Zanidatamab, a HER2-targeted bispecific antibody, in combination with tislelizumab and chemotherapy as first-line therapy for patients with advanced HER2-positive gastric/gastroesophageal junction adenocarcinoma: Preliminary results from a Phase 1b/2 study

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Conclusions

The combination of zanidatamab, tislelizumab and chemotherapy as a first-line therapy provided encouraging antitumor activity with a 75.8% confirmed objective response rate and 100% disease control rate for patients with HER2-positive gastric/gastroesophageal junction adenocarcinoma.

The combination of zanidatamab, tislelizumab and chemotherapy demonstrated a **manageable safety profile** as first-line therapy in patients with HER2-positive gastric/gastroesophageal junction adenocarcinoma with the incidence of TRAEs consistent with previous reports.[6]

Based on these results, a randomized, global Phase 3 study (HERIZON-GEA-01) has been initiated to investigate zanidatamab + chemotherapy ± tislelizumab for first-line treatment of locally advanced, unresectable, or metastatic HER2-positive gastroesophageal adenocarcinoma.[11]

Background

Over one million patients are diagnosed with gastric cancer every year worldwide, and it is the fourth most common cause of cancer-related deaths.[1] Human epidermal growth factor receptor 2 (HER2)-positive disease accounts for 15–25% of gastric cancers.[2] Zanidatamab (ZW25) is a novel HER2-targeted bispecific antibody.

Zanidatamab targets two non-overlapping extracellular domains of HER2. This results in potent antitumor activity compared to monospecific HER2 antibodies.[3,4] Zanidatamab has shown preliminary antitumor activity and tolerability in patients with HER2-positive gastroesophageal adenocarcinoma as monotherapy and with chemotherapy in Phase 1/2 studies (NCT02892123, NCT03929666).[5,6]

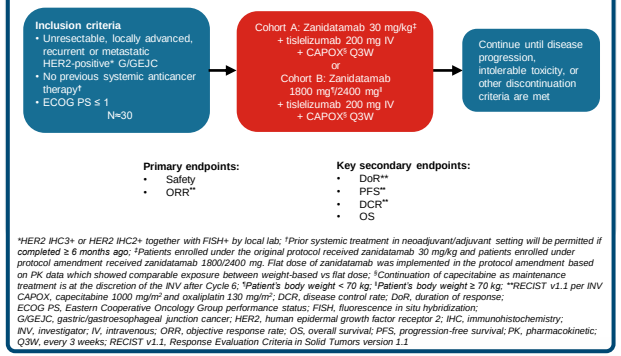
The unique binding properties of zanidatamab result in receptor clustering, internalization, and downregulation, the inhibition of growth factor-dependent and independent tumor cell proliferation, antibody-dependent cellular cytotoxicity and phagocytosis, and complement-dependent cytotoxicity.[7]

Tislelizumab, an anti-programmed cell death protein (PD)-1 antibody, is well tolerated and has antitumor activity alone and with chemotherapy in patients with advanced solid tumors.[8] Based on the mechanism of action of PD-1 inhibitors and HER2-targeted therapy, it has been hypothesized that blockade of both pathways could result in synergistic antitumor activity in HER2-positive malignancies.[9,10]

Methods

- This is an ongoing, open-label, multicenter, Phase 1b/2 study (NCT04276493; BGB-A317-ZW25-101)
- Here we describe the safety and preliminary antitumor activity of zanidatamab in combination with tislelizumab and chemotherapy in patients with advanced HER2-positive gastric/gastroesophageal junction cancer (G/GEJC) (**Figure 1**)

Figure 1. Study design



*HER2 IHC3+ or HER2 IHC2+ together with FISH+ by local lab; †Prior systemic treatment in neoadjuvant/adjuvant setting will be permitted if completed ≥ 6 months ago; ‡Patients enrolled under the original protocol received zanidatamab 30 mg/kg and patients enrolled under protocol amendment received zanidatamab 1800/2400 mg. Flat dose of zanidatamab was implemented in the protocol amendment based on PK data which showed comparable exposure between weight-based vs flat dose; §Continuation of capecitabine as maintenance treatment is at the discretion of the INV after Cycle 6; ¶Patient's body weight < 70 kg; ‖Patient's body weight ≥ 70 kg; **RECIST v1.1 per INV
CAPOX, capecitabine 1000 mg/m² and oxaliplatin 130 mg/m²; DCR, disease control rate; DoR, duration of response;
ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization;
G/GEJC, gastric/gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry;
INV, investigator; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1*

