Supplementary data

Three-year follow-up analysis of phase I/II study on tirabrutinib in patients with relapsed or refractory primary central nervous system lymphoma

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Supplementary Figure S8. QLQ-C30 in all patients and each dose group

Supplementary Figure S9. EQ-5D-3L scores in all patients and each dose group

Supplementary Table S1. Exposure and disposition

	All **n = 44**	**320 mg** **n = 20**	**480 mg** **n = 7**	**480 mg fasted** **n = 17**
Median duration of treatment, months (range)	2.7 (0.8–46.9)	2.3 (0.9–46.9)	11.1 (0.8–29.6)	7.4 (0.9–39.6)
Treatment completion, n (%)	5 (11.4)	1 (5.0)	0	4 (23.5)
Treatment discontinuation, n (%)	39 (88.6)	19 (95.0)	7 (100.0)	13 (76.5)
Reason for treatment discontinuation, n (%)				
Disease progression	31 (70.5)	14 (70.0)	5 (71.4)	12 (70.6)
Adverse event	4 (9.1)	2 (10.0)	2 (28.6)	0
Other*	4 (9.1)	3 (15.0)	0	1 (5.9)

*The investigator or sub-investigator decided that it was inappropriate to continue the study treatment. q.d., once daily.

Supplementary Table S2. Tumor responses as assessed by the central independent review committee and duration of response

	All **n = 44**	**320 mg** **n = 20**	**480 mg** **n = 7**	**480 mg fasted** **n = 17**
ORR (CR + CRu + PR), n (%) 95% CI, %	28 (63.6) 47.8–77.6	12 (60.0) 36.1–80.9	7 (100.0) 59.0–100.0	9 (52.9) 27.8–77.0
CR rate (CR + CRu), n (%) 95% CI, %	16 (36.4) 22.4–52.2	5 (25.0) 8.7–49.1	4 (57.1) 18.4–90.1	7 (41.2) 18.4–67.1
BOR, n (%)				
CR	9 (20.5)	3 (15.0)	1 (14.3)	5 (29.4)
CRu	7 (15.9)	2 (10.0)	3 (42.9)	2 (11.8)
PR	12 (27.3)	7 (35.0)	3 (42.9)	2 (11.8)
SD	7 (15.9)	4 (20.0)	0	3 (17.6)
PD	9 (20.5)	4 (20.0)	0	5 (29.4)
Median TTR, months (range)*	0.9 (0.3–1.2)	0.9 (0.9–1.2)	0.9 (0.3–1.0)	0.9 (0.8–1.0)
Median DOR, months (95% CI)*	9.2 (1.7–17.2)	3.7 (0.9–19.4)	10.2 (0.6–21.2)	12.1 (0.9–NR)
12-month DOR rate, % (95% CI)*	46.4 (27.6–63.3)	41.7 (15.2–66.5)	42.9 (9.8–73.4)	55.6 (20.4–80.5)
24-month DOR rate, % (95% CI)*	23.8 (10.0–40.9)	20.8 (3.5–47.9)	14.3 (0.7.–46.5)	33.3 (7.8–62.3)
36-month DOR rate, % (95% CI)*	19.8 (7.4–36.5)	20.8 (3.5–47.9)	0	33.3 (7.8–62.3)

*Among patients who achieved CR, CRu, or PR (n = 28, 12, 7, and 9 for all patients, 320 mg, 480 mg, and 480 mg fasted groups, respectively). BOR, best overall response; CI, confidence interval; CR, complete response; CRu, unconfirmed complete response; DOR, duration of response; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; q.d., once daily; SD, stable disease; TTR, time to response

Supplementary Table S3. Progression-free survival and overall survival in all patients and each dosage group

	All **n = 44**	**320 mg** **n = 20**	**480 mg** **n = 7**	**480 mg fasted** **n = 17**
Median PFS, months (95% CI)	2.9 (1.8–11.1)	2.1 (1.8–18.2)	11.1 (1.4–22.0)	5.8 (1.0–13.0)
12-month PFS rate, % (95% CI)	32.5 (18.9–46.9)	29.4 (11.0–50.7)	42.9 (9.8–73.4)	31.7 (11.6–54.1)
24-month PFS rate, % (95% CI)	16.7 (7.0–29.9)	14.7 (2.7–36.2)	14.3 (0.7–46.5)	19.0 (4.7–40.6)
36-month PFS rate, % (95% CI)	13.9 (5.3–26.7)	14.7 (2.7–36.2)	0	19.0 (4.7–40.6)
Median OS, months (95% CI)	NR (21.0–NR)	37.9 (11.2–NR)	NR (1.4–NR)	NR (5.5–NR)
12-month OS rate, % (95% CI)	72.7 (57.0–83.5)	75.0 (50.0–88.8)	85.7 (33.4–97.9)	64.7 (37.7–82.3)
24-month OS rate, % (95% CI)	61.4 (45.4–74.0)	60.0 (35.7–77.6)	85.7 (33.4–97.9)	52.9 (27.6–73.0)
36-month OS rate, % (95% CI)	56.7 (40.9–69.8)	55.0 (31.3–73.5)	71.4 (25.8–92.0)	52.9 (27.6–73.0)

CI, confidence interval; NR, not reached; PFS, progression-free survival; OS, overall survival.

Supplementary Table S4. OS in patients with subsequent HD-MTX-based therapy or radiotherapy

	Subsequent HD-MTX n = 18	**Subsequent WBRT n = 10**
Median OS, months (95% CI)	NR (21.0–NR)	29.0 (5.5–NR)
12-month OS, % (95% CI)	83.3 (56.8–94.3)	70.0 (32.9–89.2)
24-month OS, % (95% CI)	61.1 (35.3–79.2)	60.0 (25.3–82.7)
36-month OS, % (95% CI)	61.1 (35.3–79.2)	40.0 (12.3–67.0)

CI, confidence interval; HD-MTX, high-dose methotrexate NR, not reached; OS, over survival; WBRT, whole-brain radiotherapy.

Supplementary Table S5. Subgroup analysis of PFS at 12 months according to baseline patient characteristics

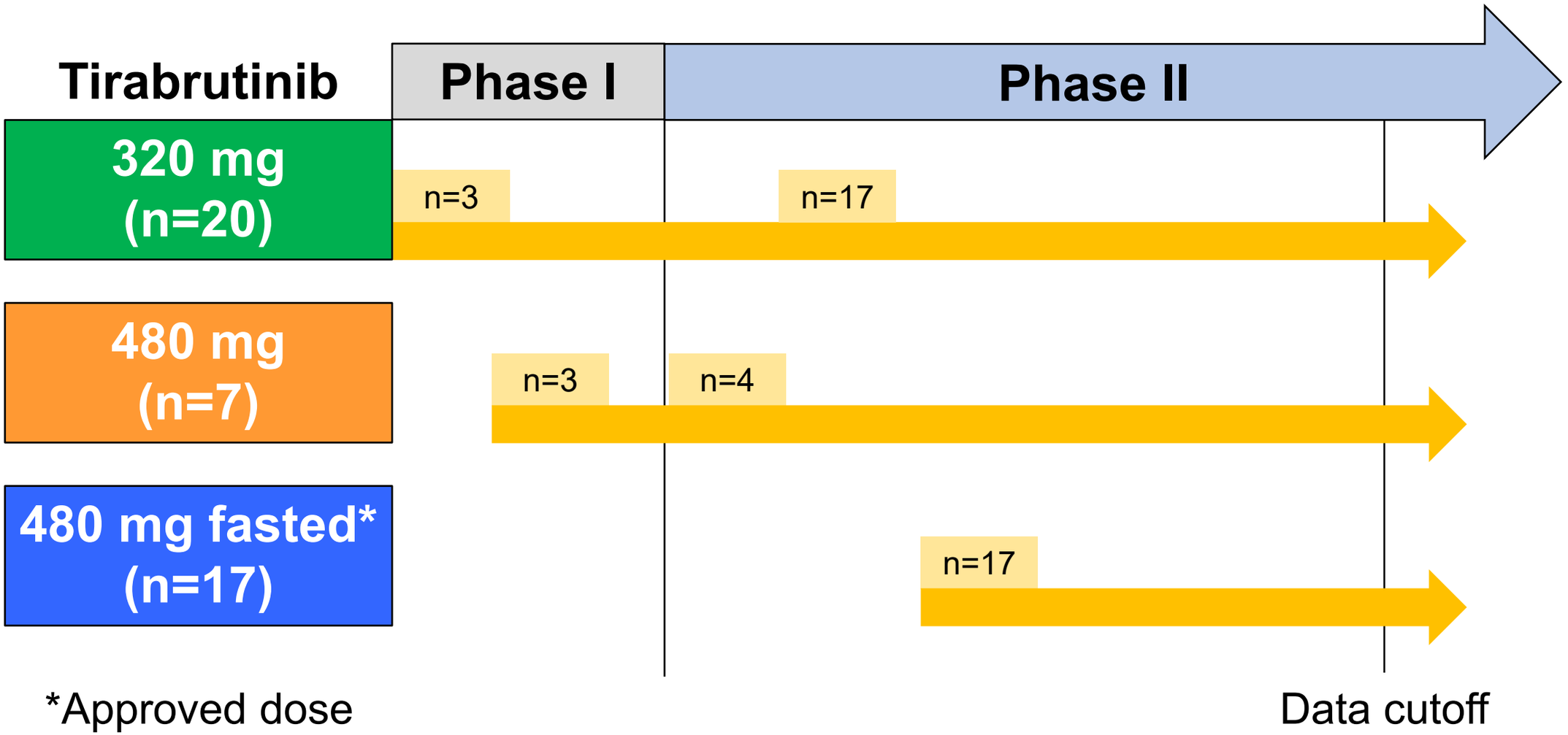
			Univariate analysis			Multivariate analysis		
Factor	**n**	**PFS events at 12 months, n (%)**	**Odds ratio**	**95% CI**	***P*-value**	**Odds ratio**	**95% CI**	***P*-value**
Age, y								
<65	22	16 (72.7)	Reference					
≥65	19	12 (63.2)	0.643	0.171–2.413	0.5126			
KPS								
70–80	21	18 (85.7)	5.999	1.333–26.996	0.0196*	5.993	1.202–29.876	0.0289*
90–100	20	10 (50.0)	Reference			Reference		
Number of previous lines of treatment								
1	17	9 (52.9)	Reference			Reference		
≥2	24	19 (79.2)	3.378	0.858–13.296	0.0817	3.292	0.701–15.451	0.1310
Previous rituximab								
Yes	23	16 (69.6)	1.143	0.305–4.289	0.8431			
No	18	12 (66.7)	Reference					
Previous WBRT								
Yes	27	21 (77.8)	3.500	0.875–13.995	0.0764	3.051	0.634–14.671	0.1639
No	14	7 (50.0)	Reference			Reference		
Previous HCT-ASCT								
Yes	5	4 (80.0)	2.000	0.201–19.914	0.5544			
No	36	24 (66.7)	Reference					
Disease status								
Relapse	32	21 (65.6)	Reference					
Refractory	7	6 (85.7)	3.143	0.335–29.493	0.2603			
Unknown	2	1 (50.0)	0.524	0.030–9.203	0.4241			
CNS involvement								
CSF								
Positive	9	7 (77.8)	1.833	0.324–10.367	0.4929			
Negative	32	21 (65.6)	Reference					
IOL								
Positive	3	2 (66.7)	0.870	0.070–10.728	0.9553			
Minor RPE abnormality	5	3 (60.0)	0.652	0.094–4.525	0.7485			
Negative	33	23 (69.7)	Reference					
GCB subtype								
GCB	13	8 (61.5)	0.640	0.160–2.559	0.5279			
Non-GCB	28	20 (71.4)	Reference					
Gene mutation (*CARD11*)								
Yes	16	10 (62.5)	0.648	0.170–2.467	0.5249			
No	25	18 (72.0)	Reference					
Gene mutation (*CD79B*)								
Yes	15	9 (60.0)	0.553	0.143–2.128	0.3886			
No	26	19 (73.1)	Reference					
Gene mutation (*MYD88*)								
Yes	29	21 (72.4)	1.875	0.459–7.659	0.3812			
No	12	7 (58.3)	Reference					
SPD at target lesion, mm^2								
<400	23	15 (65.2)	0.721	0.189–2.759	0.6330			
≥400	18	13 (72.2)	Reference					

*P <0.05. After excluding 3 patients who were censored at 12 months without PD or death, 41 patients were included in this analysis. The variables for the multivariate analysis of PFS (KPS, number of previous lines of treatment, and previous WBRT) were chosen with the step-wise method. CI, confidence interval; CNS, central nervous system; CSF, cerebrospinal fluid; GCB, germinal center B-cell-like; IOL, intraocular lymphoma; HCT-ASCT, high-dose chemotherapy followed by autologous stem cell transplantation; PD, progressive disease; PFS, progression-free survival; RPE, retinal pigment epithelial; SPD, sum of the products of the greatest diameters; WBRT, whole-brain radiotherapy.

