A phase 1 study to characterize the safety and tolerability of MP0317, a tumor targeting FAP dependent CD40 agonist DARPin, in patients with refractory solid tumors

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Background and Rationale

Activation of the innate immune system is an increasingly important cornerstone in the treatment of advanced tumors, and CD40 agonism has proven to be particularly powerful, however off target systemic toxicity has presented a challenge. DAR Pins are small (15kDa) engineered binding proteins designed around the natural ankyrin repeat protein scaffold. A DARPin can be tuned to bind almost any biological target with high affinity and selectivity, and can be concatenated with linkers, as in the case of MP0317.

MP0317 is a tri-specific fibroblast activation protein (FAP) x CD40 DARPin drug candidate that combines high potency for CD40 activation with FAP tumor targeting and tumor-restricted receptor engagement and immune cell activation, as well as half life extension through inclusion of specific human serum albumin binding DARPin domains. This combines the functions into a single tri-specific molecule, resulting in agonistic binding effects as well as FAP targeting.

Following a good preclinical safety profile observed in vivo toxicity and in vitro safety studies,1 the first-in-human study of MP0317 in patients with relapsed/refractory high FAP expressing solid tumors has been initiated in France and The Netherlands to investigate the safety and tolerability of MP0317 as a single agent, as well as provide preliminary information regarding anti-tumor effects.

Study Information

Protocol number: MP0317-CP101
Status: Recruiting
Lead Investigator: Philippe Cassier, Centre Léon Bérard, Lyon, France
Clinical Trials Identification: NCT05098405, EUĐRACT 2020-005516-22
Recruiting Sites and Countries :The Netherlands (2), France (2)
Sponsor and Funding: Molecular Partners AG, Switzerland

Study design

A multicenter, open label, study in two parts; a dose escalation part to determine maximum tolerated dose (MTD) or Recommended Dose for Expansion (RDE), followed by a safety expansion at the RDE or MTD.

Dose Escalation by Bayesian Logistic Regression Model

Dose-escalation is guided by an adaptive Bayesian Logistic Regression Model (BLRM)2 based on dose-limiting toxicity (DLT) observed during the evaluation period. The BLRM is an established method to estimate the RDE/MTD in cancer patients. The BLRM will be guided by the Escalation With Overdose Control principle2 to control the risk of DLT in patients at escalated dose levels. The method incorporates available information and updates the model parameters based upon new data for any DLTs observed during the study. The model’s estimation of the probability of DLT and the recommendation of the next dose level will be performed at each escalation step and will utilize the entire history of all available data from previous cohorts. A dose-escalation review committee (DERC) will monitor safety and govern all cohort dosing decisions.

Study treatment will be administered every 3 weeks (q3w) as an intravenous (IV) infusion until progressive disease (PD), unacceptable toxicity, or discontinuation through other causes. However, based on the recommendation of the BLRM, the DERC may advise exploration of an alternative dosing schedule (e.g., every week) after review of available clinical safety data.

The safety expansion cohort will open to confirm safety in a larger population (15 patients) once the MTD or RDE has been determined.

Key Patient Eligibility Criteria

• ≥18y old. advanced, histologically-proven solid tumor* for whom approved therapies have been exhausted
• Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1
• Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
• Mandatory paired (pre and on-treatment) tumor biopsies

Primary Outcomes and Endpoints

Determination of MTD or RDE
• Based on incidence of DLTs within an adaptive study design following Bayesian Logistic Regression Model (BLRM)
Characterize the safety and tolerability of MP0317
• Type, incidence and severity of AEs and serious adverse events (SAEs) National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0
• Changes between screening and post-screening laboratory parameters and vital signs

Secondary Outcomes

to describe the PK, evaluate the immunogenicity, and evaluate preliminary antitumor activity and clinical benefit of MP0317 as a monotherapy in patients with advanced solid tumors.

Conclusions and Outlook

Targeting CD40 a immune cell activation to the tumor microenvironment via FAP binding is hoped to provide an avenue for enhanced CD40 driven immune cell activation while reducing off target toxicity effects. This study is expected to provide data that will pave the way for further phase 2 studies in specific indications as well as potential combination studies with immune checkpoint inhibitors such as anti-PDL1.

Abstract

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Background

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