Abstract : PF596

MP0250 IN COMBINATION WITH BORTEZOMIB AND DEXAMETHASONE IN PATIENTS WITH RELAPSED-AND-REFRACTORY MULTIPLE MYELOMA: FIRST SAFETY AND EARLY EFFICACY ANALYSIS OF MP0250-CP201

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MP0250 Mechanism of Action

MP0250 is a novel biological therapeutic agent that selectively inhibits two signalling pathways (VEGF/VEGFR and HGF/c-MET) that are key regulators in the development and progression of multiple myeloma. These pathways affect tumour cell growth directly but also shape the tumour microenvironment by promoting bone marrow angiogenesis, bone destruction and mediating drug resistance to e.g. proteasome inhibitors or IMIDs[1].

We have shown in preclinical models that combining bortezomib and MP0250 has an additive effect and breaks resistance to bortezomib.

MP0250 is a first-in-class, tri-specific DARPin drug candidate with several ankyrin repeat binding domains that simultaneously neutralizes VEGF-A and HGF as well as binds to human serum albumin (HSA) resulting in an increased plasma half-life and potentially enhanced tumor penetration (Figure 1).

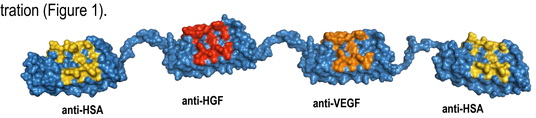


Figure 1. Model of MP0250 with binding surfaces in colour.

MP0250-CP201 Study Design

This study is a Phase II open-label, single-arm, multicenter trial of MP0250 plus bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma containing a dose escalation (Part 1) and expansion (Part 2) part.

Objectives:

- **Primary:** overall response rate (ORR)
- **Secondary**: safety, immunogenicity, progression free survival (PFS) and duration of the response (DOR)
- **Exploratory**: Overall survival (OS); PK of MP0250 when administered together with bortezomib + dexamethasone; potential biomarkers relevant for MM and the mechanism of action of MP0250.

Patient Population: MM patients 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.

Sample size: N = 40 Patients

Part 1: 12 in two dose cohorts (8 mg/Kg and 12 mg/Kg q3w - 6 patients each)

Part 2: additional 28 (for a total of 34 patients in the target dose).

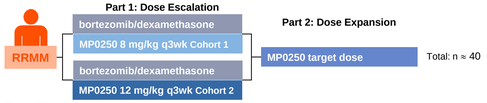


Figure 2. Enrollment Schedule

Methods

Study MP0250-CP201 (NCT03136653) is being conducted at 9 centres in three European countries (Germany, Italy and Poland).

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 ≥0.5 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.

Statistical Analyses and Assessments

- Patients who received ≥1 administration of study treatment were included in the safety analysis (N=10)
- Response rates were based on the response-evaluable population:
  - Patients in the response-evaluable population had measurable disease at screening visit, received ≥ 1 study treatment, and had adequate post-baseline disease assessments or discontinued treatment due to progressive disease
  - Response is based on International Myeloma Working Group Consensus criteria

Results

- Up-to-date into Cohort 1 (8 mg/kg MP0250) 8 patients have been treated
- Cohort 2 is ongoing; to date, 2 patients have been treated with 12 mg/kg MP0250.

Table 1. Patient Characteristics

Characteristics		Cohort 1 MP0250 (8mg/Kg) + Vd (n=8)	Cohort 2 MP0250 (12 mg/Kg) + Vd (n=2)
Age	Median (years)	57.6	58
	< 65 years	6 (75%)	2 (100%)
	65-74 years	2 (25%)	0
	>75 years	0	0
Gender	Male	4 (50%)	0
	Female	4 (50%)	2(100%)
ECOG status, n(%)	0	4 (50%)	1(50%)
	1	4 (50%)	1 (50%)
Median Time Since First Diagnosis		5.3 years	7.2 years
Prior lines of anti-myeloma treatment		3.3 (2-5)	4 (3-5)
PI refractory		4 (50%)	0%

