# Interim analysis of a phase 1 study with MP0317, a tumor targeting FAP dependent CD40 agonist DARPin, in patients with relapsed/refractory solid tumors

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## Could tumor-localized CD40 activation through FAP crosslinking mitigate systemic toxicity?

### MP0317, a Tumor-Targeted CD40 Agonist

Limited clinical efficacy has been observed with systemic CD40 agonists[1-4] in solid tumor patients due to:

- Dose-limiting toxicity (DLT) arising from systemic CD40 activation
- Limited exposure due to peripheral target-mediated drug disposition

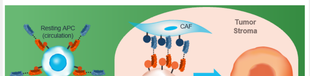
By binding Fibroblast Activation Protein (FAP), MP0317 is designed to induce tumor-localized CD40-mediated activation of APC and B cells, while avoiding extra-tumoral immune activation

**MP0317: FAP-dependent CD40 activation**

**Tumor-localized CD40 activation**

**↓**

**Improved Therapeutic Window**







Here we present emerging data from the first-in-human trial of MP0317, a biomarker-focused study designed to demonstrate MP0317 safety and tolerability profile, while elucidating its mechanisms of action in the tumor and in the circulation

### Study Design

NCT05098405 is a phase 1, first-in-human, multicenter, dose escalation study followed by a safety expansion part, evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of MP0317 monotherapy in adult patients with advanced solid tumors

Dose selection was guided by a translational PK/PD model that accounted for MP0317 biodistribution and linked affinity data with target baseline expression levels and turnover rates

#### Primary Objectives

- To characterize the safety and tolerability of MP0317
- To determine the recommended dose for expansion and subsequent combination

#### Exploratory Objective

- To evaluate PD effects in peripheral blood and tissue

#### Secondary Objectives

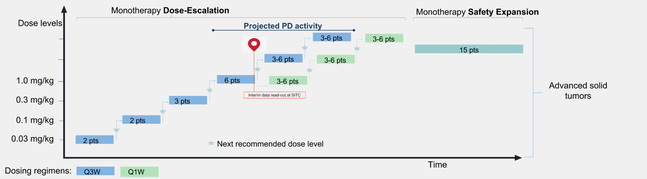
- To describe the PK of MP0317
- To evaluate preliminary antitumor activity
- To evaluate preliminary clinical benefits

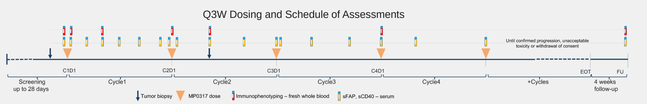
#### Key Inclusion Criteria

- Advanced solid tumor of a type known to express FAP, for which approved therapies have been exhausted - Documented FAP expression not required
- ECOG status 0 or 1
- Life expectancy > 12 weeks
- Measurable disease according RECIST v1.1

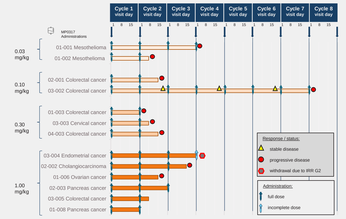
#### Key Exclusion Criteria

- Autoimmune diseases
- Inflammatory diseases that may have upregulated FAP expression
- Serious or non-healing wound, skin ulcer or non-healing bone fracture
- Abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months before screening




### MP0317 Dose Escalation Ongoing – Interim Clinical Data




| Characteristic | Patients (*N* = 13) |
|---|---|
| Age, median (range), y | 55 (35 –75) |
| Female (%) | 7 (54) |
| ECOG PS, *n* (%) | |
| 0 | 7 (54) |
| 1 | 6 (46) |
| Median prior regimens (range) | 3 (1–13) |

Patients were escalated from 0.03 mg/kg to 1 mg/kg Q3W as per protocol, with additional Q3W and Q1W cohorts recruiting

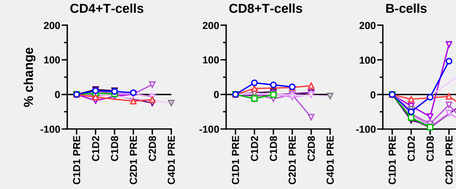
### At Data Cut-off, MP0317 Is Safe and Well-tolerated

