Integrating New Advances into the Care of Patients with Cancer

A Multitumor Symposium in Partnership with the American Oncology Network

CME/MOC, NCPD and ACPE Accredited

Saturday, November 8, 2025
10:00 AM – 3:00 PM CT

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1 — Lung Cancer: *Drs Gainor, Langer and Shields*

Module 2 — Chronic Lymphocytic Leukemia: *Dr Rogers*

Module 3 — Ovarian Cancer: *Dr Konecny*

Module 4 — Gastroesophageal Cancers: *Dr Shah*

Gastroesophageal Cancers Faculty

Manish A Shah, MD
Professor of Medicine
Bartlett Family Professor of Gastrointestinal Oncology
Chief, Solid Tumor Oncology
Weill Cornell Medicine/NewYork-Presbyterian Hospital
New York, New York

MODERATOR
Stephen "Fred" Divers, MD
Chief Medical Officer
American Oncology Network
Hot Springs, Arkansas

RTP
RESEARCH
TO PRACTICE

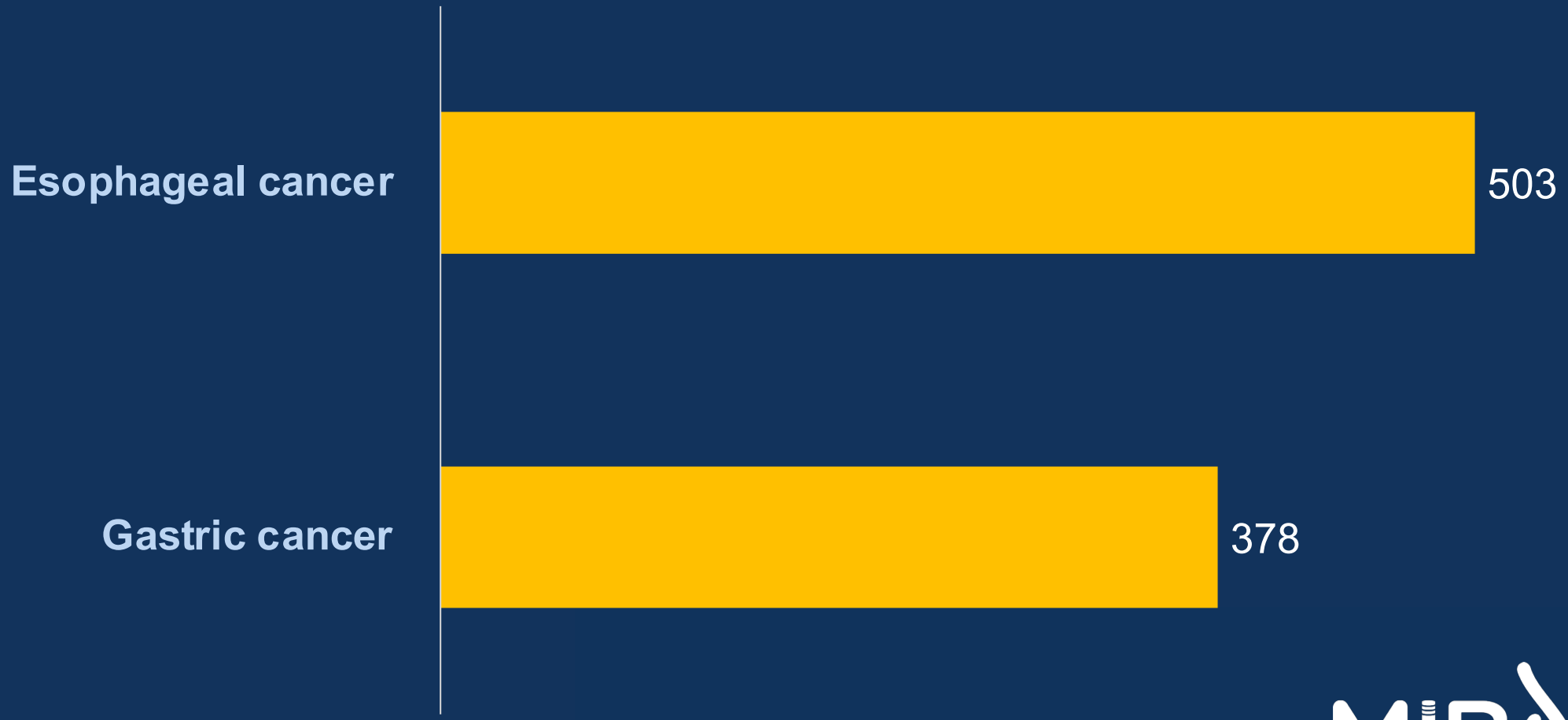
Dr Shah — Disclosures

No relevant conflicts of interest to disclose.

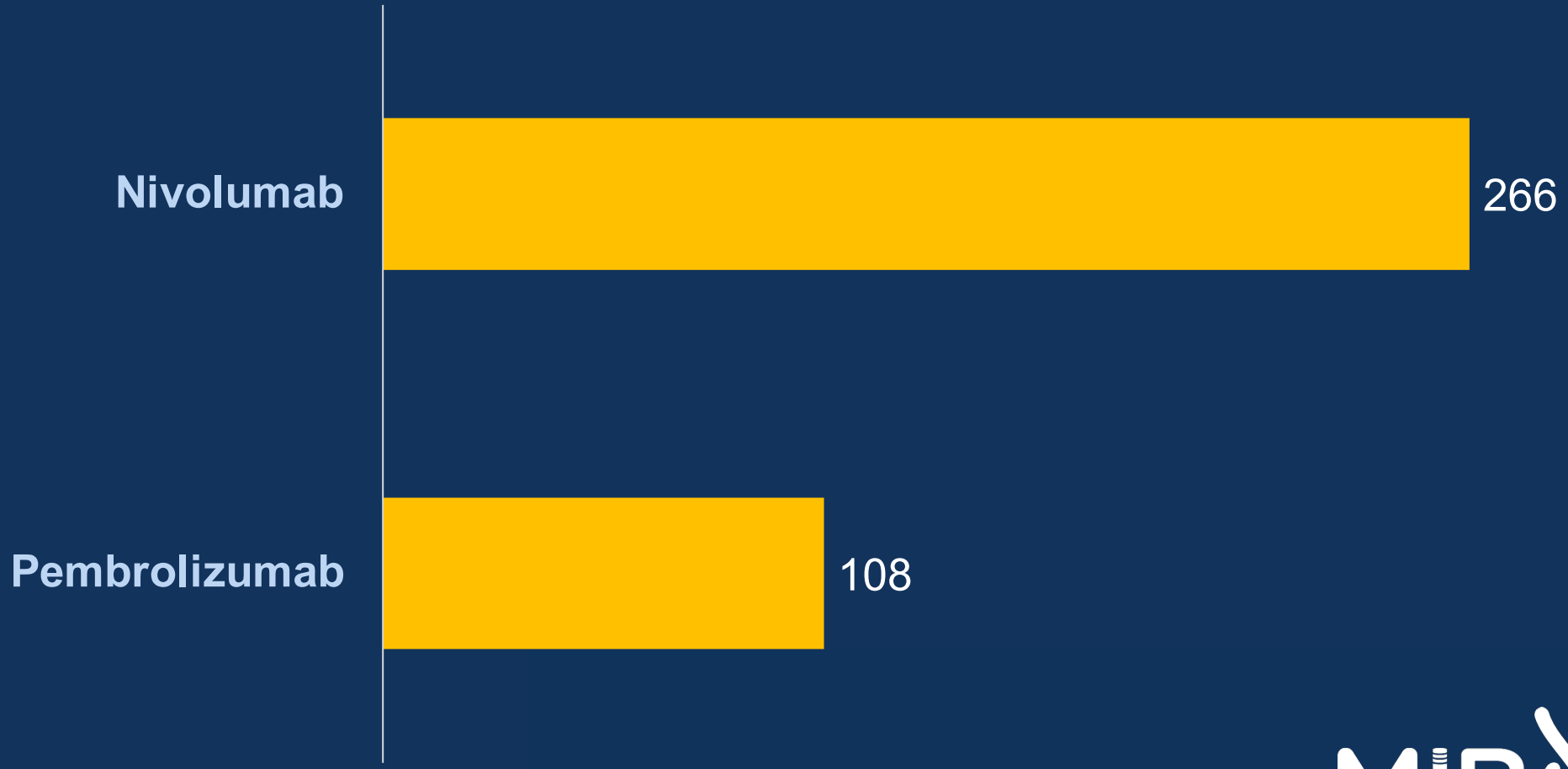
Dr Divers — Disclosures

Advisory Committees	Daiichi Sankyo Inc

Snapshot of AON Practice
Gastroesophageal Cancers



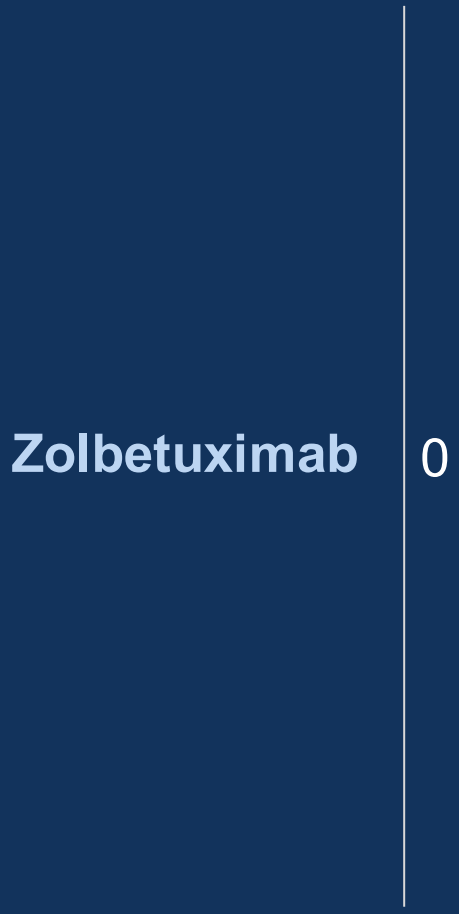
Snapshot of AON Practice
Gastroesophageal Cancers — Immunotherapy



Snapshot of AON Practice
Gastroesophageal Cancers — Chemotherapy

Snapshot of AON Practice
Gastroesophageal Cancers — HER2-Positive

Snapshot of AON Practice
Gastroesophageal Cancers – CLDN18.2-Positive

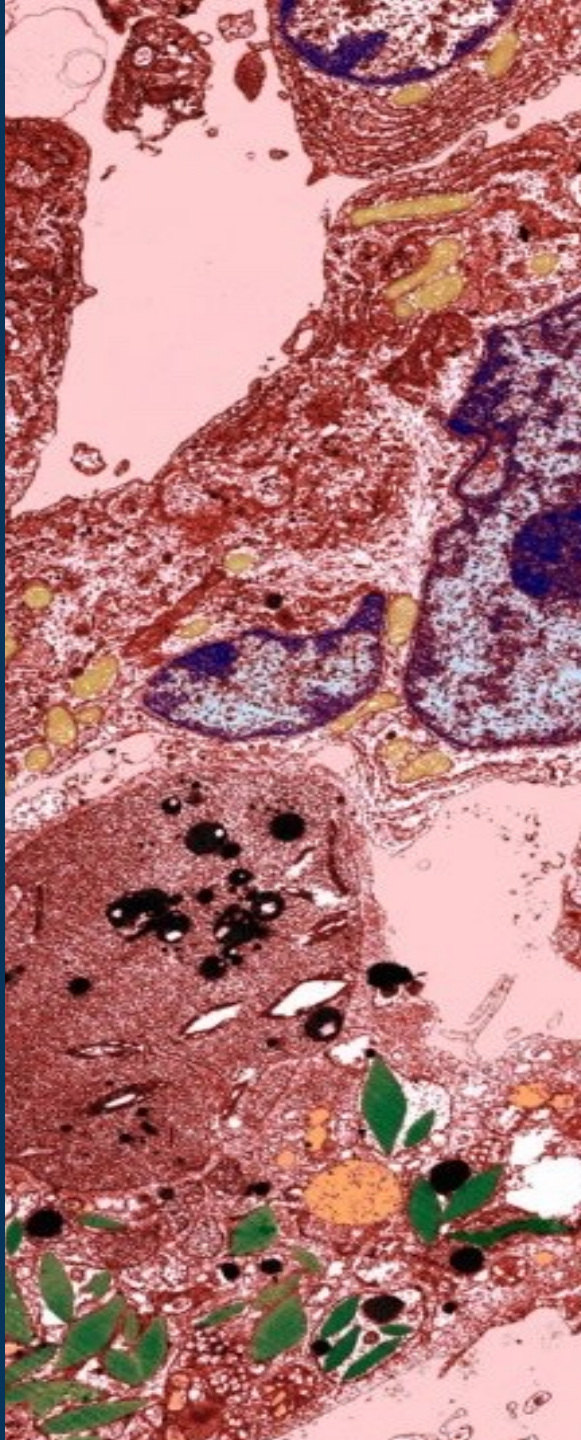


Highlights and Principals of Management of Metastatic Gastric/GEJ Adenocarcinoma

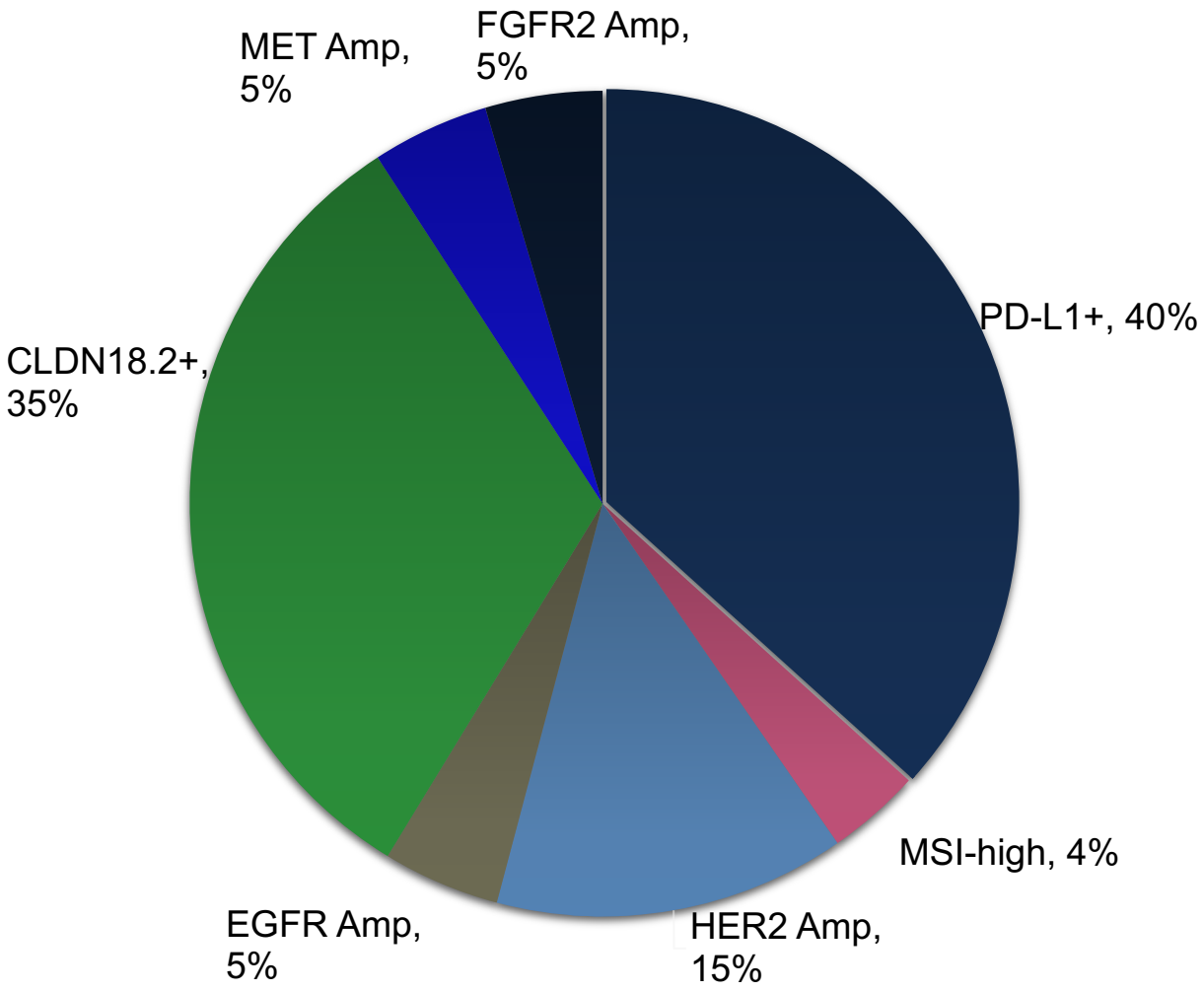
AON Annual Meeting
Dallas, Texas
November 8, 2025

Manish A. Shah, MD FASCO
Weill Cornell Medicine/ New York-Presbyterian
mas9313@med.cornell.edu

Biomarkers in Gastroesophageal Adenocarcinoma



Key Biomarkers in Gastroesophageal Cancer



AMP = amplification; CPS = combined positive score; EGFR = epidermal growth factor receptor; FGFR2 = fibroblast growth factor receptor 2; HER = human epidermal growth factor receptor

