HERIZON-GEA-01: A Phase 3 Study of Zanidatamab in Combination With Chemotherapy With or Without Tislelizumab in First-Line Human Epidermal Growth Factor Receptor 2 Positive (HER2+) Advanced/Metastatic Gastroesophageal Adenocarcinoma (GEA)

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Background

- Gastroesophageal adenocarcinomas (GEAs), including gastric, esophageal, and gastroesophageal junction (GEJ) adenocarcinomas, are common cancers with high morbidity and mortality
- HER2 is overexpressed or amplified in ~20% of patients with GEA, and trastuzumab + chemotherapy is the standard of care first-line therapy for these patients in the locally advanced or metastatic setting[1]
- Current median survival for advanced HER2+ GEA remains <2 years[2] and ongoing research with novel agents is attempting to improve outcomes
- Preliminary reports from recent studies suggest that dual targeting of the HER2 and PD-1 pathways may improve upon the results achieved with targeting either HER2 or PD-1 alone[3]

Zanidatamab

- Zanidatamab (also known as ZW25) is a novel, bispecific HER2-targeted monoclonal antibody that binds to two non-overlapping extracellular domains (ECD4 and ECD2) on HER2
- This unique bispecific binding results in multiple mechanisms of action, including formation of HER2 clusters and receptor internalization resulting in downregulation of HER2 on the cell surface, inhibition of growth factor-dependent and -independent tumor cell proliferation, as well as activation of antibody-dependent cellular cytotoxicity (ADCC), cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC)[4-6]
- In early-phase studies, zanidatamab has demonstrated encouraging antitumor activity in HER2-expressing cancers, including HER2+ GEA
  - In a phase 2 study in the first-line setting (NCT03929666), preliminary results of zanidatamab + chemotherapy demonstrated a confirmed ORR of 75.0% and a tolerable safety profile (**Table 1, Figure 1**[7])

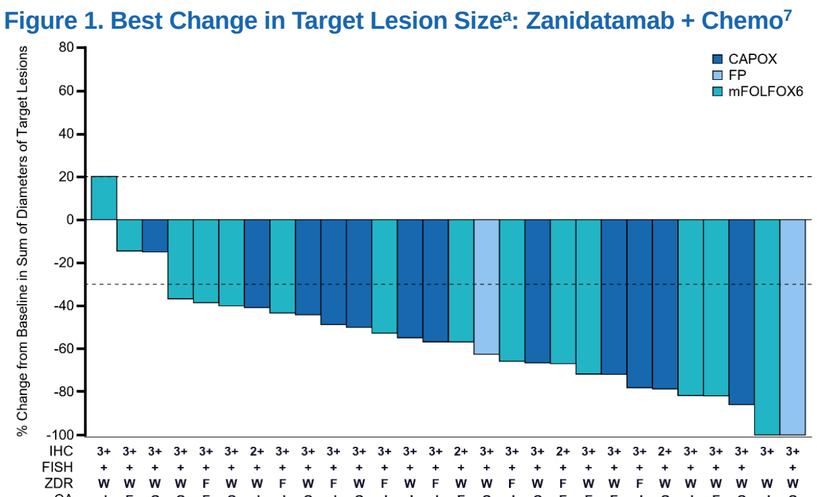
Table 1. Zanidatamab + Chemo: Efficacy and Safety[7]

	Total patients[a] (N=28)
Confirmed ORR, % (95% CI)	75.0 (55.1-89.3)
Median DOR, months (range)	16.4 (1.4-19.8+)
Median PFS, months (95% CI)	12.0 (6.9-NE)
Most common TRAEs (in ≥50% patients), n (%)	
Diarrhea	34 (94)
Nausea	27 (75)
Peripheral neuropathy	19 (53)

[a]Efficacy-evaluable population, defined as all HER2+ (IHC 3+ or IHC 2+/ISH+) patients who had ≥1 evaluable postbaseline disease assessment or discontinued study treatment due to death or clinical progression.

Abbreviations: CI, confidence interval; DOR, duration of response; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; TRAEs, treatment-related adverse events.

Figure 1. Best Change in Target Lesion Size[a]: Zanidatamab + Chemo[7]



[a]Per RECIST v1.1 by investigators.

