

March 19, 2024

Zanidatamab R&D Day

Differentiated and De-Risked



Transforming Lives. Redefining Possibilities.

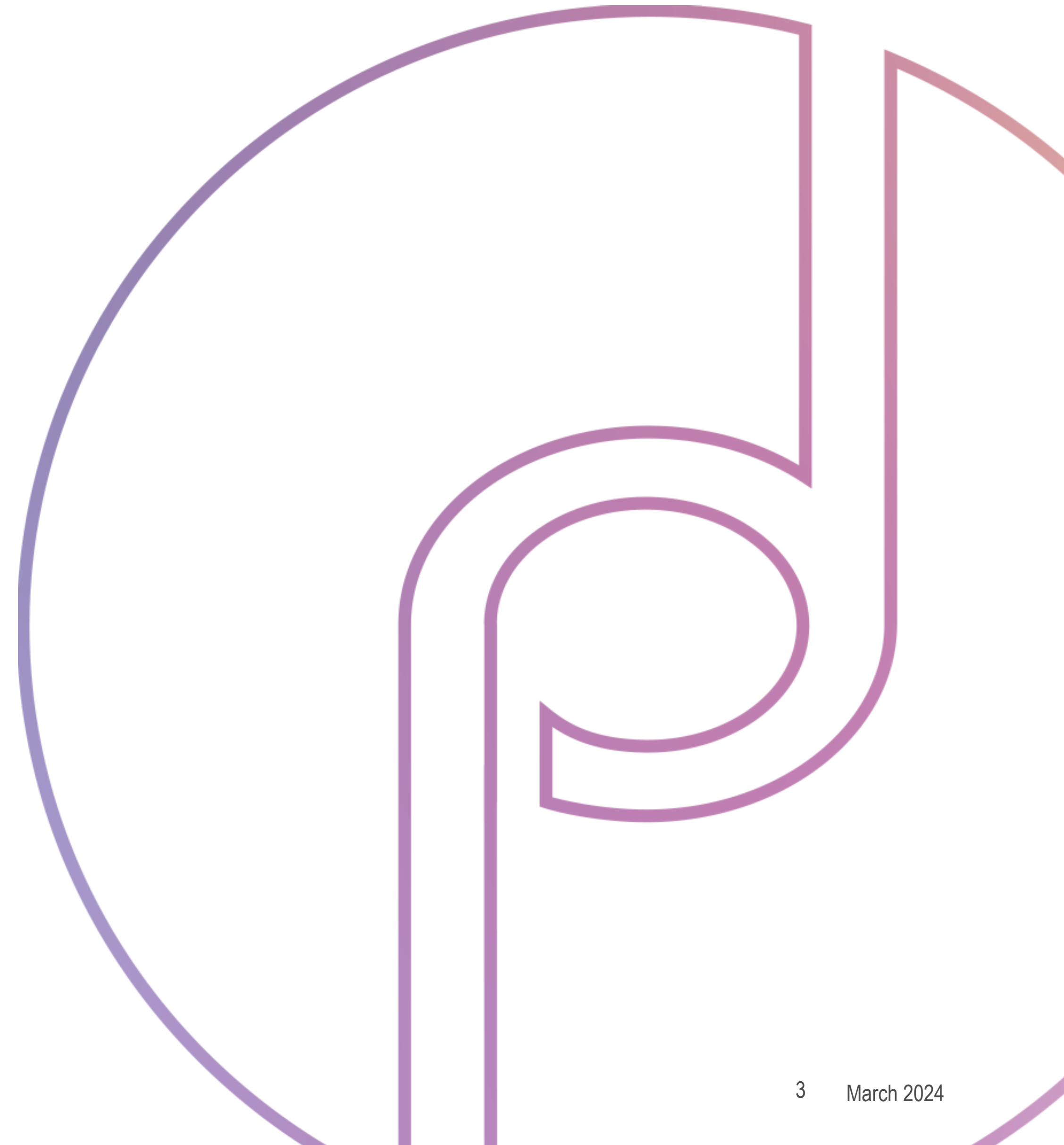
Caution Concerning Forward-Looking Statements

This presentation contains forward-looking statements and financial targets, including, but not limited to, statements related to: the Company's growth prospects and future financial and operating results, including planned or anticipated clinical trial events, including with respect to initiations, enrollment and data read-outs, and the anticipated timing thereof, and planned or anticipated regulatory submissions and filings; the Company's expectations with respect to its products and product candidates and the potential of the Company's products and product candidates, including expectations with respect to zanidatamab's de-risked, near term opportunity, the potential of zanidatamab to be more than a two billion dollar market opportunity with the potential to raise the standard of care for patients and create long-term value for the Company, and the potential regulatory path related thereto; and other statements that are not historical facts. These forward-looking statements are based on the Company's current plans, objectives, estimates, expectations and intentions and inherently involve significant risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation, risks and uncertainties associated with: the successful completion of development and regulatory activities with respect to the Company's product candidates; obtaining and maintaining adequate coverage and reimbursement for the Company's products; the time-consuming and uncertain regulatory approval process, including the risk that the Company's current and/or planned regulatory submissions may not be submitted, accepted or approved by applicable regulatory authorities in a timely manner or at all; the costly and time-consuming pharmaceutical product development and the uncertainty of clinical success, including risks related to failure or delays in successfully initiating or completing clinical trials and assessing patients such as those experienced, and expected to be experienced, by the Company; protecting and enhancing the Company's intellectual property rights and the Company's commercial success being dependent upon its obtaining, maintaining and defending intellectual property protection for its products and product candidates; delays or problems in the supply or manufacture of the Company's products and product candidates; complying with applicable U.S. and non-U.S. regulatory requirements, including those governing the research, development, manufacturing and distribution of controlled substances; government investigations, legal proceedings and other actions; and other risks and uncertainties affecting the Company, including those described from time to time under the caption "Risk Factors" and elsewhere in the Company's Securities and Exchange Commission filings and reports, including the Company's Annual Report on Form 10-K for the year ended December 31, 2023, and its future filings and reports. Other risks and uncertainties of which the Company is not currently aware may also affect its forward-looking statements and may cause actual results and the timing of events to differ materially from those anticipated. The forward-looking statements made in this presentation are made only as of the date hereof or as of the dates indicated in the forward-looking statements, even if they are subsequently made available by the Company on its website or otherwise. The Company undertakes no obligation to update or supplement any forward-looking statements to reflect actual results, new information, future events, changes in its expectations or other circumstances that exist after the date as of which the forward-looking statements were made.



Agenda

1. Mechanism of Action
2. Zanidatamab in BTC
3. Zanidatamab in GEA: Dr. Geoffrey Ku
4. Zanidatamab in Breast Cancer
 - Late-Stage: Dr. Sara Hurvitz
 - HER2+/HR+: Dr. Santiago Escrivá-de-Romaní
 - Early-Stage Breast Cancer: Dr. Paula Pohlmann
5. Roadmap to Success



Zanidatamab

Bispecific HER2-Targeted mAb




Zanidatamab Has the Potential to Transform HER2-Targeted Therapies

Zanidatamab is a highly active, differentiated HER2-targeted bispecific mAb with early compelling survival data




Novel and Differentiated MOA



Best-in-Class Profile Addresses Unmet Need



Compelling Clinical Data Supports Fast to Market Strategy



\$2B+ Commercial Opportunity



Zanidatamab

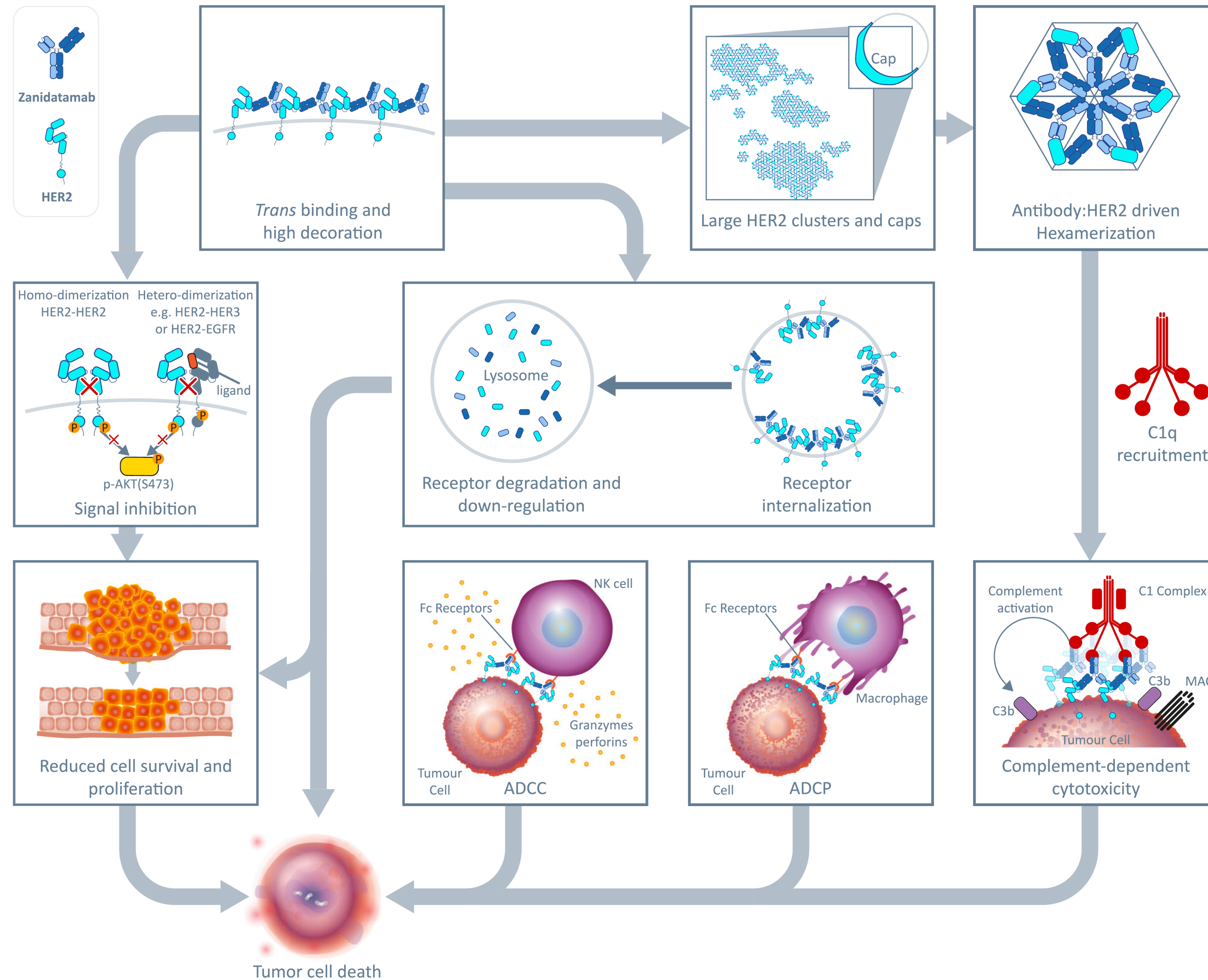
Differentiated Leader in the HER2 space

Rob Iannone, M.D., M.S.C.E.

**Executive Vice President,
Global Head of Research & Development**



Zanidatamab's Biparatopic Binding Drives Unique MOA and Clinical Activity



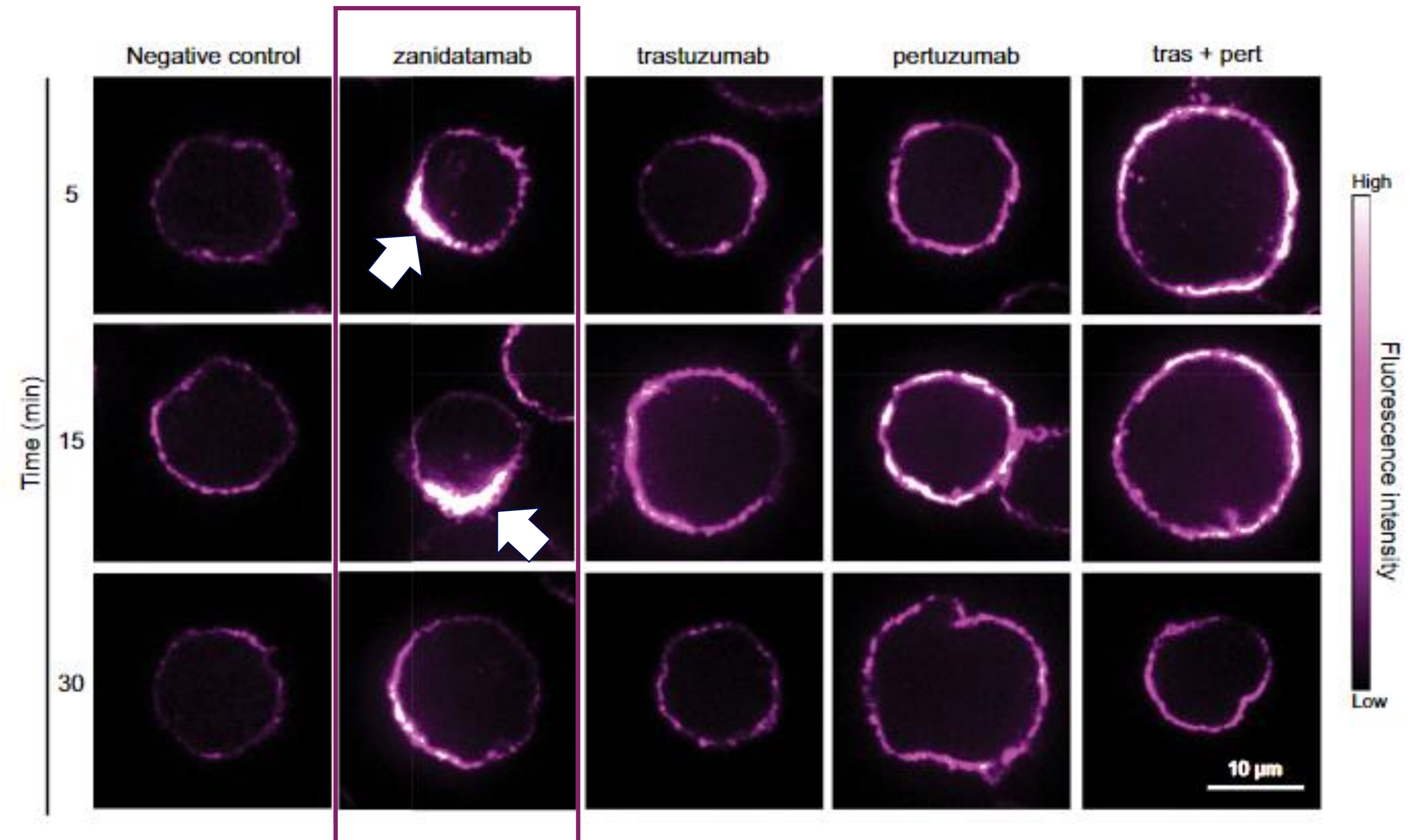
- Zanidatamab simultaneously binds **two non-overlapping extracellular domains** of HER2 (biparatopic binding)
- **Unique geometry and binding properties** result in multiple mechanisms of action



Zanidatamab's Biparatopic Binding Drives Unique MOA and Clinical Activity

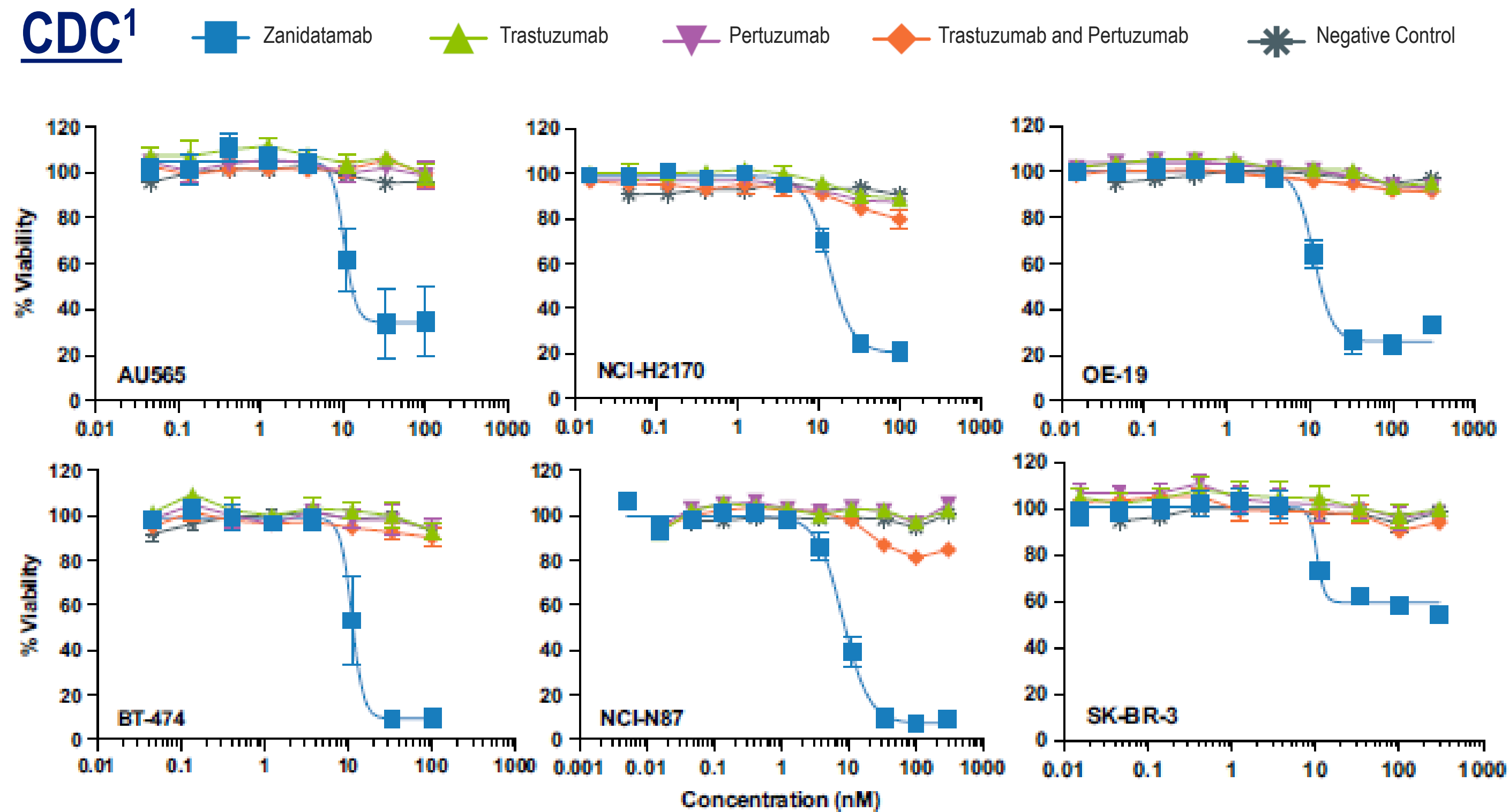
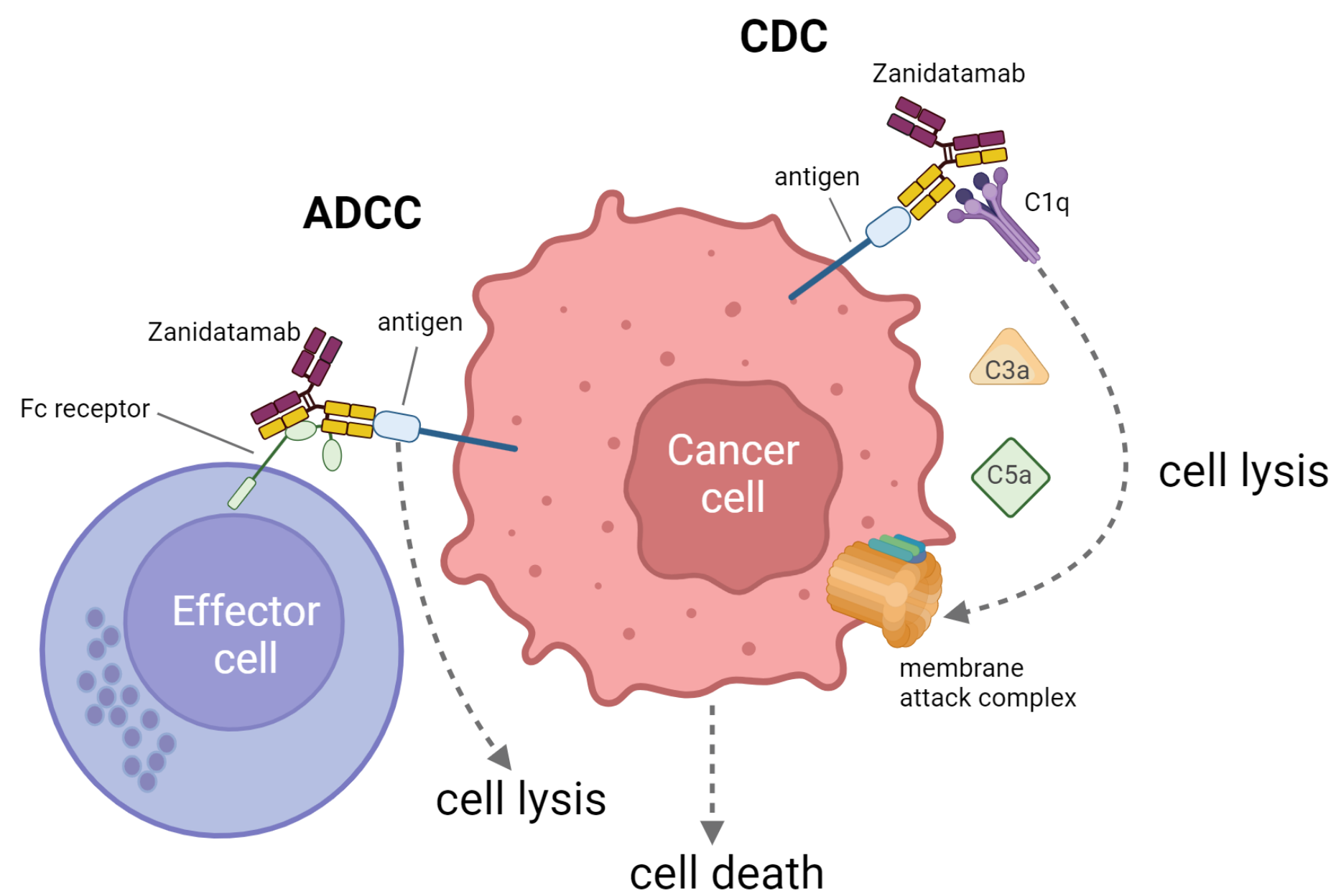
- Binding properties of zanidatamab are believed to form the **foundation of the unique and diverse mechanisms of action** observed preclinically and clinically to-date
- **Biparatopic binding** and engagement of HER2 in *trans* results in formation of **distinct and large HER2 caps / clusters** on cell surface
- Trastuzumab (tras), pertuzumab (pert), or the combination of tras + pert **were not observed** to mediate the formation of HER2 caps, clusters or CDC

Zanidatamab Clusters HER2 Receptors on Cell Surface¹

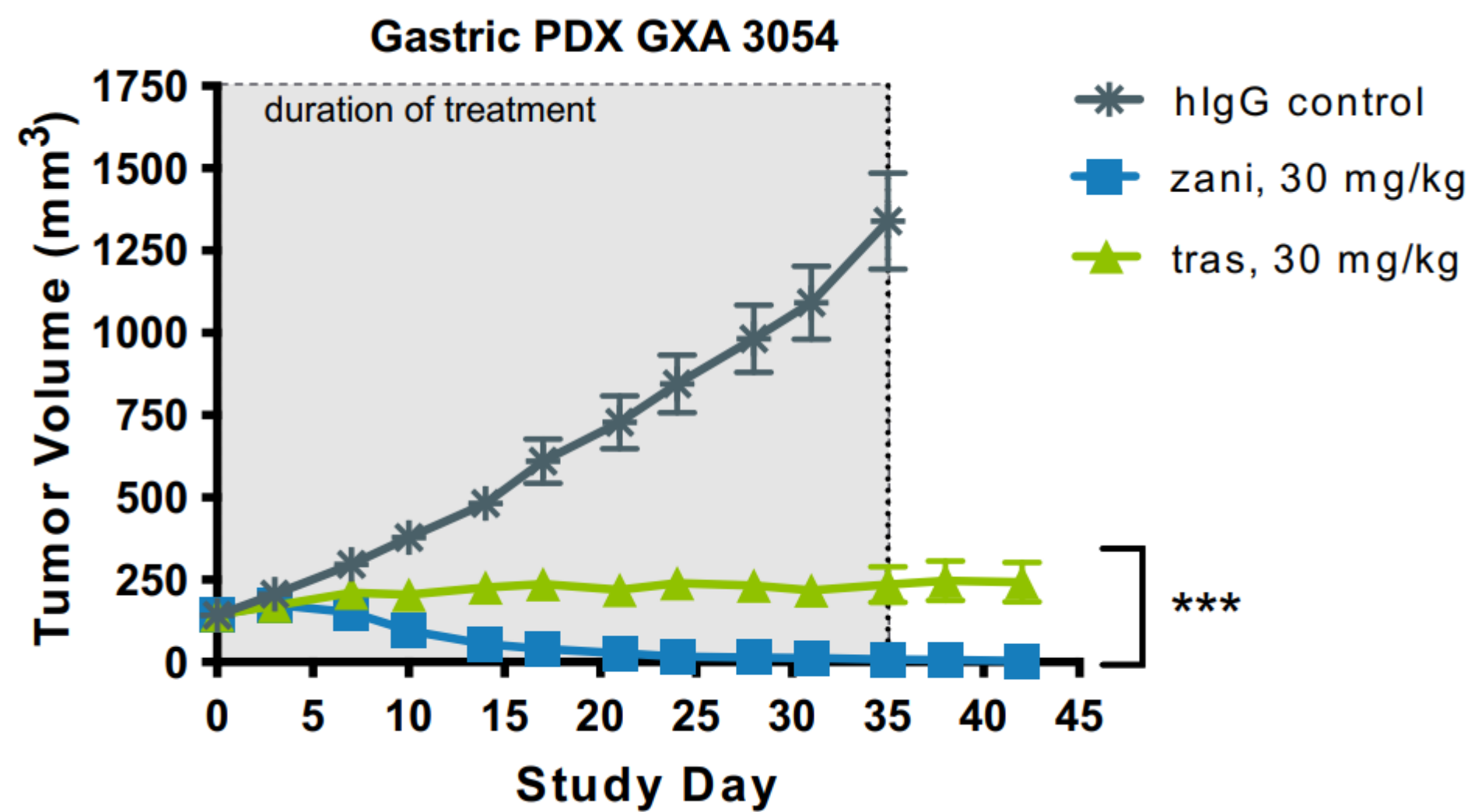


Zanidatamab's Biparatopic Binding Drives Unique MOA and Clinical Activity

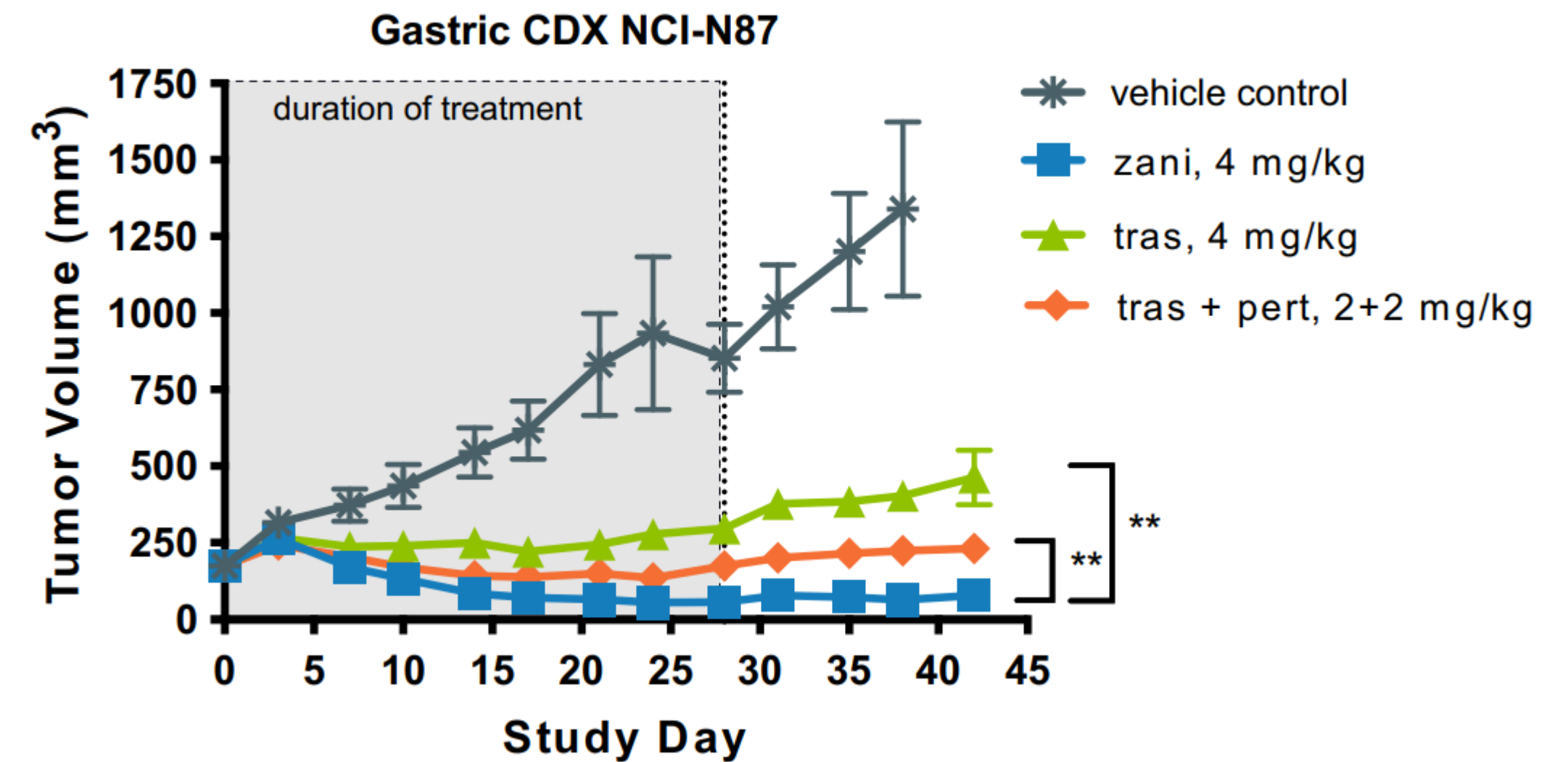
- Cap formation is believed to induce **better effector activity**¹
- Zanidatamab exhibits **strong activation of complement-dependent cytotoxicity (CDC)**¹



