Zanidatamab, a HER2-targeted bispecific antibody, in combination with docetaxel as first-line therapy for patients with advanced HER2-positive breast cancer: Preliminary results from a Phase 1b/2 study

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Abstract No: 1031 presented at ASCO, Chicago, IL, June 2022

Conclusions

Zanidatamab and docetaxel demonstrated encouraging antitumor activity as first line therapy for advanced HER2-positive breast cancer.

Treatment with zanidatamab and docetaxel resulted in a **90.5% confirmed objective response rate suggesting promising efficacy.**

The combination of zanidatamab and docetaxel had a **manageable safety profile,** with the incidence of treatment-related adverse events consistent with previous reports.[12]

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.[1,2] Human epidermal growth factor receptor 2 (HER2)-targeted agents have improved outcomes in HER2-positive breast cancer, but most patients in first-line therapy do not respond to current therapies, eventually relapse or develop resistance.[3,4]

HER2-positive breast cancer accounts for approximately 20% of all breast cancers.[5–7] 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 to trastuzumab, a monospecific HER2 antibody.[8,9]

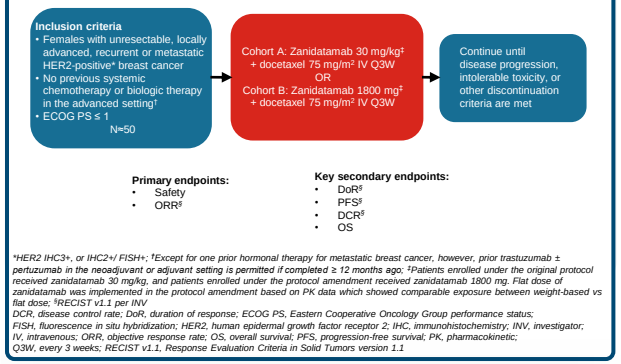
Zanidatamab's unique binding properties result in receptor clustering, internalization and downregulation, inhibition of growth factor -dependent and -independent tumor cell proliferation, and antibody-dependent cellular cytotoxicity and phagocytosis, and complement-dependent cytotoxicity.[10]

In a Phase 1 trial (NCT02892123), zanidatamab had a tolerable safety profile and demonstrated preliminary antitumor activity as monotherapy/with chemotherapy in patients with pre-treated advanced HER2-positive breast cancer.[11]

Methods

- This is an ongoing, open-label, multicenter, Phase 1b/2 study (NCT04276493)
- Here we describe the preliminary safety and antitumor activity of zanidatamab in combination with docetaxel in patients with advanced HER2-positive breast cancer (**Figure 1**)

Figure 1. Study design



HER2 IHC3+, or IHC2+/ FISH+; †Except for one prior hormonal therapy for metastatic breast cancer, however, prior trastuzumab ± pertuzumab in the neoadjuvant or adjuvant setting is permitted if completed ≥ 12 months ago; ‡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 PK data which showed comparable exposure between weight-based vs flat dose; §RECIST v1.1 per INV
DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, 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

- As of November 26, 2021, 25 female patients were enrolled in the study. Patients included in this analysis received 30 mg/kg (n=10) or 1800 mg (n=14) zanidatamab, in combination with docetaxel (**Table 1**)
- Three patients without any post-baseline tumor assessments were excluded from the efficacy evaluable analysis set. One patient was excluded from both the safety and efficacy analysis sets due to rediagnosis of her metastatic lesion
- At the data cutoff, 16 patients (66.7%) remained on treatment. This study is ongoing
- Median study follow-up was 7.0 months (range: 1.1–17.4) and the median number of treatment cycles was 10.0 (range: 2–20)

