Poster number: ABCL-482

Five-year subgroup analysis of tafasitamab + lenalidomide from the Phase II L-MIND study in patients with relapsed or refractory diffuse large B-cell lymphoma

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OBJECTIVE

To analyze the final 5-year efficacy of tafasitamab + lenalidomide (LEN) followed by tafasitamab monotherapy for patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) in the Phase II L-MIND study (NCT02399085)[1] according to exploratory subgroups of clinical interest

SUMMARY

> The 5-year analysis of L-MIND showed durable responses and long-term clinical benefit across all subgroups of clinical interest, including patients with poor prognosis risk factors

> Positive prognostic factors, such as lack of bulky disease, low International Prognostic Index (IPI) score, low lactate dehydrogenase (LDH) levels, and higher natural killer (NK) cell count at baseline were correlated with better outcomes
- Kaplan–Meier estimates showed durable remissions can be achieved in patients with a range of poor prognostic factors, albeit at lower rates than in those with favorable ones
- In regression analyses, after adjusting for important covariates of interest, NK cell count remained significantly associated with both progression-free survival (PFS) and overall survival (OS), with similar prognostic power to that of more established clinical parameters

> These exploratory results indicate that patients' immune fitness may contribute to the response to tafasitamab + LEN treatment, in accordance with its immunotherapeutic mode of action

> The long-term data from L-MIND suggest that this immunotherapy may have curative potential, which is being explored in further studies
- Even though clinical benefit was observed across subgroups, the results support continued exploration of which patients are most likely to experience a durable response

Acknowledgments: Thank you to the patients, caregivers, and study investigators. This study was funded by MorphoSys AG. Medical writing assistance was provided by Pavitra Joshi, MS, of Syneos Health, UK, and funded by MorphoSys AG.

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About Tafasitamab: Tafasitamab is a humanized Fc-modified cytolytic CD19-targeting monoclonal antibody. In 2010, MorphoSys licensed exclusive worldwide rights to develop and commercialize tafasitamab from Xencor, Inc. Tafasitamab incorporates an XmAb® engineered Fc domain, which mediates B-cell lysis through apoptosis and immune effector mechanisms including antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). In January 2020, MorphoSys and Incyte entered into a collaboration and licensing agreement to further develop and commercialize tafasitamab globally. Following accelerated approval by the U.S. Food and Drug Administration in July 2020, tafasitamab is being co-commercialized by MorphoSys and Incyte in the United States. Conditional/accelerated approvals were granted by the European Medicines Agency and other regulatory authorities. Incyte has exclusive commercialization rights outside the United States. XmAb® is a registered trademark of Xencor, Inc.

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BACKGROUND

> As historically limited treatment options for patients with R/R DLBCL begin to widen, it becomes increasingly important to understand which subgroups of patients can derive maximum benefit from particular treatments
- Tafasitamab + LEN has been granted accelerated approval in the USA[2] and conditional authorization in Europe[3] for patients with R/R DLBCL ineligible for autologous stem cell transplant (ASCT) following the primary (1-year) results of the Phase II L-MIND study (NCT02399085)[1–3]
- 2- and 5-year time points are considered important milestones of prolonged remission
- Five-year efficacy and safety results from the whole L-MIND cohort are reported in Poster ABCL-450 at this congress

> Here, we report exploratory analyses of the final 5-year efficacy in subgroups of interest
- Subgroups of interest that are based on prognostic factors, such as IPI score, lack of bulky disease, and late relapse, may correlate with the efficacy of immunotherapy
- NK cells have been described as critical contributors to the immune control of cancer cells and are correlated to prognostic benefit in patients[4]

METHODS

> L-MIND was an open-label, single-arm, multicenter, global Phase II study of tafasitamab + LEN (administered as per label), followed by tafasitamab monotherapy, in patients with R/R DLBCL and not eligible for ASCT (see Poster ABCL-450 for details of study design)

> Efficacy outcomes (objective response rate [ORR], PFS, OS, duration of response [DoR]) were evaluated in exploratory analyses in subgroups of clinical interest:
- Time to progression after first-line therapy (<12 vs ≥12 months, analyzed only in patients with only one prior line of therapy [pLoT]);
- Patient age (≤70 vs >70 years);
- IPI score at baseline (0–2 vs 3–5);
- Presence of bulky disease (longest lesion diameter ≥7.5 cm, by central radiologic assessment) at screening;
- Cell of origin (COO; germinal center B [GCB] vs non-GCB);
- NK cell count (<100 vs ≥100/µL peripheral blood, as analyzed at baseline by flow cytometry)

