Abstract 1041 TiP

MP0250 – a dual inhibitor of VEGF and HGF - plus bortezomib + dexamethasone in a Phase 2 open-label, single-arm, multicenter trial in patients with refractory and relapsed multiple myeloma (RRMM)

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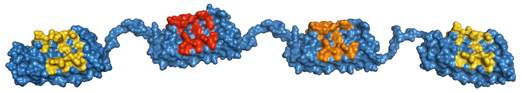
Background

Despite recent advances in the treatment of multiple myeloma (MM), 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 and linked to poor prognosis through different mechanisms such as stimulation of angiogenesis, bone destruction, and myeloma cell proliferation and migration[1,2].
MP0250 is a first-in-class, tri-specific multi-domain DARPin® drug candidate neutralizing VEGF and HGF as well as binding to human serum albumin (HSA) to increase plasma half-life. MP0250 shows activity in multiple preclinical tumor models amongst them an MM model in which it enhances the effects of bortezomib on e.g. M protein production and bone lysis[3]. MP0250 has shown a favorable safety profile in a Phase 1 clinical trial in advanced solid tumors[5].

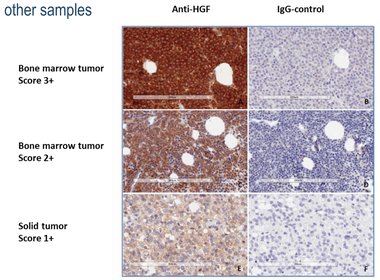


MP0250 is the first systemically administered DARPin® drug candidate. Like other DARPin® proteins, MP0250 can be easily manufactured and is very stable. DARPin® molecules are very versatile, can bind to virtually any defined target, and can be easily formatted in a multi-specific way to block several biological activities.

HGF expression in MM

HGF is highly overexpressed in bone marrow biopsies of MM

- HGF was highly overexpressed (3+) in 6 out of 8 MM samples and moderately expressed (2+) in the two other samples



IHC for HGF in bone marrow biopsies of MM

HGF expression was tested on FFPE material from MM bone marrow biopsies with representative strong, moderate, and weak HGF-immuno-reactivity in human bone marrow tumours and solid tumour. Digital scans demonstrate the range of HGF-immuno-reactivity in human tumour samples. Sections incubated with anti-HGF antibody (left) and concentration matched non-immune IgG control (right) are shown. Strong 3+, moderate 2+ and weak 1+ cytoplasmic HGF-immuno-reactivity was observed in human tumour cells. No non-specific immunoreactivity was seen in the IgG control or in the absence of primary antibody (data not shown).

Clinical Rationale

MP0250 is a novel biological therapeutic agent that selectively inhibits two signalling pathways (VEGF/VEGFR and HGF/c-MET) involved in multiple myeloma[4]. The HGF/c-MET pathway is upregulated in plasma cells as well as in bone marrow endothelial cells of multiple myeloma (MM) patients refractory to proteasome inhibitor (e.g. bortezomib) and/or IMiD (e.g. lenalidomide) treatment. This leads to increased bone marrow angiogenesis, tumour growth and metastatic spread and mediates multi-drug resistance. Inhibition of the c-MET pathway has been shown to impair several activities including chemotaxis, motility, adhesion, spreading, and whole angiogenesis in bone marrow endothelial cells significantly when combined with bortezomib or lenalidomide, both *in vitro* and *in vivo*[1].

Study Protocol

Study summary and objectives

Phase II single-arm, multi-center, open-label study to assess the efficacy, safety, pharmacokinetics and immunogenicity of MP0250 plus bortezomib (BTZ) + dexamethasone (DEX) in patients with refractory and relapsed multiple myeloma (RRMM).

Primary objective:

- Estimate the efficacy of MP0250 plus bortezomib (BTZ) + dexamethasone (DEX) based on overall response rate (ORR) in patients with MM who have received ≥ 2 lines of therapy, including bortezomib and an immunomodulatory drug (IMiD), and have shown no response to, or have progressed on the most recent treatment, or within 60 days of the most recent therapy.

Secondary objectives:

- Determine the safety profile of MP0250 plus bortezomib + dexamethasone
- Characterize the immunogenicity of MP0250
- Estimate the efficacy of MP0250 plus bortezomib + dexamethasone in terms of progression free survival (PFS) and duration of the response (DOR)

Exploratory objectives:

- Estimate efficacy in terms of overall survival (OS)
- Characterize the PK of MP0250 when administrated together with bortezomib + dexamethasone
- Exploration of potential biomarkers, relevant for MM and the mechanism of action for MP0250.

Sample size:

- N = 40 Patients
  - Part 1: 12 (2 x 6) patients / two dose cohorts
  - Part 2: additional 28 (for a total of 34 patients in the target dose).

Patients and Methods

Patients with RRMM treated with ≥ 2 prior lines of therapy will be included. 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. Responses will be assessed using the modified IMWG response criteria and toxicities graded using CTCAE v4.03 or higher.

Key inclusion criteria:

Presence of a measurable disease with at least one of the following criteria:

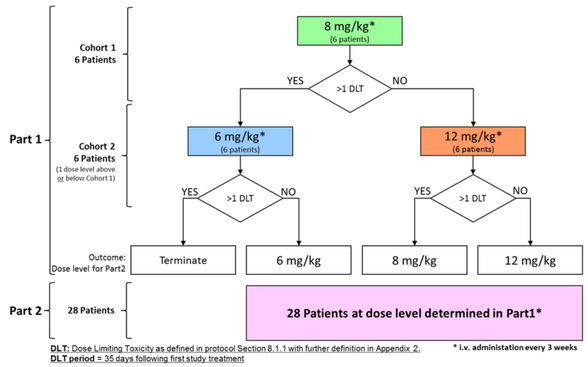
- Serum M protein ≥1 g/dL (10 g/L),
- Urine M protein ≥200 mg/24 h,
- Patients without detectable serum or urine M protein, serum FLC >100 mg/L (involved light chain) and an abnormal serum κ/λ ratio, or
- for IgA patients whose disease can only be reliably measured by serum quantitative immunoglobulin A (qIgA), a qIgA of ≥750 mg/dL (0.75 g/dL).

Key exclusion criteria:

Patients with the following conditions are excluded:

- 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)
- Uncontrolled hypertension, active congestive heart failure (New York Heart Association [NYHA] Class III to IV), symptomatic cardiac ischemia or myocardial infarction within 6 months of screening
- Clinical signs or documented leptomeningeal or cerebral involvement of MM.

Dose Escalation



In the safety lead-in and dose escalation part 1, up to two dose levels of MP0250 (i.v.) 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 2, the selected dose cohort of MP0250 determined in part 1 will be expanded by additional 28 patients to a total of 34 patients.

Study Progress

Since May 23, 2017, 2 participants have been recruited to receive MP0250 plus BTZ + DEX (1 female, 1 male) with a median of 2.5 lines (range 2-3) of prior treatment.

References

1) Ferrucci A. et al (2014). A HGF/c-MET autocrine loop is operative in multiple myeloma bone marrow endothelial cells and may represent a novel therapeutic target. Clin Cancer Res 20(22): 5796–807.
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5) M.R. Middleton, A. Azaro, S. Kumar et al (2016) Interim results from the completed first-in-human Phase I dose escalation study evaluating MP0250, a multi-DARPin® blocking HGF and VEGF, in patients with advanced solid tumors.

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