Key markers in advanced disease

HER2 positive: 15%-20% of patients; improved survival with chemo + HER2-targeting trastuzumab

MSI high: 3%-5% of patients, high response rates to immunotherapies ± chemo

PD-L1 positive: 30%-50% of patients; identifies those more likely to benefit from immunotherapy; likely gradation within PD-L1+ (CPS)

CLDN18.2 high: 30%-35% of patients; response predictor for CLDN18.2-targeting agent

Investigational biomarkers

FGFR2 amp: 5%-10% of patients; multiple trials of inhibitors

FGFR2 high: May be up to 30% of HER2 negative

EGFR amp: 5%-7%; may predict response to EGFR agents

Tumor agnostic

Mismatch repair deficiency (or MSI-H)

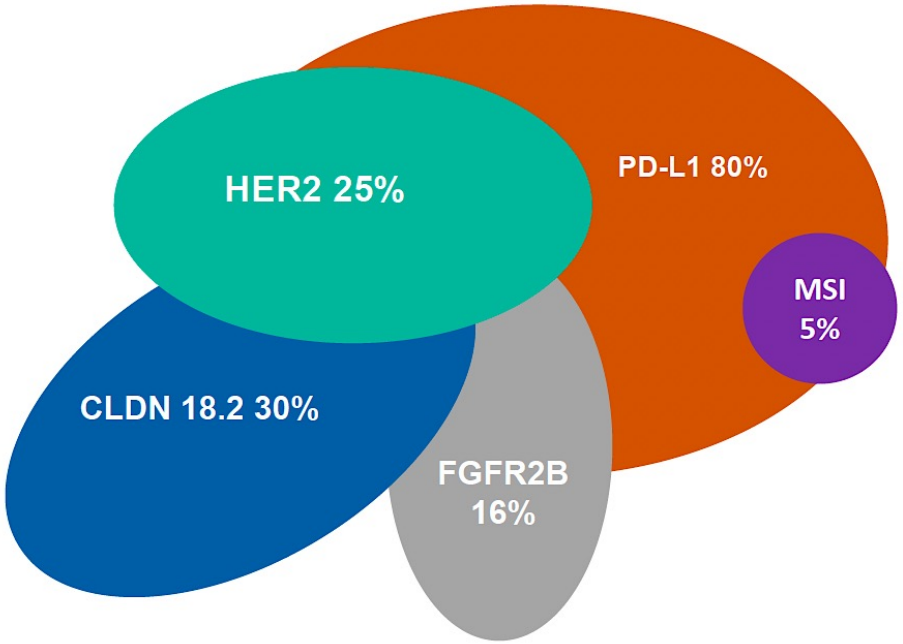
Tumor mutation burden

NTRK fusion

Kuwata T. *Pathol Int*. 2024 Jun;74(6):301-316.

Biomarkers don’t neatly fit in a pie!

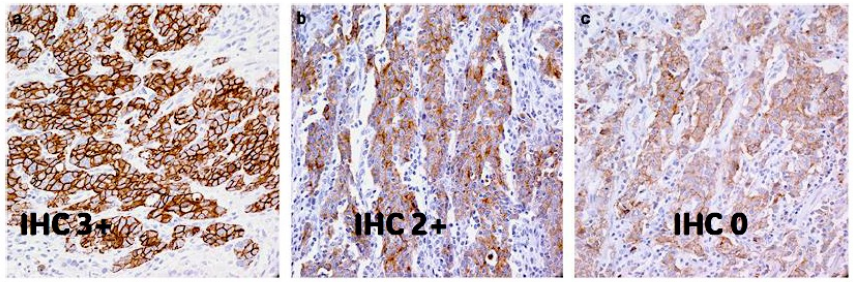
- TP53mut is an early event driving CIN in GEC
- Co-occurring alterations making it difficult to target individual oncogenes
- Rely on IHC and FISH to define clinical targets



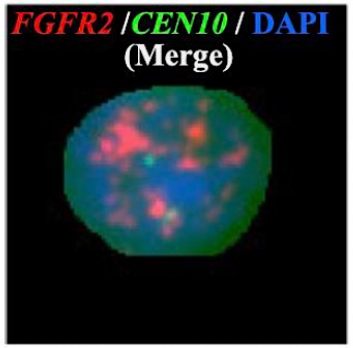
*overlapping between biomarkers may vary among studies

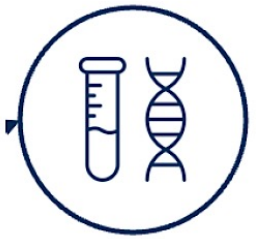
Fibroblast Growth Factor Receptor 2 (FGFR2) testing

FGFR2b ≥10% IHC 2/3+ in 16% GEC



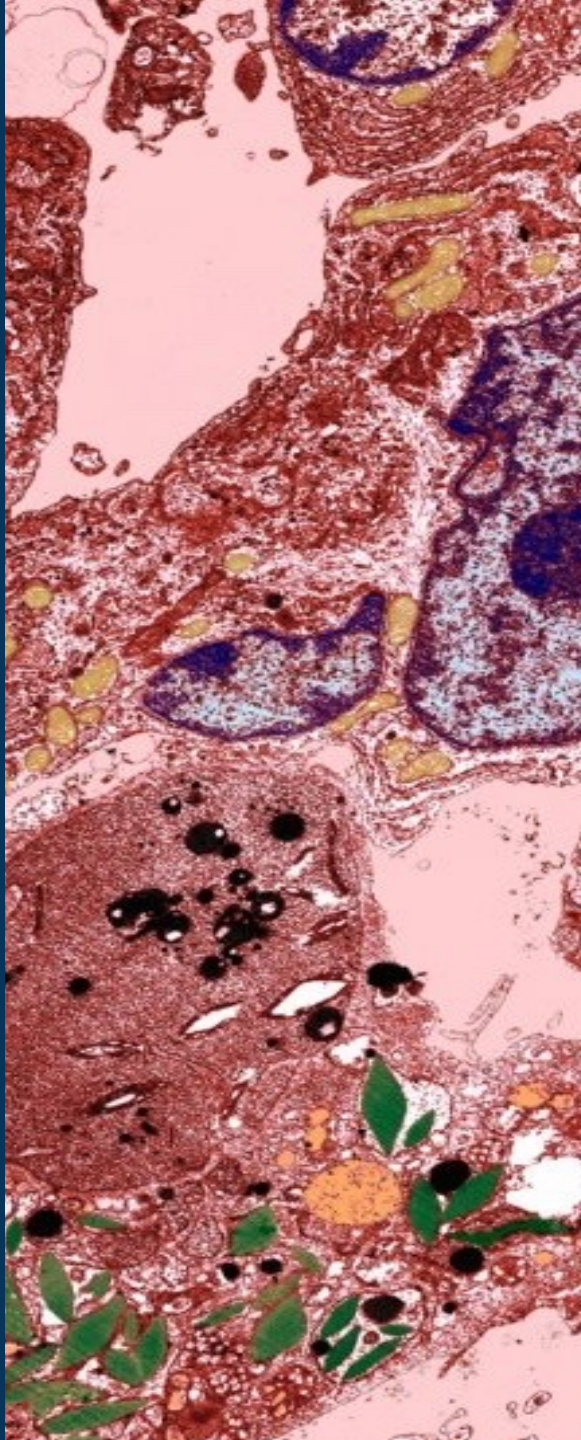
FISH and ctDNA testing: *FGFR* amplifications 5%





Yashiro Nature Scientific Reports 2021, *Sato S et al, ESMO Open 2025, Rha et al JCO PO 2025*

Immunotherapy in Gastroesophageal Adenocarcinoma



Overview of Select Trials of Immunotherapy in Upper GI Cancers: Increasing Complexity

Parameter	CheckMate -649[2]	KEYNOTE-859[3]	Rationale-05
Disease location	Gastric, GEJ, esophagus	Gastric, GEJ	Gastric, GEJ
Histology	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma
Agent	Nivolumab + chemo vs chemo	Pembrolizumab + chemo vs chemo	Tislelizumab + chemotherapy vs chemo
Setting	1L advanced	1L advanced	1L advanced
ORR, %	60 vs 45 (CPS ≥5)	51.3 vs 42	50 vs 43 (TAP ≥5)
PFS HR	0.68 (CPS ≥5)	0.76	0.67 (TAP ≥5)
OS Δ, mo	3.3 (CPS ≥5), 2.7 (CPS ≥1), 2.2 (all patients)	1.4	4.6 mo (TAP ≥5)

[a] Results from prespecified interim analysis of the first 264 patients.

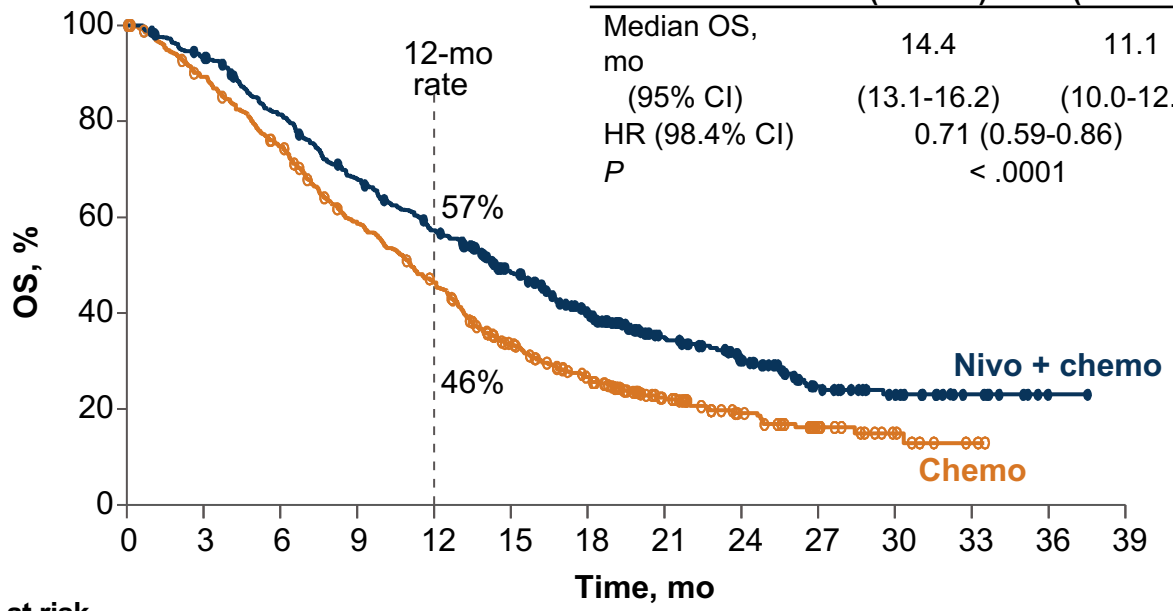
1. Janjigian YY et al. *Lancet*. 2021;398:27-40. 2. Rha SY et al. ESMO 2023. Abstract VP1-2023. 3. Xu R-H, et al. Oral presentation at ESMO 2023. Abstract LBA80.

CheckMate-649 Global Phase 3 Trial: Nivolumab Plus Chemotherapy Improved Survival[1,2]

- **FDA-approved April 2021**

PD-L1 CPS ≥5

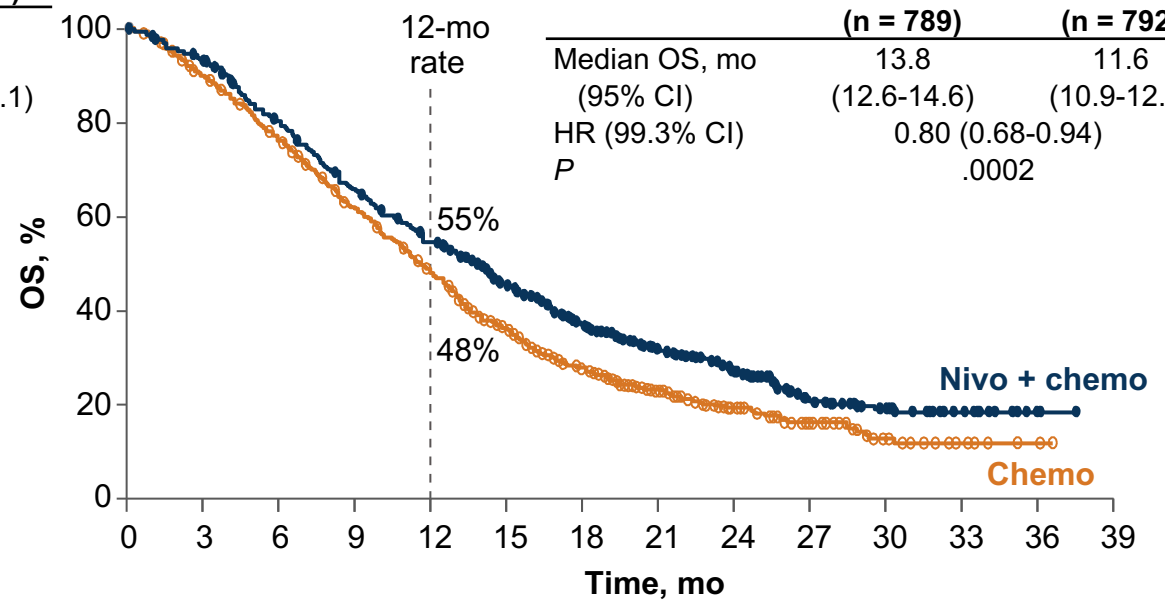
	Nivo + Chemo (n = 473)	Chemo (n = 482)
Median OS, mo	14.4	11.1
(95% CI)	(13.1-16.2)	(10.0-12.1)
HR (98.4% CI)	0.71 (0.59-0.86)	
P	< .0001	



No. at risk														
Nivo + chemo	473	438	377	313	261	198	149	96	65	33	22	9	1	0
Chemo	482	421	350	271	211	138	98	56	34	19	8	2	0	0

All randomized

	Nivo + Chemo (n = 789)	Chemo (n = 792)
Median OS, mo	13.8	11.6
(95% CI)	(12.6-14.6)	(10.9-12.5)
HR (99.3% CI)	0.80 (0.68-0.94)	
P	.0002	



789	731	621	506	420	308	226	147	100	49	34	14	2	0
792	697	586	469	359	239	160	94	59	35	15	7	2	0

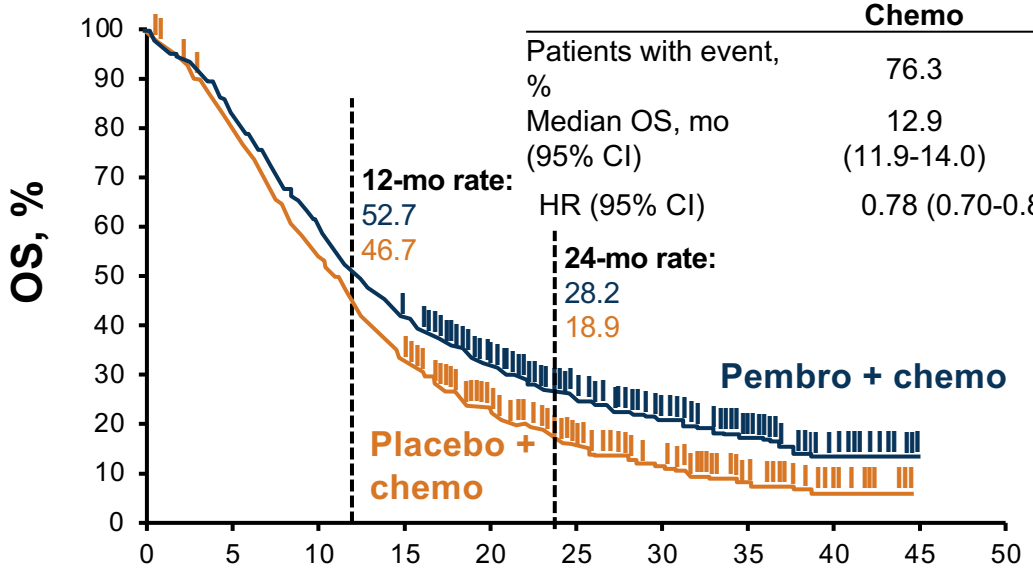
- Grade 3-4 TRAEs were reported in 59% of patients in the nivolumab + chemo arm and 44% of patients in the chemo arm
- Treatment-related deaths occurred in 16 (2%) and 4 (1%) of patients in the nivolumab + chemo and chemo arms, respectively

Adapted with permission from Yelena Y. Janjigian, MD.

1. Nivolumab Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125554Orig1s121lbl.pdf.
2. Janjigian YY et al. *Lancet*. 2021;398:27-40.

