



Webcast: HERIZON-GEA-01 Pivotal Trial Design and Zanidatamab GI Cancers Commercial Strategy

November 9th

4:15pm ET (1:15pm PT)

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 clinical development of our product candidates, related clinical trials, anticipated study design, anticipated timelines and interactions with regulators, potential therapeutic effects of zanidatamab alone or in combination with other treatments, ability to obtain regulatory approval for zanidatamab, anticipated addressable market, the commercial potential of zanidatamab, including its potential to achieve blockbuster status, potential to achieve leadership share in the market, factors affecting potential pricing, our preclinical pipeline, 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 the impact of the COVID-19 pandemic on our business, research and clinical development plans and timelines and results of operations, including impact on our clinical trial sites, collaborators, and contractors who act for or on our behalf, may be more severe and more prolonged than currently anticipated; clinical trials may not demonstrate safety and efficacy of any of our or our collaborators’ product candidates; our ongoing discovery and pre-clinical efforts may not yield additional product candidates; any of our or our collaborators’ product candidates may fail in development, may not receive required regulatory approvals, or may be delayed to a point where they are not commercially viable; even if approved, the commercial success of our product candidates may fail to meet our expectations due to factors outside of our control, including the impact of competition; we may not achieve additional milestones in our proprietary or partnered programs; regulatory agencies may impose additional requirements or delay the initiation of clinical trials; regulatory agencies may be delayed in reviewing, commenting on or approving any of our or our collaborators’ clinical development plans as a result of the COVID-19 pandemic, which could further delay development timelines; the impact of competition; the impact of expanded product development and clinical activities on operating expenses; impact of new or changing laws and regulations; adverse conditions in the general domestic and global economic markets; as well as the other risks identified in the "Risk Factors" and other sections of our public filings with the Securities and Exchange Commission and Canadian securities regulators.

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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.



Introduction

Ali Tehrani, Ph.D.
President & CEO



Zanidatamab in Gastrointestinal (GI) Cancers

Neil Josephson, M.D.
Chief Medical Officer

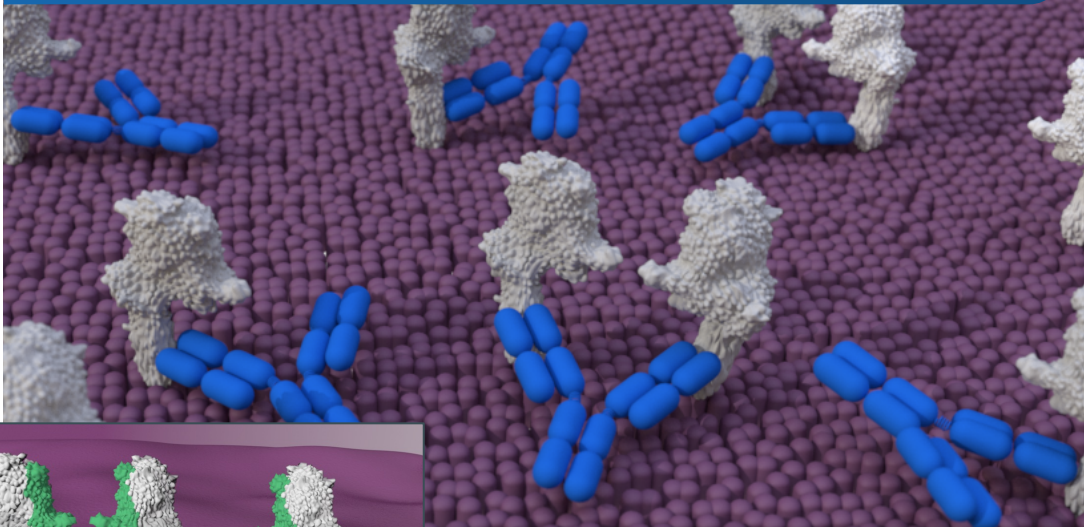


Dual HER2-Binding of Zanidatamab Drives Unique MOA

Zanidatamab's unique binding geometry promotes:

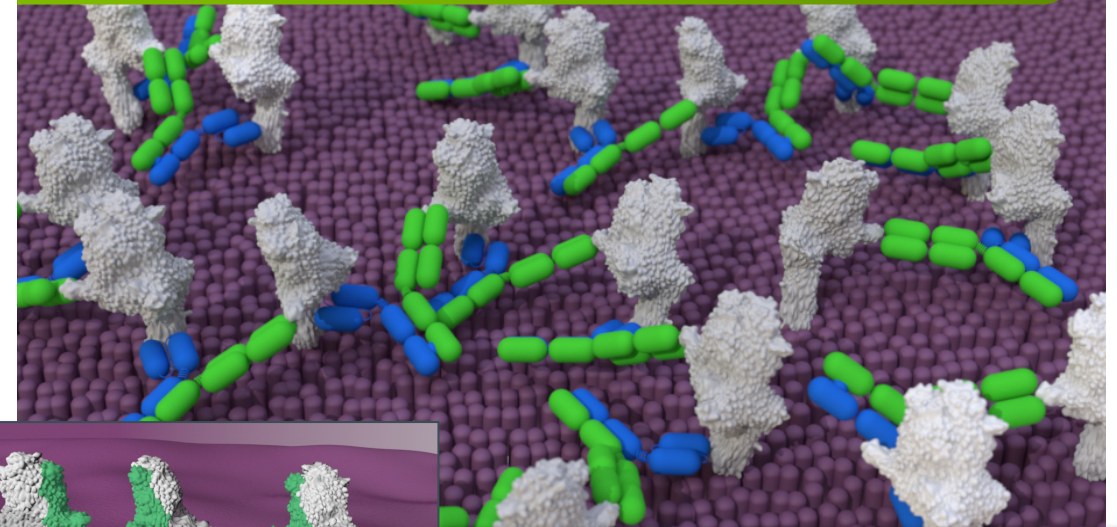
- Binding to HER2 across a range of expression levels (low to high)
- HER2-receptor clustering, internalization, and downregulation
- Inhibition of growth factor-dependent and -independent tumor cell proliferation
- Antibody-dependent cellular cytotoxicity and phagocytosis; and complement-dependent cytotoxicity

Typical Monoclonal (Trastuzumab) Binding



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

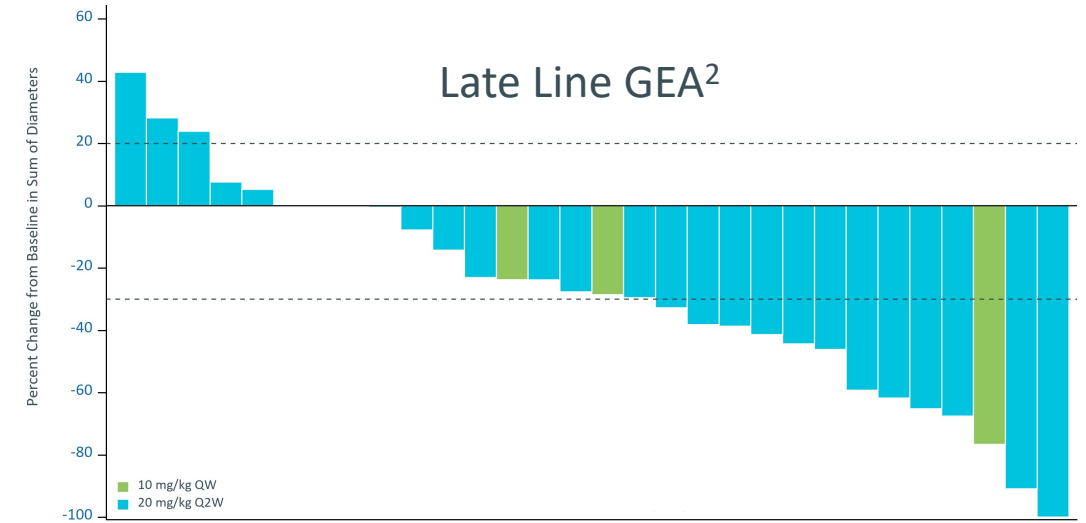
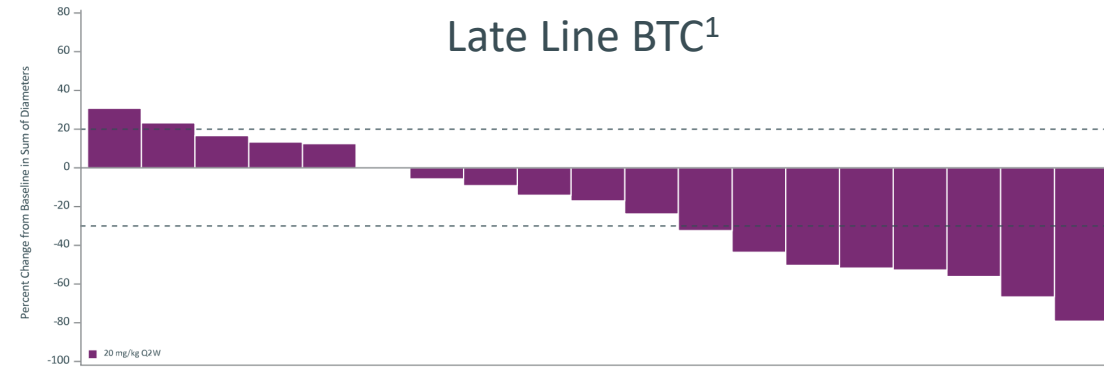
Zanidatamab Promotes Receptor Clustering



