Poster # 232

Pre-clinical antitumor activity, tumor localization and pharmacokinetics of MP0274, an apoptosis inducing, biparatopic HER2-targeting DARPin® drug candidate

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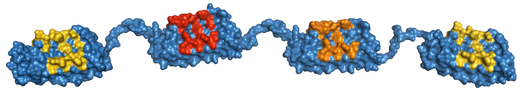
Background

HER2 positivity is an important predictive factor for treatment with anti-HER2 agents in several cancers. However, currently available monoclonal antibody and tyrosine kinase inhibitor drugs rarely achieve full disease control. We have developed a new HER2-targeting molecule with a unique proapoptotic mode of action that may provide additional benefit to patients. The DARPin® MP0274 binds to two distinct non-overlapping HER2 epitopes and also to human serum albumin for half-life extension. As previously shown*, in vitro, MP0274 induces apoptosis and inhibits proliferation of cells expressing HER2 (IHC3+, IHC2+ and IHC1+) and potently inhibits HER2/HER3 downstream signaling. To support clinical development of MP0274, we tested the potency of MP0274 in several HER2-expressing patient-derived xenograft (PDX) models and investigated tumor localization. In addition, pharmacokinetics (PK) analysis was performed in cynomolgus monkeys.

DARPin® molecules (designed ankyrin repeat proteins) are small genetically engineered proteins that bind to specific targets with very high affinity and which can be combined in a modular fashion (cartoon shown below with target binding sites in color).



MP0274 is a systemically delivered DARPin® drug candidate. Like other DARPin® molecules, MP0274 is very stable.
DARPin® is a registered trademark owned by Molecular Partners AG.

Methods

Antitumor activity of MP0274 was tested in breast and gastric cancer HER2-expressing PDX mouse models and was compared to standard of care therapies. Briefly, tumor fragments were obtained from xenografts in serial passage in nude mice. After removal from donor mice, tumors were cut into fragments (4-5 mm diameter) and placed in PBS until subcutaneous implantation. 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. MP0274 was dosed at 60mg/kg 3x weekly (i.v.); lapatinib at 100 mg/kg daily (p.o.); trastuzumab and pertuzumab as well as the combination of both at at 10mg/kg 3x weekly. Tumor growth was monitored by two-dimensional measurement with a caliper on the day of randomization and then twice weekly. Relative volumes of individual tumors (individual RTVs) for Day x were calculated by dividing the individual tumor volume on Day x (Tx) by the individual volume of the same tumor on Day 0 (T0) multiplied by 100.

Tumor localization of MP0274 was studied using an Indium-111 (Ind-111) labeled version of MP0274 in a human ovarian adenocarcinoma (SKOV-3) xenograft model by whole-body SPECT/CT imaging. Briefly, MP0274 was functionalised with the bifunctional chelator 2-(4-isothiocyanatobenzyl)-diethylenetriaminepentaacetic acid (p-SCN-Bn-DTPA) with an average chelator-MP0274 radio of 1.8. Subsequent QC assays confirmed no deviation of the molecules properties compared to non-conjugated MP0274. Female CD1 (nu/nu) mice were inoculated subcutaneously in right shoulder with $5x10^6$ SKOV-3 cells. Tumors were allowed to grow until Ø-size of ~600 mm^3 and mice were randomized. 4 mg/kg Ind-111 labelled MP0274-DTPA (activity: 9.5 MBq) was intravenously injected per mouse. Distribution of Ind-111 labelled MP0274-DTPA was monitored using Mediso's NanoSPECT/CT®PLUS pre-clinical imager.

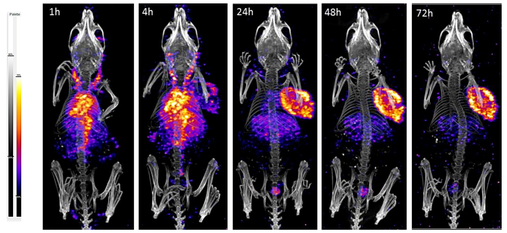
The PK of MP0274 was studied in cynomolgus monkeys using MP0274 with an N-terminal His-tag. MP0274 is cross-reactive to the cynomolgus HER2 receptor. Single animals were intravenously infused once with 1, 5 or 10 mg/kg over 30 minutes. Serum samples were taken at intervals after dosing over a 10 day period. Serum concentrations were measured using a DARPin®-specific sandwich ELISA method. PK evaluation was performed using non-compartmental analysis.

