第27届全国临床肿瘤学大会
暨2024年CSCO学术年会
2024年9月25日-29日 中国·厦门

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

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Conclusions

- **Zanidatamab in combination with docetaxel demonstrated encouraging antitumor activity as first-line therapy for advanced human epidermal growth factor receptor 2 (HER2)-positive breast cancer**
- **Efficacy was similar in both cohorts following 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 consistent with previous reports[1]**

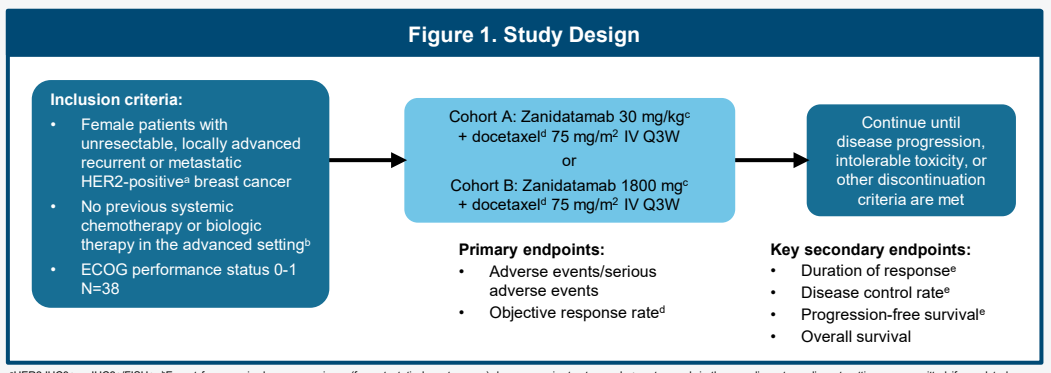
Background

- 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]
- Human epidermal growth factor receptor 2 (HER2)-targeted agents have improved outcomes in HER2-positive breast cancer, but some patients receiving first-line 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]
- 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[7-9]
- Zanidatamab's unique binding properties result in multiple mechanisms of action, including: receptor clustering, internalization, and downregulation; inhibition of growth factor-dependent and -independent tumor cell proliferation; complement-dependent cytotoxicity; and antibody-dependent cellular cytotoxicity and phagocytosis[7]
- Zanidatamab, in combination with chemotherapy, has demonstrated antitumor activity and a manageable safety profile in advanced HER2-positive breast cancer[10] and HER2-positive gastric/gastroesophageal junction adenocarcinoma[11,12]
- In advanced HER2-positive breast cancer, zanidatamab is being evaluated with docetaxel as first-line therapy (NCT04276493)[10]

Methods

- This is an open-label, multicenter, phase 1b/2 study
- 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



[a]HER2 IHC3+ or IHC2+/FISH+. [b]Except for one prior hormone regimen (for metastatic breast cancer); however, prior trastuzumab ± pertuzumab in the neoadjuvant or adjuvant setting was permitted if completed ≥12 months ago. [c]Patients enrolled under the original protocol received zanidatamab 30 mg/kg, and patients enrolled under the protocol amendment received zanidatamab 1800 mg. Flat dose of zanidatamab was implemented in the protocol amendment based on pharmacokinetic data, which showed comparable exposure between weight-based and flat dosing. [d]Continuation of docetaxel treatment was at the discretion of the investigator after Cycle 6. [e]Per Response Evaluation Criteria In Solid Tumors version 1.1 per investigator.
ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenous; Q3W, every 3 weeks.

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: 1.1-29.3) and the median number of treatment cycles was 13 (range: 1-37)
- 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			
Chinese	3 (30.0)	24 (88.9)	27 (73.0)
Korean	7 (70.0)	3 (11.1)	10 (27.0)
ECOG performance status			
0	4 (40.0)	6 (22.2)	10 (27.0)
1	6 (60.0)	21 (77.8)	27 (73.0)
HER2 status[b]			
IHC3+	8 (80.0)	24 (88.9)	32 (86.5)
IHC2+/FISH+	2 (20.0)	3 (11.1)	5 (13.5)
HR status			
Positive	5 (50.0)	16 (59.3)	21 (56.8)
Negative	5 (50.0)	11 (40.7)	16 (43.2)
Brain metastasis[c]	0 (0)	2 (7.4)	2 (5.4)
Prior anticancer systemic therapy[d]	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)

