorders	Number of subjects with events, n (%)	20 (4.5)	8 (3.6)
	Number of censored subjects, n (%)	426 (95.5)	212 (96.4)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	1.091	
	95% CI	0.480, 2.480	
	p-value	0.8349	
	Odds Ratio	1.244	
	95% CI	0.539, 2.871	
	p-value	0.6087	
	Relative Risk	1.233	
	95% CI	0.552, 2.755	
	p-value	0.6093	
	Risk Difference	0.848	
	95% CI	-2.284, 3.980	
	p-value	0.5956	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Renal and urinary disorders - PT:Urinary retention*		
Number of subjects with events, n (%)	2 (0.4)	1 (0.5)
Number of censored subjects, n (%)	444 (99.6)	219 (99.5)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	0.940	
95% CI	0.085, 10.370	
p-value	0.9595	
Odds Ratio	0.986	
95% CI	0.089, 10.939	
p-value	0.9912	
Relative Risk	0.987	
95% CI	0.090, 10.821	
p-value	0.9912	
Risk Difference	-0.006	
95% CI	-1.090, 1.078	
p-value	0.9912	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1		Darolutamide (N=446)	Placebo (N=220)
SOC: Respiratory, thoracic and mediastinal disorders*	Number of subjects with events, n (%)	6 (1.3)	7 (3.2)
	Number of censored subjects, n (%)	440 (98.7)	213 (96.8)
	Time to Event (Month)		
	25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
	75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
	Unstratified Analysis		
	Hazard Ratio	0.332	
	95% CI	0.111, 0.992	
	p-value	0.0380	
	Odds Ratio	0.415	
	95% CI	0.138, 1.250	
	p-value	0.1179	
	Relative Risk	0.423	
	95% CI	0.144, 1.243	
	p-value	0.1177	
	Risk Difference	-1.837	
	95% CI	-4.390, 0.717	
	p-value	0.1587	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
N: Number of participants, CI: Confidence Interval, NE: Not estimable
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.
95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

BAY 1841788 / 21140 - 10JAN2025
Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Vascular disorders		
Number of subjects with events, n (%)	27 (6.1)	10 (4.5)
Number of censored subjects, n (%)	419 (93.9)	210 (95.5)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.153	
95% CI	0.557, 2.388	
p-value	0.7015	
Odds Ratio	1.353	
95% CI	0.643, 2.848	
p-value	0.4257	
Relative Risk	1.332	
95% CI	0.657, 2.702	
p-value	0.4272	
Risk Difference	1.508	
95% CI	-2.024, 5.040	
p-value	0.4026	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Study population
Table 3.3.3
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm)
(safety analysis set)

Final

System organ class (SOC) / Preferred term (PT) in MedDRA version 27.1	Darolutamide (N=446)	Placebo (N=220)
SOC: Vascular disorders - PT:Hypertension		
Number of subjects with events, n (%)	20 (4.5)	8 (3.6)
Number of censored subjects, n (%)	426 (95.5)	212 (96.4)
Time to Event (Month)		
25%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Median (95%-CI)	NE (NE, NE)	NE (NE, NE)
75%-ile (95%-CI)	NE (NE, NE)	NE (NE, NE)
Unstratified Analysis		
Hazard Ratio	1.064	
95% CI	0.468, 2.421	
p-value	0.8826	
Odds Ratio	1.244	
95% CI	0.539, 2.871	
p-value	0.6087	
Relative Risk	1.233	
95% CI	0.552, 2.755	
p-value	0.6093	
Risk Difference	0.848	
95% CI	-2.284, 3.980	
p-value	0.5956	

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

N: Number of participants, CI: Confidence Interval, NE: Not estimable

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Odds Ratio, Relative Risk, Risk Difference were constructed using proc freq. In case of zero frequencies 0.5 is added to every cell as correction.

95% CI for Odds Ratio, Relative Risk, Risk Difference were constructed using normal approximation (Wald). P-values for Odds Ratio, Relative Risk, Risk Difference were calculated using Wald test.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Median in months based on Kaplan-Meier estimate. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model, without stratification. P-Value for hazard ratio from 2-sided log-rank test.

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Table 3.3.3.1
Summary of Frequent Adverse Events of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) - Subgroup analysis (safety analysis set)

Final

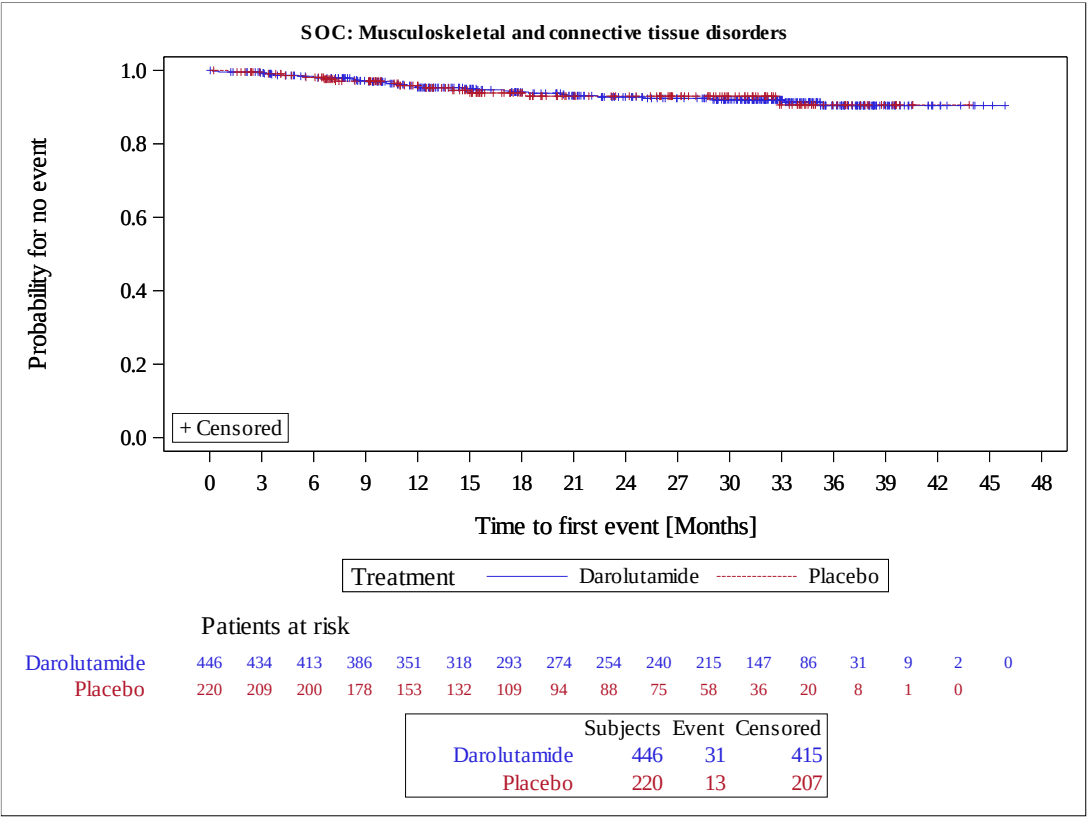
!!! There are no Observations for this Report !!!

Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug. After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm. N: Number of participants, N[s]: Number of participants in subgroup, CI: Confidence Interval, NE: Not estimable
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Hazard ratio with 95% Wald confidence interval was estimated by Cox regression model without stratification. P-Value for hazard ratio from 2-sided log-rank test.
p-Value for interaction from Cox proportional hazard model with treatment, subgroup and treatment by subgroup interaction as covariates.
Subgroup analysis was done for SOC's / PTs with significant overall treatment effect (significant log-rank test).
Effect measures are calculated if each subgroup level comprises at least 10 participants and at least 10 events occurred in one of the subgroup levels.
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Figure 3.3.3.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) (safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.
* SOC/PT is included in analysis due to indirect comparison versus TITAN.
Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.
Subgroup analysis was done for SOC / PTs with significant overall treatment effect (significant log-rank test).
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).
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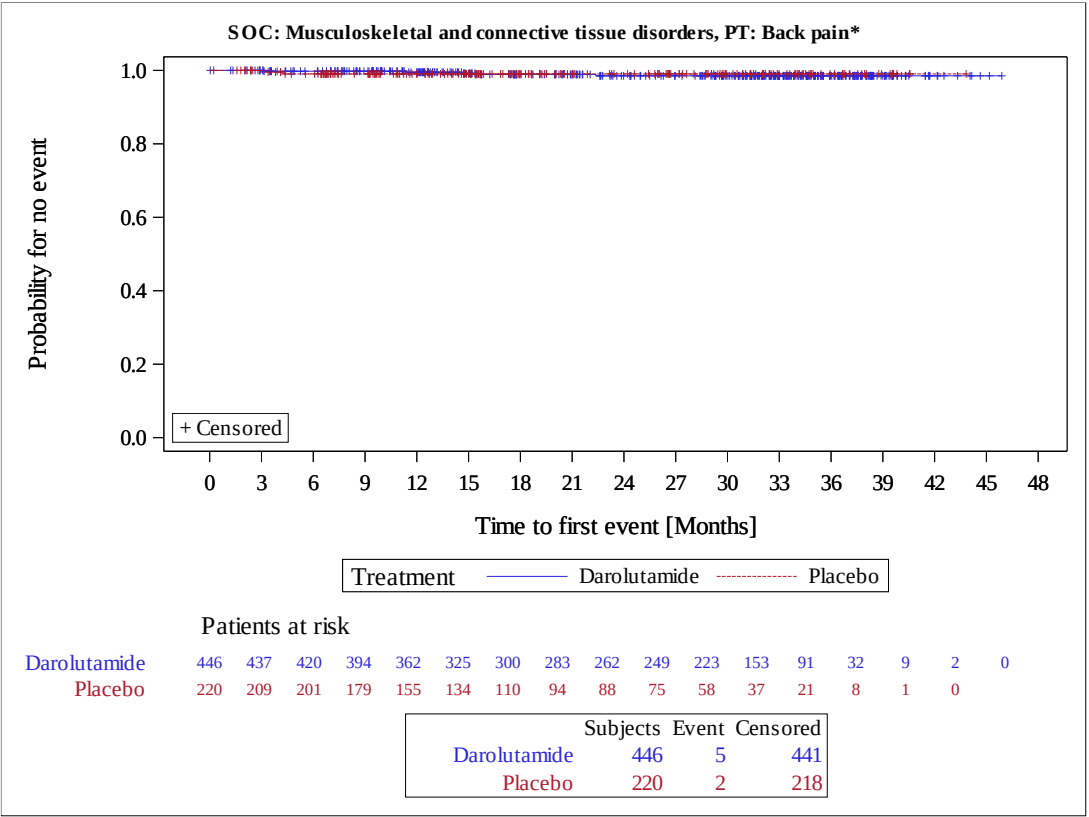
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Study population

Figure 3.3.3.2

Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) (safety analysis set)

Final



Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

After primary completion patients on study treatment (darolutamide or placebo) were offered to receive darolutamide through open-label treatment. There are 59 crossover participants in the placebo arm.

* SOC/PT is included in analysis due to indirect comparison versus TITAN.

Participants without events are censored at the study drug stop date plus 30 days, last known alive date, and cutoff date, whichever comes earlier.

Subgroup analysis was done for SOC / PTs with significant overall treatment effect (significant log-rank test).

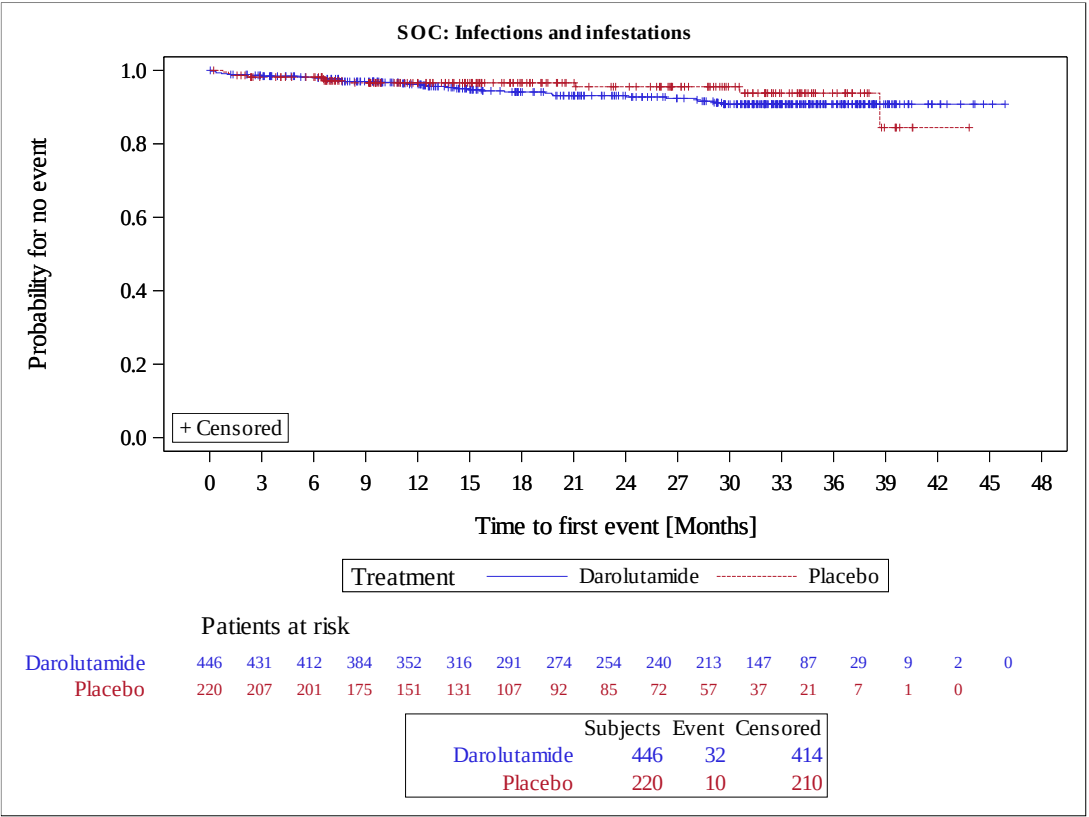
Kaplan-Meier Plots for subgroups are generated if p-value for interaction is significant (alpha<=0.05).

