Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

Gastroesophageal Cancers

Thursday, February 8, 2024
5:00 PM – 6:00 PM ET

Faculty

Yelena Y Janjigian, MD

Zev Wainberg, MD, MSc

Moderator

Neil Love, MD

RTP Year in Review 2024

Faculty

Yelena Y Janjigian, MD
Chief of Gastrointestinal Oncology Service
Department of Medicine
Memorial Sloan Kettering Cancer Center
New York, New York

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

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

Commercial Support

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

Dr Love — Disclosures

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Dr Janjigian — Disclosures

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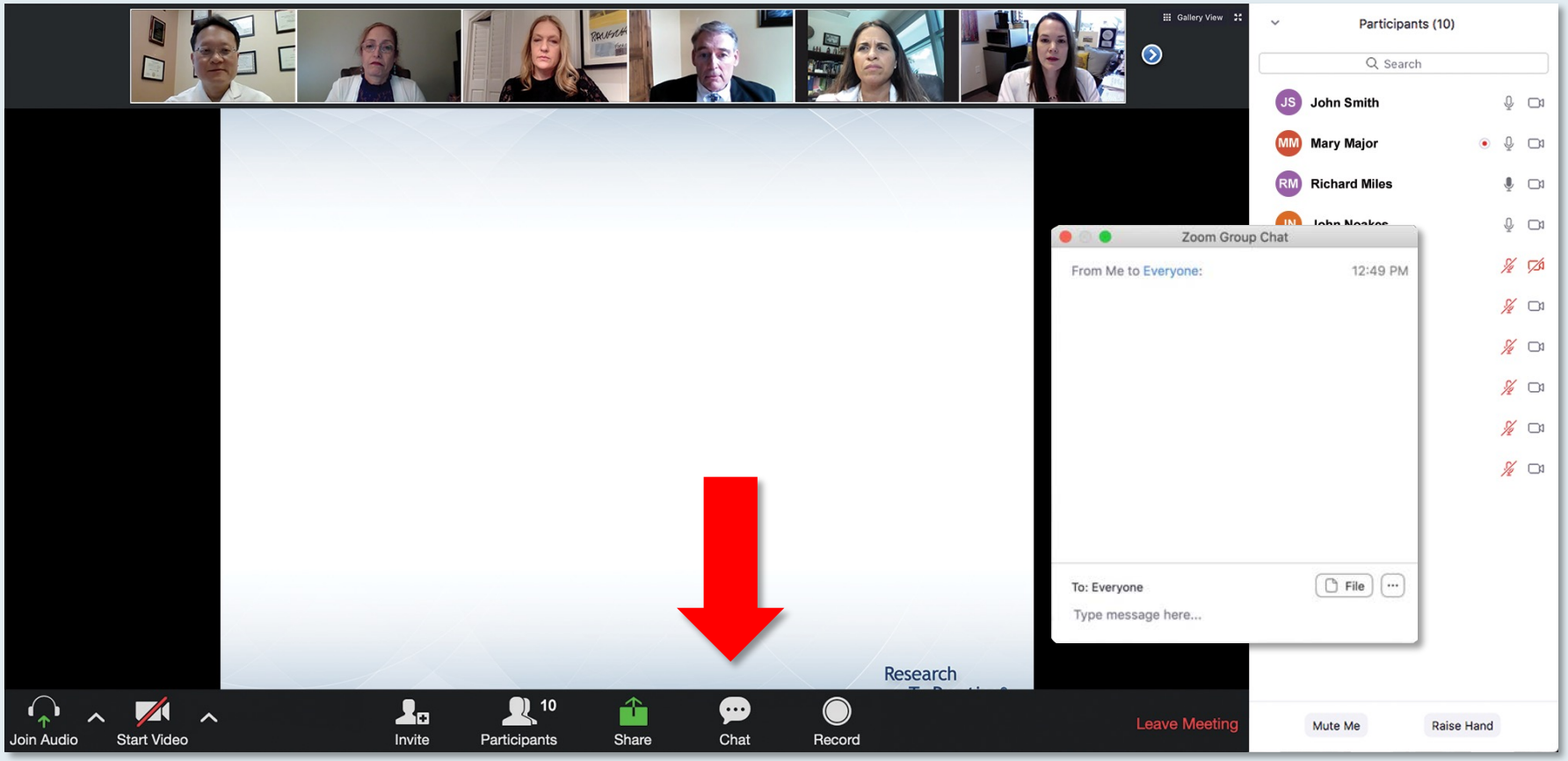
We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

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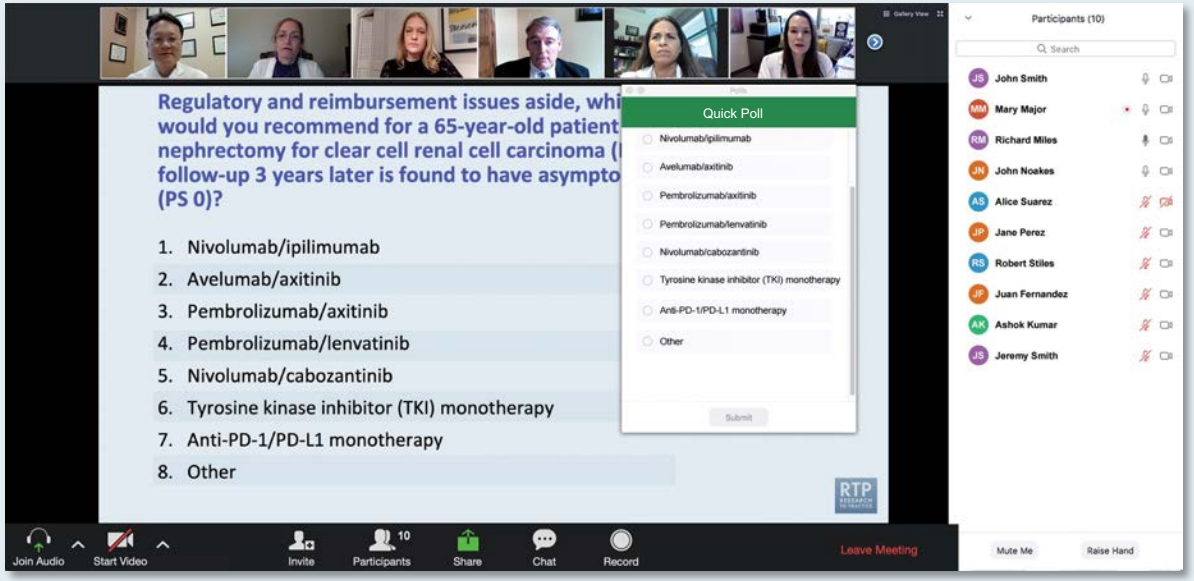
Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys



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ONCOLOGY TODAY

WITH DR NEIL LOVE

Meet The Professor: Optimizing the Management of Gastroesophageal Cancers — Part 3 of a 3-Part Series

DR SAMUEL J KLEMPNER

MASSACHUSETTS GENERAL HOSPITAL

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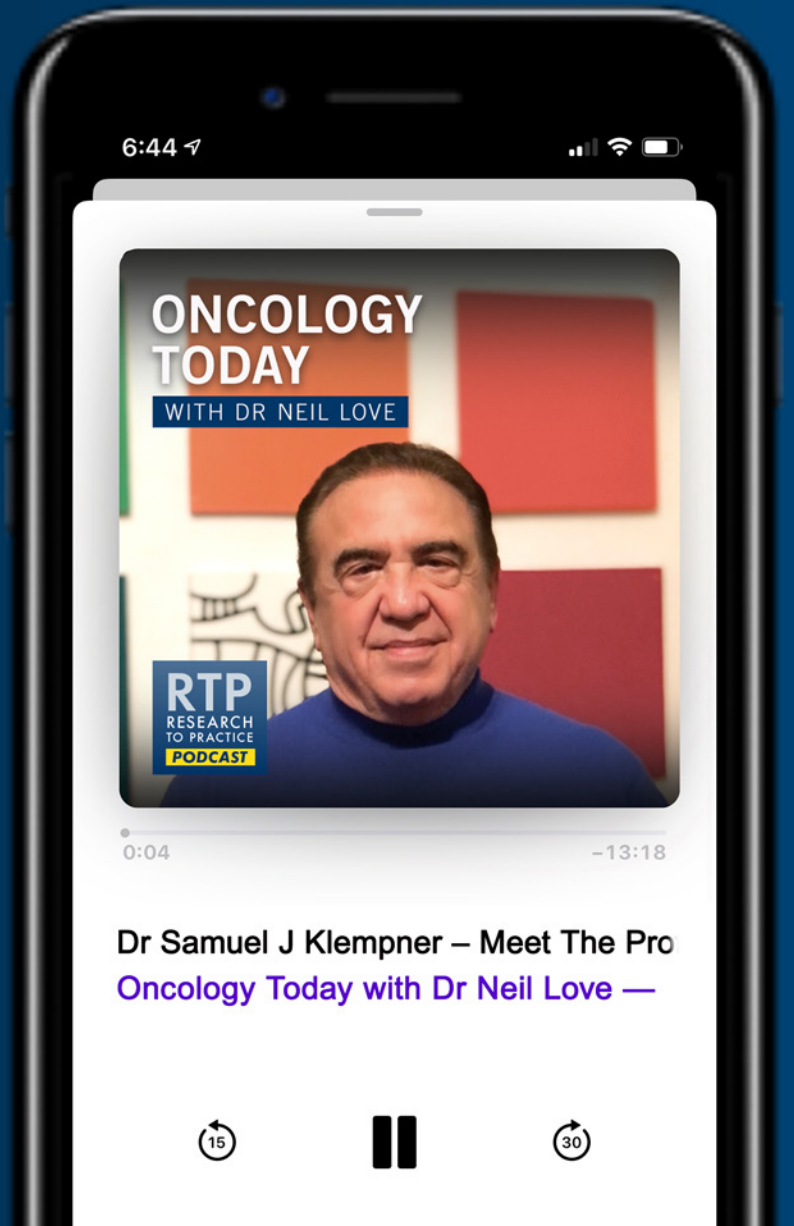

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Lymphoma

Tuesday, February 13, 2024
5:00 PM – 6:00 PM ET

Faculty

Andrew M Evens, DO, MBA, MSc
Sonali M Smith, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

Consensus or Controversy? Investigator Perspectives on the Current and Future Role of Immune Checkpoint Inhibitors in the Management of Hepatobiliary Cancers — A 2024 Post-ASCO Gastrointestinal Cancers Symposium Review

A CME-Accredited Virtual Event

Thursday, February 15, 2024
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Urothelial Bladder Cancer

Thursday, February 22, 2024
5:00 PM – 6:00 PM ET

Faculty

Shilpa Gupta, MD

Thomas Powles, MBBS, MRCP, MD

Moderator

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Prostate Cancer

Wednesday, February 28, 2024
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Faculty

Andrew J Armstrong, MD, ScM

Maha Hussain, MD, FACP, FASCO

Moderator

Neil Love, MD

RTP Year in Review 2024

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Agenda

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MODULE 1: Updates on Immunotherapy in GE Cancers

MODULE 2: Targeting HER2

- **First-Line Treatment**
- **Trastuzumab Deruxtecan**
- **Zanidatamab**

MODULE 3: Targeting Claudin 18.2 — Zolbetuximab

MODULE 4: Faculty Journal Club

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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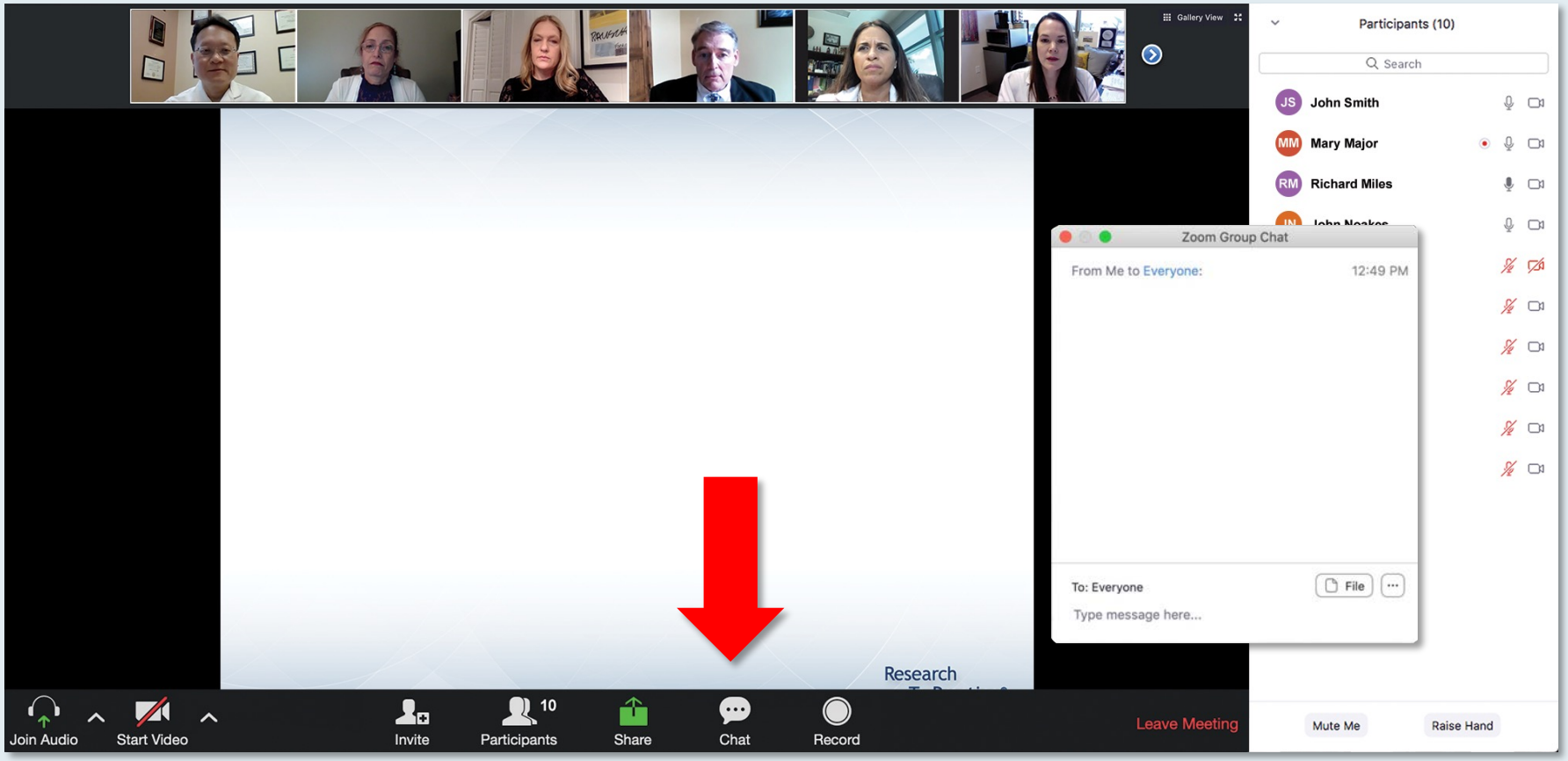

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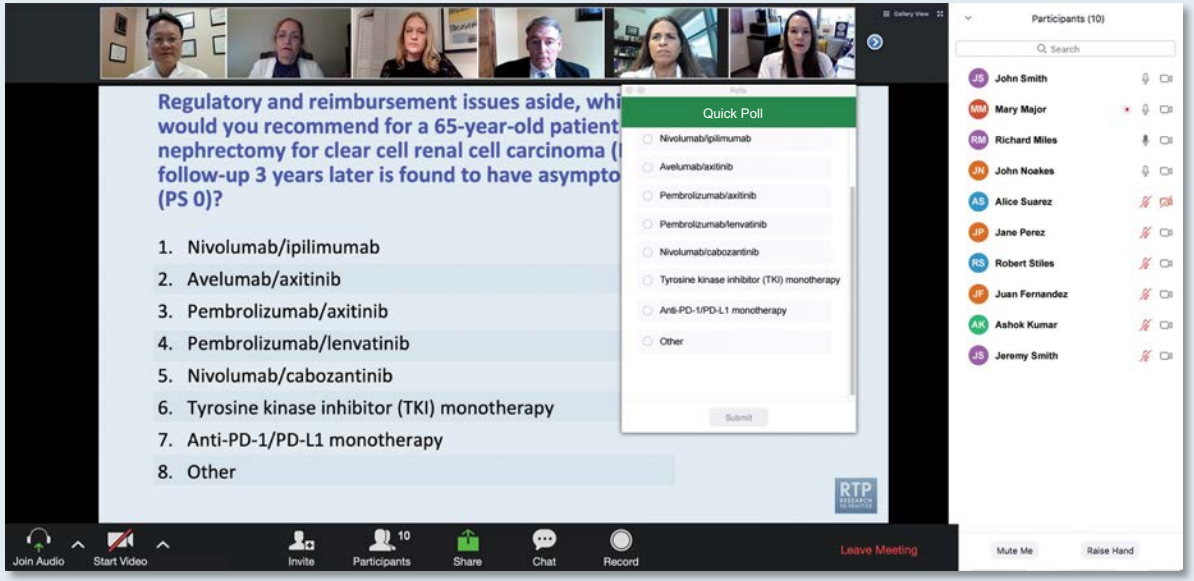

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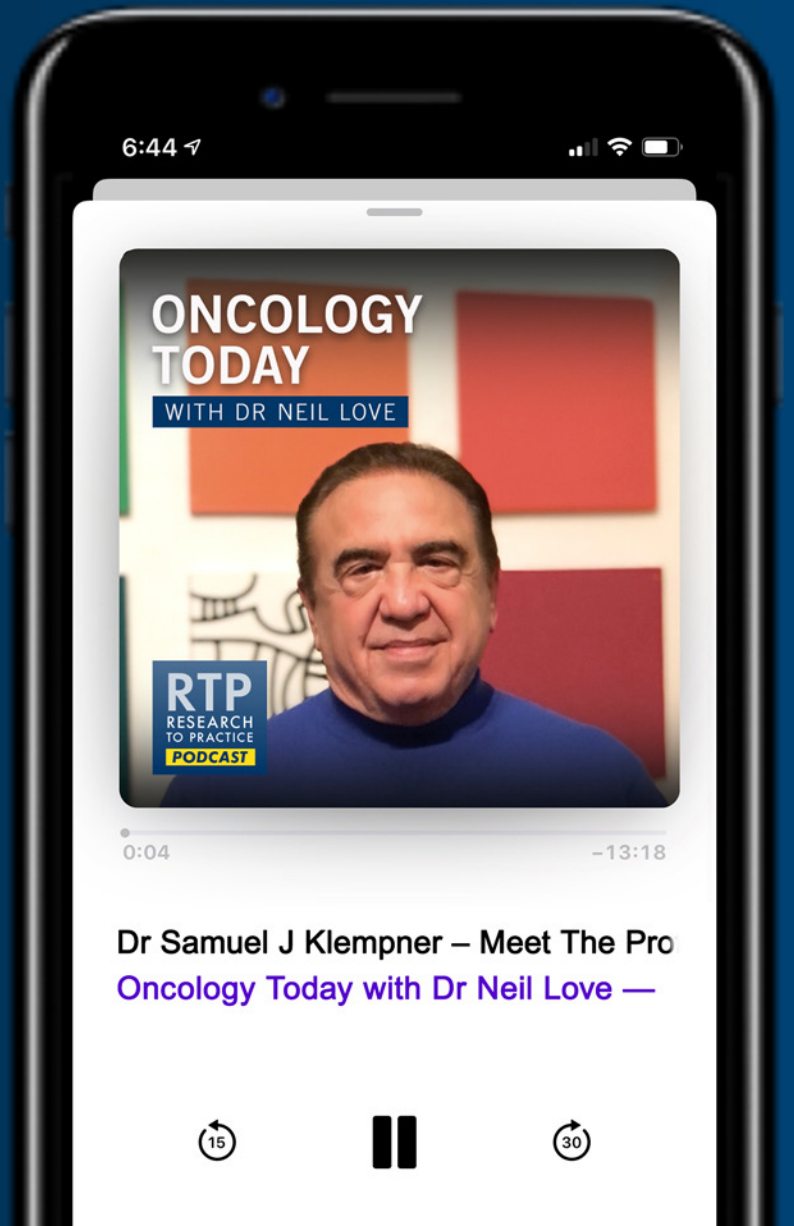

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Third Annual **National General Medical Oncology Summit**

Friday, March 22, 2024

6:30 PM – 7:00 PM

Welcome Reception

7:00 PM – 9:00 PM

Keynote Session: ER-Positive Metastatic Breast Cancer

Erika Hamilton, MD
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD
Hope S Rugo, MD

Special Feature: Clinicians with Breast Cancer

Third Annual **National General Medical Oncology Summit**

Saturday, March 23, 2024

7:30 AM – 9:10 AM

Hodgkin and Non-Hodgkin Lymphoma

Ann S LaCasce, MD, MMSc
Matthew Lunning, DO
Kami Maddocks, MD
Andrew D Zelenetz, MD, PhD

9:30 AM – 10:20 AM

Gynecologic Cancers

Bradley J Monk, MD
David M O'Malley, MD

10:20 AM – 11:10 AM

Localized Breast Cancer; SABCS 2023 Review

Virginia Kaklamani, MD, DSc
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD

11:10 AM – 12:00 PM

Metastatic Breast Cancer, Triple-Negative Breast Cancer, HER2-Positive Breast Cancer; SABCS 2023 Review

Erika Hamilton, MD
Virginia Kaklamani, MD, DSc
Hope S Rugo, MD

Third Annual **National General Medical Oncology Summit**

Saturday, March 23, 2024

12:30 PM – 1:20 PM

Prostate Cancer

Emmanuel S Antonarakis, MD
Rana R McKay, MD

1:20 PM – 2:10 PM

Urothelial Bladder Cancer

Matthew D Galsky, MD
Jonathan E Rosenberg, MD

2:10 PM – 3:00 PM

Renal Cell Carcinoma

Eric Jonasch, MD
Brian Rini, MD

3:20 PM – 4:10 PM

Targeted Therapy for Non-Small Cell Lung Cancer

Ibiayi Dagogo-Jack, MD
Helena Yu, MD

4:10 PM – 5:00 PM

Nontargeted Treatments for Lung Cancer

Edward B Garon, MD, MS
Corey J Langer, MD

Third Annual **National General Medical Oncology Summit**

Sunday, March 24, 2024

7:30 AM – 8:20 AM

Multiple Myeloma

Natalie S Callander, MD
Paul G Richardson, MD

8:20 AM – 9:10 AM

Gastroesophageal Cancers

Yelena Y Janjigian, MD
Samuel J Klempner, MD

9:30 AM – 10:20 AM

Hepatobiliary Cancers

Ghassan Abou-Alfa, MD, MBA
Richard S Finn, MD

10:20 AM – 11:10 AM

Colorectal Cancer

Kristen K Ciombor, MD, MSCI
John Strickler, MD

11:10 AM – 12:00 PM

Pancreatic Cancer

Andrew H Ko, MD
Eileen M O'Reilly, MD

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Dr Wainberg — Disclosures

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Immunotherapy in Gastroesophageal Cancers

Yelena Y. Janjigian, MD
Attending Physician

Chief, Gastrointestinal Oncology Service
Memorial Sloan Kettering Cancer Center

Email: janjigiy@mskcc.org

Monday, February 5th | 30 minutes
3:00 – 3:30 pm

Other Treatment Approaches for Gastroesophageal Cancers

Zev A. Wainberg
Professor of Medicine and Surgery
UCLA School of Medicine
Los Angeles, California

Key Data Sets

Yelena Y Janjigian, MD

- Shitara K et al. **Neoadjuvant and adjuvant pembrolizumab plus chemotherapy in locally advanced gastric or gastro-oesophageal cancer** (**KEYNOTE-585**): An **interim analysis** of the multicentre, double-blind, randomised phase 3 study. *Lancet Oncol* 2023;[Online ahead of print].
- Janjigian YY et al. **Pathological complete response (pCR)** to 5-fluorouracil, leucovorin, oxaliplatin and docetaxel **(FLOT) with or without durvalumab (D)** in **resectable** gastric and gastroesophageal junction cancer (**GC/GEJC**): Subgroup analysis by region from the phase 3, randomized, double-blind **MATTERHORN** study. Gastrointestinal Cancers Symposium 2024;Abstract LBA246.
- Li Y et al. **Chemotherapy plus camrelizumab** versus chemotherapy alone as **neoadjuvant treatment** for resectable **esophageal squamous cell carcinoma (ESCORT-NEO)**: A multi-center, randomized phase III trial. Gastrointestinal Cancers Symposium 2024;Abstract LBA244.
- Kelly R et al. **Adjuvant nivolumab** vs placebo in **resected esophageal** or gastroesophageal junction cancer **following neoadjuvant chemoradiotherapy**: First report of **comprehensive biomarker analyses from CheckMate 577**. World Congress on Gastrointestinal Cancer 2023;Abstract O-7.

Key Data Sets

Yelena Y Janjigian, MD (continued)

- Shitara K et al. **Nivolumab (NIVO) + chemotherapy (chemo)** vs chemo as **first-line (1L) treatment** for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (**GC/GEJC/EAC**): **4-year (yr) follow-up of CheckMate 649**. Gastrointestinal Cancers Symposium 2024;Abstract 306.
- Rha SY et al. **Pembrolizumab plus chemotherapy** versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (**KEYNOTE-859**): A multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol* 2023;24(11):1181-95.
- Lei M et al. **Nivolumab (NIVO) plus (+) chemotherapy (chemo)** or ipilimumab (IPI) vs chemo as **1L treatment for advanced esophageal squamous cell carcinoma (ESCC)**: First comprehensive biomarker analyses from **CheckMate 648.** Gastrointestinal Cancers Symposium 2024;Abstract 252.
- Shah MA et al. **First-line pembrolizumab (pembro) plus chemotherapy (chemo)** for advanced **esophageal** cancer: **5-year outcomes from the phase 3 KEYNOTE-590** study. Gastrointestinal Cancers Symposium 2024;Abstract 250.

Key Data Sets

Yelena Y Janjigian, MD (continued)

- Xu R-H et al. **Tislelizumab (TIS) plus chemotherapy (Chemo)** vs placebo (PBO) plus chemo as **first-line (1L)** treatment of advanced gastric or gastroesophageal junction adenocarcinoma (**GC/GEJC**): **Final analysis results of the RATIONALE-305 study**. ESMO 2023;Abstract LBA80.
- Hubner R et al. Randomized, global, **phase III** study of **tislelizumab (TIS) + chemotherapy (chemo)** vs placebo (PBO) + chemo **as first-line (1L) treatment** for advanced/metastatic **esophageal** squamous cell carcinoma (ESCC): **RATIONALE-306 update**. ESMO 2023;Abstract 1514P.
- Janjigian YY et al. **Pembrolizumab plus trastuzumab and chemotherapy** for **HER2-positive gastric** or gastro-oesophageal junction adenocarcinoma: **Interim analyses from the phase 3 KEYNOTE-811** randomised placebo-controlled trial. *Lancet* 2023;402(10418):2197-208.
- Hsu C et al. **SKYSCRAPER-08:** A phase III, randomized, double-blind, placebo-controlled study of **first-line (1L) tiragolumab (tira) + atezolizumab (atezo) and chemotherapy (CT)** in patients (pts) with **esophageal** squamous cell carcinoma (ESCC). Gastrointestinal Cancers Symposium 2024;Abstract 245.

