Update of the single-arm phase II L-MIND study of MOR208 (Tafasitamab) + lenalidomide (LEN) in relapsed/refractory diffuse large B-cell lymphoma (R-R DLBCL): High overall response rates (ORR) achieved in patient subgroups with poor prognosis

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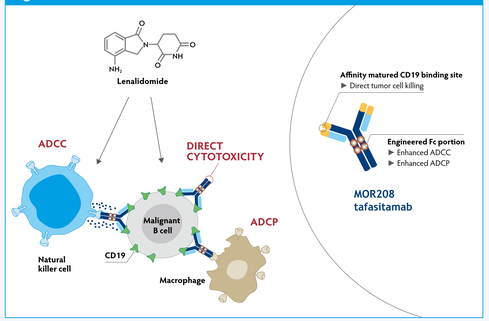
Introduction

- CD19 is broadly and homogeneously expressed across different B-cell malignancies including DLBCL, and enhances B-cell receptor (BCR) signaling and tumor cell proliferation.[1,2]
- MOR208 (Tafasitamab) is an Fc-enhanced, humanized, monoclonal antibody that targets CD19 on tumor cells leading to natural killer (NK) cell-mediated antibody-dependent cell-mediated cytotoxicity (ADCC), macrophage-mediated antibody-dependent cell-mediated phagocytosis (ADCP) and direct cytotoxicity (**Figure 1**).

Figure 1. MOR208 and LEN modes of action



- LEN is an immunomodulatory drug [IMiD®], and has both antiproliferative and antiangiogenic properties, and stimulates the activity of effector cells such as NK cells.[5]
- Both MOR208 and LEN have demonstrated single agent activity in patients with R-R DLBCL.[4,6]
- Encouraging activity has been recently reported from the MOR208 + LEN combination (preliminary results, Salles et al, ASH 2018).

Study Endpoints

Primary

- Objective response rate (ORR) assessed by independent review committee (IRC), based on Cheson 2007 criteria[7].

Secondary

- Progression-free survival (PFS), Duration of response (DoR), Overall survival (OS), safety, biomarker-based analyses.

Methods

Patients

Key inclusion criteria

- Patients aged ≥18 years with histologically confirmed relapsed and/or refractory DLBCL, and who were not candidates for high-dose chemotherapy followed by ASCT.
- 1 – 3 previous systemic therapies for DLBCL, including at least one CD20-targeted therapy (e.g., rituximab).
- Patients with grade 3b follicular lymphoma, or histological transformation from indolent lymphoma into DLBCL with subsequent relapse were eligible.

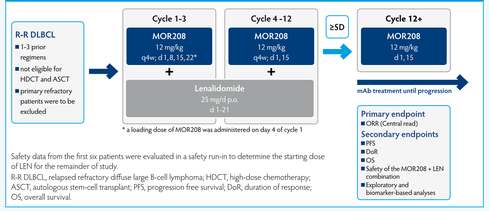
Key exclusion criteria

- Patients with a primary refractory DLBCL (no response to or progression during or within 6 months of the frontline therapy – this was applicable for protocol amendment 2 and onwards).
- Double/triple hit DLBCL if known (FISH testing was not a prerequisite per protocol).
- Central nervous system lymphoma involvement .
- Prior therapy with an iMID and / or CD19 targeted treatment.

Study design

- Phase II, single-arm, open-label, multicenter study (NCT02399085; **Figure 2**).
- Recruitment is complete with 81 patients.

Figure 2. Study design and dosing scheme



Safety data from the first six patients were evaluated in a safety run-in to determine the starting dose of LEN for the remainder of study.
R-R DLBCL, relapsed refractory diffuse large B-cell lymphoma; HDCT, high-dose chemotherapy; ASCT, autologous stem-cell transplant; PFS, progression free survival; DoR, duration of response; OS, overall survival.

Results

- Here we report an update of the L-MIND data with primary endpoint and subgroup analyses of key endpoints (cut off June 5, 2018, median follow-up duration of 12 months). Baseline characteristics are shown in **Table 1**.

Table 1. Baseline characteristics

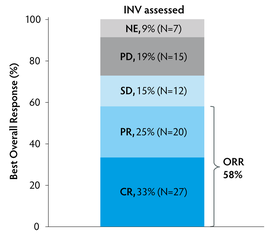
Characteristic	Specification	n=81 (%)
Age, years	Median (range)	72 (41-87)
Sex	Male	44 (54)
	Female	37 (46)
Ann-Arbor	I-II	20 (25)
	III-IV	59 (73)
	Unknown	2 (2)
Risk (IPI)	0-2	39 (48)
	3-5	42 (52)
Elevated LDH	Yes	45 (56)
	No	35 (43)
	Unknown	1 (1)
Prior Lines	Median (range)	2 (1 to 4)
	1	40 (49)
	2	35 (43)
	3	4 (5)
	4	2 (2)
Primary Refractory*	Yes	14 (17)
	No	67 (83)
Refractory to previous therapy line	Yes	34 (42)
	No	47 (58)
Prior SCT	Yes	8 (10)
	No	73 (90)
Cell of Origin (by Immunohistochemistry-IHC)	GCB	40 (49)
	Non-GCB	21 (26)
	Unknown	20 (25)

*Assesesed as primary refractory as per applicable protocol amendment.
IPI, international prognostic index; LDH, lactate dehydrogenase; SCT, stem-cell transplantation; GCB, germinal center B-cell.