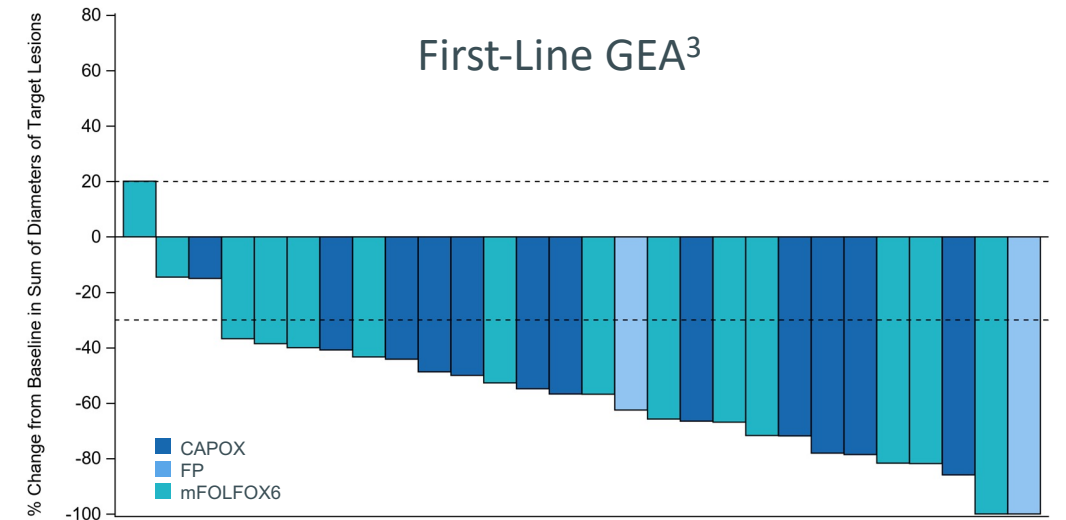
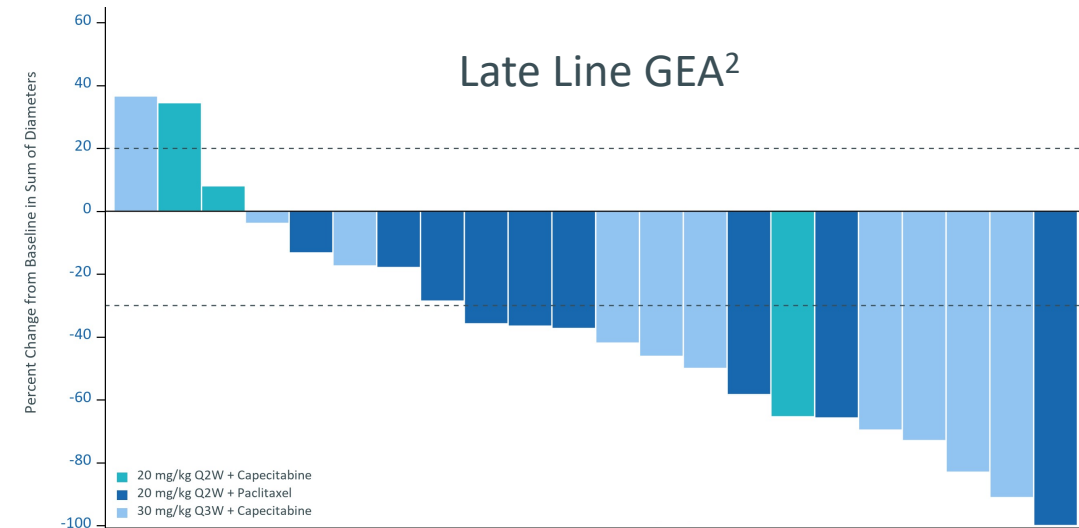
Biparatopic *Trans* Binding –
Each HER2 receptor can be targeted by two zanidatamab antibodies

Zanidatamab is Active in HER2-Expressing GI Cancers

Monotherapy



In Combination with Chemotherapy

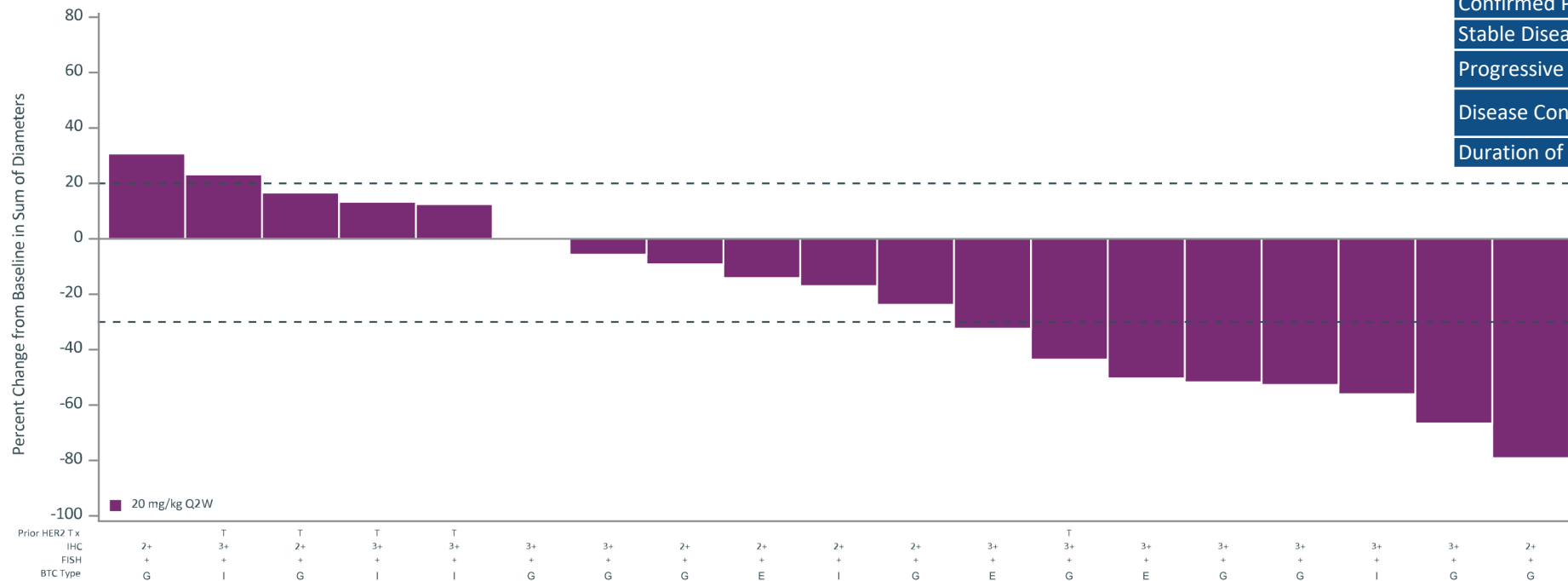


1. Funda Meric-Bernstam, et al. Zanidatamab (ZW25) in HER2-positive biliary tract cancers (BTCs): Results from a phase I study. *Journal of Clinical Oncology* 2021 39:3_suppl, 299-299
 2. Funda Meric-Bernstam, et al. Zanidatamab (ZW25) in HER2-expressing gastroesophageal adenocarcinoma (GEA): Results from a phase I study., *Journal of Clinical Oncology* 2021 39:3_suppl, 164-164
 3. G. Ku, et al. Phase (Ph) II study of zanidatamab + chemotherapy (chemo) in first-line (1L) HER2 expressing gastroesophageal adenocarcinoma (GEA), *Annals of Oncology*, Volume 32, S1044 - S1045
 BTC: biliary tract cancer; GEA: gastroesophageal adenocarcinoma; GI: gastrointestinal

Zanidatamab Monotherapy in HER2-Expressing Late-Line BTC



Data supports pivotal trial now enrolling in Second-Line Biliary Tract Cancer (HERIZON-BTC-01; NCT04466891)



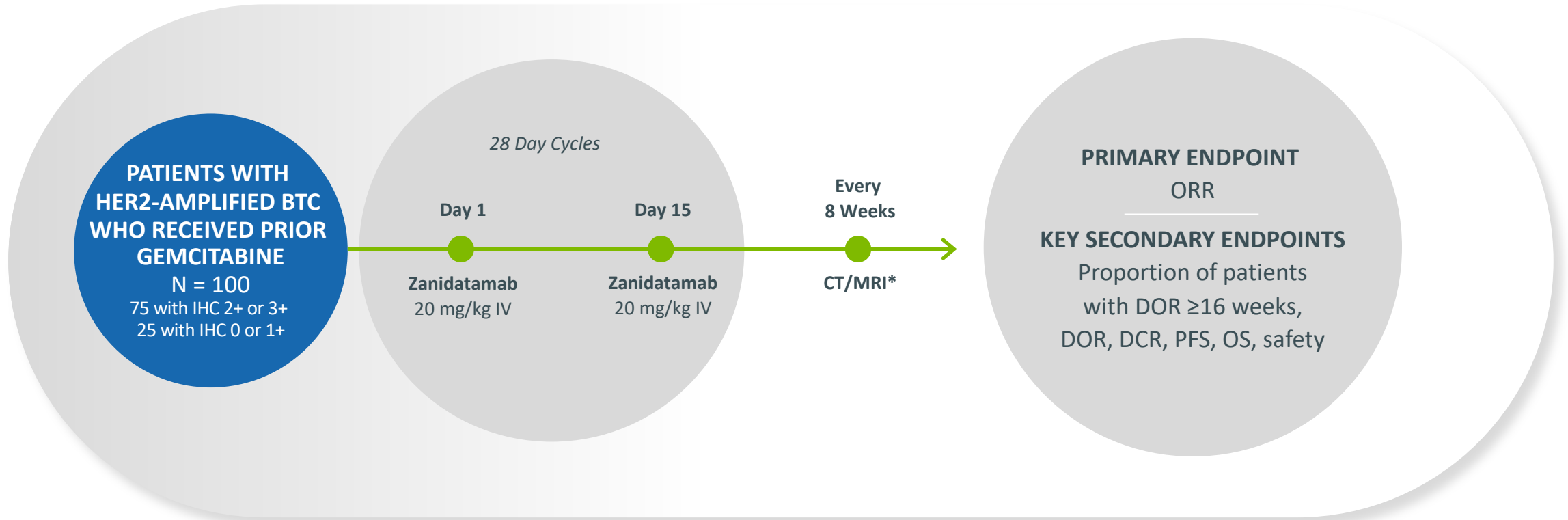
(N = 20)
n (%)

Confirmed Partial Response (cPR)	8 (40)
Stable Disease (SD)	5 (25)
Progressive Disease (PD)	7 (35)
Disease Control Rate (cPR+SD)	13 (65)
Duration of response	7.4 months

Zanidatamab was well-tolerated in BTC patients with no patient experiencing a Grade 3 or higher zanidatamab-related AE

BTC = biliary tract cancer, E = Extrahepatic Cholangiocarcinoma, FISH = fluorescence in situ hybridization; I = Intrahepatic Cholangiocarcinoma; IHC = immunohistochemistry; G = Gallbladder; T = trastuzumab; Trt = treatment.
 Response-evaluable: 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. Note: One patient was not response evaluable because they withdrew from the study. One patient in the response-evaluable set died prior to the post-baseline tumor measurement and is not included in the plot (counted as PD). Data snapshot from unlocked database 16 November 2020 and subject to change.
 Source: Funda Meric-Bernstam, et al. Zanidatamab (ZW25) in HER2-positive biliary tract cancers (BTCs): Results from a phase I study. Journal of Clinical Oncology 2021 39:3_suppl, 299-299

HERIZON-BTC-01 Study Design and Key Endpoints






BTC: biliary tract cancer; CT: computed tomography; DCR: disease control rate; DOR: duration of response; ICR: independent central review; IHC: immunohistochemistry; IV: intravenous; MRI: magnetic resonance imaging; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; Q2W: every 2 weeks; RECIST: Response Evaluation Criteria in Solid Tumors.

