First-MIND: Final Analysis from a Phase Ib, Open-Label, Randomized Study to Assess Safety of Tafasitamab or Tafasitamab + Lenalidomide in Addition to R-CHOP in Patients with Newly Diagnosed Diffuse Large B-Cell Lymphoma

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Background

- First-line (1L) standard of care for diffuse large B-cell lymphoma (DLBCL) comprises six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy[1]
- Approximately 15–20% of treatment-naïve patients with DLBCL have low CD20 expressing tumors, which are associated with poor response to rituximab-based regimens[2,3]
- CD19 is broadly expressed across many B-cell malignancies, including ~90% of DLBCL tumors, and is, therefore, an attractive therapeutic target[2,4]
- 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[5,6]
- In combination with lenalidomide (LEN), tafasitamab has been granted accelerated approval in the United States (July 2020)[5] and conditional marketing authorization in Europe (August 2021)[6] and other countries for treatment of adult patients with relapsed/refractory (R/R) DLBCL not otherwise specified (NOS), including DLBCL arising from low grade lymphoma, who are ineligible for autologous stem cell transplant, and is a preferred regimen in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) in this setting[1]
- A treatment strategy targeting both of these B-cell surface molecules, and supplemented by LEN to enhance the cytotoxicity activity of tafasitamab and rituximab, may limit target evasion and reduce resistance to R-CHOP
- First-MIND (NCT04134936) is a Phase Ib, open-label, randomized study of R-CHOP + tafasitamab ± LEN in intermediate- to high-risk (International Prognostic Index score [IPI] 2–5) patients with newly diagnosed DLBCL NOS
- The primary analysis demonstrated the feasibility of adding tafasitamab + LEN to R-CHOP without impairing its dosing and scheduling, with toxicities similar to those expected with R-CHOP alone[7]
- The combination of tafasitamab + LEN plus R-CHOP (T/L+R-CHOP) as first-line therapy is being investigated further in the global, randomized, Phase III frontMIND study (NCT04824092) in untreated patients with DLBCL and an IPI score of 3–5

Objectives

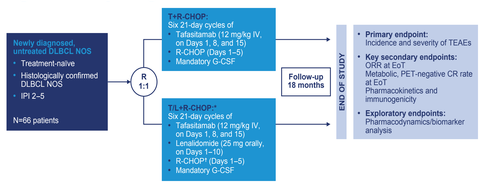
- To present the final safety analysis with ≥18 months' follow-up from the First-MIND study in all patients, and in patients treated with T/L+R-CHOP and an IPI score of 3–5
- To report the efficacy data of T/L+R-CHOP in all patients and the patient subgroup with an IPI score of 3–5
- To explore the value of minimal residual disease (MRD) data in 1L DLBCL treatment

Methods

Study design

- The First-MIND study comprises two treatment arms (**Figure 1**):
  - T+R-CHOP arm: tafasitamab (12 mg/kg intravenously [IV], Days 1, 8, and 15) + R-CHOP
  - T/L+R-CHOP: tafasitamab (12 mg/kg IV, Days 1, 8, and 15) + LEN (25 mg orally, Days 1–10) + R-CHOP

Figure 1. Study design



*In the lenalidomide arm, venous thromboembolism prophylaxis with either low-molecular weight heparins or aspirin is mandatory (according to institutional guidelines).

†Rituximab (375 mg/m²) and CHOP chemotherapy included cyclophosphamide (750 mg/m² IV), doxorubicin (50 mg/m² IV), and vincristine (1.4 mg/m² [maximum dose = 2 mg] IV) on Day 1 of every 21-day cycle and prednisone/prednisolone (100 mg/day PO) on Days 1 to 5. The Day 1 steroid dose being part of CHOP (100 mg prednisone/prednisolone, or equivalent, PO or IV) could be used as a further component of premedication prior to the tafasitamab infusion.

