frontMIND: A Phase III, randomized, double-blind study of tafasitamab + lenalidomide + R-CHOP vs R-CHOP alone for newly diagnosed high-intermediate and high-risk diffuse large B-cell lymphoma

Umberto Vitolo[1], Grzegorz S. Nowakowski[2], John M. Burke[3], Christopher P. Fox[4], Marek Trneny[5], Annalisa Chiappella[6], Maeve Waldron-Lynch[7], Nira Hadar[7], Alok Pachori[7], Georg Lenz[8]

[1]Candiolo Cancer Institute, FPO-IRCCS, Candiolo (Torino), Italy; [2]Division of Hematology, Mayo Clinic, Rochester, MN, USA; [3]Department of Hematology, US Oncology Research and Rocky Mountain Cancer Centers, Aurora, CO, USA; [4]Department of Clinical Hematology, Nottingham University Hospitals NHS, Nottingham, UK; [5]1st Department of Medicine, First Medical Faculty, Charles University and General University Hospital, Prague, Czech Republic; [6]Division of Hematology & Stem Cell Transplant, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy; [7]MorphoSys US, Boston, MA, USA; [8]Department of Medicine A – Haematology and Oncology, University Hospital Münster, Münster, Germany

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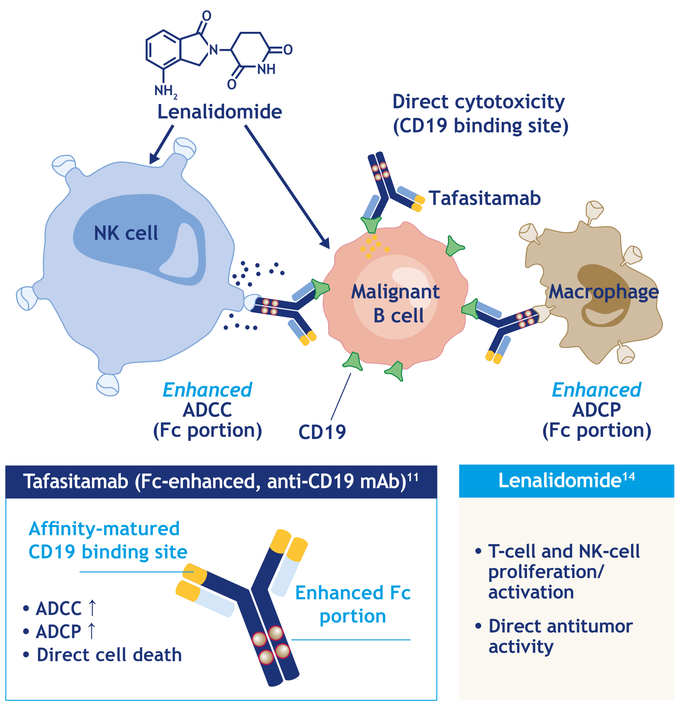
Background

