Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study

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Summary

Background Patients with relapsed or refractory diffuse large B-cell lymphoma who are ineligible for autologous stem-cell transplantation have poor outcomes and few treatment options. Tafasitamab (MOR208) is an Fc-enhanced, humanised, anti-CD19 monoclonal antibody that has shown preclinical and single-agent activity in patients with relapsed or refractory B-cell malignancies. Preclinical data suggested that tafasitamab might act synergistically with lenalidomide. We aimed to assess the antitumour activity and safety of tafasitamab plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma who were ineligible for autologous stem-cell transplantation.

Methods In this multicentre, open-label, single-arm, phase 2 study (L-MIND), patients older than 18 years with histologically confirmed diffuse large B-cell lymphoma, who relapsed or had refractory disease after previous treatment with one to three systemic regimens (with at least one anti-CD20 therapy), were not candidates for high-dose chemotherapy and subsequent autologous stem-cell transplantation, had an Eastern Cooperative Oncology Group performance status of 0–2, and had measurable disease at baseline were recruited from 35 academic and community hospitals in ten countries. Patients received coadministered intravenous tafasitamab (12 mg/kg) and oral lenalidomide (25 mg/day) for up to 12 cycles (28 days each), followed by tafasitamab monotherapy (in patients with stable disease or better) until disease progression. The primary endpoint was the proportion of patients with an objective response (centrally assessed), defined as a complete or partial response according to the 2007 International Working Group response criteria for malignant lymphoma. Antitumour activity analyses are based on all patients who received at least one dose of both tafasitamab and lenalidomide; safety analyses are based on all patients who received at least one dose of either study medication. Recruitment is complete, and the trial is in follow-up. This trial is registered with ClinicalTrials.gov, NCT02399085.

Findings Between Jan 18, 2016, and Nov 15, 2017, 156 patients were screened: 81 were enrolled and received at least one dose of either study medication, and 80 received at least one dose of both tafasitamab and lenalidomide. Median follow-up was 13·2 months (IQR 7·3–20·4) as of data cutoff on Nov 30, 2018. 48 (60%; 95% CI 48–71) of 80 patients who received tafasitamab plus lenalidomide had an objective response: 34 (43%; 32–54) had a complete response and 14 (18%; 10–28) had a partial response. The most common treatment-emergent adverse events of grade 3 or worse were neutropenia (39 [48%] of 81 patients), thrombocytopenia (14 [17%]), and febrile neutropenia (ten [12%]). Serious adverse events occurred in 41 (51%) of 81 patients. The most frequently reported serious adverse events (in two or more patients) were pneumonia (five [6%]), febrile neutropenia (five [6%]), pulmonary embolism (three [4%]), bronchitis (two [2%]), atrial fibrillation (two [2%]), and congestive cardiac failure (two [2%]).

Interpretation Tafasitamab in combination with lenalidomide was well tolerated and resulted in a high proportion of patients with relapsed or refractory diffuse large B-cell lymphoma ineligible for autologous stem-cell transplantation having a complete response, and might represent a new therapeutic option in this setting.

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Introduction

Diffuse large B-cell lymphoma is the most common subtype of non-Hodgkin lymphoma.[1] Since the introduction of the anti-CD20 antibody rituximab as a treatment for this disease in 2006, approximately 50–70% of patients are disease-free long-term survivors with initial standard-of-care immunochemotherapy.[2] However, for patients with disease that is refractory to or that relapses after frontline therapy, prognosis is poor.[3] Salvage chemotherapy followed by high-dose chemotherapy and autologous stem-cell transplantation has little benefit in this setting and is associated with substantial toxicities.[4] Moreover, most patients are ineligible for this approach and have few treatment options.[3] Therapeutic advances during the past

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Research in context

Evidence before this study

With the aim of gaining a greater understanding of the current treatment landscape for diffuse large B-cell lymphoma, we searched PubMed for reports published in English from Jan 1, 2017, to Dec 31, 2019, using the terms "treatment guidelines" and ("recurrent" or "relapsed" or "previously treated") and ("diffuse large B-cell lymphoma" or "diffuse large B cell lymphoma" or "DLBCL"). Current treatment options for patients with relapsed or refractory diffuse large B-cell lymphoma are usually some form of platinum-based salvage chemotherapy followed by high-dose chemotherapy and autologous stem-cell transplantation, which many patients are ineligible for because of comorbidities or age. Such therapies are associated with substantial toxicities. There is no standard of care for patients with relapsed or refractory diffuse large B-cell lymphoma who are ineligible for high-dose chemotherapy and autologous stem-cell transplantation, representing an unmet medical need. Novel therapeutic approaches are being developed to address this problem.

We also searched PubMed for reports published in English from Jan 1, 2017, to Dec 31, 2019, using the terms "antibody" and ("recurrent" or "relapsed" or "previously treated") and ("B cell" or "B-cell") and "lymphoma". We did similar searches in PubMed, adding the terms ("CD19" or "CD-19") or ("anti-CD19" or "anti CD-19") or ("diffuse large B-cell lymphoma" or "diffuse large B cell lymphoma" or "DLBCL"). The CD19 antigen, which is expressed broadly across the B-cell lineage and in virtually all types of diffuse large B-cell lymphoma, is an important therapeutic target of interest as evidenced by the recent emergence and regulatory approval of CD19-directed chimeric antigen receptor (CAR) T-cell therapies.

Tafasitamab (MOR208), an Fc-enhanced (increased affinity for Fcγ receptors through the introduction of two amino acid modifications within the Fc region), humanised, anti-CD19 monoclonal antibody, in combination with the immunomodulatory agent lenalidomide led to increased antitumour effects, both in vitro and in vivo. The combination has potential for a synergistic activity in the treatment of diffuse large B-cell lymphoma.

Added value of this study

In a patient population with high median age, with multiple comorbidities, and ineligible for high-dose chemotherapy or autologous stem-cell transplantation, tafasitamab in combination with lenalidomide followed by tafasitamab until progression, was well tolerated and showed promising clinical activity. Durable responses with promising overall survival were observed in a substantial proportion of patients, including patients with disease that was refractory to their previous therapies, such as CD20-directed immunochemotherapy.

Implications of all of the available evidence

The CD19 CAR-T therapies were approved in patients for whom two or more previous systemic therapies have failed. However, cell-based therapies have important limitations preventing a broad application, including manufacturing challenges, high cost of delivery, substantial toxicities, and need for patient referral to specialised treatment centres. Polatuzumab in combination with bendamustine and rituximab represents another approved option that provides an encouraging progression-free survival, but is associated with several haematological toxicities.

Tafasitamab in combination with lenalidomide is a novel approach that might offer a potentially effective, well tolerated, immunomodulatory treatment option for patients with relapsed or refractory diffuse large B-cell lymphoma who are ineligible for salvage chemotherapy followed by high-dose chemotherapy and autologous stem-cell transplantation.

