Tafasitamab for patients with relapsed or refractory diffuse large B-cell lymphoma: final 5-year efficacy and safety findings in the phase II L-MIND study

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Supplemental Information

Supplemental Methods

Exposure-adjusted Comparison of Treatment Emergent Adverse Events (TEAE) Frequency

Patients in the L-MIND study ended tafasitamab + lenalidomide combination therapy at different time points, owing to study design and patient disposition, and consequently continued with tafasitamab monotherapy for varying durations. We examined treatment exposure during three periods, corresponding to combination therapy, short-term tafasitamab monotherapy, and long-term tafasitamab monotherapy:

Combined therapy or lenalidomide
Period of tafasitamab + lenalidomide treatment, or in the event that tafasitamab is stopped before lenalidomide, up to the last time point of lenalidomide treatment.
Population: 80 patients, with a total combined exposure of 44.06 person years

Tafasitamab monotherapy up to 2 years
Period after discontinuation of lenalidomide until up to 2 years from the start of study treatment (also includes one patient who did not receive any lenalidomide).
Population: 52 patients, with a total exposure of 35.67 person years of tafasitamab

Tafasitamab monotherapy beyond 2 years
A subgroup of patients with long duration of treatment.
Population: 27 patients, with a total exposure of 64.01 person years of tafasitamab

TEAEs were classified into the applicable periods according to the following rules:

Combined therapy or lenalidomide
- For patients with no tafasitamab monotherapy period (last treatment exposure is to lenalidomide), all TEAEs were counted, including events that occurred after the end of treatment but were classified as treatment emergent
- For patients with a tafasitamab monotherapy period after ending lenalidomide treatment, all TEAEs that started before the last date of exposure to lenalidomide were counted

Tafasitamab monotherapy up to 2 years
- For patients with a monotherapy period and total tafasitamab exposure <2 years, TEAEs with a start date after the end of lenalidomide exposure, as well as TEAEs that started in the prior combination therapy phase and either ended in the monotherapy phase or do not have an end date, were counted
- For patients with a monotherapy period and total tafasitamab exposure >2 years, TEAEs that started after the end of lenalidomide exposure and within 2 years since start of combination therapy phase, as well as TEAEs that started in the prior combination therapy phase and either ended in the 2 years since the start of combination therapy or continued beyond the 2-year cut-off, were counted

Tafasitamab monotherapy beyond 2 years
- For patients with total tafasitamab exposure >2 years, TEAEs that started after 2 years from the start of study treatment, as well as TEAEs that started before 2 years but either ended after the 2 year period or do not have an end date, were counted

Based on these rules, a single TEAE might be counted in one, two or all three periods; thus, TEAEs were partially overestimated for some individuals. However, this method provides conservative and statistically robust estimates of the frequency of TEAEs per unit of treatment exposure time across the three periods. It does not distinguish between individuals having more or less events, but given the distribution of patients and treatment exposure across the periods, we consider event rate as a more reliable estimate for comparing safety outcomes than the proportion of individuals having specific safety outcomes.

Exploratory Subgroup Analyses

Regression Analysis

Regression analyses were performed for objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) based on important covariates of interest: Age group (≤70 years vs >70 years); Prior lines of treatment (1 vs ≥2); Lactate dehydrogenase (LDH) level (High vs Low); Bulky Disease (Yes vs No); International Prognostic Index (IPI) score (0–2 vs 3–5); and natural killer (NK) cell count at baseline (≥100 vs <100 cells/µL). Univariate analyses for each individual covariate were followed by a multiple covariate adjusted (multivariate) model to explore the association effects that remain after adjusting for other covariates. IPI score was not included in the multivariate models as this score is derived from other characteristics (LDH level, Bulky Disease, Prior lines of treatment and Age).

For ORR, a binary outcome of Response (complete response [CR] or partial response [PR]) Yes vs. No, logistic regression analysis using the logit link function was used to obtain the odds ratio (OR) to describe the association between the covariate and the likelihood of response versus no response. OR values >1 indicate greater likelihood of response.

For the time-to-event outcomes (PFS and OS), Cox Proportional Hazards models were used to obtain estimates of the Hazard Ratio (HR) for each covariate for the outcome. HR values >1 indicate longer time without disease progression, or longer survival.

Binary Outcome Proportions

For binary outcomes such as ORR, PR, and CR outcomes as Yes/No based on the covariates of interest (such as prior lines of treatment or best response or NK cell count) summaries of the proportions were obtained using the underlying Binomial distribution for the outcomes. The corresponding confidence intervals for the estimated proportions were based on the Clopper-Pearson method derived using the cumulative probabilities of the binomial distribution.

Survival Rate Estimates

For time-to-event outcomes such as PFS, duration of response (DoR), duration of complete response (DoCR) and OS based on the covariates of interest (such as prior lines of treatment or best response or NK cell count), summary of the survival rate estimates were obtained using non-parametric methods like Kaplan-Meier Estimator or the Kaplan–Meier estimates of quantiles of the (observed time to event) survival time distribution. Time under follow-up for the specific time to events were obtained using the inverse Kaplan–Meier estimates. The confidence intervals for the estimates were obtained using the complimentary log-log transformation for the standard errors.

