TRIAL IN PROGRESS: 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 (Treg) are essential in maintaining self tolerance, but they can also suppress anti-tumor immunity in the tumor microenvironment (TME). Treg are recruited into tumors by C-C motif chemokine ligand 17 (CCL17), and 22 (CCL22), which are produced by tumor cells and other cells in the TME. These chemokines serve as a "homing signal" to Treg by binding to their cognate receptor, C-C chemokine receptor type 4 (CCR4), the predominant chemokine receptor on human Treg.^{1 2 3} FLX475, is an orally available and selective small-molecule antagonist of CCR4. In preclinical studies it has demonstrated potent inhibition of CCL17- and CCL22-induced CCR4-mediated chemotaxis, an increase in the intratumoral Teff/Treg ratio, and anti-tumor efficacy as a single agent and in combination with checkpoint inhibitors. In a first-in-human healthy volunteer study, the orally-available CCR4 antagonist was well tolerated, with solid safety profile. A receptor occupancy (RO) pharmacodynamic (PD) assay using peripheral blood Treg demonstrated the ability to safely achieve exposure levels predicted to maximally inhibit Treg recruitment into tumors.⁴ The proposed mechanism of action, pharmacokinetics (PK), PD, and safety profile of FLX475 have enabled the optimized design of an ongoing Phase 2 study to assess the safety, efficacy of FLX475 in combination with pembrolizumab in patients with advanced or metastatic gastric cancer.

Methods This clinical trial 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 (NCT04768686). Approximately 90 subjects may be enrolled across 2 cohorts to examine the safety and efficacy when administered 100mg PO QD of FLX475 with 200mg IV Q3W of pembrolizumab. In cohort 1, checkpoint inhibitor naïve Epstein-Barr Virus (EBV)-negative gastric cancer subjects who have progressed on at least 2 prior systemic treatments for advanced or metastatic gastric cancer will be enrolled, and in cohort 2, checkpoint inhibitor naïve EBV-positive gastric cancer subjects who had at least 1 prior systemic treatment for advanced or metastatic gastric cancer will be enrolled. Both EBV negative and positive gastric cancer are predicted to express high levels of CCR4 ligands and enriched in Treg (i.e. 'charged tumor'). The study is planned initially as a 2-stage design for each cohort, and an interim analysis reviewing efficacy and safety results as well as available PK and PD data for both cohorts will be performed prior to stage 2.

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Trial Registration NCT04768686

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