

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

by Johannes Duell, Pau Abrisqueta, Marc Andre, Gianluca Gaidano, Eva Gonzales-Barca, Wojciech Jurczak, Nagesh Kalakonda, Anna Marina Liberati, Kami J. Maddocks, Tobias Menne, Zsolt Nagy, Olivier Tournilhac, Christian Kuffer, Abhishek Bakuli, Aasim Amin, Konstantin Gurbanov, and Gilles Salles

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

Tafasitamab + lenalidomide in R/R DLBCL: 5-yr data

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Johannes Duell,¹ Pau Abrisqueta,² Marc Andre,³ Gianluca Gaidano,⁴ Eva Gonzales-Barca,⁵ Wojciech Jurczak,⁶ Nagesh Kalakonda,⁷ Anna Marina Liberati,⁸ Kami J Maddocks,⁹ Tobias Menne,¹⁰ Zsolt Nagy,¹¹ Olivier Tournilhac,¹² Christian Kuffer,¹³ Abhishek Bakuli,¹³ Aasim Amin,¹³ Konstantin Gurbanov,¹³ Gilles Salles¹⁴

¹Medizinische Klinik und Poliklinik II, Universitätsklinik Würzburg, Würzburg, Germany

²Department of Hematology, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain

³Centre Hospitalier Universitaire CHU UCL Namur, Belgium

⁴Division of Hematology, Department of Translational Medicine University of Eastern Piedmont and Ospedale Maggiore della Carità, Novara, Italy

⁵Department of Hematology, Institut Català d'Oncologia, Hospitalet de Llobregat, IDIBELL, Univeristat de Barcelona, Barcelona, Spain

⁶Department of Clinical Oncology, Maria Skłodowska-Curie National Research Institute of Oncology, Kraków, Poland

⁷Department of Molecular and Clinical Cancer University of Liverpool, Liverpool, United Kingdom

⁸Università degli Studi di Perugia, Azienda Ospedaliera Santa Maria di Terni, Terni, Italy

⁹Department of Internal Medicine, Arthur G James Comprehensive Cancer Center, Ohio State University Wexner Medical Center, Columbus, OH, USA

¹⁰Freeman Hospital, The Newcastle upon Tyne Hospitals, Newcastle upon Tyne, United Kingdom

¹¹Semmelweis University, Budapest, Hungary

¹²CHU de Clermont-Ferrand, Lyon, France

¹³MorphoSys AG, Planegg, Germany

¹⁴Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Corresponding author: Johannes Duell

Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Klinikstraße 6, 97070 Würzburg, Germany, Duell_J@ukw.de [+4993120144912]

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The phase II L-MIND study of tafasitamab + lenalidomide followed by tafasitamab monotherapy enrolled patients with ASCT-ineligible R/R DLBCL, who historically have low chance of prolonged remission. This final 5-year analysis, which validates previous primary and 3-year outcomes of sustained responses, meaningful OS, and no new safety concerns, while further showing that median DoR was not reached overall or in subgroup of patients with either 1 or ≥ 2 prior lines of therapy, suggests that this immunotherapy may have curative potential in R/R DLBCL, which is to be explored in further studies.

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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.

Data-sharing statement

Data sharing requests by qualified researchers pertaining to L-MIND study will be considered only for non-commercial use on a case-by-case basis (to be approved by MorphoSys; Daniel.Moik@morphosys.com), starting 12 months from acceptance of the manuscript and until 36 months thereafter; approval may be subject to a data access agreement.

Author contributors

Conceptualization

Johannes Duell, Pau Abrisqueta, Marc Andre, Gianluca Gaidano, Eva Gonzales-Barca, Wojciech Jurczak, Nagesh Kalakonda, Anna Marina Liberati, Kami J Maddocks, Tobias Menne, Zsolt Nagy, Olivier Tournilhac, Christian Kuffer, Abhishek Bakuli, Aasim Amin, Konstantin Gurbanov, Gilles Salles

Data curation

Abhishek Bakuli, Johannes Duell, Christian Kuffer, Aasim Amin, Konstantin Gurbanov

Formal analysis

Abhishek Bakuli, Johannes Duell, Christian Kuffer, Aasim Amin, Konstantin Gurbanov

Funding acquisition

MorphoSys AG

Investigation

Johannes Duell, Pau Abrisqueta, Marc Andre, Gianluca Gaidano, Eva Gonzales-Barca, Wojciech Jurczak, Nagesh Kalakonda, Anna Marina Liberati, Kami J Maddocks, Tobias Menne, Zsolt Nagy, Olivier Tournilhac, Konstantin Gurbanov, Gilles Salles

Methodology

Abhishek Bakuli, Christian Kuffer, Aasim Amin, Konstantin Gurbanov

Project administration

Aasim Amin

Resources

Abhishek Bakuli, Christian Kuffer, Aasim Amin, Konstantin Gurbanov

Supervision

Abhishek Bakuli, Johannes Duell, Christian Kuffer, Aasim Amin, Konstantin Gurbanov

Validation

Abhishek Bakuli

Writing – original draft

Johannes Duell, Abhishek Bakuli, Christian Kuffer, Aasim Amin, Konstantin Gurbanov, Nagesh Kalakonda

Writing – review & editing

Johannes Duell, Pau Abrisqueta, Marc Andre, Gianluca Gaidano, Eva Gonzales-Barca, Wojciech Jurczak, Nagesh Kalakonda, Anna Marina Liberati, Kami J Maddocks, Tobias Menne, Zsolt Nagy, Olivier Tournilhac, Christian Kuffer, Abhishek Bakuli, Aasim Amin, Konstantin Gurbanov, Gilles Salles

Conflict of interest disclosures

Johannes Duell: Research funding: MorphoSys AG, Regeneron. **Pau Abrisqueta:** Honoraria: Janssen, Celgene, AbbVie, AstraZeneca, Gilead, Incyte; consulting/advisory: Janssen, Celgene, AbbVie, AstraZeneca; speakers' bureau: Janssen, Celgene, AbbVie, AstraZeneca, Gilead. **Marc Andre:** Advisory board: Takeda, Bristol Myers Squibb, Karyopharm, Gilead, Incyte; research Grants: Roche, Johnson & Johnson, Takeda; travel Grants: Roche, Bristol Myers Squibb, Celgene, Gilead, AbbVie, AstraZeneca. **Gianluca Gaidano:** Advisory Board: AbbVie, AstraZeneca, BeiGene, Incyte, Janssen, Roche; speaker's bureau: AbbVie, Janssen. **Eva González Barca:** Consultancy: Janssen, AbbVie, Gilead, Kiowa, EUSAPharma, Incyte, Lilly, BeiGene; speakers' bureau: Janssen, AbbVie, Takeda, Kiowa, Roche, EUSAPharma, Incyte, BeiGene; travel costs: Janssen, AbbVie, EUSAPharma. **Wojciech Jurczak:** Consulting/advisory: Mei pharma, Debiopharm, Loxo, Takeda, AstraZeneca, BeiGene; Research funding: GSK, Acerta, BeiGene, Nordic Nanovector, Incyte, Debiopharm, Incyte, Genentech, Janssen, Loxo, Mei Pharma, MorphoSys AG, Takeda, TG Therapeutics. **Anna Marina Liberati:** Honoraria: Bristol Myers Squibb, Servier, Celgene, AbbVie, Amgen; Consulting/ advisory: Incyte; research funding: Novartis, Janssen, AbbVie, Roche, Amgen, Sanofi Genzyme, Celgene, Bristol Myers Squibb, Servier, Incyte, Pfizer, IQVIA, Doxopharma, Verastem, BeiGene, Oncopeptides, Karyopharm, Archigen, CTI BioPharma, Debiopharm, MorphoSys AG, FibroGen, MEI Pharma, Regeneron, Dr Reddy's Laboratories Spa. **Kami J Maddocks:** Honoraria: Pharmacyclics, MorphoSys AG, Bristol Myers Squibb, Karyopharm Therapeutics, Kite Pharma/Gilead Company, ADC Therapeutics, AbbVie, AstraZeneca, BeiGene, Genmab, Genentech, Janssen, Lilly, Incyte; research funding: Pharmacyclics, Merck, Bristol Myers Squibb. **Tobias Menne:** Travel grants: Amgen, Jazz, Pfizer, Bayer, Kyowa Kirin, Celgene/BMS, Kite/Gilead, Janssen, Takeda; honoraria for advisory board meetings:

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Abstract (248 words)

Tafasitamab, an anti-CD19 immunotherapy, is used with lenalidomide for patients with autologous stem cell transplant-ineligible relapsed/refractory diffuse large B-cell lymphoma (DLBCL) based on the results of the phase II L-MIND study (NCT02399085). We report the final 5-year analysis. Eighty patients (≥ 18 years, 1–3 prior systemic therapies, ECOG PS 0–2) received co-administered tafasitamab and lenalidomide for up to 12 cycles, followed by tafasitamab monotherapy until disease progression (PD) or unacceptable toxicity. Primary endpoint was best objective response rate (ORR). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. Exploratory analyses evaluated efficacy endpoints by prior lines of therapy (pLoT). At data cut-off on November 14, 2022, ORR was 57.5%, with complete response (CR) of 41.3% (n=33), which was consistent with prior analyses. With median follow-up (mFU) of 44.0 months, median DoR was not reached. Median PFS was 11.6 months [95% CI, 5.7–45.7] (mFU 45.6), and median OS was 33.5 months [95% CI, 18.3–NR] (mFU 65.6). Patients with 1 pLoT (n=40) showed higher ORR (67.5%; 52.5% CR) compared with patients with ≥ 2 pLoT (n=40; 47.5%; 30% CR), but median DoR was not reached in either subgroup. Other exploratory analyses revealed consistent long-term efficacy results across subgroups. Adverse events were consistent with previous reports and manageable, and their frequency decreased during tafasitamab monotherapy, with no new safety concerns. This final 5-year analysis of L-MIND demonstrates that this immunotherapy combination is well tolerated and has long-term clinical benefit with durable responses.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL).¹ First-line standard of care immunotherapy for newly diagnosed DLBCL consists primarily of rituximab, an anti-CD20 antibody, with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or variations thereof, which may be curative in up to 60–70% of patients.^{2,3} However, 30–40% of patients experience relapsed or refractory (R/R) disease after first-line R-CHOP.^{4,5}

