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MP0250, a bispecific VEGF- and HGF-blocking multi-DARPin*, in combination with bortezomib in multiple myeloma: preclinical rationale and phase 2 study outline

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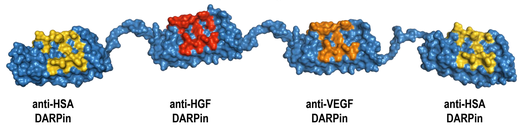
Background

Despite advances in the treatment of multiple myeloma (MM), there is no cure. Patients eventually relapse, requiring multiple lines of treatment. Upregulation of both the vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) pathways has been implicated in loss of response to therapy. VEGF and HGF are increasingly overexpressed with MM progression and have been linked to poor prognosis: they are known to be able to stimulate neovascularization, bone destruction, and myeloma proliferation, migration, and adhesion in the bone marrow. Preclinical studies have shown that refractory, high HGF-expressing MM cell lines can be re-sensitized to treatment by inhibiting HGF/cMET signaling.

MP0250 is a multi-DARPin with three specificities, able to simultaneously neutralize the activities of vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) and also to bind to human serum albumin (HSA) to give an increased plasma half-life and potentially enhanced tumor penetration.

DARPins® (designed ankyrin repeat proteins) are small genetically engineered proteins that bind to specific targets with very high affinity (i.e. picomolar; cartoon shown below with target binding sites in color).



MP0250 is the first systemically delivered DARPin. Like other DARPins, MP0250 can be easily manufactured and is very stable. DARPins are very versatile, can bind to virtually any target, and can be easily formatted in a multi-specific way to block several biological activities.

Objective

We are presenting the preclinical rationale for using MP0250 in combination with the proteasome inhibitor bortezomib (BTZ), a mainstay of MM therapy, in a planned phase 2 study in MM patients.

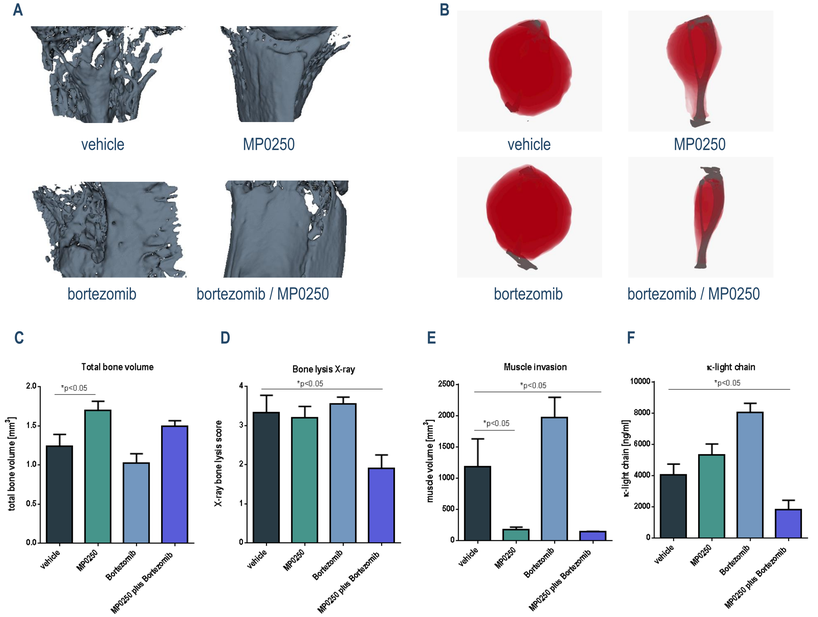
Methods

MP0250 and BTZ, alone and in combination, were tested in an orthotopic murine xenograft model in which human MM cells were implanted in murine tibial bone marrow. The model was performed at VivoPharm. Briefly, NCI-H929 cells (2.5 Mio per mouse) were implanted orthotopically into the right tibiae of 12 SCID mice per group. Vehicle control (PBS) and MP0250 (40 mg/kg) were administered once every three days via intravenous tail vein injection (i.v.), bortezomib (0.6 mg/kg) was administered twice weekly via intraperitoneal injection (i.p.), combinations were administered in the manner described above. Treatments commenced on Day 0 and continued over a period of 40 days. Invasion of tumor cells into the surrounding muscle of the inoculated leg was measured using calipers during the study and by CT at the end of the study. Images of the tumor/muscle in and around the tibiae were acquired with micro-CT. Bone lysis due to tumor growth was monitored by x-ray images taken on Days 7, 35 and 41 post-initial treatment. Visual assessment of bone lysis on the inoculated right tibiae was made from each x-ray image using a scoring system developed to indicate severity of lysis: 0 - no bone lysis; 1 - onset/mild bone lysis; 2 - moderate bone lysis; 3 - severe bone lysis; 4 - very severe bone lysis. Micro-CT analysis was performed on tibiae excised at the end of the study for analysis of bone lysis parameters: total bone volume (TBV), cortical bone volume (CBV) and trabecular bone volume (Tb.BV). Ex vivo analysis included the determination of serum M protein levels monitored by detection of κ-light chain using a human kappa ELISA kit (LubioSciences, No. E88-115).

