Phase (Ph) 2 Study of Zanidatamab + Chemotherapy in First-line (1L) HER2-expressing Gastroesophageal Adenocarcinoma (GEA)

1380P

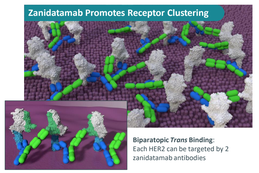
Geoffrey Ku, MD,[1*] Elena Elimova, MD, MSc,[2] Crystal S. Denlinger, MD, FACP,[3] Rutika Mehta, MD, MPH,[4] Keun-Wook Lee, MD, PhD,[5] Syma Iqbal, MD,[6] Yoon-Koo Kang, MD, PhD,[7] Do-Youn Oh, MD, PhD,[8] Sun Young Rha, MD, PhD,[9] Yeul Hong Kim, MD, PhD,[10] Young Mi Seol, MD, PhD,[11] Lisa Boyken, PhD,[12] Jonathan Grim, MD, PhD,[12] Jaffer Ajani, MD[13]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Princess Margaret Cancer Center, Toronto, ON, Canada; [3]Fox Chase Cancer Center, Philadelphia, PA, USA; [4]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [5]Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea; [6]University of Southern California, Los Angeles, CA, USA; [7]Asan Medical Center, Seoul, South Korea; [8]Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea; [9]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; [10]Korea University Anam Hospital, Seoul, South Korea; [11]Pusan National University Hospital, Busan, South Korea; [12]Zymeworks Inc., Vancouver, BC, Canada; [13]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background

- Human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 20% of GEAs[1,2]
- Metastatic HER2-positive GEA has high morbidity and mortality, and treatments are limited[3]
- 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[4] (Figure 1)
- Zanidatamab's unique binding properties result in:[4]
  - 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 a phase 1 study (NCT02892123), zanidatamab monotherapy was evaluated in 35 subjects, generating durable responses and showing good tolerability in subjects with heavily pretreated advanced or metastatic HER2-expressing GEA[5]
  - The most frequent treatment-related adverse events (TRAEs) were diarrhea (46%) and infusion-related reaction (34%); all were grades 1 and 2, with the exception of grade 3 diarrhea in 1 (3%) subject
  - 33% confirmed objective response rate (cORR) and a median duration of response (DOR) of 6.0 months
- Another ongoing phase 1b/2 study (NCT04276493) is evaluating zanidatamab + chemotherapy (capecitabine plus oxaliplatin [CAPOX]) + tislelizumab) in subjects with advanced HER2-positive gastric/gastroesophageal junction adenocarcinoma[6]

Figure 1: Unique Binding Properties of Zanidatamab

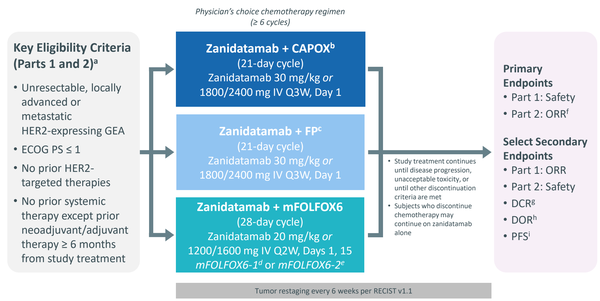


Methods

Study Design

- Study ZWI-ZW25-201 (NCT03929666) is an ongoing multicenter, global, phase 2, open-label study to investigate the safety, tolerability, and antitumor activity of zanidatamab + standard first-line combination chemotherapy regimens in subjects with locally advanced, unresectable, or metastatic HER2-expressing gastrointestinal cancers, including GEA[7]
- Zanidatamab was administered according to either a weight-based or a two-tiered flat dosing regimen
  - 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-ZW25-201 Study Design for Subjects with HER2-expressing GEA



