Expert Second Opinion: Current and Future Roles of Immunotherapy and Targeted Therapy in the Management of Advanced Gastroesophageal Cancers

A CME Symposium Held Adjunct to the 2026 ASCO® Gastrointestinal Cancers Symposium

Friday, January 9, 2026

6:00 PM – 8:00 PM PT

Faculty

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Rutika Mehta, MD, MPH

John Strickler, MD

Moderator

Samuel J Klempner, MD

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Dr Ajani — Disclosures
Faculty

Advisory Committees and Consulting Agreements	AstraZeneca Pharmaceuticals LP, BeOne, Bristol Myers Squibb, Daiichi Sankyo Inc, Gilead Sciences Inc, Henlius, Jazz Pharmaceuticals Inc, Merck, Taiho Oncology Inc, Zymeworks Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, BeOne, Bristol Myers Squibb, Henlius, I-Mab Biopharma, Jazz Pharmaceuticals Inc, Merck, Servier Pharmaceuticals LLC

Dr Ilson — Disclosures
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Consulting Agreements	Astellas

Dr Mehta — Disclosures
Faculty

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Consulting Agreements	Jazz Pharmaceuticals Inc, Lilly, Replimune
Data and Safety Monitoring Boards/Committees	Arcus Biosciences, Gilead Sciences Inc
Nonrelevant Financial Relationships	Robert A Winn Career Development Award

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Dr Strickler — Disclosures
Faculty

Advisory Committees	AbbVie Inc, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeOne, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Cytovation ASA, Daiichi Sankyo Inc, GE Healthcare, Genentech, a member of the Roche Group, GSK, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Jazz Pharmaceuticals Inc, Johnson & Johnson, Leap Therapeutics Inc, Lilly, Merck, Natera Inc, Pfizer Inc, Pheon Therapeutics, Quanta Therapeutics, Regeneron Pharmaceuticals Inc, Sanofi, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Triumvira Immunologics, Xilio Therapeutics
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Commercial Support

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Save The Date

Fifth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, April 24 to 26, 2026

The Ritz-Carlton Orlando, Grande Lakes | Orlando, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

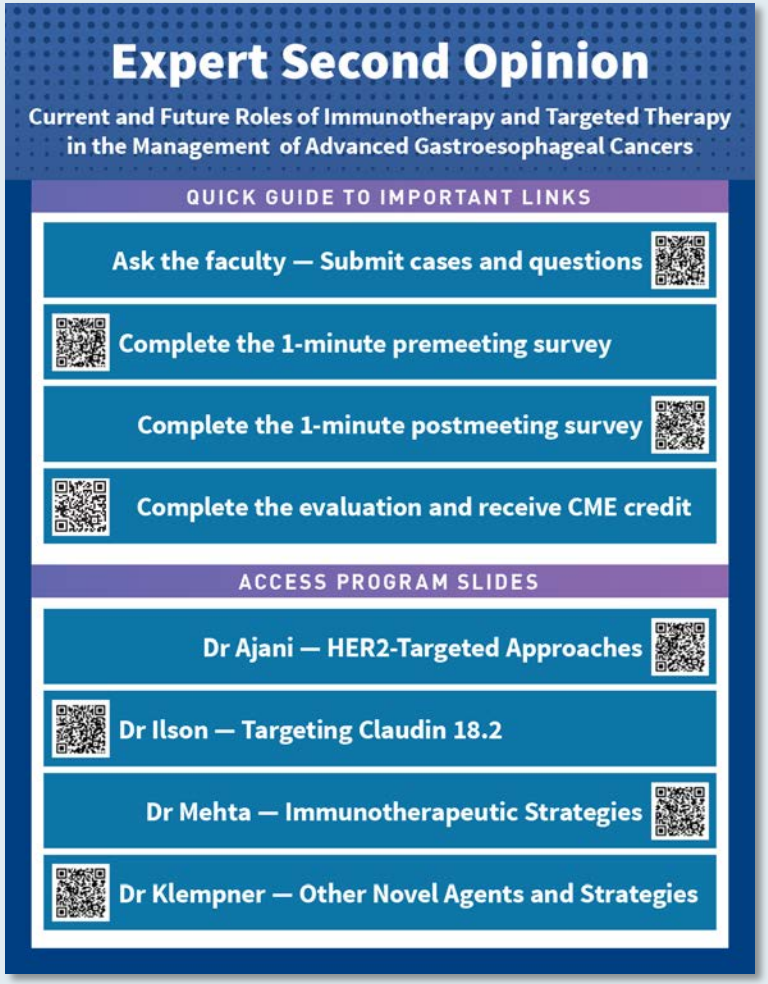
Please refer to the printed handout provided with your meeting syllabus, and scan the corresponding QR code to

Review and Download Program Slides.

Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: We will aim to address as many questions as possible during the program.

Get CME Credit: Complete the course evaluation.



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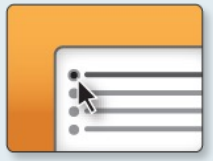
Clinicians Attending via Zoom

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



Answer Survey Questions: Complete the pre- and postmeeting surveys.

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

Get CME Credit: A credit link will be provided in the chat room at the conclusion of the program.

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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.
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Agenda

Module 1: HER2-Targeted Approaches for Advanced Gastroesophageal Cancers — Dr Ajani

Module 2: Targeting Claudin 18.2 in Advanced Gastroesophageal Cancers — Dr Strickler

Module 3: Optimal Incorporation of Immunotherapeutic Strategies into Treatment for Patients with Metastatic Gastroesophageal Tumors — Dr Mehta

Module 4: Other Novel Agents and Strategies Under Evaluation for Advanced Gastroesophageal Cancers — Dr Klempner

Survey of 50 Community-Based General Medical Oncologists

December 22, 2025 – January 7, 2026

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Agenda

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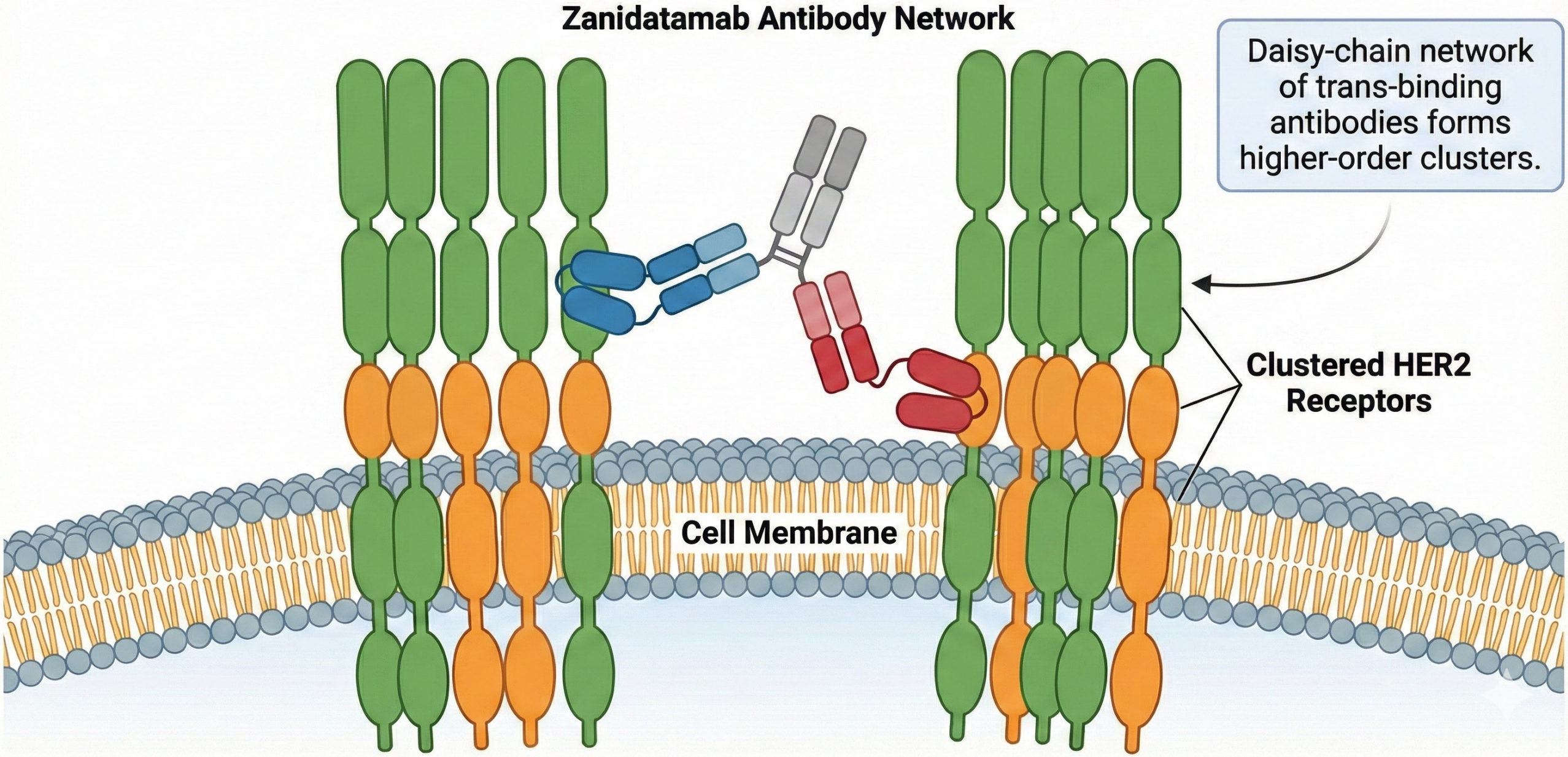
Her2-Targeting Therapeutics for Advanced Gastroesophageal Cancers

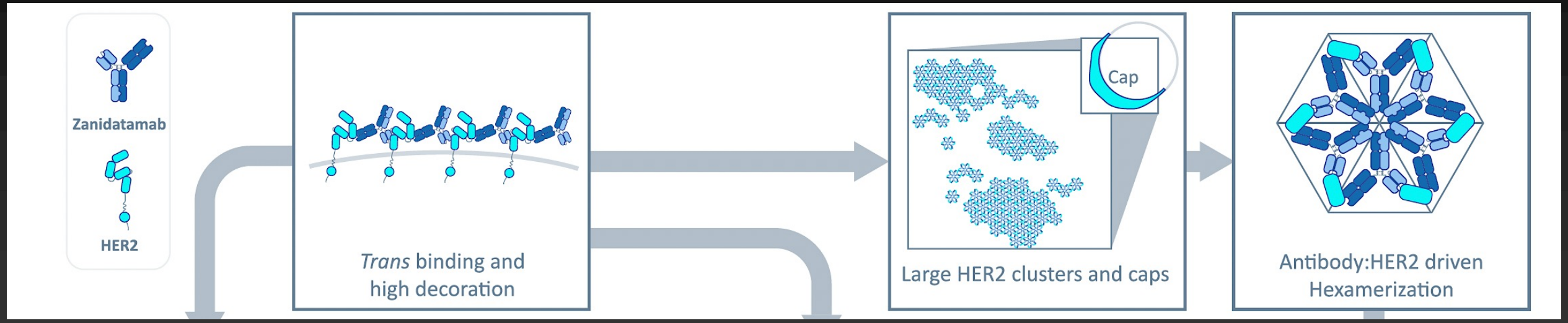
Recent Developments

Jaffer A. Ajani January 08, 2026

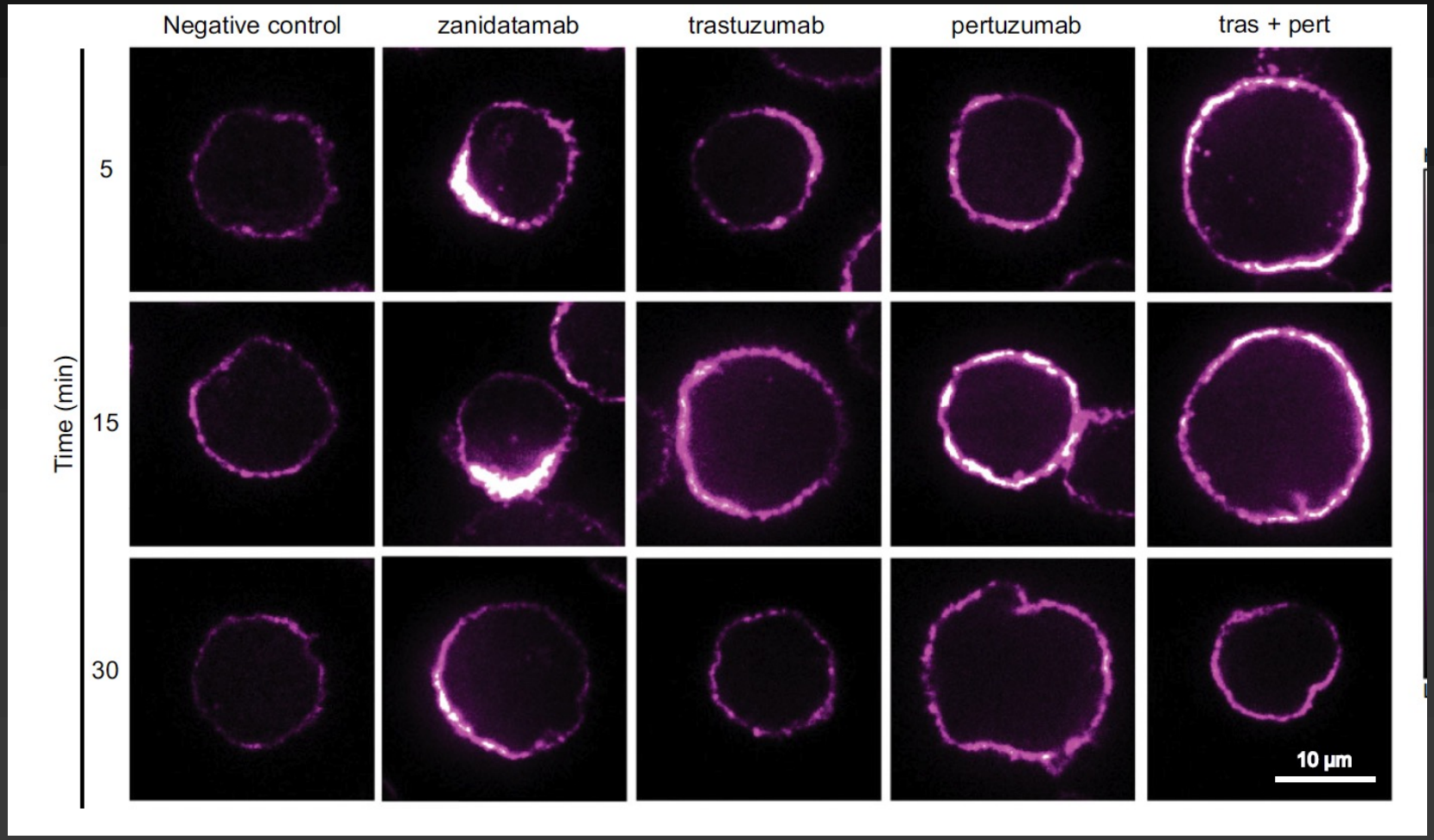
Zanidatamab-Mediated Clustering of HER2 Receptors

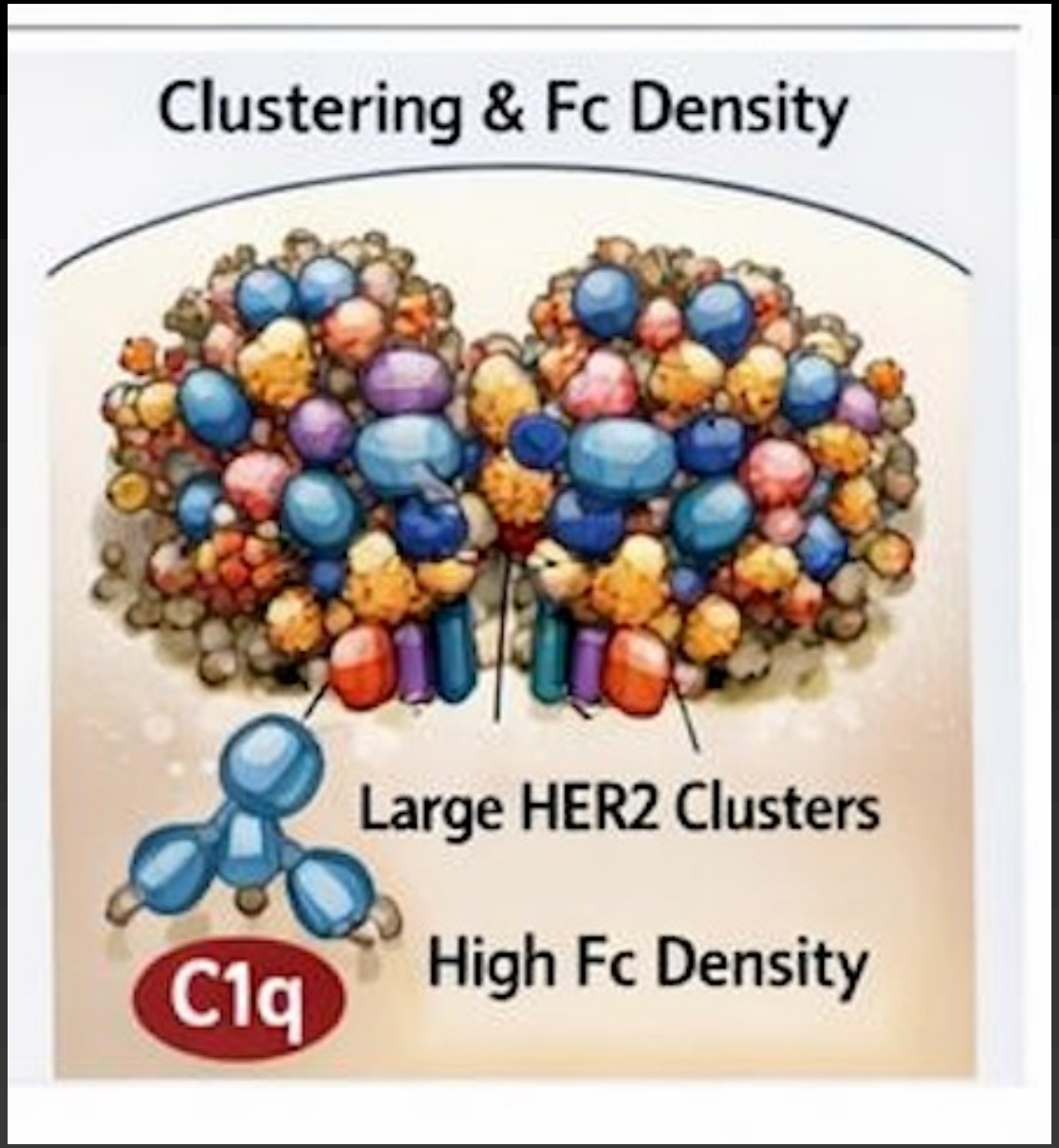


Consequences of Zani binding Her2 receptor



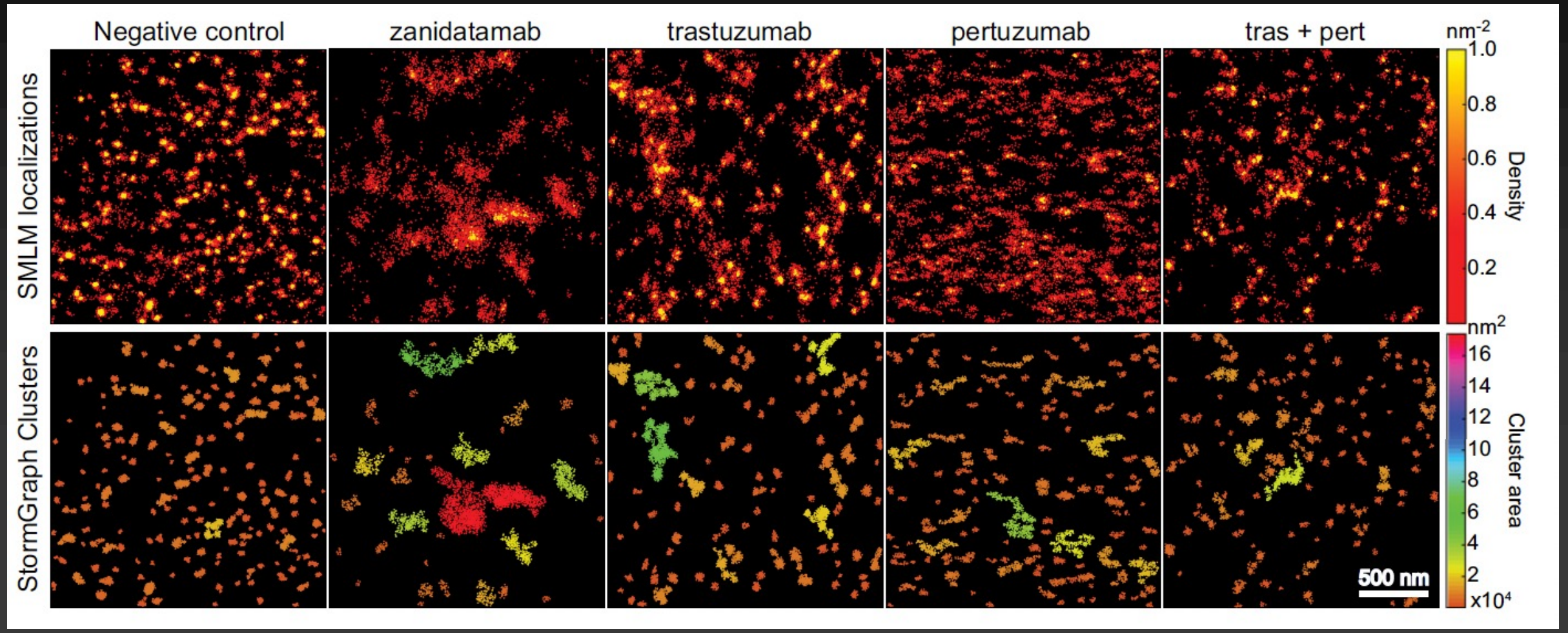
Zani forming “Caps” compared to others




Clustering & Fc Density
Large HER2 Clusters
High Fc Density
C1q

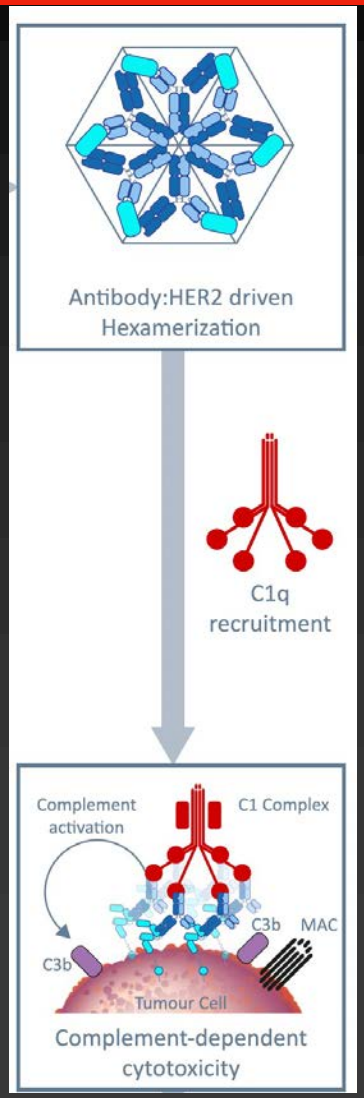
Zani-induced Clustering compared to others

SMLM, single molecule localization microscopy
dSTORM, Stochastic optical reconstruction microscopy



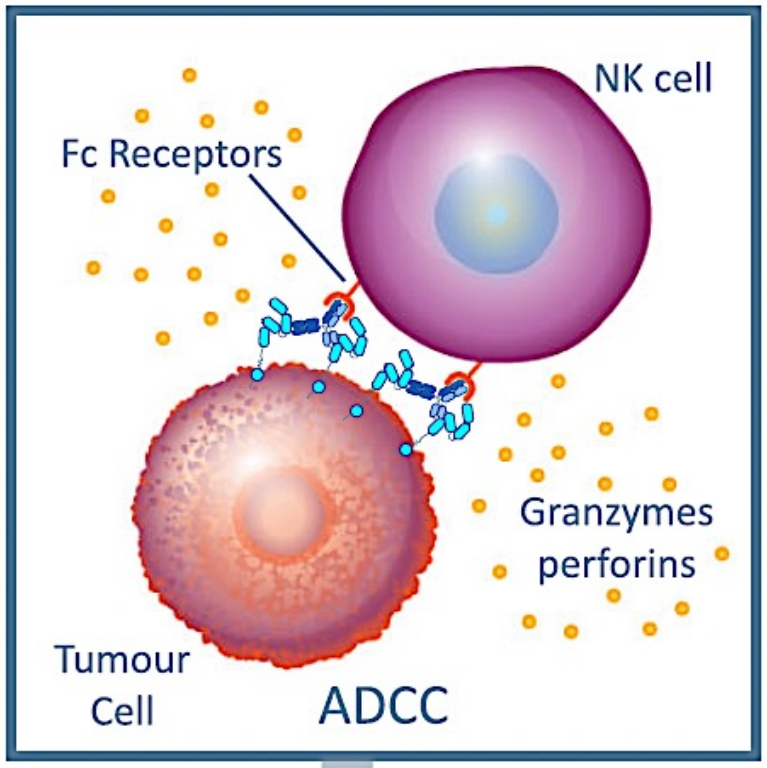
Hexamerization attracts key CDC protein, C1q

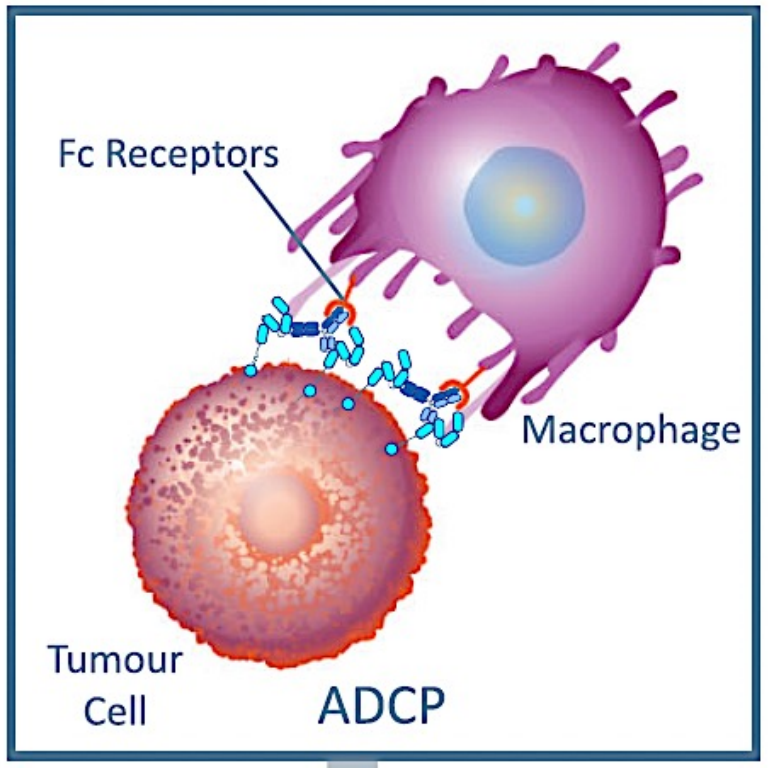
C1q cannot recruit other C3 members unless 6 FC domains are exposed

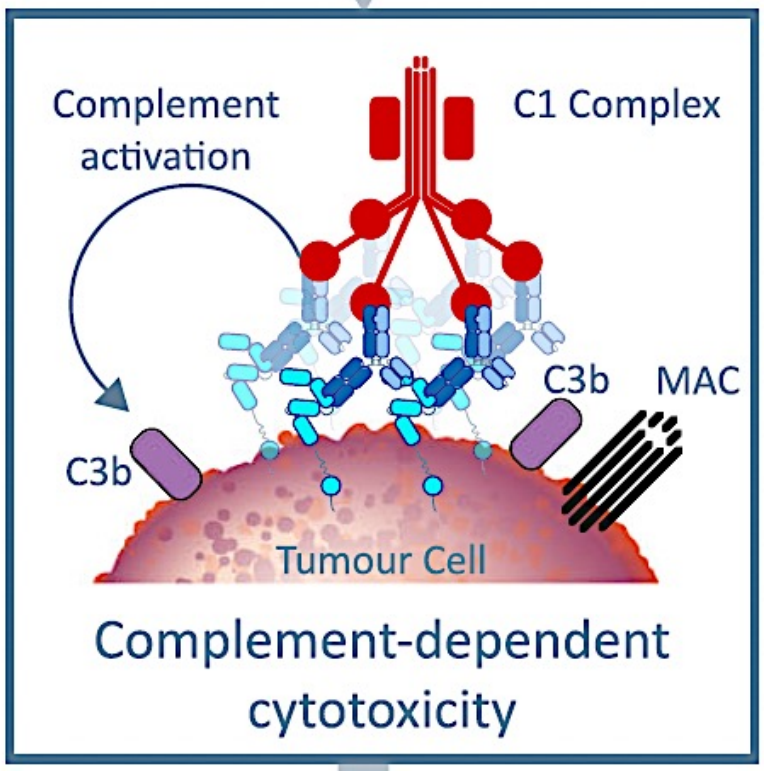


CDC is unique to Zani

Zani-induced immune-mediated cancer cell killing







Summary of Zanidatamab's effects on engaging Her2 receptors

1. Engages Her2 in *TRANS* configuration leading to extensive, ordered, receptor clustering (or lattice) on cancer cell membrane
2. Reorganizes the Her2 receptor landscape (staples Her2 receptor) forming Her2 receptor caps
3. High avidity. Ordered complexes are stable. Forming a ring structure (receptor/Zani). Clusters project Fc domains critical for C1q engagement.
4. Major CDC effects. Formation of MACs (membrane attack complexes). MACs cause cell membrane pores and osmolytic lysis of cancer cells (independent of the immune system).
5. Cross-linked cluster promotes internalization (endocytosis) and trafficking away from endosomes (which cannot handle large size) to lysosomes (preventing recycling). Depletes Her2 density and biogenesis.
6. Blocks other oncogene activation (ERK/AKT/EGFR, others)

Nat Communication

Article

https://doi.org/10.1038/s41467-025-59279-z

Zanidatamab monotherapy or combined with chemotherapy in HER2-expressing gastroesophageal adenocarcinoma: a phase 1 trial

Received: 24 July 2024

Accepted: 15 April 2025

Published online: 08 May 2025

Funda Meric-Bernstam[1], Sun Young Rha[2], Erika Hamilton[3], Yoon-Koo Kang[4], Diana L. Hanna[5], Syma Iqbal[5], Keun-Wook Lee[6], Jeeyun Lee[7], Muralidhar Beeram[8], Do-Youn Oh[9], Jorge Chaves[10], Rachel A. Goodwin[11], Jaffer A. Ajani[12], Lin Yang[13], Rajen Oza[13] & Elena Elimova[14]

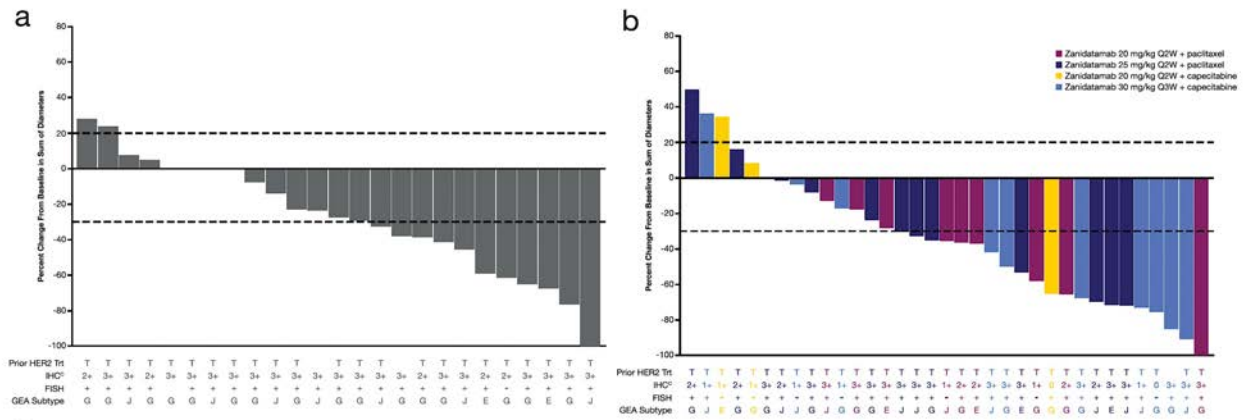
Nat Communication 2025

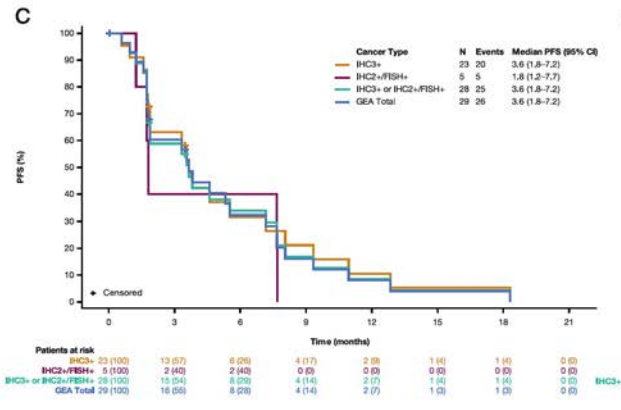
Table 3 | Antitumor activity in patients with HER2-expressing GEA (response evaluable analysis set)

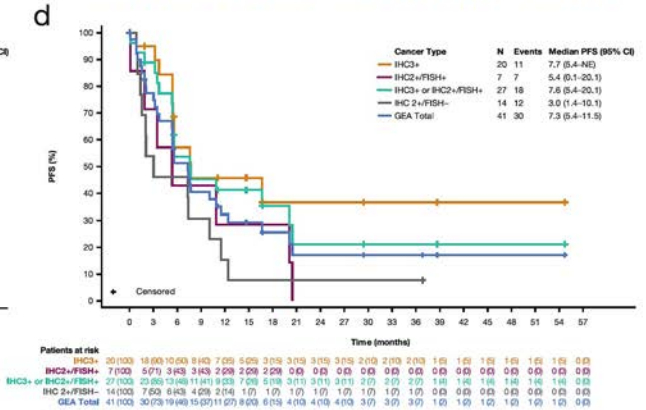
	Zanidatamab monotherapy[a]		Zanidatamab plus chemotherapy[b]	
	All GEA patients (*N* = 28)	Patients with HER2 + GEA (*n* = 27)	All GEA patients (*N* = 37)	Patients with HER2 + GEA (*n* = 26)
cORR, *n* (%) [95% CI]	9 (32.1) [15.9–52.4]	8 (29.6) [13.8–50.2]	18 (48.6) [31.9–65.6]	13 (50.0) [29.9–70.1]
cBOR, *n* (%)				
CR	–	–	2 (5.4)	2 (7.7)
PR	9 (32.1)	8 (29.6)	16 (43.2)	11 (42.3)
SD	8 (28.6)	8 (29.6)	12 (32.4)	10 (38.5)
PD	11 (39.3)	11 (40.7)	7 (18.9)	3 (11.5)
CBR,[c] *n* (%)	11 (39.3)	10 (37.0)	21 (56.8)	16 (61.5)
[95% CI]	[21.5–59.4]	[19.4–57.6]	[39.5–72.9]	[40.6–79.8]
DCR,[d] *n* (%)	17 (60.7)	16 (59.3)	30 (81.1)	23 (88.5)
[95% CI]	[40.6–78.5]	[38.8–77.6]	[64.8–92.0]	[69.8–97.6]
DOR, median (95% CI) mo,	6.7 (1.9–11.1)	7.4 (1.9–11.1)	18.3 (5.6–NE)	18.9 (3.7–NE)
[*n*]	[9]	[8]	[18]	[13]
PFS,[e] median (95% CI) mo	3.6 (1.8–7.2)	3.6 (1.8–7.2)	7.3 (5.4–11.5)	7.6 (5.4–20.1)
Had event, *n*/*n* (%)	26/29 (89.7)	25/28 (89.3)	30/41 (73.2)	18/27 (66.7)
Censored, *n*/*n* (%)	3/29 (10.3)	3/28 (10.7)	11/41 (26.8)	9/27 (33.3)

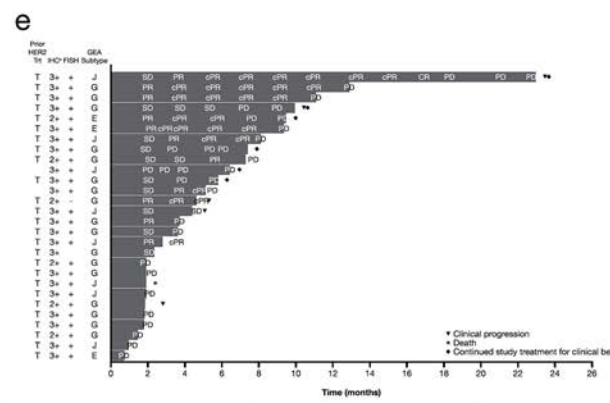
Nat Communication 2025

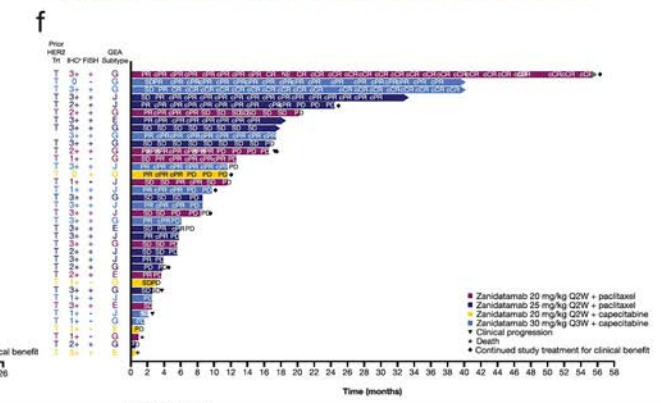
https://doi.org/10.1038/s41467-025-59279-z











Zanidatamab plus chemotherapy as first-line treatment for patients with HER2-positive advanced gastro-oesophageal adenocarcinoma: primary results of a multicentre, single-arm, phase 2 study

Elena Elimova, Jaffer Ajani, Howard Burris, Crystal S Denlinger, Syma Iqbal, Yoon-Koo Kang, Jwa Hoon Kim, Keun-Wook Lee, Bruce Lin, Rutika Mehta, Do-Youn Oh, Sun Young Rha, Young Mi Seol, Lin Yang, Mark A Ozog, Phillip M Garfin, Geoffrey Ku

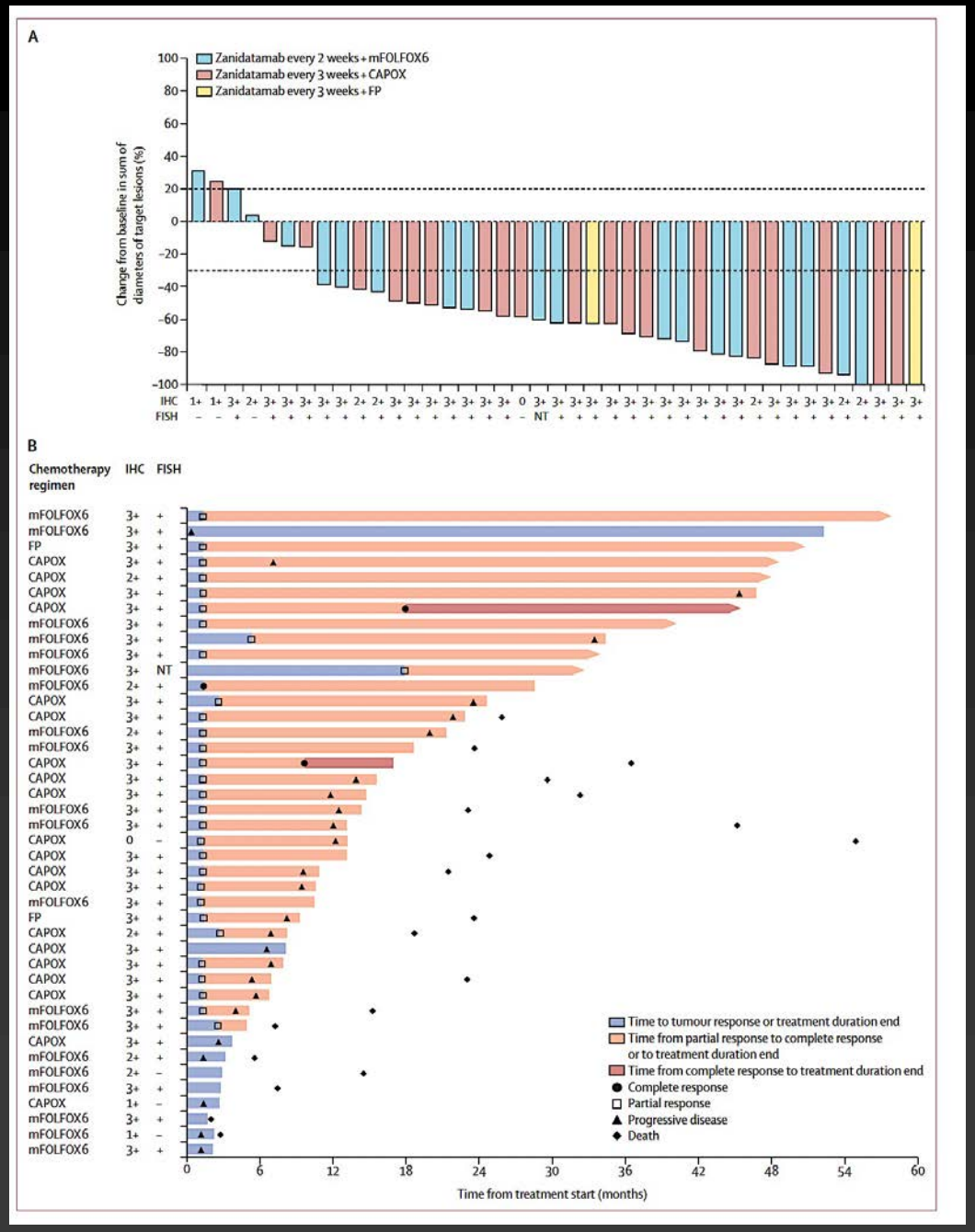
Lancet Oncol 2025; 26: 847–59

Published Online

Summary

Background Zanidatamab, a dual human epidermal growth factor receptor 2 (HER2)-targeted bispecific antibody, previously demonstrated encouraging antitumour activity and a manageable safety profile in patients with treatment-

Lancet Oncology 2025



Lancet Oncology 2025

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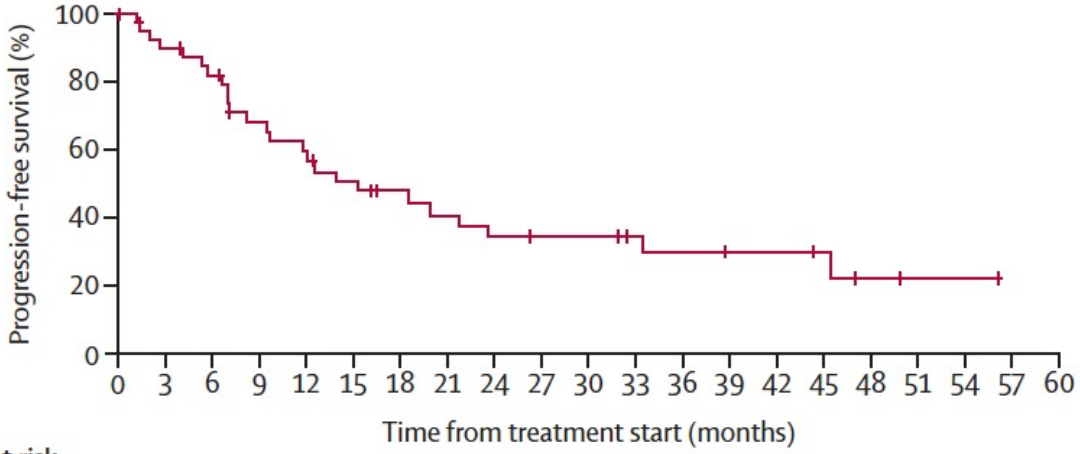
	Patients with ccHER2-positive advanced GEA (n=41)
Number of events, (%)	25 (61%)
Zanidatamab + mFOLFOX6	10/21 (48%)
Zanidatamab + CAPOX	14/18 (78%)
Zanidatamab + FP	1/2 (50%)
Patients censored, n (%)	16 (39%)
Median progression-free survival, months (95% CI)	15·2 (9·5–33·4)

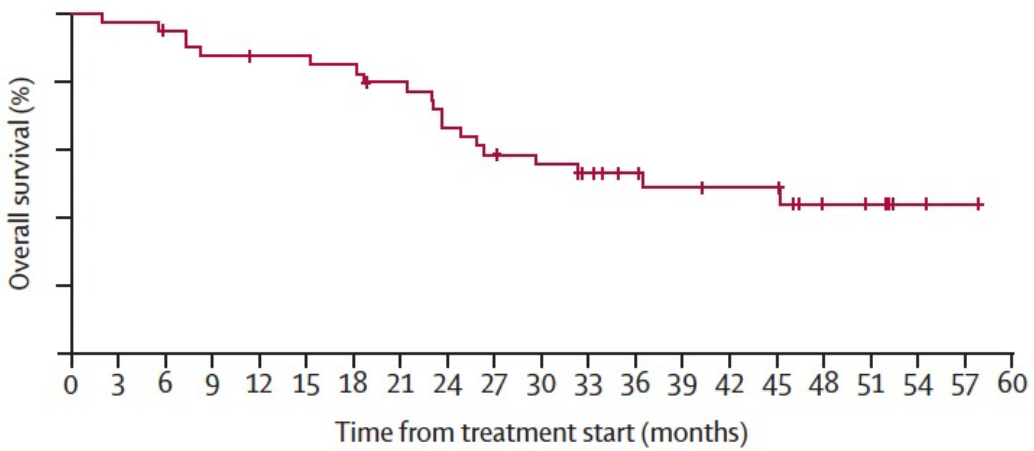


Number at risk (censored)

Total	41	35	31	24	21	17	14	12	10	9	9	7	6	5	5	4	2	1	1	0	..
	(0)	(2)	(3)	(5)	(5)	(6)	(8)	(8)	(8)	(9)	(9)	(11)	(11)	(12)	(12)	(13)	(14)	(15)	(15)	(16)	(..)
Zanidatamab + mFOLFOX6	21	16	14	12	12	10	8	6	6	5	5	3	2	1	1	1	1	1	1	0	..
	(0)	(2)	(3)	(5)	(5)	(5)	(6)	(6)	(6)	(7)	(7)	(9)	(9)	(10)	(4)	(4)	(4)	(4)	(4)	(5)	(..)
Zanidatamab + CAPOX	18	17	15	11	8	6	5	5	3	3	3	3	3	3	3	2	0	..	..	..	..
	(0)	(0)	(0)	(0)	(0)	(1)	(2)	(2)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(2)	(..)	(..)	(..)	(..)
Zanidatamab + FP	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	..	..	..
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(..)	(..)	(..)

