Ongoing Phase 1 study of MP0317, a FAP-CD40 DARPin, shows a favorable safety profile and early evidence of tumor-localized CD40 activation in patients with advanced solid tumors

Poster #721

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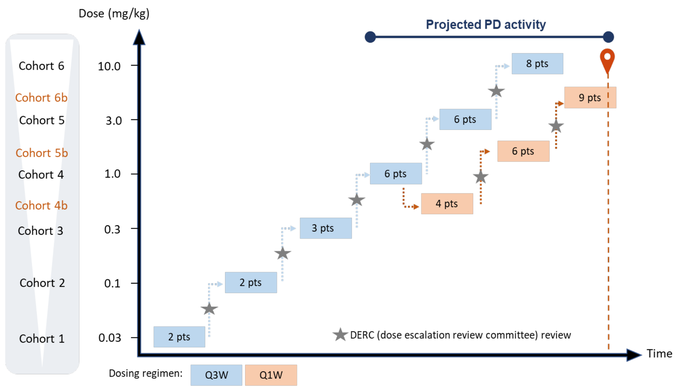
Study design

Phase 1, first-in-human, multicenter, dose-escalation study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of MP0317 monotherapy in adult patients with advanced solid tumors (NCT05098405).



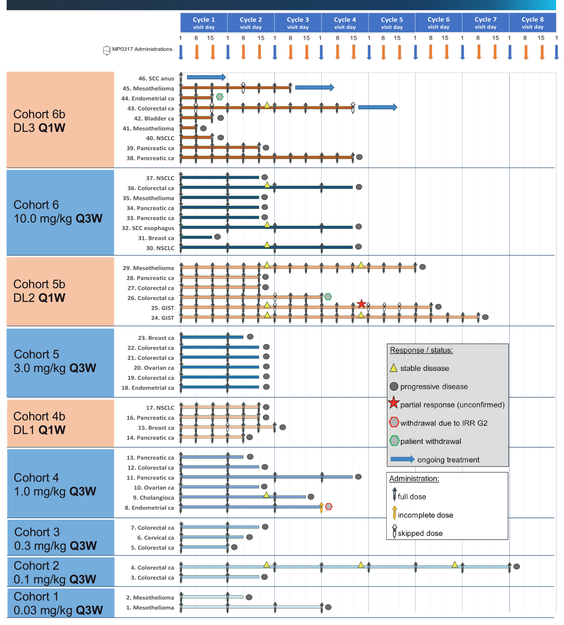
As of 6 October 2023, enrollment in all 9 cohorts was complete. In total, 46 patients were treated with MP0317 at least once, at doses of 0.03–10 mg/kg (Q3W and Q1W schedules).

Patient characteristics

Baseline characteristics	Patients (N=46)
Age (y), median (range)	63 (35 –79)
Sex (%)	
Female	24 (52)
Male	22 (48)
ECOG PS, n (%)	
0	22 (48)
1	24 (52)
Prior regimens, median (range)	4 (1–13)
Cancer types, n (%)	
Colorectal	12 (27)
Pancreatic	9 (20)
Mesothelioma	6 (13)
NSCLC	4 (9)
Breast	3 (7)
Endometrial	3 (7)
GIST	2 (4)
Ovarian	2 (4)
Cervical	1 (2)
Cholangiocarcinoma	1 (2)
SCC of esophagus	1 (2)
Bladder	1 (2)
SCC of anus	1 (2)

Data cut-off: 10 Oct 2023. GIST, gastrointestinal stromal tumor; NSCLC, non-small cell lung cancer; SCC, squamous cell cancer.

