Poster CT149

MP0250, a VEGF- and HGF-blocking multi-DARPin® drug candidate, in combination with tyrosine-kinase-inhibitors targeting EGFR-mutated NSCLC - Preclinical rational and Phase 1b/2 study -

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Background

Relapse of patients with EGFR-mutated NSCLC treated with TKI regimens is most often due to TK mutation but also in a significant number of cases due to upregulation of bypass pathways, the most common being the HGF/cMET signaling pathway. Osimertinib, a third generation TKI, is currently approved for T790M-mutated NSCLC but options for treatment following relapse are unsatisfactory. Hence, there is a high medical need for therapies overcoming EGFR-TKI resistance, including inhibition of bypass mechanisms. In this respect, we are investigating combination of HGF/cMET pathway inhibition with EGFR-TKI therapy. MP0250 is a multi-DARPin® drug candidate, specifically neutralizing HGF and VEGF, with the potential to block HGF-mediated bypass of EGFR-TKI inhibition in addition to exerting EGFR-independent antitumor activity via dual HGF and VEGF inhibition.
MP0250 has shown a favorable safety profile in a Phase 1 clinical trial in advanced solid tumors[1] and is currently being tested in combination with bortezomib + dexamethasone in a Phase 2 open-label, single-arm, multicenter trial in patients with refractory and relapsed multiple myeloma (RRMM, NCT03136653).

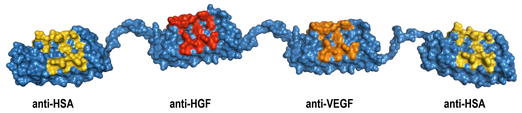


Figure 1: Cartoon of MP0250
MP0250 is the first systemically administered DARPin® drug candidate. Like other DARPin® proteins, MP0250 can be easily manufactured and is very stable. DARPin® molecules are very versatile, can bind to virtually any defined target, and can be formatted in a multi-specific way to block several biological activities[2].

Activity of MP0250 in NSCLC in PDX models

MP0250 is an efficient inhibitor of tumor growth in NSCLC patient-derived-xenograft (PDX) models and acts together with EGFR targeting tyrosine-kinase inhibitors

- MP0250 shows single agent activity in all tested HGF-autocrine NSCLC PDX models
- MP0250 shows an enhanced effect in combination with erlotinib in an erlotinib-resistant model (LU6472)

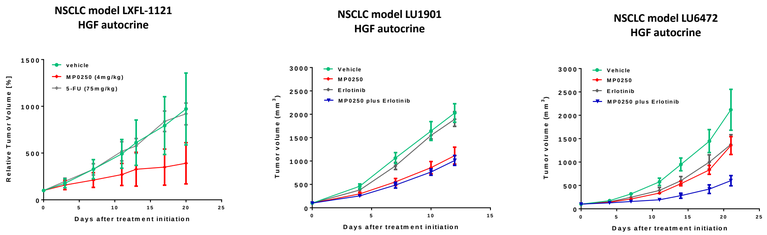


Figure 2: Inhibition of tumor cell growth in EGFR-positive NSCLC patient-derived xenograft models
The figure shows growth inhibition in PDX models treated with MP0250 and/or 5FU/erlotinib . The graphs show the relative tumor volume plotted against the days of treatment. Mice were randomized into groups when tumors reached a volume of approximately 100 – 120 mm³. The day of randomization and treatment initiation is designated as day 0 in each experiment. MP0250 was dosed at 4 mg/kg 3x weekly (i.v.), erlotinb at 50 mg/kg daily (p.o.) and 5FU at 75 mg/kg daily (i.p.).

HGF and cMET expression in human tumors

HGF is overexpressed in most tested human tumors while cMet is only moderately expressed

- HGF was highly expressed in 4 out of 5 lung cancer samples
- cMET was moderately expressed in 2 out of 5 lung cancer samples and absent in 3 out of 5 samples

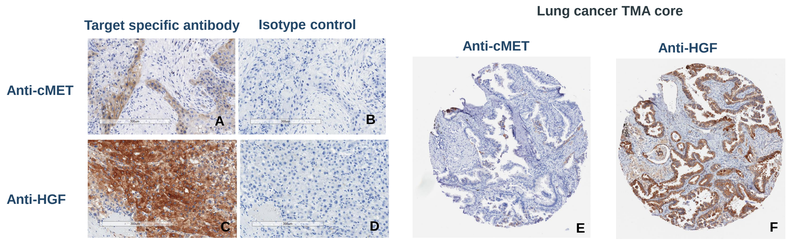


Figure 3: IHC for HGF and cMET
Panel A-D show representative cMET-immune reactivity in human lung tumor (panel A) and concentration-matched non-immune IgG control (panel B) and a representative HGF-immune reactivity in a human liver tumor (panel C) and the respective and matched non-immune IgG control (panel D).
Panels E and F show representative staining for cMET (E) and HGF (F) expression in FFPE sections of multi-tumor tissue micro arrays comprised of duplicate tissue cores from a total of 72 donors with an age range of 22-80 years, of which 30 were female and 42 were male.

