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

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Background Dose-limiting toxicity (DLT) due to systemic CD40 activation and peripheral target-mediated drug disposition are major challenges in clinical development of CD40 agonists. MP0317, a CD40-agonistic DARPin (designed ankyrin repeat protein), is exclusively active in the presence of fibroblast activation protein (FAP) expressed by cancer-associated fibroblasts in the tumor microenvironment (TME). This mode of action enables tumor-localized CD40 activation, while reducing systemic toxicity.

Methods This ongoing Phase 1, multicenter, open-label, dose-escalation study aims to establish safety/tolerability, pharmacokinetics/pharmacodynamics, and preliminary antitumor activity of MP0317 monotherapy (NCT05098405). The dose-escalation scheme uses an adaptive Bayesian logistic regression model guided by the escalation with overdose control principle to determine the recommended dose. Eligible adult patients with selected advanced solid tumors (based on anticipated FAP expression) are enrolled into 9 sequentially-escalating dose cohorts of MP0317 (0.03–10 mg/kg), administered IV 3-weekly (Q3W) or 1-weekly (Q1W) until disease progression or unacceptable toxicity. The study was approved by the Dutch and French Ethics Boards.

Results As of data cut-off (02 May 2023), 36 patients received ≥1 MP0317 dose across 8 cohorts, including 19 women (53%) and 17 men (47%). The median age at enrollment was 63 years (range 35–79) and patients received a median number of 3.5 prior treatments (range 1–13). Colorectal cancer was the most frequent tumor type (11 patients, 31%). One patient experienced a DLT (asymptomatic Grade 3 elevation of alanine and aspartate aminotransferases), at the highest planned dose of MP0317 (10 mg/kg Q3W). Grade 2 infusion-related reaction was the most frequently observed adverse reaction (7 patients, 19%), followed by Grade ≤2 fatigue, nausea and vomiting in 9, 6, and 4 patients, respectively. One patient achieved unconfirmed partial response, and stable disease was observed in 5 patients. Paired tumor biopsies confirmed colocalization of MP0317 with FAP and CD40. MP0317 detection in tumor biopsies was associated with an increase in abundance of antigen-presenting cells (dendritic cells, B cells and plasma cells) and IFNγ signature in the TME. Increases in CXCL10 serum levels post-MP0317 treatment support these findings.

Conclusions These data of 36 patients, dosed across 8 dose levels (0.03–10 mg/kg, Q3W and Q1W schedules), confirmed a favorable safety profile of MP0317 monotherapy with limited systemic inflammation compared to other CD40 agonists. Analysis of paired tumor biopsies and peripheral biomarkers provided evidence of target occupancy and pharmacodynamic modulation in the TME, consistent with tumor-localized CD40 activation. These data support continued clinical evaluation of MP0317, including combination studies.

Trial Registration This study is registered at ClinicalTrials.gov: NCT05098405

Ethics Approval The study was approved by the Dutch and French Ethics Boards.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0721