Key Data Sets

Zev Wainberg, MD, MSc

- Ajani JA et al. **Updated efficacy and safety** results from **phase III SPOTLIGHT** study evaluating **zolbetuximab + mFOLFOX6 as first-line (1L)** treatment for patients with claudin-18 isoform 2-positive **(CLDN18.2+)**, HER2−, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (**mG/GEJ**) adenocarcinoma. ESMO 2023;Abstract LBA82.
- Lordick F et al. **Updated efficacy and safety** results from **phase III GLOW** study evaluating **zolbetuximab + CAPOX as first-line (1L) treatment** for patients with claudin-18 isoform 2-positive **(CLDN18.2+)**, HER2−, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (**mG/GEJ**) adenocarcinoma. ESMO 2023;Abstract LBA81.
- Shitara K et al. **Management of nausea and vomiting** (N/V) following first-line (1L) **zolbetuximab** + chemotherapy treatment in claudin-18.2 **(CLDN18.2)**+, HER2−, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (**mG/GEJ**) adenocarcinoma: **Analysis from the phase 3 SPOTLIGHT and GLOW studies**. Gastrointestinal Cancers Symposium 2024;Abstract 372.
- Klempner SJ et al. **ILUSTRO**: Phase II **multicohort trial of zolbetuximab** in patients with advanced or metastatic **claudin 18.2-positive** gastric or gastroesophageal junction adenocarcinoma. *Clin Cancer Res* 2023;29(19):3882-91.

Key Data Sets

Zev Wainberg, MD, MSc (continued)

- Wang Y et al. **First-in-human dose escalation and expansion study** of **SYSA1801, an antibody-drug conjugate targeting claudin 18.2** in patients with resistant/refractory solid tumors. ASCO 2023; Abstract 3016.
- Van Cutsem E et al. **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. *Lancet Oncol* 2023;24(7):744-56.
- Yamaguchi K et al. **Trastuzumab deruxtecan** in anti-human epidermal growth factor receptor 2 treatment-naive patients with **human epidermal growth factor receptor 2-low** gastric or gastroesophageal junction adenocarcinoma: Exploratory cohort results in a Phase II trial. *J Clin Oncol* 2023;41(4):816-25.
- Lee K et al. **Zanidatamab (zani) plus chemotherapy (chemo) and tislelizumab (tis) as first-line (1l)** therapy for patients (pts) with advanced **HER2-positive** (+) gastric/gastroesophageal junction adenocarcinoma (**GC/GEJC**): Updated results from a phase Ib/II study. ESMO 2023;Abstract 1518P.

Key Data Sets

Zev Wainberg, MD, MSc (continued)

- Chakrabarti S et al. **Anti-HER2 therapy following ctDNA-identified ERBB2 amplification** for patients with advanced gastric cancer: Exploration of real-world outcomes and resistance mechanisms. World Congress on Gastrointestinal Cancer 2023;Abstract PD-9.
- Lorenzen S et al. **Ramucirumab plus irinotecan/leucovorin/5-FU** versus ramucirumab plus paclitaxel in patients with advanced or metastatic adenocarcinoma of the **stomach or gastroesophageal junction**, who failed one prior line of palliative chemotherapy: The **phase II/III RAMIRIS study** (AIO-STO-0415). *BMC Cancer* 2023;23(1):561.
- Shitara K et al. **Effects of prior therapies on outcomes with trifluridine/tipiracil** in patients with metastatic gastric/gastroesophageal junction cancer in a randomized **phase III trial (TAGS)**. *J Cancer Res Clin Oncol* 2023;149(11):9361-74.

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MODULE 1: Updates on Immunotherapy in GE Cancers

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- **First-Line Treatment**
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Cancer Management and Research

Open Access Full Text Article

REVIEW

Role of PD-1 Inhibitors in the Treatment of Esophagogastric Adenocarcinoma: Patient Selection and Reported Outcomes

Raisa Epistola[1], Rubens Sperandio[2], Zev Wainberg[3], Syma Iqbal[4], Joseph Chao[5]

Cancer Manag Res 2023;15:265-75.

asco special articles

Immunotherapy and Targeted Therapy for Advanced Gastroesophageal Cancer: ASCO Guideline

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J Clin Oncol 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Negative Gastric Adenocarcinoma: First-Line Immunotherapy

"For human epidermal grown factor receptor 2 (HER2)-negative patients with gastric adenocarcinoma and programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥ 5, first-line therapy with nivolumab and chemotherapy (CT) is recommended."

Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Negative Esophageal or GEJ Adenocarcinoma: First-Line Immunotherapy

"For HER2-negative patients with esophageal or gastroesophageal junction (GEJ) AC and PD-L1 CPS ≥ 5, first-line therapy with nivolumab and CT is recommended.

First-line therapy with pembrolizumab and CT is recommended for HER2-negative patients with esophageal or GEJ AC and PD-L1 ≥ 10."

Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Negative Esophageal Squamous Cell Carcinoma: First-Line Immunotherapy

"For patients with esophageal squamous cell carcinoma and PD-L1 tumor proportion score ≥ 1%, nivolumab plus CT, or nivolumab plus ipilimumab is recommended; for patients with esophageal squamous cell carcinoma and PD-L1 CPS ≥ 10, pembrolizumab plus CT is recommended."

Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Negative Esophageal or GEJ Adenocarcinoma: Second-Line Therapy

"For patients with advanced gastroesophageal or GEJ AC whose disease has progressed after first-line therapy, ramucirumab plus paclitaxel is recommended."

Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

Frequently Asked Clinical Questions About GE Cancers

In the first-line metastatic setting, how do you integrate primary tumor location, histology and PD-1 level to decide whether to add an immunotherapy (IO)?

Which IO? Which chemotherapy?

Agenda

INTRODUCTION: First-Line Therapy for Metastatic Gastroesophageal (GE) Cancers — the Bottom Line

MODULE 1: Updates on Immunotherapy in GE Cancers

MODULE 2: Targeting HER2

- **First-Line Treatment**
- **Trastuzumab Deruxtecan**
- **Zanidatamab**

MODULE 3: Targeting Claudin 18.2 — Zolbetuximab

MODULE 4: Faculty Journal Club

Neoadjuvant/Adjuvant Immunotherapy

- Kelly R et al. **Adjuvant nivolumab** vs placebo in resected esophageal or gastroesophageal junction cancer **following neoadjuvant chemoradiotherapy**: First report of **comprehensive biomarker analyses from CheckMate 577**. World Congress on Gastrointestinal Cancer 2023;Abstract O-7.
- Shitara K et al. **Neoadjuvant and adjuvant pembrolizumab plus chemotherapy in locally advanced gastric or gastro-oesophageal cancer** (**KEYNOTE-585**): An **interim analysis** of the multicentre, double-blind, randomised phase 3 study. *Lancet Oncol* 2023;[Online ahead of print].
- Al-Batran S et al. Pathological complete response (pCR) to **durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT)** in resectable gastric and gastroesophageal junction cancer (GC/GEJC): **Interim results** of the global, phase III **MATTERHORN** study. ESMO 2023;Abstract LBA73.
- Li Y et al. **Chemotherapy plus camrelizumab** versus chemotherapy alone as **neoadjuvant treatment** for resectable **esophageal squamous cell carcinoma (ESCORT-NEO)**: A multi-center, randomized phase III trial. Gastrointestinal Cancers Symposium 2024;Abstract LBA244.

Frequently Asked Clinical Questions About GE Cancers

For which patients with GE cancers do you use neoadjuvant treatment?

How do you integrate primary tumor location, histology and PD-1 level to decide whether or not to use an adjuvant IO?

Which IO and for how long?

Frequently Asked Clinical Questions About GE Cancers

Does the use of corticosteroid prophylaxis for the GI toxicity associated with chemotherapy interfere with the efficacy of immunotherapy?

Frequently Asked Clinical Questions About GE Cancers

What has been seen with the use of neoadjuvant/adjuvant IO in gastric/GEJ adenocarcinoma, and what will need to be seen to bring it to the clinic?

Do you currently use adjuvant IO in any situations for these patients?

Neoadjuvant and adjuvant pembrolizumab plus chemotherapy in locally advanced gastric or gastro-oesophageal cancer (KEYNOTE-585): an interim analysis of the multicentre, double-blind, randomised phase 3 study

*Kohei Shitara, Sun Young Rha, Lucjan S Wyrwicz, Takashi Oshima, Nina Karaseva, Mikhail Osipov, Hisateru Yasui, Hiroshi Yabusaki, Sergey Afanasyev, Young-Kyu Park, Salah-Eddin Al-Batran, Takaki Yoshikawa, Patricio Yanez, Maria Di Bartolomeo, Sara Lonardi, Josep Tabernero, Eric Van Cutsem, Yelena Y Janjigian, Do-Youn Oh, Jianming Xu, Xiao Fang, Chie-Schin Shih, Pooja Bhagia, Yung-Jue Bang, on behalf of the KEYNOTE-585 investigators**

Courtesy of Yelena Y Janjigian, MD

KEYNOTE-585: Event-Free and Overall Survival

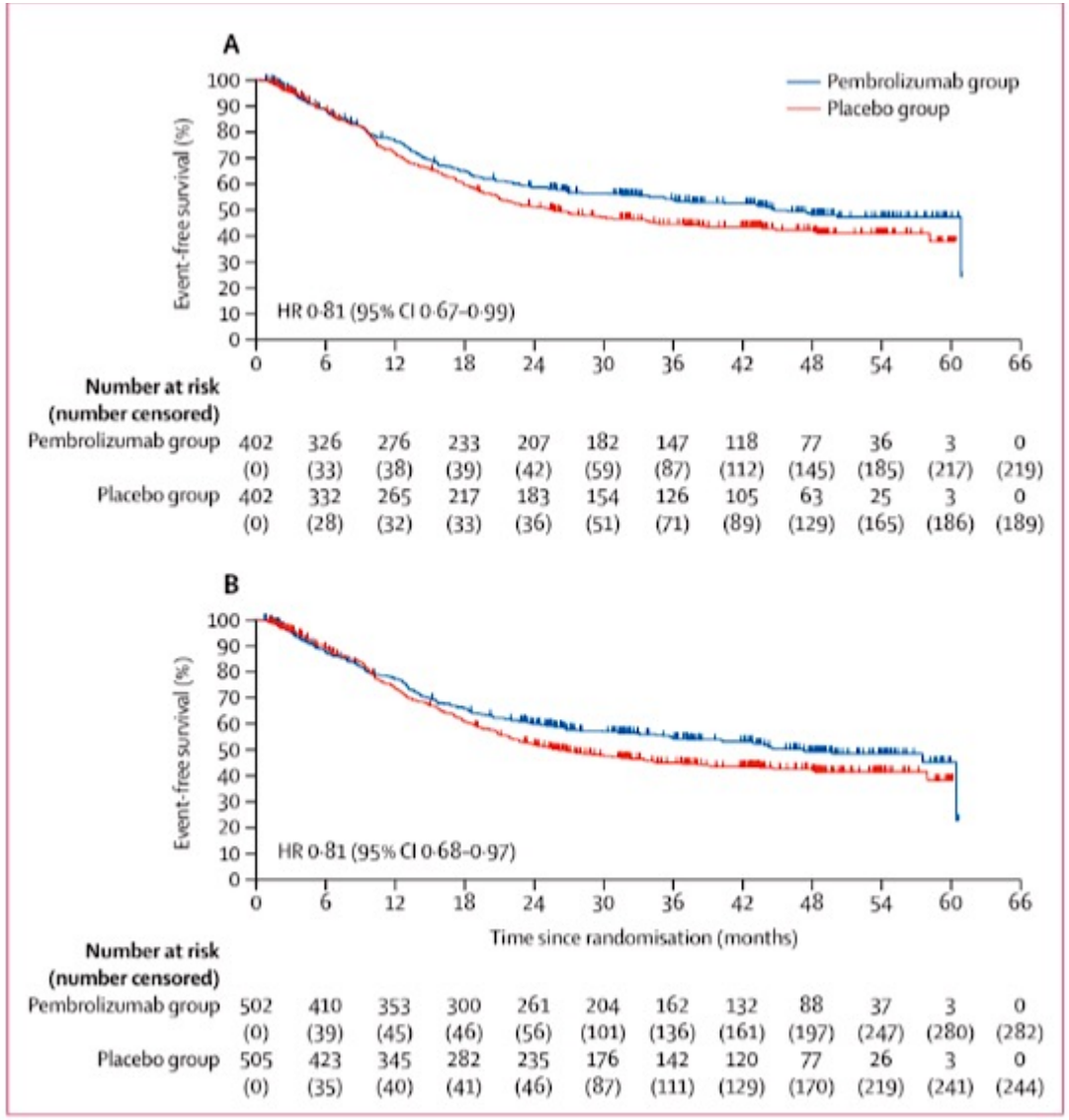

Figure 2: **Kaplan-Meier estimates of event-free survival**
(A) Main cohort. (B) Main plus FLOT cohort. Event-free survival was based on Response Evaluation Criteria in Solid Tumours (version 1.1) as assessed by the investigator.

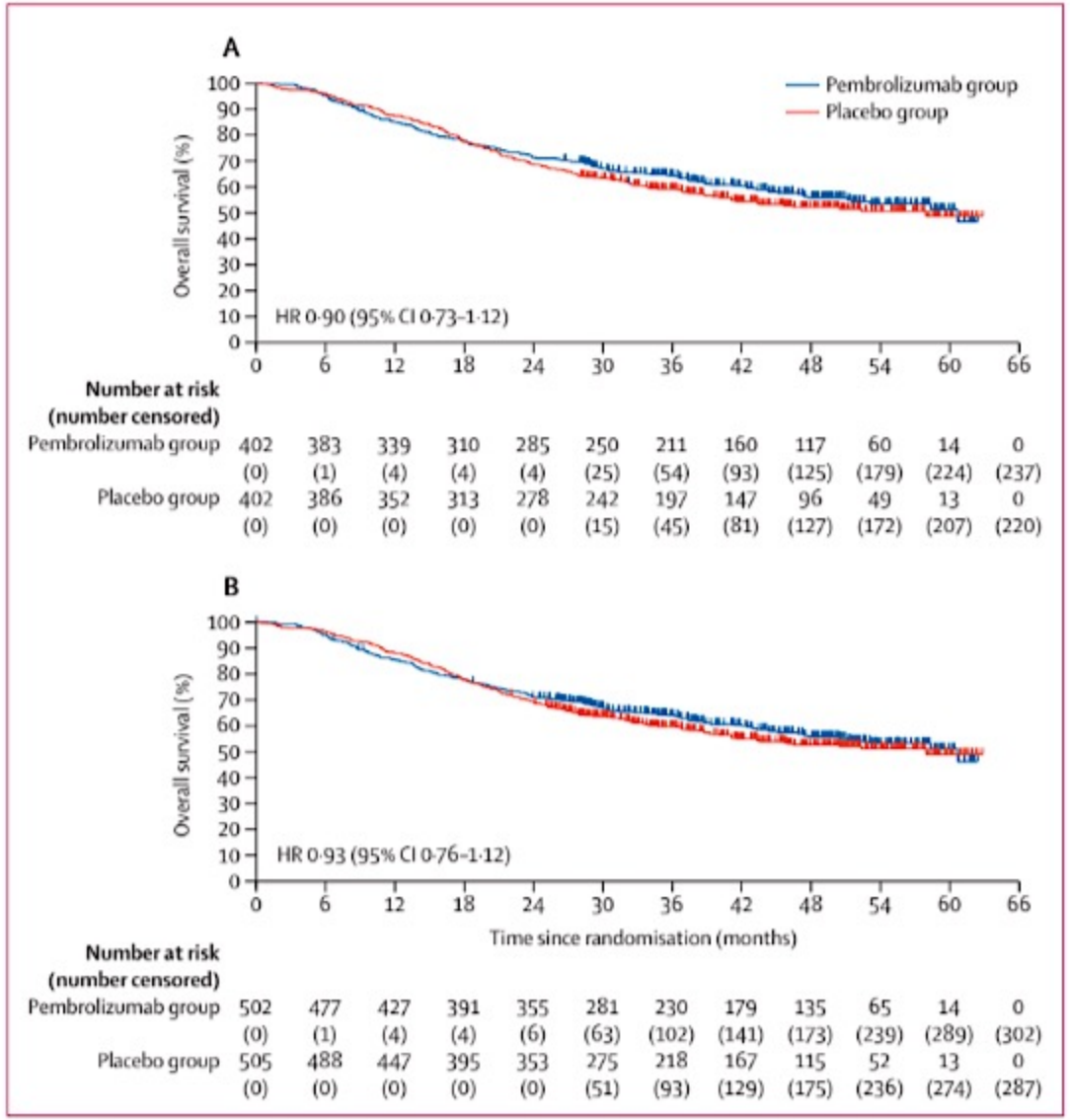

Figure 3: **Kaplan-Meier estimates of overall survival**
(A) Main cohort. (B) Main plus FLOT cohort.

Shitara K et al. *Lancet Oncol* 2023;[Online ahead of print].

Courtesy of Yelena Y Janjigian, MD

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Pathological complete response to 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) with or without durvalumab in resectable gastric and gastroesophageal junction cancer: subgroup analysis by region from the Phase 3, randomized, double-blind MATTERHORN study

Yelena Y. Janjigian, MD

Yelena Y. Janjigian[1], Salah-Eddin Al-Batran[2], Zev A. Wainberg[3], Eric Van Cutsem[4], Daniela Molena[5], Kei Muro[6], Woo Jin Hyung[7], Lucjan Wyrwicz[8], Do-Youn Oh[9], Takeshi Omori[10], Markus Moehler[11], Marcelo Garrido[12], Sulene C.S. Oliveira[13], Moishe Liberman[14], Victor Castro Oliden[15], Mehmet Bilici[16], John F. Kurland[17], Ioannis Xynos[18], Helen Mann[18], Josep Tabernero[19]

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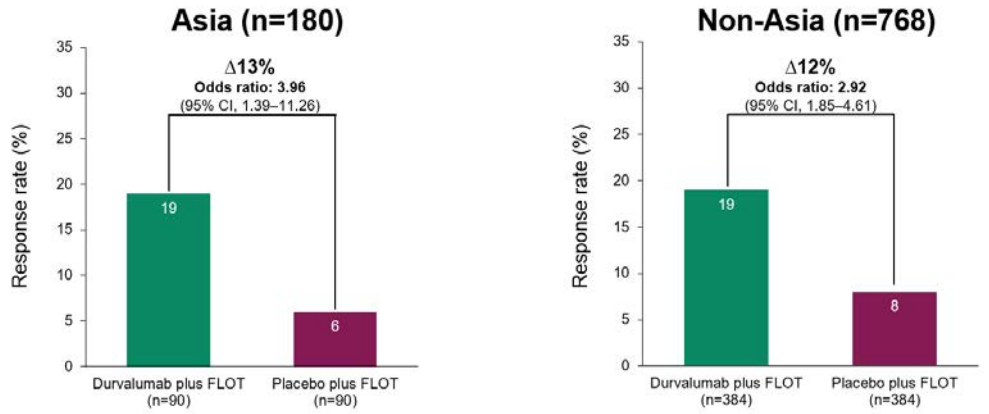
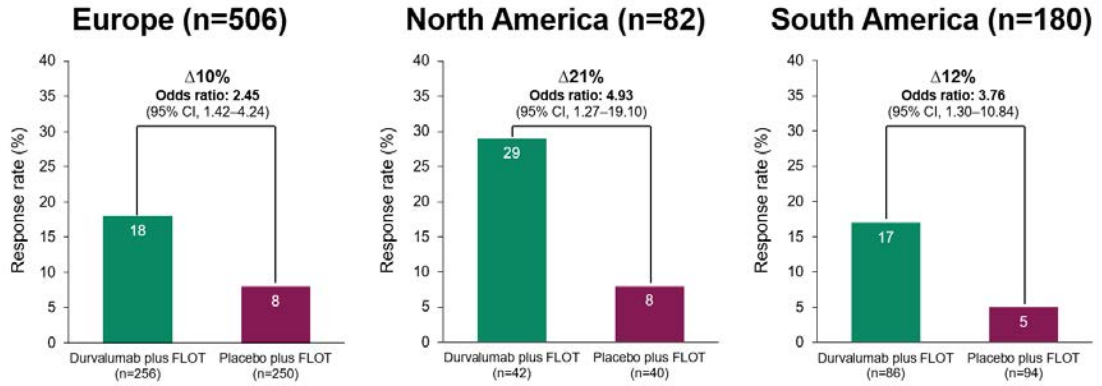
MATTERHORN: Response

Pathological complete response in Asia and non-Asia



Participants achieve pathological complete response if there is no residual viable tumor cells found at primary tumor and resected lymph nodes at the time of resection, meaning a pathological regression of 100%, based on central assessment. Central review of pathological complete response was scored using modified Ryan criteria.
CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel.

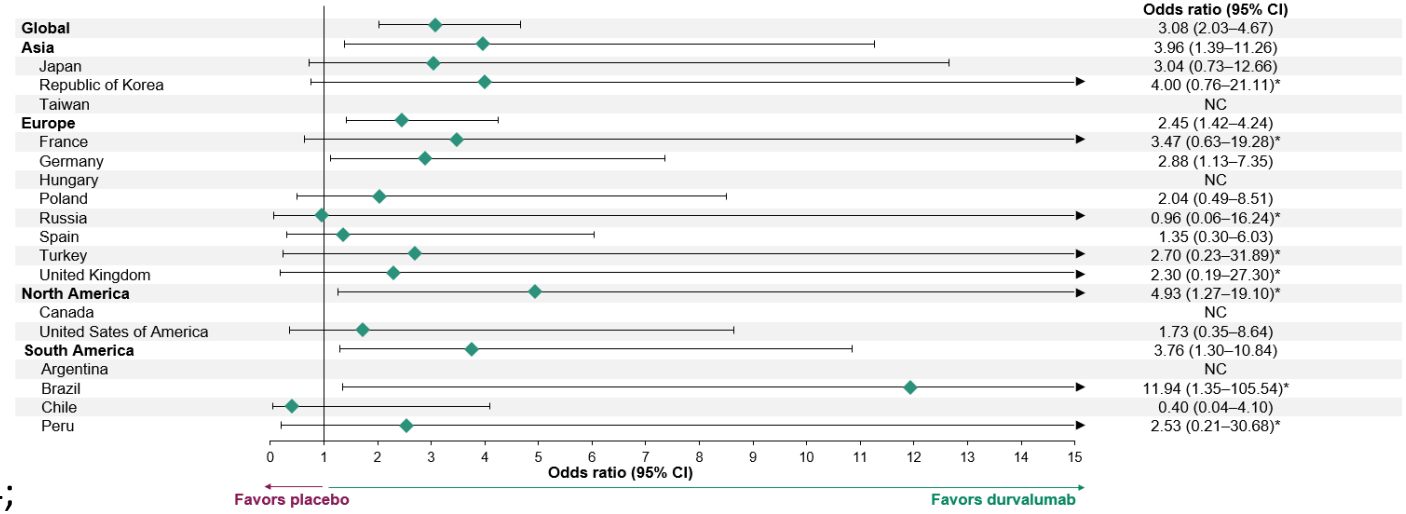
Pathological complete response by region (non-Asia)



Participants achieve pathological complete response if there is no residual viable tumor cells found at primary tumor and resected lymph nodes at the time of resection, meaning a pathological regression of 100%, based on central assessment. Central review of pathological complete response was scored using modified Ryan criteria.
CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel.

Pathological complete response

Countries with ≥20 randomized participants are shown

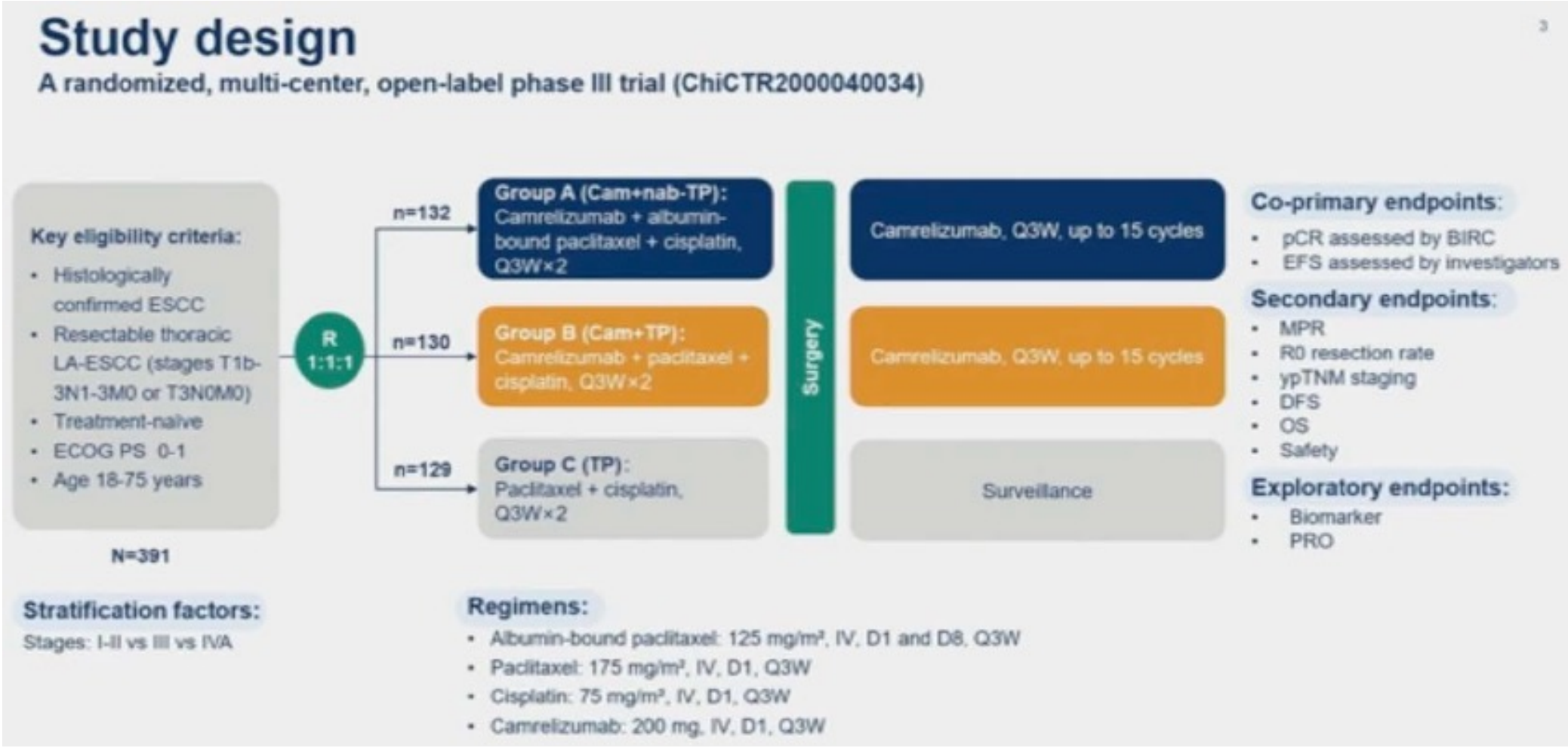


Participants achieve pathological complete response if there is no residual viable tumor cells found at primary tumor and resected lymph nodes at the time of resection, meaning a pathological regression of 100%, based on central assessment. Central review of pathological complete response was scored using modified Ryan criteria. Pathological complete response presented for countries with ≥20 randomized participants across both arms; Belgium, Denmark, and Netherlands excluded for Europe. The odds ratio is NC in a subgroup where there are <5 participants or 0 responses in either arm.
*Upper CIs exceeding a ratio of 15 are truncated for the figure.
CI, confidence interval; NC, not calculated.