*For tumor assessment per RECIST v1.1.2

Zanidatamab Clinical Results in 3L+ HER2-Positive GEA



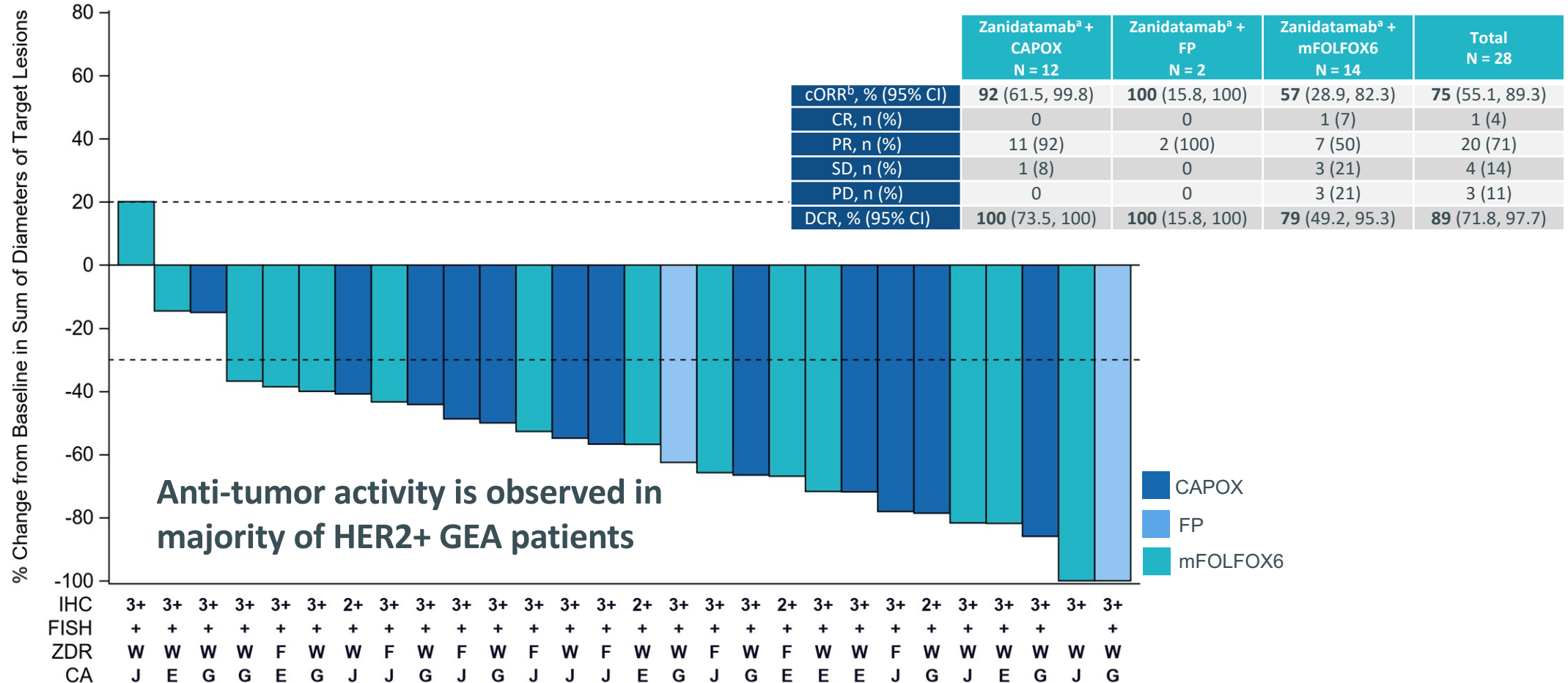
	 Zanidatamab Monotherapy (N = 33)	 Zanidatamab + Single Agent Chemotherapy (N = 24)	 Enhertu DESTINY-GASTRIC-02 (N = 79)
	Median 3 prior lines of therapy	Median 2-3 prior lines of therapy	2L
Current Phase	Phase I	Phase I	Phase II
ORR	33% cORR ~40% unconfirmed ORR	54% cORR (overall) Paclitaxel 50% cORR Capecitabine 57% cORR	38% cORR
mDOR	6.0m mDOR	8.9m mDOR (overall)	8.1m mDOR
mPFS	3.6m mPFS	5.6m mPFS (overall)	5.5m mPFS
Reference	Funda Meric-Bernstam et al., "Zanidatamab (ZW25) in HER2-expressing Gastroesophageal Adenocarcinoma (GEA): Results from a Phase 1 Study" ASCO GI 2021	Funda Meric-Bernstam et al., "Zanidatamab (ZW25) in HER2-expressing Gastroesophageal Adenocarcinoma (GEA): Results from a Phase 1 Study" ASCO GI 2021	Eric Van Cutsem et al., "Primary analysis of a phase II single-arm trial of trastuzumab deruxtecan (T-DXd)..." ESMO Congress 2021

Zanidatamab Plus Chemotherapy in HER2+ First-Line GEA

Activity



93% cORR for Proposed Phase 3 Regimen (zanidatamab + CAPOX or FP)



Source: G. Ku, et al. Phase (Ph) II study of zanidatamab + chemotherapy (chemo) in first-line (1L) HER2 expressing gastroesophageal adenocarcinoma (GEA), Annals of Oncology, Volume 32, S1044 - S1045

^aHER2-positive was defined as IHC 3+ or IHC 2+/FISH+. ^bcORR 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. Data were extracted on July 28, 2021, from an unlocked database

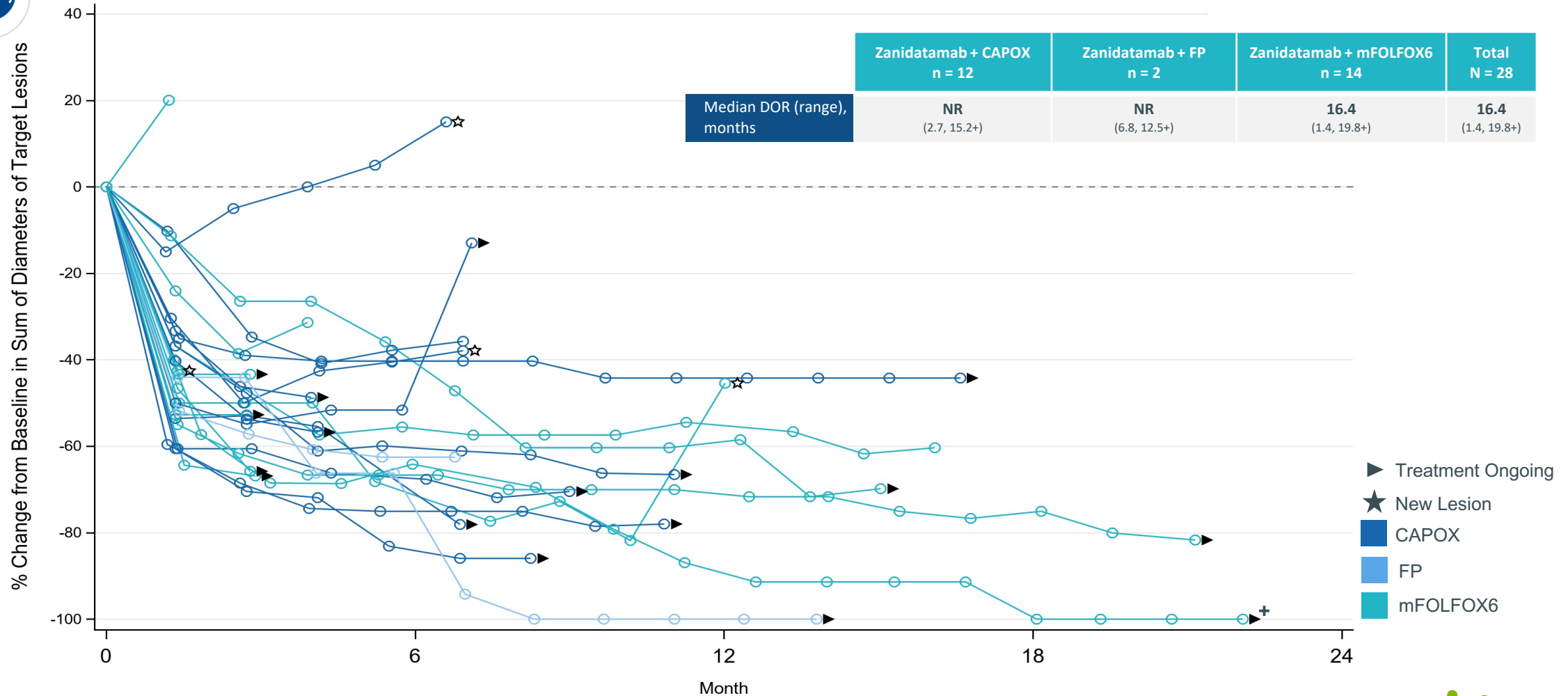
5-FU = 5-fluorouracil; CAPOX = capecitabine plus oxaliplatin; cORR = confirmed objective response rate; CR = complete response; DCR = disease control rate; E = esophageal cancer; F = flat dosing; FISH = fluorescence in situ hybridization; FP = 5-FU and cisplatin; G = gastric cancer;

IHC = immunohistochemistry; J = gastroesophageal junction cancer; 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; W = weight-based dosing; ZDR = zanidatamab dosing regimen.

Change in Target Lesion Size Over Time



Median Progression Free Survival of 12.0 months



Source: G. Ku, et al. Phase (Ph) II study of zanidatamab + chemotherapy (chemo) in first-line (1L) HER2 expressing gastroesophageal adenocarcinoma (GEA), Annals of Oncology, Volume 32, S1044 - S1045.

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

Zanidatamab Plus Chemotherapy in HER2+ First-Line GEA








Safety

- Zanidatamab plus chemotherapy in first-line GEA has a manageable safety profile
- Majority of treatment-related adverse events (TRAEs) considered mild to moderate in severity (grade 1 or 2)
- Most common grade ≥ 3 TRAE was diarrhea, which was manageable in outpatient settings
 - Introduction of prophylactic loperamide reduced incidence of grade 3 diarrhea in Cycle 1 from 44% to 18%
- No severe (grade ≥ 3) infusion-related reactions or cardiac events observed

Relevant Trials in First-Line HER2-Positive Gastric Cancer



	 Zanidatamab ESMO '21 zanidatamab + chemo [FP/CAPOX/mFOLFOX6] N = 36	 BeiGene zanidatamab + tislelizumab + chemo [CAPOX]	 KEYNOTE-811 trastuzumab + pembrolizumab + chemo [FP/CAPOX/SOX] N = 264	 JACOB trastuzumab + pertuzumab + chemo [XP/FP] N = 780	 TOGA trastuzumab + chemo [XP/FP] N = 594			
Current Phase	Ph II	Ph II	Conditionally Approved (US) First-Line HER2+ mGC/GEJC	Not Approved	Approved First-Line HER2+ SOC GEA			
ORR	zanidatamab + chemo 89% DCR 75% ORR	-	trastuzumab + pembrolizumab + chemo 74% ORR	trastuzumab + chemo 52% ORR	trastuzumab + pertuzumab + chemo 56.7% ORR	trastuzumab + chemo 48.3% ORR	trastuzumab + chemo 47% ORR	chemo 35% ORR
mDOR	16.4m mDOR	-	10.6m mDOR	9.5m mDOR	10.2m mDOR	8.4 m mDOR	6.9m mDOR	4.8m mDOR
mPFS	12.0m mPFS	-	-	-	8.5m mPFS	7.0m mPFS	6.7m mPFS	5.5m mPFS
mOS	-	-	-	-	17.5m mOS	14.2m mOS	13.1m mOS ¹	11.7m mOS ¹
Reference	Geoffrey Ku et al., "Phase (Ph) 2 Study of Zanidatamab + Chemo...", ESMO Congress (2021)	ClinicalTrials.gov Identifier: NCT04276493	Yelena Y. Janjigian et al., "Pembrolizumab plus trastuzumab and chemotherapy...", Journal of Clinical Oncology (2021)	Tabernero, Josep et al., "Pertuzumab plus trastuzumab and chemotherapy...", The Lancet. Oncology (2018)	Yung-Jue Bang et al., "Trastuzumab in combination with chemotherapy...", Lancet (2010)			

¹ As per updated OS reported in FDA Label as accessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5250lbl.pdf
 DCR: disease control rate; GEA: gastroesophageal adenocarcinoma; ESMO: European Society of Medical Oncology; GEJC: gastroesophageal junction cancer; mDOR: median duration of response; mGC: metastatic gastric cancer; mOS: median overall survival;
 mPFS: median progression-free survival; ORR: overall response rate; SOC: standard of care
 Note: Table includes cross-trial comparisons and is not meant to be indicative of comparisons made in double-blind, randomized trials.