3 years, such as chimeric antigen receptor (CAR) T-cell therapy and the antibody–drug conjugate polatuzumab vedotin, have the potential to improve patient outcomes.[5–7] Despite these advances, there is a substantial need to provide effective and tolerable treatment options for patients with relapsed or refractory diffuse large B-cell lymphoma, particularly for those who are ineligible for autologous stem-cell transplantation.[8]

CD19 is broadly and homogeneously expressed across B-cell malignancies, and enhances B-cell receptor signalling and tumour cell proliferation.[9,10] Previous approaches with CD19-directed antibodies (either naked antibody or antibody–drug conjugate) were not successful due to low activity and associated toxicities.[11–14] Tafasitamab (MOR208, previously XmAb5574) is an Fc-enhanced (increased affinity for Fcγ receptors through the introduction of two amino acid modifications within the Fc region),[15] humanised, anti-CD19 monoclonal antibody, which mediates antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, and exerts direct cytotoxicity.[15,16] Preclinical studies have shown potent in-vitro and in-vivo activity of tafasitamab in lymphoma and leukaemia models.[15,16] Single-agent tafasitamab was well tolerated and showed encouraging activity in patients with relapsed or refractory B-cell malignancies; several patients had durable responses.[17] Lenalidomide has direct antineoplastic activity, and stimulates proliferation and activation of natural killer cells.[18] Additionally, lenalidomide enhances natural killer cell-meditated, antibody-dependent cellular cytotoxicity with tafasitamab in vitro.[16] In view of the promising outcomes achieved with single-agent lenalidomide and tafasitamab in patients with relapsed or refractory diffuse large B-cell lymphoma, we hypothesise that the combination of these two drugs has synergistic potential.[17,19,20] In this study, we aimed to assess the antitumour activity and safety of tafasitamab plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma who are ineligible for autologous stem-cell transplantation.

Methods

Study design and participants

This multicentre, open-label, single-arm, phase 2 study (L-MIND) enrolled patients from 35 academic and community hospitals (appendix p 2) in ten countries (Belgium, Czech Republic, France, Germany, Hungary, Italy, Poland, Spain, the UK, and the USA).

Eligible patients were older than 18 years, with histologically confirmed diffuse large B-cell lymphoma (including transformed indolent lymphoma with a subsequent diffuse large B-cell lymphoma relapse); had disease that relapsed after or was refractory to at least one, but no more than three systemic regimens (with at least one anti-CD20 therapy); and were not candidates for high-dose chemotherapy and subsequent autologous stem-cell transplantation. Relapsed disease was defined as the appearance of any new lesions or an increase in size of at least 50% of previously involved sites from nadir, according to the 2007 International Working Group response criteria, after the most recent systemic therapy. Refractory disease was defined as disease progression as per International Working Group response criteria, showing less than a partial response or disease recurrence or progression within less than 6 months from the completion of first-line therapy, or showing less than a partial response to the most recently administered systemic therapy. Patients considered ineligible for high-dose chemotherapy and subsequent autologous stem-cell transplantation included: patients older than 70 years, patients with organ dysfunction or comorbidities precluding the use of high-dose chemotherapy or autologous stem-cell transplantation on the basis of unacceptable risk of treatment, those who had failed previous autologous stem-cell transplantation, patients who did not respond to salvage therapy, patients who refused autologous stem-cell transplantation, and those who were unable to receive autologous stem-cell transplantation because of an inability to successfully collect peripheral blood stem cells. Additional inclusion criteria were adequate organ function, Eastern Cooperative Oncology Group performance status of 0–2, and measurable disease at baseline. Patients must also have had an absolute neutrophil count of at least $1{\cdot}5\times10^9$/L and a platelet count of at least 90×10^9/L (unless either was secondary to bone marrow involvement by diffuse large B-cell lymphoma as shown by recent bone marrow aspiration and bone marrow biopsy); a total serum bilirubin concentration of less than 2·5 times the upper limit of normal (ULN) unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma (patients with Gilbert's syndrome or documented liver involvement by lymphoma could be included if their total bilirubin concentration was up to 5 times ULN); alanine transaminase, aspartate aminotransferase and alkaline phosphatase concentrations of up to 3 times ULN or less than 5 times ULN in patients with documented liver involvement; a serum creatinine clearance of at least 60 mL per min either measured or calculated using a standard Cockcroft and Gault formula. Exclusion criteria included any other histological type of lymphoma; a history of double-hit or triple-hit diffuse large B-cell lymphoma if already known (simultaneous detection of *MYC* with *BCL2* or *BCL6* [or both] translocation[s]); previous treatment with anti-CD19 therapy or immunomodulatory drugs such as thalidomide or lenalidomide; primary refractory diffuse large B-cell lymphoma, defined as no response to, or progression during or within 6 months of frontline therapy; history of malignancies other than diffuse large B-cell lymphoma, unless disease-free for at least 5 years; seropositivity for hepatitis B or C virus, and seropositivity for or history of HIV; CNS lymphoma involvement; and history or evidence of clinically significant cardiovascular, CNS, or other systemic disease that would preclude or compromise study participation. Until a protocol amendment (introduced June 27, 2016), only patients whose disease relapsed within 3 months of a previous anti-CD20-containing regimen were defined as primary refractory and excluded.[21] Thus, patients with disease that relapsed or progressed between 3 and 6 months of frontline therapy were recruited before the protocol amendment, and considered as primary-refractory patients as per B-cell lymphoma National Comprehensive Cancer Network guidelines.[22]

See Online for appendix

This study was approved by the institutional review boards at each study site and was done in accordance with the International Conference on Harmonisation good clinical practice guidelines and the Declaration of Helsinki. All patients provided written informed consent. The study protocol is available in the appendix (p 25). Follow-up to assess safety, duration of response, and survival is ongoing.

Procedures

Treatment comprised coadministration of tafasitamab and lenalidomide for up to 12 cycles (28 days each), followed by tafasitamab monotherapy (in patients with stable disease or better) until disease progression. Tafasitamab was administered intravenously at a dose of 12 mg/kg, over approximately 2 h. For cycles 1–3, tafasitamab was administered weekly on days 1, 8, 15, and 22; an additional loading dose was administered on day 4 of cycle 1. From cycle 4, tafasitamab was administered every 14 days,[17] on days 1 and 15 of each cycle. Premedication (as prophylaxis for infusion-related reactions for tafasitamab) comprised antipyretics, histamine (H1 and H2) receptor blockers, glucocorticoids, and meperidine. Tafasitamab was interrupted for any grade 2–4 infusion-related reactions or other protocol-defined toxicities. Patients discontinued tafasitamab if they had a grade 4 infusion-related reaction. Patients self-administered lenalidomide capsules orally, starting with 25 mg daily on days 1–21 of each 28-day cycle. A stepwise dose reduction (decrease by 5 mg per day in each step, only once per cycle, without re-escalation) of lenalidomide was done in cases of protocol-defined toxicities.

Central laboratory assessments were done at ICON Central Laboratories (Ireland and the USA) on day 1 of cycle 1, day 1 of cycles 2 and 3 (plus or minus 1 day), and day 1 of cycles 4–24 (plus or minus 2 days). Tumour assessment was based on CT scans done after cycles 2, 4, 6, and 9, and on PET scans, which were mandatory at baseline and after cycle 12. Patients could be withdrawn from the study because of adverse events, abnormal laboratory values, abnormal test procedure results, protocol violation, patient withdrawal of consent, loss to follow-up, administrative problems, radiologically confirmed disease progression, or withdrawal of a patient at the specific request of the sponsor. All adverse events were recorded at each visit. Adverse events of special interest were tumour flares, tumour lysis syndrome, secondary primary malignancies, infusion-related reactions and allergic reactions to study drug of grade 3 or worse, cytokine release syndrome, and overdoses. Central pathology review of fresh or archived biopsy material (immunohistochemistry using Hans' algorithm and fluorescence in situ hybridisation for *c-MYC* translocations, done at Department of Pathology, University of Würzburg, Germany; and gene expression profiling using the Lymph2X NanoString panel [NanoString, Seattle, WA, USA]) was done retrospectively.