Data cutoff: November 22, 2022. Data are n (%) unless otherwise specified. [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 a local lab. [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).
ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; HER, human epidermal growth factor receptor; 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 increased blood bilirubin. Two patients (5.4%) discontinued treatment due to TRAEs and two patients (5.4%) experienced TRAEs leading to dose reduction. No TRAEs led to death (**Table 2**)

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

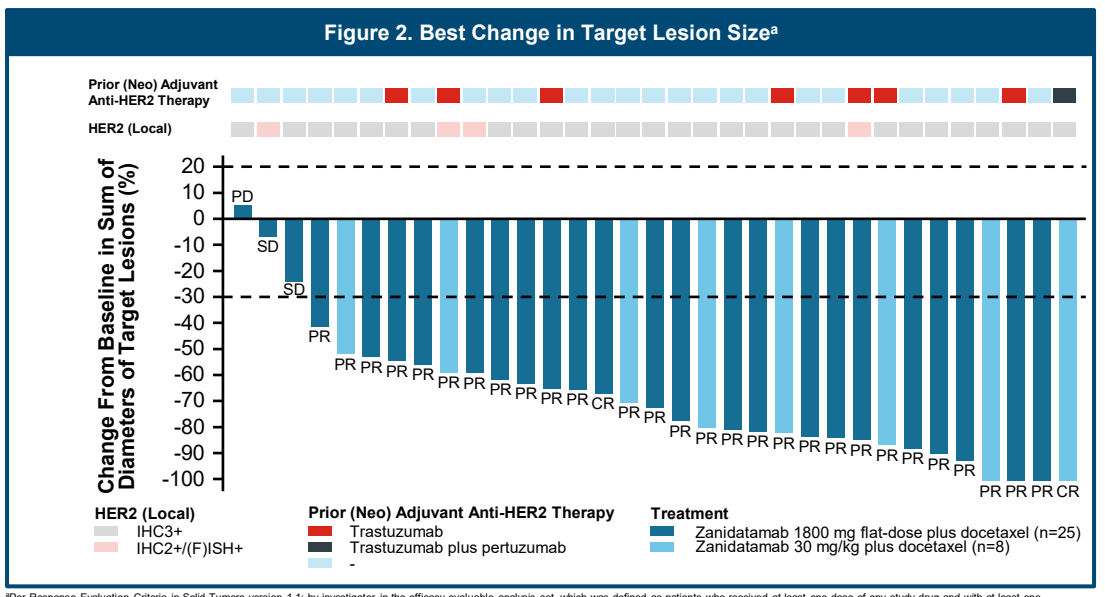
	Cohort A (n=10)		Cohort B (n=27)		Total (N=37)	
Patients with at least one event	9 (90.0)		27 (100.0)		36 (97.3)	
Grade ≥3 TRAEs	9 (90.0)		16 (59.3)		25 (67.6)	
Serious TRAEs	1 (10.0)		5 (18.5)		6 (16.2)	
TRAEs leading to death	0 (0)		0 (0)		0 (0)	
TRAEs leading to treatment discontinuation[b]	0 (0)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

Data are n (%). Adverse events were recorded using the Medical Dictionary for Regulatory Activities version 25.0, with severity graded by the investigator using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. [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.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; 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**). The treatment duration and response is 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)

