The MP0250-CP201 MiRRoR Study: A Phase 2 Study Update of MP0250 Plus Bortezomib and Dexamethasone in Relapsed/Refractory Multiple Myeloma (RRMM) Patients Previously Exposed to Proteasome Inhibitors and Immunomodulatory Drugs

#1899

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Background

Bone marrow neovascularization is a hallmark of multiple myeloma (MM) and progression is associated with a substantial increase in pro-angiogenic factors that promote bone marrow angiogenesis, including vascular endothelial growth factor (VEGF-A) and hepatocyte growth factor (HGF). Currently no agents blocking these two hallmarks are in clinical development in MM.

MP0250, A TRI-SPECIFIC DARPIN® DRUG CANDIDATE, selectively inhibits two signaling pathways (VEGF/VEGFR and HGF/c-MET) that are key regulators in the development and progression of MM. These pathways directly affect tumor cell growth, and also shape the tumor microenvironment by promoting bone marrow angiogenesis and bone destruction, as well as mediating drug resistance to proteasome inhibitors (PI) and immunomodulatory drugs (IMIDs)[1,2]. MP0250 contains four designed ankyrin repeat domains, two that bind to HGF and VEGF with high specificity and sensitivity, and two that bind to human serum albumin (HSA) in order to increase plasma half-life (Fig.1).

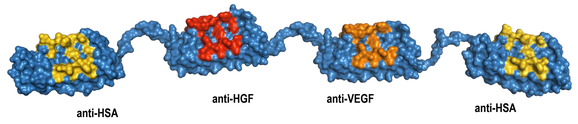

Figure 1. Model of MP0250 (binding surfaces shown in colour)

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Preclinically, MP0250 enhanced sensitivity of MM cells to bortezomib, inhibited tumor growth and reduced bone destruction[3]. A phase 1/2 open-label, single-arm study of MP0250 plus bortezomib and dexamethasone (triple combination) in patients with relapsed/refractory MM (RRMM) was initiated in May 2017 (NCT03136653). The initial phase 1 dose escalation (part 1) is completed and 8 mg/kg MP0250, q3w was established as the recommended Phase 2 dose for the triple combination. The phase 2 dose-expansion (part 2) is ongoing, evaluating safety, tolerability and efficacy of the triple combination at the selected MP0250 dose in patients with RRMM who have progressed after bortezomib and an IMiD either alone or in combination. Preliminary data for patients treated with 8 mg/kg MP0250 are reported.

Study Design

Study MP0250-CP201 is being conducted in 9 centers in Germany, Italy and Poland. Eligible patients are aged ≥18 years with an ECOG performance status ≤1, RRMM with measurable disease (serum M protein ≥0.5 g/dL or urine M protein ≥200 mg/24 h), ≥2 prior treatment regimens including bortezomib and an IMiD and have shown no response to, or progression on or within 60 days of, the most recent therapy. Patients with peripheral neuropathy grade ≥2, uncontrolled hypertension, active congestive heart failure, and/or myocardial infarction within 6 months are ineligible.

Patients receive MP0250 8 mg/kg, IV on day 1, subcutaneous bortezomib 1.3 mg/m² on days 1, 4, 8, and 11, and oral dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12, of each 21-day cycle. Up to 43 patients will be enrolled at this dose in the phase 2 part.

The primary efficacy endpoint is the overall response rate (ORR) per International Myeloma Working Group Uniform Response (IMWG) criteria. Secondary endpoints include safety and duration of response. Exploratory endpoints include pharmacokinetics (PK) parameters. Efficacy was analyzed in patients who had at least 1 dose of the triple combination and an on-treatment tumor assessment. Safety was analyzed in patients who received at least 1 dose of the triple combination.

Patients, Treatment & Safety

As of 01 September 2019, 20 patients were treated with 8 mg/kg MP0250, q3w (8 in Part 1, 12 in Part 2), 5 of whom were ongoing. Of the 15 patients who discontinued, 10 were due to disease progression, 3 were due to adverse events (AEs), 1 patient died (from complications of sepsis), and 1 patient withdrew consent. Patients received a median of 7 cycles of the MP0250 triple combination (range 1 to 35), and 5 patients received ≥10 cycles.