[a]Part 1 used local or central assessment of HER2 status and allowed HER2 IHC 3+ or IHC 2+ regardless of HER2 FISH status. Part 2 included only subjects with HER2-positive cancer (IHC 3+ or IHC 2+/FISH+). [b]CAPOX: capecitabine 1,000 mg/m^2 PO BID, Days 1-15; oxaliplatin 130 mg/m^2 IV Q2W, Day 1. [c]FP: cisplatin 80 mg/m^2 IV Q3W, Day 1; 5-FU 800 mg/m^2/day IV, continuous Days 1-5. [d]mFOLFOX6-1: leucovorin 400 mg/m^2 IV Q2W, Days 1, 15; oxaliplatin 85 mg/m^2 IV Q2W, Days 1, 15; 5-FU 1200 mg/m^2/day IV, continuous Days 1-2 and 15-16, and 400 mg/m^2 IV Q2W, Days 1, 15. [e]mFOLFOX6-2 is identical to mFOLFOX6-1 but omits the 5-FU 400 mg/m^2 IV Q2W dose on Days 1 and 15. [f]Part 2 focused on antitumor activity of zanidatamab plus combination chemotherapy in subjects with HER2-positive cancer. [g]DCR was defined as a best response of CR, PR, or SD. [h]DOR was defined as time from first objective response that is subsequently confirmed to documented PD or death ≤ 30 days of last study treatment from any cause. IPFS was defined as the time from the first dose of study treatment to the date of documented disease progression, clinical progression, or death from any cause.
5-FU = 5-fluorouracil; DCR = disease control rate; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; FISH = fluorescence in situ hybridization; GEA = gastroesophageal adenocarcinoma; IHC = immunohistochemistry; ORR = objective response rate; PD = progressive disease; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SD = stable disease.

Results

Data were extracted on July 28, 2021, from an unlocked database

- Of 36 subjects with GEA enrolled, 19 (53%) continue on study treatment
- 12 (33%) subjects have discontinued treatment due to disease progression, 4 (11%) due to treatment-related AE, and 1 (3%) due to physician decision

Table 1: Demographics and Baseline Characteristics

		Subjects (N = 36)
Median age (range), years		58 (27–77)
Male sex, n (%)		32 (89)
Race, n (%)	Asian	11 (32)
	White	25 (68)
ECOG performance status, n (%)	0	23 (64)
	1	13 (36)
Primary tumor location, n (%)	Esophageal	9 (25)
	Gastroesophageal junction	14 (39)
	Gastric	13 (36)
Stage IV disease at initial diagnosis, n (%)		29 (81)
HER2-positive, n (%)[a]		32 (89)
	IHC 3+	28 (78)
	IHC 2+/FISH+	4 (11)

[a]HER2-positive was defined as IHC 3+ or IHC 2+/FISH+.
ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry.