- No DLTs reported (Cohorts 1-4) & none of the grade ≥3 AEs were related to study treatment
- Of all AESIs that were pre-specified per protocol, only infusion-related reactions (IRR) were observed in more than one patient

| | Number of Treatment-Emergent Events (Number of Patients Affected) | | | | |
|---|---|---|---|---|---|
| MP0317 Dose Level | 0.03 mg/kg | 0.1 mg/kg | 0.3 mg/kg | 1 mg/kg | Total |
| Number of patients | 2 | 2 | 3 | 6 | 13 |
| AEs | 17 (2) | 20 (2) | 21 (3) | 27 (5) | 85 (12) |
| Related AEs | 1 (1) | 10 (2) | 4 (3) | 17 (4) | 29 (10) |
| Grade ≥3 AEs | 4 (2) | 0 (0) | 2 (2) | 0 (0) | 6 (4) |
| IRR AEs - all Grade 2 | 1 (1) | 1 (1) | 0 (0) | 3 (1) | 5 (3) |
| SAEs | 2 (2) | 0 (0) | 2 (2) | 1 (1) | 5 (5) |
| Related SAEs | 0 (0) | 0 (0) | 0 (0) | 1* (1) | 1 (1) |

* IRR Grade 2 with hospitalization for patient monitoring

### MP0317 Induces B Cell Margination and No Systemic T Cell Changes

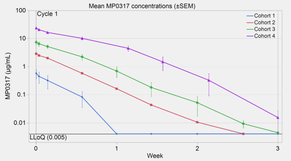



% change represent % change from baseline of immune cell populations of lymphocytes measured by flow cytometry (fresh whole blood)

Immunophenotyping results were not evaluable for 4 subjects (1 in Cohort 1, 1 in Cohort 2, 2 in Cohort 3)

- No significant changes in CD4+ / CD8+T-cell frequencies (Cohorts 1-4) and in circulating cytokines (Cohorts 1-3) were detected, including IL-6, IL-8, IL-10, TNFa, IFNg, IL-13, IL-2, IL-4, IL-1β, and IL-12p70 (data not shown), corroborating the clinical safety data
- A transient and dose-dependent B-cell margination was observed in peripheral blood, aligned with CD40 agonist mode of action

### Serum PK Shows MP0317 Half-Life Extended Properties Suitable for Q3W Dosing

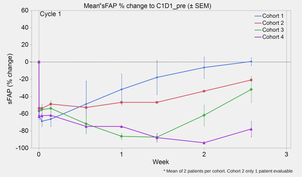



| MP0317 PK parameters Mean (range) | Cohort 1 (0.03 mg/kg) N=2 | Cohort 2 (0.1 mg/kg) N=1* | Cohort 3 (0.3 mg/kg) N=3 | Cohort 4 (1 mg/kg) N=4 |
|---|---|---|---|---|
| $t_{1/2}$, during mono-exp. elimination (hours) | 35.3 (32.1 – 38.6) | 39.7 | 45.9 (42.3 – 53.0) | 70.5 (54.5 – 85.2) |
| $C_{max,1}$ (µg/mL) | 0.570 (0.370 – 0.780) | 2.87 | 7.37 (4.66 – 9.68) | 23.6 (19.3 – 27.2) |
| $AUC_{0\text{-}21days}$ (hr µg/mL) | 25.1 (13.3 – 37.0) | 172 | 531 (337 – 746) | 2110 (1620 – 2430) |

* PK parameters and PK data of patient 03-002 (cohort 2) were not included as PK data suggest a 10-fold higher dose than nominally assigned in cycle 1

- Emerging MP0317 PK data (n=10, 4 IV dose cohorts) are consistent with a half-life extended DARPin ($t_{1/2}$ ranging from 32 to 85 hours) suitable for Q3W dosing with evidence of target-mediated drug disposition over 0.03 mg/kg – 1 mg/kg, suggestive of CD40 engagement

### MP0317 Shows Peripheral Target Engagement with sFAP

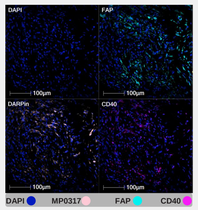



* Mean of 2 patients per cohort. Cohort 2 only 1 patient evaluable

- Soluble FAP decreased rapidly following MP0317 administration in a dose-dependent manner (n=7, 4 dose cohorts)
- Soluble CD40 did not show meaningful changes post-treatment over 0.03 – 1 mg/kg Q3W