Second-line options depend on patients' responses to first-line therapy; those with refractory disease or who experience early relapse (≤ 12 months) can receive chimeric antigen receptor T-cell (CAR-T) therapy, with event-free survival in 40–62% of patients.^{4,5} Patients relapsing after >1 year are potential candidates for high-dose chemotherapy and autologous stem cell transplant (ASCT).⁶ Many patients, however, are ineligible for intensive treatment due to advanced age and/or comorbidities,^{3,7} and about 50% do not proceed to ASCT due to failure of salvage therapy. A further 40–65% experience relapse following ASCT.^{6,8,9}

Tafasitamab is a CD19-targeted immunotherapy that elicits direct cytotoxicity, antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis via Fc domain interactions.¹⁰ Primary analysis of the phase II L-MIND study (NCT02399085), showed that the combination of tafasitamab and lenalidomide resulted in an objective response rate (ORR) of 60%, complete response (CR) rate of 43%, and a median duration of response (DoR) of 21.7 months in patients with R/R DLBCL ineligible for ASCT.¹¹ Based on these data, tafasitamab was approved in combination with lenalidomide followed by tafasitamab monotherapy under accelerated approval in the USA (July 2020) and conditional marketing authorization in Europe (August 2021) for the treatment of adult patients with R/R DLBCL (detailed in the US label as not otherwise specified, including DLBCL arising from low-grade lymphoma), and who are ineligible for ASCT, and is now a standard second-line therapy in this setting.^{12,13}

Durable responses were seen after approximately 3 years of follow-up from L-MIND, with an ORR of 57.5%, CR rate of 40%, and median DoR of 43.9 months.¹⁴ We now present the final 5-year efficacy and safety outcomes from the L-MIND study.

Methods

L-MIND was an open-label, single-arm, global, multicenter, phase II study (NCT02399085).¹¹ The study was approved by institutional review boards at each study site and conducted in accordance with the International Council for Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Study design and patients

Full details of the L-MIND study methods and patient eligibility criteria have been previously described.^{11,14} Briefly, patients were aged ≥ 18 years with ASCT-ineligible R/R DLBCL, 1–3 prior systemic therapies (including ≥ 1 targeting CD20) and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2. Patients with primary refractory disease were excluded, but because the definition changed while the study was active, some were eligible and included. At study set-up, primary refractory disease was defined as no response to, or progression/relapse within 3 months of a previous anti-CD20-containing regimen. In a protocol amendment in June 2016, this definition was updated to within 6 months of a previous anti-CD20-containing regimen. Therefore, patients who experienced relapse within the first 3–6 months of completing prior therapy (and had primary refractory disease according to the updated definition) were initially eligible to enroll in the study. Patients received tafasitamab and lenalidomide for up to 12 cycles (28 days each), followed by tafasitamab monotherapy (once every 2 weeks) in patients with stable disease (SD) or better, until progressive disease (PD). Tafasitamab (12 mg/kg intravenously) was administered according to the label.^{12,13} Lenalidomide (25 mg orally) was self-administered on days 1–21 of each 28-day cycle.

We now present data following 5 years of follow-up from enrollment of the last patient.

Study outcomes

The primary endpoint was ORR (CR plus partial response [PR]), assessed by an independent review committee (IRC), according to the 2007 International Working Group response criteria for malignant lymphoma.¹⁵ Secondary endpoints included DoR (time from initial CR or PR to first observation of PD), progression-free survival (PFS; time from first dose to PD or death), overall survival (OS; time from first dose to date of death), time to progression (TTP), time to next treatment (TTNT), and incidence and severity of adverse events (AEs).

Statistical analyses

The primary analysis occurred when all patients had completed a minimum of 12 months follow-up (data cut-off: November 30, 2018)¹¹; the 3-year follow-up had a data cut-off date of October 30, 2020.¹⁴ The data cut-off for the present, pre-specified 5-year analysis was November 14, 2022.

Efficacy outcomes were analyzed in the full analysis set (FAS; patients who received ≥ 1 dose of both tafasitamab and lenalidomide), and safety was assessed in those who received any study medication.

The frequency of treatment emergent adverse events (TEAEs) per unit of treatment exposure time was analyzed across three periods; details are provided in **Supplemental Methods**.

Exploratory subgroup analyses

Efficacy outcomes (ORR, PFS, OS, DoR, and/or duration of CR [DoCR]) were also evaluated in exploratory analyses in subgroups of clinical interest: number of prior lines of therapy (pLoT, 1 vs ≥ 2); time to progression after first-line therapy (< 1 vs ≥ 1 year, in patients with only one pLoT); patient age (≤ 70 vs > 70 years); International Prognostic Index (IPI) score at baseline (0–2 vs 3–5); presence of bulky disease (longest lesion diameter ≥ 7.5 cm, by central radiological assessment) at screening; cell of origin (COO; germinal center B [GCB] vs non-GCB); and natural killer (NK) cell count (< 100 vs $\geq 100/\mu\text{L}$ peripheral blood). NK cell counts were analyzed at baseline by flow cytometry; details are provided in **Supplemental Methods**. We also examined outcomes in patients who ended treatment while they had a CR or PR, in patients who received tafasitamab ≥ 2 years, in patients with OS > 5 years, and according to the best response experienced during the study. Regression analyses were used to explore associations with the likelihood of ORR (CR or PR vs no response) and duration of OS or PFS after adjusting for important covariates of interest; details are provided in **Supplemental Methods**. Efficacy outcomes were also analyzed in a subset of patients with centrally-confirmed diagnoses of DLBCL, which aligns with the population according to the US prescribing information (USPI population).

Results

Patients and treatment

The FAS comprised 80 patients whilst 81 were included in the safety analysis set (patient disposition for treatment is shown in **Supplemental Figure 1**). The median age of enrolled

patients was 72 years (range 41–86). Fifty percent of patients in the FAS had one pLoT at study entry; half had two or more pLoT. Fifty percent of patients had an IPI score of 3–5. Nine patients had received prior stem-cell transplant. Baseline characteristics for patients in the FAS and according to the number of pLoT are shown in **Table 1** (equivalent data in the USPI population are shown in **Supplemental Table 1**). Fifteen (18.8%) patients had primary refractory disease (DoR to first-line therapy of 3–6 months).

The 5-year follow-up period commenced from when the last enrolled patient began screening (maximum screening period 28 days), some patients had slightly less than 60 months' follow-up available before data cut-off. 26 patients had >59 months survival follow-up (23 reached end of study [EoS], three withdrew owing to AEs) and 21 had >60 months (18 reached EoS, three withdrew owing to AEs). Among those with long-term follow-up, eight received tafasitamab until EoS per protocol. In total, 27 patients received tafasitamab therapy for ≥2 years (see Safety outcomes for treatment duration).

Efficacy outcomes

At this 5-year analysis, the IRC-assessed best ORR was 57.5% (46/80; 95% CI, 45.9–68.5), with a CR rate of 41.3% (n = 33) and a PR rate of 16.3% (n = 13), which was consistent with prior analyses (**Table 2**). SD as best response was observed in 16.3% of patients (n = 13). Overall, five best responses altered in the 5-year versus 3-year analyses (two CR to PR, three PR to CR). One response deepened from PR to CR, whereas the other changes resulted from re-adjudications following inter-reader variance and/or change of personnel.

After a median follow-up of 44.0 months (95% CI, 29.9–57.0), median DoR was not reached (NR) (**Figure 1A**); the curve suggests a plateau after approximately 12 months, although number of patients at risk is limited. Median PFS was 11.6 months (95% CI, 5.7–45.7) with a median follow-up of 45.6 months (95% CI, 22.9–57.6) (**Figure 1B**), and median OS was 33.5 months (95% CI, 18.3–NR) following a median follow-up of 65.6 months (95% CI, 59.9–70.3) (**Figure 1C**). After a median follow-up of 32.7 months (95% CI, 24.4–53.6), median DoCR was not reached (**Figure 1D**); the 5-year DoCR estimate was 80.7% (95% CI, 59.1–91.6).

Figure 1E shows the impact of response quality on OS; whereas median OS was not reached in patients with CR or PR (95% CI, 45.5 months–NR) and NR (NR–NR) in patients with best response of CR, it was 18.6 months (8.6–45.5) in patients with PR as best response.

The median time to response was 2.0 months (range 1.7–16.8), which coincided with the first evaluation as per protocol, and the median time to CR was 8.1 months (range 1.7–64.9).

Twenty-six patients stopped treatment while their disease was in response, 23 with CR and three with PR (**Figure 2**). Among them, 19 patients were alive with their disease in response at EoS (eight were on treatment until EoS while 11 had previously discontinued tafasitamab), two patients later died from PD (both had previous CR but <12 months treatment, both remained off therapy for over 1 year after study treatment and thereafter went on to receive another anti-lymphoma therapy before they died), and three died from other causes (two with PR and one CR as best response). Two patients experienced disease relapse after discontinuation of treatment and were alive at the end of study participation.

Among the nine patients with prior stem-cell transplant, four had a best response of CR. Three were alive at the ~60-month follow-up (all had previously discontinued tafasitamab), the fourth withdrew after <2 months owing to an AE and died after 31 months. Three of the nine patients had a best response of PR; two of them later had PD and died, the third was alive and on treatment at EoS. Two of the nine had a best response of PD; one died and one was lost to follow-up.

Outcomes and response assessments for the 26 patients with >59 months survival follow-up are shown in **Supplemental Figure 2A**. Twenty-two had CR as best response, two PR, and one each had SD and PD.

Efficacy outcomes in the USPI population are shown in **Supplemental Table 2** and **Supplemental Figure 3**.

Exploratory subgroup analyses

Median time on study treatment was 11.4 months (range 0.7–78.0) for patients with one pLoT and 6.1 months (range 0.1–65.9) for patients with ≥ 2 pLoT in the FAS. Patients with one pLoT had higher ORR (67.5%, with 52.5% CR and 15.0% PR) compared with patients with ≥ 2 pLoT (47.5%, with 30.0% CR and 17.5% PR). Similarly, and as expected, median PFS and median OS were longer in patients with one pLoT compared with those with ≥ 2 pLoT (**Table 2, Figures 1B & 1C**). However, median DoR and DoCR were not reached in either subgroup, indicating comparable long-term efficacy in patients whether receiving tafasitamab + lenalidomide as second or later-line therapy (**Table 2, Figure 1A & 1D**).

