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

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] and Gilles Salles[14]

[1]Medizinische Klinik und Poliklinik II, Universitätsklinik Würzburg, Würzburg, Germany; [2]Department of Hematology, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; [3]Centre Hospitalier Universitaire CHU UCL Namur, Namur, Belgium; [4]Division of Hematology, Department of Translational Medicine University of Eastern Piedmont and Ospedale Maggiore della Carità, Novara, Italy; [5]Department of Hematology, Institut Català d'Oncologia, Hospitalet de Llobregat, IDIBELL, Universitat de Barcelona, Barcelona, Spain; [6]Department of Clinical Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Kraków, Poland; [7]Department of Molecular and Clinical Cancer, University of Liverpool, Liverpool, UK; [8]Università degli Studi di Perugia, Azienda Ospedaliera Santa Maria di Terni, Terni, Italy; [9]Department of Internal Medicine, Arthur G James Comprehensive Cancer Center, Ohio State University Wexner Medical Center, Columbus, OH, USA; [10]Freeman Hospital, The Newcastle upon Tyne Hospitals, Newcastle upon Tyne, UK; [11]Semmelweis University, Budapest, Hungary; [12]Centre Hospitalier Universitaire de Clermont-Ferrand, Lyon, France; [13]MorphoSys AG, Planegg, Germany and [14]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Correspondence: J. Duell
Duell_J@ukw.de

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Abstract

Tafasitamab, an anti-CD19 immunotherapy, is used with lenalidomide for patients with autologous stem cell transplant-ineligible relapsed/refractory diffuse large B-cell lymphoma based on the results of the phase II L-MIND study (NCT02399085). We report the final 5-year analysis of this study. Eighty patients ≥18 years who had received one to three prior systemic therapies, and had Eastern Cooperative Oncology Group performance status 0-2 received up to 12 cycles of co-administered tafasitamab and lenalidomide, followed by tafasitamab monotherapy until disease progression or unacceptable toxicity. The primary endpoint was the best objective response rate. Secondary endpoints included duration of response, progression-free survival, overall survival, and safety. Exploratory analyses evaluated efficacy endpoints by prior lines of therapy. At data cutoff on November 14, 2022, the objective response rate was 57.5%, with a complete response rate of 41.3% (n=33), which was consistent with prior analyses. With a median follow-up of 44.0 months, the median duration of response was not reached. The median progression-free survival was 11.6 months (95% confidence interval [95% CI]: 5.7-45.7) with a median follow-up of 45.6 months. The median overall survival was 33.5 months (95% CI: 18.3-not reached) with a median follow-up of 65.6 months. Patients who had received one prior line of therapy (n=40) showed a higher objective response rate (67.5%; 52.5% complete responses) compared to patients who had received two or more prior lines of therapy (n=40; 47.5%; 30% complete responses), but the median duration of response was not reached in either subgroup. Other exploratory analyses revealed consistent long-term efficacy results across subgroups. Adverse events were consistent with those described in previous reports, were manageable, and their frequency decreased during tafasitamab monotherapy, with no new safety concerns. This final 5-year analysis of L-MIND demonstrates that the immunotherapy combination of tafasitamab and lenalidomide 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.[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 more than 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 because of failure of salvage therapy. A further 40-65% 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] The 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%, a complete response (CR) rate of 43%, and a median duration of response 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 received conditional marketing authorization in Europe (August 2021) for the treatment of adult patients with R/R DLBCL (detailed in the USA label as not otherwise specified, including DLBCL arising from low-grade lymphoma) 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 of the L-MIND study, with an ORR of 57.5%, a CR rate of 40%, and median duration of response 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 to participation in the study.

Study design and patients

Full details of the L-MIND study methods and patients' eligibility criteria have been described previously.[11,14] Briefly, patients were aged ≥18 years with ASCT-ineligible R/R DLBCL, had received one to three prior systemic therapies (including ≥1 targeting CD20) and had an Eastern Cooperative Oncology Group performance status 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 relapsed within the first 3-6 months after 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 or better, until progressive disease. 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 the ORR (CR plus partial response [PR]), assessed by an independent review committee, according to the 2007 International Working Group response criteria for malignant lymphoma.[15] Secondary endpoints included duration of response (time from initial CR or PR to first observation of progressive disease), progression-free survival (PFS; time from first dose to progressive disease or death), overall survival (OS; time from first dose to date of death), time to progression, time to next treatment, and incidence and severity of adverse events (AE).

Statistical analyses

The primary analysis occurred when all patients had completed a minimum of 12 months follow-up (data cutoff: November 30, 2018);[11] the 3-year follow-up had a data cutoff date of October 30, 2020.[14] The data cutoff for the present, pre-specified 5-year analysis was November 14, 2022.

Efficacy outcomes were analyzed in the full analysis set (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 (TEAE) per unit of treatment exposure time was analyzed across three periods; details are provided in the *Online Supplementary Methods*.

Exploratory subgroup analyses

Efficacy outcomes (ORR, PFS, OS, duration of response, and/or duration of CR) were also evaluated in exploratory analyses in subgroups of clinical interest, defined by the number of prior lines of therapy (1 *vs.* ≥2); time to progression after first-line therapy (<1 *vs.* ≥1 year, in patients who had received only 1 prior line of therapy); patients' 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 (germinal center B cell *vs.* non-germinal center B cell); and natural killer (NK) cell count (<100 cells/μL *vs.* ≥100 cells/μL peripheral blood). NK cell counts were analyzed at baseline by flow cytometry; details are provided in the *Online Supplementary 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 the *Online Supplementary 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).

Table 1. Baseline characteristics of the patients in the full analysis set and by prior lines of therapy.

Characteristics	All patients: full analysis set	1 prior line of therapy	≥2 prior lines of therapy
N	80	40	40
Age in years, median (range)	72.0 (41.0-86.0)	72.0 (53.0-86.0)	70.5 (41.0-82.0)
Age >70 years, N (%)	45 (56.3)	25 (62.5)	20 (50.0)
Sex, N (%) Female Male	 37 (46.3) 43 (53.8)	 19 (47.5) 21 (52.5)	 18 (45.0) 22 (55.0)
Ann Arbor stage, N (%) I-II III-IV	 20 (25.0) 60 (75.0)	 11 (27.5) 29 (72.5)	 9 (22.5) 31 (77.5)
IPI score, N (%) 0-2 3-5	 40 (50.0) 40 (50.0)	 25 (62.5) 15 (37.5)	 15 (37.5) 25 (62.5)
Elevated LDH, N (%) Yes No	 44 (55.0) 36 (45.0)	 18 (45.0) 22 (55.0)	 26 (65.0) 14 (35.0)
Prior lines, N (%) 1 2 3 4	 40 (50.0) 34 (42.5) 5 (6.3) 1 (1.3)	 - - - -	 - - - -
Primary refractory*, N (%) Yes No	 15 (18.8) 65 (81.3)	 6 (15.0) 34 (85.0)	 9 (22.5) 31 (77.5)
Refractory to previous line of therapy, N (%) Yes No	 35 (43.8) 45 (56.3)	 6 (15.0) 34 (85.0)	 29 (72.5) 11 (27.5)
Prior ASCT, N (%) Yes No	 9 (11.3) 71 (88.8)	 2 (5.0) 38 (95.0)	 7 (17.5) 33 (82.5)
Cell of origin (by IHC), N (%) GCB Non-GCB Unknown/NE	 38 (47.5) 22 (27.5) 20 (25.0)	 16 (40.0) 14 (35.0) 10 (25.0)	 22 (55.0) 8 (20.0) 10 (25.0)

*Patients with primary refractory disease had a response lasting 3-6 months after first-line therapy. IPI: International Prognostic Index; LDH: lactate dehydrogenase; ASCT: autologous stem cell transplant; IHC: immunohistochemistry; GCB: germinal center B cell; NE: not evaluated.

