Consensus or Controversy? Documenting and Discussing Investigators' Approaches to the Management of Advanced Gastroesophageal Cancers

Friday, May 29, 2026

11:30 AM – 1:00 PM CT (12:30 PM – 2:00 PM ET)

Faculty

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Eric Van Cutsem, MD, PhD

Moderator

Yelena Y Janjigian, MD

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Faculty

No relevant financial relationships to disclose.

Prof Van Cutsem — Disclosures
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Dr Janjigian — Disclosures
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Dr Kim — Disclosures
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Nonrelevant Financial Relationships	Debbie's Dream Foundation, Degregorio Family Foundation, Gastric Cancer Foundation, National Cancer Institute/National Institutes of Health, NCCN (member of Gastric and Esophageal Guidelines Committees), Stand Up 2 Cancer/AACR, Torrey Coast Foundation

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Dr Wainberg — Disclosures
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Contracted Research	Arcus Biosciences, Bristol Myers Squibb
Data and Safety Monitoring Boards/Committees	AstraZeneca Pharmaceuticals LP, Pfizer Inc

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Research To Practice President Neil Love, MD — Disclosures

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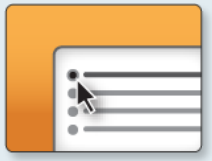

Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

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

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

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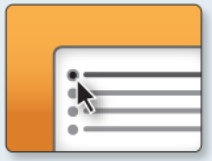

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Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

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About the Enduring Program

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

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Friday May 29	**Gastroesophageal Cancers** 11:30 AM – 1:00 PM CT (12:30 PM – 2:00 PM ET)
	Non-Small Cell Lung Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	Chronic Lymphocytic Leukemia 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	Colorectal Cancer 6:30 PM – 8:00 PM CT (7:30 PM – 9:00 PM ET)
Saturday May 30	**Ovarian Cancer** 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Small Cell Lung Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday May 31	**Oral SERDs and Agents Targeting the PI3K/AKT/mTOR Pathway for Breast Cancer** 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Endometrial Cancer 7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)
	CAR T-Cell Therapy and Bispecific Antibodies for Non-Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 1	**ADCs for Breast Cancer** 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Novel Therapies for Non-Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Relapsed/Refractory Multiple Myeloma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 2	**Myelofibrosis (Webinar)**

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Agenda

Module 1: HER2-Targeted Approaches in Advanced Gastroesophageal Cancers — Prof Van Cutsem

Module 2: Targeting CLDN18.2 in Advanced Gastroesophageal Cancers — Dr Shah

Module 3: Available Immunotherapeutic Strategies for Advanced Gastroesophageal Cancers — Dr Janjigian

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Agenda

Module 1: HER2-Targeted Approaches in Advanced Gastroesophageal Cancers — Prof Van Cutsem

Module 2: Targeting CLDN18.2 in Advanced Gastroesophageal Cancers — Dr Shah

Module 3: Available Immunotherapeutic Strategies for Advanced Gastroesophageal Cancers — Dr Janjigian

UZ LEUVEN

HER2-Targeted Approaches in Advanced Gastroesophageal Cancers

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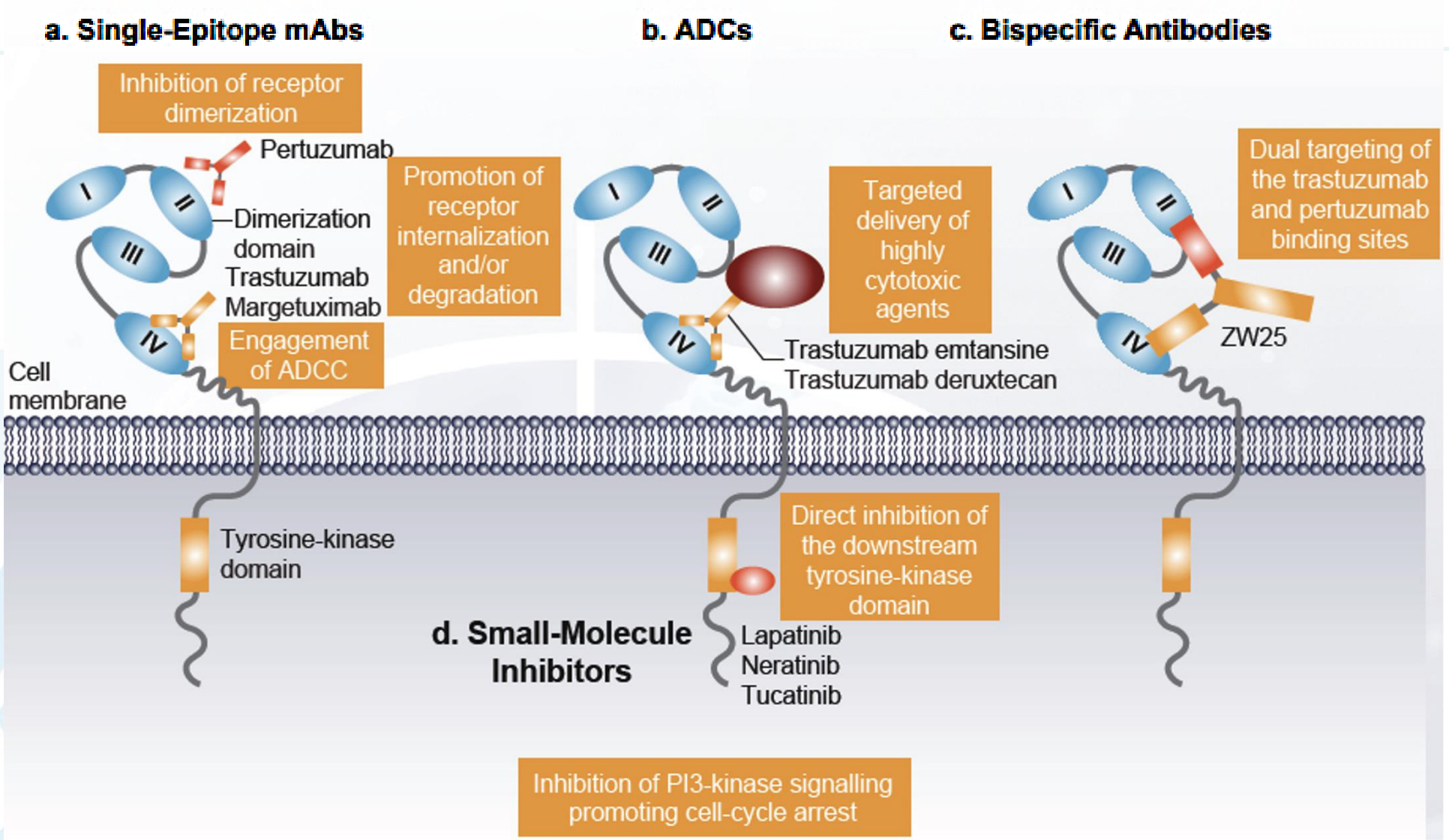
Mechanism of Action of HER2-Targeting Therapies



Oh DY, Bang YJ. Nat Rev Clin Oncol. 2020;17:33-48.

KEYNOTE-811 Global Cohort: Randomized, Double-Blind, Phase 3 Study of dual PD-1 & HER2 blockade

Key Eligibility Criteria

- Unresectable or metastatic gastric or GEJ adenocarcinoma
- No prior systemic therapy in advanced setting
- HER2-positive tumor by central review (IHC 3+ or IHC 2+ ISH+)
- ECOG PS 0 or 1

Stratification Factors

- Geographic region (Australia/Europe/ Israel/North America vs Asia vs ROW)
- PD-L1 CPS (≥1 vs <1)
- Chemotherapy choice (FP vs CAPOX)

R 1:1
N ≈ 692

Pembrolizumab 200 mg IV Q3W
+
Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Placebo IV Q3W
+
Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

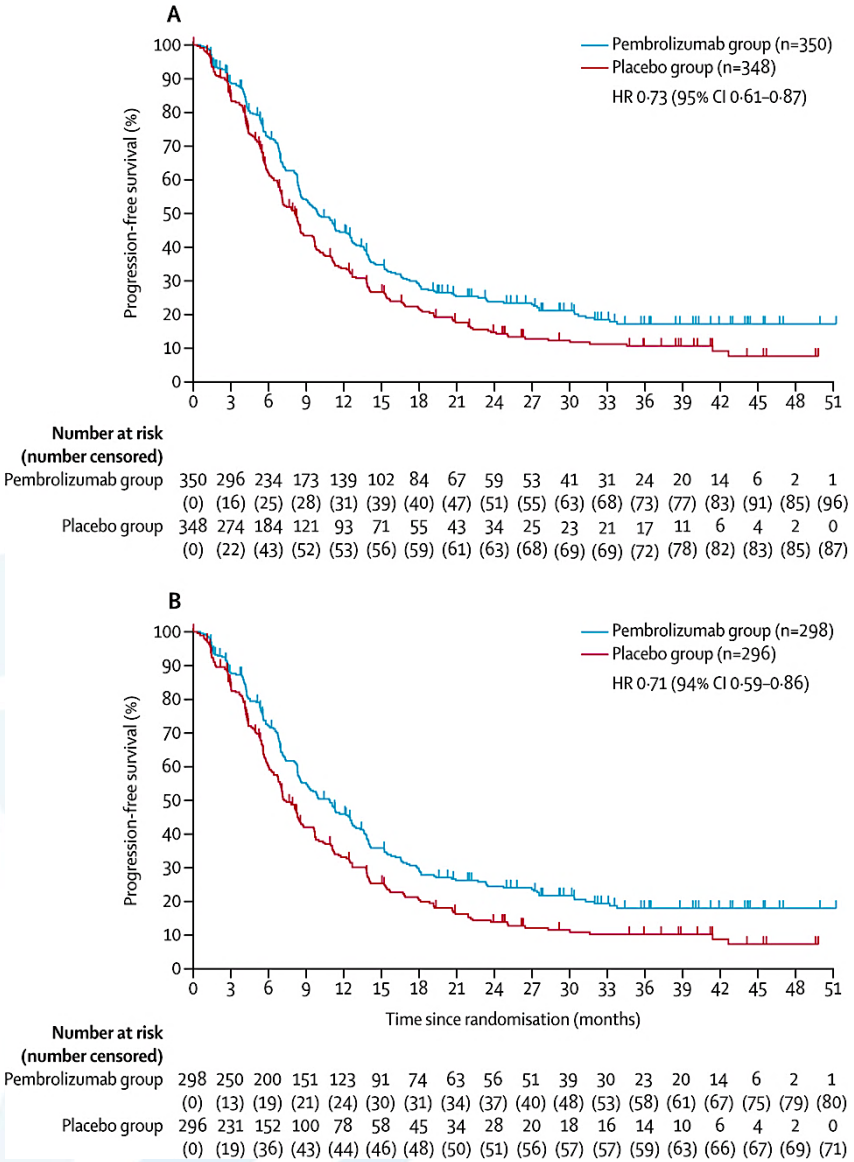
End Points

- **Dual primary:** OS and PFS per RECIST v1.1 by BICR
- **Key secondary:** ORR and DOR per RECIST v1.1 by BICR and safety

[a]Trastuzumab: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W.
BICR, blinded independent central review; CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100). KEYNOTE-811 ClinicalTrials.gov identifier, NCT03615326.

Yanjigan Y, …. Van CutsemE et al, ESMO GI/WCIGC Ann Onc 2021,LBA4 & Nature Medicine dec 2021

KEYNOTE-811 Global Cohort: Randomized, Double-Blind, Phase 3 Study of dual PD-1 & HER2 blockade



Progression-free survival in the intention-to-treat population at the third interim analysis

Kaplan-Meier estimates of progression-free survival in all patients (A) and in the subgroup of patients with tumours with a PD-L1 combined positive score of 1 or more (B). The HR for progression or death is provided on each graph. Tick marks on the Kaplan-Meier curves represent data censored at the time of last imaging assessment HR=hazard ratio.

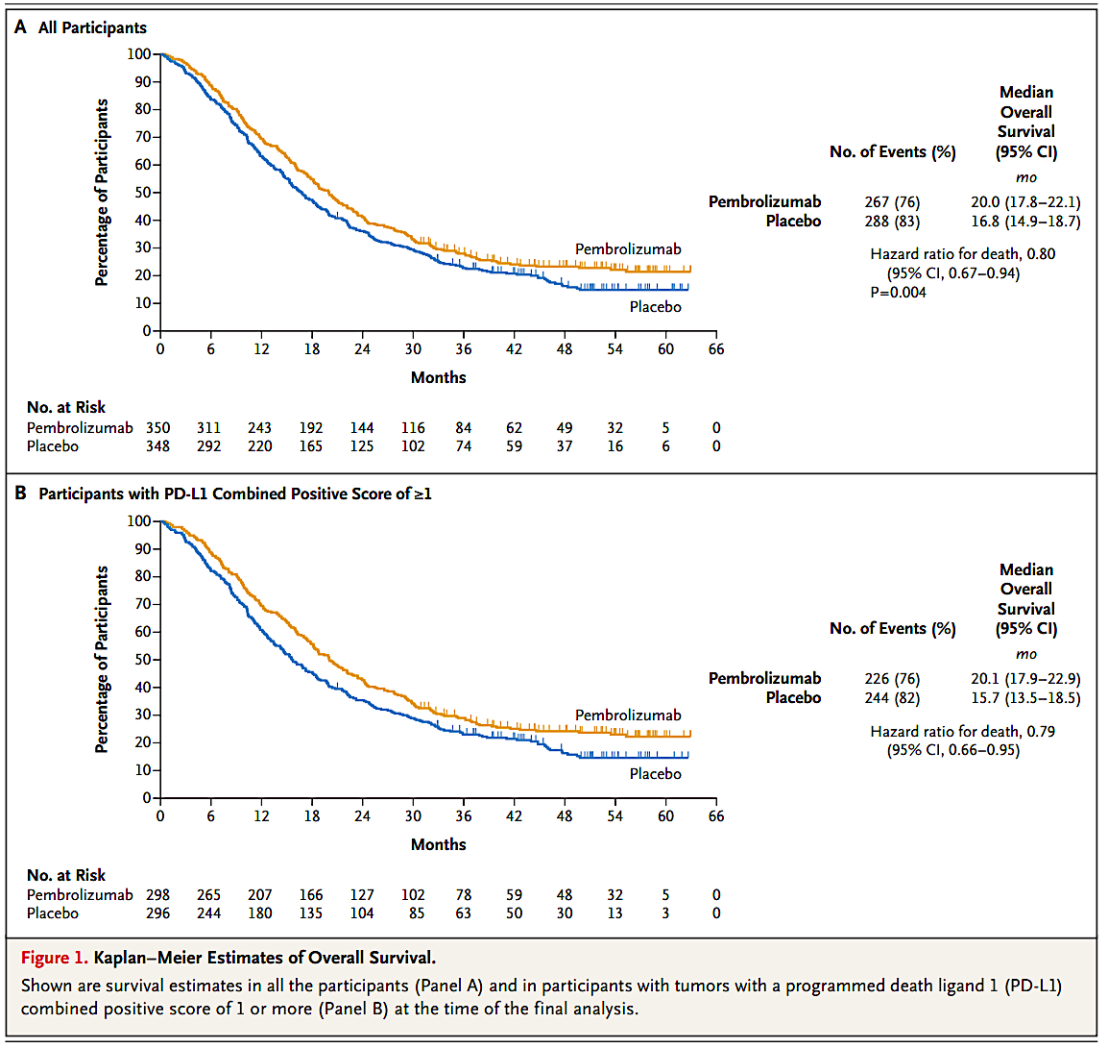


Figure 1. Kaplan–Meier Estimates of Overall Survival.
Shown are survival estimates in all the participants (Panel A) and in participants with tumors with a programmed death ligand 1 (PD-L1) combined positive score of 1 or more (Panel B) at the time of the final analysis.

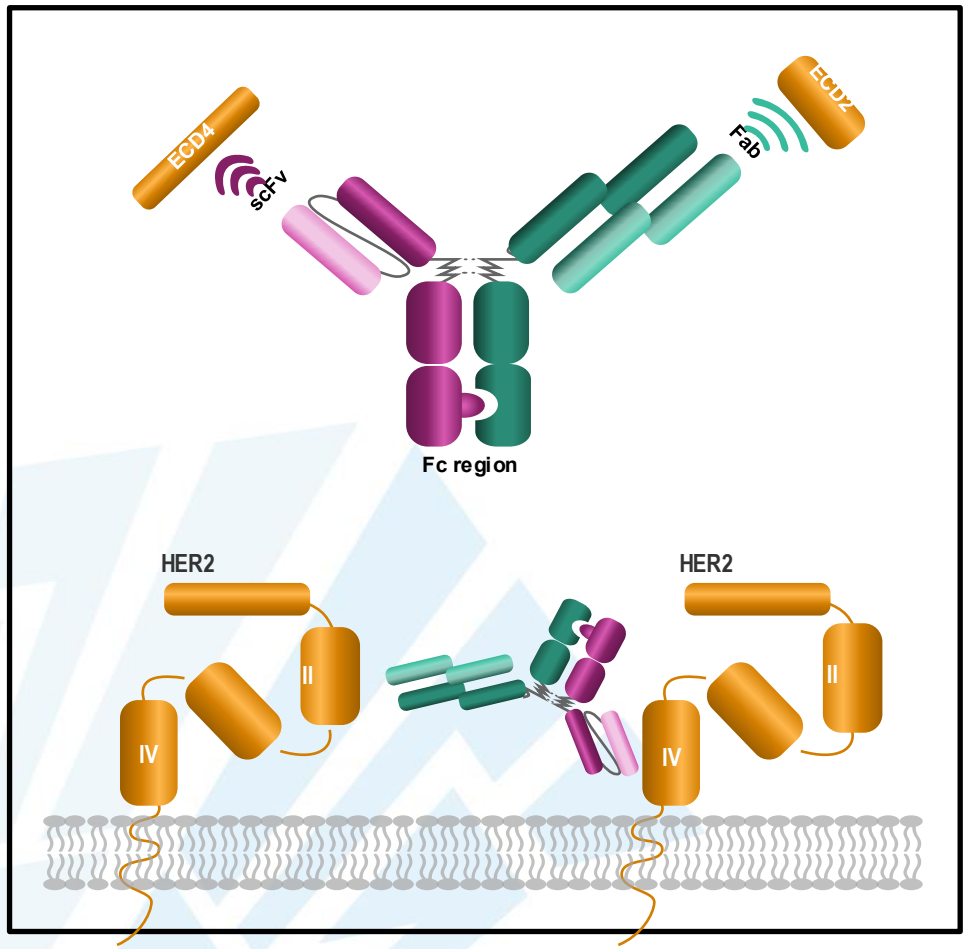
Janjigian Y…. Van Cutsem E et al, Lancet 2023
Janjigian Y…Van Cutsem E et al, New Engl J Med 2024

KEYNOTE-811: 6-year median follow-up

	ITT N = 698		PD-L1 CPS ≥1 n = 594	
	Pembro group n = 350	**Placebo group n = 348**	**Pembro group n = 298**	**Placebo group n = 296**
OS, median (95% CI), months	20.0 (17.8-22.1)	16.8 (14.9-18.7)	20.1 (17.9-22.9)	15.7 (13.5-18.5)
HR (95% CI)	0.81 (0.69-0.95)		0.79 (0.66-0.94)	
PFS, median (95% CI), months	10.0 (8.6-12.2)	8.1 (7.0-8.5)	10.9 (8.5-12.5)	7.3 (6.8-8.4)
HR (95% CI)	0.73 (0.61-0.87)		0.72 (0.60-0.87)	
ORR, % (95% CI)	72.6 (67.6-77.2)	60.1 (54.7-65.2)	73.2 (67.7-78.1)	58.4 (52.6-64.1)
DOR, median (range), months	11.3 (1.1+ to 80.0+)	9.5 (1.4+ to 79.6+)	11.3 (1.1+ to 80.0+)	9.6 (1.4+ to 79.6+)

Kawazoe A… Van Cutsem E et al, ASCO 2026: A4040

HER-2 directed bispecific antibody: Zanidatamab



- Zanidatamab is a humanized dual HER2-targeted bispecific IgG1-like antibody that binds to the HER2 juxtamembrane domain (ECD4) and dimerization domain (ECD2)
- This biparatopic binding enables zanidatamab to crosslink neighboring HER2 proteins, leading to receptor clustering
- The clustering induces potent complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC)

Zanidatamab: FDA& EMA-approved for HER2+ BTC (IHC=3+, previously treated)

Weisser N, et al. Nat Commun. 2023.

HERIZON
GEA-301

HERIZON-GEA-01 Study Design

Global phase 3 trial of zanidatamab + chemotherapy ± tislelizumab vs trastuzumab + chemotherapy in previously untreated patients with HER2+ mGEA

Key Eligibility Criteria

- Age ≥18 years
- Unresectable, locally advanced, recurrent or metastatic GEA
- HER2 IHC 3+ or IHC 2+/ISH+ per central testing
- ECOG PS 0 or 1
- No prior treatment for locally advanced or metastatic disease
- No prior HER2-targeted agents or immunotherapy in any setting

Stratification Factors

- Geographic region
- HER2 status
- ECOG PS

R 1:1:1

N = 914

Arm A: Trastuzumab + chemotherapy[a]

Arm B: Zanidatamab 1800 mg (<70 kg)/2400 mg (≥70 kg) IV Q3W + chemotherapy[a]

Arm C: Zanidatamab 1800 mg (<70 kg)/2400 mg (≥70 kg) IV Q3W + tislelizumab[b] + chemotherapy[a]

Prophylaxis to prevent IRR and diarrhea was mandatory in the zanidatamab-containing arms

CT/MRI[c] Q6W

Treatment until disease progression/death/unacceptable toxicity
Chemotherapy could be discontinued after 6 cycles

Dual Primary Endpoints

- PFS (per BICR)
- OS

Select Secondary Endpoints

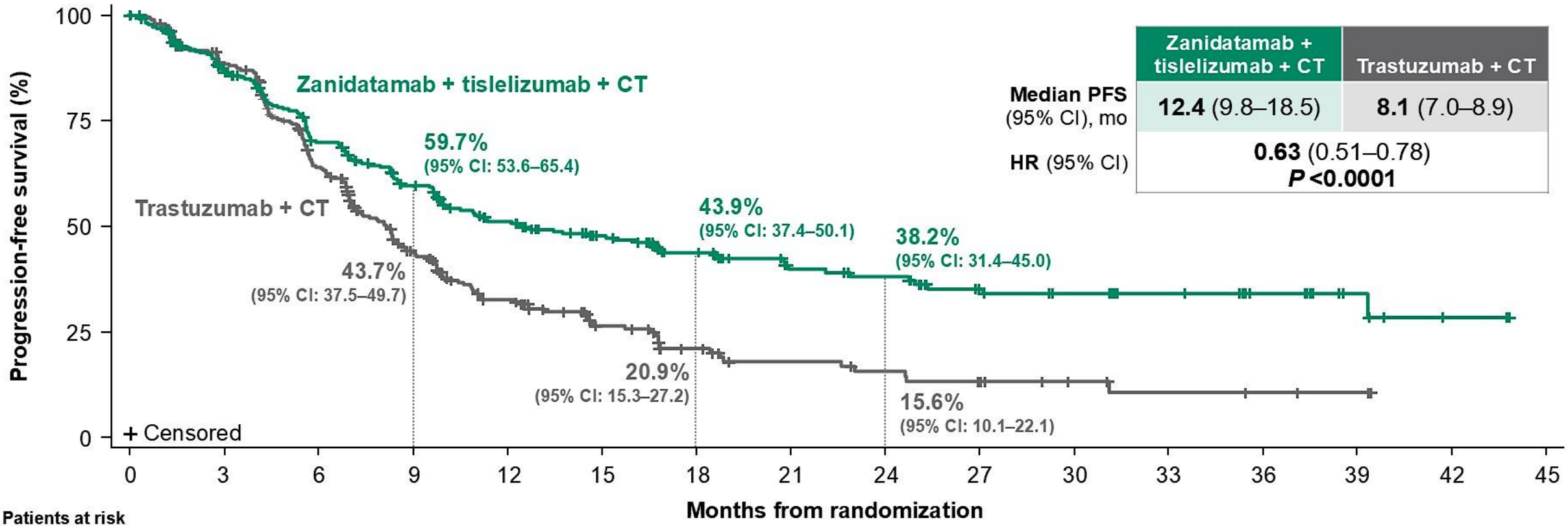
- cORR (per BICR)
- Frequency and severity of AEs

ClinicalTrials.gov: NCT05152147

[a]Physician's choice of capecitabine plus oxaliplatin or 5-fluorouracil plus cisplatin. Chemotherapy was administered for at least 6 cycles or until disease progression, unacceptable toxicity, or another criterion for treatment discontinuation was met.
[b]Tislelizumab 200 mg was administered IV Q3W. [c]CT/MRI scans were performed every 6 weeks for the first 54 weeks, then every 9 weeks.
AE, adverse event; BICR, blinded independent central review; cORR, confirmed objective response rate; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRR, infusion-related reaction; ISH, in situ hybridization; IV, intravenously; mGEA, advanced or metastatic GEA; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomization.

Primary Endpoint: PFS per BICR

Statistically significant and clinically meaningful improvement in PFS with zanidatamab + tislelizumab + CT vs trastuzumab + CT (>4-month prolongation in median PFS)



	Zanidatamab + tislelizumab + CT	Trastuzumab + CT
Median PFS (95% CI), mo	**12.4** (9.8–18.5)	**8.1** (7.0–8.9)
HR (95% CI)	**0.63** (0.51–0.78) ***P*** **<0.0001**	

Patients at risk

Zani + TIS + CT	302	240	183	147	113	90	65	46	42	30	27	20	13	6	2	0
Tras + CT	308	247	168	97	63	37	23	16	13	10	6	4	3	2	0	

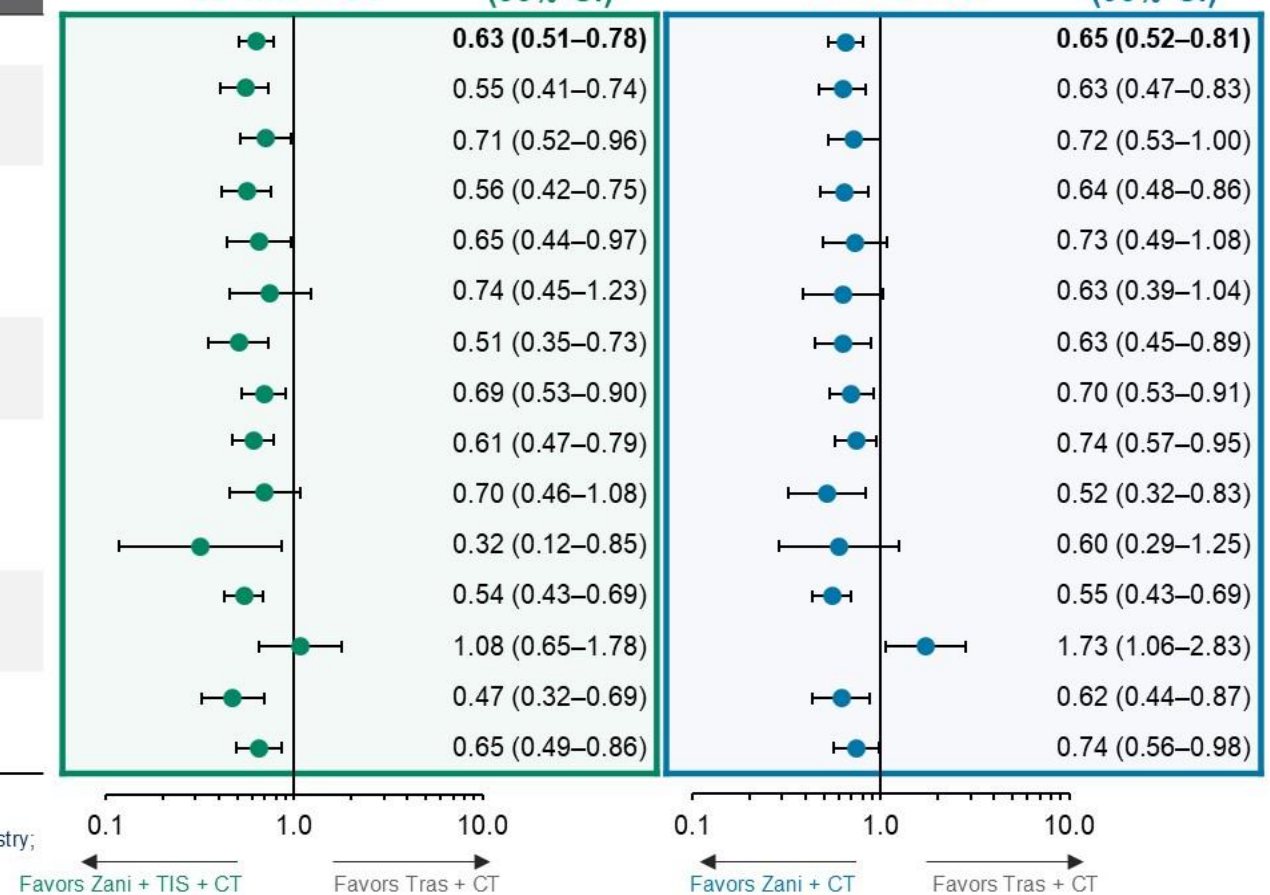
BICR, blinded independent central review; CT, chemotherapy; HR, hazard ratio; PFS, progression-free survival; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

HERIZON
GEA-301

PFS in Key Prespecified Subgroups

Improvements in PFS were generally consistent across major prespecified subgroups

Subgroup	Category	Events/patients: Zanidatamab + tislelizumab + CT	Zanidatamab + CT	Trastuzumab + CT	Zani + TIS + CT vs Tras + CT: PFS HR[a] (95% CI)	Zani + CT vs Tras + CT: PFS HR[a] (95% CI)
All patients		**154/302**	**160/304**	**196/308**	**0.63 (0.51–0.78)**	**0.65 (0.52–0.81)**
Age, years	<65	79/163	94/174	105/162	0.55 (0.41–0.74)	0.63 (0.47–0.83)
	≥65	75/139	66/130	91/146	0.71 (0.52–0.96)	0.72 (0.53–1.00)
Geographic region	Asia	78/159	81/163	106/165	0.56 (0.42–0.75)	0.64 (0.48–0.86)
	EU/NA	47/95	49/91	55/93	0.65 (0.44–0.97)	0.73 (0.49–1.08)
	ROW	29/48	30/50	35/50	0.74 (0.45–1.23)	0.63 (0.39–1.04)
ECOG PS	0	51/121	63/134	74/120	0.51 (0.35–0.73)	0.63 (0.45–0.89)
	1	103/180	97/170	122/188	0.69 (0.53–0.90)	0.70 (0.53–0.91)
Anatomical subtype	Gastric	105/208	112/204	140/226	0.61 (0.47–0.79)	0.74 (0.57–0.95)
	GEJ	43/74	29/61	44/60	0.70 (0.46–1.08)	0.52 (0.32–0.83)
	Esophageal	6/20	19/39	12/22	0.32 (0.12–0.85)	0.60 (0.29–1.25)
HER2 status	IHC 3+	121/251	125/251	167/255	0.54 (0.43–0.69)	0.55 (0.43–0.69)
	IHC 2+/ISH+	33/51	35/51	29/52	1.08 (0.65–1.78)	1.73 (1.06–2.83)
PD-L1 status	TAP <1%	47/90	61/108	71/98	0.47 (0.32–0.69)	0.62 (0.44–0.87)
	TAP ≥1%	91/187	94/178	114/188	0.65 (0.49–0.86)	0.74 (0.56–0.98)



