First-MIND: 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

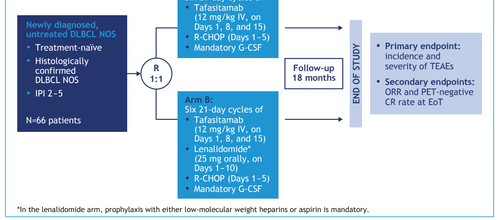
- First-line standard-of-care for diffuse large B-cell lymphoma (DLBCL) comprises six cycles of rituximab, cyclophosphamide, doxorubicin, prednisone, and vincristine (R-CHOP) chemotherapy[1]
- Approximately 15–20% of treatment-naïve patients with DLBCL have low CD20 expressing tumors, which are associated 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 enhances antibody dependent cellular cytotoxicity and phagocytosis[5]
- Tafasitamab in combination with lenalidomide is United States Food and Drug Administration-approved under accelerated approval for the treatment of adult patients with relapsed or refractory DLBCL not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant
- First-MIND (NCT04134936) is a Phase Ib, open label, randomized study of tafasitamab or tafasitamab + lenalidomide alongside R-CHOP in patients with newly diagnosed DLBCL not otherwise specified
- Enrollment is completed and the study is ongoing. We report here preliminary safety and efficacy data based on an interim snapshot (data cut-off: 22 March 2021). Primary completion data will be presented at a scientific conference in Q4 2021

Methods

Study design

- The study consists of two treatment arms (**Figure 1**)
  - Arm A: R-CHOP + tafasitamab (12 mg/kg intravenously [IV], Day [D] 1, 8, and 15)
  - Arm B: R-CHOP + tafasitamab (12 mg/kg IV, D1, 8, and 15) + lenalidomide (25 mg orally, D1–10)
  - Granulocyte-colony stimulating factor prophylaxis was mandatory in both arms and venous thromboembolism prophylaxis mandatory only in Arm B, according to the institutional guidelines

Figure 1. Study design



*In the lenalidomide arm, prophylaxis with either low-molecular weight heparins or aspirin is mandatory.

CR, complete response; EoT, end of treatment; DLBCL, diffuse large B-cell lymphoma; G-CSF, granulocyte-colony stimulating factor; IPI, international prognostic index; IV, intravenous; NOS, not otherwise specified; ORR, objective response rate; PET, positron emission tomography; R, randomized; R-CHOP, rituximab, cyclophosphamide, doxorubicin, prednisone, and vincristine; TEAEs, treatment-emergent adverse events.

Key eligibility criteria

- Eligible patients were ≥18 years, treatment-naïve, with histologically confirmed DLBCL not otherwise specified, international prognostic index (IPI) 2–5, Eastern Cooperative Oncology Group (ECOG) performance status (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

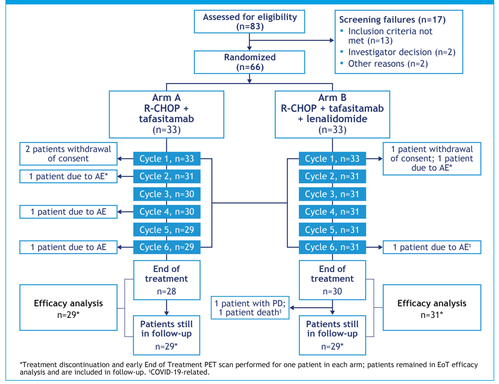
Study endpoints

- The primary endpoint is safety
- Key secondary endpoints include objective response rate (ORR) by independent review committee and PET-negative complete response (CR) rate at the end of treatment (EoT)

Results

- From December 2019 to August 2020, 83 patients across 34 sites (Europe and US) were screened. A total of 66 underwent randomization; 33 were allocated to each arm (**Figure 2**)

Figure 2. FIRST-MIND patient disposition



*Treatment discontinuation and early End of Treatment PET scan performed for one patient in each arm; patients remained in EoT efficacy analysis and are included in follow-up. †COVID-19-related.