NK cell count

NK cell analysis was performed centrally using a fit-for-purpose validated method. Whole blood samples were shipped at ambient temperature to the central lab where staining and measurement was carried out. NK cells were identified as $SSC^{low}CD45^{+}CD13^{-}CD3^{-}CD16/56^{+}$. Absolute NK cell counts were determined using Trucount tubes.

Table: Antibody-fluorochrome combination used to identify NK cells

Fluorochrome	FITC	PE	PerCP	APC
Antigen	CD3	CD16/CD56	CD45	CD13

Rationale for NK cell threshold

Several published studies have evaluated clinical outcomes in relation to high or low baseline NK cell count (NKCC) in patients receiving first-line therapy, e.g., patients newly diagnosed with diffuse large B-cell lymphoma (DLBCL)[1,2] or previously untreated patients with follicular lymphoma (FL).[2,3] A cut-off of 100 cells/µL showed independent prognostic value and was generally based on maximized differences in PFS and/or OS between patients with baseline NKCC-low and NKCC-high. Similarly, in a Phase IIa study of tafasitamab in patients with relapsed or refractory DLBCL or FL (NCT01685008), a cut-off 100 NK cells/µL was prognostic for treatment outcome.[4]

1. Kim JK, Chung JS, Shin HJ, et al. Influence of NK cell count on the survival of patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood Res 2014;49(3):162–169.
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4. Jurczak W, Zinzani PL, Gaidano G, et al. Phase IIa study of the CD19 antibody MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. Ann Oncol 2018;29(5):1266–1272.

Supplemental Table 1. Baseline characteristics in USPI population in the safety analysis set and by pLoT subgroups

	Patients in the USPI population in the safety analysis set	1 prior line of therapy	2+ prior lines of therapy
N	71	35	36
Median age, years (range)	71.0 (41.0–86.0)	72.0 (53.0–86.0)	68.5 (41.0–82.0)
Age >70 years, n (%)	39 (54.9)	23 (65.7)	16 (44.4)
Sex, n (%)			
Female	32 (45.1)	16 (45.7)	16 (44.4)
Male	39 (54.9)	19 (54.3)	20 (55.6)
Ann Arbor stage, n (%)			
I–II	16 (22.5)	8 (22.8)	8 (22.2)
III–IV	55 (77.4)	27 (77.1)	28 (77.7)
IPI score, n (%)			
0–2	34 (47.8)	21 (60.0)	13 (36.1)
3–5	37 (52.1)	14 (40.0)	23 (63.8)
Elevated LDH, n (%)			
Yes	40 (56.3)	16 (45.7)	24 (66.7)
No	31 (43.7)	19 (54.3)	12 (33.3)
Prior lines, n (%)			
1	35 (49.3)		
2	31 (43.7)		
3	4 (5.6)		
4	1 (1.4)		
Primary refractory*, n (%)			
Yes	14 (19.7)	5 (14.3)	9 (25.0)
No	57 (80.3)	30 (85.7)	27 (75.0)
Refractory to previous therapy line, n (%)			
Yes	32 (45.1)	5 (14.3)	9 (25.0)
No	39 (54.9)	30 (85.7)	27 (75.0)
Prior ASCT, n (%)			
Yes	9 (12.7)	2 (5.7)	7 (19.4)
No	62 (87.3)	33 (94.3)	29 (80.6)
Cell of origin (by IHC), n (%)			
GCB	39 (54.9)	16 (45.7)	23 (63.9)
Non-GCB	22 (31.0)	14 (40.0)	8 (22.2)
Unknown / NE	10 (14.1)	5 (14.3)	5 (13.9)

ASCT, autologous stem cell transplant; GCB, germinal center B; IHC, immunohistochemistry; LDH, lactate dehydrogenase; NE, not estimable; pLoT, prior line of therapy; USPI, US prescribing information.

Supplemental Table 2. Efficacy outcomes in the 5-year follow-up analyses in the USPI population at baseline

	Combined (n=71)	**Patients with 1 pLoT (n=35)**	**Patients with ≥2 pLoT (n=36)**
Best ORR, n (%) [95% CI]	38 (53.5) [41.3–65.5]	22 (62.9) [44.9–78.5]	16 (44.4) [27.9–61.9]
CR rate, n (%) [95% CI]	26 (36.6) [25.5–48.9]	17 (48.6) [31.4–66.0]	9 (25.0) [12.1–42.2]
PR rate, n (%) [95% CI]	12 (16.9) [9.0–27.7]	5 (14.3) [4.8–30.3]	7 (19.4) [8.2–36.0]
Median DoR, months [95% CI]	NR [21.7–NR]	NR [9.1–NR]	NR [4.4–NR]
Median PFS, months [95% CI]	8.7 [4.7–45.5]	16.2 [5.3–NR]	5.7 [2.1–28.0]
Median OS, months [95% CI]	24.8 [14.8–45.7]	45.7 [19.3–NR]	13.1 [7.6–31.6]

Data cut-off date: November 14, 2022. CI, confidence interval; CR, complete response; DoR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pLoT, prior line of therapy; PR, partial response; USPI, US prescribing information.

