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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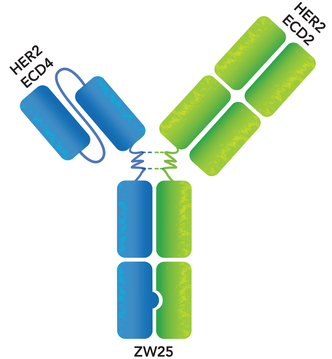
BACKGROUND

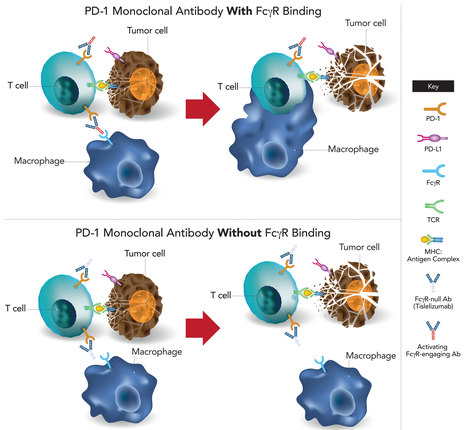
- Although HER2 overexpression has been correlated with aggressive tumors characterized by poor survival and lack of therapeutic responses, current treatment options remain limited for patients with HER2-positive metastatic breast cancer or gastric/gastroesophageal junction adenocarcinoma (GC/GEJC)[1,2]
- HER2-targeted therapies have improved treatment outcomes in some patients with breast cancer and GC/GEJC, but many patients develop resistance and/or relapse[3,4]
- ZW25 is a novel Azymetric bispecific antibody that targets HER2 domains ECD2 and ECD4, resulting in multiple differentiated and unique mechanisms of action, including improved receptor internalization and downregulation relative to trastuzumab (Figure 1)

Figure 1: Structure of ZW25



- In a phase 1 dose-escalation and expansion study, single-agent ZW25 was generally well tolerated and showed antitumor activity in patients with advanced HER2-positive cancers; patients with gastroesophageal cancer and breast cancer had objective response rates of 39% and 33%, respectively[5,6]
- Combining HER2-targeted agents with chemotherapy has resulted in improved survival and the highly immunogenic nature of HER2 tumors has led to the development of therapies combining anti-HER2 therapies with immune checkpoint blockade[7]
- Tislelizumab was specifically engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti PD-1 therapy (Figure 2)[8,9]
  - Previous reports indicate that tislelizumab was generally well tolerated and had antitumor activity alone and in combination with chemotherapy in patients with advanced solid tumors[10,11]

Figure 2: Lack of FcγR Binding May Help Prevent Macrophage-Mediated T-Cell Clearance



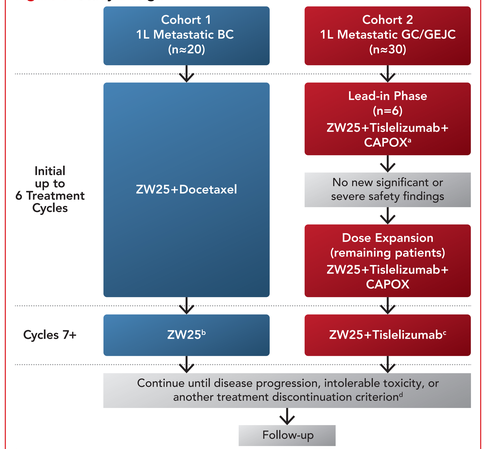
Abreviations: Ab, antibody; MHC, major histocompatibility complex; PD-1, programmed death-1 receptor; PD-L1, programmed death ligand-1; TCR, T-cell receptor.

