A phase I/IIa study of the human anti-CD38 antibody MOR202 (MOR03087) in relapsed or refractory multiple myeloma (rrMM)

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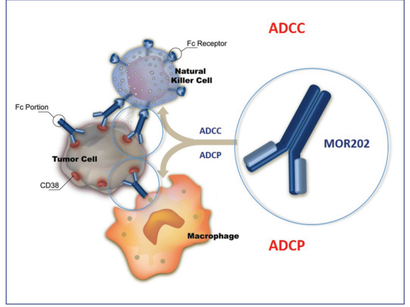
Introduction

- CD38 is a 45 kDa type II transmembrane glycoprotein widely expressed in many hematologic malignancies including multiple myeloma (MM).[1–5]
- MOR202 is a HuCAL-derived human immunoglobulin G1 anti-CD38 antibody that has demonstrated high *in vitro* and *in vivo* efficacy in preclinical models of MM.
- The main mode of action for MOR202-induced lysis of MM cells comprises antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP).[6–7]

Figure 1. MOR202 mode of action



ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis.

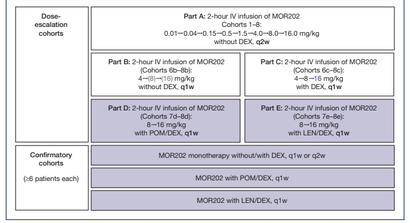
Study objectives

- To evaluate MOR202 in adult patients with relapsed or refractory MM (rrMM).
- **Primary outcome measures:**
  - Maximum tolerated dose (MTD) and/or recommended dose/schedule of MOR202 as monotherapy with and without dexamethasone (DEX), and in combination with pomalidomide (POM)/DEX and lenalidomide (LEN)/DEX (see Figure 2 footnote)
  - Safety: Incidence and severity of adverse events (AEs)
  - Immunogenicity of MOR202.
- **Secondary outcome measures:**
  - Pharmacokinetics (PK) of MOR202 without and with POM/DEX and LEN/DEX
  - Overall response rate, duration of response, time-to-progression, and progression-free survival.

Overall study design

- This is a phase I/IIa open-label, multicenter, dose-escalation study (3 + 3 design; Figure 2).

Figure 2. Study design



q1w, weekly; q2w, every 2 weeks; DEX, dexamethasone; IV, intravenous; LEN, lenalidomide; POM, pomalidomide. Cohorts of part C (weekly cohort 8c), parts D-E (cohorts 7d/e-8d/e) and the 3 confirmation cohorts are planned (see blue text and area shaded blue). Cohort 7b and 8b (8 and 16 mg/kg w/o DEX) did not take place according to Data Monitoring Committee recommendation. During cycle 1 patients in all cohorts received/will receive a loading dose on day 4.

- Parts A–C were conducted in patients with rrMM who had failed 2 previous therapies including an immunomodulatory drug and a proteasome inhibitor.
- Duration of treatment:
  - Patients from part A (cohorts 1–6) were treated for up to 2 cycles only (2 × 28 days)
  - Patients from subsequent cohorts were/will be treated until disease progression (PD) for up to 2 years.
- Route of MOR202 administration: 2-hour intravenous (IV) infusion.
- Premedication: antipyretic, histamine H1 receptor blocker.
- On completion of parts A–E, confirmatory cohorts (of ≥6 patients each) are planned to validate the MTD and/or recommended dose/schedule of MOR202 as monotherapy with and without DEX (q1w or q2w), and in combination with POM/DEX and LEN/DEX (q1w).

Patients and methods

- **Main inclusion criteria:**
  - Adult patients with rrMM who had failed ≥2 previous therapies, including an immunomodulatory agent and a proteasome inhibitor (parts A–C)
  - Documented progression during or after the last prior therapy for MM
  - Serum M-protein ≥0.5 g/100 mL and/or urine M-protein ≥200 mg/24-hour period; absolute neutrophil count (ANC) ≥1,000/mm³.
- **Main exclusion criteria:** primary refractory MM; solitary plasmacytoma or plasma cell leukemia; previous allogenic stem cell transplant.

Results

- This is the first report of safety, preliminary PK and efficacy data for patients in part A and most patients in parts B and C.
- This study is ongoing and higher doses of MOR202 will be evaluated in patients as monotherapy with and without DEX in parts B–C, with immunomodulatory agents in patients in parts D–E, and in phase IIa confirmatory cohorts (Figure 2).
- As of April 13, 2015, 42 patients had been treated; 14 and 28 patients in cohorts 1–4 and 5–8, respectively (Table 1).

Table 1. Patient baseline characteristics

Cohorts Dosing (mg/kg) Patients treated	1–4 0.01–0.5 14	5–8 1.5–16 28	Total 42
Median age (years)	70	69.5	69.5
Gender, %			
Female	42.9	28.6	33.3
Male	57.1	71.4	66.7
Ethnicity, %			
Caucasian	100	100	100
Median Karnofsky PS, %	90	90	90
Median number of prior therapy lines (range)	4 (2–10)	4 (2–11)	4 (2–11)
ASCTs, %	93	75	81
Prior therapies, % (selection)			
Bortezomib	100	100	100
Lenalidomide	100	96.4	97.6
Melphalan	100	96.4	97.6
Cyclophosphamide	64.3	82.1	76.2
Doxorubicin	57.1	60.7	59.5
Thalidomide	35.7	39.3	38.1
Pomalidomide	0	21.4	14.3
Carfilzomib	0	7.1	4.8

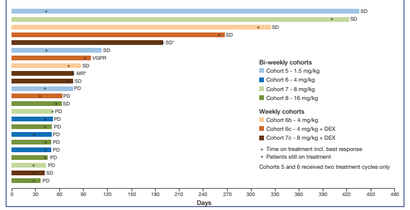
ASCTs, autologous stem cell transplants; PS, performance status.