Supplemental Table 3. Kaplan–Meier 5-year rate estimates for time-to-event endpoints in subgroups of clinical interest

		N	Median PFS	Median OS	N	Median DoR
FAS		80	11.6 [5.7–45.7]	33.5 [18.3–NR]	46	NR [33.8–NR]
Age	≤70 yr	35	23.5 [5.3–NR]	45.2 [22.5–NR]	21	NE [21.7– NE]
	>70 yr	45	10.9 [4.3–NR]	24.8 [12.1–NR]	25	NE [9.1–NE]
Number of pLoT	1	40	23.5 (7.4–NR)	NR (24.6–NR)	27	NR (9.1–NR)
	≥2	40	7.6 (2.7–45.5)	15.5 (8.6–45.5)	19	NR (26.1–NR)
IPI score	0–2	40	NE [10.9–NE]	NE [33.5–NE]	27	NE
	3–5	40	5.7 [03.6–11.6]	14.8 [8.6–24.6]	19	21.7 [4.4–NE]
Bulky disease (≥7.5 cm)	Yes	14	5.7 [1.3–NE]	26.4 [1.7–NE]	6	NE [3.9–NE]
	No	65	12.1 [7.4–NE]	34.1 [18.6–NE]	40	NE [33.5–NE]
Time to progression after 1L therapy†	<12 mo‡	20	9.1 [3.9–NE]	34.6 [13.8–NE]	10	NE [1.8–NE]
	≥12 mo	20	45.7 [10.9–NE]	NE [24.6–NE]	17	NE [8.1–NE]

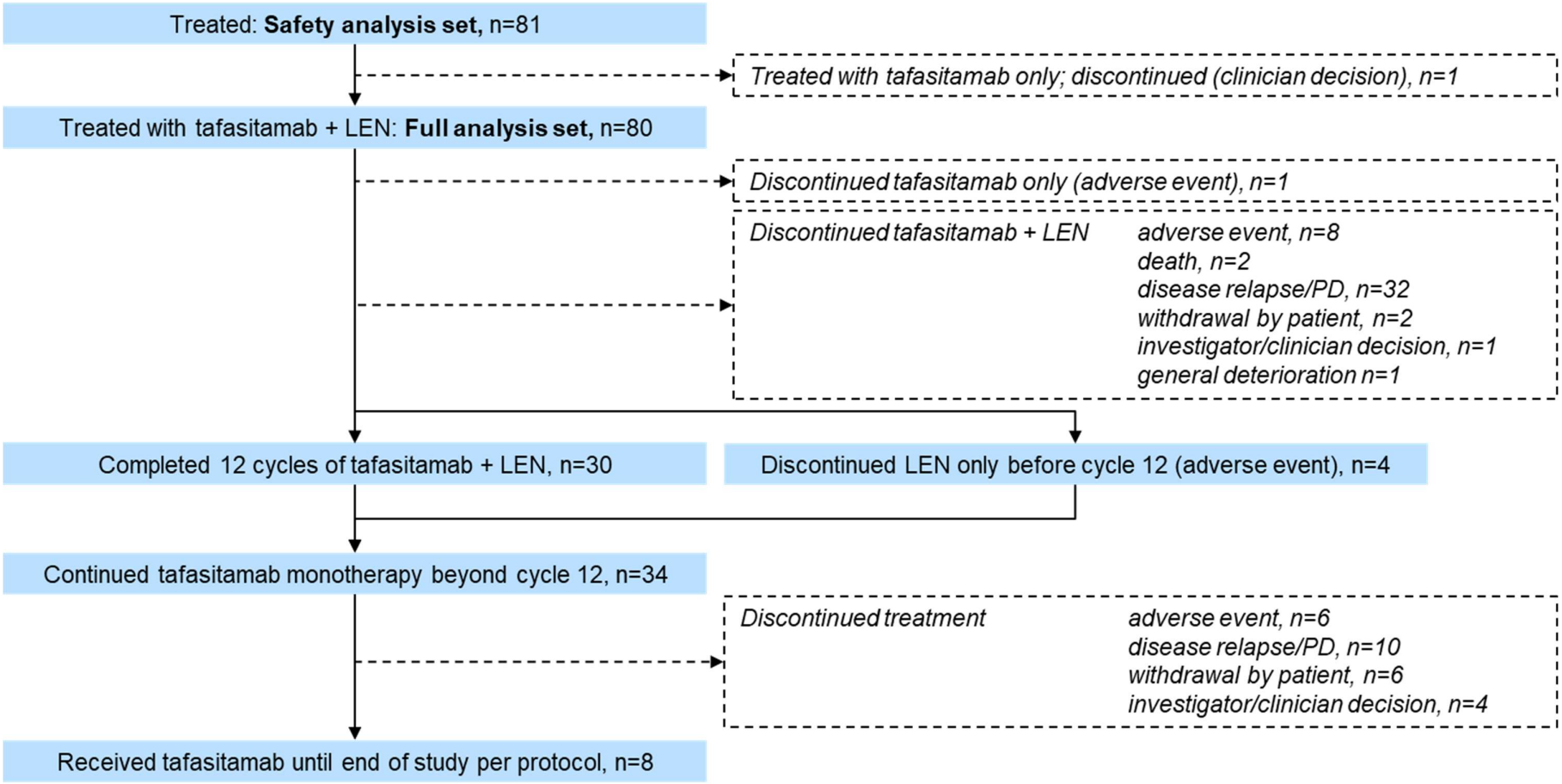
†Patients with 1 prior line of therapy. ‡Includes primary refractory. 1L, first line; DoR, duration of response; FAS, full analysis set; IPI, International Prognostic Index; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; pLoT, prior line of therapy.

