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ORIGINAL ARTICLE

Zanidatamab in combination with docetaxel in first-line HER2-positive breast cancer: results from an open-label, multicenter, phase Ib/II study

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Background: Most patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer develop resistance or relapse. Zanidatamab is a novel, humanized, dual-HER2-targeted bispecific antibody with antitumor activity and a manageable safety profile as monotherapy in HER2-positive cancers. This trial evaluated the efficacy and safety of zanidatamab with docetaxel as first-line treatment in HER2-positive breast cancer.

Methods: Cohort 1 of this open-label, multicenter, phase Ib/II trial enrolled adult patients from China or South Korea with histologically or cytologically confirmed unresectable, locally advanced, recurrent or metastatic HER2-positive breast cancer. Patients received intravenous zanidatamab 30 mg/kg with docetaxel 75 mg/m^2 or a flat dose of zanidatamab 1800 mg with docetaxel 75 mg/m^2 once every 3 weeks. Primary objectives were to evaluate the preliminary antitumor activity, safety, and tolerability of zanidatamab with docetaxel.

Results: At data cut-off (7 December 2023), 38 patients were enrolled in cohort 1; median study follow-up was 24.8 months. The confirmed objective response rate was 90.9%, disease control rate was 97.0%, and median duration of response was 23.5 months. Median time to response was 5.9 weeks. Median progression-free and overall survival were 22.1 months and 36.9 months, respectively. All patients experienced one or more treatment-emergent adverse events (TEAE), and 71.1% experienced grade $\geq$3 TEAEs. All patients had one or more treatment-related AE (TRAE), and 97.4% experienced zanidatamab-related TRAEs. Serious TEAEs were reported for 31.6% of patients: 18.4% had serious TRAEs, all of which were zanidatamab related. One death due to respiratory failure was recorded but was assessed as not related to study treatment. TEAEs and TRAEs leading to treatment discontinuation were recorded for 10.5% and 7.9% of patients, respectively.

Conclusion: Zanidatamab demonstrated efficacy and a manageable and tolerable safety profile with docetaxel as first-line treatment in patients with HER2-positive breast cancer. These data support the further development of zanidatamab in this patient population.

Key words: zanidatamab, HER2, breast cancer, phase Ib/II, anti-HER2 therapy, bispecific

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer worldwide and is the leading cause of cancer deaths in women, with >665 000 deaths in 2022.[1] In China, the age-standardized incidence rate of breast cancer in women has increased over time (17.84 per 100 000 in 1990 versus 37.00 per 100 000 in 2021, respectively), but the age-standardized mortality rate has decreased slightly (8.98 per 100 000 versus 8.24 per 100 000, respectively).[2] In Korea, the age-standardized incidence rate was 60.5 per 100 000 in 2019, and the age-standardized mortality rate for breast cancer in women was 5.5 per 100 000.[3] About 30%-40% of patients will have disease progression within 1 year of treatment of advanced disease, and the 5-year survival rate following metastatic diagnosis is ∼30%.[4,5]

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer accounts for ∼20% of all breast cancers.[6,7]

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Expression of HER2 on the cell surface, with or without overexpression or gene amplification, results in the activation of oncogenic pathways and an increase in tumor growth.[8-10] The availability of effective anti-HER2 agents, including the antibodies trastuzumab, pertuzumab, and margetuximab; the antibody—drug conjugates trastuzumab, deruxtecan, and trastuzumab emtansine; and the HER2-directed tyrosine kinase tucatinib, has dramatically improved clinical outcomes in all disease stages.[11-14] Despite the introduction of targeted therapies and encouraging treatment responses, most patients with HER2-positive breast cancer who receive first-line therapy develop resistance or eventually relapse.[6,15,16]

Trastuzumab and pertuzumab are recommended in the (neo)adjuvant setting for HER2-positive node-positive or high-risk node-negative breast cancer.[17] The first-line treatment of patients with recurrent and metastatic disease after prior exposure to perioperative trastuzumab is trastuzumab; the inclusion of pertuzumab depends on regional availability.[18,19] First-line trastuzumab and pertuzumab-containing treatment regimens have been reported to be less effective in patients with failure of adjuvant trastuzumab compared with trastuzumab-naive patients.[15,20,21] Therefore, there remains a large unmet medical need for new effective and tolerable treatments for patients with HER2-positive breast cancer, including those who received prior (neo)adjuvant anti-HER2 therapy.

Zanidatamab (also known as ZW25) is a novel, humanized, immunoglobulin G isotype 1-like HER2-targeted bispecific antibody that simultaneously binds to extracellular domain (ECD)4 and ECD2 of HER2. Zanidatamab's unique binding properties, with increased saturation of the tumor cells, result in HER2 receptor clustering and capping, internalization, and downregulation; inhibition of growth factor-dependent and -independent tumor cell proliferation; and antibody-dependent cellular cytotoxicity, phagocytosis, and complement-dependent cytotoxicity.[22] In a previous phase I clinical trial, zanidatamab demonstrated promising antitumor activity and a manageable safety profile as a single agent in patients with HER2-positive cancers, including advanced breast cancer, and in patients who received prior anti-HER2 therapies.[23]

Here, we report efficacy and safety data from an open-label, multicenter, phase Ib/II trial investigating zanidatamab in combination with docetaxel as first-line treatment in patients with unresectable locally advanced or metastatic HER2-positive breast cancer (cohort 1).