D

	Patients with ccHER2-positive advanced GEA (n=41)
Number of events, (%)	20 (49%)
Zanidatamab + mFOLFOX6	11/21 (52%)
Zanidatamab + CAPOX	8/18 (44%)
Zanidatamab + FP	1/2 (50%)
Patients censored, n (%)	21 (51%)
Median overall survival, months (95% CI)	36·5 (23·6–NE)



	41	40	38	35	34	34	33	30	25	22	20	17	14	12	11	11	6	5	2	1	0
	(0)	(0)	(1)	(1)	(2)	(2)	(2)	(3)	(3)	(3)	(4)	(6)	(9)	(10)	(11)	(11)	(15)	(16)	(19)	(20)	(21)
	21	20	19	16	16	16	15	14	12	11	10	9	7	6	5	5	4	4	2	1	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(4)	(5)	(6)	(0)	(0)	(0)	(2)	(3)	(4)
	18	18	17	17	16	16	16	14	12	10	9	7	6	5	5	5	1	1	0	..	..
	(0)	(0)	(1)	(1)	(2)	(2)	(2)	(3)	(3)	(3)	(3)	(4)	(5)	(5)	(1)	(1)	(5)	(5)	(6)	(..)	(..)
	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	0	..	..	..
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(..)	(..)	(..)

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

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

Dual Primary Endpoints

- PFS (per BICR)
- OS

Select Secondary Endpoints

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

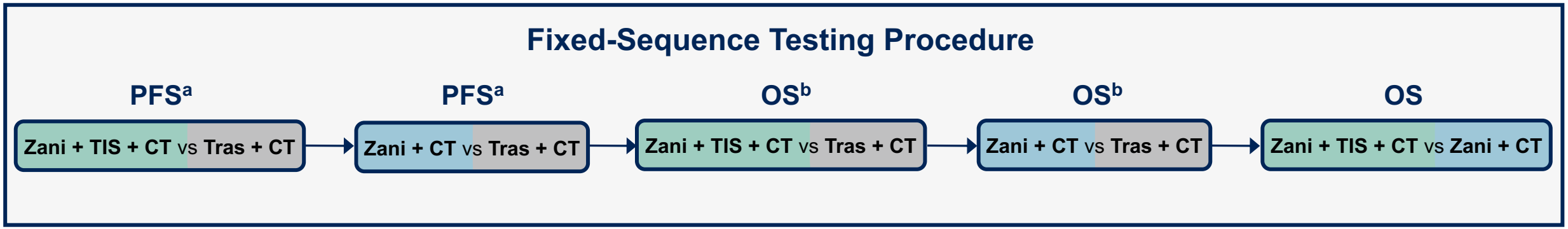
ClinicalTrials.gov: NCT05152147

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

[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.

Statistical Design

- **Dual primary endpoints (PFS and OS): Analyzed in the intent-to-treat population using log-rank tests with a 2-sided α = 0.05**
  - **Primary PFS analysis**: After target event count was reached and patients had ≥7 months of follow-up
  - **First interim OS analysis:** Performed at the time of data cutoff for the primary PFS analysis



[a]For the primary analysis of PFS, the 2-sided alpha was 0,05. [b]For the first interim analysis of OS, the 2-sided alpha was 0.020.
CT, chemotherapy; OS, overall survival; PFS, progression-free survival; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

Patient Disposition

A total of 914 patients were randomized, and median follow-up was >2 years

Randomized
N = 914

Zanidatamab + CT	Zanidatamab + tislelizumab + CT	Trastuzumab + CT
n = 304; 300 patients treated[a]	n = 302; 299 patients treated[a]	n = 308; 302 patients treated
Ongoing treatment, n = 69 (23%)	**Ongoing treatment**, n = 88 (29%)	**Ongoing treatment**, n = 37 (12%)
Discontinued treatment, n = 231 (76%)	**Discontinued treatment**, n = 211 (70%)	**Discontinued treatment**, n = 265 (86%)
• Progressive disease, n = 132	• Progressive disease, n = 117	• Progressive disease, n = 200
• Adverse event, n = 25	• Adverse event, n = 27	• Adverse event, n = 10
• Death, n = 27	• Death, n = 26	• Death, n = 17
• Withdrawal by patient, n = 23	• Withdrawal by patient, n = 26	• Withdrawal by patient, n = 20
• Physician decision, n = 19	• Physician decision, n = 13	• Physician decision, n = 13
• Other, n = 5[b]	• Other, n = 2[b]	• Other, n = 5[b]
Survival follow-up, n = 69 (23%)	**Survival follow-up**, n = 58 (19%)	**Survival follow-up**, n = 81 (26%)
Median (range) follow-up 26.0 (7.6–46.0) months	**Median (range) follow-up** 25.9 (7.9–45.5) months	**Median (range) follow-up** 25.8 (7.5–45.6) months

[a]Treated includes all randomized patients who received any amount of any study treatment and does not necessarily reflect the safety analysis set. Five patients assigned to the zanidatamab-tislelizumab-chemotherapy arm did not receive tislelizumab and are included in the safety analysis set for the zanidatamab-chemotherapy arm. [b]Includes protocol violations and "other" reasons.
CT, chemotherapy.

HERIZON GEA-301

Baseline Demographics and Disease Characteristics

Demographics and clinical characteristics were balanced across all 3 treatment arms

	Zanidatamab + CT (n = 304)	Zanidatamab + tislelizumab + CT (n = 302)	Trastuzumab + CT (n = 308)
Age, median (range), years	62.5 (25–87)	63.0 (22–81)	64.0 (21–84)
Male sex	244 (80.3)	244 (80.8)	238 (77.3)
Geographic region			
Asia	163 (53.6)	159 (52.6)	165 (53.6)
EU/North America	91 (29.9)	95 (31.5)	93 (30.2)
Rest of the world	50 (16.4)	48 (15.9)	50 (16.2)
ECOG PS[a]			
0	134 (44.1)	121 (40.1)	120 (39.0)
1	170 (55.9)	180 (59.6)	188 (61.0)
Disease status			
Metastatic	295 (97.0)	284 (94.0)	299 (97.1)
Unresectable locally advanced	9 (3.0)	18 (6.0)	9 (2.9)

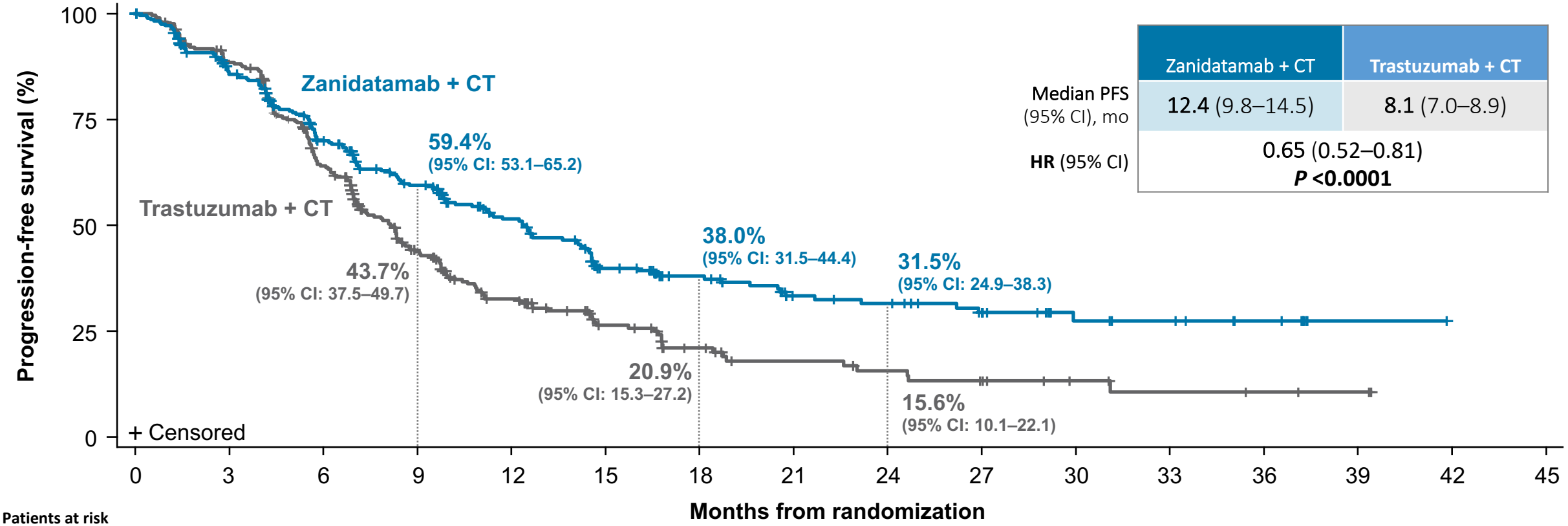
	Zanidatamab + CT (n = 304)	Zanidatamab + tislelizumab + CT (n = 302)	Trastuzumab + CT (n = 308)
Anatomical subtype			
Gastric	204 (67.1)	208 (68.9)	226 (73.4)
GEJ	61 (20.1)	74 (24.5)	60 (19.5)
Esophageal	39 (12.8)	20 (6.6)	22 (7.1)
HER2 IHC 3+	251 (82.6)	251 (83.1)	255 (82.8)
PD-L1 status[b]			
TAP score <1%	108 (35.5)	90 (29.8)	98 (31.8)
TAP score ≥1%	178 (58.6)	187 (61.9)	188 (61.0)
Choice of chemotherapy backbone			
CAPOX	276 (90.8)	273 (90.4)	282 (91.6)
FP	28 (9.2)	29 (9.6)	26 (8.4)

All data are shown as n (%) unless otherwise indicated.
[a]One patient in the zanidatamab-tislelizumab-chemotherapy arm had an ECOG PS score of 2 at baseline. [b]PD-L1 status was missing for 7.1% (n = 65) of patients across arms.
CAPOX, capecitabine and oxaliplatin; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; FP, 5-fluorouracil (5-FU) plus cisplatin; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PD-L1, programmed death-ligand 1; TAP, tumor area positivity.

HERIZON
GEA-301

Primary Endpoint: PFS per BICR

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



	Zanidatamab + CT	Trastuzumab + CT
Median PFS (95% CI), mo	12.4 (9.8–14.5)	8.1 (7.0–8.9)
HR (95% CI)	0.65 (0.52–0.81)	
	***P* <0.0001**	

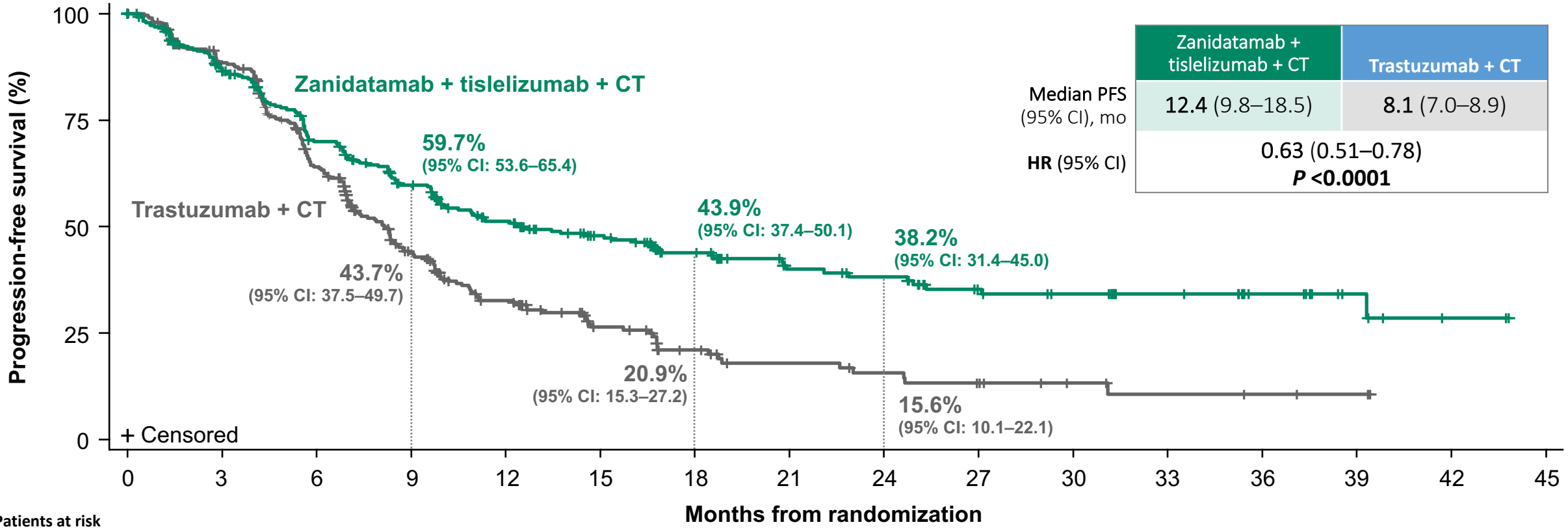
Patients at risk

Zani + CT	304	231	175	137	105	70	53	37	34	26	14	12	8	1	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; Tras, trastuzumab; Zani, zanidatamab.

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

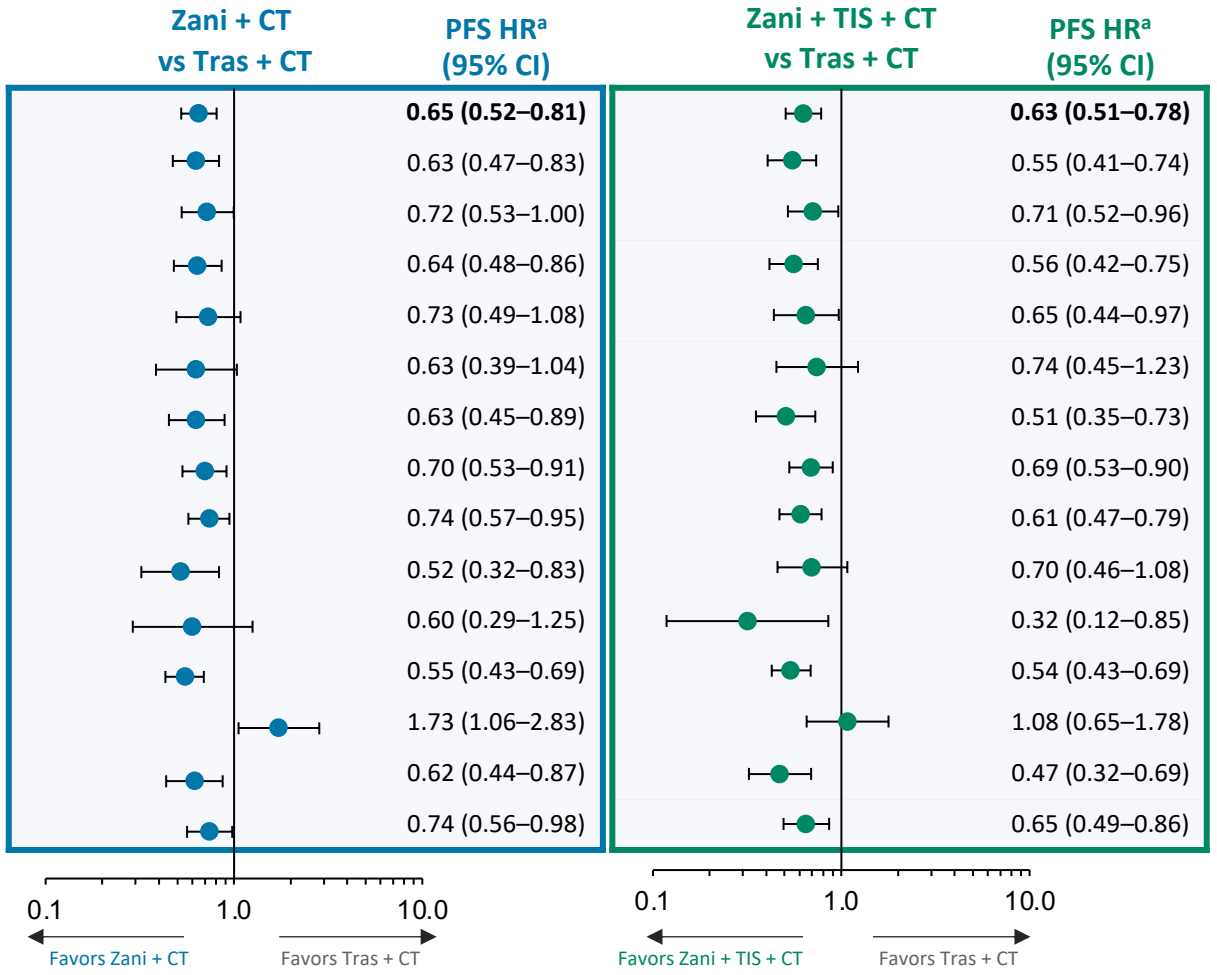
Zani + TIS + CT	302	240	183	147	113	90	65	46	42	30	27	20	13	6	2	0
Tras + CT	308	247	168	97	63	37	23	16	13	10	6	4	3	2	0	

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

HERIZON GEA-301

PFS in Key Prespecified Subgroups

Subgroup	Category	Zanidatamab + CT	Zanidatamab + tislelizumab + CT	Trastuzumab + CT
All patients		**160/304**	**154/302**	**196/308**
Age, years	<65	94/174	79/163	105/162
	≥65	66/130	75/139	91/146
Geographic region	Asia	81/163	78/159	106/165
	EU/NA	49/91	47/95	55/93
	ROW	30/50	29/48	35/50
ECOG PS	0	63/134	51/121	74/120
	1	97/170	103/180	122/188
Anatomical subtype	Gastric	112/204	105/208	140/226
	GEJ	29/61	43/74	44/60
	Esophageal	19/39	6/20	12/22
HER2 status	IHC 3+	125/251	121/251	167/255
	IHC 2+/ISH+	35/51	33/51	29/52
PD-L1 status	TAP <1%	61/108	47/90	71/98
	TAP ≥1%	94/178	91/187	114/188

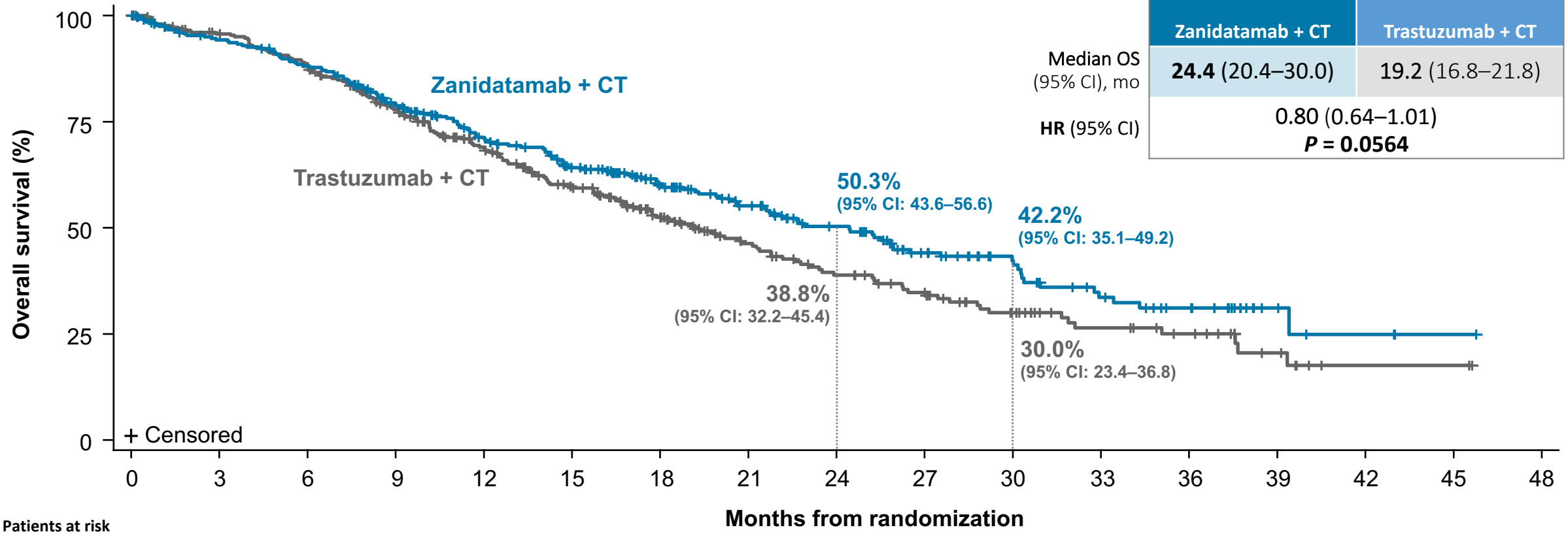


[a]The widths of the confidence intervals were not adjusted for multiplicity and cannot be used to infer treatment effects.
CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union;
GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 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.

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.

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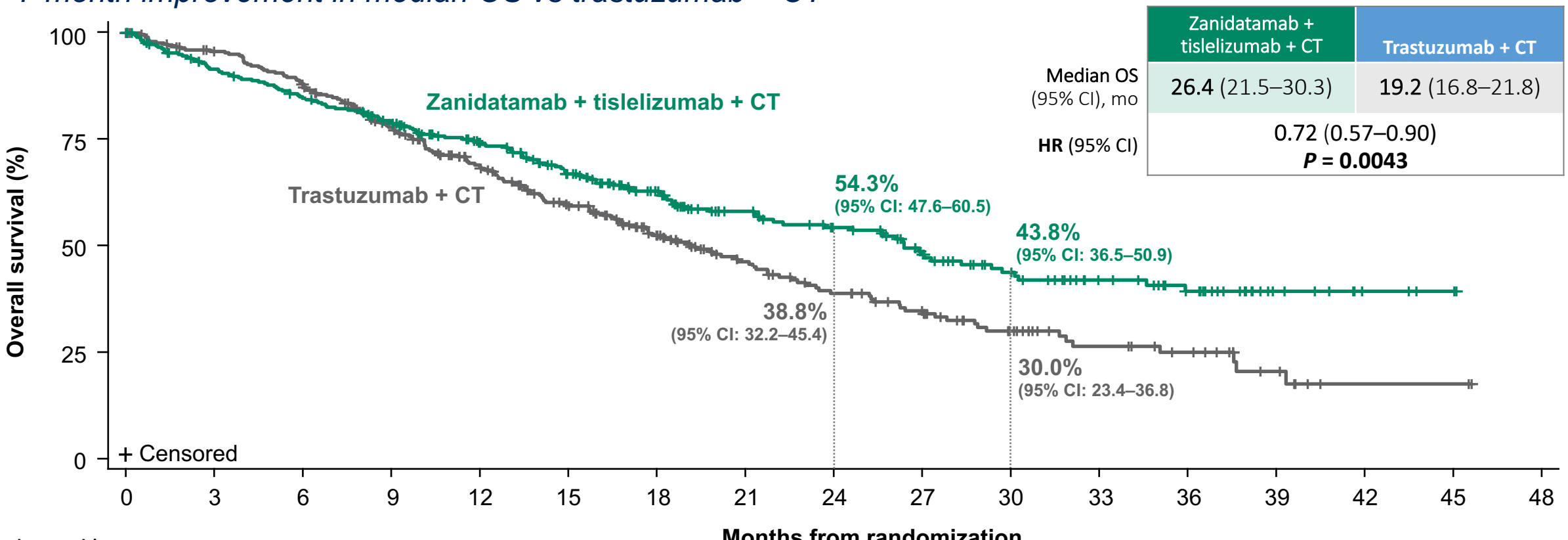
GEA-301

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**	

Patients at risk

Zani + TIS + CT	302	267	246	222	190	157	125	96	82	64	49	36	27	10	4	2	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; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

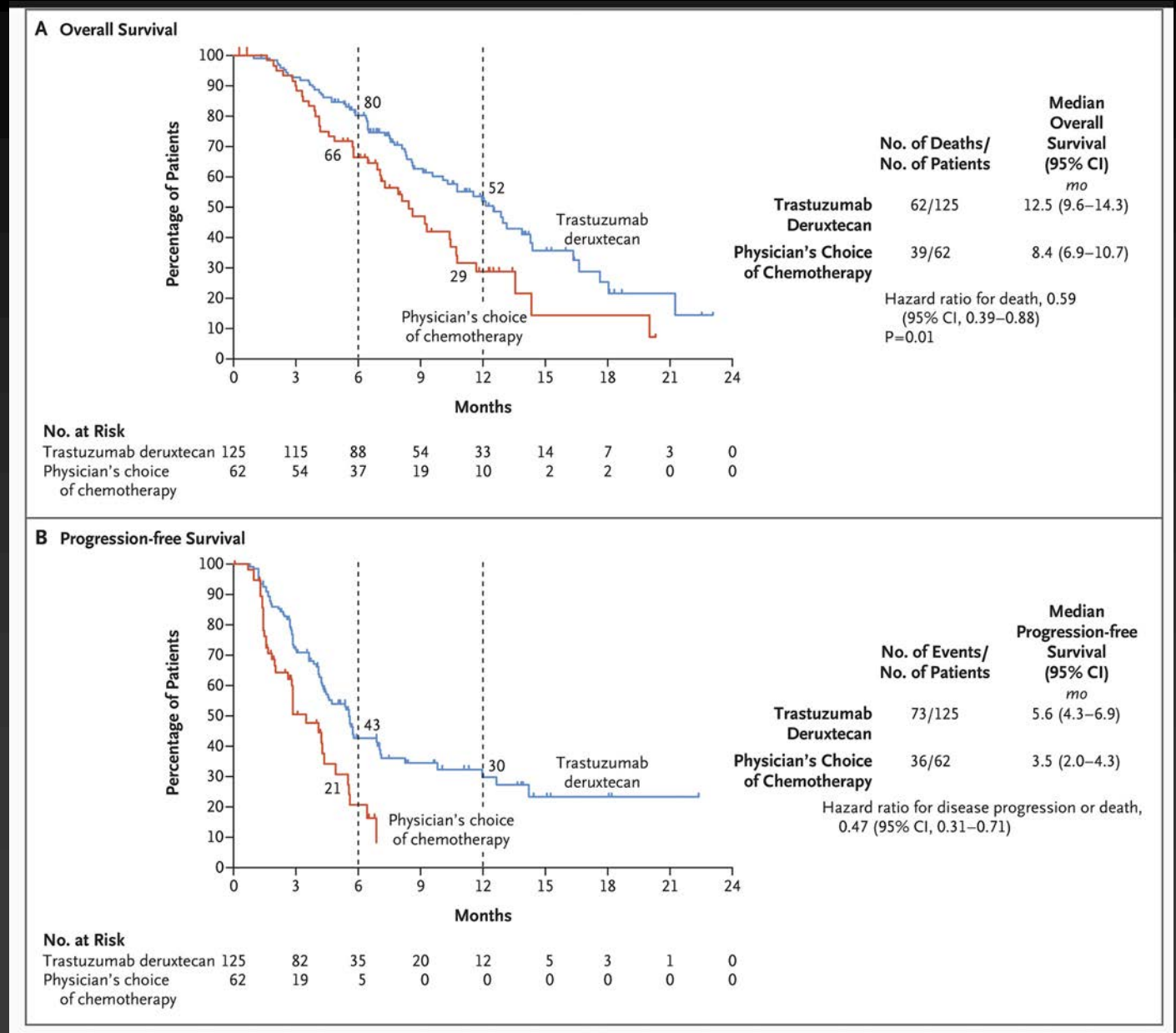
First Line Therapeutic Landscape of Her2 targeting Phase 3 Studies at Present

Trial # Pts	Median OS	HR (95% CI)	Median PFS	HR (95% CI)	ORR	Year
ToGA 594	**13.8** v 11.1	0.74 (60-91)	**6.7** v 5.5	0.71 (59-85)	47% v 35%	2010
KN811 698 PDL-1+ only	**20.0** v 16.8	0.79 (66-95)	**10.0** v 8.1	0.73 (61-87)	72% v 60%	2023
Herizon-GEA01 914 **Arm C**	**26.4** v 19.2	0.72 (57-90)	**12.4** v 8.1	0.65 (52-81)	71% v 65%	2026

January 2026 (J. Ajani)

NEJM 2020:18:2419-2430

Destiny Gastric01



Destiny Gastric04

NEJM 2025:336-348. (Interim Analysis)

Total recruited

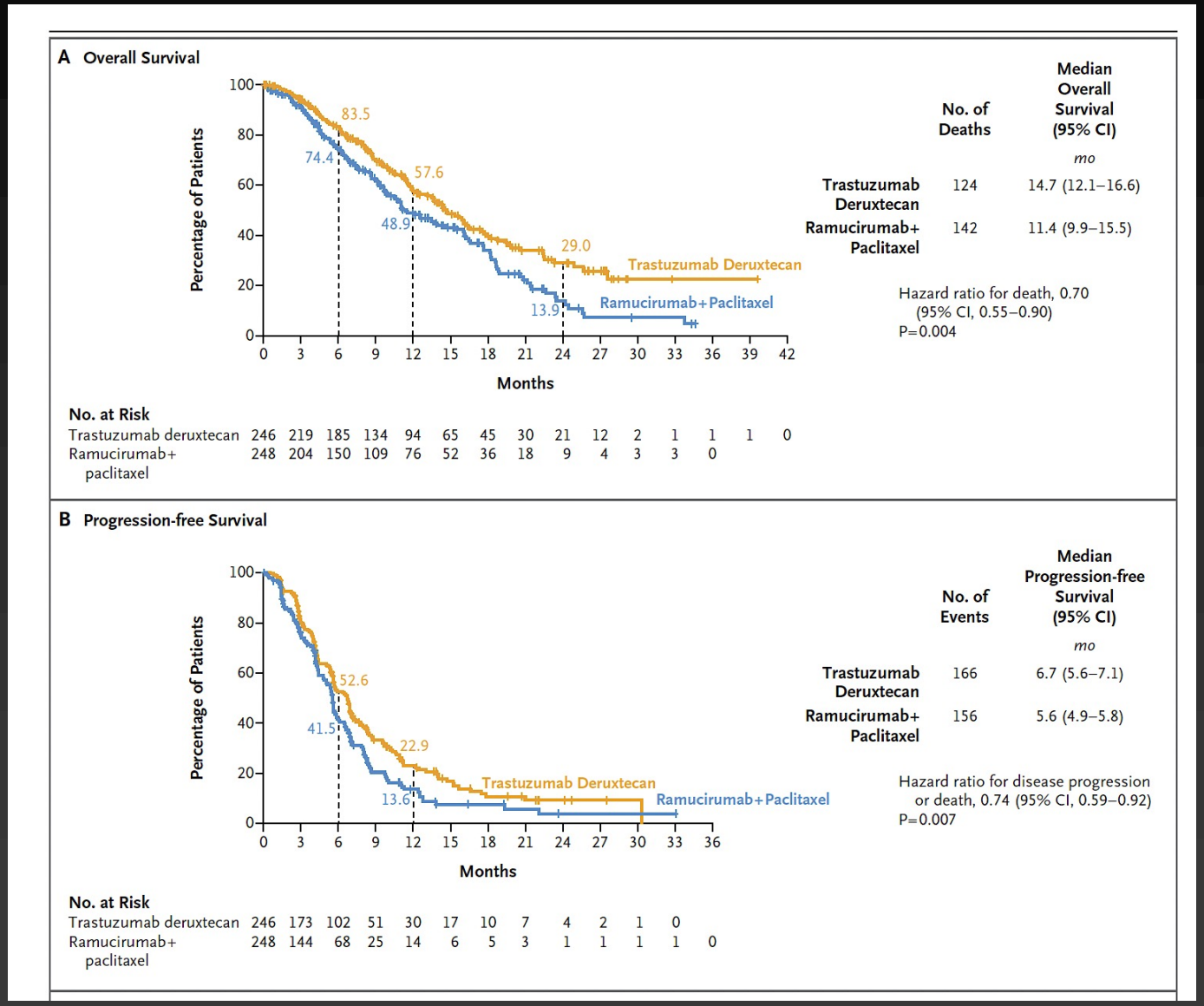
n= 494

Analyzed here

n=248

Her2 3+ = 84%

Her2 2+/+ = 15%



ORR

44 vs 29

Asians = 24%

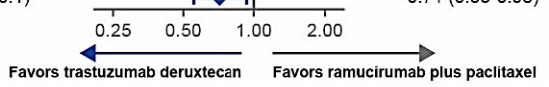
EU = 53%

Median FU

16.8 mo

Destiny Gastric04-Less effective in Diffuse Type

	No. of Events/No. of Patients		OS, median (95% CI), mo		Hazard Ratio (95% CI)
	Trastuzumab deruxtecan	Ramucirumab plus paclitaxel	Trastuzumab deruxtecan	Ramucirumab plus paclitaxel	
HER2 IHC status					
IHC 2+/ISH+	17/39	25/40	17.7 (9.1-NE)	7.4 (4.5-10.7)	0.35 (0.18-0.66)
IHC 3+	107/207	117/208	14.4 (11.9-16.4)	13.4 (10.8-16.5)	0.79 (0.61-1.03)
Geography					
Asia	31/57	34/60	14.4 (10.5-19.4)	16.1 (10.8-18.9)	0.82 (0.50-1.34)
Western Europe	67/140	79/139	15.7 (11.9-18.8)	11.1 (8.7-15.5)	0.62 (0.45-0.86)
Mainland China/Rest of world	26/49	29/49	14.8 (8.7-NE)	9.7 (7.4-16.0)	0.78 (0.46-1.33)
Time to progression on first line					
<6 months	38/61	38/61	10.2 (8.1-14.4)	7.3 (5.0-10.1)	0.70 (0.45-1.10)
≥6 months	86/185	104/187	16.3 (13.7-19.4)	13.5 (11.0-17.6)	0.68 (0.51-0.91)
Age					
<65 years	69/140	75/130	15.7 (12.1-18.1)	11.1 (9.6-16.1)	0.68 (0.49-0.94)
≥65 years	55/106	67/118	13.7 (10.5-17.5)	11.5 (8.9-16.6)	0.73 (0.51-1.05)
Region					
Asia (including mainland China)	52/97	54/95	14.4 (11.5-18.1)	14.6 (9.7-18.2)	0.85 (0.58-1.24)
Europe	60/123	80/140	15.9 (12.5-19.5)	11.0 (8.6-13.9)	0.58 (0.41-0.81)
Rest of world	12/26	8/13	7.8 (4.7-22.4)	12.2 (3.0-17.6)	0.81 (0.32-2.04)
ECOG PS					
0	38/97	45/88	18.1 (13.1-27.6)	17.6 (12.6-20.6)	0.68 (0.44-1.05)
1 or 2	86/149	96/159	13.9 (10.2-16.0)	9.9 (7.7-11.4)	0.71 (0.53-0.96)
Primary tumor location					
Gastric	83/153	83/149	11.9 (10.1-14.8)	11.4 (9.6-16.1)	0.86 (0.64-1.17)
GEJ	41/93	59/99	18.0 (14.7-22.5)	11.5 (9.2-16.2)	0.49 (0.33-0.74)
Histological subtype					
Intestinal	35/69	38/66	16.6 (11.5-20.5)	12.6 (9.9-18.3)	0.74 (0.47-1.18)
Diffuse	15/25	11/19	9.4 (7.9-16.0)	8.7 (4.6-16.1)	0.74 (0.34-1.64)
Others	74/152	93/163	14.7 (11.9-19.4)	11.1 (9.2-16.1)	0.66 (0.49-0.90)
Number of metastatic sites					
<2	36/73	44/75	13.6 (10.1-22.4)	15.5 (10.8-17.6)	0.85 (0.55-1.33)
≥2	88/173	98/173	14.7 (11.9-17.7)	10.4 (8.7-13.5)	0.64 (0.48-0.86)
Prior treatment with immune checkpoint inhibitors					
Yes	18/39	24/38	16.3 (10.2-NE)	10.1 (7.4-18.6)	0.59 (0.32-1.10)
No	106/207	118/210	14.4 (11.9-17.5)	12.6 (9.9-16.1)	0.71 (0.55-0.93)



Conclusions

1. Her2 space for gastric and gastroesophageal cancers is evolving rapidly
2. Zanidatamab is impressively superior to trastuzumab (should replace it)
3. Zani-induced toxicities are manageable
4. Tislelizumab improved PFS and OS in the HerizonGEA01 study establishing a new benchmark in first line (never been achieved before).
5. TDXd is solidly established in 2nd line
6. Looking forward to results of Destiny Gastric01, Artemide Gastric01, and HLX-Gastric-01 trials in first line.

Questions from General Medical Oncologists — HER2-Targeted Approaches for Advanced GE Cancers

56 yr old with de novo metastatic gastric cancer, HER2-positive, CPS 2. Would you use zanidatamab in the front-line setting? What are your thoughts regarding tislelizumab? Any differentiating features from other IO agents? How does tislelizumab compare to pembro/nivo?

62 y/o female with Stage IV GEJ adenocarcinoma, PD-L1 CPS of 5, HER2 IHC 3+. Before being seen by us, pt was treated with FLOT x 3 cycles with stable disease. Pt prefers to be treated by our med onc service from this point on. Should I give pembro + trastuzumab + FLOT? Or is it better to proceed with pembro + trastuzumab + FOLFOX?

RTP RESEARCH TO PRACTICE

Questions from General Medical Oncologists — HER2-Targeted Approaches for Advanced GE Cancers

80 y/o F with de novo HER2+ GEJ cancer with extensive liver mets presented w/ weight loss and FTT, ECOG PS 2 bordering on 3. What 1L rx would you offer this pt, if any (assuming she's interested)?

87 yr old male treated with front-line 5-FU with pembro and trastuzumab now with progressive disease with borderline functional status. In an elderly patient such as this, how do we decide what may be the most effective option but also tolerable?

Questions from General Medical Oncologists — HER2-Targeted Approaches for Advanced GE Cancers

52 y/o M with DM, HTN, active tobacco use (40 pack-years) and GEJ adenocarcinoma, HER2 3+, PD-L1 22%, with lymph node involvement only, including R supraclavicular, R hilar, R mediastinal and gastrohepatic LN regions on PET/CT. Patient wants to pursue surgery but plan is to start with neoadjuvant therapy. Would you offer this patient neoadjuvant therapy with FLOT + durva? Or would you consider this patient inoperable with metastatic disease and use FOLFOX + trastuzumab + IO? What about zanidatamab/chemotherapy +/- tislelizumab?

RTP
RESEARCH
TO PRACTICE

Questions from General Medical Oncologists — HER2-Targeted Approaches for Advanced GE Cancers

73-year-old female with 6-month history of dysphagia found on endoscopy to have semi-obstructive GEJ adenocarcinoma, HER2+ by IHC and FISH, no nodal or distant spread on imaging. What neoadjuvant approach would you recommend?

65 y/o with locally advanced HER2+ GEJ cancer. Is there a role for HER2-targeted therapy in locally advanced HER2+ GEJ cancer?

Questions from General Medical Oncologists — HER2-Targeted Approaches for Advanced GE Cancers

77-year-old male, taken for radical gastrectomy without preop oncology consult, found to have Stage IIIA disease but tumor HER2 overexpressed. Adjuvant therapy recommendations?

35 y/o M with dysphagia and weight loss with GEJ mass. EGD confirms HER2+ dz, PAC placed and diagnostic laparoscopy reveals no peritoneal dz but small peripheral liver lesion, also bx+ for HER2+ adenocarcinoma of GEJ origin. Quadruplet 1L systemic Rx, f/b restaging and resection of oligomet?