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Figure 3.3.3.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) (safety analysis set)

Final

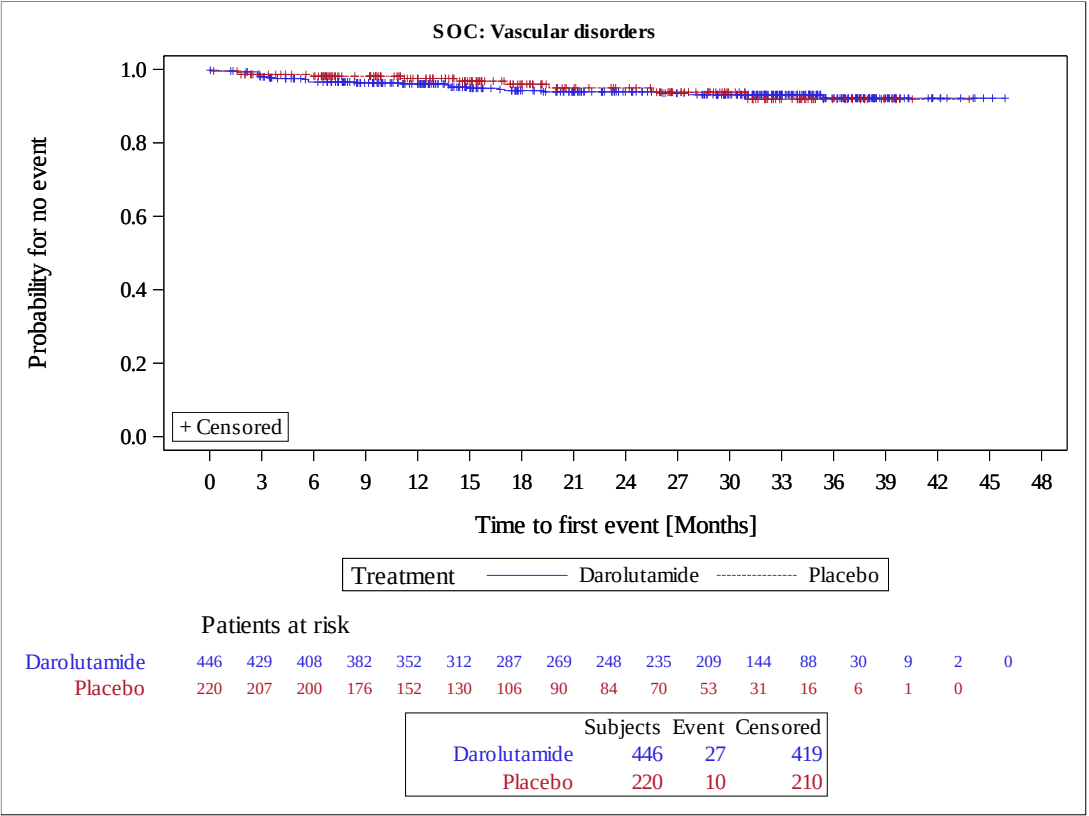


Analysis based on Treatment-Emergent Adverse Events (TEAEs). TEAEs are defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.
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Figure 3.3.3.2
Kaplan-Meier Plot of Time to First Frequent Adverse Event of CTCAE Grade >=3 by SOC and PT (incidence in either arm >= 5% or both incidence >=1% and >=10 participants affected in either arm) (safety analysis set)

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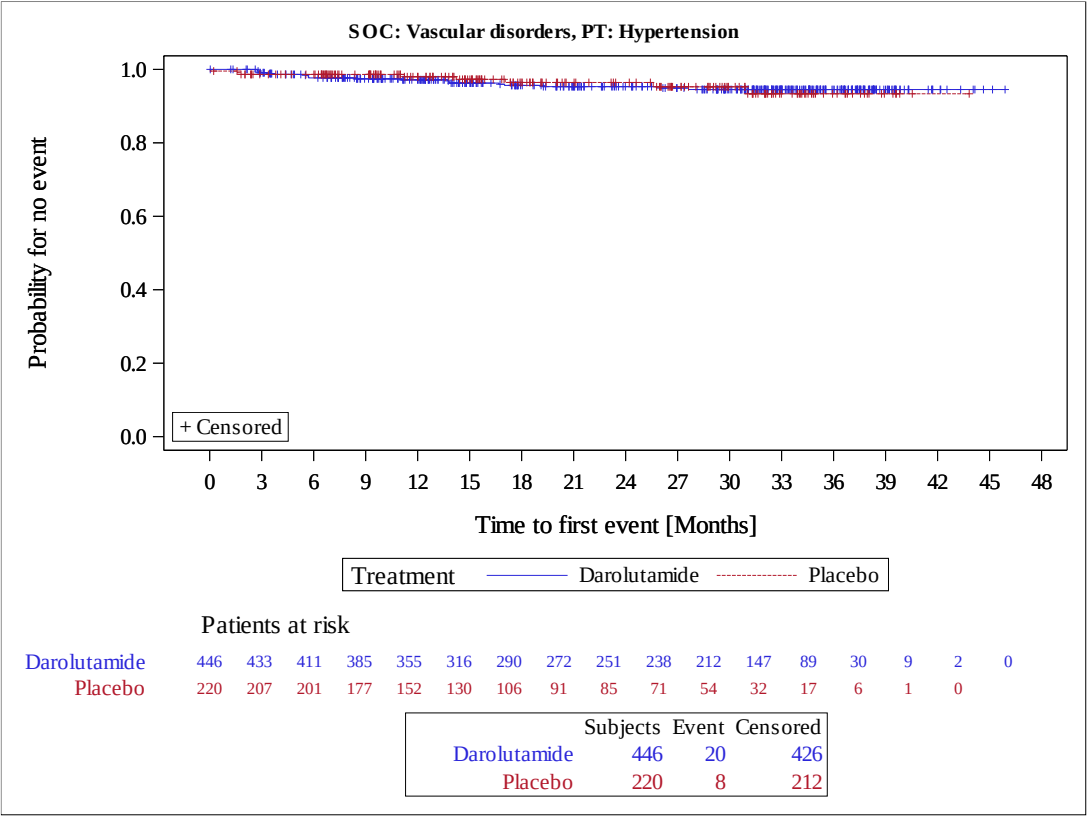
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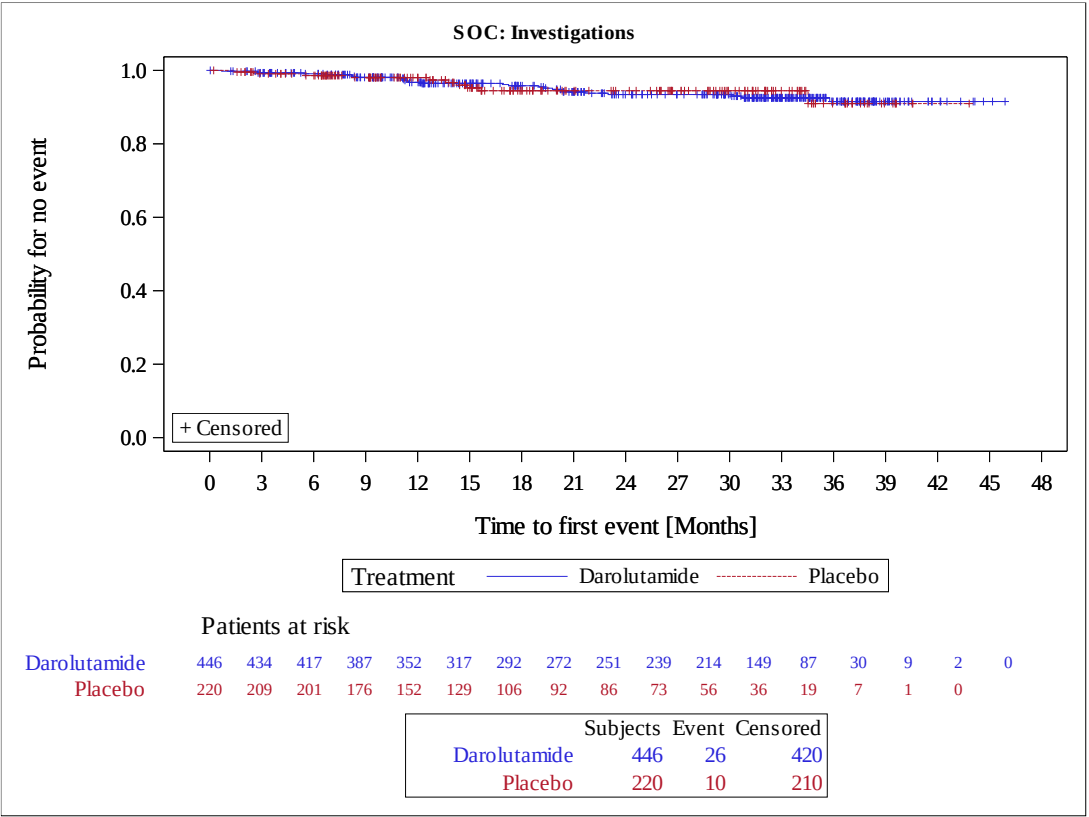
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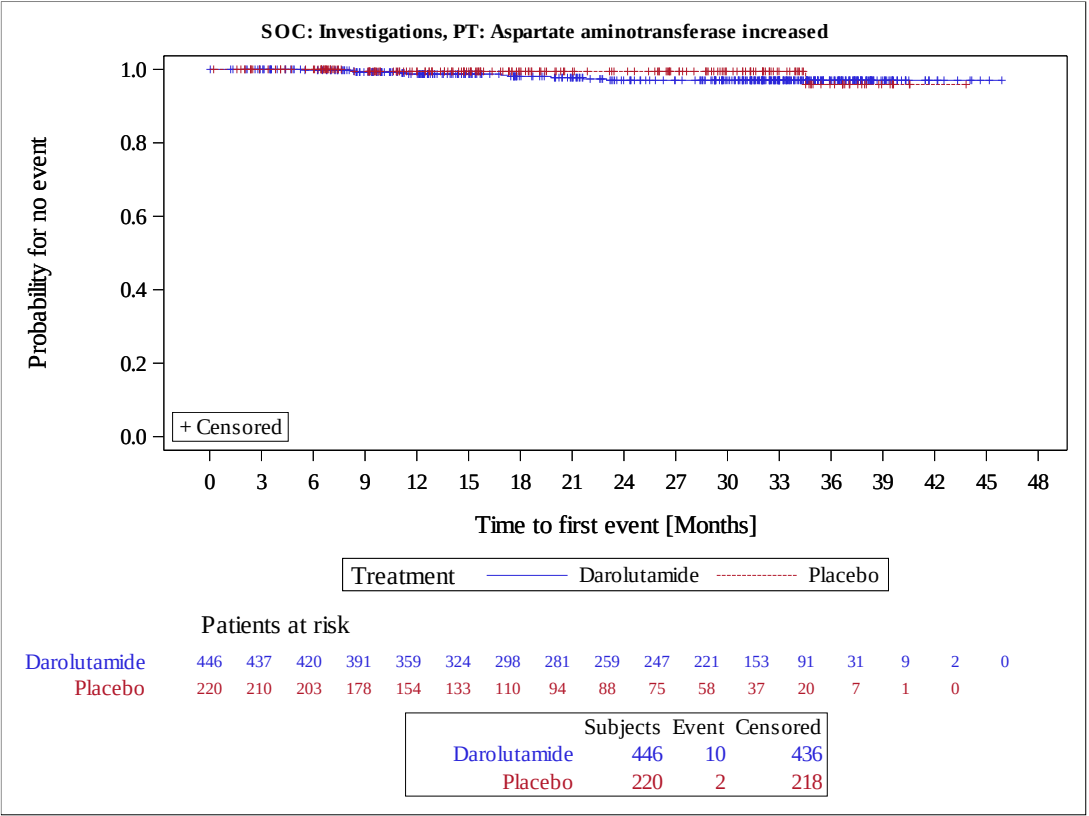


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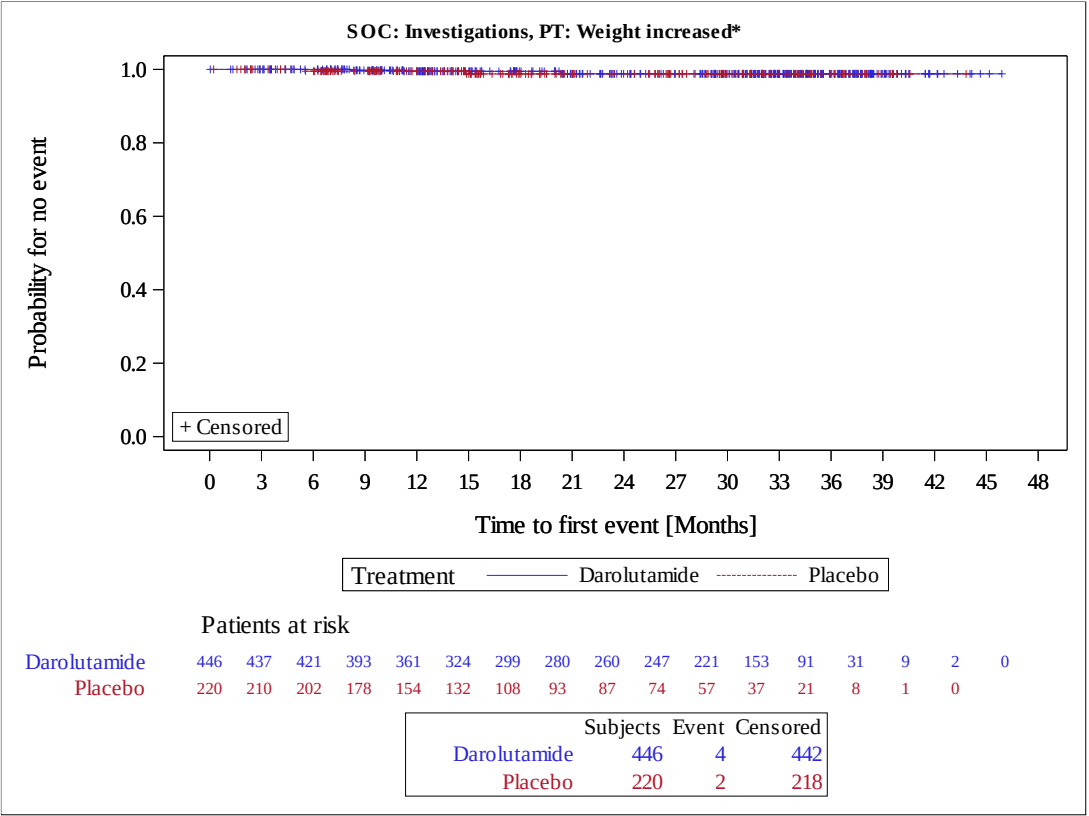
BAY 1841788 / 21140 - 10JAN2025

