RE-MIND: Comparing Tafasitamab + Lenalidomide (L-MIND) with a Real-world Lenalidomide Monotherapy Cohort in Relapsed or Refractory Diffuse Large B-cell Lymphoma

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ABSTRACT

Purpose: Tafasitamab, an Fc-modified, humanized, anti-CD19 monoclonal antibody, in combination with lenalidomide, demonstrated efficacy in transplant-ineligible patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL), in the single-arm, phase II L-MIND study (NCT02399085). RE-MIND, a retrospective observational study, generated a historic control for L-MIND to delineate the contribution of tafasitamab to the efficacy of the combination.

Patients and Methods: Data were retrospectively collected from patients with R/R DLBCL treated with lenalidomide monotherapy for comparison with tafasitamab + lenalidomide–treated patients (L-MIND). Key eligibility criteria were aligned with L-MIND. Estimated propensity score–based Nearest Neighbor 1:1 Matching methodology balanced the cohorts for nine prespecified prognostic baseline covariates. The primary endpoint was investigator-assessed best overall response rate (ORR). Secondary endpoints included complete response (CR) rate, progression-free survival (PFS), and overall survival (OS).

Results: Data from 490 patients going through lenalidomide monotherapy were collected; 140 qualified for matching with the L-MIND cohort. The primary analysis included 76 patients from each cohort who received a lenalidomide starting dose of 25 mg/day. Cohort baseline covariates were comparable. A significantly better ORR of 67.1% (95% confidence interval, 55.4–77.5) was observed for the combination therapy versus 34.2% (23.7–46.0) for lenalidomide monotherapy [odds ratio, 3.89 (1.90–8.14); $P < 0.0001$]. Higher CR rates were achieved with combination therapy compared with lenalidomide monotherapy [39.5% (28.4–51.4) vs. 13.2% (6.5–22.9)]. Survival endpoints favored combination therapy. Lenalidomide monotherapy outcomes were similar to previously published data.

Conclusions: RE-MIND enabled the estimation of the additional treatment effect achieved by combining tafasitamab with lenalidomide in patients with R/R DLBCL.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive subtype of non–Hodgkin lymphoma, with more than 18,000 cases diagnosed in the United States every year (1). Although 50% to 60% of patients might be cured with first-line chemo-immunotherapy, the prognosis in relapsed or refractory (R/R) disease is poor, with long-term remission being achieved in a minority of cases following high-dose chemotherapy (HDC) and autologous stem-cell transplantation (ASCT; ref. 2). In an analysis of 244 patients who relapsed after anthracycline-based first-line therapy for DLBCL from 2002 to 2012, median overall survival (OS) in 141 patients unable to undergo ASCT was 6.8 months from first relapse, with a 2-year OS rate of 19% (3).

Although options for patients with R/R DLBCL have historically been limited with poor rates of response, recent studies have shown more promise. Overall response rates (ORR) of 52% [95% confidence interval (CI), 41–62; ref. 4] and 82% (95% CI, 72–89; ref. 5) have been associated with chimeric antigen receptor (CAR) T-cell therapy in this population, and an ORR of 45% [including a complete response (CR) rate of 40%] was observed with the combination of polatuzumab vedotin plus bendamustine and rituximab in transplant-ineligible patients (6).

The immunomodulatory agent lenalidomide is also an option, although not approved, in the United States and the European Union (EU), with or without rituximab, especially in the ASCT-ineligible

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Translational Relevance

Tafasitamab plus lenalidomide was effective in transplant-ineligible patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) in the single-arm phase II L-MIND study (NCT02399085). However, the absence of a control arm precluded evaluation of the contribution of tafasitamab to the efficacy of combination therapy. RE-MIND established a matched real-world comparative lenalidomide-monotherapy cohort with similar prognostic baseline characteristics to the L-MIND cohort. Comparison of the RE-MIND monotherapy cohort with L-MIND confirmed the significant clinical contribution of tafasitamab to combination therapy in patients with R/R DLBCL who were not candidates for transplant. This approach demonstrates the value of real-world evidence to support drug development. Tafasitamab plus lenalidomide, followed by tafasitamab monotherapy, provides a valuable additional treatment option for a difficult-to-treat population, and has recently been approved by the FDA and included in the National Comprehensive Cancer Network treatment guidelines.

setting. Lenalidomide monotherapy has shown moderate activity in this population, with best ORRs of up to 28%, albeit with CR rates of 7% to 12% across three prospective phase II clinical trials (7–9). Median progression-free survival (PFS) and duration of response (DoR) with single-agent lenalidomide in R/R DLBCL have been reported as 2.7 months and 4.6 months, respectively (8), and 13.6 weeks and 73.9 weeks [95% CI, 16.4–not reached (NR)], respectively (9). An Italian observational study of lenalidomide monotherapy reported an ORR of 29.4% (with CR rates of 23.5%), a median PFS of 6 months, and higher response rates in patients ≥65 years old (37 responders/110 patients vs. 8 responders/43 patients <65 years; ref. 10). A retrospective cohort study using the Flatiron Health database ($N = 83$) reported a median event-free survival (EFS) of 6.8 months (95% CI, 3.8–11.9) and a median OS of 15.4 months (95% CI, 9.3–24.2; ref. 11).

Lenalidomide is active in DLBCL via direct cytotoxicity and stimulating the proliferation and activation of natural killer cells (12). Tafasitamab is a humanized, Fc-modified, CD19-targeting monoclonal antibody mediating antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and direct cytotoxicity (13, 14). Preclinical data suggest that lenalidomide enhances tafasitamab-associated cytotoxicity in lymphoma-cell models (15). The open-label, single-arm phase II L-MIND study (NCT02399085) investigated lenalidomide combined with tafasitamab for 12 cycles in adults with R/R DLBCL ineligible for ASCT, followed by tafasitamab monotherapy (16). In the primary analysis, the independent review committee (IRC)-assessed primary endpoint of ORR was 60% (95% CI, 48–71), including a CR rate of 43% (95% CI, 32–54), with a median DoR of 21.7 months (95% CI, 21.7–NR) and a median PFS of 12.1 months (95% CI, 5.7–NR), after a median follow-up of 17.3 months [median OS, NR (95% CI, 18.3–NR)]. These data led to the recent US approval of tafasitamab plus lenalidomide for patients with R/R DLBCL who are ineligible for ASCT and the inclusion of this regimen into the NCCN treatment guidelines (17, 18). To better delineate the contribution of tafasitamab to the efficacy of the combination with lenalidomide, real-world data on a patient-level basis were collected and utilized to generate a matched control cohort of lenalidomide monotherapy.