Time-to-response curves for the 27 patients who received tafasitamab treatment for ≥ 2 years are shown in **Supplemental Figure 2B**, with outcomes and response assessments for this subgroup in **Supplemental Figure 2C**. Twenty-four had best response of CR and three had PR.

ORR was generally comparable between subgroups of clinical interest (**Figure 3**), although numerically favorable in all patients with positive prognostic factors, such as lack of bulky

disease, lower IPI score, only one pLoT, and late relapse (late relapse was defined as time to relapse/PD ≥ 12 months after first-line therapy, and its influence was investigated only in the subgroup of patients with one pLoT). ORR in the USPI population between subgroups of clinical interest was also favorable in all patients with positive prognostic factors (**Supplemental Figure 4**). ORR was comparable. Similarly, 5-year rate estimates for DoR, PFS and OS suggest long-term clinical activity in all patient subgroups (**Supplemental Table 3**).

NK cell count at baseline was significantly related to survival; median OS was NR (95% CI, 19.3–NR) in patients with NK ≥ 100 cells/ μ L, compared with 18.3 months (95% CI, 8.6–45.5) in patients with NK < 100 cells/ μ L (**Figure 1F**). In regression analysis, NK cell count was not significantly associated with the odds of ORR in univariate or multivariate models, but NK cell count ≥ 100 cells/ μ L at baseline was significantly associated with both longer PFS and longer OS (**Supplemental Table 4**). Reflecting the small sample size, none of the factors in the regression analysis were significantly associated with ORR. IPI score was significantly associated with PFS and OS in univariate analysis but was excluded from the multivariate model as it is derived from other included factors. For PFS and OS, few known prognostic factors besides NK cells remained significant in the multivariate models: low lactate dehydrogenase (LDH) levels were associated with longer PFS and younger age with longer OS. Although limited in power, this analysis supports further investigation of potential patient profiles combining specific characteristics in larger studies to determine differential outcomes following tafasitamab therapy.

Safety outcomes

The median duration of exposure to study treatment (either lenalidomide or tafasitamab) in the safety analysis set was 9.2 months (range 0.23–78.46). The median duration of exposure to tafasitamab monotherapy (following discontinuation of lenalidomide at any time [n=52]) was 13.9 months [range 0.23–67.2]) versus median tafasitamab exposures of 4.1 months (range 0.1–20.8) in the primary analysis¹¹ and 9.2 months (range 0.2–54.7) at the 3-year analysis.¹⁴

An overview of the exposure-adjusted frequency of all TEAEs, hematologic and non-hematologic TEAEs, and important TEAEs of interest for three periods of the study (combination therapy, tafasitamab monotherapy up to 2 years, and tafasitamab monotherapy >2 years) is presented in **Figure 4**, showing that for all these categories of TEAEs, frequencies reduced with tafasitamab monotherapy compared with tafasitamab + lenalidomide combination therapy. Most TEAEs of special interest were hematologic events during the tafasitamab + lenalidomide combination period; incidences of infusion-related

reactions and grade ≥ 3 infections and infestations were low. Nine patients experienced at least one secondary primary malignancy: one with grade 1 and two with grade 2 basal cell carcinoma; one with grade 2 Bowen's disease; one with grade 2 breast cancer; one with grade 3 lung adenocarcinoma; one with grade 3 recurrent marginal zone lymphoma; one with grade 3 prostate cancer and grade 2 squamous cell carcinoma; and one other with grade 2 squamous cell carcinoma. The most common non-hematologic TEAEs were diarrhea and peripheral edema during the combination therapy phase, and most TEAEs were grade 1/2.

TEAEs are summarized by incidence and severity in **Table 3**. Treatment emergent serious adverse events (SAEs) were reported in 47 (58.0%) patients; with most frequent being pneumonia (seven patients [8.6%]), febrile neutropenia (five patients [6.2%]), neoplasms (four patients [4.9%]), pulmonary embolism and COVID-19 infections (three patients [3.7%] each), bronchitis, lower respiratory tract infection, dyspnea, atrial fibrillation and congestive cardiac failure (two patients [2.5%] each). Among these events, COVID-19 infections, dyspnea, and benign neoplasms were newly observed compared with the 3-year analysis.

Median durations of neutropenia and thrombocytopenia (all grades) were 9 and 13 days, respectively. Infections and infestations had a median duration of 12 days (18 days for infective pneumonia, 10.5 days for urinary tract infection, 9 days for sepsis, and 20 days for opportunistic infections).

A total of 45 patients had died at the time of this analysis, among whom 32 (39.5%) died due to PD, 12 (14.8%) for reasons unrelated to PD, and one (1.2%) with role of PD not established. Eight of the 45 patients (9.9%) died while on treatment, among whom five (6.2%) died due to PD, and three (3.7%) for reasons unrelated to PD. Among the 37 patients (45.7%) who died after treatment completion, 27 (33.3%) died due to PD, nine (11.1%) died due to reasons unrelated to PD, and one (1.2%) with role of PD not established. Six (7.4%) patients died due to AEs, none of which were considered related to study drugs.

Temporary tafasitamab interruptions occurred in 65 patients, of which 50 patients (76.9%) had 171 interruptions (52.5%) due to TEAEs. Twenty-eight patients required dose interruption of lenalidomide from the starting dose of 25 mg during combination therapy, of which 25 (89.3%) were due to AEs. Interruptions due to unacceptable toxicity occurred in one patient for each of the study drugs.

A total of 16 (19.8%) and 18 (22.2%) patients discontinued tafasitamab and lenalidomide due to AEs, respectively. AEs leading to tafasitamab discontinuations were COVID-19, bronchitis, pneumonia, progressive multifocal leukoencephalopathy, varicella zoster virus infection, pyrexia, sudden death, recurrent marginal zone lymphoma, prostate cancer,

cerebrovascular accident, cognitive disorder, pulmonary embolism, respiratory failure, thrombocytopenia, congestive cardiac failure, allergic dermatitis, and deep vein thrombosis.

Discussion

The final 5-year analysis of the phase II L-MIND study continues to demonstrate clinical benefit with tafasitamab + lenalidomide combination therapy followed by long-term tafasitamab monotherapy, in patients with R/R DLBCL ineligible for ASCT, in all subgroups of clinical interest. The ORR of 57.5% and other efficacy outcomes are consistent with previous results.¹⁴ Median DoR was not reached after a median 44.0 months of follow-up.

Long-term tafasitamab therapy was well tolerated, consistent with its established safety profile, and no new safety concerns were observed at the 5-year analysis. The incidence of all-grade and grade ≥ 3 AEs decreased as patients transitioned from combination therapy to tafasitamab monotherapy and decreased further in the tafasitamab monotherapy phase from 2 years onwards.

The importance of depth of response was apparent in the 5-year probability of OS of 72.7% in patients with best response of CR, compared with 18.3% in those with best response of PR. As would be expected, analyses by pLoT showed better outcomes in patients receiving tafasitamab + lenalidomide in second line rather than third-line or later therapy.

Nevertheless, median DoR was not reached in either subgroup; that is, durable responses were also seen with use in second- and later lines of therapy. Other subgroup analyses indicated that durable remissions can be achieved in patients with a range of poor prognostic factors, albeit at lower rates than in those with other favorable prognostic factors including lower IPI score. Exploratory analysis by NK cell count at baseline showed survival benefit and better odds of PFS and OS for patients with ≥ 100 cells/ μ L peripheral blood compared with < 100 cells. Together with the suggestion of plateau in the Kaplan–Meier curves for DoR, PFS and OS after approximately 12–18 months, these results are consistent with an immunotherapeutic mode of action for tafasitamab + lenalidomide.

Outcomes in the subgroup of patients who ended treatment while in response build further on these findings, and suggest that this immunotherapy may have curative potential for patients with R/R DLBCL ineligible for ASCT. Treatment in this setting has not historically been with curative intent, and these five-year data in a limited number of patients do not definitively confirm that tafasitamab + lenalidomide may be curative. Furthermore, no comparison with age- and sex-matched general population data has been performed. Nevertheless, durable responses were maintained in many patients after discontinuing

treatment (including at least eight who discontinued tafasitamab more than 6 months before EoS). Positron emission tomography (PET) and computed tomography (CT) scans are not sufficiently sensitive to fully ascertain disease eradication; novel assessment methods are needed to better understand whether patients whose disease remains in long-term remission without treatment are cured. Similarly, patients with long-term CR while continuing treatment are of unknown cure status.

Long-term follow-up data are also emerging in studies of CAR-T therapy. The phase II JULIET study of tisagenlecleucel [tisa-cel] was in 115 patients with R/R DLBCL ineligible for or progressing after ASCT¹⁶; 14 of 24 (58%) patients maintained a response at the 5-year analysis, including 46% with a CR, and median DoR was 61.4 months (95% CI, 3.2–not estimable).¹⁷ The 5-year follow-up of ZUMA-1 (phase I/II study of axicabtagene ciloleucel [axi-cel] in 101 patients with refractory LBCL¹⁸), was recently published under the title of ‘curative potential’.¹⁹ Supportive data include 30% of patients having ongoing CR at data cut-off, after a median follow-up of 63.1 months, with a median DoCR of 62.2 months (95% CI, 12.9–not estimable), and an estimated 51.0% rate of disease-specific survival (excludes deaths unrelated to disease progression).¹⁹

Data on next anti-lymphoma therapy were not systematically collected as part of the L-MIND 5-year survival follow-up, but two patients were documented to have later received CAR-T therapy. One with 44.7 months in treatment, a best response of CR and subsequent investigator-assessed PD received CAR-T therapy approximately 10 months after end of treatment (EoT) and was alive at the OS follow-up at 59.9 months. Another patient had a best response of PR and subsequent centrally-confirmed PD with 7 months in treatment, received CAR-T therapy approximately 12 months after EoT and died 4 months post-CAR-T therapy. Previously, a case report was published of a patient with best response of SD in L-MIND who went on to experience CR with axi-cel.²⁰

In a real-world study of 82 patients from nine academic institutions, 91% of patients would not have been eligible for L-MIND, including 23% with prior anti-CD19 therapy (21% with prior CAR-T therapy).²¹ The population had challenging disease characteristics, substantial comorbidity, and were heavily pretreated with best possible care including experimental treatments (28% with ≥ 3 pLoT, 51% with IPI 3–5, 46% with primary refractory disease and 33% with renal dysfunction); accordingly, clinical outcomes with tafasitamab + lenalidomide were lower than in L-MIND. Nevertheless, one of six patients with refractory disease to CAR-T therapy had CR with tafasitamab + lenalidomide, and four of 11 with relapsed disease after CAR-T therapy achieved a CR, suggesting it can provide a feasible approach in a post-CAR-T therapy setting.²¹

Safety and tolerability are important factors in eligibility for and selection of second-line and later therapies, with some patients ineligible for CAR-T therapies owing to the associated toxicity, including adverse hematologic events. The 5-year safety data from L-MIND are reassuring; and prolonged responses observed in the study were not offset by any detrimental long-term treatment-related adverse events. The reduced exposure-adjusted incidences of hematologic and non-hematologic TEAEs that were previously reported with the transition from tafasitamab + lenalidomide combination therapy to tafasitamab monotherapy up to 2 years were maintained or further reduced with tafasitamab monotherapy beyond 2 years.

