PD18-10

Antitumor Activity of Zanidatamab with Palbociclib and Fulvestrant in HER2+ Hormone-Receptor Positive (HR+) Metastatic Breast Cancer

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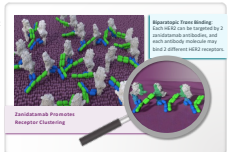
BACKGROUND

- HER2+ metastatic breast cancer (mBC) remains incurable, driving the ongoing clinical need to develop new HER2-targeted therapies, including chemotherapy-free regimens
- Zanidatamab is a novel, bispecific, monoclonal antibody targeting 2 nonoverlapping extracellular domains (ECD4 and ECD2) on HER2 (Figure 1)[1]
- Zanidatamab's unique binding properties result in:[1]
  - 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
- Zanidatamab has shown encouraging antitumor activity with a manageable safety profile in patients with HER2+ mBC as both a monotherapy[2] and in combinations[3]
- Approximately 50% of HER2+ BC is also positive for the estrogen receptor (ER+)[4]. Signaling through HER2 and ER, along with cyclin D-CDK4 kinase, contributes to tumor growth and resistance to therapy. Targeting all 3 pathways may be of benefit to patients
- Here we explore the combination of zanidatamab with palbociclib (a CDK 4/6 inhibitor) plus fulvestrant (a selective ER down-regulator) as a novel chemotherapy-free treatment option

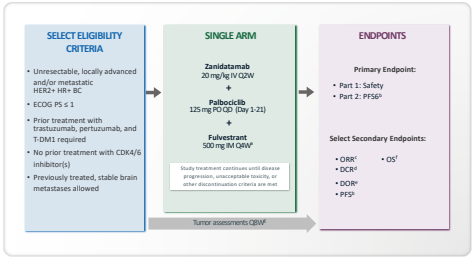
Figure 1: Unique Binding Properties of Zanidatamab



METHODS

- Study ZWI-ZW25-202 (NCT04224272) is an ongoing single-arm, open-label, international (Canada, Spain & USA), Phase 2 study of zanidatamab combined with palbociclib plus fulvestrant to treat patients with HER2+ HR+ mBC (Figure 2)
- Part 1 of the study evaluated safety and tolerability of zanidatamab in combination with palbociclib plus fulvestrant. A safety monitoring committee (SMC) reviewed safety data and assessed dose-limiting toxicities (DLTs) in Part 1 to confirm recommended doses (RDs) for Part 2
- Part 2 of the study is evaluating anti-tumor activity of the combination at the RD level determined in Part 1
  - Per protocol, patients treated at the RD in Part 1 were included in the efficacy analysis
- Total enrollment will be up to approximately 58 patients

Figure 2: ZWI-ZW25-202 Study Design (Parts 1 and 2 combined)



BC = breast cancer; CDK = cyclin-dependent kinase; CR = complete response; DCR = disease control rate; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor 2; HR = hormone receptor; IM = intramuscular; IV = intravenous; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PO = by mouth; PR = partial response; SD = stable disease; QD = daily; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; T-DM1 = ado-trastuzumab emtansine.
a After loading doses of 500 mg IM on Days 1, 15, 28, 9 PFS was defined as the time from first dose of study treatment to the date of documented disease progression per RECIST v1.1, clinical progression, or death from any cause; PFS at 6 months was defined as the percentage of patients having a PFS time of ≥ 24 weeks. c ORR was defined as the percentage of patients with a best overall response of CR or PR per RECIST v1.1. d DCR was defined as a best response of CR, PR, non-CR/non-PD (for patients who have only non-target lesions), or SD per RECIST v1.1. e DOR was defined as time from first objective response (CR or PR) to documented PD per RECIST v1.1 or death from any cause within 30 days of last dose of study treatment. f OS was defined as the time from first dose of study treatment until death from any cause. g Patients who discontinue treatment for reasons other than progressive disease or start of subsequent anticancer therapy will continue tumor assessment Q8W.

RESULTS

Disposition

- Data were extracted on 31 August 2022 from an unlocked database
- 45 patients have been enrolled and treated in the study:
  - 19 (42%) patients continue on zanidatamab treatment
  - 26 (58%) patients discontinued zanidatamab treatment: 22 due to disease progression, 2 due to physician decision, 1 due to death, and 1 patient withdrew from the treatment