METHODS

Study design and participants

This is an open-label, multicenter, phase Ib/II trial (NCT04276493) investigating the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of zanidatamab in combination with chemotherapy, with or without tislelizumab, in patients with unresectable locally advanced or metastatic HER2-positive breast cancer (cohort 1) or gastric/gastroesophageal junction adenocarcinoma (cohort 2).

Cohort 1 of the trial enrolled female patients from China or South Korea aged $\geq$18 years with histologically or cytologically confirmed unresectable, locally advanced, recurrent or metastatic breast carcinoma who were candidates for chemotherapy. Patients were HER2 immunohistochemistry (IHC) 3+ or were *in situ* hybridization positive on archival tumor tissue or a fresh biopsy sample and had not received previous systemic anticancer therapy for locally advanced unresectable or metastatic disease. Prior systemic treatment in the neoadjuvant or adjuvant setting was permitted if the disease-free interval from completion of the systemic treatment (excluding hormonal therapy) to diagnosis of locally advanced recurrent or metastatic disease was $\geq$12 months. Patients had one or more measurable lesions as defined per RECIST version 1.1, Eastern Cooperative Oncology Group performance status (ECOG PS) $\leq$1, and adequate organ function defined by laboratory screening. Exclusion criteria included a history of approved or investigative tyrosine kinase/HER inhibitors in any treatment setting, except trastuzumab with or without pertuzumab used in the neoadjuvant or adjuvant setting, and a history of cardiovascular risk factors. Patients with a history of exposure to cumulative anthracycline doses leading to an increased risk of cardiotoxicity were excluded; clinical criteria for exclusion were met if patients received any of the following: doxorubicin or liposomal doxorubicin $>$360 mg/m^2; epirubicin $>$720 mg/m^2; mitoxantrone $>$120 mg/m^2 and idarubicin $>$90 mg/m^2; other anthracycline exceeding the equivalent of 360 mg/m^2 of doxorubicin; or, if more than one anthracycline had been used, then the cumulative dose must not have exceeded the equivalent of 360 mg/m^2 of doxorubicin.

Treatments and procedures

Patients enrolled in cohort 1A received zanidatamab 30 mg/kg intravenously (i.v.) in combination with docetaxel 75 mg/m^2 i.v. once every 3 weeks (q3w); those enrolled in cohort 1B received a flat dose of zanidatamab 1800 mg i.v. in combination with docetaxel 75 mg/m^2 i.v. q3w. The 30 mg/kg dosing for zanidatamab was chosen based on data from a previous first-in-human study.[23] The flat dose of zanidatamab was selected based on population pharmacokinetic analysis, which suggested that 1800 mg q3w was considered to be equivalent to 30 mg/kg q3w for breast cancer patients with a typical body weight of 60 kg.[24] All patients received acetaminophen, diphenhydramine, and a corticosteroid 30-60 min before infusion of zanidatamab as prophylactic treatment of infusion-related reactions (IRRs). Zanidatamab plus docetaxel was administered for an initial period of up to six cycles. After cycle 6, continuation of docetaxel treatment was at the discretion of the investigator. Zanidatamab was administered until disease progression, intolerable toxicity, or another criterion for treatment discontinuation was met.

Table 1. Baseline characteristics and disease history

Characteristic	Cohort 1A (n = 11)	Cohort 1B (n = 27)	Total (N = 38)
Median age (years)	60.0	55.0	56.0
Min, max	45, 80	33, 67	33, 80
Female	11 (100.0)	27 (100.0)	38 (100.0)
Childbearing potential, *n* (%)			
Yes	5 (45.5)	12 (44.4)	17 (44.7)
No	6 (54.5)	15 (55.6)	21 (55.3)
Race, *n* (%)			
Asian	11 (100.0)	27 (100.0)	38 (100.0)
Chinese	4 (36.4)	24 (88.9)	28 (73.7)
Korean	7 (63.6)	3 (11.1)	10 (26.3)
Median weight (kg)	59.8	59.0	59.4
Min, max	45.0, 91.7	43.0, 86.0	43.0, 91.7
ECOG performance status, *n* (%)			
0	5 (45.5)	6 (22.2)	11 (28.9)
1	6 (54.5)	21 (77.8)	27 (71.1)
Metastatic disease at study entry, *n* (%)			
Yes	11 (100.0)	26 (96.3)	37 (97.4)
Median time from initial diagnosis to study entry (months)	58.7	1.7	13.6
Min, max	0.2, 195.3	0.4, 165.1	0.2, 195.3
Metastatic sites at study entry[a], *n* (%)			
Bone	5 (45.5)	13 (48.1)	18 (47.4)
Liver	4 (36.4)	15 (55.6)	19 (50.0)
Lung	5 (45.5)	16 (59.3)	21 (55.3)
Brain	0 (0.0)	2 (7.4)	2 (5.3)
Lymph nodes	6 (54.5)	22 (81.5)	28 (73.7)
Soft tissue	1 (9.1)	2 (7.4)	3 (7.9)
Skin	1 (9.1)	0 (0.0)	1 (2.6)
Other[b]	2 (18.2)	9 (33.3)	11 (28.9)
Prior anticancer systemic therapy, *n* (%)	6 (54.5)	10 (37.0)	16 (42.1)
Prior (neo)adjuvant anti-HER2 therapy	4 (36.4)	4 (14.8)	8 (21.1)
Trastuzumab[c]	3 (27.3)	4 (14.8)	7 (18.4)
Trastuzumab + pertuzumab[c]	1 (9.1)	0 (0.0)	1 (2.6)
Prior regimens, *n* (%)			
1	2 (18.2)	6 (22.2)	8 (21.1)
2	3 (27.3)	1 (3.7)	4 (10.5)
≥3	1 (9.1)	3 (11.1)	4 (10.5)
Treatment setting of prior therapies[d], *n* (%)			
Neoadjuvant	2 (18.2)	4 (14.8)	6 (15.8)
Adjuvant	6 (54.5)	9 (33.3)	15 (39.5)
Locally advanced	0 (0.0)	0 (0.0)	0 (0.0)
Metastatic	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (3.7)	1 (2.6)
Hormone ER responsiveness, *n* (%)			
Positive	5 (45.5)	15 (55.6)	20 (52.6)
Negative	6 (54.5)	12 (44.4)	18 (47.4)
Not done	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Hormone PR responsiveness, *n* (%)			
Positive	4 (36.4)	9 (33.3)	13 (34.2)
Negative	7 (63.6)	18 (66.7)	25 (65.8)
Not done	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
HER2 status by central lab, *n* (%)			
IHC3+	6 (54.5)	23 (85.2)	29 (76.3)
IHC2+/(F)ISH+[e]	4 (36.4)	3 (11.1)	7 (18.4)
Negative	0 (0.0)	1 (3.7)	1 (2.6)
NA	1 (9.1)	0 (0.0)	1 (2.6)
HER2 status by local lab, *n* (%)			
IHC3+	9 (81.8)	24 (88.9)	33 (86.8)
IHC2+/(F)ISH+[e]	2 (18.2)	3 (11.1)	5 (13.2)

