Zanidatamab (ZW25) in HER2-expressing Gastroesophageal Adenocarcinoma (GEA): Results from a Phase 1 Study

Funda Meric-Bernstam[1]; Erika Hamilton[2]; Murali Beeram[3]; Diana Hanna[4]; Anthony El-Khoueiry[4]; Yoon-Koo Kang[5]; Keun-Wook Lee[6]; Jeeyun Lee[7]; Sun Young Rha[8]; Jose Chaves[9]; Do-Youn Oh; Rachel Goodwin[11]; Jaffer Ajani[1]; Todd Gray[12]; Joseph Woolery[12]; Elena Elimova[13]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA;[2]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA;[3]The START Center for Cancer Care, San Antonio, TX, US;[4]USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA;[5]Asan Medical Center, Seoul, South Korea;[6]Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea;[7]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul Korea;[8]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea;[9]Northwest Medical Specialties, Tacoma, WA, USA;[10]Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea;[11]University of Ottawa Cancer Centre, Ottawa, ON, Canada;[12]Zymeworks Inc., Vancouver, BC, Canada;[13]Princess Margaret Cancer Centre, Toronto, ON, Canada

Corresponding author: fmeric@mdanderson.org

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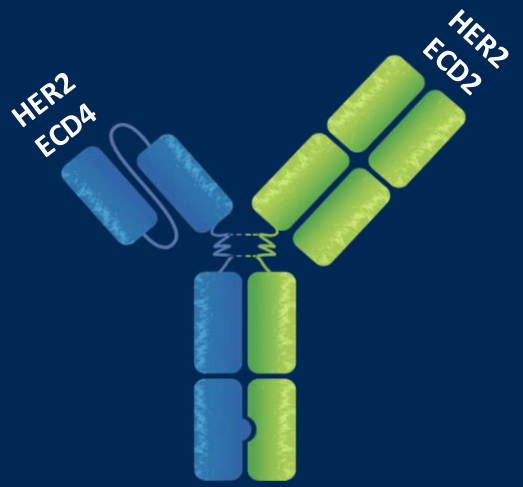
Background

- Human epidermal growth factor receptor 2 (HER2) is overexpressed in ~20% of gastroesophageal adenocarcinoma (GEA)[1,2]
- For patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma:
  - trastuzumab in combination with chemotherapy is the only approved HER2-targeted therapy[3]
  - treatment options are limited if disease progression occurs after HER2-targeted therapy

Zanidatamab: Bispecific HER2-targeted Antibody

- A biparatopic antibody that simultaneously binds two distinct sites on HER2: ECD4 (trastuzumab-targeted domain) and ECD2 (pertuzumab-targeted domain)
- Unique trans-binding results in multiple mechanisms of action by zanidatamab, including enhanced receptor clustering and internalization



ECD=extracellular domain.

1, Abrahao-Machado, *et al*. World J Gastroenterol . 2016 May 21;22(19):4619-25; 2, Van Cutsem, *et al*. Gastric Cancer. 2015 Jul;18(3):476-84;
3, HERCEPTIN® (trastuzumab). South San Francisco (CA): Genentech, Inc.; 2018. Prescribing Information.

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ZW25-101 (NCT02892123)

Key Study Objectives

- To characterize the safety and tolerability, and potential anti-tumor effects of zanidatamab, both as monotherapy and in combination with select chemotherapy

Patient Population

- Patients with HER2-expressing cancers, including GEA
- Progression after standard of care therapy
- ECOG performance status of 0 or 1
- Measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Fresh or archived tumor tissue available for central review of HER2 status