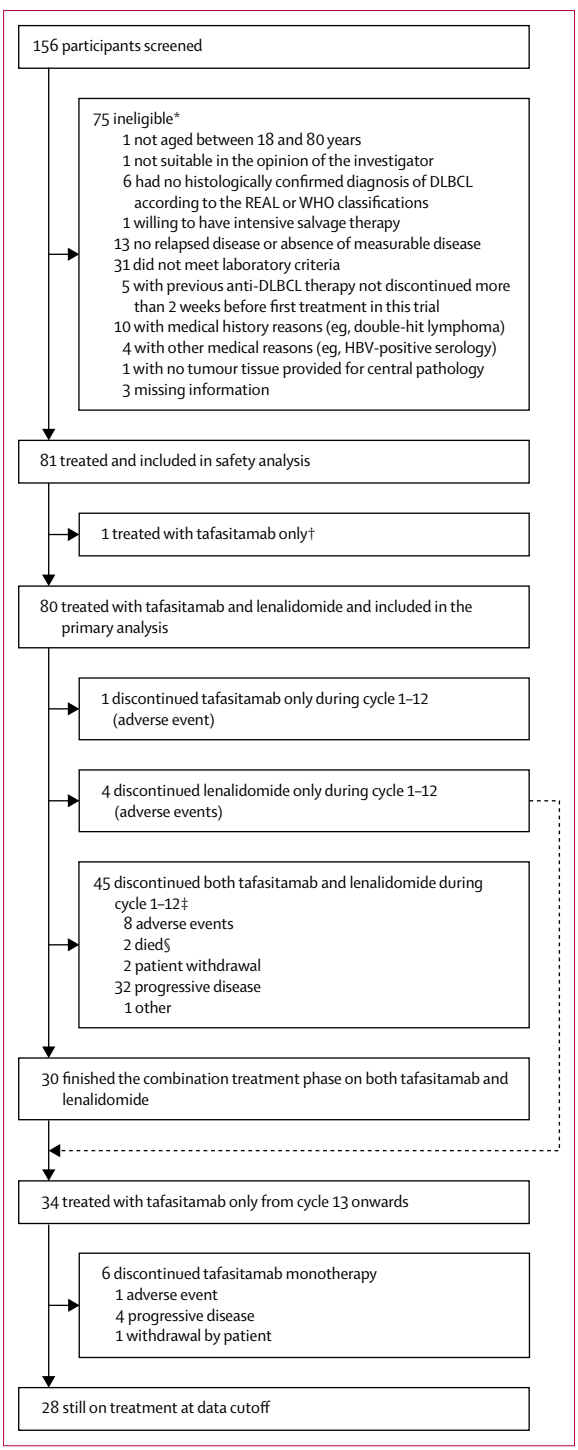

Figure 1: **Trial profile**
DLBCL=diffuse large B-cell lymphoma. HBV=hepatitis B virus. REAL=Revised European American Lymphoma. *A single patient can be counted under more than one reason for screening failure. †Patient discontinued treatment due to physician decision; the patient received tafasitamab on days 1 and 4 of cycle 1 and discontinued because of progressive disease. No lenalidomide was administered because of acute kidney injury. ‡Two scenarios are covered in this instance: (1) discontinuation of both drugs at the same time and (2) sequential discontinuation (only the reason for the later discontinuation is reported). §Two patients discontinued treatment with both study drugs because of a non-progressive disease-related death (sudden death; respiratory failure); a further six deaths were reported; however, these six were classified as having discontinued both drugs because of progressive disease (five patients) or discontinued both drugs because of adverse events (one patient; discontinued because of pulmonary embolism but died from a cerebrovascular accident and was therefore considered to have died while on treatment because it was within 30 days after treatment discontinuation).

Outcomes

The primary endpoint was the proportion of patients with an objective response, defined as the proportion of patients with a complete response plus those with a partial response, as assessed by an independent review committee, according to the 2007 International Working Group response criteria for malignant lymphoma (the concordance in best response between central and investigator assessments was calculated).[23] Overall response was analysed in the following patient subgroups: those with one previous line of therapy; those with a history of two or more previous therapies; those with disease that was refractory to their most recent therapy; and those with a history of primary refractory diffuse large B-cell lymphoma. The secondary endpoints were the proportion of patients with disease control (complete response plus partial response plus stable disease); the duration of response (the time between the initial point of complete or partial response and the first date of recurrence of progressive disease); time to next treatment (the time from first dosing to the initiation of next therapy for any reason); progression-free survival (the time between first dosing and lymphoma

	Patients in safety population (n=81)
Median age, years	72 (62–76)
Sex	
Male	44 (54%)
Female	37 (46%)
Race	
Asian	2 (2%)
White	72 (89%)
Other	1 (1%)
Data missing	6 (7%)
Median time since first DLBCL diagnosis, months	26·9 (17–51)
Previous lines of systemic therapy	
Median (range)	2 (1–4)
1	40 (50%)
2	35 (43%)
3	5 (6%)
4	1 (1%)
Previous anti-CD20 therapy	
Yes	81 (100%)
No	0 (0%)
Previous anthracycline therapy	
Yes	81 (100%)
No	0 (0%)
Primary refractory	
Yes	15 (19%)
No	66 (81%)
Rituximab refractory	
Yes	34 (42%)
No	46 (57%)
Unknown	1 (1%)
Refractory to most recent previous therapy	
Yes	36 (44%)
No	45 (56%)
Previous ASCT	
Yes	9 (11%)
No	72 (89%)
Ann Arbor stage at screening	
I or II	20 (25%)
III or IV	61 (75%)
ECOG performance status	
0	29 (36%)
1	45 (56%)
2	7 (9%)
IPI score at screening	
0–2 (low and low–intermediate risk)	40 (49%)
3–5 (intermediate–high and high risk)	41 (51%)
(Table 1 continues in next column)	
(Continued from previous column)	
Bulky disease*	
Present	15 (19%)
Absent	65 (80%)
Data missing	1 (1%)
Lactate dehydrogenase concentrations at screening	
Elevated	45 (56%)
Within reference range	36 (44%)
Cell of origin by immunohistochemistry	
Germinal centre B cell	38 (47%)
Non-germinal centre B cell	21 (26%)
Unknown	22 (27%)
Cell of origin by gene-expression profiling	
Germinal centre B cell	7 (9%)
Non-germinal centre B cell	19 (24%)
Unclassified	6 (7%)
Unknown	49 (60%)
Patients with DLBCL arising from a previous indolent lymphoma	7 (9%)
Reasons for ASCT ineligibility	
Aged >70 years	37 (46%)
Chemorefractory†	19 (23%)
Refusal	13 (16%)
Comorbidities‡	11 (14%)
Other§	1 (1%)

Data are median (IQR) or n (%) unless otherwise stated. ASCT=autologous stem-cell transplantation. DLBCL=diffuse large B-cell lymphoma. ECOG=Eastern Cooperative Oncology Group. IPI=International Prognostic Index. R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone. *Defined as having a longest lesion diameter of ≥7·5 cm (by central radiological assessment). †Patients without a partial or complete response with salvage therapy or who had ASCT before enrolment. ‡All patients who are not chemorefractory and who have comorbidities (comorbidities are listed in appendix p 23). §Other reasons include inability to successfully collect stem cells.