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; (F)ISH, (fluorescence) *in situ* hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; lab, laboratory; Max, maximum; Min, minimum; NA, not applicable; PR, progesterone receptor.

[a]A patient could have multiple metastatic sites.

[b]Other metastatic sites were the contralateral breast and pleural effusion, dura, adrenal gland, ovary, pleura, chest, mediastinum, and spleen.

[c]Patients treated with only trastuzumab were counted in 'Trastuzumab', and patients treated with trastuzumab and pertuzumab were counted in 'Trastuzumab + pertuzumab'.

[d]A patient could have multiple treatment settings.

[e]Patients with IHC 2+ and (F)ISH+.

Table 2. Efficacy outcomes

Response category	Cohort 1A (n = 8)	Cohort 1B (n = 25)	Total (N = 33)
Best overall response, *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 (0.0)	2 (8.0)	2 (6.1)
Progressive disease	0 (0.0)	1 (4.0)	1 (3.0)
Not evaluable	0 (0.0)	0 (0.0)	0 (0.0)
Not assessable	0 (0.0)	0 (0.0)	0 (0.0)
cORR, *n* (%)	8 (100.0)	22 (88.0)	30 (90.9)
95% CI (%)[a]	63.1-100.0	68.8-97.5	75.7-98.1
DCR, *n* (%)	8 (100.0)	24 (96.0)	32 (97.0)
95% CI (%)[a]	63.1-100.0	79.6-99.9	84.2-99.9
Median DoR[b,c], months	12.4	23.5	23.5
95% CI (%)	5.5-NE	11.3-NE	11.3-NE
Median TTR, weeks			5.86
Min, max			5.0-18.3
Median PFS[c], months	13.7	22.1	22.1
95% CI (%)	6.8-NE	12.7-NE	12.7-NE
Median OS[c], months	NE	NE	36.9
95% CI (%)	36.9-NE	(NE-NE)	36.9-NE
OS event-free rate at 12 months[d], %	100.0	95.8	96.9
95% CI	63.1-100.0	73.9-99.4	79.8-99.6
OS event-free rate at 24 months[d], %	100.0	87.5	90.5
95% CI	63.1-100.0	66.1-95.8	73.4-96.8

Complete response and partial response were confirmed per RECIST v1.1.
CI, confidence interval; DCR, disease control rate; DoR, duration of response; cORR, confirmed objective response rate; NE, not estimable; OS, overall survival; PFS, progression-free survival; TTR, time to response.
[a]95% CI estimated using the Clopper—Pearson method.
[b]Assessed in 8 confirmed responders in cohort 1A, 22 confirmed responders in cohort 1B, and 30 confirmed responders in total.
[c]Median estimated using the Kaplan—Meier method with 95% CIs estimated using the Brookmeyer and Crowley method.
[d]Event-free rates estimated using the Kaplan—Meier method with 95% CIs estimated using the Greenwood formula. When the estimated event-free rate was 100%, the 95% CI was estimated using the Clopper—Pearson method instead.

Trial assessments

Physical examinations, assessments of vital signs and ECOG PS, and 12-lead electrocardiograms were carried out during screening, at cycle 1, and every 21 days from cycle 3 until the end of treatment. Echocardiograms (ECHOs)/multiple gated acquisition scans (MUGA) were carried out during screening, 6 weeks after cycle 1 day 1, then every 12 weeks within a ±7-day window until the end of treatment. Tumor imaging was carried out during screening and every 6 weeks (±7 days) from cycle 1 day 1 for the first 36 weeks and then every 12 weeks (±7 days) until the end of the follow-up period. Adverse events (AEs) were recorded throughout the trial and follow-up period according to National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

Endpoints

The primary antitumor activity endpoint was confirmed objective response rate (cORR), assessed by investigator per RECIST v1.1. The primary safety endpoint was the type, frequency, and severity of AEs and serious AEs, as graded by NCI-CTCAE v5.0. Selected secondary endpoints included duration of response (DoR), time to response (TTR), progression-free survival (PFS), and disease control rate (DCR), all assessed by investigator per RECIST v1.1, and overall survival (OS), defined as the time from the start date of study drug to the date of death due to any cause.

