Zanidatamab in 1L HER2+ GEA
ESMO Webcast

September 16th
7:30am ET (4:30am PT)

NYSE: ZYME
www.zymeworks.com

Forward-Looking Statements

Ryan Dercho, PhD

Senior Director, Corporate Affairs

Legal Disclaimer

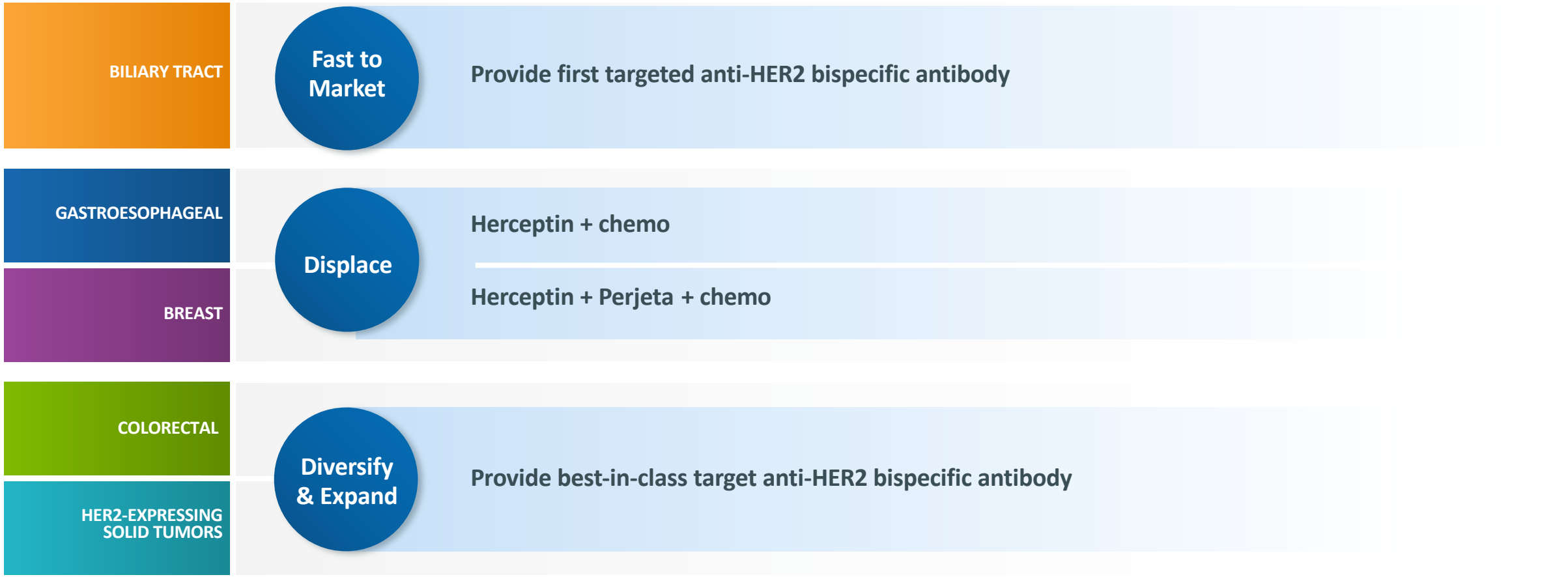
This presentation includes “forward-looking statements” within the meaning of the U.S. Private Securities Litigation Reform Act of 1995 and “forward-looking information” within the meaning of Canadian securities laws, or collectively, forward looking statements. Forward-looking statements include statements that may relate to our plans, objectives, goals, strategies, future events, future revenue or performance, capital expenditures, financing needs and other information that is not historical information. Forward-looking statements can often be identified by the use of terminology such as “subject to,” “believe,” “anticipate,” “plan,” “expect,” “intend,” “estimate,” “project,” “may,” “will,” “should,” “would,” “could,” “can,” the negatives thereof, variations thereon and similar expressions, or by discussions of strategy. In addition, any statements or information that refer to expectations, beliefs, plans, projections, objectives, performance or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking. All forward-looking statements, including, without limitation, our examination of historical operating trends, are based upon our current expectations and various assumptions. We may not realize our expectations, and our beliefs may not prove correct. Actual results could differ materially from those described or implied by such forward-looking statements as a result of risks and uncertainties, including those described in the "Risk Factors" and other sections of our public filings with the Securities and Exchange Commission and Canadian securities regulators.

These forward-looking statements are made only as of the date hereof, and Zymeworks Inc. undertakes no obligation to update or revise the forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

Opening Remarks

Ali Tehrani, PhD
President & CEO

Zanidatamab Development Strategy



Zanidatamab Background & Current Standard of Care

Neil Josephson, MD

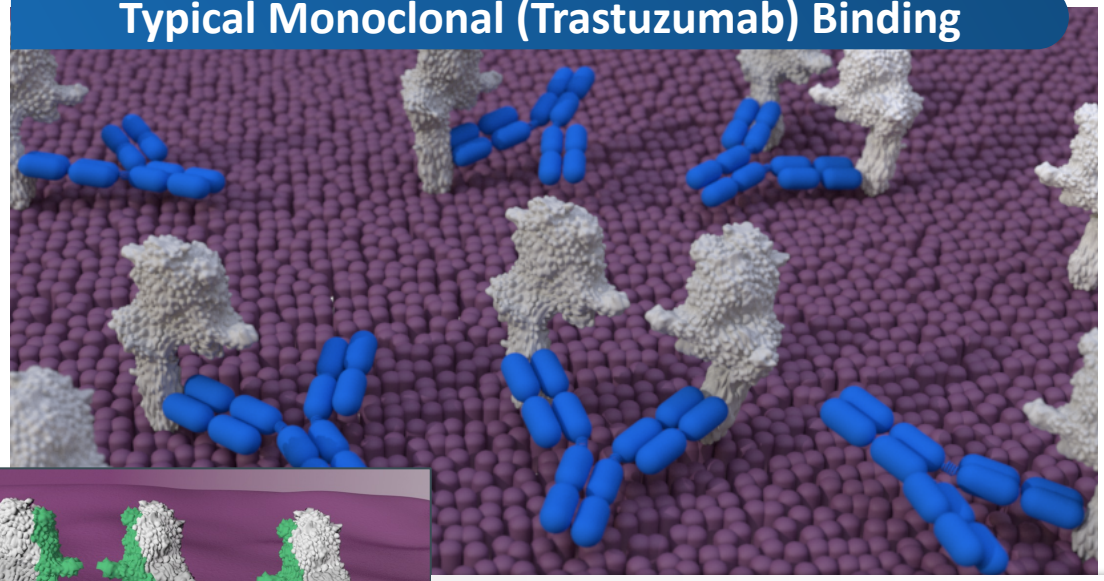
Interim CMO & SVP, Clinical Research

Dual HER2-Binding of Zanidatamab Drives Unique MOA

Zanidatamab's unique binding geometry promotes:

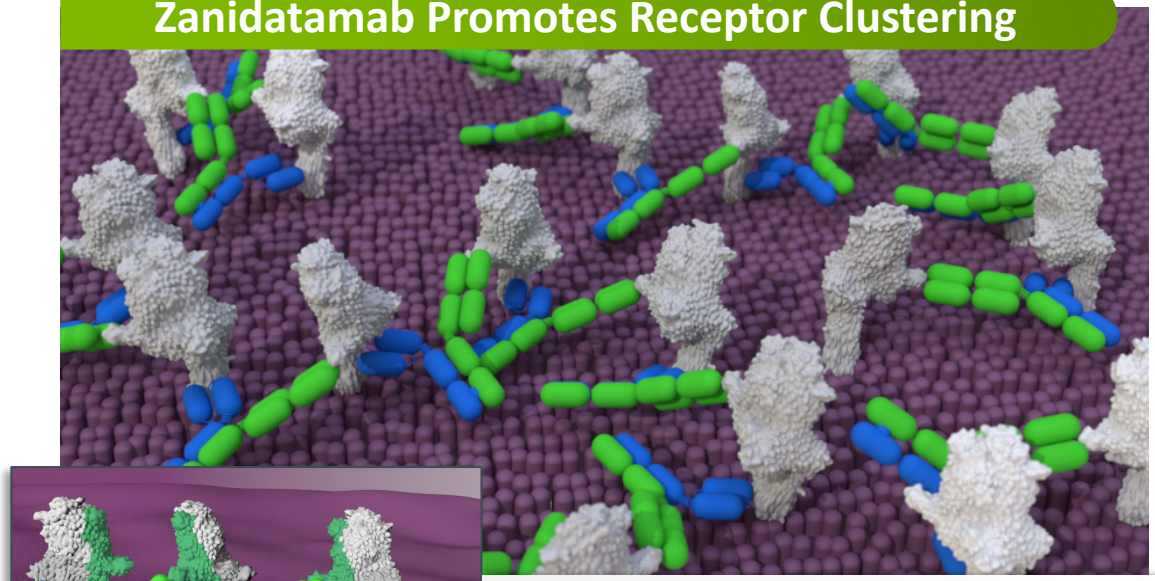
- Binding to HER2 across a range of expression levels (low to high)
- HER2-receptor clustering, internalization, and downregulation
- Inhibition of growth factor-dependent and -independent tumor cell proliferation
- Antibody-dependent cellular cytotoxicity and phagocytosis; and complement-dependent cytotoxicity

Typical Monoclonal (Trastuzumab) Binding



Monoclonal Binding –
Each HER2 receptor can only be bound by one monoclonal antibody

Zanidatamab Promotes Receptor Clustering



Biparatopic *Trans* Binding –
Each HER2 receptor can be targeted by two Zanidatamab antibodies

MOA: Mechanism of Action

zymeworks

GEA Cancer Incidence Rate by Geography

HER2 is overexpressed in approximately 20% of GEAs[1,2]

EU28

Incidence Rate Per 100K Population[3]

Gastric	GEJ	Esophageal	GEA Total
9.3	5.0	4.6	18.9

Japan

Incidence Rate Per 100K Population[3]

Gastric	GEJ	Esophageal	GEA Total
47.2	25.4	10.2	82.8

US

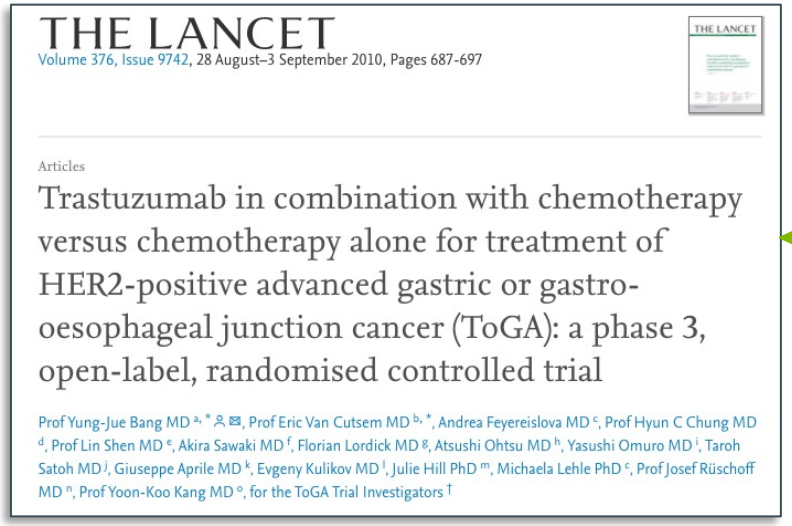
Incidence Rate Per 100K Population[3]

Gastric	GEJ	Esophageal	GEA Total
4.2	2.2	4.0	10.4

1. Abrahao-Machado LF, et al. *World J Gastroenterol*. 2016;22(19):4619-4625.
2. Van Cutsem E, et al. *Gastric Cancer*. 2015;18(3):476-484.
3. SEER 13 Crude Incidence; GLOBOCAN

zymeworks

First-Line Metastatic HER2+ GEA Registrational Studies



THE LANCET

Volume 376, Issue 9742, 28 August–3 September 2010, Pages 687-697

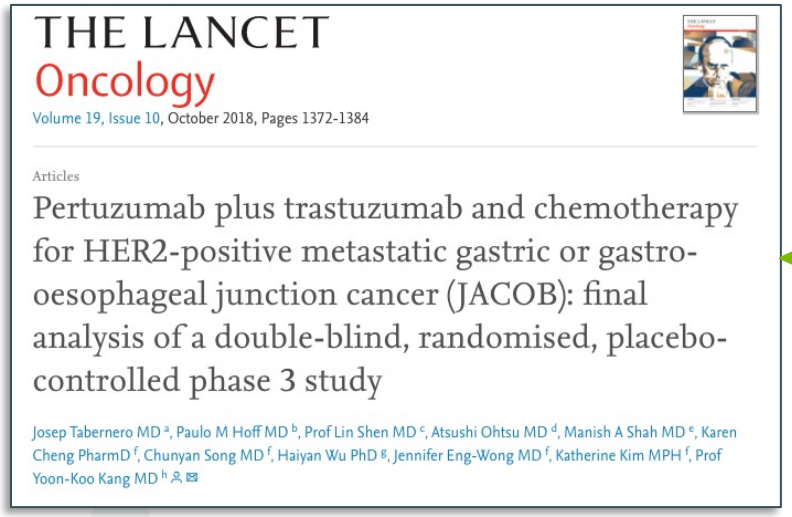
Articles

Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial

Prof Yung-Jue Bang MD [a, *], Prof Eric Van Cutsem MD [b, *], Andrea Feyereislova MD [c], Prof Hyun C Chung MD [d], Prof Lin Shen MD [e], Akira Sawaki MD [f], Florian Lordick MD [g], Atsushi Ohtsu MD [h], Yasushi Omuro MD [i], Taroh Satoh MD [j], Giuseppe Aprile MD [k], Evgeny Kulikov MD [l], Julie Hill PhD [m], Michaela Lehle PhD [c], Prof Josef Rüschoff MD [n], Prof Yoon-Koo Kang MD [o], for the ToGA Trial Investigators [†]