Janjigian YY et al.
GI Cancers Symposium 2024;
Abstract LBA246.

Courtesy of Yelena Y Janjigian, MD

Chemotherapy plus camrelizumab versus chemotherapy alone as neoadjuvant treatment for resectable esophageal squamous cell carcinoma (ESCORT-NEO): A multicenter, randomized phase III trial.



Li Y et al. GI Cancers Symposium 2024;Abstract LBA244.

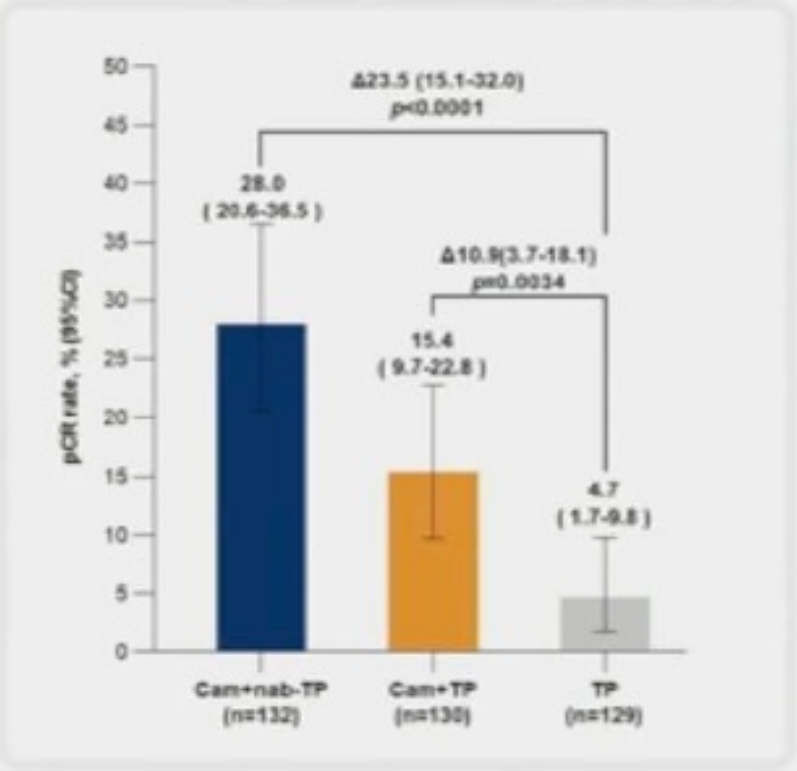
Courtesy of Yelena Y Janjigian, MD

Chemotherapy plus camrelizumab versus chemotherapy alone as neoadjuvant treatment for resectable esophageal squamous cell carcinoma (ESCORT-NEO): A multicenter, randomized phase III trial.

Primary endpoint: pCR rate assessed by BIRC in ITT population

	Group A: Cam+nab-TP (n=132)	Group B: Cam+TP (n=130)	Group C: TP (n=129)
pCR rate, % (95%CI)[a]	28.0 (20.6, 36.5)	15.4 (9.7, 22.8)	4.7 (1.7, 9.8)
Difference (vs. Group C), % (95%CI)[b]	23.5 (15.1, 32.0)	10.9 (3.7, 18.1)	
OR (vs. Group C) (95%CI)[b]	8.11 (3.28, 20.06)	3.81 (1.48, 9.80)	
p value (vs. Group C)[c]	<0.0001	0.0034	

a 95%CI were calculated based on the Clopper-Pearson method.
b 95%CI for the stratification factor-adjusted rate differences were derived using the Mantel-Haenszel method.
c The CMH test, stratified by clinical staging (stage I/II vs. III/IVA), was used to compare between groups.



Li Y et al. GI Cancers Symposium 2024;Abstract LBA244.

Courtesy of Yelena Y Janjigian, MD

First-Line Immunotherapy

- Shitara K et al. **Nivolumab (NIVO) + chemotherapy (chemo)** vs chemo as **first-line (1L) treatment** for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): **4 year (yr) follow-up of CheckMate 649**. Gastrointestinal Cancers Symposium 2024;Abstract 306.
- Rha SY et al. **Pembrolizumab plus chemotherapy** versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (**KEYNOTE-859**): A multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol* 2023;24(11):1181-95.
- Lei M et al. **Nivolumab (NIVO) plus (+) chemotherapy (chemo)** or ipilimumab (IPI) vs chemo as **1L treatment for advanced esophageal squamous cell carcinoma (ESCC)**: First comprehensive biomarker analyses from **CheckMate 648.** Gastrointestinal Cancers Symposium 2024;Abstract 252.
- Shah MA et al. **First-line pembrolizumab (pembro) plus chemotherapy (chemo)** for advanced esophageal cancer: **5-year outcomes from the phase 3 KEYNOTE-590** study. Gastrointestinal Cancers Symposium 2024;Abstract 250.

ASCO Gastrointestinal Cancers Symposium

Nivolumab plus chemotherapy or ipilimumab vs chemotherapy as first-line treatment for advanced esophageal squamous cell carcinoma: first comprehensive biomarker analyses from CheckMate 648

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[1]Bristol Myers Squibb, Princeton, NJ; [2]Osaka University Graduate School of Medicine, Osaka, Japan; [3]Keio University School of Medicine, Tokyo, Japan; [4]National Cancer Center Hospital, Tokyo, Japan; [5]Royal Marsden Hospital, London & Surrey, UK; [6]Department of Gastrointestinal Oncology, The Fifth Medical Center, Chinese PLA General Hospital, Beijing, China; [7]Klinika Onkologii i Radioterapii, Narodowy Instytut Onkologii, Warszawa, Poland; [8]Akita University Hospital, Akita, Japan; [9]Kanagawa Cancer Center, Kanagawa, Japan; [10]Kindai University Faculty of Medicine, Osakasayama, Japan; [11]National Taiwan University Hospital, Taipei, Taiwan; [12]Institut du Cancer de Montpellier, Montpellier, France; [13]Centre Oscar Lambret, Lille, France; [14]Istituto Nazionale Tumori, Milan, Italy; [15]Institute of Cancer of São Paulo, University of São Paulo, São Paulo, Brazil; [16]Odense University Hospital, Odense, Denmark; [17]The University of Texas MD Anderson Cancer Center, Houston, TX

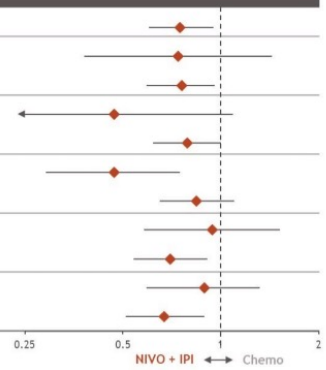
Abstract number 252

Courtesy of Yelena Y Janjigian, MD

CheckMate 648: Overall Survival Subgroup Analyses

OS by select gene alterations: NIVO + IPI

Gene alteration status[a]	Median OS, months		Unstratified HR (95% CI)
	NIVO + IPI	Chemo	
WES-evaluable (n = 390)	15.1	10.8	0.75 (0.60-0.95)
CDKN2A mutation (n = 46)	18.3	10.7	0.74 (0.38-1.44)
CDKN2A wildtype (n = 344)	15.1	11.0	0.76 (0.59-0.96)
PIK3CA mutation (n = 35)	21.2	9.9	0.47 (0.20-1.09)
PIK3CA wildtype (n = 355)	15.1	11.0	0.79 (0.62-1.00)
NFE2L2 mutation (n = 91)	13.1	8.6	0.47 (0.29-0.75)
NFE2L2 wildtype (n = 299)	15.5	12.9	0.84 (0.65-1.10)
NOTCH1 mutation (n = 83)	9.8	12.8	0.94 (0.58-1.52)
NOTCH1 wildtype (n = 307)	17.0	10.2	0.70 (0.54-0.91)
CCND1 amplification (n = 128)	16.2	11.9	0.89 (0.59-1.32)
CCND1 non-amplification (n = 262)	15.1	10.2	0.67 (0.51-0.89)



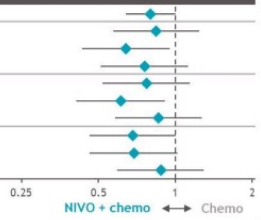
- OS benefit was observed with NIVO + IPI vs chemo regardless of genetic alteration status, although the HR for patients with *NOTCH1* mutations was close to 1

[a]Genetic alterations of *CDKN2A*, *PIK3CA*, *NFE2L2*, and *NOTCH1* were defined as mutant if non-synonymous somatic mutations with moderate to high impact were predicted by SnpEff[1] and WES-evaluable patients who were not identified as mutant were considered wildtype for the gene of interest. *CCND1* was defined as amplified if 6 or more copies were identified, and WES-evaluable patients with fewer than 6 copies were considered non-amplified. 1. Cingolani P, et al. *Fly (Austin)* 2012;6:80-92.

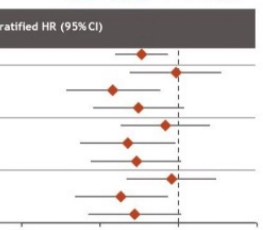
7

OS by stromal GES

Category	GES	Signature score tertile	Median OS, months		Unstratified HR (95% CI)
			NIVO + chemo	Chemo	
GES-evaluable (n = 383)	N/A	N/A	14.4	10.1	0.80 (0.64-1.00)
Stromal	15-gene fibroblast	High (n = 128)	14.0	11.9	0.84 (0.57-1.24)
		Medium (n = 127)	15.7	8.8	0.64 (0.43-0.95)
		Low (n = 128)	15.8	9.4	0.76 (0.51-1.12)
	9-gene TGF-β	High (n = 128)	15.5	12.6	0.77 (0.52-1.14)
		Medium (n = 127)	16.6	9.4	0.61 (0.41-0.91)
		Low (n = 128)	11.9	8.8	0.86 (0.58-1.27)
	51-gene Stroma/EMT/TGF-β	High (n = 128)	15.7	11.9	0.68 (0.46-1.00)
		Medium (n = 127)	15.8	8.8	0.69 (0.46-1.02)
		Low (n = 128)	11.9	9.0	0.88 (0.59-1.29)



Category	GES	Signature score tertile	Median OS, months		Unstratified HR (95% CI)
			NIVO + IPI	Chemo	
GES-evaluable (n = 380)	N/A	N/A	13.9	9.5	0.72 (0.57-0.91)
Stromal	15-gene fibroblast	High (n = 127)	11.3	11.9	0.98 (0.65-1.46)
		Medium (n = 126)	17.2	8.6	0.56 (0.37-0.85)
		Low (n = 127)	19.3	9.3	0.70 (0.47-1.05)
	9-gene TGF-β	High (n = 127)	11.7	12.6	0.89 (0.60-1.32)
		Medium (n = 126)	17.8	9.3	0.64 (0.42-0.97)
		Low (n = 127)	17.7	8.8	0.69 (0.46-1.02)
	51-gene Stroma/EMT/TGF-β	High (n = 127)	10.7	11.9	0.94 (0.63-1.39)
		Medium (n = 126)	17.8	8.8	0.60 (0.40-0.91)
		Low (n = 127)	19.3	9.0	0.68 (0.45-1.02)

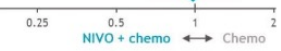


- No obvious or consistent association was observed between stromal GES scores and OS benefit with NIVO + chemo vs chemo
- Lower stromal GES scores were associated with improved OS benefit with NIVO + IPI vs chemo

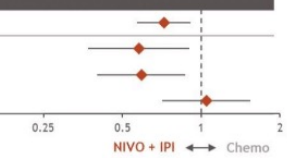
9

OS by inflammatory GES

Category	GES	Signature score tertile	Median OS, months		Unstratified HR (95% CI)
			NIVO + chemo	Chemo	
GES-evaluable (n = 383)	N/A	N/A	14.4	10.1	0.80 (0.64-1.00)
Inflammatory	4-gene inflammatory	High (n = 128)	22.0	12.6	0.63 (0.41-0.96)
		Medium (n = 127)	12.5	8.6	0.68 (0.46-0.98)
		Low (n = 128)	13.4	9.6	0.98 (0.66-1.43)



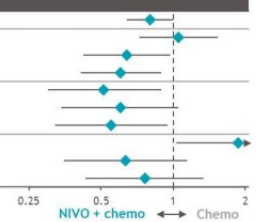
Category	GES	Signature score tertile	Median OS, months		Unstratified HR (95% CI)
			NIVO + IPI	Chemo	
GES-evaluable (n = 380)	N/A	N/A	13.9	9.5	0.72 (0.57-0.91)
Inflammatory	4-gene inflammatory	High (n = 127)	23.1	12.1	0.58 (0.37-0.90)
		Medium (n = 126)	16.2	8.6	0.59 (0.40-0.87)
		Low (n = 127)	9.7	9.6	1.05 (0.71-1.54)



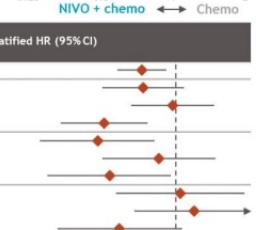
- Higher inflammatory GES scores were associated with improved OS benefit for NIVO + chemo and NIVO + IPI vs chemo

OS by β-catenin GES

Category	GES	Signature score tertile	Median OS, months		Unstratified HR (95% CI)
			NIVO + chemo	Chemo	
GES-evaluable (n = 383)	N/A	N/A	14.4	10.1	0.80 (0.64-1.00)
β-catenin (all randomized)	6-gene β-catenin	High (n = 128)	11.1	9.9	1.05 (0.72-1.54)
		Medium (n = 127)	19.1	10.2	0.64 (0.42-0.97)
		Low (n = 128)	15.8	9.1	0.60 (0.41-0.89)
β-catenin (TC PD-L1 ≥ 1%)	6-gene β-catenin	High (n = 68)	15.8	8.6	0.51 (0.30-0.89)
		Medium (n = 67)	18.0	7.8	0.60 (0.34-1.05)
		Low (n = 67)	18.5	9.4	0.55 (0.32-0.95)
β-catenin (TC PD-L1 < 1%)	6-gene β-catenin	High (n = 60)	11.1	11.9	1.87 (1.03-3.37)
		Medium (n = 60)	19.3	10.9	0.63 (0.35-1.14)
		Low (n = 60)	10.3	10.2	0.76 (0.43-1.34)



Category	GES	Signature score tertile	Median OS, months		Unstratified HR (95% CI)
			NIVO + IPI	Chemo	
GES-evaluable (n = 380)	N/A	N/A	13.9	9.5	0.72 (0.57-0.91)
β-catenin (all randomized)	6-gene β-catenin	High (n = 127)	13.5	9.9	0.73 (0.49-1.08)
		Medium (n = 126)	10.9	10.7	0.97 (0.65-1.44)
		Low (n = 127)	18.3	9.1	0.50 (0.33-0.76)
β-catenin (TC PD-L1 ≥ 1%)	6-gene β-catenin	High (n = 68)	17.4	8.6	0.47 (0.27-0.81)
		Medium (n = 67)	11.3	9.5	0.85 (0.49-1.46)
		Low (n = 68)	19.3	8.6	0.53 (0.29-0.95)
β-catenin (TC PD-L1 < 1%)	6-gene β-catenin	High (n = 58)	11.9	11.9	1.04 (0.56-1.93)
		Medium (n = 58)	9.7	12.4	1.19 (0.67-2.12)
		Low (n = 58)	17.6	11.0	0.58 (0.32-1.06)



- Lower β-catenin GES scores were generally associated with improved OS benefit with NIVO + chemo and NIVO + IPI vs chemo in all randomized patients and patients with tumor cell PD-L1 < 1%

10

Lei M et al. Gastrointestinal Cancers Symposium 2024;Abstract 252.

Courtesy of Yelena Y Janjigian, MD

Novel Immunotherapy Regimens

- Xu R-H et al. **Tislelizumab (TIS) plus chemotherapy (Chemo)** vs placebo (PBO) plus chemo as **first-line (1L)** treatment of advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJC): **Final analysis results of the RATIONALE-305 study**. ESMO 2023;Abstract LBA80.
- Hubner R et al. Randomized, global, **phase III** study of **tislelizumab (TIS) + chemotherapy (chemo)** vs placebo (PBO) + chemo **as first-line (1L) treatment** for advanced/metastatic esophageal squamous cell carcinoma (ESCC): **RATIONALE-306 update**. ESMO 2023;Abstract 1514P.

Frequently Asked Clinical Questions About GE Cancers

In choosing between IOs for GE cancers, in general the results from trials evaluating the more recently developed agents (ie, tislelizumab, sintilimab) are indirectly so similar to those of the commonly used agents that if there is a difference in cost or ability to access specific IOs, I have no problem using a novel agent. Agree or disagree?

Courtesy of Yelena Y Janjigian, MD

MADRID 2023 ESMO congress

Tislelizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy as First-line Treatment of Advanced Gastric or Gastroesophageal Junction Adenocarcinoma: Final Analysis Results of the RATIONALE-305 Study

Rui-Hua Xu[1], Do-Youn Oh[2], Ken Kato[3], Hendrik-Tobias Arkenau[4], Josep Tabernero[5], Marcia Cruz Correa[6], Anastasia V. Zimina[7], Yuxian Bai[8], Jianhua Shi[9], Keun-Wook Lee[10], Hidekazu Hirano[3], David R. Spigel[11], Lucjan Wyrwicz[12], Roberto Pazo Cid[13], Liyun Li[14], Yaling Xu[15], M. Brent McHenry[16], Silu Yang[14], Markus Moehler[17]

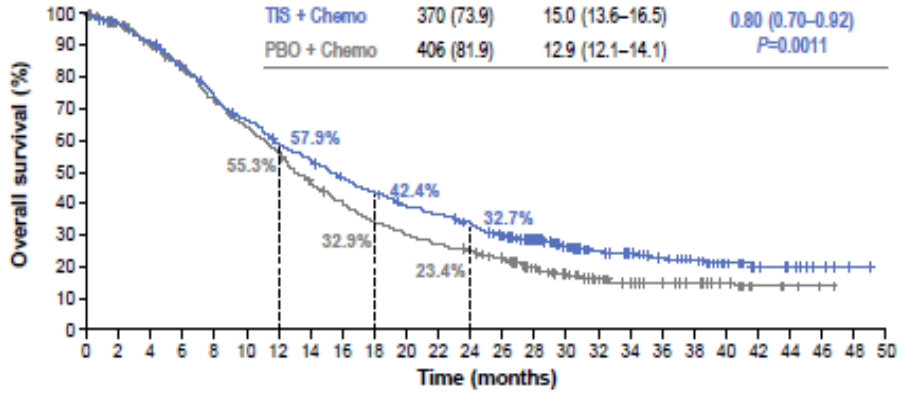
[1]*Sun Yat-sen University Cancer Center State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Department of Medical Oncology, Guangzhou, China;* [2]*Seoul National University Hospital Cancer Research Institute, Seoul National University College of Medicine, Department of Internal Medicine, Seoul, Republic of Korea;* [3]*National Cancer Center Hospital, Department of Gastrointestinal Medical Oncology, Tokyo, Japan;* [4]*Sarah Cannon Research Institute, Department of Drug Development, University College London, Cancer Institute, London, United Kingdom;* [5]*Vall d'Hebron Hospital Campus and Institute of Oncology (VHIO), Department of Medical Oncology, Barcelona, Spain;* [6]*University of Puerto Rico, School of Medicine, San Juan, Puerto Rico;* [7]*BIH Of Omsk Region, Clinical Oncology Dispensary, Omsk Oblast, Russia;* [8]*Harbin Medical University Cancer Hospital, Department of Gastrointestinal Oncology, Harbin, China;* [9]*Linyi Cancer Hospital, Department II of Medical Oncology, Linyi, China;* [10]*Seoul National University Bundang Hospital, Seoul National University College of Medicine, Department of Internal Medicine, Seongnam, Republic of Korea;* [11]*Tennessee Oncology, Department of Thoracic Medical Oncology, Nashville, TN, United States;* [12]*Maria Sklodowska-Curie National Cancer Center and Institute of Oncology, Department of Oncology and Radiotherapy, Warsaw, Poland;* [13]*Hospital Universitario Miguel Servet, Department of Medical Oncology, Zaragoza, Spain;* [14]*BeiGene (Beijing) Co., Ltd., Beijing, China;* [15]*BeiGene (Shanghai) Co., Ltd., Shanghai, China;* [16]*BeiGene USA, Inc., Cambridge, MA, United States;* [17]*Johannes Gutenberg-University Clinic, Department of Internal Medicine I, Mainz, Germany*

RATIONALE-305: Survival – Final Analysis

Overall Survival

ITT Population

	Events, n (%)	Median OS (95% CI), Months	Stratified* HR (95% CI) Log-Rank Test *P*-value
TIS + Chemo	370 (73.9)	15.0 (13.6–16.5)	0.80 (0.70–0.92) *P*=0.0011
PBO + Chemo	406 (81.9)	12.9 (12.1–14.1)	

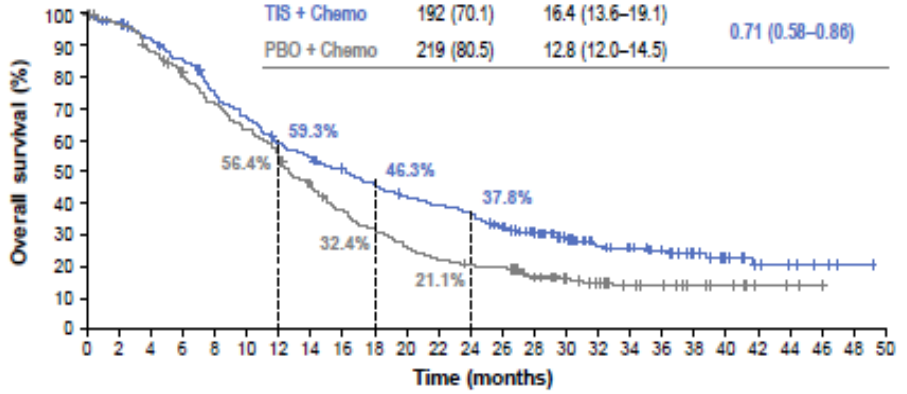


Number of patients at risk

TIS + Chemo	501	477	445	404	355	316	278	254	226	202	179	165	152	130	107	77	59	53	43	31	22	13	10	4	1	0
PBO + Chemo	496	472	431	398	344	304	264	218	186	155	136	119	109	96	73	52	39	29	25	20	15	6	3	2	0	0

PD-L1 Score ≥5% Population

	Events, n (%)	Median OS (95% CI), Months	Stratified* HR (95% CI)
TIS + Chemo	192 (70.1)	16.4 (13.6–19.1)	0.71 (0.58–0.86)
PBO + Chemo	219 (80.5)	12.8 (12.0–14.5)	



Number of patients at risk

TIS + Chemo	274	263	247	228	199	178	156	145	133	120	109	102	97	84	68	50	38	34	27	19	14	9	7	3	1	0
PBO + Chemo	272	261	236	215	190	168	148	120	99	83	69	59	53	51	39	29	23	16	14	9	7	3	2	1	0	0

- **TIS + Chemo as first-line treatment of advanced GC/GEJC demonstrated a statistically significant and clinically meaningful improvement in OS over PBO + Chemo in the ITT population at the final analysis**
- **Updated OS results in the PD-L1 score ≥5% population remained consistent with those observed at the interim analysis (HR 0.74 [95%CI 0.59–0.94] *P*=0.0056) after an additional 17 months of follow-up, showing a clinically meaningful improvement in OS**

Data cutoff: 28 February 2023.

*Log-rank and Cox regression models were stratified by regions (Asia vs Europe/North America), PD-L1 expression (ITT population analysis only), and presence of peritoneal metastasis. *P*-values are one-sided and based on the stratified log-rank test. *P*-value boundary at final analysis is 0.0226.

Medians were estimated by the Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. OS rates were estimated by the Kaplan-Meier method.

Abbreviations: Chemo, chemotherapy; CI, confidence interval; GC/GJEC, gastric or gastro-oesophageal junction adenocarcinoma; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; TIS, tislelizumab.

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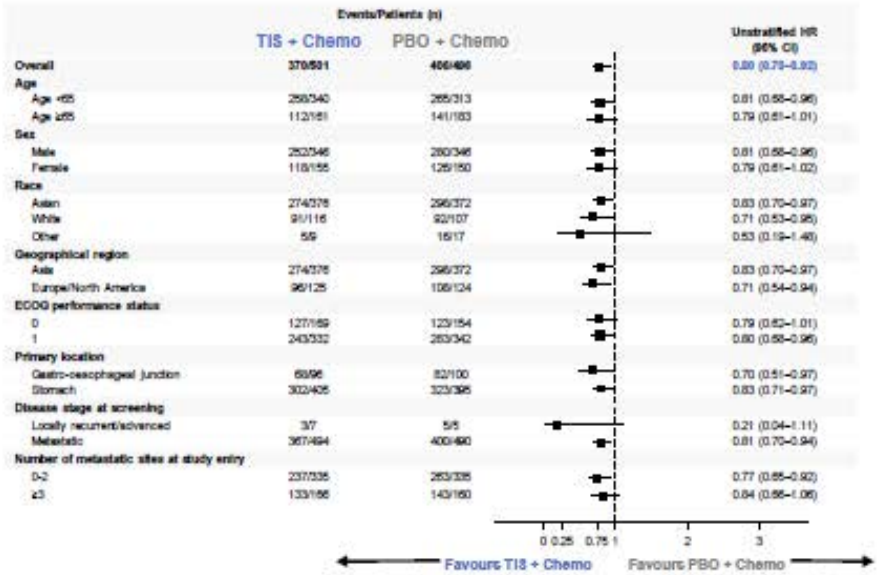
Rui-Hua Xu

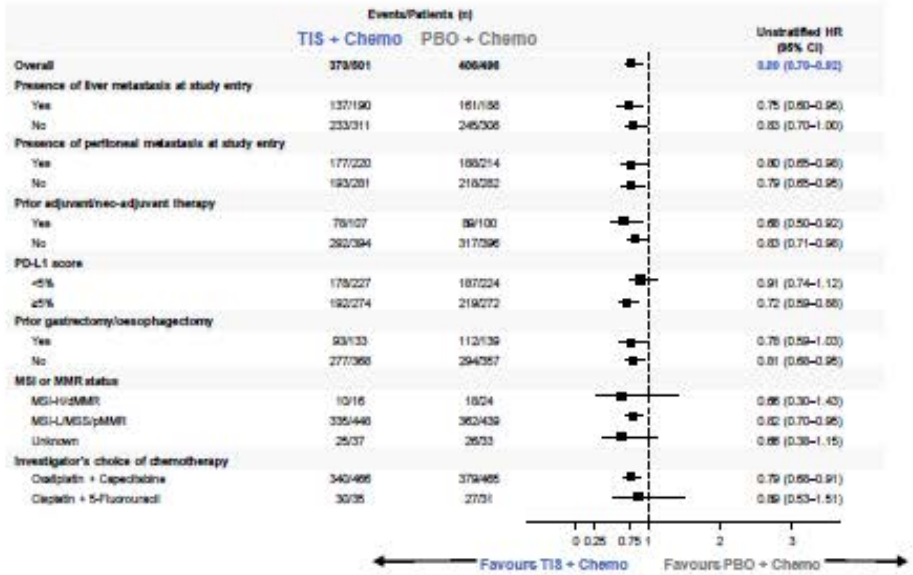
Xu R-H et al. ESMO 2023;Abstract LBA80.

