L-MIND: A safety and efficacy analysis of tafasitamab in patients with relapsed/refractory diffuse large B-cell lymphoma receiving treatment for at least 2 years

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Background

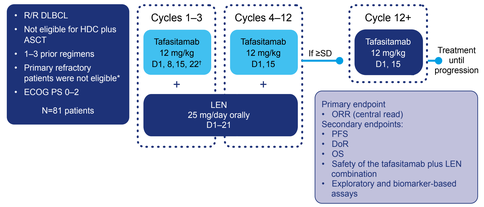
- R-CHOP is curative in 60–70% of patients with diffuse large B-cell lymphoma (DLBCL),[1,2] while 30–40% experience a relapsed/refractory (R/R) disease course[2,3]
  - Patients with R/R disease are often ineligible for second-line CAR T-cell therapy or intensive chemotherapy and autologous stem-cell transplant (ASCT) due to advanced age or comorbidities;[3–7] additionally, 40–65% of patients relapse after ASCT or CAR T-cell therapy[8–10]
- Tafasitamab is a humanized, Fc-modified, anti-CD19 monoclonal antibody that functions as an immunotherapy through direct cytotoxicity, antibody-dependent cellular cytotoxicity and antibody-dependent cell-mediated phagocytosis[11,12]
- Tafasitamab + lenalidomide (LEN) demonstrated efficacy in ASCT-ineligible patients with R/R DLBCL in the ongoing, open-label, multicenter, single-arm Phase II L-MIND study (NCT02399085)[13]
- In combination with LEN, tafasitamab has been granted accelerated approval in the United States (July 2020)[11] and conditional/accelerated approval by the European Medicines Agency (August 2021)[12] and other regulatory authorities for the treatment of adult patients with R/R DLBCL not otherwise specified, including DLBCL arising from low-grade lymphoma, and who are ineligible for ASCT, and is a preferred regimen in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) in this setting[14]
- A long duration of response (DoR), meaningful overall survival (OS), and a well-defined safety profile was reported in L-MIND patients after ≥35 months' follow-up (overall response rate: 57.5% [46/80 patients]; median DoR: 43.9 months; median OS: 33.5 months)[15]
- Here, we report efficacy and safety data for tafasitamab + LEN in patients with R/R DLBCL enrolled on L-MIND who received treatment for ≥2 years and those patients in follow-up for ≥5 years

Methods

Study design

- Patients aged ≥18 years with R/R DLBCL (1–3 prior systemic therapies, including ≥1 CD20-targeting regimen), with an Eastern Cooperative Oncology Group performance status of 0–2, and who were ineligible for ASCT were enrolled[11] (**Figure 1**)
- Patients received tafasitamab + LEN, followed by tafasitamab monotherapy
  - Tafasitamab was administered over 28-day cycles (12 mg/kg intravenously), once weekly during Cycles (C) 1–3, with a loading dose on Day 4 of C1, then every 2 weeks (Q2W) during C4–12
  - LEN (25 mg orally) was administered on Days 1–21 of C1–12
  - Following Cycle 12, progression-free patients received tafasitamab Q2W until disease progression
- The primary endpoint was objective response rate (ORR), assessed by an independent review committee, based on the 2007 International Working Group response criteria[16]
- Secondary endpoints included investigator-assessed ORR, DoR, progression-free survival (PFS), and OS; safety endpoints included incidence and severity of adverse events (AEs)

Figure 1. Study design



*Primary refractory is defined as no response to, or progression/relapse during or within 6 months of, front-line therapy; 15 refractory patients were included under an early version of the protocol.
†A loading dose of tafasitamab was administered on Day 4 of Cycle 1.

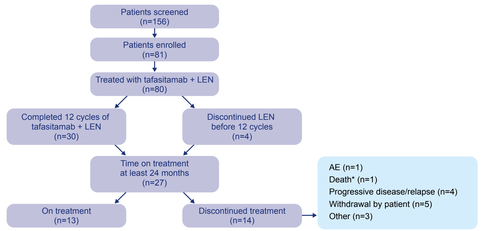
ASCT, autologous stem cell transplant; D, days; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HDC, high-dose chemotherapy; LEN, lenalidomide; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed or refractory; SD, stable disease.