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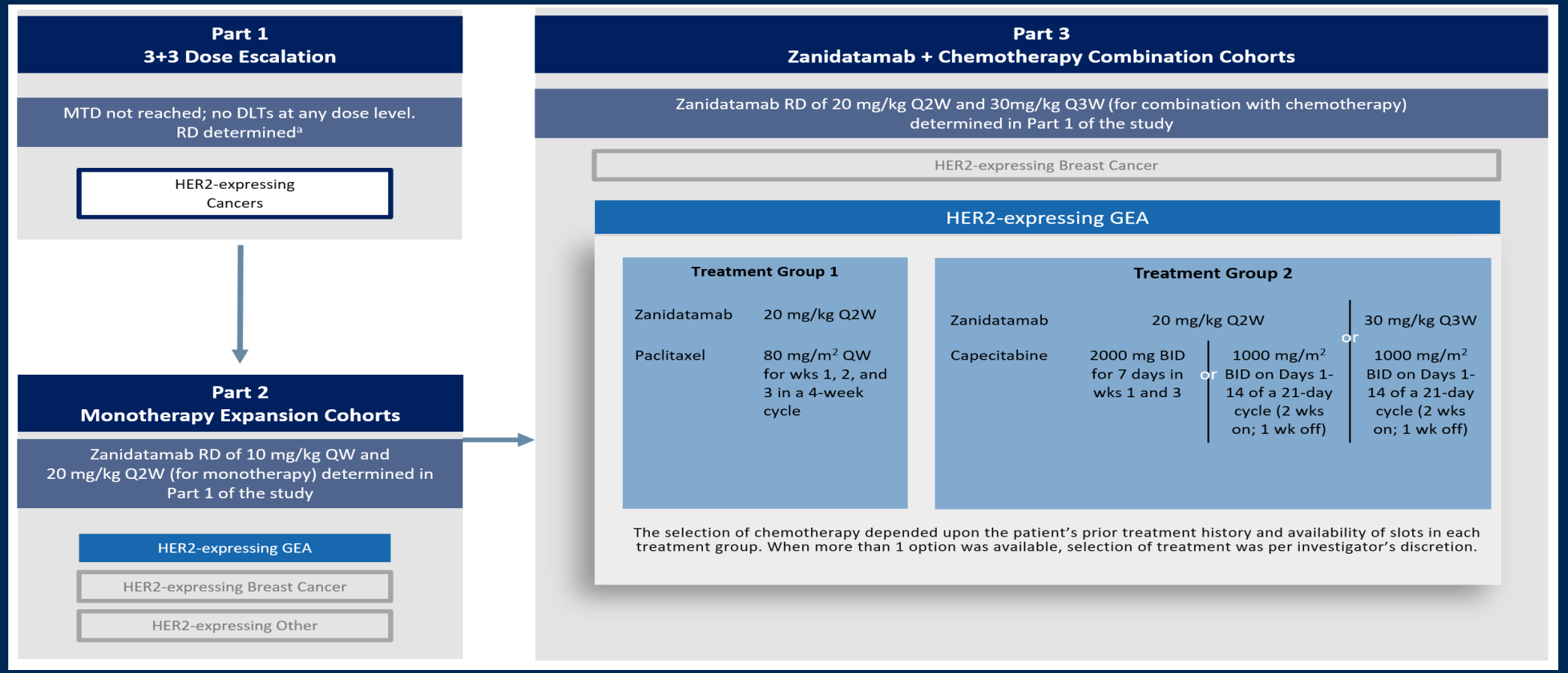
Study Design (GEA Focused)



BID=twice daily; DLT=dose-limiting toxicity; GEA=gastroesophageal adenocarcinoma; IV=intravenous; MTD=maximum-tolerated dose; PS=performance status; QW=weekly; Q2W=every 2 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; RD=recommended dose; wks=weeks.