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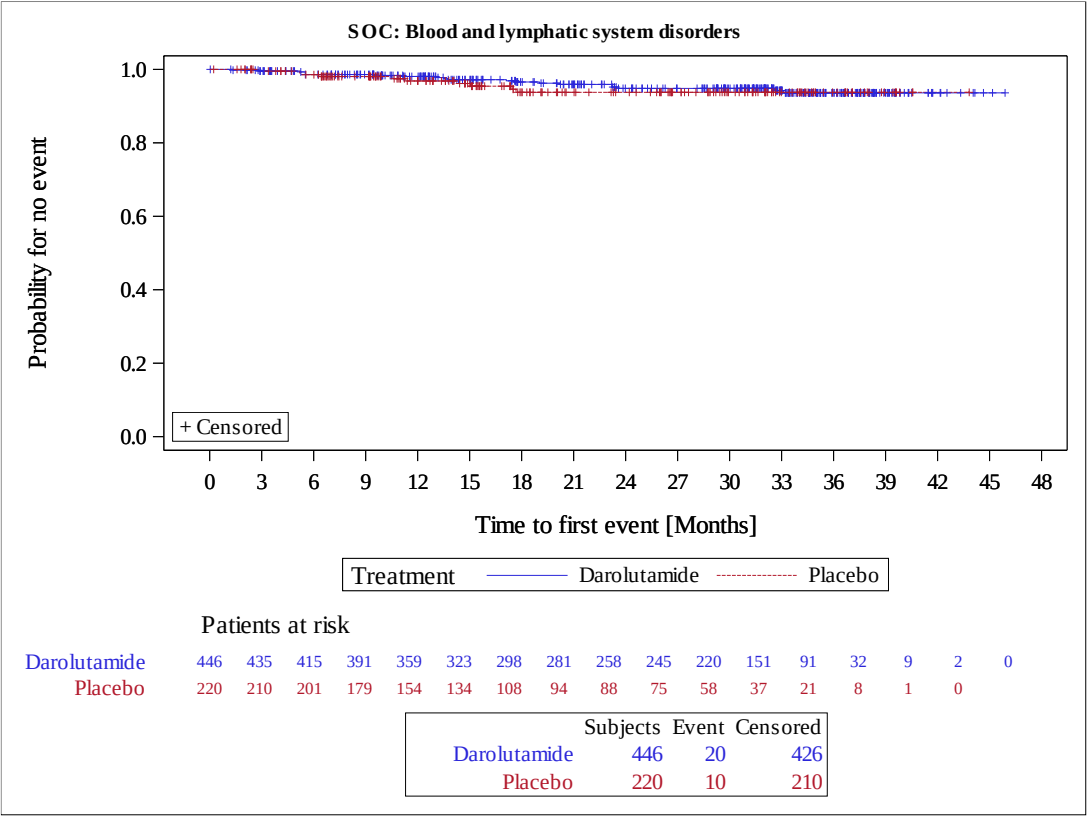
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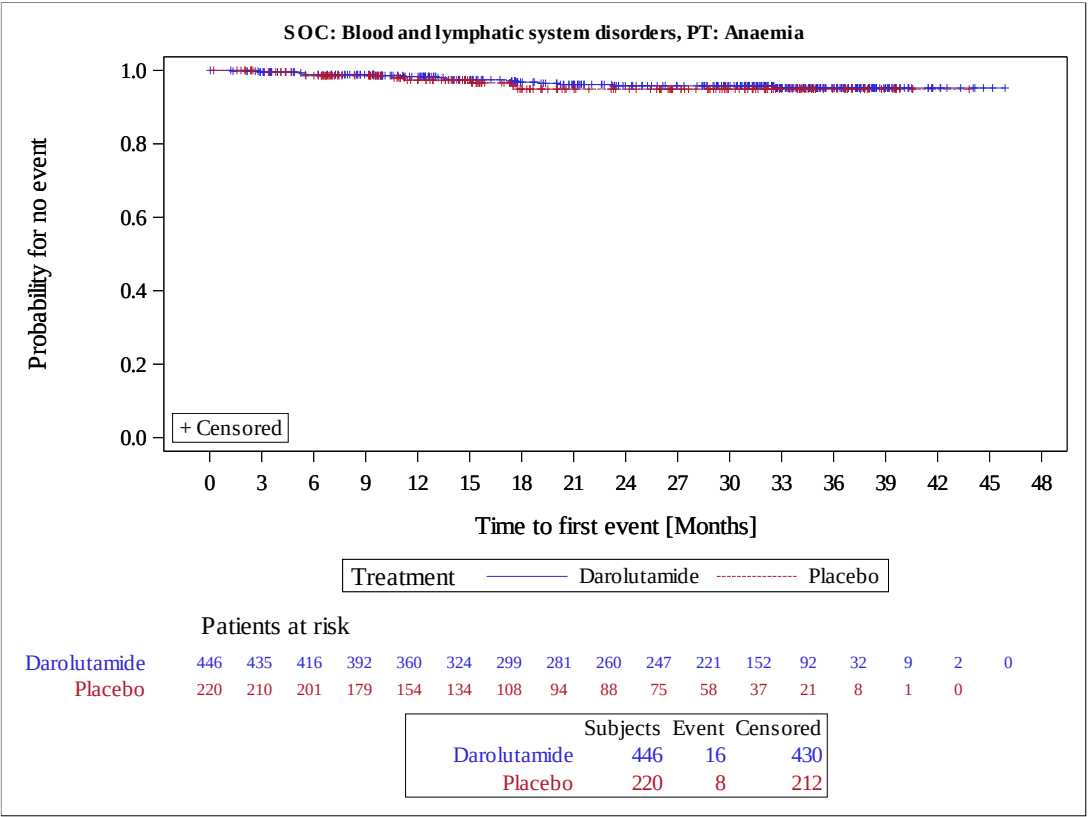


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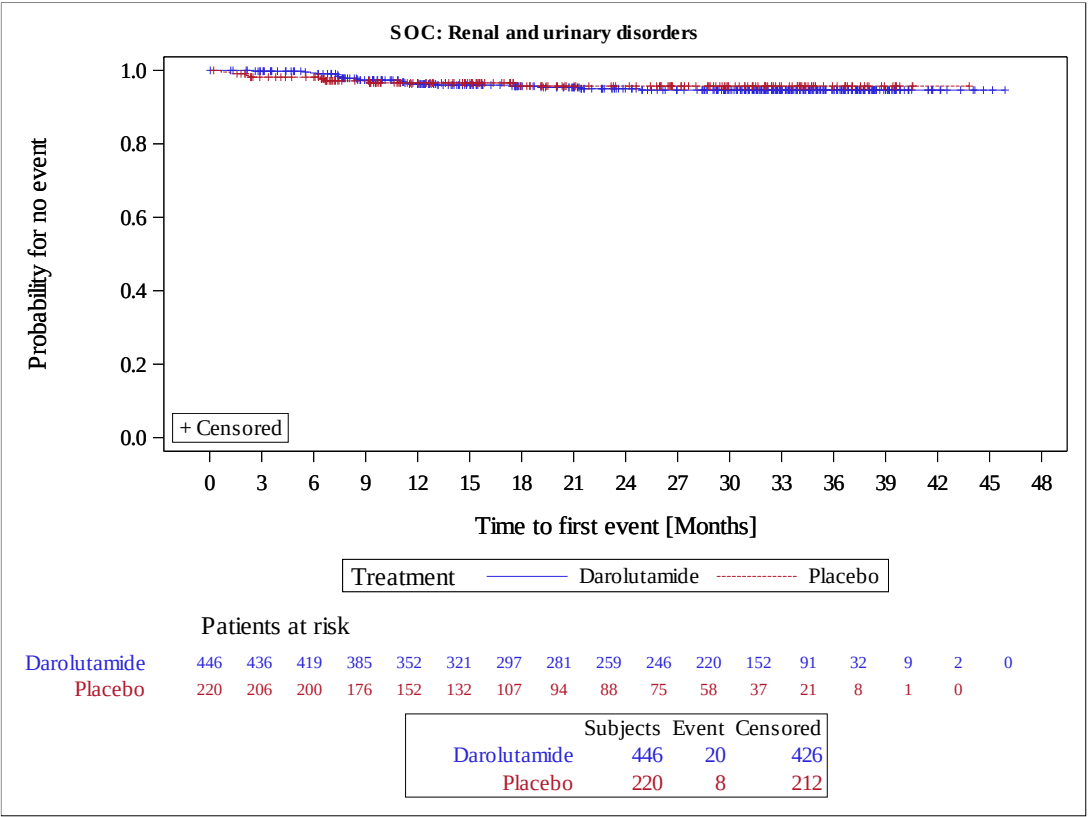


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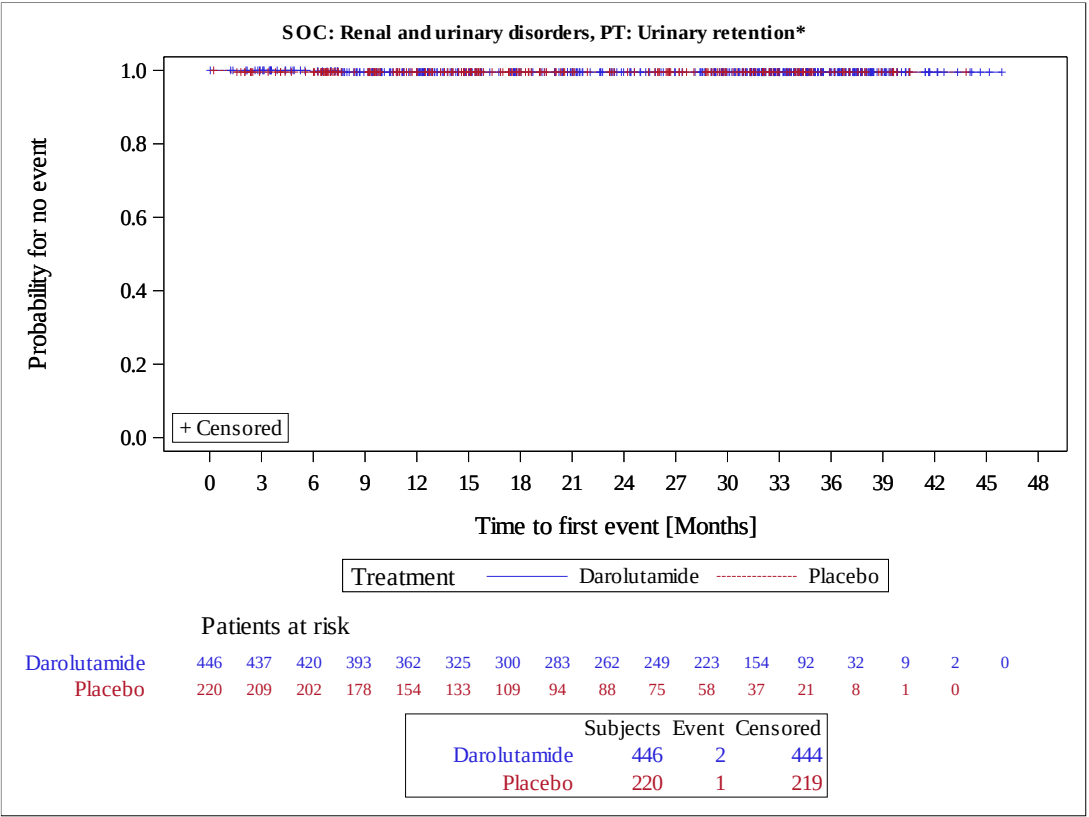
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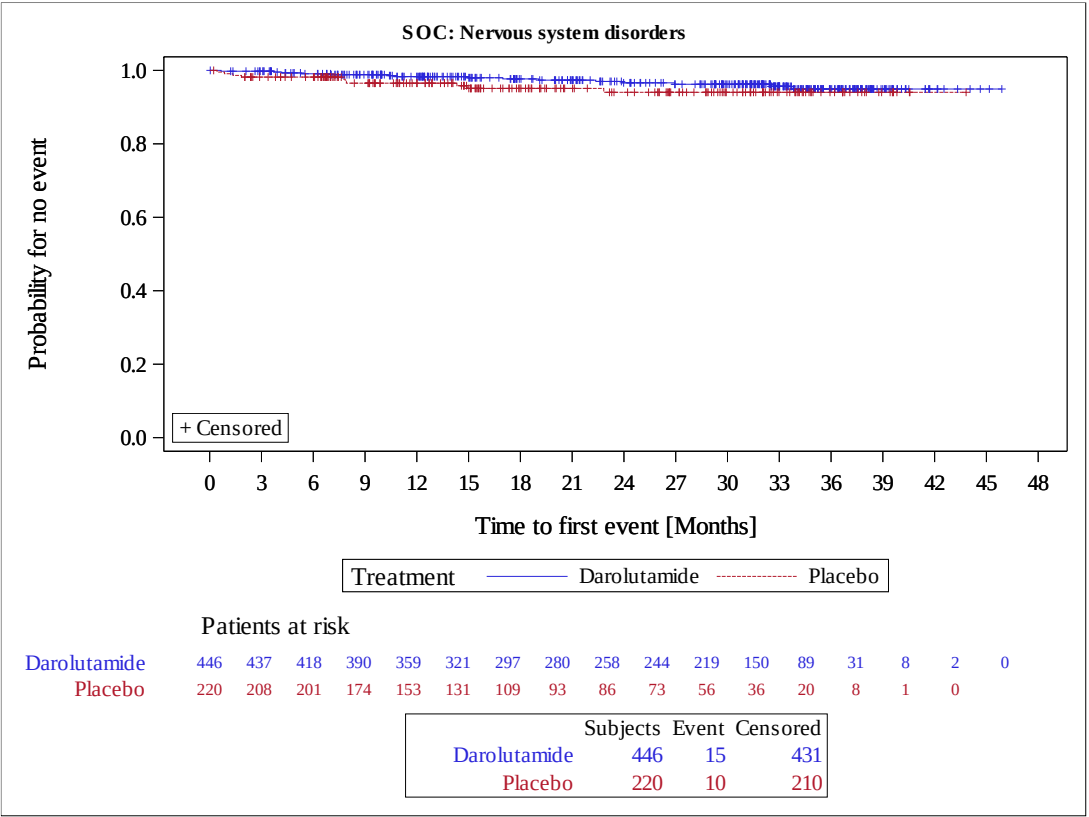
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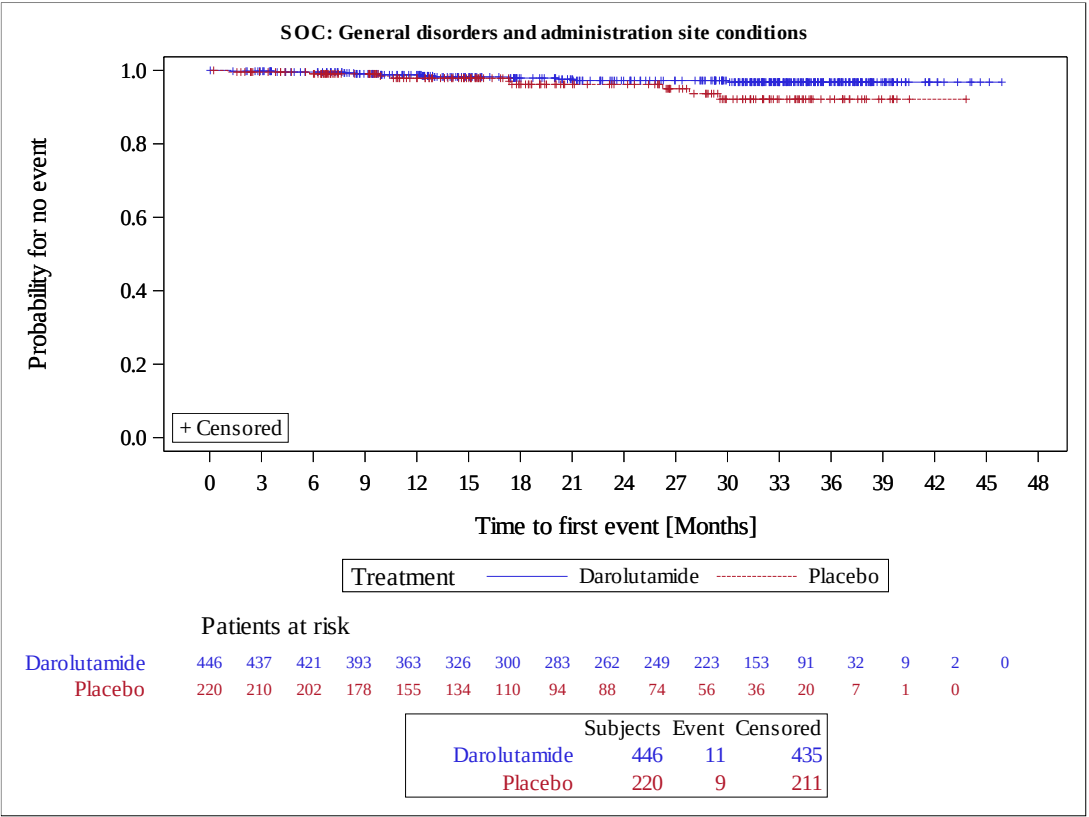