These outcomes in second line and beyond indicate a potential first-line applicability, which is supported by results from the phase Ib firstMIND study of tafasitamab + lenalidomide combined with standard R-CHOP therapy (NCT04134936). ORR at EoT was 25/33 patients (75.8% [95% CI, 57.7–88.9]).²² The phase III frontMIND study of tafasitamab + lenalidomide + R-CHOP versus R-CHOP in newly diagnosed patients with high-intermediate and high-risk DLBCL (NCT04824092) is now fully accrued, with primary completion due in 2025.²³

Testing for minimal residual disease (MRD) based on circulating tumor DNA is among promising new avenues for optimizing future outcomes in DLBCL, especially in light of new advanced methods.²⁴ Preliminary data suggest that MRD-negativity may be a surrogate biomarker for clinical benefit of tafasitamab + lenalidomide + R-CHOP,²⁵ but it remains to be seen whether it will have potential applications beyond first line, including whether it could support a decision to stop therapy in patients with durable CR in the R/R DLBCL setting.²⁴

In conclusion, the final 5-year analysis of L-MIND showed clinically significant and enduring responses with tafasitamab + lenalidomide combination therapy, followed by long-term tafasitamab monotherapy, in patients with R/R DLBCL ineligible for ASCT. Median DoR was not reached after 44.0 months median follow-up, with the appearance of plateau in survival curves after 12–18 months, albeit with limited patient numbers at later timepoints. Long-term clinical benefit was observed across subgroups of clinical interest, including patients with poor prognosis risk factors. No new safety signals were identified, confirming the tolerability profile observed with earlier data cuts, and the incidence of AEs declined during prolonged tafasitamab monotherapy. Together, these long-term results suggest that this immunotherapy combination may have curative potential, which is being explored in further studies.

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Tables

Table 1. Baseline characteristics for patients in the FAS and by pLoT

	All patients (FAS)	1 pLoT	≥2 pLoT
N	80	40	40
Median age, years (range)	72.0 (41.0–86.0)	72.0 (53.0–86.0)	70.5 (41.0–82.0)
Age >70 years, n (%)	45 (56.2)	25 (62.5)	20 (50.0)
Sex, n (%)			
Female	37 (46.2)	19 (47.5)	18 (45.0)
Male	43 (53.8)	21 (52.5)	22 (55.0)
Ann Arbor stage, n (%)			
I–II	20 (25.0)	11 (27.5)	9 (22.5)
III–IV	60 (75.0)	29 (72.5)	31 (77.5)
IPI score, n (%)			
0–2	40 (50.0)	25 (62.5)	15 (37.5)
3–5	40 (50.0)	15 (37.5)	25 (62.5)
Elevated LDH, n (%)			
Yes	44 (55.0)	18 (45.0)	26 (65.0)
No	36 (45.0)	22 (55.0)	14 (35.0)
Prior lines, n (%)			
1	40 (50.0)		
2	34 (42.5)		
3	5 (6.3)		
4	1 (1.3)		
Primary refractory*, n (%)			
Yes	15 (18.8)	6 (15.0)	9 (22.5)
No	65 (81.2)	34 (85.0)	31 (77.5)
Refractory to previous therapy line, n (%)			
Yes	35 (43.8)	6 (15.0)	29 (72.5)
No	45 (56.2)	34 (85.0)	11 (27.5)
Prior ASCT, n (%)			
Yes	9 (11.2)	2 (5.0)	7 (17.5)
No	71 (88.8)	38 (95.0)	33 (82.5)
Cell of origin (by IHC), n (%)			
GCB	38 (47.5)	16 (40.0)	22 (55.0)
Non-GCB	22 (27.5)	14 (35.0)	8 (20.0)
Unknown/NE	20 (25.0)	10 (25.0)	10 (25.0)

*Patients with primary refractory disease had a DoR after first-line therapy of 3–6 months.

ASCT, autologous stem cell transplant; DoR, duration of response; IHC, immunohistochemistry; IPI, International Prognostic Index; FAS, full analysis set; GCB, germinal center B; LDH, lactate dehydrogenase; pLoT, prior lines of therapy.

Table 2. Efficacy outcomes in the primary, 3-year and 5-year follow-up analyses in the FAS (N=80)

	Primary analysis	3-year follow-up	Final 5-year data	5-year data in patients with 1 pLoT (n = 40)	5-year data in patients with ≥2 pLoT (n = 40)
Data cut-off date	Nov 30, 2018	Oct 30, 2020	Nov 14, 2022	Nov 14, 2022	Nov 14, 2022
Best ORR, n (%) [95% CI]	48 (60.0) [48.4–70.9]	46 (57.5) [45.9–68.5]	46 (57.5) [45.9–68.5]	27 (67.5) [50.9–81.4]	19 (47.5) [31.5–63.9]
CR rate, n (%) [95% CI]	34 (42.5) [32.0–54.0]	32 (40.0) [29.2–51.6]	33 (41.3) [30.4–52.8]	21 (52.5) [36.1–68.5]	12 (30.0) [16.6–46.5]
PR rate, n (%) [95% CI]	14 (17.5) [10.0–28.0]	14 (17.5) [9.9–27.6]	13 (16.3) [8.9–26.2]	6 (15.0) [5.7–29.8]	7 (17.5) [7.3–32.8]
Median DoR, months [95% CI]	21.7 [21.7–NR]	43.9 [26.1–NR]	NR [33.8–NR]	NR [9.1–NR]	NR [26.1–NR]
Median PFS, months [95% CI]	12.1 [5.7–NR]	11.6 [6.3–45.7]	11.6 [5.7–45.7]	23.5 [7.4–NR]	7.6 [2.7–45.5]
Median OS, months [95% CI]	NR [18.3–NR]	33.5 [18.3–NR]	33.5 [18.3–NR]	NR [24.6–NR]	15.5 [8.6–45.5]

CI, confidence interval; CR, complete response; DoR, duration of response; FAS, full analysis set; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; pLoT, prior lines of therapy.

Table 3. 5-year safety summary: TEAEs occurring in ≥10% of patients or Grade 3–5 TEAEs in >1 patient (safety analysis set)

n, %	All grades	Grade ≥3
Any TEAE	74 (91.4)	52 (64.2)
Hematologic		
Neutropenia	40 (49.4)	39 (48.1)
Anemia	30 (37.0)	6 (7.4)
Thrombocytopenia	23 (28.4)	13 (16.0)
Febrile neutropenia	10 (12.3)	10 (12.3)
Leukopenia	10 (12.3)	8 (9.9)
Non-hematologic		
Asthenia	21 (25.9)	2 (2.5)
Edema peripheral	20 (24.7)	0
Pyrexia	19 (23.5)	0
Fatigue	14 (17.3)	2 (2.5)
Diarrhea	30 (37.0)	1 (1.2)
Constipation	15 (18.5)	0
Nausea	12 (14.8)	0
Vomiting	12 (14.8)	0
Bronchitis	13 (16.0)	1 (1.2)
Urinary tract infection	11 (13.6)	2 (2.4)
Pneumonia	10 (12.3)	8 (9.9)
Respiratory tract infection	9 (11.1)	0
Decreased appetite	18 (22.2)	0
Hypokalemia	15 (18.5)	5 (6.2)
Cough	24 (29.6)	1 (1.2)
Dyspnea	11 (13.6)	2 (2.5)
Back pain	16 (19.8)	3 (3.7)
Muscle spasms	12 (14.8)	0
C-reactive protein increased	9 (11.1)	0

TEAE, treatment emergent adverse event.

Legend to Figures

Figure 1. Kaplan–Meier curves of time-to-event endpoints

CI, confidence interval; CR, complete response; DoCR, duration of complete response; DoR, duration of response; FAS, full analysis set; mDoR, median DoR; mFU, median follow-up; mOS, median OS; mPFS, median PFS; NK, natural killer; NR, not reached; OS, overall survival; PFS, progression-free survival; pLoT, prior line of therapy; PR, partial response.

Figure 2. Time under treatment and outcomes in patients who ended treatment with a response (N=26)

Per protocol, the first CT or MRI scan for tumor measurement and disease assessment (local) was on cycle 3 day 1 (~2 months), and the first disease and disease response assessment (CT/PET) was on cycle 12 day 28.