KEYNOTE-859: 1L Pembrolizumab + Chemotherapy Improves Survival for Advanced G/GEJ Cancer[1]

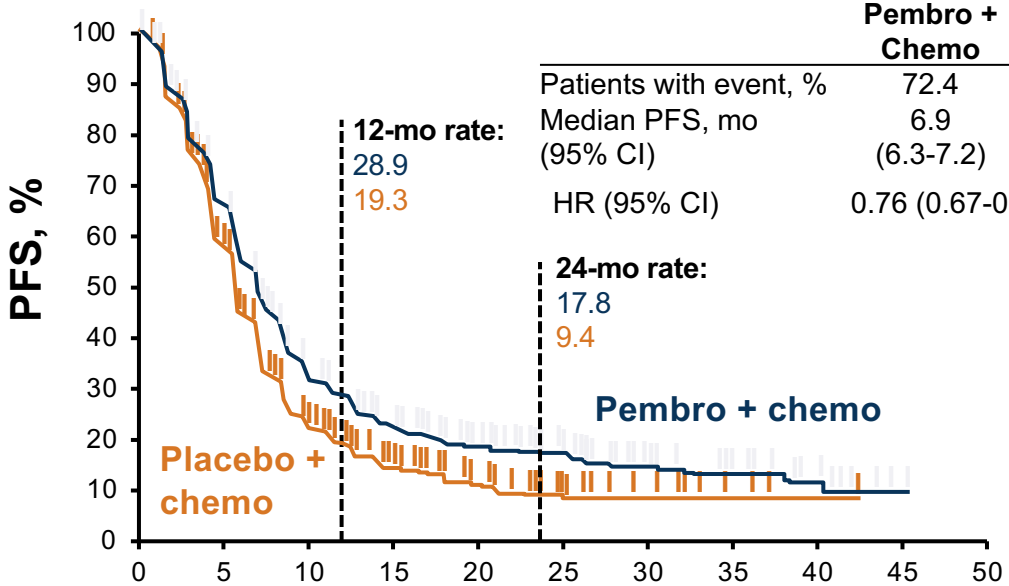
ITT Population OS



	Pembro + Chemo	Placebo + Chemo
Patients with event, %	76.3	84.4
Median OS, mo (95% CI)	12.9 (11.9-14.0)	11.5 (10.6-12.1)
HR (95% CI)	0.78 (0.70-0.87); *P* < .0001	

No. at Risk											
Pembro + chemo	790	663	490	343	240	143	95	55	19	3	0
Placebo + chemo	789	636	434	274	169	95	58	26	10	0	0

ITT Population PFS



	Pembro + Chemo	Placebo + Chemo
Patients with event, %	72.4	77.1
Median PFS, mo (95% CI)	6.9 (6.3-7.2)	5.6 (5.5-5.7)
HR (95% CI)	0.76 (0.67-0.85); *P* < .0001	

No. at Risk											
Pembro + chemo	790	461	199	131	94	63	36	22	9	1	0
Placebo + chemo	789	407	130	71	41	19	11	3	1	0	0

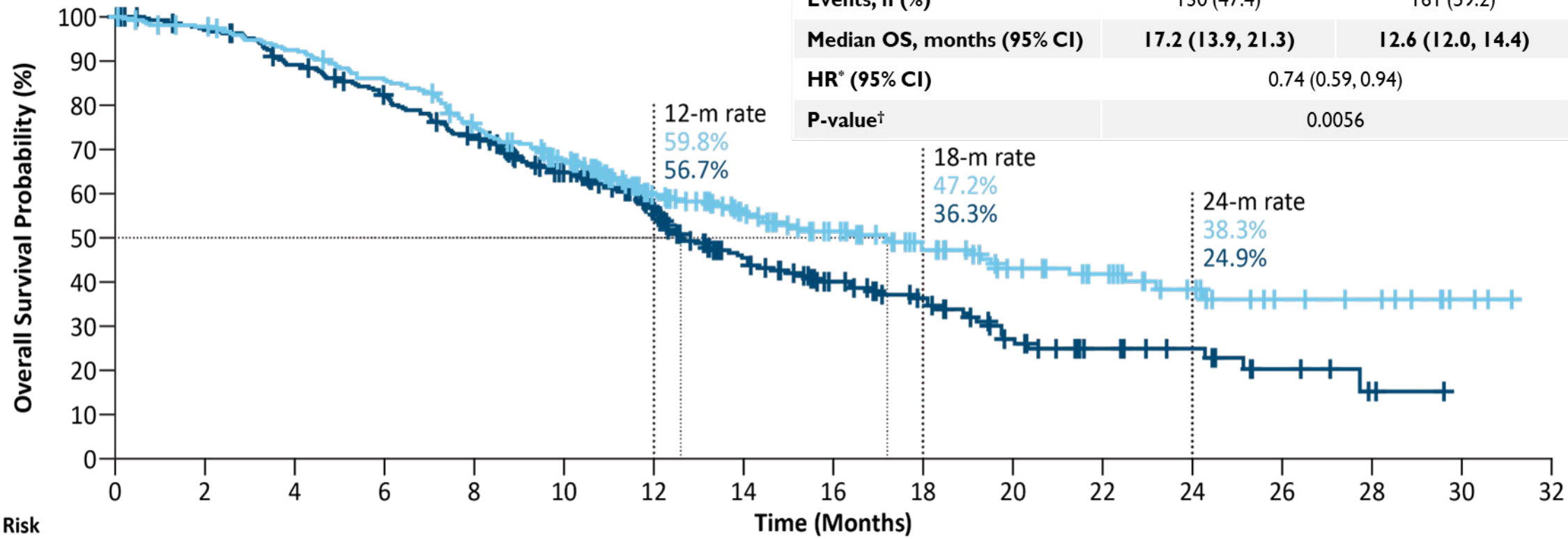
In addition to higher ORR (51.3% vs 42.0%), responses were also more durable in pembrolizumab arm (median DOR, 8.0 vs 5.7 months)

1. Rha SY et al. ESMO 2023. Abstract VP1-2023.

RATIONALE-305: Interim Analysis

Tislelizumab plus chemotherapy demonstrated statistically significant improvement in OS vs placebo plus chemotherapy

	Tislelizumab + chemo	Placebo + chemo
Events, n (%)	130 (47.4)	161 (59.2)
Median OS, months (95% CI)	**17.2 (13.9, 21.3)**	**12.6 (12.0, 14.4)**
HR* (95% CI)	0.74 (0.59, 0.94)	
P-value†	0.0056	



Number at Risk																	
TIS+chemo	274	262	246	227	196	167	122	93	70	52	38	30	19	11	9	3	0
Placebo+chemo	272	261	237	215	189	156	118	80	57	44	26	16	12	6	2	0	0

Data cutoff: October 08, 2021.

*Primary OS analysis: Stratified by regions (east Asia vs rest of the world) and presence of peritoneal metastasis. †One-sided stratified log-rank test. 116 (42.3%) patients and 147 (54.0%) patients in tislelizumab plus chemotherapy arm and placebo plus chemotherapy arm received subsequent anticancer systemic therapies, respectively. Of those, 19 (6.9%) patients and 38 (14.0%) patients received immunotherapy.

CI=confidence interval, HR=hazard ratio, OS=overall survival, m=month

Moehler M et al. ASCO-GI 2023 abstract no. 286 Jan19-21, 2023

FFDA ODAC Meeting – September 24, 2024

	Nivolumab CheckMate-649 April 16, 2021	Pembrolizumab Keynote-859 November 16, 2023	Tislelizumab Rationale-305 Under review
Intent to Treat	**N = 1581**	**N=1579**	**N=997**
Median OS - ICI + Chemo arm, mos (95% CI) - Chemo arm, mos (95% CI)	 13.8 (12.6, 14.6) 11.6 (10.9, 12.5)	 12.9 (11.9, 14.0) 11.5 (10.6, 12.1)	 15.0 (13.6, 16.5) 12.9 (12.1, 14.1)
OS HR (95% CI)	**0.80** (0.71, 0.90)	**0.78** (0.70, 0.87)	**0.80** (0.70, 0.92)
Pre-specified analysis for PD-L1 group 1	**CPS ≥ 1** **N = 1296**	**CPS ≥ 1** **N = 1235**	**TAP ≥ 5** **N = 576**
Median OS - ICI + Chemo arm, mos (95% CI) - Chemo arm, mos (95% CI)	 14.0 (12.6, 15.0) 11.3 (10.6, 12.3)	 13.0 (11.6, 14.2) 11.4 (10.5, 12.0)	 17.2 (13.9, 21.3) 12.6 (12.0, 14.4)
OS HR (95% CI)	**0.77** (0.68, 0.88)	**0.74** (0.65, 0.84)	**0.74** (0.59, 0.94)
Pre-specified analysis for PD-L1 group 2	**CPS ≥ 5** **N = 955**	**CPS ≥ 10** **N = 551**	NA
Median OS - ICI + Chemo arm, mos (95% CI) - Chemo arm, mos (95% CI)	 14.4 (13.1, 16.2) 11.1 (10.0, 12.1)	 15.7 (13.8, 19.3) 11.8 (10.3, 12.7)	NA
OS HR (95% CI)	**0.71** (0.61, 0.83)	**0.65** (0.53, 0.79)	NA

Adapted from slide made by Dr. Vaibhav Kumar

Abbreviations: CPS combined positive score; TAP tumor area positivity; ICI immune checkpoint inhibitor; mos months; OS overall survival

Gastric Cancer Applications

Pre-Specified PD-L1 groups

	Nivolumab CheckMate-649 April 16, 2021		Pembrolizumab Keynote-859 November 16, 2023		Tislelizumab Rationale-305 Under review	
Pre-specified analysis for PD-L1 group 1	**CPS ≥ 1 N = 1296**	**CPS < 1 N = 265**	**CPS ≥ 1 N = 1235**	**CPS < 1 N = 344**	**TAP ≥ 5 N = 576**	**TAP < 5 N = 451**
Median OS - ICI + Chemo arm, mos - Chemo arm, mos	 14.0 11.3	 13.1 12.5	 13.0 11.4	 12.7 12.2	 17.2 12.6	 14.1 12.9
OS HR (95% CI)	**0.77** (0.68, 0.88)	**0.85** (0.63, 1.15)	**0.74** (0.65, 0.84)	**0.92 (0.73, 1.17)**	**0.74** (0.59, 0.94)	**0.91** (0.74, 1.12)
Pre-specified analysis for PD-L1 group 2	**CPS ≥ 5 N = 955**	**CPS < 5 N = 606**	**CPS ≥ 10 N = 551**		NA	
Median OS - ICI + Chemo arm, mos (95% CI) - Chemo arm, mos (95% CI)	 14.4 11.1	 12.4 12.3	 15.7 11.8		NA	
OS HR (95% CI)	**0.71** (0.61, 0.83)	**0.94** (0.78, 1.14)	**0.65** (0.53, 0.79)		NA	

Abbreviations: CPS combined positive score; TAP tumor area positivity; ICI immune checkpoint inhibitor; mos months; OS overall survival

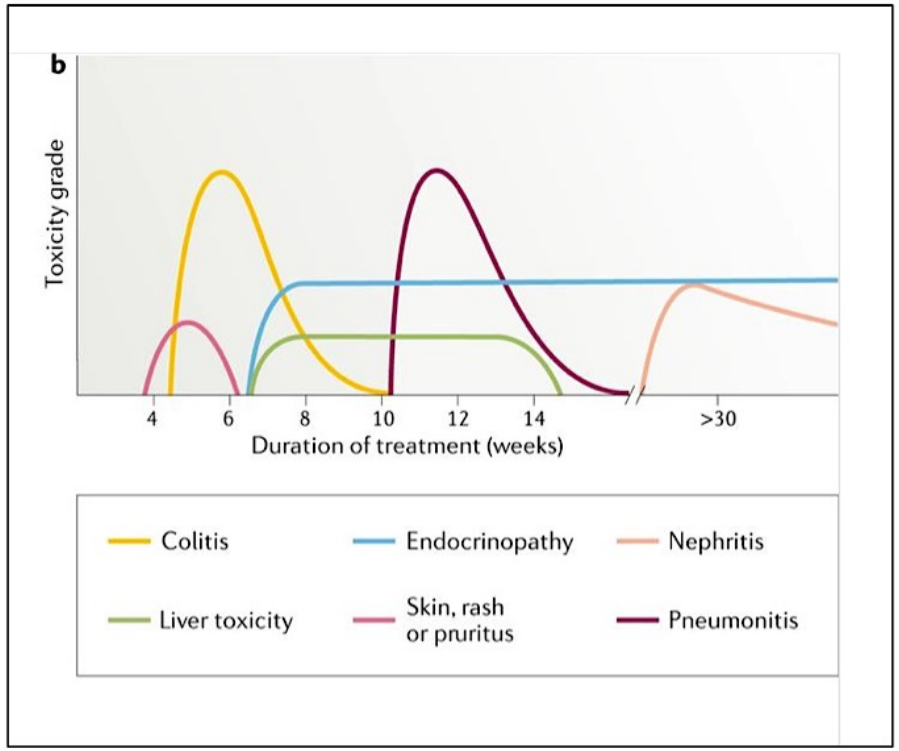
Adapted from slide made by Dr. Vaibhav Kumar and information from product labeling and/or BLA submissions

Safety – Immune Related Adverse Events (anti-PD-1)

Incidence of immune related adverse reactions (IMARs)

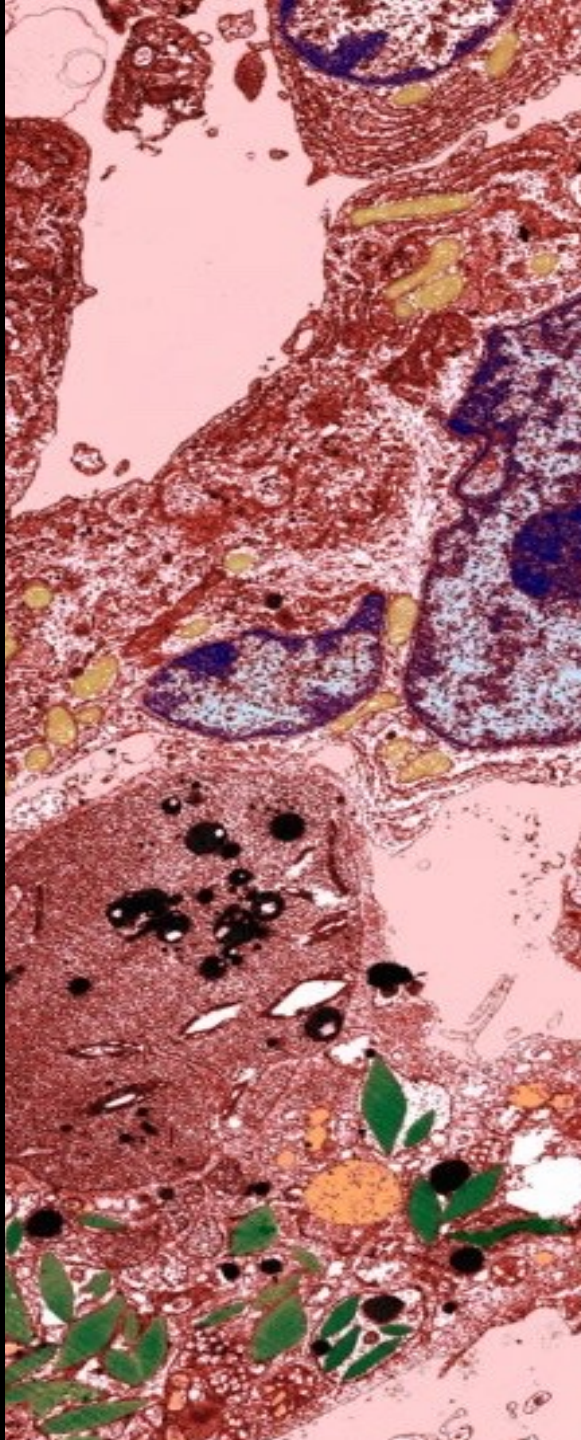
	All Grade	≥ 3
Diarrhea	6 to 19%	1%
Colitis	1 to 4%	0.3 to 2%
Pulmonary	1.5 to 5%	0 to 2%
Rash	9 to 16%	0.2 to 3.5%
Neurological	NR to 0.3%	NR to 0.3%
Endocrinopathy	7.3 to 23.4%	0 to 2%
Hepatic	0.3 to 10.8%	0 to 1.5%
Renal	NR to 2%	0 to 0.5%

