Effect of MP0317, a FAP x CD40 DARPin, on safety profile and tumor-localized CD40 activation in a phase 1 study in patients with advanced solid tumors

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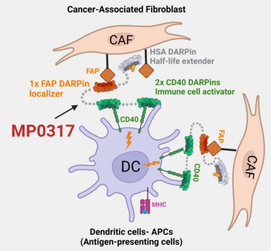
MP0317 (FAP x CD40 DARPin) scientific rationale

- Local CD40 pathway-dependent immune cell activation in the tumor microenvironment (TME) by binding to fibroblast activation protein (FAP) on cancer-associated fibroblasts (CAFs)
- Circumvent severe toxicities in peripheral organs compared to systemic CD40 activation approaches
- Suitable for combination with agents relying on antigen-presenting cell (APC) activation and benefiting from TME remodeling (e.g. checkpoint inhibitors)



Study design

- Phase 1, multicenter, open-label, dose-escalation study (NCT05098405)
- Aim to assess safety/tolerability, pharmacokinetics/pharmacodynamics (PK/PD), and preliminary antitumor activity of MP0317 monotherapy in patients with advanced solid tumors
- MP0317 administered intravenously weekly (Q1W) or every 3 weeks (Q3W) in 9 dose cohorts
- Final results are presented (46 patients)

Patient baseline characteristics and cancer types* (N=46)

Age (y), median (range)	63 (35 –79)
Female / Male, n (%)	24 (52) / 22 (48)
ECOG PS 0 / 1 , n (%)	22 (48) / 24 (52)
Prior regimens, median (range)	4 (1–13)

Colorectal	12 (27)
Pancreatic	9 (20)
Mesothelioma	6 (13)
NSCLC	4 (9)
Breast	3 (7)
Endometrial	3 (7)

*Additional cancer types: GIST and ovarian in 2 patients (4%) each; cervical, cholangiocarcinoma, SCC of esophagus or anus, bladder in 1 patient (2%) each.
ECOG, European Cooperative Oncology Group; PS, performance status; GIST, gastrointestinal stromal tumor; NSCLC, non-small cell lung cancer; SCC, squamous cell cancer.

MP0317 has a favorable safety profile across all tested doses

- DLT was observed in only one 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 and IRRs of grade 1–2

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

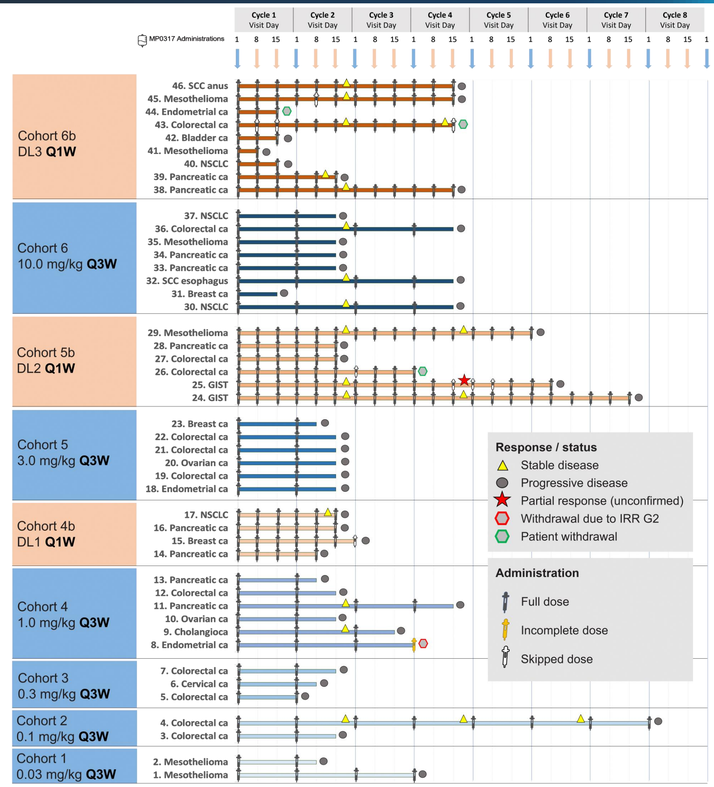
Cohort no.	1	2	3	4	4b	5	5b	6	6b	
MP0317 dose level (mg/kg) and schedule	0.03 Q3W	0.1 Q3W	0.3 Q3W	1.0 Q3W	DL1 Q1W	3.0 Q3W	DL2 Q1W	10 Q3W	DL3 Q1W	**Total**
No. of patients / cohort	2	2	3	6	4	6	6	8	9	46
Adverse Reactions (ARs)	1 (1)	10 (2)	4 (3)	20 (5)	13 (3)	5 (4)	29 (6)	25 (6)	10 (7)	117 (37)
Grade ≥3 ARs	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	1 (1)	3 (1)	0 (0)	6 (4)
Most frequent ARs										
Fatigue	0 (0)	1 (1)	0 (0)	2 (2)	1 (1)	1 (1)	5 (5)	4 (2)	3 (3)	17 (15)
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 elevations; DLT; upgraded to serious AR by Sponsor.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity; IRR, infusion-related reaction.