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GEA Patient Characteristics

- The majority of patients had received at least two prior systemic regimens, including trastuzumab

	Zanidatamab Monotherapy[a] (N = 35)	Zanidatamab + Chemotherapy Combination	
		Zanidatamab[b] + Pac (N = 11)	Zanidatamab[c] + Cape (N = 17)
Median age, year (range)	62 (24–86)	61 (25–80)	63 (26–79)
Sex: Male, n (%)	28 (80)	10 (91)	12 (71)
Race, n (%)			
White	19 (54)	7 (64)	10 (59)
Asian	12 (34)	4 (36)	7 (41)
Other	5 (14)[d]	0	0
Initial diagnosis, n (%)			
Esophageal	5 (14)	2 (18)	2 (12)
Gastroesophageal junction	9 (26)	2 (18)	6 (35)
Gastric	21 (60)	7 (64)	9 (53)
HER2: IHC3+ or IHC2+/FISH+, n (%)	31 (89)	7 (64)	8 (47)
Median prior systemic therapies (range)	3 (0–7)	3 (1–7)	2 (1–5)
Patients with prior HER2-targeted therapies, n (%)	32[e] (91)	10[f] (91)	15[f] (88)

Note: Data extracted on: Nov 16, 2020 (data are from an unlocked database and subject to change). Cape= capecitabine; Pac=paclitaxel.
a, included 10 mg/kg QW and 20 mg/kg Q2W; b, 20 mg/kg Q2W; c, included 20 mg/kg Q2W and 30 mg/kg Q3W; d, included Black or African (n=2), American Indian or Alaska Native (n=2), and unknown (n=1); e, all of these patients received prior trastuzumab, 1 patient each also received prior neratinib and T-DM1; f, all received prior trastuzumab.

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Safety: Treatment-related[a] (AEs)

- The majority[a] of treatment-related[b] AEs were Grade 1 or 2 in severity and manageable in the outpatient setting

	Zanidatamab Monotherapy (N = 35)		Zanidatamab + Chemotherapy Combination			
			Zanidatamab + Pac (N = 11)		Zanidatamab + Cape (N = 17)	
	Any Grade	Grade 3 or higher	Any Grade	Grade 3 or higher	Any Grade	Grade 3 or higher
Patients with treatment-emergent AEs, n (%)	34 (97)	17 (49)	11 (100)	9 (82)	17 (100)	10 (59)
Patients with treatment-related AEs	25 (71)	4 (11)	11 (100)	7 (64)	15 (88)	2 (12)
Most common AEs[c]						
Diarrhea	16 (46)	1 (3)	7 (64)	0	10 (59)	0
Infusion-related reaction	12 (34)	0	3 (27)	0	0	0
Nausea	4 (11)	0	4 (36)	0	3 (18)	0
Fatigue	4 (11)	0	7 (64)	2 (18)	3 (18)	0

- Treatment-related serious AEs reported in 3 patients: Grade 3 diarrhea (zanidatamab monotherapy), Grade 5 pneumonitis (zanidatamab + paclitaxel), and Grade 2 creatinine increased (zanidatamab + capecitabine)

AE=adverse event.

a, 95% of treatment-related AEs with zanidatamab monotherapy or zanidatamab + capecitabine, and 80% with zanidatamab + paclitaxel, were Grade 1 or 2 in severity; b, related to zanidatamab and/or chemotherapy; c, zanidatamab-related AEs occurring in ≥ 10% of patients in the zanidatamab monotherapy group.