COO, cell of origin; CT, computed tomography; GCB, germinal center B; LastL, disease refractory to last line of therapy (but not primary refractory); miss., missing; MRI, magnetic resonance imaging; PET, positron emission tomography; Prim., primary refractory disease

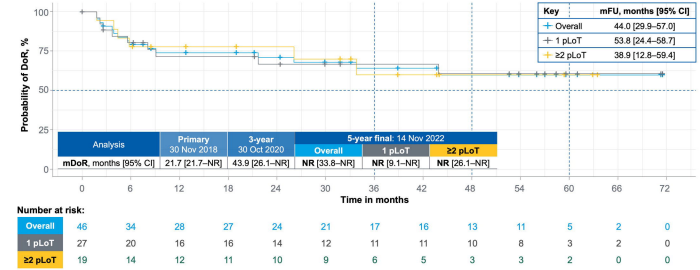
Figure 3. 5-year ORR in subgroups of clinical interest

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

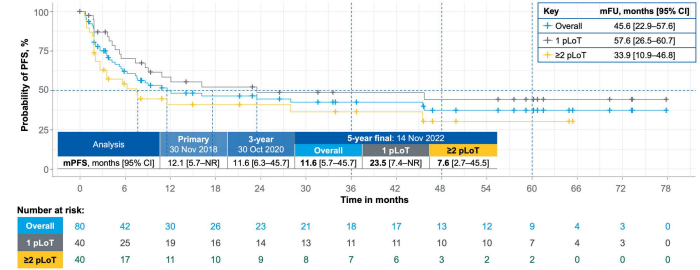
Figure 4. Exposure-adjusted comparison of TEAE frequency during the combined tafasitamab + LEN treatment period, tafasitamab monotherapy up to 2 years, and tafasitamab monotherapy beyond 2 years

TEAE, treatment-emergent adverse event; LEN, lenalidomide

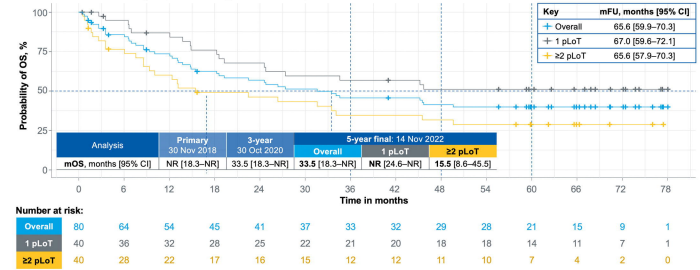
A. DoR in the FAS and in subgroups according to number of pLoT



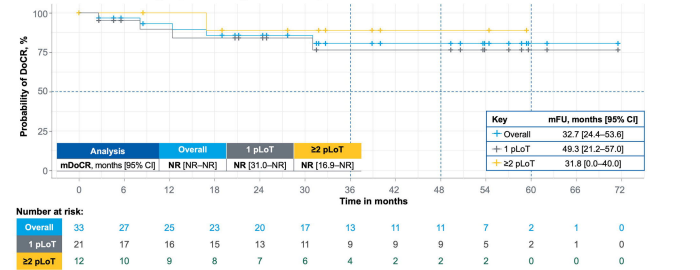
B. PFS in the FAS and in subgroups according to number of pLoT



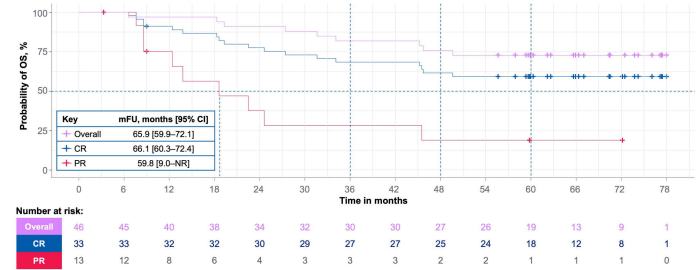
C. OS in the FAS and in subgroups according to number of pLoT



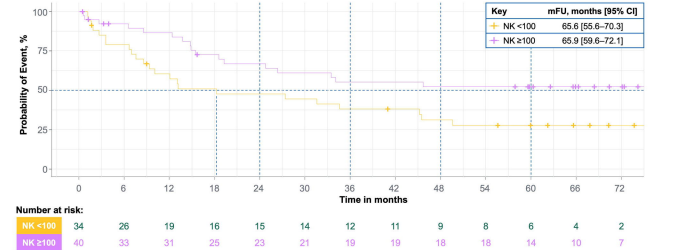
D. DoCR in the FAS and in subgroups according to number of pLoT

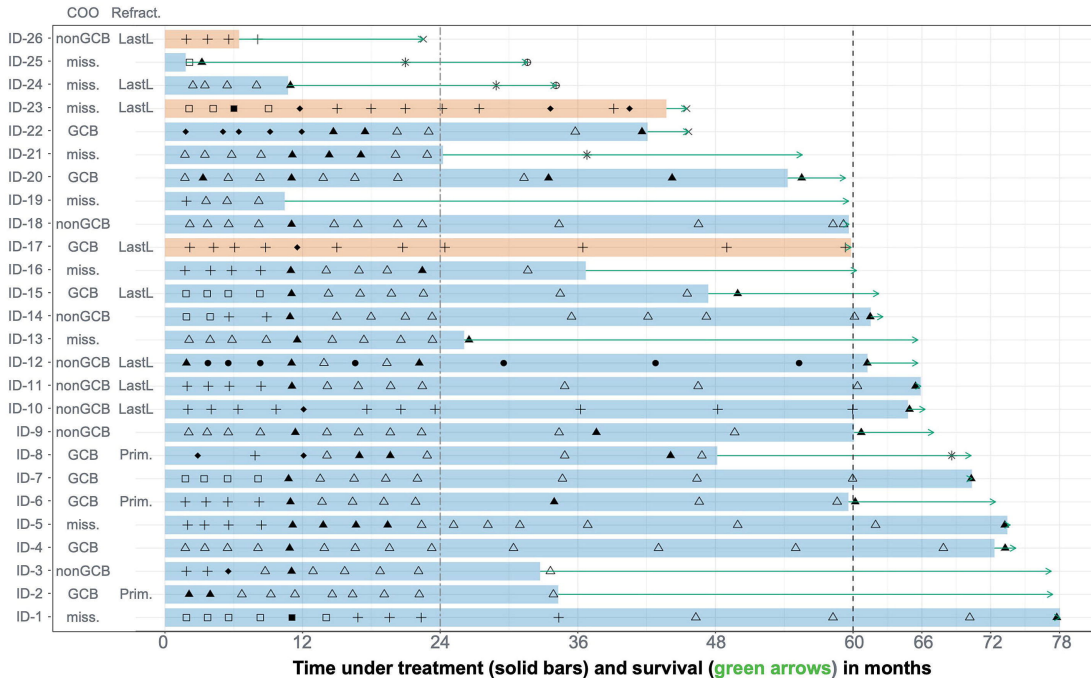


E. OS according to best response in patients with a best response of CR or PR in the FAS



F. OS according to NK cell count ≥100 cells/μL peripheral blood in the FAS



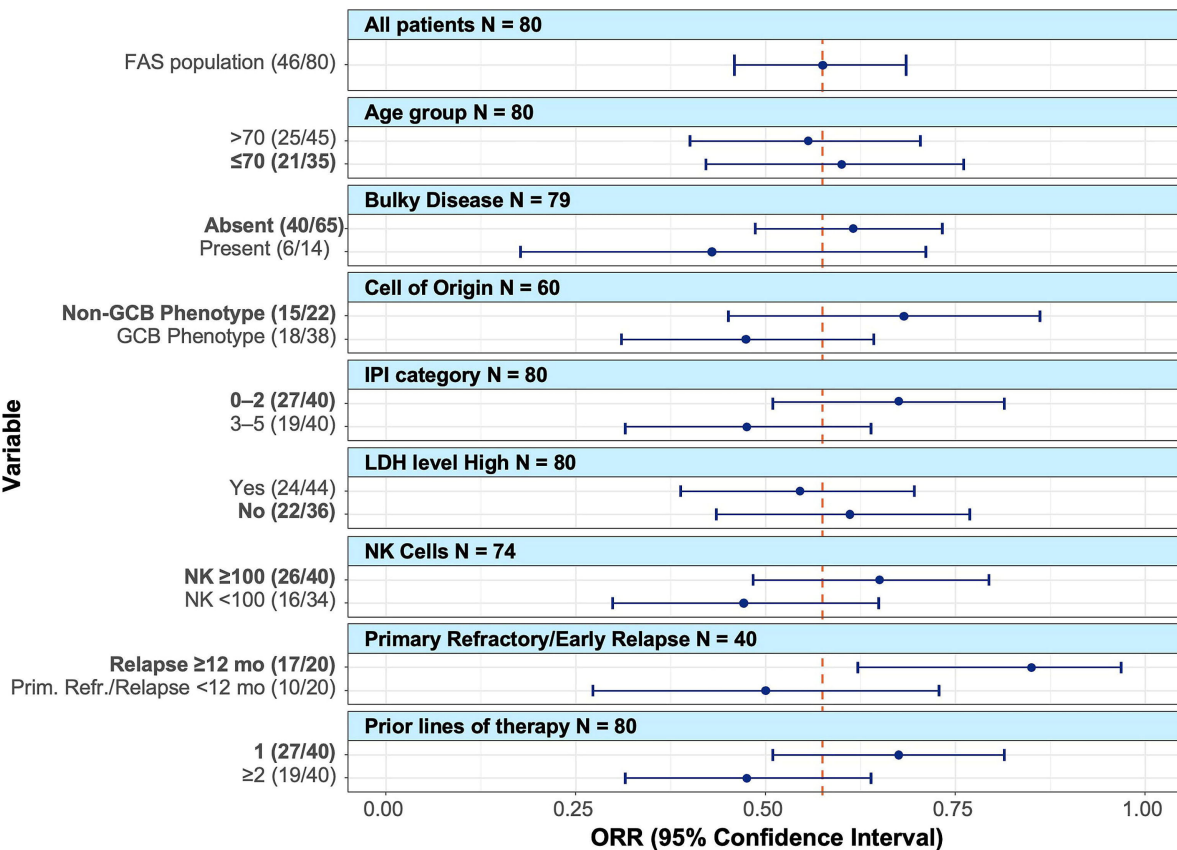


Outcomes/Response Assessment

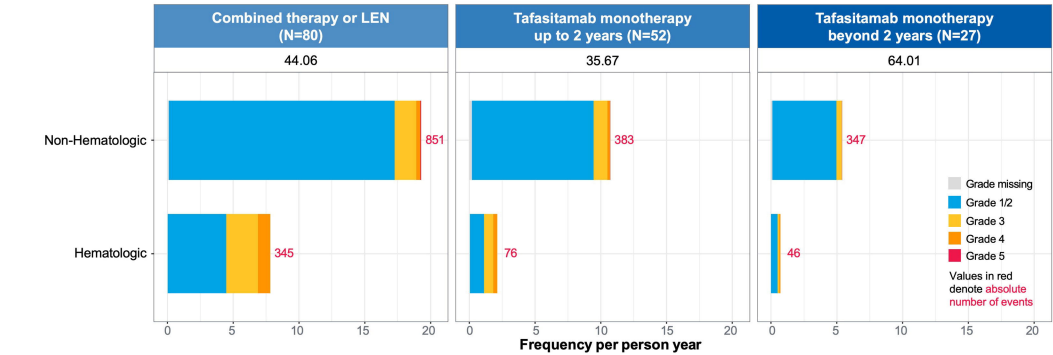
- △ Complete Response–nonPET
- ▲ Complete Response–PET
- + Partial Response–nonPET
- ◆ Partial Response–PET
- Stable Disease–nonPET
- Stable Disease–PET
- Other–nonPET
- ⊕ Death from progressive disease
- × Death from other reasons
- * Next anti-lymphoma therapy