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

Tislelizumab

- Tislelizumab is a humanized monoclonal antibody against programmed cell death protein 1 (PD-1) that is under clinical development for the treatment of several cancer types
- Tislelizumab binds to the extracellular domain of human PD-1 with high specificity and affinity and competitively blocks PD-L1 and PD-L2 binding, thus inhibiting PD-1-mediated negative signaling in T cells[8,9]
- Tislelizumab was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a potential mechanism of resistance to anti-PD-1 therapy[9]
- Tislelizumab in combination with zanidatamab and chemotherapy has demonstrated encouraging antitumor activity in HER2+ gastric/GEJ adenocarcinoma
  - In a phase 1b/2 trial in the first-line setting (NCT04276493), preliminary results of zanidatamab + chemotherapy + tislelizumab demonstrated a confirmed ORR of 75.8%[10] (**Table 2, Figure 2**). Immune-mediated AEs did not affect the overall safety assessment[10]

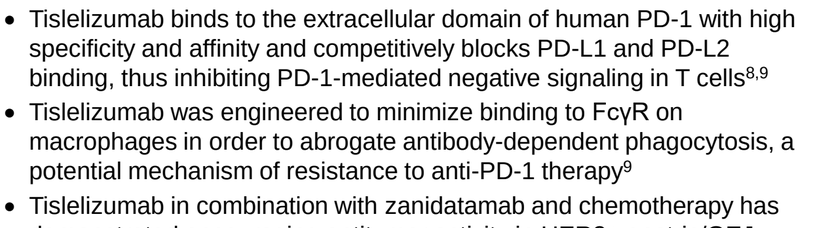
Table 2. Zanidatamab + Chemo + Tislelizumab: Efficacy and Safety[10]

	Total patients (N=33)
Confirmed ORR, % (95% CI)	75.8 (57.7-88.9)
DCR, % (95% CI)	100 (89.4-100.0)
DOR (months), min, max[a]	2.1+, 18.2+
Most common TRAEs (in ≥50% patients), n (%)	
Diarrhea	32 (97.0)
Nausea	21 (63.6)

[a]28% of patients with a confirmed response had DOR events.

Abbreviations: CI, confidence interval; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; TRAEs, treatment-related adverse events.

Figure 2. Best Change in Target Lesion Size[a]: Zanidatamab + Chemo + Tislelizumab[10]



[a]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.

Abbreviations: HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NA, not available; PD-L1, programmed death-ligand 1.

- Given the encouraging results from early-phase studies, the HERIZON-GEA-01 study will further investigate the efficacy and safety of first-line zanidatamab + chemotherapy ± tislelizumab in patients with advanced/metastatic HER2+ GEA

