Zanidatamab (ZW25), a HER2-targeted Bispecific Antibody, in Combination with Chemotherapy (chemo) for HER2-positive Breast Cancer (BC): Results from a Phase 1 Trial

P2-13-07

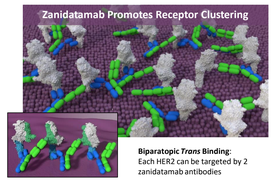
Philippe L. Bedard,[1]* Seock-Ah Im,[2] Elena Elimova,[1] SY Rha,[3] Rachel Goodwin,[4] Cristiano Ferrario,[5] Keun-Wook Lee,[6] Diana Hanna,[7] Funda Meric-Bernstam,[8] Jose Mayordomo,[9] Murali Beeram,[10] Erika Hamilton,[11] Jorge Chaves,[12] Melody Cobleigh,[13] Tony Mwatha,[14] Joseph Woolery,[14] Do-Youn Oh[2]

[1]Princess Margaret Cancer Centre, Toronto, ON, Canada; [2]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea; [3]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea; [4]University of Ottawa Cancer Centre, Ottawa, ON, Canada; [5]Jewish General Hospital Montréal, QC, Canada; [6]Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea; [7]USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [8]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [9]University of Colorado Cancer Center, Aurora, CO, USA; [10]The START Center for Cancer Care, San Antonio, TX, USA; [11]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; [12]Northwest Medical Specialists, Tacoma, WA, USA; [13]Rush University Medical Center, Chicago, IL, USA; [14]Zymeworks Inc., Vancouver, BC, Canada.

BACKGROUND

- After progression with other available HER2-targeted therapies, the treatment for patients with advanced HER2-positive BC is generally a regimen comprised of a HER2-targeted monoclonal antibody (e.g., trastuzumab) combined with a single chemotherapeutic agent[1]
  - Based on a recent phase 3 trial of previously treated patients (1-3 prior therapies) the overall response rate with such therapy is < 25% with median progression-free survival (PFS) < 6 months, and the median overall survival for these patients is < 2 years[2]
- Zanidatamab (also known as ZW25) is a humanized, bispecific, immunoglobulin G isotype 1 (IgG1)-like antibody directed against the juxtamembrane domain (ECD4) and the dimerization domain (ECD2) of HER2 (Figure 1)[3]
- Zanidatamab's unique binding properties result in:[3]
  - Receptor clustering, internalization, and downregulation
  - Inhibition of growth factor-dependent and -independent tumor cell proliferation
  - Antibody-dependent cellular cytotoxicity and phagocytosis, and complement-dependent cytotoxicity
- In ongoing phase 1 and 2 trials, zanidatamab monotherapy has been well tolerated with durable responses in subjects with heavily pretreated metastatic HER2-positive BC,[4] and HER2-expressing cancers, including gastroesophageal adenocarcinoma and biliary tract cancer[5-7]

Figure 1: Unique Binding Properties of Zanidatamab

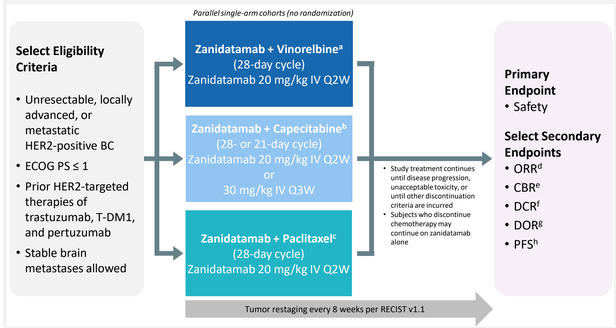


METHODS

Trial Design

- In Part 3 of this ongoing phase 1 trial (NCT02892123),[8] we evaluated the safety and antitumor activity of zanidatamab in combination with chemotherapy in patients with HER2-positive metastatic BC (monotherapy BC data from Parts 1 and 2 previously reported[4])
- Zanidatamab dosing was based on subject weight
  - To prevent or minimize infusion-related reactions, all subjects received prophylactic treatment with acetaminophen, diphenhydramine, and corticosteroid prior to administration of zanidatamab