Time course of immune related adverse events



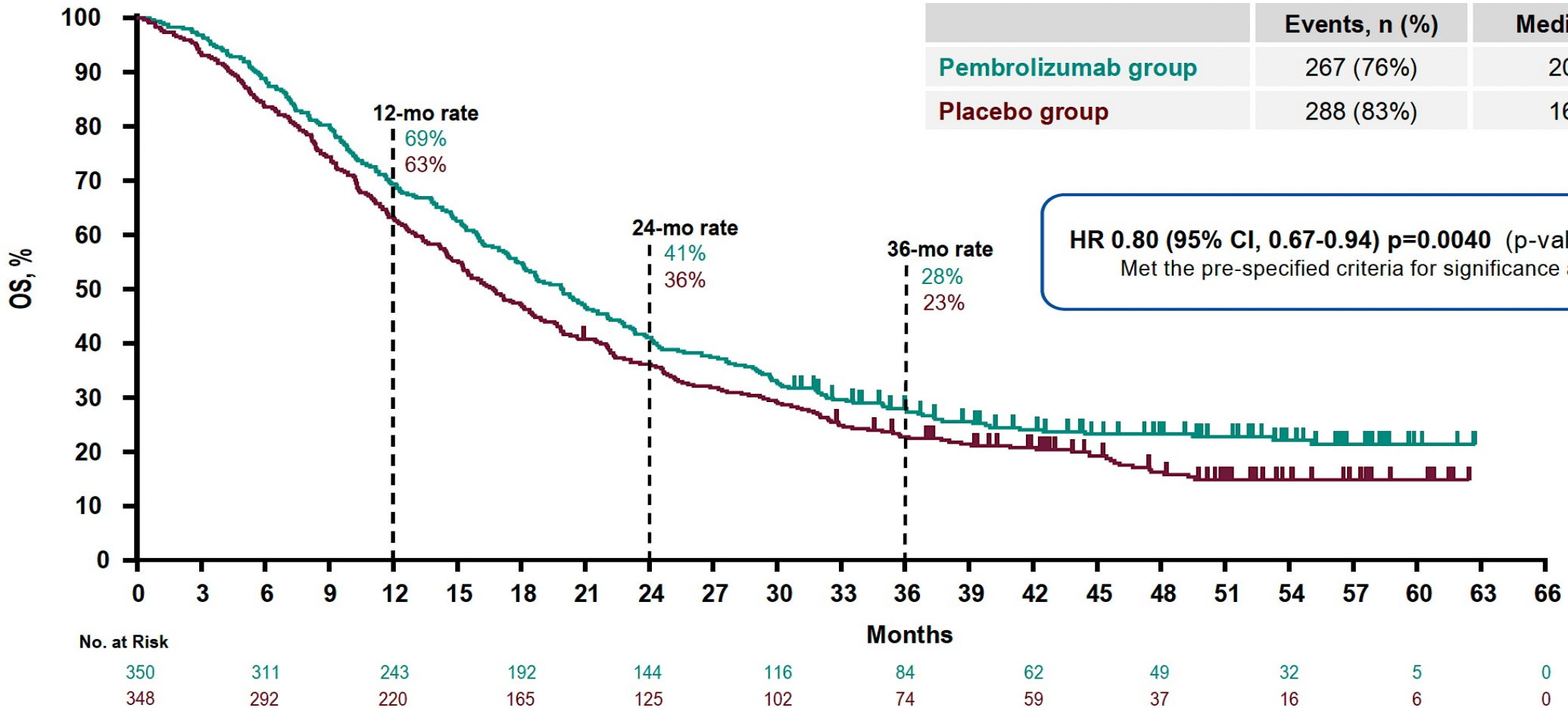
Source: (Adapted-Table and Copied-Figure) Martins et al., Nature Reviews, 2019

Targeting HER2 in Gastroesophageal Junction Adenocarcinoma



KN 811 HER2+ Overall Survival at Final Analysis

Dual HER2 and PD-1 Blockade in Advanced Disease



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

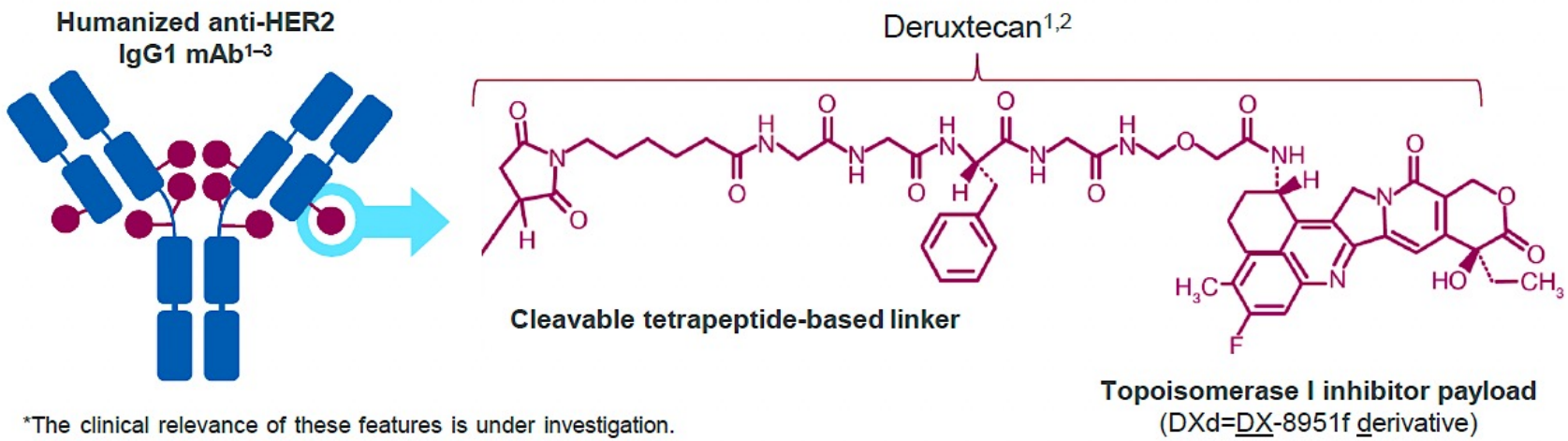
HR 0.80 (95% CI, 0.67-0.94) p=0.0040 (p-value bound 0.0201)
Met the pre-specified criteria for significance at final analysis

Janjigian YY et al. ESMO 2024. Abstract 1400O

T-DXd was designed with seven key attributes

T-DXd is an ADC composed of three components[1,2]:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab, covalently linked to
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker



*The clinical relevance of these features is under investigation.

- Payload mechanism of action: topoisomerase I inhibitor[1,2,*]
- High potency of payload[1,2,*]
- High drug-to-antibody ratio ≈ 8[1,2,*]
- Payload with short systemic half-life[1,2,*]
- Stable linker-payload[1,2,*]
- Tumour-selective cleavable linker[1,2,*]
- Bystander antitumour effect[1,4,*]

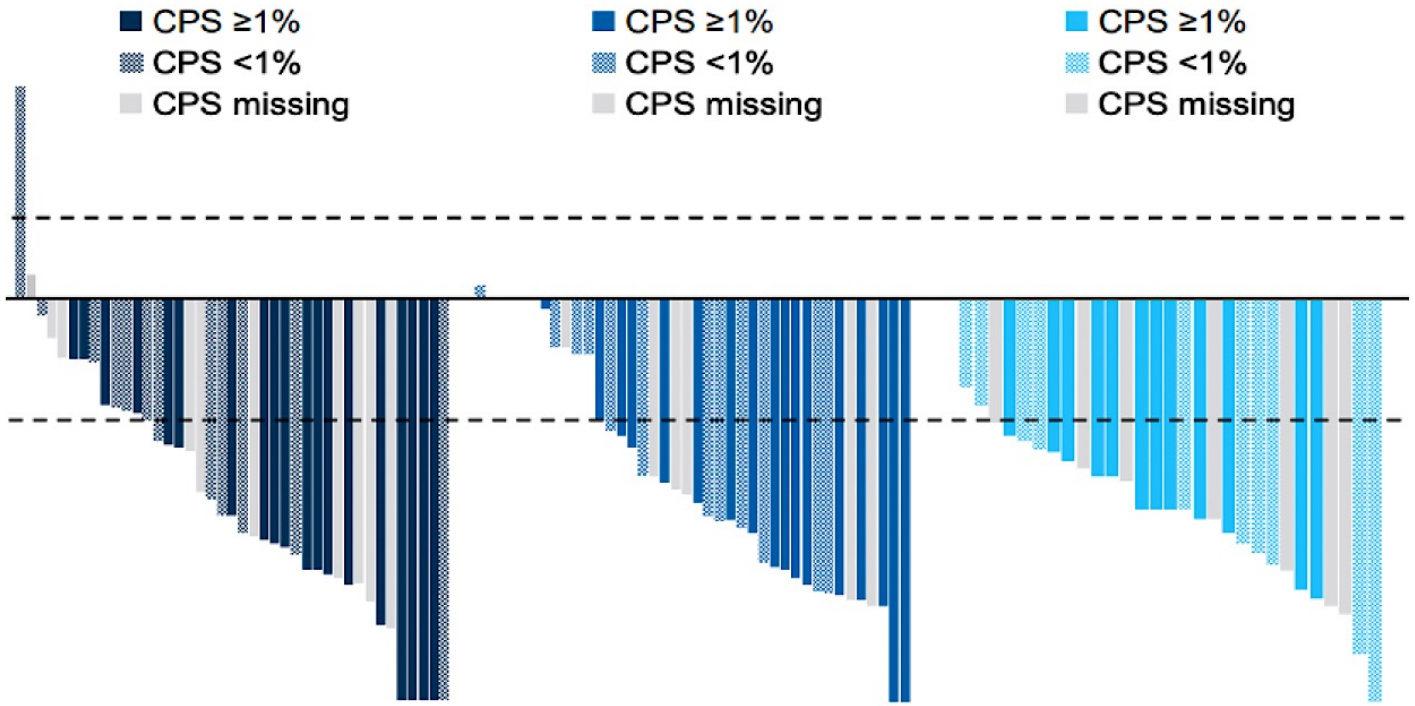
1. Nakada T, et al. *Chem Pharm Bull (Tokyo)* 2019;67:173–185. 2. Ogitani Y, et al. *Clin Cancer Res* 2016;22:5097–5108. 3. Trail PA, et al. *Pharmacol Ther* 2018;181:126–142.
4. Ogitani Y, et al. *Cancer Sci* 2016;107:1039–1046.

ADC, antibody-drug conjugate; DXd, deruxtecan; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; mAB, monoclonal antibody; T-DXd, trastuzumab deruxtecan.

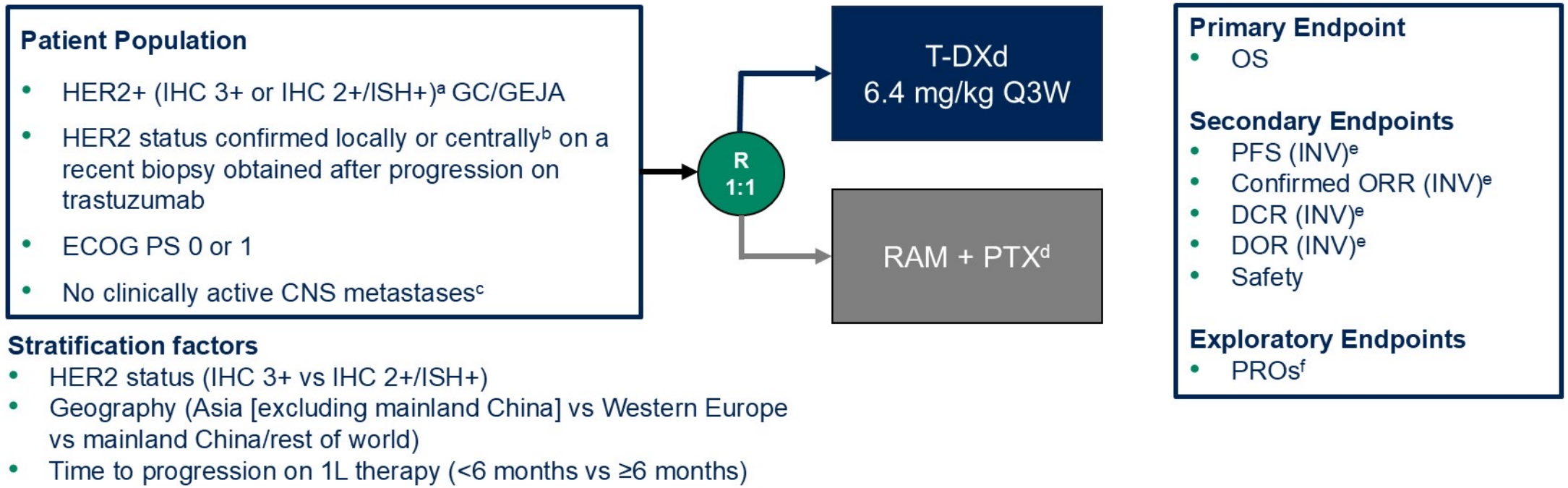
DESTINY-Gastric03: 1L T-DXd plus chemo +/- anti-PD1

Trastuzumab Deruxtecan with PD-1 Blockade Safe and Effective

T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² + pembro n=43	T-DXd 6.4 mg/kg + pembro n=41	T-DXd 5.4 mg/kg + 5-FU/cape 750 mg/m² + pembro n=32
17	15	5
17 (8, NE)	18 (5, 21)	NE (2, NE)
58 (42, 73)	63 (46, 78)	59 (40, 77)
70	78	62
39	44	46



Phase III DESTINY-Gastric04 Study Design

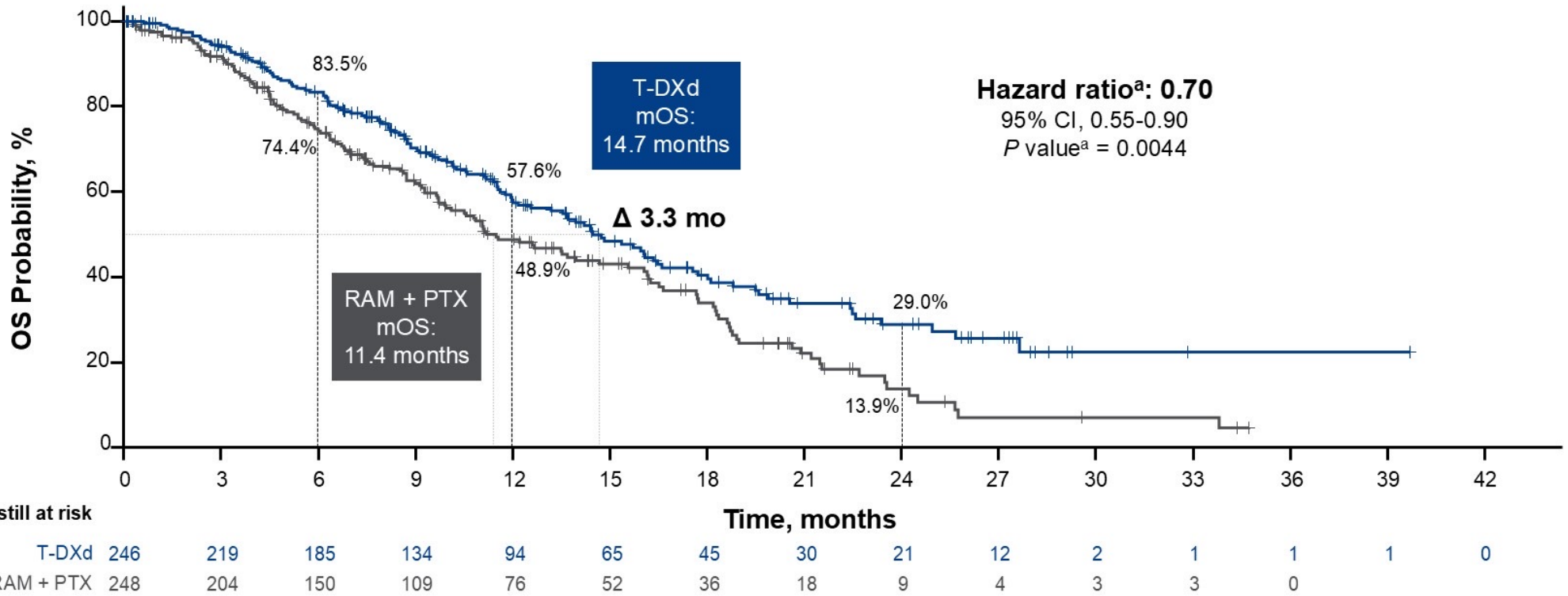


1L, first-line; ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; CNS, central nervous system; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-Dimension, 5-Level; FACT-Ga, Functional Assessment of Cancer Therapy-gastric; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; INV, investigator; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; PTX, paclitaxel; Q3W, every 3 weeks; R, randomization; RAM, ramucirumab; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; T-DXd, trastuzumab deruxtecan; VAS, visual analog scale.

[a]As classified by the 2017 ASCO-CAP guidelines for HER2 testing in gastroesophageal adenocarcinoma. [b]Study protocol originally mandated HER2 status be determined centrally but was later amended to allow local determination. [c]Clinically active CNS metastases were defined as being untreated and symptomatic or requiring therapy with corticosteroids or anticonvulsants. Patients with clinically inactive CNS metastases could be enrolled. [d]RAM administered as 8 mg/kg on days 1 and 15 of each 28-day cycle and PTX administered as 80 mg/m^2 on days 1, 8, and 15 of each 28-day cycle. [e]Determined by investigator-based assessment on RECIST v1.1. [f]Based on EORTC EQ-5D-5L VAS and FACT-Ga subscales.

Shitara K et al. ASCO 2025;Abstract LBA4002.

Phase III DESTINY-Gastric04: OS (Primary Endpoint)



Patients still at risk

T-DXd	246	219	185	134	94	65	45	30	21	12	2	1	1	1	0
RAM + PTX	248	204	150	109	76	52	36	18	9	4	3	3	0		

T-DXd demonstrated a statistically significant and clinically meaningful improvement in OS compared with RAM + PTX in HER2+ GC/GEJA, showing a 30% reduction in risk of death

DCO, data cutoff; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; mOS, median overall survival; OS, overall survival; PTX, paclitaxel; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan.

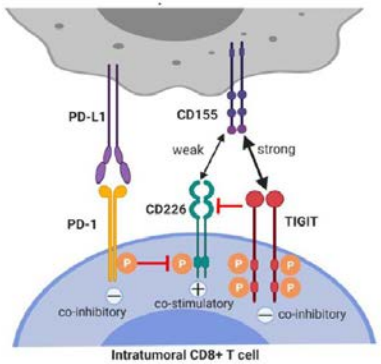
At DCO (October 24, 2024), the median duration of OS follow-up was 16.8 months for T-DXd and 14.4 months for RAM + PTX. Boundary for superiority: 2-sided $P < 0.0228$.