Zanidatamab Demonstrates Improved Antitumor Activity in Gastric Cancer Xenograft Tumors Compared to Trastuzumab Plus Pertuzumab Combination



Mean tumor volume of patient-derived gastric xenograft model GXA 3054 implanted in nude mice. Tumor bearing mice treated with indicated test articles at 30 mg/kg, IV, twice weekly for five weeks, n = 10 per group. ***p value = 3.17e-07



Mean tumor volume of patient-derived gastric xenograft model GXA 3054 implanted in nude mice. Tumor bearing mice treated with indicated test articles at 30 mg/kg, IV, twice weekly for five weeks, n = 10 per group. ***p value = 3.17e-07



Zanidatamab: Recent Data De-Risks Potential Opportunity

Meaningful data generation and rapid progression 15 months post-transaction 

Announced MD Anderson Collaboration

Studying zanidatamab as **monotherapy and in combination** in:

- Early-stage BC
- Cancers where other HER2-targeted therapies failed
- Rare, tissue agnostic cancers

Transaction Announced

- Option to in-license zanidatamab ahead of BTC data

Monotherapy Activity

- Positive monotherapy pivotal data¹ in previously treated HER2-amplified BTC
- Jazz confirms opt-in

BTC Data Presented at ASCO

- Voted **Best of ASCO** presentation

Activity in Combination

- First triplet data presented in 1L GEA at ESMO⁴
- Zanidatamab + chemotherapy + tislelizumab
- Demonstrated **promising activity in combination**

Promising Early OS Data

- Zanidatamab + chemotherapy **doublet data at ASCO GI**²
- Announced **inclusion in I-SPY 2 Trial**³

Activity Post Prior HER2 Treatment

- **Promising late-line mBC data at SABCS shows activity** in patients previously treated with HER2-targeted agents⁵
- Zanidatamab + Palbociclib + Fulvestrant
- Activity in **novel chemo-free combination regimen**

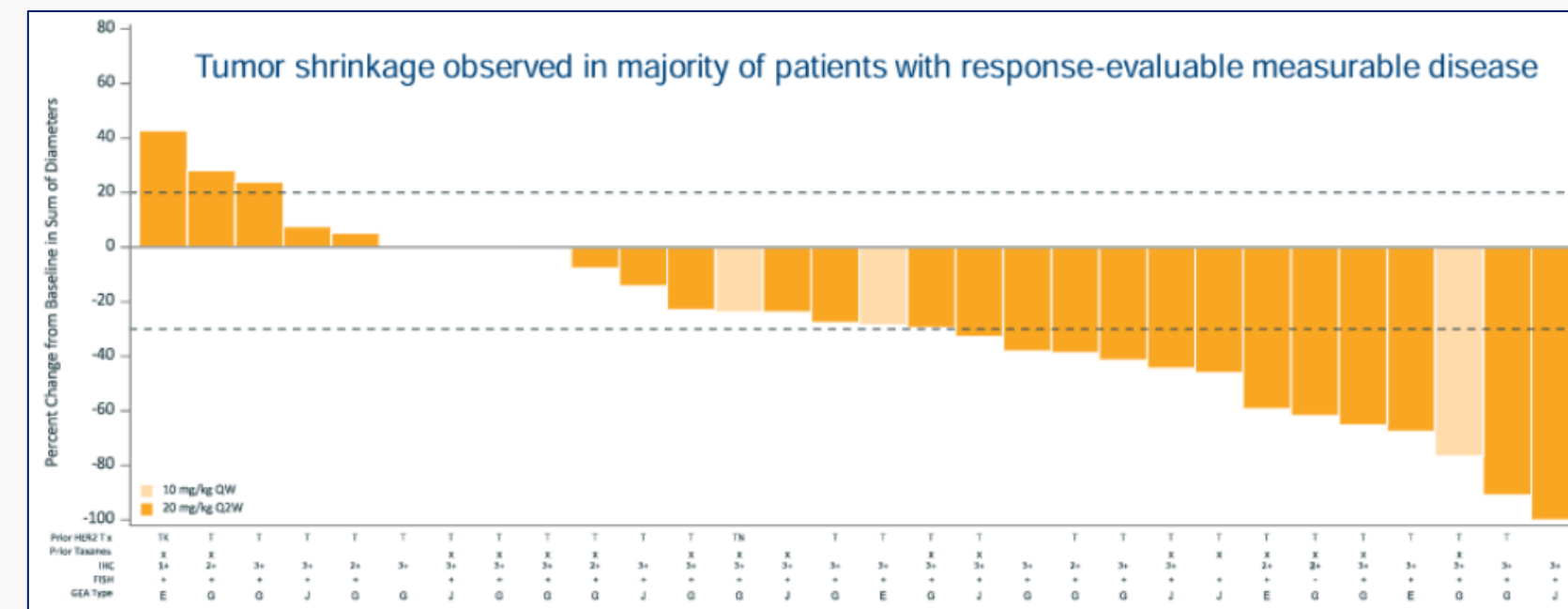
1L = first line; ASCO = American Society of Clinical Oncology; BC = breast cancer; BTC = biliary tract cancer; ESMO = European Society for Medical Oncology; GEA = gastroesophageal adenocarcinoma; GI = gastrointestinal; HER2 = human epidermal growth factor receptor 2; mBC = metastatic breast cancer; OS = overall survival; SABCS = San Antonio Breast Cancer Symposium. ¹DOI: 10.1200/JCO.2023.41.16_suppl.1044 Journal of Clinical Oncology 41, no. 16_suppl (June 01, 2023) 1044-1044; ² DOI: 10.1200/JCO.2023.41.4_suppl.347 Journal of Clinical Oncology 41, no. 4_suppl (February 01, 2023) 347-347; ³NCT01042379, in collaboration with QuantumLeap Healthcare Collaborative; ⁴Poster presented by partner BeiGene; Harpreet Wasan, et al. Zanidatamab (zani) plus chemotherapy (chemo) and tislelizumab (TIS) as first-line (1L) therapy for patients (pts) with advanced HER2-positive (+) Gastric/gastroesophageal junction adenocarcinoma (GC/GEJC): updated results from a phase 1b/2 study, ESMO, 2023; ⁵Santiago Escrivá-de-Romani, et al., Primary Results From a Phase 2a Study of Zanidatamab (zani) + Palbociclib (palbo) + Fulvestrant (fulv) in HER2+/HR+ Metastatic Breast Cancer (mBC), SABCS, 2023.



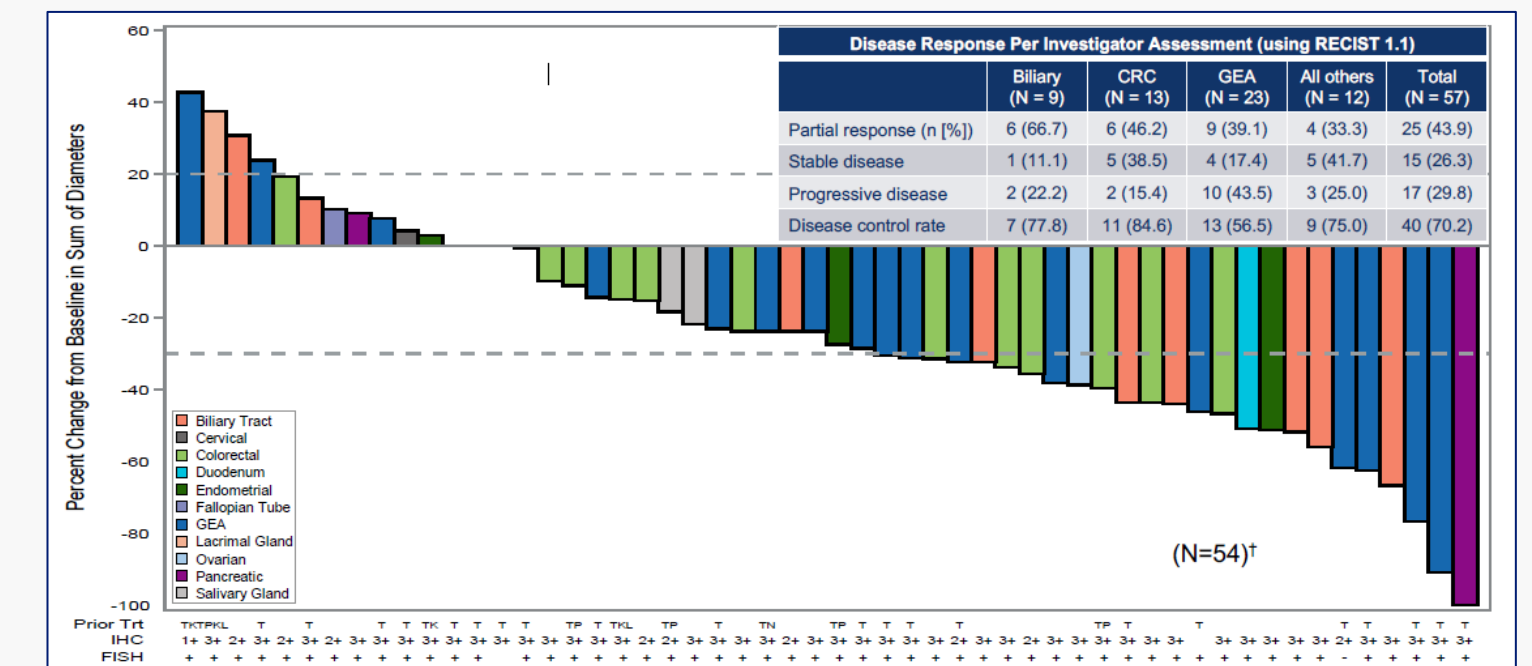
Zanidatamab Has Demonstrated Compelling Monotherapy Activity

Zanidatamab has shown monotherapy activity across a broad range of **HER2-expressing tumor types** in multiple lines of therapy

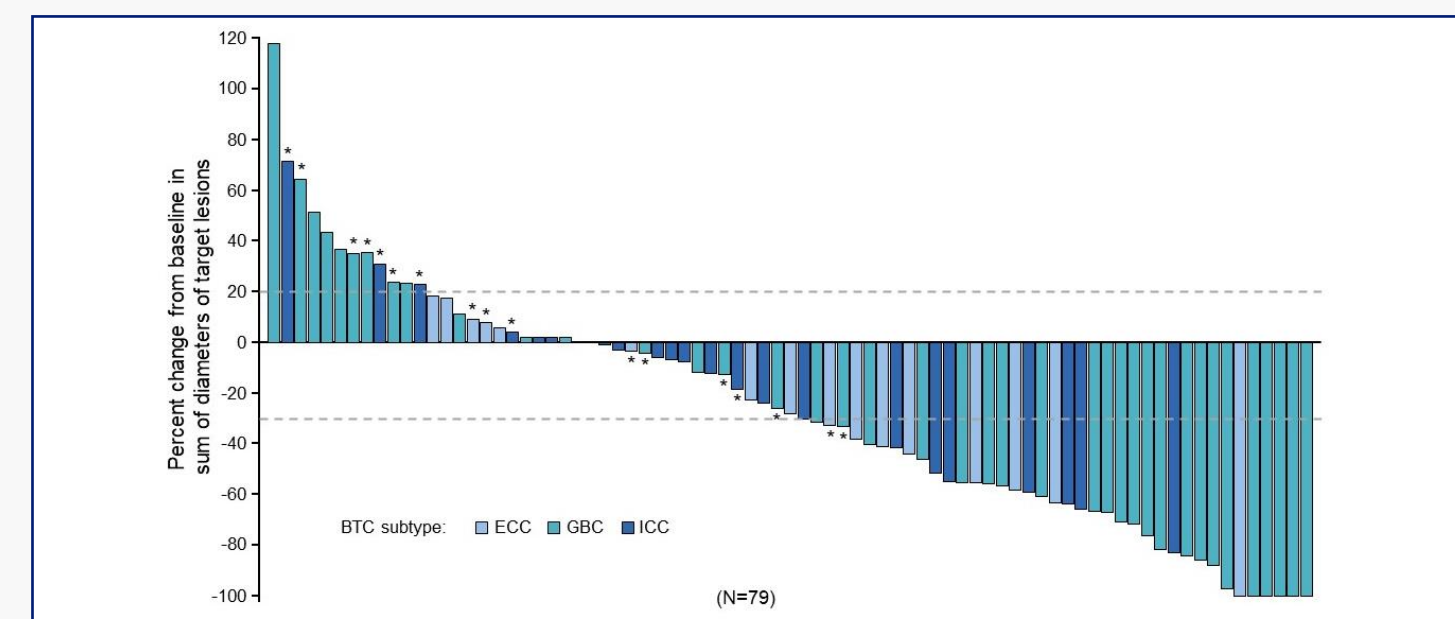
3L+ GEA: Phase 1 Monotherapy¹



4L+ Basket: Phase 1 Monotherapy²



2L+ BTC Pivotal: Phase 2 Monotherapy³

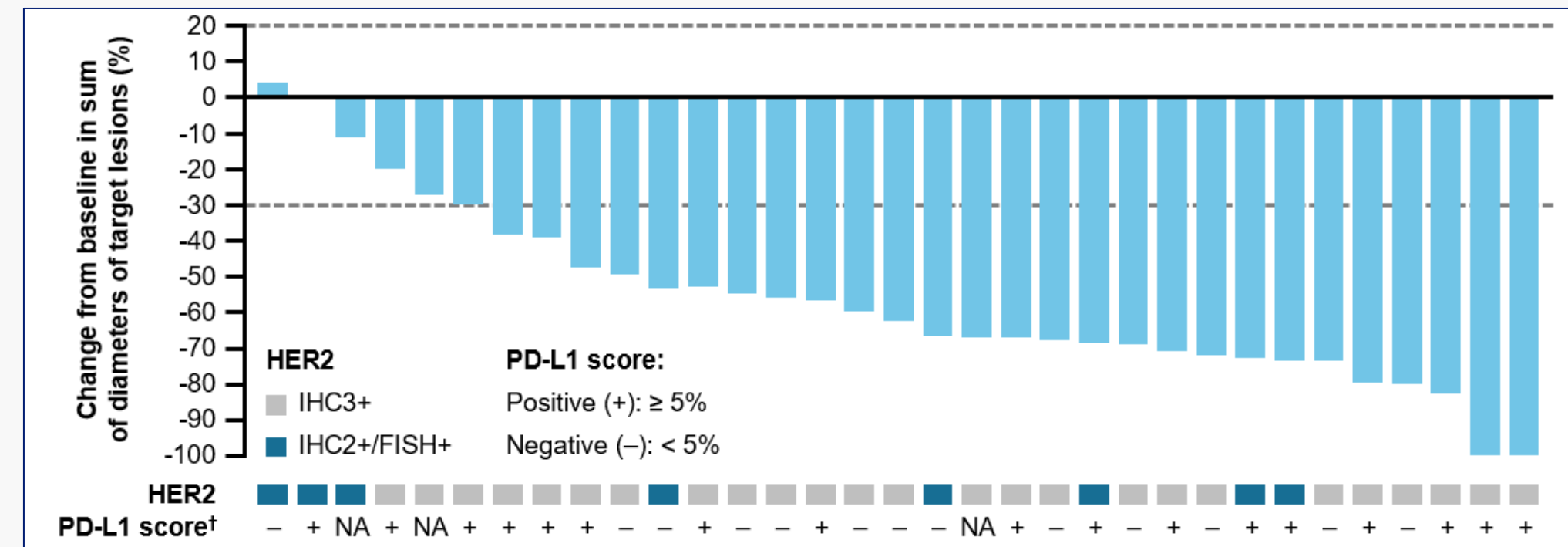


Zanidatamab is Effective in Multiple Combination Therapies

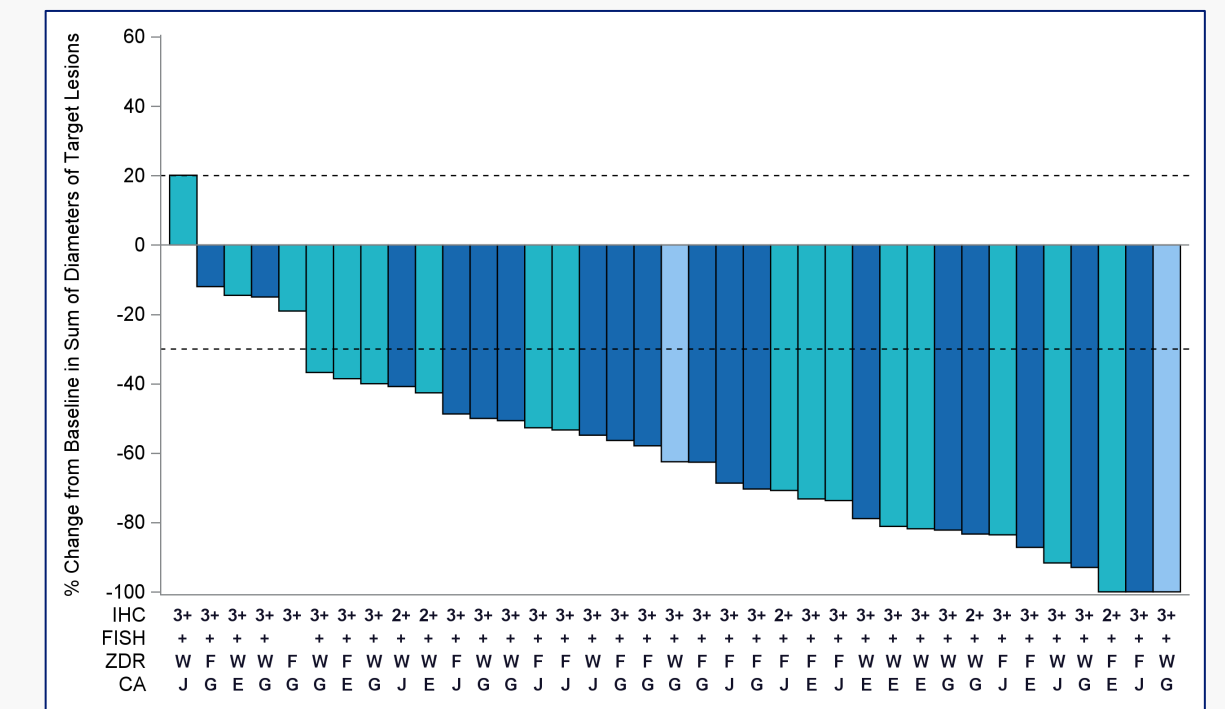
Zanidatamab **combines effectively** with multiple agents

In early- and late-line therapy, **combination therapy shows effective antitumor activity**

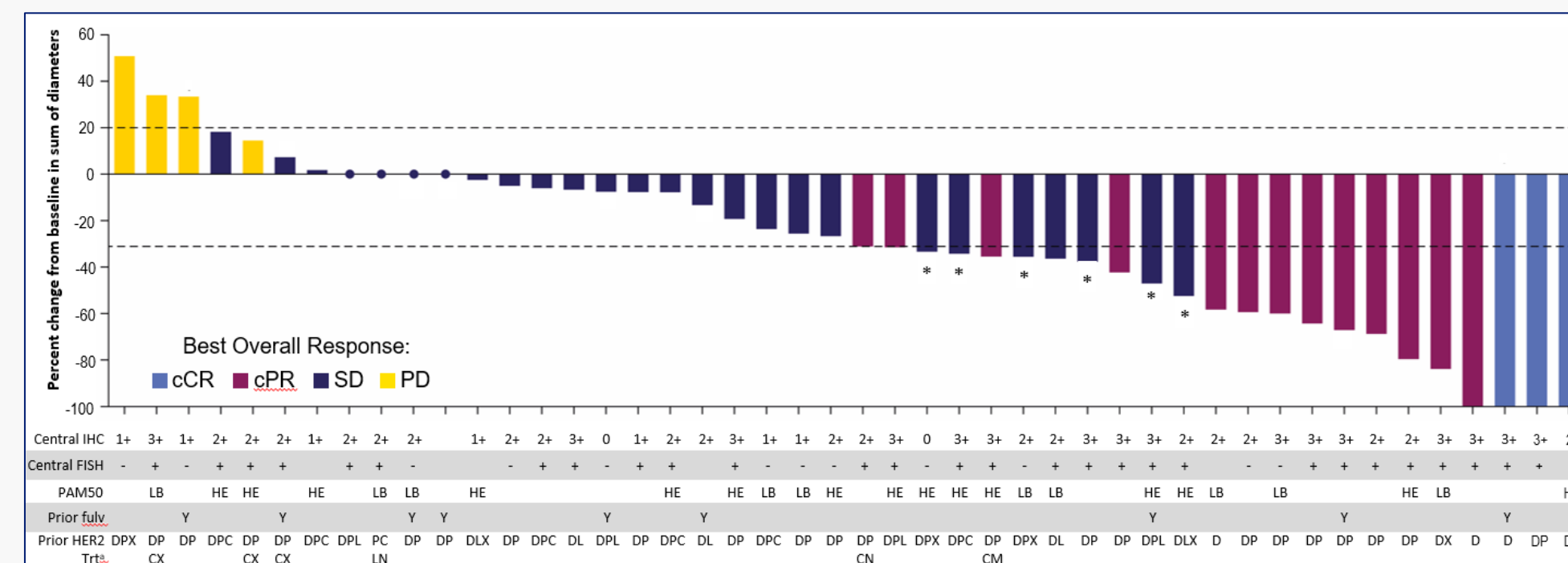
1L GEA: Phase 2 Zanidatamab + Chemotherapy + Tislelizumab¹



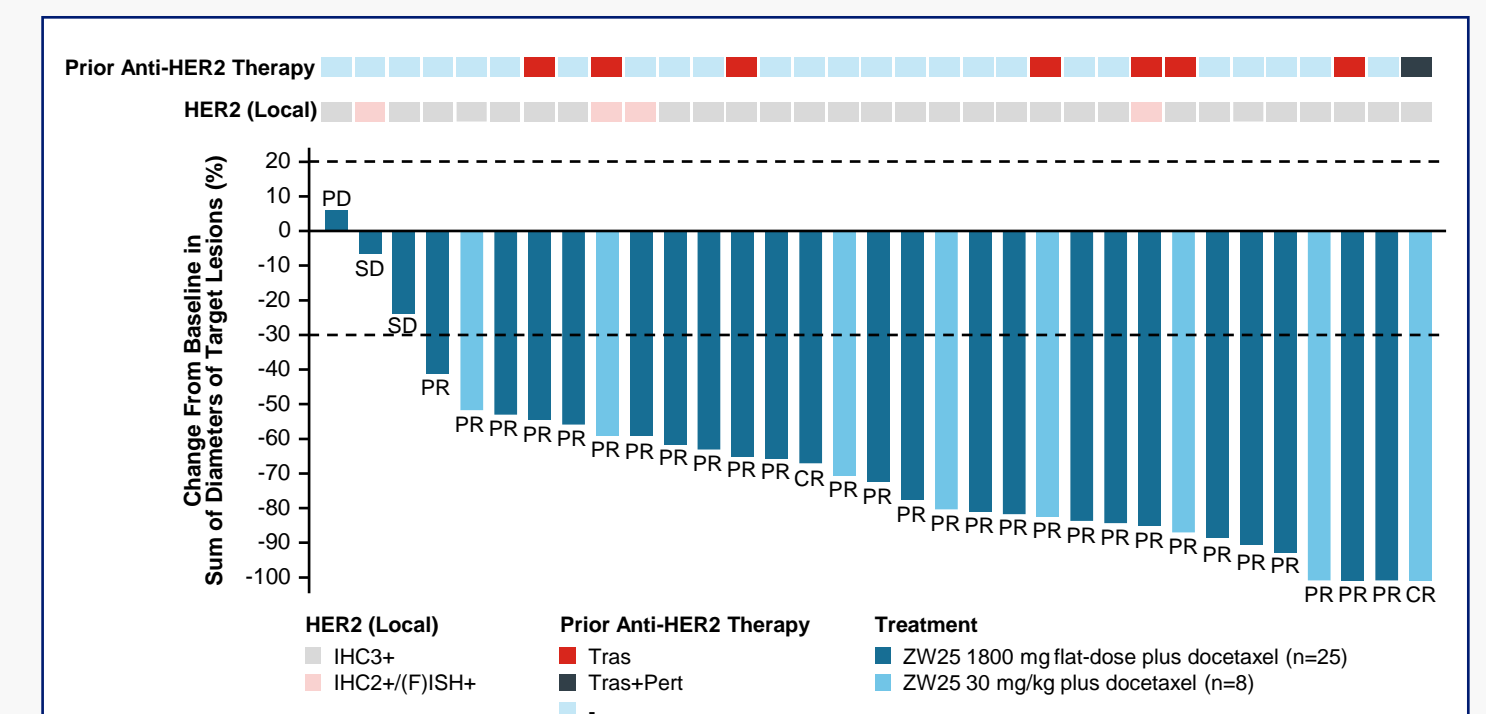
1L GEA: Phase 2 Zanidatamab + Chemotherapy²



Late-Line HR+/HER2+ BC: Phase 2 Zanidatamab + Palbociclib + Fulvestrant³



1L BC: Phase 2 Zanidatamab + Docetaxel⁴

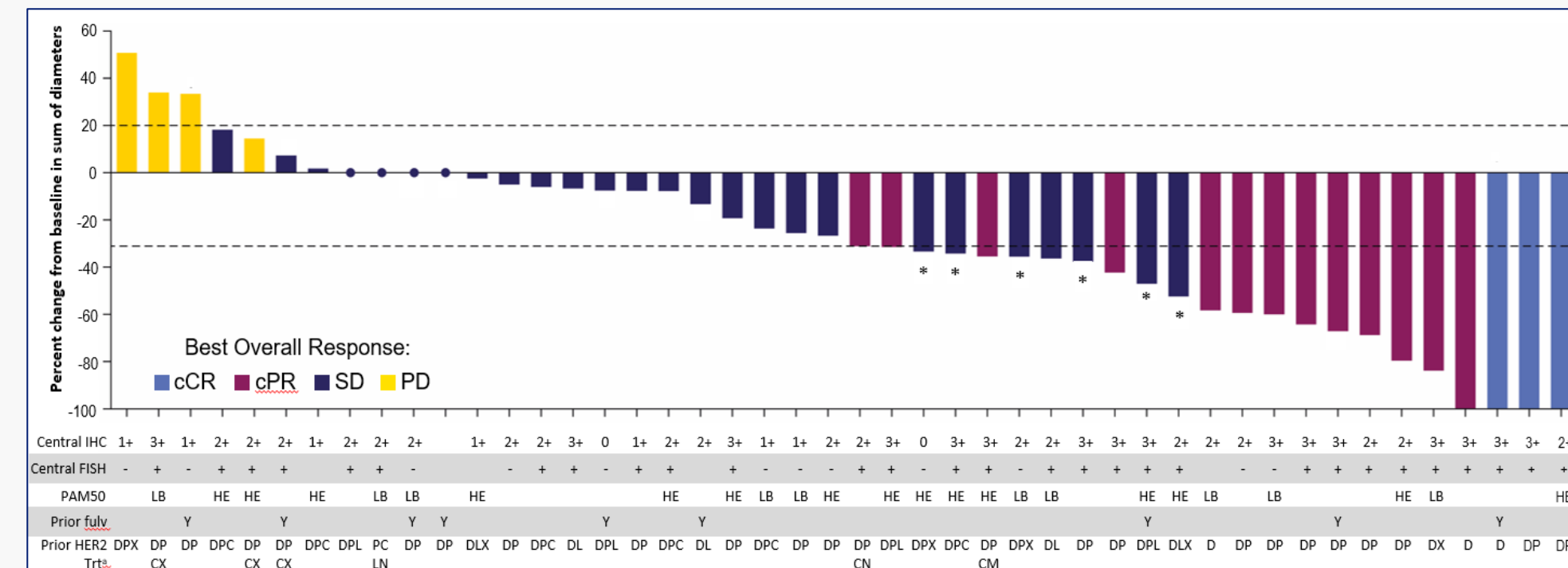


Zanidatamab has Demonstrated Activity After Progression on Other HER2 Therapies

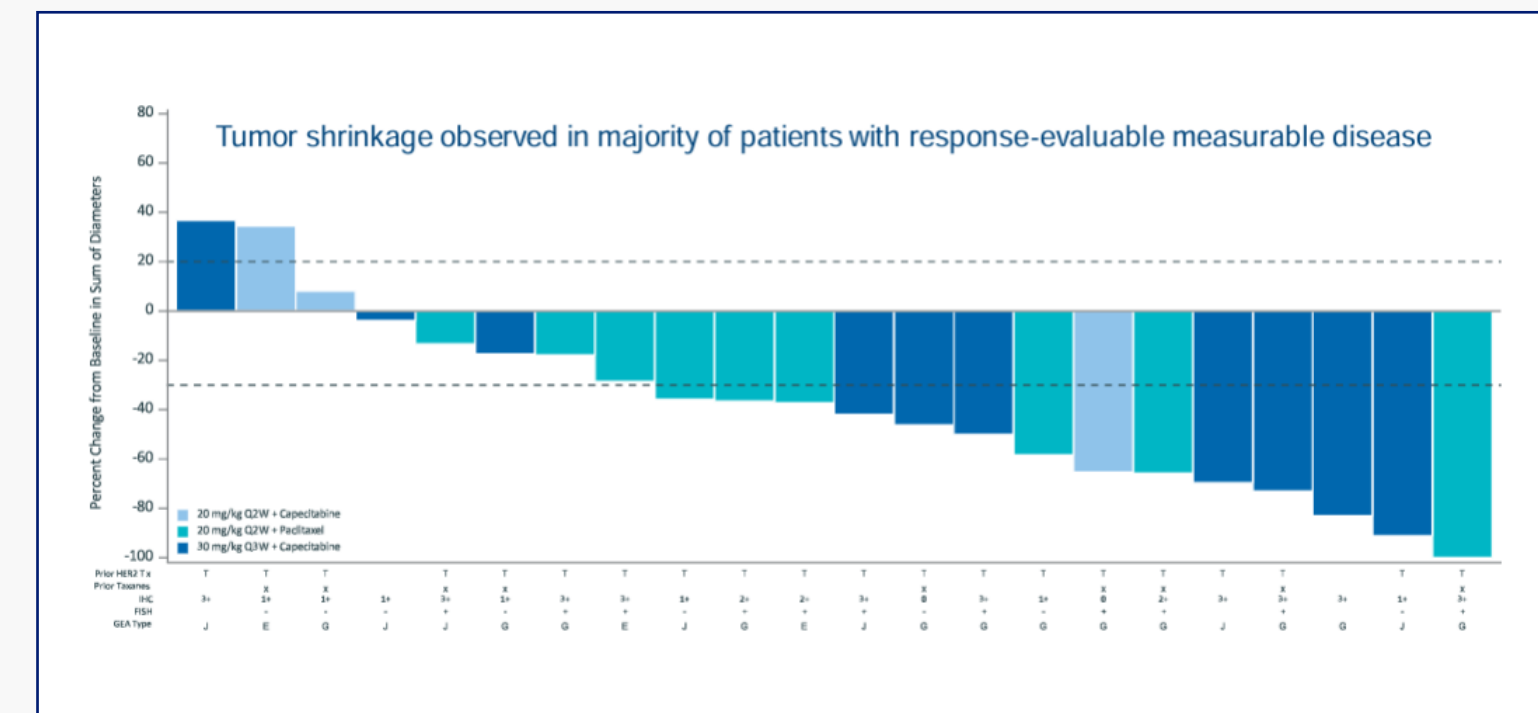
Zanidatamab has shown activity after treatment with HER2-targeted therapies:

- T-DXd
- T-DM1
- Trastuzumab
- Pertuzumab
- Tucatinib
- Lapatinib
- Neratinib
- Margetuximab

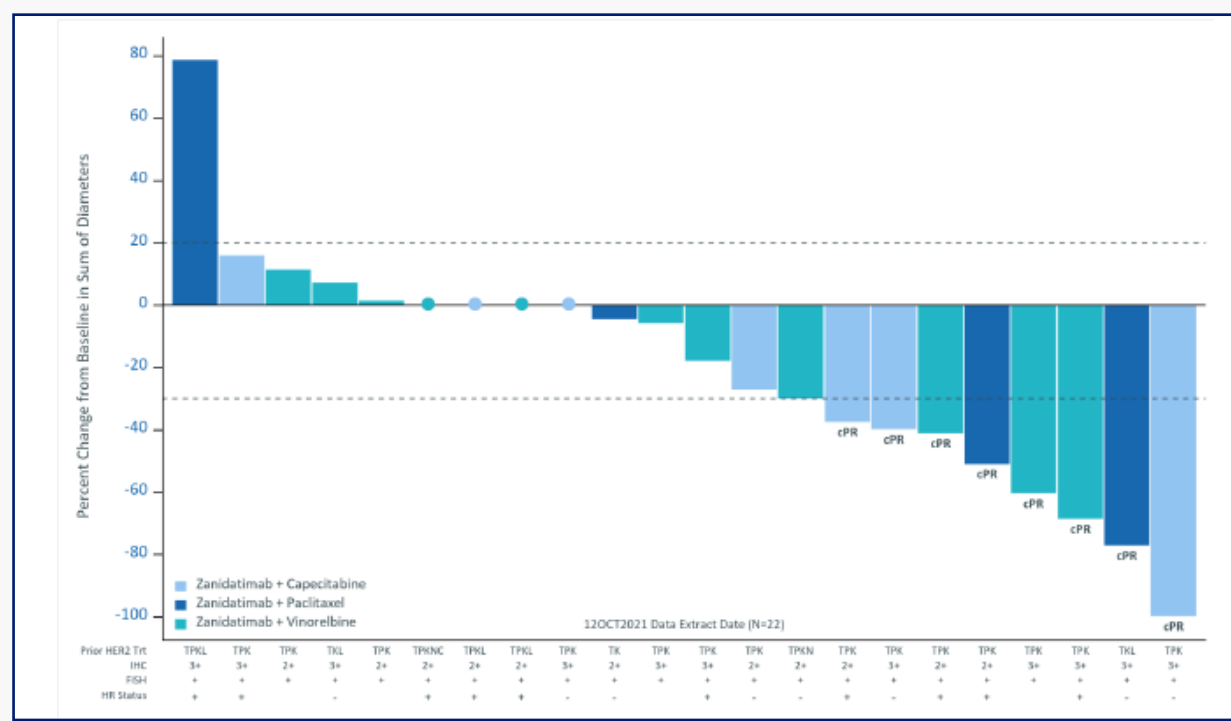
Late-Line HR+/HER2+ BC: Phase 2 Zanidatamab + Palbociclib + Fulvestrant¹



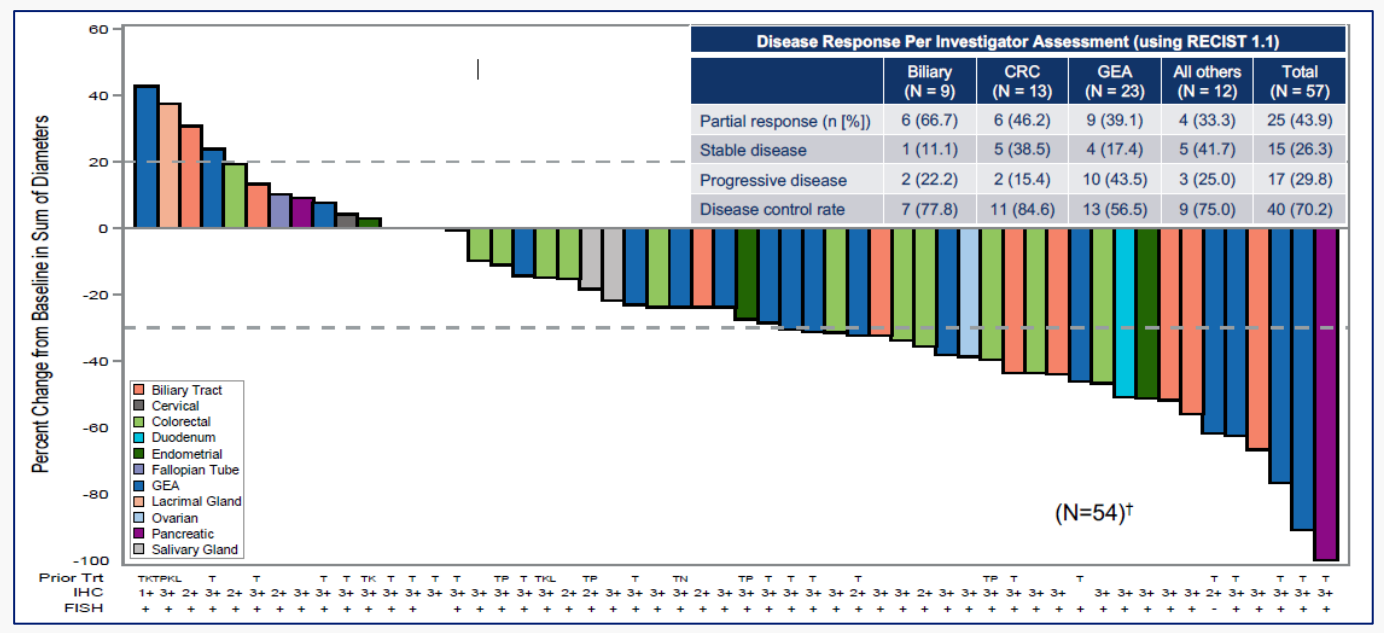
3L+ GEA: Phase 1 Chemo Combination²



Late-Line BC: Phase 1 Chemo Combination³

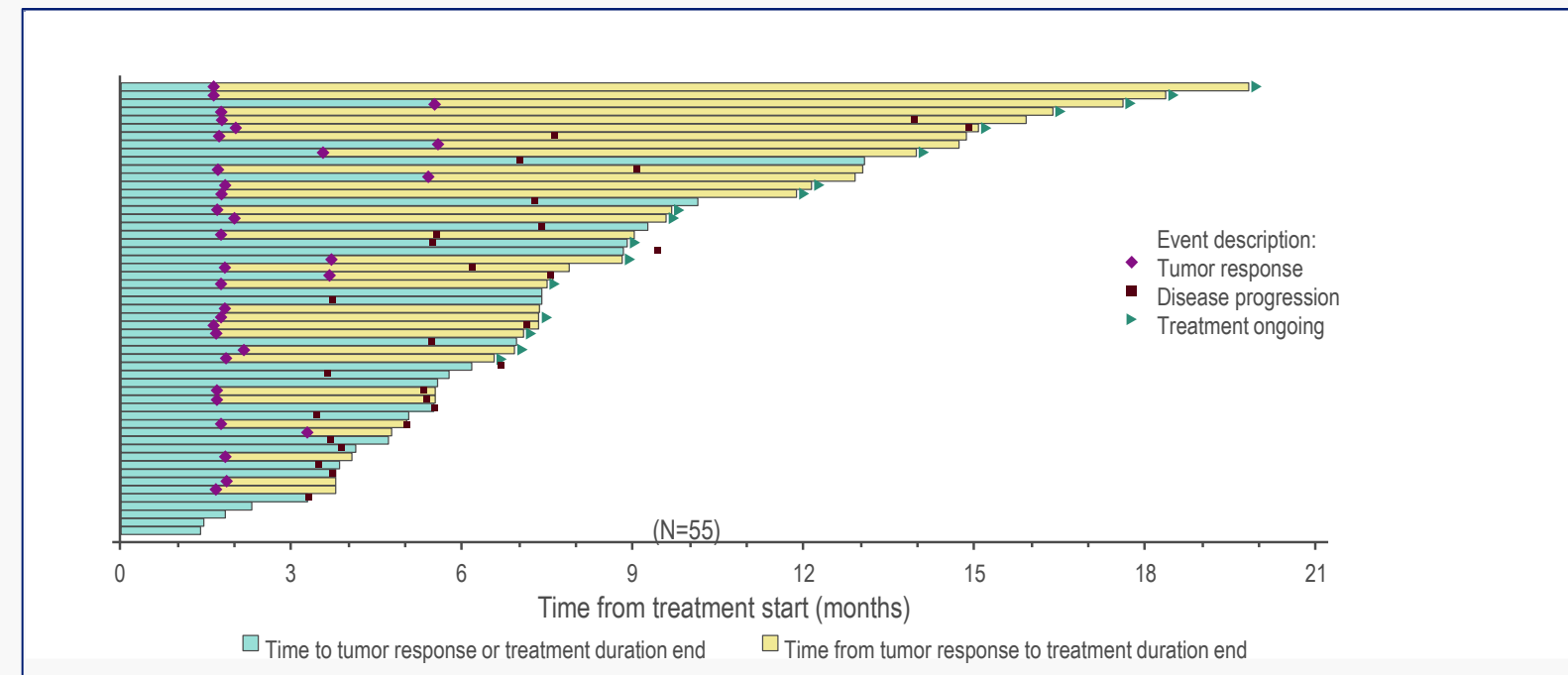


4L+ Basket: Phase 1 Monotherapy⁴

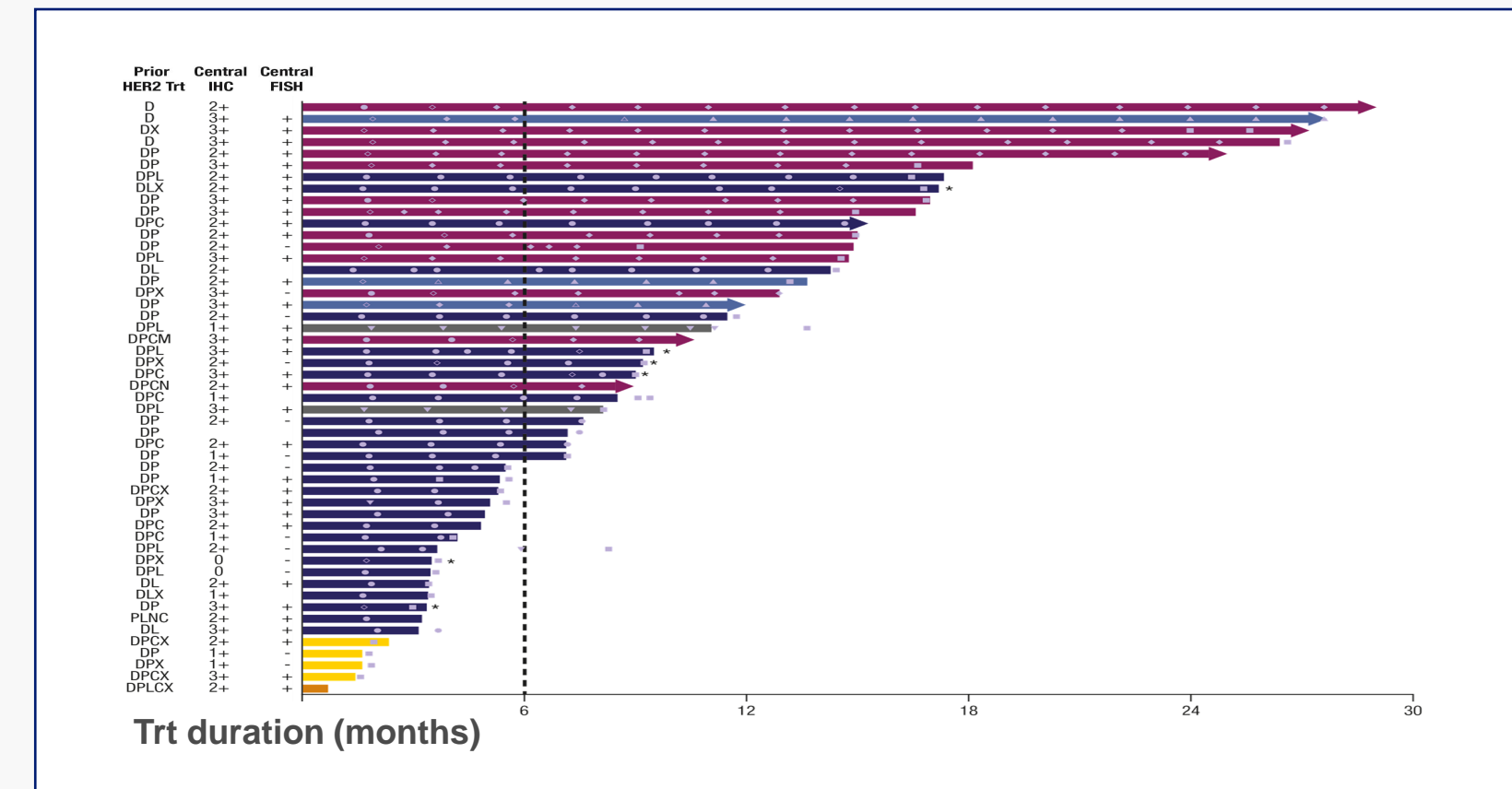


Zanidatamab has Demonstrated Durable Activity in Multiple Indications

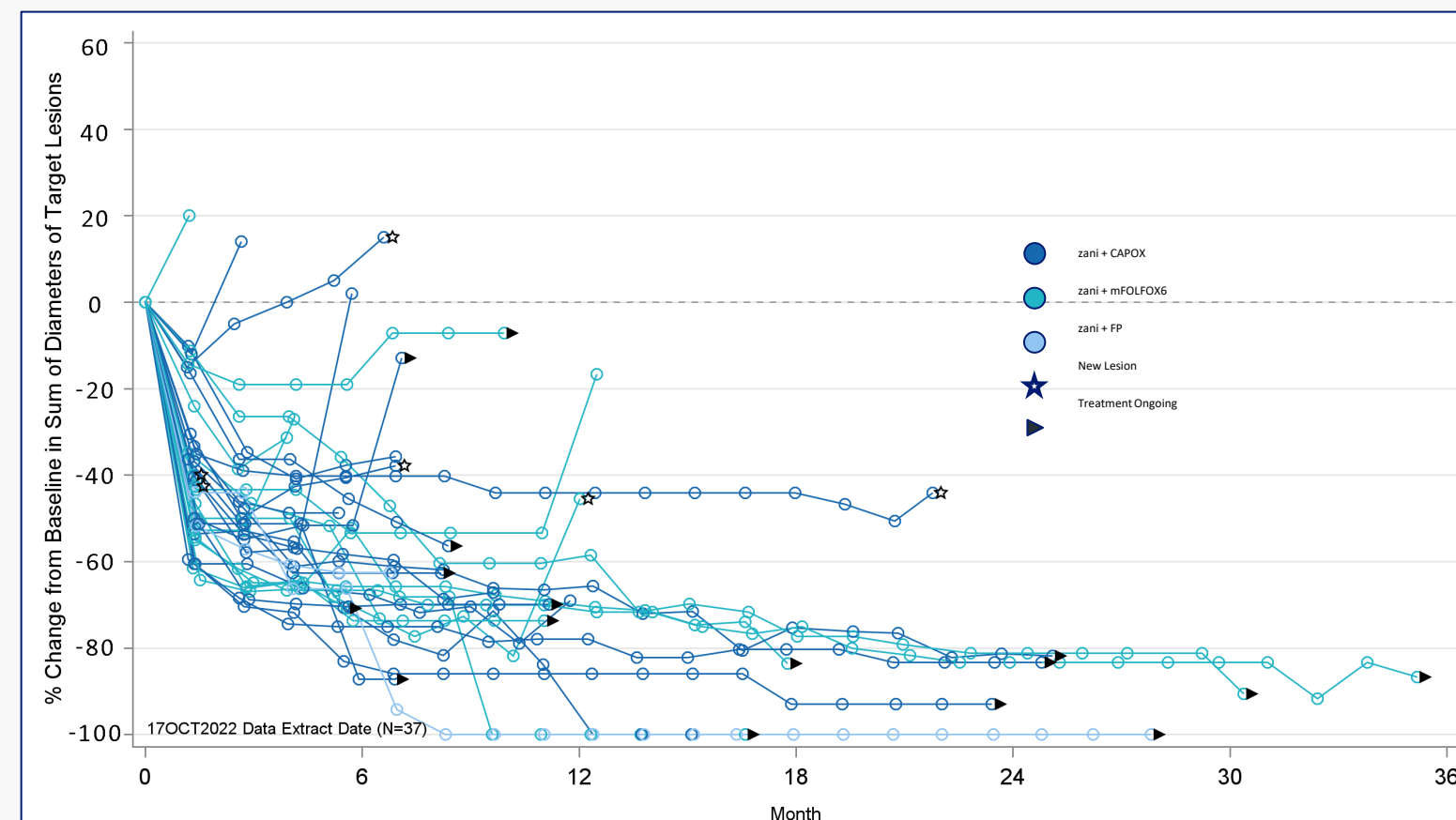
2L+ BTC Pivotal: Phase 2 Zanidatamab Monotherapy¹



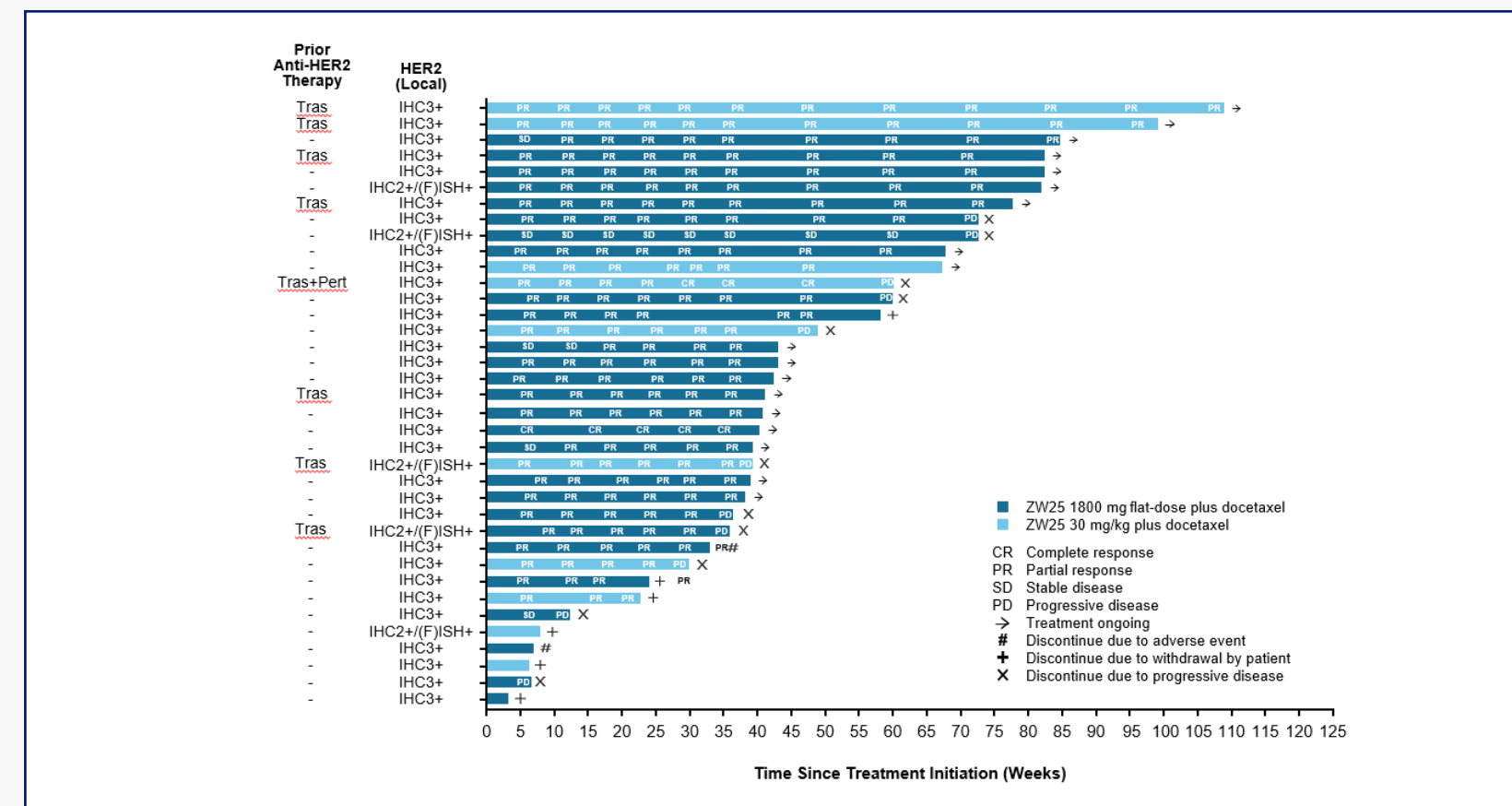
Late-Line HR+/HER2+ BC: Phase 2 Zanidatamab + Palbociclib + Fulvestrant²



1L GEA: Phase 2 Zanidatamab + Chemo³



1L BC: Phase 2 Zanidatamab + Chemo⁴



1/2L = first / second line; BC = breast cancer; BTC = biliary tract cancer; GEA = gastroesophageal adenocarcinoma; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.

¹Pant et. al., ASCO 2023; ²Escriva-de-Romani et. al., SABCS 2023; ³Elimova et. al., ASCO GI 2023; ⁴Wang et. al., ASCO 2023.

Zanidatamab in BTC

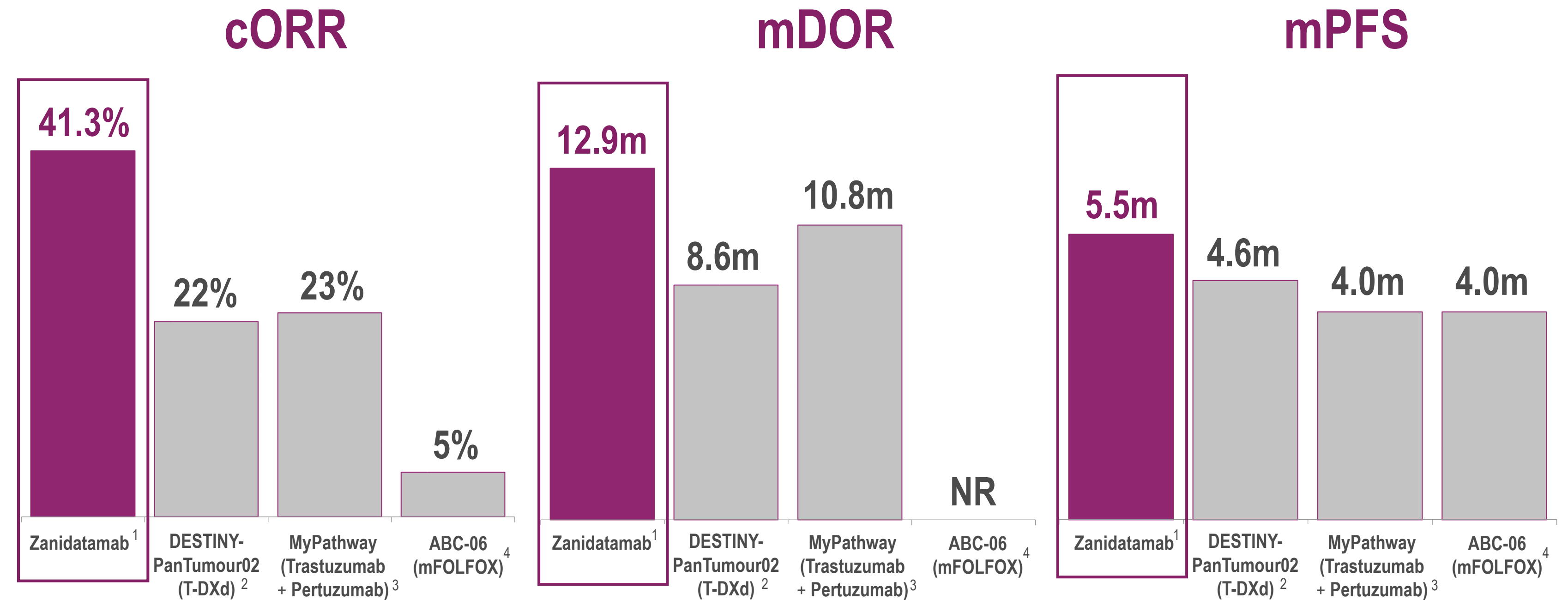
Potential to be the First Approved HER2-Targeted Therapy

Unmet Need in BTC: No Approved HER2-Targeted Therapies

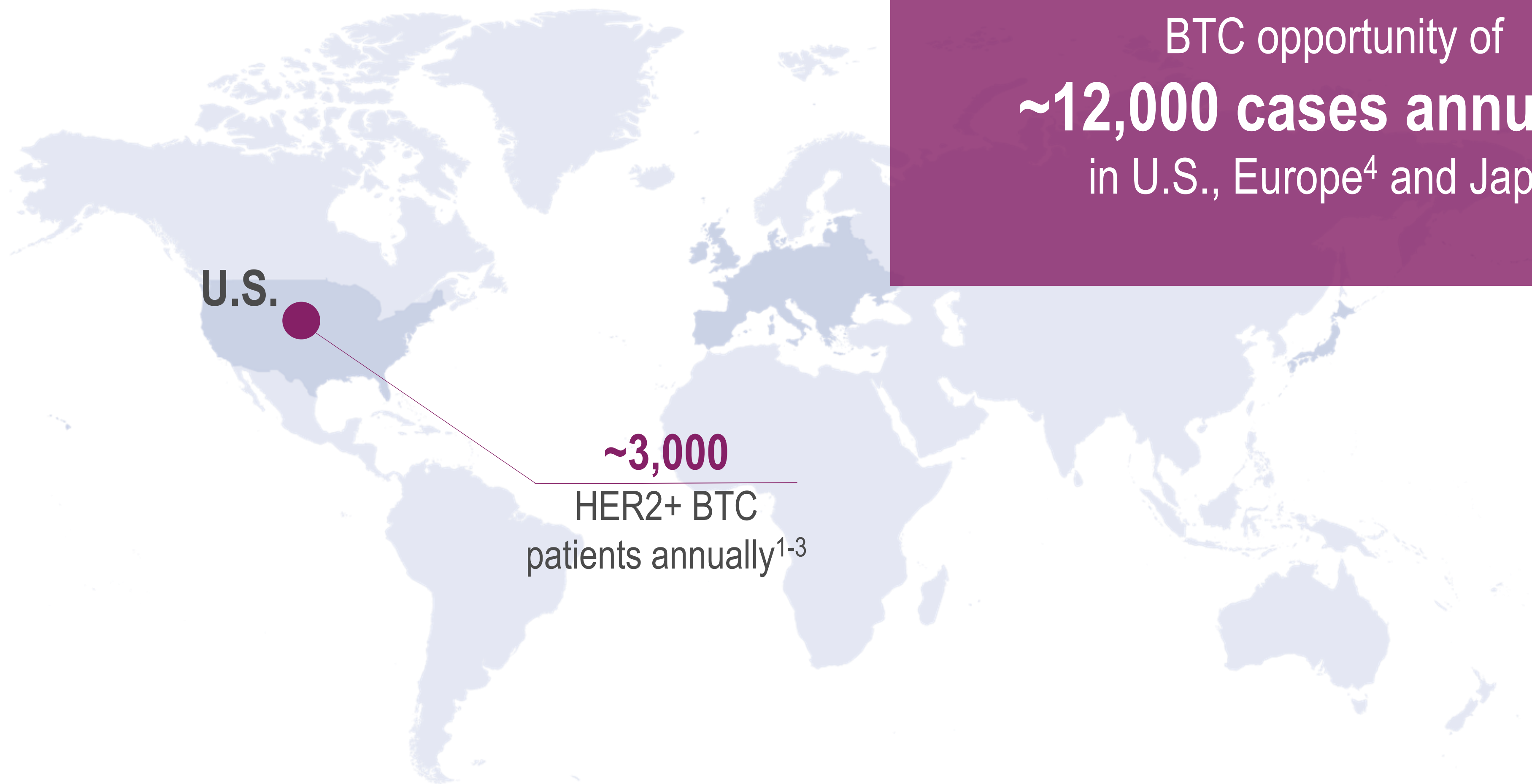
ASCO Annual Meeting Positive HERIZON-BTC-01 Trial Results

