Phase I study of MP0317, a FAP-dependent DARPin for tumor-localized CD40 activation in patients with advanced solid tumors

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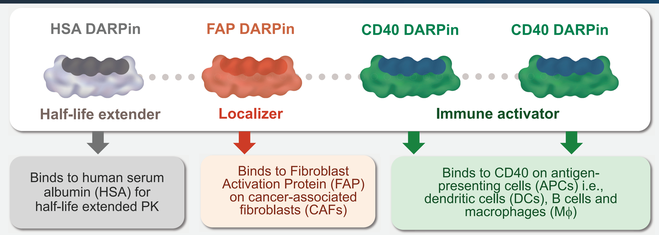
Poster #426

MP0317 DARPin: a tumor-FAP-targeted CD40 agonist

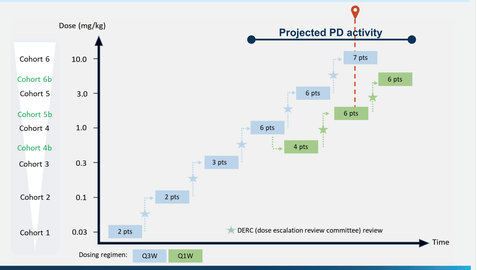


- Small size (69.5 KDa) implying good biodistribution properties
- Designed to induce tumor-FAP-localized CD40-mediated activation of APCs

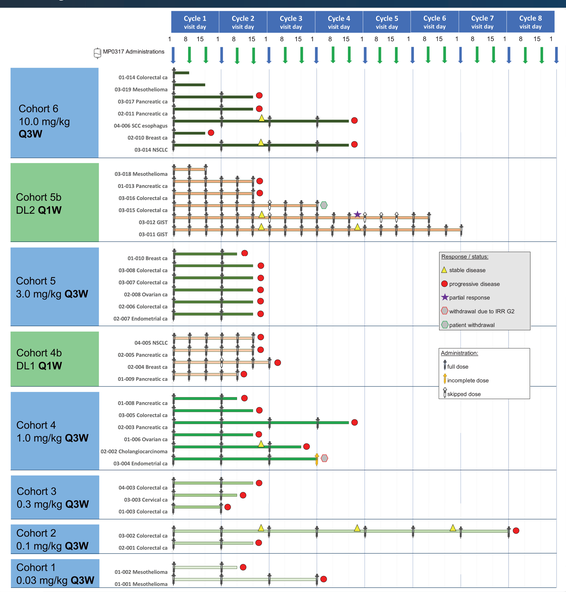
Study design

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

Study objectives	
Primary	• MP0317 safety and tolerability • Recommended dose for expansion and combination
Secondary	• PK • Antitumor activity • Preliminary clinical benefits
Exploratory	• PD



Study status



Characteristic	Patients (N = 36)
Age (y), median (range)	63 (35 –79)
Female (%)	19 (53)
ECOG PS, n (%)	
0	17 (47)
1	19 (53)
Prior regimens, median (range)	3.5 (1–13)
Cancer type, n (%)	
Colorectal	11 (31 %)
Pancreatic	7 (19 %)
Mesothelioma	4 (11 %)
Breast	3 (8 %)
GIST	2 (6 %)
Ovarian	2 (6 %)
Endometrial	2 (6 %)
NSCLC	2 (6 %)
Cervical	1 (3 %)
Cholangiocarcinoma	1 (3 %)
SCC of esophagus	1 (3 %)

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Key takeaways

Hypothesis

Tumor-localized CD40 agonism can overcome the limitations of systemic CD40 agonists (toxicities and low anti-tumor activity) by:

- Reaching safe, therapeutically relevant doses
- Activating innate immune cells intratumorally

Hypothesis confirmed in ongoing Phase 1 study

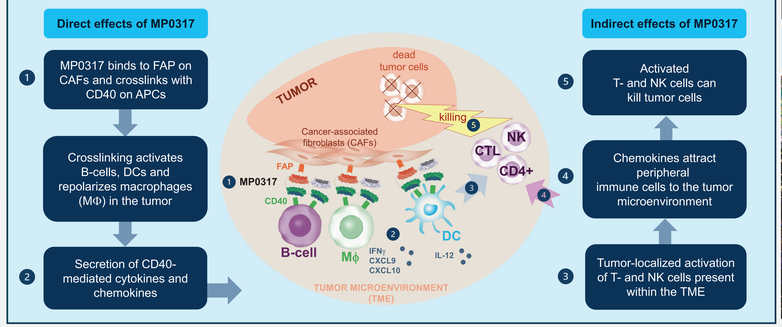
✓MP0317 has a favorable safety profile in 36 patients dosed with 0.03 mg/kg – 10 mg/kg (Q3W and Q1W schedules)

✓Tumor biopsies show target occupancy and activation of APCs (increase in B cell, plasma cell and DC abundance), and IFNγ production in the tumor microenvironment

✓Increased serum levels of CXCL10 corroborate these findings

The present data support planning of future combination studies

Proposed mechanism of action of MP0317



MP0317 safety profile

Number of treatment-emergent adverse reactions (patients)