[a]Two-sided P value from stratified log-rank test and stratified Cox proportional hazards model adjusted for stratification factor: HER2 status (IHC 3+ or IHC 2+/ISH+).

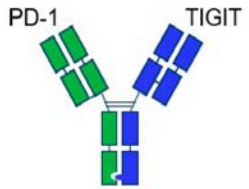
Shitara K et al. ASCO 2025;Abstract LBA4002.

Rilvegostomig (AZD2936) is designed to dual blockade PD-1 and TIGIT pathway

Ligation of PD-1 & TIGIT delivers negative signals to T cells to suppress antitumour immunity



A monovalent bispecific antibody



Affinity to human TIGIT: 15 pM

Affinity to human PD-1: 0.4 nM

Fc isotype: human IgG1-TM (reduced ADCC)

Adapted from Ge Z, et al. *Front Immunol* 2021;12:699895.

ADCC, antibody-dependent cell-mediated cytotoxicity; CD, cluster of differentiation; Fc, fragment crystallizable; IgG1, immunoglobulin G1; ITIM, immunoreceptor tyrosine-based inhibitory motif; nM, nanomolar; PD-1, programmed cell death-1; pM, picomolar; TIGIT, T cell immunoreceptor with Ig and ITIM domains.

Study Design

ARTEMIDE-Gastric 01 Study

Participant population	Intervention	Endpoints
• Histologically confirmed locally advanced or metastatic gastric GEJ • No prior treatment • HER2+ (HER2 3+ or 2+/ISH-positive) • CPS ≥ 1	N = 840 → R 1:1:1 Arm A: T-DXd + 5FU / Cape+ Rilve (N = 280) Arm C: Trastuzumab + CTx + Rilve (N = 280) Arm B: Trastuzumab + CTx + pembro (N = 280)	**Primary Endpoints** (Arm A vs Arm B) PFS, OS **Key Secondary Endpoints** (Arm C vs Arm B) PFS, OS **Secondary Endpoints** other efficacy parameters, PK, Safety, Immunogenicity, PROs

Stratification Factors

- HER2 status (IHC 3+ vs IHC 2+ plus ISH-positive)
- Geographic region (Japan/South Korea vs Rest of Asia [including China] vs North America/EU/ROW)
- PD L1 expression (CPS ≥ 10 vs CPS < 10).

Treatment arms

Arm A (treatment arm): T-DXd (dosed at 5.4 mg/kg), fluoropyrimidine (capecitabine [Investigators Choice of 750 mg/m2 twice-daily (BD) for 14 days] or 5-FU [600 mg/m2/day over 5 days]), and Rilvegostomig (dosed at 750 mg);
Arm B (control arm): Trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg for subsequent cycles), with Investigators Choice of either cisplatin/5-FU (cisplatin dosed at 80 mg/m2 and 5-FU dosed at 800 mg/m2/day over 5 days) or CapeOx (capecitabine dosed at 1000 mg/m2 BD for 14 days and oxaliplatin dosed at 130 mg/m2) and pembrolizumab (dosed at 200 mg).
Arm C (CoC arm): Trastuzumab and chemotherapy the same as control arm, Rilvegostomig (dosed at 750mg)

Phase 3 Study: T-DXd+FP+pembro (DESTINY-Gastric05)

Patient population (N = 726)

- Locally advanced or metastatic gastric or GEJ cancer
- No systemic therapy in the unresectable, locally advanced or metastatic setting or relapse ≥6 months after the last dose of perioperative or neoadjuvant therapy
- Centrally assessed HER2+ (IHC3+ or IHC2+/ISH+)
- ECOG PS 0 or 1

CPS ≥1 → R 1:1

- **Main Cohort (N = 576)**
  - **Arm M1[a]**: T-DXd + 5-FU or capecitabine + pembrolizumab
  - **Arm M2[b]**: Trastuzumab + platinum-based chemotherapy (cisplatin + 5-FU or oxaliplatin + capecitabine) + pembrolizumab

CPS <1 → R 1:1

- **Exploratory Cohort (N = 150)**
  - **Arm E1[c]**: T-DXd + 5-FU or capecitabine
  - **Arm E2[d]**: Trastuzumab + platinum-based chemotherapy (cisplatin + 5-FU or oxaliplatin + capecitabine)

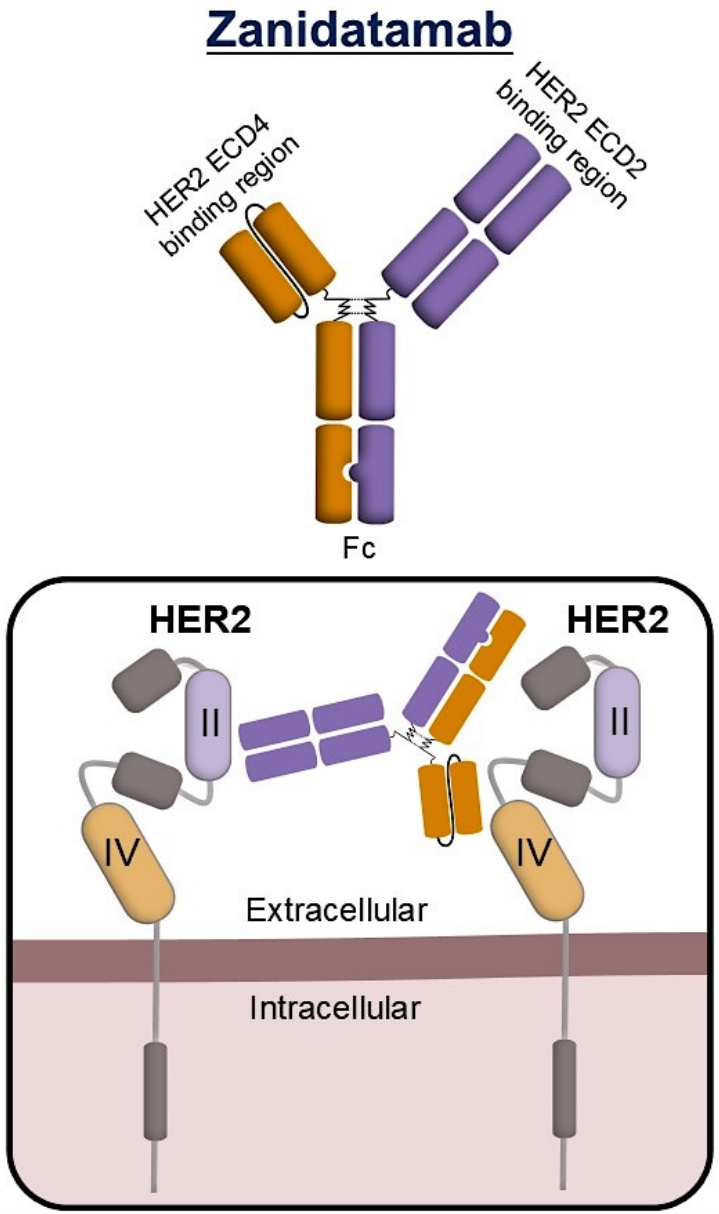
[a]T-DXd 5.4 mg/kg Q3W on day 1 plus 5-FU 600 mg/m²/day IV on days 1 to 5 or capecitabine 750 mg/m² PO BID on days 1 to 14 plus pembrolizumab 200 mg IV Q3W on day 1.

[b]Trastuzumab loading dose of 8 mg/kg IV followed by 6 mg/kg IV Q3W plus platinum-based chemotherapy (cisplatin 80 mg/m²/day IV on day 1 plus 5-FU 800 mg/m²/day IV on days 1 to 5 or oxaliplatin 130 mg/m²/day IV on day 1 plus capecitabine 1000 mg/m² PO BID on days 1 to 14) plus pembrolizumab 200 mg IV Q3W on day 1.

[c]T-DXd 5.4 mg/kg IV Q3W on day 1 plus 5-FU 600 mg/m²/day IV on days 1 to 5 or capecitabine 750 mg/m² PO BID on days 1 to 14.

[d]Trastuzumab loading dose of 8 mg/kg IV followed by 6 mg/kg IV Q3W plus platinum-based chemotherapy (cisplatin 80 mg/m²/day IV on day 1 plus 5-FU 800 mg/m²/day IV on days 1 to 5 or oxaliplatin 130 mg/m²/day IV on day 1 plus capecitabine 1000 mg/m² PO BID on days 1 to 14).

HER2-Targeted Bispecific mAb: Zanidatamab + chemo 1L



- Zanidatamab is a dual HER2-targeted bispecific antibody that drives multiple antitumor MOAs, including[1]:
  - Facilitation of HER2 internalization and subsequent degradation
  - Reduction of HER2 on the cell surface
  - Inhibition of HER2 signaling pathways
  - Activation of immune-mediated effects (CDC, ADCC, and phagocytosis)

Eligibility criteria

- Aged ≥18 years at the time of signing informed consent
- HER2-expressing advanced or metastatic GEA
  - Part 1: IHC 3+ or IHC 2+ regardless of FISH status **per local or central assessment**
  - Part 2: IHC 3+ or IHC 2+/FISH+ **per central assessment**
- Measurable disease per RECIST v1.1[1]
- Baseline ECOG PS 0 or 1
- No prior HER2-targeted treatment

Single arm trial: Zanidatamab + clinician's choice of chemotherapy

Zanidatamab[a,b] IV Q3W + CAPOX[c]

Zanidatamab[a,b] IV Q3W + FP[d]

Zanidatamab[b,e] IV Q2W + mFOLFOX6[f]

After the first 25 patients were enrolled and treated, antidiarrheal prophylaxis[g] was added for all subsequent patients

CT/MRI scans Q6W per RECIST v1.1[1]

Plasma ctDNA samples at baseline and on treatment using NGS testing (Guardant360)

Primary endpoint

- Investigator-assessed confirmed ORR

Select secondary endpoints

- DOR
- PFS
- OS
- Rate and severity of AEs

Exploratory endpoint

- Potential biomarkers for prognostic prediction

[a]Zanidatamab 30 mg/kg, 1800 mg (patients <70 kg) or 2400 mg (patients ≥70 kg); [b]Chemotherapy was required for 6 cycles except for intolerability or disease progression. Patients who discontinued chemotherapy due to reasons not related to zanidatamab toxicity without disease progression could continue treatment with zanidatamab monotherapy; [c]Capecitabine 1000 mg/m^2 PO BID on days 1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W; [d]Cisplatin 80 mg/m^2 IV Q3W + 5-FU 800 mg/m^2/day IV on days 1-5 Q3W; [e]Zanidatamab 20 mg/kg, 1200 mg (patients <70 kg) or 1600 mg (patients ⩾70 kg) IV Q2W; [f]Leucovorin 400 mg/m^2 IV Q2W + oxaliplatin 85 mg/m^2 IV Q2W + 5-FU 1200 mg/m^2/day continuous IV infusion for 48 hours Q2W; [g]Loperamide 4 mg BID starting on cycle 1 day 1 and continuing for ≥7 days.

5-FU, 5-fluorouracil; AE, adverse event; BID, twice daily; CAPOX, capecitabine plus oxaliplatin; CT, computed tomography; ctDNA, circulating tumor DNA; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FP, 5-FU plus cisplatin; FISH, fluorescence in situ hybridization; GEA, gastroesophageal adenocarcinoma; IHC, immunohistochemistry; IV, intravenous; mFOLFOX6, modified 5-FU plus oxaliplatin; MRI, magnetic resonance imaging; PFS, progression-free survival; PO, by mouth; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

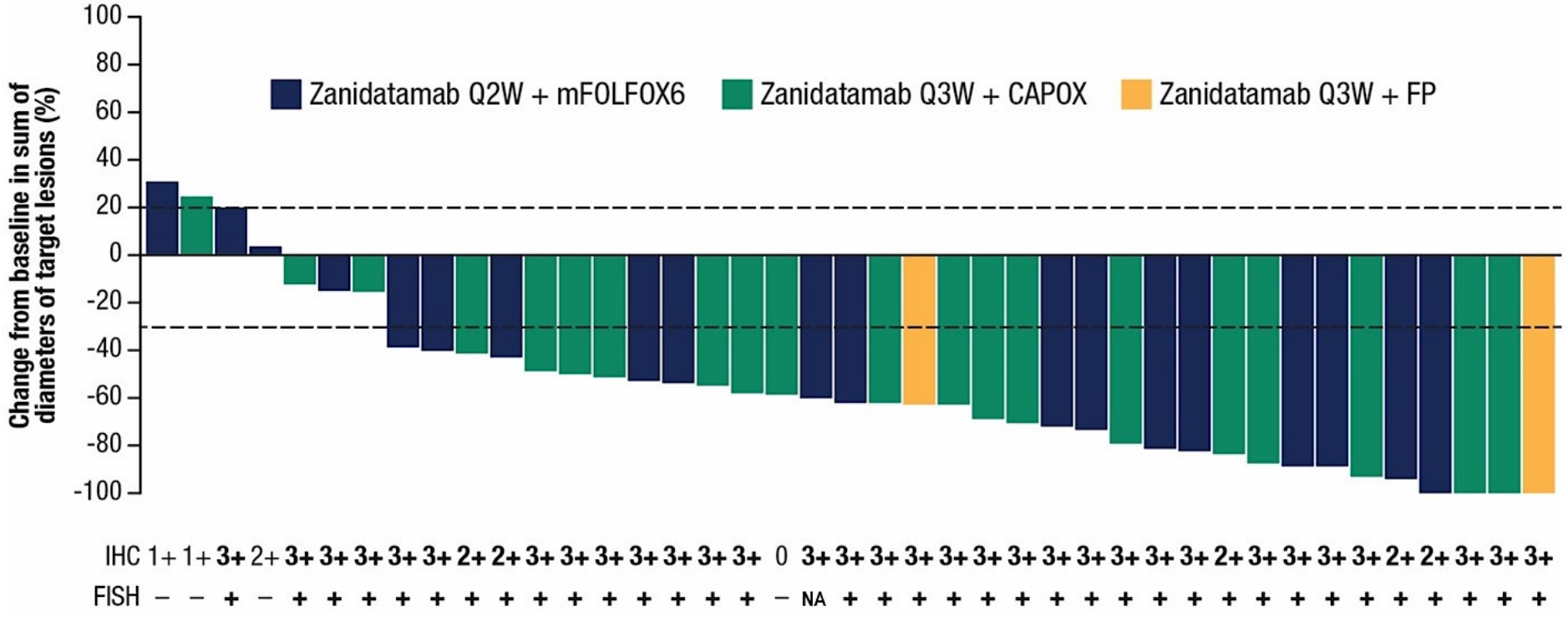
1. Eisenhauer EA et al. *Eur J Cancer*. 2009;45(2):228-247.

Elimova E et al. ASCO 2025;Abstract 4013

HERIZON-GEA-01: Antitumor Activity

- Nearly all response-evaluable patients (90%) had a decrease in target lesions from baseline

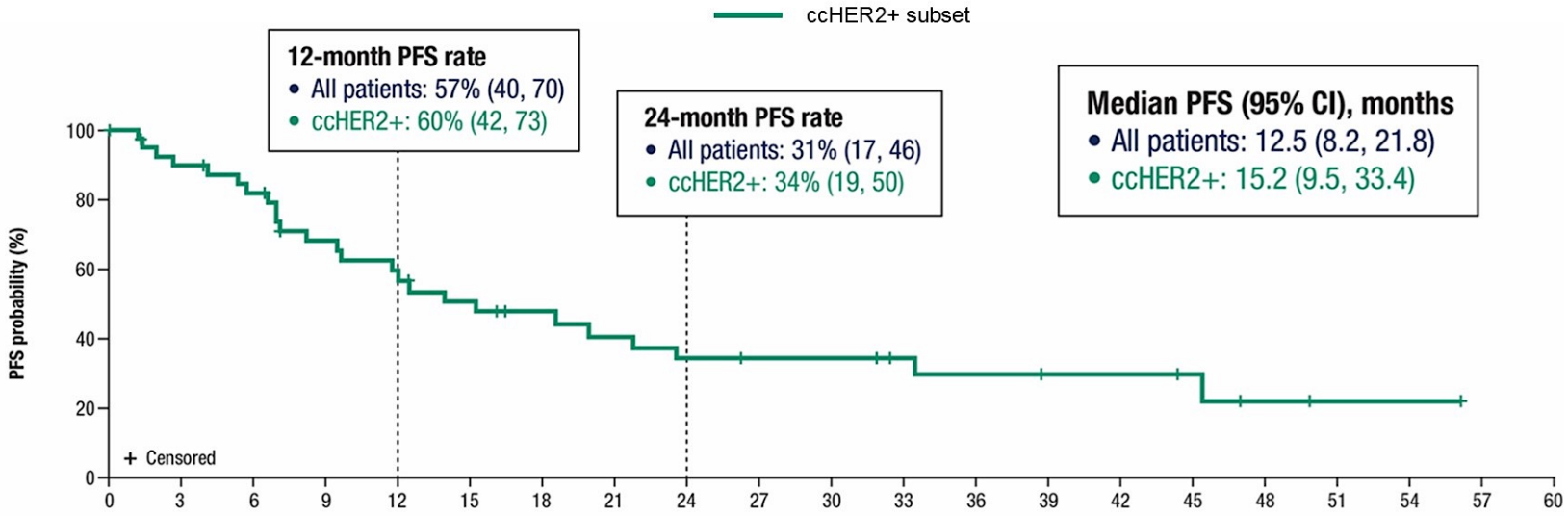
	All Patients (N = 42)	ccHER2+ Subset (n = 37)
cORR		
n (%)	32 (76)	31 (84)
95% CI	60, 88	68, 94
cBOR,[a] n (%)		
CR	3 (7)	3 (8)
PR	29 (69)	28 (76)
SD	5 (12)	4 (11)
PD	5 (12)	2 (5)
DCR[b]		
n (%)	37 (88)	35 (95)
95% CI	74, 96	82, 99
CBR[c]		
n (%)	33 (79)	32 (86)
95% CI	63, 90	72, 96



