

# Year in Review: Novel Treatments and Strategies in Gastroesophageal Cancer

*A Multitumor CME/MOC-Accredited Live Webinar*

**Wednesday, April 10, 2024  
5:00 PM – 6:00 PM ET**

## **Faculty**

**Eric Van Cutsem, MD, PhD**

## **Moderator**

**Neil Love, MD**

# Faculty



## **FACULTY**

**Eric Van Cutsem, MD, PhD**  
Professor of Medicine  
Digestive Oncology  
University Hospitals Leuven  
Leuven, Belgium



## **MODERATOR**

**Neil Love, MD**  
Research To Practice  
Miami, Florida



## **CONSULTING FACULTY**

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

## Commercial Support

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

# Dr Love — Disclosures

**Dr Love** is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI Biopharma, a Sobi company, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Grail Inc, GSK, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kronos Bio Inc, Legend Biotech, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Mural Oncology Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, R-Pharm US, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Sumitomo Dainippon Pharma Oncology Inc, Syndax Pharmaceuticals, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc, and Zymeworks Inc.

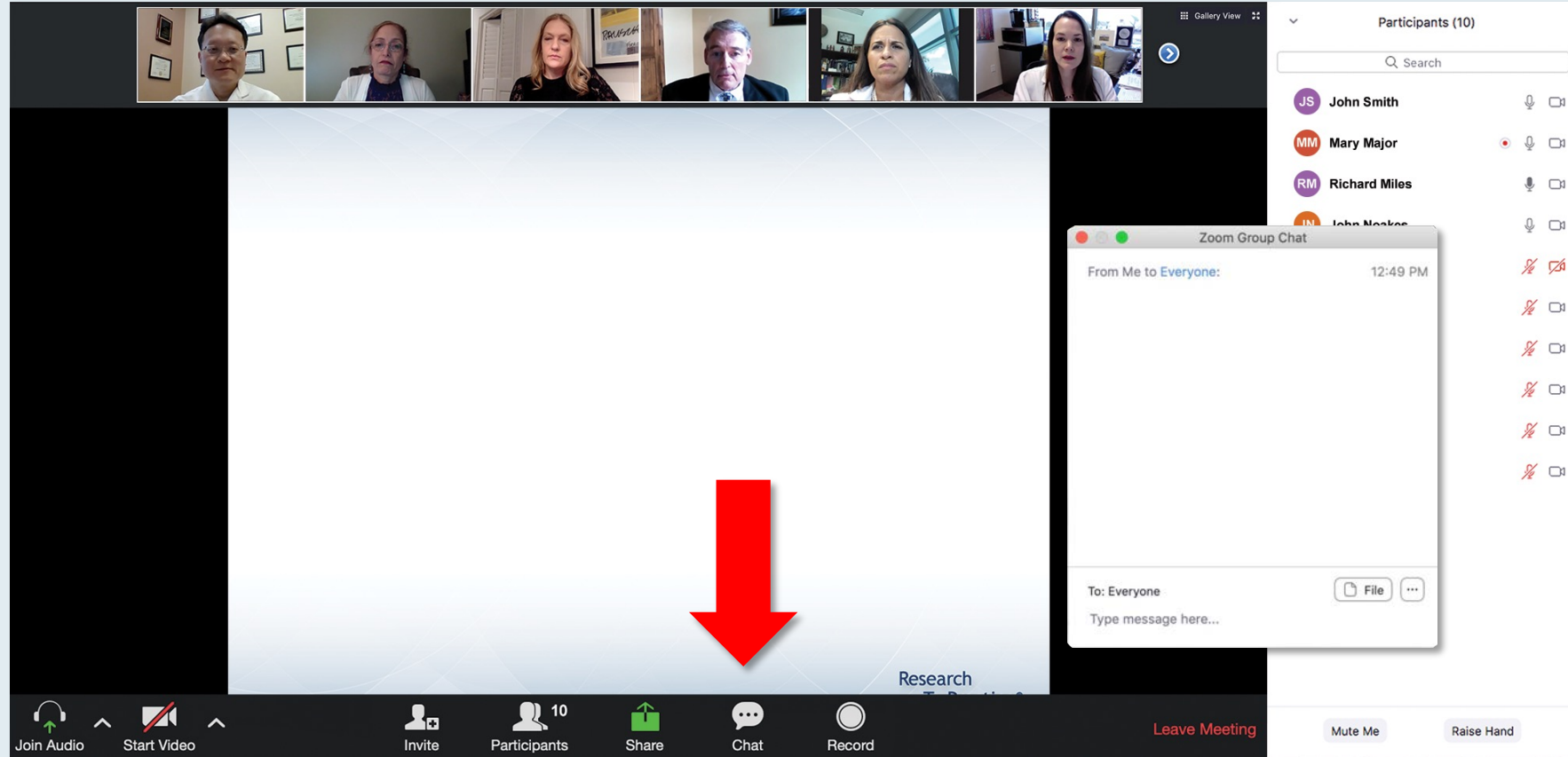
# Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

# Prof Van Cutsem — Disclosures

<b>Consulting Agreements</b>	AbbVie Inc, Agenus Inc, ALX Oncology, Amgen Inc, Arcus Biosciences, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BioNTech SE, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Daiichi Sankyo Inc, Debiopharm, Eisai Inc, ElmediX, Galapagos NV, GSK, Hookipa Pharma Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Lilly, Merck KGaA, MSD, Mirati Therapeutics Inc, Nordic Pharma, Novartis, Pfizer Inc, Pierre Fabre, Roche Laboratories Inc, Seagen Inc, Servier Pharmaceuticals LLC, Simcere, Taiho Oncology Inc, Takeda Pharmaceutical Company Limited, Terumo Medical Corporation
<b>Nonrelevant Financial Relationship</b>	Bexon Clinical Consulting

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

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

The screenshot shows a Zoom meeting interface. At the top, there is a video gallery with six participants. Below the gallery is a large text overlay for a meeting titled "Meet The Prof... Optimizing the Selection and... of Therapy for Patients with Gastrointestinal Ca...". The meeting is scheduled for Wednesday, August 25, from 5:00 PM to 6:00 PM. The faculty member is Wells A Messersmith, and the moderator is Neil Love, MD. A "Quick Survey" pop-up window is displayed in the center, listing various treatment combinations with radio button options. The survey options include: Carfilzomib +/- dexamethasone, Pomalidomide +/- dexamethasone, Carfilzomib + pomalidomide +/- dexamethasone, Eltuzumab + lenalidomide +/- dexamethasone, Eltuzumab + pomalidomide +/- dexamethasone, Daratumumab + lenalidomide +/- dexamethasone, Daratumumab + pomalidomide +/- dexamethasone, Daratumumab + bortezomib +/- dexamethasone, and Isazomib + Rd. A "Submit" button is at the bottom of the survey. On the right side, a "Participants (10)" list shows names and icons for John Smith, Mary Major, Richard Miles, John Noakes, Alice Suarez, Jane Perez, Robert Stiles, Juan Fernandez, Ashok Kumar, and Jeremy Smith. The bottom toolbar includes icons for Join Audio, Start Video, Invite, Participants (10), Share, Chat, Record, Leave Meeting, Mute Me, and Raise Hand.

The screenshot shows a Zoom meeting interface. At the top, there is a video gallery with six participants. Below the gallery is a large text overlay for a meeting titled "Regulatory and reimbursement issues aside, which would you recommend for a 65-year-old patient... nephrectomy for clear cell renal cell carcinoma (if follow-up 3 years later is found to have asymptomatic PS 0)?". A "Quick Poll" pop-up window is displayed in the center, listing eight treatment options with radio button options. The poll options include: Nivolumab/ipilimumab, Avelumab/axitinib, Pembrolizumab/axitinib, Pembrolizumab/lenvatinib, Nivolumab/cabozantinib, Tyrosine kinase inhibitor (TKI) monotherapy, Anti-PD-1/PD-L1 monotherapy, and Other. A "Submit" button is at the bottom of the poll. On the right side, a "Participants (10)" list shows names and icons for John Smith, Mary Major, Richard Miles, John Noakes, Alice Suarez, Jane Perez, Robert Stiles, Juan Fernandez, Ashok Kumar, and Jeremy Smith. The bottom toolbar includes icons for Join Audio, Start Video, Invite, Participants (10), Share, Chat, Record, Leave Meeting, Mute Me, and Raise Hand.



# ONCOLOGY TODAY

WITH DR NEIL LOVE

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



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MEMORIAL SLOAN KETTERING CANCER CENTER



**DR ZEV WAINBERG**  
UCLA JONSSON COMPREHENSIVE CANCER CENTER



# Year in Review: Acute Myeloid Leukemia

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**Wednesday, April 17, 2024**

**5:00 PM – 6:00 PM ET**

## **Faculty**

**Naval Daver, MD**

**Courtney D DiNardo, MD, MSCE**

## **Moderator**

**Neil Love, MD**

# What I Tell My Patients: Integrating New Research Information into Current Clinical Care

*A Complimentary NCPD Hybrid Symposium Series Held During the 49<sup>th</sup> Annual ONS Congress April 24-27*

## **Hormone Receptor-Positive Breast Cancer**

**Wednesday, April 24, 2024**

6:00 PM – 8:00 PM ET

### **Faculty**

Harold J Burstein, MD, PhD

Kelly Fischer, MSN, FNP-BC

Komal Jhaveri, MD, FACP

Melissa Rikal, FNP-BC, AOCNP

## **Antibody-Drug Conjugates**

**Thursday, April 25, 2024**

12:15 PM – 1:45 PM ET

### **Faculty**

Jamie Carroll, APRN, MSN, CNP

Kelly EH Goodwin, MSN, RN, ANP-BC

Erika Hamilton, MD

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## **Endometrial Cancer**

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Meetal Dharia, NP-C, AOCNP

Robert L Ferris, MD, PhD

Robert Haddad, MD

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# Agenda

**MODULE 1: Immune Checkpoint Inhibitors in Localized Gastroesophageal (GE) Cancers**

**MODULE 2: HER2-Positive GE Cancers**

**MODULE 3: First-Line Treatment of Metastatic Gastric and GEJ Adenocarcinoma**

- **Zolbetuximab for Claudin 18.2 GE Cancer**
- **Immunotherapy with Chemotherapy**



*Thank you for joining us!*

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

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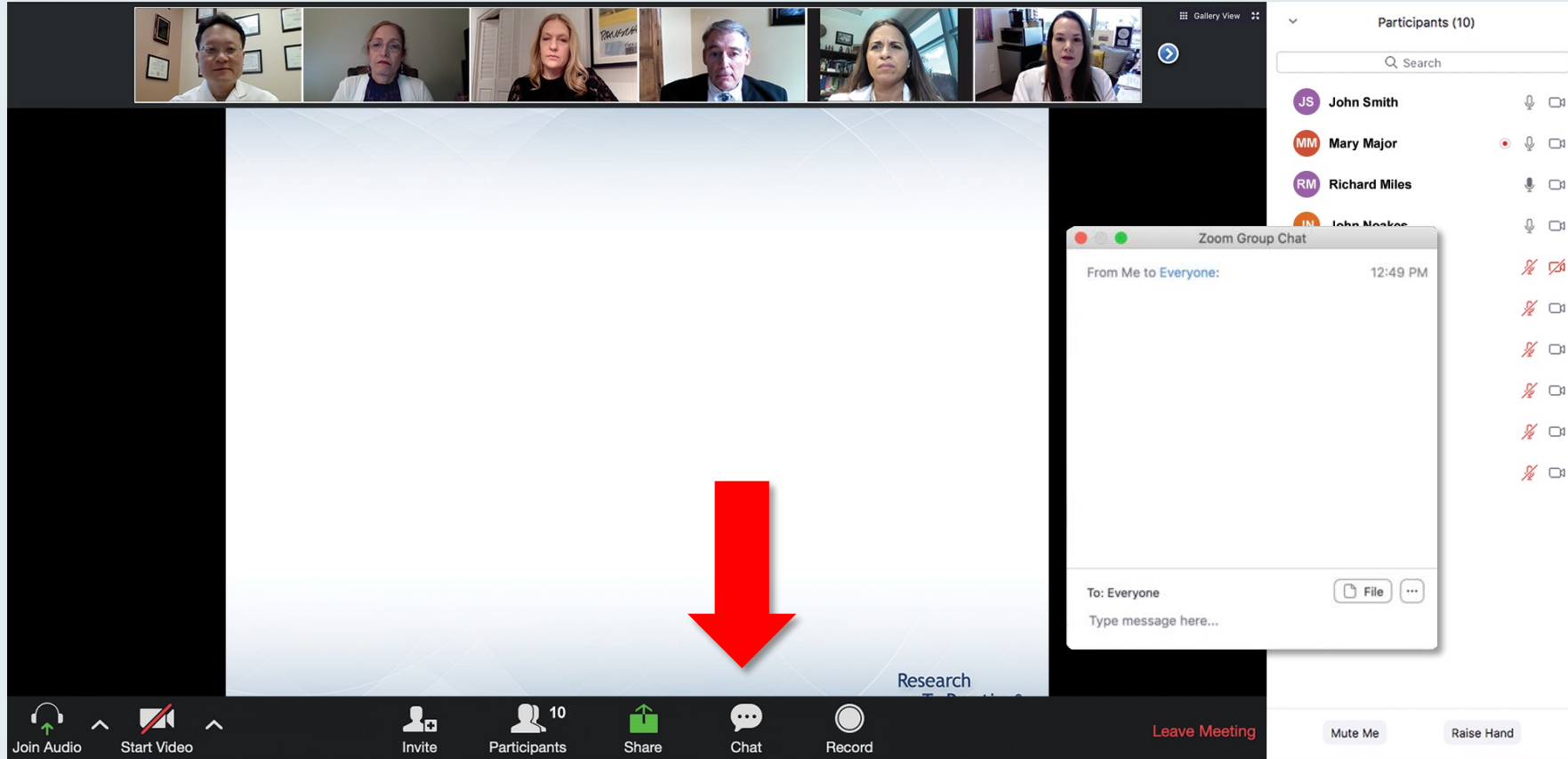
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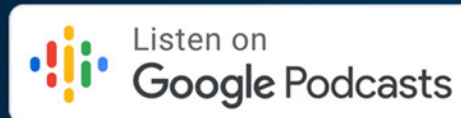
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**This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.**



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Sunnie Kim, MD  
GI Medical Oncology  
Associate Professor  
University of Colorado Cancer Center  
[UCHealth](#)



# Key Data Sets

## Sunnie Kim, MD

- Al-Batran SE et al. **Pembrolizumab plus FLOT vs FLOT as neoadjuvant and adjuvant therapy in locally advanced gastric and gastroesophageal junction cancer: Interim analysis of the phase 3 KEYNOTE-585 study.** *Gastrointestinal Cancers Symposium 2024*;Abstract 247.
- Shitara K et al. **Neoadjuvant and adjuvant pembrolizumab plus chemotherapy in locally advanced gastric or gastro-oesophageal cancer (KEYNOTE-585): An interim analysis of the multicentre, double-blind, randomised phase 3 study.** *Lancet Oncol* 2024 February;25(2):212-24.
- Janjigian YY et al. **Pathological complete response (pCR) to 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) with or without durvalumab (D) in resectable gastric and gastroesophageal junction cancer (GC/GEJC): Subgroup analysis by region from the phase 3, randomized, double-blind MATTERHORN study.** *Gastrointestinal Cancers Symposium 2024*;Abstract LBA246.
- Smyth EC et al. **Mismatch repair deficiency, microsatellite instability, and survival: An exploratory analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial.** *JAMA Oncol* 2017 September 1;3(9):1197-203.