Patients and Methods

The study was conducted in accordance with the International Conference on Harmonization Good Pharmacoepidemiology Practice Guidelines and the Declaration of Helsinki. Where the patient was alive, and where required by local law or regulations, informed consent (approved by independent ethics committee/institutional review board) was obtained prior to data collection.

Study design and patients

Study sites were selected according to geographic distribution in L-MIND (EU and United States), data completeness, and number of available patients. Between April and August 2019, data were collected retrospectively from health records of patients treated for non–transplant-eligible R/R DLBCL in real-world, compassionate-use and/or completed clinical trials within the observational period of January 2005 to July 2019. Data were collected using electronic data capture (Medidata RAVE electronic case report form, Cardinal Health survey tool) and electronic health record data extraction, including disease-specific medical history, reasons for ASCT ineligibility, dosing information, treatment response, and survival. Safety data were not collected except to document the reason for change in lenalidomide treatment. To ensure a comparable follow-up time with the L-MIND study (maximum follow-up, 32 months at primary-analysis cut-off), an analysis window from index date (i.e., start of lenalidomide monotherapy) to 32 months was applied.

Eligibility criteria were aligned with the L-MIND study. Eligible patients were aged ≥18 years with histologically confirmed DLBCL (including transformed indolent lymphoma with a subsequent relapse), were R/R after 1 to 3 prior systemic therapies (including ≥1 CD20-targeting regimens), and were not candidates for HDC and subsequent ASCT.

Exclusion criteria included central nervous system lymphoma involvement; receiving lenalidomide in combination with another anti-lymphoma therapy, including radiation; prior treatment with anti-CD19 therapy or immunomodulatory drugs, such as thalidomide or lenalidomide; previous ASCT; known 'double/triple-hit' DLBCL; or a prior history of malignancies other than DLBCL (unless disease-free for ≥5 years).

Cohort balancing

For relevant baseline patient and disease characteristics, balance between cohorts was achieved using propensity score-matching and weighting to minimize confounding effects (19). To enable adequate cohort balancing, a sample size of 500 patients was projected for the lenalidomide-monotherapy cohort. Estimated propensity score (ePS)-based Nearest Neighbor 1:1 Matching methodology (19) was used to balance the two cohorts for nine prespecified baseline covariates of prognostic importance, on the advice of regulatory authorities: age (<70 vs. ≥70 years; refs. 5, 6, 20, 21, 22), Ann Arbor stage (I/II vs. III/IV; refs. 5, 6, 20, 22), refractoriness to last therapy line [progressive disease (PD) or stable disease (SD) as best overall response to the most recent therapy, progression during treatment, or progression within ≤6 months from the completion of the most recent therapy line; yes vs. no; refs. 6, 20, 23], number of prior lines of therapy (1 vs. 2 or 3; refs. 6, 24, 25, 9), history of primary refractoriness (PD or SD as best response to first-line treatment, or PD or disease progression within ≤6 months from the completion of first-line therapy; yes vs. no; refs. 5, 20, 26, 3, 27), prior ASCT (yes

vs. no; refs. 5, 9), elevated lactate dehydrogenase [LDH; LDH >upper limit of normal (ULN) vs. LDH ≤ULN; refs. 21, 22], neutropenia [absolute neutrophil count (ANC) $<1.5 \times 10^9$/L vs. ANC $\geq 1.5 \times 10^9$/L; refs. 9, 28], and anemia [hemoglobin (Hb) <10 g/dL vs. Hb ≥10 g/dL; refs. 9, 28]. Eastern Cooperative Oncology Group performance status (ECOG PS) was included as a tenth baseline covariate in a prespecified sensitivity analysis.

Each patient in the combination cohort was propensity score-matched with a single patient in the lenalidomide-monotherapy cohort. The resulting primary analysis set [matched analysis set 25 (MAS25)] included matched patients who met the inclusion/exclusion criteria, received a lenalidomide starting dose of 25 mg/day, had complete data on all nine covariates, and had ≥6 months' follow up. The 6-month follow-up rule was applied to prevent an overestimation of the rate of nonresponders in the lenalidomide-monotherapy cohort, thereby avoiding bias in favor of the combination cohort. The rule was met if a patient responded to treatment at any time, or progressed or died within 6 months from the start of treatment without a documented response. Patients with unknown response to lenalidomide or nonresponding patients with first tumor assessment after 6 months were ineligible.

The standardized mean difference (SMD) was calculated to assess the balance of nine covariates used for matching both the cohorts. SMD was defined as the ratio of the difference of proportions of a baseline characteristic to the standard deviation of the pooled difference.

Independent validation of response assessment

Investigator-assessed best response to lenalidomide monotherapy was validated for a subset of patients by an independent committee (comprising a radiologist and a clinical hemato-oncologist). The committee assessed treatment response using the International Working Group criteria (ref. 29; as used for L-MIND) to evaluate available radiographic scans and relevant clinical data (e.g., biopsy and histopathologic results). A radiological review was followed by the clinical review, comprising the response assessment for this analysis. The criteria for inclusion in the validation set included: availability of baseline and postbaseline scans and required clinical data, a lenalidomide starting dose of 20 or 25 mg/day, and fulfilling the 6-month follow-up definition. Combined concordance between the independent committee and investigator-reported tumor-response assessments was measured by percent agreement of responding [CR plus partial response (PR)] versus nonresponding (SD plus PD) patients to lenalidomide monotherapy.

Sample-size calculation

With 81 patients enrolled in L-MIND, the ePS-based 1:1 matching would result in a sample size of maximum $n = 2 \times 81$. With an assumed difference of 23% in ORR for lenalidomide monotherapy (35%) versus the tafasitamab–lenalidomide combination (58%), the achieved power was 80% and the minimal detectable statistical difference in ORR was 17% using Fisher's exact test for unpaired data. To enable adequate cohort balancing (SMD of ≤0.2 for all covariates), a sample size of 500 patients was projected for the lenalidomide-monotherapy cohort.

Outcomes

The primary endpoint was best ORR (CR or PR as best response) as assessed by the investigator. Best ORR were considered to be those occurring within the analysis window or between the index date and the date of initiation of a new anti-DLBCL medication or death.