Results

Patients and treatment

The full analysis set comprised 80 patients while 81 were included in the safety analysis set. The patients' disposition for treatment is shown in *Online Supplementary Figure S1*. The median age of enrolled patients was 72 years (range, 41-86). Fifty percent of patients in the full analysis set had received one prior line of therapy at study entry; half had been given two or more prior lines of therapy. Fifty percent of patients had an IPI score of 3-5. Nine patients had undergone prior stem-cell transplantation. The baseline characteristics of patients in the full analysis set and according to the number of prior lines of therapy are shown in Table 1 (equivalent data in the USPI population are shown in *Online Supplementary Table S1*). Fifteen (18.8%) patients had primary refractory disease, with a duration of response 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 cutoff. Twenty-six patients had more than 59 months of follow-up for survival (23 reached the end of the study, 3 withdrew because of AE) and 21 had more than 60 months (18 reached the end of the study, 3 withdrew because of AE). Among those with long-term follow-up, eight received tafasitamab until the end of the study as per protocol. In total, 27 patients received tafasitamab therapy for 2 or more years (see Safety outcomes for treatment duration).

Efficacy outcomes

At this 5-year analysis, the best ORR, assessed by an independent review committee, was 57.5% (46/80; 95% confidence interval [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). Stable disease as the best response was observed in 16.3% of patients (n=13). Overall, five best responses altered in the 5-year *versus* 3-year analyses (t2 CR to PR, 3 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.

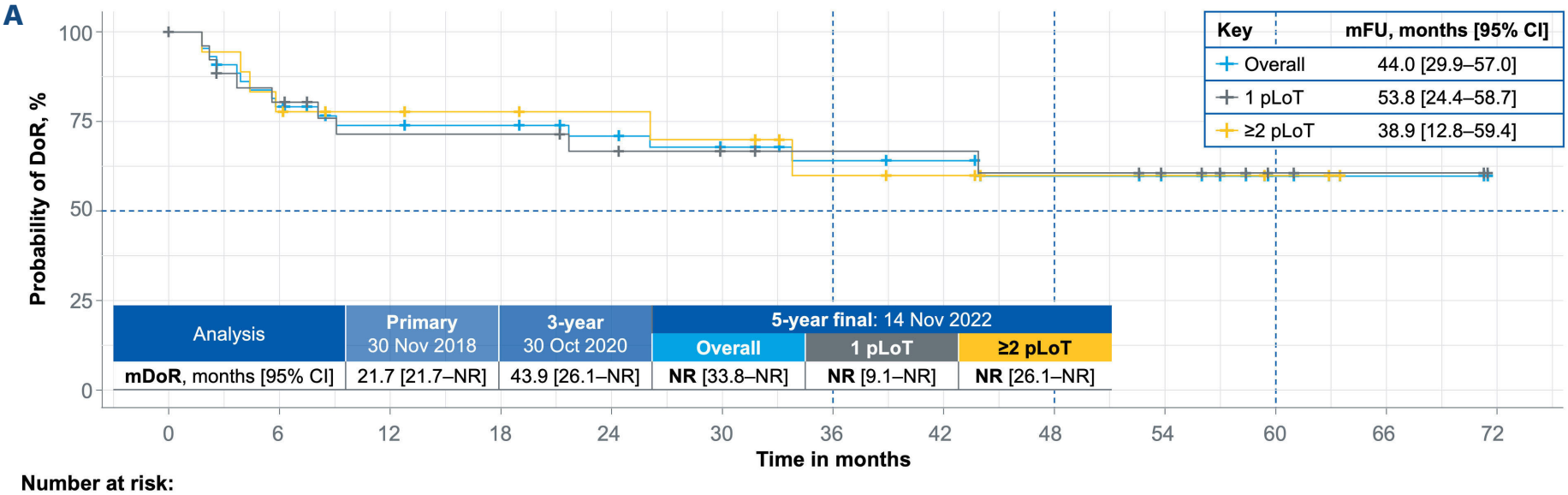
After a median follow-up of 44.0 months (95% CI: 29.9-57.0), the median duration of response was not reached (NR) (Figure 1A); the curve suggests a plateau after approximately 12 months, although the number of patients at risk is limited. The median PFS was 11.6 months (95% CI: 5.7-45.7) with a median follow-up of 45.6 months (95% CI: 22.9-57.6) (Figure 1B), and the 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), the median duration of CR was not reached (Figure 1D); the 5-year duration of CR was estimated to be 80.7% (95% CI: 59.1-91.6). Figure 1E shows the impact of response quality on OS; whereas the median OS was not reached in patients with CR or PR (95% CI: 45.5 months-NR) and in patients with a best response of CR (NR-NR), it was 18.6 months (95% CI: 8.6-45.5) in patients with PR as their best response. The median time to response was 2.0 months (range, 1.7-16.8), which coincided with the first evaluation as per

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

Characteristics	Primary analysis	3-year follow-up	Final 5-year data	5-year data for patients with 1 prior line of therapy, N=40	5-year data for patients with ≥2 prior lines of therapy, 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 in 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 in 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 in 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]

ORR: objective response rate; 95% CI: 95% confidence interval; CR: complete response; PR: partial response; DoR: duration of response; NR: not reached; PFS: progression-free survival; OS: overall survival.

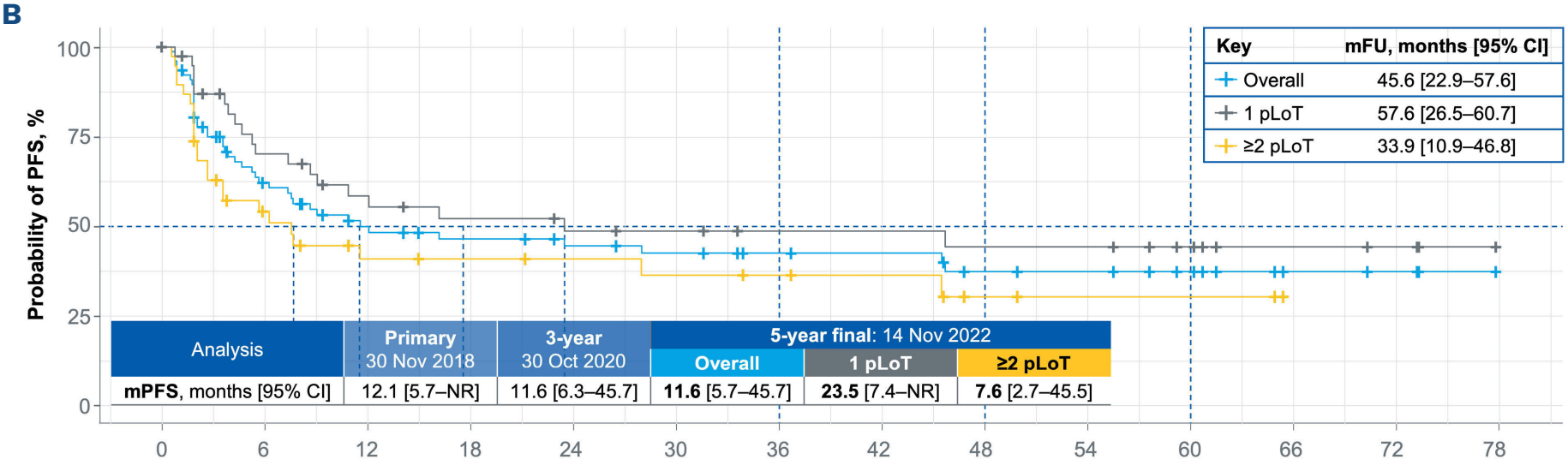
A



Number at risk:

Overall	46	34	28	27	24	21	17	16	13	11	5	2	0
1 pLoT	27	20	16	16	14	12	11	11	10	8	3	2	0
≥2 pLoT	19	14	12	11	10	9	6	5	3	3	2	0	0