Supplemental Table 4: Univariate and multivariate analysis of efficacy outcomes according to potential prognostic factors

	N	ORR: OR		PFS: HR		OS: HR	
OR or HR (95% CI); p-value		Univariate	**Multivariate**	Univariate	**Multivariate**	Univariate	**Multivariate**
Age >70 years	80	0.83 (0.34–2.04); 0.7	0.63 (0.22–1.73); 0.4	1.13 (0.61– 2.08); 0.7	1.71 (0.85–3.41); 0.13	1.41 (0.77–2.58); 0.27	**2.26** (1.10–4.63); 0.027
IPI 3–5	80	0.44 (0.17–1.07); 0.073	NA	**2.99** (1.57–5.67); <0.001	NA	**3.03** (1.63–5.64); <0.001	NA
≥2 Prior lines of therapy	80	2.3 (0.94–5.80); 0.073	2.0 (0.74–5.61); 0.2	0.6 (0.33–1.11); 0.1	0.78 (0.41–1.48); 0.4	**0.5** (0.27–0.91); 0.022	0.63 (0.33–1.21); 0.2
High LDH	80	0.76 (0.31–1.86); 0.6	1.08 (0.39–3.06); 0.9	**2.3** (1.21–4.39); 0.011	**2.05** (1.04–4.07); 0.039	**2.28** (1.22–4.27); 0.01	1.75 (0.89– 3.44); 0.11
Bulky-disease	79	0.47 (0.14–1.50); 0.2	0.57 (0.16–2.02); 0.4	1.57 (0.72–3.39); 0.26	1.49 (0.67–3.36); 0.3	1.54 (0.71–3.33); 0.27	1.76 (0.77– 3.99); 0.2
<100 NK cells/µL	74	0.48 (0.18–1.21); 0.12	0.51 (0.19–1.35); 0.2	**1.94** (1.03–3.67); 0.04	**2.12** (1.08–4.18); 0.029	**1.99** (1.06–3.74); 0.032	**2.14** (1.11–4.14); 0.024

IPI score is not included in the multivariate model as the score is derived from other characteristics. Statistically significant associations (p<0.05) are emphasized in bold text. CI, confidence interval; HR, hazard ratio; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NA, not available; NK cell, natural killer cell; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

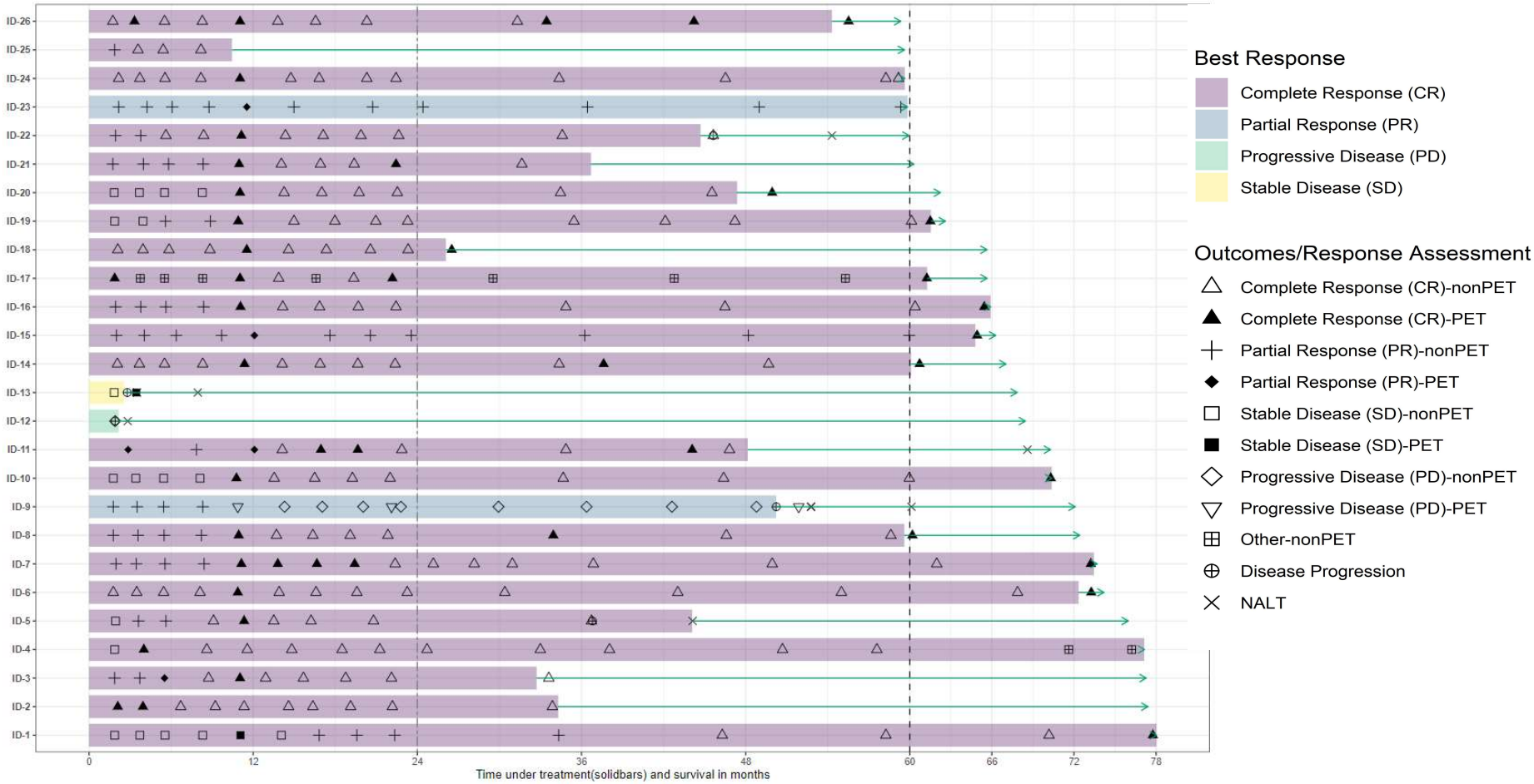
Supplemental Figure 1. Patient disposition