METHODS

Overall Design and Study Objectives

- This open-label, 2-cohort phase 1B/2 study (NCT04276493) is designed to evaluate ZW25 plus chemotherapy ± tislelizumab as first-line therapy in ≈50 patients across 12 centers in Asian countries (Figure 3)
  - In Cohort 1, patients (n=20) with HER2-positive (IHC3+ or in situ hybridization [ISH] amplified) metastatic breast cancer must be treatment-naïve for metastatic disease
  - In Cohort 2, patients (n=30) must be treatment-naïve with HER2-positive (IHC3+ or IHC2+ with ISH amplification) advanced GC/GEJC
- A safety lead-in phase is designed for the first six patients in Cohort 2, followed by dose expansion after review by a safety monitoring committee
- Primary objectives are to assess the safety/tolerability and preliminary antitumor activity (as measured by objective response rate) of ZW25 in combination with docetaxel (Cohort 1) and ZW25 in combination with tislelizumab and chemotherapy (Cohort 2)
- Secondary objectives are to further evaluate the preliminary antitumor activity in each cohort as measured by duration of response, time to response, progression-free survival, disease control rate, and overall survival, as well as to characterize the pharmacokinetics and immunogenicity of ZW25

Figure 3: Study Design



[a]CAPOX is a multi-agent chemotherapy regimen consisting of capecitabine and oxaliplatin.
[b]Cohort 1 continuation of docetaxel treatment is at the discretion of the investigator after Cycle 6.
[c]Cohort 2 continuation of capecitabine as maintenance treatment is at the discretion of the investigator after Cycle 6.
[d]Treatment beyond initial investigator-assessed Response Evaluation Criteria in Solid Tumors v1.1-defined progression is only permitted if the tislelizumab-treated patient in Cohort 2 has evidence of "pseudoprogression," and after discussion with sponsor and re-consent of patient.
Abreviations: 1L, first-line; BC, breast cancer; GC/GEJC, gastric/gastroesophageal junction adenocarcinoma.

Study Population

- All eligible patients must have histologically/cytologically confirmed locally advanced, recurrent, or metastatic HER2-positive breast cancer (Cohort 1) or HER-2 positive GC/GEJC (Cohort 2), ≥1 measurable lesion per Response Evaluation Criteria in Solid Tumors v1.1, and an Eastern Cooperative Oncology Group performance status ≤1
- In Cohort 1, patients must have HER2 IHC3+ (or ISH positive) disease and be treatment-naïve for previous systemic anticancer therapy; locally recurrent disease must not be amenable to resection with curative intent
  - Patients cannot have a history of exposure to certain cumulative doses of anthracyclines in the adjuvant/neoadjuvant setting or tyrosine kinase/HER inhibitors in any treatment setting, ***except*** trastuzumab with or without pertuzumab used in neoadjuvant or adjuvant setting
- In Cohort 2, patients must have HER2 IHC3+ (or HER2 IHC2+ together with ISH positive) disease and not have active autoimmune diseases or a history of autoimmune diseases that may relapse
  - Patients must not have received prior allogeneic stem cell or organ transplantation or previous systemic anticancer therapy (including agents targeting EGFR or tyrosine kinase/HER inhibitors)
- Prior therapy with any antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways is not allowed and patients cannot have a condition requiring systemic treatment with corticosteroids or immunosuppressive medication ≤14 days before the first dose of study drug