Study status



MP0317 has a favorable safety profile within 0.03–10 mg/kg range

- **Only one dose-limiting toxicity (DLT) was observed in a patient treated with MP0317 at the highest planned dose of 10 mg/kg (Q3W regimen; Grade 3 AST and ALT increase)**
- **The most frequently observed adverse reactions were fatigue of Grade 1–2 and infusion related reactions (IRR) of Grade 2**

Number of treatment-emergent adverse reactions (No. of patients)

Cohort no.	1	2	3	4	4b	5	5b	6	6b	Total
MP0317 dose level	0.03 mg/kg Q3W	0.1 mg/kg Q3W	0.3 mg/kg Q3W	1 mg/kg Q3W	DL1 Q1W	3 mg/kg Q3W	DL2 Q1W	10 mg/kg Q3W	DL3 Q1W	
Number of patients / cohort	2	2	3	6	4	6	6	8	9	**46**
Adverse Reactions (ARs)	1 (1)	10 (2)	4 (3)	21 (5)	14 (3)	5 (4)	29 (6)	27 (7)	8 (5)	119 (36)
Grade ≥3 ARs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	2 (1)
Most frequent ARs										
Fatigue	0 (0)	1 (1)	0 (0)	2 (2)	1 (1)	1 (1)	5 (5)	4 (2)	2 (2)	16 (14)
IRR	1 (1)	1 (1)	0 (0)	3 (1)	2 (1)	1 (1)	1 (1)	2 (1)	1 (1)	12 (8)
Liver enzyme(s) increased	0 (0)	0 (0)	0 (0)	2 (2)	1 (1)	0 (0)	0 (0)	6 (1)	1 (1)	10 (5)
Nausea	0 (0)	0 (0)	0 (0)	2 (2)	1 (1)	0 (0)	1 (1)	3 (3)	0 (0)	7 (7)
Anorexia	0 (0)	1 (1)	0 (0)	2 (2)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	5 (5)
Vomiting	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	3 (2)	1 (1)	0 (0)	5 (4)
Serious ARs	0 (0)	0 (0)	0 (0)	1* (1)	1** (1)	0 (0)	0 (0)	2*** (1)	1* (1)	5 (4)

* IRR Grade 2 with hospitalization for patient monitoring
** Heart failure Grade 1
*** Isolated asymptomatic Grade 3 AST and ALT elevation; DLT

Data cut-off: 10 Oct 2023

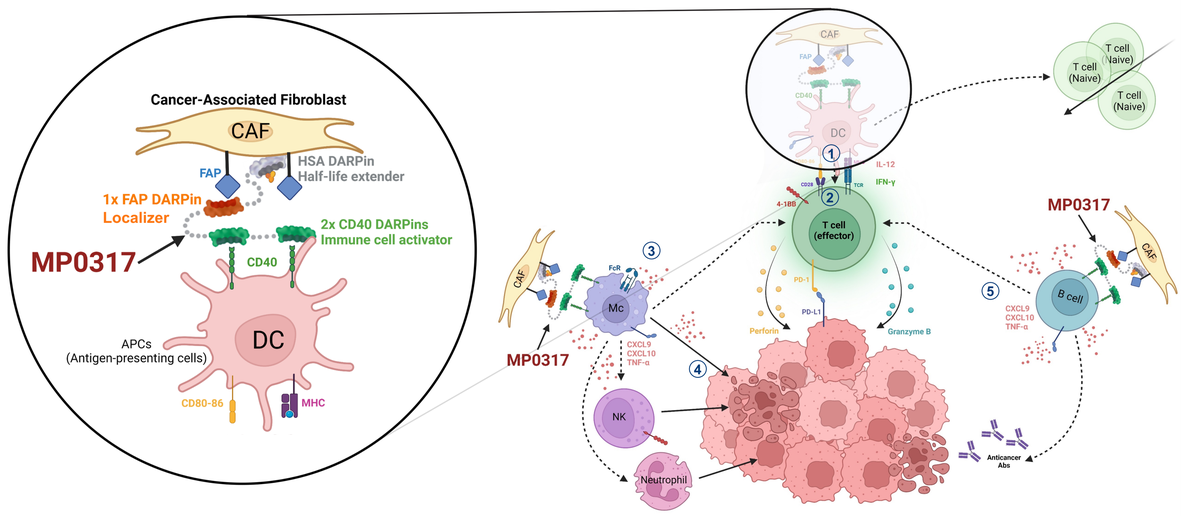
Hypothesis and proposed mechanism of action of MP0317

MP0317 (FAPxCD40) scientific rationale:

- Local CD40 pathway activation in tumor microenvironment (TME) by FAP binding on CAFs leading to immune cell activation
- Circumvent severe toxicities in peripheral organs
- Suitable for combination with agents relying on APC activation and benefiting from TME remodeling (e.g., checkpoint inhibitors)