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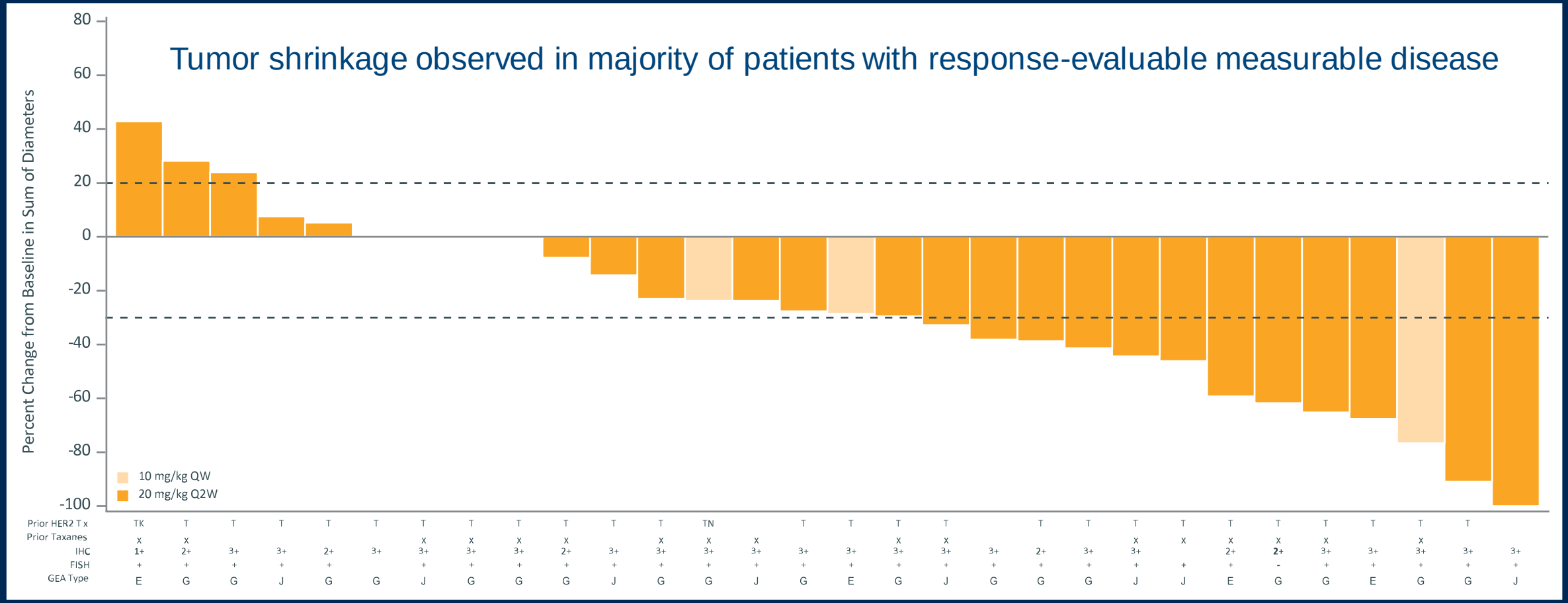
Anti-tumor Activity: Zanidatamab Monotherapy



E=esophageal; FISH=fluorescence in situ hybridization; G=gastric; IHC=immunohistochemistry; J=gastroesophageal junction; K=T-DM1; N=Neratinib; T=trastuzumab; Tx=treatment.
33 (94%) patients were response-evaluable; 3 patients had no post-baseline tumor measurements and are not included in this plot.