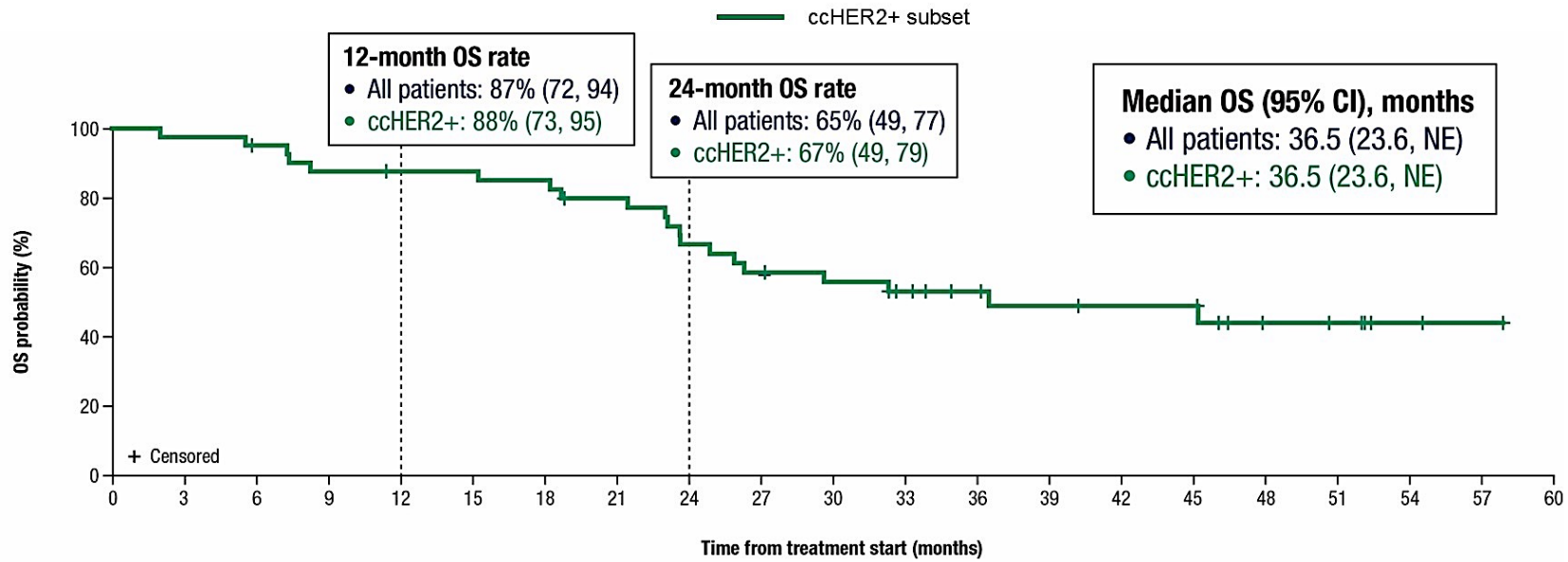
Response-evaluable patients were those who underwent at least 1 post-baseline response assessment per RECIST v1.1 or discontinued treatment due to clinical progression or death. One patient in the response-evaluable analysis set had a new lesion detected (deemed PD) on an unscheduled visit before the first scheduled tumor scan; however, measurements of this lesion were not available. Hence, this patient was not included in the waterfall plot given the missing post-baseline measurements.
[a]BOR is defined as the best response documented between the date of first dose and the date of investigator-assessed objectively documented progression, the date of subsequent anticancer therapy, any-cause death, loss to follow-up, or study discontinuation, whichever occurred first. Confirmed BOR is the BOR of a CR or PR per RECIST v1.1 confirmed ≥28 days after the first documentation; [b]Disease control was defined as a BOR of SD or confirmed CR or PR; [c]Defined as achieving a BOR of SD, non-CR, or non-PD for ≥24 weeks or confirmed CR or PR.
BOR, best overall response; cBOR, confirmed BOR; CBR, clinical benefit rate; CI, confidence interval; cORR, confirmed ORR; CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; NA, not available; SD, stable disease.

Elimova E et al. ASCO 2025;Abstract 4013

HERIZON-GEA-01: Survival



PFS



OS

Elimova E et al. ASCO 2025;Abstract 4013

HERIZON-GEA-01: Safety Outcomes

	All Patients (N = 46)	
TRAEs (any component)[a], n (%)	**Any grade**	**Grade 3 or 4**
Any	46 (100)	30 (65)
Serious	8 (17)	8 (17)
Most Common[b]		
Diarrhea	43 (93)	18 (39)
Nausea	37 (80)	3 (7)
Peripheral sensory neuropathy	30 (65)	0
Fatigue	24 (52)	2 (4)
Decreased appetite	21 (46)	0
Vomiting	16 (35)	4 (9)
Hypokalemia	14 (30)	10 (22)
Stomatitis	13 (28)	0
Anemia	12 (26)	1 (2)
Dysgeusia	11 (24)	0
Decreased neutrophil count	10 (22)	2 (4)
Hypomagnesaemia	10 (22)	1 (2)
PPE syndrome	10 (22)	1 (2)
IRRs	10 (22)	0

- **There were no treatment-related deaths**
- **AESIs:**
  - IRRs (10 [22%])
  - Non-infectious pulmonary toxicities (1 [2%])
  - No left ventricular dysfunction or grade ≥2 heart failure

After the first 25 patients were enrolled, protocol was amended to omit 5-FU bolus (mFOLFOX6) and to introduce mandatory antidiarrheal prophylaxis (all patients)

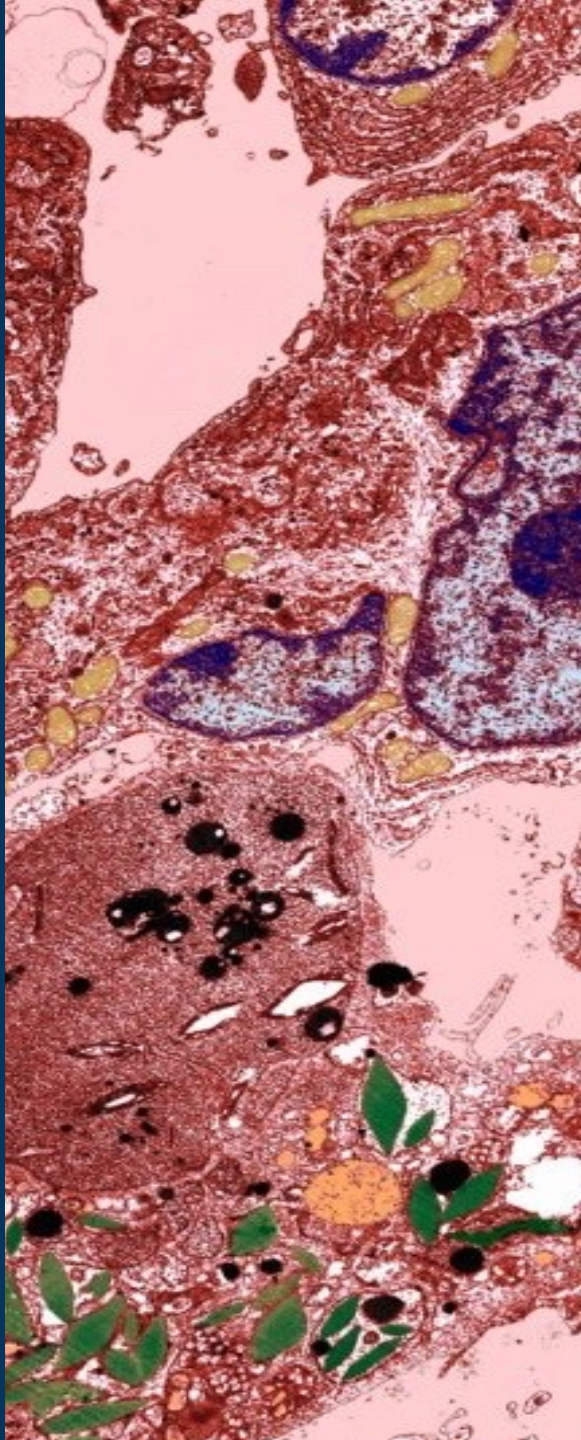
- Loperamide 4 mg twice daily starting on the first treatment day of cycle 1 and continuing for at least 7 days

After introduction of mandatory antidiarrheal prophylaxis, patients had:

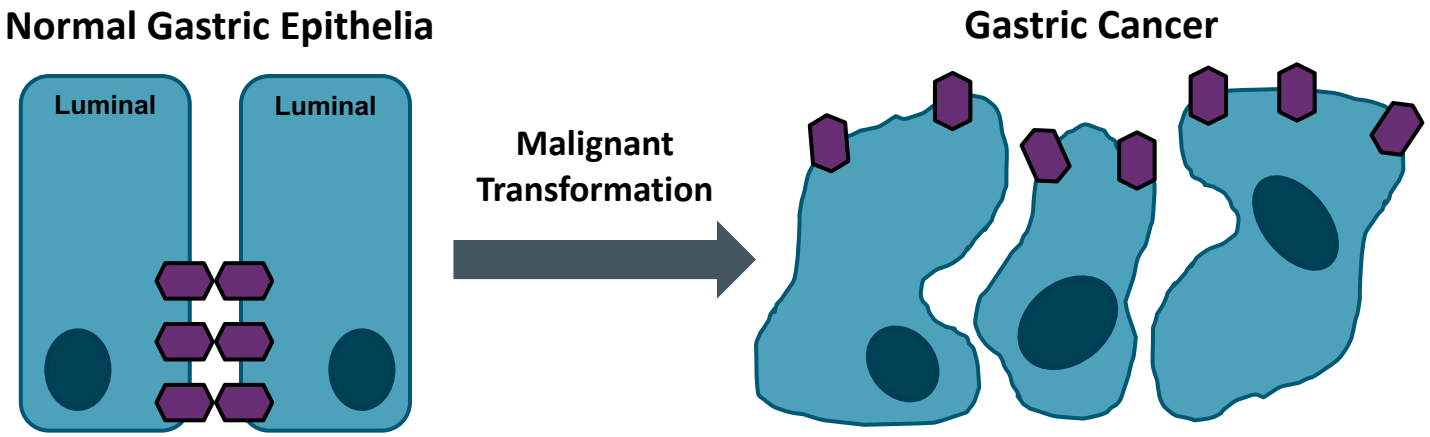
- Lower incidence of any-cause grade 3 diarrhea (56% before vs 24% after)
- No discontinuations due to diarrhea (2 patients before vs 0 patients after)

[a]TRAEs could be related to zanidatamab and/or chemotherapy; [b]Any-grade TRAEs occurred in ≥20% of all patients.
AESI, adverse event of special interest; IRR, infusion-related reactions; PPE, palmar-plantar erythrodysesthesia; TRAE, treatment-related adverse event.

Targeting Claudin18.2 in Gastroesophageal Adenocarcinoma



Claudin18.2: Leveraging Biology

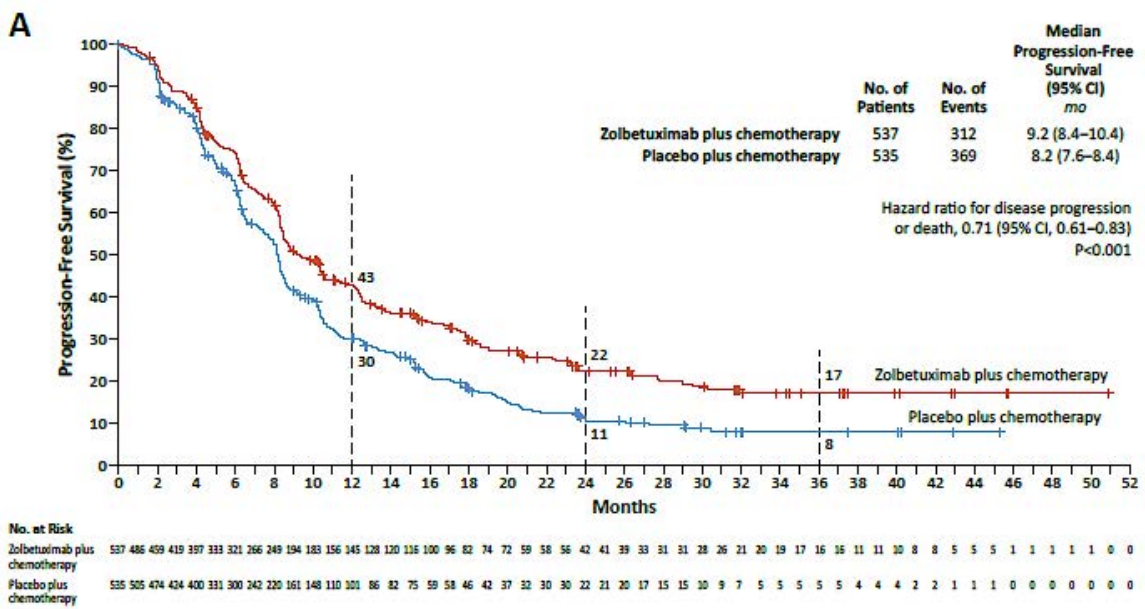


- Claudin18.2 is a major structural component of intercellular tight junctions
- Not routinely expressed in any normal tissue outside gastric mucosa (cancer-restricted antigen)
- Broadly expressed in several tumor types including gastric, GEJ, biliary, and pancreatic

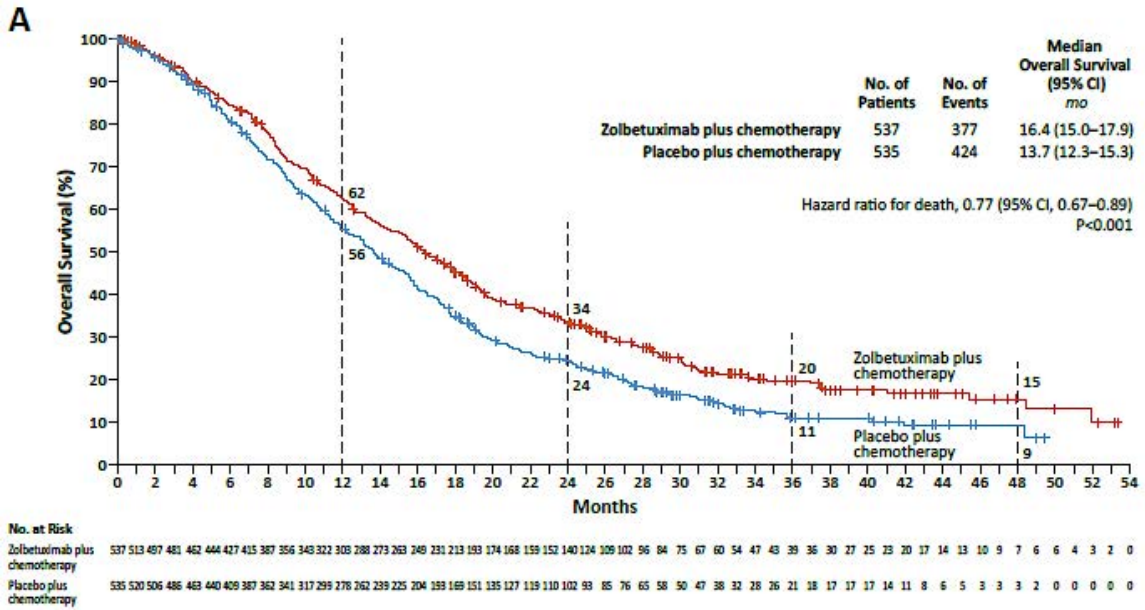
Baek. Anticancer Res. 2019;39:6973.