Table 1: **Baseline characteristics of the safety population**

progression or death from any cause); overall survival (the time from first dosing until the date of death from any cause); time to progression (the time from the day of enrolment until documented lymphoma progression or death as a result of lymphoma); incidence and severity of adverse events; immunogenicity (presence of anti-tafasitamab antibodies); pharmacokinetics; and measurements over time of B cells, T cells, and natural killer cells. Exploratory and diagnostic biomarker analyses (including gene-expression profiling for cell of origin subtyping; CD19, CD20, BCL-2, and BCL-6 expression; CD16 expression on natural killer cells; antibody-dependent cellular cytotoxicity capacity; and evaluation of adverse events and objective response stratified by FcγRIIIa and FcγRIIa polymorphism) were incomplete and are not reported because of limited sample availability.

Statistical analysis

Earlier studies of tafasitamab and lenalidomide were used to calculate assumptions on response rates for the purpose of sample size calculation.[20,24] Sample size was determined assuming that combination treatment could improve the proportion of patients with an

	Patients treated with tafasitamab plus lenalidomide (n=80)*
Best objective response	
Complete response	34 (43%; 32–54)
Partial response	14 (18%; 10–28)
Stable disease	11 (14%; 7–23)
Progressive disease	13 (16%; 9–26)
Not evaluable†	8 (10%; 4–19)
PET-confirmed complete response	30/34 (88%; 73–97)
Objective response‡	48 (60%; 48–71)
Disease control§	59 (74%; 63–83)

Data are n (%; 95% CI) or n/N (%). *One patient received tafasitamab only. †Patients had no valid postbaseline response assessments. ‡Complete response plus partial response. §Complete response plus partial response plus stable disease.

Table 2: **Best objective response according to independent radiology committee or clinical review committee**

objective response from 20% (monotherapy) to 35% (combination therapy). Applying an exact binomial test with a two-sided significance level of 5% and a power of 85%, the estimated sample size was 73 patients. Assuming 10% drop-out, a total sample size of 80 patients was estimated.

The primary endpoint was analysed when all patients had completed a minimum of 12 months of follow-up. Antitumour activity analyses are based on the full analysis set comprising all patients who received at least one dose of both tafasitamab and lenalidomide; safety analyses are based on patients who received at least one dose of either study medication. Patients without adequate postbaseline assessment were considered as non-evaluable in the overall response analysis. There was no interim analysis. For both primary and secondary outcomes, descriptive statistics were used to summarise response rates, disease control rates, and safety. Progression-free survival, overall survival, duration of response, time to next treatment, and time to progression were analysed using the Kaplan-Meier method. The median follow-up time for progression-free survival and overall survival was calculated using the reverse Kaplan-Meier method. Post-hoc subgroup analyses were done for *c-MYC* translocation presence, progression-free survival after discontinuation of lenalidomide (Kaplan-Meier method), and overall best response by reason for autologous stem-cell transplantation ineligibility (descriptive statistics). Statistical analysis was done using SAS (version 9.4 or later). This study is registered with ClinicalTrials.gov, NCT02399085.

Role of the funding source

The sponsor participated in the study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Jan 18, 2016, and Nov 15, 2017, 156 patients were screened. 81 patients were enrolled, received at least one dose of either study medication, and were evaluated for safety; 80 received at least one dose of both tafasitamab and lenalidomide and were evaluated for activity (one patient who received tafasitamab only was excluded from the activity analysis; figure 1). The most common reasons for ineligibility were not meeting laboratory criteria, not having protocol-defined relapsed or refractory disease or having an absence of measurable disease, and having other histological types of lymphoma, primary refractory diffuse large B-cell lymphoma inconsistent with the protocol, or a history of double-hit or triple-hit diffuse large B-cell lymphoma (figure 1). The median age of enrolled patients was 72 years (IQR 62–76) and all patients received R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone) or equivalent anthracycline-containing immunochemotherapy before study entry (table 1).

The data cutoff for primary analysis was Nov 30, 2018. The median follow-up was 13·2 months (IQR 7·3–20·4) and minimum follow-up was 0·5 months. 30 (37%) of 80 patients completed 12 cycles of tafasitamab and lenalidomide therapy and 28 (35%) were receiving tafasitamab monotherapy at data cutoff. Lenalidomide dose reductions are described in the appendix (p 16). The median duration of exposure to study treatment was 9·3 months (IQR 0·2–32·1); median duration of exposure to combination treatment or lenalidomide was 6·2 months (IQR 2·1–10·9), and to tafasitamab monotherapy (following discontinuation of lenalidomide) was 4·1 months (IQR 0·4–12·6).

48 (60%; 95% CI 48–71) of 80 patients who received tafasitamab plus lenalidomide had an objective response according to the independent review committee, including 34 (43%; 32–54) with a complete response and 14 (18%; 10–28) with a partial response (table 2). The median time to initial response (partial or complete) was 2·0 months (IQR 1·9–3·1). 59 (74%; 95% CI 63–83) of 80 patients had disease control. The overall concordance between centrally assessed and investigator-assessed objective response was high (appendix p 17). 30 (88%; 95% CI 73–97) of the 34 patients with a CT-assessed complete response had a PET scan at the same or a subsequent timepoint, which confirmed the results of the CT scan in all 30 patients. For the remaining four patients with CT-assessed complete response, a confirmatory PET scan was not available because these patients had discontinued before a PET scan was done.

A prespecified exploratory subgroup analysis of objective response by baseline characteristics indicated high and consistent proportions of patients with a response across most subgroups (appendix p 9).

The results of the post-hoc analysis of the proportion of patients with an objective response by reasons for autologous stem-cell transplantation ineligibility are

shown in the appendix (p 18). Additionally, seven patients had diffuse large B-cell lymphoma arising from a previous indolent lymphoma. All seven of these patients responded to the tafasitamab plus lenalidomide treatment (two [29%] of seven patients had a complete response and five [71%] had a partial response); the two patients who had a complete response as best response were still in remission at data cutoff.

The median duration of response in the 48 patients who achieved an objective response was 21·7 months (95% CI 21·7 to not reached; 13 [27%] patients had a progression-free survival event after initially having an objective response). The proportion of patients with a response lasting 12 months was 72% (95% CI 55–83; figure 2A). Among the 34 patients with a complete response, the median duration of response was not reached (three [9%] patients had a progression-free survival event after initially having a complete response; figure 2B); the proportion of patients with a response lasting 12 months and 18 months was the same at 93% (95% CI 75–98). For the 14 (18%) of 80 patients with a partial response, the median duration of response was 4·4 months (95% CI 2·0–9·1; ten [71%] of 14 patients had a progression-free survival event after initially having a partial response; figure 2B). A post-hoc subgroup analysis of patients with a response lasting 12 months is shown in the appendix (p 10).

