Abstract #2520

First-in-class phase I study evaluating MP0250, a VEGF and HGF neutralizing DARPin® molecule, in patients with advanced solid tumors

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Introduction

Vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) and hepatocyte growth factor (HGF) *c-MET* pathways are key mediators in growth and progression in solid and liquid cancers, as they modulate and drive the interaction of tumor cells and the tumor microenvironment as well as mediate treatment resistance. MP0250 is a first-in-class, tri-specific DARPin® drug candidate containing several engineered ankyrin repeat domains which simultaneously neutralizes VEGF-A and HGF, and binds to human serum albumin (HSA), resulting in an increased plasma half-life and potentially enhanced tumor penetration (Figure 1). MP0250 is a potent inhibitor of tumor growth in preclinical tumor models (Fiedler *et al. Oncotarget* 2017;8:98371–83).

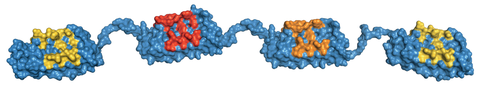

Figure 1. Model of MP0250; colored areas are the binding surfaces.

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HGF, hepatocyte growth factor; HSA, human serum albumin; VEGF-A, vascular endothelial growth factor A.

Study protocol

Study summary and objectives

This study is a first-in-man, phase I, multicenter, open-label, repeated-dose, dose-escalation study assessing safety, tolerability and pharmacokinetics (PK) of intravenous (i.v.) MP0250 in patients with advanced solid tumors (Clinical Trials.gov NCT02194426).

Primary objectives:
- To evaluate the safety and tolerability of MP0250
- To determine the maximum tolerated dose (MTD), recommended biological dose (RBD) and dose-limiting toxicities (DLTs) of MP0250
- To characterize the PK of MP0250

Secondary objectives:
- To characterize the immunogenicity of MP0250

Exploratory objectives:
- To make a preliminary assessment of biomarkers, genetic markers and anti-tumor activity of MP0250
- To assess efficacy in patients with measurable disease

Patients and methods

Key inclusion criteria:
- Histologically confirmed advanced or metastatic solid tumor refractory to ≥1 prior regimen of standard treatment or for which no curative therapy is available
- Progressive or stable disease radiologically documented in the 4 weeks prior to screening
- Presence of a measurable tumor or a tumor evaluable per RECIST v1.1
- Serum albumin ≥30 g/L

Key exclusion criteria:
- Hematological malignancy or other secondary malignancy
- Known untreated or symptomatic brain metastases
- Predominantly squamous non-small cell lung cancer (NSCLC)
- Anti-tumor treatment <4 weeks prior to first MP0250 infusion
- Proteinuria defined as ≥1+ on urinalysis dipstick confirmed by ≥1 g on 24-h urinalysis
- Uncontrolled hypertension

Study design and treatment

- 3+3 dose escalation phase
  - Cohorts 1–5: 0.5 mg/kg, 1.5 mg/kg, 4 mg/kg, 8 mg/kg, 12 mg/kg administered by 3-h i.v. infusion every other week
- Single-arm dose expansion phase (based on MTD determined from 3+3 escalation phase)
  - Cohort 6: 8 mg/kg administered by 1-h i.v. infusion every 2 weeks (q2w)
  - Cohort 7: 12 mg/kg administered by 1-h i.v. infusion every 3 weeks (q3w)
- Treatment continued until disease progression, DLT or other reason for withdrawal
  - Patients were allowed to continue treatment for >12 (>8 for Cohort 7) infusions if clinical benefit observed

PK analyses

PK assessments were performed for all 45 patients and shown for the 24 patients who completed the dose escalation phase (Cohorts 1–5).

Results

A total of 295 infusions of MP0250 were administered in 45 patients; the median number (range) of infusions was 6.5 (1–31).
A summary of demographic and patient characteristics is presented in Table 1.

Table 1. Demographics and baseline characteristics of enrolled patients.

