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

Background Regulatory T-cells (Treg) 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 Treg and is responsible for migration and accumulation of Treg in the TME. FLX475 is an orally available and selective small-molecule antagonist of CCR4 which demonstrated potent inhibition of FLX475 mediated chemotaxis, an increase in the intratumoral Teff/Treg ratio, and anti-tumor efficacy as a single agent and in combination with checkpoint inhibitors. 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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RPT 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.

ClinicalTrials.gov Identifier: NCT04768686

REFERENCES

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