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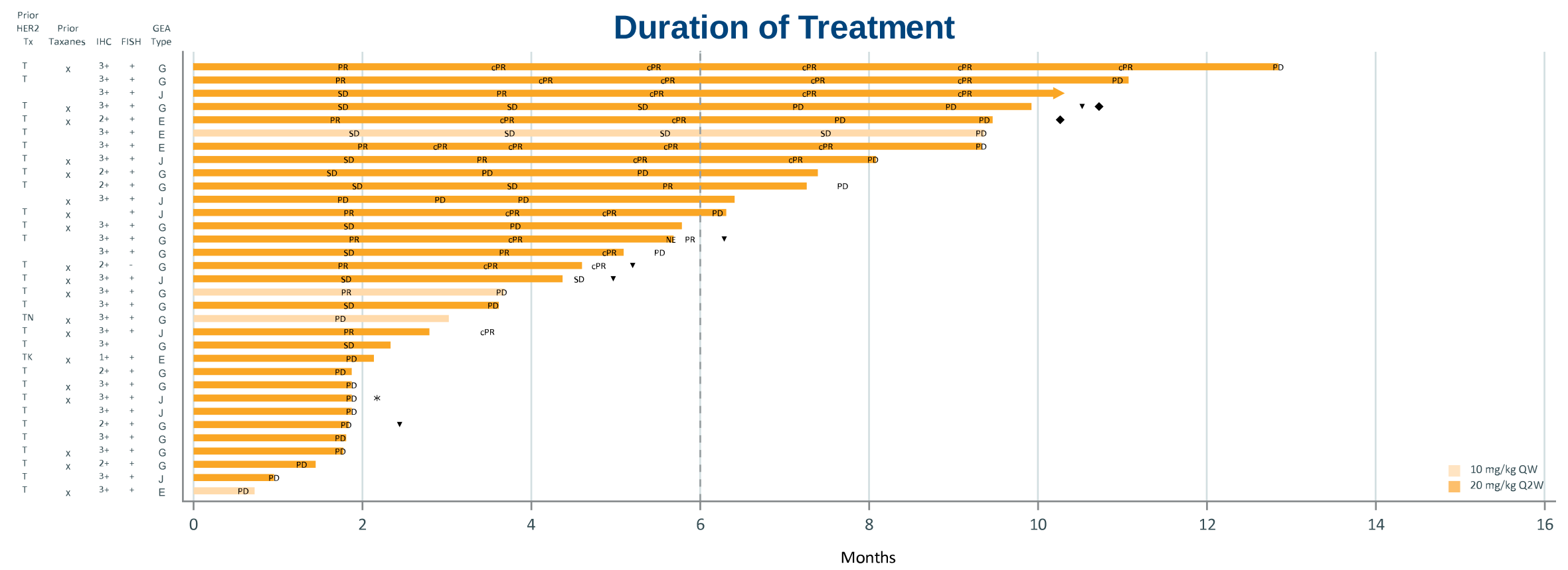
Duration of Treatment: Zanidatamab Monotherapy



(c)PR=(confirmed) partial response; E=esophageal; FISH=fluorescence in situ hybridization; G=gastric; IHC=Immunohistochemistry; J=gastroesophageal junction; K=T-DM1; N=Neratinib; PD=progressive disease; SD=stable disease; T=Trastuzumab; Tx=treatment.

▼, Clinical progression; *, Death; ◆, Continued study treatment for clinical benefit.

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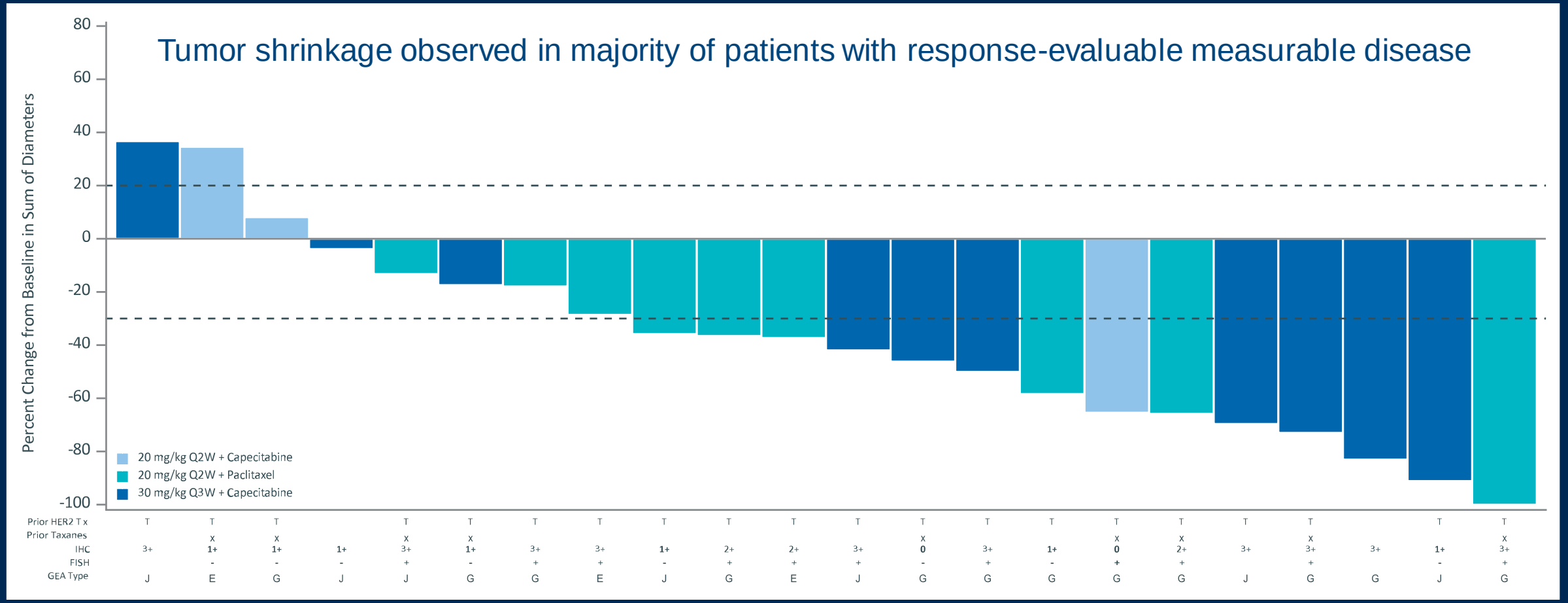
Anti-Tumor Activity: Zanidatamab + Chemotherapy