CD40 activation in APCs promotes:

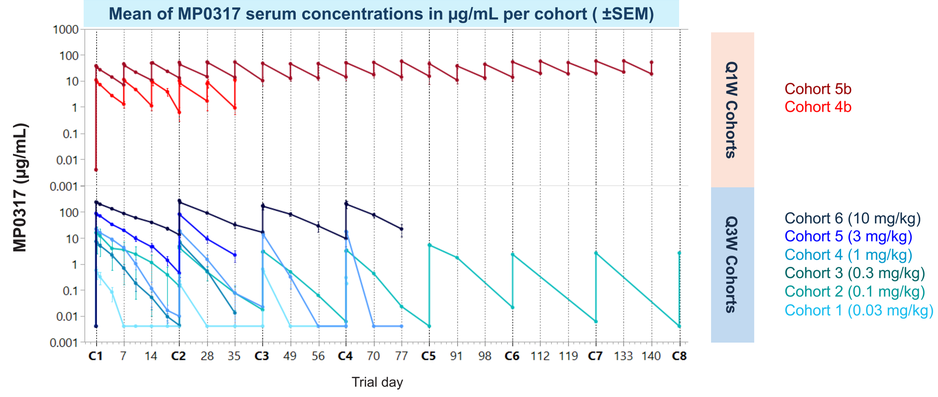
① Upregulation of activation markers and cytokines / chemokines release
② Tumor-antigen presentation and T-cell priming
③ Down-regulation of suppressive macrophages
④ Antitumor macrophage activity
⑤ B cell activation



Conclusions: MP0317 has a favorable safety profile up to the highest planned dose and shows clinical evidence of tumor-targeted CD40 activation leading to TME remodeling

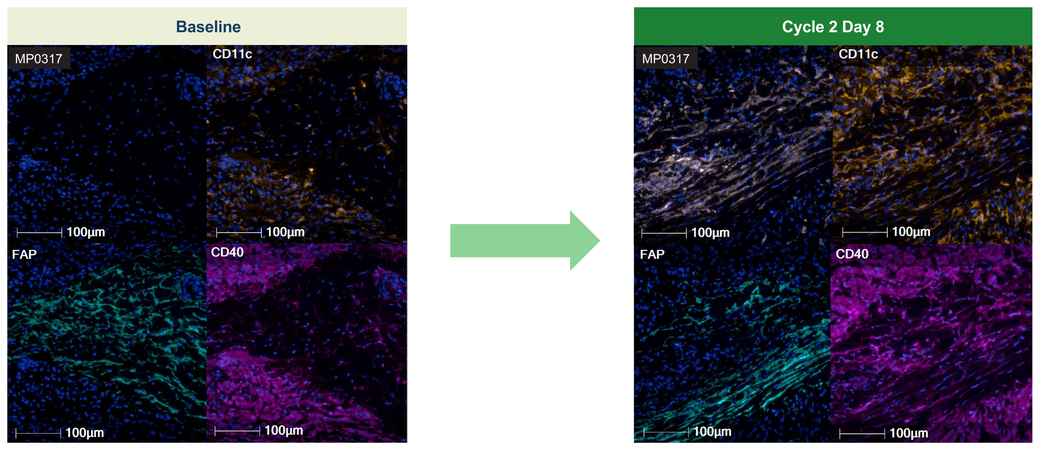
- ✓ **MP0317 has a favorable safety profile in 46 patients at each of the tested dose levels (0.03–10 mg/kg, Q3W & Q1W)**
- ✓ **MP0317 shows target occupancy in tumor biopsies and leads to TME remodeling (increase in plasma cells, T follicular helper cells, DC abundance, IFNγ production and DC maturation)**
- ✓ **Serum PK shows MP0317 half-life extended properties**
- ✓ **Increased serum levels of CXCL10 and changes in soluble biomarkers (sFAP & sCD40) corroborate these findings**
- ➢ **These data support continued clinical evaluation of MP0317, including combination studies**

MP0317 serum PK is suitable for Q3W and Q1W dosing



PK profile is consistent with half-life extended properties of DARPins. MP0317 serum exposure shows dose proportionality in C_{max} through the treatment period analysed. Sustained exposure is observed at higher doses in both Q1W and Q3W regimens overcoming the CD40-mediated antigen sink and the impact of anti-drug antibodies on PK.