Table 2. Drug Exposure

	Cohort 1 MP0250 (8 mg/Kg) + Vd (n=8)	Cohort 2 MP0250 (12 mg/Kg) + Vd (n=2)
Total n° of Cycles	5 (1-12 cycles)	2 (1-2)
Dose interruptions	2 out 8 (25%)	1 (50%)
Reason for Dose Interruption (n,%)		
AE	2 (25%)	1 (50%)
Other (including withdrawn)	0	0
Dose Reductions	2	0
Discontinuation of Treatment (n,%)	5 (62.5%)	0
Reason for discontinuation (n,%)		
Progressive Disease	3 (37.5%)	0
AE	1 (12.5%)	0
Other (including withdrawn)	1 (12.5%)	0

Table 3. Treatment Emergent Adverse Event* reported in safety population (N=10)

AE Preferred Term	AE [n]	Patients with AE [n]	AE Grade 3 [n]	Patients with AE grade 3 [n]
Hypertension	8	3	5	2**
Thrombocytopenia	6	4	3	2
Upper Respiratory Tract Infection	5	3	-	
Dyspnoea	2	2		
Respiratory Tract Infection	2	2		
ALT increased	2	1	2	1
GGT increased	2	1	2	1
Anaemia	1	1	1	1
Neutropenia	1	1	1	1
Proteinuria	1	1	1	1***
Urinary Retention	1	1		

* Any grade AEs reported in ≥2 patients or grade ≥3 AEs reported in any patient.
** Hypertension Grade 3 in one single patient represents the only DLT reported in cohort 1 [8 mg/Kg MP0250-CP201].
*** One patient discontinued treatment due to Proteinuria Grade 3.

- ORR among 8 evaluable patients in Cohort 1 was 62.5%. Four patients (50%) achieved a PR and one patient achieved a VGPR. Follow-up in Cohort 2 is very short; to date, 1 pt achieved MR

Figure 3. Time on Study & Best Response

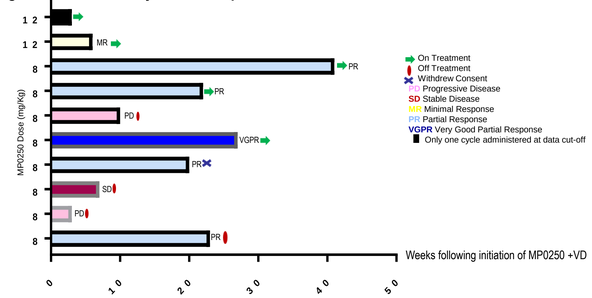
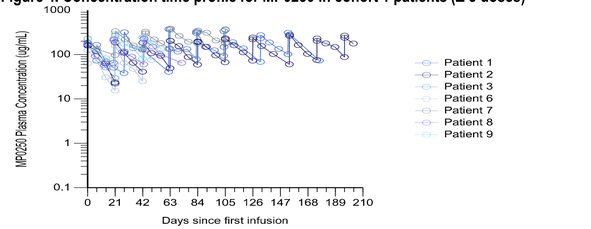


Figure 4. Concentration time profile for MP0250 in cohort 1 patients (≥ 3 doses)



- Repeated dosing in cohort 1 patients shows sustained exposure to MP0250
- Preliminary analysis of PK data indicate a mean half-life of around 11 days for MP0250 in cohort 1 patients

Conclusions

Early data from patients treated in cohorts 1 and 2 with MP0250 plus bortezomib + dex show an acceptable safety profile and promising activity in RRMM patients.

Study enrolment continues across Europe with the 12 mg/kg dose and additional safety and efficacy data are expected at the end of 2018.

Acknowledgment

We thank the patients, their families and clinical research staff from the study centers.

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References

1) Fiedler U, Ekawardhani S, Cornelius A, et al. Targeting angiogenesis in multiple myeloma by the VEGF and HGF blocking DARPin protein MP0250: a preclinical study. Oncotarget. 2017;8(58):98371-83.