Best Response

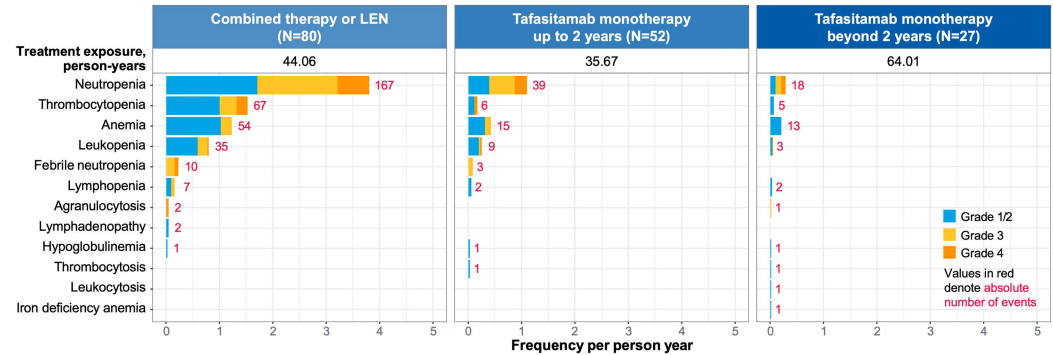
- Complete Response
- Partial Response



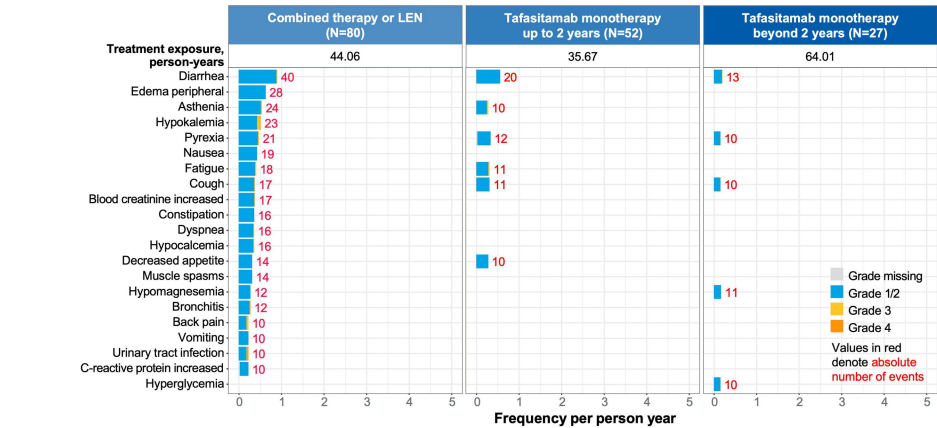
A. All TEAEs



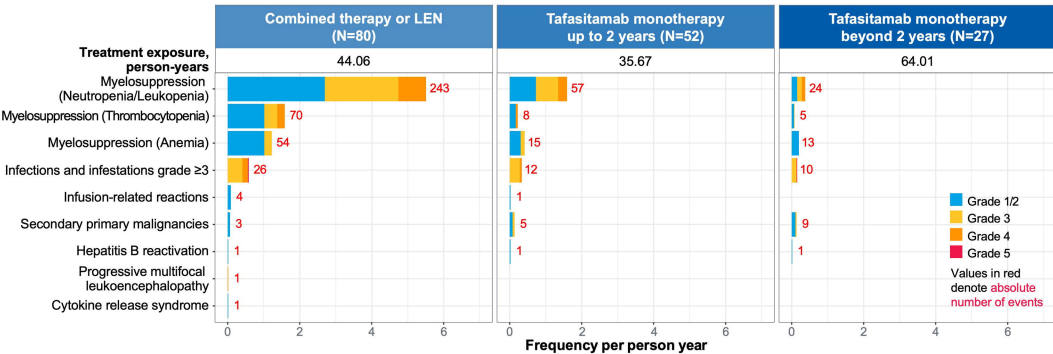
B. Hematologic TEAEs



C. Non-hematologic TEAEs (cut-off: ≥10 events in any treatment period)



D. Important TEAEs of interest



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/ μ L). 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/ μ L 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/ μ L 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.
2. Klanova M, Oestergaard MZ, Trněný M, et al. Prognostic impact of natural killer cell count in follicular lymphoma and diffuse large B-cell lymphoma patients treated with immunochemotherapy. *Clin Cancer Res* 2019;25(15):4634–4643.
3. He L, Zhu HY, Qin SC, et al. Low natural killer (NK) cell counts in peripheral blood adversely affect clinical outcome of patients with follicular lymphoma. *Blood Cancer Journal* 2016;6(8): e457.
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)

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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.

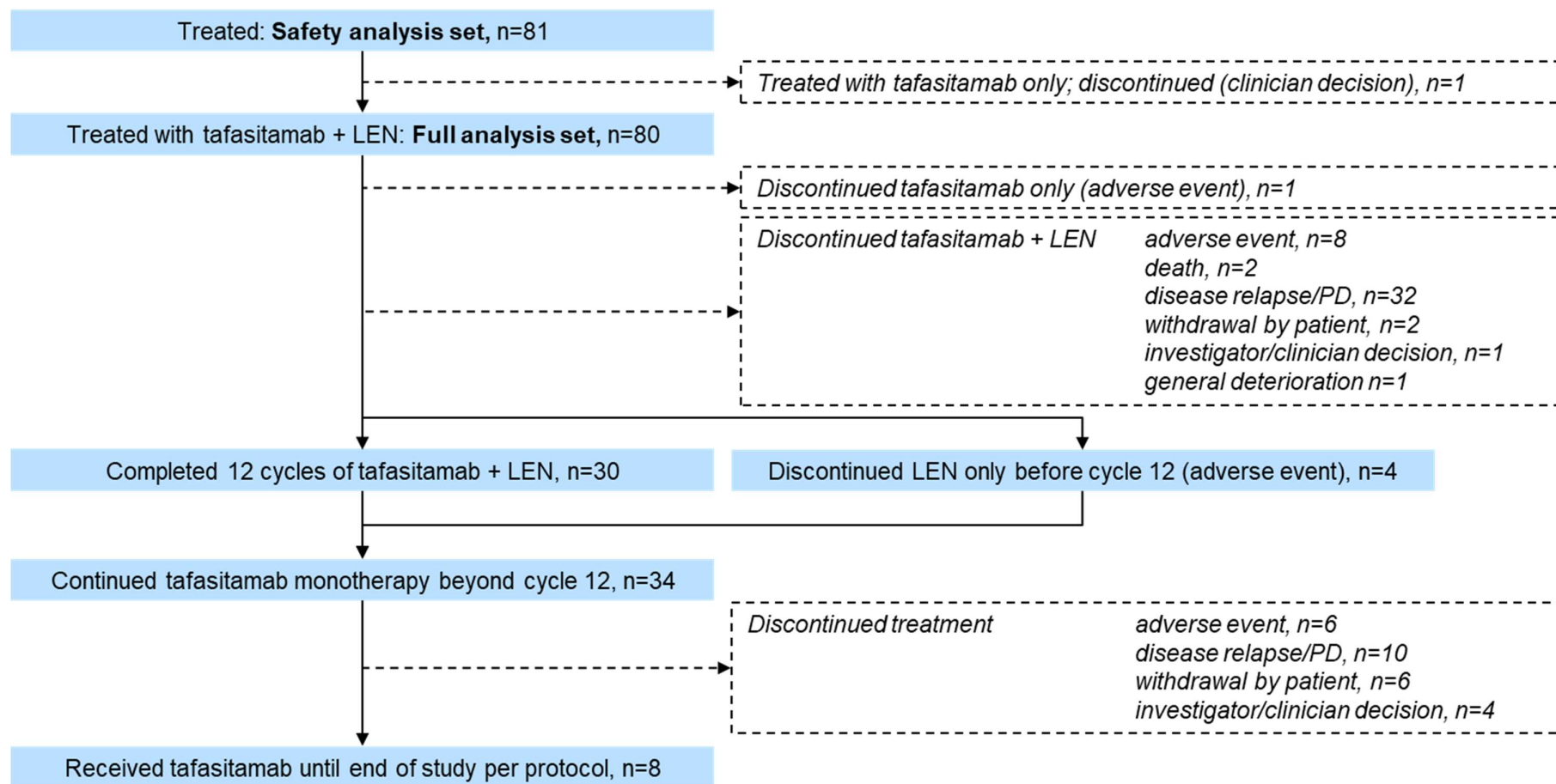
Supplemental Table 4: Univariate and multivariate analysis of efficacy outcomes according to potential prognostic factors

	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.