Courtesy of Yelena Y Janjigian, MD

RATIONALE-305: Survival – Final Analysis

Overall Survival: Subgroup Analysis (ITT Population)





OS benefit of TIS + chemo was observed across multiple patient subgroups

Data cutoff: 28 February 2023.
Hazard ratios and their 95% CI were estimated from an unstratified Cox regression model including treatment as covariate. The race subcategory 'Other' includes Not Reported, Unknown and Other.
Abbreviations: Chemo, chemotherapy; dMMR, deficient mismatch repair; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MSI-L/H, microsatellite instability low/high; MSS, microsatellite stable; PBO, placebo; PD-L1, programmed death-ligand 1; pMMR, proficient mismatch repair; TIS, tislelizumab

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Rui-Hua Xu

Xu R-H et al. ESMO 2023;Abstract LBA80.

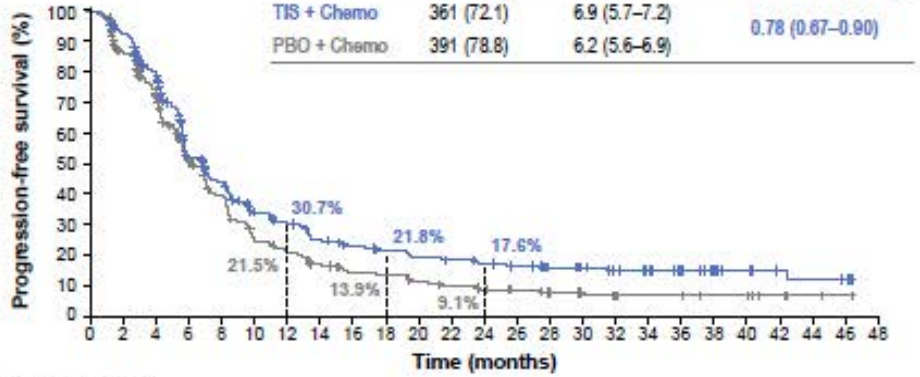
Courtesy of Yelena Y Janjigian, MD

RATIONALE-305: Survival – Final Analysis

Progression-Free Survival and Tumour Responses (ITT Population)

Progression-Free Survival

	Events, n (%)	Median PFS (95% CI), Months	Stratified[a] HR (95% CI)
TIS + Chemo	361 (72.1)	6.9 (5.7–7.2)	0.78 (0.67–0.90)
PBO + Chemo	391 (78.8)	6.2 (5.6–6.9)	

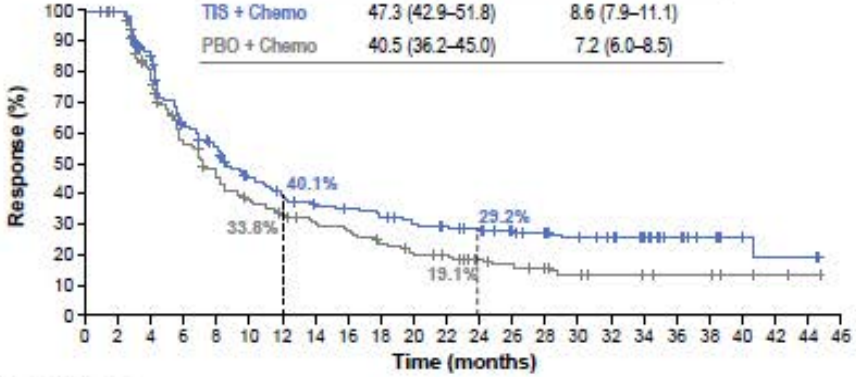


Number of patients at risk

TIS + Chemo	501	434	361	226	184	136	120	97	86	79	72	67	60	55	41	37	32	27	21	16	12	5	4	3	0
PBO + Chemo	496	399	327	211	161	100	85	67	55	51	42	37	31	26	21	16	13	11	10	8	7	4	2	1	0

Tumour Response

	ORR (95% CI)[b]	Median DoR[c] (95% CI), months
TIS + Chemo	47.3 (42.9–51.8)	8.6 (7.9–11.1)
PBO + Chemo	40.5 (36.2–45.0)	7.2 (6.0–8.5)



Number of patients at risk

TIS + Chemo	237	234	192	138	120	94	81	73	68	64	59	52	49	44	35	30	28	24	14	10	5	3	3	0
PBO + Chemo	201	193	146	101	84	66	57	50	46	39	32	29	23	19	17	12	9	9	7	7	4	2	1	0

TIS + Chemo was associated with improved PFS, higher ORR and a more durable response vs PBO + Chemo

Data cutoff: 28 February 2023. Confirmed tumour responses assessed by investigators as per RECIST version 1.1.
[a] Cox regression model stratified by regions (Asia vs Europe/North America), PD-L1 expression and presence of peritoneal metastasis.
[b] Exact Clopper-Pearson two-sided confidence interval.
[c] Among patients who achieved a confirmed CR or PR only
Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. PFS rates were estimated by Kaplan-Meier method.
Abbreviations: Chemo, chemotherapy; CI, confidence interval; DoR, duration of response; HR, hazard ratio; ITT, intent-to-treat; ORR, objective response rate; PBO, placebo; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TIS, tislelizumab.

MADRID 2023 ESMO congress

Rui-Hua Xu

Xu R-H et al. ESMO 2023;Abstract LBA80.

Courtesy of Yelena Y Janjigian, MD

Randomized, Global, Phase 3 Study of Tislelizumab + Chemotherapy Versus Placebo + Chemotherapy as First-line Treatment for Advanced/Metastatic Esophageal Squamous Cell Carcinoma: 2-year Follow-up From RATIONALE-306

Richard Hubner,[1*] Jianming Xu,[2] Ken Kato,[3] Eric Raymond,[4] Yongqian Shu,[5] Yueyin Pan,[6] Yi Jiang,[7] Jingdong Zhang,[8] Sook Ryun Park,[9] Takashi Kojima,[10] Chen-Yuan Lin,[11] Evgeny Gotovkin,[12] Lucjan Wyrwicz,[13] Ryu Ishihara,[14] Hongqian Wu,[15] Yanyan Peng,[16] Lei Wang,[17] Liyun Li,[17] Harry H. Yoon[18]

FPN: 1514P presented at ESMO, Madrid, Spain, October 20-24, 2023

[1]Department of Medical Oncology, The Christie NHS Foundation Trust/Division of Cancer Sciences, University of Manchester, Manchester, United Kingdom; [2]Fifth Medical Center, Chinese PLA General Hospital, Beijing, China; [3]National Cancer Center Hospital, Tokyo, Japan; [4]Centre Hospitalier Paris Saint-Joseph, Paris, France; [5]The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [6]Anhui Provincial Hospital, Hefei, China; [7]Cancer Hospital of Shantou University Medical College, Shantou, China; [8]Liaoning Cancer Hospital, Shenyang, China; [9]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of (South) Korea; [10]National Cancer Center Hospital East, Chiba, Japan; [11]China Medical University Hospital and China Medical University, Taichung, Taiwan; [12]Ivanovo Regional Oncology Dispensary, Ivanovo, Russia; [13]Maria Sklodowska-Curie National Cancer Research Institute, Warsaw, Poland; [14]Osaka International Cancer Institute, Osaka, Japan; [15]Global Statistics and Data Science, BeiGene USA, Inc., Ridgefield Park, NJ, United States; [16]Clinical Biomarker, BeiGene (Shanghai) Co., Ltd., Shanghai, China; [17]Clinical Development, BeiGene (Beijing) Co., Ltd., Beijing, China; [18]Mayo Clinic, Rochester, MN, United States. *Presenting author.

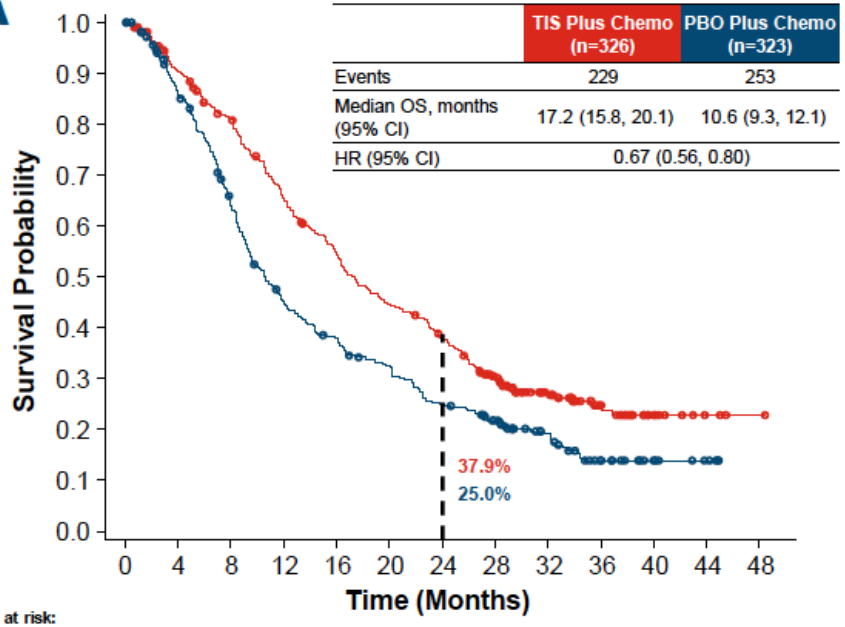
Conclusions

Tislelizumab (TIS) plus chemotherapy (chemo) showed clinically meaningful improvements in overall survival (OS) and progression-free survival (PFS), and durable antitumor response, compared with placebo (PBO) plus chemo in the first-line (1L) treatment of advanced or metastatic esophageal squamous cell carcinoma (ESCC) after a minimum of 2 years of follow-up in RATIONALE-306.

Consistent with the results of the interim analysis (IA), the results of the 2-year follow-up provide additional evidence of sustained efficacy and a manageable safety profile, supporting the treatment benefit of TIS plus chemo compared with PBO plus chemo in the 1L treatment of ESCC.

Kaplan-Meier Curves of OS for (A) All Patients; (B) Patients With PD-L1 TAP Score ≥10%; and (C) <10 (ITT Analysis Set)

A

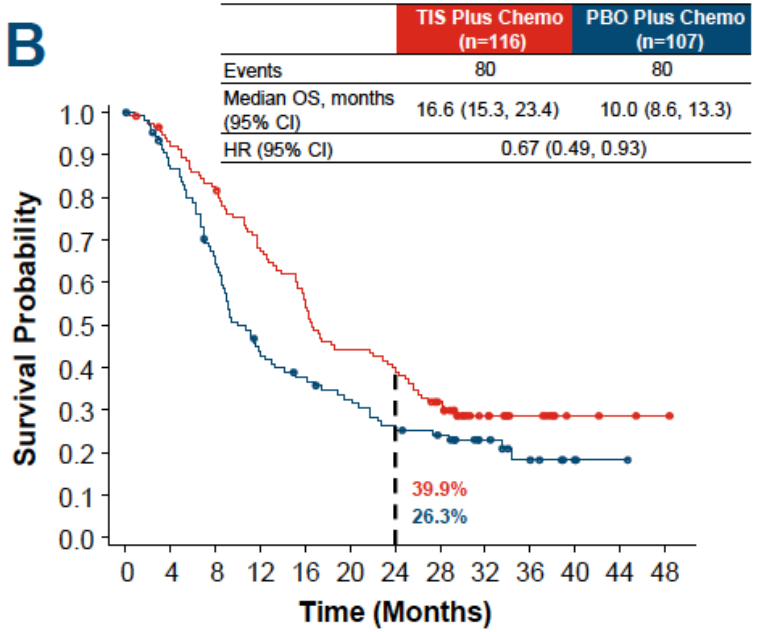


	TIS Plus Chemo (n=326)	PBO Plus Chemo (n=323)
Events	229	253
Median OS, months (95% CI)	17.2 (15.8, 20.1)	10.6 (9.3, 12.1)
HR (95% CI)	0.67 (0.56, 0.80)	

No. at risk:

TIS Plus Chemo	326	287	253	201	168	137	114	82	50	27	10	3	1
PBO Plus Chemo	323	268	195	135	113	95	73	56	36	18	8	4	0

B

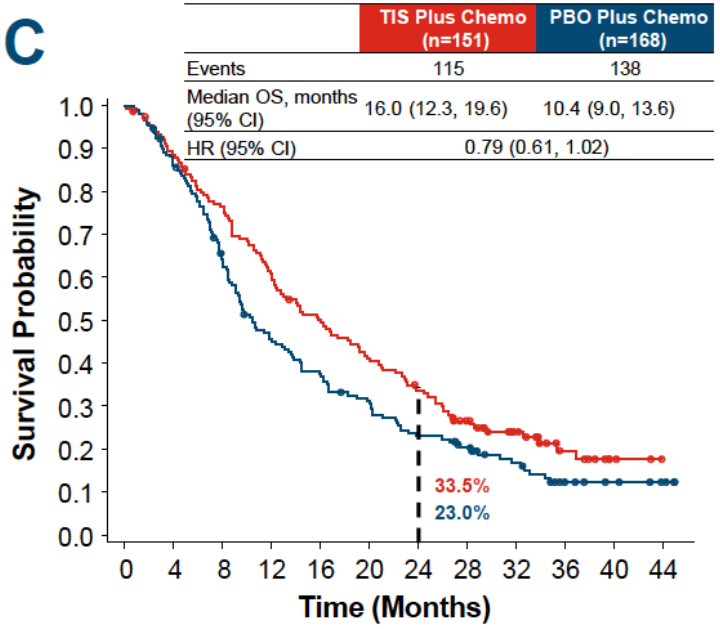


	TIS Plus Chemo (n=116)	PBO Plus Chemo (n=107)
Events	80	80
Median OS, months (95% CI)	16.6 (15.3, 23.4)	10.0 (8.6, 13.3)
HR (95% CI)	0.67 (0.49, 0.93)	

No. at risk:

TIS Plus Chemo	116	105	94	76	63	50	45	32	16	9	3	2	1
PBO Plus Chemo	107	90	66	43	37	31	25	21	12	7	2	1	0

C



	TIS Plus Chemo (n=151)	PBO Plus Chemo (n=168)
Events	115	138
Median OS, months (95% CI)	16.0 (12.3, 19.6)	10.4 (9.0, 13.6)
HR (95% CI)	0.79 (0.61, 1.02)	

No. at risk:

TIS Plus Chemo	151	132	113	88	73	60	48	33	21	10	3	0
PBO Plus Chemo	168	143	103	73	60	49	36	28	19	9	6	3

Hubner R et al. ESMO 2023;Abstract 1514P.

Courtesy of Yelena Y Janjigian, MD

Randomized, Global, Phase 3 Study of Tislelizumab + Chemotherapy Versus Placebo + Chemotherapy as First-line Treatment for Advanced/Metastatic Esophageal Squamous Cell Carcinoma: 2-year Follow-up From RATIONALE-306

Richard Hubner,[1*] Jianming Xu,[2] Ken Kato,[3] Eric Raymond,[4] Yongqian Shu,[5] Yueyin Pan,[6] Yi Jiang,[7] Jingdong Zhang,[8] Sook Ryun Park,[9] Takashi Kojima,[10] Chen-Yuan Lin,[11] Evgeny Gotovkin,[12] Lucjan Wyrwicz,[13] Ryu Ishihara,[14] Hongqian Wu,[15] Yanyan Peng,[16] Lei Wang,[17] Liyun Li,[17] Harry H. Yoon[18]

[1]Department of Medical Oncology, The Christie NHS Foundation Trust/Division of Cancer Sciences, University of Manchester, Manchester, United Kingdom; [2]Fifth Medical Center, Chinese PLA General Hospital, Beijing, China; [3]National Cancer Center Hospital, Tokyo, Japan; [4]Centre Hospitalier Paris Saint-Joseph, Paris, France; [5]The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [6]Anhui Provincial Hospital, Hefei, China; [7]Cancer Hospital of Shantou University Medical College, Shantou, China; [8]Liaoning Cancer Hospital, Shenyang, China; [9]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of (South) Korea; [10]National Cancer Center Hospital East, Chiba, Japan; [11]China Medical University Hospital and China Medical University, Taichung, Taiwan; [12]Ivanovo Regional Oncology Dispensary, Ivanovo, Russia; [13]Maria Sklodowska-Curie National Cancer Research Institute, Warsaw, Poland; [14]Osaka International Cancer Institute, Osaka, Japan; [15]Global Statistics and Data Science, BeiGene USA, Inc., Ridgefield Park, NJ, United States; [16]Clinical Biomarker, BeiGene (Shanghai) Co., Ltd., Shanghai, China; [17]Clinical Development, BeiGene (Beijing) Co., Ltd., Beijing, China; [18]Mayo Clinic, Rochester, MN, United States. *Presenting author.

FPN: 1514P presented at ESMO, Madrid, Spain, October 20-24, 2023

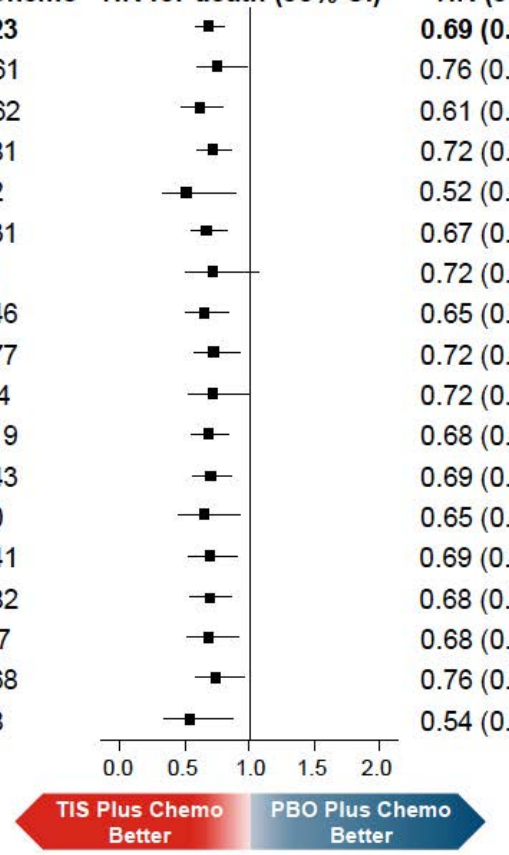
Conclusions

Tislelizumab (TIS) plus chemotherapy (chemo) showed clinically meaningful improvements in overall survival (OS) and progression-free survival (PFS), and durable antitumor response, compared with placebo (PBO) plus chemo in the first-line (1L) treatment of advanced or metastatic esophageal squamous cell carcinoma (ESCC) after a minimum of 2 years of follow-up in RATIONALE-306.

Consistent with the results of the interim analysis (IA), the results of the 2-year follow-up provide additional evidence of sustained efficacy and a manageable safety profile, supporting the treatment benefit of TIS plus chemo compared with PBO plus chemo in the 1L treatment of ESCC.

Forest Plot of OS by Subgroup (ITT Analysis Set)

Subgroup		Event/Total: TIS Plus Chemo	Event/Total: PBO Plus Chemo	HR for death (95% CI)	HR (95% CI)
Overall		**229/326**	**253/323**		**0.69 (0.57, 0.82)**
Age	<65 years	129/176	121/161		0.76 (0.59, 0.97)
	≥65 years	100/150	132/162		0.61 (0.47, 0.80)
Sex	Male	205/282	224/281		0.72 (0.59, 0.87)
	Female	24/44	29/42		0.52 (0.30, 0.90)
Smoking status	Former/Current smoker	179/247	188/231		0.67 (0.55, 0.83)
	Non-smoker	43/68	55/81		0.72 (0.49, 1.08)
ICC options per CRF	Platinum with fluoropyrimidine	101/147	117/146		0.65 (0.49, 0.84)
	Platinum with paclitaxel	128/179	136/177		0.72 (0.57, 0.92)
ECOG PS	0	73/109	77/104		0.72 (0.52, 0.99)
	1	156/217	176/219		0.68 (0.55, 0.84)
Region	Asia	169/243	188/243		0.69 (0.56, 0.86)
	Rest of World	60/83	65/80		0.65 (0.46, 0.92)
Prior Definitive Therapy per CRF	Yes	98/143	108/141		0.69 (0.53, 0.91)
	No	131/183	145/182		0.68 (0.54, 0.86)
Baseline PD-L1 status	PD-L1 score ≥10%	80/116	80/107		0.68 (0.50, 0.93)
	PD-L1 score <10%	115/151	138/168		0.76 (0.59, 0.97)
	Unknown	34/59	35/48		0.54 (0.34, 0.87)



Hubner R et al. ESMO 2023;Abstract 1514P.

Courtesy of Yelena Y Janjigian, MD

RATIONALE-306: Progression-Free Survival and Select Adverse Events

Table 1. Efficacy Endpoints (ITT Analysis Set)

	TIS Plus Chemo (n=326)	PBO Plus Chemo (n=323)
Median PFS (95% CI), months	7.3 (6.9, 8.3)	5.6 (4.9, 6.0)
HR (95% CI)	0.61 (0.51, 0.73)	
24-month PFS rate, % (95% CI)	18.1 (13.6, 23.1)	7.2 (4.4, 11.0)
ORR, % (95% CI)	63.5 (58.0, 68.7)	42.4 (37.0, 48.0)
Median DoR (95% CI), months	7.1 (6.1, 8.1)	5.7 (4.4, 7.1)
24-month DoR rate, % (95% CI)	19.6 (13.9, 25.9)	10.1 (5.0, 17.1)

Data cutoff: December 31, 2022. Listed endpoints assessed by investigator. **Abbreviations**: Chemo, chemotherapy; CI, confidence interval; DoR, duration of response; HR, hazard ratio; ITT, intent-to-treat; ORR, objective response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; TIS, tislelizumab.

Table 2. Summary of TEAEs and TRAEs (Safety Analysis Set)

	TIS Plus Chemo (n=324)	PBO Plus Chemo (n=321)
Patients with at least one TRAE, n (%)	313 (96.6)	309 (96.3)
Grade ≥3	216 (66.7)	207 (64.5)
Serious	95 (29.3)	63 (19.6)
Leading to death	6 (1.9)	4 (1.2)
Patients with at least one TEAE leading to any treatment discontinuation, n (%)	103 (31.8)	71 (22.1)
Patients with at least one TEAE leading to any dose modification, n (%)	247 (76.2)	229 (71.3)

Data cutoff: December 31, 2022. TRAEs include TEAEs that were considered by the investigator to be related to study drug or TEAEs with a missing causality. **Abbreviations:** Chemo, chemotherapy; PBO, placebo; TEAE, treatment-emergent adverse event; TIS, tislelizumab; TRAE, treatment-related adverse event.

Hubner R et al. ESMO 2023;Abstract 1514P.

Courtesy of Yelena Y Janjigian, MD

A Phase 2 Study (DisTinGuish) of DKN-01 in Combination with Tislelizumab + Chemotherapy as First-Line (1L) Therapy in Patients with Advanced Gastric or GEJ Adenocarcinoma (GEA)

Klempner SL et al.
ASCO 2023;Abstract 4027.

Agenda

INTRODUCTION: First-Line Therapy for Metastatic Gastroesophageal (GE) Cancers — the Bottom Line

MODULE 1: Updates on Immunotherapy in GE Cancers

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- **First-Line Treatment**
- **Trastuzumab Deruxtecan**
- **Zanidatamab**

MODULE 3: Targeting Claudin 18.2 — Zolbetuximab

MODULE 4: Faculty Journal Club

Targeting HER2 – First-Line Treatment

- Janjigian YY et al. **Pembrolizumab plus trastuzumab and chemotherapy** for **HER2-positive gastric** or gastro-oesophageal junction adenocarcinoma: **Interim analyses from the phase 3 KEYNOTE-811** randomised placebo-controlled trial. *Lancet* 2023;402(10418):2197-208.

Frequently Asked Clinical Questions About GE Cancers

Which specific criteria do you use to define “HER2-positive”?

What is your usual first-line treatment for metastatic HER2-positive GE cancer? How does PD-L1 level factor in?

What do you see as the future of neoadjuvant and adjuvant anti-HER2 therapy in GE cancers?