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



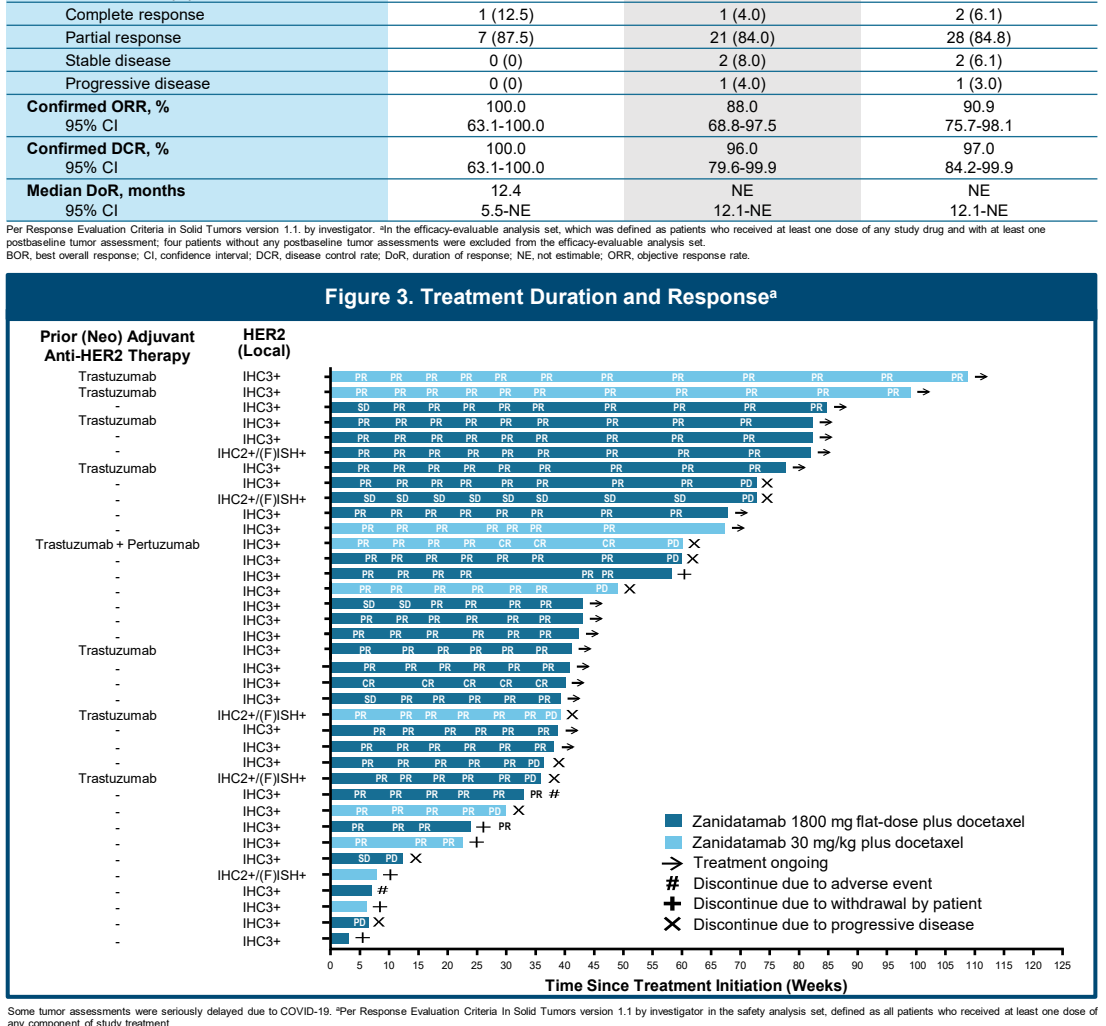
[a]Per Response Evaluation Criteria in Solid Tumors version 1.1; by investigator in the efficacy-evaluable analysis set, which was defined as patients who received at least one dose of any study drug and with at least one postbaseline tumor assessment.
CR, complete response; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PD, progressive disease; PR, partial response; SD, stable disease.

Table 3. Disease Response[a]

	Cohort A (n=8)	Cohort B (n=25)	Total (N=33)
Confirmed BOR, 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, %	100.0	88.0	90.9
95% CI	63.1-100.0	68.8-97.5	75.7-98.1
Confirmed DCR, %	100.0	96.0	97.0
95% CI	63.1-100.0	79.6-99.9	84.2-99.9
Median DoR, months	12.4	NE	NE
95% CI	5.5-NE	12.1-NE	12.1-NE

Per Response Evaluation Criteria in Solid Tumors version 1.1. by investigator. [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; four patients without any postbaseline tumor assessments were excluded from the efficacy-evaluable analysis set.
BOR, best overall response; CI, confidence interval; DCR, disease control rate; DoR, duration of response; NE, not estimable; ORR, objective response rate.

Figure 3. Treatment Duration and Response[a]



Some tumor assessments were seriously delayed due to COVID-19. [a]Per Response Evaluation Criteria In Solid Tumors version 1.1 by investigator in the safety analysis set, defined as all patients who received at least one dose of any component of study treatment.
CR, complete response; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PD, progressive disease; PR, partial response; SD, stable disease.

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Acknowledgments

We would like to thank the investigators, site support staff, and especially the patients, for participating in this study.

Funding

This study is sponsored by BeiGene, Ltd. Medical writing support under the direction of the authors, was provided by Gemma Walker, BSc, of Ashfield MedComms, an Inizio company, and was funded by BeiGene. Editorial support, under the direction of the authors, was provided by Envision Pharma Inc., and was funded by BeiGene.

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