> Regression analyses were used to explore associations with the likelihood of ORR (complete response [CR] or partial response [PR] vs no response) and duration of OS or PFS after adjusting for important covariates of interest

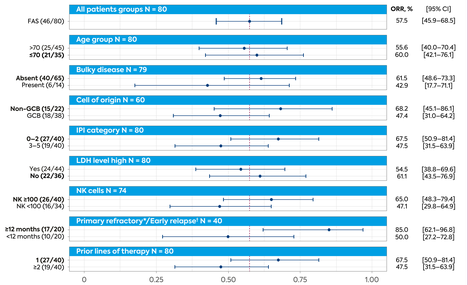
RESULTS

> Eighty patients received tafasitamab + LEN and comprised the full analysis set (FAS)

> Fifty percent of patients had an IPI score of 3–5; 50% of patients had one pLoT, and 50% of those with one pLoT had <12 months to progression after first-line therapy

> ORR was generally comparable between subgroups, albeit numerically favoring patients with positive prognostic factors, such as lack of bulky disease, lower IPI score, one pLoT, and late relapse **(Figure 1)**

Figure 1. 5-year ORR in the FAS population, in subgroups of clinical interest



*Patients with primary refractory disease were excluded, but because the definition changed (to progression/relapse within 6 months instead of within 3 months of a previous anti-CD20–containing regimen) while the study was active, some patients (n=15) with progression within 3–6 months were eligible and included. †Early relapse is defined as occurring ≤12 months after the first line of therapy.

CI, confidence interval; FAS, full analysis set; GCB, germinal center B cell; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NK, natural killer; ORR, objective response rate.

> Similarly, 5-year Kaplan–Meier estimates for DoR, PFS, and OS suggest long-term clinical activity in all patient subgroups **(Table 1)**

> Kaplan–Meier curves according to NK cell count at baseline **(Figure 2)** show a substantial relationship with durable response and survival; median DoR and median OS were not reached in patients with NK ≥100 cells/µL

Table 1. 5-year efficacy outcomes 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–NE]	46	NE [33.8–NE]
Age	≤70 years	35	23.5 [5.3–NE]	45.2 [22.5–NE]	21	NE [21.7–NE]
	>70 years	45	10.9 [4.3–NE]	24.8 [12.1–NE]	25	NE [9.1–NE]
Number of pLoT	1	40	23.5 [7.4–NE]	NE [24.6–NE]	27	NE [9.1–NE]
	≥2	40	7.6 [2.7–45.5]	15.5 [8.6–45.5]	19	NE [26.1–NE]
IPI score	0–2	40	NE [10.9–NE]	NE [33.5–NE]	27	NE [NE–NE]
	3–5	40	5.7 [3.6–11.6]	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 months†	20	9.1 [3.9–NE]	34.6 [13.8–NE]	10	NE [1.8–NE]
	≥12 months	20	45.7 [10.9–NE]	NE [24.6–NE]	17	NE [8.1–NE]
NK cell count at baseline	<100 cells/µL	34	7.6 [2.1–23.5]	18.3 [8.6–45.5]	16	33.8 [5.8–NE]
	≥100 cells/µL	40	45.7 [6.3–NE]	NE [19.3–NE]	26	NE [43.9–NE]

Data are months [95% CI]. *Patients with one prior line of therapy. †Includes primary refractory. 1L, first line; CI, confidence interval; DoR, duration of response; FAS, full analysis set; IPI, International Prognostic Index; NE, not estimable; NK, natural killer; OS, overall survival; PFS, progression-free survival; pLoT, prior line of therapy.

> In regression analyses **(Table 2)**:
- Lower IPI score was significantly associated with longer PFS and OS in univariate analysis, but IPI was excluded from the multivariate model as it is derived from other included factors
- In multivariate model, low lactate dehydrogenase levels were associated with longer PFS, and younger age with longer OS
- NK cell count ≥100 cells/µL at baseline was significantly associated with both longer PFS and longer OS in multivariate analysis
- No factors were significantly associated with greater odds of objective response, perhaps owing to the small sample size

