Zanidatamab, a HER2-Targeted Bispecific Antibody, in Combination With Docetaxel as First-Line Therapy for Patients With Advanced HER2-Positive Breast Cancer: Updated Results From a Phase 1b/2 Study

Keun Seok Lee,[1]* Xiaojia Wang,[2] Xiaohua Zeng,[3] Tao Sun,[4] Young-Hyuck Im,[5] Huiping Li,[6] Kun Wang,[7] Ping Zhou,[8] Yuanyuan Bao,[8] Zefei Jiang[9]†

[1]Department of Oncology, National Cancer Center, Goyang-si, Republic of Korea; [2]Department of Oncology, Zhejiang Cancer Hospital, Hangzhou, China; [3]Department of Breast Oncology, Chongqing University Cancer Hospital, Chongqing, China; [4]Department of Breast Oncology, Liaoning Cancer Hospital, Liaoning, China; [5]Department of Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [6]Department of Breast Oncology, Beijing Cancer Hospital, Beijing, China; [7]Department of Breast Cancer, Cancer Center, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China; [8]Clinical Development, BeiGene (Shanghai) Co. Ltd., Shanghai, China; [9]The Fifth Medical Center of Chinese PLA General Hospital, Beijing, China.
*Presenting author; †Corresponding author.

Abstract No: FP-0330 presented at KSMO 2023, Seoul, Korea

Conclusions

Zanidatamab in combination with docetaxel demonstrated encouraging antitumor activity as first-line (1L) therapy for advanced human epidermal growth factor receptor 2 (HER2)-positive breast cancer.

Efficacy was similar in both cohorts receiving different doses of zanidatamab in combination with docetaxel.

The combination of zanidatamab and docetaxel had a manageable safety profile in patients with HER2-positive breast cancer, with the incidence of treatment-related adverse events (TRAEs) consistent with previous reports.[1]

Background

Worldwide, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths in women, with over 650,000 deaths in 2020.[2,3] HER2-targeted agents have improved outcomes in HER2-positive breast cancer, but most patients receiving 1L therapy do not respond to current therapies, develop resistance, or eventually relapse.[4,5]

HER2-positive breast cancer accounts for approximately 20% of all breast cancers.[6,7] Zanidatamab, also known as ZW25, is a novel HER2-targeted bispecific antibody that binds in a trans fashion to two non-overlapping extracellular domains of HER2, resulting in more potent effector function compared with trastuzumab, a monospecific HER2 antibody.[8-10]

Zanidatamab's unique binding properties result in: receptor clustering, internalization and downregulation; inhibition of growth factor-dependent and -independent tumor cell proliferation; antibody-dependent cellular cytotoxicity, phagocytosis, and complement-dependent cytotoxicity.[8]

Zanidatamab, both with chemotherapy and as a single agent, has demonstrated antitumor activity and a manageable safety profile in advanced HER2-positive breast cancer[11] and HER2-positive gastric/gastroesophageal junction adenocarcinoma.[12,13] In advanced HER2-positive breast cancer, zanidatamab is being evaluated with docetaxel as 1L therapy (NCT04276493).[11]

Methods

- This is an open-label, multicenter, phase 1b/2 study (NCT04276493).
- Here we present updated data on the safety and antitumor activity of zanidatamab in combination with docetaxel as 1L treatment for advanced HER2-positive breast cancer, following enrollment completion (**Figure 1**).

Figure 1. Study Design

Inclusion criteria
- Females with unresectable, locally advanced recurrent or metastatic HER2-positive[a] breast cancer
- No previous systemic chemotherapy or biologic therapy in the advanced setting[b]
- ECOG PS 0-1

↓

Cohort A: Zanidatamab 30 mg/kg[c] + docetaxel 75 mg/m^2 IV Q3W
or
Cohort B: Zanidatamab 1800 mg[c] + docetaxel 75 mg/m^2 IV Q3W

↓

Continue until disease progression, intolerable toxicity, or other discontinuation criteria are met

Primary endpoints:
- AEs
- ORR[d]

Key secondary endpoints:
- DoR[d]
- DCR[d]
- PFS[d]
- OS

[a]HER2 IHC3+ or IHC2+/(F)ISH+; [b]Except for one prior hormone regimen (for metastatic breast cancer); however, prior trastuzumab ± pertuzumab in the neoadjuvant or adjuvant setting is permitted if completed ≥12 months prior; [c]Patients enrolled under the original protocol received zanidatamab 30 mg/kg, and patients enrolled under the protocol amendment received zanidatamab 1800 mg. Flat dosing of zanidatamab was implemented in the protocol amendment based on PK data, which showed comparable exposure between weight-based and flat dosing; [d]Per RECIST v1.1 per INV.
Abbreviations: AEs, adverse events; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; (F)ISH, (fluorescence) in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; INV, investigator; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Results