# Key Data Sets

## Sunnie Kim, MD (continued)

- André T et al. **Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in localized deficient mismatch repair/microsatellite instability-high gastric or esophagogastric junction adenocarcinoma**: The GERCOR **NEONIPIGA** Phase II Study. *J Clin Oncol* 2023 January 10;41(2):255-65.
- Pietrantonio F et al. **INFINITY**: A multicentre, single-arm, multi-cohort, phase II trial of **tremelimumab** and **durvalumab** as **neoadjuvant** treatment of patients with **microsatellite instability-high (MSI) resectable gastric or gastroesophageal junction adenocarcinoma (GAC/GEJAC)**. Gastrointestinal Cancers Symposium 2023;Abstract 264.
- Shen L et al. **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 September 10;40(26):3065-76.
- Xu J et al. **Tislelizumab plus chemotherapy** versus placebo plus chemotherapy as **first-line** treatment for advanced or **metastatic oesophageal squamous cell carcinoma (RATIONALE-306)**: A global, randomised, placebo-controlled, **phase 3** study. *Lancet Oncol* 2023 May;24(5):483-95.

# Key Data Sets

## Sunnie Kim, MD (continued)

- Kato K et al. **Nivolumab (NIVO) plus chemotherapy (chemo) or ipilimumab (IPI) vs chemo as first-line (1L) treatment for advanced esophageal squamous cell carcinoma (ESCC): 29-month (mo) follow-up from **CheckMate 648**. Gastrointestinal Cancers Symposium 2023;Abstract 290.**
- Moehler MH et al. **RATIONALE 305: Phase 3 study of tislelizumab plus chemotherapy vs placebo plus chemotherapy as first-line treatment (1L) of advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJC)**. Gastrointestinal Cancers Symposium 2023;Abstract 286.
- Shitara K et al. **Nivolumab (NIVO) + chemotherapy (chemo) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): 4-year (yr) follow-up of **CheckMate 649**. Gastrointestinal Cancers Symposium 2024;Abstract 306.**
- Rha SY et al. **Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): A multicentre, randomised, double-blind, phase 3 trial**. *Lancet Oncol* 2023;24(11):1181-95.

# Key Data Sets

## Sunnie Kim, MD (continued)

- Shitara K et al. **Zolbetuximab + mFOLFOX6** as **first-line** (1L) treatment for patients (pts) with **claudin-18.2+ (CLDN18.2+)** / HER2– locally advanced (LA) unresectable or **metastatic gastric** or **gastroesophageal junction** (mG/GEJ) adenocarcinoma: Primary results from **phase 3 SPOTLIGHT** study. Gastrointestinal Cancers Symposium 2023;Abstract LBA292.
- Shah MA et al. **Zolbetuximab** plus **CAPOX** in **CLDN18.2-positive gastric** or **gastroesophageal junction adenocarcinoma**: The randomized, **phase 3 GLOW** trial. *Nat Med* 2023 August;29(8):2133-41.
- Shah MA et al. Network **meta-analysis** of global trials of **1L therapies** in locally advanced (LA) unresectable or **metastatic gastric** or **gastroesophageal junction** (mG/GEJ) adenocarcinoma. Gastrointestinal Cancers Symposium 2024;Abstract 325.
- Shitara K et al; **DESTINY-Gastric01** investigators. **Trastuzumab deruxtecan** in previously treated **HER2-positive gastric cancer**. *N Engl J Med* 2020 June 18;382(25):2419-30.
- Yamaguchi K et al. **Trastuzumab deruxtecan** (T-DXd; DS-8201) in patients with **HER2–positive advanced gastric** or **gastroesophageal junction** (GEJ) adenocarcinoma: **Final overall survival** (OS) results from a randomized, multicenter, open-label, phase 2 study (**DESTINY-Gastric01**). Gastrointestinal Cancers Symposium 2022;Abstract 242.

# Key Data Sets

## Sunnie Kim, MD (continued)

- Van Cutsem E et al. **Trastuzumab deruxtecan** in patients in the USA and Europe with **HER2-positive advanced gastric or gastroesophageal junction** cancer with disease progression on or after a trastuzumab-containing regimen (**DESTINY-Gastric02**): Primary and **updated analyses** from a single-arm, phase 2 study. *Lancet Oncol* 2023 July;24(7):744-56.
- Elimova E et al. **Zanidatamab + chemotherapy** as **first-line** treatment for **HER2-expressing metastatic gastroesophageal adenocarcinoma** (mGEA). Gastrointestinal Cancers Symposium 2023;Abstract 347.

# Agenda

**MODULE 1: Immune Checkpoint Inhibitors in Localized Gastroesophageal (GE) Cancers**

**MODULE 2: HER2-Positive GE Cancers**

**MODULE 3: First-Line Treatment of Metastatic Gastric and GEJ Adenocarcinoma**

- **Zolbetuximab for Claudin 18.2 GE Cancer**
- **Immunotherapy with Chemotherapy**



# Agenda

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# Immune Checkpoint Inhibitors in Localized Disease

- Al-Batran SE et al. **Pembrolizumab plus FLOT vs FLOT as neoadjuvant and adjuvant therapy in locally advanced gastric and gastroesophageal junction cancer**: Interim analysis of the **phase 3 KEYNOTE-585** study. *Gastrointestinal Cancers Symposium 2024*;Abstract 247.
- Shitara K et al. **Neoadjuvant and adjuvant pembrolizumab plus chemotherapy in locally advanced gastric or gastro-oesophageal cancer (KEYNOTE-585)**: An interim analysis of the multicentre, double-blind, randomised **phase 3** study. *Lancet Oncol* 2024 February;25(2):212-24.
- Janjigian YY et al. **Pathological complete response (pCR) to 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) with or without durvalumab (D) in resectable gastric and gastroesophageal junction cancer (GC/GEJC)**: Subgroup analysis by region from the **phase 3**, randomized, double-blind **MATTERHORN** study. *Gastrointestinal Cancers Symposium 2024*;Abstract LBA246.
- Smyth EC et al. **Mismatch repair deficiency, microsatellite instability, and survival**: An **exploratory analysis** of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (**MAGIC**) trial. *JAMA Oncol* 2017 September 1;3(9):1197-203.

# Immune Checkpoint Inhibitors in Localized Disease (Continued)

- André T et al. **Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in localized deficient mismatch repair/microsatellite instability-high gastric or esophagogastric junction adenocarcinoma**: The GERCOR **NEONIPIGA** Phase II Study. *J Clin Oncol* 2023 January 10;41(2):255-65.
- Pietrantonio F et al. **INFINITY**: A multicentre, single-arm, multi-cohort, phase II trial of **tremelimumab** and **durvalumab** as **neoadjuvant** treatment of patients with **microsatellite instability-high (MSI) resectable gastric or gastroesophageal junction adenocarcinoma (GAC/GEJAC)**. Gastrointestinal Cancers Symposium 2023;Abstract 264.

# Case Presentation: 55-year-old man with localized, poorly differentiated signet ring, MMR-deficient advanced gastric adenocarcinoma



**Dr Sunnie Kim (Aurora, Colorado)**

# What was the patient's occupation?

- a. Physician
- b. Nurse
- c. Elementary school teacher
- d. Attorney
- e. Electrician

# NEONIPIGA and INFINITY: Perioperative dual immune checkpoint inhibition

NEONIPIGA: A Phase II trial evaluating the efficacy of **neoadjuvant nivolumab and ipilimumab** followed by **adjuvant nivolumab** in patients with **resectable MSI-H/dMMR esophagogastric adenocarcinoma**.

## Key Eligibility Criteria:

- Aged 18-75 years
- T2-T4, Nx, M0
- dMMR or MSI-H
- ECOG 0-1 (0 if >70 yr)
- Treatment-naïve

Neoadjuvant treatment  
6 cycles = 12 weeks

Nivolumab 240  
mg Q2W  
+  
Ipilimumab 1  
mg/kg Q6W

→  
5±1  
weeks

Surgery

Adjuvant treatment  
9 cycles = 9 months

Nivolumab 480  
mg Q4W

## Endpoints

### Primary Endpoint:

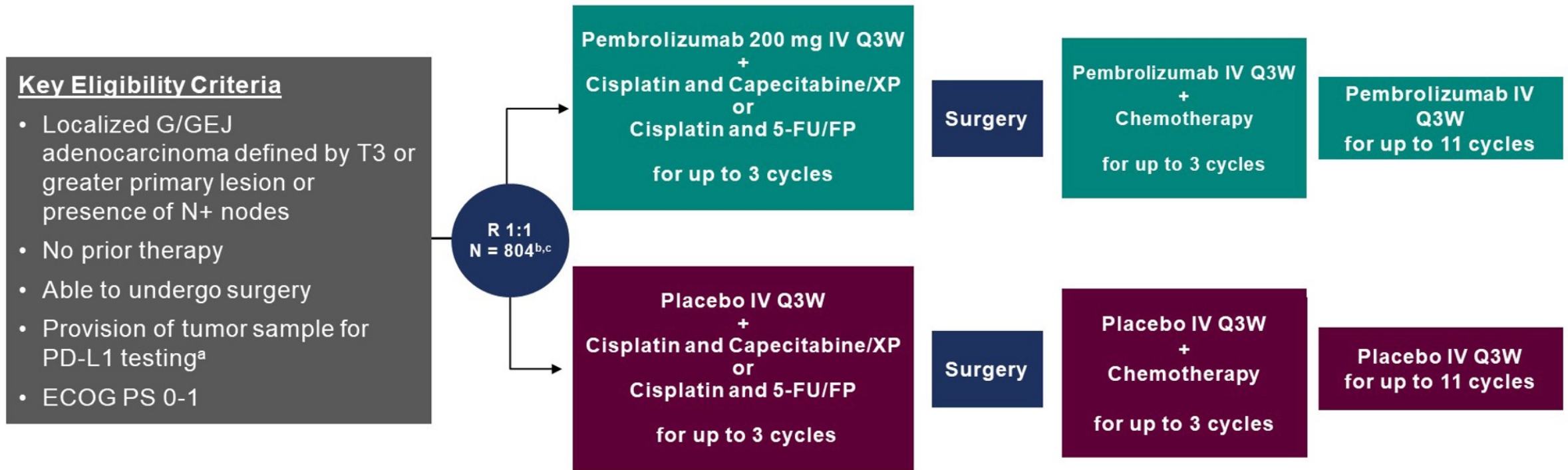
- cPRR

### Secondary Endpoints:

- DFS
- OS
- TRAEs
- Biomarkers

# KEYNOTE-585 Study Design

Randomized, Double-Blind, Phase 3 Trial of Neoadjuvant and Adjuvant Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy in G/GEJ Adenocarcinoma (**Main Cohort**)



## Stratification factors

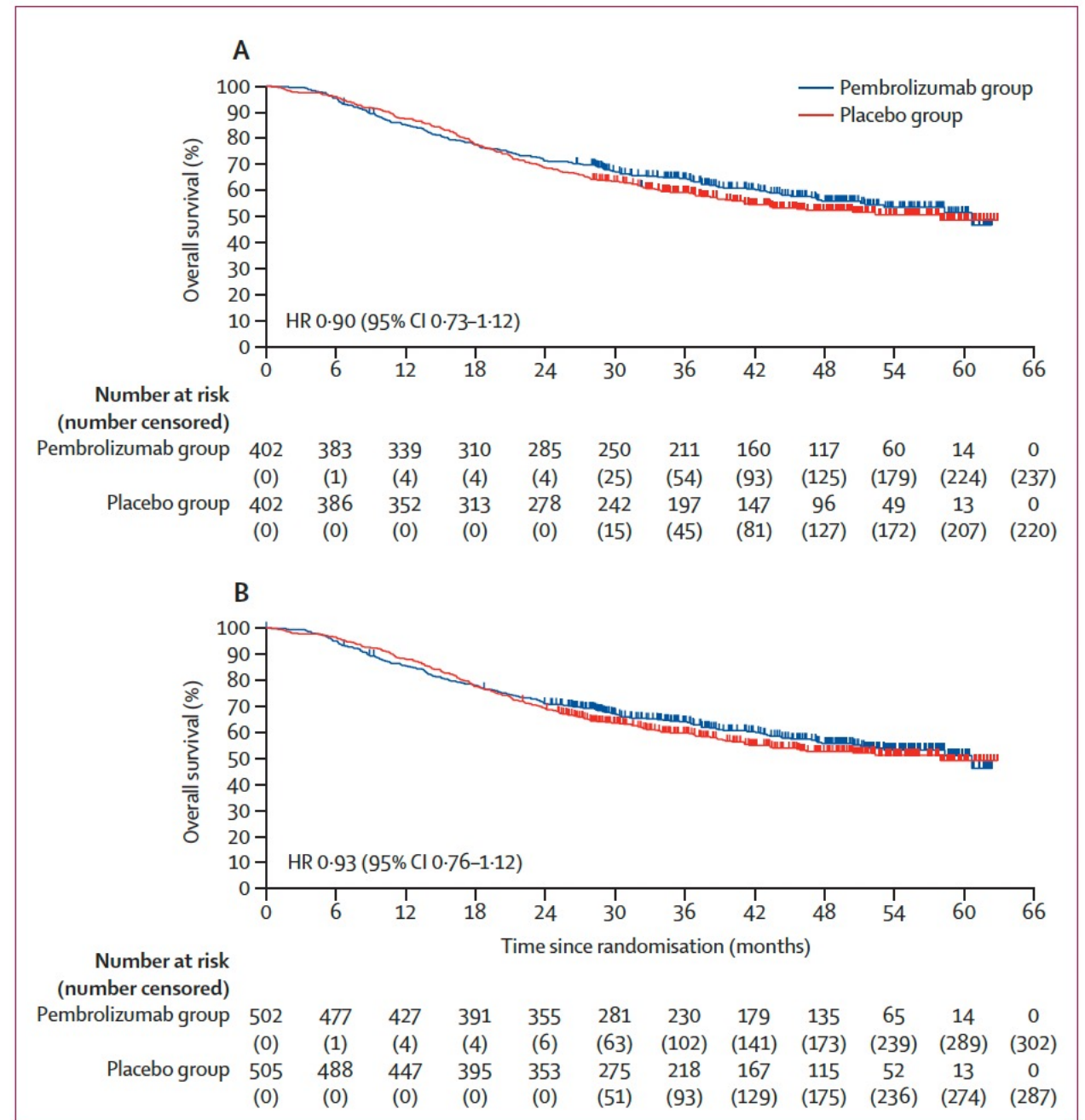
- Geographic region (Asia versus non-Asia)
- Tumor staging (II vs III vs IVa)
- Chemotherapy backbone (XP/FP vs FLOT)