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)
Male, n (%)	17 (89.5)	12 (85.7)	29 (87.9)
Race, n (%)			
Chinese	4 (21.1)	4 (28.6)	8 (24.2)
Korean	15 (78.9)	10 (71.4)	25 (75.8)
ECOG PS, n (%)			
0	5 (26.3)	6 (42.9)	11 (33.3)
1	14 (73.7)	8 (57.1)	22 (66.7)
Primary tumor location, n (%)			
Gastroesophageal junction	4 (21.1)	1 (7.1)	5 (15.2)
Stomach	15 (78.9)	13 (92.9)	28 (84.8)
HER2 status*, n (%)			
IHC3+	16 (84.2)	9 (64.3)	25 (75.8)
IHC2+/FISH+	3 (15.8)	5 (35.7)	8 (24.2)
PD-L1 score†, n (%)			
≥ 5%	12 (63.2)	5 (35.7)	17 (51.5)
< 5%	7 (36.8)	6 (42.9)	13 (39.4)
Liver metastases‡, n (%)	11 (57.9)	7 (50.0)	18 (54.5)

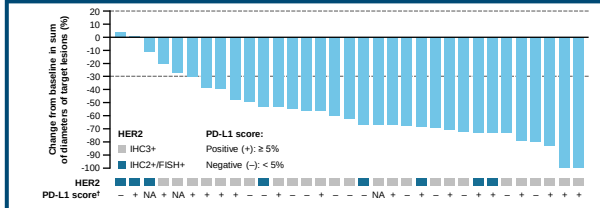
*All subjects had HER2 status confirmed by a local lab; †Assessed by tumor area positive score, which is defined as the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining, and tumor-associated immune cells with PD-L1 staining, at any intensity, as visually estimated using VENTANA PD-L1 (SP263) assay; the PD-L1 results of three patients were unavailable by data cut off and retested; ‡At study entry
ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization;
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PD-L1, programmed death-ligand 1*

Table 2. TRAEs occurring in ≥ 20% of patients

	Cohort A (n=19)		Cohort B (n=14)		Total (N=33)	
Events, n (%)	**Any grade**	**≥ Grade 3**	**Any grade**	**≥ Grade 3**	**Any grade**	**≥ Grade 3**
Patients with at least one event	19 (100.0)	12 (63.2)	14 (100.0)	8 (57.1)	33 (100.0)	20 (60.6)
Diarrhea	18 (94.7)	7 (36.8)	14 (100.0)	1 (7.1)	32 (97.0)	8 (24.2)
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)
Hypokalemia	6 (31.6)	2 (10.5)	3 (21.4)	0 (0)	9 (27.3)	2 (6.1)
Palmar-plantar erythrodysesthesia syndrome	6 (31.6)	1 (5.3)	2 (14.3)	0 (0)	8 (24.2)	1 (3.0)
Fatigue	4 (21.1)	1 (5.3)	3 (21.4)	1 (7.1)	7 (21.2)	2 (6.1)
Stomatitis	5 (26.3)	0 (0)	2 (14.3)	0 (0)	7 (21.2)	0 (0)
Weight decrease	4 (21.1)	0 (0)	3 (21.4)	0 (0)	7 (21.2)	0 (0)

*Adverse events were recorded using the Medical Dictionary for Regulatory Activities (MedDRA), with severity graded by investigators using NCI CTCAE v5.0. Two subjects experienced Grade 5 TRAEs; one subject developed Grade 5 pneumonitis and pneumonia, and one subject experienced sudden death
NCI CTCAE, National Cancer Institute common terminology criteria for adverse events; TRAE, treatment-related adverse event*

Figure 2. Best change in target lesion size*



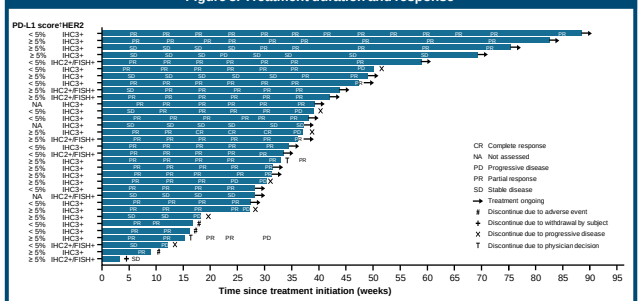
*per RECIST v1.1 by investigators; †Assessed by tumor area positive score, which is defined as the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining, and tumor-associated immune cells with PD-L1 staining, at any intensity, as visually estimated using VENTANA PD-L1 (SP263) assay
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NA, not available; PD-L1, programmed death-ligand 1*