- Oral presentation of top-line BTC data
Voted Best of ASCO 2023
- Safety profile was consistent with that observed in previous monotherapy studies

- **Initiated BLA submission in 2L BTC for potential accelerated approval**
- **Initiated 1L BTC Confirmatory Trial**



BTC Represents a Significant Unmet Need



BTC opportunity of
~12,000 cases annually²
in U.S., Europe⁴ and Japan

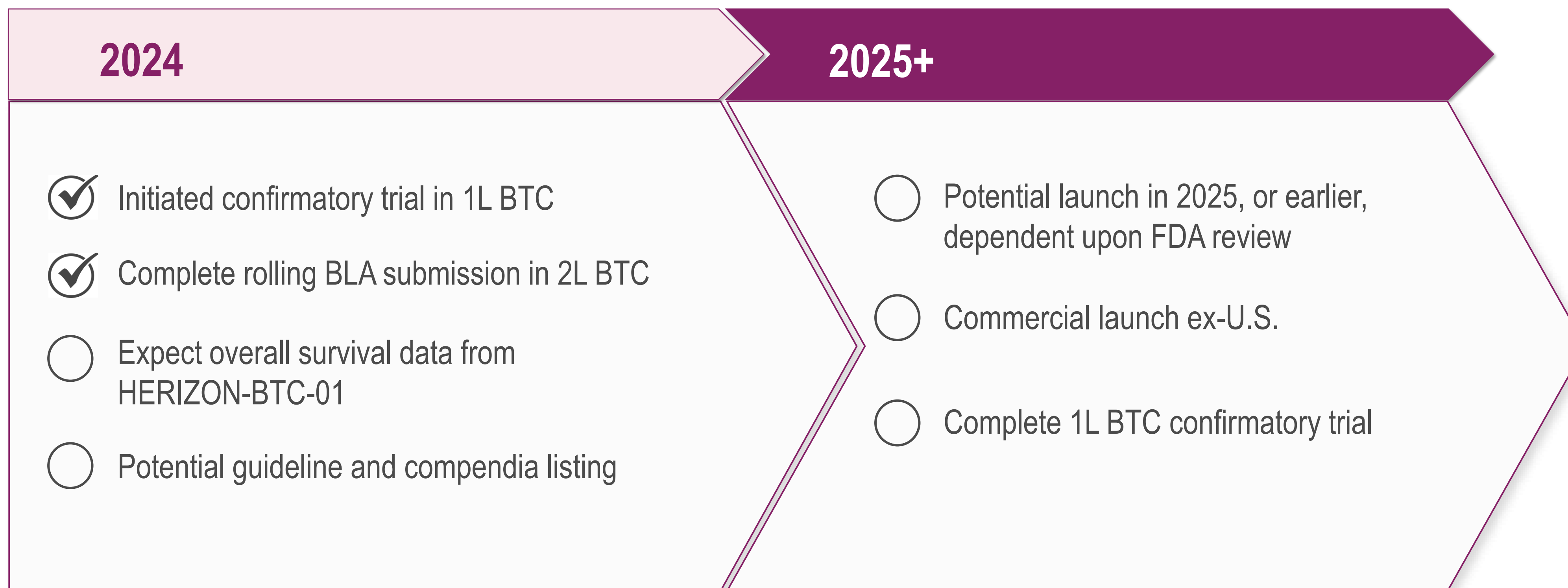
U.S.

~3,000

HER2+ BTC
patients annually¹⁻³



Zanidatamab Development Timeline in BTC



De-Risked Expansion Opportunity in 1L BTC



Key Inclusion Criteria:

- BTC: GBC, ICC, ECC
- HER2-positivity
 - IHC 3+ or IHC 2+/ISH+
- No PD-1/PD-L1 expression required
- No prior treatment in the locally advanced or metastatic setting

**Zanidatamab +
Gem/Cis +/-
PD-1/PD-L1 Inhibitor**

1:1 Randomization
N = 286

**Gem/Cis +/-
PD-1/PD-L1 Inhibitor**

Primary Endpoint:

- PFS (IHC3+)

Secondary / Exploratory Endpoints:

- PFS (allcomers)
- OS
- ORR
- DOR
- Safety
- HEOR/QOL
- Biomarkers



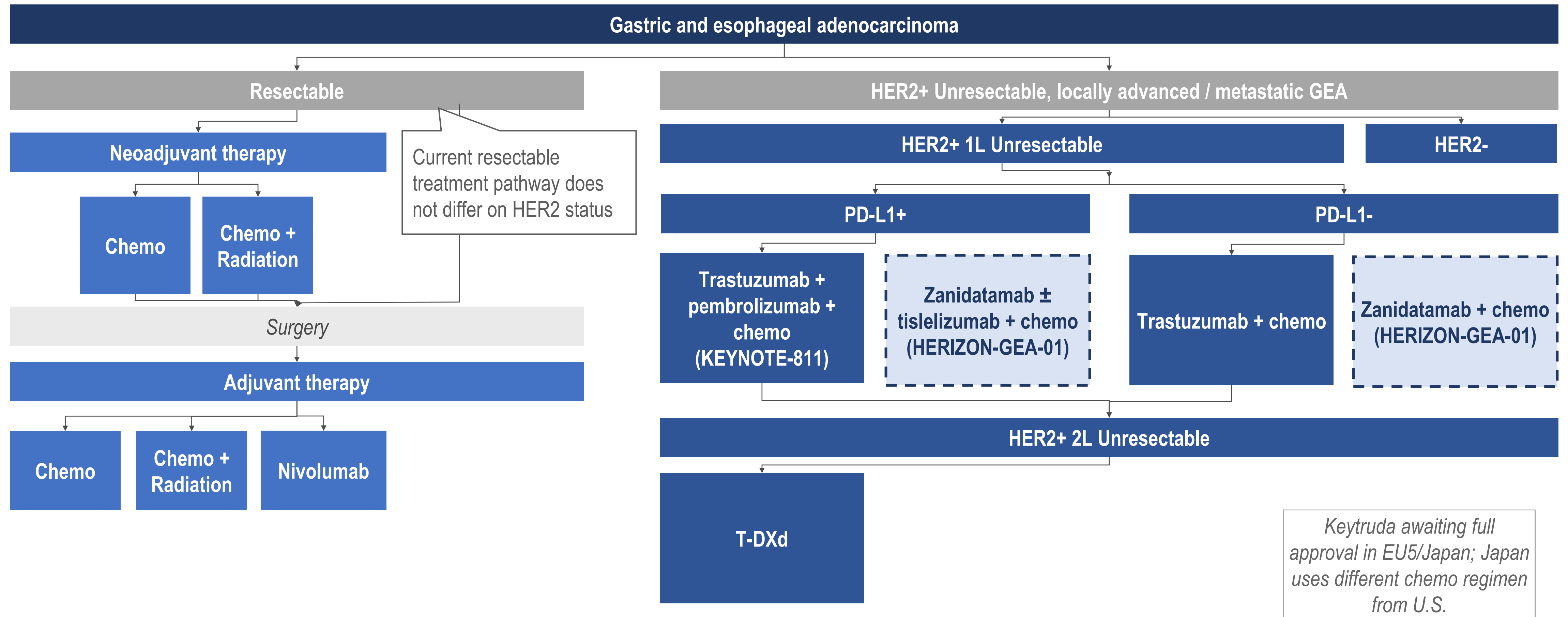
Zanidatamab in GEA

Geoffrey Ku, M.D.

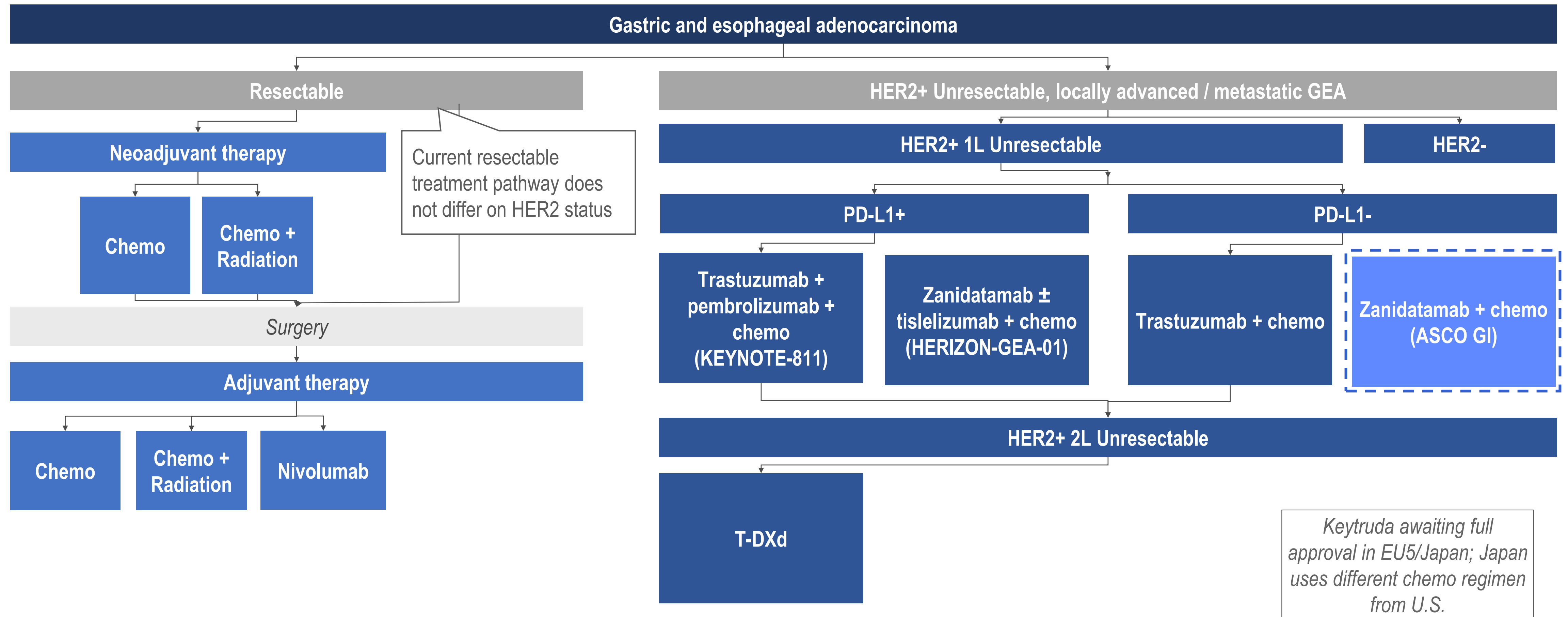
Head of Esophagogastric Section on the Gastrointestinal Oncology Service
Memorial Sloan Kettering Cancer Center Department of Medicine



GEA Treatment Paradigm Highlights Unmet Need

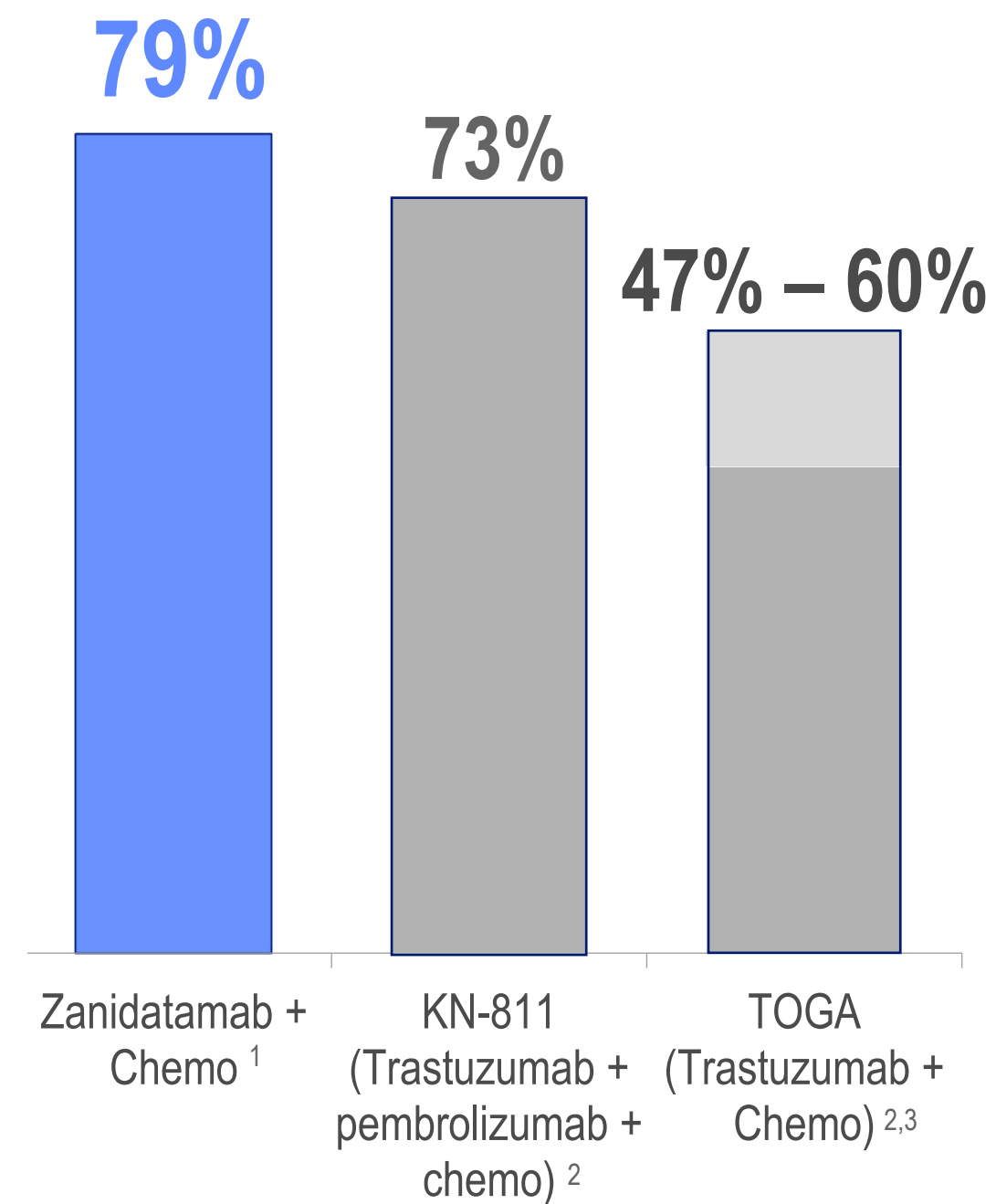


GEA Treatment Paradigm Highlights Unmet Need

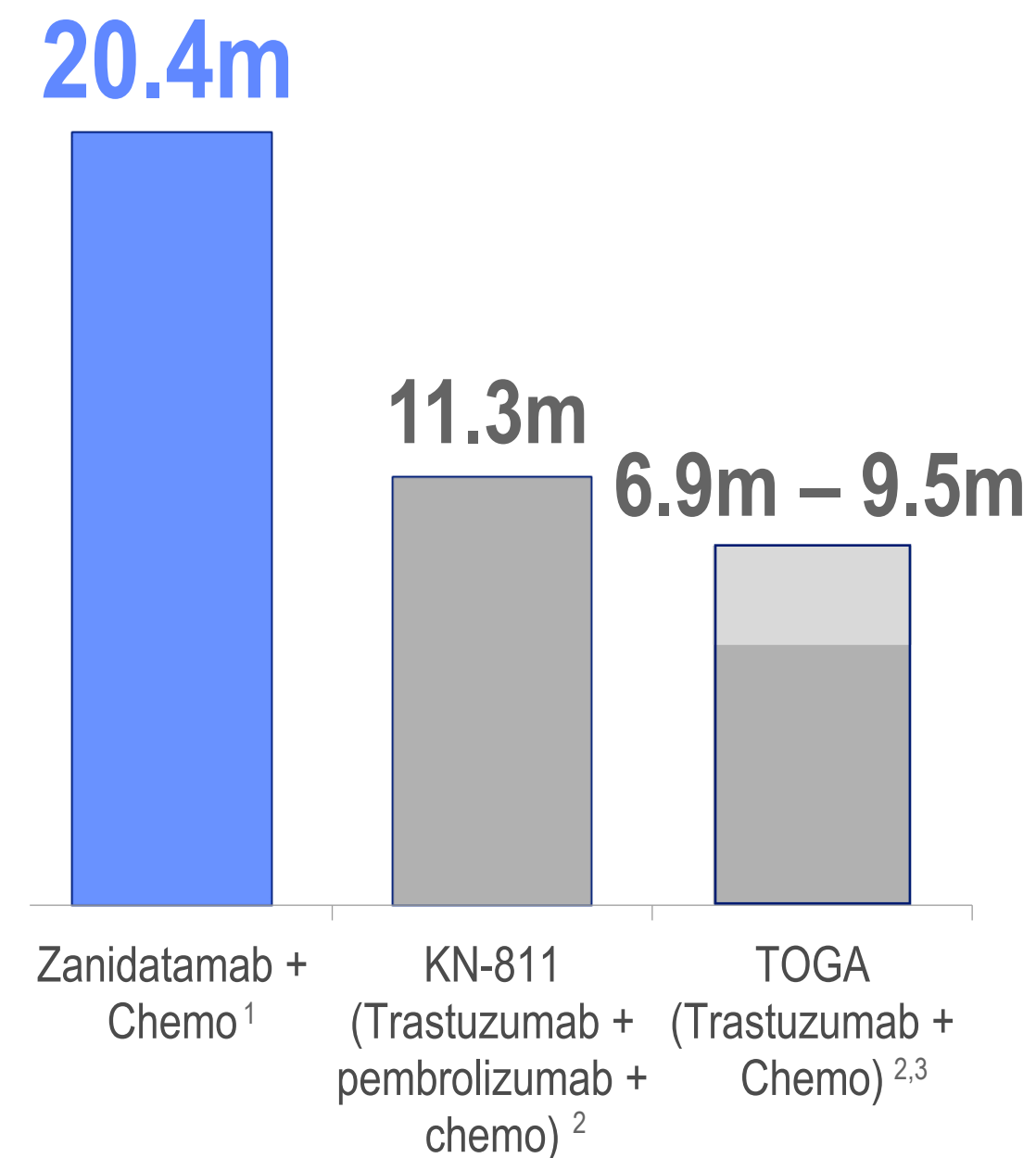


Zanidatamab + Chemo in 1L GEA: Observed Clinical Activity and Benchmarks

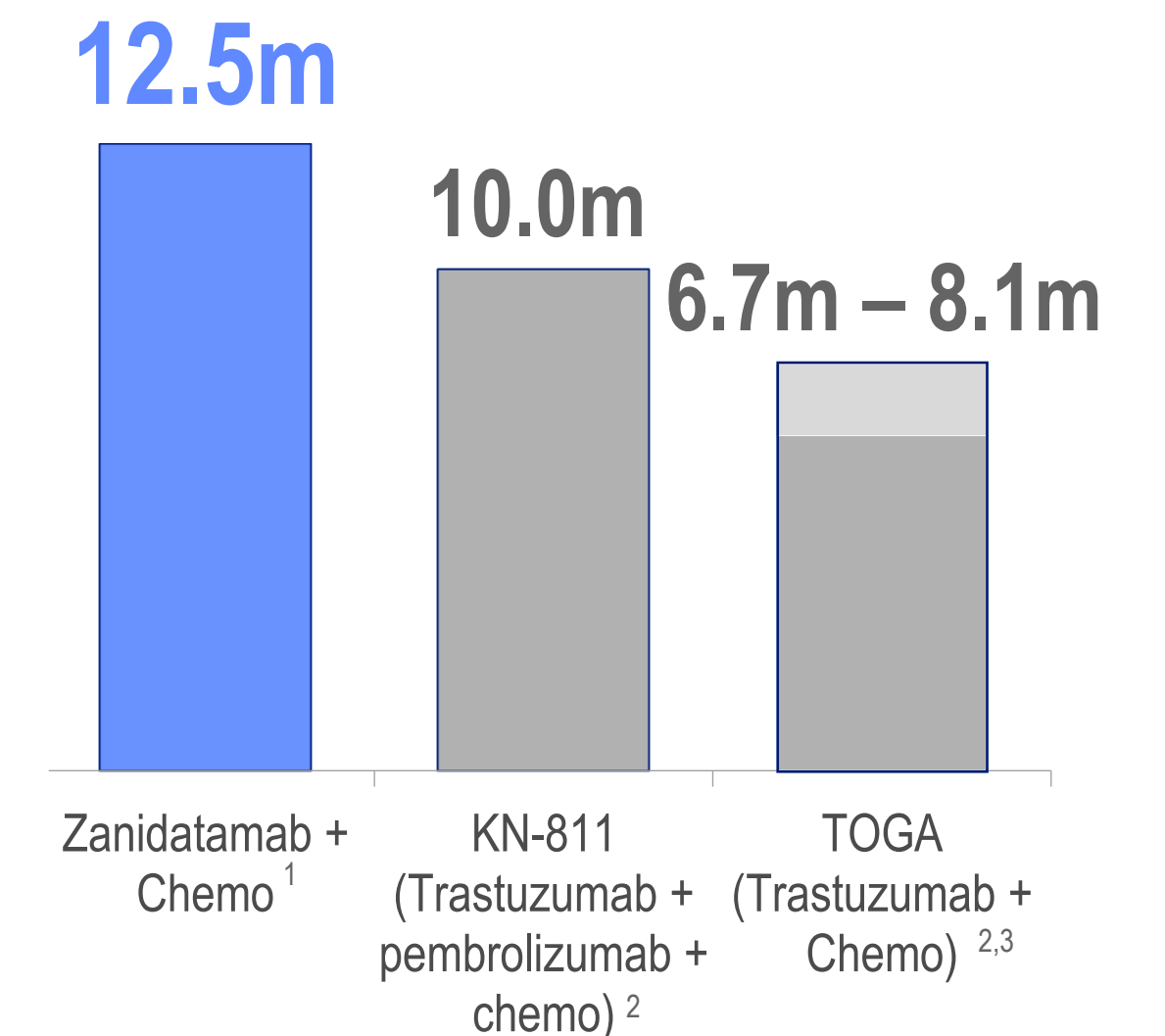
cORR



mDOR

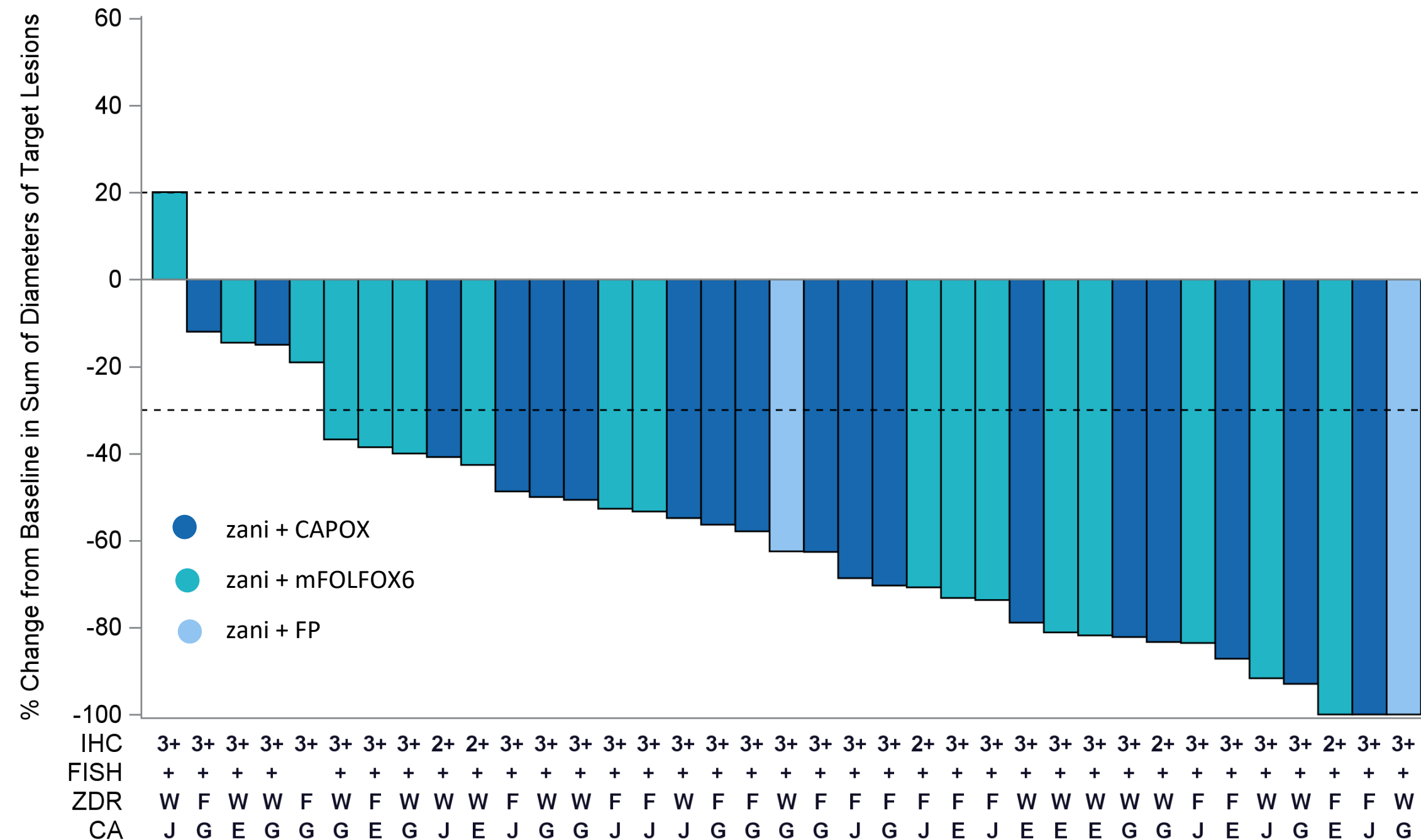


mPFS

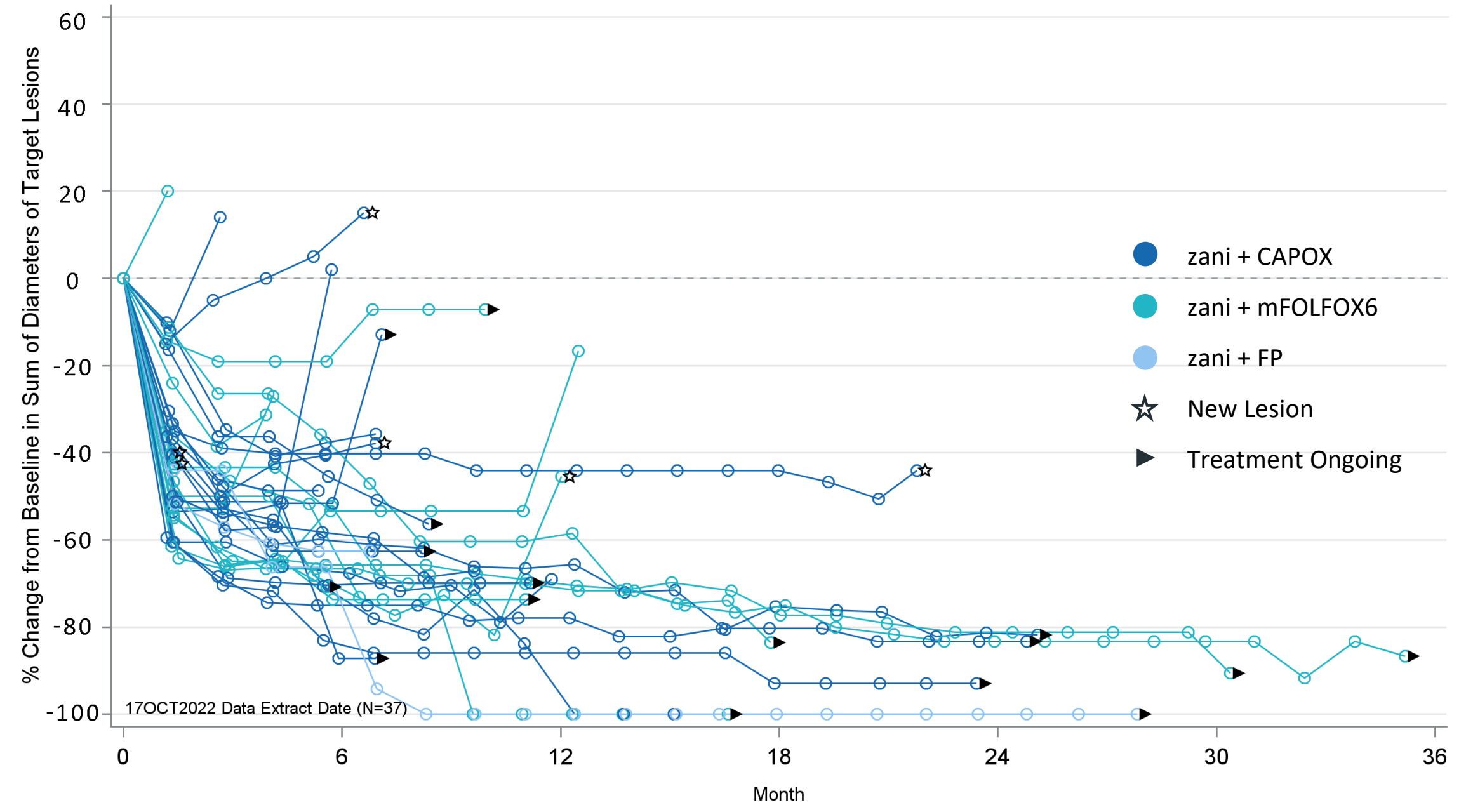


Zanidatamab + Chemo Demonstrated Promising Antitumor Activity in HER2+ 1L GEA Patients