Table 1. Patient and disease characteristics

	N = 20
Age (years), Median (range)	63 (46-76)
Males, n (%)	10 (50%)
ECOG, n (%) 0	7 (35%)
1	13 (65%)
Hematologic values, Median (range)	
β2-microglobulin (mg/L)	3.2 (1.5-11.1)
Hemoglobin (g/dL)	11.4 (5.8-13.8)
Platelets (x10⁹/L)	191 (38-327)
ANC (x10⁹/L)	2.9 (1.2-6.4)
Cytogenetics, n (%)	
1q gain	7 (35%)
t(4;14)(p16;q32)	4 (20%)
p53 deletion	2 (10%)
1p deletion	1 (5%)

	N = 20
Time from diagnosis (years), Median (range)	6.7 (1.3-15.9)
N prior lines of treatment, Median (range)	4 (2-9)
2-3 lines, n (%)	9 (45%)
≥ 4 lines, n (%)	11 (55%)
Last therapy prior to MP0250, n (%)	
IMiD	7 (35%)
IMiD + PI	3 (15%)
anti-CD38 ± PI	5 (25%)
PI	5 (25%)
RR to last therapy prior to MP0250, n (%)	15(75%)
IMiD	4 (20%)
IMiD + PI	3 (15%)
anti-CD38 ± PI	5 (25%)
PI	3 (15%)
Prior ASCT, n (%)	17 (85%)

The most frequent grade 3-4 AEs were hypertension, thrombocytopenia, anemia, hyperuricemia and proteinuria, as anticipated for the underlying disease and the anti-VEGF mode of action. Discontinuations due to AEs occurred in 3 patients (2 proteinuria; 1 asthenia). Of note, no treatment-related deaths or infusion-related reactions occurred; 3 patients had peripheral edema, all of which were grade 1 (2 of whom had associated hypoalbuminemia).

Table 2. Treatment-emergent adverse events in ≥2 patients (N=20)

	Any Grade		Grade ≥ 3	
	N	(%)	N	(%)
Hypertension	15	75	9	45
Thrombocytopenia	12	60	8	40
Infection (local/organ)	9	45	0	0
Diarrhea	6	30	1	5
Fatigue	5	25	0	0
Polyneuropathy	5	25	0	0
Anemia	4	20	4	20
Abdominal pain	3	15	0	0
Cataract	3	15	2	10
Dyspnea	3	15	0	0
Edema peripheral	3	15	0	0
Hyperuricemia	3	15	3	15
Insomnia	3	15	1	5
Proteinuria	3	15	3*	15
Conjunctivitis	2	10	0	0
Decreased appetite	2	10	0	0
Dehydration	2	10	0	0
Dysphonia	2	10	0	0
Epistaxis	2	10	1	5
Herpes zoster	2	10	1	5
Hypercholesterolemia	2	10	0	0
Leukopenia	2	10	1	5
Lymphopenia	2	10	1	5
Mucosal inflammation	2	10	0	0
Nausea	2	10	0	0
Peripheral neuropathy/sensory	2	10	0	0
Pneumonia	2	10	1	5

*≥2 g albumin/24 h urine collection

Efficacy

At the efficacy cut-off date of 05 November 2019, all 20 patients were evaluable for tumor response. One patient achieved a complete response (CR), 3 patients achieved very good partial responses (VGPR) and 5 patients achieved partial responses (PR) per investigator assessment (Table 3), giving an ORR of 45%.

Six of nine patients who were relapsed or refractory to a PI-based regimen prior to the triple combination achieved CR, VGPR or PR (Fig. 2). Median duration of response was 5 months (range, 2 to 24). The patient with CR and 2 patients with VGPR have been on treatment for more than 9 months.