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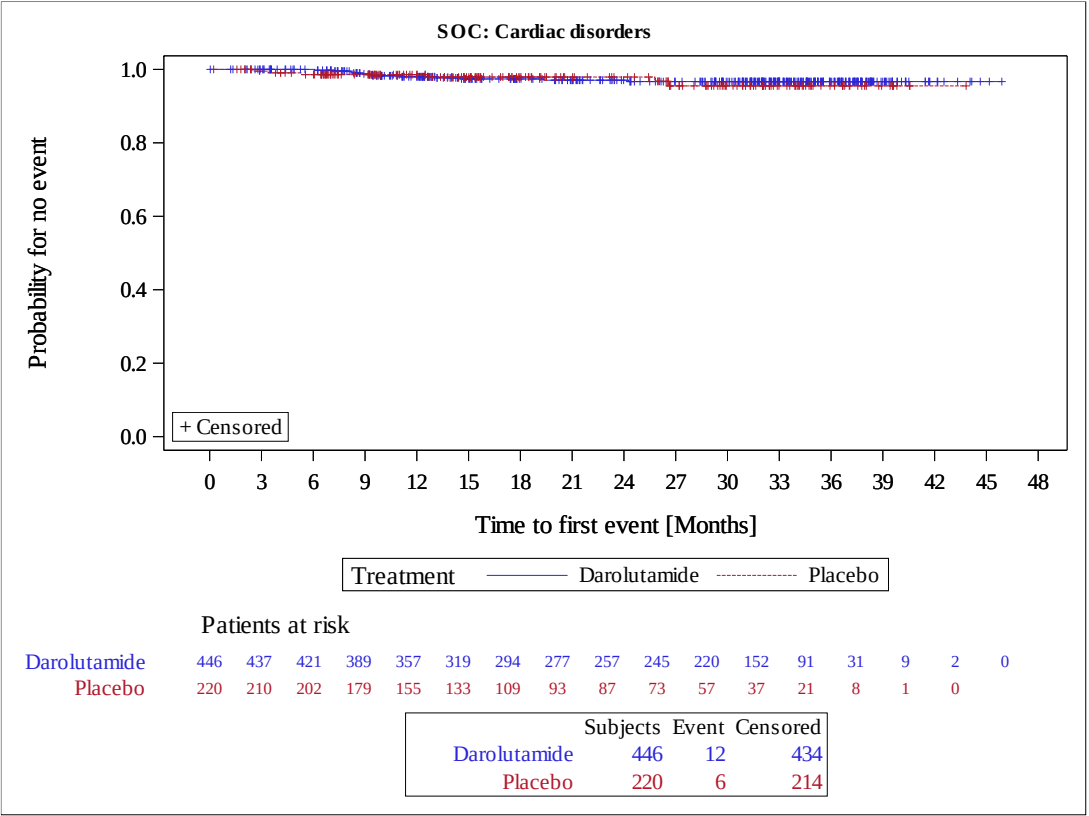


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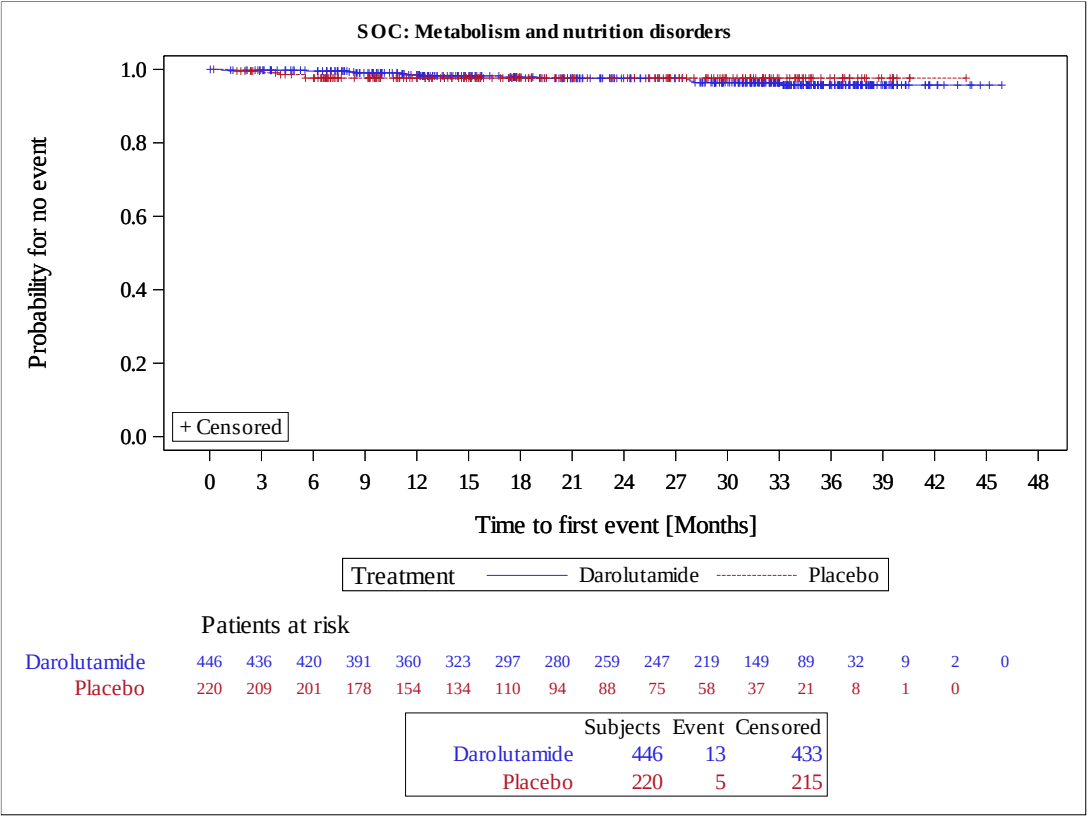


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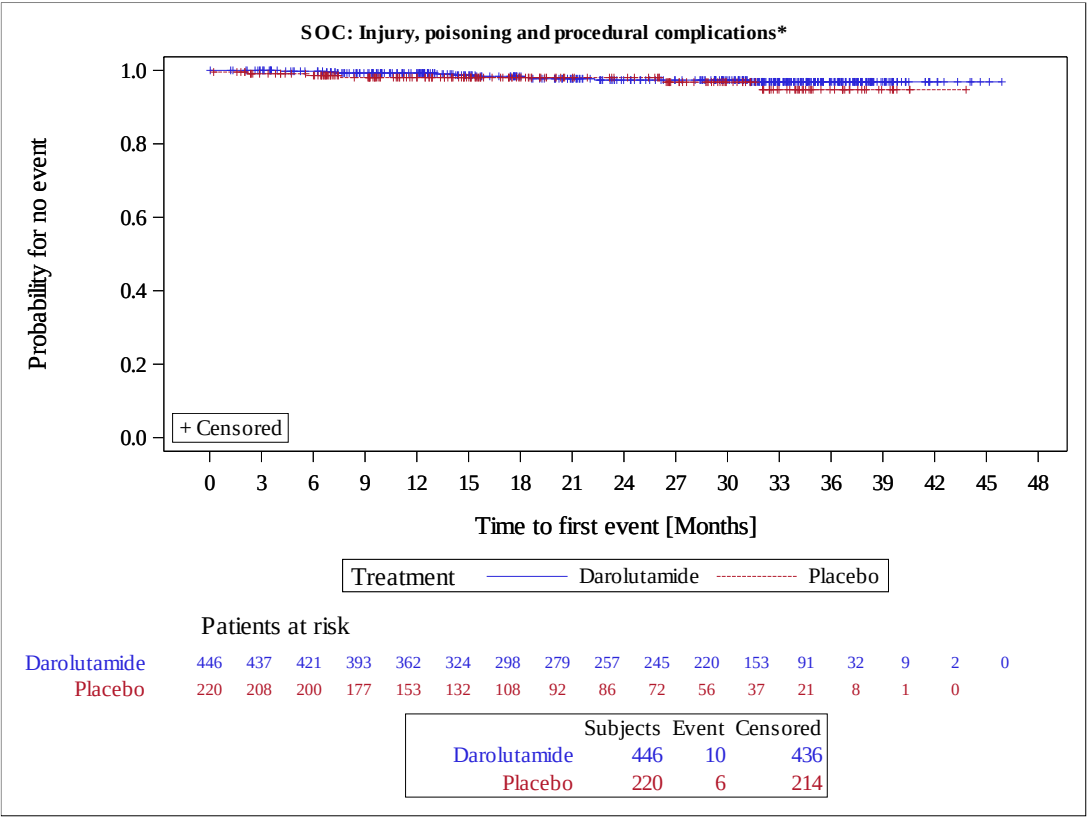


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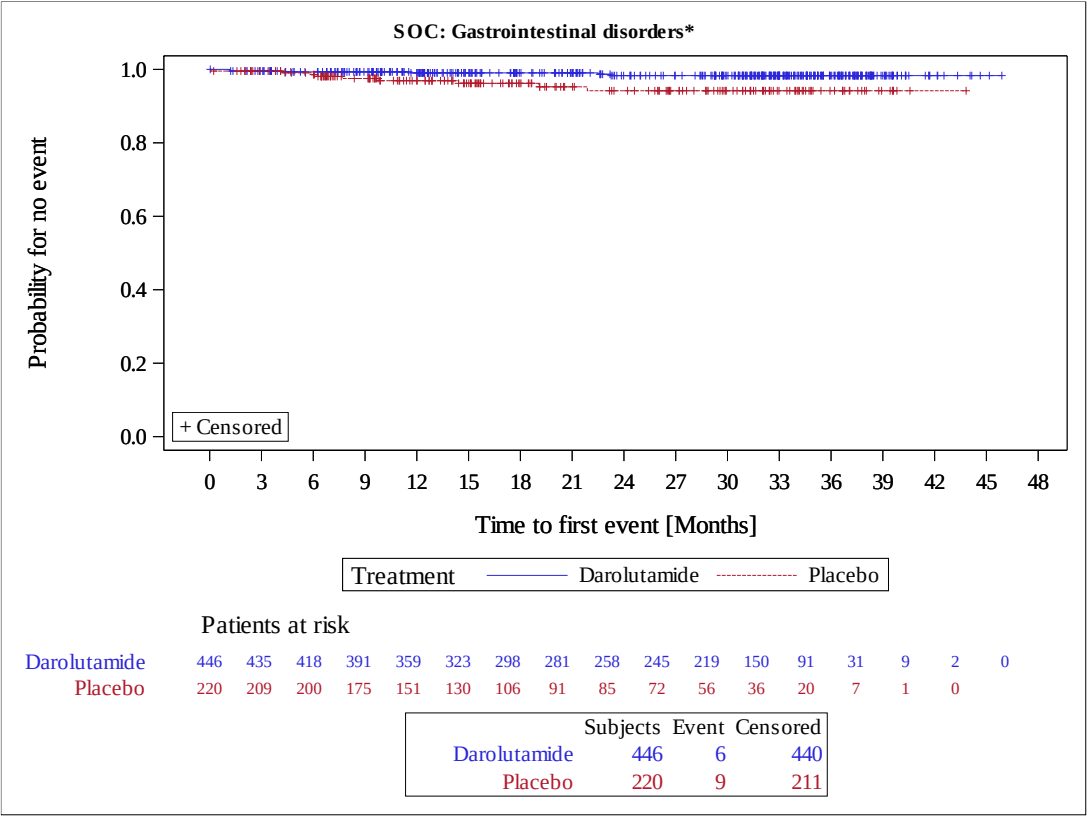
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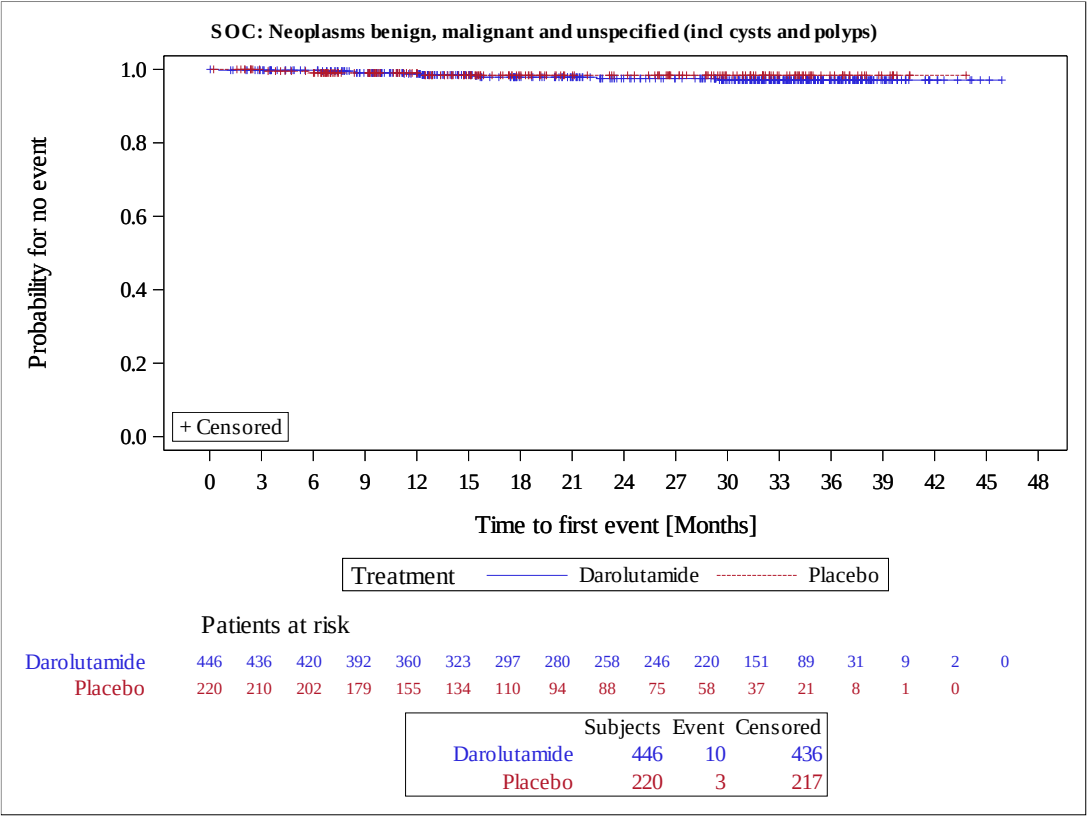
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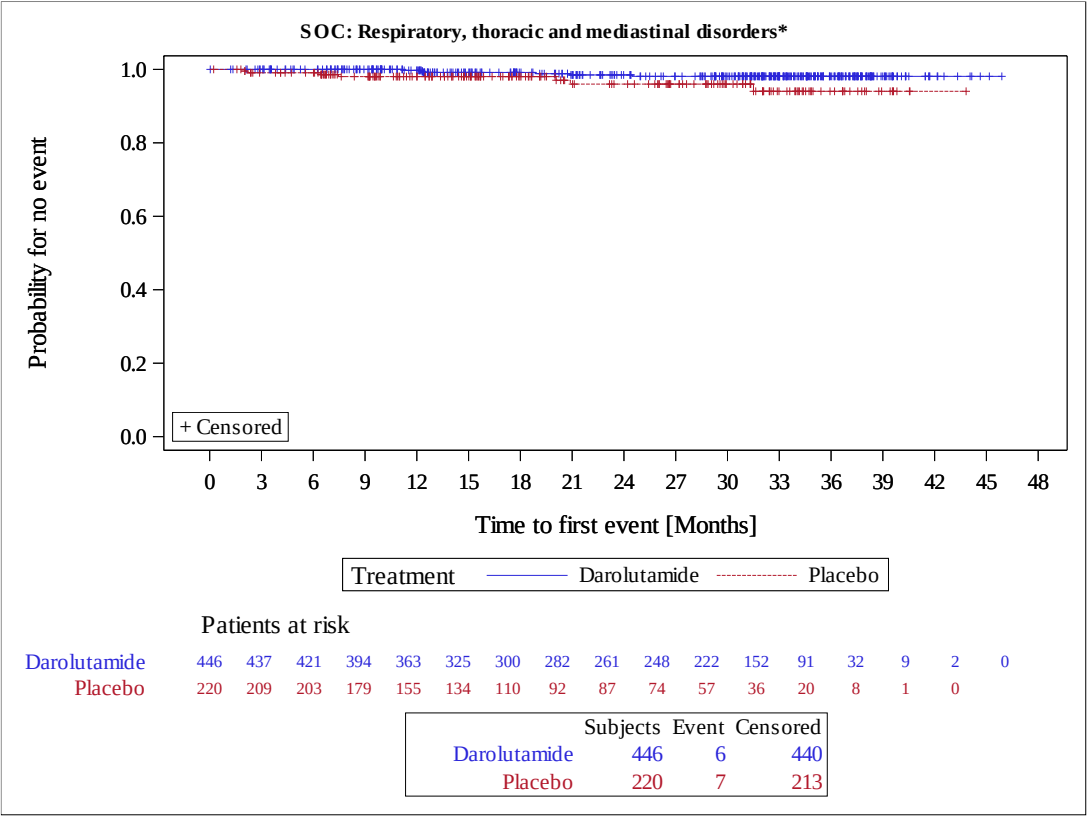
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Anhang 4-G3: Ergänzende Kaplan-Meier Kurven der RCT TITAN

