Practical Perspectives: Experts Review Actual Cases of Patients with Advanced Gastroesophageal Cancers

A CME/MOC-Accredited Live Webinar

Wednesday, May 21, 2025
5:00 PM – 6:00 PM ET

Faculty

Geoffrey Y Ku, MD
Zev Wainberg, MD, MSc

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

Faculty

Geoffrey Y Ku, MD
Associate Attending Physician
Head, Esophagogastric Section
Gastrointestinal Oncology Service
Member, Cellular Therapy Service
Department of Medicine
Memorial Sloan Kettering Cancer Center
New York, New York

Zev Wainberg, MD, MSc
Co-Director, GI Oncology Program
Director of Early Phase Clinical Research
Jonsson Comprehensive Cancer Center
UCLA School of Medicine
Los Angeles, California

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Jazz Pharmaceuticals Inc, and Merck.

Dr Love — Disclosures

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Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, CARsgen Therapeutics, Daiichi Sankyo Inc, I-Mab Biopharma, Jazz Pharmaceuticals Inc, Merck, Oncolys BioPharma, Pieris Pharmaceuticals Inc, Triumvira Immunologics, Zymeworks Inc
Travel Support	DAVA Oncology, I-Mab Biopharma

Dr Wainberg — Disclosures

Consulting Agreements	AbbVie Inc, Alligator Bioscience, Amgen Inc, Arcus Biosciences, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BridgeBio, Daiichi Sankyo Inc, EMD Serono Inc, Genentech, a member of the Roche Group, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Lilly, Merck, Novartis, Phanes Therapeutics Inc
Data and Safety Monitoring Boards/Committees	AstraZeneca Pharmaceuticals LP, Compass Therapeutics, Pfizer Inc

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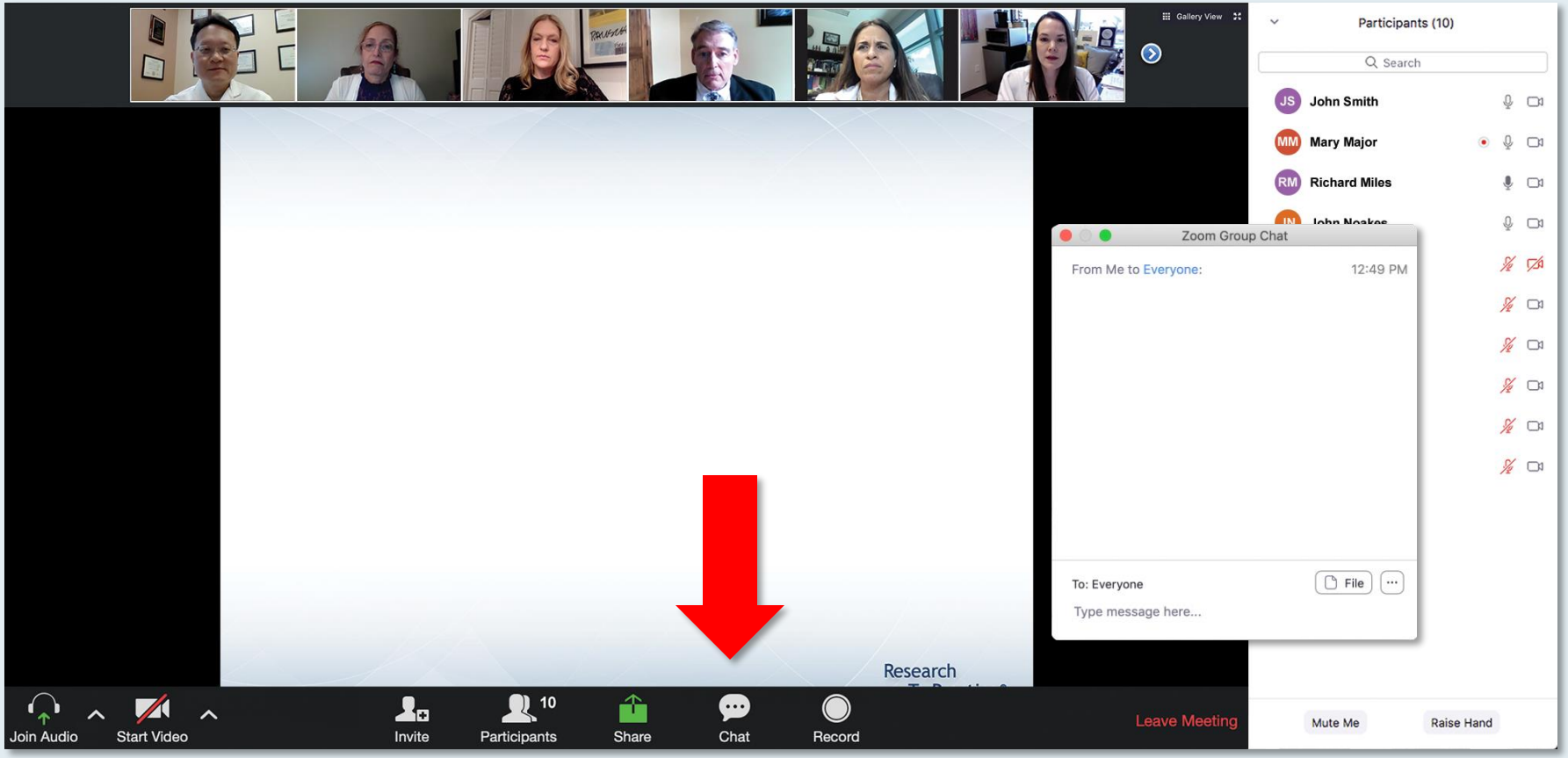

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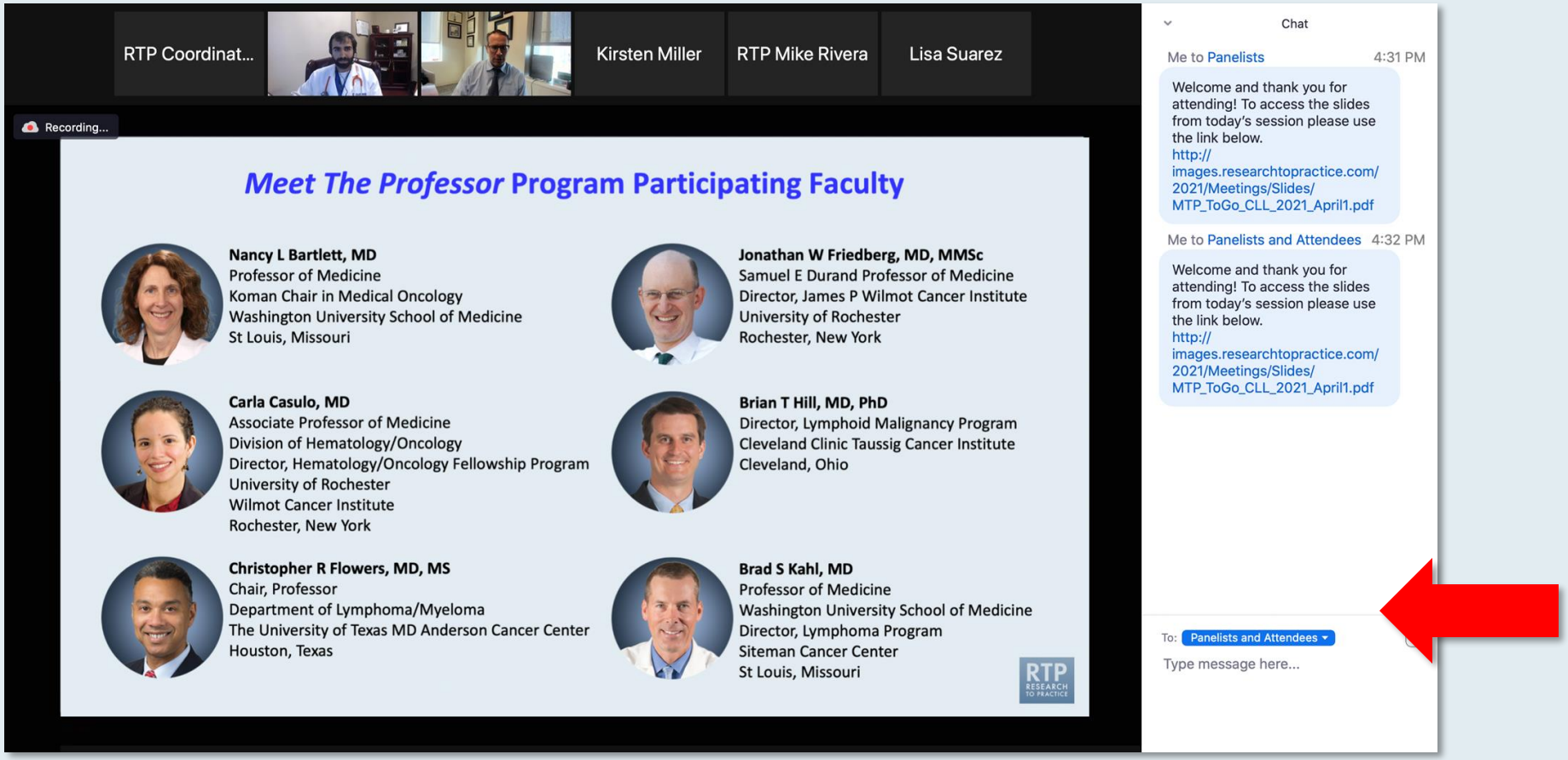

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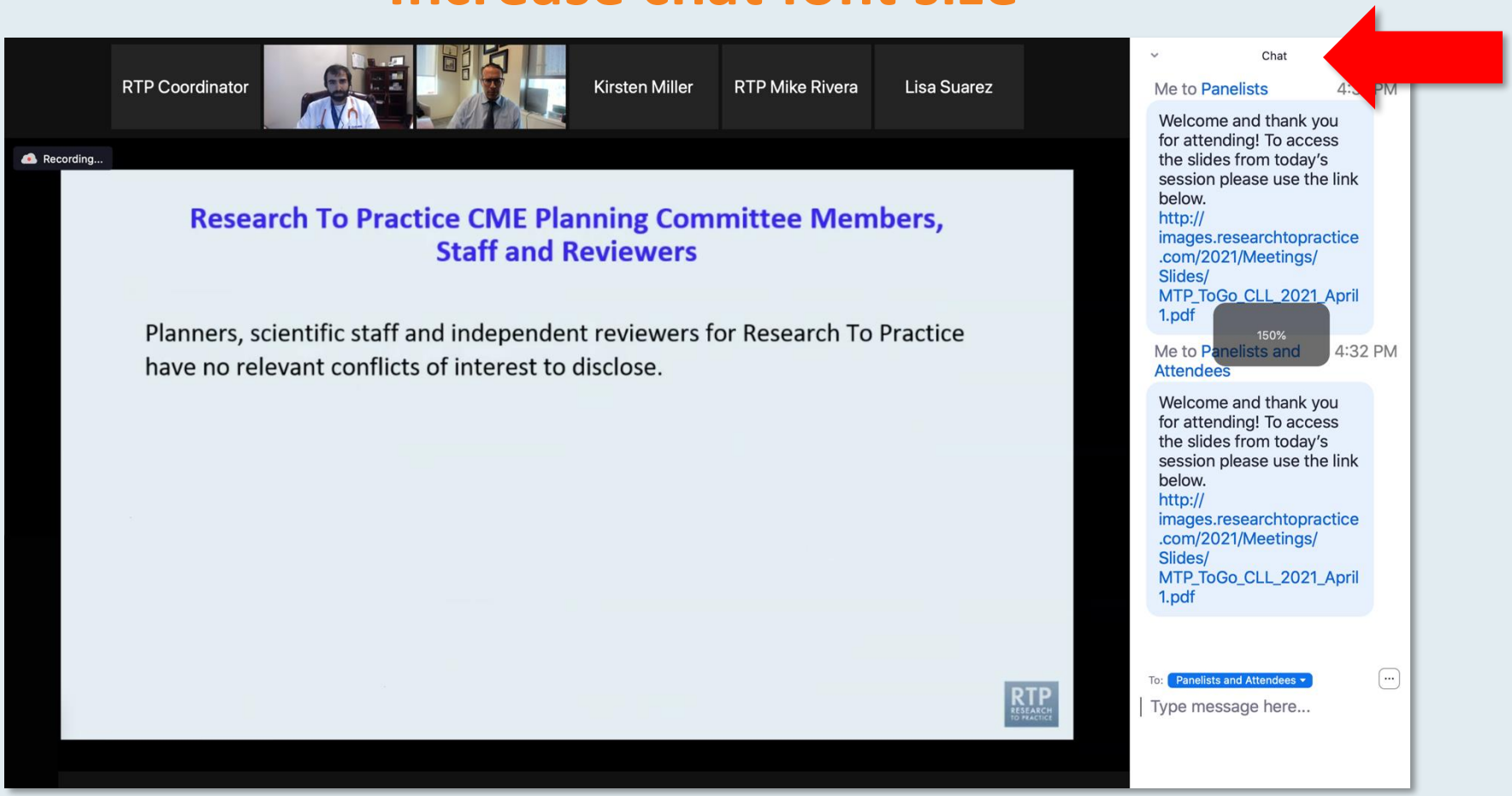

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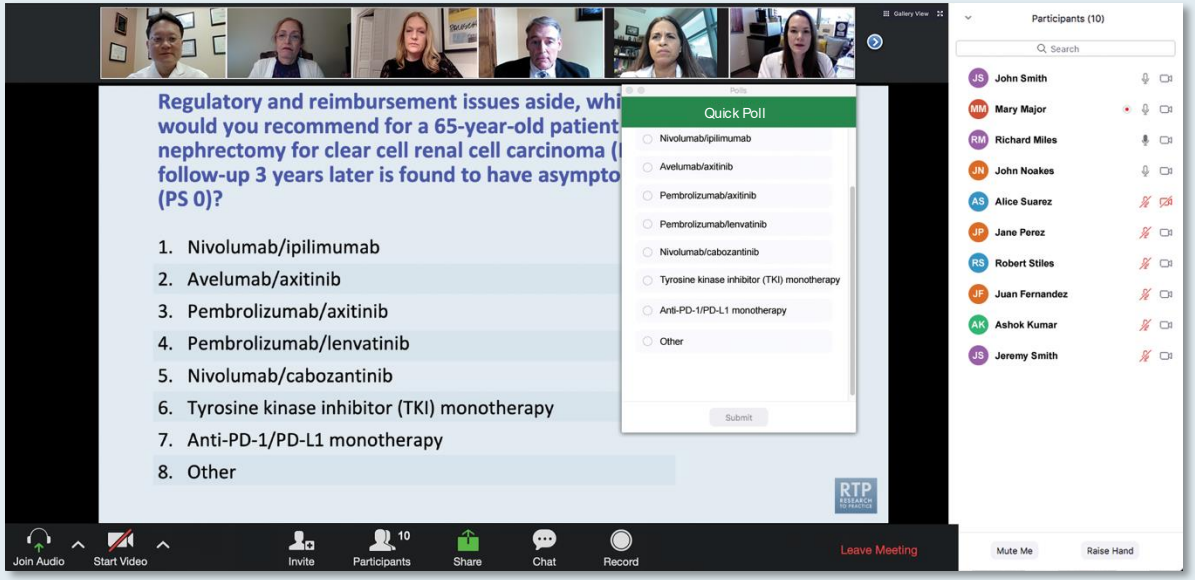
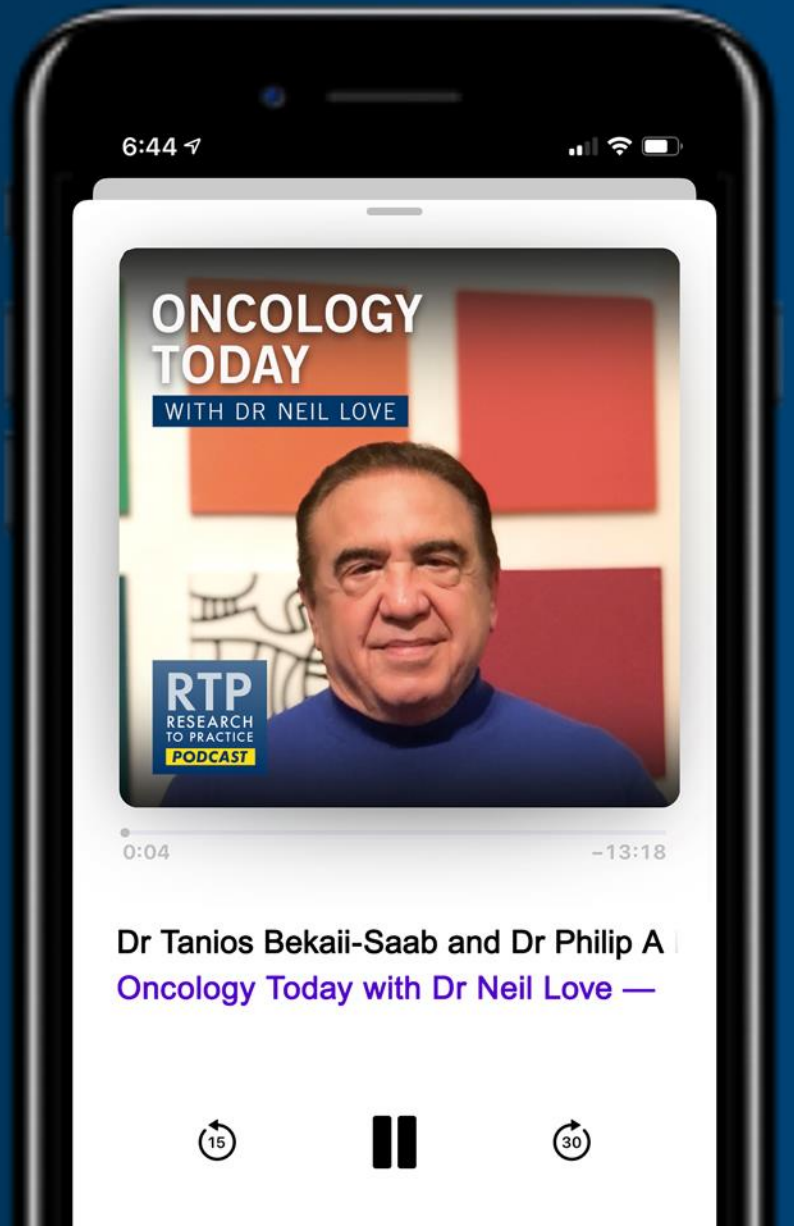


The Implications of Recent Datasets for the Current and Future Management of Gastrointestinal Cancers — An ESMO Congress 2024 Review

DR TANIOS BEKAII-SAAB
MAYO CLINIC

DR PHILIP A PHILIP
HENRY FORD CANCER



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Friday, May 30, 2025

Immunotherapy and Antibody-Drug Conjugates in Lung Cancer

11:15 AM – 12:45 PM CT (12:15 PM – 1:45 PM ET)

Faculty

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John V Heymach, MD, PhD
Professor Solange Peters, MD, PhD

Moderator

Jacob Sands, MD

Colorectal Cancer

6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)

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Andrea Cercek, MD
Arvind Dasari, MD, MS
Pashtoon Kasi, MD, MS
Eric Van Cutsem, MD, PhD

Moderator

J Randolph Hecht, MD

EGFR Mutation-Positive Non-Small Cell Lung Cancer

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Suresh S Ramalingam, MD
Joshua K Sabari, MD

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Christopher Flowers, MD, MS
Ann LaCasce, MD, MMSc
Matthew Lunning, DO
Tycel Phillips, MD, FASCO

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Andrew J Armstrong, MD, ScM
Himisha Beltran, MD
Fred Saad, MD

Moderator

Rana R McKay, MD

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Shannon N Westin, MD, MPH, FASCO, FACOG

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Metastatic Breast Cancer

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Harold J Burstein, MD, PhD
Javier Cortés, MD, PhD
Rebecca A Dent, MD, MSc
Kevin Kalinsky, MD, MS
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Faculty

Rashmi Chugh, MD

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Thank you for joining us! Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us.

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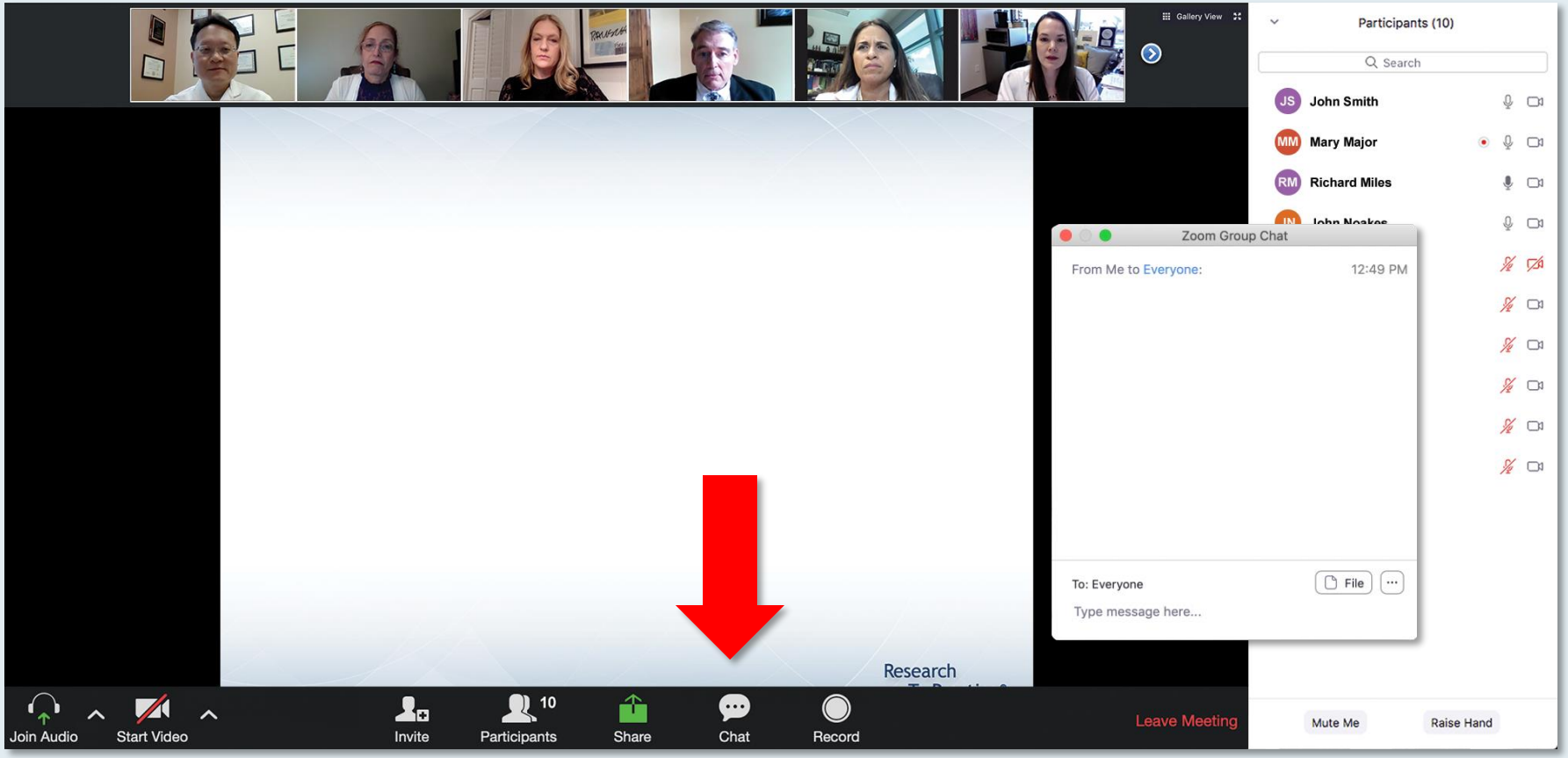

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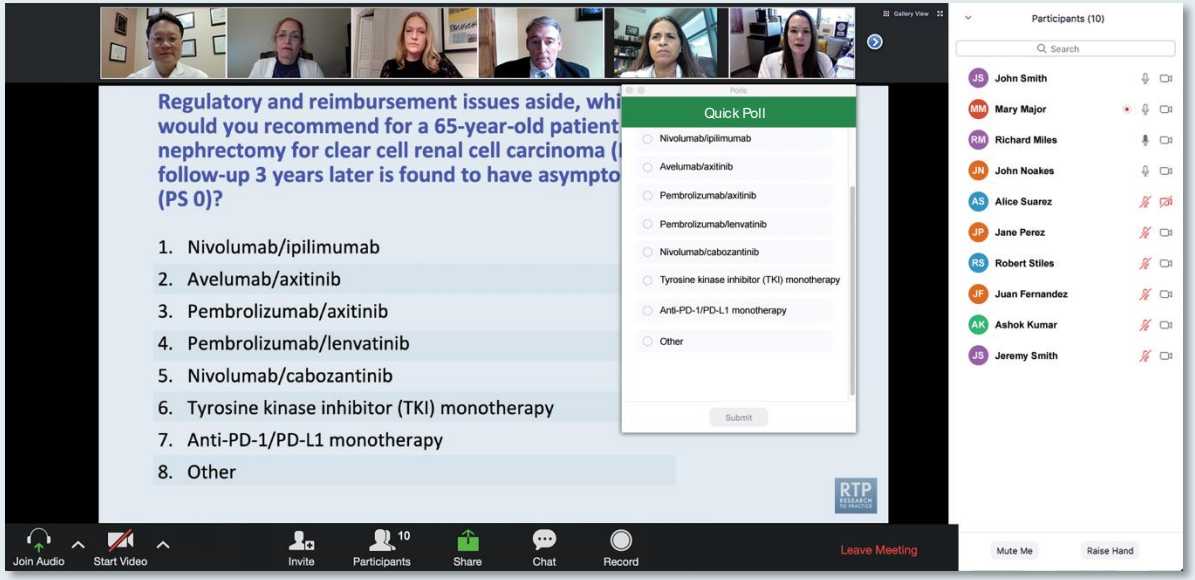

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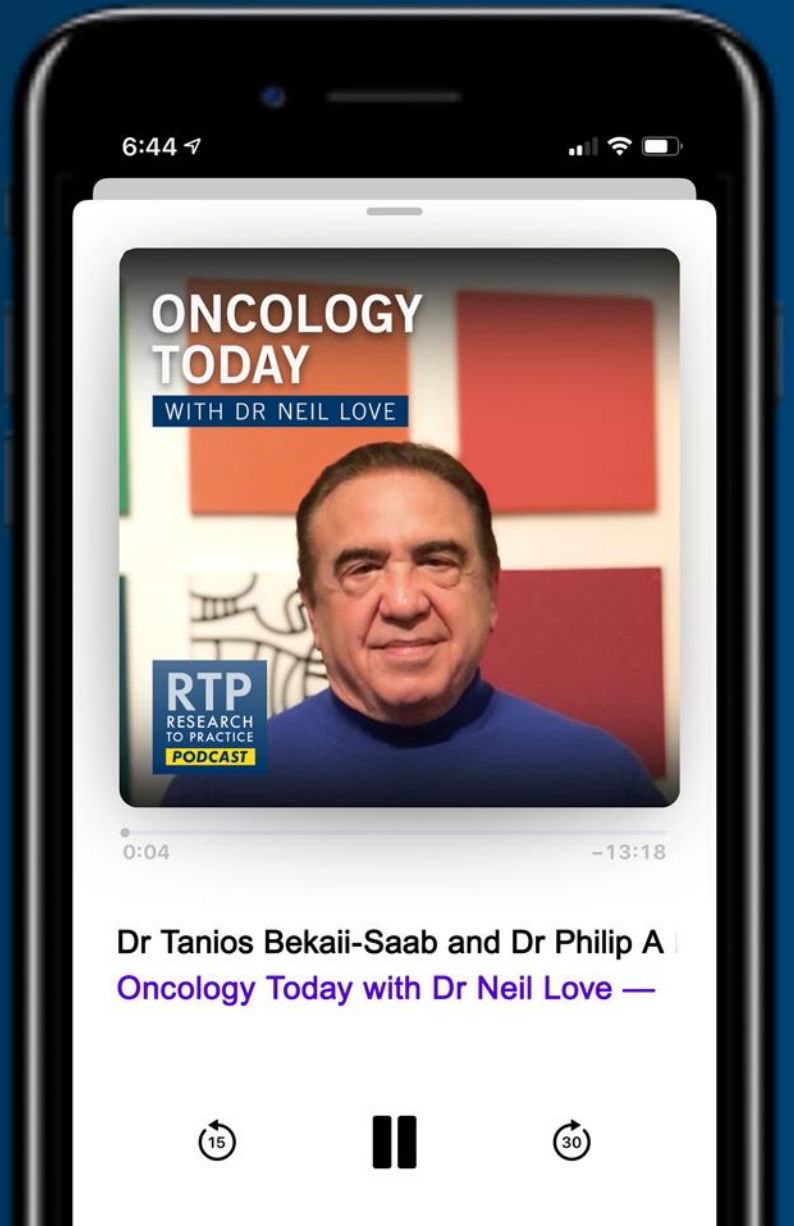

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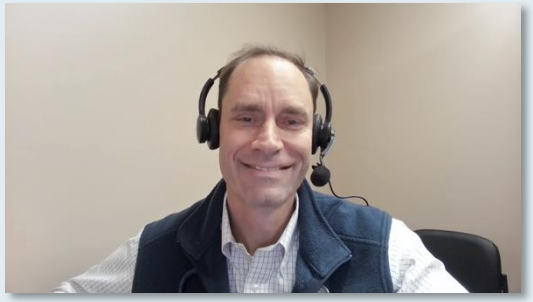
Contributing General Medical Oncologists

Warren S Brenner, MD
Lynn Cancer Institute
Boca Raton, Florida

Henna Malik, MD
Texas Oncology
Houston, Texas



Stephen “Fred” Divers, MD
American Oncology Network
Hot Springs, Arkansas

Brian P Mulherin, MD
American Oncology Network
Indianapolis, Indiana

Victoria Giffi, MD
Meritus Hematology and
Oncology Specialists
Hagerstown, Maryland

Shachar Peles, MD
Florida Cancer Specialists &
Research Institute
Lake Worth, Florida

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RESEARCH
TO PRACTICE

Agenda

Introduction: ASCO Preview

Module 1: HER2-Positive Gastroesophageal Cancers

Module 2: Immunotherapy in HER2-Negative Advanced Gastroesophageal Cancers

Module 3: Immunotherapy in Microsatellite Instability-High Gastroesophageal Cancers