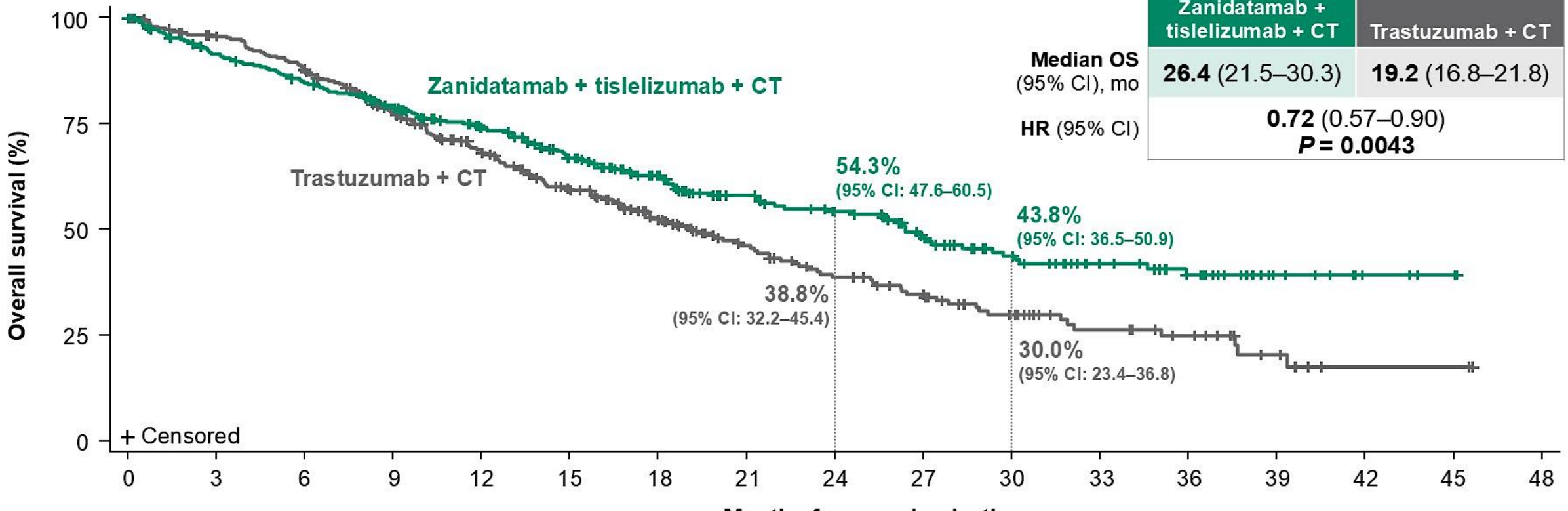
[a]The widths of the confidence intervals were not adjusted for multiplicity and cannot be used to infer treatment effects.
CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridization; NA, North America; PD-L1, programmed death-ligand 1; PFS, progression-free survival; ROW, rest of world; TAP, tumor area positivity; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

HERIZON
GEA-301

Primary Endpoint: Overall Survival

Zanidatamab + tislelizumab + CT demonstrated a statistically significant and clinically meaningful OS benefit with a >7-month improvement in median OS vs trastuzumab + CT

	Zanidatamab + tislelizumab + CT	Trastuzumab + CT
Median OS (95% CI), mo	**26.4** (21.5–30.3)	**19.2** (16.8–21.8)
HR (95% CI)	**0.72** (0.57–0.90)	
	***P* = 0.0043**	



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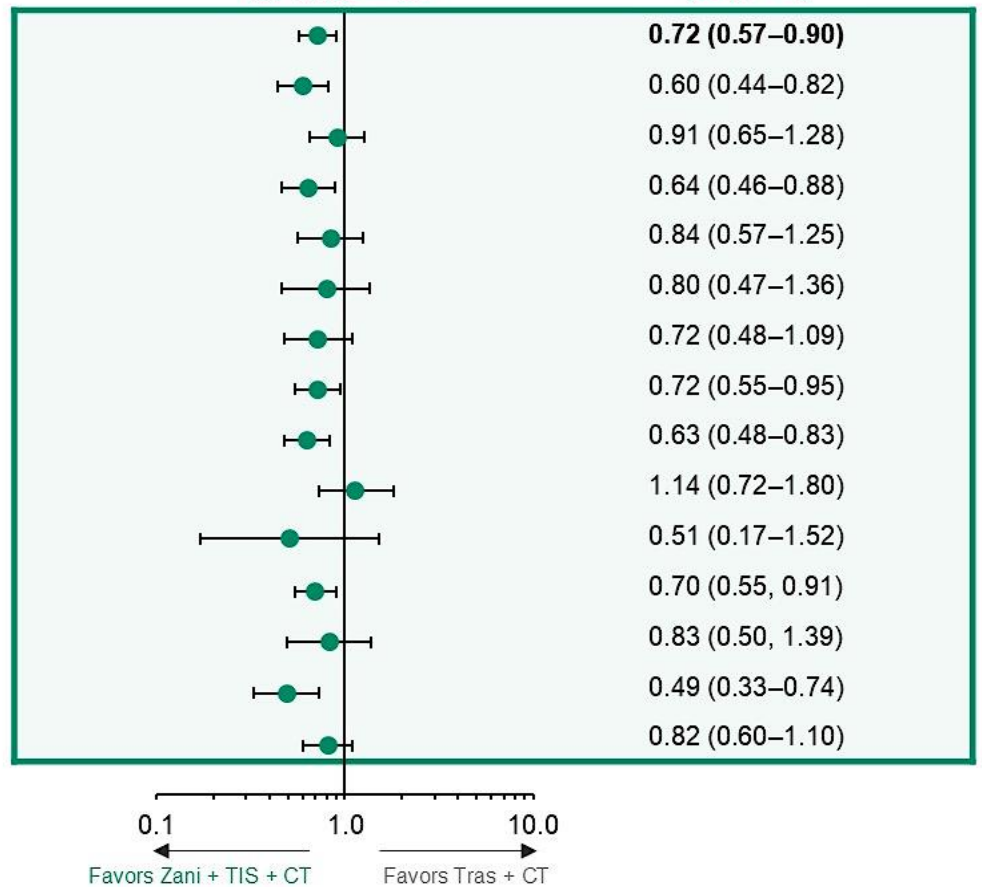
Tras + CT	308	284	261	219	178	140	106	77	61	50	33	22	17	8	2	2	0

CT, chemotherapy; HR, hazard ratio; OS, overall survival; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

OS in Key Prespecified Subgroups

Improvements in OS occurred across major prespecified subgroups, including regions and PD-L1 TAP scores

Subgroup	Category	Events/patients: Zanidatamab + tislelizumab + CT	Events/patients: Trastuzumab + CT	Zani + TIS + CT vs Tras + CT: OS HR[a] (95% CI)
All patients		**134/302**	**170/308**	**0.72 (0.57–0.90)**
Age, years	<65	68/163	99/162	0.60 (0.44–0.82)
	≥65	66/139	71/146	0.91 (0.65–1.28)
Geographic region	Asia	63/159	89/165	0.64 (0.46–0.88)
	EU/NA	46/95	52/93	0.84 (0.57–1.25)
	ROW	25/48	29/50	0.80 (0.47–1.36)
ECOG PS	0	41/121	52/120	0.72 (0.48–1.09)
	1	92/180	118/188	0.72 (0.55–0.95)
Anatomical subtype	Gastric	87/208	127/226	0.63 (0.48–0.83)
	GEJ	42/74	33/60	1.14 (0.72–1.80)
	Esophageal	5/20	10/22	0.51 (0.17–1.52)
HER2 status	IHC 3+	106/251	138/255	0.70 (0.55, 0.91)
	IHC 2+/ISH+	28/51	31/52	0.83 (0.50, 1.39)
PD-L1 status	TAP <1%	38/90	65/98	0.49 (0.33–0.74)
	TAP ≥1%	79/187	92/188	0.82 (0.60–1.10)



[a]The widths of the confidence intervals were not adjusted for multiplicity and cannot be used to infer treatment effects.
CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridization; NA, North America; OS, overall survival; PD-L1, programmed death-ligand 1; ROW, rest of world; TAP, tumor area positivity; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

PD-L1 subgroup analysis from HERIZON-GEA-01.

	Zanidatamab + Tislelizumab + CT	Tras + CT
ITT		
N	302	308
mPFS (95% CI), mo	12.4 (9.8, 18.5)	8.1 (7.0, 8.9)
mOS (95% CI), mo	26.4 (21.5, 30.3)	19.2 (16.8, 21.8)
TAP <1%		
n (%)	90 (29.8)	98 (31.8)
mPFS (95% CI), mo	18.5 (9.7, 25.2)	7.9 (5.8, 9.6)
mOS (95% CI), mo	29.7 (24.7, NE)	15.8 (12.6, 21.4)
CPS <1		
n (%)	78 (25.8)	80 (26.0)
mPFS (95% CI), mo	18.5 (9.7, 25.2)	8.1 (5.8, 9.8)
mOS (95% CI), mo	30.3 (25.7, NE)	15.7 (12.6, 21.4)

- With 26 mo median follow-up, PFS (HR, 0.63; *P* <0.001) and OS (HR, 0.72; *P* = 0.004) were significantly prolonged with zanidatamab + tislelizumab + CT vs tras + CT in the ITT population.
- In pts treated with zanidatamab + tislelizumab + CT, similarly prolonged PFS and OS were observed in PD-L1–negative and PD-L1–positive pts

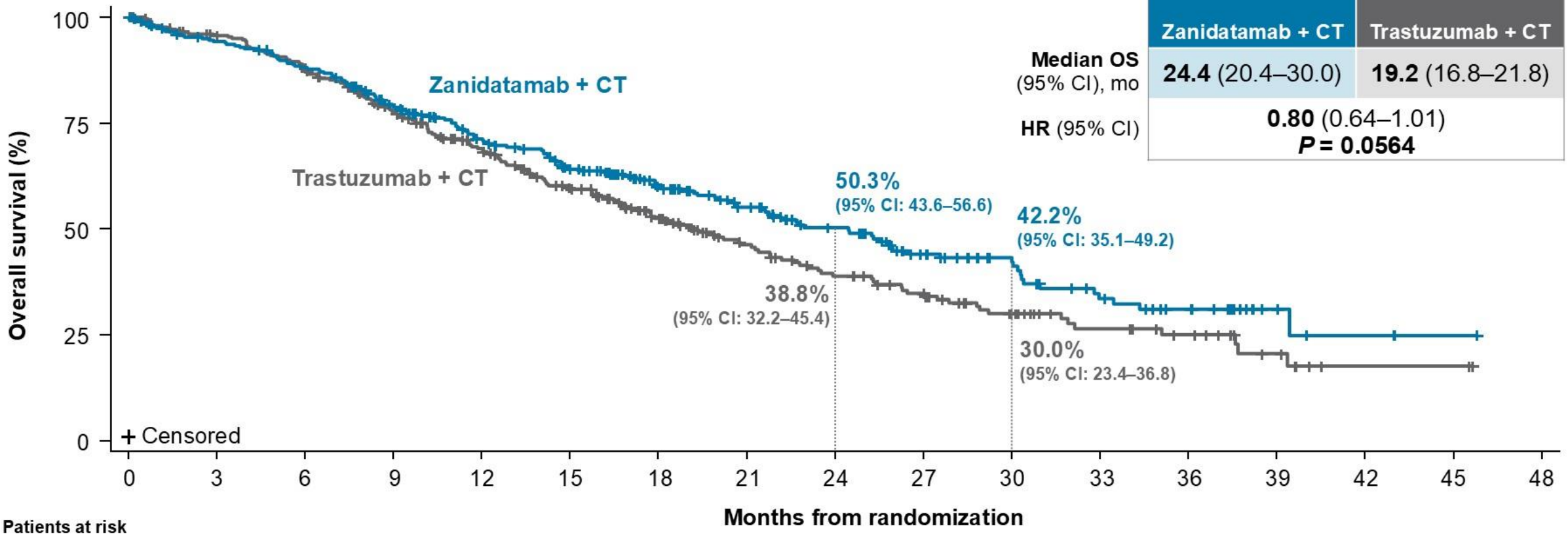
TAP ≥1%		
n (%)	187 (61.9)	188 (61.0)
mPFS (95% CI), mo	11.3 (9.6, 18.5)	8.3 (6.9, 9.7)
mOS (95% CI), mo	26.4 (18.7, 35.9)	21.2 (17.7, 25.2)
CPS ≥1		
n (%)	198 (65.6)	206 (66.9)
mPFS (95% CI), mo	12.3 (9.7, 18.5)	8.2 (6.9, 9.1)
mOS (95% CI), mo	26.4 (18.7, 34.6)	20.8 (17.3, 23.9)

Rha S et al, ASCO 2026, A4010

HERIZON
GEA-301

Primary Endpoint: Overall Survival

At this interim analysis, there was a strong trend toward significance for OS favoring zanidatamab + CT vs trastuzumab + CT (5-month improvement in median OS)



	Zanidatamab + CT	Trastuzumab + CT
Median OS (95% CI), mo	**24.4** (20.4–30.0)	**19.2** (16.8–21.8)
HR (95% CI)	**0.80** (0.64–1.01) ***P* = 0.0564**	

Patients at risk

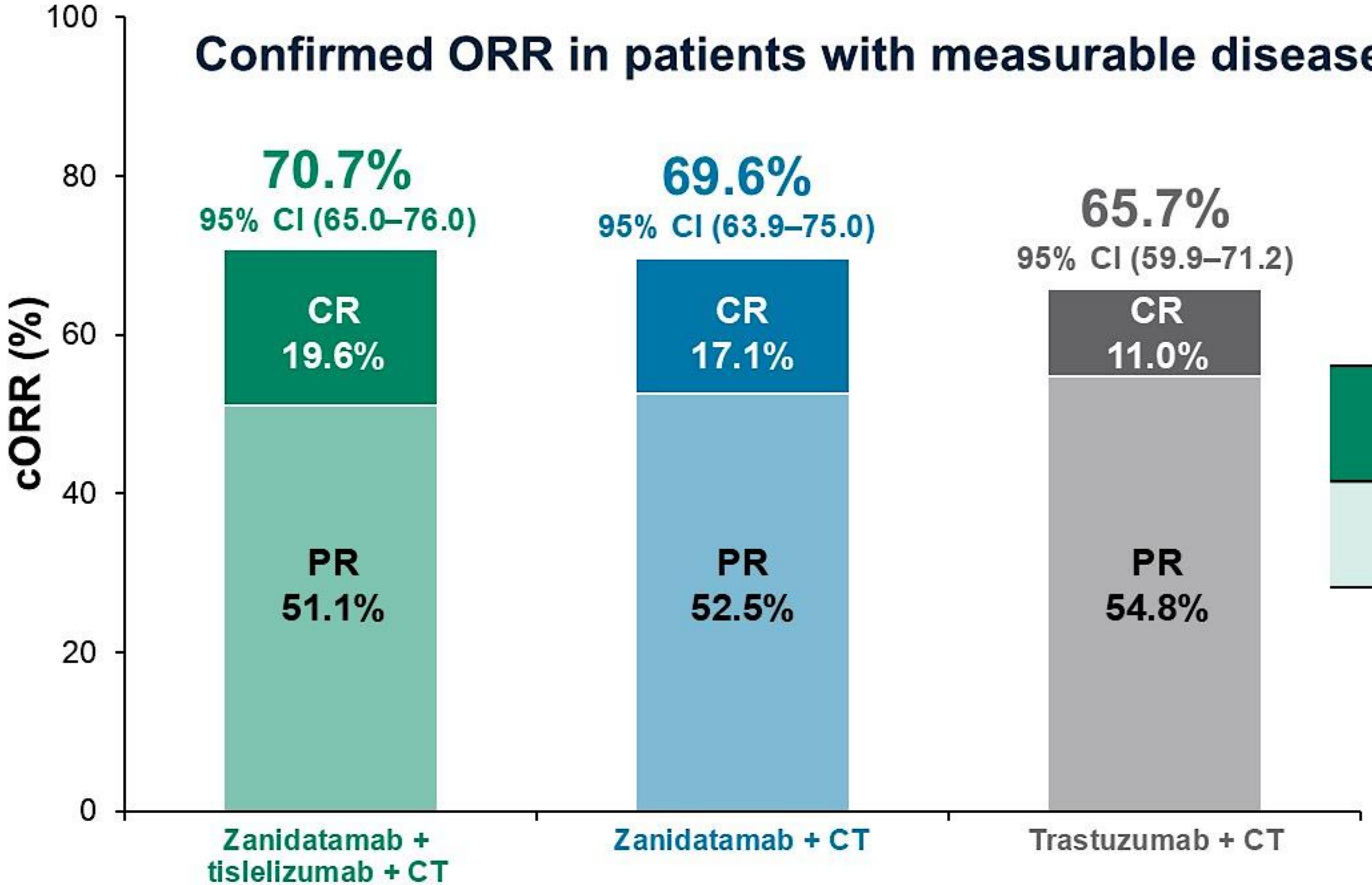
Zani + CT	304	277	257	222	187	156	121	98	78	56	41	28	21	6	3	1	0
Tras + CT	308	284	261	219	178	140	106	77	61	50	33	22	17	8	2	2	0

CT, chemotherapy; HR, hazard ratio; OS, overall survival; Tras, trastuzumab; Zani, zanidatamab.

HERIZON
GEA-301

Key Secondary Endpoint: Antitumor Activity

Responses were deeper and more durable in the zanidatamab-containing arms vs the trastuzumab + CT arm



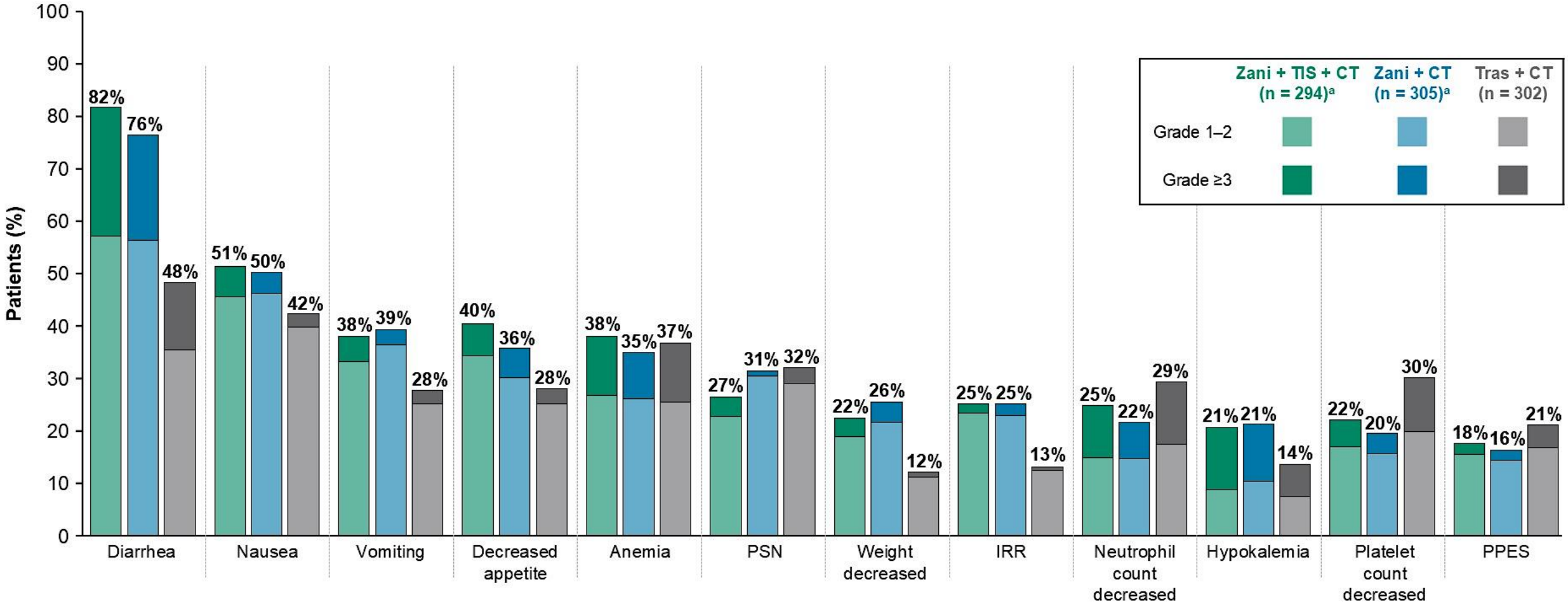
Median DOR (95% CI), mo

Zanidatamab + tislelizumab + CT (n = 195)	Zanidatamab + CT (n = 186)	Trastuzumab + CT (n = 198)
20.7 (12.6–37.7)	**14.3** (11.5–21.9)	**8.3** (6.7–9.8)

cORR was defined as the proportion of patients achieving a best overall response of CR or PR, as determined by BICR using RECIST v1.1, with the response confirmed at a subsequent visit ≥28 days after the initial assessment. DOR was assessed among patients with measurable disease at baseline who achieved a confirmed objective response by BICR per RECIST v1.1. The widths of the confidence intervals were not adjusted for multiplicity and cannot be used to infer treatment effects.
BICR, blinded independent central review; cORR, confirmed ORR; CR, complete response; CT, chemotherapy; DOR, duration of response; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Common TRAEs (≥20% of Patients in Any Arm)

Diarrhea was the most common TRAE in all treatment arms



[a]Five patients who were assigned to the zanidatamab-tislelizumab-chemotherapy arm did not receive tislelizumab. Data from these patients are summarized in the zanidatamab-chemotherapy arm.
CT, chemotherapy; IRR, infusion-related reaction; PPES, palmar-plantar erythrodysesthesia syndrome; PSN, peripheral sensory neuropathy; TIS, tislelizumab; TRAE, treatment-related adverse event; Tras, trastuzumab; Zani, zanidatamab.

Characterization of gastrointestinal adverse events

Diarrhea	Zanidatamab + Tislelizumab + CT n = 294	Zanidatamab + CT n = 305	Tras + CT n = 302
Any-grade, n (%)	244 (83.0)	241 (79.0)[a]	161 (53.3)
Grade 1	79 (26.9)	80 (26.2)	84 (27.8)
Grade 2	92 (31.3)	99 (32.5)	38 (12.6)
Grade ≥3	73 (24.8)	61 (20.0)	39 (12.9)
Time to first onset, n (%), wk			
≤3	188 (77.0)	192 (79.7)	108 (67.1)
>3 to ≤6	25 (10.2)	27 (11.2)	22 (13.7)
>6 to ≤9	7 (2.9)	14 (5.8)	11 (6.8)
>9 to ≤12	4 (1.6)	4 (1.7)	2 (1.2)
>12 to ≤18	8 (3.3)	3 (1.2)	7 (4.3)
>18	12 (4.9)	1 (0.4)	11 (6.8)
Duration of first onset, median (95% CI), wk	2.0 (1.6, 2.6)	2.4 (1.9, 2.9)	1.4 (1.0, 2.1)

- In zanidatamab-treated pts, most diarrhea events were grade 1/2, and first-onset events tended to occur in cycle 1 and resolved in <3 wk.
- Diarrhea rarely led to zanidatamab discontinuation.
- The safety of zanidatamab-containing regimens appears favorable given the survival benefits;
- Diarrhea should be managed with prophylactic loperamide and CT dose modifications as needed.

Elimova E et al, ASCO 2026, A 4042

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan or Ramucirumab plus Paclitaxel in Gastric Cancer

K. Shitara,[1] E. Van Cutsem,[2,3] M. Gümüş,[4,5] S. Lonardi,[6] C. de la Fouchardière,[7] C. Coutzac,[7] J. Dekervel,[2,3] D. Hochhauser,[8] L. Shen,[9,10] W. Mansoor,[11] B. Liu,[12] L. Fornaro,[13] M.-H. Ryu,[14,15] J. Lee,[16] C. Faustino,[17] J.-P. Metges,[18] J. Tabernero,[19,20] F. Franke,[21] Y.Y. Janjigian,[22] F. Souza,[23] L. Jukofsky,[23] Y. Zhao,[23] T. Kamio,[23] A. Zaanan,[24,25] and F. Pietrantonio,[26] for the DESTINY-Gastric04 Trial Investigators*

ABSTRACT

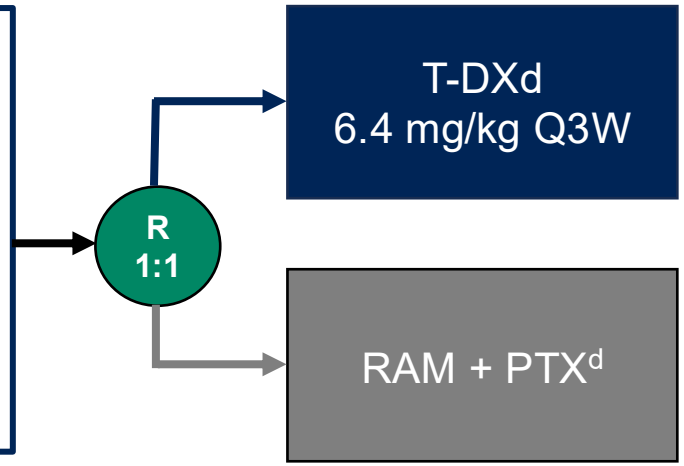
DESTINY Gastric04

Study Design

DESTINY-Gastric04: A Global, Multicenter, Randomized, Phase 3 Trial (NCT04704934)

Patient Population

- HER2+ (IHC 3+ or IHC 2+/ISH+)[a] GC/GEJA
- HER2 status confirmed locally or centrally[b] on a recent biopsy obtained after progression on trastuzumab
- ECOG PS 0 or 1
- No clinically active CNS metastases[c]



Primary Endpoint

- OS

Secondary Endpoints

- PFS (INV)[e]
- Confirmed ORR (INV)[e]
- DCR (INV)[e]
- DOR (INV)[e]
- Safety

Exploratory Endpoints

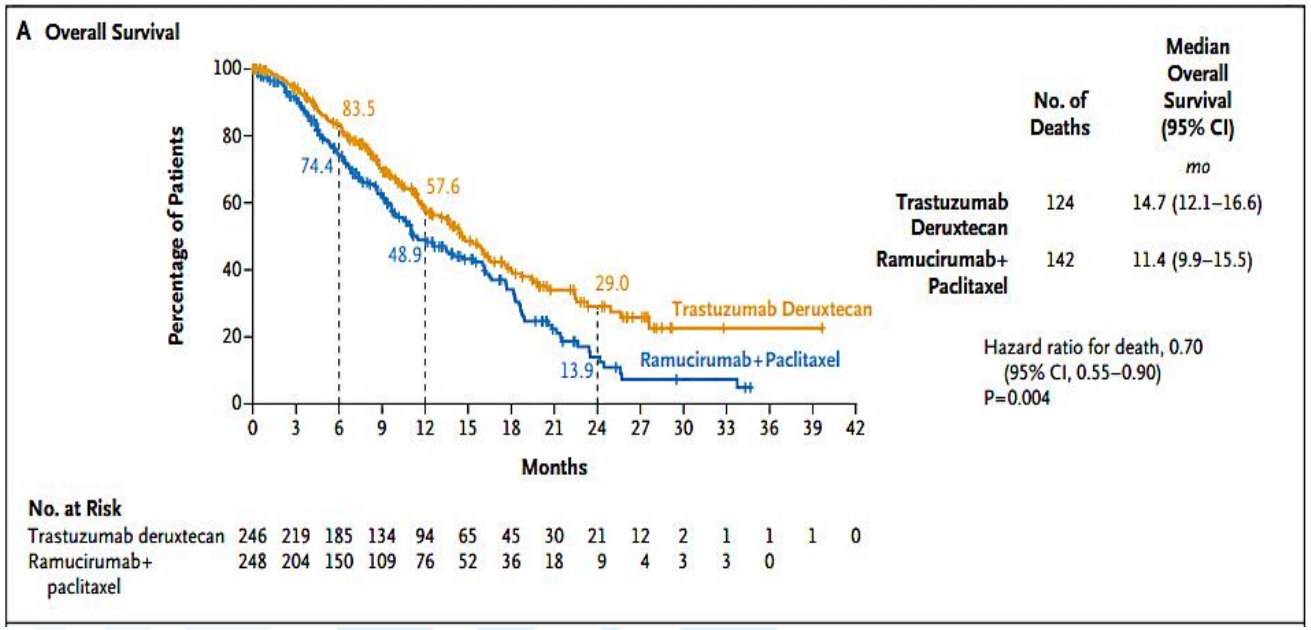
- PRO[f]

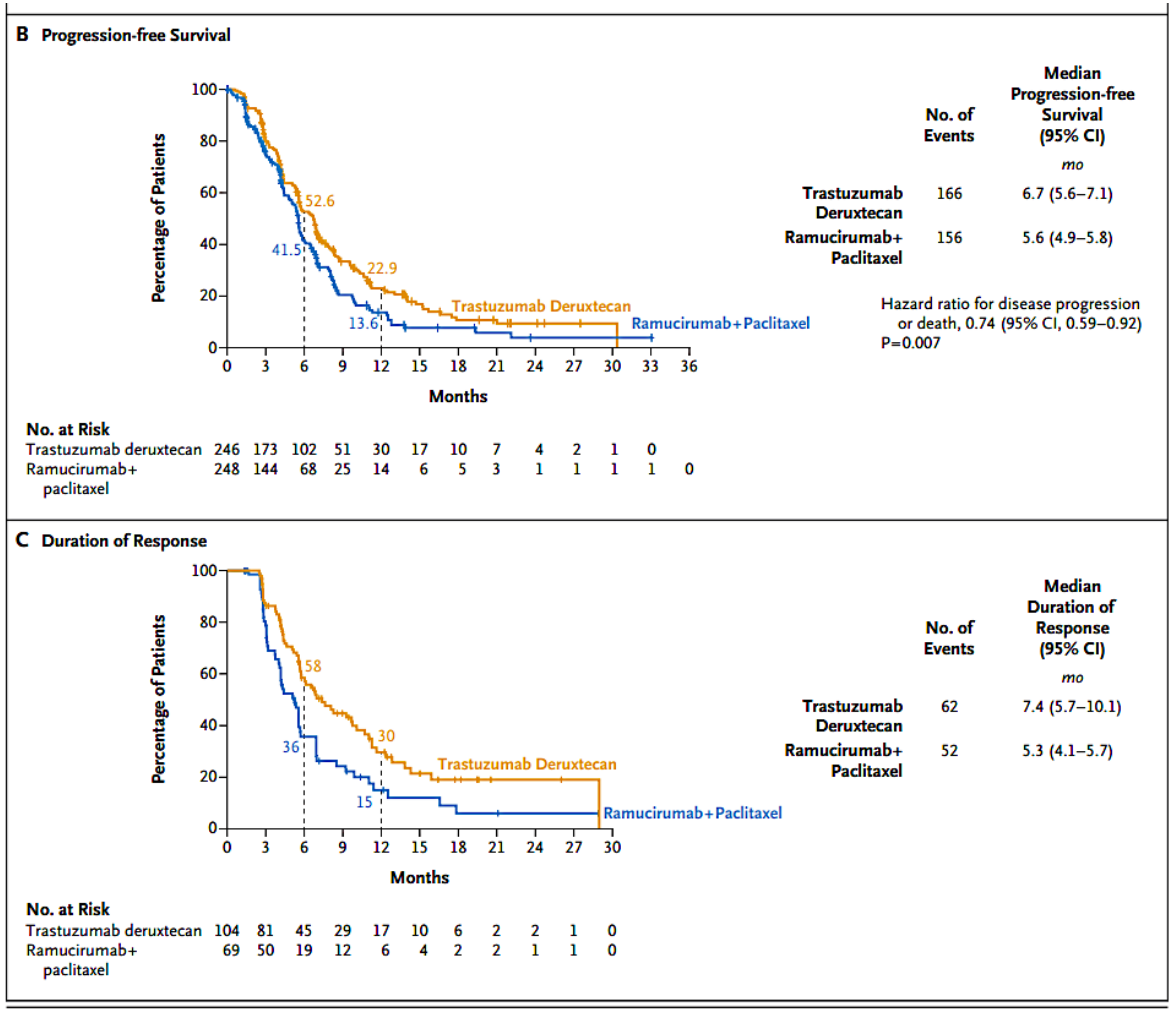
Stratification factors

- HER2 status (IHC 3+ vs IHC 2+/ISH+)
- Geography (Asia [excluding mainland China] vs Western Europe vs mainland China/rest of world)
- Time to progression on 1L therapy (<6 months vs ≥6 months)

[a]As classified by 2018 ASCO/CAP guidelines. [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.

