658 A PHASE 2 STUDY TO ASSESS THE SAFETY, EFFICACY OF FLX475 COMBINED WITH PEMBROLIZUMAB IN PATIENTS WITH ADVANCED OR METASTATIC GASTRIC CANCER

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Background Regulatory T-cells (T_{reg}) maintain homeostasis and self-tolerance, but can also suppress anti-tumor immunity in the tumor microenvironment (TME), correlating with poor clinical outcomes. C-C chemokine receptor type 4 (CCR4), the cognate receptor of the secreted proteins C-C motif chemokine ligand 17 (CCL17), and 22 (CCL22), is the predominant chemokine receptor on human T_{reg} and is responsible for migration and accumulation of T_{reg} in the TME.[1, 2, 3] FLX475 is an orally available and selective small-molecule antagonist of CCR4 which demonstrated potent inhibition of CCL17- and CCL22-induced CCR4-mediated chemotaxis, an increase in the intratumoral T_{eff}/T_{reg} ratio, and anti-tumor efficacy as a single agent and in combination with checkpoint inhibitors.[4] Given the proposed mechanism of action, a Phase 2 study investigating the safety, efficacy of FLX475 in combination with pembrolizumab in patients with advanced or metastatic gastric cancer is being conducted.

Methods This is a Phase 2, open-label study to assess the safety and efficacy of FLX475 in combination with pembrolizumab in patients with advanced or metastatic gastric cancer. Patients were treated across 2 cohorts administered with 100mg PO QD of FLX475 and 200mg IV Q3W of pembrolizumab. In cohort 1, checkpoint inhibitor (CPI) naïve Epstein-Barr Virus (EBV)-negative gastric cancer patients who have progressed on at least 2 prior systemic treatments for advanced or metastatic gastric cancer were enrolled, and in cohort 2, CPI-naïve EBV-positive gastric cancer patients who had at least 1 prior systemic treatment for advanced or metastatic gastric cancer were enrolled.

Results Initial analysis of cohorts was performed when the first 10 patients of each cohort completed 4 cycles or after 2nd response assessment (Cut-off date: 11 Oct 2021 (cohort 1), 15 Apr 2022 (cohort 2)). Overall, FLX475 in combination with pembrolizumab was well-tolerated, with no new safety signal detected. The most common treatment-emergent adverse events (all grade) occurred in more than 20% of patients across cohorts were QTc prolongation, pruritus, anaemia, headache, abdominal pain, fatigue, and aspartate aminotransferase increased. There were no responses observed in the EBV-negative cohort of 10 patients. However, 6 partial responses (ORR: 60.0%, all confirmed) from EBV-positive cohort were reported. Pharmacokinetic data demonstrated that majority of patients achieved the target minimum FLX475 exposure level of 130 ng/mL after 1 week of dosing. Pharmacodynamic biomarker changes were observed in tumor demonstrating biological activity of FLX475.

Conclusions FLX475 in combination with pembrolizumab was well-tolerated and exhibited promising anti-tumor efficacy in patients with advanced or metastatic EBV-positive gastric cancer.

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RAPT Therapeutics, Inc., South San Francisco, CA, USA is providing FLX475 for the study.

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA is providing pembrolizumab for the study.

Trial Registration ClinicalTrials. gov Identifier: NCT04768686

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Ethics Approval This study has been approved by the Institutional Review Board at each investigational site.

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