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

Table 1. Baseline characteristics

Characteristics		Arm A R-CHOP + tafasitamab (n=33)	Arm B R-CHOP + tafasitamab + lenalidomide (n=33)	Overall (N=66)
Age (years)	Median (min,max)	66.0 (43,86)	64.0 (20,79)	64.5 (20,86)
Age categories (years) n (%)	<60	12 (36.4)	11 (33.3)	23 (34.8)
	≥60	21 (63.6)	22 (66.7)	43 (65.2)
Sex, n (%)	Male	15 (45.5)	13 (39.4)	28 (42.4)
	Female	18 (54.5)	20 (60.6)	38 (57.6)
Ann Arbor disease stage, n (%)	Stage I	2 (6.1)	1 (3.0)	3 (4.5)
	Stage II	0	1 (3.0)	1 (1.5)
	Stage III	7 (21.2)	7 (21.2)	14 (21.2)
	Stage IV	23 (69.7)	24 (72.7)	47 (71.2)
	Missing	1 (3.0)	0	1 (1.5)
IPI risk score, n (%)	IPI 2	11 (33.3)	9 (27.3)	20 (30.3)
	IPI 3	14 (42.4)	15 (45.5)	29 (43.9)
	IPI 4	8 (24.2)	8 (24.2)	16 (24.2)
	IPI 5	0	1 (3.0)	1 (1.5)
Bulky disease, n (%)	Present	14 (42.4)	15 (45.5)	29 (43.9)
	Absent	19 (57.6)	18 (54.5)	37 (56.1)
ECOG PS at baseline, n (%)	ECOG 0	20 (60.6)	11 (33.3)	31 (47.0)
	ECOG 1	10 (30.3)	19 (57.6)	29 (43.9)
	ECOG 2	3 (9.1)	3 (9.1)	6 (9.1)
Reference diagnosis DLBCL (central pathology review), n (%)	DLBCL	30 (90.9)	30 (90.9)	60 (90.9)
	Other	1 (3.0)	3 (9.1)	4 (6.1)
	Missing	2 (6.1)	0	2 (3.0)

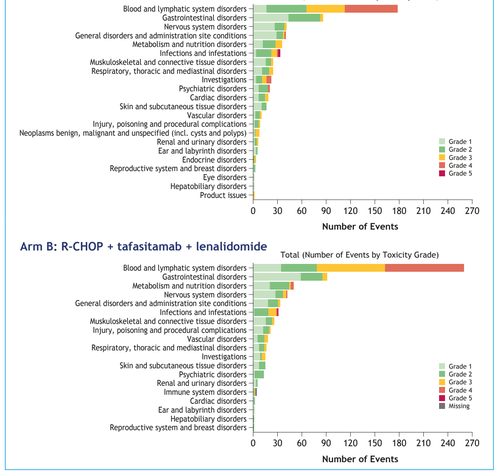
CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, international prognostic index; IV, intravenous; NOS, not otherwise specified; R-CHOP, rituximab, cyclophosphamide, doxorubicin, prednisone, and vincristine.

- Baseline characteristics were balanced between the treatment arms, with a slight imbalance of ECOG PS 0 and 1 between arm A and B (**Table 1**)
- Median age was 64.5 years (range 20–86)
- Overall, 65.2% (43/66) of patients were ≥60 years and many had high-risk disease: 30.3% with IPI 2 and 69.7% with IPI ≥3; ECOG PS: 47.0% of patients had ECOG PS 0, 43.9% PS 1, and 9.1% PS 2
- Most patients had Stage III/IV disease (92%) and 44% had bulky disease

Safety

- The most frequent treatment-emergent adverse events (TEAEs) by system organ class were blood and lymphatic system disorders (90.0% of patients overall), experienced by 29 patients in arm A (87.9%) and 31 patients in arm B (93.9%)
  - More events occurred in arm B than in arm A, with a higher incidence of Grade ≥3 events in arm B vs arm A (**Figure 3**)
- The time course of median absolute platelet count and median neutrophil count were similar in both treatment arms (**Figure 4**), with a higher incidence of Grade ≥3 neutropenia and thrombocytopenia in arm B (**Table 2**)
- The frequency of febrile neutropenia was comparable in both treatment arms (18.2%; **Table 2**)
- Overall, 6 patients received platelet transfusions; 3 patients in each arm

Figure 3. TEAEs by system organ class and toxicity grade



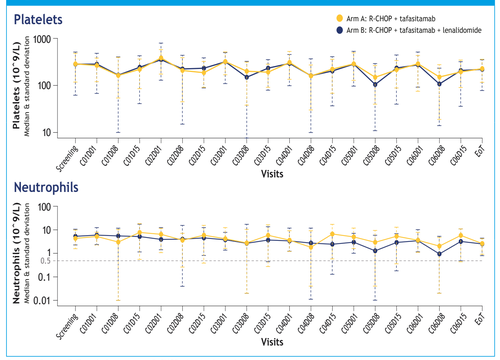
R-CHOP, rituximab, cyclophosphamide, doxorubicin, prednisone, and vincristine; TEAEs, treatment-emergent adverse events.

