# Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Gastroesophageal Cancers

*Part 1 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 ASCO Gastrointestinal Cancers Symposium*

**Thursday, January 18, 2024**

**6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)**

## Faculty

**David H Ilson, MD, PhD**

**Rutika Mehta, MD, MPH**

**Markus Moehler, MD**

**Manish A Shah, MD**

## Moderator

**Harry H Yoon, MD, MHS**

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# Faculty

**David H Ilson, MD, PhD**
Attending Physician, Member
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Professor of Medicine
Weill Cornell Medical College
New York, New York

**Rutika Mehta, MD, MPH**
Associate Member in the Department of Gastrointestinal Oncology
Moffitt Cancer Center
Associate Professor in the Department of Oncologic Sciences
University of South Florida
Tampa, Florida

**Markus Moehler, MD**
Head, Gastrointestinal Oncology
Research Center for Immunotherapy (FZI)
Past Chair of EORTC Gastrointestinal Cancer Group
Johannes Gutenberg-University Clinic
Mainz, Germany

**Manish A Shah, MD**
Chief, Solid Tumor Oncology Service
Director, Gastrointestinal Oncology Program
Co-Director, Center for Advanced Digestive Care
Bartlett Family Professor of Gastrointestinal Oncology
Weill Cornell Medicine/NewYork-Presbyterian Hospital
New York, New York

**Moderator**
**Harry H Yoon, MD, MHS**
Professor of Oncology
Enterprise Co-Leader
Gastrointestinal and Hepatobiliary/Pancreatic Cancer Research Program
Enterprise Vice-Chair, Gastrointestinal Cancer Disease Group
Mayo Clinic Comprehensive Cancer Center
Rochester, Minnesota

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# Dr Ilson — Disclosures
# Faculty

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# Dr Mehta — Disclosures
# Faculty

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| **Consulting Agreement** | Lilly |
| **Data and Safety Monitoring Board/Committee** | Arcus Biosciences |

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# Dr Moehler — Disclosures
# Faculty

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| **Contracted Research (With My University Clinic)** | Leap Therapeutics Inc, MSD, Taiho Oncology Inc |
| **Data and Safety Monitoring Board/Committee** | Transcenta |
| **Speakers Bureau** | Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Bristol Myers Squibb, MSD, Sanofi, Servier Pharmaceuticals LLC |
| **Nonrelevant Financial Relationship** | Triptych |

# Dr Shah — Disclosures
# Faculty

| | |
|---|---|
| **Contracted Research** | Bristol Myers Squibb, Merck, Oncolys BioPharma |

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# Dr Yoon — Disclosures
# Moderator

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| **Contracted Research** | Amgen Inc, BeiGene Ltd, Bristol Myers Squibb, CARsgen Therapeutics, MacroGenics Inc, Merck |

# Dr Ajani — Disclosures
# Survey Participant

| | |
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| **Data and Safety Monitoring Board/Committee** | BeiGene Ltd |

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# Dr Kim — Disclosures
# Survey Participant

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| **Contracted Research** | Merck |

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# Consensus or Controversy? Clinical Investigators Provide Perspectives on Biomarker Assessment and Related Treatment Decision-Making for Patients with Colorectal Cancer

*Part 2 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 ASCO Gastrointestinal Cancers Symposium*

**Friday January 19, 2024**

**6:15 PM – 8:15 PM PT (9:15 PM – 11:15 PM ET)**

## Faculty

**Tanios Bekaii-Saab, MD**

**Andrea Cercek, MD**

**Cathy Eng, MD**

**John Strickler, MD**

## Moderator

**Christopher Lieu, MD**

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# Consensus or Controversy? Investigator Perspectives on the Current and Future Role of Immune Checkpoint Inhibitors in the Management of Hepatobiliary Cancers

*A CME-Accredited Virtual Event Held in Conjunction with the 2024 ASCO Gastrointestinal Cancers Symposium*

**Saturday, January 20, 2024**

**8:30 AM – 9:30 AM ET (5:30 AM – 6:30 AM PT)**

## Faculty

**Ahmed Omar Kaseb, MD, CMQ**

**Arndt Vogel, MD, PhD**

## Moderator

**Neil Love, MD**

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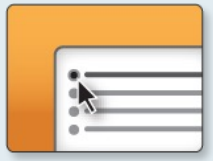
# Clinicians in the Meeting Room

**Networked iPads are available.**

**Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.**



**Answer Survey Questions: Complete the premeeting survey.**

**Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.**

**Complete Your Evaluation: Tap the CME/NCPD Evaluation button to complete your evaluation electronically to receive credit for your participation.**

***For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.***

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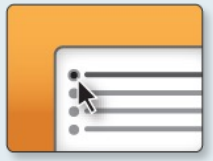
# Clinicians Attending via Zoom

**Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.**



**Answer Survey Questions: Complete the premeeting survey at the beginning of each module.**

**Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.**

**Get CME/NCPD Credit: CME and NCPD credit links will be provided in the chat room at the conclusion of the program. MOC and ONCC credit information will be emailed to attendees within the next 2-3 business days.**

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# About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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## Moderator

**Harry H Yoon, MD, MHS**

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# Agenda

**Module 1 – Recent Developments in the Management of Localized or Locally Advanced Gastroesophageal Cancers – Dr Ilson**

**Module 2 – Incorporation of First-Line Immunotherapeutic Strategies for Patients with Metastatic Gastroesophageal Tumors – Dr Yoon**

**Module 3 – Emerging Role of Therapy Targeting Claudin 18.2 in Advanced Gastric/GEJ Adenocarcinoma – Dr Shah**

**Module 4 – Current Considerations in the Care of Patients with HER2-Positive Gastroesophageal Cancers – Dr Moehler**

**Module 5 – Selection and Sequencing of Therapy for Patients with Relapsed/Refractory (R/R) HER2-Negative Gastroesophageal Cancers – Dr Mehta**

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# Consulting Faculty

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

**Sunnie Kim, MD**
GI Medical Oncologist
Associate Professor
University of Colorado Cancer Center
Aurora, Colorado

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# MODULE 1: Recent Developments in the Management of Localized or Locally Advanced Gastroesophageal Cancers – Dr Ilson

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# Adjuvant nivolumab: (1) patients with a pathologic CR after CRT, and (2) patients who refuse surgery

Sunnie Kim, MD

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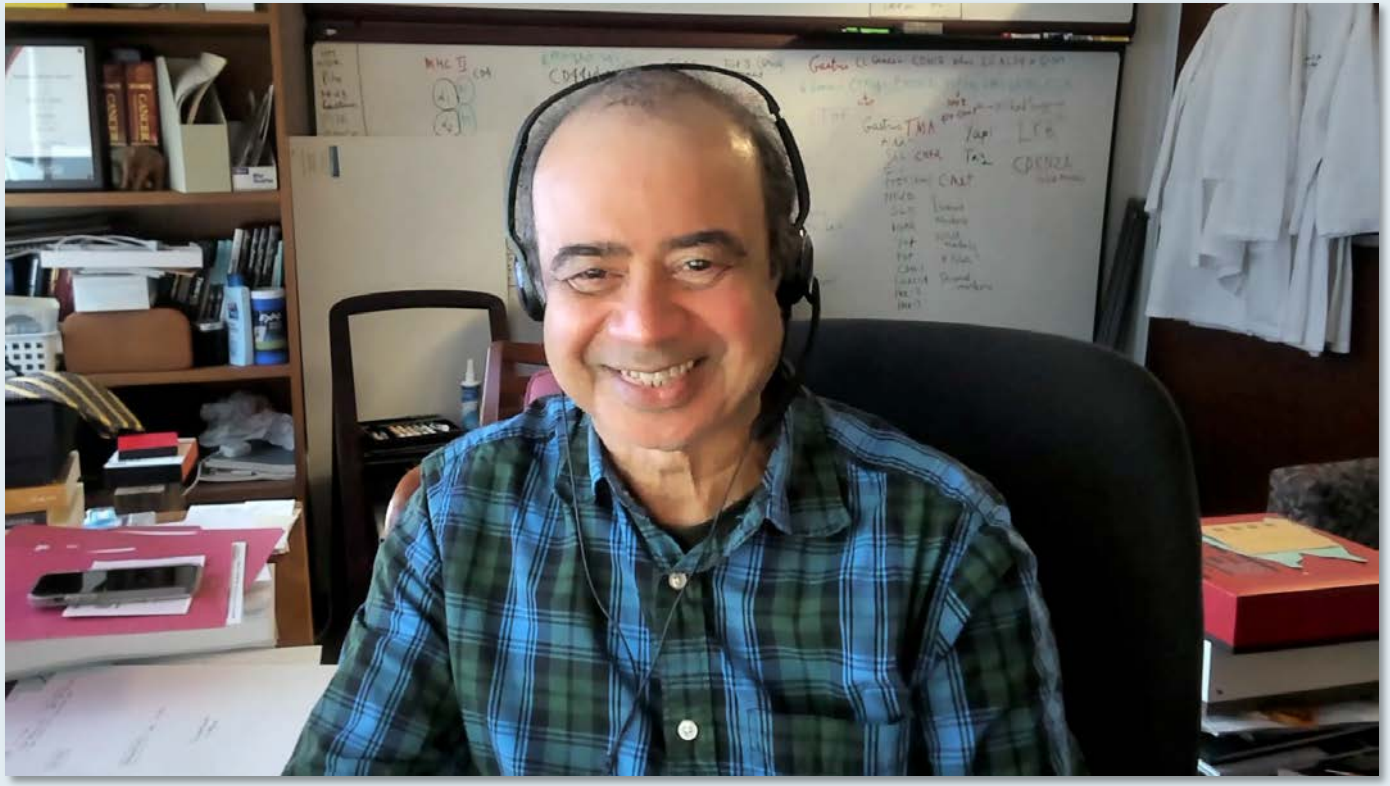
# QUESTIONS FOR THE FACULTY

**Sunnie Kim, MD**

***Would you offer adjuvant nivolumab to a patient who received neoadjuvant chemoradiation therapy and then refused or was deemed ineligible for surgery?***

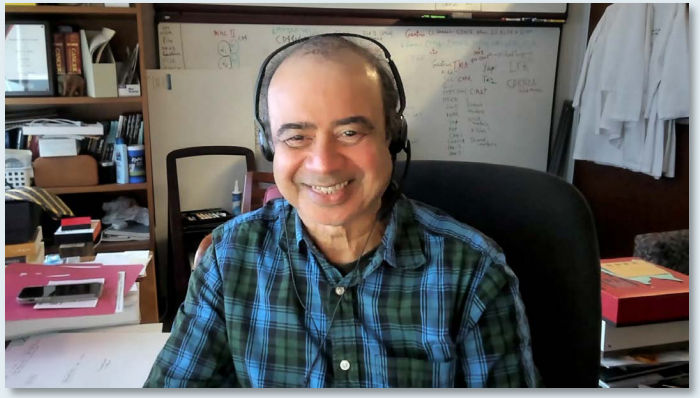
***Would you offer adjuvant nivolumab to a patient who received neoadjuvant chemoradiation therapy and had a pathologic complete response?***

# Immunotherapy for GE squamous cell carcinoma versus adenocarcinoma



**Jaffer A Ajani, MD**

# QUESTIONS FOR THE FACULTY



**Jaffer A Ajani, MD**

***What are the predictors of response of IO benefit (eg, histology) in patients with previously untreated metastatic gastroesophageal cancers?***

***Is there a tail on the IO curve? (Is cure a realistic goal?)***

**Which adjuvant systemic therapy would you currently recommend to a patient with HER2-negative, microsatellite-stable (MSS) squamous cell carcinoma of the esophagus who received neoadjuvant carboplatin/paclitaxel and concurrent radiation therapy and had residual disease at surgery? Does PD-L1 level affect your treatment choice? Approximately what proportion of patients receiving adjuvant immunotherapy in this setting complete treatment?**

| | Adjuvant Tx | PD-L1 level affect Tx? | Proportion who complete adjuvant IO |
|---|---|---|---|
|  Dr Ilson | Nivolumab – 1 year | No | 75% |
|  Dr Mehta | Nivolumab – 1 year | No | 50% |
|  Dr Moehler | Nivolumab – 1 year | No | 75% |
|  Dr Shah | Nivolumab – 1 year | No | 80% |
|  Dr Yoon | Nivolumab – 1 year | Yes, if CPS <5, lower threshold to hold or discontinue | 50% |
|  Dr Ajani | Nivolumab – 1 year | No | 75% |
|  Dr Kim | Nivolumab – 1 year | No | 60% |

IO = immunotherapy

**A patient with HER2-negative, microsatellite instability (MSI)-high gastric adenocarcinoma receives preoperative fluorouracil/leucovorin/oxaliplatin/docetaxel (FLOT), undergoes resection and has significant residual disease at surgery. Regulatory and reimbursement issues aside, which postoperative approach would you generally recommend?**

| | |
|---|---|
|  Dr Ilson | Switch to anti-PD-1/PD-L1 antibody monotherapy |
|  Dr Mehta | I would not offer FLOT in this setting — I would have started with a checkpoint inhibitor |
|  Dr Moehler | Continue FLOT |
|  Dr Shah | Continue FLOT |
|  Dr Yoon | Switch to FOLFOX/nivolumab or pembrolizumab monotherapy |
|  Dr Ajani | Switch to nivolumab or nivolumab/ipilimumab |
|  Dr Kim | Continue FLOT and add atezolizumab |

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

| | |
|---|---|
|  Dr Ilson | Give as definitive local therapy to avoid surgery, chemotherapy and radiation therapy |
|  Dr Mehta | Per NCCN: Either nivolumab/ipilimumab → nivolumab, pembrolizumab or durvalumab/tremelimumab for neoadjuvant only |
|  Dr Moehler | Only with MTB decision; not resectable "palliative" disease CPS+; argue for chemotherapy + IO |
|  Dr Shah | Patients with advanced disease, ie, borderline resectable |
|  Dr Yoon | Most |
|  Dr Ajani | Per NCCN: Either nivolumab/ipilimumab → nivolumab, pembrolizumab or durvalumab/tremelimumab for neoadjuvant only |
|  Dr Kim | Nivolumab/ipilimumab as perioperative treatment |

MTB = molecular tumor board

## If you would attempt to access an anti-PD-1/PD-L1 antibody as part of neoadjuvant therapy for a patient with MSI-high gastroesophageal cancer, what would be your preferred regimen?

| | |
|---|---|
|  Dr Ilson | Single-agent nivolumab or pembrolizumab |
|  Dr Mehta | Pembrolizumab |
|  Dr Moehler | FLOT/nivolumab (CPS ≥5), FLOT/pembrolizumab (CPS ≥1) |
|  Dr Shah | FOLFOX/nivolumab or FOLFOX/pembrolizumab |
|  Dr Yoon | FOLFOX/nivolumab |
|  Dr Ajani | Nivolumab/ipilimumab |
|  Dr Kim | Nivolumab/ipilimumab |

# Immune Checkpoint Inhibitors in Localized Gastric Cancer

David H. Ilson, MD PhD FASCO FACP

Attending Physician, Member, Professor

Memorial Sloan Kettering Cancer Center

Weill Cornell Medical College

New York, NY

# Adjuvant Chemo is Effective in Gastric Cancer

- Pre and post op chemo
  - FLOT (FLOT-4)
- After D2 resection: Adjuvant Chemo
  - S-1 for 1 year (ACTS-GC)
  - CAPOX for 6 months (CLASSIC)
- After D2 resection: Stage III / Node Positive
  - Combination chemo is superior to S-1
    - Docetaxel + S-1 > S-1 Stage III (JACCRO GC-07)
    - 6 months of SOX > S-1 Node Positive (ARTIST 2)

JCO 29: 4387; 2011  Lancet Oncol 15: 1389; 2014 Gastric Cancer 25: 188; 2022  Ann Onc 32: 368; 2021 NEJM 355: 1; 2006 Lancet 393: 1948; 2019

# MSI high prognostic in Gastric Cancer, Surgery ± Chemo

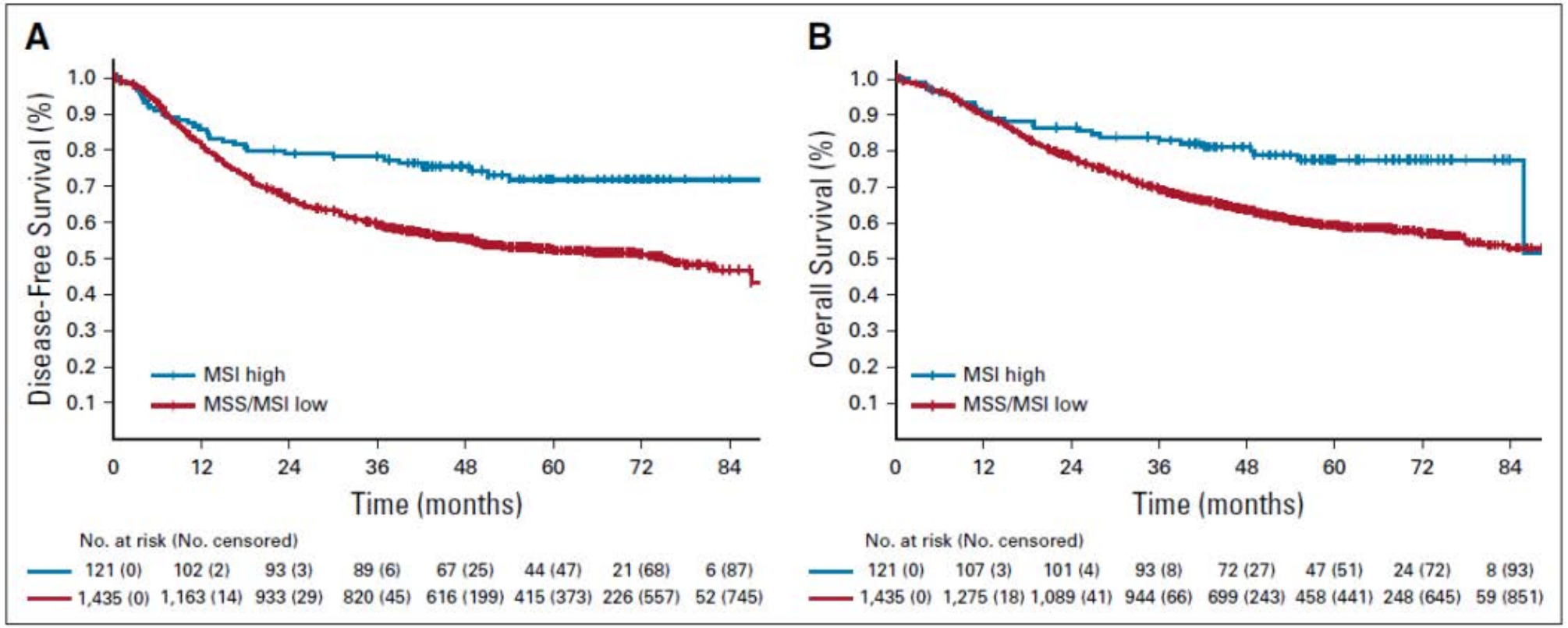



**FIG 2.** Kaplan-Meier curves of (A) disease-free survival and (B) overall survival according to microsatellite-instability (MSI) status (microsatellite stable [MSS]/MSI-low *v* MSI-high).

MAGIC, CLASSIC, ARTIST, ITACA-S

Smyth JCO 37: 3392; 2019

# Pooled Analysis: MSI High patients, Surgery ± Chemo

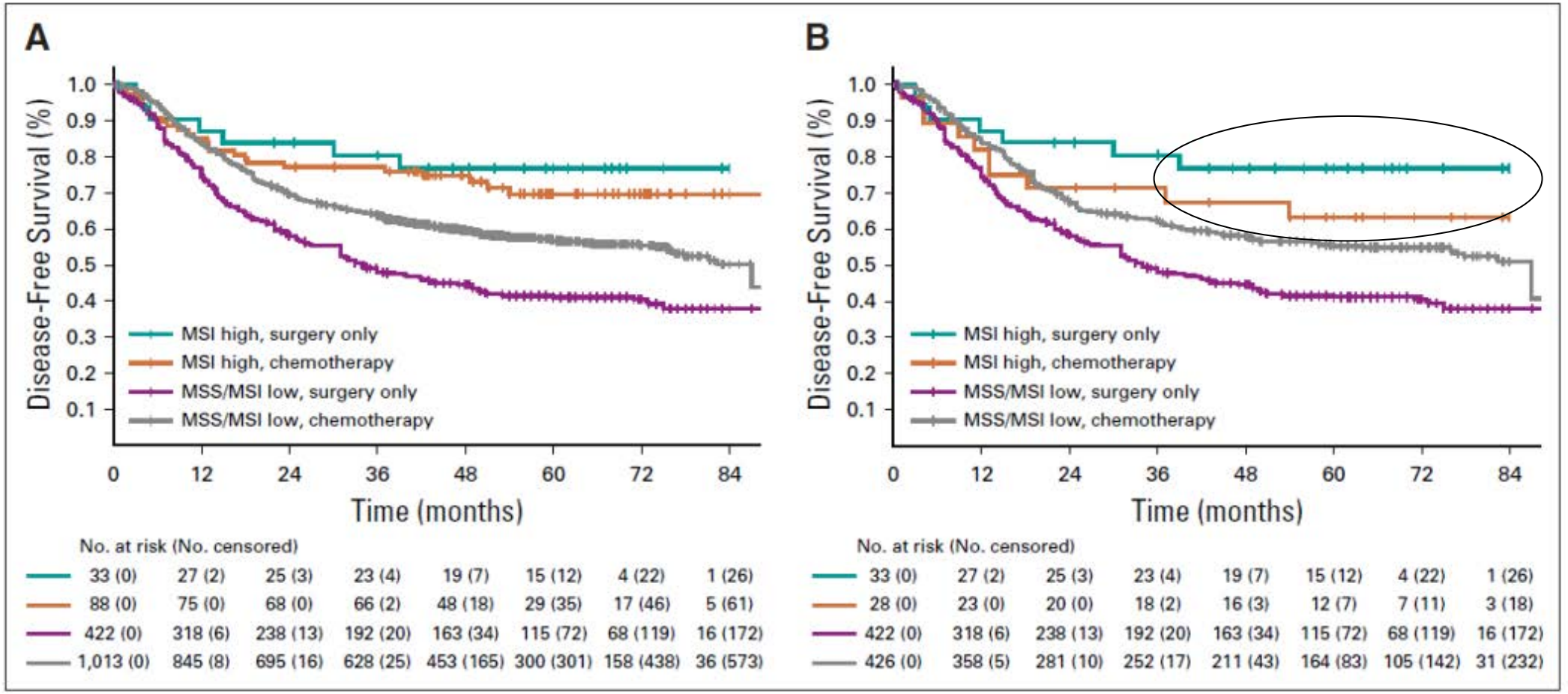
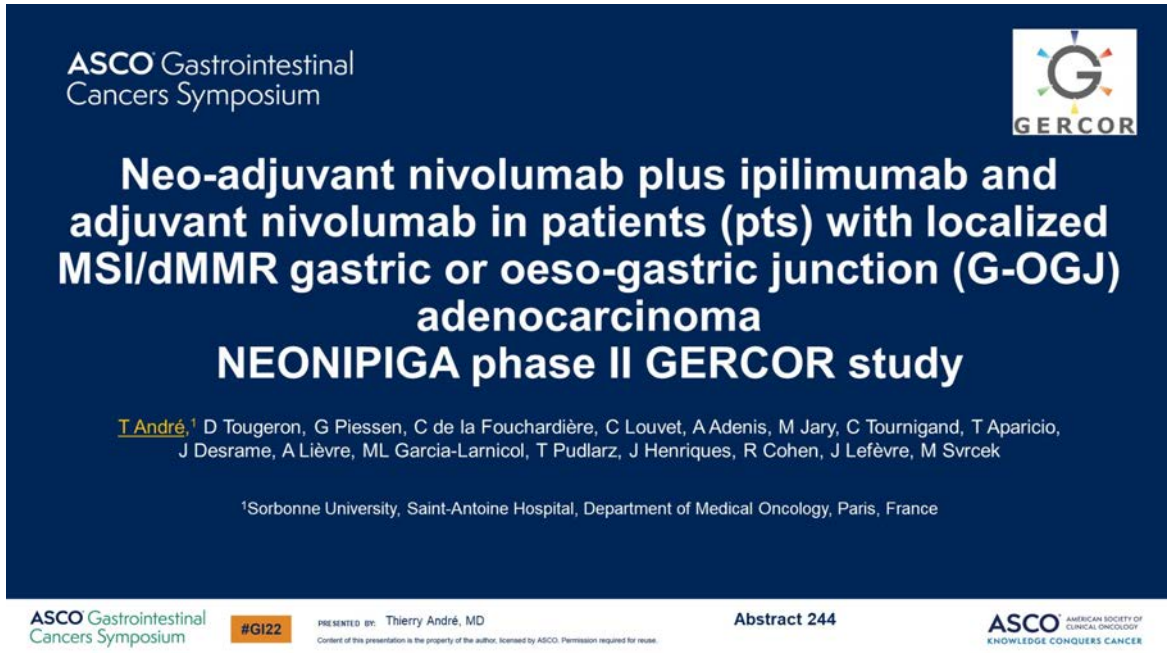



**FIG 3.** Kaplan-Meier curves of disease-free survival according to treatment (surgery plus chemotherapy *v* surgery only) and microsatellite-instability (MSI) status (MSI-high *v* microsatellite stable [MSS]/MSI-low) in (A) whole trial population and (B) MAGIC and CLASSIC trials only.

Surgery alone without chemo for MSI high patients

Smyth JCO 37: 3392; 2019

# Preoperative CPI therapy in MSI High Gastric Cancer




André T et al. ASCO GI 2022; Abstract 244.
André T et al. *J Clin Oncol* 2023;41(2):255-65.


Pietrantonio F et al. ASCO GI 2023; Abstract 358.

# Preoperative CPI therapy in MSI High Gastric Cancer

## Results (1): Surgery and TNM and Tumor Regression Grading (TRG)

| Type of surgery (N=29) | N | % |
|---|---|---|
| R0 | 29 | 100 |
| Total oesogastrectomy | 1 | 3,5 |
| Total gastrectomy | 7 | 24 |
| 4/5 gastrectomy | 9 | 31 |
| Lewis-Santy procedure | 11 | 38 |
| Pancreaticoduodenectomy | 1 | 3,5 |

| ypT stage (N=32) | |
|---|---|
| ypT0* | 19 |
| ypT1a | 1 |
| ypT1b | 2 |
| ypT2 | 2 |
| ypT3 | 5 |
| unknown** | 3 |
| **ypN stage (N=32)** | |
| ypN0 | 23 |
| ypN1 | 6 |
| unknown* | 3 |

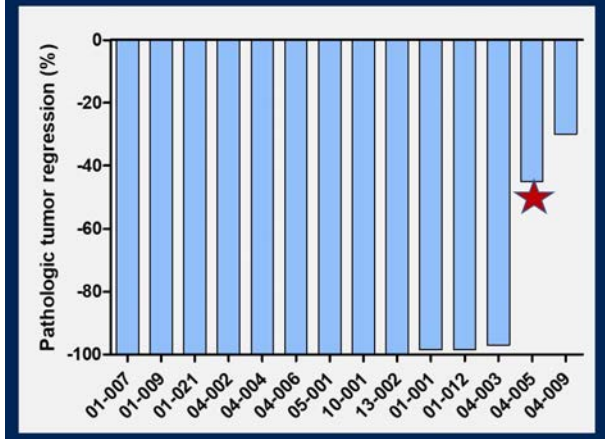
| TRG Mandard (N=29) | N | % |
|---|---|---|
| TRG 1: complete regression/fibrosis with no tumor cells | 17 | 58.6 |
| TRG 2: fibrosis with scattered tumor cells | 4 | 13.8 |
| TRG 3: fibrosis and tumor cells with a dominance of fibrosis | 2 | 6.9 |
| TRG 4: fibrosis & tumor cells with dominance of tumor cells | 4 | 13.8 |
| TRG 5: tumor without evidence of regression | 2 | 6.9 |
| **TRG Becker (N=29)** | | |
| TRG 1a: complete tumor regression without residual tumor | 17 | 58.6 |
| TRG 1b: < 10% residual tumor per tumor bed | 4 | 13.8 |
| TGR 2: 10% to 50% residual tumor | 2 | 6.9 |
| TRG 3: > 50% residual tumor cells | 6 | 21.7 |

- * 2 patients ypT0 and ypN1 (residual tumoral cells < 10% in only one node)
- ** 3 patients without surgery, 1 in metastatic PD and 2 in complete response in endoscopy with no tumoral cell on biopsy

ASCO Gastrointestinal Cancers Symposium #GI22 PRESENTED BY: Thierry André, MD Abstract 244 ASCO KNOWLEDGE CONQUERS CANCER

André T et al. ASCO GI 2022; Abstract 244.
André T et al. *J Clin Oncol* 2023;41(2):255-65.

## Primary endpoint




| TRG Becker | N = 15 | % |
|---|---|---|
| 1a | 9 | 60% |
| 1b | 3 | 20% |
| 3 | 2 | 13% |

*1 patient did not undergo surgery for PD*

Among evaluable patients, rate of pCR was 60% and rate of major to complete pathological response (<10% viable cells) was 80%.

★ Heterogeneous pMMR/dMMR status at surgery

ASCO Gastrointestinal Cancers Symposium #GI23 PRESENTED BY: Filippo Pietrantonio, MD ASCO KNOWLEDGE CONQUERS CANCER

Pietrantonio F et al. ASCO GI 2023; Abstract 358.

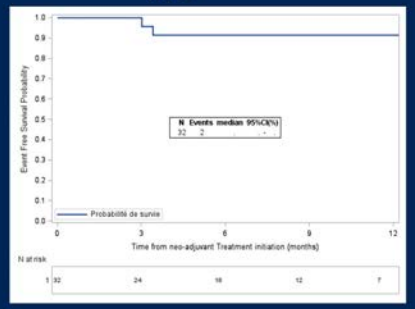
Pathologic CR 59% (17/29) and 60% (9/15), Near pCR 14-20%

# Preoperative CPI therapy in MSI High Gastric Cancer

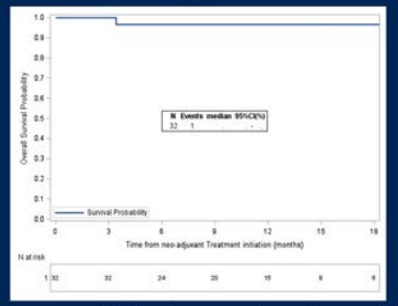
## Results (2)

- With a median follow-up of 12 months (95%CI: 7.8-14.2), 2 patients had events (death or relapse)
  - one death at day 3 post surgery*
  - one progressive disease with metastatic disease PD after 6 cycles (surgery not performed)
  - 31 patients alive and 30 without relapse

EFS



OS



* History of severe cardio vascular co-morbidity and sudden death

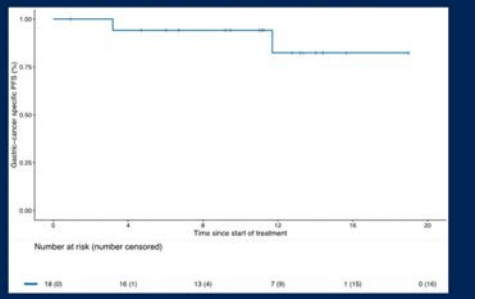
ASCO Gastrointestinal Cancers Symposium #GI22 — Abstract 244 — ASCO KNOWLEDGE CONQUERS CANCER

André T et al. ASCO GI 2022; Abstract 244.
André T et al. *J Clin Oncol* 2023;41(2):255-65.

## Survival endpoints

| | PFS event | OS event | |
|---|---|---|---|
| 01-020 | Yes | No | CR to CAPOX |
| 04-005 | Yes | Yes | Heterogeneous pMMR/dMMR status |
| 13-002 | No | Yes | Late postoperative complications |
| 01-009 | No | Yes | Late postoperative complications |
| 05-001 | No | Yes | Second primary brain cancer |

Gastric cancer-specific PFS



Data cutoff date: 16th December 2022, with a median follow up of 13.4 (IQR 9.7-14.2) months

ASCO Gastrointestinal Cancers Symposium #GI23 — ASCO KNOWLEDGE CONQUERS CANCER

Pietrantonio F et al. ASCO GI 2023; Abstract 358.

# High Rates of pCR: Nonoperative Management?

# Immunotherapy Neoadjuvant/Adjuvant Trials

- **ATTRACTION-5: Nivolumab + Post op S-1 or CAPE-OX: Negative trial**
- **CheckMate 577: Nivolumab post op after chemo, RT, surgery: Positive trial**
- **KEYNOTE-585: Pembro + Perioperative Cape or 5-FU cisplatin: Negative trial**
- **MATTERHORN: Durvalumab + Perioperative FLOT**
- **Other European Trials**
  - AIO DANTE: FLOT ± Atezolizumab
  - EORTC VESTIGE: post op Ipi/Nivo vs Chemo in high risk patients: Ipi/Nivo inferior

Lorenzen JCO EPUP 2023; Smyth Ann Onc 2023

2023 ASCO ANNUAL MEETING

ADJUVANT NIVOLUMAB?

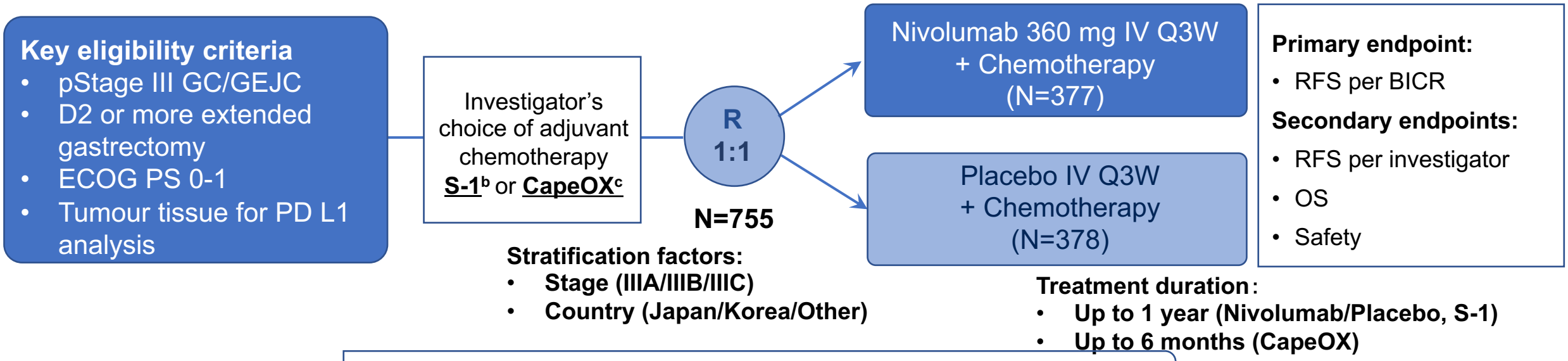
# ATTRACTION-5: A Phase 3 study of nivolumab plus chemotherapy as postoperative adjuvant treatment for pathological stage III gastric or gastroesophageal junction cancer

Masanori Terashima[1], Yoon-Koo Kang[2], Young-Woo Kim[3], Narikazu Boku[4], Hyun Cheol Chung[5], Jen-Shi Chen[6], Jiafu Ji[7], Ta-Sen Yeh[8], Li-Tzong Chen[9], Min-Hee Ryu[2], Jong Gwang Kim[10], Takeshi Omori[11], Sun-Young Rha[5], Tae Yong Kim[12], Keun Won Ryu[3], Shinichi Sakuramoto[13], Yasunori Nishida[14], Norimasa Fukushima[15], Takanobu Yamada[16], Mitsuru Sasako[17]

[1]Shizuoka Cancer Center, Japan; [2]Asan Medical Center, Republic of Korea; [3]National Cancer Center, Republic of Korea; [4]The Institute of Medical Science, The University of Tokyo, Japan; [5]Yonsei Cancer Center, Yonsei University Health System, Republic of Korea; [6]Linkou Chang Gung Memorial Hospital, Taiwan; [7]Beijing Cancer Hospital, China; [8]Chang Gung Memorial Hospital, Taiwan; [9]Kaohsiung Medical University Hospital, Taiwan; [10]Kyungpook National University Chilgok Hospital, Republic of Korea; [11]Osaka International Cancer Institute, Japan; [12]Seoul National University Hospital, Republic of Korea; [13]Saitama Medical University International Medical Center, Japan; [14]Keiyukai Sapporo Hospital, Japan; [15]Yamagata Prefectural Central Hospital, Japan; [16]Kanagawa Cancer Center, Japan; [17]Yodogawa Cristian Hospital, Japan

# Study design

- Phase 3, double-blind, placebo-controlled study of Asian patients (Japan, Korea, Taiwan, China)[a]

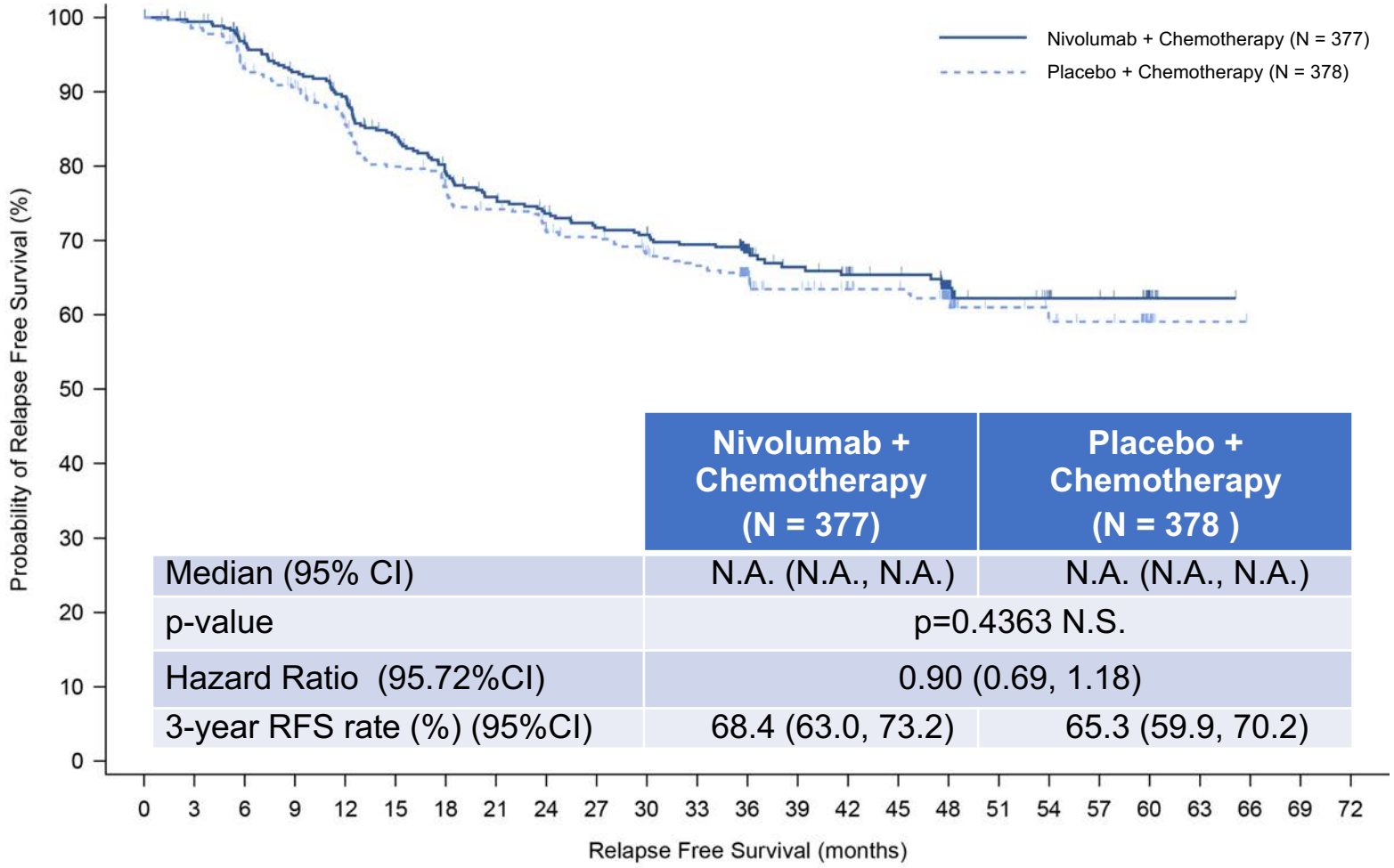



- Planned sample size: 700 patients (assuming HR=0.67; 3-year RFS, 71% vs 60%)
- Patients were randomized from February 2017 to August 2019
- All data are based on a clinical data cutoff of August 2022, at which point the minimum follow-up after the last patient randomized was 36 months

[a]ClinicalTrials.gov number, NCT03006705; [b]**S-1 therapy:** S-1 40 mg/m$^2$/dose orally twice daily (day1-28) , Q6W; [c]**CapeOX therapy:** Oxaliplatin 130 mg/m$^2$ IV once daily (day1), and Capecitabine 1000 mg/m$^2$/dose orally twice daily (day1-14), Q3W.

Abbreviations: BICR, blinded independent central review; CapeOX, capecitabine/oxaliplatin; GC, gastric cancer; GEJC, gastroesophageal junction cancer; IV, intravenous; Q3W, every 3 weeks; Q6W, every 6 weeks; S-1, tegafur/gimeracil/oteracil; BICR, blinded independent central review

# Primary endpoint: RFS per BICR



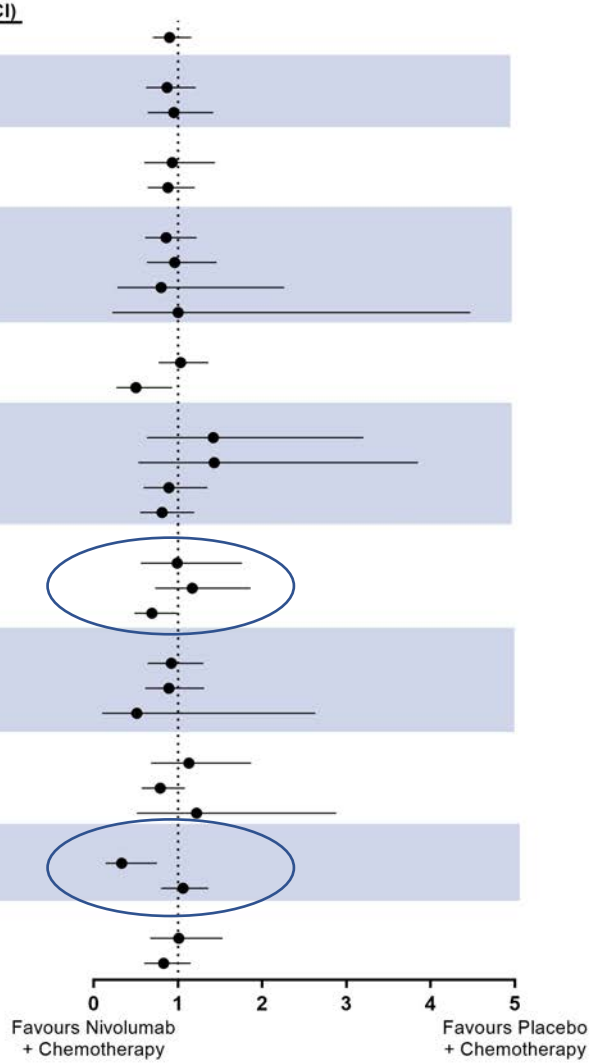

| | Nivolumab + Chemotherapy (N = 377) | Placebo + Chemotherapy (N = 378 ) |
|---|---|---|
| Median (95% CI) | N.A. (N.A., N.A.) | N.A. (N.A., N.A.) |
| p-value | p=0.4363 N.S. | |
| Hazard Ratio (95.72%CI) | 0.90 (0.69, 1.18) | |
| 3-year RFS rate (%) (95%CI) | 68.4 (63.0, 73.2) | 65.3 (59.9, 70.2) |

At Risk

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab + Chemotherapy | 377 | 349 | 326 | 310 | 297 | 273 | 255 | 241 | 231 | 223 | 219 | 214 | 162 | 127 | 120 | 114 | 58 | 33 | 28 | 24 | 9 | 1 | 0 | 0 | 0 |
| Placebo + Chemotherapy | 378 | 353 | 324 | 311 | 288 | 267 | 254 | 242 | 228 | 223 | 212 | 204 | 148 | 118 | 110 | 107 | 57 | 33 | 30 | 26 | 10 | 1 | 0 | 0 | 0 |

# RFS per BICR in subgroups

| | Nivolumab + Chemotherapy No. of events | Placebo + Chemotherapy No. of events | Unstratified HR (95%CI) |
|---|---|---|---|
| **Overall** | 113/377 | 124/378 | 0.90 (0.70-1.16) |
| **Age** | | | |
| <65 years | 63/212 | 78/222 | 0.87 (0.62-1.21) |
| ≥65years | 50/165 | 46/156 | 0.95 (0.64-1.42) |
| **Sex** | | | |
| Female | 39/110 | 43/115 | 0.93 (0.60-1.44) |
| Male | 74/267 | 81/263 | 0.88 (0.64-1.20) |
| **Country** | | | |
| Japan | 60/182 | 67/183 | 0.86 (0.61-1.22) |
| Korea | 44/157 | 44/155 | 0.96 (0.63-1.46) |
| Taiwan | 6/23 | 9/24 | 0.80 (0.28-2.26) |
| China | 3/15 | 4/16 | 1.00 (0.22-4.47) |
| **ECOG PS** | | | |
| 0 | 98/299 | 95/294 | 1.03 (0.77-1.36) |
| 1 | 15/78 | 29/84 | 0.50 (0.27-0.93) |
| **Primary sites** | | | |
| GEJ | 10/21 | 14/31 | 1.42 (0.63-3.20) |
| Gastric fundus | 9/26 | 7/25 | 1.43 (0.53-3.85) |
| Gastric corpus | 44/161 | 46/154 | 0.89 (0.59-1.35) |
| Gastric antrum and pylorus | 50/169 | 57/168 | 0.81 (0.55-1.19) |
| **Pathological stage** | | | |
| IIIA | 23/110 | 24/111 | 0.99 (0.56-1.76) |
| IIIB | 37/127 | 33/129 | 1.17 (0.73-1.86) |
| IIIC | 53/140 | 67/138 | 0.69 (0.48-0.99) |
| **Type of surgery** | | | |
| Total gastrectomy | 61/164 | 64/164 | 0.92 (0.64-1.30) |
| Distal gastrectomy | 50/204 | 55/199 | 0.89 (0.61-1.31) |
| Others | 2/9 | 5/15 | 0.51 (0.10-2.63) |
| **Histology** | | | |
| Intestinal type | 31/134 | 29/140 | 1.13 (0.68-1.87) |
| Diffuse type | 71/213 | 83/209 | 0.79 (0.57-1.08) |
| Others | 11/30 | 10/26 | 1.22 (0.51-2.88) |
| **Tumor cell PD-L1 expression** | | | |
| ≥1% | 9/52 | 15/34 | 0.33 (0.14-0.75) |
| <1% | 103/309 | 106/333 | 1.06 (0.81-1.40) |
| **Chemotherapy regimen** | | | |
| S-1 | 46/132 | 45/135 | 1.01 (0.67-1.53) |
| CapeOX | 67/245 | 79/243 | 0.83 (0.60-1.15) |



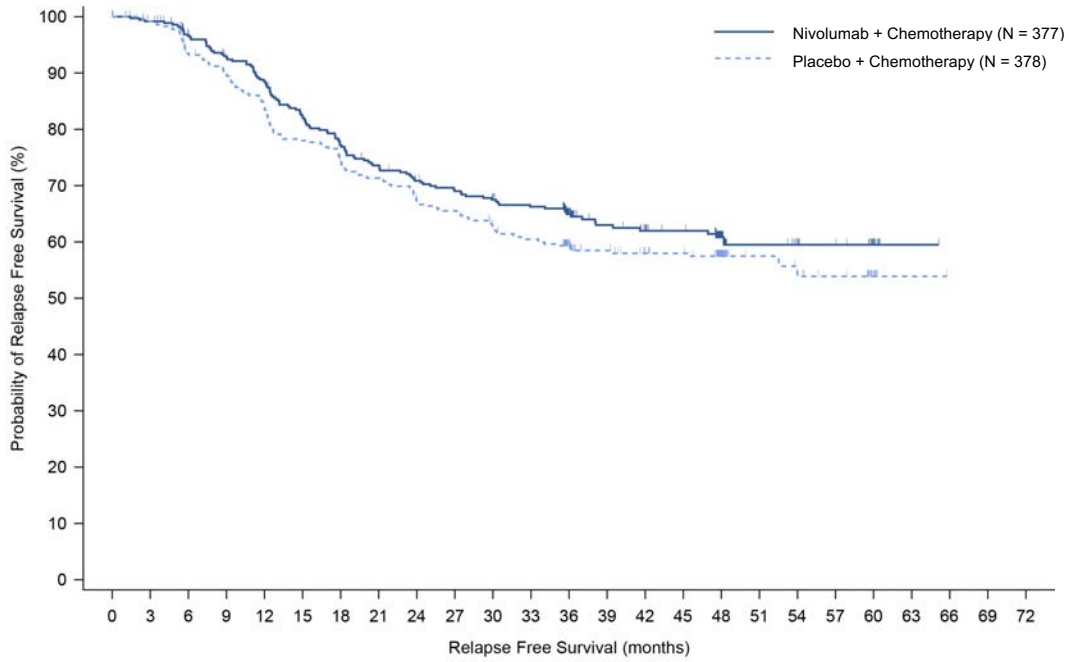

TPS ≥ 1% 14%

60-80% of TPS negative will be CPS Positive

MSI not studied

# Secondary endpoints: RFS per investigator and OS

## RFS per investigator

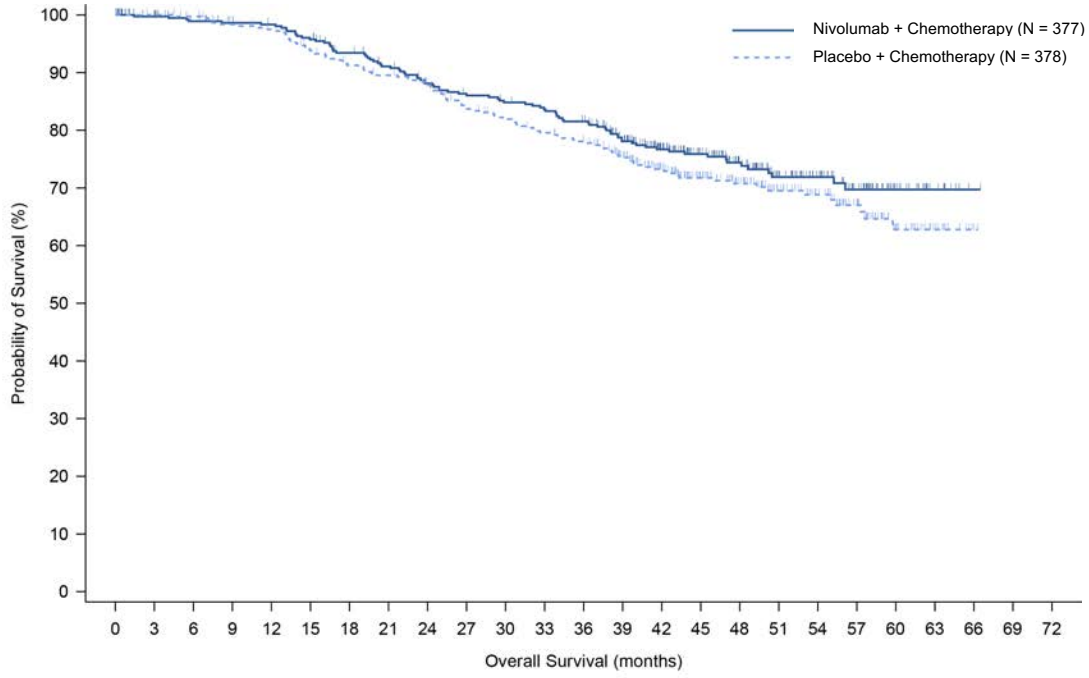



At Risk

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab + Chemotherapy | 377 | 349 | 328 | 313 | 298 | 275 | 257 | 244 | 233 | 226 | 219 | 213 | 159 | 125 | 118 | 112 | 57 | 32 | 27 | 23 | 8 | 1 | 0 | 0 | 0 |
| Placebo + Chemotherapy | 378 | 354 | 326 | 312 | 290 | 271 | 256 | 246 | 230 | 225 | 213 | 204 | 148 | 119 | 110 | 107 | 58 | 33 | 30 | 26 | 10 | 1 | 0 | 0 | 0 |

| | Nivolumab + Chemotherapy (N = 377) | Placebo + Chemotherapy (N= 378 ) |
|---|---|---|
| Median (95% CI) | N.A. (N.A., N.A.) | N.A. (52.53, N.A.) |
| p-value | – | |
| Hazard ratio (95%CI) | 0.87 (0.69, 1.11) | |
| 3-year RFS rate (%) (95%CI) | 64.9 (59.5, 69.8) | 59.3 (54.0, 64.3) |

## OS




At Risk

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab + Chemotherapy | 377 | 368 | 356 | 347 | 343 | 334 | 320 | 309 | 296 | 289 | 283 | 278 | 270 | 244 | 203 | 166 | 131 | 101 | 79 | 57 | 27 | 9 | 1 | 0 | 0 |
| Placebo + Chemotherapy | 378 | 367 | 364 | 352 | 345 | 329 | 318 | 311 | 304 | 285 | 277 | 267 | 259 | 236 | 199 | 160 | 132 | 104 | 85 | 60 | 30 | 12 | 2 | 0 | 0 |

| | Nivolumab + Chemotherapy (N = 377) | Placebo + Chemotherapy (N = 378 ) |
|---|---|---|
| Median (95% CI) | N.A. (N.A., N.A.) | N.A. (N.A., N.A.) |
| p-value | – | |
| Hazard ratio (95%CI) | 0.88 (0.66, 1.17) | |
| 3-year OS rate (%) (95%CI) | 81.5 (77.0, 85.3) | 78.0 (73.3, 82.1) |

# CheckMate 577: Positive Trial for Adjuvant Nivolumab after CRT/Surgery in ESO/GEJ AC and SCC

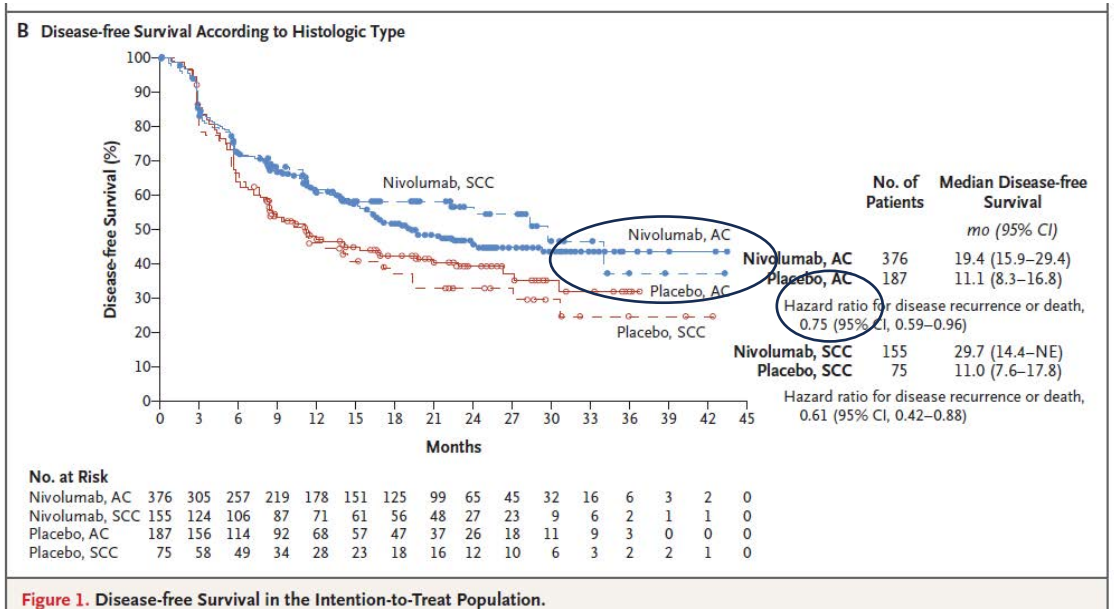



Figure 1. Disease-free Survival in the Intention-to-Treat Population.

| | | | | |
|---|---|---|---|---|
| Tumor-cell PD-L1 expression | | | | |
| ≥1% | 129 | 19.7 | 14.1 | 0.75 (0.45–1.24) |
| <1% | 570 | 21.3 | 11.1 | 0.73 (0.57–0.92) |
| Indeterminate or could not be evaluated | 95 | Not reached | 9.5 | 0.54 (0.27–1.05) |
| **PD-L1 CPS expression** | | | | |
| ≥5 (n = 371) | | 29.4 | 10.2 | 0.62 (0.46–0.83) |
| <5 (n = 295) | | 16.3 | 11.1 | 0.89 (0.65–1.22) |
| Tumor location at trial entry | | | | |
| Esophagus | 462 | 24.0 | 8.3 | 0.61 (0.47–0.78) |
| Gastroesophageal junction | 332 | 22.4 | 20.6 | 0.87 (0.63–1.21) |

72% TPS negative
47% CPS ≥ 5%

Kelly RJ et al. *N Engl J Med* 2021;384(13):1191-1203.