ToGA Trial – Standard of Care in 1L GEA

- Indication: 1L HER2-positive advanced gastric or gastroesophageal junction cancer
- Drugs Tested: Herceptin + chemo (XP/FP) vs. SOC chemo
- ORR: 47% (up to 52% in recent control arms)
- mDOR: 6.9 months
- mPFS: 6.7 months
- mOS: 13.8 months



THE LANCET Oncology

Volume 19, Issue 10, October 2018, Pages 1372-1384

Articles

Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study

Josep Tabernero MD [a], Paulo M Hoff MD [b], Prof Lin Shen MD [c], Atsushi Ohtsu MD [d], Manish A Shah MD [e], Karen Cheng PharmD [f], Chunyan Song MD [f], Haiyan Wu PhD [g], Jennifer Eng-Wong MD [f], Katherine Kim MPH [f], Prof Yoon-Koo Kang MD [h]

JACOB Trial – Not Approved by FDA in 1L GEA

- Indication: 1L HER2-positive metastatic gastric or gastroesophageal junction cancer
- Drugs Tested: Herceptin + Perjeta + chemo (Cisplatin / Capecitabine) vs. Herceptin + chemo
- ORR: 56.7% vs. 48.3% control
- mDOR: 10.2 months vs. 8.4 months control
- mPFS: 8.5 months vs. 7.0 months control
- mOS: 17.5 months vs. 14.2 months control

zymeworks

First-Line Metastatic HER2+ GEA Registrational Studies

Journal of Clinical Oncology
An American Society of Clinical Oncology Journal

Enter words / phrases / DOI / ISBN / authors / keywords / etc.

Newest Articles | Issues | Special Content | Authors | Subscribers | About | ASC

Journal of Clinical Oncology > List of Issues > Volume 39, Issue 15 suppl >

GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

Pembrolizumab plus trastuzumab and chemotherapy for HER2+ metastatic gastric or gastroesophageal junction (G/GEJ) cancer: Initial findings of the global phase 3 KEYNOTE-811 study.

Check for updates

Yelena Y. Janjigian, Akihito Kawazoe, Patricio Eduardo Yanez, Suxia Luo, Sara Lonardi, Oleksii Kolesnik, ...

Show More

Abstract Disclosures

Keynote 811 Trial – Conditional Approval 1L GEA

- Indication: 1L HER2-positive advanced gastric or gastro-esophageal junction cancer
- Drugs Tested: Herceptin + Keytruda + chemo (FP/CAPOX/SOX) vs. SOC (Herceptin + chemotherapy)
- ORR: 74% vs. 52% control
- mDOR: 10.6 months vs. 9.5 months control

zymeworks

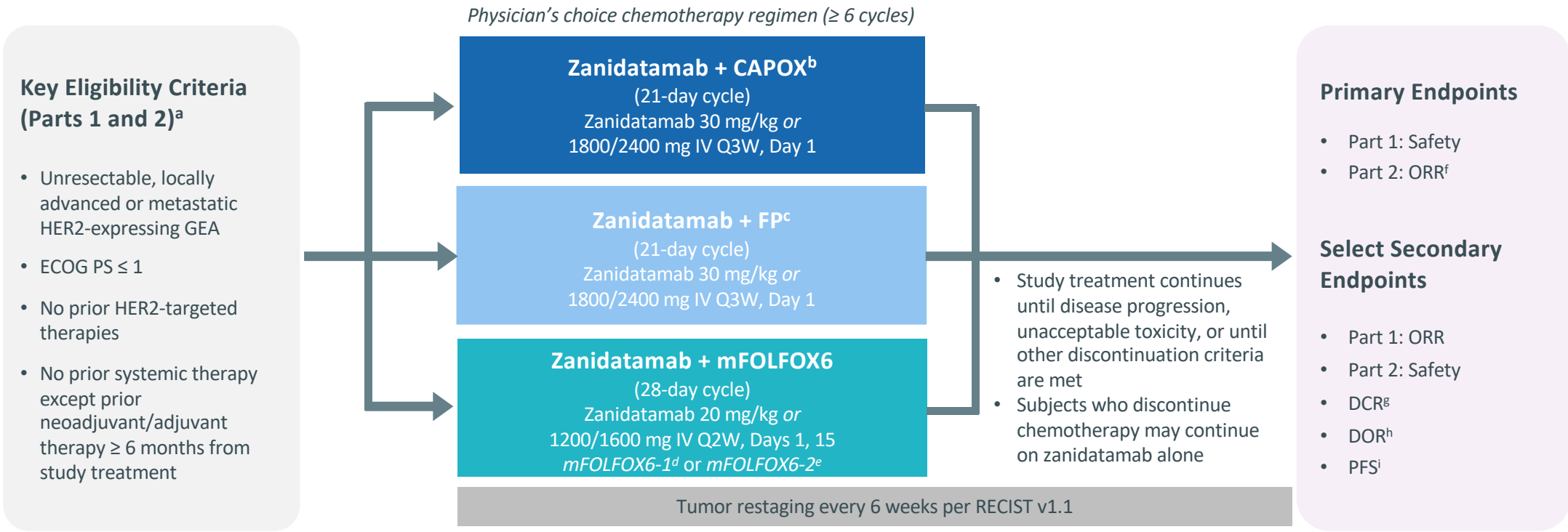
Phase 2 Study of Zanidatamab + Chemotherapy in First-line (1L) HER2-expressing Gastroesophageal Adenocarcinoma (GEA)

European Society of Medical Oncology (ESMO)

Geoffrey Ku, M.D.

Medical Oncologist and Principal Investigator, Memorial Sloan Kettering Cancer Center

ZWI-ZW25-201 Study Design for Subjects with HER2-expressing GEA



[a] Part 1 used local or central assessment of HER2 status and allowed HER2 IHC 3+ or IHC 2+ regardless of HER2 FISH status. Part 2 included only subjects with HER2-positive cancer (IHC 3+ or IHC 2+/FISH+). [b] CAPOX: capecitabine 1,000 mg/m2 PO BID, Days 1-15; oxaliplatin 130 mg/m2 IV Q3W, Day 1. [c]FP: cisplatin 80 mg/m2 IV Q3W, Day 1; 5-FU 800 mg/m2/day IV, continuous Days 1-5. [d]mFOLFOX6-1: leucovorin 400 mg/m2 IV Q2W, Days 1, 15; oxaliplatin 85 mg/m2 IV Q2W, Days 1, 15; 5-FU 1200 mg/m2/day IV, continuous Days 1-2 and 15-16, and 400 mg/m2 IV Q2W, Days 1, 15. [e]mFOLFOX6-2 is identical to mFOLFOX6-1 but omits the 5-FU 400 mg/m2 IV Q2W dose on Days 1 and 15. [f]Part 2 focused on antitumor activity of zanidatamab plus combination chemotherapy in subjects with HER2-positive cancer. [g]DCR was defined as a best response of CR, PR, or SD. [h]DOR was defined as time from first objective response that is subsequently confirmed to documented PD or death ≤ 30 days of last study treatment from any cause. [i]PFS was defined as the time from the first dose of study treatment to the date of documented disease progression, clinical progression, or death from any cause. 5-FU = 5-fluorouracil; DCR = disease control rate; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; FISH = fluorescence in situ hybridization; GEA = gastroesophageal adenocarcinoma; IHC = immunohistochemistry; ORR = objective response rate; PD = progressive disease; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SD = stable disease.