- The chemoimmunotherapy R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) is first-line standard-of-care (SoC) for patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL)[1,2]
  - While curative in 60–70% of patients, 30–40% experience a relapsed/refractory (R/R) disease course,[2,3] whilst for patients with high-risk DLBCL (International Prognostic Index 3–5) 5-year overall survival (OS) is 32%[4]
- There remains an unmet need to improve the efficacy of R-CHOP despite numerous investigations over the past two decades[2]
  - Substitution of polatuzumab vedotin for vincristine in the R-CHOP regimen (pola-R-CHP; POLARIX) was associated with a modest improvement in progression-free survival (PFS) but no OS benefit[5]
  - Co-administration of lenalidomide with R-CHOP improved both PFS and OS in the ECOG-ACRIN E1412 trial.[6] The Phase III ROBUST study, in which a lower dose of lenalidomide was used, did not meet the primary end point of PFS in all patients but showed a positive trend toward 2-year PFS in a subgroup analysis[7]
- Tafasitamab, a humanized, Fc-modified, anti-CD19 monoclonal antibody, in combination with lenalidomide has been granted accelerated approval in the United States (July 2020)[8] and conditional marketing authorization in Europe and Canada (August 2021)[9,10] for treatment of R/R DLBCL in adult patients ineligible for autologous stem cell transplant (ASCT)
  - The combination, with a potentially synergistic mode of action (**Figure 1**), is a preferred regimen in the NCCN guidelines for ASCT-ineligible patients with R/R DLBCL[1,11]
  - This chemo-free immunotherapy demonstrated efficacy in the single-arm, Phase II L-MIND study (NCT02399085), with outcomes sustained at ≥35 months' follow-up (overall response rate: 57.5% [46/80 patients]; median duration of response: 43.9 months; median OS: 33.5 months)[12]
- In the context of improved outcomes observed with R-CHOP + lenalidomide for patients with treatment-naïve DLBCL in the ECOG-ACRIN E1412 trial[6] and the efficacy of the tafasitamab + lenalidomide combination for R/R DLBCL,[12] the addition of tafasitamab + lenalidomide to R-CHOP represents a novel approach that may improve outcomes for patients with newly diagnosed DLBCL
- The primary analysis of the Phase Ib First-MIND study (NCT04134936) demonstrated that the addition of tafasitamab ± lenalidomide to first-line SoC does not impair dosing and scheduling of R-CHOP in patients with previously untreated and newly diagnosed DLBCL, with toxicities similar to those expected with R-CHOP alone[13]
- The Phase III frontMIND study (NCT04824092) will investigate the efficacy and safety of R-CHOP + tafasitamab + lenalidomide versus R-CHOP alone in previously untreated patients with high-intermediate and high-risk DLBCL in urgent need of treatment

Figure 1. Mode of action of tafasitamab plus lenalidomide



Adapted from Salles et al. Expert Opin Biol Ther 2021.[11]
ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cell-mediated phagocytosis; mAb, monoclonal antibody; NK, natural killer.

Objective

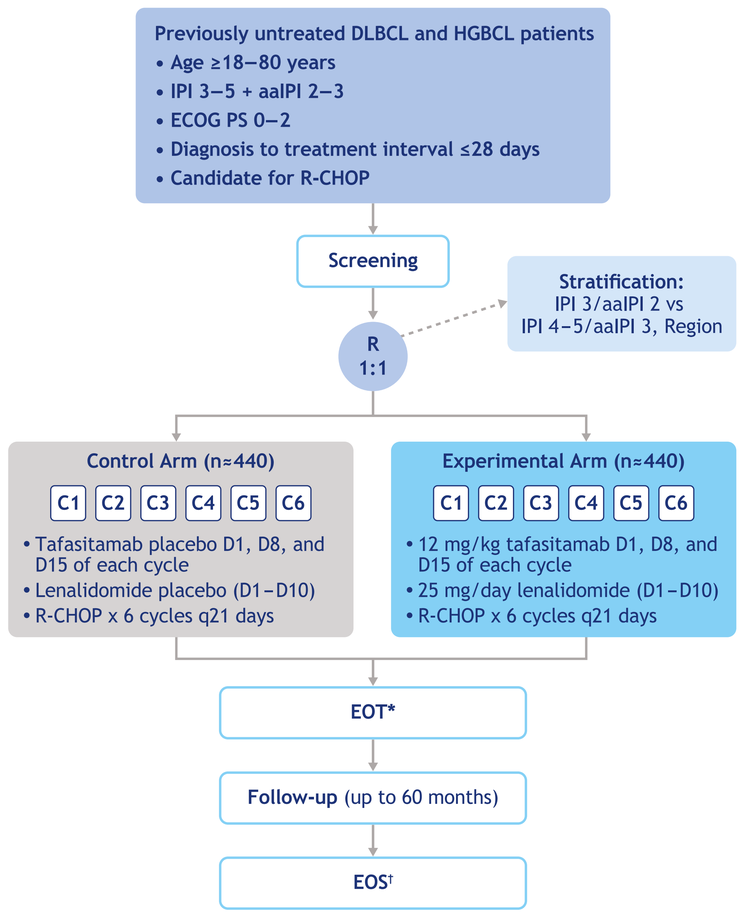
- frontMIND (NCT04824092, EudraCT number 2020-002990-84) is a trial in progress, assessing the efficacy and safety of tafasitamab plus lenalidomide plus R-CHOP versus R-CHOP alone in previously untreated, high-intermediate, and high-risk patients with newly diagnosed DLBCL