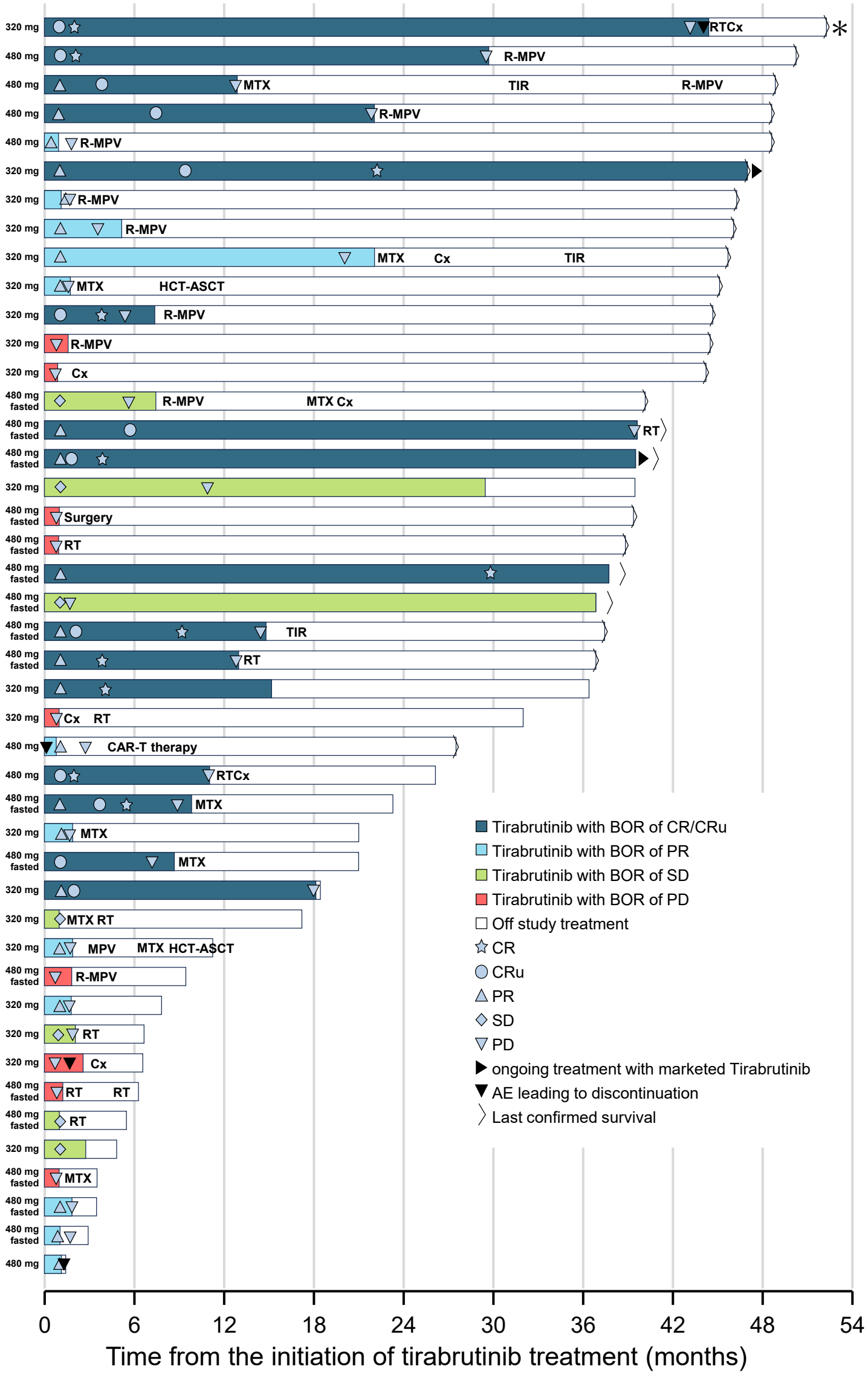
Supplementary Table S6. Outcome of treatment-related adverse events of special interest and treatment status of tirabrutinib in overall population

TRAEs of special interest	Onset, n (%)	Median time to onset, days (range)	Recovered or recovering, n (%)*	Median time to recovered or recovering, days (range)	Tirabrutinib treatment, n (%)*		Medical intervention for the TRAEs, n (%)*
Skin	24 (54.5)	13.0 (1–121)	20 (83.3)	35.5 (6–635)	Dose not changed	15 (62.5)	20 (83.3)
					Dose reduced	1 (4.2)	
					Drug interrupted	6 (25.0)	
					Drug withdrawn	2 (8.3)	
					Unknown	0	
Cytopenia	19 (43.2)	15.0 (2–813)	15 (78.9)	30.0 (14–682)	Dose not changed	17 (89.5)	1 (5.3)
					Dose reduced	0	
					Drug interrupted	2 (10.5)	
					Drug withdrawn	0	
					Unknown	0	
Infection	7 (15.9)	130.0 (32–346)	5 (71.4)	18.0 (6–25)	Dose not changed	1 (14.3)	7 (100)
					Dose reduced	0	
					Drug interrupted	4 (57.1)	
					Drug withdrawn	1 (14.3)	
					Unknown	1 (14.3)	
Haemorrhage	3 (6.8)	29.0 (10–109)	3 (100)	48.0 (18–190)	Dose not changed	2 (66.7)	0
					Dose reduced	0	
					Drug interrupted	1 (33.3)	
					Drug withdrawn	0	
					Unknown	0	
Diarrhoea	1 (2.3)	2.0 (2–2)	1 (100)	2.0 (2–2)	Dose not changed	1 (100)	0
					Dose reduced	0	
					Drug interrupted	0	
					Drug withdrawn	0	
					Unknown	0	

*Among those who developed each TRAE. TRAE, treatment-related adverse events.

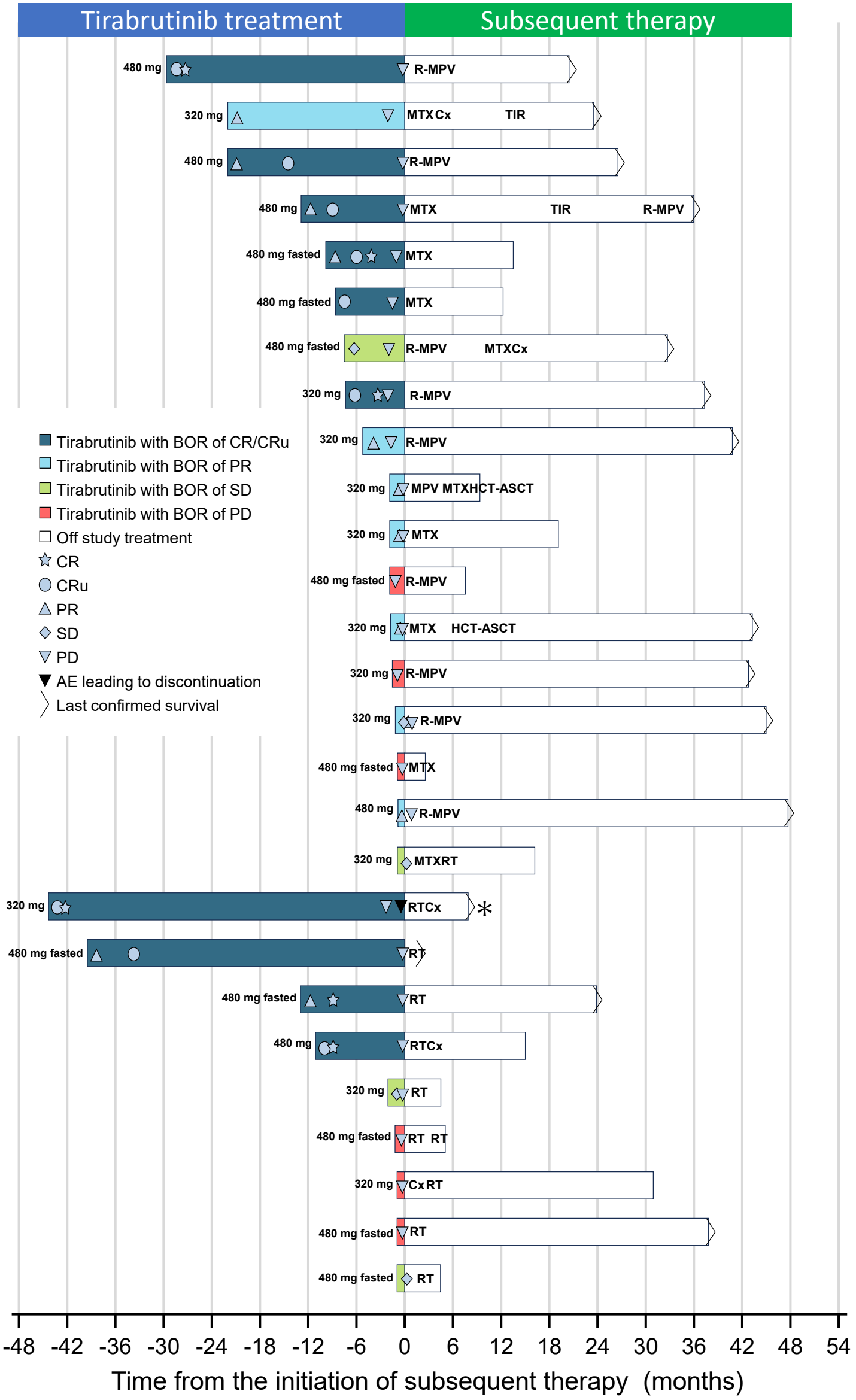


Supplementary Figure S1. Timeline of the study



Supplementary Figure S2. Subsequent therapy and survival outcomes

BOR is per central assessment and duration of treatment is per investigators' assessment. *The patient developed an adverse event on a date on which he or she had centrally confirmed PD. AE, adverse event; BOR, best overall response; CR, complete response; CRu, unconfirmed complete response; Cx, chemotherapy except HD-MTX-based therapy; HCT-ASCT, high-dose chemotherapy followed by autologous stem cell transplantation; HD-MTX, high-dose methotrexate; MTX, HD-MTX-based therapy excluding R-MPV and MPV; MPV, methotrexate, procarbazine, and vincristine; R-MPV, rituximab plus MPV; SD, stable disease; TIR, Tirabrutinib re-challenged; PD, progressive disease; PR, partial response; RT, radiotherapy.

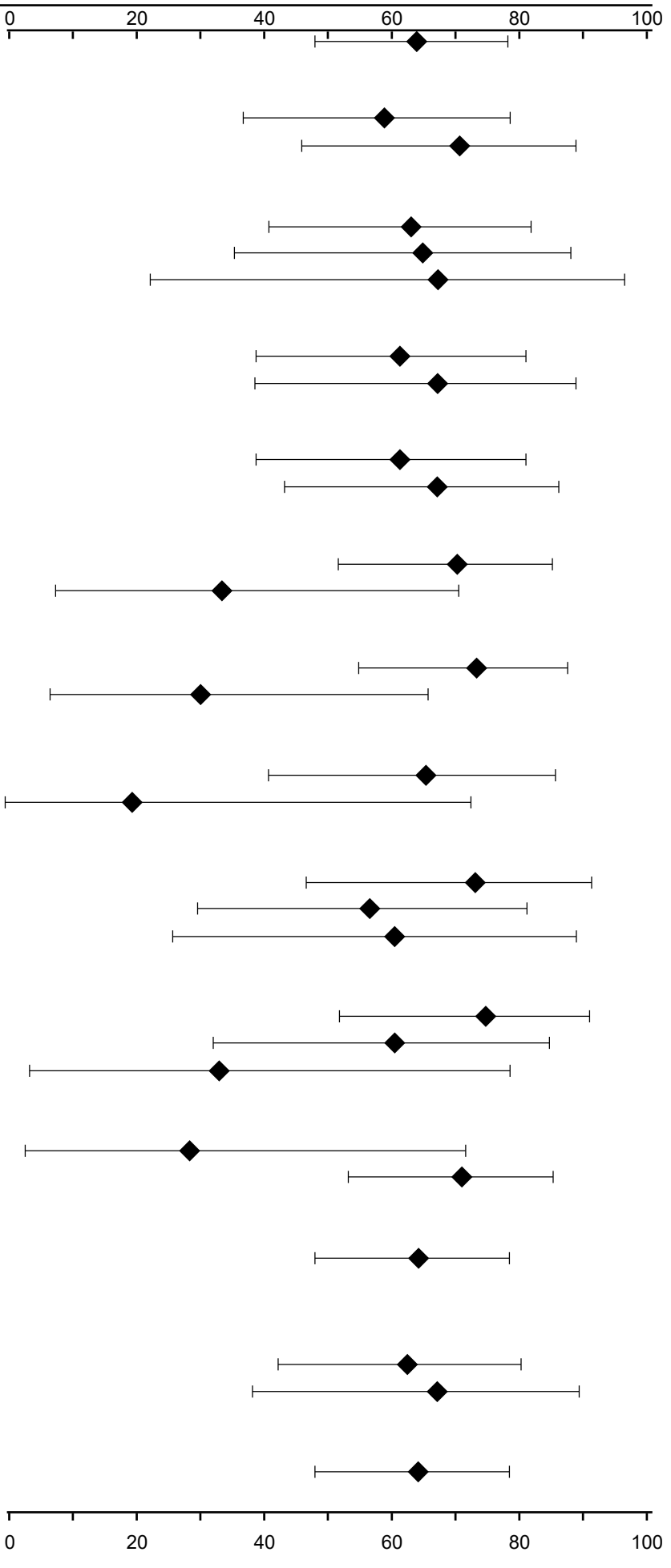


Supplementary Figure S3. Subsequent therapy and survival outcomes of those who received HD-MTX-based therapy and those who received radiotherapy