Secondary endpoints included: CR rate; disease control rate (DCR; CR plus PR plus SD), DoR (time between the initial response and the first date of tumor progression or death), OS (time between index date and death), PFS [time between index date and investigator-reported tumor progression (confirmed by a radiology assessment or positive bone marrow aspiration/biopsy or tissue biopsy) or death], EFS [time between index date and disease progression (irrespective of the method used), death or initiation of a new anti-DLBCL therapy], and time-to-next-treatment (TTNT; time from index date to the start of the next anti-DLBCL therapy or death).

Statistical analysis

The objective of RE-MIND was to characterize the effectiveness of lenalidomide monotherapy and to compare a matched cohort with the efficacy outcomes observed for tafasitamab plus lenalidomide combination therapy in L-MIND. The primary endpoint of best ORR was compared between the two matched cohorts using Fisher's exact test. The odds ratio for response (CR or PR) was estimated using logistic regression and the resulting odds ratio and associated 95% CI were estimated. CR rate and DCR were analyzed similarly to ORR.

All time-to-event endpoints were analyzed using standard Kaplan–Meier methodology. The difference between the two arms was compared using a log–rank test, and hazard ratios (HRs) and their 95% CIs were estimated using a Cox proportional hazard model. Best ORR, OS, and PFS in patient subgroups defined by age, Ann Arbor stage, refractoriness, prior lines of therapy, and prior ASCT were compared with the overall population.

Multiple sensitivity analyses were performed to demonstrate the robustness of the comparison. These analyses included: using the assumption of correlated data for matched datasets using Nearest Neighbor 1:1 matching; analysis of PFS and EFS with different censoring rules; matching with application of caliper to achieve a higher degree of balance for baseline characteristics (SMD ≤0.1); analyses of ORR, PFS, and OS with cohorts balanced using overlap weights constructed from the ePS; Nearest Neighbor 1:1 matching performed after multiple imputation of missing baseline covariates; inclusion of ECOG PS as a tenth covariate; modified analysis sets not considering the 6-month follow-up rule; and the application of the 'doubly robust' method to address any residual imbalance. See Supplemental 1 for further details on the sensitivity analyses methods.

Statistical analysis was conducted using SAS® (version 9.3 or later).

Results

Patients

Data from 524 patient charts were collected from 42 centers (Italy, 33; United States, 4; Spain, 3; France, 2) and physicians and sites from three healthcare companies (Cardinal Health, The Feinstein Institute for Medical Research, and Flatiron Health) between April 12 and August 25, 2019 (Supplementary Fig. S1). Following medical review, data for 34 patients from three centers (including all data from The Feinstein Institute and Flatiron Health) were excluded due to incomplete data, lack of R/R condition, lack of ASCT ineligibility reason, or double/triple-hit DLBCL; overall, included data came from 28 academic and 30 nonacademic centers. Of the data collected for 490 included patients, data for 140 patients fulfilled the inclusion criteria, received a lenalidomide starting dose of 25 mg, fulfilled the 6-month follow-up criteria, and had data on the prespecified baseline covariates available at baseline (**Figure 1**).

Of the 81 patients enrolled in L-MIND, 5 were excluded from the analysis ($n = 1$ did not receive lenalidomide and $n = 4$ did not meet the 6-month follow-up criterion). Following ePS-based Nearest

Table 1. Baseline characteristics (MAS25).

Characteristics		Tafasitamab + lenalidomide (*N* = 76)	Lenalidomide monotherapy (*N* = 76)
Balancing characteristics			
Age group, *n* (%)	<70 years old	33 (43.4)	31 (40.8)
	≥70 years old	43 (56.6)	45 (59.2)
Ann Arbor stage, *n* (%)	I/II	19 (25.0)	12 (15.8)
	III/IV	57 (75.0)	64 (84.2)
Refractoriness to last prior therapy, *n* (%)	Yes	34 (44.7)	34 (44.7)
	No	42 (55.3)	42 (55.3)
Number of prior systemic treatment lines, *n* (%)	1	39 (51.3)	28 (36.8)
	2–3	37 (48.7)	48 (63.2)
Primary refractoriness, *n* (%)	Yes	14 (18.4)	16 (21.1)
	No	62 (81.6)	60 (78.9)
Prior ASCT, *n* (%)	Yes	9 (11.8)	6 (7.9)
	No	67 (88.2)	70 (92.1)
Elevated LDH (>ULN), *n* (%)	Yes	41 (53.9)	45 (59.2)
	No	35 (46.1)	31 (40.8)
Neutropenia (cut-off <1.5 × 10^9/L), *n* (%)	Yes	2 (2.6)	2 (2.6)
	No	74 (97.4)	74 (97.4)
Anemia (cut-off Hb <10 g/dL), *n* (%)	Yes	6 (7.9)	5 (6.6)
	No	70 (92.1)	71 (93.4)
Other characteristics			
ECOG PS (0–4), *n* (%)	0	29 (38.2)	5 (6.6)
	1	41 (53.9)	36 (47.4)
	2	6 (7.9)	19 (25.0)
	3	0	6 (7.9)
	≥2	6 (7.9)	25 (32.9)
	Missing	0	10 (13.2)
Age at index date (years)	Mean (Standard Deviation)	69.1 (9.71)	70.0 (8.65)
	Median (Q1, Q3)	71.5 (62.0, 76.0)	71.0 (64.5, 76.0)
	Range (min–max)	41–86	41–86
Sex, *n* (%)	Female	36 (47.4)	33 (43.4)
	Male	40 (52.6)	43 (56.6)
Weight (kg)	*n*	75	64
	Missing	1	12
	Mean (Standard Deviation)	77.9 (17.45)	77.0 (17.64)
	Median (Q1, Q3)	75.5 (67.0, 87.9)	78.5 (63.7, 87.5)
	Range (min–max)	43–145	37–117
Race, *n* (%)	Black or African American	0	4 (5.3)
	American Indian or Alaska Native	0	1 (1.3)
	Native Hawaiian or Other Pacific Islander	0	0
	White	70 (98.6)	50 (65.8)
	Unknown	0	18 (23.7)
	Other	1 (1.4)	3 (3.9)
	Missing	5 (6.6)	0
Ann Arbor stage, *n* (%)	I	4 (5.3)	0
	II	15 (19.7)	12 (15.8)
	III	14 (18.4)	12 (15.8)
	IV	43 (56.6)	52 (68.4)
IPI Score, *n* (%)	0–2	40 (52.6)	16 (21.1)
	3–5	36 (47.4)	32 (42.1)
	Missing	0	28 (36.8)
Number of prior systemic treatment lines, *n* (%)	1	39 (51.3)	28 (36.8)
	2	32 (42.1)	42 (55.3)
	3	5 (6.6)	6 (7.9)
Relapse after first-line treatment, *n* (%)	Relapse ≤12 months	32 (42.1)	32 (42.1)
	Relapse >12 months	41 (53.9)	39 (51.3)
	Missing	3 (3.9)	5 (6.6)
Cell of origin (IHC), *n* (%)	GCB	34 (44.7)	14 (18.4)
	Non-GCB	20 (26.3)	16 (21.1)
	Missing	22 (28.9)	46 (60.5)