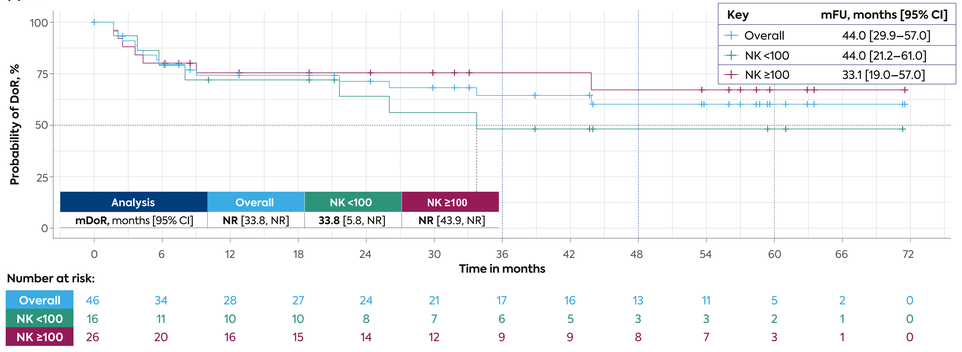
Table 2. Univariate and multivariate analysis of efficacy outcomes according to potential prognostic factors

	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
Elevated 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

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 applicable; NK, natural killer; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Figure 2. Kaplan–Meier curves of time-to-event endpoints according to NK cell count at baseline

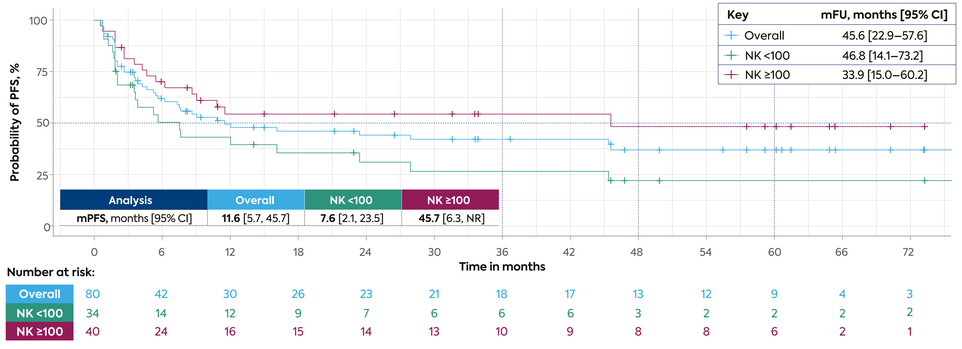
(A) DoR



Number at risk:

Overall	46	34	28	27	24	21	17	16	13	11	5	2	0
NK <100	16	11	10	10	8	7	6	5	3	3	2	1	0
NK ≥100	26	20	16	15	14	12	9	9	8	7	3	1	0

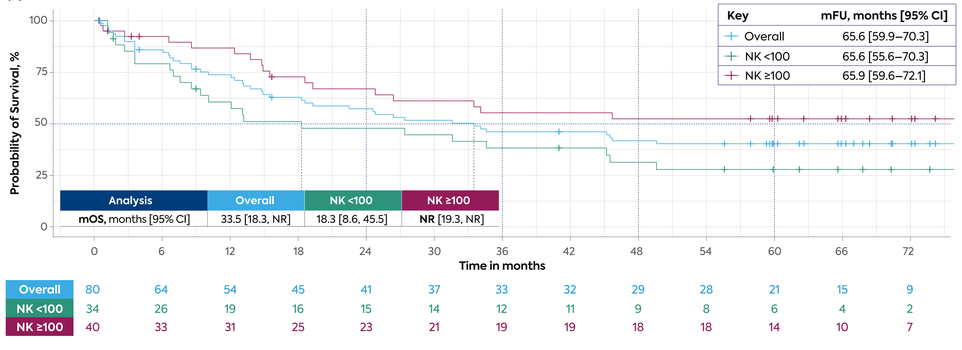
(B) PFS



Number at risk:

Overall	80	42	30	26	23	21	18	17	13	12	9	4	3
NK <100	34	14	12	9	7	6	6	6	3	2	2	2	2
NK ≥100	40	24	16	15	14	13	10	9	8	8	6	2	1

(C) OS



Overall	80	64	54	45	41	37	33	32	29	28	21	15	9
NK <100	34	26	19	16	15	14	12	11	9	8	6	4	2
NK ≥100	40	33	31	25	23	21	19	19	18	18	14	10	7

CI, confidence interval; DoR, duration of response; mFU, median follow up; NK, natural killer; NR, not reached; OS, overall survival; PFS, progression-free survival.

Presented at the Society of Hematologic Oncology (SOHO) 2023 Hybrid Annual Meeting, September 6–9, 2023.