DESTINY-Gastric 04: efficacy





Shitara K, Van Cutsem E et al, NEJM 2025

DESTINY-Gastric 04

Table 2. Efficacy Summary.

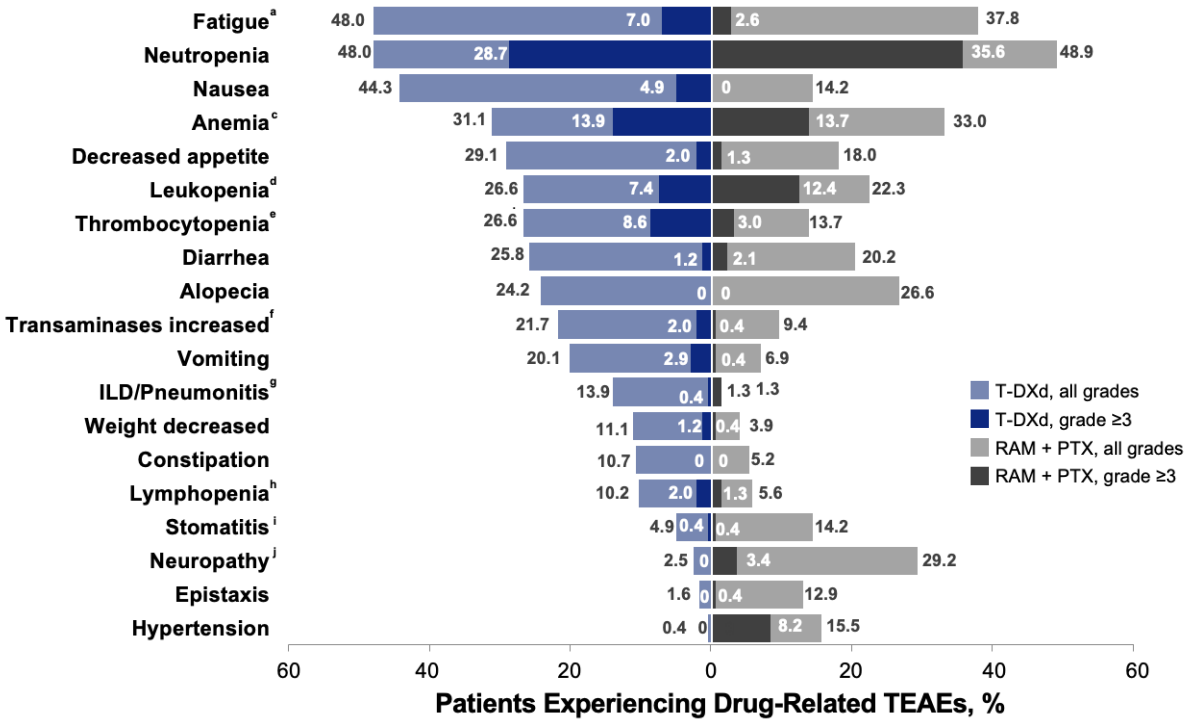
End Point	Trastuzumab Deruxtecan (N=246)	Ramucirumab + Paclitaxel (N=248)	Treatment Effect (95% CI)*	P Value†
Overall survival (95% CI)‡				
Median — mo	14.7 (12.1–16.6)	11.4 (9.9–15.5)	0.70 (0.55–0.90)	0.004
At 6 mo — %	83.5 (78.0–87.7)	74.4 (68.0–79.7)		
At 12 mo — %	57.6 (50.3–64.2)	48.9 (41.5–55.9)		
At 24 mo — %	29.0 (21.3–37.2)	13.9 (7.8–21.8)		
Progression-free survival (95% CI)§				
Median — mo	6.7 (5.6–7.1)	5.6 (4.9–5.8)	0.74 (0.59–0.92)	0.007
At 6 mo — %	52.6 (45.7–59.1)	41.5 (34.3–48.7)		
At 12 mo — %	22.9 (16.9–29.6)	13.6 (8.4–20.0)		
Response				
Confirmed objective response¶				
No. of patients with response/total no.	104/235	69/237		
Percent of patients with response (95% CI)	44.3 (37.8–50.9)	29.1 (23.4–35.3)	15.1 (6.1–24.2)	<0.001
Confirmed best overall response — no./total no. (%)				
Complete response	7/235 (3.0)	3/237 (1.3)		
Partial response	97/235 (41.3)	66/237 (27.8)		
Stable disease**	112/235 (47.7)	111/237 (46.8)		
Progressive disease	13/235 (5.5)	22/237 (9.3)		
Could not be evaluated	6/235 (2.6)	35/237 (14.8)		
Disease control¶				
No. of patients with disease control/total no.	216/235	180/237		
Percent of patients with disease control (95% CI)	91.9 (87.7–95.1)	75.9 (70.0–81.2)	16.0 (9.1–22.9)	
Duration of response (95% CI)††				
Median — mo	7.4 (5.7–10.1)	5.3 (4.1–5.7)		
At 6 mo — %	58 (47–68)	36 (24–48)		
At 12 mo — %	30 (19–41)	15 (7–26)		

Shitara K, Van Cutsem E et al
This article was published on May 31, 2025, at NEJM.org.

DOI: 10.1056/NEJMoa2503119

DESTINY-Gastric04: Safety

Drug-related TEAEs in ≥10% of patients



- Most common drug-related TEAEs with T-DXd included fatigue or AEs of gastrointestinal or hematologic nature; for RAM + PTX, they included fatigue, neuropathy, and hematologic AEs.

AEs of special interest

Adjudicated drug-related ILD/pneumonitis

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 244)	7 (2.9)	26 (10.7)	1 (0.4)	0	0	34 (13.9)
RAM + PTX (n = 233)	0	0	2 (0.9)	0	1 (0.4)	3 (1.3)

Left ventricular dysfunction[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 244)	0	3 (1.2)	3 (1.2)	0	0	6 (2.5)
RAM + PTX (n = 233)	2 (0.9)	2 (0.9)	0	0	0	4 (1.7)

- ILD/pneumonitis events in the T-DXd arm were mainly low-grade, with no grade 4 or 5 events
- Incidence of left ventricular dysfunction was similar across both arms

Shitara K, Van Cutsem E et al, NEJM 2025

Additional health-related quality of life (HRQoL) analysis from DESTINY-Gastric04 (DG-04),

	T-DXd n=246	RAM + PTX n=248	HR (95% CI) Nominal *P* Value
EQ-5D-5L VAS, median TTFD (95% CI), mo	3.5 (2.7-5.0)	3.0 (2.1-3.5)	0.79 (0.62-1.01) 0.063
FACT-Ga scale, median TTFD (95% CI), mo			
FACT-G (EWB + FWB + PWB + SWB)	3.5 (2.2-4.4)	2.8 (2.1-3.5)	0.74 (0.58-0.95) 0.015
FACT-Ga total score (FACT-G + GaCS)	4.4 (3.5-5.7)	4.4 (3.5-6.5)	0.95 (0.73-1.24) 0.700
EWB	5.1 (4.2-8.7)	3.7 (2.4-5.0)	0.74 (0.57-0.97) 0.026
FWB	2.3 (2.1-3.2)	2.3 (2.1-3.5)	0.89 (0.70-1.13) 0.338
PWB	2.8 (2.1-3.7)	2.2 (2.1-3.1)	0.79 (0.62-1.00) 0.052
SWB	3.8 (2.6-5.3)	2.5 (2.1-3.5)	0.71 (0.55-0.91) 0.006
GaCS	4.9 (3.7-6.3)	5.8 (4.8-7.4)	1.11 (0.84-1.47) 0.462

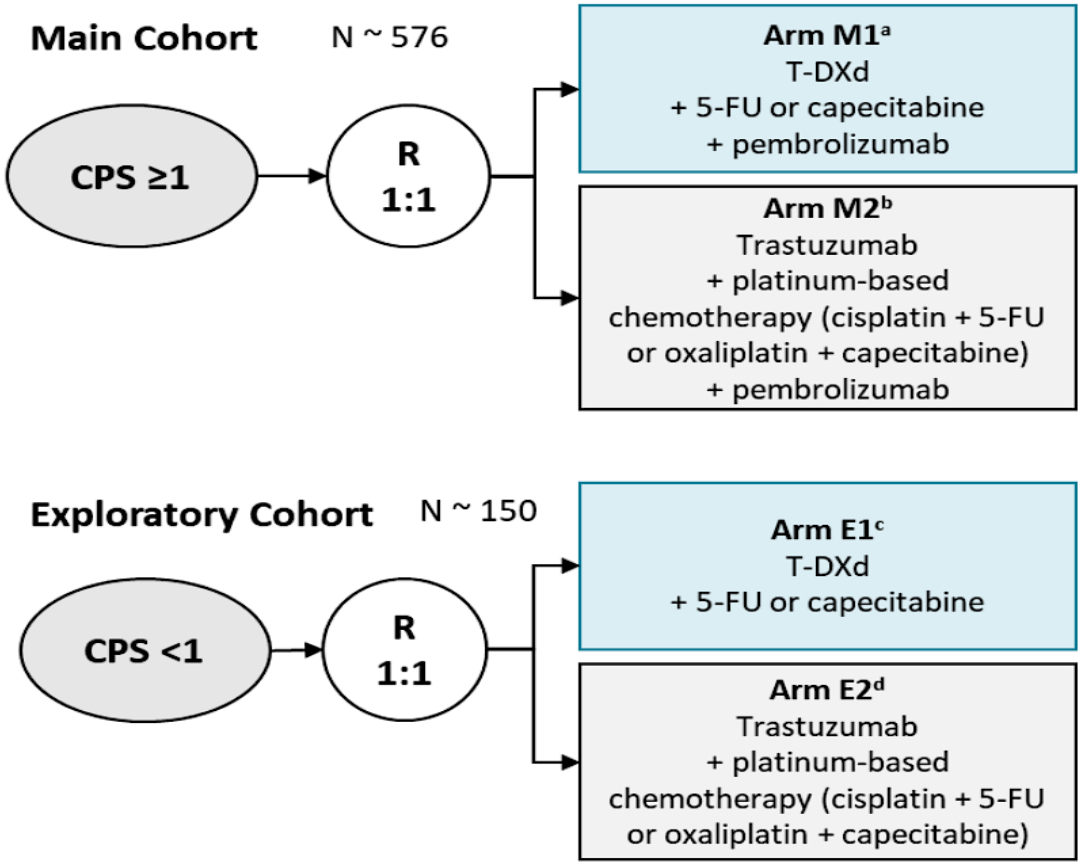
- These findings support patient-reported HRQoL was maintained with T-DXd in pts with HER2+ unresectable/metastatic GC/GEJA.
- Time to first deterioration (TTFD) was not negatively impacted with T-DXd
- Mean change from baseline (CFB) in all FACT-Ga subscales showed pt symptoms and functioning remained stable, with some subscales favoring T-DXd vs RAM + PTX.

Shitara K,…Van Cutsem et al, ASCO 2026, A4011

DESTINY-Gastric05: study design

Key Eligibility Criteria:

- Locally advanced or metastatic GC or GEJ adenocarcinoma
- No systemic therapy for the unresectable, locally advanced or metastatic setting or relapse more than 6 months after the last dose of perioperative or neoadjuvant therapy
- HER2-positive: IHC3+ or IHC2+/ISH-positive (central assessment)
- ECOG PS 0 or 1



Stratification factors:

- HER2 status: IHC 3+ vs IHC 2+/ISH-positive
- Geographic region: Japan/South Korea vs Rest of Asia (including China) vs North America/EU/ROW

Primary endpoint

- PFS (BICR)

Secondary endpoints

- OS (key secondary)
- ORR
- PFS (Inv)
- DOR
- Safety
- PRO

https://clinicaltrials.gov/study/NCT06731478

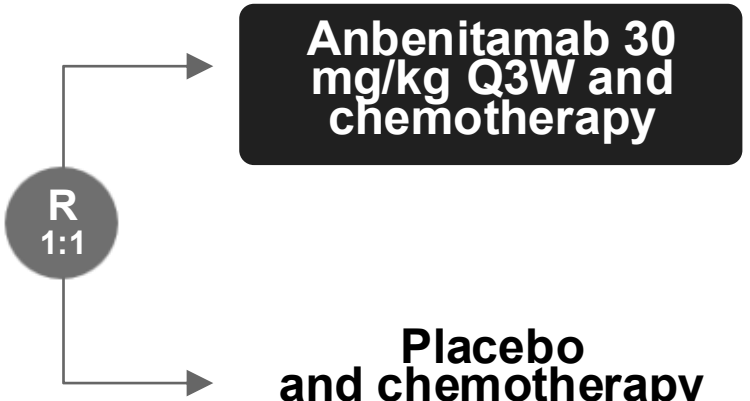
Chemo +/- Anbenitamab in pretreated advanced HER2 + gastric adenocarcinoma

Population studied :

- GC/GEJC HER2 positive centrally confirmed
- Progression under treatment prior containing trastuzumab
- ECOG PS of 0 or 1

Stratification factors :

- Type of chemotherapy (taxanes [paclitaxel and docetaxel] or irinotecan)
- HER2 expression (IHC 3+ or IHC2+/FISH+)
- Number of previous lines (1 or ≥2)



Primary objective :

- IRC assessed PFS
- OS

Secondary objectives:

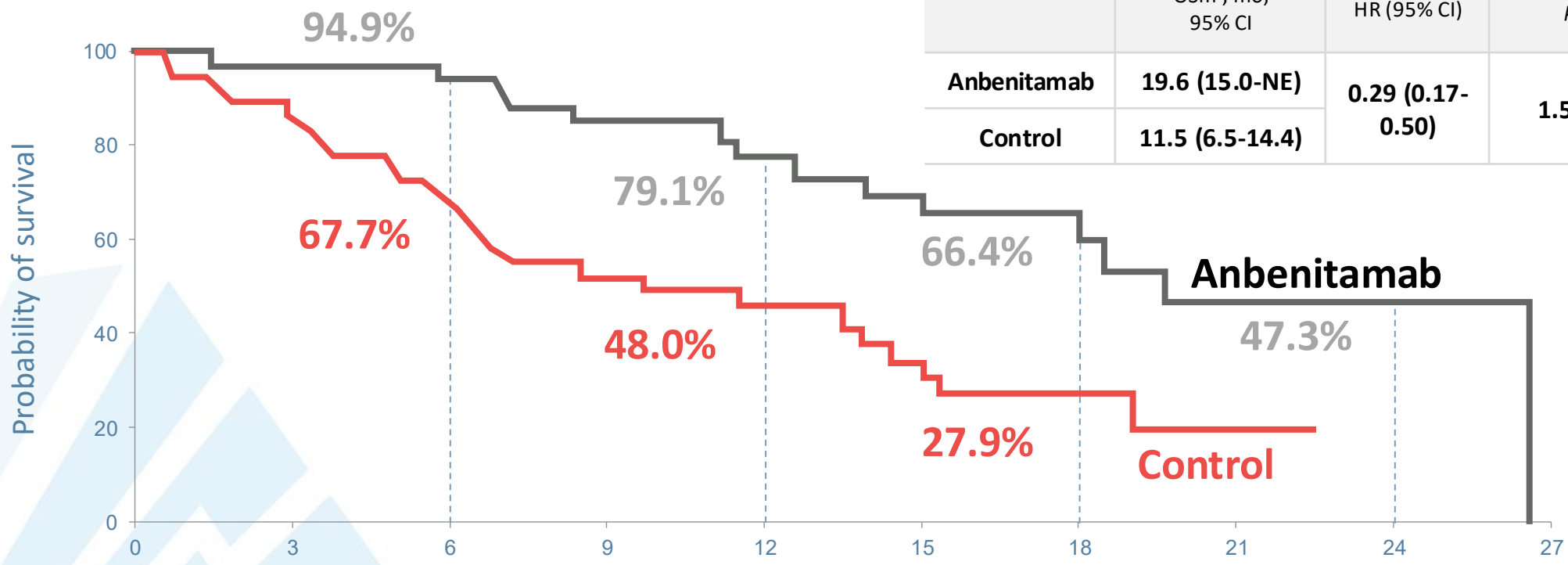
- The IRC and the investigator have assessed the objective response rate (ORR), duration of response (DoR), disease control rate (DCR), progression-free survival (PFS), and safety.

Xu J et al., ESMO 2025, Abs #LBA78; Liu R et al, Ann Onc 2026

Chemo +/- Anbenitamab in pretreated advanced HER2 + gastric adenocarcinoma

Compared with chemotherapy alone, anbenitamab plus chemotherapy significantly reduced the risk of death by 71%, meeting the predefined statistical criterion (alpha threshold of 0.00001).

	OSm , mo, 95% CI	HR (95% CI)	*p-value*
Anbenitamab	**19.6 (15.0-NE)**	**0.29 (0.17-0.50)**	**1.56 x 10 $^{-6}$**
Control	**11.5 (6.5-14.4)**		



Number at risk

Anbenitamab	**95**	**81**	**63**	**40**	**29**	**19**	**12**	**5**	**3**	**0**
Control	93	72	44	26	18	10	4	1	0	0

Positive study with impressive results of Anbenitamab efficacy. To be confirmed in non-Asian population

Xu J et al., ESMO 2025, Abs #LBA78; Liu R et al, Ann Onc 2026

Regulatory and reimbursement issues aside, what first-line treatment would you most likely recommend for a 65-year-old patient presenting with metastatic CLDN18.2-negative, HER2-positive, MSS gastric adenocarcinoma with PD-L1 CPS 0?

 Dr Janjigian	Zanidatamab/chemotherapy
 Dr Shah	Zanidatamab/chemotherapy
 Prof Van Cutsem	FOLFOX/trastuzumab
 Dr Kim	Zanidatamab/chemo/tislelizumab
 Dr Klempner	Zanidatamab/chemo ± tislelizumab
 Dr Wainberg	Zanidatamab/chemo/tislelizumab

MSS = microsatellite-stable; CPS = combined positive score

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what first-line treatment would you most likely recommend for a 65-year-old patient presenting with metastatic CLDN18.2-negative, HER2-positive, MSS gastric adenocarcinoma with PD-L1 CPS 1?

 Dr Janjigian	Zanidatamab/chemo/tislelizumab
 Dr Shah	Zanidatamab/chemo/tislelizumab
 Prof Van Cutsem	Zanidatamab/chemo/tislelizumab
 Dr Kim	Zanidatamab/chemo/tislelizumab
 Dr Klempner	Zanidatamab/chemo/tislelizumab
 Dr Wainberg	Trastuzumab/chemo/pembrolizumab

MSS = microsatellite-stable; CPS = combined positive score

RTP RESEARCH TO PRACTICE

For a patient for whom you have elected to employ zanidatamab/chemotherapy in combination with an anti-PD-1 antibody, how will you approach the selection of anti-PD-1 antibody?

 Dr Janjigian	I will use any of the anti-PD-1 antibodies
 Dr Shah	I will use any of the anti-PD-1 antibodies
 Prof Van Cutsem	I will use tislelizumab per the trial
 Dr Kim	I will use tislelizumab per the trial
 Dr Klempner	I will use any of the anti-PD-1 antibodies
 Dr Wainberg	I will use tislelizumab per the trial

RTP RESEARCH TO PRACTICE

In general, which targeted strategy would you prioritize for a patient with newly diagnosed CLDN18.2-positive, HER2-positive gastric/GEJ adenocarcinoma?

 Dr Janjigian	HER2-targeted therapy
 Dr Shah	HER2-targeted therapy
 Prof Van Cutsem	HER2-targeted therapy
 Dr Kim	HER2-targeted therapy
 Dr Klempner	HER2-targeted therapy
 Dr Wainberg	HER2-targeted therapy

What preemptive treatment, if any, are you recommending to prevent gastrointestinal toxicities with zanidatamab?

 Dr Janjigian	Loperamide, tramadol
 Dr Shah	Loperamide
 Prof Van Cutsem	Loperamide
 Dr Kim	Loperamide
 Dr Klempner	Loperamide
 Dr Wainberg	Loperamide

Faculty Discussion

- **Regulatory and reimbursement issues aside, what first-line treatment would you most likely recommend for a 65-year-old patient presenting with metastatic CLDN18.2-negative, HER2-positive, MSS gastric adenocarcinoma with PD-L1 CPS 0? PD-L1 CPS 1?**
- **For a patient for whom you have elected to employ zanidatamab/chemotherapy in combination with an anti-PD-1 antibody, how will you approach the selection of anti-PD-1 antibody?**
- **In general, which targeted strategy would you prioritize for a patient with newly diagnosed CLDN18.2-positive, HER2-positive gastric/GEJ adenocarcinoma?**
- **What preemptive treatment, if any, are you recommending to prevent gastrointestinal toxicities with zanidatamab?**

Regulatory and reimbursement issues aside, what would you most likely recommend as second-line therapy for a patient with metastatic CLDN18.2-negative, HER2-positive, MSS gastric adenocarcinoma, a PD-L1 CPS of ≥1 and PD on zanidatamab/chemotherapy/tislelizumab?

 Dr Janjigian	Trastuzumab deruxtecan
 Dr Shah	Trastuzumab deruxtecan
 Prof Van Cutsem	Trastuzumab deruxtecan
 Dr Kim	Trastuzumab deruxtecan
 Dr Klempner	Trastuzumab deruxtecan
 Dr Wainberg	Trastuzumab deruxtecan

RTP RESEARCH TO PRACTICE

Outside of a clinical trial, would you offer zanidatamab to a patient with HER2-positive gastric/GEJ adenocarcinoma who had PD on first-line FOLFOX/trastuzumab/pembrolizumab and second-line trastuzumab deruxtecan?

 Dr Janjigian	No
 Dr Shah	No
 Prof Van Cutsem	No
 Dr Kim	Yes
 Dr Klempner	Yes
 Dr Wainberg	Yes

Outside of a clinical trial, have you administered or would you administer trastuzumab deruxtecan to a patient with HER2-low (IHC 2+ or 1+) gastric/GEJ adenocarcinoma?

 Dr Janjigian	I have not but would for the right patient
 Dr Shah	I have not but would for the right patient
 Prof Van Cutsem	I have not and would not
 Dr Kim	I have not but would for the right patient
 Dr Klempner	I have not and would not
 Dr Wainberg	I have not and would not

RTP RESEARCH TO PRACTICE

Faculty Discussion

- **Regulatory and reimbursement issues aside, what would you most likely recommend as second-line therapy for a patient with metastatic CLDN18.2-negative, HER2-positive, MSS gastric adenocarcinoma, a PD-L1 CPS of ≥1 and PD on zanidatamab/chemotherapy/tislelizumab?**
- **Outside of a clinical trial, would you offer zanidatamab to a patient with HER2-positive gastric/GEJ adenocarcinoma who had PD on first-line FOLFOX/trastuzumab/pembrolizumab and second-line trastuzumab deruxtecan?**
- **Outside of a clinical trial, have you administered or would you administer trastuzumab deruxtecan to a patient with HER2-low (IHC 2+ or 1+) gastric/GEJ adenocarcinoma?**

Agenda

Module 1: HER2-Targeted Approaches in Advanced Gastroesophageal Cancers — Prof Van Cutsem

Module 2: Targeting CLDN18.2 in Advanced Gastroesophageal Cancers — Dr Shah

Module 3: Available Immunotherapeutic Strategies for Advanced Gastroesophageal Cancers — Dr Janjigian

RTP RESEARCH TO PRACTICE

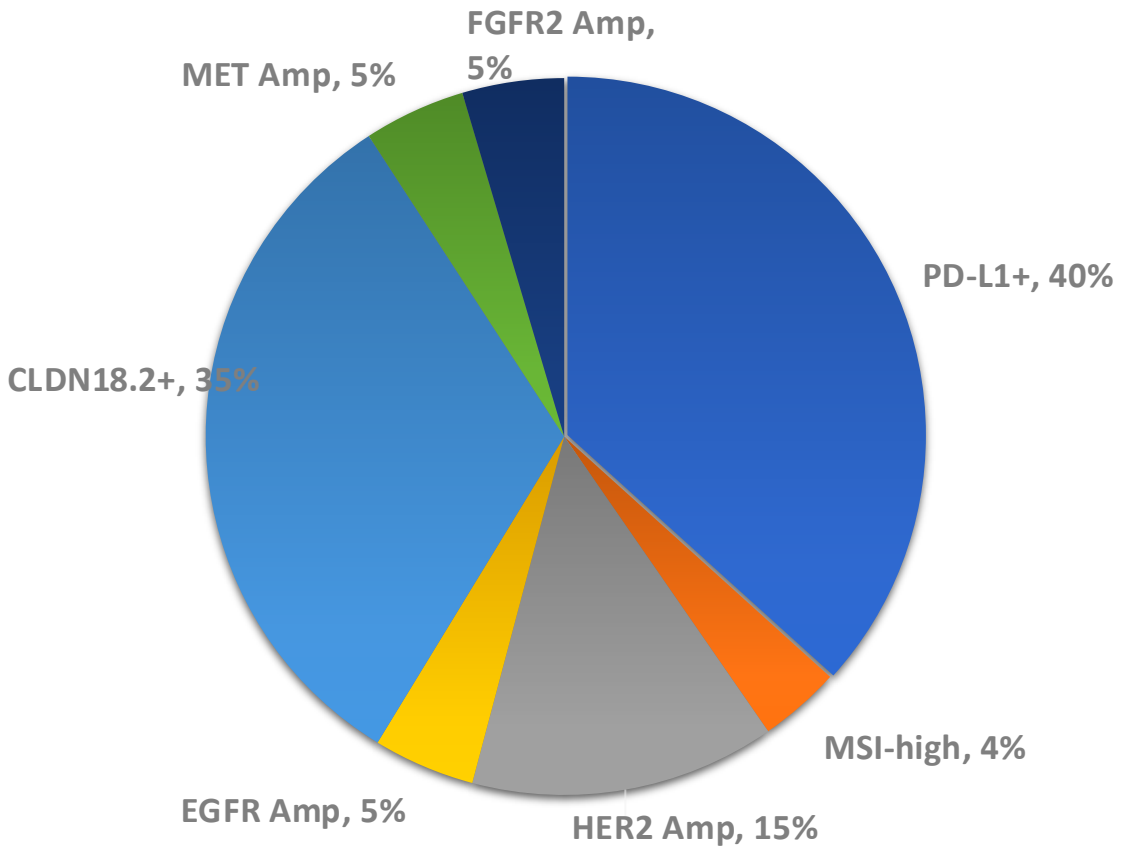
The Evolving Role of Targeting CLDN18.2 in Gastroesophageal Cancers

Research To Practice Satellite Symposium

May 29, 2026

Manish A. Shah, MD
@MDManishShah

Key Biomarkers in Gastroesophageal Cancer



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

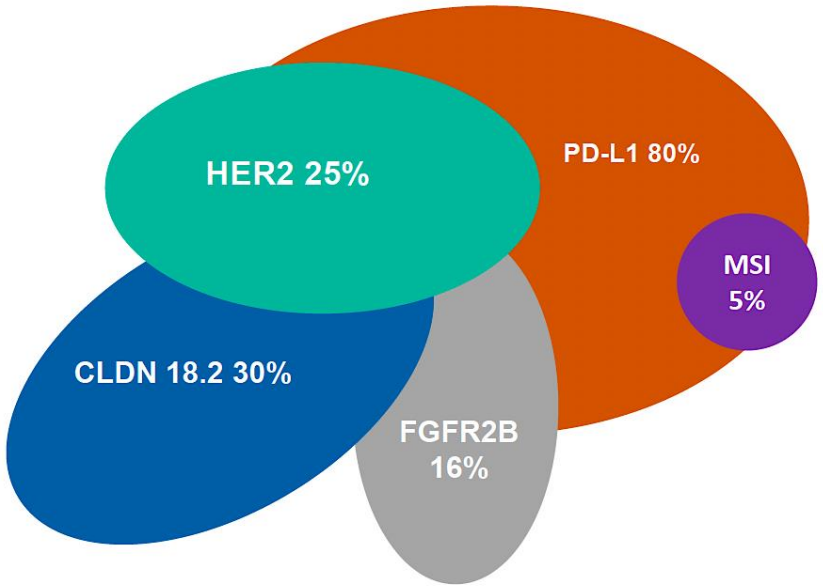
Tumor agnostic
Mismatch repair deficiency (or MSI-H)
Tumor mutation burden
NTRK fusion

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

Kuwata T. *Pathol Int*. 2024; online ahead of print

Biomarkers don’t neatly fit in a pie!