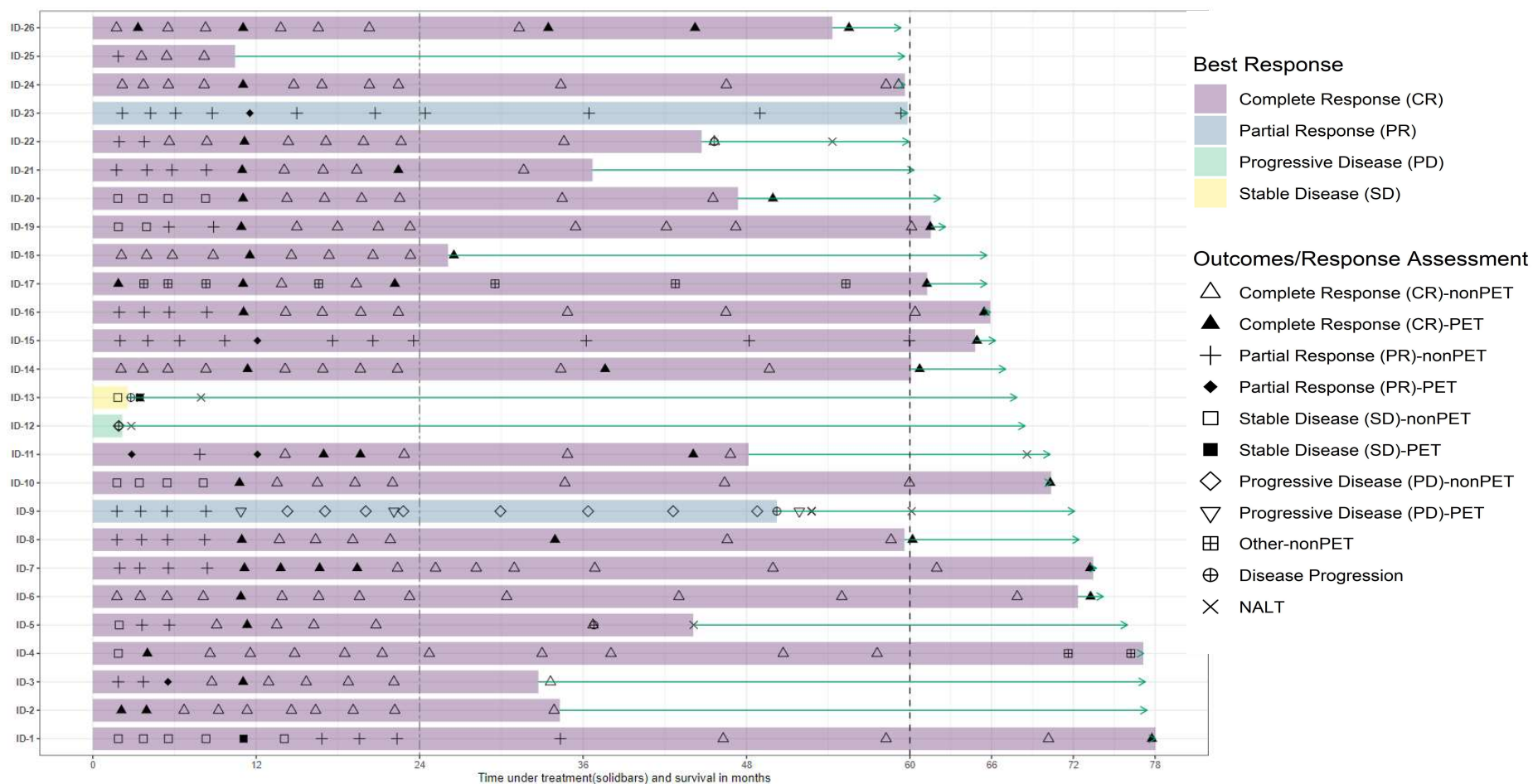
Supplemental Figure 1. Patient disposition



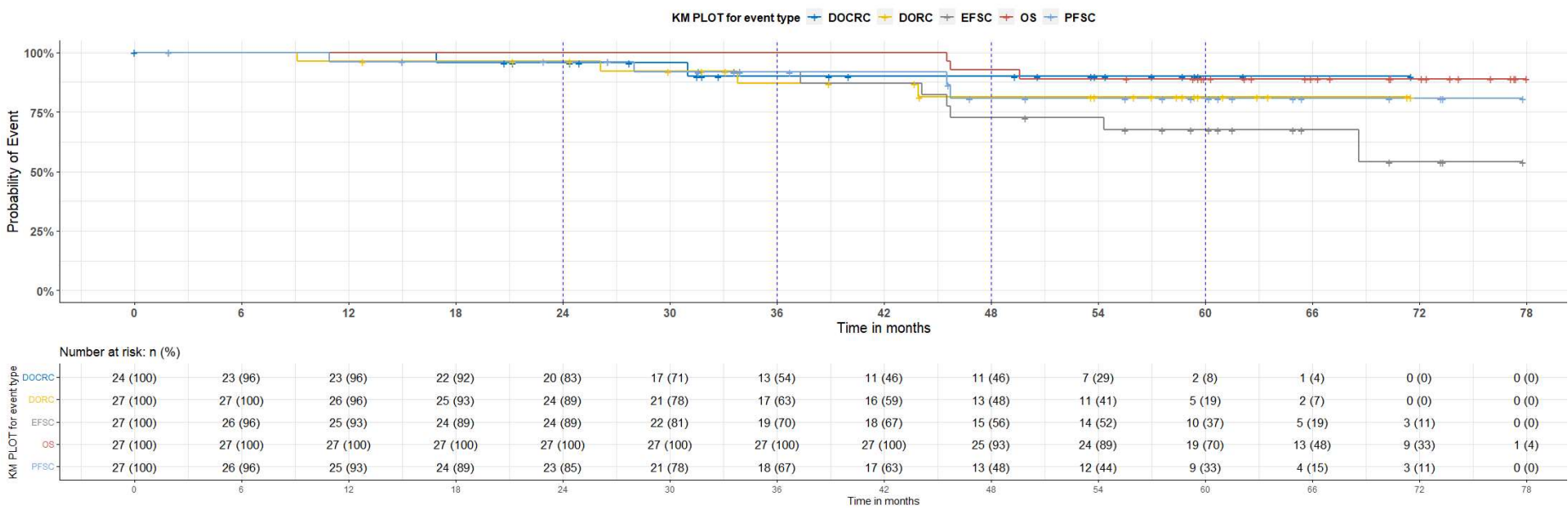
LEN, lenalidomide; PD, progressive disease.

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

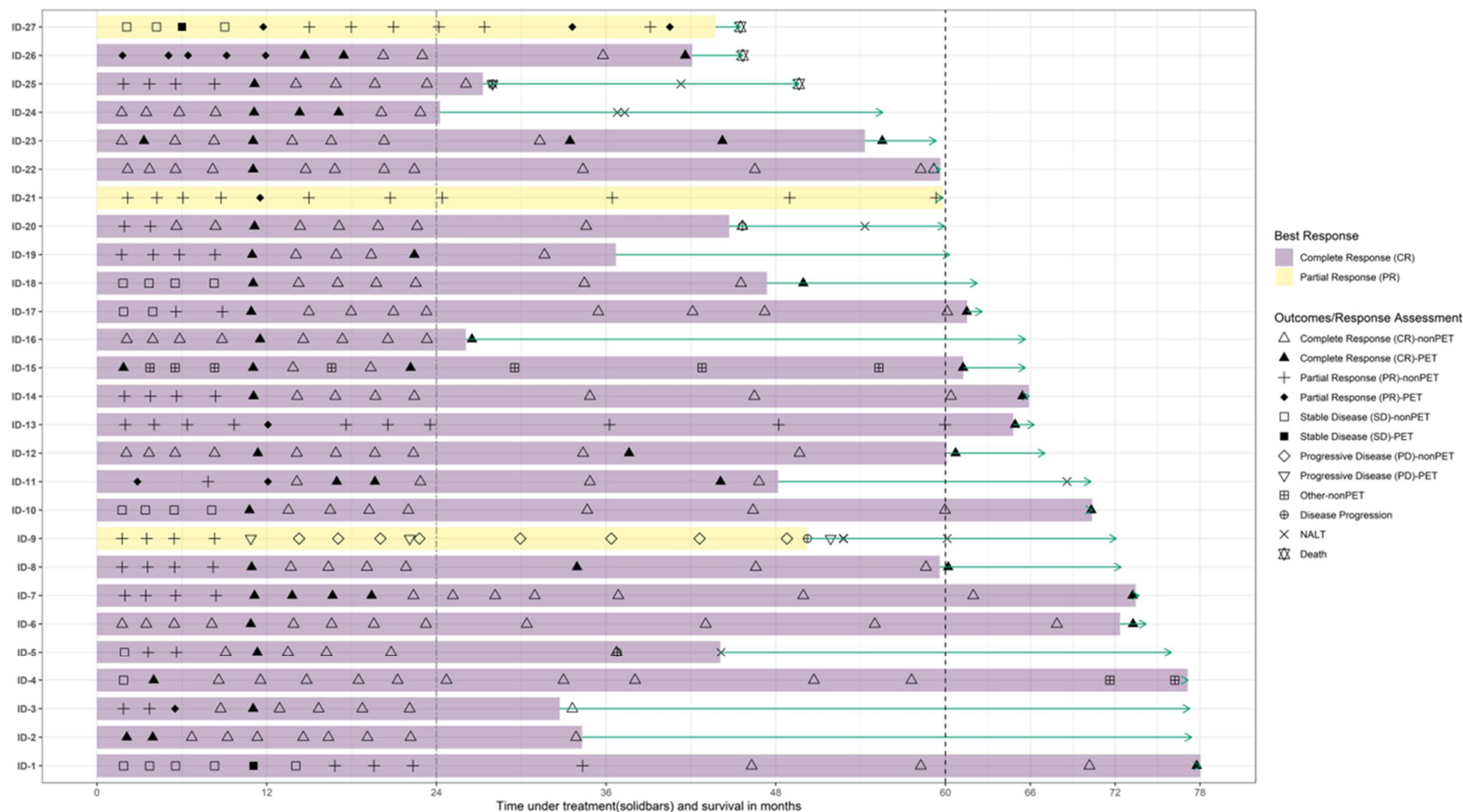
(A) Time under treatment and outcomes in patients with OS follow-up >59 months (n=26)