* U. Fiedler et al. SABC 2013. Abstract# 1094 & Poster# P4-12-30

Tumor localization of MP0274

MP0274 localizes efficiently *in vivo* to a Her2-expressing tumor

- MP0274 localizes efficiently to the Her2-expressing SKOV-3 tumor
- MP0274 localizes to the tumor within 24 h



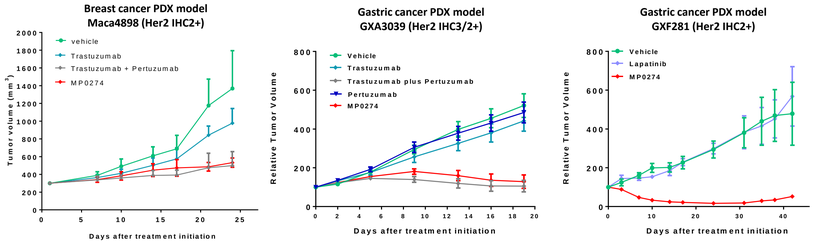
Localization of MP0274 in SKOV3 tumors by SPECT/CT imaging

The figure shows ventro-dorsal whole-body SPECT/CT images of female CD1 (nu/nu) mice bearing SKOV-3 human ovarian adenocarcinomas after injection of Ind-111 labelled **MP0274-DTPA conjugate** at 4 mg/kg. Representative for n=3 animals/group.

Preclinical efficacy in patient-derived xenografts

MP0274 is an efficient inhibitor of tumor growth in *in vivo* models

- MP0274 inhibits tumor growth in Her2 3+ and 2+ PDX models of breast and gastric cancer
- MP0274 shows superior efficacy compared to trastuzumab and lapatinib
- MP0274 shows equivalent efficacy compared to a combination of trastuzumab and pertuzumab
  - In contrast to the antibodies, MP0274 cannot induce ADCC



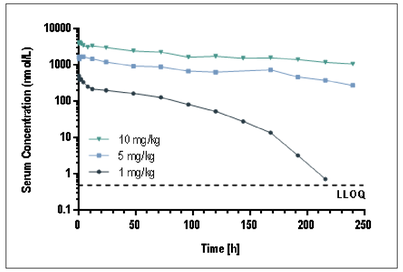
Inhibition of tumor cell growth in Her2 positive patient-derived xenograft models

The figure shows examples for growth inhibition of PDX models of breast cancer (Maca4898) and two gastric cancer models (GXA3039 and GXF281). The graphs show either the absolute tumor volume (Maca4898) or the relative tumor volume plotted against the days of treatment.

Pharmacokinetics of MP0274 in monkeys

MP0274 PK behavior in monkeys is indicative for TMDD as expected for HER2 binding drugs

- Non-dose linear PK behavior in the dose range between 1 and 5 mg/kg indicates that MP0274 exhibits target-mediated drug disposition (TMDD) which is in line with a saturable binding process to HER2 receptors associated with a saturable elimination process such as receptor-mediated endocytosis.
- Approximately dose-proportional PK behavior at dose levels above 5 mg/kg with long half-life values (≥ 5 days)



Parameter	Unit	Values		
		1 mg/kg	5 mg/kg	10 mg/kg
AUCinf_D	(hr*nmol*kg)/(L*mg)	20371	49029	71993
Cmax	nmol/L	512	1722	4319
Cmax_D	(nmol*kg)/(L*mg)	512	344	432
Cl_pred	mL/hr/kg	0.82	0.34	0.23
Vss_pred	mL/kg	43	58	53
Half-life	hr	11.3 (0.47 days)	120 (5 days)	161 (6.7 days)

PK characteristics of His-MP0274 in monkeys

Figure to the left shows conc.-time traces of His-MP0274 following single intravenous 30 min infusions at dose levels of 1, 5, and 10 mg/kg. His-MP0274 serum concentrations were determined by sandwich ELISA.

Table above lists PK parameters calculated from the conc.-time data provided in the figure using non-compartmental analysis. Dose in mg/kg were used to calculate dose-normalized values of AUCinf_D and Cmax_D, whereas dose in nmol/kg were used to calculate Cl and Vss.

Planned phase I a/b clinical trial design

MP0274-CP101 will be a first-in-human, single-arm, multi-center, multinational, open-label, repeated-dose, dose-escalation study in patients with HER2 positive solid cancers who have progressed after standard therapy for advanced disease. The primary objective is to evaluate the safety and tolerability of MP0274. Secondary and exploratory objectives include assessment of pharmacokinetics, immunogenicity, and anti-tumor efficacy. The primary endpoint is incidence and severity of adverse events, secondary and exploratory endpoints include serum-concentration profiles of MP0274, incidence of anti-drug antibodies, clinical benefit and response rates, progression free and overall survival parameters.

Major inclusion criteria are recently documented HER2 positive solid tumor disease after standard therapies, HER2 assessment according to published guidelines, measureable disease according to RECIST v1.1, adequate cardiac and other organ function, and additional established phase 1 study criteria.

Trial design: Dose escalation follows a standard 3+3 study design up to achieving Recommended Dose (RD). At RD additional patients will be included to further evaluate anti-tumor activity in particular.

The first regulatory submission is planned Q1 2017.

Conclusion

MP0274, with its unique proapoptotic mode of action, demonstrates excellent activity in HER2-expressing PDX models, fast localization to HER2-expressing tumors and a PK profile consistent with a compound binding to HER2 receptors. MP0274 was well tolerated in all studies. These results suggest that MP0274 has the potential to provide additional clinical benefit to patients with HER2-expressing tumors. A GLP repeated dose toxicology study in cynomolgus monkeys has been completed and a phase I clinical trial is in preparation.

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