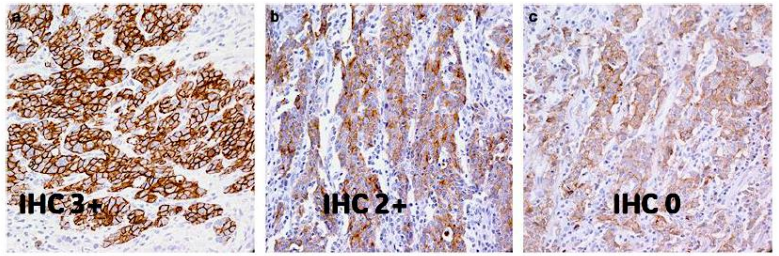
- TP53mut is an early event driving CIN in GEC
- Co-occurring alterations making it difficult to target individual oncogenes
- Rely on IHC and FISH to define clinical targets



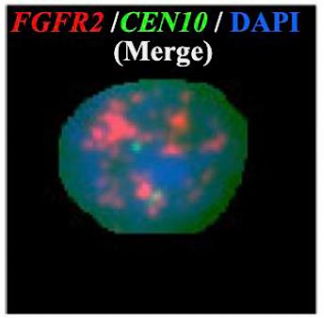
*overlapping between biomarkers may vary among studies

Fibroblast Growth Factor Receptor 2 (FGFR2) testing

FGFR2b ≥10% IHC 2/3+ in 16% GEC

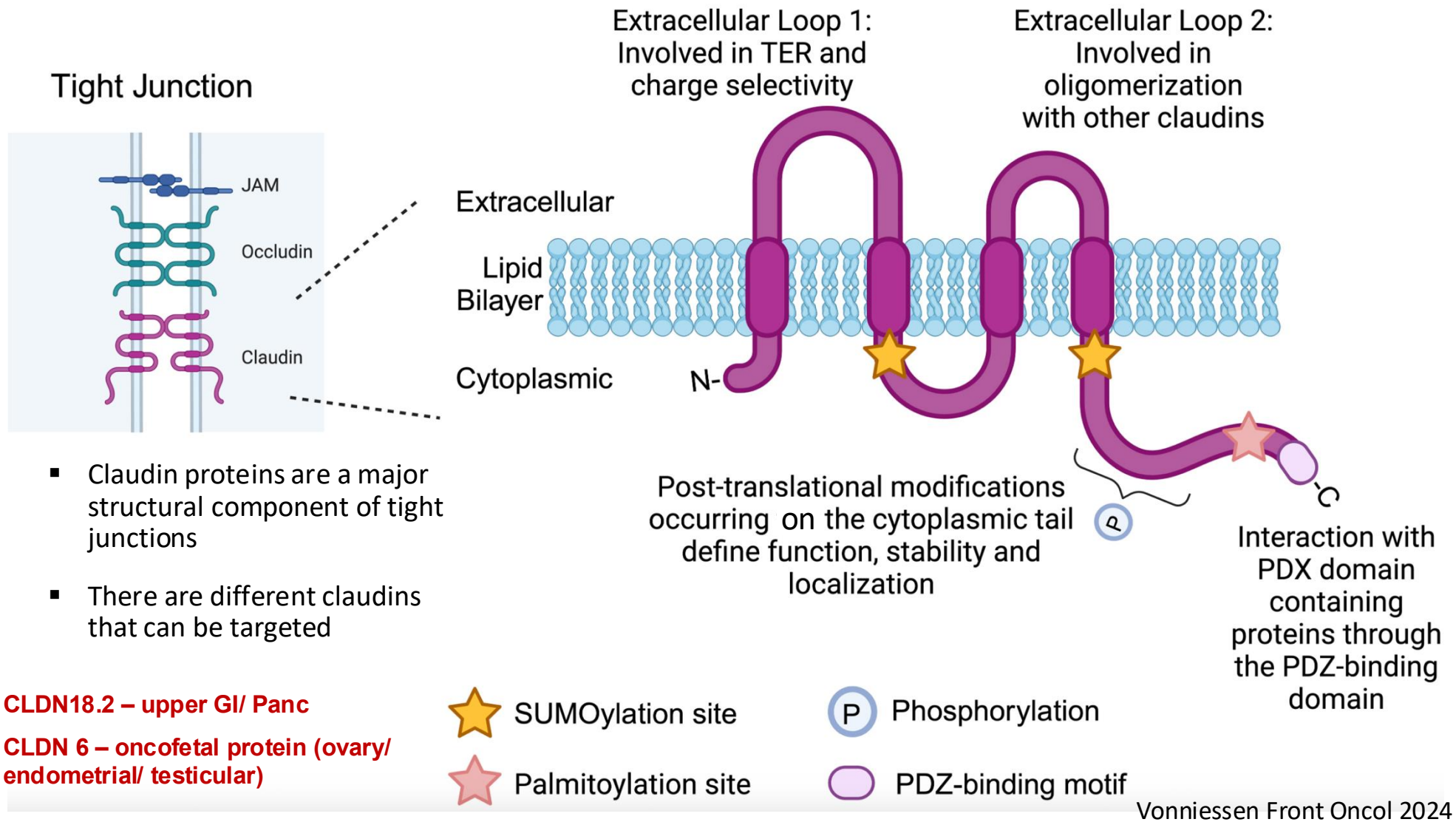


FISH and ctDNA testing: *FGFR* amplifications 5%



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

Claudin 18.2 – A New Target in Upper GI Cancers



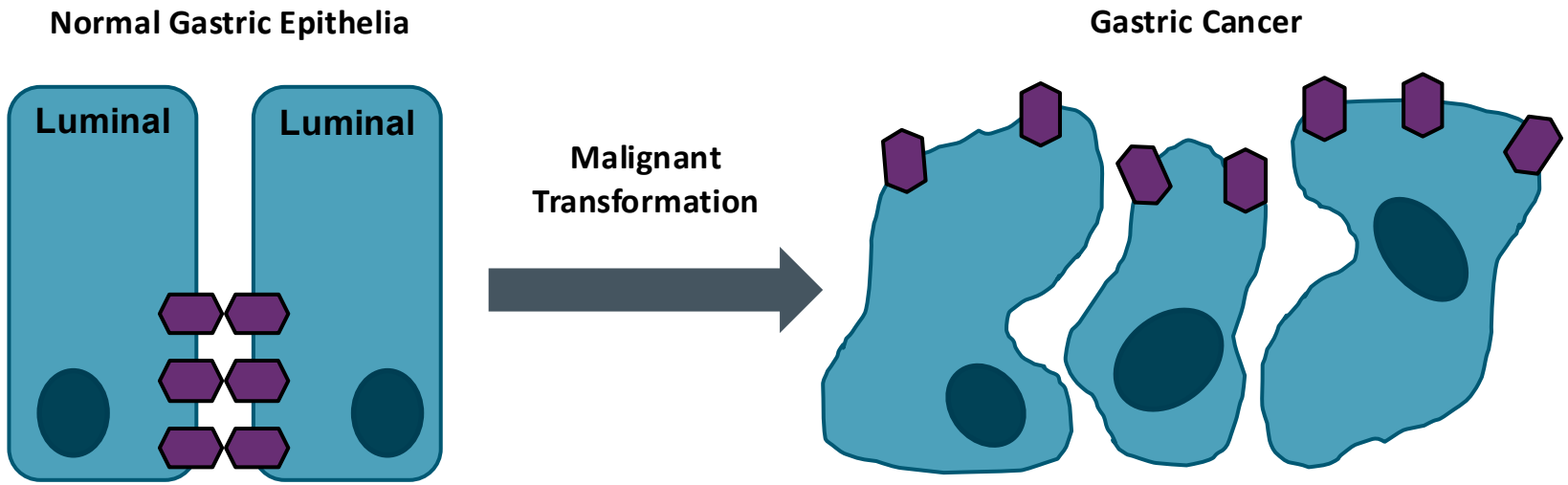
- Claudin proteins are a major structural component of tight junctions
- There are different claudins that can be targeted

CLDN18.2 – upper GI/ Panc

CLDN 6 – oncofetal protein (ovary/ endometrial/ testicular)

Vonniessen Front Oncol 2024

Claudin18.2: Leveraging Biology



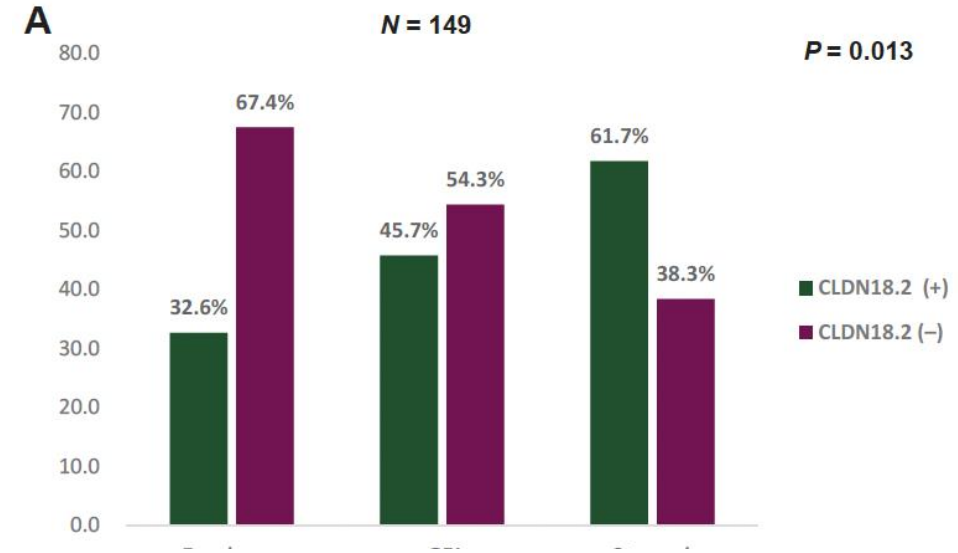
- Claudin18.2 is a major structural component of intercellular tight junctions
- Not routinely expressed in any normal tissue outside gastric mucosa (cancer-restricted antigen)
- Broadly expressed in several tumor types including gastric, GEJ, biliary, and pancreatic

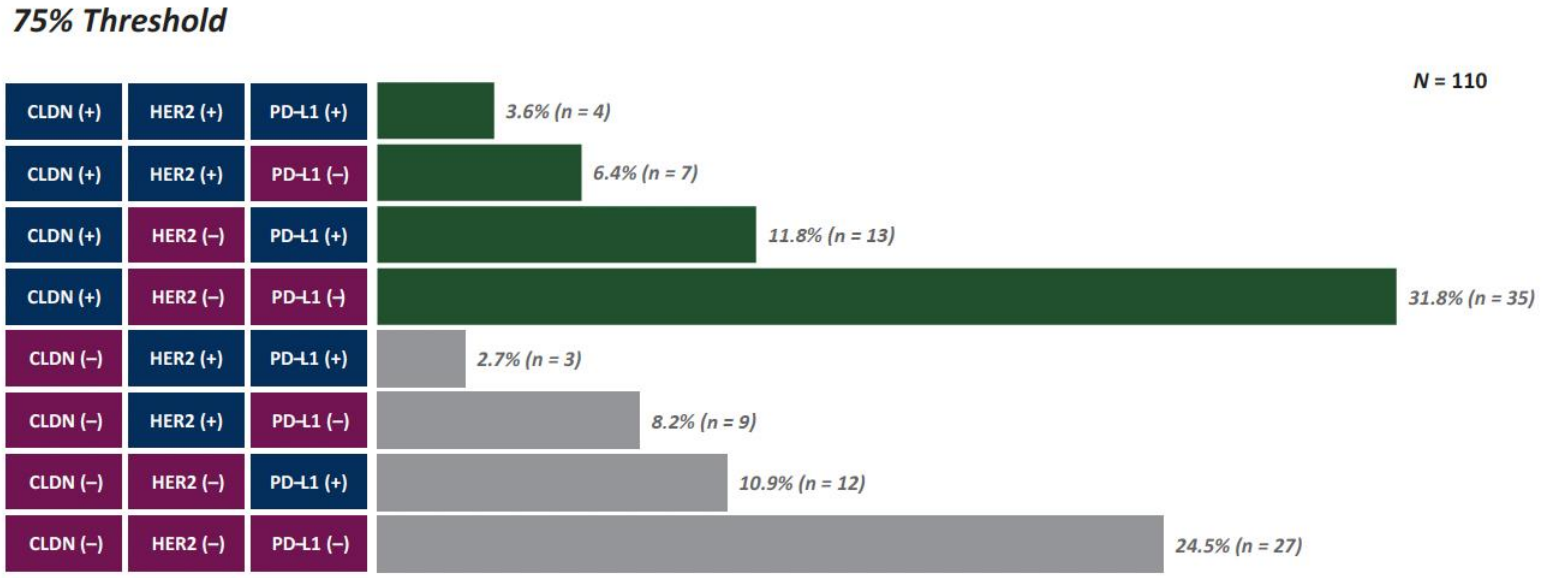
Baek. Anticancer Res. 2019;39:6973.

Claudin18.2: Characteristics and Overlap

More prevalent in GC

~30% sole biomarker

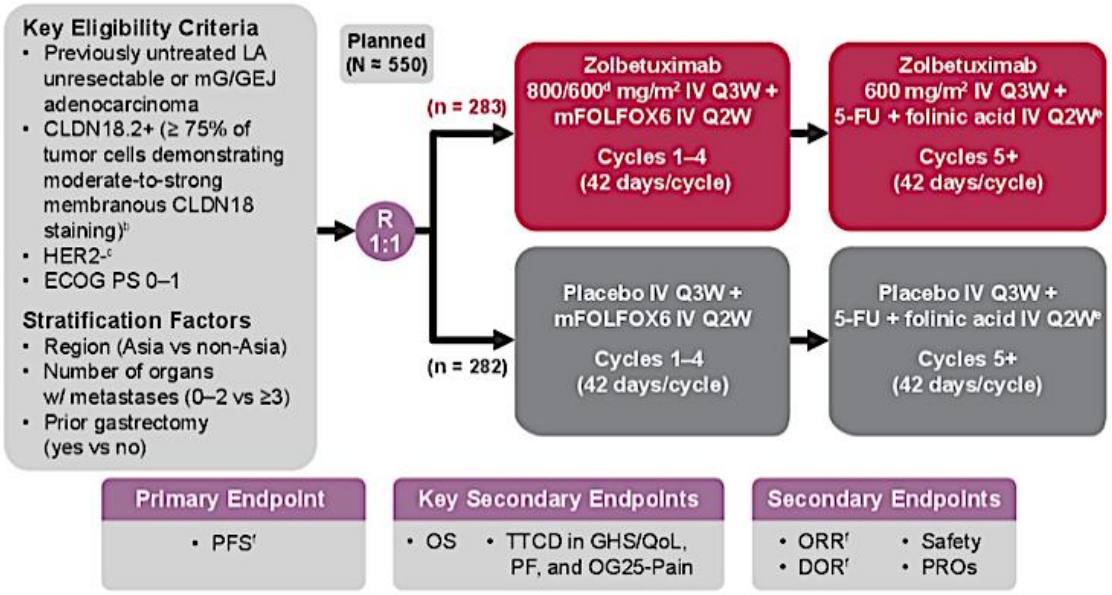




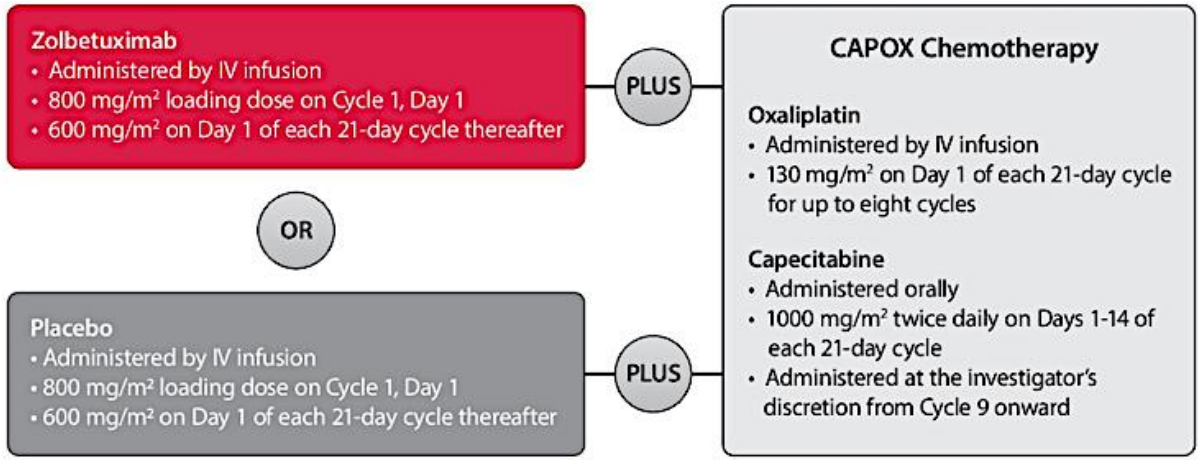
Maeng et al. ESMO Gastro Onc 2026

SPOTLIGHT/GLOW Study Design

SPOTLIGHT

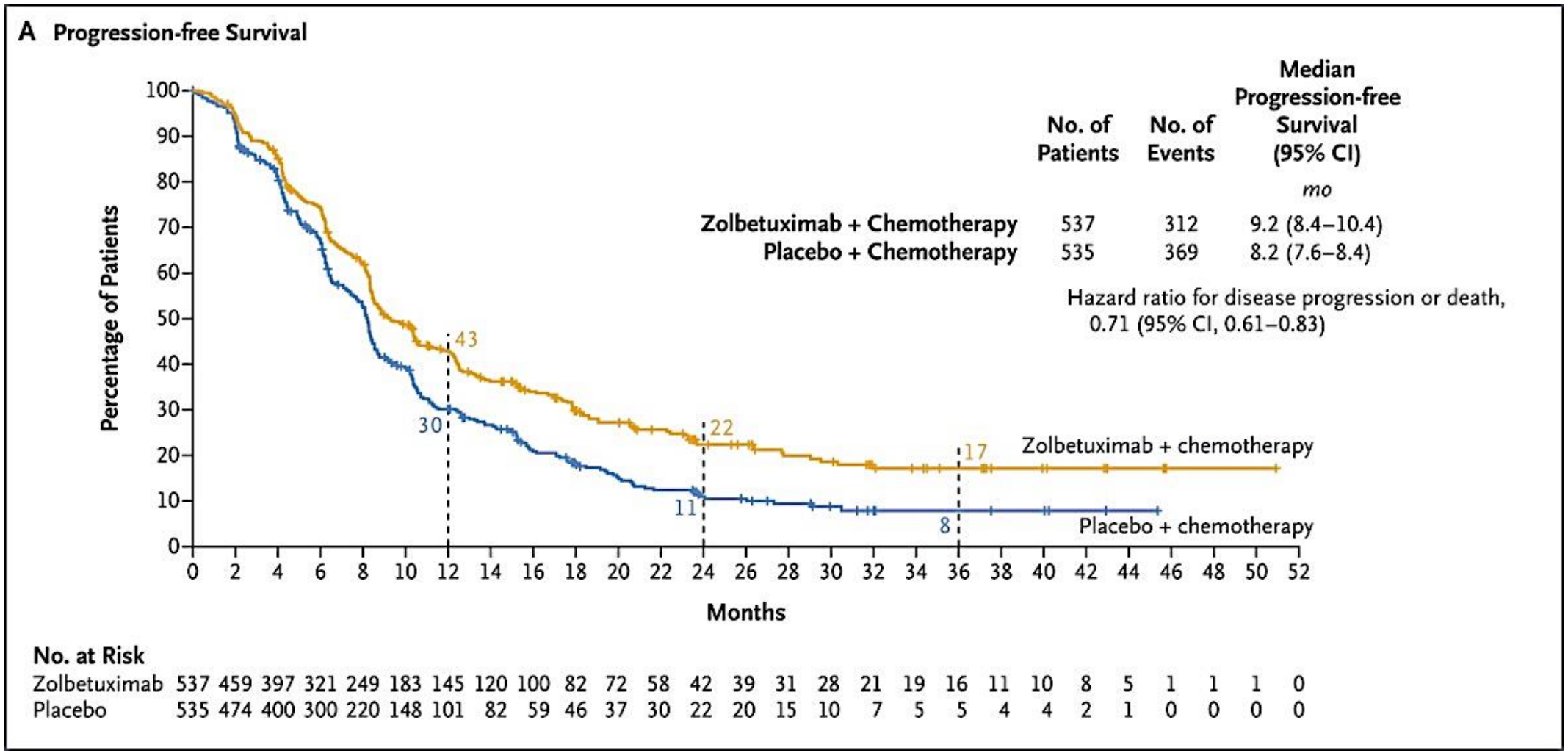


GLOW



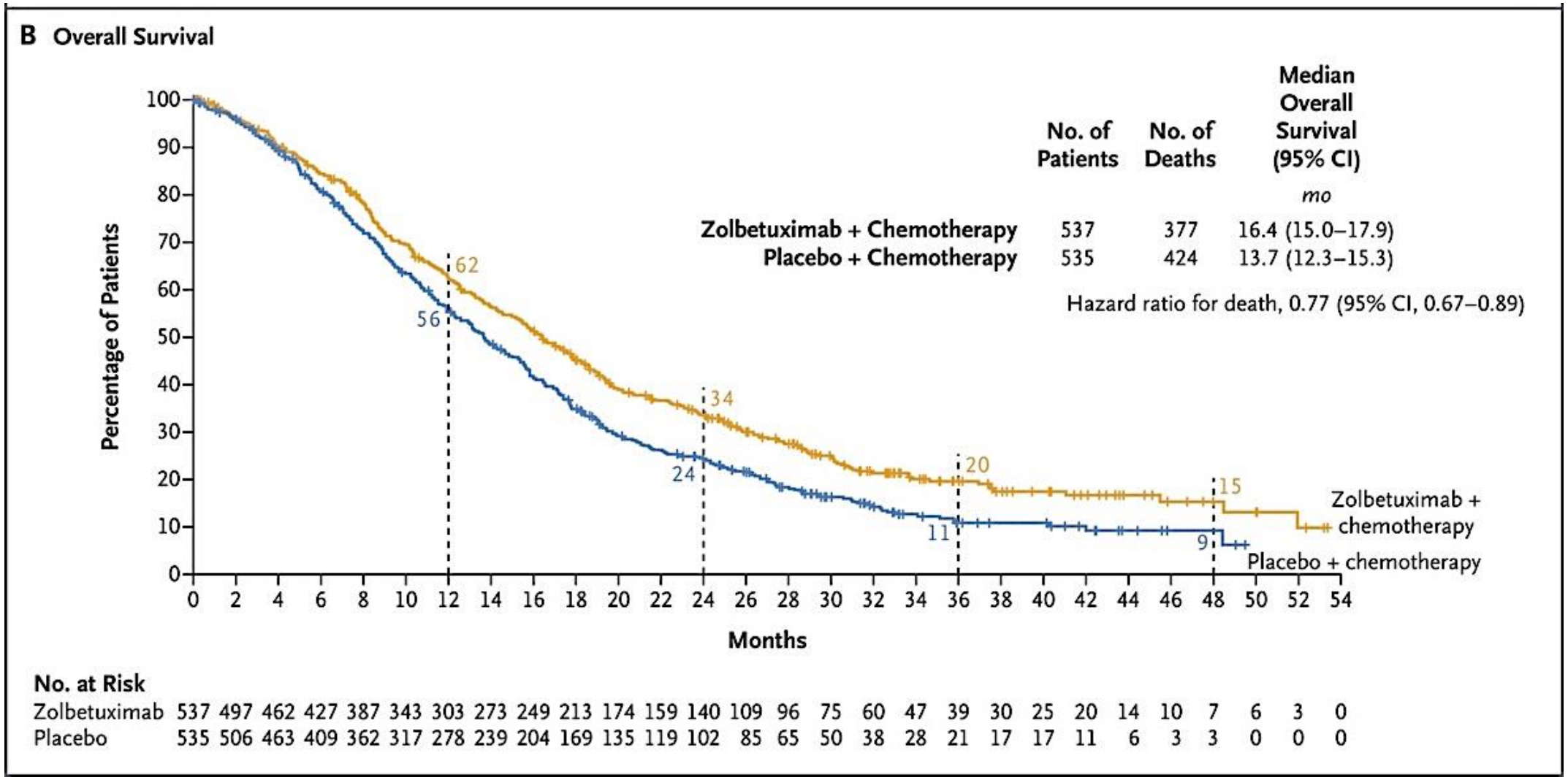
Shitara K et al. *N Engl J Med*. 2024;391(12):1159-1163.

SPOTLIGHT/GLOW Combined PFS



Shitara K et al. *N Engl J Med.* 2024;391(12):1159-1163.

SPOTLIGHT/GLOW Combined OS

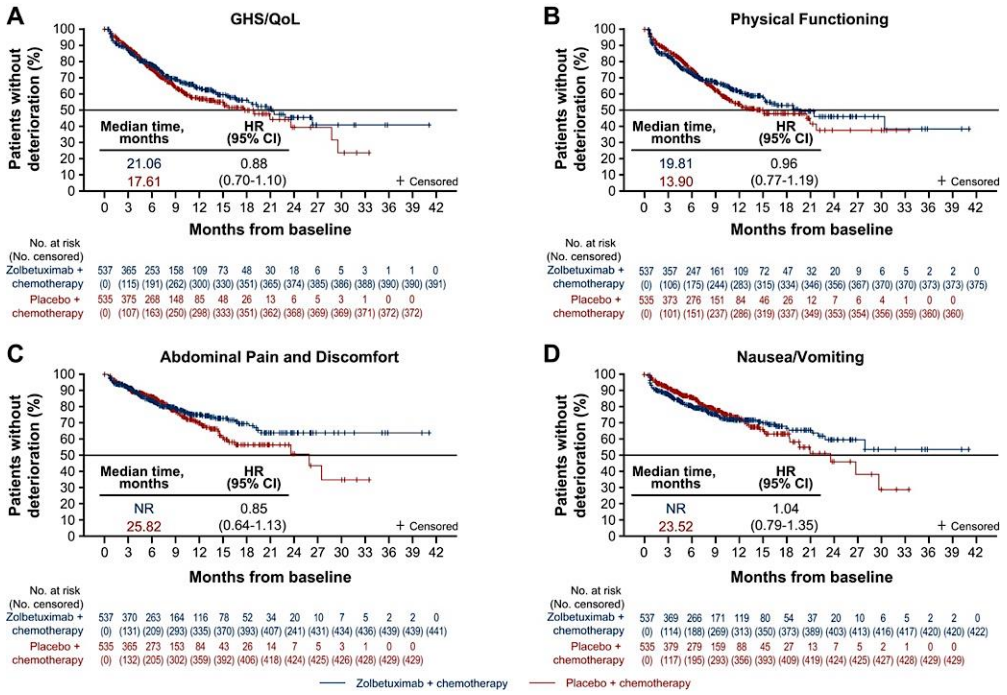


Shitara K et al. *N Engl J Med.* 2024;391(12):1159-1163.

SPOTLIGHT/GLOW Adverse Events

Table S10. Adverse Events in the Safety Analysis Set in SPOTLIGHT and in GLOW

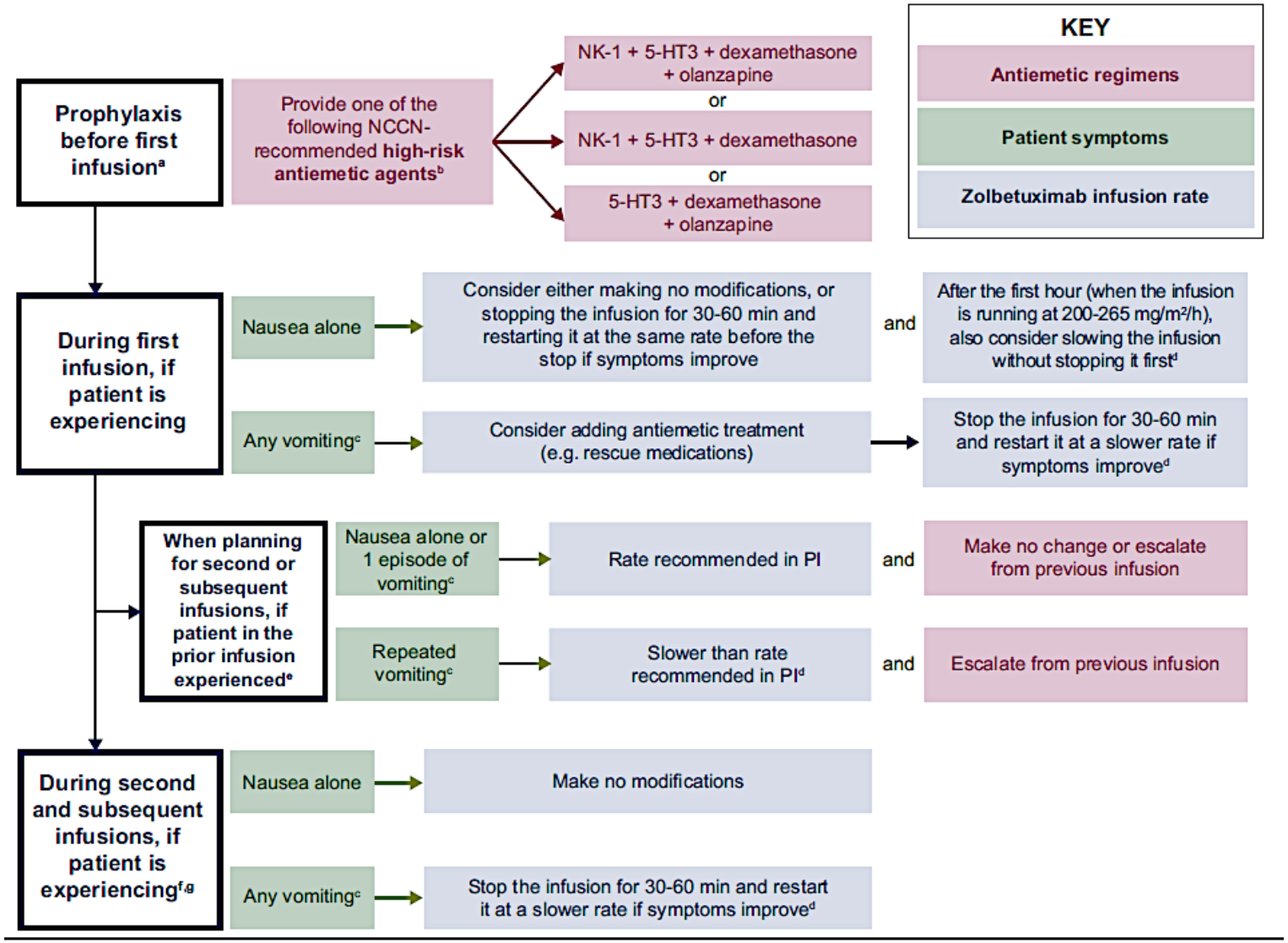
Event – no. (%)	SPOTLIGHT		GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)
Treatment-emergent adverse events				
All	278 (99.6)	277 (99.6)	251 (98.8)	244 (98.0)
Grade ≥3	244 (87.5)	219 (78.8)	186 (73.2)	175 (70.3)
Serious	133 (47.7)	129 (46.4)	123 (48.4)	126 (50.6)
Treatment-related adverse events				
Leading to dose interruption of any study drug	217 (77.8)	130 (46.8)	168 (66.1)	108 (43.4)
Leading to dose interruption of zolbetuximab or placebo	172 (61.6)	61 (21.9)	114 (44.9)	39 (15.7)
Leading to discontinuation of any study drug	108 (38.7)	83 (29.9)	56 (22.0)	40 (16.1)
Leading to discontinuation of zolbetuximab or placebo	38 (13.6)	7 (2.5)	18 (7.1)	11 (4.4)
Leading to death	5 (1.8)	5 (1.8)	6 (2.4)	7 (2.8)
Treatment-emergent adverse events* by preferred terms†				
	All grade	**Grade ≥3**	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**
Nausea	230 (82.4)	45 (16.1)	171 (61.5)	19 (6.8)	175 (68.9)	22 (8.7)	125 (50.2)	6 (2.4)
Vomiting	188 (67.4)	45 (16.1)	101 (36.3)	17 (6.1)	168 (66.1)	31 (12.2)	79 (31.7)	9 (3.6)
Decreased appetite	136 (48.7)	17 (6.1)	97 (34.9)	9 (3.2)	105 (41.3)	17 (6.7)	86 (34.5)	4 (1.6)
Anemia	106 (38.0)	24 (8.6)	107 (38.5)	26 (9.4)	93 (36.6)	29 (11.4)	92 (36.9)	28 (11.2)
Diarrhea	114 (40.9)	12 (4.3)	125 (45.0)	10 (3.6)	83 (32.7)	15 (5.9)	87 (34.9)	18 (7.2)
Neutrophil count decreased	96 (34.4)	69 (24.7)	91 (32.7)	69 (24.8)	71 (28.0)	26 (10.2)	59 (23.7)	24 (9.6)



- Change from baseline trends for key PRO domains were similar with zolbetuximab + chemotherapy and placebo + chemotherapy.
- Nausea/vomiting worsened in early cycles but later returned to baseline levels without clinically meaningful deterioration.