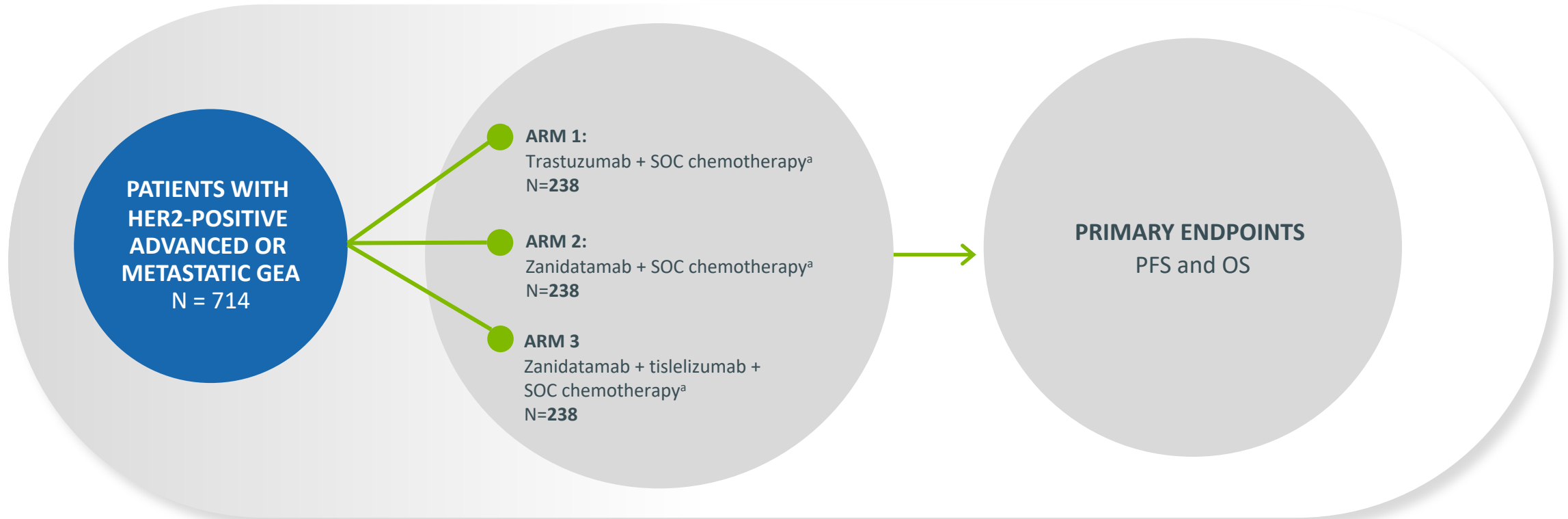


HERIZON-GEA-01 Trial Design

Neil Josephson, M.D.

Chief Medical Officer



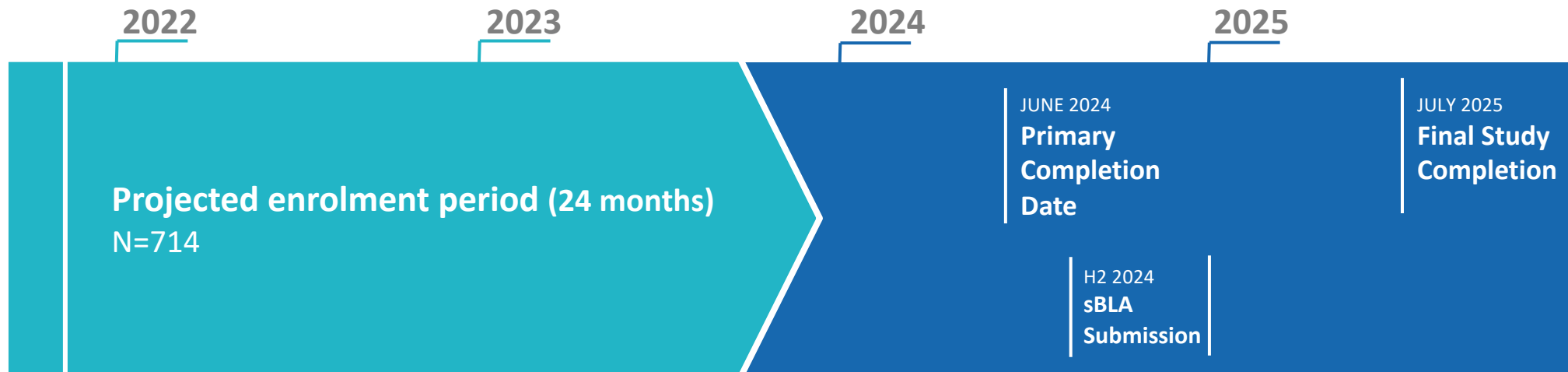


- Global Study
- Open-label with disease assessments per Blinded Independent Central Review (BICR)
- First HER2 pivotal trial to study complete GEA spectrum
 - Patient population includes gastric, esophageal, and gastroesophageal junction cancers
- Three-arm design
 - 1:1:1 randomization to show the contributions of zanidatamab (HER2-bispecific) and tislelizumab (PD1 inhibitor)
- Stratification by geographic region, HER2 IHC 2+ vs 3+, and ECOG performance status
- PD-L1 non-selected
- Dual Primary endpoints: PFS and OS



Designed to support an indication for **zanidatamab and chemotherapy with or without tislelizumab as first-line treatment for HER2-positive gastric, esophageal, and gastroesophageal junction cancers**

HERIZON-GEA-01 Study Timeline



~300 Sites Across 38 Countries



North America

Canada
Mexico

South America

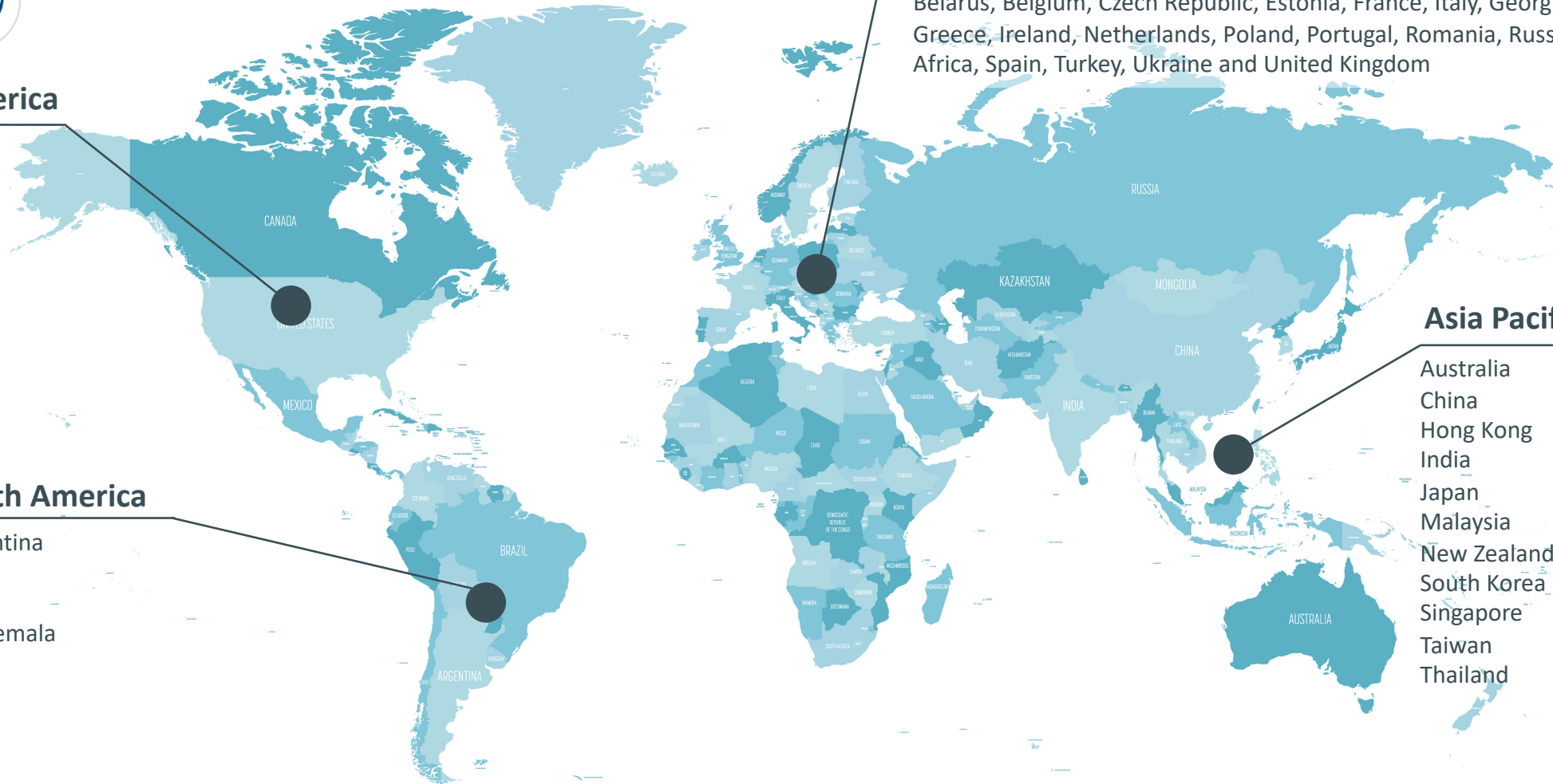
Argentina
Brazil
Chile
Guatemala
Peru

Europe, Middle East and Africa (EMEA)