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Dossier zur Nutzenbewertung – Modul 4 A

Stand: 24.02.2020

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

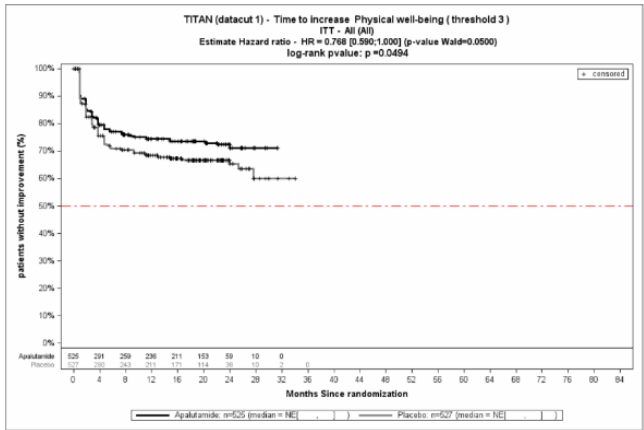


Abbildung 50: FACT-P (PWB; MCID 3) – Verbesserung

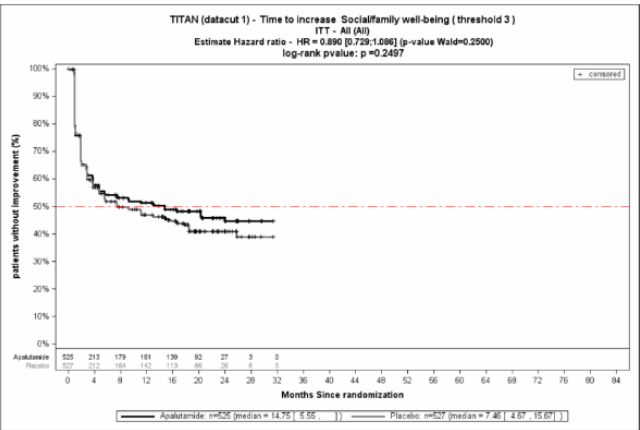


Abbildung 52: FACT-P (SFWB; MCID 3) – Verbesserung

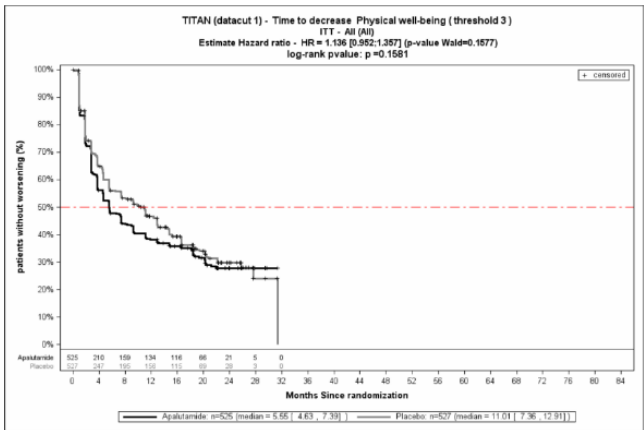


Abbildung 51: FACT-P (PWB; MCID 3) – Verschlechterung

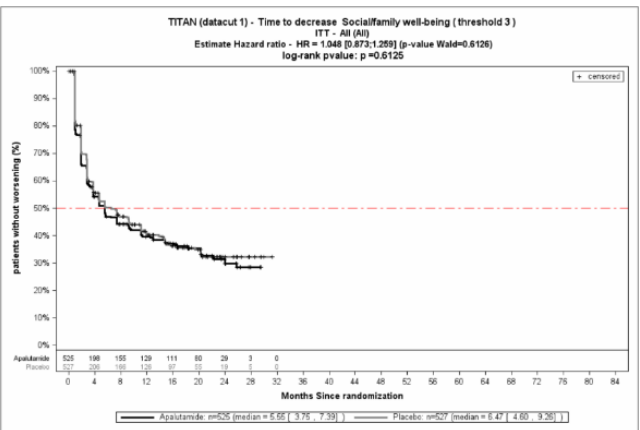


Abbildung 53: FACT-P (SFWB; MCID 3) – Verschlechterung

Dossier zur Nutzenbewertung – Modul 4 A

Stand: 24.02.2020

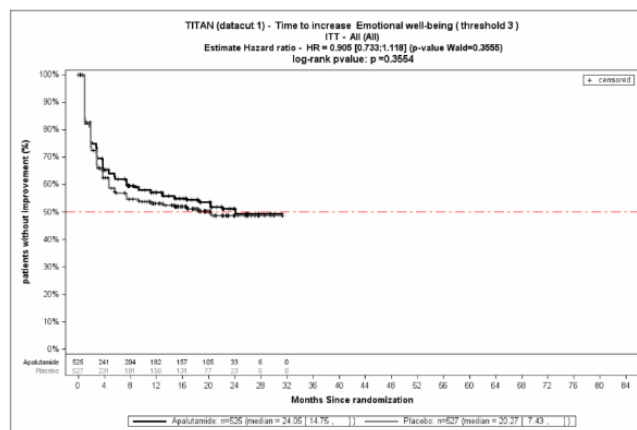


Abbildung 54: FACT-P (EWB; MCID 3) – Verbesserung

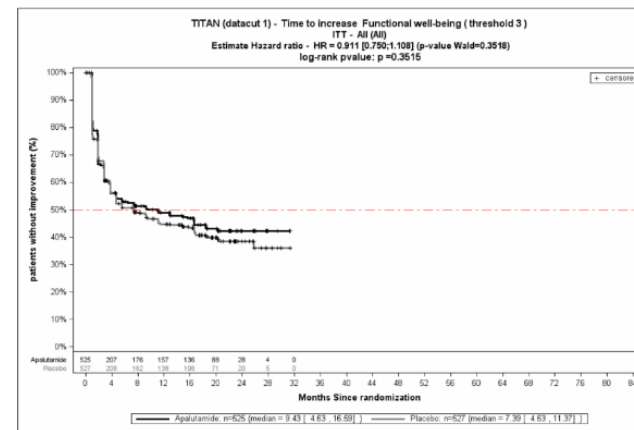


Abbildung 56: FACT-P (FWB; MCID 3) – Verbesserung

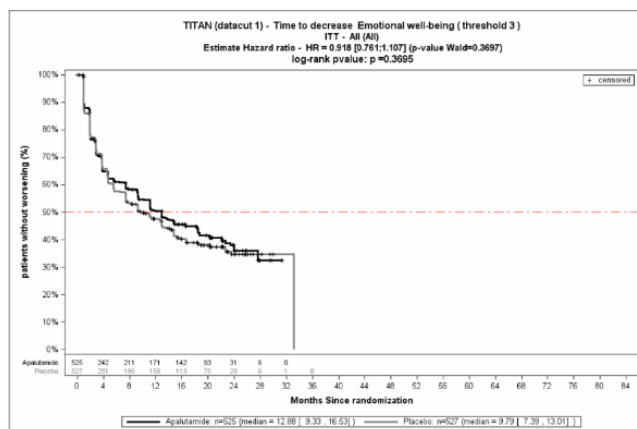


Abbildung 55: FACT-P (EWB; MCID 3) – Verschlechterung

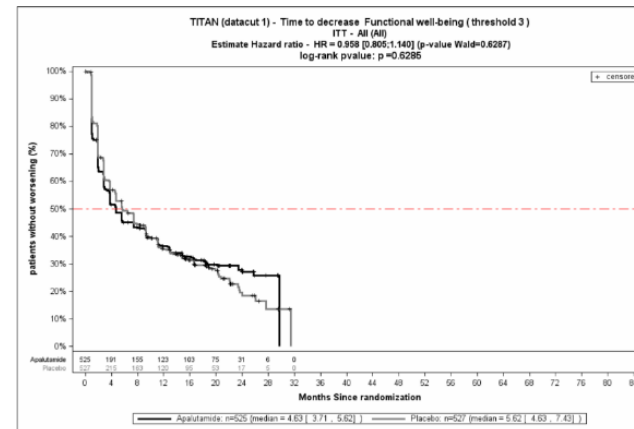


Abbildung 57: FACT-P (FWB; MCID 3) – Verschlechterung

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

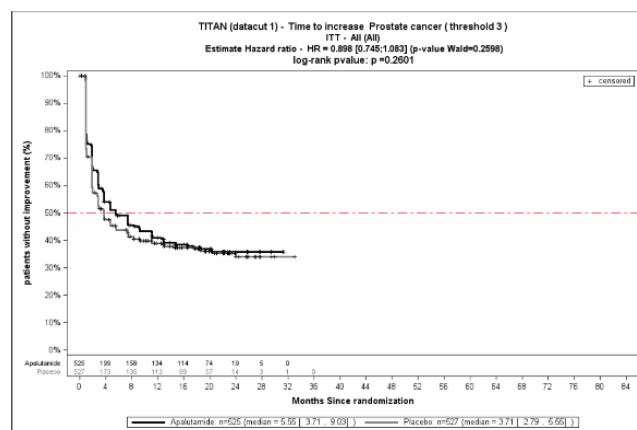


Abbildung 58: FACT-P (PCS; MCID 3) – Verbesserung

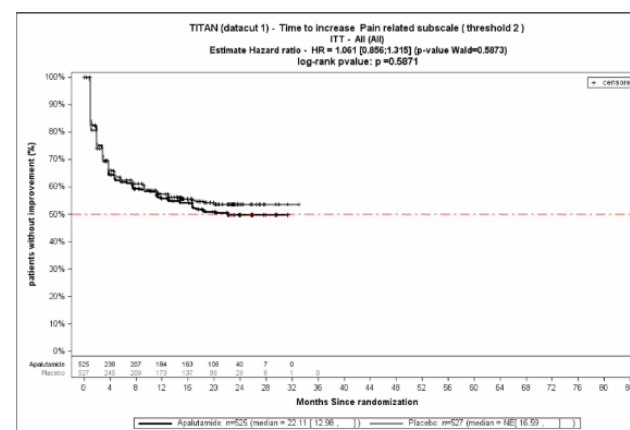


Abbildung 60: FACT-P (PRS; MCID 2) – Verbesserung

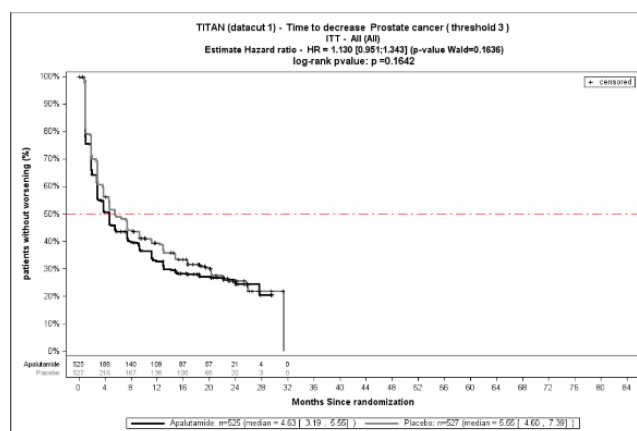


Abbildung 59: FACT-P (PCS; MCID 3) – Verschlechterung

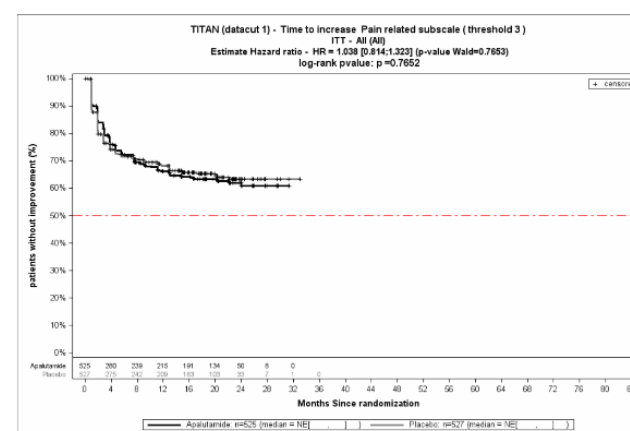


Abbildung 61: FACT-P (PRS; MCID 3) – Verbesserung

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Kaplan-Meier-Kurven

Im Folgenden werden für die TITAN Studie die Kaplan-Meier-Kurven der unerwünschten Ereignisse von speziellem Interesse dargestellt. Alle anderen Kaplan-Meier-Kurven der TITAN Studie sind in Abschnitt 4.3.1 dargestellt.

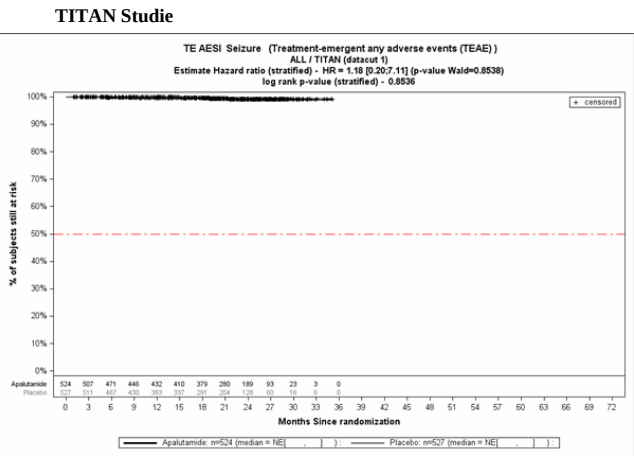


Abbildung 286 (Anhang): Kaplan-Meier-Kurve des unerwünschten Ereignisses von speziellem Interesse Krampfanfall – Jegliche unerwünschten Ereignisse aus TITAN

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Dossier zur Nutzenbewertung – Modul 4 A
Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

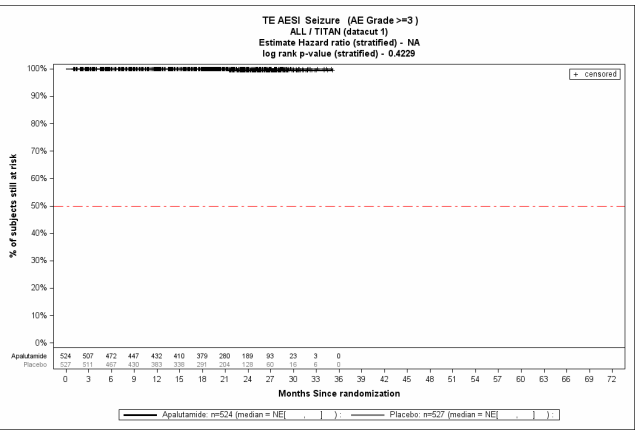


Abbildung 287 (Anhang): Kaplan-Meier-Kurve des unerwünschten Ereignisses von speziellem Interesse Krampfanfall – Schwere unerwünschte Ereignisse (CTCAE ≥ 3) aus TITAN

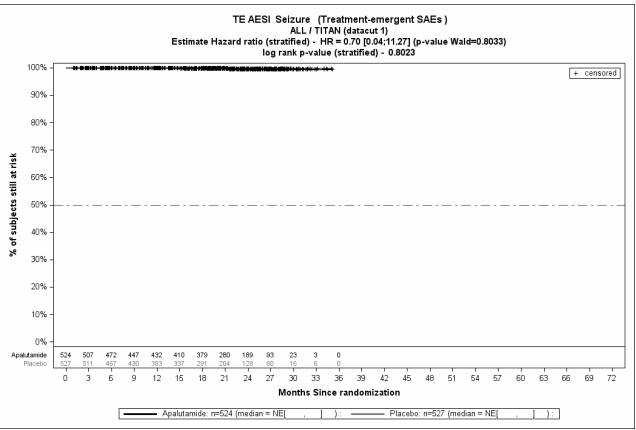


Abbildung 288 (Anhang): Kaplan-Meier-Kurve des unerwünschten Ereignisses von speziellem Interesse Krampfanfall – Schwerwiegende unerwünschte Ereignisse aus TITAN