Shitara K et al. *N Engl J Med.* 2024;391(12):1159-1163; Lordick F et al. *ESMO Open.* 2024;9(8):103663.

Zolbetuximab: Management of Nausea and Vomiting



Klempner SJ et al. *ESMO Gastro Oncol*. 2025;7:100131.

ILUSTRO Cohort 4 Study Design

Key Eligibility Criteria

- Previously untreated LA unresectable or mG/GEJ adenocarcinoma
- CLDN18.2+ (moderate-to-strong CLDN18 staining in ≥ 50% of tumor cells)[a]
  - Intermediate expression: ≥ 50 – < 75% of cells
  - High: ≥ 75% of cells
- HER2−[b]
- ECOG PS 0–1

Cohort 4A: Safety Lead-In Phase[c] (n = 12)

Cycles 1–4 (~5.5 months):
Zolbetuximab[c] 600/400 mg/m² OR 800/400 mg/m² + nivolumab 240 mg + mFOLFOX6 Q2W

Cycles 5+:
Zolbetuximab 400 mg/m² + nivolumab 240 mg + 5-FU/FA[e] Q2W

Cohort 4B: Expansion Phase (n = ~65)

Cycles 1–4 (~5.5 months):
Zolbetuximab 800/400[d] mg/m² + nivolumab 240 mg + mFOLFOX6 Q2W

Cycles 5+:
Zolbetuximab 400 mg/m² + nivolumab 240 mg + 5-FU/FA[e] Q2W

Endpoints and Analyses

PFS, ORR, DCR, DOR, OS, safety and tolerability

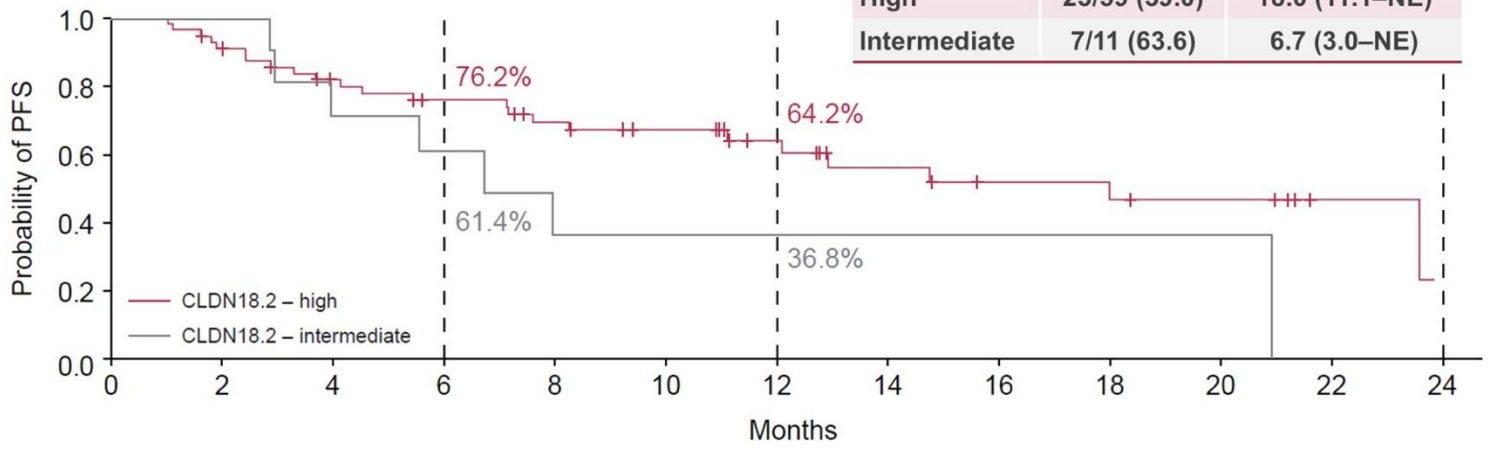
Preplanned analyses by CLDN18.2 and ad-hoc analyses by PD-L1 CPS[f]

Shitara ASCO GI 2026, Abs 284

PFS Stratified by CLDN18.2 Expression in Cohort 4B

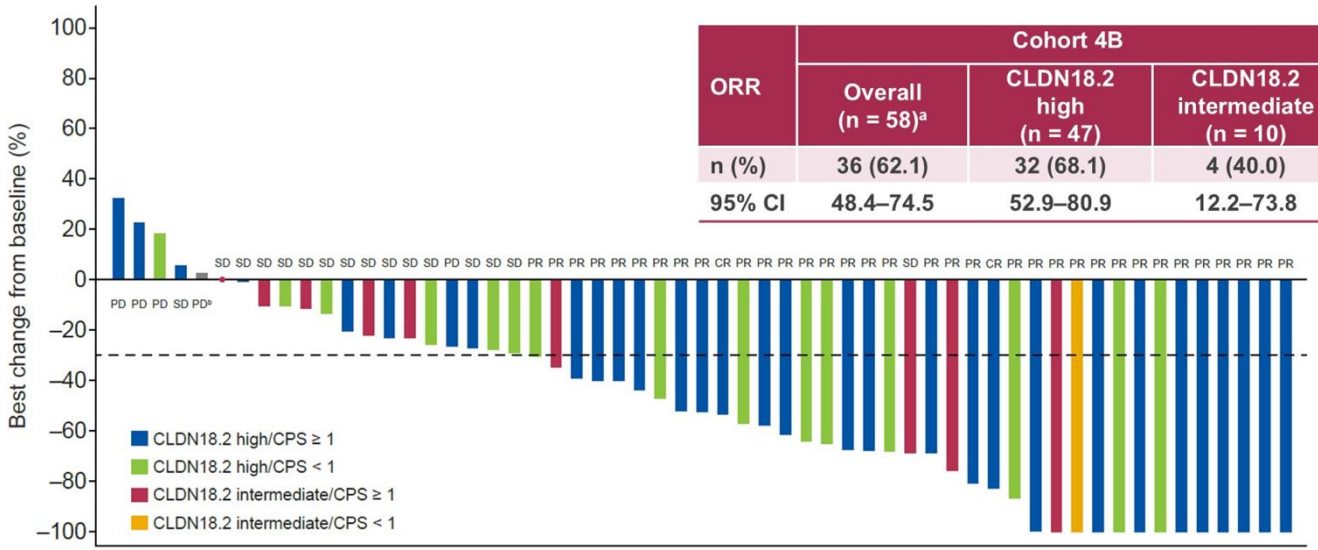
Median PFS was 18.0 months in the CLDN18.2-high population

CLDN18.2	Events/n (%)	Median PFS, months (95% CI)
High	23/59 (39.0)	18.0 (11.1–NE)
Intermediate	7/11 (63.6)	6.7 (3.0–NE)



ORR was 68.1% in patients in the CLDN18.2-high group

ORR	Cohort 4B		
	Overall (n = 58)[a]	CLDN18.2 high (n = 47)	CLDN18.2 intermediate (n = 10)
n (%)	36 (62.1)	32 (68.1)	4 (40.0)
95% CI	48.4–74.5	52.9–80.9	12.2–73.8



Shitara ASCO GI 2026, Abs 284

ILUSTRO Safety Profile in Cohorts 4A + 4B

The safety profile was manageable with no unexpected signals

Event, n (%)	Cohort 4A + 4B (N = 77)
TEAEs leading to discontinuation of any study drug	38 (49.4)
TEAEs leading to discontinuation of zolbetuximab	4 (5.2)
TEAEs leading to discontinuation of nivolumab	6 (7.8)
TEAEs leading to discontinuation of mFOLFOX6 component Oxaliplatin Fluorouracil bolus Fluorouracil infusion	 27 (35.1) 20 (26.0) 2 (2.6)
TEAEs leading to dose adjustment of zolbetuximab	3 (3.9)
TEAEs leading to dose adjustment of nivolumab	0
TEAEs leading to dose adjustment of mFOLFOX6 component Oxaliplatin Fluorouracil bolus Fluorouracil infusion	 43 (55.8) 29 (37.7) 36 (46.8)

- The median (range) duration of treatment was 288.5 days (1–1271) for zolbetuximab and 226.0 days (1–872) for nivolumab
- Mean (standard deviation) relative dose intensity of zolbetuximab was 97.1% (11.6) and nivolumab was 97.0% (7.1)

Shitara K et al. ASCO GI 2026. LBA284

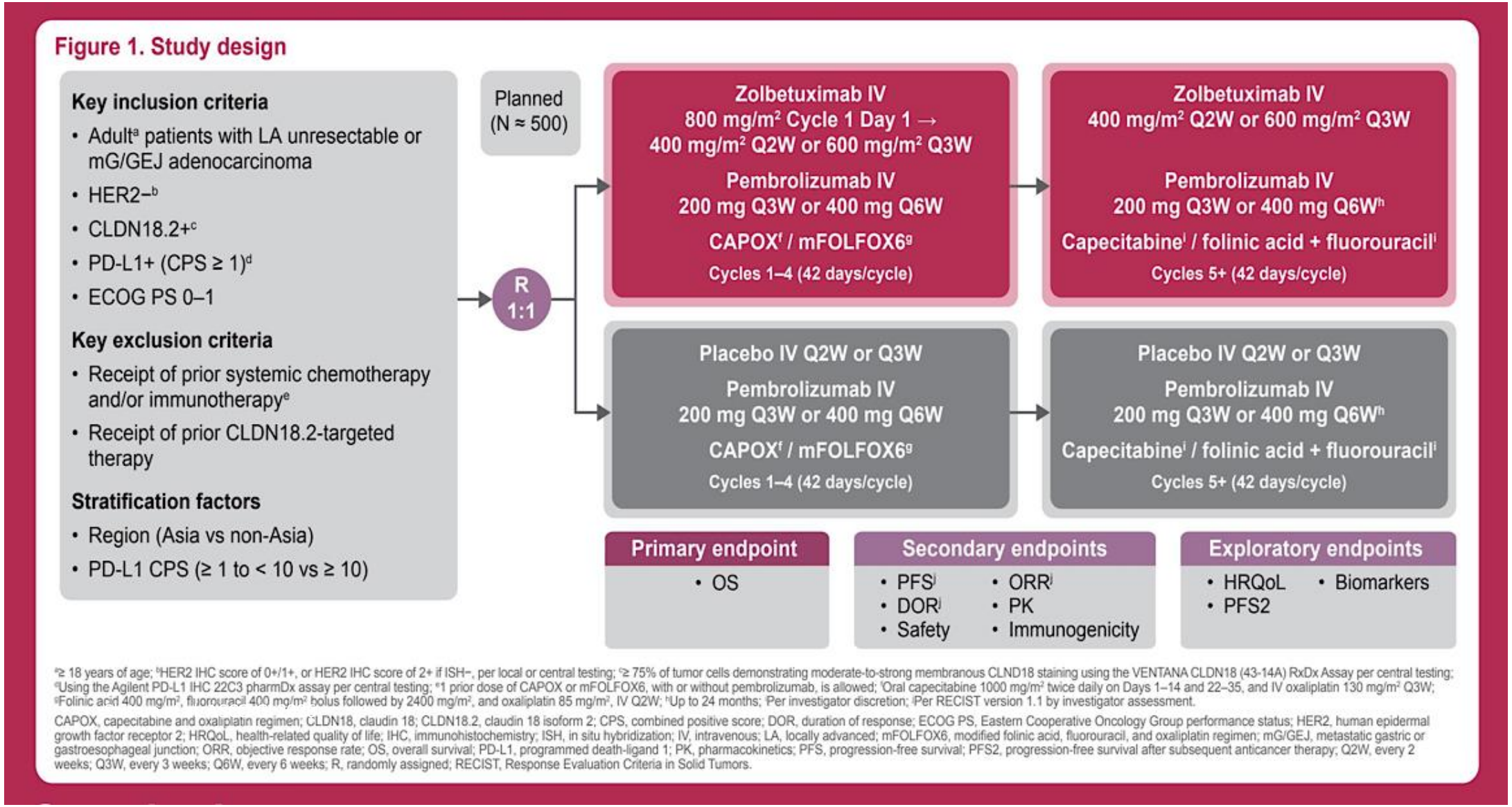
ILUSTRO TEAEs in ≥20% of Patients in All Treated Patients from Cohorts 4A + 4B

Most common adverse event was nausea; all events were low grade

Event, n (%)	Cohort 4A + 4B (N = 77)	
Any grade Related to any study drug	76 (98.7) 76 (98.7)	
Grade ≥ 3	51 (66.2)	
Serious Related to any study drug	29 (37.7) 18 (23.4)	
TEAEs in ≥ 20% of patients by preferred terms, *n* (%)	**Any grade**	**Grade ≥ 3**
Nausea	62 (80.5)	0
Decreased appetite	56 (72.7)	6 (7.8)
Neutrophil count decreased	35 (45.5)	25 (32.5)
Peripheral sensory neuropathy	35 (45.5)	2 (2.6)
Vomiting	29 (37.7)	3 (3.9)
Diarrhea	28 (36.4)	1 (1.3)
Pyrexia	24 (31.2)	0
Anemia	19 (24.7)	2 (2.6)
Constipation	17 (22.1)	0

Shitara K et al. ASCO GI 2026. LBA284

Phase 3 LUCERNA Study

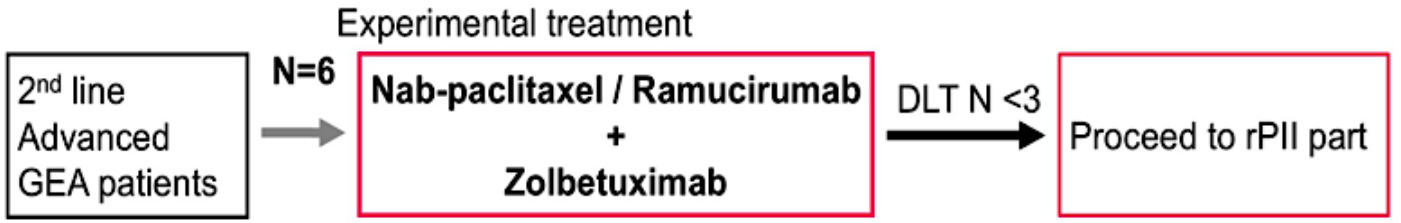


[a]≥ 18 years of age; [b]HER2 IHC score of 0+/1+, or HER2 IHC score of 2+ if ISH−, per local or central testing; [c]≥ 75% of tumor cells demonstrating moderate-to-strong membranous CLND18 staining using the VENTANA CLDN18 (43-14A) RxDx Assay per central testing; [d]Using the Agilent PD-L1 IHC 22C3 pharmDx assay per central testing; [e]1 prior dose of CAPOX or mFOLFOX6, with or without pembrolizumab, is allowed; [f]Oral capecitabine 1000 mg/m² twice daily on Days 1–14 and 22–35, and IV oxaliplatin 130 mg/m² Q3W; [g]Folinic acid 400 mg/m², fluorouracil 400 mg/m² bolus followed by 2400 mg/m², and oxaliplatin 85 mg/m², IV Q2W; [h]Up to 24 months; [i]Per investigator discretion; [j]Per RECIST version 1.1 by investigator assessment.

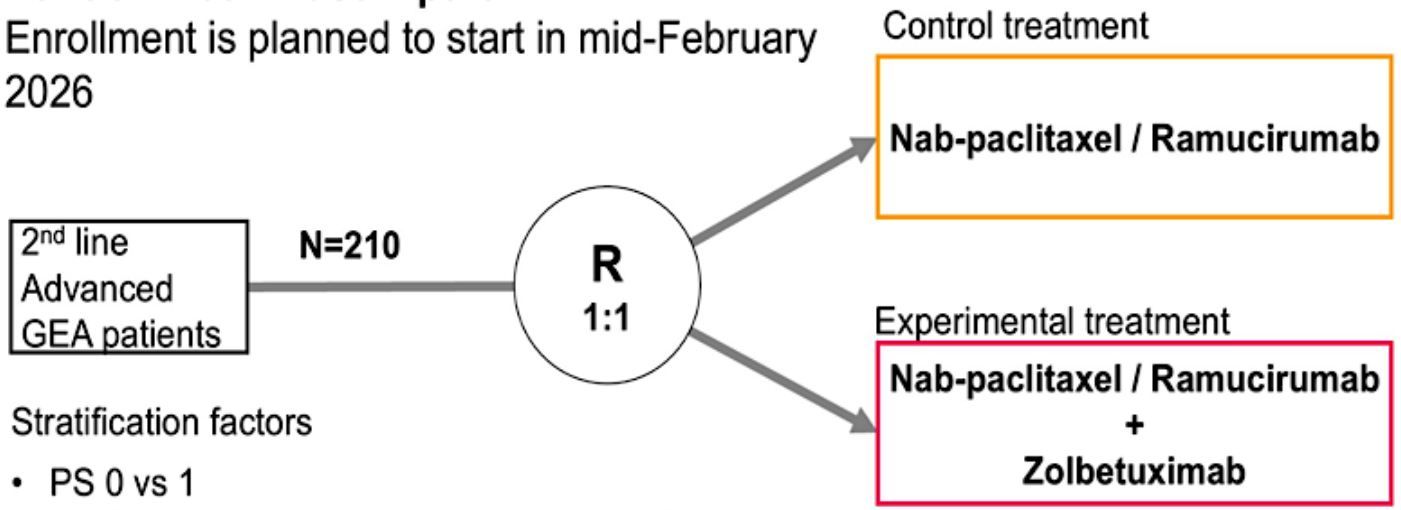
CAPOX, capecitabine and oxaliplatin regimen; CLDN18, claudin 18; CLDN18.2, claudin 18 isoform 2; CPS, combined positive score; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenous; LA, locally advanced; mFOLFOX6, modified folinic acid, fluorouracil, and oxaliplatin regimen; mG/GEJ, metastatic gastric or gastroesophageal junction; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PK, pharmacokinetics; PFS, progression-free survival; PFS2, progression-free survival after subsequent anticancer therapy; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomly assigned; RECIST, Response Evaluation Criteria in Solid Tumors.

Phase I/II ZELDA Study

Safety lead-in part;
Recruitment has been completed in December 2025



Randomized Phase II part
Enrollment is planned to start in mid-February 2026



Stratification factors

- PS 0 vs 1
- Gastric cancer vs. Esophagogastric junction cancer
- Presence or absence of resection of the primary tumor

ASCO
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KNOWLEDGE CONQUERS CANCER

ASCO Annual Meeting

Abstract #: TPS4243

Poster Session

Phase II RAINSPOT: A multicentric open label trial of zolbetuximab-paclitaxel-ramucirumab in second-line setting for CLDN18.2-positive gastro-esophageal adenocarcinoma.

Authors: Filip Van Herpe, Ana-Maria Bucalau, Eduard Callebout, Marc Van Den Eynde, Timon Vandamme, Pieter Vandecandelaere, Mieke De Wit, Kristien Dumon, Gabriela Chiritescu, Frederik Deman, Roberto Salgado, Gertjan Rasschaert, Jeroen Dekervel

Methods:

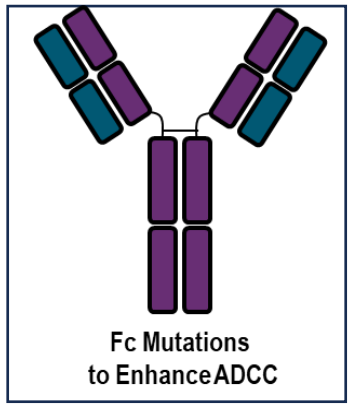
RAINSPOT is a national, multicentre, phase II, open-label study with a prospective single-arm cohort and a matched retrospective cohort across six Belgian centres. The prospective cohort will include 100 patients (≥18 years, ECOG 0–1) with metastatic or locally advanced disease progressing after one prior systemic line. Tumours must be CLDN18.2-positive (≥75% moderate-to-strong membranous staining; Ventana 43-14A assay). A fresh biopsy at progression is obtained when feasible. Treatment consists of zolbetuximab (800 mg/m² loading, then 400 mg/m² q2w), paclitaxel (80 mg/m² weekly ×3 q28d) and ramucirumab (8 mg/kg q2w). Treatment continues until progression or unacceptable toxicity. HRQoL is assessed every 4 weeks (EORTC QLQ-C30, QLQ-OG25).

The retrospective cohort includes patients treated with second-line paclitaxel–ramucirumab (2021–2023) with archived tissue reassessed for CLDN18.2; only baseline-positive patients are eligible. Propensity score matching (1:1; SMD ≤0.05) uses age, sex, tumour location, gastrectomy, peritoneal

CLDN18.2 Targeted Therapies

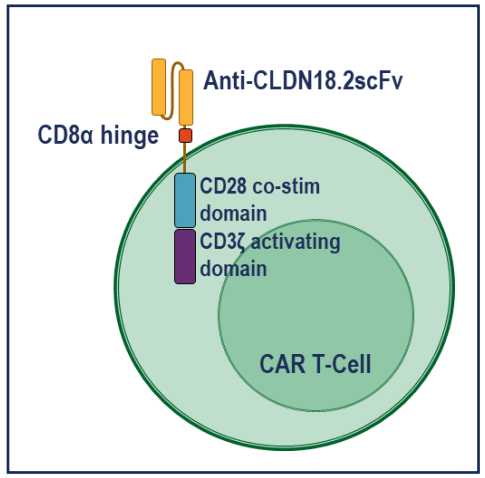
Monoclonal antibody

- Humanized mAb
- Engineered mAb



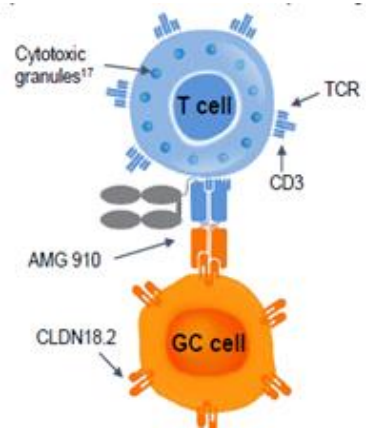
Zolbetuximab
TST-001
ABI011, MIL93, ZL1211
etc.

CAR-T



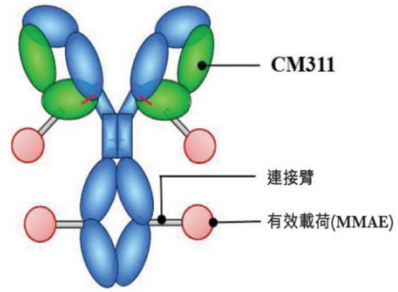
CT-041
LCAR-C18S
LY011

Bispecific



AMG910/ASP2138 (CD3)
TJ-CD4B (4-1BB)
PT886 (CD47)
Q-1802 (PD-L1)
IBI 389

ADCs



CMG901, EO-3021
TORL-2800
TPX4589
RC118
LM302
SOT102
SKB315
JS107
IBI343

Regulatory and reimbursement issues aside, what first-line treatment would you most likely recommend for a 65-year-old patient presenting with metastatic CLDN18.2-positive, HER2-negative, MSS gastric adenocarcinoma with PD-L1 CPS 0?

 Dr Janjigian	Chemotherapy + zolbetuximab
 Dr Shah	Chemotherapy + zolbetuximab
 Prof Van Cutsem	Chemotherapy + zolbetuximab
 Dr Kim	Chemotherapy + zolbetuximab
 Dr Klempner	Chemotherapy + zolbetuximab
 Dr Wainberg	Chemotherapy + zolbetuximab

MSS = microsatellite-stable; CPS = combined positive score

Regulatory and reimbursement issues aside, what first-line treatment would you most likely recommend for a 65-year-old patient presenting with metastatic CLDN18.2-positive, HER2-negative, MSS gastric adenocarcinoma with PD-L1 CPS 1?

 Dr Janjigian	Chemotherapy + anti-PD-1/PD-L1 antibody
 Dr Shah	Chemotherapy + zolbetuximab
 Prof Van Cutsem	Chemotherapy + zolbetuximab
 Dr Kim	Chemotherapy + zolbetuximab
 Dr Klempner	Chemotherapy + zolbetuximab and anti-PD-1/PD-L1 antibody
 Dr Wainberg	Chemotherapy + zolbetuximab and anti-PD-1/PD-L1 antibody

MSS = microsatellite-stable; CPS = combined positive score

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what first-line treatment would you most likely recommend for a 65-year-old patient presenting with metastatic CLDN18.2-positive, HER2-negative, MSS gastric adenocarcinoma with PD-L1 CPS 10?

 Dr Janjigian	Chemotherapy + anti-PD-1/PD-L1 antibody
 Dr Shah	Chemotherapy + anti-PD-1/PD-L1 antibody
 Prof Van Cutsem	Chemotherapy + anti-PD-1/PD-L1 antibody
 Dr Kim	Chemotherapy + anti-PD-1/PD-L1 antibody
 Dr Klempner	Chemotherapy + anti-PD-1/PD-L1 antibody
 Dr Wainberg	Chemotherapy + zolbetuximab and anti-PD-1/PD-L1 antibody

MSS = microsatellite-stable; CPS = combined positive score

RTP RESEARCH TO PRACTICE

Faculty Discussion

- **Regulatory and reimbursement issues aside, what first-line treatment would you most likely recommend for a 65-year-old patient presenting with metastatic CLDN18.2-positive, HER2-negative, MSS gastric adenocarcinoma with PD-L1 CPS 0? PD-L1 CPS 1? PD-L1 CPS 10?**

How would you indirectly compare the global efficacy of zolbetuximab and chemotherapy to that of an anti-PD-1 antibody and chemotherapy for patients with newly diagnosed gastric/GEJ adenocarcinoma who are eligible for both treatments?

 Dr Janjigian	An anti-PD-1 antibody/chemotherapy is more efficacious
 Dr Shah	About the same
 Prof Van Cutsem	About the same
 Dr Kim	An anti-PD-1 antibody/chemotherapy is more efficacious
 Dr Klempner	About the same
 Dr Wainberg	About the same

RTP RESEARCH TO PRACTICE

What premedication(s), if any, do you generally recommend for a patient who is about to begin treatment with zolbetuximab?

 Dr Janjigian	Standard quadruple regimen
 Dr Shah	Full antiemetics: ondansetron, aprepitant, steroids
 Prof Van Cutsem	Triple antiemetic: steroid (dexamethasone), 5HT3 and NK1 receptor blocker (+ evt olanzapine)
 Dr Kim	IV aprepitant, palonsetron, dexamethasone and olanzapine
 Dr Klempner	Palonsetron IV, dexamethasone IV, fosaprepitant IV, olanzapine or lorazepam added commonly, and sometimes IV diphenhydramine
 Dr Wainberg	The kitchen sink!

RTP RESEARCH TO PRACTICE

Outside of a clinical trial, have you administered or would you administer both zolbetuximab and an anti-PD-1/PD-L1 antibody in combination with first-line chemotherapy for a patient with newly diagnosed gastric/GEJ adenocarcinoma?

 Dr Janjigian	I have
 Dr Shah	I have not and would not
 Prof Van Cutsem	I have not and would not
 Dr Kim	I have not but would for the right patient
 Dr Klempner	I have
 Dr Wainberg	I have

RTP RESEARCH TO PRACTICE

In which situations, if any, would you attempt to employ zolbetuximab as second- or later-line treatment, and what would you feel comfortable combining it with?

 Dr Janjigian	None
 Dr Shah	For high CLDN18.2 expressors, after 2nd line
 Prof Van Cutsem	Generally none — no data
 Dr Kim	Unlikely
 Dr Klempner	Rare situations due to lack of data
 Dr Wainberg	After progression on FOLFOX/nivolumab, I have done with 5-FU

RTP RESEARCH TO PRACTICE

Faculty Discussion

- How would you indirectly compare the global efficacy and tolerability of zolbetuximab and chemotherapy to that of an anti-PD-1 antibody and chemotherapy for patients with newly diagnosed gastric/GEJ adenocarcinoma who are eligible for both treatments?
- What premedication(s), if any, do you generally recommend for a patient who is about to begin treatment with zolbetuximab?
- Outside of a clinical trial, have you administered or would you administer both zolbetuximab and an anti-PD-1/PD-L1 antibody in combination with first-line chemotherapy for a patient with newly diagnosed gastric/GEJ adenocarcinoma?
- In which situations, if any, would you attempt to employ zolbetuximab as second- or later-line treatment, and what would you feel comfortable combining it with?

