Poster #1980

MP0250 COMBINED WITH BORTEZOMIB AND DEXAMETHASONE IN MULTIPLE MYELOMA PATIENTS PREVIOULSY EXPOSED TO PROTEASOME INHIBITORS AND IMMUNOMODULATORY DRUGS

Stefan Knop[1], Hartmut Goldschmidt[2], Marc. S. Raab[2], Monika Szarejko[3], Artur Jurczyszyn[4], Jan Duerig[5], Sara Bringhen[6], Barbara Gamberi[7], Angelo Vacca[8], Jorge Acosta[9], Guy Lemaillet[9], Cédric Cortijo[9], Sudhir Bansod[9], Norbert Grzasko[10].

[1]Department of Medicine II, University Hospital Wurzburg, Germany, [2]Department of Hematology, Oncology, and Rheumatology, Heidelberg University Hospital, Germany, [3]University Clinical Centre, Department of Hematology and Transplantology Gdansk, Poland, [4]University Hospital, Clinical Department of Hematology, Krakow, Poland, [5]Department of Hematology, University Hospital Essen, Germany, [6]Department of Oncology and Hematology, Clinical trials in onco-hematology and multiple myeloma, City of Health and Science of Turin, Italy, [7]Hematology Complex Operative Unit, Senior Hospital Santa Maria Nuova, Reggio Emilia, Italy, [8]Department of Biomedical Sciences and Human Oncology, Section of Internal Medicine, University of Bari Medical School, Bari, Italy, [9]Molecular Partners AG, Zürich, Switzerland, [10]Department of Hematology, Centre of Oncology of the Lublin Region, Poland.

MP0250 Mechanism of Action

MP0250 is a first-in-class selective tri-specific multi-DARPin® drug candidate neutralizing VEGF-A and HGF as well as binding to human serum albumin to increase its plasma half-life (Figure 1). Preclinical studies have shown that MP0250 enhances sensitivity of Multiple Myeloma (MM) cells to bortezomib, inhibits tumour growth and reduces bone destruction[1].

In this clinical phase 2 trial we are investigating the safety, tolerability and efficacy of the combination of MP0250 plus bortezomib and dexamethasone (dex) in patients (pts) with relapsed/refractory (RR) MM previously exposed to proteasome inhibitors (PI) and immunomodulatory drugs (IMiD).

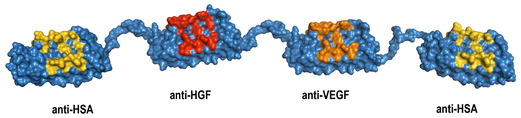


Figure 1. Model of MP0250 with binding surfaces in colour.

DARPin® is a registered trademark owned by Molecular Partners AG

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. A dose-escalation phase (part 1) consisting of two cohorts will define a safe dose of the combination of MP0250 plus bortezomib + dex followed by a dose-expansion phase (part 2).

This trial is recruiting adults ≥18 years of age with RRMM who have progressed after at least two prior treatment regimens including bortezomib and an IMiD. A dose-escalation phase (part 1) consisting of two cohorts will define a safe dose of the combination of MP0250 plus bortezomib + dex followed by a dose-expansion phase (part 2).

Enrolled patients receive iv MP0250 on day 1 + subcutaneous bortezomib 1.3 mg/m² on days 1, 4, 8, 11, oral dexamethasone (dex) 20 mg on days 1-2, 4-5, 8-9, 11-12 of each 21-day cycle. Up to 40 patients will be enrolled. Patients will receive treatment until there is documented disease progression or unacceptable toxicity.

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

Methods

Eligible patients were aged ≥ 18 years with an Eastern Cooperative Oncology Group performance status of ≤ 1 and documented diagnosis of RRMM with measurable disease by serum M protein ≥0.5 g/dL or urine M protein ≥200 mg/24 h.

Patients with a history of the previously have peripheral neuropathy ≥ 2 or active congestive heart failure, myocardial infarction within 6 months prior to screening and/or uncontrolled hypertension are ineligible.

The primary endpoint is overall response rate (ORR) per International Myeloma Working Group Uniform Response criteria. Secondary endpoints include safety, immunogenicity, progression free survival, and duration of response. Exploratory endpoints include overall survival and pharmacokinetics. The safety analysis set is defined as patients who have received at least 1 dose of the combination of MP0250 plus bortezomib + dexamethasone.