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Dossier zur Nutzenbewertung – Modul 4 A
Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

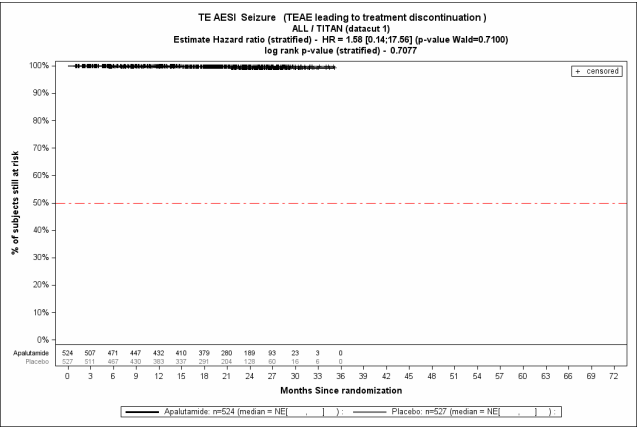


Abbildung 289 (Anhang): Kaplan-Meier-Kurve des unerwünschten Ereignisses von speziellem Interesse Krampfanfall – Unerwünschte Ereignisse, die zum Therapieabbruch der Studienmedikation führen aus TITAN

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Dossier zur Nutzenbewertung – Modul 4 A
Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

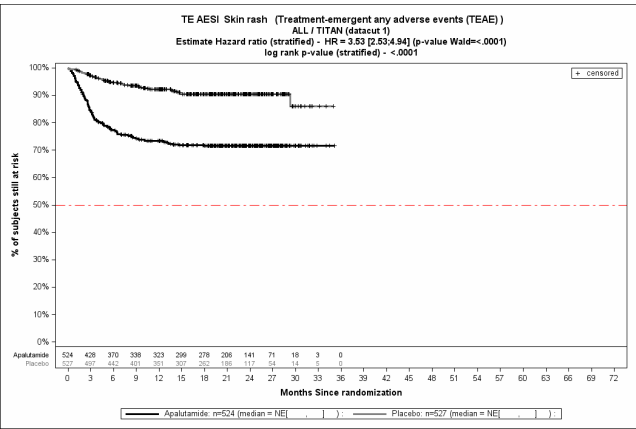


Abbildung 290 (Anhang): Kaplan-Meier-Kurve des unerwünschten Ereignisses von
speziellem Interesse Hautausschlag – Jegliche unerwünschte Ereignisse aus TITAN

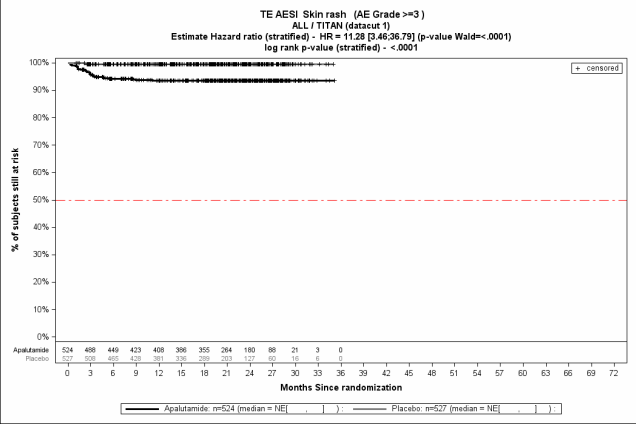


Abbildung 291 (Anhang): Kaplan-Meier-Kurve des unerwünschten Ereignisses von
speziellem Interesse Hautausschlag – Schwere unerwünschte Ereignisse (CTCAE ≥ 3) aus
TITAN

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Dossier zur Nutzenbewertung – Modul 4 A
Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

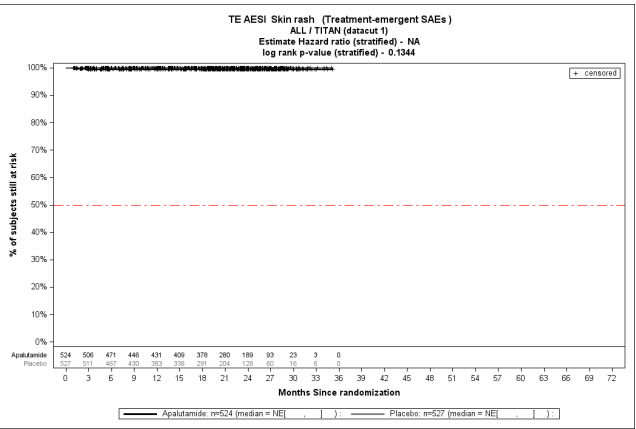


Abbildung 292 (Anhang): Kaplan-Meier-Kurve des unerwünschten Ereignisses von
speziellem Interesse Hautausschlag – Schwerwiegende unerwünschte Ereignisse aus TITAN

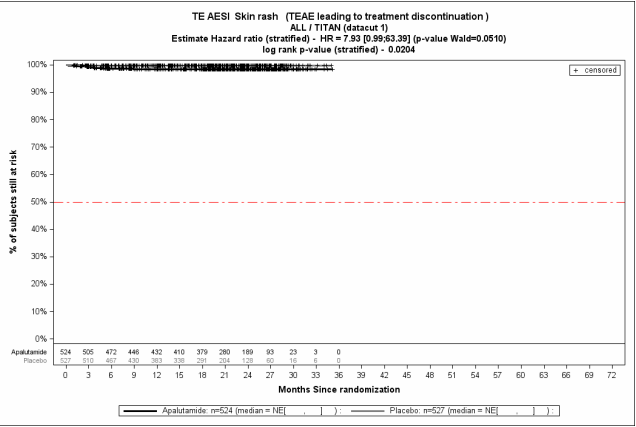


Abbildung 293 (Anhang): Kaplan-Meier-Kurve des unerwünschten Ereignisses von
speziellem Interesse Hautausschlag – Unerwünschte Ereignisse, die zum Therapieabbruch der
Studienmedikation führen aus TITAN

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

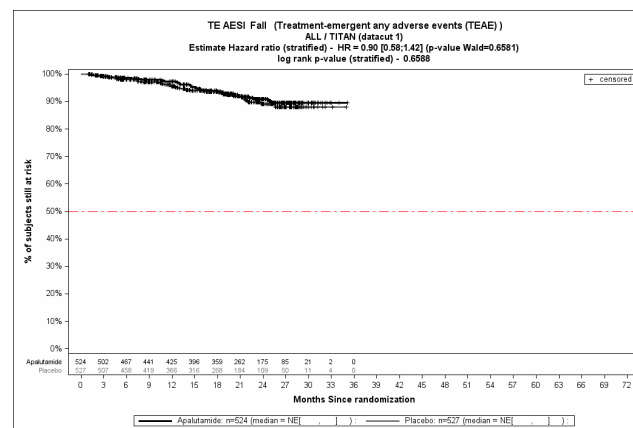


Abbildung 294 (Anhang): Kaplan-Meier-Kurve des unerwünschten Ereignisses von speziellem Interesse Stürze – Jegliche unerwünschte Ereignisse aus TITAN

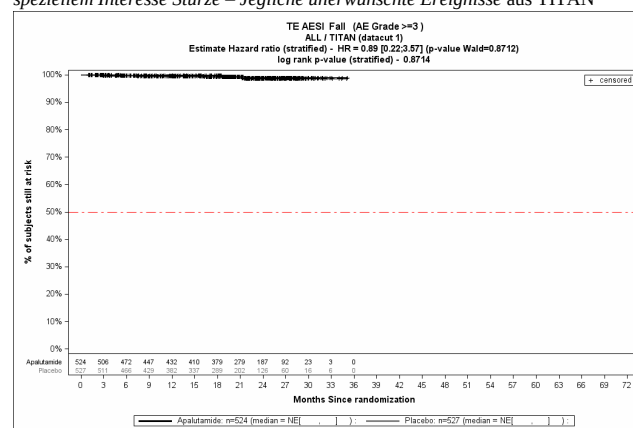


Abbildung 295 (Anhang): Kaplan-Meier-Kurve des unerwünschten Ereignisses von speziellem Interesse Stürze – Schwere unerwünschte Ereignisse (CTCAE ≥3) aus TITAN

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Dossier zur Nutzenbewertung – Modul 4 A
Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

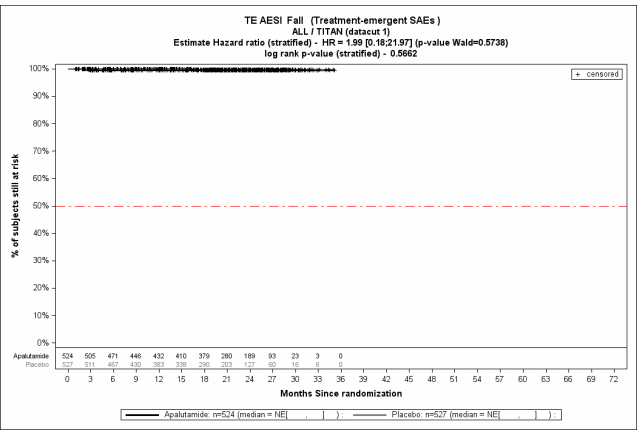


Abbildung 296 (Anhang): Kaplan-Meier-Kurve des unerwünschten Ereignisses von speziellem Interesse Stürze – Schwerwiegende unerwünschte Ereignisse aus TITAN

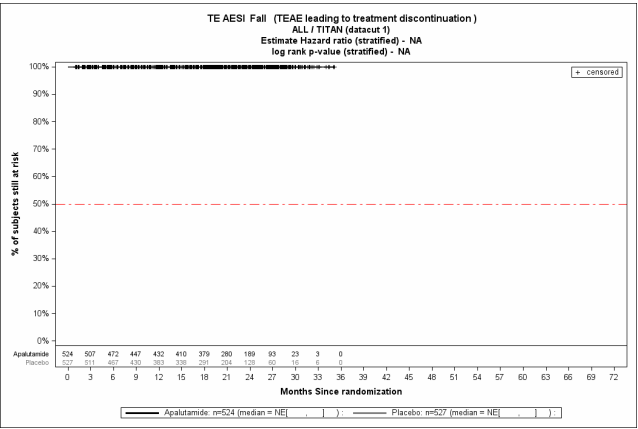


Abbildung 297 (Anhang): Kaplan-Meier-Kurve des unerwünschten Ereignisses von speziellem Interesse Stürze – Unerwünschte Ereignisse, die zum Therapieabbruch der Studienmedikation führen aus TITAN

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Dossier zur Nutzenbewertung – Modul 4 A
Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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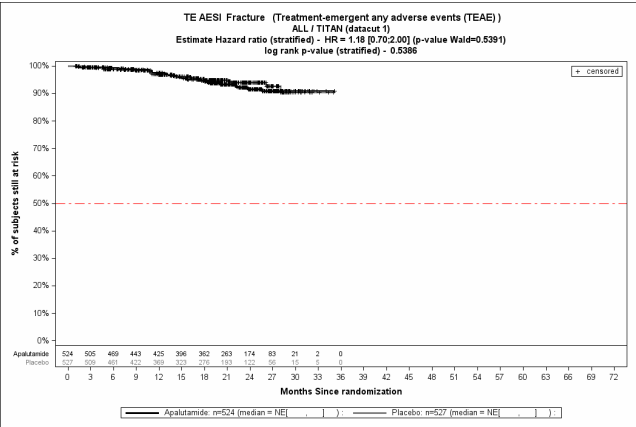


Abbildung 298 (Anhang): Kaplan-Meier-Kurve des unerwünschten Ereignisses von
speziellem Interesse Frakturen – Jegliche unerwünschte Ereignisse aus TITAN

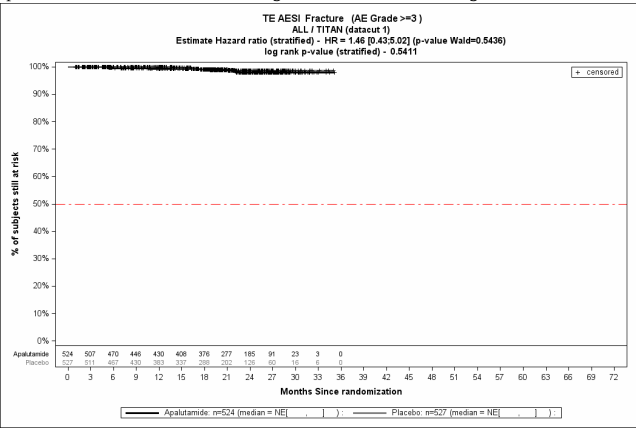


Abbildung 299 (Anhang): Kaplan-Meier-Kurve des unerwünschten Ereignisses von
speziellem Interesse Frakturen – Schwere unerwünschte Ereignisse (CTCAE >=3) aus TITAN

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

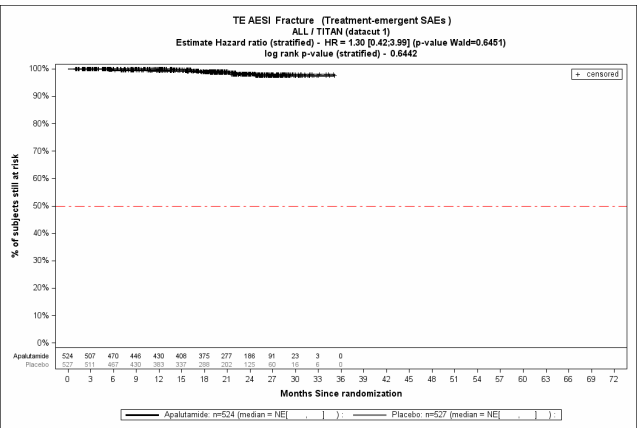


Abbildung 300 (Anhang): Kaplan-Meier-Kurve des unerwünschten Ereignisses von
speziellem Interesse Frakturen – Schwerwiegende unerwünschte Ereignisse aus TITAN

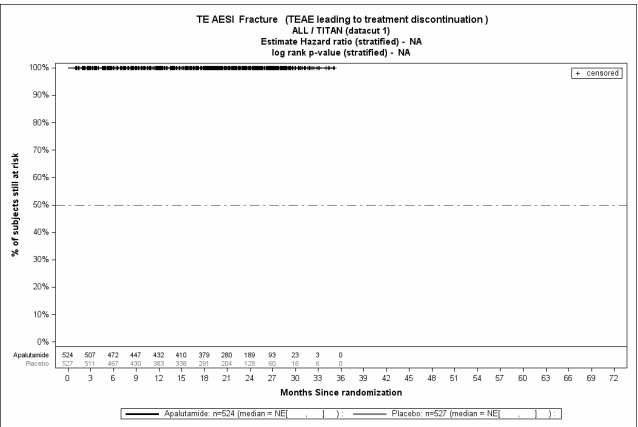


Abbildung 301 (Anhang): Kaplan-Meier-Kurve des unerwünschten Ereignisses von
speziellem Interesse Frakturen – Unerwünschte Ereignisse, die zum Therapieabbruch der
Studienmedikation führen aus TITAN

