Meet The Professor
Optimizing the Management of Gastroesophageal Cancers

Thursday, September 28, 2023
5:00 PM – 6:00 PM ET

Faculty

Peter C Enzinger, MD

Moderator

Neil Love, MD

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Commercial Support

This activity is supported by educational grants from Astellas, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Daiichi Sankyo Inc, and Novartis.

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Nonrelevant Financial Relationship	American Gastroenterological Association, Degregorio Family Foundation, National Cancer Institute/National Institutes of Health, Stand Up 2 Cancer/AACR

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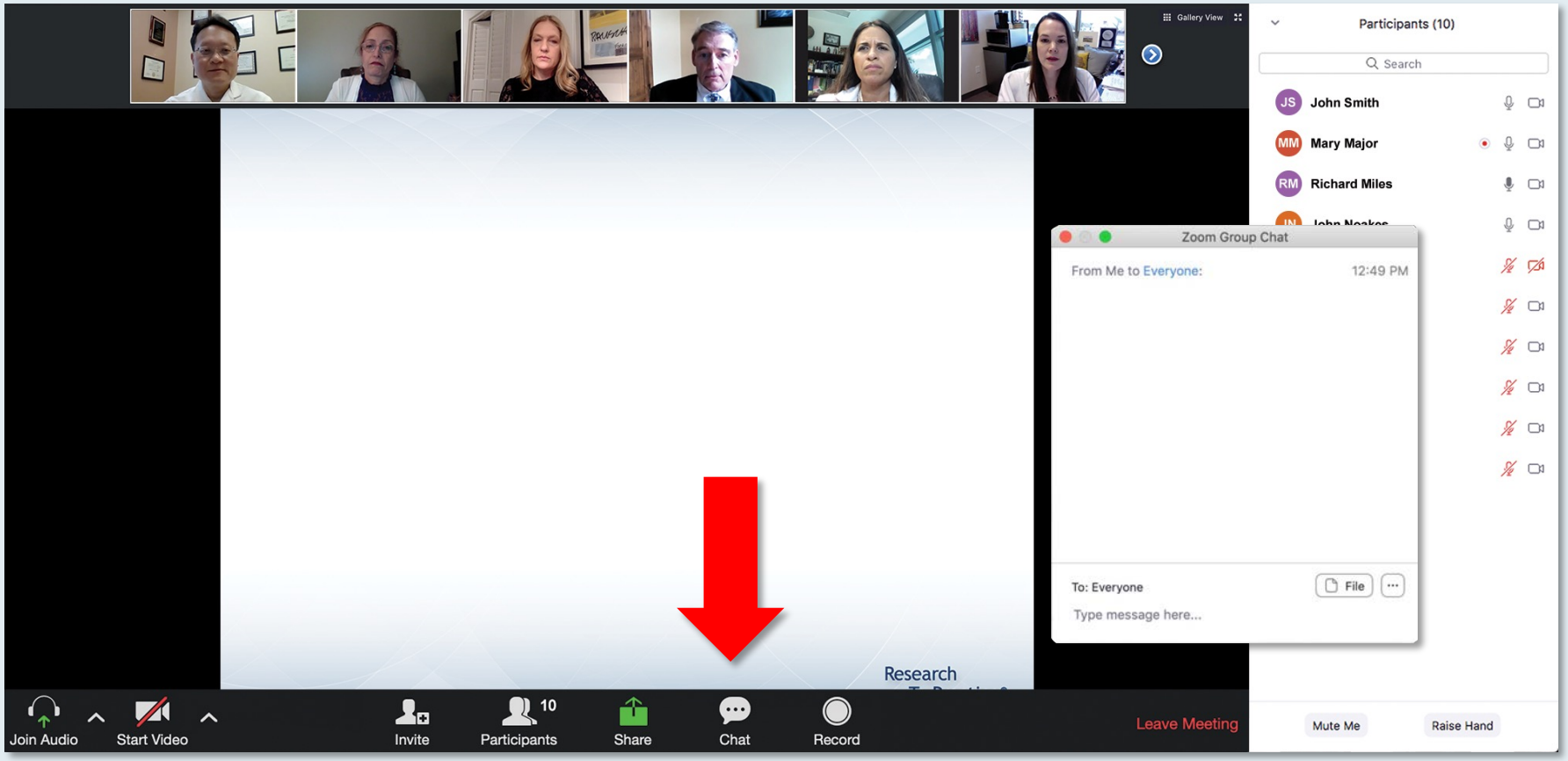

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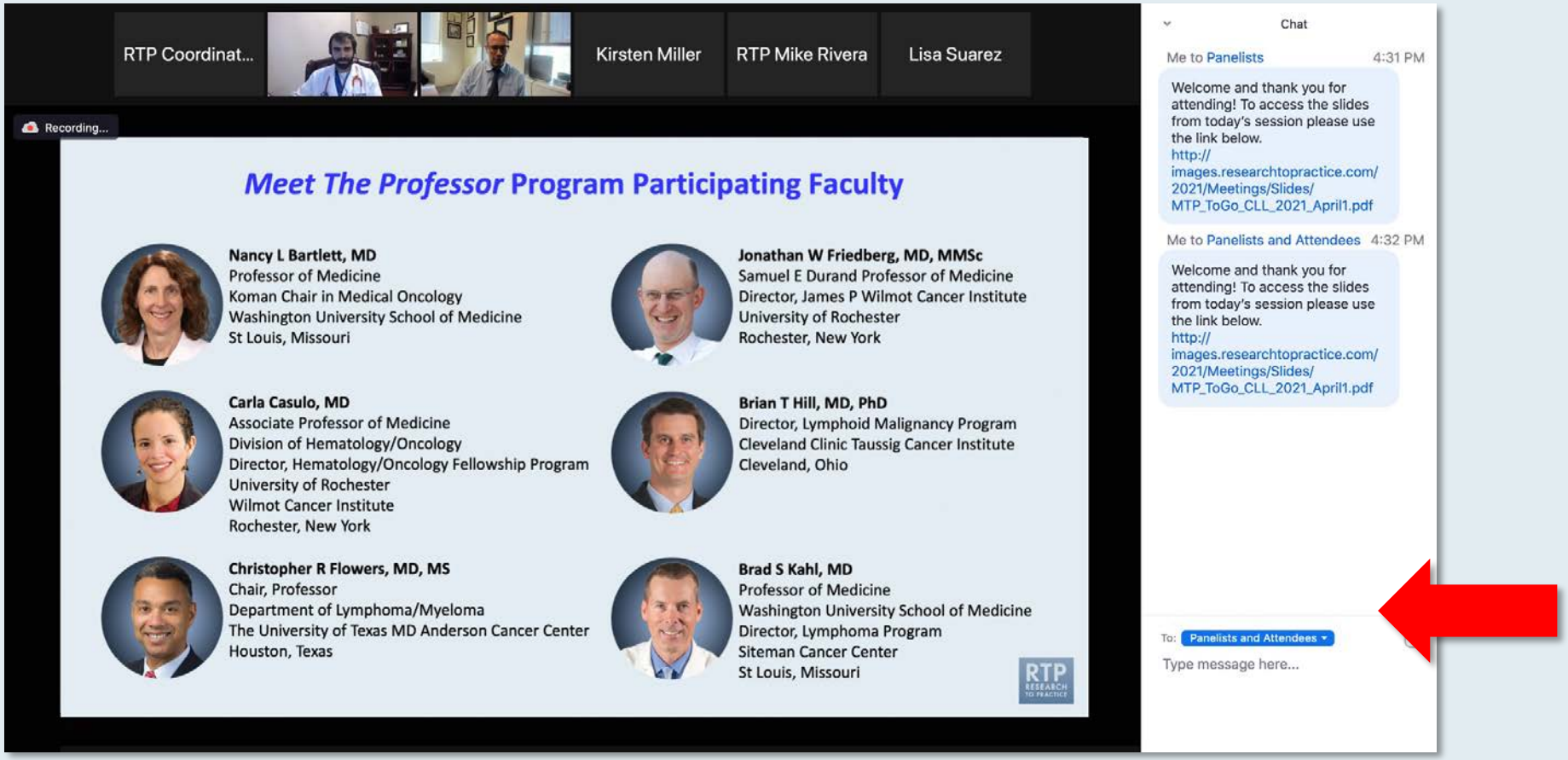

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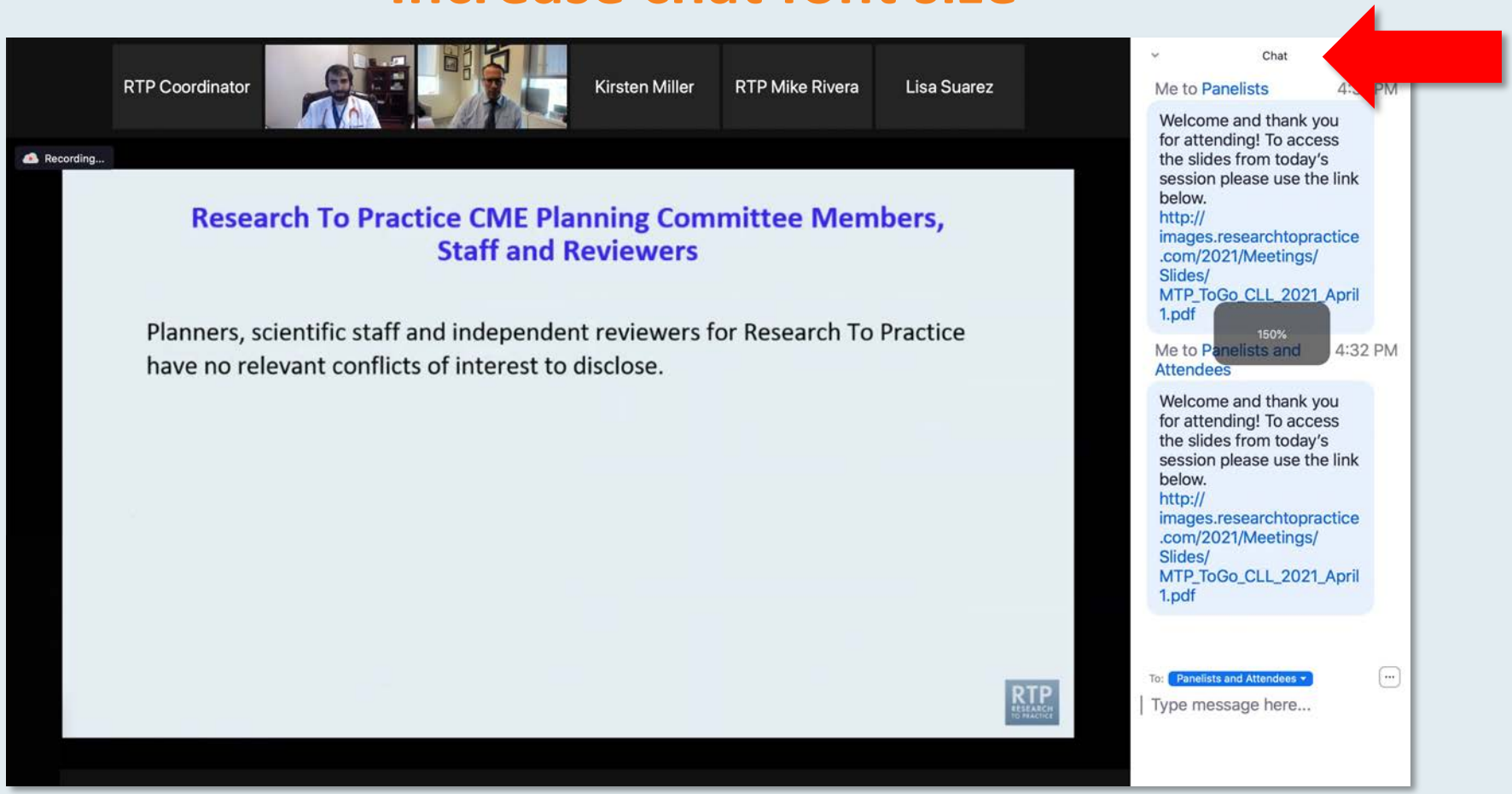

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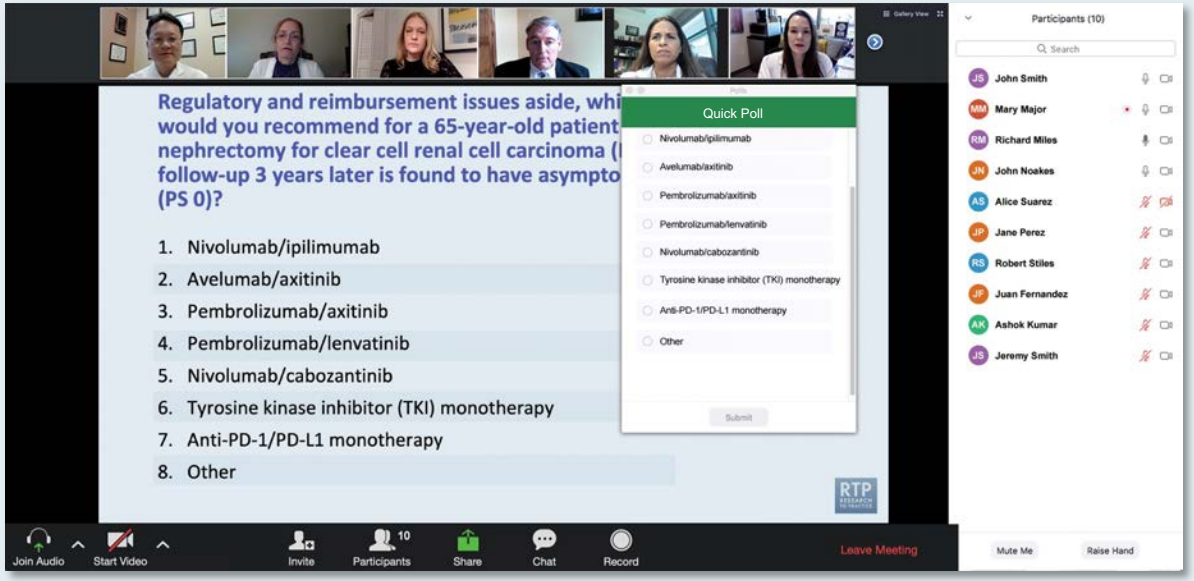

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Optimizing the Management of Metastatic Pancreatic Cancer

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MEMORIAL SLOAN KETTERING CANCER CENTER

DR ZEV WAINBERG

UCLA JONSSON COMPREHENSIVE CANCER CENTER

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Inside the Issue: Optimizing the Management of Nonmelanoma Skin Cancer

A CME/MOC-Accredited Live Webinar

Tuesday, October 3, 2023
5:00 PM – 6:00 PM ET

Faculty

Nikhil I Khushalani, MD
Anna C Pavlick, DO, MBA

Moderator

Neil Love, MD

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7:15 AM – 8:15 AM ET

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Lymphoma

9:30 AM – 10:30 AM PT
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Ann S LaCasce, MD, MMSc

Urothelial Bladder Cancer and Renal Cell Carcinoma

10:30 AM – 11:30 AM PT
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Peter C Enzinger, MD
Director
Center for Esophageal and Gastric Cancer
Dana-Farber/Brigham and Women's Cancer Center
Institute Physician, Dana-Farber Cancer Institute
Associate Professor, Harvard Medical School
Boston, Massachusetts

Meet The Professor Program Participating Faculty

Jaffer A Ajani, MD
Professor of Medicine
Department of Gastrointestinal Medical Oncology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Peter C Enzinger, MD
Director
Center for Esophageal and Gastric Cancer
Dana-Farber/Brigham and Women's Cancer Center
Institute Physician, Dana-Farber Cancer Institute
Associate Professor, Harvard Medical School
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Sunnie Kim, MD
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Samuel J Klempner, MD
Associate Professor
Massachusetts General Hospital
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Boston, Massachusetts

Eric Van Cutsem, MD, PhD
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Digestive Oncology
University Hospitals Leuven
Leuven, Belgium

Harry H Yoon, MD, MHS
Professor of Oncology
Enterprise Co-Leader
Gastrointestinal and Hepatobiliary
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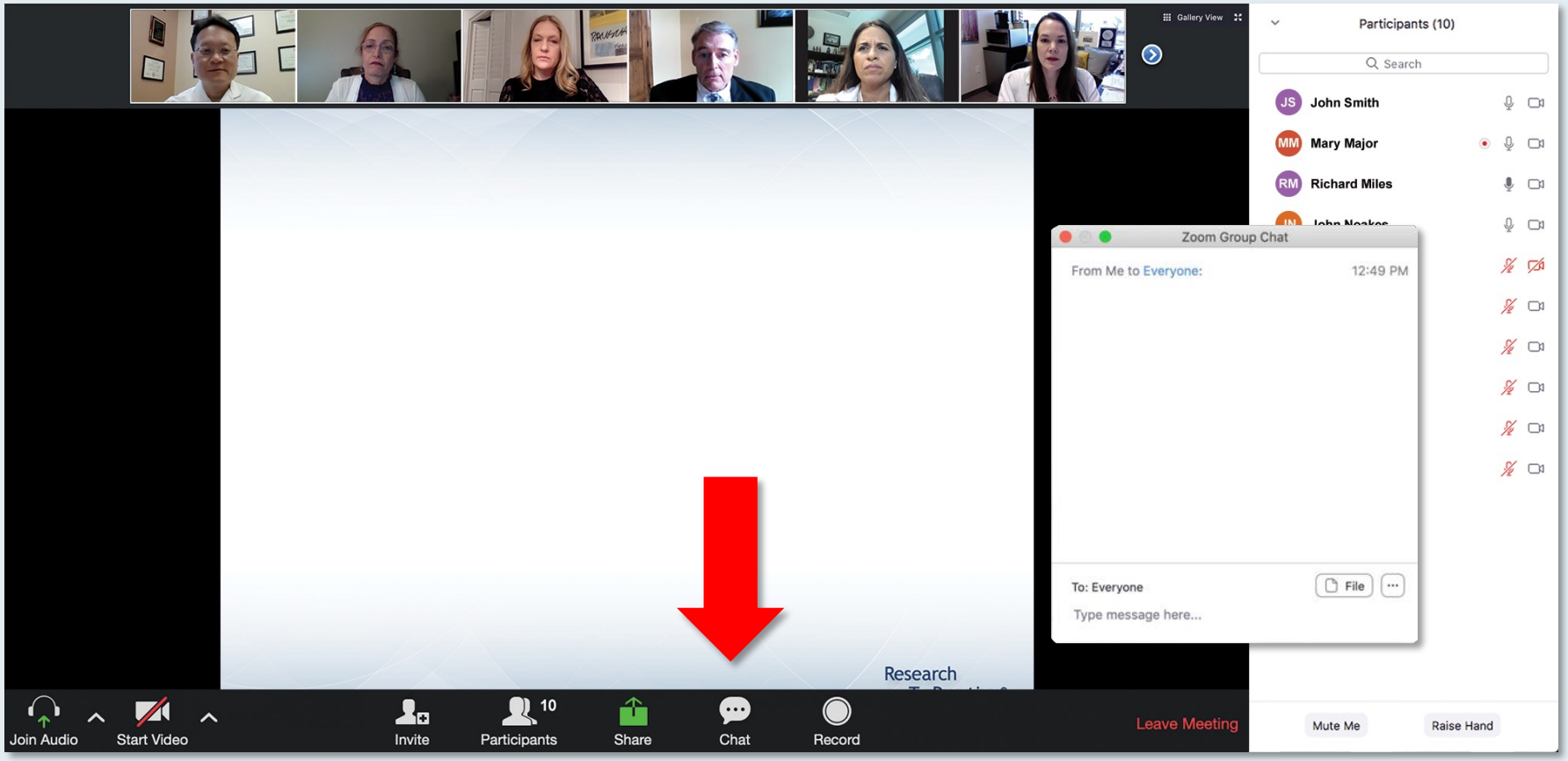

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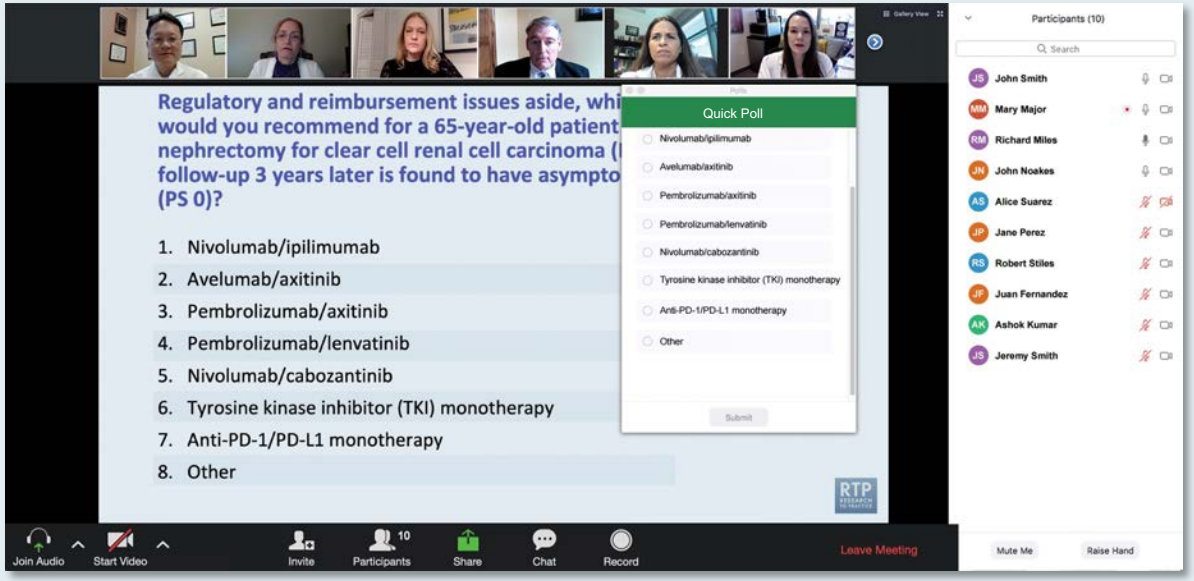

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Florida Cancer Specialists
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Eric H Lee, MD, PhD
Compassionate Cancer Care Medical Group
Fountain Valley, California

Jennifer L Dallas, MD
Oncology Specialists of Charlotte
Charlotte, North Carolina

Priya Rudolph, MD, PhD
Georgia Cancer Specialists
Athens, Georgia

Farshid Dayyani, MD, PhD
Stern Center for Cancer Clinical Trials and Research
Orange, California

Matthew R Strickland, MD
Massachusetts General Hospital Cancer Center
Boston, Massachusetts

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Meet The Professor with Dr Enzinger

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INTRODUCTION

MODULE 1: HER2-Positive Gastroesophageal Cancer

MODULE 2: Immunotherapy for HER2-Negative Disease

MODULE 3: Investigational Approaches – Zolbetuximab, Bemarituzumab

MODULE 4: Journal Club with Dr Enzinger

MODULE 5: Appendix

Open access Original research

BMJ Open Sport & Exercise Medicine

Physical activity in older adults with metastatic gastrointestinal cancer: a pilot and feasibility study

Justin C Brown ,[1,2] Elizabeth Brighton,[3] Nancy Campbell,[3] Nadine J McCleary,[3] Thomas A Abrams,[3] James M Cleary,[3] Peter C Enzinger,[3] Kimmie Ng,[3] Douglas Rubinson,[3] Brian M Wolpin,[3] Matthew B Yurgelun,[3] Jeffrey A Meyerhardt[3]

2022;8(2):e001353

Baseline-Informed versus Tumor-Agnostic Minimal Residual Disease (MRD) Concordance Study in Patients with HER2+ Gastroesophageal Adenocarcinoma

Du P et al.

ESMO 2023;Abstract 2262P.

Meet The Professor with Dr Enzinger

Case Presentation: 64-year-old man with HER2-positive metastatic SCC of the esophagus develops PD after treatment with 5-FU/cisplatin/trastuzumab – PD-L1 CPS 10

Dr Eric Lee (Fountain Valley, California)

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Primary Endpoint of PFS Met with First-Line Pembrolizumab/ Trastuzumab and Chemotherapy in KEYNOTE-811 Trial

Press Release: June 16, 2023

"[The] Phase 3 KEYNOTE-811 trial investigating pembrolizumab ... in combination with trastuzumab and chemotherapy met one of its dual primary endpoints of progression-free survival (PFS) for the first-line treatment of human epidermal growth factor receptor 2 (HER2)-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma.