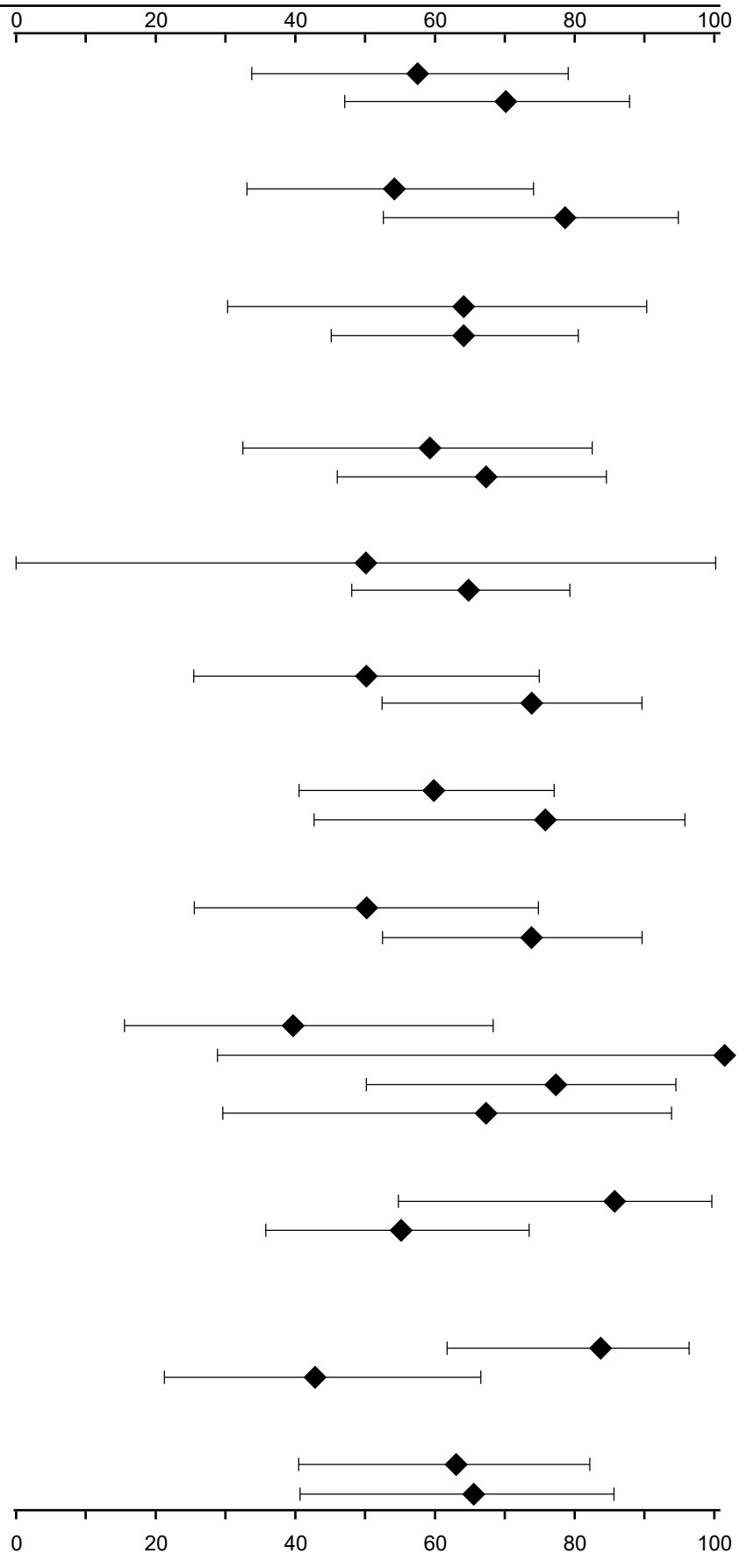
BOR is per central assessment and duration of treatment is per investigators' assessment. *The patient developed an adverse event on a date on which he or she had centrally confirmed PD. AE, adverse event; BOR, best overall response; CR, complete response; CRu, unconfirmed complete response; Cx, chemotherapy except HD-MTX-based therapy; HCT-ASCT, high-dose chemotherapy followed by autologous stem cell transplantation; HD-MTX, high-dose methotrexate; MTX, HD-MTX-based therapy excluding R-MPV and MPV; MPV, methotrexate, procarbazine, and vincristine; R-MPV, rituximab plus MPV; SD, stable disease; TIR, Tirabrutinib re-challenged; PD, progressive disease; PR, partial response; RT, radiotherapy.

Supplementary Figure S4. See the figure legend on the next page

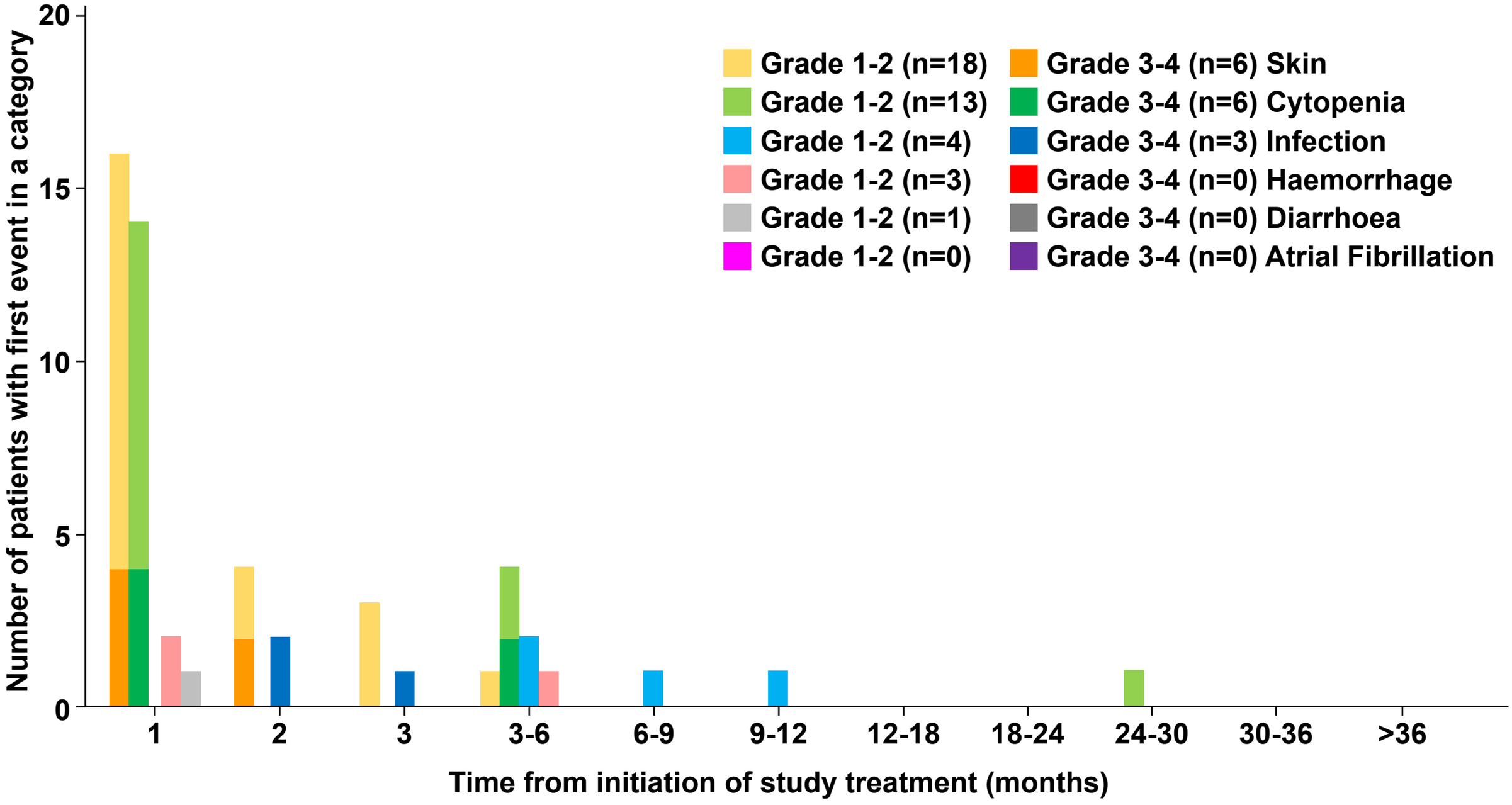
	n	ORR (%)	[95% CI]*
All	**44**	**28 (63.6)**	**[47.8, 77.6]**
Sex			
Male	24	14 (58.3)	[36.6, 77.9]
Female	20	14 (70.0)	[45.7, 88.1]
Age (years)			
<65	24	15 (62.5)	[40.6, 81.2]
65 to <75	14	9 (64.3)	[35.1, 87.2]
≥75	6	4 (66.7)	[22.3, 95.7]
Time from the diagnosis of PCNSL to enrollment (initial onset) (months)			
<35	23	14 (60.9)	[38.5, 80.3]
≥35	15	10 (66.7)	[38.4, 88.2]
Time from the diagnosis of PCNSL to enrollment (last onset) (months)			
<0.5	23	14 (60.9)	[38.5, 80.3]
≥0.5	21	14 (66.7)	[43.0, 85.4]
Recurrent or refractory after last treatment for PCNSL			
Recurrent	33	23 (69.7)	[51.3, 84.4]
Refractory	9	3 (33.3)	[7.5, 70.1]
Recurrent or refractory after last methotrexate therapy for PCNSL			
Recurrent	33	24 (72.7)	[54.5, 86.7]
Refractory	10	3 (30.0)	[6.7, 65.2]
Recurrent or refractory after last rituximab therapy for PCNSL			
Recurrent	20	13 (65.0)	[40.8, 84.6]
Refractory	5	1 (20.0)	[0.5, 71.6]
Number of previous lines of treatments			
1	18	13 (72.2)	[46.5, 90.3]
2–3	16	9 (56.3)	[29.9, 80.2]
≥4	10	6 (60.0)	[26.2, 87.8]
Number of previous lines of chemotherapies			
1	23	17 (73.9)	[51.6, 89.8]
2–3	15	9 (60.0)	[32.3, 83.7]
≥4	6	2 (33.3)	[4.3, 77.7]
Treatment history for PCNSL (HCT-ASCT)			
Yes	7	2 (28.6)	[3.7, 71.0]
No	37	26 (70.3)	[53.0, 84.1]
Treatment history for PCNSL (chemotherapies)			
Yes	44	28 (63.6)	[47.8, 77.6]
No	0	-	-
Treatment history for PCNSL (WBRT)			
Yes	29	18 (62.1)	[42.3, 79.3]
No	15	10 (66.7)	[38.4, 88.2]
Treatment history for PCNSL (methotrexate)			
Yes	44	28 (63.6)	[47.8, 77.6]
No	0	-	-



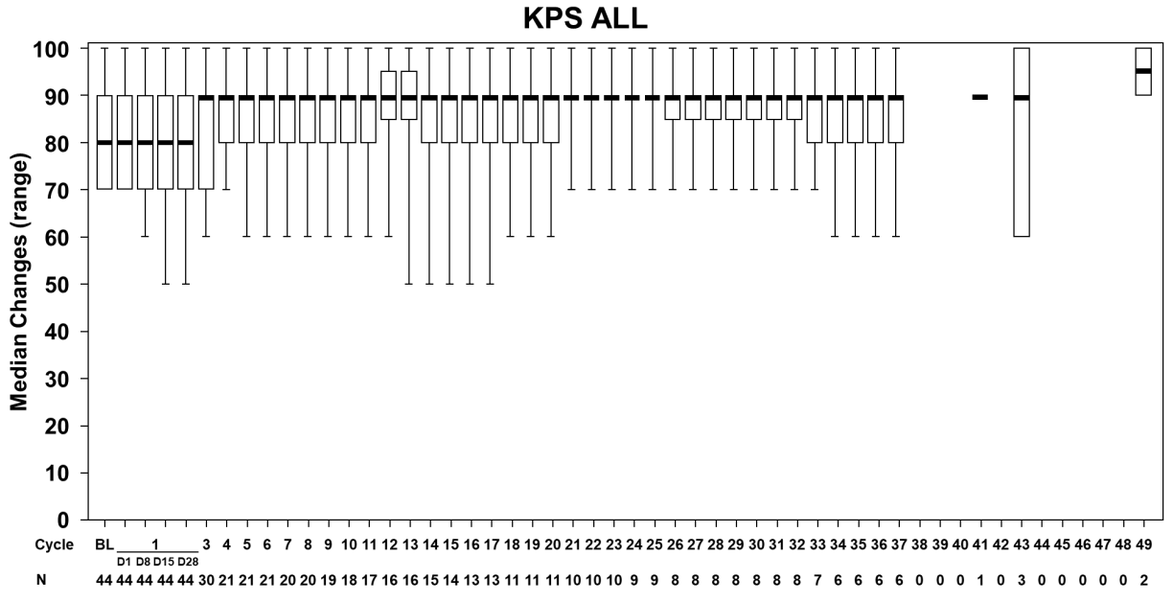
	n	ORR (%)	[95% CI]*
Treatment history for PCNSL (cytarabine)			
Yes	21	12 (57.1)	[34.0, 78.2]
No	23	16 (69.6)	[47.1, 86.8]
Treatment history for PCNSL (rituximab)			
Yes	26	14 (53.8)	[33.4, 73.4]
No	18	14 (77.8)	[52.4, 93.6]
Prognostic factors (Recursive partitioning analysis scoring system)			
Class 1	11	7 (63.6)	[30.8, 89.1]
Class 2	33	21 (63.6)	[45.1, 79.6]
Class 3	0	-	-
Gene mutation (CARD11)			
Yes	17	10 (58.8)	[32.9, 81.6]
No	27	18 (66.7)	[46.0, 83.5]
Gene mutation (CD79A)			
Yes	2	1 (50.0)	[1.3, 98.7]
No	42	27 (64.3)	[48.0, 78.4]
Gene mutation (CD79B)			
Yes	18	9 (50.0)	[26.0, 74.0]
No	26	19 (73.1)	[52.2, 88.4]
Gene mutation (MYD88)			
Yes	32	19 (59.4)	[40.6, 76.3]
No	12	9 (75.0)	[42.8, 94.5]
Gene mutation (CD79A/B)**			
Yes	18	9 (50.0)	[26.0, 74.0]
No	26	19 (73.1)	[52.2, 88.4]
Gene mutation (CD79B and MYD88)			
Yes-Yes	15	6 (40.0)	[16.3, 67.7]
Yes-No	3	3 (100.0)	[29.2, 100.0]
No-Yes	17	13 (76.5)	[50.1, 93.2]
No-No	9	6 (66.7)	[29.9, 92.5]
PCNSL subtype			
GCB	13	11 (84.6)	[54.6, 98.1]
Non-GCB	31	17 (54.8)	[36.0, 72.7]
Unknown	0	-	-
SPD at target lesion (mm^2) (central review)			
<400	23	19 (82.6)	[61.2, 95.0]
≥400	21	9 (42.9)	[21.8, 66.0]
Karnofsky Performance Status			
≤80	24	15 (62.5)	[40.6, 81.2]
90–100	20	13 (65.0)	[40.8, 84.6]