### MP0317 Colocalizes and Occupies FAP and CD40 in Tumor

(Cohorts 1-3)




Representative multiplex immunofluorescence images of MP0317 colocalization with FAP and CD40 in a tumor verified area (pan cytokeratin positive) for subject 03-003, a cervical cancer patient dosed at 0.3 mg/kg

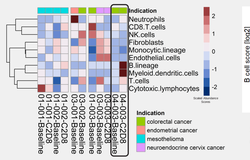
| DARPin target occupancy in tumor with FAP and CD40 | | | | |
|---|---|---|---|---|
| Subject | Cohort | % FAP at baseline | % FAP occupied by MP0317 | % CD40 occupied by MP0317 |
| 01-001 | 1 | 18.0 | 3.6 | 33.4 |
| 01-002 | 1 | 38.3 | ND | ND |
| 02-001 | 2 | 0.2 | ND | ND |
| 03-002 | 2 | 47.8 | 6.4 | 27.0 |
| 01-003* | 3 | 0.2 | no sample | no sample |
| 03-003 | 3 | 22.8 | 26.0 | 47.1 |
| 04-003 | 3 | pending | pending | pending |

*No Cycle 2 Day 8 sample collected; ND: not detected; For patient 04-003, multiplex immunofluorescence paired biopsy data are pending bioanalysis (together with cohort 4 batch)

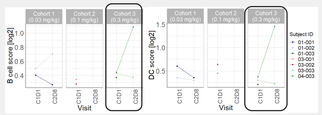
- Multiplex immunofluorescence data show colocalization of MP0317 with FAP and CD40 in 3 out of 5 eligible paired tumor biopsies, demonstrating preferential tumor targeting through FAP, and CD40 target occupancy
- More data and orthogonal validation across PD biomarkers are required to determine a FAP threshold for patient selection

### MP0317 Impact on Tumor Immune Microenvironment

(Cohorts 1-3)




Heatmap of Immune cell abundance scores for main tumor infiltrating immune cell types, fibroblasts and endothelial cells (bulk RNA sequencing data), computed using MCPCounter[5], and scaled around the mean




Scatterplot of abundance scores (unscaled) for immune cell populations expected to be increased by by MP0317

- Preliminary gene expression data suggest an increase from baseline at C2D8 in B cell and dendritic cell abundance (n=1) in the tumor microenvironment as expected for MP0317 mode of action and dose level. Baseline biopsies with no evaluable or missing post-treatment paired biopsies are included to better assess inter-patient variability

### Key Points

**Enrollment**

- Four cohorts fully enrolled (n=13)
- Cohorts 1-3 completed study (n=7)

**Exposure and Safety**

- Clinical data, immunophenotyping and cytokine panel biomarker data show no signs of systemic cytotoxicity
- Preliminary PK data show all patients were exposed to MP0317 and confirmed half-life extension

**Target Engagement and PD Effects**

- A dose-dependent soluble FAP decrease indicates target engagement in the periphery
- Multiplexed immunofluorescence data confirms tumor exposure combined with FAP and CD40 colocalization in 3 out of 5 evaluable paired tumor biopsies
- Transient dose-dependent B-cell peripheral decrease (n=9) indicates B-cell margination
- Preliminary gene expression analysis showed an increase from baseline in B-cell and dendritic cell abundance (n=1) as expected for MP0317 mode of action and dose level

### Conclusions

- As of Oct 2022, MP0317 is well-tolerated and shows no sign of systemic toxicity or DLT in the first 13 patients enrolled across 4 dose levels (0.03 mg/kg – 1 mg/kg Q3W)
- Emerging PK data are consistent with a half-life extended DARPin suitable for a Q3W dosing with evidence of target-mediated drug disposition, suggestive of CD40 engagement
- Preliminary biomarker data show evidence of target occupancy and PD modulation in the tumor microenvironment, consistent with the expected mode of action of tumor-localized CD40-mediated activation
- Enrollment at higher Q3W doses and at Q1W is ongoing to validate those preliminary observations and define the recommended dose for expansion

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