Statistical analysis

The efficacy evaluable analysis set included all patients who received one or more doses of the study drug, had measurable disease at baseline according to RECIST v1.1, and had at least one postbaseline tumor response assessment unless any clinical progressive disease or death occurred within 10 weeks after the first dose. One patient with primary lung carcinoma was removed from the efficacy evaluable analysis set due to violation of inclusion criteria; the resulting per-protocol analysis set was used for efficacy analyses. The cORR was determined from confirmed best overall response (BOR) assessments of complete response (CR) or partial response (PR) by investigator per RECIST v1.1. The DCR was determined from confirmed BOR assessments of CR, PR, or stable disease. The two-sided Clopper—Pearson 95% confidence intervals (CIs) for cORR and DCR were calculated for each cohort. PFS, DoR, and OS were estimated using the Kaplan—Meier method. TTR was estimated descriptively using the subset of patients who achieved a confirmed CR or PR.

The safety analysis set included all patients who received one or more doses of any component of study treatment. Descriptive summary statistics were used to analyze safety data. Zanidatamab AEs of special interest (AESI) were defined as treatment-emergent AEs with a start date <30 days after the last dose of zanidatamab. These AESIs included zanidatamab-related IRRs, potential cardiac events [defined as grade ≥2 AEs in the Broad Cardiac Failure Standardised Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) or ECHO/MUGA results indicating a postbaseline decrease in the left ventricular ejection fraction (LVEF) of ≥10% from pretreatment baseline and a value of <50%], confirmed cardiac events (defined as the subset of potential cardiac events that had been clinically reviewed by the sponsor and determined to be consistent with cardiac events of absolute decrease in LVEF of ≥10% from pretreatment baseline and absolute value of <50%, and/or grade ≥2 heart failure), and noninfectious pulmonary toxicities (defined by the broad interstitial lung disease SMQ). Selected zanidatamab AEs included treatment-emergent diarrhea, defined using the MedDRA preferred term of 'diarrhoea', and treatment-emergent embryo-fetal toxicity, defined using the modified pregnancy and neonatal topics SMQ, which excluded the sub-SMQ lactation-related topics, including neonatal exposure through breast milk.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All patients provided written informed consent before enrollment. The protocol was approved by the institutional review board/independent ethics committee in conformance with Good Clinical Practice (GCP) and applicable regulatory requirements (8 January 2020; approval number 2019-10-169-002). The trial was conducted in accordance

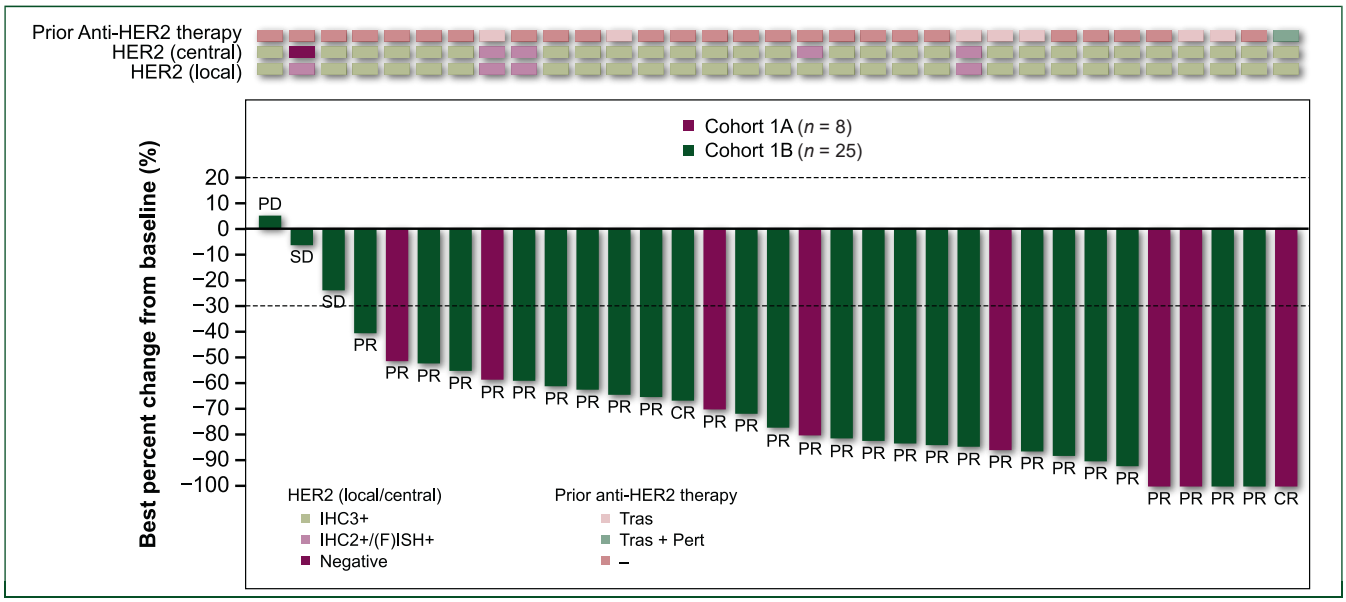

Figure 1. Best percent change from baseline in target lesion sum of diameters by best overall response per investigator.
CR, complete response; (F)ISH, (fluorescence) *in situ* hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PD, progressive disease; Pert, pertuzumab; PR, partial response; SD, stable disease; Tras, trastuzumab.

with sponsor procedures, which comply with the principles of GCP, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guidelines, the Declaration of Helsinki, and applicable local regulatory requirements.