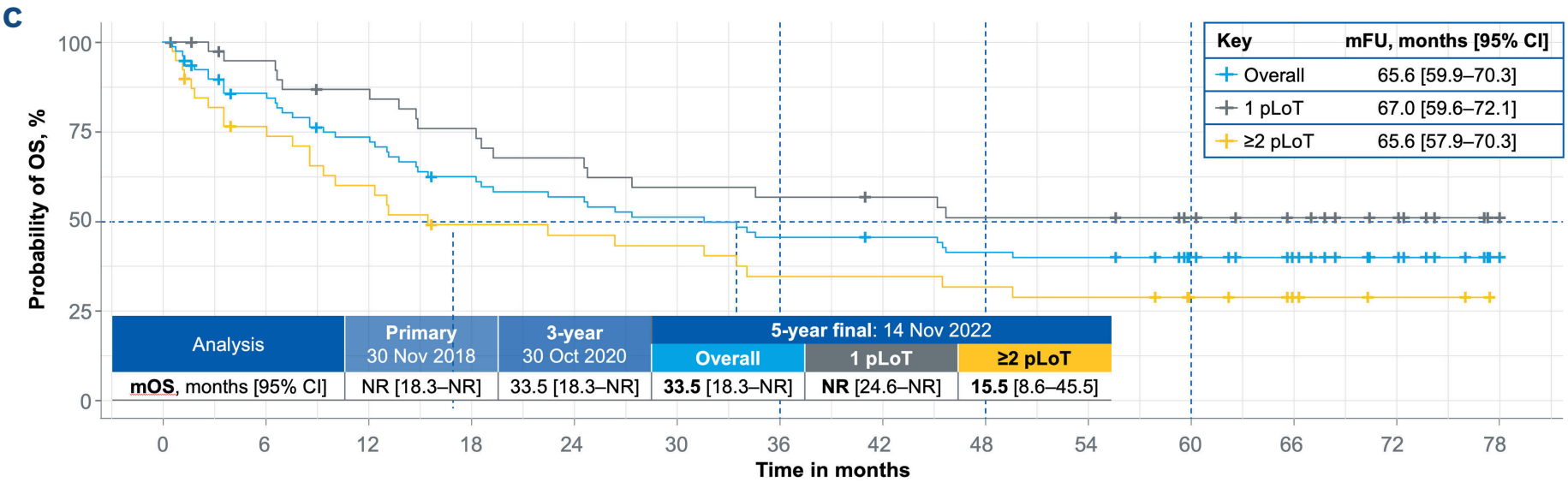
B



Number at risk:

Overall	80	42	30	26	23	21	18	17	13	12	9	4	3	0
1 pLoT	40	25	19	16	14	13	11	11	10	10	7	4	3	0
≥2 pLoT	40	17	11	10	9	8	7	6	3	2	2	0	0	0

C



Number at risk:

Overall	80	64	54	45	41	37	33	32	29	28	21	15	9	1
1 pLoT	40	36	32	28	25	22	21	20	18	18	14	11	7	1
≥2 pLoT	40	28	22	17	16	15	12	12	11	10	7	4	2	0

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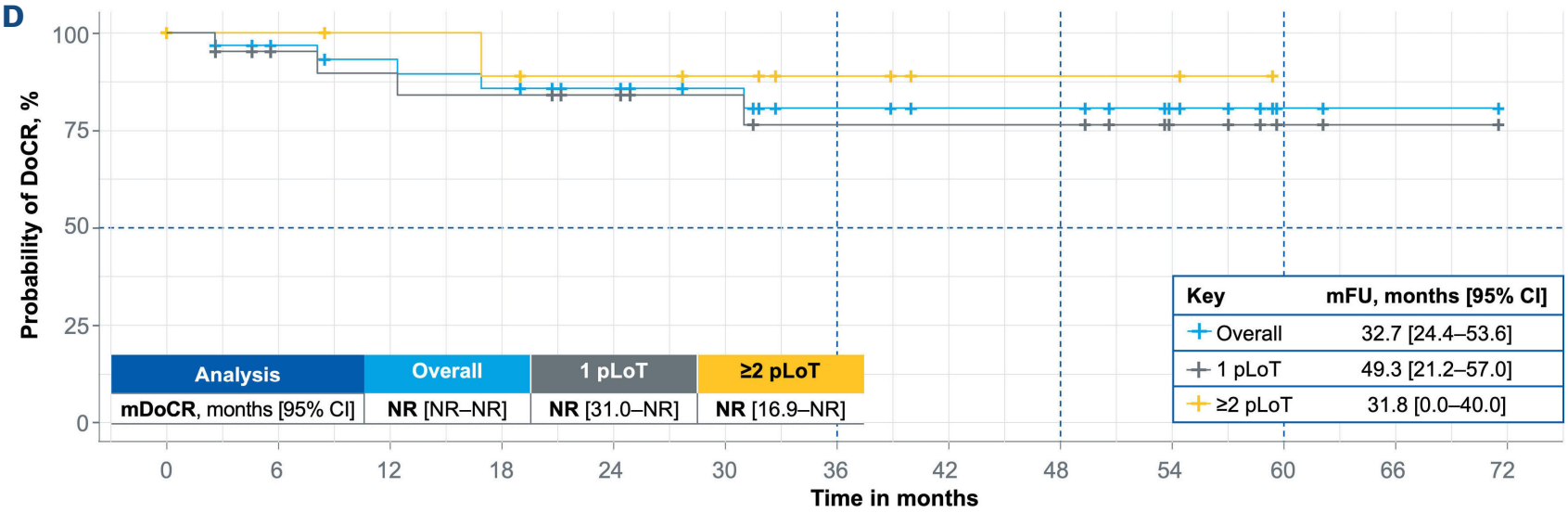
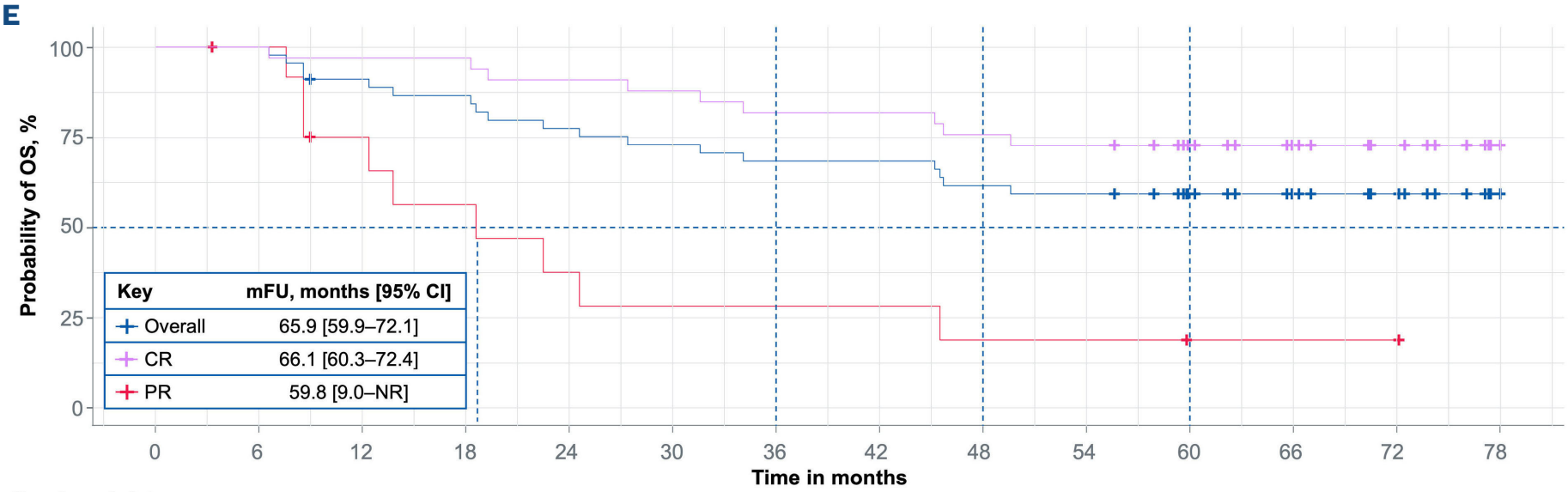
D