Patients

- The last patient was enrolled on March 3, 2022. In total, 38 patients were enrolled in the study and one patient was subsequently excluded due to non-metastatic breast cancer histology. Patients included in this analysis received 30 mg/kg (n=10) or 1800 mg (n=27) zanidatamab in combination with docetaxel (**Table 1**).
- As of November 22, 2022, 18 patients (48.6%) remained on treatment.
- Median study follow-up was 15.5 months (range: 1.1 to 29.3) and the median number of treatment cycles was 13 (range: 1 to 37).
- Four patients without any postbaseline tumor assessments were excluded from the efficacy-evaluable analysis set.

Table 1. Demographics and Baseline Characteristics

	Cohort A (n=10)	Cohort B (n=27)	Total (N=37)[a]
Median age, years (range)	59.5 (45-80)	55.0 (33-67)	55.0 (33-80)
Race, n (%)			
Chinese	3 (30.0)	24 (88.9)	27 (73.0)
Korean	7 (70.0)	3 (11.1)	10 (27.0)
ECOG PS, n (%)			
0	4 (40.0)	6 (22.2)	10 (27.0)
1	6 (60.0)	21 (77.8)	27 (73.0)
HER2 status[b], n (%)			
IHC3+	8 (80.0)	24 (88.9)	32 (86.5)
IHC2+/(F)ISH+	2 (20.0)	3 (11.1)	5 (13.5)
HR status, n (%)			
Positive	5 (50.0)	16 (59.3)	21 (56.8)
Negative	5 (50.0)	11 (40.7)	16 (43.2)
Brain metastases[c], n (%)	0 (0)	2 (7.4)	2 (5.4)
Prior anti-cancer systemic therapy[d], n (%)	6 (60.0)	10 (37.0)	16 (43.2)
(Neo)adjuvant anti-HER2 therapy	4 (40.0)	4 (14.8)	8 (21.6)
Trastuzumab	4 (40.0)	4 (14.8)	8 (21.6)
Pertuzumab	1 (10.0)	0 (0)	1 (2.7)

[a]Of 38 enrolled, one patient was excluded because they received a biopsy after the end of treatment and the metastatic lesion in the lung was pathologically confirmed as "pulmonary sarcomatoid carcinoma, spindle cell carcinoma"; [b]All patients had HER2 status confirmed by local laboratory; [c]At study entry, must be asymptomatic and radiologically stable for inclusion; [d]Patients had neoadjuvant/adjuvant therapy and/or one prior hormone regimen (for metastatic breast cancer).
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; (F)ISH, (fluorescence) in situ hybridization; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry.

Safety

- In total, 36 patients (97.3%) experienced at least one TRAE, and 25 patients (67.6%) experienced at least one ≥grade 3 TRAE (**Table 2**).
- The most common TRAEs were neutrophil count decreased (59.5%), anemia (54.1%), and diarrhea (51.4%); the most common ≥grade 3 TRAEs were neutrophil count decreased (48.6%) and white blood cell count decreased (18.9%; **Table 2**).
- Serious TRAEs occurred in six patients (16.2%), with two patients (5.4%) experiencing a serious TRAE of blood bilirubin increased. Two patients (5.4%) discontinued treatment due to TRAEs and two patients (5.4%) experienced TRAEs leading to dose reduction of any component of the study treatment. No TRAEs led to death (**Table 2**).

Table 2. Summary of Treatment-Related[a] Adverse Events

Category, n (%)	Cohort A (n=10)	Cohort B (n=27)	Total (N=37)
Patients with at least one event	9 (90.0)	27 (100.0)	36 (97.3)
≥Grade 3 event	9 (90.0)	16 (59.3)	25 (67.6)
Serious TRAEs	1 (10.0)	5 (18.5)	6 (16.2)
TRAEs leading to death	0 (0)	0 (0)	0 (0)
TRAEs leading to treatment discontinuation[b]	0 (0)	2 (7.4)	2 (5.4)
TRAEs leading to dose reduction[c]	2 (20.0)	0 (0)	2 (5.4)