Patients and treatments

Data cut off was 02 November 2018. 8 pts have been treated in cohort 1 (8 mg/Kg q3w) and 3 pts in cohort 2 (12 mg/Kg q3w). Part 2, is currently open and recruiting patients to receive 8 mg/kg q3w (the recommend Part 2 dose). At cut-off date, two patients have enrolled in part 2.

Table 1. Patient demography and baseline characteristics

Demographics	Part 1 Escalation		Part 2 Expansion
	Cohort 1 (8 mg/Kg) n = 8	Cohort 2 (12 mg/Kg) n = 3	8 mg/Kg n = 2
Median age (y)	57.75	55.66	62
Gender (F/M)	4 / 4	2 / 1	2 / 0
ECOG, n (%) 0	4	2	1
1	4	1	1
B2-microglobulin (mg/L) Median (range)	3.65 (2.2-6.9)	3.36 (2.5-5.1)	2.35 (1.6 – 3.1)
Haemoglobin (g/L) Median (range)	120.5 (95-143)	121.66 (101-134)	117 (97-137)
Platelets, x10^9/L Median (range)	181.1 (72-327)	153.6 (111-219)	245.5 (146-345)
ANC, x10 ^{9}/L Median (range)	2.68 (1.3-4.4)	3.03 (2.3-3.8)	2 (1.3-2.7
Median prior lines of treatment (range)	3.25 (2-5)	3.5 (3-5)	4.5 (3-6)
Time from initial diagnosis (y) Median (range)	4.7 (1.3-10)	5.5 (2.5-9)	10 (8-12)
PI Refractory , n (%)	4 (50%)	3 (100%)	1 (50%)
Prior SCT, n (%)	7 (87.5%)	3 (100%)	2 (100%)

Table 2. Patient Disposition

	Part 1: Dose Escalation		Part 2: Expansion
	Cohort 1: 8 mg/Kg (n =8)	Cohort 2: 12 mg/Kg (n = 3)	8 mg/Kg (n = 2)
On treatment, n (%)	1	0	2
Discontinued, n (%)			
PD	4	2	0
Consent withdrawn	1	0	0
AE	2	1	0
Death	0	0	0

Table 3. Treatment Emergent Adverse Event reported (N=11)

Most common adverse events during treatment				
Adverse Event	Part 1: Dose escalation			
	Cohort 1: 8 mg/Kg (n=8)		Cohort 2: 12 mg/Kg (n=3)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Hematologic adverse events				
Neutropenia	-	-	3 AE (1 pt.)	2 AEs (1 pt.)
Thrombocytopenia	4 AEs (3 pts.)	1 AE (1 pt.)	12 AEs (3 pts.)	8 AEs (3 pts.)
Anaemia	-		8 AEs (2 pts.)	4 AEs (2 pts.)
Non-hematologic adverse events				
Epistaxis	-	-	5 AEs (1 pt.)	1 AE (1 pt.)*
Peripheral Sensory Neuropathy	2 AE (1 pt.)	-	1 AE (1 pt.)	-
Hypertension	5 AEs (5 pts.)	3 AE (3 pt.)	3 AEs (3 pt.)	1 AE (1 pt.)
Proteinuria	1 AE (1 pt.)	1 AE (1 pt.)	2 AEs (2 pt.)	1 AE (1 pt.)**
Nausea	1 AE (1 pt.)	1 AE (1 pt.)	3 AEs (1 pt.)	-
Respiratory tract infection	1 AE (1 pt.)	1 AE (1 pt.)	1 AE (1 pt.)	-
ALT elevation	2 AEs (1 pt.)	1 AE (1 pt.)	-	-
AST elevation	1 AE (1 pt.)	-	-	-
GGT elevation	1 AE (1 pt.)	1 AE (1 pt.)	-	-
Diarrhoea	-	-	1 AE (1 pt.)	-

- No AEs reported in 2 patients enrolled in Part 2 Expansion phase (8 mg/kg) at data cut-off.
- The most frequent drug-related grade ≥ 3 AEs: hypertension in 4 pts, thrombocytopenia in 4 pts, proteinuria in 2 pts and transient liver enzyme elevation in 1 patient.
- 2 Dose Limiting Toxicity events were observed in cohort 2 (grade 3 epistaxis*, grade 3 proteinuria**), enrollment stopped at 12 mg/Kg and the next lower dose level (8 mg/kg) is considered the MTD.