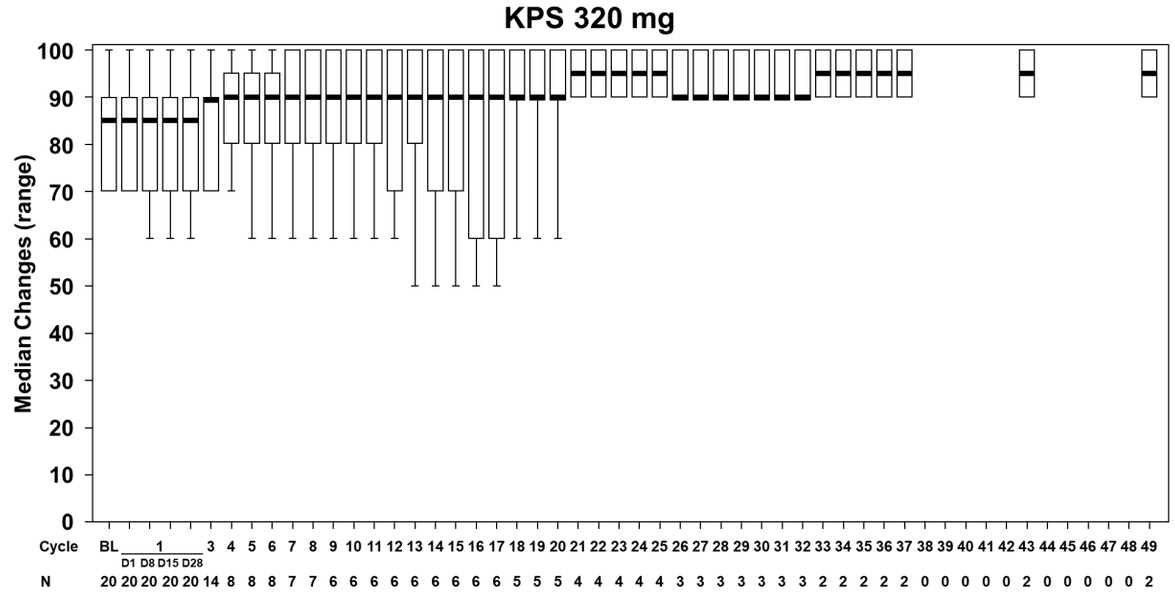


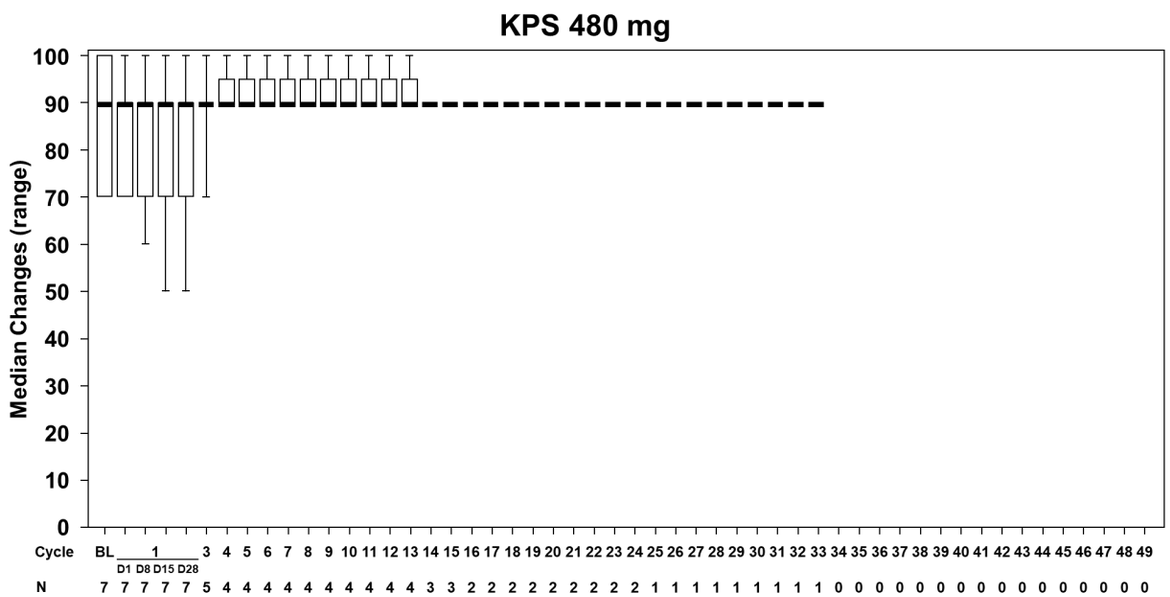
Supplementary Figure 4. Subgroup analysis of ORR by patient characteristics.
The best overall response was assessed according to the International PCNSL Collaborative Group (IPCG) criteria.
*The two-sided 95% confidence interval was calculated using the Clopper-Pearson method.
** "Yes" indicates that the patient had mutation in CD79A or CD79B. "No" indicates that the patient had no mutation in either gene.
CI, confidence interval; GCB, germinal center B-cell-like; HCT-ASCT, high-dose chemotherapy followed by autologous stem cell transplantation; ORR, overall response ratio; PCNSL, primary central nervous system lymphoma; SPD sum of the products of the greatest diameters; WBRT, whole-brain radiotherapy.

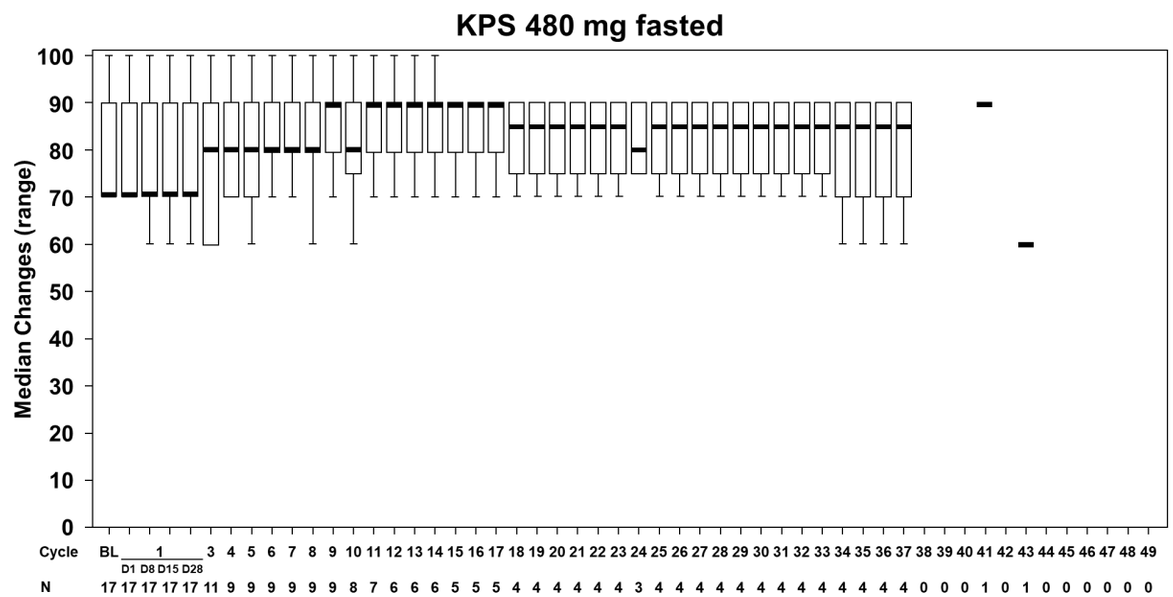


Supplementary Figure S5. Time to first onset of treatment-related AEs of special interest
AE, adverse events.



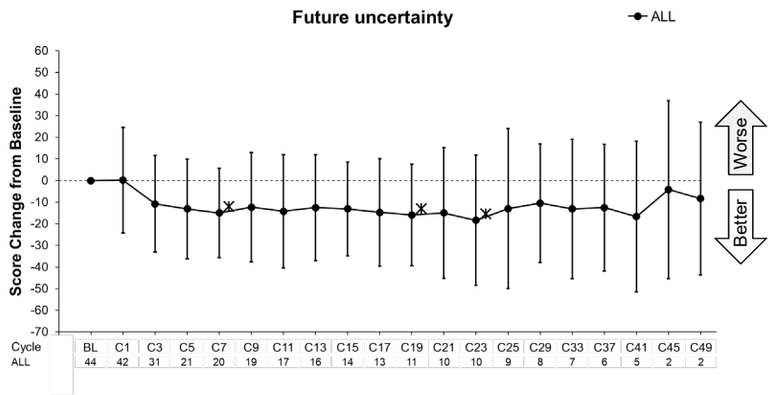


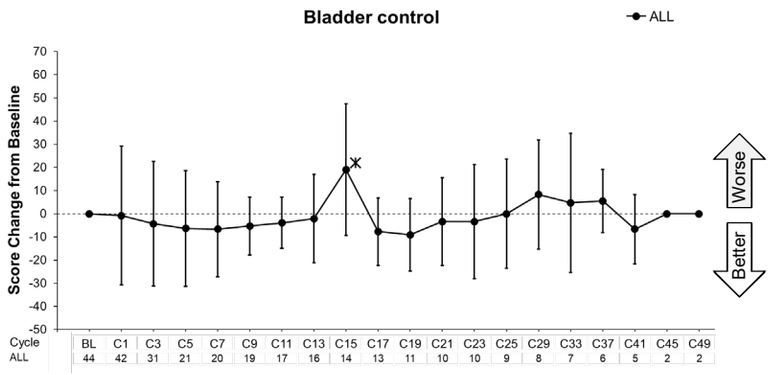


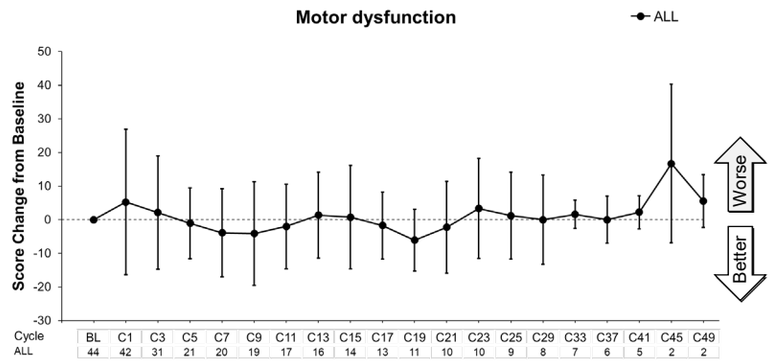


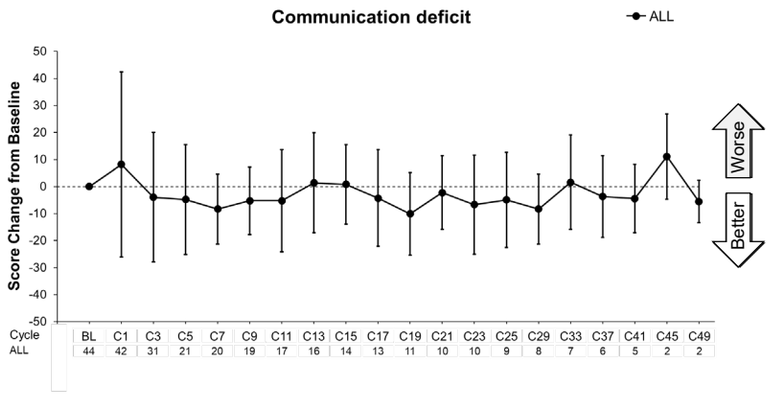
Supplementary Figure S6. KPS in all patients and each dose group
Boxplot diagrams for the KPS scores in each cycle of treatment. The boxes, thick line inside the boxes, and whiskers indicate the interquartile ranges, medians, and ranges, respectively. BL, baseline.

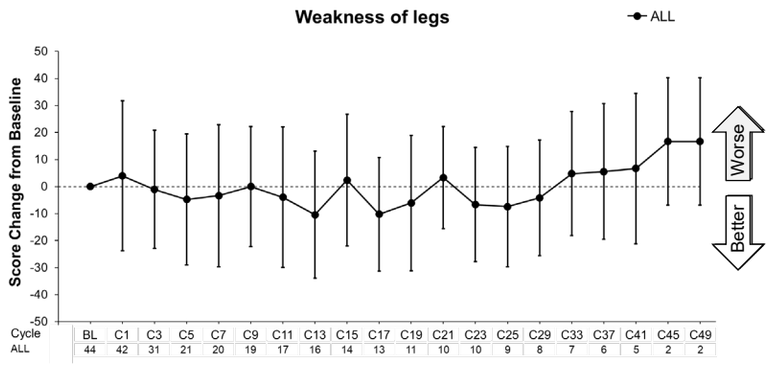
Supplementary Figure S7. See figure legend for the later page











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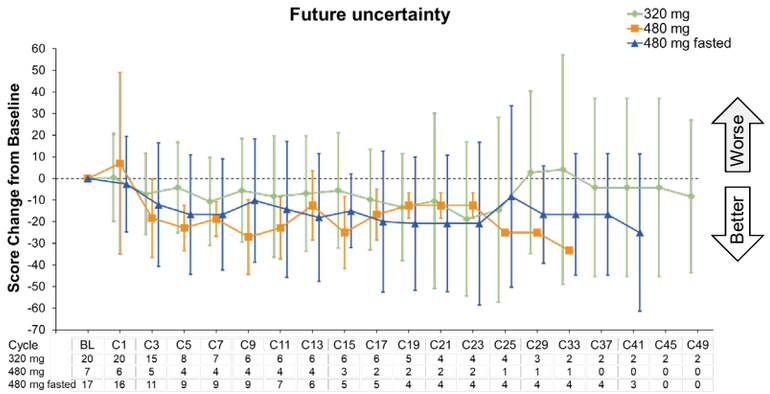

