Pharmacokinetics and pharmacodynamics in First-MIND: A Phase Ib, open-label, randomized study of tafasitamab ± lenalidomide + R-CHOP in patients with newly diagnosed diffuse large B-cell lymphoma

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Background

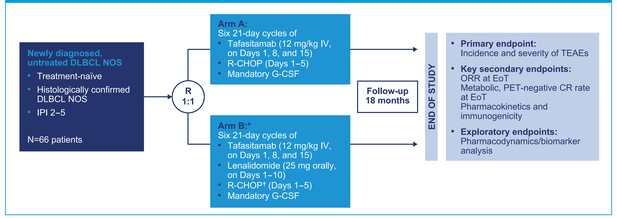
- First-line (1L) standard of care for diffuse large B-cell lymphoma (DLBCL) comprises six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy[1]
  - Approximately 15–20% of treatment-naïve patients with DLBCL have low CD20-expressing tumors, which are 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, a humanized, Fc-modified, anti-CD19 monoclonal antibody, in combination with lenalidomide, 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 the treatment of adult patients with relapsed or refractory (R/R) DLBCL not otherwise specified, including DLBCL arising from low-grade lymphoma, who are ineligible for autologous stem cell transplant, and is a preferred treatment option in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) in this setting[1]
- First-MIND (NCT04134936) is a Phase Ib, open-label, randomized study of R-CHOP + tafasitamab ± lenalidomide in patients with newly diagnosed intermediate- to high-risk (International Prognostic Index score [IPI] 2–5) DLBCL not otherwise specified
  - Previously reported data show a tolerable safety profile for the addition of tafasitamab ± lenalidomide to R-CHOP, and that the addition of tafasitamab + lenalidomide does not impair dosing and scheduling of R-CHOP, as indicated by the consistent median average relative dose intensity of R-CHOP in both arms[7]
  - Toxicities were similar to those expected with R-CHOP alone and in combination with lenalidomide[7]
  - The objective response rate (ORR) at end of treatment (EoT) suggests that patients with treatment-naïve DLBCL may achieve clinically meaningful efficacy with tafasitamab and lenalidomide in addition to R-CHOP[7]
- An assessment of the pharmacokinetic (PK) and pharmacodynamic (PD) profile for tafasitamab and its potential immunogenicity may provide insight into patient response to treatment
- B-cell depletion with anti-CD20 immunosuppressive monoclonal antibodies such as rituximab has been associated with impaired humoral response to infection and vaccination[8–11]
  - Recovery of B-cell count post-treatment may support return of immune system function against infection, long-term immunity, and vaccination response[12]
- Here, we report assessments of PK, PD, immunogenicity, and hematologic biomarkers in patients from the First-MIND study

Methods

Study design

- The First-MIND study comprises two treatment arms (**Figure 1**)
  - Arm A: R-CHOP + tafasitamab
  - Arm B: R-CHOP + tafasitamab + lenalidomide

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 counted 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; NOS, not otherwise specified; ORR, overall response rate; PET, positron emission tomography; PO, orally; R, randomized; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; TEAEs, treatment-emergent adverse events.

Key eligibility criteria

- Eligible patients were ≥18 years, treatment-naïve, with histologically confirmed DLBCL not otherwise specified, 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 is incidence and severity of treatment-emergent adverse events
- Key secondary endpoints include assessment of efficacy, PK, immunogenicity, and exploratory assessment of biomarkers and PD