Table 3. Characteristics of responders

Pt #	Gender	Age (years)	Durie/Salmon stage at diagnosis	High-risk cytogenetics	N prior therapies	PI-based regimen prior to MP0250	N cycles MP0250	Response on MP0250
1	M	66	Stage 2	1q gain	4	Yes	14+	CR
2	F	64	UNK	No	3	Yes	39+	VGPR
3	M	62	Stage 2	No	4	Yes	14+	VGPR
4	F	67	Stage 2	No	5	No	11	VGPR
5	F	69	Stage 1	No	4	No	10	PR
6	F	63	UNK	1q gain	3	Yes	8	PR
7	F	56	Stage 3A	t(4;14)(p16;q32)	3	No	3	PR
8	M	67	Stage 3A	No	2	Yes	8+	PR
9	M	74	Stage 3A	No	3	Yes	7	PR

Case study: The patient with the longest MP0250 treatment duration and refractory to all prior treatments is depicted: Patient #2, was diagnosed with IgG kappa MM in May 2016. She received 3 prior lines of treatment (cyclophosphamide-thalidomide-dexamethasone; bortezomib-dexamethasone; bortezomib-lenalidomide- dexamethasone), with a best response of SD for each line. She started MP0250 triple therapy in August 2017 and experienced a VGPR lasting 24+ months. Treatment is ongoing.

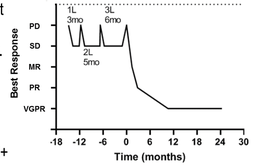
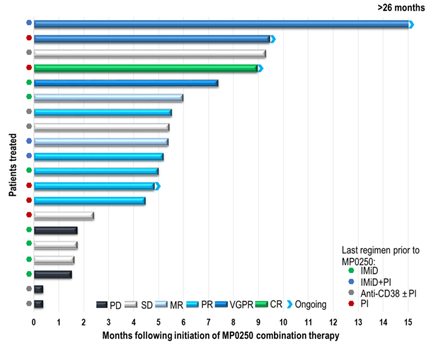


Figure 2. Treatment duration

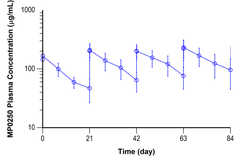


Pharmacokinetics

Repeated MP0250 dosing led to sustained drug exposure throughout the treatment periods that were analyzed (Fig. 3).

Steady state PK of MP0250 in combination with bortezomib and dexamethasone is characterized by a mean half-life of ~2 weeks and a limited accumulation ratio of ~1.5 (based on C_{min}, C_{max} and AUC; Table 4). This ratio was as expected according to the dosing schedule and the half-life of MP0250 when administered as monotherapy.

Figure 3. Plasma concentration (mean, SD) vs time profile over four MP0250 doses (8 mg/kg)



N patients analyzed per dose: 1st n=14, 2nd n=10, 3rd n=6, 4th n=5)

Table 4. Non-compartmental analysis of MP0250 plasma concentration vs time

	C_{max} [µg/mL] Mean (range, n)	C_{min} [µg/mL] Mean (range, n)	AUC [h*mg/mL] Mean (range, n)	Half-life [days] Mean (range, n)
First infusion	170 (112–248, n=19)	48 (15–97, n=19)	45 (29–69, n=19)	13.0 (6.0-19.9, n=14)
Steady state (third infusion)	199 (159–248, n=6)	67 (49–91, n=6)	60 (47–82, n=6)	14.3 (12.6-16.9, n=5)

Plasma sampling: pre-infusion, 5 ± 10 min after end of infusion, 2 h ± 1 h after end of infusion.

Conclusions

- MP0250 administered at a dose of 8 mg/kg q3w is adequately tolerated when combined with bortezomib and dexamethasone in patients with RRMM, with no unexpected AEs reported to date.
- Preliminary efficacy results are encouraging with a 45% ORR in heavily pretreated RRMM patients, including in patients refractory/relapsed on the last PI-based therapy prior to MP0250 plus bortezomib and dexamethasone.
- Recruitment and evaluation are ongoing of MP0250 in combination with bortezomib plus dexamethasone in MM patients who are relapsed/refractory to their last treatment regimen which must have included a PI (carfilzomib or bortezomib).

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