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inMIND: A Phase 3 Study of Tafasitamab Plus Lenalidomide and Rituximab Versus Placebo Plus Lenalidomide and Rituximab for Relapsed/Refractory Follicular Lymphoma or Marginal Zone Lymphoma

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Introduction

- Follicular lymphoma (FL) and marginal zone lymphoma (MZL) are indolent subtypes of non-Hodgkin lymphoma (NHL)[1] that account for 22% and 8% of NHL cases in the Western world, respectively[2]
  - Most patients respond to first-line treatment but relapse is common, and there is no single standard treatment for patients with relapsed/refractory (R/R) disease[3,4]
  - Approved therapies include R[2] (rituximab plus lenalidomide [LEN]),[5] the phosphoinositide 3-kinase inhibitor, copanlisib,[6] and the enhancer of zeste homolog 2 inhibitor, tazemetostat[7]
  - Additional treatment options with improved clinical outcomes and safety are needed for these patients
- CD19 is broadly expressed in FL and MZL, and regulates B-cell proliferation via B-cell receptor signaling[8,9]
- Tafasitamab is a humanized anti-CD19 monoclonal antibody (mAb) that is Fc-engineered for increased affinity to Fcγ receptors on immune effector cells
  - Tafasitamab triggers malignant B-cell death by binding to CD19 and inducing direct cytotoxicity as well as by enhancing immune-mediated mechanisms, ie, natural killer cell–mediated antibody-dependent cell-mediated cytotoxicity and macrophage-mediated antibody-dependent cellular phagocytosis
- Tafasitamab demonstrated preclinical activity in NHL cell lines in combination with anti-CD20 mAb rituximab and the immunomodulator LEN[10]
- In the United States, tafasitamab received accelerated approval by the US Food and Drug Administration in combination with LEN for adult patients with R/R diffuse large B-cell lymphoma not otherwise specified, including diffuse large B-cell lymphoma arising from low-grade lymphoma, who are not eligible for autologous stem cell transplantation based on data from L-MIND, an ongoing phase 2, single-arm study (NCT02399085)[11,12]
  - In the primary analysis of L-MIND (November 2018 data cutoff), tafasitamab plus LEN was associated with an objective response rate (ORR) of 60% (95% confidence interval [CI], 48-71)[11]
  - In a subsequent analysis (November 2019 data cutoff), after a median follow-up of 31.8 months, the median duration of response (DOR) was 34.6 months (95% CI, 26.1-not reached [NR]) and median overall survival was 31.6 months (95% CI, 18.3-NR)[13]
  - In an additional analysis (October 2020 data cutoff), after a median follow-up of ≥35 months, the median DOR was 43.9 months (95% CI, 26.1-NR)[14]
- In a phase 2a study in patients with R/R NHL (NCT01685008), tafasitamab monotherapy was associated with an investigator-assessed ORR of 29% (n/N=10/34) in patients with FL and 33% (n/N=3/9) in patients with MZL[15]
- These clinical findings, along with preclinical observations, suggest a potential for clinical benefit of tafasitamab plus LEN and rituximab for patients with R/R FL or MZL

Objective

- inMIND is designed to investigate whether tafasitamab plus LEN as an add-on to rituximab provides improved clinical benefit compared with LEN alone as an add-on to rituximab in R/R FL or R/R MZL

Study Design

- inMIND (NCT04680052; EudraCT2020-004407-13) is a global, phase 3, double-blind, placebo-controlled, randomized study in patients with R/R FL of grade 1 to 3a, or R/R MZL
- Approximately 528 R/R FL and 60 to 90 R/R MZL patients eligible for enrollment will be randomized 1:1 with stratification to receive either:
  - Tafasitamab (12 mg/kg intravenous [IV] on days 1, 8, 15, and 22 of a 28-day cycle [cycles 1-3], then days 1 and 15 [cycles 4-12]) plus LEN (20 mg orally once daily [PO QD; 10 mg PO QD if creatinine clearance ≥30 to <60 mL/min], days 1-21/cycle for 12 cycles), and rituximab (375 mg/m^2 IV on days 1, 8, 15, and 22 of cycle 1, then day 1 of cycles 2-5)

    OR

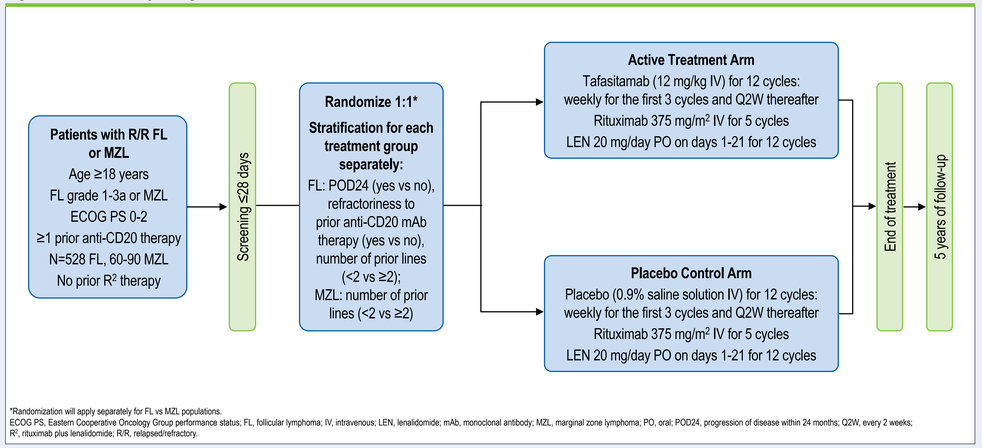
  - Placebo (0.9% saline solution IV) plus LEN and rituximab
- Stratified randomization will be performed separately for patients with R/R FL and R/R MZL