# CheckMate 577: Safety Profile

**Table 2. Adverse Events in the Safety Population.***

| Event | Nivolumab (N = 532) | | Placebo (N = 260) | |
|---|---|---|---|---|
| | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 |
| | *number of patients with event (percent)* | | | |
| Any adverse event† | 510 (96) | 183 (34) | 243 (93) | 84 (32) |
| Serious adverse event | 158 (30) | 107 (20) | 78 (30) | 53 (20) |
| Adverse event leading to discontinuation of trial regimen | 68 (13) | 38 (7) | 20 (8) | 16 (6) |
| Any adverse event related to nivolumab or placebo†‡ | 376 (71) | 71 (13) | 119 (46) | 15 (6) |
| Serious adverse event related to nivolumab or placebo‡ | 40 (8) | 29 (5) | 7 (3) | 3 (1) |
| Related adverse event leading to discontinuation of trial regimen‡ | 48 (9) | 26 (5) | 8 (3) | 7 (3) |
| Adverse event related to nivolumab or placebo in ≥5% of patients in either group† | | | | |
| Fatigue | 90 (17) | 6 (1) | 29 (11) | 1 (<1) |
| Diarrhea | 88 (17) | 2 (<1) | 39 (15) | 2 (<1) |
| Pruritus | 53 (10) | 2 (<1) | 9 (3) | 0 |
| Rash | 52 (10) | 4 (<1) | 10 (4) | 1 (<1) |
| Hypothyroidism | 50 (9) | 0 | 4 (2) | 0 |
| Nausea | 47 (9) | 0 | 13 (5) | 0 |
| Hyperthyroidism | 35 (7) | 0 | 1 (<1) | 0 |
| Arthralgia | 30 (6) | 1 (<1) | 4 (2) | 0 |
| Increase in AST level | 29 (5) | 2 (<1) | 10 (4) | 0 |
| Asthenia | 28 (5) | 0 | 4 (2) | 0 |
| Decreased appetite | 26 (5) | 0 | 5 (2) | 0 |

Kelly RJ et al. *N Engl J Med* 2021;384(13):1191-203.

# Preoperative CPI Improves Path CR: Phase 2

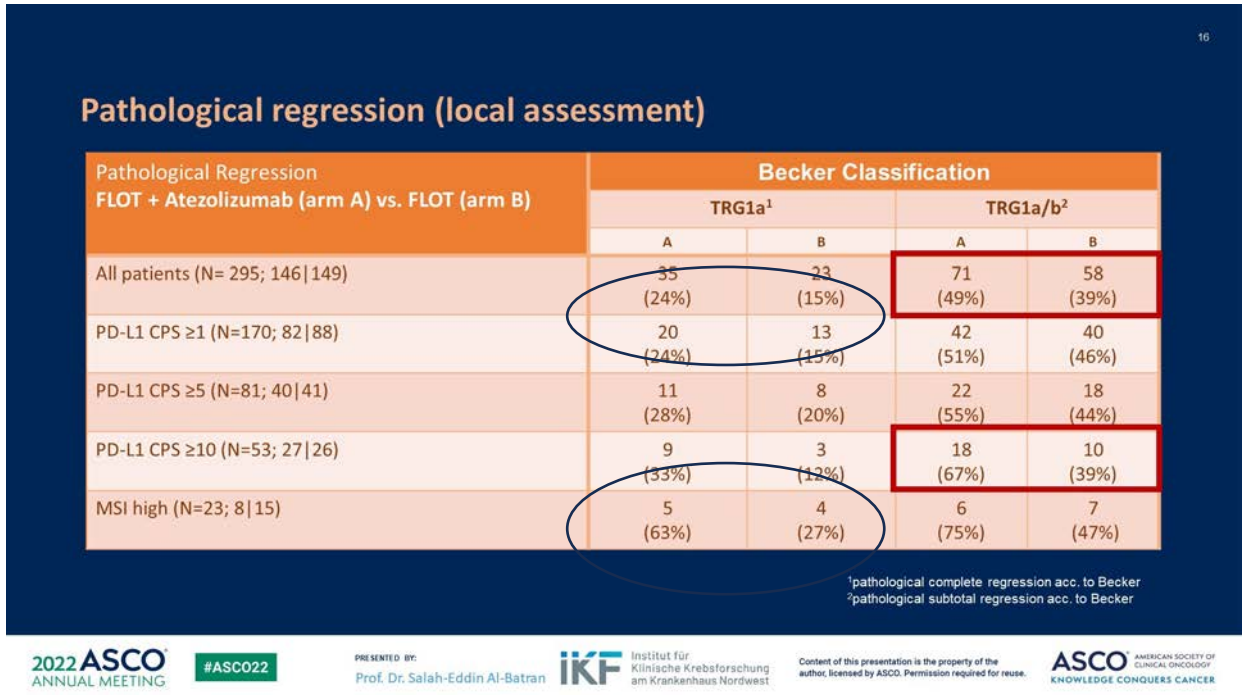


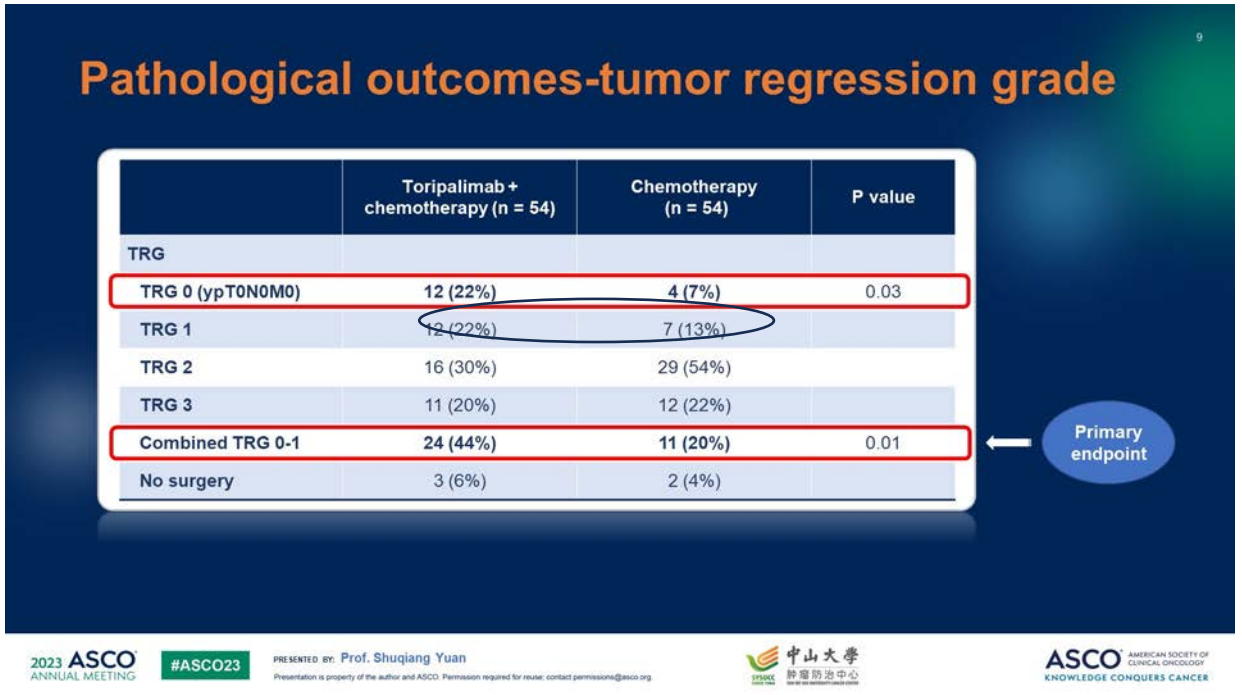




Al-Batran et al. ASCO 2022; Abstract 4003.
Lorenzen S et al. J Clin Oncol 2023; November 14 [Online ahead of print].
Yuan et al. ASCO 2023; Abstract 4001.

# Preoperative CPI Improves Path CR



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Al-Batran et al. ASCO 2022; Abstract 4003.
Lorenzen S et al. J Clin Oncol 2023; November 14 [Online ahead of print].
Yuan et al. ASCO 2023; Abstract 4001.

# KEYNOTE-585: Preop CF/FLOT ± Pembrolizumab

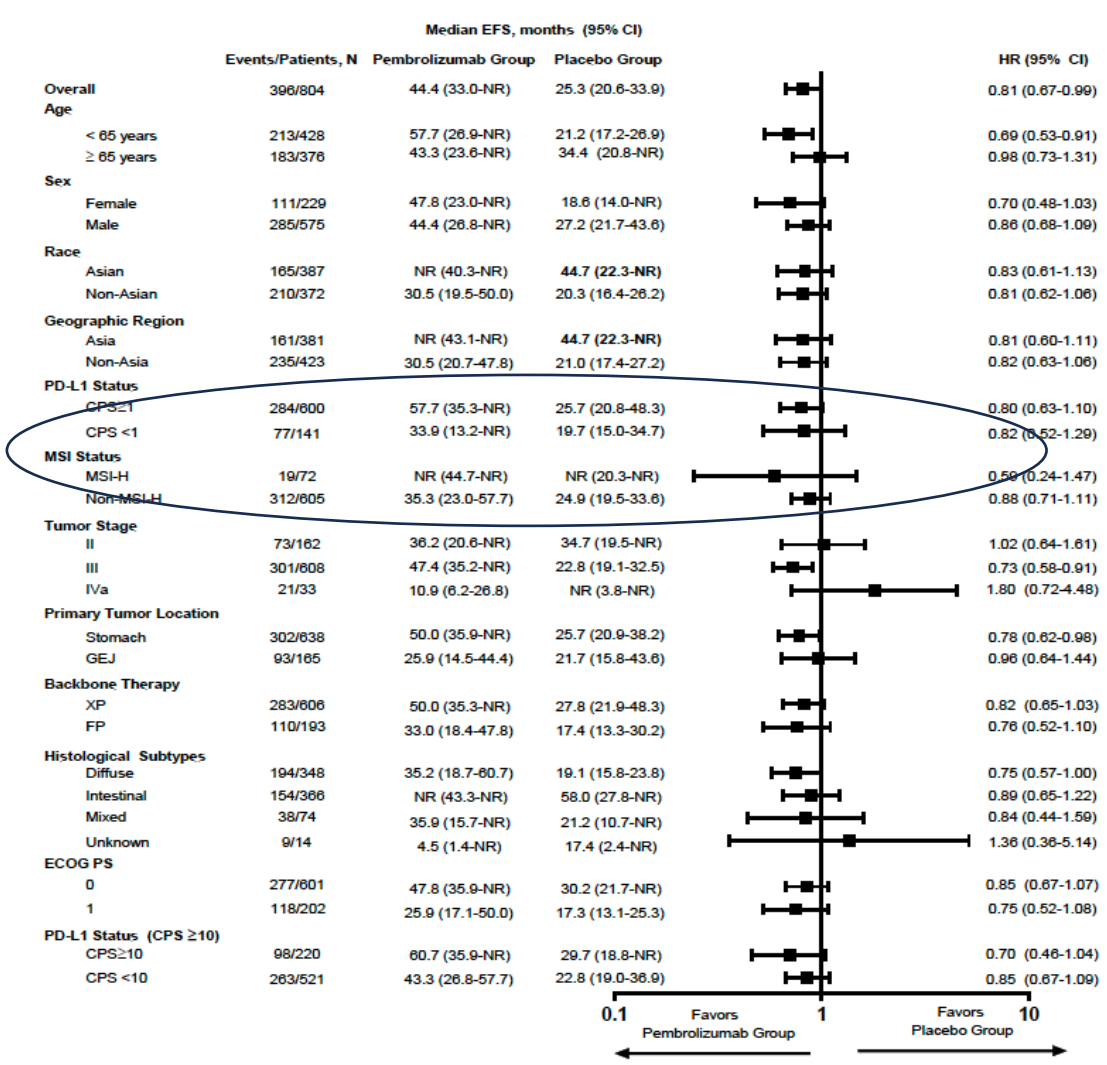
- Over 1000 patients, 80% gastric , 75% CPS ≥ 1%
  - 9% MSI high
- Most received CF, 20% FLOT
- Co-primary endpoints of EFS and OS, pathologic CR
- Improved pCR with pembrolizumab: 13.0 % vs 2.4%
  - CF: 12.9% vs 2.0%
  - CF + FLOT: 13.0% vs 2.4%
- Trend toward improved EFS, non-significant for pembrolizumab
  - CF + FLOT: 45.8 months vs 25.7 months (HR 0.81)
  - No difference in CF, combined FLOT cohorts
- No difference in OS
  - CF: 60.7 months vs 58.0 months (HR 0.90)
  - CF + FLOT: 60.7 months vs median not reached (HR 0.93)
- Supplement:  Differences driven by MSI high patients

Shitara K et al. *Lancet Oncol* 2023; December 19 [Online ahead of print].

# MSI STATUS DRIVES EFS DIFFERENCES

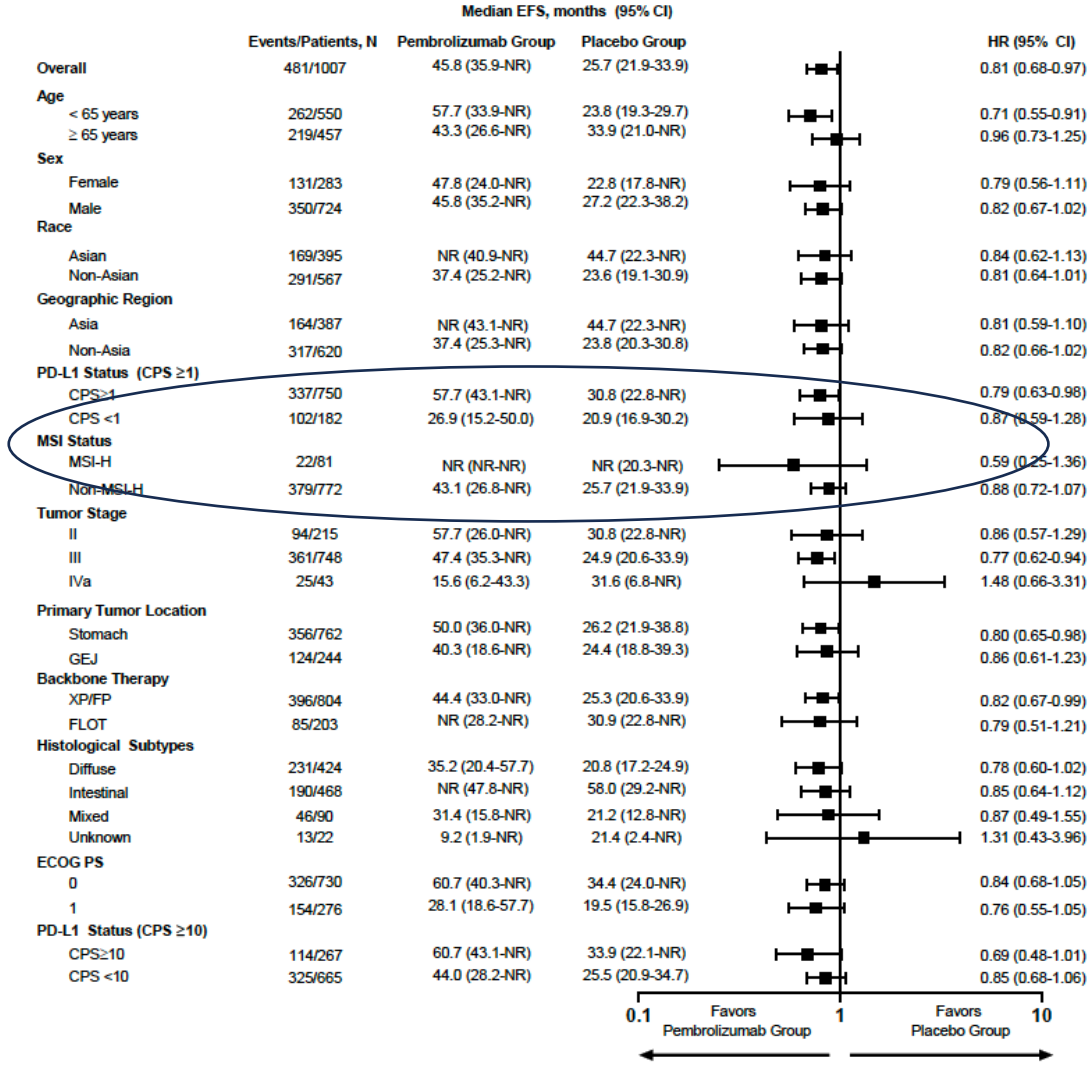
## CF Cohort

**Figure S3.** Forest plot of event-free survival across pre-specified subgroups in the main cohort



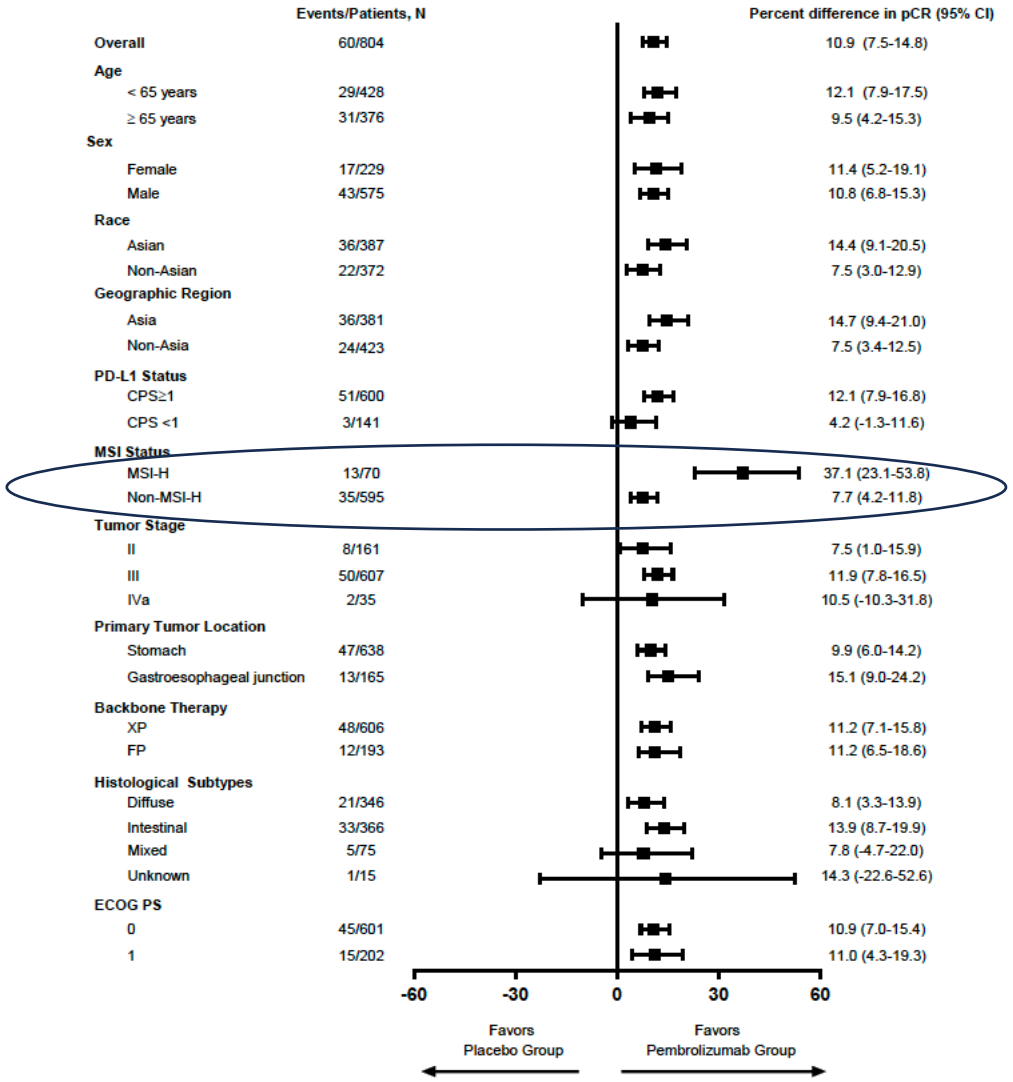

## CF + FLOT Cohort

**Figure S4.** Forest plot of event-free survival across pre-specified subgroups in the main plus FLOT cohort




Shitara K et al. *Lancet Oncol* 2023; December 19 [Online ahead of print].

**Figure S2.** Forest plot of difference in pathological complete response across pre-specified subgroups in the main cohort



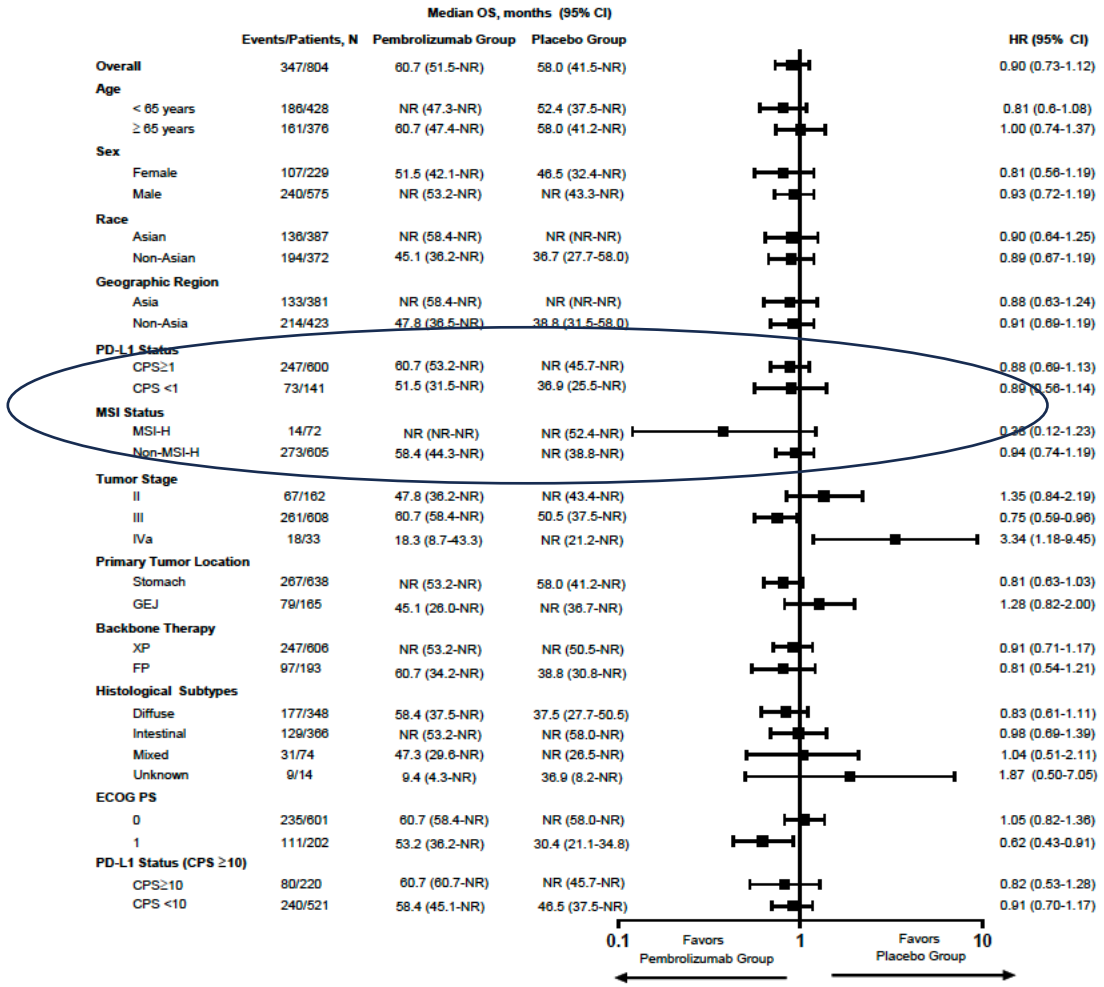

# MSI Status Drives Increased Path CR Rate

Shitara K et al. *Lancet Oncol* 2023; December 19 [Online ahead of print].

# MSI STATUS DRIVES OS DIFFERENCES

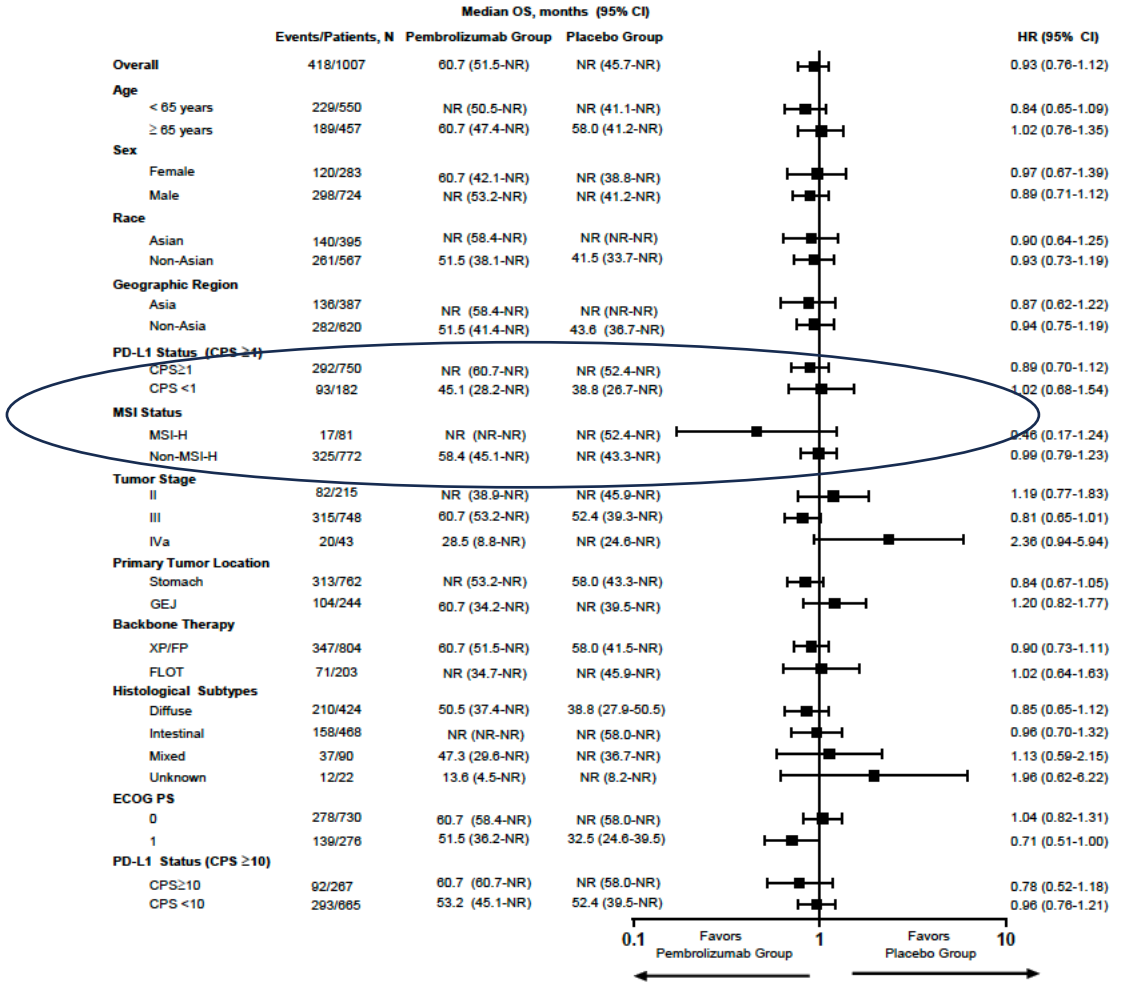
## CF Cohort

**Figure S5.** Forest plot of overall survival across pre-specified subgroups in the main cohort




## CF + FLOT Cohort

**Figure S6.** Forest plot of overall survival across pre-specified subgroups in the main plus FLOT cohort

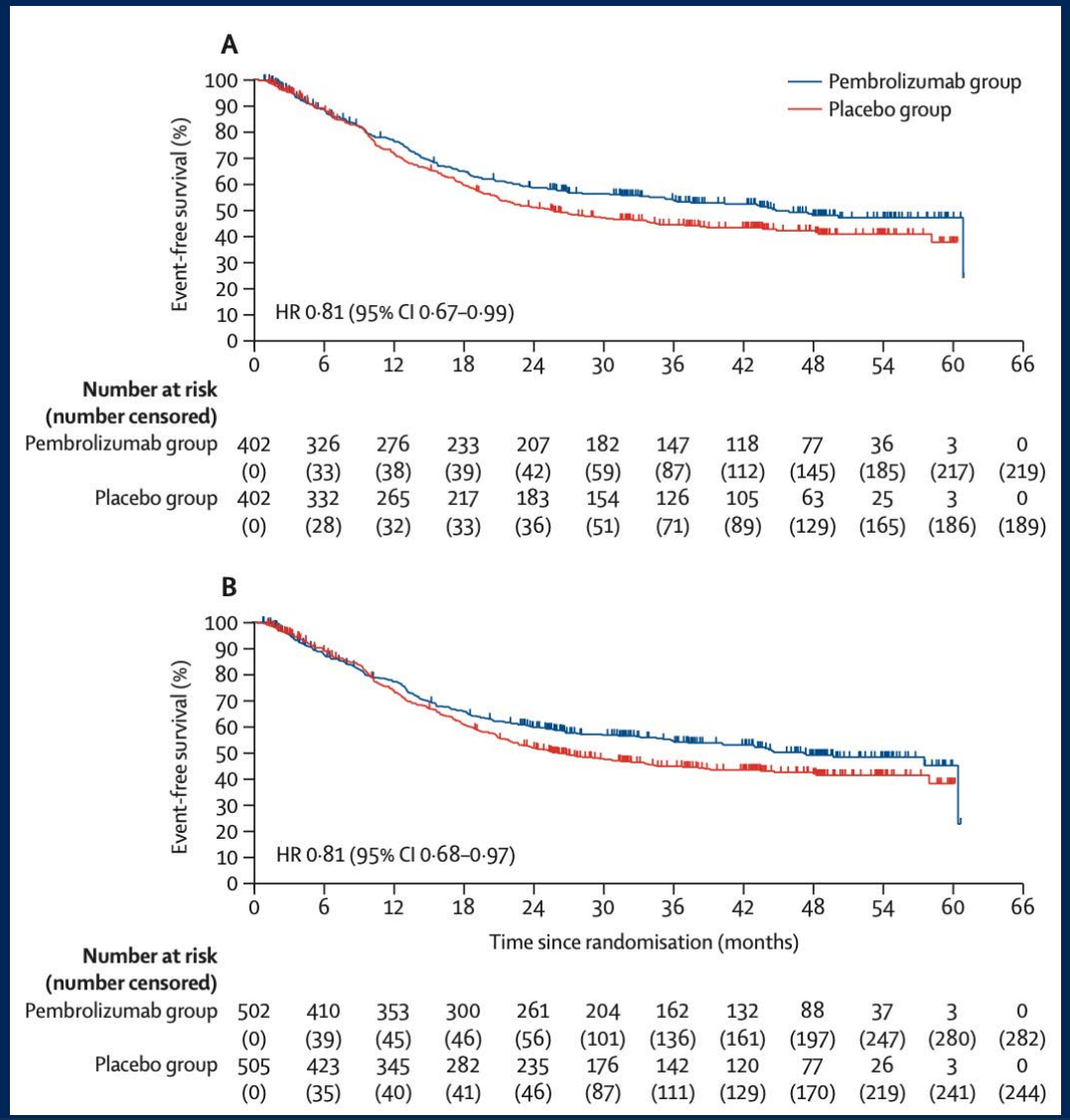


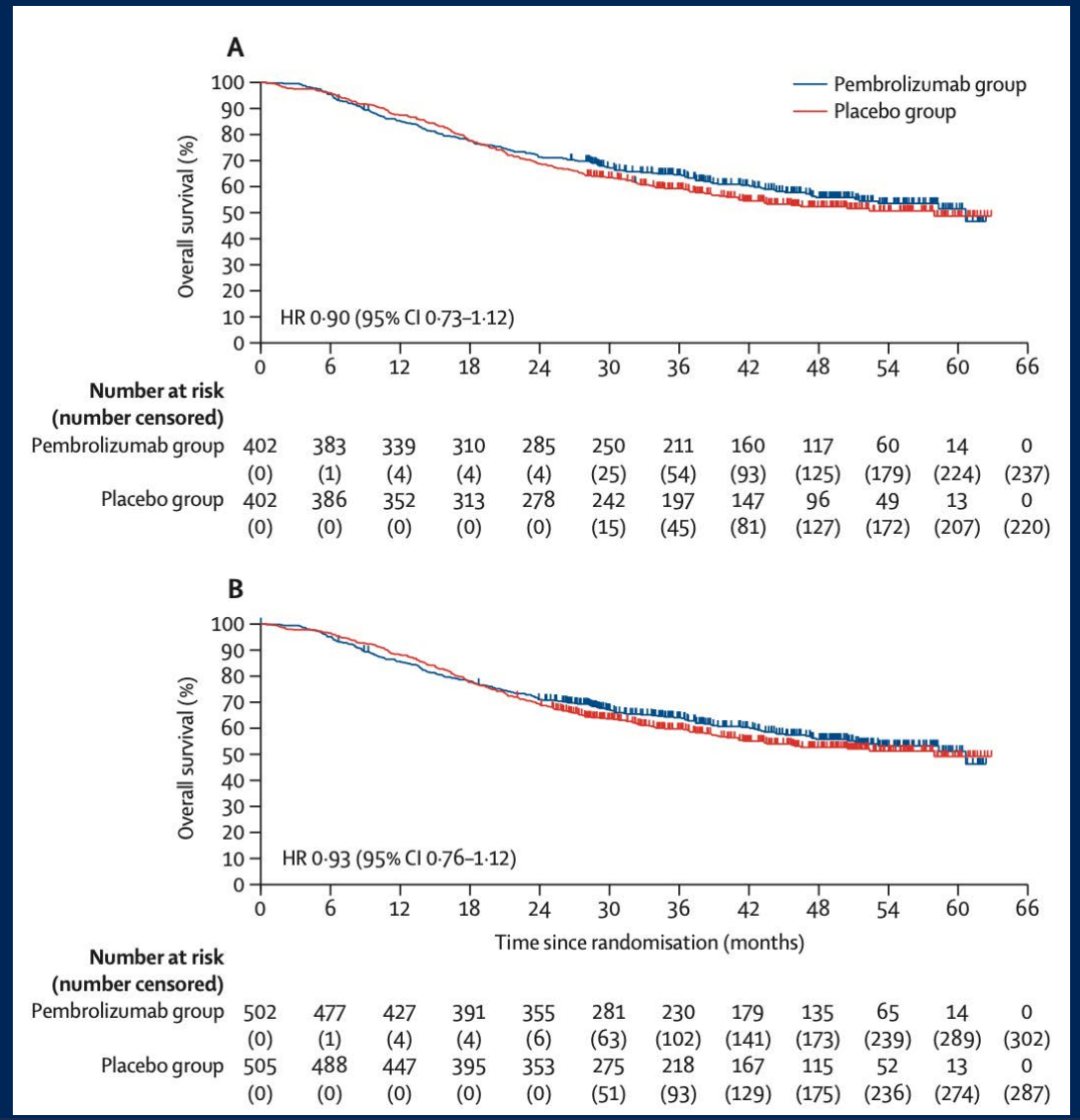

Shitara K et al. *Lancet Oncol* 2023; December 19 [Online ahead of print].

# KEYNOTE-585: Preop CF/FLOT +/- Pembrolizumab

CF

CF + FLOT




EFS

OS

Shitara K et al. *Lancet Oncol* 2023; December 19 [Online ahead of print].

# Methods

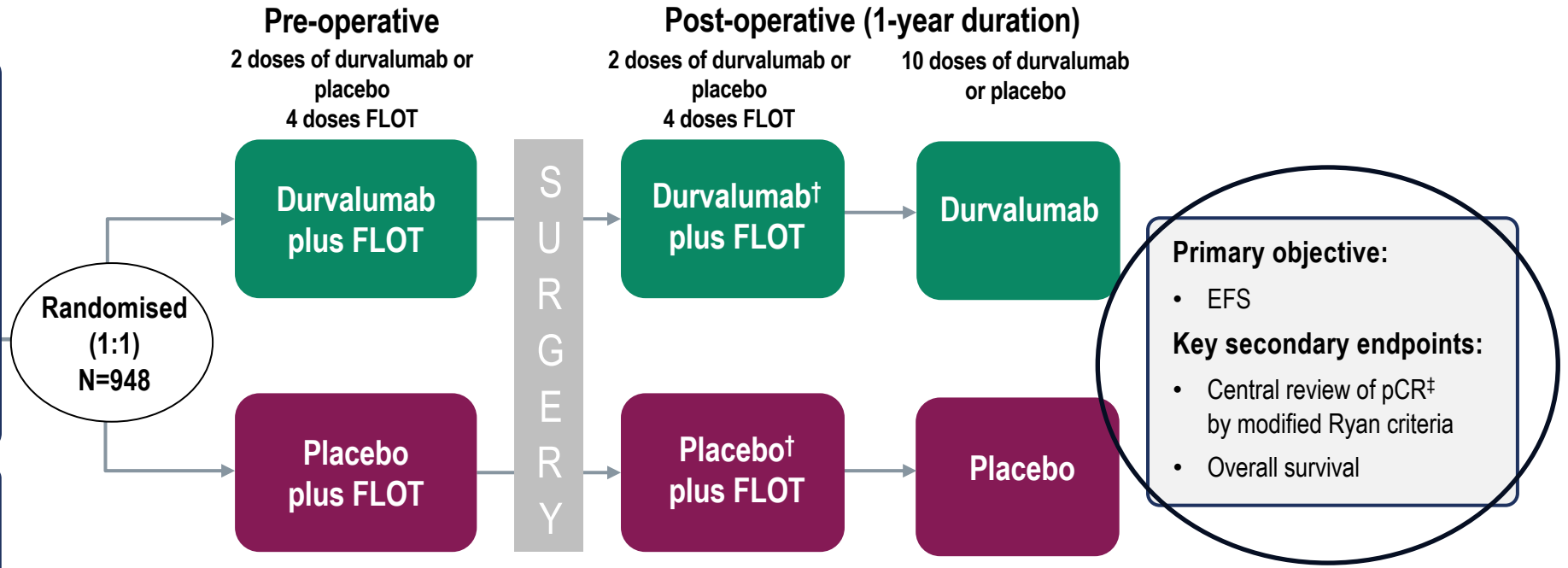
MATTERHORN is a global, Phase 3, randomised, double-blind, placebo-controlled study

**Study population**

- Gastric and GEJ adenocarcinoma
- Stage II, III and IVA (>T2 N0-3 M0 or T0-4 N+ M0)
- No evidence of metastasis
- No prior therapy
- ECOG PS 0 or 1
- Global enrolment from Asia, Europe, North America and South America

**Stratification factors**

- Geographic region: Asia versus non-Asia
- Clinical lymph node status: positive versus negative
- PD-L1 status: TAP <1% versus TAP ≥1%*




Durvalumab 1500 mg or placebo Q4W (Day 1) plus FLOT Q2W (Days 1 and 15) for 4 cycles (2 doses of durvalumab or placebo plus 4 doses of FLOT pre- and post-operative) followed by durvalumab or placebo Q4W (Day 1) for 10 further cycles

*Measured by VENTANA PD-L1 (SP263) assay. †Durvalumab or placebo monotherapy may be continued if post-operative FLOT is discontinued due to toxicity. ‡pCR was scored using modified Ryan criteria by central review.
FLOT: 5-fluorouracil 2600 mg/m², oxaliplatin 85 mg/m², docetaxel 50 mg/m², leucovorin 200 mg/m² on Days 1 and 15 Q4W, 2 doses (two cycles) pre- and post-operative; durvalumab: 1500 mg on Day 1 Q4W, 2 doses (two cycles) of durvalumab or placebo pre- and post-operative.
ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; GEJ, gastro-oesophageal junction; PD-L1, programmed cell death-ligand 1; PS, performance status; pCR, pathological complete response; PD-L1, programmed cell death ligand-1; Q2W, every 2 weeks; Q4W, every 4 weeks; TAP, tumour area positivity.

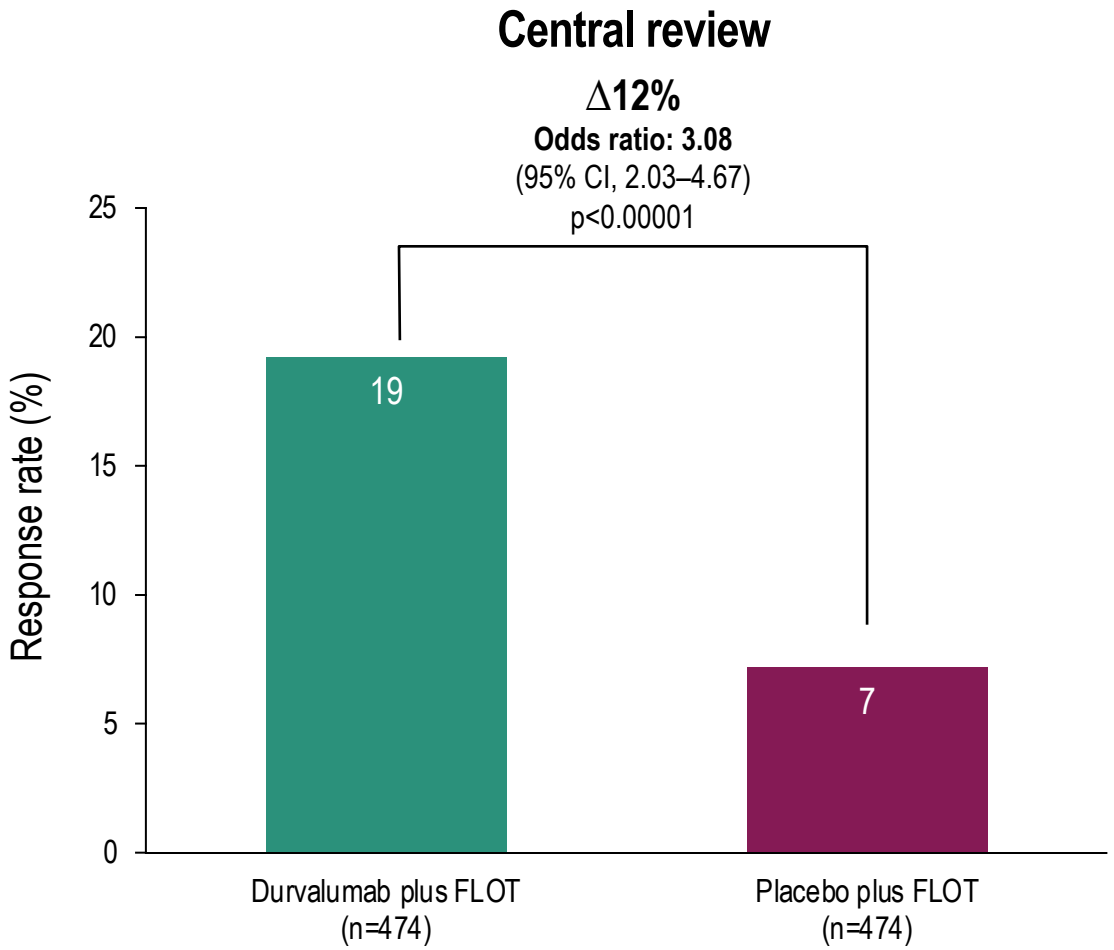
# Baseline characteristics

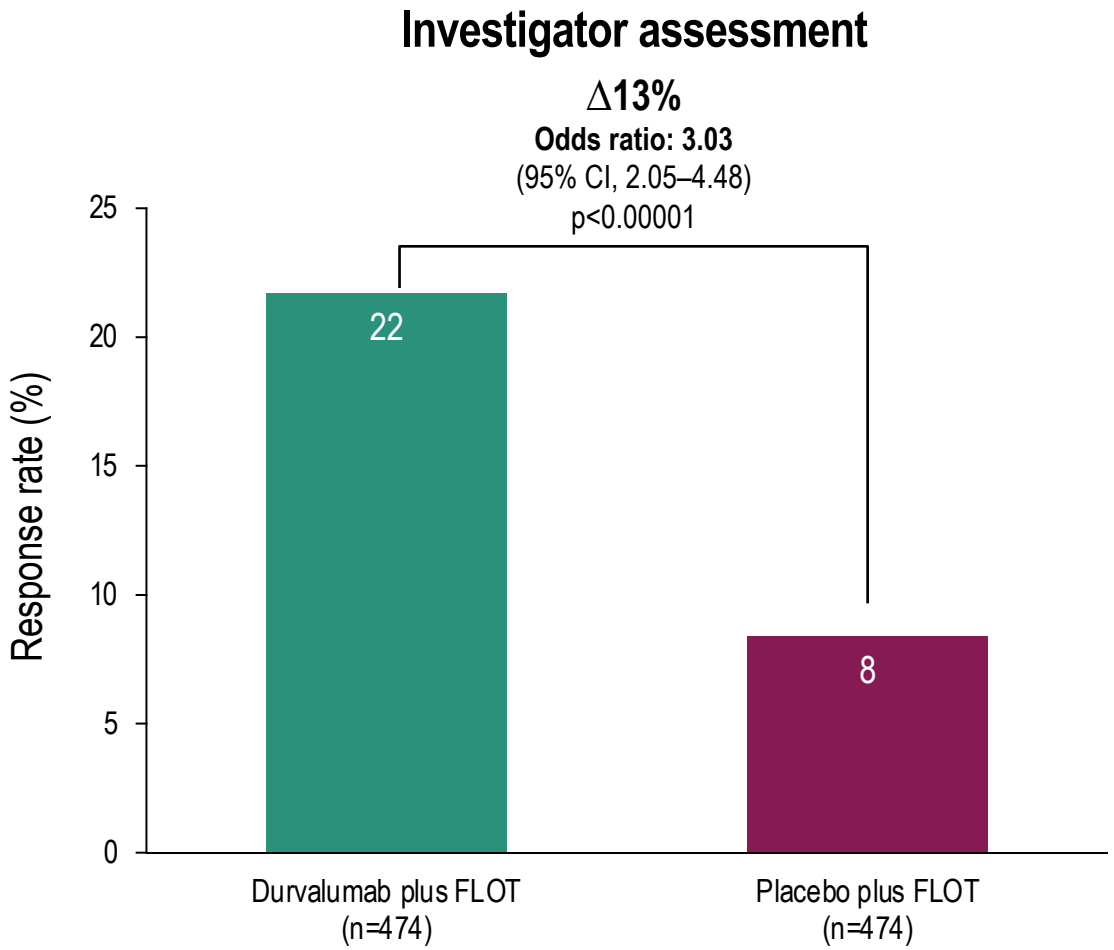
MSI High Status Not Reported

| | | Durvalumab plus FLOT (n=474) | Placebo plus FLOT (n=474) |
|---|---|---|---|
| **Median age, (range) years** | | 62 (26–84) | 63 (28–83) |
| **Male, n (%)** | | 326 (69) | 356 (75) |
| **Region of enrolment, n (%)** | Asia | 90 (19) | 90 (19) |
| | Non-Asia | 384 (81) | 384 (81) |
| **ECOG PS, n (%)** | 0 | 337 (71) | 366 (77) |
| | 1 | 137 (29) | 108 (23) |
| **Primary tumour location, n (%)** | Gastric | 324 (68) | 316 (67) |
| | GEJ | 150 (32) | 158 (33) |
| **Siewert status, n (%)** | Type 1 | 44 (9) | 55 (12) |
| | Type 2 | 72 (15) | 68 (14) |
| | Type 3 | 34 (7) | 35 (7) |
| **Primary tumour stage, n (%)** | T0–T1a | 6 (1) | 0 |
| | T1b–T2 | 44 (9) | 36 (8) |
| | T3 | 307 (65) | 321 (68) |
| | T4a | 101 (21) | 103 (22) |
| | T4b | 16 (3) | 14 (3) |
| **Clinical lymph node status,* n (%)** | Positive | 329 (69) | 330 (70) |
| | Negative | 145 (31) | 144 (30) |
| **PD-L1 expression status by TAP,† n (%)** | <1% | 48 (10) | 47 (10) |
| | ≥1% | 426 (90) | 427 (90) |
| | <5% | 236 (50) | 230 (49) |
| | ≥5% | 238 (50) | 244 (52) |
| **Histology type, n (%)** | Intestinal | 174 (37) | 168 (35) |
| | Diffuse | 104 (22) | 85 (18) |
| | Unspecified adenocarcinoma or other | 196 (41) | 221 (47) |

*Stratification factor data. †Measured by VENTANA PD-L1 (SP263) assay.
ECOG, Eastern Cooperative Oncology Group; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; GEJ, gastro-oesophageal junction; PD-L1, programmed cell death ligand-1; PS, performance status.