Figure 2: ZWI-ZW25-101 Trial Design for Patients with HER2-positive BC in Part 3



CBR = clinical benefit rate; CR = complete response; DCR = disease control rate; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; ORR = objective response rate; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.
[a]Vinorelbine: vinorelbine 25 mg/m^2 QW on days 1, 8, 15, 22. [b]Capecitabine: with zanidatamab 20 mg/kg Q2W, 2000 mg twice daily for 7 days in weeks 1 and 3 or 1000 mg/m^2 twice daily on days 1-14 on a 21-day cycle; with zanidatamab 30 mg/kg Q3W, 1000 mg/m^2 twice daily on days 1-14 on a 21-day cycle. [c]Paclitaxel: paclitaxel 80 mg/m^2 QW for weeks 1-3. [d]ORR was defined as the percentage of subjects who have ≥ 1 overall tumor responses of CR/PR by RECIST v1.1. [e]CBR was defined as a best overall response of CR/PR, or SD or non-CR/non-PD≥ 24 weeks. [f]DCR was defined as a best response of CR, PR, or SD. [g]DOR was defined as time from first confirmed objective response until PD or death in subjects who had a CR/PR followed by ≥ 1 additional response assessment. [h]PFS was defined as time from first dose of zanidatamab to the date of documented disease progression per RECIST v1.1, clinical progression, or death from any cause.

RESULTS

Data were extracted on October 12, 2021 from an unlocked database.

- Of 24 subjects with HER2-positive BC enrolled in Part 3 of this trial, 10 (42%) continue on treatment
- 13 (54%) subjects have discontinued treatment due to disease progression and 1 (4%) due to an adverse event (AE; treatment-related grade 3 diarrhea)

Table 1: Demographics and Baseline Characteristics

	Subjects (N = 24)
Median age (range), years	55 (37–72)
Female sex, n (%)	24 (100)
Race, n (%)	
Asian	15 (63)
White	9 (38)
ECOG PS, n (%)	
0	12 (50)
1	12 (50)
HER2 positive,[a] n (%)	24 (100)
HR status, n (%)	
HR positive[b]	10 (42)
HR negative	10 (42)
Not reported	4 (17)
Prior history of brain metastases, n (%)	9 (38)
Prior systemic cancer regimens in the metastatic setting, median (range)	2.0 (0-6)
Patients with prior HER2-targeted therapies, n (%)	23 (96)[c]
Trastuzumab	23 (96)
T-DM1	23 (96)
Pertuzumab[d]	20 (83)
Lapatinib	5 (21)
Neratinib	2 (8)
Tucatinib/placebo[e]	2 (8)
Margetuximab	1 (4)
Tucatinib	1 (4)

ECOG PS = Eastern Cooperative Oncology Group performance status; ER = estrogen receptor; HR = hormone receptor.
[a]All subjects had HER2 status centrally confirmed. [b]All subjects had ER-positive tumors. [c]At time of data extraction, 1 subject was missing information on prior HER2-targeted therapies. [d]Three subjects did not have access to pertuzumab and were allowed to enroll after consultation with the trial sponsor per protocol. [e]Possibly treated with investigational tucatinib.

Safety

Table 2: Zanidatamab and/or Chemotherapy TRAEs

	Zanidatamab + Vinorelbine (n = 12)		Zanidatamab + Capecitabine (n = 8)		Zanidatamab + Paclitaxel (n = 4)		Total (N = 24)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
TRAE,[a] n (%)	11 (92)	7 (58)	8 (100)	3 (38)	3 (75)	3 (75)	22 (92)	13 (54)
Treatment-related SAE	0	0	0	0	0	0	0	0
TRAEs leading to treatment discontinuation[b]	1 (8)	1 (8)	1 (13)	0	0	0	2 (8)	1 (4)
TRAEs occurring in ≥ 20% of subjects and/or Grade ≥ 3 TRAEs in > 1 subject								
Diarrhea	10 (83)	1 (8)	5 (63)	1 (13)	2 (50)	0	17 (71)	2 (8)
Nausea	3 (25)	0	5 (63)	0	0	0	8 (33)	0
Stomatitis	2 (17)	0	4 (50)	0	1 (25)	0	7 (29)	0
Fatigue	3 (25)	0	3 (38)	0	0	0	6 (25)	0
Peripheral neuropathy	1 (8)	0	2 (25)	0	3 (75)	1 (25)	6 (25)	1 (4)
PPE	0	0	6 (75)	0	0	0	6 (25)	0
Neutrophil count decreased	6 (50)	6 (50)	0	0	0	0	6 (25)	6 (25)
Neutropenia	2 (17)	1 (8)	0	0	2 (50)	2 (50)	4 (17)	3 (13)
AESI in any subject								
Infusion-related reaction	1 (8)	0	1 (13)	0	1 (25)	0	3 (13)	0
Cardiac events[c]	1 (8)	0	1 (13)	0	0	0	2 (8)	0
Pneumonitis	1 (8)	0	0	0	0	0	1 (4)	0