Module 4: CLDN18.2-Positive Advanced Gastroesophageal Cancers

Agenda

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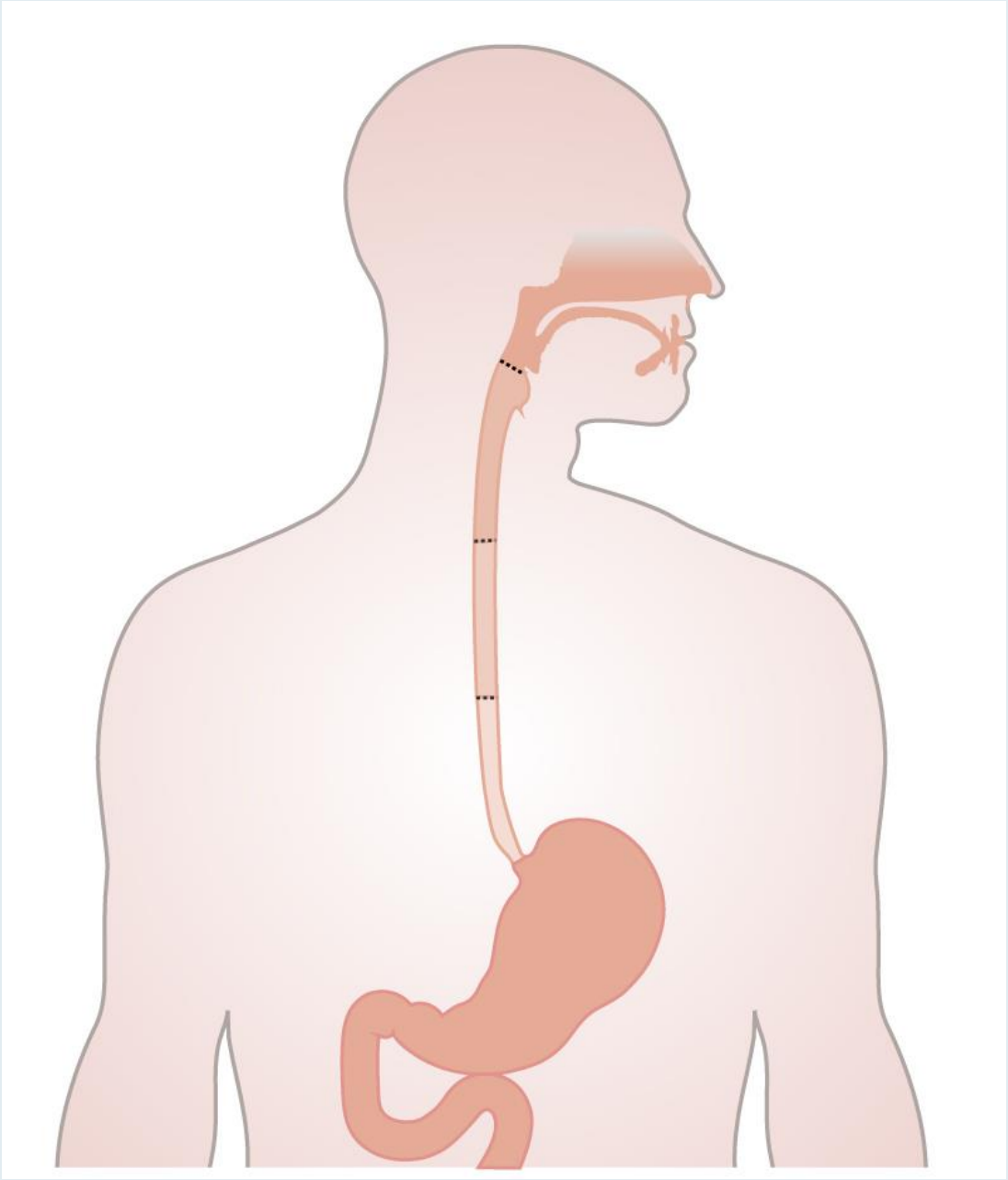
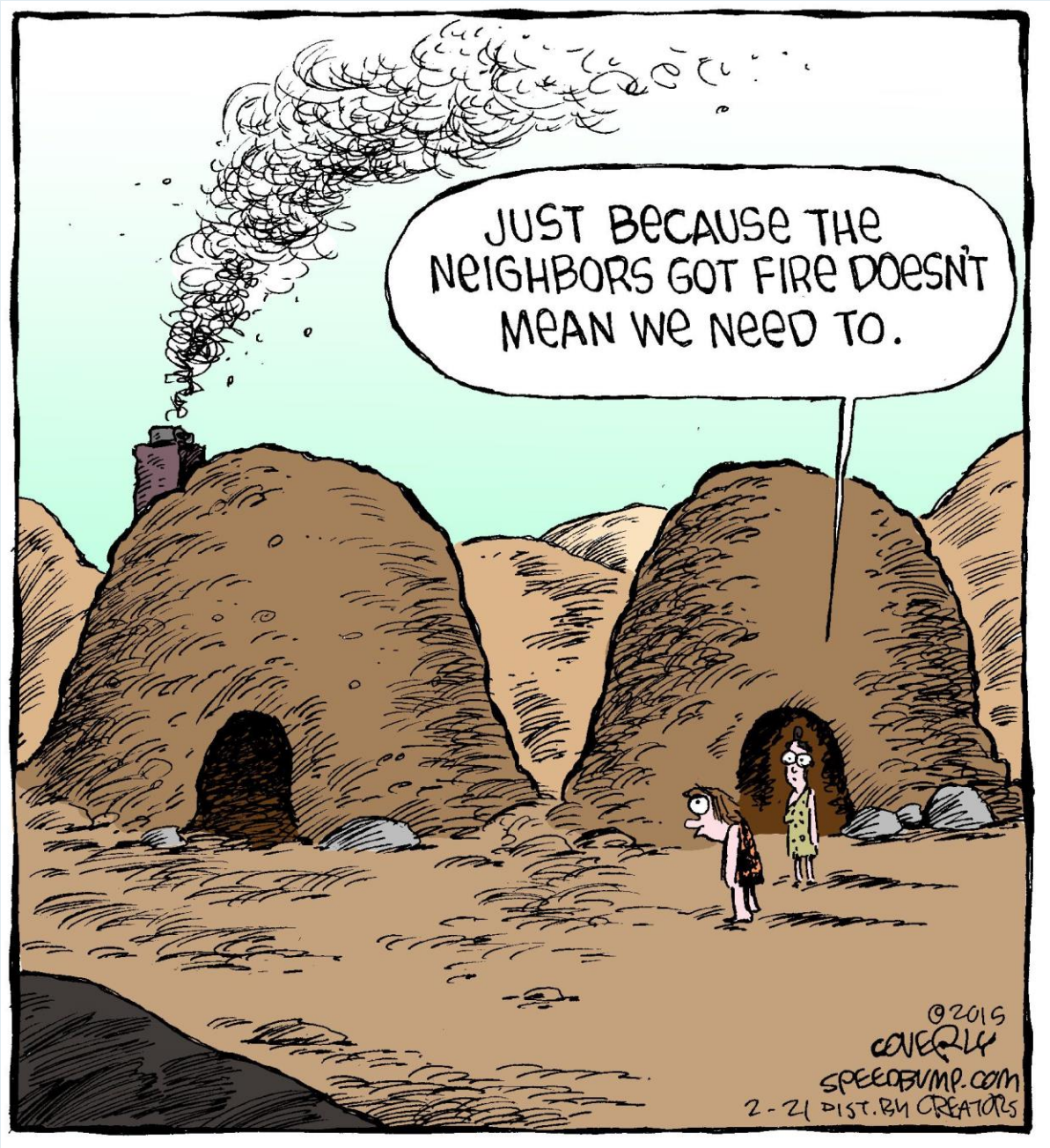
Anatomy Involved with Gastroesophageal Cancers




JUST BECAUSE THE NEIGHBORS GOT FIRE DOESN'T MEAN WE NEED TO.
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Case Presentation: 73-year-old man with HER2-negative, MSS, localized T3N2M0 GEJ adenocarcinoma (somatic BRCA mutation) receives neoadjuvant FLOT followed by surgery

Dr Stephen “Fred” Divers (Hot Springs, Arkansas)

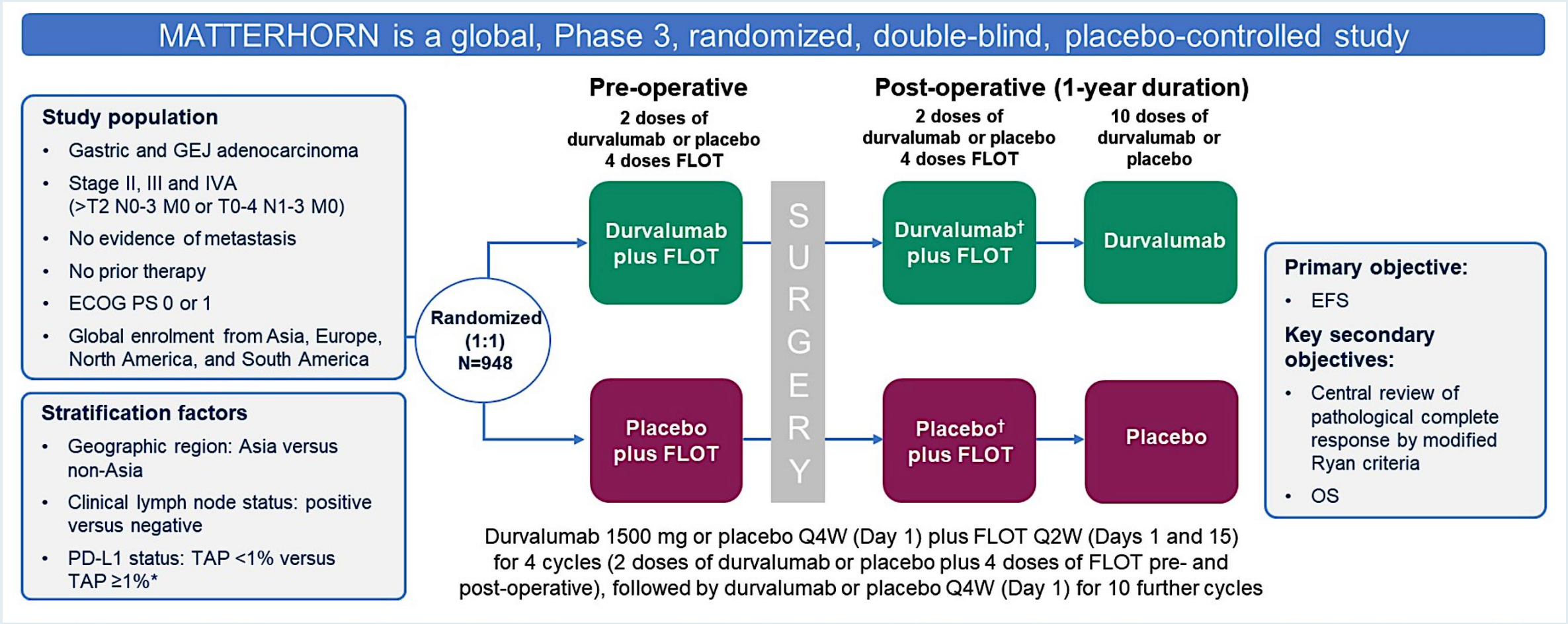
RTP RESEARCH TO PRACTICE

Event-Free Survival (EFS) in MATTERHORN: A Randomized, Phase 3 Study of Durvalumab plus 5-Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel Chemotherapy (FLOT) in Resectable Gastric/ Gastroesophageal Junction Cancer (GC/GEJC)

Janjigian Y et al.
ASCO 2025;Abstract LBA5.

June 1, 2025
Hall B1| 3:13 PM CT

MATTERHORN: Phase III Study of FLOT with or without Durvalumab for Resectable Gastroesophageal Adenocarcinoma



Janjigian Y et al. Gastrointestinal Cancers Symposium 2024;Abstract LBA246.

Durvalumab-Based Regimen Demonstrated Statistically Significant and Clinically Meaningful Improvement in Event-Free Survival in Resectable Early-Stage Gastric and Gastroesophageal Junction Cancers

Press Release: March 7, 2025

Positive high-level results from the MATTERHORN Phase III trial showed perioperative treatment with durvalumab in combination with standard-of-care FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) chemotherapy demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of event-free survival (EFS).

Patients were treated with neoadjuvant durvalumab in combination with chemotherapy before surgery, followed by adjuvant durvalumab in combination with chemotherapy, then durvalumab monotherapy. The trial evaluated this regimen versus perioperative chemotherapy alone for patients with resectable, early-stage and locally advanced (Stages II, III, IVA) gastric and gastroesophageal junction (GEJ) cancers.

For the secondary endpoint of overall survival (OS), a strong trend was observed in favour of the durvalumab-based regimen at this interim analysis. The trial will continue to follow OS, which will be formally assessed at the final analysis.

RTP RESEARCH TO PRACTICE

https://www.astrazeneca.com/media-centre/press-releases/2025/imfinzi-improved-efs-in-early-stage-gastric-cancer.html

Lenvatinib plus Pembrolizumab and Chemotherapy versus Chemotherapy in Advanced, Metastatic Gastroesophageal Adenocarcinoma: The Phase 3, Randomized LEAP-015 Study

Rha S et al.
ASCO 2025;Abstract 4001.

May 31, 2025
Hall D1| 3:12 PM CT

Randomized Trial of Standard Chemotherapy Alone or Combined with Atezolizumab as Adjuvant Therapy for Patients with Stage III Deficient DNA Mismatch Repair (dMMR) Colon Cancer (Alliance A021502; ATOMIC)

Sinicrope F et al.
ASCO 2025;Abstract LBA1.

June 1, 2025
Hall B1| 1:05 PM CT

Trastuzumab Deruxtecan (T-DXd) vs Ramucirumab (RAM) + Paclitaxel (PTX) in Second-Line Treatment of Patients (Pts) with Human Epidermal Growth Factor Receptor 2-Positive (HER2+) Unresectable/Metastatic Gastric Cancer (GC) or Gastroesophageal Junction Adenocarcinoma (GEJA): Primary Analysis of the Randomized, Phase 3 DESTINY-Gastric04 Study

Shitara K et al.
ASCO 2025;Abstract LBA4002.

May 31, 2025
Hall D1| 3:24 PM CT

T-DXd Demonstrated Statistically Significant and Clinically Meaningful Improvement in OS for Patients with HER2-Positive Metastatic Gastric Cancer at Interim Analysis of the DESTINY-Gastric04 Phase III Trial

Press Release: March 3, 2025

"Positive topline results from the DESTINY-Gastric04 phase 3 trial showed trastuzumab deruxtecan (T-DXd) demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of overall survival (OS) compared to ramucirumab and paclitaxel in patients with second-line HER2 positive (IHC 3+ or IHC 2+/ISH+) unresectable and/or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma.

The safety profile seen in DESTINY-Gastric04 is consistent with the established safety profile of T-DXd.

Data from DESTINY-Gastric04 will be presented at an upcoming medical meeting and shared with global regulatory authorities."

https://daiichisankyo.us/press-releases/-/article/enhertu-demonstrated-statistically-significant-and-clinically-meaningful-improvement-in-overall-survival-in-patients-with-her2-positive-metastatic-gas

RTP RESEARCH TO PRACTICE

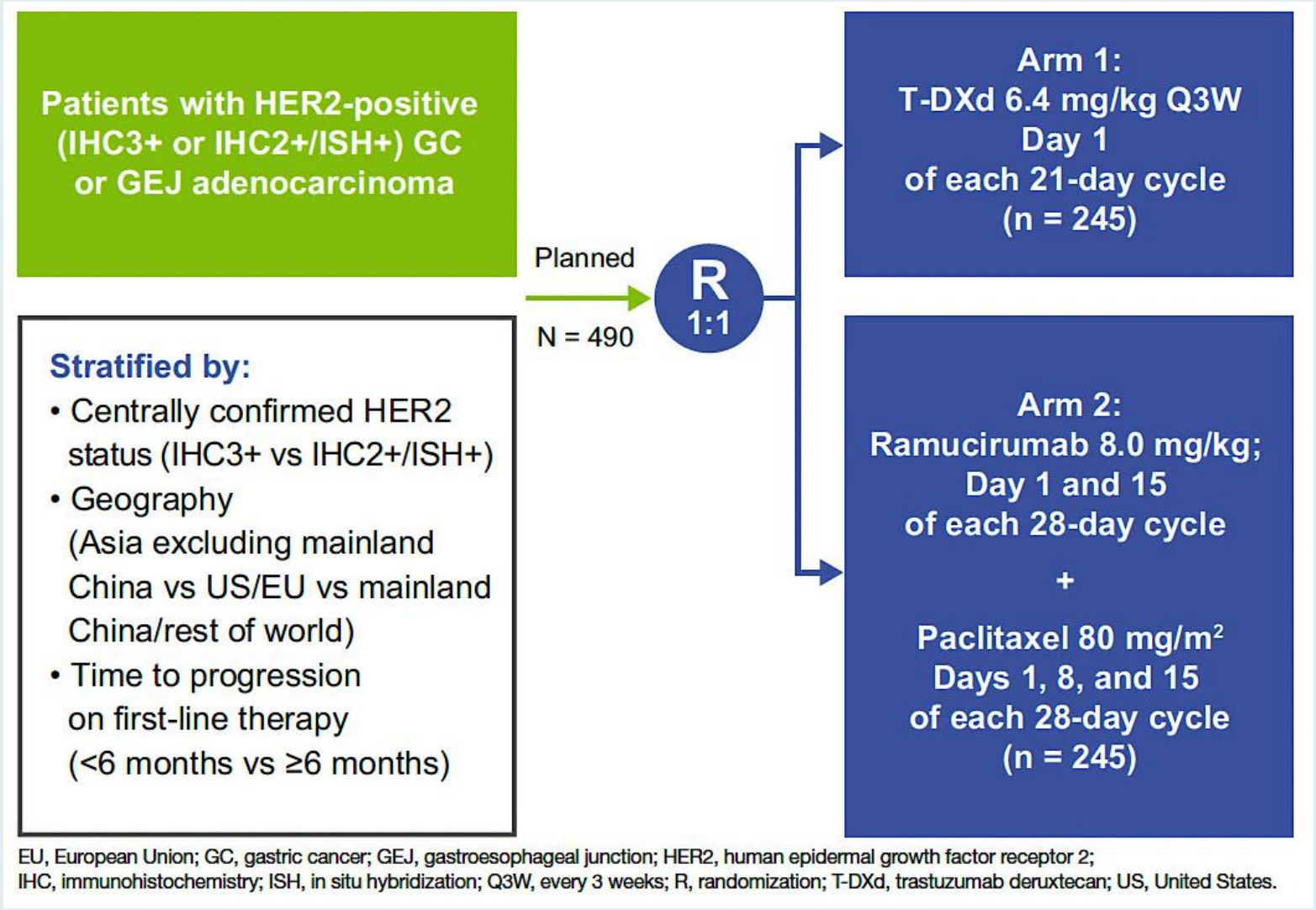
DESTINY-Gastric04 Phase III Study Design

Key Inclusion Criteria

- Adults (according to local regulation) and able to provide informed consent
- Unresectable, locally advanced, or metastatic GC or GEJ adenocarcinoma
- Progression on or after previous first-line treatment including trastuzumab-containing therapy
- Centrally confirmed HER2-positive status (IHC3+ or IHC2+/ISH+) on a tumor biopsy obtained after progression on or after a trastuzumab-containing regimen
- ECOG PS of 0 or 1
- LVEF ≥50% within 28 days before randomization

Key Exclusion Criteria

- Anticancer therapy after trastuzumab-containing therapy
- Myocardial infarction ≤6 months before randomization or symptomatic CHF
- History of ILD/pneumonitis that required steroids, current ILD/pneumonitis, or suspected ILD/pneumonitis that cannot be ruled out by imaging at screening
- Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disease



EU, European Union; GC, gastric cancer; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; US, United States.

Janjigian Y et al. Gastrointestinal Cancers Symposium 2025;Abstract 448.

Agenda

Introduction: ASCO Preview

Module 1: HER2-Positive Gastroesophageal Cancers

Module 2: Immunotherapy in HER2-Negative Advanced Gastroesophageal Cancers

Module 3: Immunotherapy in Microsatellite Instability-High Gastroesophageal Cancers

Module 4: CLDN18.2-Positive Advanced Gastroesophageal Cancers

Case Presentation: 64-year-old man with HER2-positive (IHC 3+) and HER2-mutant (exon 20), TP53-mutant metastatic GEJ adenocarcinoma (PD-L1 0) receives pembrolizumab/trastuzumab/chemotherapy

Dr Brian Mulherin (Indianapolis, Indiana)

RTP RESEARCH TO PRACTICE

Case Presentation: 86-year-old man with HER2-positive (IHC 3+) metastatic esophageal cancer (PD-L1 CPS 10) with s/p chemotherapy/pembrolizumab/trastuzumab and maintenance 5-FU/pembrolizumab/trastuzumab, now with brain metastases

Dr Warren S Brenner (Boca Raton, Florida)

FDA Amends Pembrolizumab's Gastric Cancer Indication

Press Release: November 7, 2023

"On November 7, 2023, the Food and Drug Administration revised the existing indication of pembrolizumab with trastuzumab, fluoropyrimidine, and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.

This updated indication, which remains approved under accelerated approval regulations, **restricts its use to patients whose tumors express PD-L1 (CPS ≥ 1)** as determined by an FDA-approved test.

In a recent, prespecified interim analysis of the fully enrolled [KEYNOTE-811] trial (N=698), in a subgroup analysis conducted in patients with PD-L1 CPS <1 (N= 104), the hazard ratio (HR) for OS and PFS were 1.41 (95% CI 0.90, 2.20) and 1.03 (95% CI 0.65, 1.64), respectively."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-amends-pembrolizumabs-gastric-cancer-indication

RTP RESEARCH TO PRACTICE

FDA Approves Pembrolizumab for HER2-Positive Gastric or Gastroesophageal Junction Adenocarcinoma Expressing PD-L1 (CPS ≥1)

Press Release: March 19, 2025

"The Food and Drug Administration granted traditional approval to pembrolizumab with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1).

Pembrolizumab previously received accelerated approval for this indication on May 5, 2021.

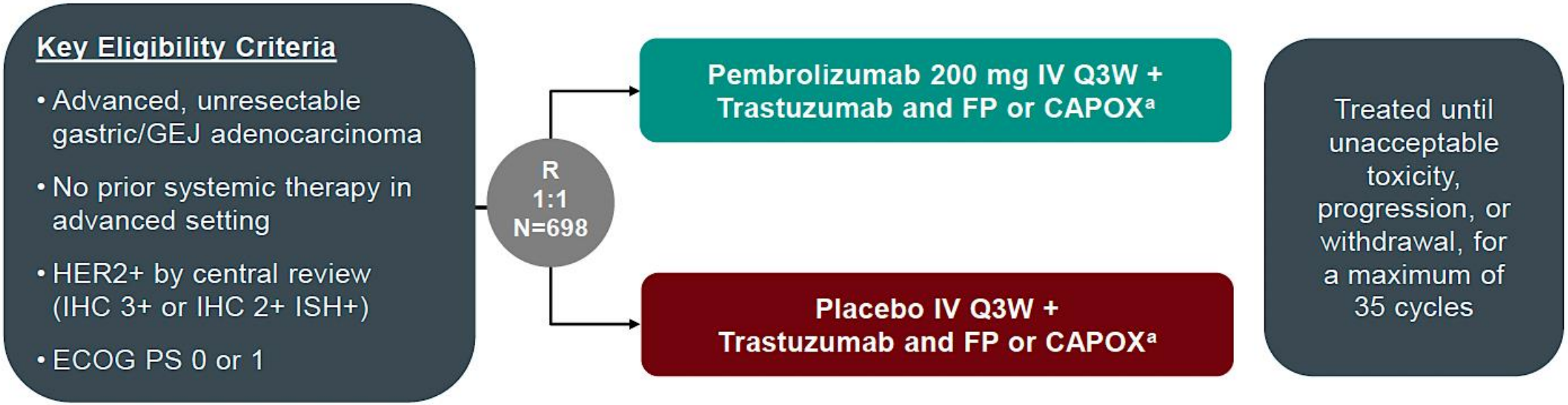
Efficacy was evaluated in KEYNOTE-811 (NCT03615326), a multicenter, randomized, double-blind, placebo-controlled trial enrolling 698 patients with HER2-positive advanced gastric or GEJ adenocarcinoma not previously treated with systemic therapy for metastatic disease.

In patients with tumors that were PDL1 CPS≥1, median PFS was 10.9 months (95% CI: 8.5, 12.5) in the pembrolizumab arm and 7.3 months (95% CI: 6.8, 8.4) in the placebo arm (Hazard ratio [HR] 0.72 [95% CI: 0.60, 0.87]). Median OS was 20.1 months (95% CI: 17.9, 22.9) and 15.7 months (95% CI: 13.5, 18.5) in the respective arms (HR 0.79 [95% CI: 0.66, 0.95]."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-her2-positive-gastric-or-gastroesophageal-junction-adenocarcinoma

RTP RESEARCH TO PRACTICE

KEYNOTE-811: Phase III Study of First-Line Pembrolizumab with Trastuzumab and Chemotherapy for HER2-Positive Gastroesophageal Cancers



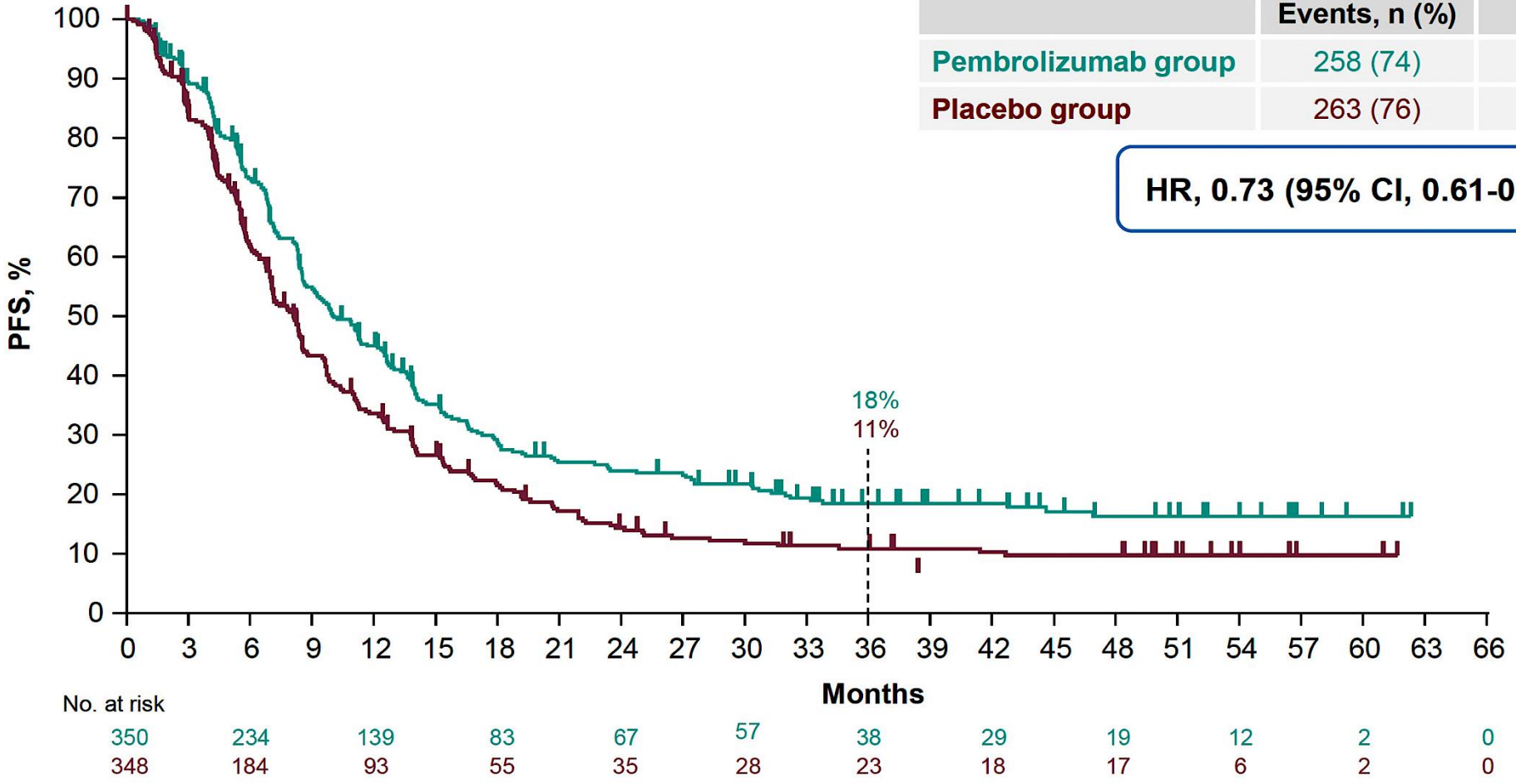
FP = fluorouracil and cisplatin; CPS = combined positive score; OS = overall survival; PFS = progression-free survival; ORR = objective response rate; DOR = duration of response

Rha S et al. ESMO 2024;Abstract 128MO.

KEYNOTE-811: Phase III Study of First-Line Pembrolizumab with Trastuzumab and Chemotherapy for HER2-Positive Gastroesophageal Cancers – PFS

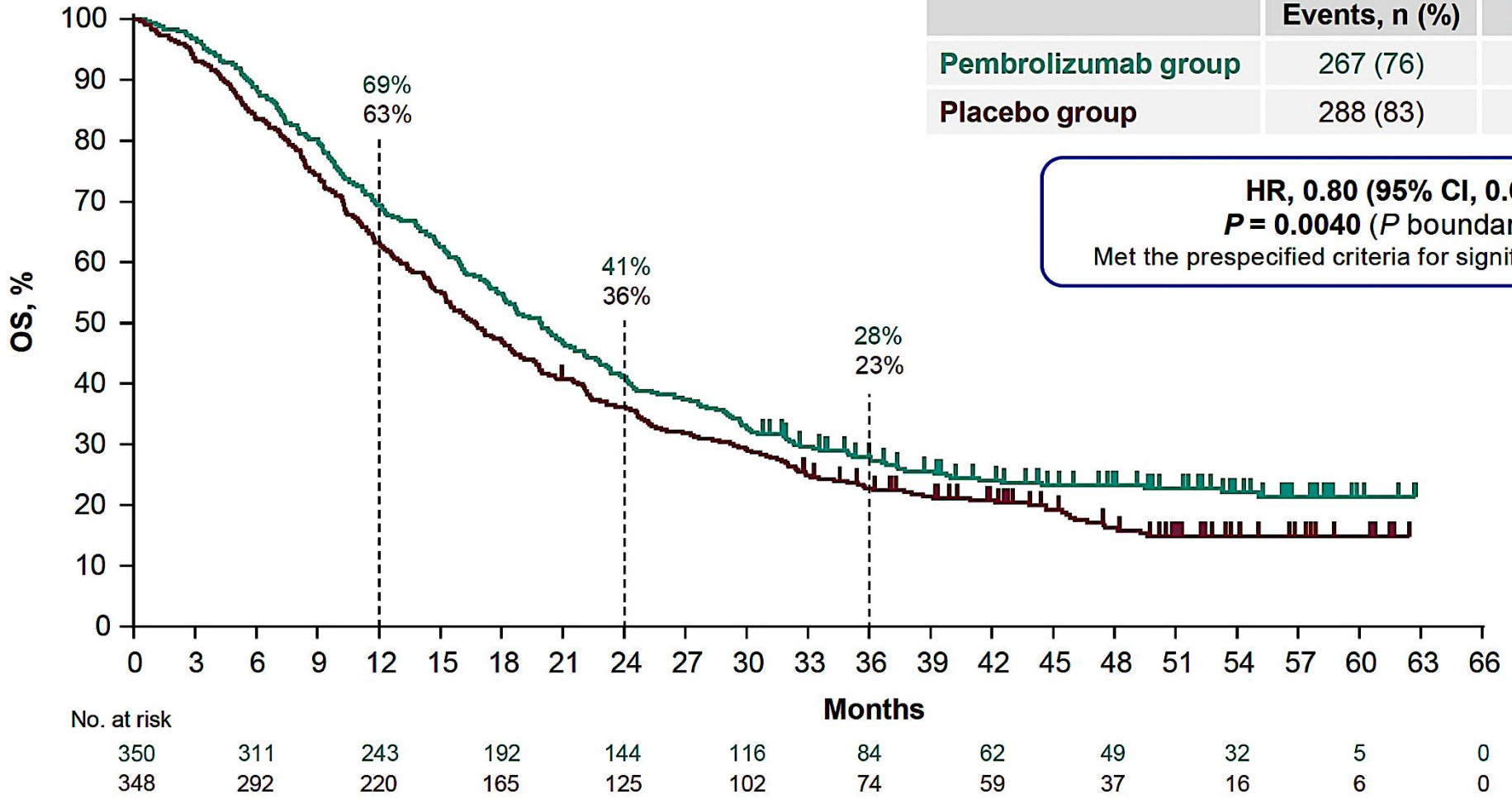
	Events, n (%)	Median (95% CI), mo
Pembrolizumab group	258 (74)	10.0 (8.6-12.2)
Placebo group	263 (76)	8.1 (7.0-8.5)

HR, 0.73 (95% CI, 0.61-0.87)



Rha S et al. ESMO 2024;Abstract 128MO.

KEYNOTE-811: Phase III Study of First-Line Pembrolizumab with Trastuzumab and Chemotherapy for HER2-Positive Gastroesophageal Cancers – OS



	Events, n (%)	Median (95% CI), mo
Pembrolizumab group	267 (76)	20.0 (17.8-22.1)
Placebo group	288 (83)	16.8 (14.9-18.7)

HR, 0.80 (95% CI, 0.67-0.94);
***P* = 0.0040** (*P* boundary, 0.0201)
Met the prespecified criteria for significance at final analysis

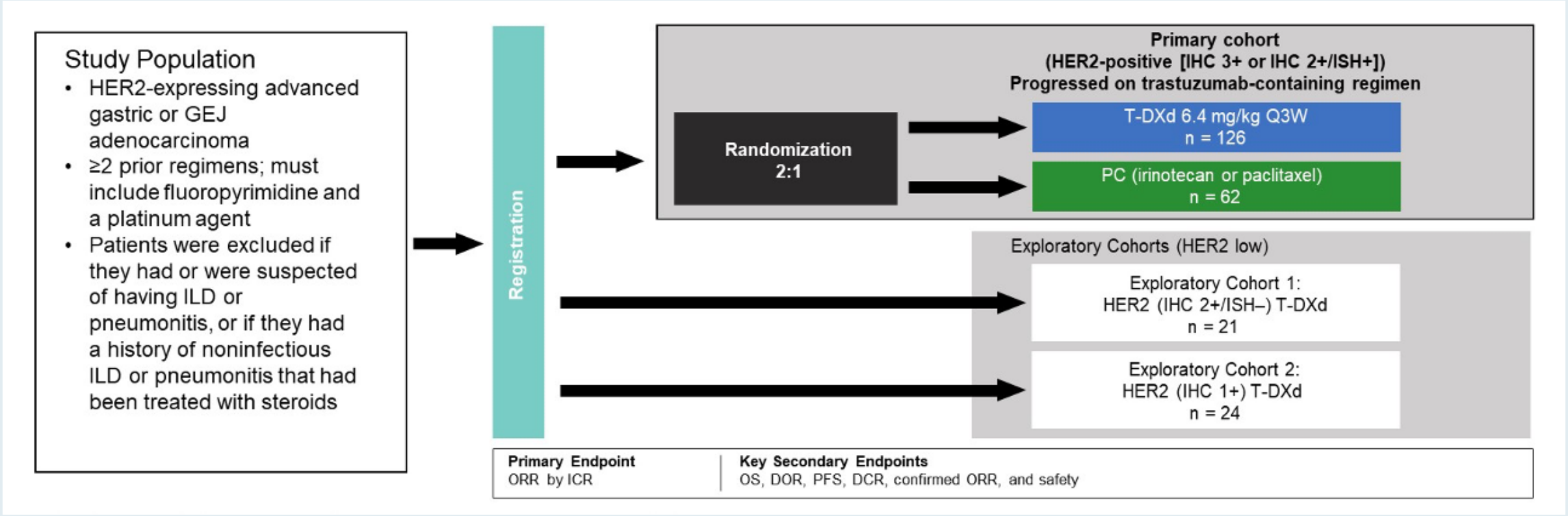
Rha S et al. ESMO 2024;Abstract 128MO.

