

frontMIND: A Phase III, randomized, double-blind, placebo-controlled study comparing efficacy and safety of tafasitamab plus lenalidomide plus R-CHOP versus R-CHOP alone for newly diagnosed high-intermediate and high-risk diffuse large B-cell lymphoma

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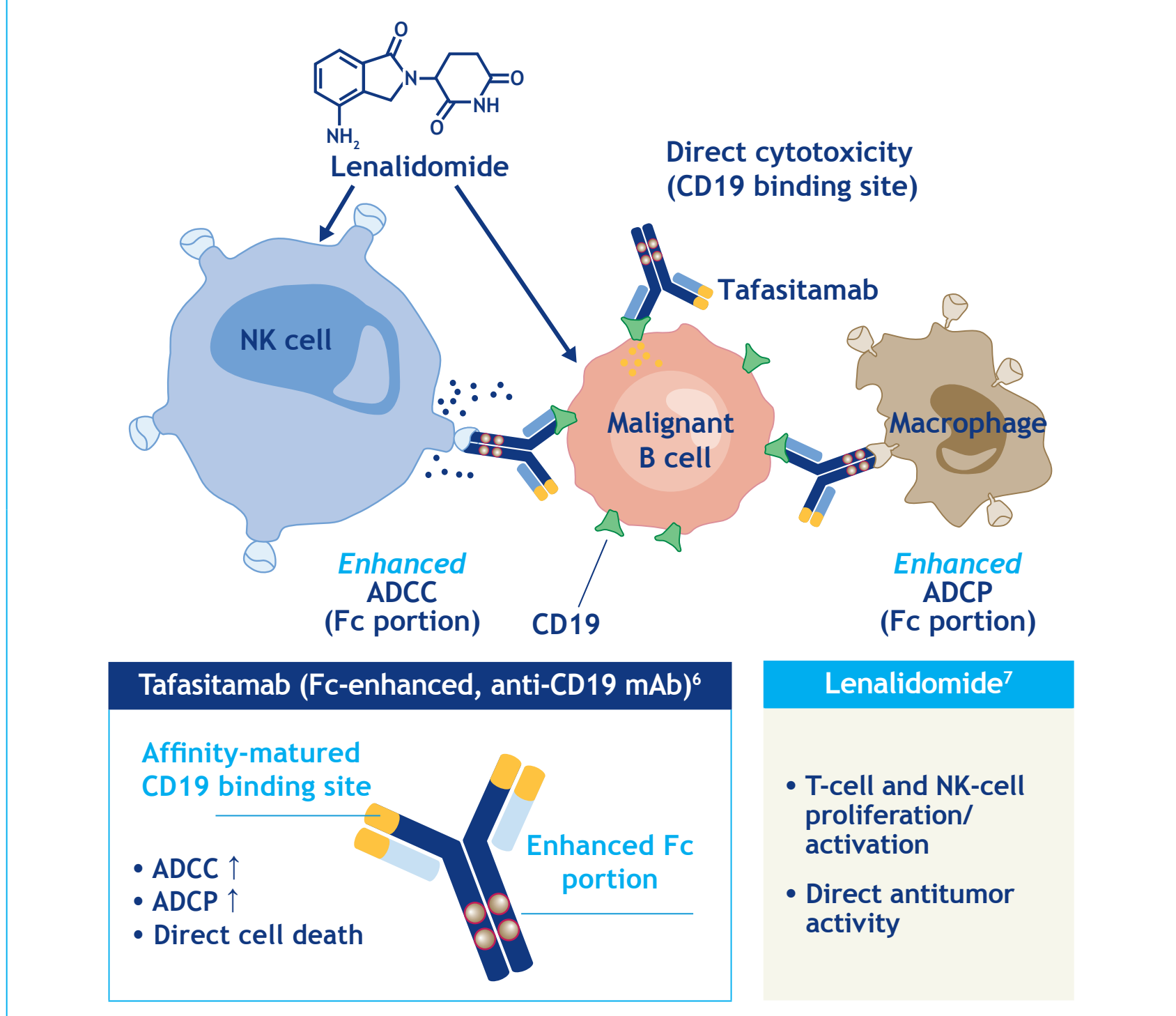
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Background