# Pathological complete response



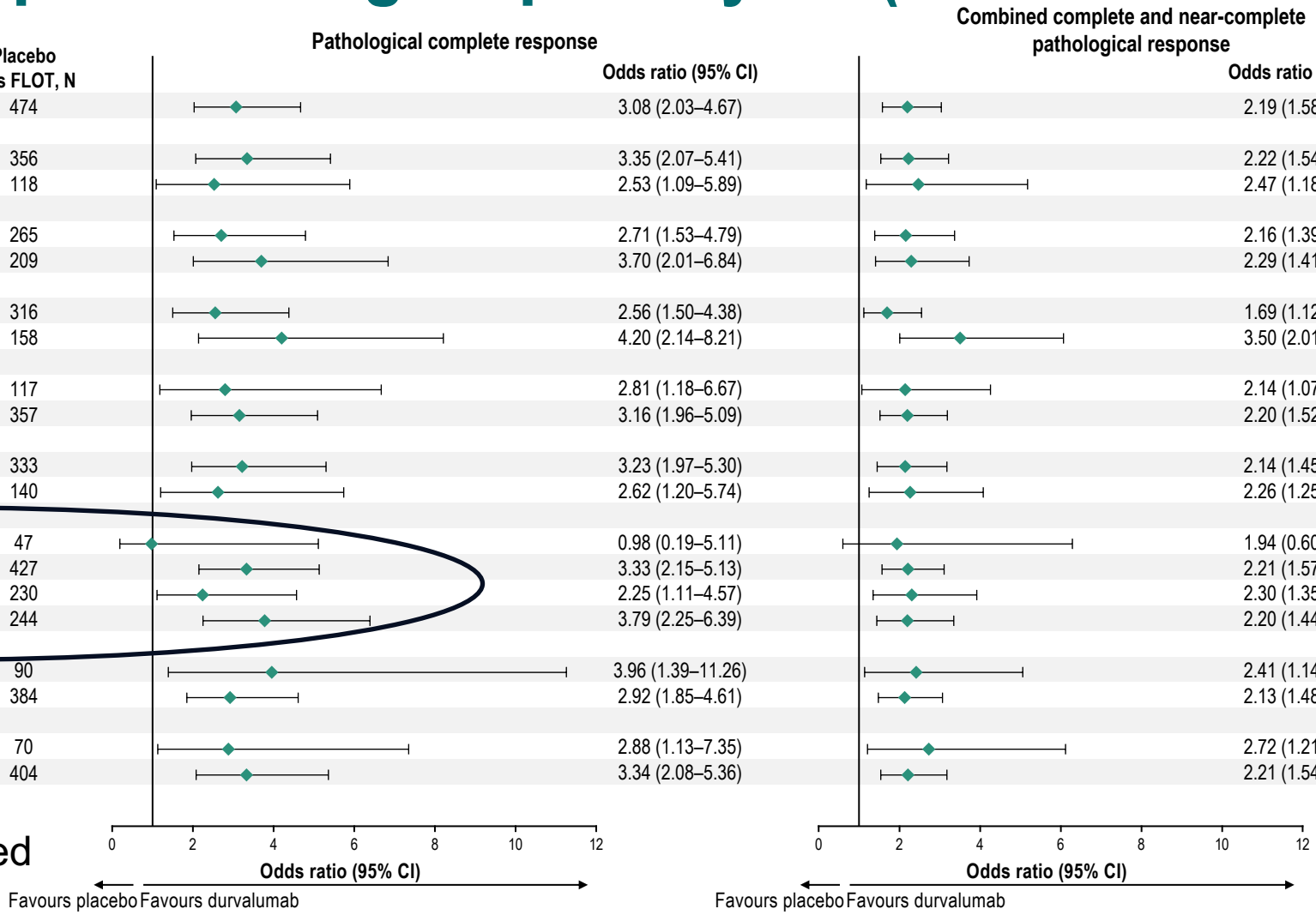




Participants achieve pCR if there is no residual viable tumour cells found at primary tumour and resected lymph nodes at the time of resection, meaning a pathological regression of -100%, based on central (or local) assessment. Central review of pCR was scored using modified Ryan criteria which assess both the primary tumour and lymph nodes.

CI, confidence interval; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; pCR, pathological complete response.

# Pathological response subgroup analysis (central review)

| | Durvalumab plus FLOT, N | Placebo plus FLOT, N | Pathological complete response: Odds ratio (95% CI) | Combined complete and near-complete pathological response: Odds ratio (95% CI) |
|---|---|---|---|---|
| **All participants** | 474 | 474 | 3.08 (2.03–4.67) | 2.19 (1.58–3.04) |
| **Sex** | | | | |
| Male | 326 | 356 | 3.35 (2.07–5.41) | 2.22 (1.54–3.22) |
| Female | 148 | 118 | 2.53 (1.09–5.89) | 2.47 (1.18–5.18) |
| **Age group** | | | | |
| <65 years | 291 | 265 | 2.71 (1.53–4.79) | 2.16 (1.39–3.37) |
| ≥65 years | 183 | 209 | 3.70 (2.01–6.84) | 2.29 (1.41–3.73) |
| **Location at screening** | | | | |
| GC | 324 | 316 | 2.56 (1.50–4.38) | 1.69 (1.12–2.55) |
| GEJC | 150 | 158 | 4.20 (2.14–8.21) | 3.50 (2.01–6.07) |
| **TNM classification** | | | | |
| T4 | 117 | 117 | 2.81 (1.18–6.67) | 2.14 (1.07–4.26) |
| Non-T4 | 357 | 357 | 3.16 (1.96–5.09) | 2.20 (1.52–3.19) |
| **Clinical lymph node status** | | | | |
| Positive | 334 | 333 | 3.23 (1.97–5.30) | 2.14 (1.45–3.18) |
| Negative | 137 | 140 | 2.62 (1.20–5.74) | 2.26 (1.25–4.08) |
| **PD-L1 expression at baseline** | | | | |
| <1% | 48 | 47 | 0.98 (0.19–5.11) | 1.94 (0.60–6.29) |
| ≥1% | 426 | 427 | 3.33 (2.15–5.13) | 2.21 (1.57–3.11) |
| <5% | 236 | 230 | 2.25 (1.11–4.57) | 2.30 (1.35–3.92) |
| ≥5% | 238 | 244 | 3.79 (2.25–6.39) | 2.20 (1.44–3.35) |
| **Region** | | | | |
| Asia | 90 | 90 | 3.96 (1.39–11.26) | 2.41 (1.14–5.06) |
| Non-Asia | 384 | 384 | 2.92 (1.85–4.61) | 2.13 (1.48–3.07) |
| **Country** | | | | |
| Germany | 47 | 70 | 2.88 (1.13–7.35) | 2.72 (1.21–6.12) |
| Non-Germany | 427 | 404 | 3.34 (2.08–5.36) | 2.21 (1.54–3.18) |




MSI High Status Not Reported

Participants achieve pCR if there is no residual viable tumour cells found at primary tumour and resected lymph nodes at the time of resection, meaning a pathological regression of -100%, based on central (or local) assessment. Central review of pCR was scored using modified Ryan criteria.
CI, confidence interval; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; pCR, pathological complete response; PD-L1, programmed cell death ligand-1.

# Ongoing Pre/Post Op CPI Trials

- ECOG/ACRIN EA2174 [NCT03604991] Phase 2/3:
  - Chemoradiotherapy ± Nivolumab in Esophageal and GEJ Cancer, Adjuvant Nivolumab ± Ipilimumab
- ECOG/ACRIN EA2212 [NCT05836584]: Phase 2:
  - MSI high, peri-op Atezolizumab ± (FLOT or mFOLFOX or CAPOX)
- Multiple Chinese trials: Nivolumab, Toripalimab, Sintilimab + pre/post op chemo
- Pilots in HER2 positive disease

# CPI in Locally Advanced Esophagogastric Adenocarcinoma

- MSI high gastric cancer
  - Surgery alone given better prognosis, ? Detriment of chemo
  - Preop CPI therapy: high rate of path CR➔ Non operative management
- Pre and Post op CPI
  - Adjuvant nivolumab did not improve EFS or OS (ATTRACTION-5)
  - CheckMate 577: Adjuvant nivolumab standard after CRT/Surgery in esophageal and GEJ cancer
  - Preop CPI + Chemo improves path CR
    - Benefit in CPS +, MSI high
  - Trends toward improved EFS, no difference OS (KEYNOTE-585)
    - EFS improvement driven by MSI high patients
  - MATTERHORN (FLOT): EFS primary endpoint, pending
- CPI Trials: Analyze with exclusion of MSI high patients

# MODULE 2: Incorporation of First-Line Immunotherapeutic Strategies for Patients with Metastatic Gastroesophageal Tumors – Dr Yoon

RTP
RESEARCH
TO PRACTICE

# Neoadjuvant immunotherapy for dMMR gastric cancer

Sunnie Kim, MD

RTP
RESEARCH
TO PRACTICE

# QUESTIONS FOR THE FACULTY

**Sunnie Kim, MD**

***What is your preferred immunotherapy regimen for younger and older patients with MSI-high localized and metastatic disease?***

***What has been your experience with the toxicity of anti-PD-1/anti-CTLA-4 combination regimens?***

RTP
RESEARCH
TO PRACTICE

# Prevention and management of immunotherapy-associated pneumonitis

**Sunnie Kim, MD**

RTP
RESEARCH
TO PRACTICE

# QUESTIONS FOR THE FACULTY

**Sunnie Kim, MD**

***How do you approach the workup of patients with pulmonary symptoms or imaging alterations while receiving IOs?***

***How do you manage IO-associated pneumonitis, and in what situations, if any, would you consider rechallenge?***

**Please describe the last patient in your practice with HER2-negative metastatic gastroesophageal cancer who received first-line chemotherapy in combination with immunotherapy. What was their CPS? What was their MSI/mismatch repair/PD-L1 status? What treatment regimen did the patient receive?**

| | CPS | MSI/mismatch repair/PD-L1 | Tx received |
|---|---|---|---|
|  Dr Ilson | 5 | MSS | FOLFOX/nivolumab |
|  Dr Mehta | 6 | MSS | FOLFOX/nivolumab |
|  Dr Moehler | 7 | MSS | FLOT/nivolumab |
|  Dr Shah | 10 | MSS | FOLFOX/nivolumab |
|  Dr Yoon | 10 | MSS | FOLFOX/nivolumab |
|  Dr Ajani | 6 | MSS | FOLFOX/nivolumab |
|  Dr Kim | 5 | pMMR | FOLFOX/nivolumab |

pMMR = proficient mismatch repair

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

| | CPS 0 | CPS 1 |
|---|---|---|
|  Dr Ilson | FOLFOX/nivolumab | FOLFOX/nivolumab |
|  Dr Mehta | FOLFOX | FOLFOX |
|  Dr Moehler | FOLFOX; FLOT + resection if oligometastatic | FOLFOX/pembrolizumab |
|  Dr Shah | FOLFOX | FOLFOX |
|  Dr Yoon | FOLFOX | FOLFOX |
|  Dr Ajani | Chemotherapy | Chemotherapy |
|  Dr Kim | FOLFOX | FOLFOX |

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

| | CPS 5 | CPS 10 |
|---|---|---|
|  Dr Ilson | FOLFOX/nivolumab | FOLFOX/nivolumab |
|  Dr Mehta | FOLFOX/nivolumab | FOLFOX/nivolmuab |
|  Dr Moehler | FOLFOX/nivolumab; FLOT/nivolumab + resection if oligometastatic | FOLFOX/nivolumab; FLOT/nivolumab + resection if oligometastatic |
|  Dr Shah | FOLFOX/nivolumab | FOLFOX/pembrolizumab |
|  Dr Yoon | FOLFOX/nivolumab | FOLFOX/nivolumab |
|  Dr Ajani | Chemotherapy with nivolumab | Chemotherapy with either pembrolizumab or nivolumab |
|  Dr Kim | FOLFOX/nivolumab | FOLFOX/nivolumab |

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

| | |
|---|---|
|  Dr Ilson | Pembrolizumab |
|  Dr Mehta | Pembrolizumab |
|  Dr Moehler | FOLFOX/nivolumab; FLOT/nivolumab + resection if oligometastatic |
|  Dr Shah | FOLFOX/nivolumab or FOLFOX/pembrolizumab |
|  Dr Yoon | FOLFOX/nivolumab |
|  Dr Ajani | Nivolumab/ipilimumab |
|  Dr Kim | FOLFOX/nivolumab if symptomatic; pembrolizumab if asymptomatic/low disease burden |

## Do you believe that the additional anti-PD-1 antibodies that have been evaluated for advanced gastroesophageal cancer (eg, sintilimab, tislelizumab) are essentially equivalent to pembrolizumab and nivolumab in terms of efficacy and tolerability?

| | |
|---|---|
|  Dr Ilson | Yes |
|  Dr Mehta | Yes |
|  Dr Moehler | Yes |
|  Dr Shah | Yes |
|  Dr Yoon | Yes |
|  Dr Ajani | Yes |
|  Dr Kim | Yes |

RTP RESEARCH TO PRACTICE

**If the additional anti-PD-1 antibodies that have been evaluated for advanced gastroesophageal cancer (eg, sintilimab, tislelizumab) were available and were priced 50% less than pembrolizumab and nivolumab, would you preferentially use them?**

| | |
|---|---|
|  Dr Ilson | Yes |
|  Dr Mehta | Yes |
|  Dr Moehler | Yes |
|  Dr Shah | Yes |
|  Dr Yoon | Yes |
|  Dr Ajani | Yes |
|  Dr Kim | Yes |

RTP RESEARCH TO PRACTICE

MAYO CLINIC

# Incorporation of First-Line Immunotherapeutic Strategies for Patients with Metastatic Gastroesophageal Tumors

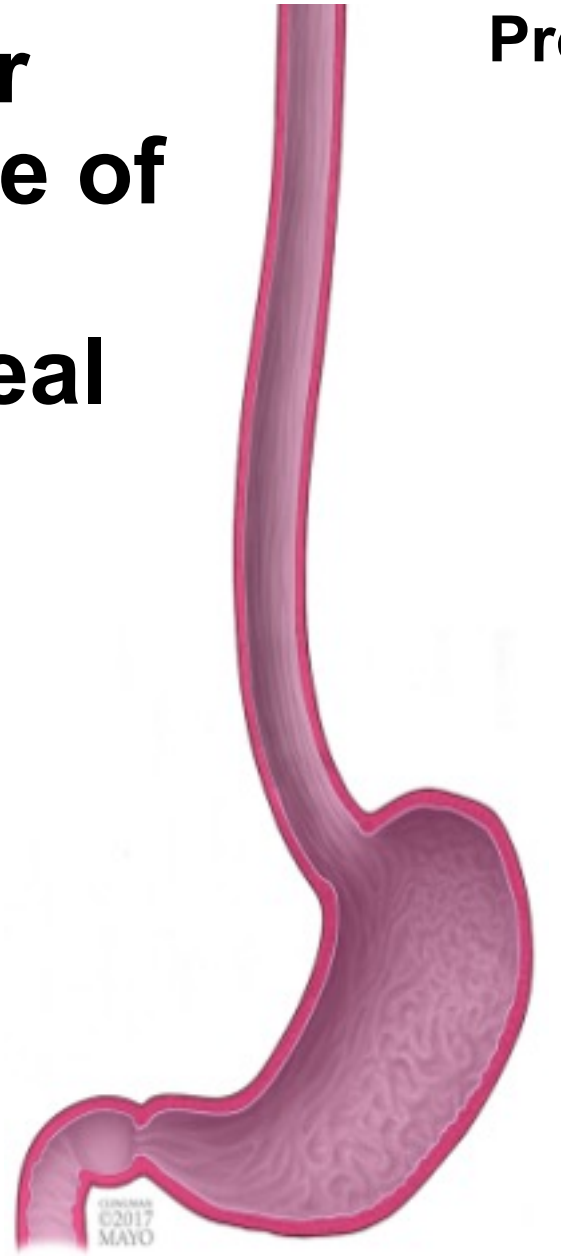

**Harry H Yoon, MD MHS**
Professor of Oncology
Enterprise Co-Leader, GI/Hepatobiliary/Pancreatic Cancer Research
Enterprise Vice-Chair, GI Disease Group
Mayo Clinic
Rochester, MN; Phoenix, AZ; Jacksonville, FL; and Health Systems

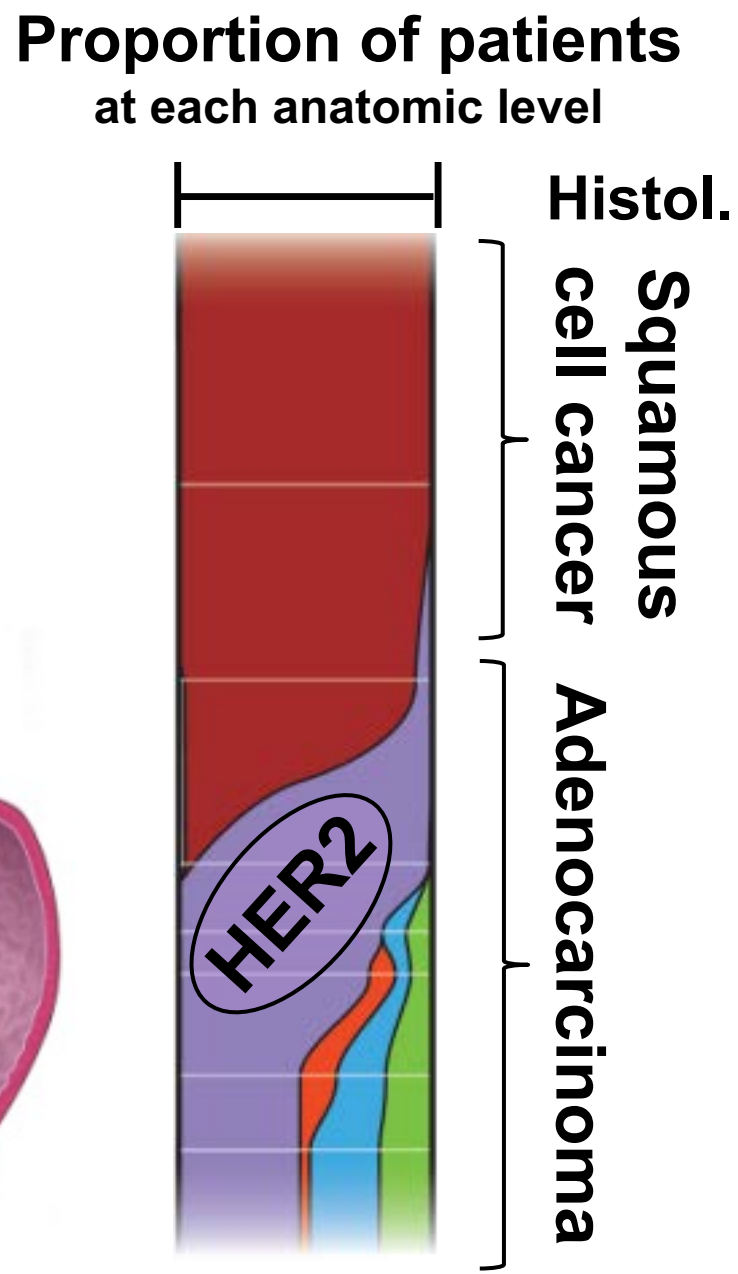


Research To Practice Symposium Focused on the Management of Gastroesophageal Cancers in conjunction with ASCO GI 2024
Thursday, January 18, 2024
San Francisco, CA


# Molecular landscape of gastro-esophageal cancer

TCGA,
*Nature* 2017




Mol. Signature

**SCC signature**
*~15%*

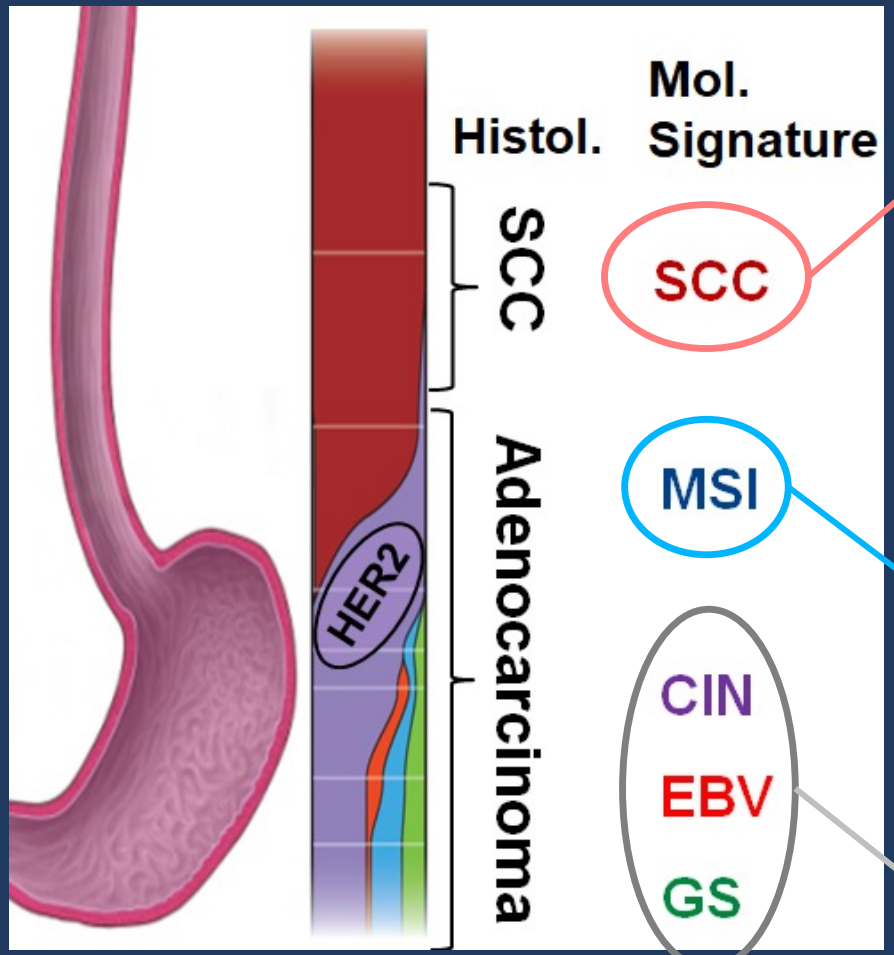
**MSI** *~5-10%*

**Chromosomal instability (CIN)**
*~60-70%*

**EBV** *<5%*

**Genomically stable** *~5-10%*

# 2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal cancer (NCCN Category 1 or 2A)




Any PD-L1 status
Nivo + oxaliplatin/FP
Nivo + IPI

PD-L1 CPS ≥ 10
Pembro + oxaliplatin/FP

Pembro +/- chemo
Nivo + FOLFOX
Nivo + IPI
Dostarlimab

PD-L1 CPS ≥ 5-10 (CPS ≥ 1 ?)
Nivo or pembro + platin/FP

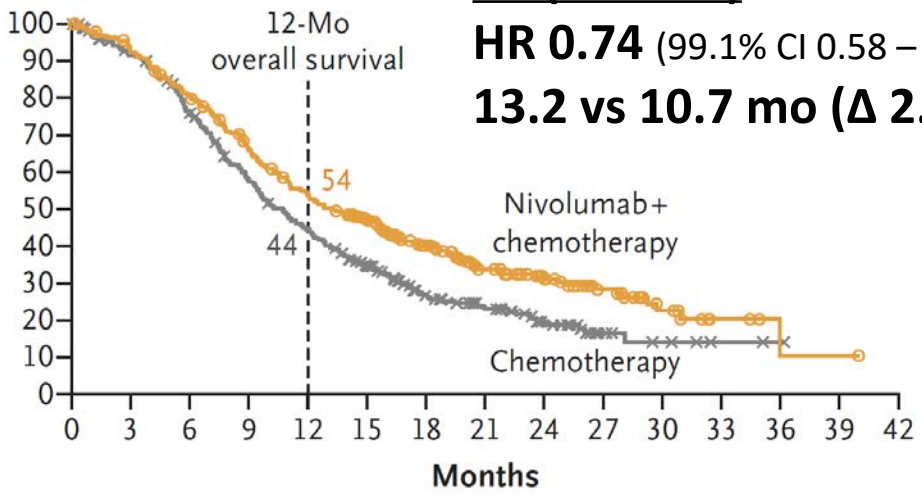
CPS, Combined positive score; FP, fluoropyrimidine; nivo, nivolumab; pembro, pembrolizumab; ICI, immune checkpoint inhibition; IPI, ipilimumab

# CM-648: Nivo improves OS in 1st-line esophageal SCC

**Primary endpoints: OS and PFS in TPS ≥ 1**

**All**

## Nivo + chemo

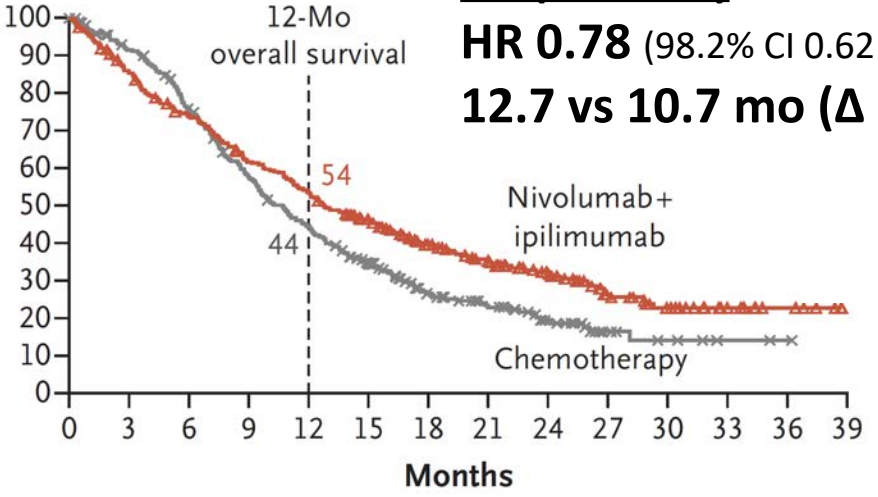



**All (N = 645)**

**HR 0.74** (99.1% CI 0.58 – 0.96)

**13.2 vs 10.7 mo (Δ 2.5)**

## Nivo + IPI




**All (N = 649)**

**HR 0.78** (98.2% CI 0.62 – 0.98)

**12.7 vs 10.7 mo (Δ 2.0)**

Doki Y et al. *N Engl J Med* 2022;386(5):449-462.

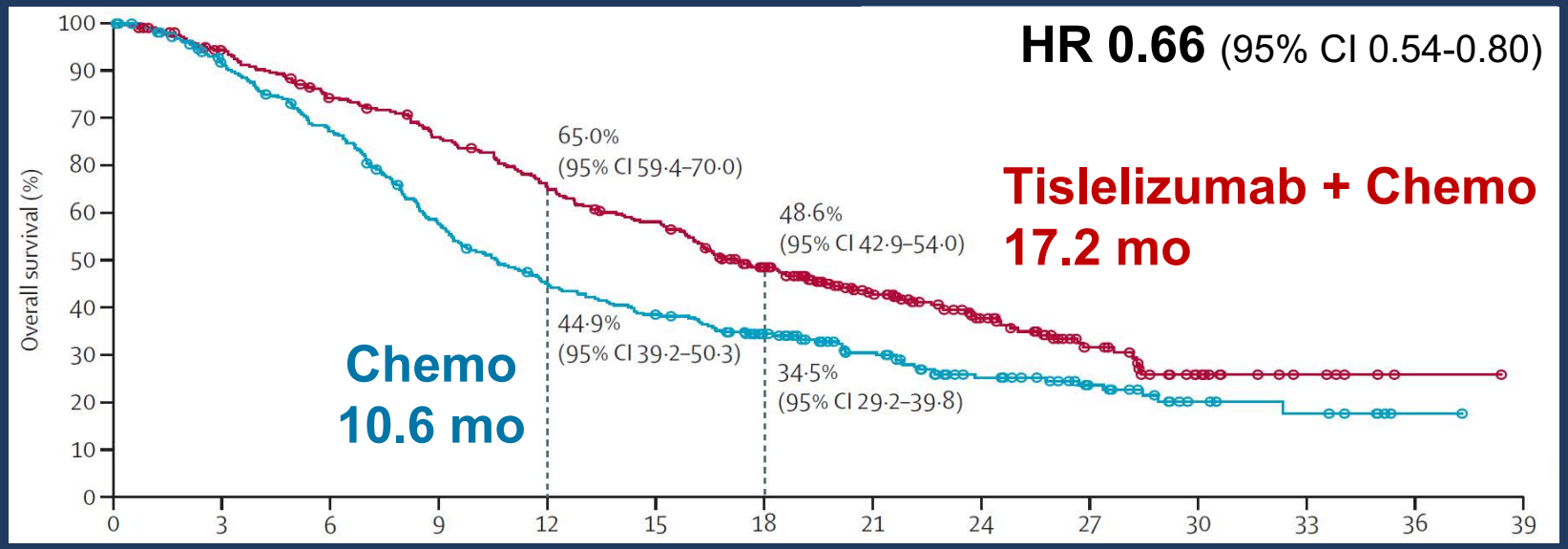
SCC, squamous cell carcinoma; TPS, tumor proportion score; OS, overall survival; PFS, progression free survival; nivo, nivolumab;; IPI, ipilimumab

# RATIONALE-306: Most recent global phase 3 in esophageal SCC

## Overall survival shown

**Tislelizumab**

Anti-PD-1 Ab, mechanism comparable to commercially available anti-PD-1/-L1 Abs




**Primary endpoint: overall survival in intent to treat population (any PD-L1 status)**

**First SCC study to allow >1 chemo backbone:**

- Cisplatin/oxaliplatin + fluoropyrimidine
- Cisplatin/oxaliplatin + paclitaxel


**Xu J … Yoon HH et al. *Lancet Oncol* 2023;24(5):483-495.**

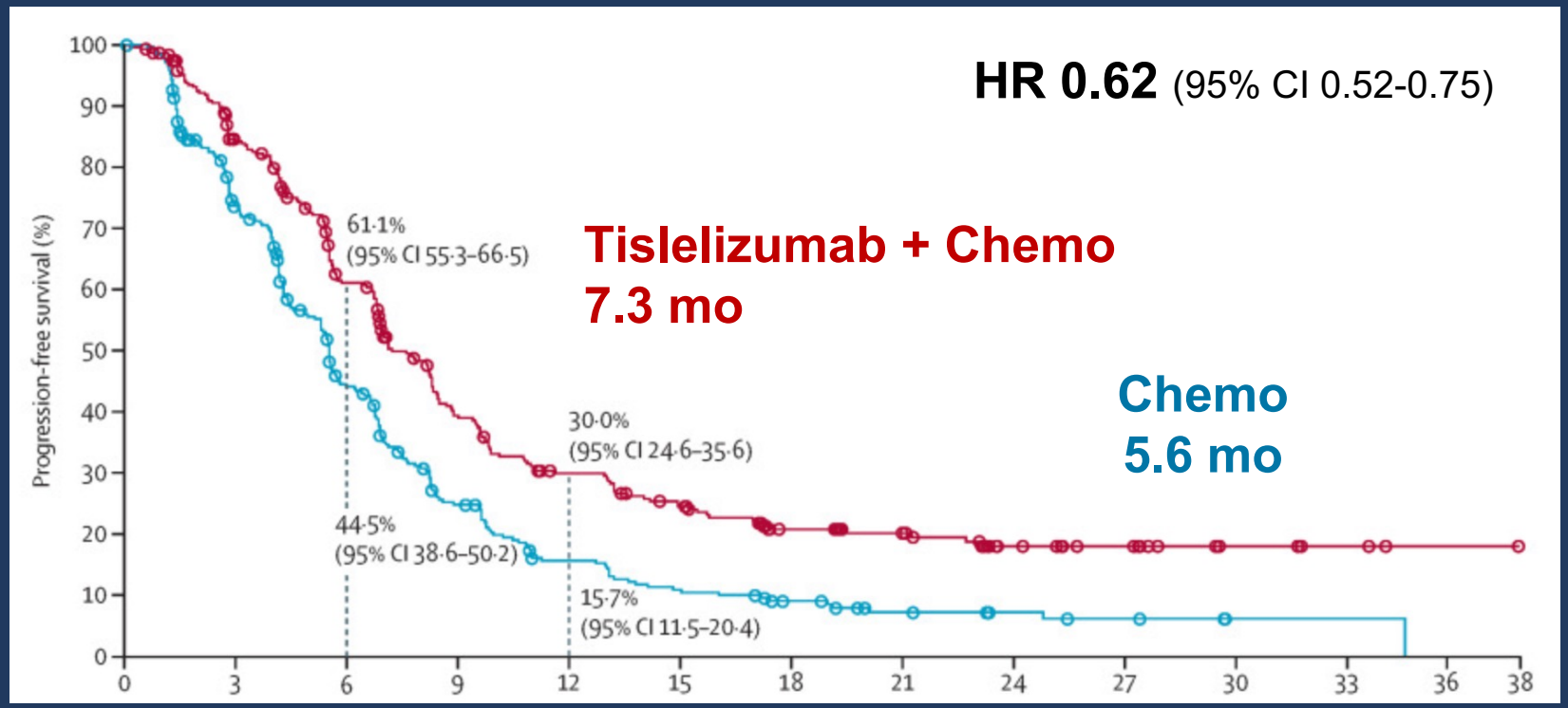

SCC, squamous cell carcinoma

# RATIONALE-306: Most recent global phase 3 in esophageal SCC

## Progression-free survival shown

**Tislelizumab**

Anti-PD-1 Ab, mechanism comparable to commercially available anti-PD-1/-L1 Abs




**Secondary endpoint: progression-free survival in intent to treat population (any PD-L1 status)**

**First SCC study to allow >1 chemo backbone:**

- Cisplatin/oxaliplatin + fluoropyrimidine
- Cisplatin/oxaliplatin + paclitaxel


**Xu J … Yoon HH et al. *Lancet Oncol* 2023;24(5):483-495.**


SCC, squamous cell carcinoma

# RATIONALE-306: Most recent global phase 3 in esophageal SCC

## Safety data shown

### Tislelizumab

Anti-PD-1 Ab, mechanism comparable to commercially available anti-PD-1/-L1 Abs

| | Tislelizumab plus chemotherapy group (n=324) | | | | Placebo plus chemotherapy group (n=321) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1–2 | Grade 3 | Grade 4 | Grade 5* | Grade 1–2 | Grade 3 | Grade 4 | Grade 5* |
| Any event | 97 (30%) | 153 (47%) | 56 (17%) | 7 (2%) | 102 (32%) | 148 (46%) | 53 (17%) | 6 (2%) |
| Anaemia | 126 (39%) | 46 (14%) | 1 (<1%) | 0 | 114 (36%) | 41 (13%) | 0 | 0 |
| Decreased white blood cell count | 108 (33%) | 31 (10%) | 4 (1%) | 0 | 107 (33%) | 45 (14%) | 5 (2%) | 0 |
| Decreased appetite | 107 (33%) | 9 (3%) | 0 | 0 | 108 (34%) | 7 (2%) | 0 | 0 |
| Nausea | 104 (32%) | 8 (2%) | 0 | 0 | 125 (39%) | 5 (2%) | 0 | 0 |
| Peripheral sensory neuropathy | 63 (19%) | 10 (3%) | 0 | 0 | 54 (17%) | 7 (2%) | 0 | 0 |
| Alopecia | 58 (18%) | 0 | 0 | 0 | 63 (20%) | 0 | 0 | 0 |
| Diarrhoea | 54 (17%) | 9 (3%) | 0 | 0 | 54 (17%) | 5 (2%) | 0 | 0 |
| Decreased neutrophil count | 54 (17%) | 72 (22%) | 27 (8%) | 0 | 47 (15%) | 70 (22%) | 35 (11%) | 0 |

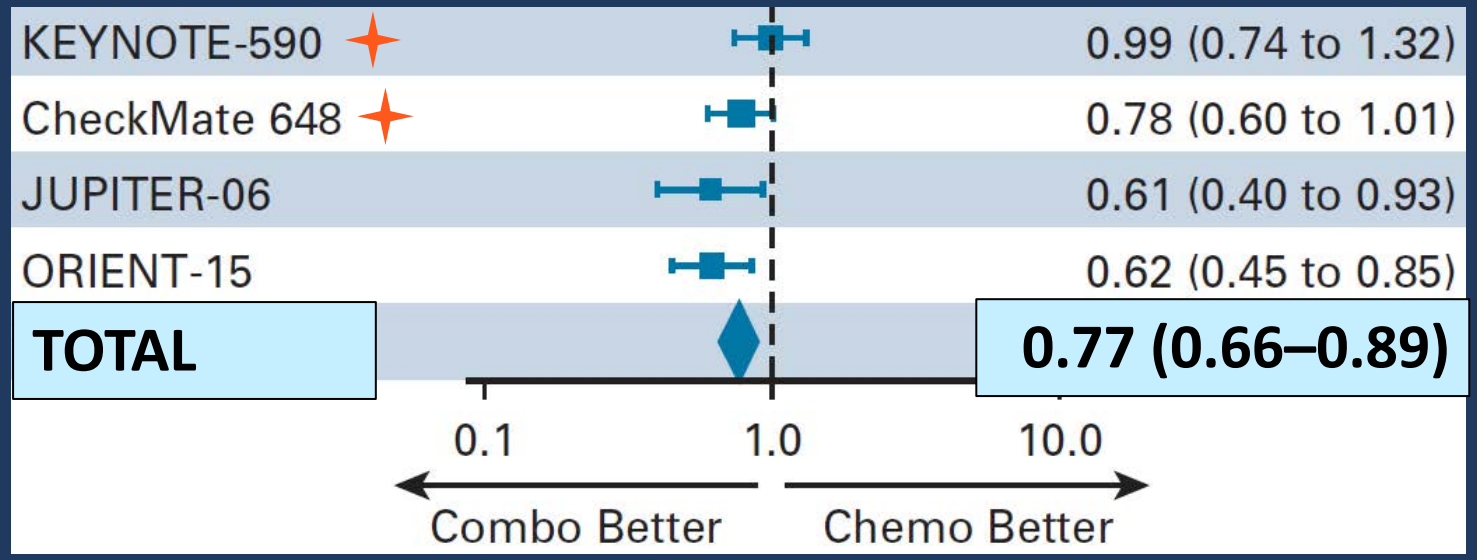
Xu J … Yoon HH et al. *Lancet Oncol* 2023;24(5):483-495.

SCC, squamous cell carcinoma

# Most phase 3 trials in esophageal SCC show meaningfully improved OS with ICI + chemo, even in PD-L1-low tumors

## Overall Survival in CPS <10

**Meta-analysis [1]**




**Subsequent trials [2-3]**

| | |
|---|---|
| RATIONALE-306 ✦ | 0.82 (0.62 to 1.08) |
| ASTRUM-007 [a] | 0.74 (0.54 to 1.03) |

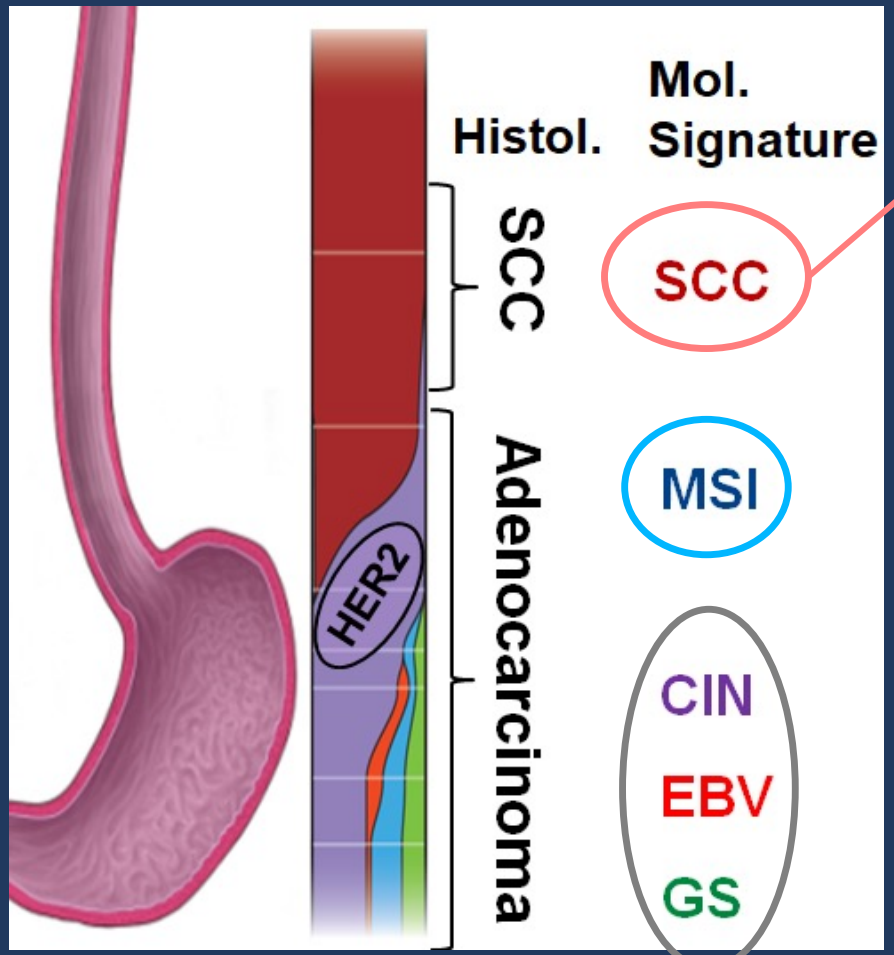
✦ Study population was global (ie, includes non-Asia)

[a] ASTRUM-007 reported only CPS 1-9 (not CPS <10 and not TPS)

SCC, squamous cell carcinoma ICI, immune checkpoint inhibition; OS, overall survival; CPS, combined positive score

1. Wu H-X et al, JCO 2022; 2. Xu J … Yoon HH et al, Lancet Oncol 2023; 3. Song Y et al, Nat Med 2023

# 2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal cancer (NCCN Category 1 or 2A)

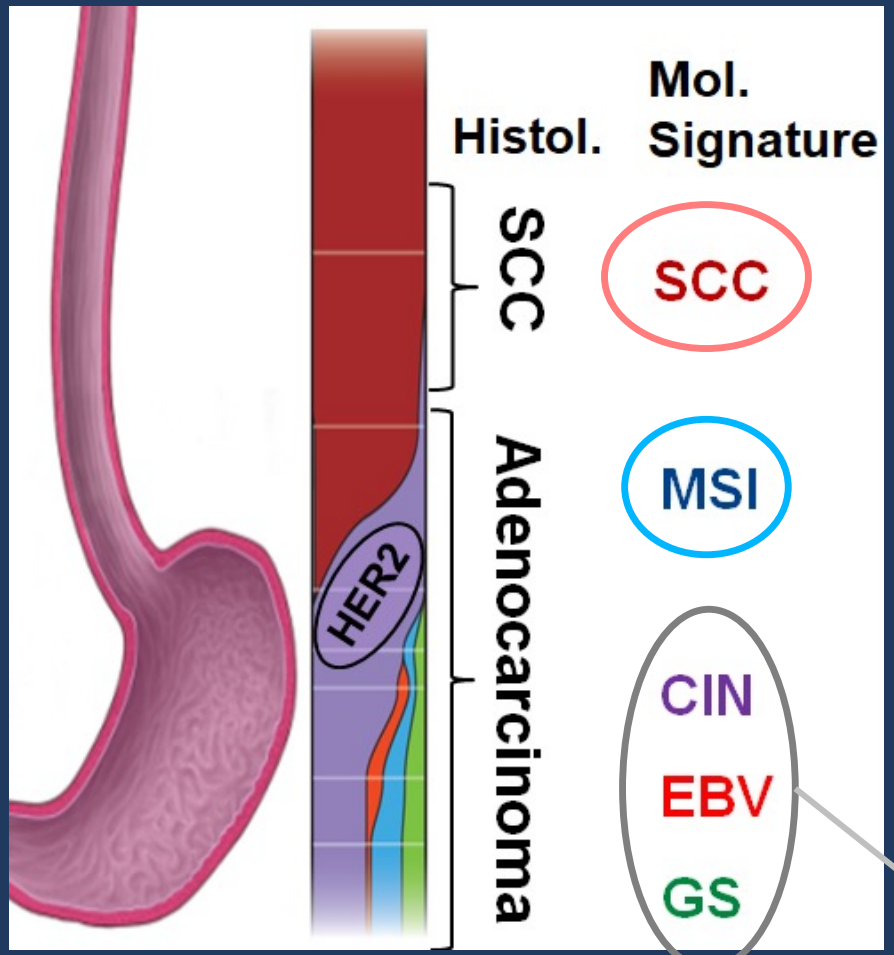



Any PD-L1 status
Nivo + oxaliplatin/FP
Nivo + IPI

PD-L1 CPS ≥ 10
Pembro + oxaliplatin/FP

CPS, Combined positive score; FP, fluoropyrimidine; nivo, nivolumab; pembro, pembrolizumab; ICI, immune checkpoint inhibition; IPI, ipilimumab

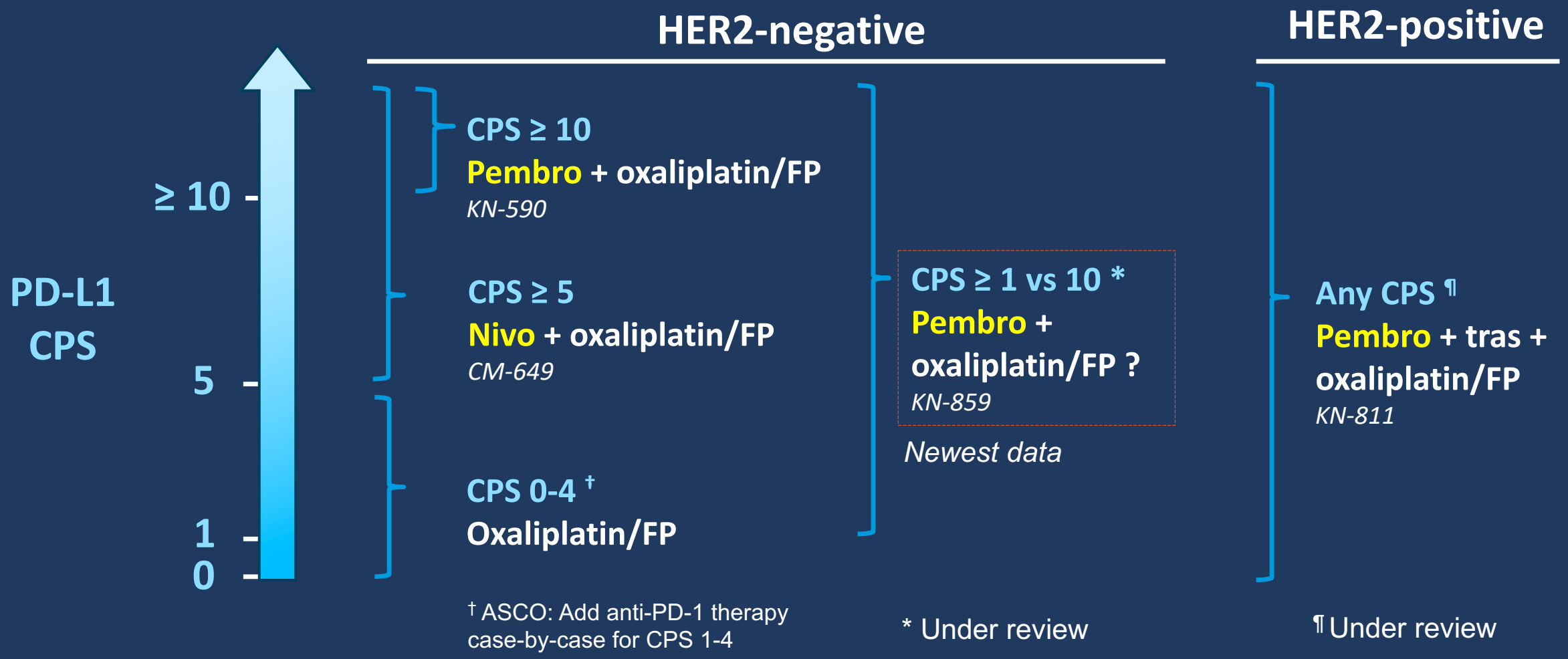
# 2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal cancer (NCCN Category 1 or 2A)




PD-L1 CPS ≥ 5-10 (CPS ≥ 1 ?)
Nivo or pembro + platin/FP

CPS, Combined positive score; FP, fluoropyrimidine; nivo, nivolumab; pembro, pembrolizumab; ICI, immune checkpoint inhibition; IPI, ipilimumab

# 2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal MSS adenocarcinoma (NCCN Category 1 or 2A)




† ASCO: Add anti-PD-1 therapy case-by-case for CPS 1-4

* Under review

¶ Under review

† Shah MA et al. JCO 2023

CPS, Combined positive score; FP, fluoropyrimidine; MSS, microsatellite stable; nivo, nivolumab; pembro, pembrolizumab; Tras, trastuzumab

# CM-649: Nivo improves overall survival in CPS ≥ 5

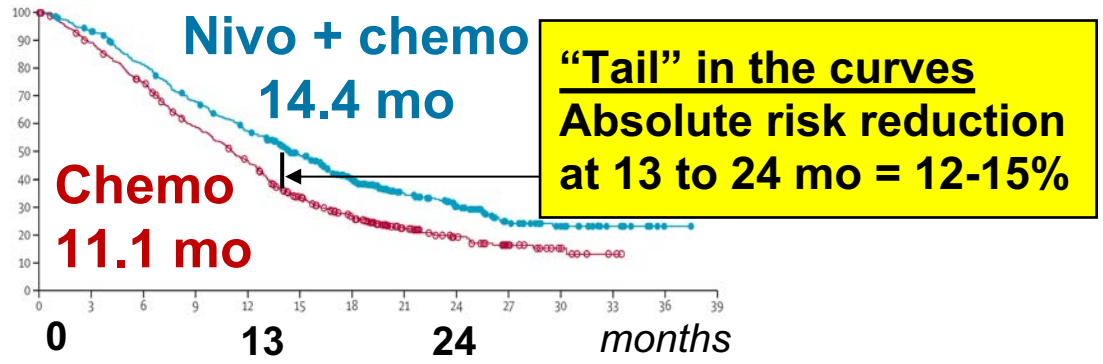
## Gastric/GEJ adenocarcinoma (1st-line FOLFOX/CAPOX +/- nivo)

Primary endpoints = OS in CPS ≥ 5 and PFS in CPS ≥ 5 (IHC Ab 28-8)

**CPS ≥ 5**
**HR 0.71** (98.4% CI 0.59–0.86)

n = 955

OS



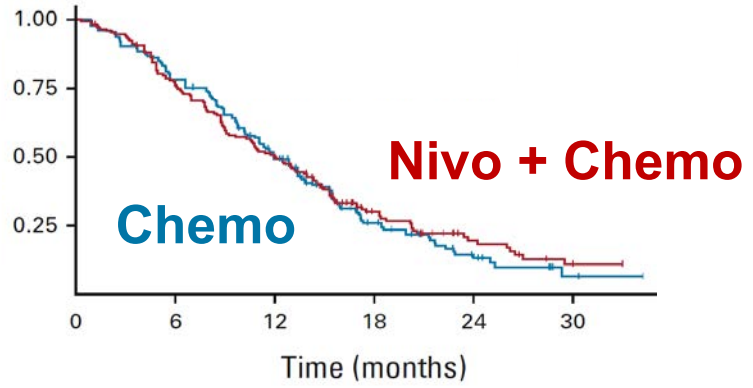

**PFS = 8.1 vs 6.1 mo; HR 0.70** (95% CI 0.60–0.81) [a]
**ORR = 60% vs 45%**

Janjigian YY, et al. *Lancet*. 2021;398(10294):27-40.

