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Abstract# 3573

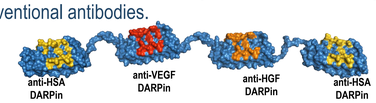
Interim results from the completed FIH Phase I dose escalation study evaluating MP0250, a multi-DARPin® drug candidate blocking HGF and VEGF, in patients with advanced solid tumors

M.R. Middleton[1], A. Azaro[2], S. Kumar[3], P. Niedermann[4], J. Rodon[2], K. H. Herbschleb[1], J. Steiner[5], C. Zitt[6], D. Feurstein[6], S. A. Schreiner[6], D. Turner[6], K. M. Dawson[6], K. Tadjalli Mehr[6], E. vom Baur[6], M. T. Stumpp[6], A. Harstrick[6], R.D. Baird[3], A. Omlin[4].

[1]Oxford University Hospitals NHS Foundation Trust, Churchill Hospital, Oxford, UK; [2]Vall d'Hebron, Institute of Oncology, Barcelona, Spain; [3]Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge, UK; [4]Kantonsspital St Gallen, St Gallen, Switzerland; [5]Oxford Therapeutics Consulting Ltd, Crowthorne, UK; [6]Molecular Partners, Zurich, Switzerland

Background

DARPin®* proteins are small genetically engineered proteins that bind to specific targets with very high affinity (i.e. picomolar). MP0250 is a multi-DARPin with three specificities, able to simultaneously neutralize the activities of vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) and also to bind to human serum albumin (HSA) to give an increased plasma half-life and potentially enhanced tumor penetration (below: 3D-model with binding surfaces in color). VEGF/VEGFR and HGF/cMet pathways are implicated in tumor survival, growth, angiogenesis, invasion, metastasis and the development of resistance to anti-cancer treatments. MP0250 is a potent inhibitor of tumor growth in several patient-derived xenograft models (liver, kidney, stomach, lung, multiple myeloma). MP0250 is the first systemically delivered DARPin® protein. Like other DARPin® proteins, MP0250 can be easily manufactured with high yields and is very stable. DARPin® proteins can be easily formatted in a multi-specific way to block several biological activities unlike conventional antibodies.



Study Protocol

Study summary and objectives

Phase I first-in-human multi-center, open-label, repeated-dose, dose-escalation (3+3 design) study to assess safety, tolerability, pharmacokinetics and immunogenicity of i.v. MP0250 in patients with advanced solid tumors.

Primary objectives:

- Evaluate the safety and tolerability of MP0250
- Determine the Maximum Tolerated Dose (MTD), Recommended Biological Dose (RBD) and Dose Limiting Toxicities (DLTs) of MP0250
- Characterize the pharmacokinetics of MP0250

Secondary objectives:

- Characterize the immunogenicity of MP0250
- Exploratory assessment of biomarkers
- Evaluate the anti-tumor activity of MP0250

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 documented radiologically in the 4 weeks prior to screening; Presence of a measurable tumor or a tumor evaluable per RECIST v1.1; Serum albumin concentration ≥ 30 g/L.

Key exclusion criteria: Hematological malignancies or other secondary malignancy; Known untreated or symptomatic brain metastases; Predominantly squamous non-small cell lung carcinoma; Anti-tumor treatment less than 4 weeks prior to the first infusion of MP0250, such as chemotherapy, experimental or targeted therapy, biologics, hormonal therapy and radiotherapy; Proteinuria; Uncontrolled hypertension.

Study treatment:

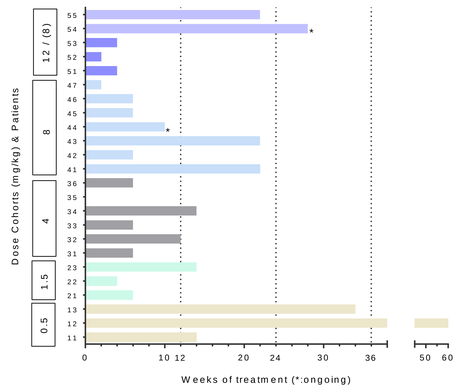
- Five dose cohorts: 0.5, 1.5, 4, 8, 12 mg/kg
- Up to 12 intravenous infusions of MP0250 without pre-treatment: every two weeks administered over 3 hours
- Treatment until disease progression, DLT or other reasons for withdrawal.
- Patients are allowed to continue treatment >12 infusions in case of benefit