Study design

- frontMIND is a Phase III, multicenter, randomized, double-blind, placebo-controlled trial
- With an assumed true hazard ratio of experimental over control arm of 0.7, approximately 880 patients from nearly 350 study centers in North and South America, Europe, and Asia-Pacific will be enrolled in this study
- Patients will be randomized 1:1 to receive either
  - Six 21-day cycles of tafasitamab (12 mg/kg intravenous [IV] on Day [D] 1, 8, and 15) plus lenalidomide (25 mg orally, D1–10) plus R-CHOP

  OR
  - Six 21-day cycles of tafasitamab placebo (0.9% saline solution IV, D1, 8, and 15) plus lenalidomide placebo (orally, D1–10) plus R-CHOP (**Figure 2**)
- Pre-planned central nervous system (CNS) prophylaxis with intravenous methotrexate is allowed at the end of treatment in patients at high-risk of CNS recurrence
- After the end of treatment, patients will enter the follow-up period of up to 60 months

Figure 2. frontMIND study design



*EOT is defined as D21 of the last treatment cycle the patient started. †EOS is expected to occur approximately 5 years after the first patient is enrolled, to allow all patients a minimum of 3 years follow-up post-treatment.
aaIPI, age-adjusted International Prognostic Index (patients ≤60 years); C, cycle; D, Day; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; EOS, end of study; HGBCL, high-grade B-cell lymphoma; IPI, International Prognostic Index (patients >60 years); R, randomization; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; q, every.

- Eligible patients will be aged ≥18–80 years, with previously-untreated CD20-positive DLBCL (International Prognostic Index [IPI] status of 3–5 for patients >60 years or age-adjusted IPI 2–3 for patients ≤60 years of age), and Eastern Cooperative Oncology Group performance status 0–2 (**Table 1**)

Table 1. Key patient eligibility criteria

Inclusion criteria	Exclusion criteria
• Age 18–80 years • Previously-untreated DLBCL and HGBCL* • Time from diagnosis to treatment start ≤28 days • Local biopsy-proven CD20-positive DLBCL and HGBCL • IPI 3–5 (for patients >60 years) or aaIPI 2–3 (for patients ≤60 years) • Up to six of the largest target nodes, nodal masses, or other lymphomatous lesions should be identified by local assessment • ECOG PS 0–2	• Any other histological type of lymphoma, according to WHO 2016 classification of lymphoid neoplasms • History of radiation therapy to ≥25% of the bone marrow for other diseases • History of prior non-hematologic malignancy • Active systemic infection • Known CNS lymphoma • Pregnancy or lactation

*HGBCL patients can be enrolled if deemed not eligible for a more aggressive treatment.
aaIPI, age-adjusted International Prognostic Index; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; HGBCL, high-grade B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; WHO, World Health Organization.

- The primary endpoint is PFS, while key secondary endpoints include investigator-assessed event-free survival (EFS), OS, and safety (**Table 2**)
- Exploratory analyses of biomarkers will be performed to assess the pharmacodynamics, prognostic and/or predictive value of candidate biomarkers, as well as potential resistance to treatment in relationship with selected efficacy or safety outcomes (**Table 2**)

Table 2. Key study endpoints*

Primary endpoint	• PFS† as assessed by the investigator
Key secondary endpoints	• EFS as assessed by the investigator • OS
Other secondary endpoints	• Metabolic, PET-negative CR rate at EOT as assessed by the investigator • ORR at EOT as assessed by the investigator • OS rate at 3 years • Health-related quality of life • Safety (incidence and severity of TEAE)
Exploratory endpoints	• Biomarkers for correlative analyses: – Immunophenotyping including immune cell enumeration – Gene expression analysis of tumor tissue – CD19 and CD20 expression on tumor cells

*All clinical efficacy endpoints will be assessed according to the revised response criteria for malignant lymphoma based on the guidelines of the Lugano Classification.[15] †Defined as the time from randomization to the first occurrence of disease progression or relapse, or death from any cause, whichever occurs earlier.
CR, complete response; EFS, event-free survival; EOT, end of treatment; ORR, objective response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; TEAE, treatment emergent adverse events.