Belarus, Belgium, Czech Republic, Estonia, France, Italy, Georgia, Germany, Greece, Ireland, Netherlands, Poland, Portugal, Romania, Russia, Serbia, South Africa, Spain, Turkey, Ukraine and United Kingdom

Asia Pacific (APAC)

Australia
China
Hong Kong
India
Japan
Malaysia
New Zealand
South Korea
Singapore
Taiwan
Thailand





- Zanidatamab is a novel HER2-targeted bispecific antibody with a binding geometry that drives multiple mechanisms of action
- Clinical data demonstrates that zanidatamab monotherapy has potent anti-tumor activity in HER2-expressing BTC and GEA
- In GEA, zanidatamab in combination with chemotherapy produces high overall response rates with durable tumor control
- HERIZON-BTC-01 is Zymeworks' first pivotal study; it is enrolling well and will support submission of a Biologics License Application for previously treated advanced/unresectable or metastatic HER2-expressing BTC in 2023
- HERIZON-GEA-01 is open for enrollment; this 3-arm study will evaluate zanidatamab in combination with SOC chemotherapy with and without tislelizumab for the treatment of 1L HER2-positive gastroesophageal adenocarcinoma

Zanidatamab Commercial Opportunity in HER2-Positive Gastrointestinal Cancers

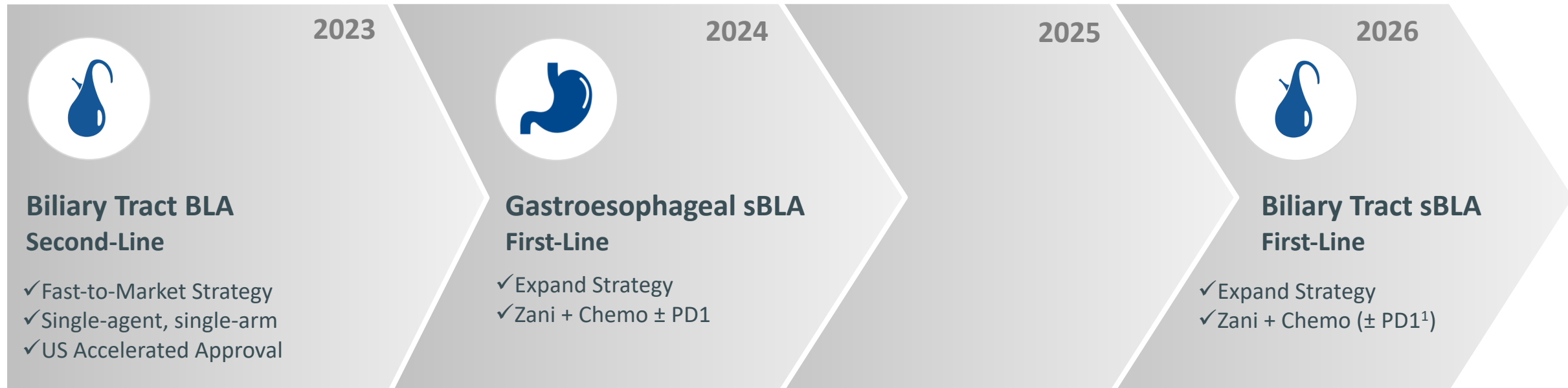
James Priour, MBA

Chief Commercial Officer



Zanidatamab Has Blockbuster Peak Sales Potential in Biliary Tract Cancer and Gastroesophageal Adenocarcinoma if Approved

3 BLAs in Gastrointestinal Cancers in Next 5 Years



New Backbone Antibody for the treatment of HER2-positive cancers

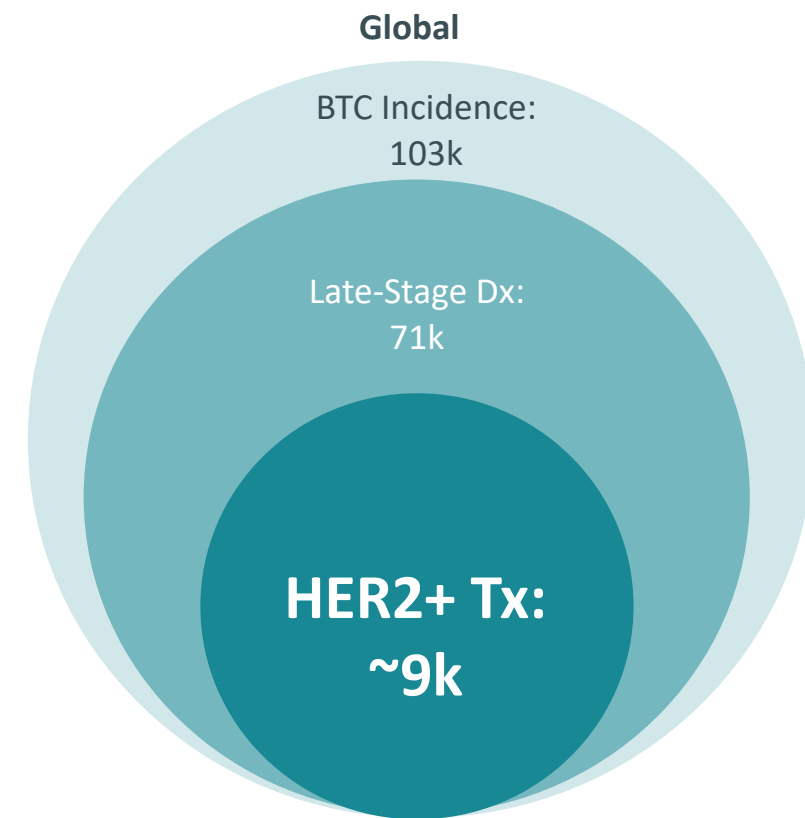
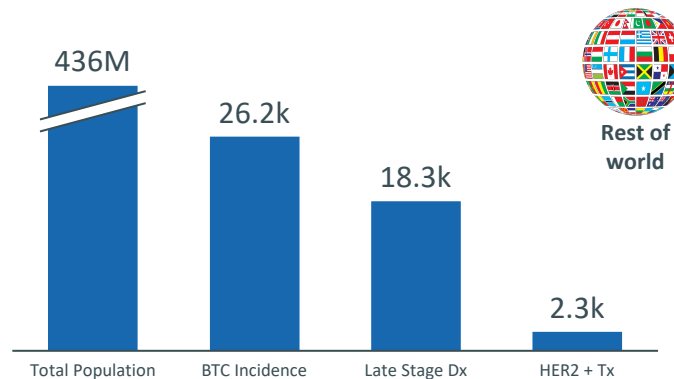
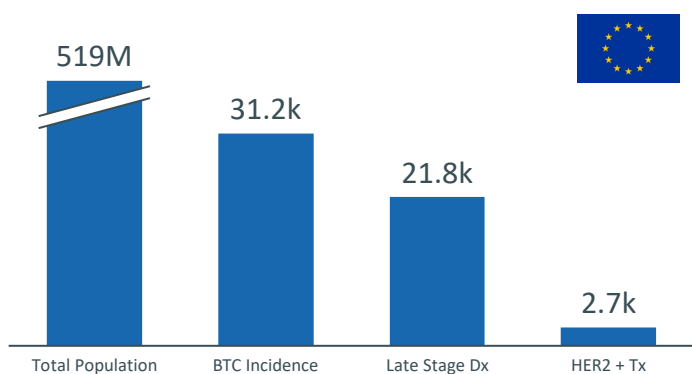
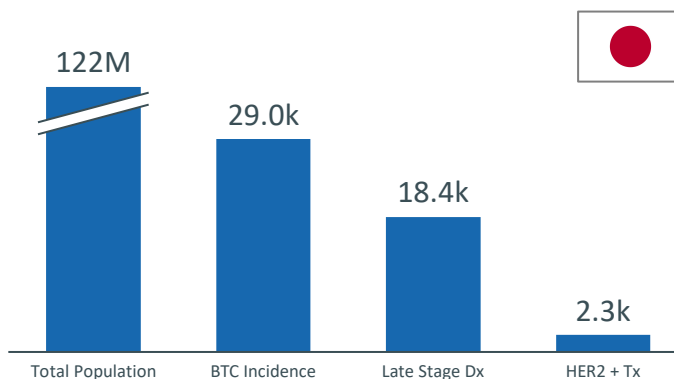
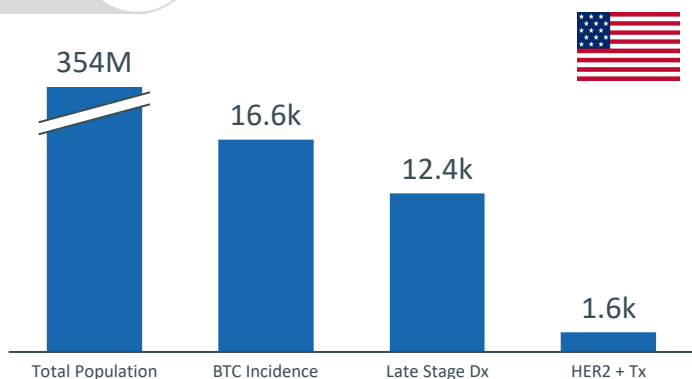
- >50,000 new patients/year with HER2+ Biliary Tract & Gastroesophageal Adenocarcinoma
- Superior product profile emerging across the 2 tumor types drives leadership position
- Favorable Pricing & Reimbursement of new targeted medicines in BTC to anchor launch price
- Familiarization with the drug in 2L BTC bolsters uptake in 1L GEA

Biliary Tract Cancer Commercial Value Drivers

James Priour, MBA
Chief Commercial Officer



HER2+ Biliary Tract Cancers Represent ~18% of Total Zanidatamab Opportunity and Acts as springboard to 1L GEA adoption



Potential Addressable Patients
1L & 2L Combined (Peak Year Est.):
~9K

Biliary tract cancers are orphan, heterogenous tumors that have an aggressive disease course and a poor clinical outcome. They usually present at an advanced stage (> 90% cases are adenocarcinomas) and only approx. 20% of tumors are considered resectable. Mean overall survival rate for patients with cholangiocarcinoma is less than 24 months and gallbladder cancer is 6 months

Source: bioStrategies Forecast Model; SEER Stage Distribution (2000-2015); GLOBOCAN; ROW calculated using 84% EU scale up factor; Epidemiology excludes APAC royalties from BeiGene; BTC HER2 + Incidence rate of 9.4% Source: Roche HER2 Screening Data Feb 2021. Dx: disease; Est: estimated; Tx: treated

Current Standard of Care for Metastatic BTC



Biliary Tract Cancer

Unresectable and Metastatic Disease		
First-Line	Second-Line	Third-Line
Chemotherapy (Gemcitabine + Cisplatin) ± PD1 or PD-L1	FOLFOX	Clinical Trial
	Targeted agents (pemigatinib, infigratinib, ivosidenib)	Palliation/ Hospice