Table 3. Disease response*

	Cohort A (n=19)	Cohort B (n=14)	Total (N=33)
Confirmed ORR, n (%) **95% CI**	15 (78.9) 54.4, 94.0	10 (71.4) 41.9, 91.6	25 (75.8) 57.7, 88.9
Complete response, n (%)	1 (5.3)	0 (0)	1 (3.0)
Partial response, n (%)	14 (73.7)	10 (71.4)	24 (72.7)
Stable disease†, n (%)	4 (21.1)	4 (28.6)	8 (24.2)
Progressive disease, n (%)	0 (0)	0 (0)	0 (0)
DCR, n (%) **95% CI**	19 (100.0) 82.4, 100.0	14 (100.0) 76.8, 100.0	33 (100.0) 89.4, 100.0
DoR (months), min, max†	2.1+, 18.2+	4.2+, 7.2+	2.1+, 18.2+

*per RECIST v1.1 by investigators; †28% of patients with a confirmed response had DoR events
+, censored; CI, confidence interval; DCR, disease control rate; DoR, duration of response; ORR, objective response rate*

Figure 3. Treatment duration and response*



*per RECIST v1.1 by investigators; †Assessed by tumor area positive score, which is defined as the total percentage of the tumor area covered by 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
CR, complete response; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NA, not assessed; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease*

Results

Patients

- As of January 5, 2022, 33 patients were enrolled in the study. Patients received 30 mg/kg (n=19) or 1800/2400 mg (n=14) zanidatamab, in combination with tislelizumab and CAPOX (**Table 1**)
- The last patient in the study was enrolled on June 28, 2021. The study is ongoing
- Median study follow-up was 9.0 months (range: 2.1–20.3) and the median number of treatment cycles was 11 (range: 1–30). At the data cutoff, 20 patients (60.6%) remained on treatment

Safety

- All patients experienced at least one treatment-related adverse event (TRAE), and 20 patients (60.6%) experienced at least one ≥ Grade 3 TRAE
- The most common TRAEs (considered by the investigator to be related to any component of the study treatment) were diarrhea (32 patients; 97.0%), nausea (21 patients; 63.6%), decreased appetite (16 patients; 48.5%); the most common ≥ Grade 3 TRAEs were diarrhea (eight patients; 24.2%) (**Table 2**), and lipase increased (three patients; 9.1%)
- Immune-mediated AEs (imAEs) occurred in nine patients (27.3%) of which seven (21.2%) were ≥ Grade 3. Lipase increase was the only ≥ Grade 3 imAE to occur in more than one patient (two patients; 6.1%). ImAEs which led to tislelizumab discontinuation occurred in three patients, and included pneumonitis and immune hepatitis
- Due to early onset of Grade 3 diarrhea in some subjects, mandatory prophylaxis with loperamide (4 mg twice daily × ≥ 7 days) was initiated for the first treatment cycle and if subjects developed ≥ Grade 2 diarrhea during cycle 1 of therapy, prophylaxis should be continued with subsequent cycles (implemented October 30, 2020)
  - In the nine subjects who initiated treatment without antidiarrheal prophylaxis, the incidence of Grade 3 diarrhea and serious diarrhea was 33.3% (three patients) and 22.2% (two patients), respectively
  - In the 24 subjects who initiated treatment with antidiarrheal prophylaxis, the incidence of Grade 3 diarrhea and serious diarrhea was 20.8% (five patients) and 4.2% (one patient), respectively

Efficacy

- The best percentage change in target lesion size is shown in **Figure 2**
- Confirmed objective response rate was 75.8% (95% CI: 57.7, 88.9) and the disease control rate was 100% (95% CI: 89.4, 100.0) (**Table 3**). The treatment duration with overall response is shown in **Figure 3**
- At the data cutoff, median progression-free survival (PFS) was 10.9 months (95% CI: 8.2, non-estimable), with 36.4% of patients having PFS events

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