ZW25, 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.

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Background:
ZW25 is a novel HER2-targeted antibody that binds two distinct extracellular domains of HER2, allowing for multiple mechanisms of action, including activation of ADCC and inhibition of ligand-dependent and -independent cellular growth. ZW25 is well tolerated and showed single-agent antitumor activity in patients (pts) with advanced HER2-positive cancers. Previous reports suggested that tislelizumab, an investigational anti-PD-1 antibody engineered to minimize binding of FcgR on macrophages in order to abrogate antibody-dependent phagocytosis, was generally well tolerated and had antitumor activity alone and in combination with chemotherapy in pts with advanced solid tumors. Combining HER2-targeted agents with chemotherapy has resulted in improved survival; 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 is designed to evaluate ZW25 plus chemotherapy ± tislelizumab as first-line therapy in pts (n≈50) with HER2-positive metastatic breast cancer (mBC; cohort 1) or advanced gastric/gastroesophageal junction adenocarcinoma (GC/GEJC; cohort 2). In cohort 1, pts with HER2-positive (IHC3+ or ISH amplified) mBC must be treatment-naïve for metastatic disease and will receive intravenous (IV) ZW25 30 mg/kg plus docetaxel 75 mg/m^2 IV once every 3 weeks (Q3W). In cohort 2, treatment-naïve pts with HER2-positive (IHC3+ or IHC2+ with ISH amplification) advanced GC/GEJC will receive ZW25 30 mg/kg plus tislelizumab 200 mg IV and chemotherapy (CAPOX regimen: capecitabine 1000 mg/m^2 twice daily and oxaliplatin 130 mg/m^2 IV) Q3W. A safety lead-in phase is designed for the first six pts in cohort 2, followed by dose expansion after a safety monitoring committee review. Primary endpoints are the safety/tolerability profile and objective response rate; secondary endpoints include duration of response, time to response, progression-free survival, disease control rate, and overall survival. Clinical trial information: Registered, NCT number pending will provide as soon as available.