A Phase 1 Study of Zanidatamab Monotherapy in Japanese Patients With Metastatic or Unresectable HER2-Expressing Cancers

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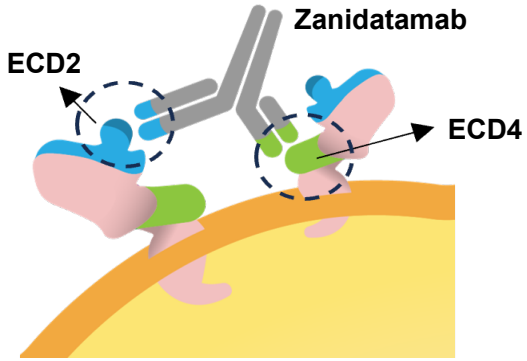
Background & Objectives

- HER2-targeted therapies have improved outcomes for patients with HER2-altered solid tumors, including breast cancer, gastric/GEJ cancer, CRC, and NSCLC[1-5]
- Zanidatamab is a HER2-targeted bispecific antibody that binds to two non-overlapping HER2 domains and crosslinks neighboring HER2 proteins[6]
  - Leading to HER2 internalization and downregulation, inhibition of HER2 signaling, and immune-mediated effects, including CDC, ADCP, and ADCC

Zanidatamab binding to HER2[6]



- Zanidatamab has shown encouraging antitumor activity with a manageable safety profile in non-Japanese patients with HER2-expressing solid tumors, including gastroesophageal adenocarcinoma (GEA) and biliary tract cancer (BTC)[5,7-8]

This ongoing phase 1 study is evaluating the safety, pharmacokinetics, and preliminary antitumor activity of zanidatamab in Japanese patients with treatment-refractory, HER2-expressing solid tumors

1. Tolaney SM, et al. *Lancet Oncol*. 2020;21(6):763-775. 2. Ciruelos E, et al. *Clin Cancer Res*. 2020;26(22):5820-29. 3. Bang YJ, et al. *Lancet*. 2010;376(9742):687-97. 4. Hofheinz RD, et al. *Int J Cancer*. 2021;149(6):1322-31. 5. Meric-Bernstam F, et al. *Lancet Oncol*. 2022;23(12):1558-70. 6. Weisser NE, et al. *Nat Commun*. 2023;14(1394). 7. Meric-Bernstam F, et al. *J Clin Oncol*. 2021;39(3_suppl):164. 8. Harding JJ, et al. *Lancet Oncol*. 2023;24(7):772-782.

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; CRC, colorectal cancer; ECD, extracellular domain; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer.

Study Design

Select Eligibility Criteria

- Advanced unresectable and/or metastatic treatment-refractory, HER2-expressing (IHC1+, 2+, or 3+) solid tumors[a]
- Adults ≥20 years
- Evaluable disease per RECIST v1.1
- ECOG PS ≤1
- Adequate organ and hematologic function
- Adequate cardiac function

Zanidatamab
Weight-Based Dosing

20 mg/kg Q2W

Or

30 mg/kg Q3W

Or 2-Tiered Flat Dosing

1800 mg Q3W for pts <70 kg
2400 mg Q3W for pts ≥70 kg

Tumor assessments Q8W

Includes dose escalation followed by dose expansion (all dose groups)

Select Primary Endpoints:

- Frequency of DLTs, AEs, AESIs, SAEs, LVEF abnormalities

Select Secondary Endpoints:

- ORR (per RECIST v1.1)
- DOR
- PFS

[a]Enrollment was based on local assessment of fresh or archived tumors for HER2 and reassessed centrally; eligible tumor types include but are not limited to GEA, BTC, breast, ovarian, colorectal, and NSCLC.

Clinical trial ID: jRCT2031210161

AE, adverse event; AESI, adverse event of special interest; BTC, biliary tract cancer; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; LVEF, left ventricular ejection fraction; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; pts, patients; Q2W, every 2 weeks; Q3W, every 3 weeks; Q8W, every 8 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse events.