CR, complete response; DLBCL, diffuse large B-cell lymphoma; EoT, end of treatment; G-CSF, granulocyte colony stimulating factor; IPI, International Prognostic Index; IV, intravenous; L, lenalidomide; NOS, not otherwise specified; ORR, overall response rate; PET, positron emission tomography; PO, orally; R, randomized; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; T, tafasitamab; TEAEs, treatment-emergent adverse events.

Key eligibility criteria

- Eligible patients were ≥18 years, treatment-naïve, with histologically confirmed DLBCL NOS, IPI 2–5, Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2, and eligible for treatment with R-CHOP
- Patients were ineligible if they had known double- or triple-hit lymphoma, transformed non-Hodgkin's lymphoma, evidence of composite lymphoma, history of radiation therapy to ≥25% of the bone marrow for other diseases, history of anthracycline therapy, known central nervous system involvement, or active hepatitis B/C infection

Study endpoints

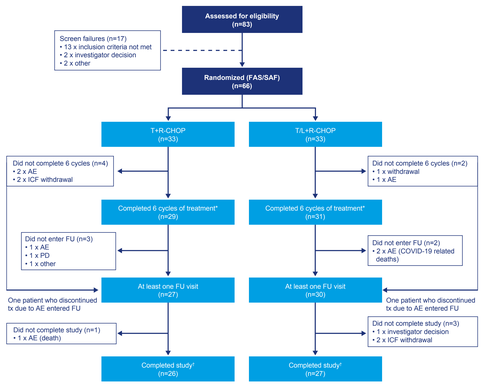
- The primary endpoint in First-MIND is incidence and severity of treatment-emergent adverse events (TEAEs)
- Secondary endpoints included overall response rate (ORR) and positron emission tomography (PET)-negative complete response (CR) rate at end of treatment (EoT)
  - Tumor measurements by PET/computed tomography or PET/magnetic resonance imaging at EoT were performed according to Lugano 2014 criteria[8]
  - MRD was assessed using immunoglobulin gene next-generation sequencing in cell-free DNA extracted from plasma

Results

Patient disposition and baseline demographics

- From December 2019 to August 2020, 83 patients across 54 sites (Europe and United States) were screened
- A total of 17 patients failed screening and 66 underwent randomization; 33 were allocated to each arm (**Figure 2**)

Figure 2. First-MIND patient disposition



Of note, also some patients with PD at EoT have entered the FU period.

*Completed treatment: patient completed treatment on at least one study drug in Cycle 6.

†Completed study: all FU visits completed

AE, adverse event; COVID-19, coronavirus disease 2019; EoT, end of treatment; FAS, full analysis set; FU, follow up; ICF, informed consent form; L, lenalidomide; PD, progressive disease; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; SAF, safety analysis set; T, tafasitamab; Tx, treatment.

- The final analysis was conducted on August 10, 2022, and included ≥18 months' follow-up after the EoT visit for all patients
- At the data cut-off, of the 66 patients randomized (T+R-CHOP, n=33; T/L+R-CHOP, n=33), a total of 60 patients (90.9%) had completed six cycles of treatment (T+R-CHOP, n=29; T/L+R-CHOP, n=31)
- Baseline characteristics were balanced between the treatment arms (**Table 1**)
- 60.6% of patients in T+R-CHOP and 66.7% in T/L+R-CHOP had an IPI score of 3–5; 94.0% and 87.9% had an ECOG PS of 0–1, respectively; and 93.9% of patients in both arms were Ann Arbor stage III/IV