Table 2. Most frequently occurring hematologic TEAEs (≥10% of patients)

Hematologic TEAEs, n (%)	Arm A R-CHOP + tafasitamab (n=33) Any Grade	Arm A R-CHOP + tafasitamab (n=33) Grade ≥3	Arm B R-CHOP + tafasitamab + lenalidomide (n=33) Any Grade	Arm B R-CHOP + tafasitamab + lenalidomide (n=33) Grade ≥3	Total (n=66) Any Grade	Total (n=66) Grade ≥3
Neutropenia	20 (60.6)	19 (57.6)	28 (84.8)	28 (84.8)	48 (72.7)	47 (71.2)
Anemia	18 (54.5)	7 (21.2)	20 (60.6)	9 (27.3)	38 (57.6)	16 (24.2)
Thrombocytopenia	6 (18.2)	3 (9.1)	13 (39.4)	11 (33.3)	19 (28.8)	14 (21.2)
Leukopenia	9 (27.3)	6 (18.2)	9 (27.3)	9 (27.3)	18 (27.3)	15 (22.7)
Febrile neutropenia	6 (18.2)	6 (18.2)	6 (18.2)	6 (18.2)	12 (18.2)	12 (18.2)
Lymphopenia	4 (12.1)	4 (12.1)	7 (21.2)	7 (21.2)	11 (16.7)	11 (16.7)

R-CHOP, rituximab, cyclophosphamide, doxorubicin, prednisone, and vincristine; TEAEs, treatment-emergent adverse events.

Figure 4: Platelet and absolute neutrophil counts by cycle



C, cycle; D, day; EoT, end of treatment; R-CHOP, rituximab, cyclophosphamide, doxorubicin, prednisone, and vincristine.

- The most frequently reported non-hematologic events are summarized in **Table 3**

Table 3. Most frequently occurring non-hematologic TEAEs (≥10% of patients)

Non-hematologic TEAEs, n (%)	Arm A R-CHOP + tafasitamab (n=33) Any Grade	Arm A R-CHOP + tafasitamab (n=33) Grade ≥3	Arm B R-CHOP + tafasitamab + lenalidomide (n=33) Any Grade	Arm B R-CHOP + tafasitamab + lenalidomide (n=33) Grade ≥3	Total (n=66) Any Grade	Total (n=66) Grade ≥3
Diarrhea	9 (27.3)	1(3.0)	11 (33.3)	2 (6.1)	20 (30.3)	3 (4.5)
Hypokalemia	7 (21.2)	3 (9.1)	11 (33.3)	2 (6.1)	18 (27.3)	5 (7.6)
Nausea	10 (30.3)	0	7 (21.2)	0	17 (25.8)	0
Peripheral neuropathy	6 (18.2)	0	10 (30.3)	1 (3.0)	16 (24.2)	1 (1.5)
Vomiting	11 (33.3)	1 (3.0)	5 (15.2)	0	16 (24.2)	1 (1.5)
Constipation	8 (24.2)	0	8 (24.2)	1 (3.0)	16 (24.2)	1 (1.5)
Asthenia	7 (21.2)	1 (3.0)	8 (24.2)	0	15 (22.7)	1 (1.5)
Fatigue	9 (27.3)	1 (3.0)	5 (15.2)	0	14 (21.2)	1 (1.5)
Insomnia	9 (27.3)	0	5 (15.2)	0	14 (21.2)	0
Stomatitis	6 (18.2)	1 (3.0)	7 (21.2)	0	13 (19.7)	1 (1.5)
Hypotension	5 (15.2)	1 (3.0)	7 (21.2)	3 (9.1)	12 (18.2)	4 (6.1)
Infusion related reaction	6 (18.2)	0	6 (18.2)	1 (3.0)	12 (18.2)	1 (1.5)
Pyrexia	7 (21.2)	0	4 (12.1)	0	11 (16.7)	0
Abdominal pain	5 (15.2)	0	5 (15.2)	1 (3.0)	10 (15.2)	1 (1.5)
Pain in extremity	3 (9.1)	0	5 (15.2)	0	8 (12.1)	0
Dysgeusia	4 (12.1)	0	3 (9.1)	0	7 (10.6)	0
Headache	3 (9.1)	0	4 (12.1)	0	7 (10.6)	0
Alopecia	5 (15.2)	0	2 (6.1)	0	7 (10.6)	0

R-CHOP, rituximab, cyclophosphamide, doxorubicin, prednisone, and vincristine; TEAE, treatment-emergent adverse event.