- Tafasitamab is an Fc-modified, humanized anti-CD19 monoclonal antibody, which enhances *in vitro* antibody-dependent cell-mediated cytotoxicity and antibody-dependent cell-mediated phagocytosis^{1,2}
- In the United States, tafasitamab in combination with the immunomodulatory drug lenalidomide received accelerated approval (July 2020) by the Food and Drug Administration for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, who are not eligible for autologous stem cell transplantation³
- The tafasitamab plus lenalidomide treatment combination, with a potentially synergistic mode of action (Figure 1), resulted in a high proportion of patients having a complete response (CR, 43%; n=34/80) in the pivotal L-MIND study (NCT02399085)^{4,5}

Figure 1. Mode of action of tafasitamab plus lenalidomide



Adapted from Salles et al. Expert Opin Biol Ther 2021.⁶
ADCC, antibody-dependent cell-mediated cytotoxicity; ADP, antibody-dependent cell-mediated phagocytosis; mAb, monoclonal antibody; NK, natural killer.

- The National Comprehensive Cancer Network[®] guidelines recommend R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) as the preferred first-line treatment regimen for patients with newly diagnosed DLBCL⁹
 - Cure rates with R-CHOP range from 60% to 70%⁹
- Preliminary data from the Phase Ib First-MIND (NCT04134936) study in patients with newly diagnosed DLBCL suggest that tafasitamab plus lenalidomide in addition to R-CHOP is effective (objective response rate, 93.5%) and tolerable in patients with treatment-naïve DLBCL¹⁰