## Endpoints:

- Primary: pathCR rate per BICR, EFS per investigator, OS (main cohort), safety (FLOT)
- Key secondary: safety (main cohort), safety, OS, EFS (main plus FLOT cohort)

# KEYNOTE-585: Overall Results

- With median follow up of 47.7 mos, pembrolizumab was superior to placebo for pCR (12.9% versus 2%)
- Median event free survival was 44.4 mos versus 25.3 mos
- In main cohort, mOS 60.7 mos versus 58 mos (HR 0.90, 95% CI 0.73 to 1.12; p=0.174)





# MATTERHORN: Study Design

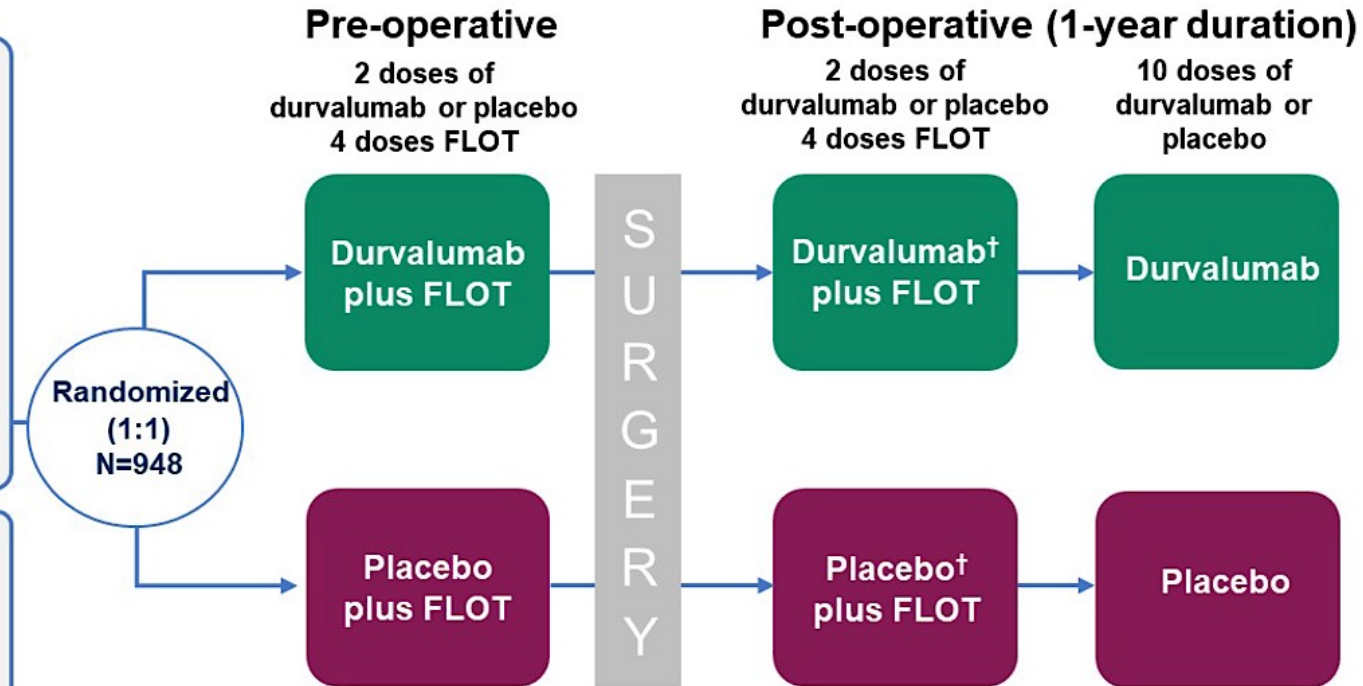
MATTERHORN is a global, Phase 3, randomized, double-blind, placebo-controlled study

## Study population

- Gastric and GEJ adenocarcinoma
- Stage II, III and IVA (>T2 N0-3 M0 or T0-4 N1-3 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

## Primary objective:

- EFS

## Key secondary objectives:

- Central review of pathological complete response by modified Ryan criteria
- OS

# What is the role of MMR Deficiency/MSI in Resectable Gastric and GEJ Cancers?

JAMA Oncology | **Original Investigation**

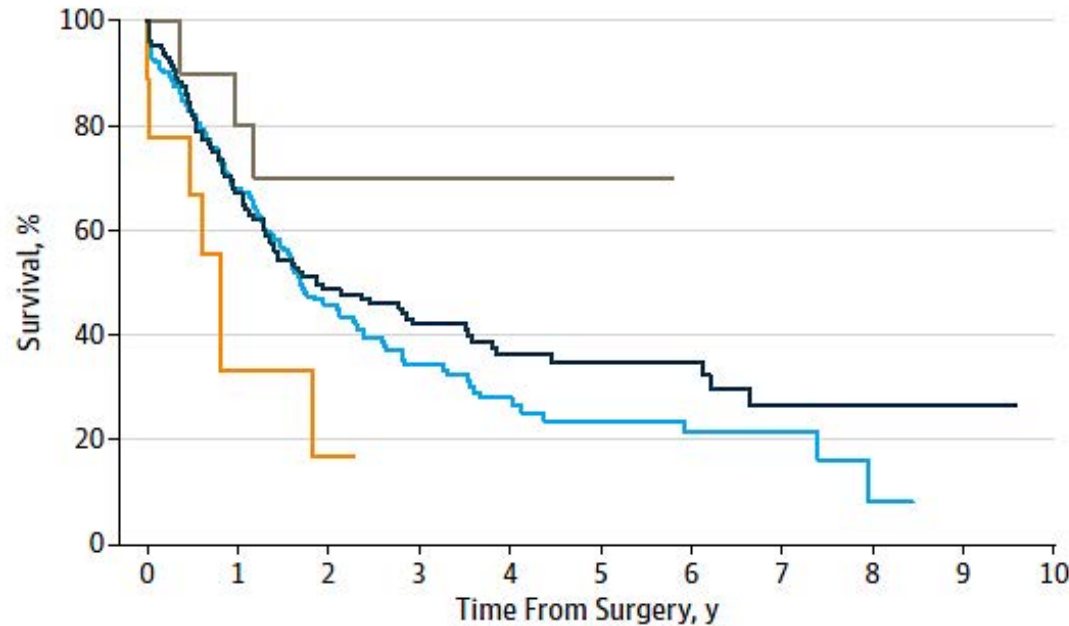
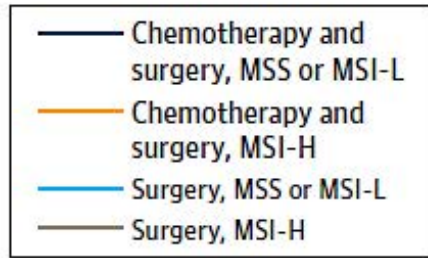
## Mismatch Repair Deficiency, Microsatellite Instability, and Survival

### An Exploratory Analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial

Elizabeth C. Smyth, MB, BCh, MSc; Andrew Wotherspoon, MD; Clare Peckitt, MSc; David Gonzalez, PhD; Sanna Hulkki-Wilson, BSc, MSc; Zakaria Eltahir, PhD; Matteo Fassan, MD, PhD; Massimo Rugge, MD, FACP; Nicola Valeri, MD, PhD; Alicia Okines, MD; Madeleine Hewish, MD, PhD; William Allum, MD; Sally Stenning, MSc; Matthew Nankivell, MSc; Ruth Langley, MD, PhD; David Cunningham, MD, FMedSci

- Secondary post hoc analysis of the MAGIC trial to evaluate the roles of MSI and dMMR with survival
- Of 503 study patients:
  - MMR status analyzed in 288 patients
    - 246 with pMMR
    - 22 with dMMR (7.6%)
  - MSI results available for 303 patients
    - 283 with MSS or MSI-L
    - 20 with MSI-H (6.6%)

# MAGIC Trial: MSI-H has a Negative Prognostic Effect in Patients Treated with Chemotherapy



No. at risk	0	1	2	3	4	5	6	7	8	9	10
Chemotherapy and surgery, MSI-negative patients	129	85	58	42	27	22	15	6	3	1	
Chemotherapy and surgery, MSI-positive patients	9	3	1								
Surgery, MSI-negative patients	151	100	58	37	21	13	9	7	1		
Surgery, MSI-positive patients	10	8	6	3	1	1					

## ★ Surgery + Chemotherapy

- ★ MSI-H or dMMR
  - **mOS 9.6 months** (95% CI, 0.1-22.5 months)
- MSS, MSI-L or pMMR
  - mOS 19.5 months (95%CI, 15.4-35.2 months; HR, 2.18; 95%CI, 1.08-4.42;  $P = .03$ )

## ★ Surgery alone

- ★ MSI-H or dMMR
  - **mOS not reached** (95%CI, 11.5 months to not reached)
- MSS, MSI-L or pMMR
  - mOS 20.5 months (95%CI, 16.7-27.8 months; HR, 0.42; 95%CI, 0.15-1.15;  $P = .09$ ).

# Trials in Progress: Localized Disease

- Ishigami H et al. Combined intraperitoneal and systemic chemotherapy as adjuvant or perioperative chemotherapy for patients with type 4 scirrhous gastric cancer: PHOENIX-GC2 trial. ASCO GI 2023;Abstract TPS477.
- Kinoshita T et al. Single-arm phase II trial to evaluate the safety of laparoscopic/robotic total gastrectomy with spleen-preserving splenic hilar dissection for locally advanced proximal gastric cancer that invades the greater curvature: JCOG1809. ASCO GI 2023;Abstract TPS479.
- McLaughlin RA et al. A prospective translational study investigating the association of gut microbiome (GM) diversity with pathological complete response (pCR) after neoadjuvant treatment in early stage rectal and esophageal cancers. ASCO GI 2023;Abstract TPS819.
- Wang M et al. Perioperative penpulimab plus anlotinib combined with chemotherapy for locally advanced gastric cancer: A single arm, multicenter, phase II clinical trial. ASCO GI 2023;Abstract TPS485.
- Yen C et al. Efficacy and safety of XELOX combined with anlotinib and penpulimab vs XELOX as adjuvant therapy in ctDNA-positive gastric and esophagogastric junction adenocarcinoma: A protocol for a randomized, controlled, multicenter phase II clinical trial — EXPLORING study. ASCO GI 2023;Abstract TPS486.

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- Immunotherapy with Chemotherapy

# HER2-Positive GE Cancers

- Shitara K et al; **DESTINY-Gastric01** investigators. **Trastuzumab deruxtecan** in previously treated **HER2-positive gastric cancer**. *N Engl J Med* 2020 June 18;382(25):2419-30.
- Yamaguchi K et al. **Trastuzumab deruxtecan** (T-DXd; DS-8201) in patients with **HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma: Final overall survival (OS) results** from a randomized, multicenter, open-label, phase 2 study (**DESTINY-Gastric01**). Gastrointestinal Cancers Symposium 2022;Abstract 242.
- Van Cutsem E et al. **Trastuzumab deruxtecan** in patients in the USA and Europe with **HER2-positive advanced gastric or gastroesophageal junction** cancer with disease progression on or after a trastuzumab-containing regimen (**DESTINY-Gastric02**): Primary and **updated analyses** from a single-arm, phase 2 study. *Lancet Oncol* 2023 July;24(7):744-56.
- Elimova E et al. **Zanidatamab + chemotherapy** as **first-line** treatment for **HER2-expressing metastatic gastroesophageal adenocarcinoma** (mGEA). Gastrointestinal Cancers Symposium 2023;Abstract 347.

**Case Presentation: 72-year-old man with HER2-positive gastroesophageal junction (GEJ) adenocarcinoma and disease progression on FOLFOX/trastuzumab (PD-L1 CPS 0)**



**Dr Sunnie Kim (Aurora, Colorado)**

# FDA grants accelerated approval to trastuzumab deruxtecan for unresectable or metastatic HER2-positive solid tumors

Press Release: April 5, 2024

On April 5, 2024, the US Food and Drug Administration (FDA) granted accelerated approval to trastuzumab deruxtecan (T-DXd) for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options. Efficacy was evaluated in 192 adult patients with previously treated unresectable or metastatic HER2-positive (IHC 3+) solid tumors who were enrolled in one of three multicenter trials: DESTINY-PanTumor02 (NCT04482309), DESTINY-Lung01 (NCT03505710), and DESTINY-CRC02 (NCT04744831). All three trials excluded patients with a history of interstitial lung disease (ILD)/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening and clinically significant cardiac disease. Patients were also excluded for active brain metastases or ECOG performance status >1. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity.