39 (49%) of 80 patients had a progression-free survival event (disease progression or death). At a median follow-up of 17·3 months (IQR 11·5–21·2) for progression-free survival, median progression-free survival was 12·1 months (95% CI 5·7 to not reached; figure 2C). 12-month progression-free survival was 50% (95% CI 38–61) and 18-month progression-free survival was 46% (33–57). Post-hoc analysis showed median progression-free survival after discontinuation of lenalidomide was 12·7 months (95% CI 2·3 to not reached). Median time to progression was 16·2 months (95% CI 7·4 to not reached), with disease progression events occurring in 35 (44%) of 80 patients. Median time to next treatment was 15·4 months (95% CI 7·6 to not reached; 43 [54%] of 80 patients received subsequent treatment). Two patients subsequently received salvage treatment consolidation with stem-cell transplantation: one patient each with autologous stem-cell transplantation and allogeneic stem-cell transplantation. One other patient subsequently received CD19 CAR T-cell therapy after disease progression in this study, had a complete response, and was in remission at the time of this report.

At a median follow-up of 19·6 months (IQR 15·3–21·9) for overall survival, 29 (36%) of 80 patients had died; median overall survival was not reached (95% CI

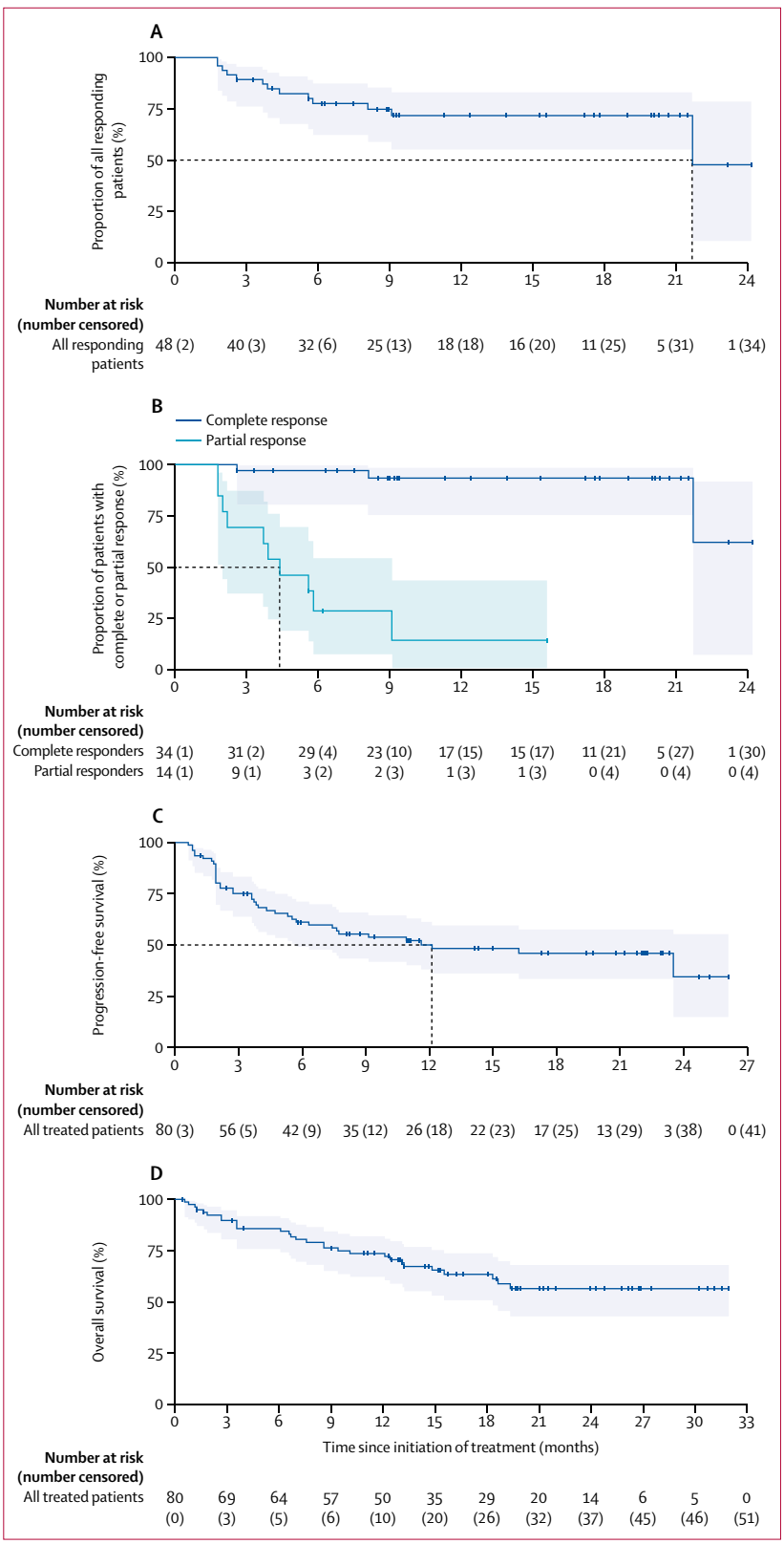

Figure 2: **Patient outcomes**

(A) Duration of response in all responding patients. (B) Duration of response by best response achieved. (C) Progression-free survival in the full analysis set. (D) Overall survival in the full analysis set. Shaded areas indicate 95% CIs.

	Grade 1–2	Grade 3	Grade 4	Grade 5
Haematological events				
Neutropenia	1 (1%)	22 (27%)	17 (21%)	0
Anaemia	22 (27%)	6 (7%)	0	0
Thrombocytopenia	11 (14%)	10 (12%)	4 (5%)	0
Leukopenia	5 (6%)	6 (7%)	1 (1%)	0
Febrile neutropenia	0	8 (10%)	2 (2%)	0
Lymphopenia	2 (2%)	2 (2%)	1 (1%)	0
Agranulocytosis	0	0	1 (1%)	0
Non-haematological events				
All rash*	22 (27%)	7 (9%)	0	0
Diarrhoea	26 (32%)	1 (1%)	0	0
Asthenia	17 (21%)	2 (2%)	0	0
Cough	17 (21%)	1 (1%)	0	0
Peripheral oedema	18 (22%)	0	0	0
Pyrexia	16 (20%)	1 (1%)	0	0
Decreased appetite	16 (20%)	0	0	0
Hypokalaemia	10 (12%)	4 (5%)	1 (1%)	0
Back pain†	11 (14%)	2 (2%)	0	0
Fatigue	12 (15%)	2 (2%)	0	0
All urinary tract infection*	9 (11%)	3 (4%)	1 (1%)	0
Constipation	13 (16%)	0	0	0
Muscle spasms	12 (15%)	0	0	0
Nausea	12 (15%)	0	0	0
Bronchitis	10 (12%)	0	1 (1%)	0
Vomiting	11 (14%)	0	0	0
Dyspnea	9 (11%)	1 (1%)	0	0
Abdominal pain	7 (9%)	1 (1%)	0	0
Upper respiratory tract infection	6 (7%)	2 (2%)	0	0
Hypertension	4 (5%)	3 (4%)	0	0
Increased blood creatinine†	5 (6%)	1 (1%)	0	0
Mucosal inflammation	5 (6%)	1 (1%)	0	0
Pneumonia	1 (1%)	5 (6%)	0	0
Hypocalcaemia	4 (5%)	1 (1%)	0	0
Hypogammaglobulinaemia	4 (5%)	1 (1%)	0	0
Increased γ-glutamyltransferase	4 (5%)	1 (1%)	0	0
Atrial fibrillation	1 (1%)	2 (2%)	1 (1%)	0
Pulmonary embolism	0	2 (2%)	2 (2%)	0
Sinusitis	3 (4%)	1 (1%)	0	0
Deep vein thrombosis	2 (2%)	0	1 (1%)	0
Hyperbilirubinaemia	2 (2%)	1 (1%)	0	0
Increased blood bilirubin	2 (2%)	1 (1%)	0	0
Increased transaminases	1 (1%)	2 (2%)	0	0
Lower respiratory tract infection	2 (2%)	1 (1%)	0	0
Renal failure	1 (1%)	2 (2%)	0	0
Syncope	2 (2%)	1 (1%)	0	0
Tumour flare	2 (2%)	1 (1%)	0	0
Cataract	1 (1%)	1 (1%)	0	0
Congestive cardiac failure	0	2 (2%)	0	0
Muscular weakness	1 (1%)	1 (1%)	0	0
Urinary incontinence	1 (1%)	1 (1%)	0	0
Arthritis	0	1 (1%)	0	0
Atrial flutter	0	1 (1%)	0	0