Agenda

Module 1: HER2-Targeted Approaches for Advanced Gastroesophageal Cancers — Dr Ajani

Module 2: Targeting Claudin 18.2 in Advanced Gastroesophageal Cancers — Dr Strickler

Module 3: Optimal Incorporation of Immunotherapeutic Strategies into Treatment for Patients with Metastatic Gastroesophageal Tumors — Dr Mehta

Module 4: Other Novel Agents and Strategies Under Evaluation for Advanced Gastroesophageal Cancers — Dr Klempner

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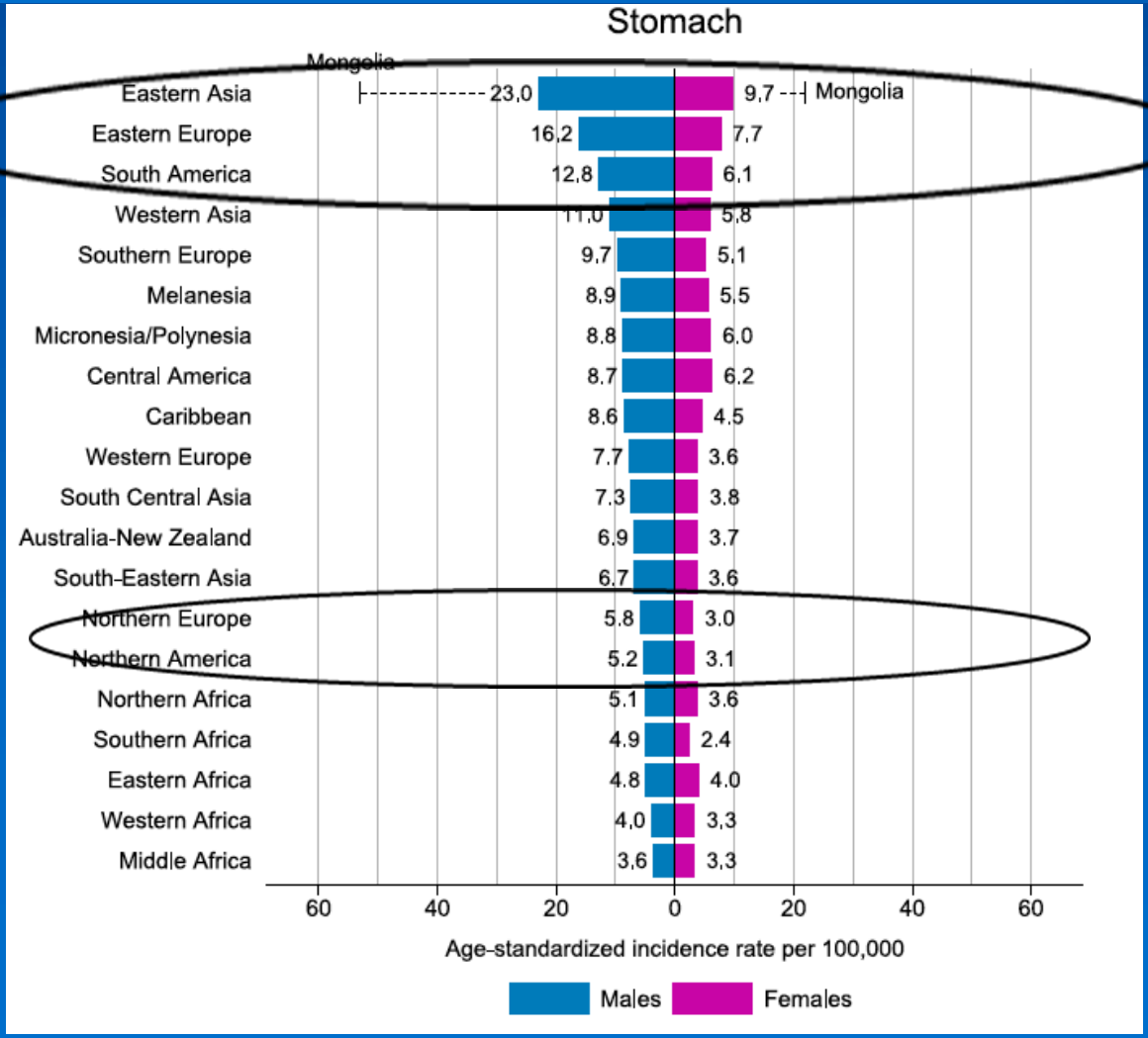
TARGETING CLAUDIN 18.2 (CLDN18.2) IN ADVANCED GASTROESOPHAGEAL CANCERS

John Strickler, MD
Professor of Medicine
Associate Director, Clinical Research – GI
Co-Leader, Molecular Tumor Board
Duke University
Durham, North Carolina

Courtesy of David H. Ilson, MD PhD, FASCO, FACP

Gastric Cancer: Global Incidence: 2022



- 5th leading cause of cancer
- 5th leading cause of cancer related death
- Uncommon in the U.S. and Europe
- No effective screening or early detection

Bray et al CA J Clin 74: 229; 2024

Metastatic Disease: NCCN Endorsed Chemo

- **2 drug regimens**
  - FOLFOX, CAPE-OX or CIS, FOLFIRI
- **3 drug regimens + docetaxel (DCF, mDCF, FLOT) not recommended**
  - No survival benefit for FLOT over FLO, patients 65 or older: FLOT65
  - No survival benefit for Doc + S-1/Cisplatin: JCOG 1013
  - TFOX > FOLFOX in French FFCD / Prodige 51 Trial
  - ARMANI: Early change to paclitaxel ramucirumab from FOLFOX
    - Access to Ramucirumab second line limited in both studies

JNCCN 23: 169;2025 EJC 49: 835; 2013 Lancet Gastroenterol Hepatol 4: 501;2019 Lancet Onc 26: 732; 2025 Lancet Onc 25: 1539; 2024

Metastatic Disease: NCCN Endorsed Chemo

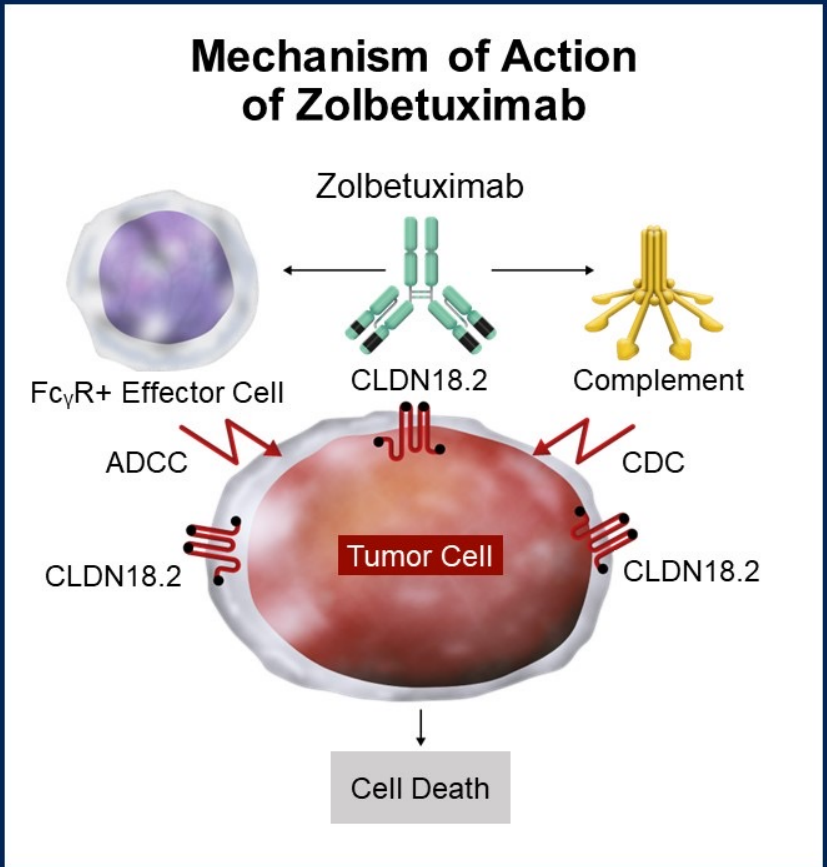
- Add trastuzumab in HER2+, add pembro in CPS > = 1%
- Add Nivo to chemo in CPS > = 1%
- Add Pembro to chemo in CPS > = 1%
- Add Tislelizumab to chemo in CPS > = 1%
- Add Zolbetuximab if Claudin 18.2 positive at > = 75%
- MSI High: First line use of CPI + / - chemo

JNCCN 23: 169; 2025

Minimum biomarker testing in a newly diagnosed M1 Esophagogastric Cancer

- **1) IHC for HER2**
- **2) IHC for DNA mismatch repair protein deficiency**
  - Esophageal cancer: < 1%
  - Gastric cancer: 7%
- **3) IHC for PDL-1, Combined positive score**
- **4) IHC for Claudin 18.2**
- **NGS**
  - Blood based genomic testing if tissue unavailable
  - Covers gene amplification and Validates MSI
  - Tests for rare but targetable genes
    - NTRK gene fusion, BRAF V600E, RET gene fusion
  - Assesses TMB

Introduction: Rationale for Zolbetuximab in Patients With LA Unresectable or mG/GEJ Adenocarcinoma



- CLDN18.2 is a tight junction protein expressed in normal and malignant gastric mucosa cells[1–8]
- During malignant transformation, CLDN18.2 may become exposed on the surface of G/GEJ adenocarcinoma cells, making it a promising target[2–8]
- Zolbetuximab is a first-in-class chimeric IgG1 monoclonal antibody that targets CLDN18.2 and induces ADCC/CDC[4–8]
- Zolbetuximab is currently being evaluated in combination with oxaliplatin-based chemotherapy regimens in 2 global, phase 3 studies
  - SPOTLIGHT: zolbetuximab + mFOLFOX6[9]
  - GLOW: zolbetuximab + CAPOX

1. Niimi T et al. *Mol Cell Biol.* 2001;21:7380–90; 2. Sahin U et al. *Clin Cancer Res.* 2008;14:7624–34; 3. Moran D et al. *Ann Oncol.* 2018;29:viii14-viii57; 4. Sahin U et al. *Eur J Cancer.* 2018;100:17–26; 5. Rhode C et al. *Jpn J Clin Oncol.* 2019;49:870–6; 6. Türeci Ö et al. *Ann Oncol.* 2019;30:1487-95; 7. Pellino A et al. *J Pers Med.* 2021; 11(11):1095; 8. Sahin U et al. *Ann Oncol.* 2021;32:609–19; 9. Shitara et al. *J Clin Onocol.* 2023;41:4_suppl, LBA292-LBA292.

Prevalence and Impact of CLDN18.2 Expression

- **Single Institution series from Japan, 408 patients 2015-2019**
- **CLDN18.2 by IHC with Clone 43-14A Roche Ventana antibody, + > = 75%**
- **CLDN18.2 expression similar across tumor subtypes**
  - 24% were positive including MMR-D (20.8%), EBV + (26.7%), HER2 + (26.7%), and “all negative” (23.8%)
  - CPS > = 5% 41.9% of CLDN18.2 +
  - No change in CLDN18.2 expression before and after first line chemo
- **For first and second line chemo, CLDN18.2 had no effect on PFS or OS**
- **For later line CPI therapy, CLDN18.2 had no effect on outcome**

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CLDN18.2 Expression Similar Across Tumor Subtypes

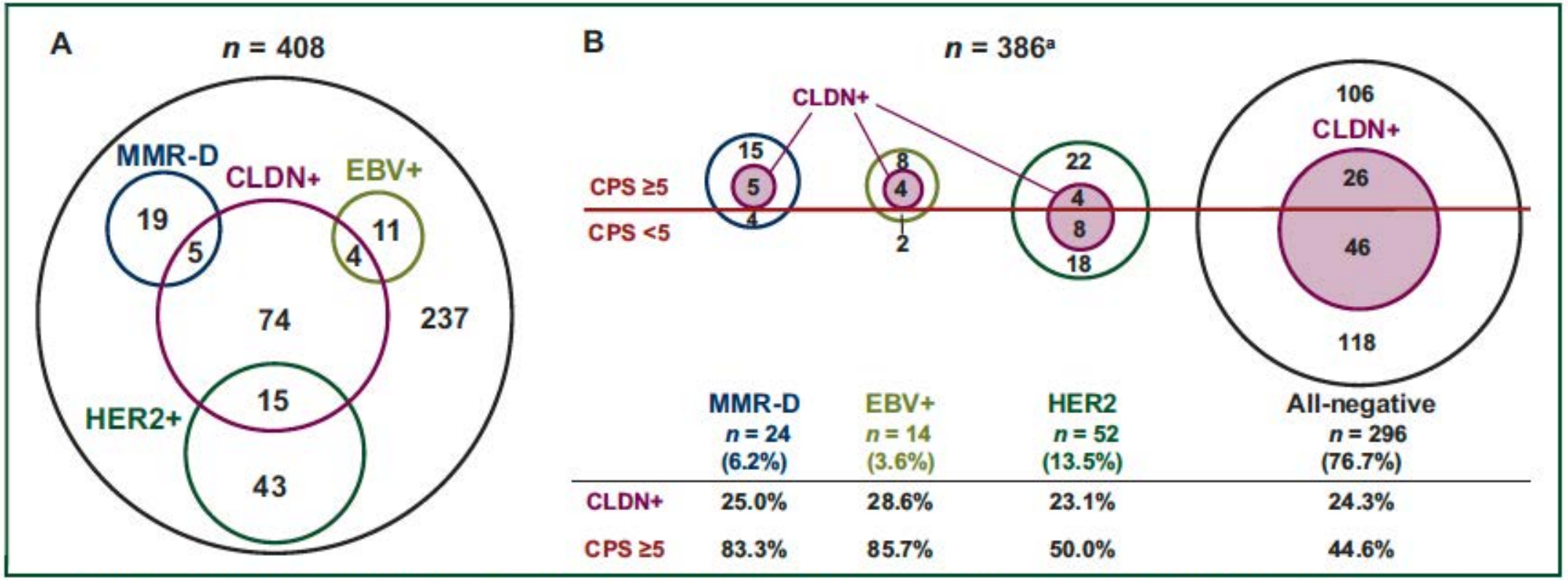

Figure 2. Relationship between CLDN and other biomarkers (A) and PD-L1 CPS (B). All-negative: negative for neither MMR-D, EBV nor HER2.
CLDN, claudin; CPS, combined positive score; EBV, Epstein–Barr virus; HER2, human epidermal growth factor receptor 2; MMR-D, mismatch repair deficient; MMR-P, mismatch repair proficient.
[a]Patients with available CPS results.

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CLDN18.2 and OS with First Line Chemo

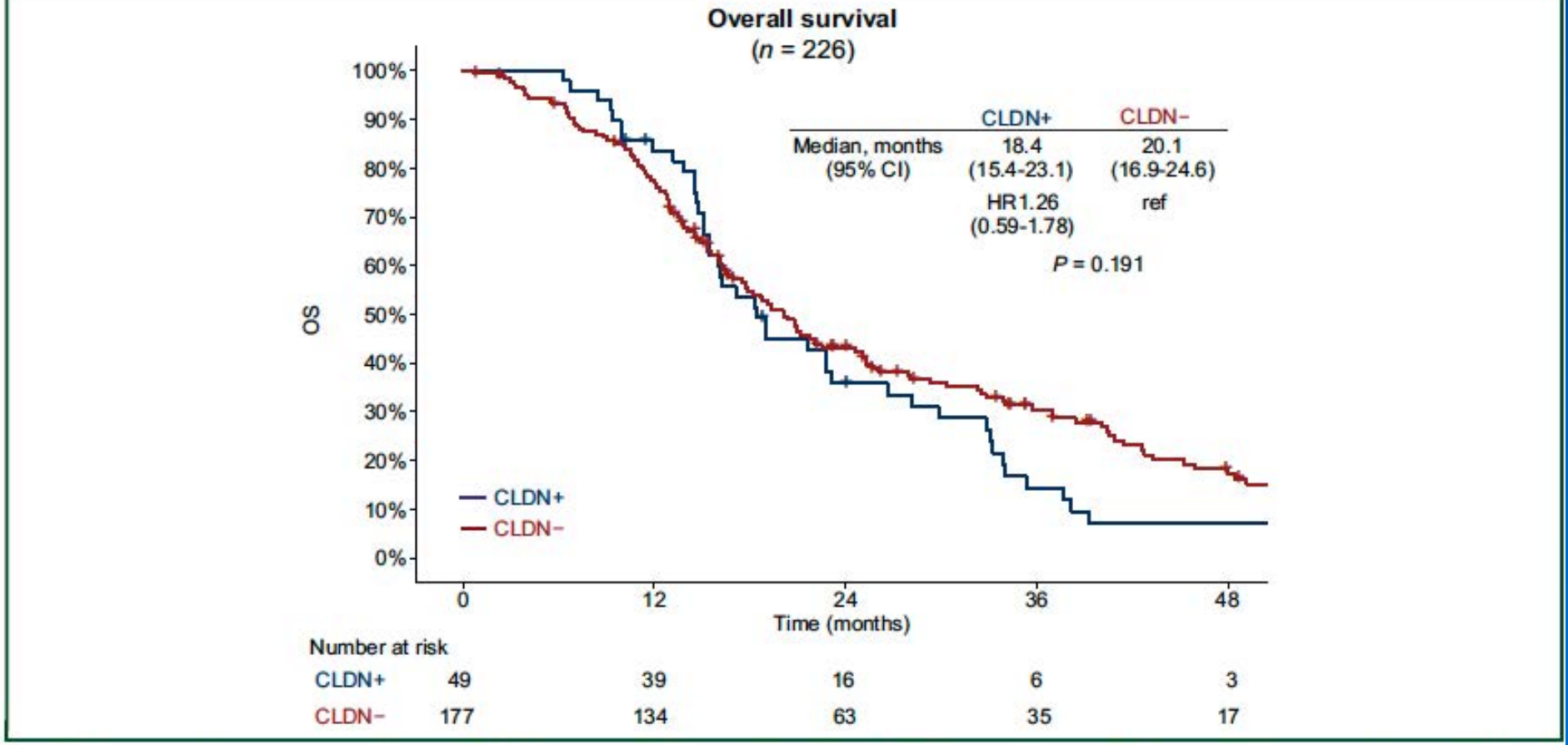


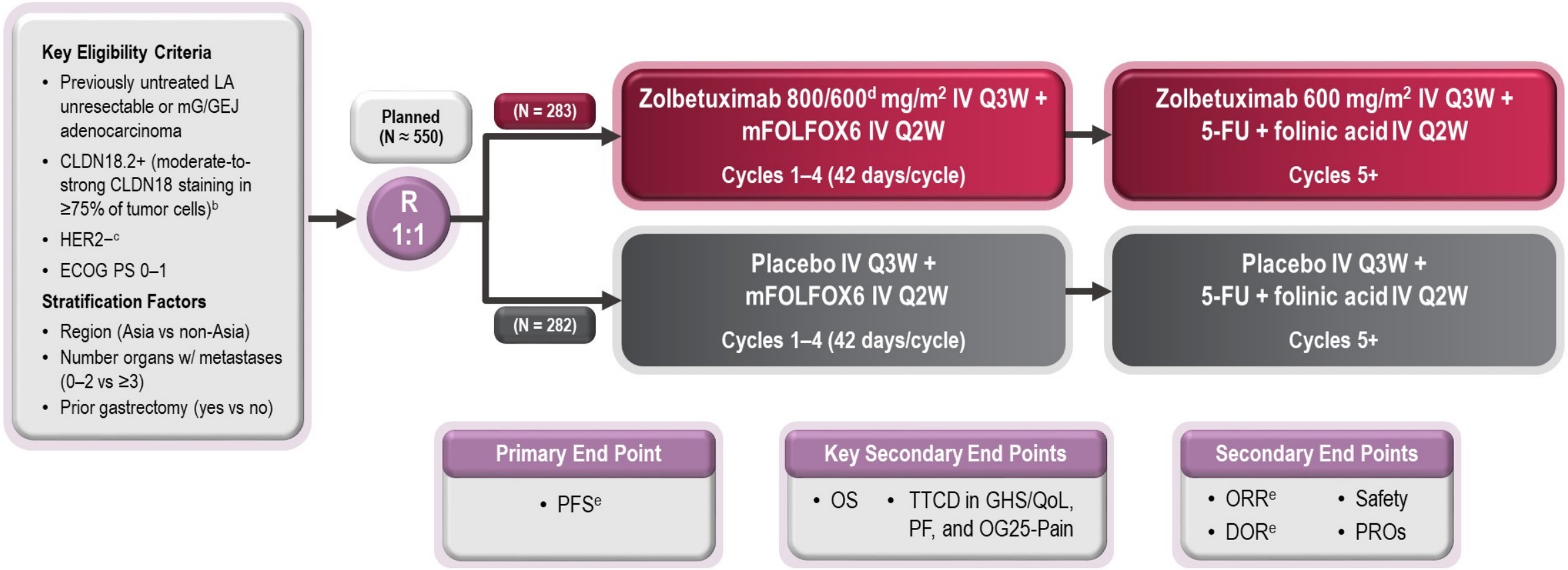
Figure 4. Kaplan–Meier plots of overall survival (OS) in patients who received standard first-line chemotherapy (platinum + fluoropyrimidine, *n* = 226).
HR, hazard ratio; ref, reference.

Kubota and Shitara ESMO Open 8: 1; 2023

Study Design: SPOTLIGHT

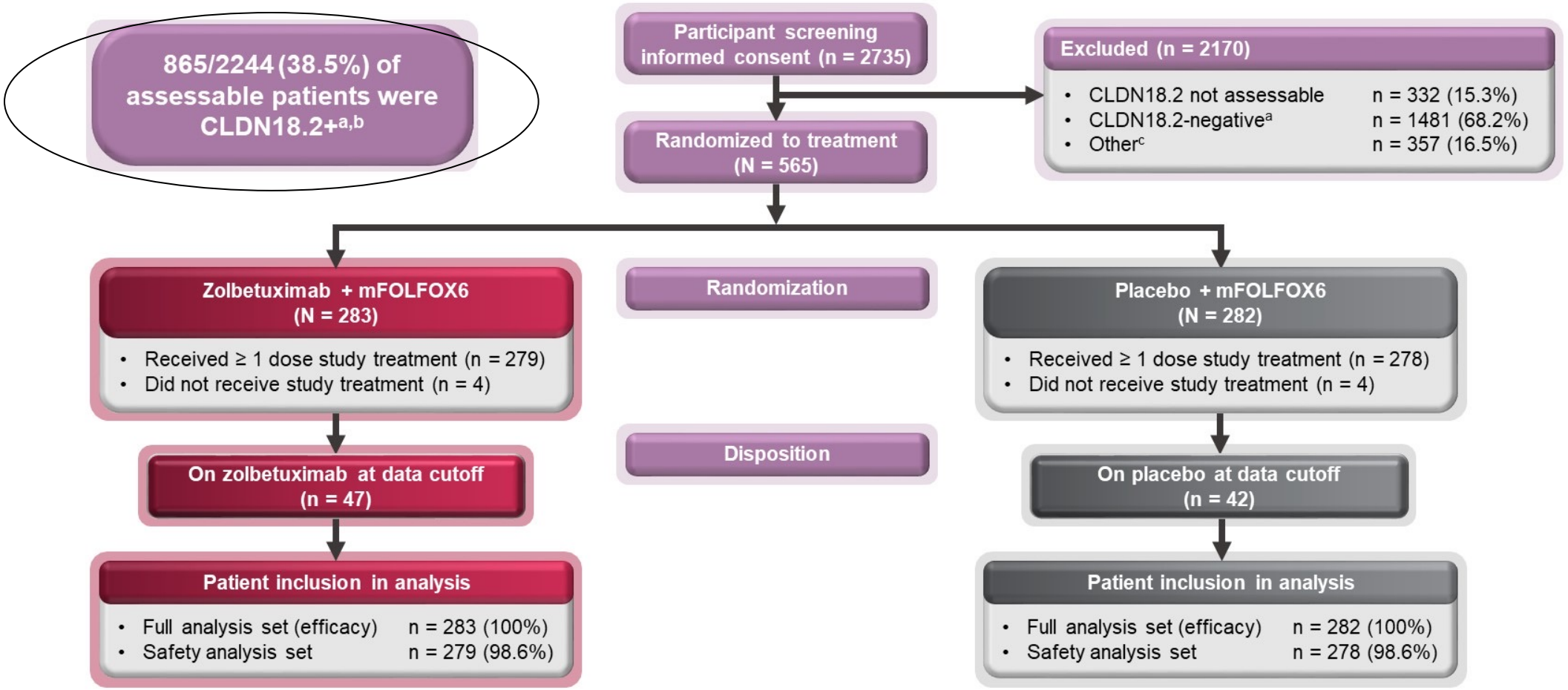
Shitara Lancet 401: 1655; 2023

Global[a], randomized, double-blinded, placebo-controlled, phase 3 trial



[a]Study was conducted at 215 sites in 20 countries across Australia, Asia, Europe, N. America, and S. America; [b]By central IHC using the analytically validated VENTANA CLDN18 (43-14A) RxDx Assay; [c]By central or local HER2 testing; [d]800 mg/m² at cycle 1 day 1 followed by 600 mg/m² on cycle 1 day 22 and days 1 and 22 of subsequent cycles; [e]Per RECIST v1.1 by independent review committee.

Patient Disposition



Data cutoff: September 9, 2022; Recruitment period: June 21, 2018–April 1, 2022.

[a]CLDN18.2+ was defined as moderate-to-strong CLDN18 staining in ≥75% of tumor cells by central IHC using the analytically validated VENTANA CLDN18 (43-14A) RxDx Assay. [b]These data exclude Chinese patients. [c]"Other" represents reasons including withdrawal by subject, laboratory findings, HER2-expression status, and ECOG PS score.

Baseline Characteristics

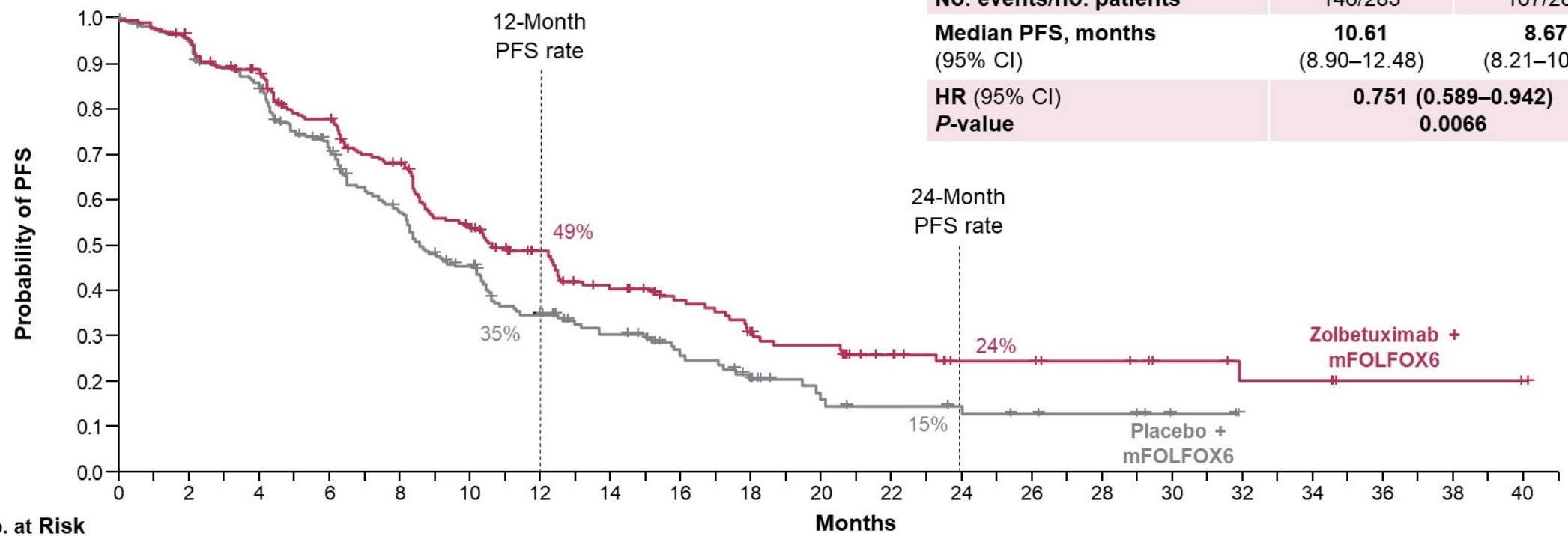
		Zolbetuximab + mFOLFOX6 (N = 283)	Placebo + mFOLFOX6 (N = 282)
Age, years (range)	Median	62.0 (27–83)	60.0 (20–86)
Sex, n (%)	Male	176 (62.2)	175 (62.1)
Region, n (%)	Asia	88 (31.1)	89 (31.6)
	Non-Asia	195 (68.9)	193 (68.4)
Organs with metastases, n (%)	0–2	219 (77.4)	219 (77.7)
	≥3	64 (22.6)	63 (22.3)
Prior gastrectomy, n (%)	Yes	84 (29.7)	82 (29.1)
	No	199 (70.3)	200 (70.9)
Primary site, n (%)	Stomach	219 (77.4)	210 (74.5)
	GEJ	64 (22.6)	72 (25.5)
Lauren classification, n (%)	Diffuse	82 (29.1)	117 (42.1)
	Intestinal	70 (24.8)	66 (23.7)
	Mixed/others[a]	130 (45.9)	95 (33.7)
ECOG PS[b,c], n (%)	0	125 (44.8)	115 (41.4)
	1	153 (54.8)	163 (58.6)

- As an ad hoc analysis, 41/311 (13.2%) of assessable patients had tumors with PD-L1 CPS ≥5[d]
- Subsequent anticancer therapies were administered to 48% of patients in the zolbetuximab arm and 53% in the placebo arm

[a]Patients with Lauren classification "Mixed/others" include those classified as "mixed," "other," or "unknown" (unknown represents patients with adenocarcinoma without Lauren classification); [b]A patient in the zolbetuximab arm with ECOG PS 2 at baseline who was enrolled with ECOG PS 1 at screening is not shown here; [c]Four patients in each arm with ECOG PS missing at baseline who were enrolled with ECOG PS 0 or 1 at screening are not shown here (did not receive treatment and therefore did not have baseline measurements at C1D1); [d]Using the Dako PD-L1 IHC 28-8 pharmDx assay for samples within test stability and with subject consent.

Primary End Point: PFS by Independent Review Committee[a]

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	146/283	167/282
Median PFS, months (95% CI)	**10.61** (8.90–12.48)	**8.67** (8.21–10.28)
HR (95% CI)	**0.751 (0.589–0.942)**	
***P*-value**	**0.0066**	



No. at Risk

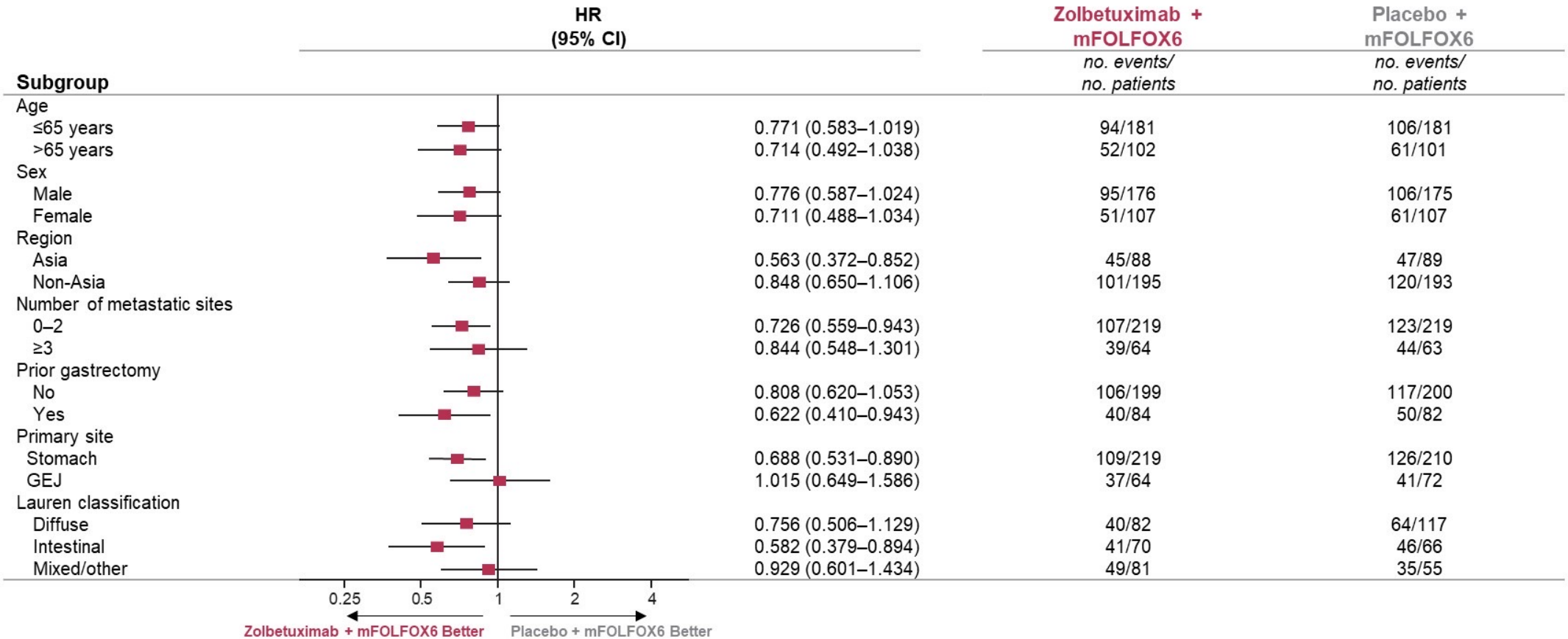
Zolbetuximab + mFOLFOX6	283	263	254	232	226	190	187	148	143	108	102	84	78	59	56	53	43	40	33	28	28	21	19	17	12	12	12	10	10	9	7	7	5	5	5	2	2	2	2	2	1	0
Placebo + mFOLFOX6	282	273	260	237	226	183	168	136	122	91	83	60	56	43	40	38	26	25	19	14	12	9	9	9	8	7	6	5	5	4	2	2	0	0	0	0	0	0	0	0	0	0

- PFS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

Data cutoff: September 9, 2022; Median follow-up = 12.94 months (zolbetuximab + mFOLFOX6) vs 12.65 months (placebo + mFOLFOX6).

[a]Per RECIST version 1.1.

Primary End Point: PFS[a] Subgroup Analysis



Subgroup	HR (95% CI)	Zolbetuximab + mFOLFOX6 *no. events/ no. patients*	Placebo + mFOLFOX6 *no. events/ no. patients*
Age			
≤65 years	0.771 (0.583–1.019)	94/181	106/181
>65 years	0.714 (0.492–1.038)	52/102	61/101
Sex			
Male	0.776 (0.587–1.024)	95/176	106/175
Female	0.711 (0.488–1.034)	51/107	61/107
Region			
Asia	0.563 (0.372–0.852)	45/88	47/89
Non-Asia	0.848 (0.650–1.106)	101/195	120/193
Number of metastatic sites			
0–2	0.726 (0.559–0.943)	107/219	123/219
≥3	0.844 (0.548–1.301)	39/64	44/63
Prior gastrectomy			
No	0.808 (0.620–1.053)	106/199	117/200
Yes	0.622 (0.410–0.943)	40/84	50/82
Primary site			
Stomach	0.688 (0.531–0.890)	109/219	126/210
GEJ	1.015 (0.649–1.586)	37/64	41/72
Lauren classification			
Diffuse	0.756 (0.506–1.129)	40/82	64/117
Intestinal	0.582 (0.379–0.894)	41/70	46/66
Mixed/other	0.929 (0.601–1.434)	49/81	35/55

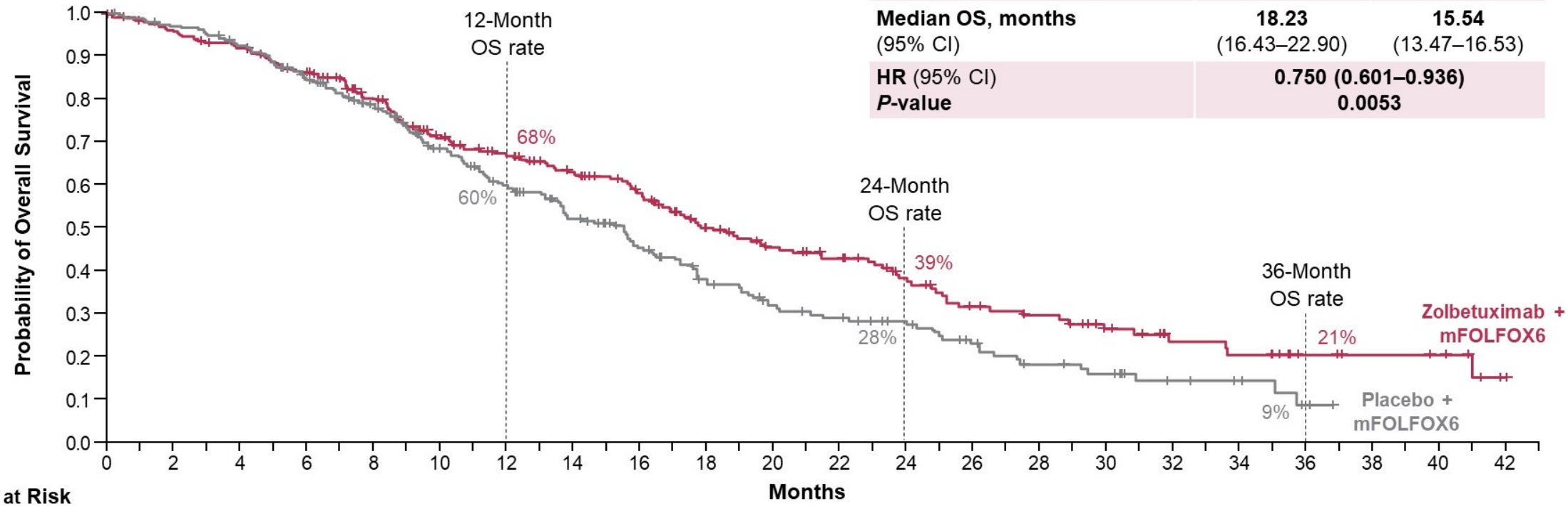
- PFS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 across most subgroups

Data cutoff: September 9, 2022.

[a]Per RECIST version 1.1 by independent review committee.

Key Secondary End Point: OS

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	149/283	177/282
Median OS, months (95% CI)	**18.23** (16.43–22.90)	**15.54** (13.47–16.53)
HR (95% CI)	**0.750 (0.601–0.936)**	
***P*-value**	**0.0053**	



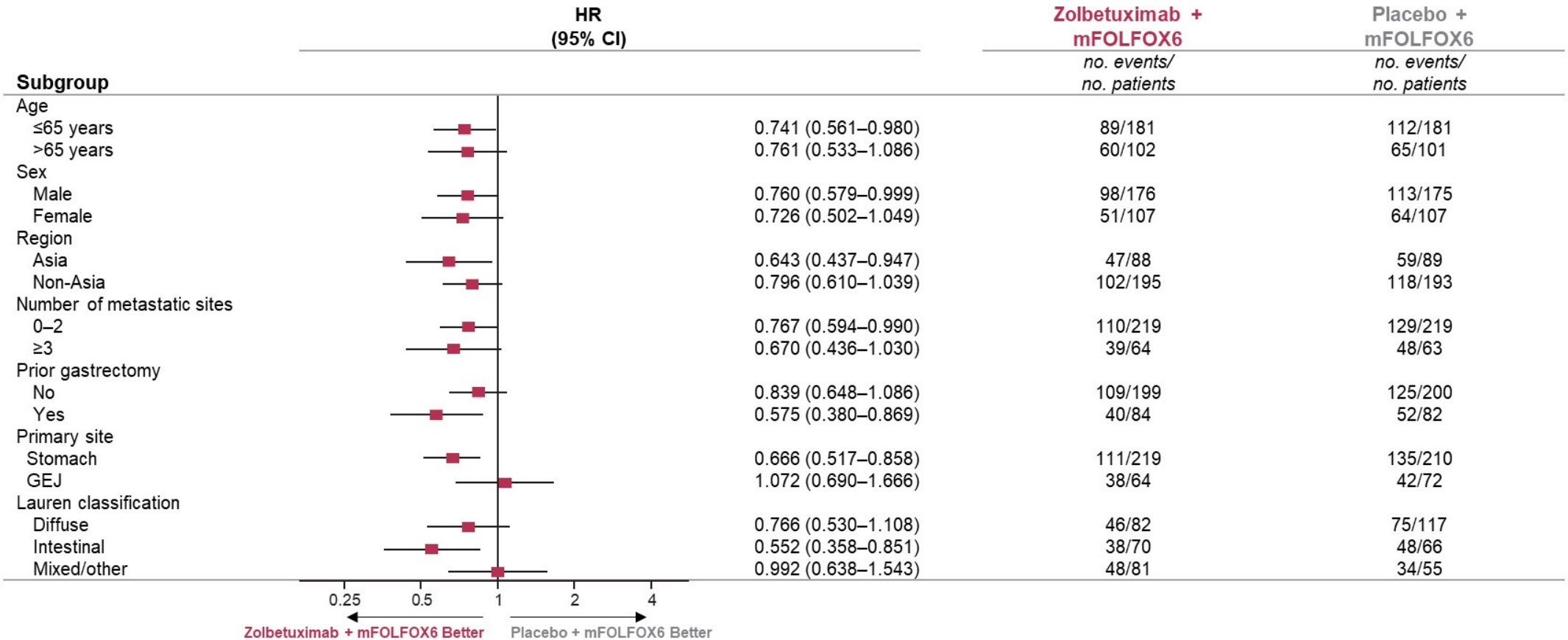
No. at Risk

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

- OS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

Data cutoff: September 9, 2022; Median follow-up = 22.14 months (zolbetuximab + mFOLFOX6) vs 20.93 months (placebo + mFOLFOX6).

Key Secondary End Point: OS Subgroup Analysis



- OS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 across most subgroups

Data cutoff: September 9, 2022.

Secondary End Points

	Zolbetuximab + mFOLFOX6 (N = 211)	Placebo + mFOLFOX6 (N = 211)
Patients[a], n	128	131
ORR[b], % (95% CI)	60.7 (53.72–67.30)	62.1 (55.17–68.66)
BOR[c,d], n (%)		
CR	12 (5.7)	7 (3.3)
PR	116 (55.0)	124 (58.8)
SD	45 (21.3)	52 (24.6)
PD	14 (6.6)	14 (6.6)
Median DOR[b], months, (95% CI)	8.51 (6.80–10.25)	8.11 (6.47–11.37)
3rd quartile, months (95% CI)	29.9 (10.41–NE)	15.5 (13.27–NE)

- Response rates were similar between treatment arms
- Formal analysis of PROs is pending
  - Initial descriptive analysis did not indicate differences between treatment arms

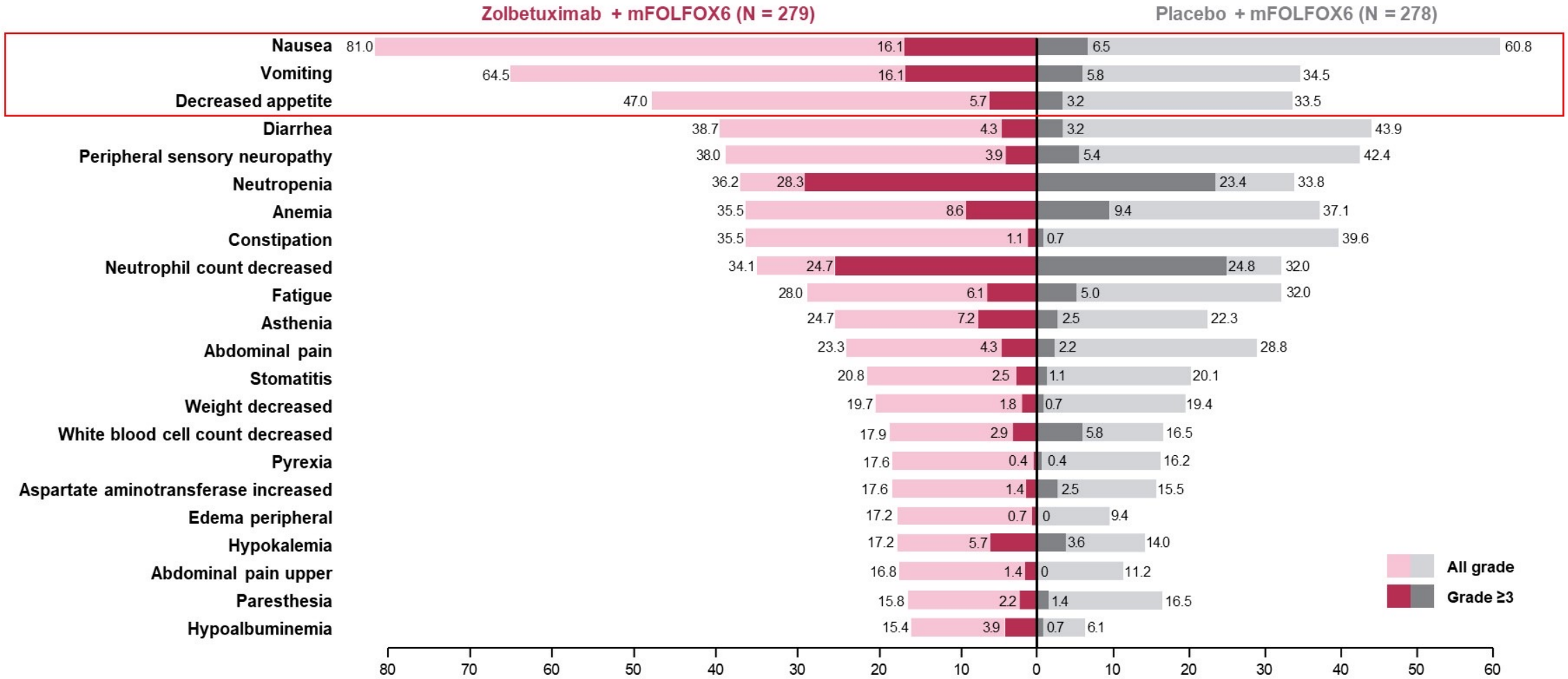
[a]Patients with measurable disease. [b]Per RECIST version 1.1 by independent review committee; [c]Patients with non-CR/non-PD, no disease, missing data, or who could not be evaluated are not shown; [d]Patients with missing data had no post-baseline imaging assessment.