The recommended T-DXd dosage for this indication is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. This tumor agnostic indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).



# Summary of Trastuzumab deruxtecan

- FDA approved as 2L and beyond therapy for HER2+ gastric/GEJ cancers
- DESTINY-Gastric02
  - Phase II study (n=79) from **Europe** and the **United States** who had progressed on one trastuzumab-containing regimen.
    - Median age: 61
    - HER2 expression of mostly 3+ (86%),
    - Primarily gastroesophageal junction cancer (66%)
  - ORR: 42%
  - Four patients (5%) had complete responses
  - At a median follow-up of 10.2 months (data cutoff: 11/8/2021)
    - Median DOR: 8.1 months
    - Median PFS: 5.6 months
- DESTINY-Gastric04 ongoing (ram/paclitaxel versus T-DXd)

# KEYNOTE-811

## Study Design

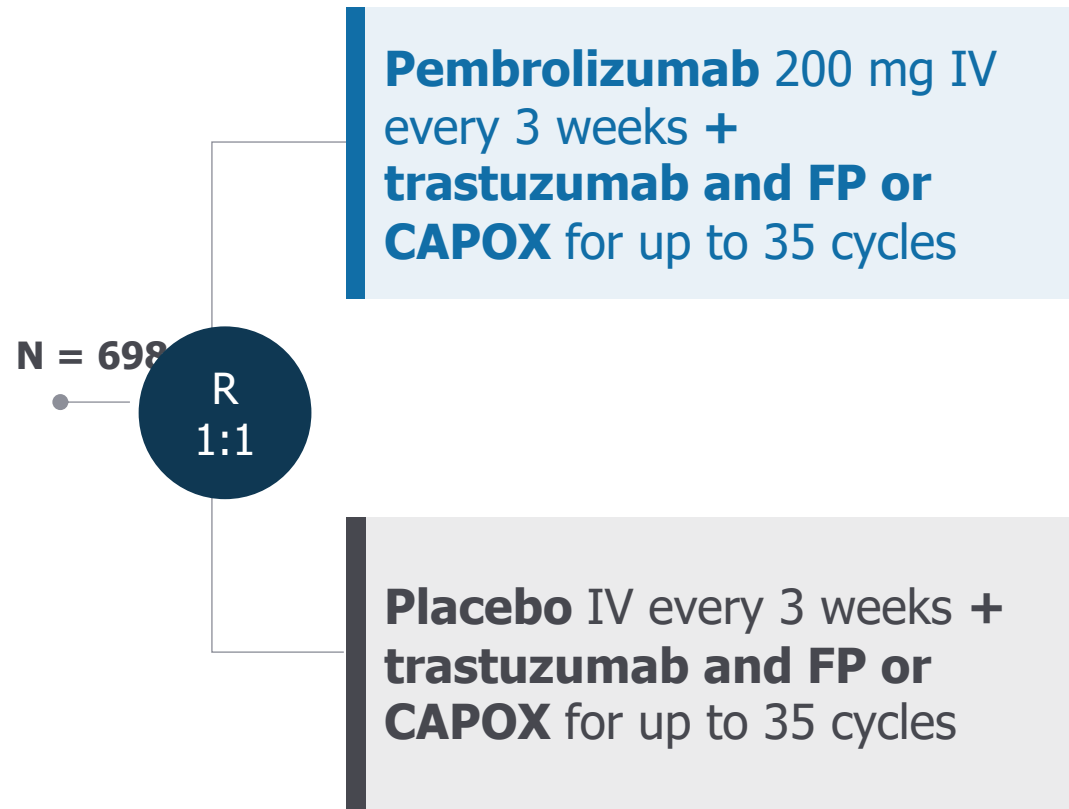
### Phase 3, randomized, double-blind study

#### Key eligibility criteria:

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

#### Stratification:

- Geographic region
- PD-L1 CPS
- Chemotherapy choice



#### Primary endpoints:

- OS
- PFS (RECIST v1.1 per BICR)

#### Secondary endpoints:

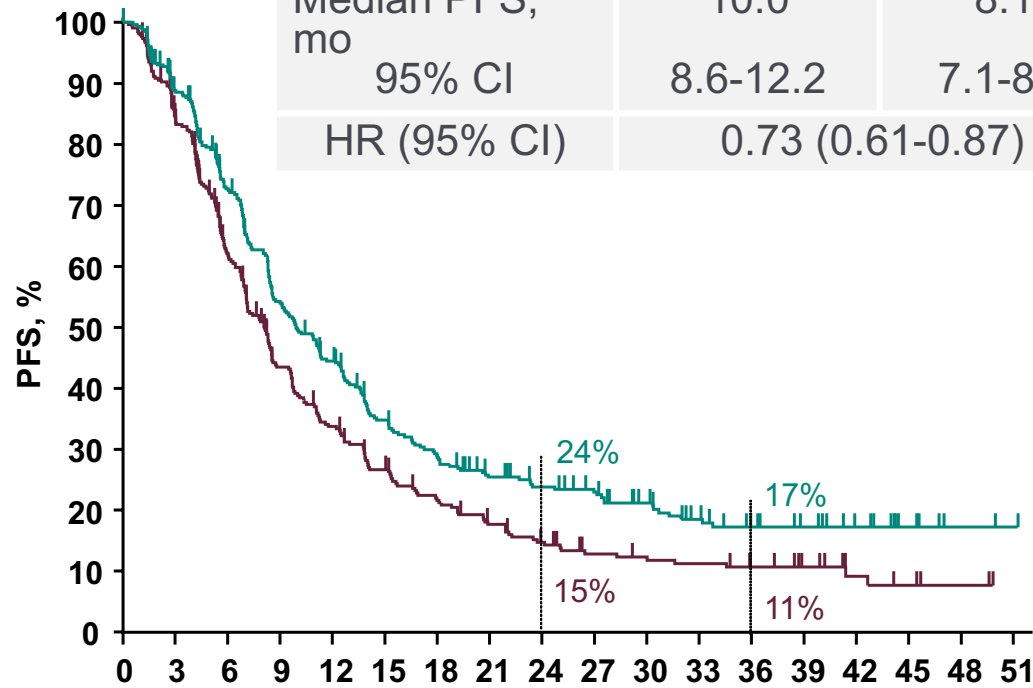
- ORR (RECIST v1.1 per BICR)
- DOR (RECIST v1.1 per BICR)
- Safety

# KEYNOTE-811

## PFS at IA3: 38.5 Months of Follow Up

### All patients

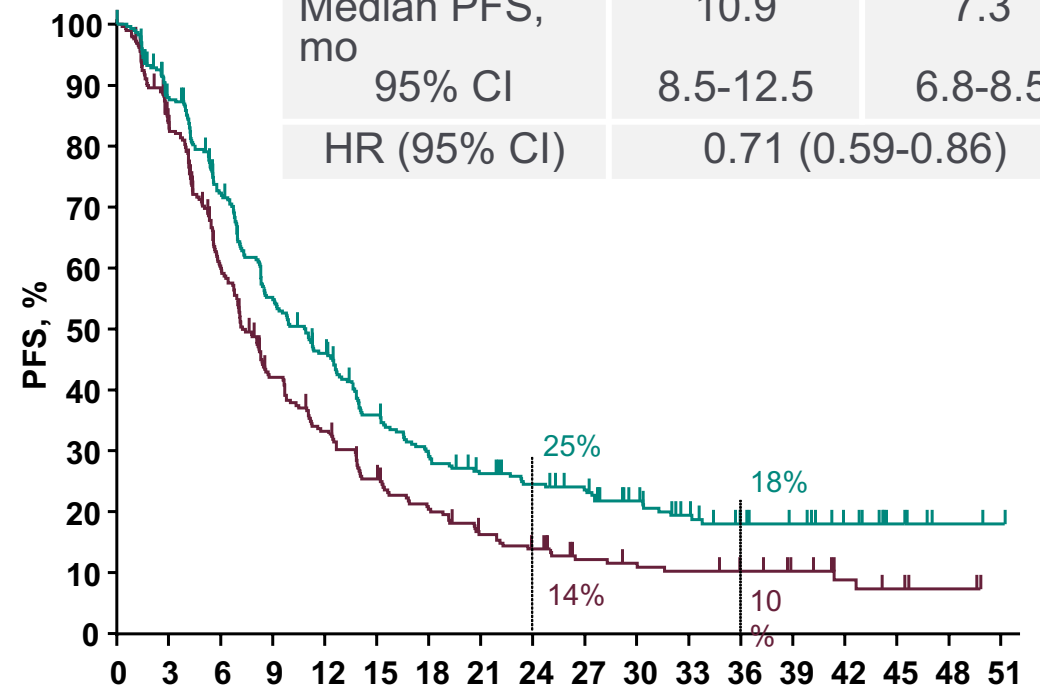
	Pembro	Placebo
Median PFS, mo	10.0	8.1
95% CI	8.6-12.2	7.1-8.6
HR (95% CI)	0.73 (0.61-0.87)	



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Pembrolizumab gp	350	296	234	173	139	102	84	67	59	53	41	31	24	20	14	6	2	1
Placebo gp	348	274	184	121	93	71	55	43	34	25	23	21	17	11	6	4	2	0

### PD-L1 CPS ≥1

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



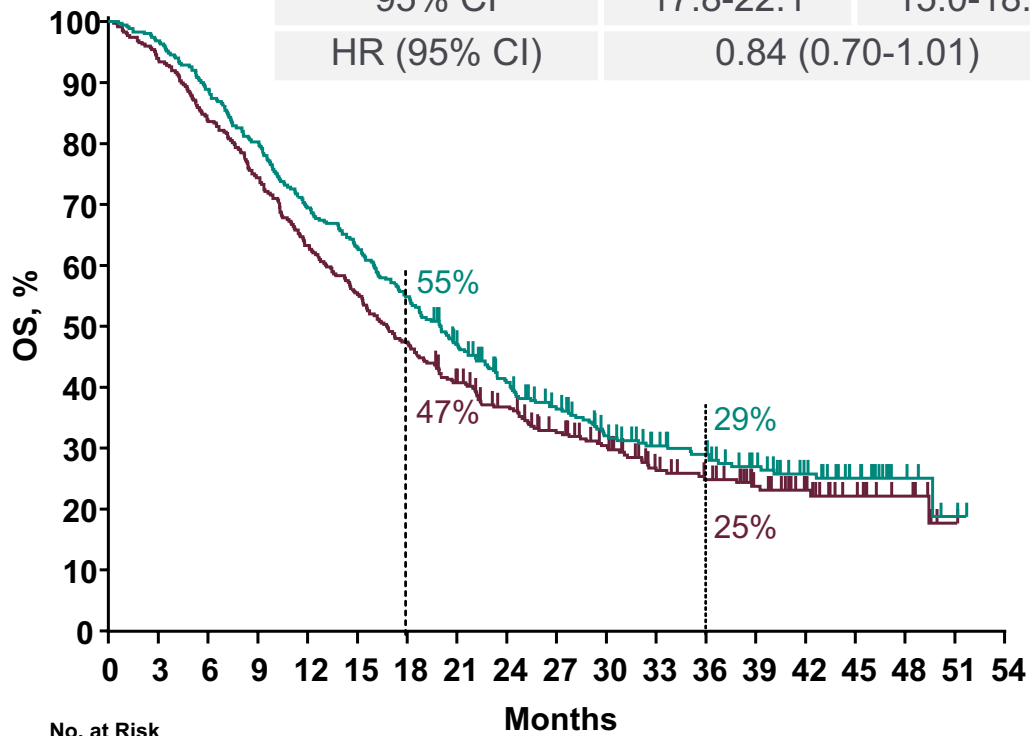
No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Pembrolizumab gp	298	250	200	151	123	91	74	63	56	51	39	30	23	20	14	6	2	1
Placebo gp	296	231	152	100	78	58	45	34	28	20	18	16	14	10	6	4	2	0

# KEYNOTE-811

## OS at IA3

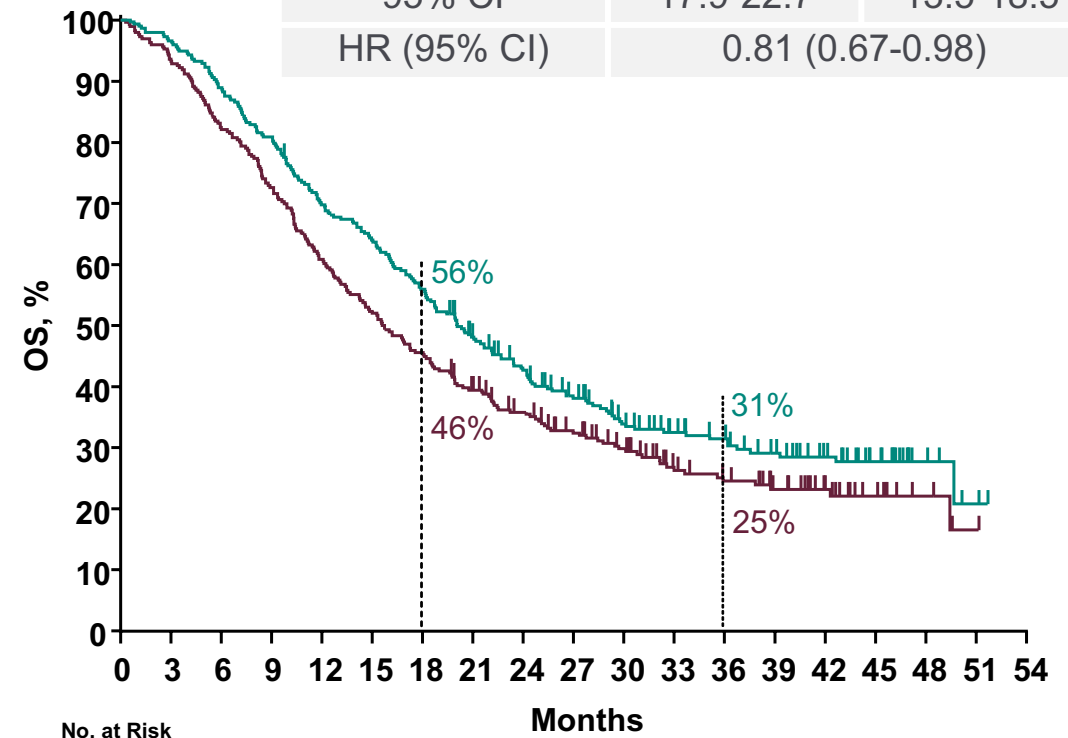
### All patients

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

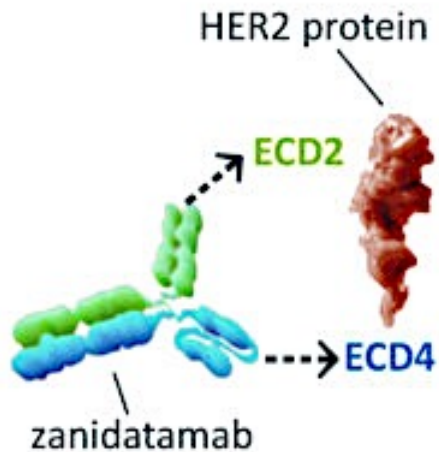


### PD-L1 CPS ≥1

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



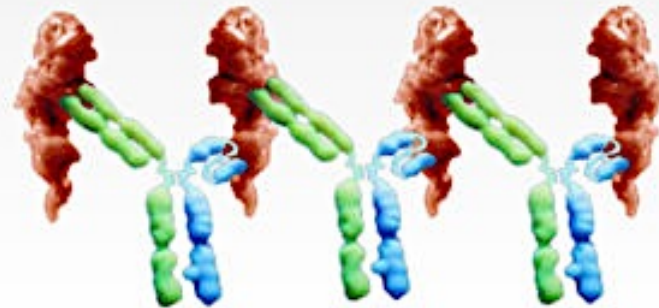
# Zanidatamab: A Biparatopic Bispecific Antibody for HER2-Expressing Cancers