Characteristic	Patients (N=45)
Age, mean (SD) [range], years	59.5 (12.3) [20–78]
M:F	19:26
Tumor types	
Colorectal	14
Ovarian/fallopian tube	6
Head and neck	4
Lung	4
Adenocarcinoma NOS	3
Renal	3
Breast	2
Endometrial	2
Gallbladder	2
Spindle cell	2
Cervical	1
Melanoma	1
Small bowel	1
Prior lines of systemic therapy, median (range)	3 (0–13)

Maximum tolerated dose (MTD)

The MTD determined from the findings of this study was 8 mg/kg q2w or 12 mg/kg q3w.

Dose-limiting toxicities (DLT)

There were a total of nine dose-limiting toxicities reported in six patients. These are summarized by cohort in Figure 2.

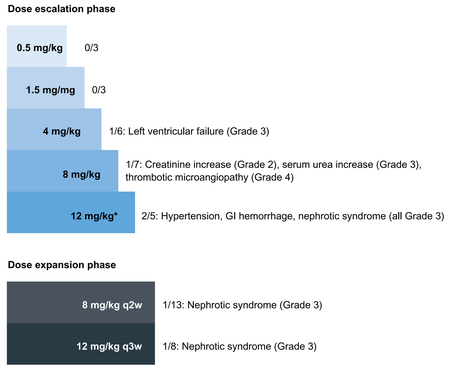

Figure 2. Dose-limiting toxicities by cohort.

* Two patients had a dose reduction to 8 mg/kg
GI, gastrointestinal.

Safety and tolerability

- All patients experienced at least one adverse event (AE).
  - A summary of the most frequently reported AEs (reported in ≥5 patients irrespective of cohort) is presented in Table 2
- A total of 44 serious adverse events (SAEs) were reported in 26 (57.8%) patients.
- SAEs reported in more than one patient (excluding tumor progression) were:
  - Nephrotic syndrome (four patients)
  - Venous thromboembolism (three patients)
  - Anemia (two patients)
  - Dyspnea (two patients)
- A total of 12 (26.7%) patients prematurely discontinued the study as a result of an AE (n=4) or SAE (n=8).
  - AEs leading to premature discontinuation: ascites, hemoptysis, hypertension, proteinuria
  - SAEs leading to premature discontinuation: nephrotic syndrome (four patients), acute left ventricular failure, gastrointestinal hemorrhage, Streptococcus B infection, thrombotic microangiopathy
- Most common treatment-related AEs were: hypertension 64.4% (grade 3: 31.1%), proteinuria 51.1% (grade 3: 4.4%), diarrhea 28.9% (grade 3: 2.2%), hypoalbuminemia 20.0% (grade 3: 2.2%), fatigue 17.8% (grade 3: 2.2%), headache 15.6% (grade 3: 0%), nausea 13.3% (grade 3: 0%), vomiting 13.3% (grade 3: 0%), blood creatine phosphokinase increased 11.1% (grade 3: 2.2%) and platelet count decreased 11.1% (grade 3: 0%).

Table 2. Most frequently reported AEs* reported in safety population (N=45).

*Any grade AEs reported in ≥5 patients or grade ≥3 AEs reported in ≥2 patients.
AE, adverse event.

Adverse events as coded by MedDRA (version 17.0) Preferred term (PT)	Any grade		Grade ≥3	
	Number of AEs	Number (%) of patients with AE	Number of AEs	Number (%) of patients with AE
Total	593	45 (100)	112	37 (82.2)
Hypertension	74	31 (68.9)	31	16 (35.6)
Proteinuria	41	23 (51.1)	3	3 (6.7)
Diarrhea	27	16 (35.6)	1	1 (2.2)
Nausea	17	16 (35.6)	2	2 (4.4)
Fatigue	21	14 (31.1)	1	1 (2.2)
Decreased appetite	14	12 (26.7)		
Vomiting	15	12 (26.7)	1	1 (2.2)
Cough	12	11 (24.4)		
Hypoalbuminemia	18	11 (24.4)	1	1 (2.2)
Headache	16	10 (22.2)	1	1 (2.2)
Pyrexia	12	9 (20.0)		
Back pain	11	8 (17.8)		
Platelet count decreased	9	8 (17.8)	1	1 (2.2)
Abdominal pain	12	7 (15.6)		
Anemia	11	7 (15.6)	5	5 (11.1)
Blood creatinine increased	7	7 (15.6)		
Alanine aminotransferase increased	6	6 (13.3)	1	1 (2.2)
Blood creatine phosphokinase increased	8	6 (13.3)	1	1 (2.2)
Constipation	6	6 (13.3)	1	1 (2.2)
Dyspnea	7	6 (13.3)	2	2 (4.4)
Asthenia	8	5 (11.1)		
Ascites	6	4 (8.9)	2	2 (4.4)
Nephrotic syndrome	4	4 (8.9)	4	4 (8.9)
Embolism	3	3 (6.7)	2	2 (4.4)
Lipase increased	3	3 (6.7)	2	2 (4.4)
Hyponatremia	2	2 (4.4)	2	2 (4.4)