KEYNOTE-811: First-Line Pembrolizumab with Trastuzumab and Chemotherapy – Survival by PD-L1 CPS

	PD-L1 CPS ≥1		PD-L1 CPS <1	
	Pembrolizumab n = 298	Placebo n = 296	Pembrolizumab n = 52	Placebo n = 52
PFS, median (95% CI), mo	10.9 (8.5-12.5)	7.3 (6.8-8.4)	9.5 (8.3-12.6)	9.5 (7.9-13.0)
HR (95% CI)	0.72 (0.60-0.87)		0.99 (0.62-1.56)	
OS, median (95% CI), mo	20.1 (17.9-22.9)	15.7 (13.5-18.5)	18.2 (13.9-22.9)	20.4 (16.4-24.7)
HR (95% CI)	0.79 (0.66-0.95)		1.10 (0.72-1.68)	

Rha S et al. ESMO 2024;Abstract 128MO.

DESTINY-Gastric01 Randomized, Phase II Study Design

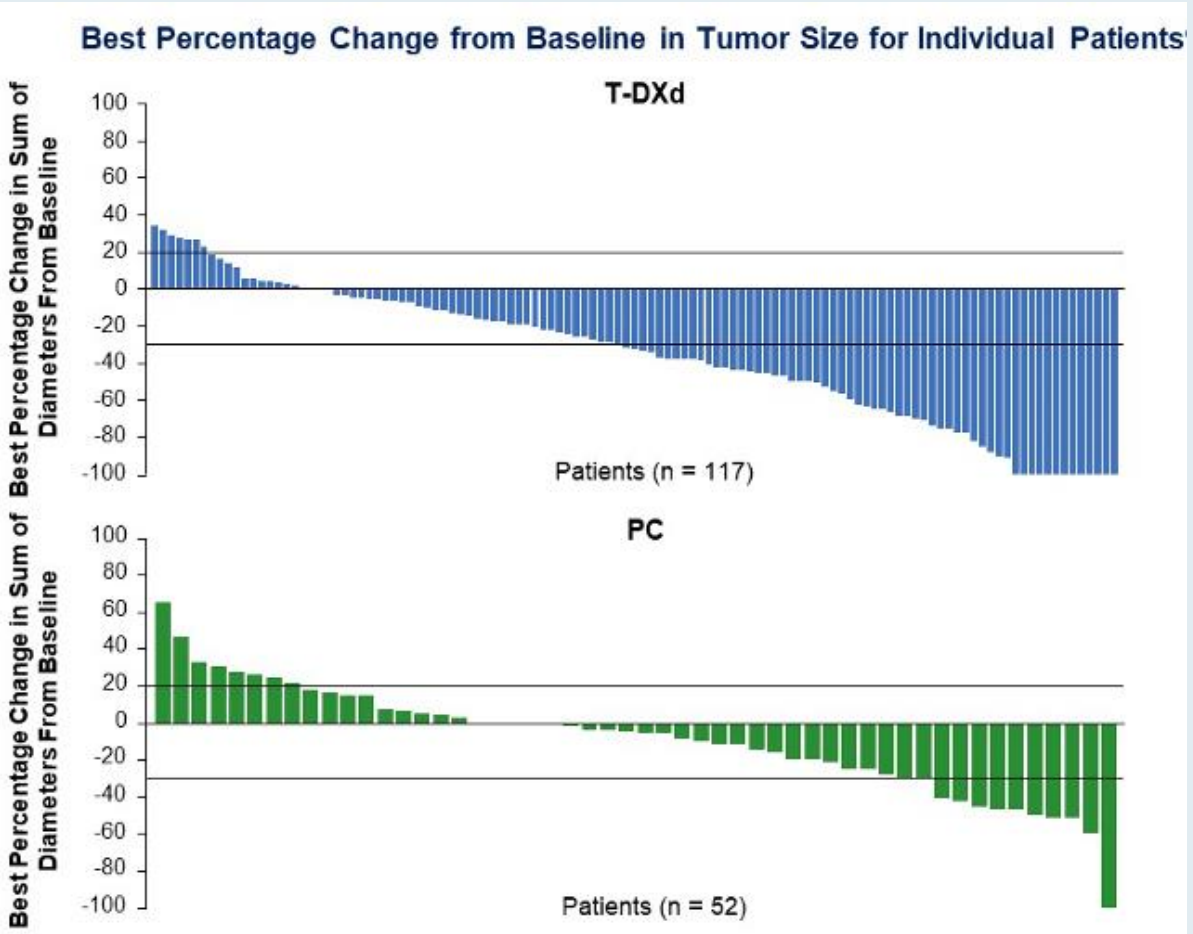


GEJ = gastroesophageal junction; ILD = interstitial lung disease; T-DXd = trastuzumab deruxtecan; PC = treatment of physician's choice; ICR = independent central review; DCR = disease control rate

Yamaguchi K et al. Gastrointestinal Cancers Symposium 2022;Abstract 242.

DESTINY-Gastric01: Antitumor Activity

	T-DXd n = 119	PC Overall n = 56
ORR (CR + PR) by ICR, n (%)[a]	**61 (51.3) 95% CI, 41.9-60.5**	**8 (14.3) 95% CI, 6.4-26.2**
	P < 0.0001[b]	
CR	11 (9.2)	0
PR	50 (42.0)	8 (14.3)
SD	42 (35.3)	27 (48.2)
PD	14 (11.8)	17 (30.4)
Not evaluable	2 (1.7)	4 (7.1)
Confirmed ORR (CR + PR) by ICR, n (%)[a]	50 (42.0) 95% CI, 33.0-51.4	7 (12.5) 95% CI, 5.2-24.1
CR	10 (8.4)	0
PR	40[c] (33.6)	7 (12.5)
SD	52 (43.7)	28 (50.0)
PD	14 (11.8)	17 (30.4)
Not evaluable	3 (2.5)	4 (7.1)
Confirmed DCR (CR + PR + SD), n (%)[a]	102 (85.7) 95% CI, 78.1-91.5	35 (62.5) 95% CI, 48.5-75.1
Confirmed DOR, median, months	12.5 95% CI, 5.6-NE	3.9 95% CI, 3.0-4.9
TTR, median, months	1.5 95% CI, 1.4-1.7	1.6 95% CI, 1.3-1.7

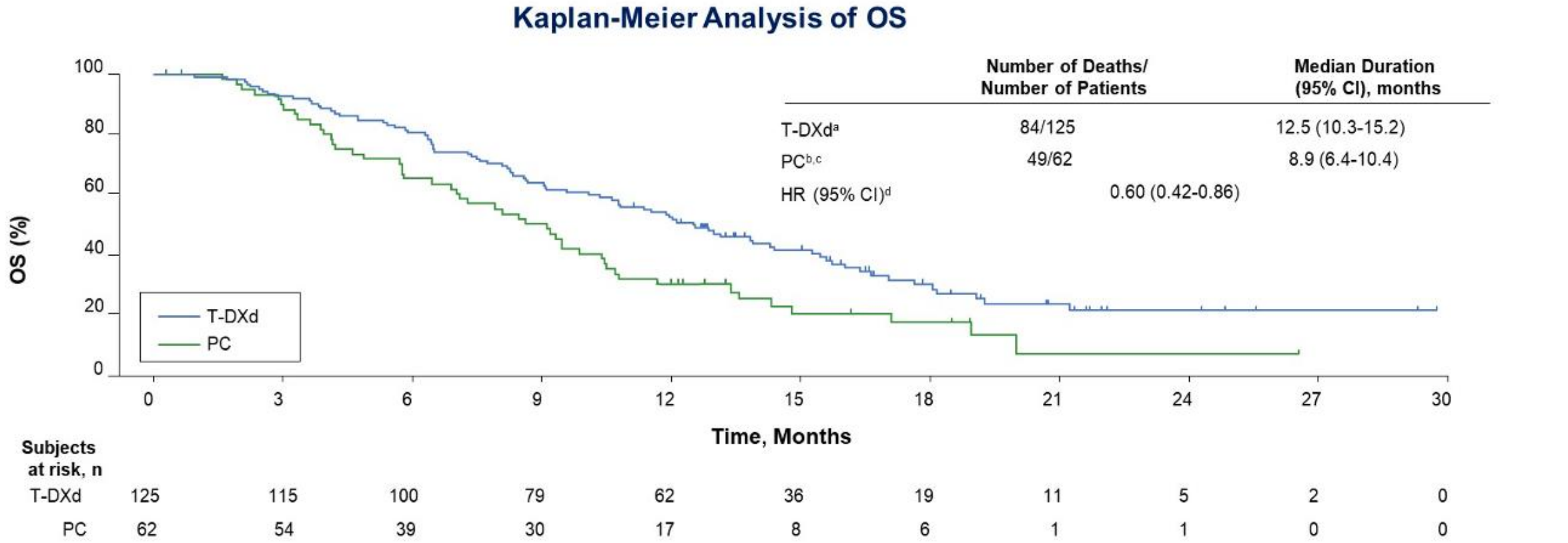


CR = complete response; PR = partial response; SD = stable disease; PD = disease progression; TTR = time to response

Yamaguchi K et al. Gastrointestinal Cancers Symposium 2022;Abstract 242.

RTP RESEARCH TO PRACTICE

DESTINY-Gastric01: Final Overall Survival (OS)



As in the primary analysis (101 OS events; 54.0% maturity), in this updated analysis (133 OS events; 71.1% maturity), T-DXd showed superior antitumor activity compared to PC

Yamaguchi K et al. Gastrointestinal Cancers Symposium 2022;Abstract 242.

DESTINY-Gastric01: Select Adverse Events

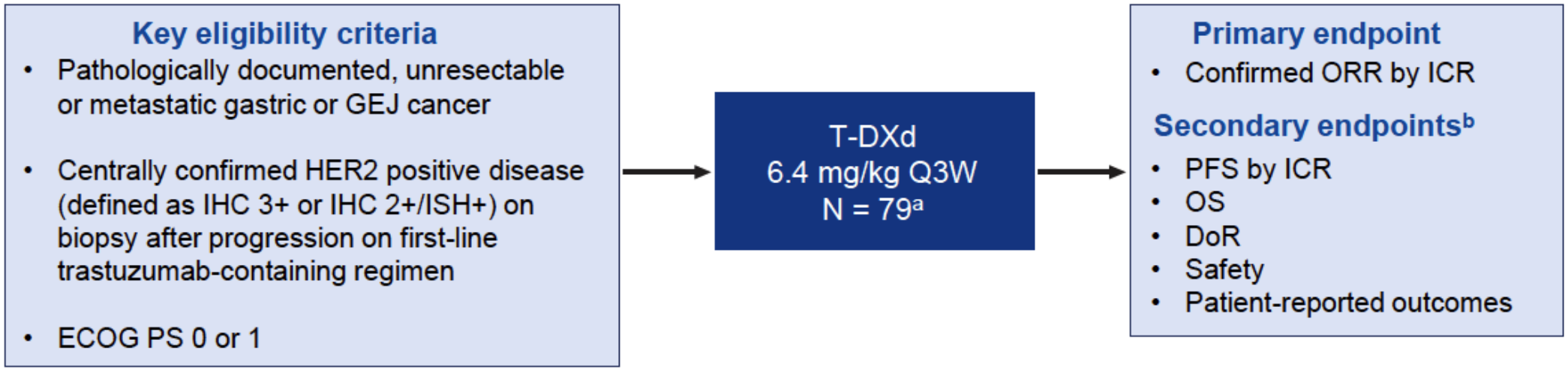
Adverse Event	T-DXd (n = 125)		PC Overall (n = 62)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutrophil count decreased	65%	51%	36%	24%
Nausea	63%	6%	47%	2%
Decreased appetite	61%	17%	45%	13%
Anemia	58%	38%	31%	23%
Platelet count decreased	40%	11%	7%	3%
WBC count decreased	38%	21%	36%	11%
Lymphocyte count decreased	23%	12%	3%	2%

16 patients (13%) had T-DXd-related interstitial lung disease/pneumonitis

- 13/16 were Grade 1 or 2
- Median time to first onset: 102.5 days

Yamaguchi K et al. Gastrointestinal Cancers Symposium 2022;Abstract 242.

DESTINY-Gastric02 Phase II Study Design



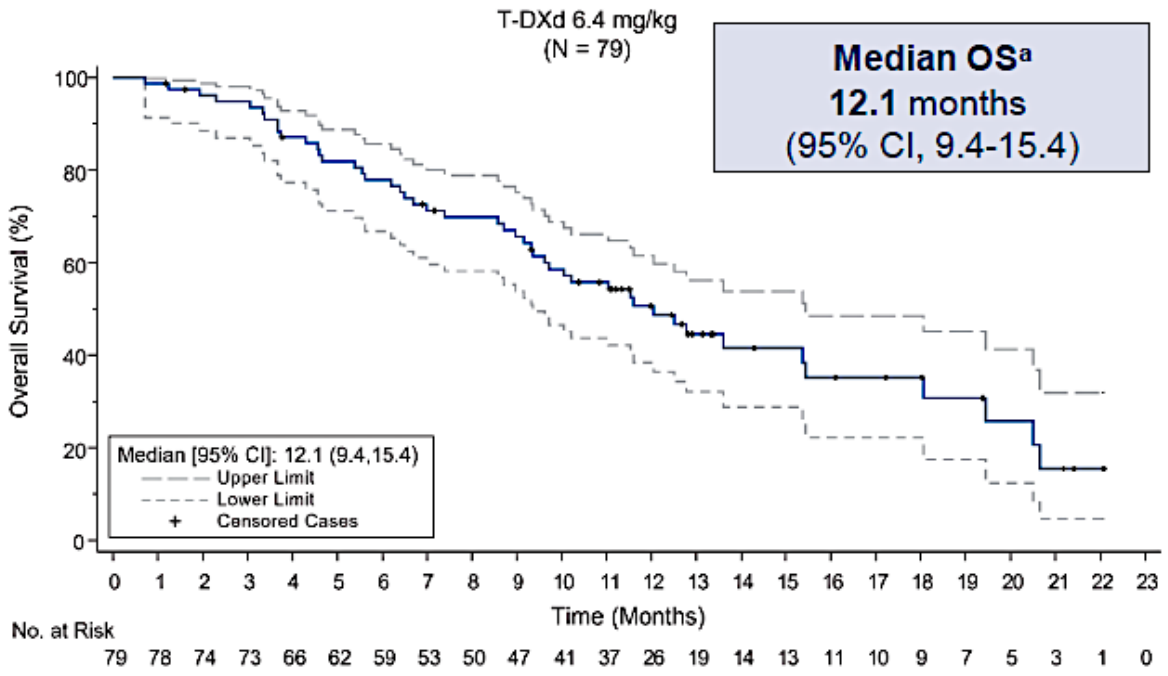
- Primary results of DESTINY-Gastric02 (data cutoff, April 9, 2021; median follow up 5.9 months) demonstrated a cORR of **38.0%** (95% CI, 27.3-49.6), and safety consistent with the established T-DXd safety profile[1]
- Here, we report OS and updated efficacy and safety results, with 7 additional months of follow-up (data cutoff, November 8, 2021)

cORR, confirmed ORR; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; Q3W, every 3 weeks.
[a]Enrollment of 80 patients was planned; actual enrollment was 79 patients. [b]Other secondary endpoints were ORR, PFS, and DoR by investigator assessment, pharmacokinetics, and anti-drug antibodies.
1. Van Cutsem E et al. *Ann Oncol*. 2021 32(suppl_5):S1283-S346.

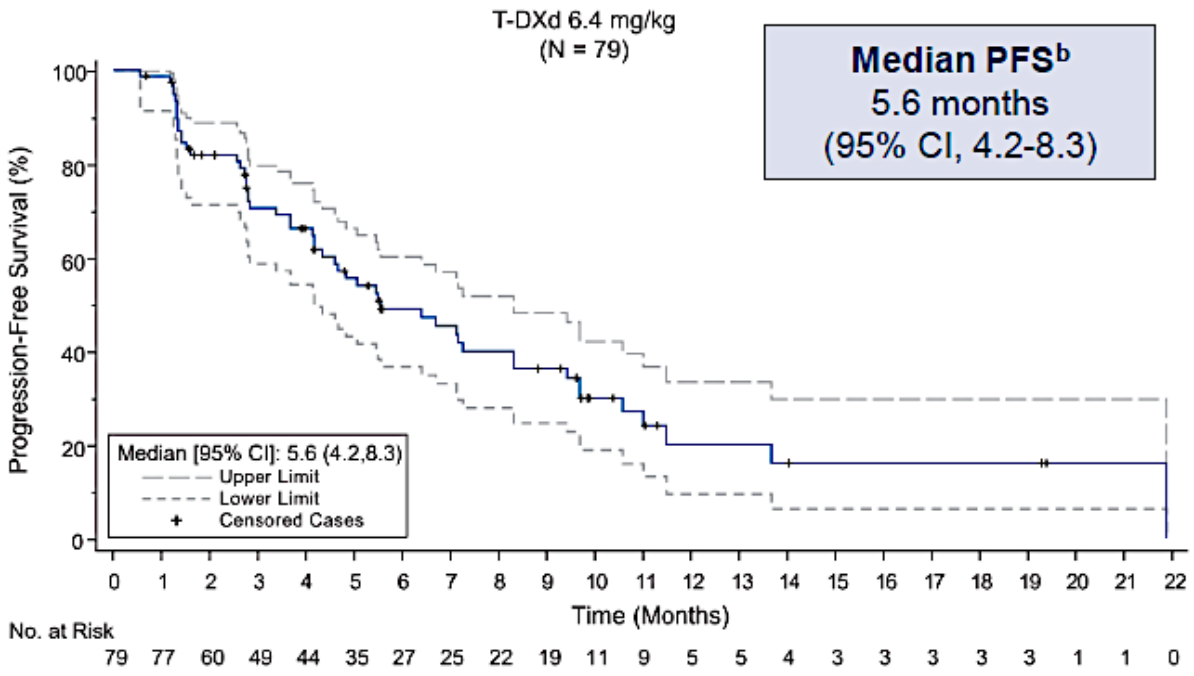
Ku GY et al. ESMO 2022;Abstract 1205MO.

DESTINY-Gastric02: OS and PFS

Kaplan-Meier Plot of OS



Kaplan-Meier Plot of PFS by ICR



Ku GY et al. ESMO 2022;Abstract 1205MO. Van Cutsem E et al. *Lancet Oncol* 2023;24:744-56.

DESTINY-Gastric02: Overall Safety Summary and ILD/Pneumonitis

% (n)	Patients (N = 79)
Any TEAE	100 (79)
Drug-related	94.9 (75)
TEAE grade ≥3	55.7 (44)
Drug-related	30.4 (24)
Serious TEAE	41.8 (33)
Drug-related	12.7 (10)
TEAE associated with study drug discontinuation	19.0 (15)
Drug-related	12.7 (10)
TEAE associated with dose reduction	21.5 (17)
Drug-related	17.7 (14)
TEAE associated with an outcome of death	13.9 (11)
Drug-related	2.5 (2)
Adjudicated drug-related ILD/pneumonitis	10.1 (8)[a]
Adjudicated drug-related ILD/pneumonitis grade 5	2.5 (2)

- Median treatment duration was 4.3 months (range, 0.7-22.1 months)
- The most common TEAEs were nausea (67.1%), vomiting (44.3%), and fatigue (41.8%)
- Grade 1 adjudicated drug-related ILD/pneumonitis occurred in 2 patients (2.5%), grade 2 in 4 patients (5.1%), and grade 5 in 2 patients (2.5%)
- Median time to onset of adjudicated drug-related ILD/pneumonitis was 80.5 days (range, 42-344 days), with a median duration of 36.0 days (range, 15-142 days)
- Of the 2 fatal ILD/pneumonitis cases, 1 occurred 171 days after drug initiation and the second after 353 days

ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.
Cutoff date: November 8, 2021.
[a]Of the 6 grade 1/2 ILD/pneumonitis cases, 3 patients had recovered or were recovering at the time of data cutoff, 1 had recovered with sequelae, 1 had not recovered, and 1 had an outcome that was unknown.

Ku GY et al. ESMO 2022;Abstract 1205MO. Van Cutsem E et al. *Lancet Oncol* 2023;24:744-56.

DESTINY-Gastric03: Phase Ib/II Study of First-Line T-DXd with Pembrolizumab and Fluoropyrimidine for HER2-Positive GEJ Cancer (Arms D and F)

Figure 1. Study design (DESTINY-Gastric03 Part 2, arms D and F only)

Patient population

- Adults ≥18 years of age
- Unresectable, locally advanced or metastatic GC, GEJA, or esophageal adenocarcinoma
- HER2+ (IHC 3+ or IHC 2+/ISH+ per local assessment)
- Treatment naïve for metastatic disease
- ECOG PS of 0 or 1

→

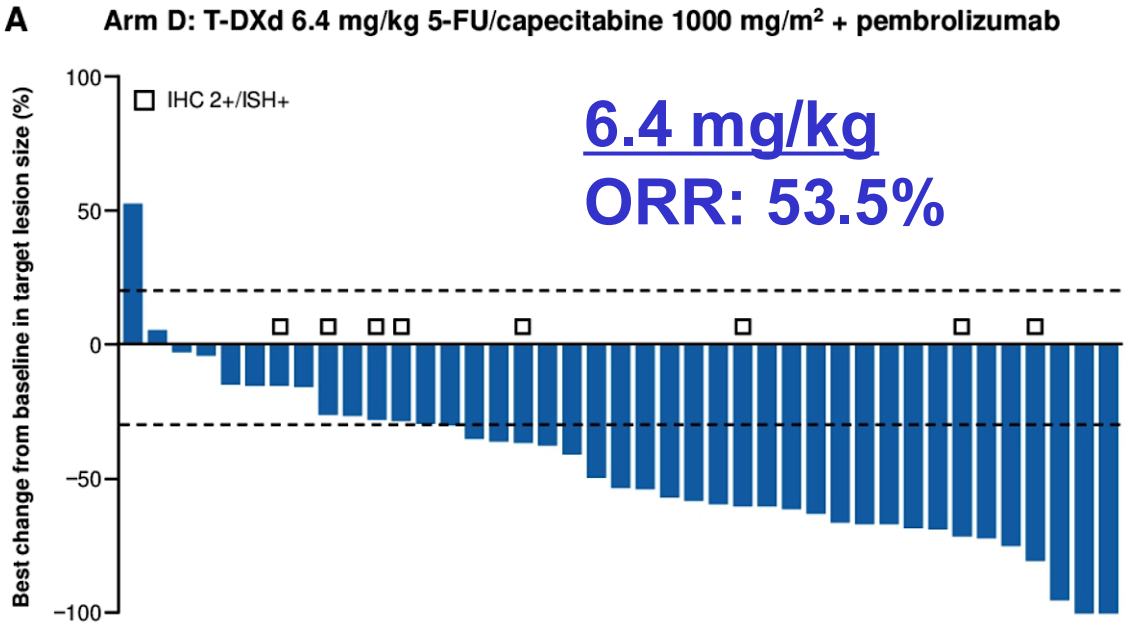
Arm D (n=43): T-DXd 6.4 mg/kg* + 5-FU 600 mg/m²†‡ or capecitabine 1000 mg/m²‡§ + pembrolizumab 200 mg*

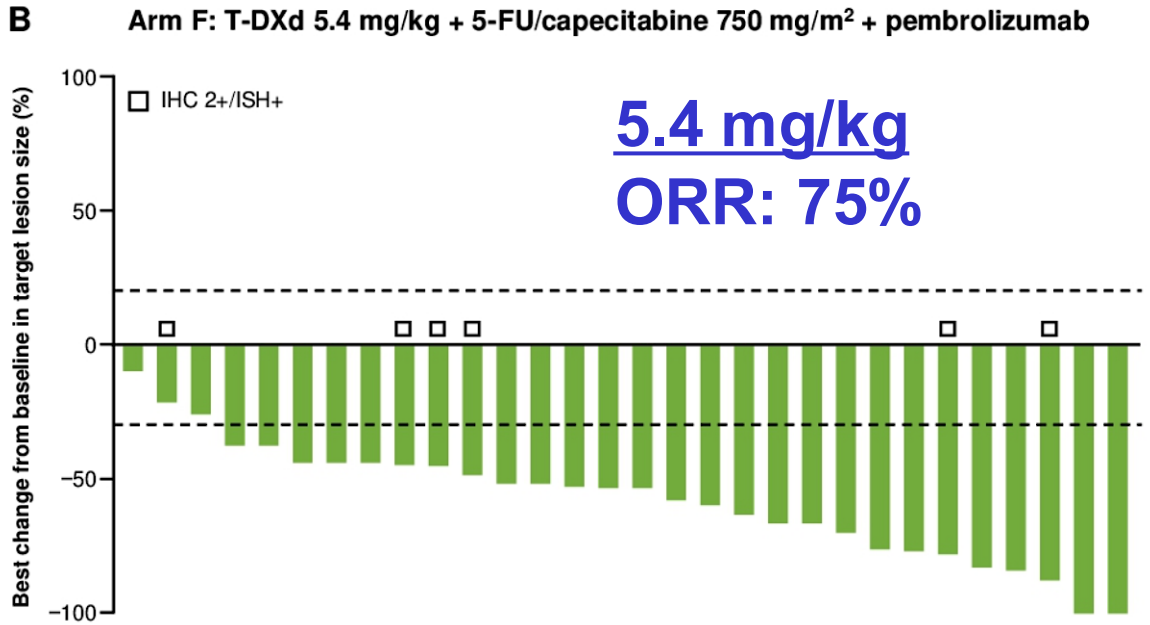
Arm F (n=32): T-DXd 5.4 mg/kg* + 5-FU 600 mg/m²†‡ or capecitabine 750 mg/m²‡§ + pembrolizumab 200 mg*

GC = gastric cancer; GEJA = gastroesophageal junction adenocarcinoma; 5-FU = 5-fluorouracil

Janjigian Y et al. Gastrointestinal Cancers Symposium 2025;Abstract 448.

DESTINY-Gastric03: Phase Ib/II Study of First-Line T-DXd with Pembrolizumab and Fluoropyrimidine for HER2-Positive GEJ Cancer (Arms D and F) – Response

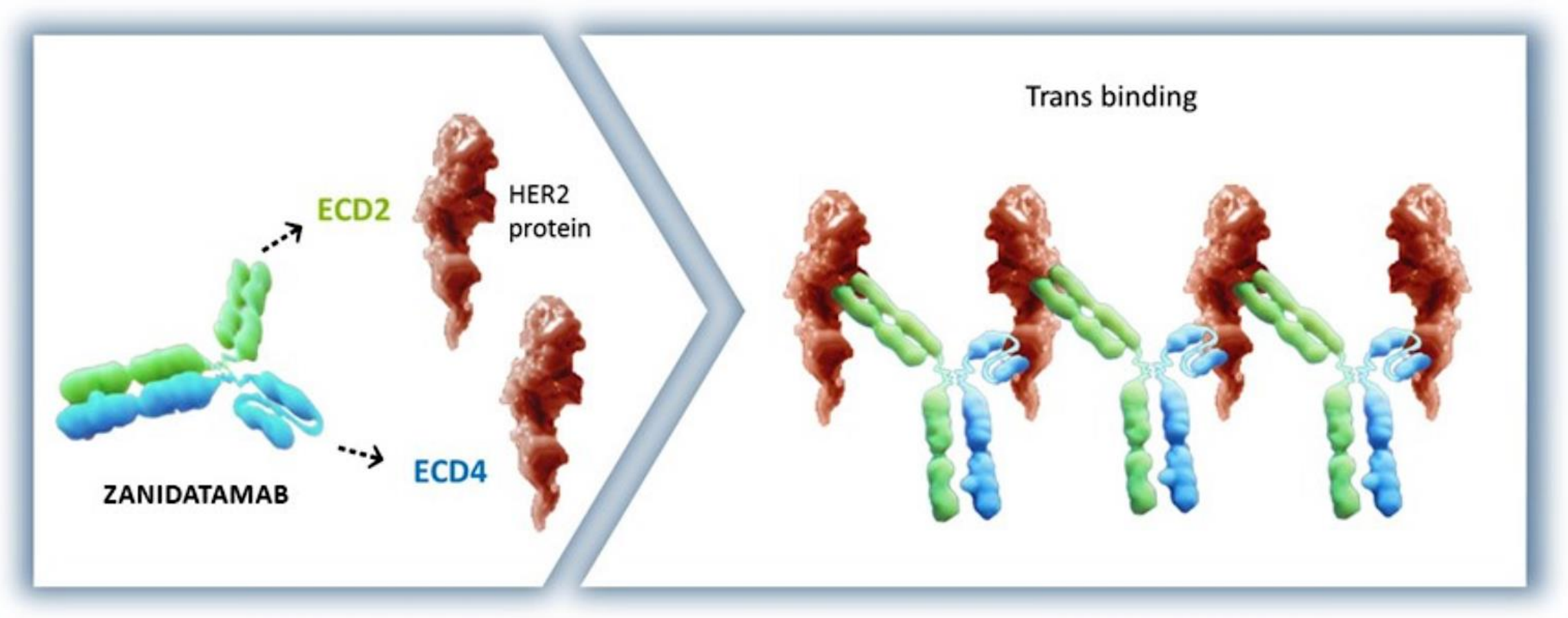




- At similar periods of follow up, the confirmed ORR by investigator assessment was 53.5% in the T-DXd 6.4 mg/kg triplet combination arm (**Figure 2A**) and 75.0% in the 5.4 mg/kg triplet combination arm (**Figure 2B**)
  - In the T-DXd 6.4 mg/kg triplet combination arm, the ORR (n/N) was 55.9% (19/34) in patients with IHC 3+ and 44.4% (4/9) in patients with IHC 2+/ISH+
  - In the T-DXd 5.4 mg/kg triplet combination arm, the ORR (n/N) was 73.1% (19/26) in patients with IHC 3+ and 83.3% (5/6) in patients with IHC 2+/ISH+

Janjigian Y et al. Gastrointestinal Cancers Symposium 2025;Abstract 448.

Zanidatamab: Mechanism of Action



Pant S et al. ASCO 2023;Abstract 4008.

Zanidatamab Clinical Development Across Multiple Tumor Types

Author/Unique Protocol Id; Phase; Trial No	Drugs	Zanidatamab Dose	Tumors Included	Number of Patients	Investigations
Harding et al. (HERIZON-BTC-01); phase IIb; NCT04466891 [44]	Zanidatamab	20 mg/kg IV every 2 weeks	locally advanced or metastatic, HER2+ve BTC (IHCh, ECC and GBC)	87	IHC
Lumish et al.; phase II; NCT04513665 [50]	Zanidatamab	20 mg/kg IV every 2 weeks	recurrent or persistent HER2+ve endometrial carcinoma and carcinosarcoma	16	IHC, FISH
Lee et al.; Phase 1b/2; NCT04276493 [48]	Zanidatamab + chemotherapy / Zanidatamab + chemotherapy + Tislelizumab	Cohort A: 30 mg/kg IV, Cohort B: 1800 mg IV (weight < 70 kg) or 2400 mg IV (weight ≥ 70 kg)	unresectable, locally advanced, recurrent, or metastatic HER2+ve Breast Cancer or Gastric cancer or GEJA	71	IHC, FISH
ZWI-ZW25-202, phase II; NCT04224272 [46]	Zanidatamab + Palbociclib + Fulvestrant	NR	unresectable, locally advanced, or metastatic disease HER2+ve breast cancer	51	NR

Kanwal W et al. *BMC Cancer* 2025;25(1):382.