Change in Target Lesion Size in Response-evaluable Patients with HER2-positive mGEA



Change in Target Lesion Size Over Time in Response-evaluable Patients with HER2-positive mGEA

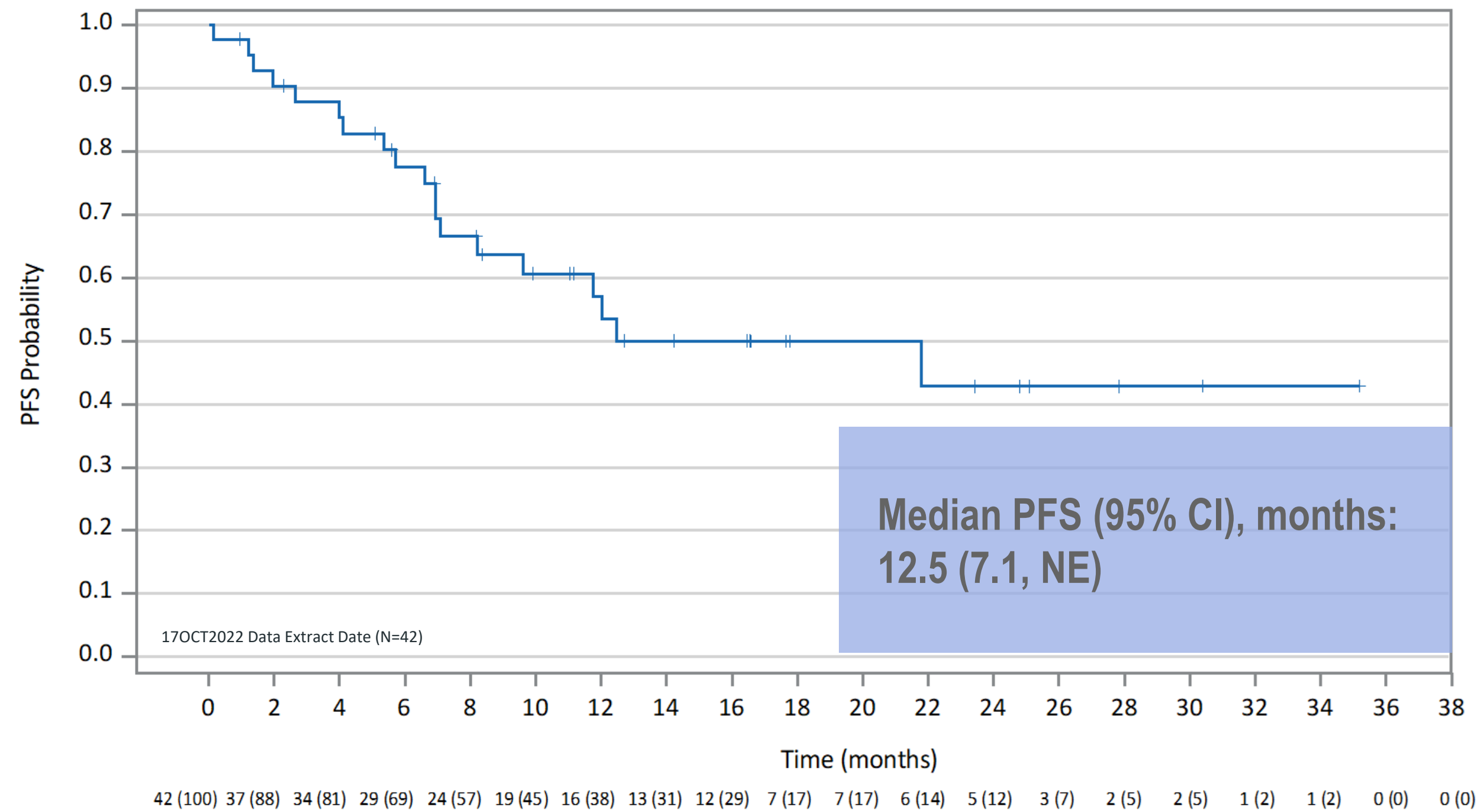


Dotted lines indicate 20% increase and 30% decrease in sum of diameters of target tumors.
 CA = primary tumor type; E = esophageal cancer; F = flat dosing regimen; FISH = fluorescence *in situ* hybridization; G = gastric cancer; IHC = immunohistochemistry; J = gastroesophageal junction adenocarcinoma; W = weight-based dosing regimen; ZDR = zanidatamab dosing regimen; zani = zanidatamab*1 patient is excluded from the figure because they did not have a postbaseline assessment of target lesions.

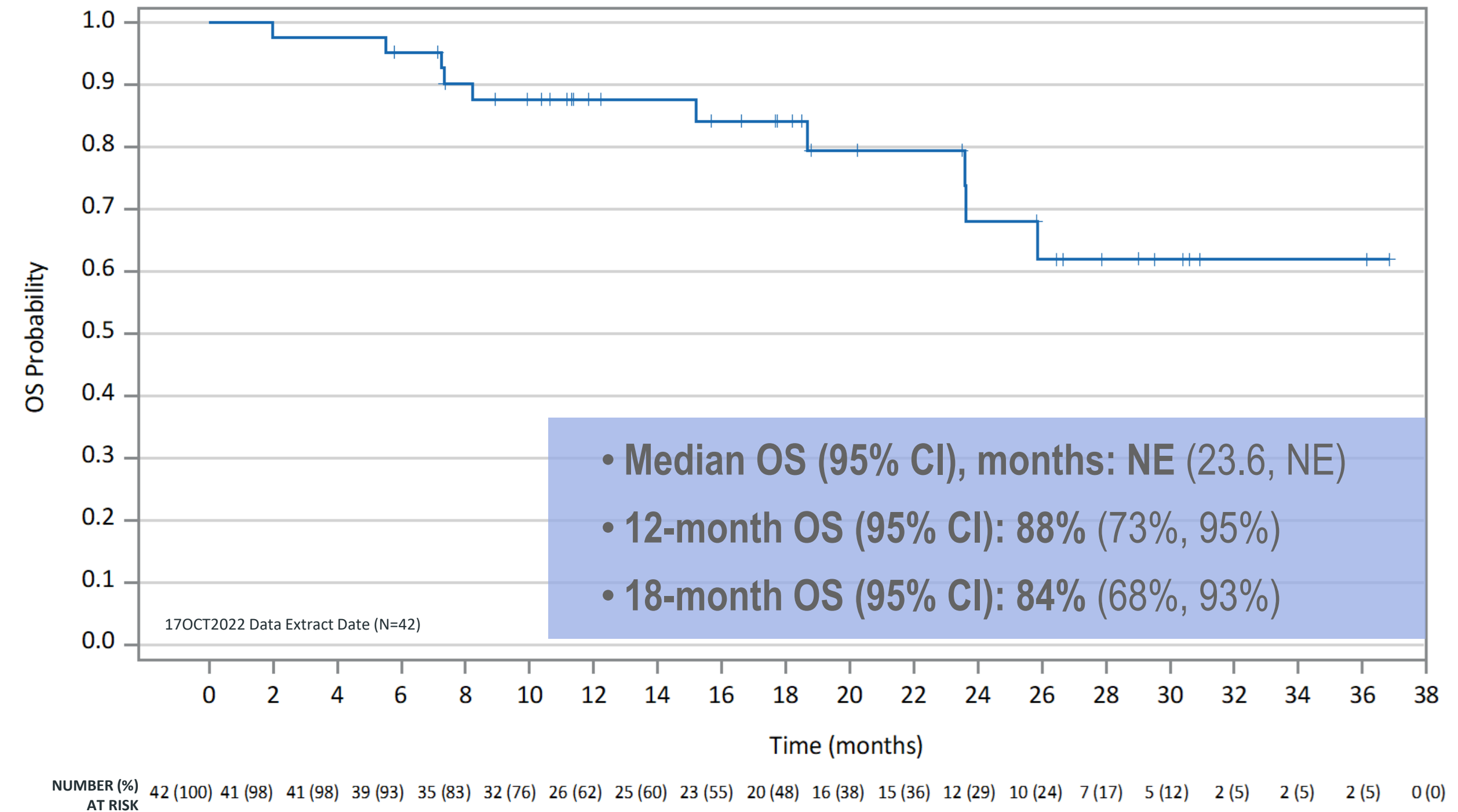
Dotted line indicates no change from baseline in sum of diameters of target tumor. zani = zanidatamab.
 *1 patient is excluded from the figure because they did not have a postbaseline assessment of target lesions.

Zanidatamab + Chemo Demonstrated Promising Early Overall Survival in HER2+ 1L GEA Patients

Progression-free Survival in Patients with HER2-positive mGEA

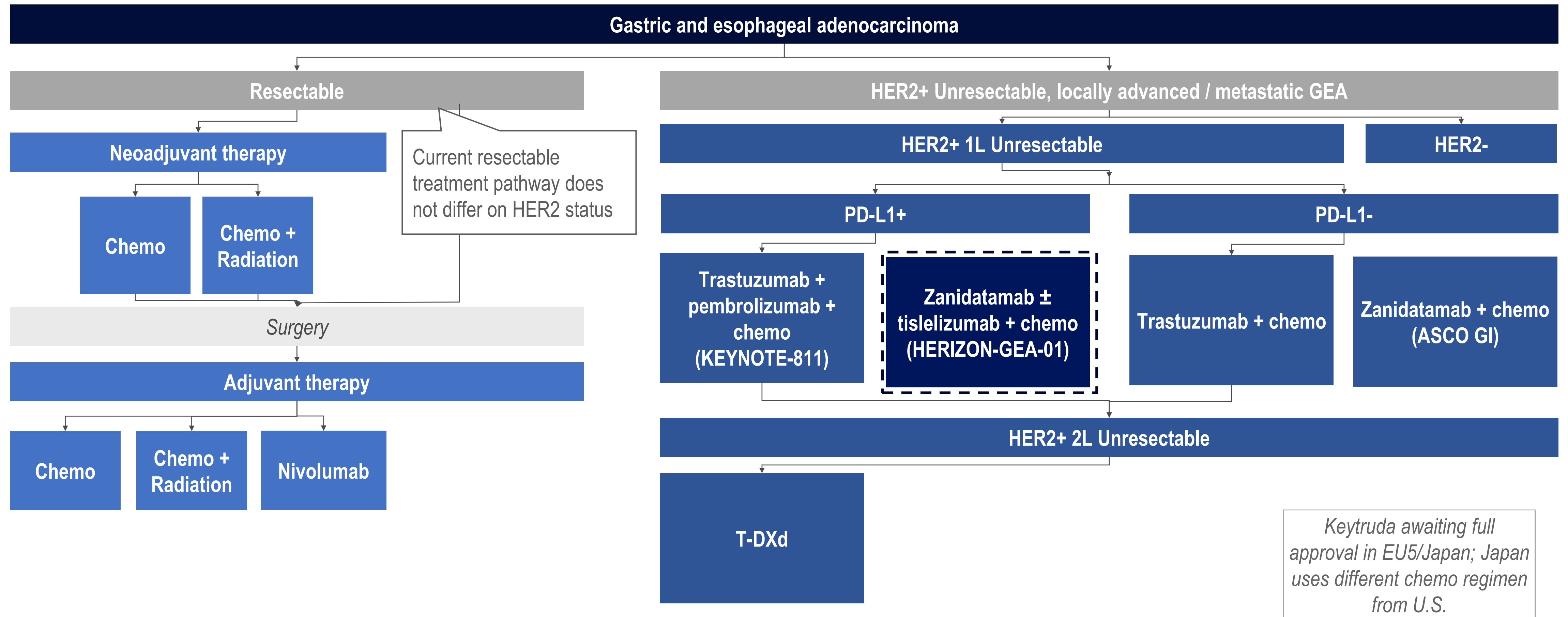


Overall Survival in Patients with HER2-positive mGEA




Source: Elimova et al, ASCO GI 2023. CI = confidence interval; GEA = gastroesophageal adenocarcinoma; HER2 = human epidermal growth factor receptor 2; NE = not evaluable; OS = overall survival; PFS = progression-free survival.

GEA Treatment Paradigm Highlights Unmet Need

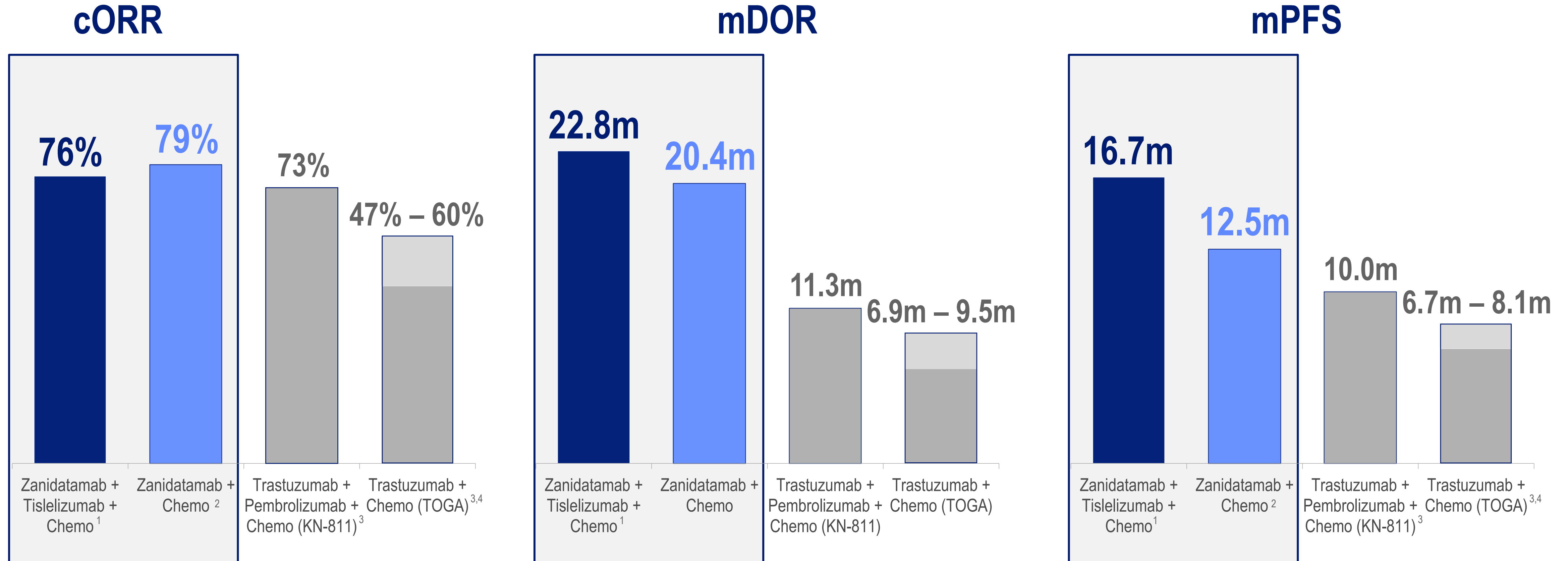


Keytruda awaiting full approval in EU5/Japan; Japan uses different chemo regimen from U.S.

 Key ongoing Jazz trials

Source: NCCN Guidelines. 1L = first line; ASCO GI = American Society of Clinical Oncology Gastrointestinal; EU5: Major EU markets, U.K, France, Germany, Spain, Italy; GEA = gastroesophageal adenocarcinoma; HER2 = human epidermal growth factor receptor 2; PD-L1 = programmed cell death protein 1; T-DXd = trastuzumab deruxatecan, or Enhertu®.

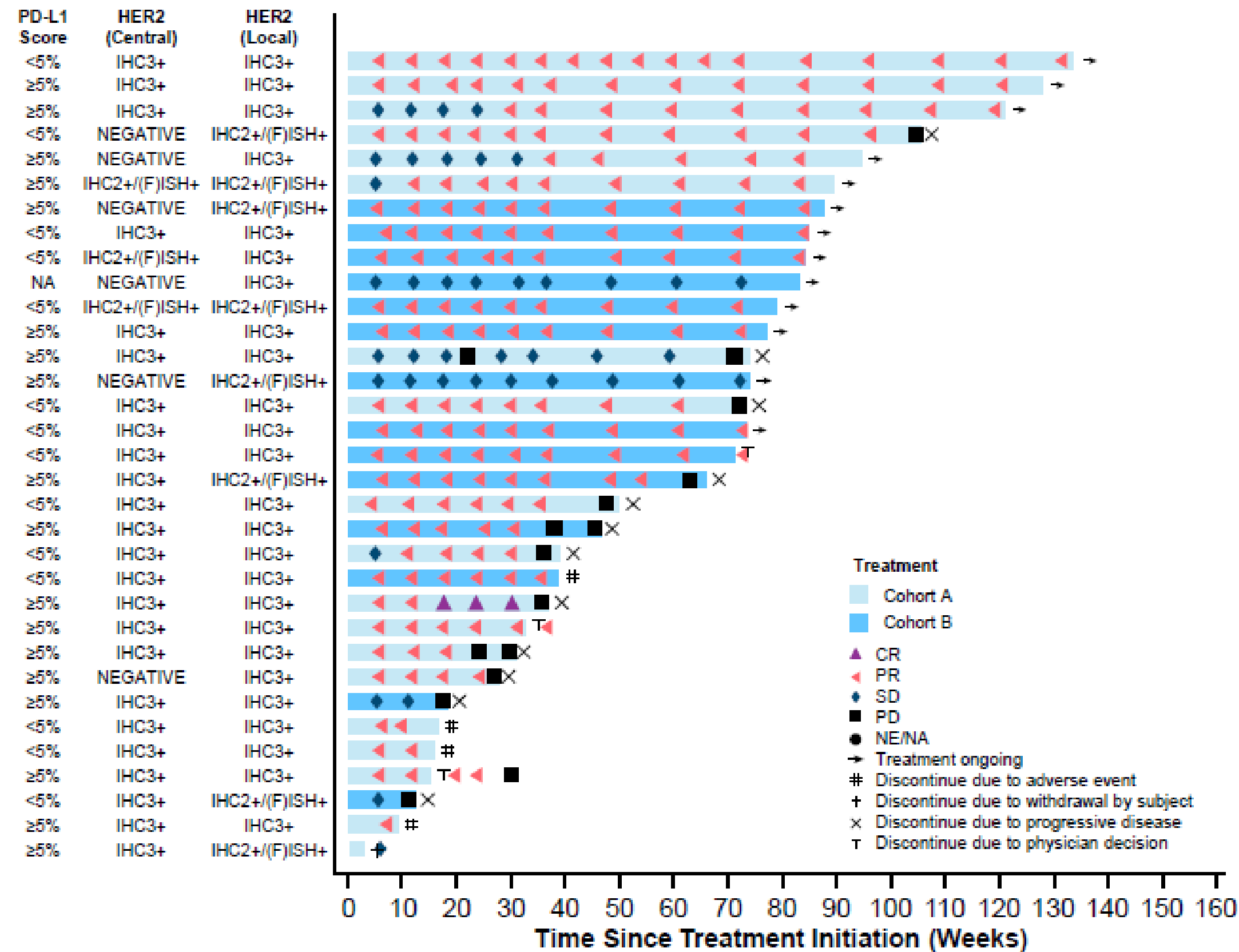
Zanidatamab + Tislelizumab + Chemo in 1L GEA: Observed Clinical Activity and Benchmarks



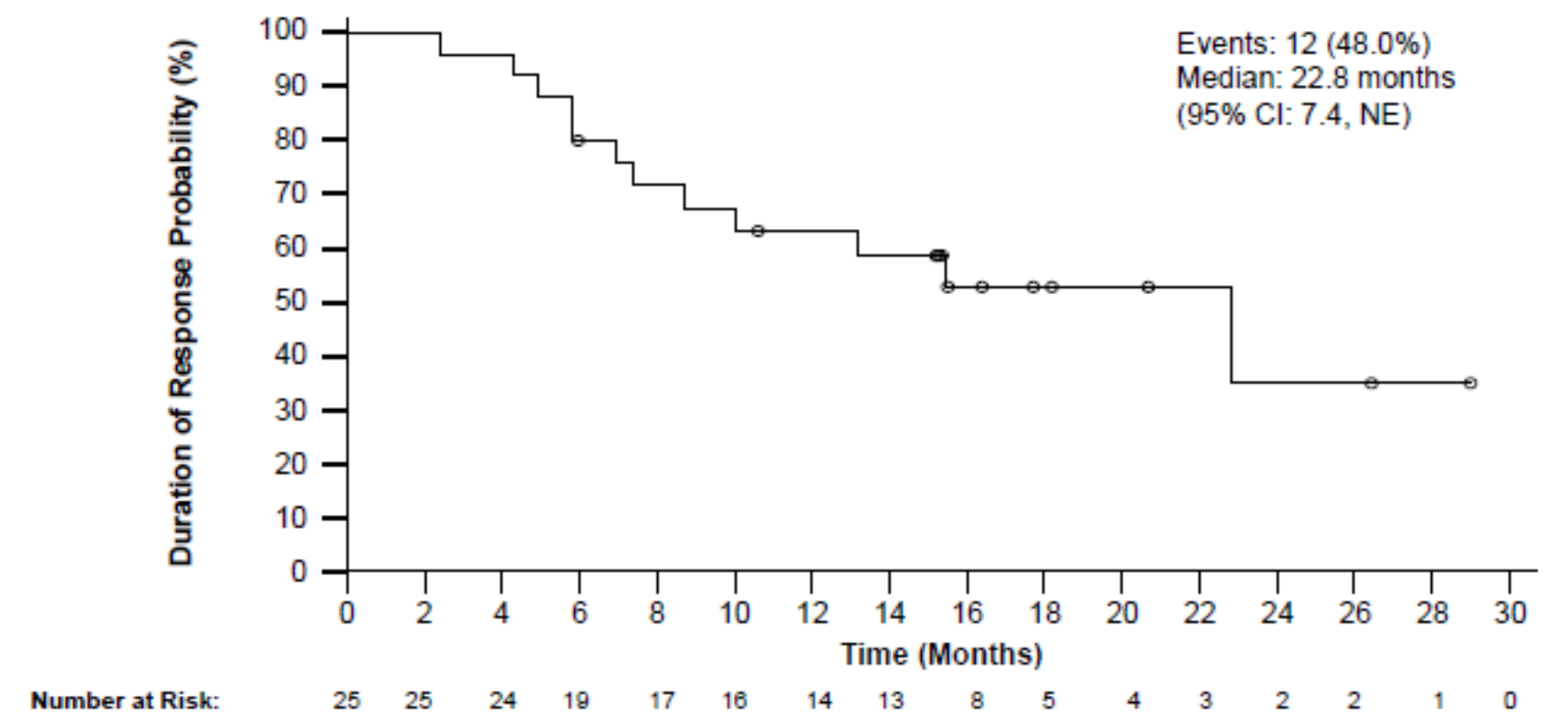
1L = first line; cORR = confirmed objective response rate; GEA = gastroesophageal adenocarcinoma; mDOR = median duration of response; mPFS = median progression-free survival. ¹Zanidatamab + tislelizumab + chemotherapy study done in collaboration with partner BeiGene. Lee et. al., ESMO 2023; ²Elimova et al, ASCO GI 2023; ³Janjigian et. al., Lancet Oncol. 2023; ⁴Bang et. al., Lancet Oncol. 2010.

Zanidatamab + Chemo + Tislelizumab Improves Durability

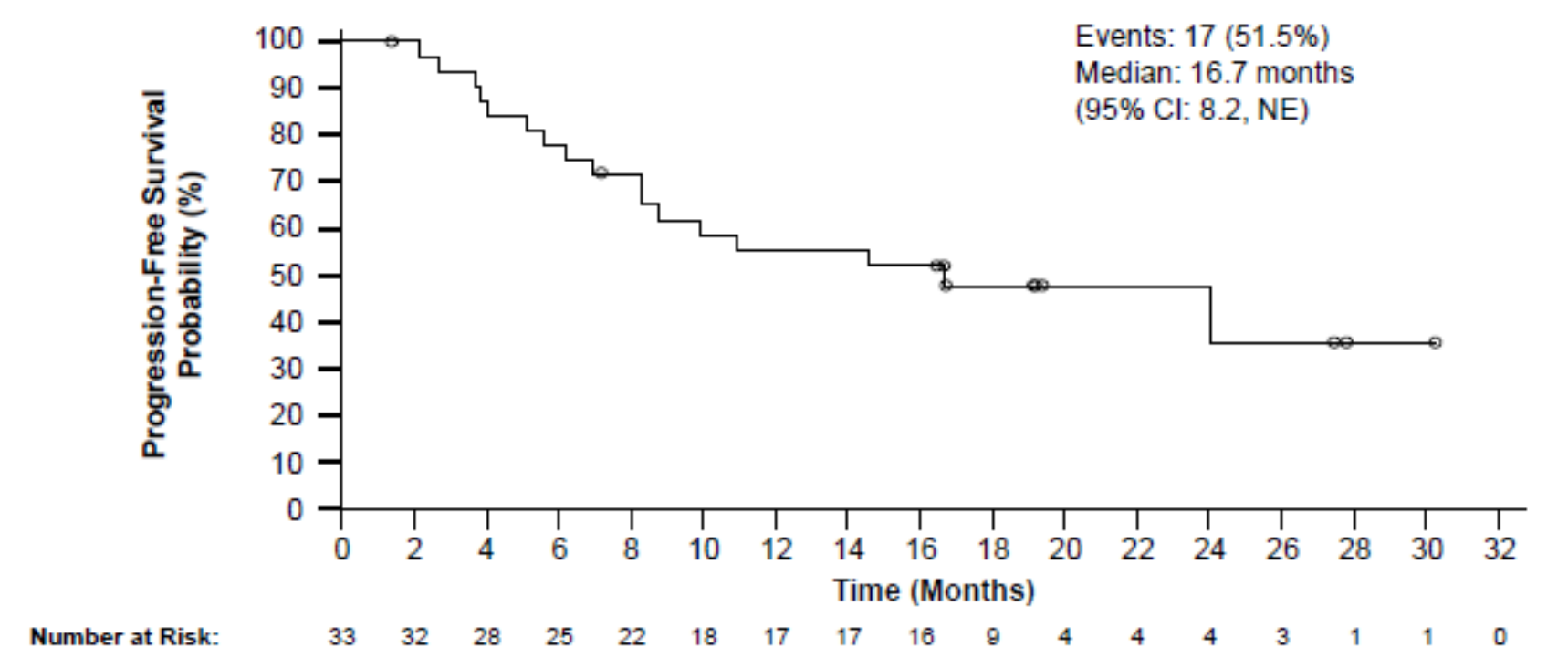
Treatment Duration and Response



Duration of Response



Progression-Free Survival

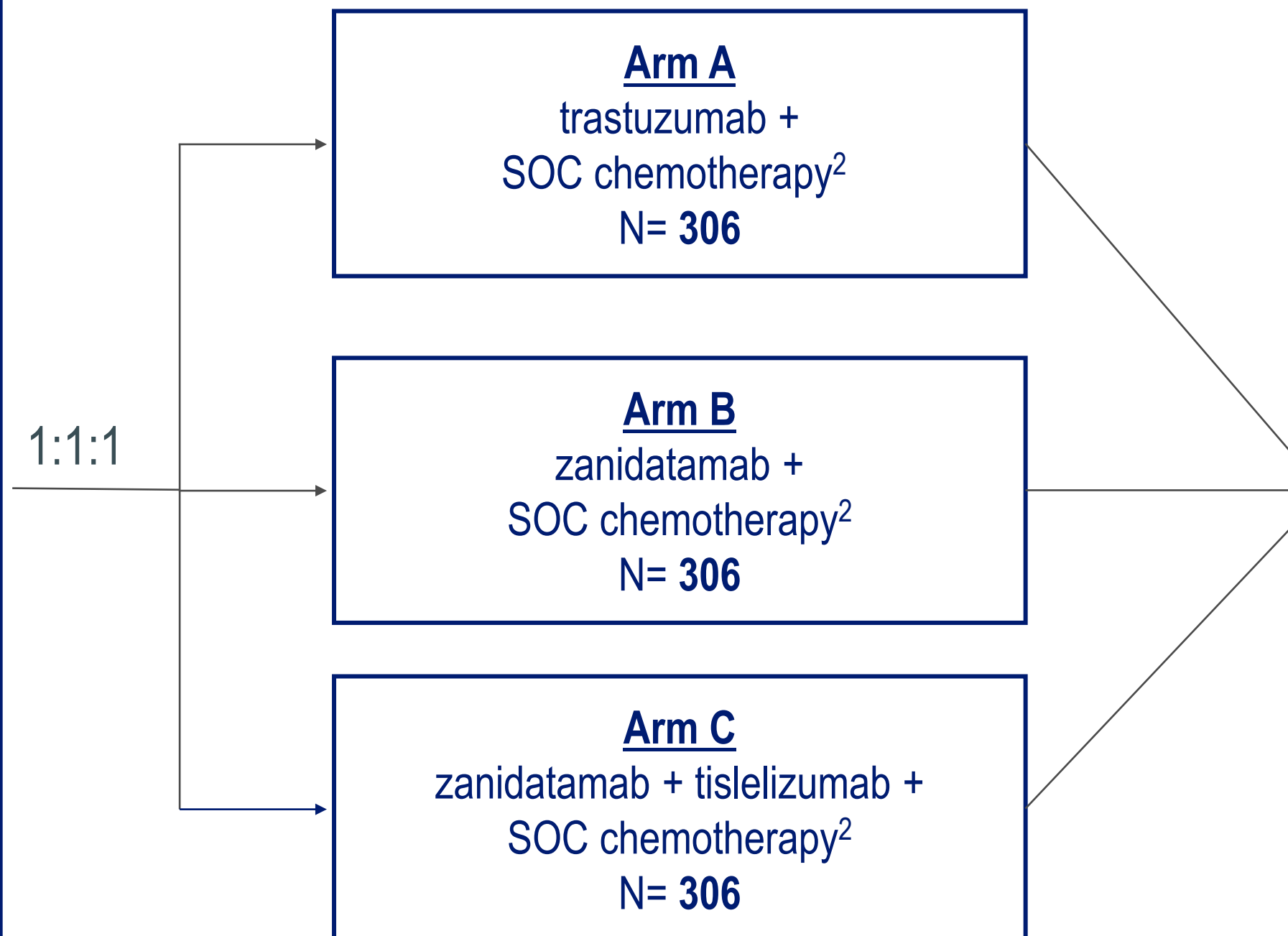


CI = confidence interval; CR = complete response; (F)ish = (fluorescence) in-situ hybridization; HER2 = Human epidermal growth factor receptor 2; IHC = immunohistochemistry; NA = not applicable; NE/NA = not evaluable / not assessed; PD = progressive disease; PD-L1 = programmed death-ligand 1. Note: Zanidatamab + tislelizumab + chemotherapy study done in collaboration with partner BeiGene. Lee et. al., ESMO 2023.