Agenda

Module 1: HER2-Targeted Approaches in Advanced Gastroesophageal Cancers — Prof Van Cutsem

Module 2: Targeting CLDN18.2 in Advanced Gastroesophageal Cancers — Dr Shah

Module 3: Available Immunotherapeutic Strategies for Advanced Gastroesophageal Cancers — Dr Janjigian

RTP RESEARCH TO PRACTICE

Memorial Sloan Kettering Cancer Center

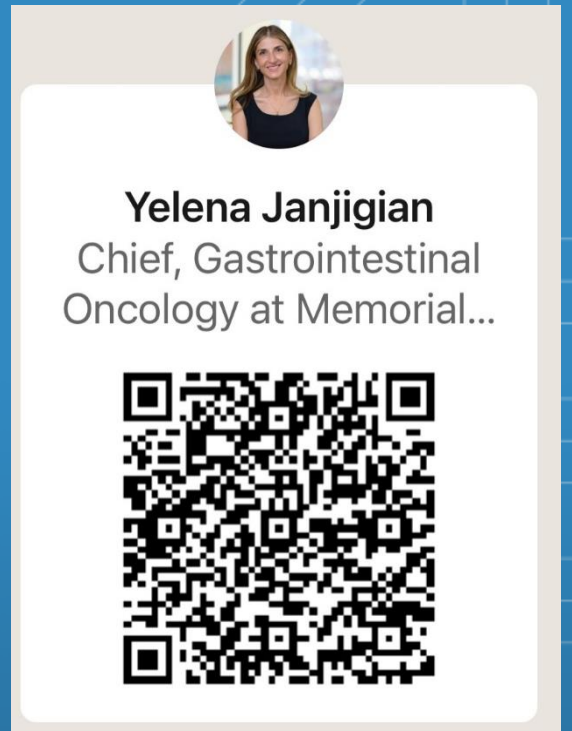
Available Immunotherapeutic Strategies for Advanced Gastroesophageal Cancers

Yelena Y. Janjigian, MD
Chief Attending Physician
Carroll & Milton Petrie Chair

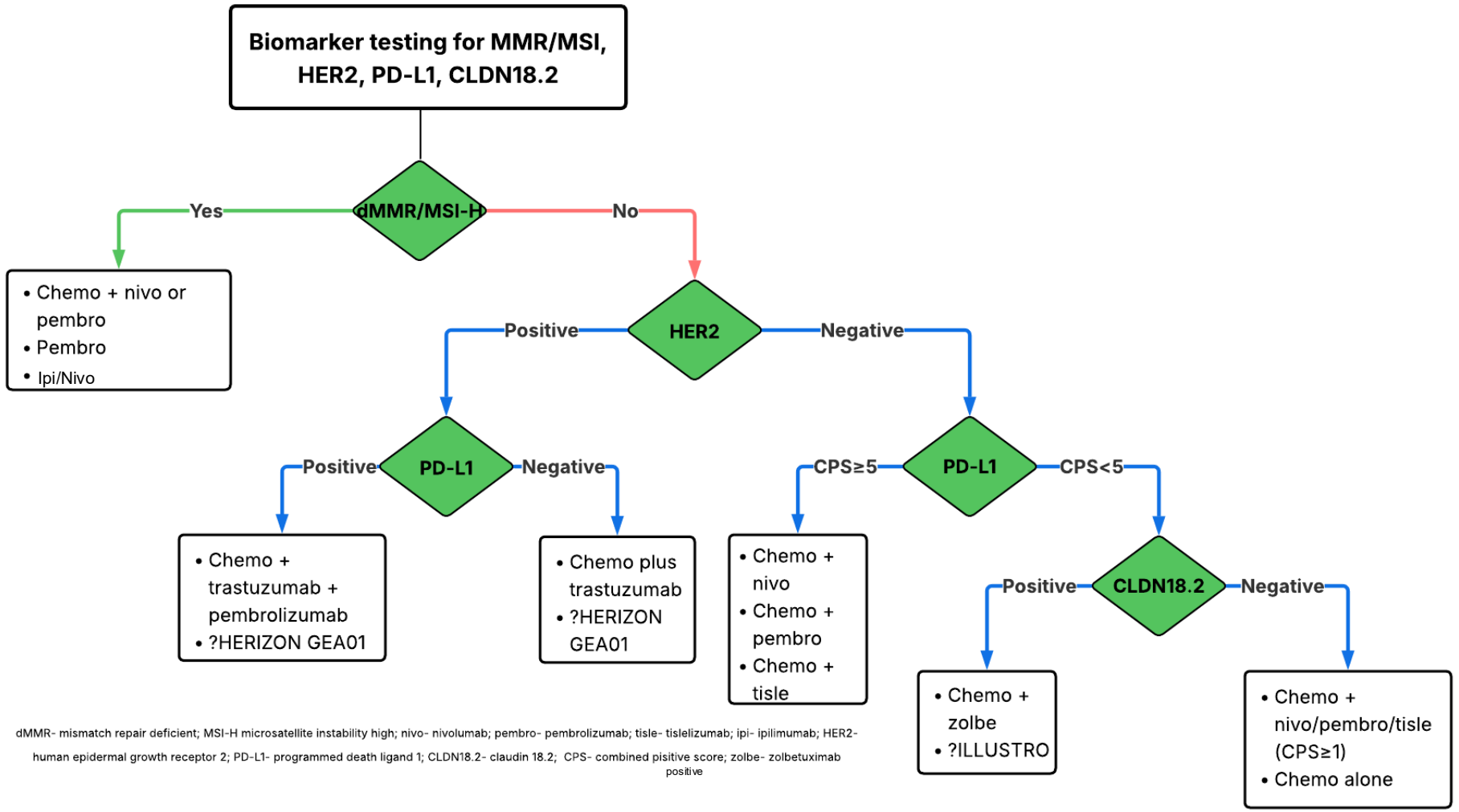
Gastrointestinal Oncology Service
Memorial Sloan Kettering Cancer Center

Email: janjigiy@mskcc.org

Friday, May 29th | 10 minutes



Approach to 1L Treatment of Gastroesophageal Cancers



dMMR- mismatch repair deficient; MSI-H microsatellite instability high; nivo- nivolumab; pembro- pembrolizumab; tisle- tislelizumab; ipi- ipilimumab; HER2- human epidermal growth receptor 2; PD-L1- programmed death ligand 1; CLDN18.2- claudin 18.2; CPS- combined pisitive score; zolbe- zolbetuximab positive

Janjigian Y et al. The Lancet 2021; Chao J. *JAMA Oncol* 2021; Rha S et al, *The Lancet Oncol* 2023; Qiu MZ et al. *BMJ* 2024; Janjigian Y et al. *NEJM* 2024; Shitara K et al. *The Lancet* 2023; Shah MA et al. *Nat Med* 2023.

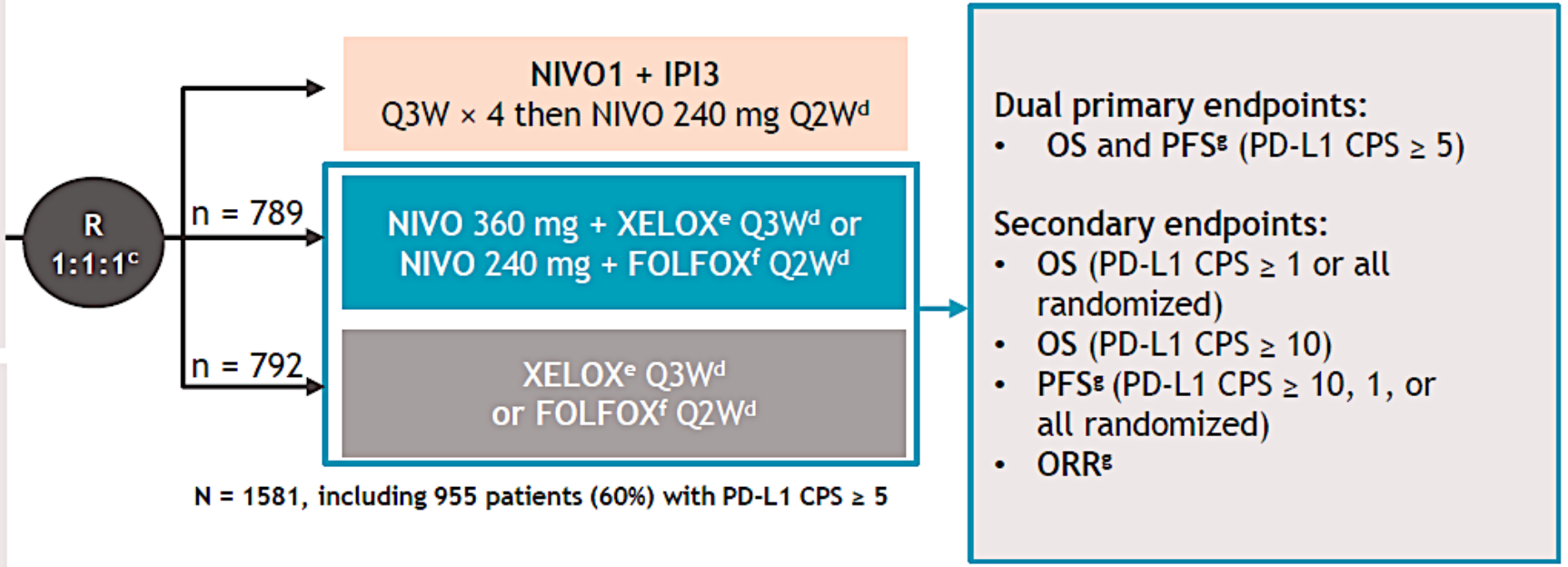
Courtesy of Rutika Mehta, MD, MPH

CheckMate-649

- CheckMate 649 is a randomized, open-label, phase 3 study[a]

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/ esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0-1

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)

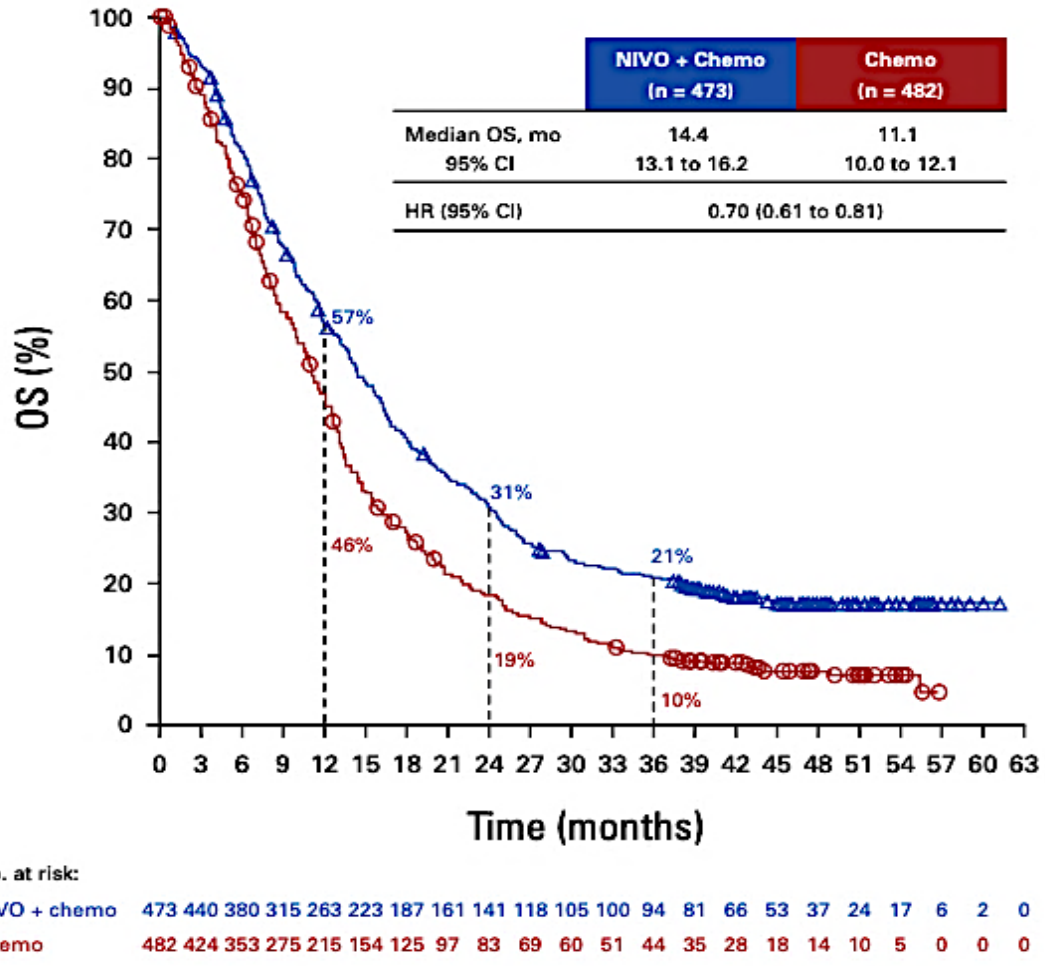


70%- GASTRIC; 16-17%- GEJ; 13-14%- EAC

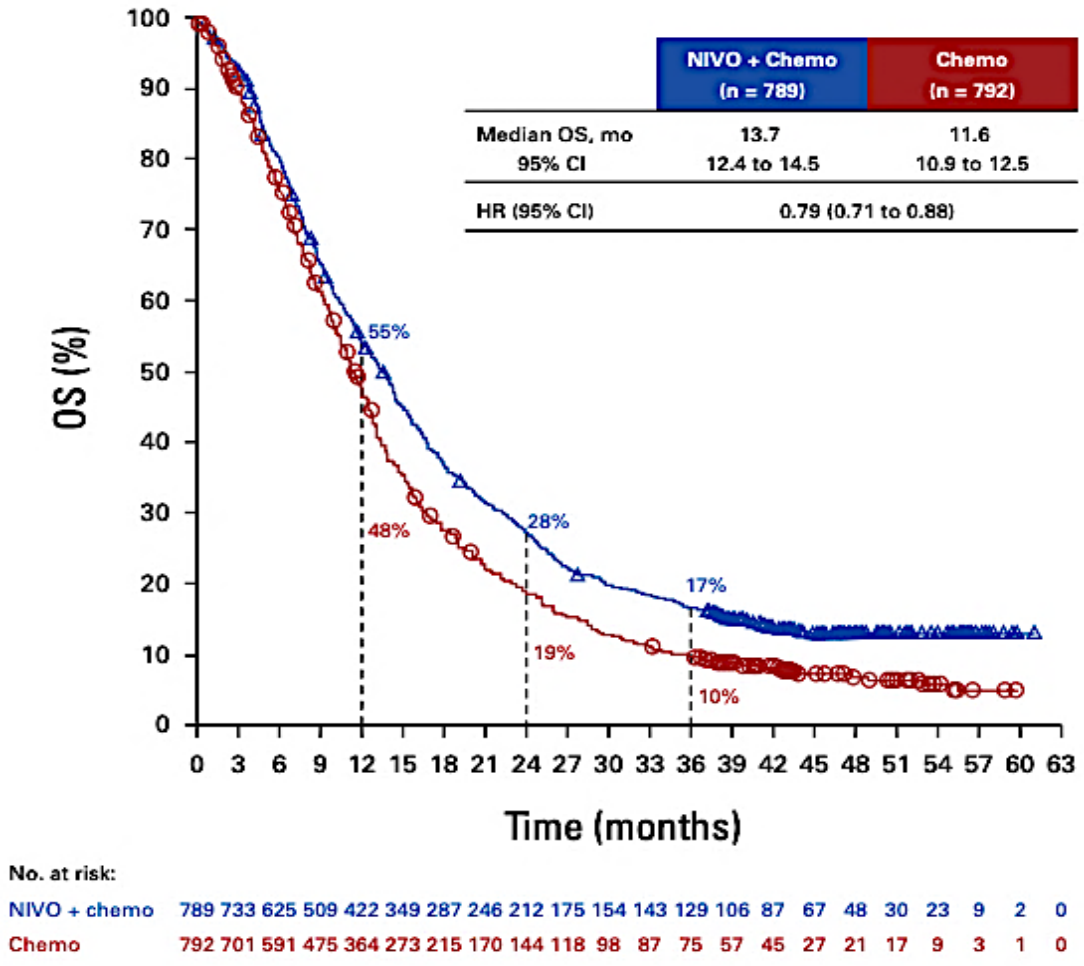
Moehler et al. *Annals of Oncology* 2020.

Courtesy of Rutika Mehta, MD, MPH

Addition of Nivolumab Improves OS



PD-L1 CPS ≥5

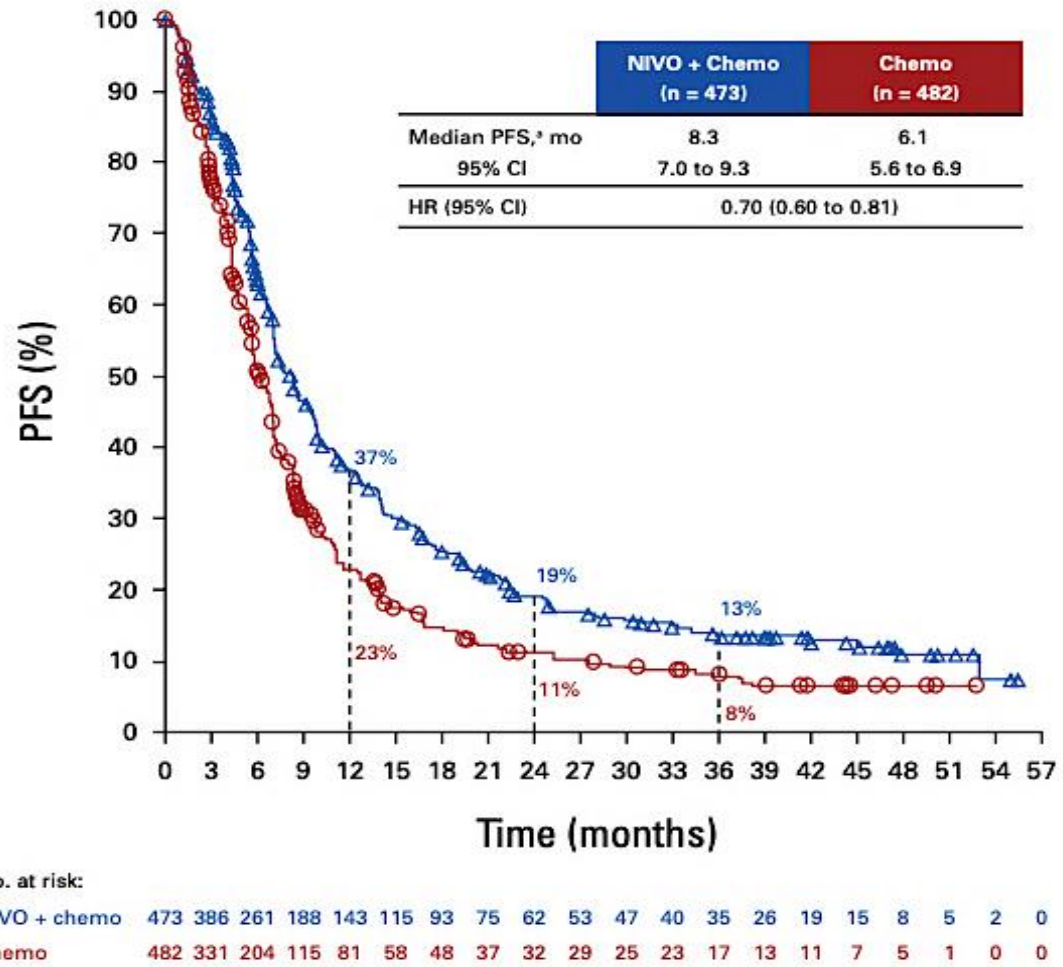


All randomized patients

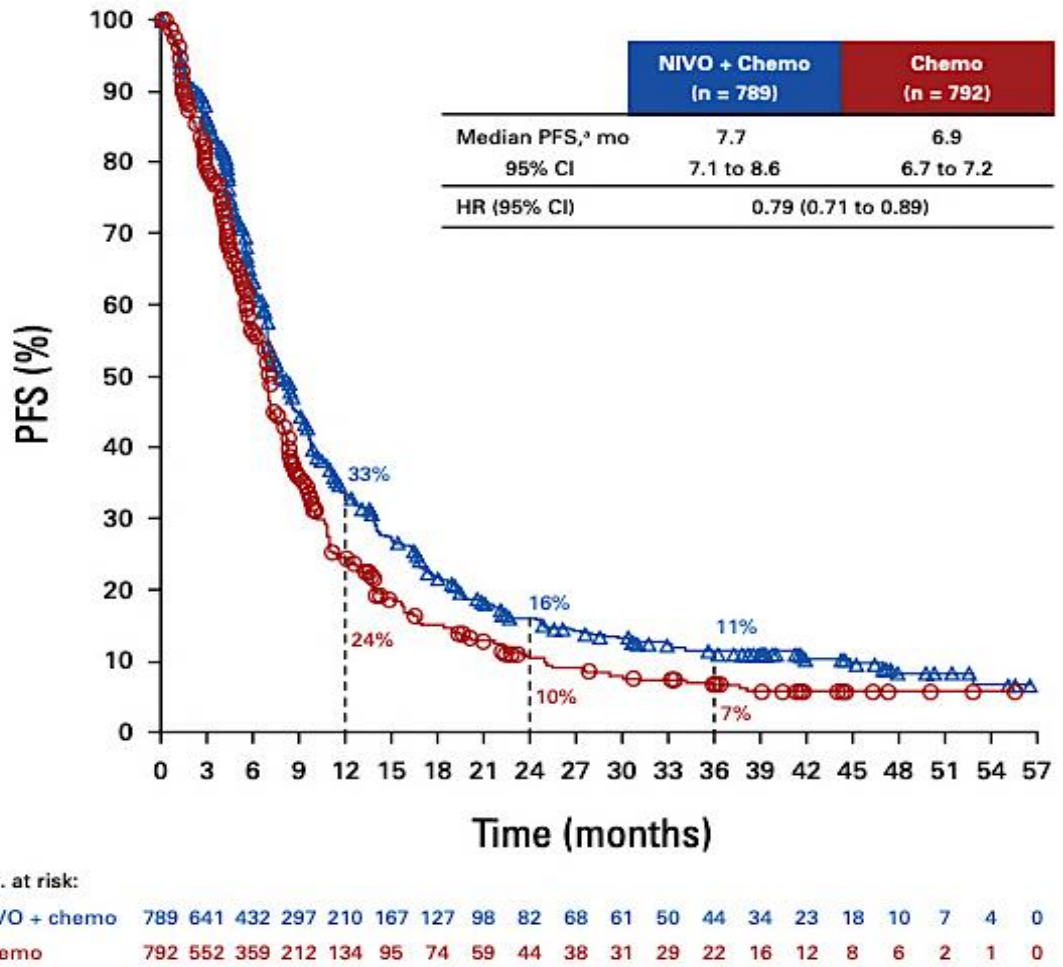
Janjigian Y et al. *J Clin Oncol* 2024.

Courtesy of Rutika Mehta, MD, MPH

Addition of Nivolumab Improves PFS



PD-L1 CPS ≥5

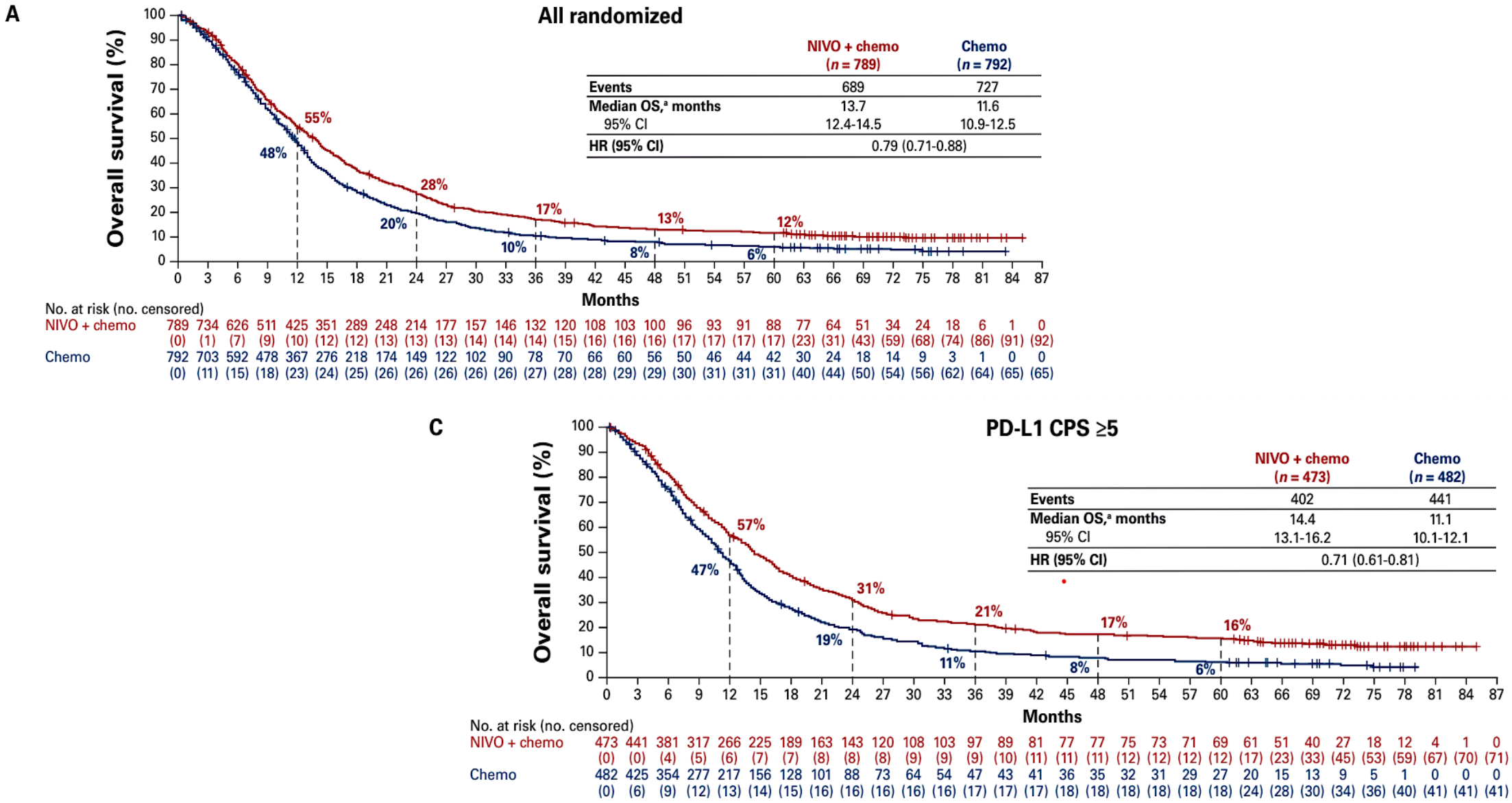


All randomized patients

Janjigian Y et al. *J Clin Oncol* 2024.

Courtesy of Rutika Mehta, MD, MPH

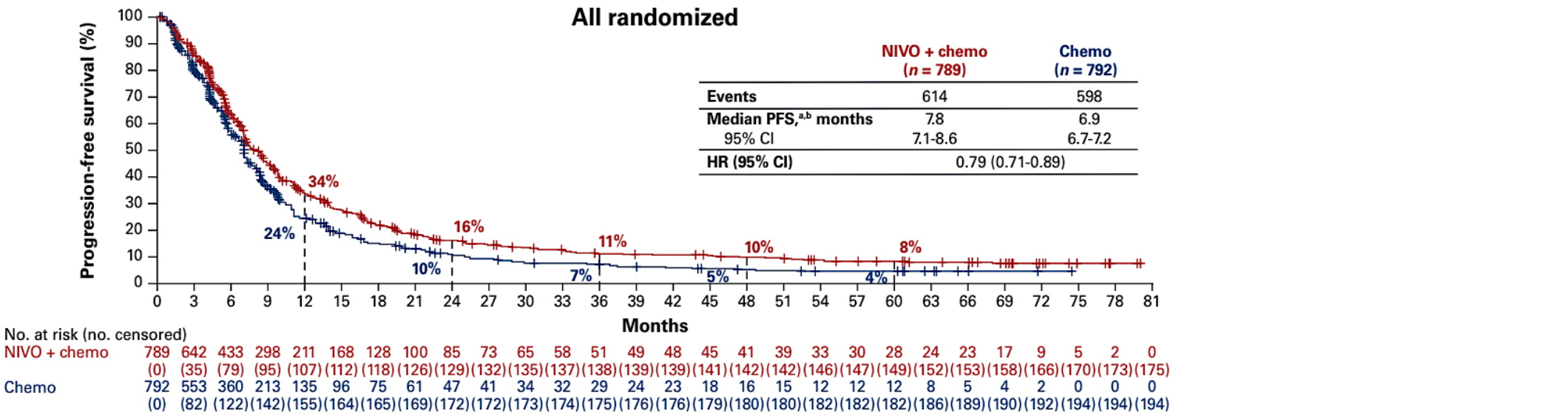
Five-Year OS Results



Janjigian Y et al. *Ann Oncol* 2026.