PK and immunogenicity

PK data

- Mean MP0250 plasma concentration increased in a dose-proportional manner over the dose range 1.5–12 mg/kg (Figure 3).

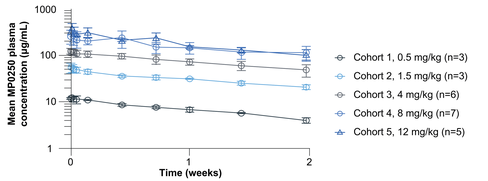

Figure 3. Mean plasma concentration–time profiles for patients in Cohorts 1–5 following first dose of MP0250.

- Sustained exposure was observed for all patients throughout the treatment periods analyzed (up to 12 months).
- Mean half-life calculated for patients in the dose escalation phase was approximately 12 days (range 9–18 days).
- Slight accumulation (by a factor of 1.3–3, based on C_{max}, C_{min} and area under the curve [AUC]) was observed following q2w repeated infusions.
- Reducing the infusion time from 3 h to 1 h had no obvious impact on the PK characteristics, with the range of C_{max}, C_{min} and AUC values being similar at similar dose levels.
- Consistent PK characteristics were observed for the different dosing schemes of repeated infusions either q2w (e.g. Cohort 5) or q3w (Cohort 7 [not shown]).

Immunogenicity

Of the 24 patients included in the dose escalation phase only one patient developed anti-drug antibodies, which were >10-fold above background with no effect on PK.

Anti-tumor activity

Out of a total of 45 patients with a median of 6.5 lines of MP0250 treatment, two patients achieved a partial response (PR) (one confirmed PR in a 64-year-old female patient with metastatic squamous cell anal cancer, one clinically defined PR in a 63-year-old female patient with metastatic ovarian cancer). Prolonged stable disease was seen in four patients (between 28 and 60 weeks).

Duration of therapy

- <3 months: 25 (55.6%) patients
- 3 – <6 months: 16 (35.6%) patients
- 6 – <12 months: 3 (6.7%) patients
- ≥12 months: 1 (2.2%) patient

Overall median duration of therapy was 6 weeks.
Duration of therapy by patient and cohort is shown in Figure 4.

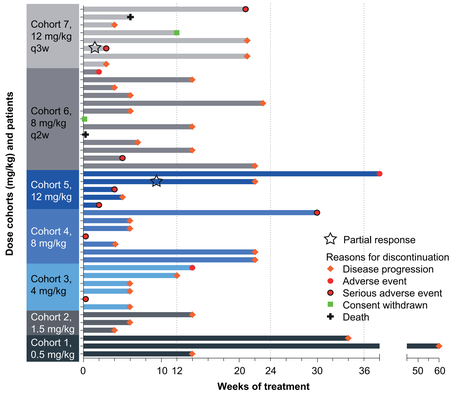

Figure 4. Duration of therapy.

PR, partial response; q2w, every 2 weeks; q3w, every 3 weeks.

Conclusions

- In this phase I study, MP0250 was well tolerated, with most AEs being consistent with potent inhibition of the VEGF pathway.
- The MTD / RBD was 8 mg/kg q2w or 12 mg/kg q3w.
- Exposure was dose-proportional and sustained throughout the dosing period for all patients.
- Signs of single agent anti-tumor activity were observed; phase II studies of MP0250 in NSCLC and multiple myeloma are ongoing.

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