Table 1: Demographics and Baseline Characteristics

	Patients (N=45)
Median age (range), years	54 (36 – 77)
Female sex, n (%)	43 (96)
Race, n (%)	
White	37 (82)
Asian	2 (4)
Other[a]	6 (13)
ECOG PS, n (%)	
0	23 (51)
1	22 (49)
HER2[b]+/HR+, n (%)	25 (56)
HER2+[b] by central testing	25 (56)[c]
HR+ by local testing	45 (100)
Prior history of brain metastases, n (%)	7 (16)
De novo metastatic disease, n (%)	16 (36)
Prior systemic anti-cancer therapy regimens in metastatic setting[d], median (range)	4 (1 – 10)
Prior systemic HER2 therapy in metastatic setting[d], median (range)	3 (1 – 9)
Percent of patients with prior endocrine therapy in metastatic setting[d], n (%)	35 (78)
Median (range)	1 (0 – 5)
Percent of patients with prior fulvestrant therapy, n (%)	9 (20)
Percent of patients with prior HER2 therapy , n(%)	45 (100)
Trastuzumab	45 (100)
T-DM1	44 (98)
Pertuzumab	36 (80)[e]
Lapatinib	13 (29)
T-DXd	11 (24)
Tucatinib	7 (16)
Neratinib	1 (2)

ECOG PS = Eastern Cooperative Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor 2; HR = hormone receptor; T-DM1 = ado-trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.
a Other included: Black or African American (n=1), Not Reported (n=1), Unknown (n=3), and Other (n=1). b Patients were allowed to enroll based on local HER2 results. Central laboratory HER2 analysis was performed after enrollment. c Per central testing, 11 patients had results that were HER2 negative, and 9 had results that were inconclusive/not evaluable (central biopsy was not received for 6 of these patients). d Includes (neo)adjuvant regimen if patient progressed on or within 6 months of completion of therapy. e Per protocol, prior pertuzumab therapy was not required in regions where it was not available or not the standard of care.

Safety

Part 1:

- A DLT of Grade 4 neutropenia lasting > 7 days occurred in 1 of 7 DLT-evaluable patients, assessed by the investigator as related to palbociclib. All 3 agents were held; zanidatamab and fulvestrant resumed after 3 weeks, whereas palbociclib was resumed after 4 weeks at a reduced dose and when the neutropenia resolved to Grade ≤ 2
- The SMC recommended that the starting doses (Figure 2) administered in Part 1 be used in Part 2 of the study

Parts 1 and 2 (N=45):

- Most treatment-related (related to zanidatamab, palbociclib and/or fulvestrant) adverse events (AEs) were Grade ≤ 2
  - The most common were diarrhea and neutropenia/neutrophil count decreased
    - 34 (76%) patients experienced diarrhea of any grade vs 4 (9%) patients experienced Grade 3 diarrhea
    - 28 (62%) patients experienced any grade of neutropenia/neutrophil count decreased, and 25 (56%) experienced a Grade 3 or Grade 4 event
- One zanidatamab- and palbociclib-related serious adverse event (SAE) of Grade 3 increased transaminases occurred in 1 patient
  - This event led to discontinuation of palbociclib
- There were no discontinuations of zanidatamab or fulvestrant due to an AE
- Dose reduction of zanidatamab due to an AE occurred in 2 patients: one had Grade 3 diarrhea and the other had Grade 3 increased transaminases
- Six deaths occurred and none were related to treatment: 5 due to disease progression (for 2 patients, cause of death was updated from "unknown" and "other" [respectively] to disease progression after the data cut off date) and 1 due to an unrelated AE of COVID 19

Table 2: TRAEs and AESIs

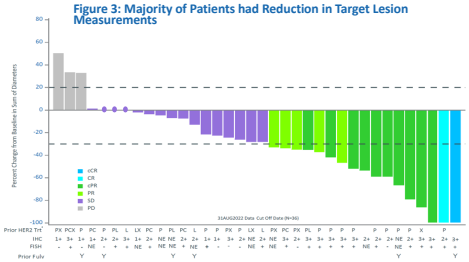
	Patients (N=45)	
	Any Grade	Grade ≥ 3[a]
Any TRAE (related to zanidatamab, palbociclib and/or fulvestrant), n (%)	44 (98)	27 (60)
Serious TRAE	1 (2)	1 (2)
TRAE in > 20% of patients and/or Grade ≥ 3 TRAE in > 1 patient		
Diarrhea	34 (76)	4 (9)
Neutropenia/neutrophil count decreased	28 (62)	25 (56)
Nausea	16 (36)	1 (2)
Stomatitis	15 (33)	1 (2)
Asthenia	11 (24)	0
Anemia	10 (22)	3 (7)
Vomiting	9 (20)	1 (2)
Thrombocytopenia	8 (18)	2 (4)
Treatment-related AESI		
Cardiac events[b]	4 (9)	1 (2)
Infusion-related reaction	1 (2)	0
Noninfectious pulmonary toxicity	0	0

AESI = adverse event of special interest; ECHO = echocardiogram; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition scan; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event; SMQ = Standardized MedDRA Query.
a All events were Grade 3 in severity with the exception of 3 patients who had Grade 4 events of neutropenia or neutrophil count decreased. b Potential cardiac events are defined as either ECHO/MUGA scan results for LVEF decrease ≥ 10 percentage points from pretreatment baseline and result value < 50%, and/or Grade ≥ 2 TEAEs meeting the broad cardiac failure SMQ.