Number at risk:

Overall	33	27	25	23	20	17	13	11	11	7	2	1	0
1 pLoT	21	17	16	15	13	11	9	9	9	5	2	1	0
≥2 pLoT	12	10	9	8	7	6	4	2	2	2	0	0	0

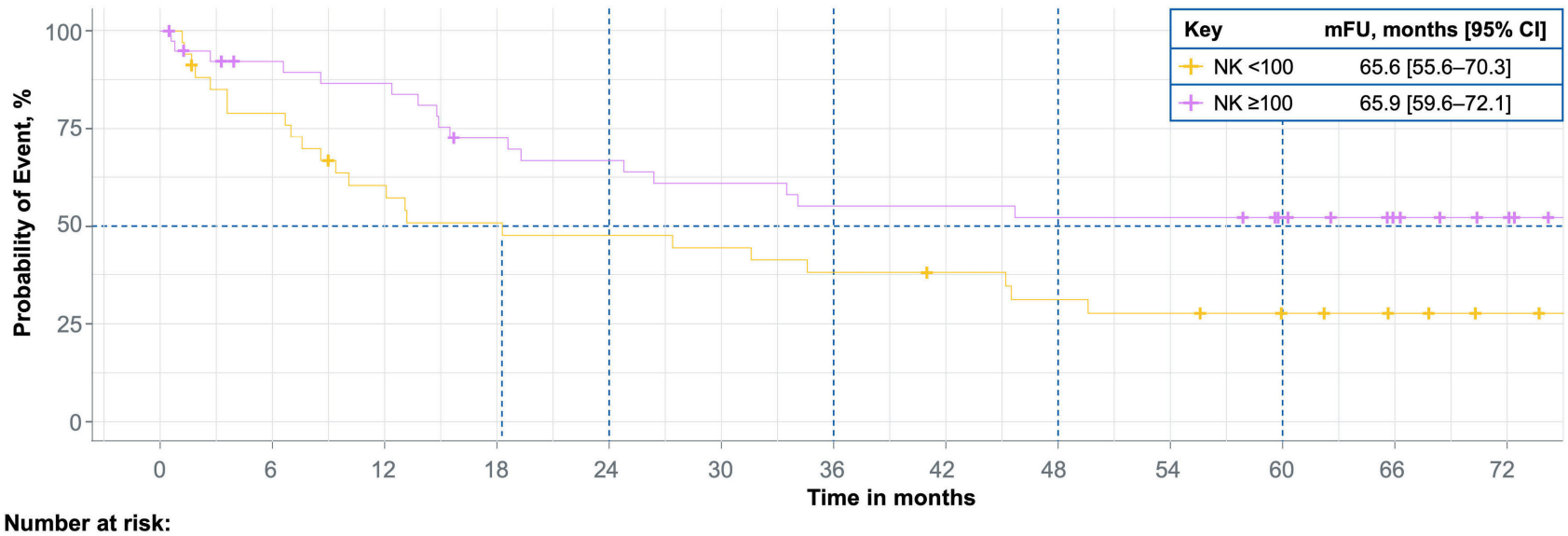
E



Number at risk:

Overall	46	45	40	38	34	32	30	30	27	26	19	13	9	1
CR	33	33	32	32	30	29	27	27	25	24	18	12	8	1
PR	13	12	8	6	4	3	3	3	2	2	1	1	1	0

F



Number at risk:

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

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Figure 1. Kaplan-Meier curves of time-to-event endpoints. (A) Duration of response in the overall group and in subgroups divided according to the number of prior lines of therapy. (B) Progression-free survival in the overall group and in subgroups divided according to the number of prior lines of therapy. (C) Overall survival in the overall group and in subgroups divided according to the number of prior lines of therapy. (D) Duration of complete response in the overall group and in subgroups divided according to the number of prior lines of therapy. (E) Overall survival according to best response in patients with a best response of complete response or partial response in the overall group. (F) Overall survival according to natural killer cell count < or ≥100 cells/μL of peripheral blood. DoR: duration of response; mFU: median follow-up; 95% CI: 95% confidence interval; pLoT: prior line(s) of therapy; mDoR: median DoR; NR: not reached; PFS: progression-free survival; mPFS: median PFS; OS: overall survival; mOS: median OS; DoCR: duration of complete response; mDoCR: median DoCR; CR: complete response; PR: partial response; NK: natural killer cell count.

protocol. 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 the end of the study (8 were on treatment until the end of the study, while 11 had previously discontinued tafasitamab), two patients later died from progressive disease (both had previous CR but <12 months of 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 (2 with PR and 1 with CR as best response). Two patients experienced disease relapse after discontinuation of treatment and were alive at the end of participation in the study.

Among the nine patients who had previously undergone stem-cell transplantation, 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 less than 2 months because of an AE and died after 31 months. Three of the nine patients had a best response of PR; two of them later had progressive disease and died, the third was alive and on treatment at the end of the study. Two of the nine had a best response of progressive disease; one died and one was lost to follow-up.

Outcomes and response assessments for the 26 patients with a follow-up for survival of more than 59 months are shown in *Online Supplementary Figure S2A*. Twenty-two had CR as their best response, two PR, and one each had stable disease and progressive disease.

Efficacy outcomes in the USPI population are shown in *Online Supplementary Table S2* and *Online Supplementary Figure S3*.

Exploratory subgroup analyses

The median time on study treatment was 11.4 months (range, 0.7-78.0) for patients who had received one prior line of therapy and 6.1 months (range, 0.1-65.9) for those who had received two or more prior lines of therapy in the full analysis set. Patients who had received only one prior line of therapy had a higher ORR (67.5%, with 52.5% CR and 15.0% PR) compared to patients who had received two or more prior lines of therapy (47.5%, with 30.0% CR and 17.5% PR). Similarly, and as expected, the median PFS and median OS were longer in patients who had received one prior line of therapy compared with those who had received two or more prior lines of therapy (Table 2, Figure 1B, C). However, the median duration of response and duration of CR were not reached in either subgroup, indicating comparable long-term efficacy in patients who received the combination of tafasitamab + lenalidomide as second or later lines of therapy (Table 2, Figure 1A, D).

Time-to-response curves for the 27 patients who received tafasitamab treatment for 2 or more years are shown in *Online Supplementary Figure S2B*, with outcomes and response assessments for this subgroup in *Online Supplementary Figure S2C*. The best response was a CR in 24 and PR in three patients.

The 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 prior line of therapy, and late relapse (defined as time to relapse/progressive disease ≥12 months after first-line therapy, and its influence was investigated only in the subgroup of patients given 1 prior line of therapy). The ORR in the USPI population between subgroups of clinical interest was also favorable in all patients with positive prognostic factors (*Online Supplementary Figure S4*). Similarly, 5-year rate estimates for duration of response, PFS and OS suggest long-term clinical activity in all subgroups of patients (*Online Supplementary Table S3*).

