Zanidatamab (ZW25), a HER2-Targeted Bispecific Antibody, in Combination With Chemotherapy and Tislelizumab in Patients With Advanced HER2-Positive Gastric/Gastroesophageal Junction Adenocarcinoma: Updated Results From a Phase 1b/2 Study

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Conclusions

Zanidatamab, in combination with tislelizumab and capecitabine-oxaliplatin (CAPOX), showed promising antitumor activity as a first-line therapy for patients with gastric and gastroesophageal junction cancer (GC/GEJC).

This combination therapy regimen had a tolerable safety profile with durable responses. The phase 3 HERIZON-GEA-01 trial (NCT05152147) evaluating the regimen of zanidatamab and CAPOX, with or without tislelizumab, is ongoing.[1]

Background

Gastric cancers are among the most common cancers globally, with over one million new cases estimated to have been diagnosed in 2020.[2] Targeted therapy is an option in patients with human epidermal growth factor receptor 2 (HER2) overexpression, which occurs in 12-25% of GC/GEJC and up to 30% of GEJC.[3,4]

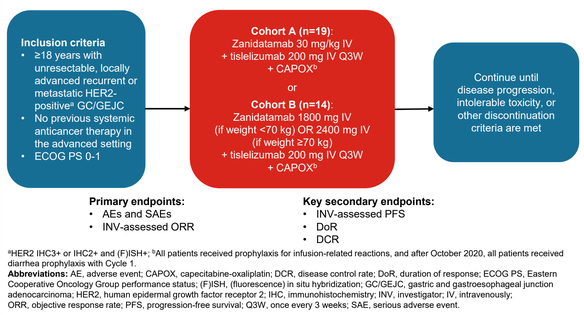
Zanidatamab (ZW25) is a humanized, bispecific, monoclonal antibody in development for the treatment of HER2-expressing cancers, including HER2-positive GC/GEJC.[1] Zanidatamab has been shown to be well tolerated and have durable antitumor activity in combination with chemotherapy as first-line therapy for GC/GEJC.[5]

Tislelizumab is a humanized immunoglobulin G4 monoclonal antibody with high affinity and binding specificity for programmed cell death protein 1 (PD-1).[6] Preliminary results from a phase 1b/2 study demonstrated promising efficacy outcomes and a tolerable safety profile in patients with HER2-positive GC/GEJC receiving zanidatamab in combination with tislelizumab and standard first-line chemotherapy (NCT04276493).[7]

Here we present updated data from the phase 1b/2 study on the safety and antitumor activity of zanidatamab in combination with tislelizumab and CAPOX for untreated, unresectable, locally advanced/metastatic HER2-positive GC/GEJC, following enrollment completion.

Methods

Figure 1. Study Design



[a]HER2 IHC3+ or IHC2+ and (F)ISH+; [b]All patients received prophylaxis for infusion-related reactions, and after October 2020, all patients received diarrhea prophylaxis with Cycle 1.
Abbreviations: AE, adverse event; CAPOX, capecitabine-oxaliplatin; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; (F)ISH, (fluorescence) in situ hybridization; GC/GEJC, gastric and gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; INV, investigator; IV, intravenously; ORR, objective response rate; PFS, progression-free survival; Q3W, once every 3 weeks; SAE, serious adverse event.

Results

Patients

- Baseline characteristics and demographics are presented in **Table 1**
- At data cutoff (November 22, 2022), a total of 13 patients (39.4%) remained on treatment after a median study follow-up of 18.2 months (range: 2.1-30.9)

Safety

- Twenty-two patients (66.7%) experienced at least one grade ≥3 treatment-related adverse event (TRAE) (**Table 2**)
- Two patients (6.1%) died as a result of TRAEs (one from lung infection and pneumonitis and the other of sudden death)
- The most common TRAEs of any grade were diarrhea (100%), nausea (63.6%), and decreased appetite (48.5%) (**Table 2**). Nine patients (27.3%) experienced immune-mediated adverse events