HERIZON-GEA-01: Randomized Phase 3 Study of Zanidatamab + Chemotherapy \pm I/O vs Trastuzumab + Chemotherapy in 1L Metastatic GEA

Study Design

- Unresectable locally advanced or metastatic gastroesophageal adenocarcinoma (stomach, GEJ, esophagus)
- HER2 status:
 - IHC3+ or ICH2+/ISH+¹
 - Any PD-L1 status
- No prior therapy for advanced disease
- Open-label with disease assessments per Blinded Independent Central Review (BICR)
- 1:1:1 randomization (total N = 918)
- Investigator choice of chemotherapy
- Stratification by region, HER2 status, and ECOG performance status



Primary Endpoint:

- PFS
- OS

Secondary / Exploratory Endpoints:

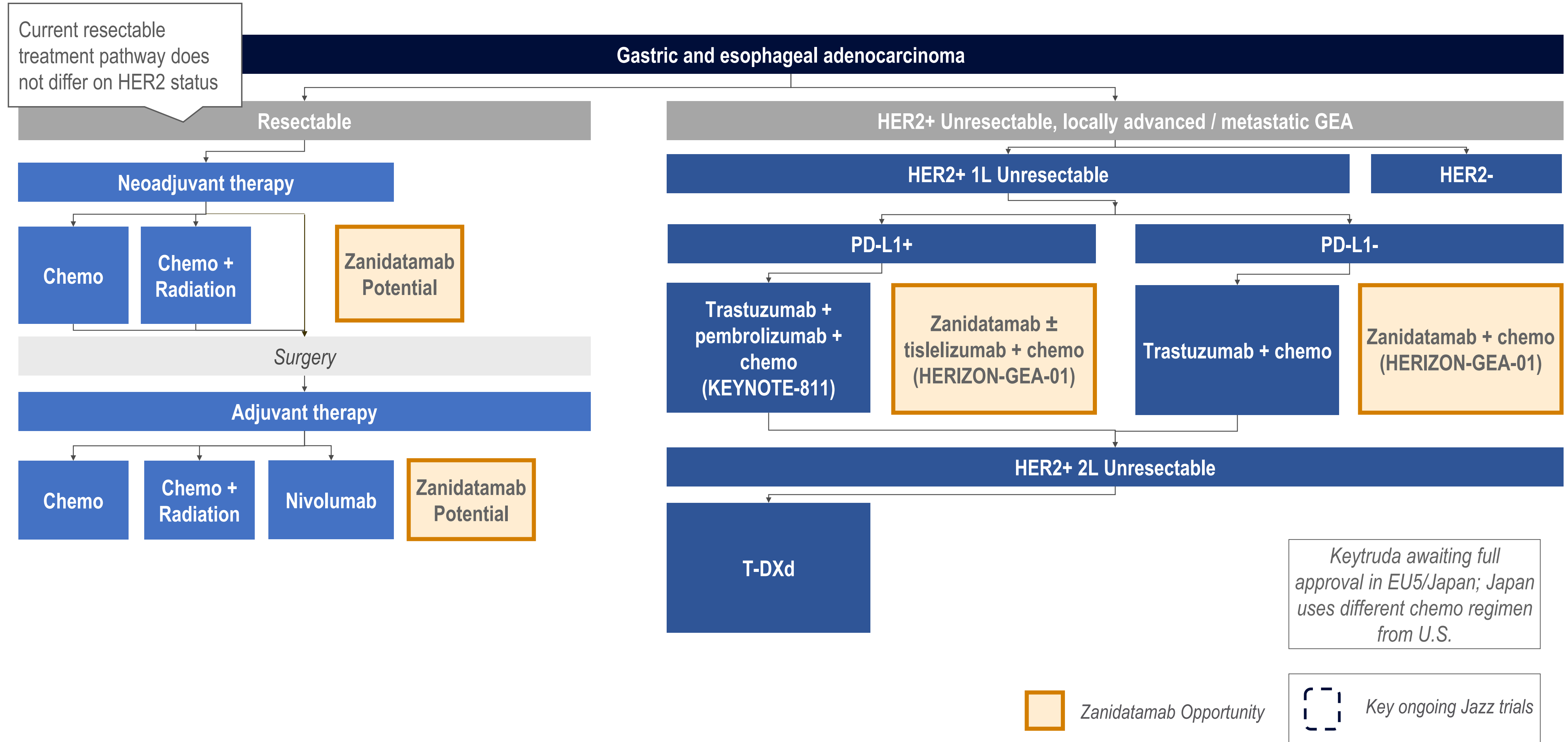
- ORR
- DOR
- Safety
- HRQoL

Rob Iannone, M.D., M.S.C.E.

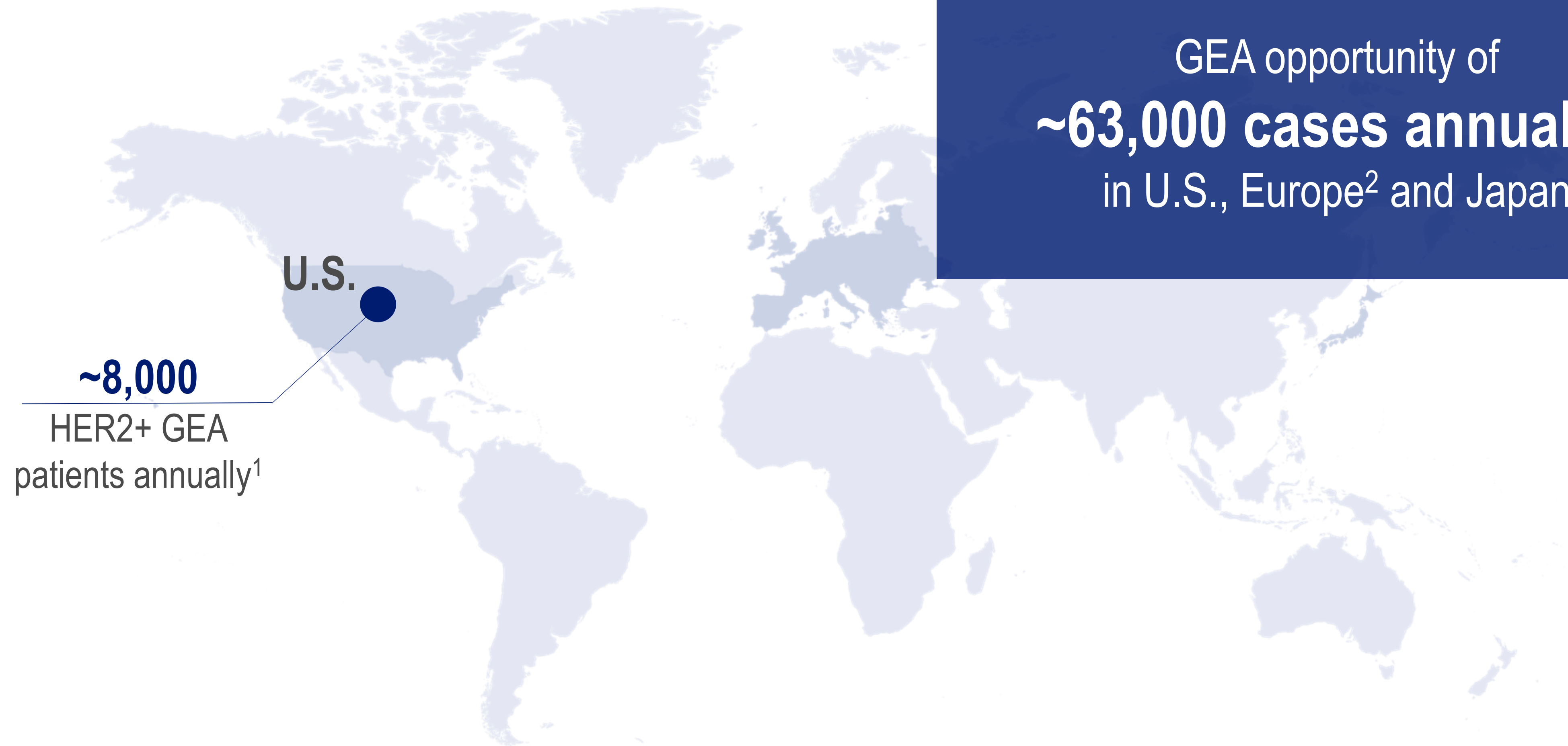
**Executive Vice President,
Global Head of Research & Development**



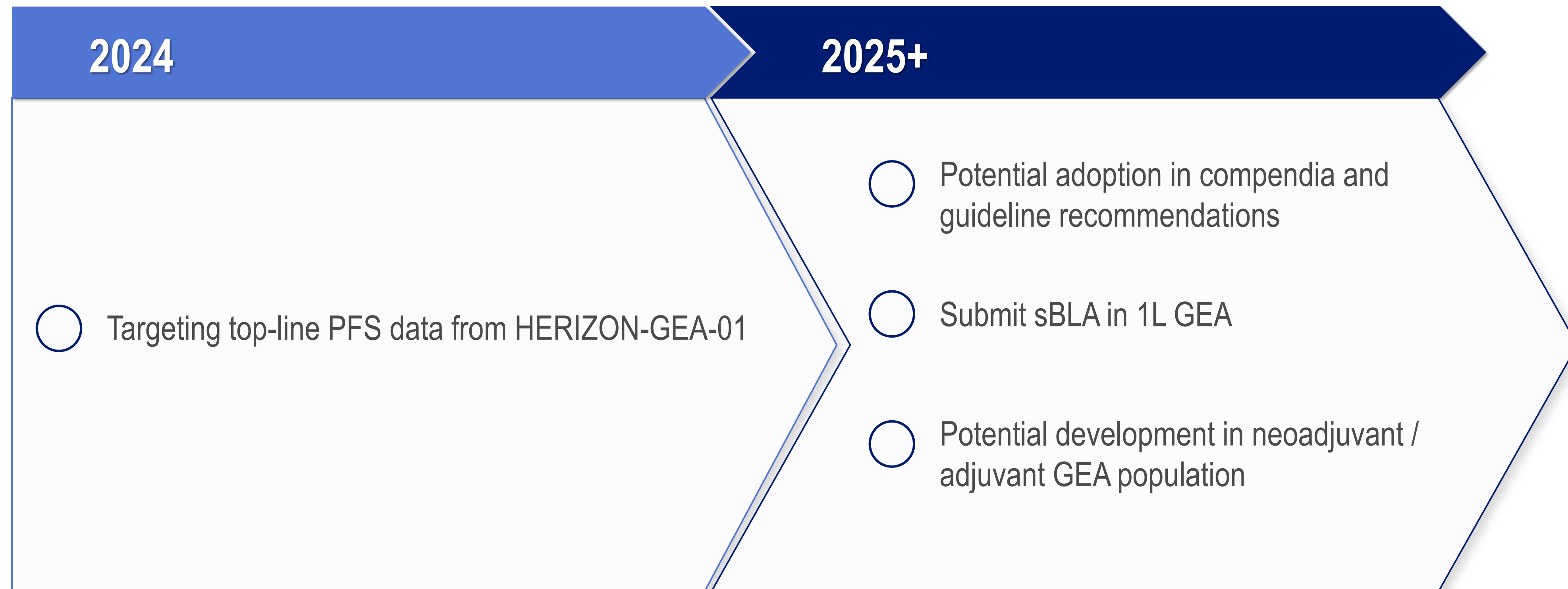
GEA Treatment Paradigm Highlights Unmet Need



GEA Represents a Significant Unmet Need



Zanidatamab Development Timeline in GEA



Zanidatamab in Breast Cancer

Significant Potential in Early- to Late-Line Breast Cancer

Zanidatamab Opportunity in Early- and Late-Stage Breast Cancer

Expect to initiate Phase 3 breast cancer trial in patients who have progressed on T-DXd in 2H24

	Advanced Breast Cancer		Early Breast Cancer
	Zanidatamab + Physician's Choice Chemotherapy	Zanidatamab + CDK4/6i + fulvestrant	Neoadjuvant Therapy
Scientific Rationale	Preclinical data: Additive antitumor effects when zanidatamab combined with wide range of chemo agents	CyclinD1-CDK4 pathway interacts with HER2 and ER pathways, mediating resistance to HER2 therapy	Opportunity to improve pCR rate and reduce toxicity of post-surgery therapy in the curative setting Zanidatamab: Favorable safety profile as monotherapy and in combination
Clinical Rationale	<p><u>ZW25-101 trial: zanidatamab + chemo¹</u></p> <ul style="list-style-type: none"> • HER2+ metastatic BC • Median of 2 prior regimens (n = 24) • Included patients refractory to trastuzumab + pertuzumab, T-DXd, other <ul style="list-style-type: none"> • cORR: 36.4% • mPFS: 7.3 months • Activity of other anti-HER2 agents not defined after progression on T-DXd 	<p><u>ZW25-202 Trial: zanidatamab + CDK4/6i + fulvestrant²</u></p> <ul style="list-style-type: none"> • Late-stage metastatic population • cORR: 35% • mDOR: 15 months • mPFS: 12 months • Chemo-free regimen; manageable toxicity profile address HER2 and ER biology 	<p><u>POC trial: node neg, early-stage HER2+ BC³</u></p> <ul style="list-style-type: none"> • Zanidatamab neoadjuvant therapy prior to surgery • Significant efficacy: 30% pCR rate



Zanidatamab in Advanced mBC

Potential to Address Unmet Need After Progression on T-DXd

Sara Hurvitz, M.D., FACP

Head, Division of Hematology and Oncology

SVP, Clinical Research Division

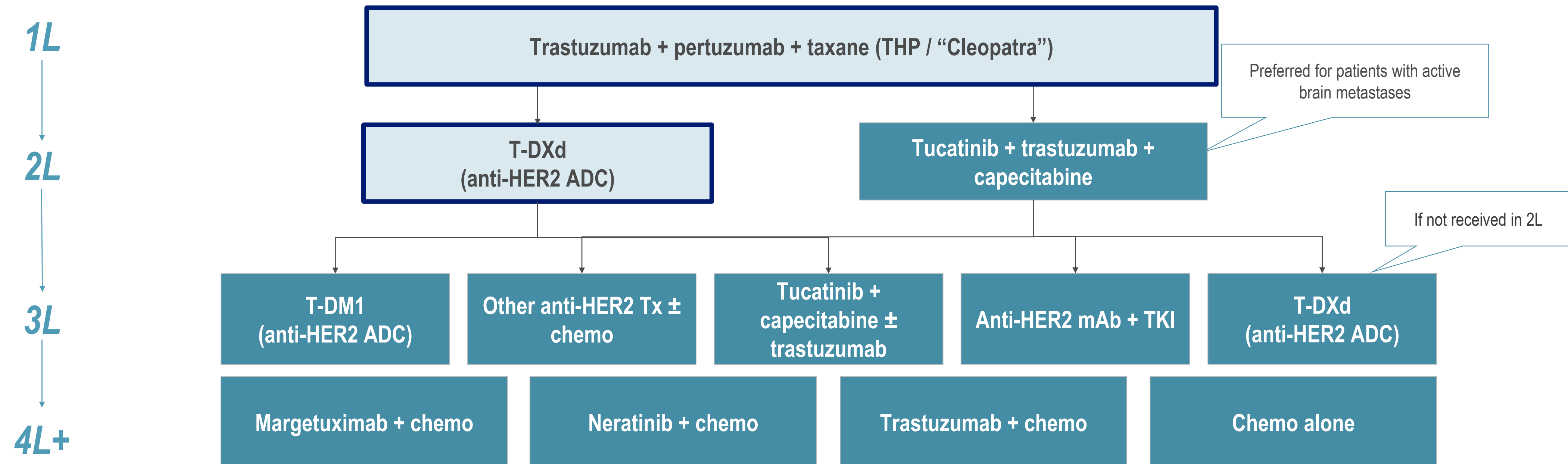
Department of Medicine, UW Medicine |

Fred Hutchinson Cancer Center



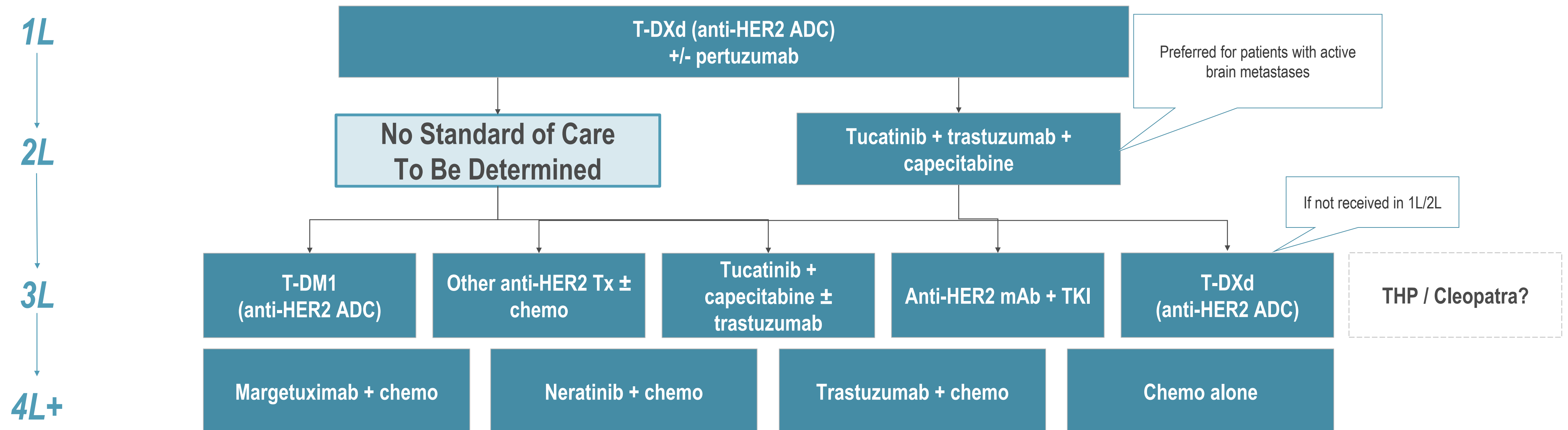
Current HER2+ Advanced Breast Cancer Treatment Paradigm

Cleopatra regimen and T-DXd currently favored in current HER2+ advanced treatment paradigm



Activity of Other Anti-HER2 Agents not Defined After Progression on T-DXd

- If T-DXd becomes 1L SoC as expected, 2L treatment will be undefined as currently having no approved HER2-targeted options to have demonstrated efficacy in this setting
- There will be a need for an **effective post T-DXd therapy in 2L** advanced BC



Zanidatamab is Active in HER2+ mBC Patients Across Multiple Lines of Treatment Regardless of HR Status or Combination Therapy

		1L mBC	3L+ mBC	
		BGB-A317-ZW25-101 (BC Cohorts 1a & 1b) ¹	ZW25-101 (Part 3) ²	ZW25-202 ³
HER2 and HR status		HER2+, HR+/-	HER2+, HR+/-	HER2+, HR+
Regimen		zanidatamab + docetaxel	zanidatamab + select chemotherapies ⁴	zanidatamab + palbociclib + fulvestrant
N (HER2+)		37 (33 evaluable)	24 (22 evaluable)	51 (32 ccHER2+)
cORR	n (%)	19 (90.9)	8 (36.4)	16 (35)
	(95% CI)	(75.7, 98.1)	(13.9, 54.9)	(21, 50)
DOR, months	Median	NE	NA	15
	(95% CI)	(12.1, NE)	(1.6, 22.1+)	(12, 25)
PFS, months	Median	NA	7.3	12
	(95% CI)	NA	(3.6, NE)	NA

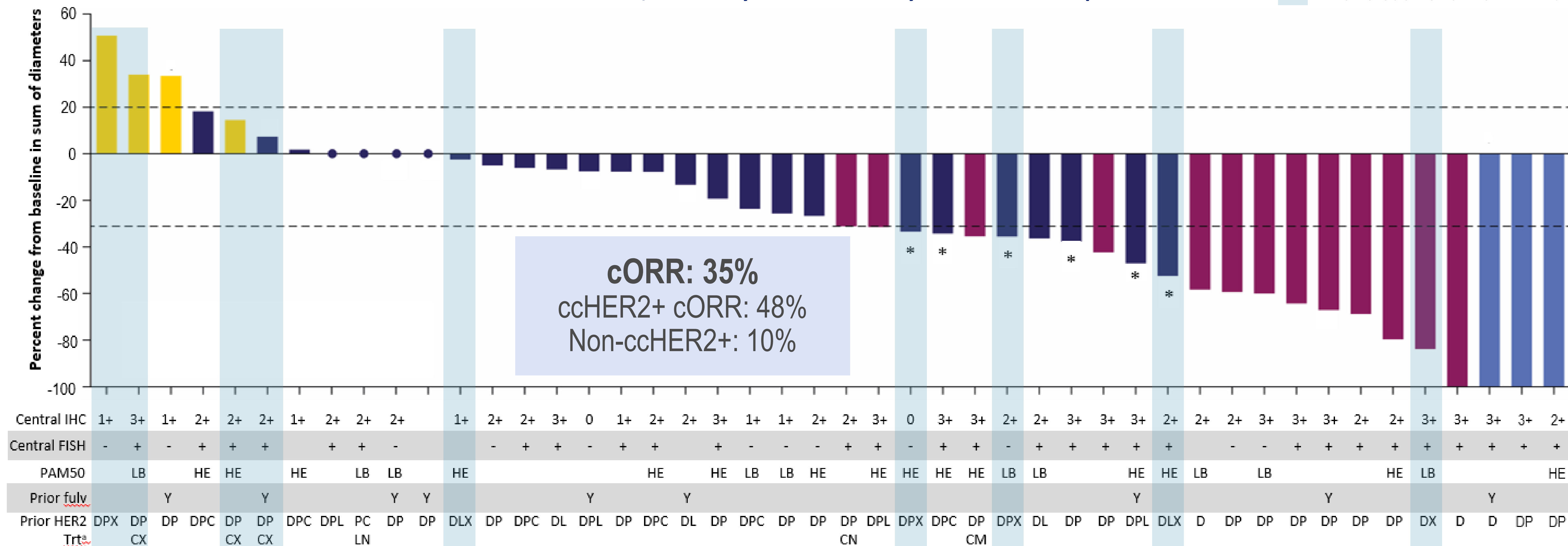
Zanidatamab Plus Chemo is Active in Heavily Pre-treated HER2+ mBC Patients Compared to Other Regimens

	ZW25-101 ¹	Sophia Study ²	
Regimen	Zanidatamab + chemotherapy	trastuzumab + chemotherapy	margetuximab + chemotherapy
N	24 (22 evaluable)	270	266
ORR	36.4% (CI 13.9 – 54.9)	14%	25%
mDOR	NE (1.6 - 22.1+)	7.0 months	6.9 months
mPFS	7.3 months (95% CI: 3.6-NE)	4.4 months (95% CI: 4.1-5.5)	5.7 months (95% CI: 5.2-7.0)

Phase 2 Data Demonstrates Activity in Patients Previously Treated with HER2-Targeted Therapies, Including T-DXd

Zanidatamab + Fulvestrant + CDK4/6i Efficacy of Treatment by Best Overall Response

Prior treatment with T-DXd



Prior HER2 Treatment: C = tucatinib; D = T-DM1; L = Lapatinib; M = margetuximab; N = neratinib; X = T-DXd; PAM50 subtype: HE = HER2-enriched; LB = Luminal B

Best Overall Response
cCR cPR SD PD

Note: Best overall response includes patients with measurable disease. ^aAll patients received prior trastuzumab and taxane. ^{*}Indicates patients with unconfirmed partial responses. Dotted lines indicate -30% and +20% change in tumor size. Source: Escrivá-de-Romani S et al, SABCS 2023. T-DXd = trastuzumab deruxatecan, or Enhertu®.

Treatment After Progression on T-DXd is an Uncharted Space of Unmet Need

1

Opportunity: Patients want a better treatment option that is effective and maintains quality of life

Zanidatamab: MOA, clinical efficacy, and safety profile are advantageous for use after progression on T-DXd

2

Opportunity: Physicians are looking for an answer to the sequencing dilemma and therapies indicated after progression on T-DXd

Zanidatamab: Goal of generating robust zanidatamab data to fill gaps in sequencing gap after progression T-DXd

3

Opportunity: Zanidatamab has potential to be the 1st HER2-targeted therapy to demonstrate efficacy and safety after progression on T-DXd

Zanidatamab: Plan to launch Phase 3 study in patients who have progressed on T-DXd

Randomized Phase 3 Study of Zanidatamab + Chemotherapy in Post T-DXd Patients with HER2+ Advanced BC



EMPOWHER
BC-303

Inclusion Criteria:

- Patients with HER2+ BC whose disease has progressed on previous T-DXd treatment
- No more than 4 prior lines of HER2-directed therapies in metastatic setting
- Based on the patient eligibility, institutional and local guidelines, and physician's choice, all approved treatments are allowed as post T-DXd therapy, including pertuzumab, tucatinib-containing regimen, and T-DM1 prior to enrollment in the trial
- Patients with history of treated-CNS metastasis who are clinically stable are eligible
- At least 1 measurable lesion per RECIST version 1.1
- ECOG PS 0 or 1

R 1:1
N=550

zanidatamab +
physician's choice
chemotherapy

trastuzumab +
physician's choice
chemotherapy

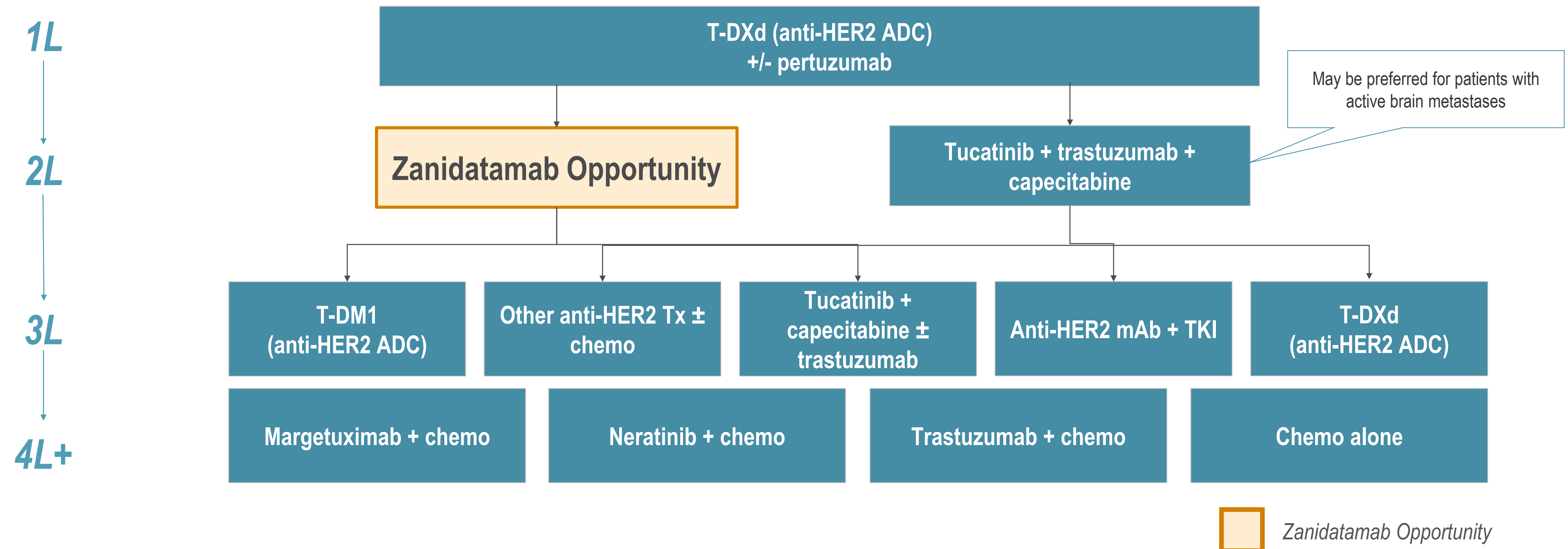
Primary Endpoint:

- PFS

Secondary / Exploratory Endpoints:

- OS
- ORR
- Safety

Potential HER2+ Advanced BC Treatment Paradigm: Post T-DXd Uncharted Space of Unmet Need



Sources: UpToDate, NCCN Guidelines 2023.1/2/3/4L = First/second/third/fourth line; ADC = antibody drug conjugate; \HER2 = human epidermal growth factor receptor 2; T-DM1 = trastuzumab emtansine, Kadcyra®; T-DXd = trastuzumab deruxatecan, or Enhertu®; TKI: tyrosine kinase inhibitor.