At a pre-specified interim analysis conducted by an independent Data Monitoring Committee, pembrolizumab in combination with trastuzumab and chemotherapy demonstrated a statistically significant improvement in PFS compared to placebo in combination with trastuzumab and chemotherapy in the intention-to-treat (ITT) study population. Based on a pre-specified subgroup analysis by PD-L1 expression, the improvement in PFS observed in the ITT population was limited to patients whose tumors were PD-L1 positive (Combined Positive Score [CPS] ≥1). In the study, more than 80% of patients had tumors that were PD-L1 positive."

These findings have been discussed with the US Food and Drug Administration (FDA) and efforts are underway to update the current indication for pembrolizumab in HER2-positive gastric or GEJ adenocarcinoma to those patients whose tumors are PD-L1 positive. In addition, these results will be presented at an upcoming medical meeting and shared with regulatory authorities worldwide.

https://www.businesswire.com/news/home/20230616585453/en/KEYTRUDA®-pembrolizumab-Plus-Trastuzumab-and-Chemotherapy-Met-Primary-Endpoint-of-Progression-Free-Survival-as-First-Line-Treatment-in-Patients-With-HER2-Positive-Advanced-Gastric-or-Gastroesophageal-Junction-GEJ-Adenocarcinoma

Case Presentation: 64-year-old man with HER2-positive metastatic SCC of the esophagus develops PD after treatment with 5-FU/cisplatin/trastuzumab – PD-L1 CPS 10 (continued)

Dr Eric Lee (Fountain Valley, California)

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Questions and Comments: Role of HER2-targeted therapy for locally advanced gastroesophageal cancer; trastuzumab deruxtecan and ILD

Dr Matthew Strickland (Boston, Massachusetts)

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RESEARCH
TO PRACTICE

Dear Dr Love,

I am a general oncologist in Germany and I need help with the following case:

40-year-old female from Russia, two young kids, colon cancer with liver and lung metastasis. Primary and samples from liver and lung show KRAS G13D and HER2 overexpression (3+).

She progressed quickly on TAS 102 and is now receiving FOLFIRI + ramucirumab. Would the experts recommend T-DXd despite the KRAS mutation?

So far, I have not been able to get her on a clinical trial and the insurance declined payment of T-DXd. The patient is very informed and wants to receive T-DXd. She would be willing to cover the costs herself.

Kind Regards,
Dr Mithun Scheytt

Abstract 1205MO

PARIS 2022 ESMO congress

Updated Analysis of DESTINY-Gastric02: a Phase 2 Single-Arm Trial of Trastuzumab Deruxtecan (T-DXd) in Western Patients with HER2-Positive Unresectable/Metastatic Gastric/Gastroesophageal Junction (GEJ) Cancer Who Progressed on or After Trastuzumab-Containing Regimen

Presentation 1205MO

Geoffrey Ku,[a] Maria di Bartolomeo, Eliza
Ian Chau, Haeseong Park, Salvatore Sier
Zev A. Wainberg, Jaffer Ajani, Joseph Chao, F
Yoshinori Kawaguchi, Amy Qin, Jasmeet Sing
Gerold Meinhardt, Eric Van Cutsem

On behalf of the DESTINY-Gastric02 in

[a]Memorial Sloan Kettering Cancer Center, New
Paris, France, September 9-13, 2022

Lancet Oncol 2023;24:744-56

Trastuzumab deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastroesophageal junction cancer with disease progression on or after a trastuzumab-containing regimen (DESTINY-Gastric02): primary and updated analyses from a single-arm, phase 2 study

Eric Van Cutsem, Maria di Bartolomeo, Elizabeth Smyth, Ian Chau, Haeseong Park, Salvatore Siena, Sara Lonardi, Zev A Wainberg, Jaffer Ajani, Joseph Chao, Yelena Janjigian, Amy Qin, Jasmeet Singh, Ferdous Barlaskar, Yoshinori Kawaguchi, Geoffrey Ku

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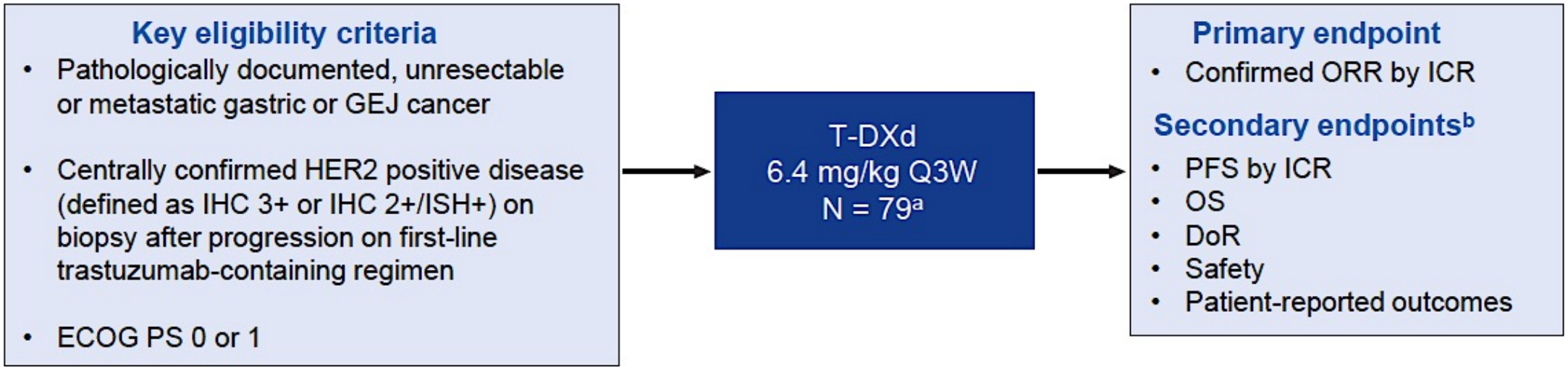
DESTINY-Gastric02 Phase II Study Design



- 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 G et al. ESMO 2022;Abstract 1205MO.

DESTINY-Gastric02: Efficacy Endpoints

	April 9, 2021, data cutoff; patients (N=79)	Nov 8, 2021, data cutoff; patients (N=79)
Confirmed objective response	30 (38%; 27·3–49·6)	33 (42%; 30·8–53·4)
Confirmed best overall response		
Complete response	3 (4%)	4 (5%)
Partial response	27 (34%)	29 (37%)
Stable disease	34 (43%)	31 (39%)
Progressive disease	13 (16%)	13 (16%)
Not evaluable	2 (3%)	2 (3%)
Median progression-free survival, months	5·5 (4·2–7·2)*	5·6 (4·2–8·3)†
Patients with events	44 (56%)	51 (65%)
Progressive disease	37 (47%)	44 (56%)
Death	7 (9%)	7 (9%)
Median overall survival, months	12·1 (8·6–NE)‡	12·1 (9·4–15·4)§
Patients with events	26 (33%)	46 (58%)
Patients without events (censored)	53 (67%)	33 (42%)
Alive	46 (58%)	26 (33%)
Lost to follow-up	7 (9%)	7 (9%)
Confirmed disease control	64 (81%; 70·6-89·0)	64 (81%; 70·6–89·0)
Median time to response, months	1·4 (1·4–2·6)	1·4 (1·4–2·7)
Median duration of response, months	8·1 (4·1–NE)¶	8·1 (5·9–NE)‖

Ku G 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.

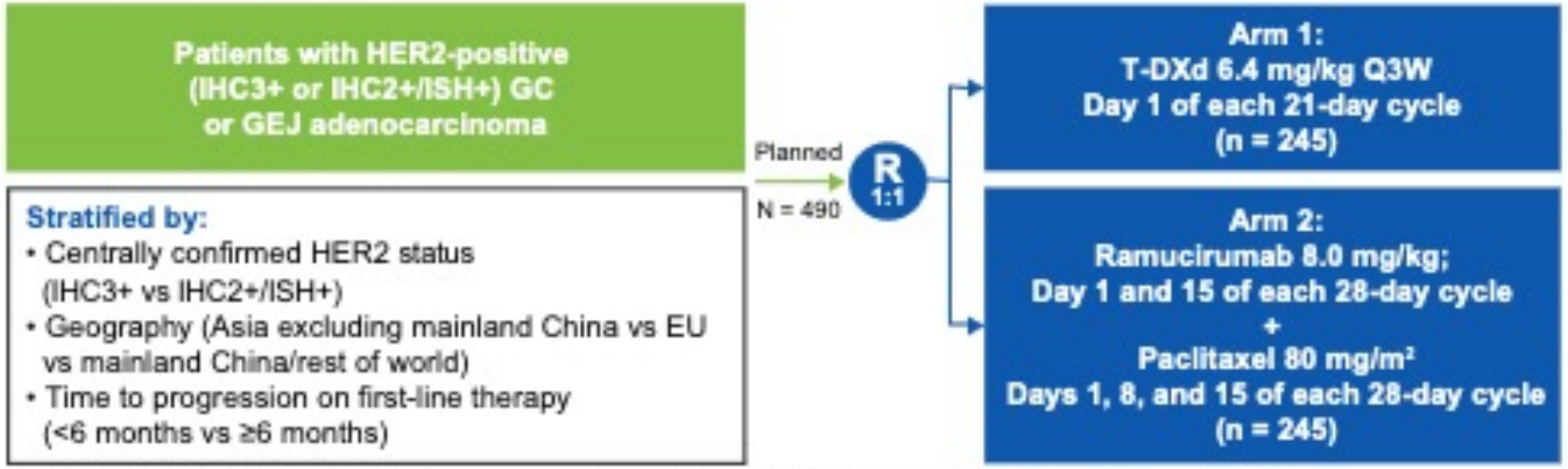
Ku G et al. ESMO 2022;Abstract 1205MO. Van Cutsem E et al. *Lancet Oncol* 2023;24:744-56.

DESTINY-Gastric04 Ongoing Phase III Trial Schema

Study Design and Population

- DESTINY-Gastric04 is a global, multicenter, 2-arm, randomized, open-label phase 3 study (**Figure 2**)

Figure 2. Study Design



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.

Primary endpoint: Overall survival
Secondary endpoints: PFS, ORR, DOR, DCR

Shitara K et al. World Congress on Gastrointestinal Cancer 2022;Abstract P-159.

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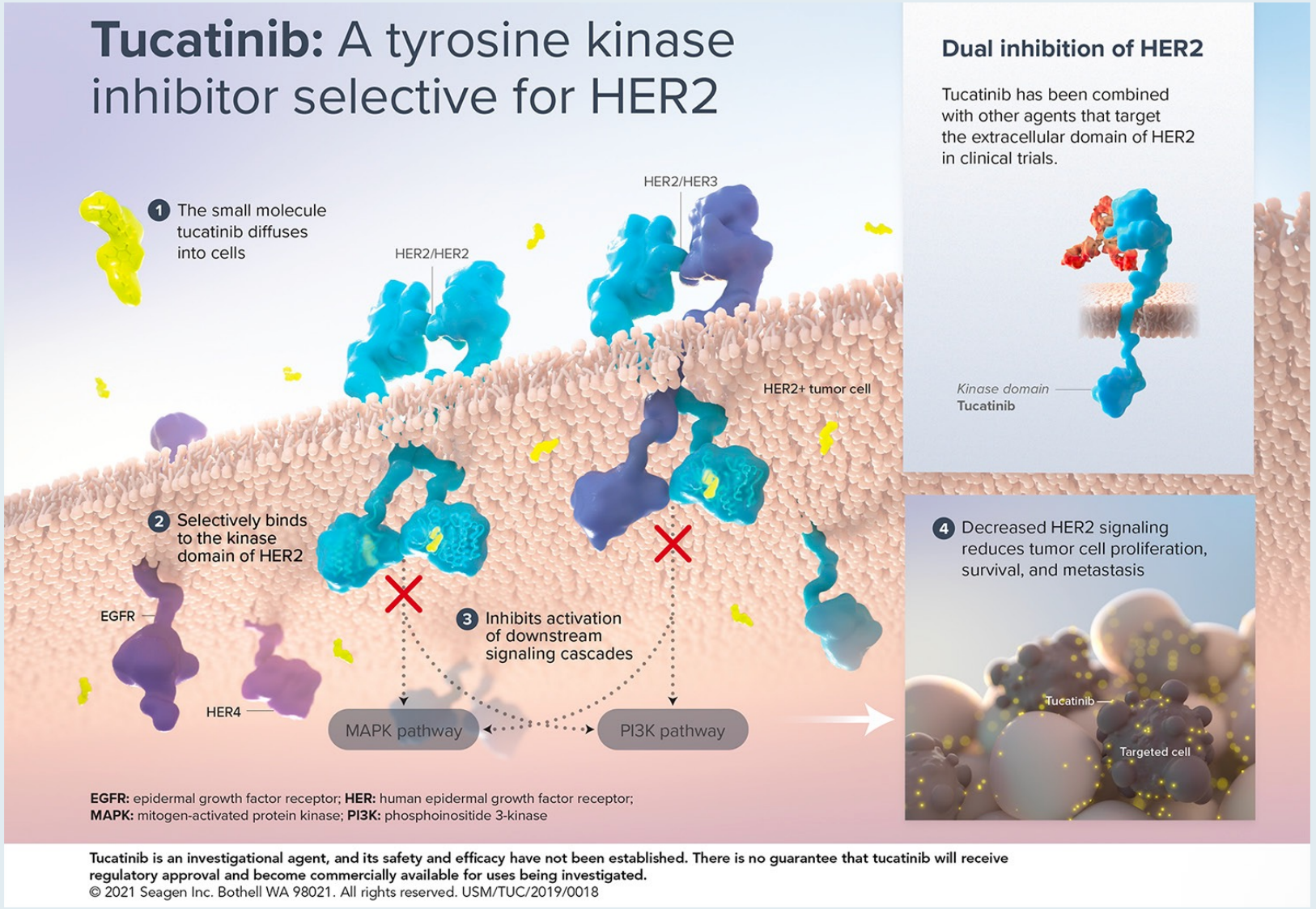
Tucatinib Proposed Mechanism of Action



Tucatinib is an investigational agent, and its safety and efficacy have not been established. There is no guarantee that tucatinib will receive regulatory approval and become commercially available for uses being investigated.

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

FDA Grants Accelerated Approval to Tucatinib with Trastuzumab for Colorectal Cancer

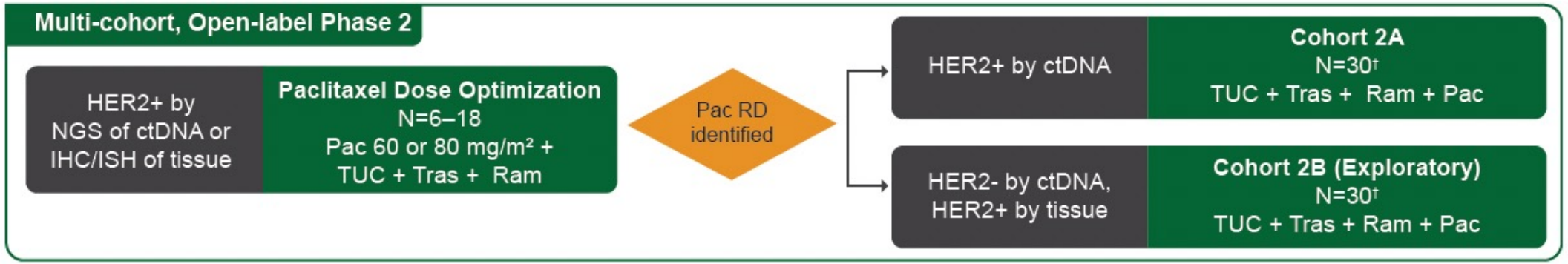
Press Release: January 19, 2023

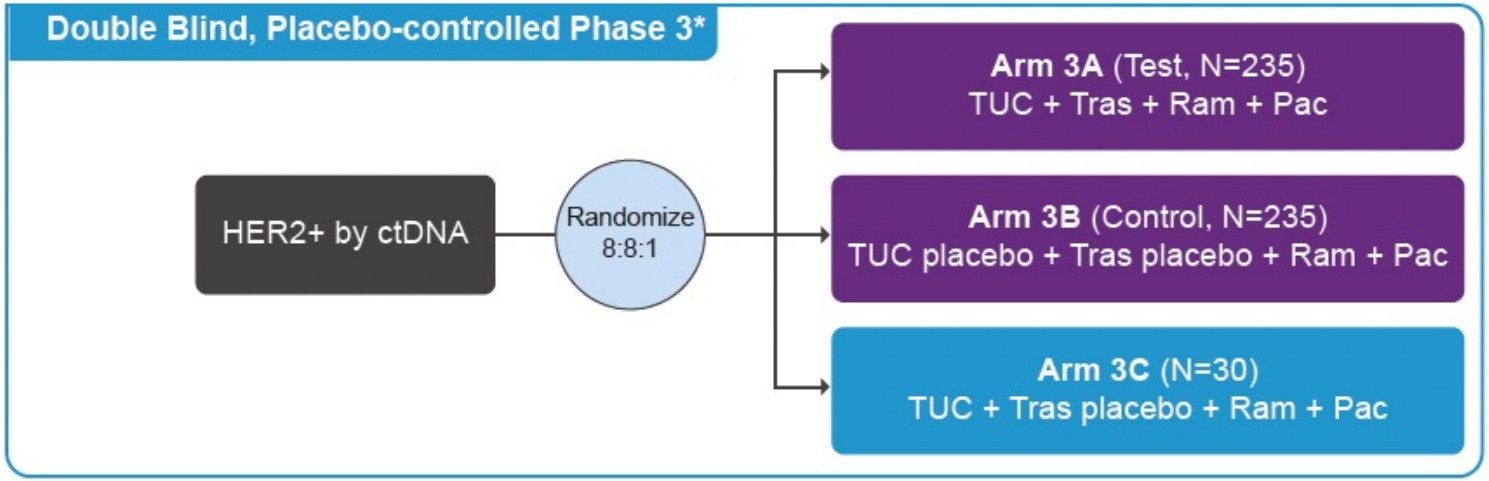
"On January 19, 2023, the Food and Drug Administration (FDA) granted accelerated approval to tucatinib in combination with trastuzumab for RAS wild-type HER2-positive unresectable or metastatic colorectal cancer that has progressed following fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

Efficacy was evaluated in 84 patients in MOUNTAINEER (NCT03043313), an open-label, multicenter trial. Patients were required to have HER2-positive, RAS wild-type, unresectable or metastatic colorectal cancer and prior treatment with fluoropyrimidine, oxaliplatin, irinotecan, and an anti-vascular endothelial growth factor (VEGF) monoclonal antibody (mAb). Patients whose tumors were deficient in mismatch repair (dMMR) proteins or were microsatellite instability-high (MSI-H) must also have received an anti-programmed cell death protein-1 mAb. Patients who received prior anti-HER2 targeting therapy were excluded."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tucatinib-trastuzumab-colorectal-cancer

MOUNTAINEER-02 Phase II/III Study of Tucatinib, Trastuzumab, Ramucirumab and Paclitaxel as Second-Line Therapy for HER2-Positive Gastric Cancer: Design





† Subjects in the dose optimization stage will be counted towards the sample size for these cohorts, if they received the recommended dose and are response-evaluable.

Formal statistical comparisons to be made between Arms 3A and 3B

Randomization stratified by Asia vs Rest of World, Time to Progression, Prior Gastrectomy

* The SMC may recommend proceeding to phase 3 if the regimen is safe and tolerable and an ORR ≥36% is observed in all response-evaluable patients treated at the Pac RD who have HER2+ disease by NGS assay of ctDNA.

NGS = next-generation sequencing; TUC = tucatinib; Tras = trastuzumab; Ram = ramucirumab; Pac = paclitaxel; RD = recommended dose; ctDNA = circulating tumor DNA

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

In general, which biomarkers and assays do you believe oncologists in community practice should evaluate or use for patients with newly diagnosed advanced gastroesophageal cancer?

 Dr Ajani	PD-L1, MSI, HER2
 Dr Enzinger	PD-L1, MSI, HER2
 Dr Kim	PD-L1, MSI, HER2, claudin 18.2, NGS
 Dr Klempner	PD-L1, MSI, HER2, NGS, liquid biopsy
 Prof Van Cutsem	PD-L1, MSI, HER2
 Dr Yoon	PD-L1, MSI, HER2

MSI = microsatellite instability; NGS = next-generation sequencing

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Regulatory and reimbursement issues aside, what would be your preferred first-line treatment for a patient with newly diagnosed metastatic HER2-positive, MSS gastric adenocarcinoma if their PD-L1 CPS was 0? CPS ≥1?

	PD-L1 CPS 0	PD-L1 CPS ≥1
 Dr Ajani	FOLFOX/trastuzumab	Trastuzumab/mFOLFOX6/ pembrolizumab
 Dr Enzinger	FOLFOX/trastuzumab	Trastuzumab/chemotherapy/ pembrolizumab (KN-811)
 Dr Kim	FOLFOX/trastuzumab	FOLFOX/trastuzumab
 Dr Klempner	FOLFOX/trastuzumab	Trastuzumab/FOLFOX/ pembrolizumab
 Prof Van Cutsem	FOLFOX/trastuzumab	Trastuzumab/FOLFOX6/ pembrolizumab
 Dr Yoon	FOLFOX/trastuzumab	Trastuzumab/FOLFOX/ pembrolizumab

Regulatory and reimbursement issues aside, what would you currently recommend as second-line therapy for a patient with metastatic HER2-positive, MSS gastric adenocarcinoma (PD-L1 CPS ≥1) who experienced disease progression on FOLFOX/trastuzumab?

 Dr Ajani	Trastuzumab deruxtecan
 Dr Enzinger	Trastuzumab deruxtecan
 Dr Kim	Trastuzumab deruxtecan
 Dr Klempner	Trastuzumab deruxtecan or ramucirumab/paclitaxel
 Prof Van Cutsem	Trastuzumab deruxtecan
 Dr Yoon	Trastuzumab deruxtecan

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Regulatory and reimbursement issues aside, what would you currently recommend as second-line therapy for a patient with metastatic HER2-positive, MSS gastric adenocarcinoma (PD-L1 CPS ≥1) who experienced disease progression on FOLFOX/trastuzumab/pembrolizumab?

 Dr Ajani	Trastuzumab deruxtecan
 Dr Enzinger	Trastuzumab deruxtecan
 Dr Kim	Trastuzumab deruxtecan
 Dr Klempner	Trastuzumab deruxtecan or ramucirumab/paclitaxel
 Prof Van Cutsem	Trastuzumab deruxtecan
 Dr Yoon	Trastuzumab deruxtecan

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At what grade of ILD would you permanently discontinue therapy with trastuzumab deruxtecan for a patient with HER2-positive gastric/GEJ adenocarcinoma?

 Dr Ajani	Grade 1
 Dr Enzinger	Grade 2
 Dr Kim	Grade 2
 Dr Klempner	Grade 2
 Prof Van Cutsem	Grade 2
 Dr Yoon	Grade 2

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Have you offered or would you offer trastuzumab deruxtecan to a patient with HER2-low gastric/GEJ adenocarcinoma outside of a clinical trial?

 Dr Ajani	I have not and would not
 Dr Enzinger	I have not and would not
 Dr Kim	I have not and would not
 Dr Klempner	I have not but would for the right patient
 Prof Van Cutsem	I have not and would not
 Dr Yoon	I have not and would not

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Meet The Professor with Dr Enzinger

Case Presentation: 53-year-old man with HER2-negative, MSS esophageal cancer and mediastinal lymphadenopathy receives concurrent chemoradiation (CROSS trial regimen)

Dr Jennifer Dallas (Charlotte, North Carolina)

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Dr Priya Rudolph
(Athens, Georgia)

Case Presentation: 83-year-old frail woman with PMH of cardiac issues is diagnosed with localized GEJ adenocarcinoma

Dr Mamta Choksi
(New Port Richey, Florida)

Questions and Comments: Impacts of chemotherapy shortages

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original reports

Neoadjuvant Nivolumab Plus Ipilimumab and Adjuvant Nivolumab in Localized Deficient Mismatch Repair/Microsatellite Instability–High Gastric or Esophagogastric Junction Adenocarcinoma: The GERCOR NEONIPIGA Phase II Study

Thierry André, MD[1]; David Tougeron, MD, PhD[2]; Guillaume Piessen, MD, PhD[3]; Christelle de la Fouchardière, MD[4]; Christophe Louvet, MD, PhD[5]; Antoine Adenis, MD, PhD[6]; Marine Jary, MD[7]; Christophe Tournigand, MD, PhD[8]; Thomas Aparicio, MD, PhD[9]; Jérôme Desrame, MD[10]; Astrid Lièvre, MD, PhD[11]; Marie-Line Garcia-Larnicol, MD[12]; Thomas Pudlarz, MD[1]; Romain Cohen, MD, PhD[1]; Salomé Memmi, MD, PhD[13]; Dewi Vernerey, PhD[14,15]; Julie Henriques, MSc[14,15]; Jérémie H. Lefevre, MD, PhD[16]; and Magali Svrcek, MD, PhD[13]

J Clin Oncol 2023 January 10;41(2):255-65

RTP RESEARCH TO PRACTICE

NEONIPIGA: Efficacy

N = 32		
Underwent surgery	**R0 resection**	**pCR**
29/32*	29/29 (100%)	17/29 (58.6%)

* Three patients did not have surgery and had a complete endoscopic response with tumor-free biopsies and normal CT scans.

pCR = pathologic complete response

André T et al. *J Clin Oncol* 2023 January 10;41(2):255-65.

