ASCO Breakthrough

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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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 (HER)2-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[3,4]
- HER2-positive breast cancer accounts for approximately 20% of all breast cancers[5]
- 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[6-8]
- 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[6]
- Zanidatamab, in combination with chemotherapy, has demonstrated antitumor activity and a manageable safety profile in advanced HER2-positive breast cancer[9] and HER2-positive gastric/gastroesophageal junction adenocarcinoma[10,11]
- In advanced HER2-positive breast cancer, zanidatamab is being evaluated with docetaxel as first-line therapy (NCT04276493)[9]

1. Bray F, et al. *CA Cancer J Clin.* 2018;68(6):394-424; 2. WHO 2020. https://www.iarc.who.int/news-events/current-and-future-burden-of-breast-cancer-global-statistics-for-2020-and-2040/ Accessed June 26, 2023;
3. Ayoub NM, et al. *Breast Cancer (Dove Med Press).* 2019;11:53-69; 4. Rier HN, et al. *Oncologist.* 2017;22(8):901-909; 5. Wolff AC, et al. *Arch Pathol Lab Med.* 2007;131(1):18-43; 6. Weisser N, et al. *Nat Commun.* 2023;14:1394;
7. Kahraman S, Yalcin S. *Onco Targets Ther.* 2021;14:4149-4162; 8. Bedard PL, et al. (Poster P2-13-07) [presented at SABCS 2021]; 9. Lee K-S, et al. *J Clin Oncol.* 2022;40(suppl 16) (Abs 1031) [presented at ASCO 2022];
10. Meric-Bernstam F, et al. *J Clin Oncol.* 2021;39(suppl 3):164; 11. Lee KW, et al. *J Clin Oncol.* 2022;40(suppl 16). **Abbreviation:** HER, human epidermal growth factor receptor.

Study Design

Open-label, multicenter, phase 1b/2 study

Inclusion criteria

- Female patients 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[d] 75 mg/m^2 IV Q3W
or
Cohort B: Zanidatamab 1800 mg[c] + docetaxel[d] 75 mg/m^2 IV Q3W

→

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

Primary endpoints:

- Adverse events/serious adverse events
- Objective response rate[d]

Key secondary endpoints:

- Duration of response[e]
- Disease control rate[e]
- Progression-free survival[e]
- Overall survival

[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 is 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 PK data, which showed comparable exposure between weight-based and flat dosing. [d]Continuation of docetaxel treatment is at the discretion of the investigator after Cycle 6. [e]Per Response Evaluation Criteria In Solid Tumors version 1.1 per investigator. **Abbreviations:** ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenous; PK, pharmacokinetic; Q3W, every 3 weeks.

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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 PS			
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 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). **Abbreviations:** 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.

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 v25.0, with severity graded by INV 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. **Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; INV, investigator; TRAE, treatment-related adverse event; WBC, white blood cell.

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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, % 95% CI	100.0 63.1, 100.0	88.0 68.8, 97.5	90.9 75.7, 98.1
Confirmed DCR, % 95% CI	100.0 63.1, 100.0	96.0 79.6, 99.9	97.0 84.2, 99.9
Median DoR, months 95% CI	12.4 5.5, NE	NE 12.1, NE	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. **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.