KEYNOTE-811
Study Design

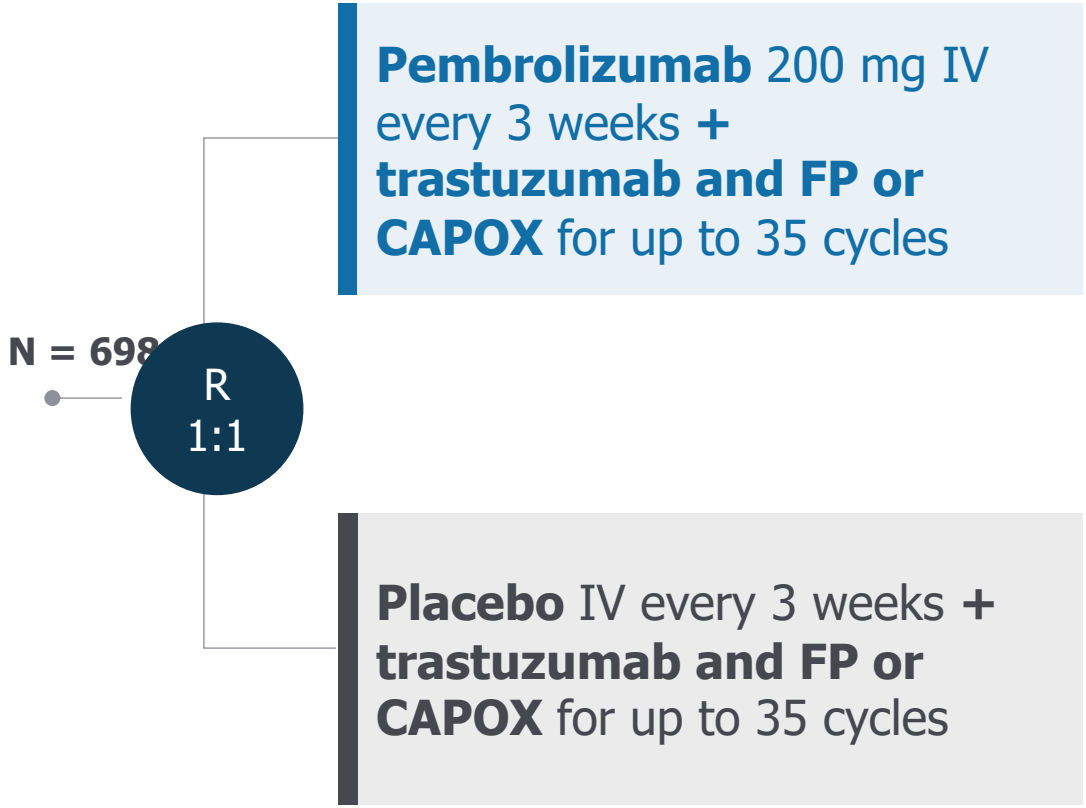
Phase 3, randomized, double-blind study

Key eligibility criteria:

- Advanced G/GEJ adenocarcinoma
- No prior therapy in advanced setting
- HER2-positive
- ECOG PS 0 or 1

Stratification:

- Geographic region
- PD-L1 CPS
- Chemotherapy choice



Primary endpoints:
- OS
- PFS (RECIST v1.1 per BICR)

Secondary endpoints:
- ORR (RECIST v1.1 per BICR)
- DOR (RECIST v1.1 per BICR)
- Safety

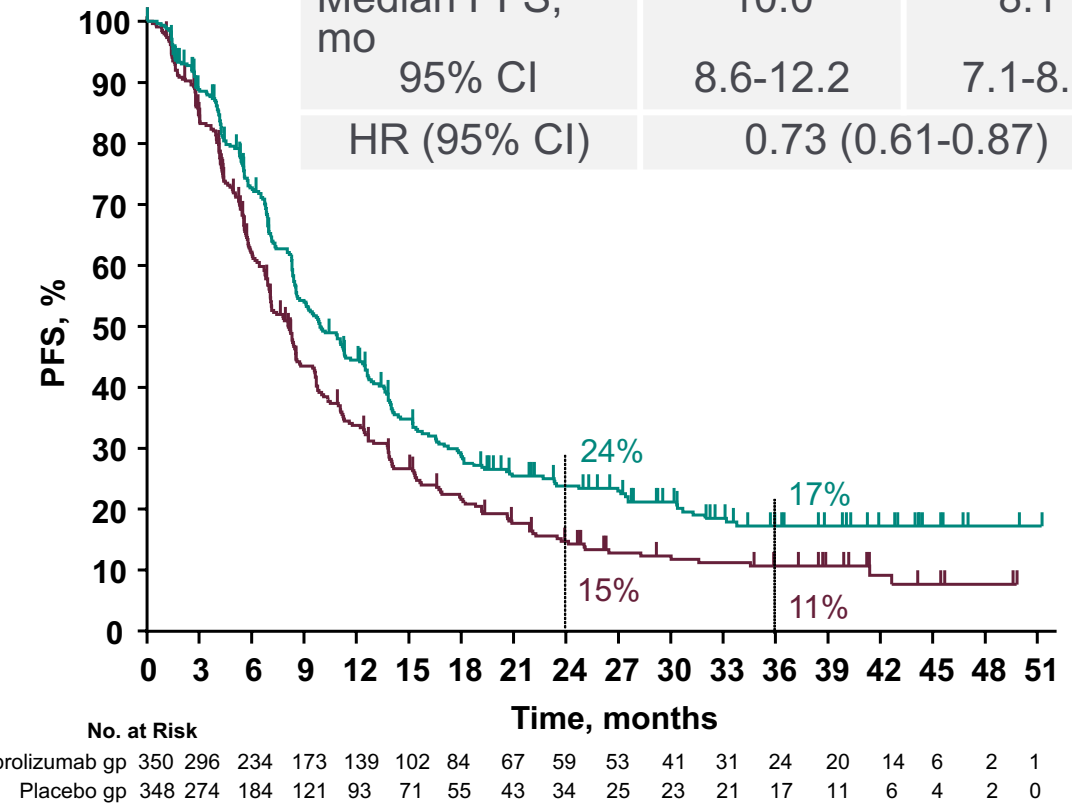
BICR, blinded independent central review; CAPOX, capecitabine plus oxaliplatin; DOR, duration of response.
Janjigian YY, et al. Nature. 2021;600:727-730. Janjigian YY, et al. Lancet, 2023; 402:2197-2208.

Courtesy of Zev Wainberg, MD, MSc

KEYNOTE-811
PFS at IA3: 38.5 Months of Follow Up

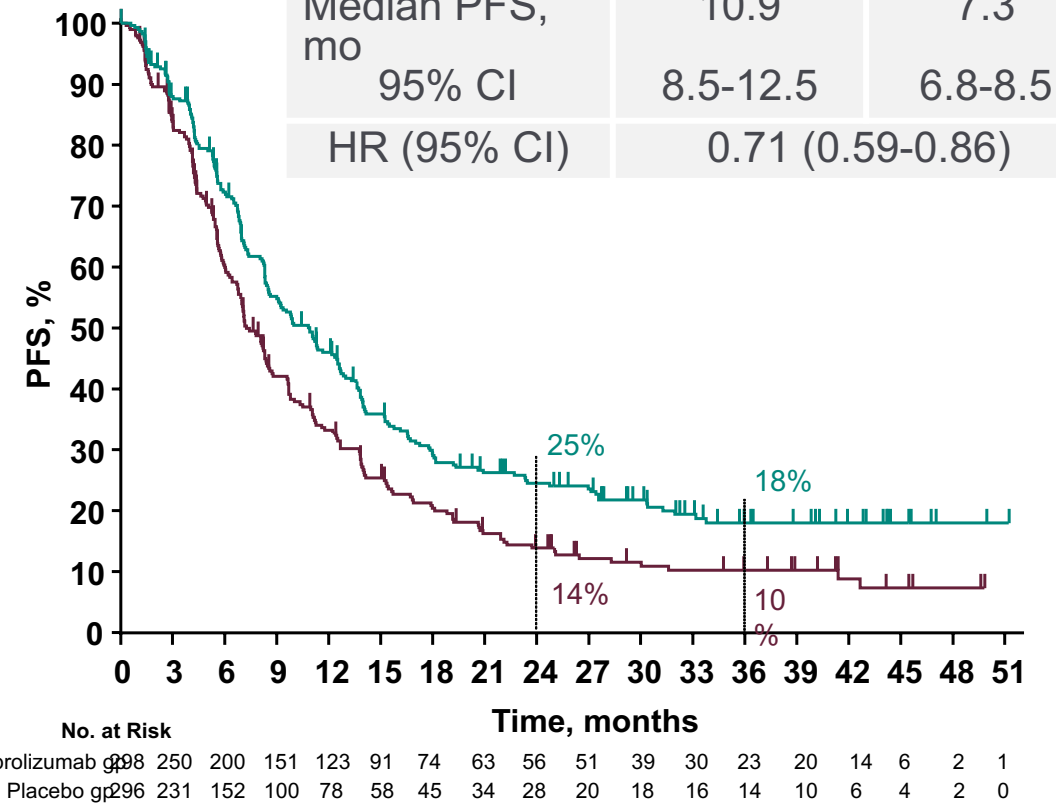
All patients

	Pembro	Placebo
Median PFS, mo	10.0	8.1
95% CI	8.6-12.2	7.1-8.6
HR (95% CI)	0.73 (0.61-0.87)	



PD-L1 CPS ≥1

	Pembro	Placebo
Median PFS, mo	10.9	7.3
95% CI	8.5-12.5	6.8-8.5
HR (95% CI)	0.71 (0.59-0.86)	



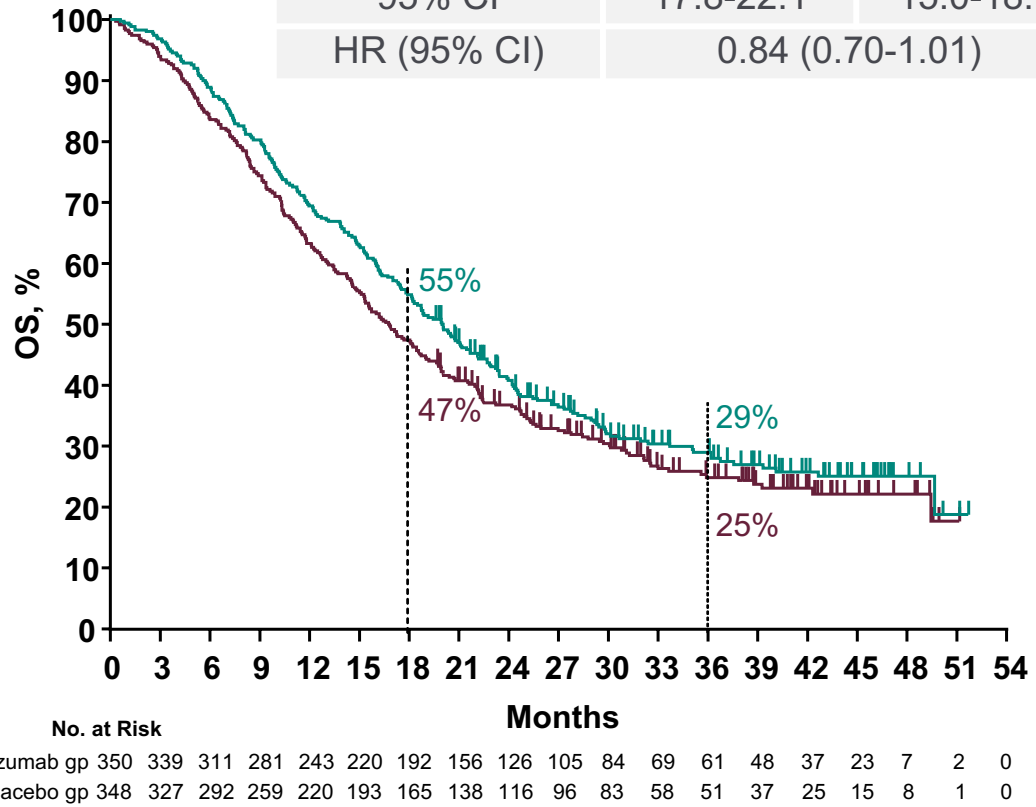
Janjigian YY, et al. Lancet, 2023; 402:2197-2208.

Courtesy of Zev Wainberg, MD, MSc

KEYNOTE-811
OS at IA3

All patients

	Pembro	Placebo
Median OS, mo 95% CI	20.0 17.8-22.1	16.8 15.0-18.7
HR (95% CI)	0.84 (0.70-1.01)	

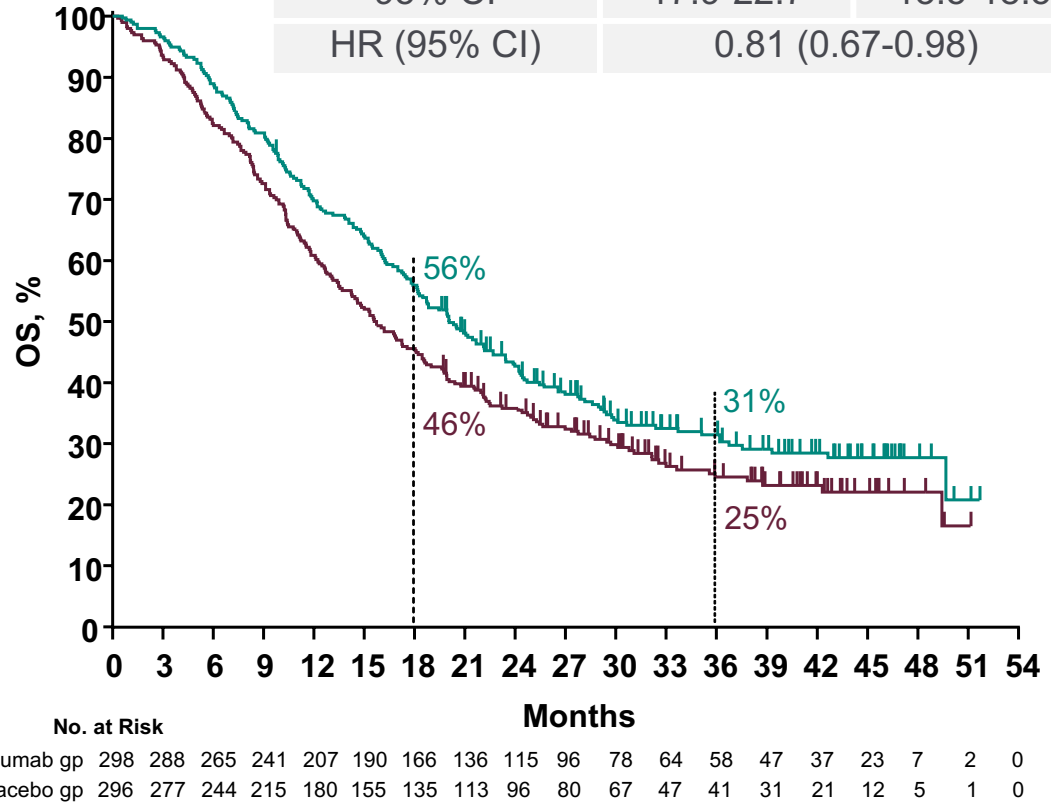


No. at Risk

Pembrolizumab gp	350	339	311	281	243	220	192	156	126	105	84	69	61	48	37	23	7	2	0
Placebo gp	348	327	292	259	220	193	165	138	116	96	83	58	51	37	25	15	8	1	0

PD-L1 CPS ≥1

	Pembro	Placebo
Median OS, mo 95% CI	20.0 17.9-22.7	15.7 13.5-18.5
HR (95% CI)	0.81 (0.67-0.98)	



No. at Risk

Pembrolizumab gp	298	288	265	241	207	190	166	136	115	96	78	64	58	47	37	23	7	2	0
Placebo gp	296	277	244	215	180	155	135	113	96	80	67	47	41	31	21	12	5	1	0

Janjigian YY, et al. Lancet, 2023; 402:2197-2208.

Courtesy of Zev Wainberg, MD, MSc

asco special articles

Immunotherapy and Targeted Therapy for Advanced Gastroesophageal Cancer: ASCO Guideline

Manish A. Shah MD[1]; Erin B. Kennedy MHSc[2]; Ashley E. Alarcon-Rozas MD MBA[3]; Thierry Alcindor MD[4]; Angela N. Bartley MD[5]; Aubrey Belk Malowany BS[6]; Nishin A. Bhadkamkar MD[7]; Dana C. Deighton BA[8]; Yelena Janjigian MD[9]; Asha Karippot MD[10]; Uqba Khan MD[1]; Daniel A. King MD PhD[11]; Kelsey Klute MD[12]; Jill Lacy MD[13]; James J. Lee MD PhD[14]; Rutika Mehta MD MPH[15]; Sarbajit Mukherjee MD MS[16]; Arun Nagarajan MD[17]; Haeseong Park MD MPH[18]; Anwaar Saeed MD[19]; Thomas J. Semrad MD MAS[20]; Kohei Shitara MD[21]; Elizabeth Smyth MD[22]; Nataliya V. Uboha MD PhD[23]; Melani Vincelli[24]; Zev Wainberg MD[25]; and Lakshmi Rajdev MD[26]

J Clin Oncol 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Positive Gastric or GEJ Adenocarcinoma: First-Line Immunotherapy and Targeted Therapy

"For patients with HER2-positive gastric or GEJ previously untreated, unresectable or metastatic AC, trastuzumab plus pembrolizumab is recommended, in combination with CT."

Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Positive Gastric or GEJ Adenocarcinoma: Second-Line Therapy

"For HER2-positive patients with gastric or GEJ AC who have progressed after first-line therapy, trastuzumab deruxtecan is recommended."

Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

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MODULE 4: Faculty Journal Club

Targeting HER2 – Trastuzumab Deruxtecan

- Van Cutsem E et al. **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. *Lancet Oncol* 2023;24(7):744-56.
- Yamaguchi K et al. **Trastuzumab deruxtecan** in anti-human epidermal growth factor receptor 2 treatment-naive patients with **human epidermal growth factor receptor 2-low** gastric or gastroesophageal junction adenocarcinoma: Exploratory cohort results in a Phase II trial. *J Clin Oncol* 2023;41(4):816-25.

Frequently Asked Clinical Questions About GE Cancers

What is your usual second-line treatment for metastatic HER2-positive GE cancer?

How do you manage the GI toxicities associated with trastuzumab deruxtecan?

In general, what is your approach to screening for ILD (interstitial lung disease) in patients who are receiving trastuzumab deruxtecan?

DESTINY-Gastric02 Study Design

An open-label, multicenter phase 2 study in Western patients with HER2+ gastric or GEJ cancer (NCT04014075)

Key eligibility criteria

- Pathologically documented, unresectable or metastatic gastric or GEJ cancer
- Centrally confirmed HER2 positive disease (defined as IHC 3+ or IHC 2+/ISH+) on biopsy after progression on first-line trastuzumab-containing regimen
- ECOG PS 0 or 1

T-DXd
6.4 mg/kg Q3W
N = 79[a]

Primary endpoint

- Confirmed ORR by ICR

Secondary endpoints[b]

- PFS by ICR
- OS
- DOR by ICR
- Safety and tolerability

- DESTINY-Gastric02 is the first study focused only on second-line T-DXd monotherapy in Western patients with HER2+ gastric/GEJ cancer who have progressed on a trastuzumab-containing regimen
  - It is the follow-on study to DESTINY-Gastric01, which evaluated T-DXd third-line or later in Asian patients[1]
- Patients were enrolled in Europe (Belgium, Great Britain, Italy, Spain) and the United States (data cutoff: April 9, 2021)

[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, anti-drug antibodies, and patient-reported outcomes.

1. Shitara K et al. *N Engl J Med*. 2020;382:2419-30.

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.

Courtesy of Zev Wainberg, MD, MSc

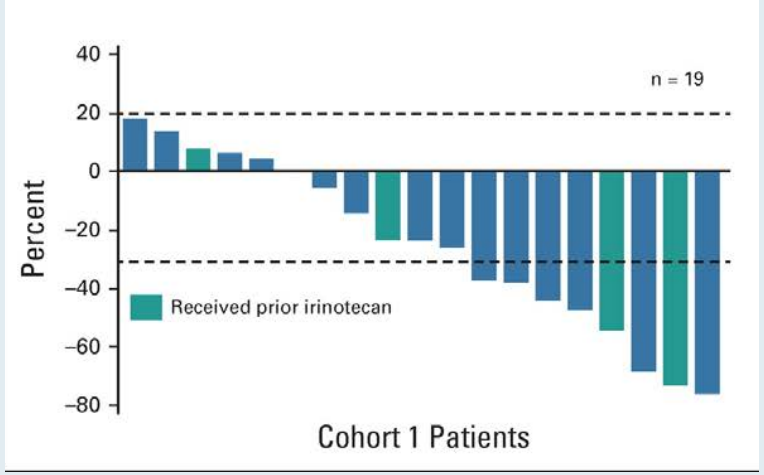
Efficacy Endpoints

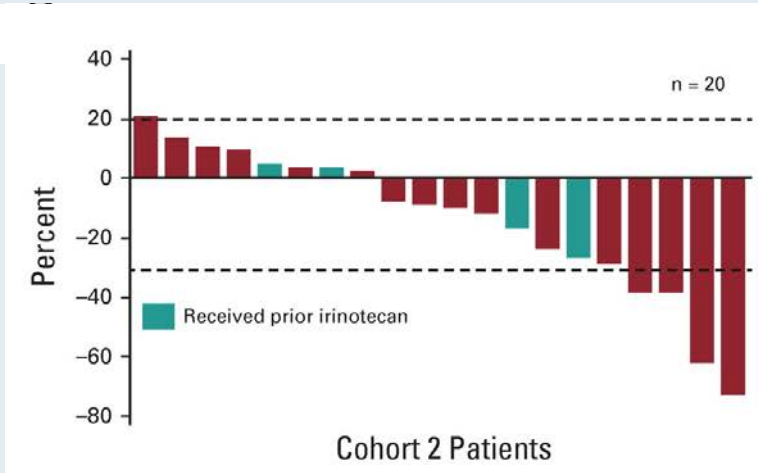
	Patients (N = 79)
Confirmed ORR[a], n (%)	**33 (42)** (95% CI, 27.3-49.6)
Confirmed best overall response, n (%)	
CR	**4 (5)**
PR	**29 (37)**
SD	**31 (39)**
PD	**13 (16)**
Not evaluable	**2 (3)**
Median DOR,[b] months	8.1 (95% CI, 5.9-NE)
Median PFS,[d] months	5.6 (95% CI, 4.2-7.3)
Median OS, months	12.1 (95% CI, 9.4-15.4)
Median follow up, months	10.2 (range, 5.6-12.9)

Van Cutsem et al Lancet Oncology 2023

Courtesy of Zev Wainberg, MD, MSc

Phase II DESTINY-Gastric01: Responses

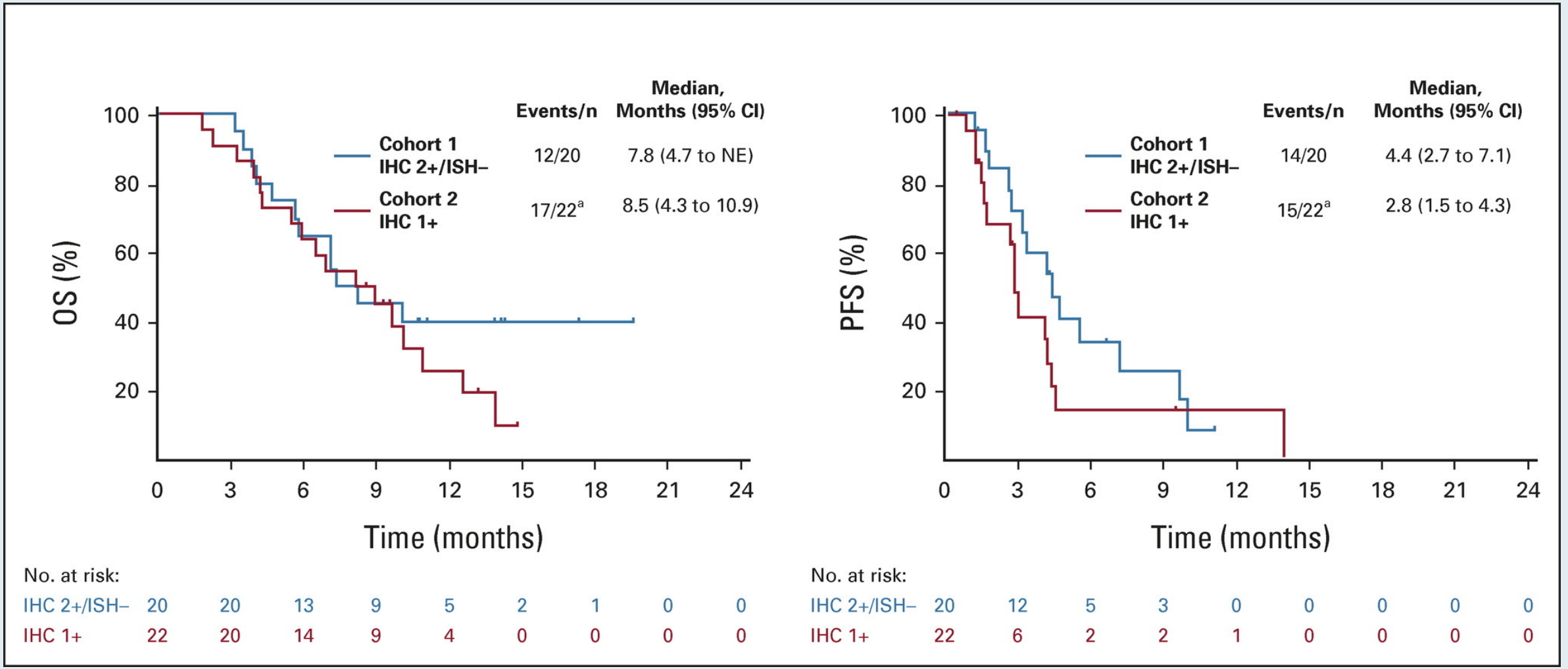




End Point	Cohort 1 (HER2 IHC 2+/ISH−; n = 19)	Cohort 2 (HER2 IHC 1+; n = 21)
Confirmed[a] ORR by ICR, % (95% CI)[b]	26.3 (9.1 to 51.2) n = 5	9.5 (1.2 to 30.4) n = 2
Confirmed[a] BOR by ICR, No. (%)[b]		
CR	0	0
PR	5 (26.3)	2 (9.5)
SD	12 (63.2)	13 (61.9)
PD	2 (10.5)	6 (28.6)
DCR based on ICR, % (95% CI)[b,c]	89.5 (66.9 to 98.7) n = 17	71.4 (47.8 to 88.7) n = 15
Individual DoR per patient, months[d]	9.7	8.1
	6.8	12.5
	8.3	
	2.4	
	4.1	

Yamaguchi K et al. *J Clin Oncol* 2023;41(4):816-25.

Phase II DESTINY-Gastric01: Survival



Yamaguchi K et al. *J Clin Oncol* 2023;41(4):816-25.

RTP RESEARCH TO PRACTICE

Phase II Dose Optimization Results from MOUNTAINEER-02: A Study of Tucatinib, Trastuzumab, Ramucirumab, and Paclitaxel for HER2+ Gastroesophageal Cancer (GEC)

Tehfe M et al.

ESMO 2023;Abstract 1523P.

Agenda

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Targeting HER2 – Zanidatamab

- Lee K et al. **Zanidatamab (zani) plus chemotherapy (chemo) and tislelizumab (tis) as first-line (1l)** therapy for patients (pts) with advanced **HER2-positive** (+) gastric/gastroesophageal junction adenocarcinoma (GC/GEJC): Updated results from a phase Ib/II study. ESMO 2023;Abstract 1518P.
- Chakrabarti S et al. **Anti-HER2 therapy following ctDNA-identified ERBB2 amplification** for patients with advanced gastric cancer: Exploration of real-world outcomes and resistance mechanisms. World Congress on Gastrointestinal Cancer 2023;Abstract PD-9.

Frequently Asked Clinical Questions About GE Cancers

What is known about the efficacy of zanidatamab alone and in combination with chemotherapy?

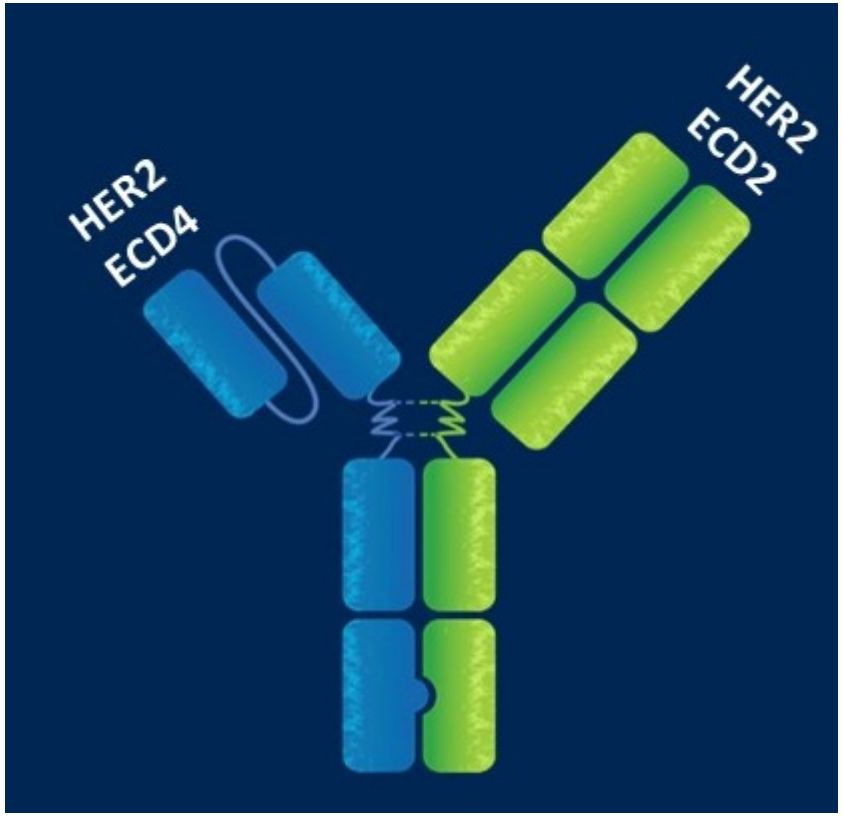
What are the primary toxicities associated with zanidatamab?