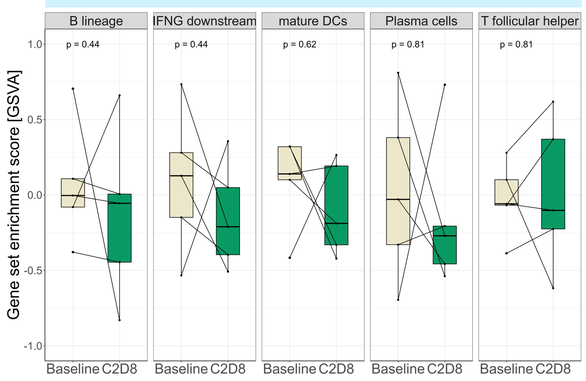
MP0317 co-localizes with FAP and CD40 in tumors – concomitant increase in intra-tumoral DCs observed



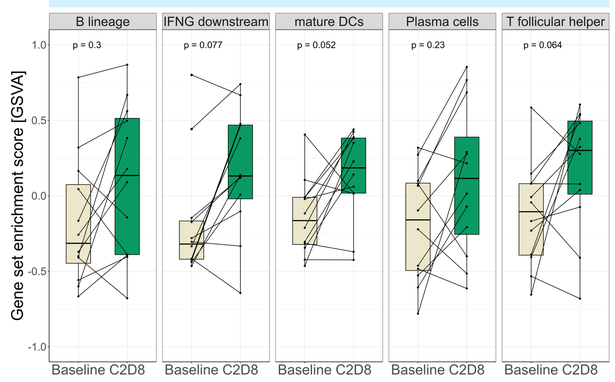
Representative multiplex immunofluorescence (mIF) images at screening and Cycle 2 Day 8 (C2D8) in tumor verified areas (H&E and pan cytokeratin positive) from GIST metastasis showing MP0317 colocalization with FAP and CD40. TME analysis verified an increase in DC (CD11c+) cell numbers at C2D8.

Immune cell infiltration, DC maturation and IFNγ production in tumors post-MP0317 treatment

MP0317 low doses⊖ or not detected in tumor (n=5)

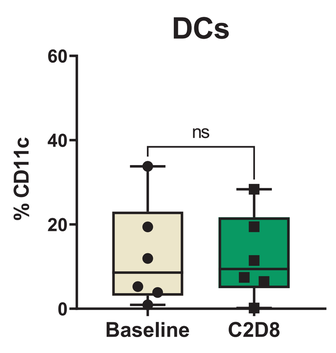


MP0317 higher doses⊕ and detected in tumor (n=12)

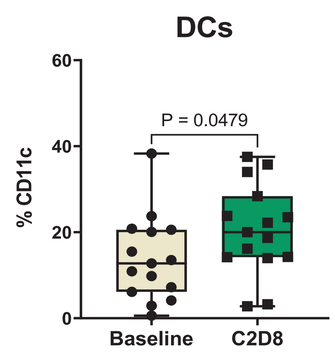


Treated patients up to Cohort 6 with evaluable paired biopsies for transcriptomics (n=17).
⊖Low doses = ≤0.1 mg/kg; ⊕Higher doses = ≥0.3 mg/kg. Statistical analysis was done using a signed rank Wilcoxon test.

MP0317 low doses⊖ or not detected in tumor (n=6)

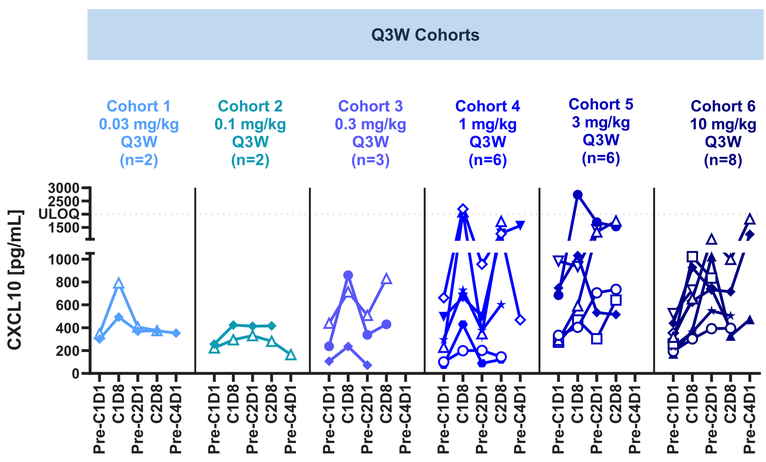


MP0317 higher doses⊕ and detected in tumor (n=15)



