Phase IIa study of single-agent MOR208 in patients with relapsed or refractory B-cell non-Hodgkin’s lymphoma

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Introduction

CD19, a B-lymphocyte lineage specific surface antigen, is the earliest and most broadly expressed of the selective B-cell markers, and is highly expressed in most B-cell non-Hodgkin’s lymphomas (B-NHL).1,2 Consequently, a CD19 antibody may have clinical utility as a new therapeutic approach to NHL treatment.

Phase I results confirmed an Fc-engineered monoclonal antibody that targets CD19 (Figure 1).

A phase I/II study has shown MOR208 to be generally safe and well tolerated, with encouraging single-agent activity in patients with chronic lymphocytic leukemia (CLL) – encountered intravenous dosing, 12 mg/kg, monthly.

Methods

- Phase I/II non-randomized multicenter study (Figure 2).

- 2-stage design:
  - Stage 1: 10 patients to be enrolled into each of 4 NHL subtype cohorts, differing large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and no NHL cohort. PR: partial response (PR) according to any NHL criteria.

- Stage 2: 2 cohorts: 3 responses complete or partial or expanded by at least 25 additional patients.

- Key inclusion criteria:
  - Aged >18 years
  - Histologically confirmed DLBCL, FL, other NHL, or MCL

- NHL-processed after at least one prior rituximab-containing therapy

- Eastern Cooperative Oncology Group performance status ≤2

- Adequate bone marrow, total and liver function

- All patients provided written informed consent prior to study entry.

Results

Patients

- Data cutoff November 11, 2015.

- Two cohorts were expanded (DLBCL and FL) leading to an overall enrollment of 92 patients (Table 1).

- Other NHL cohort not expanded as response was deemed too heterogeneous between different lymphoma subtypes (Table 2).

- PR: partial response (PR) according to any NHL criteria.

- Paired baseline characteristics are summarized in Table 1.

Efficacy

- Responses are presented in Table 2 and Figures 4 to 6.

- Median progression-free survival time was 6 months (Figure 6).

- Median overall survival time was 6 months for all NHL and 7 months for DLBCL (Figure 5).

- 12-month overall survival rate for DLBCL was 30% (Figure 6).

- Complete and partial responses in DLBCL and MCL were observed in 60% and 40% of patients, respectively.

- Clinical benefit: 78% of patients received clinical benefit (Figure 5).

- 5 complete responses in the combined iNHL cohort.

- 2 complete responses in the DLBCL cohort.

- 2 complete responses in the combined NHL cohort.

- Longest DIF to date was 29.3 months for DLBCL, and 20.3 months for iNHL (both ongoing).

Pharmacokinetics

- Estimated mean terminal elimination half-life: 15 days.

- Steady state (Cmax ~ 500 µg/mL) was reached after 6 to 8 weeks (Figure 7).

- Optimized loading dose of 12 mg/kg weekly led to rapid and nongaussian exposure with an initial weekly dosing.

- Only 1 of 92 patients has so far tested positive for anti-drug antibodies during treatment with MOR208.

Safety

- The employed dosing regimen at 12 mg/kg was safe and well tolerated and will be continued in a randomized confirmatory phase 3 study.

- No significant immunogenicity detected: 10% of patients showed detectable anti-drug antibodies during treatment with MOR208.

- No significant immunogenicity detected; only 1 of 92 patients has so far tested positive for anti-drug antibodies during treatment with MOR208.

- The MOR208 exposures showing clinical efficacy are mainly reached at 12 mg/kg with an initial weekly dosing.

- Encouraging single-agent activity for MOR208, an Fc-engineered CD19 antibody, in patients with relapsed or refractory NHL.

- Promising objective response rates observed; ≥20% in the DLBCL cohort and ≥27% in the combined iNHL cohort.

- Safety

- Tolerability

- Pharmacokinetics and pharmacodynamics

Conclusions

- The MOR208 exposures showing clinical efficacy are mainly reached at 12 mg/kg with an initial weekly dosing.

- The most common treatment emergent adverse events (TEAEs) were headache and upper respiratory tract infection.

- Infusion-related reactions were reported in 5% (10/202) of patients:
  - Grade 1 or 2 in 6 patients; grade 4 response in 1 patient.

- The most common grade 3 treatment emergent adverse events are summarized in Table 3.

- No severe toxicity or treatment related death.

- Table 2. Response

- Table 3. Adverse events

- Table 3. AEs (all patients)

- Reference


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