How will you likely integrate zanidatamab into clinical practice?

What do you anticipate the results of the HERIZON-GEA-01 study will show?

Zanidatamab: Bispecific HER2-Targeted Antibody

- A biparatopic antibody that binds 2 distinct sites on HER2 at the same time: ECD4 and ECD2 (trastuzumab-targeted domain and pertuzumab-targeted domain, respectively)
- Exclusive trans-binding leads to enhanced receptor clustering and internalization by zanidatamab

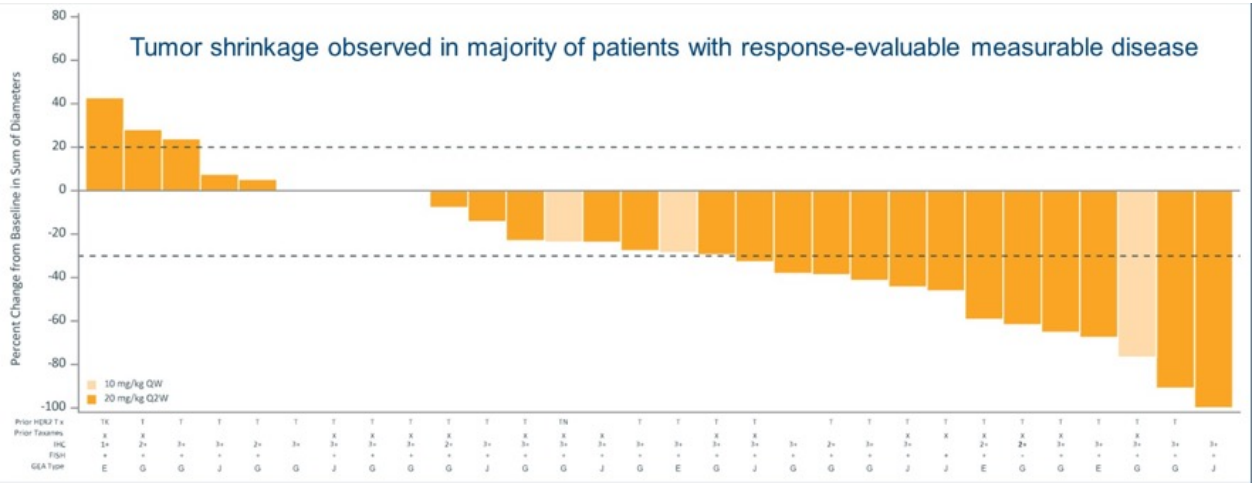


Meric-Bernstam F, et al. J Clin Oncol. 2021;39(suppl 3): Abs 164.

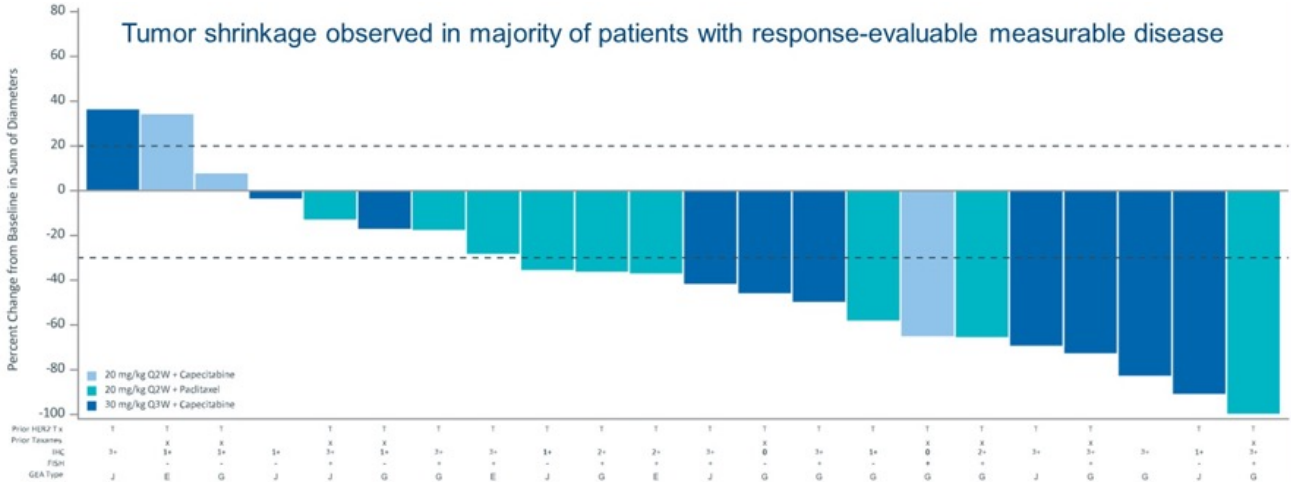
Courtesy of Zev Wainberg, MD, MSc

Zanidatamab: Phase 1, Dose Escalation and Expansion Study: Antitumor Activity

Zani monotherapy



Zani + chemotherapy



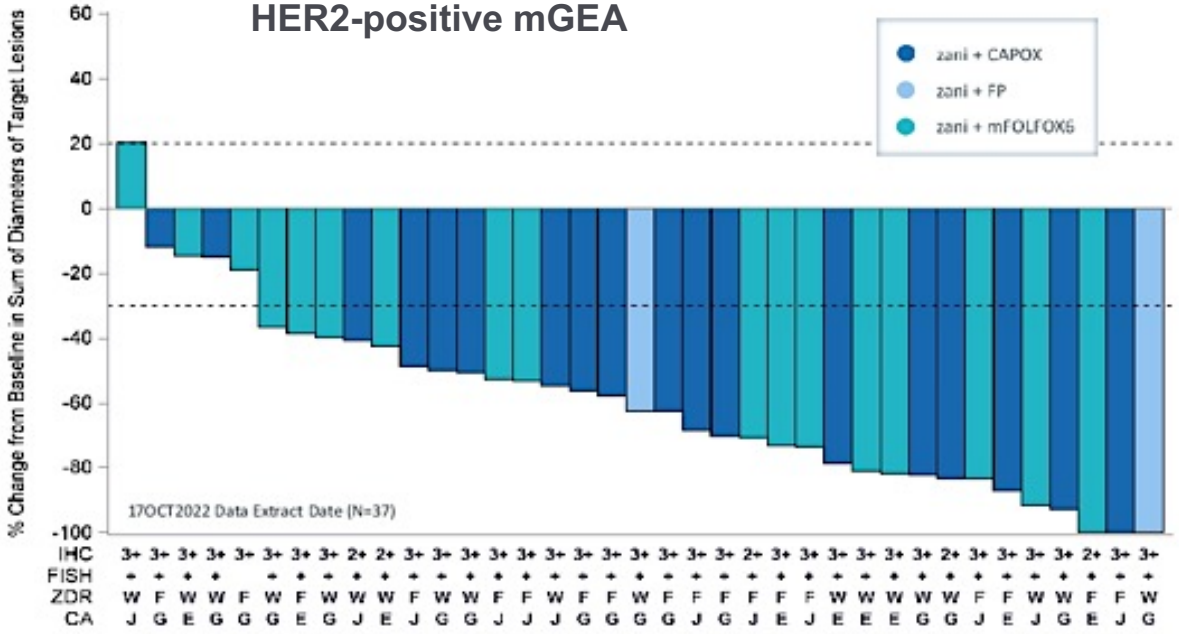
Meric-Bernstam F, et al. J Clin Oncol. 2021;39(suppl 3): Abs 164.

Courtesy of Zev Wainberg, MD, MSc

Zanidatamab + Chemotherapy as First Line Treatment for HER2-Expressing mGEA: Phase 2 Results

The majority of patients treated with zanidatamab (Zan) + chemo have reduced target lesion size and have durable objective responses

Change in target lesion size in response-evaluable patients with HER2-positive mGEA



	Zan + CAPOX (n =18)	Zan + mFOLFOX6 (n = 18)	Zan + FP (n = 2)	Total N = 38
cORR, %	89	67	100	79
Confirmed best overall response, %				
CR	2	1	0	3
PR	14	11	2	27
SD	2	3	0	5
PD	0	3	0	3
DCR	100	83	100	92
mDOR, months	10.4	NE	NE	20.4

Elimova E, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 347)

Courtesy of Zev Wainberg, MD, MSc

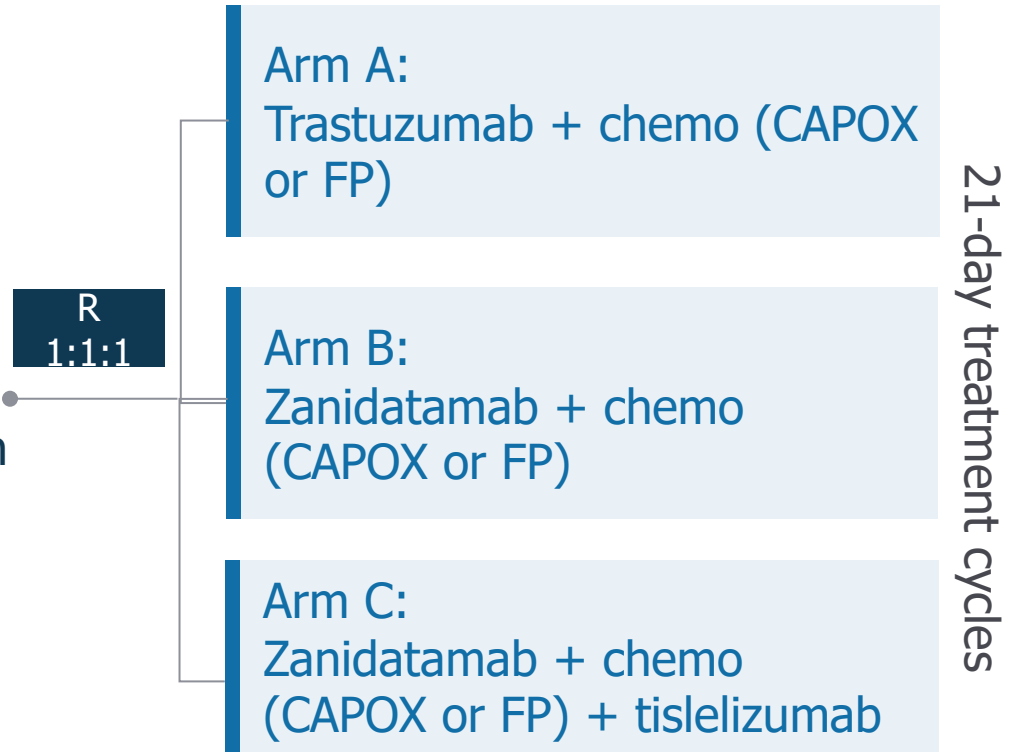
HERIZON-GEA-01

Global, randomized, open-label, active comparator, phase 3 trial (NCT05152147):

- Evaluate and compare the efficacy and safety of zanidatamab plus chemotherapy with or without tislelizumab to the standard of care (trastuzumab plus chemotherapy)
- As first-line treatment for patients with advanced/metastatic HER2-positive GEAs

Unresectable, locally advanced or metastatic GEA

- HER2+
- No prior therapy in the advanced/metastatic setting
- No prior treatment with HER2 agents or checkpoint inhibitors
- Any PD-L1 status
- ECOG PS ≤ 1



Primary Endpoints
PFS, OS

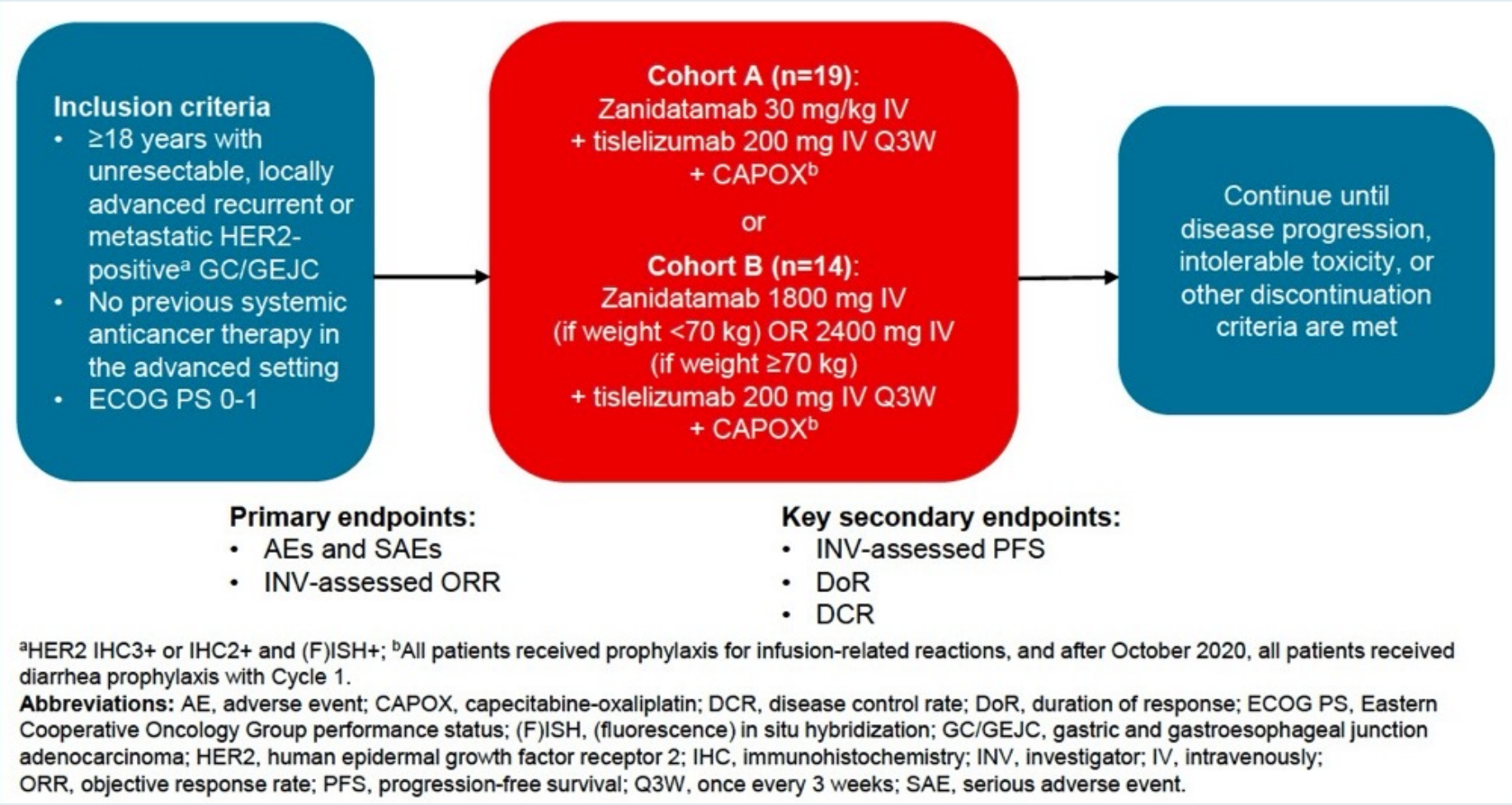
Secondary Endpoints
ORR, frequency and severity of AEs, change in HRQOL from baseline

CAPOX, Capecitabine + oxaliplatin; FP: 5-fluorouracil + cisplatin

Tabernero J, et al. Future Oncol. 2022;18:3255-3266.

Courtesy of Zev Wainberg, MD, MSc

Phase Ib/II NCT04276493: Study Design



[a]HER2 IHC3+ or IHC2+ and (F)ISH+; [b]All patients received prophylaxis for infusion-related reactions, and after October 2020, all patients received diarrhea prophylaxis with Cycle 1.

Abbreviations: AE, adverse event; CAPOX, capecitabine-oxaliplatin; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; (F)ISH, (fluorescence) in situ hybridization; GC/GEJC, gastric and gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; INV, investigator; IV, intravenously; ORR, objective response rate; PFS, progression-free survival; Q3W, once every 3 weeks; SAE, serious adverse event.

Lee K et al. ESMO 2023;Abstract 1518P.

HER2+ Disease

- Clinical Trials:
  - KEYNOTE-811: Chemo + Trastuzumab + Pembro now approved for HER2+ in PD-L1+
  - DS8201 approved for 2nd line (and beyond) HER2+ disease
    - Await randomized Phase III data in 2nd line (DESTINY-Gastric04)
    - Pneumonitis, which patients? Is 5.4 a better dose?
  - Zanidatamab: Promising preliminary results, results expected 2025
- Future Directions:
  - ctDNA: Probably as sensitive for HER2 as tissue (Chakrabarti et al, ESMO GI 2023)
  - Front line therapies beyond chemo + trastuzumab/pembro
  - HER2 Low: RR of 26% in HER2 2+, 9% in HER2 1+ (Yamaguchi et al, JCO, 2023)

Courtesy of Zev Wainberg, MD, MSc

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RTP Year in Review 2024

Targeting Claudin 18.2 — Zolbetuximab

- Ajani JA et al. **Updated efficacy and safety** results from **phase III SPOTLIGHT** study evaluating **zolbetuximab + mFOLFOX6 as first-line (1L)** treatment for patients with claudin-18 isoform 2-positive **(CLDN18.2+)**, HER2−, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma. ESMO 2023;Abstract LBA82.
- Lordick F et al. **Updated efficacy and safety** results from **phase III GLOW** study evaluating **zolbetuximab + CAPOX as first-line (1L) treatment** for patients with claudin-18 isoform 2-positive **(CLDN18.2+)**, HER2−, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma. ESMO 2023;Abstract LBA81.
- Shitara K et al. **Management of nausea and vomiting** (N/V) following first-line (1L) **zolbetuximab** + chemotherapy treatment in claudin-18.2 **(CLDN18.2)**+, HER2−, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma: **Analysis from the phase 3 SPOTLIGHT and GLOW studies**. Gastrointestinal Cancers Symposium 2024;Abstract 372.
- Klempner SJ et al. **ILUSTRO**: Phase II **multicohort trial of zolbetuximab** in patients with advanced or metastatic **claudin 18.2-positive** gastric or gastroesophageal junction adenocarcinoma. *Clin Cancer Res* 2023;29(19):3882-91.
- Wang Y et al. **First-in-human dose escalation and expansion study** of **SYSA1801, an antibody-drug conjugate targeting claudin 18.2** in patients with resistant/refractory solid tumors. ASCO 2023;Abstract 3016.

Frequently Asked Clinical Questions About GE Cancers

How do you measure claudin 18.2 in patients with GE cancer?

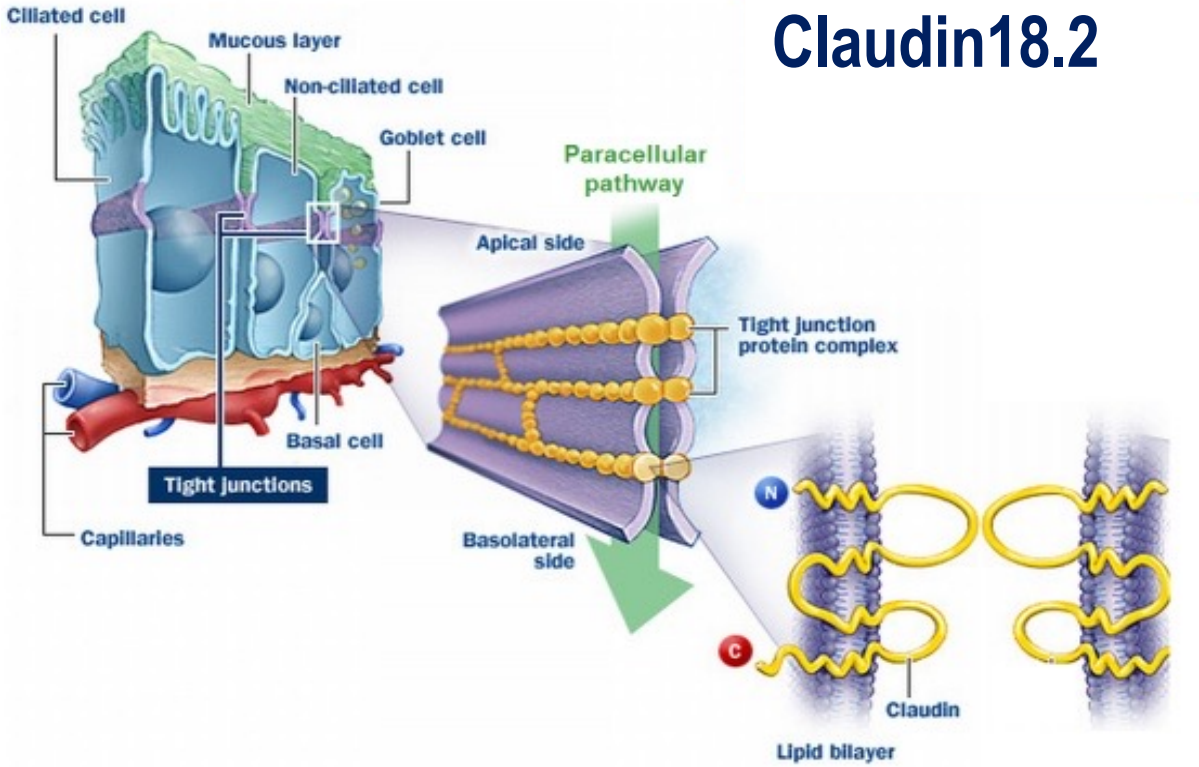
What is your usual treatment approach for a patient with GE cancer that is both claudin 18.2- and PD-L1-positive?

How do you manage the nausea and vomiting associated with zolbetuximab?

What other anti-claudin 18.2 targeted agents are under investigation?

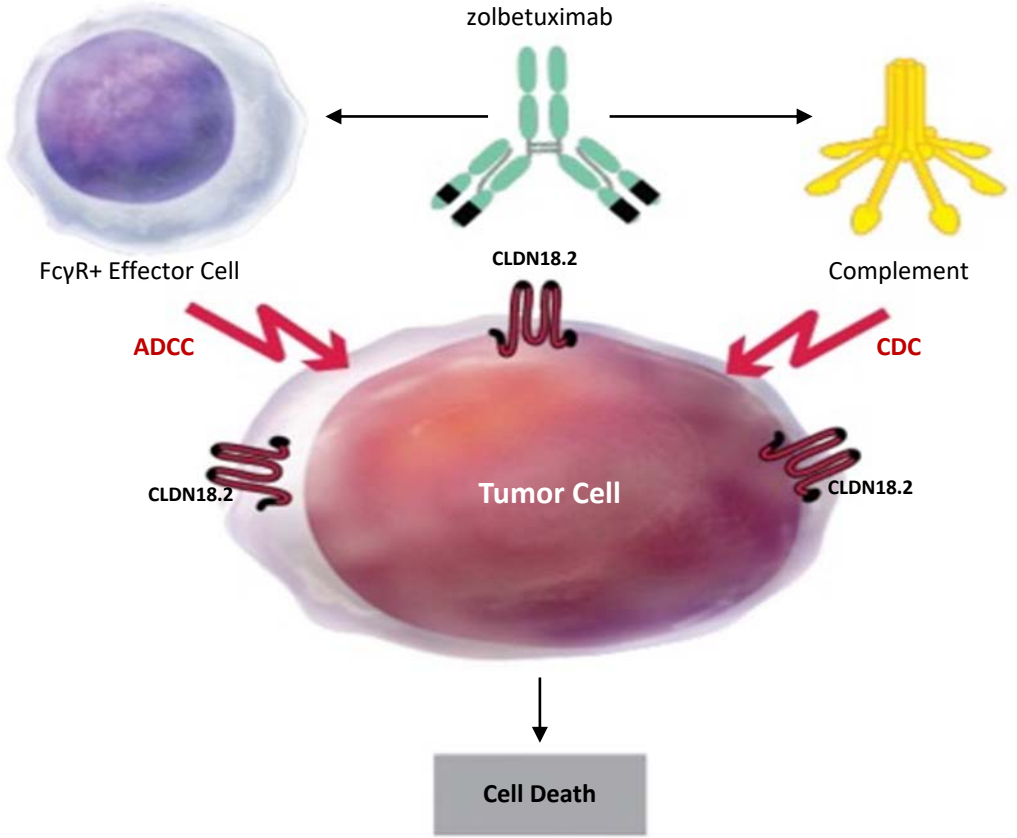
CLAUDIN18.2 – A NOVEL TARGET

Claudin18.2



- Member of the claudin family
- Major structural component of tight junctions
- Seals intercellular space in epithelial sheets
- Not expressed in any healthy tissues, except: stomach mucosa

Mechanism of Action of Zolbetuximab

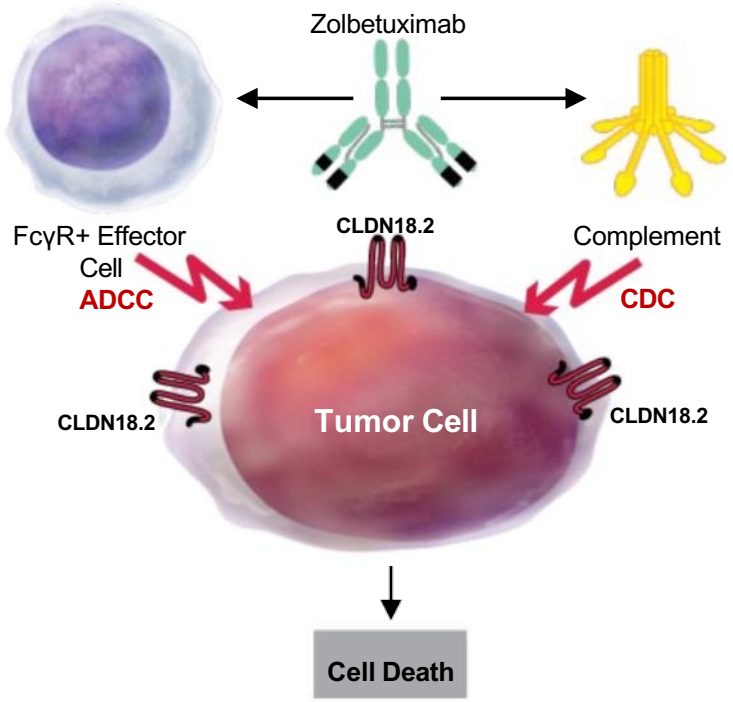


Sahin U et al. *Ann Oncol.* 2021 May;32(5):609-619

Courtesy of Zev Wainberg, MD, MSc

Zolbetuximab in Patients With mG/GEJ Adenocarcinoma

Mechanism of Action of Zolbetuximab



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

- CLDN18.2, a tight junction protein, expressed in normal and malignant gastric mucosa cells, becomes exposed on the surface of G/GEJ adenocarcinoma cells during malignant transformation, making it a promising target[8,12–18]
- Zolbetuximab is a first-in-class chimeric IgG1 monoclonal antibody that targets CLDN18.2 and induces ADCC/CDC[8,15–18]
- Zolbetuximab is a targeted treatment that continues to be evaluated in 2 ongoing global, phase 3 studies, SPOTLIGHT and GLOW[19,20]
  - Primary analyses of both studies showed that treatment with zolbetuximab in combination with oxaliplatin-based chemotherapy regimens prolonged survival compared with the placebo group[19,20]

1. Van Cutsem et al. *Lancet*. 2016; 388(10060):2654–2664; 2. Lordick F et al. *Ann Oncol*. 2022; 33(10):1005–1020; 3. Obermannová R et al. *Ann Oncol*. 2022; 33(10):992–1004; 4. JGCA. *Gastric Cancer.* 2021; 24(1):1–21; 5. Kelly RJ et al. *N Engl J Med*. 2021; 384(13):1191–1203; 6. NHCPRC. *Chin J Cancer Res*. 2022; 34(3):207–237; 7. Bang Y-J et al. *Lancet*. 2010; 376(9742):687–697; 8. Pellino et al. *J Pers Med*. 2021;11(11):1095; 9. Shah MA et al. *J Clin Oncol*. 2023; 41(7):1470–1491; 10. Janjigian YY et al. *Lancet*. 2021; 398(10294):27–40; 11. Shitara K et al. *Nature*. 2022; 603(7903):942–948; 12. Niimi T et al. *Mol Cell Biol.* 2001;21(21):7380–7390; 13. Sahin U et al. *Clin Cancer Res.* 2008;14(23):7624–7634; 14. Moran D et al. *Ann Oncol.* 2018;29(suppl_8):viii14-viii57; 15. Sahin U et al. *Eur J Cancer.* 2018;100:17–26; 16. Rhode C et al. *Jpn J Clin Oncol.* 2019;49(9):870–876; 17. Türeci Ö et al. *Ann Oncol.* 2019;30(9):1487–1495; 18. Sahin U et al. *Ann Oncol.* 2021;32(5):609–619; 19. Shitara K et al. *Lancet.* 2023;401(10389):1655–1668; 20. Shah MA et al. *Nat Med*. 2023; 29(8):2133–2141.