Zanidatamab Has Potential to Be the First to Open a New Lane for HER2+ BTC



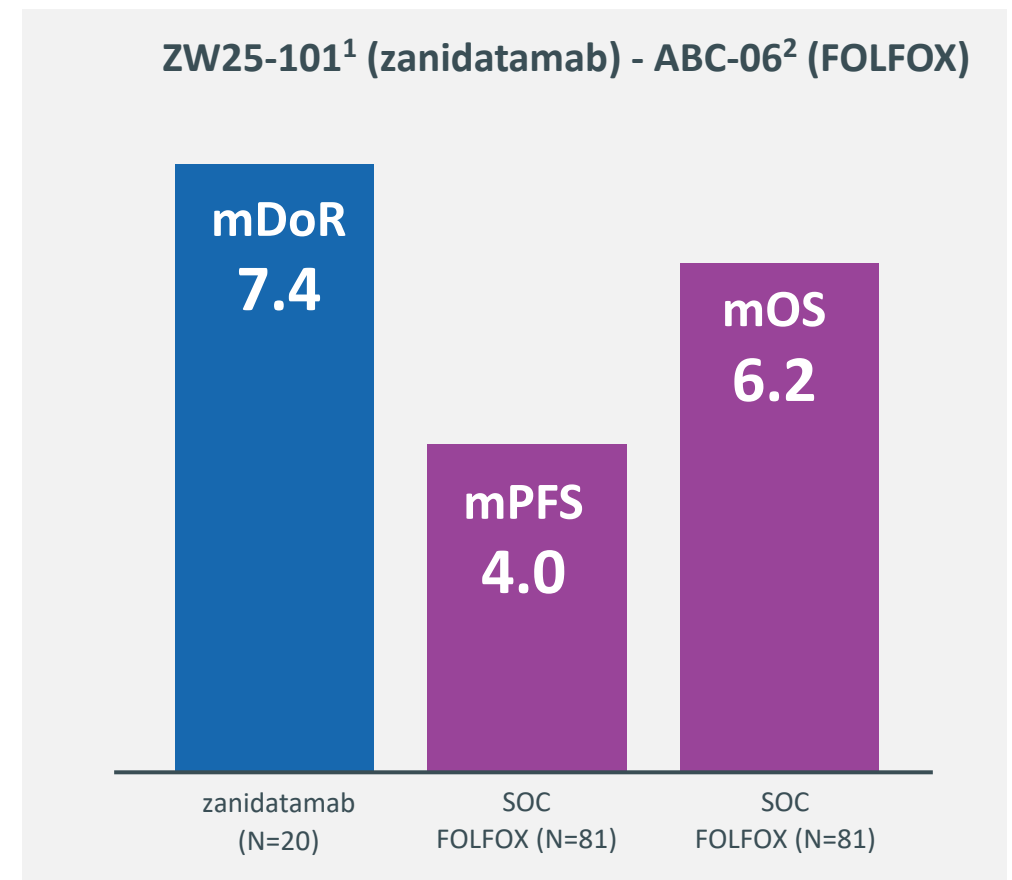
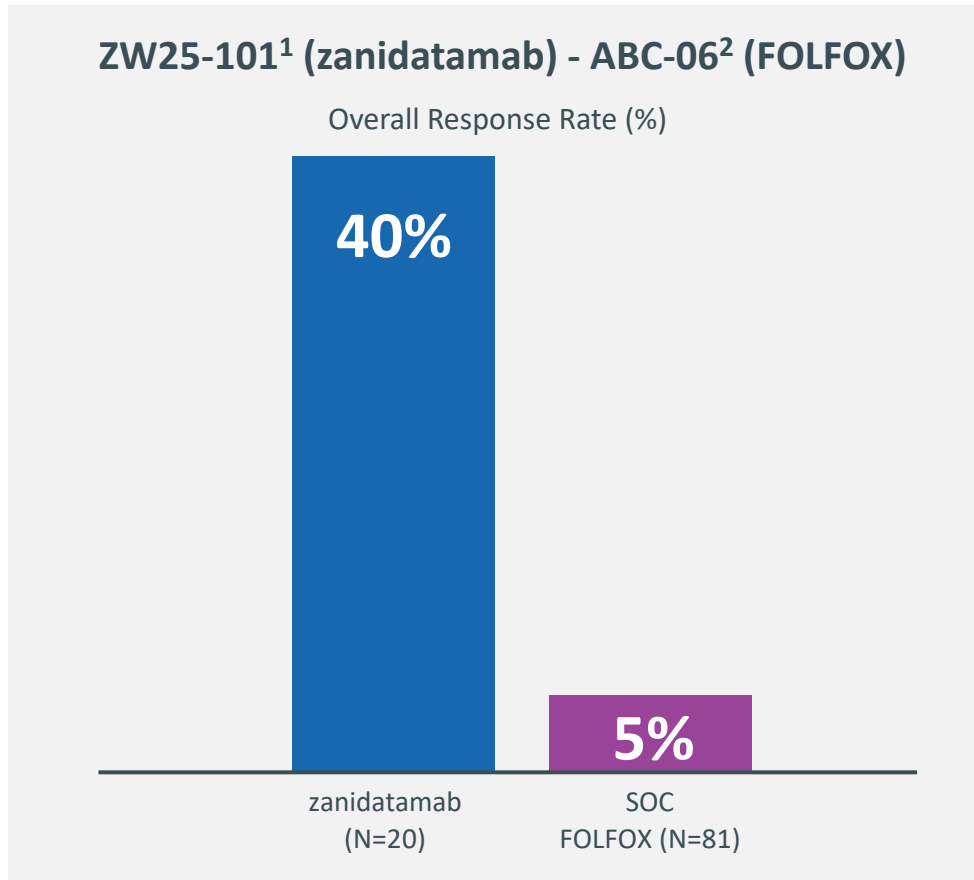
HER2-negative
Biliary Tract Cancer

Unresectable and Metastatic Disease		
First-Line	Second-Line	Third-Line
Chemotherapy (Gemcitabine + Cisplatin) ± PD1 or PD-L1	FOLFOX	Clinical trial
	Targeted agents (pemigatinib, infigratinib, ivosidenib)	Palliation / Hospice

HER2-positive
Biliary Tract Cancer

<p>Zanidatamab Opportunity #2</p> <p>HERIZON-BTC-02 (planned)</p>	<p>Zanidatamab Monotherapy Opportunity #1</p> <p>HERIZON-BTC-01 (enrolling)</p>
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Phase 1 Data Drive Confidence Zanidatamab Could Become the 1st Approved Chemo-Free HER2-Targeted Therapy for 2L BTC and New Standard of Care

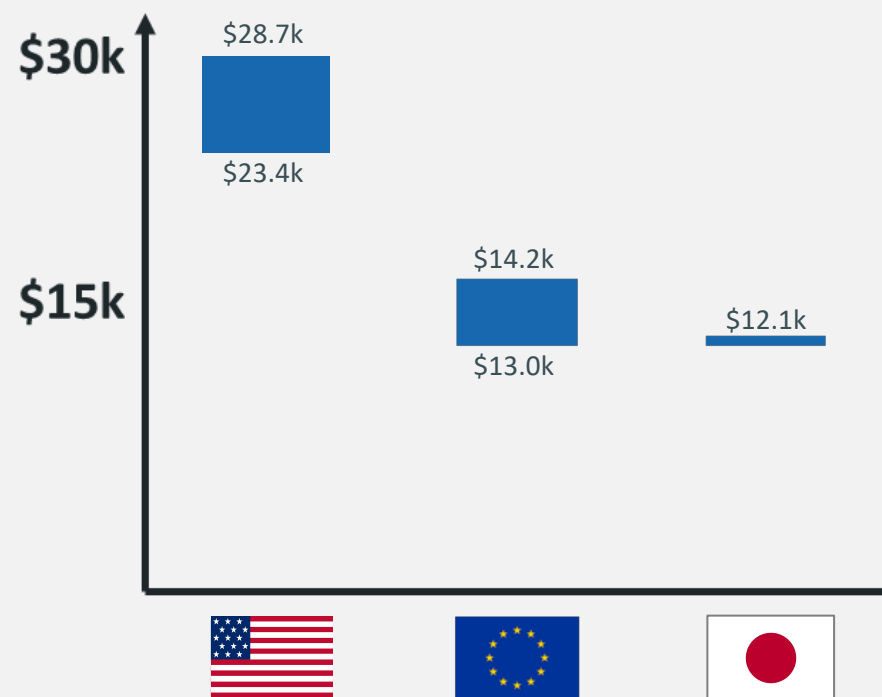


1. Pant S, et al. ASCO.GI. 2021, DOI 10.1200/JCO.2021.39.3_suppl.299
2. Lamarca A, et al Lancet Oncology / Published online March 30, 2021 [https://doi.org/10.1016/S1470-2045\(21\)00027-9](https://doi.org/10.1016/S1470-2045(21)00027-9)

Note: Chart includes cross-trial comparisons and is not meant to be indicative of comparisons made in double-blind, randomized trials.
BTC: biliary tract cancer; mDOR: median duration of response; mOS: median overall survival; mPFS: median progression-free survival; SOC: standard of care

Payers Recognize Value of the New Targeted Therapies for Cholangiocarcinoma, Highlighting the Potential for Zanidatamab

Monthly List Prices of Recently-Approved Targeted Therapies for Cholangiocarcinoma



Source: PriCentric Database. Prices for Pemazyre, Tibsovo, and Truseltiq where available. Accessed 26.Oct.2021.