ASCO Gastrointestinal Cancers Symposium 2023

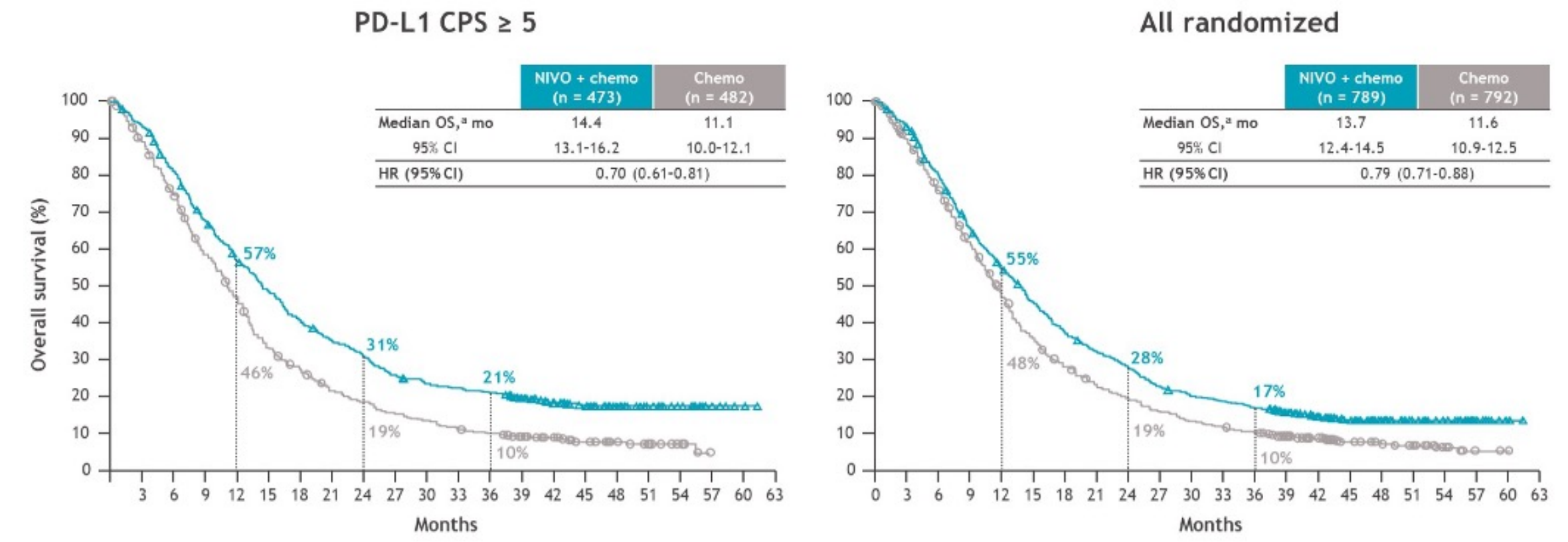
Nivolumab plus chemotherapy vs chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: 3-year follow-up from CheckMate 649

Yelena Y. Janjigian,[1] Kohei Shitara,[2] Markus Moehler,[3] Marcelo Garrido,[4] Carlos Gallardo,[5] Lin Shen,[6] Kensei Yamaguchi,[7] Lucjan Wyrwicz,[8] Tomasz Skoczylas,[9] Arinilda Bragagnoli,[10] Tianshu Liu,[11] Mustapha Tehfe,[12] Elena Elimova,[13] Ricardo Bruges,[14] James M. Cleary,[15] Michalis Karamouzis,[16] Samira Soleymani,[17] Ming Lei,[17] Carlos Amaya Chanaga,[17] Jaffer A. Ajani[18]

[1]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; [2]National Cancer Center Hospital East, Kashiwa, Japan; [3]Johannes-Gutenberg University Clinic, Mainz, Germany; [4]Clinica San Carlos de Apoquindo, Pontificia Universidad Católica, Santiago, Chile; [5]Fundación Arturo López Pérez, Providencia, Chile; [6]Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, China; [7]The Cancer Institute Hospital of JFCR, Tokyo, Japan; [8]Klinika Onkologii i Radioterapii, Narodowy Instytut Onkologii, Warszawa, Poland; [9]II Klinika Chirurgii Ogólnej, Gastroenterologicznej i Nowotworów Układu Pokarmowego, Medical University of Lublin, Lublin, Poland; [10]Fundacao Pio Xii Hosp Cancer De Barretos, Barretos, Brazil; [11]Zhongshan Hospital Fudan University, Shanghai, China; [12]Oncology Center-Centre Hospitalier de l'Universite de Montreal, Montreal, Canada; [13]Princess Margaret Cancer Centre, Toronto, Canada; [14]Instituto Nacional de Cancerologia E.S.E., Bogotá, Colombia; [15]Dana Farber Cancer Institute, Boston, MA; [16]Laiko General Hospital of Athens, Athens, Greece; [17]Bristol Myers Squibb, Princeton, NJ; [18]The University of Texas MD Anderson Cancer Center, Houston, TX

Abstract number 291

CheckMate 649: Overall Survival with Nivolumab and Chemotherapy versus Chemotherapy Alone — 36-Month Follow-Up



- Clinically meaningful improvement in OS with NIVO and chemotherapy versus chemotherapy was maintained with longer follow-up in PD-L1 CPS ≥5 and all randomized populations

CPS = combined positive score; OS = overall survival; NIVO = nivolumab

Janjigian YY et al. Gastrointestinal Cancers Symposium 2023;Abstract 291.

ASCO Gastrointestinal Cancers Symposium 2023

Nivolumab plus chemotherapy or ipilimumab vs chemotherapy as first-line treatment for advanced esophageal squamous cell carcinoma: 29-month follow-up from CheckMate 648

Ken Kato,[1] Jaffer Ajani,[2] Yuichiro Doki,[3] Jianming Xu,[4] Lucjan Wyrwicz,[5] Satoru Motoyama,[6] Takashi Ogata,[7] Hisato Kawakami,[8] Chih-Hung Hsu,[9] Antoine Adenis,[10] Farid El Hajbi,[11] Maria Di Bartolomeo,[12] Maria Ignez Braghiroli,[13] Eva Holtved,[14] Mariela Blum Murphy,[2] Apurva Patel,[15] Nan Hu,[15] Yasuhiro Matsumura,[16] Ian Chau,[17] Yuko Kitagawa[18]

[1]National Cancer Center Hospital, Tokyo, Japan; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Osaka University Graduate School of Medicine, Osaka, Japan; [4]Affiliated Hospital Cancer Center, Academy of Military Medical Sciences, Beijing, China; [5]Klinika Onkologii i Radioterapii, Narodowy Instytut Onkologii, Warszawa, Poland; [6]Japanese Red Cross Akita Hospital, Akita, Japan; [7]Kanagawa Cancer Center, Kanagawa, Japan; [8]Kindai University Faculty of Medicine, Osakasayama, Japan; [9]National Taiwan University Hospital, Taipei, Taiwan; [10]Institut du Cancer de Montpellier, Montpellier, France; [11]Centre Oscar Lambret, Lille, France; [12]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [13]Institute of Cancer of São Paulo, University of São Paulo, São Paulo, Brazil; [14]Odense University Hospital, Odense, Denmark; [15]Bristol Myers Squibb, Princeton, NJ; [16]Ono Pharmaceutical Company Ltd., Osaka, Japan; [17]Royal Marsden Hospital, London & Surrey, UK; [18]Keio University School of Medicine, Tokyo, Japan

Abstract number 290

ESMO VIRTUAL PLENARY 2023;Abstract VP1-2023

Pembrolizumab Plus Chemotherapy as First-Line Therapy for Advanced HER2-Negative Gastric or Gastroesophageal Junction Cancer: Phase 3 KEYNOTE-859 Study

S.Y. Rha,[1] L.S. Wyrwicz,[2] P.E. Yañez Weber,[3] Y. Bai,[4] M.-H. Ryu,[5] J. Lee,[6] F. Rivera,[7] G. Vasconcelos Alves,[8] M. Garrido,[9] K.-K. Shiu,[10] M. González Fernández,[11] J. Li,[12] M.A. Lowery,[13] T. Çil,[14] F.J. Silva Melo Cruz,[15] S. Qin,[16] L. Yin,[17] S. Bordia,[17] P. Bhagia,[17] D.-Y. Oh[18] on behalf of the KEYNOTE-859 Investigators

[1]Yonsei Cancer Center, Yonsei University Health System, Seoul, Republic of Korea; [2]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [3]Universidad de La Frontera, James Lind Cancer Research Center, Temuco, Chile; [4]Harbin Medical University Cancer Hospital, Harbin, China; [5]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [6]Samsung Medical Center, Seoul, South Korea; [7]University Hospital Marqués de Valdecilla, IDIVAL, Santander, Spain; [8]Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; [9]Pontificia Universidad Católica de Chile, Santiago, Chile (currently at Universidad Mayor, Santiago, Chile); [10]University College Hospital, NHS Foundation Trust, London, UK; [11]IMAT-Oncomedica, Montería, Colombia; [12]Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China; [13]Trinity St. James Cancer Institute, Dublin, Ireland; [14]Health and Science University, Adana City Hospital, Adana, Turkey; [15]Nucleo de Pesquisa e Ensino da Rede São Camilo, São Paulo, Brazil; [16]Cancer Center of People's Liberation Army, Nanjing, China; [17]Merck & Co., Inc., Rahway, NJ, USA; [18]Seoul National University College of Medicine, Seoul, Republic of Korea

KEYNOTE-859: Study Design

Randomized, Double-Blind, Phase 3 Trial

Key Eligibility Criteria

- Histologically or cytologically confirmed adenocarcinoma of the stomach or GEJ
- Locally advanced unresectable or metastatic disease
- No prior treatment
- Known PD-L1 status (assessed centrally using PD-L1 IHC 22C3)
- HER2-negative status (assessed locally)
- ECOG PS 0 or 1

R 1:1

Pembrolizumab 200 mg IV Q3W for ≤35 cycles (~2 yr) + Chemotherapy[a] (FP or CAPOX)

Placebo IV Q3W for ≤35 cycles (~2 yr) + Chemotherapy[a] (FP or CAPOX)

Stratification Factors

- Geographic region (Europe/Israel/North America/ Australia vs Asia vs rest of world)
- PD-L1 CPS (<1 vs ≥1)
- Choice of chemotherapy[a] (FP vs CAPOX)

- **Primary End Point:** OS
- **Secondary End Points:** PFS,[b] ORR,[b] DOR,[b] and safety

ESMO VIRTUAL PLENARY

[a] FP: 5-fluorouracil 800 mg/m^2/day IV continuous on days 1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 orally twice daily on days 1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W. Cisplatin and oxaliplatin could have been limited to 6 cycles as per local country guidelines.
[b] Assessed per RECIST v1.1 by blinded, independent central review.
ClinicalTrials.gov number, NCT03675737.

Rha SY et al. ESMO Virtual Plenary 2023;Abstract VP1-2023.

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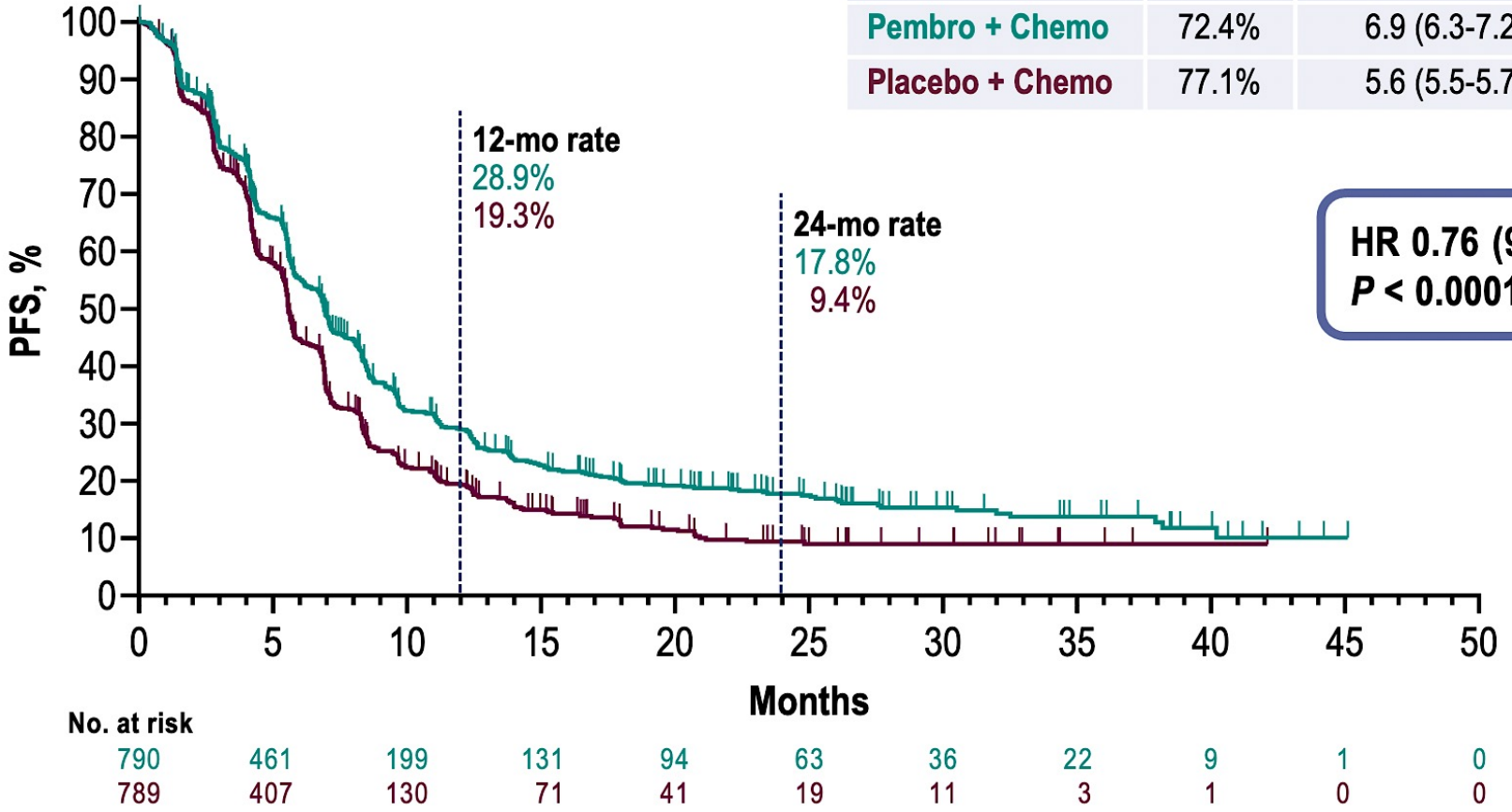
KEYNOTE-859: Progression-Free Survival (PFS) in ITT Population

	Pts w/ Event	Median, mo (95% CI)
Pembro + Chemo	72.4%	6.9 (6.3-7.2)
Placebo + Chemo	77.1%	5.6 (5.5-5.7)



HR 0.76 (95% CI, 0.67-0.85)
P < 0.0001

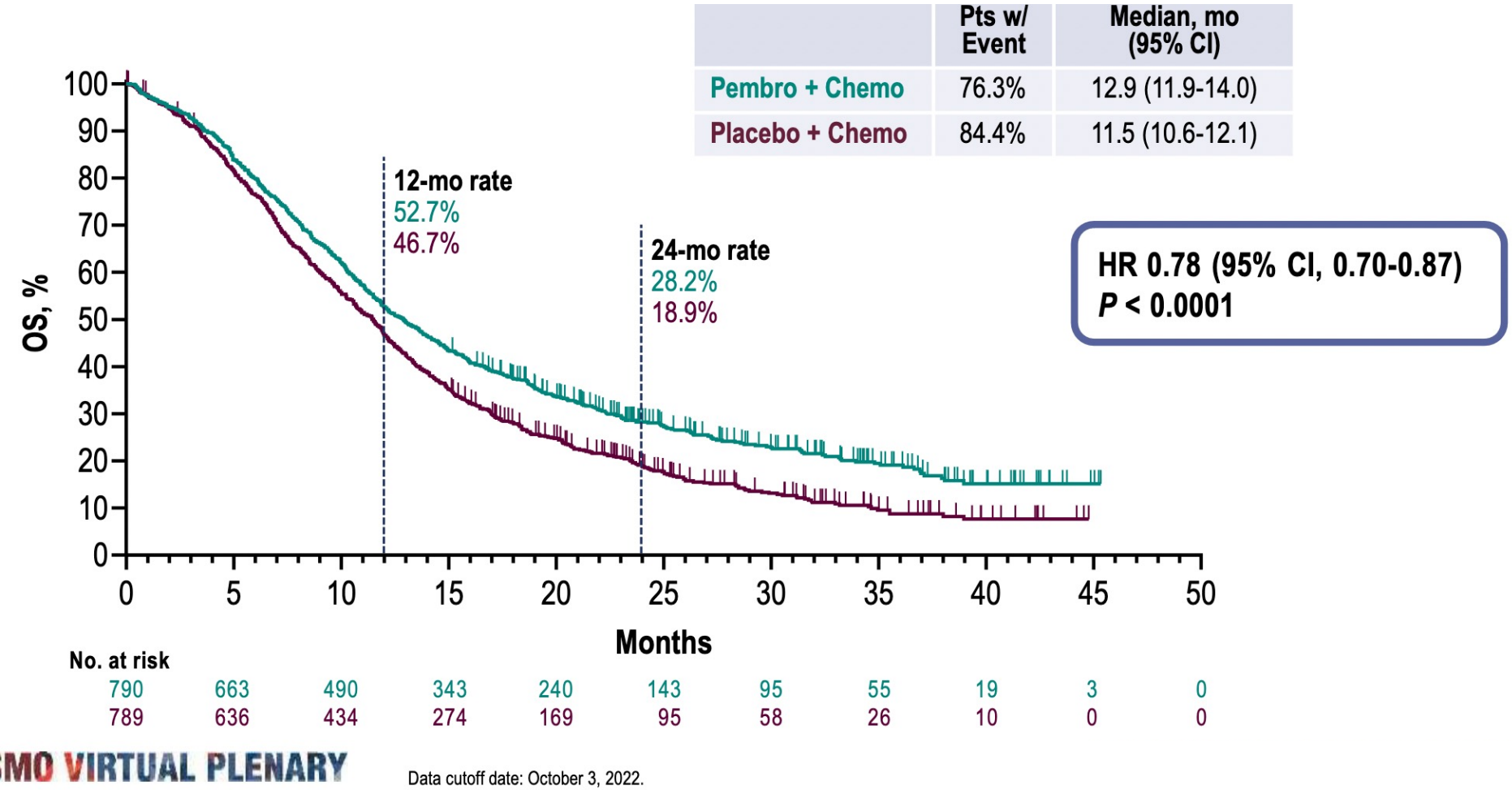
ESMO VIRTUAL PLENARY

Response assessed per RECIST v1.1 by blinded, independent central review..
Data cutoff date: October 3, 2022.

Rha SY et al. ESMO Virtual Plenary 2023;Abstract VP1-2023.

RTP RESEARCH TO PRACTICE

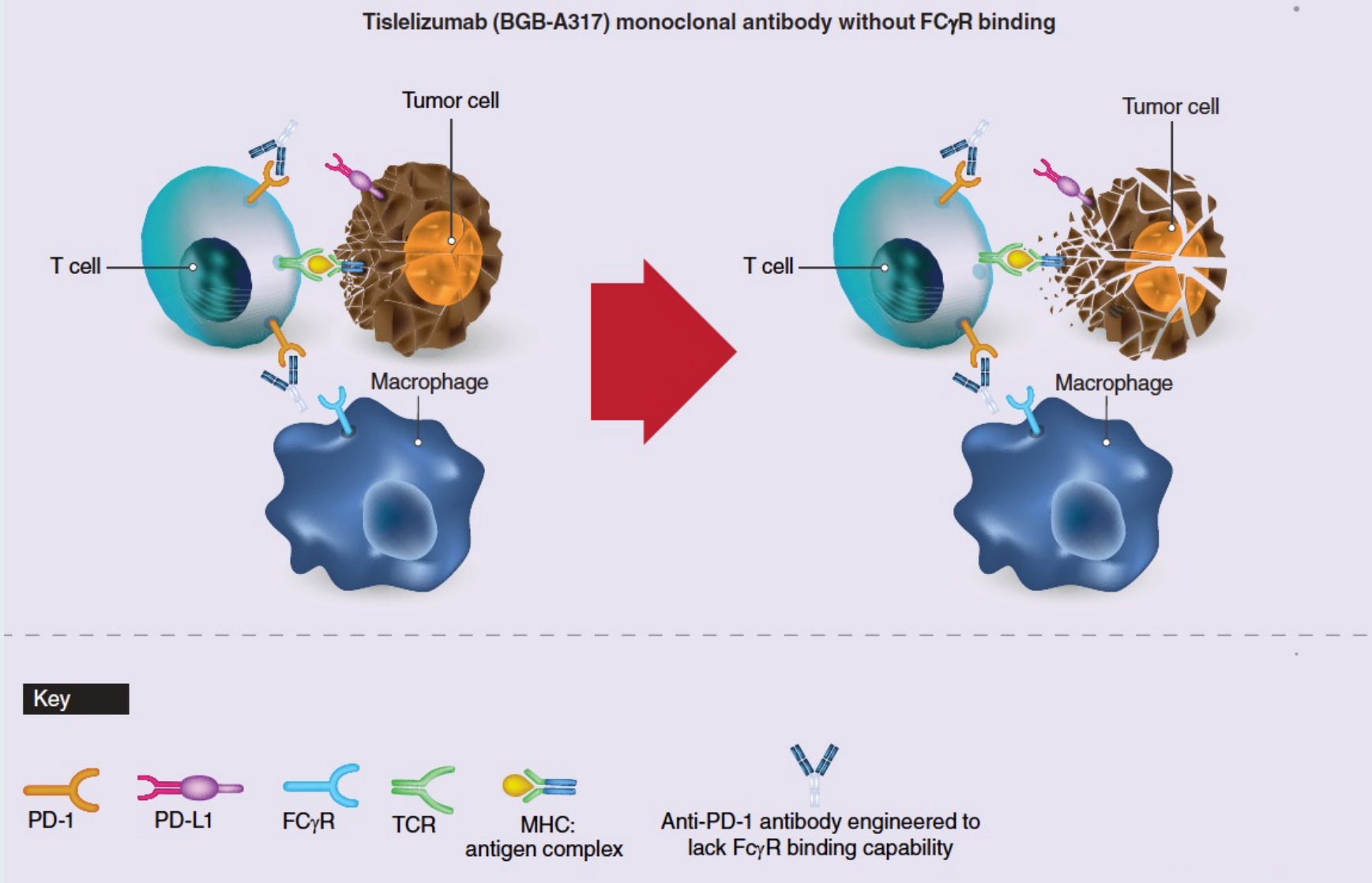
KEYNOTE-859: Overall Survival (OS) in ITT Population



OS = overall survival; ITT = intent to treat

Rha SY et al. ESMO Virtual Plenary 2023;Abstract VP1-2023.

Tislelizumab: Mechanism of Action



Qin S et al. *Future Oncol* 2019;15(16):1811-22.