RESULTS

As of the data cut-off date of 7 December 2023, a total of 38 patients were enrolled in cohort 1 of the trial (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105852); 10 (26.3%) patients remained on treatment, and median study follow-up time was 24.8 months (range 1.1-37.5 months). The primary reason for treatment discontinuation was progressive disease (16 patients, 42.1%), followed by withdrawal by patient (eight, 21.1%), and AEs (four, 10.5%). Twenty-six (68.4%) patients remained on the study. The primary reasons for study discontinuation were death and withdrawal by patient (five each, 13.2%), followed by loss to follow-up (two, 5.3%).

Demographics, baseline characteristics, and disease history

All patients enrolled in cohort 1 were Asian females with a median age of 56.0 years and a median body weight of 59.4 kg; 27 (71.1%) patients had an ECOG PS of 1 (Table 1). Thirty-seven (97.4%) patients had metastatic breast cancer at study entry; time from initial diagnosis to study entry and metastatic sites at study entry are reported in Table 1. Prior anticancer systemic therapy was recorded for 16 (42.1%) patients overall. The type, number of regimens, and setting of prior therapies are listed in Table 1. Estrogen receptor and progesterone receptor responsiveness and HER2 status are reported in Table 1.

Efficacy analysis

The efficacy analyses included 33 patients: eight from cohort 1A and 25 from cohort 1B. The cORR was 90.9% (95% CI 75.7% to 98.1%) overall: 100.0% (95% CI 63.1% to 100.0%) in cohort 1A and 88.0% (95% CI 68.8% to 97.5%) in cohort 1B (Table 2). Eight patients received prior anti-HER2 therapy (four each from cohorts 1A and 1B), all of whom achieved a BOR of confirmed CR or PR (Figure 1). Treatment duration and efficacy responses are summarized in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105852.

The DCR was 97.0% (95% CI 84.2% to 99.9%) overall: 100.0% (95% CI 63.1% to 100.0%) in cohort 1A and 96.0% (95% CI 79.6% to 99.9%) in cohort 1B (Table 2). The DoR event rate was 46.7% and the overall median DoR (mDoR) was 23.5 months (95% CI 11.3 months-not estimable [NE]) in 30 confirmed responders (Table 2 and Figure 2A). In cohort 1A, the DoR event rate was 50.0%, and mDoR was 12.4 months (95% CI 5.5 months-NE) in eight confirmed responders. The DoR event rate for cohort 1B was 45.5% and mDoR was 23.5 months (95% CI 11.3 months-NE) in 22 confirmed responders. Median TTR was 5.9 weeks (range 5.0-18.3 weeks) overall. The PFS event rate was 51.5%, and the overall median PFS was 22.1 months (95% CI 12.7 months-NE) (Table 2 and Figure 2B). The 18-month PFS event-free rate was 52.5% (95% CI 33.1% to 68.7%). In cohort 1A, the PFS event rate was 50.0%, mPFS was 13.7 months (95% CI 6.8 months-NE), and the 18-month event-free rate was 42.9% (95% CI 9.8% to 73.4%). In cohort 1B, the PFS event rate was 52.0%, mPFS was 22.1 months (95% CI 12.7 months-NE), and the 18-month event-free rate was 55.1% (95% CI 32.4% to 73.0%). Death was reported for 12.1% of patients overall, median OS was 36.9 months (95% CI 36.9 months-NE), and the OS

