New Therapeutic Approaches for Esophageal and Gastric Cancer

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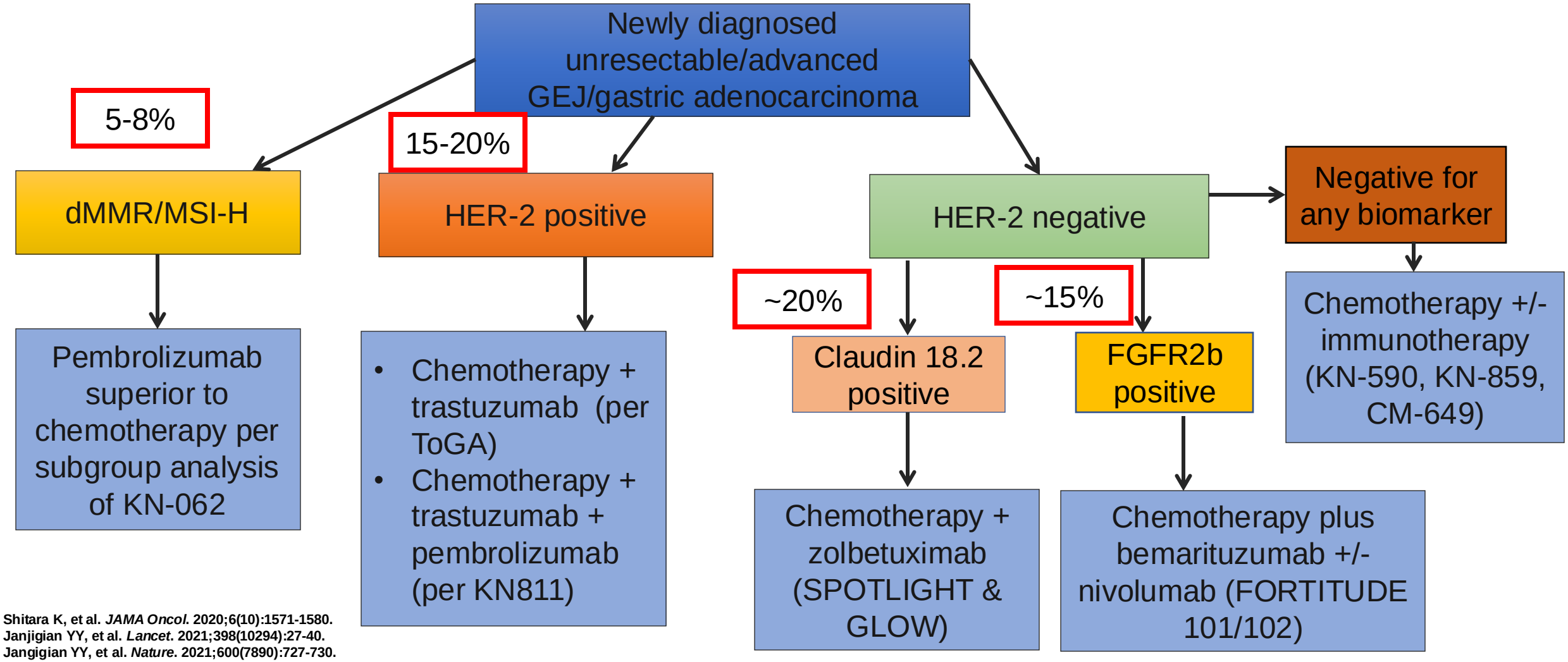
Agenda

- Current state of art of 1st line treatment of gastroesophageal cancers – Old and New developments.
- Discuss 2nd line treatment of gastroesophageal cancers

Key Biomarkers in GI Cancers

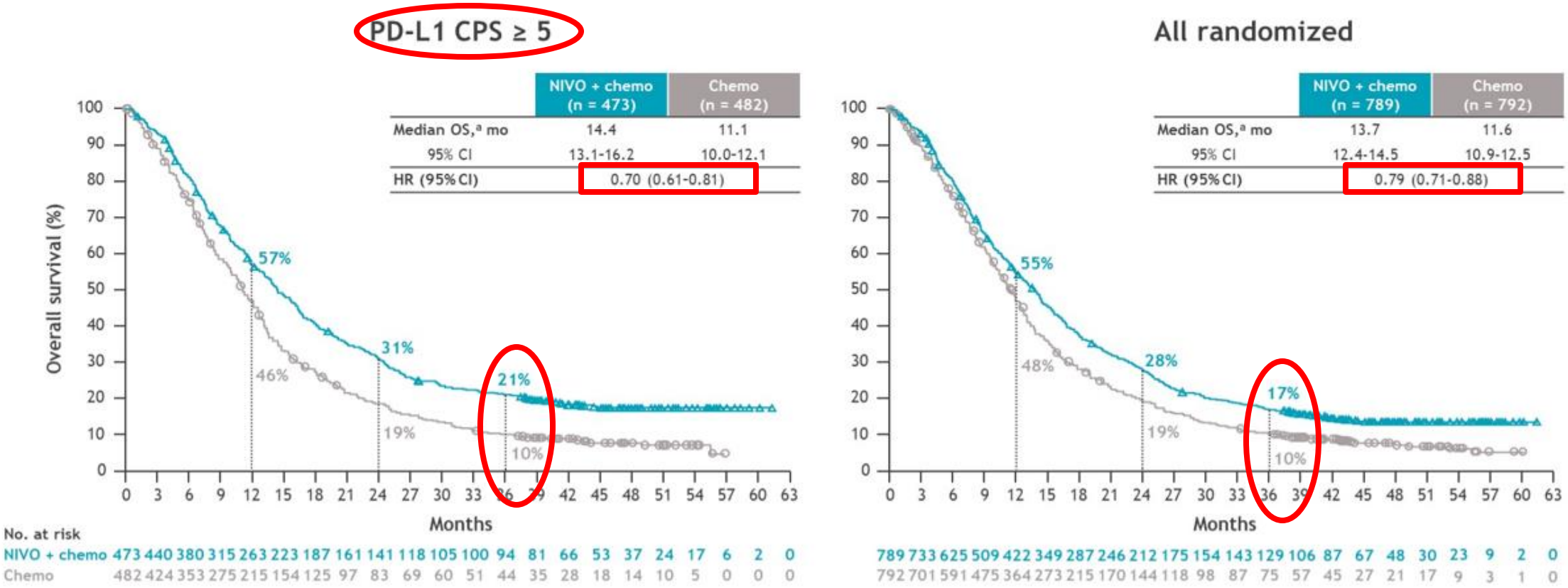
Gastric and Esophageal	Biliary Tract	Pancreatic	Colorectal	Agnostic
MMR/MSI	*FGFR* fusion	*BRCA1/2, PALB2*	MMR/MSI	MMR/MSI
HER2	*IDH*	DNA repair aberrations	*RAS*	Actionable fusion, incl. *NTRK, RET*
PD-L1	HER2	KRAS	*BRAF*	TMB
CLDN 18.2	*BRAF* V600E		HER2	HER2
FGFR2b				*BRAF* V600E