## Zanidatamab's Unique Binding Geometry Promotes:

- Biparatopic – targets two distinct HER2 epitopes and results in HER2 binding across a range of expression levels (low to high)
- HER2-receptor cross-linking, clustering, internalization, and downregulation
  - Enhanced receptor clustering on cell surface (cluster internalization, receptor downregulation)
  - Inhibition of cellular proliferation
- Fc-mediated cytotoxicity: ADCC, ADCP, CDC

## Dual HER2-Binding of Zanidatamab Drives Unique MOA

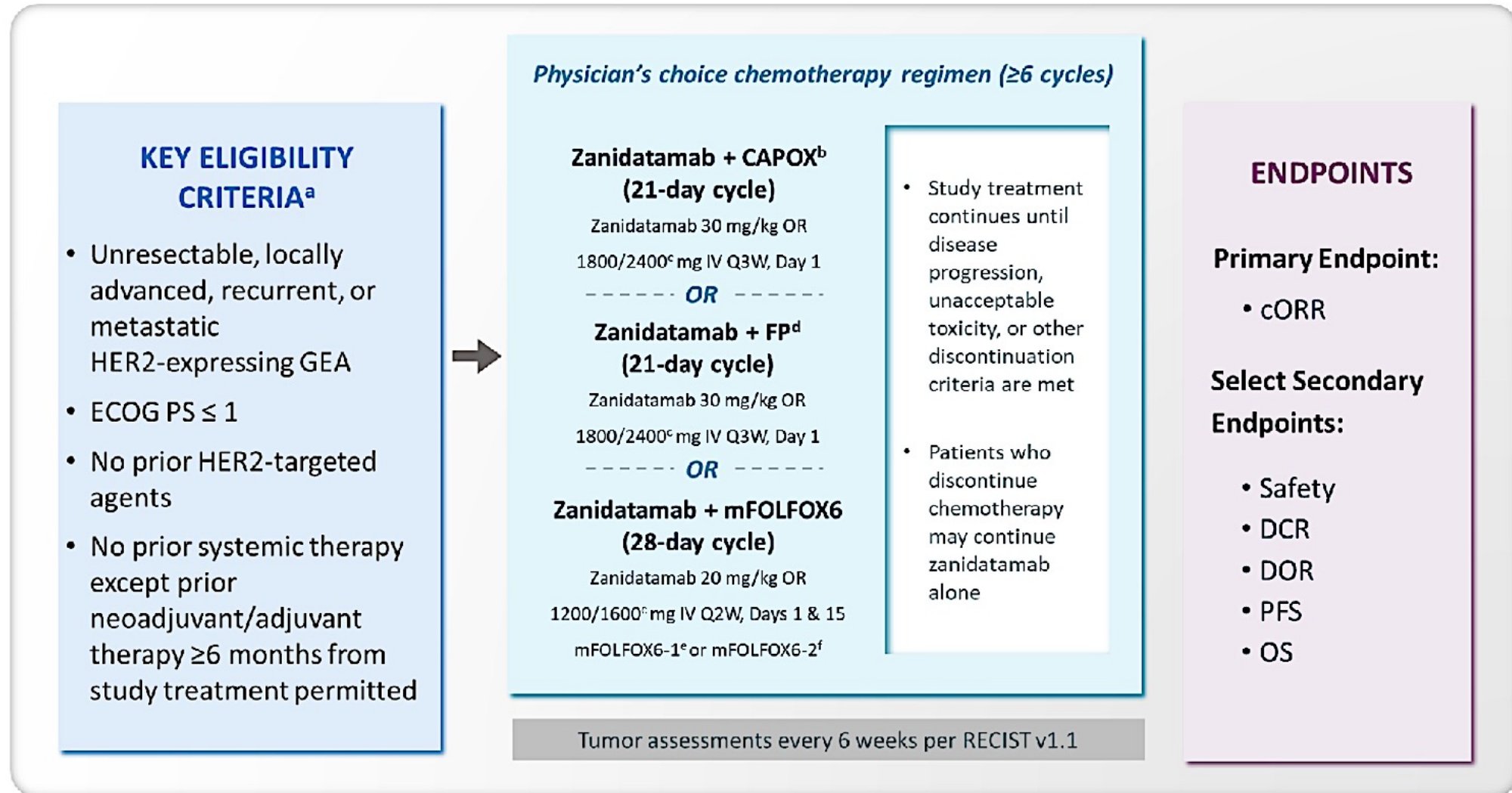


*The geometry of zanidatamab prevents it from binding to the same HER2 molecule*

Note: Zanidatamab has been granted Breakthrough Therapy designation by the FDA for patients with previously-treated HER2 gene-amplified BTC as well as two Fast Track designations, one for previously treated or recurrent HER2-positive BTC and another for first-line GEA in combination with standard of care chemotherapy. Zanidatamab also received Orphan Drug designation for the treatment of BTC and GEA in the United States and for gastric cancer and BTC in the European Union.

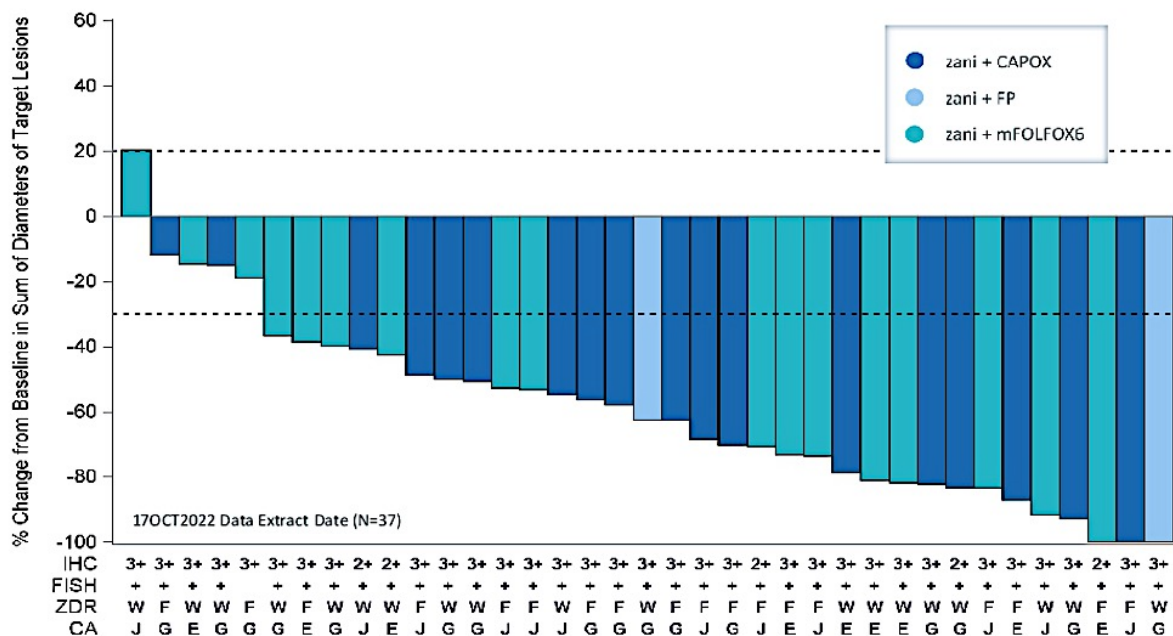
ADCC: antibody-dependent cellular cytotoxicity; ADCP: antibody-dependent cellular phagocytosis; CDC: complement-dependent cytotoxicity; ECD: extracellular domain; Fc: fragment crystallizable region of antibody; HER2: human epidermal growth factor receptor 2

# 1L Study of doublet chemo + zanidatamab



# ORR seen in majority of HER2+ GE cancers

## 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

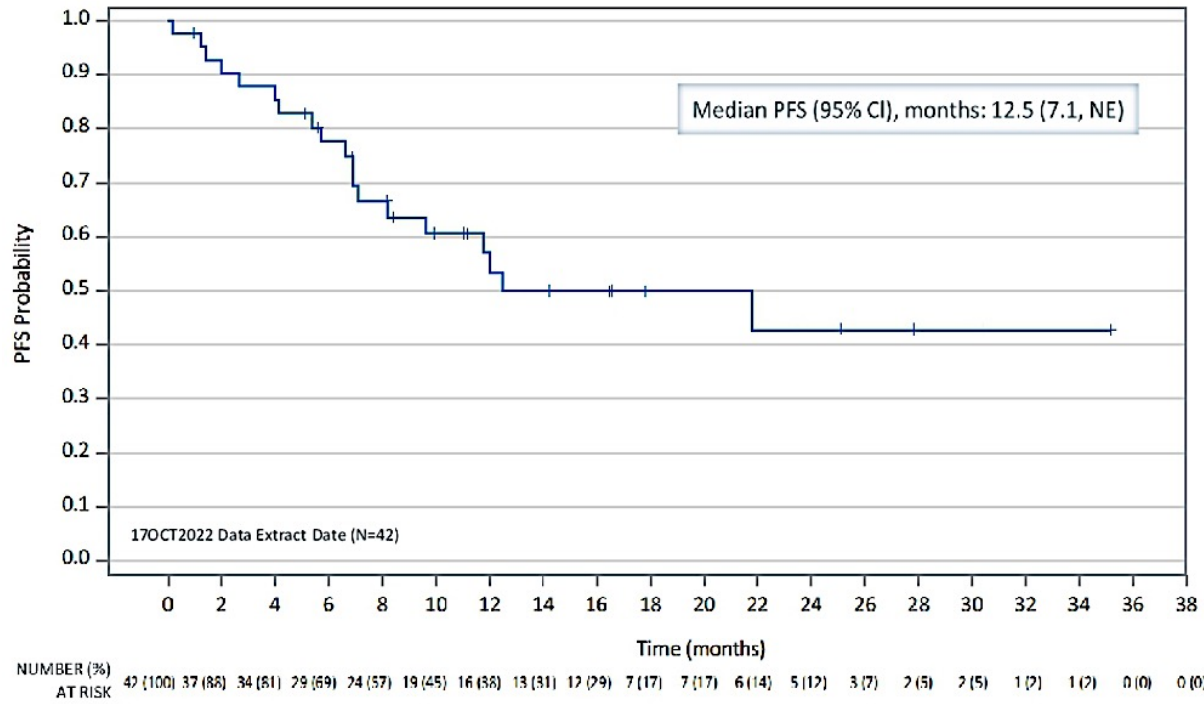
\*1 patient is excluded from the figure because they did not have a postbaseline assessment of target lesions.

## 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 <sup>a</sup> , % (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)

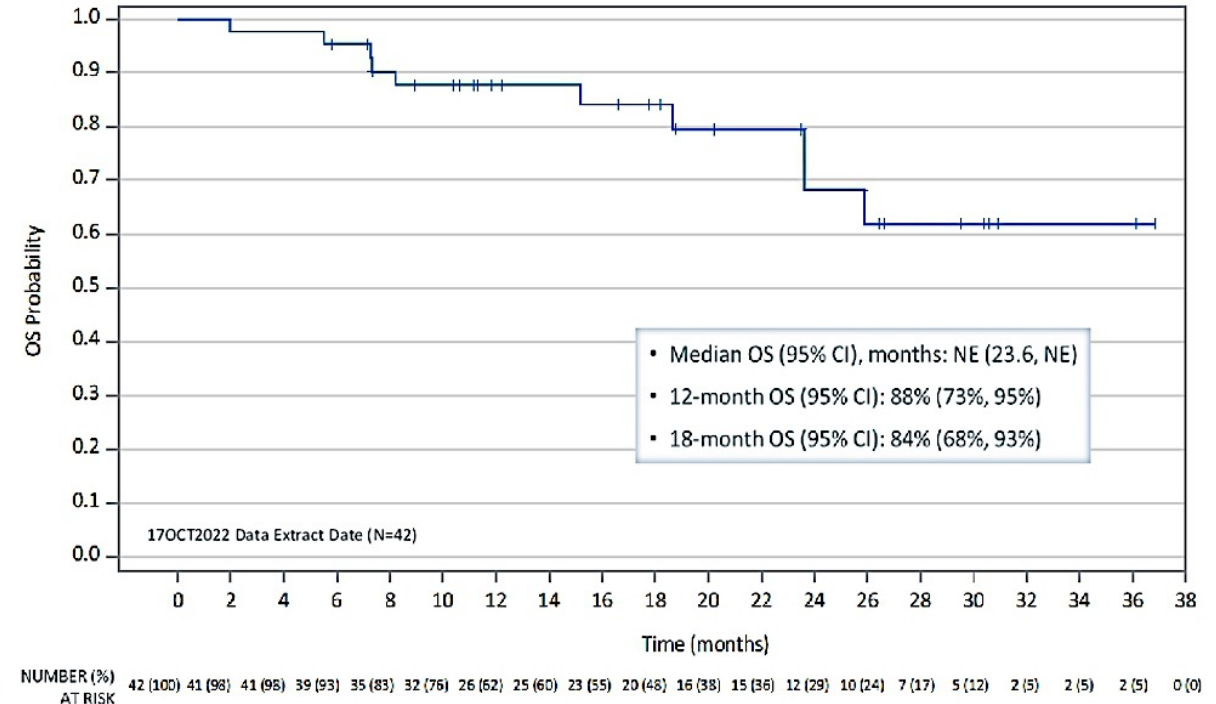
a. Based on a baseline scan and a confirmatory scan obtained  $\geq 4$  weeks following initial documentation of objective response. CI = confidence interval; DOR = duration of response; NE = not estimable.