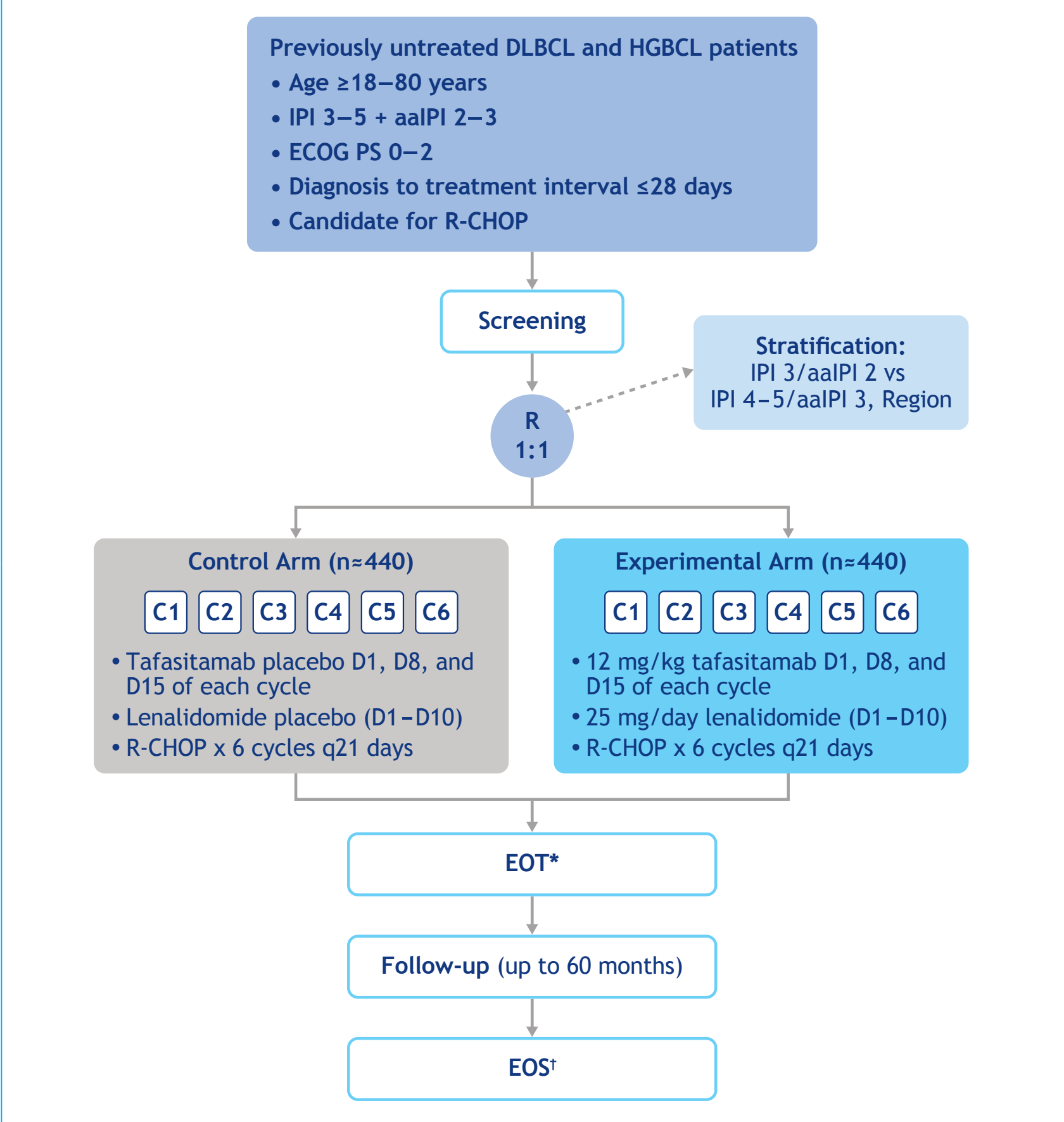
Objective

- 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 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.

- 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 aalPI 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	- 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
ECOG performance status 0–2	

*HGBCL patients can be enrolled if deemed not eligible for a more aggressive treatment.

aalPI, age-adjusted International Prognostic Index; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; HGBCL, high-grade B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; WHO, World Health Organization.

- The primary endpoint is progression-free survival (PFS), while key secondary endpoints include investigator-assessed event-free survival (EFS), overall survival (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	PFS¹ 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.¹¹ 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		
Survival follow-up [‡]																					X		
Quality of life assessment																							
EORTC-QLQ-C30, EQ-5D-5L, FACT-Lym	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 deceased 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 events; AESI, adverse events 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 events; wks, weeks.

Summary

- As 30–40% of patients relapse or are refractory to first-line therapy,⁹ 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
- 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

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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 fees from Celgene, Janssen, Incyte, Genmab, Regeneron, Gilead; lecture fees from Celgene, Janssen, Roche, Gilead, AbbVie. GS: consulting/advisory fees from Celgene, MorphoSys, Genentech, Selvita, Debiopharm Group, Kite/Gilead; research funding from Celgene, NanoString Technologies, MorphoSys. JMB: consulting/advisory fees from Genentech/Roche, AbbVie, Seattle Genetics, Bayer, AstraZeneca, Adaptive Biotechnologies, Verastem, MorphoSys, Kura, Epizyme, BeiGene, Kymera; speakers' bureau at Seattle Genetics, Beigene. CPF: trial steering committee at MorphoSys; grants from Roche, Takeda, AbbVie; personal fees from Roche, Takeda, GenMab, Janssen, AbbVie, AstraZeneca, Incyte. MT: consulting/advisory fees from Janssen, Gilead, Takeda, Bristol-Meyer Squibb, AbbVie, Roche, MorphoSys, Incyte. Celgene: honoraria from Janssen, Gilead, Takeda, Bristol-Meyer Squibb, Amgen, AbbVie, Roche, MorphoSys, Incyte; other fees from Janssen, Gilead, Takeda, Bristol-Meyer Squibb, AbbVie, Roche. AC: consulting/advisory fees from Celgene BMS, Roche, Gilead Sciences, Clingen, Takeda; lecture fees from Celgene BMS, Roche, Gilead Sciences, Clingen, Takeda, Janssen-Cilag, Novartis, Incyte. ST, AS, WB: employees of MorphoSys AG. GL: grants and personal fees from MorphoSys; personal fees from Roche, MorphoSys, AstraZeneca, Janssen, Acerta, Gilead, Bayer, Novartis, Incyte, Karyopharm, Celgene/BMS, Takeda, Nanostring, AbbVie, Genmab; grants from Roche, MorphoSys, AstraZeneca, Janssen, Acerta, Gilead, Bayer, AGIOS, AQUINOX.