Preliminary efficacy

Data of patients (cohorts 5–8) receiving ≥1 treatment cycle.

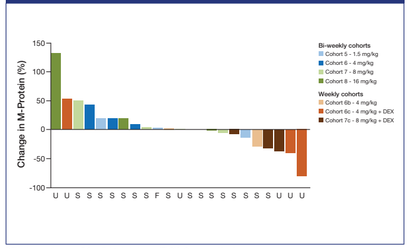
- Time on study and best response (Figure 3).
- Maximal change in M-protein (Figure 4).

Figure 3. Time on study and best response - updated data from 20 May 2015



DEX, dexamethasone; MR, minor response; PD, progressive disease; SD, stable disease; VGPR, very good partial response.

Figure 4. Maximal change in M-protein - updated data from 20 May 2015



DEX, dexamethasone; F, free light chain kappa (FLCk); S, serum; U, urine.

Safety

- 42 (100%) patients experienced AEs during treatment irrespective of causality.
- 18 (42.9%) patients discontinued treatment due to AEs, in 3 (7.1%) cases due to a suspected causal relationship.
- There have been no treatment-related deaths.
- The MTD of MOR202 has not yet been reached.

Table 2. Most frequently reported AEs

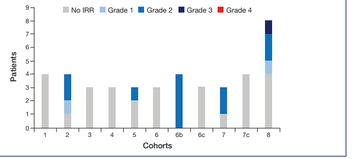
Cohorts Grades	1–4 ≥3	 All	5–8 ≥3	 All	Total ≥3	 All
Hematologic AEs* (≥10%)						
Anemia	7.1	42.9	-	28.6	2.4	33.3
Lymphocyte count decreased	-	7.1	21.4	25.0	14.3	19.0
WBC count decreased	7.1	7.1	7.1	25.0	7.1	19.0
Leukopenia	-	7.1	7.1	17.9	4.8	14.3
Neutrophil count decreased	-	0.0	3.6	17.9	2.4	11.9
Thrombocytopenia	-	0.0	7.1	17.9	4.8	11.9
Non-hematologic AEs (≥15%)						
Fatigue	-	42.9	-	28.6	-	33.3
Nausea	-	35.7	-	21.4	-	26.2
Diarrhea	-	28.6	-	14.3	-	19.0
Headache	-	42.9	-	3.6	-	16.7
Nasopharyngitis	-	28.6	-	10.7	-	16.7
Pyrexia	-	21.4	-	14.3	-	16.7

*MedDRA System Organ Classes "Blood and Lymphatic System Disorders" and "Investigations" are applicable and therefore Preferred Terms from both are included; AEs, adverse events; WBC, white blood cell.

Infusion tolerability

- A 2-hour IV infusion was feasible in all patients.
- Infusion-related reactions (IRRs) occurred in 13 (31%) patients and only in patients receiving MOR202 without DEX, mainly during the first infusion.
- All IRRs were grade 1–2 except for 1 patient (grade 3).
- No IRRs occurred in patients who received DEX.

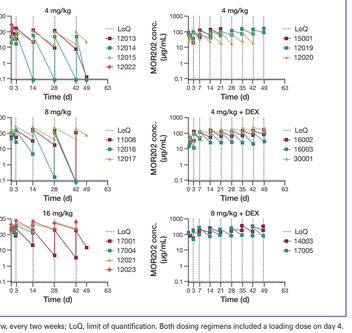
Figure 5. Infusion-related reactions



Pharmacokinetics and immunogenicity

- In most patients treated q2w, a dominant target-mediated sink effect was observed leading to low or no detectable serum trough levels (Figure 6A, ≥4 mg/kg only).
- In contrast, patients treated q1w (≥4 mg/kg) showed constant or slightly accumulating trough levels (Figure 6B).
- Data indicate that further dose-escalation might lead to full target saturation at higher dose levels.
- A terminal elimination half-life of 2–3 weeks was estimated by comparing modelled serum concentrations of MOR202 (at 4 mg/kg, q1w) with measured patient data.
- Only 1 patient (0.15 mg/kg, q2w) developed a transient anti-MOR202 antibody response.

Figure 6. MOR202 serum concentrations over time for patients dosed at ≥4mg/kg. Initial two cycles following: A. q2w dosing; B. q1w dosing.



q1w, weekly; q2w, every two weeks; LoQ, limit of quantification. Both dosing regimens included a loading dose on day 4.

Case report of a very good partial response (VGPR)

- Female, 45 years of age, Karnofsky PS 90%.
- First diagnosis: February 2006.
- MM staging: International staging system III; Salmon and Durie IIIB.
- 4 prior therapies, including an autologous stem cell transplant.
- Chromosomal aberration: del13.
- Allocated to part C, cohort 6 (4 mg/kg, q1w, with DEX).
- 15 infusions received.
- VGPR was determined after 29 days on treatment.
- The patient developed new bone lesions after 84 days on treatment.

Conclusions

- The MTD of MOR202 has not yet been reached.
- MOR202 can be safely administered as a 2-hour IV infusion and is well tolerated.
- In the cohorts without DEX the incidence of IRRs was low and mainly limited to the first infusion.
- No IRRs were reported in patients treated with MOR202 plus DEX.
- In this heavily pre-treated rrMM population, encouraging long-lasting tumor control has been observed already in early cohorts.
- PK data indicate the potential for full target occupancy in patients who receive 16 mg/kg MOR202, q1w.
- Further cohorts will evaluate doses of MOR202 up to 16 mg/kg q1w with DEX, as well as in combination with POM/DEX and LEN/DEX.

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