Zanidatamab + Chemotherapy as First-line Treatment for HER2-expressing Metastatic Gastroesophageal Adenocarcinoma (mGEA)

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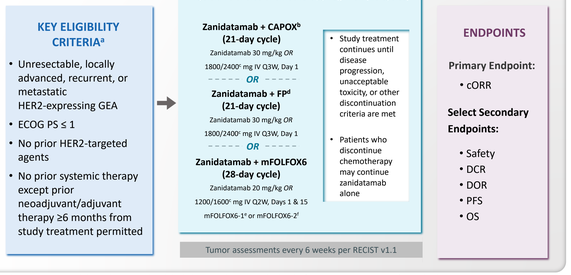
Background and Methods

- Overexpression of HER2 has been reported in approximately 20% of GEA (gastric, esophageal, and gastroesophageal junction [GEJ] adenocarcinomas), yet HER2-targeted treatments for mGEA are limited.[1,2,3]
- **Zanidatamab is a bispecific antibody (directed at ECD4 and ECD2 of HER2)** with unique binding properties and mechanisms of action that include enhanced receptor clustering, internalization & downregulation vs trastuzumab. Zanidatamab also activates immune-mediated responses, including antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity.[4,5]
- **Zanidatamab has demonstrated encouraging safety and antitumor activity in phase 1 studies,** including in patients with mGEA.[6,7]
- **The primary objective of this phase 2, open-label study** (NCT03929666) is to evaluate the antitumor activity of zanidatamab + standard first-line combination chemotherapy in patients with HER2-expressing mGEA (Figure 1).[8,9]

Figure 1: Study Design



Note: All patients received prophylaxis with acetaminophen, diphenhydramine, and corticosteroid with each infusion to prevent or attenuate infusion-related reactions.
a. The initial safety cohort 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 patients 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 Q3W, Day 1. **c.** Two-tiered flat dose for subjects <70 kg/≥70 kg. **d.** FP: cisplatin 80 mg/m^2 IV Q3W, Day 1; 5-fluorouracil (5-FU) 800 mg/m^2/day IV, continuous Days 1-5. **e.** mFOLFOX6-1: leucovorin 400 mg/m^2 IV Q2W, Days 1 and 15; oxaliplatin 85 mg/m^2 IV Q2W, Days 1 and 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 and 15. **f.** mFOLFOX6-2 is the same as mFOLFOX6-1 but omits the 5-FU 400 mg/m^2 IV Q2W dose on Days 1 and 15.
cORR = confirmed objective response rate; CR = complete response; DCR = disease control rate (defined as best response of CR, PR, or SD); DOR = duration of response (defined as time from first objective response that is subsequently confirmed until documented PD or death from any cause ≤ 30 days of last study treatment); ECOG PS = Eastern Cooperative Oncology Group performance status; OS = overall survival (defined as the time from the first dose of study treatment to the date of death from any cause); PD = progressive disease; PFS = progression-free survival (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); PR = partial response; SD = stable disease.

Results

Disposition and Baseline Characteristics

Data were extracted on October 17, 2022, from an unlocked database:

- A total of 46 patients with mGEA were enrolled from 15 sites in Canada (n=8), South Korea (n=14), and the US (n=24), between August 29, 2019, and February 18, 2022; enrollment of patients with mGEA is complete.
- Median duration of follow-up was 26.5 months (interquartile range: 17.8 – 32.4 months).
- 19 patients (41%) are continuing with zanidatamab treatment and 27 patients (59%) have discontinued zanidatamab:
  - Reasons for discontinuation: disease progression (n=20); adverse event (n=5); physician decision (n=1); other (n=1)