RTP RESEARCH TO PRACTICE

ASCO Gastrointestinal Cancers Symposium

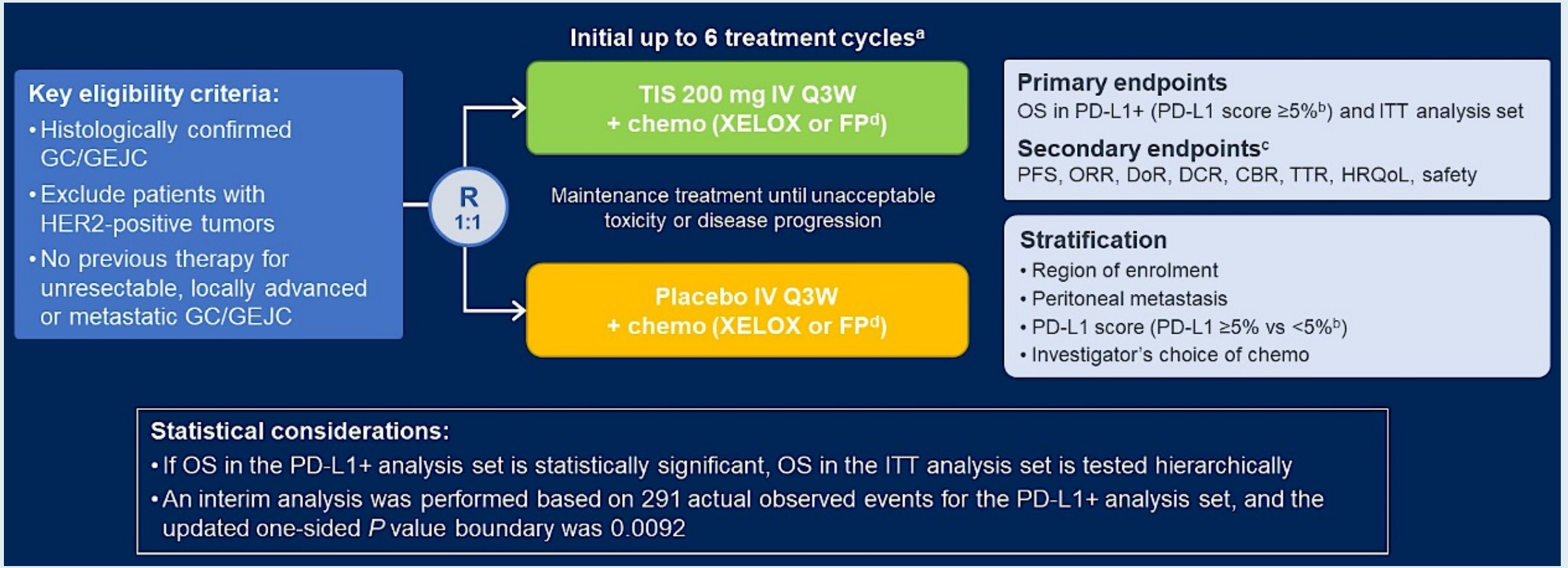
2023;Abstract 286

RATIONALE-305: Phase 3 Study of Tislelizumab + Chemotherapy vs Placebo + Chemotherapy as First-line Treatment of Advanced Gastric or Gastroesophageal Junction Adenocarcinoma

Markus Moehler,[1] Ken Kato,[2] Tobias Arkenau,[3] Do-Youn Oh,[4] Josep Tabernero,[5] Marcia Cruz Correa,[6] Hongwei Wang,[7] Hui Xu,[8] Jiang Li,[9] Silu Yang,[8] Gisoo Barnes,[10] Rui-Hua Xu[11]

[1]Johannes Gutenberg-University Clinic, Mainz, Germany; [2]National Cancer Center Hospital, Tokyo, Japan; [3]Sarah Cannon Research, London, England; [4]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine; [5]Vall d'Hebron University Hospital, Barcelona, Spain; [6]University of Puerto Rico, San Juan, Puerto Rico; [7]BeiGene, Ltd., Boston, MA, United States; [8]BeiGene (Beijing) Co., Ltd., Beijing, China; [9]BeiGene, Ltd., Ridgefield Park, NJ, United States; [10]BeiGene, Ltd., Emeryville, CA, United States; [11]Sun Yat-sen University Cancer Center State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China

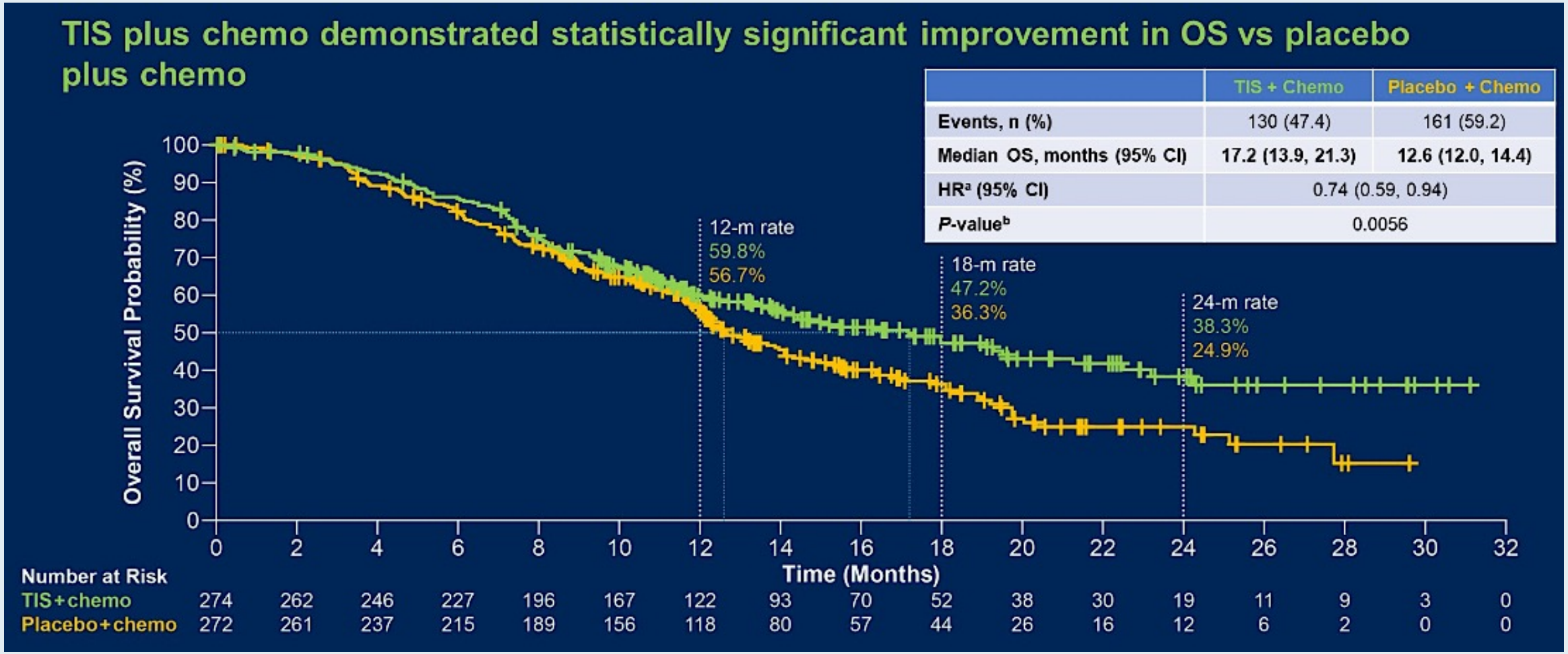
RATIONALE-305: Phase III Study Design



TIS = tislelizumab

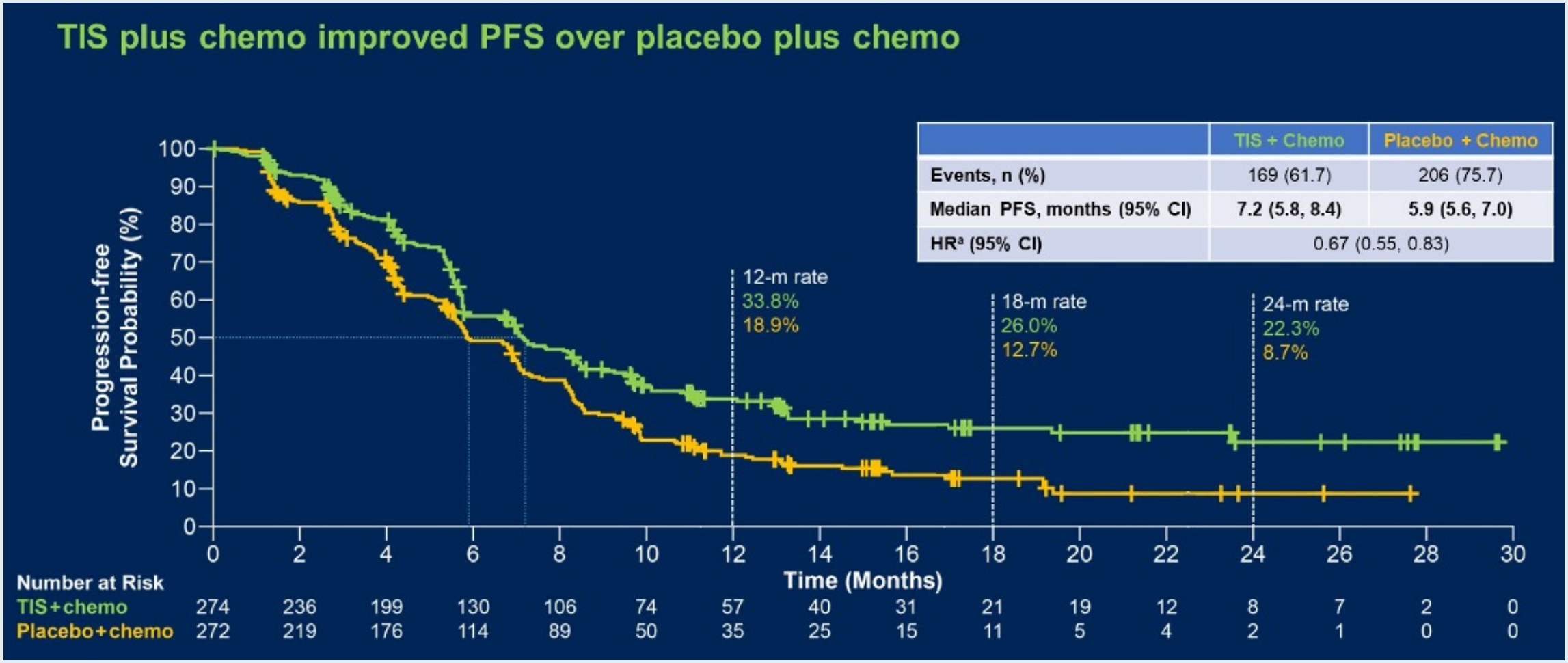
Moehler M et al. Gastrointestinal Cancers Symposium 2023;Abstract 286.

RATIONALE-305: Overall Survival in PD-L1-Positive Analysis Set (Primary Endpoint)



Moehler M et al. Gastrointestinal Cancers Symposium 2023;Abstract 286.

RATIONALE-305: Progression-Free Survival in PD-L1-Positive Analysis Set (Key Secondary Endpoint)



	TIS + Chemo	Placebo + Chemo
Events, n (%)	169 (61.7)	206 (75.7)
Median PFS, months (95% CI)	7.2 (5.8, 8.4)	5.9 (5.6, 7.0)
HR[a] (95% CI)	0.67 (0.55, 0.83)	

Moehler M et al. Gastrointestinal Cancers Symposium 2023;Abstract 286.

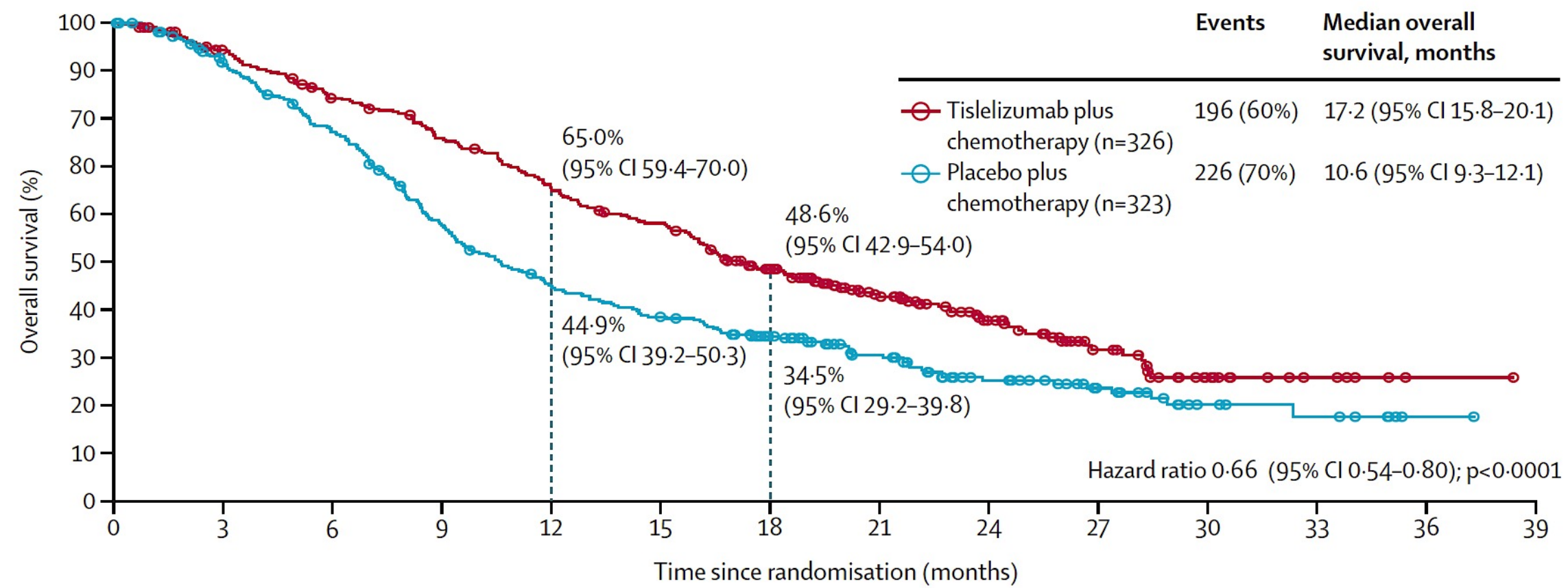
RTP RESEARCH TO PRACTICE

Lancet Oncol 2023;24(5):483-95

Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for advanced or metastatic oesophageal squamous cell carcinoma (RATIONALE-306): a global, randomised, placebo-controlled, phase 3 study

Jianming Xu, Ken Kato, Eric Raymond, Richard A Hubner, Yongqian Shu, Yueyin Pan, Sook Ryun Park, Lu Ping, Yi Jiang, Jingdong Zhang, Xiaohong Wu, Yuanhu Yao, Lin Shen, Takashi Kojima, Evgeny Gotovkin, Ryu Ishihara, Lucjan Wyrwicz, Eric Van Cutsem, Paula Jimenez-Fonseca, Chen-Yuan Lin, Lei Wang, Jingwen Shi, Liyun Li, Harry H Yoon

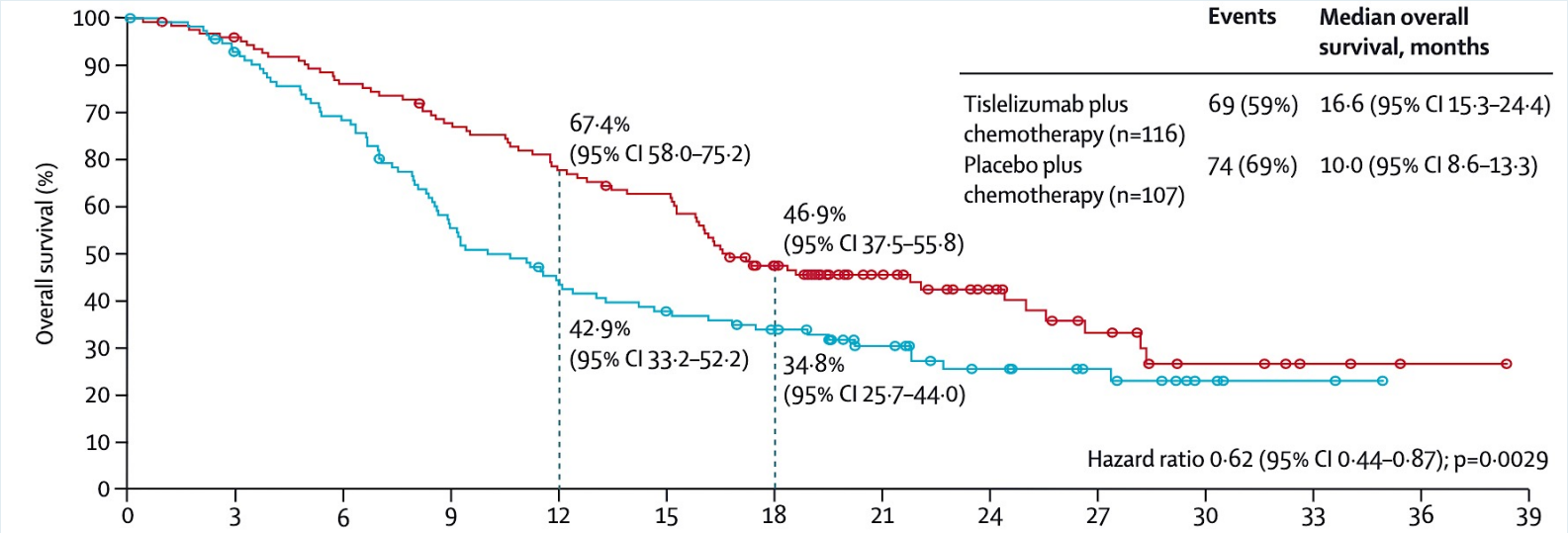
RATIONALE-306: Overall Survival in ITT Population



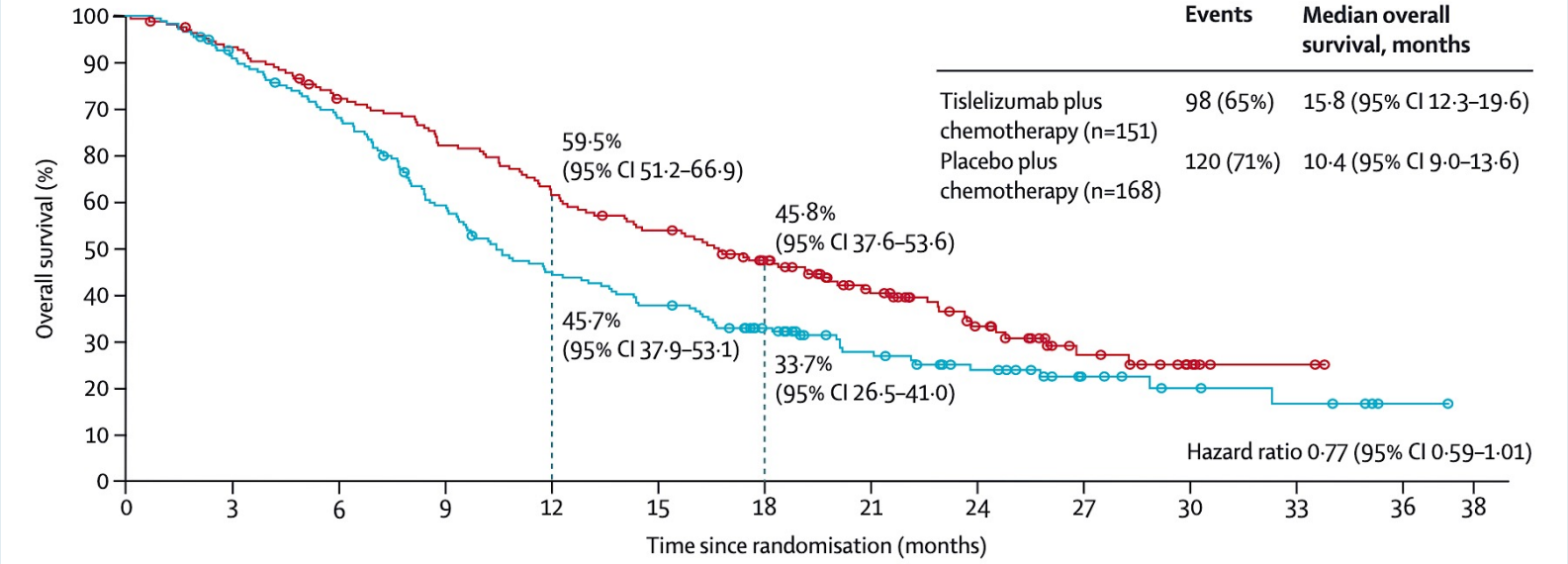
Xu J et al. *Lancet Oncol* 2023;24(5):483-95.

RATIONALE-306: Overall Survival by PD-L1 Tumor Area Positivity (TAP) Score

PD-L1 TAP ≥10%



PD-L1 TAP <10%



Xu J et al. *Lancet Oncol* 2023;24(5):483-95.

RATIONALE-306: Select Adverse Events

Adverse event (%)	Tislelizumab + chemo (n = 324)			Placebo + chemo (n = 321)		
	Grades 1-2	Grade 3	Grade 4	Grades 1-2	Grade 3	Grade 4
Anemia	39	14	<1	36	13	0
Decreased appetite	33	3	0	34	2	0
Nausea	32	2	0	39	2	0
Peripheral sensory neuropathy	19	3	0	17	2	0
Diarrhea	17	3	0	17	2	0
Vomiting	16	1	0	21	2	<1
Increased AST	11	1	<1	8	<1	<1
Increased ALT	11	5	0	9	1	<1
Constipation	13	0	0	12	<1	0

Xu J et al. *Lancet Oncol* 2023; 24(5):483-95.

Which adjuvant systemic therapy would you recommend to a patient with HER2-negative, microsatellite-stable (MSS) SCC of the esophagus who receives neoadjuvant carboplatin/paclitaxel and concurrent RT and has residual disease at surgery? Does PD-L1 level affect your treatment choice? For a patient to whom you opt to administer adjuvant nivolumab, how long do you continue treatment, assuming the patient is responding and tolerating it well?

	Adjuvant Tx	PD-L1 level affect Tx?	Adjuvant nivolumab duration
 Dr Ajani	Nivolumab	No	1 year
 Dr Enzinger	Nivolumab	Yes	1 year
 Dr Kim	Nivolumab	No	1 year
 Dr Klempner	Nivolumab	No	1 year
 Prof Van Cutsem	Nivolumab	No	1 year
 Dr Yoon	Nivolumab	No	1 year

RT = radiation therapy

A patient with HER2-negative, microsatellite instability (MSI)-high gastric adenocarcinoma receives preoperative FLOT, undergoes resection and has significant residual disease at surgery. Regulatory and reimbursement issues aside, what would you generally recommend?

 Dr Ajani	Pembrolizumab or nivolumab
 Dr Enzinger	Pembrolizumab or nivolumab (per GERCOR NEONIPIGA)
 Dr Kim	Nivolumab
 Dr Klempner	Pembrolizumab or nivolumab
 Prof Van Cutsem	Pembrolizumab or nivolumab
 Dr Yoon	Pembrolizumab or nivolumab

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Outside of a clinical trial, would you attempt to access an anti-PD-1/PD-L1 antibody as part of neoadjuvant therapy for a patient with MSI-high gastroesophageal cancer?

 Dr Ajani	Yes
 Dr Enzinger	Yes, if patient is willing
 Dr Kim	Yes, would attempt neoadjuvant ipilimumab/nivolumab in locally advanced gastric and esophageal cancers
 Dr Klempner	Yes, all situations
 Prof Van Cutsem	Yes, adenocarcinoma — cT3-4 or any N stage
 Dr Yoon	Yes, locally advanced

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, which first-line therapy would you most likely recommend for a 65-year-old patient presenting with metastatic HER2-negative, MSS gastric adenocarcinoma if their PD-L1 CPS was 0? CPS 1?

	PD-L1 CPS = 0	PD-L1 CPS = 1
 Dr Ajani	mFOLFOX6	mFOLFOX6
 Dr Enzinger	FOLFOX	FOLFOX
 Dr Kim	FOLFOX	FOLFOX + nivolumab
 Dr Klempner	FOLFOX	FOLFOX
 Prof Van Cutsem	FOLFOX	FOLFOX + pembrolizumab
 Dr Yoon	FOLFOX	FOLFOX

Regulatory and reimbursement issues aside, which first-line therapy would you most likely recommend for a 65-year-old patient presenting with metastatic HER2-negative, MSS gastric adenocarcinoma if their PD-L1 CPS was 5? CPS 10?