AEs in All Treated Patients

Event, n (%)	Zolbetuximab + mFOLFOX6 (N = 279)		Placebo + mFOLFOX6 (N = 278)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
All TEAEs	278 (99.6)	242 (86.7)	277 (99.6)	216 (77.7)
Serious TEAEs	125 (44.8)	-	121 (43.5)	-
TRAEs leading to discontinuation of any study drug	106 (38.0)	-	82 (29.5)	-
TRAEs leading to discontinuation of zolbetuximab or placebo	38 (13.6)	-	6 (2.2)	-
TRAEs leading to death	5 (1.8)		4 (1.4)	

- The incidence of overall TEAEs was similar between treatment arms

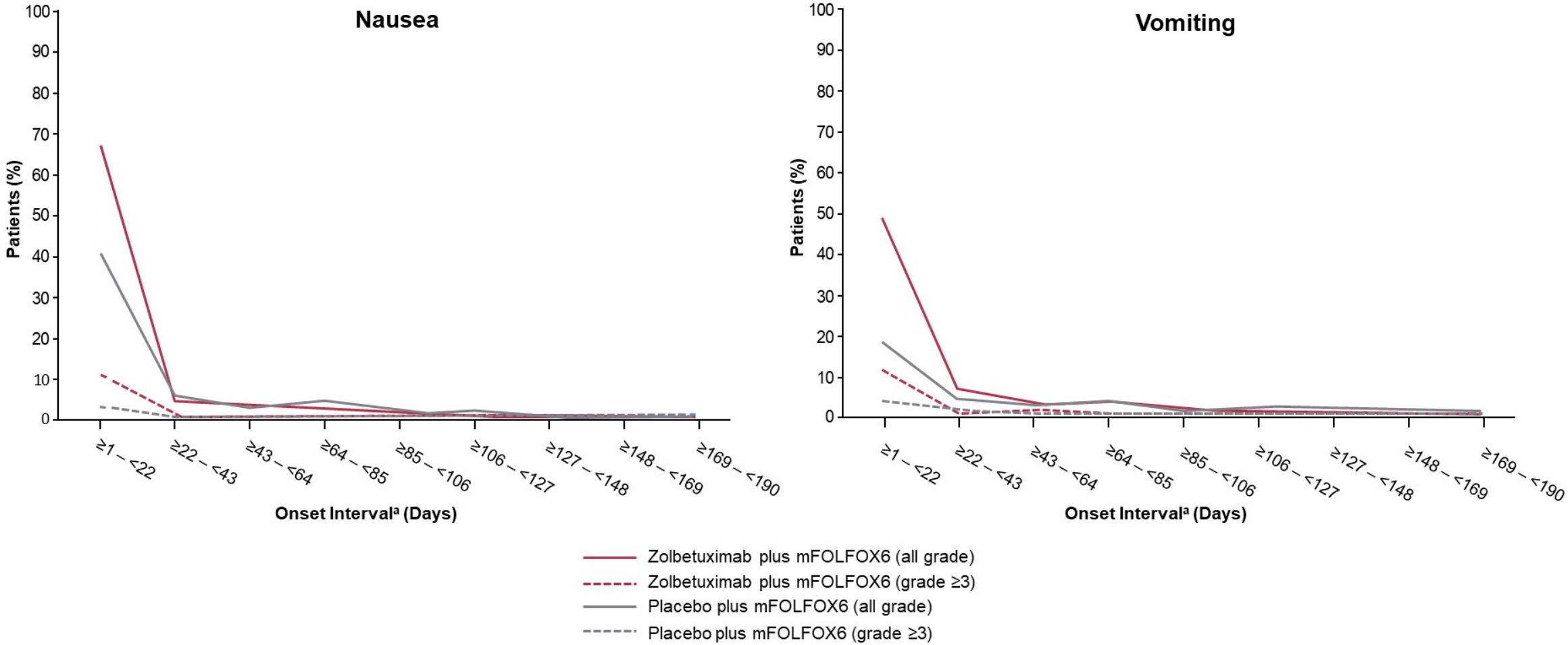
TEAEs[a] Occurring in ≥15% of All Treated Patients



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

[a]Preferred terms were defined according to the Medical Dictionary for Regulatory Activities terminology version 25.0.

First Occurrence of Nausea and Vomiting

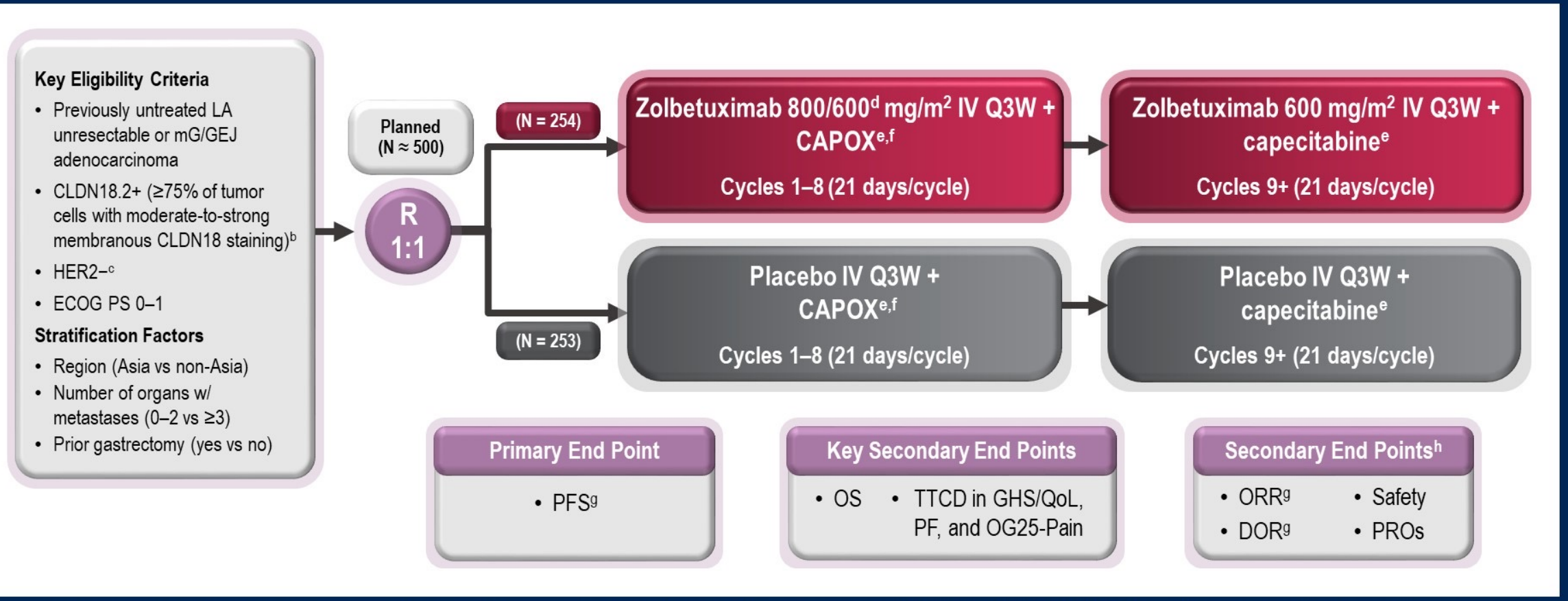


[a]The onset interval was defined as the date of onset through the date of dose plus one.

Study Design: GLOW

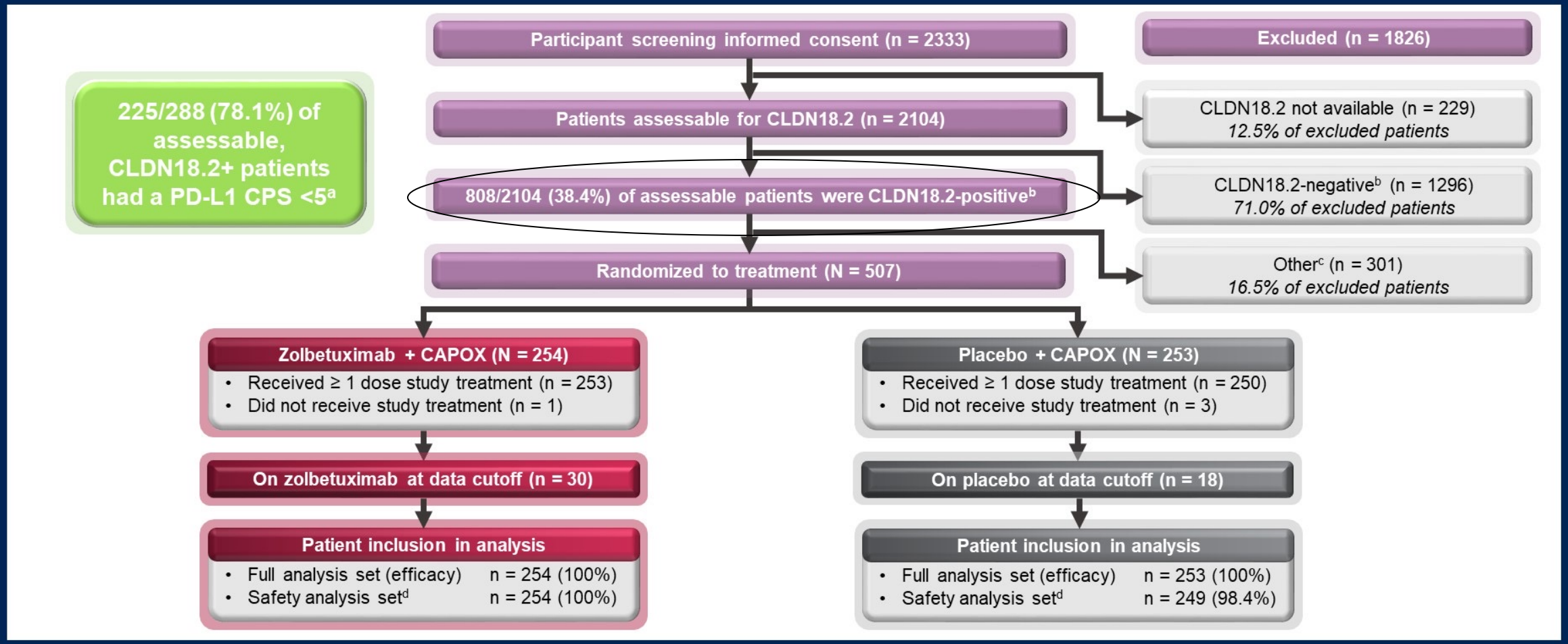
Global[a], randomized, double-blinded, placebo-controlled, phase 3 trial

Shah Nature Medicine 29: 2133; 2023



[a]Study was conducted at 166 sites in 18 countries across Asia, Europe, N. America, and S. America; [b]By central IHC using the investigational VENTANA CLDN18 (43-14A) RxDx Assay; [c]By central or local HER2 testing (IHC0–1, or IHC2/FISH–); [d]800 mg/m² at cycle 1 day 1 followed by 600 mg/m² on day 1 of subsequent cycles; [e]1000 mg/m² capecitabine orally BID on days 1–14 of each cycle; [f]130 mg/m² oxaliplatin IV on day 1 of each cycle; [g]Per RECIST v1.1 by independent review committee; [h]Select secondary end points are included here.

Patient Disposition



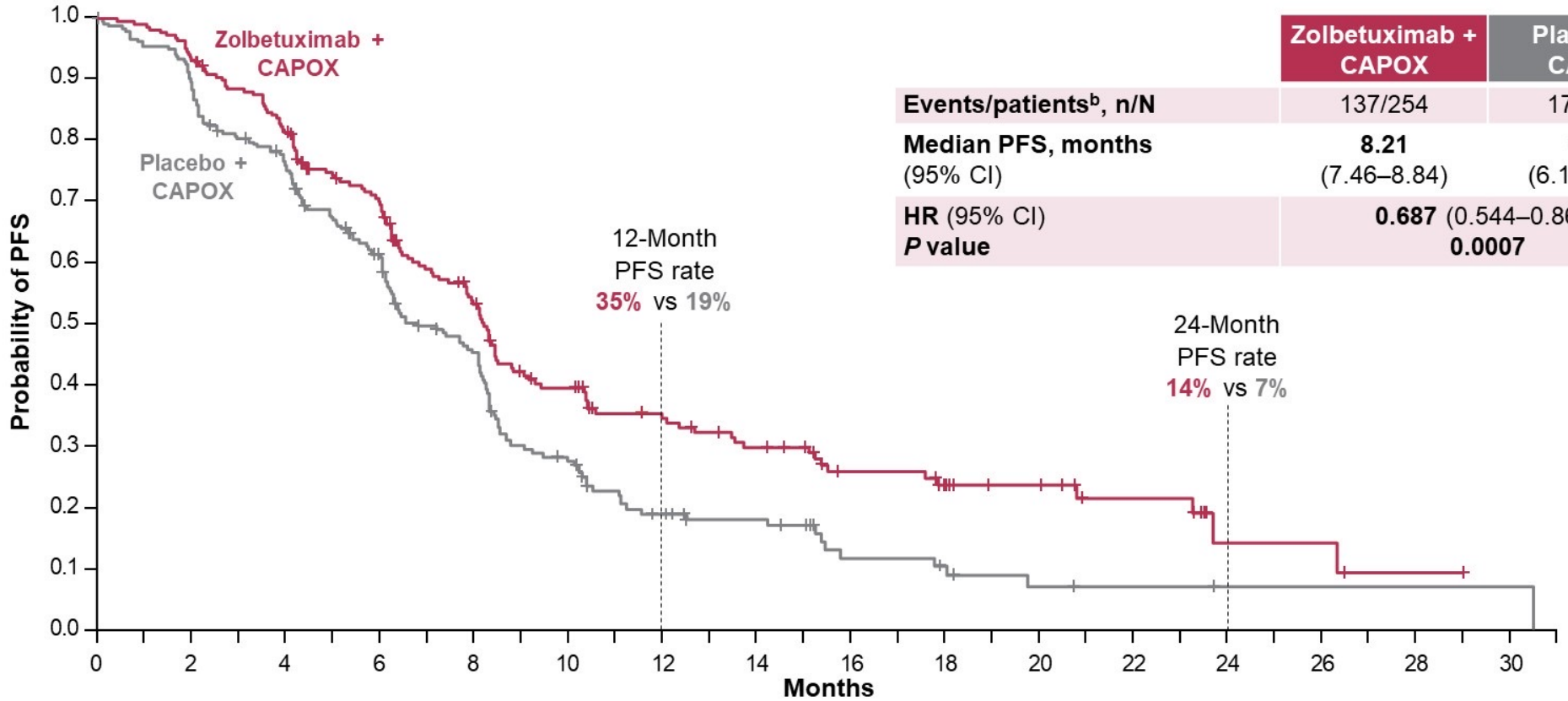
Data cutoff: October 7, 2022; Recruitment period: November 28, 2018–October 7, 2022.
[a]As an ad hoc analysis using the Dako PD-L1 IHC 28-8 pharmDx assay for samples within test stability and with subject consent, and excluding patients from China; [b]"CLDN18.2-positive" was defined as ≥75% of tumor cells with moderate-to-strong membranous CLDN18 staining by central IHC using the investigational VENTANA CLDN18 (43-14A) RxDx Assay, and "CLDN18.2-negative" was defined as <75% of tumor cells with moderate-to-strong membranous CLDN18 staining; [c]"Other" represents reasons including withdrawal by subject, laboratory findings, HER2-expression status, and ECOG PS score; [d]One patient assigned to placebo + CAPOX received 1 dose of zolbetuximab as a protocol deviation and was moved to the zolbetuximab + CAPOX group for the safety analysis set.

Baseline Characteristics

		Zolbetuximab + CAPOX (N = 254)	Placebo + CAPOX (N = 253)
Age, years (range)	Median	61.0 (22–82)	59.0 (21–83)
Sex, n (%)	Male	159 (62.6)	156 (61.7)
Region, n (%)	Asia[a]	157 (61.8)	158 (62.5)
	Non-Asia	97 (38.2)	95 (37.5)
Organs with metastases, n (%)	0–2	189 (74.4)	188 (74.3)
	≥3	65 (25.6)	65 (25.7)
Prior gastrectomy, n (%)	No	179 (70.5)	178 (70.4)
	Yes	75 (29.5)	75 (29.6)
Primary site, n (%)	Stomach	219 (86.2)	209 (82.6)
	GEJ	35 (13.8)	44 (17.4)
Lauren classification, n (%)	Diffuse	87 (34.4)	100 (39.5)
	Intestinal	36 (14.2)	41 (16.2)
	Mixed/others/unknown[b]	130 (51.2)	112 (44.3)
ECOG PS[c], n (%)	0	108 (42.7)	108 (43.2)
	1	145 (57.3)	142 (56.8)

[a]76 patients assigned to zolbetuximab + CAPOX and 69 patients assigned to placebo + CAPOX were from China; [b]Patients with Lauren classification "unknown" represents patients with adenocarcinoma without Lauren classification; [c]One patient in the zolbetuximab arm and 3 patients in the placebo arm with ECOG PS missing at baseline who were enrolled with ECOG PS 0 or 1 at screening are not shown here (did not receive treatment and therefore did not have baseline measurements at cycle 1 day 1).

Primary End Point: PFS by Independent Review Committee[a]



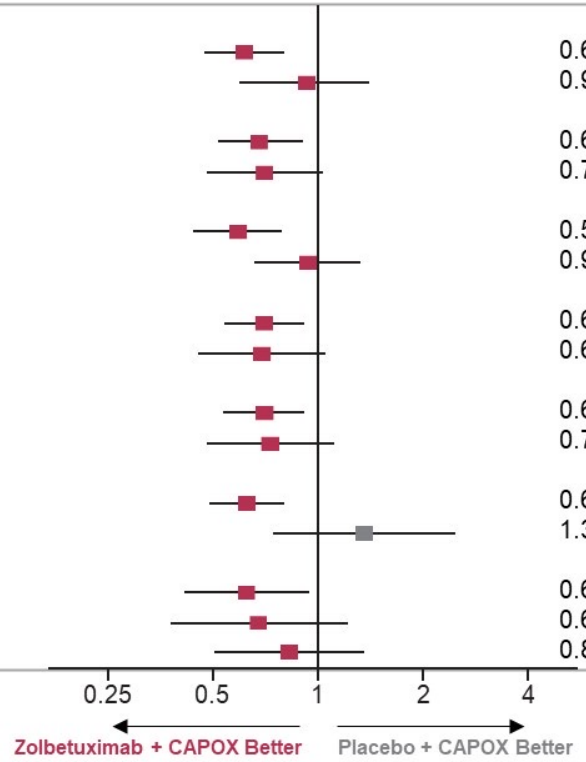
	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[b], n/N	137/254	172/253
Median PFS, months (95% CI)	**8.21** (7.46–8.84)	**6.80** (6.14–8.08)
HR (95% CI)	**0.687** (0.544–0.866)	
***P* value**	**0.0007**	

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

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

[a]Per RECIST version 1.1; [b]117/254 (46.1%) patients assigned to zolbetuximab + CAPOX and 81/253 (32.0%) of patients assigned to placebo + CAPOX were censored.

Primary End Point: PFS[a] Subgroup Analysis

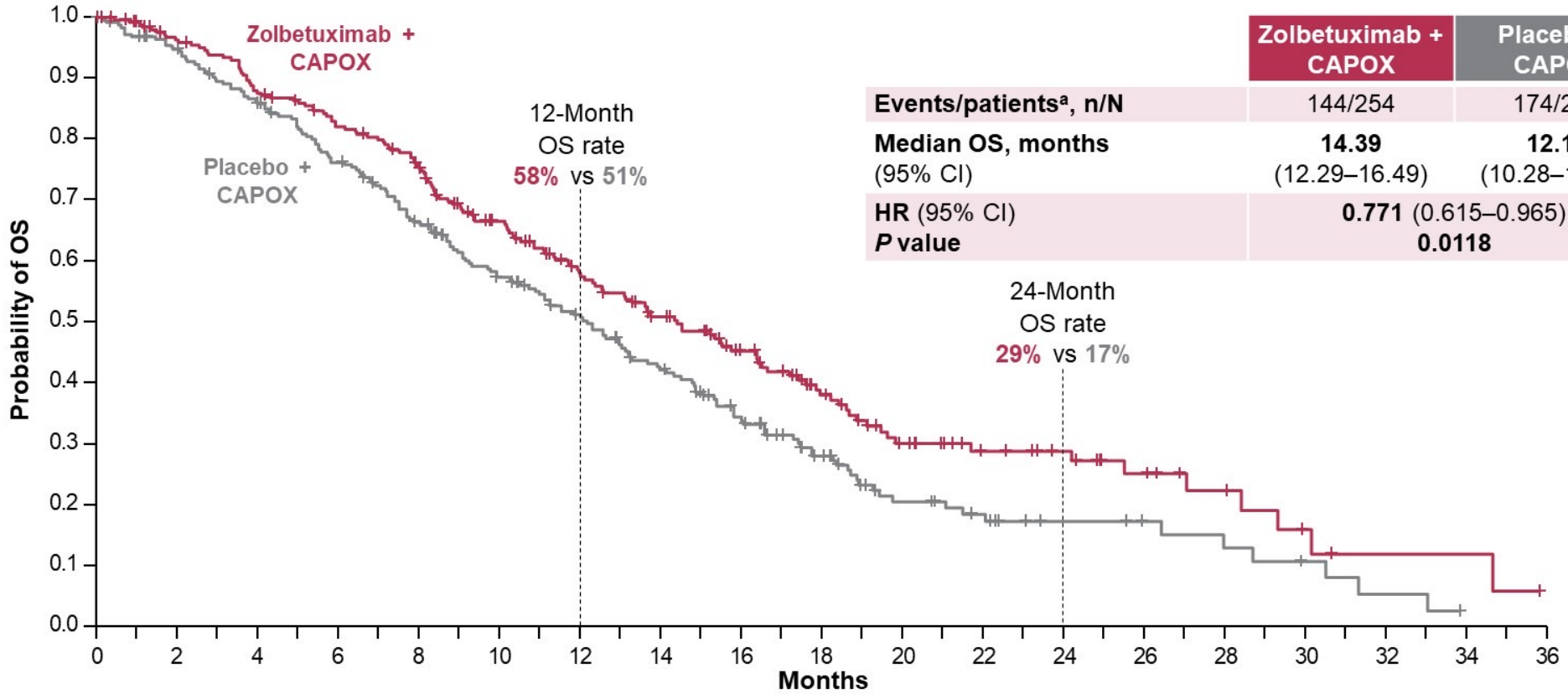


Subgroup	HR (95% CI)	Zolbetuximab + CAPOX *Events/patients, n/N*	Placebo + CAPOX *Events/patients, n/N*
Age			
≤65 years	0.606 (0.463–0.794)	92/176	130/180
>65 years	0.917 (0.596–1.410)	45/78	42/73
Sex			
Male	0.679 (0.513–0.898)	92/159	110/156
Female	0.700 (0.474–1.035)	45/95	62/97
Region			
Asia[b]	0.583 (0.436–0.781)	82/157	109/158
Non-Asia	0.928 (0.645–1.336)	55/97	63/95
Number of metastatic sites			
0–2	0.691 (0.529–0.904)	97/189	125/188
≥3	0.682 (0.445–1.045)	40/65	47/65
Prior gastrectomy			
No	0.696 (0.533–0.909)	97/179	125/178
Yes	0.726 (0.472–1.114)	40/75	47/75
Primary site			
Stomach	0.619 (0.484–0.791)	116/219	149/209
GEJ	1.351 (0.731–2.496)	21/35	23/44
Lauren classification			
Diffuse	0.620 (0.411–0.936)	38/87	60/100
Intestinal	0.675 (0.375–1.217)	21/36	26/41
Mixed/other[c]	0.824 (0.499–1.358)	28/54	36/48

PFS was significantly longer in patients treated with zolbetuximab + CAPOX across most subgroups

Data cutoff: October 7, 2022.
[a]Per RECIST version 1.1 by independent review committee; [b]76 patients assigned to zolbetuximab + CAPOX and 69 patients assigned to placebo + CAPOX were from China; [c]Patients with Lauren classification "Mixed/other" include those classified as "mixed" or "other," but does not include patients with an "unknown" or missing Lauren classification ("unknown" represents patients with adenocarcinoma without Lauren classification).

Key Secondary End Point: OS



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

No. at Risk

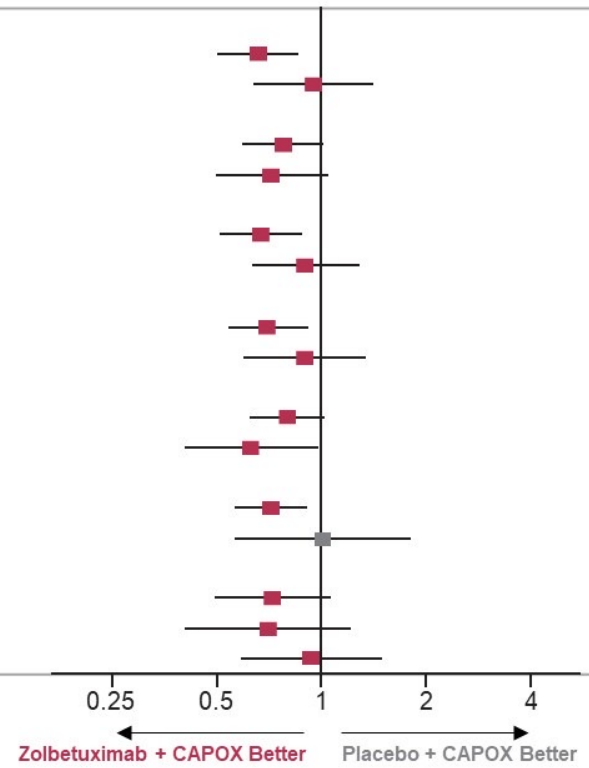
Zolbetuximab + CAPOX	254	243	233	226	211	203	193	187	171	150	138	125	108	100	87	80	68	61	47	38	31	27	22	21	18	13	12	9	8	6	4	2	2	2	2	1	0
Placebo + CAPOX	253	243	235	220	210	197	181	168	152	136	125	115	104	92	82	70	59	49	40	27	22	20	16	12	10	10	8	7	6	5	4	3	2	2	0	0	0

OS was significantly longer in patients treated with zolbetuximab + CAPOX vs placebo + CAPOX
Subsequent anticancer therapies were administered to 47% of patients in the zolbetuximab arm and 55% in the placebo arm

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

[a]110/254 (43.3%) patients assigned to zolbetuximab + CAPOX and 79/253 (31.2%) of patients assigned to placebo + CAPOX were censored.

Key Secondary End Point: OS Subgroup Analysis



Subgroup	HR (95% CI)	Zolbetuximab + CAPOX Events/patients, n/N	Placebo + CAPOX Events/patients, n/N
Age			
≤65 years	0.664 (0.507–0.869)	92/176	127/180
>65 years	0.951 (0.637–1.420)	52/78	47/73
Sex			
Male	0.779 (0.593–1.025)	94/159	114/156
Female	0.722 (0.494–1.054)	50/95	60/97
Region			
Asia[a]	0.674 (0.508–0.893)	88/157	110/158
Non-Asia	0.903 (0.630–1.294)	56/97	64/95
Number of metastatic sites			
0–2	0.708 (0.544–0.922)	100/189	126/188
≥3	0.903 (0.598–1.362)	44/65	48/65
Prior gastrectomy			
No	0.804 (0.622–1.040)	109/179	125/178
Yes	0.632 (0.408–0.982)	35/75	49/75
Primary site			
Stomach	0.718 (0.565–0.913)	124/219	146/209
GEJ	1.013 (0.563–1.823)	20/35	28/44
Lauren classification			
Diffuse	0.726 (0.493–1.069)	44/87	63/100
Intestinal	0.702 (0.403–1.222)	23/36	30/41
Mixed/other[b]	0.945 (0.594–1.502)	36/54	37/48

OS was significantly longer in patients treated with zolbetuximab + CAPOX across most subgroups

Data cutoff: October 7, 2022.
[a]76 patients assigned to zolbetuximab + CAPOX and 69 patients assigned to placebo + CAPOX were from China; [b]Patients with Lauren classification "Mixed/other" include those classified as "mixed" or "other," but does not include patients with an "unknown" or missing Lauren classification ("unknown" represents patients with adenocarcinoma without Lauren classification).

Secondary End Points: Response Outcomes[a]

	Zolbetuximab + CAPOX (N = 195)	Placebo + CAPOX (N = 205)
ORR[b], n (%)	105 (53.8)	100 (48.8)
95% CI	46.58–60.99	41.76–55.84
BOR[c,d], n (%)		
CR	6 (3.1)	3 (1.5)
PR	99 (50.8)	97 (47.3)
SD	46 (23.6)	57 (27.8)
PD	10 (5.1)	25 (12.2)
Median DOR[b,e], months (95% CI)	6.28 (5.39–8.28)	6.18 (4.53–6.41)

Response outcomes were similar between treatment arms

[a]In patients with measurable disease as an ad hoc analysis; [b]Per RECIST version 1.1 by independent review committee; [c]Patients with non-CR/non-PD, no disease, missing data, or who could not be evaluated are not shown; [d]Patients with missing data had no postbaseline imaging assessment; [e]DOR was defined as time from initial response (CR/PR) until time of PD.

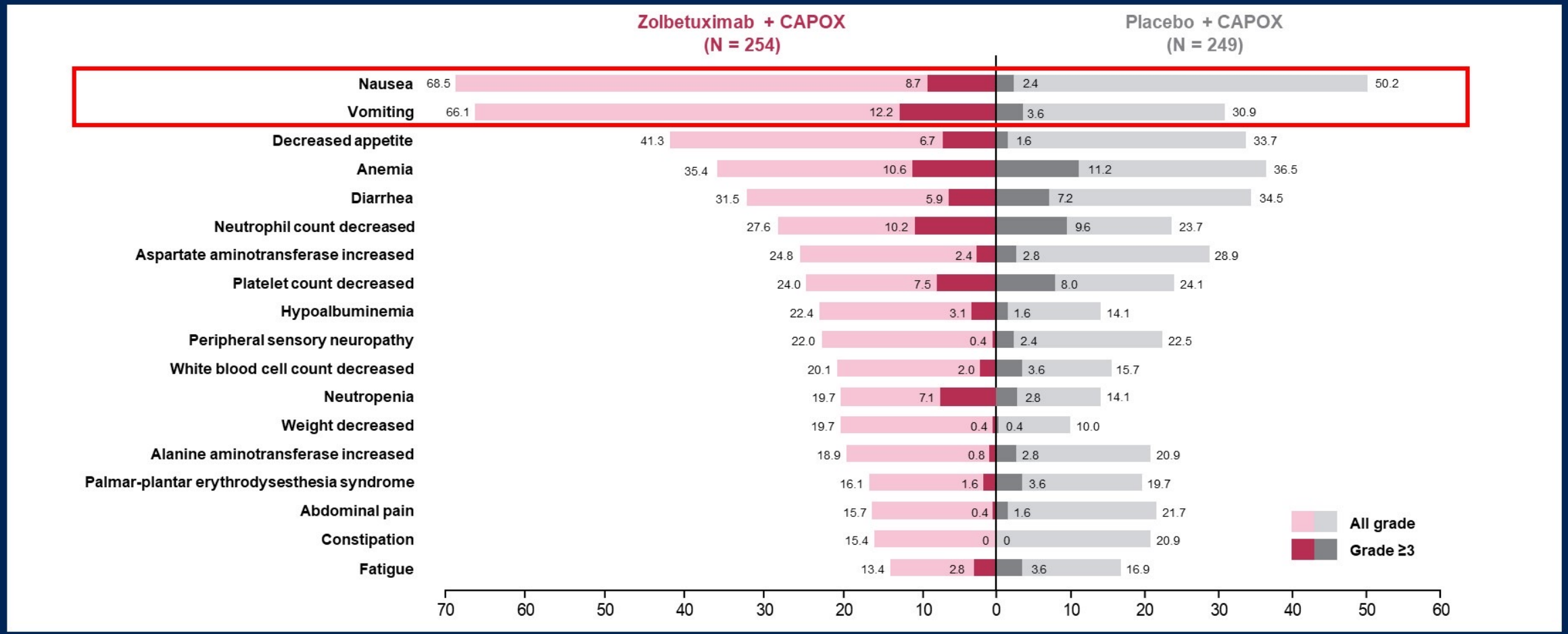
Safety: AEs in All Treated Patients

Event, n (%)	Zolbetuximab + CAPOX (N = 254)	Placebo + CAPOX (N = 249)
All TEAEs	251 (98.8)	244 (98.0)
Grade ≥3 TEAEs	185 (72.8)	174 (69.9)
Serious TEAEs	120 (47.2)	124 (49.8)
TRAEs leading to discontinuation of any study drug	55 (21.7)	39 (15.7)
TRAEs leading to discontinuation of zolbetuximab or placebo	18 (7.1)	11 (4.4)
TRAEs leading to death[a–c]	6 (2.4)	7 (2.8)

The incidence of overall TEAEs was similar between treatment arms

[a]Events in zolbetuximab + CAPOX arm (n): septic shock (1), cerebral hemorrhage (1), platelet count decreased (1), procedural complication (1), sepsis (1), syncope (1), upper gastrointestinal hemorrhage (1); [b]Events in placebo + CAPOX arm (n): septic shock (1), death (1), diarrhea (1), febrile neutropenia (1), hematemesis (1), lower respiratory tract infection viral (1), mucosal infection (1), neutropenic sepsis (1); [c]One individual in each arm experienced 2 TRAEs leading to death.

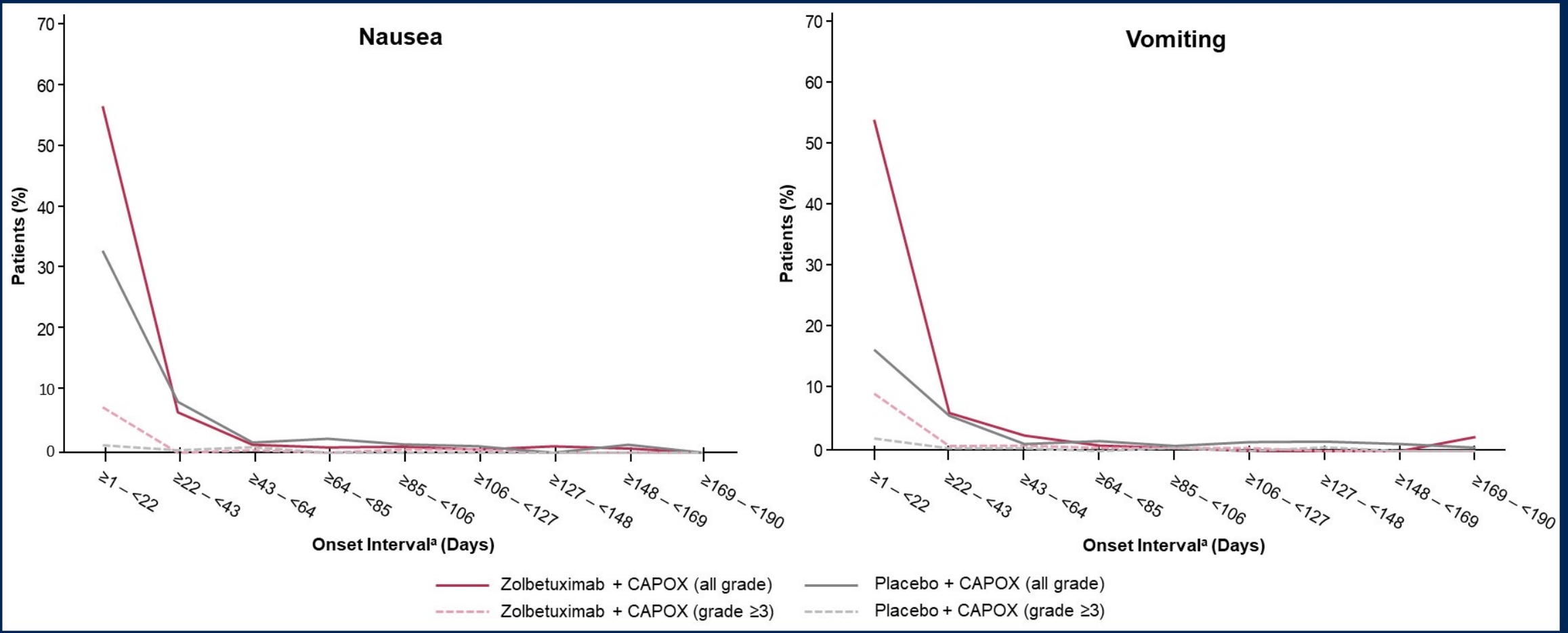
Safety: TEAEs[a] Occurring in ≥15% of All Treated Patients[b]



The most common TEAEs with zolbetuximab + CAPOX were nausea and vomiting

[a]Preferred terms were defined according to the Medical Dictionary for Regulatory Activities terminology version 25.0;
[b]Among all treated patients in either treatment arm.

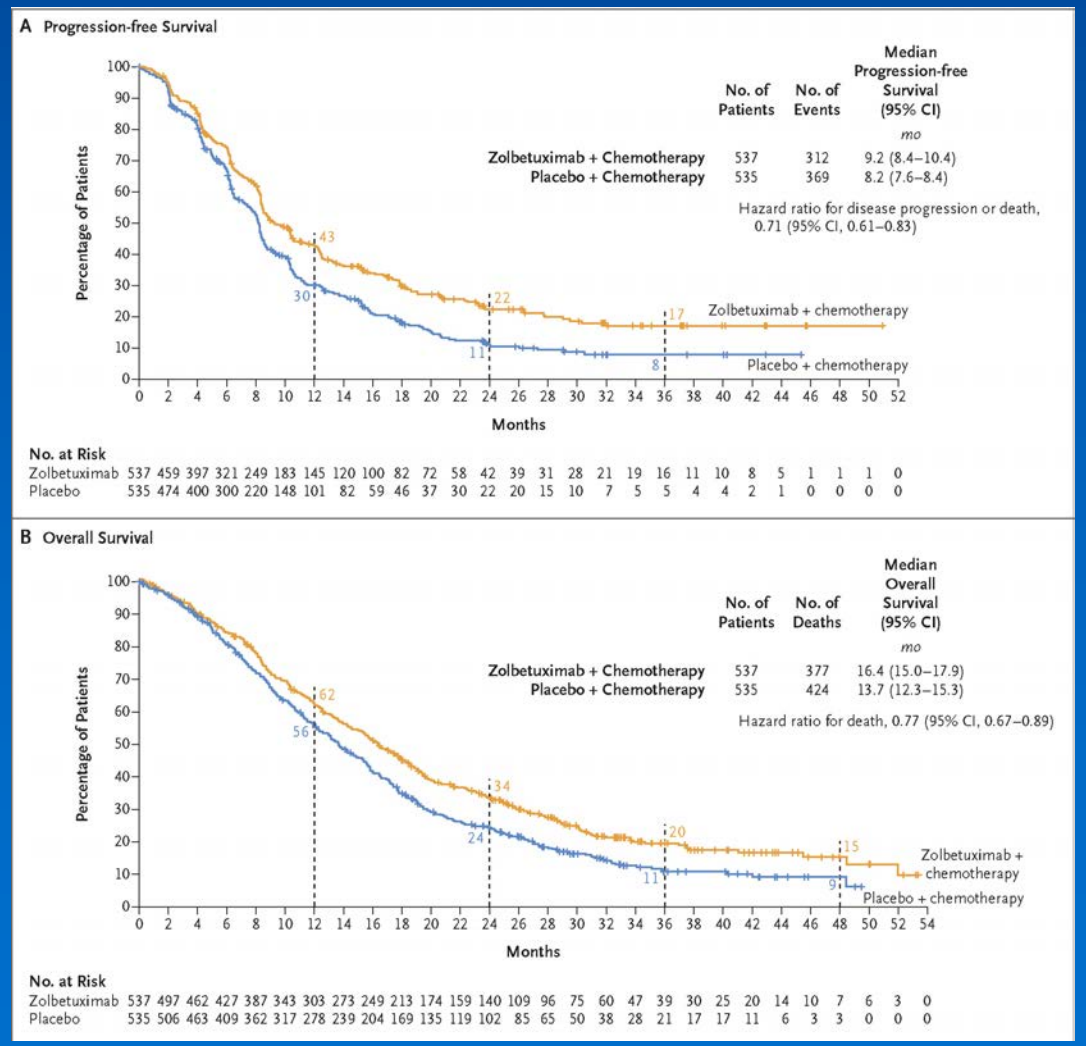
Safety: First Occurrence of Nausea and Vomiting



Nausea and vomiting first occurred most commonly during the first and second treatment cycles

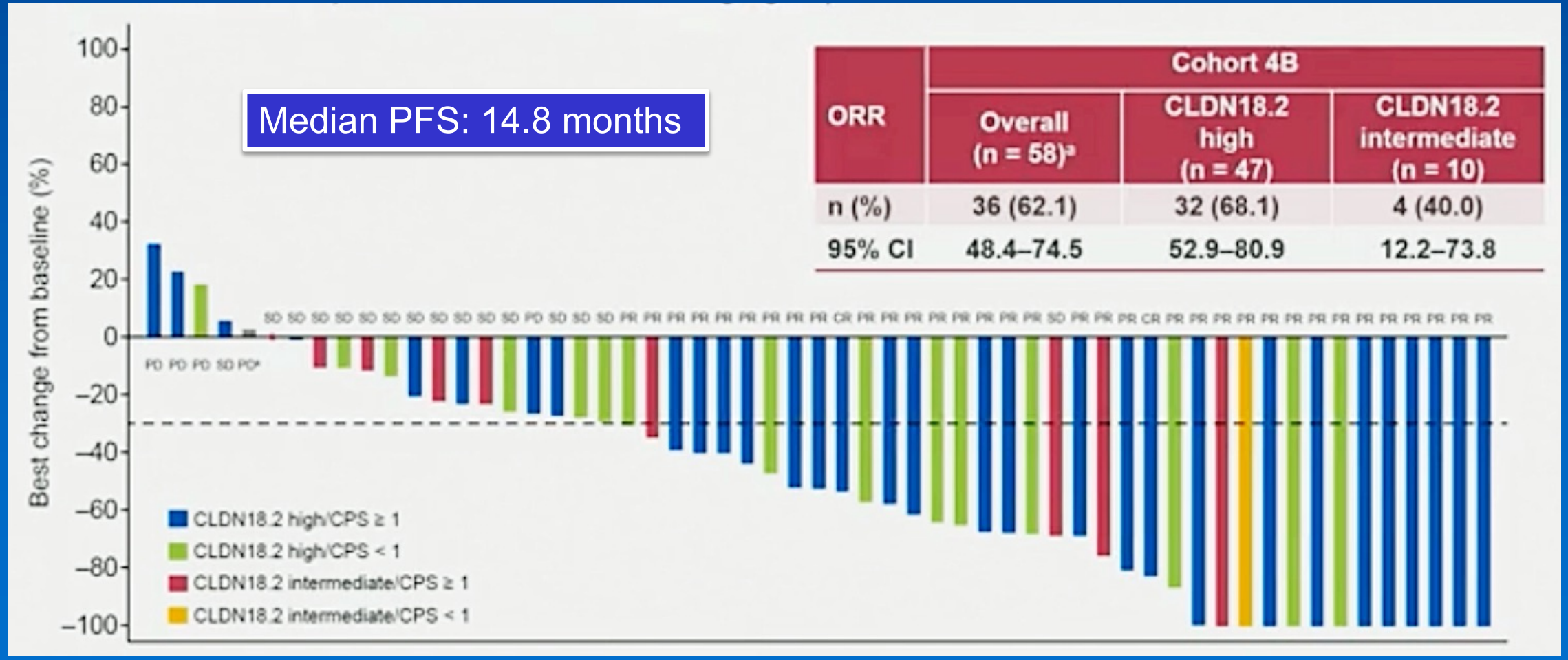
[a]The onset interval was defined as the date of onset through the date of dose + 1.

Pooled PFS and OS Results for SPOTLIGHT and GLOW



Shitara NEJM 391: 1159; 2024

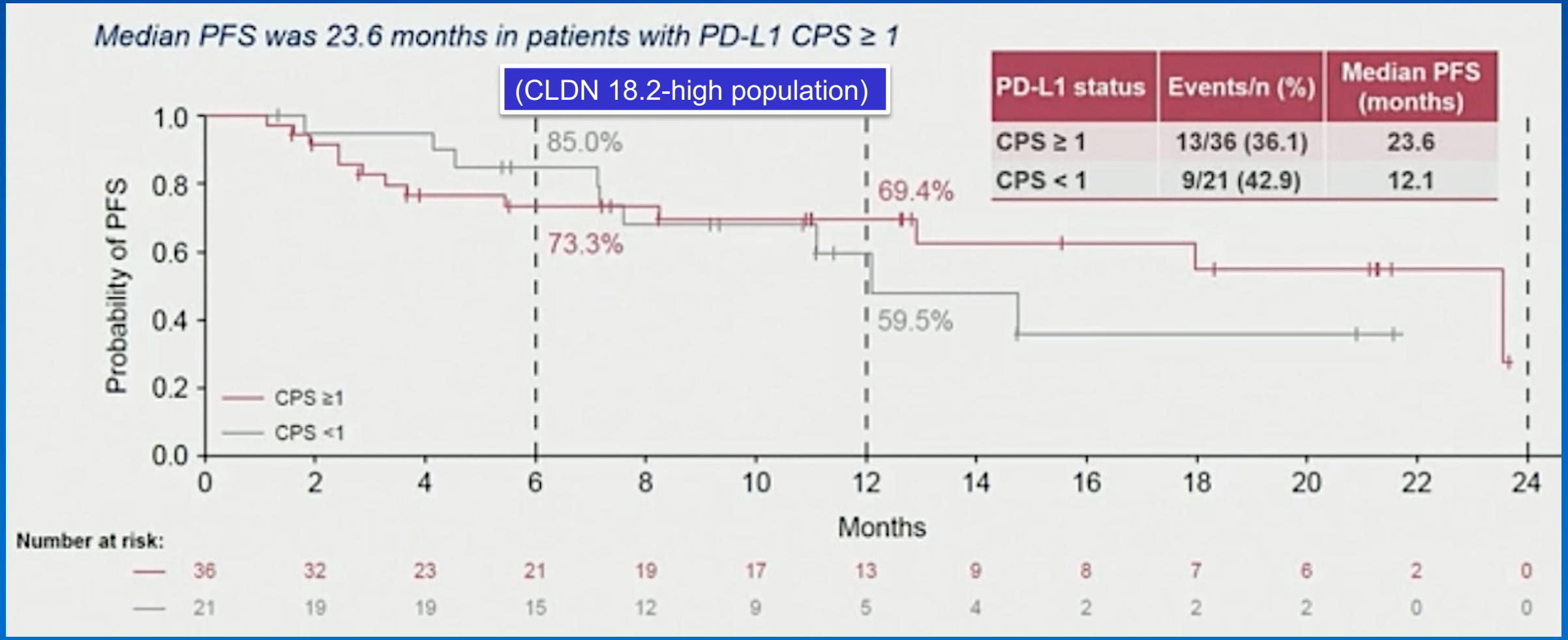
ILUSTRO: First Line Zolbetuximab + Nivolumab + mFOLFOX6



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 Gastrointestinal Cancers Symposium 2026; Abstract LBA284.