Zanidatamab in HER2+/HR+ Advanced BC

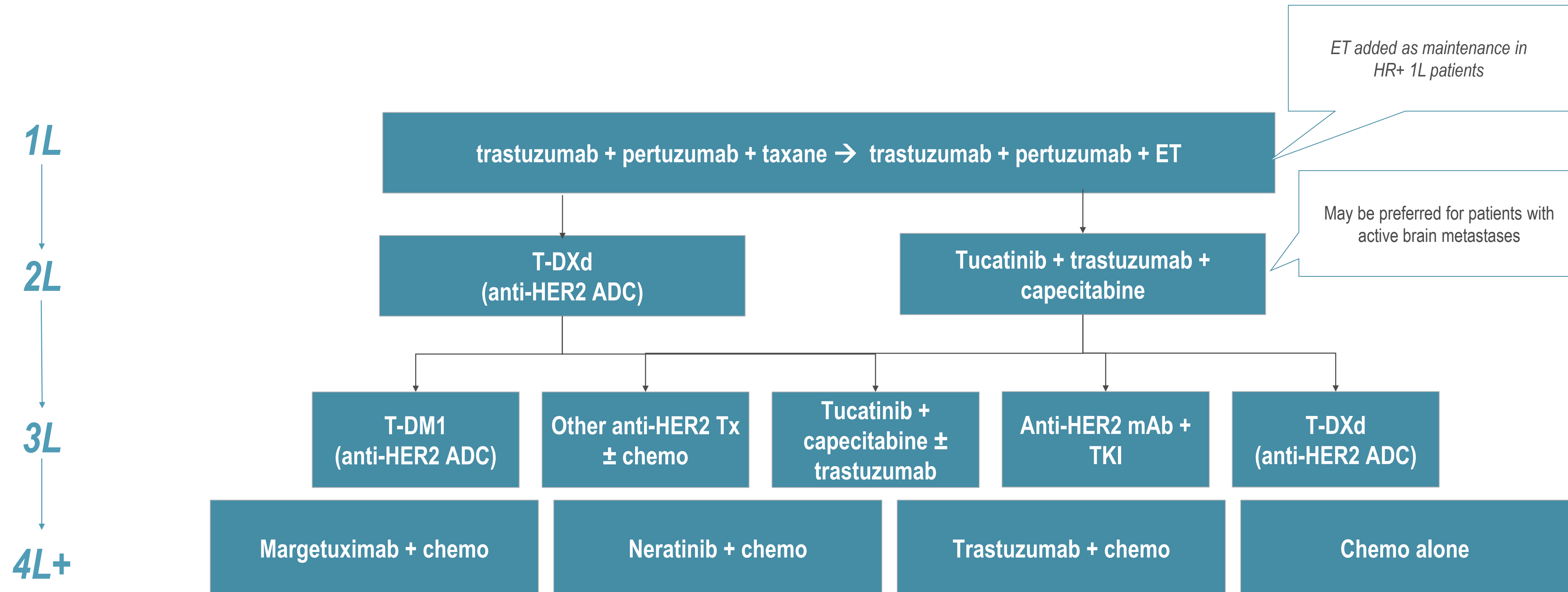
Potential Chemo-Free Option for HER2+/HR+ Patients

Santiago Escrivá-de-Romaní, M.D.

**Medical Oncologist, Breast Cancer Unit
Vall d'Hebron Institute of Oncology**



HER2+/HR+ Late-Stage Breast Cancer Treatment Paradigm

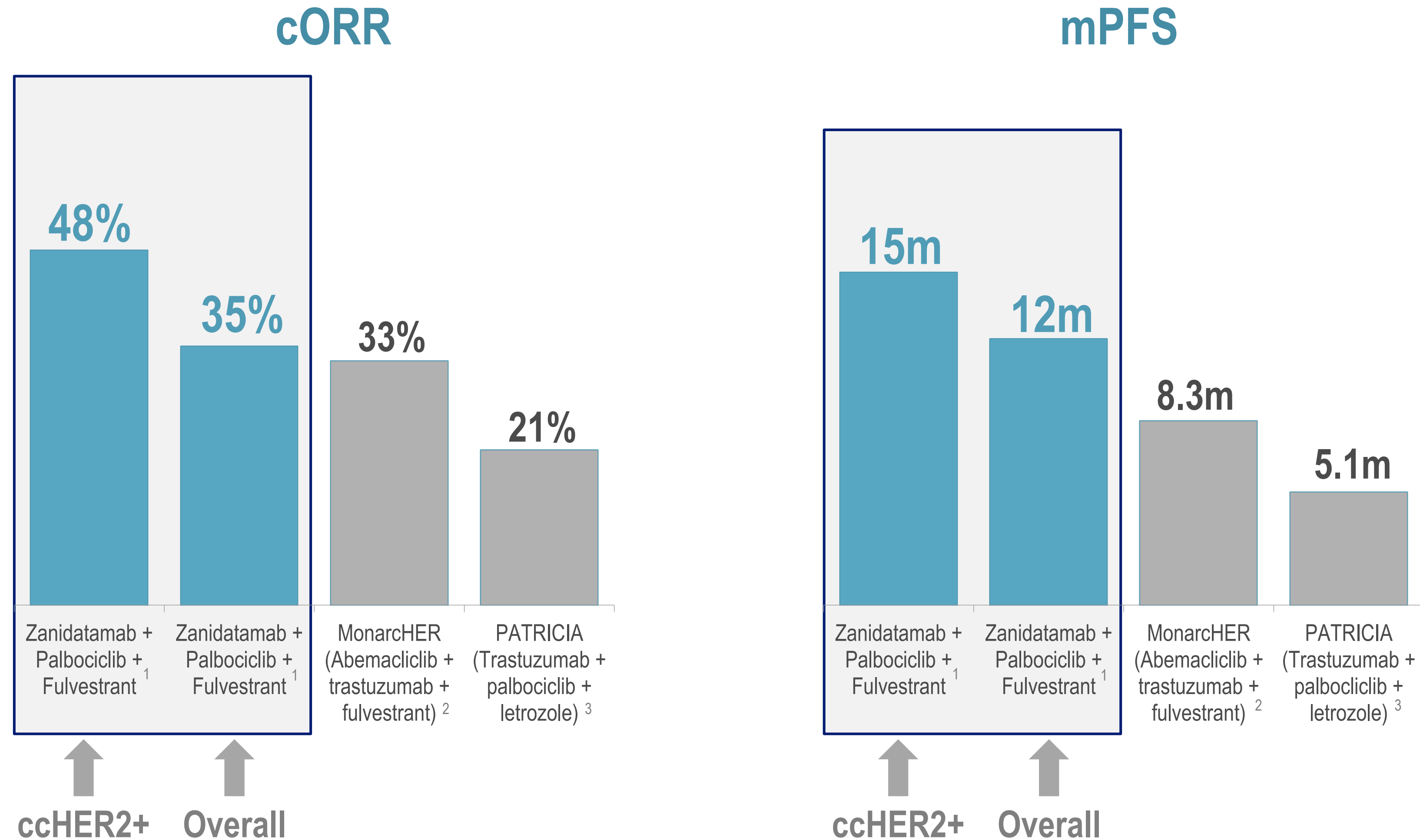


- Current treatment paradigm does not take full advantage of HR status and potential synergy between blocking HR and HER2 pathways
- Unmet need will remain following completion of PATINA* trial (1L maintenance) regardless of outcome

Note: standard approach is to treat HR+ patients with HER2+ treatment paradigm with possible addition of ET to anti-HER2 regimens

*PATINA trial evaluating efficacy and safety of the addition of Palbociclib to anti-HER2 treatment and ET maintenance after induction treatment in 1L HR+/HER2+ mBC; Sources: UpToDate, NCCN Guidelines 2023. 1/2/3/4L = First/second/third/fourth line; ADC = antibody drug conjugate; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; ET: endocrine therapy (only used for hormone receptor positive breast cancer); T-DM1 = trastuzumab emtansine, Kadcyla®; T-DXd = trastuzumab deruxatecan, or Enhertu®; TKI: tyrosine kinase inhibitor.

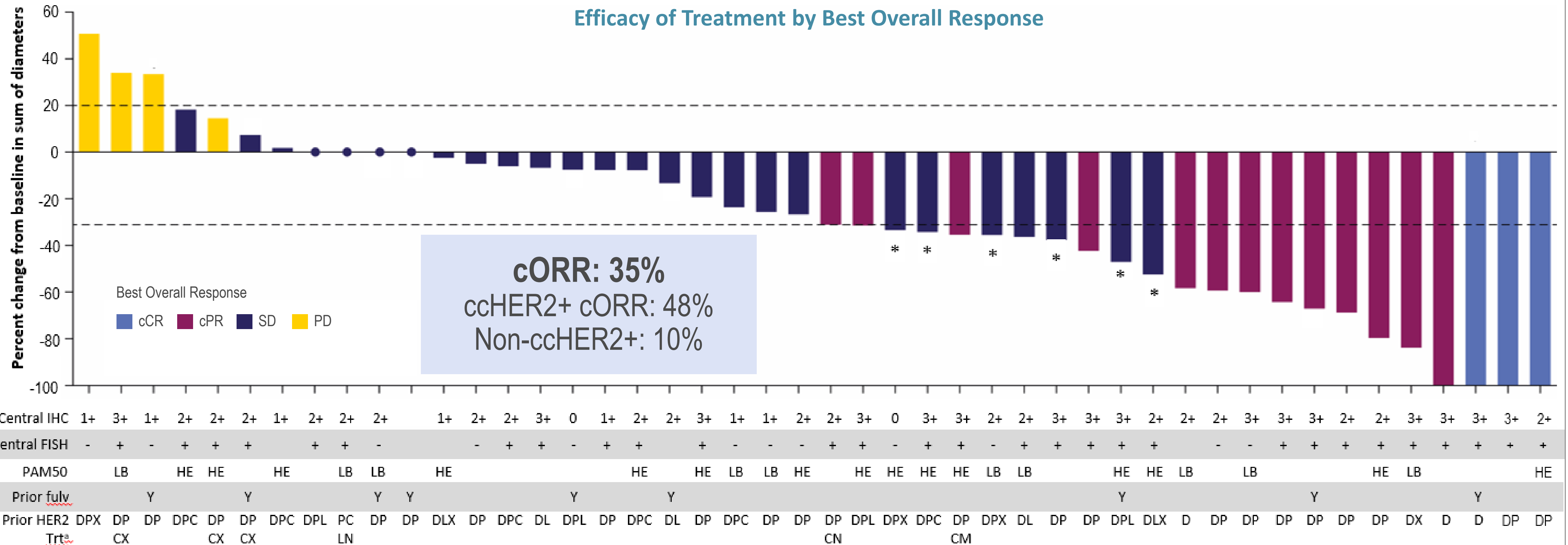
HER2+/HR+ Advanced BC: Observed Clinical Activity and Benchmarks: Phase 2 Data from Zanidatamab + Fulvestrant + CDK4/6i



BC = breast cancer; ccHER2+ = centrally confirmed HER2+; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor. ¹Escriva-de-Romani S et al. SABCS 2023; ²Tolaney SM et al. Lancet Oncol 2020; ³Ciruelos E et al. CCR 2020; * Note: Trial ongoing. Median (range) follow-up time: 16 (2-32) months.

Phase 2 Data from Zanidatamab + Fulvestrant + CDK4/6i Demonstrates Promising Antitumor Activity in Heavily Pretreated Patients Including Patients Receiving Prior T-DXd

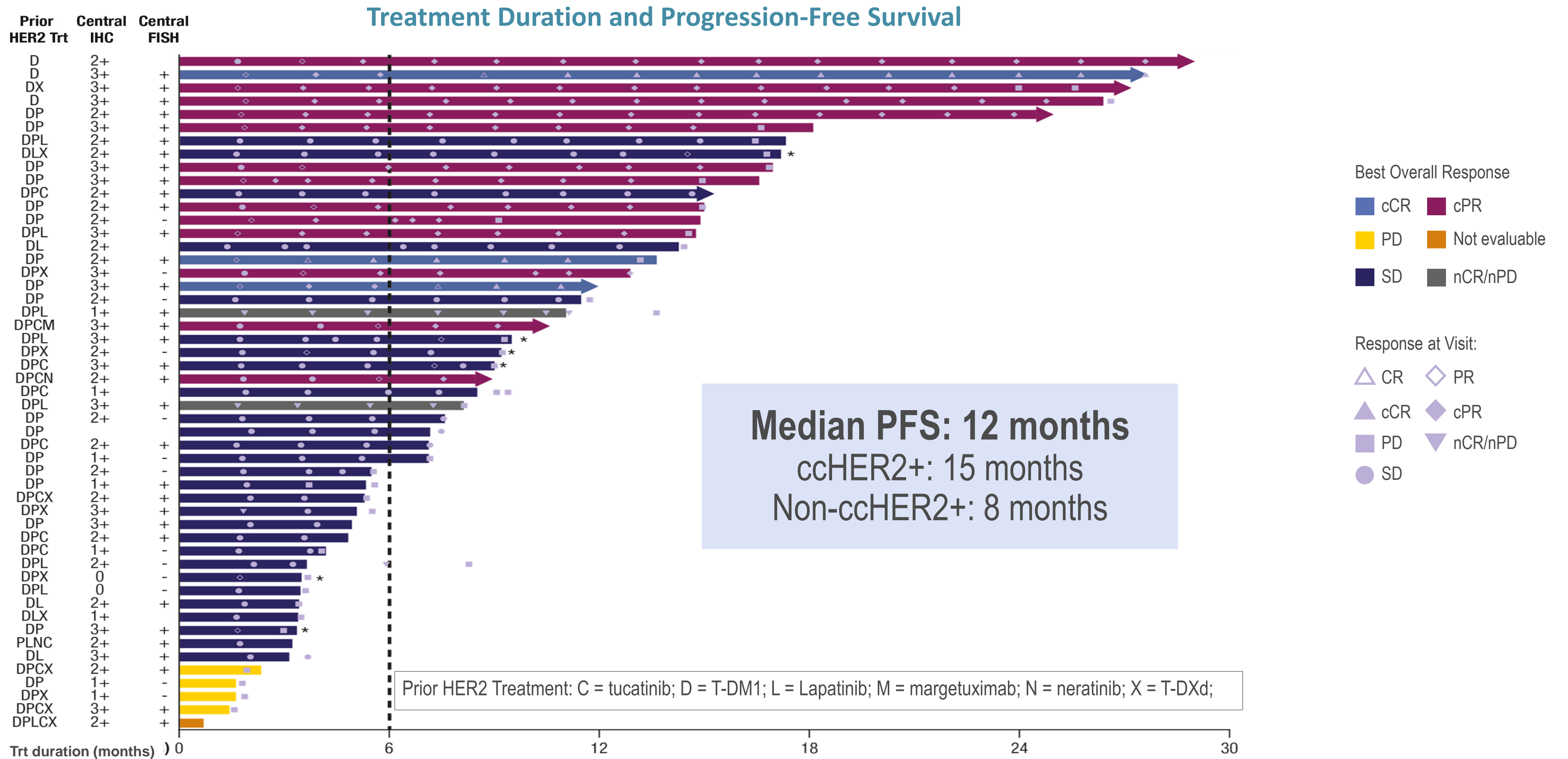
Efficacy of Treatment by Best Overall Response



Prior HER2 Treatment: C = tucatinib; D = T-DM1; L = Lapatinib; M = margetuximab; N = neratinib; X = T-DXd; PAM50 subtype: HE = HER2-enriched; LB = Luminal B

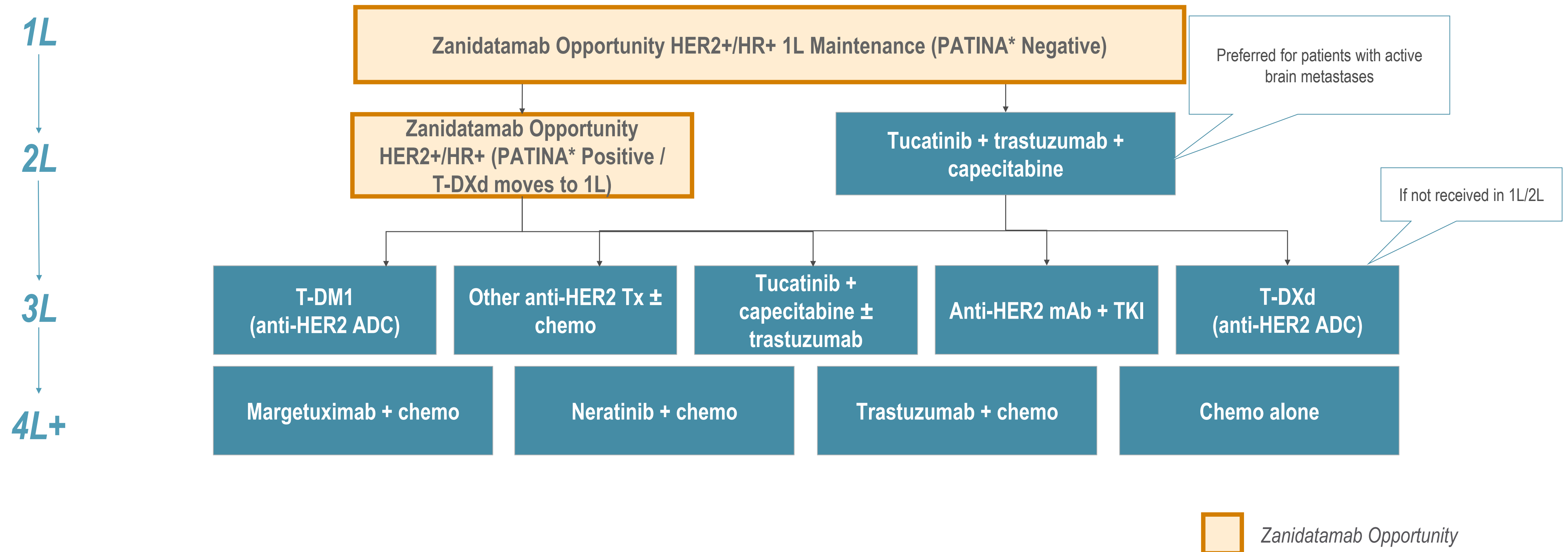
*Indicates patients with unconfirmed partial responses. Dotted lines indicate -30% and +20% change in tumor size.
^aAll patients received prior trastuzumab and taxane.

Phase 2 Data from Zanidatamab + Fulvestrant + CDK4/6i Demonstrates Promising Durability and Progression-Free Survival



*Indicates patients with unconfirmed partial responses. Dotted line indicates 6 months. Source: Escrivá-de-Romani S et al, SABCS 2023. ccHER2 = centrally confirmed HER2; cCR = confirmed complete response; cPR = confirmed partial response; HER2 = human epidermal growth factor receptor 2; PD = progressive disease; PFS = progression-free survival; SD = stable disease; nCR/nPD = near complete response / near progressive disease.

Potential HER2+/HR+ Late-Stage Breast Cancer Treatment Paradigm



*PATINA trial evaluating efficacy and safety of the addition of Palbociclib to anti-HER2 treatment and ET maintenance after induction treatment in 1L HR+/HER2+ mBC; Sources: UpToDate, NCCN Guidelines 2023. 1/2/3/4L = First/second/third/fourth line; ADC = antibody drug conjugate; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; ET: endocrine therapy (only used for hormone receptor positive breast cancer); T-DM1 = trastuzumab emtansine, Kadcyla®; T-DXd = trastuzumab deruxatecan, or Enhertu®; TKI: tyrosine kinase inhibitor.

Zanidatamab in Early-Stage Breast Cancer

Reducing Toxicity in a Curative Setting

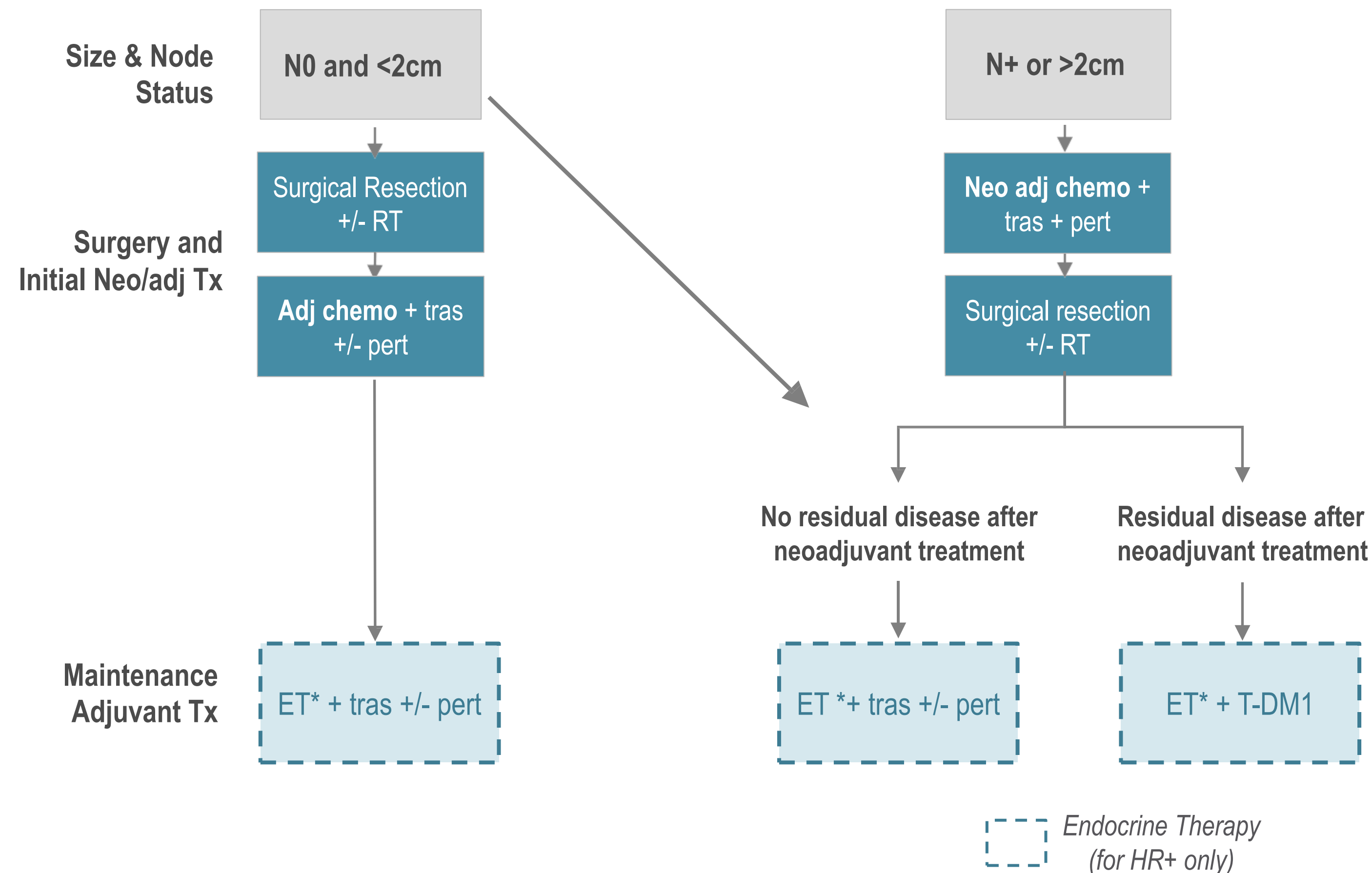
Paula Pohlmann, M.D.

Department of Breast Medical Oncology,
Division of Cancer Medicine,
University of Texas MD Anderson Cancer Center



Opportunity to Improve Outcomes and Reduce Toxicity of Systemic Therapy in the Curative Setting

HER2+ Early-Stage Treatment Paradigm



Potential long-term toxicity of cytotoxic agents:

- Heart failure
- Secondary malignancies
- Disabling peripheral neuropathy
- Cognitive dysfunction
- Premature menopause
- Sexual dysfunction
- Infertility
- Liver dysfunction

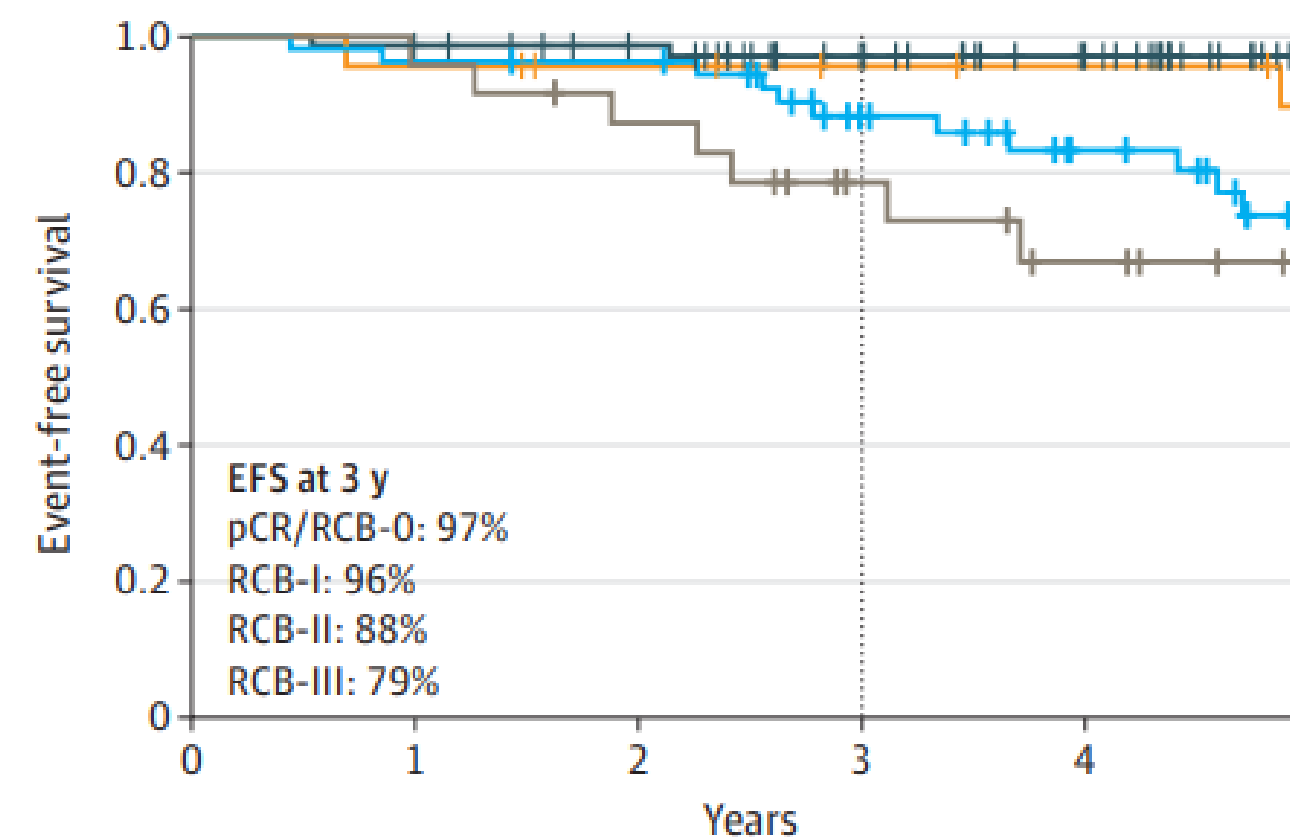
Neoadjuvant Setting Is Key to Learning and to Personalizing Treatment

- Permits timely efficacy read-out
- Allows tailoring of treatment
 - ✓ More for those who need it
 - ✓ Less for those who do not
- Facilitates improvement and investigation of 'success and failure'