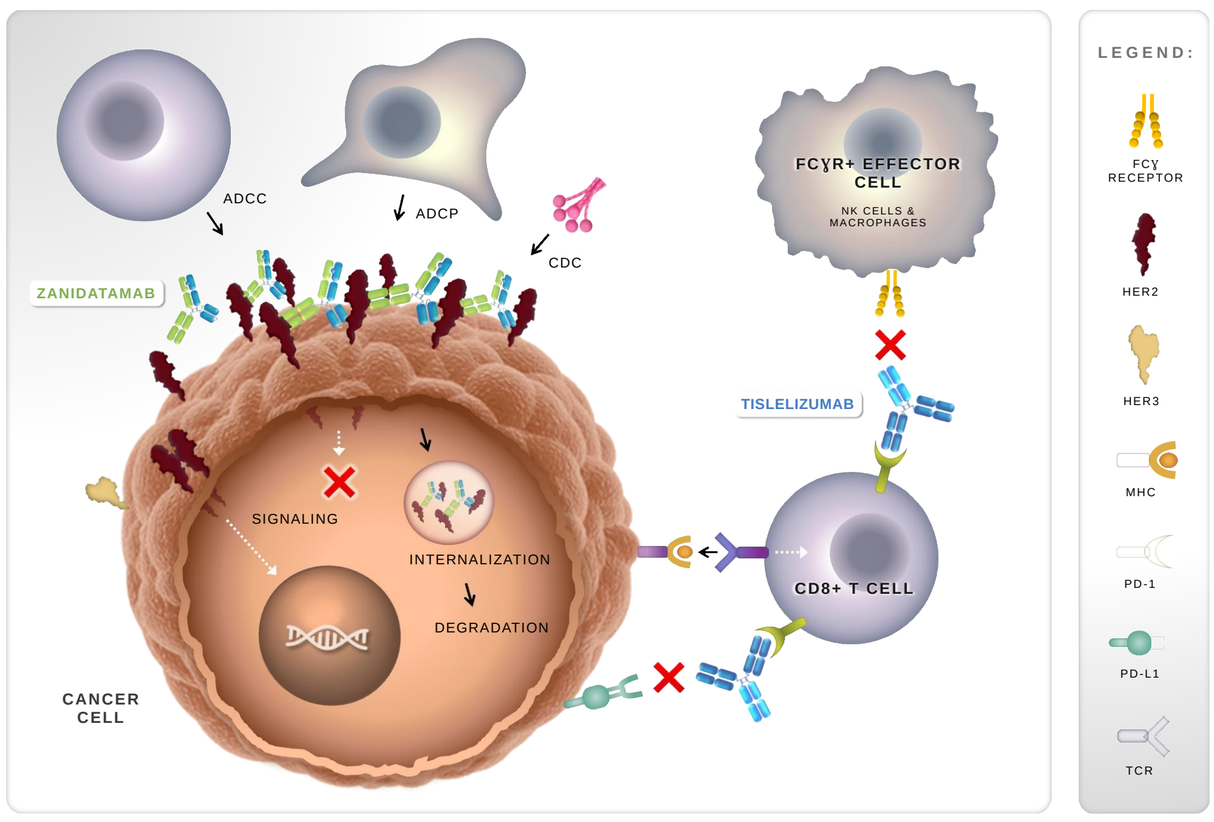
Combining Zanidatamab and Tislelizumab

- Zanidatamab and tislelizumab have differentiated and unique mechanisms of action (**Figure 3**) compared with other monoclonal antibodies targeting HER2 or PD-1, respectively

Figure 3. Proposed Mechanisms of Action of Zanidatamab and Tislelizumab

The proposed mechanisms of action of zanidatamab and tislelizumab:

- Zanidatamab binds in *trans* to two non-overlapping domains on separate HER2 proteins, leading to receptor clustering, internalization and downregulation of HER2 on the cell surface, reduction in growth factor-mediated proliferation, as well as activation of ADCC, ADCP, and CDC
- Tislelizumab binds to the extracellular domain of PD-1 and competitively blocks PD-L1 and PD-L2 binding, thus inhibiting PD-1-mediated negative signaling in T cells, minimal FcγRs binding, and abrogates ADCC, ADCP, and CDC effects in humans