ILUSTRO: First Line Zolbetuximab + Nivolumab + mFOLFOX6



Shitara ASCO Gastrointestinal Cancers Symposium 2026; Abstract LBA284.

Ongoing CLDN18.2 Development

- **LUCERNA (NCT06901531): First line FOLFOX CAPOX/Pembro + / - Zolbetuximab**
- **ZELDA: Second Line Chemo + / - Zolbetuximab**
- **CLARITY (NCT06346392): Second or later line phase 3: CLDN18.2 ADC AZD0901 vs Pac/Ram or MD choice**
- **First Line CLDN18.2 ADC AZD0901 + FU + Rilvegostomig (TIGIT/PD-1)**
- **Novel CLDN18.2 targets**
  - Bispecifics
    - Givastomig: targets CLDN18.2 and 41BB (T cells, agonist)
    - 16% response in phase 1/2 in GE cancer
    - + FOLFOX/Nivo, safe and tolerable

Ku CCR 31: 494; 2025 Klempner ESMO 2025

Conclusions

- **CLDN18.2 high expression > = 75% seen in 25%, similar across molecular subtypes and PDL-1 expression**
  - No impact on OS/PFS in first or second-line chemo
- **Zolbetuximab is approved first line in CLDN18.2 + > = 75% + chemo**
  - Nausea/Vomiting significant and requires attentive management
- **Zolbetuximab First line phase 3 + FOLFOX-CAPOX/Pembro is ongoing**
- **Ongoing development**
  - ADC's in phase 2-3, earlier line development
  - Novel constructs, CART cells
  - Exploration in neoadjuvant/adjuvant therapy

Questions from General Medical Oncologists — Targeting CLDN18.2 in Advanced GE Cancers

82 y/o M with metastatic gastric cancer and high CLDN18.2. Started FOLFOX + zolbetuximab. Used maximal antinausea regimen along with olanzapine. He has not had any nausea. When can antinausea meds be de-escalated?

62 y/o male had FLOT and esophagectomy. Cancer recurred a few months after surgery. He had zolbetuximab and low-dose FOLFOX. He tolerated treatment well, but no response. Can zolbetuximab be combined with FOLFIRI? Can it be given as second-line treatment?

58 y/o woman with HTN, Stage IV gastric cancer, s/p gastrectomy for previous bleeding ulcer 10 yrs ago, CLDN 18.2+ and PD-L1 5%. Would you offer zolbe + chemo?

RTP
RESEARCH TO PRACTICE

Questions from General Medical Oncologists — Targeting CLDN18.2 in Advanced GE Cancers

39-year-old woman with HER2-neg, PD-L1 CPS 0, Claudin 18.2 80% GEJ cancer with Grade 3 nausea on zolbetuximab. How can we give zolbetuximab so it is less emetogenic?

Can zolbetuximab first loading dose preemptively be split into 2 days to minimize severe nausea/vomiting, like we give amivantamab IV infusion?

59 y/o M with CLDN18.2-high gastric cancer, developed PE after 1 cycle of front-line zolbetuximab/FOLFOX. Is it safe to resume zolbetuximab after the pt is fully anticoagulated?

RTP
RESEARCH
TO PRACTICE

Questions from General Medical Oncologists — Targeting CLDN18.2 in Advanced GE Cancers

67 y/o male with Stage 4 metastatic GEJ adenocarcinoma, PD-L1 CPS 0, HER2, Claudin 18.2 more than 75%. We are planning to give zolbetuximab plus FOLFOX now. Any pearls for management of nausea? Can you specify your antiemetic regimen with zolbetuximab?

In the 3 patients I treated with zolbetuximab, I have found lorazepam to help with nausea more than anything else. Have you seen this? Any rationale?

Questions from General Medical Oncologists — Targeting CLDN18.2 in Advanced GE Cancers

48 y/o female with diffuse poorly differentiated Stage 4 gastric adenocarcinoma, PD-L1 CPS 4, claudin 18.2 more than 75%. Pt is very sick and in need of palliative systemic tx ASAP. Should I give zolbetuximab + chemo, or should I still to give IO + chemo?

55-year-old male with metastatic gastric cancer (peritoneal mets). Biopsy shows HER2 IHC 3+, PD-L1 CPS 10, CLDN18.2+. If patient is candidate for 1L HER2-directed tx and zolbetuximab, which is preferred and how do experts make treatment decisions?

RTP
RESEARCH TO PRACTICE

Agenda

Module 1: HER2-Targeted Approaches for Advanced Gastroesophageal Cancers — Dr Ajani

Module 2: Targeting Claudin 18.2 in Advanced Gastroesophageal Cancers — Dr Strickler

Module 3: Optimal Incorporation of Immunotherapeutic Strategies into Treatment for Patients with Metastatic Gastroesophageal Tumors — Dr Mehta

Module 4: Other Novel Agents and Strategies Under Evaluation for Advanced Gastroesophageal Cancers — Dr Klempner

Optimal Incorporation of Immunotherapeutic Strategies into Treatment for Patients with Metastatic Gastroesophageal Tumors

Rutika Mehta MD, MPH

Associate Professor, Division of Hematology/Oncology

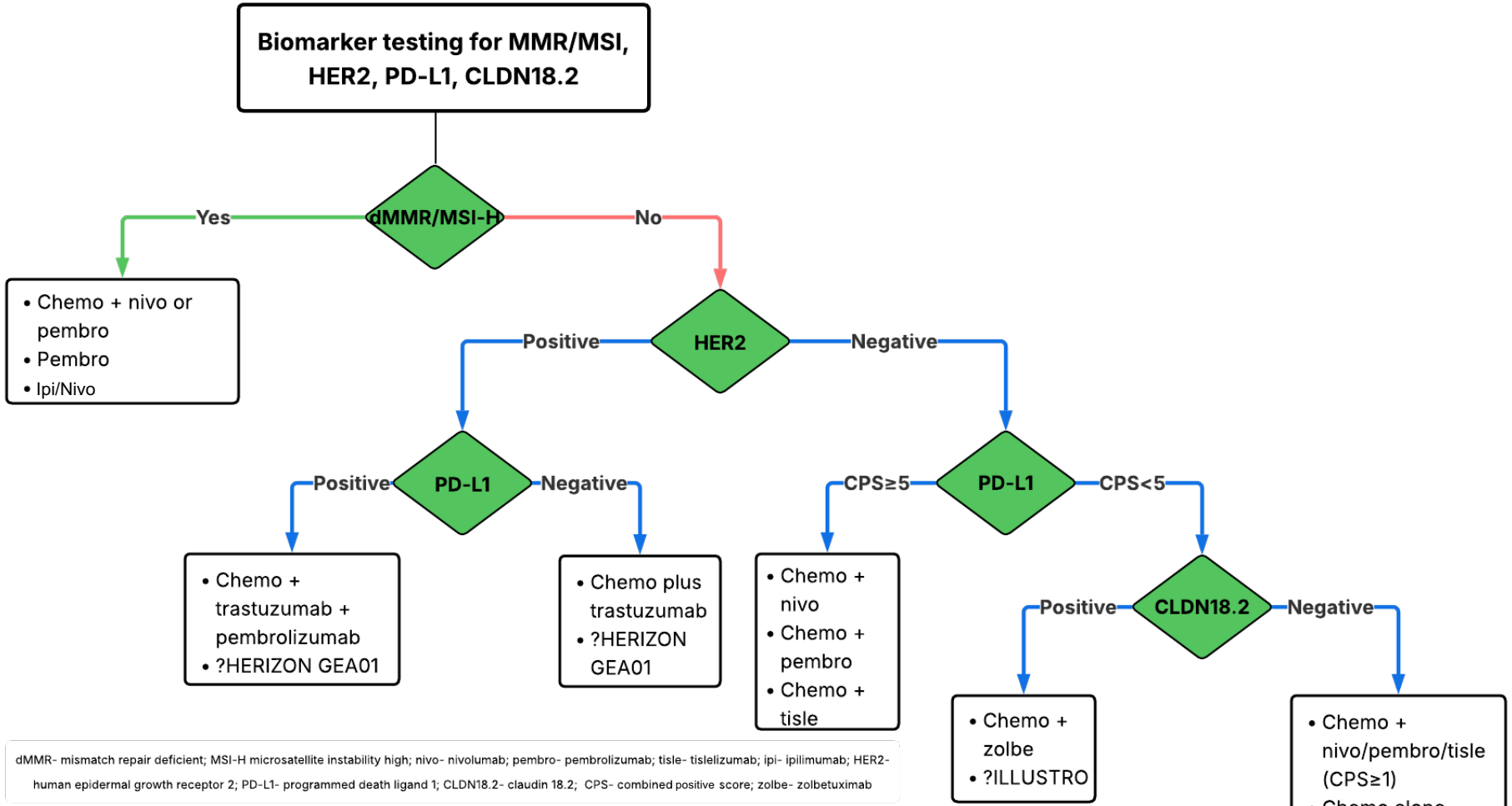
Weill Cornell Medicine/New York Presbyterian Hospital

New York, NY

Agenda

- Clinical and biological factors affecting the choice of up-front therapy for patients with metastatic gastroesophageal cancers
- Published datasets demonstrating the efficacy and safety of first-line nivolumab-, pembrolizumab- and tislelizumab-containing regimens for advanced HER2-negative gastric, GEJ and esophageal cancers; impact of PD-L1 expression on outcomes
- Long-term follow-up with the addition of pembrolizumab to chemotherapy and trastuzumab for previously untreated HER2-positive advanced gastric/GEJ adenocarcinoma; impact of PD-L1 status on outcomes
- Clinical utility, if any, of immunotherapy for relapsed/refractory gastroesophageal tumors

Approach to 1L treatment of gastroesophageal cancers



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.

Choice of chemotherapy

- Typically doublet of fluoropyrimidine and platinum
  - Either capecitabine or 5-fluorouracil
  - Oxaliplatin preferred over cisplatin
- In case of oligometastatic disease, no actionable biomarkers and potentially eligible for resection of primary and metastatic site- then can consider FLOT (triplet regimen of 5-fluorouracil, oxaliplatin and docetaxel).
- Ongoing clinical trial comparing FOLFOX +/- nivo vs FOLFIRINOX +/- nivo in Alliance **A022102**

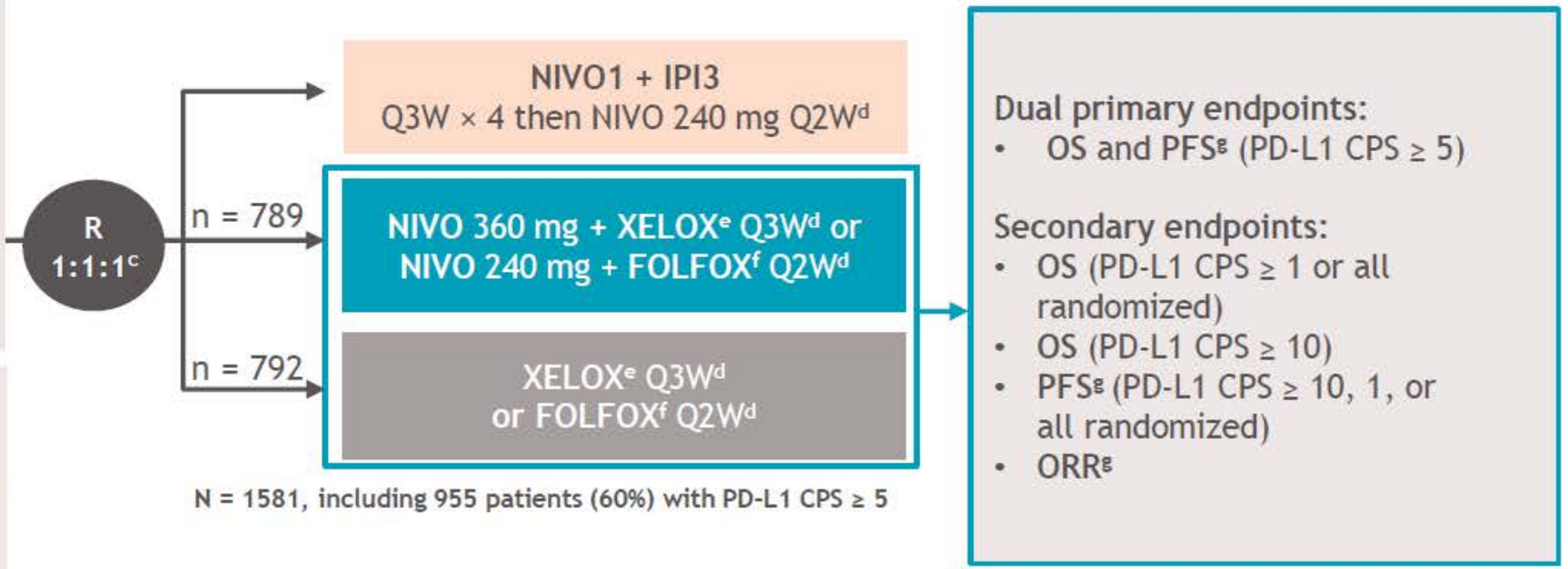
Cunningham D et al. N Engl J Med 2008; Park H et al. J Clin Oncol 2023

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

Demographics

Characteristic	Patients With PD-L1 CPS ≥5		All Randomly Assigned Patients	
	Nivolumab Plus Chemotherapy (n = 473)	Chemotherapy (n = 482)	Nivolumab Plus Chemotherapy (n = 789)	Chemotherapy (n = 792)
Age, years, median (range)	63 (18-88)	62 (23-90)	62 (18-88)	61 (21-90)
<65	266 (56)	286 (59)	473 (60)	488 (62)
≥65	207 (44)	196 (41)	316 (40)	304 (38)
Sex				
Male	331 (70)	349 (72)	540 (68)	560 (71)
Female	142 (30)	133 (28)	249 (32)	232 (29)
Race[a]				
Asian	119 (25)	117 (24)	186 (24)	189 (24)
Non-Asian	354 (75)	365 (76)	603 (76)	602 (76)
Region				
Asia	117 (25)	111 (23)	178 (23)	178 (22)
United States and Canada	67 (14)	70 (15)	131 (17)	132 (17)
Rest of the world	289 (61)	301 (62)	480 (61)	482 (61)
ECOG PS[b]				
0	193 (41)	204 (42)	327 (41)	337 (43)
1	280 (59)	278 (58)	461 (58)	452 (57)
Primary tumor location at initial diagnosis				
GC	333 (70)	334 (69)	554 (70)	556 (70)
GEJC	84 (18)	86 (18)	132 (17)	128 (16)
EAC	56 (12)	62 (13)	103 (13)	108 (14)
Tumor cell PD-L1 expression[c]				
<1%	363 (77)	361 (75)	663 (84)	661 (83)
≥1%	110 (23)	120 (25)	126 (16)	127 (16)
Previous surgery				
Yes	98 (21)	105 (22)	161 (20)	176 (22)
No	375 (79)	377 (78)	628 (80)	616 (78)
Disease stage				
Metastatic	454 (96)	461 (96)	757 (96)	756 (95)
Locally advanced	16 (3)	20 (4)	27 (3)	34 (4)
Locally recurrent	3 (<1)	1 (<1)	5 (<1)	2 (<1)
Organs with metastases				
1	99 (21)	96 (20)	165 (21)	179 (23)
≥2	374 (79)	386 (80)	624 (79)	613 (77)

Characteristic	Patients With PD-L1 CPS ≥5		All Randomly Assigned Patients	
	Nivolumab Plus Chemotherapy (n = 473)	Chemotherapy (n = 482)	Nivolumab Plus Chemotherapy (n = 789)	Chemotherapy (n = 792)
Site of metastases				
Liver	190 (40)	217 (45)	301 (38)	313 (40)
Peritoneum	102 (22)	96 (20)	188 (24)	189 (24)
CNS	1 (<1)	0	1 (<1)	0
Signet ring cell carcinoma				
Yes	72 (15)	69 (14)	145 (18)	137 (17)
No	401 (85)	413 (86)	644 (82)	655 (83)
Lauren classification				
Intestinal type	171 (36)	176 (37)	272 (34)	267 (34)
Diffuse type	137 (29)	141 (29)	254 (32)	273 (34)
Mixed	37 (8)	30 (6)	58 (7)	48 (6)
Unknown	128 (27)	135 (28)	205 (26)	204 (26)
MSI status				
MSS	424 (90)	423 (88)	696 (88)	682 (86)
MSI-H	18 (4)	16 (3)	23 (3)	21 (3)
Not reported or invalid	31 (7)	43 (9)	70 (9)	89 (11)
Chemotherapy regimen[d]				
FOLFOX	237 (51)	242 (52)	422 (54)	406 (53)
XELOX	231 (49)	223 (48)	360 (46)	361 (47)

Janjigian Y et al. J Clin Oncol 2024

Overall response rate

Outcome	Patients With PD-L1 CPS ≥5		All Randomly Assigned Patients	
	Nivolumab Plus Chemotherapy (n = 378)[a]	Chemotherapy (n = 390)[a]	Nivolumab Plus Chemotherapy (n = 602)[a]	Chemotherapy (n = 607)[a]
Objective response rate[b]	226 (60)	176 (45)	350 (58)	279 (46)
95% CI	54.7 to 64.8	40.1 to 50.2	54.1 to 62.1	41.9 to 50.0
Best overall response[c]				
Complete response	50 (13)	29 (7)	67 (11)	40 (7)
Partial response	176 (47)	147 (38)	283 (47)	239 (39)
Stable disease	106 (28)	132 (34)	171 (28)	200 (33)
Progressive disease	25 (7)	42 (11)	41 (7)	62 (10)
Not evaluable	21 (6)	40 (10)	40 (7)	66 (11)
Time to response,[d] months, median (range)	1.5 (0.8-10.2)	1.5 (1.0-13.7)	1.5 (0.8-11.2)	1.5 (0.6-13.7)
Duration of response,[d] months, median (95% CI)	9.6 (8.2 to 12.4)	7.0 (5.6 to 7.9)	8.5 (7.7 to 9.9)	6.9 (5.8 to 7.2)

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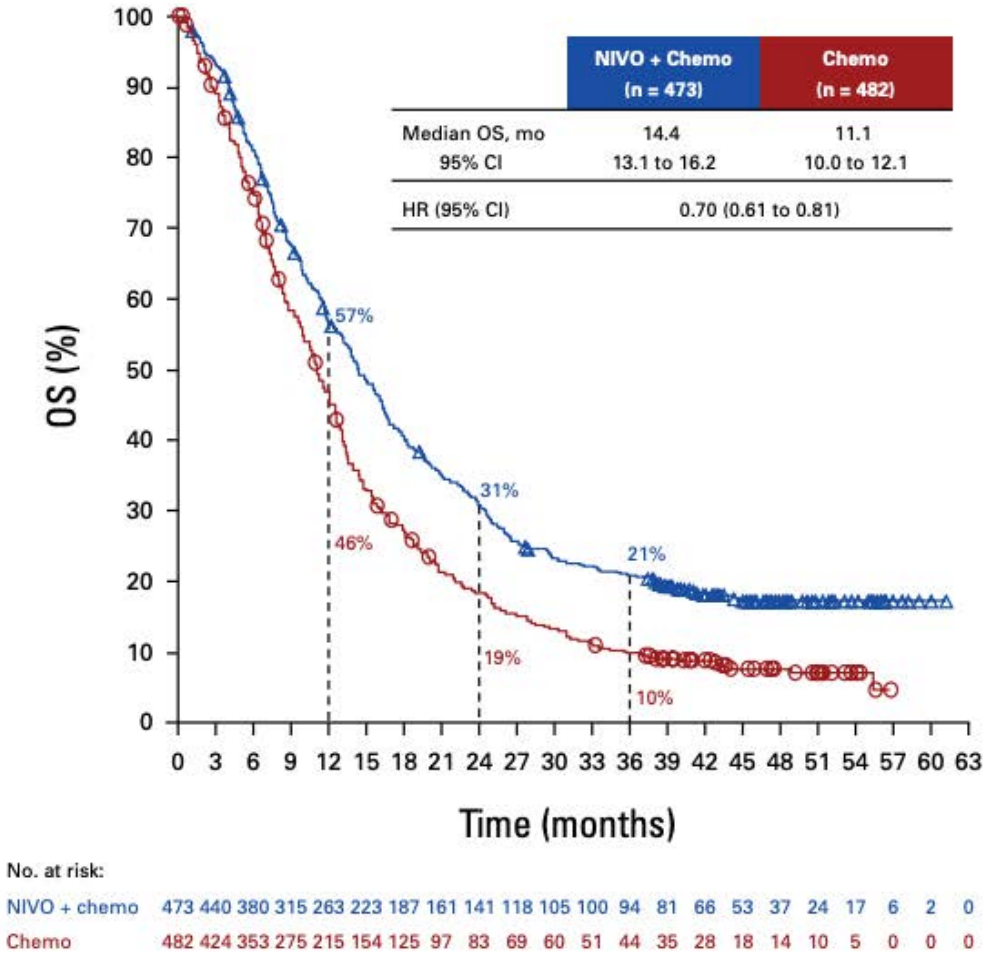
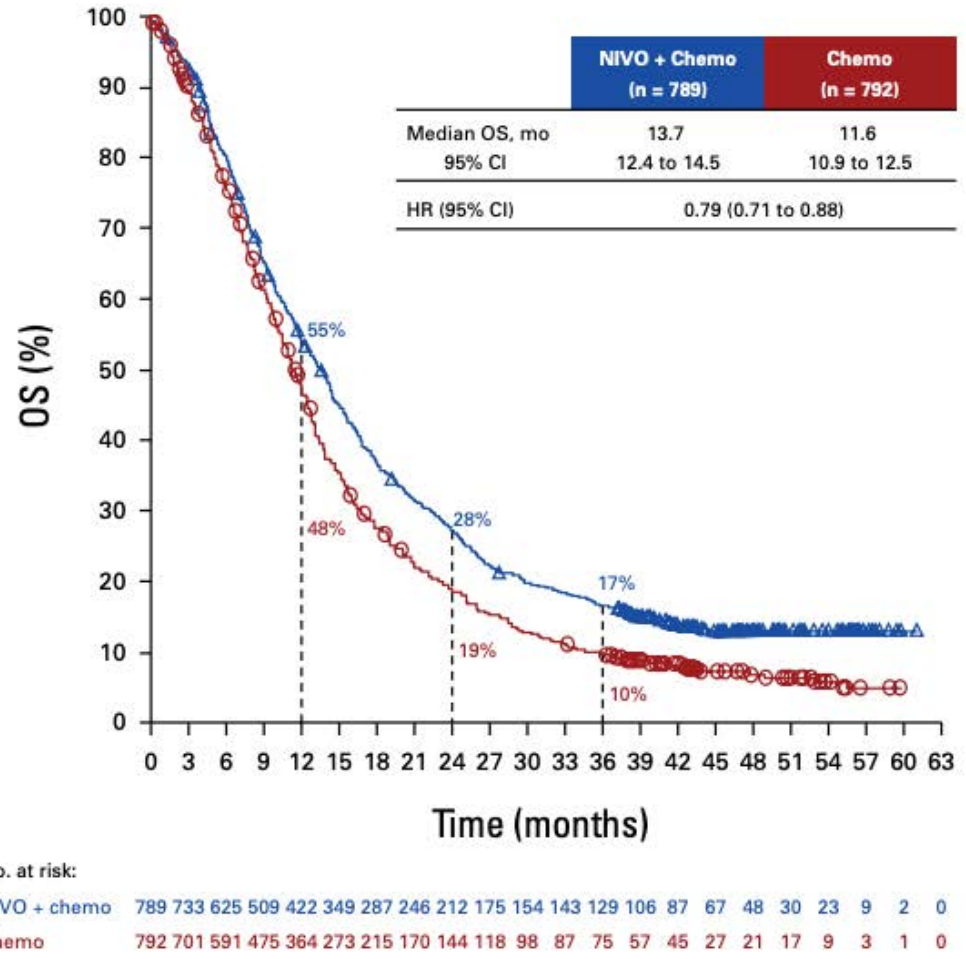
Addition of nivolumab improves OS



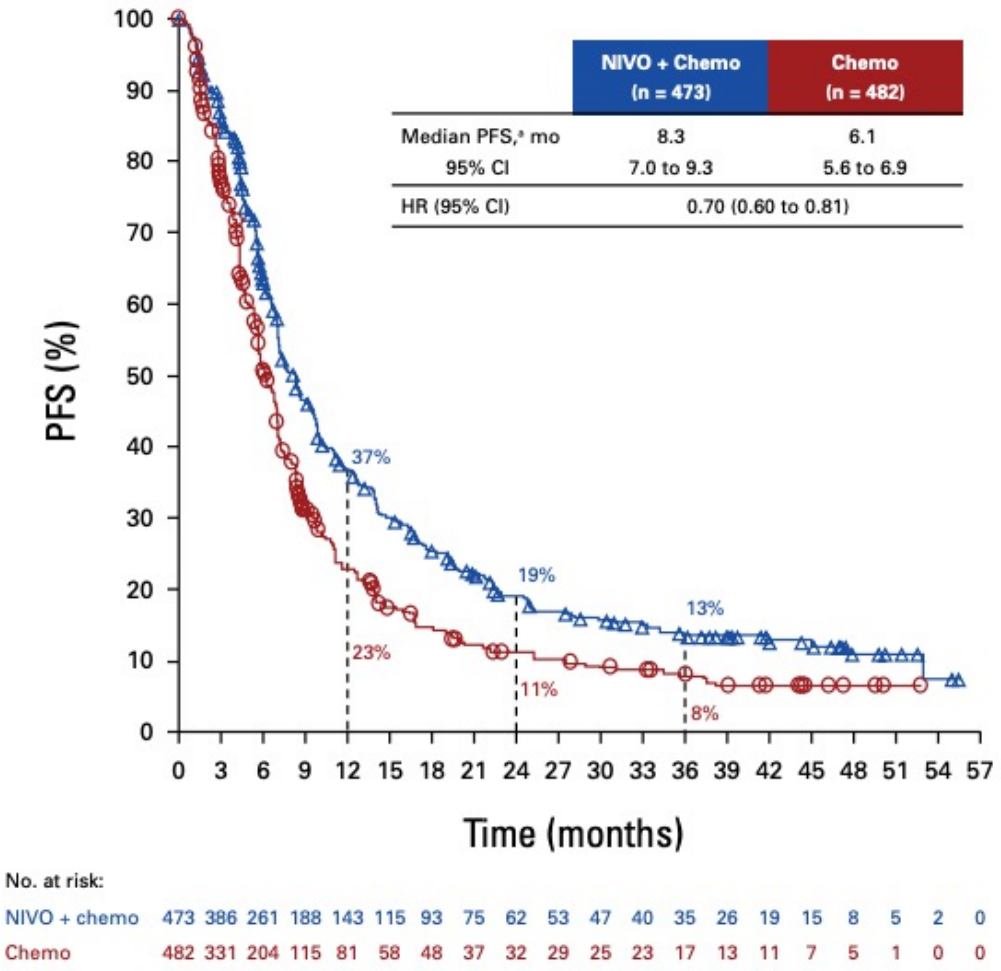
PD-L1 CPS ≥5



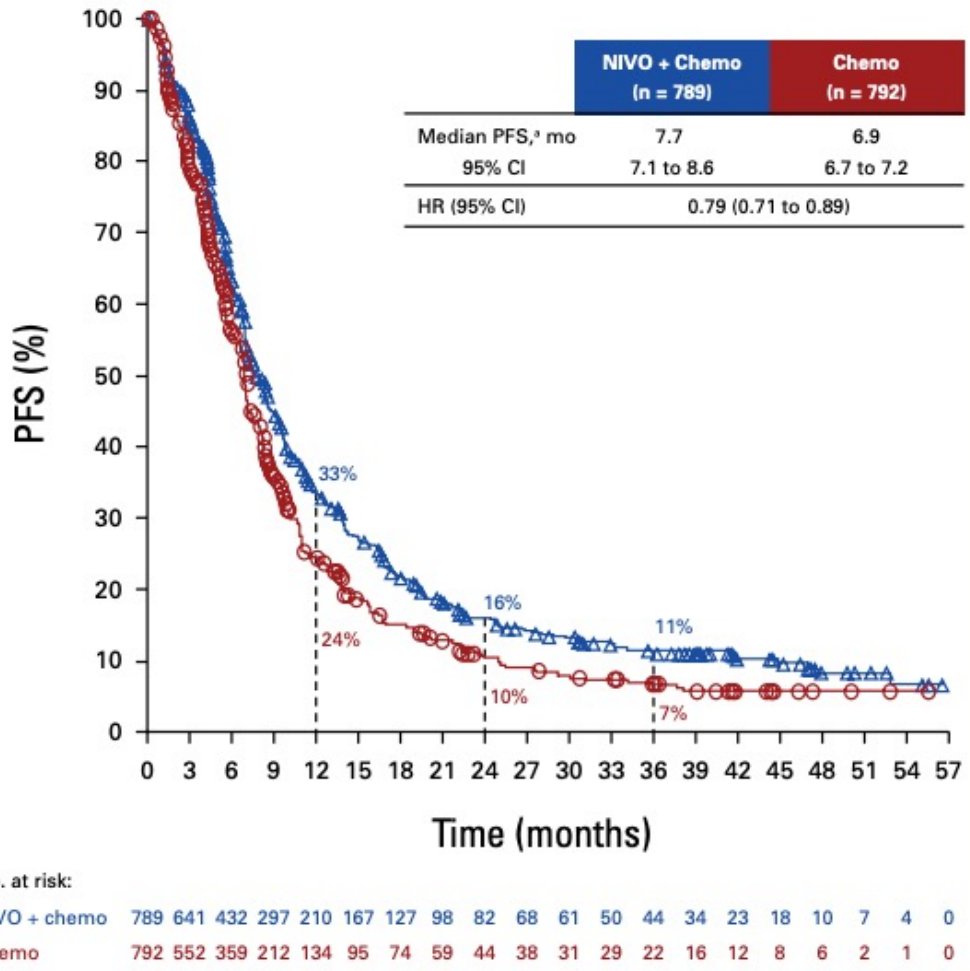
All randomized patients

Janjigian Y et al. J Clin Oncol 2024

Addition of nivolumab improves PFS



PD-L1 CPS ≥5



All randomized patients

Janjigian Y et al. J Clin Oncol 2024

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

Demographics

80% patients had gastric cancer; ~35% patients had diffuse gastric cancer

	Pembrolizumab plus chemotherapy (n=790)			Placebo plus chemotherapy (n=789)		
	ITT (n=790)	PD-L1 CPS ≥1 (n=618)	PD-L1 CPS ≥10 (n=279)	ITT (n=789)	PD-L1 CPS ≥1 (n=617)	PD-L1 CPS ≥10 (n=272)
Age, years	61 (52–67)	62 (53–68)	63 (54–69)	62 (52–69)	63 (53–69)	63 (54–69)
<65	486 (62%)	377 (61%)	161 (58%)	479 (61%)	364 (59%)	159 (58%)
≥65	304 (38%)	241 (39%)	118 (42%)	310 (39%)	253 (41%)	113 (42%)
Sex*						
Female	263 (33%)	196 (32%)	86 (31%)	245 (31%)	169 (27%)	67 (25%)
Male	527 (67%)	422 (68%)	193 (69%)	544 (69%)	448 (73%)	205 (75%)
Race*						
American Indian or Alaskan Native	31 (4%)	24 (4%)	7 (3%)	36 (5%)	29 (5%)	11 (4%)
Asian	270 (34%)	206 (33%)	98 (35%)	269 (34%)	203 (33%)	89 (33%)
Black or African American	12 (2%)	7 (1%)	2 (1%)	9 (1%)	9 (1%)	5 (2%)
Multiple	43 (5%)	32 (5%)	16 (6%)	30 (4%)	25 (4%)	8 (3%)
Native Hawaiian or other Pacific Islander	1 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	0
White	426 (54%)	342 (55%)	155 (56%)	435 (55%)	343 (56%)	157 (58%)
Missing	7 (1%)	6 (1%)	0	8 (1%)	7 (1%)	2 (1%)
Geographical region						
Asia	263 (33%)	201 (33%)	96 (34%)	262 (33%)	200 (32%)	88 (32%)
Rest of world	326 (41%)	251 (41%)	105 (38%)	325 (41%)	251 (41%)	120 (44%)
Western Europe, Israel, North America, and Australia	201 (25%)	166 (27%)	78 (28%)	202 (26%)	166 (27%)	64 (24%)
ECOG performance status						
0	281 (36%)	223 (36%)	99 (35%)	301 (38%)	228 (37%)	103 (38%)
1	509 (64%)	395 (64%)	180 (65%)	488 (62%)	389 (63%)	169 (62%)
Primary tumour location						
Gastro-esophageal junction	149 (19%)	123 (20%)	65 (23%)	185 (23%)	164 (27%)	73 (27%)
Stomach	640 (81%)	494 (80%)	214 (77%)	603 (76%)	453 (73%)	199 (73%)
Other	0	0	0	1 (<1%)	0	0
Missing	1 (<1%)	1 (<1%)	0	0	0	0
Disease status						
Locally advanced	28 (4%)	26 (4%)	14 (5%)	30 (4%)	24 (4%)	11 (4%)
Metastatic	761 (96%)	591 (96%)	265 (95%)	759 (96%)	593 (96%)	261 (96%)
Missing	1 (<1%)	1 (<1%)	0	0	0	0
Histological subtype (Lauren classification[20])						
Diffuse	318 (40%)	236 (38%)	102 (37%)	301 (38%)	220 (36%)	89 (33%)
Intestinal	284 (36%)	239 (39%)	111 (40%)	273 (35%)	215 (35%)	99 (36%)
Indeterminate	186 (24%)	141 (23%)	65 (23%)	215 (27%)	182 (29%)	84 (31%)
Unknown	1 (<1%)	1 (<1%)	1 (<1%)	0	0	0
Missing	1 (<1%)	1 (<1%)	0	0	0	0
Liver metastases						
No	475 (60%)	359 (58%)	160 (57%)	478 (61%)	364 (59%)	162 (60%)
Yes	314 (40%)	258 (42%)	119 (43%)	311 (39%)	253 (41%)	110 (40%)
Missing	1 (<1%)	1 (<1%)	0	0	0	0
Prior gastrectomy or oesophagectomy						
No	613 (78%)	506 (82%)	231 (83%)	622 (79%)	508 (82%)	231 (85%)
Yes	172 (22%)	109 (18%)	48 (17%)	162 (21%)	105 (17%)	40 (15%)
Missing	5 (1%)	3 (<1%)	0	5 (1%)	4 (1%)	1 (<1%)
Microsatellite instability status						
High	39 (5%)	35 (6%)	20 (7%)	35 (4%)	31 (5%)	16 (6%)
Low or microsatellite stable	641 (81%)	503 (81%)	227 (81%)	639 (81%)	500 (81%)	224 (82%)
Unknown	0	0	0	1 (<1%)	1 (<1%)	1 (<1%)
Missing	110 (14%)	80 (13%)	32 (11%)	114 (14%)	85 (14%)	31 (11%)
PD-L1 CPS						
≥1	618 (78%)	618 (100%)	279 (100%)	617 (78%)	617 (100%)	272 (100%)
<1	172 (22%)	0	0	172 (22%)	0	0
≥10	279 (35%)	279 (45%)	279 (100%)	272 (34%)	272 (44%)	272 (100%)
<10	509 (64%)	337 (55%)	0	517 (66%)	345 (56%)	0
Missing	2 (<1%)	2 (<1%)	0	0	0	0
Choice of chemotherapy						
Capecitabine and oxaliplatin	682 (86%)	528 (85%)	242 (87%)	681 (86%)	528 (86%)	235 (86%)
Flurouracil and cisplatin	108 (14%)	90 (15%)	37 (13%)	108 (14%)	89 (14%)	37 (14%)

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Overall response rate

	PD-L1 CPS ≥10 population		PD-L1 CPS ≥1 population		ITT population	
	Pembrolizumab plus chemotherapy group (n=279)	**Placebo plus chemotherapy group (n=272)**	**Pembrolizumab plus chemotherapy group (n=618)**	**Placebo plus chemotherapy group (n=617)**	**Pembrolizumab plus chemotherapy group (n=790)**	**Placebo plus chemotherapy group (n=789)**
Objective response, n (%)	169 (61%)	117 (43%)	322 (52%)	263 (43%)	405 (51%)	331 (42%)
Best response						
Complete response	36 (13%)	14 (5%)	61 (10%)	36 (6%)	75 (9%)	49 (6%)
Partial response	133 (48%)	103 (38%)	261 (42%)	227 (37%)	330 (42%)	282 (36%)
Stable disease[†]	70 (25%)	105 (39%)	194 (31%)	243 (39%)	256 (32%)	314 (40%)
Progressive disease	24 (9%)	28 (10%)	54 (9%)	64 (10%)	73 (9%)	87 (11%)
Not evaluable[‡]/not assessed[§]	16 (6%)	22 (8%)	48 (8%)	47 (8%)	56 (7%)	57 (7%)

Data are n (%).

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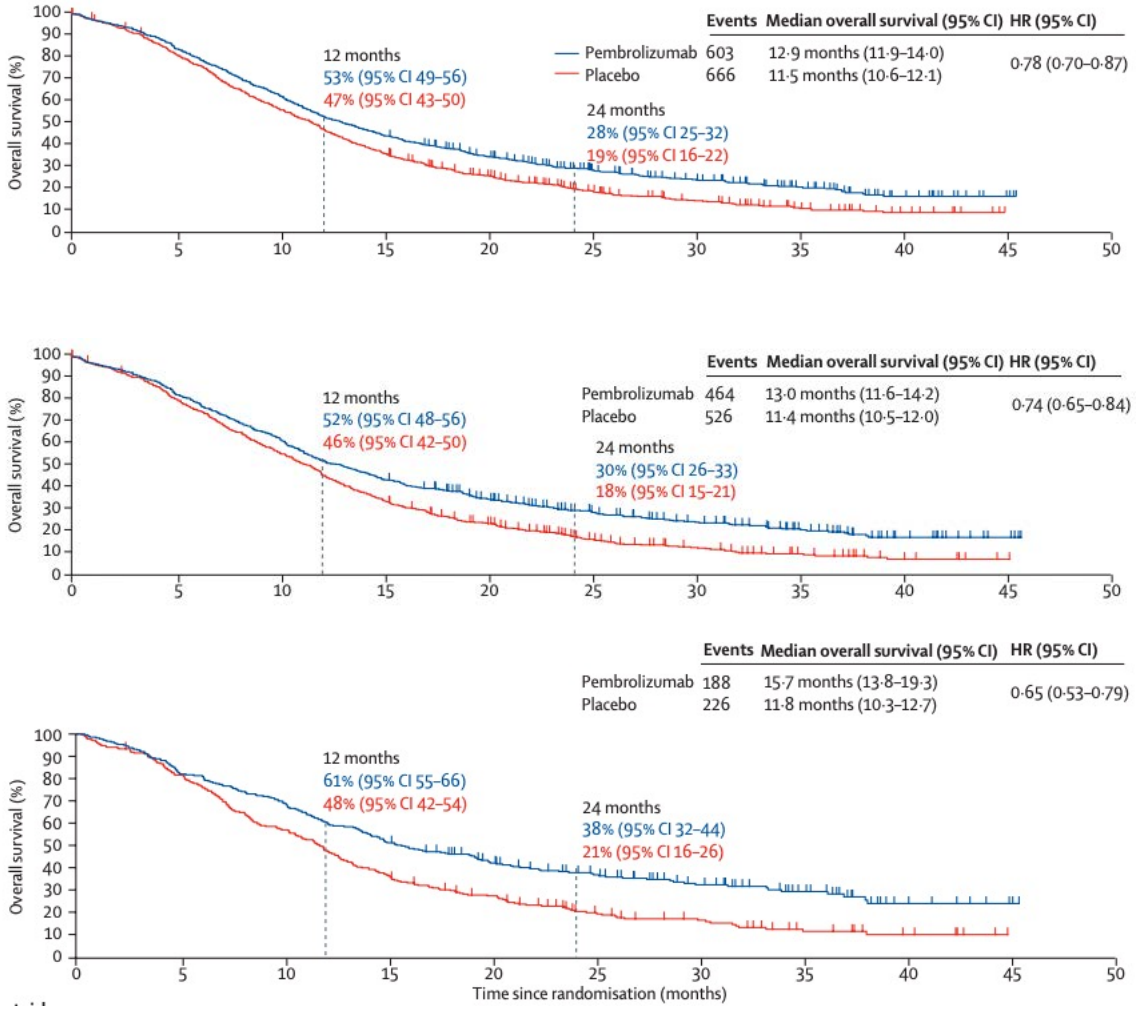
Addition of pembrolizumab improves OS



Intention-to-treat population

PD-L1 CPS ≥1

PD-L1 CPS ≥10

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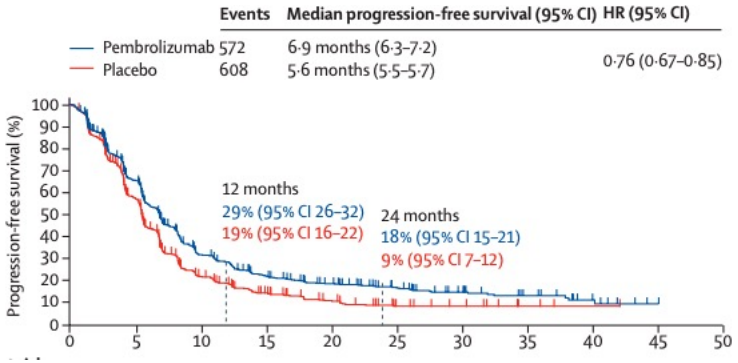
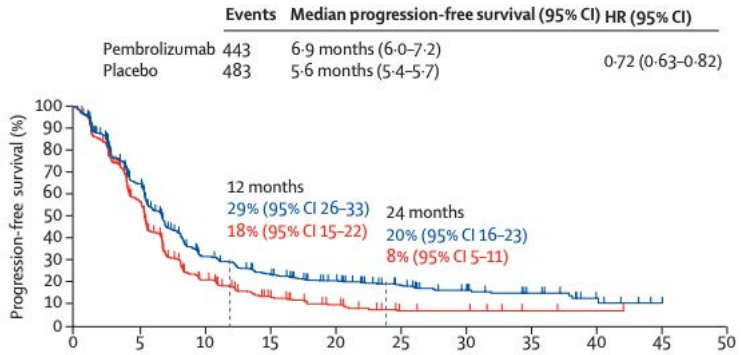
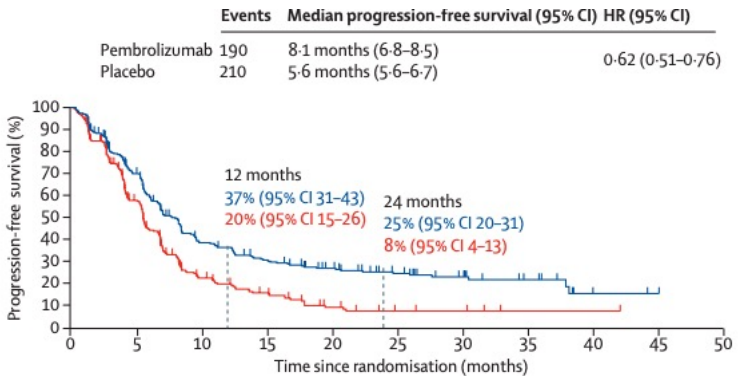
Addition of pembrolizumab improves PFS



Intention-to-treat population



PD-L1 CPS ≥1



PD-L1 CPS ≥10

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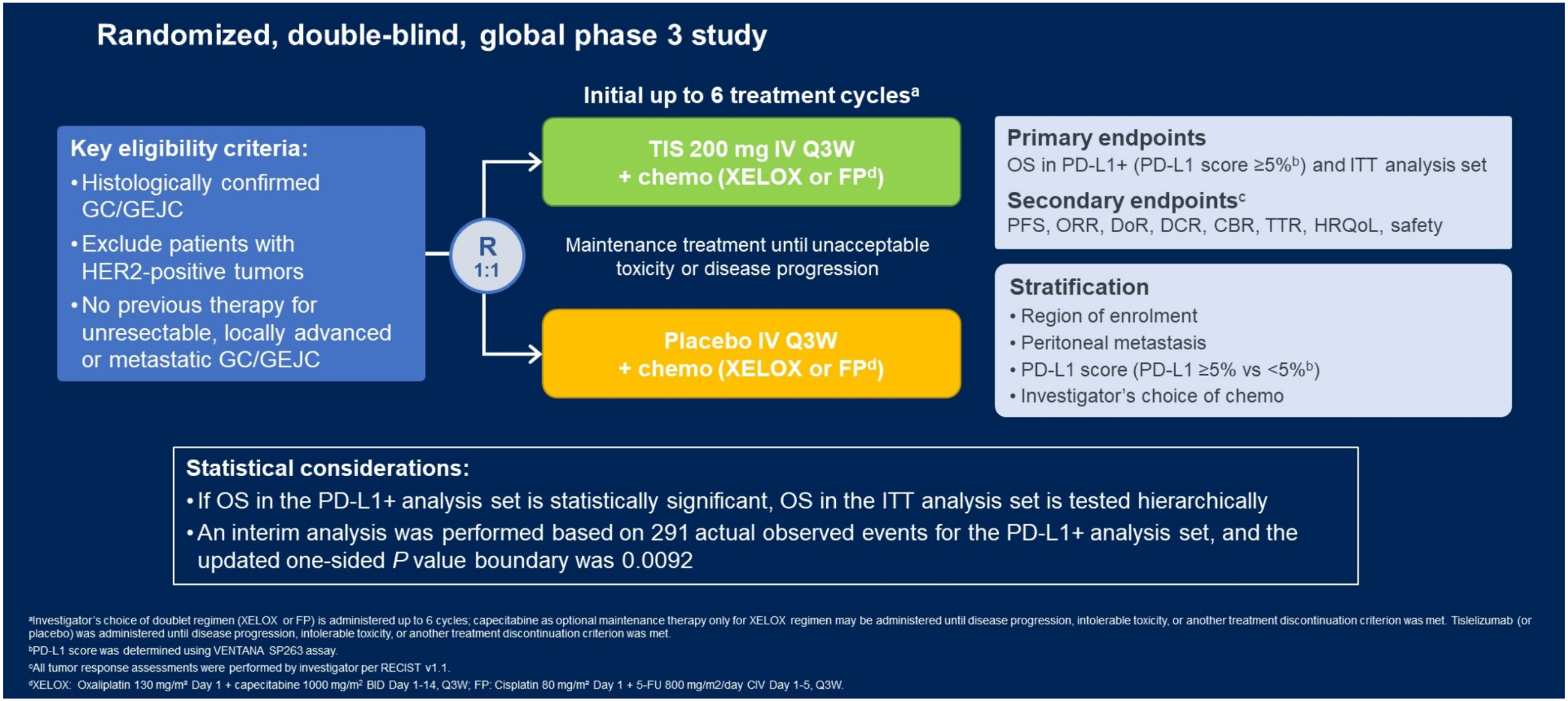
RATIONALE-305



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Demographics

TAP score, defined as total percentage of tumor area (tumor and any desmoplastic stroma) covered by tumor cells with PD-L1 membrane staining (any intensity), and tumor associated immune cells with PD-L1 staining (any intensity), visually estimated by pathologists using an investigational use only version of the Ventana PDL1 (SP263) assay (Roche Diagnostics)

CPS and TAP overall agreement 82%

Table 1 | Baseline personal and clinical characteristics of randomised patients. Values are number (percentage) unless stated otherwise

Characteristics	Tislelizumab plus chemotherapy (n=501)	Placebo plus chemotherapy (n=496)
Median (IQR) age (years)	60.0 (53.0-66.0)	61.0 (54.0-68.0)
Sex:		
Male	346 (69)	346 (70)
Female	155 (31)	150 (30)
Race/ethnicity:		
Asian	376 (75)	372 (75)
White	116 (23)	107 (22)
Other*	9 (2)	17 (3)
Geographical region:		
Asia	376 (75)	372 (75)
North America/Europe	125 (25)	124 (25)
ECOG performance status:		
0	169 (34)	154 (31)
1	332 (66)	342 (69)
Primary tumour location:		
Stomach	405 (81)	395 (80)
Gastro-oesophageal junction	96 (19)	100 (20)†
Metastatic disease	494 (99)	490 (99)
No of metastatic sites:		
0-2	335 (67)	335 (68)
≥3	166 (33)	160 (32)
Missing	0 (0)	1 (‹1)¶
Liver metastases	190 (38)	188 (38)
Peritoneal metastases	220 (44)	214 (43)
Previous adjuvant/neoadjuvant treatment	107 (21)	100 (20)
Previous gastrectomy/oesophagectomy	133 (27)	139 (28)
MSI or MMR status:		
MSI-H/dMMR	16 (3)	24 (5)
MSI-L/MSS/pMMR	448 (89)	439 (89)
Unknown	37 (7)	33 (7)
PD-L1 expression TAP score:		
‹5%	227 (45)	224 (45)
≥5%	274 (55)	272 (55)
Investigator chosen chemotherapy:		
Oxaliplatin and capecitabine	466 (93)	465 (94)
Cisplatin and 5-fluouracil	35 (7)	31 (6)

Data cut-off was 28 February 2023.
dMMR=mismatch repair-deficient; ECOG=Eastern Cooperative Oncology Group; IQR=interquartile range; MSI-H/L=microsatellite instability-high/low; MSS=microsatellite stable; PD-L1=programmed death-ligand 1; pMMR=mismatch repair-proficient; TAP=tumour area positivity.
*Includes not reported, unknown, and other.
†The diagnosis of one patient was updated from gastric adenocarcinoma to pancreatic cancer after randomisation.
¶Metastatic site was surgically removed before study entry.