	PD-L1 CPS = 5	PD-L1 CPS = 10
 Dr Ajani	mFOLFOX6 + nivolumab	FOLFOX + pembrolizumab or FOLFOX + nivolumab
 Dr Enzinger	FOLFOX + nivolumab	FOLFOX + nivolumab
 Dr Kim	FOLFOX + nivolumab	FOLFOX + nivolumab
 Dr Klempner	FOLFOX + nivolumab	FOLFOX + nivolumab
 Prof Van Cutsem	FOLFOX + pembrolizumab or FOLFOX + nivolumab	FOLFOX + nivolumab
 Dr Yoon	FOLFOX + nivolumab	FOLFOX + nivolumab

Regulatory and reimbursement issues aside, which first-line therapy would you most likely recommend for a 65-year-old patient presenting with metastatic HER2-negative, MSI-high gastric adenocarcinoma?

 Dr Ajani	Nivolumab + ipilimumab
 Dr Enzinger	Pembrolizumab or nivolumab (with FOLFOX if asymptomatic or high disease burden)
 Dr Kim	FOLFOX + nivolumab
 Dr Klempner	Pembrolizumab or nivolumab (with FOLFOX if high disease burden)
 Prof Van Cutsem	FOLFOX + pembrolizumab or nivolumab
 Dr Yoon	FOLFOX + nivolumab

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Enzinger

Case Presentation: 63-year-old man with newly diagnosed clinical Stage I lower esophageal cancer undergoes esophagectomy and pathology reveals Stage IVA disease

Dr Farshid Dayyani (Orange, California)

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TO PRACTICE

FDA Grants Priority Review for Zolbetuximab
Press Release: July 6, 2023

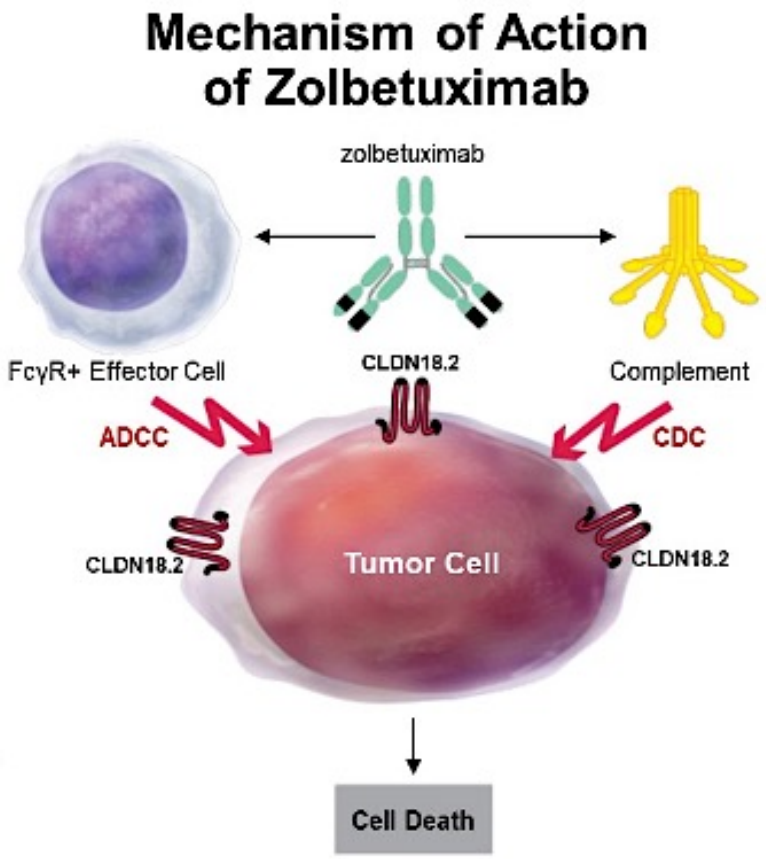
"The US Food and Drug Administration (FDA) has accepted and granted Priority Review for the company's Biologics License Application (BLA) for zolbetuximab, a first-in-class investigational Claudin 18.2 (CLDN18.2)-targeted monoclonal antibody, for first-line treatment of patients with locally advanced unresectable or metastatic HER2-negative CLDN18.2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are CLDN18.2-positive. If approved, zolbetuximab would be the first CLDN18.2-targeted therapy available in the U.S. for these patients.

Under the Prescription Drug User Fee Act (PDUFA), the FDA has set a target action date of January 12, 2024. The FDA reviewed the application under its Real-Time Oncology Review (RTOR) program, which aims to explore a more efficient review process to ensure that safe and effective treatments are available to patients as early as possible."

https://www.astellas.com/en/news/27946

Mechanism of Action of Zolbetuximab

- CLDN18.2 is a tight junction protein normally expressed in gastric mucosa cells and retained in G/GEJ adenocarcinoma[1–8]
- CLDN18.2 may become exposed on the surface of G/GEJ adenocarcinoma cells, making it a promising target[2–8]
- Zolbetuximab is a first-in-class chimeric IgG1 monoclonal antibody that targets CLDN18.2 and induces ADCC/CDC[4–8]
- In the phase 2b FAST study, EOX ± zolbetuximab prolonged survival in a subgroup of patients with higher expression of CLDN18.2 in tumor cells[8]
  - mPFS: 9.0 vs 5.7 months with zolbetuximab + EOX vs EOX alone
  - mOS: 16.5 vs 8.9 months with zolbetuximab + EOX vs EOX alone



Shitara K et al. Gastrointestinal Cancers Symposium 2023;Abstract LBA292.

nature medicine 2023;29(8):2133-41

Article

https://doi.org/10.1038/s41591-023-02465-7

Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial

Received: 5 May 2023

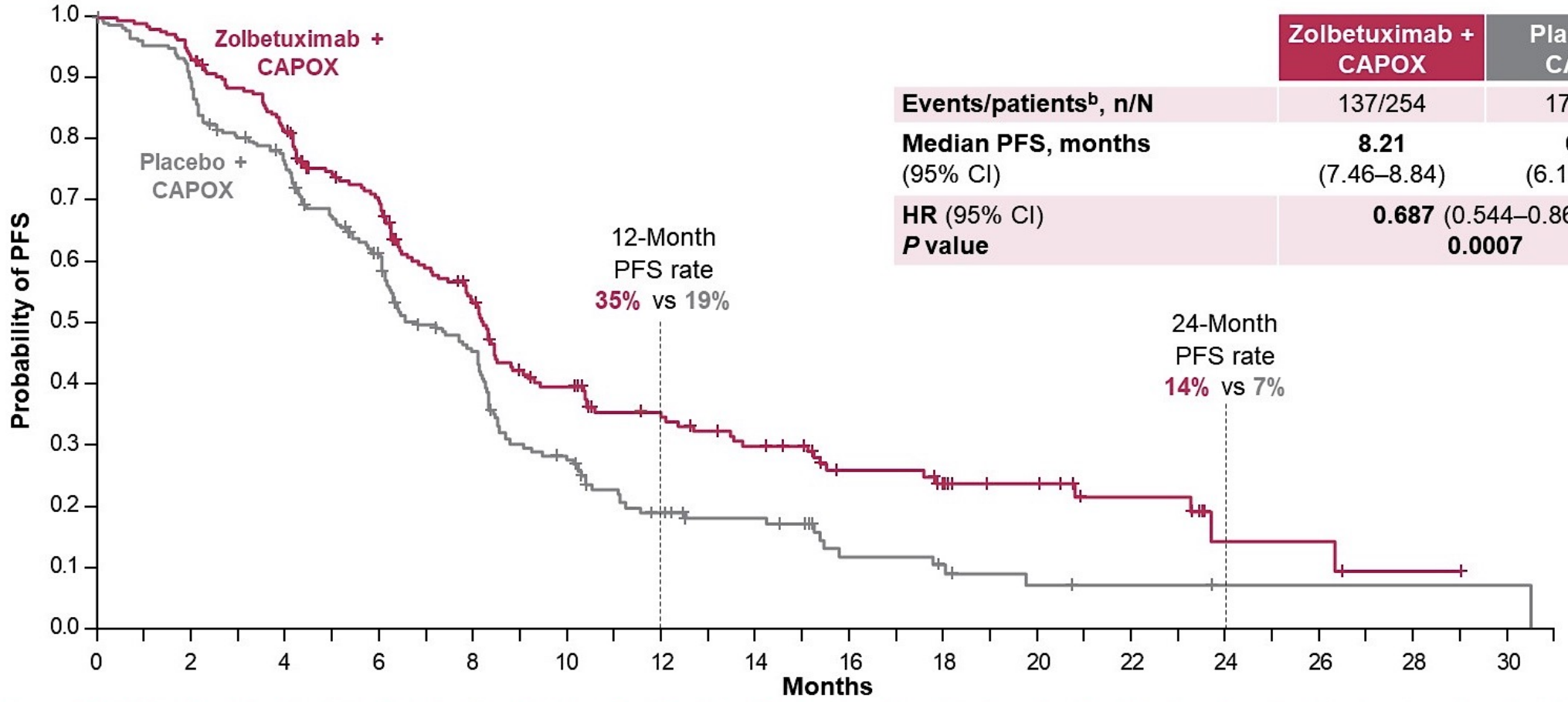
Accepted: 15 June 2023

Published online: 31 July 2023

Check for updates

Manish A. Shah[1], Kohei Shitara[2], Jaffer A. Ajani[3], Yung-Jue Bang[4], Peter Enzinger[5], David Ilson[6], Florian Lordick[7], Eric Van Cutsem[8], Javier Gallego Plazas[9], Jing Huang[10], Lin Shen[11], Sang Cheul Oh[12], Patrapim Sunpaweravong[13], Hwoei Fen Soo Hoo[14], Haci Mehmet Turk[15], Mok Oh[16], Jung Wook Park[16], Diarmuid Moran[16], Pranob Bhattacharya[16], Ahsan Arozullah[16] & Rui-Hua Xu[17]

GLOW: PFS by Independent Review Committee (Primary Endpoint)



	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[b], n/N	137/254	172/253
Median PFS, months (95% CI)	**8.21** (7.46–8.84)	**6.80** (6.14–8.08)
HR (95% CI)	**0.687** (0.544–0.866)	
***P* value**	**0.0007**	

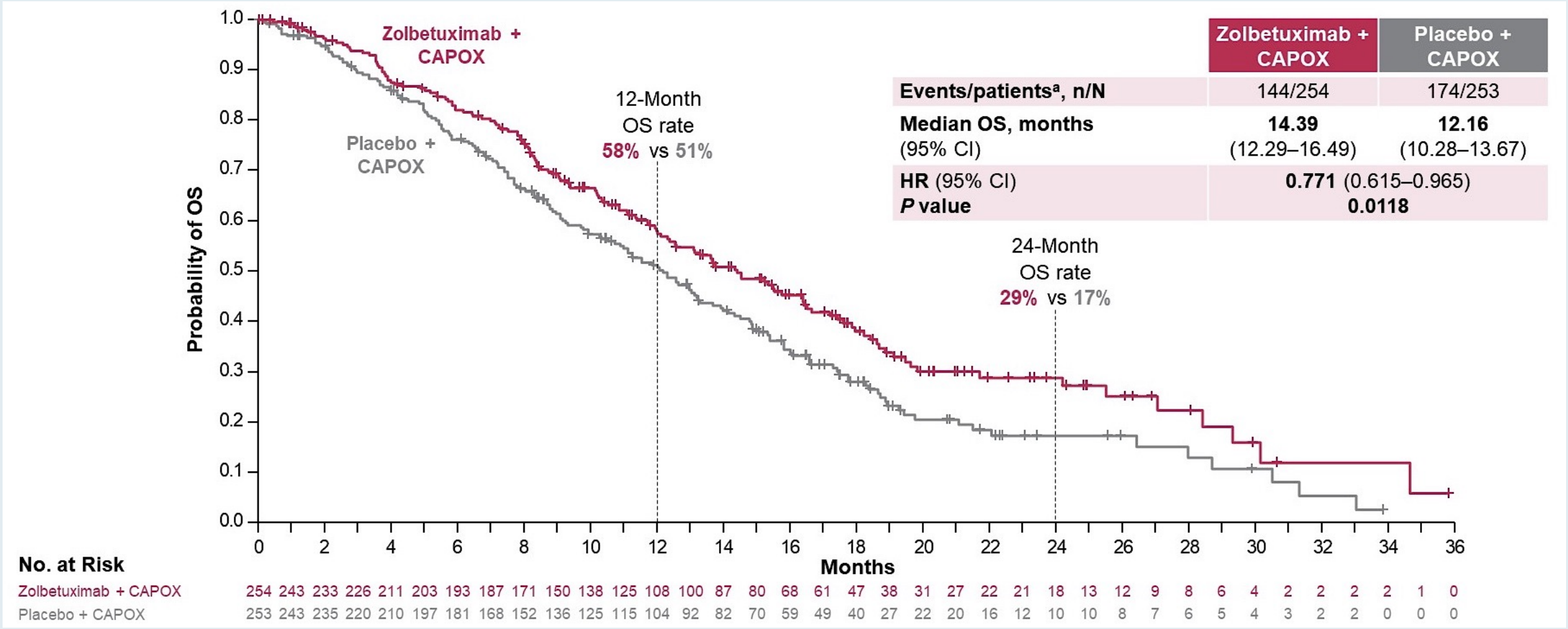
No. at Risk

Zolbetuximab + CAPOX	254	223	205	187	171	141	132	104	91	66	61	47	45	41	37	35	24	24	19	14	14	9	9	9	3	3	3	1	1	1	0	0
Placebo + CAPOX	253	233	215	188	175	146	127	93	84	48	43	30	24	19	19	17	9	9	7	5	4	2	2	2	1	1	1	1	1	1	1	0

PFS = progression-free survival

Shah MA et al. ASCO Plenary Series, March 22, 2023;Abstract 405736. Shah MA et al. *Nat Med* 2023;29(8):2133-41.

GLOW: Overall Survival (Key Secondary Endpoint)



	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[a], n/N	144/254	174/253
Median OS, months (95% CI)	**14.39** (12.29–16.49)	**12.16** (10.28–13.67)
HR (95% CI)	**0.771** (0.615–0.965)	
***P* value**	**0.0118**	

Shah M et al. ASCO Plenary Series, March 22, 2023;Abstract 405736. Shah M et al. *Nat Med* 2023;29(8):2133-41.

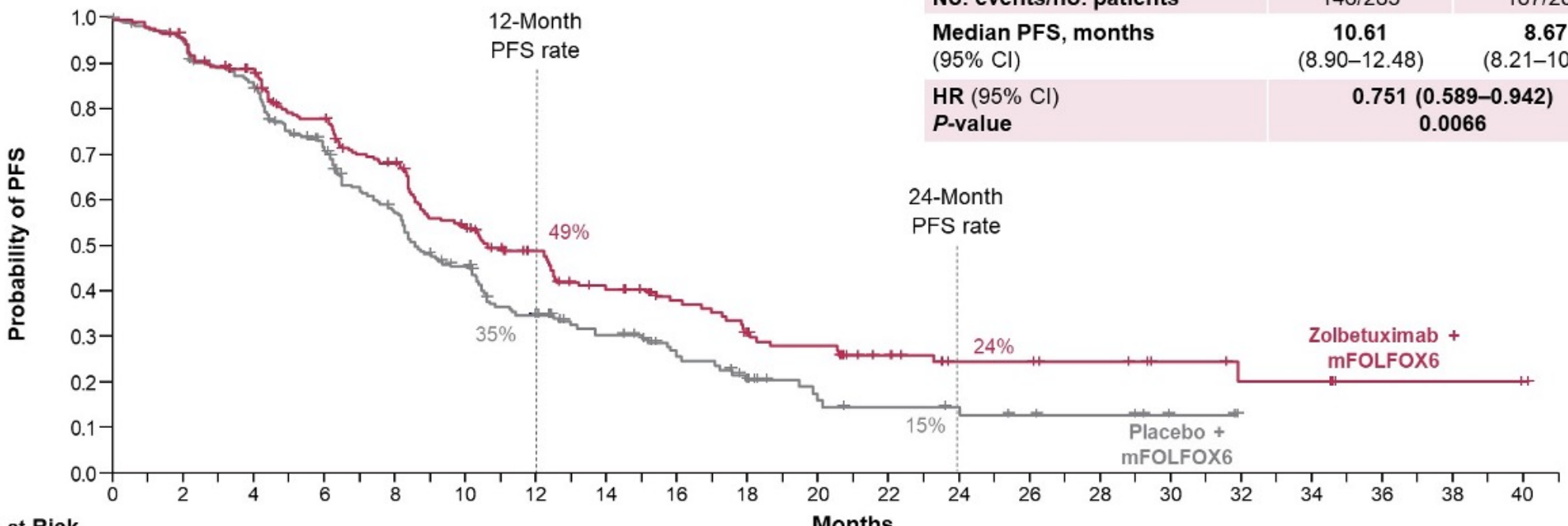
Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial

Kohei Shitara, Florian Lordick, Yung-Jue Bang, Peter Enzinger, David Ilson, Manish A Shah, Eric Van Cutsem, Rui-Hua Xu, Giuseppe Aprile, Jianming Xu, Joseph Chao, Roberto Pazo-Cid, Yoon-Koo Kang, Jianning Yang, Diarmuid Moran, Pranob Bhattacharya, Ahsan Arozullah, Jung Wook Park, Mok Oh, Jaffer A Ajani

***Lancet* 2023;401:1655-68**

SPOTLIGHT: Progression-Free Survival (Primary Endpoint)

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	146/283	167/282
Median PFS, months (95% CI)	**10.61** (8.90–12.48)	**8.67** (8.21–10.28)
HR (95% CI)	**0.751 (0.589–0.942)**	
***P*-value**	**0.0066**	



No. at Risk

Zolbetuximab + mFOLFOX6	283	263	254	232	226	190	187	148	143	108	102	84	78	59	56	53	43	40	33	28	28	21	19	17	12	12	12	10	10	9	7	7	5	5	5	2	2	2	2	2	1	0
Placebo + mFOLFOX6	282	273	260	237	226	183	168	136	122	91	83	60	56	43	40	38	26	25	19	14	12	9	9	9	8	7	6	5	5	4	2	2	0	0	0	0	0	0	0	0	0	0

- PFS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

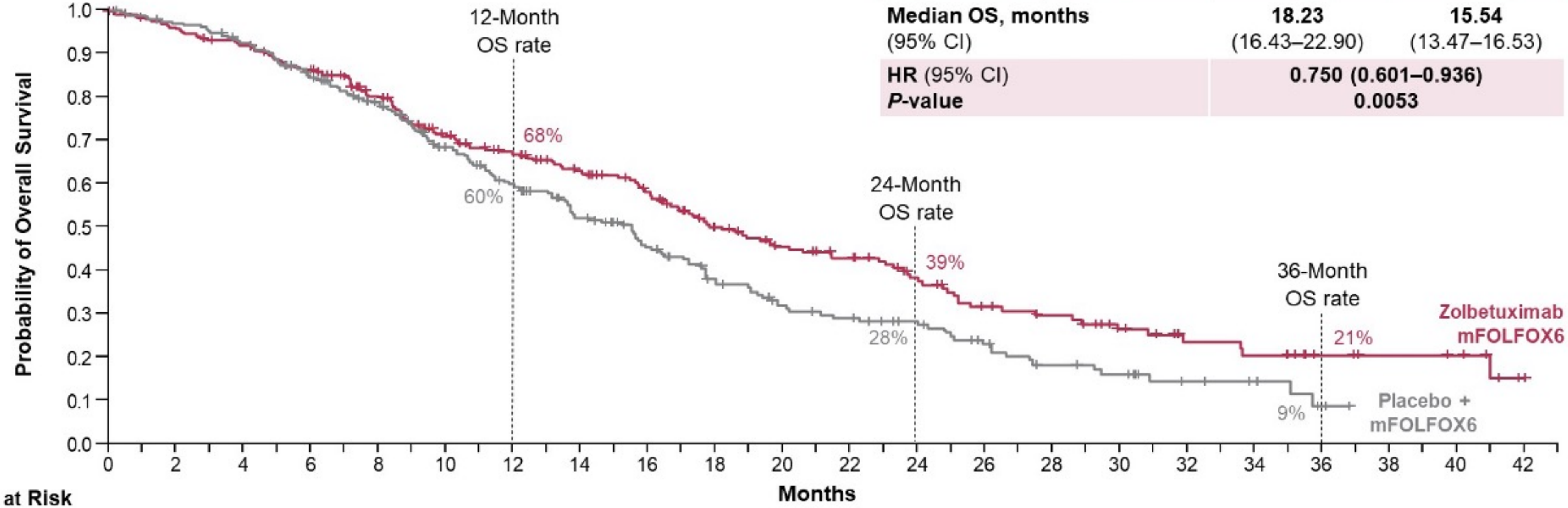
Data cutoff: September 9, 2022; Median follow-up = 12.94 months (zolbetuximab + mFOLFOX6) vs 12.65 months (placebo + mFOLFOX6).

[a]Per RECIST version 1.1.

Shitara K et al. Gastrointestinal Cancers Symposium 2023;Abstract LBA292. Shitara K et al. *Lancet* 2023;401:1655-68.

SPOTLIGHT: Overall Survival (Key Secondary Endpoint)

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	149/283	177/282
Median OS, months (95% CI)	**18.23** (16.43–22.90)	**15.54** (13.47–16.53)
HR (95% CI) ***P*-value**	**0.750 (0.601–0.936)** **0.0053**	



No. at Risk

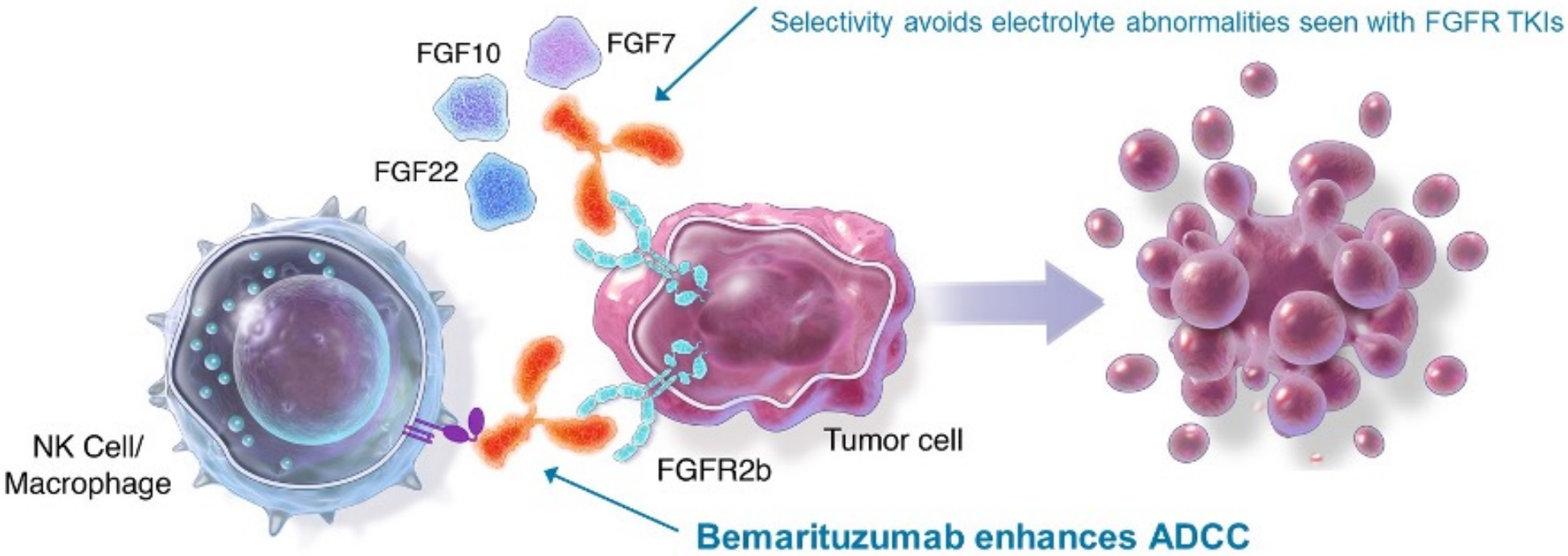
Zolbetuximab + mFOLFOX6	283	270	264	255	251	241	233	217	196	178	164	152	146	135	125	117	107	93	83	75	70	67	62	58	49	42	34	32	30	27	23	20	15	15	13	13	9	8	7	7	6	4	1	0
Placebo + mFOLFOX6	282	277	271	266	253	242	224	210	197	183	164	152	139	129	108	101	85	77	64	60	49	42	40	36	34	30	25	21	18	17	15	9	8	7	6	5	2	0	0	0	0	0	0	0

- OS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

Data cutoff: September 9, 2022; Median follow-up = 22.14 months (zolbetuximab + mFOLFOX6) vs 20.93 months (placebo + mFOLFOX6).