Demographics and Baseline Characteristics

		Subjects (N = 36)
Median age (range), years		58 (27–77)
Male sex, n (%)		32 (89)
Race, n (%)	Asian White	11 (32) 25 (68)
ECOG performance status, n (%)	0 1	23 (64) 13 (36)
Primary tumor location, n (%)	Esophageal Gastroesophageal junction Gastric	9 (25) 14 (39) 13 (36)
Stage IV disease at initial diagnosis, n (%)		29 (81)
HER2-positive, n (%)[a]	IHC 3+ IHC 2+/FISH+	32 (89) 28 (78) 4 (11)

[a]HER2-positive was defined as IHC 3+ or IHC 2+/FISH+.
ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry.

Data were extracted on July 28, 2021, from an unlocked database:

- Of 36 subjects with GEA enrolled, 19 (53%) continue on study treatment
- 12 (33%) subjects have discontinued treatment due to disease progression, 4 (11%) due to treatment-emergent AE, and 1 (3%) due to physician decision

Zanidatamab and/or Chemotherapy TRAEs

	Zanidatamab + CAPOX (n = 14)		Zanidatamab + FP (n = 2)		Zanidatamab + mFOLFOX6 (n = 20)		Total (N = 36)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
TRAE,[a] n (%)	14 (100)	8 (57)	2 (100)	1 (50)	20 (100)	16 (80)	36 (100)	25 (69)
Treatment-related SAE[b]	2 (14)	2 (14)	1 (50)	1 (50)	4 (20)	4 (20)	7 (19)	7 (19)
TRAEs leading to treatment discontinuation	0	0	0	0	4 (20)	1 (6)	4 (11)	1 (3)
TRAEs occurring in ≥ 20% of subjects and/or Grade ≥ 3 TRAEs in > 1 subject[c]								
Diarrhea	13 (93)	5 (36)	2 (100)	1 (50)	19 (95)	9 (45)	34 (94)	15 (42)
Nausea	11 (79)	1 (7)	1 (50)	0	15 (75)	1 (5)	27 (75)	2 (6)
Peripheral neuropathy	10 (71)	0	0	0	9 (45)	0	19 (53)	0
Fatigue	5 (36)	0	0	0	11 (55)	1 (5)	16 (44)	1 (3)
Decreased appetite	5 (36)	0	1 (50)	0	9 (45)	0	15 (42)	0
Hypokalemia	2 (14)	0	0	0	11 (55)	6 (30)	13 (36)	6 (17)
Vomiting	3 (21)	1 (7)	0	0	9 (45)	2 (10)	12 (33)	3 (8)
Hypomagnesemia	3 (21)	0	0	0	6 (30)	1 (5)	9 (25)	1 (3)
Dysgeusia	4 (29)	0	0	0	4 (20)	0	8 (22)	0
Stomatitis	2 (14)	0	0	0	6 (30)	0	8 (22)	0
Neutrophil count decreased	2 (14)	0	0	0	5 (25)	3 (15)	7 (19)	3 (8)
WBC decreased	0	0	0	0	6 (30)	2 (10)	6 (17)	2 (6)
Acute kidney injury	0	0	1 (50)	1 (50)	1 (5)	1 (5)	2 (6)	2 (6)
AESIs occurring in any subject								
Infusion-related reaction	4 (29)	0	1 (50)	0	0	0	5 (15)	0
Cardiac events[d]	0	0	0	0	3 (15)	0	3 (9)	0
Pneumonitis	0	0	0	0	1 (5)	0	1 (3)	0

[a]AEs were recorded using the Medical Dictionary for Regulatory Activities (MedDRA), with severity graded by investigators using NCI-CTCAE v5.0. [b]SAEs occurring in ≥ 2 subjects included 3 (9%) subjects with diarrhea, 2 (6%) with acute kidney injury, and 2 (6%) with hypokalemia. [c]Four (11%) subjects experienced grade 4 AEs: 1 (3%) lymphocyte count decreased, neutrophil count decreased, and white blood cell count decreased, and 3 (8%) hypokalemia; no treatment-related deaths were observed. [d]Includes 2 (6%) subjects with peripheral edema and 1 (3%) ejection fraction decreased.

5-FU = 5-fluorouracil; AE = adverse event; AESI = adverse event of special interest; CAPOX = capecitabine plus oxaliplatin; FP = 5-FU plus cisplatin; mFOLFOX6 = 5-FU plus oxaliplatin and leucovorin; SAE = serious adverse event; TRAE = treatment-related adverse event; WBC = white blood cell.

Diarrhea Prophylaxis

Due to early onset of grade 3 diarrhea in some subjects across all treatment regimens, mandatory prophylaxis with loperamide (4 mg BID × ≥ 7 days) was initiated for the first treatment cycle (implemented September 30, 2020)

- In the 25 subjects initiating treatment prior to implementation of antidiarrheal prophylaxis, the incidence of grade 3 diarrhea in Cycle 1 was 44% (11/25) overall (mFOLFOX6-1 46% [6/13], CAPOX 40% [4/10], FP 50% [1/2]).
- In the 11 subjects initiating treatment after implementation of antidiarrheal prophylaxis, the incidence of grade 3 diarrhea in Cycle 1 was 18% (2/11) overall (mFOLFOX6-2 29% [2/7], CAPOX 0% [0/4]).

Safety

Dose Confirmation and Dose-limiting Toxicities (DLTs) – Part 1

- **Zanidatamab + CAPOX:** No DLTs in 6 subjects; dosing of zanidatamab + CAPOX was confirmed for Part 2
- **Zanidatamab + FP:** One DLT (acute kidney injury, grade 3) in 2 subjects; FP continues to enroll in Part 1
- **Zanidatamab + mFOLFOX6-1:** Two DLTs (diarrhea, grade 3) in 13 subjects, and 8/13 (62%) with grade 3 diarrhea
  - Safety monitoring committee recommended a modified regimen (mFOLFOX6-2) that omits the 5-FU 400mg/m^2 bolus on Days 1, 15
- **Zanidatamab + mFOLFOX6-2:** One DLT (diarrhea, grade 3) in 7 subjects, and 2/7 (29%) with grade 3 diarrhea; dosing of zanidatamab + mFOLFOX6-2 was confirmed for Part 2

Efficacy

- Efficacy-evaluable population: all HER2-positive subjects with measurable disease in Parts 1 and 2
- Median follow-up time was 6.9 months across all treatment regimens in the efficacy evaluable population
- In the efficacy-evaluable population (N = 28), 17 (61%) remain on zanidatamab treatment