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



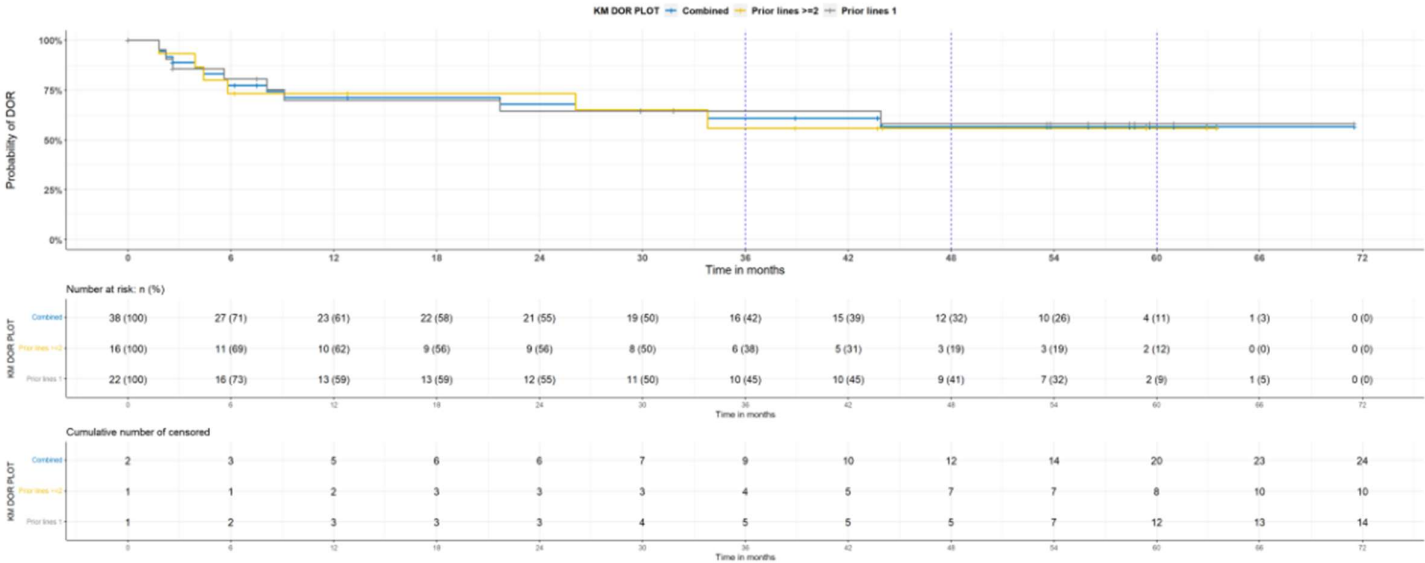
(C) Time under treatment and outcomes in patients with ≥ 2 years of therapy (N=27)



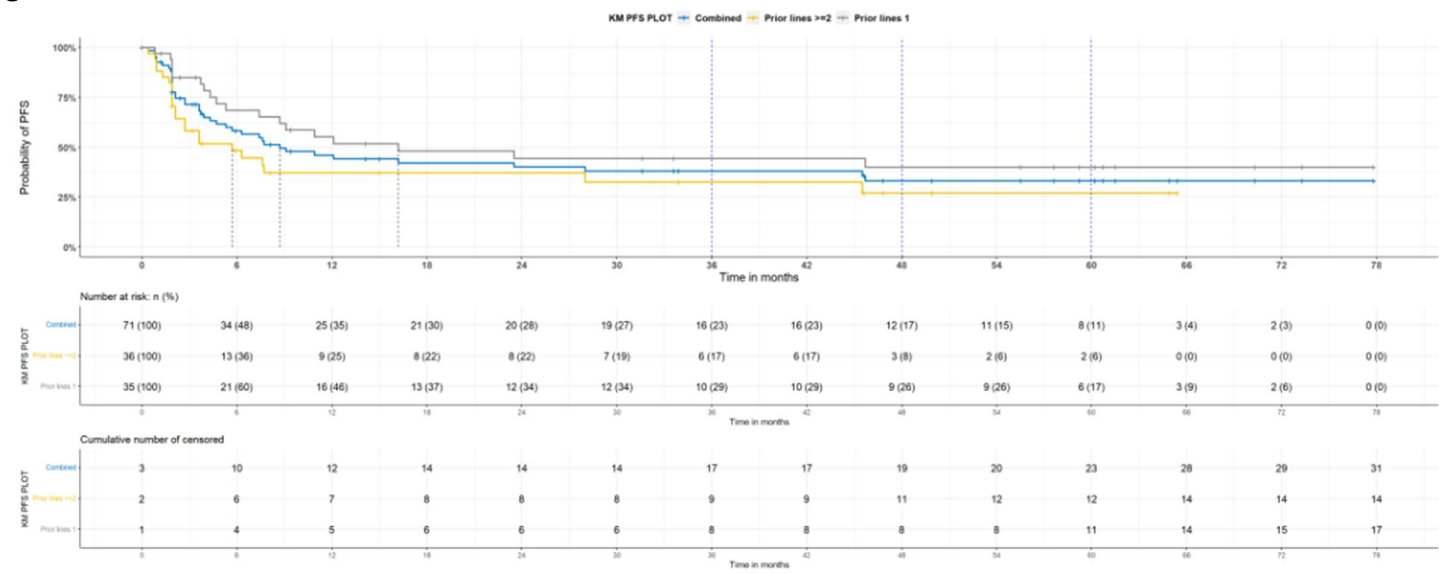
CR, complete response; FAS, full analysis set; NALT, next anti-lymphoma therapy; OS, overall survival; PFS, progression-free survival; pLoT, prior line of therapy; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.

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

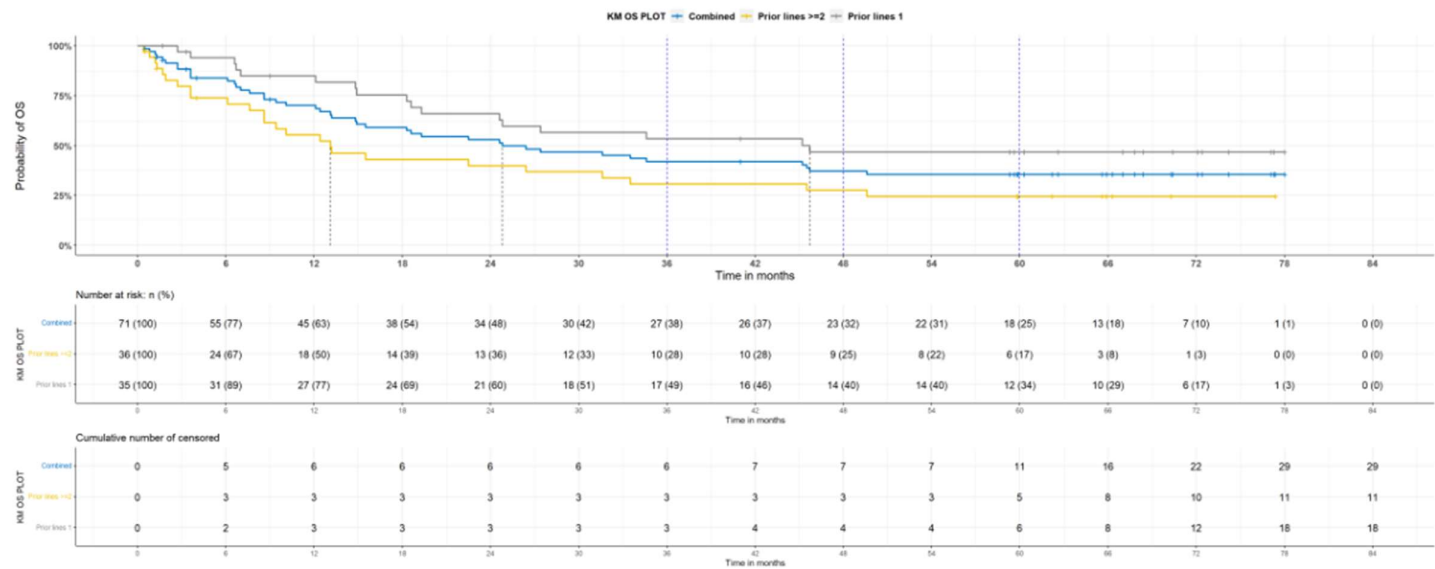
(A) DoR



(B) PFS

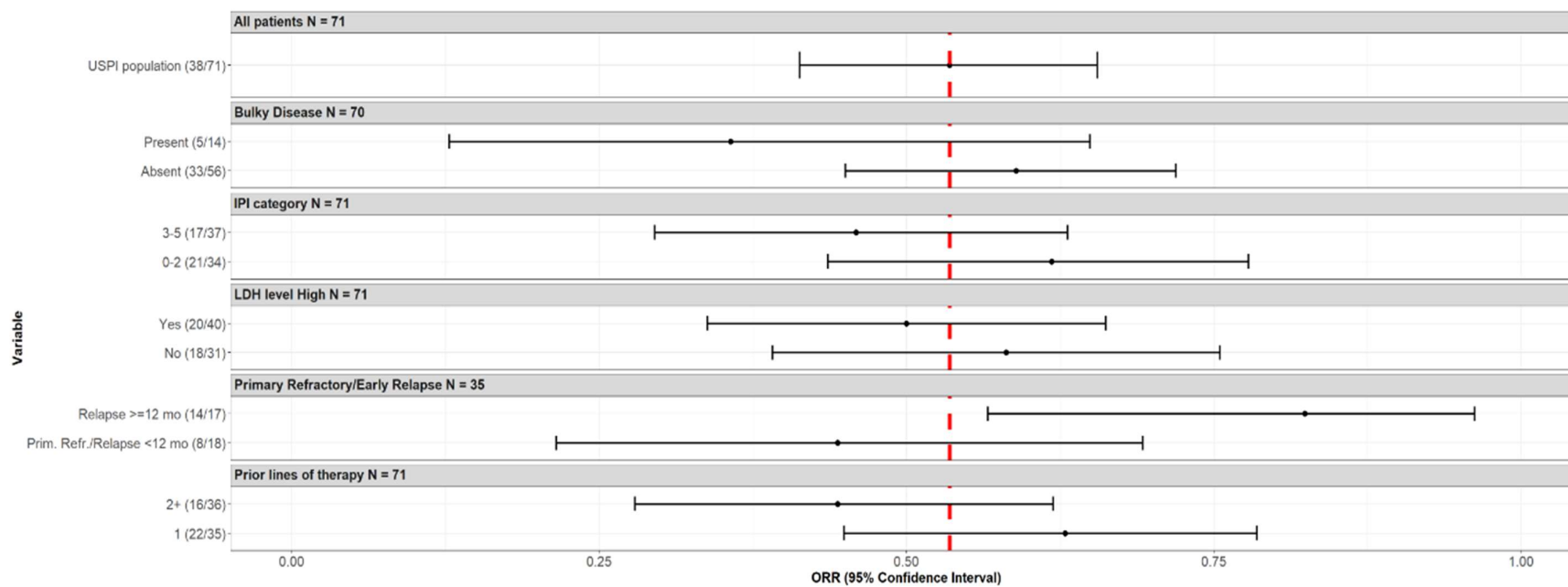


(C) OS



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.