SPOTLIGHT and GLOW – Combined Final Analysis

Progression Free Survival



Overall Survival



Total Population – 1072 (n=537 Zolbe + chemo)
PFS HR 0.71 (0.61-0.83), p < 0.001
OS HR 0.77 (0.67-0.89), p < 0.01

Measurable disease (n=820),
Complete Response - 5.2%. v. 3.1%
Partial Response - 52.2%. v. 52.2%
Overall Response Rate - 57.4%. Vs. 55.3%

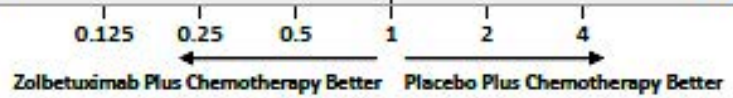
Key Toxicity

≥ Grade 3 toxicity higher than control
Nausea - 12.6%. vs. 4.7%
Vomiting 14.3%. vs. 4.9%
Decreased appetite - 6.4% vs. 2.5%

Shitara K, Shah MA NEJM Letter 2024

SPOTLIGHT and GLOW – Combined Final Analysis

Subgroup	Zolbetuximab Plus Chemotherapy (no. events/no. patients)	Placebo Plus Chemotherapy (no. events/no. patients)	Hazard Ratio (95% CI)
All patients	377/537	424/535	0.77 (0.67–0.89)
Age			
≤65 yr	241/357	284/361	0.73 (0.62–0.87)
>65 yr	136/180	140/174	0.85 (0.67–1.07)
Sex			
Male	243/335	272/331	0.78 (0.66–0.93)
Female	134/202	152/204	0.76 (0.60–0.96)
Region			
Asia	166/245	190/247	0.71 (0.58–0.88)
Non-Asia	211/292	234/288	0.83 (0.69–1.00)
Number of metastatic sites			
0–2	274/408	312/407	0.76 (0.65–0.90)
≥3	103/129	112/128	0.78 (0.59–1.02)
Prior gastrectomy			
No	276/378	303/378	0.83 (0.71–0.98)
Yes	101/159	121/157	0.65 (0.50–0.85)
Lauren classification			
Diffuse	120/169	164/217	0.82 (0.65–1.04)
Intestinal	75/106	90/107	0.65 (0.47–0.88)
Mixed/other	96/135	85/103	0.88 (0.66–1.18)
Primary site			
Stomach	301/438	331/419	0.72 (0.62–0.84)
Gastroesophageal junction	76/99	93/116	1.02 (0.76–1.39)
Race			
White	175/234	183/224	0.89 (0.72–1.09)
Asian	171/254	196/255	0.69 (0.56–0.85)



Key Points

- Broad activity
- ? GEJ resistance?
- ? White people?

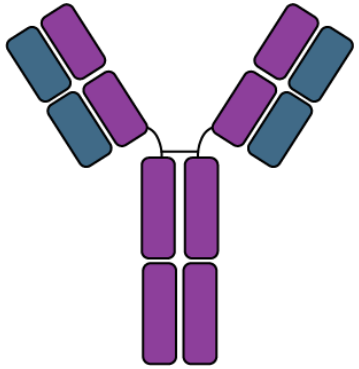
Validated Target

Shitara K, Shah MA NEJM Letter 2024

CLDN18.2 is a valid target:
Emerging CLDN18.2 Targeted Treatments

Monoclonal antibody

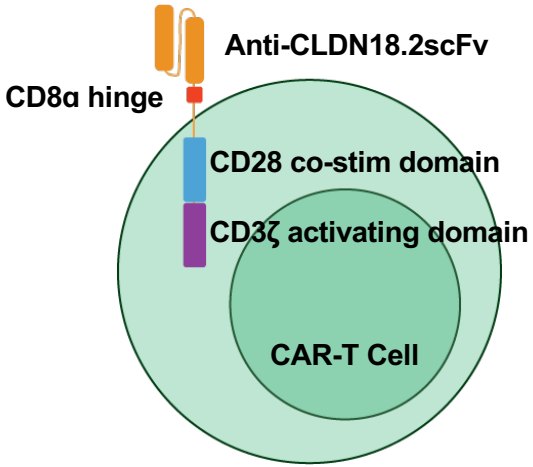
- Humanized mAb
- Engineered mAb



Fc mutations to enhance ADCC

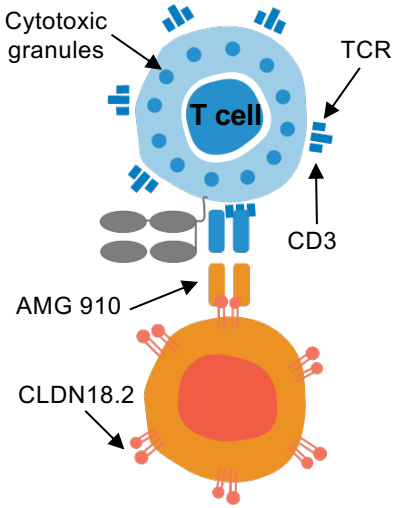
- IMAB306/zolbetuximab TST-001
- ABI011, MIL93, ZL1211

CAR-T



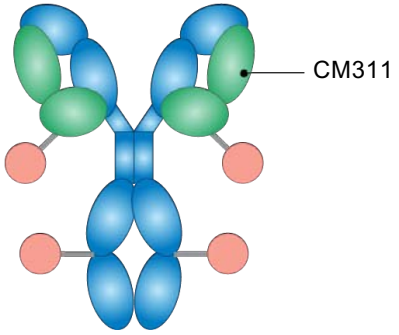
- CT-041, LCAR-C18S
- LY011

BITE Bispecific



- AMG910/ASP2138 (CD3), Q-1802 (PD-L1)
- TJCD4B (4-1BB)
- PT886 (CD47)

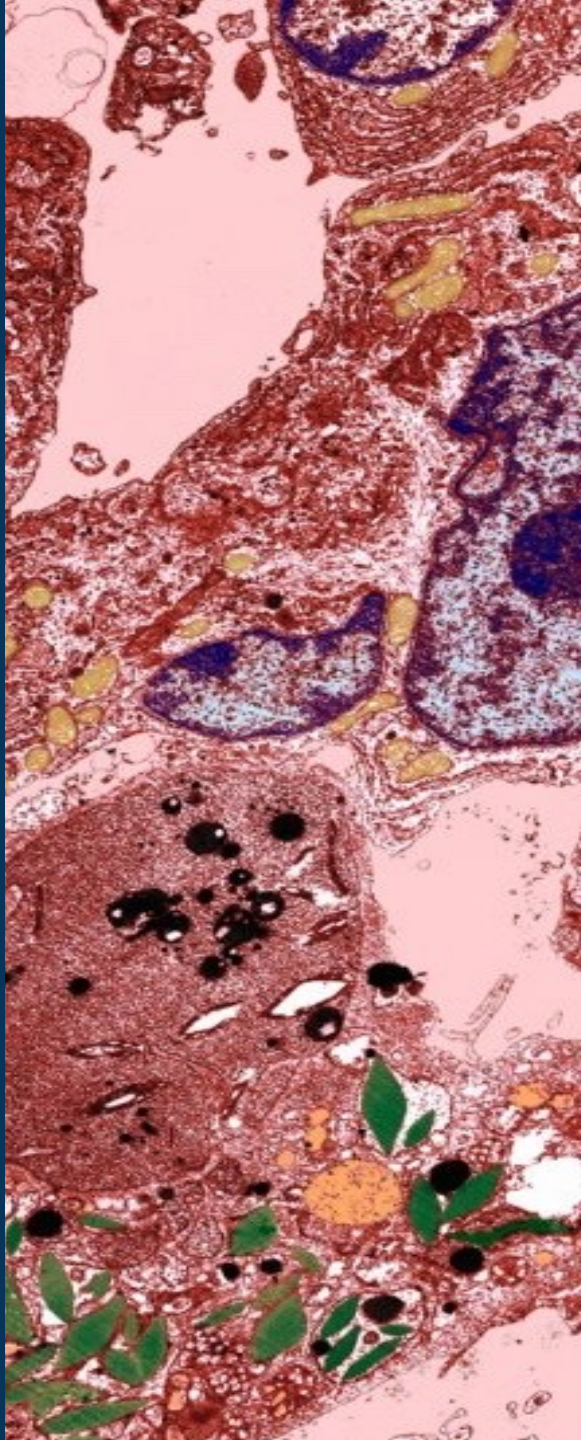
ADCs



CMG901

- CMG901, EO-3021
- TPX4589
- RC118
- LM302
- SOT102
- SKB315
- JS107
- IBI343

Targeting FGFR2 in Gastroesophageal Adenocarcinoma



FIGHT Trial Design

Key Eligibility Criteria

- No prior therapy for unresectable LA or mG/GEJ adenocarcinoma
- RECIST v1.1 evaluable disease
- FGFR2b overexpression by IHC and/or FGFR2 gene amplification by ctDNA*
- ECOG 0/1
- HER2 not positive
- May receive 1 dose of mFOLFOX6

Stratification Factors

- Geographic region
- Single dose of mFOLFOX6 during screening
- Prior adjuvant or neoadjuvant chemotherapy

R
1:1

Double blind, placebo controlled

Bema + mFOLFOX6 (n=77)

VS

Placebo + mFOLFOX6 (n=78)

Treatment Q2W†

Primary endpoint

- Investigator-assessed PFS

Secondary endpoints

- OS
- Response rate

Statistical Plan

Trial initially designed as registrational phase 3 (n=548) with 2-sided **α** 0.05 amended after enrolling n=155 to a proof-of-concept phase 2 with prespecified statistical assumptions of:

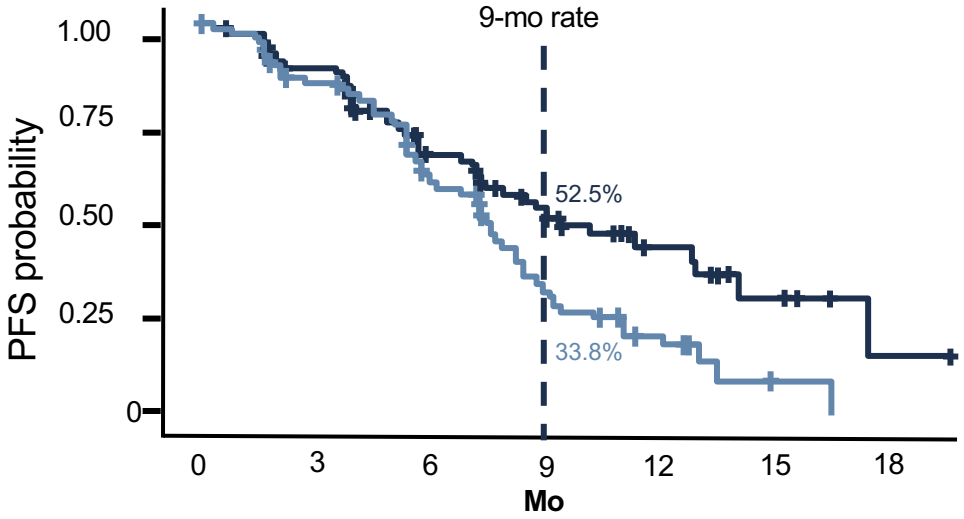
- Hierarchical sequential testing: PFS, then OS/ORR
- ≥84 events to demonstrate benefit at a HR ≤0.76 for PFS at 2-sided **α** of 0.2

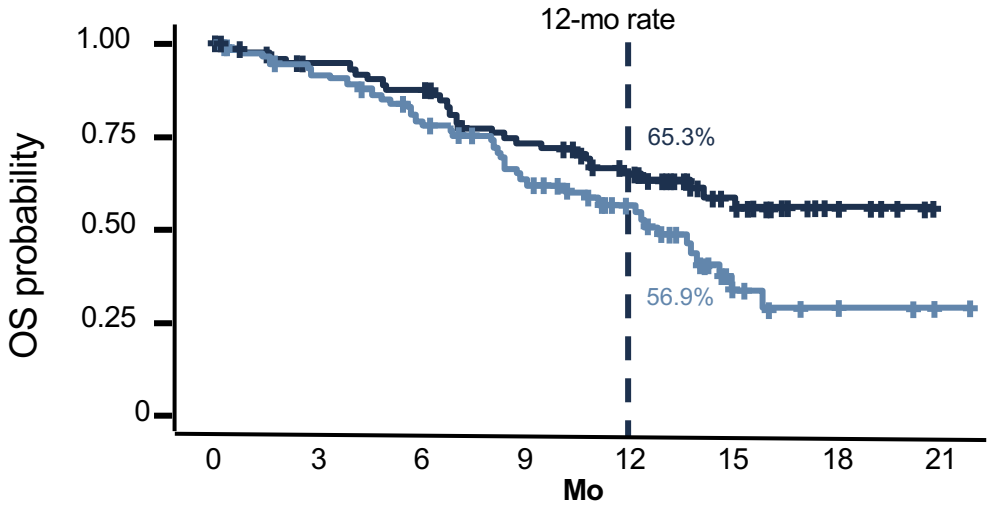
*Central testing: IHC stain (Ventana): cut-off any 2+/3+; circulating tumor DNA (PGDx): cut-off 1.5X.
†15 mg/kg Q2W with a single 7.5-mg/kg dose on Cycle 1 Day 8.

Wainberg ZA. ASCO GI 2021. Abstract LBA160. Wainberg ZA et al. *Lancet Oncol*. 2022;23(11):1430-40.

FIGHT: First-Line Bemarituzumab + mFOLFOX6 vs Placebo + mFOLFOX6 in Advanced Gastric/GEJ Cancer

- Randomized phase 2 trial of bemarituzumab (anti-FGFR2b antibody) or placebo + (both + mFOLFOX6) for patients with no prior therapy and unresectable LA or mG/GEJ adenocarcinoma with *FGFR2b* overexpression/amplification (N=155)



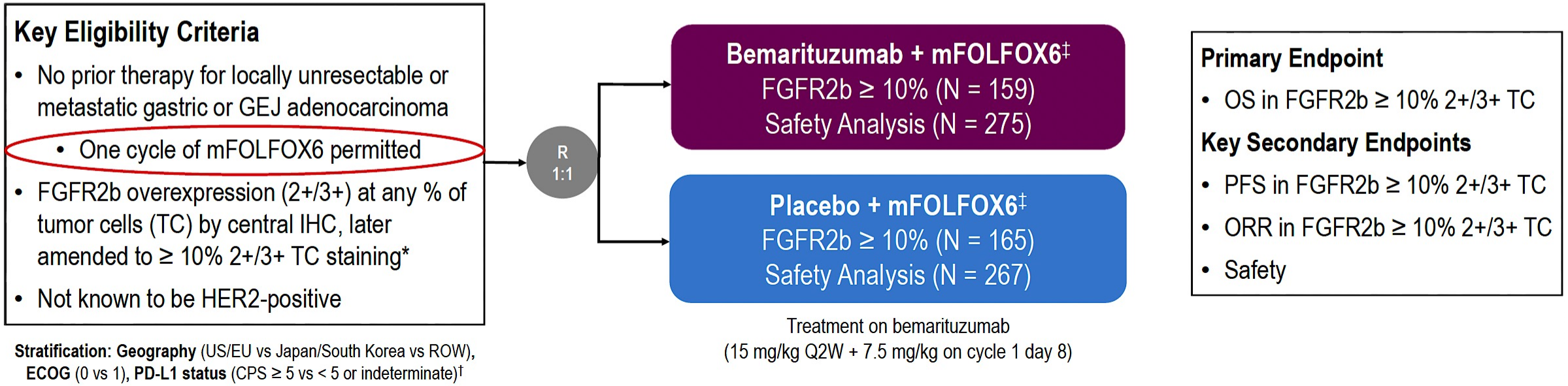


	Bema + mFOLFOX6 (n=77)	Placebo + mFOLFOX6 (n=78)	
Median PFS, mo	9.5	7.4	HR 0.68; *P*=0.0727
Median OS, mo	Not reached	12.9	HR 0.58; *P*=0.0268

Wainberg ZA. ASCO GI 2021. Abstr LBA160. Wainberg ZA et al. *Lancet Oncol*. 2022;23(11):1430-40.