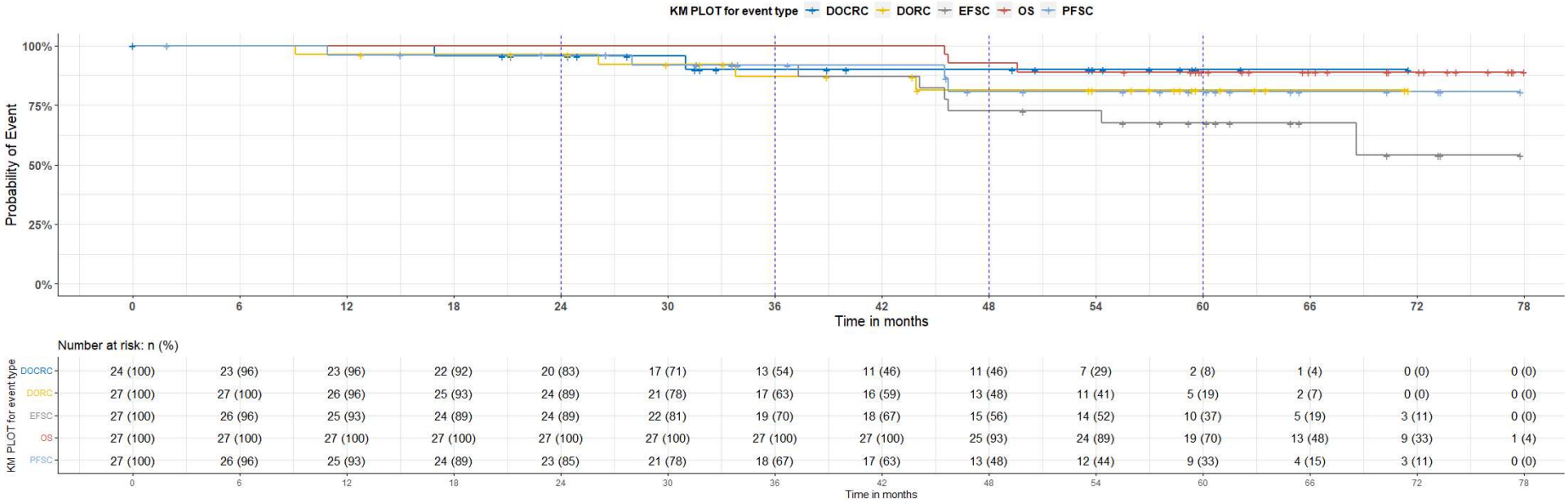
LEN, lenalidomide; PD, progressive disease.

