Safety and efficacy of ZW25, a HER2-targeted bispecific antibody, in combination with chemotherapy in patients with locally advanced and/or metastatic HER2-expressing gastroesophageal cancer

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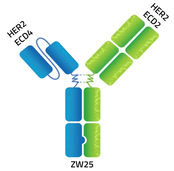
Background

- Human epidermal growth factor receptor 2 (HER2) is a validated therapeutic target for HER2+ (IHC 3+ or IHC 2+/fluorescence in situ hybridization [FISH]+) breast cancer and gastroesophageal adenocarcinoma (GEA)
- Despite 5 approved HER2-targeted therapies for HER2+ breast cancer*, only trastuzumab is approved for HER2+ GEA
- While paclitaxel and capecitabine are frequently part of standard of care 2nd line regimens for patients with GEA, including those with HER2+ disease, single-agent response rates are <20%†
- ZW25 is a HER2-targeted, bispecific antibody designed to address unmet need for patients with HER2-expressing cancers, including GEA
  - ZW25 has been granted FDA Orphan Drug designation in gastric cancer and Fast Track designation in combination with standard of care chemotherapy for 1st line treatment of HER2+ GEA
- ZW25 monotherapy has been well tolerated with promising anti-tumor activity in patients with HER2-expressing tumors, including GEA
  - Objective response rate (ORR) of 32% in patients with HER2-expressing GEA (with median of 3.5 prior treatment regimens, including trastuzumab)‡
- Based on these results, the safety and anti-tumor activity of ZW25 was evaluated in combination with paclitaxel or capecitabine in patients with HER2-expressing GEA that had progressed after at least 1 prior line of systemic therapy

* Approved HER2 agents for breast cancer include trastuzumab, pertuzumab, lapatinib, T-DM1, and neratinib
† Wilke et al. Lancet Oncology, 2014 and Koizumi et al. Oncology, 2003
‡ Meric-Bernstam et al. Annals of Oncology (ESMO Annual Meeting). 2019

ZW25: Bispecific HER2-Targeted Antibody



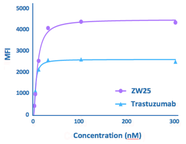
- Designed using the Azymetric™ bispecific platform
- Biparatopic – simultaneously binds two HER2 epitopes
  - ECD4 (trastuzumab binding domain)
  - ECD2 (pertuzumab binding domain)
- Unique binding configuration results in multiple mechanisms of action
  - Improved binding, clustering, and receptor internalization and downregulation
  - Inhibition of ligand-dependent and independent proliferation
  - Potent activation of antibody-dependent cellular cytotoxicity

ECD=extracellular domain

ZW25: Unique Binding Configuration Drives Novel Mechanisms of Action

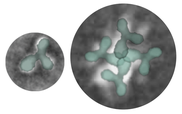
Enhanced tumor cell binding and internalization relative to trastuzumab

Increased Tumor Cell Binding



JIMT-1 (HER2 2+)

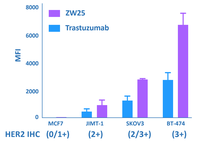
HER2 Receptor Clustering



Single ZW25 Antibody

ZW25-HER2 Cluster

Enhanced Internalization



Internalization 37°C, 24h

IHC=immunohistochemistry; MFI=mean fluorescence intensity; nM=nanoMolar

Phase 1 Study of ZW25 in Advanced HER2-Expressing Cancers (NCT02892123)

Key Study Objectives

To characterize the safety and tolerability, serum pharmacokinetics (PK) profile, and potential anti-tumor effects of ZW25 in combination with paclitaxel or capecitabine

Key Eligibility Criteria

- Patients with HER2 IHC 3+ or IHC2+ and FISH+ or - GEA based on local review
- Received at least 1 and no more than 3 prior systemic chemotherapy regimens
- Measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1*; patients with non-target lesions only could be enrolled with approval from Sponsor medical monitor
- Fresh or archived tumor tissue available for retrospective central review of HER2 status

* Eisenhauer EA, et al. Eur J Cancer. 2009

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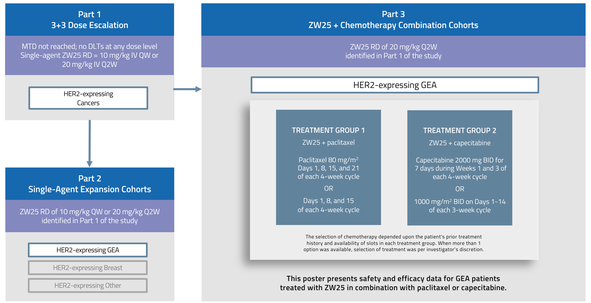
Data represent a snapshot from an unlocked database as of 18 Sept 2019 and are subject to change

Study Design



BID=twice daily; DLT=dose-limiting toxicity; GEA=gastroesophageal adenocarcinoma; IV=intravenous; MTD=maximum-tolerated dose; QW=weekly; Q2W=every 2 weeks; RD=recommended dose