Table 1: Selection and Timing of Dose Administration

Study Drug	Dose (Route)	Initial 6 Treatment Cycles	Cycle 7 and Onward
Cohort 1			
ZW25	30 mg/kg (IV)	Day 1 of each 21-day cycle: • Cycles 1 and 2: infusion over 120 to 150 minutes (60-minute monitoring period before chemotherapy) • Cycles 3 to 6: infusion for at least 120 minutes (60-minute monitoring period before chemotherapy)	Day 1 of each 21-day cycle, infusion for at least 120 minutes • 60-minute monitoring period before chemotherapy (optional[a])
Docetaxel	75 mg/m^2 (IV)	Day 1 of each 21-day cycle, infusion over 1 hour	Day 1 of each 21-day cycle, infusion over 1 hour (optional[a])
Cohort 2			
ZW25	30 mg/kg (IV)	Day 1 of each 21-day cycle: • Cycles 1 and 2: infusion over 120 to 150 minutes (60-minute monitoring period before tislelizumab) • Cycles 3 to 6: infusion for at least 120 minutes (60-minute monitoring period before tislelizumab)	Day 1 of each 21-day cycle, infusion for at least 120 minutes • 60-minute monitoring period before tislelizumab)
Tislelizumab[b]	200 mg (IV)	Schedule dependent on cycle: • Cycles 1 and 2: Day 2 of each 21-day cycle, infusion over 60 minutes (60-minute monitoring period before chemotherapy) • Cycles 3 to 6: Day 1 of each 21-day cycle, infusion over 30 minutes (30-minute monitoring period before chemotherapy)	Day 1 of each 21-day cycle, infusion over 30 minutes • 30-minute monitoring period before chemotherapy
Oxaliplatin	130 mg/m^2 (IV)	Duration of infusion follows local practice • Cycles 1 and 2: Day 2 of each 21-day cycle • Cycles 3 to 6: Day 1 of each 21-day cycle	Discontinue treatment
Capecitabine	1000 mg/m^2 (Oral)	Schedule dependent on cycle: • Twice daily Cycles 1 and 2: from the evening of Day 2 to the morning of Day 16 of each 21-day cycle • Cycle 3 to 6: from the evening of Day 1 to the morning of Day 15 of each 21-day cycle	Twice daily, from the evening of Day 1 to the morning of Day 15 of each 21-day cycle (optional[a])

[a]After Cycle 6, continuation of docetaxel treatment is at the discretion of the investigator.
[b]Reduction of tislelizumab infusion time from 60 minutes to 30 minutes is based on the 60-minute infusion time is well tolerated.
[c]After Cycle 6, continuation of capecitabine as maintenance treatment is at the discretion of the investigator.

Treatment

- For the initial six treatment cycles, patients in Cohort 1 will receive intravenous (IV) ZW25 30 mg/kg; docetaxel 75 mg/m^2 IV will be administered after a 60-minute monitoring period (Table 1)
- For the initial six treatment cycles (Q3W), patients in Cohort 2 will receive ZW25 30 mg/kg IV; after a 60-minute monitoring period, tislelizumab 200 mg IV will be administered, followed by chemotherapy (CAPOX regimen: oxaliplatin 130 mg/m^2 IV followed by oral capecitabine 1000 mg/m^2 twice daily)
- Maintenance therapy with ZW25 (Cohort 1) and ZW25 plus tislelizumab (Cohort 2) will be administered until disease progression, intolerable toxicity, or discontinuation

Study Assessments and Statistical Analysis

- Safety/tolerability will be assessed by the incidence and severity of adverse events (AEs) according to the National Cancer Institute Common Terminology Criteria for AEs v5.0, results from physical examinations, vital signs, electrocardiogram, and laboratory tests
  - The safety analysis set will be the primary analysis set for safety analyses and will include all patients receiving ≥1 dose of any component of study treatment
- Tumor assessments will occur at baseline, every 6 weeks for 36 weeks, and every 12 weeks thereafter until disease progression, withdrawal of consent, death, or the start of a new anticancer therapy
  - The efficacy evaluable analysis set will be the primary analysis set for tumor response and will include all patients receiving ≥1 dose of study drug that have measurable/evaluable disease at baseline and ≥1 postbaseline tumor response assessment, unless progressive disease or death occurs ≤10 weeks after the first dose
- Secondary efficacy objectives including duration of response, time to response, and progression-free survival, will be analyzed using the Kaplan-Meier method primarily in patients receiving study drug with evaluable disease at baseline and at least one postbaseline assessment
  - Disease control rate will be estimated on the efficacy evaluable set; sensitivity analyses will use the safety analysis set
  - Overall survival will be estimated using the Kaplan-Meier method from patients receiving one or more dose of any component of study treatment

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