(Table 3 continues on next page)

18·3 to not reached; figure 2D). 74% (62–82) of patients were alive at 12 months and 64% (51–74) of patients were alive at 18 months. 30 (38%) of 80 patients remain in remission at data cutoff for this report.

A post-hoc analysis showed that seven patients had a *c-MYC* translocation that was identified during central pathology review: three of whom had a complete response, one had a partial response, and three did not respond to therapy. Of these seven patients, one presented with a double-hit translocation and had a partial response (lasting 5·8 months) and another had a triple-hit translocation and a complete response (ongoing at 20·1 months).

Treatment-emergent adverse events of any grade occurred in all 81 patients. Neutropenia was the most common adverse event (all grades), occurring in 40 (49%) of 81 patients, and the most common grade 3 or worse adverse event, occurring in 39 (48%) patients (table 3). Neutropenia was managed by granulocyte colony-stimulating factor in 36 (44%) patients, and the majority (32 [81%] of 39 patients with grade 3 or 4 neutropenia) recovered to baseline neutrophil counts within 1 week. The next most common grade 3 or worse events were thrombocytopenia, febrile neutropenia, leukopenia, anaemia, and pneumonia (table 3; appendix pp 19–21). The majority of non-haematological adverse events were grades 1 and 2; diarrhoea was the most common, with a median duration of 8 days (IQR 3–24). 29 (36%) patients had different types of rash, most of which were grade 2 or lower (table 3; appendix p 21): seven (9%) patients had a (non-serious) rash of grade 3, which was classified as allergic dermatitis in three patients, and as maculopapular rash, erythematous rash, pruritus, and psoriasis in one patient each (appendix p 21). All of these patients with grade 3 rash recovered between 2 and 40 days after event onset, but one patient with allergic dermatitis recovered with sequelae 45 days after event onset (both study drugs were discontinued). In one patient with psoriasis, lenalidomide was discontinued because of the event, and in two patients with allergic dermatitis, lenalidomide was temporarily interrupted because of the event. Infusion-related reactions (all grade 1) were observed in five (6%) patients. All occurred once during the first infusion and no discontinuation of infusion was required.

Serious adverse events occurred in 41 (51%) of 81 patients. The most frequently reported serious adverse events (in two or more patients) were pneumonia (five [6%]), febrile neutropenia (five [6%]), pulmonary embolism (three [4%]), bronchitis (two [2%]), atrial fibrillation (two [2%]), and congestive cardiac failure (two [2%]). Serious adverse events suspected to be treatment-related by the investigators occurred in 15 (19%) patients. These were primarily infections (in eight [10%] of 81 patients: bronchitis [two patients; 2%], pneumonia [two; 2%], cytomegalovirus infection [one; 1%], lower respiratory tract infection [one; 1%], neutropenic sepsis [one; 1%], sepsis [one; 1%], streptococcal sepsis [one; 1%],

respiratory syncytial virus infection [one; 1%], and urinary tract infection [one; 1%]) or febrile neutropenia (four [5%]). Other treatment-related serious adverse events were pulmonary embolism (two [2%]), and agranulocytosis, chronic obstructive pulmonary disease, fatigue, pyrexia, atrial fibrillation, and tumour flare (one event each [1%]).

Ten (12%) of 81 patients discontinued the study during the combination therapy because of adverse events (figure 1). In total, 20 (25%) of 81 patients discontinued treatment with one or both study drugs because of adverse events during the study (appendix p 22). Seven (9%) patients had an adverse event of special interest (defined by the protocol): three with tumour flares (one each at grades 1–3), one with grade 2 basal cell carcinoma, and three with grade 3 allergic dermatitis.

30 (37%) of 81 patients died; eight during study treatment and 22 post-treatment. 23 (77%) of the 30 deaths were related to lymphoma progression and seven (23%) were unrelated to disease progression. Treatment-emergent adverse events leading to death occurred in four (13%) of 30 patients: sudden death, respiratory failure, cerebrovascular accident, and worsening of progressive multifocal leukoencephalopathy (table 3; appendix p 8). The patient with progressive multifocal leukoencephalopathy had neurological symptoms before initiation of protocol treatment, and died 68 days after the end of treatment. The investigators did not consider any of these four treatment-emergent adverse events to be related to study treatment. Three (10%) of the 30 deaths, unrelated to disease progression, occurred during the post-treatment period and were reported as intracerebral haemorrhage, lung oedema due to cardiac failure, and pneumonia.

Upon discontinuation of lenalidomide (either cycle 13 onwards as per protocol or earlier in case of toxicities), the incidence and severity of treatment-emergent adverse events decreased under tafasitamab monotherapy; grade 3 or 4 neutropenia occurred in three (6%) of 51 patients after lenalidomide discontinuation during this phase (appendix p 11). Adverse events of grade 3 or 4 were reported in 56 (70%) of 80 patients before lenalidomide discontinuation, compared with 15 (29%) of 51 patients after lenalidomide discontinuation.

Numbers of circulating B cells, T cells, and natural killer cells were analysed from baseline until cycle 8, day 15 (appendix pp 12–14): numbers of B cells decreased rapidly at day 8 of cycle 1, numbers of T cells showed transient changes, and the numbers of natural killer cells were found to be higher in patients at day 15 of cycle 8 compared with baseline at day 1 of cycle 1. In 32 patients with samples available both at baseline and cycle 8, day 15, there was a slight increase in the median number of peripheral natural killer cells, from 168 cells per µL (IQR 59–237) at baseline to 203 cells per µL (121–547) at cycle 8, day 15 (appendix p 15).

Tafasitamab showed a pharmacokinetic profile consistent with earlier studies (data not shown). No clinically relevant treatment-emergent immunogenicity was observed (data not shown; appendix p 7). Because of limited sample availability, full assessment of exploratory and diagnostic biomarkers were incomplete and are not reported; no further analyses are planned.