Patient Demographics and Baseline Characteristics

- As of the data cutoff (December 1, 2023), a total of 32 patients have been enrolled (dose escalation and expansion)

	GEA (n=13)	Non-GEA (n=19)	All Patients (N=32)
Median age (range), years	68 (33-77)	68 (42-79)	68 (33-79)
Female sex, n (%)	3 (23)	12 (63)	15 (47)
ECOG PS, n (%)			
0	11 (85)	13 (68)	24 (75)
1	2 (15)	6 (32)	8 (25)
Cancer Type, n (%)			
GEA	13 (100)	-	13 (41)
Gastric	8 (62)	-	8 (25)
GEJ	4 (31)	-	4 (13)
Esophageal	1 (8)	-	1 (3)
Non-GEA	-	19 (100)	19 (59)
BTC	-	6 (32)	6 (19)
Breast	-	5 (26)	5 (16)
Other[a]	-	8 (42)	8 (25)

	GEA (n=13)	Non-GEA (n=19)	All Patients (N=32)
Centrally confirmed HER2-positive (IHC2+/FISH+ or IHC3+)	6 (46)	7 (37)	13 (41)
Prior HER2-targeted agents,[b] n (%)			
Trastuzumab	8 (62)	5 (26)	13 (41)
T-DXd	8 (62)	2 (11)	10 (31)
T-DM1	0	3 (16)	3 (9)
Pertuzumab	0	2 (11)	2 (6)
Lapatinib	0	2 (11)	2 (6)
Tucatinib	0	1 (5)	1 (3)

[a]Other cancers include apocrine carcinoma, colorectal cancer, extramammary Paget's disease, orbital tumor, pancreatic cancer, salivary duct carcinoma, and uterine cancer.
[b]Patients could have received more than one prior therapy.

BTC, biliary tract cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; GEA, gastroesophageal adenocarcinoma; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; T-DXd trastuzumab deruxtecan; T-DM1, ado-trastuzumab emtansine.

Data cutoff date: December 1, 2023

Zanidatamab Exposure

	GEA (n=13)	Non-GEA (n=19)	All Patients (N=32)
Median number of cycles, n (range)	4 (2, 16)	4 (2, 21)	4 (2, 21)
Dose reductions due to TEAE,[a] n (%)	0	0	0
Dose interruptions due to TRAE,[b] n (%)[c]	4 (31)	3 (16)	7 (22)
Dose delays or held due to TRAE,[b] n (%)[d]	2 (15)	1 (5)	3 (23)
Treatment discontinuation due to TRAE[b,e]	0	1 (3)	1 (3)

[a]TEAEs were defined as an adverse event with onset on or after first dose of study treatment through 30 days after final dose of study treatment inclusive.
[b]TRAE relatedness is as determined by the investigator.
[c]TRAEs led to dose interruptions in seven patients (six due to IRRs and one due to chills).
[d]TRAEs led to dose delays or being held in three patients (AST increased, diarrhea, and malaise; one each).
[e]One patient discontinued due to treatment-related grade 2 paronychia.

AST, aspartate aminotransferase; DLT, dose-limiting toxicity; GEA, gastroesophageal adenocarcinoma; IRR, infusion related reaction; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Data cutoff date: December 1, 2023

Summary of Adverse Events

	GEA (n=13)	Non-GEA (n=19)	All Patients (N=32)
TEAE, n (%)			
Any	13 (100)	16 (84)	29 (91)
Grade 1-2	12 (92)	8 (42)	20 (62)
Grade 3	1 (8)	8 (42)	9 (28)
TRAE, n (%)			
Any	12 (92)	12 (63)	24 (75)
Grade 1-2	12 (92)	10 (53)	22 (69)
Grade 3[a]	0	2 (11)	2 (6)
Treatment-related SAE, n (%)	0	0	0
Treatment-related AESI, n (%)			
Infusion-related reaction	3 (23)	4 (21)	7 (22)
Non-infectious pulmonary toxicities	0	0	0
Potential cardiac events	0	0	0
Most common TRAEs, n (%)			
Diarrhea	8 (62)	5 (26)	13 (41)
Infusion-related reaction	3 (23)	4 (21)	7 (22)
ALT increased	2 (15)	3 (16)	5 (16)
AST increased	2 (15)	3 (16)	5 (16)
Malaise	3 (23)	1 (5)	4 (13)
Rash	1 (8)	3 (16)	4 (13)

- No DLTs were observed during dose escalation
- No treatment-related deaths or serious TRAEs occurred
- No grade 4 TRAEs occurred
- No AESIs of potential cardiac events or non-infectious pulmonary toxicities occurred

[a]Grade 3 TRAEs were hypokalaemia in one patient with BTC, and AST increased and ALT increased in one patient with orbital tumor.

AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BTC, biliary tract cancer; GEA, gastroesophageal adenocarcinoma; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Data cutoff date: December 1, 2023

Antitumor Activity in Evaluable Patients

	GEA (n=12)	Non-GEA (n=18)	All Patients (N=30)
Confirmed OR, n (%) 95% CI	1 (8) 0, 38	4 (22) 6, 48	5 (17) 6, 35
Confirmed BOR, n (%) CR PR SD	 - 1 (8) 7 (58)	 1 (6) 3 (17) 6 (33)	 1 (3) 4 (13) 13 (43)
DCR, n (%) 95% CI	8 (67) 35, 90	10 (56) 31, 78	18 (60) 41, 77
Median DOR,[a] months 95% CI	NE NE	7 5, NE	9 5, NE

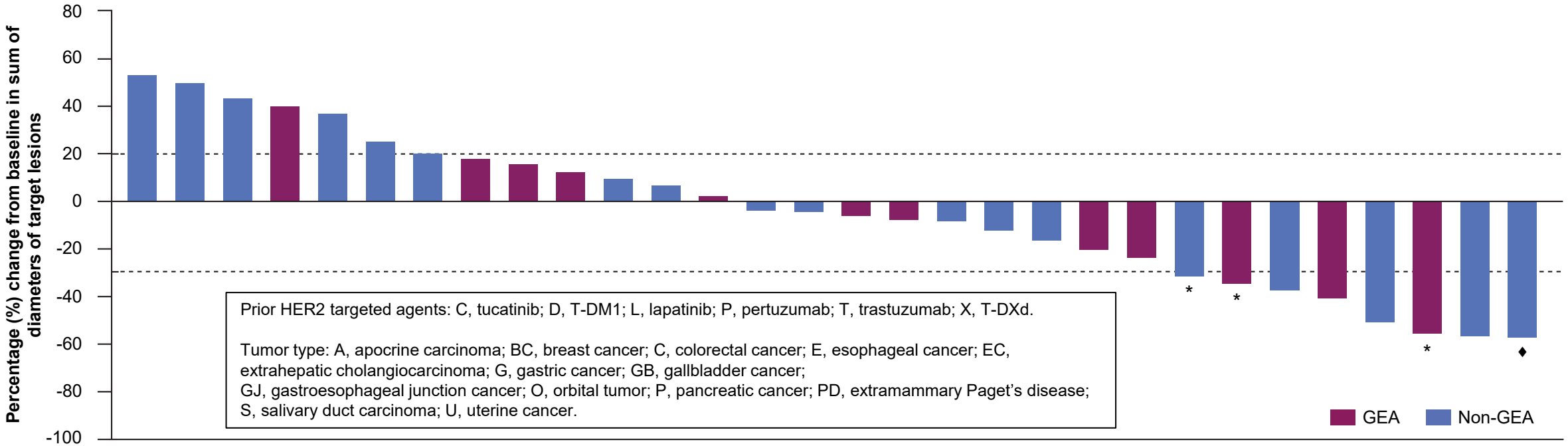
- One patient with BTC (IHC3+/FISH+) achieved a CR
- One patient with GEA who achieved a PR had a DOR of 7 months (response ongoing at data cutoff)
- Three patients with unconfirmed responses remain on treatment at time of data cutoff
  - Two newly enrolled patients with GEA had a PR at first tumor assessment
  - One ongoing patient with BTC had a PR at most recent tumor assessment

[a]Includes evaluable patients with a confirmed CR or PR (n=5 for all patients)

BOR, best overall response; BTC, biliary tract cancer; CI, confidence interval; CR, complete response, DCR, disease control rate; DOR, duration of response; FISH, fluorescence in situ hybridization; GEA, gastroesophageal adenocarcinoma; IHC, immunohistochemistry; NE, not evaluable; OR, objective response; PR, partial response; SD, stable disease.