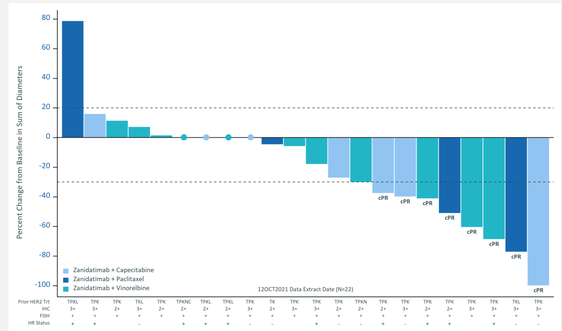
AESI = adverse event of special interest; PPE = palmar-plantar erythrodysesthesia; SAE = serious adverse event; TRAE = treatment-related adverse event. [a]AEs were recorded using the Medical Dictionary for Regulatory Activities (MedDRA), with severity graded by investigators using NCI-CTCAE v5.0. [b]One subject experience grade 1/2 nausea and abdominal pain, and 1 subject experienced grade 3 diarrhea. [c]Includes 2 subjects who experienced grade 2 ejection fraction decreased.

- Safety was formally assessed by the Safety Monitoring Committee (SMC) after the first 6 subjects were enrolled to each cohort
- Among the first 6 subjects dosed in the vinorelbine (25 mg/m^2 weekly) cohort, 2 subjects had chemotherapy dose reductions due to grade 3-4 neutrophil count decreased in Cycle 1:
  - 2 events led to vinorelbine dose reduction in 2 subjects
  - The SMC recommended vinorelbine dosing be altered from continuous weekly dosing to dosing on days 1 and 15 of a 28-day cycle
  - 1 subject (of 6) experienced grade 4 neutrophil count decreased (Cycle 1, Day 15) in the vinorelbine cohort after this dosing schedule modification
- 2 (8%) subjects experienced 3 serious AEs, none related to trial treatment:
  - 1 subject experienced upper respiratory infection and pneumonitis, and 1 subject experienced pleural effusion

Efficacy

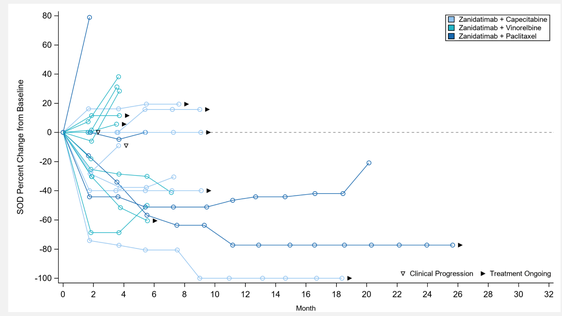
- The HER2-positive BC efficacy-evaluable population was defined as subjects with measurable disease (N = 22)
  - Median follow-up time was 7.1 months

Figure 3: Best Reduction in Target Lesions



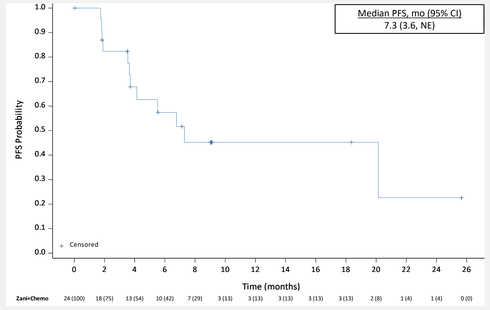
C = tucatinib; cPR, confirmed partial response; FISH = fluorescence in situ hybridization; HR = hormone receptor; IHC = immunohistochemistry; K = T-DM1; L = lapatinib; N = neratinib; P = pertuzumab; T = trastuzumab; Trt = treatment.