Demographics and Patient Characteristics

	ZW25 + Paclitaxel (N=8)	ZW25 + Capecitabine (N=6)	Total (N=14)
Male, n (%)	7 (88)	4 (67)	11 (79)
Median age (range)	60 (51–80)	61 (26–66)	60 (26–80)
Baseline ECOG			
0, n (%)	1 (13)	0	1 (7)
1, n (%)	7 (88)	6 (100)	13 (93)
HER2 status* (IHC 3+ or IHC 2+/FISH+), n (%)	6 (75)	2 (33)	8 (57)
Median number of prior systemic regimens	2.5	2.5	2.5
Median number of prior HER2 therapies	1	1	1
Prior trastuzumab treatment, n (%)	7 (88)	6 (100)	13 (93)
Prior taxane-containing regimens, n (%)	1 (13)	4 (67)	5 (36)
Paclitaxel + ramucirumab, n (%)	0	2 (33)	2 (14)
Prior capecitabine-containing regimens, n (%)	6 (75)	1 (17)	7 (50)
Capecitabine + cisplatin (XP), n (%)	4 (50)	1 (17)	5 (36)

ECOG=Eastern Cooperative Oncology Group; FISH=fluorescence in situ hybridization; IHC=immunohistochemistry
* Based on central review when available

Safety

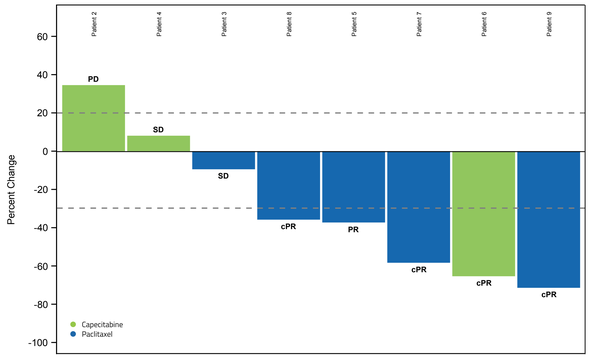
Treatment-Related Adverse Events Reported in ≥ 2 patients*

Preferred Term	ZW25 + Paclitaxel (N=8)		ZW25 + Capecitabine (N=6)		Total (N=14)	
Grade; n (%)	Any	≥ Grade 3	Any	≥ Grade 3	Any	≥ Grade 3
Diarrhea	4 (50)	0	3 (50)	0	7 (50)	0
Nausea	2 (25)	0	3 (50)	0	5 (36)	0
Alopecia	4 (50)	0	0	0	4 (29)	0
Decreased appetite	2 (25)	0	2 (33)	0	4 (29)	0
Stomatitis	2 (25)	1 (13)	2 (33)	0	4 (29)	1 (7)
Vomiting	1 (13)	0	3 (50)	0	4 (29)	0
Fatigue	3 (38)	2 (25)	0	0	3 (21)	2 (14)
Neuropathy peripheral	2 (25)	0	1 (17)	1 (17)	3 (21)	1 (7)
Neutropenia	3 (38)	2 (25)	0	0	3 (21)	2 (14)
Rash maculo-papular	2 (25)	0	1 (17)	0	3 (21)	0
Dry skin	1 (13)	0	1 (17)	0	2 (14)	0
Hypokalaemia	2 (25)	1 (13)	0	0	2 (14)	1 (7)
Infusion-related reaction	1 (13)	0	1 (17)	0	2 (14)	0
Palmar-plantar erythrodysaesthesia syndrome	0	0	2 (33)	0	2 (14)	0

* Treatment-related are events related to ZW25 and/or chemotherapy. Events occurring in 2 or more patients across both treatment groups combined are included

Anti-Tumor Activity

Maximum Change in Sum of Diameters for Response-Evaluable Patients*



cPR=confirmed partial response; FISH=fluorescence in situ hybridization; IHC=immunohistochemistry; PD=progressive disease; PR=partial response; SD=stable disease;
* Response-evaluable patients include all patients who received at least one dose of ZW25, had at least one measurable target lesion at baseline and at least one post-baseline disease assessment or discontinued the study due to death, clinical or radiologic progressive disease
Patient 1 had no post-baseline tumor measurements and is excluded from the figure

Disease Response in Response-Evaluable Patients*

	ZW25 + Paclitaxel (N=6) n (%)	ZW25 + Capecitabine (N=3) n (%)	Total (N=9) n (%)
Partial Response (PR)	4 (67)	1 (33)	5 (56)
Stable Disease (SD)	1 (17)	1 (33)	2 (22)
Progressive Disease (PD)	1 (17)	1 (33)	2 (22)
Disease Control†	5 (83)	2 (67)	7 (78)

* Response evaluable includes all patients who received at least one dose of ZW25, had at least one measurable target lesion at baseline and at least one post-baseline disease assessment or discontinued the study due to death, clinical or radiologic progressive disease. Five non-evaluable patients: 3 had no measurable disease, 1 too early, 1 unrelated AE
† Disease Control=Complete Response (CR)+PR+SD at any time on study

- ORR=56% (95% CI: 21, 86) (5/9 patients; all partial responses, with 4 confirmed to date)
  - ORR for ZW25 + paclitaxel=67% (4/6 patients); ORR for ZW25 + capecitabine=33% (1/3 patients)
- Disease control rate=78% (95% CI: 40, 97) (7/9 patients)

Safety (cont.)