Data cutoff date: December 1, 2023

Antitumor Activity in Evaluable Patients[a]



Central IHC	1+	1+	0	0	2+	1+	**2+**	1+	0	**3+**	**2+**	1+	1+	1+	2+	**2+**	0	**2+**	1+	1+	**3+**	1+	**3+**	**3+**	**3+**	1+	0	**3+**	**3+**	**3+**
Central FISH	-	-	-	-	-	-	**+**	-	-	**+**	**+**	-	-		-	**+**	-	**+**	-	+	**+**	-	**+**	**+**	**+**	+	-	**+**	**+**	**+**
Tumor type	P	BC	U	G	BC	BC	**C**	GJ	G	**G**	**BC**	O	G	GB	BC	**G**	GJ	**P**	EC	EC	**G**	GJ	**GB**	**E**	**S**	G	PD	**G**	**A**	**GB**
Zanidatamab dose[b]	FD	30	20	30	30	30	**20**	FD	FD	**FD**	**30**	20	30	30	FD	**30**	FD	**20**	30	20	**FD**	30	**FD**	**30**	**FD**	FD	20	**30**	**FD**	**FD**
Prior HER2 Trt		LT						T		**X**	**DPTX**	DT			DLPTX	**TX**				CT	**TX**	TX		**TX**		TX		**TX**		

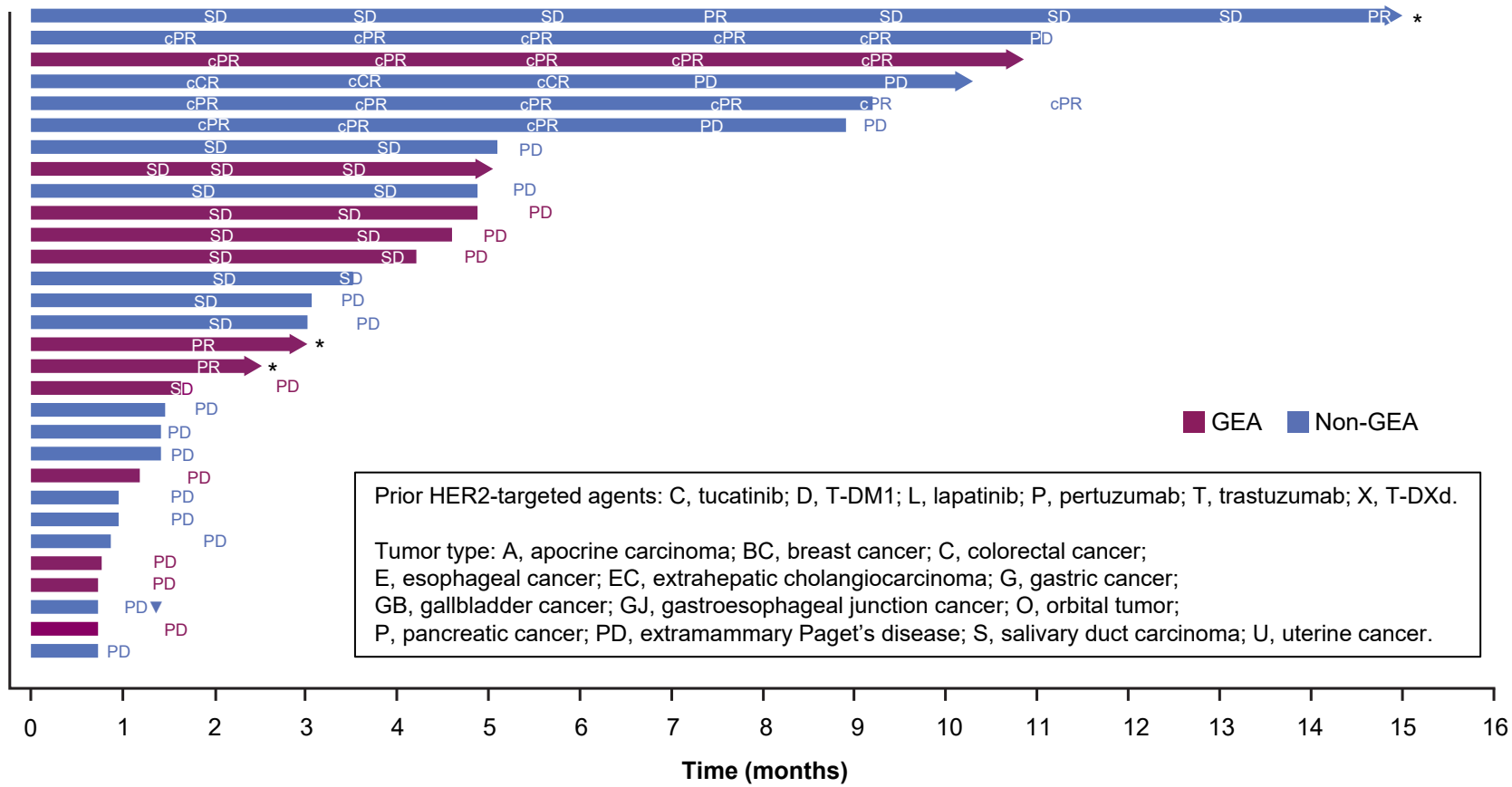
[a]Overall, 30 patients were evaluable for response.
[b]FD=1800 mg Q3W; 20=20 mg/kg Q2W; 30=30 mg/kg Q3W.
* Patient with an unconfirmed response.
♦Patient achieved a CR; the target lesion for this patient was a lymph node that became non-pathologic; per RECIST 1.1 criteria, a complete response of lymph nodes is defined as a decrease in the size of pathologic lymph nodes to a short axis of less than 10 mm.
Note: Patients in bold had centrally confirmed HER2-positive tumor.