Safety

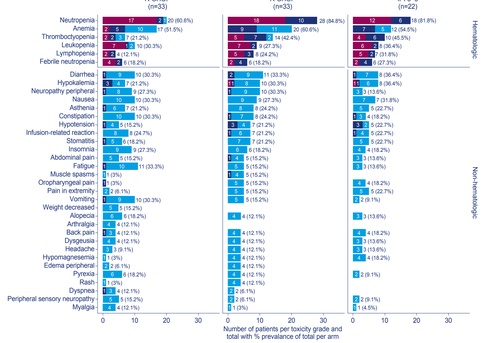
- In both treatment arms, the most common hematologic TEAEs were neutropenia, anemia, thrombocytopenia, and leukopenia (**Figure 3**); the most common non-hematologic TEAEs were fatigue, diarrhea, nausea, vomiting, constipation, peripheral neuropathy, and hypokalemia

Table 1. Patient baseline and disease characteristics

Characteristics, n (%)		T+R-CHOP (n=33)	T/L+R-CHOP (n=33)	T/L+R-CHOP IPI 3–5 (n=22)
Gender	Male/Female	15 (45.5)/ 18 (54.5)	13 (39.4)/ 20 (60.6)	10 (45.5)/ 12 (54.5)
Age (screening)	≤60 years/ >60 years	12 (36.4)/ 21 (63.6)	11 (33.3)/ 22 (66.7)	7 (31.8)/ 15 (68.2)
Race	White/Other/ Not reported	31 (93.9)/ 1 (3.0)/1 (3.0)	33 (100.0)/ 0/0	22 (100)
IPI score	2	13 (39.4)	11 (33.3)	–
	3	13 (39.4)	16 (48.5)	16 (72.7)
	4	7 (21.2)	4 (12.1)	4 (18.2)
	5	0	2 (6.1)	2 (9.1)
	3–5	20 (60.6)	22 (66.7)	22 (100)
ECOG PS	0	19 (57.6)	12 (36.4)	7 (31.8)
	1	12 (36.4)	17 (51.5)	12 (54.5)
	2	2 (6.1)	4 (12.1)	3 (13.6)
Cell of origin (assessed locally)	GCB	9 (27.3)	10 (30.3)	12 (54.5)
	Non-GCB	15 (45.5)	14 (42.4)	9 (40.9)
	Missing or not evaluable	9 (27.3)	9 (27.3)	1 (4.5)
Ann Arbor disease stage	I	2 (6.1)	1 (3.0)	–
	II	0	1 (3.0)	–
	III	8 (24.2)	7 (21.2)	3 (13.6)
	IV	23 (69.7)	24 (72.7)	19 (86.4)
	I & II	2 (6.1)	2 (6.1)	–
	III & IV	31 (93.9)	31 (93.9)	22 (100)

ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B-cell; IPI, International Prognostic Index; L, lenalidomide; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; T, tafasitamab.

Figure 3. Most frequent hematologic and non-hematologic TEAEs occurring in ≥10% of patients in either study arm



IPI, International Prognostic Index; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; TEAE, treatment-emergent adverse events.

- The frequency of Grade ≥3 TEAEs was 72.7% in the T+R-CHOP arm and 90.9% in the T/L+R-CHOP arm
- Any grade serious TEAEs categorized as infections and infestations were reported at an incidence of 18.2% (Grade 3, 18.2%) in the T+R-CHOP arm, 24.2% (Grade 3, 18.2%) in the T/L+R-CHOP arm, and 22.7% (Grade 3, 13.6%) in the T/L+R-CHOP IPI 3–5 cohort
- There were two Grade 5 events in the T+R-CHOP arm (urosepsis and sepsis) and one in the T/L+R-CHOP arm (COVID-19)

Efficacy

- ORR at EoT visit and best response across all visits were higher in the T/L+R-CHOP arm, as were 18-month duration of response (DoR), duration of complete response (DoCR), progression-free survival (PFS), and overall survival (OS) rates (**Table 2**)

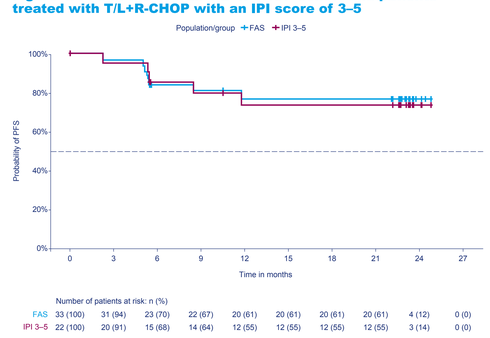
Table 2. First-MIND efficacy after ≥18 months' follow-up