Pemazyre
(pemigatinib) tablets
13.5mg+9mg+4.5mg

3Q21 Sales of \$18MM

- FDA Approved April 2020 in FGFR2-fusion positive cholangiocarcinoma
- Quarterly sales growth +117% YoY
- Annualized sales trend >\$70MM
- \$170MM consensus forecast by 2026*

* Consensus forecast from FactSet as of November 5, 2021
Pemazyre data from Incyte's 3Q21 earnings presentation from November 2, 2021
YoY: year-over-year

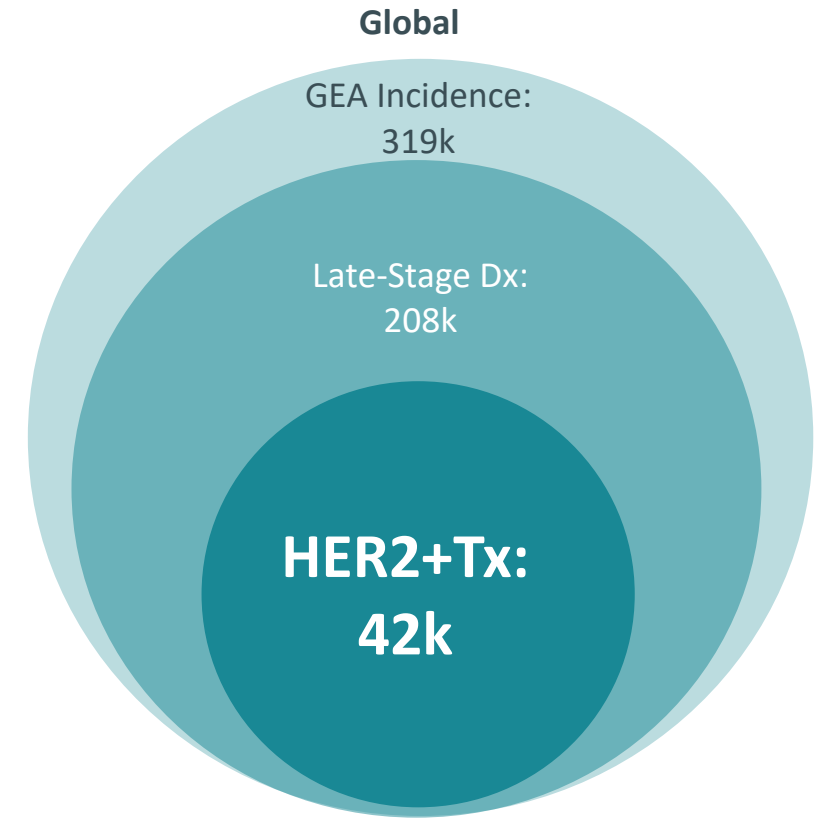
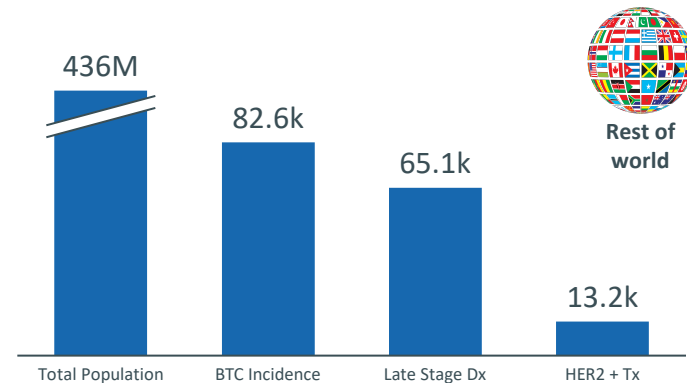
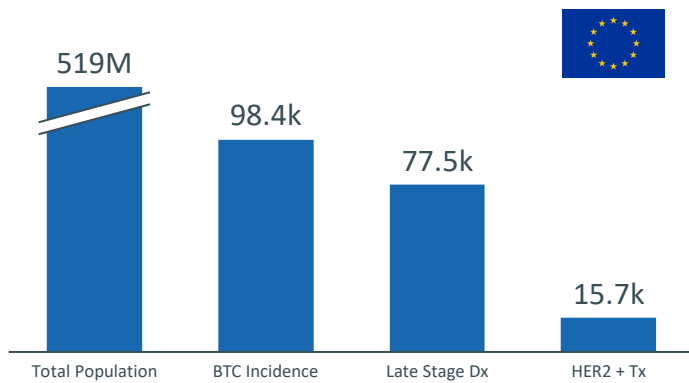
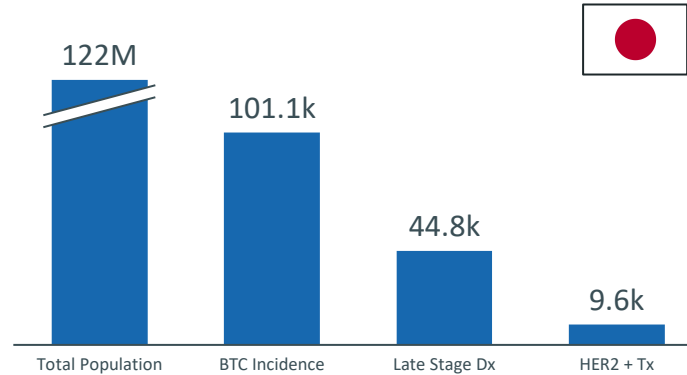
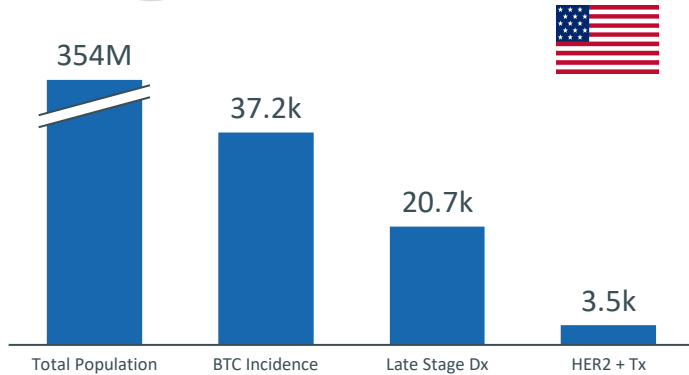
Gastroesophageal Adenocarcinoma Commercial Value Drivers

James Priour, MBA

Chief Commercial Officer



GEA has HER2-Positive Rate of >20% and Represents a Peak Opportunity in 1L of >40,000 New Patients/Year



Potential Addressable Patients in 1L (Peak Year Est.):
~42K

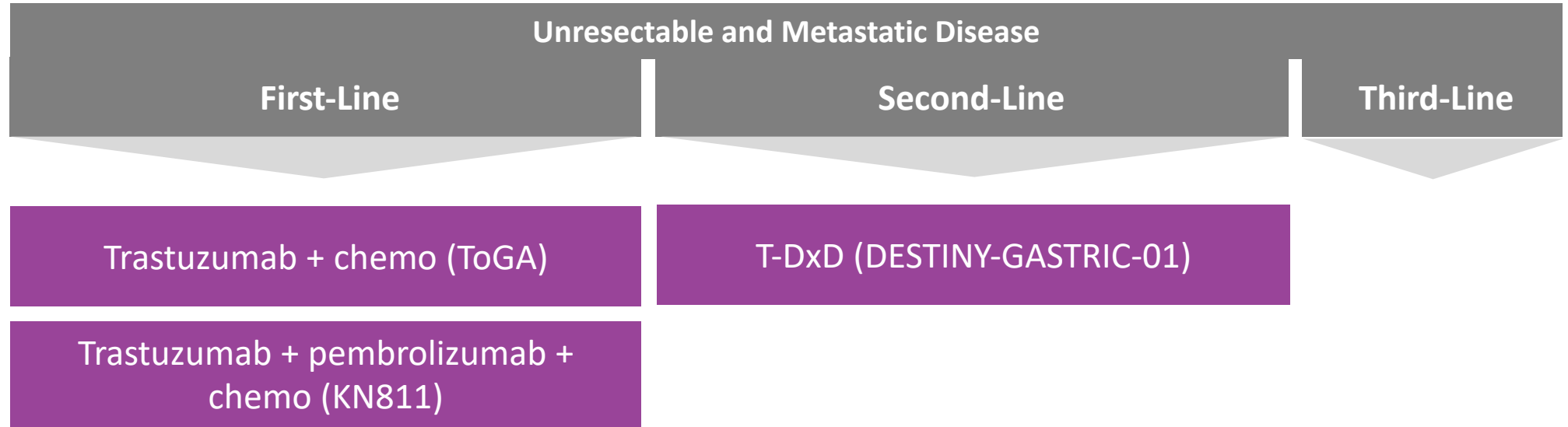
Gastric cancer accounts for 6.8% of all cancers, and the 3rd most common cause of cancer-specific mortality worldwide, it is often diagnosed at an advanced stage, defined as unresectable locoregional or metastatic disease, which has very poor prognosis with 5-year survival not exceeding 5–20%.

Source: bioStrategies Forecast Model; SEER Stage Distribution (2000-2015); GLOBOCAN; ROW calculated using 84% EU scale up factor, Epidemiology excludes BeiGene APAC Territories; GEA HER2+ Incidence rate of 21.7% ,Source: Roche HER2 Screening Data Feb 2021. Dx: disease; Est: estimated; Tx: treated

Zanidatamab Has Potential to Become the New Antibody Backbone and 1st HER2-Targeted Therapy Approved for Esophageal Patients



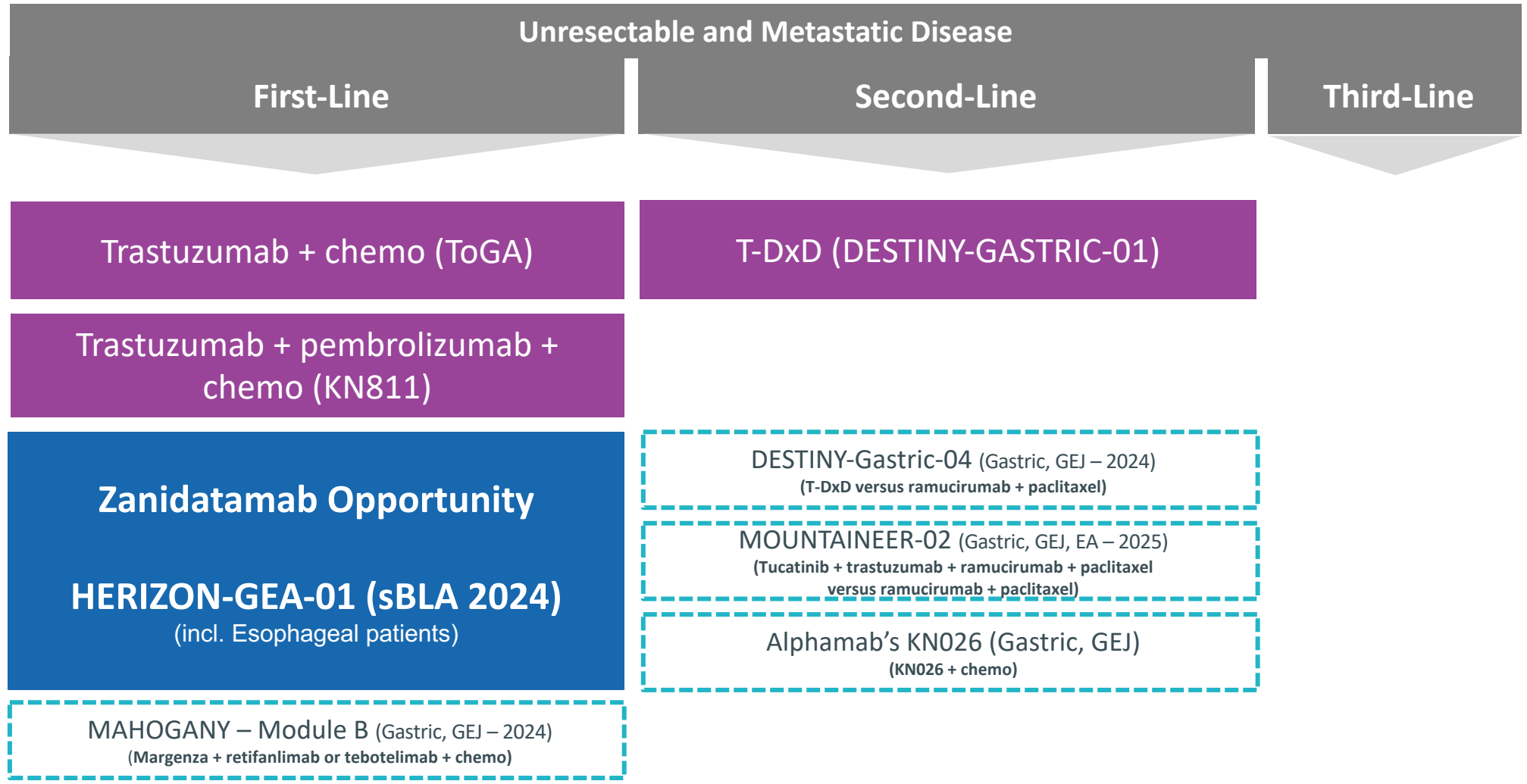
GEA



Zanidatamab Has Potential to Become the New Antibody Backbone and 1st HER2-Targeted Therapy Approved for Esophageal Patients



