

# The European Medicines Agency Review of Tafasitamab in Combination With Lenalidomide for the Treatment of Adult Patients With Relapsed/Refractory Diffuse Large B-cell Lymphoma

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## Abstract

Tafasitamab is a humanized monoclonal antibody that binds to the CD19 antigen, which is expressed in tumor cells from patients with diffuse large B-cell lymphoma (DLBCL). On June 24, 2021, a positive opinion for a conditional marketing authorization was issued by the European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) for tafasitamab, in combination with lenalidomide, for the treatment of adult patients with relapsed or refractory DLBCL who are ineligible for autologous stem cell transplantation. Tafasitamab was evaluated in the phase 2 single-arm, multicenter, open-label L-MIND clinical trial. The primary endpoint of this trial was objective response rate (ORR). The best ORR, achieved at any time during the study, was 56.8% (95% confidence interval: 45.3%–67.8%), and the median duration of response was 34.6 months (95% confidence interval: 26.1–not reached). The most frequently reported adverse events by system organ class were infections and infestations (72.8%; grade  $\geq 3$ : 29.6%), blood and lymphatic system disorders (65.4%; grade  $\geq 3$ : 56.8%), gastrointestinal disorders (64.2%; grade  $\geq 3$ : 2.5%), and general disorders and administration site conditions (58.0%; grade  $\geq 3$ : 8.6%). The aim of this article is to summarize the scientific review of the application which led to the positive opinion by the CHMP.

## Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma. In Europe, approximately 8500 new cases of DLBCL are diagnosed every year, causing around 4000 deaths.<sup>1,2</sup> The incidence of DLBCL increases with

age, ranging from  $<1/100,000$  in children to 10–15/100,000 in people older than 65 years.<sup>1</sup> Prognosis is determined by patient's age, tumor cell of origin (germinal centre B-cell versus activated B-cell) and genomic aberrations, including *TP53* abnormalities and chromosomal alterations involving the *MYC*, *BCL2*, and *BCL6* genes ("double/triple hit DLBCL").<sup>3,4</sup> The most commonly used risk assessment tool is, however, the International Prognostic Index (IPI), which considers age, disease stage, lactate dehydrogenase (LDH) levels, performance status, and extranodal involvement.<sup>5</sup>

Treatment of DLBCL consists of 6–8 courses of the anti-CD20 monoclonal antibody (mAb) rituximab and CHOP chemotherapy (R-CHOP).<sup>6</sup> Still, around 30%–40% of patients ultimately relapse and 20% are primarily refractory to R-CHOP.<sup>7</sup> For patients with relapsed or refractory (R/R) disease, the current standard of care consists of platinum- and/or gemcitabine-based salvage chemotherapy followed by autologous stem cell transplant (ASCT).<sup>6</sup> For some patients, who are not fit enough for ASCT due to advanced age or comorbidities, or in whom the ASCT is ineffective, the prognosis is very poor.<sup>8</sup> Treatment options for patients relapsing after, or ineligible for, salvage chemotherapy and ASCT are limited.<sup>6</sup> Among newer agents, chimeric antigen receptor T-cells, such as tisagenlecleucel and axicabtagene ciloleucel (and lisocabtagene marelleucel in the United States), constitute an option for patients with R/R DLBCL who have received 2 or more lines of therapy,<sup>9,10</sup> but adverse events (AEs) such as neurotoxicity and cytokine-release syndrome must be considered. Pixantrone is also an option as monotherapy for patients with multiply relapsed or refractory aggressive DLBCL<sup>11</sup> and, in January 2020, the novel antibody-drug conjugate polatuzumab vedotin received

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a conditional marketing authorization (CMA), in combination with bendamustine and rituximab, as second- or later-line therapy for patients with R/R DLBCL who are not candidates for ASCT.<sup>12</sup> Lenalidomide has also shown some efficacy in heavily pretreated patients with R/R DLBCL,<sup>13</sup> but it is not approved for this indication in the European Union (EU).

On April 30, 2020, Morphosys AG applied for a marketing authorization via the European Medicines Agency (EMA)'s centralized procedure for tafasitamab (trade name Minjuvi). Tafasitamab had been designated orphan medicine by the European Commission (EC) on January 15, 2015 for the treatment of R/R DLBCL. To qualify for orphan designation, a medicine must be intended for the treatment, prevention or diagnosis of a life-threatening or chronically debilitating disease, the prevalence of the condition in the EU must not be >5 in 10,000, and the medicine must be of significant benefit to those affected by the condition.