Table 1: Demographics and Disease Characteristics

	All Patients (N=46)
Median age (range), years	58 (26-82)
Male sex, n (%)	39 (85)
Race, n (%)	
Asian	17 (37)
White	28 (61)
Unknown	1 (2)
Ethnicity, n (%)	
Hispanic or latino	3 (7)
Not hispanic or latino	43 (93)
ECOG Performance Status, n (%)	
0	26 (57)
1	20 (43)
Primary tumor location, n (%)	
Esophageal	11 (24)
GEJ	16 (35)
Gastric	19 (41)
Stage IV disease at initial diagnosis, n (%)	38 (83)
HER2-positive[a] per central testing, n (%)	42 (91)
IHC 3+	37 (80)
IHC 2+/FISH+	5 (11)

a. HER2-positive was defined as IHC 3+ or IHC 2+/FISH+ by central review; for Part 1 local testing was permitted for enrollment followed by retrospective central review.
ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence *in situ* hybridization; IHC = immunohistochemistry.

Results

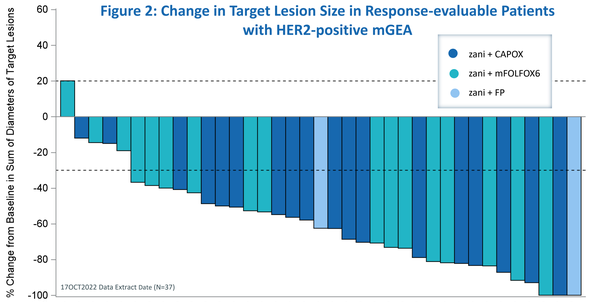
Efficacy

Table 2: Response Rates and DOR in Patients with HER2-positive mGEA (Response-evaluable)

	Zanidatamab + CAPOX (n =18)	Zanidatamab + mFOLFOX6 (n = 18)	Zanidatamab + FP (n = 2)	Total (N = 38)
Confirmed objective response rate[a], % (95% CI)	89 (65, 99)	67 (41, 87)	100 (16, 100)	79 (63, 90)
Confirmed best overall response, n (%)				
Complete response	2 (11)	1 (6)	0	3 (8)
Partial response	14 (78)	11 (61)	2 (100)	27 (71)
Stable disease	2 (11)	3 (17)	0	5 (13)
Progressive disease	0	3 (17)	0	3 (8)
Disease control rate, % (95% CI)	100 (82, 100)	83 (59, 96)	100 (16, 100)	92 (79, 98)
Median duration of response (95% CI), months	10.4 (5.7, NE)	NE (2.8, NE)	NE (6.8, NE)	20.4 (8.3, NE)

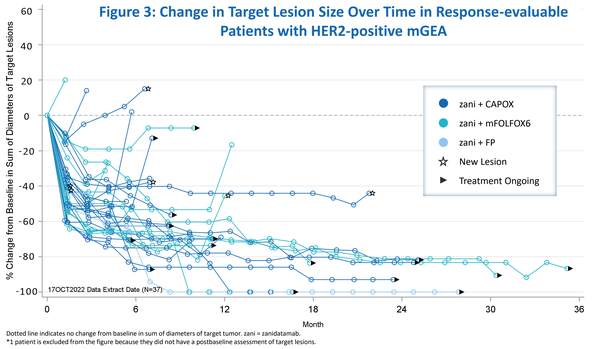
a. Based on a baseline scan and a confirmatory scan obtained ≥4 weeks following initial documentation of objective response.
CI = confidence interval; DOR = duration of response; NE = not estimable.

Figure 2: Change in Target Lesion Size in Response-evaluable Patients with HER2-positive mGEA



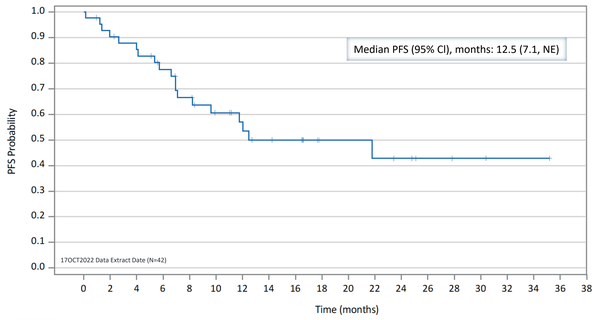
Dotted lines indicate 20% increase and 30% decrease in sum of diameters of target tumors.
CA = primary tumor type; E = esophageal cancer; F = flat dosing regimen; FISH = fluorescence in situ hybridization; G = gastric cancer; IHC = immunohistochemistry; J = gastroesophageal junction adenocarcinoma; W = weight-based dosing regimen; ZDR = zanidatamab dosing regimen; zani = zanidatamab
*1 patient is excluded from the figure because they did not have a postbaseline assessment of target lesions.