Zanidatamab Ongoing Studies

Author/Unique Protocol Id; Phase; Trial No	Drugs	Zanidatamab Dose	Tumors Included	Number of Patients
Meric-Bernstam et al.; phase I; NCT02892123 [49]	Zanidatamab + chemotherapy	5 mg/kg to 30 mg/kg every 1, 2, or 3 weeks	locally advanced or metastatic, unresectable HER2 + ve tumors, received all available approved therapies, BTC, colorectal cancer, breast cancer, ovarian cancer, GEA, NSCLC	132
Tabernero et al.; phase III; NCT05152147 [51]	Zanidatamab + chemotherapy / trastuzumab + chemotherapy / Zanidatamab + chemotherapy + tislelizumab	1,800 mg (patients < 70 kg at baseline) or 2,400 mg (patients ≥ 70 kg at baseline), intravenously on day 1 of each cycle	locally advanced or metastatic, unresectable, nonresponsive to chemoradiationHER2 + ve GEA (gastroesophageal functional tumor, gastric neoplasms, and esophageal adenocarcinoma)	714
Elimova et al.; phase II; NCT06043427 [52]	Zanidatamab + Paclitaxel and Ramucirumab	assigned at enrollment	metastatic or unresectable HER2 + ve GEA (stomach, gastroesophageal junction, or esophagus)	168
Garfin et al.; phase II; NCT03929666 [53]	Zanidatamab + chemotherapy	NR	locally advanced, recurrent, or metastatic, unresectable HER2 + ve GEA, BTC (ICC, ECC, and GBC), and colorectal cancer	74
JZP598-303; phase III; NCT06435429 [54]	Zanidatamab + chemotherapy	NR	unresectable or metastatic, HER2 + ve breast cancer	550
JZP598-302; phase III; NCT06282575 [55]	Zanidatamab + Cisplatin ± PD-1/L1 inhibitor	NR	Locally advanced unresectable or metastatic HER2 + ve BTC (ICC, ECC, and GBC)	286
RHA et al.; phase II; NCT05270889 [56]	Zanidatamab and tislelizumab	1800 mg IV (weight < 70 kg) or 2400 mg IV (weight ≥ 70 kg)	advanced HER2 + ve gastric cancer or GEJA after first-line treatment	50

Kanwal W et al. *BMC Cancer* 2025;25(1):382.

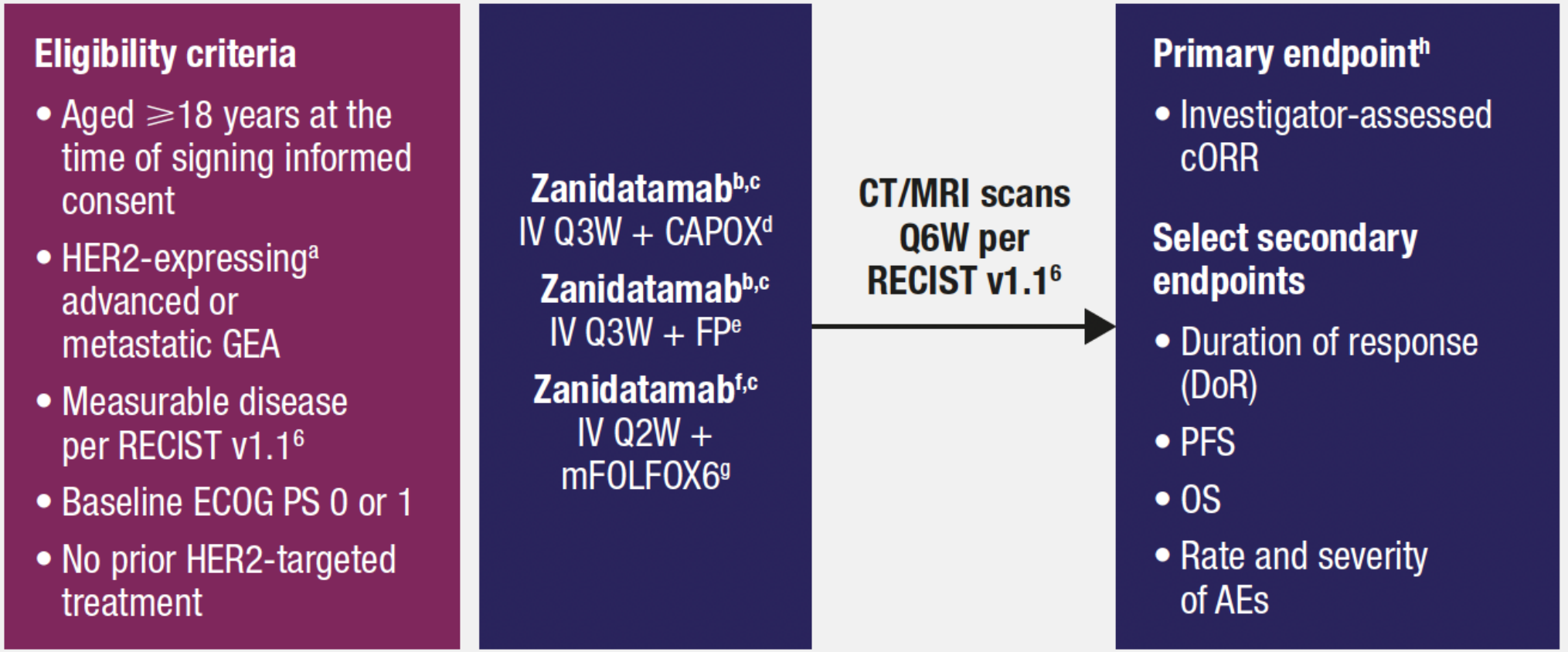
Zanidatamab Ongoing Studies (Continued)

Author/Unique Protocol Id; Phase; Trial No	Drugs	Zanidatamab Dose	Tumors Included	Number of Patients
Hurvitz et al.; phase 1b/2; NCT05027139 [57]	Zanidatamab + Evorpacept	not provided	unresectable, locally advanced, or metastatic HER2 + ve breast, HER2 + ve breast cancer and HER2 overexpressing breast cancer cancer	52
Valero et al.; phase II; NCT05035836 [58]	Zanidatamab	every 2 weeks (± 3 days) for up to 6 doses	early stage, low-risk HER2 + ve breast cancer	20
Pohlmann et al.; phase I; NCT05868226 [59]	Zanidatamab + Tucatinib	NR	Metastatic HER2 + ve Breast Cancer	54
David et al.; phase III; NCT05615818 [60]	Zanidatamab + Futibatinib + Ivosidenib + Trastuzumab + Neratinib + Encorafenib + Binimetinib + Niraparib	1800 mg IV (weight < 70 kg) or 2400 mg IV (weight ≥ 70 kg)	De novo or recurrent, locally advanced unresectable or metastatic intrahepatic, HER2 + ve perihilar or distal cholangiocarcinoma, or GBC (ampullary carcinoma excluded)	800
BGB-A317-290-LTE1; phase III; NCT04164199 [48]	Zanidatamab or Tislelizumab or Pamiparib or Sitravatinib or BGB-15025 and others	NR	advanced malignancies	300

Kanwal W et al. *BMC Cancer* 2025;25(1):382.

Phase II Study of First-Line Zanidatamab and Chemotherapy for HER2-Positive Advanced GEJ Cancers

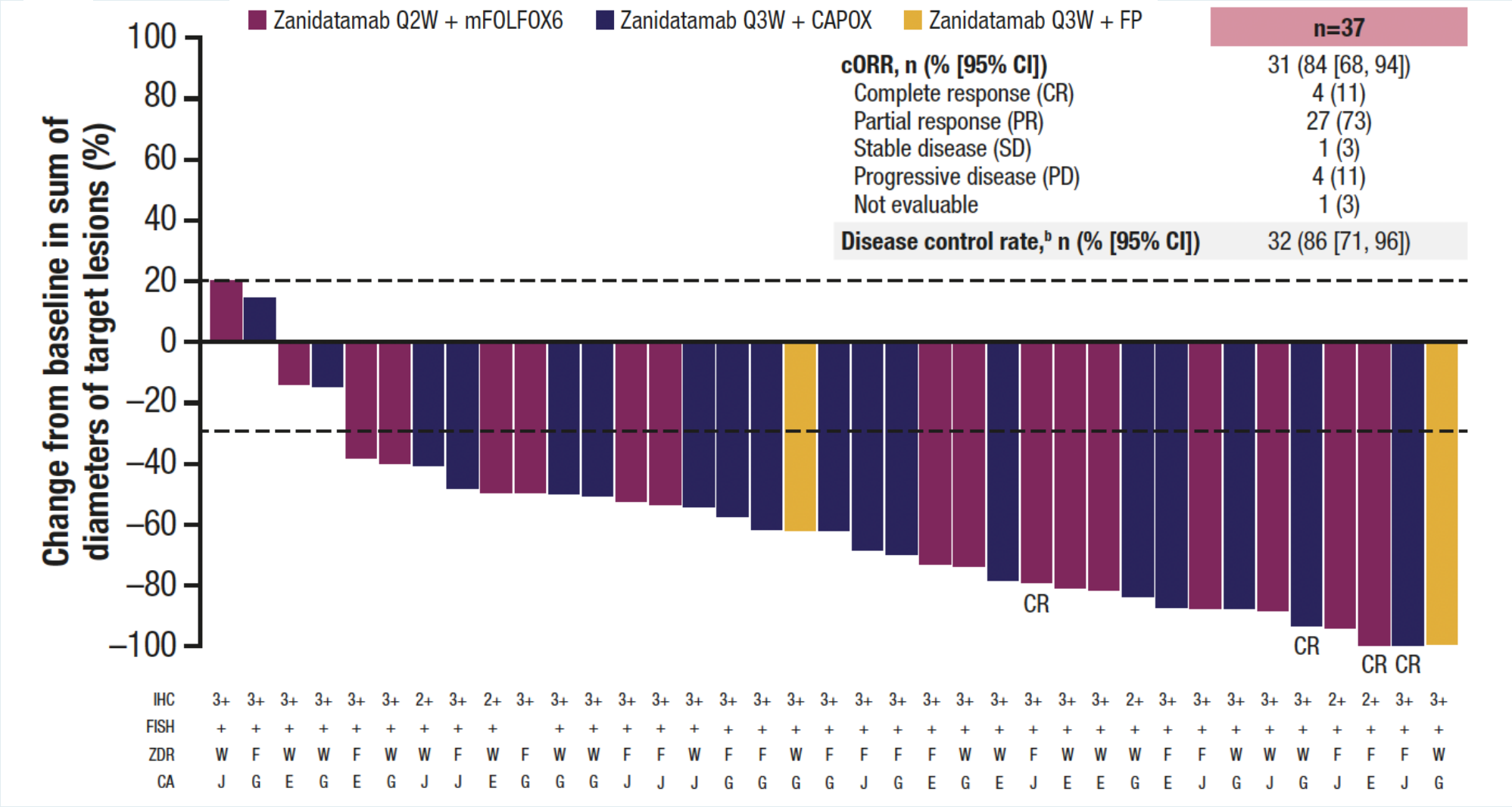
Figure 1. Study Design for the GEA Cohort



GEA = gastroesophageal adenocarcinoma

Elimova E et al. ESMO 2024;Abstract 3212.

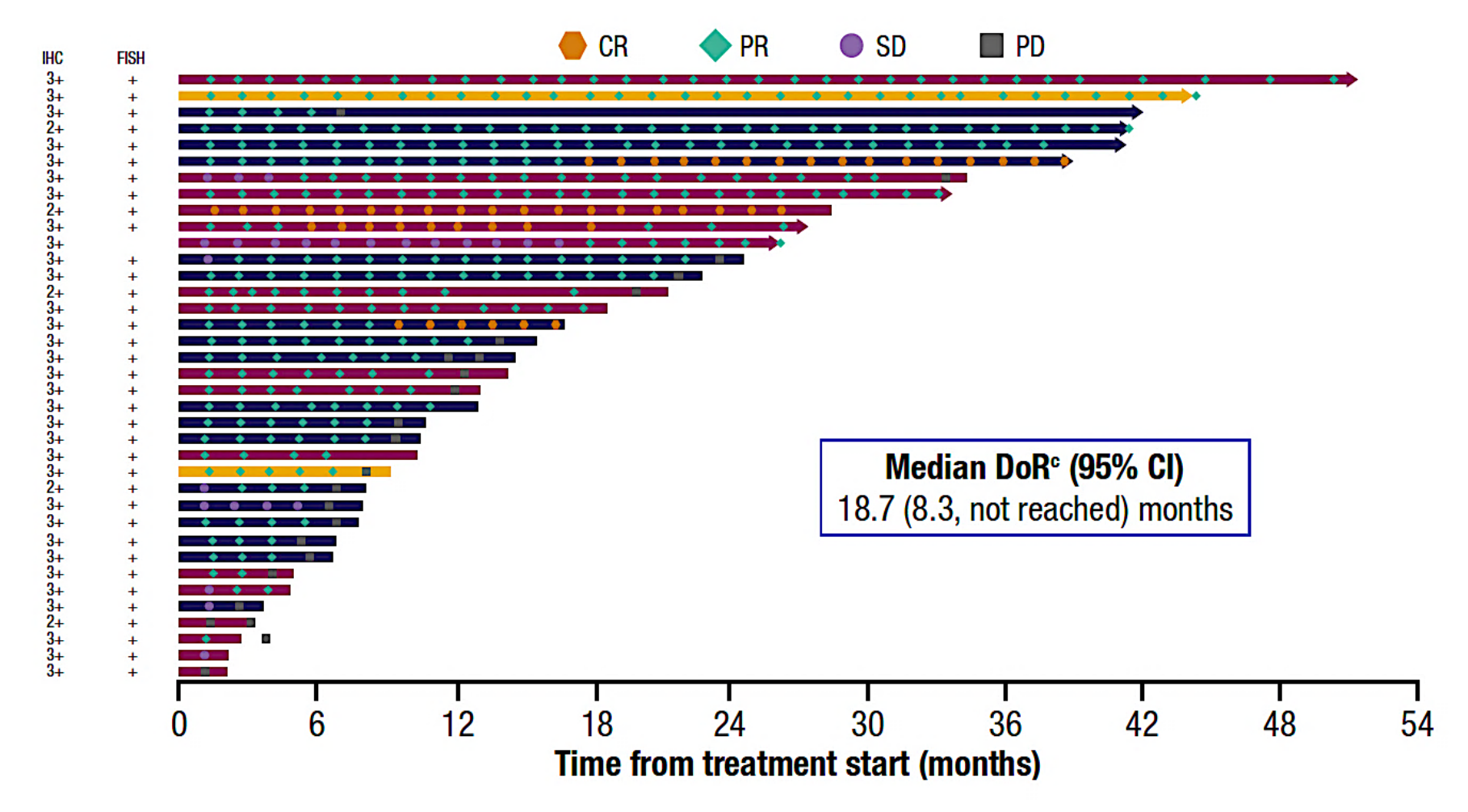
Phase II Study of First-Line Zanidatamab and Chemotherapy for HER2-Positive Advanced GEJ Cancers – ORR



	n=37
cORR, n (% [95% CI])	31 (84 [68, 94])
Complete response (CR)	4 (11)
Partial response (PR)	27 (73)
Stable disease (SD)	1 (3)
Progressive disease (PD)	4 (11)
Not evaluable	1 (3)
Disease control rate,[b] n (% [95% CI])	32 (86 [71, 96])

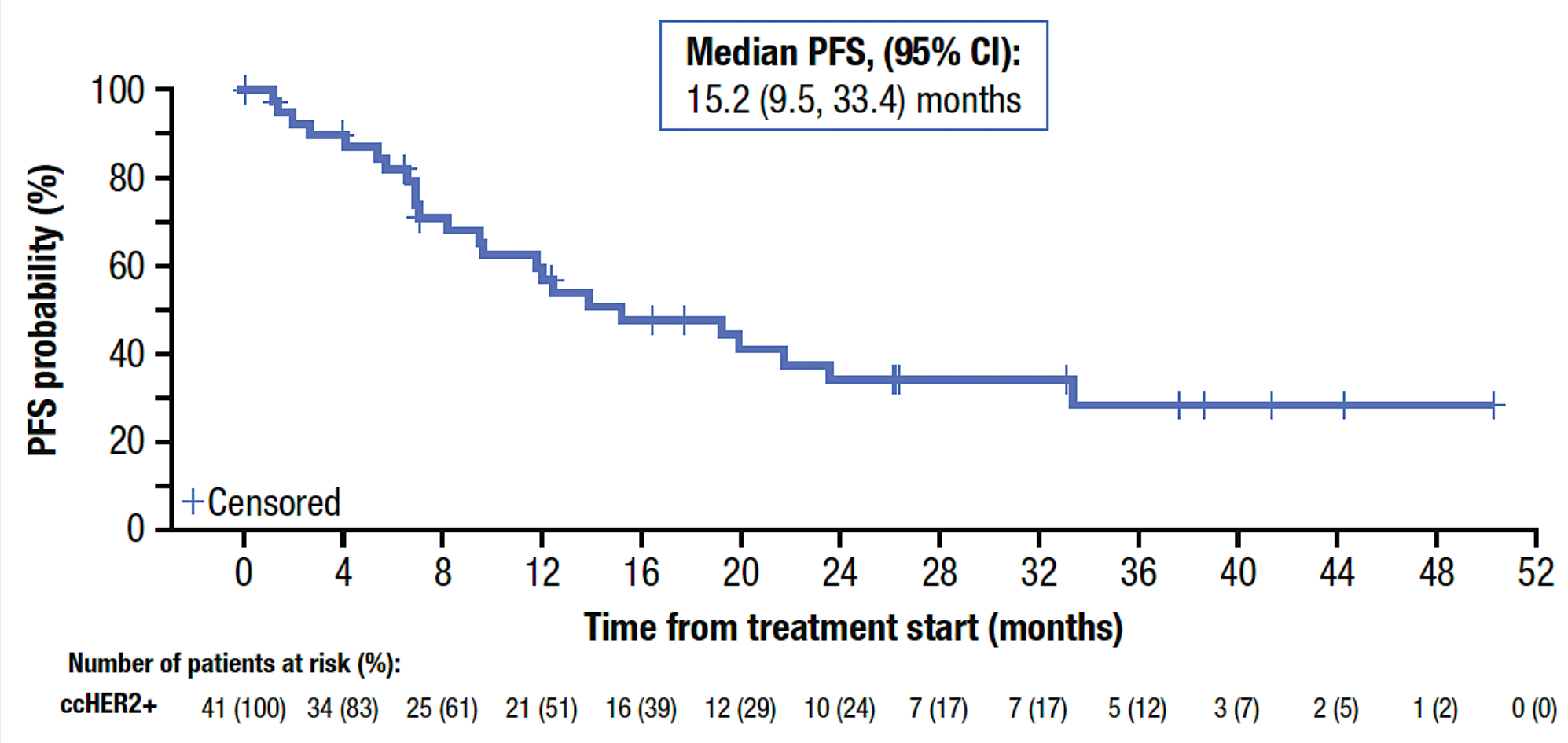
Elimova E et al. ESMO 2024;Abstract 3212.

Phase II Study of First-Line Zanidatamab and Chemotherapy for HER2-Positive Advanced GEJ Cancers – DoR



Elimova E et al. ESMO 2024;Abstract 3212.

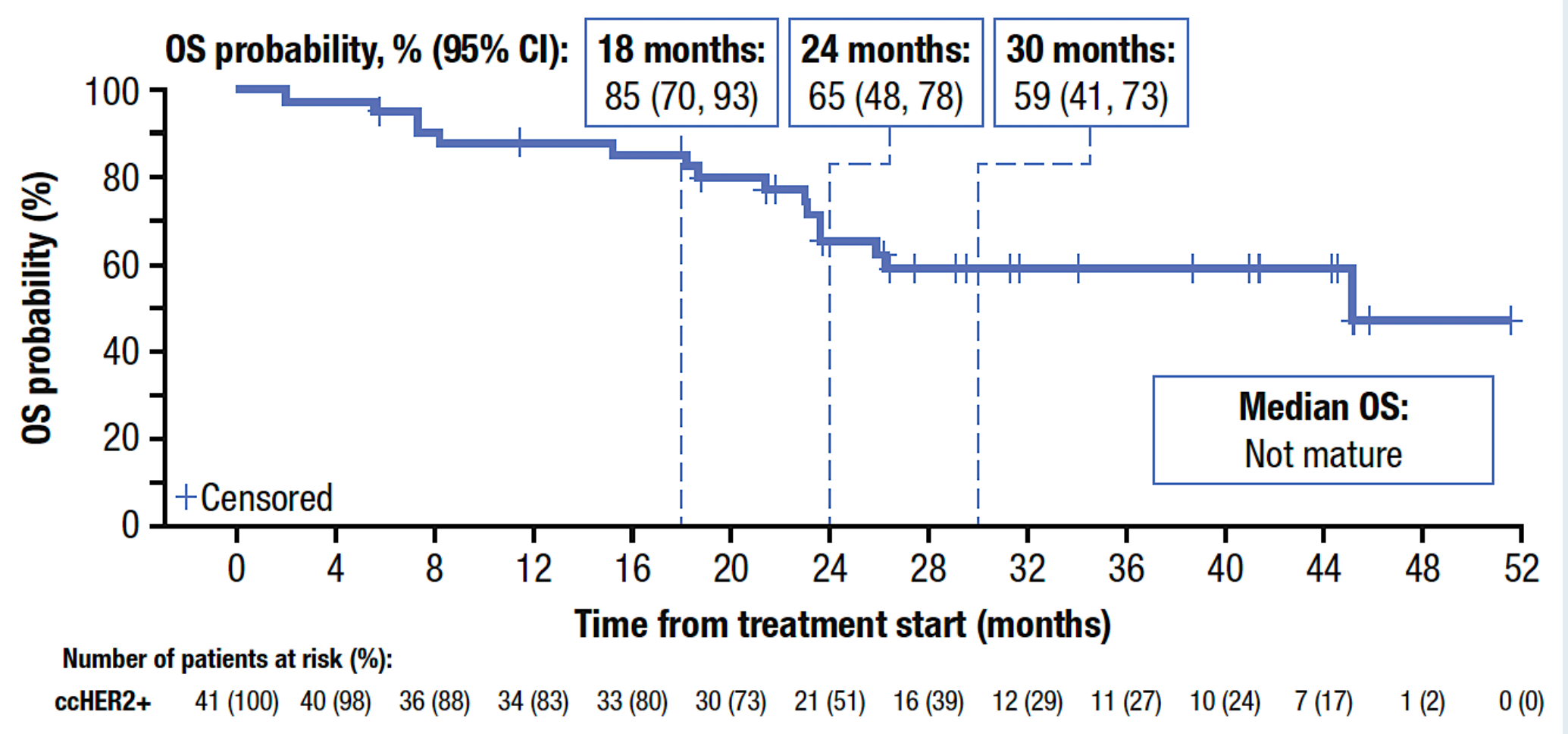
Phase II Study of First-Line Zanidatamab and Chemotherapy for HER2-Positive Advanced GEJ Cancers – PFS



ccHER2+ = centrally confirmed HER2-positive

Elimova E et al. ESMO 2024;Abstract 3212.

Phase II Study of First-Line Zanidatamab and Chemotherapy for HER2-Positive Advanced GEJ Cancers – OS



Elimova E et al. ESMO 2024;Abstract 3212.

Phase II Study of First-Line Zanidatamab and Chemotherapy – Safety

	Total (N=46)
Any-grade TRAE,[a] n (%)	46 (100)
Grades 1-2	17 (37)
Grades 3-4	29 (63)
Grade 5	0 (0)
Serious TRAE,[a] n (%)	8 (17)
TRAEs leading to zanidatamab discontinuation, n (%)	2 (4)[c]

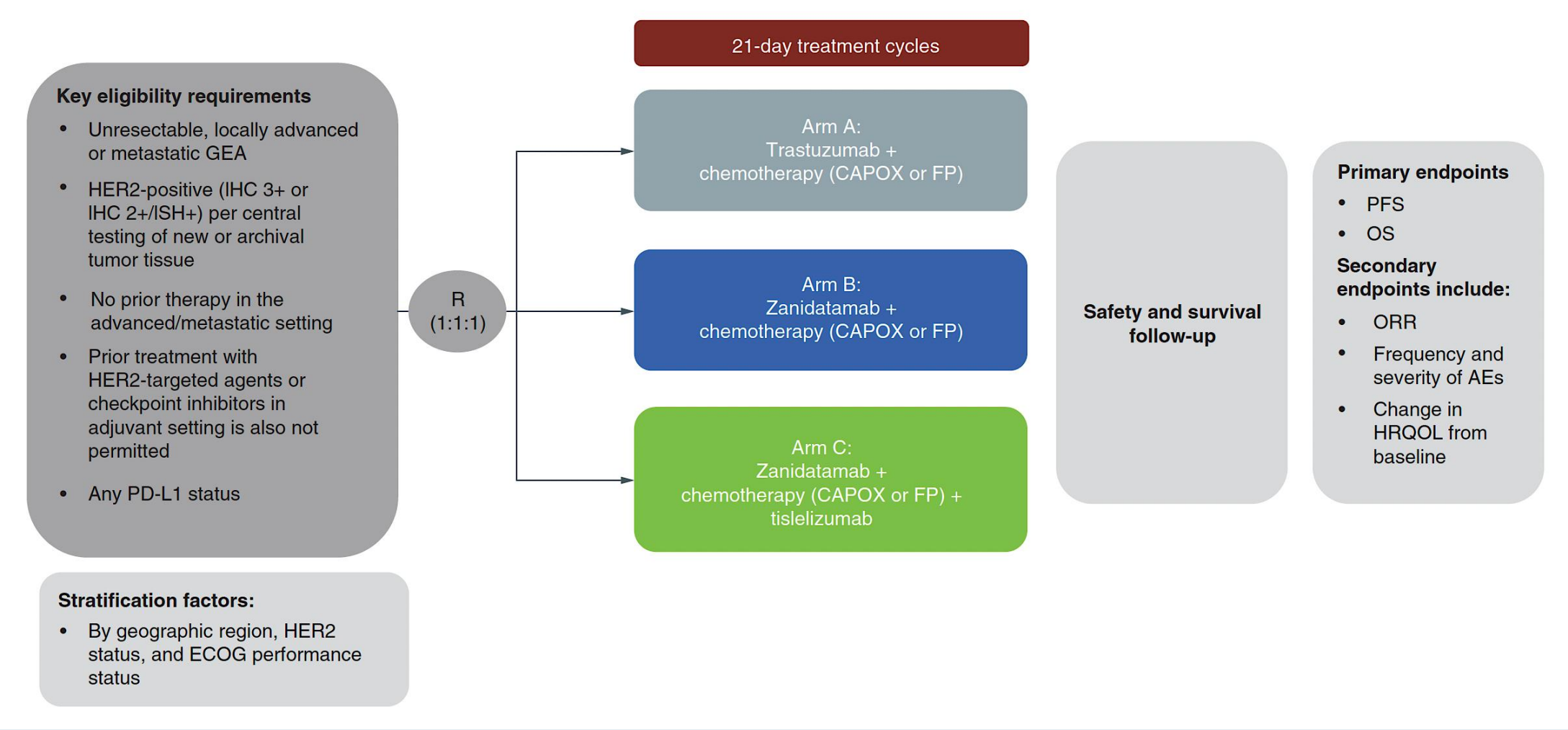
	All grades	Grade ⩾3
Most common TRAEs,[a,b] n (%)		
Diarrhoea[d]	43 (93)	16 (35)[d]
Nausea	37 (80)	3 (7)
Peripheral neuropathy	30 (65)	0 (0)
Fatigue	23 (50)	2 (4)
Decreased appetite	21 (46)	0 (0)
Vomiting	16 (35)	3 (7)
Hypokalaemia	14 (30)	10 (22)
Stomatitis	13 (28)	0 (0)
Anaemia	10 (22)	0 (0)
Dysgeusia	10 (22)	0 (0)
IRR	10 (22)	0 (0)
Decreased neutrophil count	10 (22)	2 (4)
PPE	10 (22)	1 (2)
Hypomagnesaemia	9 (20)	1 (2)
Decreased white blood cell count	7 (15)	2 (4)
Acute kidney injury	3 (7)	2 (4)
Treatment-related AESI occurring		
IRR	10 (22)	0 (0)
Ejection fraction decreased	2 (4)	0 (0)
Pneumonitis	0 (0)	0 (0)

TRAE = treatment-related adverse event;
IRR = infusion-related reaction;
AESI = adverse event of special interest

Elimova E et al. ESMO 2024;Abstract 3212.

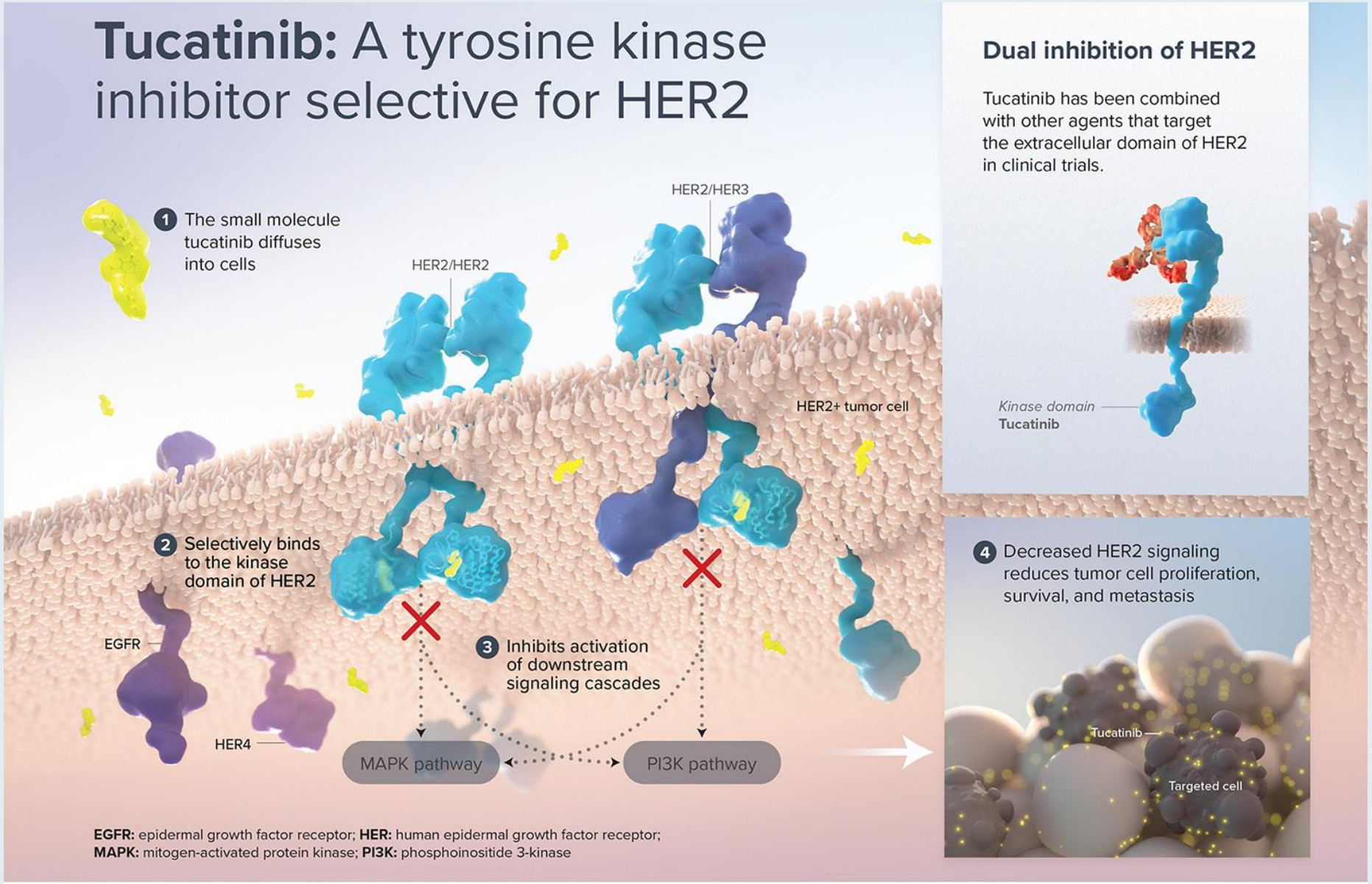
RTP RESEARCH TO PRACTICE

HERIZON-GEA-01: Phase III Study of Zanidatamab with Chemotherapy with or without Tislelizumab for First-Line Treatment of HER2-Positive GEJ Cancer



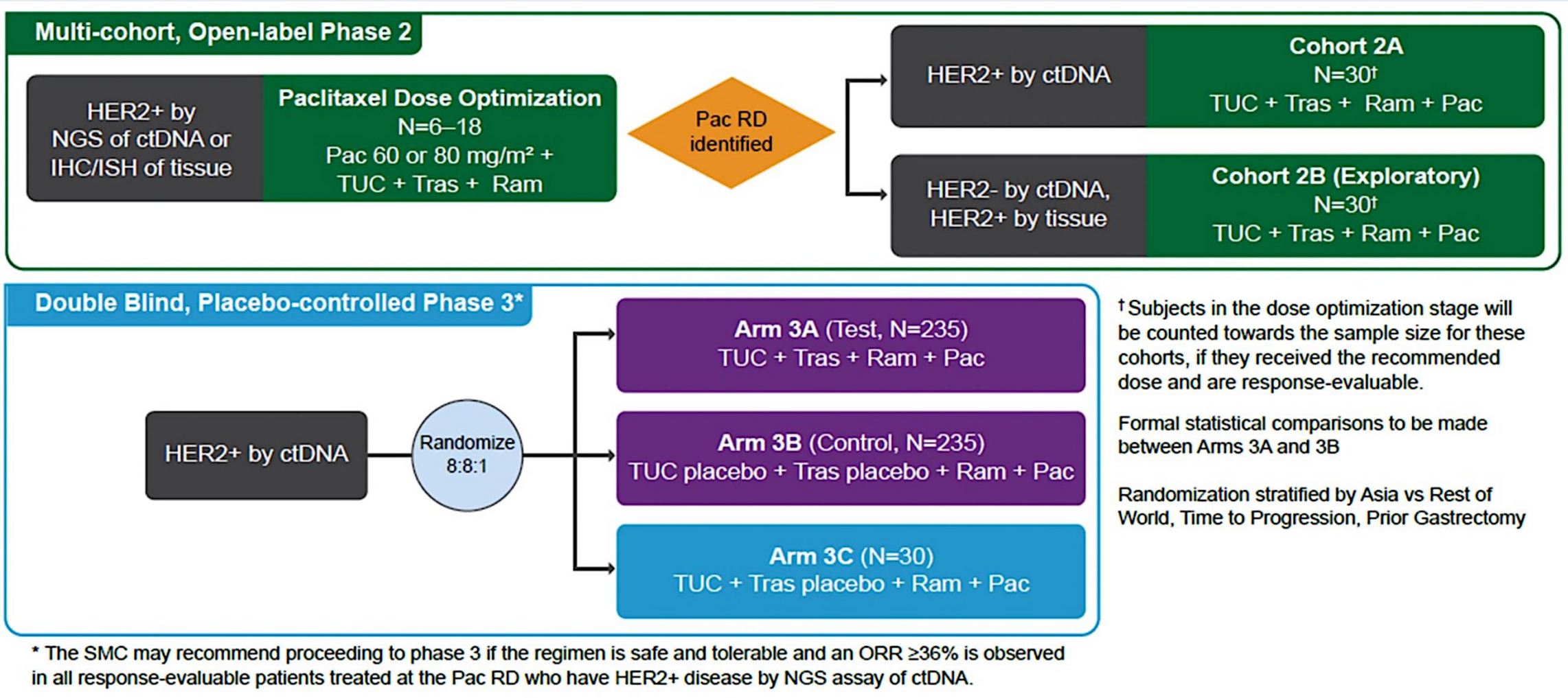
Tabernero J et al. *Future Oncol* 2022;18(29):3255-66.