**CPS 1-4**
**HR 0.95** (95% CI 0.75–1.21)

n = 341

OS




**PFS = ~9 vs ~9 m; HR 0.96** (95% CI 0.74–1.24)
**ORR = not reported**

Zhao JJ, et al. *JCO*. 2021:40:392

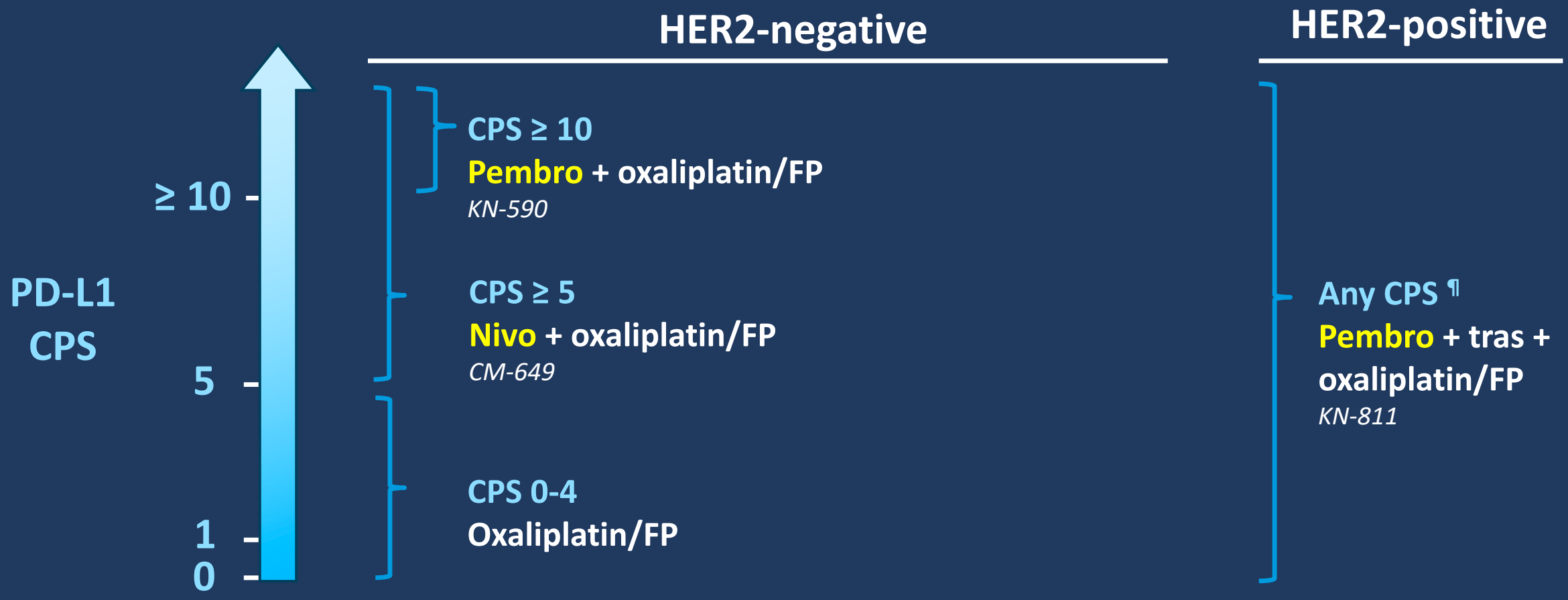
[a] For PFS, maximum absolute risk reduction is at 12 months = 14%

# Higher G3-5 Toxicity with nivolumab in CM-649

| | Nivo + Chemo | Chemo |
|---|---|---|
| **Any G3-5** | **60%**<br>1.3x | **44%**<br>ref |
| **G4-5** | **14%**<br>2x | **7%**<br>ref |
| ***Treatment duration*** | ***6.8 m***<br>*1.4x* | ***4.9 m***<br>*ref* |

Janjigian YY, et al. *Lancet*. 2021;398(10294):27-40.

# 2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal MSS adenocarcinoma (NCCN Category 1 or 2A)




¶ Under review

CPS, Combined positive score; FP, fluoropyrimidine; MSS, microsatellite stable; nivo, nivolumab; pembro, pembrolizumab; Tras, trastuzumab

# Along with CM-649, data from other phase 3 trials generally reinforced PD-L1 as predictive marker

*Therapeutic benefit should never be excluded based on a single exploratory (subgroup) analysis …*

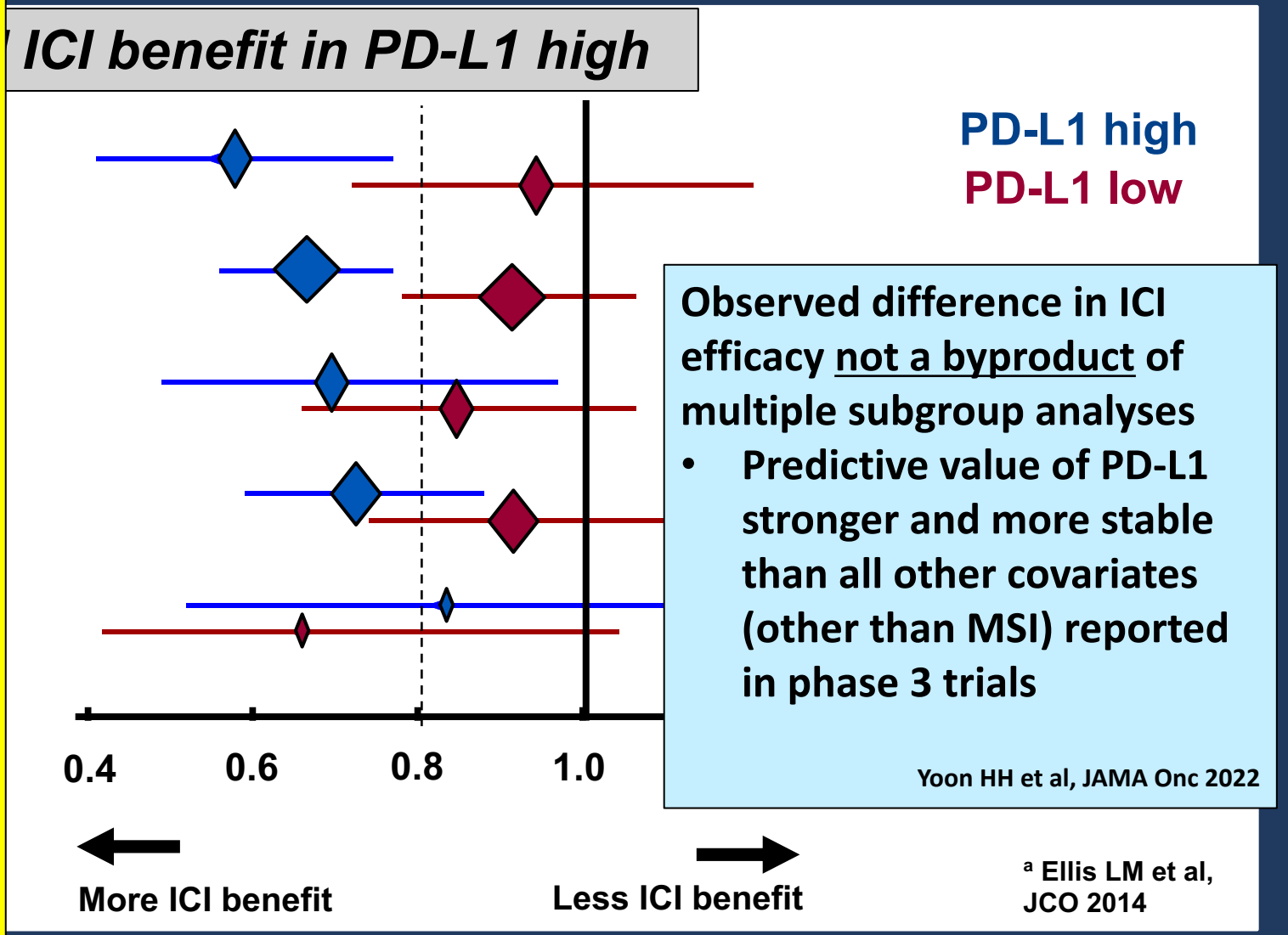
*But more evidence than that has now emerged...*

# ICI efficacy is greater in PD-L1 high (vs low) patients in 1st-line phase 3 trials of MSS HER2-negative GEA

**Complex issues regarding PD-L1 assay**

- Spatiotemporal (hetero)homogeneity
- Detection antibodies
- Interpathologist (dis)agreement
- Ideal cutpoint
- Issues common to IHC


1. Kulangara K et al, Arch Pathol Lab Med 143:330-337, 2018.
2. Kim S-W et al, Pathology 53:586-594, 2021.
3. Ahn S et al, Mod Pathol 34:1719-1727, 2021
4. Yeong J et al, Gastric Cancer 25:741-750, 2022
5. Park Y et al, Cancer Res Treat 52:661-670, 2020
6. Kim JM et al, Mol Diagn Ther 26:679-688, 2022
7. Dabbagh TZ et al, Appl Immunohisto Mol Morphol 29:462-466, 2021
8. Fernandez AI … Rimm DL. Mod Pathol 36:100128, 2023
9. Robert ME et al, Mod Pathol 36:100154, 2023
10. Zhou KI … Catenacci DVT, Clin Cancer Res 26:6453-6463, 2020
11. Catenacci DVT et al, Cancer Discov 11:308-325, 2021

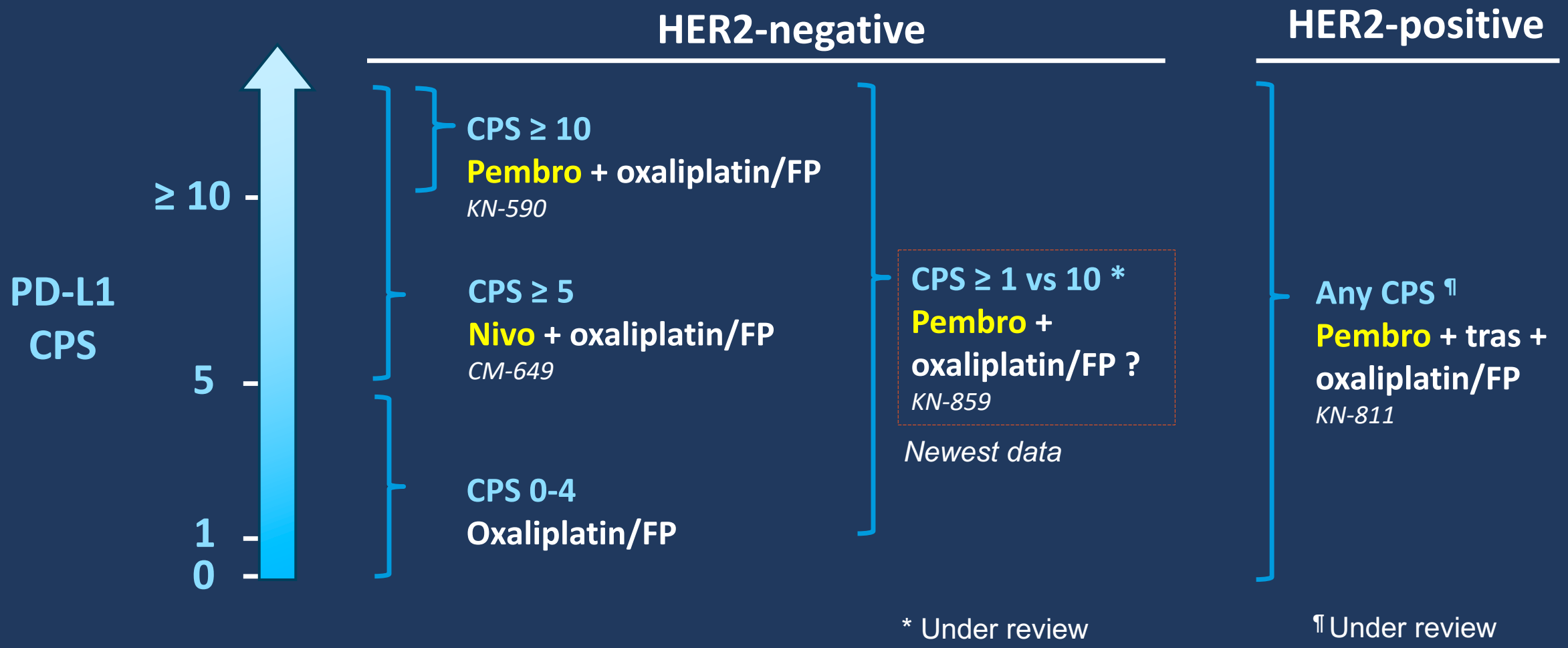

**Observed difference in ICI efficacy not a byproduct of multiple subgroup analyses**

- Predictive value of PD-L1 stronger and more stable than all other covariates (other than MSI) reported in phase 3 trials

Yoon HH et al, JAMA Onc 2022

MSS, microsatellite stable; TAP, tumor area positivity; CPS, combined positive score; GEA, gastroesophageal adenocarcinoma

# 2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal MSS adenocarcinoma (NCCN Category 1 or 2A)




* Under review

¶ Under review

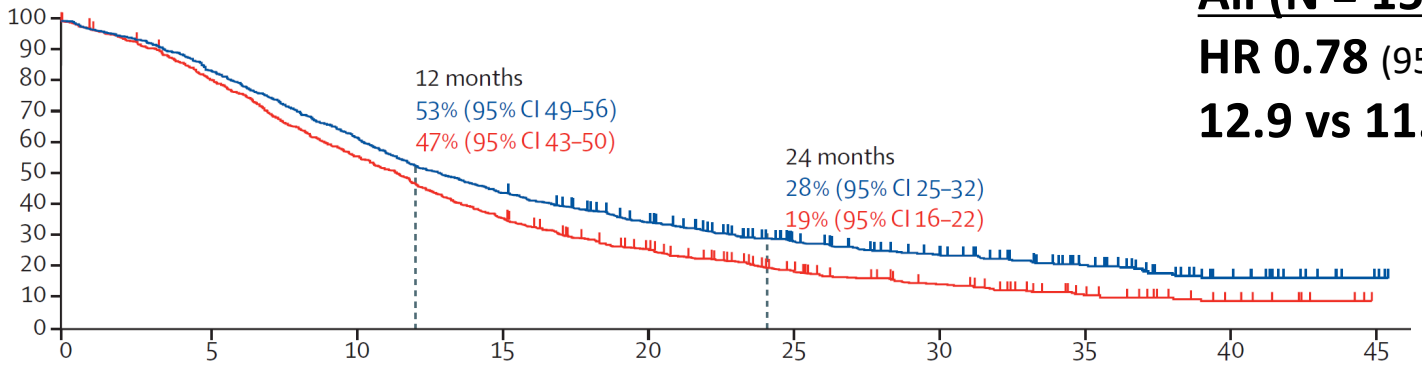
CPS, Combined positive score; FP, fluoropyrimidine; nivo, nivolumab; pembro, pembrolizumab; Tras, trastuzumab

# KN-859: pembro improves OS in 1st-line GEA

**Phase 3**
**Chemo +/- pembro**

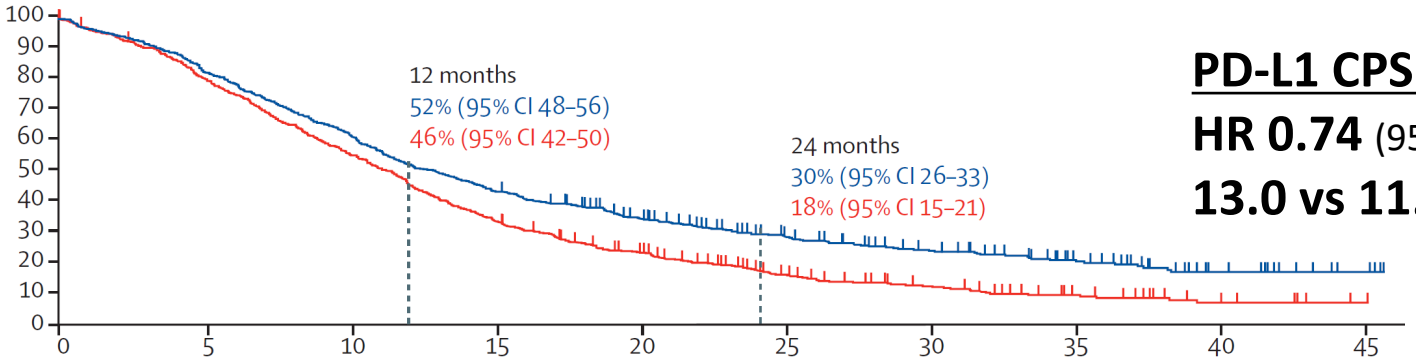
22C3 Ab

OS



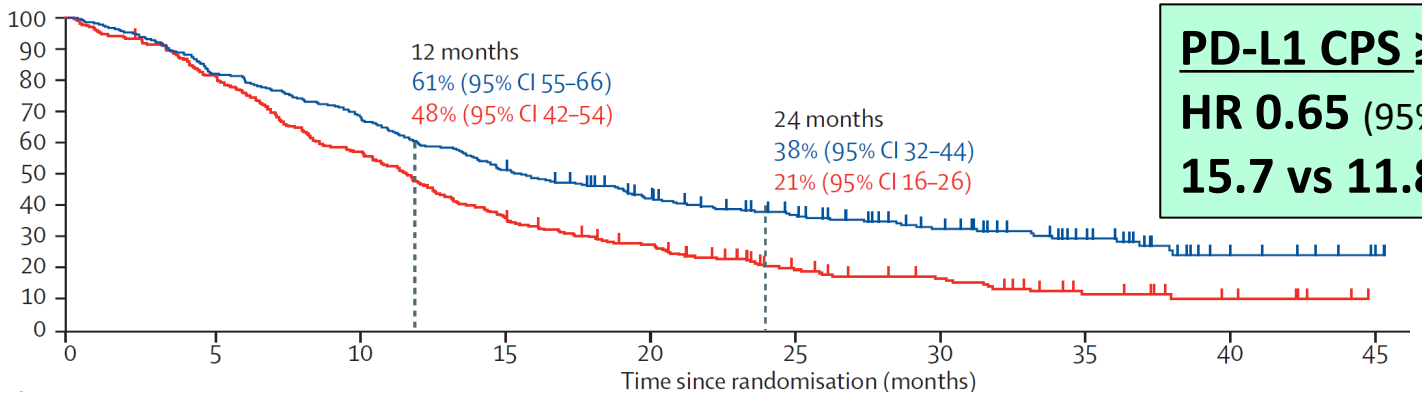

**All (N = 1579)**
**HR 0.78** (95% CI 0.70 – 0.87)
**12.9 vs 11.5 mo (Δ 1.4 [5.6 wk])**

OS




**PD-L1 CPS ≥ 1 (n = 1235)**
**HR 0.74** (95% CI 0.65 – 0.84)
**13.0 vs 11.4 mo (Δ 1.6 mo [6.4 wk])**

OS




**PD-L1 CPS ≥ 10 (n = 551)**
**HR 0.65** (95% CI 0.53 – 0.79)
**15.7 vs 11.8 mo (Δ 3.9)**

**PD-L1 CPS <1 (n = 344)**
**HR 0.92** (95% CI 0.73 – 1.17)
**Not reported (< Δ 1.4)**

**PD-L1 CPS 1-9 (n = 682)**
**HR 0.83** (95% CI 0.70 – 0.98)
**Not reported: likely < 6 wk**

**Rha SY et al, Lancet Oncol 2023**

# PD-L1 CPS 1-9 subgroup (KN-859)

## n = 682 patients, 574 deaths

| Survival endpoints | HR (95% CI) | Median | "Tail" in curves |
|---|---|---|---|
| **OS** | **0.83** (0.70 – 0.98) | Not reported<br>**Likely < 6 weeks** [a] | Not reported |
| **PFS** | **0.83** (0.70 – 0.99) | Not reported<br>**Likely < 5 weeks** [b] | Not reported |

[a] Since difference in larger CPS 1+ group was 6.4 weeks

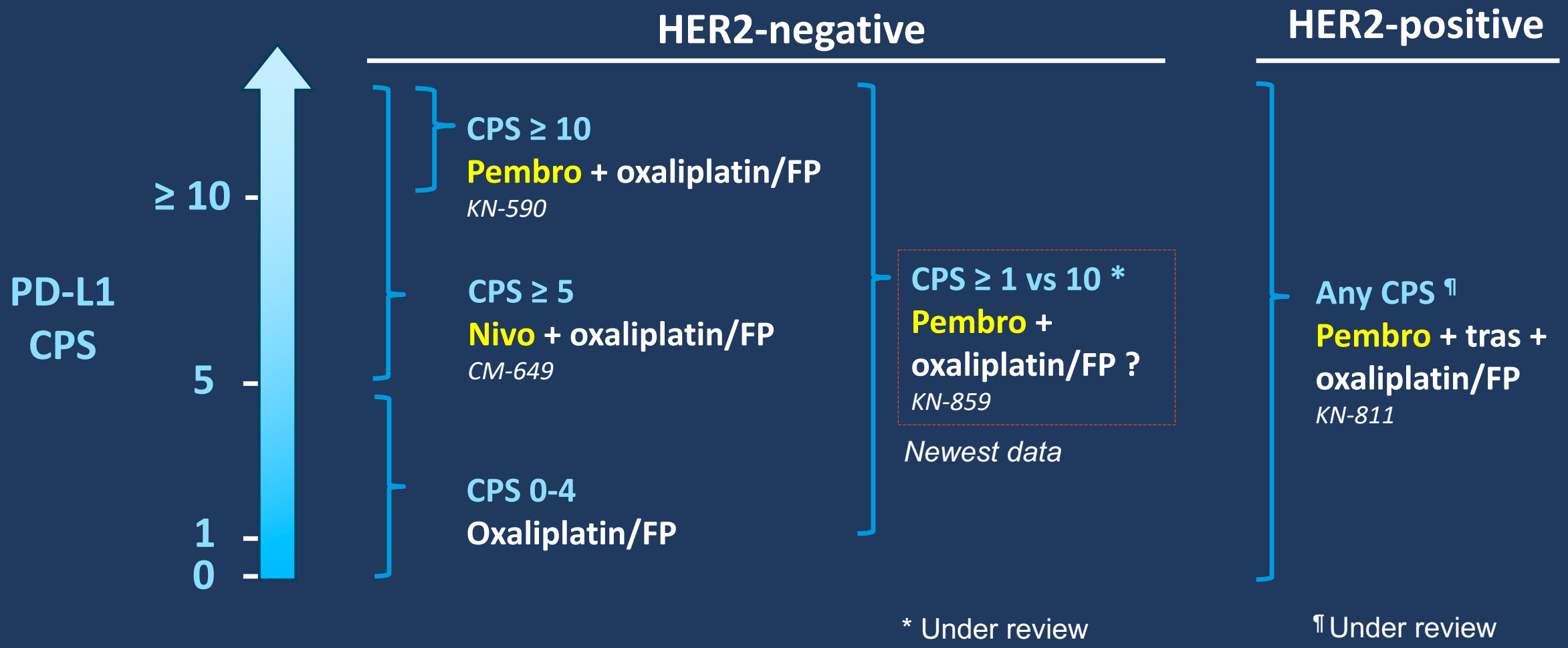
[b] Since difference in larger CPS 1+ group was ~5 weeks

| Other endpoints | |
|---|---|
| **Objective response rate** | **Δ 1%** (24.7% pembro vs 23.7% placebo; Table S3) |
| **Grade 3-5 toxicity** [c] | **Δ 9%** (60% pembro vs 51% placebo) |

[c] Reported only in total population

**Rha SY et al, Lancet Oncol 2023**

# 2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal MSS adenocarcinoma (NCCN Category 1 or 2A)

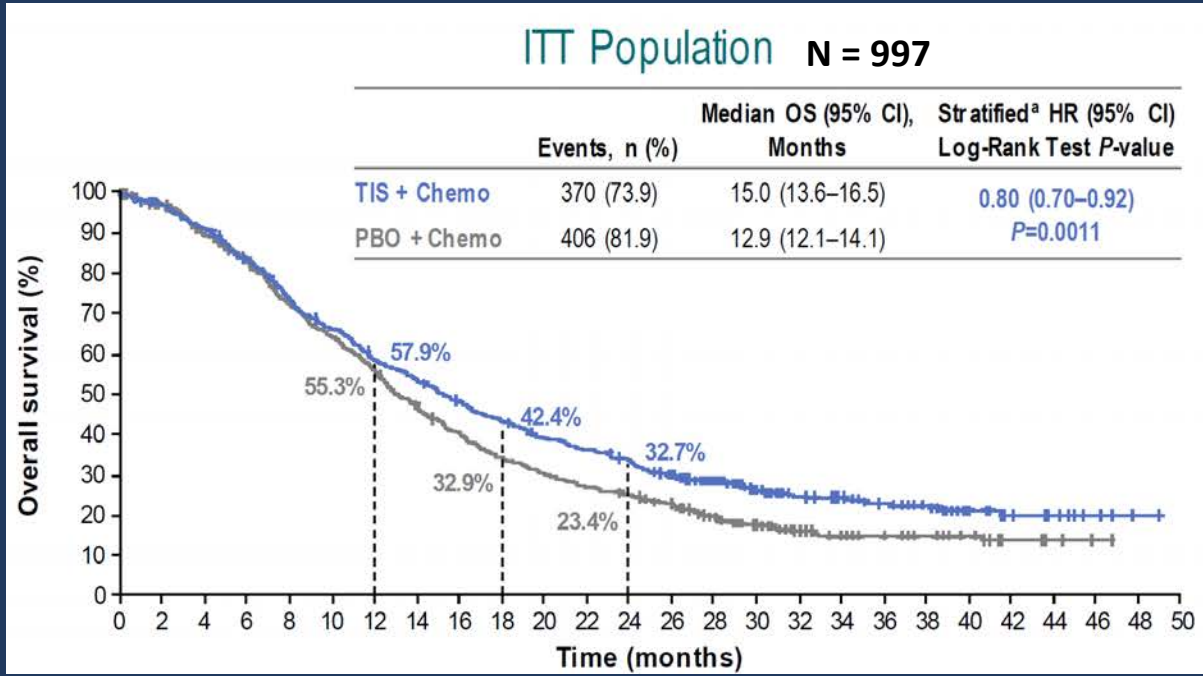


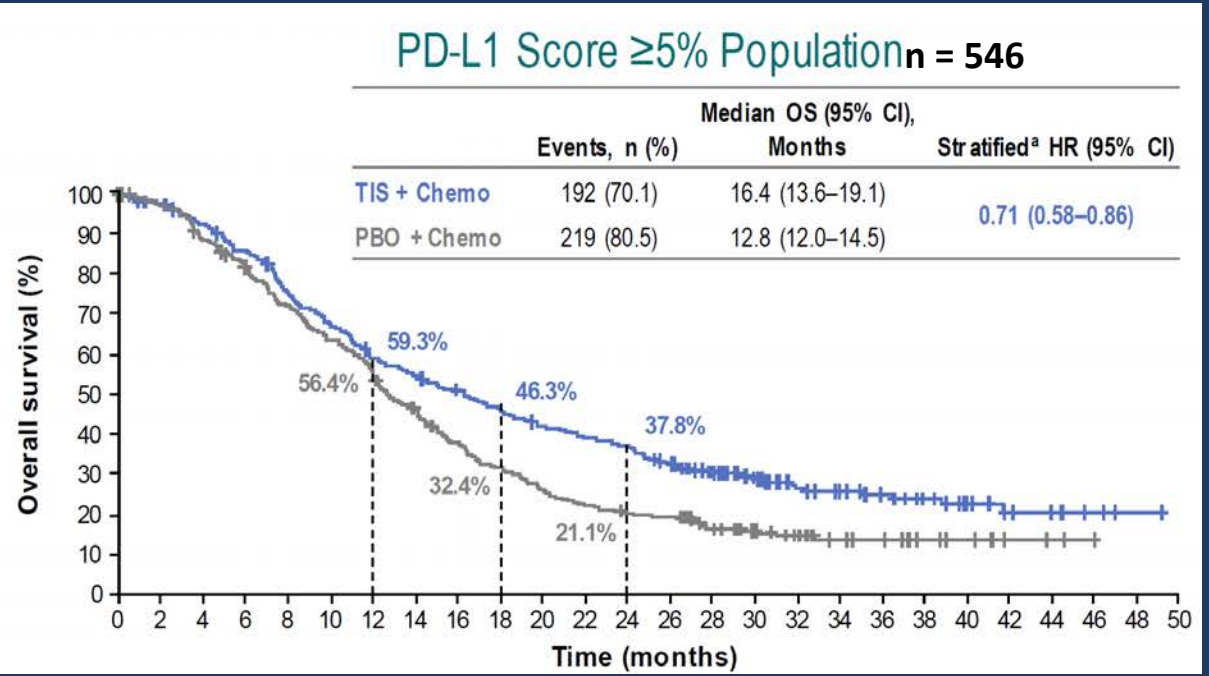

* Under review

¶ Under review

CPS, Combined positive score; FP, fluoropyrimidine; nivo, nivolumab; pembro, pembrolizumab; Tras, trastuzumab

# RATIONALE-305: Most recent phase 3 in gastroesophageal adenocarcinoma




**Primary endpoint: OS in PD-L1 TAP ≥ 5%**

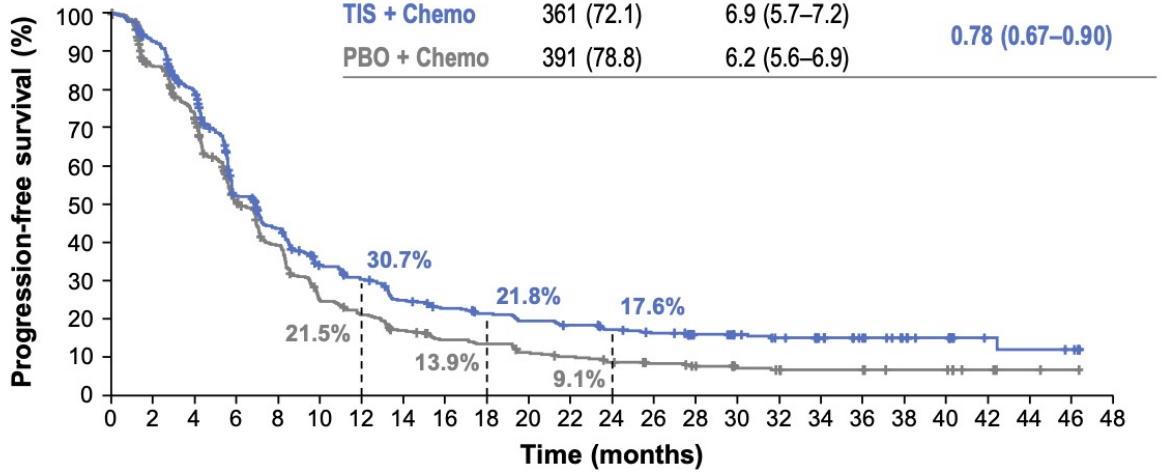
**Xu R-H et al, ESMO 2023**

SP263 assay by tumour area positivity (TAP) score

# RATIONALE-305: Most recent phase 3 in gastroesophageal adenocarcinoma

## 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) | |

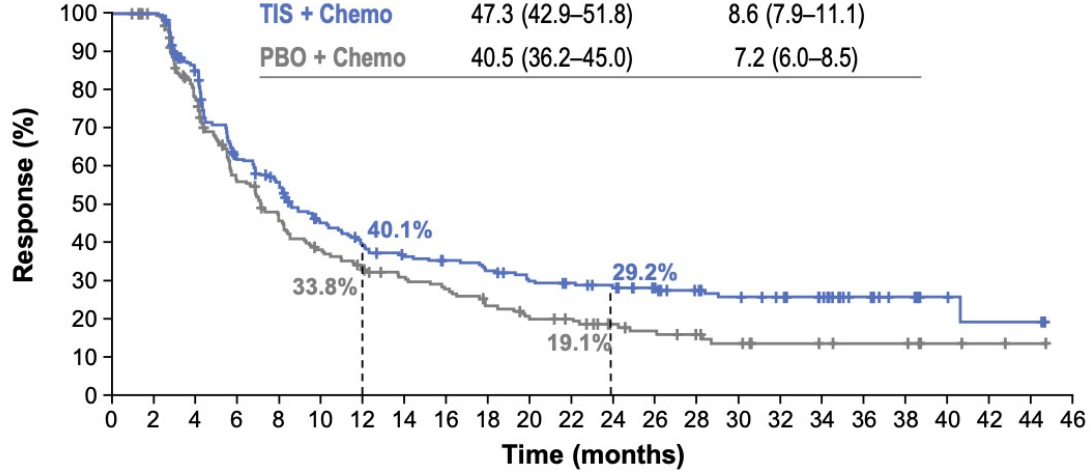



Number of patients at risk

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 |

**Key secondary endpoints: PFS, ORR**

Xu R-H et al, ESMO 2023

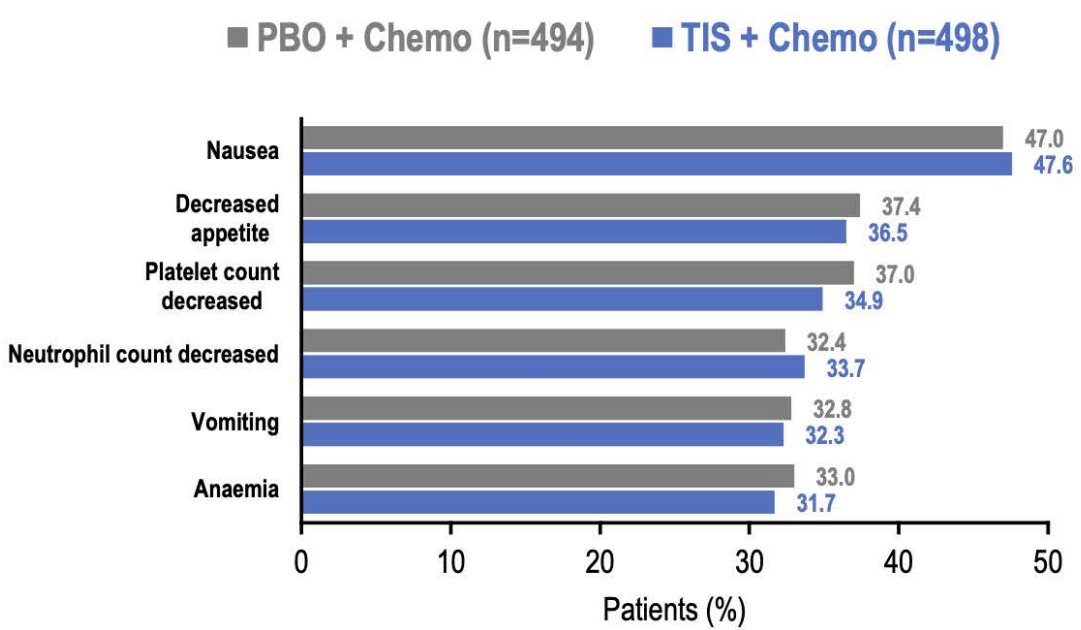
SP263 assay by tumour area positivity (TAP) score

# RATIONALE-305: Most recent phase 3 in gastroesophageal adenocarcinoma

## Summary of AE Incidence

| n (%) | TIS + Chemo (n=498) | PBO + Chemo (n=494) |
|---|---|---|
| Any TRAE | 483 (97.0) | 476 (96.4) |
| Grade ≥3 TRAEs | 268 (53.8) | 246 (49.8) |
| Serious TRAEs | 113 (22.7) | 72 (14.6) |
| Any immune-mediated AE | 154 (30.9) | 58 (11.7) |
| TRAEs leading to treatment discontinuation | 80 (16.1) | 40 (8.1) |
| TRAEs leading to death[a] | 6 (1.2) | 2 (0.4) |

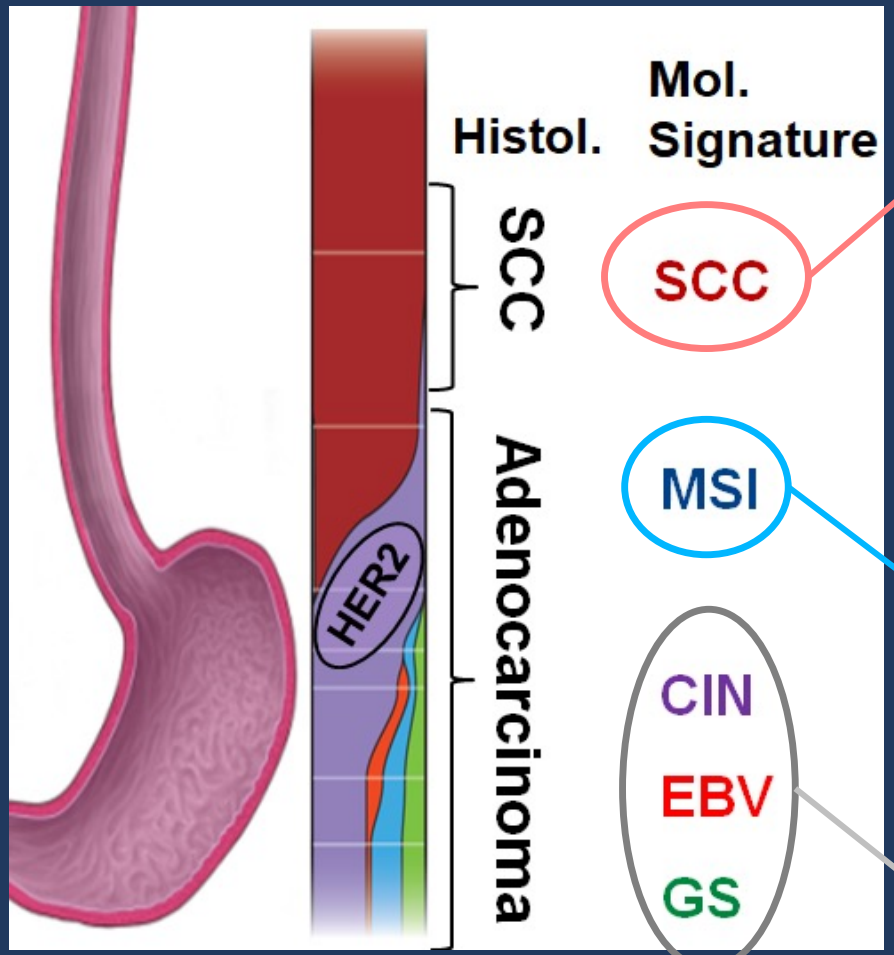
## TRAEs of Any Grade with Incidence ≥ 30%




Xu R-H et al, ESMO 2023

SP263 assay by tumour area positivity (TAP) score

# 2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal cancer (NCCN Category 1 or 2A)




Any PD-L1 status
Nivo + oxaliplatin/FP
Nivo + IPI

PD-L1 CPS ≥ 10
Pembro + oxaliplatin/FP

Pembro +/- chemo
Nivo + FOLFOX
Nivo + IPI
Dostarlimab

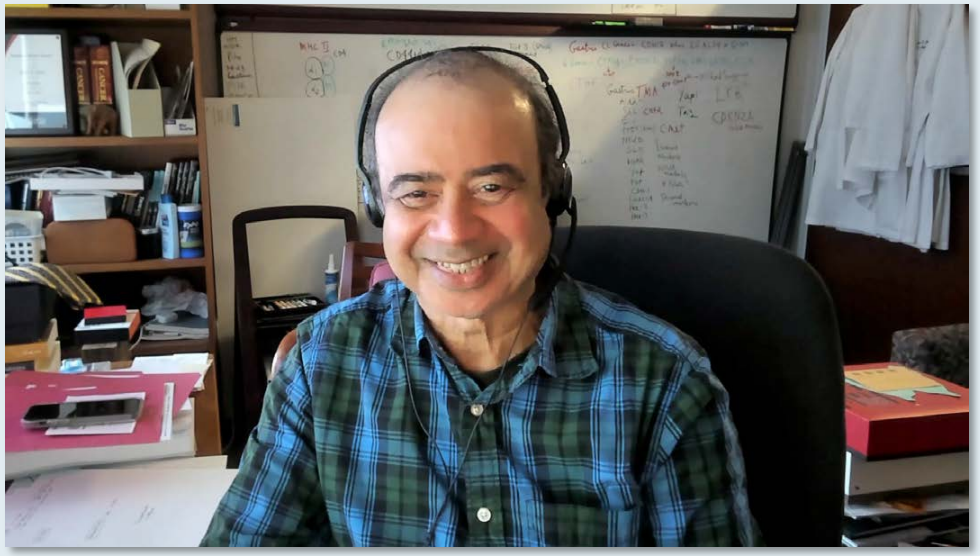
PD-L1 CPS ≥ 5-10 (CPS ≥ 1 ?)
Nivo or pembro + platin/FP

CPS, Combined positive score; FP, fluoropyrimidine; nivo, nivolumab; pembro, pembrolizumab; ICI, immune checkpoint inhibition; IPI, ipilimumab

# MODULE 3: Emerging Role of Therapy Targeting Claudin 18.2 in Advanced Gastric/GEJ Adenocarcinoma – Dr Shah

RTP
RESEARCH
TO PRACTICE

# Function of the claudin junction protein; role of zolbetuximab/IO combinations



Jaffer A Ajani, MD

Sunnie Kim, MD

RTP RESEARCH TO PRACTICE

# QUESTIONS FOR THE FACULTY

Jaffer A Ajani, MD

*What are your thoughts about the practical issues that may become evident as zolbetuximab moves forward in the regulatory process, including the types of assays and limits for claudin 18.2 positivity?*

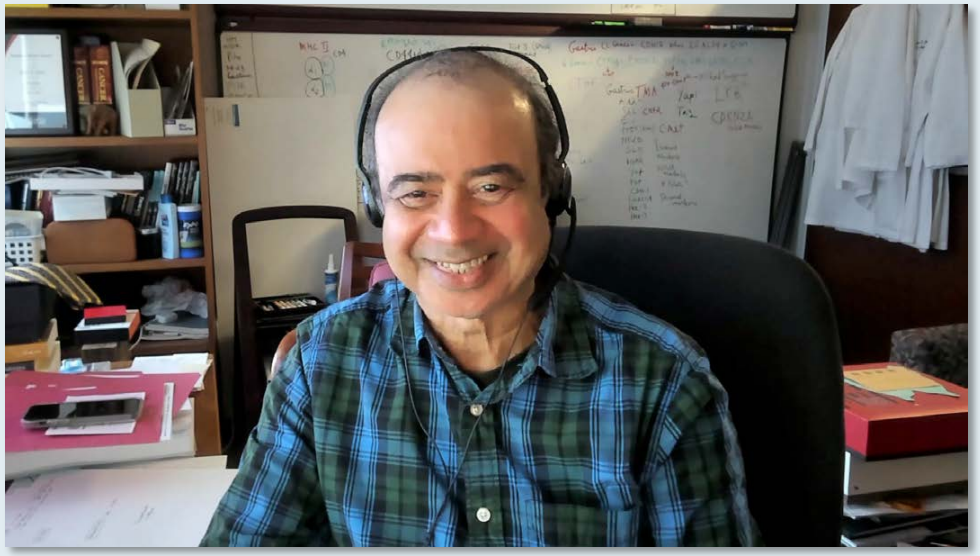
Sunnie Kim, MD

*Do you anticipate that zolbetuximab will eventually be combined with anti-PD-1 antibodies for patients with claudin 18.2-high, PD-L1-positive disease?*

RTP
RESEARCH
TO PRACTICE

# Management of zolbetuximab-associated acute GI toxicity

Sunnie Kim, MD



Jaffer A Ajani, MD

RTP
RESEARCH
TO PRACTICE

# QUESTIONS FOR THE FACULTY

Sunnie Kim, MD

***What are your strategies to prevent and manage acute zolbetuximab-associated gastrointestinal toxicities?***

Jaffer A Ajani, MD

***What is the role of prolonging infusions of zolbetuximab to mitigate nausea/vomiting?***

RTP
RESEARCH
TO PRACTICE

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

| | CPS 0 | CPS 1 |
|---|---|---|
|  Dr Ilson | Zolbetuximab | Zolbetuximab |
|  Dr Mehta | Zolbetuximab | Zolbetuximab |
|  Dr Moehler | Zolbetuximab/FOLFOX | Zolbetuximab/FOLFOX |
|  Dr Shah | Zolbetuximab | Zolbetuximab |
|  Dr Yoon | Zolbetuximab | Zolbetuximab |
|  Dr Ajani | Zolbetuximab + pembrolizumab | Zolbetuximab + pembrolizumab |
|  Dr Kim | Zolbetuximab | Zolbetuximab |

## Regulatory and reimbursement issues aside, which therapy, if any, would you add to chemotherapy as first-line treatment for a 65-year-old patient presenting with metastatic HER2-negative, CLDN18.2-positive, MSS gastric adenocarcinoma if their PD-L1 CPS was 5? CPS 10?

| | CPS 5 | CPS 10 |
|---|---|---|
|  Dr Ilson | Nivolumab | Nivolumab |
|  Dr Mehta | Zolbetuximab and if not tolerated nivolumab | Zolbetuximab and if not tolerated nivolumab |
|  Dr Moehler | FOLFOX/nivolumab | FOLFOX/nivolumab |
|  Dr Shah | Nivolumab | Nivolumab |
|  Dr Yoon | Zolbetuximab | Nivolumab |
|  Dr Ajani | Zolbetuximab + pembrolizumab | Zolbetuximab + pembrolizumab |
|  Dr Kim | Zolbetuximab + nivolumab | Zolbetuximab + nivolumab |

# Based on current available data and/or your personal experience, what is your global view of the acute emetogenic effect of zolbetuximab in terms of time of onset, prevention and treatment approaches?

| | Time of onset | Prevention | Tx approaches |
|---|---|---|---|
|  Dr Ilson | Early | Steroids, 5-HT3 and substance P inhibitors, olanzapine | NA |
|  Dr Mehta | Almost immediate | Steroids, NK-1 and 5-HT3 antagonists and olanzapine | Slower or split infusion |
|  Dr Moehler | First cycle | 5-HT3 antagonists, steroids, antidepressants | Reduce dose |
|  Dr Shah | Within 30 minutes | 5-HT3 inhibitors, steroids, aprepitant | Hold zolbetuximab and try again |
|  Dr Yoon | Within hours | Maximum | NA |
|  Dr Ajani | These are all manageable | These are all manageable | These are all manageable |
|  Dr Kim | During first cycle | Slow down infusion; maximal antiemetics | Slow down infusion; maximal antiemetics |

# Emerging Role of Therapy Targeting CLDN18.2 in Advanced Gastric/GEJ Adenocarcinoma

Manish A. Shah, MD FASCO

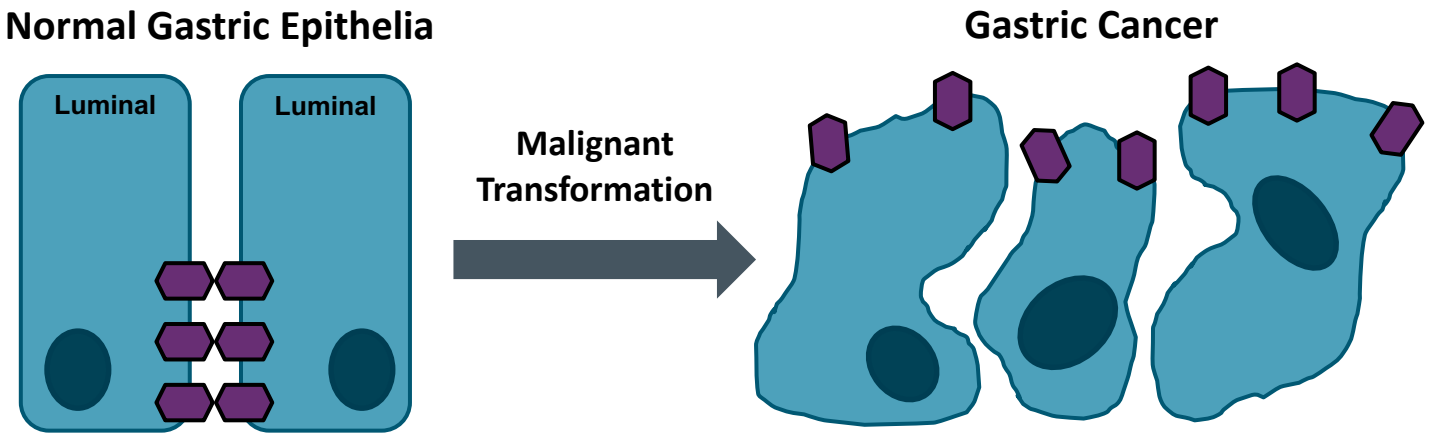
Weill Cornell Medicine/ New York-Presbyterian

January 18, 2024

# Current Options for Advanced/Metastatic Gastric Cancer

- Gastric cancer is the cause of almost 800,000 deaths worldwide yearly
- Standard of care for patients with advanced unresectable or metastatic gastric adenocarcinoma is chemotherapy, providing median OS of less than 1 year
  - There is a high unmet need in this patient group
- Genetic testing allows some patient subgroups to benefit from targeted therapy:
  - Trastuzumab: HER2+ disease
  - Nivolumab: PD-L1 combined positive score ≥5
  - CLDN18.2: Zolbetuximab with chemotherapy
- Further identification of molecular targets is needed to reach greater numbers of patients

# Claudin18.2: Leveraging Biology

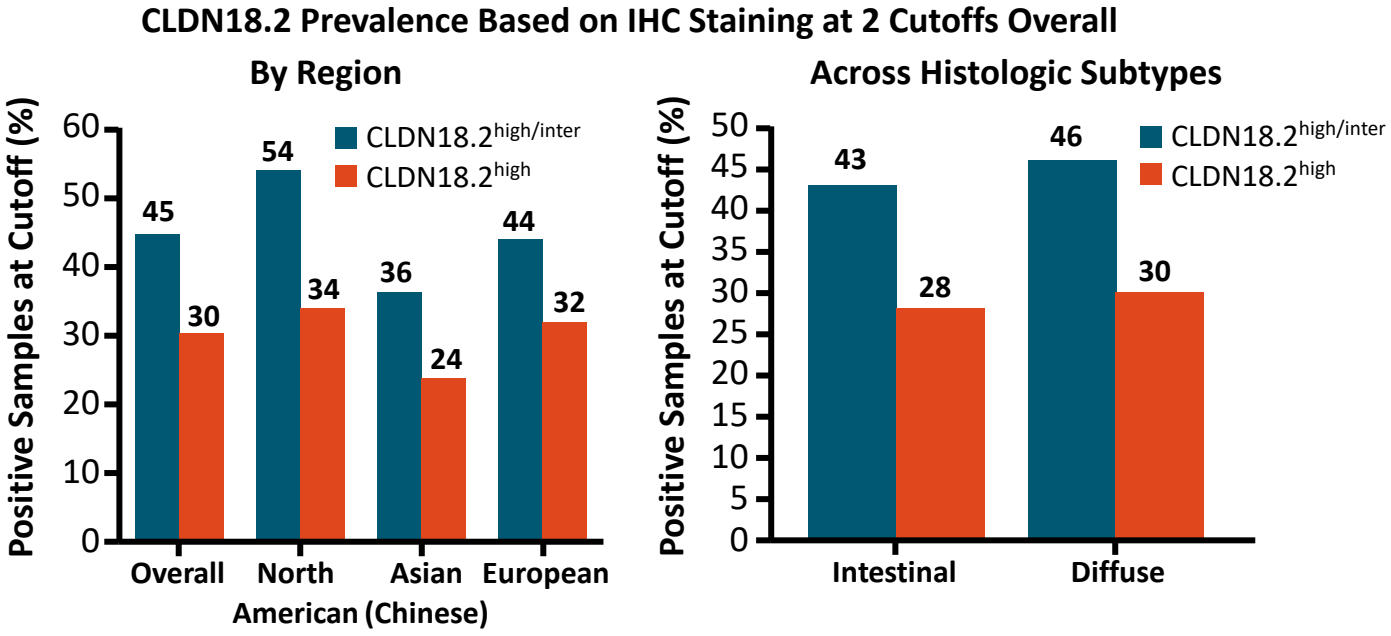


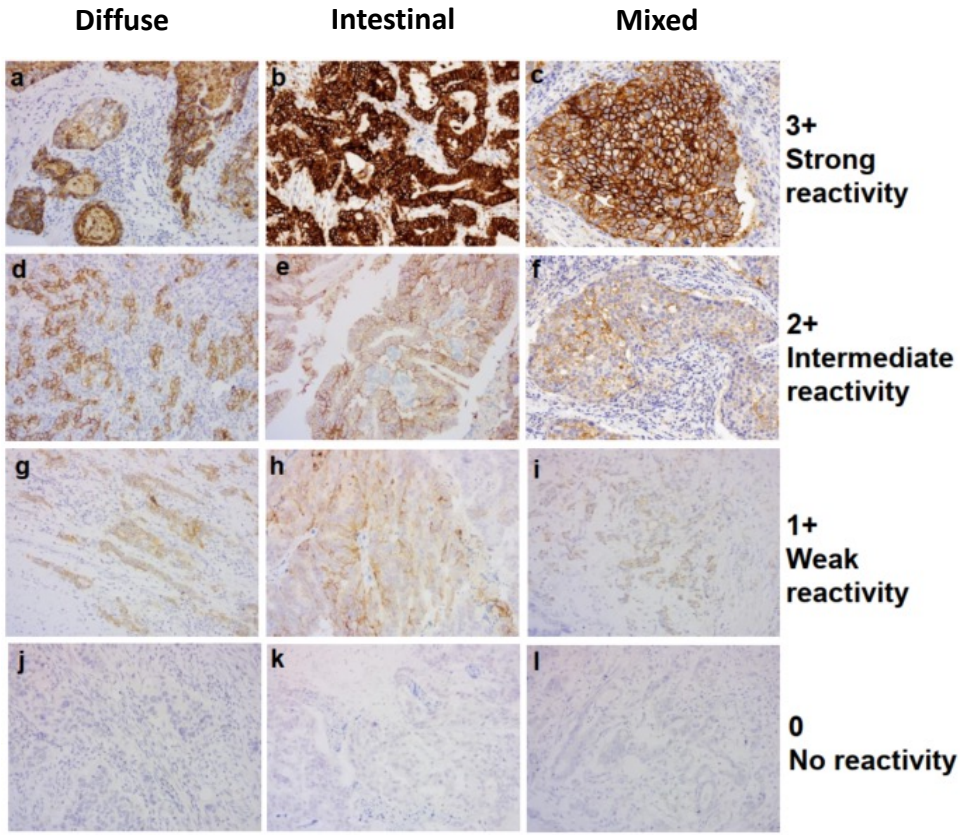

- Claudin18.2 is a major structural component of intercellular tight junctions
- Not routinely expressed in any normal tissue outside gastric mucosa (cancer-restricted antigen)
- Broadly expressed in several tumor types including gastric, GEJ, biliary, and pancreatic

Baek. Anticancer Res. 2019;39:6973.