The review of the benefit–risk balance was conducted by the Committee for Medicinal Products for Human Use (CHMP) and the positive opinion was issued on June 24, 2021. The indication approved in the EU was as follows: “Minjuvi is indicated in combination with lenalidomide followed by Minjuvi monotherapy for the treatment of adult patients with relapsed or refractory DLBCL who are not eligible for autologous stem cell transplant.” The aim of this article is to summarize the scientific review of the application leading to the regulatory approval of tafasitamab in the EU.

## Nonclinical aspects and clinical pharmacology

Tafasitamab is a humanized mAb that binds to the CD19 antigen, which is expressed throughout normal and malignant B-cell development, including tumor cells from patients with DLBCL.<sup>14</sup> A key aspect of this molecule is the modification of 2 amino acid residues from its constant region, significantly increasing its binding to Fc gamma receptors and leading to enhanced antibody-dependent cell cytotoxicity (ADCC) and phagocytosis (ADCP) compared to the unmodified antibody.<sup>15</sup> Both ADCC and ADCP were observed against tumor cell lines representative of Burkitt's lymphoma, chronic lymphocytic leukemia (CLL), hairy cell leukemia, DLBCL, and acute lymphoblastic leukemia, all of which expressed varying levels of CD19 antigen.<sup>15</sup> The enhancement of tafasitamab-mediated natural killer-cell activation and ADCC by lenalidomide was also demonstrated *in vitro*.<sup>16</sup> Genotoxicity and carcinogenicity studies were not required as per ICH S6(R1) and S9 guidelines. The absence of developmental toxicity studies in pharmacologically relevant nonhuman primates was considered reasonable considering that the patient population was mostly beyond reproductive age (median age 72 y) and the co-administration with the well-known teratogenic lenalidomide during the first 12 cycles, for which measures to avoid pregnancy in woman of childbearing potential (contraception during treatment and up to 3 mo after cessation of treatment) are included in the Summary of Product Characteristics (SmPC).

The pharmacology of tafasitamab was investigated in four clinical trials for patients with different B-cell malignancies (XmAb5574-01, MOR208C201, MOR208C202, and MOR208C203 [L-MIND]) for a total of 221 subjects.<sup>17,18</sup> The phase I dose-escalation XmAb5574-01 study showed tafasitamab to be safe, well tolerated and provided initial evidence of clinical activity,<sup>17</sup> with the highest tested intravenous dose of 12 mg/kg being recommended for phase II testing.<sup>18</sup> When combined with lenalidomide, tafasitamab exhibited a flat exposure–response relationship, leading to the conclusion that increasing the exposure to tafasitamab above that dose was unlikely to result in higher response rates. Moreover, switching the dosing frequency from once weekly to every two weeks after 12 weeks

of treatment did not have any impact on efficacy. The marketing authorization holder (MAH) also evaluated whether there was a correlation between drug exposure and the incidence of AEs of special interest (AESI) and, although this could be suspected for some AESIs, firm conclusions could not be drawn.

## Trial design

The main study was MOR208C203 (L-MIND), a phase 2 single-arm, open-label study of the efficacy and safety of tafasitamab combined with lenalidomide followed by tafasitamab monotherapy in patients with R/R DLBCL who are ineligible for or refuse ASCT.<sup>19</sup> Eligible patient had to have R/R DLBCL (at least one but no more than three prior therapies), also including grade 3b follicular lymphoma and transformed lymphoma from other low-grade entities (follicular lymphoma, marginal zone lymphoma, or CLL). Patients with a history of “double/triple hit” DLBCL were excluded, but MYC, BCL2 or BCL6 genomic testing was not formally required at screening. Prior therapy with lenalidomide, other immunomodulatory agents or CD19-targeted therapies (eg, tisagenlecleucel or axicabtagene ciloleucel) was not allowed. The primary reasons why patients were not candidates for ASCT included high age (46.3%), refractoriness to salvage chemotherapy (22.5%), comorbidities (13.8%), and refusal (16.3%). Of those who refused ASCT, only 4 had no comorbidities and refused exclusively due to personal reasons.

Tafasitamab (12 mg/kg) was administered intravenously on days 1, 8, 15, and 22 of each 28-day cycle for cycles 1–3. On day 4, cycle 1, an additional loading dose of tafasitamab was administered. Thereafter, tafasitamab was infused on days 1 and 15 of each cycle. In patients with at least stable disease after cycle 12, tafasitamab was administered until disease progression or unacceptable toxicity. A premedication consisting of paracetamol, histamine H1 receptor blockers (eg, diphenhydramine), histamine H2 receptor blockers (eg, cimetidine), or glucocorticosteroids (eg, methylprednisolone) was recommended 30 minutes to 2 hours before tafasitamab infusion. Lenalidomide (25 mg) was administered orally on days 1–21 of each 28-day cycle for a maximum of 12 cycles. The dose could be modified in the case of intolerance according to the SmPC.