Treated patients up to Cohort 6 with evaluable paired biopsies for mIF (n=21). ⊖Low doses = ≤0.1 mg/kg; ⊕Higher doses = ≥0.3 mg/kg. Upper (75%), median, and lower (25%) percentiles are indicated. P-values are derived from paired ranked sum Wilcoxon test.

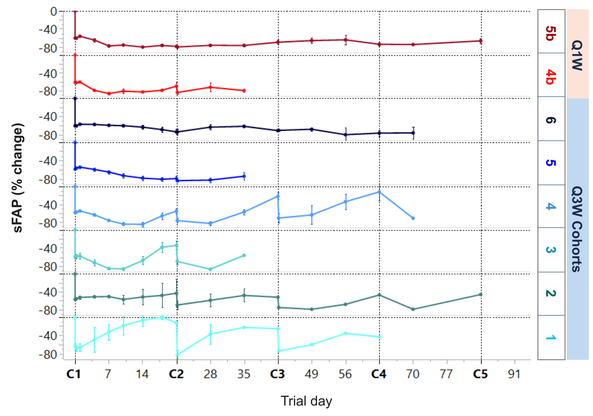
Increases in CXCL10 serum levels post-MP0317 treatment



Transient increases in circulating CXCL10 serum levels were observed after MP0317 dosing with higher fold increase observed for patients treated at projected pharmacologically active dose regimens (≥0.3 mg/kg).

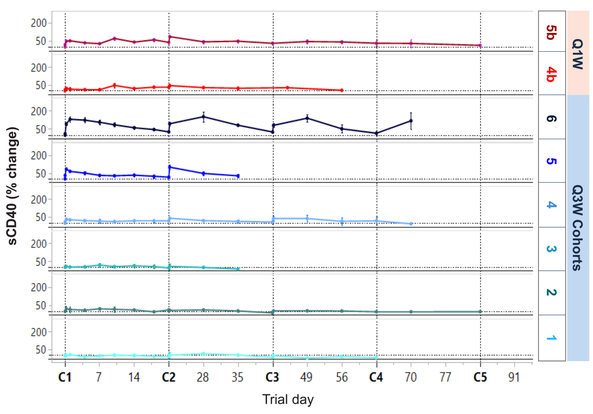
Soluble FAP and CD40 serum levels change in a dose-dependent manner

Free soluble FAP levels post-MP0317 treatment
(Mean % change from baseline per cohort [+/- SEM])



Free sFAP serum levels decreased rapidly after MP0317 administration in a dose-dependent manner. Levels return to baseline very quickly at low doses, but reduction of sFAP levels are maintained during the study treatment at high doses.

Free soluble CD40 levels post-MP0317 treatment
(Mean % change from baseline per cohort [+/- SEM])



Free sCD40 serum levels are maintained constant at lower doses and significantly increased after higher doses, suggesting a dose-dependent shedding mechanism following MP0317 engagement with CD40 on the cell surface.

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Disclosures: CGR: invited speaker for BMS, Pierre Fabre, Roche/Genentec; member of advisory board for Macomics; IDMC member for Pharmamar; steering committee member for BMS and Genentec; coordinating PI for Amunix, BMS, Hookipa, IDEAYA and Kazia Therapeutics; research grant from Roche/Genentec. NeS, EG: nothing to disclose. HDW, EF, VS, NiS, PB, JK, KI, AMF, LH, BBB, MPS, VK, AG, PL: employees and stock owners of Molecular Partners AG; PC: honorarium/fees from Ose Immunotherapeutics, Boerhinger Ingelheim, Astra Zeneca, Scenic Biotech, Amgen, BMS.

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