Table 1. Demographics and Baseline Characteristics

	Cohort A (n=19)	Cohort B (n=14)	Total (N=33)
Median age, years (range)	66.0 (29-80)	61.5 (42-72)	64.0 (29-80)
Race, Chinese/Korean, n (%)	4 (21.1)/ 15 (78.9)	4 (28.6)/ 10 (71.4)	8 (24.2)/ 25 (75.8)
Male sex, n (%)	17 (89.5)	12 (85.7)	29 (87.9)
ECOG PS, 0/1, n (%)	5 (26.3)/ 14 (73.7)	6 (42.9)/ 8 (57.1)	11 (33.3)/ 22 (66.7)
HER2 status (by local lab), n (%)			
IHC3+	16 (84.2)	9 (64.3)	25 (75.8)
IHC2+/(F)ISH+	3 (15.8)	5 (35.7)	8 (24.2)
Location of primary cancer, n (%)			
Gastroesophageal junction/Stomach	4 (21.1)/ 15 (78.9)	1 (7.1)/ 13 (92.9)	5 (15.2)/ 28 (84.8)
Visceral metastases at study entry,[a] n (%)	17 (89.5)	12 (85.7)	29 (87.9)
Liver/Lung	11 (57.9)/ 4 (21.1)	7 (50.0)/ 4 (28.6)	18 (54.5)/ 8 (24.2)
PD-L1 score, ≥5%/<5%,[b] n (%)	12 (63.2)/ 7 (36.8)	6 (42.9)/ 7 (50.0)	18 (54.5)/ 14 (42.4)

[a]Other visceral metastases were present in 12 patients in Cohort A and six in Cohort B, and included pleural and peritoneal involvement and other visceral metastases to the adrenal gland, spleen, etc; [b]PD-L1 positivity was assessed using the tumor area positivity score, which is defined as the total percentage of tumor area covered with tumor cells with PD-L1 membrane staining, and tumor-associated immune cells with PD-L1 staining, at any intensity, as visually estimated using VENTANA PD-L1 (SP263) assay. PD-L1 score was not available for one patient in Cohort B. **Abbreviations:** ECOG PS, Eastern Cooperative Oncology Group performance status; (F)ISH, (fluorescence) in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PD-L1, programmed death-ligand 1.

Table 2. Safety Summary of Adverse Events

	Cohort A (n=19)		Cohort B (n=14)		Total (N=33)	
Patients with ≥1 TRAE[a]	19 (100.0)		14 (100.0)		33 (100.0)	
Grade ≥3 TRAE	13 (68.4)		9 (64.3)		22 (66.7)	
Serious TRAEs	7 (36.8)		4 (28.6)		11 (33.3)	
TRAEs leading to treatment discontinuation[b]	2 (10.5)		0 (0)		2 (6.1)	
TRAEs leading to death	2 (10.5)		0 (0)		2 (6.1)	
Most common TRAEs[c]	**Any Grade**	**≥Grade 3**	**Any Grade**	**≥Grade 3**	**Any Grade**	**≥Grade 3**
Diarrhea	19 (100.0)	7 (36.8)	14 (100.0)	2 (14.3)	33 (100.0)	9 (27.3)
Nausea	11 (57.9)	1 (5.3)	10 (71.4)	0 (0)	21 (63.6)	1 (3.0)
Decreased appetite	10 (52.6)	2 (10.5)	6 (42.9)	0 (0)	16 (48.5)	2 (6.1)
Vomiting	7 (36.8)	0 (0)	6 (42.9)	0 (0)	13 (39.4)	0 (0)
Peripheral sensory neuropathy	8 (42.1)	0 (0)	4 (28.6)	0 (0)	12 (36.4)	0 (0)
Pyrexia	8 (42.1)	0 (0)	4 (28.6)	0 (0)	12 (36.4)	0 (0)
PPED syndrome	8 (42.1)	1 (5.3)	2 (14.3)	0 (0)	10 (30.3)	1 (3.0)

Data are n (%). Adverse events were recorded using the Medical Dictionary for Regulatory Activities version 25.0, with severity graded by the investigator 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]Any-grade TRAEs in ≥30% of patients of any grade in the total safety analysis set. **Abbreviations:** PPED, palmar-plantar erythrodysesthesia; TRAE, treatment-related adverse event.