	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)				
Biliary colic	0	1 (1%)	0	0
Bronchopulmonary aspergillosis	0	0	1 (1%)	0
Cardiac failure	0	0	1 (1%)	0
Cerebrovascular accident	0	0	0	1 (1%)
Cervicobrachial syndrome	0	1 (1%)	0	0
Cranial nerve infection	0	1 (1%)	0	0
Cytomegalovirus infection	0	1 (1%)	0	0
Device-related thrombosis	0	1 (1%)	0	0
Enterobacter bacteraemia	0	1 (1%)	0	0
Febrile infection	0	0	1 (1%)	0
Femur fracture	0	1 (1%)	0	0
Haematuria	0	1 (1%)	0	0
Hyperkalaemia	0	1 (1%)	0	0
Hypersensitivity	0	1 (1%)	0	0
Hyponatraemia	0	1 (1%)	0	0
Infected bite	0	1 (1%)	0	0
Klebsiella sepsis	0	1 (1%)	0	0
Lower limb fracture	0	1 (1%)	0	0
Lung infection	0	1 (1%)	0	0
Myocardial ischaemia	0	0	1 (1%)	0
Myositis	0	1 (1%)	0	0
Nephrolithiasis	0	1 (1%)	0	0
Neutropenic sepsis	0	1 (1%)	0	0
Osteonecrosis	0	1 (1%)	0	0
Peripheral sensorimotor neuropathy	0	1 (1%)	0	0
Progressive multifocal leukoencephalopathy	0	0	0	1 (1%)
Recurrent marginal zone lymphoma	0	1 (1)	0	0
Respiratory failure	0	0	0	1 (1%)
Respiratory syncytial virus infection	0	1 (1)	0	0
Sepsis	0	0	1 (1%)	0
Soft tissue infection	0	1 (1)	0	0
Streptococcal sepsis	0	0	1 (1%)	0
Sudden death	0	0	0	1 (1%)
Varicella zoster virus infection	0	0	1 (1%)	0
Wound complication	0	0	1 (1%)	0

Data are n (%). The table shows treatment-emergent adverse events of grade 1 or 2 occurring in at least 10% of patients and all grade 3, 4, and 5 events. *Defined by customised Medical Dictionary for Regulatory Activities query. †One report of back pain and one report of increased blood creatinine had no toxicity grading.

Table 3: **Treatment-emergent adverse events**

Discussion

In this population of patients with relapsed or refractory diffuse large B-cell lymphoma who were ineligible for stem-cell transplantation, combination treatment with

tafasitamab and lenalidomide elicited an overall objective response in 60% of patients and a complete response in 43%. Furthermore, the responses were durable, with a median duration of response of 21·7 months. Among patients with a complete response, 93% had a response lasting 18 months. With a median follow-up of 19·6 months, median overall survival had not yet been reached. Moreover, 30 (38%) of 80 patients remain in remission at data cutoff for this report.

The patients in this study were notable for being considered ineligible for autologous stem-cell transplantation and their older age (median 72 years). This study also included a substantial proportion of patients belonging to subgroups known for poor prognosis, in particular those with disease that is refractory to previous therapies; tafasitamab and lenalidomide had similar activity in patients with or without refractory disease, whether refractory to the most recent previous therapy, refractory to rituximab, or with a history of primary refractory diffuse large B-cell lymphoma. Encouraging responses were also reported in patients with germinal centre B-cell-derived disease. Given that single-agent lenalidomide is historically less active in the subgroup of patients with germinal centre B-cell-derived disease,[19,20,25] these results suggest a greater activity and synergy of the tafasitamab plus lenalidomide combination, irrespective of the cell of origin. However, a more complete interpretation is limited because the cell of origin was unknown for 27% of patients and gene-expression profiling results were not evaluable for 60% of patients, because of insufficient tumour tissue.

Based on their single-agent safety profiles, no new safety signals were identified for either drug or the combination during this study.[15,16,19,20,25–28] The study treatments were generally well tolerated in this older and pretreated population. Most adverse events were manageable; neutropenia was common, although short in duration and responsive to supportive treatment.

Previous studies in similar patient populations have reported proportions of patients with an objective response of 25% for ibrutinib monotherapy,[29] 28% for lenalidomide monotherapy,[19] and 33% for lenalidomide plus rituximab.[24] More recently, novel therapeutic options in patients with relapsed or refractory diffuse large B-cell lymphoma have been approved. Trials with CAR T-cell therapies have reported that 52–82% of patients had an objective response, but 89–95% of the patients had adverse events of grade 3 or worse.[5,6] The most common adverse event of any grade was cytokine release syndrome (58–93%). Access and eligibility to CAR T-cell therapy is a constraint for some patients.[5,6] Results from a study of polatuzumab vedotin combined with bendamustine and rituximab showed 45% of patients with an objective response (at end of treatment), 40% with a complete response, and a median progression-free survival of 9·5 months in 40 patients.[7] Median overall survival was reached at 12·4 months (95% CI 9·0 to not reached) and only seven of 40 patients (including one who had received an allogeneic stem-cell transplant) remained disease free at around 20 months.[7] In the polatuzumab combination treatment group, 33% of patients discontinued all treatment because of adverse events, most commonly thrombocytopenia and neutropenia.[7]

One of the limitations of our study is its open-label, single-arm phase 2 design, precluding comparison of outcome measures with other existing therapeutic approaches or to single-agent lenalidomide. Because of the small proportion of patients with primary refractory disease (19%) and double-hit or triple-hit lymphoma (2%) who were enrolled in this study, the results for these subgroups cannot be extrapolated wider to these patient populations who usually have a poor outcome to routinely administered therapies. Furthermore, approximately half of the patients received only one previous therapy line and were considered by investigators as transplant ineligible; however, these patients might have been considered for autologous stem-cell transplantation, despite their older ages and underlying comorbidities. Finally, the higher proportion of patients with a response among those with a low or low–intermediate risk International Prognostic Index score (0–2) suggests that the benefit of this drug combination in patients with an intermediate–high or high-risk IPI score (3–5) needs to be further confirmed.

The L-MIND study indicates the benefit provided by the addition of tafasitamab to lenalidomide, given the proportion of patients with an objective response on single-agent lenalidomide has been shown to range from 28% to 35% in patients with relapsed or refractory aggressive non-Hodgkin lymphoma (including diffuse large B-cell lymphoma),[19,20,26] and the proportion of patients with an objective response on single-agent tafasitamab has been shown to be 26% in relapsed or refractory diffuse large B-cell lymphoma.[17] The greater activity in L-MIND could potentially be due to the complementary mechanism of action of both drugs and a lenalidomide-mediated decreased activation threshold.[30] The observed increase in the number of natural killer cells during treatment might also be a contributing factor behind this synergy. CD19 appears to be a useful alternative target in patients who have failed with previous anti-CD20 immunochemotherapy, and a randomised phase 2/3 study is ongoing to explore the combination of tafasitamab with chemotherapy in patients previously exposed to rituximab (NCT02763319).

These trial data suggest that tafasitamab plus lenalidomide is a well tolerated immunomodulatory treatment option with very promising clinical activity and a high proportion of durable complete responses in patients with relapsed or refractory diffuse large B-cell lymphoma who are ineligible for autologous stem-cell transplantation.

Contributors

GS, JD, JW, MD-H, SA, and GF-R analysed and interpreted the data. All authors contributed to data acquisition, manuscript development, and approval. All authors interpreted the results and agree on accountability for all study aspects, including accuracy, integrity, and protocol adherence. All authors contributed to study design or conduct, data analyses, or manuscript writing.