Five-Year PFS Results

E

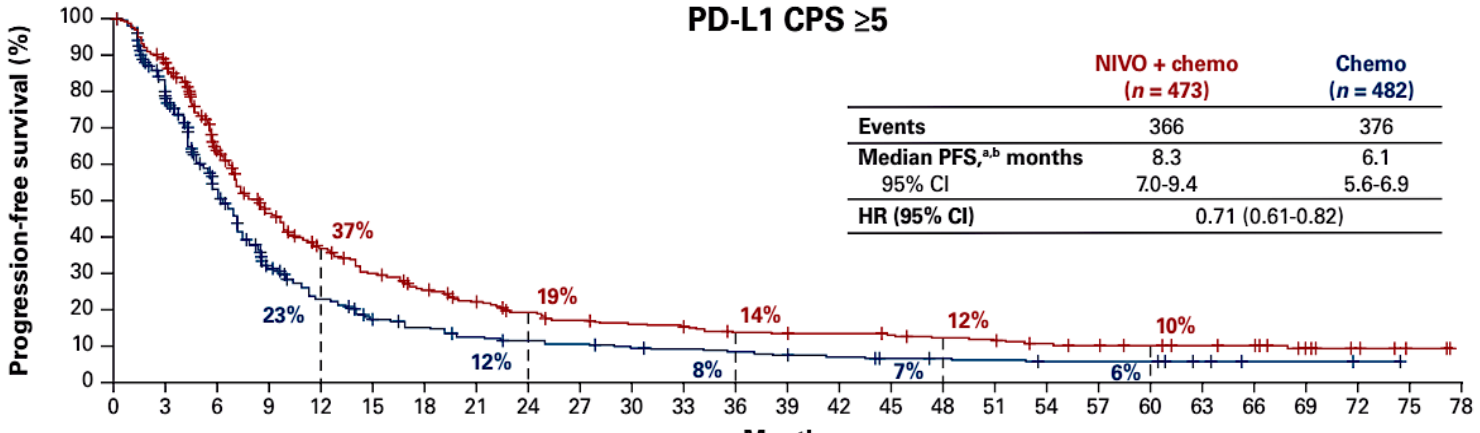


	NIVO + chemo (*n* = 789)	Chemo (*n* = 792)
Events	614	598
Median PFS,[a,b] months	7.8	6.9
95% CI	7.1-8.6	6.7-7.2
HR (95% CI)	0.79 (0.71-0.89)	

No. at risk (no. censored)

NIVO + chemo	789	642	433	298	211	168	128	100	85	73	65	58	51	49	48	45	41	39	33	30	28	24	23	17	9	5	2	0
	(0)	(35)	(79)	(95)	(107)	(112)	(118)	(126)	(129)	(132)	(135)	(137)	(138)	(139)	(139)	(141)	(142)	(142)	(146)	(147)	(149)	(152)	(153)	(158)	(166)	(170)	(173)	(175)
Chemo	792	553	360	213	135	96	75	61	47	41	34	32	29	24	23	18	16	15	12	12	12	8	5	4	2	0	0	0
	(0)	(82)	(122)	(142)	(155)	(164)	(165)	(169)	(172)	(172)	(173)	(174)	(175)	(176)	(176)	(179)	(180)	(180)	(182)	(182)	(182)	(186)	(189)	(190)	(192)	(194)	(194)	(194)

G



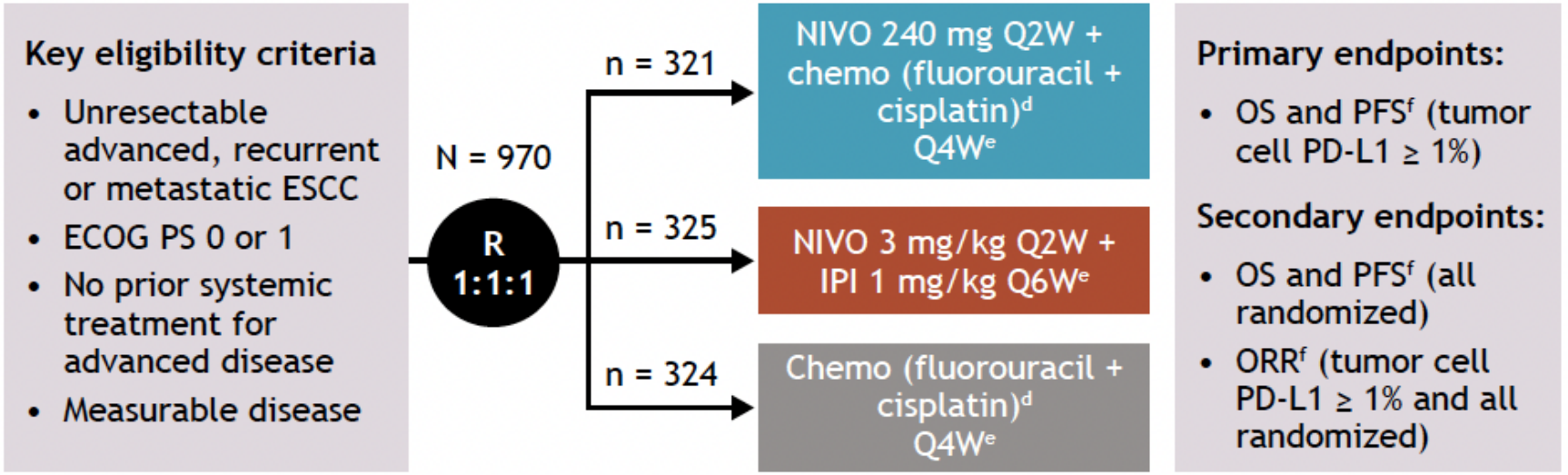
	NIVO + chemo (*n* = 473)	Chemo (*n* = 482)
Events	366	376
Median PFS,[a,b] months	8.3	6.1
95% CI	7.0-9.4	5.6-6.9
HR (95% CI)	0.71 (0.61-0.82)	

No. at risk (no. censored)

NIVO + chemo	473	387	262	189	144	116	94	77	65	56	50	47	41	39	39	37	34	32	28	25	23	20	19	13	7	3	0
	(0)	(19)	(44)	(51)	(57)	(59)	(63)	(69)	(71)	(73)	(75)	(76)	(77)	(78)	(78)	(79)	(80)	(80)	(82)	(83)	(85)	(88)	(89)	(94)	(100)	(104)	(107)
Chemo	482	331	205	116	82	59	49	39	35	32	28	26	24	20	19	15	14	13	11	11	11	7	4	4	2	0	0
	(0)	(45)	(62)	(74)	(78)	(83)	(84)	(86)	(87)	(87)	(88)	(89)	(89)	(90)	(90)	(93)	(94)	(94)	(95)	(95)	(95)	(99)	(102)	(102)	(104)	(106)	(106)

Janjigian Y et al. *Ann Oncol* 2026.

CheckMate 648: A Phase III Study of First-Line Nivolumab/ Chemotherapy or Nivolumab/Ipilimumab for Esophageal Squamous Cell Carcinoma (ESCC)



Stratification factors

- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (East Asia[c] vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- No. of organs with metastases (≤ 1 vs ≥ 2)

[a]ClinicalTrials.gov. NCT03143153. [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako). [c]East Asia includes patients from Japan, Korea, and Taiwan. [d]Fluorouracil 800 mg/m^2 IV daily (days 1-5) and cisplatin 80 mg/m^2 IV (day 1). [e]Until documented disease progression (unless consented to treatment beyond progression for NIVO + IPI or NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given alone or in combination with IPI for a maximum of 2 years. [f]Per BICR. BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; ORR, objective response rate; PFS, progression-free survival; Q×W, every × weeks; R, randomization; ROW, rest of world.

Chau I et al. ESMO 2025;Abstract 2106P.

Phase III CheckMate 648: Authors' Conclusions

- With 5 years minimum follow-up, NIVO + chemo and NIVO + IPI continued to demonstrate clinically meaningful long-term survival benefit and more durable responses vs chemo as 1L treatment for advanced ESCC
  - OS benefits were observed with NIVO + chemo and NIVO + IPI vs chemo in patients with tumor cell PD-L1 ≥ 1% and all randomized patients
  - OS favored NIVO + chemo and NIVO + IPI across most subgroups, with the greatest magnitude of benefit seen among patients with PD-L1 ≥ 1%
  - PFS benefit with NIVO + chemo vs chemo was observed in patients with tumor cell PD-L1 ≥ 1%
  - ORR was higher with NIVO + chemo regardless of PD-L1 status and was higher with NIVO + IPI in patients with PD-L1 ≥ 1%
  - Longer DOR was observed with NIVO + chemo and NIVO + IPI vs chemo
- No new safety signals were identified with NIVO + chemo or NIVO + IPI at the 5-year follow-up
  - No additional TRAEs leading to discontinuation and no new treatment-related deaths were reported with longer follow-up
- These results further support NIVO + chemo and NIVO + IPI as 1L standard of care treatments for patients with advanced ESCC

Chau I et al. ESMO 2025;Abstract 2106P.

KEYNOTE-859

Randomized, Double-Blind, Phase 3 Trial

Key Eligibility Criteria

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

R
1:1

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

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

Stratification Factors

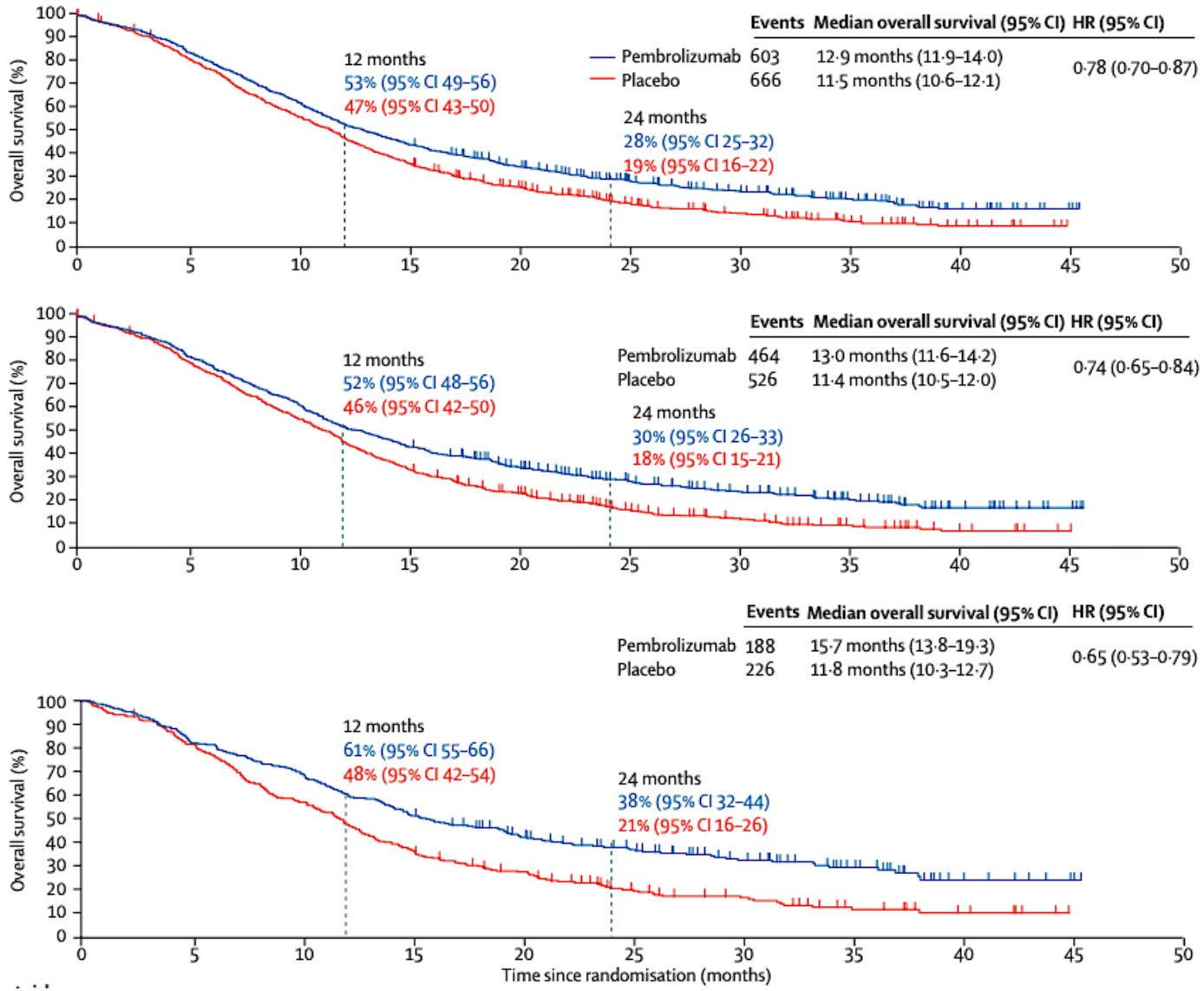
- Geographic region (Europe/Israel/North America/ Australia vs Asia vs rest of world)
- PD-L1 CPS (<1 vs ≥1)
- Choice of chemotherapy[a] (FP vs CAPOX)

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

Rha SY et al. *Lancet Oncol* 2023.

Courtesy of Rutika Mehta, MD, MPH

Addition of Pembrolizumab Improves OS



Intention-to-treat population

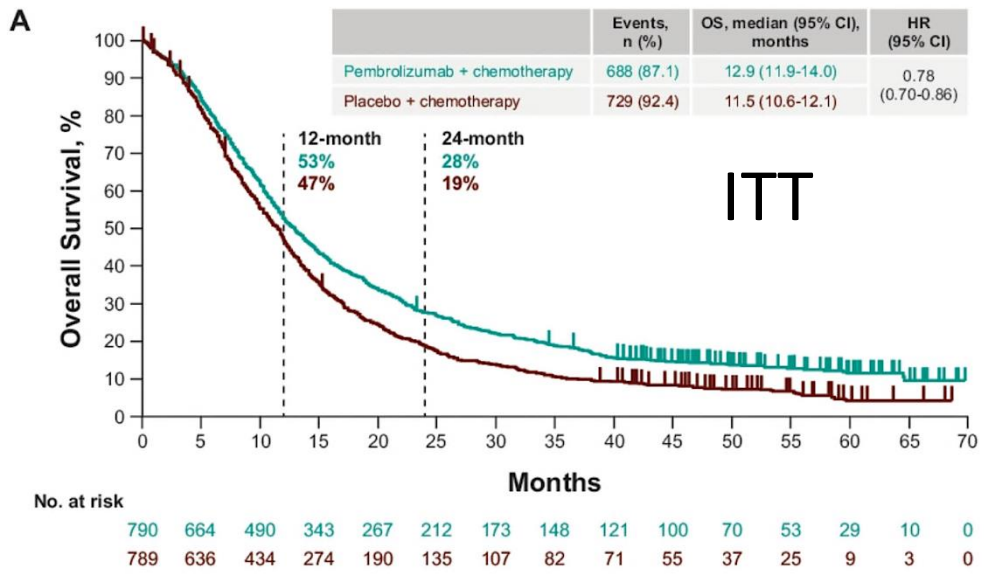
PD-L1 CPS ≥1

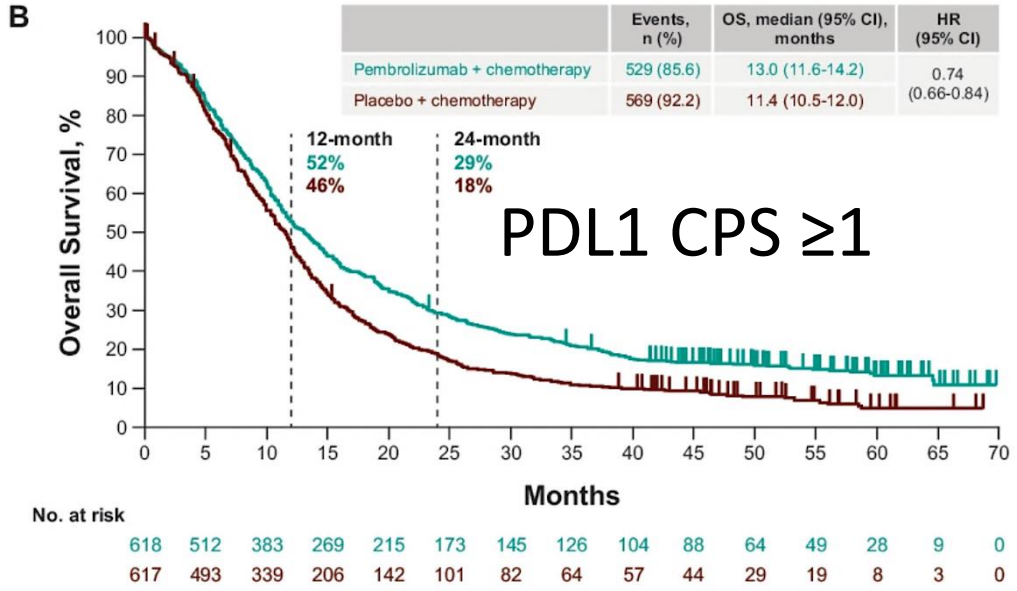
PD-L1 CPS ≥10

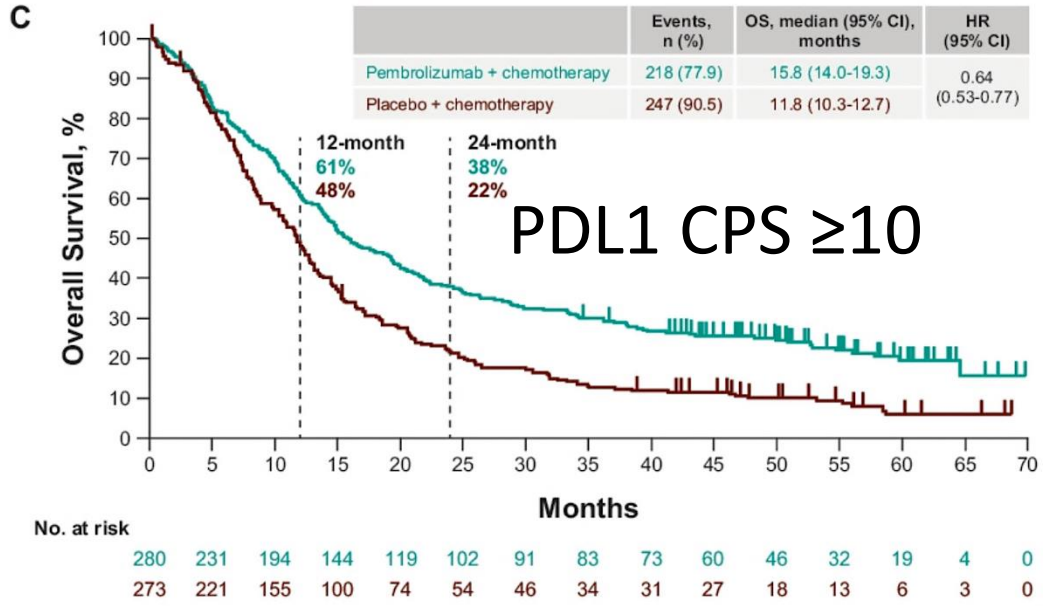
Rha SY et al. *Lancet Oncol* 2023.

Courtesy of Rutika Mehta, MD, MPH

OS Benefit Maintained at 4.5 Year Follow-Up

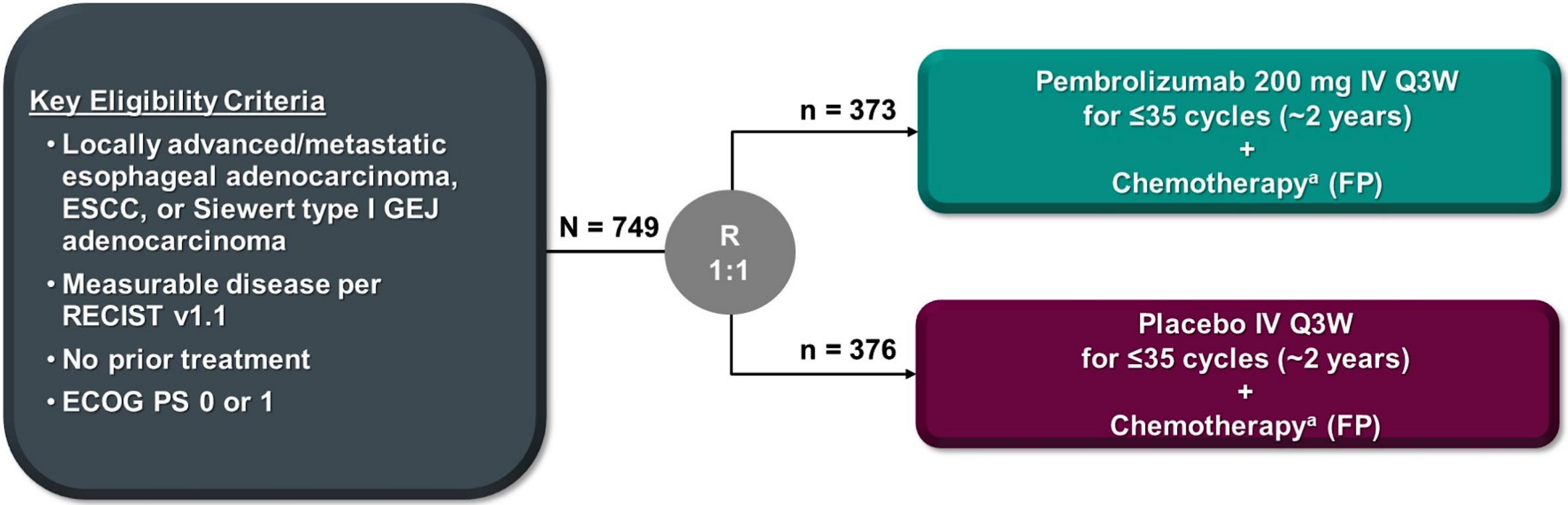






Rha SY et al. ASCO 2025.

KEYNOTE-590: A Phase III Study of First-Line Pembrolizumab and Chemotherapy for GE Cancers



Stratification Factors

- Geographic region (Asia vs rest of world)
- Histology (adenocarcinoma vs squamous cell carcinoma)
- ECOG PS (0 vs 1)

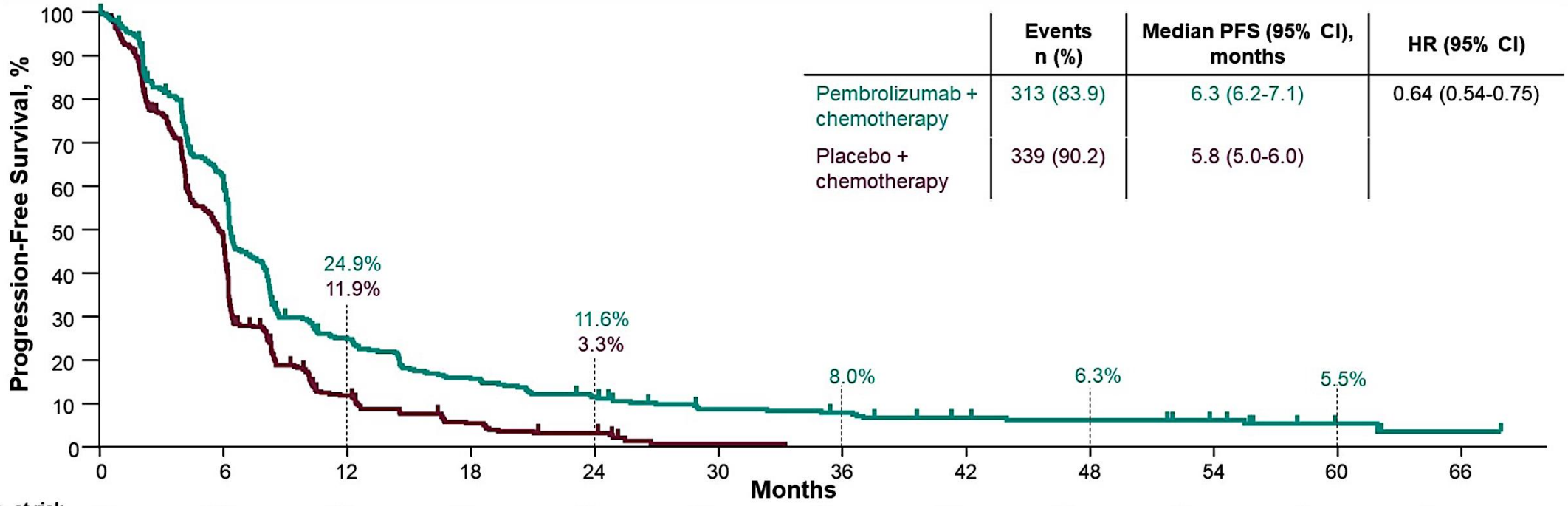
End Points

- Primary: OS,[b] PFS[c,d]
- Secondary: ORR[d], DOR[d], safety, PROs[e]

PROs = patient-reported outcomes

Shah M et al. Gastrointestinal Cancers Symposium 2024;Abstract 250.

KEYNOTE-590: PFS in the Intent-to-Treat Population



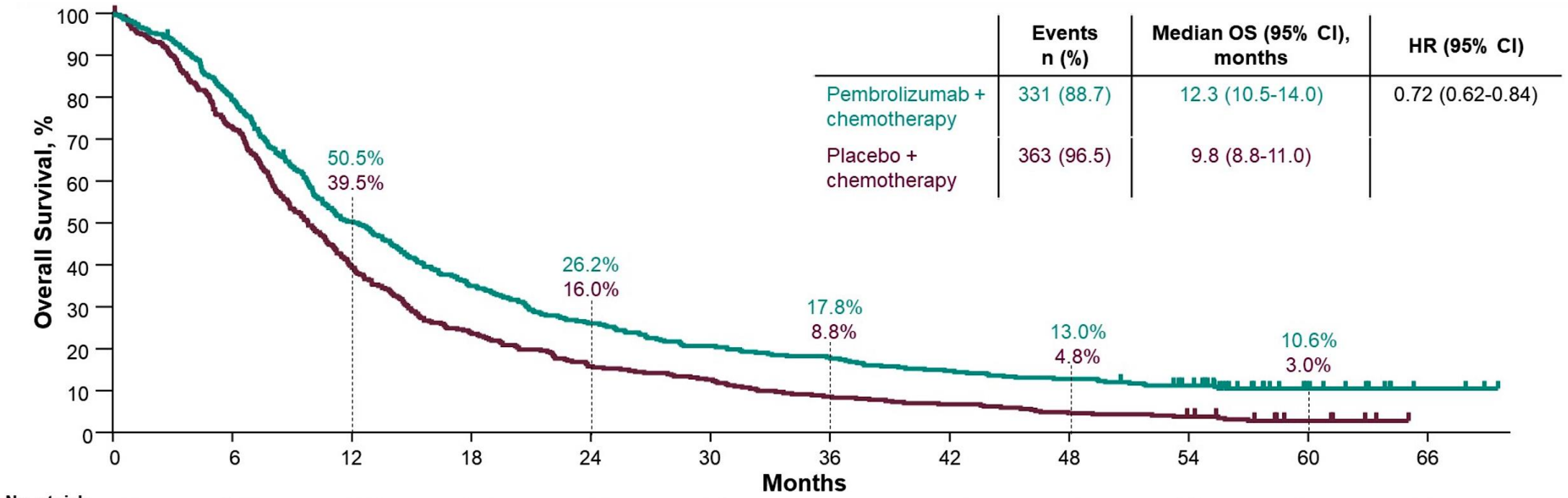
	Events n (%)	Median PFS (95% CI), months	HR (95% CI)
Pembrolizumab + chemotherapy	313 (83.9)	6.3 (6.2-7.1)	0.64 (0.54-0.75)
Placebo + chemotherapy	339 (90.2)	5.8 (5.0-6.0)	

	CPS ≥10		ESCC		ESCC and CPS ≥10	
	Pembro + chemo n = 186	Placebo + chemo n = 197	Pembro + chemo n = 274	Placebo + chemo n = 274	Pembro + chemo n = 143	Placebo + chemo n = 143
PFS HR (95% CI)	0.51 (0.40-0.64)		0.65 (0.54-0.78)		0.53 (0.41-0.69)	
5-y PFS rate,[a] %	7.5	0	6.7	0	9.1	0

[a]Kaplan-Meier estimate. Data cutoff: July 10, 2023.

Shah M et al. Gastrointestinal Cancers Symposium 2024;Abstract 250.

KEYNOTE-590: OS in the Intent-to-Treat Population



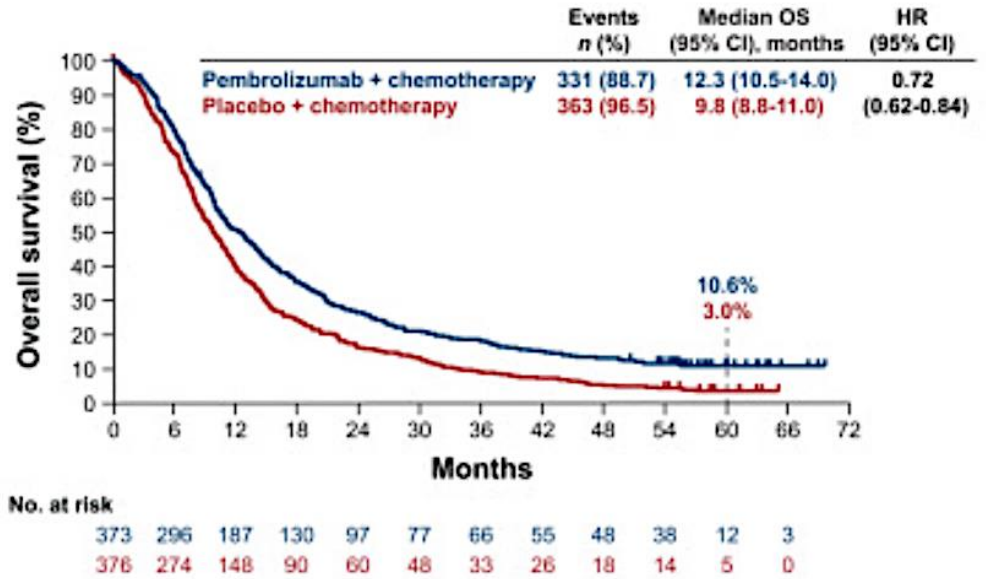
	Events n (%)	Median OS (95% CI), months	HR (95% CI)
Pembrolizumab + chemotherapy	331 (88.7)	12.3 (10.5-14.0)	0.72 (0.62-0.84)
Placebo + chemotherapy	363 (96.5)	9.8 (8.8-11.0)	

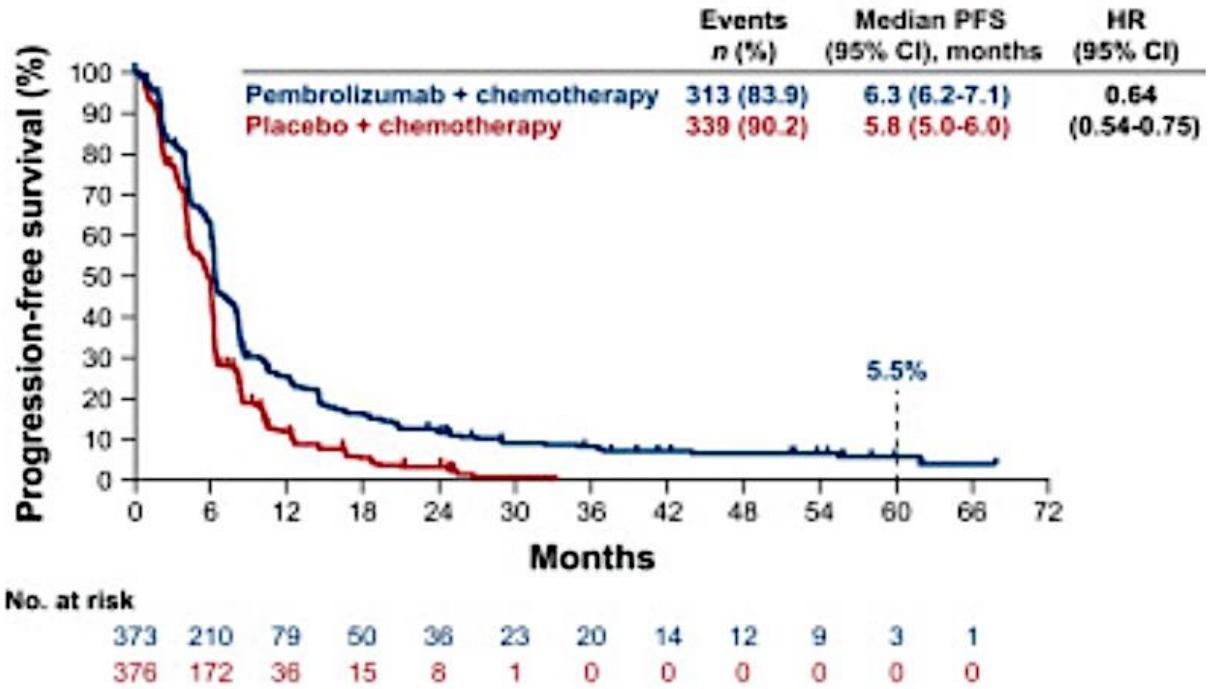
	CPS ≥10		ESCC		ESCC and CPS ≥10	
	Pembro + chemo n = 186	Placebo + chemo n = 197	Pembro + chemo n = 274	Placebo + chemo n = 274	Pembro + chemo n = 143	Placebo + chemo n = 143
OS, HR (95% CI)	0.64 (0.52-0.80)		0.71 (0.60-0.85)		0.60 (0.46-0.76)	
5-y OS rate,[a] %	12.8	3.8	11.8	3.4	13.8	3.7

[a]Kaplan-Meier estimate. Data cutoff: July 10, 2023.