NK cell count at baseline was significantly related to survival; the median OS was not reached (95% CI: 19.3-NR) in patients with a NK cell count of ≥100 cells/μL, compared with 18.3 months (95% CI: 8.6-45.5) in patients with a NK cell count of <100 cells/μL (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/μL at baseline was significantly associated with both longer PFS and longer OS (*Online Supplementary Table S4*). Reflecting the small sample size, none of the factors in the regression analysis was 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, a few known prognostic factors besides NK cells remained significant in the multivariate models: low lactate dehydrogenase levels were associated

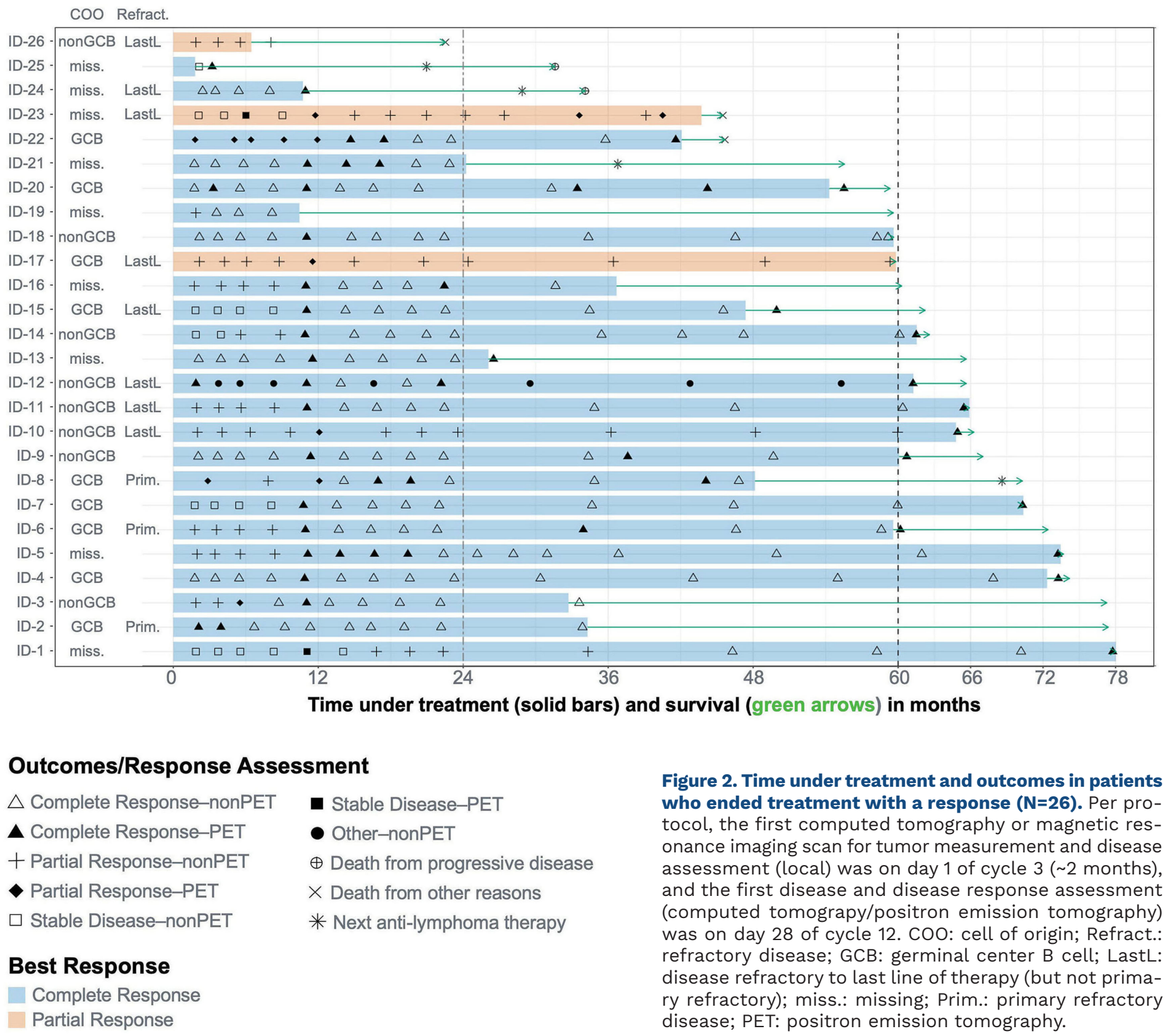


Figure 2. Time under treatment and outcomes in patients who ended treatment with a response (N=26). Per protocol, the first computed tomography or magnetic resonance imaging scan for tumor measurement and disease assessment (local) was on day 1 of cycle 3 (~2 months), and the first disease and disease response assessment (computed tomograpy/positron emission tomography) was on day 28 of cycle 12. COO: cell of origin; Refract.: refractory disease; GCB: germinal center B cell; LastL: disease refractory to last line of therapy (but not primary refractory); miss.: missing; Prim.: primary refractory disease; PET: positron emission tomography.

with longer PFS and younger age was associated 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 analysis[11] and 9.2 months (range, 0.2-54.7) at the 3-year analysis.[14]

An overview of the exposure-adjusted frequency of all TEAE, hematologic and non-hematologic TEAE, and important TEAE 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 TEAE, frequencies were less common with tafasitamab monotherapy than with tafasitamab + lenalidomide combination therapy. Most TEAE of special interest during the tafasitamab + lenalidomide combination period were hematologic events; the 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

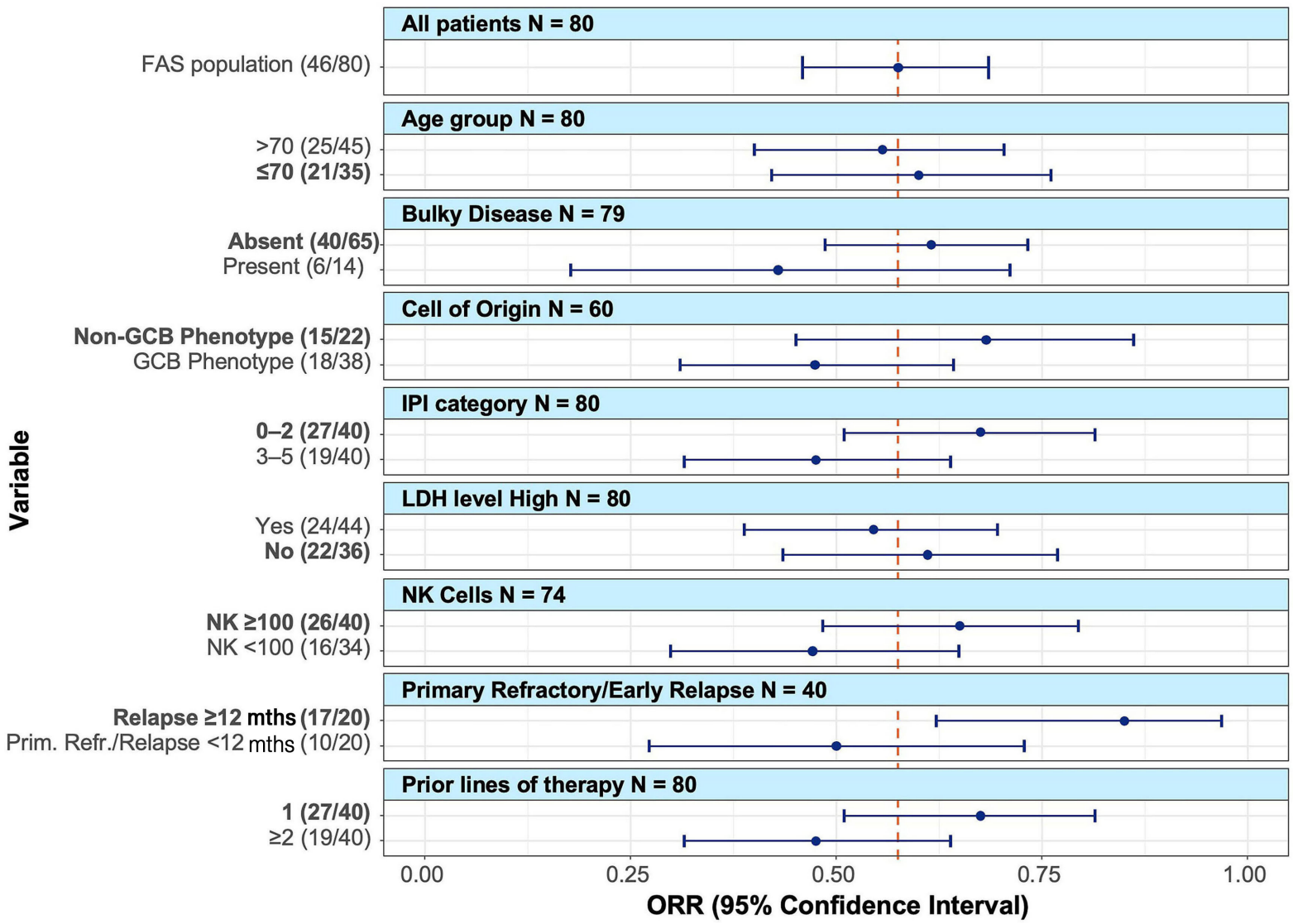


Figure 3. Five-year objective response rate in subgroups of clinical interest. FAS: full analysis set; GCB: germinal center B cell; IPI: International Prognostic Index; LDH: lactate dehydrogenase; NK: natural killer; Prim. Refr.: primary refractory; mths: months; ORR: objective response rate.