# Claudin18.2: Scoring in Gastric Cancer

- IHC staining
- Common tumor cell expression thresholds:
  - ≥40%: moderate or intermediate
  - ≥70%: high
- No correlation with PD-L1
  - In fact, ~15-20% CLDN18.2 high tumors have PD-L1 CPS ≥5

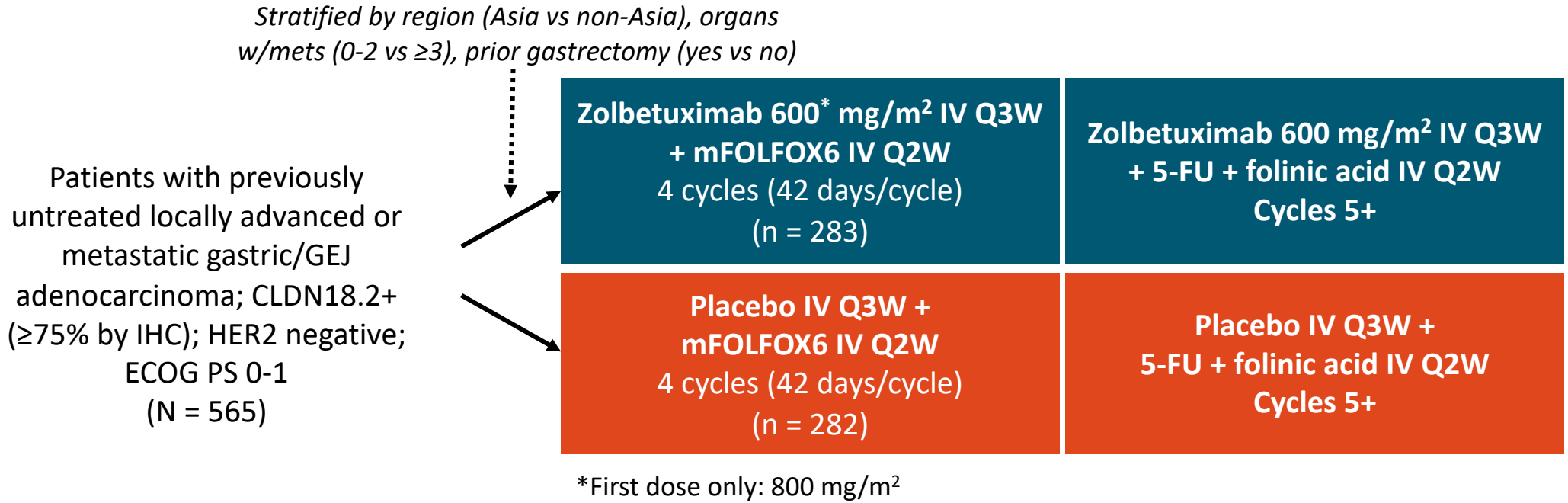



Baek. Anticancer Res. 2019;39:6973. Mao. SITC 2022. Abstr 105.

# SPOTLIGHT: Zolbetuximab + mFOLFOX6 in CLDN18.2+ Treatment Naive G/GEJ Cancer

- Global, randomized, double-blind phase III trial



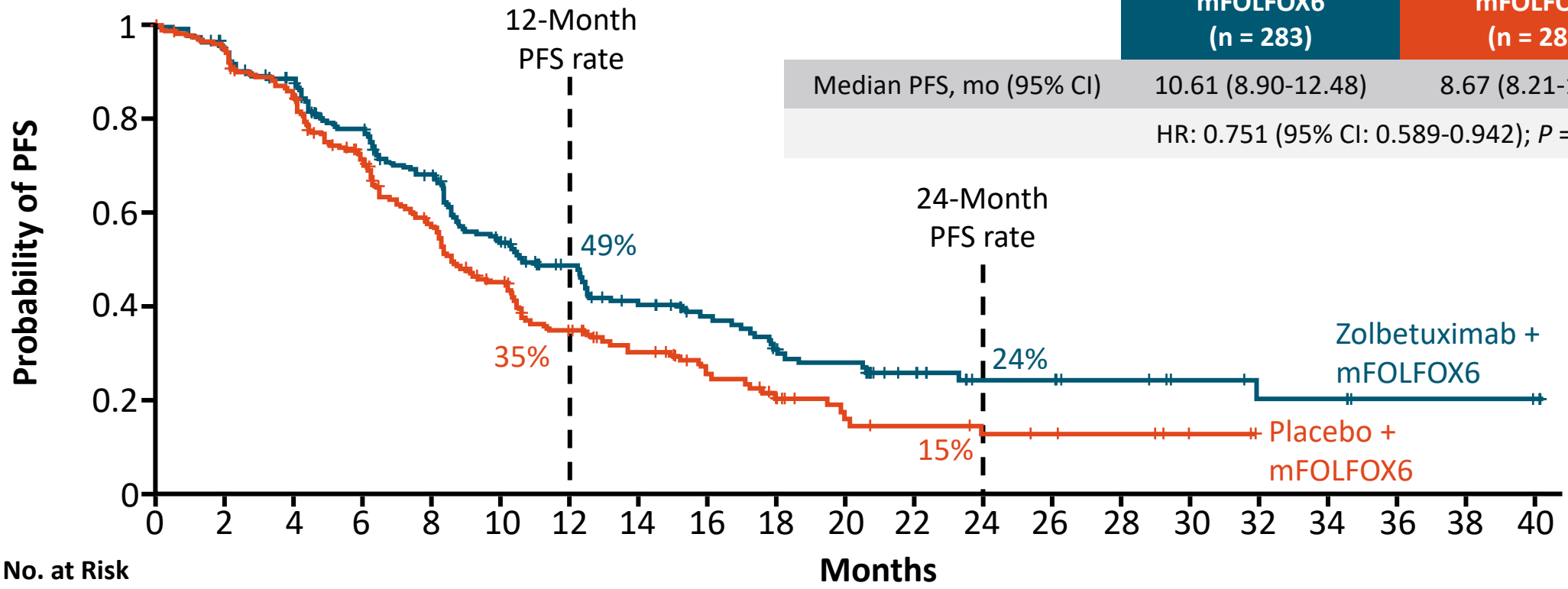

*First dose only: 800 mg/m²

- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, TTCD (GHS/QoL, PF, and QLQ-OG25-Pain score)
- **Additional endpoints:** ORR, DoR, safety, PROs

Shitara K et al. ASCO GI 2023. Abstr LBA292. Shitara K et al. *Lancet* 2023;401(10389):1655-1668.

# SPOTLIGHT: IRC-assessed PFS

| | Zolbetuximab + mFOLFOX6 (n = 283) | Placebo + mFOLFOX6 (n = 282) |
|---|---|---|
| Median PFS, mo (95% CI) | 10.61 (8.90-12.48) | 8.67 (8.21-10.28) |
| | HR: 0.751 (95% CI: 0.589-0.942); *P* = .0066 | |




**No. at Risk**

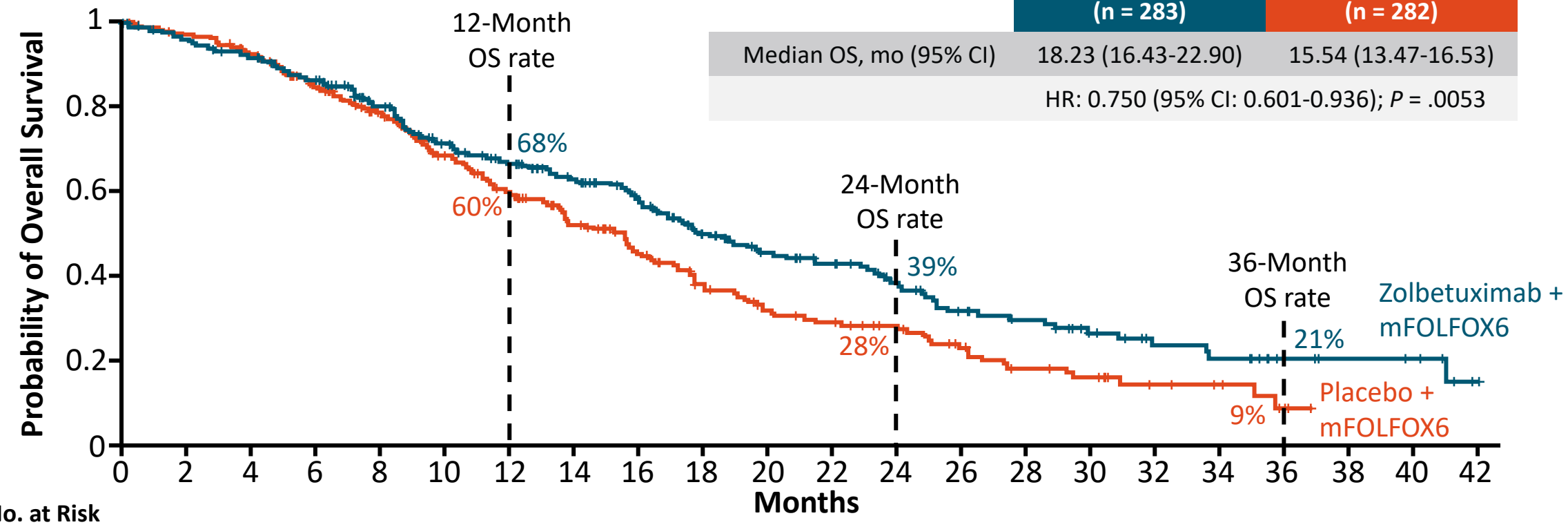
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zolbetuximab + mFOLFOX6 | 283 | 263 | 254 | 232 | 226 | 190 | 187 |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

Data cut-off: September 9, 2022. Median follow-up: 12.94 mo (zolbetuximab + FOLFOX6) vs 12.65 mo (placebo + FOLFOX6).

Shitara K et al. ASCO GI 2023. Abstr LBA292. Shitara K et al. *Lancet* 2023;401(10389):1655-1668.

# SPOTLIGHT: OS

| | Zolbetuximab + mFOLFOX6 (n = 283) | Placebo + mFOLFOX6 (n = 282) |
|---|---|---|
| Median OS, mo (95% CI) | 18.23 (16.43-22.90) | 15.54 (13.47-16.53) |
| | HR: 0.750 (95% CI: 0.601-0.936); *P* = .0053 | |




**No. at Risk**

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

Data cut-off: September 9, 2022. Median follow-up: 22.14 mo (zolbetuximab + FOLFOX6) vs 20.93 mo (placebo + FOLFOX6).

Shitara K et al. ASCO GI 2023. Abstr LBA292. Shitara K et al. *Lancet* 2023;401(10389):1655-1668.

# SPOTLIGHT: Response

| Characteristic | Zolbetuximab + mFOLFOX6 (n = 211) | Placebo + mFOLFOX6 (n = 211) |
|---|---|---|
| Pts with measurable disease, n | 128 | 131 |
| ORR, % (95% CI) | 60.7 (53.72-67.30) | 62.1 (55.17-68.66) |
| Best overall response, n (%) | | |
| ▪ CR | 12 (5.7) | 7 (3.3) |
| ▪ PR | 116 (55.0) | 124 (58.8) |
| ▪ SD | 45 (21.3) | 52 (24.6) |
| ▪ PD | 14 (6.6) | 14 (6.6) |
| Median DOR, mo (95% CI) | 8.51 (6.80-10.25) | 8.11 (6.47-11.37) |

Shitara K et al. ASCO GI 2023. Abstr LBA292. Shitara K et al. *Lancet* 2023;401(10389):1655-1668.

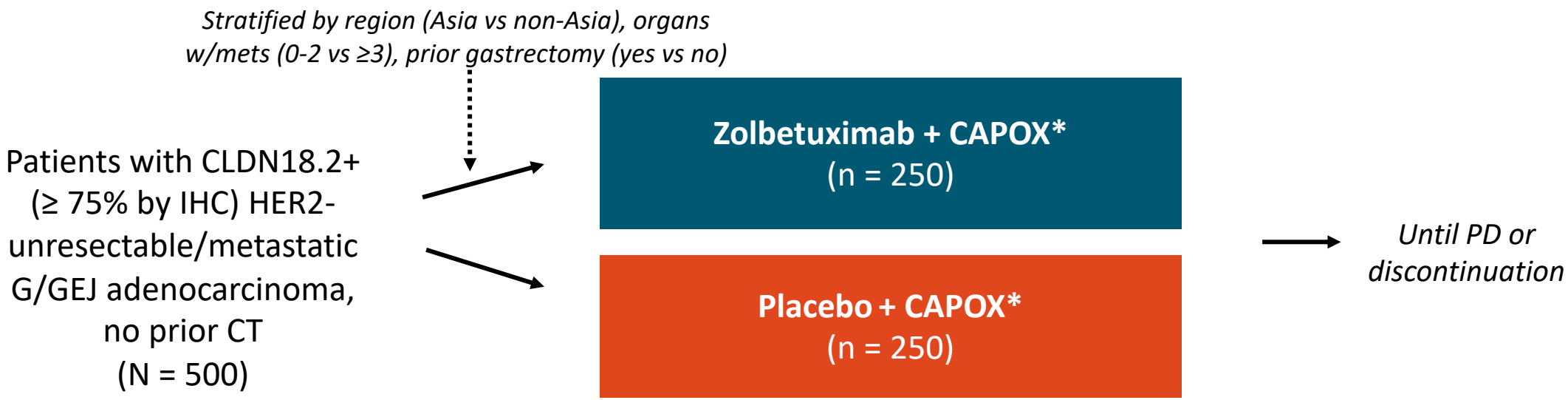
# SPOTLIGHT: Safety

| Event, n (%) | Zolbetuximab + mFOLFOX6 (n = 279) | | Placebo + mFOLFOX6 (n = 278) | |
|---|---|---|---|---|
| | All Grade | Grade ≥3 | All Grade | Grade ≥3 |
| All TEAEs | 278 (99.6) | 242 (86.7) | 277 (99.6) | 216 (77.7) |
| ▪ Nausea | 226 (81.0) | 45 (16.1) | 169 (60.8) | 18 (6.5) |
| ▪ Vomiting | 180 (64.5) | 45 (16.1) | 96 (34.5) | 16 (5.8) |
| ▪ Decreased appetite | 131 (47.0) | 16 (5.7) | 93 (33.5) | 9 (3.2) |
| Serious TEAEs | 125 (44.8) | - | 121 (43.5) | - |
| TRAEs leading to discontinuation of any study drug | 106 (38.0) | - | 82 (29.5) | - |
| TRAEs leading to discontinuation of zolbetuximab or placebo | 38 (13.6) | - | 6 (2.2) | - |
| TRAEs leading to death | 5 (1.8) | | 4 (1.4) | |

Shitara K et al. ASCO GI 2023. Abstr LBA292. Shitara K et al. *Lancet* 2023;401(10389):1655-1668.

# GLOW: Zolbetuximab + CAPOX in CLDN18.2+ G/GEJ Cancer

- Global, double-blind, placebo-controlled, randomized phase III study

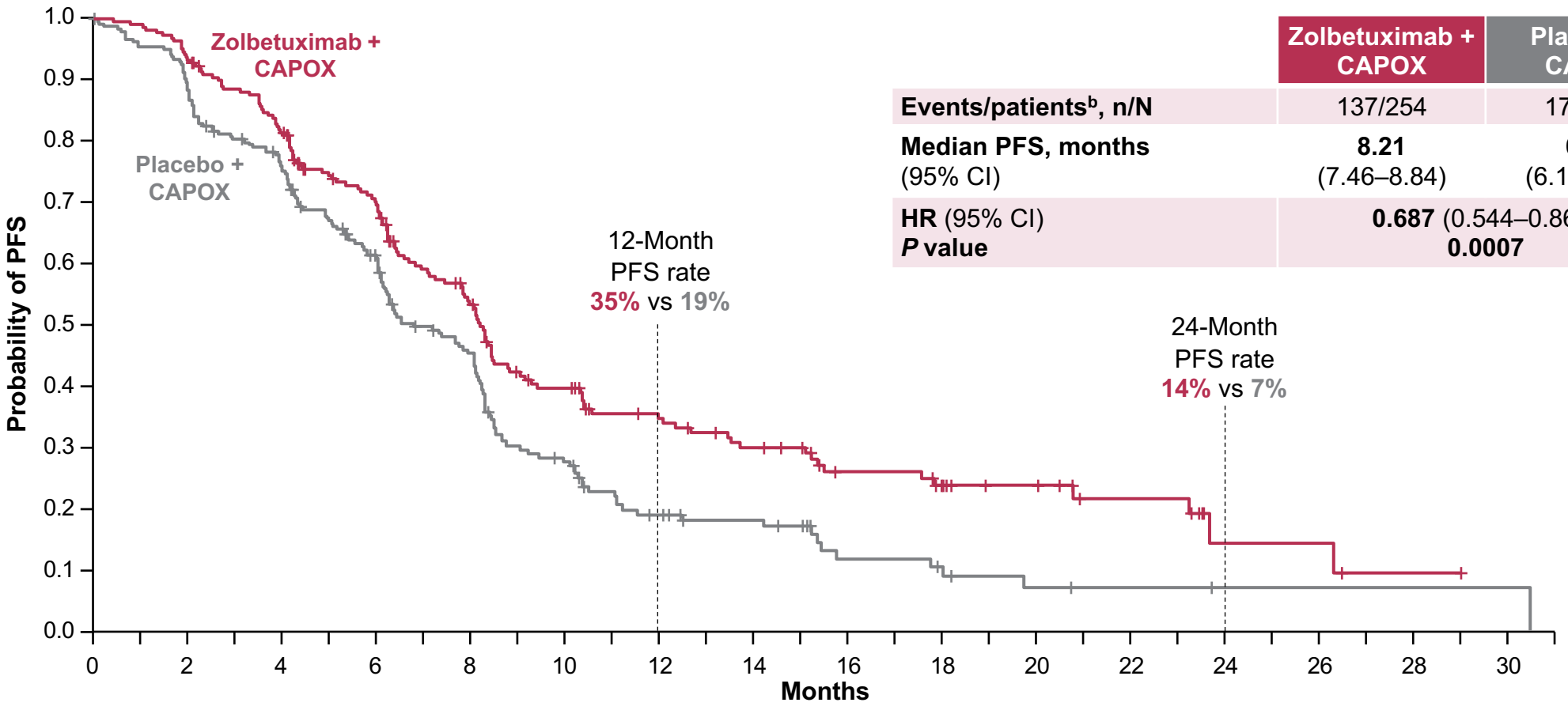



* Zolbetuximab dosed initially as 800 mg/mm$^2$ IV followed by 600 mg/mm$^3$ IV Q3W. CAPOX dosed as 21d cycles of oxaliplatin 130 mg/mm$^2$ IV up to 8 cycles and capecitabine at investigator's discretion cycle 9+.

- **Primary endpoint:** IRC-assessed PFS
- **Secondary endpoints:** OS, ORR, DOR, safety, PK, QoL

Shah MA et al. ASCO GI 2022. Abstr TPS365. NCT03653507. Shah MA et al. *Nat Med* 2023;29(8):2133-2141.

# Primary End Point: PFS by Independent Review Committee




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

**No. at Risk**

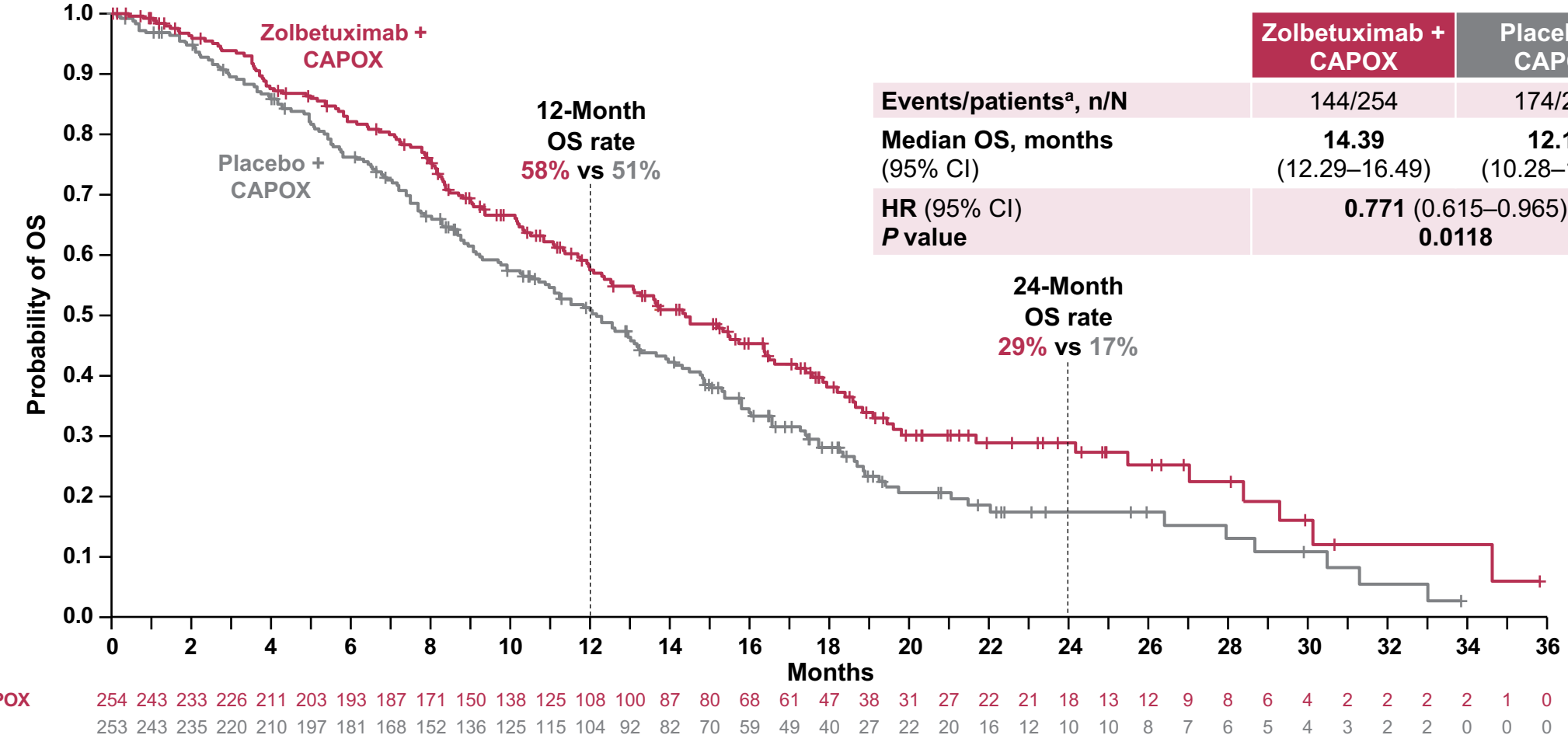
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zolbetuximab + CAPOX | 254 | 223 | 205 | 187 | 171 | 141 | 132 | 104 | 91 | 66 | 61 | 47 | 45 | 41 | 37 | 35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

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

**Data cutoff: October 7, 2022; Median follow-up = 12.62 months (zolbetuximab + CAPOX) vs 12.09 months (placebo + CAPOX).**

Shah MA et al. *Nat Med* 2023;29(8):2133-2141.

# Key Secondary End Point: OS




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

**No. at Risk**

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zolbetuximab + CAPOX | 254 | 243 | 233 | 226 | 211 | 203 | 193 | 187 | 171 | 150 | 138 | 125 | 108 | 100 | 87 | 80 | 68 | 61 | 47 | 38 | 31 | 27 | 22 | 21 | 18 | 13 | 12 | 9 | 8 | 6 | 4 | 2 | 2 | 2 | 2 | 1 | 0 |
| Placebo + CAPOX | 253 | 243 | 235 | 220 | 210 | 197 | 181 | 168 | 152 | 136 | 125 | 115 | 104 | 92 | 82 | 70 | 59 | 49 | 40 | 27 | 22 | 20 | 16 | 12 | 10 | 10 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 2 | 0 | 0 | 0 |

**OS was significantly longer in patients treated with zolbetuximab + CAPOX vs placebo + CAPOX**

**Subsequent anticancer therapies were administered to 47% of patients in the zolbetuximab arm and 55% in the placebo arm**

**Data cutoff: October 7, 2022; Median follow-up = 17.71 months (zolbetuximab + CAPOX) vs 18.43 months (placebo + CAPOX).**

Shah MA et al. *Nat Med* 2023;29(8):2133-2141.

# Zolbetuximab and Pembrolizumab (Cohort 3A): Response Data

| | Cohort 1A Zolbetuximab Monotherapy ($n = 27$[a]) | Cohort 2 Zolbetuximab + mFOLFOX6 ($n = 21$) | Cohort 3A Zolbetuximab + Pembrolizumab ($n = 3$) |
|---|---|---|---|
| Best overall response, *n* (%)[b] | | | |
| Confirmed CR | 0 | 0 | 0 |
| Confirmed PR | 0 | 15 (71.4) | 0 |
| Unconfirmed CR | 0 | 0 | 0 |
| Unconfirmed PR | 0 | 1 (4.8) | 0 |
| Stable disease | 6 (22.2) | 2 (9.5) | 1 (33.3) |
| Non-CR/non-progressive disease | 6 (22.2) | 3 (14.3) | 1 (33.3) |
| Progressive disease | 12 (44.4) | 0 | 1 (33.3) |
| Not evaluable | 3 (11.1) | 0 | 0 |
| ORR (confirmed) | | | |
| ORR, *n* (%) | 0 | 15 (71.4) | 0 |
| 95% CI (%)[c] | (0.00–12.77) | (47.82–88.72) | (0.00–70.76) |
| ORR (confirmed and unconfirmed) | | | |
| ORR, *n* (%) | 0 | 16 (76.2) | 0 |
| 95% CI (%)[c] | (0.00–12.77) | (52.83–91.78) | (0.00–70.76) |
| DCR (confirmed) | | | |
| DCR, *n* (%)[d] | 12 (44.4) | 21 (100.0) | 2 (66.7) |
| 95% CI (%)[c] | (25.48–64.67) | (83.89–100.00) | (9.43–99.16) |
| DCR (confirmed and unconfirmed) | | | |
| DCR, *n* (%)[d] | 15 (55.6) | 21 (100.0) | 2 (66.7) |
| 95% CI (%)[c] | (35.33–74.52) | (83.89–100.00) | (9.43–99.16) |

Klempner SJ et al. *Clin Cancer Res* 2023;29(19):3882-91.

# Zolbetuximab and Pembrolizumab (Cohort 3A): PFS Analysis

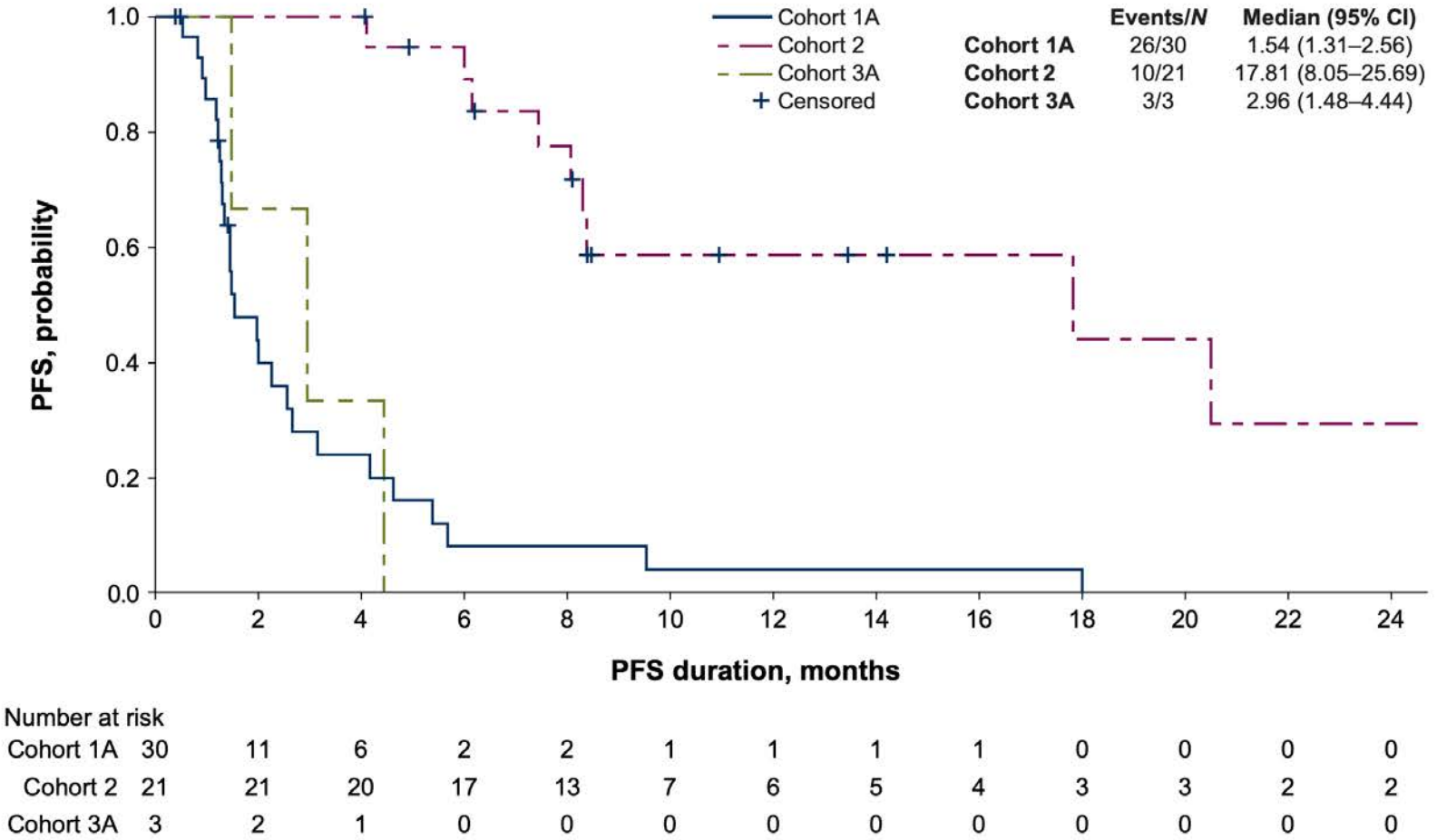
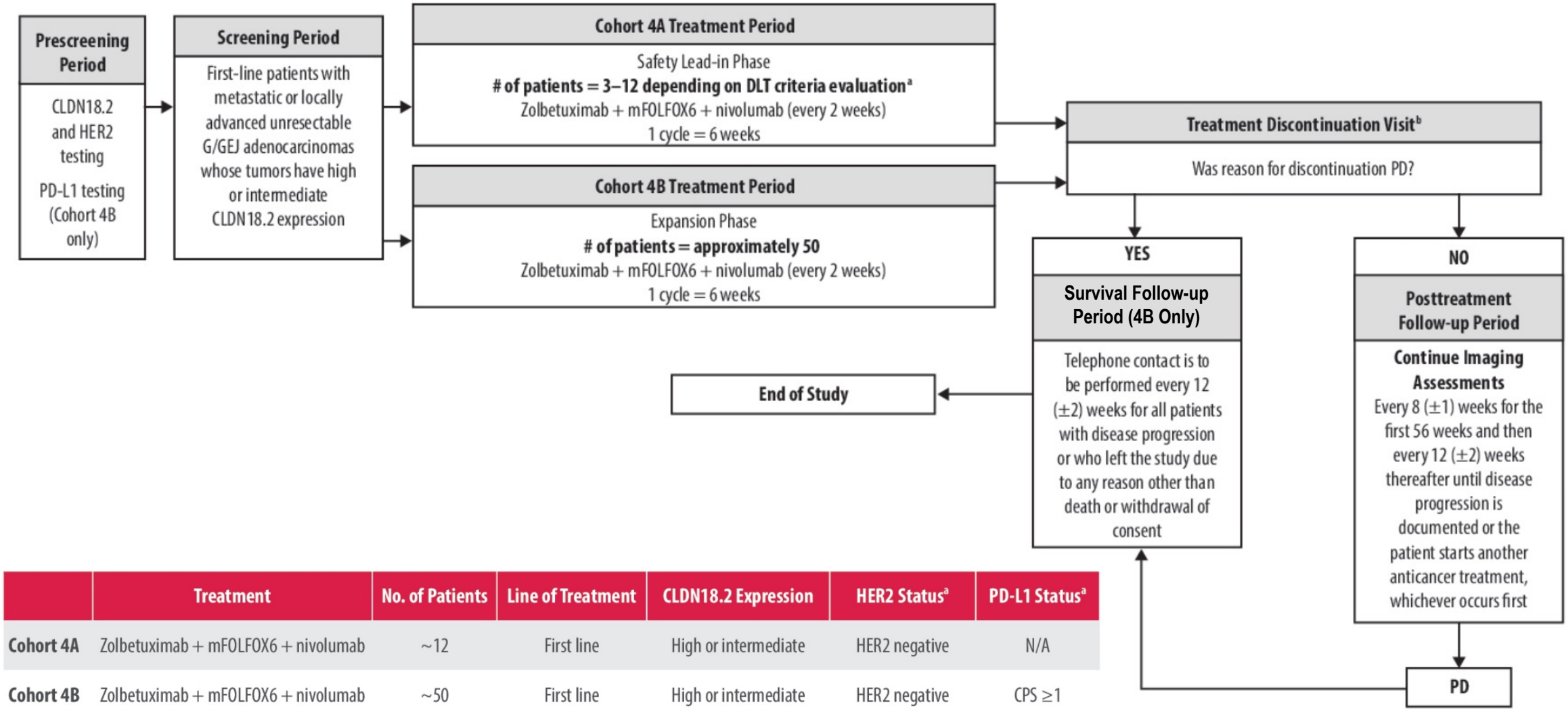



**Figure 1.**

PFS based on Independent Review in the Safety Population (Kaplan–Meier). Cohort 1A, zolbetuximab monotherapy ($n = 30$); Cohort 2, zolbetuximab + mFOLFOX6 ($n = 21$); Cohort 3A, zolbetuximab + pembrolizumab ($n = 3$).

Klempner SJ et al. *Clin Cancer Res* 2023;29(19):3882-91.

# Zolbetuximab and Nivolumab: Cohort 4A/4B in ILUSTRO Study




| | Treatment | No. of Patients | Line of Treatment | CLDN18.2 Expression | HER2 Status[a] | PD-L1 Status[a] |
|---|---|---|---|---|---|---|
| **Cohort 4A** | Zolbetuximab + mFOLFOX6 + nivolumab | ~12 | First line | High or intermediate | HER2 negative | N/A |
| **Cohort 4B** | Zolbetuximab + mFOLFOX6 + nivolumab | ~50 | First line | High or intermediate | HER2 negative | CPS ≥1 |

Shitara K et al. ASCO 2023;Abstract TPS4173.

# FDA Issues Complete Response Letter for Zolbetuximab for Advanced CLDN18.2+ Gastric Cancer

## Press Release: January 9, 2024

“The FDA has issued a complete response letter for a biologics license application for zolbetuximab (IMAB362) as a treatment for those with Claudin 18.2 (CLDN18.2)–positive, locally advanced, unresectable or metastatic, HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma.

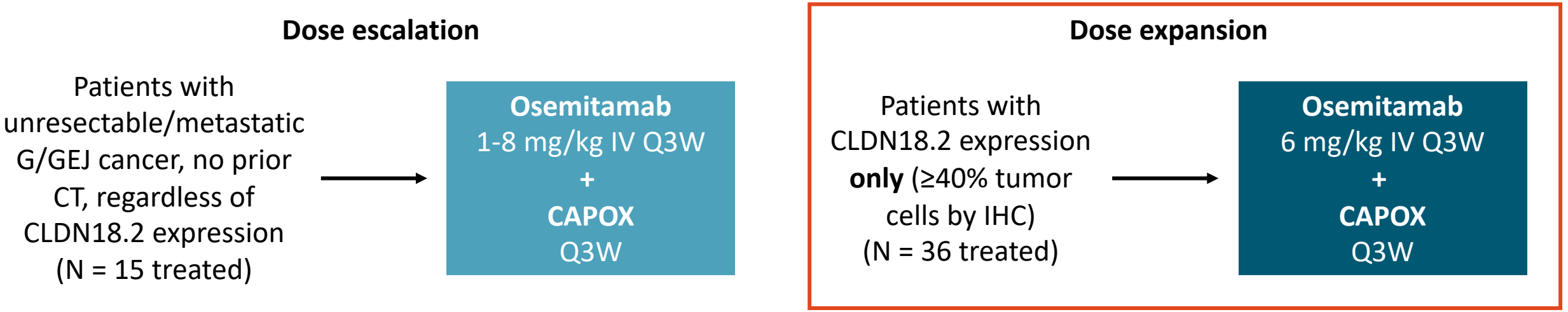
The regulatory agency highlighted that it could not approve the application for zolbetuximab in this indication due to insufficiencies pertaining to a pre-license inspection at a third-party manufacturing site for the agent.

Moreover, no additional clinical data or studies were requested to affirm the agent’s efficacy or safety. Developers are collaborating with the FDA and the third-party manufacturer to meet the concerns associated with the inspection.”

https://www.cancernetwork.com/view/fda-issues-crl-for-zolbetuximab-in-advanced-cldn18-2-gastric-cancer

# Anti-CLDN18.2 Antibody Osemitamab (TST001) in CLND18.2+ G/GEJ Cancer

- Recombinant humanized anti-CLDN18.2 monoclonal IgG1 antibody
- 2-part, open-label, multicenter, phase I study in China
  - Part 1 established RP2D for osemitamab monotherapy; Part 2 evaluates combination therapies
  - Other trial cohorts include pancreatic, BTC, CRC, and NSCLC




- **Primary endpoints:** Safety, MTD, RP2D, DLTs
- **Secondary endpoints:** PK/PD, immunogenicity, ORR, DOR, CBR, PFS

Gong. ESMO 2022. Abstr 3520. NCT04495296.

2023 ASCO® ANNUAL MEETING

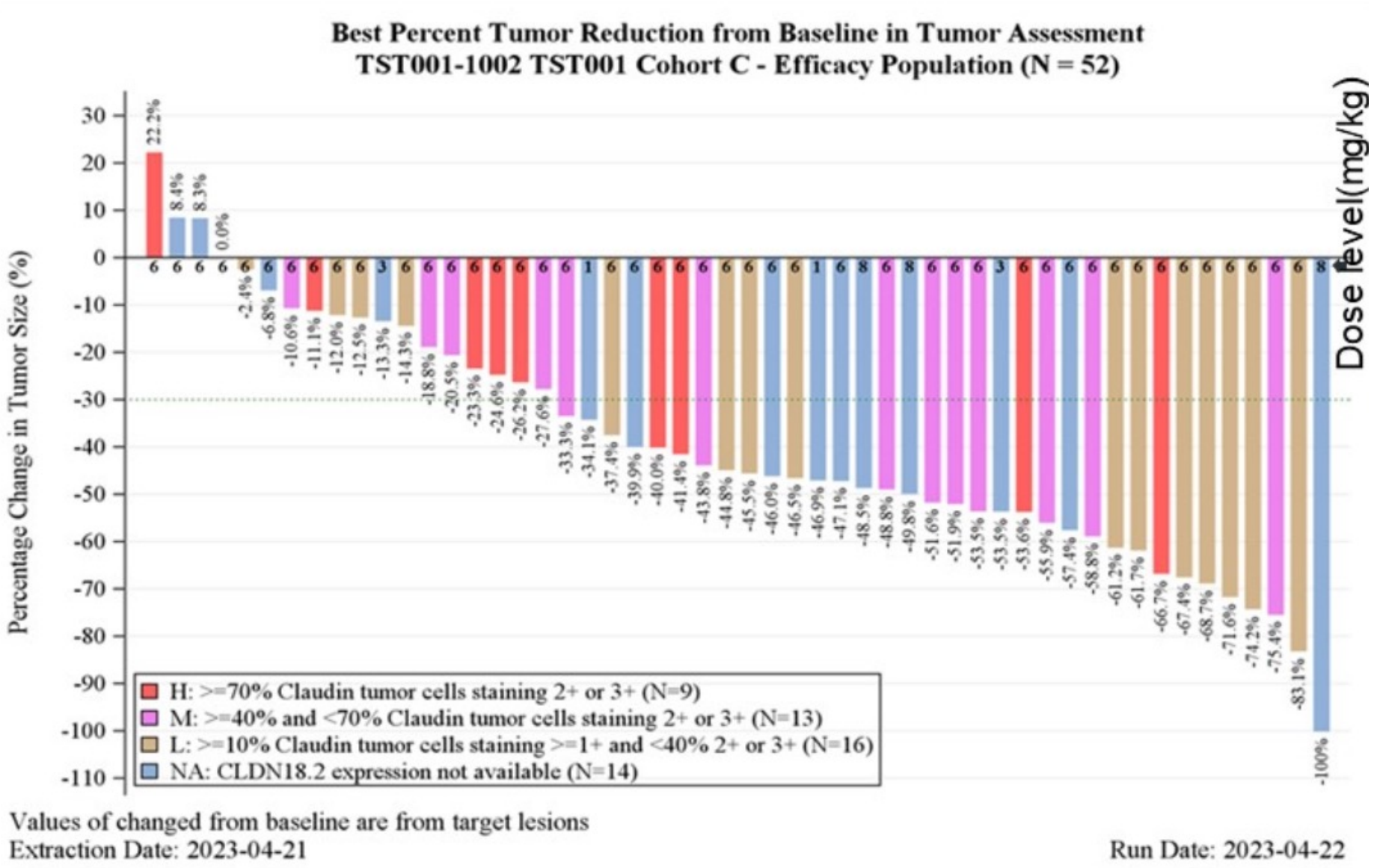
**Abstract 4046:**

# TST001 in Combination with Capecitabine and Oxaliplatin (CAPOX) as a First-Line Treatment of Advanced G/GEJ Cancer

## -updated data of Cohort C from a Phase I/IIa, Multi-center Study (TranStar102/TST001-1002)

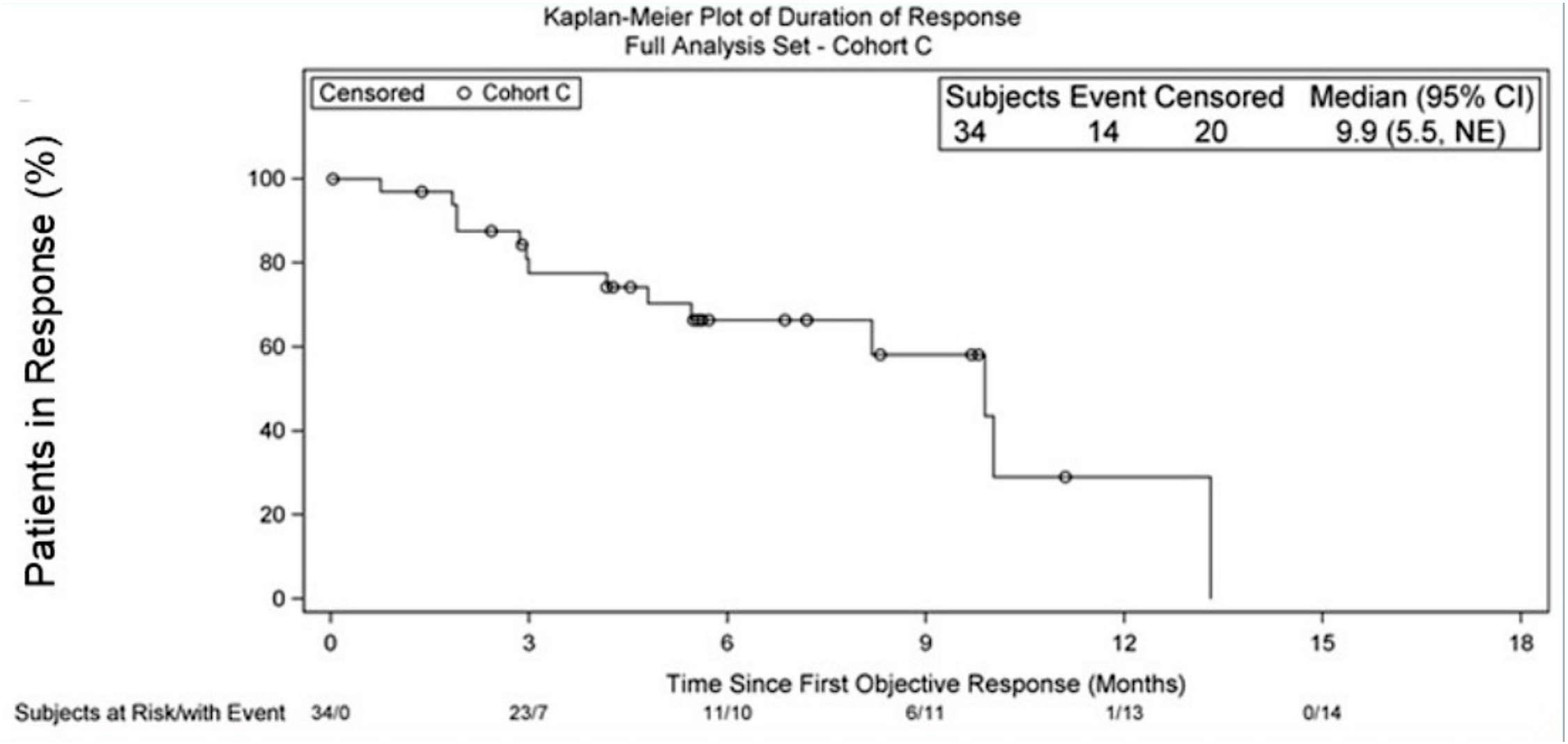
Authors: Lin Shen, Dan Liu, Ning Li, Weijian Guo, Tianshu Liu, Hongli Li, Jiayi Li, Yuxian Bai, Yanhong Deng, Zhi-xiang Zhuang, Meili Sun, Qingxia Fan, Fuyou Zhao, Liang Han, Zhenzhong Xia, Jianming Wang, Chuan Qi, Li Xu, Xueming Qian, Caroline Germa

# Osemitamab and CAPOX for First-Line GEJ



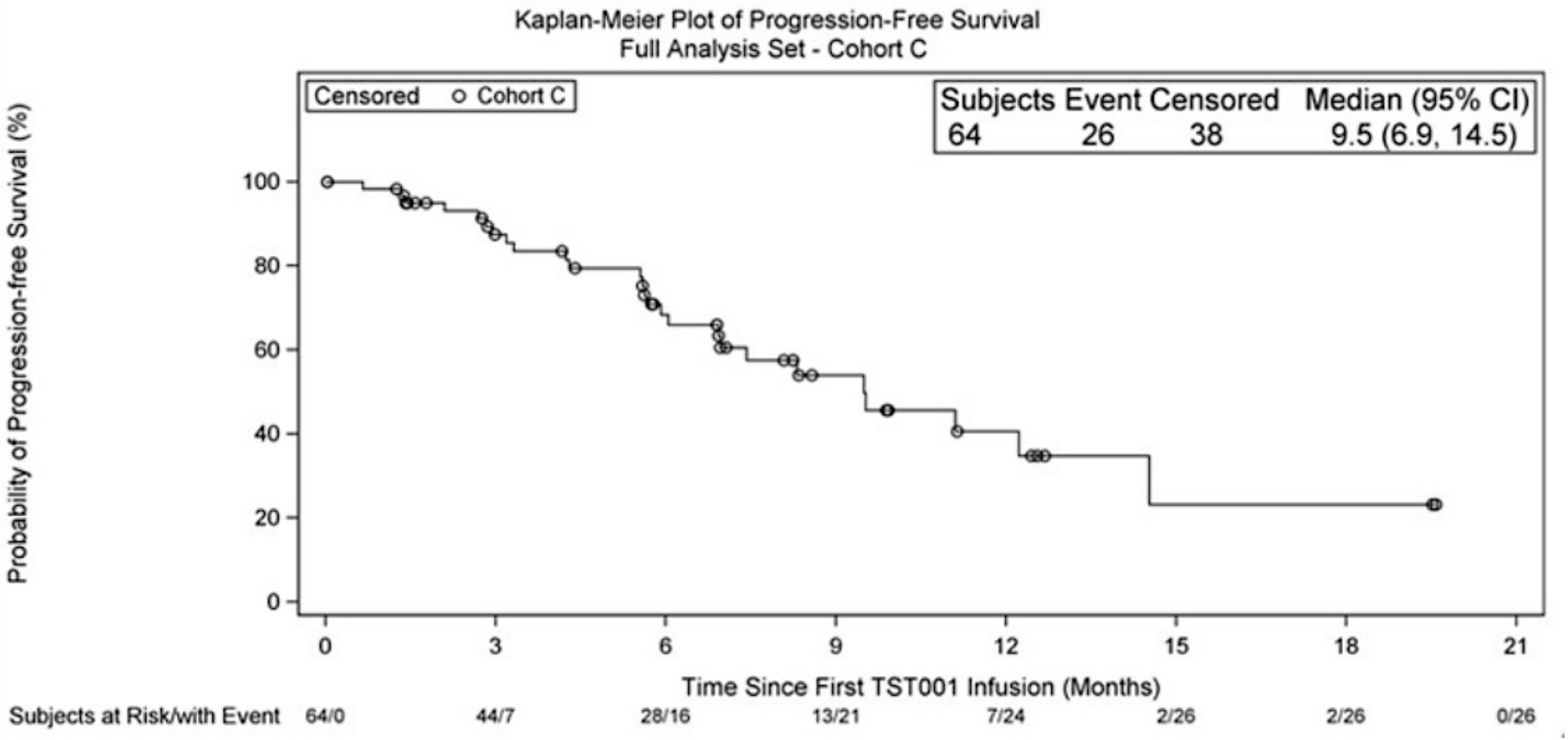

Shen L et al. ASCO 2023;Abstract 4046.