Results

Patients

- Of 81 patients enrolled in L-MIND, 80 received ≥1 dose of tafasitamab + LEN and were included in the full analysis set (FAS) for efficacy; all 81 patients were included in the safety analysis
- At the data cut-off date (February 15, 2022), 30 patients completed 12 cycles of tafasitamab + LEN and four patients discontinued LEN before 12 cycles; 27 (34%) received treatment for ≥2 years (median: 4.3 years) (**Figure 2**)
- Of these 27 patients, 23 are confirmed alive, one died from an unknown cause, two died following AEs unrelated to study treatment, and one was lost to follow-up
- Thirteen patients remain on treatment; 14 patients discontinued the treatment

Figure 2. Patient disposition



*COVID-related.
AE, adverse event; LEN, lenalidomide.

- Baseline characteristics between the safety analysis set and the patients who received treatment for ≥2 years were similar
- In the patients who received treatment for ≥2 years, median age was 71 years (range, 41–81 years), eight patients (30%) had high-risk disease (International Prognostic Index score 3–5), and 19 patients (70%) had Ann Arbor stage III–IV disease (**Table 1**)
- The proportion of patients who were primary refractory, refractory to previous therapy, or who had received prior ASCT were similar between patients who received treatment for ≥2 years and the FAS (**Table 1**)

Table 1. Baseline and disease characteristics

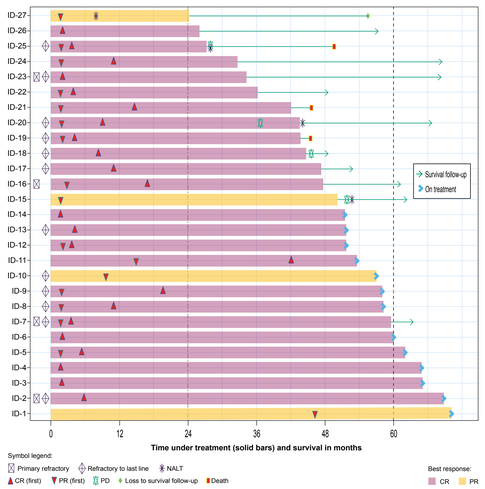
Characteristic	Specification	Treatment ≥2 years N=27	Safety analysis set N=81
Age, years*	Median (range)	71 (41–81)	72 (41–86)
Sex, n (%)	Male Female	12 (44) 15 (56)	44 (54) 37 (46)
Ann Arbor stage, n (%)*	I–II III–IV	8 (30) 19 (70)	20 (25) 61 (75)
Risk (IPI), n (%)*	0–2 3–5	19 (70) 8 (30)	40 (49) 41 (51)
Elevated LDH, n (%)*	Yes No	12 (44) 15 (56)	45 (56) 36 (44)
Prior lines, n (%)*	1 2 3 4	16 (59) 10 (37) 1 (4) –	40 (49) 35 (43) 5 (6) 1 (1)
Primary refractory, n (%)*	Yes No	4 (15)‡ 23 (85)	15 (19) 66 (81)
Refractory to previous therapy line, n (%)*†	Yes No	12 (44) 15 (56)	36 (44) 45 (56)
Prior SCT, n (%)	Yes No	4 (15) 23 (85)	9 (11) 72 (89)
Cell of origin (by IHC), n (%) (Centrally assessed – Hans algorithm)	GCB Non-GCB Unknown	11 (41) 9 (33) 7 (26)	37 (46) 20 (25) 24 (29)

*At study entry. †Refractory to previous line is defined as having less than a partial response to the most recent systemic therapy. ‡Primary refractory defined as no response to or progression/relapse during or within 6 months of front-line therapy; primary refractory patients had a DoR to 1L of 3–6 months.
1L, first line; DoR, duration of response; GCB, germinal center B-cell; IHC, immunohistochemistry; IPI, International Prognostic Index; LDH, lactate dehydrogenase; SCT, stem cell transplant.