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 TEAE were diarrhea and peripheral edema during the combination therapy phase, and most TEAE were grade 1/2.

TEAE are summarized by incidence and severity in Table 3. Treatment-emergent serious AE were reported in 47 (58.0%) patients, with the most frequent being pneumonia (7 patients, 8.6%), febrile neutropenia (5 patients, 6.2%), neoplasms (4 patients, 4.9%), pulmonary embolism and COVID-19 infections (3 patients, 3.7%, each), bronchitis, lower respiratory tract infection, dyspnea, atrial fibrillation and congestive cardiac failure (2 patients, 2.5%, each). Among these events, COVID-19 infections, dyspnea, and benign neoplasms were newly observed compared with those recorded at the 3-year analysis.

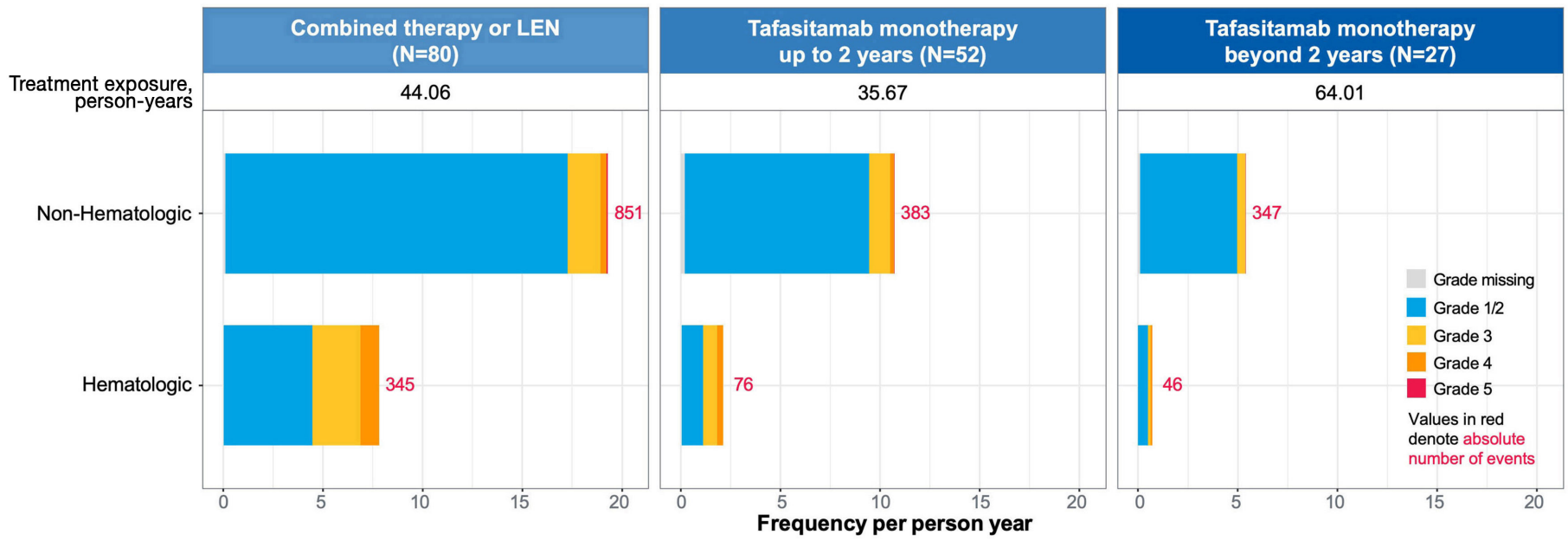
The median duration of neutropenia and thrombocytopenia (all grades) was 9 and 13 days, respectively. Infections and infestations had a median duration of 12 days (18 days for infectious pneumonia, 10.5 days for urinary tract infection, 9 days for sepsis, and 20 days for opportunistic infections).

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

Temporary tafasitamab interruptions occurred in 65 patients, of whom 50 patients (76.9%) had 171 interruptions (52.5%) due to TEAE. Twenty-eight patients required dose interruption of lenalidomide from the starting dose of 25 mg during combination therapy, with these interruptions being due to AE in 25 (89.3%) patients. 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, respectively, due to AE. AE leading to tafasitamab discontinuations were COVID-19,

A



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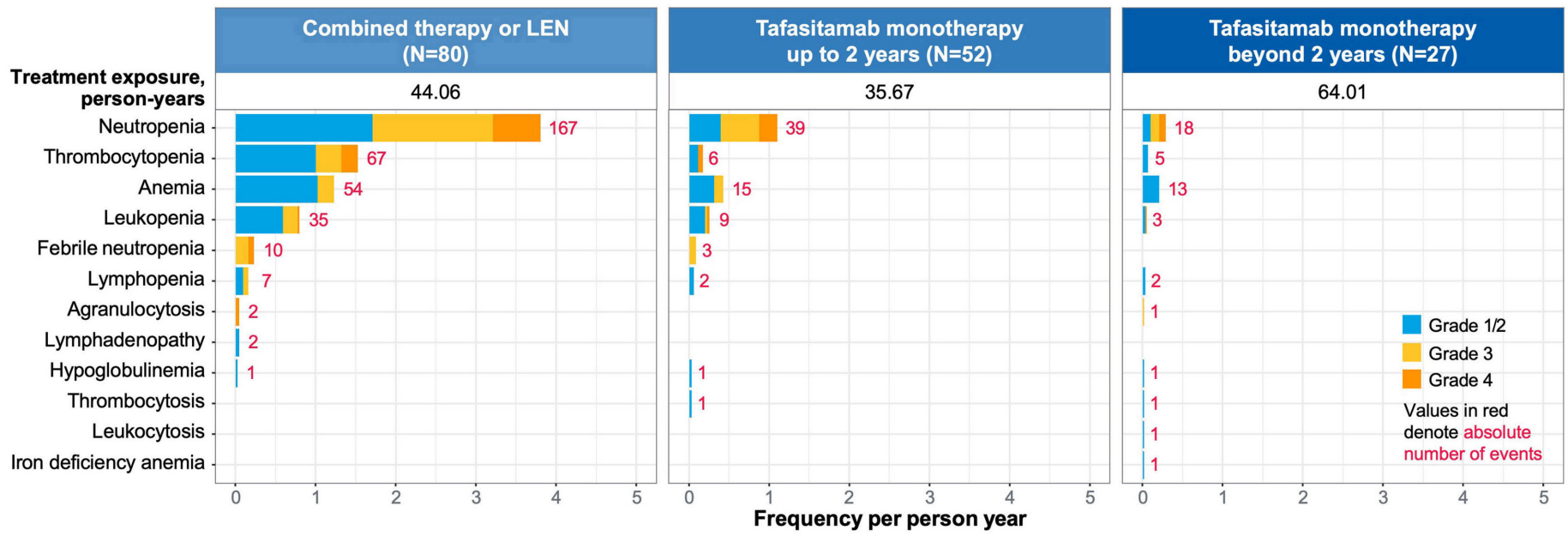