Table 2: Zanidatamab and/or Chemotherapy TRAEs

	Zanidatamab + CAPOX (n = 14)		Zanidatamab + FP (n = 2)		Zanidatamab + mFOLFOX6 (n = 20)		Total (N = 36)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
TRAE,[a] n (%)	14 (100)	8 (57)	2 (100)	1 (50)	20 (100)	16 (80)	36 (100)	25 (69)
Treatment-related SAE[b]	2 (14)	2 (14)	1 (50)	1 (50)	4 (20)	4 (20)	7 (19)	7 (19)
TRAEs leading to treatment discontinuation	0	0	0	0	4 (20)	1 (6)	4 (11)	1 (3)
TRAEs occurring in ≥ 20% of subjects and/or Grade ≥ 3 TRAEs in > 1 subject[c]								
Diarrhea	13 (93)	5 (36)	2 (100)	1 (50)	19 (95)	9 (45)	34 (94)	15 (42)
Nausea	11 (79)	1 (7)	1 (50)	0	15 (75)	1 (5)	27 (75)	2 (6)
Peripheral neuropathy	10 (71)	0	0	0	9 (45)	0	19 (53)	0
Fatigue	5 (36)	0	0	0	11 (55)	1 (5)	16 (44)	1 (3)
Decreased appetite	5 (36)	0	1 (50)	0	9 (45)	0	15 (42)	0
Hypokalemia	2 (14)	0	0	0	11 (55)	6 (30)	13 (36)	6 (17)
Vomiting	3 (21)	1 (7)	0	0	9 (45)	2 (10)	12 (33)	3 (8)
Hypomagnesemia	3 (21)	0	0	0	6 (30)	1 (5)	9 (25)	1 (3)
Dysgeusia	4 (29)	0	0	0	4 (20)	0	8 (22)	0
Stomatitis	2 (14)	0	0	0	6 (30)	0	8 (22)	0
Neutrophil count decreased	2 (14)	0	0	0	5 (25)	3 (15)	7 (19)	3 (8)
WBC decreased	0	0	0	0	6 (30)	2 (10)	6 (17)	2 (6)
Acute kidney injury	0	0	1 (50)	1 (50)	1 (5)	1 (5)	2 (6)	2 (6)
AESIs occurring in any subject								
Infusion-related reaction	4 (29)	0	1 (50)	0	0	0	5 (15)	0
Cardiac events[d]	0	0	0	0	3 (15)	0	3 (9)	0
Pneumonitis	0	0	0	0	1 (5)	0	1 (3)	0

[a]AEs were recorded using the Medical Dictionary for Regulatory Activities (MedDRA), with severity graded by investigators using NCI-CTCAE v5.0. [b]SAEs occurring in ≥ 2 subjects included 3 (9%) subjects with diarrhea, 2 (6%) with acute kidney injury, and 2 (6%) with hypokalemia. [c]our (11%) subjects experienced grade 4 AEs: 1 (3%) lymphocyte count decreased, neutrophil count decreased, and white blood cell count decreased, and 3 (8%) hypokalemia; no treatment-related deaths were observed. [d]Includes 2 (6%) subjects with peripheral edema and 1 (3%) ejection fraction decreased.
5-FU = 5-fluorouracil; AE = adverse event; AESI = adverse event of special interest; CAPOX = capecitabine plus oxaliplatin; FP = 5-FU plus cisplatin; mFOLFOX6 = 5-FU plus oxaliplatin and leucovorin; SAE = serious adverse event; TRAE = treatment-related adverse event; WBC = white blood cell.

Safety

Dose Confirmation and Dose-limiting Toxicities (DLTs) – Part 1

- **Zanidatamab + CAPOX:** No DLTs in 6 subjects; dosing of zanidatamab + CAPOX was confirmed for Part 2
- **Zanidatamab + FP:** One DLT (acute kidney injury, grade 3) in 2 subjects; FP continues to enroll in Part 1
- **Zanidatamab + mFOLFOX6-1:** Two DLTs (diarrhea, grade 3) in 13 subjects, and 8/13 (62%) with grade 3 diarrhea
  - Safety monitoring committee recommended a modified regimen (mFOLFOX6-2) that omits the 5-FU 400 mg/m^2 bolus on Days 1, 15
- **Zanidatamab + mFOLFOX6-2:** One DLT (diarrhea, grade 3) in 7 subjects, and 2/7 (29%) with grade 3 diarrhea; dosing of zanidatamab + mFOLFOX6-2 was confirmed for Part 2

Diarrhea Prophylaxis

- Due to early onset of grade 3 diarrhea in some subjects across all treatment regimens, mandatory prophylaxis with loperamide (4 mg BID × ≥ 7 days) was initiated for the first treatment cycle (implemented September 30, 2020)
  - In the 25 subjects initiating treatment prior to implementation of antidiarrheal prophylaxis, the incidence of grade 3 diarrhea in Cycle 1 was 44% (11/25) overall (mFOLFOX6-1 46% [6/13], CAPOX 40% [4/10], and FP 50% [1/2])
  - In the 11 subjects initiating treatment after implementation of antidiarrheal prophylaxis, the incidence of grade 3 diarrhea in Cycle 1 was 18% (2/11) overall (mFOLFOX6-2 29% [2/7] and CAPOX 0% [0/4])