Tucatinib Proposed Mechanism of Action



Catenacci DV et al. ESMO 2021;Abstract 1434TiP.

MOUNTAINEER-02: A Phase II/III Study of Second-Line Tucatinib, Trastuzumab, Ramucirumab, and Paclitaxel for HER2-Positive Gastroesophageal Cancers



ctDNA = circulating tumor DNA

Catenacci D et al. Gastrointestinal Cancers Symposium 2022;Abstract TPS371.

Agenda

Introduction: ASCO Preview

Module 1: HER2-Positive Gastroesophageal Cancers

Module 2: Immunotherapy in HER2-Negative Advanced Gastroesophageal Cancers

Module 3: Immunotherapy in Microsatellite Instability-High Gastroesophageal Cancers

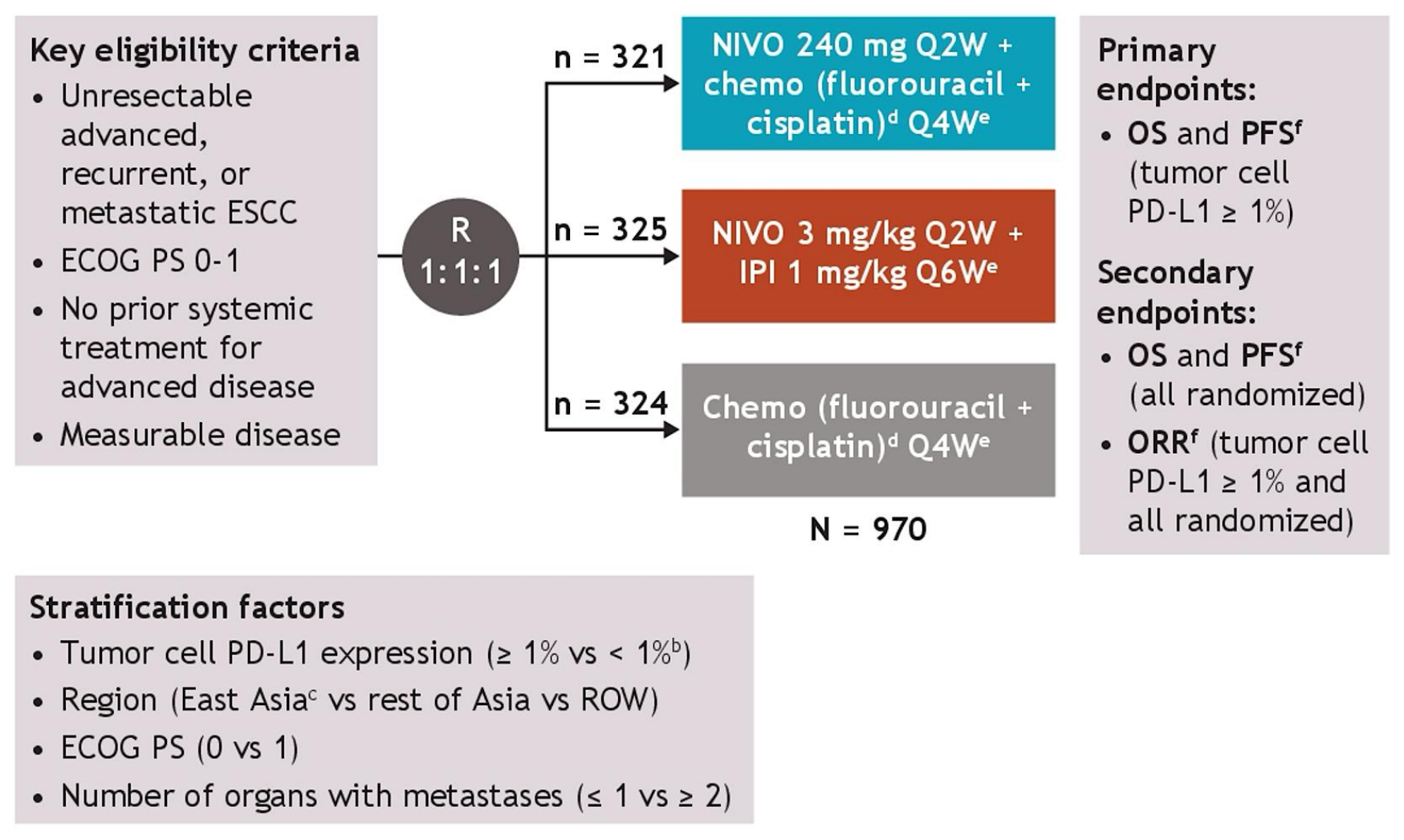
Module 4: CLDN18.2-Positive Advanced Gastroesophageal Cancers

Case Presentation: 75-year-old man with HER2-negative metastatic esophageal adenocarcinoma (PD-L1 5%) receives mFOLFOX/nivolumab followed by nivolumab maintenance with CR for 3.5 years

Dr Victoria Giffi (Hagerstown, Maryland)

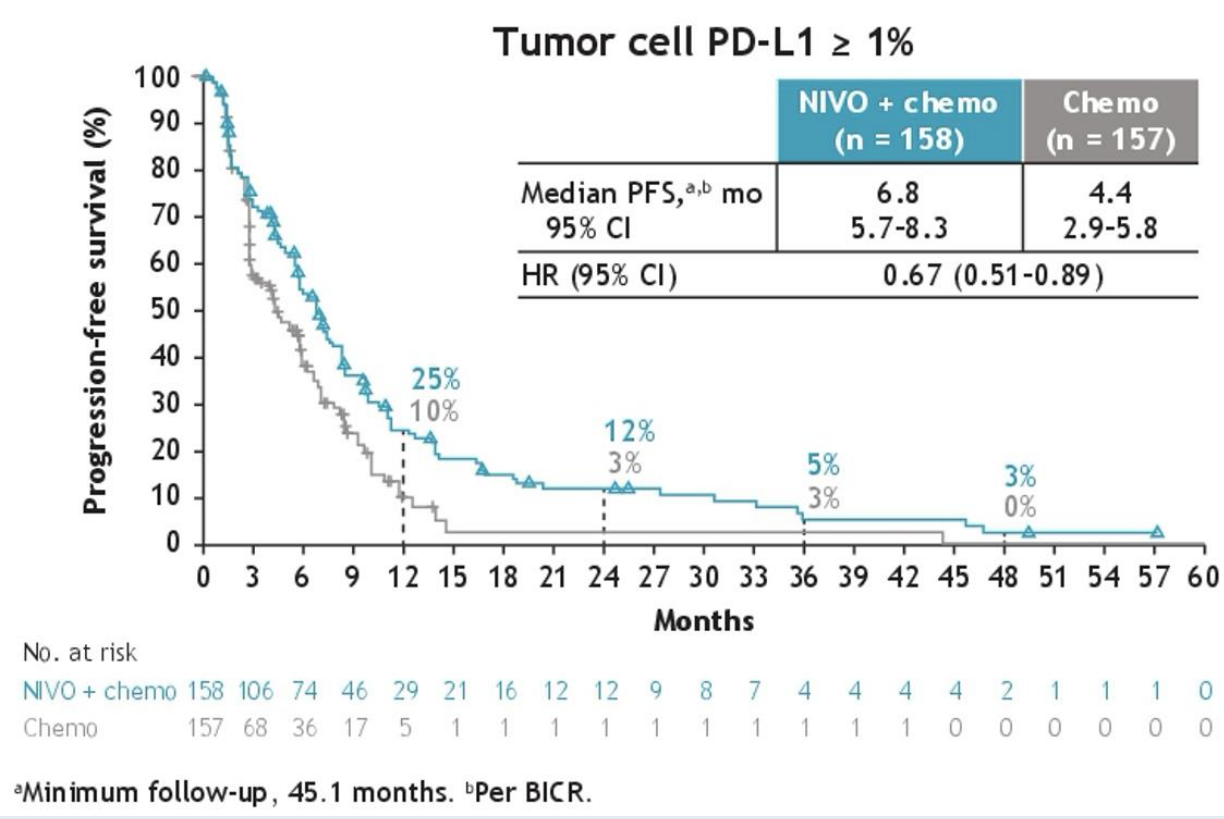
RTP RESEARCH TO PRACTICE

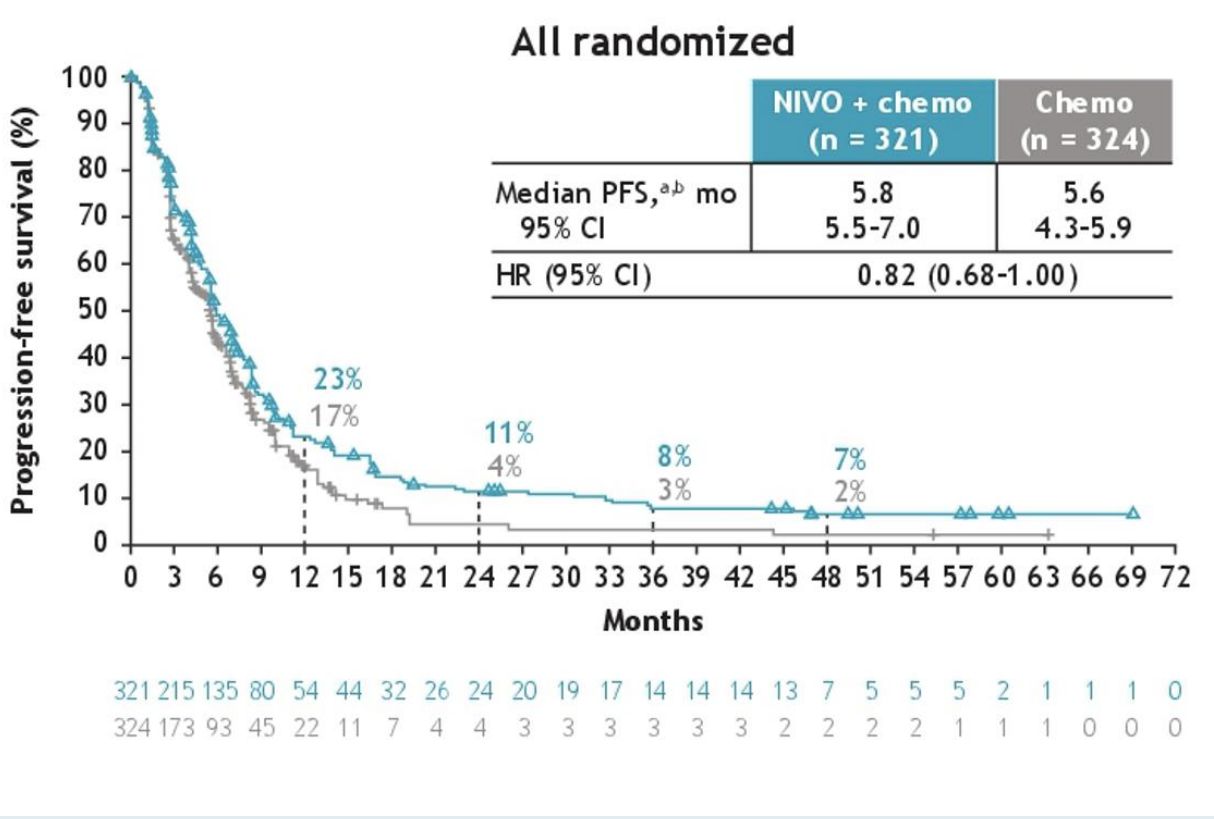
CheckMate 648: Phase III Study of First-Line Nivolumab/ Chemotherapy or Nivolumab/Ipilimumab for Esophageal Squamous Cell Carcinoma (ESCC)



Chau I et al. ASCO 2024;Abstract 4034.

CheckMate 648: Phase III Study of First-Line Nivolumab and Chemotherapy for ESCC – PFS

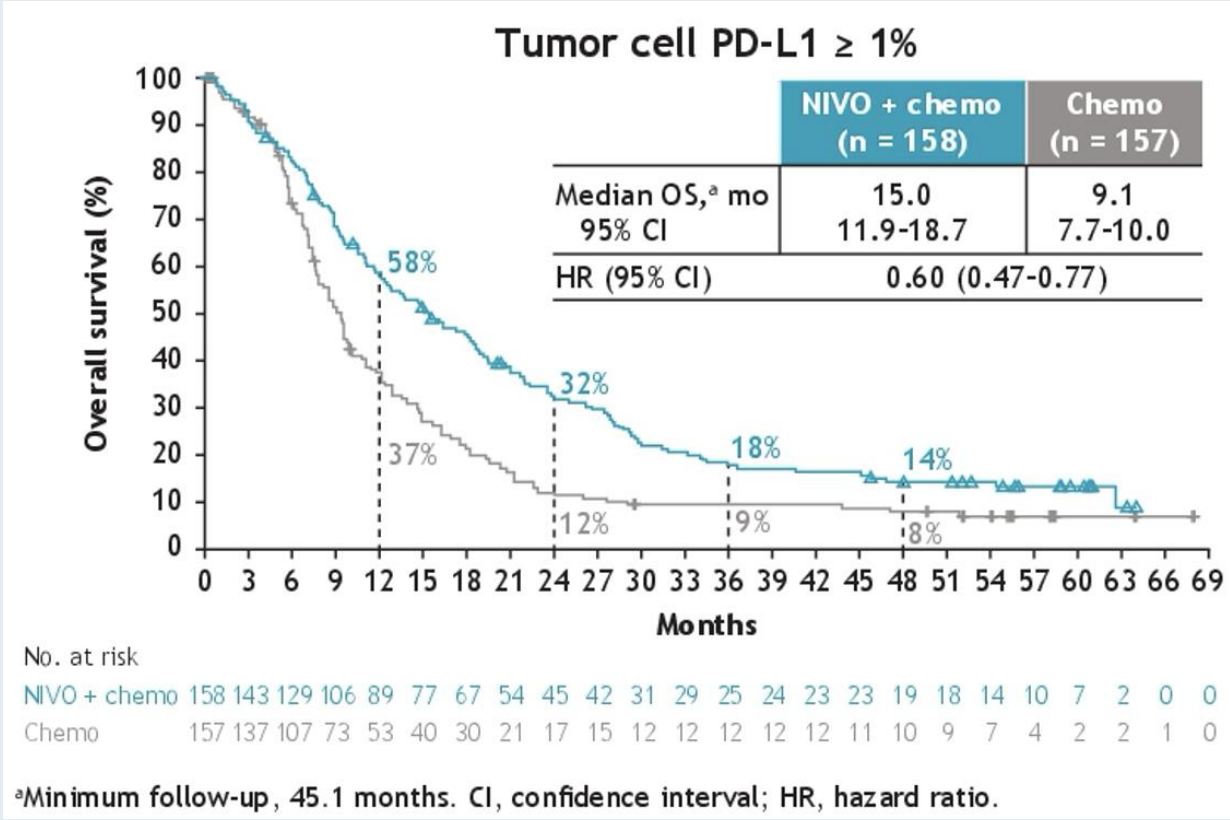


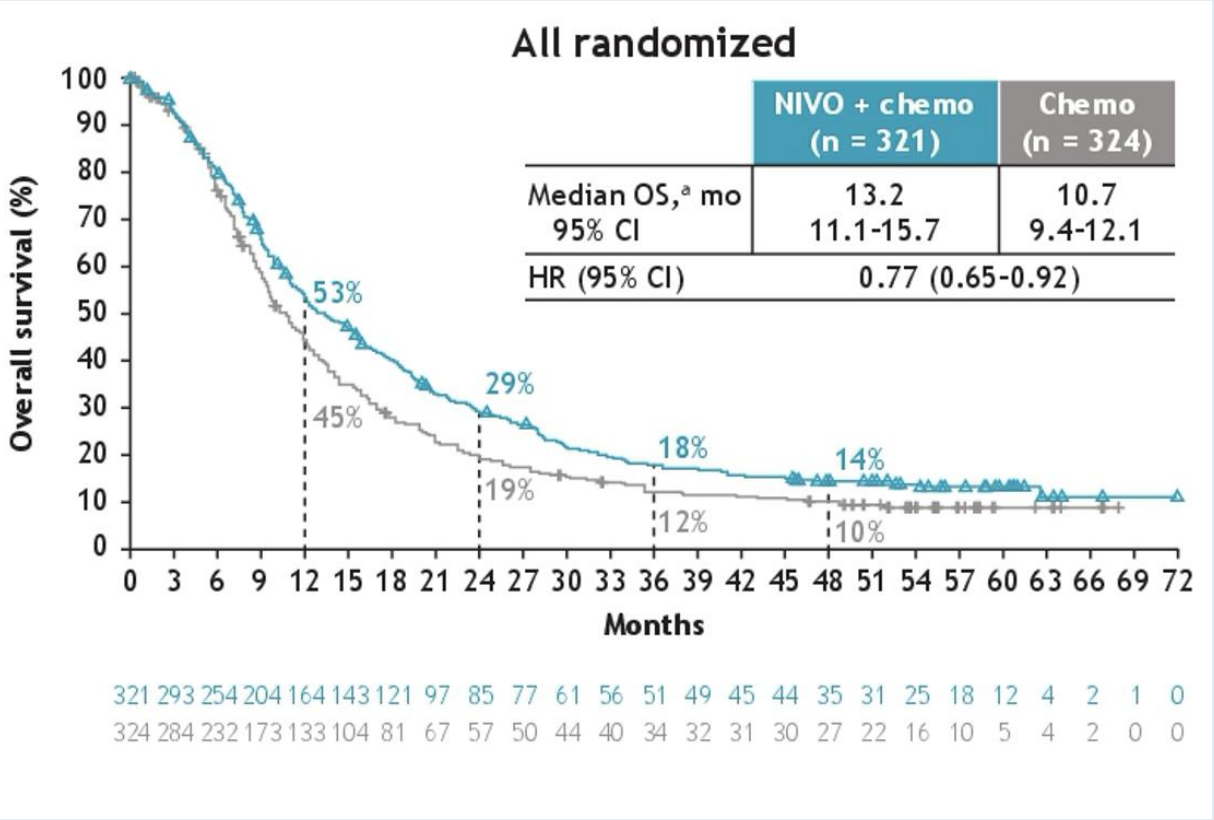


[a]Minimum follow-up, 45.1 months. [b]Per BICR.

Chau I et al. ASCO 2024;Abstract 4034.

CheckMate 648: Phase III Study of First-Line Nivolumab and Chemotherapy for ESCC – OS

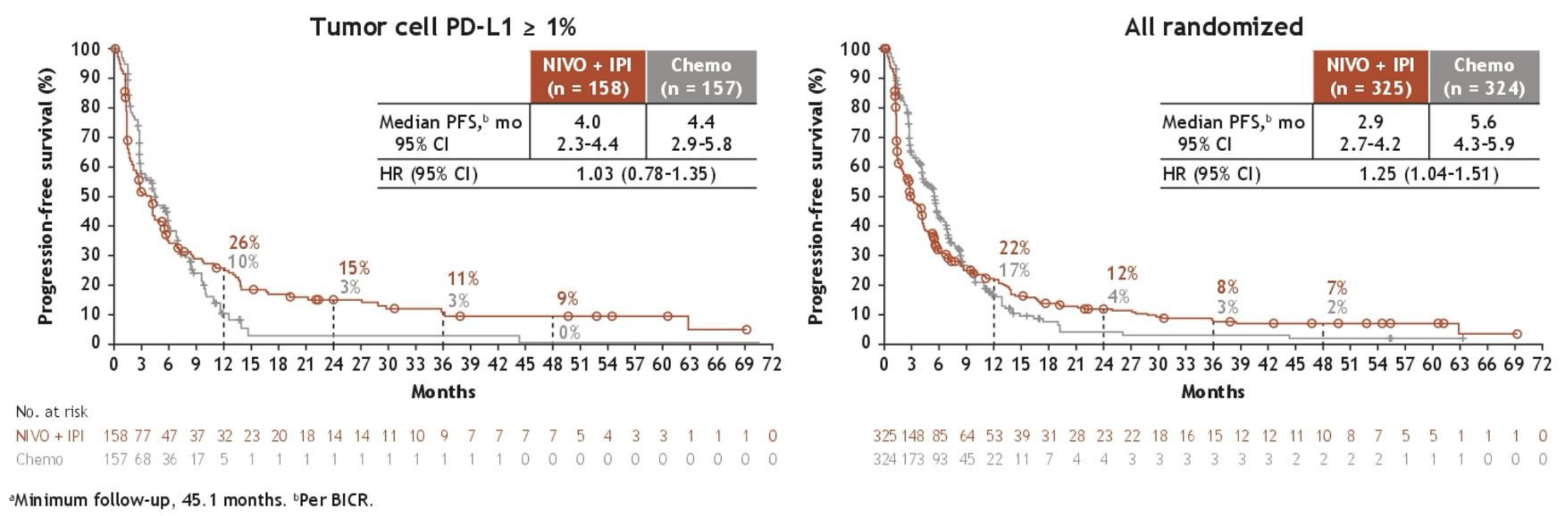




[a]Minimum follow-up, 45.1 months. CI, confidence interval; HR, hazard ratio.

Chau I et al. ASCO 2024;Abstract 4034.

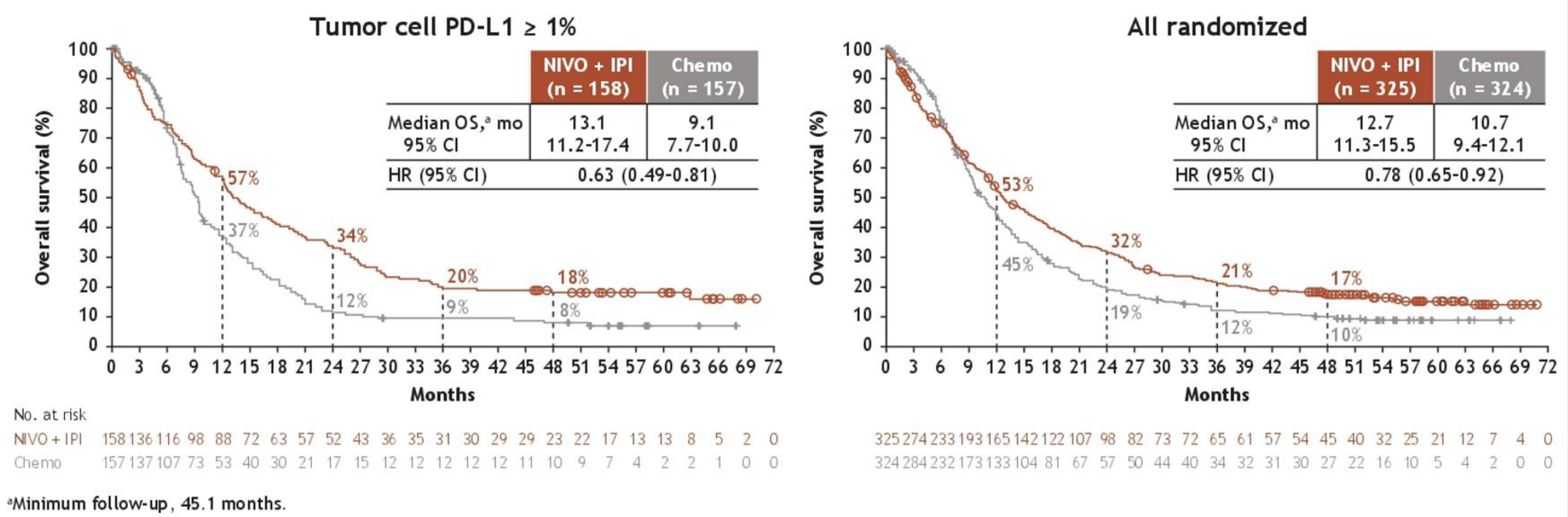
CheckMate 648: Phase III Study of First-Line Nivolumab and Ipilimumab for ESCC – PFS



[a]Minimum follow-up, 45.1 months. [b]Per BICR.

Chau I et al. ASCO 2024;Abstract 4034.

CheckMate 648: Phase III Study of First-Line Nivolumab and Ipilimumab for ESCC – OS



[a]Minimum follow-up, 45.1 months.

Chau I et al. ASCO 2024;Abstract 4034.

CheckMate 648: Phase III Study of First-Line Nivolumab/ Chemotherapy or Nivolumab/Ipilimumab for ESCC – Overall Safety

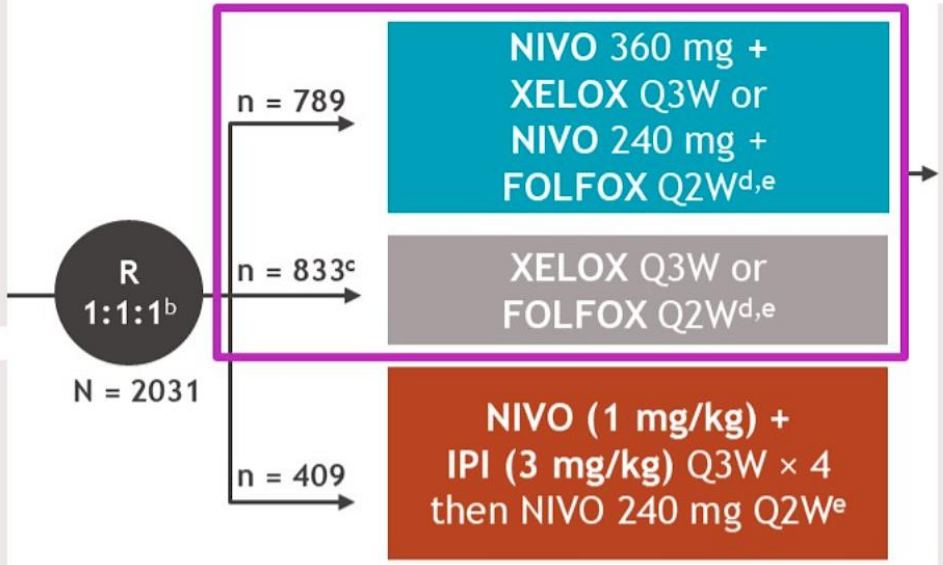
All treated,[a] n (%)	NIVO + chemo (n = 310)		NIVO + IPI (n = 322)		Chemo (n = 304)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TRAEs[b]	297 (96)	151 (49)	256 (80)	105 (33)	275 (90)	111 (37)
Serious TRAEs[b]	74 (24)	58 (19)	105 (33)	75 (23)	49 (16)	41 (13)
TRAEs leading to discontinuation[b,c]	107 (35)	30 (10)	60 (19)	44 (14)	63 (21)	18 (6)
Treatment-related deaths[d]	5 (2)[e]		7 (2)[f]		5 (2)[g]	

Chau I et al. ASCO 2024;Abstract 4034.

CheckMate 649: Phase III Study of First-Line Nivolumab and Chemotherapy for Gastroesophageal Adenocarcinomas

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic GC/GEJC/EAC
- No known HER2-positive status
- ECOG PS 0-1

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[a])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



Dual primary endpoints:
- **OS** and **PFS**[f] (PD-L1 CPS ≥ 5)

Secondary endpoints:
- **OS** (PD-L1 CPS ≥ 1, all randomized)
- **OS** (PD-L1 CPS ≥ 10)
- **PFS**[f] (PD-L1 CPS ≥ 10, ≥ 1, all randomized)
- **ORR**[f]

Exploratory endpoints:
- **Safety**
- **Quality of life**

- At data cutoff (May 28, 2024), the minimum follow-up (time from concurrent randomization of the last patient to clinical data cutoff) was 60.1 months
- No patients in the NIVO + chemo or chemo arms were receiving ongoing study treatment at data cutoff

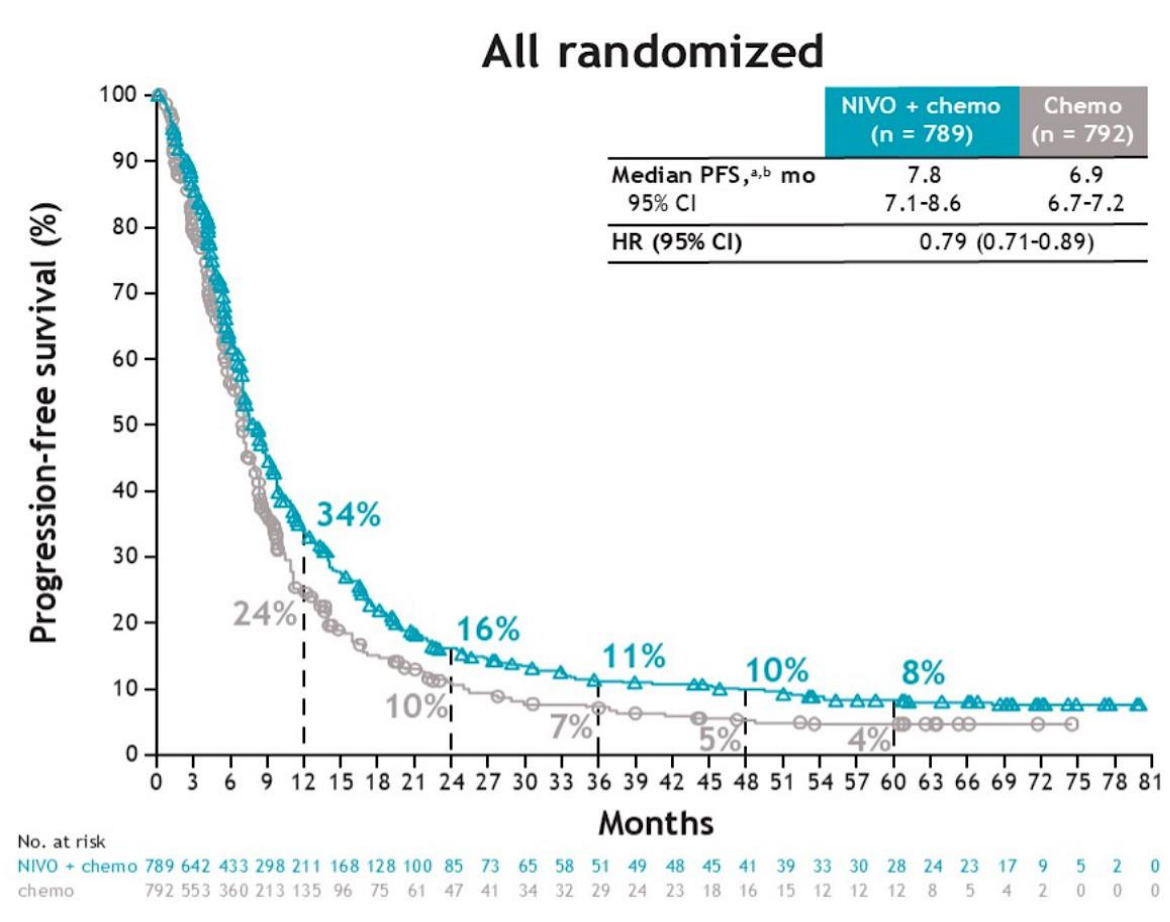
Janjigian Y et al. Gastrointestinal Cancers Symposium 2025;Abstract 398.