# Osemitamab and CAPOX for First-Line GEJ




Shen L et al. ASCO 2023;Abstract 4046.

# Osemitamab and CAPOX for First-Line GEJ




Shen L et al. ASCO 2023;Abstract 4046.

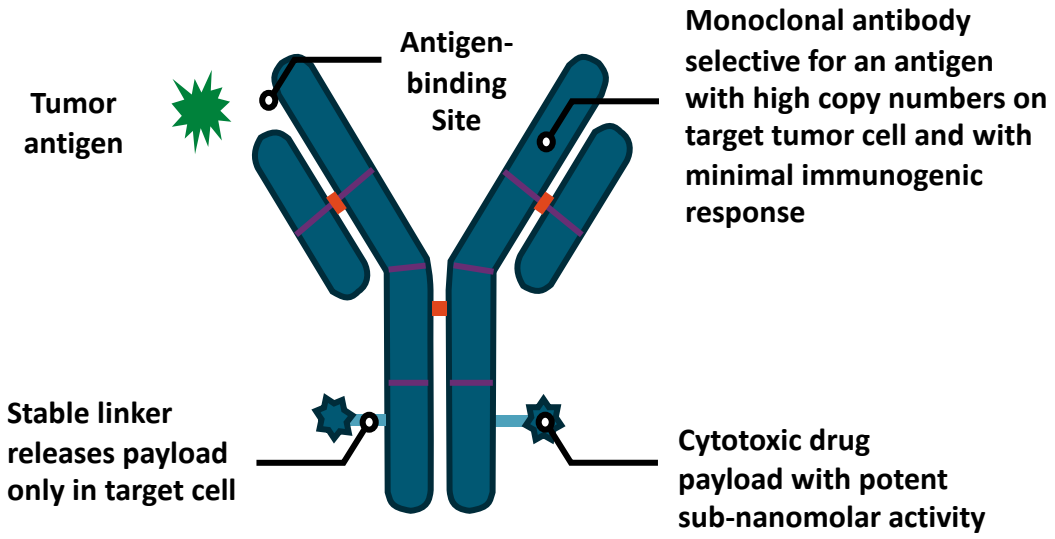
# Enrolling Trials of CLDN18.2 mAbs

| Agent | Trial | Phase | G/GEJ Patient Criterion | Location |
|---|---|---|---|---|
| Zolbetuximab + pembrolizumab | ILUSTRO Cohort 3 NCT03505320 [1] | II | CLDN18.2 expression in ≥50% of tumor cells (IHC) | US, Europe, Asia |
| Osemitamab (TST001) + nivolumab | NCT04396821 [2] | I/IIa | **Dose-finding:** CLDN18.2 expression not required **Dose expansion:** CLDN18.2 expression required | US |
| Osemitamab (TST001) + CAPOX or paclitaxel | NCT04495296 [3] | I/IIa | CLDN18.2 expression in ≥40% of tumor cells (IHC) **CAPOX combination:** HER2-, no prior systemic therapy **Paclitaxel combination:** ≥1 prior systemic therapy | China |

1. Klempner. ASCO GI 2021. Abst TPS260. 2. Gabrail. ASCO GI 2022. Abstr TPS375. 3. Shen L. ASCO 2023. Abstr 4046.

# Antibody Drug Conjugates (ADC)

- Monoclonal antibody linked to a cytotoxic drug designed to widen the therapeutic window by focusing delivery to specific cells




- Payload:
  - DAR (drug antibody ratio)[2]
  - Topo I inhibitors, MMAE derivatives (microtubule interference), other cytotoxics, other active moieties[2]
- Antibody epitope: associated ‘extras’
  - Signaling interference via ligand blocking, dimerization interference, internalization, and degradation[2]
  - ADCC[3]
- Linker: primarily influences circulating free-drug vs release in cells[2,3]

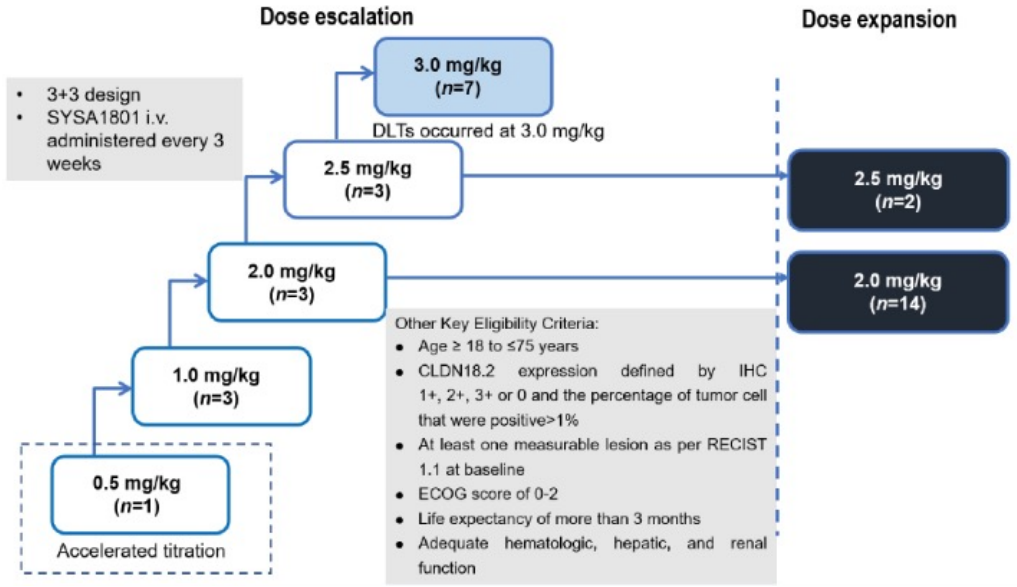
1. Drago. Nat Rev Clin Oncol. 2021;18:327. 2. Rinnerthaler. Int J Mol Sci. 2019;20:1115. 3. Nejadmoghaddam. Avicenna J Med Biotechnol. 2019;11:3.

# SYSA1801 (EO-3021): CLDN18.2-Targeted ADC

- Payload: MMAE with bystander killing, ADCC, and complement-dependent cytotoxicity
- Ongoing phase Ia/Ib, multicenter, open-label, single-arm study in China

**Phase Ia dose escalation**

Patients with advanced/metastatic solid tumors (N = 33 treated)




- Interim data as of Nov 5, 2022:
  - 33 patients treated up to dose 3.0 mg/kg
  - 2 DLTs at 3.0 mg/kg (Nausea and vomiting). Grade 3 or higher TRAEs occurred in 24%

Wang ASCO 2023. Abstr 3016.

# SYSA1801 (EO-3021): CLDN18.2-Targeted ADC

- Payload: MMAE with bystander killing, ADCC, and complement-dependent cytotoxicity
- Ongoing phase Ia/Ib, multicenter, open-label, single-arm study in China

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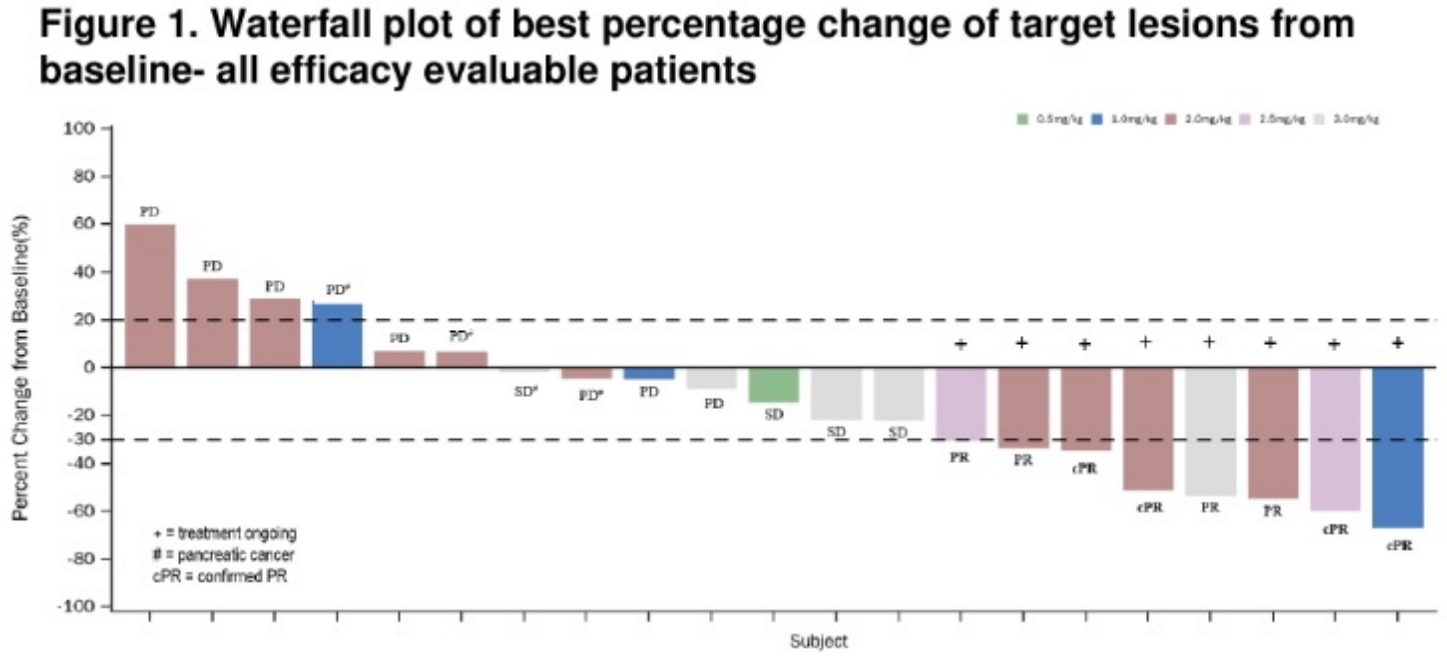



- Interim data as of Nov 5, 2022:
  - Among 17 pts with gastric cancer, ORR was 47.1%
  - 1 patient who failed previous anti-CLDN18.2 Ab therapy achieved PR with SYSA1801 2.0 mg/kg

Wang ASCO 2023. Abstr 3016.

# Enrolling Trials of CLDN18.2 ADCs

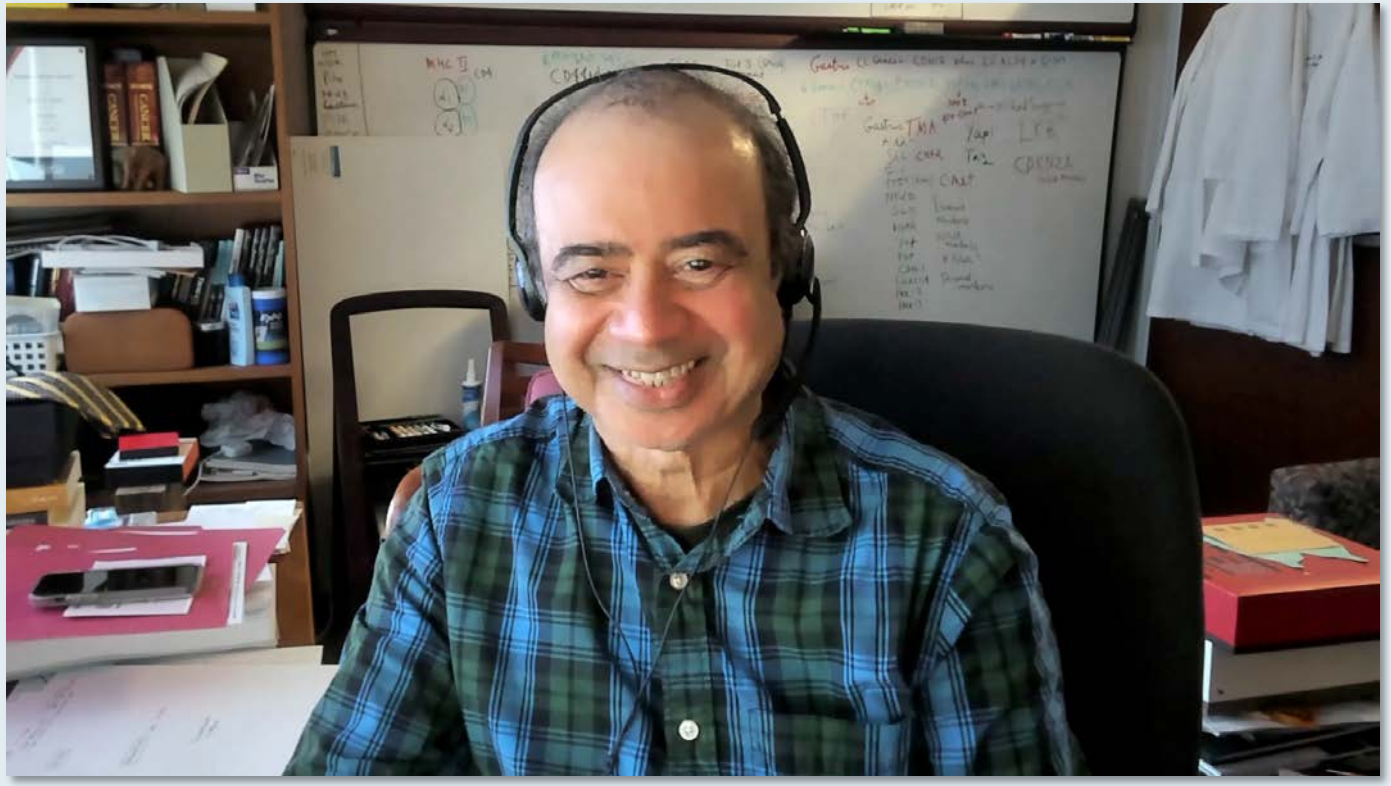
| Agent | Trial | Phase | G/GEJ Patient Criterion | Location |
|---|---|---|---|---|
| TPX-4589/ LM-302 (Payload: MMAE) | NCT05001516 | I/II | **Dose-finding:** CLDN18.2 expression not required **Dose expansion:** CLDN18.2 expression required (≥10% by IHC) | US |
| EO-3021/ SYSA1801 (Payload: MMAE) | NCT05009966 | I | **Dose-finding:** CLDN18.2 expression not required **Dose expansion:** CLDN18.2 expression required (≥40% by IHC) | China |

# Conclusions

- CLDN18.2 is a validated target in upper GI cancers
- CLDN18.2 is expressed in about 30-40% of gastric/GEJ tumors
  - Minimal overlap with PD-L1 CPS positive tumors
- Zolbetuximab in combination with chemotherapy is a new standard of care for CLDN18.2 positive gastric/GEJ tumors
- New molecules targeting CLDN18.2 are under development and have already shown encouraging activity

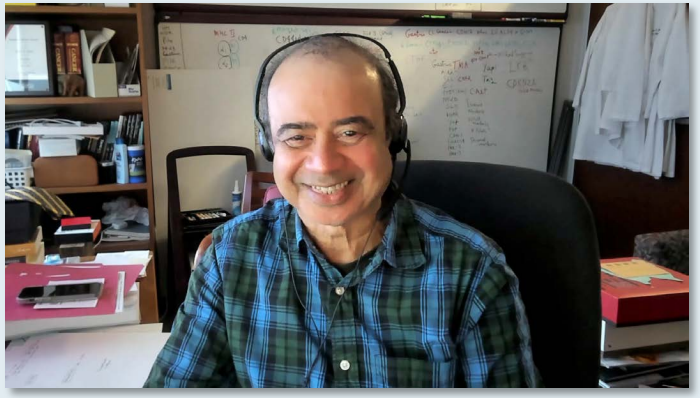
# MODULE 4: Current Considerations in the Care of Patients with HER2-Positive Gastroesophageal Cancers – Dr Moehler

# Choice of second-line treatment; screening for ILD in patients receiving trastuzumab deruxtecan



**Jaffer A Ajani, MD**

# QUESTIONS FOR THE FACULTY



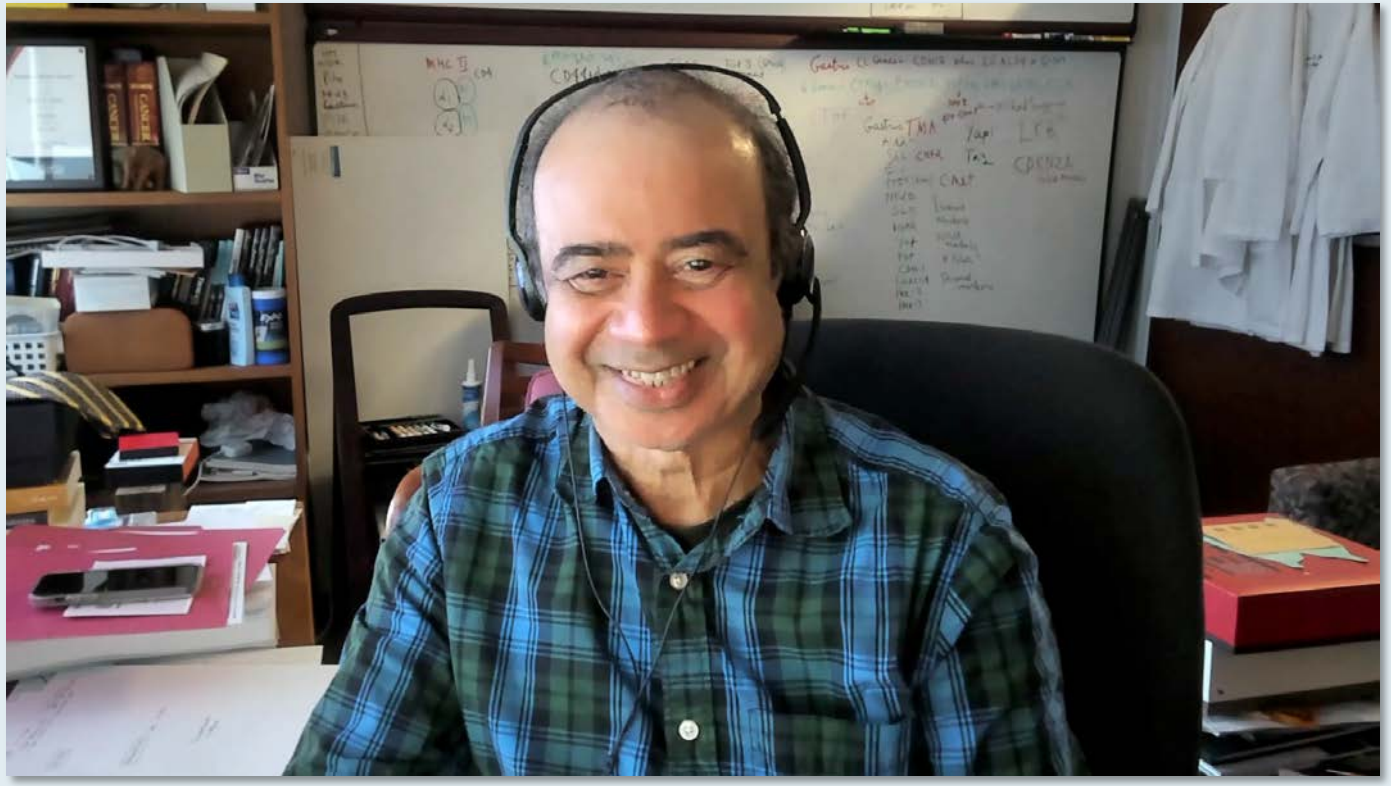
Jaffer A Ajani, MD

*How do you think through the sequencing of anti-HER2 therapies in advanced gastroesophageal cancers?*

*What is your approach to HER2 testing, and do you repeat testing in patients with progressive disease?*

*What is your approach to the prevention and management of trastuzumab deruxtecan-associated ILD?*

# Novel HER2-targeted bispecific antibody zanidatamab



Jaffer A Ajani, MD

RTP
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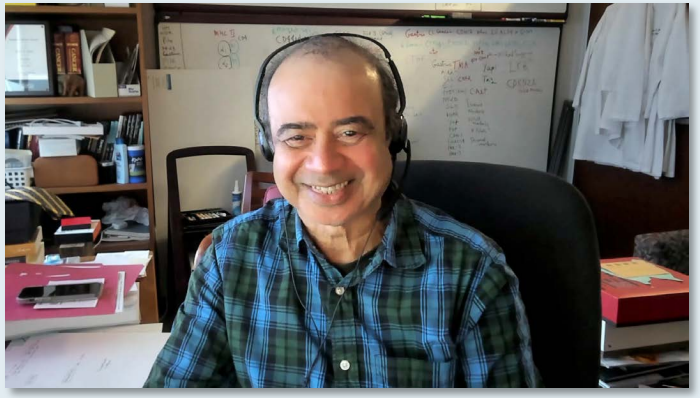
TO PRACTICE

# QUESTIONS FOR THE FACULTY



**Jaffer A Ajani, MD**

***What is the future of zanidatamab in advanced gastroesophageal cancers?***

***What has been your personal experience with zanidatamab in this disease?***

RTP
RESEARCH
TO PRACTICE

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

| | |
|---|---|
|  Dr Ilson | Trastuzumab deruxtecan |
|  Dr Mehta | Trastuzumab deruxtecan if still HER2+, ramucirumab/paclitaxel if HER2- |
|  Dr Moehler | Ramucirumab/paclitaxel |
|  Dr Shah | Ramucirumab/paclitaxel |
|  Dr Yoon | Trastuzumab deruxtecan or ramucirumab/paclitaxel |
|  Dr Ajani | Trastuzumab deruxtecan |
|  Dr Kim | Trastuzumab deruxtecan if still HER2+, ramucirumab + either paclitaxel or FOLFIRI if HER2- |

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

| | |
|---|---|
|  Dr Ilson | Trastuzumab deruxtecan |
|  Dr Mehta | Trastuzumab deruxtecan if still HER2+, ramucirumab/paclitaxel if HER2- |
|  Dr Moehler | Ramucirumab/paclitaxel |
|  Dr Shah | Trastuzumab deruxtecan |
|  Dr Yoon | Trastuzumab deruxtecan or ramucirumab/paclitaxel |
|  Dr Ajani | Trastuzumab deruxtecan |
|  Dr Kim | Trastuzumab deruxtecan if still HER2+, ramucirumab/paclitaxel or ramucirumab/FOLFIRI if HER2- |

RTP RESEARCH TO PRACTICE

# At which grade of interstitial lung disease would you permanently discontinue therapy with trastuzumab deruxtecan for a patient with HER2-positive gastric/GEJ adenocarcinoma?

| | |
|---|---|
|  Dr Ilson | Grade 2 |
|  Dr Mehta | Grade 2 |
|  Dr Moehler | Grade 3 |
|  Dr Shah | Grade 2 |
|  Dr Yoon | Grade 2 |
|  Dr Ajani | Grade 2 and above |
|  Dr Kim | Grade 2 |

RTP RESEARCH TO PRACTICE

# Current Considerations in the Care of Patients with HER2-Positive Gastroesophageal Cancers

Markus Moehler, MD

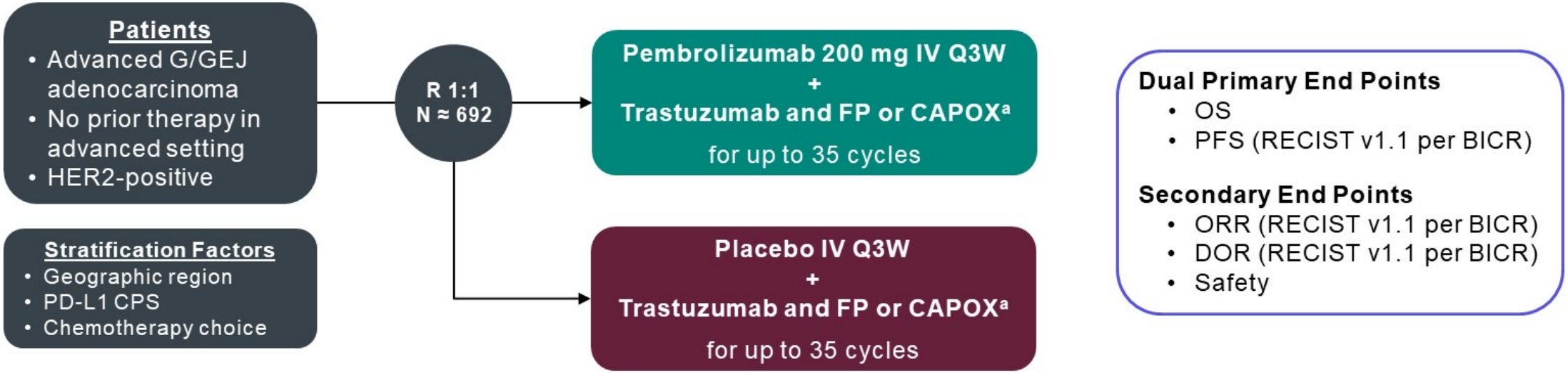
Johannes Gutenberg-University Clinic, Mainz, Germany

# Agenda

- Available data from the Phase III KEYNOTE-811 trial evaluating the addition of pembrolizumab to chemotherapy and trastuzumab for previously untreated HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma
- Efficacy and safety findings from the DESTINY-Gastric01 and DESTINY-Gastric02 studies evaluating trastuzumab deruxtecan for patients with progressive HER2-positive gastric/GEJ cancer
- Mechanism of action of the novel HER2-targeted bispecific antibody zanidatamab
- Published findings with zanidatamab/chemotherapy as first-line treatment for advanced HER2-positive gastroesophageal adenocarcinoma
- Design, eligibility criteria and key efficacy and safety endpoints of the Phase III HERIZON-GEA-01 trial of up-front zanidatamab and chemotherapy with or without tislelizumab for HER2-positive gastroesophageal adenocarcinoma

# KEYNOTE-811: Study Design

## Double-Blind Phase 3 Study of Pembrolizumab + Trastuzumab and Chemotherapy vs Placebo + Trastuzumab and Chemotherapy as First-Line Therapy For HER2-Positive Unresectable or Metastatic G/GEJ Cancer (NCT03615326)




[a]Trastuzumab dose: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP dose: 5-fluorouracil 800 mg/m$^2$ IV on D1-5 Q3W + cisplatin 80 mg/m$^2$ IV Q3W. CAPOX dose: capecitabine 1000 mg/m$^2$ BID on D1-14 Q3W + oxaliplatin 130 mg/m$^2$ IV Q3W.
BICR, blinded independent central review; CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100).

Janjigian YY et al. ASCO 2021;Abstract 4013.

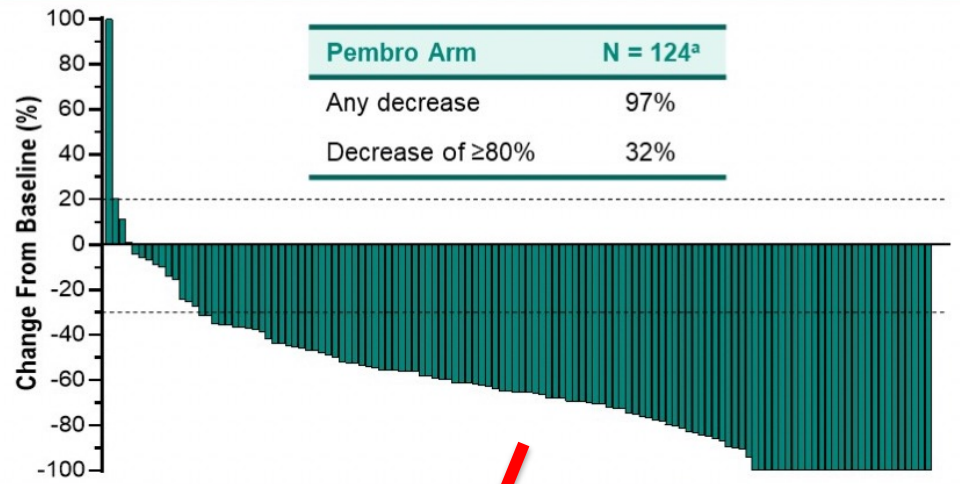
# KEYNOTE-811: First Results 2021

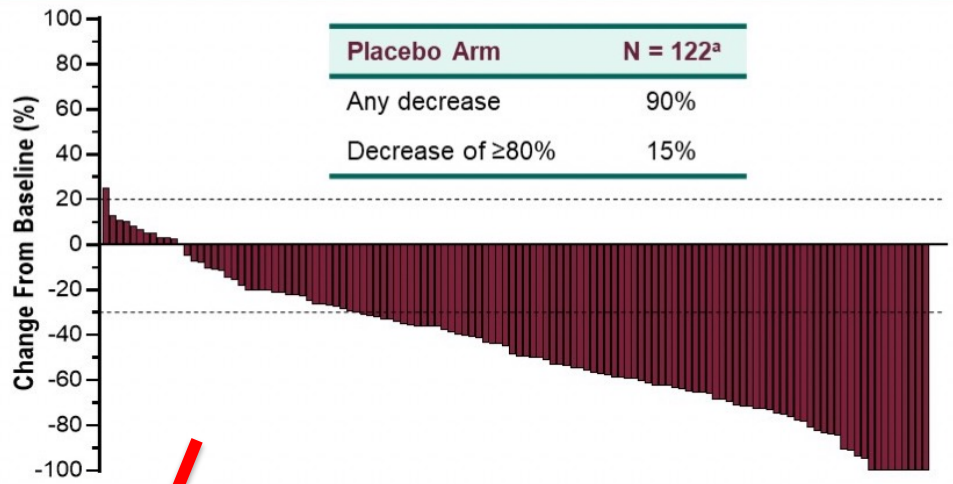
**US FDA APROVAL 2021**
**EMA APPROVAL 2023**

**PHASE III KEYNOTE-811**

**FIRST PRE-PLANNED INTERIM ANALYSIS (N=264)**

The primary endpoint was unconfirmed ORR by independent central review




| ORR and DCR, % (95% CI) | Pembro Arm (N = 133) | Placebo Arm (N = 131) |
|---|---|---|
| **ORR** | **74.4% (66.2-81.6)** | **51.9% (43.0-60.7)** |
| **ORR difference[b]** | **22.7% (11.2-33.7) *P* = 0.00006** | |
| DCR | 96.2% (91.4-98.8) | 89.3% (82.7-94.0) |

| Best Response, n (%) | Pembro Arm (N = 133) | Placebo Arm (N = 131) |
|---|---|---|
| **CR** | **15 (11%)** | **4 (3%)** |
| **PR** | **84 (63%)** | **64 (49%)** |
| SD | 29 (22%) | 49 (37%) |
| PD | 5 (4%) | 7 (5%) |
| Not evaluable | 0 | 2 (2%) |
| Not assessed | 0 | 5 (4%) |

| Duration of Response[c] | Pembro Arm (N = 99) | Placebo Arm (N = 68) |
|---|---|---|
| Median[d] | 10.6 mo | 9.5 mo |
| Range | 1.1+ to 16.5+ | 1.4+ to 15.4+ |
| ≥6-mo duration[d] | 70.3% | 61.4% |
| ≥9-mo duration[d] | 58.4% | 51.1% |

Janjigian YY et al. ASCO 2021;Abstract 4013.

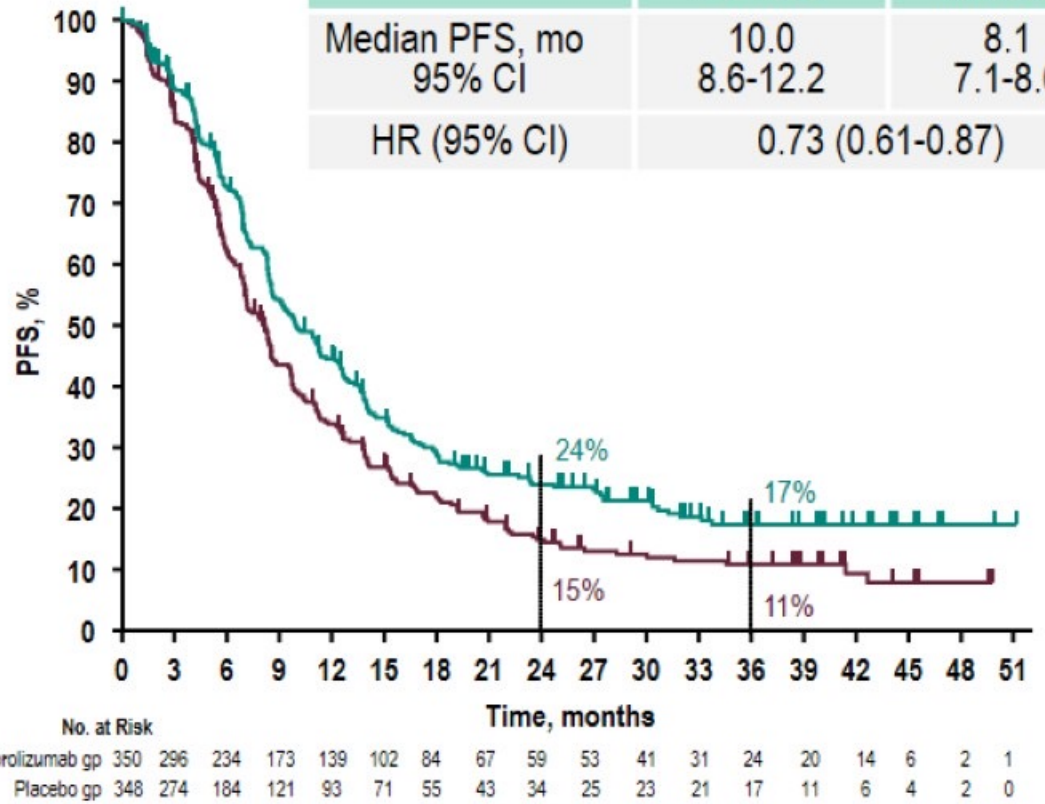
ORR = objective response rate; DCR = disease control rate

# Progression-Free Survival at IA3: 38.5 months of follow-up[a]

RECIST V1.1, BICR

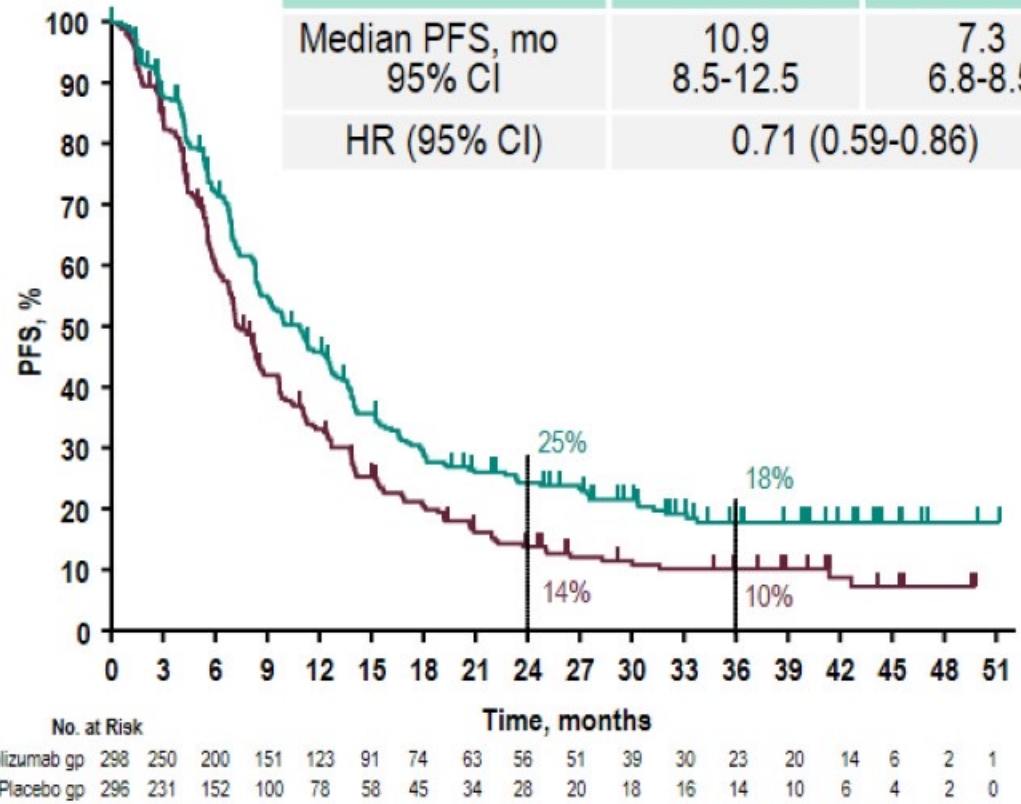
## All patients

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




## PD-L1 CPS ≥1[b]

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

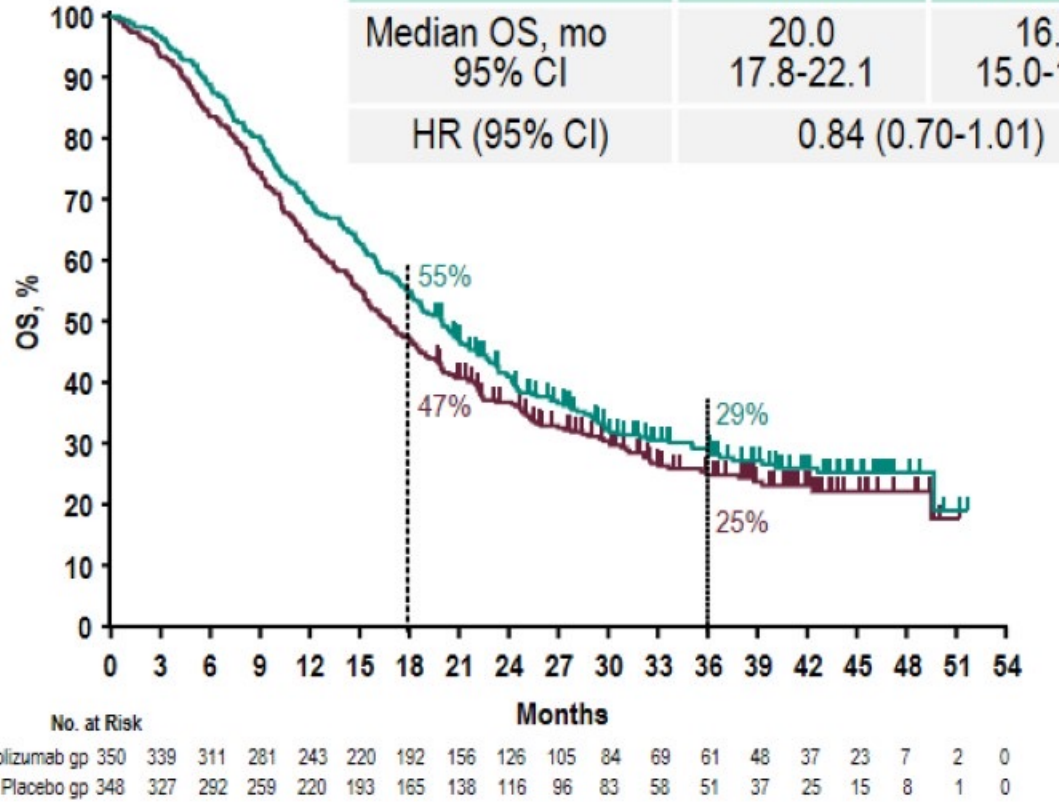



Data cut-off: March 29, 2023. [a]Median follow-up. [b]Not a prespecified endpoint.

# Overall Survival at IA3

## All patients

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

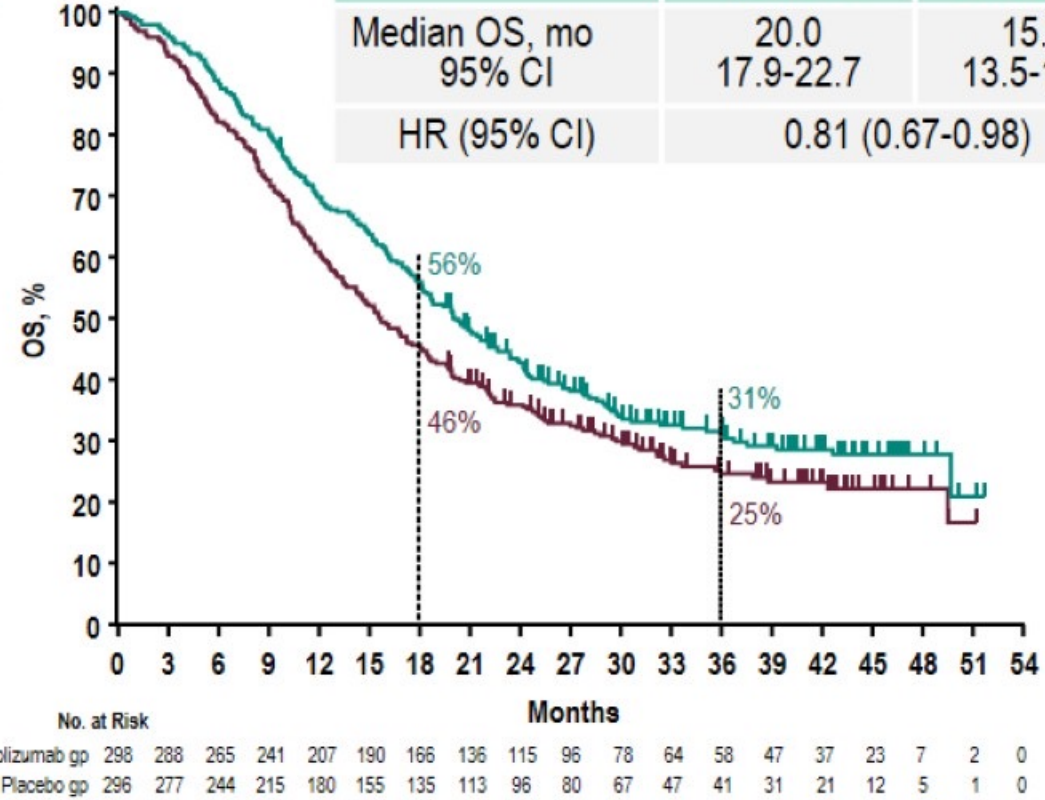



No. at Risk

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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[a]

| | Pembro | Placebo |
|---|---|---|
| Median OS, mo<br>95% CI | 20.0<br>17.9-22.7 | 15.7<br>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 |

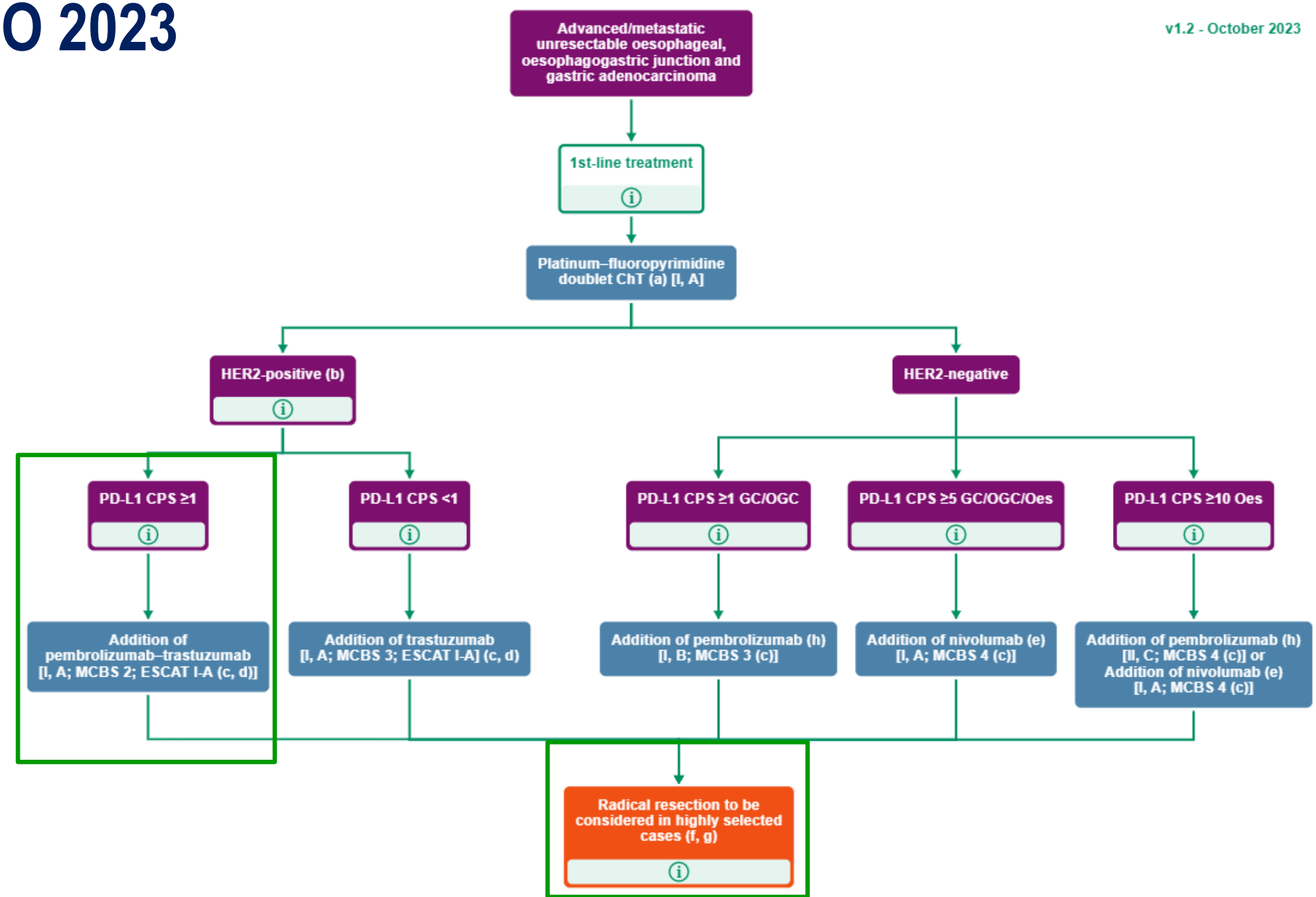
Data cut-off: March 29, 2023. OS did not meet the prespecified criteria for significance at IA3 and will be retested at final analysis. [a]Not a prespecified endpoint.