Pharmacokinetics and Immunogenicity

Figure 2. Concentration x time profile for MP0250 in cohort 1 patients (≥ 3 doses) [n = 7]

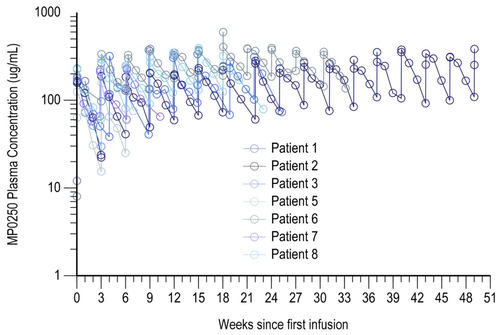
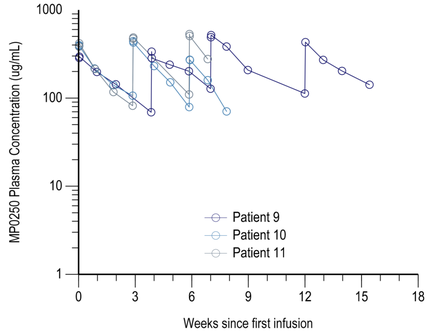


Figure 3. Concentration x time profile for MP0250 in cohort 2 patients [n = 3]



- Repeated MP0250 dosing led to sustained drug exposure throughout the treatment periods analysed, the longest to-date being 12 months; MP0250 exposure for cohort 1 and cohort 2 is proportional to dose.
- MP0250 in combination with bortezomib and dexamethasone has a half-life of ca. 11 days (range: 6-17 days) and shows only slight accumulation upon repeated dosing (factor 1.4-3.1 based on C_{min}, C_{max} and AUC); pharmacokinetics are similar to those previously observed with single agent administration of MP0250
- All 11 patients in the dose-escalation portion were assessed for anti-drug antibody (ADA) formation; 2 patients were found to be ADA positive with very low and stable titer (range 1-4) and no impact on PK profile or exposure to MP0250.

Efficacy

All 11 patients in the dose escalation portion were evaluable for tumour response (Fig.4). The ORR (better than or equal to PR) for all treated patients was 45.5%.

Figure 4. Response outcomes

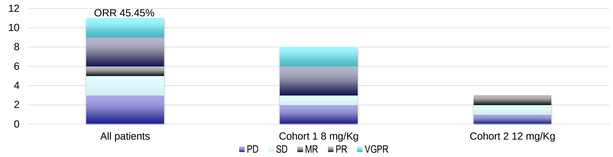
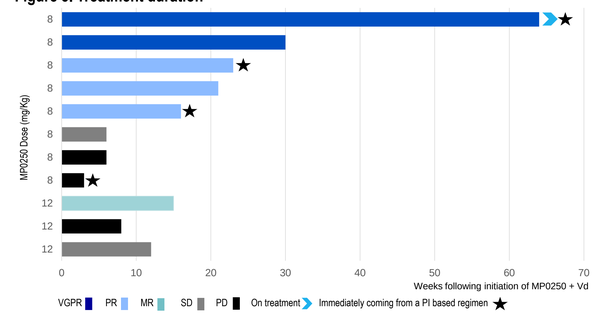


Figure 5. Treatment duration



- Tree out of four patients who were coming immediately from a PI based regimen achieved a response. One patient has been on treatment longer than 12 months and achieved VGPR (Fig.5).
- Duration of follow-up for Part 2 patients is too short.

Conclusions

Data from cohort 1 (8 mg/Kg q3w) suggest that MP0250 can be safely combined with bortezomib and dex in patients with relapsed and refractory MM.

While the number of patients treated is still small, early responses observed in bortezomib-refractory patients are promising and justify further evaluation of MP0250 therapy in combination with bortezomib plus dex in RRMM.

Acknowledgment

We thank the patients and families who contributed to this study, as well as the study investigators, nurses and clinical research personnel from the study centres across Europe. This study is sponsored by Molecular Partners AG.

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.