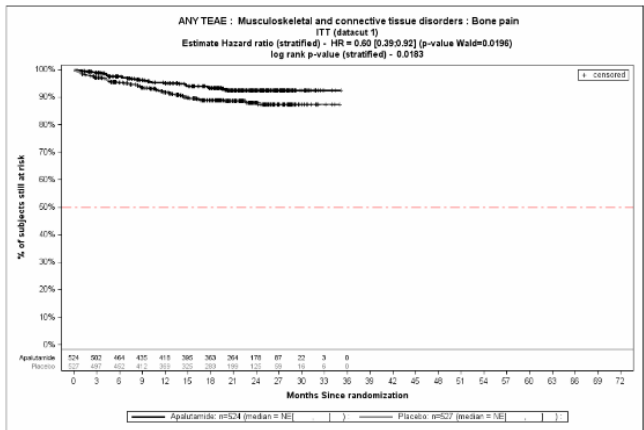


Abbildung 79: Kaplan-Meier Kurve der Jeglichen UE SOC Knochenschmerzen

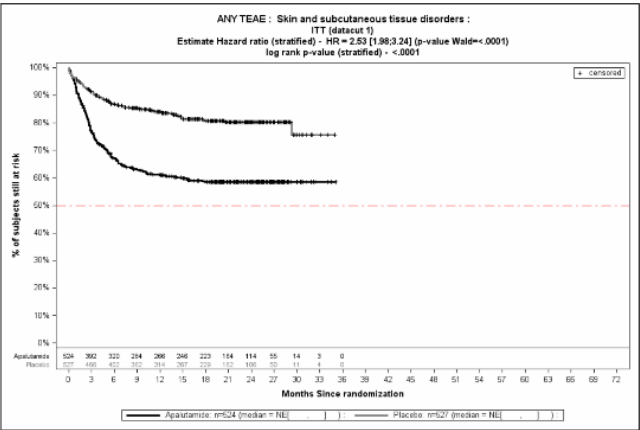


Abbildung 81: Kaplan-Meier Kurve der Jeglichen UE SOC Erkrankungen der Haut und des Unterhautgewebes

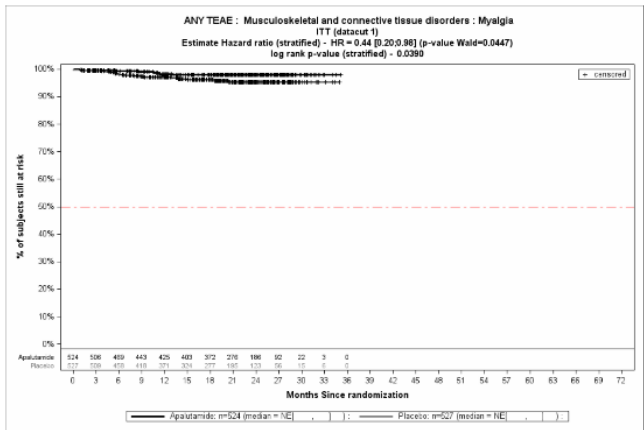


Abbildung 80: Kaplan-Meier Kurve der Jeglichen UE PT Myalgie

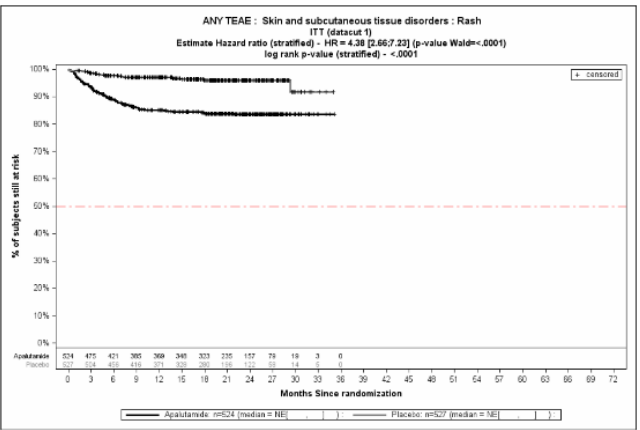


Abbildung 82: Kaplan-Meier Kurve der Jeglichen UE PT Ausschlag

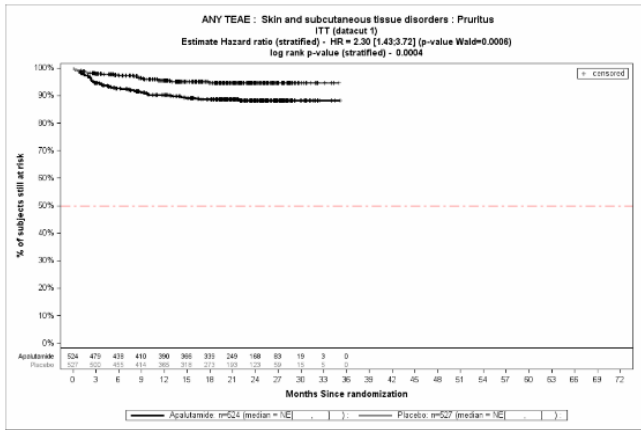


Abbildung 83: Kaplan-Meier Kurve der Jeglichen UE PT Pruritus

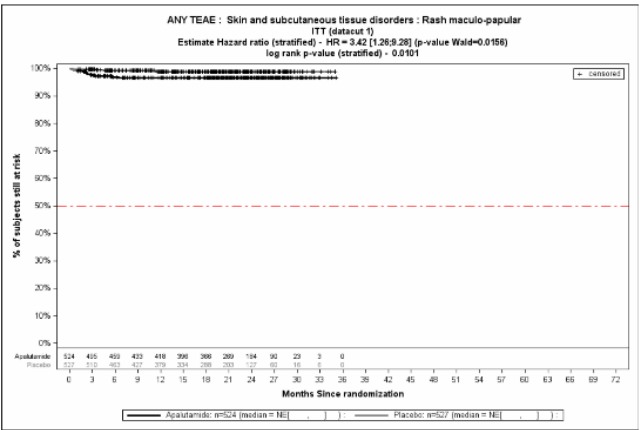


Abbildung 85: Kaplan-Meier Kurve der Jeglichen UE PT Ausschlag makulo-papulös

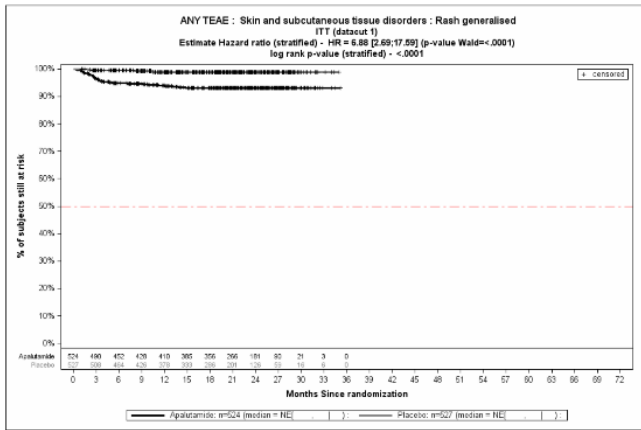


Abbildung 84: Kaplan-Meier Kurve der Jeglichen UE PT Ausschlag generalisiert

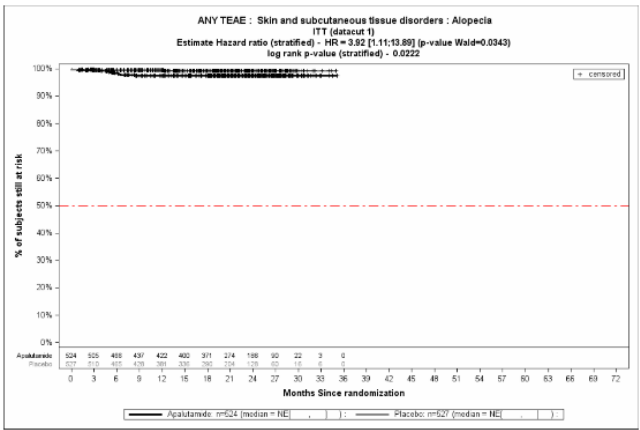


Abbildung 86: Kaplan-Meier Kurve der Jeglichen UE PT Alopezie

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

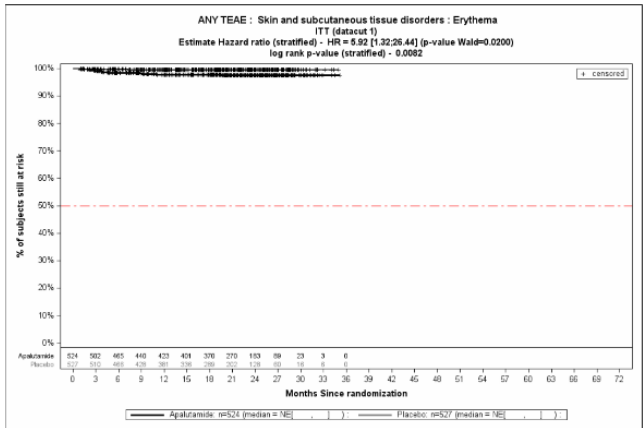


Abbildung 87: Kaplan-Meier Kurve der Jeglichen UE PT Erythem

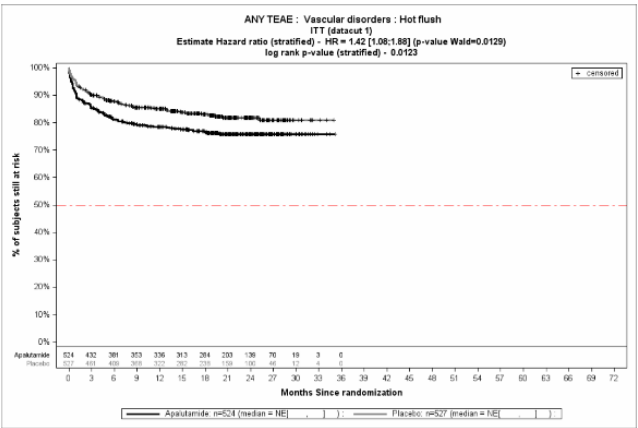


Abbildung 89: Kaplan-Meier Kurve der Jeglichen UE PT Hitzewallung

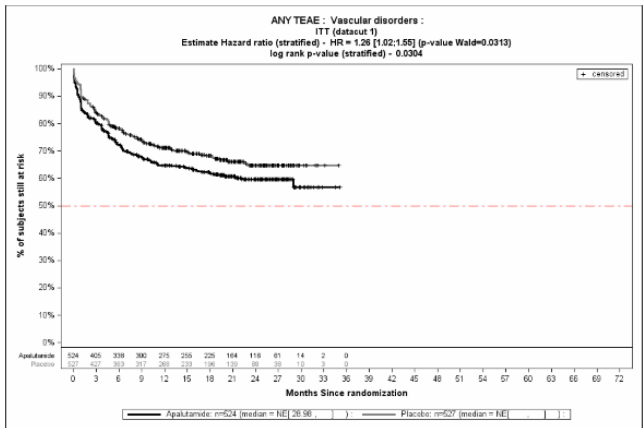


Abbildung 88: Kaplan-Meier Kurve der Jeglichen UE SOC Gefäßerkrankungen

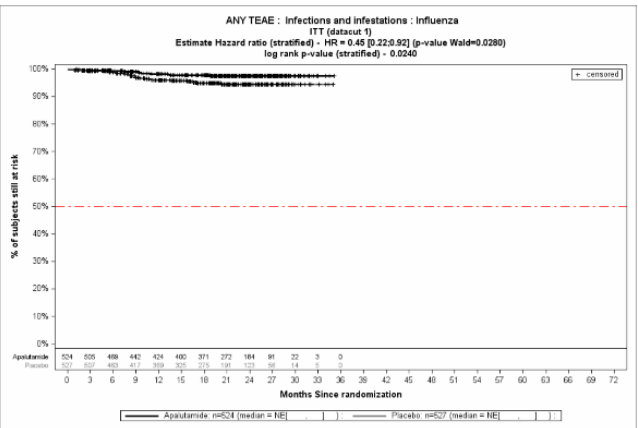


Abbildung 90: Kaplan-Meier Kurve der Jeglichen UE PT Grippe

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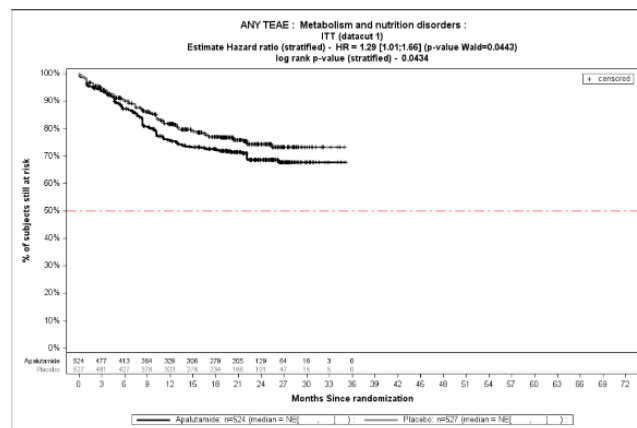


Abbildung 91: Kaplan-Meier Kurve der Jeglichen UE SOC Stoffwechsel- und Ernährungsstörung

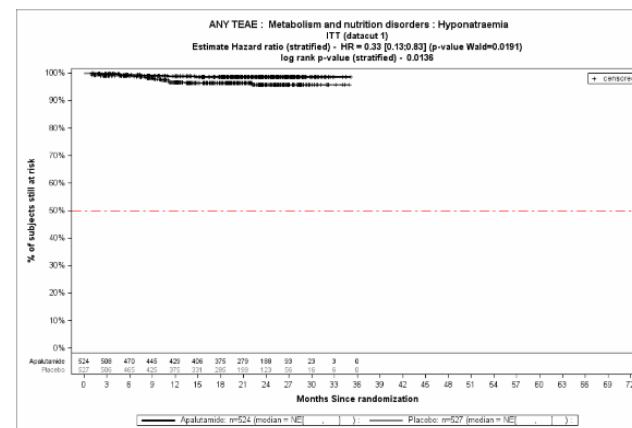


Abbildung 93: Kaplan-Meier Kurve der Jeglichen UE PT Hyponatriämie

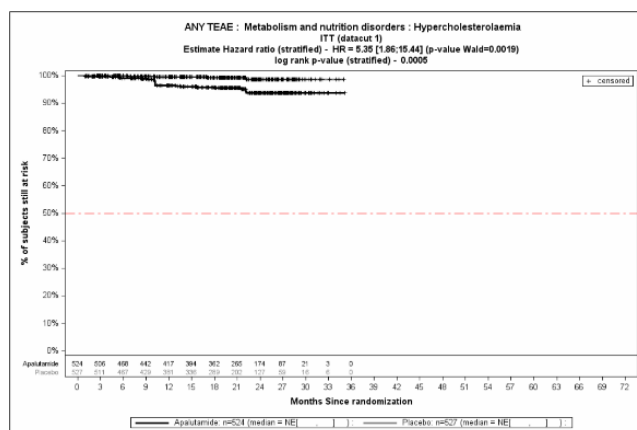


Abbildung 92: Kaplan-Meier Kurve der Jeglichen UE PT Hypercholesterinämie

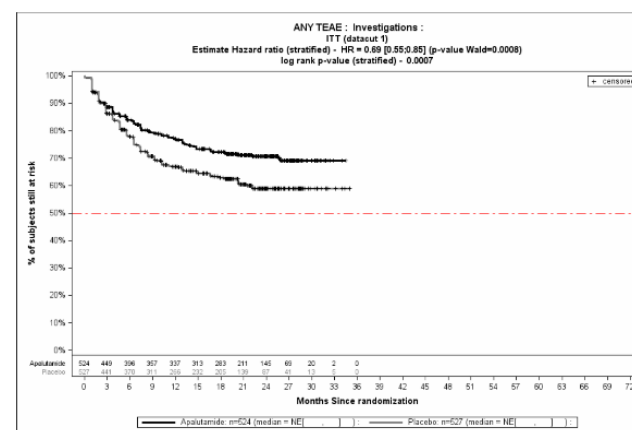


Abbildung 94: Kaplan-Meier Kurve der Jeglichen UE SOC Untersuchungen

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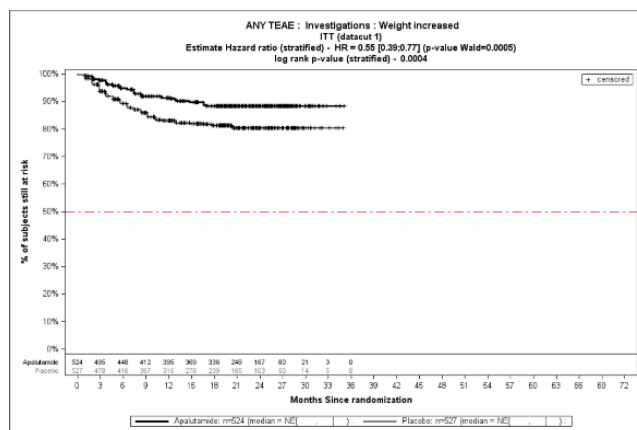