Declaration of interests

GS has received personal fees for consultancy from Epizyme; advisory board participation or symposia from MorphoSys, Amgen, Acerta, Autolus, Bristol-Myers Squibb, Merck, AbbVie, Janssen, Novartis, Gilead/Kite, Servier, Celgene, Roche, Pfizer, and Takeda outside of the submitted work; and has a patent issued (WO2012010561A1: characterisation of another anti-CD19 monoclonal antibody, having antibody-dependent cellular cytotoxicity function, and developed in collaboration with iDD-biotech; this antibody and the company has no relationship with the anti-CD19 antibody described in the current paper (tafasitamab) and has not been licensed to any third party). EGB has received personal fees for consultancy from Janssen, Gilead, Sandoz, Celltrion, Keona, and Celgene, and honoraria from Roche, Janssen, AbbVie, and Takeda, outside of the submitted work. OT has received personal fees from Roche, Gilead, AbbVie, Celgene, Janssen, Sandoz, and Iquone, and travel grants from Roche, Gilead, AbbVie, Celgene, and Janssen outside of the submitted work. WJ has received research funding from MorphoSys during the conduct of the study, and from Roche, Sandoz, and Celltrion, outside of the submitted work. GG has received personal fees for advisory board participation from AbbVie, Janssen, AstraZeneca, and Sunesys, and for participation in a speaker bureau from Janssen, outside of the submitted work. NK has received research funding from Celgene, outside of the submitted work. MD has received an institutional research grant from Celgene; personal fees for advisory board participation from Celgene and MorphoSys; and speaker fees from Celgene, all outside of the submitted work. JW, MD-H, SA, and G-FR are employees of MorphoSys, Planegg, Germany. KM has received personal fees for advisory board participation from MorphoSys during the conduct of the study, and from Pharmacyclics, Teva, AstraZeneca, Celgene, and Seattle Genetics, outside of the submitted work. All other authors declare no competing interests.

Data sharing

Additional documents and data sharing will be considered only for non-commercial use on a case-by-case basis (to be approved by MorphoSys; sumeet.ambarkhane@morphosys.com), starting 12 months from acceptance of the manuscript and until 36 months.

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References

1 Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. *CA Cancer J Clin* 2016; **66:** 443–59.

2 Coiffier B, Sarkozy C. Diffuse large B-cell lymphoma: R-CHOP failure-what to do? *Hematology Am Soc Hematol Educ Program* 2016; **2016:** 366–78.

3 Hitz F, Connors JM, Gascoyne RD, et al. Outcome of patients with primary refractory diffuse large B cell lymphoma after R-CHOP treatment. *Ann Hematol* 2015; **94:** 1839–43.

4 Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol* 2010; **28:** 4184–90.

5 Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med* 2019; **380:** 45–56.

6 Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med* 2017; **377:** 2531–44.

7 Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol* 2020; **38:** 155–65.

8 Salles GA, Pettengell R, Cordoba R, Długosz-Danecka M, Jurczak W, Tilly H. Treatment of aggressive B-cell non-Hodgkin lymphoma beyond frontline therapy in patients not eligible for stem cell transplantation: a structured review. *Leuk Lymphoma* 2019; **60:** 1610–25.

9 Olejniczak SH, Stewart CC, Donohue K, Czuczman MS. A quantitative exploration of surface antigen expression in common B-cell malignancies using flow cytometry. *Immunol Invest* 2006; **35:** 93–114.

10 Poe JC, Minard-Colin V, Kountikov EI, Haas KM, Tedder TF. A c-Myc and surface CD19 signaling amplification loop promotes B cell lymphoma development and progression in mice. *J Immunol* 2012; **189:** 2318–25.

11 Trněný M, Verhoef G, Dyer MJS, et al. A phase II multicenter study of the anti-CD19 antibody drug conjugate coltuximab ravtansine (SAR3419) in patients with relapsed or refractory diffuse large B-cell lymphoma previously treated with rituximab-based immunotherapy. *Haematologica* 2018; **103:** 1351–58.

12 Ohmachi K, Ogura M, Suehiro Y, et al. A multicenter phase I study of inebilizumab, a humanized anti-CD19 monoclonal antibody, in Japanese patients with relapsed or refractory B-cell lymphoma and multiple myeloma. *Int J Hematol* 2019; **109:** 657–64.

13 Kahl BS, Hamadani M, Radford J, et al. A phase I study of ADCT-402 (loncastuximab tesirine), a novel pyrrolobenzodiazepine-based antibody–drug conjugate, in relapsed/ refractory B-cell non-Hodgkin lymphoma. *Clin Cancer Res* 2019; **25:** 6986–94.

14 Ryan MC, Palanca-Wessels MC, Schimpf B, et al. Therapeutic potential of SGN-CD19B, a PBD-based anti-CD19 drug conjugate, for treatment of B-cell malignancies. *Blood* 2017; **130:** 2018–26.

15 Horton HM, Bernett MJ, Pong E, et al. Potent in vitro and in vivo activity of an Fc-engineered anti-CD19 monoclonal antibody against lymphoma and leukemia. *Cancer Res* 2008; **68:** 8049–57.

16 Awan FT, Lapalombella R, Trotta R, et al. CD19 targeting of chronic lymphocytic leukemia with a novel Fc-domain-engineered monoclonal antibody. *Blood* 2010; **115:** 1204–13.

17 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:** 1266–72.

18 Gribben JG, Fowler N, Morschhauser F. Mechanisms of action of lenalidomide in B-cell non-Hodgkin lymphoma. *J Clin Oncol* 2015; **33:** 2803–11.

19 Czuczman MS, Trněný M, Davies A, et al. A phase 2/3 multicenter, randomized, open-label study to compare the efficacy and safety of lenalidomide versus investigator's choice in patients with relapsed or refractory diffuse large B-cell lymphoma. *Clin Cancer Res* 2017; **23:** 4127–37.

20 Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. *Ann Oncol* 2011; **22:** 1622–27.

21 Tarella C, Gueli A, Delaini F, et al. Rate of primary refractory disease in B and T-cell non-Hodgkin's lymphoma: correlation with long-term survival. *PLoS One* 2014; **9:** e106745.

22 National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: B-cell lymphomas. 2018. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf (accessed Feb 20, 2020).

23 Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007; **25:** 579–86.

24 Wang M, Fowler N, Wagner-Bartak N, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: a phase II clinical trial. *Leukemia* 2013; **27:** 1902–09.

25 Witzig TE, Nowakowski GS, Habermann TM, et al. A comprehensive review of lenalidomide therapy for B-cell non-Hodgkin lymphoma. *Ann Oncol* 2015; **26:** 1667–77.

26 Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. *J Clin Oncol* 2008; **26:** 4952–57.

27 Rodgers TD, Baran AM, Reagan PM, et al. Outcomes of lenalidomide in diffuse large B-cell (DLBCL) and high-grade NHL (HGBCL): a single-center retrospective analysis. *Proc Am Soc Clin Oncol* 2019; **37:** 7547.

28 Broccoli A, Casadei B, Chiappella A, et al. Lenalidomide in pretreated patients with diffuse large B-cell lymphoma: an Italian observational multicenter retrospective study in daily clinical practice. *Oncologist* 2019; **24:** 1246–52.

29 Wilson WH, Young RM, Schmitz R, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nat Med* 2015; **21:** 922–26.

30 Lagrue K, Carisey A, Morgan DJ, Chopra R, Davis DM. Lenalidomide augments actin remodeling and lowers NK-cell activation thresholds. *Blood* 2015; **126:** 50–60.