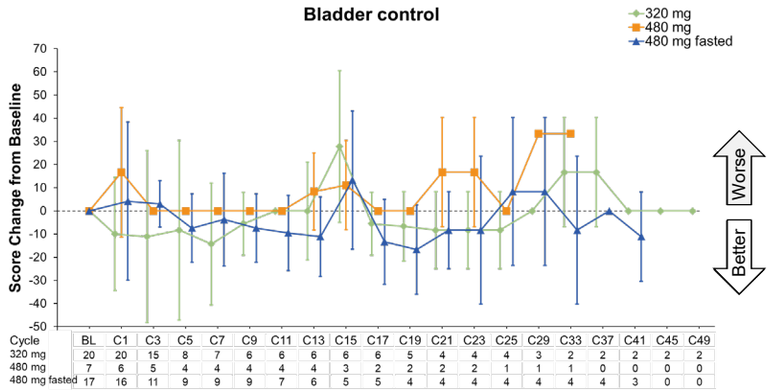

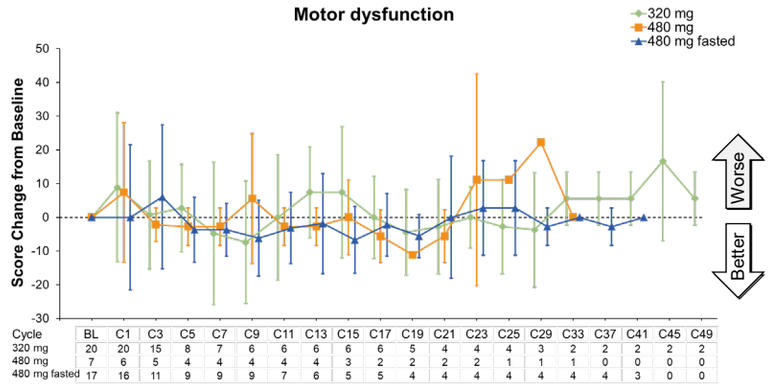

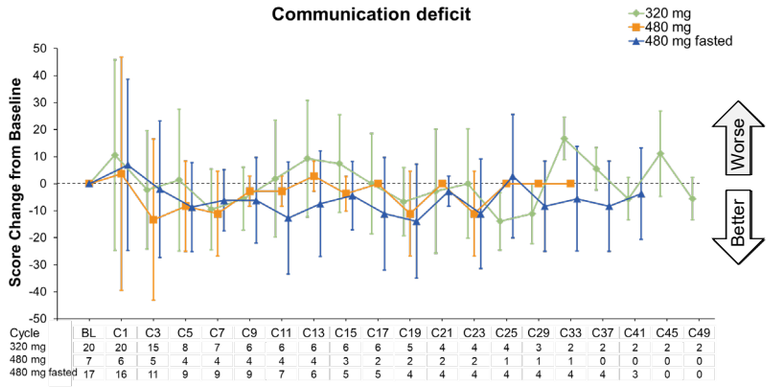

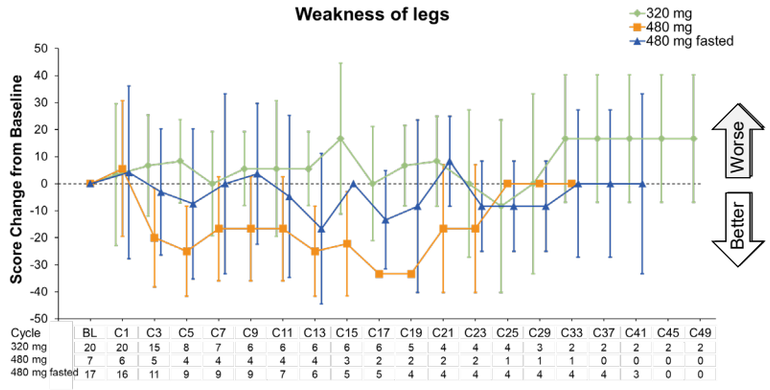

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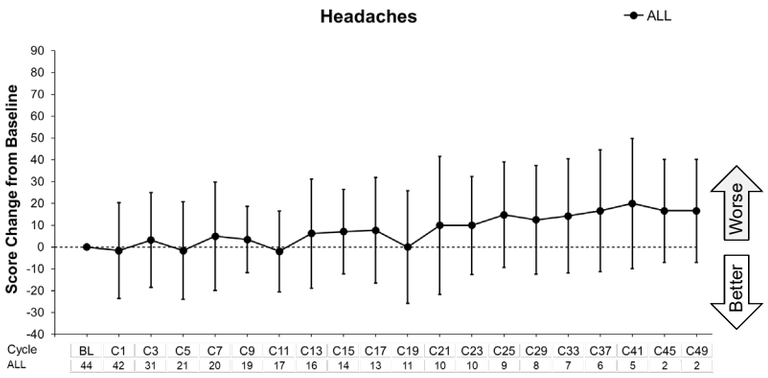
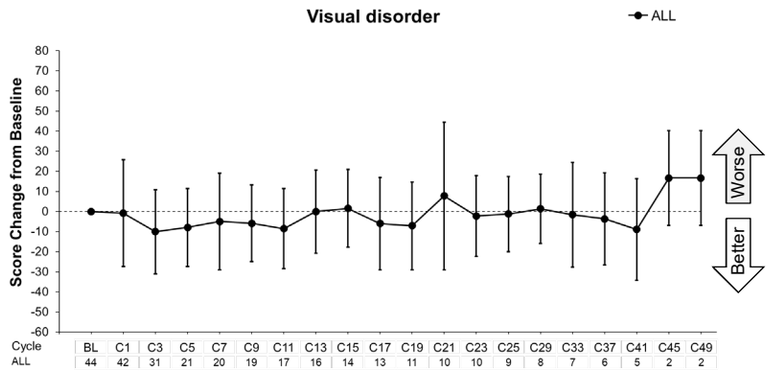
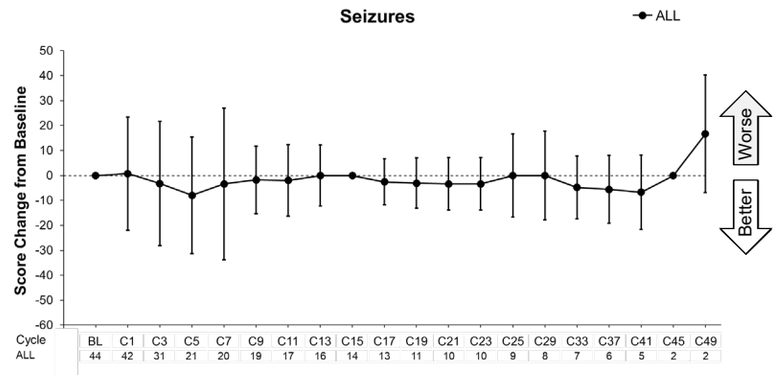
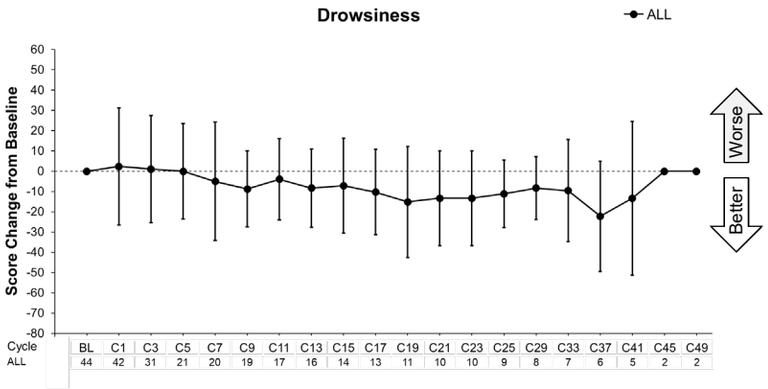
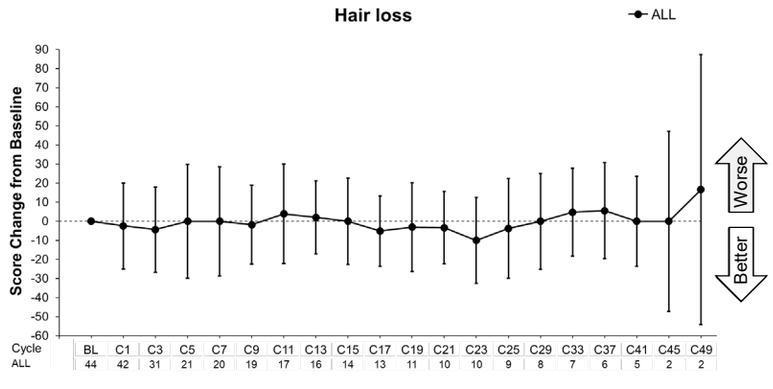
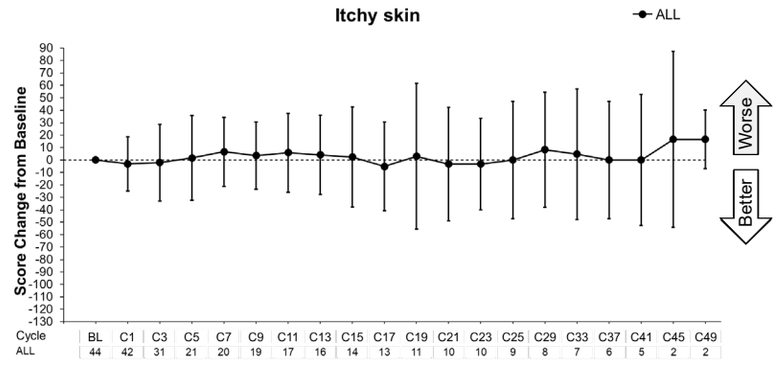