Preliminary efficacy analysis

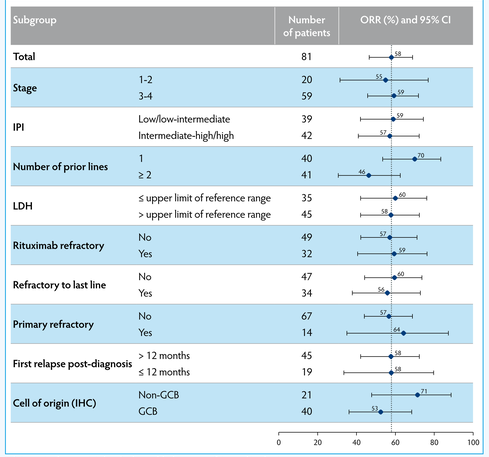
- The IRC-assessed objective response rate was 54% with a complete response rate of 32% (**Figure 3**) and was similar to investigator assessments.
- Encouraging activity was observed in in most patient subgroups of interest associated with poor outcome, including patients who were refractory to their previous therapies (**Figure 4 Subgroup Analysis for ORR**).
- The median time to response, or to complete response were 1.8 months and 3.4 months, respectively (**Figure 6**).
- Median Duration of Response (DoR) was not reached, and the 12-month DoR rate for patients with CR was 87% (**Figure 5**).

Figure 3. Best overall response [ITT analysis]



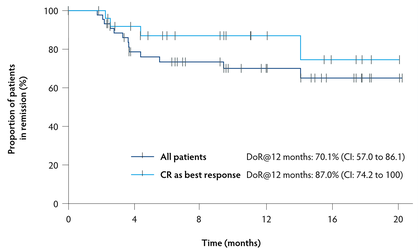
Seven patients were not evaluable (NE) as they did not have a post-baseline response assessment due to: adverse event (n=1, Herpes zoster), withdrawal of consent (n=1), non-compliance (n=1), Clinical decision (n=1) or death (n=3: disease progression, sudden death, respiratory failure).

Figure 4. Subgroup analysis for ORR (investigator assessment)



IPI, international prognostic index; LDH, lactate dehydrogenase; IHC, immunohistochemistry.

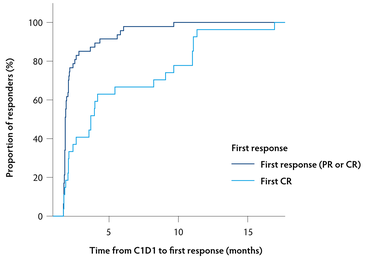
Figure 5. Duration of response (investigator assessment)



Number of patients at risk						
All patients	47	30	23	15	8	2
CR as best response	27	19	13	8	4	1

CR, complete response; NR, not reached.

Figure 6. Time to response [ITT analysis] as per investigator assessment

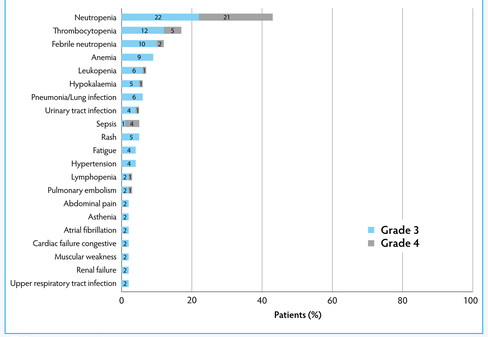


CR, complete response; PR, partial response.

Safety

- MOR208 plus LEN combination was well tolerated.
- No unexpected toxicities were observed compared to the known toxicity profiles of LEN or MOR208.
- Most common treatment-emergent adverse events (TEAEs) of grade ≥3 are shown in **Figure 7**.
- Neutropenia, the most frequent grade ≥3 TEAE, was well manageable and the majority of the patients (81%) recovered within 1 week .
- Treatment-related serious adverse events were mainly infections (10%) or febrile neutropenia (5%).
- 4 (5%) patients permanently discontinued treatment with both MOR208 and LEN due to an adverse event.
- 41 (51%) patients required a LEN dose reduction due to an adverse event.

Figure 7. Most common TEAEs of grade ≥3 reported in ≥2% of patients



TEAEs, treatment-emergent adverse events.

Conclusions

- MOR208 (Tafasitamab) in combination with LEN showed encouraging activity in patients with R-R DLBCL.
- Tafasitamab + LEN achieved high ORR and CR rates even in patient subgroups of poor prognosis such as, high age, primary refractory and refractory to prior therapies.
- Tafasitamab in combination with LEN was well tolerated.
- Primary analysis of study results are currently ongoing.

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Disclosures

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