Table 1. Demographics and baseline characteristics

	Cohort A (n=10)	Cohort B (n=14)	Total (N=24*)
Median age, years (range)	59.5 (45–80)	56.0 (33–67)	57.0 (33–80)
Race, n (%)			
Chinese	3 (30.0)	11 (78.6)	14 (58.3)
Korean	7 (70.0)	3 (21.4)	10 (41.7)
ECOG PS, n (%)			
0	4 (40.0)	3 (21.4)	7 (29.2)
1	6 (60.0)	11 (78.6)	17 (70.8)
HER2 status†, n (%)			
IHC3+	8 (80.0)	11 (78.6)	19 (79.2)
IHC2+/FISH+	2 (20.0)	3 (21.4)	5 (20.8)
HR status, n (%)			
Positive	5 (50.0)	9 (64.3)	14 (58.3)
Negative	5 (50.0)	5 (35.7)	10 (41.7)
Brain metastases‡, n (%)	0 (0)	1 (7.1)	1 (4.2)
Prior systemic therapy§, n (%)	6 (60.0)	7 (50.0)	13 (54.2)
(Neo)adjuvant anti-HER2 therapy	4 (40.0)	3 (21.4)	7 (29.2)
Trastuzumab	4 (40.0)	3 (21.4)	7 (29.2)
Pertuzumab	1 (10.0)	0 (0)	1 (4.2)

*One patient was excluded because she 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'; †All subjects had HER2 status confirmed by local lab; ‡At study entry, must be asymptomatic and radiologically stable for inclusion; §Patients had neoadjuvant/adjuvant therapy and/or one prior hormone regimen (for metastatic breast cancer)
ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry

Safety

- In total, 22 patients (91.7%) experienced at least one treatment-related adverse event (TRAE; considered by the investigator to be related to any component of the study treatment), and 16 patients (66.7%) experienced at least one ≥ Grade 3 TRAE (**Table 2**)
- The most common TRAEs were neutrophil count decreased (13 patients; 54.2%), diarrhea (13 patients; 54.2%), and anemia (nine patients; 37.5%); and the most common ≥ Grade 3 TRAEs were neutrophil count decreased (12 patients; 50.0%), diarrhea (three patients; 12.5%), and white blood cell count decreased (two patients; 8.3%)
- Serious TRAEs occurred in two (8.3%) patients. One patient experienced febrile neutropenia, cholangitis, and diarrhea, and the other patient experienced decreased platelet count and an infusion-related reaction, in which the last one led to treatment discontinuation in one (4.2%) patient

Table 2. TRAEs occurring in ≥ 20% of patients

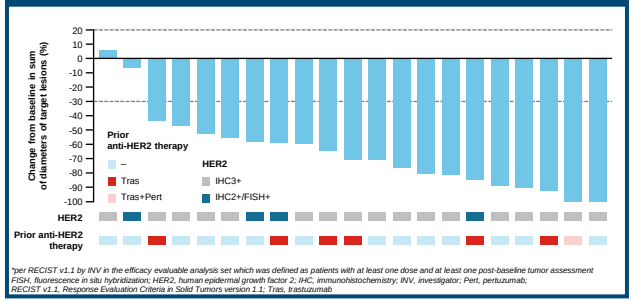
Events, n (%)	Cohort A (n=10)		Cohort B (n=14)		Total (N=24)	
	Any grade	≥ Grade 3	Any grade	≥ Grade 3	Any grade	≥ Grade 3
Patients with at least one event	9 (90.0)	9 (90.0)	13 (92.9)	7 (50.0)	22 (91.7)	16 (66.7)
Neutrophil count decreased	7 (70.0)	7 (70.0)	6 (42.9)	5 (35.7)	13 (54.2)	12 (50.0)
Diarrhea	7 (70.0)	3 (30.0)	6 (42.9)	0 (0)	13 (54.2)	3 (12.5)
Anemia	1 (10.0)	1 (10.0)	8 (57.1)	0 (0)	9 (37.5)	1 (4.2)
Chest discomfort	2 (20.0)	0 (0)	5 (35.7)	1 (7.1)	7 (29.2)	1 (4.2)
Nausea	4 (40.0)	0 (0)	3 (21.4)	0 (0)	7 (29.2)	0 (0)
Alopecia	1 (10.0)	0 (0)	5 (35.7)	0 (0)	6 (25.0)	0 (0)
Aspartate aminotransferase increased	1 (10.0)	0 (0)	5 (35.7)	0 (0)	6 (25.0)	0 (0)
Alanine aminotransferase increased	1 (10.0)	0 (0)	4 (28.6)	0 (0)	5 (20.8)	0 (0)
Decreased appetite	2 (20.0)	0 (0)	3 (21.4)	0 (0)	5 (20.8)	0 (0)
Platelet count decreased	0 (0)	0 (0)	5 (35.7)	0 (0)	5 (20.8)	0 (0)
White blood cell count decreased	0 (0)	0 (0)	5 (35.7)	2 (14.3)	5 (20.8)	2 (8.3)