Clinical Rationale

- **MP0250 in combination with an EGFR-targeting therapeutic (e.g. TKI) breaks resistance to the therapeutic**
- **HGF/cMET pathway inhibition restores sensitivity to EGFR-directed treatment**
- **VEGFR and cMET pathway inhibition inhibits angiogenesis and induces blood vessel normalization resulting in a better delivery of e.g. the EGFR-targeting therapeutic**

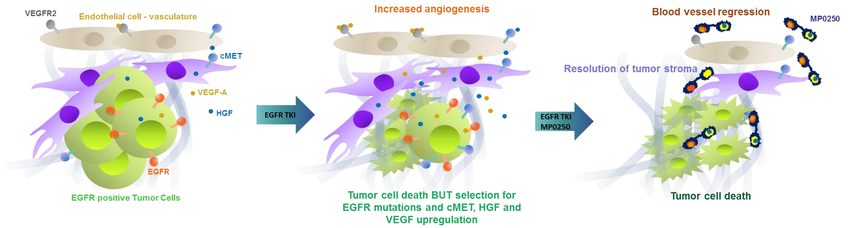
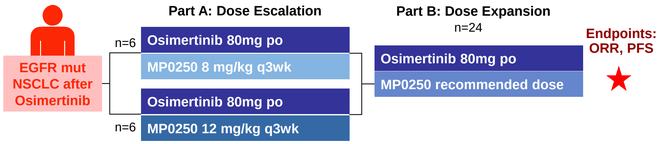


Figure 4. Cartoon of the mode-of-action of MP0250 in breaking resistance to EGFR TKIs

Trial Design Study Protocol (NCT03418532)

Study summary and description
This is a Phase 1b/2, single-arm, open-label, multi-center study of MP0250 in combination with osimertinib in patients with EGFR-mutated non-squamous non-small cell lung cancer (NSCLC) pretreated with osimertinib.
The primary objective is to estimate the antitumor efficacy, as measured by Objective Response Rate (ORR) after 8 cycles of treatment with MP0250 i.v. every 3 weeks in combination with osimertinib 80mg orally once daily, when administered to patients with EGFR mutated, advanced, non-squamous NSCLC after tumor progression on osimertinib and on or after the most recent therapy.
The secondary objective is to determine safety, tolerability, progression-free survival (PFS), duration of response (DOR), overall survival (OS), time to response (TTR), pharmacokinetics and immunogenicity. Exploratory endpoints include analysis of tissue and blood biomarkers that may be correlated with antitumor efficacy of MP0250.
An initial dose escalation safety lead-in part, Part A, is intended to establish a safe recommended dose (RD) of MP0250 in combination with osimertinib. A treatment expansion phase (part B) will further evaluate efficacy and safety at the RD of MP0250 in combination with osimertinib.

Trial design:



Key Exclusion and inclusion criteria:

Inclusion Criteria:
- Histologically confirmed metastatic or unresectable locally advanced non-squamous NSCLC with documented EGFR mutation-positive disease
- Radiologically documented disease progression on previous osimertinib treatment or after most recent antitumor therapy.
- Measurable disease according to RECIST 1.1 and ECOG performance status (PS) 0 2.
- Adequate hematological, hepatic and renal function prior to first dose
- Serum albumin concentration ≥30 g/L

Exclusion Criteria:
- Necrotic tumors or tumors close to large blood vessels that may impose an increased bleeding risk when treated with anti-VEGF agents.
- Second malignancy that is currently clinically significant or required active intervention during the period of 12 months prior to Screening, except early stage non-melanoma skin cancer treated with curative intent.
- Known pre-existing interstitial or inflammatory lung disease.
- Clinical signs of or documented leptomeningeal carcinomatosis.

Study progress:
The study is recruiting patients in the United States of America, the first patient will be treated in April 2018.

References

[1] Interim results from the completed FIH Phase I dose escalation study evaluating MP0250, a multi-DARPin® blocking HGF and VEGF, in patients with advanced solid tumors; Middleton et al. ESMO 2016: poster 361PD
[2] Fiedler et al., Oncotarget 2017

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