Most common TRAEs[d]	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3
Neutrophil count decreased	7 (70.0)	7 (70.0)	15 (55.6)	11 (40.7)	22 (59.5)	18 (48.6)
Anemia	1 (10.0)	1 (10.0)	19 (70.4)	0 (0)	20 (54.1)	1 (2.7)
Diarrhea	7 (70.0)	3 (30.0)	12 (44.4)	0 (0)	19 (51.4)	3 (8.1)
WBC count decreased	0 (0)	0 (0)	16 (59.3)	7 (25.9)	16 (43.2)	7 (18.9)
Alopecia	1 (10.0)	0 (0)	12 (44.4)	0 (0)	13 (35.1)	0 (0)
ALT increased	1 (10.0)	0 (0)	10 (37.0)	1 (3.7)	11 (29.7)	1 (2.7)
AST increased	1 (10.0)	0 (0)	9 (33.3)	0 (0)	10 (27.0)	0 (0)
Nausea	4 (40.0)	0 (0)	6 (22.2)	0 (0)	10 (27.0)	0 (0)

Adverse events were recorded using the Medical Dictionary for Regulatory Activities v25.0, with severity graded by INV using National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. [a]Treatment-related is defined as related to any component of study treatment; [b]Treatment discontinuation is defined as discontinuation of all components of study treatment; [c]Dose reduction is defined as dose reduction of any component of the study treatment; [d]Occurring in ≥25% of patients in the total analysis population.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INV, investigator; TRAE, treatment-related adverse event; WBC, white blood cell.

Efficacy

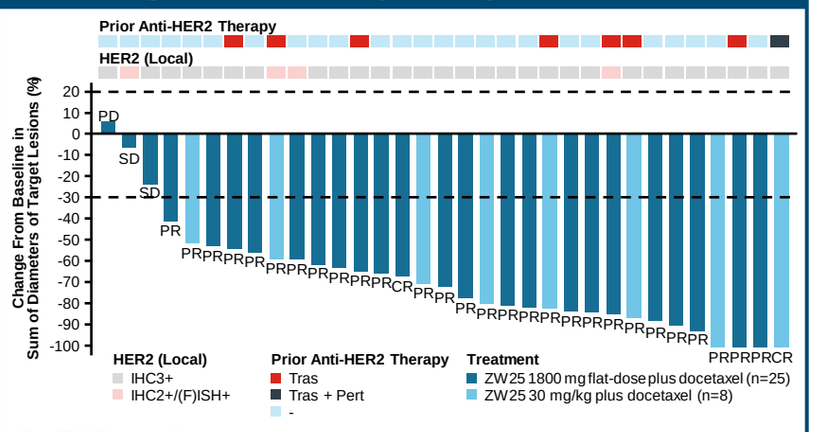
- The best percentage change in target lesion size is shown in **Figure 2.**
- Of the 33 efficacy-evaluable patients, the confirmed objective response rate was 90.9% (95% confidence interval [CI]: 75.7, 98.1; **Table 3**). Treatment duration and response are shown in **Figure 3.**
- The disease control rate was 97.0% (95% CI: 84.2, 99.9).
- The median duration of response was not estimable (95% CI: 12.1, not estimable).
- The 6-month progression-free survival rate was 93.9% (95% CI: 77.9, 98.4) and the 12-month rate was 73.3% (95% CI: 50.7, 86.7).

Table 3. Disease Response[a]

	Cohort A (n=8)	Cohort B (n=25)	Total (N=33)
Confirmed BOR[b], n (%)			
Complete response	1 (12.5)	1 (4.0)	2 (6.1)
Partial response	7 (87.5)	21 (84.0)	28 (84.8)
Stable disease	0 (0)	2 (8.0)	2 (6.1)
Progressive disease	0 (0)	1 (4.0)	1 (3.0)
Confirmed ORR[b], % 95% CI	100.0 63.1, 100.0	88.0 68.8, 97.5	90.9 75.7, 98.1
Confirmed DCR[b], % 95% CI	100.0 63.1, 100.0	96.0 79.6, 99.9	97.0 84.2, 99.9
Median DoR[b], months 95% CI	12.4 5.5, NE	NE 12.1, NE	NE 12.1, NE