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ORR, DCR and DoR

	PD-L1 TAP score ≥5% population*		All randomised patients†	
	Tislelizumab plus chemotherapy arm (n=274)	Placebo plus chemotherapy arm (n=272)	Tislelizumab plus chemotherapy arm (n=501)	Placebo plus chemotherapy arm (n=496)
Confirmed objective response rate, n (% (95% CI))	138 (50 (44 to 56))	117 (43 (37 to 49))	237 (47 (43 to 52))	201 (41 (36 to 45))
Odds ratio (95% CI)¶	1.36 (0.97 to 1.92); P=0.08		1.33 (1.03 to 1.72)	
Best overall response, n (%)				
Complete response	9 (3)	5 (2)	19 (4)	19 (4)
Partial response	129 (47)	112 (41)	218 (44)	182 (37)
Stable disease‡	104 (38)	109 (40)	213 (43)	212 (43)
Progressive disease	12 (4)	32 (12)	23 (5)	55 (11)
Undetermined**	20 (7)	14 (5)	28 (6)	28 (6)
Disease control rate, n (% (95% CI))	242 (88 (84 to 92))	226 (83 (78 to 87))	450 (90 (87 to 92))	413 (83 (80 to 86))
Clinical benefit rate, n (% (95% CI))	176 (64 (58 to 70))	161 (59 (53 to 65))	316 (63 (59 to 67))	292 (59 (54 to 63))
Median duration of response, months (95% CI)§	9.0 (8.2 to 19.4)	7.1 (5.7 to 8.3)	8.6 (7.9 to 11.1)	7.2 (6.0 to 8.5)
Median time to response, months (range)§	1.4 (0.9 to 11.3)	1.4 (1.0 to 17.5)	1.4 (0.9 to 13.4)	1.4 (1.0 to 17.5)

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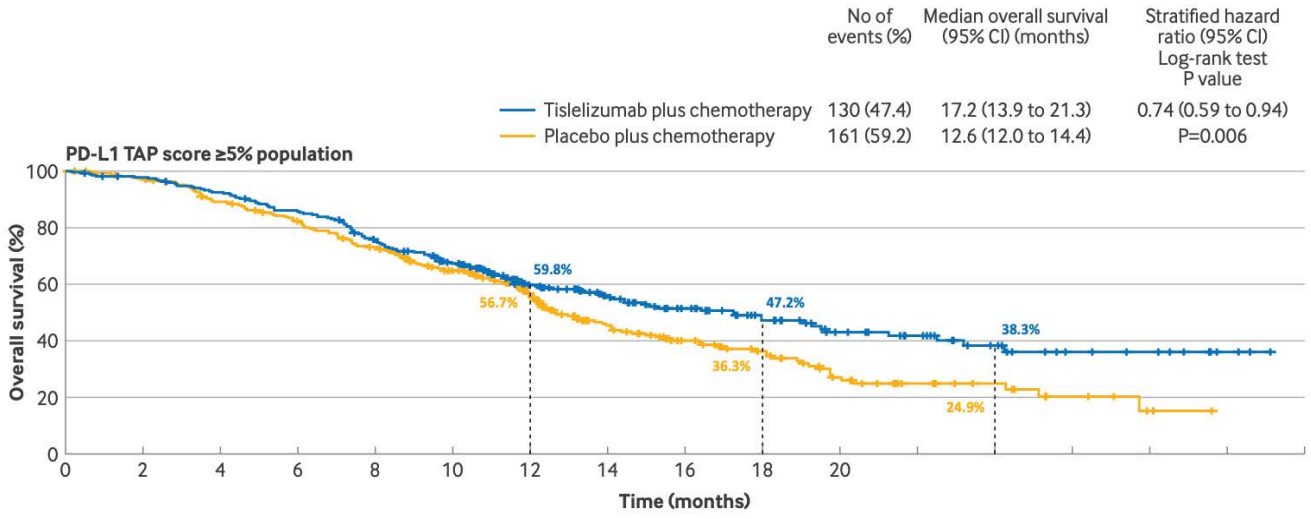
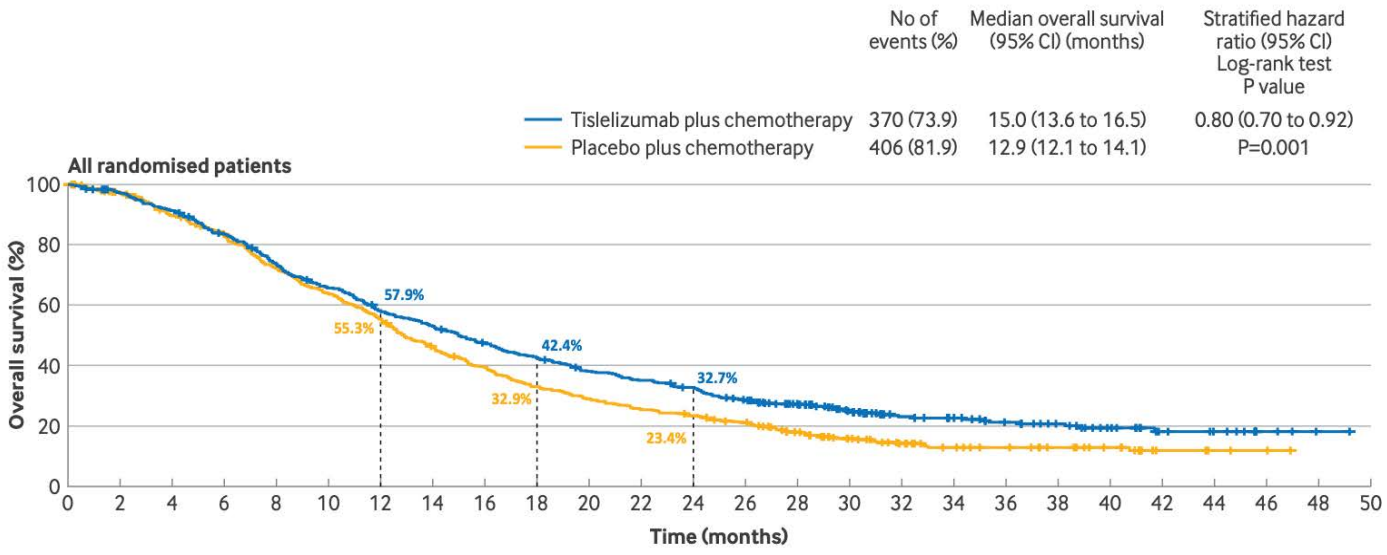
Addition of tislelizumab showed OS benefit



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)



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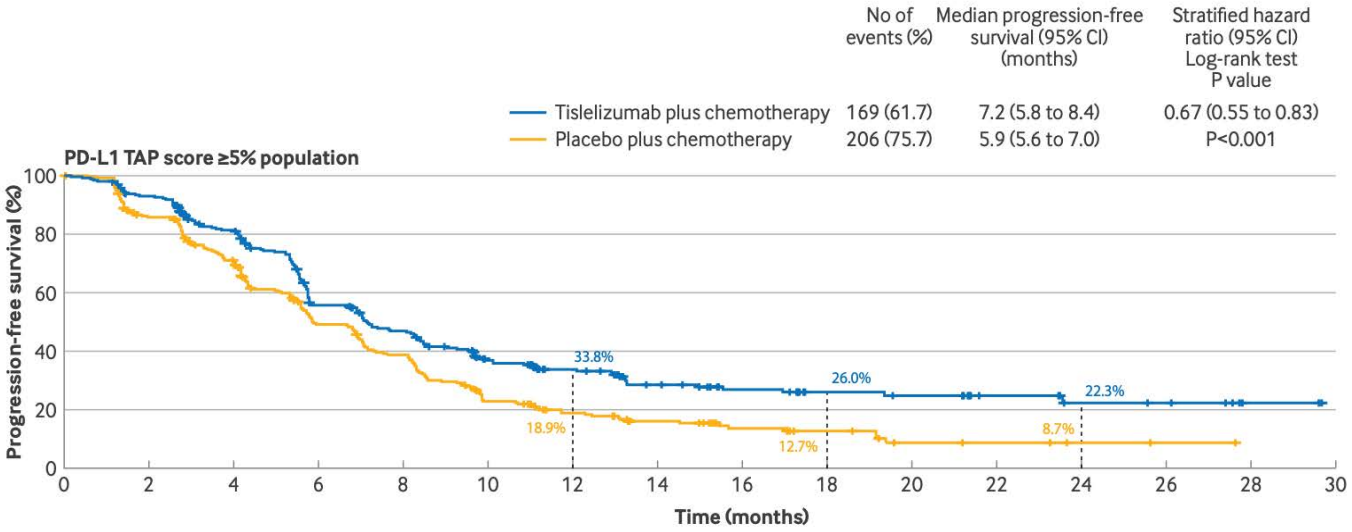
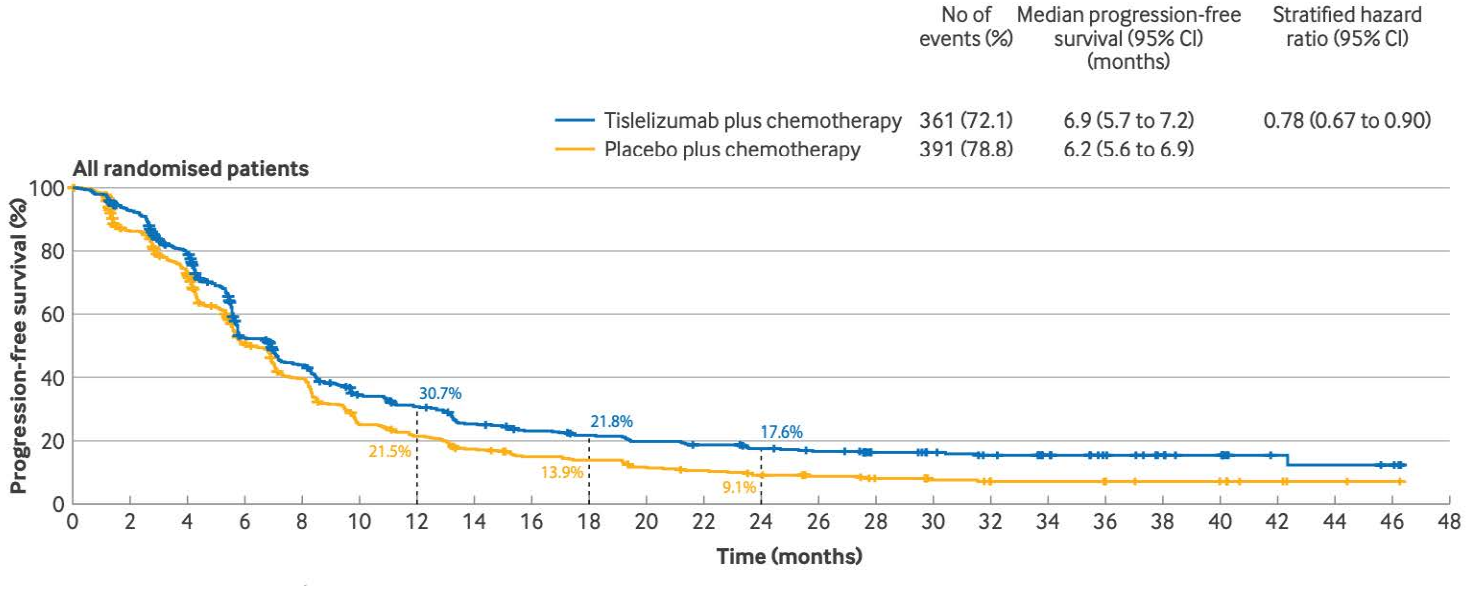
Addition of tislelizumab showed PFS benefit



In TAP ≥5%, median PFS of C + tisle vs C alone was 7.2 mos vs 5.9 mos (HR 0.67; p<0.001)

In all randomized patients, median PFS of C + tisle vs C alone was 6.9 mos vs 6.2 mos (HR 0.67; p<0.001)



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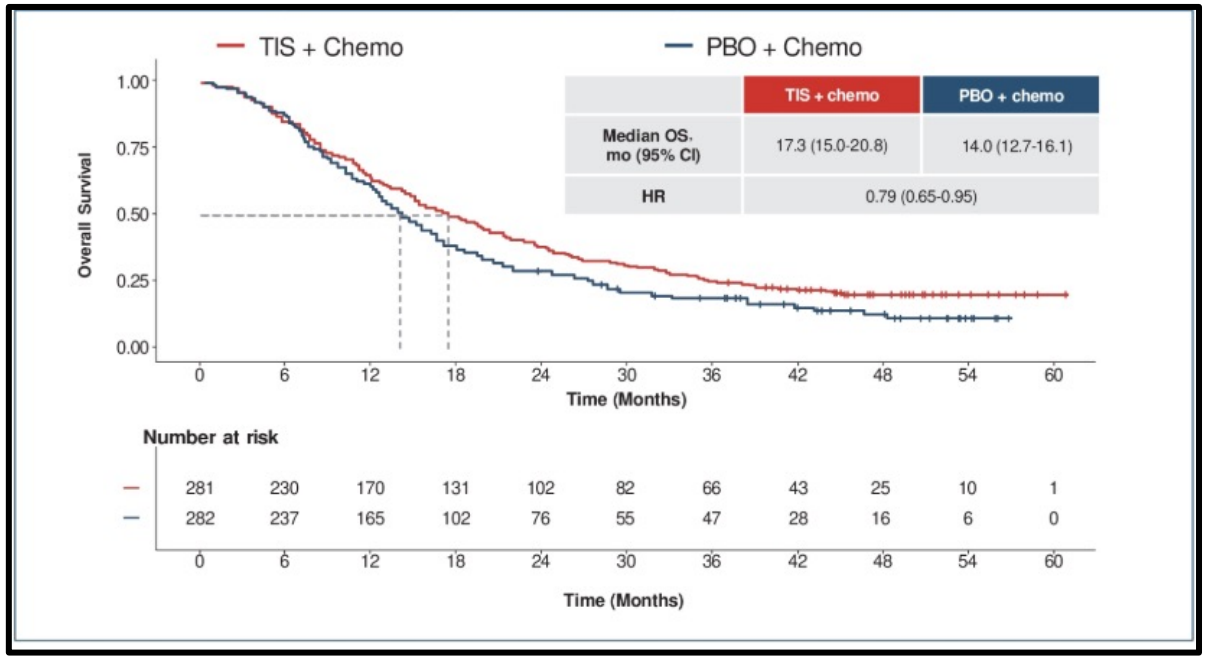
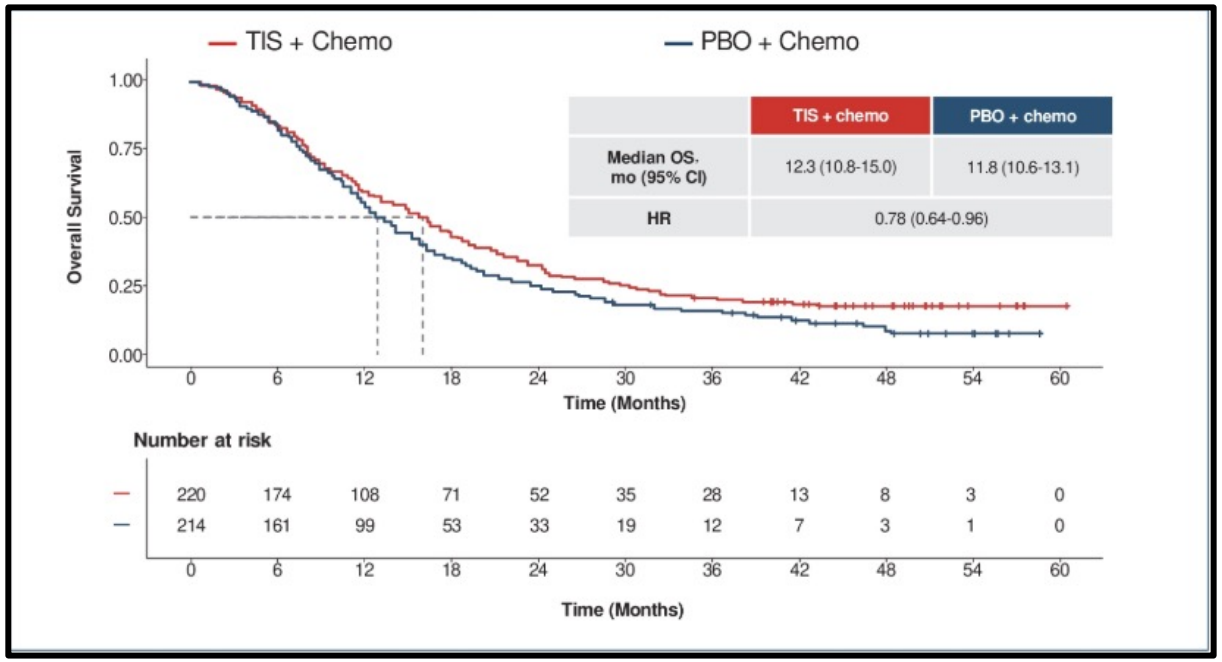
Chemo plus tislelizumab better than chemo regardless of peritoneal metastasis

OS in patients without peritoneal metastasis



OS in patients with peritoneal metastasis

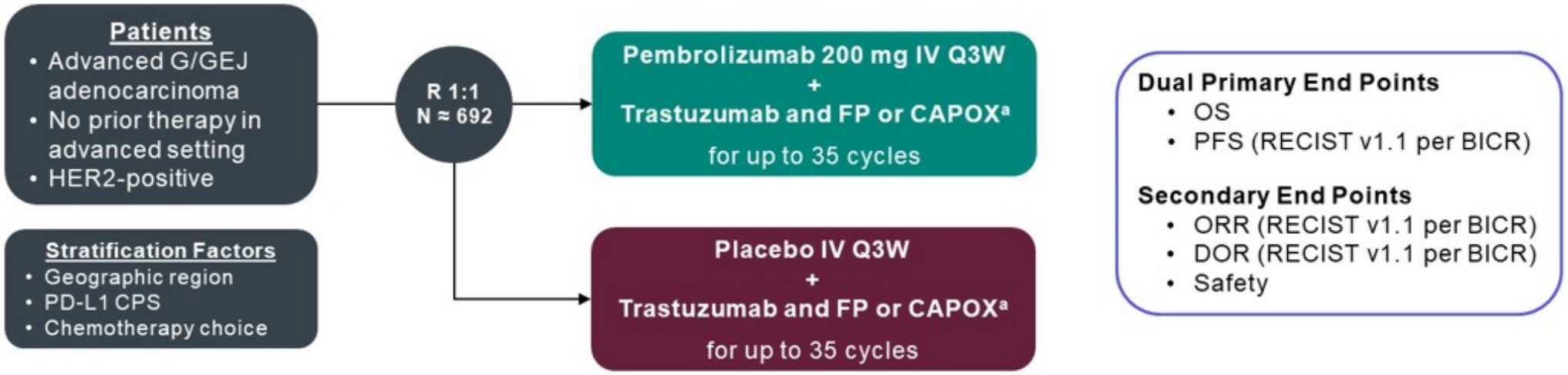


Qiu M et al. J Clin Oncol (2025)

KEYNOTE-811: 1L HER2-POS mGC/GEJ

KEYNOTE-811 Global Cohort

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



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KEYNOTE-811

Protocol-Specified First Interim Analysis (IA1)

Key Points

- Timing: to occur when first 260 participants enrolled had ≥8.5 mo of follow-up
- Objective: to assess whether adding pembrolizumab to trastuzumab and chemotherapy significantly improves ORR
- Superiority boundary: $P = 0.002$ (one-sided)
- Data cutoff date: June 17, 2020
  - 434 participants enrolled

Efficacy Population

- First 264 participants enrolled
- Follow-up duration[a]
  - Median: 12.0 mo
  - Range: 8.5-19.4 mo
- Continuing any study treatment
  - Pembro arm: 40.6%
  - Placebo arm: 28.5%

Safety Population

- 433 participants who received ≥1 dose of study medication
- Follow-up duration[a]
  - Median: 9.9 mo
  - Range: 0.1-19.4 mo
- Continuing any study treatment
  - Pembro arm: 58.5%
  - Placebo arm: 48.1%

[a]Follow-up duration was defined as the time from randomization to the data cutoff date.
Aus, Australia; EU, Europe; Isr, Israel; NAm, North America; ROW, rest of world.
The treatment regimen in both arms included trastuzumab and chemotherapy.

Baseline Characteristics – Efficacy Population

	Pembro Arm (N = 133)	Placebo Arm (N = 131)
Age, median (range)	62 y (19-84)	61 y (32-83)
Male sex	84%	79%
Region of enrollment		
Aus/EU/Isr/NAm	31%	34%
Asia	30%	30%
ROW	39%	37%
ECOG PS 1	51%	55%
Primary location of stomach	72%	68%
Histologic subtype		
Diffuse	21%	20%
Intestinal	61%	48%
Indeterminate	18%	32%
PD-L1 CPS ≥1	88%	85%
HER2 status		
IHC 2+, ISH positive	18%	21%
IHC 3+	82%	79%
Choice of chemotherapy		
CAPOX	86%	88%
FP	14%	12%

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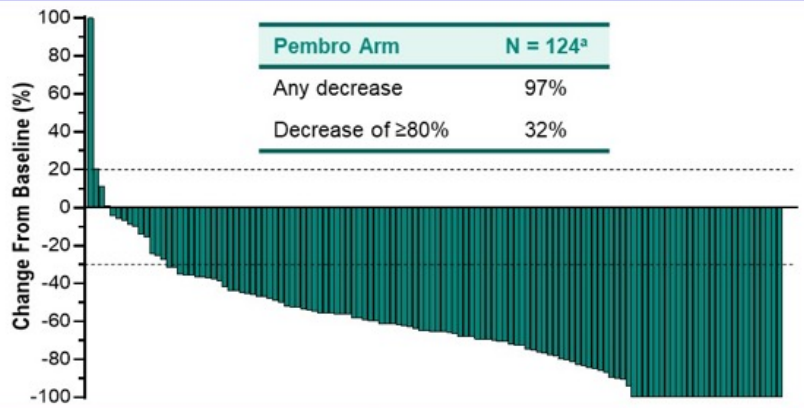
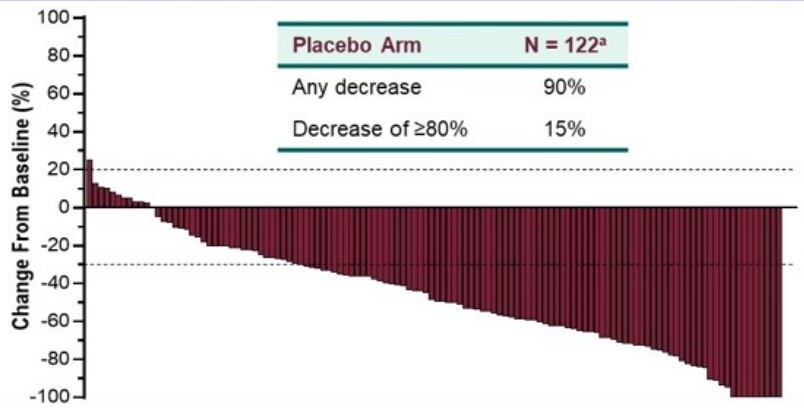
KEYNOTE-811

Confirmed Response at IA1





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

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

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

[a]Participants with RECIST-measurable disease at baseline and ≥1 post-baseline measurement evaluable for change from baseline in target lesions. [b]Calculated using the Miettinen and Nurminen method stratified by the randomization stratification factors. [c]Calculated in participants with best response of CR or PR. [d]Kaplan-Meier estimation. The treatment regimen in both arms included trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

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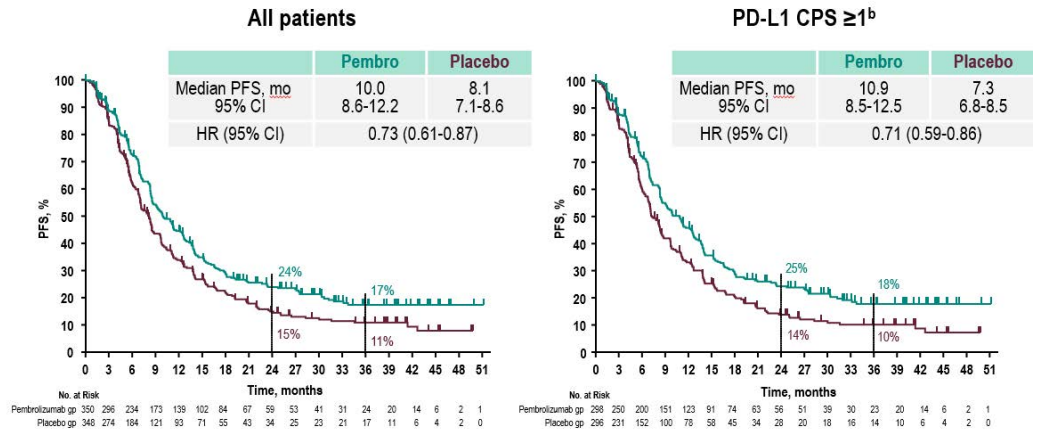
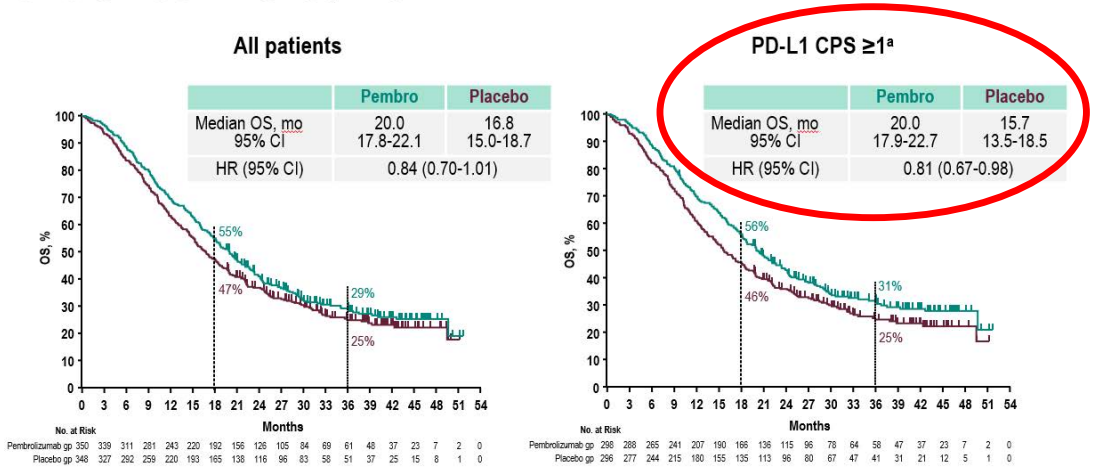
KEYNOTE-811 assessing addition of pembrolizumab to chemotherapy plus trastuzumab in HER2 positive gastroesophageal cancers
Previously shown to improve ORR with addition of pembrolizumab and combination was FDA approved in 2021.

Progression-Free Survival at IA3: 38.5 months of follow-up

RECIST V1.1, BICR



Overall Survival at IA3



The overall survival benefit of adding pembrolizumab was limited to PD-L1 CPS ≥1 patients

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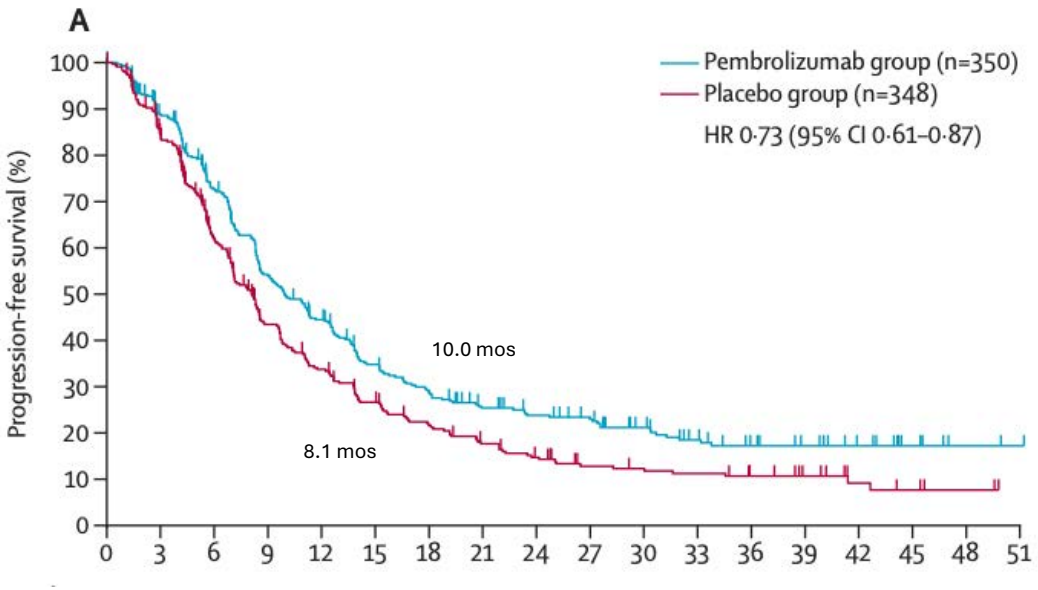
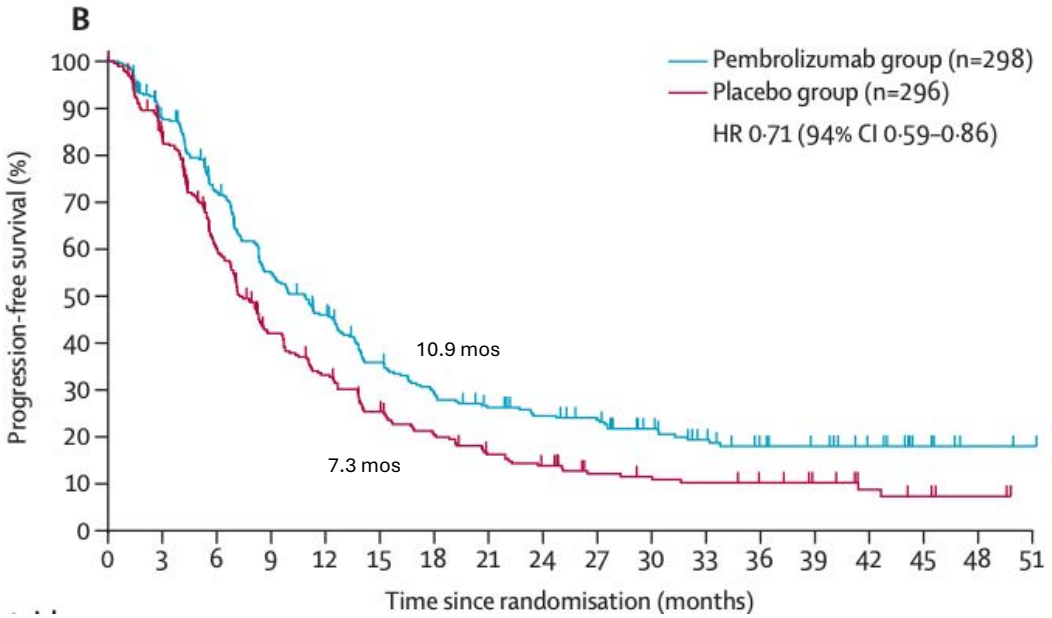
Pembrolizumab improves PFS in 1L HER2 pos



All randomized patients



PD-L1 CPS ≥1

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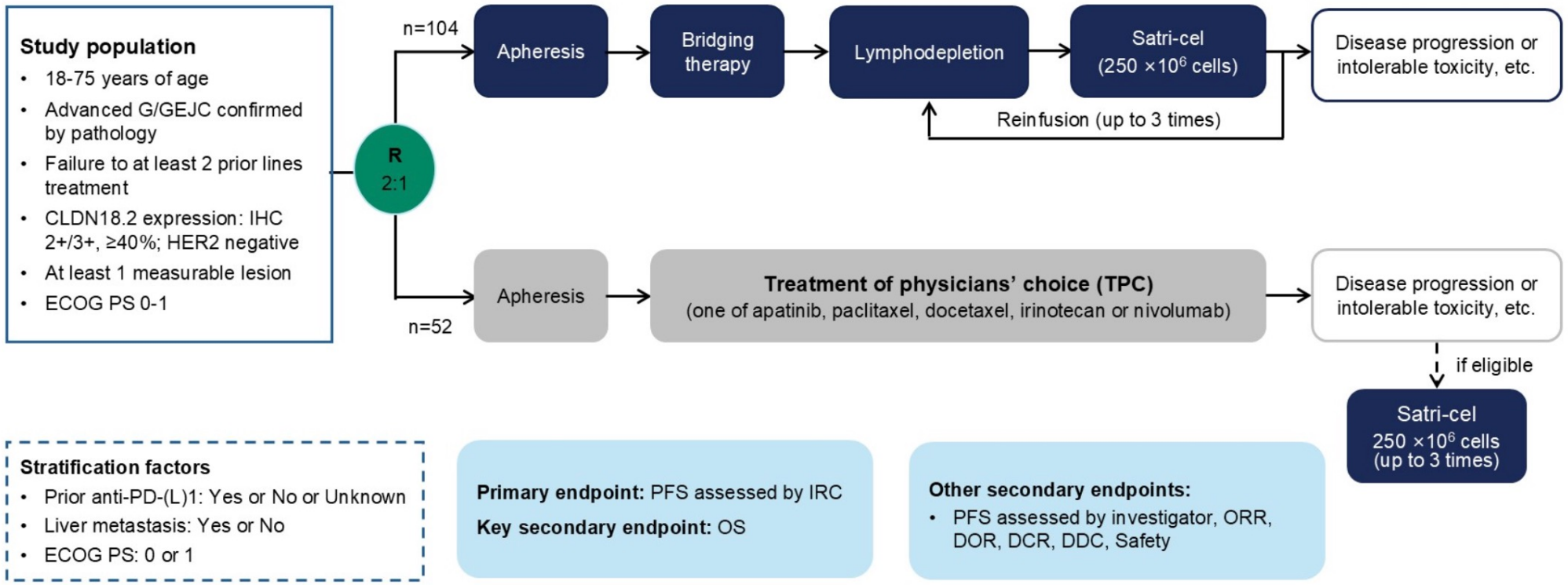
CAR-T therapy in refractory gastric cancer

Trial Design and Procedure schema

An open-label, multicenter, randomized controlled trial conducted in China.



Qi. ASCO 2025

Results

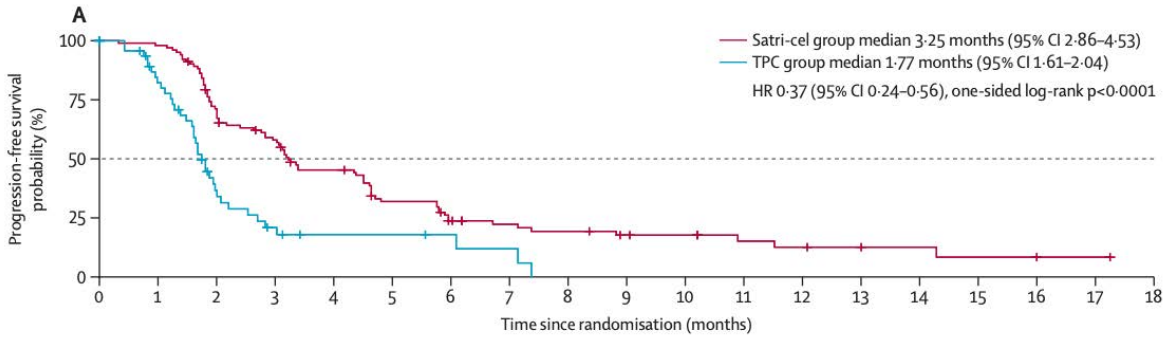
	Satri-cel group (n=104)	TPC group (n=52)
Median age, years	53·5 (45·0–60·0)	50·5 (43·0–58·0)
Sex		
Male	56 (54%)	31 (60%)
Female	48 (46%)	21 (40%)
Ethnicity		
Chinese	104 (100%)	52 (100%)
ECOG performance status		
0	17 (16%)	8 (15%)
1	87 (84%)	44 (85%)
History of smoking		
Yes	29 (28%)	15 (29%)
No	75 (72%)	37 (71%)
History of alcohol use		
Yes	23 (22%)	13 (25%)
No	81 (78%)	39 (75%)
Primary tumour site		
Gastric	88 (85%)	48 (92%)
Gastro-oesophageal junction	16 (15%)	4 (8%)
Previous gastrectomy		
Yes	49 (47%)	31 (60%)
No	55 (53%)	21 (40%)
Lauren histological classification		
Intestinal type	21 (20%)	12 (23%)
Diffuse type	45 (43%)	26 (50%)
Mixed type	29 (28%)	8 (15%)
Unknown	9 (9%)	6 (12%)
WHO histological classification		
Signet-ring cell carcinoma*	41 (39%)	27 (52%)
Non-signet-ring cell carcinoma	63 (61%)	25 (48%)
CLDN18.2 expression†		
Medium expression	24 (23%)	10 (19%)
High expression	80 (77%)	42 (81%)

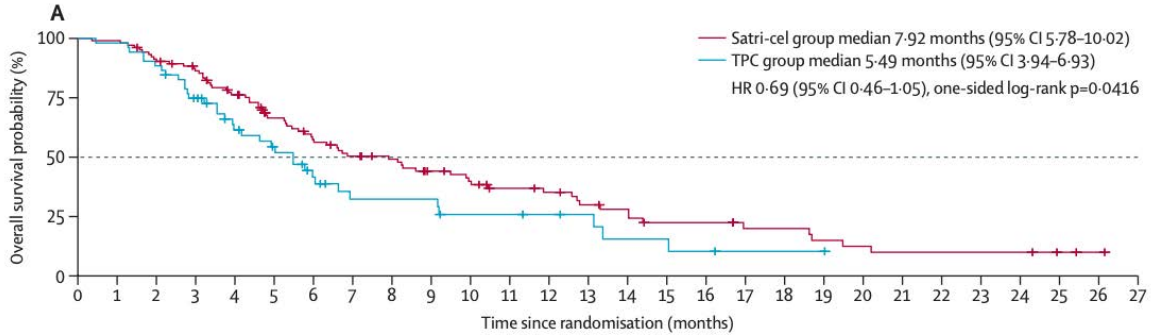
(Table 1 continues in next column)

	Satri-cel group (n=104)	TPC group (n=52)
(Continued from previous column)		
Number of previous lines of therapy‡		
2	76 (73%)	42 (81%)
≥3	28 (27%)	10 (19%)
Previous systemic therapies		
Fluorouracil or analogues and derivatives	101 (97%)	52 (100%)
Taxanes	96 (92%)	47 (90%)
Platinum	103 (99%)	50 (96%)
Anti-PD-1 or anti-PD-L1	81 (78%)	42 (81%)
Number of organs with metastasis		
≤2	53 (51%)	25 (48%)
≥3	51 (49%)	27 (52%)
Organs with metastasis		
Liver	21 (20%)	10 (19%)
Lung	9 (9%)	7 (13%)
Peritoneum	72 (69%)	31 (60%)
Bone	8 (8%)	9 (17%)

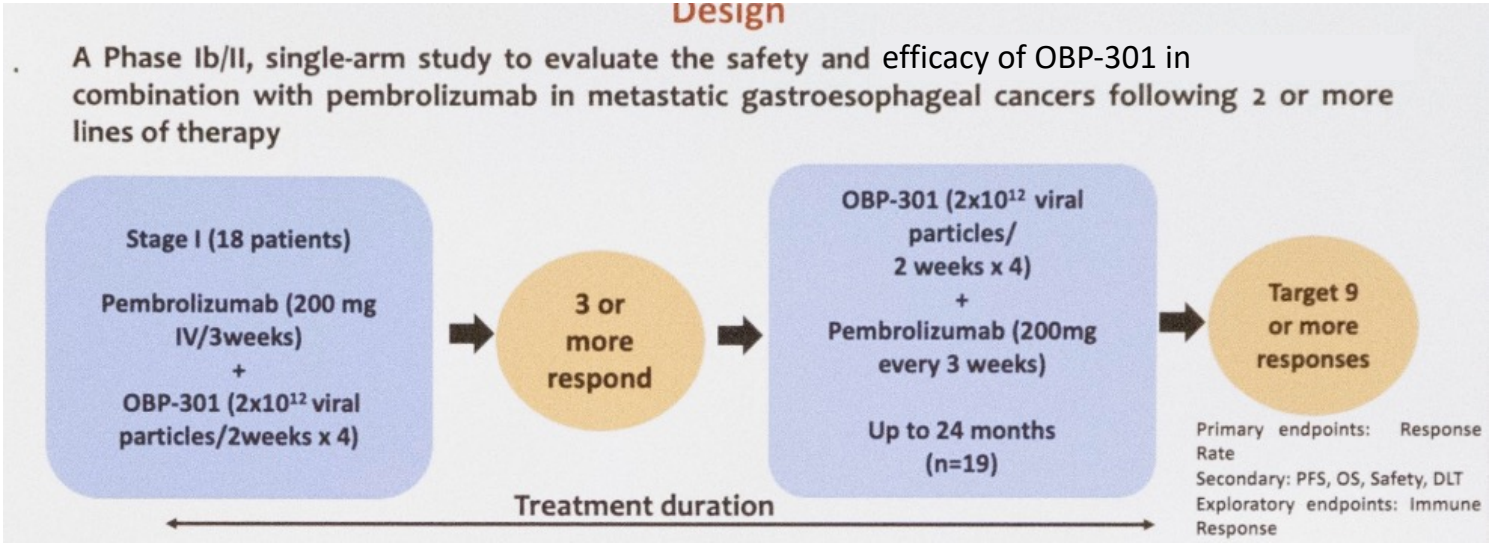
The calculation of percentages is based on the number of participants in the corresponding analysis set for each treatment group. Baseline is defined as the measurement taken on the day of randomisation or the most recent evaluable measurement before randomisation. CLDN18.2=claudin-18 isoform 2. ECOG=Eastern Cooperative Oncology Group. TPC=treatment of physician's choice. *Inclusion of signet-ring cell carcinoma components includes those with WHO classification of signet-ring cell carcinoma or any component of signet-ring cell carcinoma. †Defined according to the sum of the percentages of tumour cells with 3+ and 2+ CLDN18.2 expression; high expression is a sum ≥70%; medium expression is a sum ≥40% and <70%. ‡Second-line treatment includes all second-line treatments and first-line treatments that concurrently used three chemotherapeutic drugs, namely taxane (or anthracycline), platinum, and fluorouracil.