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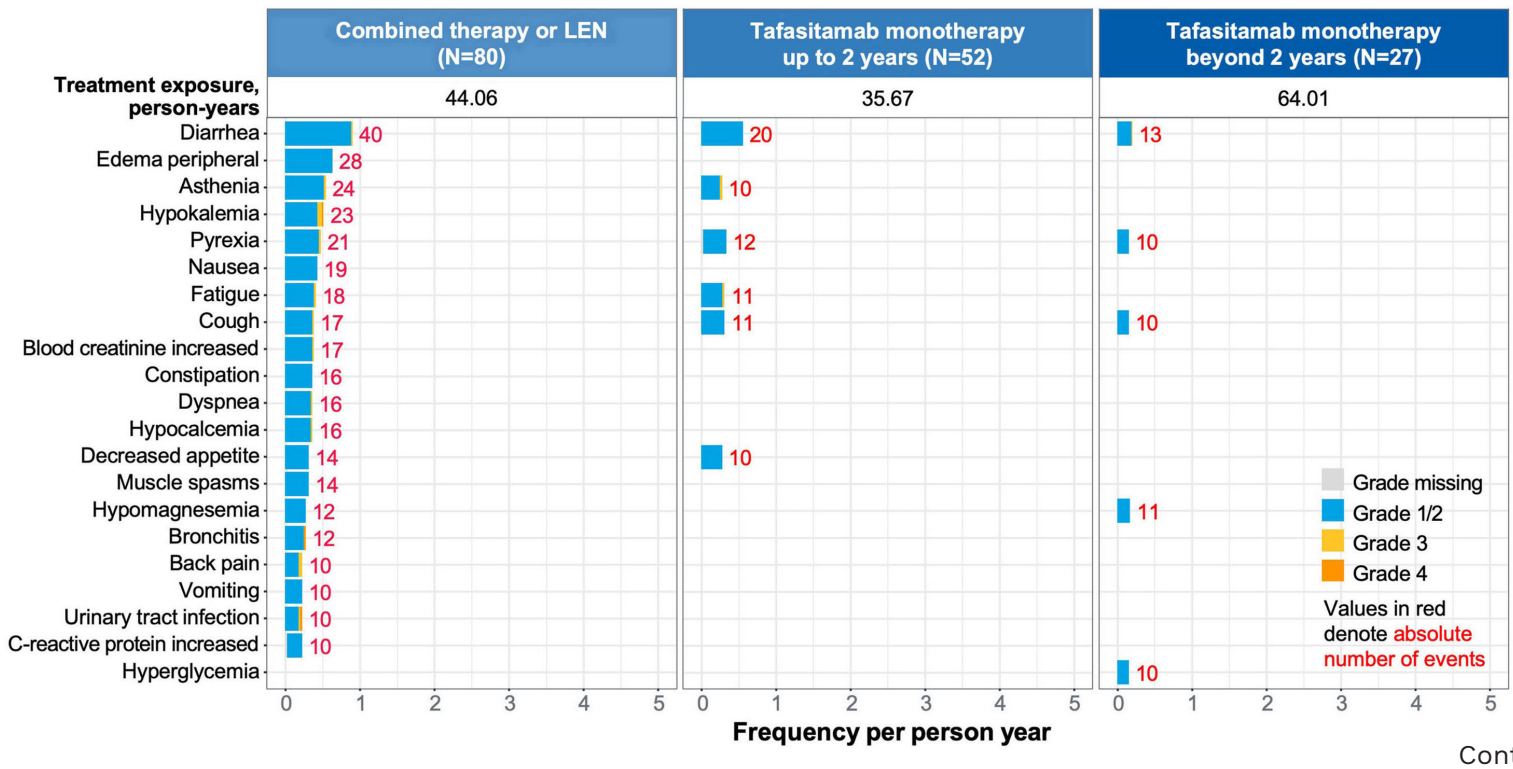

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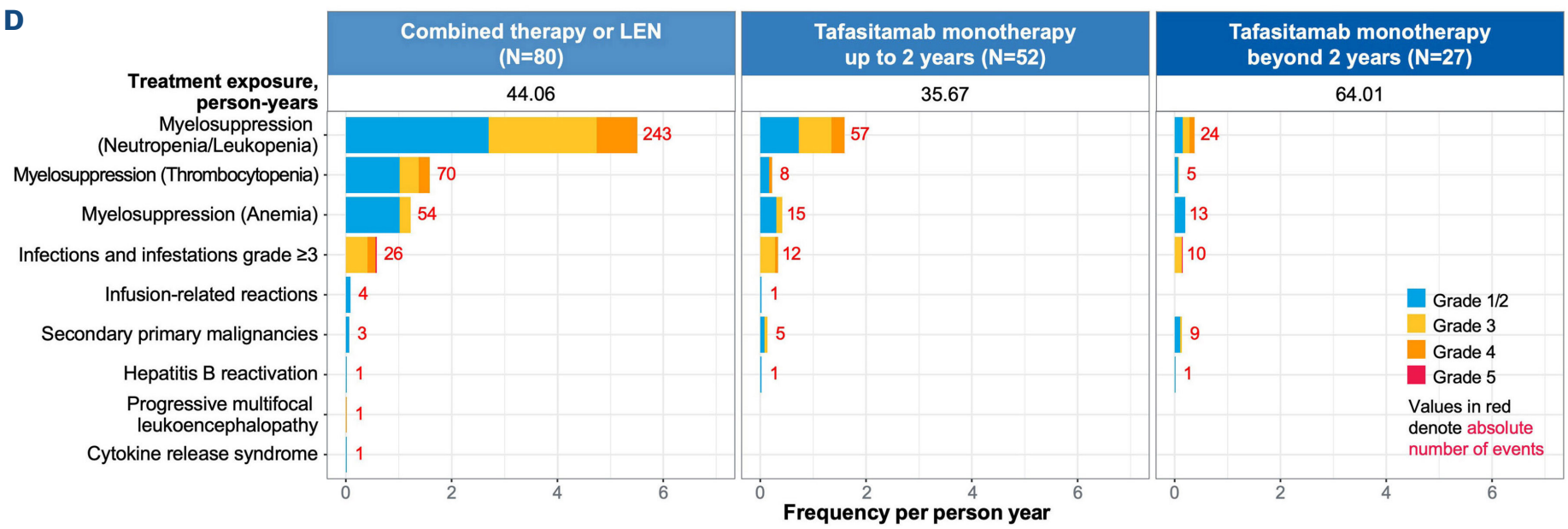

Figure 4. Exposure-adjusted comparison of the frequencies of treatment-emergent adverse events during the combined tafasitamab + lenolamide treatment period, during tafasitamab monotherapy up to 2 years, and during tafasitamab monotherapy beyond 2 years. (A) All treatment-emergent adverse events (TEAE). (B) Hematologic TEAA. (C) Non-hematologic TEAE (cutoff: ≥10 events in any treatment period. (D) Important TEAE of interest. LEN: lenalidomide.

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.

Table 3. Five-year safety summary: treatment-emergent adverse events occurring in ≥10% of patients or grade 3-5 treatment-emergent adverse events in >1 patient (safety analysis set)

	All grades, N (%)	Grade ≥3, N (%)
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)
Peripheral edema	20 (24.7)	0
Pyrexia	19 (23.5)	1 (1.2)
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.