Supplemental Figure 2. Efficacy outcomes in subgroups of patients in the FAS

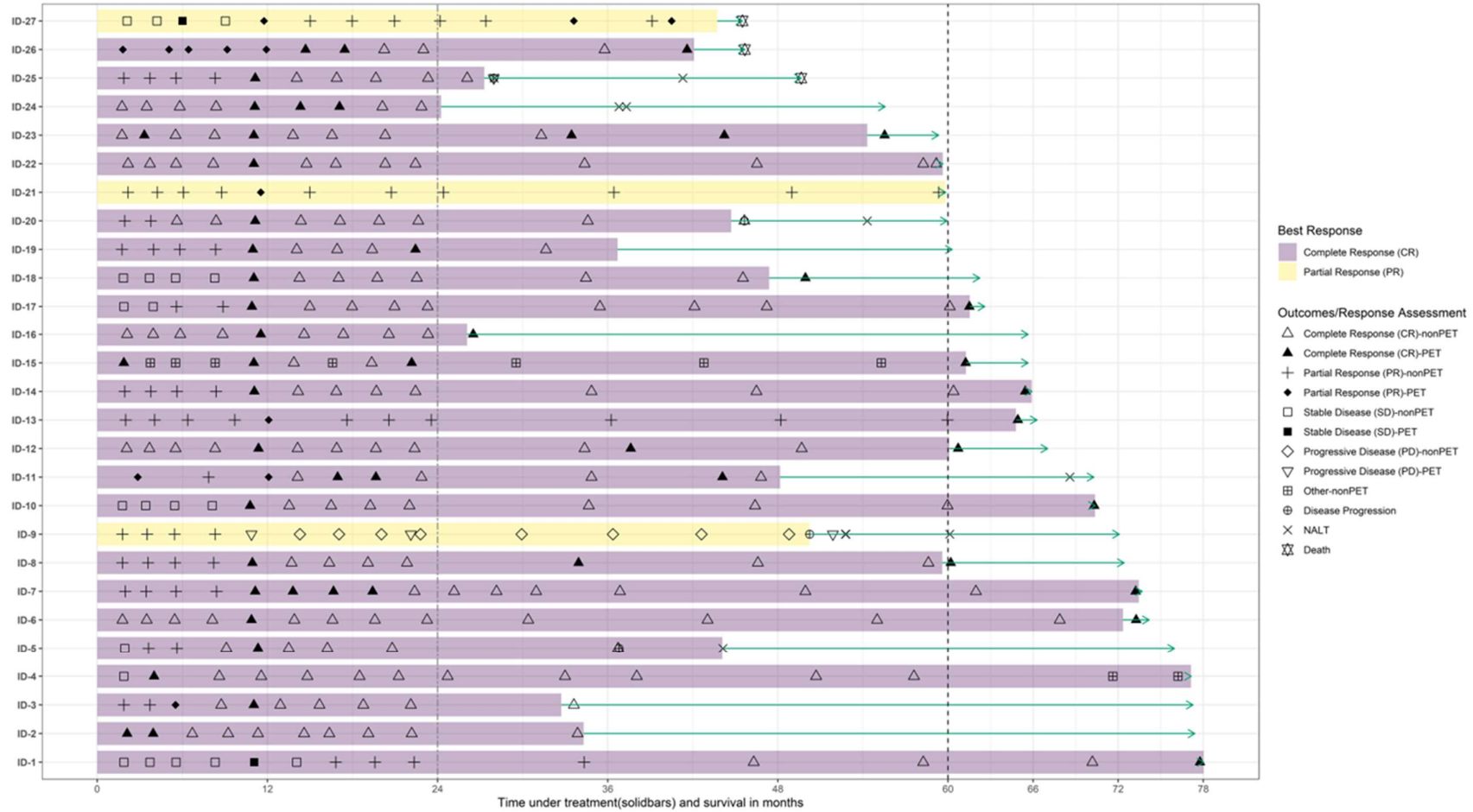
(A) Time under treatment and outcomes in patients with OS follow-up >59 months (n=26)



(B) Kaplan–Meier plot of time-to-event endpoints in patients with ≥2 years of therapy in the FAS (N=27)



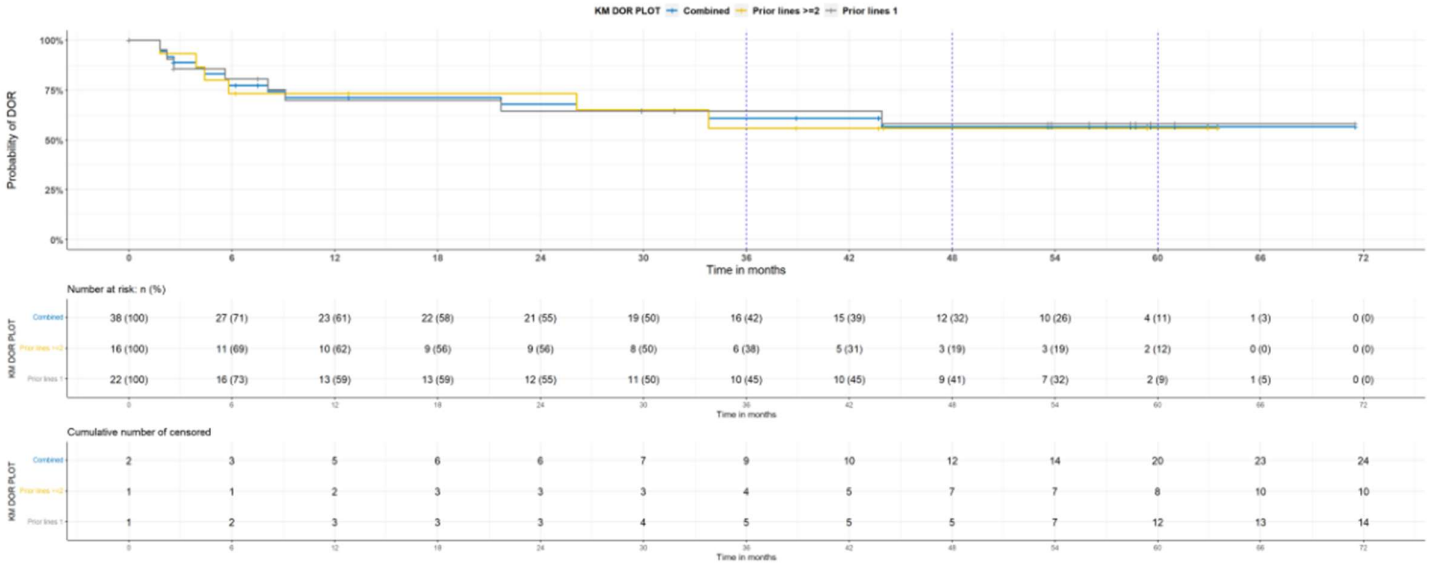
(C) Time under treatment and outcomes in patients with ≥2 years of therapy (N=27)