The primary efficacy endpoint was objective response rate (ORR), defined as the proportion of complete and partial responders as assessed by Independent Radiology/Clinical Review Committee (IRC). A sensitivity analysis was conducted using ORR based on the investigators' (INV) assessment. Secondary endpoints were disease control rate, defined as the proportion of patients achieving ORR or stable disease, duration of response (DOR), progression-free survival (PFS), time to progression, overall survival (OS), time to next treatment, and incidence/severity of AEs. For the sample size calculations, a 15% improvement in ORR was assumed (from 20% to 35%). A sample size of 80 subjects was considered sufficient to have an 85% statistical power assuming a 10% dropout rate.

Supportive studies were the MOR208C201 and the MOR208C206 (RE-MIND) trials. The MOR208C201 was an open-label multicentre phase 2a study of single-agent tafasitamab in adult patients with different subtypes of R/R lymphoma. Patients received tafasitamab 12 mg/kg intravenously weekly for 8 weeks (2 cycles) with the option of further bimonthly infusions in the case of clinical benefit. The MOR208C206 trial was a retrospective study of lenalidomide monotherapy in adult patients with R/R DLBCL with similar efficacy endpoints and eligibility criteria as the MOR208C203 trial. Patients from MOR208C206 trial were matched with those from the MOR208C203 trial according to age, disease stage, refractoriness to last therapy, the number of prior therapies, prior ASCT, elevated LDH, and the presence of neutropenia or anemia.

## Clinical efficacy

Eighty-one patients were enrolled in the L-MIND trial. The initial cutoff was November 30, 2018, but the current analysis is based on the subsequent cutoff of November 30, 2019, with some corrections made in October 2020 (Table 1). Half of the patients had 1 prior therapy and the other half had 2 or more. Nine (11.3%) patients had progressive disease after ASCT, while 15 (18.8%) had primary refractory disease.

The best ORR, achieved at any time during the study, was 56.8% (95% confidence interval [CI]: 45.3%–67.8%), with a complete response rate of 39.5% (95% CI: 28.8%–51.0%). The concordance rate between IRC and INV assessments were 84.4% and 71.4% for complete and partial response, respectively, leading to an 84.3% agreement in the assessment of ORR. The median DOR was 34.6 months (95% CI: 26.1–not reached [NR]), with a 2-year DOR of 71.3% (95% CI: 52.8%–83.7%), whereas the median PFS was 12.1 months (95% CI: 5.7–NR). The concordance rate between IRC and INV for PFS events and censorings was 91.4%. The Kaplan-Meier estimate for the median OS was 31.6 months (95% CI: 18.3–NR), with a 2-year OS of 56.4% (95% CI: 44.5%–66.8%).

Study MOR208C201 enrolled 35 patients with DLBCL, among other lymphoma subtypes. The ORR in the DLBCL population was 26% (95% CI: 12.5%–43.3%), with a median DOR of 20.1 months (95% CI: 1.1–NR). The RE-MIND study collected data on comparable patients treated with lenalidomide monotherapy. In total, 76 patients were matched (1:1) to L-MIND patients. The estimated ORR were 67.1% (95% CI: 55.4%–77.5%) and 34.2% (95% CI: 23.7%–46.0%) for tafasitamab + lenalidomide and lenalidomide, respectively, while estimated median DOR were 20.5 (95% CI: 3.3–13.9) versus 4.1 months (95% CI: 1.5–5.2).

## Clinical safety

Only the L-MIND study evaluated the combination of lenalidomide and tafasitamab followed by tafasitamab monotherapy, for which approval was sought. Three further studies using tafasitamab monotherapy were also included in the safety dataset (MOR208C201, MOR208C202 and XmAb5574-01 [n = 141 patients]), for a total of 222 patients, all lymphoma subtypes included. The median treatment duration was 232 days in the L-MIND study, longer than in the pooled monotherapy studies (51 d). Consequently, the cumulative dose was more than twice higher in the L-MIND study compared to pooled monotherapy studies.