Cohort no.	1	2	3	4	4b	5	5b	6	
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	Total
Number of patients / cohort	2	2	3	6	4	6	6	7	36
Related AEs	1 (1)	10 (2)	4 (3)	22 (5)	13 (3)	7 (5)	23 (4)	18 (5)	98 (28)
Grade ≥3 ARs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	2 (1)
Most frequent ARs									
IRR	1 (1)	1 (1)	0 (0)	3 (1)	2 (1)	1 (1)	1 (1)	2 (1)	11 (7)
Fatigue	0 (0)	1 (1)	0 (0)	2 (2)	1 (1)	1 (1)	3 (3)	1 (1)	9 (9)
Nausea	0 (0)	0 (0)	0 (0)	2 (2)	1 (1)	0 (0)	1 (1)	2 (2)	6 (6)
Vomiting	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	3 (2)	1 (1)	5 (4)
Related SAEs	0 (0)	0 (0)	0 (0)	1* (1)	1** (1)	0 (0)	0 (0)	2*** (1)	4 (3)

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

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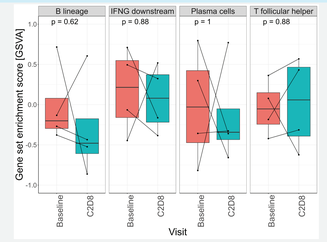
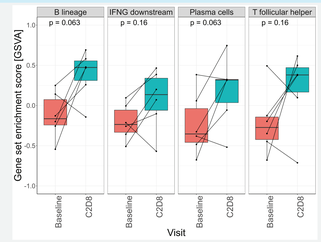
B cell — Increased B, plasma and T follicular helper cell infiltration and IFNγ production in tumors post-MP0317 treatment

MP0317 low doses* or not detected in tumor (n=4)



MP0317 higher doses# and detected in tumor (n=6)

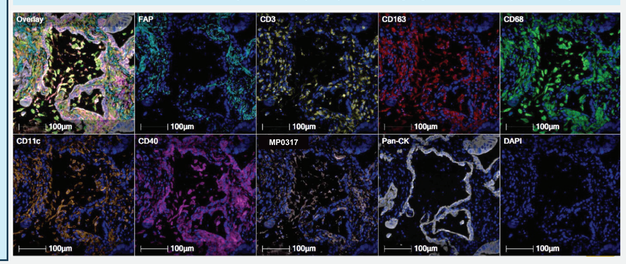


Treated patients up to Cohort 4b with evaluable paired biopsies for transcriptomics (n=10).
*Low doses = ≤0.1 mg/kg; #higher doses = ≥0.3 mg/kg. Statistical analysis was done using a signed rank Wilcoxon test.

Data cut-off Cohort 4b

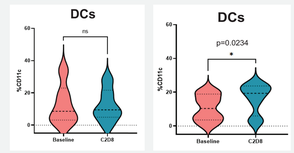
DC — A statistically significant increase in DCs in tumors post-MP0317 treatment

MP0317 detection and TME characterization in a tumor biopsy of a patient with pancreatic cancer treated every 3 weeks (Q3W) with 1 mg/kg MP0317 at Cycle 2 Day 8



Representative multiplex immunofluorescence (mIF) images in a tumor verified area (H&E and pan cytokeratin positive) from lung metastasis showing MP0317 colocalization with FAP and CD40. TME analysis verified the presence of T cells (CD3+) and myeloid cells (DCs as CD11c+ and macrophages, total as CD68+ and M2 type as CD68+ CD163+).

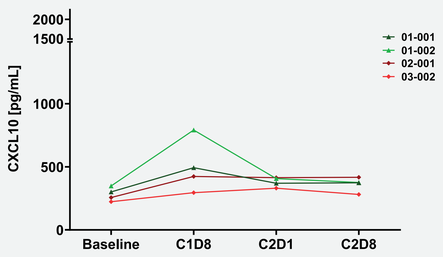
MP0317 low doses* or not detected in tumor (n=6) | **MP0317 higher doses# and detected in tumor (n=8)**



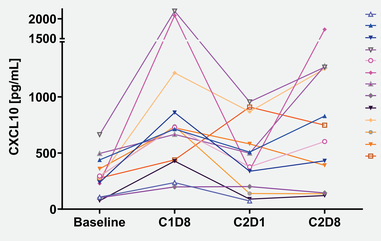
Treated patients up to Cohort 4b with evaluable paired biopsies for mIF (n=14). *Low doses = ≤0.1 mg/kg; #Higher doses = ≥0.3 mg/kg. Upper (75%), median, and lower (25%) percentiles are indicated. P-values are derived from paired ranked sum Wilcoxon test.

Increases in CXCL10 serum levels post-MP0317 treatment

Circulating CXCL10 in MP0317 low dose cohorts* (n=4)



Circulating CXCL10 in MP0317 higher dose cohorts# (n=13)



CXCL10 measured 1 week after MP0317 administration (cycles 1 and 2).
*Low doses = ≤0.1 mg/kg; #higher doses = ≥0.3 mg/kg (predicted pharmacological active doses).

Data cut-off Cohort 4b

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