# Summary and Conclusions

- The addition of pembrolizumab to first-line trastuzumab and chemotherapy led to meaningful improvement in PFS and ORR, particularly in dual HER2 and PD-L1 overexpressed tumors
  - PFS: 10.9 vs 7.3 mo, HR 0.71; ORR: 73% vs 58%; OS: 20 vs 15.7 mo, HR 0.81 in CPS ≥1 population
- AE incidence was similar between arms, and the observed AEs were as expected with no new safety concerns identified
- These data resulted in approval of pembrolizumab, trastuzumab plus chemotherapy as first-line therapy in patients with advanced unresectable or metastatic gastroesophageal cancer with HER2 and PD-L1 overexpression in Europe
- KEYNOTE-811 is continuing as planned, and the final analysis of OS will be performed per protocol

# ESMO 2023

v1.2 - October 2023



# OligoMetastatic Esophagogastric Cancer Consortium

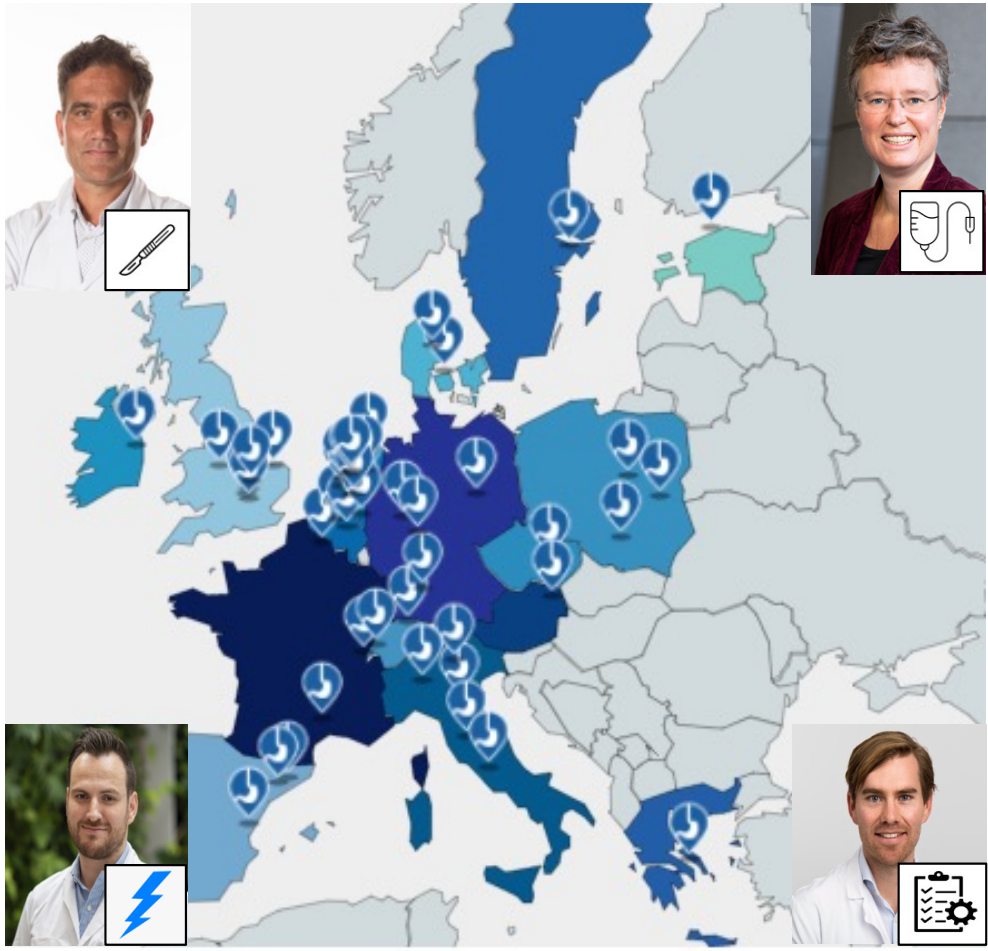
**OMEC**

www.omecproject.eu

**Goal:** Determine & overcome challenges and practice variation in

- **Definition** of oligometastasis
- **Treatment** strategies for oligometastasis

**Participants:** European multidisciplinary consortium (50 centers)



**Endorsed by:**

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

esso THE EUROPEAN SOCIETY OF SURGICAL ONCOLOGY

INTERNATIONAL GASTRIC CANCER ASSOCIATION IGCA

EORTC European Organisation for Research and Treatment of Cancer

ESTRO European Society for RADIOTHERAPY & ONCOLOGY

ESDE The European Society for Diseases of the Esophagus


Kroese TE et al. *Eur J Cancer* 2022;166:254-69
Kroese TE et al. *Eur J Cancer* 2022;164:18-29
Lordick F et al. *Ann Oncol* 2022;33(10):1005-20

# DESTINY-Gastric TRIALS

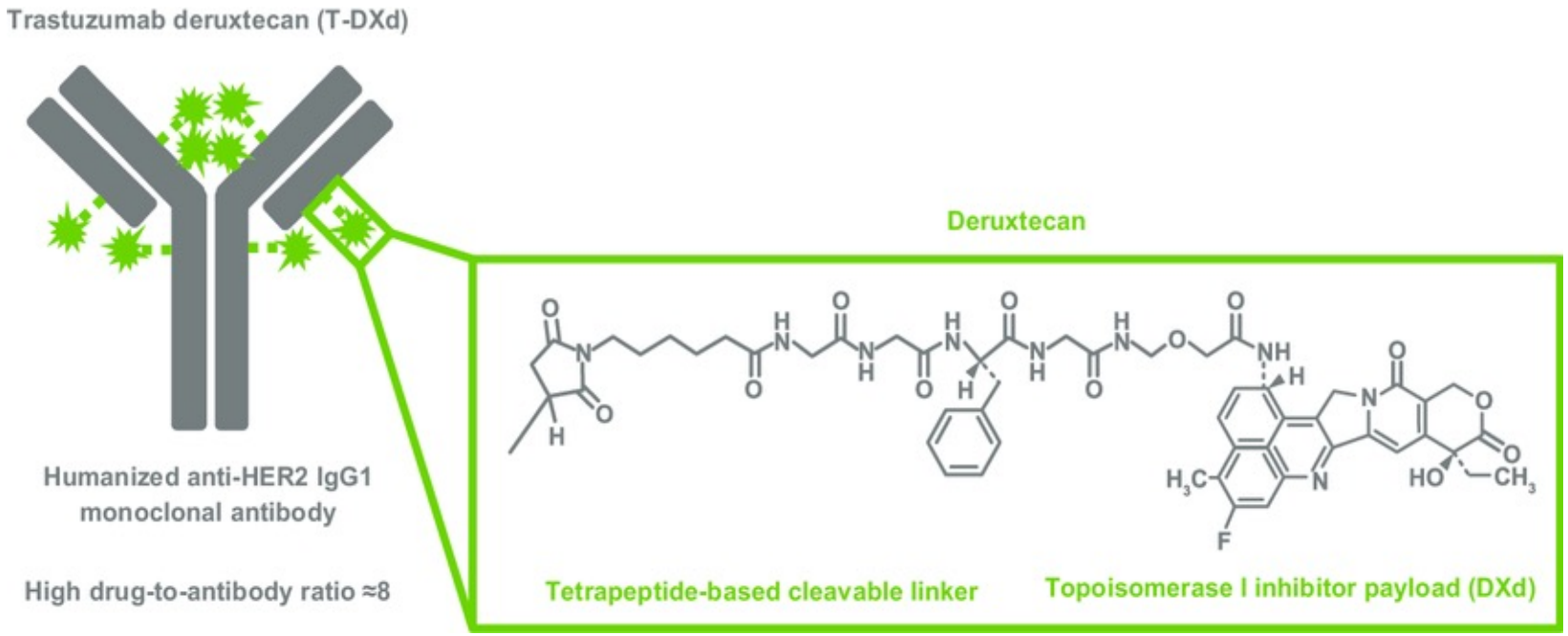
**2x Multicenter Phase II: 2L APPROVAL FDA and EMA!!**

**HER2+** patients with unresectable or metastatic gastric or GEJ cancer; **on biopsy after disease progression on first-line trastuzumab-containing regimen**
ECOG PS 0/1 (N = 79)

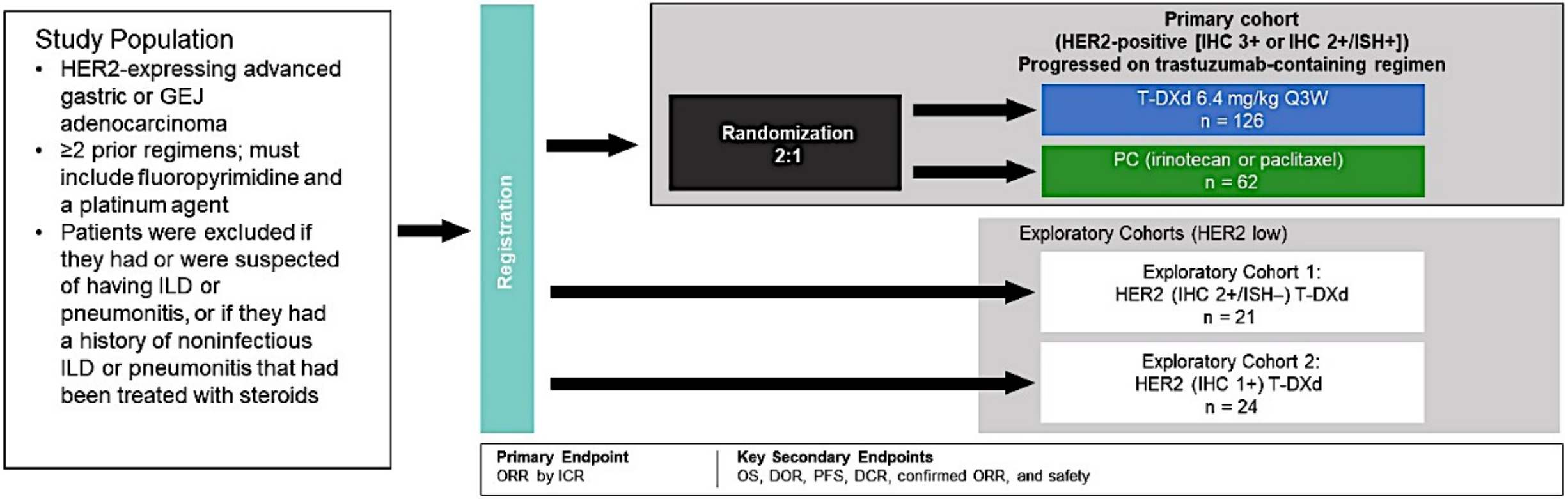
## Antibody-Drug Conjugate

**Trastuzumab Deruxtecan**

6.4 mg/kg q3wk



# DESTINY-Gastric01 Randomized, Phase II Study Design

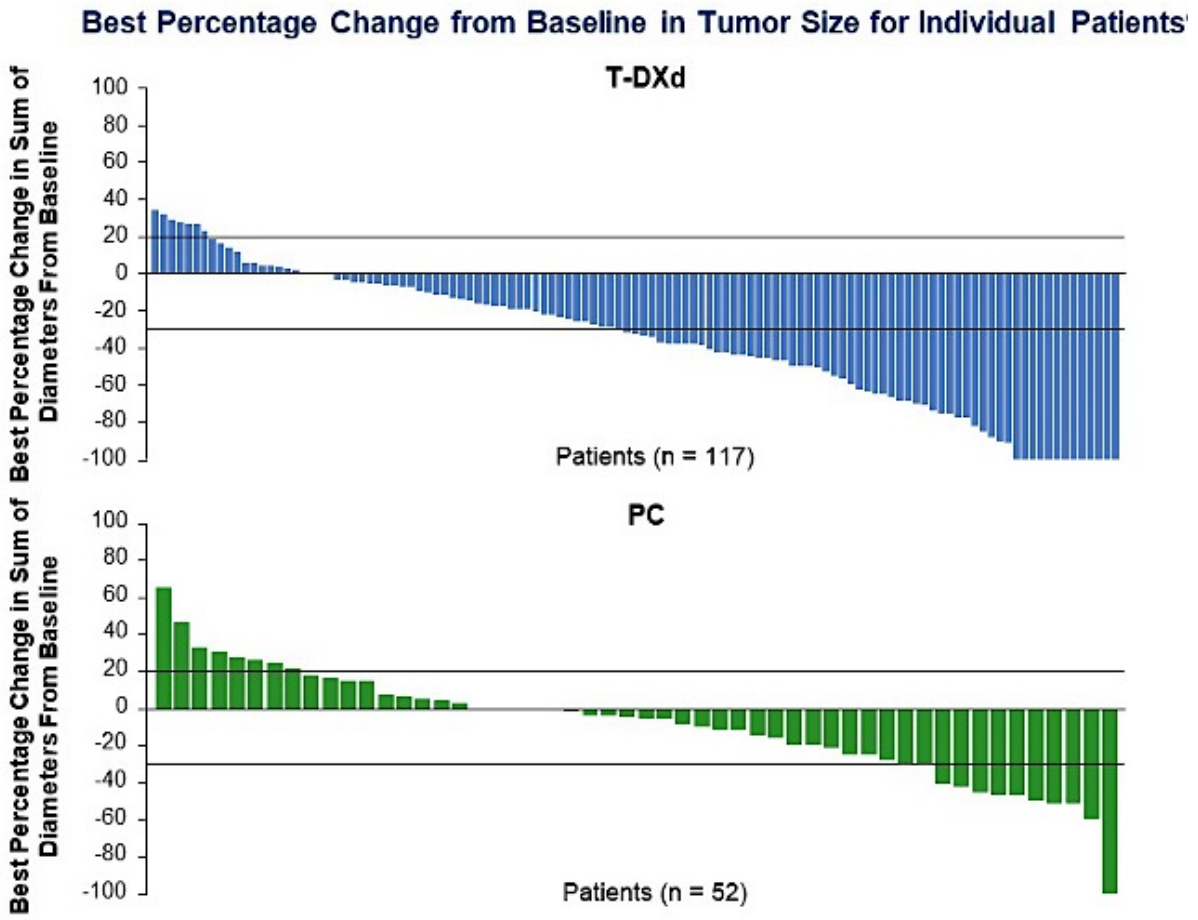



T-DXd = trastuzumab deruxtecan; PC = physician's choice

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

# DESTINY-Gastric01: Antitumor Activity

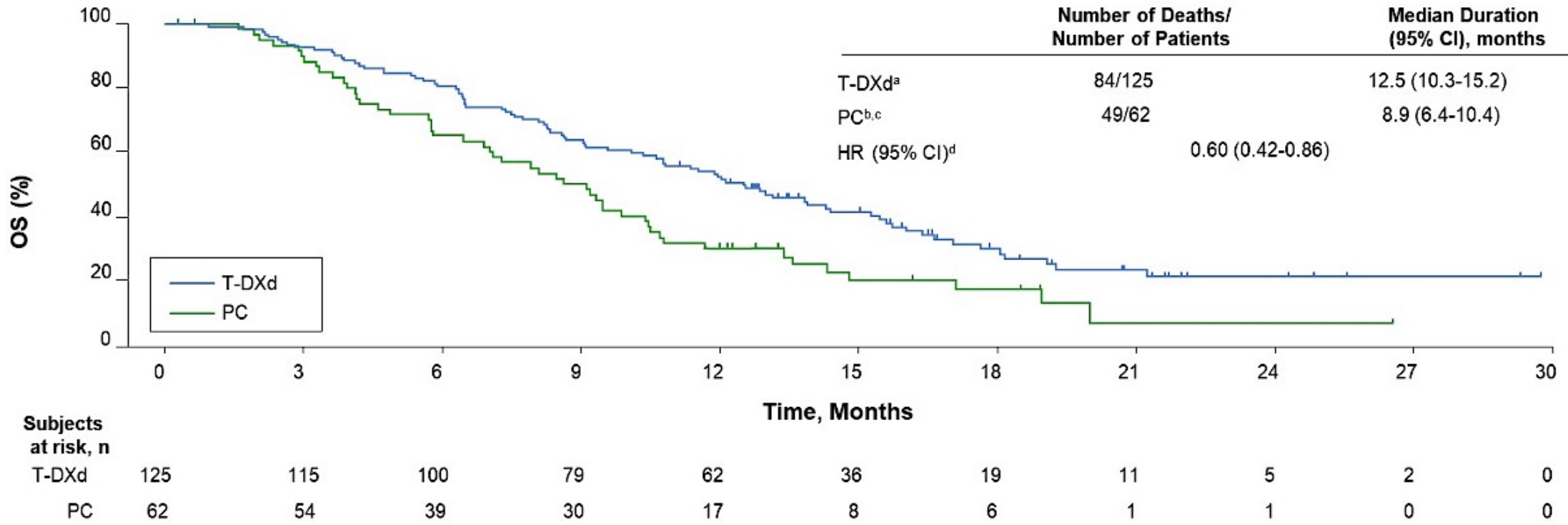
| | T-DXd n = 119 | PC Overall n = 56 |
|---|---|---|
| **ORR (CR + PR) by ICR, n (%)[a]** | **61 (51.3) 95% CI, 41.9-60.5** | **8 (14.3) 95% CI, 6.4-26.2** |
| | *P* < 0.0001[b] | |
| CR | 11 (9.2) | 0 |
| PR | 50 (42.0) | 8 (14.3) |
| SD | 42 (35.3) | 27 (48.2) |
| PD | 14 (11.8) | 17 (30.4) |
| Not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




ORR = objective response rate; ICR = independent central review

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

# DESTINY-Gastric01: Final Overall Survival (OS)



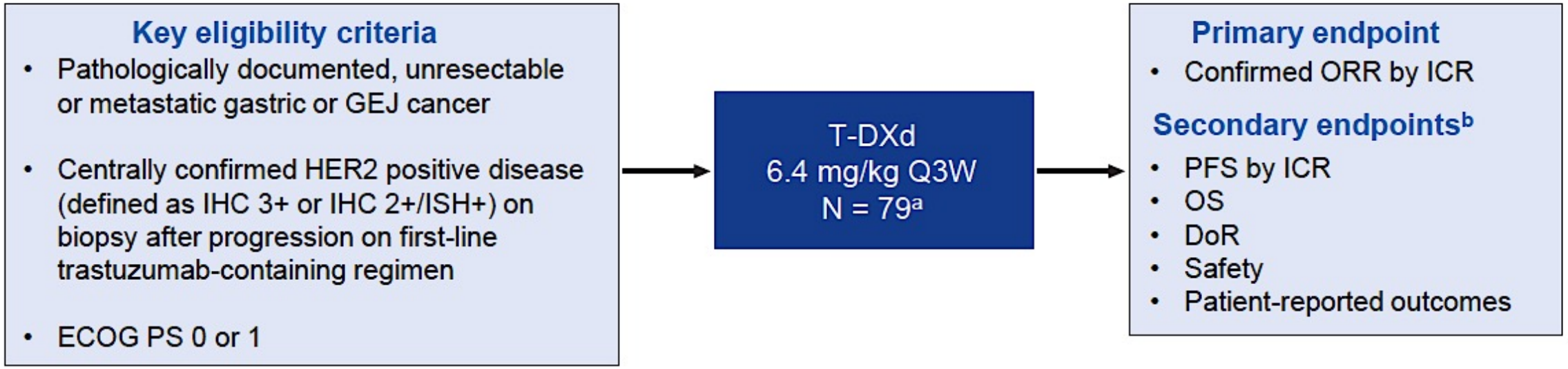

| | Number of Deaths/ Number of Patients | Median Duration (95% CI), months |
|---|---|---|
| T-DXd[a] | 84/125 | 12.5 (10.3-15.2) |
| PC[b,c] | 49/62 | 8.9 (6.4-10.4) |
| HR (95% CI)[d] | 0.60 (0.42-0.86) | |

| Subjects at risk, n | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DXd | 125 | 115 | 100 | 79 | 62 | 36 | 19 | 11 | 5 | 2 | 0 |
| PC | 62 | 54 | 39 | 30 | 17 | 8 | 6 | 1 | 1 | 0 | 0 |

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

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

# DESTINY-Gastric02 Phase II Study Design




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

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

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

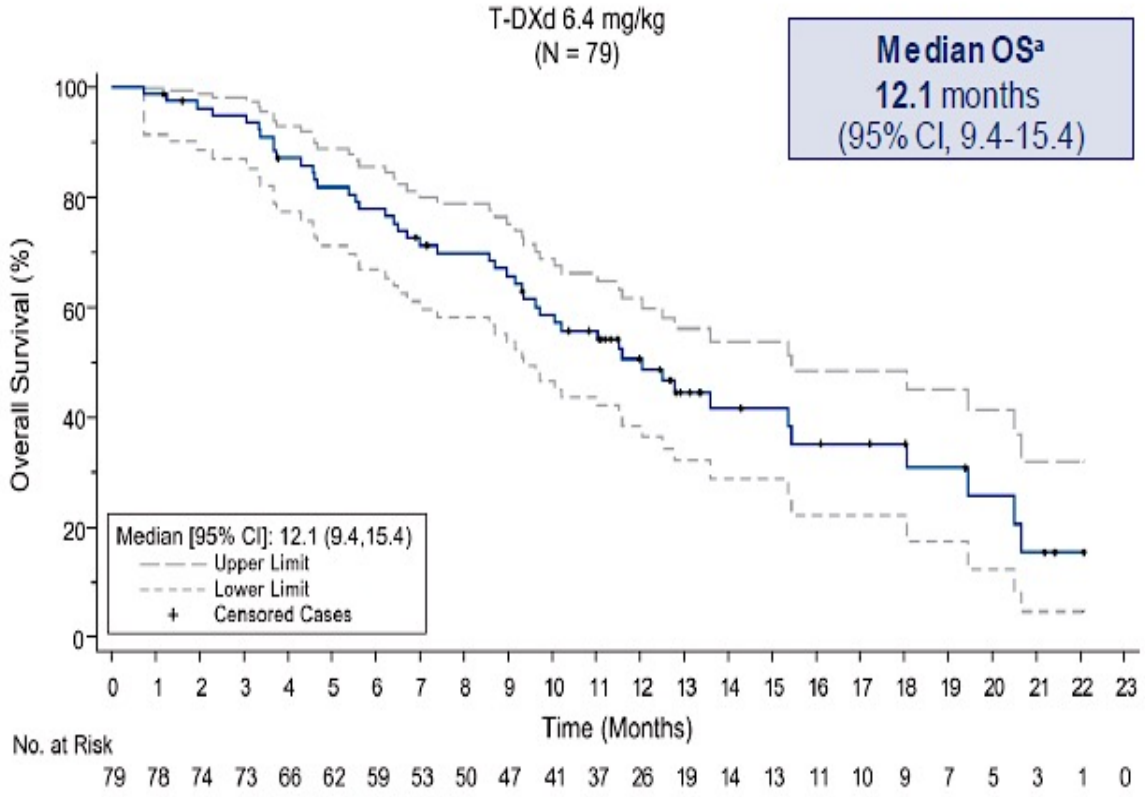
# DESTINY-Gastric02

## Antibody-Drug Conjugate

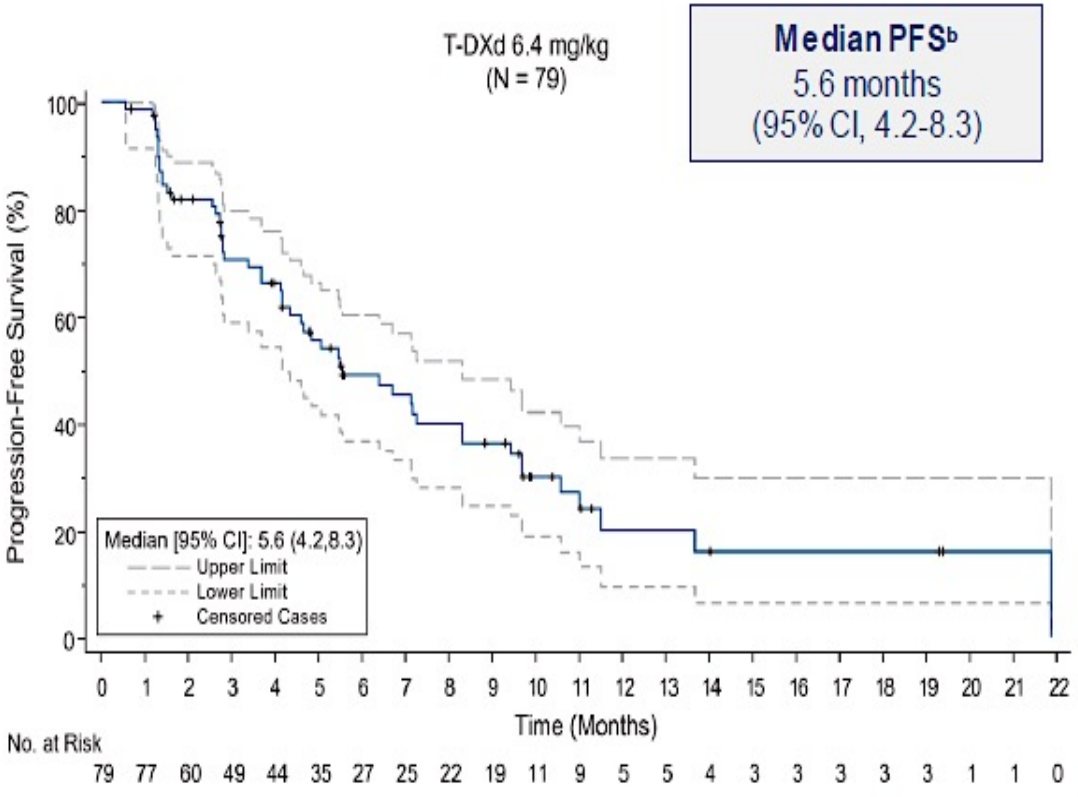
**Trastuzumab Deruxtecan**

6.4 mg/kg q3wk

### Kaplan-Meier Plot of OS

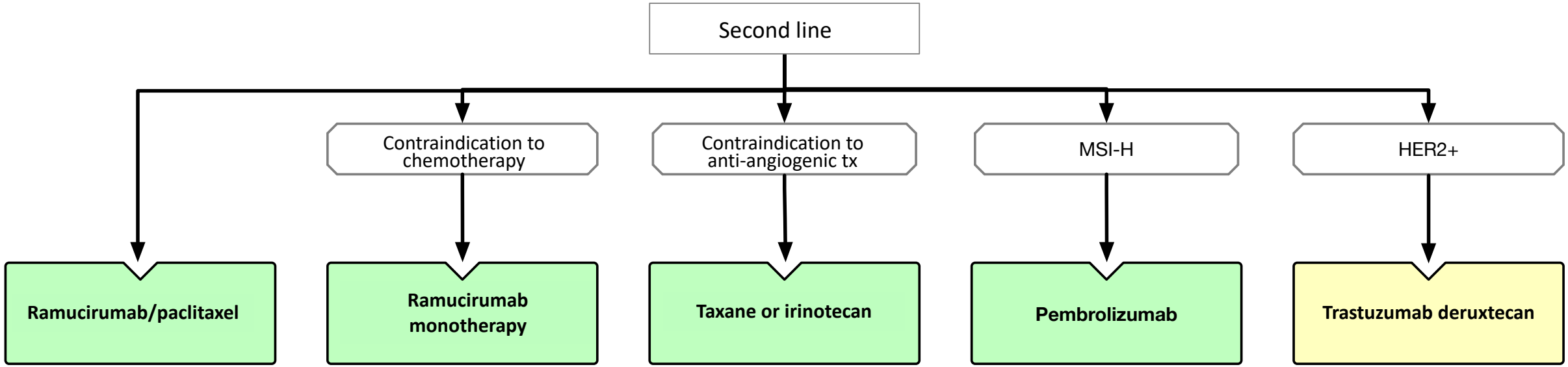



### Kaplan-Meier Plot of PFS by ICR



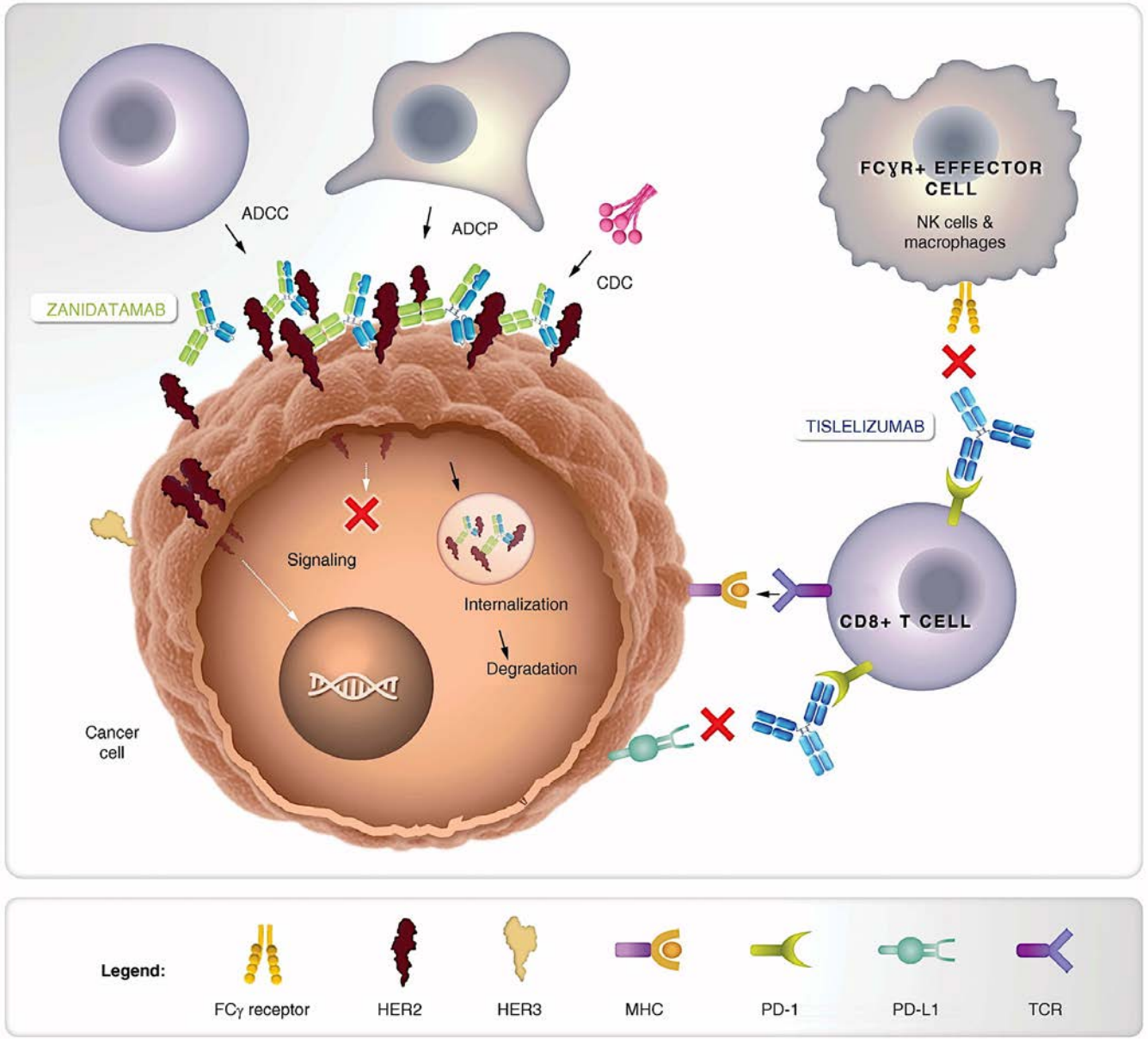
# Second-Line Treatment of Metastatic Esophagogastric Cancer The ESMO Guideline

**+ HER2 test?!**




MSI-H = High microsatellite instability

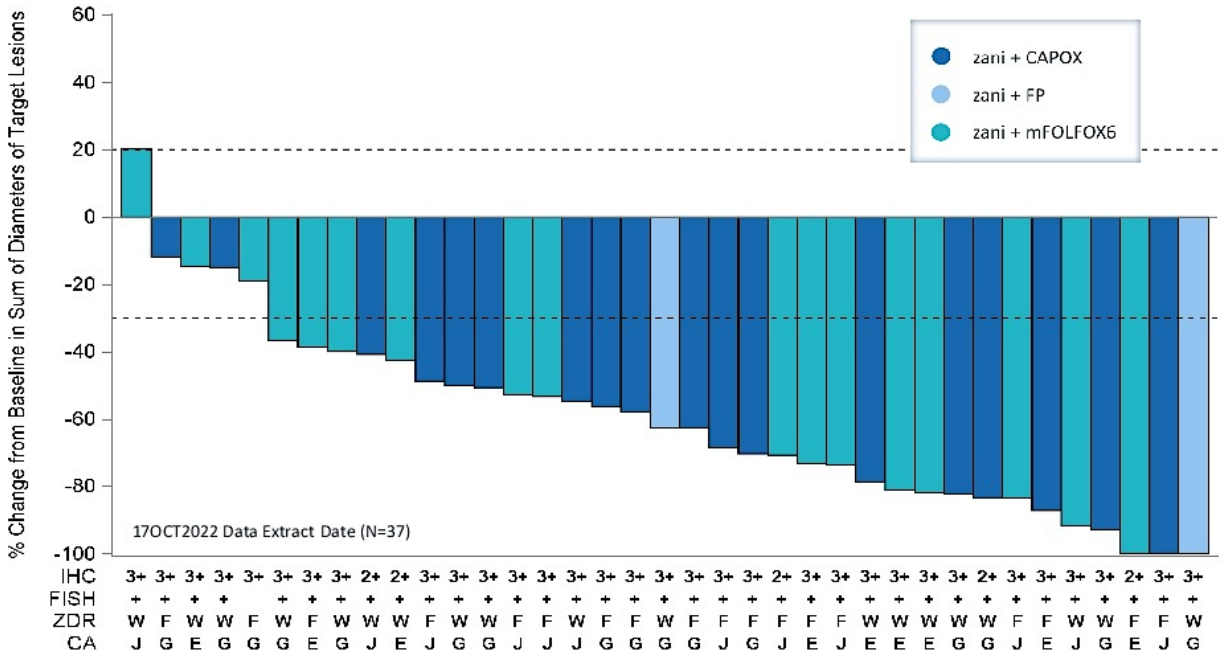
# Zanidatamab: Mechanism of Action




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

# First-Line Zanidatamab + Chemotherapy for HER2-Expressing mGEA: Antitumor Activity

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




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

## Response Rates and DOR in Response-evaluable Patients with HER2-positive mGEA

| | Zanidatamab + CAPOX (n =18) | Zanidatamab + mFOLFOX6 (n = 18) | Zanidatamab + FP (n = 2) | Total (N = 38) |
|---|---|---|---|---|
| Confirmed objective response rate[a], % (95% CI) | 89 (65, 99) | 67 (41, 87) | 100 (16, 100) | 79 (63, 90) |
| Confirmed best overall response, n (%) | | | | |
| Complete response | 2 (11) | 1 (6) | 0 | 3 (8) |
| Partial response | 14 (78) | 11 (61) | 2 (100) | 27 (71) |
| Stable disease | 2 (11) | 3 (17) | 0 | 5 (13) |
| Progressive disease | 0 | 3 (17) | 0 | 3 (8) |
| Disease control rate, % (95% CI) | 100 (82, 100) | 83 (59, 96) | 100 (16, 100) | 92 (79, 98) |
| Median duration of response (95% CI), months | 10.4 (5.7, NE) | NE (2.8, NE) | NE (6.8, NE) | 20.4 (8.3, NE) |

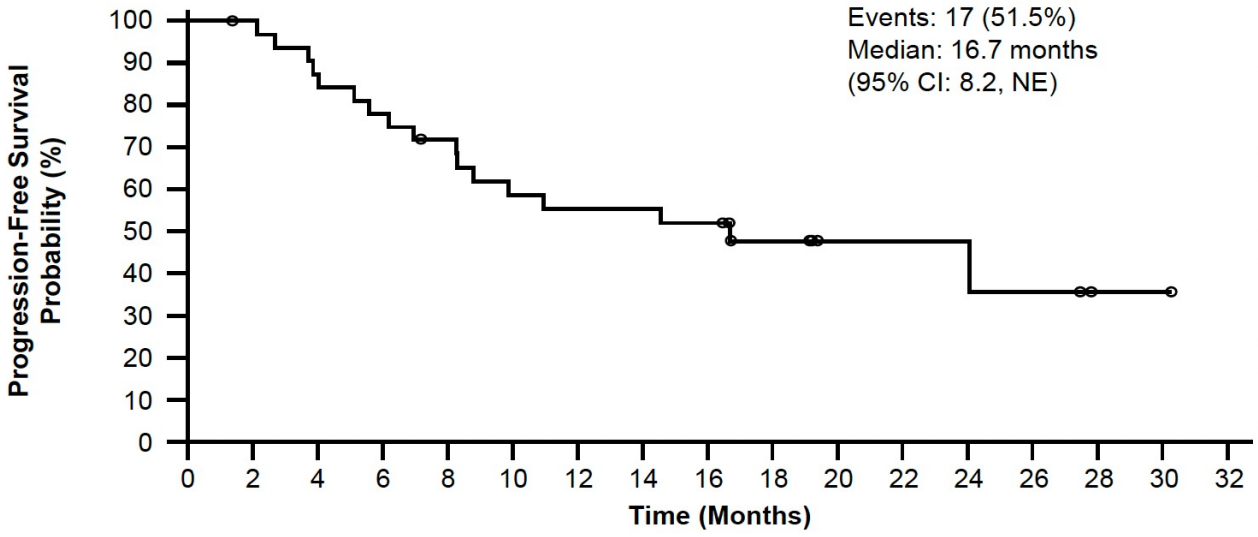
a.Based on a baseline scan and a confirmatory scan obtained ≥4 weeks following initial documentation of objective response.
CI = confidence interval; DOR = duration of response; NE = not estimable.

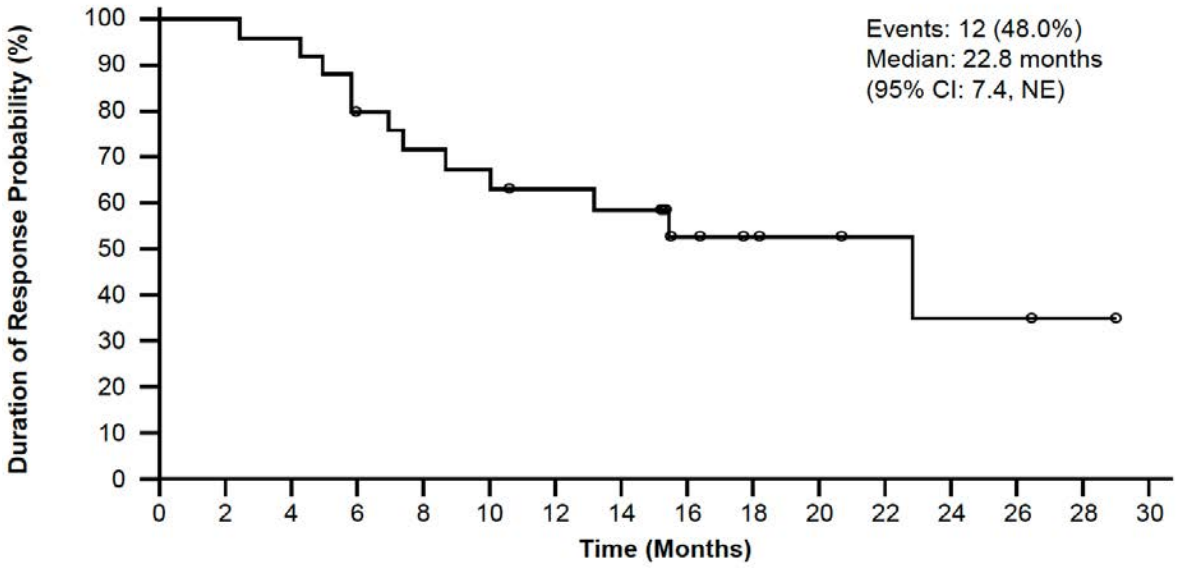
Elimova E et al. Gastrointestinal Cancers Symposium 2023;Abstract 347.

# Zanidatamab + chemotherapy + tislelizumab for advanced HER2-positive gastric/GEJ adenocarcinoma

| | Cohort A (n=19) | Cohort B (n=14) | Total (N=33) |
|---|---|---|---|
| **Confirmed BOR,[b] n (%)** | | | |
| Complete response | 1 (5.3) | 0 (0) | 1 (3.0) |
| Partial response | 14 (73.7) | 10 (71.4) | 24 (72.7) |
| Stable disease | 4 (21.1) | 4 (28.6) | 8 (24.2) |
| Progressive disease | 0 (0) | 0 (0) | 0 (0) |
| **Confirmed ORR,[b] % (95% CI)** | 78.9 (54.4, 93.9) | 71.4 (41.9, 91.6) | 75.8 (57.7, 88.9) |
| **Confirmed DCR,[b] % (95% CI)** | 100.0 (82.4, 100.0) | 100.0 (76.8, 100.0) | 100.0 (89.4, 100.0) |
| **Median DoR,[b] months (95% CI)** | 15.4 (4.9, NE) | NE (7.4, NE) | 22.8 (7.4, NE) |

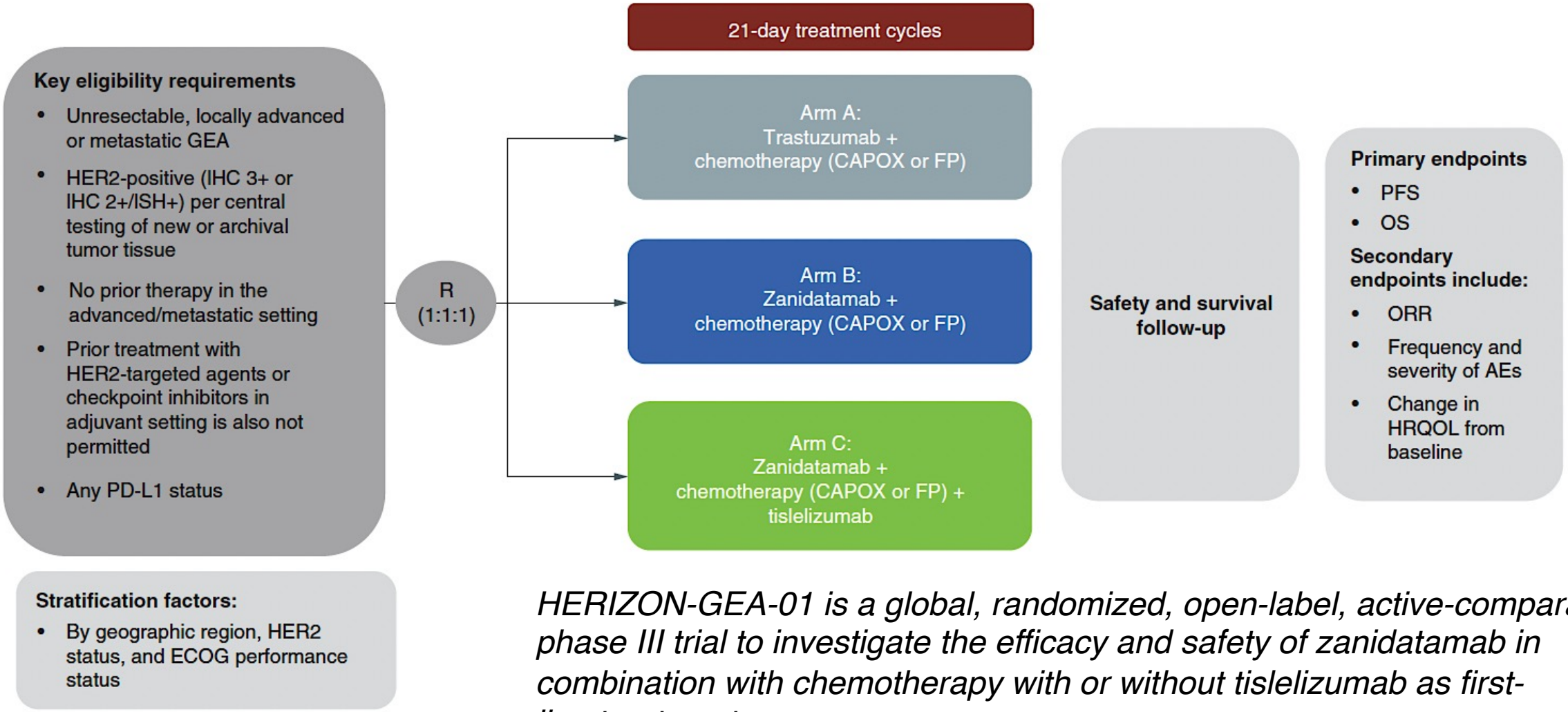
BOR = best overall response; ORR = objective response rate; DCR = disease control rate; DoR = duration of response




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

# HERIZON-GEA-01: Zanidatamab + Chemotherapy ± Tislelizumab for First-Line Treatment of HER2-Positive GEA




*HERIZON-GEA-01 is a global, randomized, open-label, active-comparator, phase III trial to investigate the efficacy and safety of zanidatamab in combination with chemotherapy with or without tislelizumab as first-line treatment.*

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

# Summary

- Phase III KEYNOTE-811 trial approved the addition of pembrolizumab to chemotherapy and trastuzumab for previously untreated HER2-positive advanced gastric/GEJ adenocarcinoma
- DESTINY-Gastric01 and DESTINY-Gastric02 studies approved trastuzumab deruxtecan for progressive HER2-positive gastric/GEJ cancer
- Mechanism of action has been established for the novel HER2-targeted bispecific antibody zanidatamab
- Zanidatamab/chemotherapy has been established but not yet approved as first-line treatment for advanced HER2-positive gastroesophageal adenocarcinoma
- Phase III HERIZON-GEA-01 trial is ongoing to evaluate up-front zanidatamab and chemotherapy with or without tislelizumab for HER2-positive gastroesophageal adenocarcinoma

# MODULE 5: Selection and Sequencing of Therapy for Patients with Relapsed/Refractory (R/R) HER2-Negative Gastroesophageal Cancers – Dr Mehta

# Rebiopsy of HER2-positive gastric cancer; selection of partner for ramucirumab

**Sunnie Kim, MD**

RTP
RESEARCH
TO PRACTICE

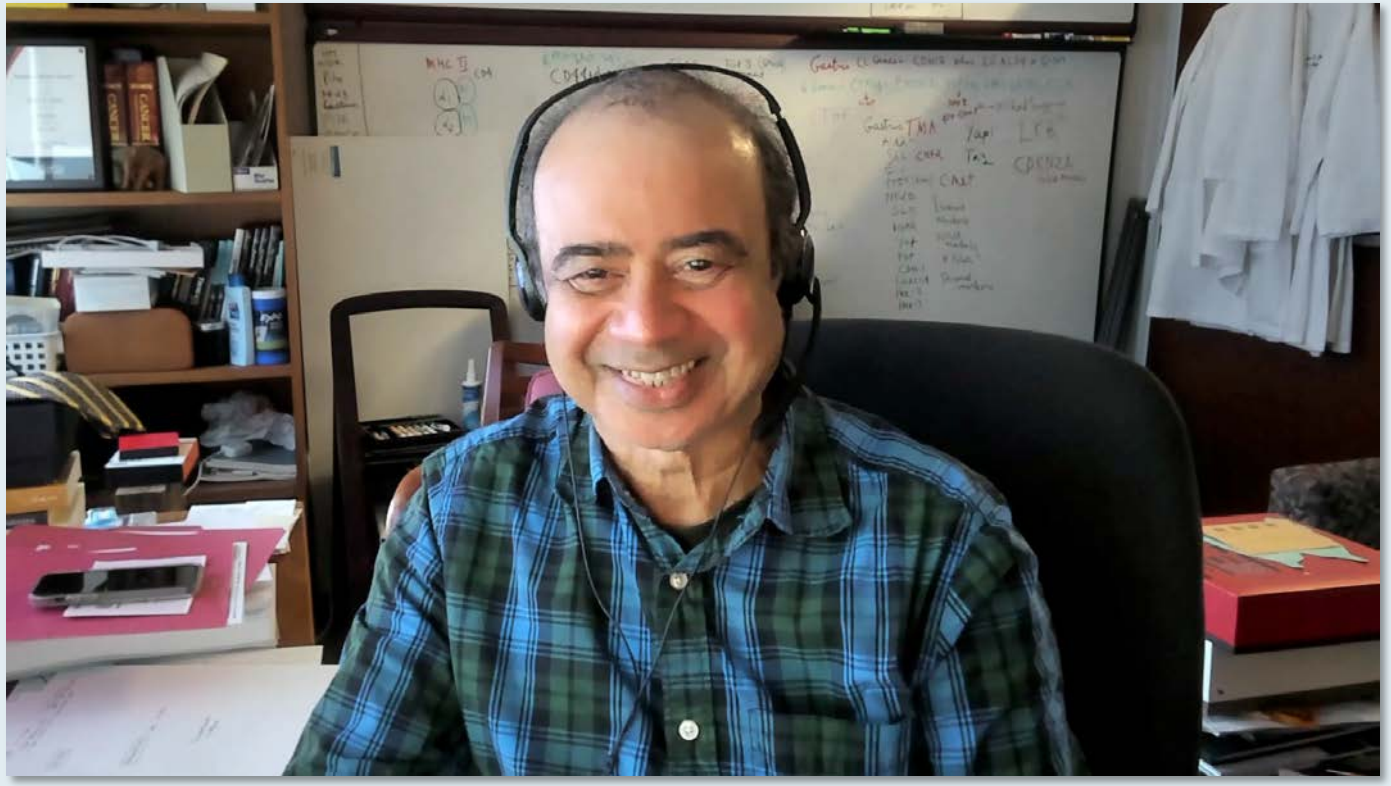
# QUESTIONS FOR THE FACULTY

**Sunnie Kim, MD**

***How do you approach the use of ramucirumab in patients with advanced gastroesophageal cancers?***

RTP
RESEARCH
TO PRACTICE

# New agents and regimens in ongoing research for GE cancer



**Jaffer A Ajani, MD**

RTP
RESEARCH
TO PRACTICE

# QUESTIONS FOR THE FACULTY

**Jaffer A Ajani, MD**

***What are your thoughts about the future of systemic therapy, including new immunotherapeutic and targeted strategies, for advanced gastroesophageal cancers?***

# What was the age of the last patient in your practice with metastatic gastroesophageal cancer who received ramucirumab? Which regimen did the patient receive? What prior treatment did the patient receive?

| | Age | Tx regimen | Prior Tx |
|---|---|---|---|
|  Dr Ilson | 72 years | Ramucirumab/paclitaxel | FOLFOX/nivolumab |
|  Dr Mehta | 67 years | Ramucirumab/FOLFIRI | FOLFOX/nivolumab |
|  Dr Moehler | 64 years | Ramucirumab/paclitaxel | FLOT; FOLFOX |
|  Dr Shah | 72 years | Ramucirumab/paclitaxel | FOLFOX/nivolumab |
|  Dr Yoon | 72 years | Ramucirumab/paclitaxel | FOLFOX |
|  Dr Ajani | 61 years | Ramucirumab/paclitaxel | FOLFOX |
|  Dr Kim | 51 years | Ramucirumab/irinotecan | FOLFOX/nivolumab |

# Beyond paclitaxel, what other chemotherapeutic agents, if any, are you comfortable combining with ramucirumab for your patients with relapsed gastroesophageal cancer?

| | |
|---|---|
|  Dr Ilson | FOLFIRI, irinotecan, docetaxel |
|  Dr Mehta | FOLFIRI |
|  Dr Moehler | FOLFIRI, irinotecan, docetaxel, S1 |
|  Dr Shah | FOLFIRI |
|  Dr Yoon | FOLFIRI |
|  Dr Ajani | None |
|  Dr Kim | Irinotecan, FOLFIRI |

RTP RESEARCH TO PRACTICE

# Selection and Sequencing of Therapy for Patients with Relapsed/Refractory (R/R) HER2-Negative Gastroesophageal Cancers

Rutika Mehta MD, MPH

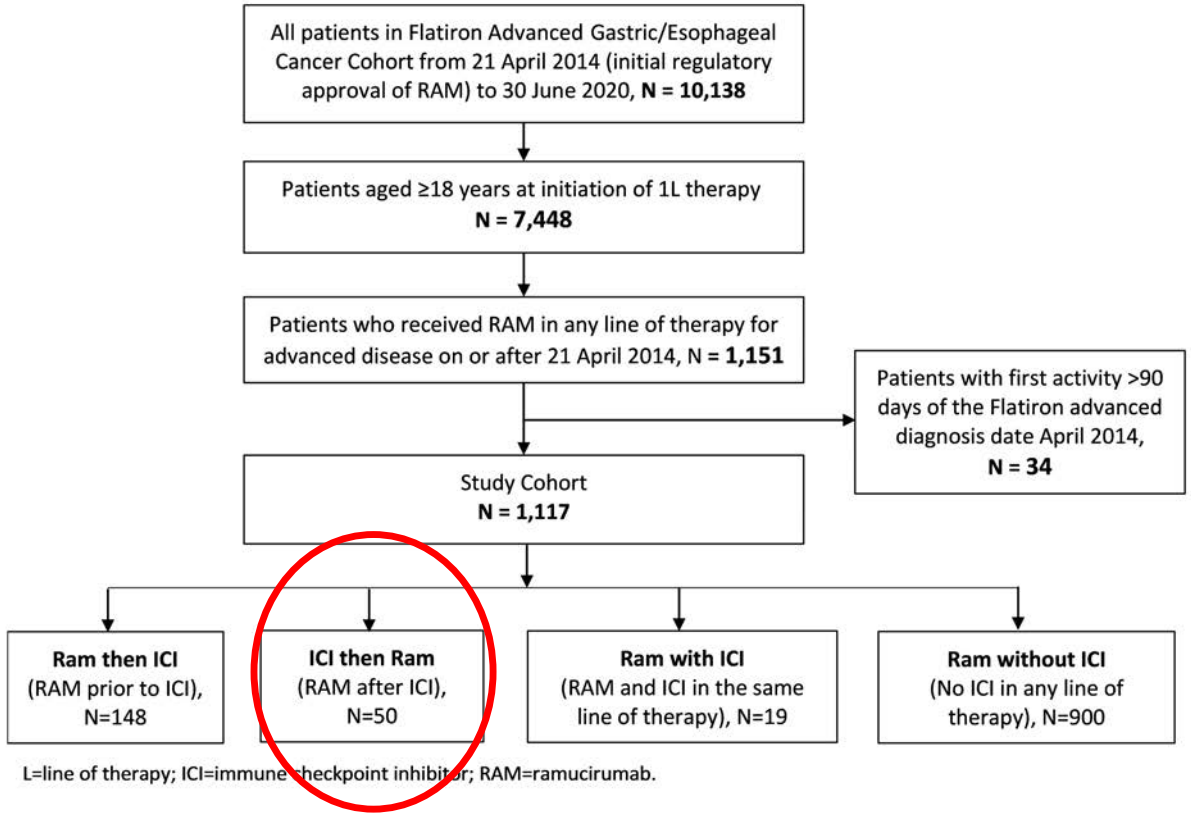
Associate Member, GI Oncology

Moffitt Cancer Center

# Sequencing ramucirumab after progression on ICI

ICI- Immune checkpoint inhibitor

# Sequencing ramucirumab after disease progression on ICI




Liepa AM, Cui ZL, Beyrer JK, Hadden EL, Chatterjee A. Real-world ramucirumab and immune checkpoint inhibitor sequences in US patients with advanced gastroesophageal cancer. Future Oncol. 2023 Jun;19(18):1277-1291.