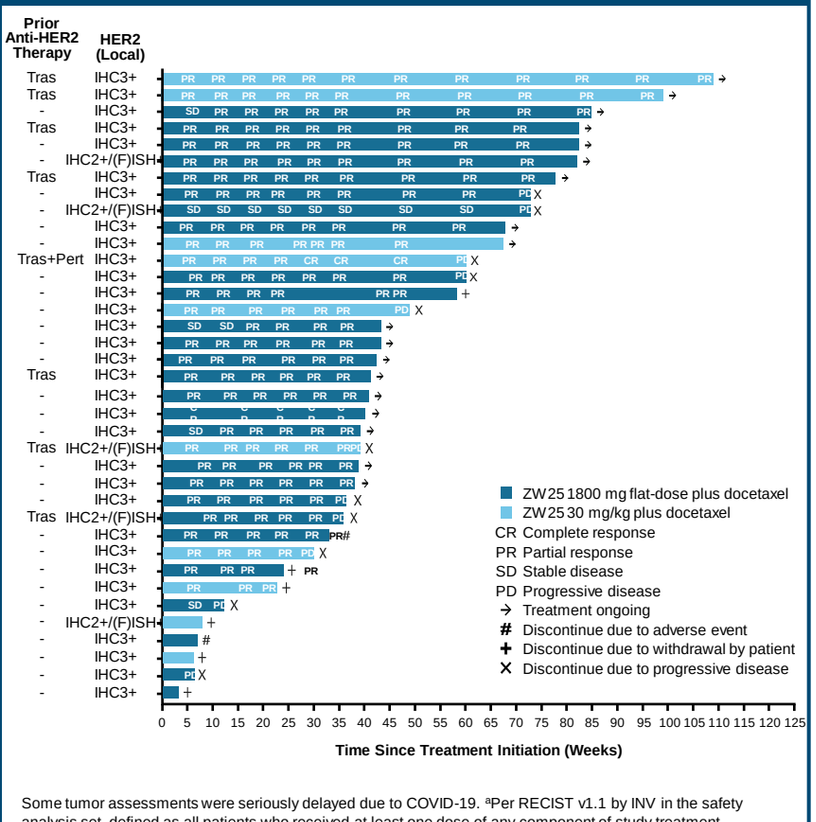
[a]In the efficacy-evaluable analysis set, which was defined as patients who received at least one dose of any study drug and with at least one postbaseline tumor assessment; [b]Per RECIST v1.1 by INV.
Abbreviations: BOR, best overall response; CI, confidence interval; DCR, disease control rate; DoR, duration of response; INV, investigator; NE, not estimable; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Figure 2. Best Change in Target Lesion Size[a]



[a]Per RECIST v1.1 by INV in the efficacy-evaluable analysis set, which was defined as patients who received at least one dose of any study drug and with at least one postbaseline tumor assessment.
Abbreviations: CR, complete response; (F)ISH, (fluorescence) in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; INV, investigator; PD, progressive disease; Pert, pertuzumab; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; Tras, trastuzumab; ZW25, zanidatamab.

Figure 3. Treatment Duration and Response[a]



Some tumor assessments were seriously delayed due to COVID-19. [a]Per RECIST v1.1 by INV in the safety analysis set, defined as all patients who received at least one dose of any component of study treatment.
Abbreviations: (F)ISH, (fluorescence) in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; INV, investigator; Pert, pertuzumab; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; Tras, trastuzumab; ZW25, zanidatamab.

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Acknowledgments

This study is sponsored by BeiGene, Ltd. Medical writing support under the direction of the authors, was provided by Emily Finn, MSc, of Ashfield MedComms, an Inizio company, and was funded by BeiGene, Ltd. Editorial support was provided by Megan Fox, BSc, of Ashfield MedComms and Elizabeth Hermans, PhD, of BeiGene, Ltd.

Author details:
Zefei Jiang
jiangzefei@csco.org.cn

Disclosures

KSL: ABL Bio; ALX Oncology; Astellas Pharma; AstraZeneca/MedImmune; Bayer; BeiGene, Ltd.; Bolt Biotherapeutics; Boryung; Bristol-Myers Squibb; Daiichi Sankyo; Five Prime Therapeutics; GC Pharma; InventisBio; ISU ABXIS; Leap Therapeutics; LSK BioPharma; MacroGenics; MedPacto; Merck KGaA; MSD; Oncologie; Ono Pharmaceutical; Pfizer; Pharmacyclics; Seagen; Taiho Pharmaceutical; Trishula Therapeutics; Y-Biologics; Vifor Pharma; Zymeworks. **XZ, YHI, HL, KW, ZJ:** have no conflicts of interest. **TS:** ABL Bio; ALX Oncology; Amgen; Arcus Biosciences; Astellas Pharma; AstraZeneca; BeiGene, Ltd.; Bold therapeutics; Daiichi Sankyo; Eisai; Indivumed; Ipsen; Leap Therapeutics; LG Bioche; Macrogenics; MedPacto; Merck KGaA; MSD; Ono pharmaceutical; Pfizer; Seagen; Taiho Pharmaceutical; Zymeworks. **XW, PZ, YB:** are employees of BeiGene, Ltd.