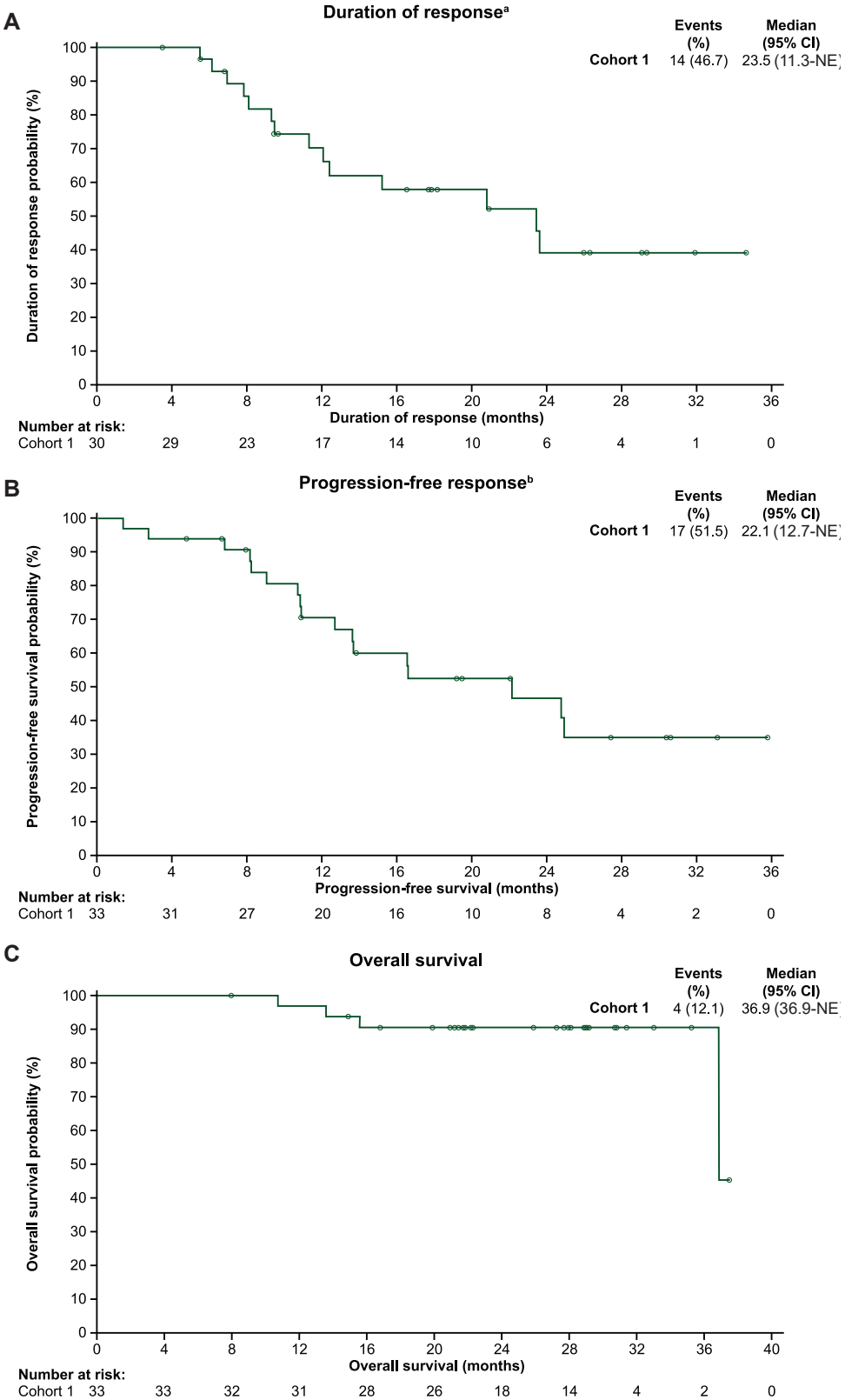

Figure 2. Kaplan–Meier plots for efficacy outcomes. Showing duration of response (A), progression-free survival (B), and overall survival (C).
CI, confidence interval; NE, not estimable.
[a]Assessed in responders by investigator.
[b]Assessed by investigator.

24-month event-free rate was 90.5% (95% CI 73.4% to 96.8%) (Table 2 and Figure 2C). Median OS was NE in cohort 1A and cohort 1B (Table 2). Death was reported for 12.5% of patients in cohort 1A, and the OS 24-month event-free rate was 100.0% (95% CI 63.1% to 100.0%). In cohort 1B, death was reported for 12.0% of patients,

Table 3. Safety outcomes and treatment-related AEs by maximum grade and preferred term

Patients, *n* (%)	Cohort 1A (*n* = 11)		Cohort 1B (*n* = 27)		Total (*N* = 38)	
Any TEAE	11 (100.0)		27 (100.0)		38 (100.0)	
Grade ≥3	10 (90.9)		17 (63.0)		27 (71.1)	
Serious	2 (18.2)		10 (37.0)		12 (31.6)	
Leading to death[a]	0 (0.0)		1 (3.7)		1 (2.6)	
Leading to treatment discontinuation	0 (0.0)		4 (14.8)		4 (10.5)	
Leading to zanidatamab discontinuation	0 (0.0)		4 (14.8)		4 (10.5)	
Leading to treatment modification	5 (45.5)		19 (70.4)		24 (63.2)	
Leading to zanidatamab dose reduction	2 (18.2)		0 (0.0)		2 (5.3)	
Treatment-related AE Preferred term	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Patients with ≥1 event	11 (100.0)	10 (90.9)	27 (100.0)	16 (59.3)	38 (100.0)	26 (68.4)
Neutrophil count decreased	8 (72.7)	7 (63.6)	15 (55.6)	11 (40.7)	23 (60.5)	18 (47.4)
Anemia	1 (9.1)	1 (9.1)	21 (77.8)	0 (0.0)	22 (57.9)	1 (2.6)
Diarrhea	8 (72.7)	4 (36.4)	13 (48.1)	0 (0.0)	21 (55.3)	4 (10.5)
White blood cell count decreased	0 (0.0)	0 (0.0)	17 (63.0)	7 (25.9)	17 (44.7)	7 (18.4)
Alopecia	3 (27.3)	0 (0.0)	12 (44.4)	0 (0.0)	15 (39.5)	0 (0.0)
Alanine aminotransferase increased	2 (18.2)	0 (0.0)	11 (40.7)	1 (3.7)	13 (34.2)	1 (2.6)
Hypokalemia	0 (0.0)	0 (0.0)	11 (40.7)	2 (7.4)	11 (28.9)	2 (5.3)
Nausea	5 (45.5)	0 (0.0)	6 (22.2)	0 (0.0)	11 (28.9)	0 (0.0)
Aspartate aminotransferase increased	1 (9.1)	0 (0.0)	9 (33.3)	0 (0.0)	10 (26.3)	0 (0.0)
Edema peripheral	0 (0.0)	0 (0.0)	8 (29.6)	0 (0.0)	8 (21.1)	0 (0.0)
Pruritus	1 (9.1)	0 (0.0)	7 (25.9)	1 (3.7)	8 (21.1)	1 (2.6)
Decreased appetite	2 (18.2)	0 (0.0)	5 (18.5)	0 (0.0)	7 (18.4)	0 (0.0)
Hypoalbuminemia	0 (0.0)	0 (0.0)	7 (25.9)	0 (0.0)	7 (18.4)	0 (0.0)
Platelet count decreased	0 (0.0)	0 (0.0)	7 (25.9)	0 (0.0)	7 (18.4)	0 (0.0)
Arthralgia	3 (27.3)	0 (0.0)	3 (11.1)	0 (0.0)	6 (15.8)	0 (0.0)
Chest discomfort	2 (18.2)	0 (0.0)	4 (14.8)	1 (3.7)	6 (15.8)	1 (2.6)
Weight decreased	1 (9.1)	0 (0.0)	5 (18.5)	0 (0.0)	6 (15.8)	0 (0.0)
Blood bilirubin increased	1 (9.1)	0 (0.0)	4 (14.8)	0 (0.0)	5 (13.2)	0 (0.0)
Blood lactate dehydrogenase increased	0 (0.0)	0 (0.0)	5 (18.5)	0 (0.0)	5 (13.2)	0 (0.0)
Insomnia	0 (0.0)	0 (0.0)	5 (18.5)	0 (0.0)	5 (13.2)	0 (0.0)
Myalgia	3 (27.3)	0 (0.0)	2 (7.4)	0 (0.0)	5 (13.2)	0 (0.0)
Abdominal distension	0 (0.0)	0 (0.0)	4 (14.8)	0 (0.0)	4 (10.5)	0 (0.0)
Fatigue	1 (9.1)	0 (0.0)	3 (11.1)	0 (0.0)	4 (10.5)	0 (0.0)
Mouth ulceration	2 (18.2)	0 (0.0)	2 (7.4)	0 (0.0)	4 (10.5)	0 (0.0)
Rash	3 (27.3)	0 (0.0)	1 (3.7)	0 (0.0)	4 (10.5)	0 (0.0)
Stomatitis	3 (27.3)	0 (0.0)	1 (3.7)	0 (0.0)	4 (10.5)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	4 (14.8)	0 (0.0)	4 (10.5)	0 (0.0)