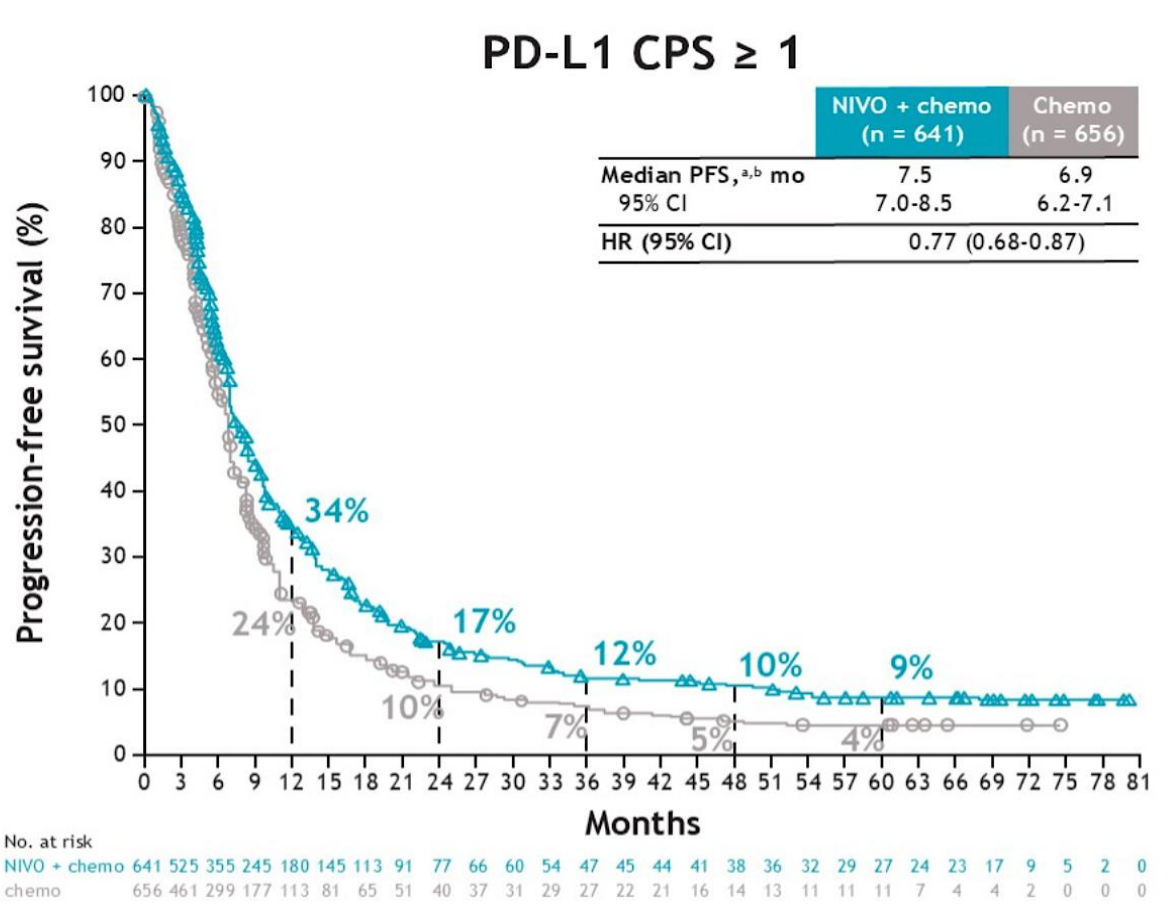
CheckMate 649: Phase III Study of First-Line Nivolumab and Chemotherapy for Gastroesophageal Adenocarcinomas – Response

Response per BICR	All randomized[a]		PD-L1 CPS ≥ 1[b]		PD-L1 CPS ≥ 5[c]		PD-L1 CPS ≥ 10[d]	
	NIVO + chemo (n = 603)[e]	Chemo (n = 609)[e]	NIVO + chemo (n = 503)[e]	Chemo (n = 515)[e]	NIVO + chemo (n = 379)[e]	Chemo (n = 391)[e]	NIVO + chemo (n = 301)[e]	Chemo (n = 319)[e]
ORR (95% CI),[b] %	58 (54-62)	46 (42-50)	60 (55-64)	46 (42-51)	60 (55-65)	45 (40-50)	59 (53-65)	45 (39-50)
CR	11	7	12	7	13	8	12	8
PR	47	39	48	40	47	37	47	37
SD	28	33	27	32	28	34	28	33
PD	7	10	7	11	7	11	6	12
Median DOR (95% CI),[f] mo	8.5 (7.7-9.9)	7.0 (6.0-7.6)	8.6 (7.9-10.5)	6.9 (5.8-7.6)	9.6 (8.3-12.4)	7.0 (5.7-8.0)	9.9 (8.4-12.7)	7.1 (5.7-8.4)

Janjigian Y et al. Gastrointestinal Cancers Symposium 2025;Abstract 398.

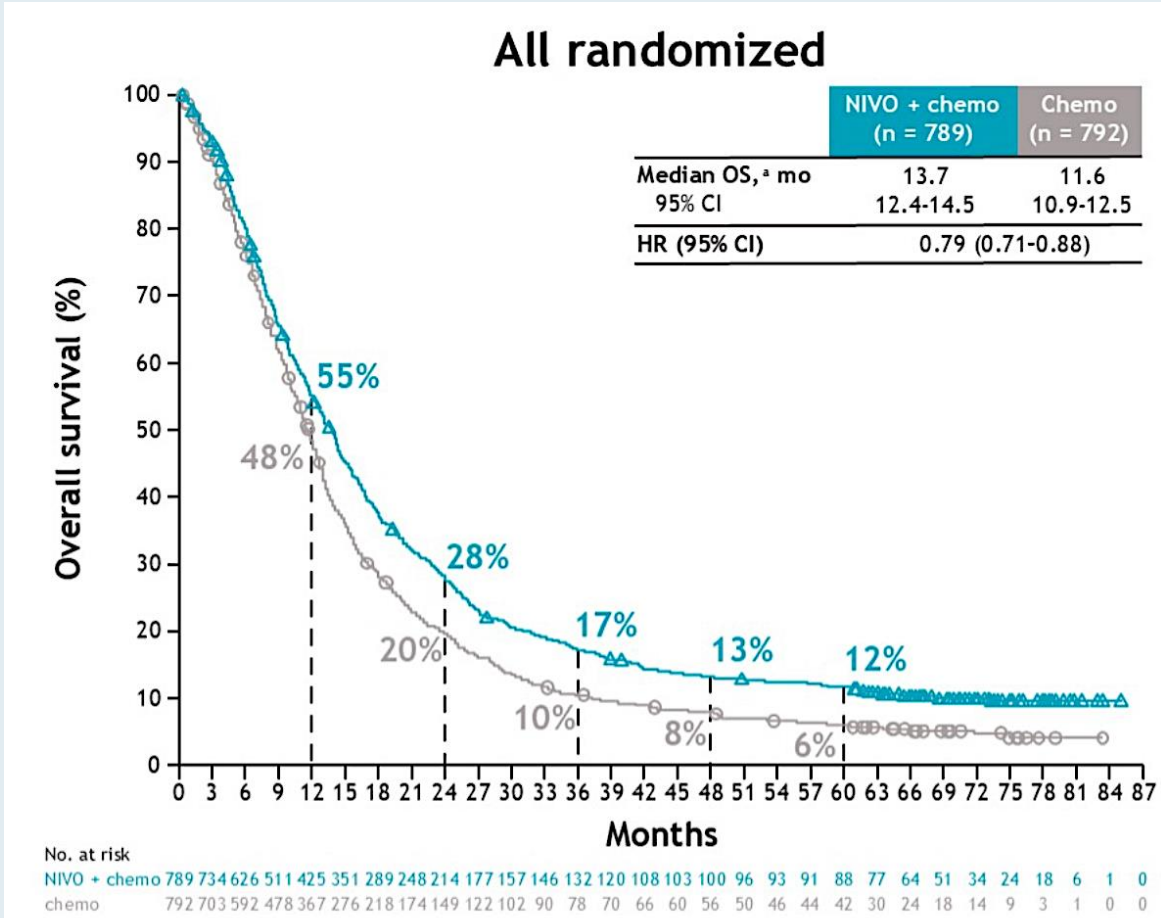
CheckMate 649: Phase III Study of First-Line Nivolumab and Chemotherapy for Gastroesophageal Adenocarcinomas – PFS

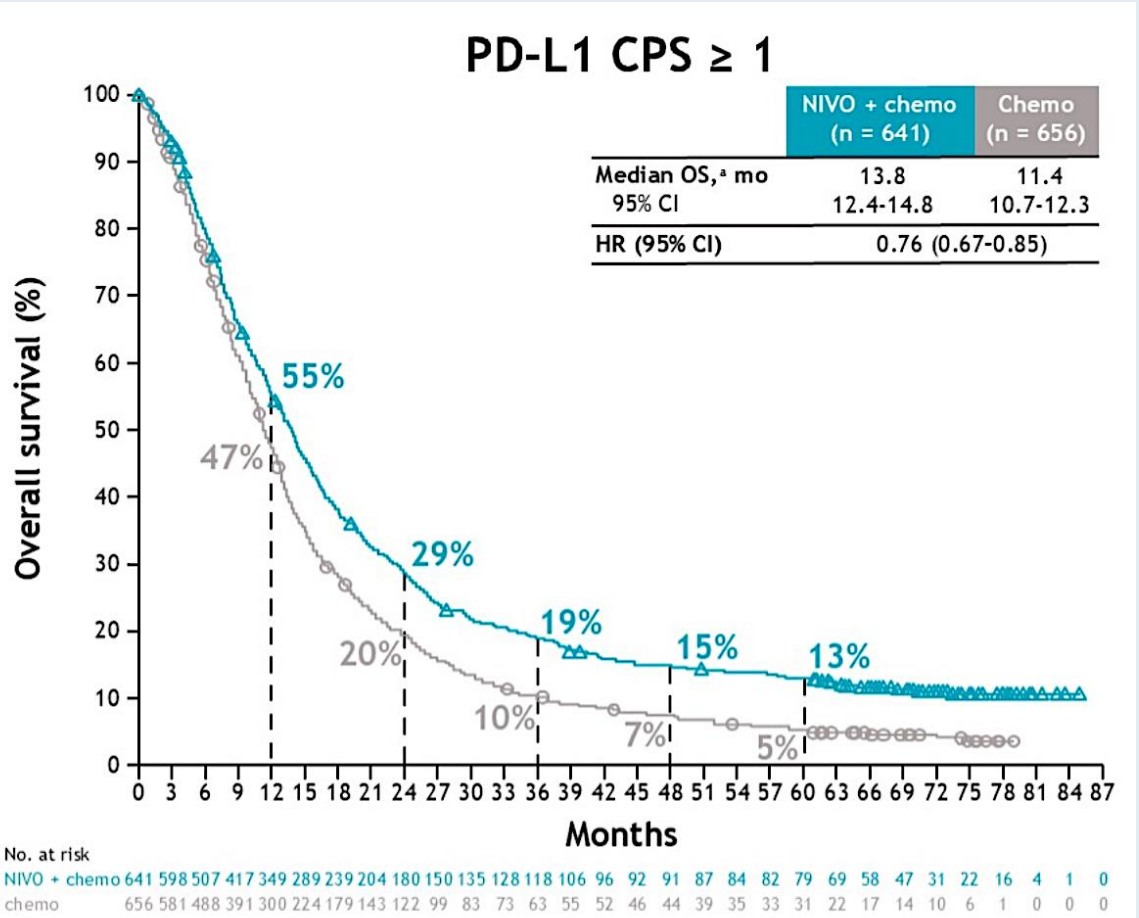




Janjigian Y et al. Gastrointestinal Cancers Symposium 2025;Abstract 398.

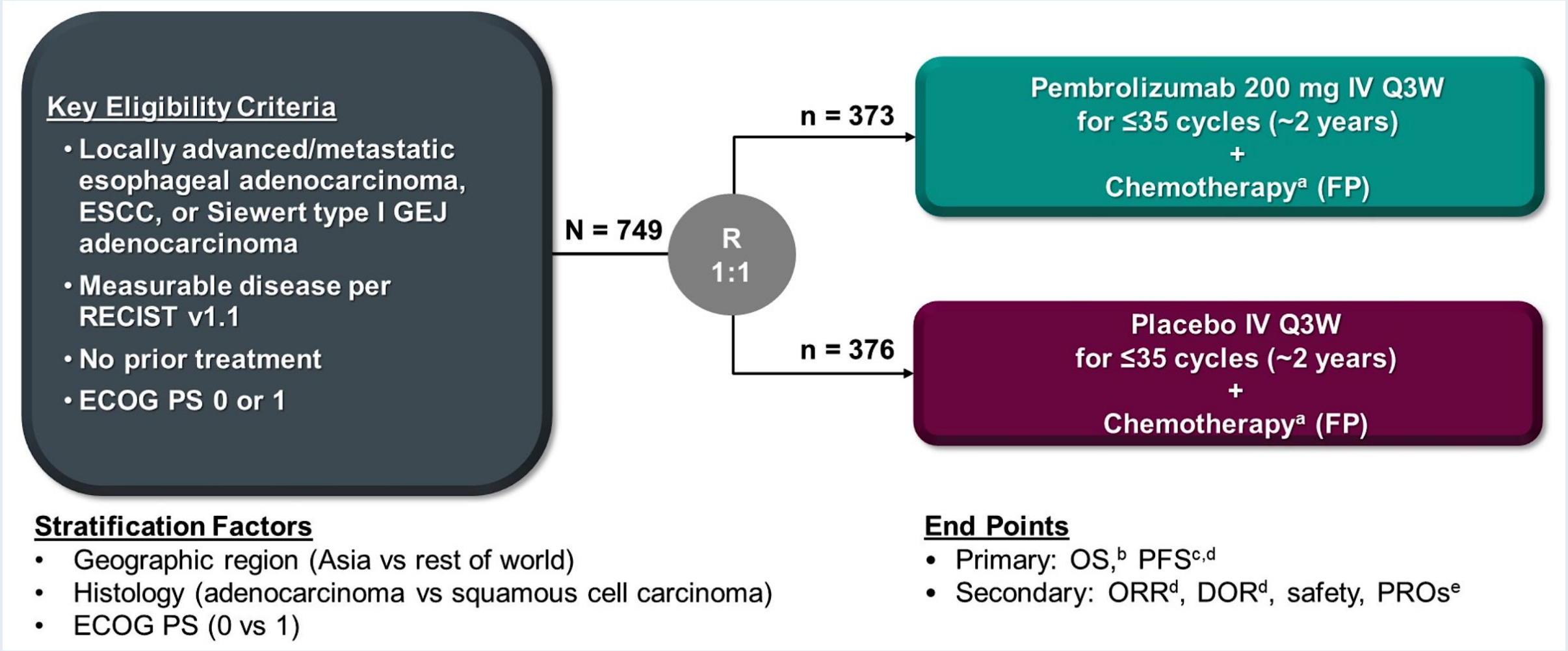
CheckMate 649: Phase III Study of First-Line Nivolumab and Chemotherapy for Gastroesophageal Adenocarcinomas – OS





Janjigian Y et al. Gastrointestinal Cancers Symposium 2025;Abstract 398.

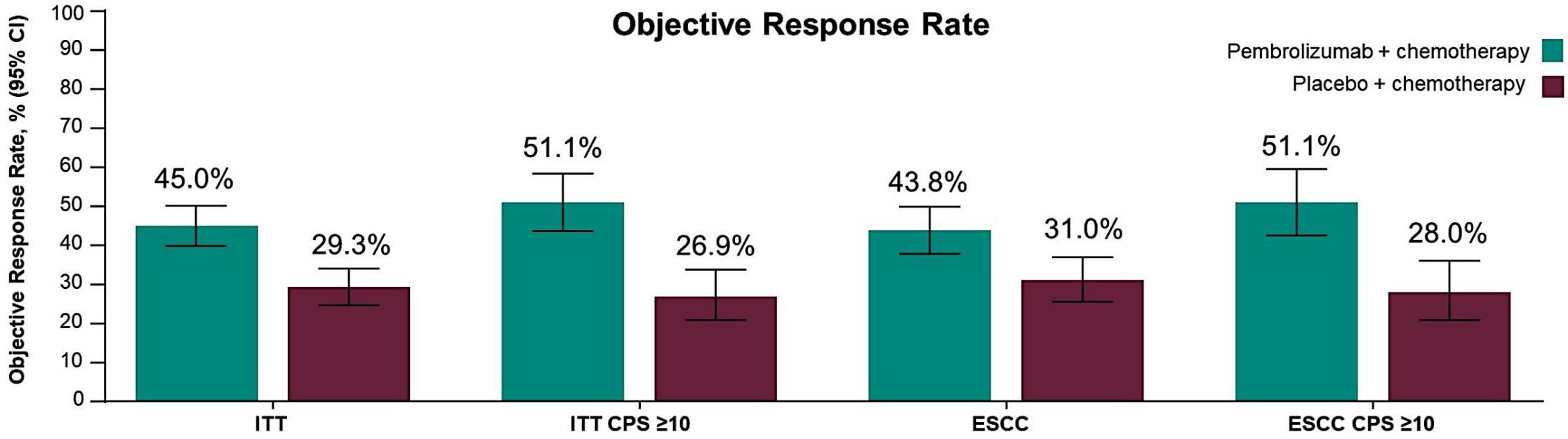
KEYNOTE-590: Phase III Study of First-Line Pembrolizumab and Chemotherapy for Gastroesophageal Cancers



PROs = patient-reported outcomes

Shah M et al. Gastrointestinal Cancers Symposium 2024;Abstract 250.

KEYNOTE-590: Phase III Study of First-Line Pembrolizumab and Chemotherapy for Gastroesophageal Cancers – Response

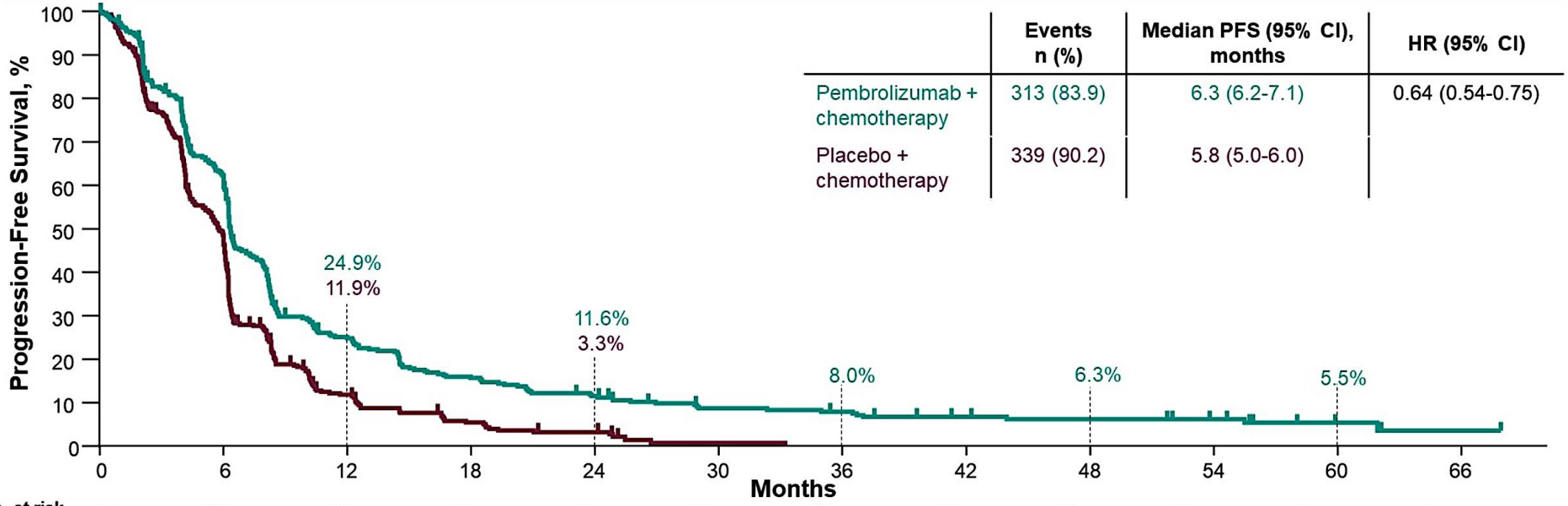


Duration of Response

	ITT		CPS ≥10		ESCC		ESCC and CPS ≥10	
	Pembro + chemo (n = 168)	Placebo + chemo (n = 110)	Pembro + chemo (n = 95)	Placebo + chemo (n = 53)	Pembro + chemo (n = 120)	Placebo + chemo (n = 85)	Pembro + chemo (n = 73)	Placebo + chemo (n = 40)
DOR,[b] median (range), months	8.3 (1.2+ to 65.9+)	6.0 (1.5+ to 31.1)	10.4 (1.9 to 65.9+)	5.6 (1.5+ to 31.1)	9.1 (1.2+ to 65.9+)	6.1 (1.5+ to 31.1)	10.4 (2.2+ to 65.9+)	4.4 (1.5+ to 31.1)

Shah M et al. Gastrointestinal Cancers Symposium 2024;Abstract 250.

KEYNOTE-590: Phase III Study of First-Line Pembrolizumab and Chemotherapy for Gastroesophageal Cancers – PFS in Intent-to-Treat Population



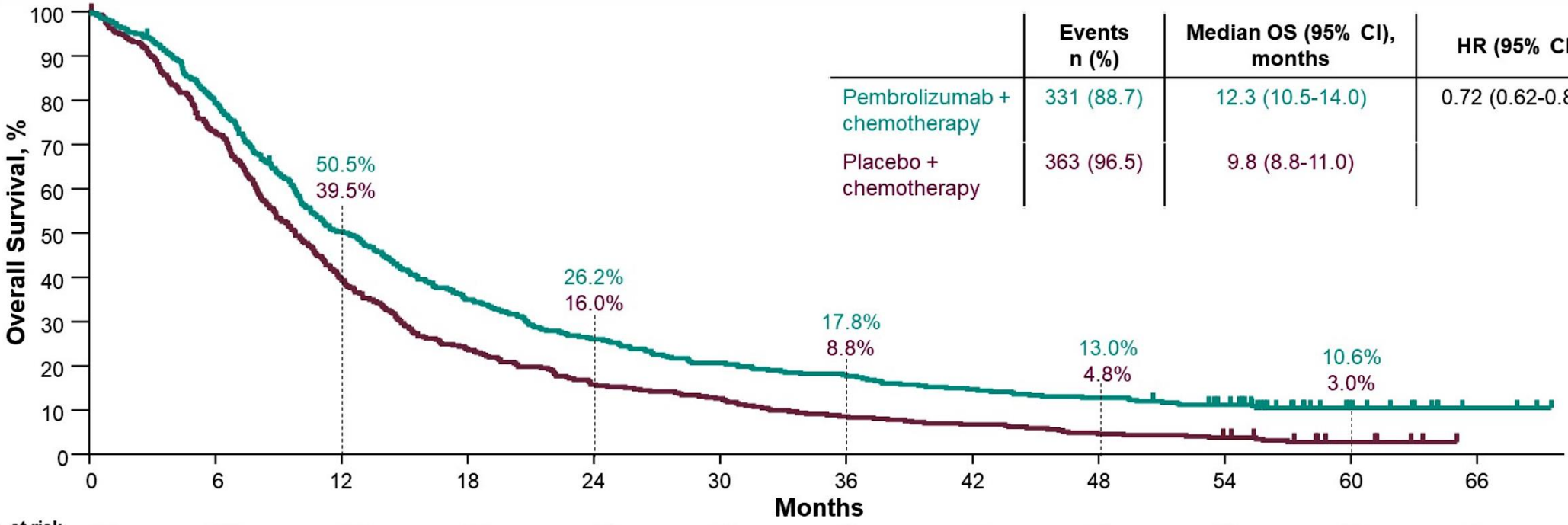
	Events n (%)	Median PFS (95% CI), months	HR (95% CI)
Pembrolizumab + chemotherapy	313 (83.9)	6.3 (6.2-7.1)	0.64 (0.54-0.75)
Placebo + chemotherapy	339 (90.2)	5.8 (5.0-6.0)	

	CPS ≥10		ESCC		ESCC and CPS ≥10	
	Pembro + chemo n = 186	Placebo + chemo n = 197	Pembro + chemo n = 274	Placebo + chemo n = 274	Pembro + chemo n = 143	Placebo + chemo n = 143
PFS HR (95% CI)	0.51 (0.40-0.64)		0.65 (0.54-0.78)		0.53 (0.41-0.69)	
5-y PFS rate,[a] %	7.5	0	6.7	0	9.1	0

[a]Kaplan-Meier estimate. Data cutoff: July 10, 2023.

Shah M et al. Gastrointestinal Cancers Symposium 2024;Abstract 250.

KEYNOTE-590: Phase III Study of First-Line Pembrolizumab and Chemotherapy for Gastroesophageal Cancers – OS in Intent-to-Treat Population



	Events n (%)	Median OS (95% CI), months	HR (95% CI)
Pembrolizumab + chemotherapy	331 (88.7)	12.3 (10.5-14.0)	0.72 (0.62-0.84)
Placebo + chemotherapy	363 (96.5)	9.8 (8.8-11.0)	

No. at risk											
	373	296	187	130	97	77	66	55	48	38	12	3
	376	274	148	90	60	48	33	26	18	14	5	0

	CPS ≥10		ESCC		ESCC and CPS ≥10	
	Pembro + chemo n = 186	Placebo + chemo n = 197	Pembro + chemo n = 274	Placebo + chemo n = 274	Pembro + chemo n = 143	Placebo + chemo n = 143
OS, HR (95% CI)	0.64 (0.52-0.80)		0.71 (0.60-0.85)		0.60 (0.46-0.76)	
5-y OS rate,[a] %	12.8	3.8	11.8	3.4	13.8	3.7

[a]Kaplan-Meier estimate. Data cutoff: July 10, 2023.

Shah M et al. Gastrointestinal Cancers Symposium 2024;Abstract 250.

Tislelizumab Combined with Chemotherapy Approved in US for First-Line Treatment of Gastric and Gastroesophageal Junction Cancers

Press Release: December 27, 2024

”[The manufacturer] today announced the US Food and Drug Administration (FDA) has approved tislelizumab-jsgr, in combination with platinum and fluoropyrimidine-based chemotherapy, for the first-line treatment of unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma (G/GEJ) in adults whose tumors express PD-L1 (≥1).

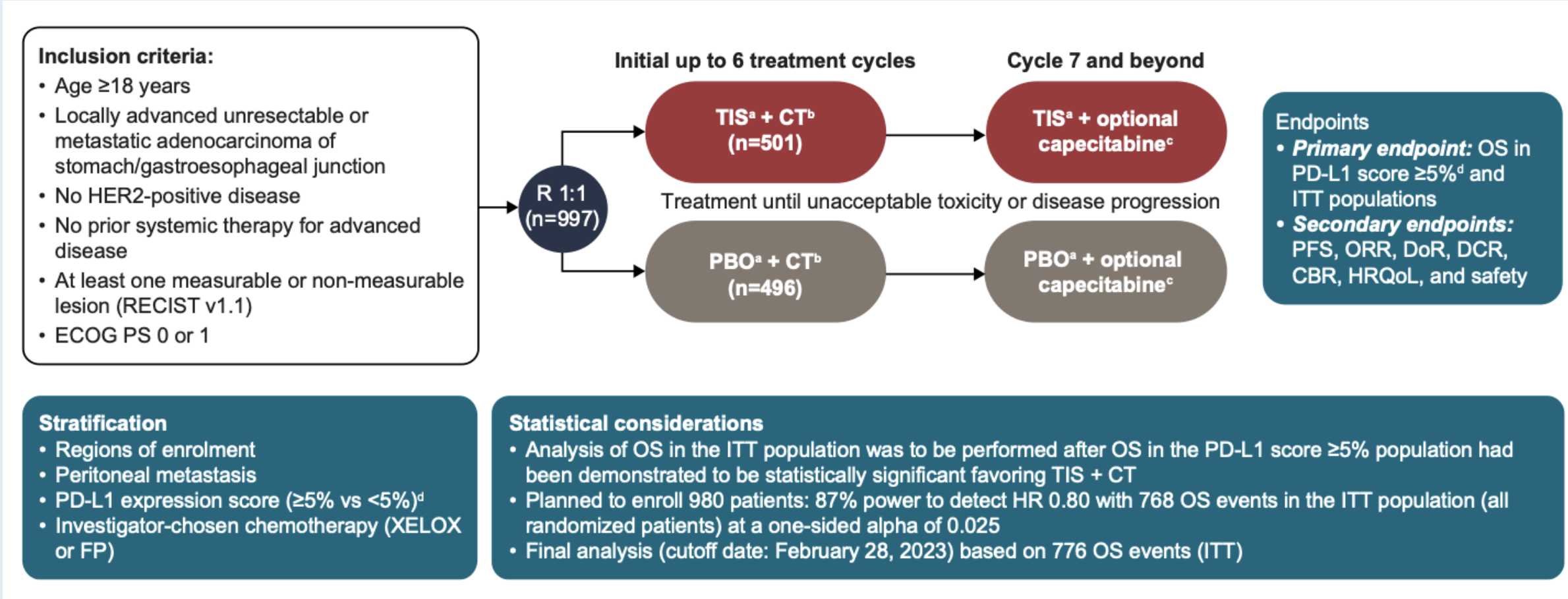
The indication for first-line G/GEJ cancers is based on results from RATIONALE-305 (NCT03777657), a randomized, double-blind, placebo-controlled, global Phase 3 trial to evaluate the efficacy and safety of tislelizumab in combination with chemotherapy as a first-line treatment for adult patients with advanced unresectable or metastatic G/GEJ cancer.

The study met its primary endpoint and demonstrated a statistically significant and clinically meaningful overall survival (OS) benefit with a median OS of 15.0 months for patients treated with tislelizumab in combination with the investigator’s choice of chemotherapy compared to 12.9 months for patients treated with placebo plus chemotherapy (n = 997; HR: 0.80 [95% CI: 0.70, 0.92]; *P* = 0.0011), resulting in a 20% reduction in the risk of death.”

https://ir.beigene.com/news/tevimbra-approved-in-u-s-for-first-line-treatment-of-gastric-and-gastroesophageal-junction-cancers-in-combination/cedb475b-fcfe-47a4-8afe-8a501d9cf849/

RTP RESEARCH TO PRACTICE

RATIONALE-305: Phase III Study of First-Line Tislelizumab and Chemotherapy for Gastroesophageal Adenocarcinomas



PBO= placebo; CBR = clinical benefit rate

Fornaro L et al. Presented at Italian Medical Oncology Association Meeting 2024.

Tislelizumab Combined with Chemotherapy Approved in US for First-Line Treatment of Advanced ESCC

Press Release: March 4, 2025

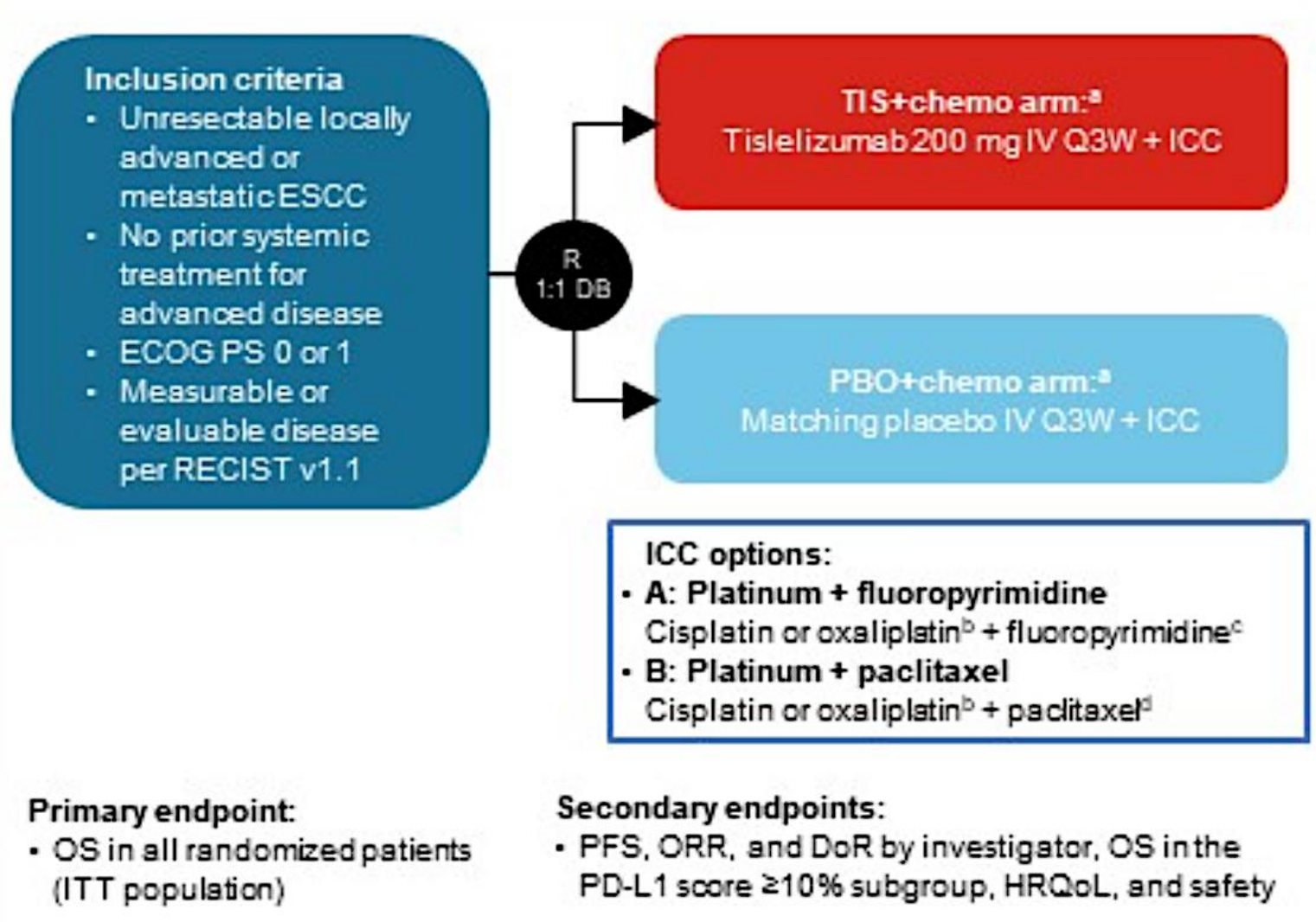
"[The manufacturer] today announced the US Food and Drug Administration (FDA) has approved tislelizumab-jsgr, in combination with platinum-containing chemotherapy, for the first-line treatment of adults with unresectable or metastatic esophageal squamous cell carcinoma (ESCC) whose tumors express PD-L1 (≥1).

