**TPS4203** **Poster Session**

# Open-label, single-arm, single-center phase 1b/2 clinical study of fruquintinib combined with trastuzumab and XELOX in the first-line treatment of advanced HER2-positive metastatic gastric or gastroesophageal junction adenocarcinoma.

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**Background:** Trastuzumab plus chemotherapy has significantly prolonged survival in patients with HER2-positive gastric and gastroesophageal junction (G/GEJ) cancer. The KEYNOTE-811 study suggested that the efficacy of adding pembrolizumab to trastuzumab and chemotherapy was superior to trastuzumab plus chemotherapy. However, only patients with a PD-L1 combined positive score (CPS) of 1 or higher could benefit, while those with PD-L1 CPS $< 1$ did not benefit from this regimen. Fruquintinib is a highly selective oral tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3. The phase 3 study FRUTIGA demonstrated fruquintinib plus paclitaxel was superior to paclitaxel alone as second-line treatment in patients with G/GEJ cancer. As anti-angiogenesis has a synergistic effect with trastuzumab, we designed this study to evaluate the safety and efficacy of fruquintinib plus trastuzumab, and CAPEOX as first-line treatment for advanced HER2-positive G/GEJ cancer. **Methods:** This is a single-center, single-arm, open-label, phase 1b/2 study. The phase 1b study will adopt a 3+3 design with escalating oral daily dose of 2 to 4 mg (1 mg per level) fruquintinib for days 1-14 in combination with trastuzumab (8mg/kg load, followed by 6mg/kg) intravenously once for day 1, capecitabine 1000mg/m$^2$ orally twice a day for days 1-14, and oxaliplatin 130mg/m$^2$ intravenously once for day 1 using a 21-day cycle. The maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of fruquintinib will be determined in the phase 1b study with a dose-limiting toxicity (DLT) period of the first cycle. Major DLTs are defined as any of the following toxicities occurring in the DLT period determined to be related to study treatment: grade $\geq 4$ hematological toxicities, grade $\geq 3$ non-hematological toxicities, and toxicities that required discontinuation of fruquintinib or trastuzumab $\geq 21$ days. 6 to 12 systematic treatment-naïve patients with advanced G/GEJ cancer are expected to be enrolled in the phase 1b study, depending on observed DLTs and the need for dose adjustments. In the phase 2 study, 39 additional patients will be enrolled with RP2D administered. Upon 6-8 cycles of treatment completed, fruquintinib plus trastuzumab and capecitabine will be administered as maintenance treatment. The treatment continues until progressive disease or intolerable toxicity. The primary endpoint of the phase 2 study is PFS. The secondary endpoints include OS, ORR, DCR, DoR, safety, and molecular biomarker exploration. Clinical trial information: ChiCTR2300074767. Research Sponsor: None.