Efficacy (investigator-assessed)

- A complete response (CR) as a best response was achieved by 23 of 27 patients, including the patients who were primary refractory (**Figure 3**)
  - Four patients achieved a partial response (PR), of which two were still on treatment
- The 48-month OS rate was 92.6%; however, the median OS, PFS, and DoR were not reached (**Figure 4A–C**)
- Of 12 patients refractory to a previous therapy line, 11 (91.7%) were in follow-up at 48 months
- Twelve patients have been in OS follow-up for ≥5 years; of these, six are still on treatment, while six have discontinued treatment
  - Of the six patients who received treatment for ≥5 years, five achieved CR (one of whom had triple-hit R/R DLBCL [patient ID-7]) and one had a PR
  - All of the primary refractory patients (n=4) are in follow-up at 60 months

Figure 3. Treatment response in patients treated for ≥2 years



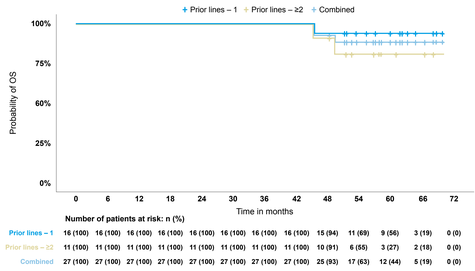
ID-19, reason for treatment discontinuation was due to withdrawal by patient. The difference in arrow type signifies the transition from on-treatment to off-treatment. Thick arrows indicate on-treatment, while thin arrows indicate off-treatment.

CR, complete response; NALT, non-protocol specified antilymphoma treatment; PD, progressive disease; PR, partial response.

Safety

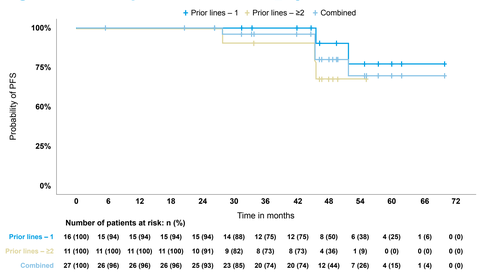
- The safety analysis of the 27 patients who received treatment for ≥2 years with tafasitamab + LEN therapy (C1–12) and tafasitamab monotherapy (C13–24) by exposure-adjusted incidence revealed a lower incidence of AEs during the tafasitamab monotherapy phase compared with the combination therapy phase; the low incidence of AEs was maintained during the tafasitamab monotherapy phase from 2 years onwards (Cycle ≥25), with no new safety signals reported (**Figure 5**)
  - The majority of AEs were Grades 1–2
  - Neutropenia, thrombocytopenia, leukopenia, and anemia were the most common hematologic AEs, while diarrhea, bronchitis, pyrexia, muscle spasms, and peripheral edema were the most common non-hematologic AEs in the combination phase
  - This incidence of all AEs substantially declined in the tafasitamab monotherapy phase
- Exposure-adjusted AE comparison showed a reduced AE frequency in the C13–24 tafasitamab monotherapy period following the C1–12 combination therapy phase

Figure 4A. OS in patients treated for ≥2 years



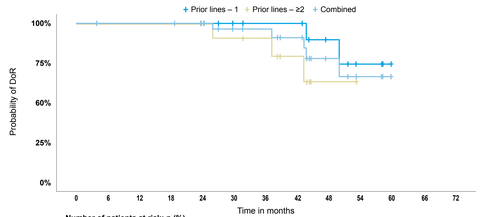
OS, overall survival.

Figure 4B. PFS in patients treated for ≥2 years



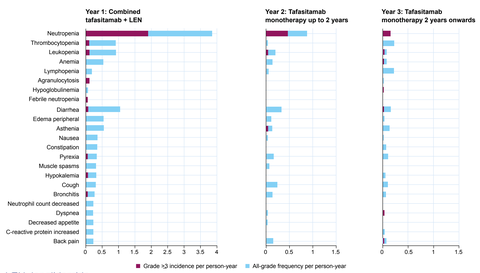
PFS, progression-free survival.