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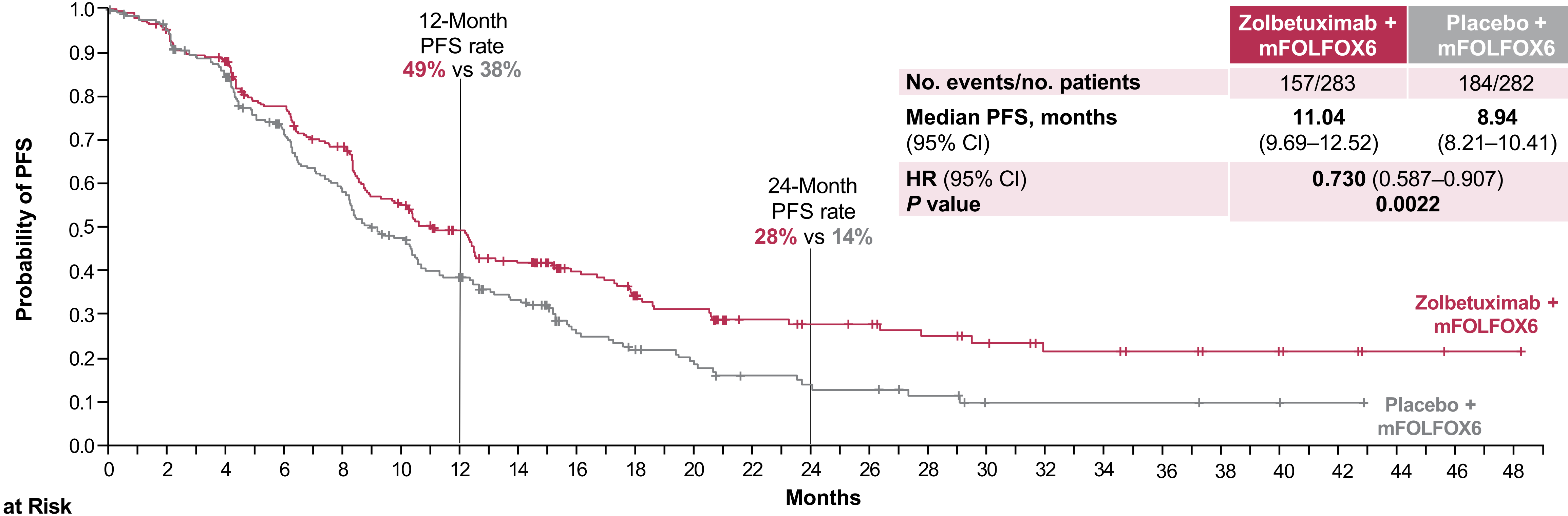
Courtesy of Zev Wainberg, MD, MSc

SPOTLIGHT Primary Endpoint: PFS by Independent Review Committee

Updated Analysis With 9.7 Months Additional Follow-Up



	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	157/283	184/282
Median PFS, months (95% CI)	**11.04** (9.69–12.52)	**8.94** (8.21–10.41)
HR (95% CI) *P* **value**	**0.730** (0.587–0.907) **0.0022**	

No. at Risk

Zolbetuximab + mFOLFOX6	283	263	254	232	227	193	190	160	155	123	117	101	93	78	75	70	58	55	46	39	39	32	29	29	24	24	23	19	18	18	15	14	11	11	11	9	9	9	7	7	5	4	4	2	2	2	1	1	1	0
Placebo + mFOLFOX6	282	273	260	237	226	186	173	148	134	107	99	77	73	60	57	48	34	33	28	26	23	18	17	17	12	11	11	10	8	8	4	4	4	4	4	4	4	4	3	3	3	1	1	0	0	0	0	0	0	0

Data cutoff: June 29, 2023; Median follow-up = 17.87 months (zolbetuximab + mFOLFOX6) vs 15.18 months (placebo + mFOLFOX6).
[a]Per RECIST version 1.1.

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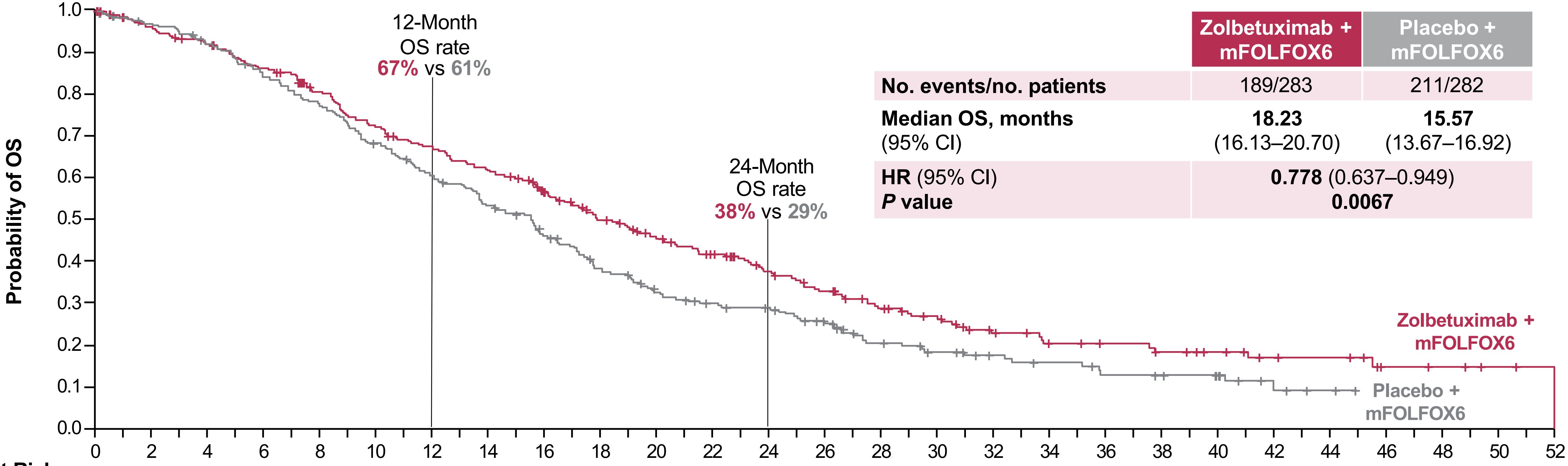
Courtesy of Zev Wainberg, MD, MSc

SPOTLIGHT Key Secondary Endpoint: OS

Updated Analysis With 9.7 Months Additional Follow-Up



	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	189/283	211/282
Median OS, months (95% CI)	**18.23** (16.13–20.70)	**15.57** (13.67–16.92)
HR (95% CI) *P* **value**	**0.778** (0.637–0.949) **0.0067**	

No. at Risk

Zolbetuximab + mFOLFOX6	283	270	264	255	251	241	234	228	211	196	189	179	174	166	160	153	139	128	116	109	99	93	85	79	72	67	60	54	49	44	41	35	31	29	23	23	21	21	18	17	15	13	11	10	10	9	5	5	4	3	2	1	0
Placebo + mFOLFOX6	282	277	271	266	253	243	228	219	209	198	184	174	162	156	142	134	117	107	91	86	73	67	63	57	56	51	45	36	32	30	25	22	20	18	17	17	13	13	12	11	10	6	4	3	2	0	0	0	0	0	0	0	0

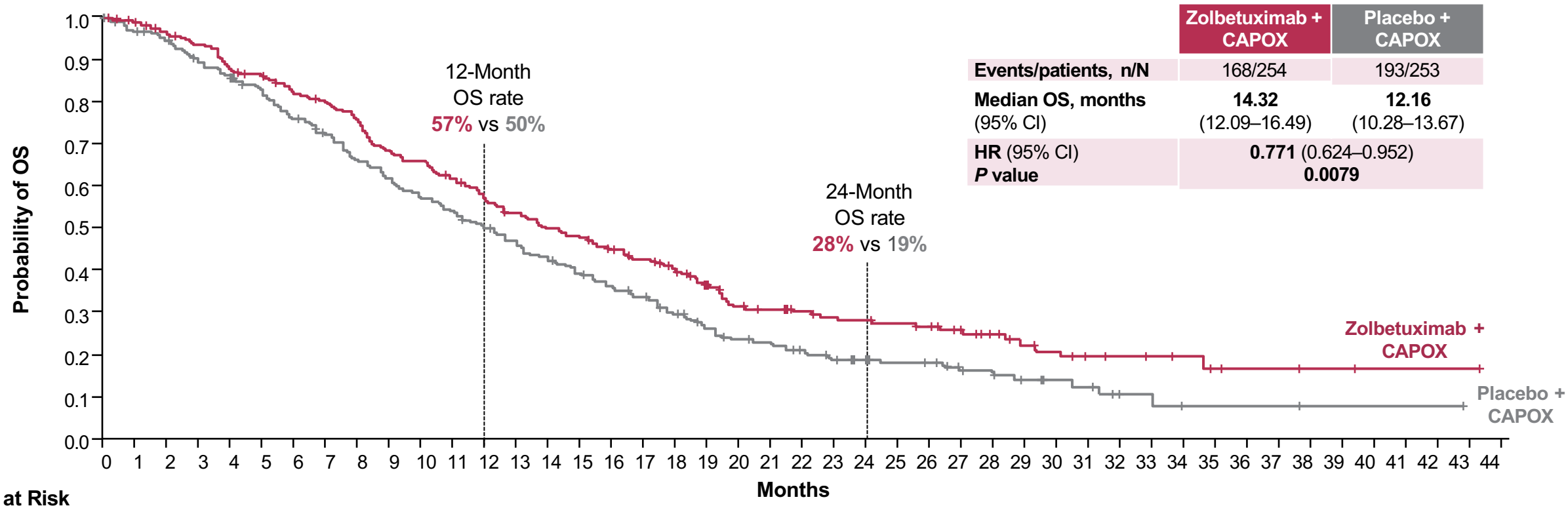
Data cutoff: June 29, 2023; Median follow-up = 31.11 months (zolbetuximab + mFOLFOX6) vs 29.57 months (placebo + mFOLFOX6).

MADRID 2023 ESMO congress

Courtesy of Zev Wainberg, MD, MSc

GLOW Key Secondary Endpoint: OS

Updated analysis with 8.7 months additional follow-up



	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**	

No. at Risk

Zolbetuximab + CAPOX	254	243	233	226	211	203	193	187	176	160	154	143	129	122	113	108	98	88	78	67	54	51	46	42	41	38	36	26	21	17	15	12	10	9	7	4	3	3	2	2	1	1	1	1	0
Placebo + CAPOX	253	243	235	220	210	197	181	168	153	143	133	125	116	106	97	89	80	74	62	52	46	43	38	33	28	25	23	17	14	11	9	8	4	4	2	2	2	2	1	1	1	1	1	0	0

MADRID 2023 ESMO congress

Data cutoff: June 29, 2023. Median follow-up = 26.09 months (zolbetuximab + CAPOX) vs 26.18 months (placebo + CAPOX).

Courtesy of Zev Wainberg, MD, MSc

SPOTLIGHT and GLOW

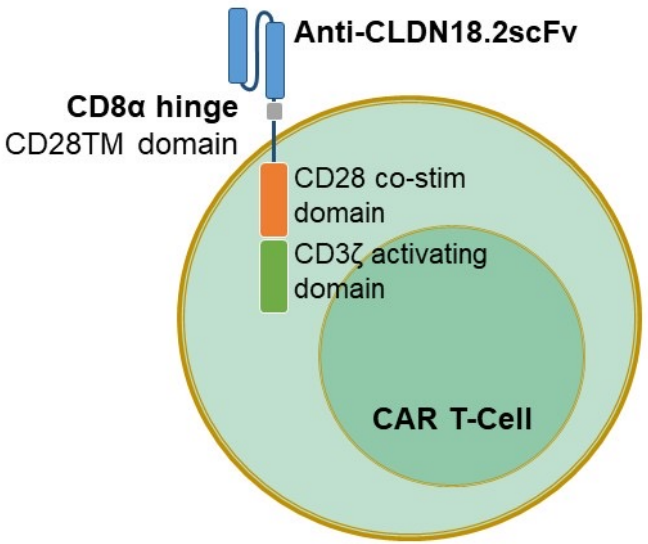
	SPOTLIGHT	GLOW
Control	FOLFOX	CapeOX
Countries	Global	Global (~50% from China)
CPS≥5	13%	22%
mPFS	10.6 vs 8.7 **+1.9** **HR 0.75**	8.2 vs 6.8 **+1.4** **HR 0.69**
mOS	18.2 vs 15.5 **+2.7** **HR 0.75**	14.4 vs 12.2 **+2.2** **HR 0.77**
ORR	61 vs 62% -1%	54 vs 49% +5%
Nausea Vomiting	81 vs 61% 65 vs 35%	69 vs 50% 66 vs 31%
Discontinuation of zolbe/pbo by AE	14 vs 2%	7 vs 4%

Shitara K, et al. ASCO-GI 2023; Lancet 2023; Xu RH, et al. ASCO Plenary series 2023
Courtesy of Zev Wainberg, MD, MSc

Major Claudin18.2 Strategies

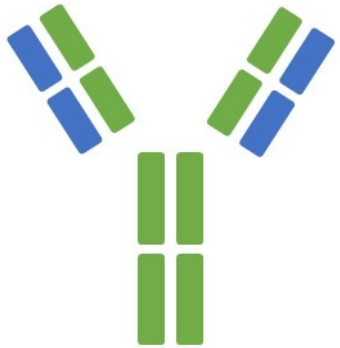
CAR T-Cell

CT041[1]



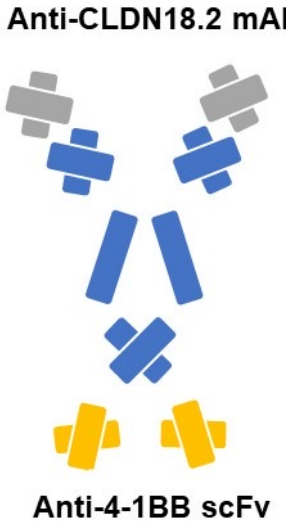
Engineered mAb

ZL-1211[2] (Humanized IgG1)



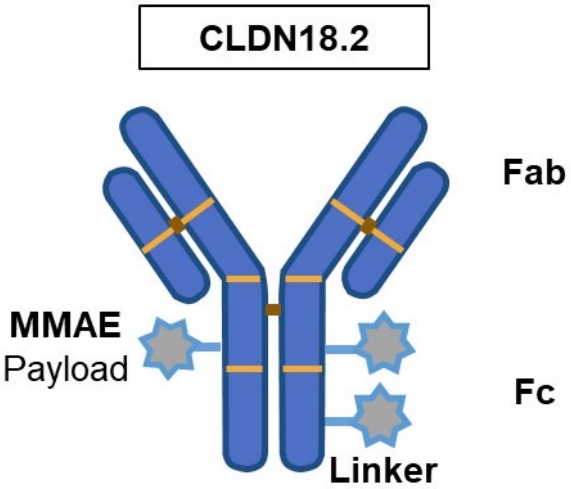
Bispecific Ab

TJ-CD4B[3]



Antibody–Drug Conjugate

CMG901[1]



Cao. Biomark Res. 2022;10:38. 2. Konno. AACR 2021. Abstr 1203. 3. Jiang. AACR 2020. Abstr 5644.

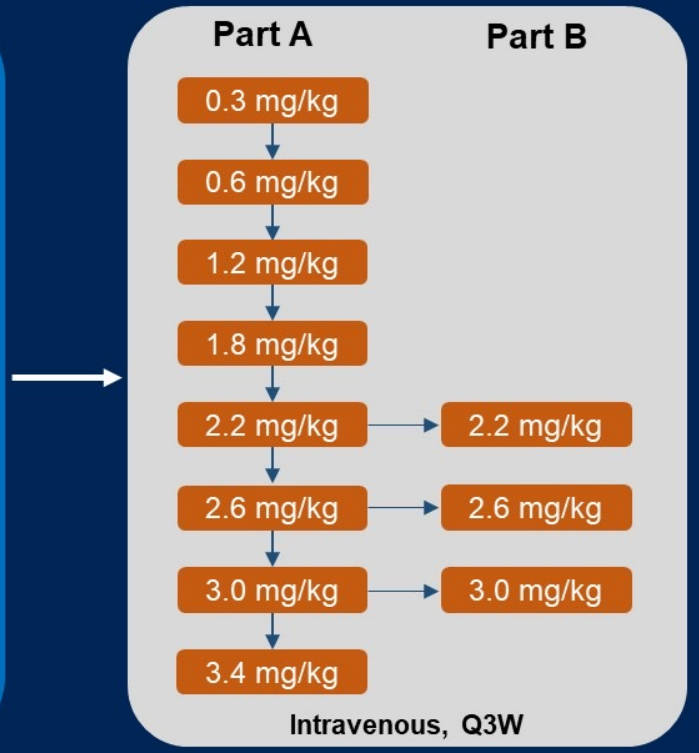
Courtesy of Zev Wainberg, MD, MSc

KYM901 Study Design

Open-label, multicenter, phase 1 trial

Key eligibility criteria:

- Pathologically confirmed advanced solid tumor, evaluable by RECIST v1.1
- Refractory/intolerant to standard therapies
- ECOG PS ≤1
- Part A dose escalation:
  - CLDN18.2 expression not required
- Part B dose expansion:
  - CLDN18.2 expression of ≥2+ membrane staining intensity in ≥5% tumor cells required



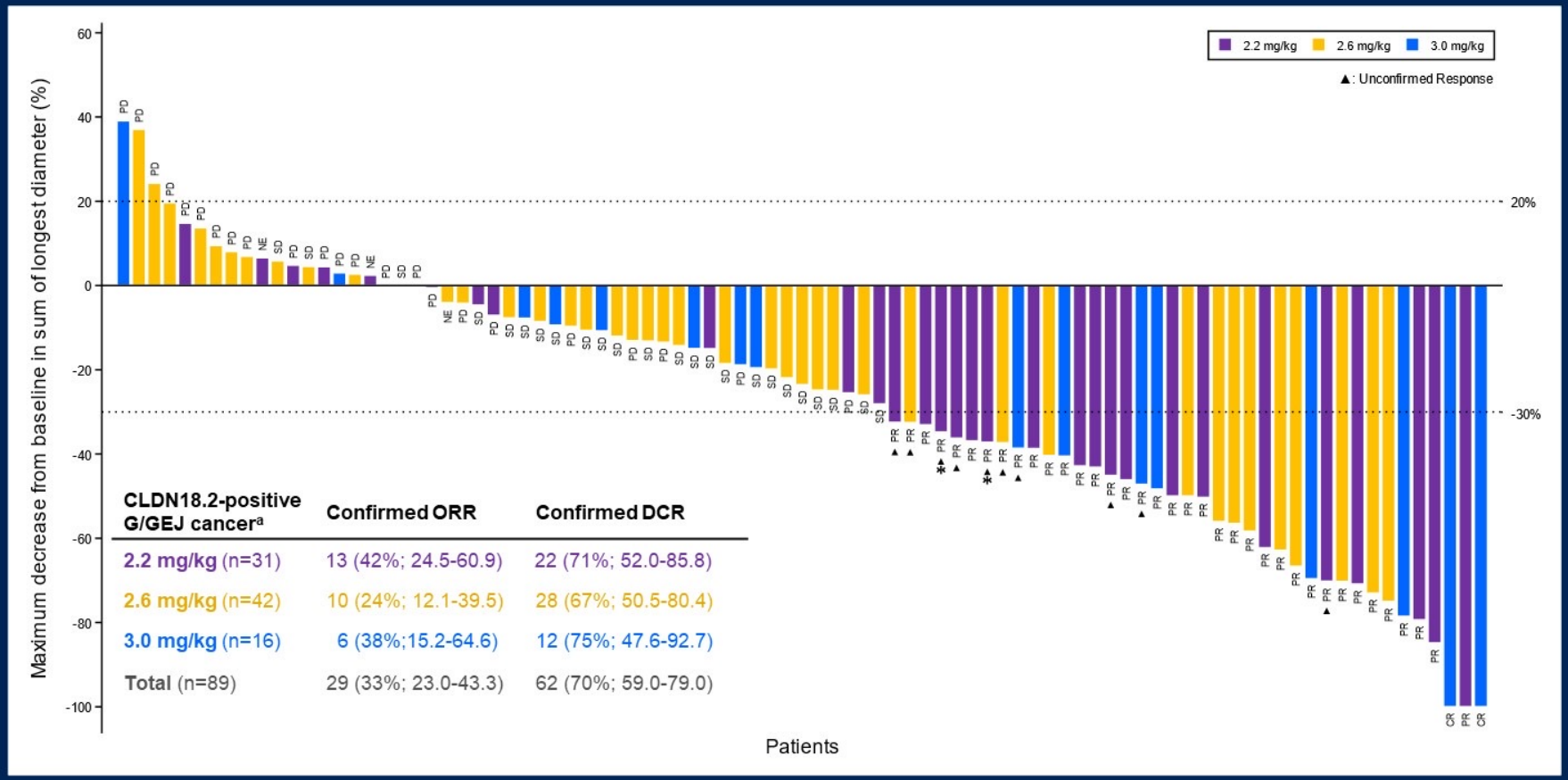
Primary endpoints
Part A: Adverse events and DLT
Part B: ORR[a] and RP2D

This presentation focuses on the 113 patients with G/GEJ cancer treated at 2.2-3.0 mg/kg cohorts (107 patients from part B, plus 6 patients from part A).

Data cut-off date: July 24, 2023. [a] Based on RECIST v1.1.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; Q3W, every 3 weeks; DLT, dose-limited toxicity; ORR, objective response rate; RP2D, recommended phase 2 dose.

Courtesy of Zev Wainberg, MD, MSc

CMG901: Best Overall Response in CLDN18.2-Positive[a] G/GEJ Cancer



CLDN18.2-positive G/GEJ cancer[a]	Confirmed ORR	Confirmed DCR
2.2 mg/kg (n=31)	13 (42%; 24.5-60.9)	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)	29 (33%; 23.0-43.3)	62 (70%; 59.0-79.0)

- Two additional patients* have ongoing unconfirmed partial response as of data-cutoff (July 24, 2023).
- One confirmed PR among 19 patients with CLDN18.2-expressing tumors that didn't meet the 20% IHC 2+/3+ threshold.

Data are presented as n (%, 95%CI). [a] In patients with CLDN18.2 expression of ≥2+ membrane staining in ≥20% tumor cells, who received one or more doses of CMG901, with at least one post-treatment evaluation.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; DCR, disease control rate; CI, confidence interval; IHC, immunohistochemistry.

Courtesy of Zev Wainberg, MD, MSc

Biomarker Overlap, what do we know?

Feature/Biomarker	Kubota Y, et al.		Pellino A, et al.		Jia K, et al.	
	CLDN18.2+ (n= 98)	CLDN18.2- (n = 310)	CLDN18.2+ (n = 117)	CLDN18.2- (n = 233)	CLDN18.2+ (n = 42)	CLDN18.2- (n = 38)
HER2-	83 (85%)	267 (85%)	100 (85%)	198 (85%)	33 (79%)	25 (66%)
HER2+	15 (15%)	43 (14%)	17 (15%)	35 (15%)	9 (21%)	13 (34%)
FGFR2b+	N/A	N/A	N/A	N/A	N/A	N/A
FGFR2b-	N/A	N/A	N/A	N/A	N/A	N/A
pMMR/MSS	93 (96%)	291 (94%)	102 (87%)	194 (83%)	36 (86%)	33 (87%)
dMMR/MSI	5 (5%)	19 (6%)	15 (13%)	39 (17%)	6 (14%)	5 (13%)
EBV+	4 (4%)	11 (4%)	7 (6%)	1 (0.4%)	8 (19%)	2 (5%)
EBV-	94 (96%)	299 (96%)	110 (94%)	232 (99.5%)	34 (81%)	36 (95%)
PD-L1- (CPS < 1)	24 (26%)	68 (23%)	87 (74%)	165 (71%)	9 (21%)	8 (21%)
PD-L1+ (CPS ≥ 1)	69 (74%)	225 (77%)	30 (26%)	68 (29%)	33 (79%)	30 (79%)
PD-L1+ (CPS ≥ 5)	39 (42%)	293 (52%)	21 (18%)	50 (21%)	N/A	N/A
PD-L1+ (CPS ≥ 10)	N/A	N/A	N/A	N/A	19 (45%)	17 (45%)
Diffuse Type	47 (48%)	137 (44%)	47 (40%)	70 (30%)	12 (29%)	22 (58%)
Intestinal Type	51 (52%)	173 (56%)	54 (46%)	132 (57%)	16 (38%)	6 (16%)

Klempner SJ, Janjigian, Wainberg Z et al, ESMO Open 2023

Courtesy of Zev Wainberg, MD, MSc

Biomarker Overlap, what do we know?

Can we combine with IO?

ILUSTRO Trial: Ongoing Now, seems to be safe, efficacy is pending

Feature/Biomarker	Kubota Y, et al.		Pellino A, et al.		Jia K, et al.	
	CLDN18.2+ (n= 98)	CLDN18.2- (n = 310)	CLDN18.2+ (n = 117)	CLDN18.2- (n = 233)	CLDN18.2+ (n= 42)	CLDN18.2- (n = 38)
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Klempner SJ, Janjigian, Wainberg Z et al, ESMO Open 2023

Courtesy of Zev Wainberg, MD, MSc

Claudin 18.2: How to Handle Unique “On Target” Toxicity

- Nausea and Vomiting reported with all Claudin 18.2 targeting agents
- Most studies suggest tachyphylaxis
- Not centrally induced nausea/vomiting
- Things that help (Shitara et al Proc GI ASCO 2024):
  - Slower infusion times
  - ? Steroids
  - ? H1/H2 blockers
  - Lorazepam

Courtesy of Zev Wainberg, MD, MSc

Agenda

INTRODUCTION: First-Line Therapy for Metastatic Gastroesophageal (GE) Cancers — the Bottom Line

MODULE 1: Updates on Immunotherapy in GE Cancers

MODULE 2: Targeting HER2

- **First-Line Treatment**
- **Trastuzumab Deruxtecan**
- **Zanidatamab**

MODULE 3: Targeting Claudin 18.2 — Zolbetuximab

MODULE 4: Faculty Journal Club

Frequently Asked Clinical Questions About GE Cancers

What research is being done to evaluate the role of the microbiome in GE cancers?