AEs were recorded using the MedDRA, with severity graded by INV using NCI CTCAE v5.0. No TRAEs led to death
AE, adverse event; INV, investigator; MedDRA, Medical Dictionary for Regulatory Activities; NCI CTCAE, National Cancer Institute common terminology criteria for adverse events; TRAE, treatment-related adverse event

Efficacy

- The best percentage change in target lesion size is shown in **Figure 2**

Figure 2. Best change in target lesion*



*per RECIST v1.1 by INV in the efficacy evaluable analysis set which was defined as patients with at least one dose and at least one post-baseline tumor assessment
FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor 2; IHC, immunohistochemistry; INV, investigator; Pert, pertuzumab; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; Tras, trastuzumab

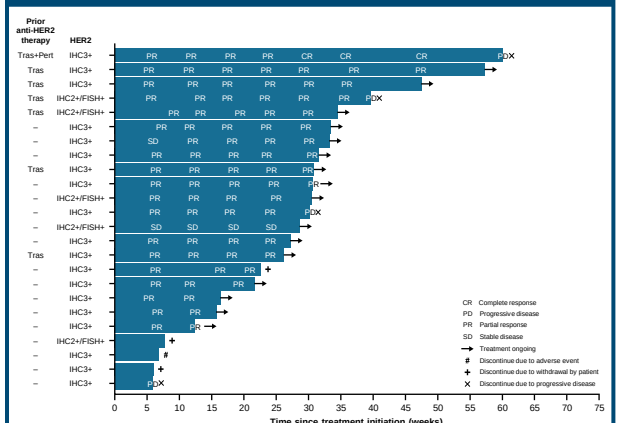
- Of the 21 efficacy evaluable patients, the confirmed objective response rate (ORR) was 90.5% (95% CI: 69.6, 98.8) (**Table 3**) with 15 patients (78.9%) who were ongoing responders. The treatment duration with overall response is shown in **Figure 3**
- The disease control rate was 95.2% (95% CI: 76.2, 99.9) (**Table 3**); 20 patients had controlled disease
- The 6-month progression-free survival rate was 95.2% (95% CI: 70.7, 99.3)

Table 3. Disease response*

	Cohort A (n=8)	Cohort B (n=13)	Total (N=21)
cORR†, %	100.0	84.6	90.5
95% CI	63.1, 100.0	54.6, 98.1	69.6, 98.8
Complete response, n (%)	1 (12.5)	0 (0)	1 (4.8)
Partial response, n (%)	7 (87.5)	11 (84.6)	18 (85.7)
Stable disease, n (%)	0 (0)	1 (7.7)	1 (4.8)
Progressive disease, n (%)	0 (0)	1 (7.7)	1 (4.8)
DCR†, %	100.0	92.3	95.2
95% CI	63.1, 100.0	64.0, 99.8	76.2, 99.9
DoR (months), min, max‡	1.4+, 12.4	1.5+, 5.6+	1.4+, 12.4

*In the efficacy evaluable analysis set; †per RECIST v1.1 by INV; ‡15.8% of patients had DoR events
+, censored; CI, confidence interval; cORR, confirmed objective response rate; DCR, disease control rate; DoR, duration of response; INV, investigator; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1*

Figure 3. Treatment duration and response*



*per RECIST v1.1 by INV in the safety analysis set
CR, complete response; FISH, 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

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Acknowledgments

This study is sponsored by BeiGene, Ltd. Medical writing support for the development of this poster, under direction of the authors, was provided by Victoria Dagwell, MSc, and Helena Crisford, MSc, of Ashfield MedComms, an Ashfield Health company, and was funded by BeiGene, Ltd.

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