Success Measurement

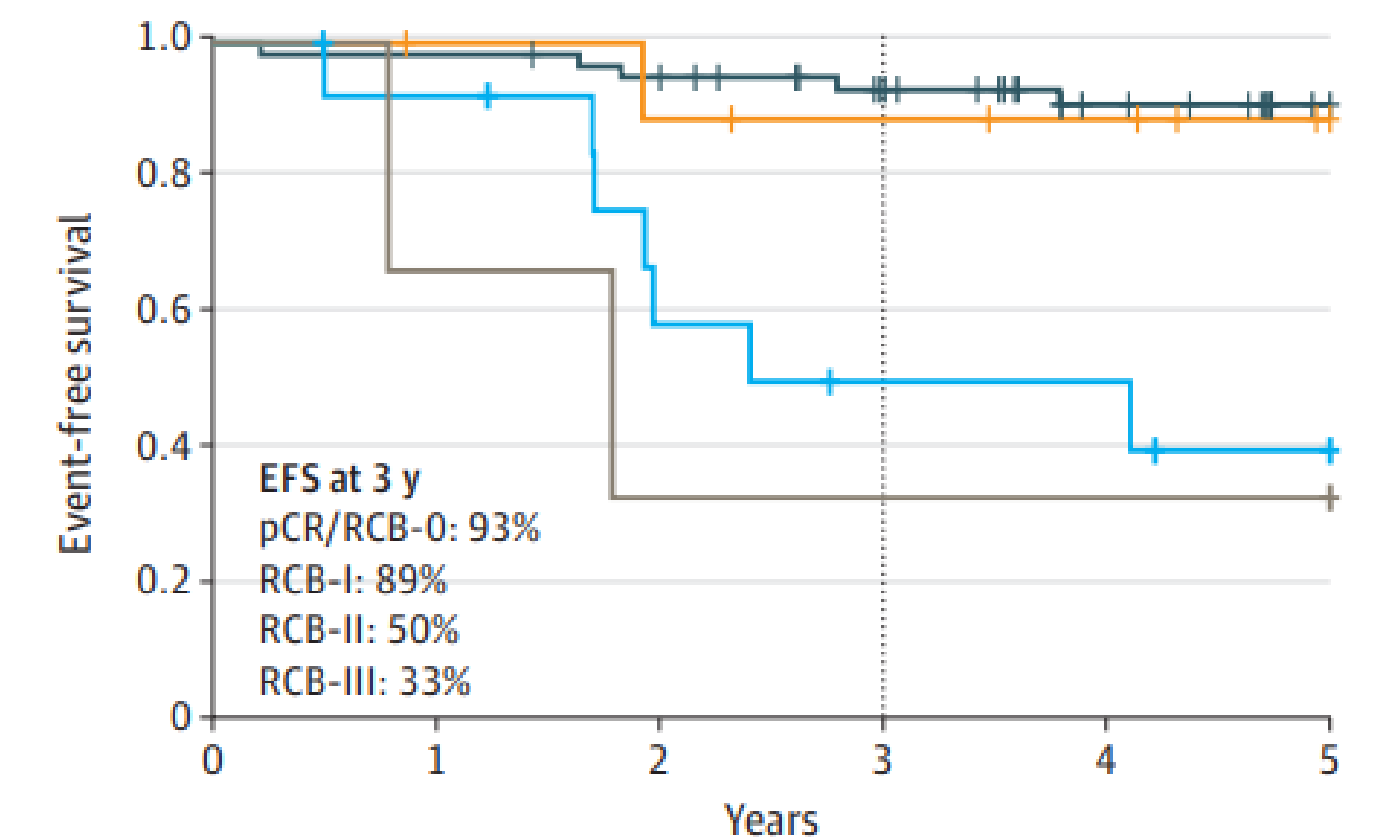
Residual Cancer Burden: Prognostic Value Beyond pCR

HR+ / HER2+



No. at risk	0	1	2	3	4	5
0	72	70	65	51	41	22
I	23	22	20	18	17	15
II	54	52	51	39	29	17
III	24	23	20	14	10	6

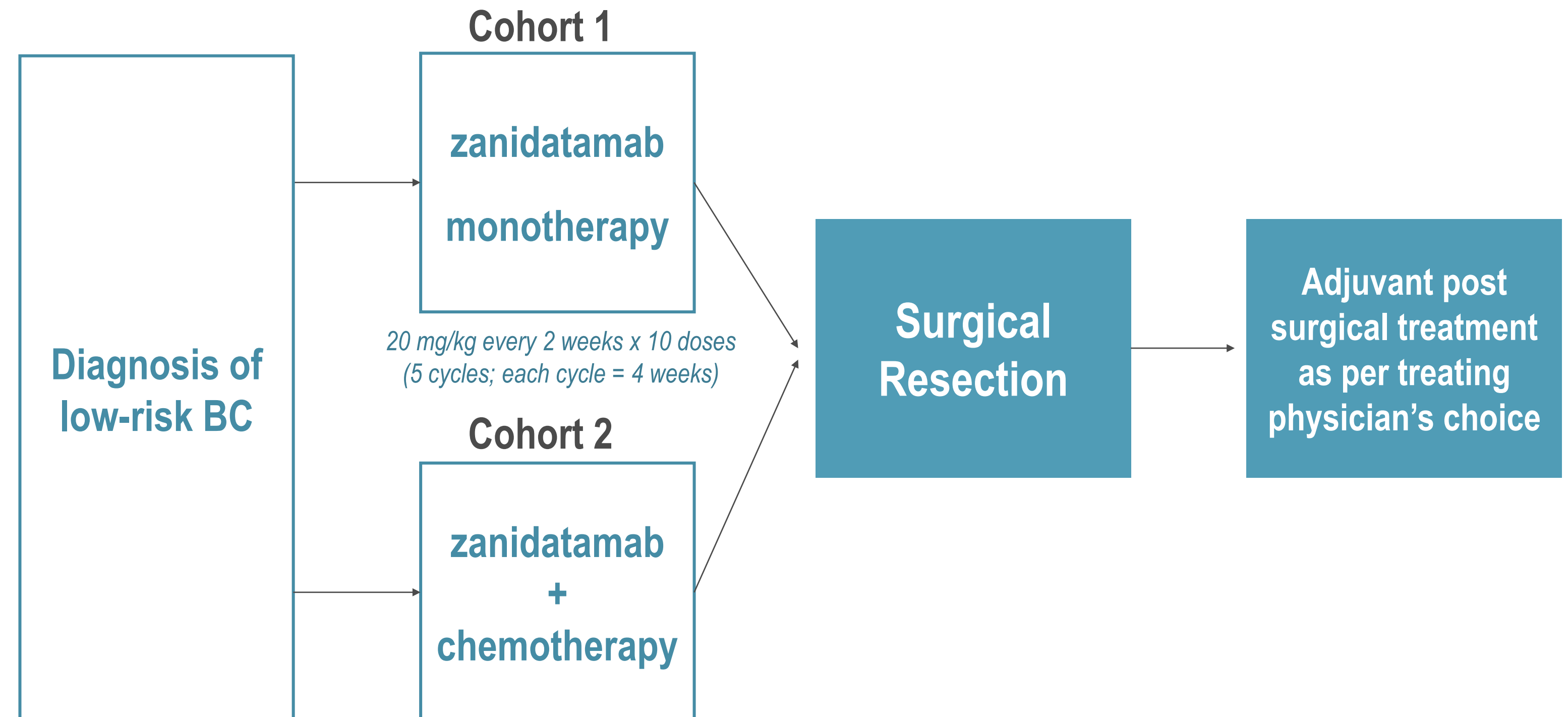
HR- / HER2+



No. at risk	0	1	2	3	4	5
0	61	60	57	49	38	28
I	10	9	8	7	6	3
II	14	12	7	5	5	3
III	3	2	1	1	1	1

MDACC Trial Design Overview

- Single-arm open label study of **zanidatamab** in N0 neoadjuvant setting
- Study Details:
 - N = 20 → 40
 - HER2+ breast cancer
 - Any HR status
 - Early Stage
 - Tumor size > 1 cm ≤ 3cm
 - Node negative



Zanidatamab Demonstrated Significant Efficacy in Early-Stage Breast Cancer

- Neoadjuvant zanidatamab for 3 cycles (6-10 doses) showed **significant efficacy** in patients with stage I node negative HER2+ BC
 - **50% pCR/RCB-1**
 - **30% pCR**
- Zanidatamab was well-tolerated with acceptable safety profile
 - **No Grade 3 or Grade 4 TRAEs**
- Trial ongoing

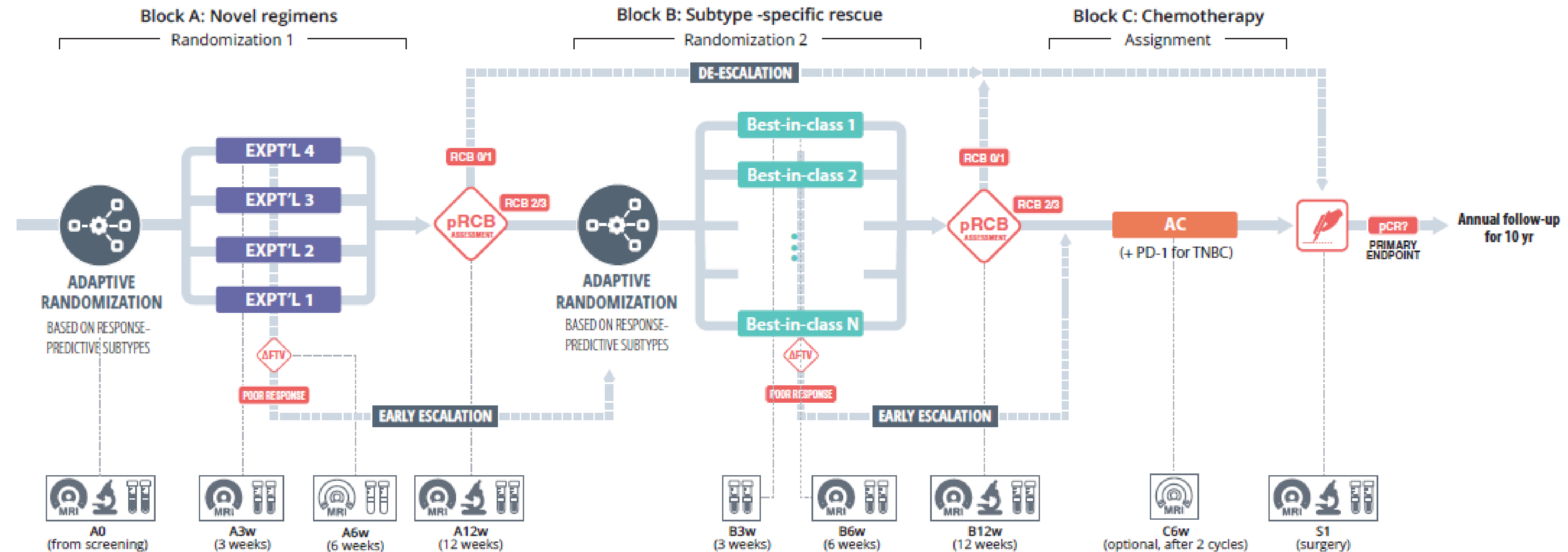
Pathologic Response and Residual Cancer Burden

	# Patients	%	
pCR/RCB-0	6	30	} RCB0/1
RCB-1	4	20	
RCB-2	9	45	
RCB-3	1	5	

Zanidatamab Selected for Inclusion in I-SPY 2 Studies

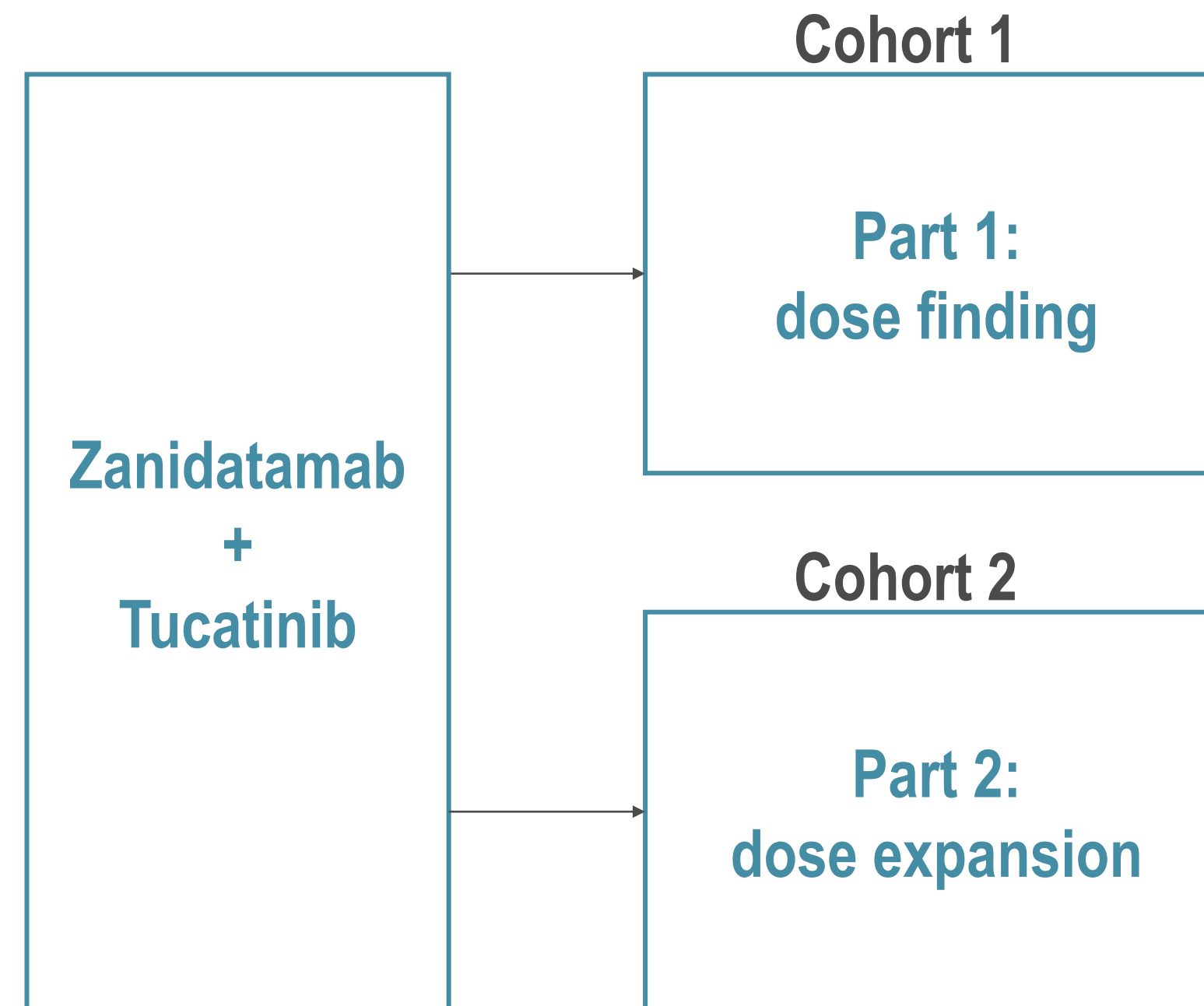
- Single agent **zanidatamab** in neoadjuvant setting (Block A)
- Planned enrollment N=100
- Will provide information on zanidatamab monotherapy in N0 and N+ patients
- I-SPY2 platform study utilizes an **adaptive trial design** and **early surrogate efficacy endpoints** (MRI functional tumor volume/FTV & pCR) allowing for efficient enrollment and **faster initial efficacy results**

I-SPY2.2 Trial Design



PRE-I-SPY 2 Study Design Evaluating Zanidatamab + Tucatinib

- PRE-ISPY/Phase 1b multisite platform to evaluate single agents or combinations in a metastatic setting to move promising drugs into the I-SPY 2 SMART Neoadjuvant Design Trial and/or other trials in a timely manner
- Studying **zanidatamab + tucatinib**
- Designed to generate proof-of-concept data for expansion in the companion I-SPY2 Trial in the neo-adjuvant setting
- N = 12 in Part 1 dose finding and N=12 in Part 2 dose expansion
- Implications for indications outside breast cancer (eg, CRC)



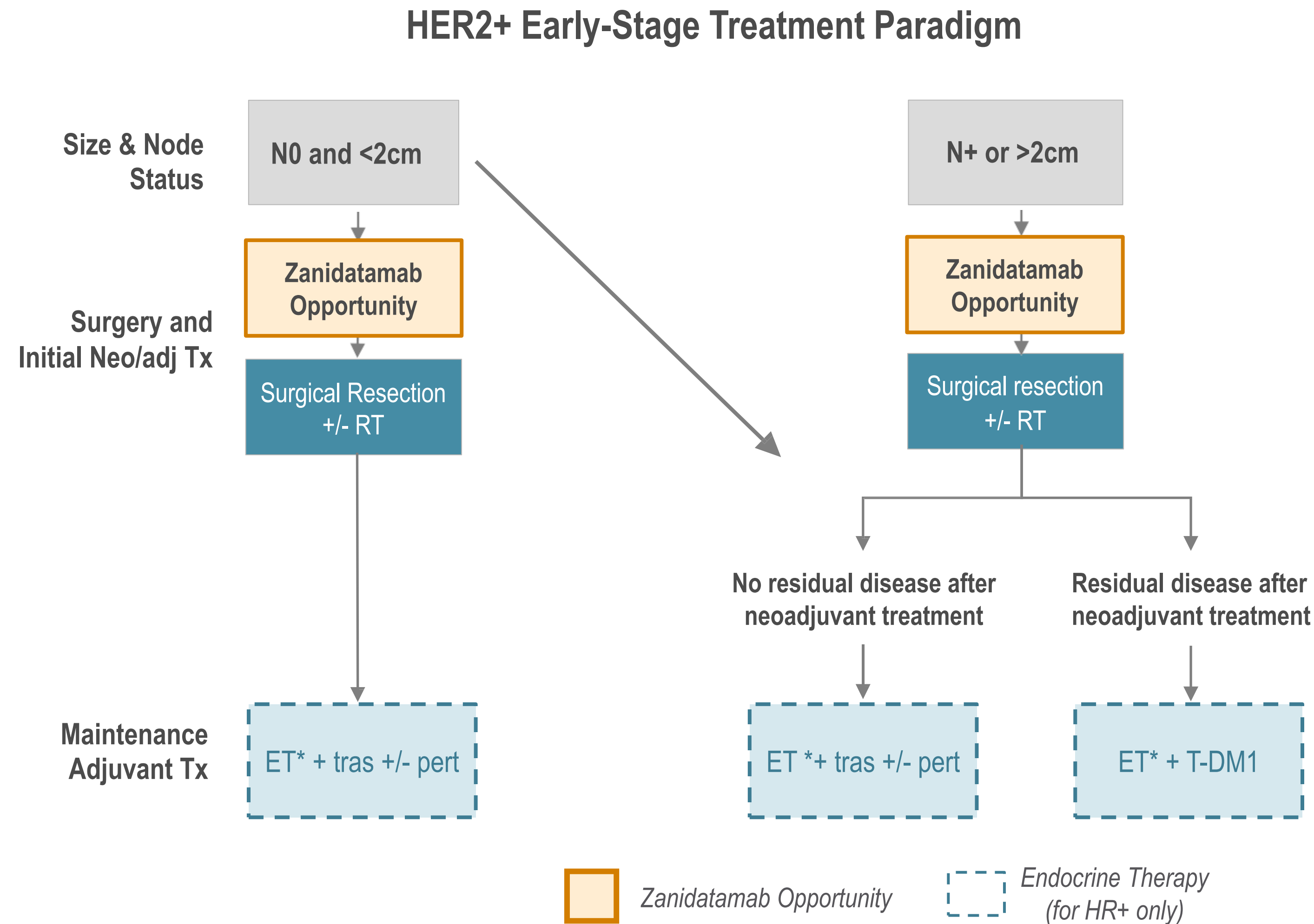
Primary Endpoint:

- Dose finding / RP2D
- Safety / tolerability
- Preliminary efficacy

Secondary / Exploratory Endpoints:

- Preliminary PFS, DOR, CBR
- PK
- Translational Biomarkers

Goal of Reducing Toxicity in a Curative Setting



Zanidatamab Development in Breast Cancer

Rob Iannone, M.D., M.S.C.E.

**Executive Vice President,
Global Head of Research & Development**

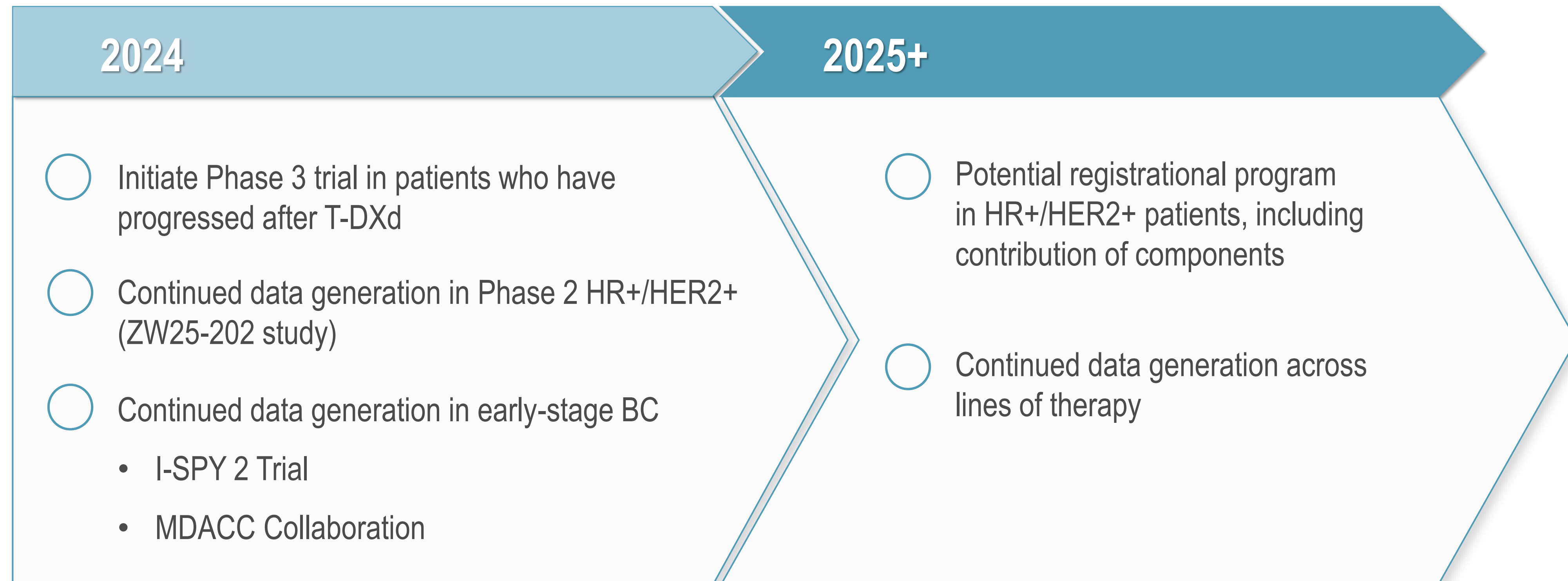


Building Patient Value in Early- and Late-Stage Breast Cancer

Program	Neoadjuvant Node-Negative	Neoadjuvant Node-Positive (I-SPY 2)	Late-Stage After Progression on T-DXd	Late-Stage Combination with CDK4/6i + Fulvestrant
Unmet Need	Goal of reducing toxicity in adjuvant setting	Patients and prescribers want to reduce chemotherapy use due to side effects, even for high-risk patients	No clinically validated treatment option for patients who progress or cannot tolerate T-DXd	In HER2+/HR+ BC, treatment is based on HER2 status with limited consideration of estrogen therapies
Strategy	ESTABLISH a new better-tolerated standard of care for low-risk patients in NeoAdj/Adj with zanidatamab monotherapy	IMPROVE pCR rates and reduce chemotherapy burden in adjuvant setting by replacing Herceptin and Perjeta and potential to de-escalate chemotherapy (chemo-free combinations)	ADDRESS high unmet need for patients who progress or cannot tolerate T-DXd in prior lines	SHIFT mindset from single HER2+ treatment focus in late-lines to Hormone Receptor (HR+) status plus HER2+ with a chemo free option



Zanidatamab Development Timeline in BC



Zanidatamab Commercial Development

Path to \$2B+ Peak Potential

Abizer Gaslightwala

Senior Vice President, Jazz Oncology

U.S. Business Unit Head



Zanidatamab: De-Risked Near-Term Opportunity with \$2B+ Peak Potential

1st to market in BTC¹

- Familiarize physicians with zanidatamab treatment
- Initiated BLA submission in 4Q23
- Initiated confirmatory trial in 1L BTC
- Commercial launch preparations for 2025 or earlier

~12,000
BTC cases annually² in U.S.,
Europe³ and Japan



1L = first line; 2L = second line; BC = breast cancer; BLA = biologics license application; BTC = biliary tract cancer; FDA = Food and Drug Administration; GEA = gastroesophageal adenocarcinoma; HER2 = human epidermal growth factor receptor 2; HR+ = hormone receptor positive; NSCLC = non-small cell lung cancer; OS = overall survival; PD-L1 = programmed cell death ligand 1; T-DXd = trastuzumab deruxtecan. ¹Pending regulatory approvals; ²Incidence sources: Kantar reports, ToGA surveillance report; SEER, cancer.gov; ClearView Analysis; GLOBOCAN, Data on file; ³Major markets: U.K, France, Germany, Spain, Italy; ⁴Incidence source estimates derived from multiple sources: Decision Resources Group, Kantar Health, Jazz Market Research, data on file; ⁵Funda Meric-Bernstam et al, Zanidatamab, a novel bispecific antibody, for the treatment of locally advanced or metastatic HER2-expressing or HER2-amplified cancers: a phase 1, dose-escalation and expansion study, The Lancet Oncology, Volume 23, Issue 12, 2022, Pages 1558-1570, ISSN 1470-2045, [https://doi.org/10.1016/S1470-2045\(22\)00621-0](https://doi.org/10.1016/S1470-2045(22)00621-0). Note: HER2+ BTC patients in Jazz controlled commercial territories, which includes Japan, and excludes other certain Asia Pacific countries licensed to BeiGene, Ltd.

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HER2-targeted agent of choice in GEA

- Address unmet need in PD-L1 negative population
- Replace trastuzumab in PD-L1 positive population
- Improved statistical power for OS analysis while maintaining PFS top-line readout target timing

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Address unmet need post-T-DXd in BC

- Phase 3 Zanidatamab + chemo in post-T-DXd patients with HER2+ mBC
- Potential registrational program in HR+/HER2+ patients, including contribution of components
- Potential further development in neoadjuvant / adjuvant BC population

~150,000
BC cases annually⁵ in U.S., Europe³ and Japan



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~150,000

BC cases annually⁴ in U.S., Europe³ and Japan

Broad potential in other HER2-targeted indications

Broad potential beyond BTC, GEA, and BC in multiple HER2-expressing indications based on compelling clinical activity from early trials⁵

- Colorectal
- NSCLC
- Ovarian
- Endometrial
- Pancreatic
- Bladder
- Salivary Gland
- Ampullary
- Other HER2-expressing solid tumors

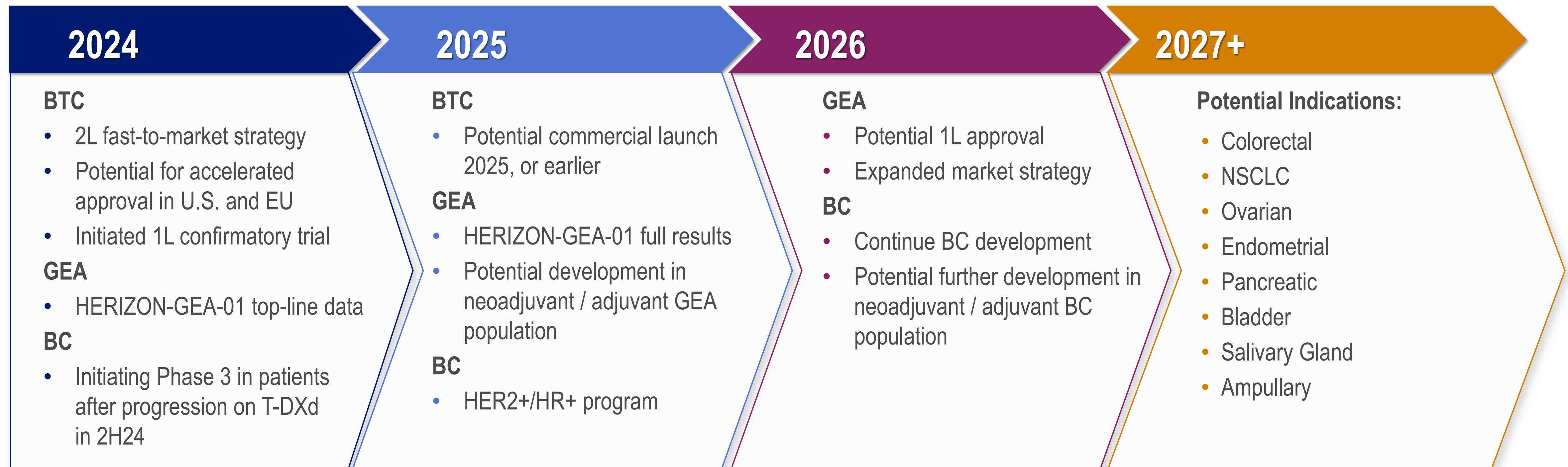
Broad Potential

Beyond BTC, GEA, and BC



1L = first line; 2L = second line; BC = breast cancer; BLA = biologics license application; BTC = biliary tract cancer; FDA = Food and Drug Administration; GEA = gastroesophageal adenocarcinoma; HER2 = human epidermal growth factor receptor 2; HR+ = hormone receptor positive; NSCLC = non-small cell lung cancer; OS = overall survival; PD-L1 = programmed cell death ligand 1; T-DXd = trastuzumab deruxtecan. ¹Pending regulatory approvals; ²Incidence sources: Kantar reports, ToGA surveillance report; SEER, cancer.gov; ClearView Analysis; GLOBOCAN, Data on file; ³Major markets: U.K, France, Germany, Spain, Italy; ⁴Incidence source estimates derived from multiple sources: Decision Resources Group, Kantar Health, Jazz Market Research, data on file; ⁵Funda Meric-Bernstam et al. Zanidatamab, a novel bispecific antibody, for the treatment of locally advanced or metastatic HER2-expressing or HER2-amplified cancers: a phase 1, dose-escalation and expansion study, The Lancet Oncology, Volume 23, Issue 12, 2022, Pages 1558-1570, ISSN 1470-2045, [https://doi.org/10.1016/S1470-2045\(22\)00621-0](https://doi.org/10.1016/S1470-2045(22)00621-0). Note: HER2+ BTC patients in Jazz controlled commercial territories, which includes Japan, and excludes other certain Asia Pacific countries licensed to BeiGene, Ltd.

Significant Commercial Opportunity with Multiple Expansion Indications



Q&A