## Progression-free Survival in Patients with HER2-positive mGEA



CI = confidence interval; NE = not estimable; PFS = progression-free survival

## Overall Survival in Patients with HER2-positive mGEA



CI = confidence interval; NE = not estimable; OS = overall survival

Diarrhea was the most common zanidatamab – and/or chemotherapy related AE

**Ongoing Phase 3 Study: HERIZON-GEA-01: Zanidatamab + chemo ± tislelizumab for 1L treatment of HER2-positive gastroesophageal adenocarcinoma**



# Trials in Progress: HER2-Positive Disease

- Lee KW et al. Zanidatamab (zani), a HER2-targeted bispecific antibody, in combination with chemotherapy (chemo) and tislelizumab (TIS) as first-line (1L) therapy for patients (pts) with advanced HER2-positive gastric/gastroesophageal junction adenocarcinoma (G/GEJC): Preliminary results from a Phase 1b/2 study. ASCO 2022;Abstract 4032.
- Price TJ et al. nextHERIZON: A phase 2 study of HER-Vaxx, a HER2-targeting peptide vaccine, in combination with chemotherapy or pembrolizumab in patients with HER2 metastatic or advanced gastric/gastroesophageal adenocarcinoma that progressed on or after trastuzumab treatment. ASCO GI 2023;Abstract TPS481.
- Gutierrez M et al. A phase I/IIa open label, nonrandomized, multicenter study of CYNK-101 in combination with trastuzumab and pembrolizumab in patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (G/GEJ) adenocarcinoma. ASCO GI 2023;Abstract TPS478.
- Blange D et al. The efficacy of the addition of TRAstuzumab and Pertuzumab to neoadjuvant chemoradiation: A randomized multi-center study in resectable HER2 overexpressing adenocarcinoma of the esophagus or gastroesophageal junction (TRAP-2). ESMO 2022;Abstract 1260TiP.

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# First-Line Treatment of Metastatic Gastric and GEJ Adenocarcinoma: Zolbetuximab for Claudin 18.2-Positive Tumors

- Shitara K et al. **Zolbetuximab + mFOLFOX6** as **first-line** (1L) treatment for patients (pts) with **claudin-18.2+ (CLDN18.2+)** / HER2– locally advanced (LA) unresectable or **metastatic gastric** or **gastroesophageal junction** (mG/GEJ) adenocarcinoma: Primary results from **phase 3 SPOTLIGHT** study. Gastrointestinal Cancers Symposium 2023;Abstract LBA292.
- Shah MA et al. **Zolbetuximab** plus **CAPOX** in **CLDN18.2-positive gastric** or **gastroesophageal junction adenocarcinoma**: The randomized, **phase 3 GLOW** trial. *Nat Med* 2023 August;29(8):2133-41.
- Shah MA et al. Network **meta-analysis** of global trials of **1L therapies** in locally advanced (LA) unresectable or **metastatic gastric** or **gastroesophageal junction** (mG/GEJ) adenocarcinoma. Gastrointestinal Cancers Symposium 2024;Abstract 325.

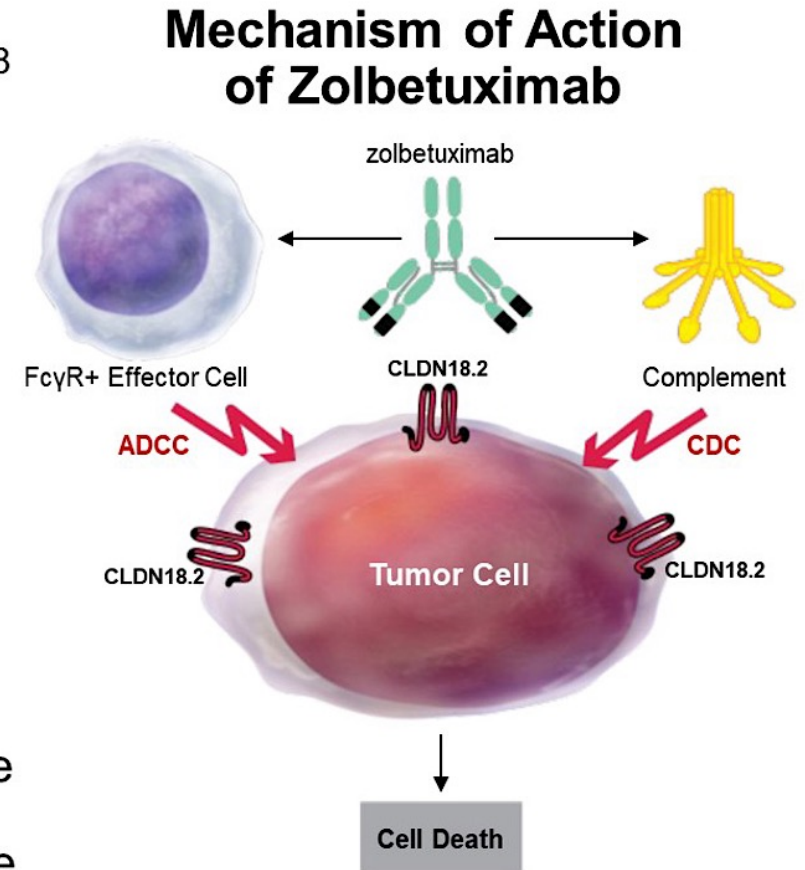
**Case Presentation: 41-year-old man who presents with metastatic GEJ adenocarcinoma (CLDN18.2-positive, PD-L1 CPS 2) in visceral crisis from lung metastases**



**Dr Sunnie Kim (Aurora, Colorado)**

# Claudin 18.2 background and rationale

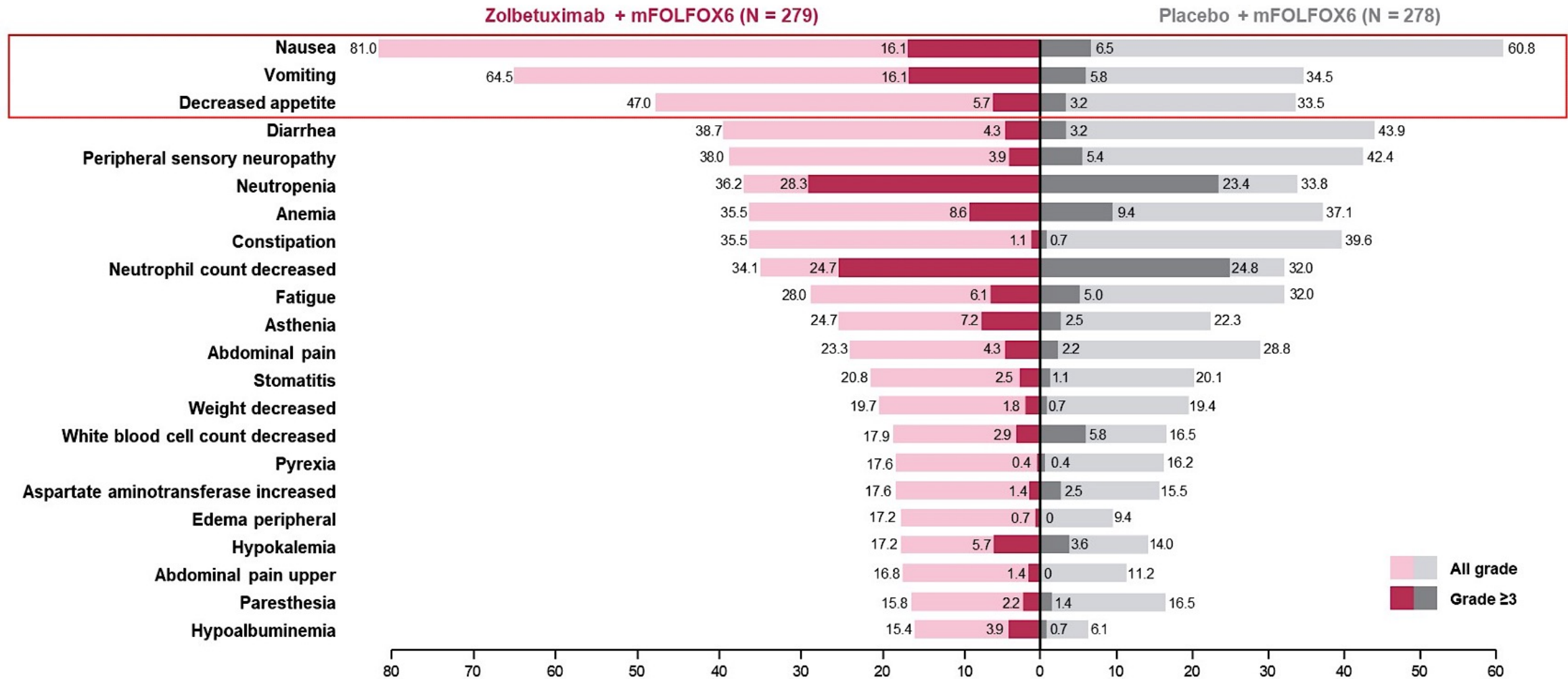
- CLDN18.2 is a tight junction protein normally expressed in gastric mucosa cells and retained in G/GEJ adenocarcinoma<sup>1-8</sup>
- CLDN18.2 may become exposed on the surface of G/GEJ adenocarcinoma cells, making it a promising target<sup>2-8</sup>
- Zolbetuximab is a first-in-class chimeric IgG1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



# SPOTLIGHT and GLOW

	SPOTLIGHT (n=550)	GLOW (n=500)
Control	FOLFOX	CapeOX
Countries	Global	Global (~50% from China)
CPS $\geq$ 5	13%	22%
mPFS	10.6 vs 8.7 <b>+1.9</b> <b>HR 0.75</b>	8.2 vs 6.8 <b>+1.4</b> <b>HR 0.69</b>
mOS	18.2 vs 15.5 <b>+2.7</b> <b>HR 0.75</b>	14.4 vs 12.2 <b>+2.2</b> <b>HR 0.77</b>
ORR	61% vs 62% -1%	54% vs 49% +5%
Nausea Vomiting	81% vs 61% 65% vs 35%	69% vs 50% 66% vs 31%
Discontinuation of zolbe/pbo by AE	14% vs 2%	7% vs 4%

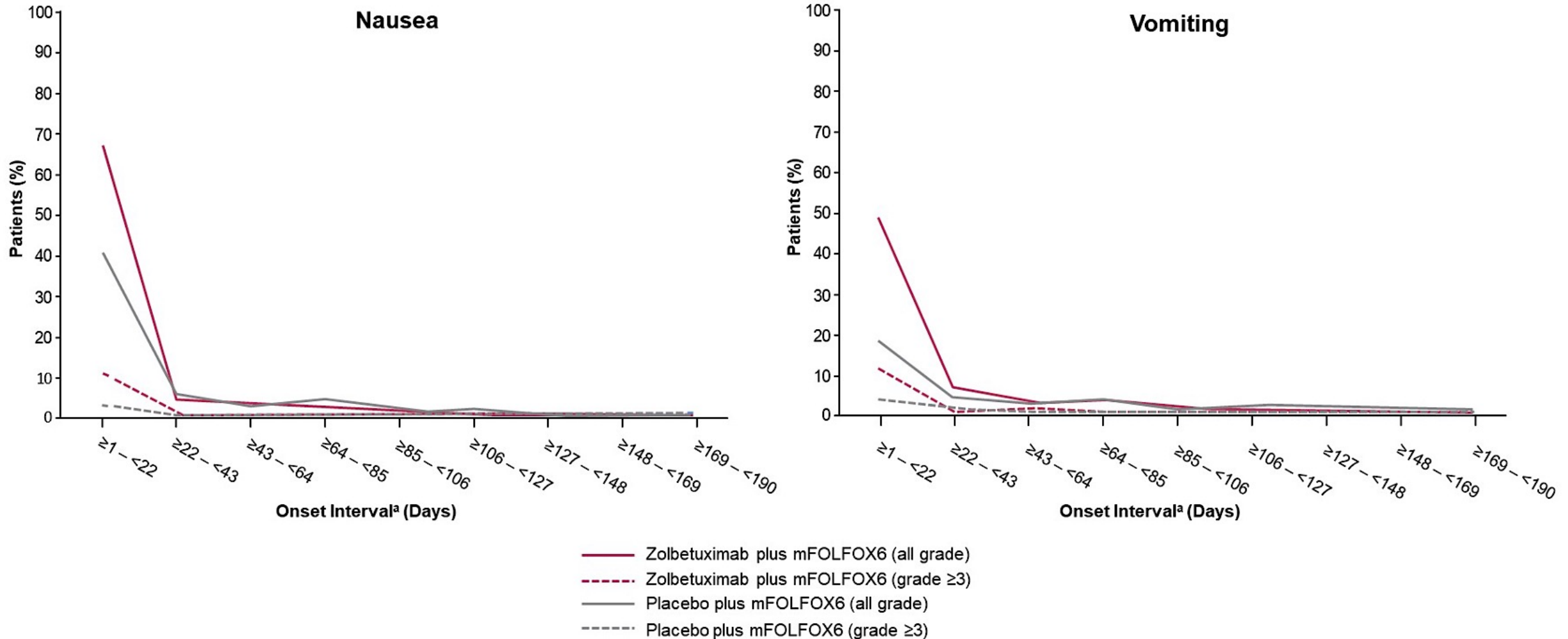
# SPOTLIGHT: Nausea, Vomiting and Anorexia are Key AEs



- The most common TEAEs with zolbetuximab + mFOLFOX6 were nausea and vomiting as on-target effects

<sup>a</sup>Preferred terms were defined according to the Medical Dictionary for Regulatory Activities terminology version 25.0.