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Table 1. Baseline characteristics (MAS25). (Cont'd)

Characteristics		Tafasitamab + lenalidomide (*N* = 76)	Lenalidomide monotherapy (*N* = 76)
Rituximab refractoriness, *n* (%)	Yes	32 (42.1)	33 (43.4)
	No	44 (57.9)	43 (56.6)
Creatinine clearance (mL/min) at baseline, *n* (%)	≥60	69 (90.8)	42 (55.3)
	Missing	7 (9.2)	34 (44.7)
Time since first DLBCL diagnosis (months)	*n*	76	75
	Missing	0	1
	Mean (Standard Deviation)	39.99 (35.96)	38.04 (35.47)
	Median (Q1, Q3)	25.92 (16.77, 54.70)	24.94 (14.49, 45.34)
	Range (min–max)	7.8–189.7	3.0–193.1
Time since discontinuation of last prior anti-DLBCL medication or ASCT (months)	*n*	76	76
	Mean (Standard Deviation)	17.39 (22.30)	13.62 (19.64)
	Median (Q1, Q3)	9.23 (5.17, 20.67)	6.46 (1.28, 14.77)
	Range (min–max)	0.6–121.9	0.1–103.2
Lenalidomide dose intensity (mg/day)	*n*	76	74
	Mean (Standard Deviation)	16.93 (4.03)	18.62 (3.31)
	Median (Q1, Q3)	17.58 (14.43, 19.15)	19.03 (17.48, 19.53)
	Range (min–max)	6.9–25.0	7.3–25.0
Imaging modality post-baseline	*n*	76	76
	Post-baseline assessments, *n*	383	130
	No radiological assessment, *n* (%)	0	15 (11.5)
	PET/CT, *n* (%)	102 (26.6)	51 (39.2)
	PET only, *n* (%)	1 (0.3)	3 (2.3)
	MRI only, *n* (%)	6 (1.6)	3 (2.3)
	CT only, *n* (%)	265 (69.2)	55 (42.3)
	Other, *n* (%)	9 (2.3)	3 (2.3)
Geographic distribution, *n* (%)	EU[a]	71 (93.4)	29 (38.2)
	US	5 (6.6)	47 (61.8)

Abbreviations: ASCT, autologous stem-cell transplantation; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; GCB, germinal center B cell; Hb, hemoglobin; IHC, immunohistochemistry; IPI, International Prognostic Index; LDH, lactate dehydrogenase; MAS25, matched analysis set 25; MRI, magnetic resonance imaging; PET, positron emission tomography; Q1, first quartile; Q3, third quartile; ULN, upper limit of normal; US, United States.

[a]Including United Kingdom. *N*, total number of patients in that cohort; *n*, number of patients with non-missing values for that variable. Percentage/statistics are calculated on the basis of the number of patients with non-missing observations in each cohort.

Neighbor 1:1 matching, the primary analysis set (MAS25) comprised 76 patients from each cohort. Of the patients in the MAS25 lenalidomide-monotherapy cohort, data for 47 patients were collected from sites in the United States and 29 patients from sites in Italy. Patients in the lenalidomide-monotherapy cohort were treated between January 2007 and April 2019, and patients in the combination-therapy cohort received treatment between March 2016 and November 2017. Most patients (63 patients; 82.9%) in the lenalidomide-monotherapy cohort commenced treatment between 2014 and 2019. Reasons for transplant ineligibility in the lenalidomide-monotherapy and combination-therapy cohorts included chemorefractoriness (35.5% vs. 21.1%), advanced age or comorbidities (53.9% vs. 60.5%), and refusal of HDC or ASCT (7.9% vs. 17.1%), respectively.

Baseline characteristics for the MAS25 are shown in **Table 1** and were generally balanced between the combination-therapy and lenalidomide-monotherapy cohorts, with SMDs ≤0.13 for seven of the nine baseline characteristics. Residual imbalance was observed for two covariates: the number of prior lines of therapy (SMD 0.29) and Ann Arbor stage (SMD 0.23; **Figure 2**). These residual imbalances were addressed in sensitivity analyses that confirmed the primary analysis (Supplementary Table S1). ECOG PS was not a balancing characteristic in the primary analysis but was included as such in one of the sensitivity analyses.

The median lenalidomide dose intensity was 17.6 mg/day [interquartile range (IQR): 14.4–19.2] versus 19.0 mg/day (IQR: 17.5–19.5), median follow-up for OS was 21.5 months (IQR: 15.1–26.5) versus 20.9 months (IQR: 15.5–29.6), and median time to first post-baseline assessment was 1.9 versus 3.1 months in the combination-therapy and lenalidomide-monotherapy cohorts, respectively. In the combination-therapy cohort, 96% of assessments were made by computed tomography (CT) only or positron emission tomography/CT, compared with 82% in the lenalidomide-monotherapy cohort; the median frequency of assessment for response in the combination-therapy cohort was 2.1 months (IQR: 1.8–2.8) and 3.2 months (IQR: 1.9–4.5) in the lenalidomide-monotherapy cohort.

During the analysis window, all patients in the combination cohort and 96.1% of patients in the lenalidomide-monotherapy cohort permanently discontinued lenalidomide. In the combination cohort, 39.5%, 31.6%, and 14.5% of lenalidomide discontinuations occurred due to PD/death, planned discontinuation, and adverse events, respectively, compared with 63.2%, 9.2%, and 9.2%, respectively, in the lenalidomide-monotherapy cohort. Patient withdrawals comprised 1.3% and 6.6% of lenalidomide discontinuations in the combination and monotherapy cohorts, respectively.