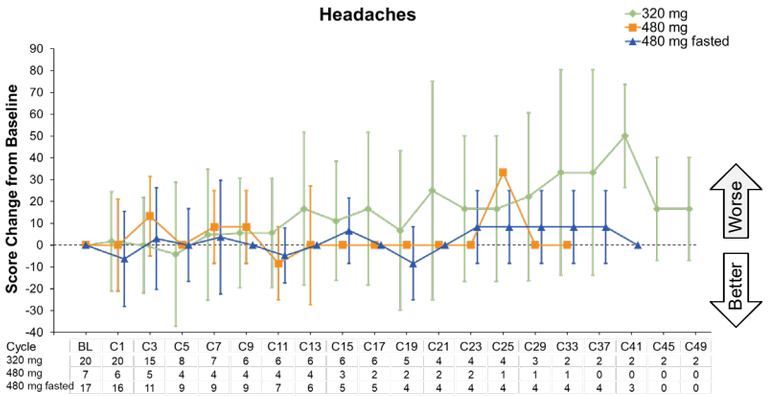


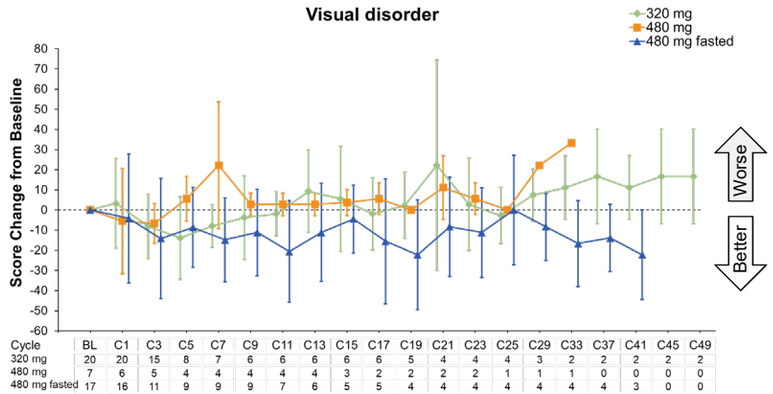


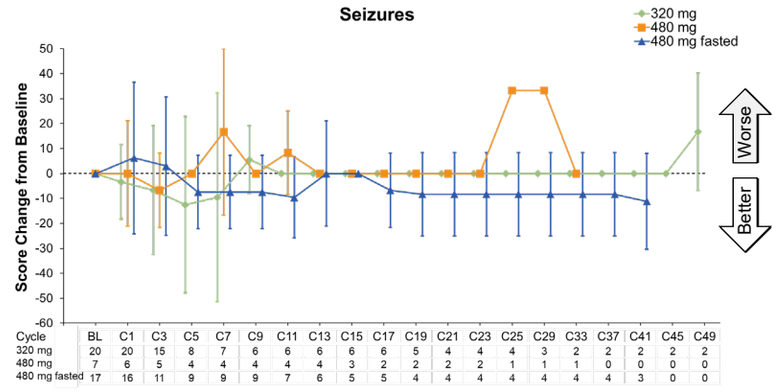


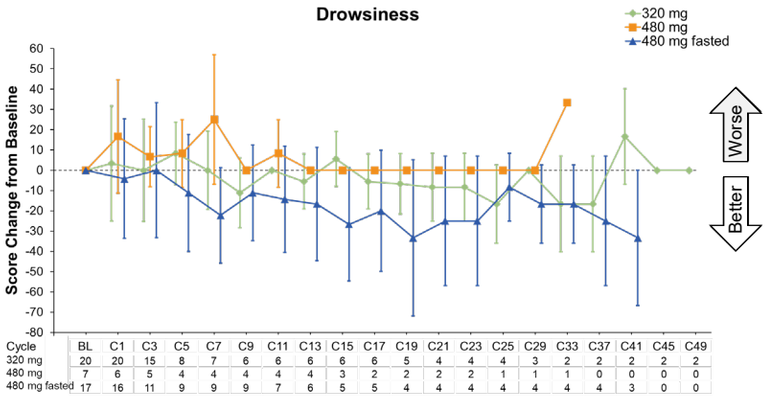


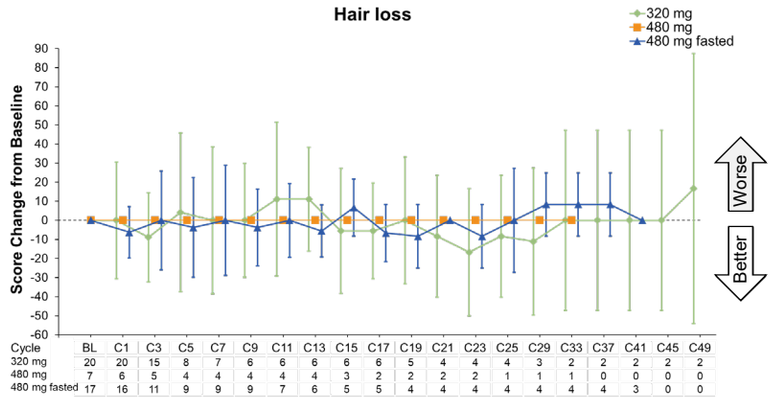


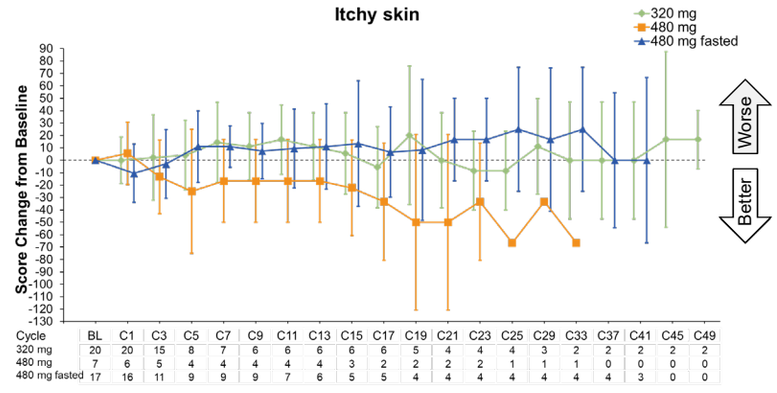








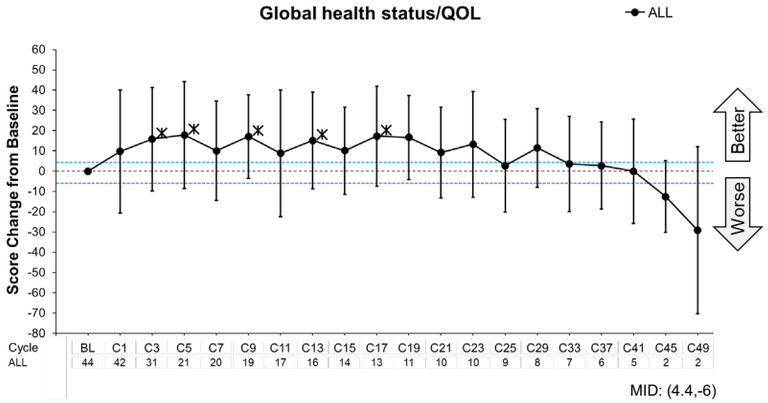


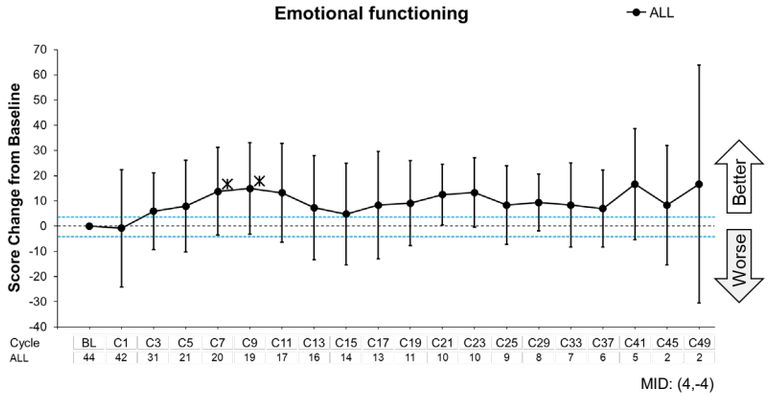


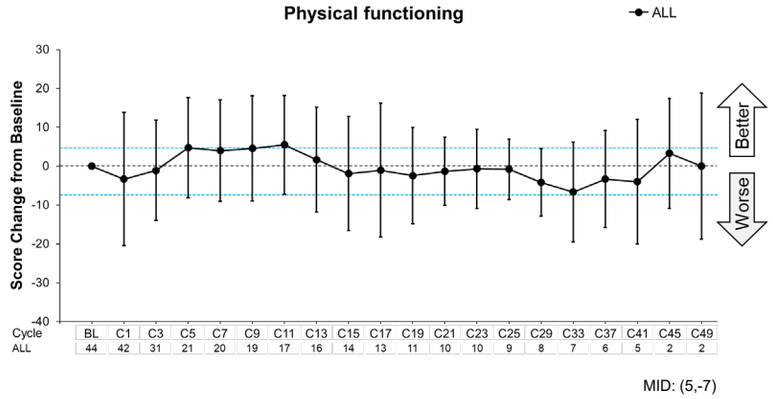
Supplementary Figure S7. QLQ-BN20 in all patients and each dose group

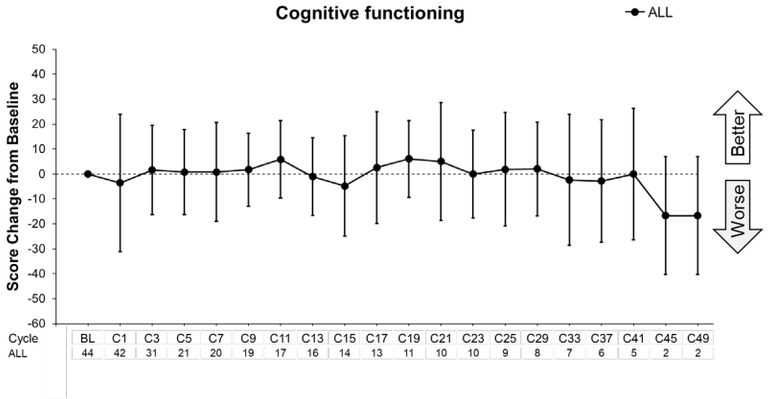
The average changes from baseline are shown. Error bars indicate the standard deviation. The horizontal dotted black lines show the baselines. *P <0.05 in the Dunnett's test in comparison with the baselines. BL, baseline; QLQ-BN20, the core QoL questionnaires-BN20.

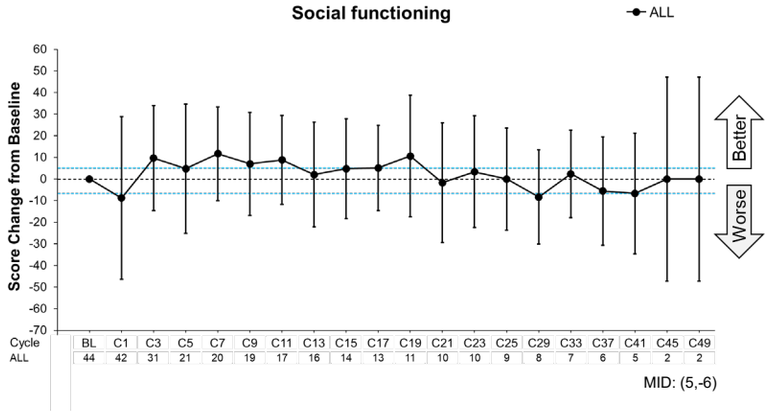
Supplementary Figure S8. See figure legend for the later page

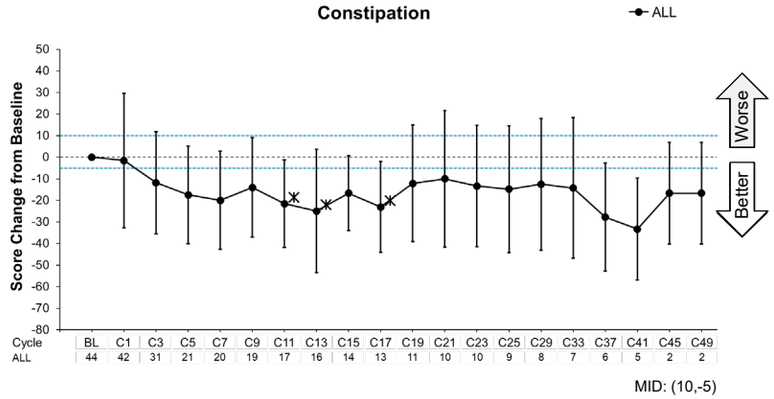


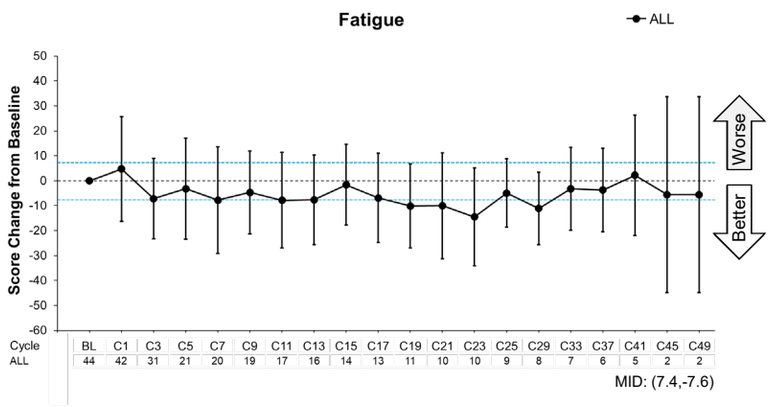












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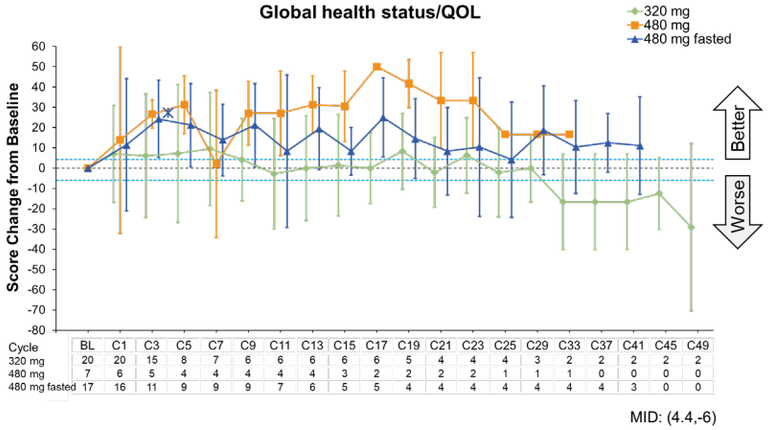

