MOR202, a Human Anti-CD38 Monoclonal Antibody, Mediates Potent Tumoridal Activity In Vivo and Shows Synergistic Efficacy in Combination with Different Antineoplastic Compounds

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Abstract

Background:
MOR202, a human anti-CD38 monoclonal antibody, is currently being evaluated in a phase I/II clinical trial for the treatment of multiple myeloma (MM). Pharmacologically, MOR202 exerts its tumoricidal effect by eliciting antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). Aside from a promising single-agent activity profile, experimental in-vitro indicate additive or synergistic effects of MOR202 in combination with different types of standard care compounds in MM such as lenalidomide (LEN), bortezomb (BOR).

Aims:
To compare in-vivo the ADCP activity of MOR202 on MM cells and normal hematopoietic cells with the respective profiles of two other anti-CD38 antibodies in clinical development: daratumumab and isatuximab. To determine the tumoricidal efficiency of MOR202 in vivo in combination with either LEN, BOR or melphalan (MEL), representing immunomodulatory drugs (IMiDs), proteasome inhibitors, and alkylating agents, respectively.

Methods:
The in vitro ADCP activity of the antibodies was assessed by fluorescence activated cell sorting using a panel of CD38+ MM cell lines in presence of non-tumor cell cultures. The potential for cytotoxicity was assessed in normal hematopoietic cells was tested on purified natural killer (NK) cells by measuring NK-NK killing. In the in-vivo studies, two independent mouse models were employed to assess therapeutic effects. Firstly, as a model for MM, NCI-H929 cells were inoculated intravenously into the bone marrow to establish an orthotopic model characterized by prolymphocyctic hematopoiesis of the disease, such as bone lysis, and the emergence of serum M protein. Bone density, evaluated by microcomputed tomography (µCT), and M protein serum levels were used as endpoints for the antitumor activity of the single agents. Secondly, for the disseminated xenograft model, Ramos non-Hodgkin lymphoma cells were intravenously injected into immunodeficient mice. Survival served as the primary endpoint, reflecting the success of the combination. Combinatorial drug interactions were evaluated according to Clarke, 1997 (Breast Cancer Res Treat, 46:255-76) and Chou, 2006 (Pharmac Res, 58:621-81).

Results:
In the in vitro ADCP studies on MM cell lines, the maximum killing of MOR202 was equivalent to the tested comparator antibodies (Figure 2A). In contrast, the potential to induce killing of normal NK cells expressing low levels of CD38 was significantly reduced for MOR202 compared with surrogates of daratumumab and isatuximab (n=10 donors, median of 7% specific killing vs 30% and 37%, respectively). This appeared to be independent of FcγRIIA receptor polymorphism status (Figure 2B). In the in vivo MM model, MOR202 administration at 3 mg/kg significantly reduced bone lysis by up to 72.5%, relative to vehicle control. Treatment with LEN, BOR, or MEL alone also decreased bone lysis significantly, as compared with vehicle control. However, coadministration of MOR202 with LEN, BOR, or MEL completely abolished or dramatically reduced bone lysis (Figure 4A). Drug interaction analyses indicated synergistic efficacy. The markedly reduced bone lysis seen with combination therapy was accompanied by a reduction (>50%) of serum M protein levels indicating a significant decrease in tumor load (Figure 4B). In the disseminated lymphoma model, LEN or BOR administration had no impact on survival time as compared with vehicle control. In contrast, MOR202 treatment resulted in significantly improved survival compared with vehicle control (median 25 vs 42 and 43.5 days respectively, in two independent experiments) (Figure 6). Notably, coadministration of MOR202/LEN, or MOR202/BOR further improved survival, with LEN or BOR alone demonstrating no effect. The combination of LEN/MOR202/BOR improved survival time beyond the single agents, on account of its immunomodulatory effect, as well as improved efficacy in the expression of β2 integrins (i.e., a sub-set of synergy). Of note, all mice receiving monotherapy finally succumbed to the tumor. In contrast, 37.5% of mice treated with MOR202/LEN and 40% of mice treated with MOR202/BOR were completely free of tumor until study termination at day 58.

Conclusions:
MOR202 shows equivalent ADCC to CD38 high expressing MM cells as compared with surrogates of daratumumab and isatuximab, while providing significantly reduced off-target killing of CD38 low expressing normal NK cells. In addition, MOR202 synergistically works in combination with different compounds representative of classes of agents commonly used in the treatment of hematologic malignancies.

Summary and Conclusion
- MOR202 shows equivalent ADCC activity towards CD38 high expressing MM cells (on-tumor) compared with surrogates of daratumumab and isatuximab
- MOR202 spares CD38 low expressing cells e.g. NK effector cells (off-tumor) in contrast to surrogates of daratumumab and isatuximab
- MOR202 reduces bone lysis and M protein serum levels in an experimental mouse model of multiple myeloma
- MOR202 improves survival rates in an experimental disseminated lymphoma mouse model
- MOR202 shows synergistic efficacy in vivo in combination with relevant standard of care compounds in MM, i.e., IMiDs, proteasome inhibitors, and alkylating agents