Figure 3: Change in Target Lesion Size Over Time in Response-evaluable Patients with HER2-positive mGEA



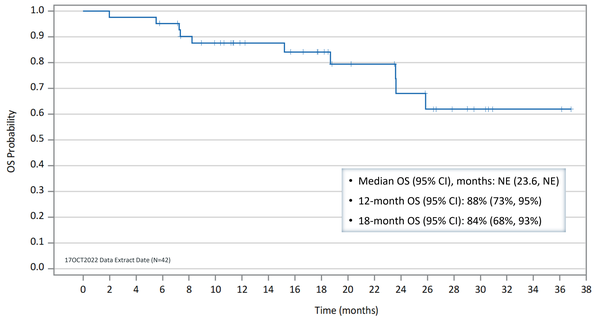
Dotted line indicates no change from baseline in sum of diameters of target tumor. zani = zanidatamab.
*1 patient is excluded from the figure because they did not have a postbaseline assessment of target lesions.

Figure 4: Progression-free Survival in Patients with HER2-positive mGEA



CI = confidence interval; NE = not estimable; PFS = progression-free survival

Figure 5: Overall Survival in Patients with HER2-positive mGEA



CI = confidence interval; NE = not estimable; OS = overall survival

Safety

- Similar to previous reports[8], diarrhea was the most common treatment (zanidatamab and/or chemotherapy)-related AE (Table 3).
- Antidiarrheal prophylaxis (loperamide ≥ 7 days during Cycle 1) was implemented after the first 25 patients were treated, which reduced the incidence of treatment-related Grade ≥3 diarrhea:
  - Incidence before vs after use of antidiarrheal prophylaxis was mandated: 13/25 (52%) patients vs 3/21 (14%) patients
- Events of treatment-related Grade ≥3 diarrhea predominantly occurred in Cycle 1 and the median duration of events in all cycles was 3 days (interquartile range: 2-5).

Table 3: Summary of Treatment (Zanidatamab and/or Chemotherapy)-related Adverse Events (TRAEs)

	Zanidatamab + CAPOX (n =20)		Zanidatamab + mFOLFOX6 (n = 24)		Zanidatamab + FP (n = 2)		Total (N = 46)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any TRAE[a]	20 (100)	9 (45)	24 (100)	18 (75)	2 (100)	1 (50)	46 (100)	28 (61)
Treatment-related SAE	2 (10)	2 (10)	5 (21)	5(21)	1 (50)	1 (50)	8 (17)[b]	8(17)
TRAEs leading to zanidatamab DC	0	0	3 (13)	1 (4)	0	0	3 (7)[c]	1 (2)
TRAEs, any Grade occurring in ≥ 20% of patients or Grade ≥ 3 in ≥ 2 patients (based on the Total group)								
Diarrhea	18 (90)	6 (30)	23 (96)	9 (38)	2 (100)	1 (50)	43 (93)	16 (35)
Nausea	15 (75)	1 (5)	20 (83)	2 (8)	1 (50)	0	36 (78)	3 (7)
Peripheral neuropathy	14 (70)	0	14 (58)	0	0	0	28 (61)	0
Fatigue	6 (30)	0	14 (58)	2 (8)	0	0	20 (43)	2 (4)
Decreased appetite	7 (35)	0	12 (50)	0	1 (50)	0	20 (43)	0
Vomiting	4 (20)	1 (5)	11 (46)	3 (13)	0	0	15 (33)	4 (9)
Hypokalemia	2 (10)	0	11 (46)	7 (29)	0	0	13 (28)	7 (15)
Stomatitis	2 (10)	0	9 (38)	0	0	0	11 (24)	0
Neutrophil count decr.	3 (15)	0	7 (29)	3 (13)	0	0	10 (22)	3 (7)
Hypomagnesemia	3 (15)	0	6(25)	1 (4)	0	0	9 (20)	1 (2)
Dysgeusia	4 (20)	0	5(21)	0	0	0	9 (20)	0
Acute kidney injury	0	0	2(8)	1 (4)	1 (50)	1 (50)	3 (7)	2 (4)
WBC count decreased	0	0	7 (29)	3 (13)	0	0	7 (15)	3 (7)
Treatment-related AESIs occurring in any patient								
Infusion-related reaction	6 (30)	0	3 (13)	0	1 (50)	0	10 (22)	0
Ejection fraction decr.	0	0	2 (8)	0	0	0	2 (4)	0
Pneumonitis	0	0	0	0	0	0	0	0