Table 1: **Demographics and baseline clinical characteristics**





Immunotherapy in refractory settings



Tolerance and Toxicity

OBP-301 direct tumor injection was well tolerated, with median OBP-301 injections of 3 (range 1-5).

Toxicity	Grade 2	Grade 3	Total G2-3 Toxicity (%)
Upper GI bleed		1 (6.25%)	6.25%
Anemia		1 (6.25%)	6.25%
Nausea	1 (6.25%)		6.25%
Elevated LFT	1 (6.25%)	1 (6.25%)	12.5%
Fatigue	5 (31.25%)	1 (6.25%)	37.5%
Fever	1 (6.25%)	1 (6.25%)	12.5%
Maculopapular Rash	1 (6.25%)		6.25%
Mucositis	1 (6.25%)		6.25%

OBP-301 is a novel, replication-selective adenoviral construct that incorporates the hTERT promoter to regulate the expression of the early adenoviral genes, E1A and E1B.

Three of 16 patients (19%) had a partial response.

A formal Phase 2 study is currently enrolling (NCT06340711).

Shah MA et al. J Clin Oncol 2023

Conclusions

- Key biomarkers MMR/MSI, HER2, PD-L1, CLDN18.2 dictate standard 1L treatment for advanced/metastatic gastroesophageal adenocarcinomas.
- Doublet chemotherapy is preferred over triplet combination.
- Nivolumab, pembrolizumab and tislelizumab have all shown improvement in OS and PFS when added to chemo. Incremental benefit seen with higher PD-L1 cut-offs.
- In 1L HER2 positive patients, addition of pembrolizumab to chemo plus trastuzumab is limited to PD-L1 CPS ≥1 patients.
- Limited benefit of checkpoint inhibitors in refractory settings. But, oncolytic viruses and cellular therapies being explored.

Questions from General Medical Oncologists — Incorporation of Immunotherapeutic Strategies into Treatment of Metastatic GE Tumors

72 y/o with CHF and stage IV esophageal SCC, PD-L1 7, treated with FOLFOX and nivolumab. What is the minimum PD-L1 level for using an ICI for both SCC and adenocarcinoma?

60M with squamous gastric cancer (not GEJ) PD-L1 85%. Started FOLFOX plus nivolumab, excellent response gaining weight, disease shrinking. How would you compare the sensitivity to ICI of squamous gastric cancer versus GEJ cancer?

Questions from General Medical Oncologists — Incorporation of Immunotherapeutic Strategies into Treatment of Metastatic GE Tumors

70-year-old man with a history of hypertension, Type 2 DM with peripheral neuropathy and mild COPD presents with dysphagia, weight loss, and fatigue. Imaging: multiple liver metastases, enlarged perigastric nodes. ECOG performance status 2. Endoscopy and biopsy: gastric adenocarcinoma, intestinal type HER2-negative, PD-L1 CPS = 25, MSI-stable. What treatment would you most likely recommend?

Questions from General Medical Oncologists — Incorporation of Immunotherapeutic Strategies into Treatment of Metastatic GE Tumors

Age: 62, Sex: Male, Diagnosis/stage: Metastatic GEJ adenocarcinoma (liver mets), HER2-negative, PD-L1 CPS 10. Comorbidities: Diabetes, mild CKD. Major therapies: Newly diagnosed – planning FOLFOX + nivolumab. At what PD-L1 CPS threshold is the benefit of adding checkpoint inhibitor to chemotherapy clinically meaningful?

RTP RESEARCH TO PRACTICE

Questions from General Medical Oncologists — Incorporation of Immunotherapeutic Strategies into Treatment of Metastatic GE Tumors

79-year-old woman with HER2 positive GEJ cancer, PD-L1 CPS 30, also has a history of moderately controlled rheumatoid arthritis. What is the threshold of autoimmune disease that would impact the use of immunotherapy?

60F (ECOG 0) with Crohn's disease (not on any steroids or biologics and without any flares in 20+ yrs) and metastatic gastric adenocarcinoma, PDL1 55%, HER2 1+. Pending 1st line treatment. Would you offer FOLFOX + immunotherapy for a tumor with a high PD-L1 score given the patient's dormant IBD? How do you discuss immune therapy in patient with auto-immune disease and other co-morbid conditions?

RTP RESEARCH TO PRACTICE

Questions from General Medical Oncologists — Incorporation of Immunotherapeutic Strategies into Treatment of Metastatic GE Tumors

48 y/o F with metastatic gastric cancer, Claudin 18.2 positive, PD-L1 CPS is 12. What would be the better frontline therapy – FOLFOX/zolbetuximab versus FOLFOX/nivolumab?

63 y/o female pt was treated with FOLFIRI x 5 cycles in Japan, with progressive disease, then transferred here, found to be PD-L1 CPS 5, HER2 1+, and Claudin 18.2 more than 75%. Should I give FOLFOX/nivolumab or FOLFOX/zolbetuximab?

47 yr old male with Stage 4 gGEJ cancer with Claudin 18.2 of 80% and PD-L1 score of 5. How do we choose between targeting claudin vs IO?

RTP
RESEARCH
TO PRACTICE

Questions from General Medical Oncologists — Incorporation of Immunotherapeutic Strategies into Treatment of Metastatic GE Tumors

59 y/o man with Type 2 DM and Stage IV gastric adenocarcinoma, PD1 20%, TMB 10, but pt refuses chemo. Would you offer single agent anti-PD1 antibody?

Agenda

Module 1: HER2-Targeted Approaches for Advanced Gastroesophageal Cancers — Dr Ajani

Module 2: Targeting Claudin 18.2 in Advanced Gastroesophageal Cancers — Dr Strickler

Module 3: Optimal Incorporation of Immunotherapeutic Strategies into Treatment for Patients with Metastatic Gastroesophageal Tumors — Dr Mehta

Module 4: Other Novel Agents and Strategies Under Evaluation for Advanced Gastroesophageal Cancers — Dr Klempner

Other Novel Agents and Strategies Under Evaluation for Advanced Gastroesophageal Cancers

Samuel J. Klempner, MD, FASCO

MGB Cancer Institute

Boston, MA

Overview

1. Doubling Down on Checkpoint Inhibitors with TIGIT + PD-1

2. What About Bispecific Dual Checkpoint Blockade with PD-1xTIGIT

3. Getting More from CLDN18.2 with Antibody Drug Conjugates

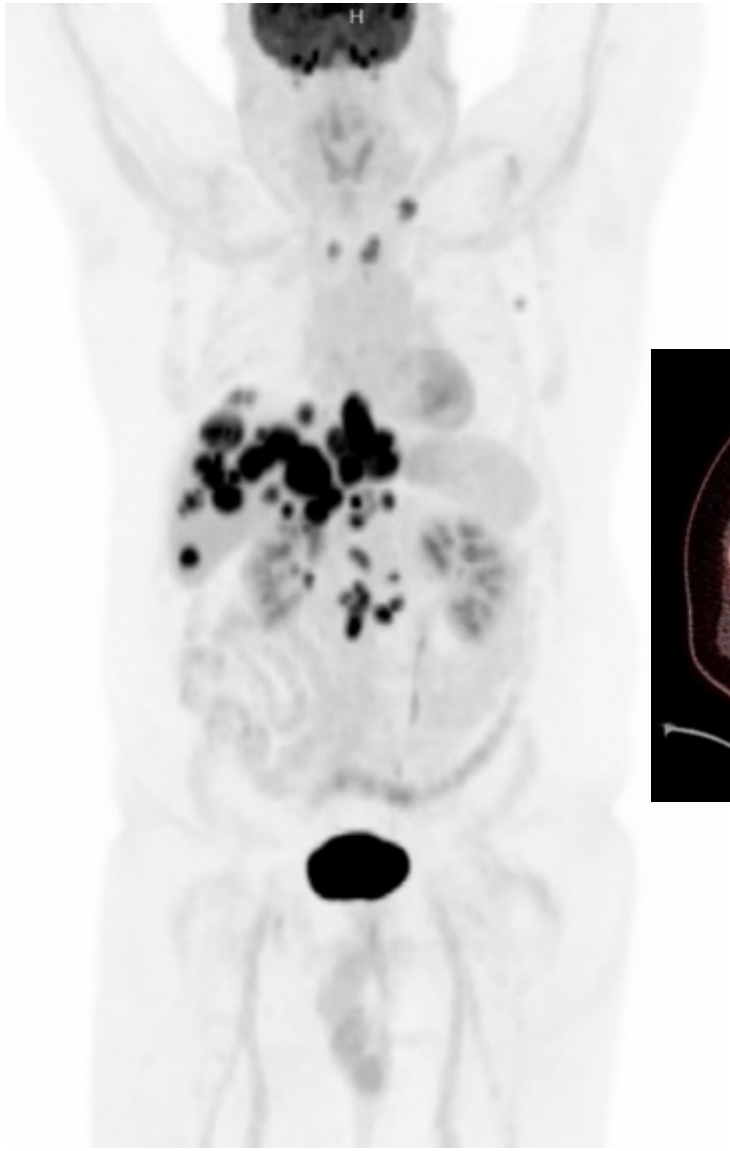
4. ADCs for Other Antigens and New Targets

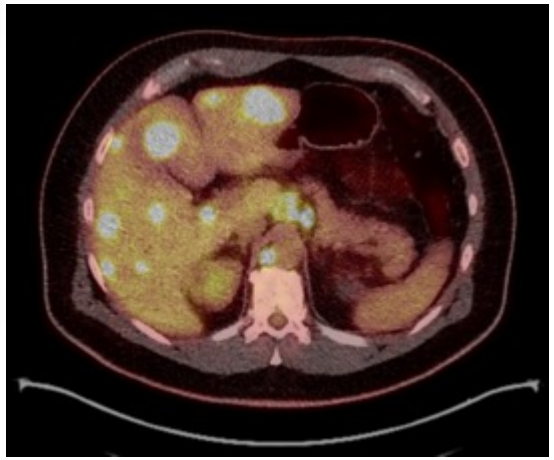
Starting in the Clinic

- HPI: 67M with limited PMH presents with increasing food sticking and 10lb weight loss.

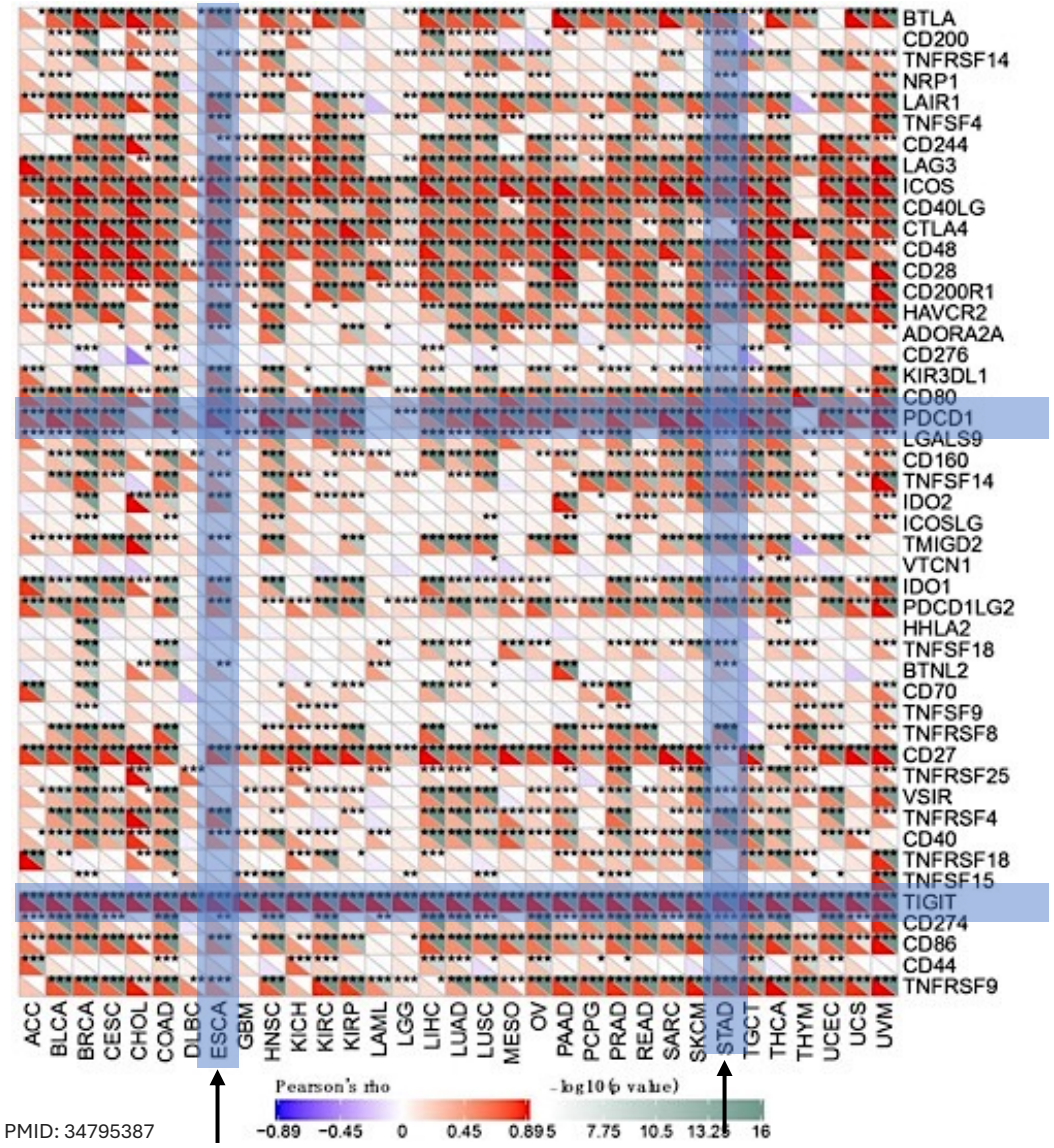
- PET-CT: Diffuse bilobar hepatic mets, widespread lymphadenopathy

- PATHOLOGY: Liver biopsy with mod-diff adenocarcinoma, pMMR, HER2 IHC 1+, PD-L1+ (CPS = 4), CLDN18.2 2+/3+ in 40% tumor cells





Starting From Biomarkers



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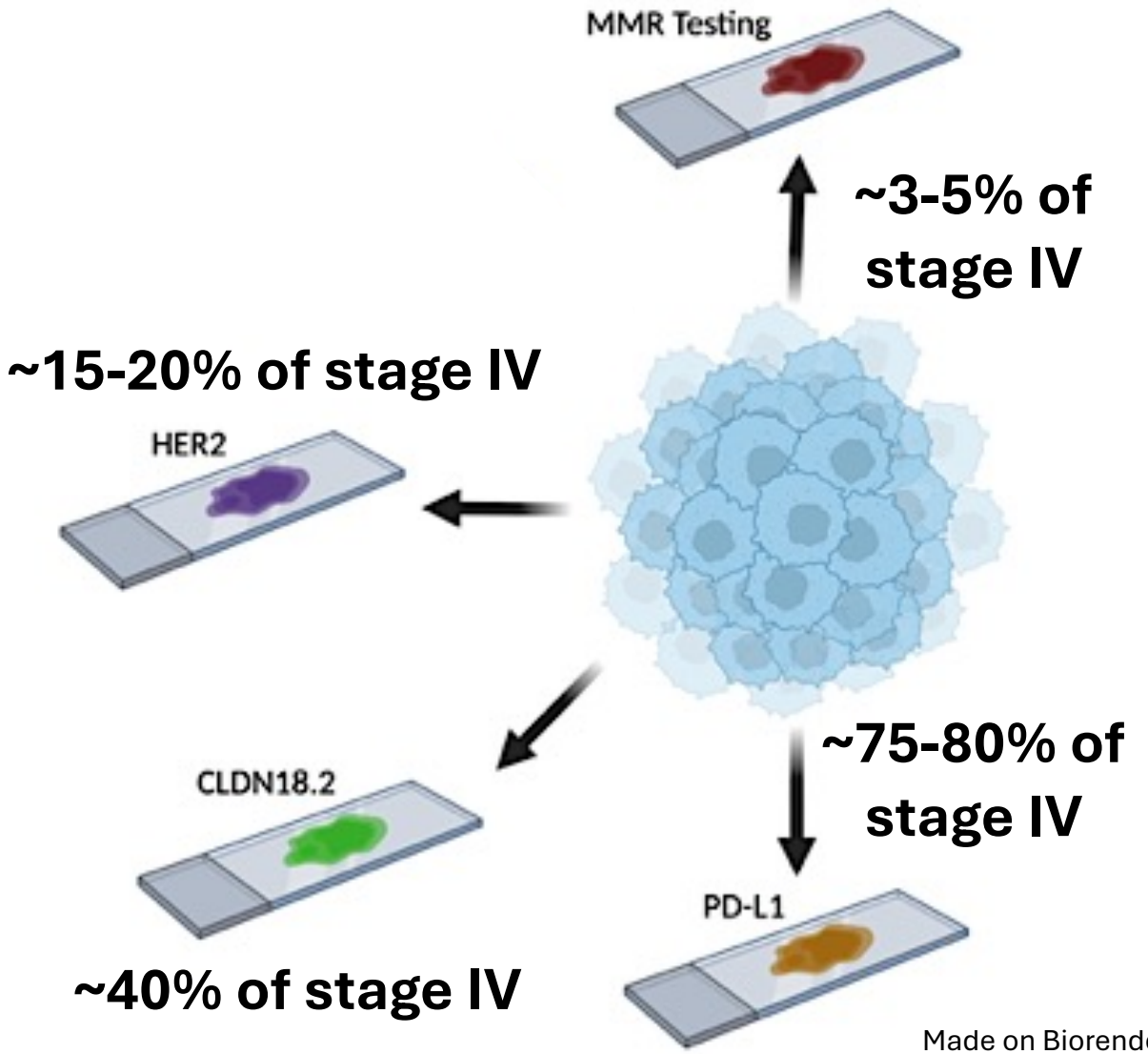

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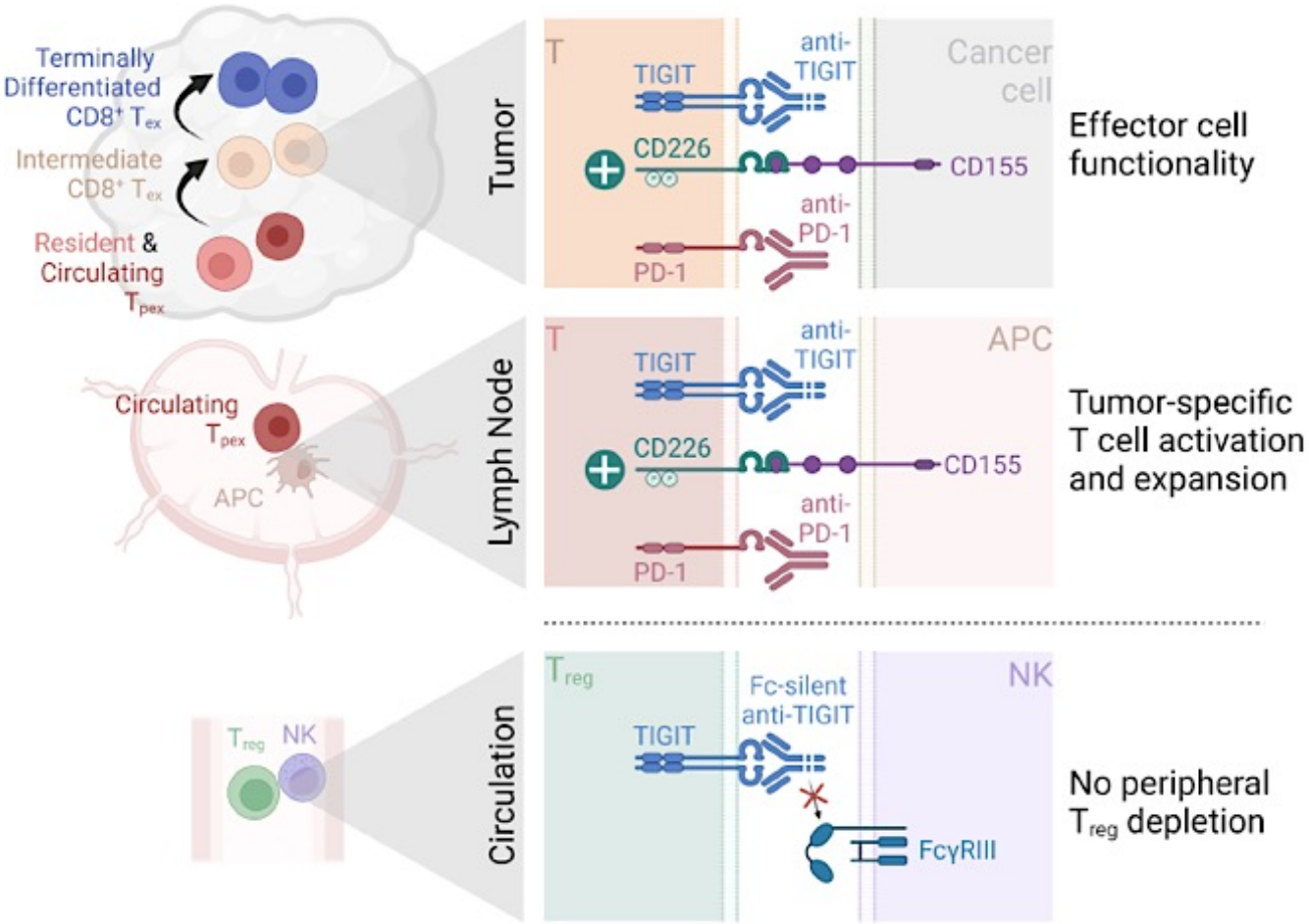
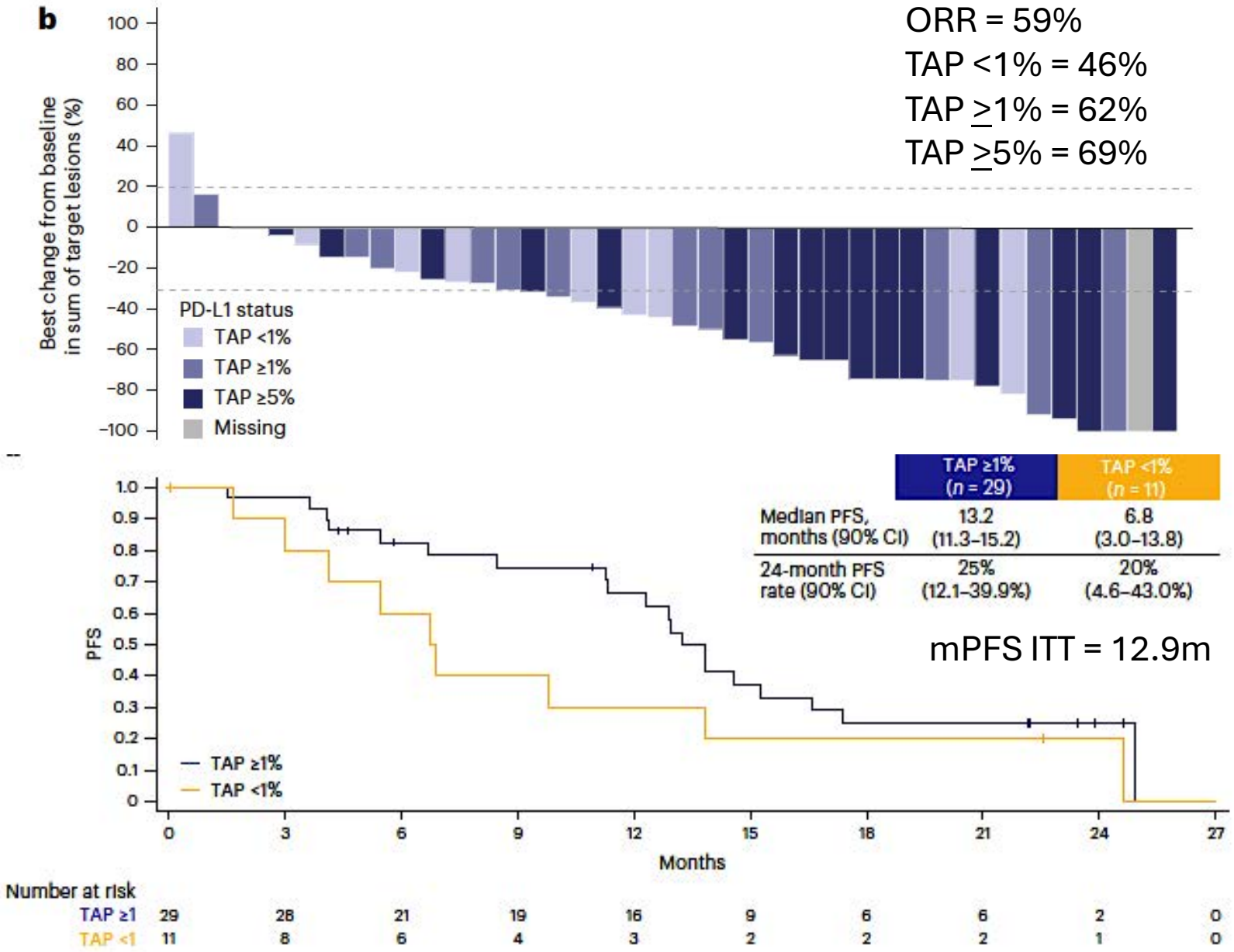
TIGIT RATIONALE



- Inhibitory checkpoint on T/NK cell subsets
- Suppresses T/NK activation partly by outcompeting CD226/DNAM-1 for shared ligand CD155/PVR
- TIGIT expression correlates with PD-1 expression, particularly in tumor-infiltrating cells
- PD-1 and TIGIT are frequently co-expressed on putative tumor-specific CD8+ T-cell in gastroesophageal

Early Enthusiasm for Dual PD-1 + TIGIT

Characteristic	Overall N=41
Median age in years (range)	62 (30–82)
Sex, *n* (%)	
Female	17 (41)
Male	24 (59)
Country, *n* (%)	
South Korea	19 (46)
USA/France	22 (54)
Race, *n* (%)	
Asian	21 (51)
White	14 (34)
Not reported	6 (15)
ECOG PS, *n* (%)	
0	16 (39)
1	25 (61)
Histologically confirmed diagnosis, *n* (%)	
GC adenocarcinoma	26 (63)
GEJC adenocarcinoma	5 (12)
EAC	10 (24)
Clinical tumor stage at study entry, *n* (%)	
III	2 (5)
IVA	10 (24)
IVB	29 (71)
Current disease status, *n* (%)	
Locally advanced unresectable	2 (5)
Metastatic	39 (95)
Liver metastases, *n* (%)	12 (29)
Peritoneal metastases, *n* (%)	18 (44)
Microsatellite instability status, *n* (%)	
High	1 (2)
Low	4 (10)
Stable	31 (76)
Unknown	5 (12)



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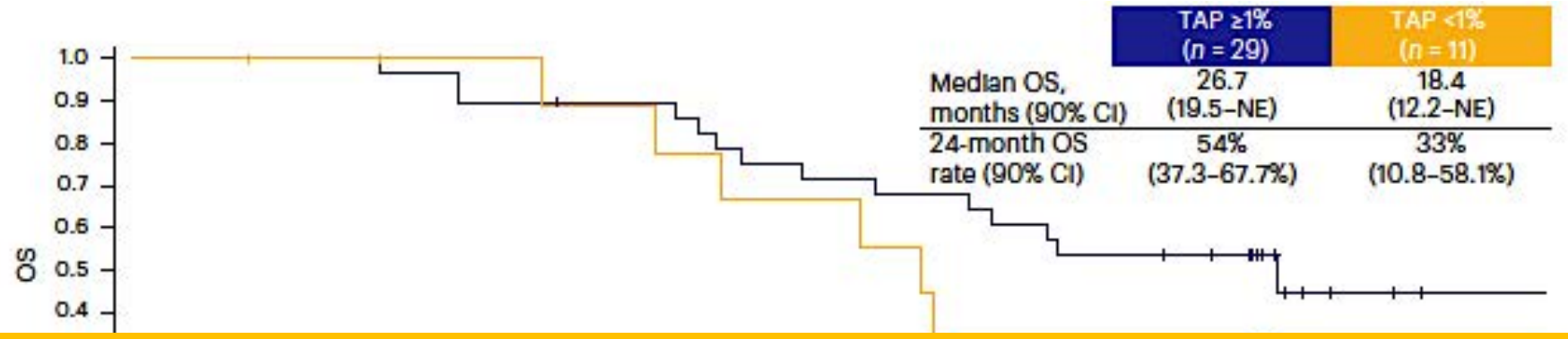
Early Enthusiasm for Dual PD-1 + TIGIT



12/12/2025: The Phase 3 STAR-221 study evaluating a domvanalimab-based combination in upper gastrointestinal cancers will be discontinued due to futility

Number at risk

TAP ≥1	29	29	28	26	25	21	19	17	15	4	1	0
TAP <1	11	10	9	9	8	6	5	3	3	0	0	0

Key Eligibility Criteria
- First-line locally advanced unresectable or metastatic without prior systemic treatment
- Measurable disease (RECIST 1.1)
- PD-L1 all comers
- Known HER-2-positive tumors excluded

N = 970

R 1:1

- Domvanalimab + Zimberelimab + PI Choice of Chemotherapy[a]
- Nivolumab + PI Choice of Chemotherapy[a]

Stratification Factors
- PD-L1 expression (TAP ≥5% or TAP <5%)
- ECOG PS (0 to 1)
- Region (US/Canada/EU5 vs Asia vs rest of world)

Dual Primary End Points
- OS ITT
- OS in TAP ≥5%

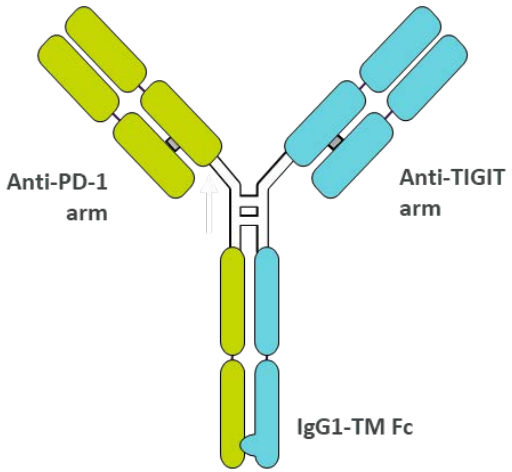
Key Secondary End Points
- PFS ITT
- PFS in TAP ≥5%

PMID: 41109921

Shifting TIGIT Hopes to Bispecifics: Rilve

Rilvegostomig

Anti-PD-1 / anti-TIGIT DuetMab[1,2]



Designed to maximise effect of PD-1 and TIGIT blockade through cooperative binding[1,2]

GEMINI-Gastric = phase 2 platform study in HER2-negative locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma

STUDY DESIGN

- Locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma
- HER2-negative tumors
- Previously untreated for advanced/ metastatic disease
- ECOG PS 0 or 1

Substudy assignment: For substudies 3 and 4, patients must have claudin18.2-positive status

- **Substudy 1 (n=40)** Volrustomig + XELOX or FOLFOX
- **Substudy 2 (n=40)** Rilvegostomig + XELOX or FOLFOX
- **Substudy 3 (n=40)** AZD0901 + volrustomig + 5-FU or capecitabine
- **Substudy 4 (n=40)** AZD0901 +rilvegostomig + 5-FU or capecitabine
- **Substudy 5 (n=40)** Sabestomig + XELOX or FOLFOX

Primary endpoint

- ORR and 6-month PFS §

Key secondary endpoints

- DoR §
- PFS (median and 12-month rate) §
- Safety and tolerability

Rivera F, et al. Presented at: ESMO 2024 [Poster 1422P].

Shifting TIGIT Hopes to Bispecifics: Rilve

Patient demographics

Demographic parameter	All patients (N=40)	
	Rilvegostomig + XELOX (n=27)	Rilvegostomig + FOLFOX (n=13)
Age, years, median (range)	63 (42–79)	
<65 years, n (%)	22 (55.0)	
≥65 years, n (%)	18 (45.0)	
Male, n (%)	23 (57.5)	
Race, n (%)		
Asian	29 (72.5)	
White	11 (27.5)	
Area of residence, n (%)		
Asia*	29 (72.5)	
Western country†	11 (27.5)	

Baseline disease characteristics

Disease characteristic	All patients (N=40)	
	Rilvegostomig + XELOX (n=27)	Rilvegostomig + FOLFOX (n=13)
ECOG PS, n (%)		
0	21 (52.5)	
1	19 (47.5)	
Primary tumor location, n (%)		
Stomach	32 (80.0)	
GEJ	8 (20.0)	
Metastatic disease, n (%)	40 (100)‡	
Metastatic sites, n (%)		
Peritoneum	16 (40.0)	
Liver	14 (35.0)	
Bone	4 (10.0)	
PD-L1 CPS, n (%)		
<5	22 (55.0)§	
≥5	16 (40.0)¶	
Missing	2 (5.0)	

Data cutoff: 4 July 2024.

*Includes mainland China (n=14), Republic of Korea (n=8), Japan (n=4), and Taiwan (n=3). †Includes Spain (n=8), Great Britain (n=2), and the USA (n=1).
‡One patient had peritoneal metastases resected before enrollment. §Includes one patient with local PD-L1 results. ¶Includes two patients with local PD-L1 results.

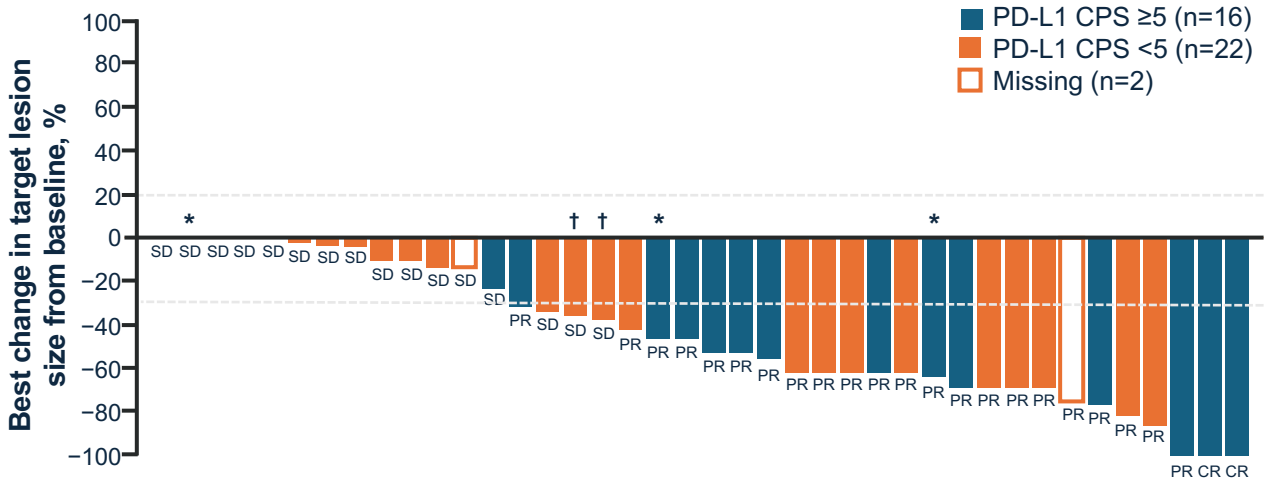
CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; GEJ, gastroesophageal junction; PD-L1, programmed cell death ligand 1; XELOX, capecitabine + oxaliplatin.

Rivera F, et al. Presented at: ESMO 2024 [Poster 1422P].

Shifting TIGIT Hopes to Bispecifics: Rilve

The ORR was 62.5% in all patients and 81.3% in patients with a PD-L1 CPS ≥5

Response outcomes



Outcome	PD-L1 CPS ≥5 (n=16)	PD-L1 CPS <5 (n=22)	All patients (N=40)
Confirmed ORR, % (95% CI)	81.3 (54.4–96.0)	50.0 (28.2–71.8)	62.5 (45.8–77.3)
Best overall confirmed response, n (%)			
CR	**2 (12.5)**	0	2 (5.0)
PR	11 (68.8)	11 (50.0)	23 (57.5)
uPR	0	2 (9.1)	2 (5.0)
SD lasting ≥5 weeks	3 (18.8)	9 (40.9)	13 (32.5)
PD	**0**	**0**	**0**
DoR for confirmed responses, months, median (95% CI)	12.2 (3.4–NC)	5.8 (4.1–7.0)	5.8 (4.2–NC)

- Two patients with a **PD-L1 CPS ≥5 had a CR**
- **All patients** demonstrated **disease control** (objective response or SD as the best overall response); none had primary PD

Figure adapted from Rivera F, et al. 2024.

*Patients with local PD-L1 results. †Unconfirmed objective responses.

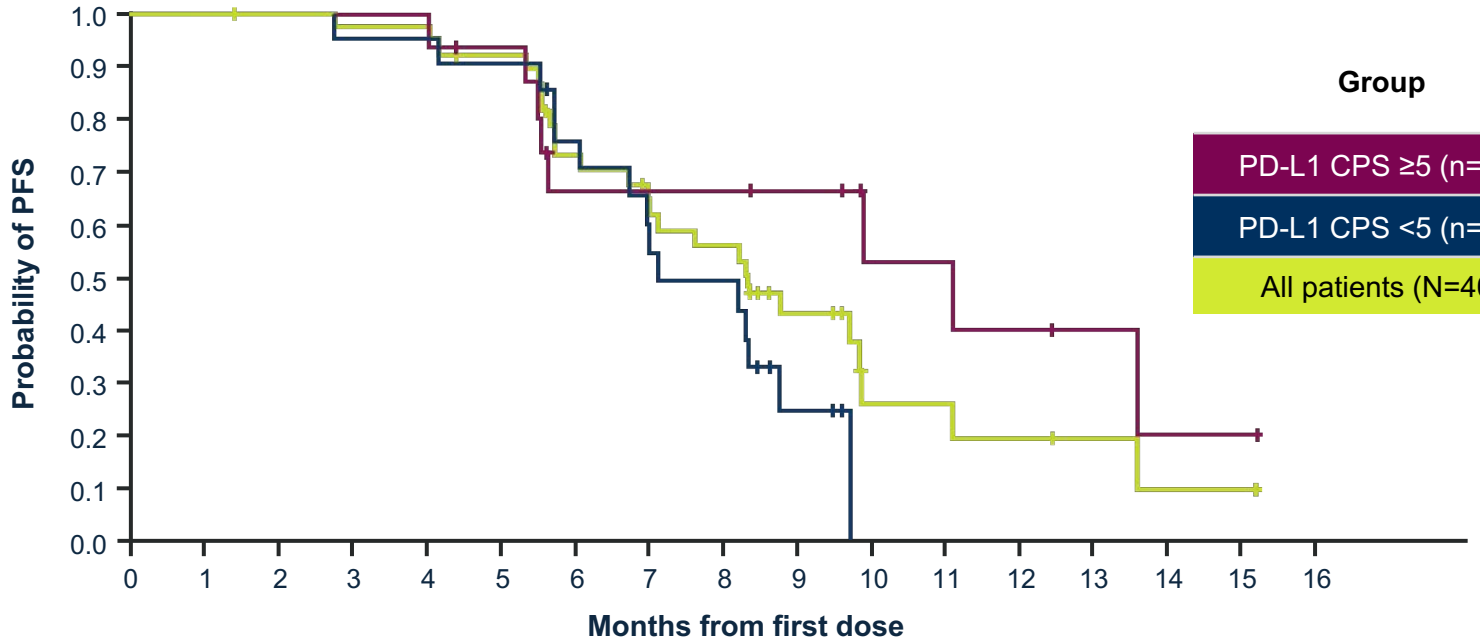
CI, confidence interval; CPS, combined positive score; CR, complete response; DoR, duration of response; NC, not calculable; ORR, objective response rate; PD, progressive disease; PD-L1, programmed cell death ligand 1; PR, partial response; SD, stable disease; uPR, unconfirmed partial response.

Rivera F, et al. Presented at: ESMO 2024 [Poster 1422P].

Frontline Chemo + PD-1xTIGIT Bispecific

Median PFS was 8.3 months in all patients and 11.1 months in patients with PD-L1 CPS ≥5

PFS based on investigator assessment



Group	Median PFS (95% CI), months
PD-L1 CPS ≥5 (n=16)	11.1 (5.6–NC)
PD-L1 CPS <5 (n=22)	7.1 (6.1–8.8)
All patients (N=40)	8.3 (7.0–9.9)

Patients at risk, n																		Events, n
PD-L1 CPS <5	22	22	21	20	20	19	15	11	9	3	0	0	0	0	0	0	0	15
PD-L1 CPS ≥5	16	16	16	16	16	14	9	9	9	7	4	4	3	2	1	1	0	8
All patients	40	40	39	38	38	35	26	22	19	11	4	4	3	2	1	1	0	25

Rivera F, et al. Presented at: ESMO 2024 [Poster 1422P].