AEs were classified based on MedDRA v26.0 and were graded based on NCI-CTCAE v5.0. Treatment discontinuation was defined as discontinuation of any study drug. Treatment modification included infusion interrupted, dose delay, infusion rate decreased, or dose reduced for zanidatamab or chemotherapy. Patients with more than one event for a given preferred term were counted once at the maximum severity for the preferred term.

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute—Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event;

[a]There was one patient with grade 5 TEAE, which was unrelated to zanidatamab.

and the OS event-free rate at 24 months was 87.5% (95% CI 66.1% to 95.8%).

Safety analysis

Safety was analyzed in 38 patients in total: 11 in cohort 1A and 27 in cohort 1B. Median duration of exposure to zanidatamab was 9.0 months for cohort 1A and 15.7 months for cohort 1B. Median relative dose intensities of zanidatamab in cohort 1A and cohort 1B were 98.0% and 95.5%, respectively.

All patients experienced one or more treatment-emergent AE (TEAE; Table 3). Most patients (27, 71.1%) experienced grade ≥3 TEAEs, including 12 (31.6%) patients with grade 3, 14 (36.8%) patients with grade 4, and 1 (2.6%) patient with grade 5 events. All patients experienced treatment-related AEs (TRAEs), and almost all experienced zanidatamab-related TRAEs (37, 97.4%). The most common (≥10% of patients overall) TRAEs are reported in Table 3. TRAEs of grade ≥3 were reported in 26 (68.4%) patients, including events related to zanidatamab reported in 12 (31.6%) patients. Serious TRAEs were reported in seven (18.4%) patients, all of which were related to zanidatamab. A total of 12 (31.6%) patients experienced serious TEAEs.

One TEAE of respiratory failure leading to death was reported for a patient in cohort 1B who had lung and other metastatic disease at baseline; this event was assessed as likely caused by COVID-19 infection and as not related to study treatment. Four (14.8%) patients in cohort 1B experienced TEAEs leading to treatment discontinuation, including three (11.1%) who experienced zanidatamab-related TEAEs events leading to treatment discontinuation (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105852). Twenty-four (63.2%) patients experienced TEAEs leading to treatment modification, including two (5.3%) who experienced TEAEs leading to dose reduction of

zanidatamab. TRAEs leading to treatment modification were reported in 17 (44.7%) patients, 16 of whom (42.1%) experienced zanidatamab-related TEAEs. The most common TRAEs leading to treatment modification (two or more patients) were chest discomfort (four, 10.5%); chills (three, 7.9%); and alanine aminotransferase increased, blood bilirubin increased, and ejection fraction decreased (two each, 5.3%).

The most common zanidatamab-related TEAE was diarrhea, reported for seven (63.6%) patients in cohort 1A and 13 (48.1%) patients in cohort 1B. Zanidatamab-related grade 3 diarrhea was reported for four (36.4%) patients in cohort 1A and no patients in cohort 1B. No grade >3 treatment-related diarrhea was reported. A zanidatamab-related TEAE of diarrhea leading to zanidatamab dose reduction was reported for one (9.1%) patient in cohort 1A. Treatment-emergent AESIs/selected AEs of zanidatamab were reported in 27 (71.1%) patients. The incidence of individual AESIs is reported in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105852. Three (7.9%) patients were identified with confirmed cardiac events, all of which were grade ≤2. All confirmed cardiac events were clinically asymptomatic, were not assessed to be serious by the investigator, and were managed without dose modification. One (3.7%) patient in cohort 1B experienced grade 3 IRRs of pruritus, oropharyngeal discomfort, palpitations, chest discomfort, and decreased heart rate, all of which were resolved with concomitant medication. No grade ≥4 IRRs were reported.