E=esophageal; FISH=fluorescence in situ hybridization; G=gastric; IHC=immunohistochemistry; J=gastroesophageal junction; K=T-DM1; N=Neratinib; T=Trastuzumab; Tx=treatment.
24 (86%) patients were response-evaluable; 2 patients had no post-baseline tumor measurements and are not included in this plot.

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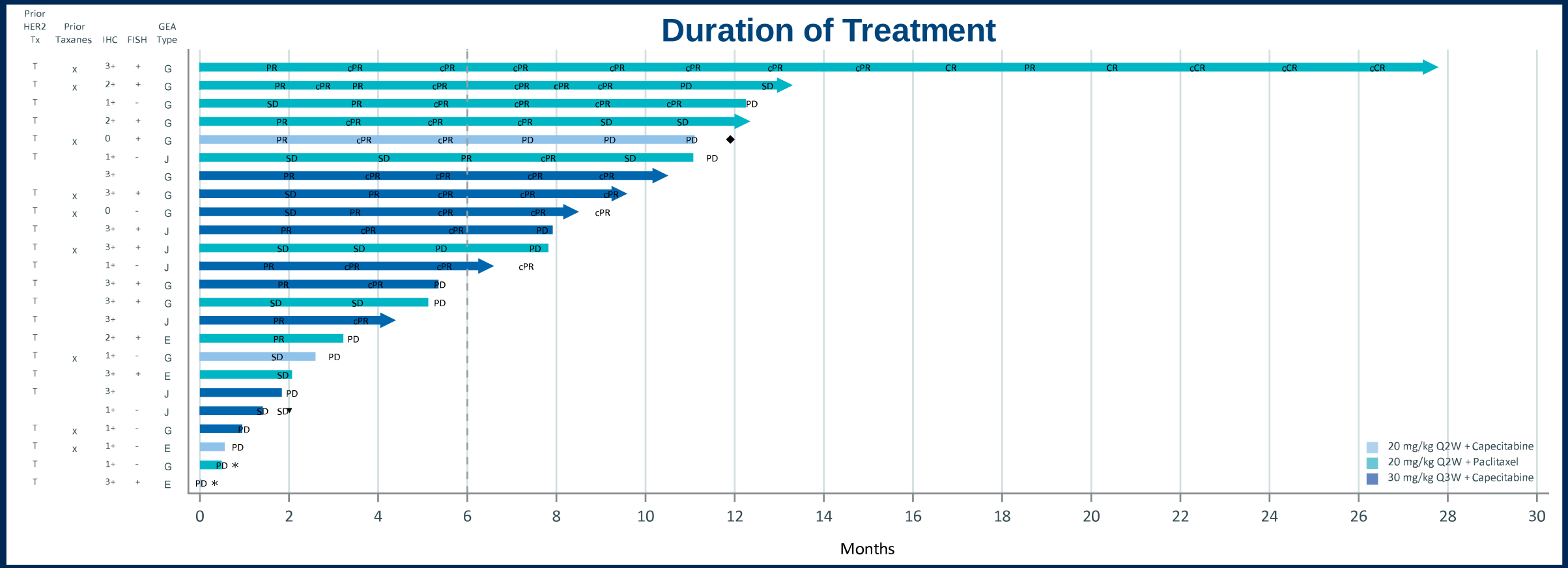
Duration of Treatment: Zanidatamab + Chemotherapy