Event	T+R-CHOP (n=33)	T/L+R-CHOP (n=33)	T/L+R-CHOP IPI 3–5 (n=22)
ORR, n (%) [95% CI]			
CR or PR (at EoT)	25 (75.8) [57.7, 88.9]	27 (81.8) [64.5, 93.0]	18 (81.8) [59.7, 94.8]
CR or PR (best response across all visits)	30 (90.9) [75.7, 98.1]	31 (93.9) [79.8, 99.3]	20 (90.9) [70.8, 98.9]
18-month DoR rate, % [95% CI]	72.7 [52.7, 85.3]	78.7 [58.5, 89.9]	76.6 [48.8, 90.5]
18-month DoCR rate, % [95% CI]	74.5 [53.8, 87.0]	86.5 [63.8, 95.5]	80.0 [50.0, 93.1]
24-month PFS rate, % [95% CI]	72.7 [52.7, 85.3]	76.8 [57.1, 88.3]	73.6 [47.3, 88.2]
24-month OS rate, % [95% CI]	90.3 [72.9, 96.8]	93.8 [77.3, 98.4]	95.2 [70.7, 99.3]

CI, confidence interval; CR, complete response; DoCR, duration of complete response; DoR, duration of response; EoT, end of treatment; IPI, International Prognostic Index; L, lenalidomide; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; T, tafasitamab.

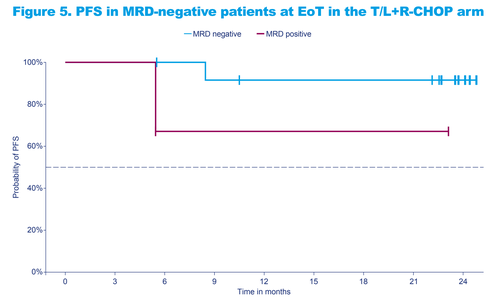
- In patients treated in the T/L+R-CHOP arm with an IPI score of 3–5 (n=22), ORR, 18-month DoR and DoCR and 24-month PFS and OS rates were comparable with the overall T/L+R-CHOP arm (**Table 2; Figure 4**)
- The 18-month PFS rate by MRD status at EoT in the T/L+R-CHOP arm was 92.3% in MRD-negative patients (n=12) and 66.6% in MRD-positive patients (n=3) (**Figure 5**)

Figure 4. PFS in the overall T/L+R-CHOP cohort and patients treated with T/L+R-CHOP with an IPI score of 3–5



FAS, full analysis set; IPI, International Prognostic Index; L, lenalidomide; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; T, tafasitamab.

Figure 5. PFS in MRD-negative patients at EoT in the T/L+R-CHOP arm



Tick marks denote censored patients. One MRD-negative patient relapsed with CNS progression only.

CNS, central nervous system; EoT, end of treatment; L, lenalidomide; MRD, minimal residual disease; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; T, tafasitamab.

Conclusions

- **The long-term safety profile of tafasitamab ± LEN when added to R-CHOP was manageable, showed no new safety signals to those reported previously, and does not impede the administration of R-CHOP**
- **The addition of LEN to T+R-CHOP appears to increase hematologic toxicity; however, the addition of tafasitamab to LEN+R-CHOP does not appear to increase toxicity compared with previous trials of LEN+R-CHOP[9,10]**
- **In treatment-naïve patients with DLBCL, the combination of T/L+R-CHOP achieved numerically higher clinical efficacy than adding tafasitamab alone**
- **Although the sample size is limited, patients with an IPI score of 3–5 treated with T/L+R-CHOP showed efficacy comparable to that of the overall treatment arm cohort**
- **Improved PFS was observed in MRD-negative patients compared with MRD-positive patients**
- **frontMIND will further evaluate T/L+R-CHOP in previously untreated patients with high-intermediate and high-risk (IPI score 3–5) DLBCL**