Table 1. Key Patient Eligibility Criteria

Inclusion Criteria
• Age ≥18 years
• Histologically confirmed FL (grade 1, 2, or 3a) or MZL (nodal, splenic, or extranodal)
– Patients with gastric MZL and evidence of *Helicobacter pylori* must have documented nonresponse to antibiotic therapy
• ≥1 prior systemic anti-CD20 therapy (anti-CD20 refractory disease is eligible)
• Documented relapsed, refractory, or PD after systemic treatment
• Need of treatment for relapsed, refractory, or PD as assessed by the investigator per GELF criteria, with ≥1 measurable lesion
• ECOG PS ≤2
• Adequate hematologic, liver, and renal function
Exclusion Criteria
• NHL histology other than FL or MZL including transformed lymphoma
• Prior rituximab plus LEN treatment
• History of nonhematologic malignancy
• Congestive heart failure (LVEF <50%)
• Active systemic infection
• Severe immunocompromised state
• Known CNS lymphoma

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GELF, Groupe d'Etude des Lymphomes Folliculaires; LEN, lenalidomide; LVEF, left ventricular ejection fraction; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PD, progressive disease.

Figure 1. inMIND Study Design



*Randomization will apply separately for FL vs MZL populations.
ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; IV, intravenous; LEN, lenalidomide; mAb, monoclonal antibody; MZL, marginal zone lymphoma; PO, oral; POD24, progression of disease within 24 months; Q2W, every 2 weeks; R^2, rituximab plus lenalidomide; R/R, relapsed/refractory.

Table 2. Key Study Assessments

	Screening	Treatment Period												
		Cycle 1 (±1 Day)				Cycles 2 and 3 (±1 Day)				Cycle ≥4 (±2 Days)		EOT (90 Days After Last Dose)	Follow-up Period
Assessments	Day −28 to Day −1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		
Safety													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	
Survival follow-up													X
Efficacy													
Bone marrow core biopsy	X											X*	
Bone marrow aspirate (for MRD)	X											X	
PET	X											X†	
CT with contrast or MRI	X									X‡,§		X‡,§	X‡
Quality-of-life questionnaires													
EORTC QLQ-C30, EQ-5D-5L, FACT-Lym		X				X				X		X	X‖

*If positive at baseline and at time of radiological CR. †Within 4 (±2) weeks to confirm a PD per CT/MRI if earlier than EOT. ‡The assessments are performed every 12 (±2) weeks in year 1, every 16 (±2) weeks in years 2 and 3, and every 24 (±3) weeks in years 4 to 6; PET and CT can be combined. §Patients with negative PET at baseline will have a CT scan or MRI only at EOT. ‖Every 6 months after EOT until PD, and 6 months after PD.
CR, complete response; CT, computed tomography; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EOT, end of treatment; EQ-5D-5L, EuroQol 5-Dimensional 5-Level Scale; FACT-Lym, Functional Assessment of Cancer Therapy – Lymphoma; MRD, minimal residual disease; MRI, magnetic resonance imaging; PD, progressive disease; PET, positron emission tomography.

Table 3. Key Study Endpoints

Primary Endpoint	• PFS by investigator assessment in the FL population
Key Secondary Endpoints	• PFS by investigator assessment in the overall population (FL + MZL) • PET-CR rate at EOT* by investigator in the FL population • OS in the FL population
Other Secondary Endpoints	• PET-CR rate at EOT* by investigator in the overall population • MRD-negativity rate (at thresholds of 10^{-4} and 10^{-5}) at EOT in the FL and overall population • ORR and DOR by investigator in the FL and overall population • OS in the overall population • HRQoL in the FL and overall population • Safety (incidence and severity of TEAEs) in the FL and overall population

All clinical efficacy endpoints will be assessed based on the Lugano 2014 (Cheson) criteria.[16]
*90 days after last dose.
DOR, duration of response; EOT, end of treatment; FL, follicular lymphoma; HRQoL, health-related quality of life; MRD, minimal residual disease; MZL, marginal zone lymphoma; ORR, objective response rate; OS, overall survival; PET-CR, positron emission tomography-complete response; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

Summary

- **inMIND (NCT04680052, EudraCT2020-004407-13) is currently enrolling patients, with a planned enrollment of 528 patients with R/R FL and 60 to 90 patients with R/R MZL**
- **Approximately 275 centers in North America, Europe, and Asia Pacific are anticipated to participate in this study**

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 US 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.

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