DISCUSSION

Treatment of patients with HER2-positive breast cancer has experienced several recent advances; however, there remains a need for effective and tolerable new therapies. This trial investigated the combination of zanidatamab with docetaxel in patients with HER2-positive breast cancer who had not received prior systemic therapies for locally advanced, unresectable, or metastatic disease. Zanidatamab with docetaxel demonstrated clinically meaningful antitumor activity with a manageable and tolerable safety profile that was consistent with the known AEs of each treatment component.

Patients with HER2-positive metastatic breast cancer who received docetaxel, trastuzumab, and pertuzumab in the randomized, double-blind, phase III CLEOPATRA trial had an ORR of 80.2% and median DoR of 20.2 months.[4,25] Median PFS was 18.5 months, median OS was 57.1 months, and the 24-month OS rate was 80.5%.[4,25,26] In the trial, 10.9% of patients received prior adjuvant or neoadjuvant chemotherapy with trastuzumab.[4] Final analysis of the phase III, randomized, double-blind, placebo-controlled PUFFIN trial reported an ORR of 79.0% and median PFS of 14.5 months in Chinese patients with previously untreated HER2-positive locally recurrent or metastatic breast cancer who received docetaxel, trastuzumab, and pertuzumab.[27] Prior adjuvant or neoadjuvant trastuzumab was received by 11.1% of patients.[27]

In the current trial, cORR by investigator was 90.9% (95% CI 75.7% to 98.1%), median DoR was 23.5 months, and median PFS was 22.1 months. OS data are immature after the median study follow-up of 24.8 months, with a 24-month OS event-free rate of 90.5%. No clinically meaningful difference in antitumor activity was observed between the body weight-based and flat dosing regimens of zanidatamab in combination with docetaxel described in this study. Prior adjuvant or neoadjuvant anti-HER2 therapy was received by 21.1% of patients. The one patient who received prior trastuzumab with pertuzumab achieved a confirmed CR, and all eight patients who received prior anti-HER2 therapy achieved a BOR of confirmed CR or PR. These data suggest patients with prior anti-HER2 therapy may respond to zanidatamab; however, this finding requires further evaluation in a randomized trial.

Safety analyses showed that zanidatamab with docetaxel was well tolerated. There was no convincing evidence of significant drug exposure differences between body weight-based dosing and flat dosing regimens. The most common (incidence ≥50%) TEAEs were decreased neutrophil count, anemia, and diarrhea, consistent with the known risks of each treatment component. The incidence of TEAEs was similar in cohort 1A and cohort 1B. The incidence of diarrhea in cohort 1A was 72.7% and 48.1% in cohort 1B. Overall, most diarrhea cases were grade ≤2 and manageable without zanidatamab discontinuation. Three (7.9%) patients were identified with confirmed cardiac events, all of which were grade ≤2, clinically asymptomatic, not assessed to be serious by the investigator, and were managed without dose modification. No patient experienced noninfectious pulmonary toxicities. The incidence of TRAEs leading to treatment discontinuation was 7.9%. TRAEs leading to treatment modification were reported for 44.7% of patients, while the incidence of TRAEs leading to zanidatamab dose reduction was 5.3%. No TRAEs leading to death were reported. Together, these data support the tolerability of zanidatamab with docetaxel.

The potential limitations of this trial include the nonrandomized design, a lack of standard-of-care comparator, a small sample size, a patient population from only China and South Korea, and immature OS data. Additionally, the study did not specify the HER2 status at initial diagnosis, so the HER2 status before study entry is unknown. Only half of the patients who received prior systemic anticancer therapy had been treated with anti-HER2 agents. Factors that may have contributed to the low proportion of patients receiving anti-HER2 treatment include changes in HER2 status over time, limited access to certain drugs, or restricted indications for trastuzumab, with or without pertuzumab, during earlier periods. Therefore, the generalizability of these trial findings should be considered carefully.

In summary, zanidatamab demonstrated clinically meaningful antitumor activity and exhibited a manageable and tolerable safety profile as first-line treatment when combined with docetaxel in patients with unresectable, locally advanced, recurrent or metastatic HER2-positive

breast cancer. The data show no clinically meaningful difference of antitumor activity between the body weight-based and flat dosing regimens of zanidatamab when combined with docetaxel in these patients. The safety profiles of the dosing regimens were similar overall. These results support further development of zanidatamab in HER2-positive breast cancer.

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DISCLOSURE

KSL received drug supply for their institution from Dong-A ST, and participated on advisory boards for Bixink, Daiichi Sankyo, Eisai, Everest Medicine, Lilly, MSD, Novartis, Pfizer, and Roche. KW reports payments made to their institution for a consulting or advisory role from Shanghai Qiangshi Information Technology, Co., Ltd. PZ, VL, and SC are employees of BeOne Medicines Ltd., and may hold stock or stock options. ZJ serves as the Editor-in-Chief of Translational Breast Cancer Research. All other authors have declared no conflicts of interest.

DATA SHARING

BeOne Medicines voluntarily shares anonymous data on completed studies responsibly and provides qualified scientific and medical researchers access to anonymous data and supporting clinical trial documentation for clinical trials in dossiers for medicines and indications after submission and approval in the United States, China, and Europe. Clinical trials supporting subsequent local approvals, new indications, or combination products are eligible for sharing once corresponding regulatory approvals are achieved. BeOne Medicines shares data only when permitted by applicable data privacy and security laws and regulations. In addition, data can only be shared when it is feasible to do so without compromising the privacy of study participants. Data requests may be submitted to ClinicalTrials@beonemed.com.

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