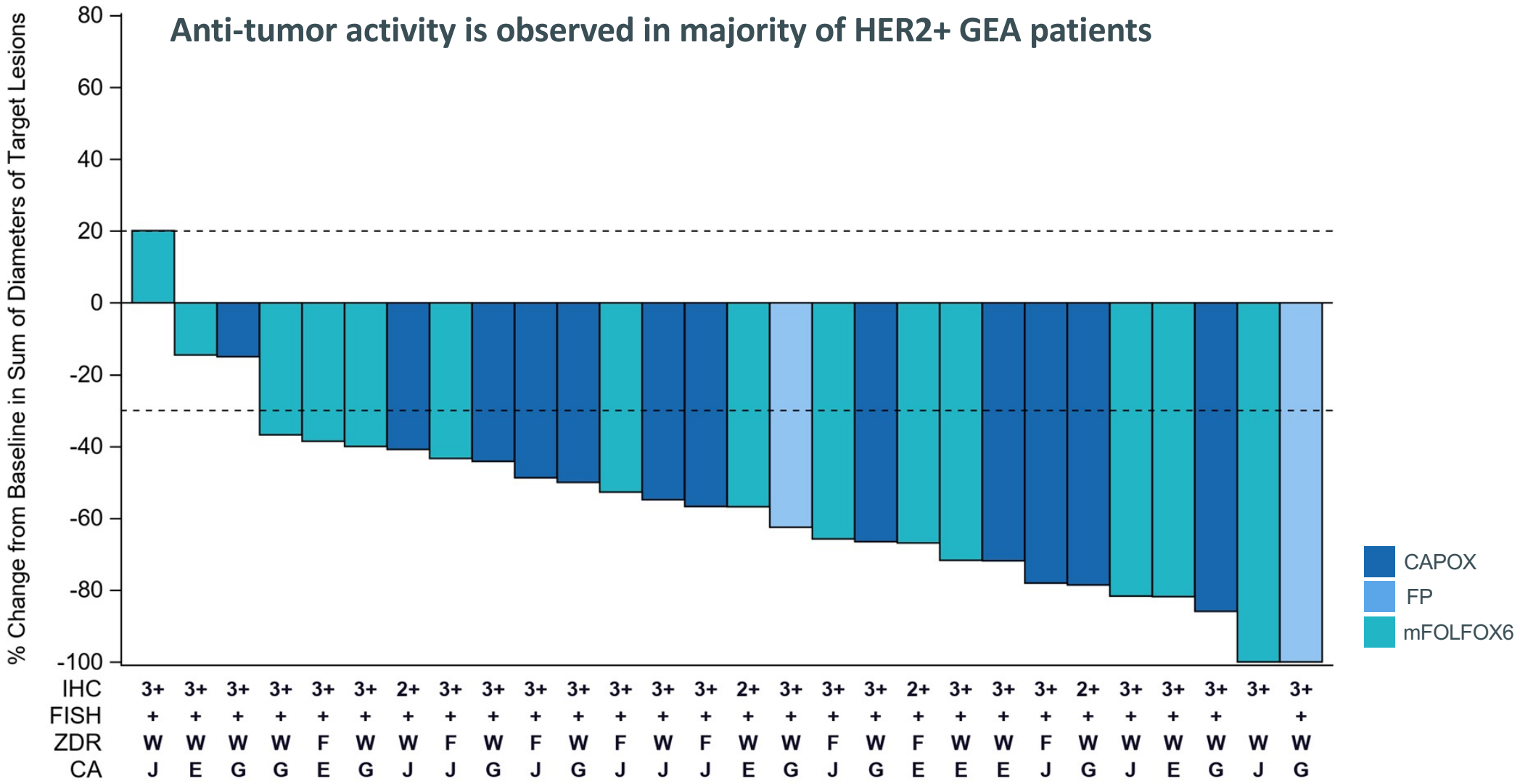
Objective Response Rate and Disease Control Rate

	Zanidatamab[a] + CAPOX N = 12	Zanidatamab[a] + FP N = 2	Zanidatamab[a] + mFOLFOX6 N = 14	Total N = 28
cORR[b], % (95% CI)	**92** (61.5, 99.8)	**100** (15.8, 100)	**57** (28.9, 82.3)	**75** (55.1, 89.3)
CR, n (%)	0	0	1 (7)	1 (4)
PR, n (%)	11 (92)	2 (100)	7 (50)	20 (71)
SD, n (%)	1 (8)	0	3 (21)	4 (14)
PD, n (%)	0	0	3 (21)	3 (11)
Disease Control Rate, % (95% CI)	**100** (73.5, 100)	**100** (15.8, 100)	**79** (49.2, 95.3)	**89** (71.8, 97.7)

[a]HER2-positive was defined as IHC 3+ or IHC 2+/FISH+. [b]cORR included a baseline scan and a confirmatory scan obtained ≥ 4 weeks following initial documentation of objective response; the efficacy-evaluable population was defined as all HER2-positive subjects who had ≥ 1 evaluable post-baseline disease assessment or discontinued study treatment due to death or clinical progression.

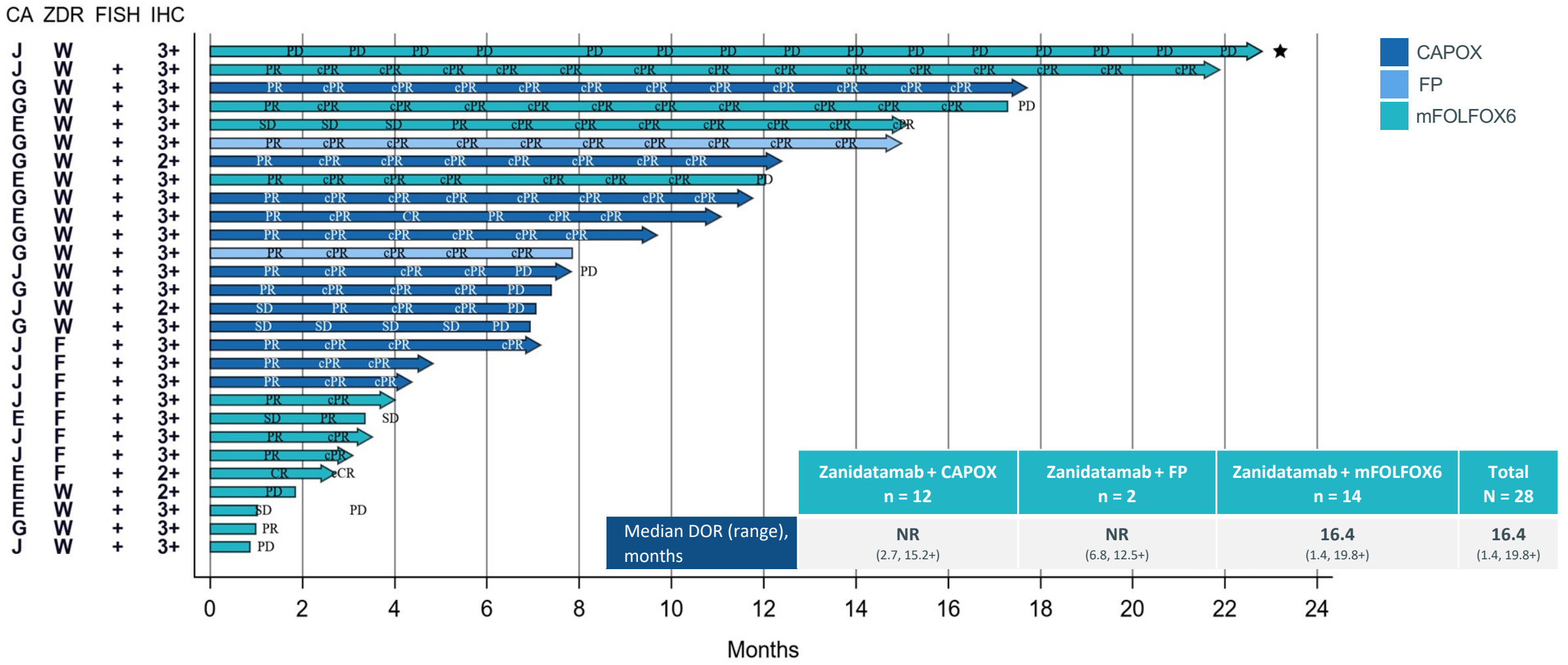
5-FU = 5-fluorouracil; CAPOX = capecitabine plus oxaliplatin; CR = complete response; DCR = disease control rate; FP = 5-FU and cisplatin; mFOLFOX6 = 5-FU plus oxaliplatin and leucovorin; NR = not reached; ORR = objective response rate (CR + PR); PD = progressive disease; PR = partial response; SD = stable disease.