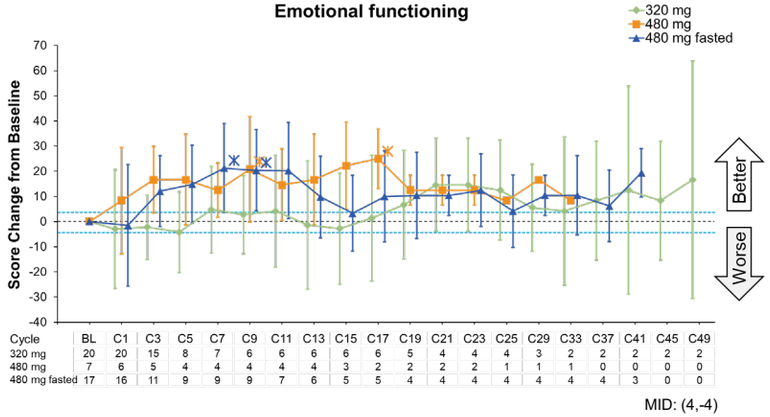

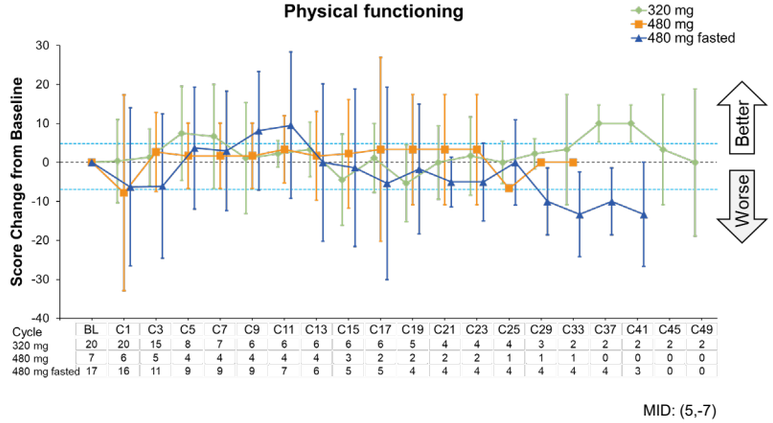

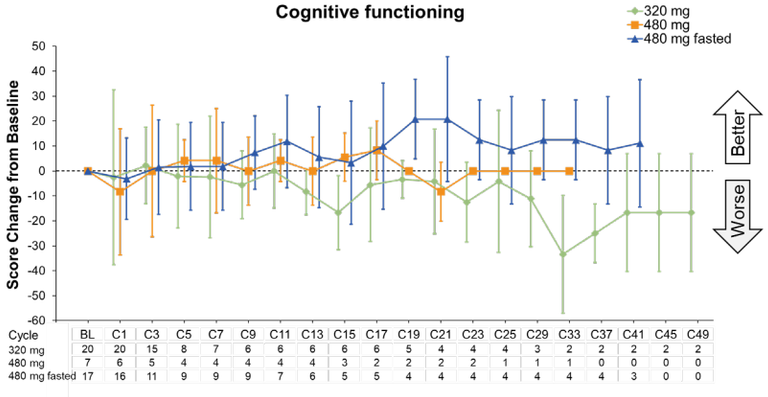

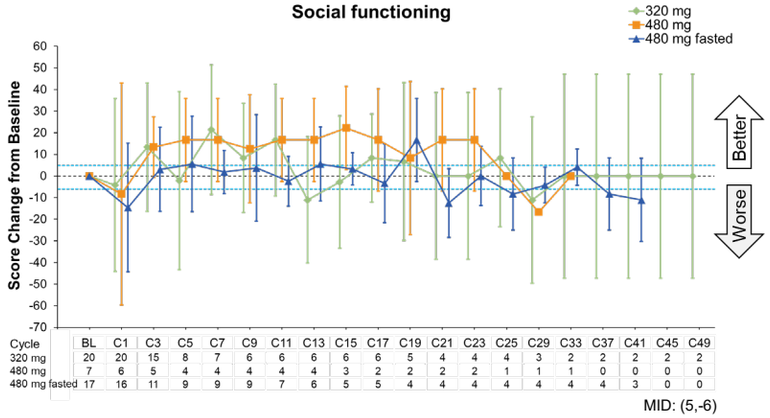

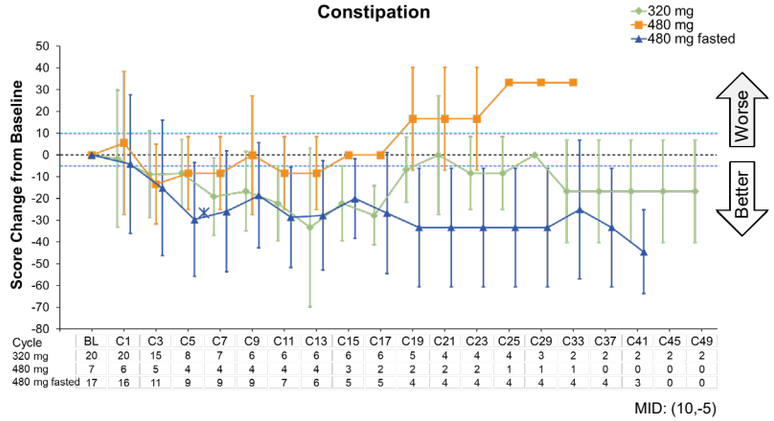

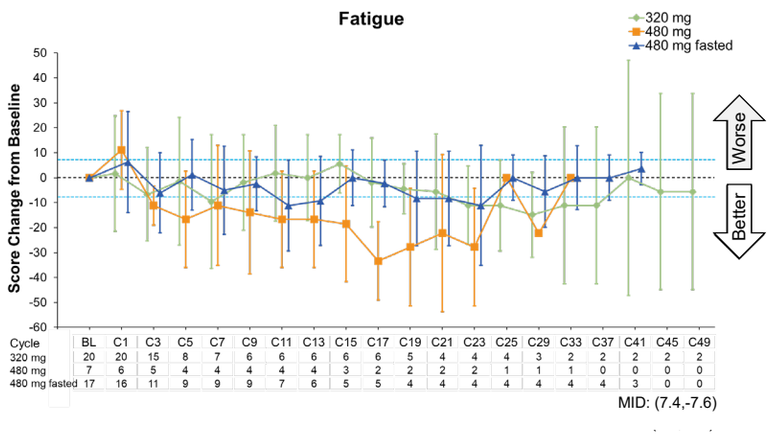

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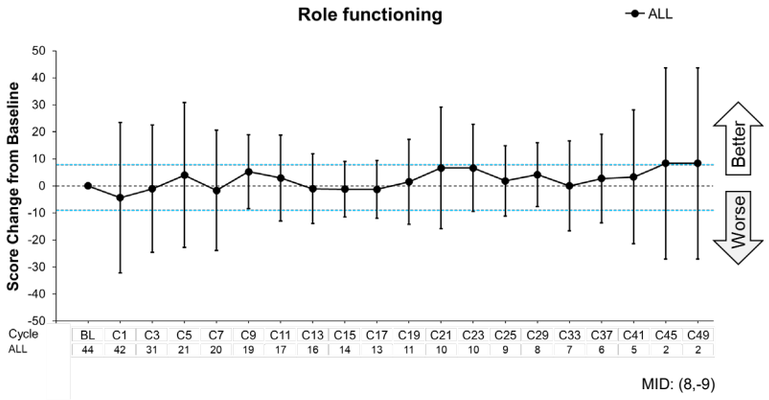
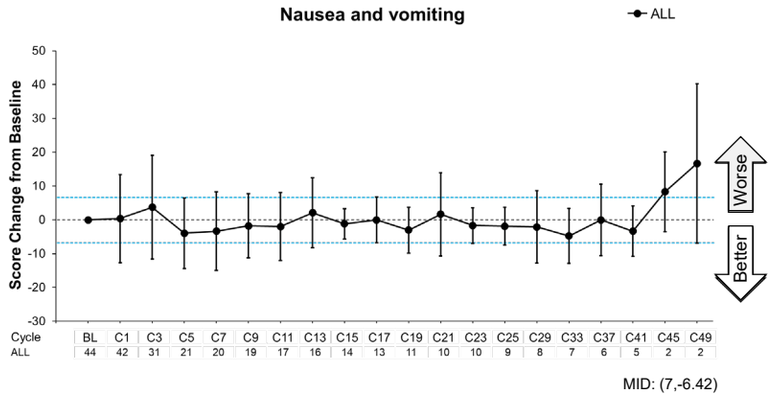
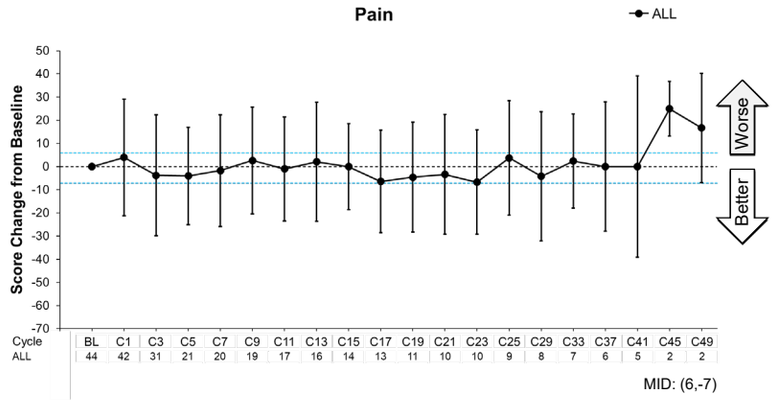
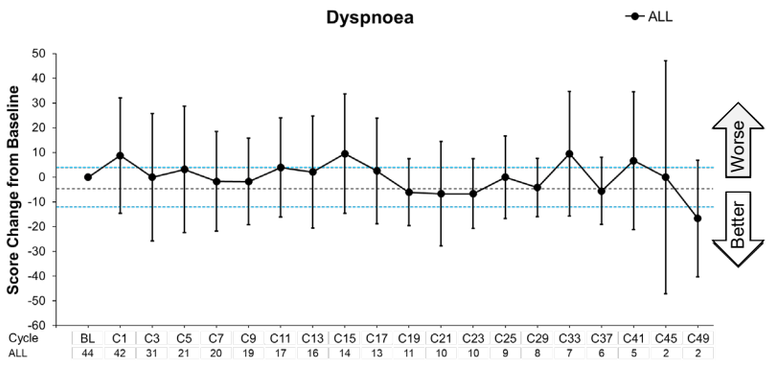
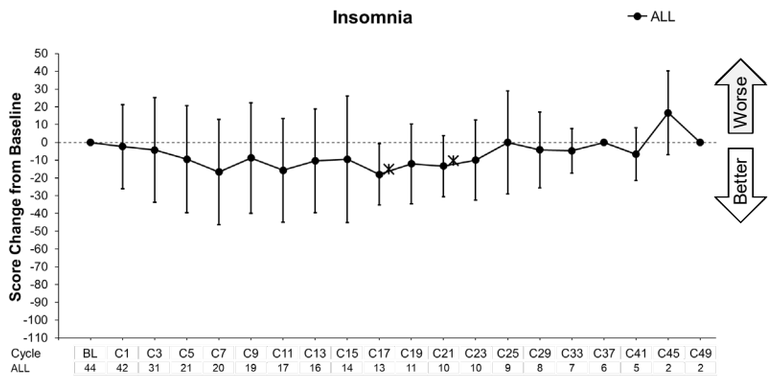
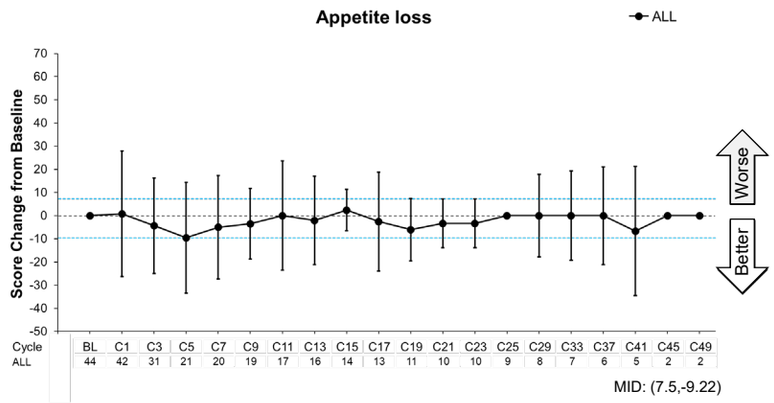


