Comprehensive biomarker analyses from a Phase 1 study reveals marked tumor microenvironment modulation in patients with advanced solid tumors treated with MP0317, a FAP-localized CD40 agonistic DARPin

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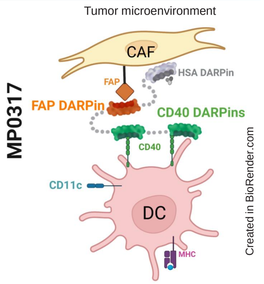
MP0317 (FAP x CD40 DARPin) tested in Phase 1 study

Scientific rationale

- MP0317, a bispecific DARPin (designed ankyrin repeat protein), selectively activates CD40 on antigen-presenting cells (APCs) within the tumor microenvironment (TME) by engaging fibroblast activation protein (FAP) on cancer-associated fibroblasts (CAFs).
- The present biomarker analyses aimed to decipher the mechanism of TME-localized CD40 pathway activation in patients treated with MP0317.



Study design

- Biomarker data obtained from a completed Phase 1 multicentre, open-label, dose-escalation trial (NCT05098405) of MP0317 monotherapy.
- MP0317 administered intravenously weekly (Q1W) or every 3 weeks (Q3W) in 9 dose cohorts (0.03-10 mg/kg) in 46 adults with advanced solid tumors, selected on literature-based predicted FAP expression.
- The presented biomarker data were analyzed on a pre-specified subgroup of pharmacologically active doses and tumor presence of MP0317 to elucidate the underlying mechanism of action of MP0317.

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

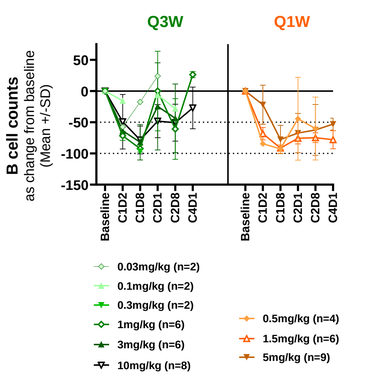
Age (y), median (range)	63 (35 –79)
Female / Male, n (%)	24 (52) / 22 (48)
ECOG PS 0 / 1 , n (%)	22 (48) / 24 (52)
Prior regimens, median (range)	4 (1–13)

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.

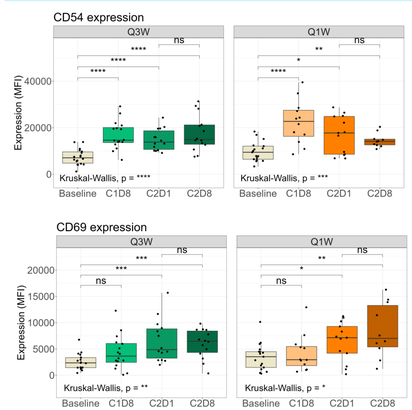
B cell trafficking and activation observed on Q3W and Q1W schedules

Transient peripheral B cell decrease



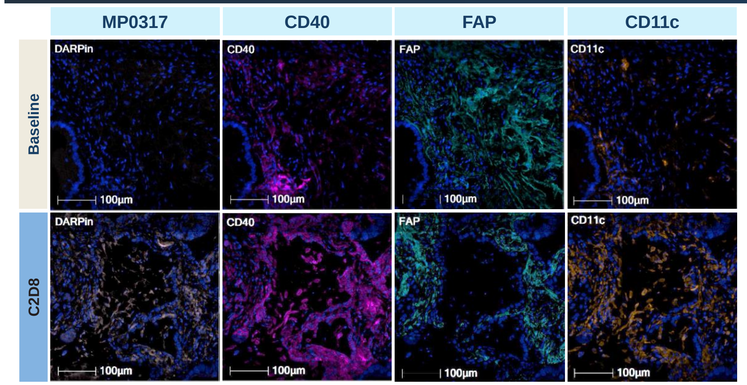
Mean of peripheral absolute B cell counts (cells/µl), quantified by flow cytometry (gated on CD3-CD19+) and presented as % change from baseline per cohort, at the indicated timepoints.

Transient peripheral B cell activation



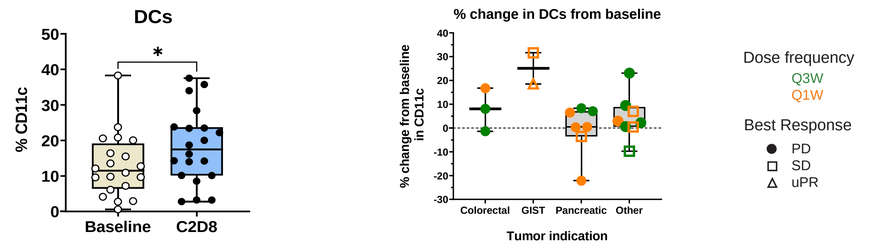
Expression levels (MFI) of CD54 and CD69 on B cells in fresh whole blood by flow cytometry at the indicated timepoints. Differences in distribution among groups was calculated by Kruskal-Wallis test by ranks (non-parametric).