PK, immunogenicity, and PD

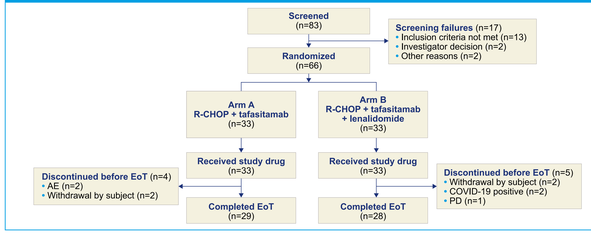
- Patients with at least one quantifiable tafasitamab serum concentration were included in the PK analysis
- Tafasitamab serum concentrations were evaluated pre- and post-dose on every first day of each cycle as well as on the EoT visit, and in the follow-up period 3 months (FU1) and 6 months (FU2) after EoT
- The formation of anti-tafasitamab antibodies was assessed pre-dose on every first day of each cycle and at the EoT, FU1 and FU2 visits, with all patients with at least one anti-tafasitamab antibody assessment evaluated for immunogenicity
- Blood and tumor samples were collected before treatment, and blood samples were collected throughout the study for assessment of exploratory biomarkers, including B-, T- and natural killer (NK) cell counts in peripheral blood
- Flow cytometry assessment was performed at Cycle (C)1 Day (D)1, 8, 15; C2 D1; C4 D1; and at the EoT and FU2 visits
- Immunoglobulin (Ig) levels (for IgA, IgG, and IgM) were assessed at C1 D1, C4 D1; and at the EoT, FU1 and FU2 visits, and the 9 months' follow-up after EoT visit (FU3)

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 were excluded and 66 underwent randomization; 33 were allocated to each arm (**Figure 2**)
- The data cut-off was March 13, 2021 for the safety, PK, immunogenicity, and Ig data analyses, including ≥1 month follow-up after the EoT visit, and August 31, 2021 for the PD analysis

Figure 2. First-MIND patient disposition



AE, adverse event; EoT, end of treatment; PD, progressive disease; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

- Baseline characteristics were balanced between the treatment arms (**Table 1**)
- Median age was 64.5 years (range, 20–86 years)
- Overall, 50% (33/66) of patients were ≥65 years and many had high-risk disease: 63.6% with IPI >2, 43.9% had bulky disease, and 71.2% had Ann Arbor Stage IV disease

Table 1. Patient baseline and disease characteristics

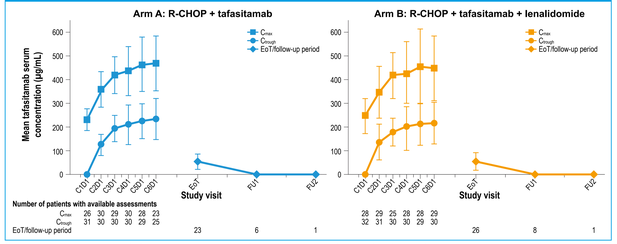
Characteristic	Arm A R-CHOP + tafasitamab (n=33)	Arm B R-CHOP + tafasitamab + lenalidomide (n=33)	Overall (n=66)
Median age, years (range)	66.0 (43–86)	64.0 (20–79)	64.5 (20–86)
Age at index date (years), n (%)			
<65	16 (48.5)	17 (51.5)	33 (50.0)
≥65	17 (51.5)	16 (48.5)	33 (50.0)
Sex, n (%)			
Male	15 (45.5)	13 (39.4)	28 (42.4)
Female	18 (54.5)	20 (60.6)	38 (57.6)
Race, n (%)			
White	31 (93.9)	33 (100.0)	64 (97.0)
Others	1 (3.0)	0	1 (1.5)
Missing	1 (3.0)	0	1 (1.5)
Ann Arbor disease stage, n (%)			
I	2 (6.1)	1 (3.0)	3 (4.5)
II	0	1 (3.0)	1 (1.5)
III	8 (24.2)	7 (21.2)	15 (22.7)
IV	23 (69.7)	24 (72.7)	47 (71.2)
IPI risk score, n (%)			
2	13 (39.4)	11 (33.3)	24 (36.4)
3	13 (39.4)	16 (48.5)	29 (43.9)
4	7 (21.2)	4 (12.1)	11 (16.7)
5	0	2 (6.1)	2 (3.0)
ECOG PS, n (%)			
0	19 (57.6)	12 (36.4)	31 (47.0)
1	12 (36.4)	17 (51.5)	29 (43.9)
2	2 (6.1)	4 (12.1)	6 (9.1)
Pre-planned radiotherapy, n (%)			
Yes	4 (12.1)	3 (9.1)	7 (10.6)
Pre-planned intrathecal chemotherapy, n (%)			
Yes	7 (21.2)	4 (12.1)	11 (16.7)
Elevated LDH levels, n (%)			
Yes	23 (69.7)	24 (72.7)	47 (71.2)
Stage III/IV disease, n (%)			
Yes	31 (93.9)	31 (93.9)	62 (93.9)
Bulky disease, n (%)			
Yes	14 (42.4)	15 (45.5)	29 (43.9)
Cell of origin,* n (%)			
GCB	18 (54.5)	19 (57.6)	37 (56.1)
Non-GCB	12 (36.4)	12 (36.4)	24 (36.4)
Missing	1 (3.0)	2 (6.1)	3 (4.5)