- The most common treatment-related AEs were primarily Grade 1 or 2 and manageable with symptomatic treatment
  - Grade 3 or higher treatment-related AEs of fatigue and neutropenia reported in 2 patients each; ALT increased, anemia, hypokalemia, neutrophil count decreased, peripheral neuropathy, pneumonitis, stomatitis, and WBC count decreased reported in 1 patient each
  - One event of Grade 5 pneumonitis in an 80 year old patient who had progressed after prior treatment with trastuzumab, cisplatin, and capecitabine; pembrolizumab and margetuximab; and DS-8201a. Radiographic findings consistent with possible interstitial lung disease were also present at baseline
- Five patients had dose reductions of paclitaxel (n=4[a]) or capecitabine (n=1[b]) due to treatment-related AEs; no dose reductions of ZW25 due to AEs
- Three patients had paclitaxel discontinued due to treatment-related AEs;[a] ZW25 was discontinued due to a treatment-related AE in 1 patient[c]
- No treatment-related changes in left ventricular ejection fraction (LVEF) >10%

* Peripheral neuropathy and diverticulitis in 1 patient, ALT and AST increased in 1 patient, and fatigue and neutropenia in 1 patient each
[a] Peripheral neuropathy
[b] Peripheral neuropathy, fatigue, and pneumonitis in 1 patient each
[c] Pneumonitis

We sincerely thank all patients and their families. Thanks to all investigators and clinical trial personnel: MD Anderson Cancer Center, Houston, TX, USA; Northwest Medical Specialties, Tacoma, WA, USA; Seoul National University Hospital, Seoul, South Korea; Samsung Medical Center, Seoul, South Korea; Asan Medical Center, Seoul, South Korea; Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; University of Colorado School of Medicine, Aurora, CO, USA; Rush Medical Center, Chicago, IL, USA; University of Alabama Cancer Center, Birmingham, AL, USA; Princess Margaret Hospital, Toronto, Ontario, Canada; and USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA

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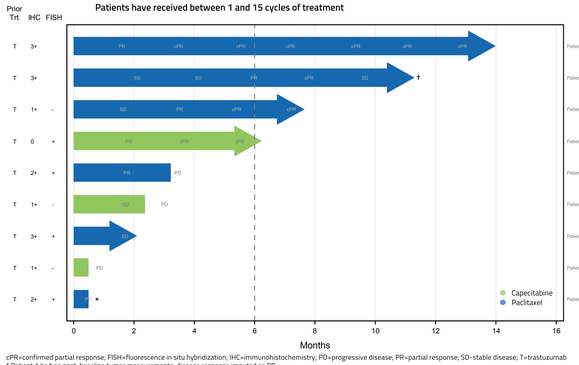
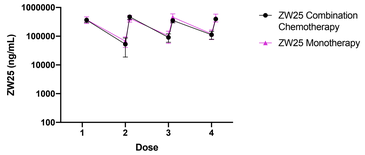
Time on Treatment for Response-Evaluable Patients



cPR=confirmed partial response; FISH=fluorescence in situ hybridization; IHC=immunohistochemistry; PD=progressive disease; PR=partial response; SD=stable disease; T=trastuzumab
* Patient 1 had no post-baseline tumor measurements; disease response imputed as PD
† Patient 8 discontinued paclitaxel due to peripheral neuropathy after Cycle 1, and remained on ZW25 alone
IHC and FISH are based on central review when available

Pharmacokinetics of 20 mg/kg ZW25 (Q2W) in Combination With Chemotherapy Compared with ZW25 Monotherapy

- The combination of ZW25 plus chemotherapy did not alter the PK of a 20 mg/kg dose of ZW25



ZW25 combination chemotherapy: N=5 patients; ZW25 monotherapy: N=56 patients
Patients had blood draws for PK analysis within 4 hours prior to ZW25 dosing and immediately following completion of ZW25 dosing for up to 4 doses

Conclusions

- Combination of ZW25 and chemotherapy manageable in outpatient setting in heavily pretreated patients with HER2-expressing GEA
  - Most treatment-related AEs Grade 1 or 2 in severity
- The overall safety profile of ZW25 plus chemotherapy was similar to that seen with chemotherapy alone
- The combination of ZW25 plus chemotherapy was associated with promising anti-tumor activity in this small series of patients with HER2-expressing GEA
  - Objective response rate of 56%
  - Disease control rate of 78%
  - Durable responses seen in patients with FISH+ and FISH- disease
- Data compare favorably with current 2nd line and later standard of care regimens
- Further evaluation of the safety and efficacy of ZW25 in combination with standard of care chemotherapy regimens has been initiated in frontline GEA (Study ZW25-201; NCT03929666)

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