Figure 4: Treatment Duration



SOD = sum of diameter

Figure 5: Progression-free Survival in All Subjects



NE = not estimable; PFS = progression-free survival.

Table 3: Response Rates and DOR

HER2-positive Subjects	Zani + Vino (n = 11)	Zani + Cape (n = 7)	Zani + Pac (n = 4)	Total (N = 22)
cORR, % (95% CI)	27.3 (6.0, 61.0)	42.9 (9.9, 81.6)	50.0 (6.8, 93.2)	36.4 (13.9, 54.9)
PR, n (%)	3 (27.3)	3 (42.9)	2 (50)	8 (36.4)
SD, n (%)	6 (54.5)	4 (57.1)	1 (25)	11 (50)
PD, n (%)	2 (18.2)	0	1 (25)	3 (13.6)
CBR,[a] % (95% CI)	27.3 (6.0, 61.0)	85.7 (42.1, 99.6)	75.0 (19.4, 99.4)	54.5[a] (32.2, 75.6)
DCR, % (95% CI)	81.8 (48.2, 97.7)	100 (59.0, 100)	75.0 (19.4, 99.4)	86.4 (65.1, 97.1)
DOR range, months	1.6–3.7	3.6–16.7+	18.4–22.1+	1.6–22.1+

Cape = capecitabine; CBR = clinical benefit rate; cORR = confirmed objective response rate; DCR = disease control rate; DOR = duration of response; Pac = paclitaxel; PD = progressive disease; PR = partial response; SD = stable disease; Vino = vinorelbine; Zani = zanidatamab.
[a]Does not include 2 subjects currently on trial treatment < 6 months with a response of SD.

CONCLUSIONS

- Zanidatamab in combination with chemotherapy demonstrates encouraging antitumor activity in heavily pretreated subjects with HER2-positive BC:
  - 36.4% confirmed objective response rate (cORR) and a median progression-free survival (PFS) of 7.3 months across all treatment regimens compare favorably to historical data[2]
  - 4 of 8 responses are ongoing with response duration range of 1.8+ to 22.1+ months
- Zanidatamab in combination with single agent chemotherapy is well tolerated:
  - Diarrhea is the most frequent treatment-related AE observed across regimens and is manageable, the majority (> 90%) being low grade
  - Few infusion-related reactions or cardiac events were observed, none severe (grade ≥ 3)
- These data support further investigation of zanidatamab + single agent chemotherapy as a novel therapeutic option for treatment of patients with HER2-positive locally advanced or metastatic breast cancer after ≥ 3 lines of prior therapy
- The capecitabine and vinorelbine cohorts continue to enroll, evaluating the combination of zanidatamab and chemotherapy

References

1. Martinez-Saez O, Prat A. *JCO Oncol Pract*. 2021;OP2100172.
2. Rugo HS, et al. *JAMA Oncol*. 2021;7(4):573-584.
3. Weisser N, et al. Presented at: American Association for Cancer Research Annual Meeting; April 10-15, May 17-21, 2021. Virtual. Abstract 1005.
4. Hamilton E, et al. Presented at: San Antonio Breast Cancer Society Symposium; December 5-9, 2017; San Antonio, TX. Abstract PS-20:06.
5. Meric-Bernstam F, et al. Presented at: American Society of Clinical Oncology Gastrointestinal Cancers Symposium; January 15-17, 2021. Virtual. Abstract 164.
6. Meric-Bernstam F, et al. Presented at: American Society of Clinical Oncology Gastrointestinal Cancers Symposium; January 15-17, 2021. Virtual. Abstract 299.
7. Ku G, et al. Presented at: European Society for Medical Oncology Congress; September 16-21, 2021. Virtual. Abstract 1380P.
8. Clinicaltrials.gov. Accessed September 26. 2021. https://clinicaltrials.gov/ct2/show/NCT02892123

Acknowledgements

We sincerely thank all patients and their families. We thank all the investigators, clinical trial researchers, personnel, and staff who contributed to the trial.
ZWI-ZW25-101 trial is sponsored by Zymeworks Inc.

*Corresponding author: Philippe.Bedard@uhn.ca

Presented at the San Antonio Breast Cancer Symposium, December 7-10, 2021, San Antonio, TX