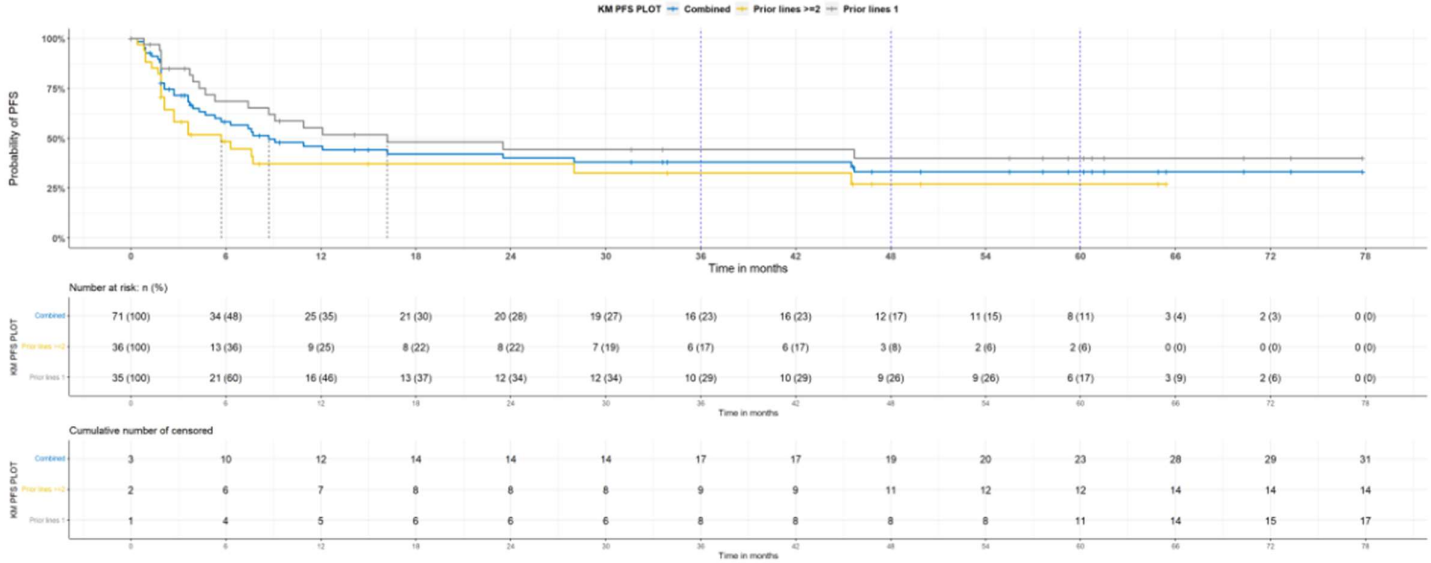
CR, complete response; FAS, full analysis set; NALT, next anti-lymphoma therapy; OS, overall survival; PFS, progression-free survival; pLoT, prior line of therapy; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.

Supplemental Figure 3. Kaplan–Meier plots of time-to-event endpoints in the USPI population, and by pLoT.

