617 A PHASE I STUDY OF A TUMOR-TARGETED, FIBROBLAST ACTIVATION PROTEIN (FAP)-CD40 AGONIST (RO7300490) IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background FAP-CD40 is a second-generation, bispecific, FAP-targeted CD40 agonist antibody, which was developed to overcome systemic toxicities and the narrow therapeutic index of conventional anti-CD40 therapeutics.

FAP-CD40 was designed to specifically activate antigen-presenting cells when CD40 is crosslinked by FAP-positive cells in the tumor.

Methods This first-in-human study evaluated the safety, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor activity of FAP-CD40 in adult patients with solid tumors considered to express FAP.

Patients diagnosed with locally advanced and/or metastatic solid tumor types that were not amenable to standard therapy, and with adequate bone marrow and organ function were eligible. FAP-CD40 was administered intravenously every 2 weeks until disease progression, unacceptable toxicity or other discontinuation criteria were met. A Bayesian model-based approach guided dose escalation.

Results Twenty-nine patients received FAP-CD40 in 6 cohorts at doses ranging from 16mg to 1100mg. Discontinuations were mainly due to progressive disease or symptomatic deterioration (79.3%).

No DLT was reported. Most adverse events (AE) were mild to moderate and non-serious. The most common treatment-related (TR) AE was low-grade arthralgia (31%). No Grade 4–5 TRAE was reported. Grade 3 TRAEs were reported in 2 patients. One single case of Grade 1 cytokine-release syndrome occurred. Three AEs led to treatment withdrawal, 2 of which were assessed related to FAP-CD40. There was no evidence of dose-related AE incidence or severity.

The best overall response was stable disease, which was achieved in 14/26 patients.

At lower doses, FAP-CD40 showed non-linear PK, which can be attributed to the saturation of peripheral CD40 binding sites, with a trend for linear PK at the higher doses. Persistent and full occupancy of CD40 receptors on circulating B cells was reached at the higher doses. A dose-dependent reduction of circulating B cells was also observed. There was no detectable effect of FAP-CD40 on peripheral cytokines and chemokines.

Conclusions FAP-CD40 was well tolerated up to the highest dose tested and the maximum tolerated dose was not reached. Toxicities were as anticipated and manageable. No objective response was achieved.

FAP-CD40 demonstrated target-mediated drug disposition with a sustained exposure at higher doses. Target engagement and peripheral PD effects aligned with expectations for a tumor-targeted mode of action.

In summary, targeting CD40 agonism to the tumor has led to a favorable safety profile at doses with strong and sustained target engagement, and supports further studies in combination with other anti-cancer therapies.

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Ethics Approval The study was approved by all relevant IRB/EC (CEIC de Navarra: EC_2021/2; HRA & HCRW: 21/FT/0031; De VK Region Hovedstaden: H-21017757; SNUH IRB: H-2104–078-1211; ASM IRB S2021–0747-0001); CPP Ile de France I: CPPIDF1–2022-DI21-cat.1)

Study participants gave informed consent prior enrollment.

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