Efficacy

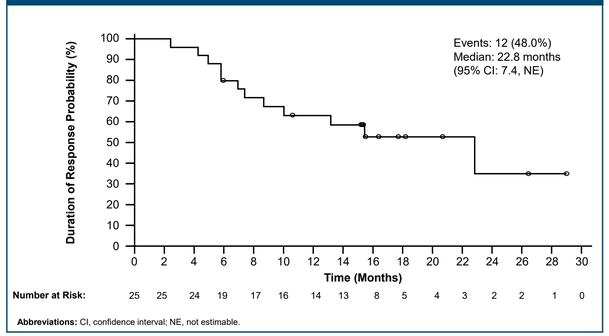
- Confirmed objective response rate by investigator (INV) was 75.8% (**Table 3**). Median duration of response was 22.8 months (95% confidence interval [CI]: 7.4, not estimable) (**Figure 2**)
- Median progression-free survival was 16.7 months (95% CI: 8.2, not estimable) (**Figure 3**)
- Treatment duration with overall response by INV is shown in **Figure 4**

Table 3. Disease Response[a]

	Cohort A (n=19)	Cohort B (n=14)	Total (N=33)
Confirmed BOR,[b] n (%)			
Complete response	1 (5.3)	0 (0)	1 (3.0)
Partial response	14 (73.7)	10 (71.4)	24 (72.7)
Stable disease	4 (21.1)	4 (28.6)	8 (24.2)
Progressive disease	0 (0)	0 (0)	0 (0)
Confirmed ORR,[b] % (95% CI)	78.9 (54.4, 93.9)	71.4 (41.9, 91.6)	75.8 (57.7, 88.9)
Confirmed DCR,[b] % (95% CI)	100.0 (82.4, 100.0)	100.0 (76.8, 100.0)	100.0 (89.4, 100.0)
Median DoR,[b] months (95% CI)	15.4 (4.9, NE)	NE (7.4, NE)	22.8 (7.4, NE)

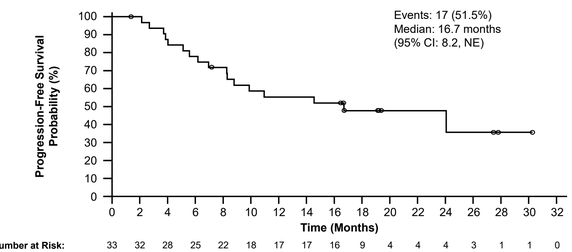
[a]In the efficacy-evaluable analysis set, which was defined as patients who received at least one dose of any study drug, had measurable disease at baseline according to RECIST version 1.1, and one or more postbaseline tumor assessment; [b]Per RECIST version 1.1 by investigator.
Abbreviations: BOR, best overall response; CI, confidence interval; DCR, disease control rate; DoR, duration of response; NE, not estimable; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours.

Figure 2. Duration of Response



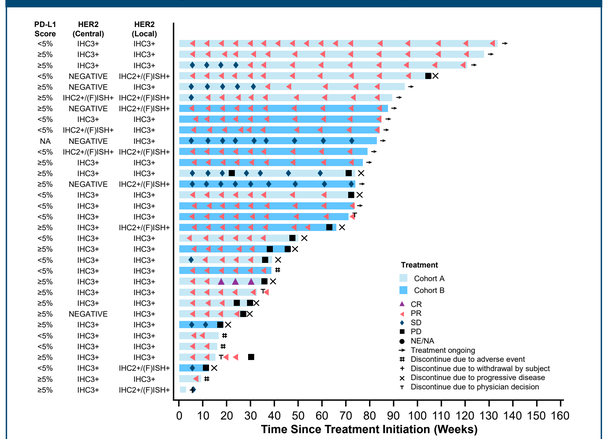
Abbreviations: CI, confidence interval; NE, not estimable.

Figure 3. Progression-Free Survival



Abbreviations: CI, confidence interval; NE, not estimable.

Figure 4. Treatment Duration and Response



Abbreviations: CR, complete response; (F)ISH, (fluorescence) in-situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NA, not applicable; NE/NA, not evaluable/not assessed; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease.

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Disclosures

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