*Assessed locally using IHC-Hans algorithm. IHC, immunohistochemistry; IPI, International Prognostic Index; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B-cell; LDH, lactate dehydrogenase; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Pharmacokinetics and immunogenicity

- Tafasitamab serum concentrations achieved steady state by C3 and declined after treatment completion, reaching levels close to or below the lower level of quantification (50 ng/mL) by FU2 (**Figure 3**)
  - Tafasitamab serum concentrations were comparable between both treatment groups, with arithmetic mean C_{trough} concentrations between C3 and C6 ranging from 194.59–234.20 µg/mL in Arm A and 180.02–217.84 µg/mL in Arm B
- Anti-tafasitamab antibodies were detected in 1/65 (1.5%) patients (**Table 2**)
  - This patient was part of the R-CHOP + tafasitamab arm (Arm A) and showed pre-existing anti-tafasitamab antibodies at baseline, which decreased during treatment
  - The presence of these anti-tafasitamab antibodies had no impact on tafasitamab PK or showed any direct effects on the patient's safety and efficacy results

Figure 3. Tafasitamab mean serum concentration



Mean values ± standard deviation are shown for C_{trough} (samples collected pre-dose) and C_{max} (samples collected 1 hour after the end of the tafasitamab infusion).
C, cycle; C_{max}, maximum concentration; C_{trough}, trough concentration; D, day; EoT, end of treatment; FU, follow-up; R-CHOP, rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone.

Table 2. Patients with anti-tafasitamab antibodies

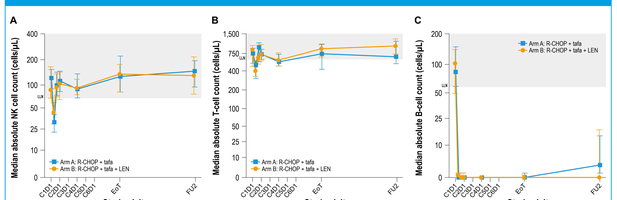
Anti-tafasitamab antibodies	Arm A R-CHOP + tafasitamab (n=32)	Arm B R-CHOP + tafasitamab + lenalidomide (n=33)
Pre-existing anti-tafasitamab antibodies, n (%)	1/32 (3.1)	0/33
No anti-tafasitamab antibodies after start of treatment, n (%)	30/31 (96.8)	31/31 (100.0)
Anti-tafasitamab antibodies after start of treatment, n (%)	1/31 (3.2)	0/31
Treatment-induced anti-tafasitamab antibodies, n (%)	0/31	0/31
Treatment-boosted anti-tafasitamab antibodies, n (%)	0/31	0/31

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Pharmacodynamics

- Median NK cell counts decreased from baseline at C1 D8, but were at baseline or higher levels by EoT visit (Arm A) and C1 D15 (Arm B) and sustained thereafter (**Figure 4A**)
- T-cell counts decreased from baseline at C1 D8 in both arms, but were at baseline level or higher by C1 D15 (Arm A) and EoT visit (Arm B) and sustained thereafter (**Figure 4B**)
- Median B-cell counts decreased from baseline to 0 cells/µL (Arm A, C1 D15; Arm B, C1 D8); at 6 months' follow-up after EoT visit (FU2), B-cell counts had recovered to measurable levels in ~50% of patients (**Figure 4C**)