Phase III FORTITUDE-101 Study Design

- **37% PDL1 CPS ≥5, no anti-PD-1 which is now SOC, 50% started with FOLFOX pre randomization**
- **57% Asia, most in China; 40% pts in last 6 months of enrollment with early censoring**
- **Primary OS amended to FGFR2b ≥10% primary OS with n=324**

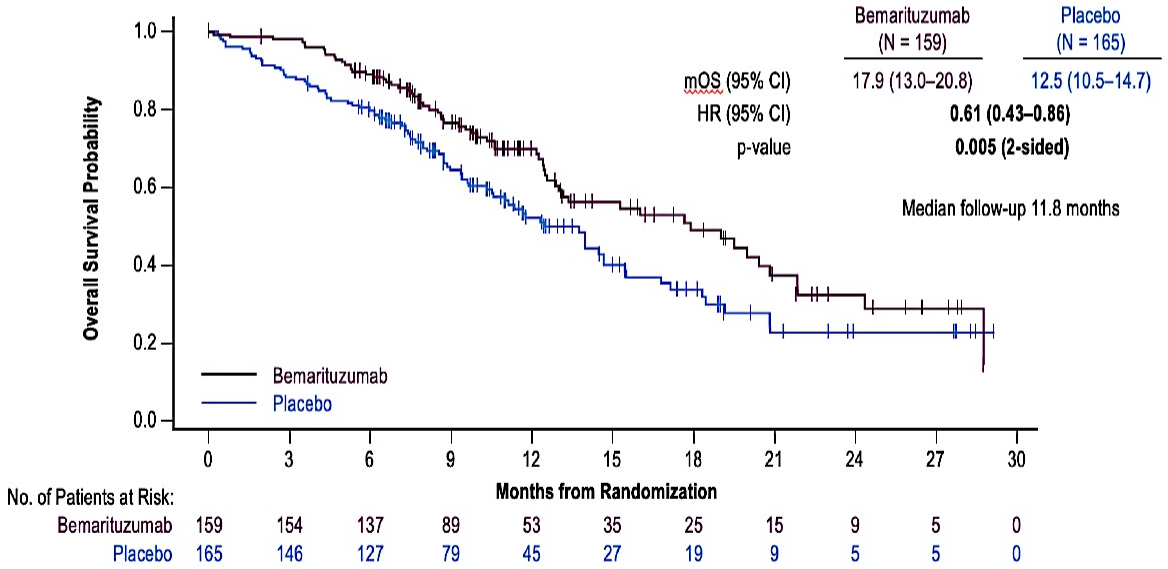


Rha SY et al. ESMO 2025;Abstract LBA10

FORTITUDE 101 KM OS Drift In FGFR2b≥10%

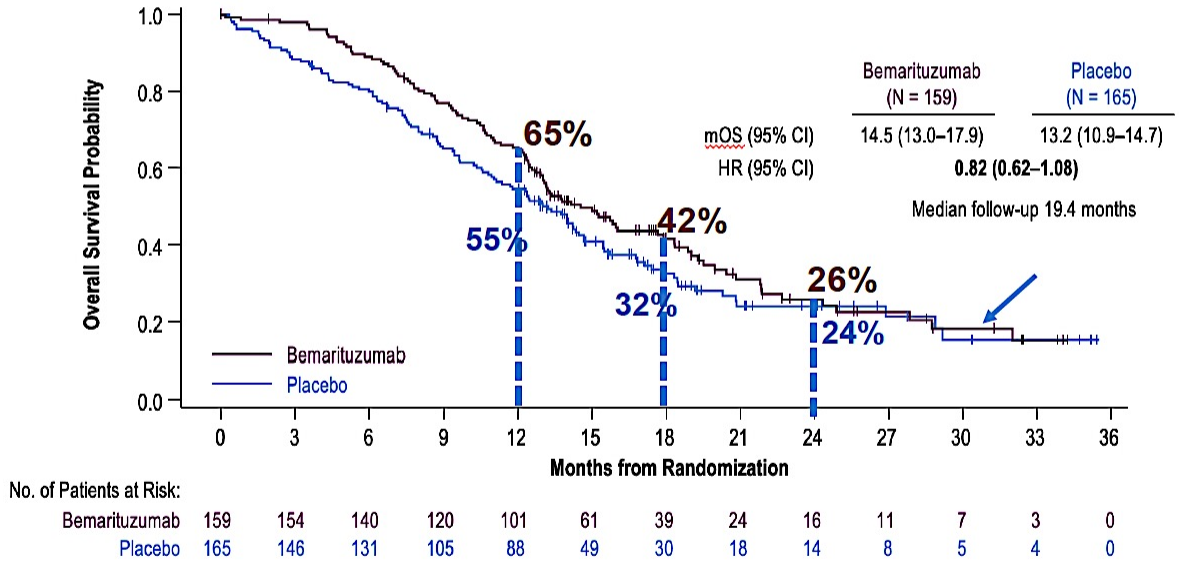
IA='FINAL' but median f/u < 1 yr

Δ 5.4 mo, HR 0.61



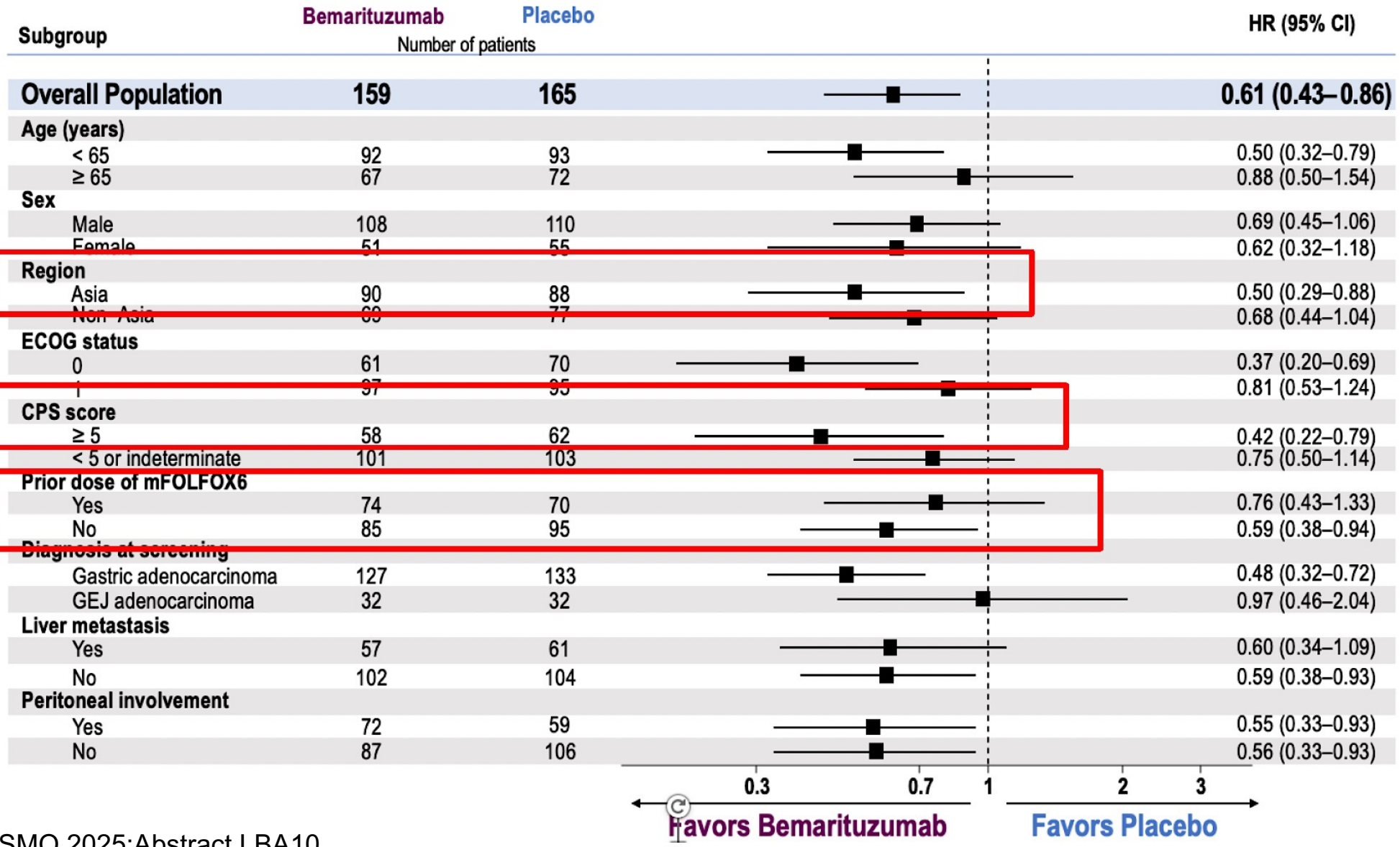
Updated w/ 7.6 months later

Δ 1.3 mo, HR 0.82



Rha SY et al. ESMO 2025;Abstract LBA10

FORTITUDE 101 Subgroup Analysis

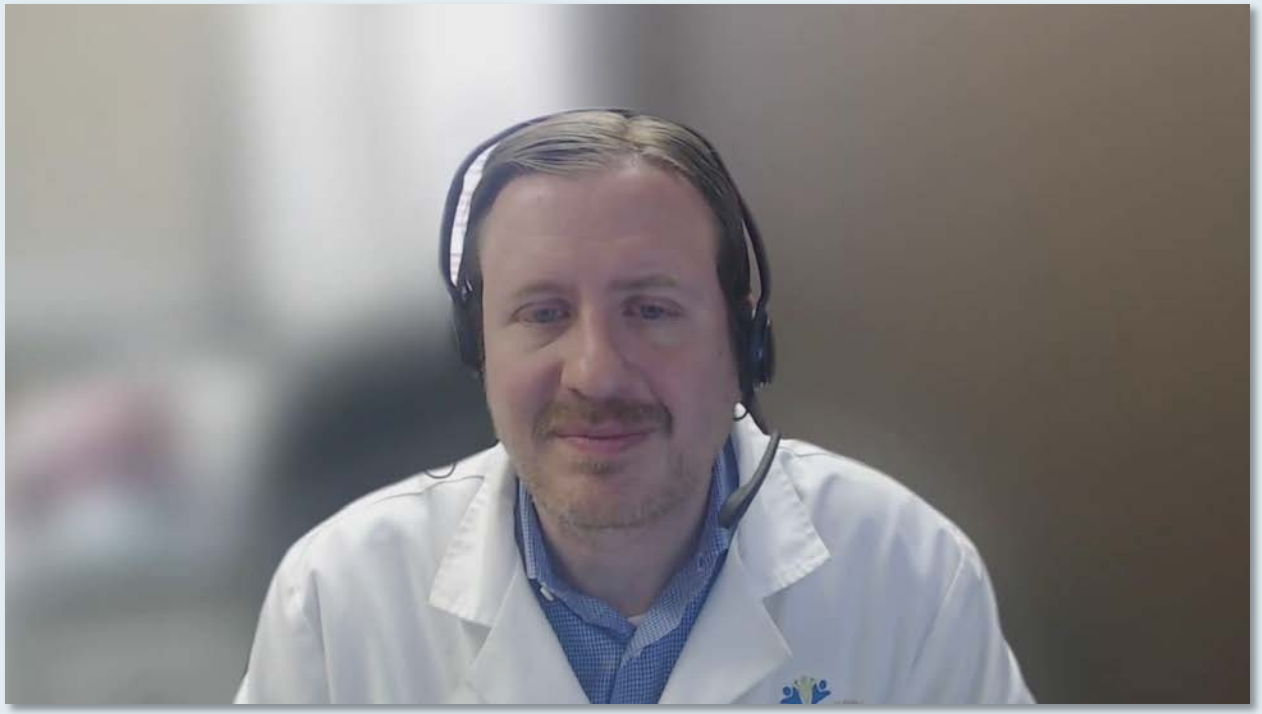


Rha SY et al. ESMO 2025;Abstract LBA10

Conclusions

- Critical to obtain Biomarkers to optimally treat advanced Gastric/ GEJ adenocarcinoma
  - PD-L1
  - HER2
  - CLDN18.2
  - FGFR2
  - TIGIT
- Immunotherapy + chemotherapy for PD-L1 positive Gastric/GEJ adeno
- CLDN18.2 positive tumors – zolbetuximab
- HER2 – chemotherapy + pembrolizumab + trastuzumab

Case Presentation: 51-year-old man with MSI-high localized esophageal adenocarcinoma



Dr Brian Mulherin (Indianapolis, Indiana)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What is the optimal approach to treatment for this patient?

If the MATTERHORN regimen were to become available, would you most likely opt for it or neoadjuvant/ perioperative immune checkpoint inhibition alone for a patient with resectable MSI-H/dMMR disease?

If this patient had received the MATTERHORN approach in the neoadjuvant setting and achieved a pCR, how would you have approached adjuvant therapy? What if he had received neoadjuvant immunotherapy only without chemotherapy?

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

If the MATTERHORN regimen were to become available for patients, in which patients will you prioritize the use of this strategy? Would you have any hesitation about adding durvalumab to FLOT for a patient with PD-L1-negative disease?

Case Presentation: 68-year-old woman with HER2-positive (IHC 3+) and HER2 TKD-mutant metastatic esophageal adenocarcinoma

Dr Sean Warsch (Asheville, North Carolina)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How would you approach maintenance therapy for this patient going forward?

Do you rebiopsy all patients with HER2-positive gastroesophageal cancers after progression on first-line HER2-targeted therapy?

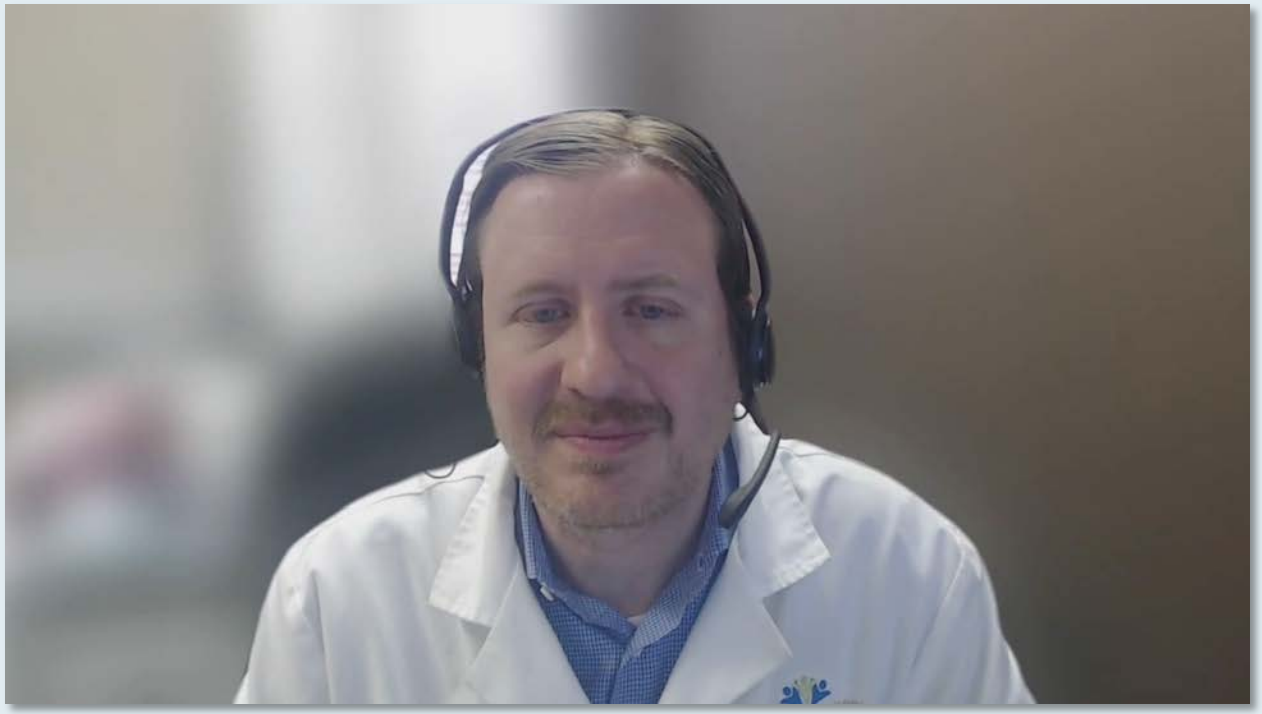
What second-line therapy would you recommend for this patient? After seeing the results of DESTINY-Gastric04, are there any situations in which you would not recommend T-DXd as second-line therapy and opt for ramucirumab/paclitaxel or something else instead?

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How do you manage nausea and other GI toxicities with T-DXd?

Case Presentation: 73-year-old woman with HER2-positive (IHC 3+), PD-L1-negative, CLDN18.2-negative metastatic gastric cancer



Dr Brian Mulherin (Indianapolis, Indiana)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How do you screen for ILD with T-DXd, and do all patients need to be monitored using scans or can they be monitoring clinically with scans ordered only for those with symptoms?

QUESTIONS FOR THE FACULTY

How do you envision zanidatamab being employed in HER2-positive gastroesophageal cancers?

If both zanidatamab and T-DXd were available for HER2-positive gastroesophageal cancers, which one would you prioritize and why? Does zanidatamab offer any mechanistic advantages, given that it is a bispecific antibody?

What are the most common side effects associated with zanidatamab, and how can they be managed? How would you indirectly compare the global tolerability/toxicity of zanidatamab to that of T-DXd?

QUESTIONS FOR THE FACULTY

Given that zanidatamab is available in biliary tract cancers, are there any situations in which you would attempt to access it for a patient with HER2-positive gastroesophageal cancer outside of a clinical trial today?

Case Presentation: 73-year-old woman with metastatic GEJ adenocarcinoma (PD-L1 CPS 15) who begins treatment with FOLFOX/nivolumab and subsequently is found to have CLDN18.2 overexpression

Dr Zanetta Lamar (Naples, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

When do you typically conduct CLDN18.2 testing for your patients with advanced gastroesophageal cancers, and what assay do you use? Is CLDN18.2 reported on commercially available NGS platforms?

For patients with newly diagnosed gastric/GEJ adenocarcinoma that expresses both CLDN18.2 and PD-L1, do you generally opt for anti-PD-1 antibody/chemotherapy or zolbetuximab/ chemotherapy? Would you ever offer both an anti-PD-1 antibody and zolbetuximab?

QUESTIONS FOR THE FACULTY

What would you most likely recommend when this patient's disease progresses? For a patient with CLDN18.2-positive disease who had already received first-line therapy, would you attempt to employ zolbetuximab in a later line?

Case Presentation: 45-year-old man with CLDN18.2-positive metastatic esophageal adenocarcinoma (PD-L1 10%) who receives mFOLFOX6 and zolbetuximab

Dr Jennifer Yannucci (Savannah, Georgia)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What has been your experience with the efficacy and tolerability of zolbetuximab/chemotherapy? Would you have treated this patient any differently?

Have you found any strategies to be particularly helpful for mitigating/managing zolbetuximab-associated nausea and vomiting?

Integrating New Advances into the Care of Patients with Cancer

A Multitumor Symposium in Partnership with the American Oncology Network

CME/MOC, NCPD and ACPE Accredited

Saturday, November 8, 2025
10:00 AM – 3:00 PM CT

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!

Your feedback is very important to us.

How to Obtain CME/MOC, NCPD and ACPE Credit

In-person attendees: Please refer to the program syllabus for the credit link or QR code.

Online/Zoom attendees: The credit link is posted in the chat room.

RTP
RESEARCH
TO PRACTICE