Zanidatamab, an anti-HER2 bispecific antibody, plus chemotherapy with/without tislelizumab as first-line treatment for patients with advanced HER2-positive breast cancer or gastric/gastroesophageal junction adenocarcinoma: A Phase 1B/2 trial-in-progress.

Keun Wook Lee, Young-Hyuck Im, Keun Seok Lee, Jae Yong Cho, Do-Youn Oh, Hyun Cheol Cheol Chung, Yee Chao, Li-Yuan Bai, Chia Jui Yen, In-Ho Kim, Sang Cheul Oh, Chia-Chi Lin, Jin Wang, Xin Wang, Huiyan Li, Yen-Yang Chen, Yoon-Koo Kang; Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea, Republic of (South); Samsung Medical Center, Sungkyunkwan University, School of Medicine, Seoul, Korea, Republic of (South); National Cancer Center, Goyang, Korea, Republic of (South); Yonsei Cancer Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, Republic of (South); Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea, Republic of (South); Department of Oncology, Taipei Veterans General Hospital, Taipei City, Taiwan; China Medical University Hospital, China Medical University, Taichung, Taiwan; National Cheng Kung University Hospital, Tainan City, Taiwan; The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, Korea, Republic of (South); Korea University Guro Hospital, Seoul, Korea, Republic of (South); National Taiwan University Hospital, Taipei, Taiwan; BeiGene (Shanghai) Co., Ltd., Shanghai, China; Kaohsiung Chang Gung Memorial Hospital, Kaohsiung City, Taiwan; Asan Medical Centre, University of Uslan College of Medicine, Seoul, Korea, Republic of (South)

Background:

Zanidatamab is a novel HER2-targeted antibody that binds two distinct extracellular domains of HER2, allowing for multiple mechanisms of action including enhanced binding, clustering, receptor internalization and downregulation; this results in inhibition of ligand-dependent and -independent proliferation and potent activation of antibody-dependent cellular cytotoxicity. Zanidatamab monotherapy is well tolerated and has shown promising anti-tumor activity in patients (pts) with pre-treated advanced HER2-positive cancers, and was well tolerated in a Phase I trial (NCT02892123). Tislelizumab is an investigational anti-programmed death-1 (PD-1) antibody engineered to minimize binding of FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, which is a potential mechanism of T-cell clearance and resistance to anti-PD-1 therapy. Tislelizumab is well tolerated and has anti-tumor activity alone and in combination with chemotherapy in pts with advanced solid tumors. The highly immunogenic nature of HER2 tumors has led to the development of therapies combining anti-HER2 therapies with immune checkpoint blockade.

Methods:

This open-label, two cohort Phase 1B/2 study (NCT04276493) is designed to evaluate zanidatamab as a first-line therapy with chemotherapy in pts with HER2-positive metastatic breast cancer (mBC; cohort 1) or with chemotherapy + tislelizumab in pts with HER2-positive advanced gastric/gastroesophageal junction adenocarcinoma (GC/GEJC; cohort 2). Weight-based dosing (cohorts 1a and 2a) and flat dosing (cohorts 1b and 2b) regimens of zanidatamab are being investigated. In cohort 1 (n = 20), pts with treatment-naïve HER2-positive (IHC3+ or ISH amplified) mBC will receive intravenous (IV) zanidatamab 30 mg/kg (cohort 1a) or 1800 mg (cohort 1b), plus IV docetaxel 75 mg/m^2 once every 3 weeks (Q3W). In cohort 2 (n = 30), treatment-naïve pts with HER2-positive (IHC3+ or IHC2+ with ISH amplification) advanced GC/GEJC will receive IV zanidatamab 30 mg/kg (cohort 2a), or 1800 mg (pts < 70kg; cohort 2b) or 2400 mg (pts ≥ 70kg; cohort 2b), plus IV tislelizumab 200 mg and chemotherapy (CAPOX regimen: oral capecitabine 1000 mg/m^2 twice daily [days 1–14] and IV oxaliplatin 130 mg/m^2 [day 1]) Q3W. For cohort 2 there is a six pt safety lead-in phase, followed by dose expansion after approval by the safety monitoring committee. Primary endpoints are the safety profile and objective response rate. Secondary endpoints include duration of response, time to response, progression-free survival, disease control rate, and overall survival.