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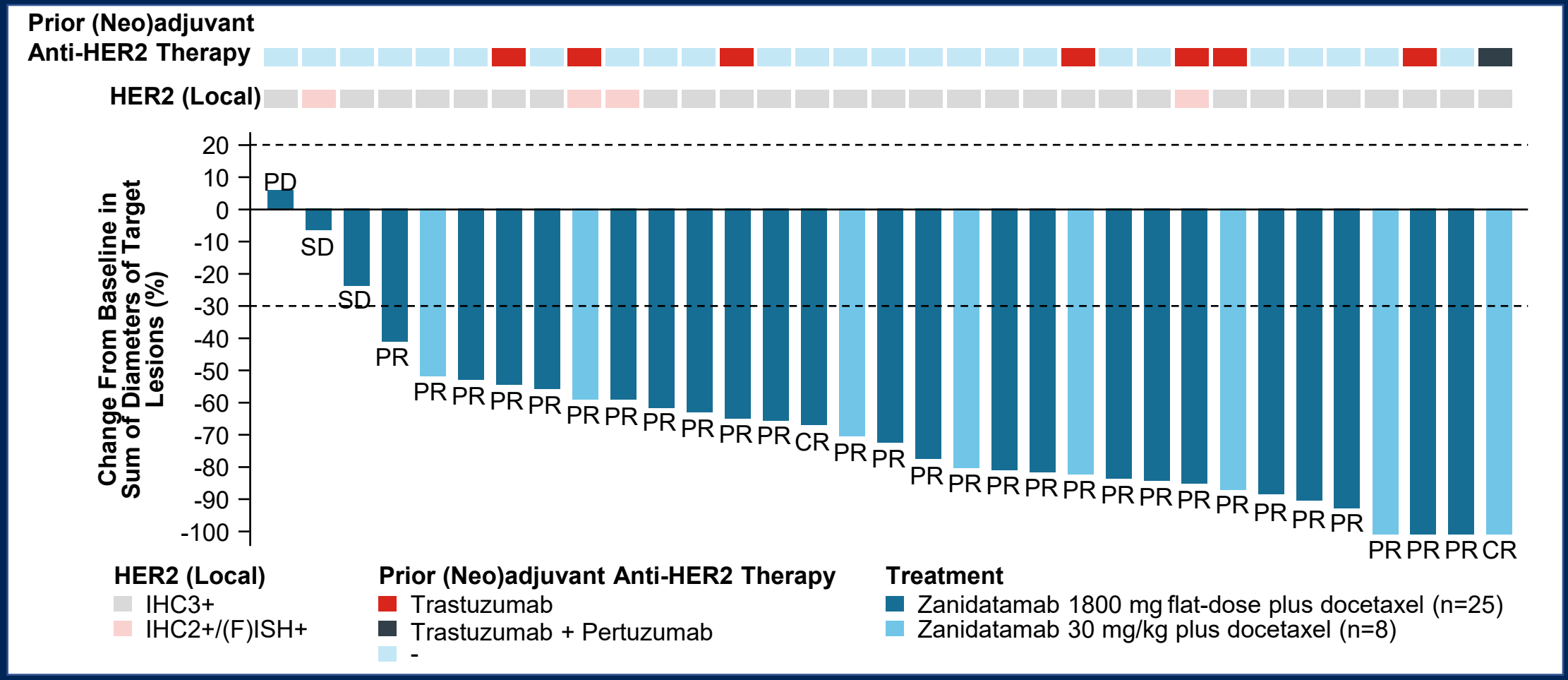
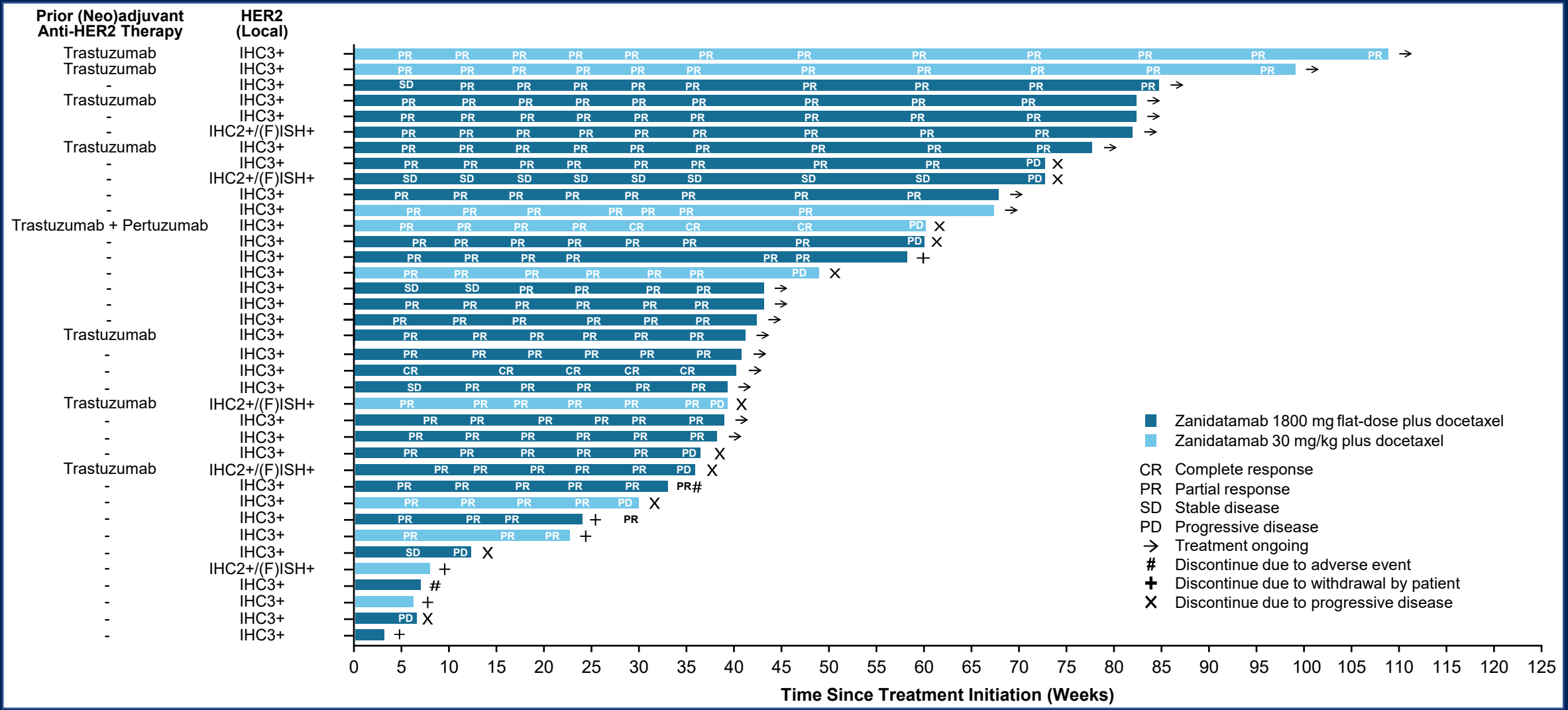
Best Change in Target Lesion Size[a]



[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.
Abbreviations: 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.

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.
Abbreviations: 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.

Conclusions

- Zanidatamab in combination with docetaxel demonstrated encouraging antitumor activity as first-line therapy for advanced 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]

1. Ku G, et al. *Ann Oncol.* 2021;32(suppl 5):S1044-S1045. **Abbreviation:** HER, human epidermal growth factor receptor.

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