Shah M et al. Gastrointestinal Cancers Symposium 2024;Abstract 250.

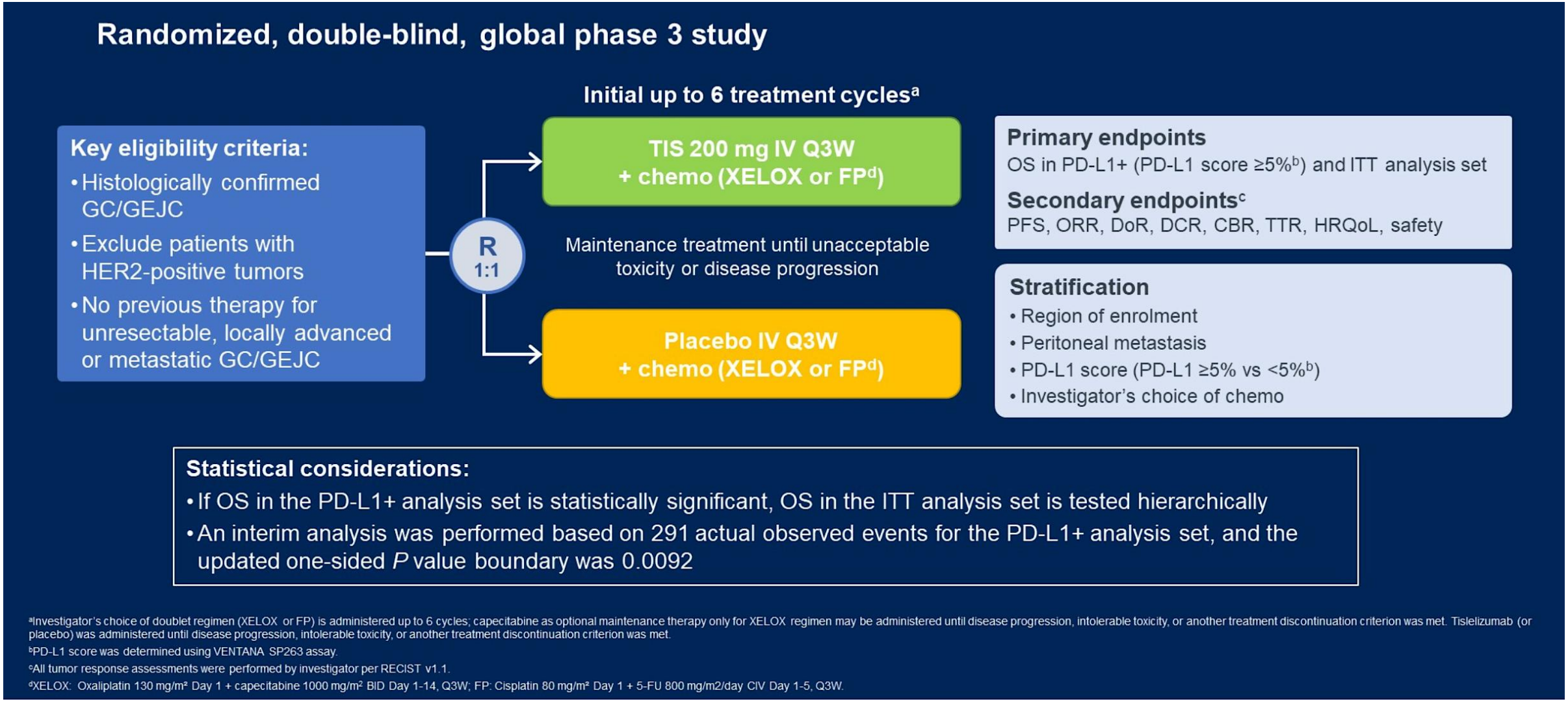
KEYNOTE-590: Benefit Maintained at 5-Year Follow-Up





Metges JP et al. ESMO Open 2025.

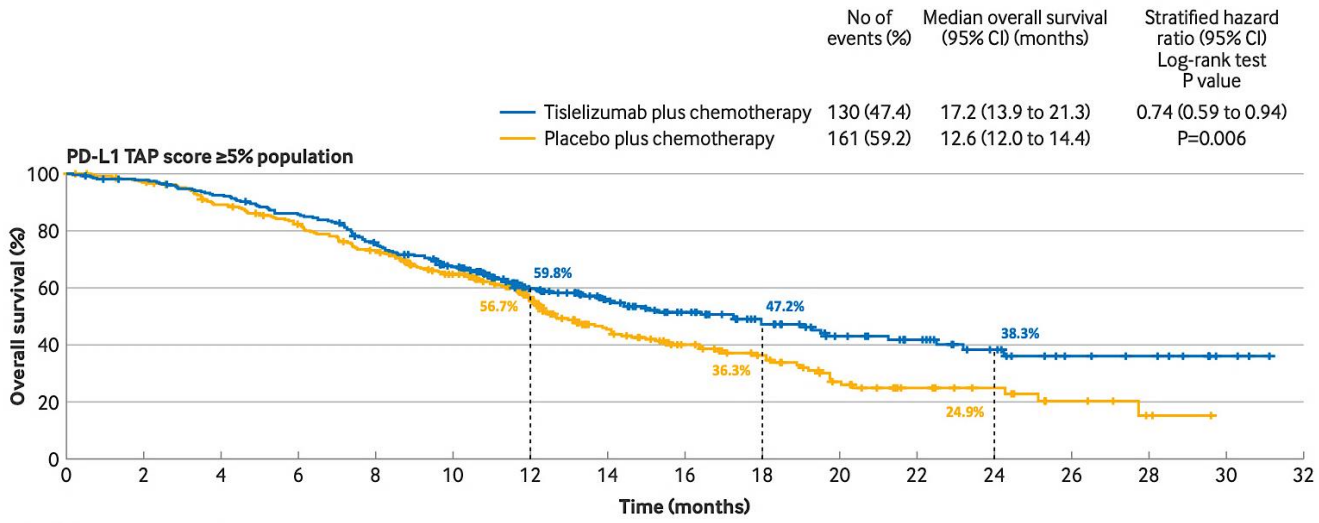
RATIONALE-305



Moehler et al. ASCO GI 2023.

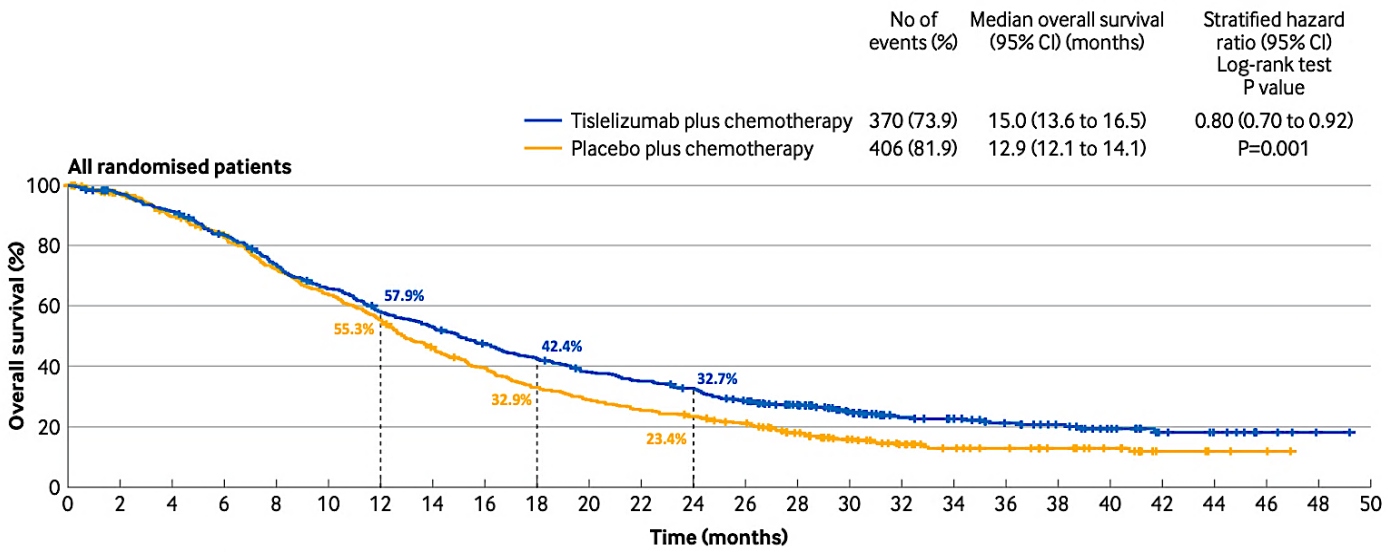
Courtesy of Rutika Mehta, MD, MPH

Addition of Tislelizumab Showed OS Benefit



In TAP ≥5%, median OS with C+ tisle vs C alone was 17.2 mos vs 12.6 mos (HR 0.74; *p* = 0.006)

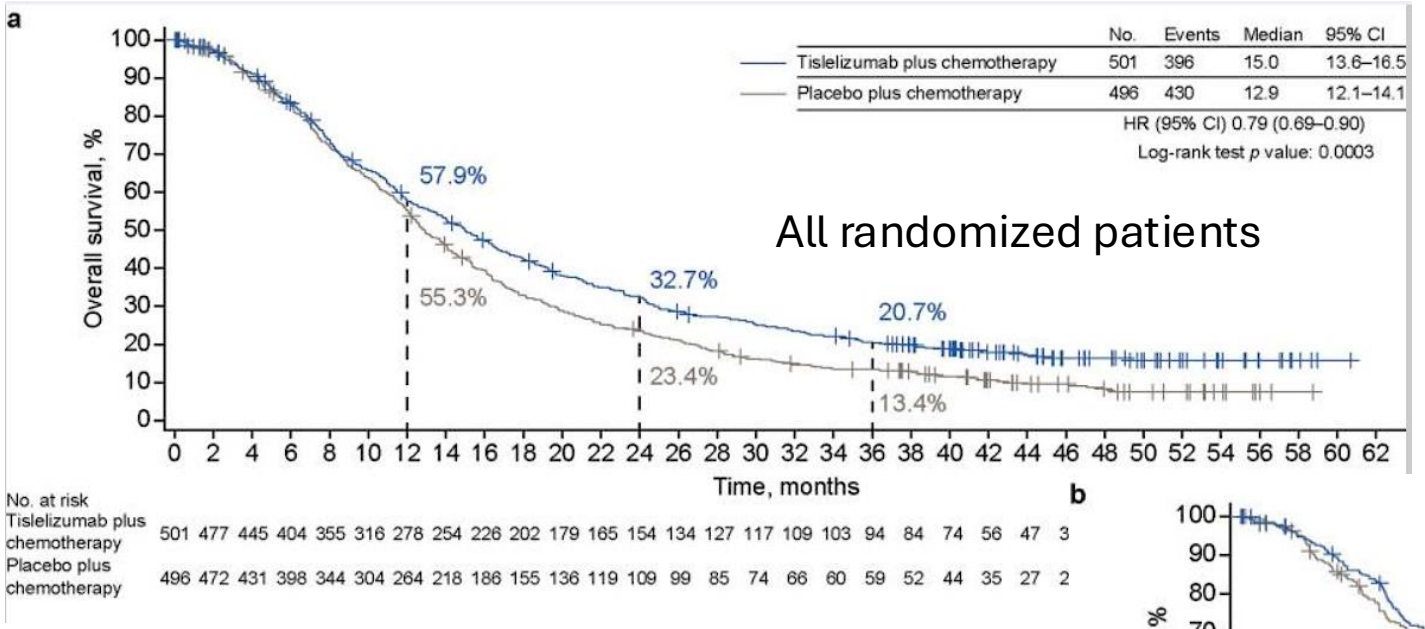
In all randomized patients, median OS with C+ tisle vs C alone was 15.0 mos vs 12.9 mos (HR 0.80; *p* = 0.001)

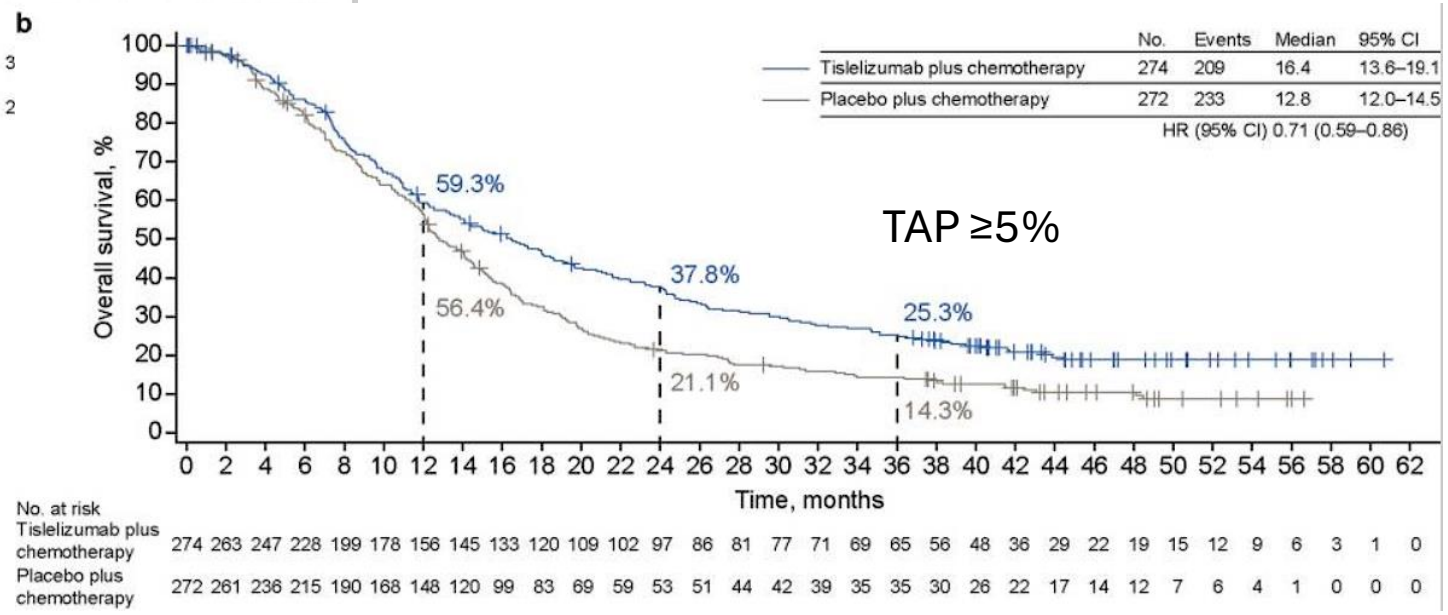


Qiu MZ et al. *BMJ* 2024.

Courtesy of Rutika Mehta, MD, MPH

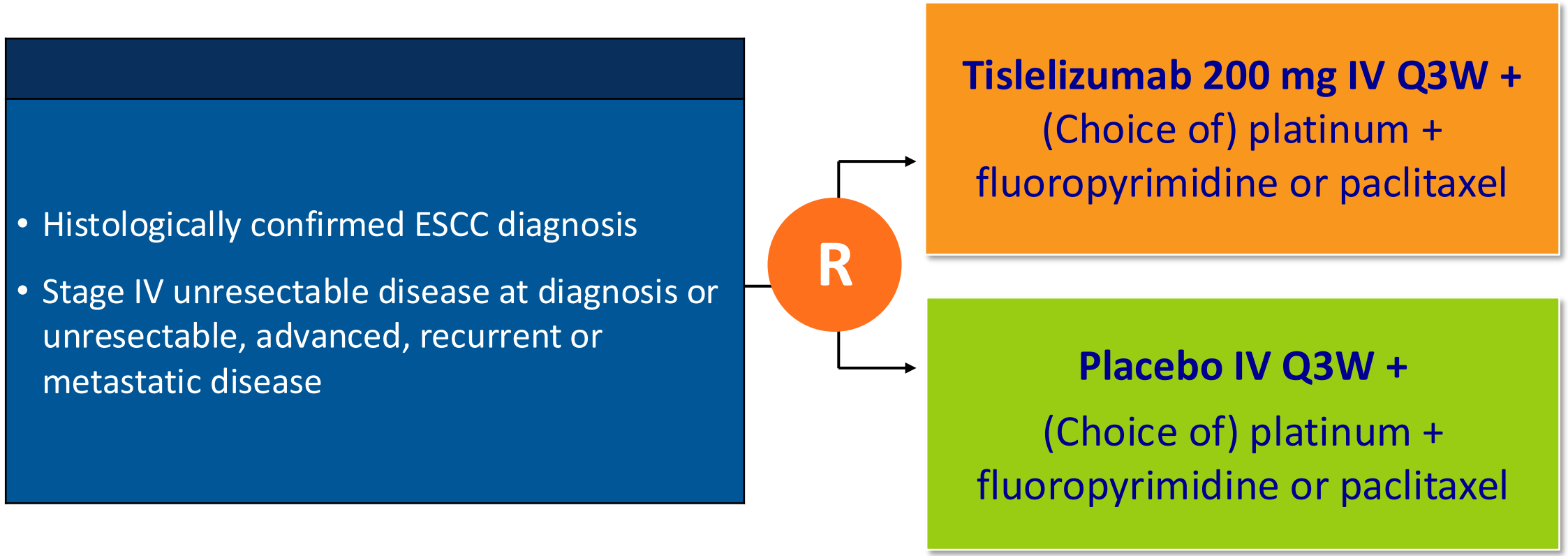
Benefit Maintained at 5-Year Follow-Up





Cruz-Correa et al. Adv Ther 2025.

RATIONALE-306 Trial Design



Primary endpoint: OS in ITT

Secondary endpoints: PFS, ORR, OS in PD-L1 ≥10%, DOR, Safety

https://clinicaltrials.gov/study/NCT03430843. Accessed May 2026.

Efficacy Benefits Maintained Through 3-Year Follow-Up

	Interim Analysis		3-Year Follow-up	
	TIS + CT (n=31)	PBO + CT (n=32)	TIS + CT (n=32)[e]	PBO + CT (n=31)[f]
Median OS, mo (95% CI)	25.6 (15.3, NE)	11.5 (9.0, 21.8)	25.6 (15.3, NE)	12.3 (9.0, 21.8)
HR (95% CI)[a]	0.36 (0.17, 0.77)	–	0.50 (0.26, 0.95)	–
Median PFS,[a] mo (95% CI)	13.2 (6.8, NE)	6.7 (4.2, 9.7)	13.2 (6.8, 27.7)	6.7 (4.2, 9.7)
HR (95% CI)[a]	0.46 (0.22, 0.96)	–	0.47 (0.23, 0.96)	–
ORR,[b,c] n (%)	18 (58.1)	10 (31.3)	19 (59.4)	10 (32.3)
Median DoR,[b,d] mo (95% CI)	Not reached (8.4, NE)	5.7 (1.5, 9.6)	22.1 (6.1, NE)	5.7 (1.5, 9.6)

Yoon HY et al. ASCO GI 2026.

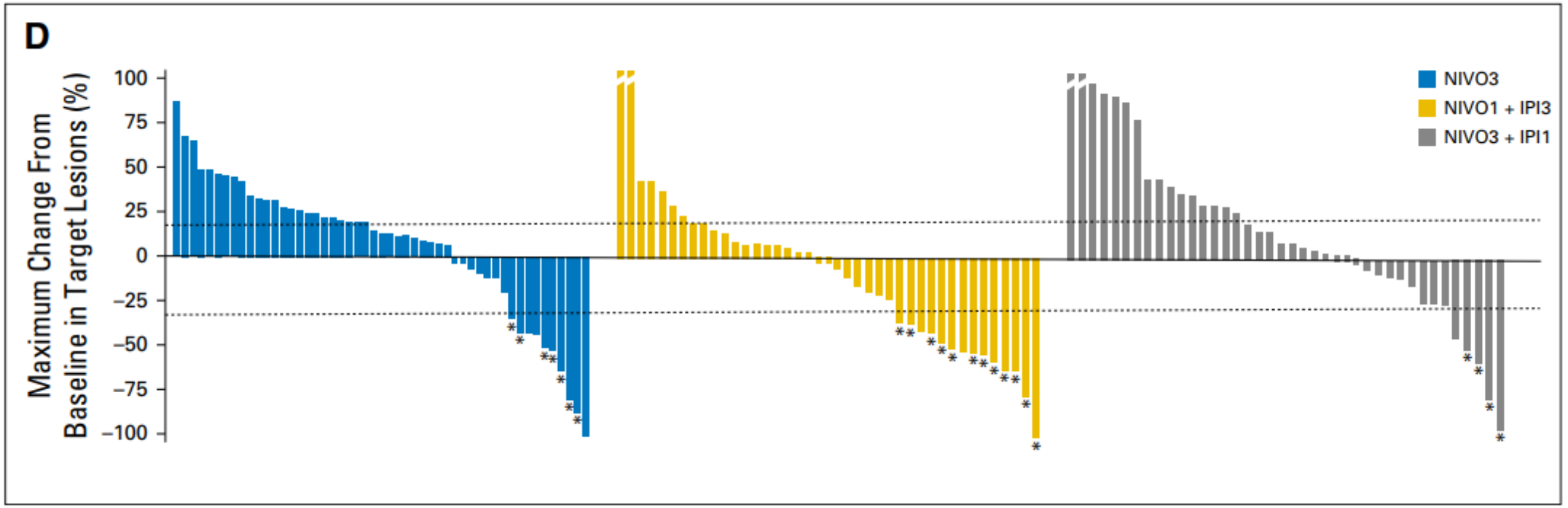
NCCN Guidelines 2.2026: Esophageal and Esophagogastric Junction Cancers

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA
Second-Line or Subsequent Therapy • Dependent on prior therapy and PS
Preferred • Nivolumab (category 1)[b,f,91] • Pembrolizumab[b,f] for PD-L1 CPS ≥10 (category 1)[50,92] • Docetaxel (category 1)[60,61] • Paclitaxel (category 1)[56,57,72] • Irinotecan (category 1)[72-75] • Tislelizumab-jsgr (category 1)[b,f,93,94] • Fluorouracil[a,g] and irinotecan[73,76,77]
Other Recommended • Irinotecan and cisplatin[42,80] • Docetaxel and irinotecan (category 2B)[84]
Useful in Certain Circumstances[c] • Entrectinib, larotrectinib, or repotrectinib[i] for *NTRK 1/2/3* gene fusion-positive tumors[85-87] • Pembrolizumab[b,f] for MSI-H/dMMR tumors[47-50] • Nivolumab and ipilimumab[b,f] for MSI-H/dMMR tumors[35] • Pembrolizumab[b,f] for TMB-H (≥10 mutations/megabase) tumors[50,88] • Dostarlimab-gxly[b,f,j] for MSI-H/dMMR tumors[51] • Dabrafenib and trametinib for *BRAF* V600E-mutated tumors[89] • Selpercatinib for *RET* gene fusion-positive tumors[90]

Dual IO Achieves Tumor Reduction in GEC



Janjigian et al. J Clin Oncol. 2018

Nivolumab plus Ipilimumab Combined with Chemotherapy as First-Line Treatment for HER2-Negative Unresectable Advanced or Recurrent Gastric/Gastroesophageal Junction Cancer: A Randomized Phase 3 Trial (ATTRACTION-6)

Oh DY et al.

ASCO 2026;Abstract 4006.

Gastrointestinal Cancer – Gastroesophageal, Pancreatic, and Hepatobiliary

MONDAY JUNE 1, 2026

Oral Abstract Session

Regulatory and reimbursement issues aside, what first-line treatment would you most likely recommend for a 65-year-old patient presenting with metastatic CLDN18.2-negative, HER2-negative, MSS GEJ adenocarcinoma with PD-L1 CPS 0?

 Dr Janjigian	Nivolumab + FOLFOX
 Dr Shah	FOLFOX
 Prof Van Cutsem	FOLFOX
 Dr Kim	FOLFOX
 Dr Klempner	FOLFOX
 Dr Wainberg	FOLFOX or CAPOX

MSS = microsatellite-stable; CPS = combined positive score

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what first-line treatment would you most likely recommend for a 65-year-old patient presenting with metastatic CLDN18.2-negative, HER2-negative, MSS GEJ adenocarcinoma with PD-L1 CPS 1?

 Dr Janjigian	Nivolumab + FOLFOX
 Dr Shah	Pembrolizumab + FOLFOX
 Prof Van Cutsem	Pembrolizumab + FOLFOX
 Dr Kim	Nivolumab + FOLFOX
 Dr Klempner	Nivolumab + FOLFOX
 Dr Wainberg	Nivolumab + FOLFOX or Pembrolizumab + CAPOX

MSS = microsatellite-stable; CPS = combined positive score

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, which first-line therapy would you most likely recommend for a 65-year-old patient presenting with metastatic CLDN18.2-negative, HER2-negative, MSI-high GEJ adenocarcinoma with a PD-L1 CPS of 1?

 Dr Janjigian	Nivolumab + ipilimumab
 Dr Shah	Nivolumab + ipilimumab
 Prof Van Cutsem	Nivolumab + FOLFOX
 Dr Kim	Would start with FOLFOX/PD-1i with low threshold to drop chemo and continue PD-1i alone
 Dr Klempner	Nivolumab + FOLFOX
 Dr Wainberg	Pembrolizumab

PD-1i = PD-1 inhibitor

RTP RESEARCH TO PRACTICE

Faculty Discussion

- **Regulatory and reimbursement issues aside, what first-line treatment would you most likely recommend for a 65-year-old patient presenting with metastatic CLDN18.2-negative, HER2-negative, MSS GEJ adenocarcinoma with PD-L1 CPS 0? PD-L1 CPS 1?**
- **Regulatory and reimbursement issues aside, which first-line therapy would you most likely recommend for a 65-year-old patient presenting with metastatic CLDN18.2-negative, HER2-negative, MSI-high GEJ adenocarcinoma with a PD-L1 CPS of 1?**

Regulatory and reimbursement issues aside, what first-line treatment would you most likely recommend for a 65-year-old patient presenting with metastatic CLDN18.2-negative, HER2-negative, MSS squamous cell carcinoma (SCC) of the esophagus with the PD-L1 CPS below?

	PD-L1 CPS 0	PD-L1 CPS 1
 Dr Janjigian	Nivolumab + FOLFOX	Nivolumab + FOLFOX
 Dr Shah	Nivolumab + FOLFOX	Pembrolizumab + FOLFOX
 Prof Van Cutsem	FOLFOX	Nivolumab + FOLFOX or Tislelizumab + FOLFOX
 Dr Kim	FOLFOX	Nivolumab + FOLFOX
 Dr Klempner	Nivolumab + FOLFOX	Nivolumab + FOLFOX
 Dr Wainberg	Nivolumab + FOLFOX or Pembrolizumab + CAPOX	Nivolumab + FOLFOX or Pembrolizumab + CAPOX

MSS = microsatellite-stable; CPS = combined positive score

Are there any situations in which you prioritize nivolumab/chemotherapy, pembrolizumab/chemotherapy or tislelizumab/chemotherapy over the others for patients with newly diagnosed CLDN18.2-negative, HER2-negative metastatic GE cancer?

 Dr Janjigian	No
 Dr Shah	Yes
 Prof Van Cutsem	Yes
 Dr Kim	No
 Dr Klempner	No
 Dr Wainberg	No

RTP RESEARCH TO PRACTICE

Are there any circumstances in which you would still offer an anti-PD-1 antibody-containing regimen to a patient with newly diagnosed metastatic gastroesophageal cancer that was PD-L1-negative?

 Dr Janjigian	Yes, if CLDN18.2-negative
 Dr Shah	No
 Prof Van Cutsem	Yes, if MSI-high/dMMR (realizing that most are PD-L1-positive)
 Dr Kim	Yes, if patient cannot tolerate chemotherapy, I would offer IO monotherapy if they were still fit and wanting further therapy
 Dr Klempner	Yes, if MSI-high or with discordant PD-L1 testing results
 Dr Wainberg	No

IO = immunotherapy

RTP RESEARCH TO PRACTICE

Faculty Discussion

- **Regulatory and reimbursement issues aside, what first-line treatment would you most likely recommend for a 65-year-old patient presenting with metastatic CLDN18.2-negative, HER2-negative, MSS squamous cell carcinoma (SCC) of the esophagus with PD-L1 CPS 0? PD-L1 CPS 1?**
- **Are there any situations in which you prioritize nivolumab/chemotherapy, pembrolizumab/chemotherapy or tislelizumab/chemotherapy over the others for patients with newly diagnosed CLDN18.2-negative, HER2-negative metastatic GE cancer?**
- **Are there any circumstances in which you would still offer an anti-PD-1 antibody-containing regimen to a patient with newly diagnosed metastatic gastroesophageal cancer that was PD-L1-negative?**

RTP RESEARCH TO PRACTICE

Cases from the Community: Investigators Discuss the Optimal Management of EGFR-Mutated Non-Small Cell Lung Cancer

A CME Symposium Held Adjunct with the 2026 ASCO® Annual Meeting

Friday, May 29, 2026

6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)

Faculty

Sarah B Goldberg, MD, MPH

Jonathan Goldman, MD

Joel W Neal, MD, PhD

Antonio Passaro, MD, PhD

Moderator

Jacob Sands, MD

RTP RESEARCH TO PRACTICE

Cases from the Community: Investigators Discuss the Optimal Management of Chronic Lymphocytic Leukemia

A CME Symposium Held Adjunct with the 2026 ASCO® Annual Meeting

Friday, May 29, 2026

6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)

Faculty

John N Allan, MD

Bita Fakhri, MD, MPH

Shuo Ma, MD, PhD

Mazyar Shadman, MD, MPH

Moderator

Jeremy S Abramson, MD, MMSc

RTP RESEARCH TO PRACTICE

Consensus or Controversy? Documenting and Discussing Investigators' Approaches to the Management of Colorectal Cancer

A CME Symposium Held Adjunct with the 2026 ASCO® Annual Meeting

Friday, May 29, 2026
6:30 PM – 8:00 PM CT (7:30 PM – 9:00 PM ET)

Faculty

Stacey A Cohen, MD
Arvind Dasari, MD, MS

Moderator

Tanios Bekaii-Saab, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!
Your feedback is very important to us.

Please complete the survey currently up on the iPads for attendees in the room and on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

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In-person attendees: Please refer to the program syllabus for the CME credit link or QR code. Online/Zoom attendees: The CME credit link is posted in the chat room.

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