CR, complete response; FD, flat dose; FISH, fluorescence in situ hybridization; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; Q2W, every 2 weeks; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; T-DM1, ado-trastuzumab; T-DXd, trastuzumab deruxtecan; Trt, treatment.

Data cutoff date: December 1, 2023

Treatment Duration in Evaluable Patients[a]

Prior HER2 Trt	Zanidatamab dose[b]	Tumor type	Central FISH	Central IHC
	FD	**GB**	**+**	**3+**
	FD	**S**	**+**	**3+**
TX	FD	G	+	1+
	FD	**GB**	**+**	**3+**
	FD	**A**	**+**	**3+**
	20	PD	-	0
CT	20	EC	+	1+
TX	30	GJ	-	1+
	30	GB		1+
	FD	GJ	-	0
T	FD	GJ	-	1+
TX	**FD**	**G**	**+**	**3+**
DLPTX	FD	BC	-	2+
	20	**P**	**+**	**2+**
	30	EC	-	1+
TX	**30**	**G**	**+**	**3+**
TX	**30**	**E**	**+**	**3+**
TX	**30**	**G**	**+**	**2+**
	30	BC	-	1+
LT	30	BC	-	1+
	20	**C**	**+**	**2+**
X	**FD**	**G**	**+**	**3+**
DT	20	O	-	1+
	20	U	-	0
	30	BC	-	2+
	30	G	-	0
	30	G	-	1+
	FD	P	-	1+
	FD	G	-	0
DPTX	**30**	**BC**	**+**	**2+**