All (100%) patients from the L-MIND study experienced treatment emergent AEs (TEAEs), 77.8% of which were grade 3 or higher (Table 1). Serious AEs (SAEs) were documented in 51.9% of patients, including 4 (4.9%) cases of fatal SAEs. These fatal AEs were cerebrovascular accident, sudden death, respiratory failure, and progressive multifocal leukoencephalopathy, all considered unrelated to the experimental therapy by the investigators. The most frequently reported AEs by system organ class (SOC) were infections and infestations (72.8%; grade  $\geq 3$ : 29.6%), blood and lymphatic system disorders (65.4%; grade  $\geq 3$ : 56.8%), gastrointestinal disorders (64.2%; grade  $\geq 3$ : 2.5%), and general disorders and administration site conditions (58.0%; grade  $\geq 3$ : 8.6%) (Table 1). The most frequently reported grade  $\geq 3$  infections were pneumonia (7%), respiratory tract infections (4.9%), urinary tract infections (4.9%), and sepsis (4.9%); and they were fatal in <1% of patients. Median time to onset and duration of grade  $\geq 3$  infections were 62.5 days (4–1014 d) and 11 days (1–392 d), respectively. Infections led to dose interruption and permanent discontinuation of tafasitamab in 27% and 4.9% of patients, respectively. After 12 cycles, 26 (76.4%) patients receiving tafasitamab monotherapy

**Table 1**

**Key Favorable and Unfavorable Effects for Tafasitamab and Lenalidomide (L-MIND trial; Efficacy Cutoff: October 30, 2020; Safety Cutoff: June 30, 2019)**

Effect	Unit	Treatment: Tafasitamab + Lenalidomide	Uncertainties/ Strength of Evidence
<b>Favorable effects</b>			
ORR by IRC	% (95% CI)	56.8 (45.3–67.8)	Uncontrolled data
Median DOR by IRC	Months (95% CI)	34.6 (25.1–NR)	
Median PFS by IRC	Months (95% CI)	12.1 (5.7–NR)	
Median OS	Months (95% CI)	31.6 (18.3–NR)	
<b>Unfavorable effects</b>			
Infections and infestations (SOC)	%	72.8 Gr. 3–5: 29.6 SAEs: 25.9	The lack of a comparator weakens the interpretation and attribution of AEs in this clinical setting
Blood and lymphatic system disorders (SOC)	%	65.4 Gr. 3–5: 56.8	
Neutropenia	%	50.6 Gr. 3–5: 49.4	
Anemia	%	35.8 Gr. 3–5: 7.4	
Thrombocytopenia	%	30.9 Gr. 3–5: 17.3	
Febrile neutropenia	%	12.3 Gr. 3–5: 12.3	
GI disorders (SOC)	%	64.2 Gr. 3–5: 2.5	
Diarrhea	%	35.8 Gr. 3–5: 1.2	
Infusion-related reactions	%	6.2 Gr. 3–5: 0	

AEs = adverse events; CI = confidence interval; DOR = duration of response; GI = gastrointestinal; IRC = independent review committee; ORR = objective response rate (complete and partial responses); OS = overall survival; NR = not reached; PFS = progression-free survival; SAEs = serious adverse events; SOC = system organ class.

experienced TEAEs (compared to 97.1% during cycles 1–12). Infections and infestations were the most common TEAEs after cycle 12 (47.1% of patients) followed by neutropenia (23.5% of patients).

AESIs were predetermined based on preclinical and/or clinical safety data for tafasitamab. No events of anaphylaxis or anaphylactoid reactions were reported, but there were 4 events of grade  $\geq 3$  allergic reactions. In two cases lenalidomide was interrupted, and in the other two cases both drugs were discontinued. There were no cases of acute renal failure or drug-induced liver injury, and only 5 cases of elevated liver enzymes, all considered unrelated to therapy. One case of QT prolongation was documented, but not attributed to therapy, while tumor flare occurred in three patients (one grade  $\geq 3$ ). No events of tumor lysis syndrome or cytokine release syndrome were reported. Three patients from the L-MIND trial developed secondary primary malignancies (SPMs), including one case of myelodysplastic syndrome. Infusion-related reactions were observed in 6.2% of patients, all grade 1 in severity. Common AEs considered to be usually associated with lenalidomide, such as nonallergic skin reactions, diarrhea, and thromboembolic events, were observed in 37.0%, 35.8%, and 13.6% of patients, respectively. Pre-existing anti-tafasitamab antibodies were detected in 6.9% of patients, with no impact on pharmacokinetics, efficacy or safety of tafasitamab.