Shitara K et al. Gastrointestinal Cancers Symposium 2023;Abstract LBA292. Shitara K et al. *Lancet* 2023;401:1655-68.

Bemarituzumab Mechanism of Action



18% overall response rate in late-line FGFR2b+ gastroesophageal cancer[1]

ADCC, antibody-dependent cell-mediated cytotoxicity; FGF, fibroblast growth factor; IgG1, immunoglobulin G1; NK, natural killer; TKIs, tyrosine kinase inhibitors.

1. Catenacci D, et al. *J Clin Oncol*. 2020.

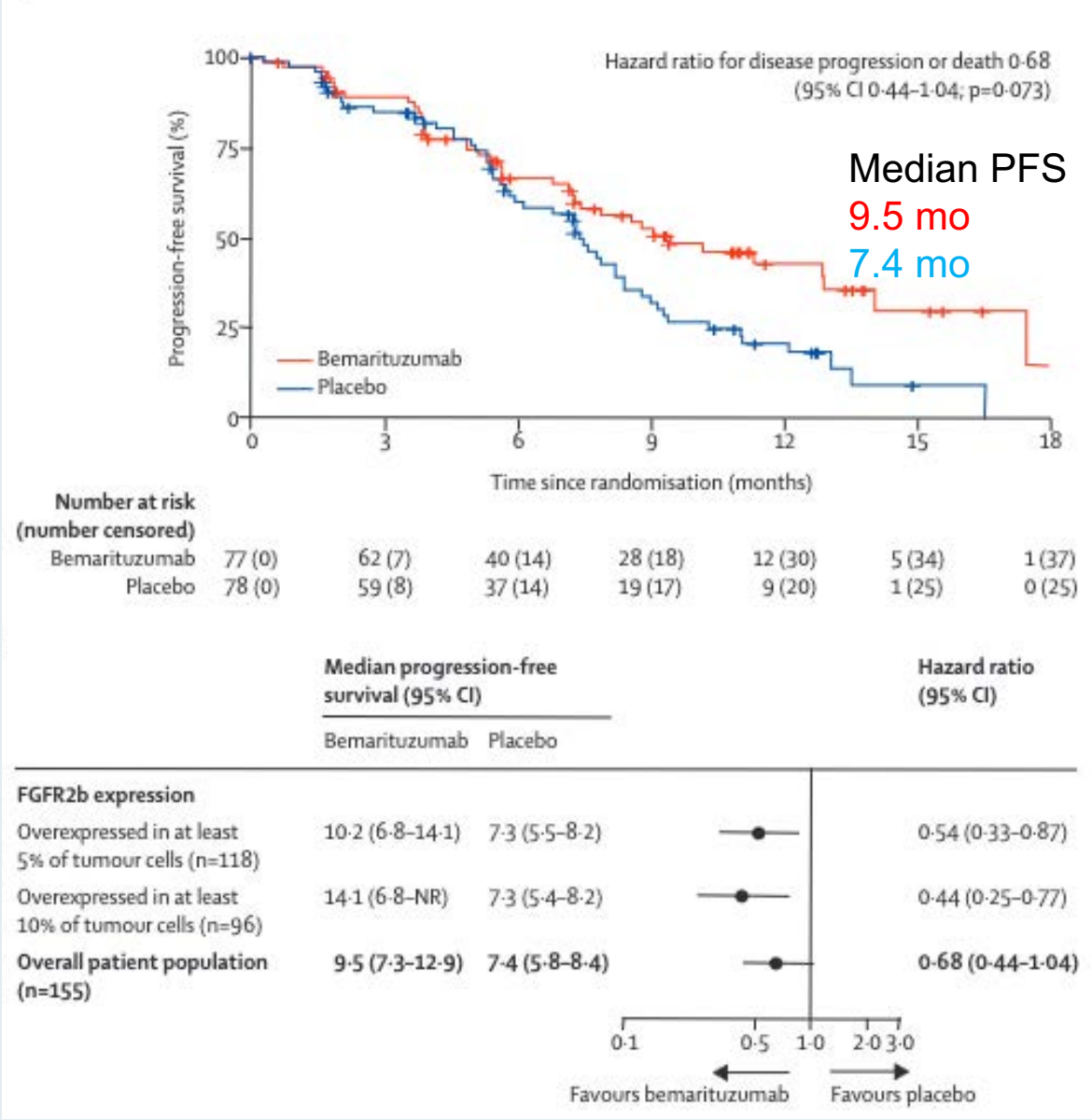
Catenacci DV et al. ASCO 2021;Abstract 4010.

Lancet Oncol 2022 November;23(11):1430-40

Bemarituzumab in patients with FGFR2b-selected gastric or gastro-oesophageal junction adenocarcinoma (FIGHT): a randomised, double-blind, placebo-controlled, phase 2 study

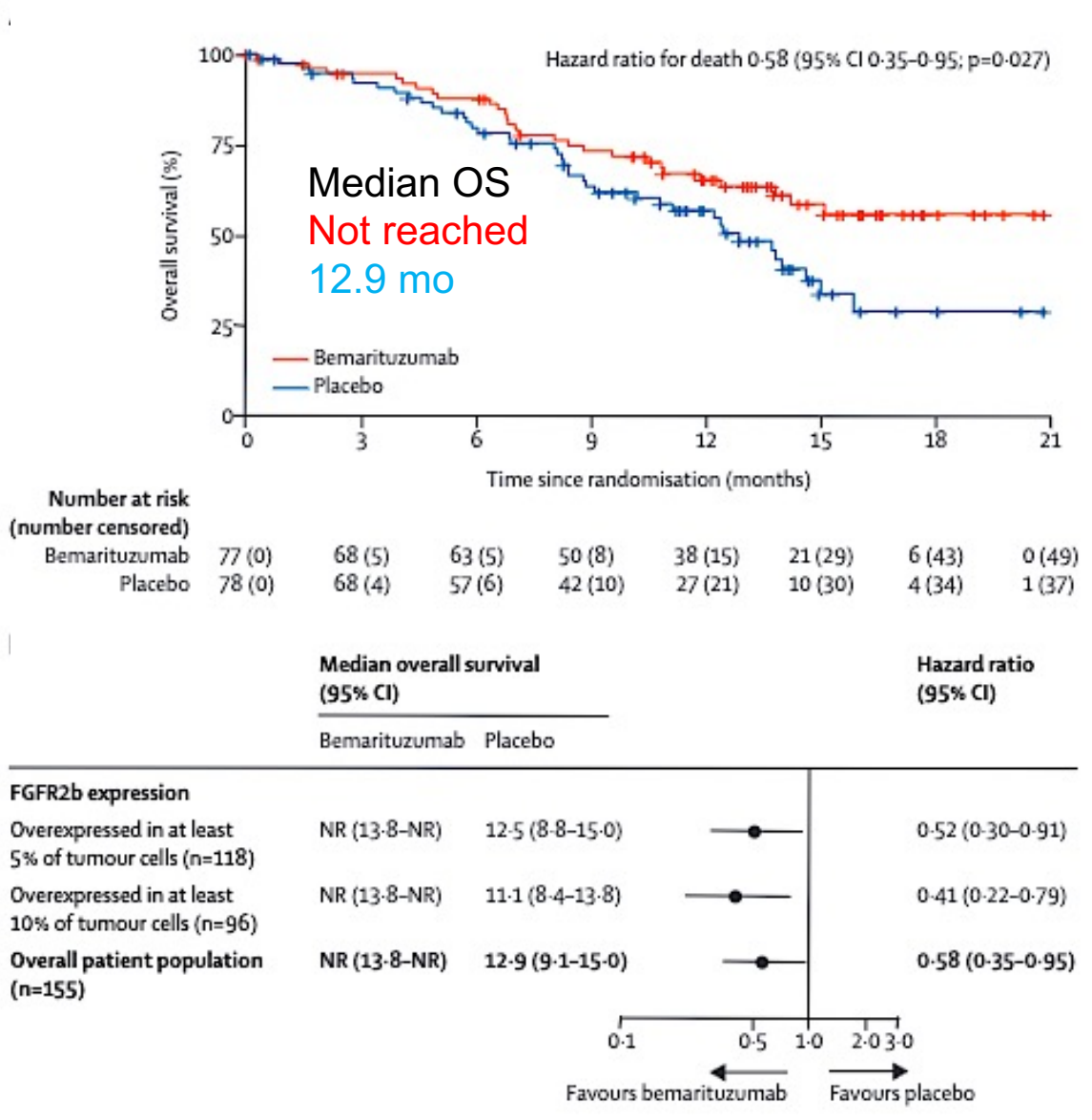
Zev A Wainberg, Peter C Enzinger, Yoon-Koo Kang, Shukui Qin, Kensei Yamaguchi, In-Ho Kim, Anwaar Saeed, Sang Cheul Oh, Jin Li, Haci Mehmet Turk, Alexandra Teixeira, Christophe Borg, Erika Hitre, Adrian A Udrea, Giovanni Gerardo Cardellino, Raquel Guardeño Sanchez, Helen Collins, Siddhartha Mitra, Yingsi Yang, Daniel V T Catenacci, Keun-Wook Lee

FIGHT Primary Endpoint: PFS (ITT)



Wainberg ZA et al. *Lancet Oncol* 2022 November;23(11):1430-40.

FIGHT: Overall Survival



Number at risk (number censored)								
Bemarituzumab	77 (0)	68 (5)	63 (5)	50 (8)	38 (15)	21 (29)	6 (43)	0 (49)
Placebo	78 (0)	68 (4)	57 (6)	42 (10)	27 (21)	10 (30)	4 (34)	1 (37)

	Median overall survival (95% CI)		Hazard ratio (95% CI)
	Bemarituzumab	Placebo	
FGFR2b expression			
Overexpressed in at least 5% of tumour cells (n=118)	NR (13·8–NR)	12·5 (8·8–15·0)	0·52 (0·30–0·91)
Overexpressed in at least 10% of tumour cells (n=96)	NR (13·8–NR)	11·1 (8·4–13·8)	0·41 (0·22–0·79)
Overall patient population (n=155)	**NR (13·8–NR)**	**12·9 (9·1–15·0)**	**0·58 (0·35–0·95)**

Wainberg ZA et al. *Lancet Oncol* 2022 November;23(11):1430-40.

To approximately how many patients with advanced claudin 18.2 (CLDN18.2)-positive gastroesophageal cancer have you administered first-line zolbetuximab/chemotherapy on protocol? What have you observed in terms of efficacy and tolerability?

	Number of patients	Efficacy, tolerability
 Dr Ajani	20	Nausea/vomiting and sometimes prolonged remissions
 Dr Enzinger	5	Some nausea and vomiting
 Dr Kim	0	N/A
 Dr Klempner	5	Experience aligns with trial; early nausea, generally during 1st infusion
 Prof Van Cutsem	10	In agreement with clinical trial data
 Dr Yoon	0	N/A

Regulatory and reimbursement issues aside, what additional therapy, if any, would you add to chemotherapy as first-line treatment for a 65-year-old patient presenting with metastatic HER2-negative, CLDN18.2-positive, MSS gastric adenocarcinoma if their PD-L1 CPS was 0? CPS 1?

	PD-L1 CPS 0	PD-L1 CPS 1
 Dr Ajani	Zolbetuximab	Zolbetuximab
 Dr Enzinger	Zolbetuximab	Zolbetuximab
 Dr Kim	Zolbetuximab	Zolbetuximab
 Dr Klempner	Zolbetuximab	Zolbetuximab
 Prof Van Cutsem	Zolbetuximab	Zolbetuximab
 Dr Yoon	Zolbetuximab	Zolbituximab

Regulatory and reimbursement issues aside, what additional therapy, if any, would you add to chemotherapy as first-line treatment for a 65-year-old patient presenting with metastatic HER2-negative, CLDN18.2-positive, MSS gastric adenocarcinoma with a PD-L1 CPS of 10?

 Dr Ajani	Pembrolizumab or nivolumab or zolbetuximab
 Dr Enzinger	Pembrolizumab or nivolumab
 Dr Kim	Nivolumab
 Dr Klempner	Nivolumab
 Prof Van Cutsem	Nivolumab
 Dr Yoon	Nivolumab

RTP RESEARCH TO PRACTICE

What is your global view on the acute emetogenic effect of zolbetuximab (time of onset, optimal prevention and treatment approaches)?

 Dr Ajani	Manageable early-onset issue that does not require treatment discontinuation
 Dr Enzinger	Manageable with appropriate steps, including slowing down infusion and NK-1 inhibitors
 Dr Kim	Do not expect it to be an issue with antiemetics and slowing down infusion rate during first cycle
 Dr Klempner	Nausea/vomiting can be quite hard for patients; good support including IVF and interrupting or slowing down infusion can help; olanzapine may be effective
 Prof Van Cutsem	Early on, sometimes severe, on target, strong antiemetic
 Dr Yoon	Fast onset, best to pretreat aggressively

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Enzinger

PharmacoEconomics (2022) 40:1247–1259
https://doi.org/10.1007/s40273-022-01196-w

ORIGINAL RESEARCH ARTICLE

Cost Effectiveness of Adding Pembrolizumab to Platinum and Fluoropyrimidine-Based Chemotherapy as First-Line Treatment for Advanced Esophageal Cancer: A US Healthcare Payer's Perspective

Tingting Qu[1] · Shujing Zhang[2] · Yichen Zhong[2] · Yang Meng[1] · He Guo[2] · Seongjung Joo[3] · Peter C. Enzinger[4]

Original Reports | Biomarkers

Highly Sensitive Circulating Tumor DNA Assay Aids Clinical Management of Radiographically Occult Isolated Peritoneal Metastases in Patients With GI Cancer

Harshabad Singh, MBBS[1,2,3]; Samuel J. Klempner, MD[3,4]; Nelya Melnitchouk, MD, MSc[3,5]; Deepak P. Chander, MD[6]; Ovidiu George Negrea, MD[7]; Anuj K. Patel, MD[1,2,3]; Benjamin L. Schlechter, MD, PhD[1,2,3]; Douglas A. Rubinson, MD, PhD[1,2,3]; Brandon M. Huffman, MD[1,2,3]; Chetan Nambiar, BS[1]; Joshua Remland, BS[1]; Elizabeth Andrews, BS[1]; Megan E. Leahy, PA-C[1]; Lauren K. Brais, BS[1]; Peter C. Enzinger, MD[1,2,3]; Harvey J. Mamon, MD, PhD[3,8]; Marios Giannakis, MD, PhD[1,2,3]; Jeffrey A. Meyerhardt, MD, MPH[1,2,3]; Kimmie Ng, MD[1,2,3]; Kimberly J. Perez, MD[1,2,3]; Andrew J. Aguirre, MD, PhD[1,2,3]; Jeffrey W. Clark, MD[3,4]; James M. Cleary, MD, PhD[1,2,3]; and Brian M. Wolpin, MD, MPH[1,2,3]

JCO Precis Oncol 2023;7:e2200572

Open access Original research

Journal for ImmunoTherapy of Cancer

G-CSF rescue of FOLFIRINOX-induced neutropenia leads to systemic immune suppression in mice and humans

Victoire Cardot-Ruffino ,[1,2] Naima Bollenrucher,[1] Luisa Delius,[1] S Jennifer Wang,[1] Lauren K Brais,[3] Joshua Remland,[3] C Elizabeth Keheler,[4] Keri M Sullivan,[4] Thomas A Abrams,[3,5] Leah H Biller,[3,5] Peter C Enzinger,[3,5] Nadine J McCleary,[3,5] Anuj K Patel,[3,5] Douglas A Rubinson ,[3,5] Benjamin Schlechter,[3,5] Sarah Slater,[3,5] Matthew B Yurgelun,[3,5] James M Cleary,[3,5] Kimberly Perez,[3,5] Michael Dougan,[4,5] Kimmie Ng,[3,5] Brian M Wolpin,[3,5] Harshabad Singh,[3,5] Stephanie K Dougan [1,2]

2023;11(6):e006589

Meet The Professor with Dr Enzinger

Localized Gastric, Gastroesophageal and Esophageal Cancers

RTP
RESEARCH
TO PRACTICE

Phase II Clinical Trial of Perioperative Pembrolizumab and Chemotherapy followed by Adjuvant Pembrolizumab for Resectable Gastric/GEJ Adenocarcinoma

Gulam Abbas Manji, MD PhD[1], Shing Lee, PhD[1], Michael May, MD[1], Armando Del Portillo, MD[1], Naomi Sender, BS[1], Sarah Sta Ana, MS[1], Katarzyna Gautier, BS[1], Emily Alouani, MD[1], Mengyu Xie, PhD[2], Amrita Sethi, MD[1], Beth Schrope, MD PhD[1], MD, Aik Choon Tan, PhD[2], Haeseong Park, MD[3], Paul E. Oberstein, MD[4], Manish A. Shah, MD[5], Alexander G. Raufi MD[6].

[1]Columbia University Irving Medical Center – NewYork-Presbyterian, [2]Moffitt Cancer Center, [3]Washington University, [4]New York University, [5]Weill Cornell Medical College – NewYork-Presbyterian, [6]Brown University

Presented by

Gulam Abbas Manji, MD PhD

Columbia University – NewYork-Presbyterian

Abstract CT009

RTP RESEARCH TO PRACTICE

Pathologic Complete Response Rate (Primary Endpoint)

Pathological Response (Central Review)	Evaluable – 34 (%)	Underwent Curative Resection – 28 (%)
Complete	**7 (20.6%)** (10.1%, 100%)	7 (25%)
Near-complete	6 (17.6%)	6 (21%)
Partial	8 (23.5%)	8 (29%)
Treatment effect present, NOS	1 (2.9%)	1 (4%)
No or minimal/poor	7 (20.6%)	7 (25%)

Pathological Complete Response
No viable cancer cells

Near-complete Pathological Response
Single/rare small groups of cancer cells

Partial Response
Residual cancer with regression
(> single/rare small groups of cancer cells)

No or Minimal/Poor Response
Treatment effect absent

The study successfully met its primary endpoint of achieving a complete pathologic response (20.6%)

Manji GA et al. AACR 2022;Abstract CT009.

RTP RESEARCH TO PRACTICE

Treatment-Related Adverse Events with Perioperative Pembrolizumab and Chemotherapy Followed by Adjuvant Pembrolizumab for Resectable Gastric/GEJ Adenocarcinoma

Number of Patients experiencing events (N – 35; >5% and > 10% subjects)

Adverse Event (Grads 3-4)	Related to Chemotherapy	Related to Pembrolizumab
Anemia	3	0
Anorexia	4	0
Dehydration	2	0
Diarrhea	6	5
Fatigue	2	1
Febrile neutropenia	2	0
Hypokalemia	2	0
Hyponatremia	0	2
Neutrophil count decreased	3	0
Rectal hemorrhage	1	1
Sepsis	2	1
Dermatitis	0	2

Grade ≥3 Attributions	N = 35 (%)
All	18 (51%)
Pembrolizumab	10 (29%)

Grade 4 Attributions	N = 35 (%)
All	4 (11%)
Pembrolizumab	2 (6%)

Manji GA et al. AACR 2022;Abstract CT009.

RTP RESEARCH TO PRACTICE

Emerging and Investigational Approaches to First-Line Therapy for Advanced Gastroesophageal Cancers

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

July 2023;[Online ahead of print]

ILUSTRO: Phase II Multicohort Trial of Zolbetuximab in Patients with Advanced or Metastatic Claudin 18.2–Positive Gastric or Gastroesophageal Junction Adenocarcinoma

Samuel J. Klempner[1], Keun-Wook Lee[2], Kohei Shitara[3], Jean-Phillippe Metges[4], Sara Lonardi[5], David H. Ilson[6], Nicola Fazio[7], Tae Yong Kim[8], Li-Yuan Bai[9], Diarmuid Moran[10], Jianning Yang[10], Ahsan Arozullah[10], Jung Wook Park[10], Jeffrey J. Raizer[11], Yung-Jue Bang[12], and Manish A. Shah[13]

ILUSTRO: Phase II Study of Zolbetuximab Alone or in Combination with Chemotherapy, Immunotherapy or Both in Metastatic or Locally Advanced Unresectable Gastric or GEJ Adenocarcinoma

Trial identifier: NCT03505320 (open)

Histologically confirmed gastric or GEJ adenocarcinoma

Locally advanced, unresectable or metastatic disease

Positivity for CLDN18.2 expression

R

- **Cohort 1A**
  Zolbetuximab
  (in third or later line)
- **Cohort 2**
  Zolbetuximab + mFOLFOX6
  (in first line)
- **Cohort 3A**
  Zolbetuximab + pembrolizumab
  (in third or later line)
- **Cohort 4A/4B**
  Zolbetuximab + mFOLFOX6
  +/- nivolumab

Primary endpoint: Objective response rate with zolbetuximab monotherapy

Secondary endpoints include PFS, pharmacokinetics, safety and tolerability

www.clinicaltrials.gov. NCT03505320. Accessed March 2022.

RTP RESEARCH TO PRACTICE

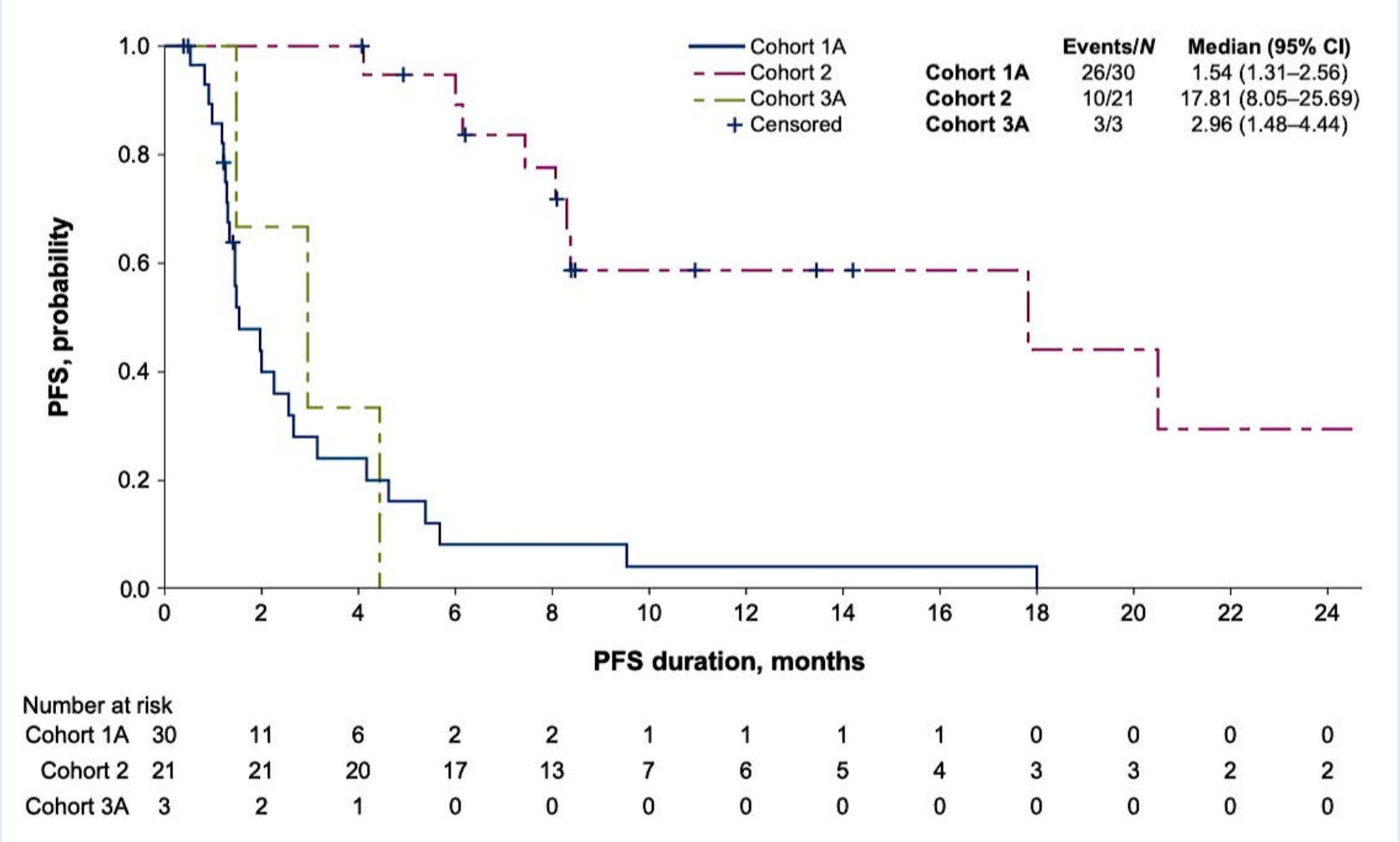
ILUSTRO: Objective Response Rates per Independent Review

Best overall response	Cohort 1A Zolbetuximab monotherapy (n = 27)	Cohort 2 Zolbetuximab + mFOLFOX6 (n = 21)	Cohort 3A Zolbetuximab + pembrolizumab (n = 3)
Confirmed CR	0	0	0
Confirmed PR	0	15 (71.4%)	0
Unconfirmed CR	0	0	0
Unconfirmed PR	0	1 (4.8%)	0

CR = complete response; PR = partial response

Klempner SJ et al. *Clin Cancer Res* 2023;[Online ahead of print].