Overall, 59.2% of patients in the combination-therapy cohort experienced relapse, progression, or death, compared with 82.9% in the lenalidomide-monotherapy cohort.

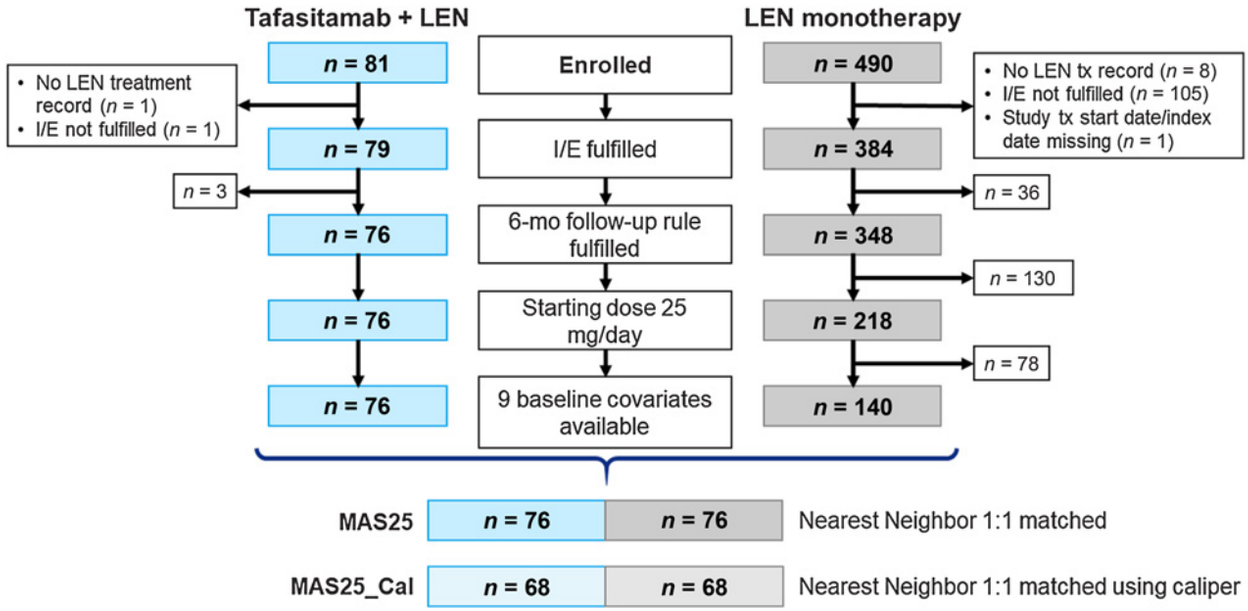

Figure 1.
RE-MIND: patient disposition. I/E, inclusion or exclusion criteria; LEN, lenalidomide; MAS25, matched analysis set 25; MAS25_Cal, matched analysis set 25 with use of caliper; mo, month; tx, treatment.

Efficacy outcomes

Best ORR of 67.1% (51/76; 95% CI, 55.4–77.5) was observed for patients in the combination-therapy cohort versus 34.2% (26/76; 95% CI, 23.7–46.0) for patients in the lenalidomide-monotherapy cohort (odds ratio, 3.89; 95% CI, 1.90–8.14; Fisher's exact test, $P < 0.0001$; McNemar's test, $P = 0.0004$; **Fig. 3**). Significantly more patients achieved a CR in the combination cohort (39.5%; 30/76; 95% CI, 28.4–51.4) compared with the lenalidomide-monotherapy cohort (13.2%; 10/76; 95% CI, 6.5–22.9). For responding patients, median DoR was 20.5 months (95% CI, 12.3–NR) in the combination cohort versus 6.6 months (95% CI, 4.1–17.2) in the lenalidomide-monotherapy cohort (Supplementary Fig. S2).

Subgroup analyses supported the primary analysis with a consistently higher ORR in the combination cohort versus the lenalidomide-monotherapy cohort regardless of age category, disease stage, treatment history, and refractoriness (**Fig. 4A**).

After a median of 21.5 months of follow-up in the combination cohort and 20.9 months in the lenalidomide-monotherapy cohort, OS was superior in the combination cohort compared with the lenalidomide-monotherapy cohort: median OS was not estimable (NE; 95% CI, 15.5 months–NE) and 9.4 months (95% CI, 5.1–20.0), respectively (HR, 0.499; 95% CI, 0.32–0.79; $P = 0.0026$; **Fig. 5A**). With a median follow-up for PFS of 19.7 and 12.6 months in the combination and lenalidomide-monotherapy cohorts, respectively, PFS was prolonged in the combination cohort (median 12.1 months; 95% CI, 5.9–NE) versus the lenalidomide-monotherapy cohort [4 months (95% CI, 3.1–7.4); HR, 0.463 (95% CI, 0.307–0.698); $P = 0.0002$; **Fig. 5B**].

After a median follow-up of 21.9 months in the combination-therapy cohort and 15.4 months in the lenalidomide-monotherapy cohort, EFS was superior in the combination cohort (median 12.1 months; 95% CI, 5.5–21.0) compared with the lenalidomide-monotherapy cohort [median 4.0 months (95% CI, 3.1–6.2); HR, 0.439 (95% CI, 0.296–0.650); $P < 0.0001$].

Median TTNT was also prolonged in the combination cohort (16.7 months; 95% CI, 7.6–NR) compared with the lenalidomide-monotherapy cohort (5.1 months; 95% CI, 4.7–7.3).

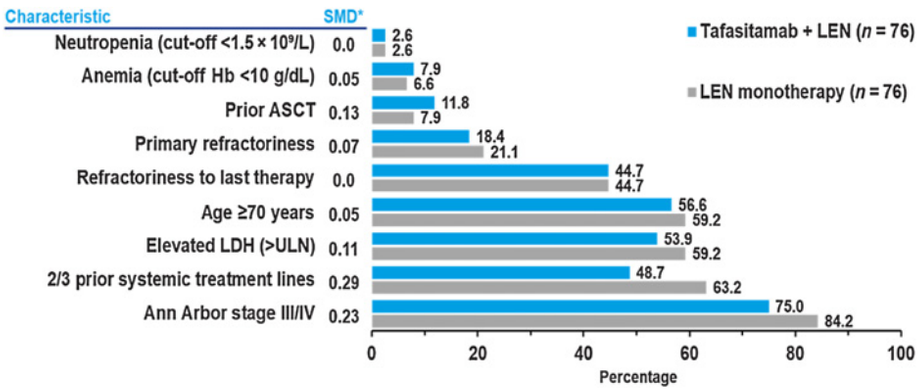

Figure 2.
Baseline characteristics used for cohort balancing (MAS25). *SMD is defined as the ratio of the difference of proportions of a baseline characteristic to the Standard Deviation of the pooled difference. This standardization allows for comparison of the relative balance achieved across different baseline characteristics occurring in a low or high proportion. ASCT, autologous stem-cell transplantation; Hb, hemoglobin; LDH, lactate dehydrogenase; LEN, lenalidomide; MAS25, matched analysis set 25; SMD, standardized mean difference; ULN, upper limit of normal.