Efficacy

In the GEA efficacy-evaluable population (defined as all HER2-positive subjects with measurable disease in Parts 1 and 2 [N = 28])

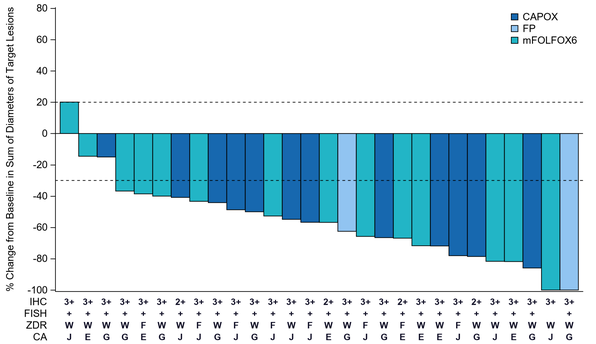
- Median follow-up time was 6.9 months across all treatment regimens
- 17 (61%) subjects remain on zanidatamab treatment

Table 3: Response Rates and DOR

HER2-positive subjects[a]	Zanidatamab + CAPOX (n = 12)	Zanidatamab + FP (n = 2)	Zanidatamab + mFOLFOX6 (n = 14)	Total (N = 28)
cORR,[b] % (95% CI)	92 (61.5, 99.8)	100 (15.8, 100)	57 (28.9, 82.3)	75 (55.1, 89.3)
CR, n (%)	0	0	1 (7)	1 (4)
PR, n (%)	11 (92)	2 (100)	7 (50)	20 (71)
SD, n (%)	1 (8)	0	3 (21)	4 (14)
PD, n (%)	0	0	3 (21)	3 (11)
DCR, % (95% CI)	100 (73.5, 100)	100 (15.8, 100)	79 (49.2, 95.3)	89 (71.8, 97.7)
Median DOR (range), months	NR (2.7, 15.2+)	NR (6.8, 12.5+)	16.4 (1.4, 19.8+)	16.4 (1.4, 19.8+)

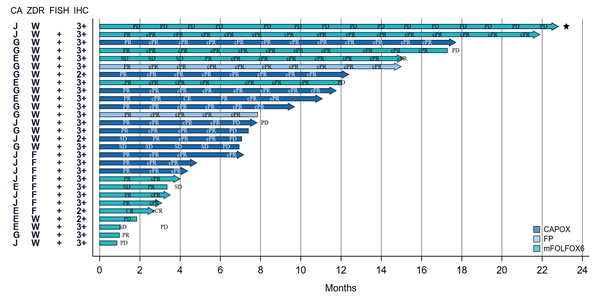
[a]HER2-positive was defined as IHC 3+ or IHC 2+/FISH+. [b]cORR included a baseline scan and a confirmatory scan obtained ≥ 4 weeks following initial documentation of objective response; the efficacy-evaluable population was defined as all HER2-positive subjects who had ≥ 1 evaluable post-baseline disease assessment or discontinued study treatment due to death or clinical progression. + indicates that the subject is in response at the time of data extraction.
5-FU = 5-fluorouracil; CAPOX = capecitabine plus oxaliplatin; CR = complete response; DCR = disease control rate; DOR = duration of response; FP = 5-FU and cisplatin; mFOLFOX6 = 5-FU plus oxaliplatin and leucovorin; NR = not reached; ORR = objective response rate (CR + PR); PD = progressive disease; PR = partial response; SD = stable disease.