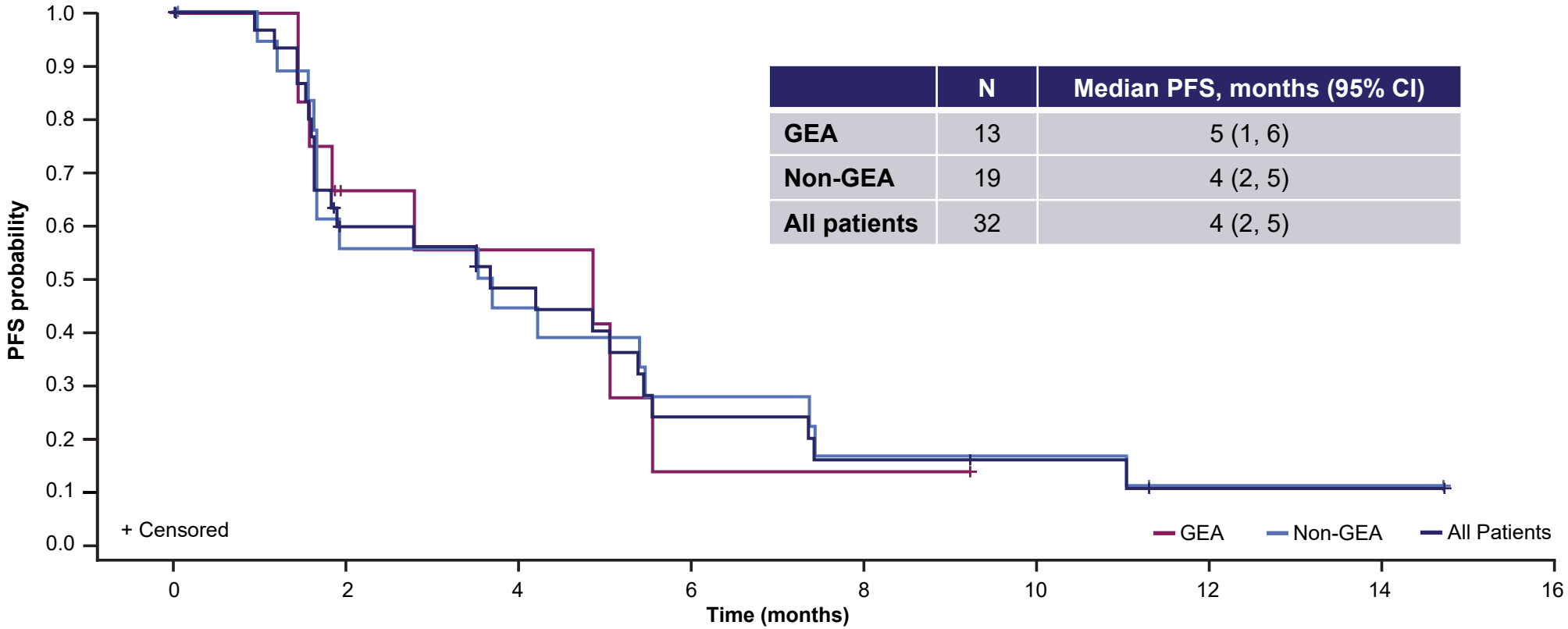


[a]Overall, 30 patients were evaluable for response.
[a]FD=1800 mg Q3W; 20=20 mg/kg Q2W; 30=30 mg/kg Q3W.
* Patient with an unconfirmed response.
▼ Death.
Note: Patients in bold had centrally confirmed HER2-positive tumor.

cCR; confirmed complete response; cPR, confirmed partial response; CR, complete response; FD, flat dose; FISH, fluorescence in situ hybridization; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PD, progressive disease; PR, partial response; SD, stable disease; Q2W, every 2 weeks; Q3W, every 3 weeks; T-DM1, ado-trastuzumab; T-DXd, trastuzumab deruxtecan; Trt, treatment.

Data cutoff date: December 1, 2023

Progression-Free Survival



	N	Median PFS, months (95% CI)
GEA	13	5 (1, 6)
Non-GEA	19	4 (2, 5)
All patients	32	4 (2, 5)

Number at risk, n (%)

GEA	13 (100)	6 (46)	4 (31)	1 (8)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)
Non-GEA	19 (100)	10 (53)	8 (42)	5 (26)	3 (16)	3 (16)	1 (5)	1 (5)	0 (0)
All Patients	32 (100)	16 (50)	12 (38)	6 (19)	4 (13)	3 (9)	1 (3)	1 (3)	0 (0)

CI, confidence interval; GEA, gastroesophageal adenocarcinoma; NE, not evaluable; PFS, progression-free survival.

Data cutoff date: December 1, 2023

Conclusions

- Zanidatamab was well-tolerated in Japanese patients with HER2-expressing solid tumors
  - Zanidatamab was previously observed to be well-tolerated in non-Japanese patients[1]
- Preliminary antitumor activity was observed, with a rapid response seen by the first assessment
  - This is consistent with previous observations in non-Japanese patients[1]
- While these data are preliminary, this study is ongoing and will continue to assess safety and antitumor activity
- Additional zanidatamab trials have been initiated in Japan and more are planned
  - The ongoing global phase 3 HERIZON-GEA-01 trial[2] investigating zanidatamab plus chemotherapy in first-line advanced HER2-positive GEA has been initiated in study sites in Japan (NCT05152147; jRCT2061230026)

1. Meric-Bernstam F, et al. *Lancet Oncol.* 2022;23(12):1558-70. 2. Tabernero J, et al. *Future Oncol*. 2022;18(29):3255-3266.

GEA, gastroesophageal adenocarcinoma;
HER2, human epidermal growth factor receptor 2.

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