Abbildung 95: Kaplan-Meier Kurve der Jeglichen UE PT Gewicht erhöht

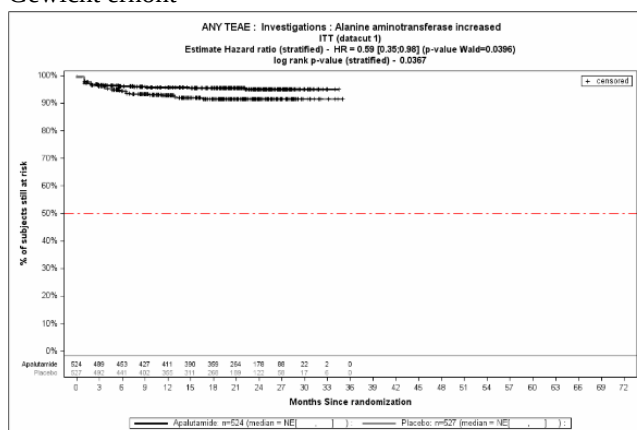


Abbildung 96: Kaplan-Meier Kurve der Jeglichen UE PT Alaninaminotransferase erhöht

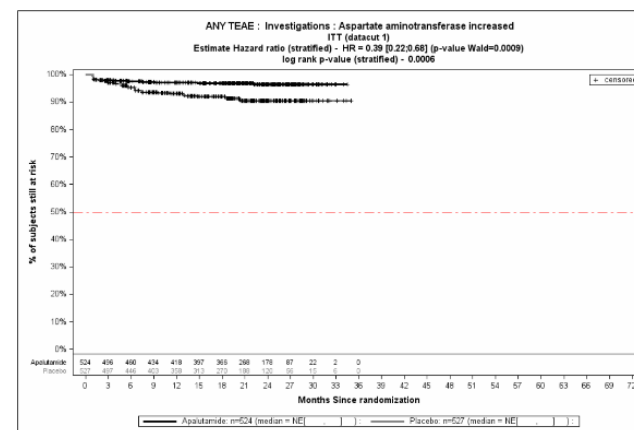


Abbildung 97: Kaplan-Meier Kurve der Jeglichen UE PT Aspartataminotransferase erhöht

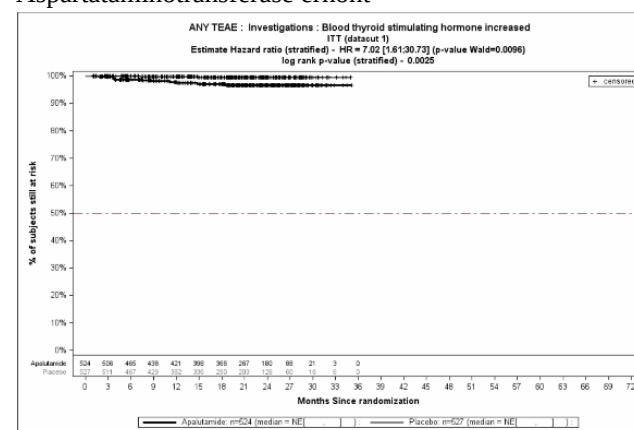


Abbildung 98: Kaplan-Meier Kurve der Jeglichen UE PT Thyreotropin im Blut erhöht

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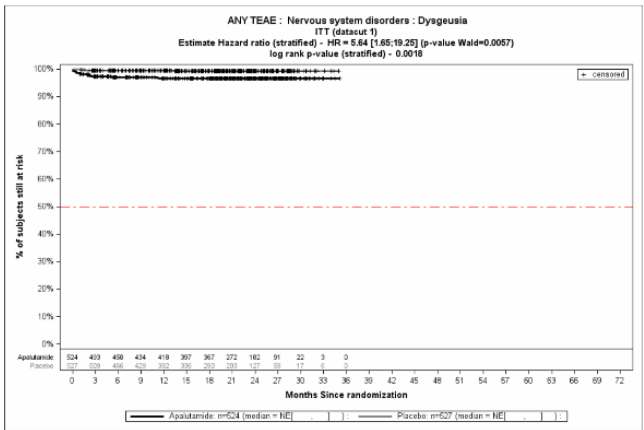


Abbildung 99: Kaplan-Meier Kurve der Jeglichen UE PT Geschmacksstörung

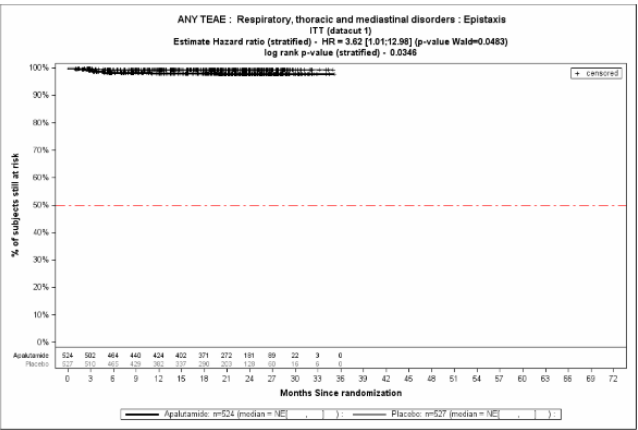


Abbildung 101: Kaplan-Meier Kurve der Jeglichen UE PT Epistaxis

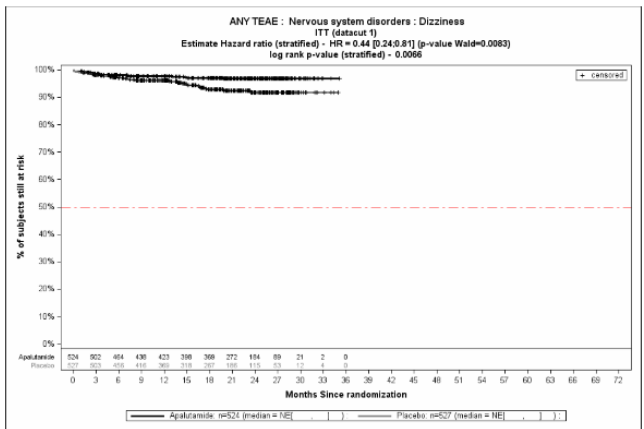


Abbildung 100: Kaplan-Meier Kurve der Jeglichen UE PT Schwindelgefühl

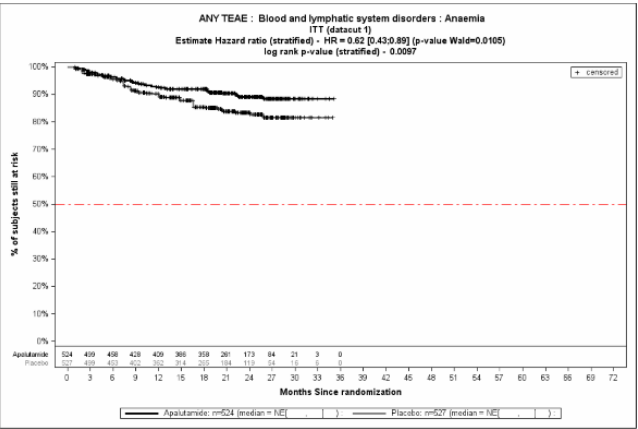


Abbildung 102: Kaplan-Meier Kurve der Jeglichen UE PT Anämie

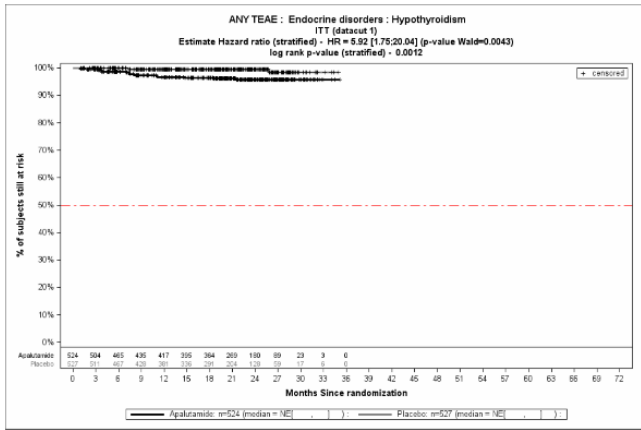
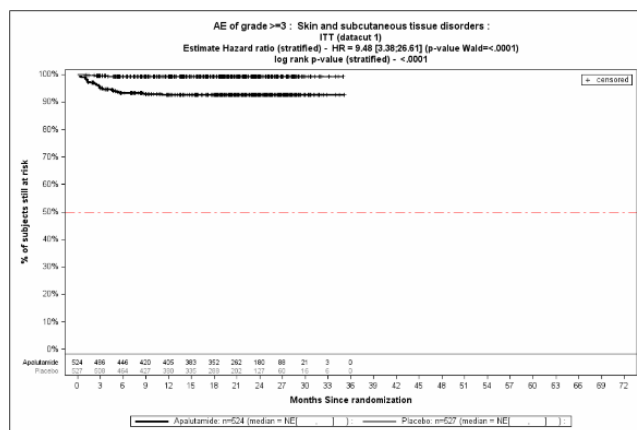
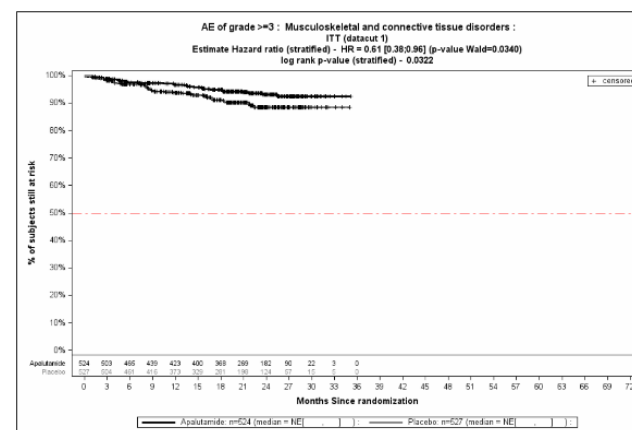
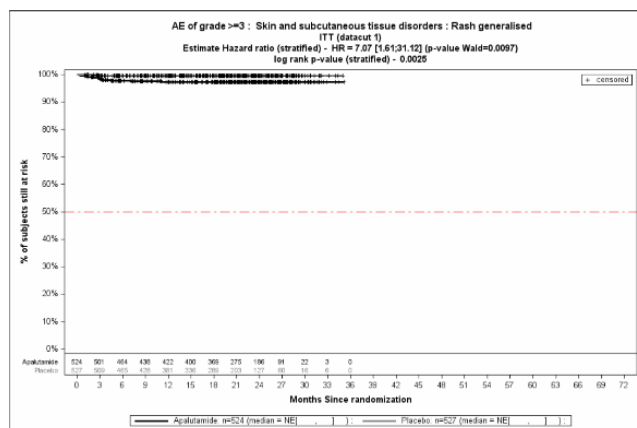
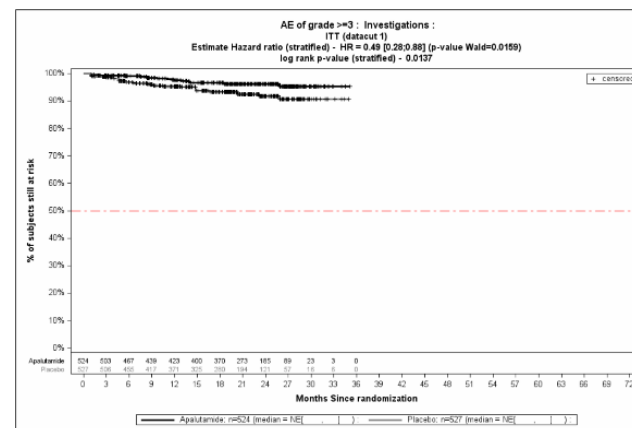


Abbildung 103: Kaplan-Meier Kurve der Jeglichen UE PT Hypothyreose

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Abbildung 105: KM: Schwere UE (CTCAE-Grad ≥ 3) SOC Erkrankungen der Haut und des UnterhautgewebesAbbildung 107: KM: Schwere UE (CTCAE-Grad ≥ 3) SOC Skelettmuskulatur-, Bindegewebs- und KnochenkrankungenAbbildung 106: Kaplan-Meier Kurve der Schwere UE (CTCAE-Grad ≥ 3) PT Ausschlag generalisiertAbbildung 108: Kaplan-Meier Kurve der Schwere UE (CTCAE-Grad ≥ 3) SOC Untersuchungen

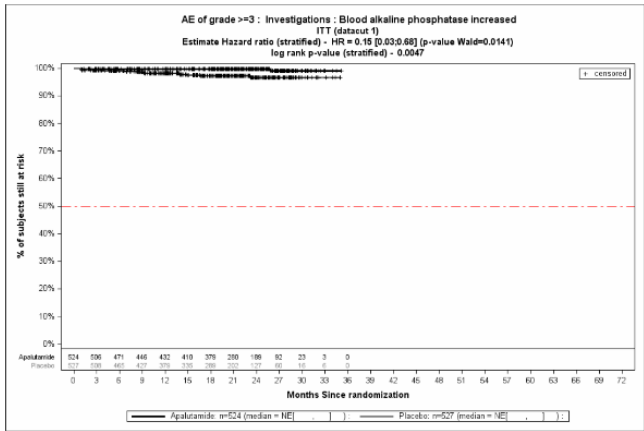


Abbildung 109: Kaplan-Meier Kurve der Schweren UE (CTCAE-Grad ≥ 3) PT Alkalische Phosphatase im Blut erhöht

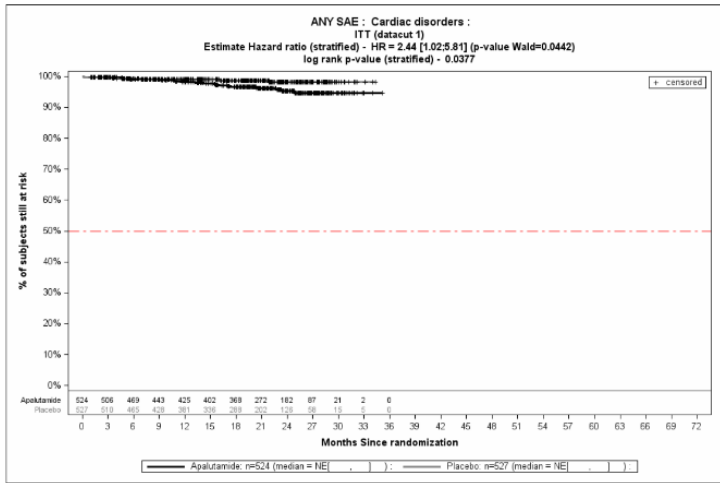


Abbildung 111: Kaplan-Meier Kurve der Schwerwiegenden UE SOC Herzerkrankungen

Quelle: *Janssen-Cilag GmbH. Dossier zur Nutzenbewertung gemäß § 35a SGB V, Apalutamid (Erleada®). Modul 4 A. 2020.*