HER2-positive GEA



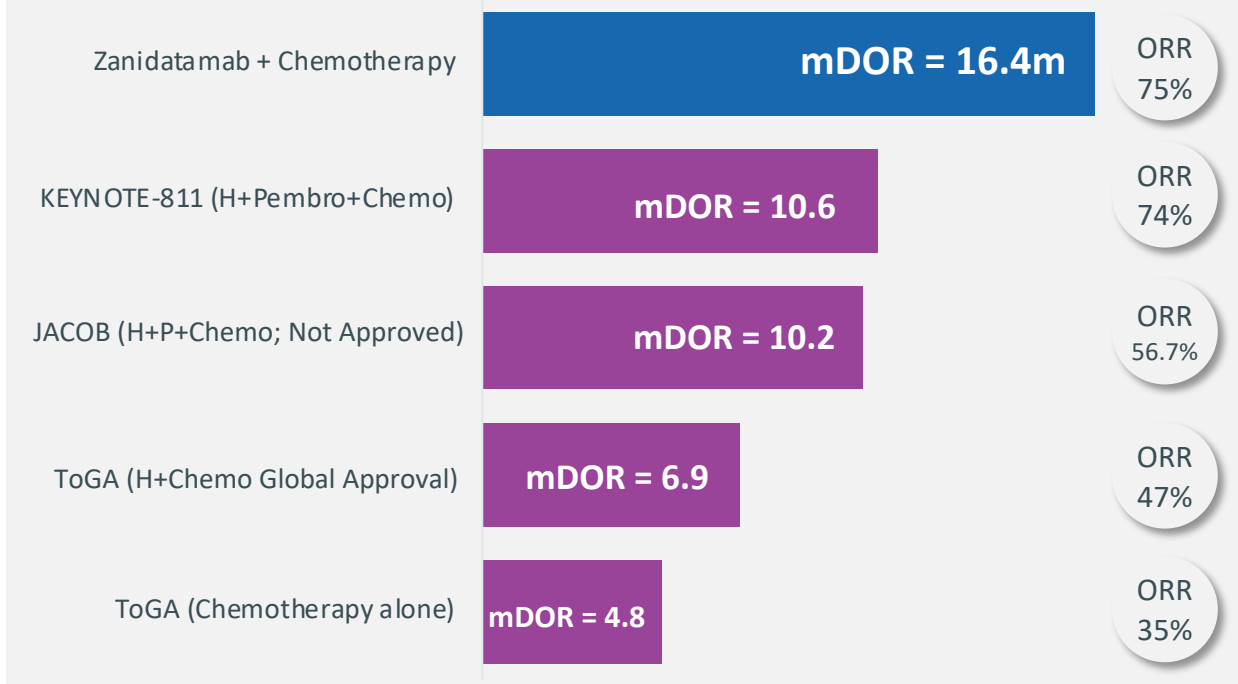
Investigational

ESMO 2021 Phase 2 Data Drives Confidence that Zanidatamab Will Deliver Superior Efficacy To Approved Standards of Care



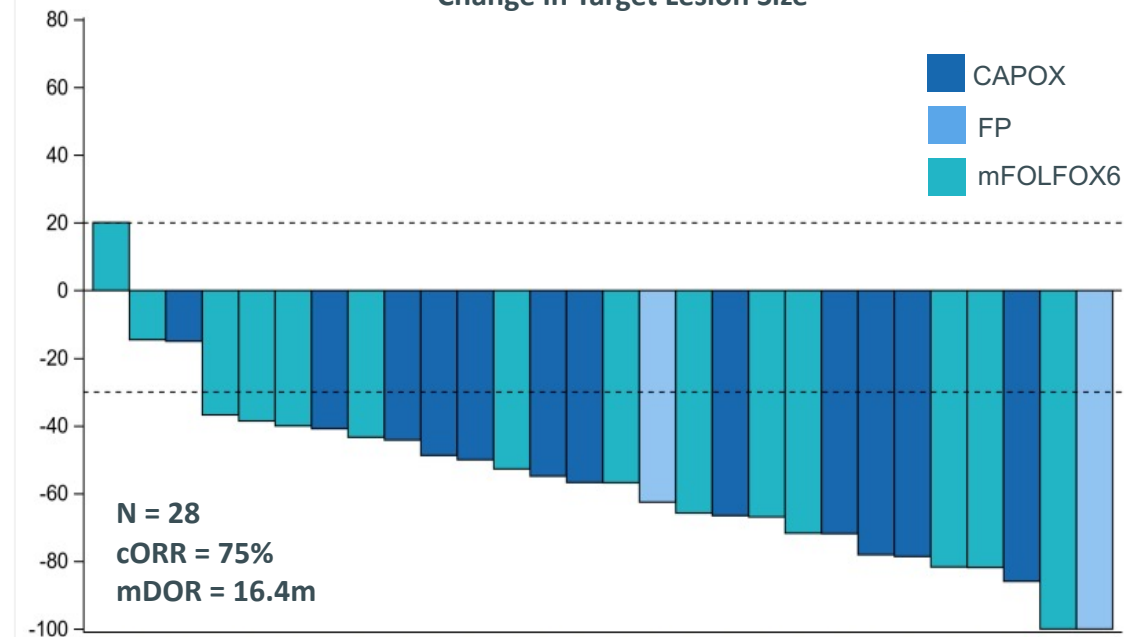
Clinical Trials in 1L HER2-Positive Gastroesophageal Adenocarcinoma

Median Duration of Response^{1, 2, 3, 4}



Zanidatamab + Chemotherapy¹

Change in Target Lesion Size



1. Ku G, et al. ESMO Congress, September 16 – 21, 2021

2. KEYTRUDA US Prescribing Information (US FDA PI), based on KEYNOTE-811

3. Tabernero, J, et al. Lancet Oncol 2018; 19: 1372–84

4. Bang Y, et al. Lancet 2010; 376: 687–97

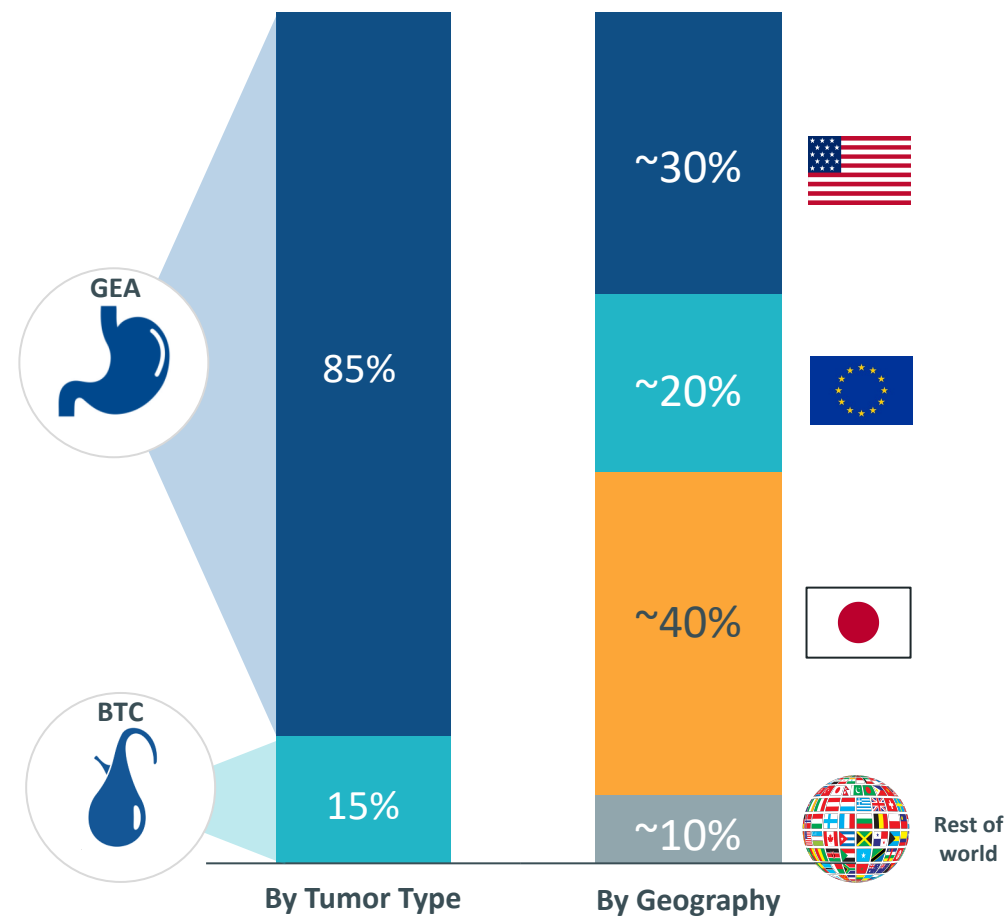
cORR: confirmed overall response rate; H: Herceptin (trastuzumab); HP: Herceptin (trastuzumab) + Perjeta (pertuzumab); mDOR: median duration of response; Pembro: Keytruda (pembrolizumab)

Note: Table includes cross-trial comparisons and is not meant to be indicative of comparisons made in double-blind, randomized trials

Zanidatamab Has a Clear Lane in BTC and GEA with Blockbuster Peak Sales Potential if Approved

Revenue Drivers	BTC + GEA
Size of HER2+ Population	✓ ✓ ✓
Access / Pricing Context	✓ ✓
Competition Intensity	Low to Medium
Zanidatamab Profile vs. SOC	✓ ✓ ✓
Potential Market Share	Leadership Position

Global Zanidatamab Peak Revenue Contribution - GEA & BTC*



Closing Remarks

Ali Tehrani, Ph.D.
President & CEO



Q&A

Ali Tehrani, PhD

President & CEO

Neil Josephson, MD

Chief Medical Officer

James Priour, MBA

Chief Commercial Officer