ILUSTRO: Progression-Free Survival



Cohort 1A, zolbetuximab monotherapy (n = 30); Cohort 2, zolbetuximab + mFOLFOX6 (n = 21); Cohort 3A, zolbetuximab + pembrolizumab (n = 3)

Klempner SJ et al. *Clin Cancer Res* 2023;[Online ahead of print].

RTP RESEARCH TO PRACTICE

ILUSTRO: Select Any-Grade and Grade ≥3 Adverse Events

Adverse event, n (%)	Cohort 1A Zolbetuximab monotherapy (n = 27)		Cohort 2 Zolbetuximab + mFOLFOX6 (n = 21)		Cohort 3A Zolbetuximab + pembrolizumab (n = 3)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Anemia	6 (20)	3 (10)	5 (23.8)	2 (9.5)	0	0
Neutropenia	0	0	8 (38.1)	6 (28.6)	0	0
Nausea	19 (63.3)	2 (6.7)	19 (90.5)	1 (4.8)	2 (66.7)	0
Vomiting	11 (36.7)	2 (6.7)	14 (66.7)	2 (9.5)	1 (33.3)	0
Abdominal pain	12 (40.0)	3 (10.0)	7 (33.3)	2 (9.5)	0	0

Klempner SJ et al. *Clin Cancer Res* 2023;[Online ahead of print].

Nature 2021;600(7890):727-30

Article

The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer

https://doi.org/10.1038/s41586-021-04161-3

Received: 25 May 2021

Accepted: 30 September 2021

Published online: 15 December 2021

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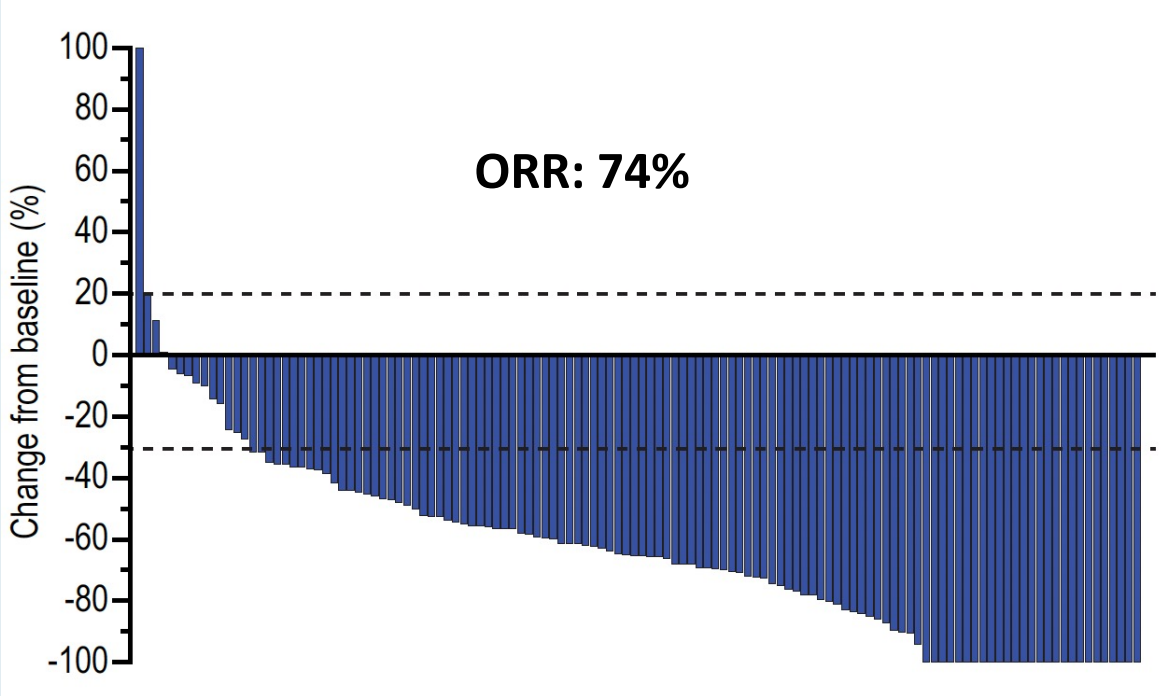
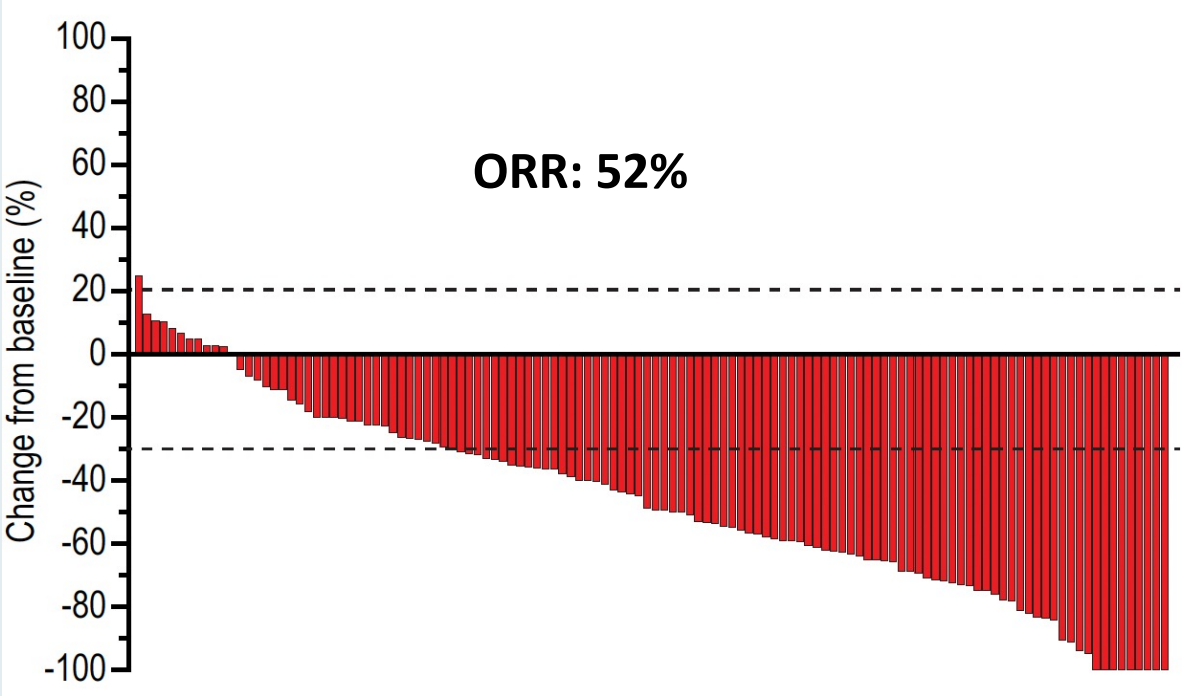
KEYNOTE-811: Overall Response Rate

Pembrolizumab



Placebo



Janjigian YY et al. *Nature* 2021;600(7890):727-30.

RTP RESEARCH TO PRACTICE

KEYNOTE-811: Summary of Adverse Events

Number of events (%)	Any cause		Immune-mediated events and infusion reactions[a]	
	Pembrolizumab group (*n* = 217)	Placebo group (*n* = 216)	Pembrolizumab group (*n* = 217)	Placebo group (*n* = 216)
Any grade	211 (97.2)	212 (98.1)	73 (33.6)	45 (20.8)
Grade 3–5	124 (57.1)	124 (57.4)	21 (9.7)	7 (3.2)
Serious	68 (31.3)	83 (38.4)	19 (8.8)	7 (3.2)
Led to death	7 (3.2)	10 (4.6)	3 (1.4)	1 (0.5)
Led to discontinuation of any drug	53 (24.4)	56 (25.9)	12 (5.5)	5 (2.3)
Pembrolizumab or placebo	12 (5.5)	15 (6.9)	7 (3.2)	2 (0.9)
Trastuzumab	12 (5.5)	16 (7.4)	7 (3.2)	2 (0.9)
Any chemotherapy	50 (23.0)	52 (24.1)	12 (5.5)	5 (2.3)
All drugs	8 (3.7)	12 (5.6)	6 (2.8)	2 (0.9)

The treatment regimen included trastuzumab and chemotherapy in both groups.

[a]Events with a possible immune-mediated cause and infusion reactions were considered regardless of attribution to study treatment or immune relatedness by the investigator and are based on a list of terms provided by the sponsor.

Janjigian YY et al. *Nature* 2021;600(7890):727-30.

Poster 242

ASCO Gastrointestinal Cancers Symposium 2022

Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients With HER2–Positive Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma: Final Overall Survival (OS) Results From a Randomized, Multicenter, Open-Label, Phase 2 Study (DESTINY-Gastric01)

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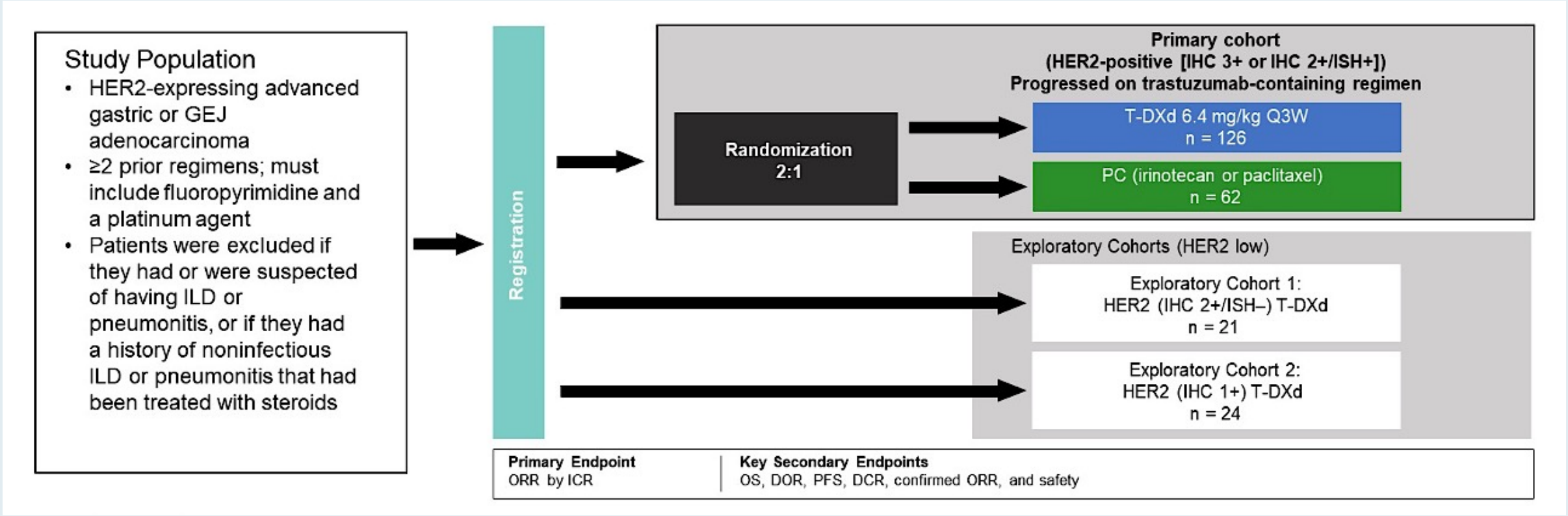
ON BEHALF OF THE DESTINY-GASTRIC01 INVESTIGATORS

Additional authors: Yung-Jue Bang, Satoru Iwasa, Naotoshi Sugimoto, Min-Hee Ryu, Daisuke Sakai, Hyun Cheol Chung, Hisato Kawakami, Hiroshi Yabusaki, Jeeyun Lee, Kaku Saito, Yoshinori Kawaguchi, Takahiro Kamio, Akihito Kojima, Masahiro Sugihara, Kohei Shitara

DESTINY-Gastric01 Randomized, Phase II Study Design

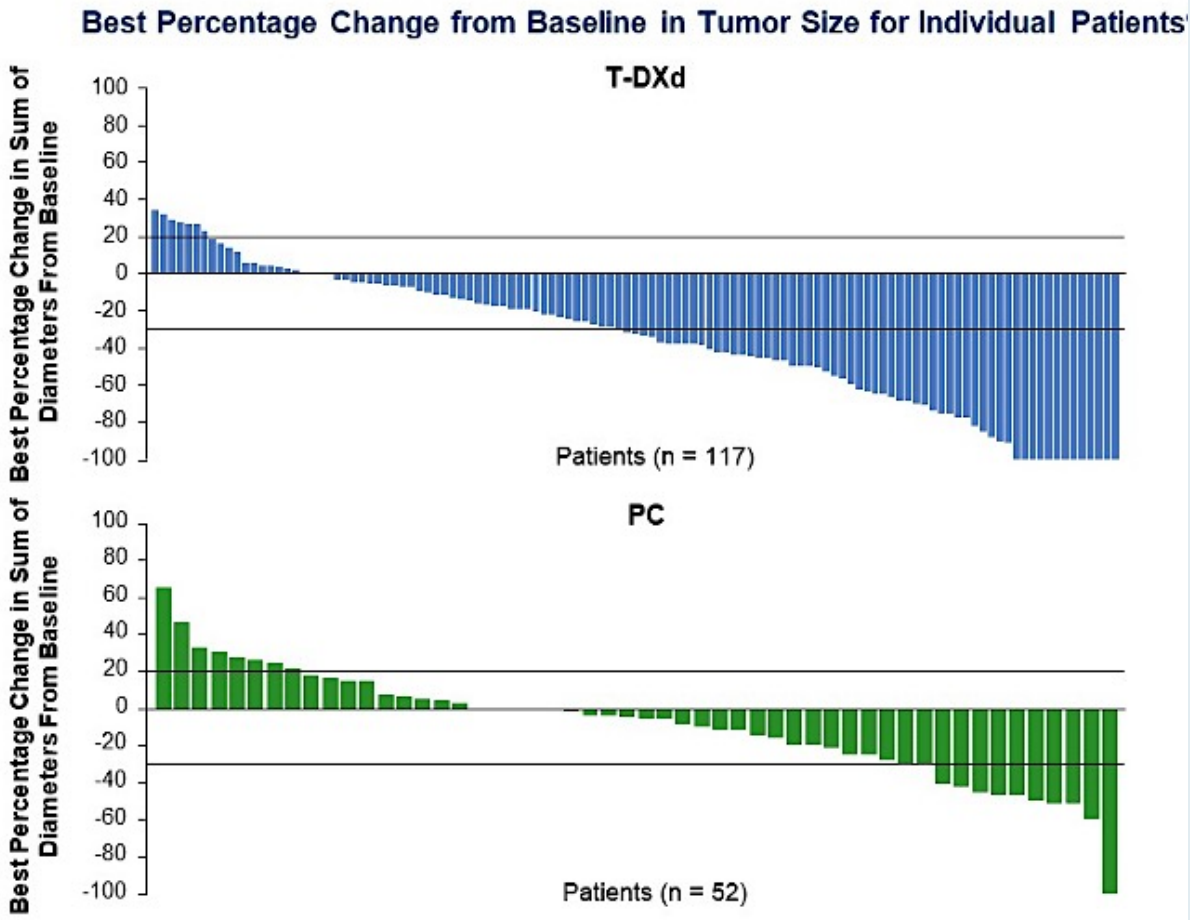


ILD = interstitital lung disease; PC = physician's choice; ORR = objective response rate; ICR = independent central review; OS = overall survival; DOR = duration of response; PFS = progression-free survival; DCR = disease control rate

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

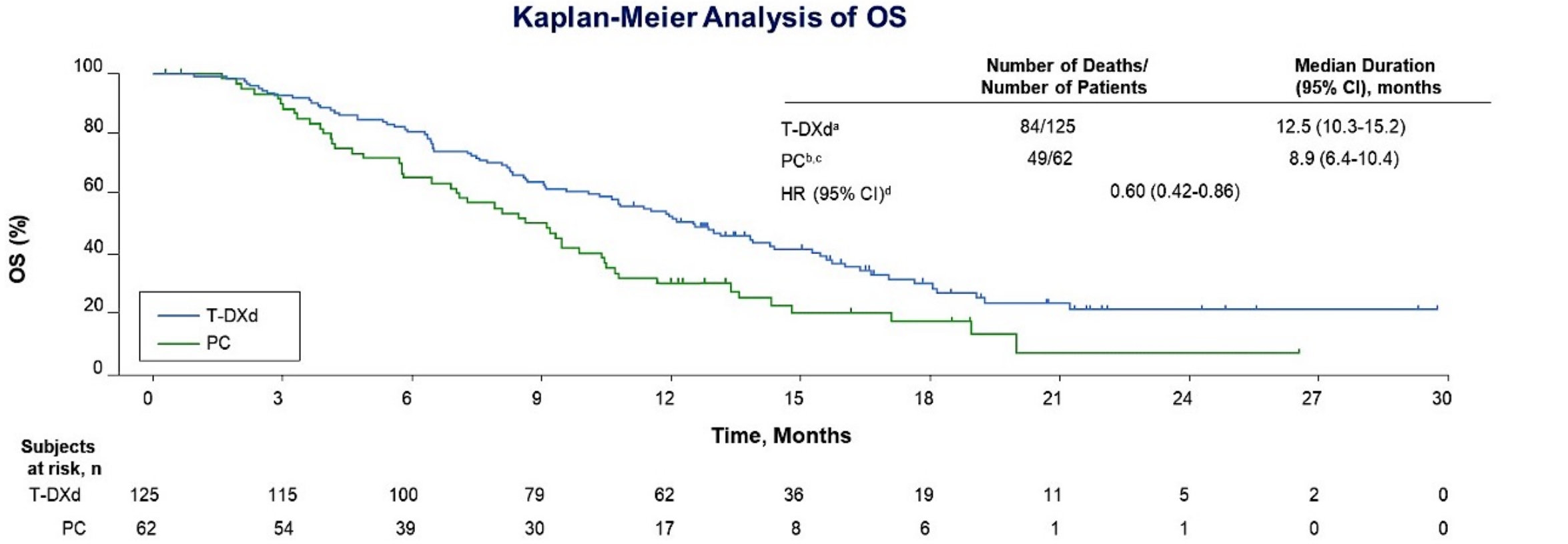
DESTINY-Gastric01: Antitumor Activity

	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



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

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.

RTP RESEARCH TO PRACTICE

2022 ASCO Gastrointestinal Cancers Symposium
Poster 295

Dose-escalation and dose-expansion study of trastuzumab deruxtecan (T-DXd) monotherapy and combinations in patients with advanced/metastatic HER2-positive gastric cancer/gastroesophageal junction adenocarcinoma: DESTINY-Gastric03

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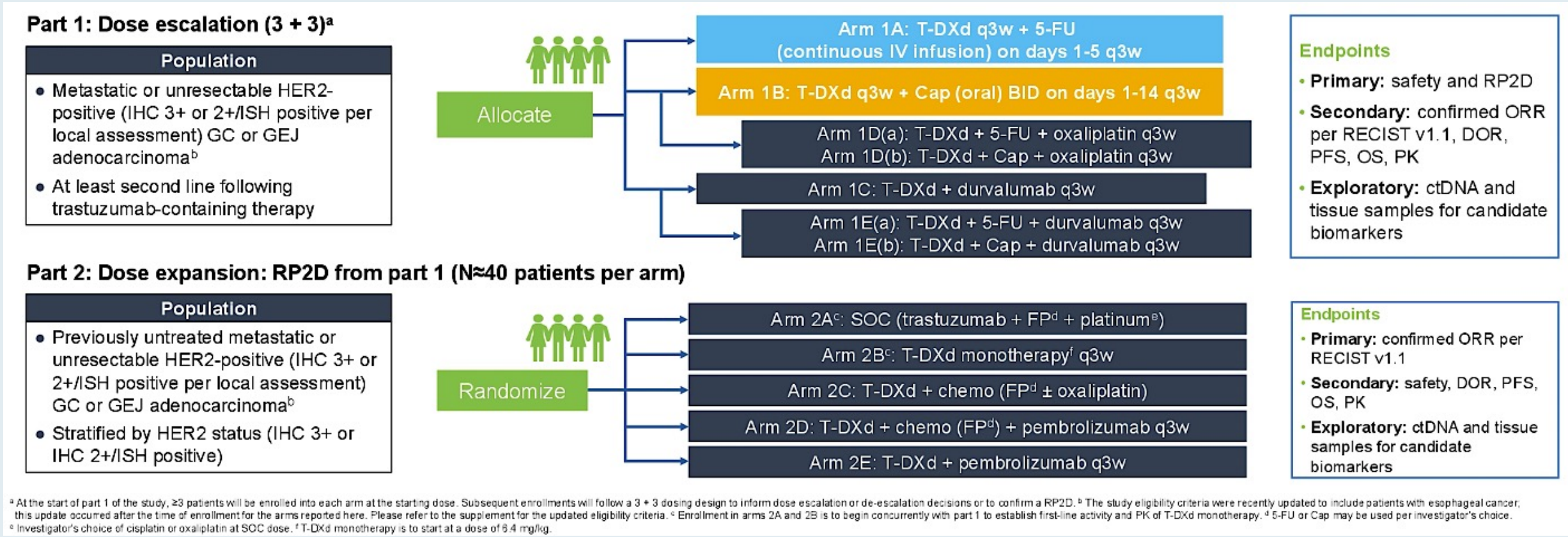
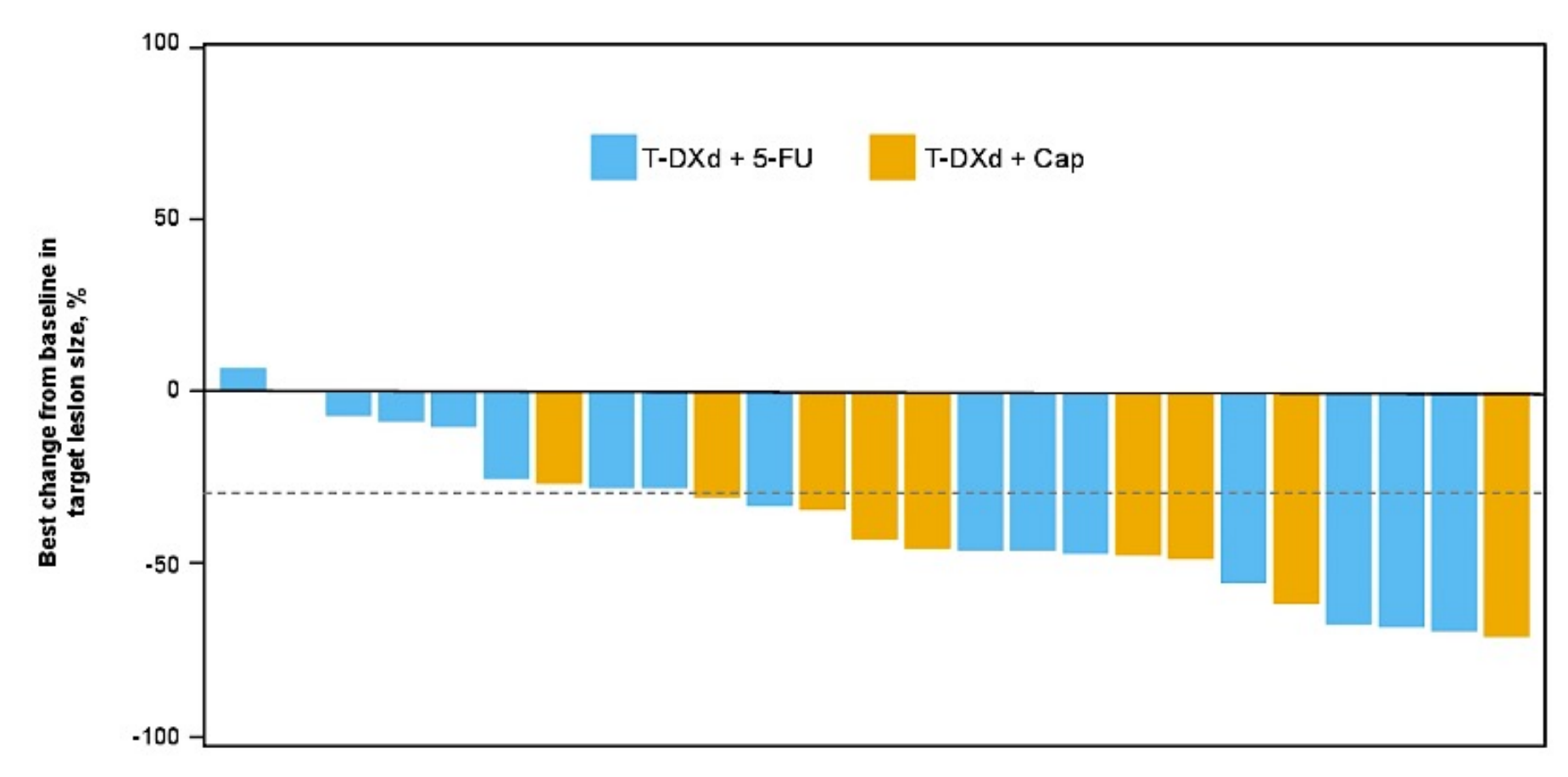
DESTINY-Gastric03 Phase Ib/II Study Design



[a] At the start of part 1 of the study, ≥3 patients will be enrolled into each arm at the starting dose. Subsequent enrollments will follow a 3 + 3 dosing design to inform dose escalation or de-escalation decisions or to confirm a RP2D. [b] The study eligibility criteria were recently updated to include patients with esophageal cancer; this update occurred after the time of enrollment for the arms reported here. Please refer to the supplement for the updated eligibility criteria. [c] Enrollment in arms 2A and 2B is to begin concurrently with part 1 to establish first-line activity and PK of T-DXd monotherapy. [d] 5-FU or Cap may be used per investigator's choice. [e] Investigator's choice of cisplatin or oxaliplatin at SOC dose. [f] T-DXd monotherapy is to start at a dose of 6.4 mg/kg.

