

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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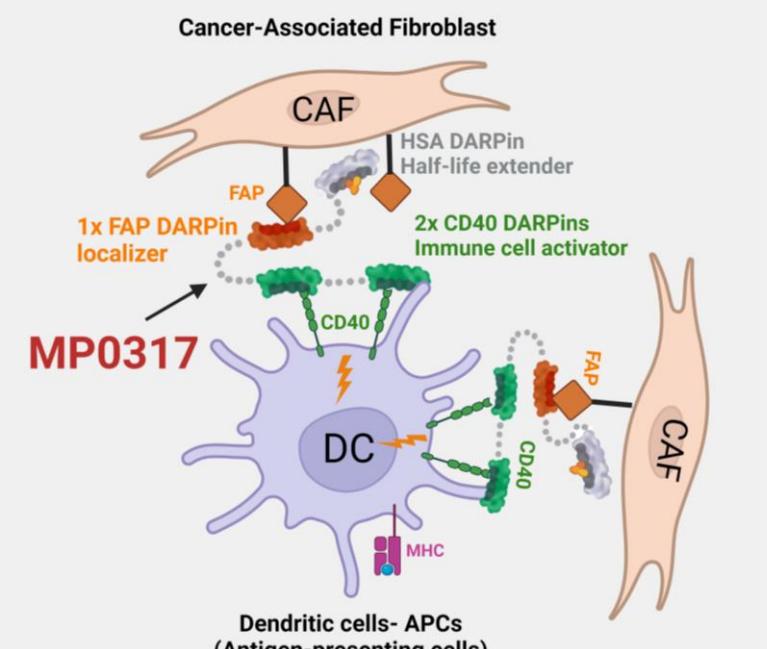
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MP0317 (FAP x CD40 DARPin) scientific rationale

- 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)	Colorectal	12 (27)
Female / Male, n (%)	24 (52) / 22 (48)	Pancreatic	9 (20)
ECOG PS 0 / 1, n (%)	22 (48) / 24 (52)	Mesothelioma	6 (13)
Prior regimens, median (range)	4 (1–13)	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	Total
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	
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)	2*** (1)	1* (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.

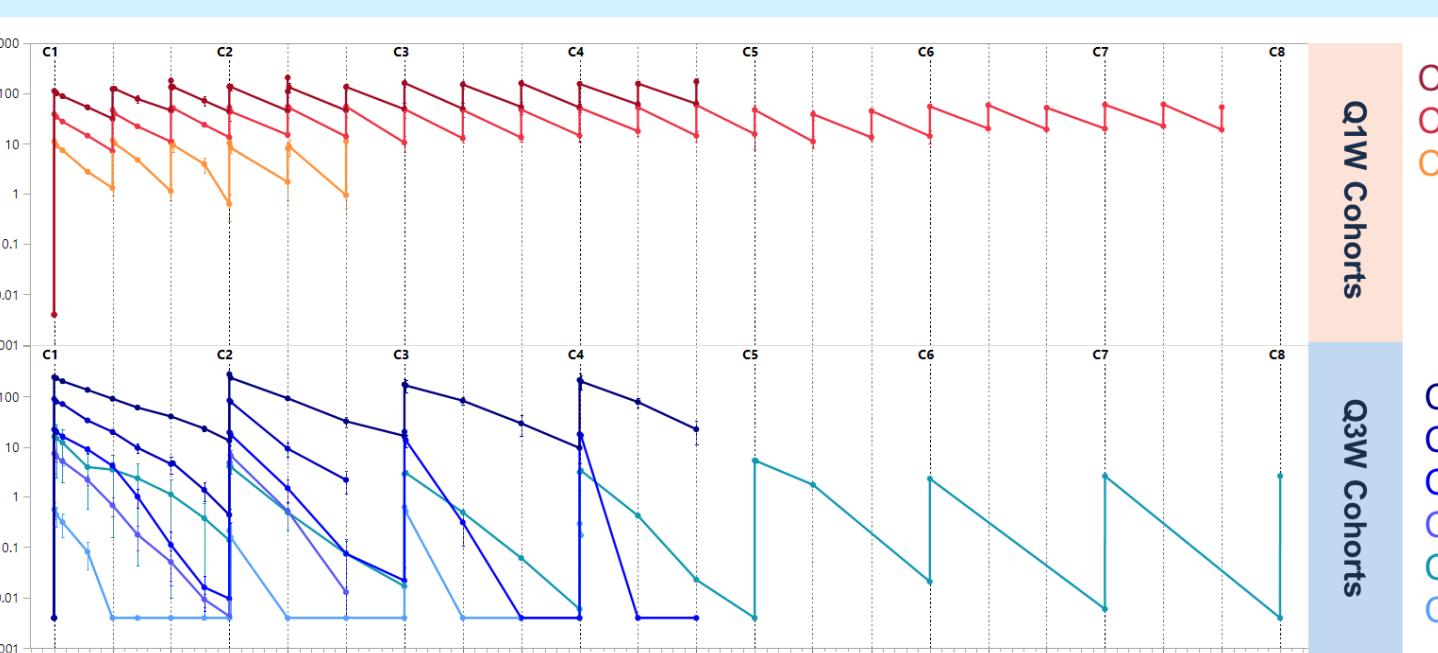
ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity; IRR, infusion-related reaction.