Main findings & conclusions

- MP0317 has a favorable safety profile in 46 patients at each of the tested dose levels (0.03–10 mg/kg, Q3W & Q1W)
- Serum PK shows MP0317 half-life extended properties and confirms that MP0317 is suited for Q3W and Q1W dosing
- MP0317 shows target occupancy in tumor biopsies and evidence of TME remodeling:
  - Increases in plasma cells, T follicular helper cells, dendritic cell (DC) abundance
  - IFNγ downstream activation
  - DC maturation gene signature score increases
- Increased CXCL10 serum levels corroborate these findings
- Dose-response analysis supports an optimal benefit-risk profile of MP0317 at doses of ≥1.5 mg/kg, with adjustable dosing frequency to match a combination dosing scheme
- These data support further clinical evaluation of MP0317 in combination with complementary anticancer therapies

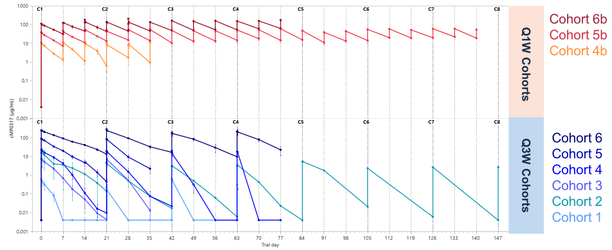
MP0317 treatment and patient outcomes



Q1W, weekly dosing; Q3W, dosing every 3 weeks; ca, carcinoma.

MP0317 serum PK is suitable for Q3W and Q1W dosing

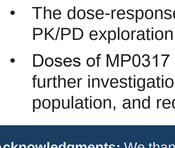
MP0317 serum concentrations (mean ± SEM)



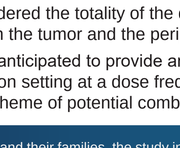
PK profile is consistent with half-life extended properties of DARPins.
MP0317 exposure shows dose proportionality throughout the treatment period analysed.
Sustained exposure is observed at higher doses in both regimens overcoming the target-mediated drug disposition and the impact of anti-drug antibodies.

MP0317 tumor-localized CD40 activation and TME modulation

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



MP0317 higher doses and detected in tumor (n=20)

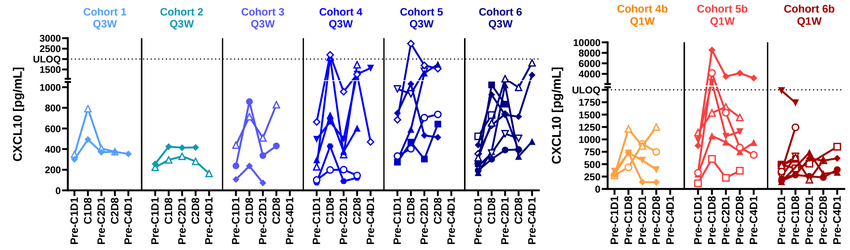


Evaluable paired tumor biopsies from treated patients were analyzed with multiplex immuno-fluorescense.
Low doses: ≤0.1mg/kg; higher doses: ≥0.3mg/kg.
Upper (75%), median, and lower (25%) percentiles are indicated. P-values are derived from paired ranked sum Wilcoxon test.

Bulk RNA sequencing in paired tumor biopsies (n=19)

- MP0317 presence tends to be associated with increase in abundance of plasma and T follicular helper cells, as well as DC maturation gene signature and IFNγ downstream activation gene signature scores

CXCL10 serum level increases post MP0317 treatment



CXCL10 chemokine serum levels per cohort show transient increases in patients dosed with MP0317, with higher magnitude of response at doses projected pharmacologically active.

MP0317 dose recommendation for potential further clinical development

- The dose-response analysis considered the totality of the data, including safety, antitumor activity, and PK/PD exploration of biomarkers in the tumor and the periphery
- Doses of MP0317 ≥1.5 mg/kg are anticipated to provide an optimal benefit-risk profile and warrant further investigation in a combination setting at a dose frequency adjustable to the disease, patient population, and required dosing scheme of potential combination regimen

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