Analyses of the Flatiron database revealed that 50 patients were treated with ICI followed by ramucirumab. Most of the patients receiving ramucirumab, received it in combination with paclitaxel as 3L (38.3%), 4L (29.6%) or 5L (47.1%) treatment.

The median time of treatment with ramucirumab (in combination or monotherapy) in the group receiving ramucirumab following ICI was similar to those receiving ramucirumab prior to ICI or ramucirumab without ICI (1.9 months with combination and 1.3 months as monotherapy).

ICI- Immune checkpoint inhibitor; 3L- 3rd line; 4L- 4th line; 5L- 5th line

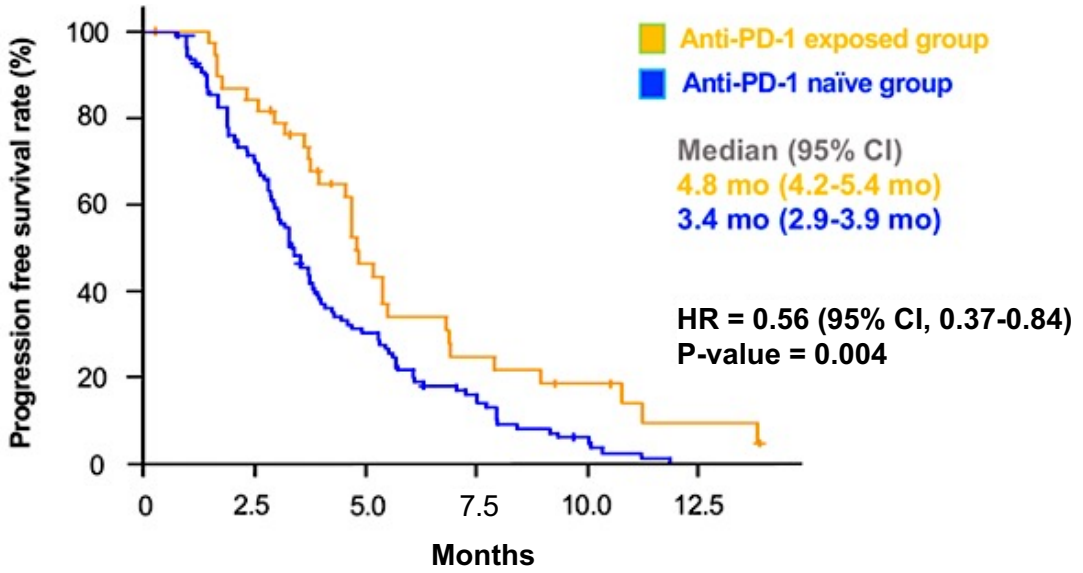
# Prior ICI use increased tumor response to ramucirumab plus taxane

| | Anti-PD-1-exposed group | Anti-PD-1-naive group | P value |
|---|---|---|---|
| Overall population | **n=56** | **n=138** | |
| CR | 0 | 0 | |
| PR | 25 (45.5%) | 27 (19.6%) | |
| SD | 20 (35.7%) | 68 (49.3%) | |
| PD | 10 (17.9%) | 43 (31.2%) | |
| NE | 1 (1.8%) | 0 (0.0%) | |
| ORR (%) | 44.6 | 19.6 | 0.001 |
| DCR (%) | 80.6 | 68.8 | 0.12 |
| Taxanes+RAM | **n=33** | **n=85** | |
| CR | 0 | 0 | |
| PR | 20 (60.6%) | 17 (20.0%) | |
| SD | 9 (27.3%) | 40 (47.1%) | |
| PD | 4 (12.1%) | 28 (32.9%) | |
| ORR (%) | 60.6 | 20.0 | <0.001 |
| DCR (%) | 87.9 | 67.1 | 0.023 |

Sasaki A, Kawazoe A, Eto T, Okunaka M, Mishima S, Sawada K, Nakamura Y, Kotani D, Kuboki Y, Taniguchi H, Kojima T, Doi T, Yoshino T, Akimoto T, Shitara K. Improved efficacy of taxanes and ramucirumab combination chemotherapy after exposure to anti-PD-1 therapy in advanced gastric cancer. ESMO Open. 2020 Jul;4(Suppl 2):e000775.

In a single institution study in Japan, 233 patients with advanced gastric cancer were identified June 2015 to April 2019.

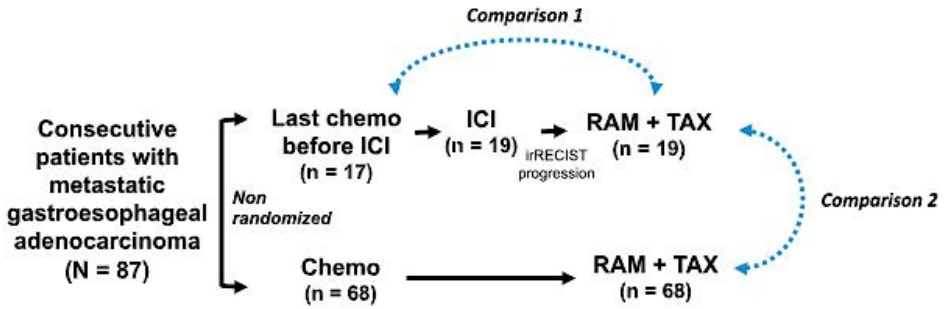
B. taxanes+RAM



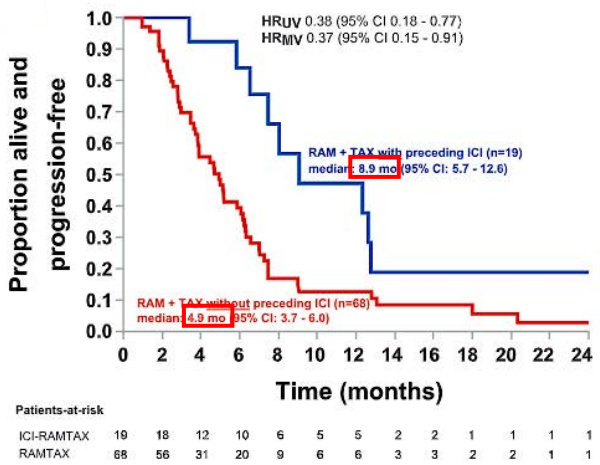

11 patients in ICI naïve group were rechallenged with ramucirumab plus taxane after exposure to ICI, and 3 of 11 showed PR.

ICI- Immune checkpoint inhibitor; PR- partial response

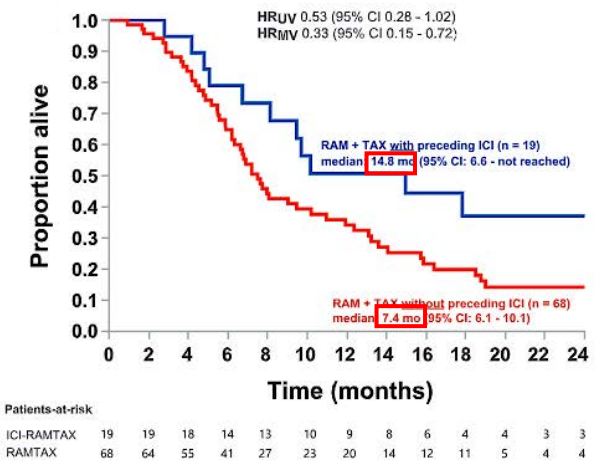
# Ramucirumab and paclitaxel after ICI



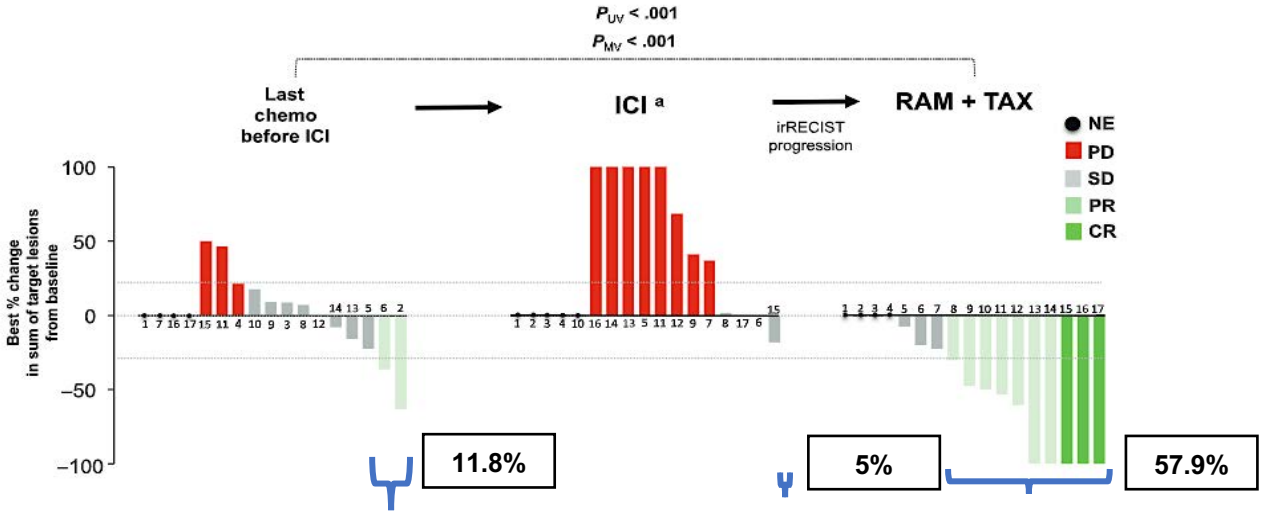

**Progression free survival**



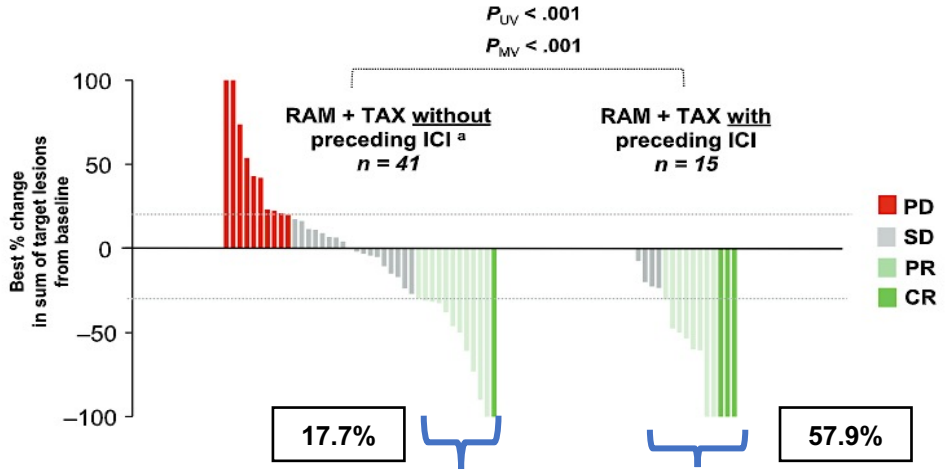

**Overall survival**




**Tumor response across treatment lines**

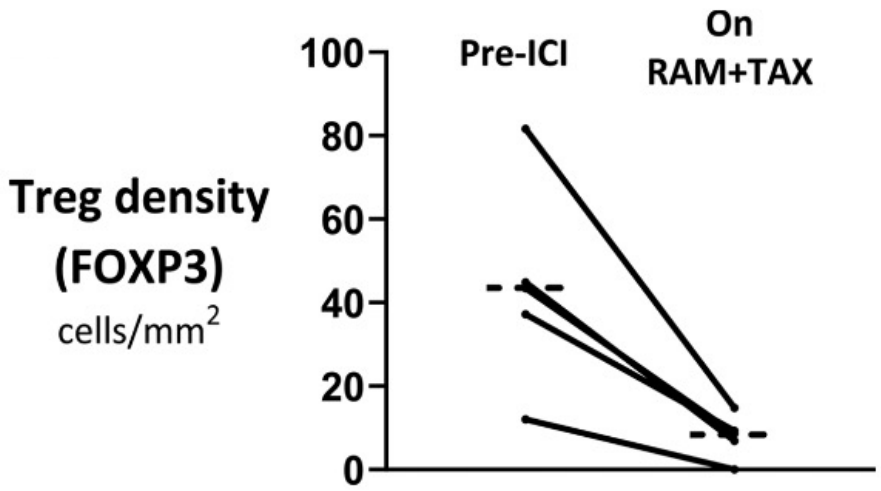


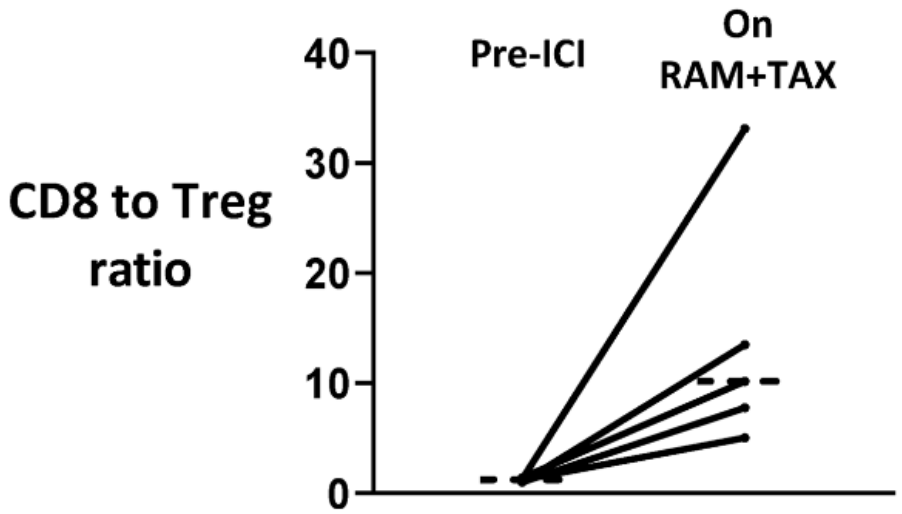

**Tumor response with ram+tax based on ICI exposure**




Kankeu Fonkoua LA, Chakrabarti S, Sonbol MB, et al. Outcomes on anti-VEGFR-2/paclitaxel treatment after progression on immune checkpoint inhibition in patients with metastatic gastroesophageal adenocarcinoma. *Int. J. Cancer*. 2021; 149: 378–386.

# Ram + Pac after ICI reduce Tregs




Mean fold-change on-ramucirumab/paclitaxel vs pre-ICI is 28.4 (95% CI,−35.7 to 92.5) for FOXP3+ Treg frequency and 11.9 (95% CI 1.0 to 22.9) for the CD8/Treg ratio.

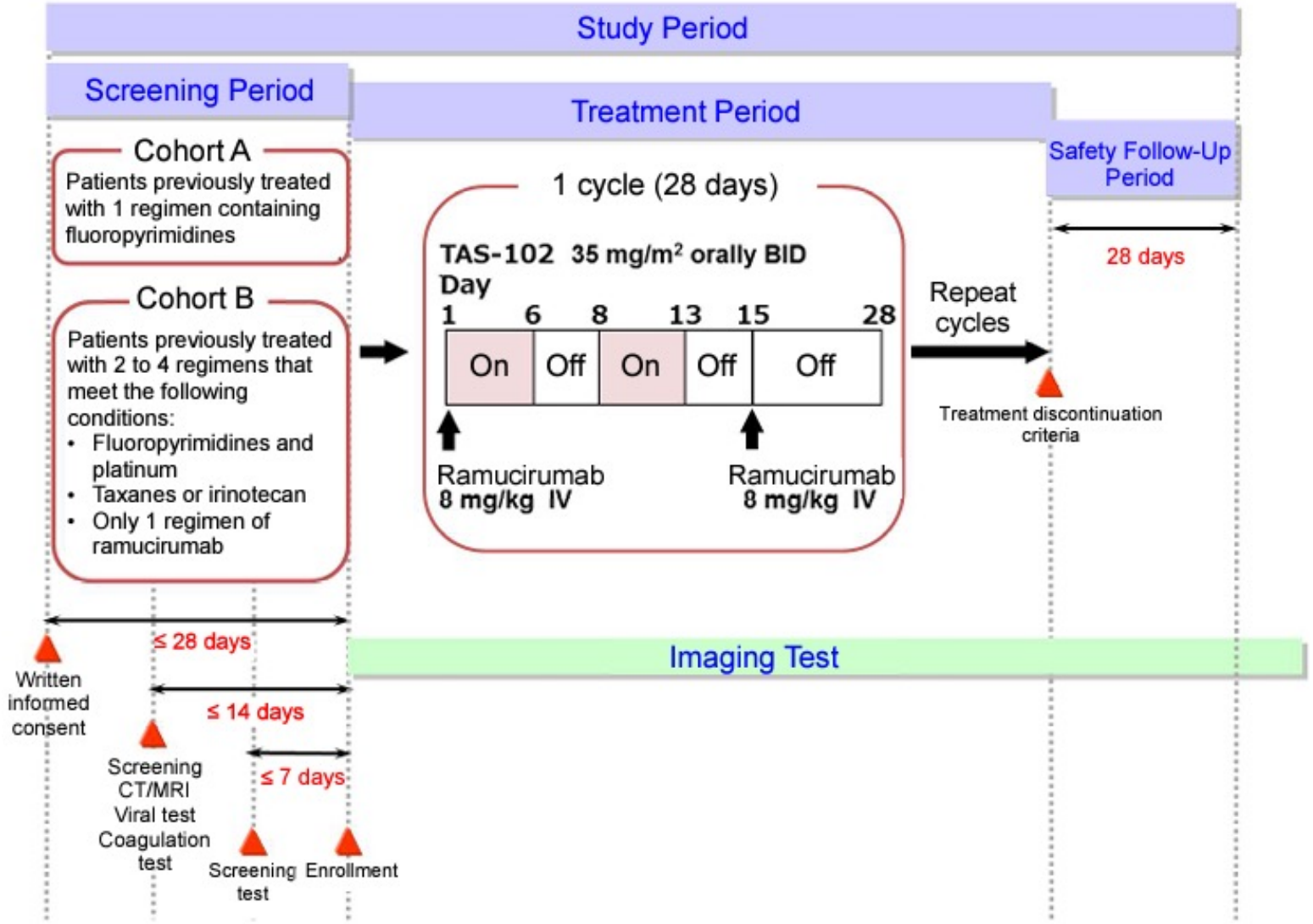
ICI- Immune checkpoint inhibitor; Ram- ramucirumab; tax- taxane; Treg- regulatory T cells.

Kankeu Fonkoua LA, Chakrabarti S, Sonbol MB, et al. *Int J Cancer*. 2021;149(2):378-86.

**Novel SEQUEnced Immunotherapy With Anti-angiogenesis and Chemotherapy in Advanced gastroesophageaL Adenocarcinoma (SEQUEL) [NCT04069273] currently recruiting patients to address this question.**

# Novel combinations with ramucirumab

# Phase II study of ramucirumab plus TAS-102




| | Cohort A (n=33) | Cohort B (n=31) |
|---|---|---|
| Sex | | |
| Male | 24 (73%) | 22 (71%) |
| Female | 9 (27%) | 9 (29%) |
| Age, years | 71·0 (67·0–76·0) | 67·0 (59·0–71·0) |
| <65 | 5 (15%) | 13 (42%) |
| ≥65 | 28 (85%) | 18 (58%) |
| ECOG PS | | |
| 0 | 20 (61%) | 27 (87%) |
| 1 | 13 (39%) | 4 (13%) |
| Primary tumour location | | |
| Gastric | 31 (94%) | 28 (90%) |
| Gastro-oesophageal junction | 2 (6%) | 3 (10%) |
| Histological type | | |
| Diffuse | 18 (55%) | 15 (48%) |
| Intestinal | 15 (45%) | 16 (52%) |
| HER2 test result | | |
| Negative | 30 (91%) | 24 (77%) |
| Positive | 3 (9%) | 7 (23%) |
| Number of metastatic organs | | |
| 1–2 | 25 (76%) | 20 (65%) |
| ≥3 | 8 (24%) | 11 (35%) |
| Metastatic organ* | | |
| Lymph node | 24 (73%) | 21 (68%) |
| Peritoneum | 13 (39%) | 17 (55%) |
| Liver | 13 (39%) | 10 (32%) |
| Lung | 4 (12%) | 7 (23%) |

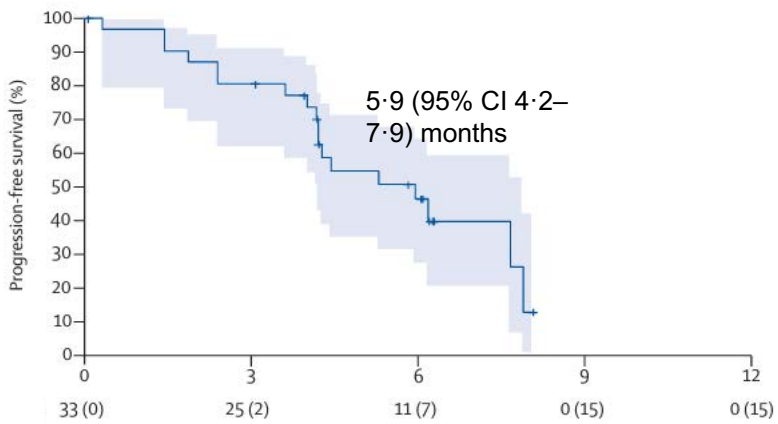
Kawazoe A, Ando T, Hosaka H, Fujita J, Koeda K, Nishikawa K, Amagai K, Fujitani K, Ogata K, Watanabe K, Yamamoto Y, Shitara K. Safety and activity of trifluridine/tipiracil and ramucirumab in previously treated advanced gastric cancer: an open-label, single-arm, phase 2 trial. Lancet Gastroenterol Hepatol. 2021 Mar;6(3):209-217

# Efficacy and Tolerability of Ram + TAS-102

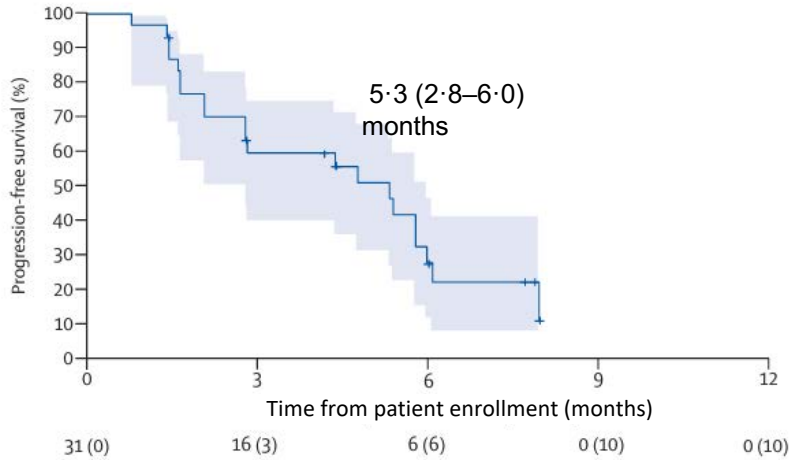
| | Cohort A (n=33) | Cohort B (n=31) |
|---|---|---|
| Complete response | 0 | 0 |
| Partial response | 3 (9%) | 5 (16%) |
| Stable disease | 25 (76%) | 19 (61%) |
| Progressive disease | 3 (9%) | 7 (23%) |
| Not evaluable | 2 (6%) | 0 |
| Overall response rate* | 3 (9%, 2–24) | 5 (16%, 6–34) |
| Disease control rate† | 28 (85%, 68–95) | 24 (77%, 59–90) |

Data are n (%) or n (%, 95% CI). *Complete response plus partial response. †Complete response plus partial response plus stable disease.

**PFS in Cohort A**




**PFS in Cohort B**




**Response rate based on ICI exposure**

| | Cohort A (n=33) | | Cohort B (n=31) | |
|---|---|---|---|---|
| | Previous use (n=7) | No previous use (n=26) | Previous use (n=15) | No previous use (n=16) |
| Overall response rate* | 2 (29%, 4–71) | 1 (4%, 0–20) | 5 (33%, 12–62) | 0 (0%, 0–21) |
| Disease control rate† | 7 (100%, 59–100) | 21 (81%, 61–93) | 10 (67%, 38–88) | 14 (88%, 62–98) |
| Progression-free survival, months | 6·1 (4·1–NA) | 5·3 (3·6–7·9) | 5·4 (1·4–NA) | 5·0 (2·1–6·1) |
| Event | 3 (43%) | 15 (58%) | 9 (60%) | 12 (75%) |
| Censored | 4 (57%) | 11 (42%) | 6 (40%) | 4 (25%) |

Data are n (%, 95% CI), n (95% CI), or n (%). NA=not available. *Complete response plus partial response. †Complete response plus partial response plus stable disease.

| | Cohort A (n=33) | | | | Cohort B (n=31) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1–2 | Grade 3 | Grade 4 | Total | Grade 1–2 | Grade 3 | Grade 4 | Total |
| Any treatment-related adverse event | 4 (12%) | 15 (45%) | 13 (39%) | 32 (97%) | 6 (19%) | 16 (52%) | 9 (29%) | 31 (100%) |
| Neutrophil count decreased | 3 (9%) | 14 (42%) | 13 (39%) | 30 (91%) | 1 (3%) | 14 (45%) | 9 (29%) | 24 (77%) |
| Decreased appetite | 17 (52%) | 2 (6%) | 0 | 19 (58%) | 19 (61%) | 1 (3%) | 0 | 20 (65%) |
| Platelet count decreased | 10 (30%) | 7 (21%) | 1 (3%) | 18 (55%) | 7 (23%) | 4 (13%) | 0 | 11 (35%) |
| White blood cell count decreased | 6 (18%) | 6 (18%) | 2 (6%) | 14 (42%) | 5 (16%) | 7 (23%) | 0 | 12 (39%) |
| Malaise | 10 (30%) | 0 | 0 | 10 (30%) | 13 (42%) | 0 | 0 | 13 (42%) |
| Nausea | 13 (39%) | 0 | 0 | 13 (39%) | 10 (32%) | 0 | 0 | 10 (32%) |
| Diarrhoea | 11 (33%) | 1 (3%) | 0 | 12 (36%) | 5 (16%) | 1 (3%) | 0 | 6 (19%) |
| Anaemia | 3 (9%) | 6 (18%) | 0 | 9 (27%) | 5 (16%) | 4 (13%) | 0 | 9 (29%) |
| Hypertension | 3 (9%) | 3 (9%) | 0 | 6 (18%) | 2 (6%) | 2 (6%) | 0 | 4 (13%) |
| Alopecia | 6 (18%) | 0 | 0 | 6 (18%) | 0 | 0 | 0 | 0 |
| Fatigue | 3 (9%) | 2 (6%) | 0 | 5 (15%) | 3 (10%) | 0 | 0 | 3 (10%) |

Kawazoe A, Ando T, Hosaka H, Fujita J, Koeda K, Nishikawa K, Amagai K, Fujitani K, Ogata K, Watanabe K, Yamamoto Y, Shitara K. Safety and activity of trifluridine/tipiracil and ramucirumab in previously treated advanced gastric cancer: an open-label, single-arm, phase 2 trial. Lancet Gastroenterol Hepatol. 2021 Mar;6(3):209-217

# FOLFIRI plus Ramucirumab- RAMIRIS Study

Phase II randomized study (2:1) to **Arm A**: FOLFIRI plus ramucirumab vs **Arm B**: ramucirumab plus paclitaxel. 110 patients randomized. 65% had prior docetaxel exposure.

Best overall response in the ITT (total population).

| Best overall response | FOLFIRI + Ramucirumab (n = 72) | Paclitaxel + Ramucirumab (n = 38) | Total (n = 110) |
|---|---|---|---|
| CR | 2 (3%) | 1 (3%) | 3 (3%) |
| PR | 14 (19%) | 3 (8%) | 17 (15%) |
| SD | 28 (39%) | 16 (42%) | 44 (40%) |
| PD | 18 (25%) | 10 (26%) | 28 (25%) |
| Not evaluable or not assessed | 10 (14%) | 8 (21%) | 18 (16%) |

Data are (%) or number (n).

**ORR 22% vs 11%; DCR 61% vs 53%**

Best overall response in docetaxel-pretreated patients.

| Best overall response | FOLFIRI + Ramucirumab (n = 48) | Paclitaxel + Ramucirumab (n = 24) | Total (n = 72) |
|---|---|---|---|
| CR | 2 (4%) | 1 (4%) | 3 (4%) |
| PR | 10 (21%) | 1 (4%) | 11 (15%) |
| SD | 19 (40%) | 7 (29%) | 26 (36%) |
| PD | 12 (25%) | 10 (42%) | 22 (31%) |
| Not evaluable or not assessed | 5 (10%) | 5 (21%) | 10 (14%) |

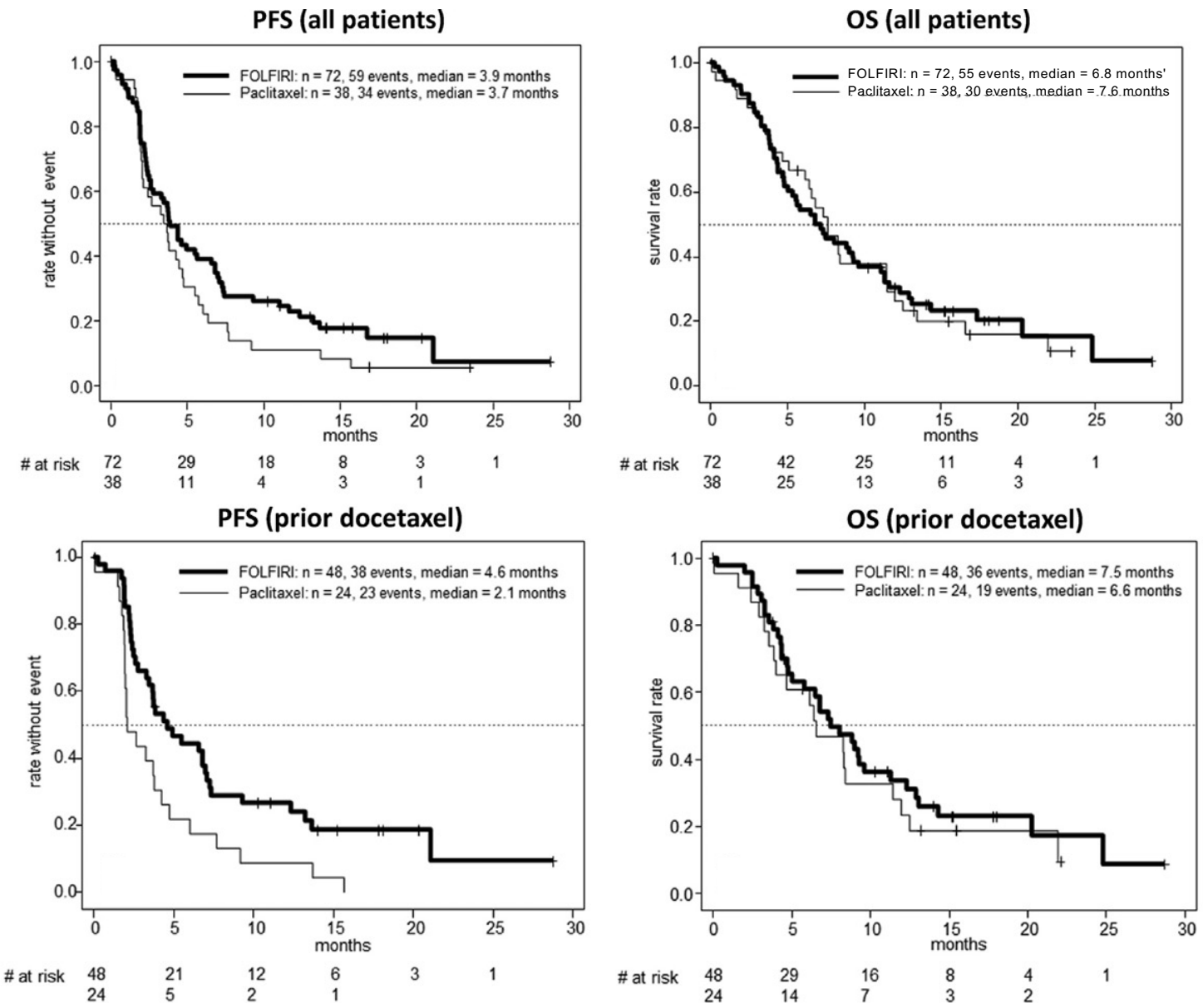
Data are (%) or number (n).

**ORR 25% vs 8%; DCR 65% vs 37%**

ORR- Objective response rate; DCR- Disease control rate

Lorenzen S, Thuss-Patience P, Pauligk C, Gökkurt E, Ettrich T, Lordick F, Stahl M, Reichardt P, Sökler M, Pink D, Probst S, Hinke A, Goetze TO, Al-Batran SE. FOLFIRI plus ramucirumab versus paclitaxel plus ramucirumab as second-line therapy for patients with advanced or metastatic gastroesophageal adenocarcinoma with or without prior docetaxel - results from the phase II RAMIRIS Study of the German Gastric Cancer Study Group at AIO. Eur J Cancer. 2022 Apr;165:48-57.

# Ph 2 RAMIRIS Study




In arm A, at least one event of grade 3-5 was recorded in 54/72 patients (75%). The corresponding finding in arm B was 23/34 (68%).

Treatment-related serious AEs were reported in 32 (30%) patients of the safety population in total, 22(31%) in the FOLFIRI group and 10(29%) in the paclitaxel group.

# Other combinations with ramucirumab

## Ramucirumab plus paclitaxel plus nivolumab

- Phase I/II study (N=43)
- 60.5% PD-L1 CPS≥1
- 90.7% of patients experienced grade ≥3 treatment-related AEs
- Median PFS was 5.1 months
- Median OS was 13.1 months
- ORR was 37.2%

## Ramucirumab plus Olaparib

- Phase I/II study (N=51)
- ORR 14%
- DOR 10 months
- Median PFS 2.8 months
- Median OS 7.3 months (13.5 months for HRD positive tumors)

PD-L1- Programmed Death ligand 1; CPS- Combined positive score; AE- adverse event; PFS- progression free survival; OS- Overall survival; ORR- objective response rate; DOR- duration of response; HRD- homologous recombination deficiency

Nakajima TE, Kadowaki S, Minashi K, Nishina T, Yamanaka T, Hayashi Y, Izawa N, Muro K, Hironaka S, Kajiwara T, Kawakami Y. Multicenter Phase I/II Study of Nivolumab Combined with Paclitaxel Plus Ramucirumab as Second-line Treatment in Patients with Advanced Gastric Cancer. Clin Cancer Res. 2021 Feb 15;27(4):1029-1036 and Cecchini M, Cleary JM, Shyr Y, Chao J, Uboha N, Cho M, Shields A, Pant S, Goff L, Spencer K, Kim E, Stein S, Kortmansky JS, Canosa S, Sklar J, Swisher EM, Radke M, Ivy P, Boerner S, Durecki DE, Hsu CY, LoRusso P, Lacy J. NCI10066: a Phase 1/2 study of olaparib in combination with ramucirumab in previously treated metastatic gastric and gastroesophageal junction adenocarcinoma. Br J Cancer. 2023 Dec 22. doi: 10.1038/s41416-023-02534-1.

# Anticipated activation of SWOG Ph II/III of 2nd Line Nivolumab + Paclitaxel + Ramucirumab versus Paclitaxel + Ramucirumab in Patients with PD-L1 CPS ≥ 1 Advanced Gastric and Esophageal Adenocarcinoma (PARAMMUNE)

# Role of anti-PD-1 monotherapy in recurrent disease

On April 29, 2021, the FDA's Oncologic Drugs Advisory Committee (ODAC) voted 6 to 2 against the continued approval of pembrolizumab for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (combined positive score [CPS] ≥1) who experienced disease progression on or after 2 or more prior lines of therapy, including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2-targeted therapy.

# Mismatch repair deficient/Microsatellite instability high tumors

**GARNET study with dostarlimab**

- 22 of 347 patients had diagnosis of gastric cancer
- Overall response rate 45.5%
- Median PFS 5.5 months
- Median OS 20.1 months

**KEYNOTE-158 with pembrolizumab**

- 42 of 321 patients had diagnosis of gastric cancer
- Overall response rate 31.0%
- Median PFS 3.2 months
- Median OS 11.0 months

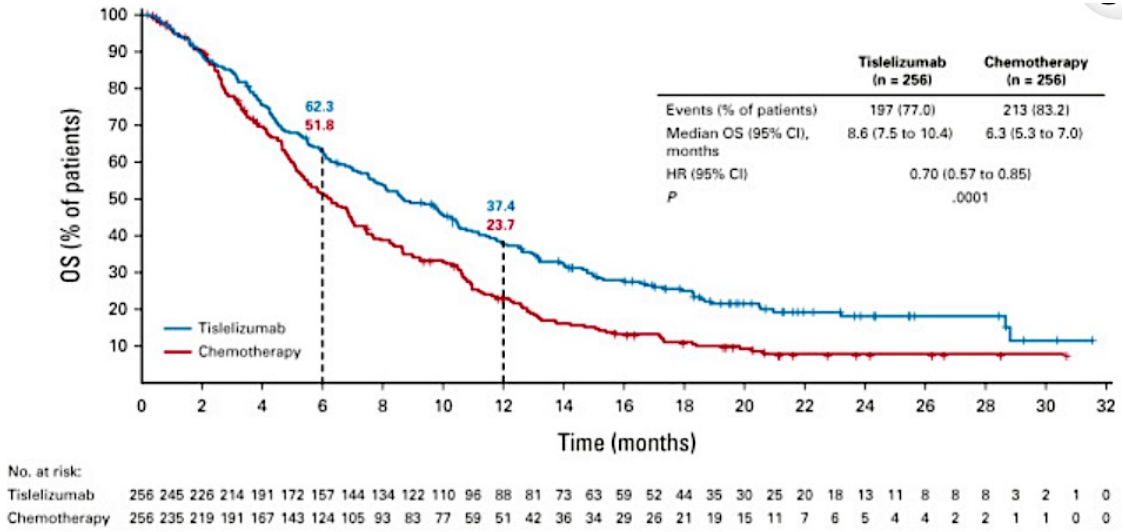
***Both are appropriate choices per NCCN guidelines***

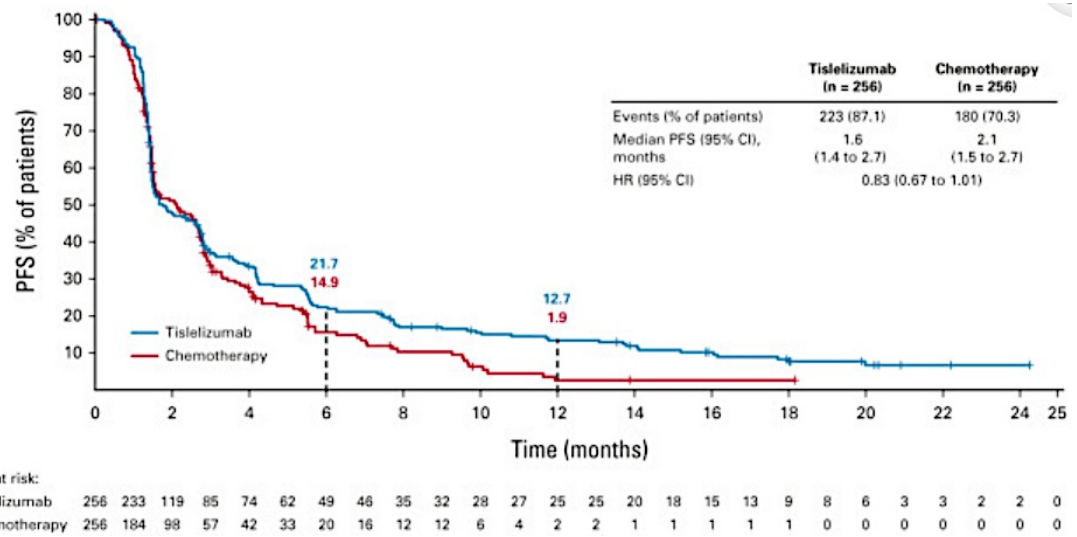
André T, Berton D, Curigliano G, et al. Antitumor Activity and Safety of Dostarlimab Monotherapy in Patients With Mismatch Repair Deficient Solid Tumors: A Nonrandomized Controlled Trial. *JAMA Netw Open.* 2023;6(11):e2341165 and Maio M, Ascierto PA, Manzyuk L, et al. Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: updated analysis from the phase II KEYNOTE-158 study. *Ann Oncol*. 2022;33(9):929-938.

# RATIONALE-302

# RATIONALE-302

Open-label phase III clinical study, patients with **advanced or metastatic ESCC**, whose tumor progressed after first-line systemic treatment, were randomly assigned (1:1) to receive intravenous tislelizumab, an anti–programmed cell death protein 1 antibody, 200 mg every 3 weeks or chemotherapy (investigator's choice of paclitaxel, docetaxel, or irinotecan). The primary end point was overall survival (OS) in all patients. Patients that received ICI previously were excluded.



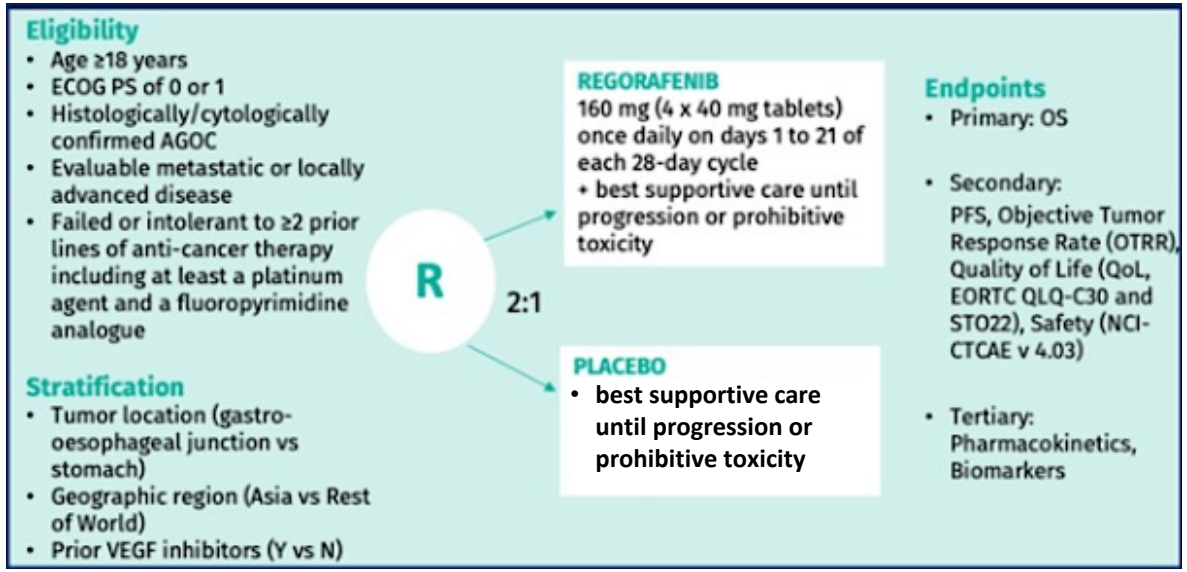




Shen L, Kato K, Kim SB, Ajani JA, Zhao K, He Z, Yu X, Shu Y, Luo Q, Wang J, Chen Z, Niu Z, Zhang L, Yi T, Sun JM, Chen J, Yu G, Lin CY, Hara H, Bi Q, Satoh T, Pazo-Cid R, Arkenau HT, Borg C, Lordick F, Li L, Ding N, Tao A, Shi J, Van Cutsem E; RATIONALE-302 Investigators. Tislelizumab Versus Chemotherapy as Second-Line Treatment for Advanced or Metastatic Esophageal Squamous Cell Carcinoma (RATIONALE-302): A Randomized Phase III Study. J Clin Oncol. 2022 Sep 10;40(26):3065-3076.

ORR 20.3% vs 9.8%. Fewer patients had ≥ grade 3 TRAEs with tislelizumab versus chemotherapy (18.8% *v* 55.8%).

# Other promising agents

# INTEGRATE IIa (REGORAFENIB)




## Results*

- REGO improved OS:
  - HR 0.70 (95% CI:0.56 to 0.87; p= 0.001) in the pooled study population (INTEGRATE and INTEGRATE IIA); no heterogeneity observed (p = 0.90).
  - After 238 events in INTEGRATE IIa, OS HR 0.68 with 12 -month survival of 19% vs 6%.
  - No statistically significant regional difference (Asia versus non-Asia), with benefit seen in all pre-specified sub-groups
- REGO improved PFS: HR=0.53; 95% CI: 0.40-0.70; p<0.0001)
- REGO delays deterioration in global QoL compared with PBO (p = 0.0043).
- REGO toxicity profile was similar to that seen in previous reports.

*Analysis uses data extracted Dec 13, 2022

| | Regorafenib (N= 166) | | | | Placebo (N= 79) | | | |
|---|---|---|---|---|---|---|---|---|
| | Gr 1-2 | Gr 3 | Gr 4 | Gr 5 | Gr 1-2 | Gr 3 | Gr 4 | Gr 5 |
| Any adverse event | 52 (31) | 92 (55) | 12 (7) | 3 (2)[a] | 37 (47) | 29 (37) | 3 (4) | 0 |
| Fatigue | 40 (24) | 15 (9) | 0 | 0 | 18 (23) | 5 (6) | 0 | 0 |
| Palmar-plantar erythrodysesthesia syndrome* | 52 (31) | 15 (9) | 0 | 0 | 4 (5) | 0 | 0 | 0 |
| Abdominal pain | 30 (18) | 6 (4) | 0 | 0 | 14 (18) | 4 (5) | 0 | 0 |
| Anorexia | 30 (18) | 7 (4) | 0 | 0 | 16 (20) | 0 | 0 | 0 |
| Oral mucositis* | 34 (20) | 1 (1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Nausea | 24 (14) | 2 (1) | 0 | 0 | 17 (22) | 3 (4) | 0 | 0 |
| Vomiting | 15 (9) | 3 (2) | 0 | 0 | 8 (10) | 3 (4) | 0 | 0 |
| Diarrhea* | 30 (18) | 6 (4) | 0 | 0 | 4 (5) | 1 (1) | 0 | 0 |
| Constipation* | 20 (12) | 1 (1) | 0 | 0 | 4 (5) | 1 (1) | 0 | 0 |
| ALT increase* | 20 (12) | 9 (5) | 0 | 0 | 3 (4) | 1 (1) | 0 | 0 |
| AST increase* | 23 (16) | 7 (4) | 2 (1) | 0 | 3 (4) | 2 (3) | 0 | 0 |
| Anemia | 6 (4) | 9 (5) | 0 | 0 | 4 (5) | 6 (8) | 0 | 0 |
| Hypertension* | 23 (16) | 13 (8) | 0 | 0 | 2 (3) | 0 | 0 | 0 |

* Toxicities more common with regorafenib; [a]One death was due to hepatic failure, and two were due to sepsis.

*Between Oct 2016 and Sep 2021, 251 patients were randomized in INTEGRATE IIa from 6 countries: 157 from Asia (Korea, Taiwan, Japan) and 94 from Australia, New Zealand and Canada). 169 patients received regorafenib and 82 placebo. The study population was well balanced in demographic and stratification factors.*

Ongoing Phase III INTEGRATE IIb comparing regorafenib plus nivolumab vs investigator-choice chemotherapy.

Nick Pavlakis et al., INTEGRATE IIa: A randomised, double-blind, phase III study of regorafenib versus placebo in refractory advanced gastro-oesophageal cancer (AGOC)—A study led by the Australasian Gastro-intestinal Trials Group (AGITG).. *JCO* **41**, LBA294-LBA294(2023).

Cinrebafusp alfa (PRS-343), a first-in-class bispecific antibody-Anticalin fusion protein, targets both HER2 on tumor cells and the receptor 4-1BB (CD137) on T cells.

Phase II, multi-center, open-label study of cinrebafusp alfa in combination with standard doses of ramucirumab and paclitaxel in HER2 positive gastric/GEJ tumors.

5 patients treated before the trial was ceased and all experienced a response.

Geoffrey Ku, Jeeyun Lee, Kayti Aviano, Tim Demuth, Laura-Carolin Hasenkamp, Shane A. Olwill; Abstract CT154: Combination of cinrebafusp alfa with ramucirumab and paclitaxel is well tolerated and elicits encouraging clinical activity in patients with HER2-positive gastric/gastroesophageal junction (GEJ) adenocarcinoma. *Cancer Res* 15 April 2023; 83 (8_Supplement): CT154.

# Consensus or Controversy? Clinical Investigators Provide Perspectives on Biomarker Assessment and Related Treatment Decision-Making for Patients with Colorectal Cancer

*Part 2 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 ASCO Gastrointestinal Cancers Symposium*

**Friday January 19, 2024**

**6:15 PM – 8:15 PM PT (9:15 PM – 11:15 PM ET)**

## Faculty

**Tanios Bekaii-Saab, MD**

**Andrea Cercek, MD**

**Cathy Eng, MD**

**John Strickler, MD**

## Moderator

**Christopher Lieu, MD**

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