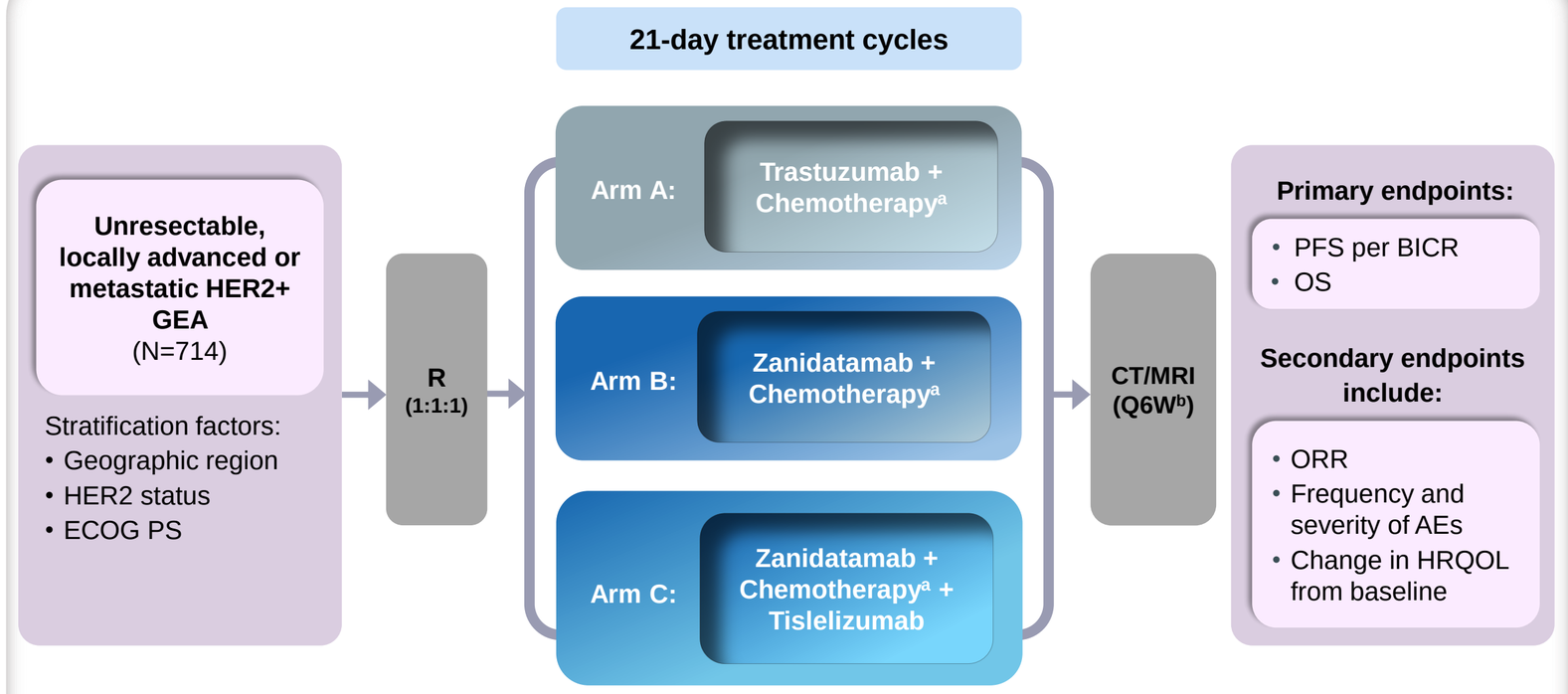


Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; CD8+ T cell, cluster of differentiation 8+ T cell; FcγR, Fc-gamma receptor; HER2, human epidermal growth factor receptor 2; MHC, major histocompatibility complex; PD-1, programmed cell death-1; T cell, thymus cell (T lymphocyte); TCR, T cell receptor.

HERIZON-GEA-01 Study

- HERIZON-GEA-01 (NCT05152147; EudraCT#: 2021 000296 36) is a global, randomized, open-label, active-comparator, phase 3 study to evaluate the efficacy and safety of zanidatamab + chemotherapy ± tislelizumab as first-line treatment for patients with advanced/metastatic HER2+ GEA (**Figure 4, Table 3**)

Figure 4. Study Design



Patients will be treated until radiographical progression per BICR, clinical progression per investigator, unacceptable toxicity, patient's or investigator's decision to stop, start of subsequent anticancer therapy, lost to follow-up, or death.

[a]Chemotherapy is physician's choice of either CAPOX or FP; [b]Disease assessments will be done using CT and/or MRI. A baseline scan is required within 28 days of enrollment; subsequent scans are required every 6 weeks for the first 54 weeks and then every 9 weeks thereafter. All scans will be submitted for BICR.

Abbreviations: AEs, adverse events; BICR, blinded independent central review; CAPOX, capecitabine + oxaliplatin; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; FP, 5 fluorouracil + cisplatin; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; HRQOL, health-related quality of life; IHC, immunohistochemistry; ISH, in situ hybridization; MRI, magnetic resonance imaging; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PS, performance status; R, randomization.

Table 3. Key Eligibility Criteria

Key Inclusion Criteria

- Age ≥18 years
- Histologically confirmed, untreated, advanced/metastatic HER2+ (IHC3+ or IHC2+/ISH+, per central testing) adenocarcinoma of the stomach, GEJ, or esophagus
- ECOG performance status of 0 or 1
- Adequate hepatic, renal, and hematologic function
- Left ventricular ejection fraction (LVEF) ≥50%
- Willing to use acceptable methods of contraception during the study and for a defined period after the study

Key Exclusion Criteria

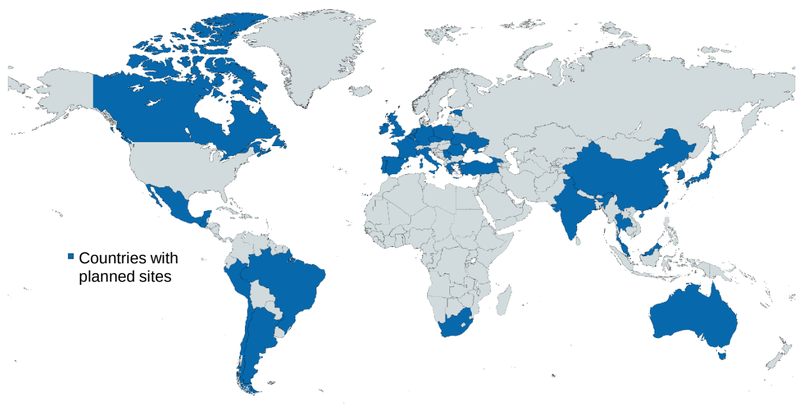
- Prior treatment with a HER2-targeted agent
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
- Prior treatment with systemic antineoplastic therapy for unresectable locally advanced, recurrent or metastatic GEA. Prior neoadjuvant/adjuvant chemotherapy permitted if completed ≥6 months before enrollment
- Untreated CNS metastases, symptomatic CNS metastases, or radiation treatment for CNS metastases within 4 weeks prior to randomization
- Clinically significant cardiac disease
- Clinically significant pulmonary disease
- Active autoimmune disease

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2.

Study Status

- The HERIZON-GEA-01 study opened to enrollment in November 2021 and is currently recruiting patients
- Recruitment will occur at ~300 sites in more than 30 countries (**Figure 5**)

Figure 5. Countries with Planned Enrollment Sites



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