Background The potential of toll-like receptor (TLR) agonists to induce anti-tumor immunity has been limited by toxicities associated with systemic administration. Recently, intratumoral TLR agonists (CMP-001, SD-101) have shown promising responses in melanoma as single agents and in combination with checkpoint blockade. Building on the concept of localized innate activation to induce systemic anti-tumor immunity and increased safety window, APR003 is a small molecule TLR7 agonist designed to concentrate in the GI/liver upon oral administration for treatment of metastatic GI malignancies. Studies in mice and monkeys demonstrated robust Type-1 Interferon pathway activation with good tolerability compared to benchmark TLR7 agonists. APR003 is also efficacious in several models of liver and colon cancer, both as single agent and in combination with anti-PDL1. APR003 is currently being evaluated in an ongoing Phase 1 dose escalation trial (NCT04645797) in relapsed/refractory colorectal cancer (CRC) patients with hepatic metastasis.

Methods APR003 was administered to patients orally once weekly either at 25 mg or 50 mg in 21-day cycles. Peripheral blood was collected at various time points post-dose on Cycle 1/Day 1 (C1D1), Cycle 1/Day 15 (C1D15), and Cycle 2/Day 1 (C2D1). Plasma was analyzed for pharmacokinetics. Plasma cytokines, including IFNa, IP-10, IL-6, and TNFa, were quantified by SIMOA® technology.

Results Between the 25 mg (n=6) and 50 mg (n=4) dose cohorts, APR003 plasma levels were low, with no dose-dependent increase in exposure. APR003 induced a transient yet robust cytokine response peaking around 6-8 hours post-dose and declining by 24 hours. After a week of recovery, all cytokines returned to baseline before the subsequent weekly dose. Cytokine induction in plasma also revealed no dose-dependency. The dose cohort combined geometric mean maximum fold induction over pre-dose of IFNa, IP-10, IL-6, and TNFa were 41-, 21-, 5-, and 2-fold on C1D1 and 107-, 28-, 6-, and 3-fold on C1D15, respectively. Comparing the cytokine levels at 6 hours on the plasma sampling days indicated slightly diminished response on C2D1 compared to C1D1; no APR003 plasma exposure accumulation or reduction was observed on C2D1.

Conclusions In an ongoing Phase 1 dose escalation trial, oral administration of APR003 elicited a strong Type I interferon response (IFNa and IP-10) over the pro-inflammatory response (IL-6 and TNFa), at well tolerated doses. The results suggest our tissue-targeted oral TLR7 agonist may have an increased safety window compared to prior (non-targeted) agents of the same class, thereby achieving Proof-of-Drug Design and warrants further investigation.

Trial Registration This study is registered on Clinicaltrials.gov: NCT04645797

REFERENCE