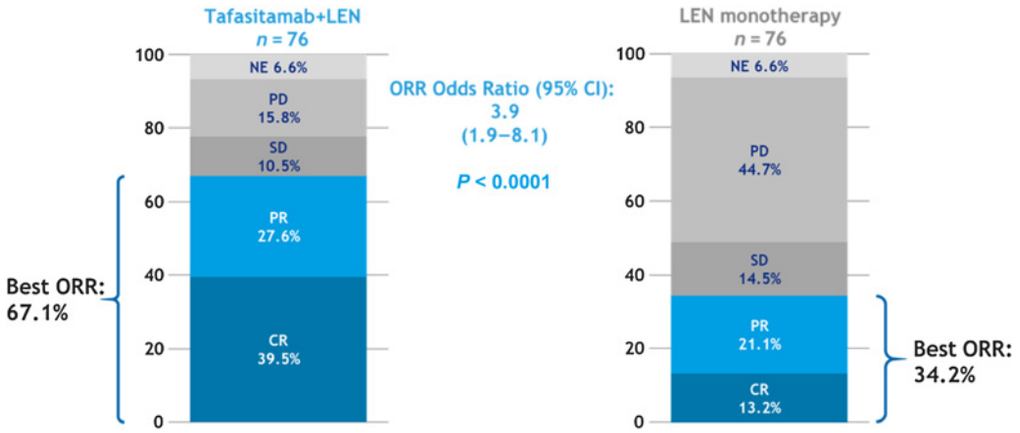

Figure 3.

Primary endpoint: Best ORR (investigator assessed; MAS25). CI, confidence interval; CR, complete response; LEN, lenalidomide; MAS25, matched analysis set 25; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

As part of the sensitivity analysis to adjust for residual imbalance, Ann Arbor stage and number of prior systemic treatments were included as covariates in the statistical models for estimating odds ratio or HR ('doubly robust estimation' Supplemental 1; Supplementary Table S2). Results for primary and secondary endpoints were consistent with the main analysis.

OS and PFS subgroup analyses were consistent with the main matched analysis across all investigated subgroups (Supplementary Table S3).

Efficacy sensitivity analyses

Odds ratios for best ORR were consistent across the primary and sensitivity analyses (**Fig. 4B**). All of the sensitivity analyses performed supported the primary analysis for best ORR, with odds ratio values of 3.8 to 6.0 in favor of combination therapy over lenalidomide monotherapy, compared with 3.9 for the primary analysis. Sensitivity analyses for secondary endpoints also supported the main analysis, with HRs ranging from 0.374 to 0.53 for OS and 0.387 to 0.495 for PFS.

Independent validation of response assessment

Seventy-nine patients fulfilled the criteria for inclusion in the validation subset, of whom 22 were also a part of the lenalidomide-monotherapy cohort in the MAS25. The combined concordance for responders (CR + PR) and nonresponders (SD + PD) between the independently-reviewed and investigator-reported assessments was 79.8%, which supports the validity of the real-world dataset.

Discussion

The phase II L-MIND study reported overall response and CR rates of 60% (95% CI, 48–71) and 43% (95% CI, 32–54), respectively, by IRC and 64% (95% CI, 52–74) and 36%, respectively, by investigator assessment with the combination of lenalidomide and tafasitamab followed by tafasitamab monotherapy in adults with R/R DLBCL ineligible for ASCT (16). A long-term follow-up analysis of L-MIND showed durable responses and a median OS of 31.6 months (95% CI, 18.3–NR; ref. 30). Similar outcomes are reported for CAR T-cell therapy: median OS of 12 months for tisagenlecleucel (4) and 25.8 months for axicabtagene ciloleucel (31). However, the single-arm design of L-MIND precludes the assessment of the contribution of tafasitamab to the observed clinical efficacy. To define the contribution of tafasitamab to the combination, the RE-MIND study was designed using ePS-based matching to retrospectively identify a patient cohort similar to that of L-MIND, but who received lenalidomide monotherapy only, and compared outcomes in the two cohorts. In the comparison set, patients who received combination therapy had significantly improved outcomes compared with lenalidomide monotherapy, in terms of ORR (67.1% vs. 34.2%; odds ratio 3.89; $P < 0.0001$), CR rate (39.5% vs. 13.2%), median DoR (20.5 months vs. 6.6 months), and median OS (NE vs. 9.4 months; HR, 0.499; $P = 0.00269$). Notably, in the subgroup analyses, the improvement in outcomes was apparent regardless of age, disease stage, treatment history, and refractoriness to prior treatment.

The lenalidomide-monotherapy cohort identified in RE-MIND compared well with historical cohorts of patients who received lenalidomide monotherapy for R/R DLBCL in clinical trials (7–9), with patients in RE-MIND being slightly older (median 71 years vs. 65–66 years), but with fewer prior treatments (median 2 vs. 3–4). Clinical outcomes were also similar, with a best ORR of 34.2% (95% CI, 23.7–46.0) in RE-MIND versus 19% to 28% historically, a CR rate of 13.2% (95% CI, 6.5–22.9) versus 7% to 12% (CR/CR unconfirmed), a median DoR of 6.6 months (95% CI, 4.1–17.2) versus 4 to 6 months, and a median PFS of 4 months (95% CI, 3.1–7.4) versus 2.7 months (7–9). A real-world cohort of patients with R/R DLBCL who received lenalidomide monotherapy ($N = 153$) was also comparable with the cohort identified in RE-MIND in regard to age (median 72 years; ref. 10) and prior therapies (median two lines). Although patient responses were of better quality in the real-world cohort than reported in clinical trials (7–9), with a CR rate of 23.5% at an ORR of 29.4%, this magnitude of improvement was not reflected in long-term outcomes, with a median PFS of 6 months and a median OS of 12 months (10). Hence, the lenalidomide-monotherapy cohort identified in RE-MIND can be considered representative of patients with R/R DLBCL and a valid comparator for patients receiving combination therapy in L-MIND.