Frontline Chemo + PD-1xTIGIT Bispecific

Safety summary for rilvegostomig + chemotherapy

Patients, n (%)	All patients (N=40)
Treatment-related AEs	40 (100.0)
Rilvegostomig-related AEs	25 (62.5)
Treatment-related grade ≥3 AEs	17 (42.5)
Rilvegostomig-related grade ≥3 AEs	4 (10.0)
Treatment-related serious AEs	5 (12.5)
Rilvegostomig-related serious AEs	1 (2.5)*
Any AE leading to treatment discontinuation	10 (25.0)
Any AEs leading to discontinuation of rilvegostomig	1 (2.5)

Grade ≥3 rilvegostomig-related AEs occurred in four patients: lipase ↑ (n=2), alkaline phosphatase ↑, platelets ↓, pneumonitis (n=1 each)

Adverse events of special interest

AESI, n (%)	All patients (N=40)	
	Any grade	Grade ≥3
Infusion-related reaction	3 (7.5)†	0
Pneumonitis	2 (5.0)‡	1 (2.5)‡
Rash	2 (5.0)‡	0
Diarrhea	1 (2.5)‡	0
Drug hypersensitivity	1 (2.5)§	0
Hyperthyroidism	1 (2.5)	0
Immune-mediated enterocolitis	1 (2.5)‡	0
Immune-mediated thyroiditis	1 (2.5)‡	0
Pruritus	1 (2.5)	0

The only grade ≥3 rilvegostomig-related AESI reported was pneumonitis, which occurred ~3 months after discontinuation of study treatment

*Two events occurred in one patient: platelet count decreased and pneumonitis. †One event was a grade 2 rilvegostomig-related AE. ‡Rilvegostomig-related events. §Oxaliplatin-related.
AE, adverse events; AESI, adverse event of special interest.
Rivera F, et al. Presented at: ESMO 2024 [Poster 1422P].

Novel-Novel Combinations to Push Forward

The Phase 3 ARTEMIDE-Gastric 01 study is ongoing, evaluating T-DXd + rilvegostomig + fluoropyrimidine in HER2+ / PD-L1 CPS≥1 GC

- Locally advanced or metastatic gastric GEJ
- No prior treatment
- HER2+ (HER2 3+ or 2+ / ISH positive)
- CPS ≥ 1
- ECOG PS 0 or 1

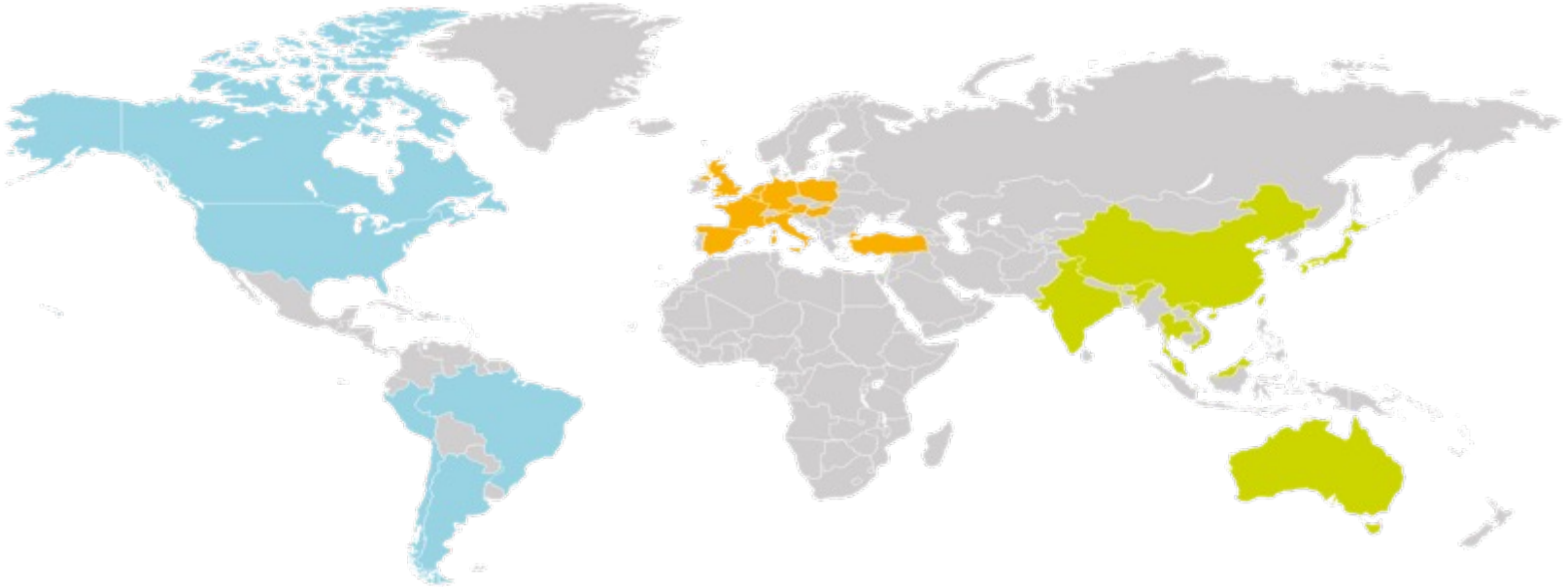
N = 840

R 1:1:1

- Rilve + T-DXd + 5FU / Cape
- Pembro + Trastuzumab + 5FU + FP / CAPOX
- Rilve + T-DXd + FP / CAPOX

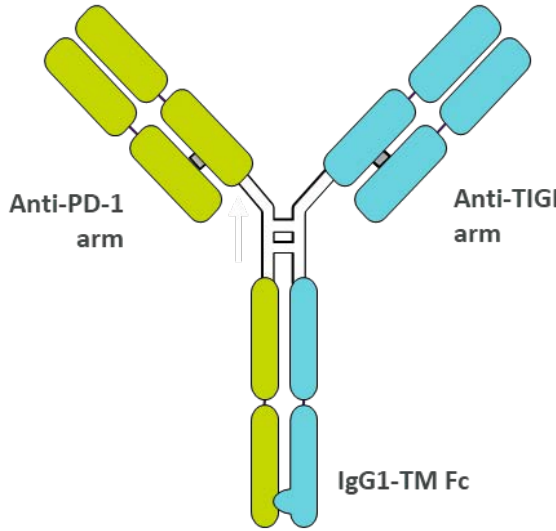
Endpoints

Primary: PFS; OS



Rilvegostomig

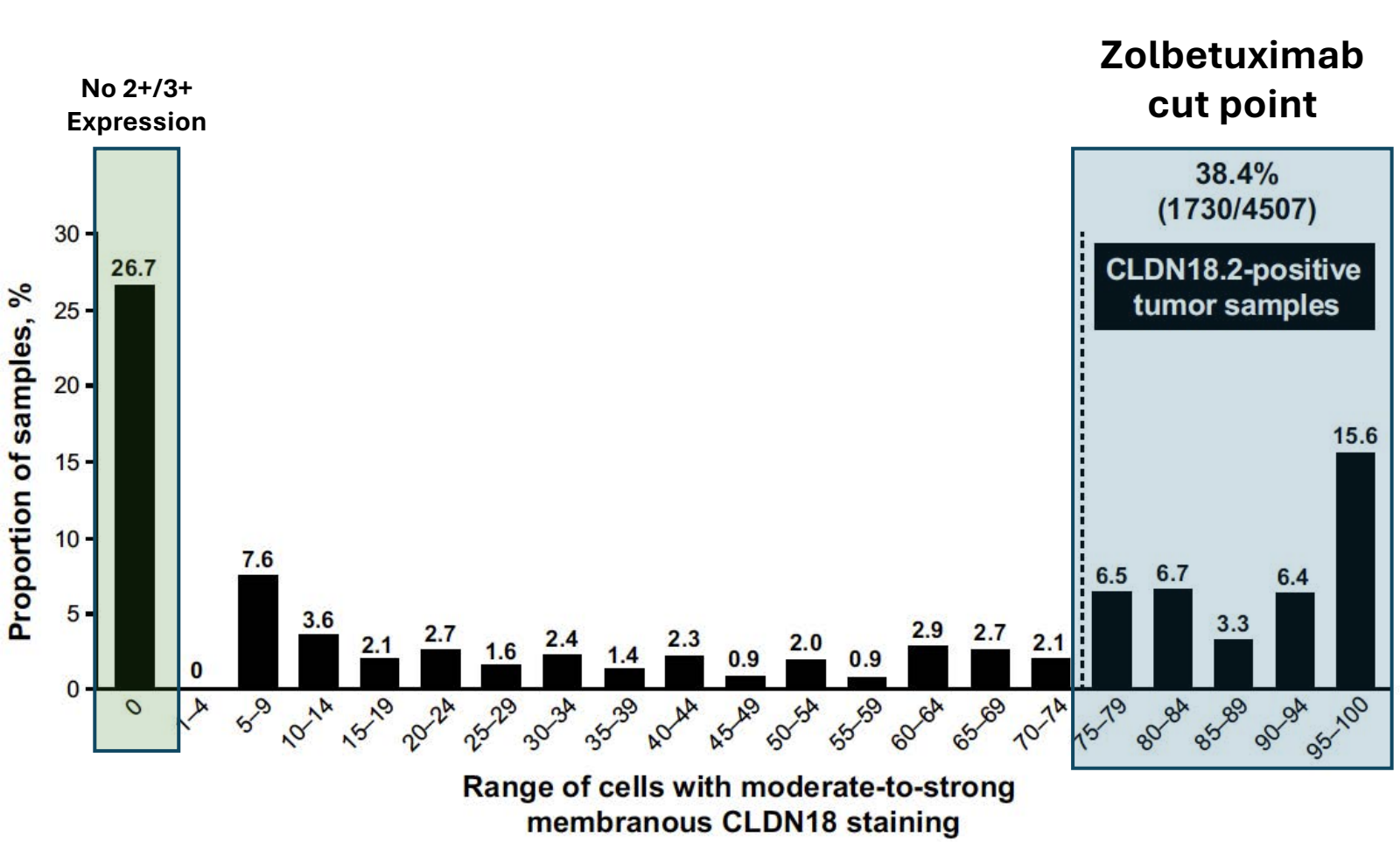
Anti-PD-1 / anti-TIGIT DuetMab[1,2]

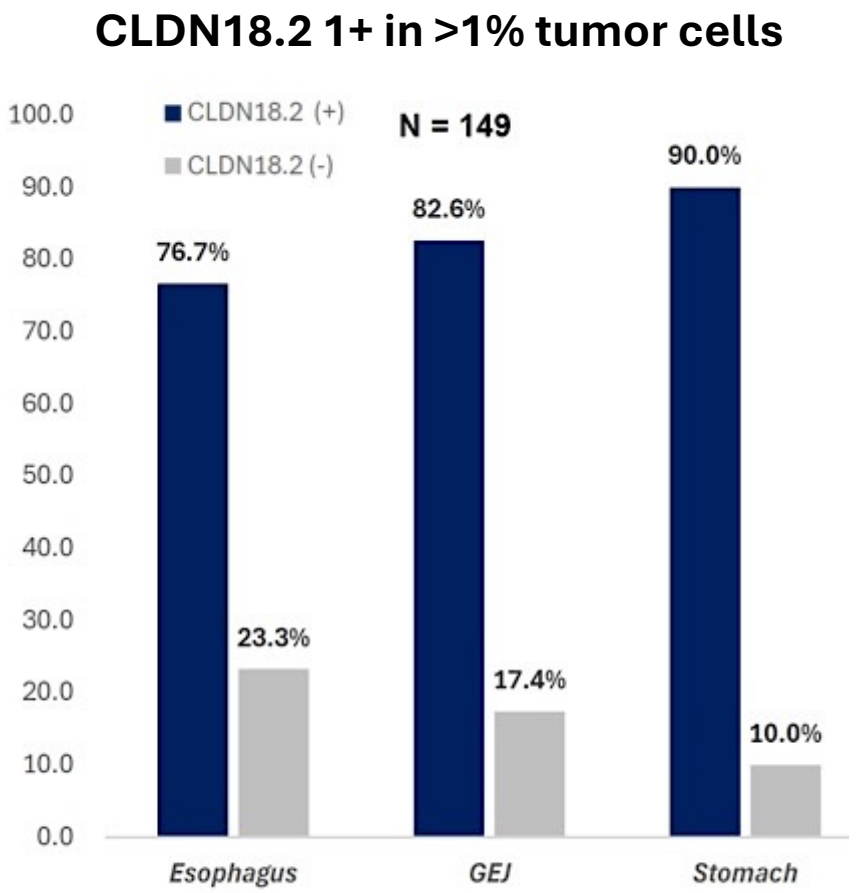


Designed to maximise effect of PD-1 and TIGIT blockade through cooperative binding[1,2]

Shah M, et al. *ASCO-GI* 2026; submitted, NCT06764875

CLDN18.2 Prevalence and Cut Points

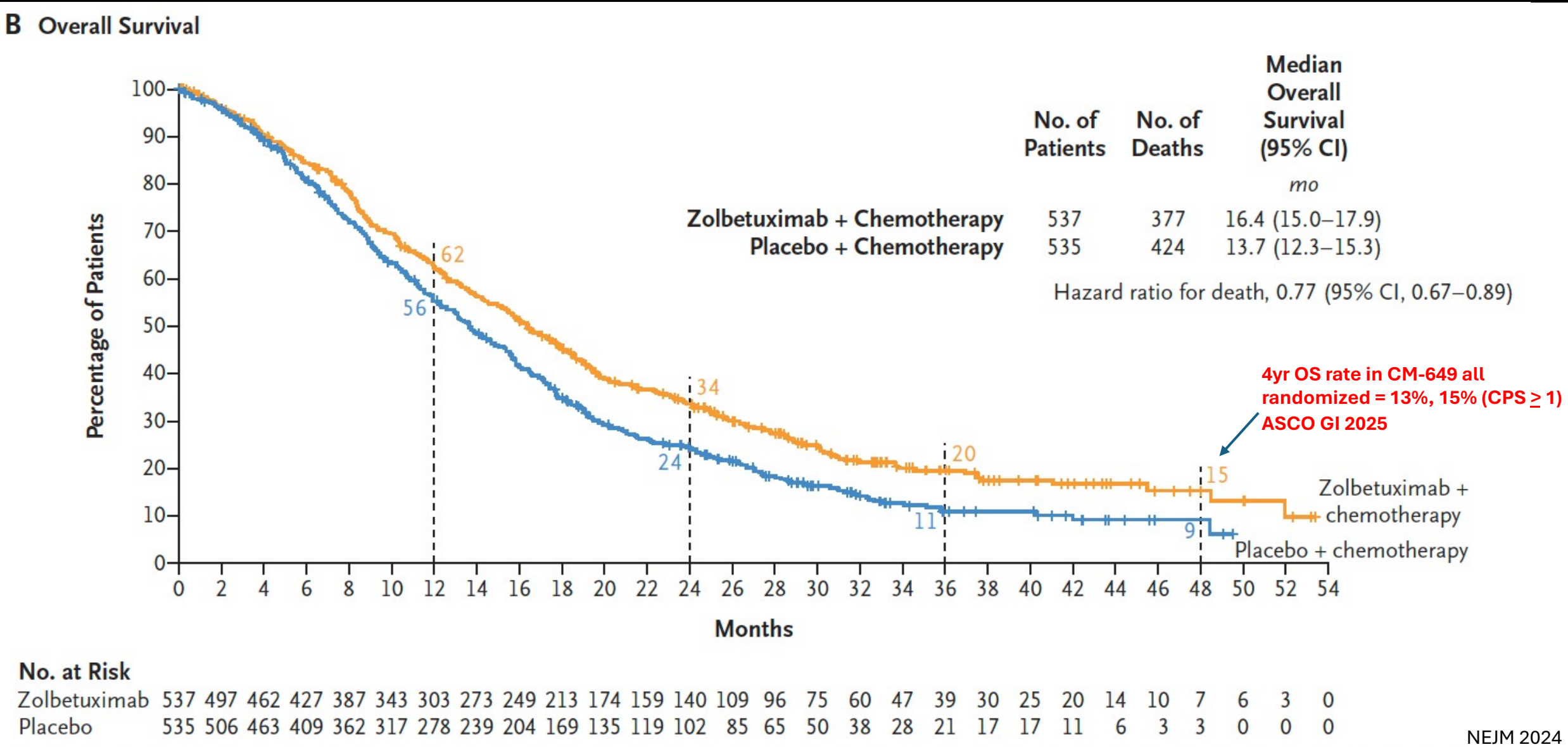




Gastric Cancer 2024, ESMO Open 2024

Maeng C, in revision, ESMO GI

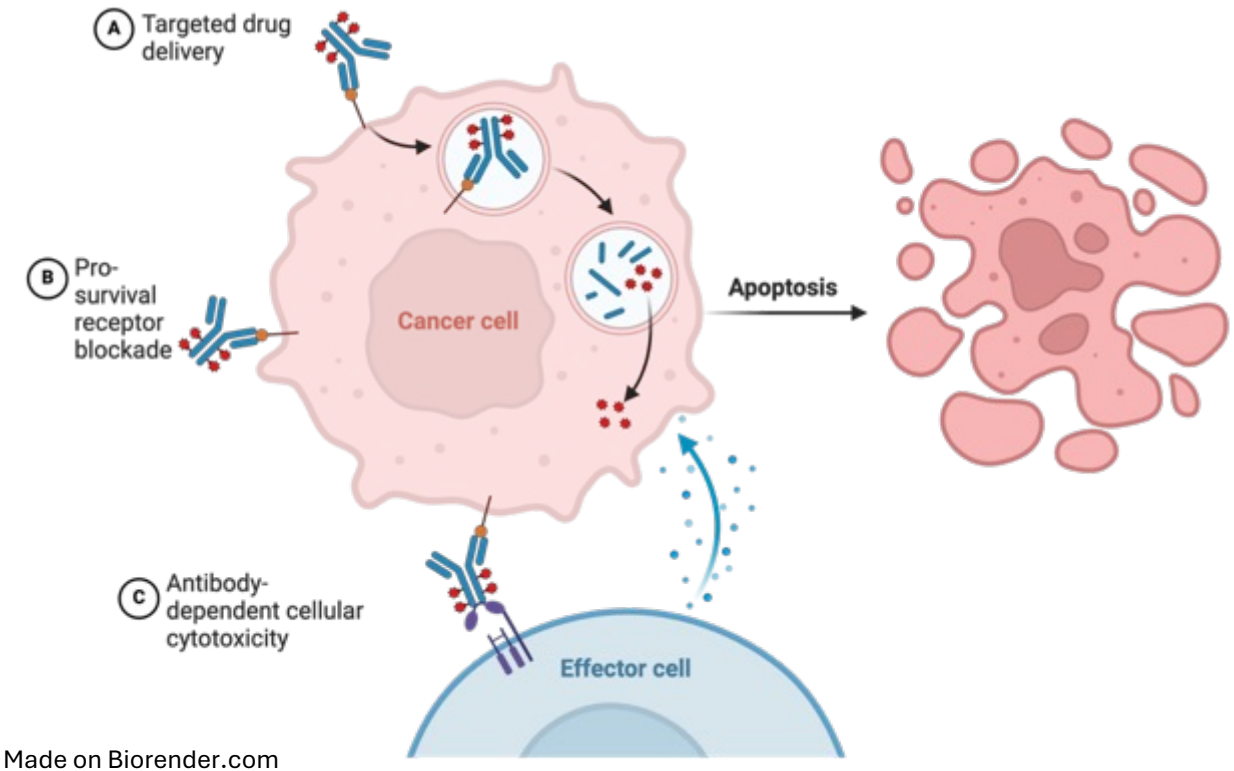
Zolbetuximab in 1L CLDN18.2+ GC/GEJ



NEJM 2024

Expanding Beyond Zolbetuximab

Antibody Drug Conjugates



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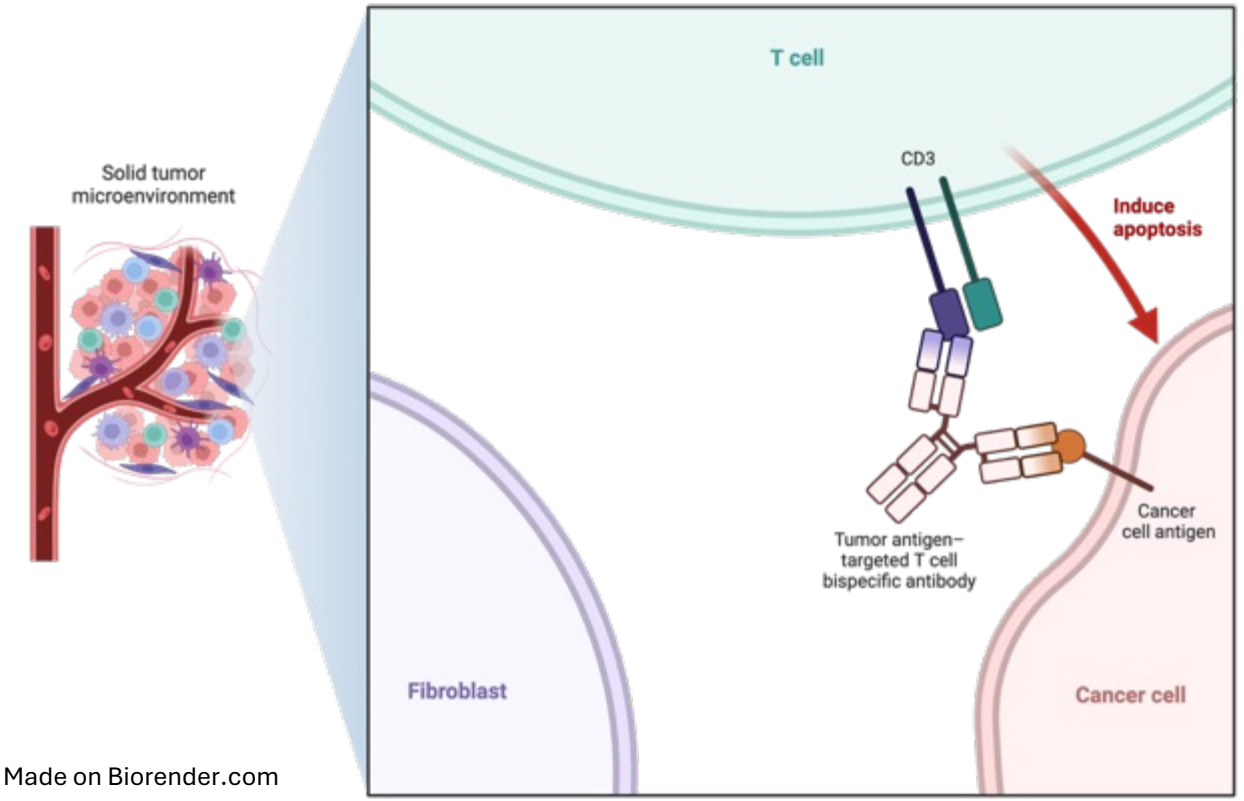
AZD0901 – CLDN18.2 ADC with **MMAE** Payload
EO-3021 – CLDN18.2 ADC with **MMAE** Payload
IBI343 -- CLDN18.2 ADC with **TOPO1** Payload
SHR-A1904 -- CLDN18.2 ADC with **TOPO1** Payload

Bispecific Antibodies and BiTEs

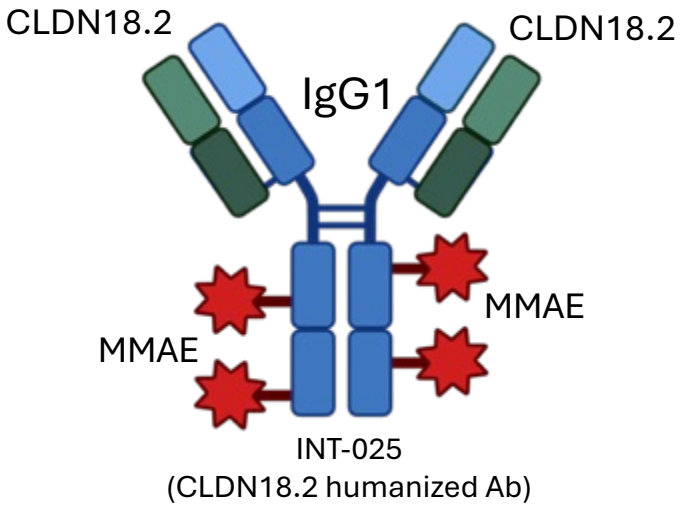


Made on Biorender.com

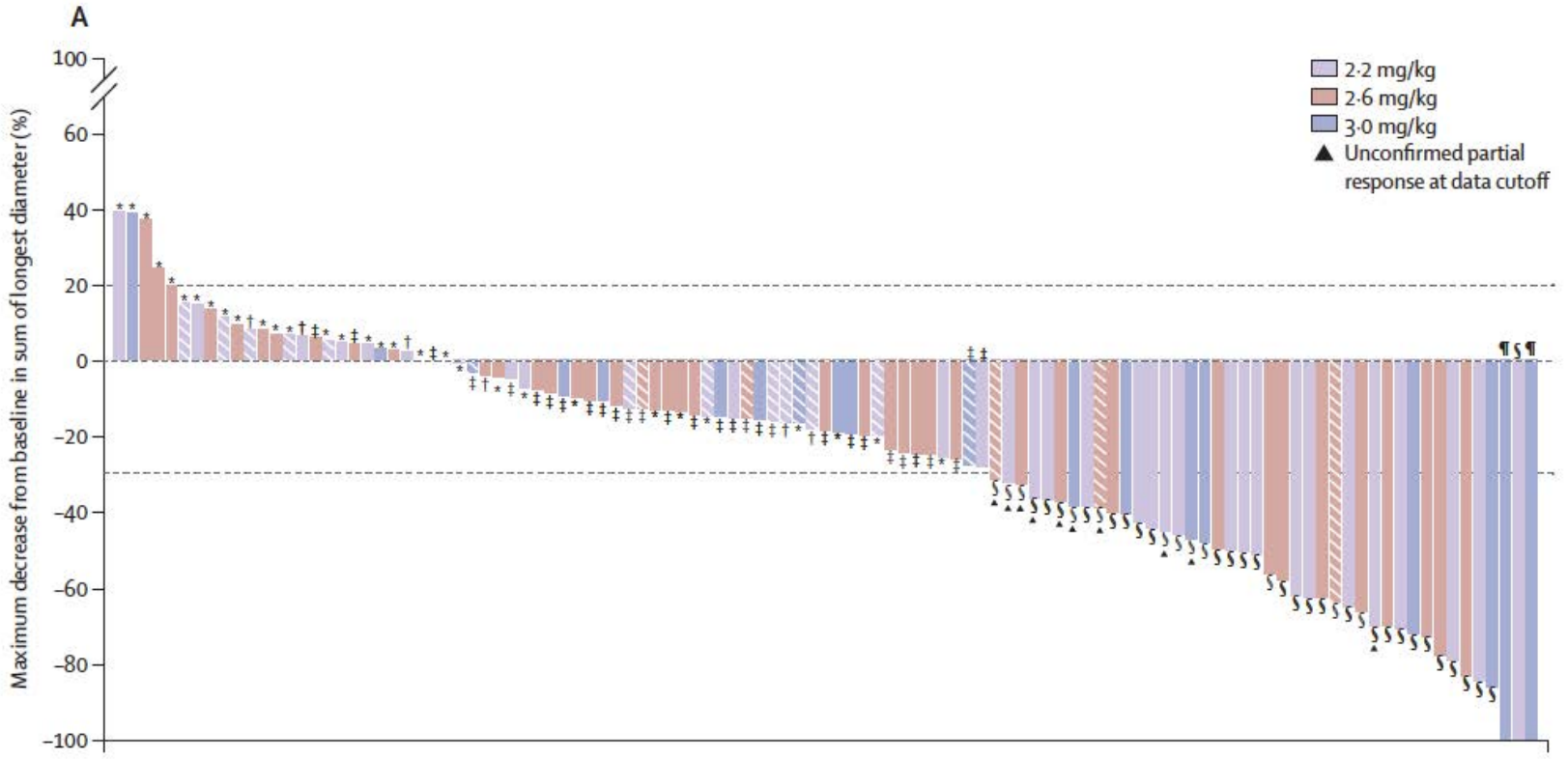
Givastomig – CLDN18.2 x 4-1BB bispecific
PT886 – CLDN18.2 x CD47 bispecific
ASP2138 – CLDN18.2 x CD3 BiTE
AZD5863 -- CLDN18.2 x CD3 BiTE

CLDN18.2 ADC Activity in GC/GEJ: AZD0901

AZD0901 (CMG901, sonesitatug vedotin)



Global phase III 2L+ CLARITY trial examining AZD0901 vs investigator-choice chemotherapy in CLDN18.2+ GC/GEJ is ongoing (NCT06346392)

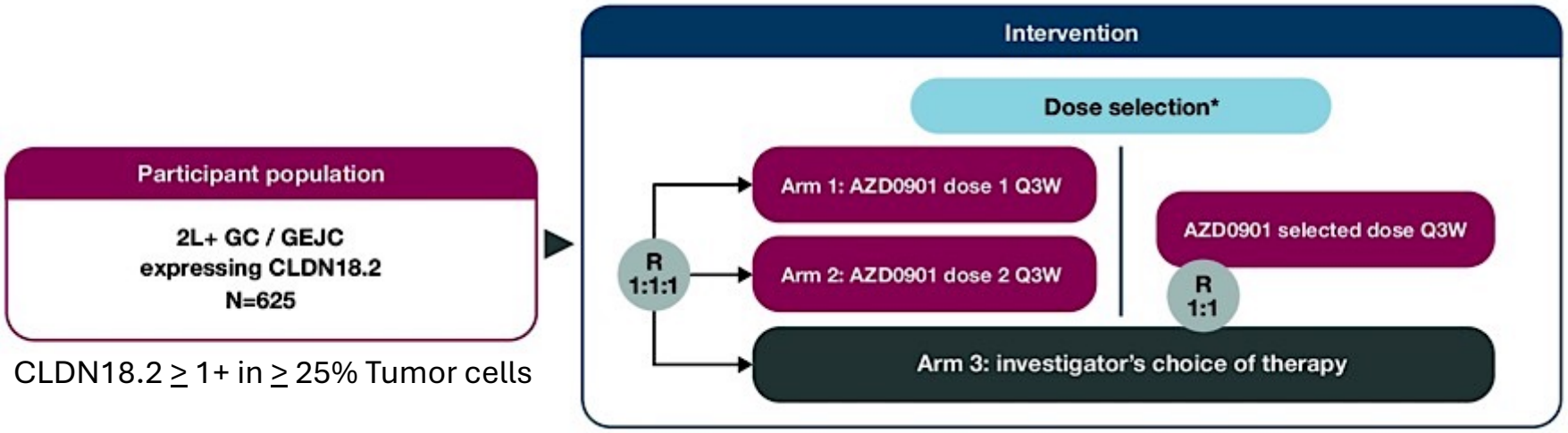


Feature	CLDN18.2-high 2.2mg/kg (n = 32)	CLDN18.2-high 2.6mg/kg (n = 45)	CLDN18.2-high 3.0mg/kg (n = 15)	CLDN18.2-high Total (n = 93)
cORR	47%	22%	38%	33%
mPFS	4.8 months	3.3 months	9.9 months	4.8 months
mOS	11.8 months	11.5 months	11.1 months	11.8 months

CLDN18.2 ≥2+ in 20% tumor cells = CLDN18.2-high

Lancet Oncology 2025

CLARITY-Gastric-01



Investigator's choice of therapy

- 2L: ramucirumab + paclitaxel
- 2L: paclitaxel (for participants with contraindication to ramucirumab only)
- 2L: docetaxel (for participants with contraindication to ramucirumab only)
- 3L+: irinotecan
- 3L+: TAS-102 (except China)
- 3L+: apatinib (China only)

Study endpoints

1°

- Progression-free survival in all randomized participants
- Overall survival in 3L+ participants (all randomized participants who had received ≥2 prior lines of systemic therapy)

2°

- Overall survival in all randomized participants
- Progression-free survival in 3L+ participants
- Overall response rate in both all randomized participants and 3L+ participants
- Duration of response in both all randomized participants and 3L+ participants
- Safety and tolerability
- Pharmacokinetics and immunogenicity

- Efficacy data will be summarized and analyzed in the intent-to-treat population
- All efficacy endpoints will assess the AZD0901 arm (selected dose) versus investigator's choice of therapy arm
- Safety and tolerability will be assessed in all participants who receive at least one dose of study treatment

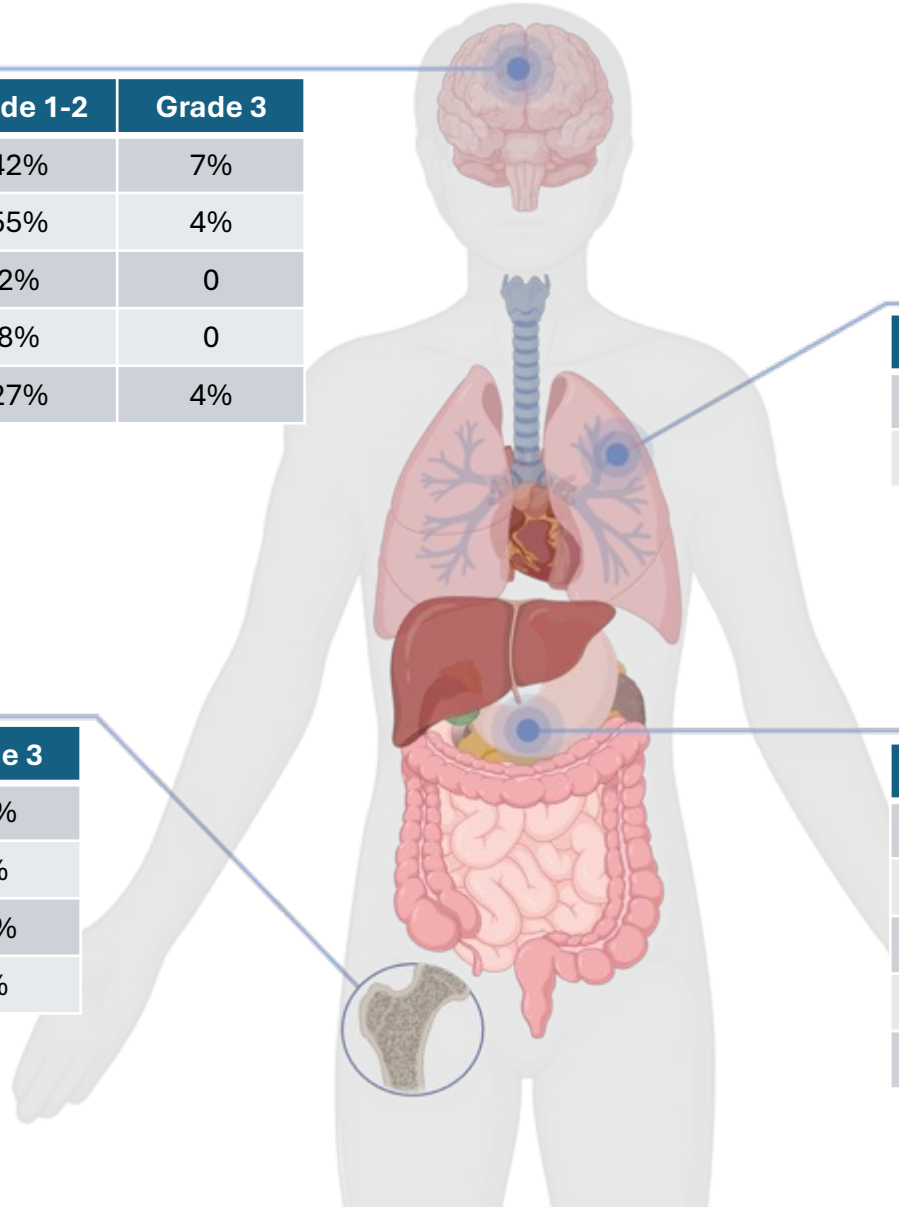
Can we move CLDN18.2 ADC into later line therapy? -- TBD

ASCO GI 2025, TPS507

CLDN18.2 ADC Toxicity in GC/GEJ: AZD0901

General

Toxicity	Grade 1-2	Grade 3
Decr. Appetite	42%	7%
Weight Loss	55%	4%
Fatigue	2%	0
Alopecia	8%	0
Asthenia	27%	4%



Pulmonary

Toxicity	Grade 1-2	Grade 3
Pneumonitis	6%	0
URI	6%	1%

Bone Marrow

Toxicity	Grade 1-2	Grade 3
Anemia	52%	13%
Low PLTs	10%	2%
Neutropenia	33%	16%
Leukopenia	43%	7%

Gastrointestinal

Toxicity	Grade 1-2	Grade 3
Vomiting	46%	10%
Nausea	53%	4%
Diarrhea	19%	1%
Abd. Pain	16%	3%
Constipation	21%	0%

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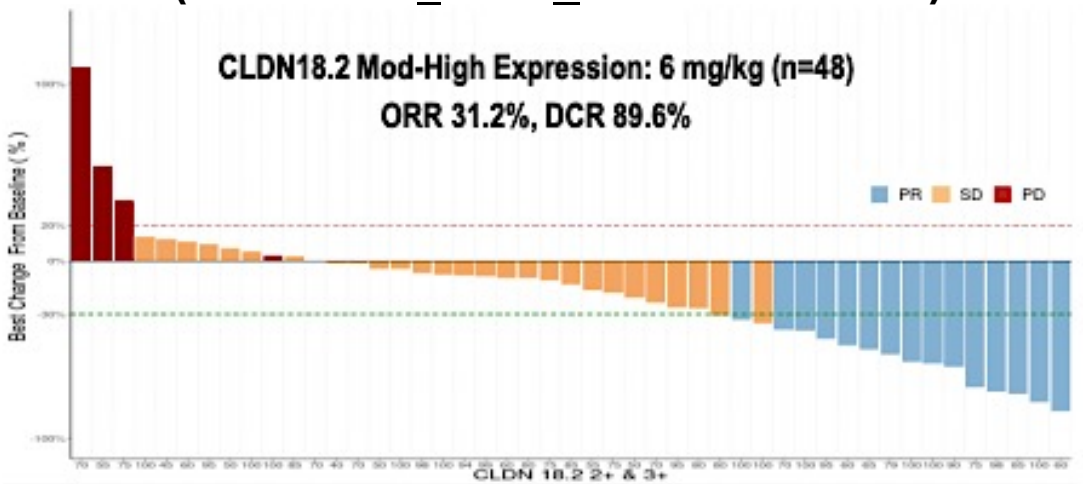
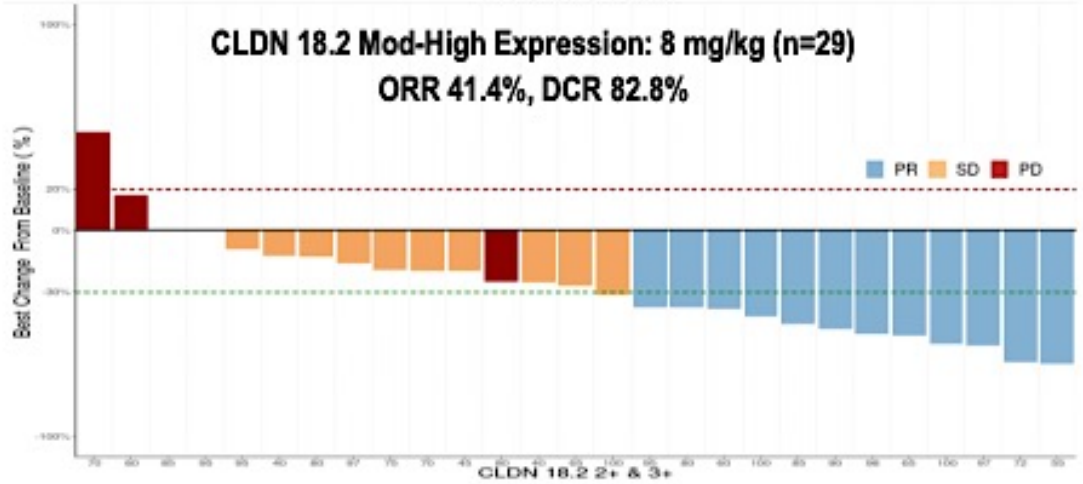
Other CLDN18.2 ADCs: IBI343 and SHR-A1904

IBI343

(CLDN18.2 ≥2+ in ≥40% tumor cells)



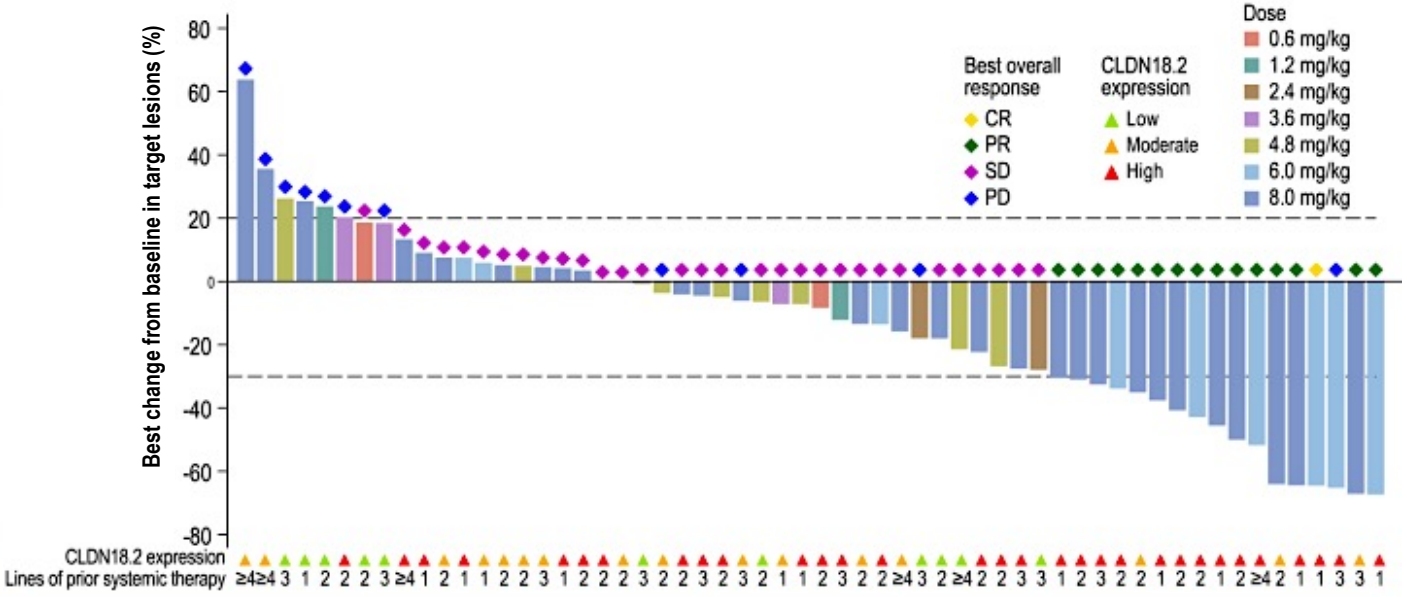


ESMO GI, 6/2024

SHR-A1904

(low = CLDN18.2 ≥1+ in 1-49% tumor cells)

(mod = CLDN18.2 ≥2+ in 50-69% tumor cells)



	6.0 mg/kg (N=9)	8.0 mg/kg (N=30)	All (N=58)
ORR, n (%; 95% CI)	5 (**55.6**; 21.2–86.3)	11 (**36.7**; 19.9–56.1)	16 (27.6; 16.7–40.9)
DCR, n (%; 95% CI)	8 (**88.9**; 51.8–99.7)	26 (**86.7**; 69.3–96.2)	47 (81.0; 68.6–90.1)

ESMO, 9/2024

Other Targets in Advanced GC/GEJ

Target/Mechanism	Approach(s)	Rationale
VEGF	PD-1 x VEGF bispecific, small molecule TKIs	Remodel TME (reduce Treg, MDSC)
YAP/TEAD, FAK	Oral Small molecules	Hippo pathway activation common in GC FAK activation in DGC
Treg depletion	Anti-CCR8	Shift TME balance by depleting inhibitory Tregs
T-cell Stimulating	IL-2 + PD-1, etc	CD8+ T-cell expansion (IL-2) + T-cell reinvigoration (PD-1)
Myeloid Targeting (TLR8, STING, etc.)	Combos with PD-1, combo with ADC	Reprogram TME
EGFR, MET, HER2, CDH17, TAG-72, CEACAM5, etc.	ADCs (bispecific EGFR x MET, etc.), mAb, biparatopic (Zanidatamab)	Targeted ADC payload delivery, improved ADCC/CDC, receptor internalization
Other cellular therapies (TILs, CAR-T, CAR-NK, etc.)	Multiple	Multiple
Personalized neoantigen vaccines	Combo with FLOT, maintenance, etc	Enhance immune recognition

Expert Second Opinion: Current and Future Roles of Immunotherapy and Targeted Therapy in the Management of Advanced Gastroesophageal Cancers

A CME Symposium Held Adjunct to the 2026 ASCO® Gastrointestinal Cancers Symposium

Friday, January 9, 2026

6:00 PM – 8:00 PM PT

Faculty

Jaffer A Ajani, MD

Rutika Mehta, MD, MPH

John Strickler, MD

Moderator

Samuel J Klempner, MD

RTP RESEARCH TO PRACTICE

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