Results

- Twenty four patients were enrolled in the dose escalation part with MP0250 at 0.5 (n=3), 1.5 (n=3), 4 (n=6), 8 (n=7), and 12 mg/kg (n=5) every two weeks.
- The MTD was reached at 8 mg/kg, two patients switched treatment from 12 to 8 mg/kg

Antitumour Activity

- Two patients showed significant reductions in tumor volume (1 confirmed as partial response, 1 with signs of response in non-measureable lesions). In addition, prolonged stable disease was seen in 6 patients (between 22 and 60 weeks).
- Treatment duration was ≥ 3 months in 10 patients (42%) with 3 patients exceeding 6 months



Safety and Tolerability

- A total of 175 infusions of MP0250 have been administered in 24 patients. Infusions were well tolerated, except for mild nausea and diarrhea occurring in some patients.
- The most frequent adverse events (AEs, CTC version 4.03) were hypertension (63%), diarrhea (42%), fatigue (46%), proteinuria, cough, nausea, and vomiting (29% each).
- In total, 7 Dose limiting toxicities (DLTs) were observed in 4 patients: Acute left ventricular failure (1 pt.), nephrotic syndrome and hypertension (1), gastrointestinal hemorrhage (1), thrombotic microangiopathy (1).
- One patient experienced a temporary drop in blood pressure and bradycardia during his first infusion which resolved spontaneously. Even though not classical, an infusion-related reaction could not be excluded in this patient.
- Patient with the DLT of acute left ventricular failure died from cardiac arrest two months after his first and only infusion. The event was assessed as possibly related and reported as SUSAR. The patient had several risk factors (hypertension, prior anthracyline therapy and mediastinal radiation).
- Nine serious unexpected adverse reactions (SUSARs) were reported in 7 patients: infusion related reaction (1 pt.), acute left ventricular failure and cardiac arrest (1), gastrointestinal hemorrhage (1), thrombotic micro-angiopathy (1), Nephrotic syndrome and hypertension (1) and pulmonary embolism (2).

Serious adverse events, SAEs (*: SUSAR; +: DLT)

SAE / Severity	none	2	3	4	5
Acute left ventricular failure			1*,+		
Ascites			1		
Back pain		2			
Billiary tract infection			1		
Cardiac arrest					1*
Device related infection	1				
Dyspnoea			1		
Embolism (pulmonary)			2*		
Gastric haemorrhage			1*,+		
Hypertension			1*,+		
Infusion related reaction		1*			
Lower respiratory tract infection			1		
Lung infection			1		
Malignant neoplasm progression			1		4
Medical device complication		1			
Metastases to CNS			1		
Nephrotic syndrome			1*,+		
Sepsis				1	
Thrombotic microangiopathy				1*,+	
Total (25 SAEs in 12 patients)	**1**	**4**	**13**	**2**	**5**

Conclusion

- This is the first demonstration of the systemic application of a DARPin® protein - MP0250 a first-in-class dual inhibitor of HGF and VEGF with potential to treat patients with various tumors
- MP0250 showed side effects expected for a VEGF inhibitor (e.g. hypertension, proteinuria)
- MP0250 is well tolerated at doses ranging from 0.5 to 8 mg/kg given as i.v. infusion every two weeks, with two patients showing significant reduction in tumor volume and 6 patients having prolonged stable disease
- MP0250 shows a long half-life of around 12 days with the potential of dosing every three weeks and beyond
- Repeated dosing led to sustained exposure throughout the treatment periods, the longest to-date being 12 months

Outlook

- The first Phase II study of MP0250 will be in Multiple Myeloma in combination with Bortezomib and Dexamethasone, since upregulation of both HGF and VEGF pathways has been implicated in loss of response to therapy
- DARPin® proteins including MP0250 could become valuable agents in oncology