(c)PR=(confirmed) partial response; CR=complete response; FISH=fluorescence in situ hybridization; IHC=Immunohistochemistry; PD=progressive disease; SD=stable disease; T=Trastuzumab; Tx=treatment.

▼, Clinical progression; *, Death; ◆, Continued study treatment for clinical benefit.

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Disease Response per RECIST 1.1 in Response-Evaluable[a] Patients

	Zanidatamab Monotherapy (N = 33)	Zanidatamab + Chemotherapy Combination		
		Zanidatamab + Pac (N = 10)	Zanidatamab + Cape (N = 14)	Combo Total (N = 24)
Confirmed objective response[b], n (%)	11 (33)	5 (50)	8 (57)	13 (54)
Complete response	0	1 (10)	0	1 (4)
Partial response	11 (33)	4 (40)	8 (57)	12 (50)
Stable disease	9 (27)	4 (40)	2 (14)	6 (25)
Progressive disease	13 (39)	1 (10)	4 (29)	5 (21)
Disease control rate, n (%)	20 (61)	9 (90)	10 (71)	19 (79)
Duration of response,[c] months	(N=11)	(N=5)	(N=8)	(N=13)
Median (95% CI)	6.0 (1.9, 9.2)	9.1 (5.6, NE)	5.8 (3.5, NE)	8.9 (5.6, NE)
PFS, months	(N=35[d])	(N=11[e])	(N=17[f])	(N=28[g])
Median (95% CI)	3.6 (1.9, 6.2)	10.9 (3.4, 12.4)	5.4 (1.5, 7.7)	5.6 (3.0, 10.9)

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

a, all treated patients with measurable disease who had at least one evaluable, post-baseline disease assessment (per RECIST 1.1) or discontinued study treatment due to death or clinical progression; b, per investigator assessment using RECIST 1.1; c, in response evaluable patients who had a confirmed complete or partial response followed by ≥1 response assessment; d, safety set (5 pts were censored); e, safety set (3 pts were censored); f, safety set (6 pts were censored); g, safety set (9 pts In total were censored).

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Conclusions

- Zanidatamab is well tolerated with promising anti-tumor activity in patients with HER2-expressing GEA that has progressed after prior therapies, including HER2-targeted agents
  - The majority of the treatment-related AEs were Grade 1 or 2 and manageable in the outpatient setting
  - Durable responses and disease control with zanidatamab as monotherapy and in combination with chemotherapy
    - Zanidatamab monotherapy: Confirmed ORR: 33%; DCR: 61%; median DOR: 6.0 months
    - Zanidatamab + chemotherapy: Confirmed ORR: 54%; DCR:79%; median DOR: 8.9 months
- Based on these data, zanidatamab is being further evaluated in patients with HER2-expressing GEA in 2 global studies:
  - ZW25-201 (Phase 2; NCT03929666): zanidatamab + 1st line chemotherapy in patients with HER2-expressing GEA
  - BGB-A317-ZW25-101 (Phase 1b/2; NCT04276493): zanidatamab in combination with chemotherapy with/without tislelizumab in patients with HER2+ GEJ adenocarcinoma and breast cancer

DOR, duration of response; DCR=disease control rate; GEJ=gastroesophageal junction, NE=not estimable; ORR=objective response rate.

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Acknowledgments and Other Information

Acknowledgments

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