- Imaging assessments of efficacy and disease response will be recorded during the course of the study and safety assessments will be monitored continuously to ensure patient safety (**Table 3**)

Table 3. Key study assessments

Assessments	Screening	Treatment Period																				EOT*/ ETD	Follow-up period
	D(−28) to D(−1)	Cycle 1 (21 days)			Cycle 2 (21 days)			Cycle 3 (21 days)				Cycle 4 (21 days)			Cycle 5 (21 days)			Cycle 6 (21 days)					
		D1	D8†	D15	D1	D8	D15	D1	D8	D15	D18	D1	D8	D15	D1	D8	D15	D1	D8	D15	6±2 wks	
Efficacy																							
Tumor tissue	X																						
PET/CT or PET/MRI‡	X																					X	
CT or MRI‡											X												
Safety																							
AE, SAE, AESI and pregnancy reporting	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Survival follow-up§																							X
Quality of life assessment																							
EORTC-QLQ-C30, EQ-5D-5L, FACT-Lym	X	X			X			X							X							X	X

*EOT visit is defined as 6±2 weeks after EOT. EOT is defined as D21 of the last treatment cycle the patient started. †A visit window of ±2 days is allowed for visits starting from C1D8 until C6D15 of R-CHOP and tafasitamab/placebo. ‡Tumor measurements by PET/CT or PET/MRI of the neck, chest, abdomen and pelvis to be performed at screening and 6±2 weeks after D21 of the last treatment cycle the patient started. A mid-treatment CT or MRI scan and tumor evaluation is required at C3D18 ±3 days prior to the end of C3. §Should the patient decease at any time, the date of death as well as cause of death should be reported (if available). In the extended follow-up period after 60 months, the patients will be contacted via telephone approximately every 6 months until close of the study.
AE, adverse event; AESI, adverse event of special interest; C, cycle; CT, computed tomography; D, day; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EOT, end of treatment; EQ-5D-5L, Euro Quality of life (QoL) 5-Dimensional 5-Level Scale; FACT-Lym, Functional Assessment of Cancer Therapy – Lymphoma; ETD, early treatment discontinuation; MRI, magnetic resonance imaging; PET, positron emission tomography; SAE, serious adverse event; wks, weeks.

Summary

- As 30–40% of patients relapse or are refractory to first-line therapy,[2] there remains a high unmet need to improve treatment options for newly diagnosed patients, particularly those with high-risk DLBCL
- The combination of tafasitamab, lenalidomide and R-CHOP may have synergistic potential and improve SoC
- The frontMIND study will further evaluate the clinical benefits and safety when adding tafasitamab plus lenalidomide to the current standard of care, in newly diagnosed patients with high-intermediate and high-risk DLBCL treated with R-CHOP
- This study is currently enrolling patients, with a planned sample size of 880 patients in ~350 centers worldwide