MP0317 co-localization with FAP and CD40 in tumors is associated with a significant increase in dendritic cell abundance in the TME



Representative multiplex Immunofluorescence (mIF) images in tumor verified areas (H&E, positive pan-cytokeratin) from one patient (pancreatic cancer with lung metastasis) showing MP0317 colocalization with FAP and CD40. TME analysis verified an increase in DC (CD11c+) cell numbers post treatment.

Tumor abundance of CD11c positive cells increased across various indications

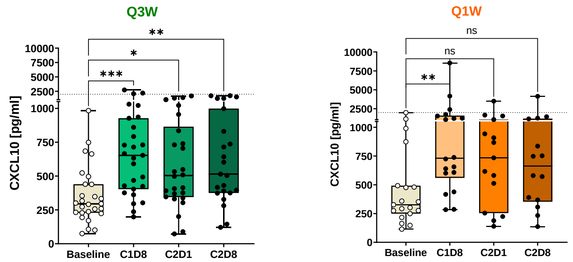


Evaluable paired tumor biopsies from treated patients were analyzed with mIF. Boxplots include patients treated with ≥0.3mg/kg and with MP0317 detected in tumors (n=20). The tumor indication, dose frequency and best clinical response are shown in the right panel. P-values are derived from paired ranked sum Wilcoxon test.

Main findings & conclusions

- Biomarker data confirmed the desired tumor-localization and activation of the CD40 pathway by MP0317.
- Evidence of TME remodeling in patients treated with pharmacologically active doses was exemplified by:
  - ✓ Increases in dendritic cells (DCs), M1 macrophages, plasma cells and T follicular helper cells abundance.
  - ✓ IFNγ downstream activation and an increased DC maturation gene signature score.
- Peripheral PD effects like increases in CXCL10 chemoattractant, transient B cell reduction and activation in blood are aligned with MP0317 mode of action.
- CD40 pathway was activated in a broad-spectrum of cancer types and various tumor locations, and MP0317 is suited for Q3W and Q1W dosing.
- These data support further clinical evaluation of MP0317 in combination with complementary immunotherapies (e.g. checkpoint inhibition).

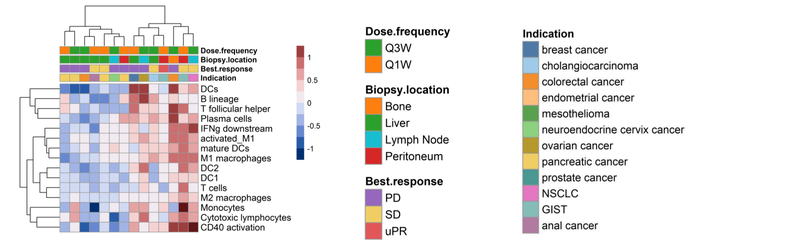
CXCL10 serum level increased post MP0317 treatment



CXCL10 serum concentration in pg/mL. Differences in distribution among Q3W and Q1W groups at the indicated timepoints was calculated by Kruskal-Wallis test.

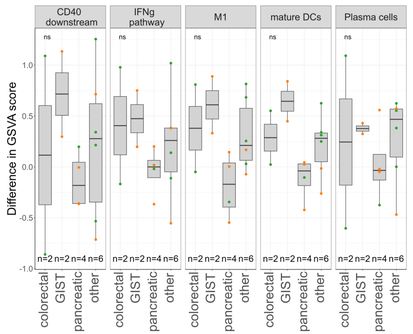
Increased abundance of myeloid and B lineage cells, and CD40 and IFNγ pathway activation were observed in patient biopsies

TME remodeling across various tumor indications, biopsy location and clinical response



Heatmap displaying changes from baseline in Gene Set Variation Analysis (GSVA) scores for biopsies taken from patients treated with MP0317. Patients included here received a dose of MP0317 ≥0.3 mg/kg and had confirmed MP0317 positivity in tumor biopsies.

Upregulation of gene signatures indicative of CD40 pathway activation in different tumor types on Q3W and Q1W schedules



Boxplot showing changes in selected GSVA scores post treatment across tumor indications, calculated using Kruskal-Wallis test.
Patients included here received a dose of MP0317 ≥0.3 mg/kg and had confirmed MP0317 positivity in a tumor biopsy.
Indications included in "others" category: anal cancer, breast cancer, cholangiocarcinoma, neuroendocrine cervix cancer, NSCLC, ovarian cancer.

Levels of statistical significance are indicated as ns (p > 0.05), * (p < 0.05), ** (p < 0.01), *** (p < 0.001), or **** (p < 0.0001).

Disclosures: all authors are employees and stock owners of Molecular Partners AG

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