Change in Target Lesion Size



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

Treatment Duration and Duration of Response

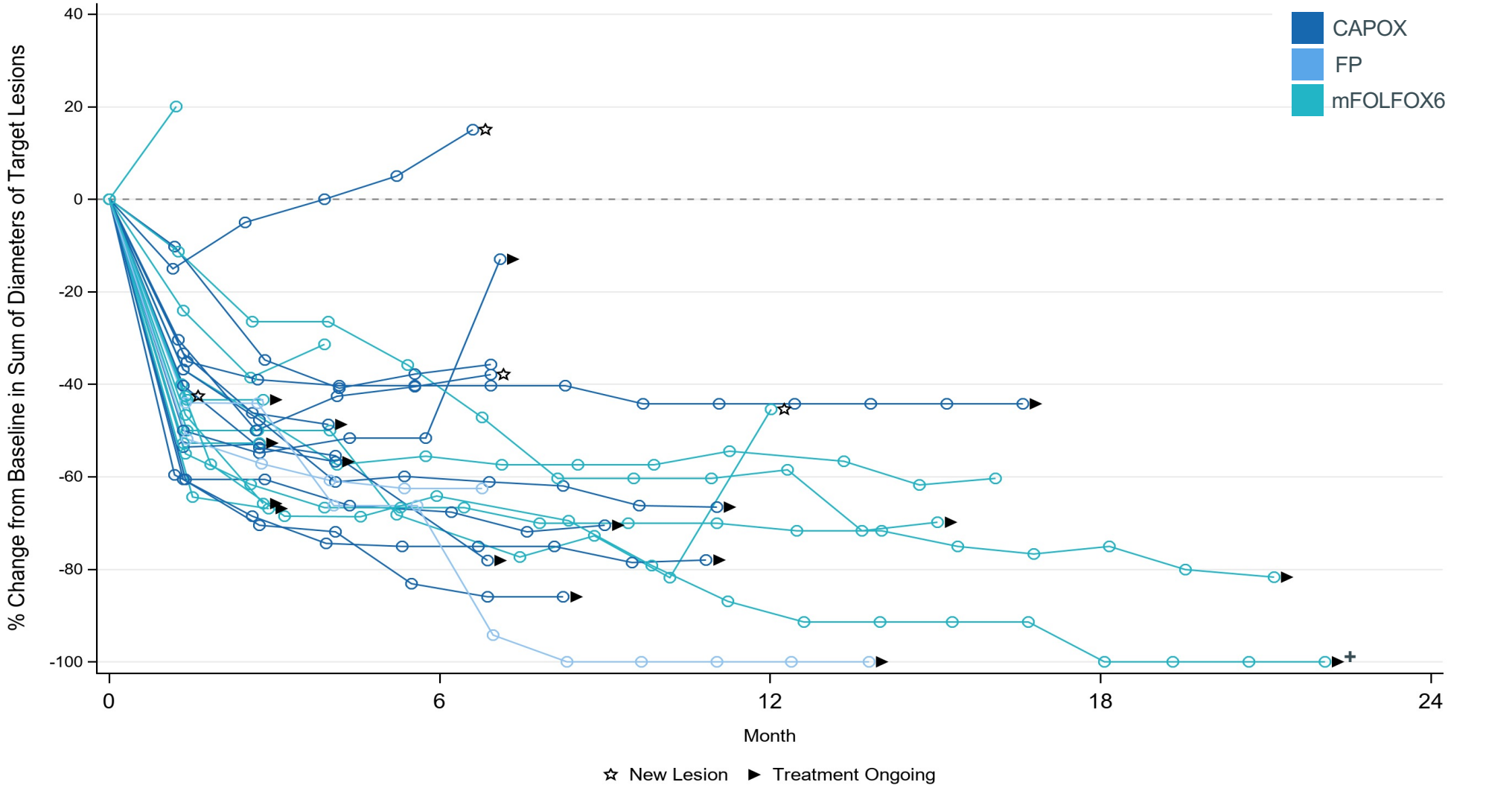


	Zanidatamab + CAPOX n = 12	Zanidatamab + FP n = 2	Zanidatamab + mFOLFOX6 n = 14	Total N = 28
Median DOR (range), months	NR (2.7, 15.2+)	NR (6.8, 12.5+)	16.4 (1.4, 19.8+)	16.4 (1.4, 19.8+)

★ An MRI performed for neurologic symptoms on Day 8 demonstrated brain metastases, which were treated with radiation therapy. Subject remained on mFOLFOX6-1 with zanidatamab and has had long term disease control since treatment of brain metastases.