References

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas V.5.2022. ®National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed October 26, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **2.** Johnson NA, et al. Blood 2009;113(16):3773–80. **3.** Prevodnik VK, et al. Diagn Pathol 2011;6(1):33. **4.** Horton HM, et al. Cancer Res 2008;68(19):8049–57. **5.** MONJUVI. Prescribing information. Boston, MA: MorphoSys. 2020. https://www.monjuvi.com/pi/monjuvi-pi.pdf. Accessed April 2022. **6.** European Medicines Agency. Minjuvi. https://www.ema.europa.eu/en/medicines/human/EPAR/minjuvi. Accessed October 2021. **7.** Belada D, et al. Blood 2020;136(Supplement 1):3028. Presented at ASH 2021. **8.** Cheson BD, et al. J Clin Oncol 2014;32(27):3059–68. **9.** Nowakowski GS, et al. J Clin Oncol 2021;39(12):1329–38. **10.** Nowakowski GS, et al. J Clin Oncol 2021;39(12):1317–28.

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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 mechanisms including antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). In January 2020, MorphoSys and Incyte entered into a collaboration and licensing agreement to further develop and commercialize tafasitamab globally. Following accelerated approval by the U.S. Food and Drug Administration in July 2020, tafasitamab is being co-commercialized by MorphoSys and Incyte in the United States. 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

GSN: Consultancy, grants and non-financial support during the conduct of the study and research funding: MorphoSys AG; consultancy, grants and other support and research funding: Bristol Myers Squibb/Celgene, Roche; consultancy: Fate Therapeutics, Incyte, TG Therapeutics, Karyopharm, Ryvu, Kymera, Zai, Kite Pharma, Bantam Pharmaceutical, Selvita, Debiopharm, Genentech, MEI Pharma, Curis, ADC Therapeutics, Seagen; consultancy and other support: AbbVie; other support: Kyte, Genmab, Blueprint Medicines, Daiichi Sankyo. **JD:** Consultancy: Incyte; consultancy and research funding: MorphoSys AG; research funding: Regeneron. **KK:** Honoraria: Novartis; stocks: Laboratories Pierre Fabre. **MT:** Consultancy, honoraria and research funding: Takeda, Hoffman-La Roche, Novartis; consultancy and honoraria: Bristol Myers Squibb, Incyte, AbbVie, Amgen, Gilead Sciences, Janssen, MorphoSys AG, Zentiva. **CP:** Research funding: MorphoSys AG, Roche; consultancy: Roche, Lilly, Novartis, Gilead, Janssen. **MK:** no disclosures. **JMB:** Consultancy: AbbVie, Adaptive Biotechnologies, AstraZeneca, BeiGene, Bristol Myers Squibb, Epizyme, Kura, Kymera, MorphoSys AG, Nurix, Roche/Genentech, Seagen, TG Therapeutics; speaker's bureau: BeiGene, Seagen; research funding: MorphoSys AG. **MWL:** Employment: MorphoSys, US, Inc., Novartis AG; stocks: Novartis AG (immediate family member). **SW:** Employment, stocks and travel expenses: MorphoSys, AG. **AM:** Employment: MorphoSys, AG. **DB:** Employment: MorphoSys AG; stocks: Bristol Myers Squibb. **DBe:** Consultancy: Gilead Sciences, Janssen-Cilag, Roche, Takeda, MorphoSys AG, Debiopharm Group; research funding: Roche, Gilead Sciences, Janssen-Cilag, Takeda, MorphoSys AG, Pharmacyclics, Archiden Biotech, Reddy; travel expenses: Gilead Sciences, Roche, Takeda.

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