# SPOTLIGHT: Nausea/Vomiting Peak with 1<sup>st</sup> Dose





# First-Line Treatment of Metastatic Gastric and GEJ Adenocarcinoma: Immunotherapy with Chemotherapy

- Shen L et al. **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 September 10;40(26):3065-76.
- Xu J et al. **Tislelizumab plus chemotherapy** versus placebo plus chemotherapy as **first-line** treatment for advanced or **metastatic oesophageal squamous cell carcinoma (RATIONALE-306)**: A global, randomised, placebo-controlled, **phase 3** study. *Lancet Oncol* 2023 May;24(5):483-95.
- Kato K et al. **Nivolumab (NIVO) plus chemotherapy (chemo) or ipilimumab (IPI) vs chemo as first-line (1L) treatment for advanced esophageal squamous cell carcinoma (ESCC)**: 29-month (mo) follow-up from **CheckMate 648**. *Gastrointestinal Cancers Symposium 2023*;Abstract 290.
- Moehler MH et al. **RATIONALE 305: Phase 3 study of tislelizumab plus chemotherapy vs placebo plus chemotherapy as first-line treatment (1L) of advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJC)**. *Gastrointestinal Cancers Symposium 2023*;Abstract 286.

# First-Line Treatment of Metastatic Gastric and GEJ Adenocarcinoma: Immunotherapy with Chemotherapy (Continued)

- Shitara K et al. **Nivolumab (NIVO) + chemotherapy (chemo)** vs chemo as **first-line (1L) treatment** for advanced **gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma** (GC/GEJC/EAC): **4-year (yr) follow-up of CheckMate 649**. Gastrointestinal Cancers Symposium 2024;Abstract 306.
- Rha SY et al. **Pembrolizumab plus chemotherapy** versus placebo plus chemotherapy for HER2-negative **advanced gastric cancer (KEYNOTE-859)**: A multicentre, randomised, double-blind, **phase 3** trial. *Lancet Oncol* 2023;24(11):1181-95.

# Case Presentation: 66-year-old man with metastatic GEJ adenocarcinoma (PD-L1 CPS 20)



**Dr Sunnie Kim (Aurora, Colorado)**

# Tislelizumab: Mechanism of Action



# FDA Approves Tislelizumab for Advanced or Metastatic ESCC After Chemotherapy

Press Release: March 14, 2024

“The FDA has approved tislelizumab as monotherapy for the treatment of adult patients with unresectable or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor.

The approval is based on the RATIONALE 302 trial, which met its primary endpoint in the intention-to-treat (ITT) population with a statistically significant and clinically meaningful survival benefit for tislelizumab compared with chemotherapy. In the ITT population, the median overall survival (OS) in the tislelizumab arm was 8.6 months (95% CI: 7.5, 10.4) compared to 6.3 months (95% CI: 5.3, 7.0) in the chemotherapy arm (p=0.0001; hazard ratio [HR]=0.70 [95% CI: 0.57, 0.85]). The safety profile of tislelizumab was favorable over chemotherapy.”

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



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

# RATIONALE-306

- Key eligibility criteria**
- Unresectable locally advanced or metastatic ESCC
  - No prior systemic treatment for advanced disease
  - ECOG PS 0 or 1
  - Measurable or evaluable disease per RECIST v1.1

R  
1:1  
DB  
N=649

**Tislelizumab 200 mg IV Q3W + investigator-chosen chemotherapy**

Treatment until disease progression, intolerable toxicity, or withdrawal for other reasons

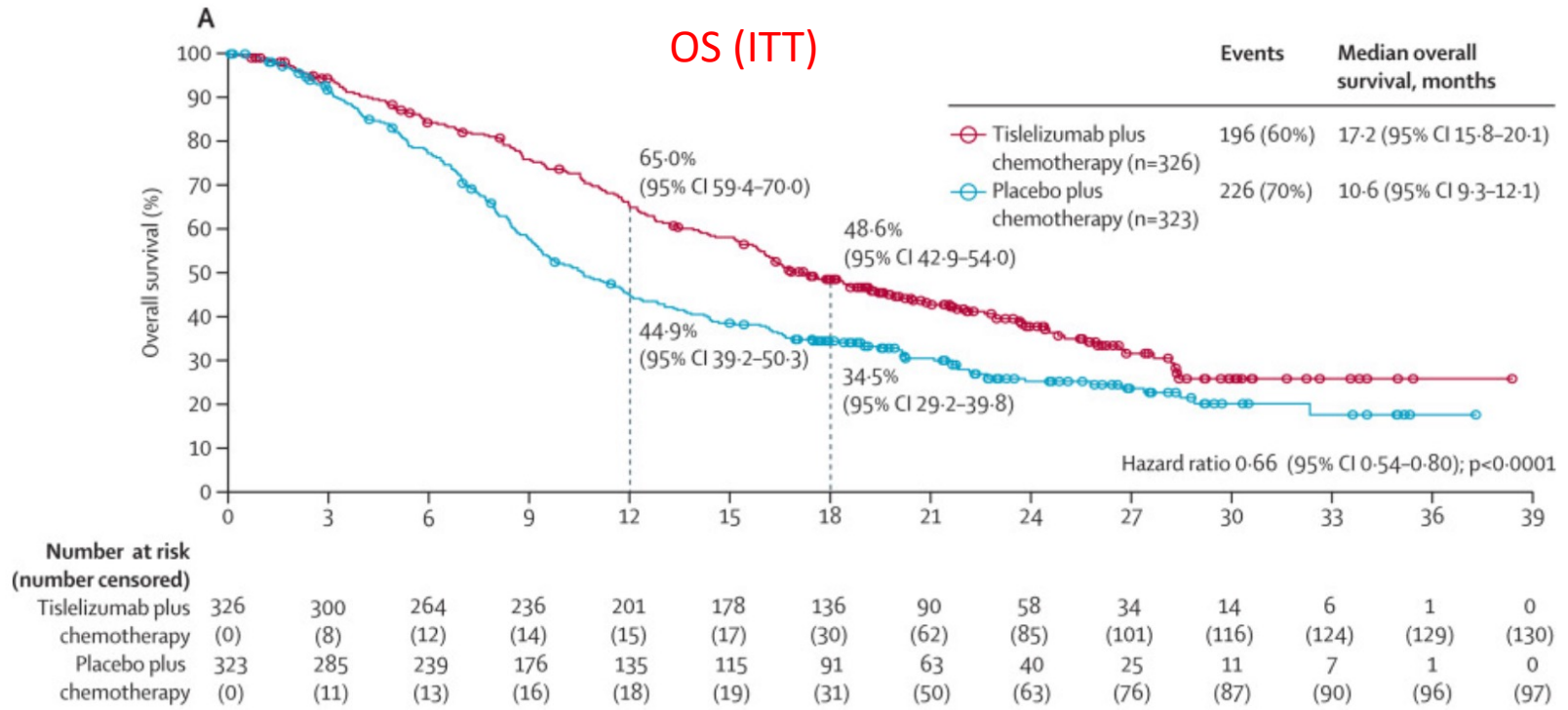
**Matching placebo IV Q3W + investigator-chosen chemotherapy**

**Investigator-chosen chemotherapy:**

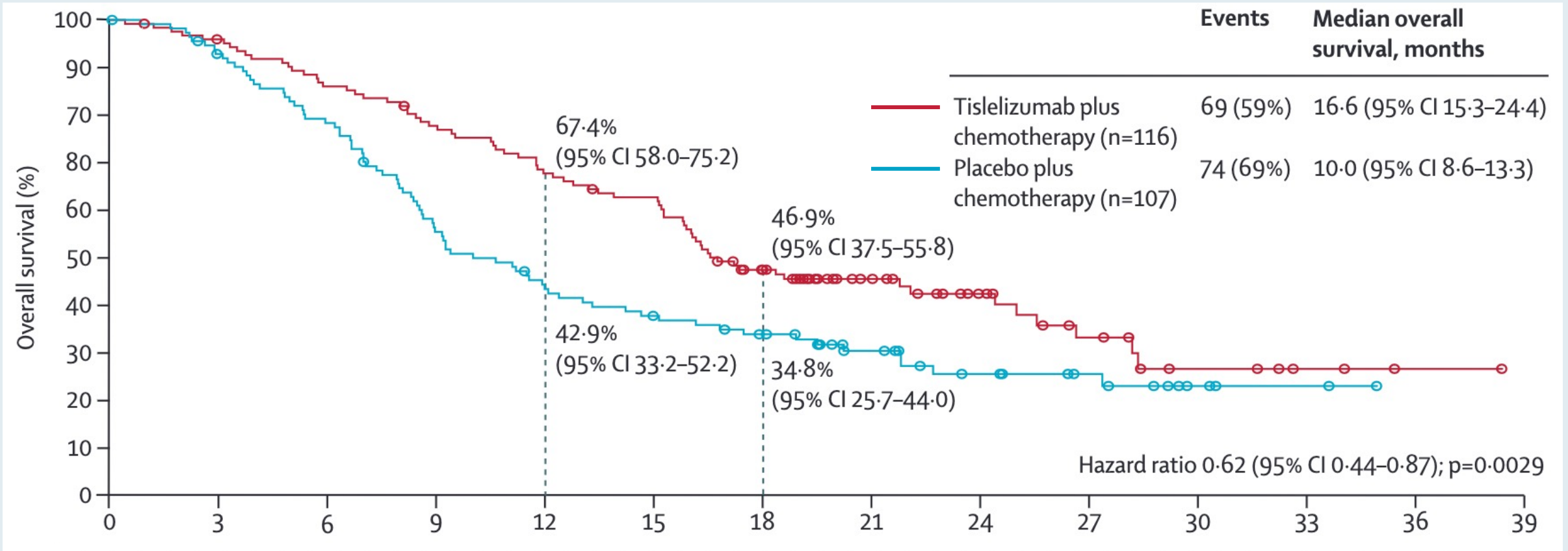
- **Option A: Platinum + fluoropyrimidine**  
Cisplatin or oxaliplatin\* + fluoropyrimidine†
- **Option B: Platinum + paclitaxel**  
Cisplatin or oxaliplatin\* + paclitaxel‡

- Stratification factors**
- Geographic region (Asia [excluding Japan] vs Japan vs Rest of World)
  - Prior definitive therapy (yes vs no)
  - Investigator-chosen chemotherapy (platinum/fluoropyrimidine vs platinum/paclitaxel)

- Endpoints**
- **Primary endpoint:** OS in all randomized patients (ITT population)
  - **Secondary endpoints:** PFS, ORR and DoR by investigator, OS in the PD-L1 score ≥ 10% subgroup<sup>§</sup>, HRQoL, and safety



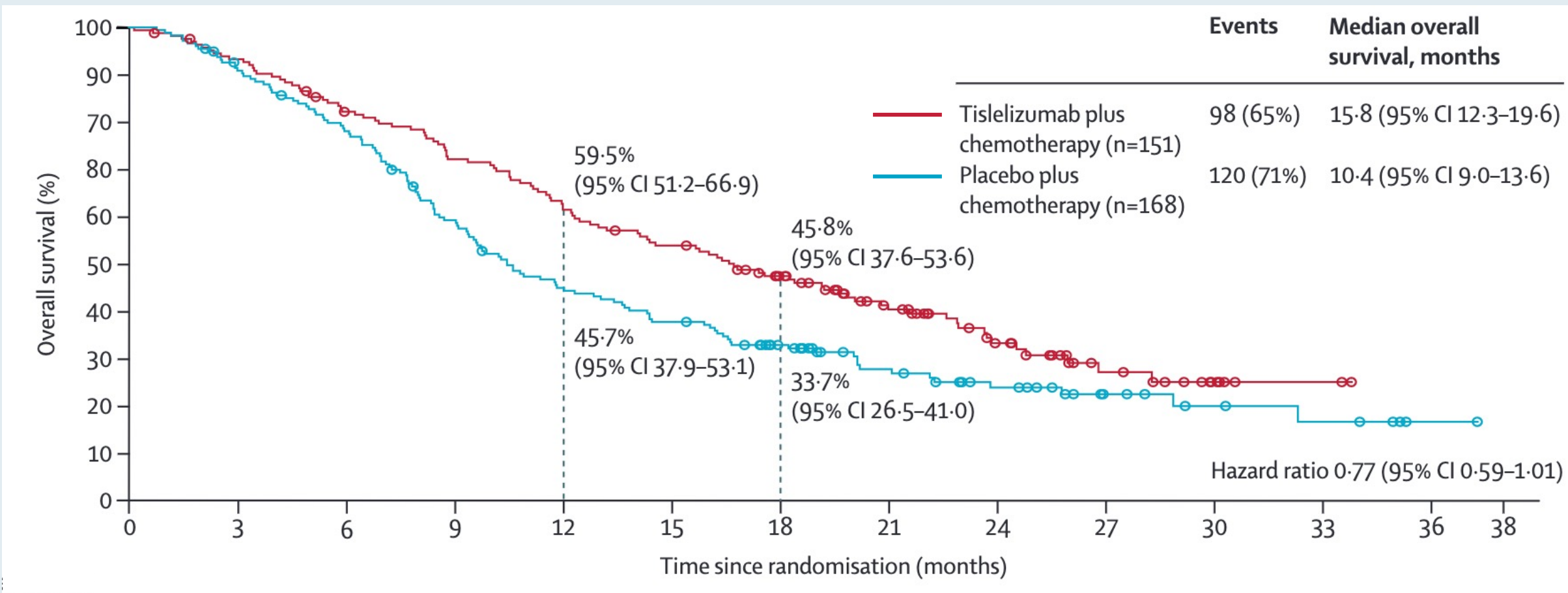
# RATIONALE-306: Overall Survival for Patients with PD-L1 TAP $\geq 10\%$