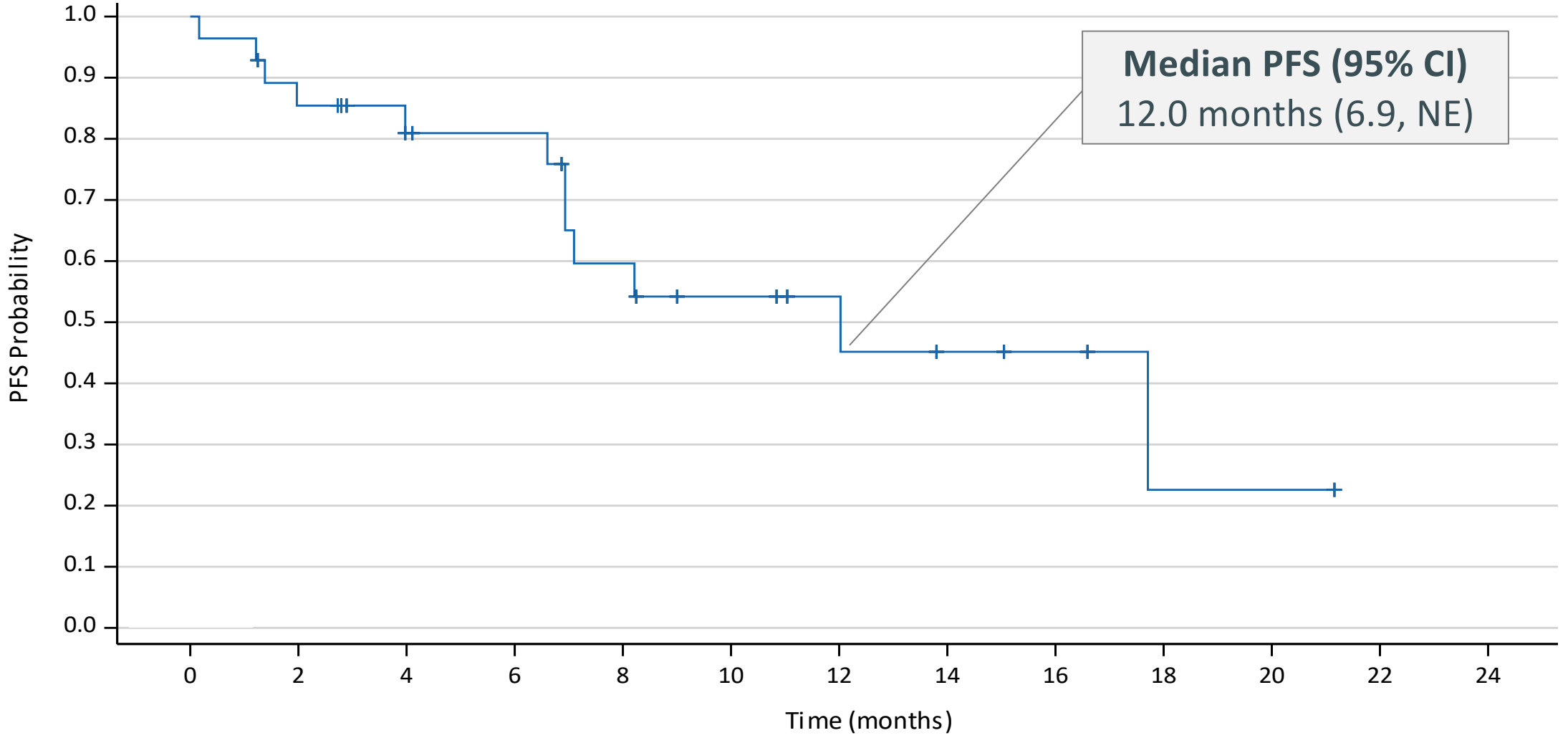
5-FU = 5-fluorouracil; CA, primary tumor location; CAPOX = capecitabine plus oxaliplatin; cCR = confirmed CR; CR = complete response; cPR = confirmed PR; DOR = duration of response; E = esophageal cancer; F = flat dosing; FISH = fluorescence in situ hybridization; FP = 5-FU plus cisplatin; G = gastric cancer; IHC = immunohistochemistry; J = gastroesophageal junction cancer; mFOLFOX6 = 5-FU plus oxaliplatin and leucovorin; NR = not reached; PD = progressive disease; PR = partial response; SD = stable disease; W = weight-based dosing; ZDR = zanidatamab dosing; + = indicates that the subject is in response at the time of data extractionregimen.

Change in Target Lesion Size Over Time



+ An MRI performed for neurologic symptoms on Day 8 demonstrated brain metastases, which were treated with radiation therapy. Subject remained on mFOLFOX6-1 with zanidatamab and has had long term disease control since treatment of brain metastases.

Progression-free Survival



NE = not estimable; PFS = progression-free survival

Conclusions

In patients with HER2-positive GEA, zanidatamab combined with standard first-line chemotherapy demonstrates encouraging antitumor activity

- 75% cORR across all treatment regimens with median DOR of 16.4 months
  - Zanidatamab + CAPOX: 92% cORR with 9 of 12 responses ongoing (range: 2.7, 15.2+ months)
  - Zanidatamab + FP: 100% cORR with 1 of 2 responses ongoing (range: 6.8, 12.5+ months)
- Median PFS was 12.0 months, with a median follow-up of 6.9 months

TRAEs are generally consistent with previous reports of zanidatamab and/or the chemotherapy regimens

- Diarrhea is the most frequent TRAE observed across treatment regimens, is manageable in the outpatient setting, and is mitigated by prophylaxis
- No severe (grade ≥ 3) infusion-related reactions or cardiac events were observed

Acknowledgements

Acknowledgments

We sincerely thank all patients and their families. We thank all the investigators, clinical trial researchers, personnel, and staff who contributed to the trial.