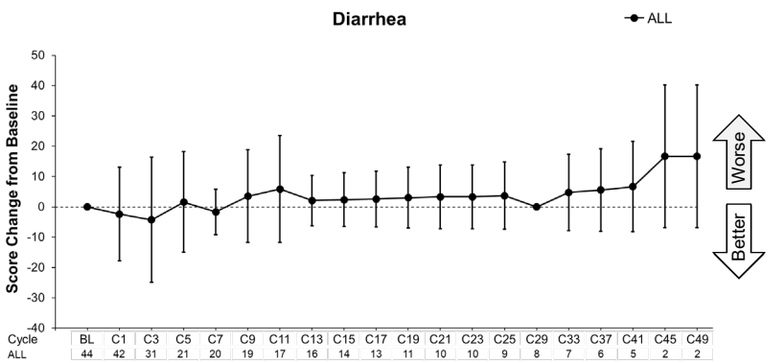


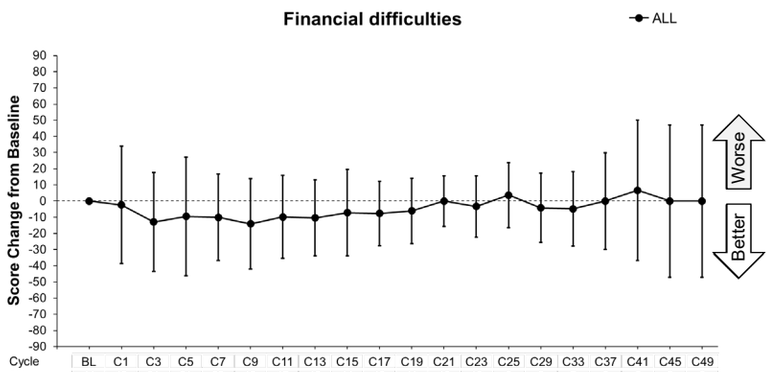


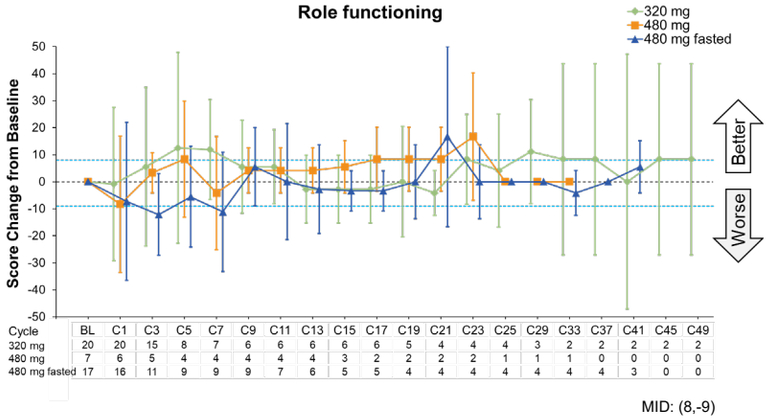


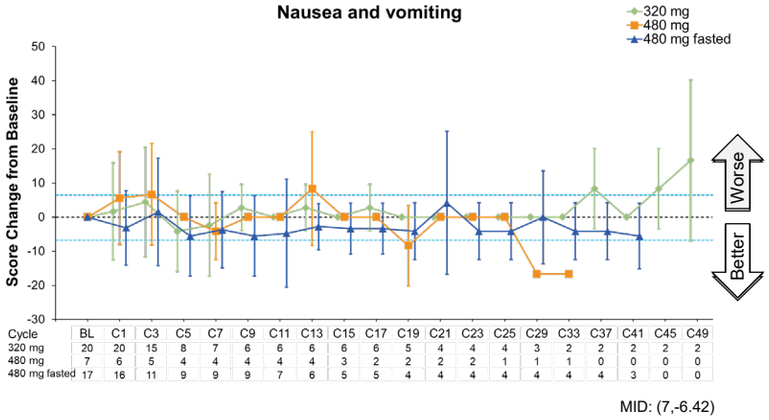


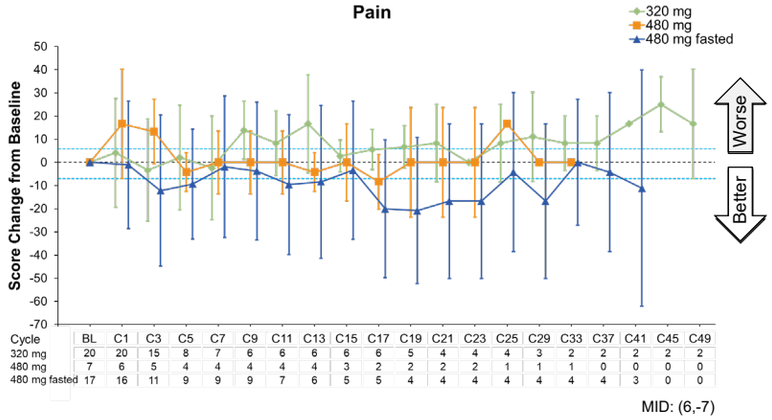


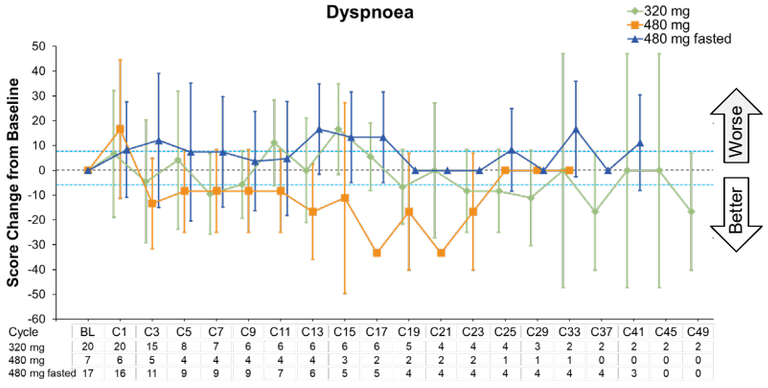


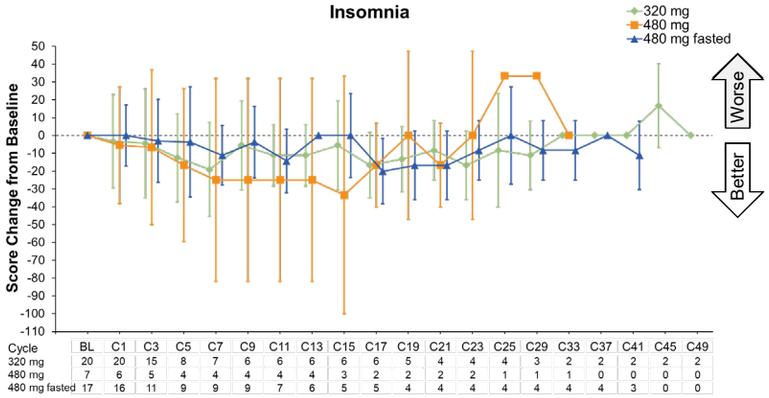


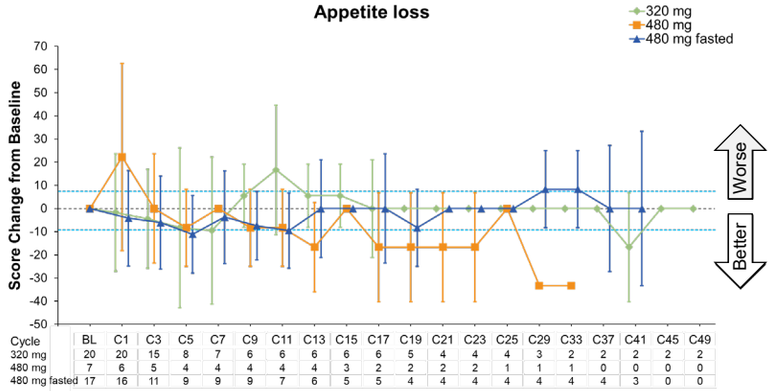


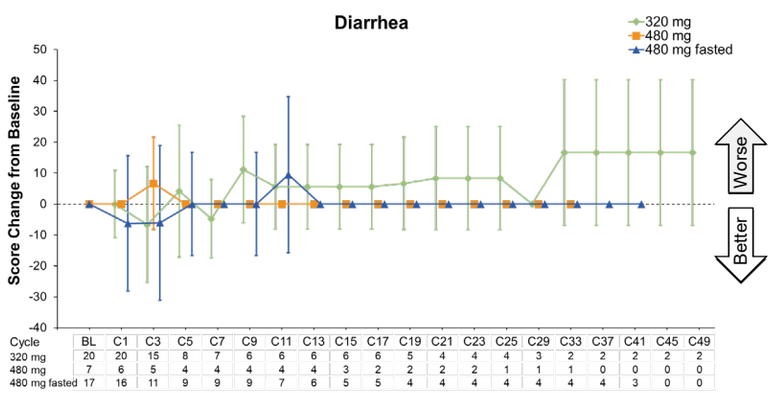


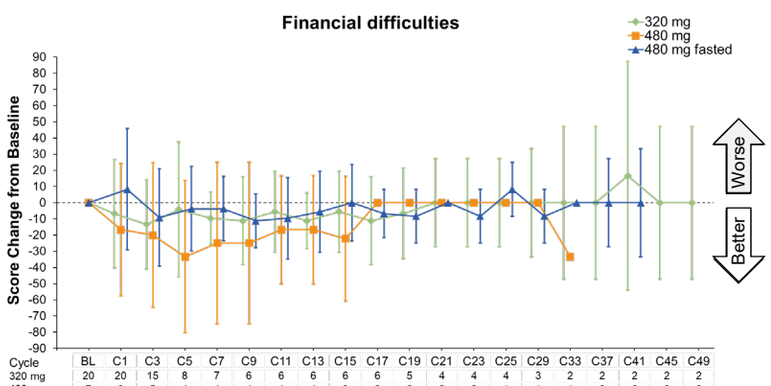






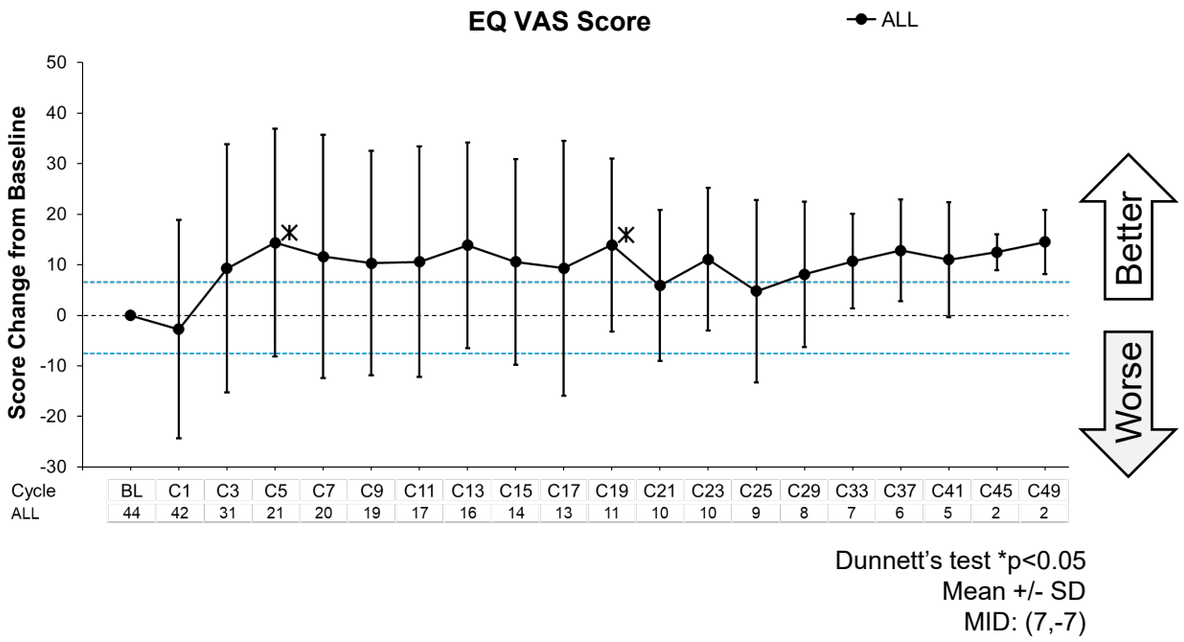


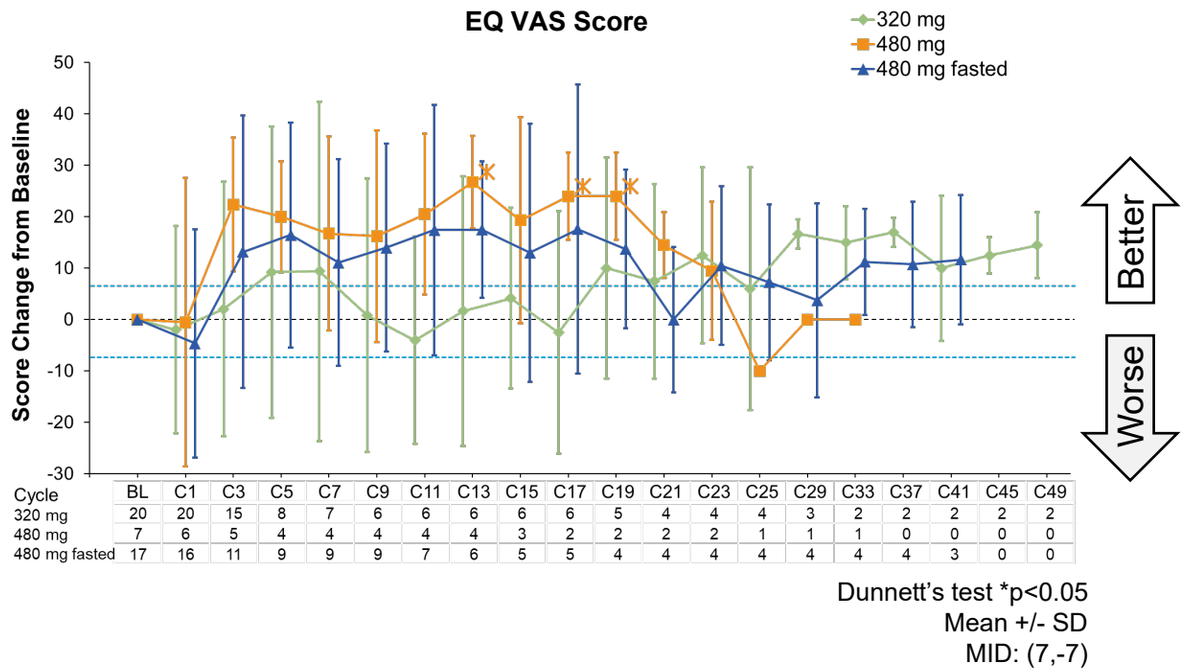


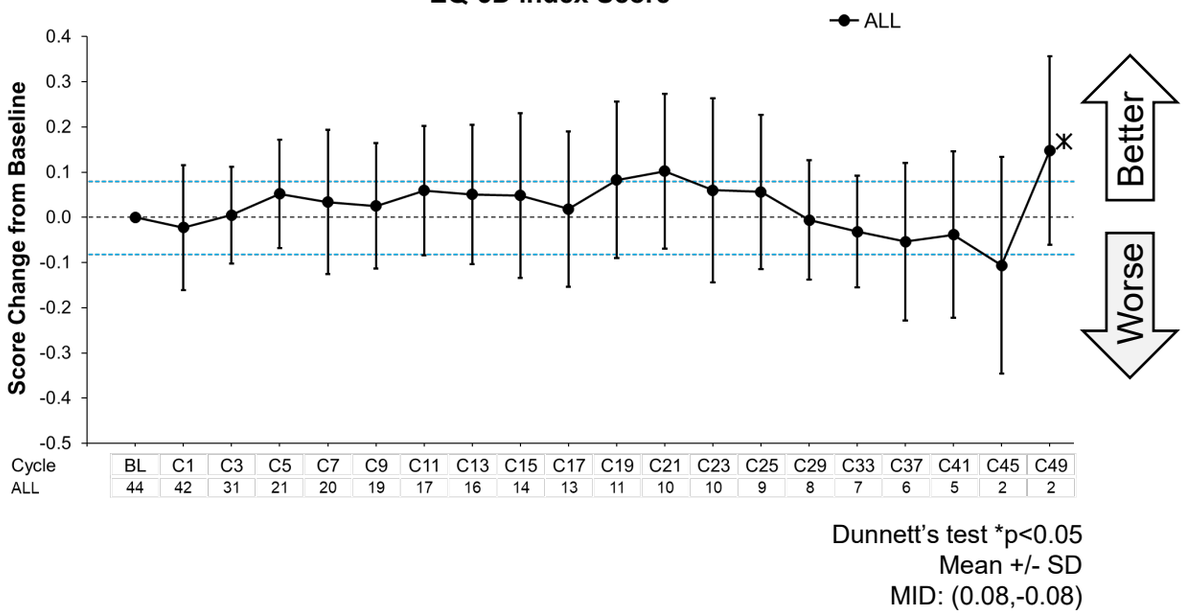


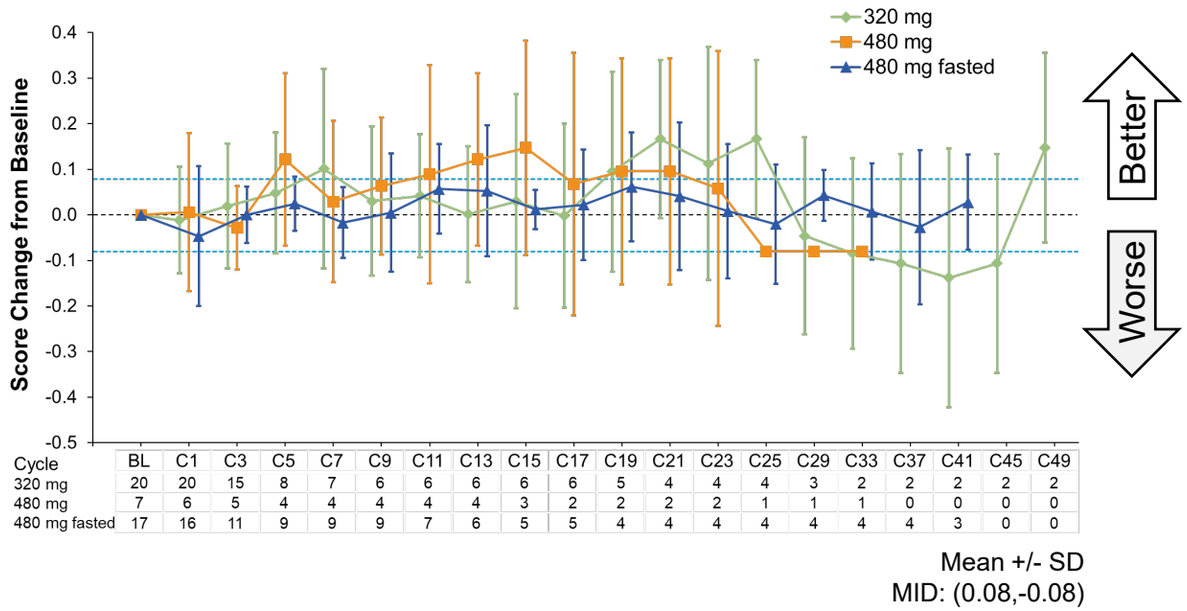
Supplementary Figure S8. QLQ-C30 in all patients and each dose group

The average changes from baseline are shown. Error bars indicate the standard deviation. The horizontal dotted black lines and dotted light blue lines show the baselines and minimally important differences, respectively. *P <0.05 in the Dunnett's test in comparison with the baselines. BL, baseline; QLQ-C30, core QoL questionnaires-C30; MID, minimally important difference.









Supplementary Figure S9. EQ-5D-3L scores in all patients and each dose group

The average changes from baseline are shown. Error bars indicate the standard deviation. The horizontal dotted black lines and dotted light blue lines show the baselines and minimally important differences, respectively. *P <0.05 in the Dunnett's test in comparison with the baselines. BL, baseline; EQ-5D-3L, the EuroQoL 5 dimensions 3-level; MID, minimally important difference; VAS, visual analog scales.