TAP = tumor area positivity score



# RATIONALE-306: Overall Survival for Patients with PD-L1 TAP <10%



# RATIONALE-306: Safety

	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
Vomiting	53 (16%)	4 (1%)	0	0	67 (21%)	6 (2%)	1 (<1%)	0
Decreased platelet count	51 (16%)	8 (2%)	1 (<1%)	0	51 (16%)	3 (1%)	0	0
Stomatitis	45 (14%)	10 (3%)	3 (1%)	0	40 (12%)	7 (2%)	0	0
Decreased weight	45 (14%)	1 (<1%)	0	0	45 (14%)	0	0	0
Increased blood creatinine	42 (13%)	1 (<1%)	0	0	27 (8%)	1 (<1%)	0	0
Constipation	42 (13%)	0	0	0	40 (12%)	1 (<1%)	0	0
Increased aspartate aminotransferase	37 (11%)	4 (1%)	1 (<1%)	0	27 (8%)	1 (<1%)	1 (<1%)	0
Increased alanine aminotransferase	36 (11%)	5 (2%)	0	0	28 (9%)	4 (1%)	1 (<1%)	0
Hypoalbuminaemia	36 (11%)	0	0	0	25 (8%)	0	0	0
Fatigue	35 (11%)	13 (4%)	0	0	45 (14%)	8 (2%)	0	0
Malaise	35 (11%)	5 (2%)	1 (<1%)	0	47 (15%)	3 (1%)	0	0
Pruritus	34 (10%)	0	0	0	19 (6%)	0	0	0
Asthenia	33 (10%)	4 (1%)	0	0	38 (12%)	1 (<1%)	0	0
Hypoaesthesia	33 (10%)	1 (<1%)	0	0	39 (12%)	1 (<1%)	0	0
Hypothyroidism	31 (10%)	0	0	0	14 (4%)	0	0	0
Neutropaenia	29 (9%)	16 (5%)	7 (2%)	0	15 (5%)	19 (6%)	12 (4%)	0
Hypokalaemia	22 (7%)	17 (5%)	1 (<1%)	0	15 (5%)	7 (2%)	2 (1%)	0
Hyponatraemia	19 (6%)	17 (5%)	5 (2%)	0	23 (7%)	9 (3%)	1 (<1%)	0

# CheckMate 648

## Key eligibility criteria

- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

## Stratification factors

- Tumor cell PD-L1 expression ( $\geq 1\%$  vs  $< 1\%$ <sup>b</sup>)
- Region (East Asia<sup>c</sup> vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases ( $\leq 1$  vs  $\geq 2$ )

R  
1:1:1

n = 321

NIVO 240 mg Q2W +  
chemo (fluorouracil + cisplatin)<sup>d</sup> Q4W<sup>e</sup>

n = 325

NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W<sup>e</sup>

n = 324

Chemo (fluorouracil + cisplatin)<sup>d</sup> Q4W<sup>e</sup>

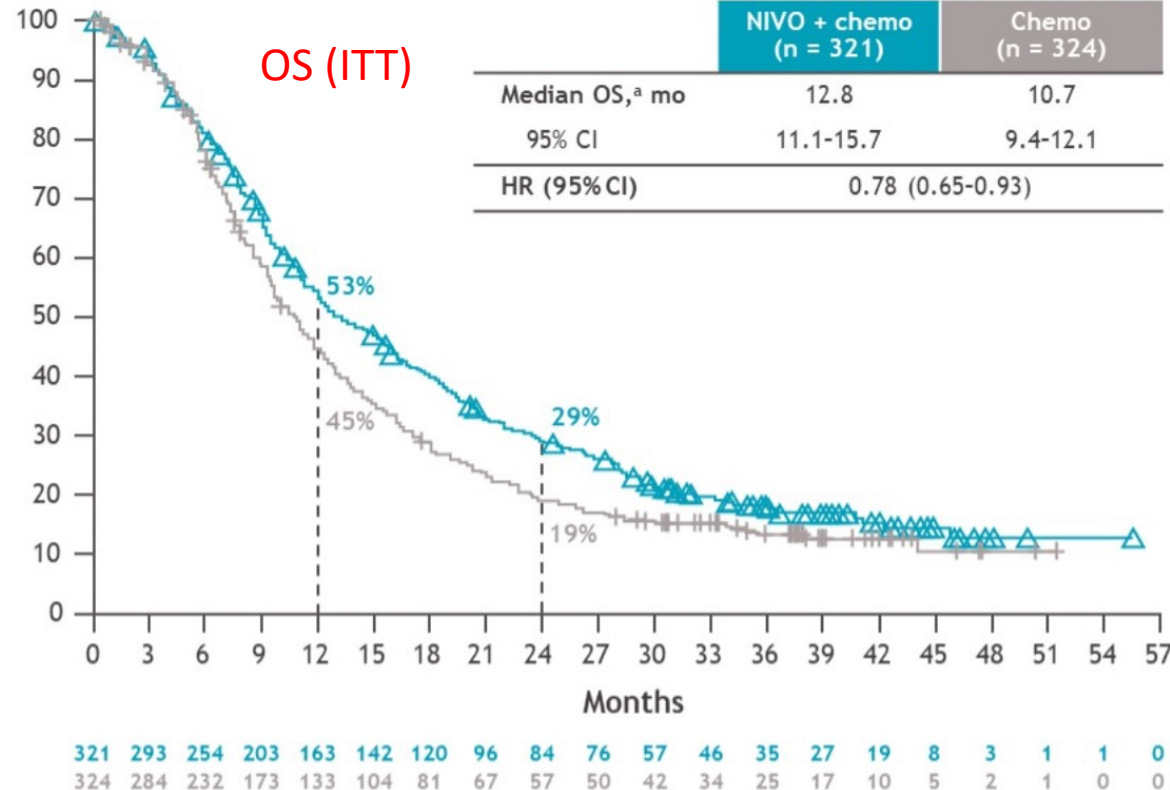
N = 970

## Primary endpoints:

- OS and PFS<sup>f</sup> (tumor cell PD-L1  $\geq 1\%$ )

## Secondary endpoints:

- OS and PFS<sup>f</sup> (all randomized)
- ORR<sup>f</sup> (tumor cell PD-L1  $\geq 1\%$  and all randomized)



# KEYNOTE-859

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

R  
1:1

Pembrolizumab 200 mg IV Q3W for ≤35 cycles (~2 yr)  
+  
Chemotherapy<sup>a</sup> (FP or CAPOX)

Placebo IV Q3W for ≤35 cycles (~2 yr)  
+  
Chemotherapy<sup>a</sup> (FP or CAPOX)

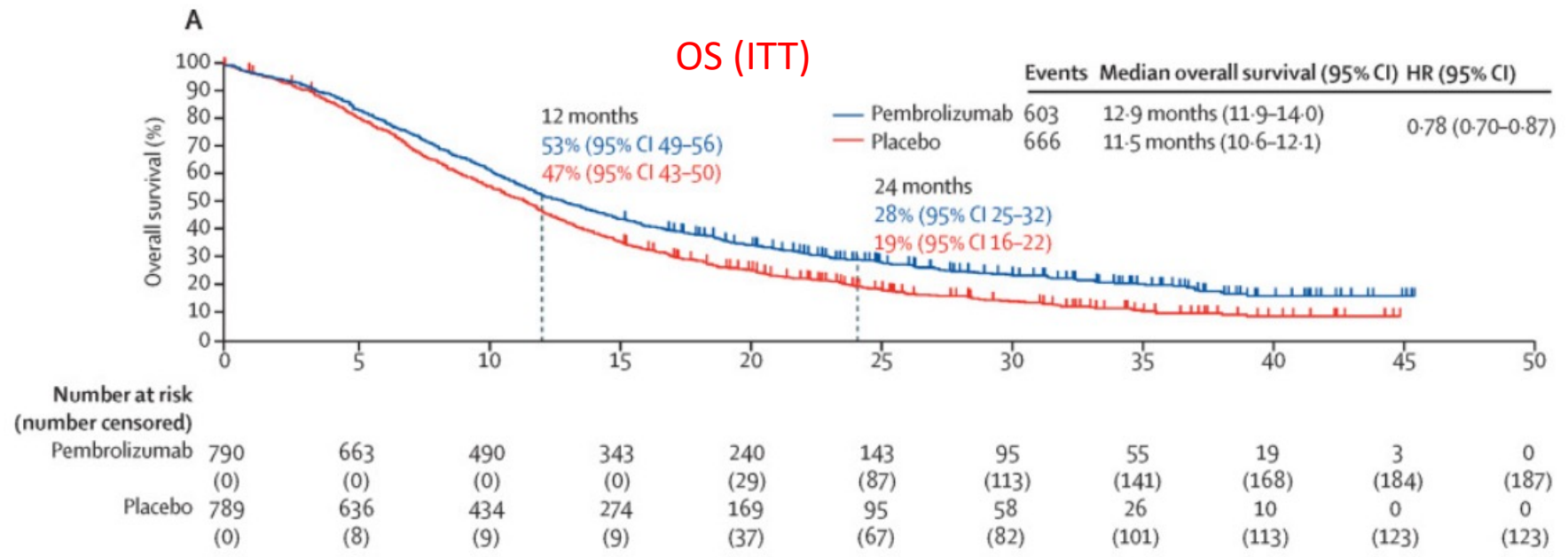
**Stratification Factors**

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

**Primary End Point:** OS

- Secondary End Points:** PFS,<sup>b</sup> ORR,<sup>b</sup> DOR,<sup>b</sup> and safety

- Alpha-controlled analyses:** OS, PFS, and ORR in the overall, PD-L1 CPS ≥1, and PD-L1 CPS ≥10 populations



# Trials in Progress: Metastatic Disease

- Klempner S et al. A phase 2 study (DisTinGuish) of DKN-01 in combination with tislelizumab + chemotherapy as first-line (1L) therapy in patients with advanced gastric or GEJ adenocarcinoma (GEA). ASCO 2023;Abstract 4027.
- Shitara K et al. Phase 2 trial of zolbetuximab in combination with mFOLFOX6 and nivolumab in patients with advanced or metastatic claudin 18.2-positive, HER2-negative gastric or gastroesophageal junction adenocarcinomas. ASCO 2023;Abstract TPS4173.
- Klempner S et al. STAR-221: A randomized, open-label, multicenter, phase 3 trial of domvanalimab, zimberelimab, and chemotherapy versus nivolumab and chemotherapy in previously untreated, locally advanced, unresectable or metastatic gastric, gastroesophageal junction, and esophageal adenocarcinoma. ASCO GI 2023;Abstract TPS481.
- Wang F et al. AdvanTIG-203: A phase 2 randomized, multicenter study of ociperlimab (OCI) + tislelizumab (TIS) in patients (pts) with unresectable, locally advanced, recurrent/metastatic esophageal squamous cell carcinoma (ESCC) and programmed cell death ligand 1 (PD-L1) positivity. ESMO 2023;Abstract 1020MO.
- Day F et al. Chemoradiotherapy with concurrent durvalumab for the palliative treatment of oligometastatic esophageal and gastroesophageal carcinoma with dysphagia: A single arm phase 2 clinical trial, PALEO. ASCO 2023;Abstract TPS4172.

# Trials in Progress: Metastatic Disease (Continued)

- Moschetta M et al. A phase I/Ib study of the Werner (WRN) helicase inhibitor HRO761 as single agent and in combination with irinotecan or tislelizumab in patients with microsatellite instability-high (MSIhi) or mismatch repair deficient (dMMR) advanced solid tumors. ESMO 2023;Abstract 719TiP.
- Obermannova R et al. CLAUDIO-01: A multicentric phase I/II trial to evaluate the safety and efficacy of SOT102 as monotherapy and in combination with standard of care (SoC) in patients with gastric, gastroesophageal junction (GEJ), and pancreatic adenocarcinoma. ESMO 2023;Abstract 722TiP.
- Guo W et al. TST001 (a high affinity humanized anti-claudin18.2 monoclonal antibody) in combination with nivolumab plus capecitabine and oxaliplatin as first-line or with nivolumab as late-line treatment in locally advanced and metastatic gastric/gastroesophageal junction (G/GEJ) cancer: Design of cohorts from a phase I/IIa study (TST001-1002). ASCO GI 2023;Abstract TPS476.
- Wang M et al. Penpulimab plus chemotherapy with or without anlotinib as first-line treatment for patients with advanced esophageal squamous cell carcinoma (ANSWER): A randomized, two-arm, clinical trial in progress. ASCO GI 2023;Abstract TPS482.

# Trials in Progress: Metastatic Disease

- Wainberg ZA et al. Trial in progress: Phase 1b/3 study of bemarituzumab + mFOLFOX6 + nivolumab versus mFOLFOX6 + nivolumab in previously untreated advanced gastric and gastroesophageal junction (GEJ) cancer with FGFR2b overexpression (FORTITUDE-102). ASCO 2022;Abstract TPS4165.
- Kelly RK et al. Phase 2 open-label study of pembrolizumab plus lenvatinib and belzutifan in patients with advanced solid tumors. ASCO 2022;Abstract TPS4173.
- Wang F et al. AdvanTIG-203: Phase 2 Randomized, Multicenter Study of Ociperlimab (OCI) + Tislelizumab (TIS) in Patients (pts) With Unresectable, Locally Advanced, Recurrent/Metastatic Esophageal Squamous Cell Carcinoma (ESCC) and Programmed Cell Death-Ligand 1 (PD-L1) Positivity. ESMO 2023;Abstract 1020MO.

# Year in Review: Acute Myeloid Leukemia

*A Multitumor CME/MOC-Accredited Live Webinar*

**Wednesday, April 17, 2024**

**5:00 PM – 6:00 PM ET**

## **Faculty**

**Naval Daver, MD**

**Courtney D DiNardo, MD, MSCE**

## **Moderator**

**Neil Love, MD**



*Thank you for joining us!*

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