Upcoming Zanidatamab Studies

Neil Josephson, MD

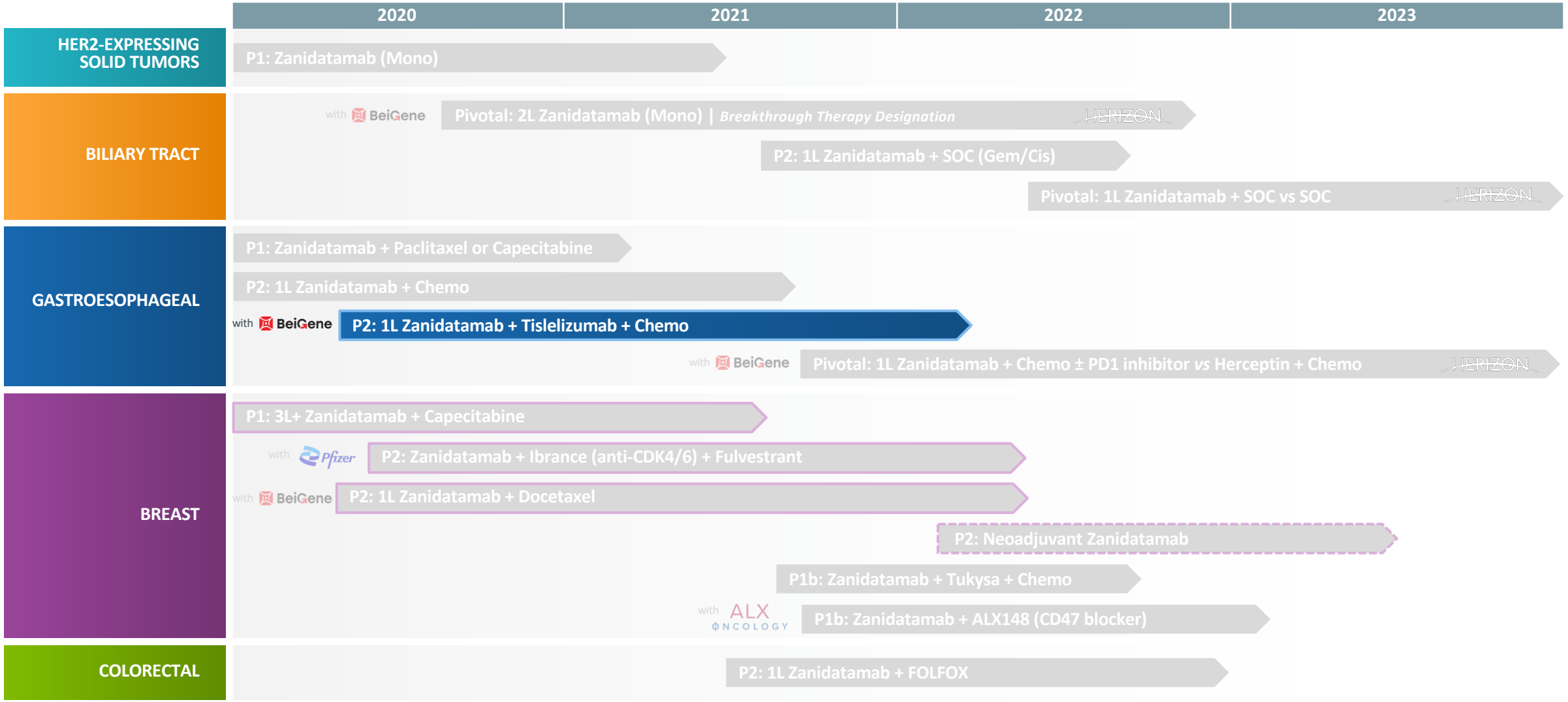
Interim CMO & SVP, Clinical Research

Zanidatamab Clinical Results in GEA

	Zani Monotherapy (N = 33)	Zani + Single Agent Chemotherapy (N = 24)		Zani + Combination Chemotherapy (N = 28)		
	Median 3 prior lines of therapy	Median 2-3 prior lines of therapy		First-Line		
Current Phase	Phase I	Phase I		Phase II		
ORR	33% cORR ~40% unconfirmed ORR	54% cORR (overall)		75% cORR (overall)		
		Paclitaxel 50% cORR	Capecitabine 57% cORR	CAPOX 92% cORR	FP 100% cORR	mFOLFOX6 57% cORR
mDOR	6.0m mDOR	8.9m mDOR (overall)		16.4m mDOR (overall)		
mPFS	3.6m mPFS	5.6m mPFS (overall)		12.0m mPFS (overall)		

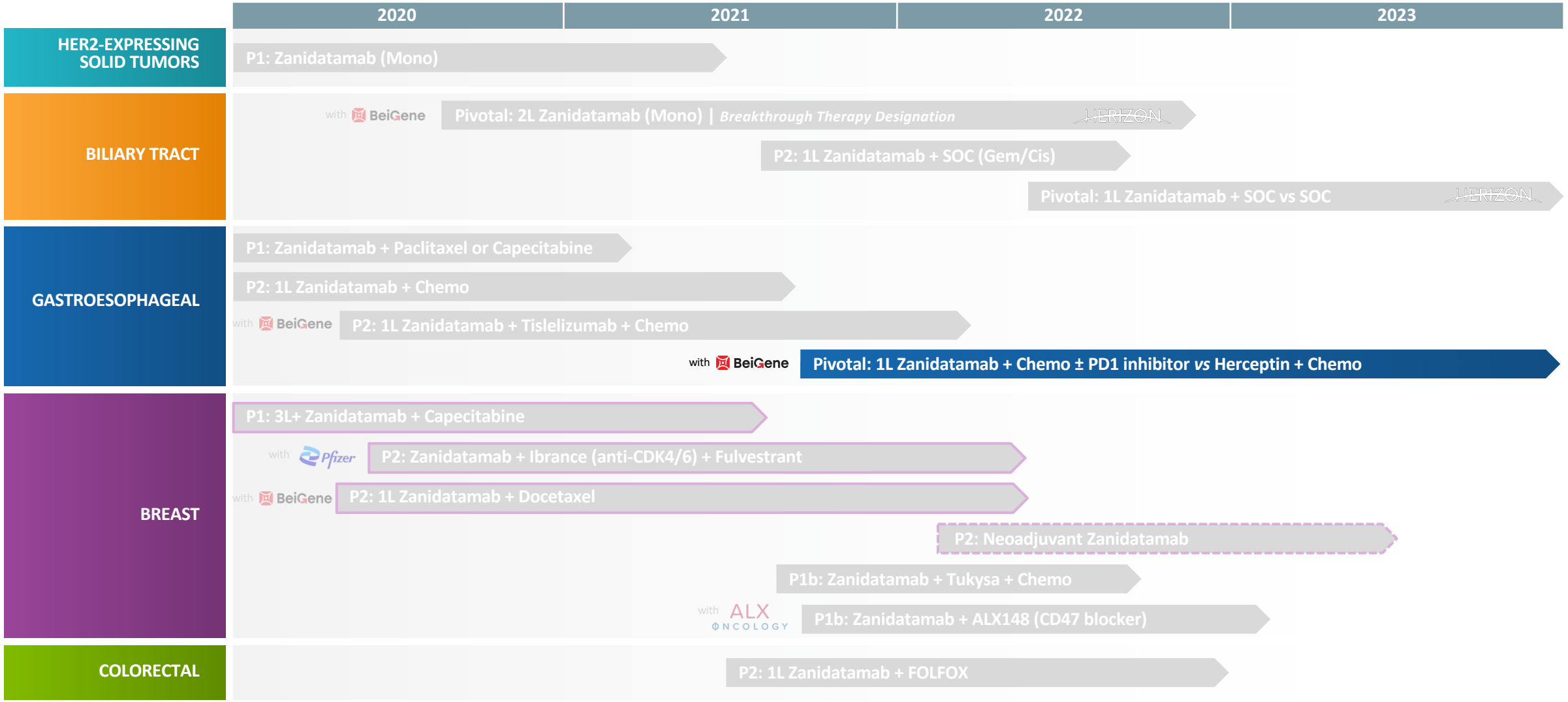
zymeworks

Zanidatamab Clinical Development



BLA-Biologics License Application | Pending Final Study Design ----- | Upcoming Zanidatamab Data Readout ——

Zanidatamab Clinical Development



BLA-Biologics License Application | Pending Final Study Design ----- | Upcoming Zanidatamab Data Readout ——

Closing Remarks

Ali Tehrani, PhD
President & CEO

Q&A

Ali Tehrani, PhD
President & CEO

Neil Josephson, MD
Interim CMO & SVP, Clinical Research

Geoffrey Ku, MD
Medical Oncologist and Principal Investigator, Memorial Sloan Kettering Cancer Center