## Benefit–risk assessment

In patients with R/R DLBCL, the main consideration for further treatment is whether the patient is eligible or not for ASCT, which may offer a second chance of cure for about 30%–40% of patients.<sup>20,21</sup> Unfortunately, however, many patients with R/R DLBCL are ineligible for ASCT due to older age or comorbidities, and therapeutic options are limited for this patient population despite the recent approval of polatuzumab vedotin.<sup>12</sup>

The main evidence of efficacy and safety submitted was the phase 2 single-arm, multicentre, open-label L-MIND clinical trial. Two supportive studies were added to the submission package to demonstrate the contribution of each agent individually. Compared with historical data with monotherapy of either tafasitamab or lenalidomide, an ORR higher than 50% with a complete response rate of almost 40% was considered highly meaningful in this context. The study also showed a high incidence of AEs in the SOC infections and infestations, blood and lymphatic system disorders (especially neutropenia), and gastrointestinal disorders. These AEs were expected in the setting of R/R DLBCL and considered manageable and reversible. The single-arm design did not, however, allow to disentangle to what extent tafasitamab contributed to the efficacy and safety of the combination.

Predefined AESI were rare in patients recruited into the L-MIND trial, including anaphylactic or allergic reactions, infusion-related reactions, tumor lysis syndrome, or cytokine release syndrome.

Three patients from the L-MIND trial developed SPMs, which were not considered associated to tafasitamab but rather to prior cytotoxic treatment. Moreover, SPMs have also been described for patients taking lenalidomide for other indications.<sup>22,23</sup>

The CHMP evaluated the results of the RE-MIND trial, a multicenter, observational, retrospective study of the efficacy of lenalidomide monotherapy in adults with R/R DLBCL. However, the heterogeneity in the study populations included in the L-MIND and RE-MIND studies, the uncertainties in the matching, and the differences in standard of care received during treatment hampered the interpretation of the results. Therefore, the results of the RE-MIND study were regarded as exploratory and not confirmatory.

All in all, the benefit–risk balance was considered positive, but the data package, being from a small single-arm trial, was not considered comprehensive. The initial application was for a full marketing authorization but, after discussions with

CHMP members, the MAH changed it during the assessment to an application for a CMA. Tafasitamab fell within the scope of Article 14a of Regulation (EC) 726/2004 concerning CMA, as the condition (R/R DLBCL not eligible for ASCT) is a serious and life-threatening disease, where there is an unmet medical need and the benefit–risk balance was concluded positive, but further clinical data are still required and can likely be collected by the MAH. Moreover, the risks associated with approving a drug based on noncomprehensive data must be outweighed by the benefits of the earlier availability of the drug.

Moreover, the need for comprehensive postauthorization data will be satisfied with the following specific obligations:

- A single-arm study of tafasitamab with lenalidomide in the approved indication, following an agreed protocol, to confirm the efficacy and safety data of tafasitamab in combination with lenalidomide in patients with R/R DLBCL. The protocol must be submitted for review by the CHMP no later than 3 months after the EC decision, and the results are expected in December 2026.
- Safety data from the B-MIND trial, an ongoing study evaluating the efficacy and safety of tafasitamab plus bendamustine versus rituximab plus bendamustine in patients with R/R DLBCL (results due in March 2025).
- A phase 3 randomized double-blind placebo-controlled trial (Front-MIND) comparing the efficacy and safety of tafasitamab and lenalidomide added to R-CHOP versus R-CHOP in previously untreated patients with DLBCL (results due in December 2025).

For a CMA to be granted, a major therapeutic advantage against existing treatments in the context of an unmet medical need must be justified. In patients with R/R DLBCL who are ineligible for ASCT, the aim of therapy is to control the disease for as long as possible, given that all patients eventually relapse and become resistant to therapy. In this context, novel agents with a positive benefit-risk balance and a new mechanism of action provide a major therapeutic advantage if they have a different safety profile or if they are efficacious when other products are not expected to be so. The mechanism of action of tafasitamab is different from that of authorized treatments, the drug in combination with lenalidomide achieves a significant ORR and prolonged DOR and possesses a distinct safety profile. Therefore, this can be considered a major therapeutic advantage for patients in the proposed target population, for whom there are very limited options.

## Conclusions

Based on the review of data on quality, safety, and efficacy, the EMA recommended the granting of a CMA for tafasitamab in the following indication: “Tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy is approved for the treatment of adult patients with R/R DLBCL who are not eligible for ASCT.”

## Disclosures

The authors have no conflicts of interest to disclose.

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