Figure 3: Change in Target Lesion Size



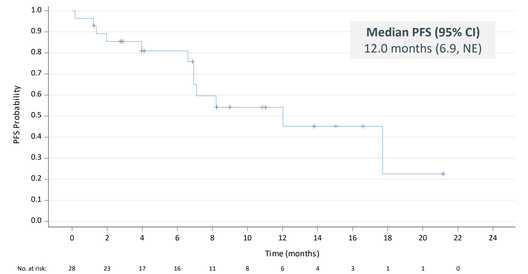
5-FU = 5-fluorouracil; CA = primary tumor location; CAPOX = capecitabine plus oxaliplatin; E = esophageal cancer; F = flat dosing; FISH = fluorescence in situ hybridization; FP = 5-FU plus cisplatin; G = gastric cancer; IHC = immunohistochemistry; J = gastroesophageal junction cancer; mFOLFOX6 = 5-FU plus oxaliplatin and leucovorin; W = weight-based dosing; ZDR = zanidatamab dosing regimen.

Figure 4: Treatment Duration



★ An MRI performed for neurologic symptoms on Day 8 demonstrated brain metastases, which were treated with radiation therapy. Subject remained on mFOLFOX6-1 with zanidatamab and has had long term disease control since treatment of brain metastases.
5-FU = 5-fluorouracil; CA, primary tumor location; CAPOX = capecitabine plus oxaliplatin; cCR = confirmed CR; CR = complete response; cPR = confirmed PR; E = esophageal cancer; F = flat dosing; FISH = fluorescence in situ hybridization; FP = 5-FU plus cisplatin; G = gastric cancer; IHC = immunohistochemistry; J = gastroesophageal junction cancer; mFOLFOX6 = 5-FU plus oxaliplatin and leucovorin; PD = progressive disease; PR = partial response; SD = stable disease; W = weight-based dosing; ZDR = zanidatamab dosing regimen.

Figure 5: Progression-free Survival



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

Conclusions

- In subjects with HER2-positive GEA, zanidatamab combined with standard first-line chemotherapy demonstrates encouraging antitumor activity
  - 75% cORR across all treatment regimens with median DOR of 16.4 months
    - Zanidatamab + CAPOX: 92% cORR with 9 of 12 responses ongoing (range: 2.7, 15.2+ months)
    - Zanidatamab + FP: 100% cORR with 1 of 2 responses ongoing (range: 6.8, 12.5+ months)
  - Median PFS was 12.0 months, with a median follow-up of 6.9 months
- TRAEs are generally consistent with previous reports of zanidatamab and/or the chemotherapy regimens
  - Diarrhea is the most frequent TRAE observed across treatment regimens, is manageable in the outpatient setting, and is mitigated by prophylaxis
  - No severe (grade ≥ 3) infusion-related reactions or cardiac events were observed
- Based on these results, a randomized, global phase 3 study (HERIZON-GEA-01) is planned to begin enrollment in 2021 and will evaluate zanidatamab + chemotherapy (CAPOX or FP) ± the PD-1 inhibitor tislelizumab for first-line treatment of locally advanced, unresectable, or metastatic HER2-positive GEA

References

1. Abrahao-Machado LF, et al. *World J Gastroenterol*. 2016;22(19):4619-4625.
2. Van Cutsem E, et al. *Gastric Cancer*. 2015;18(3):476-484.
3. Stroes CI, et al. *Cancer Treat Rev*. 2021;99:102249.
4. Weisser N, et al. Presented at: American Association for Cancer Research Annual Meeting; April 10-15, May 17-21, 2021. Virtual. Abstract 1005.
5. Meric-Bernstam F, et al. Presented at: American Society of Clinical Oncology Gastrointestinal Cancers Symposium; January 15-17, 2021. Virtual. Abstract 164.
6. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT04276493. Accessed Aug 25, 2021.
7. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03929666. Accessed Aug 25, 2021.

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-ZW25-201 study is sponsored by Zymeworks Inc.

*Corresponding author: kug@mskcc.org

Presented at the European Society for Medical Oncology (ESMO) Congress, September 16 – 21, 2021

Disclosures: KUG has disclosed the following: Speaker, consultant, advisory role for Apexigen, BMS, Eli Lilly, Merck, Pieris, Zymeworks; research funding from Arog, AstraZeneca, BM, Daiichi Sankyo, Merck, Oncolys, Pieris, Zymeworks.