RE-MIND included several measures to reduce bias and ensure that the identified lenalidomide-monotherapy cohort would provide a legitimate comparator for the L-MIND cohort. Study sites were selected from the same geographic regions (United States and EU)

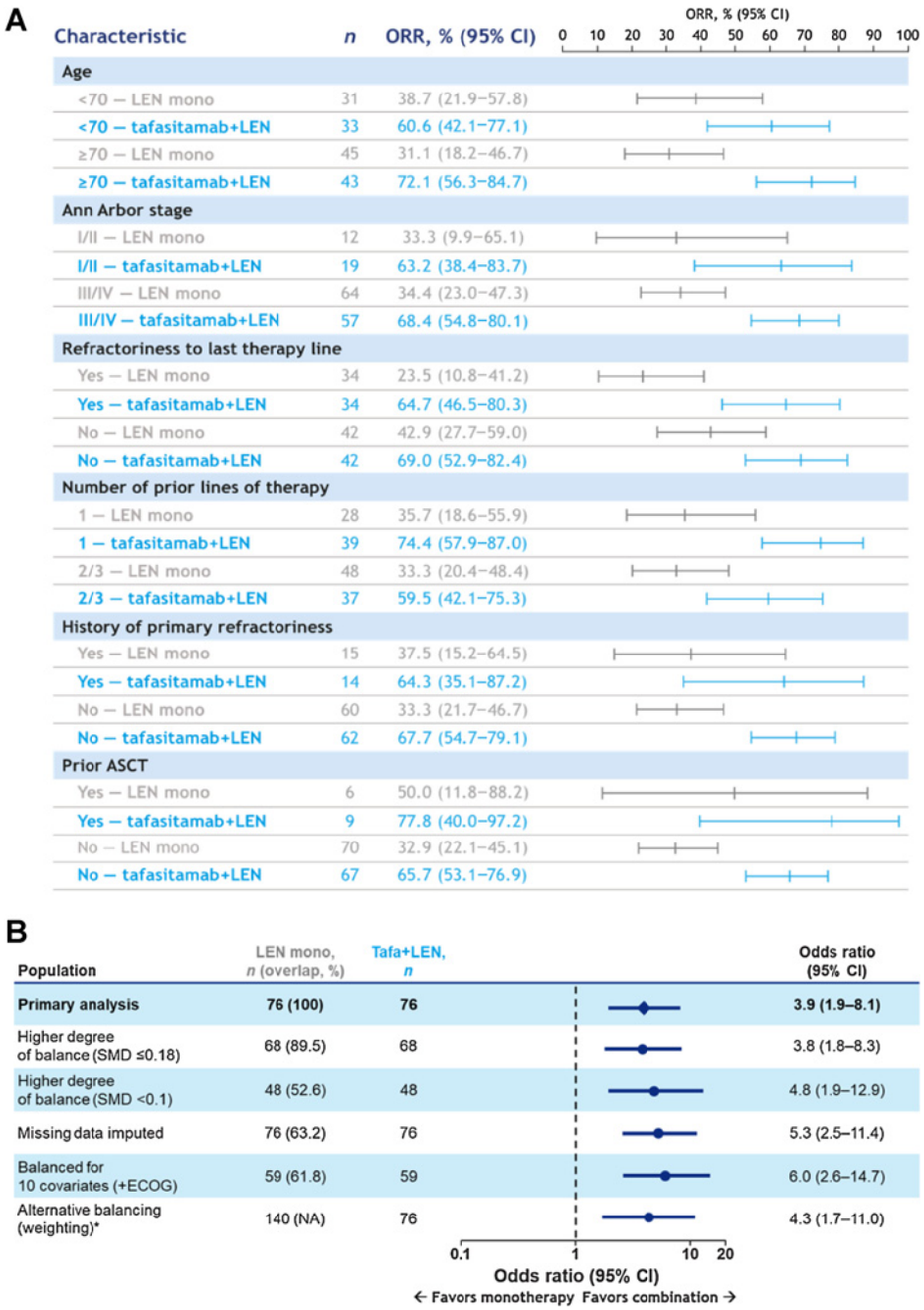

Figure 4.

A, Best ORR by subgroups (MAS25). **B,** Best ORR in the primary analysis and sensitivity analyses. Footnote for **A:** The best ORR was defined as the proportion of patients with CR or PR as best response achieved at any time within the analysis window (index to 32 months; 974 days) or between index date and date of initiation of a new anti-DLBCL medication or death. The denominator was the total number of patients included in the analysis set. ASCT, autologous stem-cell transplantation; CI, confidence interval; CR, complete response; DLBCL, diffuse large B-cell lymphoma; LEN, lenalidomide; MAS25, matched analysis set 25; ORR, overall response rate; PR, partial response. Footnote for **B**: *Balancing weight approaches use weights based on the ePS to create a sample in which the distribution of measured baseline covariates is independent of treatment assignment, and estimates the average treatment effect in this population. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ePS, estimated propensity score; LEN, lenalidomide; SMD, standardized mean difference.

as included in L-MIND. A feasibility questionnaire was used to identify sites that could provide patient data that satisfied key requirements for inclusion/exclusion criteria, patient disposition, and outcomes, with data eventually being pooled from 58 centers. The RE-MIND cohort included only patients who started lenalidomide at a dose of 25 mg/day (as in L-MIND) and ≥6 months' follow-up data were required to prevent overestimation of nonresponse in the main analysis. The comparison of response-assessment outcomes between investigator and an IRC in the validation set showed a high concordance, supporting the validity of the RE-MIND cohort.

ePS-matching is an established real-world evidence approach for balancing comparator populations where randomized data are not available, and has recently supported the development of selinexor in the STORM study in patients with R/R multiple myeloma (32), and blinatumomab in patients with R/R Philadelphia chromosome–positive acute lymphoblastic leukemia (33). The success of ePS-matching depends on the availability of a large pool of patients from which to select a closely matched population. Various potential sources of bias have been encountered in previous studies (32, 33), including a limited ability to apply similar inclusion and exclusion criteria between cohorts, difficulties with the fidelity of available patient record data, variations in outcome assessments, and differences or changes in treatment strategies across geographic regions or over the timeframe of the study parameters. The RE-MIND study was designed to mitigate