Preclinical efficacy in multiple myeloma model

Effect of MP0250 alone and in combination with low dose bortezomib in an MM *in vivo* model

- MP0250 significantly inhibited the reduction of total and cortical bone volume ($p<0.05$) and was shown to reduce erosion of the outer part of the bone; it had no significant effect on trabecular bone (shown by micro-CT imaging, Figs A & C)
- MP0250 in combination with bortezomib significantly inhibited bone lysis ($p<0.05$) (shown by X-ray, Fig D) and invasion of tumor cells into the muscle ($p<0.05$) (shown by micro-CT in Fig B & caliper measurement in Fig E)
- MP0250 in combination with bortezomib significantly ($p<0.05$) inhibited tumor cell growth (shown by κ-light chain secretion, Fig F)



Inhibition of MM tumor cell growth, bone erosion and muscle invasion

The figures show results of micro-CT and X-ray analyses and determination of secreted κ-light chain in the mouse model. Groups were: vehicle (PBS), MP0250 (40 mg/kg), bortezomib (0.6mg/kg) and the combination group of MP0250 (40mg/kg) plus bortezomib (0.6 mg/kg). Treatment of mice was initiated day 0 post tumor implantation. Mice received MP0250 for 5 weeks, 3x weekly (i.v.), and bortezomib twice weekly via i.p. injection. Figure A shows representative three-dimensional micro-CT scan images (Day 41);. Figure B shows representative leg muscle CT scan images (Day 41). Figure C shows the mean total bone volume in inoculated tibiae ± SEM determined by micro-CT scan. MP0250 alone and in combination with bortezomib significantly prevented bone erosion, p= 0.0184 (need 2 p values). Figure D shows the mean bone lysis score in inoculated tibiae ± SEM assessed by X-ray imaging on Day 41. MP0250 plus bortezomib significantly prevented bone erosion, p= 0.0228. Figure E shows the mean muscle volume (mm3) ± SEM in inoculated legs on Day 41. MP0250 as well as a combination of MP0250 and bortezomib significantly prevented tumor invasion of muscle; p=0.0214 (MP0250) and p=0.0123 (MP0250 / bortezomib). Figure F shows secreted κ-light chain in serum at the end of the study. MP0250 in combination with bortezomib significantly reduced M-protein secretion and thus tumor cell growth, p=0.0232.

Study Protocol

Rationale

It has been demonstrated that the HGF/MET pathway is upregulated in plasma cells as well as in bone marrow endothelial cells of MM patients refractory to proteasome inhibitor (e.g. bortezomib) and/or IMiD (e.g. lenalidomide) treatment. This is associated with increased bone marrow angiogenesis, tumour growth and multi-drug resistance. Nonclinical studies indicate that combined inhibition of VEGF and HGF can reverse these activities.

Study summary and objectives

This is a Phase II open-label, single-arm, multicentre trial of MP0250 plus bortezomib (BTZ)+Dexamethasone(DEX) in patients with refractory and relapsed multiple myeloma (RRMM).

Primary objectives:

- Estimate the efficacy of MP0250 plus BTZ+DEX, based on overall response rate (ORR)

Secondary objectives:

- Determine the safety profile of MP0250 plus BTZ+DEX
- Characterise the immunogenicity of MP0250
- Characterise the pharmacokinetics (PK) of MP0250 when administered together with BTZ+DEX
- Estimate the efficacy of MP0250 plus BTZ+DEX in terms of progression free survival (PFS) and duration of response (DOR)

Patients and methods:

Key inclusion criteria:

- Multiple myeloma patients who have received ≥2 lines of therapy, including BTZ and an immunomodulatory agent (IMiD), and have shown no response to or have progressed on the most recent treatment within 60 days after the most recent therapy.
- Presence of a measurable disease with at least one of the following criteria: (1) Serum M protein ≥1 g/dL (10 g/L), (2) Urine M protein ≥200 mg/24 h, (3) in patients without detectable serum or urine M protein, serum FLC >100 mg/L (involved light chain) and an abnormal serum κ/λ ratio, or (4) for IgA patients whose disease can only be reliably measured by serum quantitative immunoglobulin A (qIgA), a qIgA of ≥750 mg/dL (0.75 g/dL).

Key exclusion criteria:

- Patients with MGUS of non-IgM and IgM subtypes, light chain MGUS, Solitary plasmacytoma (alone or with minimal marrow involvement), systemic Ig light chain amyloidosis, Waldenstrom's Macroglobulinaemia, myelodysplastic syndrome, plasma cell leukaemia defined as a plasma cell count >2000/mm^3 and polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) syndrome
- Significant neuropathy (Grades 3 to 4, or Grade 2 with pain) within 14 days prior to enrolment.

Study design and treatment:

- In the safety lead-in and dose escalation part, up to three doses of MP0250 will be administered in combination with BTZ+DEX to establish a safe dose of MP0250 when given in combination with BTZ+DEX (6 patients per dose cohort).
- In the treatment part, the selected dose cohort of MP0250 will be expanded by additional 28 patients to a total of 34 patients.
- The study treatment will be based on a 21 day cycle consisting of MP0250 (D1), BTZ (Days 1, 4, 8, 11) and DEX (Days 1, 2, 4, 5, 8, 9, 11, and 12) for 8 cycles, or more in case of benefit.

Conclusion

MP0250, a multi-DARPin specifically blocking HGF and VEGF, improves the efficacy of BTZ in a preclinical MM model. Consequent to this and a favorable phase 1 study, MP0250 will be evaluated in a phase 2 study in MM in combination with BTZ+DEX.

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