Janjigian YY et al. 2022 ASCO Gastrointestinal Cancers Symposium;Abstract 295.

DESTINY-Gastric03 Part 1: Response



Arm 1A (T-DXd + 5-FU) ORR at RP2D: 3/6 (50%)
Arm 1B (T-DXd + capecitabine) ORR at RP2D: 3/7 (43%)

Janjigian YY et al. 2022 ASCO Gastrointestinal Cancers Symposium;Abstract 295.

DESTINY-Gastric03 Part 1: Safety in Arm 1A and Arm 1B

Arm 1A: T-Dxd + 5-FU

	Arm 1A all cohorts N=15	RP2D cohort n=6
Any AEs, n (%)	15 (100.0)	6 (100.0)
Grade ≥3 AEs, n (%)	14 (93.3)	5 (83.3)
Most common grade ≥3 AEs, n (%)[a]		
Anemia	6 (40.0)	3 (50.0)
Neutrophil count decreased	5 (33.3)	0
Neutropenia	2 (13.3)	2 (33.3)
Nausea	2 (13.3)	0
Stomatitis	2 (13.3)	0

[a] Occurring in >1 patient.

Arm 1B: T-Dxd + Capecitabine

	Arm 1B all cohorts N=10	RP2D cohort n=7
Any AEs, n (%)	10 (100.0)	7 (100.0)
Grade ≥3 AEs, n (%)	9 (90.0)	6 (85.7)
Most common grade ≥3 AEs, n (%)[a]		
Neutrophil count decreased	4 (40.0)	3 (42.9)
Anemia	4 (40.0)	2 (28.6)
Nausea	2 (20.0)	0

[a] Occurring in >1 patient.

AE = adverse event

Janjigian YY et al. 2022 ASCO Gastrointestinal Cancers Symposium;Abstract 295.

Management of Relapsed/Refractory HER2-Negative Gastroesophageal Cancers

RTP
RESEARCH
TO PRACTICE

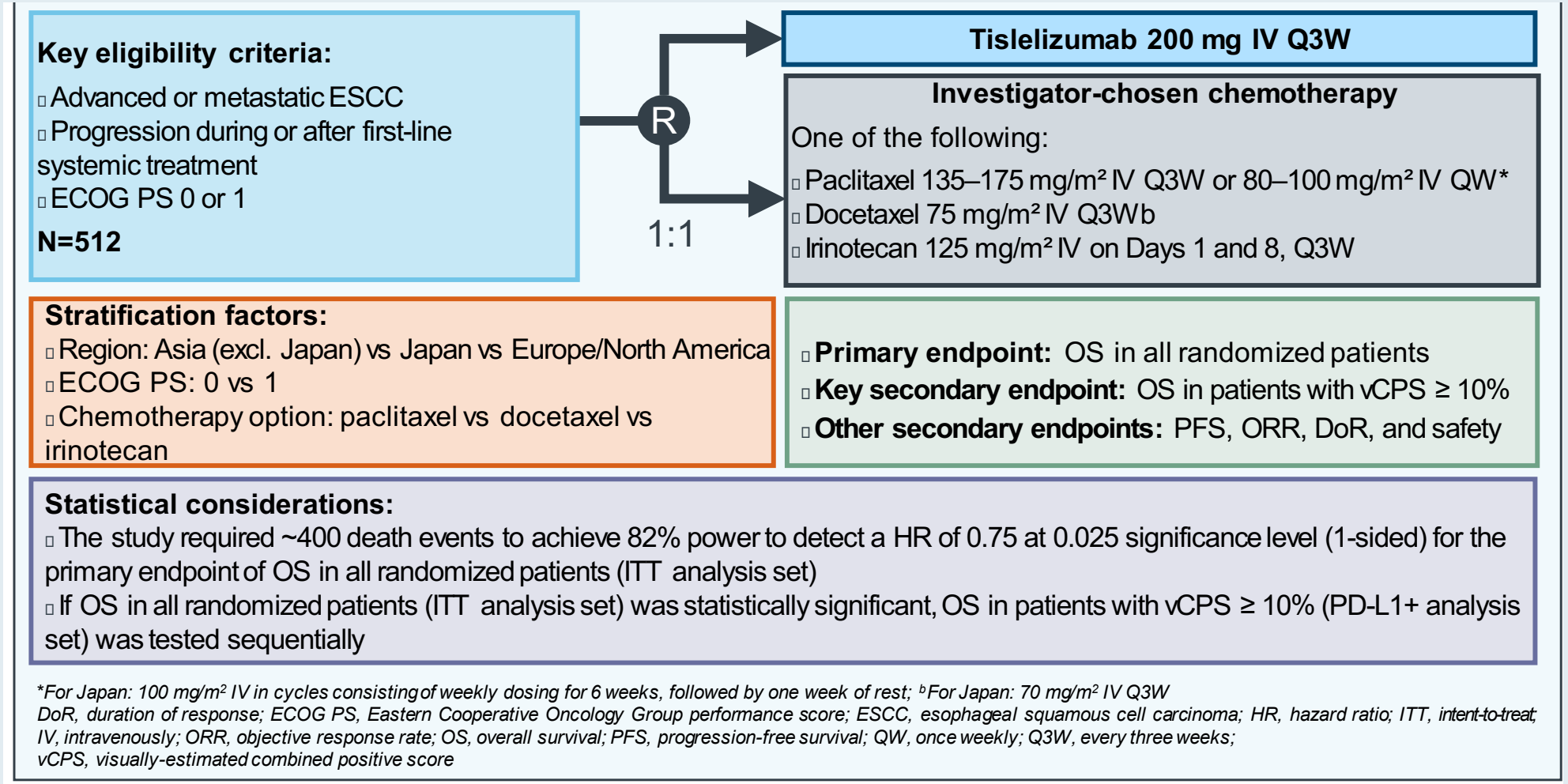
original reports

Tislelizumab Versus Chemotherapy as Second-Line Treatment for Advanced or Metastatic Esophageal Squamous Cell Carcinoma (RATIONALE-302): A Randomized Phase III Study

J Clin Oncol 2022;40:3065-76

Lin Shen, MD, PhD[1]; Ken Kato, MD, PhD[2]; Sung-Bae Kim, MD, PhD[3]; Jaffer A. Ajani, MD, PhD[4]; Kuaile Zhao, MD[5]; Zhiyong He, MD[6]; Xinmin Yu, MD[7]; Yongqian Shu, MD[8]; Qi Luo, MD[9]; Jufeng Wang, MD, PhD[10]; Zhendong Chen, MD[11]; Zuoxing Niu, MD[12]; Longzhen Zhang, MD[13]; Tienan Yi, MD[14]; Jong-Mu Sun, MD, PhD[15]; Jianhua Chen, MD, PhD[16]; Guohua Yu, MD[17]; Chen-Yuan Lin, MD, PhD[18]; Hiroki Hara, MD[19]; Qing Bi, MD[20]; Taroh Satoh, MD[21]; Roberto Pazo-Cid, MD[22]; Hendrick-Tobias Arkenau, MD, PhD[23]; Christophe Borg, MD, PhD[24]; Florian Lordick, MD, PhD[25]; Liyun Li, MD[26]; Ningning Ding, MD[26]; Aiyang Tao, PhD[26]; Jingwen Shi, PhD[26]; and Eric Van Cutsem, MD, PhD[27]; for the RATIONALE-302 Investigators

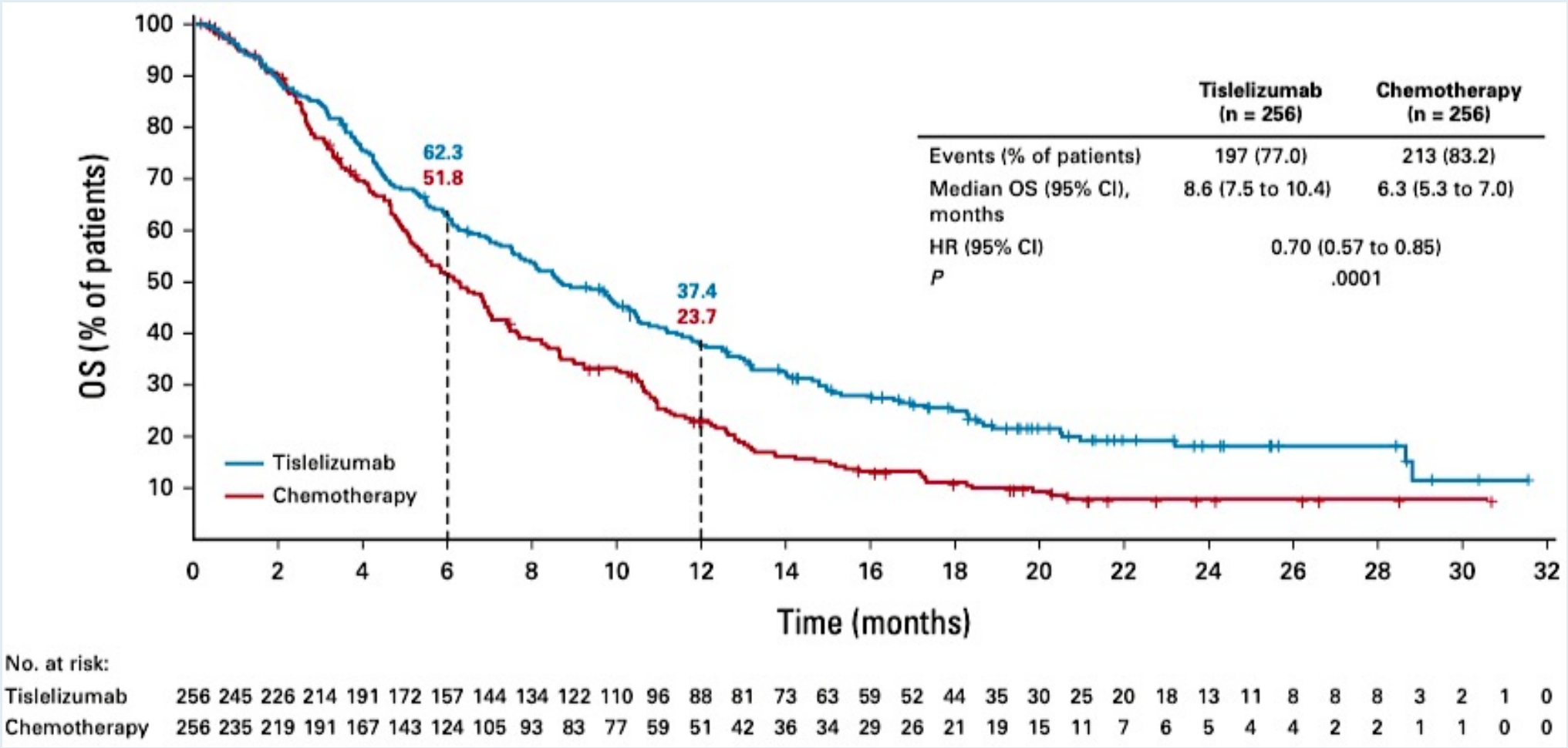
RATIONALE-302: Study Design



**For Japan: 100 mg/m² IV in cycles consisting of weekly dosing for 6 weeks, followed by one week of rest; [b]For Japan: 70 mg/m² IV Q3W*
DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; ITT, intent-to-treat; IV, intravenously; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QW, once weekly; Q3W, every three weeks; vCPS, visually-estimated combined positive score

Shen L et al. ASCO 2021;Abstract 4012.

RATIONALE-302: OS in ITT Population



	Tislelizumab (n = 256)	Chemotherapy (n = 256)
Events (% of patients)	197 (77.0)	213 (83.2)
Median OS (95% CI), months	8.6 (7.5 to 10.4)	6.3 (5.3 to 7.0)
HR (95% CI)	0.70 (0.57 to 0.85)	
P	.0001	

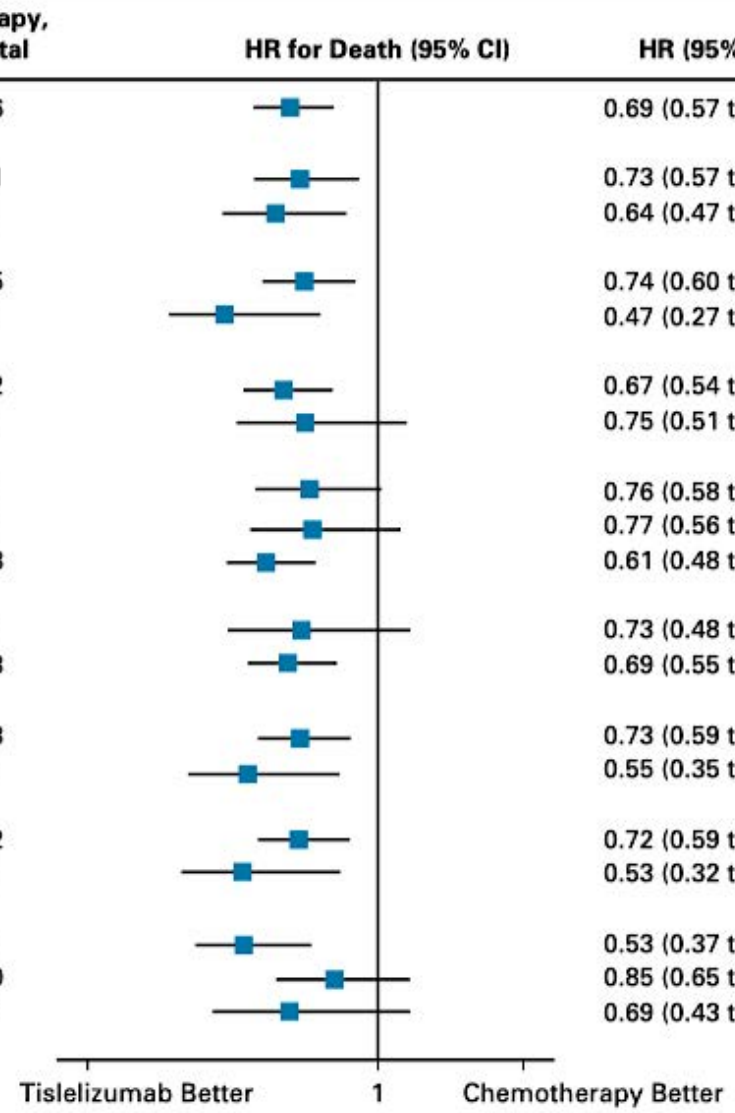
No. at risk:

Tislelizumab	256	245	226	214	191	172	157	144	134	122	110	96	88	81	73	63	59	52	44	35	30	25	20	18	13	11	8	8	8	3	2	1	0
Chemotherapy	256	235	219	191	167	143	124	105	93	83	77	59	51	42	36	34	29	26	21	19	15	11	7	6	5	4	4	2	2	1	1	0	0

Shen L et al. *J Clin Oncol* 2022;40:3065-76.

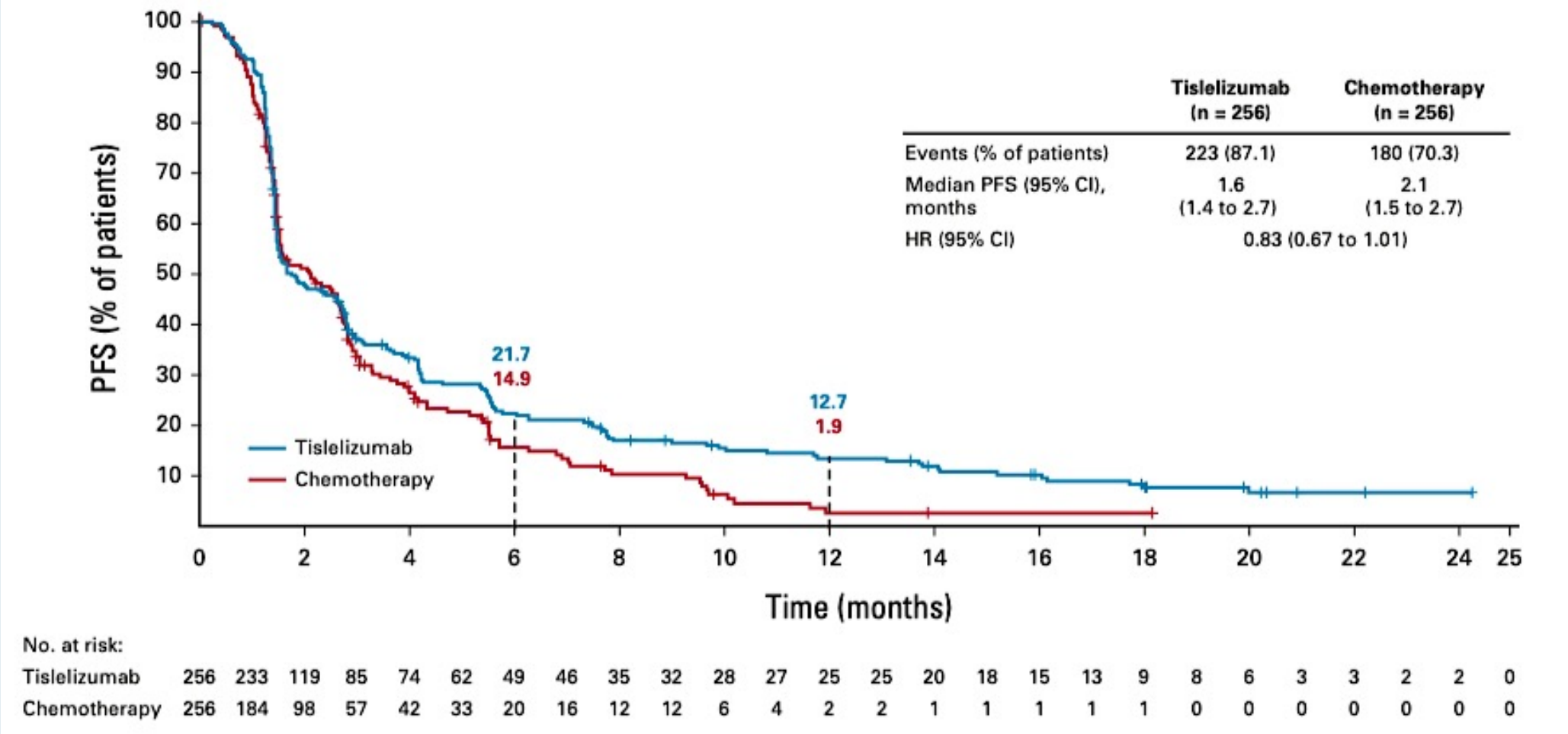
RATIONALE-302: OS Subgroup Analysis in ITT Population

Subgroup	Tislelizumab, Event/Total	Chemotherapy, Event/Total	HR (95% CI)
Overall	197/256	213/256	0.69 (0.57 to 0.84)
Age, years			
Age < 65	128/157	133/161	0.73 (0.57 to 0.93)
Age ≥ 65	69/99	80/95	0.64 (0.47 to 0.89)
Sex			
Male	171/217	178/215	0.74 (0.60 to 0.92)
Female	26/39	35/41	0.47 (0.27 to 0.80)
Smoking status			
Former/current smoker	139/188	161/192	0.67 (0.54 to 0.84)
Nonsmoker	58/68	52/63	0.75 (0.51 to 1.10)
Chemotherapy options			
Paclitaxel	197/256	68/85	0.76 (0.58 to 1.01)
Docetaxel	197/256	44/53	0.77 (0.56 to 1.07)
Irinotecan	197/256	101/118	0.61 (0.48 to 0.78)
ECOG PS			
0	45/64	45/63	0.73 (0.48 to 1.11)
1	152/192	168/193	0.69 (0.55 to 0.86)
Region			
Asia	162/201	171/203	0.73 (0.59 to 0.90)
Europe/North America	35/55	42/53	0.55 (0.35 to 0.87)
Race			
Asian and other	164/203	179/212	0.72 (0.59 to 0.90)
White	33/53	34/44	0.53 (0.32 to 0.87)
Baseline PD-L1 status			
TAP ≥ 10%	61/89	58/68	0.53 (0.37 to 0.77)
TAP < 10%	97/116	121/140	0.85 (0.65 to 1.11)
Unknown	39/51	34/48	0.69 (0.43 to 1.10)



Shen L et al. *J Clin Oncol* 2022;40:3065-76.

RATIONALE-302: PFS in ITT Population



	Tislelizumab (n = 256)	Chemotherapy (n = 256)
Events (% of patients)	223 (87.1)	180 (70.3)
Median PFS (95% CI), months	1.6 (1.4 to 2.7)	2.1 (1.5 to 2.7)
HR (95% CI)	0.83 (0.67 to 1.01)	

No. at risk:																									
Tislelizumab	256	233	119	85	74	62	49	46	35	32	28	27	25	25	20	18	15	13	9	8	6	3	3	2	2	0
Chemotherapy	256	184	98	57	42	33	20	16	12	12	6	4	2	2	1	1	1	1	1	0	0	0	0	0	0	0

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RATIONALE-302: Overall Response Rates

Antitumor Response	Tislelizumab (n = 256)	Chemotherapy (n = 256)
ORR, No. (%) [95% CI][a]	52 (20.3) [15.6 to 25.8]	25 (9.8) [6.4 to 14.1]
Odds ratio for ORR (95% CI)	2.39 (1.42 to 4.01)	
Best overall response, No. (%)		
Complete response	5 (2.0)	1 (0.4)
Partial response	47 (18.4)	24 (9.4)
Stable disease	68 (26.6)	82 (32.0)
Progressive disease	116 (45.3)	86 (33.6)
Not evaluable[b]	1 (0.4)	3 (1.2)
Not assessable[c]	19 (7.4)	60 (23.4)
DoR, months, median (95% CI)[a]	7.1 (4.1 to 11.3)	4.0 (2.1 to 8.2)
Patients with ongoing response, No./n (%)	10/52 (19.2)	0/25 (0.0)

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