The additional indication is based on results from RATIONALE-306 (NCT03783442), a randomized, placebo-controlled, double-blind, global Phase 3 study to evaluate the efficacy and safety of tislelizumab in combination with platinum-containing chemotherapy as a first-line treatment in adult patients (n = 649) with unresectable, locally advanced recurrent or metastatic ESCC. The study met its primary endpoint and demonstrated a statistically significant improvement in overall survival (OS) for adult patients randomized to tislelizumab in combination with chemotherapy compared to placebo in combination with chemotherapy.

Analysis of OS in the PD-L1 positive (≥1) population (n = 481) showed a median OS of 16.8 months for patients treated with TEVIMBRA plus chemotherapy compared to 9.6 months for patients treated with placebo plus chemotherapy (HR: 0.66, [95% CI: 0.53, 0.82]), resulting in a 34% reduction in the risk of death."

https://ir.beigene.com/news/tevimbra-approved-in-us-for-first-line-treatment-of-advanced-esophageal-squamous-cell-carcinoma-in-combination/8379a7c3-35ce-45af-82d3-164c64ecf37c

RATIONALE-306: Phase III Study of First-Line Tislelizumab and Chemotherapy for ESCC



ICC = investigator-chosen chemotherapy

Yoon H et al. ASCO 2024;Abstract 4032.

IDeate-Esophageal01 Phase III Trial of Ifinatamab Deruxtecan Initiated in Certain Patients with Pretreated Advanced or Metastatic ESCC

Press Release: May 19, 2025

"The first patient has been dosed in the IDeate-Esophageal01 Phase 3 trial evaluating the efficacy and safety of investigational ifinatamab deruxtecan (I-DXd) versus investigator's choice of chemotherapy in patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) with disease progression following treatment with a platinum-containing systemic therapy and an immune checkpoint inhibitor.

Ifinatamab deruxtecan is a specifically engineered, potential first-in-class B7-H3 directed DXd antibody drug conjugate."

https://www.merck.com/news/ideate-esophageal01-phase-3-trial-of-ifinatamab-deruxtecan-initiated-in-certain-patients-with-pretreated-advanced-or-metastatic-esophageal-squamous-cell-carcinoma/

RTP RESEARCH TO PRACTICE

Agenda

Introduction: ASCO Preview

Module 1: HER2-Positive Gastroesophageal Cancers

Module 2: Immunotherapy in HER2-Negative Advanced Gastroesophageal Cancers

Module 3: Immunotherapy in Microsatellite Instability-High Gastroesophageal Cancers

Module 4: CLDN18.2-Positive Advanced Gastroesophageal Cancers

Case Presentation: 63-year-old man with surgically unresectable MSI-high, TMB-high HER2-negative gastric adenocarcinoma (PD-L1 2%) receives FOLFOX/nivolumab

Dr Shachar Peles (Lake Worth, Florida)

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Nivolumab for Microsatellite Instability-High (MSI-H) Gastroesophageal Cancers in CheckMate 649: OS Analysis

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic GC/GEJC/EAC
- No known HER2-positive status
- ECOG PS 0-1

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[a])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)

R 1:1:1[b]
N = 2031

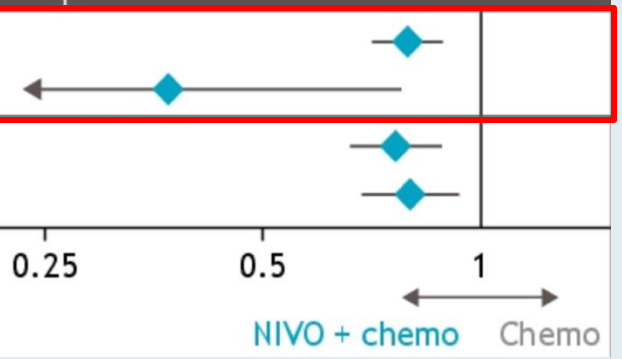
- n = 789: NIVO 360 mg + XELOX Q3W or NIVO 240 mg + FOLFOX Q2W[d,e]
- n = 833[c]: XELOX Q3W or FOLFOX Q2W[d,e]
- n = 409: NIVO (1 mg/kg) + IPI (3 mg/kg) Q3W × 4 then NIVO 240 mg Q2W[e]

Dual primary endpoints:
- **OS** and **PFS**[f] (PD-L1 CPS ≥ 5)

Secondary endpoints:
- **OS** (PD-L1 CPS ≥ 1, all randomized)
- **OS** (PD-L1 CPS ≥ 10)
- **PFS**[f] (PD-L1 CPS ≥ 10, ≥ 1, all randomized)
- **ORR**[f]

Exploratory endpoints:
- **Safety**
- **Quality of life**

Category (all randomized)	Subgroup	Median OS, months[a]		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
MSI status[e]	MSS (n = 1378)	13.8	11.5	0.79	
	MSI-H (n = 44)	38.7	12.3	0.37	
Chemo regimen	FOLFOX (n = 828)	13.6	11.8	0.77	
	XELOX (n = 721)	13.9	11.8	0.80	



Elimova E et al. ASCO 2024;Abstract 4040.

JAMA Oncology | Brief Report

Assessment of Pembrolizumab Therapy for the Treatment of Microsatellite Instability–High Gastric or Gastroesophageal Junction Cancer Among Patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 Clinical Trials

Joseph Chao, MD; Charles S. Fuchs, MD; Kohei Shitara, MD; Josep Tabernero, MD; Kei Muro, MD; Eric Van Cutsem, MD; Yung-Jue Bang, MD; Ferdinando De Vita, MD; Gregory Landers, MD; Chia-Jui Yen, MD; Ian Chau, MD; Anneli Elme, MD; Jeeyun Lee, MD; Mustafa Özgüroğlu, MD; Daniel Catenacci, MD; Harry H. Yoon, MD; Erluo Chen, MPH; David Adelberg, MD; Chie-Schin Shih, MD; Sukrut Shah, PhD; Pooja Bhagia, MD; Zev A. Wainberg, MD

2021;7(6):895-902.

Pembrolizumab for MSI-H Gastroesophageal Cancers in the KEYNOTE-059, KEYNOTE-061 and KEYNOTE-062 Studies

Table 2. Outcomes in Patients With Advanced Gastric or Gastroesophageal Junction Cancer by Line of Therapy

	KEYNOTE-059[a]	KEYNOTE-061[b]		KEYNOTE-062[c]		
Outcome	Pembrolizumab	Pembrolizumab	Chemotherapy	Pembrolizumab	Pembrolizumab plus chemotherapy	Chemotherapy
Patients with MSI-H tumors						
Total patients, No.	7	15	12	14	17	19
Objective response rate, % (95% CI)	57.1 (18.4-90.1)	46.7 (21.3-73.4)	16.7 (2.1-48.4)	57.1 (28.9-82.3)	64.7 (38.3-85.8)	36.8 (16.3-61.6)
Best overall response rate, %						
Complete	28.6	6.7	8.3	7.1	35.3	10.5
Partial	28.6	40.0	8.3	50.0	29.4	26.3
Stable disease	14.3	40.0	58.3	21.4	17.6	42.1
Progressive disease	0	6.7	0	14.3	0	10.5
Duration of response, median (range), mo	NR (20.0[d]-26.8[d])	NR (5.5-26.0[d])	NR (2.2[d]-12.2[d])	21.2 (1.4[d]-33.6[d])	NR (1.6[d]-34.5[d])	7.0 (2.0-30.4[d])
Survival, median (95% CI), mo						
Progression-free	NR (1.1-NR)	17.8 (2.7-NR)	3.5 (2.0-9.8)	11.2 (1.5-NR)	NR (3.6-NR)	6.6 (4.4-8.3)
Overall	NR (1.1-NR)	NR (5.6-NR)	8.1 (2.0-16.7)	NR (10.7-NR)	NR (3.6-NR)	8.5 (5.3-20.8)
Estimated overall survival rate, % (95% CI)						
12 mo	71 (NA)	73 (44-89)	25 (6-50)	79 (47-92)	71 (43-87)	47 (24-67)
24 mo	57 (NA)	59 (31-79)	NA	71 (41-88)	65 (38-82)	26 (10-57)

Chao J et al. *JAMA Oncol* 2021;7(6):895-902.

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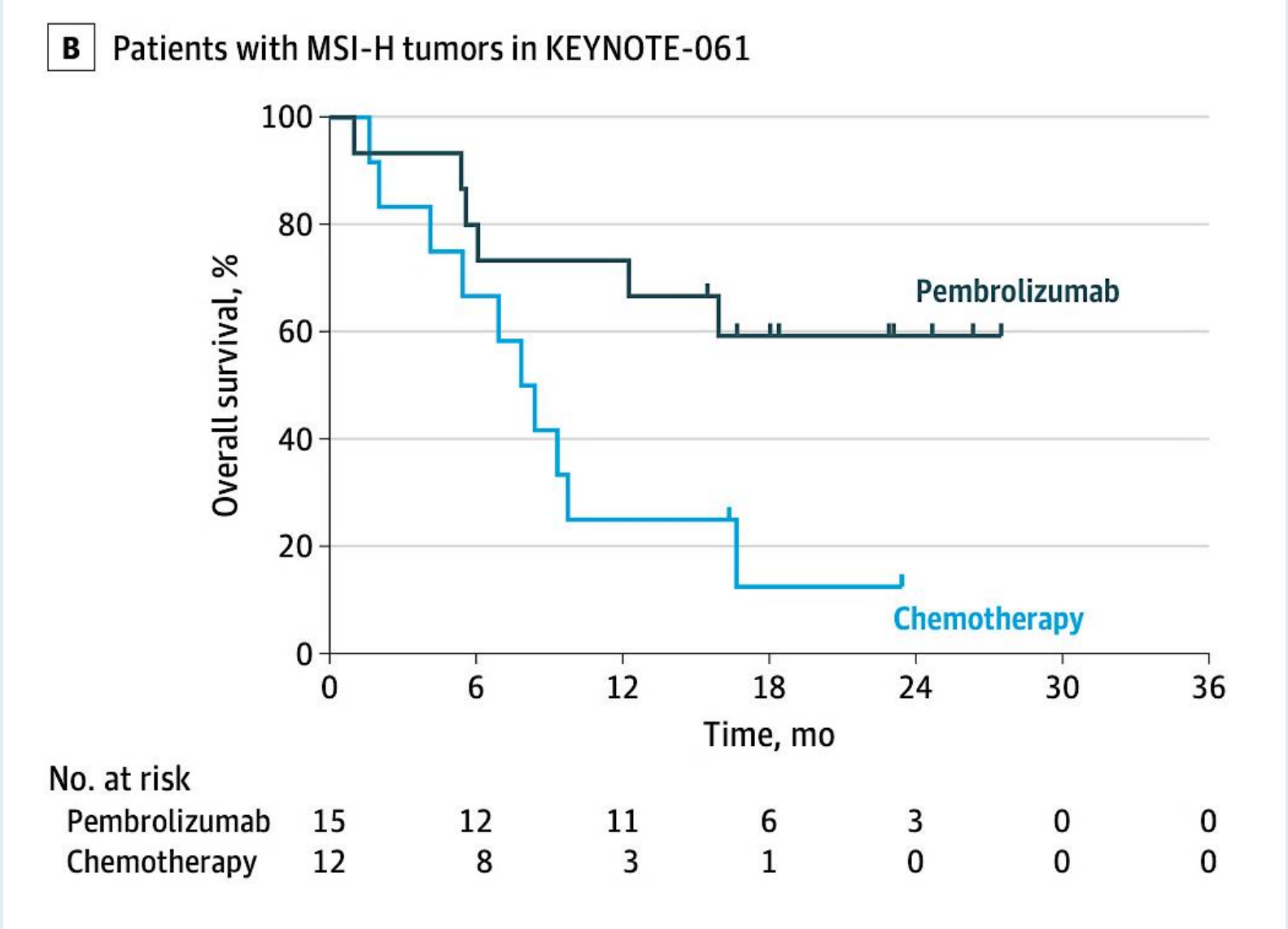
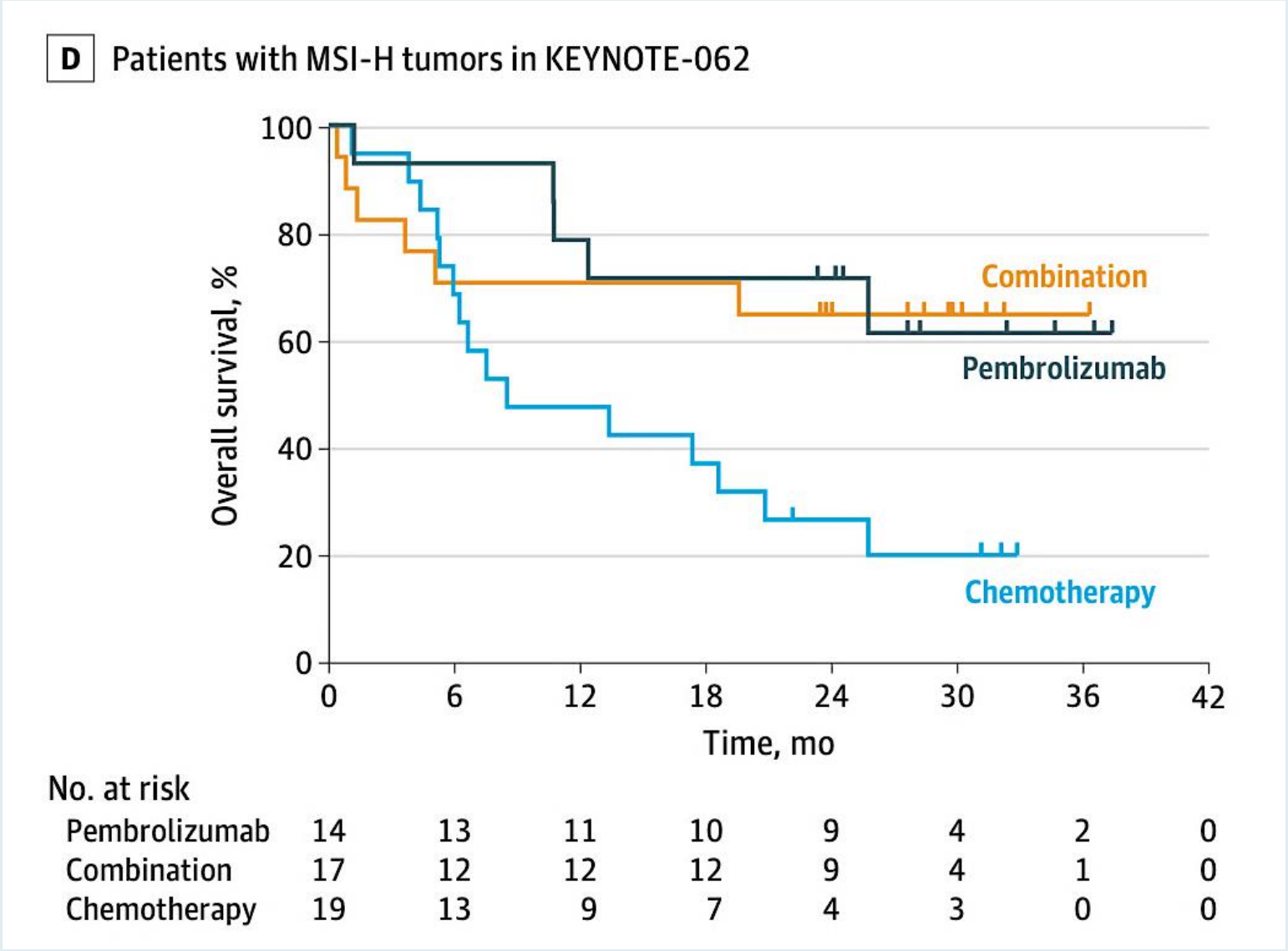
Pembrolizumab for MSI-H Gastroesophageal Cancers in KEYNOTE-061



Chao J et al. *JAMA Oncol* 2021;7(6):895-902.

Pembrolizumab for MSI-H Gastroesophageal Cancers in KEYNOTE-062



Chao J et al. *JAMA Oncol* 2021;7(6):895-902.

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Module 4: CLDN18.2-Positive Advanced Gastroesophageal Cancers

Case Presentation: 82-year-old man with recurrent HER2-negative (HER2 IHC 2+/FISH-negative) metastatic esophageal adenocarcinoma (PD-L1 CPS 20, CLDN 18.2-positive) receives zolbetuximab with chemotherapy

Dr Henna Malik (Houston, Texas)

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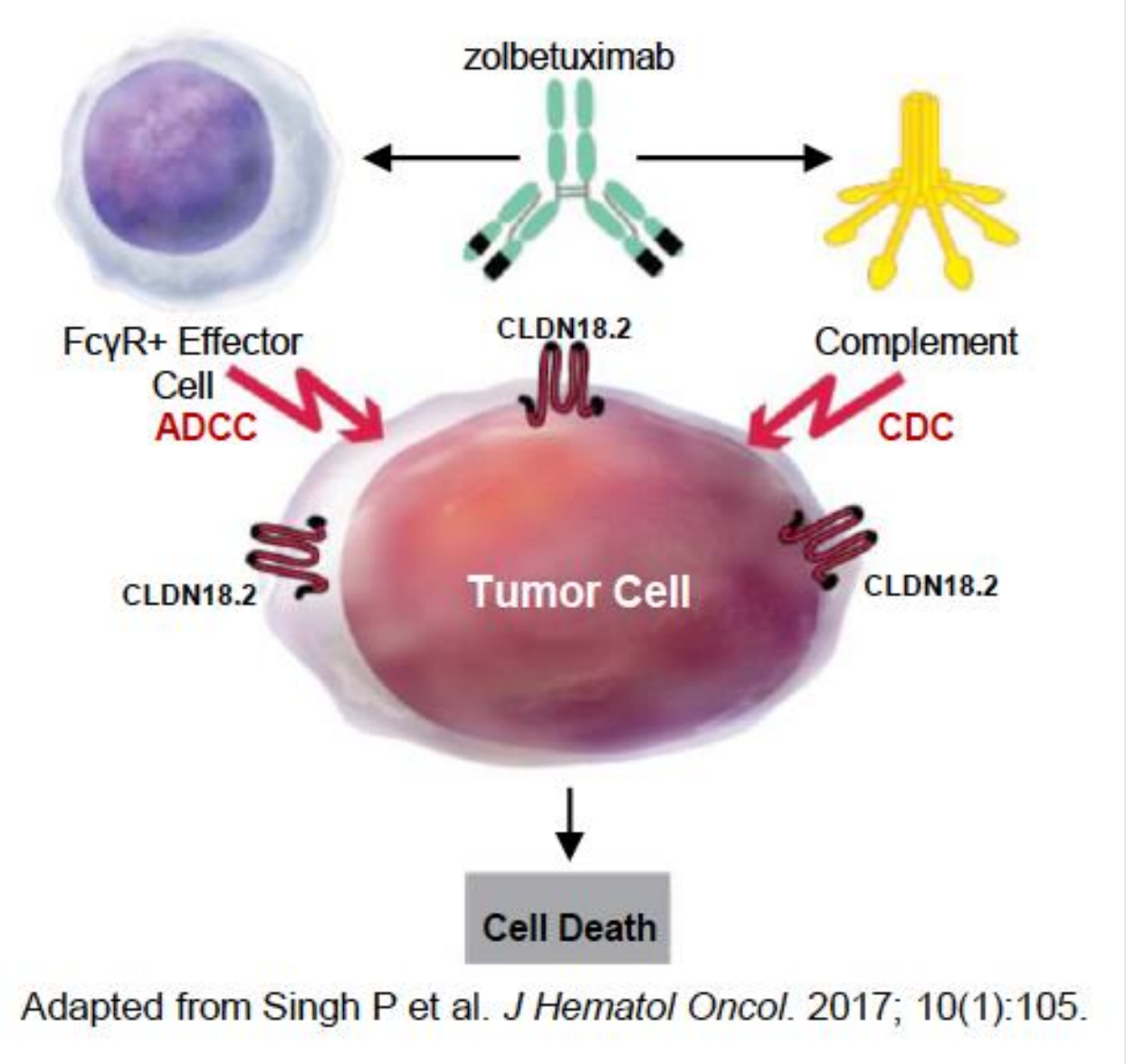
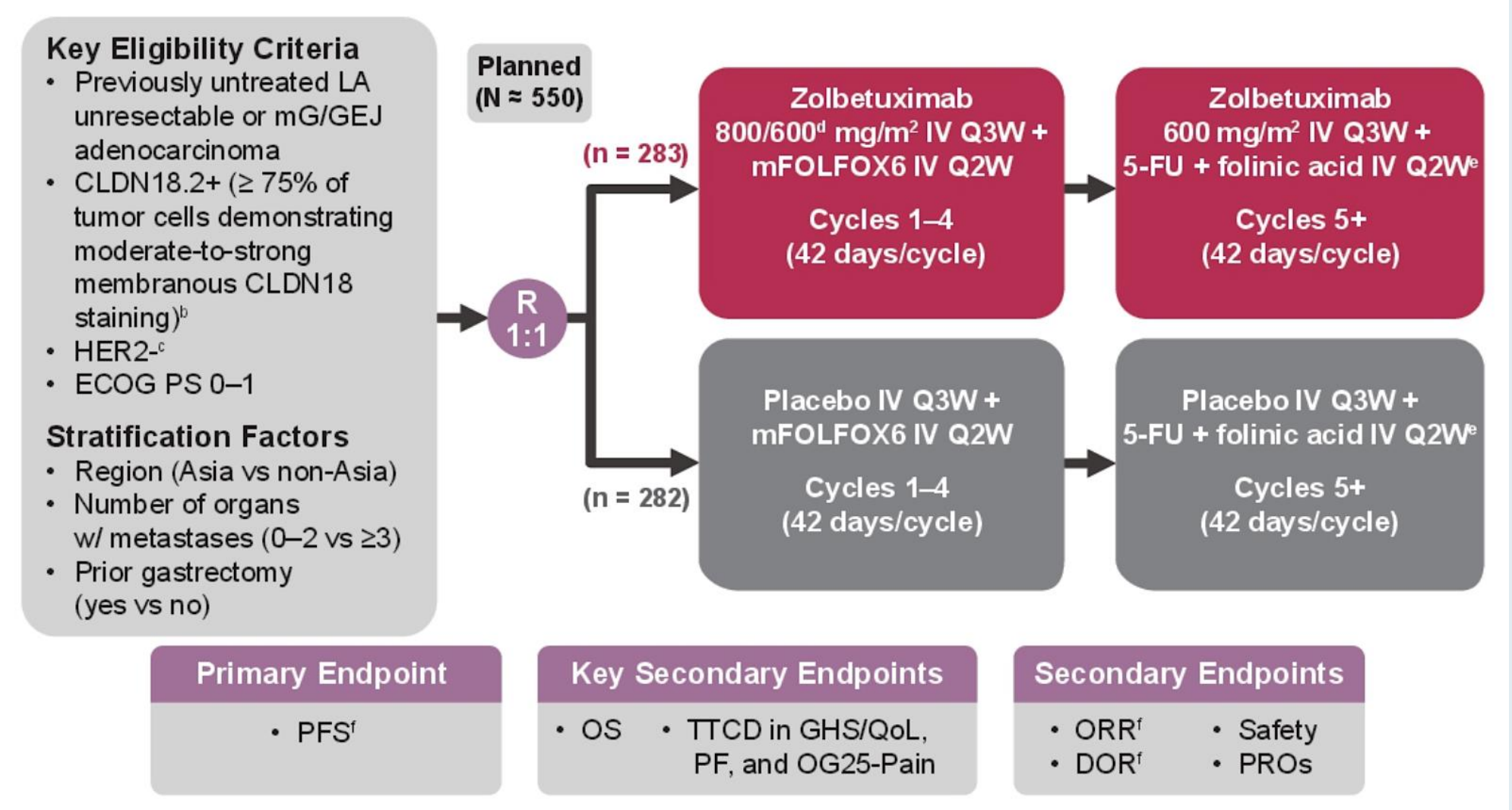
Mechanism of Action of Zolbetuximab



Adapted from Singh P et al. *J Hematol Oncol*. 2017; 10(1):105.

Lordick F et al. ESMO 2024;Abstract 134MO.

SPOTLIGHT: Phase III Study of First-Line Zolbetuximab and mFOLFOX6 for CLDN18.2-Positive Gastroesophageal Adenocarcinoma

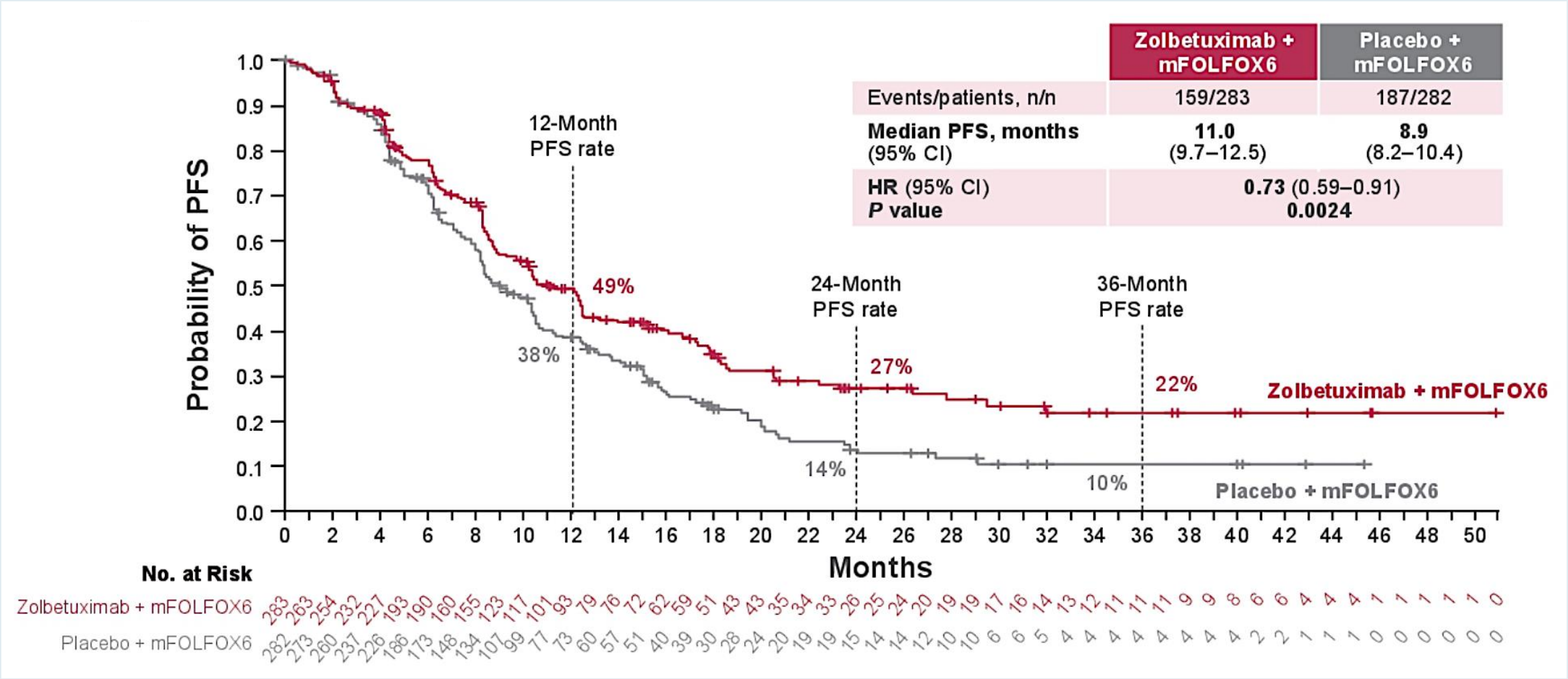


TTCD = time to confirmed deterioration; GHS/QoL = global health status/quality of life; PF = physical functioning; OG25-Pain = Oesophago-gastric Questionnaire on Abdominal Pain and Discomfort

Shitara K et al. ASCO 2024;Abstract 4036.

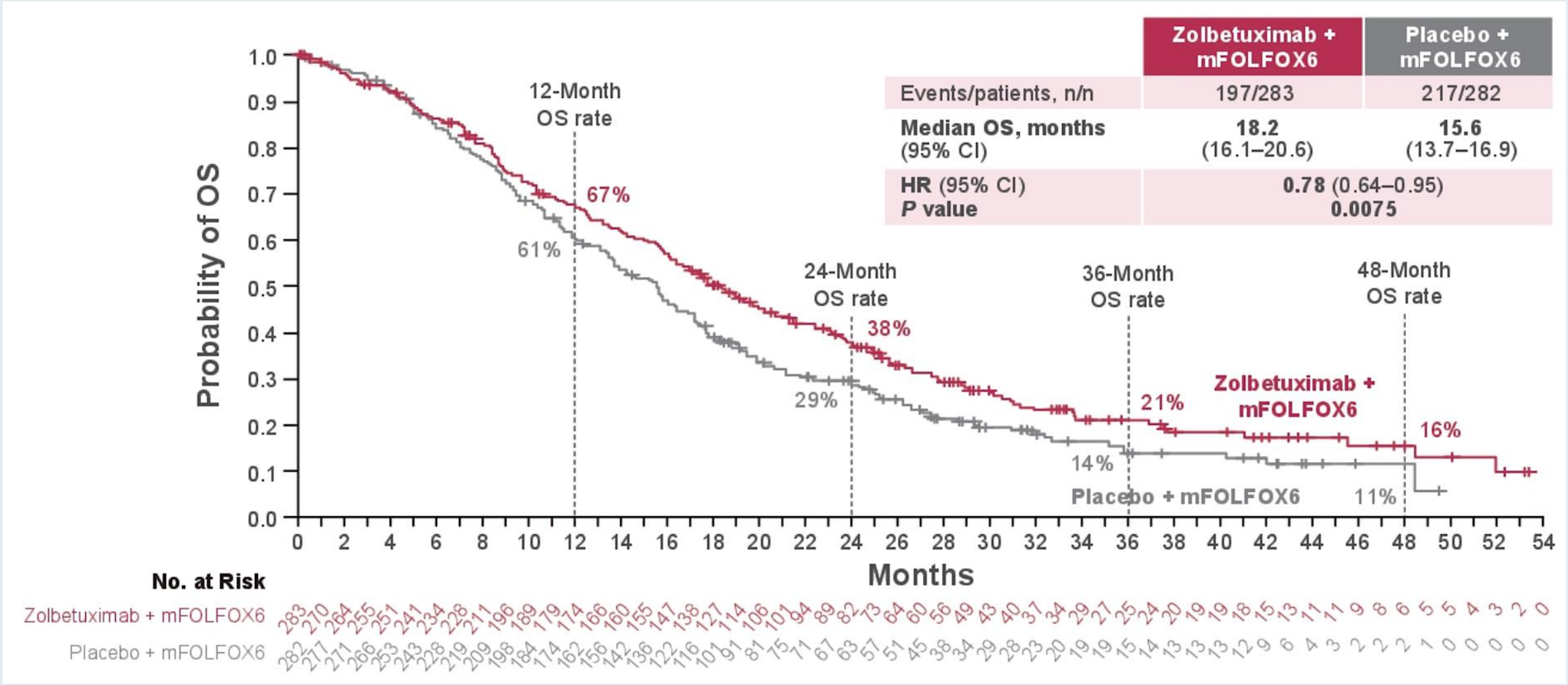
RTP RESEARCH TO PRACTICE

SPOTLIGHT: Phase III Study of First-Line Zolbetuximab and mFOLFOX6 for CLDN18.2-Positive Gastroesophageal Adenocarcinoma – PFS



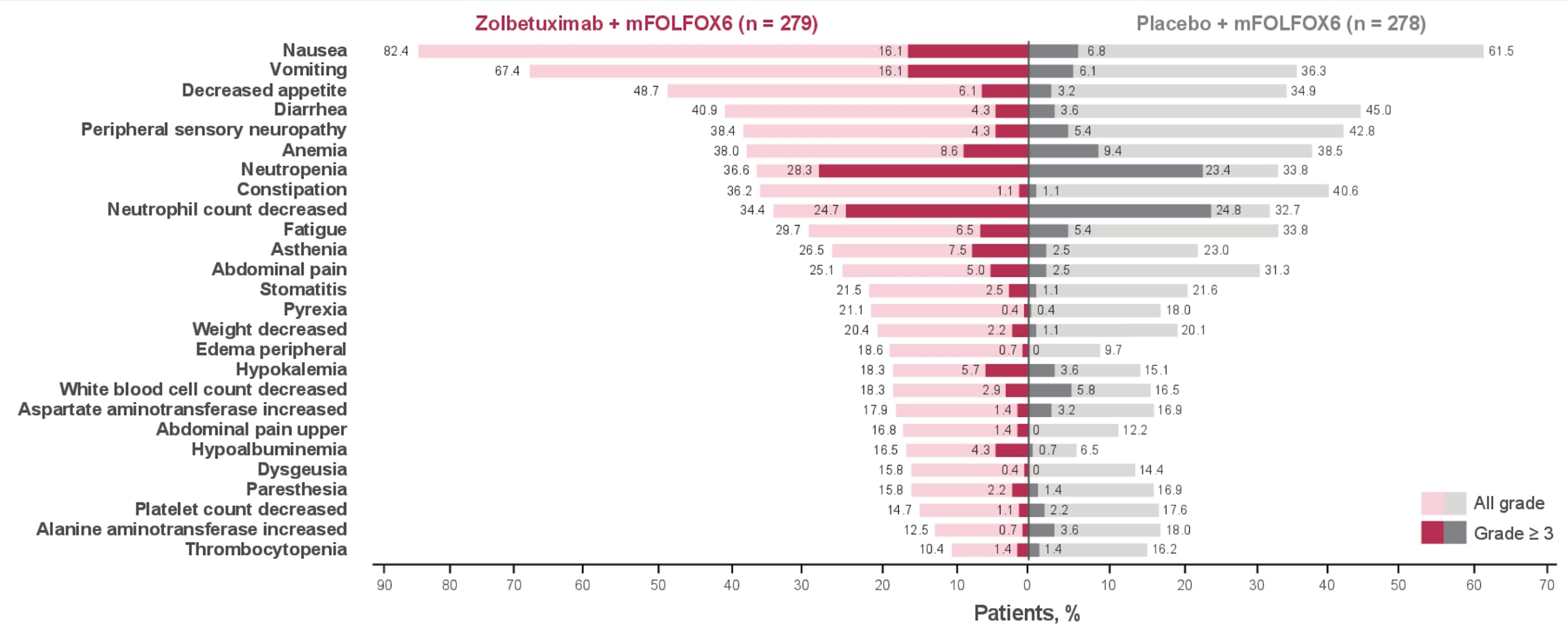
Shitara K et al. ASCO 2024;Abstract 4036.