Discussion

The final 5-year analysis of the phase II L-MIND study continues to demonstrate clinical benefit from the 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] The median duration of response was not reached after a median follow-up of 44.0 months. Long-term tafasitamab therapy was well tolerated, consistent with the drug's established safety profile, and no new safety concerns were observed at the 5-year analysis. The incidence of all-grade and grade ≥3 AE 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 whose best response was CR, compared with 18.3% in those whose best response was PR. As would be expected, analyses by prior lines of therapy showed better outcomes in patients receiving tafasitamab + lenalidomide as second-line therapy rather than third or later lines of therapy. Nevertheless, the median duration of response 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 favorable prognostic factors

including lower IPI score. Exploratory analysis by NK cell count at baseline showed a survival benefit and better odds of PFS and OS for patients with ≥100 cells/μL peripheral blood compared with <100 cells/μL. Together with the suggestion of a plateau in the Kaplan-Meier curves for duration of response, 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 5-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 8 who discontinued tafasitamab more than 6 months before the end of the study). Positron emission tomography and computed tomography 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 status with regard to being cured. Long-term follow-up data are also emerging from studies of CAR-T therapy. The phase II JULIET study of tisagenlecleucel was conducted in 115 patients with R/R DLBCL ineligible for or progressing after ASCT;[16] 14 of 24 (58%) patients maintained a response at the 5-year analysis, including 46% with a CR, and the median duration of response was 61.4 months (95% CI: 3.2-not estimable).[17] The 5-year follow-up of ZUMA-1 (a phase I/II study of axicabtagene ciloleucel in 101 patients with refractory large B-cell lymphoma[18]), was recently published under the title of 'curative potential'.[19] Data supporting this claim included the 30% of patients with ongoing CR at data cutoff, after a median follow-up of 63.1 months, with a median duration of CR of 62.2 months (95% CI: 12.9-not estimable), and an estimated 51.0% rate of disease-specific survival, which excluded 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 on treatment, a best response of CR and subsequent investigator-assessed progressive disease received CAR-T therapy approximately 10 months after the end of treatment and was alive at the OS follow-up at 59.9 months. Another patient, who had a best response of PR and subsequent centrally-confirmed progressive disease with 7 months on treatment, received CAR-T therapy approximately 12 months after the end of treatment and died 4 months after CAR-T therapy. Previously, a case report was published of a patient with a best response of stable disease in L-MIND who went on to experience CR with axicabtagene ciloleucel.[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% who had received 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 prior lines of therapy, 51% with IPI scores of 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 that the combination immunotherapy can provide a feasible approach in a post-CAR-T therapy setting.[21]

Safety and tolerability are important factors when considering the eligibility for and selection of second-line and later therapies, with some patients being ineligible for CAR-T therapies because of 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 AE. The reduced exposure-adjusted incidences of hematologic and non-hematologic TEAE 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 of second-line treatment 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). An objective response at the end of treatment was documented in 25/33 patients, with an ORR of 75.8% (95% CI: 57.7-88.9).[22] Accrual into 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 finished, with primary completion of the study due in 2025.[23]

Testing for minimal residual disease based on circulating tumor DNA is among promising new avenues for optimizing future outcomes in DLBCL, especially in the light of new advanced methods.[24] Preliminary data suggest that negativity for minimal residual disease 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 the first-line setting, 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 to tafasitamab

+ lenalidomide combination therapy, followed by long-term tafasitamab monotherapy, in patients with R/R DLBCL ineligible for ASCT. The median duration of response had not been reached after a median of 44.0 months follow-up, with the appearance of a plateau in survival curves after 12-18 months, although the numbers of patients at later timepoints were limited. 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 cutpoints, and the incidence of AE 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.

Disclosures

JD has received research funding from MorphoSys AG and Regeneron. PA has received honoraria from Janssen, Celgene, AbbVie, AstraZeneca, Gilead, and Incyte; has played a consulting or advisory role for Janssen, Celgene, AbbVie, and AstraZeneca; and participated in speakers' bureau for Janssen, Celgene, AbbVie, AstraZeneca, and Gilead. MA has sat on advisory boards for Takeda, Bristol Myers Squibb, Karyopharm, Gilead, and Incyte; has received research grants from Roche, Johnson & Johnson, and Takeda; and has received travel grants from Roche, Bristol Myers Squib, Celgene, Gilead, AbbVie, and AstraZeneca. GG has sat on advisory boards for AbbVie, AstraZeneca, BeiGene, Incyte, Janssen, and Roche and participated in speakers' bureau for AbbVie and Janssen. EG-B has provided consultancy for Janssen, AbbVie, Gilead, Kiowa, EUSAPharma, Incyte, Lilly, and BeiGene; participated in speakers' bureau for Janssen, AbbVie, Takeda, Kiowa, Roche, EUSAPharma, Incyte, and BeiGene; and received travel costs from Janssen, AbbVie, and EUSAPharma. WJ has provided consulting/advisory services for Mei Pharma, Debiopharm, Loxo, Takeda, AstraZeneca, BeiGene; and has received research funding from GSK, Acerta, BeiGene, Nordic Nanovector, Incyte, Debiopharm, Incyte, Genentech, Janssen, Loxo, Mei Pharma, MorphoSys AG, Takeda, and TG Therapeutics. AML has received honoraria from Bristol Myers Squibb, Servier, Celgene, AbbVie, and Amgen; provided consulting or advisory services for Incyte; and received research funding from 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, and Dr Reddy's Laboratories Spa. KJM has received honoraria from Pharmacyclics, MorphoSys AG, Bristol Myers Squibb, Karyopharm Therapeutics, Kite Pharma/Gilead Company, ADC Therapeutics, AbbVie, AstraZeneca, BeiGene, Genmab, Genentech, Janssen, Lilly, Incyte; and research funding from Pharmacyclics, Merck, and Bristol Myers Squibb. TM has received travel grants from Amgen, Jazz, Pfizer, Bayer, Kyowa Kirin, Celgene/BMS, Kite/Gilead, Janssen, and Takeda; honoraria for advisory board meetings from Kite/Gilead, Amgen, Novartis, Pfizer, Celgene/BMS, Daiichi Sankyo, Atara, Roche, and Janssen; honoraria for lectures from Kite/Gilead, Takeda, Janssen, Roche, Servier, Novartis, Celgene/BMS, and Pfizer; and research funding from Janssen, AstraZeneca, and Novartis. ZN has provided consulting/advisory services for Takeda, Janssen, AbbVie, Roche, Amgen, Servier, and Astellas. OT has provided consulting/advisory services for Takeda, AstraZeneca, BeiGene, Incyte, Janssen, Gilead, AbbVie, Roche, Sandoz, and Blueprint. CK and KG are employees of MorphoSys AG. AB is an employee of MorphoSys AG and a statistical consultant for Ludwig-Maximilians-University Hospital, Munich, Germany. AA is an employee of MorphoSys AG and holds stock in Paion AG. GS has provided consulting services for Roche/Genentech, Gilead Sciences, Janssen, Celgene, Novartis, MorphoSys AG, Epizyme, Alimera Sciences, Genmab, Debiopharm Group, VelosBio, Bristol Myers Squibb, BeiGene, Miltenyi Biotec, and Ipsen; and has received honoraria from Roche/Genentech, Janssen, Celgene, Gilead Sciences, Novartis, AbbVie, and MorphoSys AG.

Contributions

JD, PA, MA, GG, EG-B, WJ, NK, AML, KJM, TM, ZN, OT, CK, AB, AA, KG, and GS conceived the study. JD, PA, MA, GG, EG-B, WJ, NK, AML, KJM, TM, ZN, OT, KG and GS were responsible for the investigation. AB, CK, AA, and KG were responsible for methodology and resources. AA was the project administrator. AA, AB, JD, CK, and KG supervised the study, and curated and analyzed the data. AB was responsible for validation. JD, AB, CK, AA, KG, and NK wrote the original draft of the article. JD, PA, MA, GG, EG-B, WJ, NK, AML, KJM, TM, ZN, OT, CK, AB, AA, KG, and GS reviewed and edited the original draft.

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Data-sharing statement

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

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