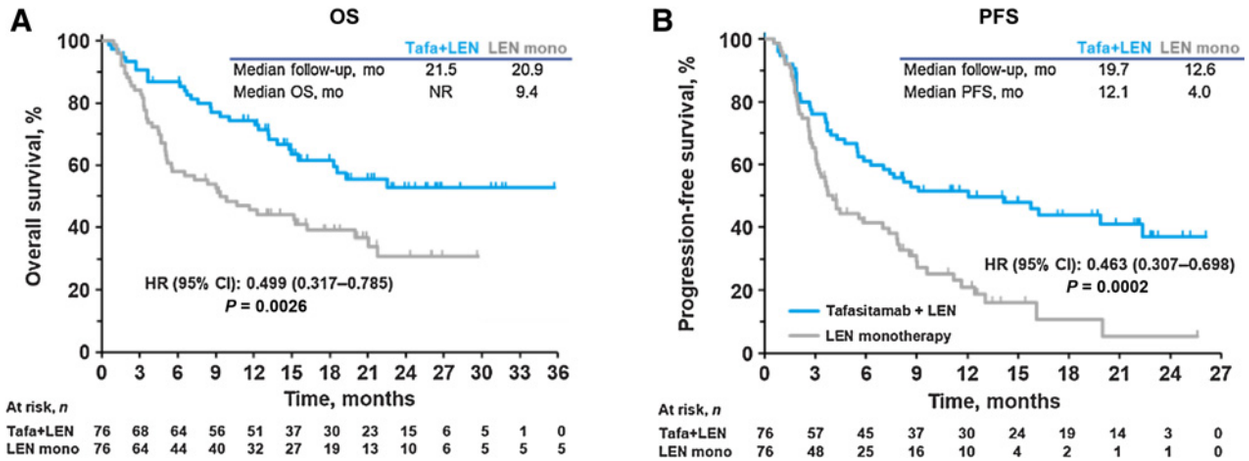

Figure 5.

Secondary endpoints: OS (**A**) and PFS (**B**; MAS25). CI, confidence interval; HR, hazard ratio; LEN, lenalidomide; MAS25, matched analysis set 25; mo, month; NR, not reached; OS, overall survival; PFS, progression-free survival.

these limitations by including a large pool of patients from clinical centers with good data fidelity from the same geographic regions as L-MIND. Patients were treated at similar times, enabling the strict application of inclusion and exclusion criteria.

The propensity matching method is not a replacement for a randomized, controlled study, but mitigates the risk of potential bias for a cross-trial comparison without randomization. The high number of selected baseline covariates for matching in RE-MIND focused on nine clinically relevant outcome and laboratory parameters. Residual imbalances observed in baseline characteristics were addressed in sensitivity analyses that confirmed the primary analysis ('doubly robust' method and application of caliper to achieve a higher degree of balance). Disease characteristics not formally included as balancing covariates, such as ECOG PS, were included as balancing covariates in sensitivity analyses confirming the primary analysis (**Fig. 4B**).

The impact of potential remaining unmeasured confounding factors was assessed in tipping-point analyses and indicated a low likelihood of hidden bias to an extent that would change the inferential statistics for the primary analysis (data not shown).

Bias arising from exclusion of patients with missing data in baseline characteristics could be ruled out by sensitivity analyses applying multiple imputation techniques and confirming the primary analysis. Differences in response assessment frequency or not capturing response to lenalidomide monotherapy in daily clinical practice is an additional source of bias and was minimized by applying the 6-months follow-up rule. As a result, the frequency of response assessment was comparable in the two cohorts.

In conclusion, the RE-MIND study provides a valuable comparator cohort to demonstrate the significant clinical benefit of adding tafasitamab to a lenalidomide treatment regimen for patients with R/R DLBCL who are not candidates for transplant. Tafasitamab plus lenalidomide, followed by tafasitamab monotherapy, provides an additional treatment option for a difficult-to-treat population with a historically poor prognosis, and has been approved by the FDA, providing an important addition to the available treatment options in clinical guidelines, such as the NCCN. Furthermore, the approach taken in RE-MIND highlights the value of real-world evidence to support clinical trials and drug development.

Disclaimers

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 mechanism 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. Incyte has exclusive commercialization rights outside the United States.

XmAb® is a registered trademark of Xencor Inc.

Authors' Disclosures

T. Rodgers reports other support from MorphoSys AG during the conduct of the study, as well as personal fees from MJH Life Sciences outside the submitted work. N.H. Fowler reports personal fees from Celgene and Epizyme during the conduct of the study. G. Salles reports personal fees from MorphoSys AG during the conduct of the study, as well as personal fees from AbbVie, BeiGene, BMS/Celgene, Debiopharm, Epizyme, Genentech/Roche, Genmab, Incyte, Janssen, Kite/Gilead, Miltenyi, Novartis, Regeneron, and VelosBio outside the submitted work. B. Feinberg reports other support from Cardinal Health outside the submitted work. N.C. Kurukulasuriya reports personal fees from MorphoSys AG during the conduct of the study, as well as personal fees from MorphoSys AG outside the submitted work. S. Tillmanns reports personal fees from MorphoSys AG during the conduct of the study. D. Dey reports other support from MorphoSys AG during the conduct of the study. G. Fingerle-Rowson reports personal fees from MorphoSys AG outside the submitted work. S. Ambarkhane reports other support from MorphoSys AG during the conduct of the study, as well as other support from MorphoSys AG outside the submitted work. M. Winderlich reports other support from Syneos Health and Parexel during the conduct of the study, as well as other support from MorphoSys AG outside the submitted work; in addition, M. Winderlich has a patent for WO2017207574A1 pending to MorphoSys AG and a patent for WO2013024095A1 pending to MorphoSys AG. G.S. Nowakowski reports grants and other support from MorphoSys AG and Incyte during the conduct of the study; G.S. Nowakowski also reports grants and other support from BMS and Roche, as well as other support from Ryvu, Karyopharm, Bantham, Daiichi Sankyo, Zai Laboratory, Kymera, TG Therapeutics, and Blueprint Medicines outside the submitted work. No disclosures were reported by the other authors.

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