Efficacy

- 36 patients with measurable disease (defined as patients with at least 1 measurable target lesion at baseline and at least 1 post-baseline disease assessment or discontinued study due to death, progressive disease, or an AE) were evaluable for response
  - Median follow-up time was 14 months
  - Number of efficacy-evaluable patients with measurable disease still on treatment: 19 (53%)
  - 9 of 12 confirmed responses ongoing; with response duration range of 2.1+ to 14.9+ months

Figure 3: Majority of Patients had Reduction in Target Lesion Measurements



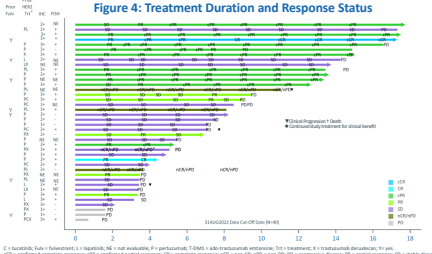
C = tucatinib; Fulv = fulvestrant; L = lapatinib; NE = not evaluable; P = pertuzumab; T-DM1 = ado-trastuzumab emtansine; Trt = treatment; X = trastuzumab deruxtecan; Y = yes.
cCR= confirmed complete response; cPR = confirmed partial response; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
*All patients had received prior trastuzumab and T-DM1 treatments.

Table 3: Response Rates and DOR

	Patients (N=36)[a]
cORR (CR + PR), n (%)	12 (33)
(95% CI)	(18.6, 51.0)
cBOR,	
CR, n (%)	1 (3)
PR, n (%)	11 (31)[b]
SD, n (%)	21 (58)
PD, n (%)	3 (8)
DCR (CR, PR, or SD), n (%)	33 (92)
(95% CI)	(77.5, 98.2)
DOR, (range)	(2.1+ – 14.9+)[c]

BOR = best overall response; cBOR = confirmed best overall response; cORR = confirmed objective response rate; CR = complete response; DCR = disease control rate; DOR = duration of response; PD = progressive disease; PR = partial response; SD = stable disease.
a Includes evaluable patients with measurable disease. b An additional 4 patients have unconfirmed PR and are included as SD; 1 patient with confirmed PR has since had an 8OR of unconfirmed CR. c Among 12 patients included in the analysis.

Figure 4: Treatment Duration and Response Status



C = tucatinib; Fulv = fulvestrant; L = lapatinib; NE = not evaluable; P = pertuzumab; T-DM1 = ado-trastuzumab emtansine; Trt = treatment; X = trastuzumab deruxtecan; Y= yes.
cCR = confirmed complete response; cPR = confirmed partial response; CR = complete response; nCR = non-CR; nPD = non-PD; PD = progressive disease; PR = partial response; SD = stable disease.
* All patients had received prior trastuzumab and T-DM1 treatments; An overall response of SD erroneously reported for this patient was subsequently corrected to nCR/nPR.

- The primary endpoint of PFS6 could not be determined in this interim data analysis with study enrollment ongoing
- Interim median PFS (n=40 for mITT*) was 9.6 months (95% CI: 7.2, 16.6), range 1.58 to 16.72+

*mITT = modified Intent-to-Treat analysis set, defined as all patients in the safety analysis set who had at least one identifiable (target and/or non-target) lesion at baseline and at least one post-baseline disease assessment or discontinued all study treatment and are no longer being followed for efficacy.

CONCLUSIONS

- Interim analyses of activity and safety data of zanidatamab combined with palbociclib plus fulvestrant in heavily pretreated patients with advanced/metastatic HER2+ HER+ BC are encouraging
- The regimen shows encouraging antitumor activity; in patients with response evaluable disease:
  - Most demonstrated reduction in the size of their target lesions
  - 33% achieved a confirmed response
- Durable disease control was demonstrated with a median PFS of 9.6 months in the mITT data set:
  - 9 of 12 patients with a confirmed response remained progression-free on therapy for > 1 year, including 7 still on treatment at the time of data cut
  - Of patients with a best response of stable disease, 3 remained progression free on therapy for > 1 year, and an additional 5 remained progression free on therapy for > 6 months
- Zanidatamab in combination with palbociclib plus fulvestrant is well tolerated and shows a manageable safety profile
- These results support further investigation of zanidatamab in combination with palbociclib plus fulvestrant, and enrollment in the study is continuing

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