Figure 4C. DoR in patients treated for ≥2 years



DoR, duration of response.

Figure 5. Exposure-adjusted adverse events



LEN, lenalidomide.

Summary

- **These long-term data in patients treated for ≥2 years suggest that tafasitamab + LEN can achieve prolonged remission and survival of 5 years or longer in patients with R/R DLBCL ineligible for ASCT**
- **Long-term tafasitamab therapy (up to 60 months) was well tolerated and consistent with the established safety profile of tafasitamab**
- **These data suggest that the long-term administration of tafasitamab + LEN in patients with R/R DLBCL is feasible and has the potential to yield favorable clinical benefit, with a marked decrease in AEs in the monotherapy phase of the regimen**

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Disclosures

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 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. Conditional/accelerated approvals were granted by the European Medicines Agency and other regulatory authorities. Incyte has exclusive commercialization rights outside the United States. XmAb® is a registered trademark of Xencor, Inc.

Conflicts of interest
JD: research funding: MorphoSys AG, Regeneron. **WJ:** consulting/advisory: Mei pharma, Debiopharm, Loxo, Takeda, AstraZeneca, BeiGene; research funding: GlaxoSmithKline, Acerta, BeiGene, Nordic Nanovector, Debiopharm, Incyte, Genentech, Janssen, Loxo, Mei Pharma, MorphoSys AG, Takeda, TG Therapeutics. **AML:** honoraria: Bristol-Myers Squibb, Servier, Celgene, AbbVie, Amgen; consulting/advisory: Incyte; research funding: Novartis, Janssen, AbbVie, Roche, Amgen, Sanofi Genzyme, Celgene, Bristol-Myers Squibb, Servier, Incyte, Pfizer, IQVIA, Doxopharma, Verastem, BeiGene, Oncopeptides, Karyopharm, Archigen, CTI BioPharma, Debiopharm, MorphoSys AG, FibroGen, MEI Pharma, Regeneron, Dr Reddy's Laboratories Spa. **JH:** no disclosures. **EPC:** no disclosures. **PA:** honoraria: Janssen, Celgene, AbbVie, AstraZeneca, Gilead; consulting/advisory: Janssen, Celgene, AbbVie, AstraZeneca; speakers' bureau: Janssen, Celgene, AbbVie, AstraZeneca, Gilead. **KJM:** honoraria: Pharmacyclics, Celgene, Seattle Genetics, MorphoSys AG, Bristol-Myers Squibb, Karyopharm Therapeutics, Kite Pharma/Gilead Company, ADC Therapeutics and Genmab, Genentech, Lilly, Epizyme, Incyte; research funding: Pharmacyclics, Merck, Bristol-Myers Squibb. **MD:** research funding (institution): AbbVie, Bayer, Celgene, Janssen-Cilag, Roche; consulting/advisory: Acerta Pharma/AstraZeneca, Bayer/Vital, Celgene/Jazz, Gilead, Janssen-Cilag, Novartis, Roche, BeiGene, Genmab, Incyte; speakers' bureau: Amgen, Bayer, BeiGene, Celgene, Gilead, Janssen-Cilag, Roche; travel, accommodation, expenses: Celgene, Janssen-Cilag, Roche. **AR:** no disclosures. **AB:** employment: MorphoSys AG; consultancy: External Affiliate Statistical Consultant - Division of Infectious Diseases and Tropical Medicine, University Hospital, Ludwig-Maximilians-Universität (LMU) Munich. **AA:** employment: MorphoSys AG; stock: Paion AG. **KG:** employment: MorphoSys AG. **GS:** consultancy: Roche/Genentech, Gilead Sciences, Janssen, Celgene, Novartis, MorphoSys AG, Epizyme, Alimera Sciences, Genmab, Debiopharm Group, Velosbio, Bristol-Myers Squibb, BeiGene, Incyte, Miltenyi Biotec, Ipsen; honoraria: Roche/Genentech, Janssen, Celgene, Gilead Sciences, Novartis, AbbVie, MorphoSys AG.

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