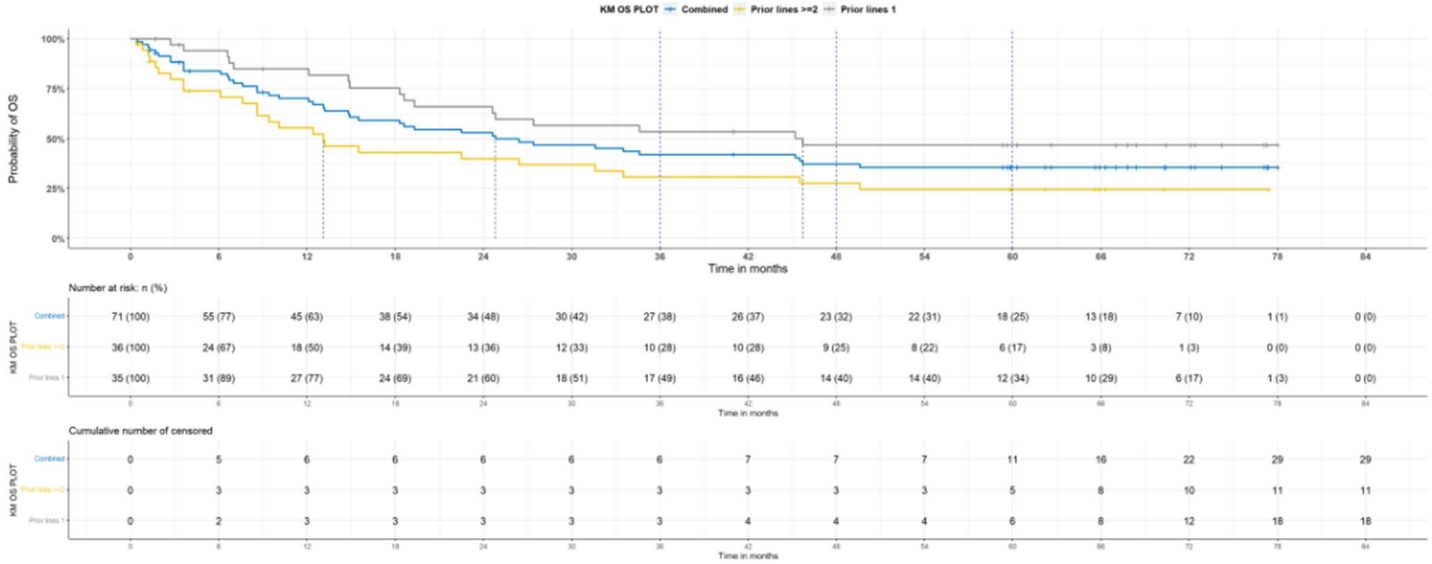
(A) DoR



(B) PFS

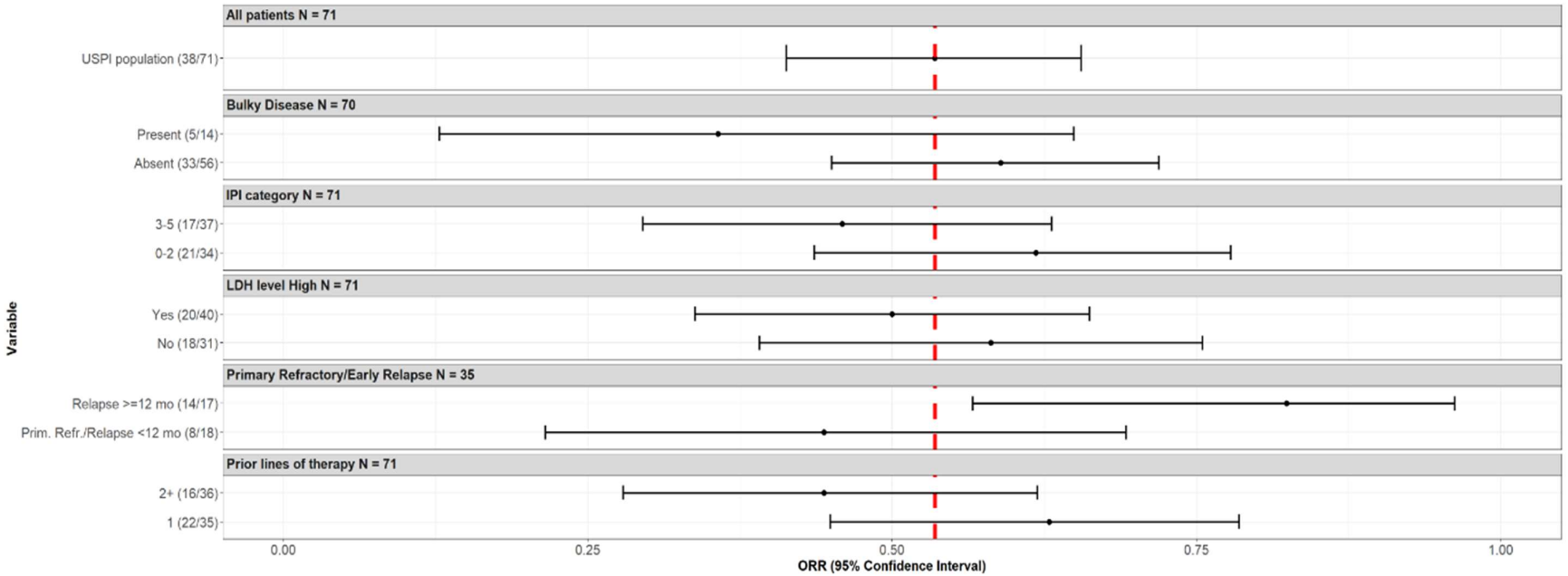

KM PFS PLOT Combined Prior lines >=2 Prior lines 1
Probability of PFS
100%
75%
50%
25%
0%
0 6 12 18 24 30 36 42 48 54 60 66 72 78
Time in months
Number at risk: n (%)
KM PFS PLOT
Combined 71 (100) 34 (48) 25 (35) 21 (30) 20 (28) 19 (27) 16 (23) 16 (23) 12 (17) 11 (15) 8 (11) 3 (4) 2 (3) 0 (0)
Prior lines >=2 36 (100) 13 (36) 9 (25) 8 (22) 8 (22) 7 (19) 6 (17) 6 (17) 3 (8) 2 (6) 2 (6) 0 (0) 0 (0) 0 (0)
Prior lines 1 35 (100) 21 (60) 16 (46) 13 (37) 12 (34) 12 (34) 10 (29) 10 (29) 9 (26) 9 (26) 6 (17) 3 (9) 2 (6) 0 (0)
Time in months
Cumulative number of censored
KM PFS PLOT
Combined 3 10 12 14 14 14 17 17 19 20 23 28 29 31
Prior lines >=2 2 6 7 8 8 8 9 9 11 12 12 14 14 14
Prior lines 1 1 4 5 6 6 6 8 8 8 8 11 14 15 17
Time in months

(C) OS



DoR, duration of response; OS, overall survival; PFS, progression-free survival; pLoT, prior line of therapy; USPI, US prescribing information.

Supplemental Figure 4. 5-year ORR in the USPI population, in subgroups of clinical interest



IPI, International Prognostic Index; LDH, lactate dehydrogenase; ORR, objective response rate; USPI, US prescribing information.