Data are reported as number of patients, n (%). **a.** All AEs were recorded using the Medical Dictionary for Regulatory Activities (MedDRA) with severity graded by investigators according to the National Cancer institute Common Terminology Criteria for Adverse Events version 5.0. **b.** Treatment-related SAEs: diarrhea (3 patients), acute kidney injury (2 patients), vomiting (2 patients), hypokalemia (2 patients), hypomagnesemia (1 patient), nausea (1 patient), stomatitis (1 patient), upper GI hemorrhage (1 patient) **c.** Treatment-related adverse events that led to discontinuation of zanidatamab: diarrhea (2 patients), vomiting (1 patient).
AESI = adverse event of special interest; DC = discontinuation; SAE = serious adverse event; WBC = white blood cell.

Conclusions

- Zanidatamab combined with standard chemotherapy is a highly active treatment regimen for first-line therapy of patients with HER2-positive metastatic or advanced GEA.
  - This maturing data set demonstrates durable disease control with encouraging cORR, DOR, PFS, and OS
  - With a median follow-up of 26.5 months, median OS is not yet reached
- The safety profile of zanidatamab + standard first-line chemotherapy with antidiarrheal prophylaxis is manageable and consistent with the observed safety profiles for other standard combination regimens for patients with HER2-positive GEA.
- A global phase 3 study (HERIZON-GEA-01; NCT05152147; EudraCT 2020-000459) to evaluate zanidatamab + physician's choice of chemotherapy with or without the PD-1 inhibitor tislelizumab for first-line treatment of locally advanced, unresectable, or metastatic HER2-positive GEA is currently enrolling.

References and Acknowledgements

1. Abrahao-Machado LF, et al. *World J Gastroenterol*. 2016;22(19):4619-4625; 2. Van Custem 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. Weisser N, et al. Presented at: American Association for Cancer Research Annual Meeting; Apr 1-5, 2017. Washington, DC. Abstract 31; 6. Meric-Bernstam F, et al. Presented at: American Society of Clinical Oncology Gastrointestinal Cancers Symposium; January 15–17, 2021. Virtual. Abstract 164; 7. Lee K-W, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 3-7, 2022. Chicago, IL. Abstract 4032; 8. Ku G, et al. Presented at: European Society of Medical Oncology Congress; September 16-21, 2021. Abstract 1380P; 9. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03929666. Accessed October 31, 2022.

We sincerely thank all patients and their families. We thank all the investigators, clinical study researchers, personnel, and staff who contributed to the various study activities.

ZW25-201 study is sponsor Zymeworks BC Inc.

Abstract #: 347

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Presented at the ASCO Gastrointestinal Cancers Symposium in San Francisco, CA from January 19-21, 2023

E. Elimova has disclosed the following: consulting or advisory roles with Bristol-Myers Squibb, Zymeworks, Adaptimmune, and BeiGene; research funding from Bristol-Myers Squibb, Zymeworks, AstraZeneca Canada, and Bold Therapeutics; a direct family member is employed by Merck.