- Serious TEAEs occurred in 42.4% (arm A) and 51.5% (arm B) of patients
- There were three TEAEs with fatal outcome, none of which were related to tafasitamab and/or lenalidomide; two in arm A (sepsis, urosepsis) and one in arm B (COVID-19 pneumonia)

Dosing

- The median average relative dose intensity (ARDI) of R-CHOP remained unchanged during the six treatment cycles, with a median ARDI of 100% in both arms
- Some of the patients in each cycle experienced treatment delay for each cycle (**Table 4**)

Table 4. Number (%) of patients with a treatment cycle delay

Cycle number	Arm A R-CHOP + tafasitamab (n=33)	Arm B R CHOP + tafasitamab + lenalidomide (n=33)	Total (n=66)
Cycle 2	4 (12.1)	2 (6.1)	6 (9.1)
Cycle 3	1 (3.0)	0	1 (1.5)
Cycle 4	4 (12.1)	2 (6.1)	6 (9.1)
Cycle 5	1 (3.0)	3 (9.1)	4 (6.1)
Cycle 6	1 (3.0)	3 (9.1)	4 (6.1)

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

Preliminary efficacy (response assessment at EoT)

- For the 60 patients with a tumor assessment at EoT across both arms combined, the ORR was 83.3% (50/60; 95% confidence interval [CI], 71.5–91.7) and the CR rate was 75.0% (45/60; 95% CI, 62.1–85.3)

Conclusions

- This ongoing study suggests that the addition of tafasitamab or tafasitamab + lenalidomide to R-CHOP is tolerable in patients with newly diagnosed DLBCL
- As of data cut-off, there were no unexpected toxicities or new safety signals
- Grade 3 or higher neutropenia and thrombocytopenia events were more frequent in arm B than arm A but rates of febrile neutropenia were similar between the arms
- The incidence of other TEAEs was comparable between the two treatment arms; safety profiles were as expected for R-CHOP alone[7] or in combination with lenalidomide (R2-CHOP)[8,9]
- The relative dose intensity and scheduling of R-CHOP was unaffected by the addition of tafasitamab (arm A) or tafasitamab and lenalidomide (arm B)
- At EoT, ORR for evaluable patients (both arms combined) was 83.3% and the CR rate was 75.0% (efficacy analysis set)
- The combination of R-CHOP + tafasitamab + lenalidomide is being further investigated in previously untreated patients with high-intermediate and high-risk DLBCL (Phase III randomized, double-blind study; 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 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. XmAb® is a trademark of Xencor, Inc.

DB: consultancy fees from: Gilead Sciences, Janssen-Cilag, Roche, Takeda, MorphoSys AG, Debiopharm Group; research institution funding from: Roche, Gilead Sciences, Janssen-Cilag, Takeda, MorphoSys AG, Pharmacyclics, Archiden Biotech, Reddy; Travel expenses from: Gilead Sciences, Roche, Takeda. **KK:** no disclosures. **JMB:** no disclosures. **MA:** no disclosures. **EPP:** consultancy fees from: Celgene/Bristol Myers Squibb, Amgen, Janssen-Cilag, GlaxoSmithKline; speaker fees from: Roche, Celgene/Bristol Myers Squibb, Amgen, Janssen-Cilag, AbbVie, Takeda, Sanofi; travel expenses from: Roche, Celgene/Bristol Myers Squibb, Janssen-Cilag, AbbVie, Jazz Pharmaceuticals, Amgen. **PP:** no disclosures. **PK:** employee of MorphoSys AG. **BB:** employee of MorphoSys AG. **EL:** employee of MorphoSys AG. **AL:** employee of MorphoSys AG. **NS:** employee of MorphoSys AG. **WB:** employee of MorphoSys AG. **JB:** consultancy fees from: Genentech/Roche, AbbVie, Seattle Genetics, Bayer, AstraZeneca, Adaptive Biotechnologies, Verastem, MorphoSys AG, Kura Oncology, Epizyme, BeiGene, Kymera; speaker fees from: Seattle Genetics, BeiGene. **GN:** consultancy fees from: Celgene, MorphoSys AG, Genentech, Selvita, Debiopharm Group, Kite/Gilead; research institution funding from: Celgene, MorphoSys, NanoString Technologies.

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