References

1. NCCN Clinical Practice Guidelines: B-Cell Lymphomas V1.2022. **2.** Sehn LH, et al. N Engl J Med 2021;384(9):842–58. **3.** Sarkozy C, et al. Ann Lymphoma 2019;3:10. **4.** Candelaria M, Dueñas-Gonzalez A. Ther Adv Hematol 2021;12:2040620721989579. **5.** Tilly H, et al. N Engl J Med 2022; 386(4):351–63. **6.** Nowakowski GS, et al. J Clin Oncol 2021;39(12):1329–38. **7.** Nowakowski GS, et al. J Clin Oncol 2021;39(12):1317–28. **8.** MONJUVI Prescribing information. Boston, MA: MorphoSys. https://www.monjuvi.com/pi/monjuvi-pi.pdf. Accessed April 2022. **9.** European Medicines Agency. Minjuvi. https://www.ema.europa.eu/en/medicines/human/EPAR/minjuvi. Accessed April 2022. **10.** Health Canada. Minjuvi. https://health-products.canada.ca/dpd-bdpp/info.do?lang=en&code=100793. Accessed April 2022. **11.** Salles G, et al. Expert Opin Biol Ther 2021;21(4):455–63. **12.** Duell J, et al. Haematologica 2021;106(9):2417–26. **13.** Belada D, et al. Blood 2021;138(Supplement 1):3556. **14.** Gribben JG, et al. J Clin Oncol 2015; 33(25):2803–11. **15.** Cheson BD, et al. J Clin Oncol 2014;32(27):3059–68

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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 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. Incyte has exclusive commercialization rights outside the United States. XmAb® is a trademark of Xencor, Inc.

Conflicts of interest

UV: Consulting/advisory: Seagen, Genmab, Incyte, Costellation, Bayer, Regeneron; Speakers' bureau: AbbVie, Incyte, Janssen, Gilead Sciences. **GSN:** Consultancy: Celgene, MorphoSys AG, Genentech, Selvita, Debiopharm Group, Kite/Gilead Sciences; Research funding: Celgene, NanoString Technologies, MorphoSys AG; Membership on an entity's Board of Directors or advisory committees: Celgene, MorphoSys AG, Genentech, Selvita, Debiopharm Group, Kite/Gilead Sciences. **JMB:** Consulting/advisory: Genentech/Roche, AbbVie, Seattle Genetics, Bayer, AstraZeneca, Adaptive Biotechnologies, Verastem, MorphoSys AG, Kura, Epizyme, BeiGene, Kymera, Novartis, Bristol-Myers Squibb, TG Therapeutics, Lilly; Speakers' bureau: Seattle Genetics, BeiGene. **CPF:** Consulting/advisory: AbbVie, AstraZeneca, Atarabio, Celgene-BMS, Genmab, Kite/Gilead Sciences, MorphoSys AG, Ono, Orion, Roche, Takeda; Speakers' bureau: Gilead Sciences, Takeda, Roche, Incyte, Janssen; Research funding: BeiGene. **MT:** Honoraria: Takeda, Novartis, Janssen, AbbVie, Gilead Sciences, Roche, Bristol-Myers Squibb, Amgen, MorphoSys AG; Consulting/advisory: Roche, Bristol-Myers Squibb, Amgen, Gilead Sciences, Novartis, Incyte, MorphoSys AG, Takeda, AbbVie, Janssen; Travel, accommodations, expenses: Gilead Sciences, Bristol-Myers Squibb, Janssen, Takeda, Roche, AbbVie. **AC:** Consulting/advisory: Celgene-BMS, Clinigen, Kite/Gilead Sciences, Janssen-Cilag, Roche, Secura BIO, Takeda; Lecture fees/educational activities: AstraZeneca, Celgene-BMS, Clinigen, Gilead Sciences, Incyte, Janssen-Cilag, Novartis, Roche, Secura BIO, Takeda. **MWL:** Employment and stocks: MorphoSys, US. Inc., Novartis AG (immediate family member). **NH:** Employment: MorphoSys AG; Stocks: Novartis; **AP:** Employment and stocks: Novartis, MorphoSys AG. **GL:** Consulting/advisory: Roche, MorphoSys AG, Incyte, Karyopharm, Bayer, Bristol-Myers Squibb, AstraZeneca, Constellation, ADC Therapeutics, Janssen, Gilead Sciences, Novartis, AbbVie, Genmab; Honoraria: Roche, MorphoSys AG, Incyte, Karyopharm, Bayer, Bristol-Myers Squibb, AstraZeneca, Constellation, ADC Therapeutics, Janssen, Gilead Sciences, Novartis, AbbVie, Genmab; Research funding: Roche, Gilead Sciences, Janssen.

Correspondence: Dr MD Umberto Vitolo (umberto.vitolo@ircc.it)