What role, if any, does ctDNA assessment have in the management of GE cancers?

How do you currently detect and integrate CHiP analysis?

Ann Surg. 2022 October 01; 276(4): 605–615. doi:10.1097/SLA.0000000000005587.

A Novel Microbiome Signature in Gastric Cancer: A Two Independent Cohort Retrospective Analysis

Miseker Abate, MD MPH[1,2,3], Elvira Vos, MD, PhD[1], Mithat Gonen, PhD[4], Yelena Y. Janjigian, MD[5], Mark Schattner, MD[7], Monika Laszkowska, MD[6], Laura Tang, MD PhD[7], Steven B. Maron, MD[5], Daniel G. Coit, MD[1], Santosh Vardhana, MD PhD[2], Chad Vanderbilt, MD[7,*], Vivian E. Strong, MD[1,*]

Cell Free DNA (cfDNA) Assessment of Esophagogastric (EG) Cancer Using MSK-ACCESS

Cytryn SL et al.
ASCO 2023;Abstract 4036.

Cell Free DNA (cfDNA) Assessment of Esophagogastric (EG) Cancer Using MSK-ACCESS

Cytryn SL et al.
Gastrointestinal Cancers Symposium 2024;Abstract 406.

JAMA Network Open

2023;6(2):e2254221

Original Investigation | Genetics and Genomics

Clinical Importance of Clonal Hematopoiesis in Metastatic Gastrointestinal Tract Cancers

Bill H. Diplas, MD, PhD; Ryan Ptashkin, MS; Joanne F. Chou, MPH; Shalom Sabwa, MPH; Michael B. Foote, MD; Benoit Rousseau, MD, PhD; Guillem Argilés, MD; James Robert White, PhD; Caitlin M. Stewart, PhD; Kelly Bolton, MD, PhD; Sree B. Chalasani, MD; Avni M. Desai, MD; Zoe Goldberg, MD; Ping Gu, MD, PhD; Jia Li, MD, PhD; Marina Shcherba, DO; Alice Zervoudakis, MD; Andrea Cercek, MD; Rona Yaeger, MD; Neil H. Segal, MD, PhD; David H. Ilson, MD, PhD; Geoffrey Y. Ku, MD; Ahmet Zehir, PhD; Marinela Capanu, PhD; Yelena Y. Janjigian, MD; Luis A. Diaz Jr, MD; Steven B. Maron, MD, MSc

OXFORD

JNCI: Journal of the National Cancer Institute, 2023, **00(0)**, 1–10

https://doi.org/10.1093/jnci/djad186

Advance Access Publication Date: September 12, 2023

Article

Clinical and molecular characteristics of early-onset vs average-onset esophagogastric cancer

Melissa A. Lumish, MD,[1,2] Henry Walch, MS,[3,4] Steven B. Maron, MD, MSc,[1,2] Walid Chatila, PhD,[3,4] Yelena Kemel, MS, ScM,[5] Anna Maio, RN, BSN,[5] Geoffrey Y. Ku, MD,[1,2] David H. Ilson, MD, PhD,[1,2] Elizabeth Won, MD,[1,2] Jia Li, MD, PhD,[1,2] Smita S. Joshi, MD,[1,2] Ping Gu, MD, PhD,[1,2] Mark A. Schattner, MD,[6] Monika Laszkowska, MD, MS,[6] Hans Gerdes, MD,[6] David R. Jones, MD,[7] Smita Sihag, MD, MPH,[7] Daniel G. Coit, MD,[7] Laura H. Tang, MD, PhD,[8] Vivian E. Strong, MD,[7] Daniela Molena, MD,[7] Zsofia K. Stadler, MD,[1,2,5] Nikolaus Schultz, PhD,[3,4] Yelena Y. Janjigian, MD,[1,2,‡] Andrea Cercek, MD[1,2,*,‡]

Open access Original research

Journal for ImmunoTherapy of Cancer

Impact of *Helicobacter pylori* infection status on outcomes among patients with advanced gastric cancer treated with immune checkpoint inhibitors

Patrick T Magahis ,[1] Steven B Maron,[2] Darren Cowzer ,[2] Stephanie King,[3] Mark Schattner,[3] Yelena Janjigian,[2] David Faleck ,[3] Monika Laszkowska[3]

2023;11(10):e007699

Immune Checkpoint Blockade and Targeted Therapies in Esophageal Cancer

Jessica Yang, MD[a,b,*], Yelena Y. Janjigian, MD[a,b,1]

Thorac Surg Clin 2022;32(4):467-78

Open access Original research

Journal for ImmunoTherapy of Cancer

Association between gene expression signatures and clinical outcomes of pembrolizumab versus paclitaxel in advanced gastric cancer: exploratory analysis from the randomized, controlled, phase III KEYNOTE-061 trial

Kohei Shitara ,[1,2] Maria Di Bartolomeo,[3] Mario Mandala ,[4] Min-Hee Ryu,[5] Christian Caglevic,[6] Tomasz Olesinski ,[7] Hyun Cheol Chung,[8] Kei Muro,[9] Eray Goekkurt,[10] Raymond S McDermott,[11] Wasat Mansoor,[12] Zev A Wainberg,[13] Chie-Schin Shih,[14] Julie Kobie,[14] Michael Nebozhyn,[14] Razvan Cristescu,[14] Z Alexander Cao,[14] Andrey Loboda,[14] Mustafa Özgüroğlu[15]

J Immunother Cancer 2023;11(6):e006920.

SWOG S2303: Randomized Phase II/III Trial of 2nd Line Nivolumab + Paclitaxel + Ramucirumab versus Paclitaxel + Ramucirumab in Patients with PD-L1 CPS ≥1 Advanced Gastric and Esophageal Adenocarcinoma (PARAMUNE)

Saeed A et al.

Gastrointestinal Cancers Symposium 2024;Abstract TPS430.

Appendix

asco special articles

Immunotherapy and Targeted Therapy for Advanced Gastroesophageal Cancer: ASCO Guideline

Manish A. Shah MD[1]; Erin B. Kennedy MHSc[2]; Ashley E. Alarcon-Rozas MD MBA[3]; Thierry Alcindor MD[4]; Angela N. Bartley MD[5]; Aubrey Belk Malowany BS[6]; Nishin A. Bhadkamkar MD[7]; Dana C. Deighton BA[8]; Yelena Janjigian MD[9]; Asha Karippot MD[10]; Uqba Khan MD[1]; Daniel A. King MD PhD[11]; Kelsey Klute MD[12]; Jill Lacy MD[13]; James J. Lee MD PhD[14]; Rutika Mehta MD MPH[15]; Sarbajit Mukherjee MD MS[16]; Arun Nagarajan MD[17]; Haeseong Park MD MPH[18]; Anwaar Saeed MD[19]; Thomas J. Semrad MD MAS[20]; Kohei Shitara MD[21]; Elizabeth Smyth MD[22]; Nataliya V. Uboha MD PhD[23]; Melani Vincelli[24]; Zev Wainberg MD[25]; and Lakshmi Rajdev MD[26]

J Clin Oncol 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Negative Gastric Adenocarcinoma: First-Line Immunotherapy

"For human epidermal grown factor receptor 2 (HER2)-negative patients with gastric adenocarcinoma and programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥ 5, first-line therapy with nivolumab and chemotherapy (CT) is recommended."

Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Negative Gastric Adenocarcinoma: First-Line Immunotherapy*

Recommendation 1.1. For human epidermal growth factor receptor 2 (HER2)–negative patients with gastric adenocarcinoma (AC) and programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥ 5, first-line therapy with nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy (CT) is recommended (Type: Evidence based; benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

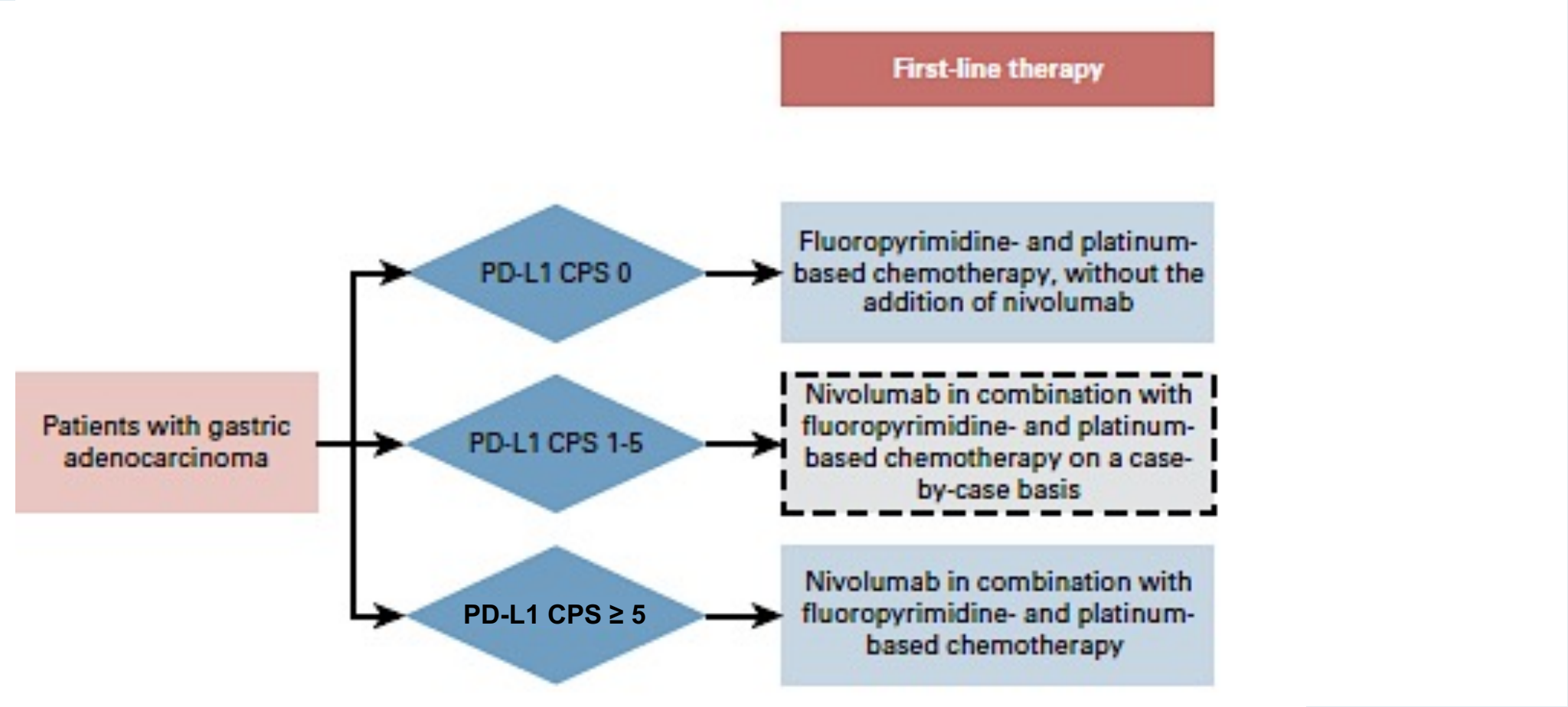
Qualifying statements:

- For HER2-negative patients with gastric AC and PD-L1 CPS 1-5, first-line therapy with nivolumab in combination with fluoropyrimidine- and platinum-based CT may be considered on a case-by-case basis.
- For HER2-negative patients with gastric AC and PD-L1 CPS 0, first-line therapy with fluoropyrimidine- and platinum-based CT, without the addition of nivolumab, is recommended.

* The PD-L1 cutoffs are based on subgroup analyses presented in included studies. All possible cutoffs have not been assessed; therefore, optimal PD-L1 cutoffs are unknown. Several additional studies of immunotherapy with PD-1 inhibitors plus CT, compared with placebo plus CT have shown efficacy; however, these therapy options are not currently US Food and Drug Administration-approved.

Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Negative Gastric Adenocarcinoma: First-Line Immunotherapy



Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Negative Esophageal or GEJ Adenocarcinoma: First-Line Immunotherapy

"For HER2-negative patients with esophageal or gastroesophageal junction (GEJ) AC and PD-L1 CPS ≥ 5, first-line therapy with nivolumab and CT is recommended.

First-line therapy with pembrolizumab and CT is recommended for HER2-negative patients with esophageal or GEJ AC and PD-L1 ≥ 10."

Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Negative Esophageal or GEJ Adenocarcinoma: First-Line Immunotherapy*

Recommendation 1.2. For HER2-negative patients with esophageal or gastroesophageal junction (GEJ) AC, first-line therapy with nivolumab for patients with PD-L1 CPS ≥ 5, or pembrolizumab for PD-L1 CPS ≥ 10, in combination with fluoropyrimidine- and platinum-based CT is recommended (Type: Evidence based; benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong).

Qualifying statements:

- For HER2-negative patients with esophageal or GEJ AC, first-line therapy with nivolumab for patients with PD-L1 CPS 1-5, or pembrolizumab for patients with PD-L1 CPS 1-10, in combination with fluoropyrimidine- and platinum-based CT may be recommended on a case-by-case basis.
- For HER2-negative patients with gastric AC and PD-L1 CPS 0 or PD-L1 tumor proportion score (TPS) 0%, first-line therapy with fluoropyrimidine- and platinum-based CT, without the addition of programmed cell death protein 1 inhibitors, is recommended.

* The PD-L1 cutoffs are based on subgroup analyses presented in included studies. All possible cutoffs have not been assessed; therefore, optimal PD-L1 cutoffs are unknown. Several additional studies of immunotherapy with PD-1 inhibitors plus CT, compared with placebo plus CT have shown efficacy; however, these therapy options are not currently US Food and Drug Administration-approved.

Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Negative Esophageal or GEJ Adenocarcinoma: Second-Line Therapy

"For patients with advanced gastroesophageal or GEJ AC whose disease has progressed after first-line therapy, ramucirumab plus paclitaxel is recommended."

Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Negative Esophageal or GEJ Adenocarcinoma: Second-Line Therapy

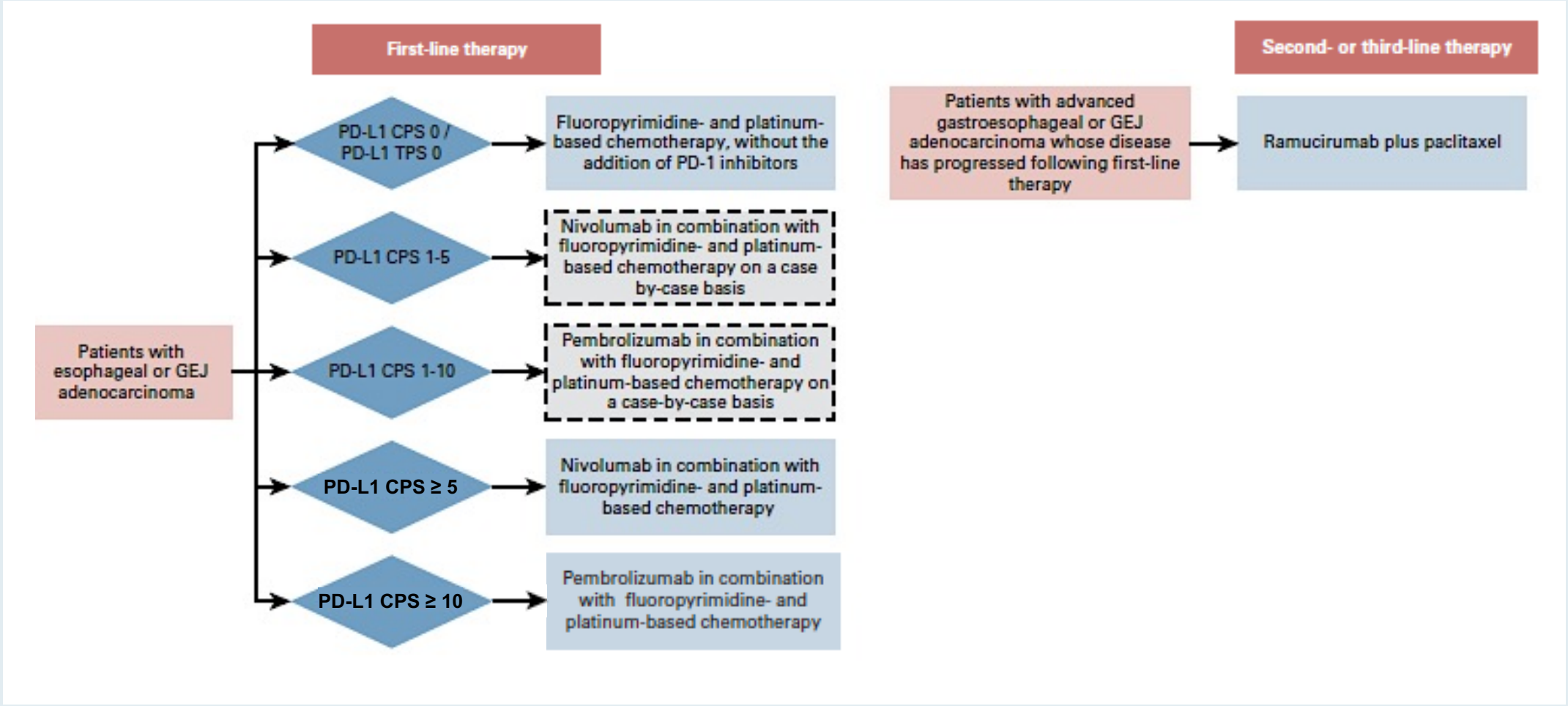
Recommendation 2.1. For patients with advanced gastroesophageal or GEJ AC whose disease has progressed after first-line therapy, ramucirumab plus paclitaxel is recommended (Type: Evidence based; benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Qualifying statement:

- Although outside the scope of this review, for patients with gastric or GEJ AC, trifluridine and tipiracil may be offered after progression on second-line therapy.

Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Negative Esophageal or GEJ Adenocarcinoma: First-Line Immunotherapy and Subsequent Lines of Therapy



Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Negative Esophageal Squamous Cell Carcinoma: First-Line Immunotherapy

"For patients with esophageal squamous cell carcinoma and PD-L1 tumor proportion score ≥ 1%, nivolumab plus CT, or nivolumab plus ipilimumab is recommended; for patients with esophageal squamous cell carcinoma and PD-L1 CPS ≥ 10, pembrolizumab plus CT is recommended."

Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Negative Esophageal Squamous Cell Carcinoma: First-Line Immunotherapy*

Recommendation 1.3. For patients with HER2-negative esophageal squamous cell carcinoma (ESCC) and PD-L1 CPS ≥ 10, pembrolizumab plus fluoropyrimidine- and platinum-based CT is recommended (Type: Evidence based; benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 1.4. For patients with HER2-negative ESCC and PD-L1 TPS ≥ 1%, nivolumab plus fluoropyrimidine- and platinum-based CT or nivolumab plus ipilimumab is recommended (Type: Evidence based; benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

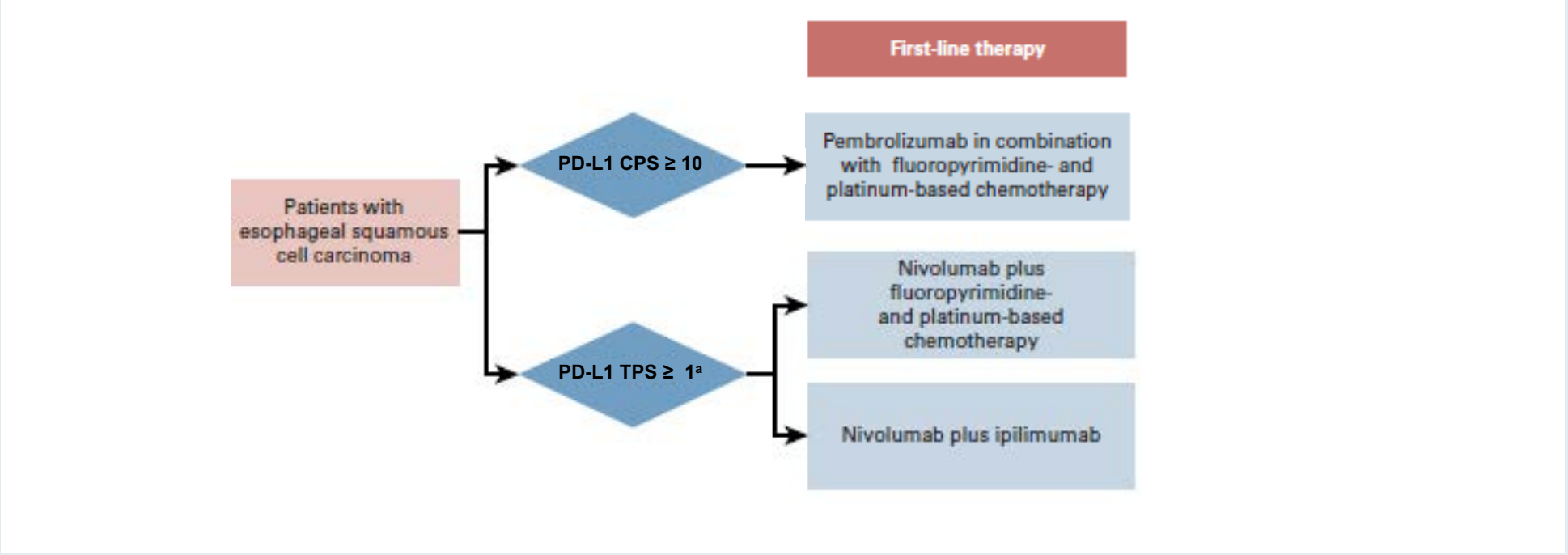
Qualifying statement:

- Data from the primary analysis of CheckMate 648 supports Recommendation 1.4 in patients with ESCC and PD-L1 TPS ≥ 1%. Additional exploratory analyses from CheckMate 648 found that 91% of patients across three study arms had PD-L1 CPS ≥ 1; therefore, CPS ≥ 1 may be used as a threshold for treatment decision making if TPS is not available.

* The PD-L1 cutoffs are based on subgroup analyses presented in included studies. All possible cutoffs have not been assessed; therefore, optimal PD-L1 cutoffs are unknown. Several additional studies of immunotherapy with PD-1 inhibitors plus CT, compared with placebo plus CT have shown efficacy; however, these therapy options are not currently US Food and Drug Administration-approved.

Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Negative Esophageal Squamous Cell Carcinoma: First-Line Immunotherapy



[a] Data from primary analysis of CheckMate 648 supports recommendation in patients with ESCC and PD-L1 TPS ≥1%. Additional exploratory analyses for CheckMate 648 found that 915 of patients across 3 study arms had PD-L1 CPS ≥ 1; therefore CPS ≥ 1 may be used as a threshold for treatment decision making if TPS is not available.

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ASCO Guideline for Advanced HER2-Positive Gastric or GEJ Adenocarcinoma: First-Line Immunotherapy and Targeted Therapy

"For patients with HER2-positive gastric or GEJ previously untreated, unresectable or metastatic AC, trastuzumab plus pembrolizumab is recommended, in combination with CT."

Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Positive Gastric or GEJ Adenocarcinoma: First-Line Immunotherapy and Targeted Therapy

Recommendation 1.5. For patients with HER2-positive gastric or GEJ previously untreated, unresectable or metastatic AC, trastuzumab plus pembrolizumab is recommended, in combination with fluoropyrimidine- and oxaliplatin-based CT (Type: Evidence based; benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong).

Qualifying statements:

- Recommendation 1.5 is applicable irrespective of CPS or TPS levels; however, the Expert Panel notes that PD-L1 CPS was ≥ 1 in 87% of patients included in the KEYNOTE-811 randomized controlled trial.
- HER2 positivity was defined in KEYNOTE-811 as immunohistochemistry 3+ or immunohistochemistry 2+ with positive in-situ hybridization (details of testing methodology are contained in the Literature review and analysis section).
- Trastuzumab plus pembrolizumab and CT is recommended based on an interim analysis showing a response benefit in the first 264 patients enrolled in KEYNOTE-811.[12] We await the analysis of primary outcomes overall survival and progression-free survival.

Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Positive Gastric or GEJ Adenocarcinoma: Second-Line Therapy

"For HER2-positive patients with gastric or GEJ AC who have progressed after first-line therapy, trastuzumab deruxtecan is recommended."

Shah MA et al. *J Clin Oncol* 2023;41:1470-91.

ASCO Guideline for Advanced HER2-Positive Gastric or GEJ Adenocarcinoma: Second-Line Therapy

Recommendation 2.2. For HER2-positive patients with gastric or GEJ AC who have progressed after first-line therapy, trastuzumab deruxtecan is recommended (Type: Evidence based; benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Note. Although the key evidence for this recommendation includes patients who received therapy in the third-line setting, this option is US Food and Drug Administration–approved as a second-line and later therapy option.

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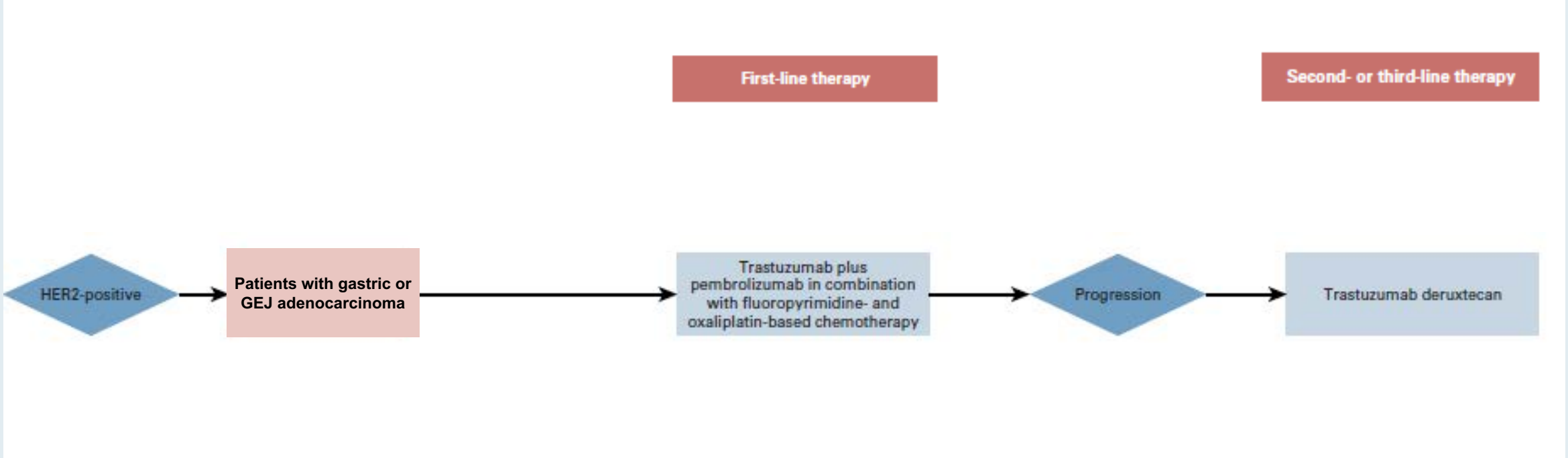
ASCO Guideline for Advanced HER2-Positive Gastric or GEJ Adenocarcinoma: First-Line Immunotherapy and Targeted Therapy and Second-Line Treatment



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