SPOTLIGHT: Phase III Study of First-Line Zolbetuximab and mFOLFOX6 for CLDN18.2-Positive Gastroesophageal Adenocarcinoma – OS



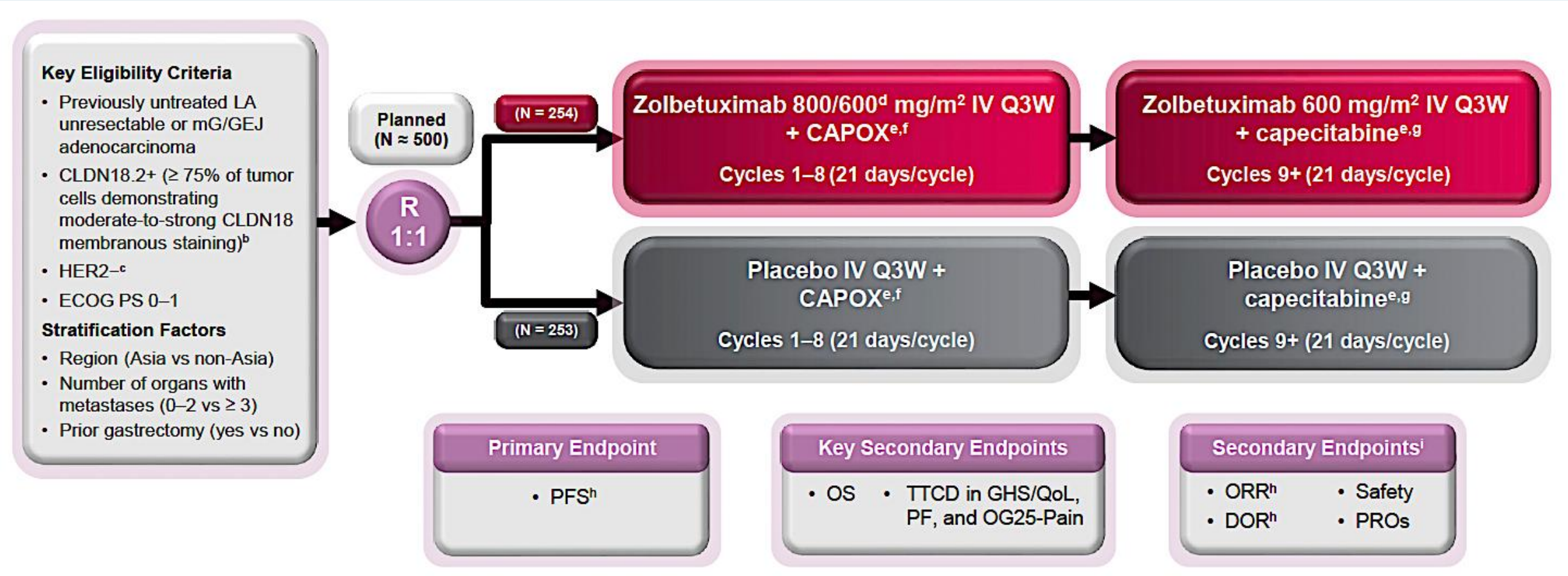
Shitara K et al. ASCO 2024;Abstract 4036.

SPOTLIGHT: Phase III Study of First-Line Zolbetuximab and mFOLFOX6 for CLDN18.2-Positive Gastroesophageal Adenocarcinoma – Safety



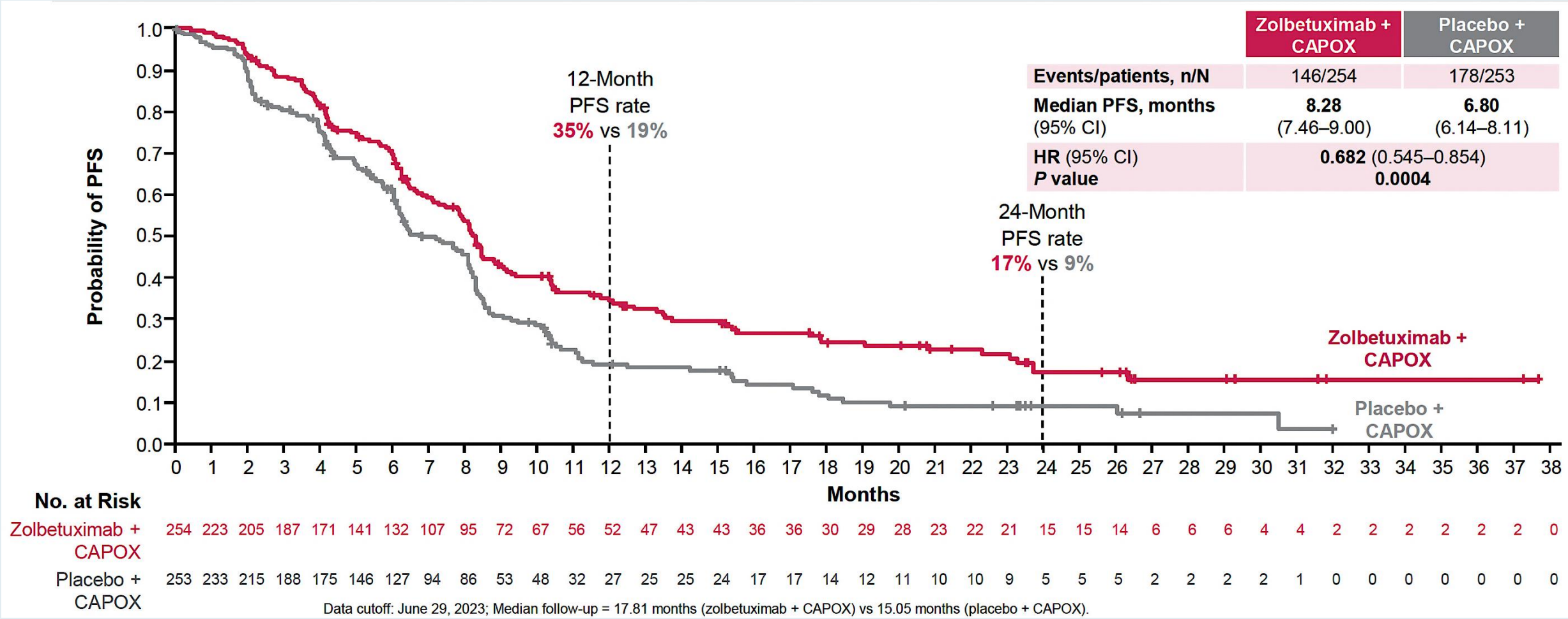
Shitara K et al. ASCO 2024;Abstract 4036.

GLOW: Phase III Study of First-Line Zolbetuximab and CAPOX for CLDN18.2-Positive Gastroesophageal Adenocarcinoma



Lordick F et al. ESMO 2024;Abstract 134MO.

GLOW: Phase III Study of First-Line Zolbetuximab and CAPOX for CLDN18.2-Positive Gastroesophageal Adenocarcinoma – PFS



	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients, n/N	146/254	178/253
Median PFS, months (95% CI)	**8.28** (7.46–9.00)	**6.80** (6.14–8.11)
HR (95% CI)	**0.682** (0.545–0.854)	
***P* value**	**0.0004**	

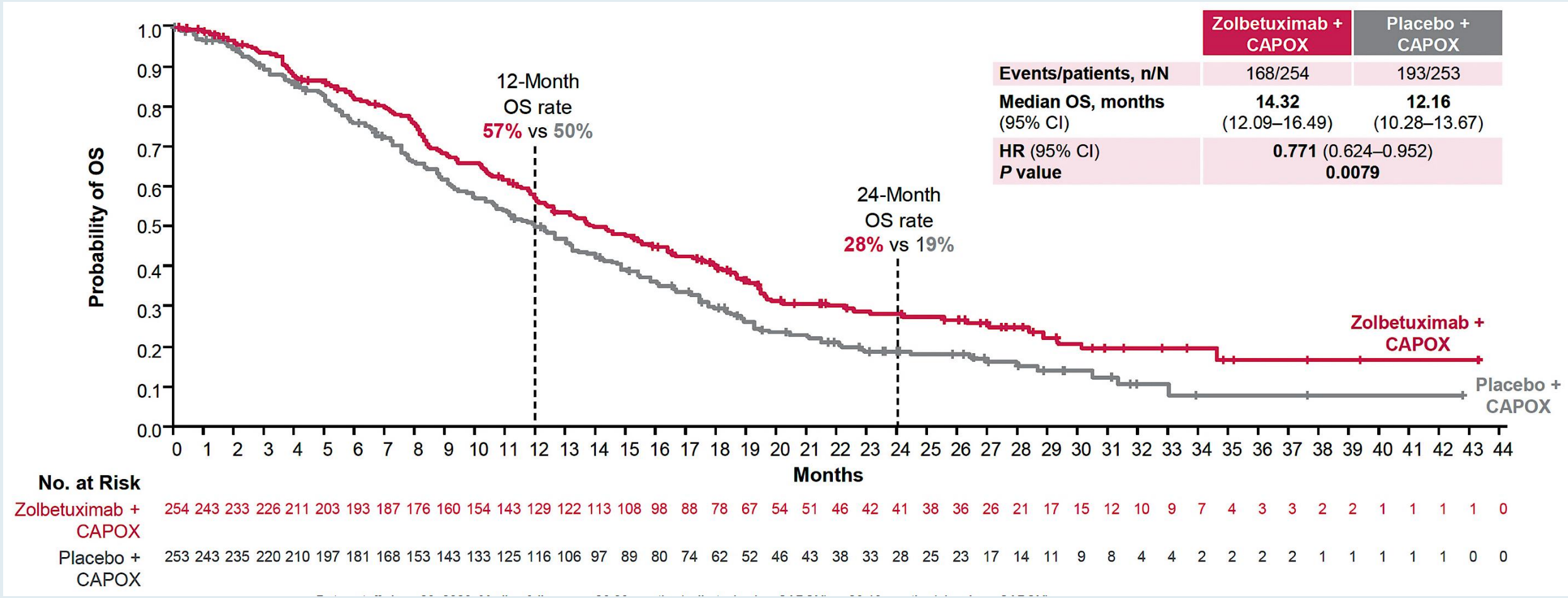
No. at Risk

Zolbetuximab + CAPOX	254	223	205	187	171	141	132	107	95	72	67	56	52	47	43	43	36	36	30	29	28	23	22	21	15	15	14	6	6	6	4	4	2	2	2	2	2	2	0
Placebo + CAPOX	253	233	215	188	175	146	127	94	86	53	48	32	27	25	25	24	17	17	14	12	11	10	10	9	5	5	5	2	2	2	2	1	0	0	0	0	0	0	0

Data cutoff: June 29, 2023; Median follow-up = 17.81 months (zolbetuximab + CAPOX) vs 15.05 months (placebo + CAPOX).

Lordick F et al. ESMO 2024;Abstract 134MO.

GLOW: Phase III Study of First-Line Zolbetuximab and CAPOX for CLDN18.2-Positive Gastroesophageal Adenocarcinoma – OS

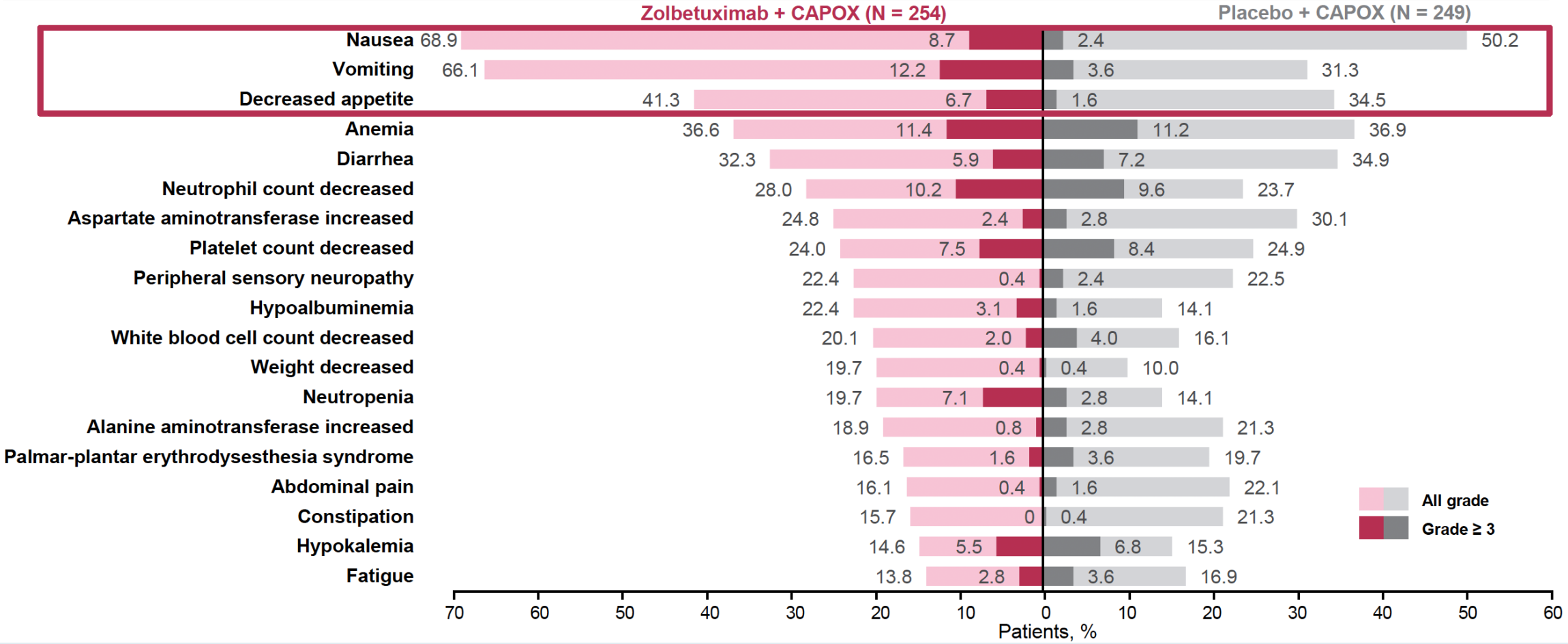


	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients, n/N	168/254	193/253
Median OS, months (95% CI)	**14.32** (12.09–16.49)	**12.16** (10.28–13.67)
HR (95% CI)	**0.771** (0.624–0.952)	
***P* value**	**0.0079**	

Lordick F et al. ESMO 2024;Abstract 134MO.

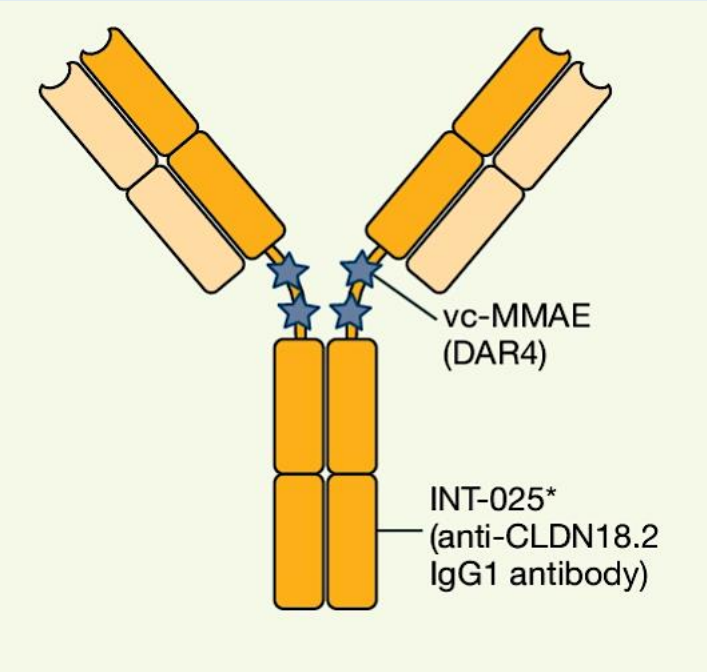
GLOW: Phase III Study of First-Line Zolbetuximab and CAPOX for CLDN18.2-Positive Gastroesophageal Adenocarcinoma – Safety

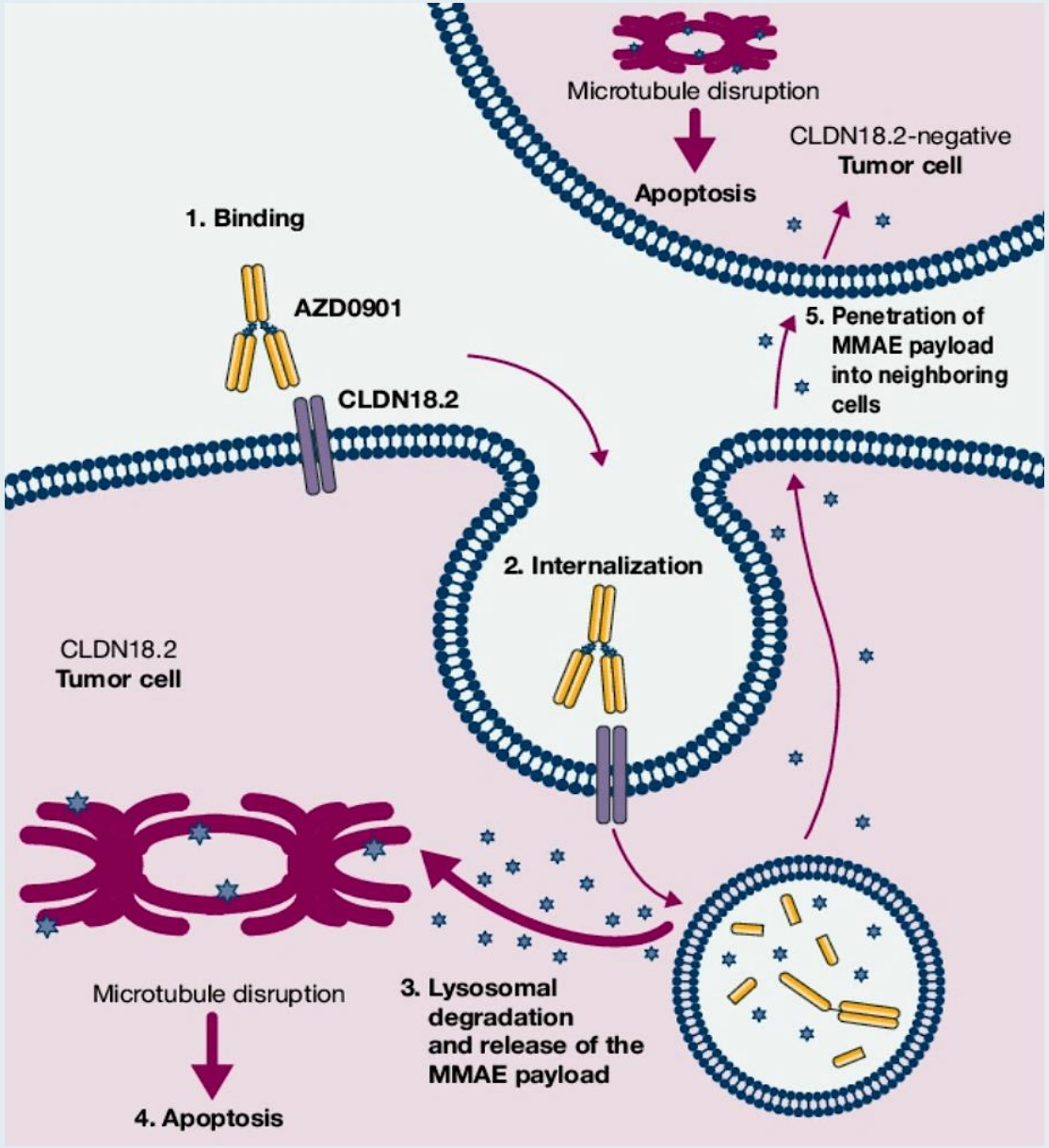
The most common TEAEs with zolbetuximab + CAPOX were nausea, vomiting, and decreased appetite as on-target effects
Nausea and vomiting occurred mostly during the first zolbetuximab cycle[1]



Lordick F et al. ESMO 2024;Abstract 134MO.

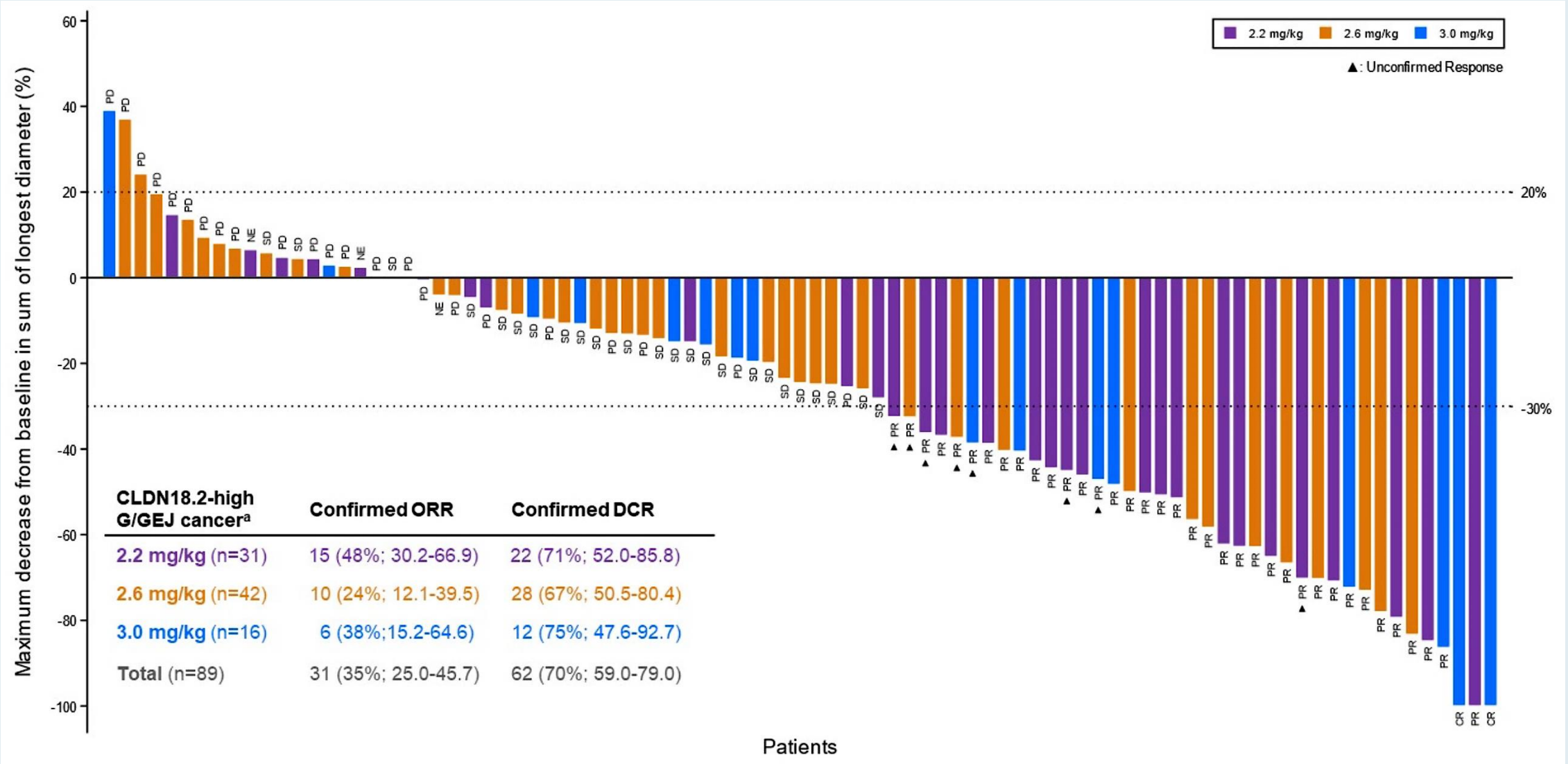
AZD0901: Anti-CLDN18.2 Antibody-Drug Conjugate





Janjigian Y et al. Gastrointestinal Cancers Symposium 2025;Abstract TPS507.

Phase I Study of AZD0901 for CLDN18.2-Positive Gastroesophageal Cancers: ORR



CLDN18.2-high G/GEJ cancer[a]	Confirmed ORR	Confirmed DCR
2.2 mg/kg (n=31)	15 (48%; 30.2-66.9)	22 (71%; 52.0-85.8)
2.6 mg/kg (n=42)	10 (24%; 12.1-39.5)	28 (67%; 50.5-80.4)
3.0 mg/kg (n=16)	6 (38%;15.2-64.6)	12 (75%; 47.6-92.7)
Total (n=89)	31 (35%; 25.0-45.7)	62 (70%; 59.0-79.0)

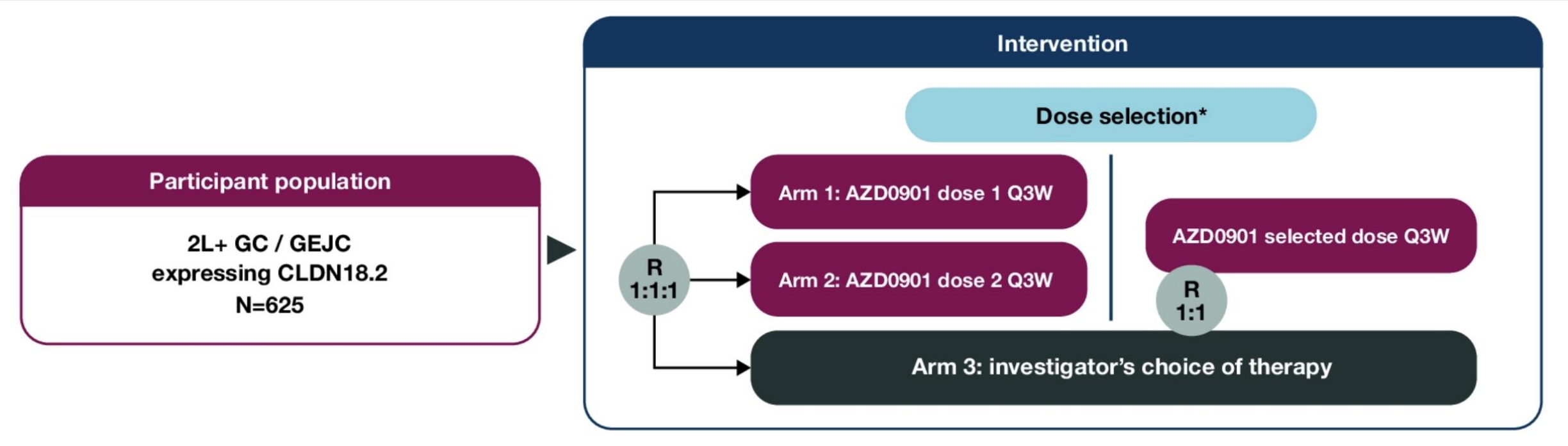
Xu R-H et al. ASCO 2024;Abstract 434420.

Phase I Study of AZD0901 for CLDN18.2-Positive Gastroesophageal Cancers: Safety

	2.2 mg/kg (n=44)		2.6 mg/kg (n=50)		3.0 mg/kg (n=19)		Total (n=113)	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Anaemia	27 (61%)	6 (14%)	31 (62%)	8 (16%)	13 (68%)	1 (5%)	71 (63%)	15 (13%)
Vomiting	23 (52%)	5 (11%)	30 (60%)	4 (8%)	12 (63%)	2 (11%)	65 (58%)	11 (10%)
Hypoalbuminaemia	26 (59%)	0	27 (54%)	0	12 (63%)	0	65 (58%)	0
Weight decreased	18 (41%)	0	29 (58%)	2 (4%)	15 (79%)	1 (5%)	62 (55%)	3 (3%)
Nausea	19 (43%)	0	28 (56%)	3 (6%)	15 (79%)	1 (5%)	62 (55%)	4 (4%)
Neutrophil count decreased	18 (41%)	5 (11%)	28 (56%)	11 (22%)	13 (68%)	5 (26%)	59 (52%)	21 (19%)
White blood cell count decreased	17 (39%)	4 (9%)	28 (56%)	4 (8%)	12 (63%)	0	57 (50%)	8 (7%)
Decreased appetite	19 (43%)	6 (14%)	26 (52%)	1 (2%)	10 (53%)	1 (5%)	55 (49%)	8 (7%)
Aspartate aminotransferase increased	19 (43%)	0	18 (36%)	0	10 (53%)	0	47 (42%)	0
Asthenia	13 (30%)	3 (7%)	12 (24%)	0	8 (42%)	1 (5%)	33 (29%)	4 (4%)
Proteinuria	10 (23%)	0	11 (22%)	1 (2%)	9 (47%)	0	30 (27%)	1 (1%)
Alanine aminotransferase increased	14 (32%)	0	11 (22%)	0	6 (32%)	0	31 (27%)	0
Hyponatraemia	9 (20%)	0	15 (30%)	0	5 (26%)	0	29 (26%)	0
Diarrhoea	7 (16%)	0	10 (20%)	1 (2%)	7 (37%)	0	24 (21%)	1 (1%)

Xu R-H et al. ASCO 2024;Abstract 434420.

CLARITY Gastric 01: A Randomized Phase III Study of AZD0901 for Second-Line or Later Therapy for CLDN18.2-Positive Gastroesophageal Cancers



Janjigian Y et al. Gastrointestinal Cancers Symposium 2025;Abstract TPS507.

Data + Perspectives: Clinical Investigators Discuss the Current and Future Role of Immunotherapy and Antibody-Drug Conjugates in Lung Cancer

A CME Symposium Held in Conjunction with the 2025 ASCO® Annual Meeting

Friday, May 30, 2025

11:15 AM – 12:45 PM CT (12:15 PM – 1:45 PM ET)

Faculty

Marina Chiara Garassino, MBBS

John V Heymach, MD, PhD

Professor Solange Peters, MD, PhD

Moderator

Jacob Sands, MD

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Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open for 5 minutes after the meeting ends.

Information on how to obtain CME, ABIM MOC and ABS credit is provided in the Zoom chat room. Attendees will also receive an email in 1 to 3 business days with these instructions.

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