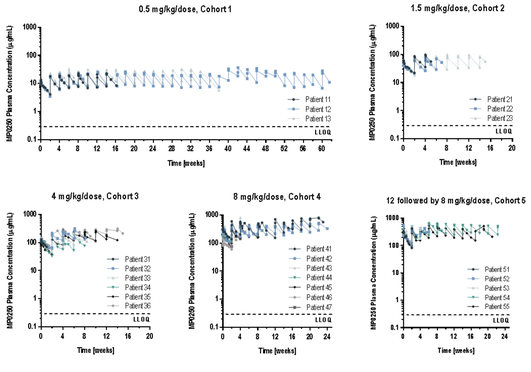
Most Frequent Adverse Events

Most frequent adverse events (reported in more than 2 patients) by dose cohort and grade (CTC v4.03)

Cohort	0.5 mg/kg						1.5 mg/kg						4 mg/kg						8 mg/kg						12/8 mg/kg						12 mg/kg					
No. Patients	3						3						6						7						2						3					
Adverse Events / CTC grade	1	2	3	4	5	∑ %	1	2	3	4	5	∑ %	1	2	3	4	5	∑ %	1	2	3	4	5	∑ %	1	2	3	4	5	∑ %	1	2	3	4	5	∑ %
Hypertension									1		1	33%		1	3			4 67%		4	2			6 86%		1	1			2 100%		1	1			2 67%
Diarrhoea	1					1 33%	1	1			2	67%	2					2 33%	2	1				3 43%	1					1 50%	1					1 33%
Fatigue	1					1 33%		2			2	67%		1				1 17%	2	2				4 57%	1					1 50%	1	1				2 67%
Proteinuria																			1	3				4 57%	2					2 100%		1				1 33%
Cough	1					1 33%	1				1	33%	1					1 17%	2	1				3 43%	1					1 50%						
Nausea							1				1	33%	2	1				3 50%	3					3 43%												
Vomiting	1					1 33%								2				2 33%	3	1				4 57%												
Malignant neoplasm progression															1		2	3 50%				1	1	14%											1	1 33%
Dyspnoea							1				1	33%	1					1 17%		2				2 29%											1	1 33%
Decreased appetite	1					1 33%							2					2 33%	1					1 14%							1					1 33%
Platelet count decreased																1		1 17%	2	1				3 43%												
Abdominal pain														1				1 17%	2					2 29%							1					1 33%
Back Pain	1					1 33%							1					1 17%	1					1 14%								1				1 33%
Headache													1					1 17%	1					1 14%	1					1 50%	1					1 33%
Pyrexia							1				1	33%	1					1 17%	1					1 14%	1					1 50%						
Dysphonia	1					1 33%	1				1	33%	1					1 17%							1					1 50%						
Blood bilirubin increased													1	1				2 33%	1					1 14%												
Blood creatinine increased													2					2 33%		1				1 14%												
Hypoalbuminemia														1				1 17%	1					1 14%	1					1 50%						

PK and Immunogenicity

- Sustained exposure was observed for all patients throughout the treatment periods analyzed, the longest to date being 12 months.
- MP0250 exposure (AUC, Cmax) increased with dose in a dose-proportional manner in the dose range of 1.5 to 12 mg/kg.
- MP0250 shows a mean half-life of approx. 12 days (range 9-18 days) with slight accumulation (factors 1.3 - 3, based on Cmax, Cmin, and AUC).
- All 24 patients were assessed for anti drug antibody (ADA) formation. Only one patient developed ADAs, which were >10-fold above background with no effect on PK.



* DARPin® is a registered trademark of Molecular Partners AG

See also Special Symposium: Drugs you will be using in 2020 on 10 Oct 2016, 14:45 - 16:15, Athens
M. Stumpp. Engineered peptide therapeutics and other protein therapies

Molecular Partners AG, Wagistrasse 14, 8952 Zurich-Schlieren, Switzerland – www.molecularpartners.com – info@molecularpartners.com – phone: +41 44 755 77 00