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
 - IFN γ 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 serum PK is suitable for Q3W and Q1W dosing

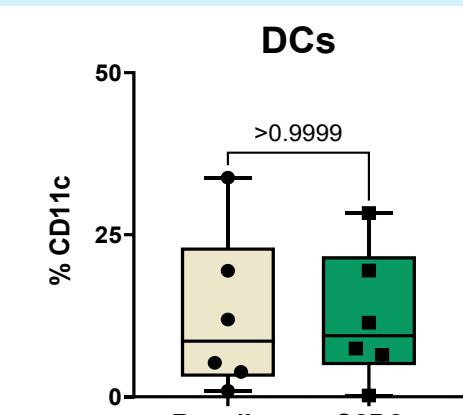
MP0317 serum concentrations (mean ± SEM)



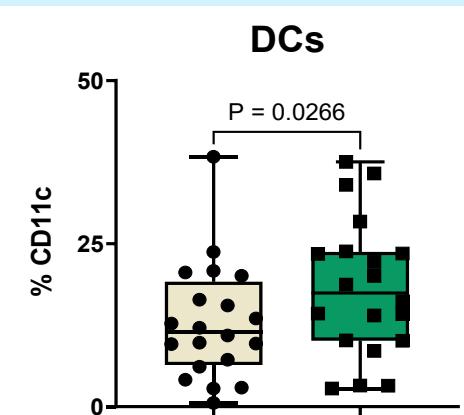
PK profile is consistent with half-life extended properties of DARPin. MP0317 exposure shows dose proportionality throughout the treatment period analysed. Sustained exposure is observed at higher doses in both regimens overcoming the target-mediated drug disposition and the impact of anti-drug antibodies.

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)

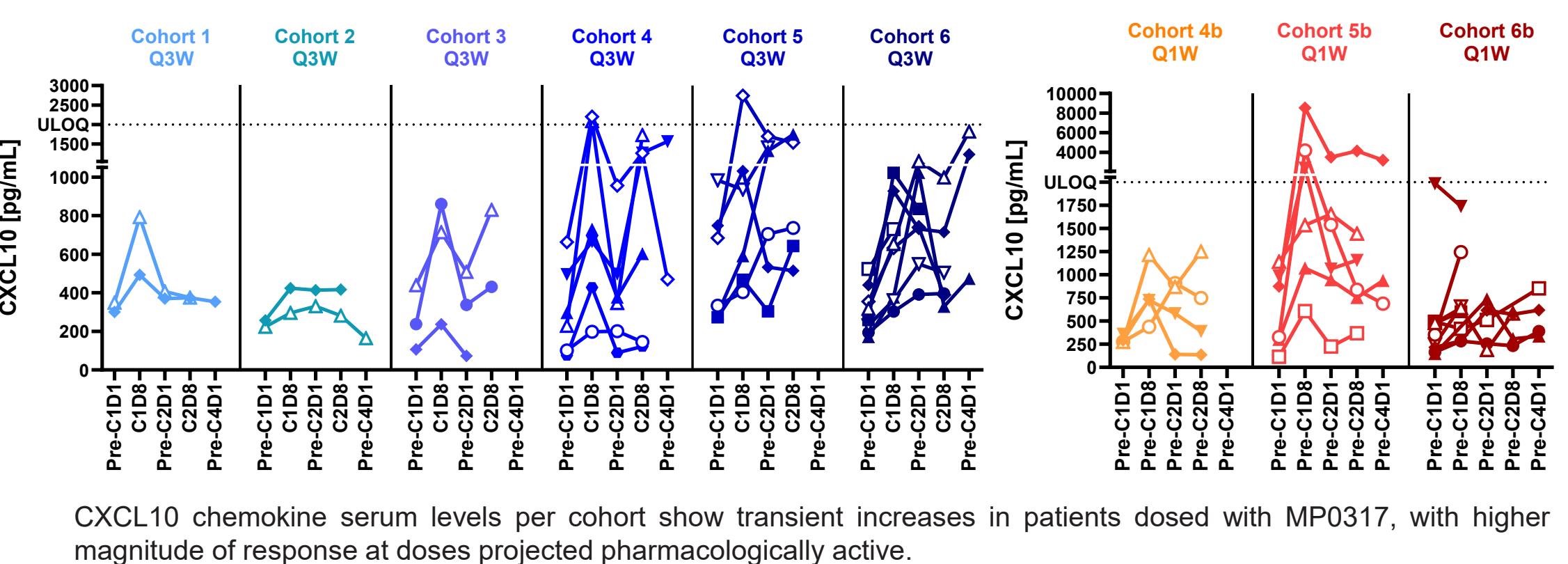


Evaluable paired tumor biopsies from treated patients were analyzed with multiplex immuno-fluorescence. Low doses: ≤0.1 mg/kg; higher doses: ≥0.3 mg/kg. Upper (75%), median, and lower (25%) percentiles are indicated. P-values are derived from paired ranked sum Wilcoxon test.

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 IFN γ downstream activation gene signature scores

CXCL10 serum level increases post MP0317 treatment



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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For any questions, please contact: info@molecularpartners.com / attention of Vaia Stavropoulou

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