Figure 4. Absolute cell count for (A) NK cells, (B) T cells, (C) B cells (error bars indicate 95% CI)

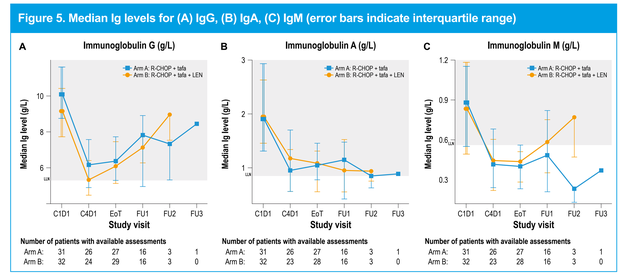


Normal range in healthy adults in selected countries (2.5–97.5%): NK cells, 70–801 cells/µL; CD3+ T-cells, 683–2,904 cells/µL; CD19+ B-cells, 57–1,491 cells/µL.[13]
C, cycle; CI, confidence interval; D, day; EoT, end of treatment; FU, follow-up; LEN, lenalidomide; NK, natural killer; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; tafa, tafasitamab.

Change in Ig levels

- Decreases from baseline in IgA, IgG, and IgM were reported in both arms at EoT (**Figure 5**)
  - A return toward baseline was observed in both treatment arms from C4 D1 for IgG (**Figure 5A**) and in Arm B (R-CHOP + tafasitamab + lenalidomide) from EoT for IgM (**Figure 5C**)

Figure 5. Median Ig levels for (A) IgG, (B) IgA, (C) IgM (error bars indicate interquartile range)



Normal range in healthy adults: IgG, 5.65–17.65 g/L; IgA, 0.85–3.85 g/L; IgM, 0.55–3.75 g/L.[13]
C, cycle; D, day; EoT, end of treatment; FU, follow-up; Ig, immunoglobulin; LEN, lenalidomide; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; tafa, tafasitamab.

Conclusions

- Tafasitamab serum concentration reached and maintained a therapeutic dose level during treatment and declined in line with known tafasitamab half-life (~16 days) after treatment completion
- None of the patients (n=65) developed treatment-induced or treatment-boosted anti-tafasitamab antibodies
- The combination of R-CHOP + tafasitamab + lenalidomide is being further investigated in previously untreated patients with high-intermediate and high-risk DLBCL (frontMIND; NCT04824092)

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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

DB: consultancy: Gilead Sciences, Janssen-Cilag, Roche, Takeda, MorphoSys AG, Debiopharm Group; research institution funding: Roche, Gilead Sciences, Janssen-Cilag, Takeda, MorphoSys AG, Pharmacyclics, Archiden Biotech, Reddy; travel expenses: Gilead Sciences, Roche, Takeda. **KK:** stocks: Viatris; consultancy: Pierre Fabre; travel expenses: Bayer. **JMB:** no disclosures. **DS:** no disclosures. **GN:** consultancy fees: Celgene, MorphoSys AG, Genentech, Selvita, Debiopharm Group, Kite/Gilead; research institution funding: Celgene, MorphoSys AG, NanoString Technologies. **MW-L:** employment: MorphoSys US, Inc.; Novartis; stocks: Novartis. **NH:** employment: MorphoSys US, Inc. **AM:** employment: MorphoSys AG. **CL:** employment: MorphoSys AG. **DBl:** employment: MorphoSys AG; stocks: BMS. **MD:** research support (institution): AbbVie, Bayer, BMS/Celgene, Gilead/Kite, Janssen, Roche; honoraria: Amgen, AstraZeneca, Bayer, BMS/Celgene, Gilead/Kite, Incyte, Janssen, Novartis, Roche; advisory board: AstraZeneca, Bayer, BeiGene, BMS/Celgene, Genmab, Gilead/Kite, Incyte, Janssen, Lilly/Loxo, MorphoSys AG, Novartis, Roche.

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