Paradigm of treatment for treatment naïve stage IV GEJ/gastric cancer patients



Shitara K, et al. *JAMA Oncol.* 2020;6(10):1571-1580.
Janjigian YY, et al. *Lancet.* 2021;398(10294):27-40.
Jangigian YY, et al. *Nature.* 2021;600(7890):727-730.
Sun JM, et al. The Lancet. 2021; 398(10302): 759-771

CheckMate-649: Overall Survival at 36 Months



- Clinically meaningful improvement in OS with NIVO + chemo vs chemo was maintained with longer follow-up in PD-L1 CPS ≥ 5 and all randomized populations

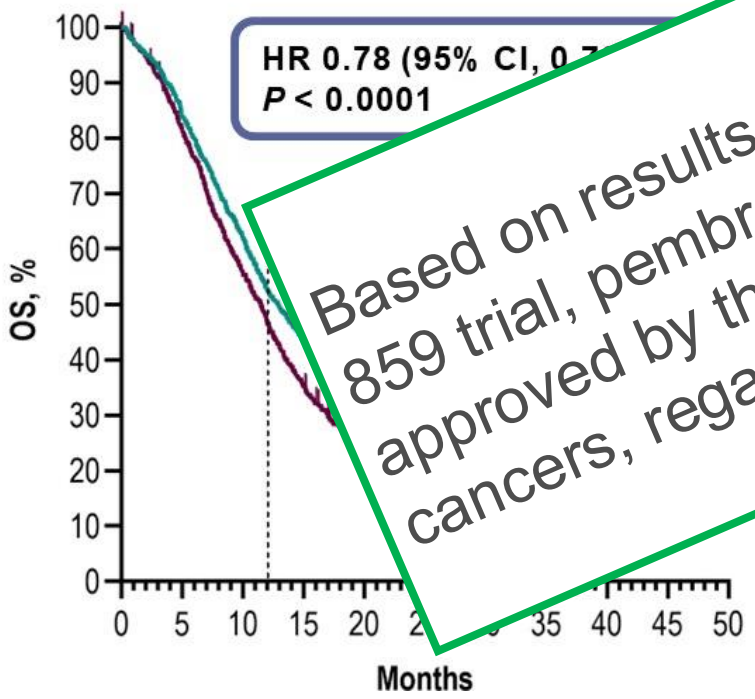
[a]Minimum follow-up, 36.2 months.

- Janjigian, Y., et al. GI ASCO (2023).

KEYNOTE-859 Primary Endpoint: Overall Survival

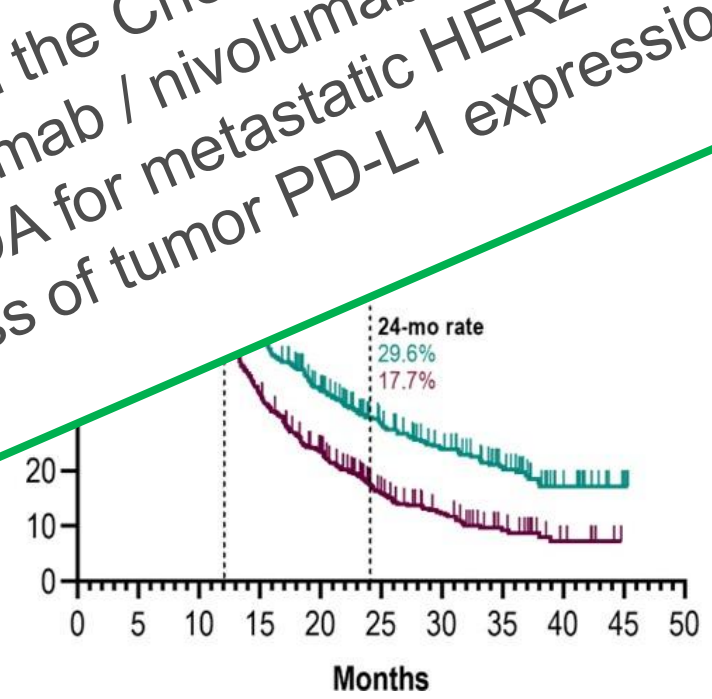
Overall

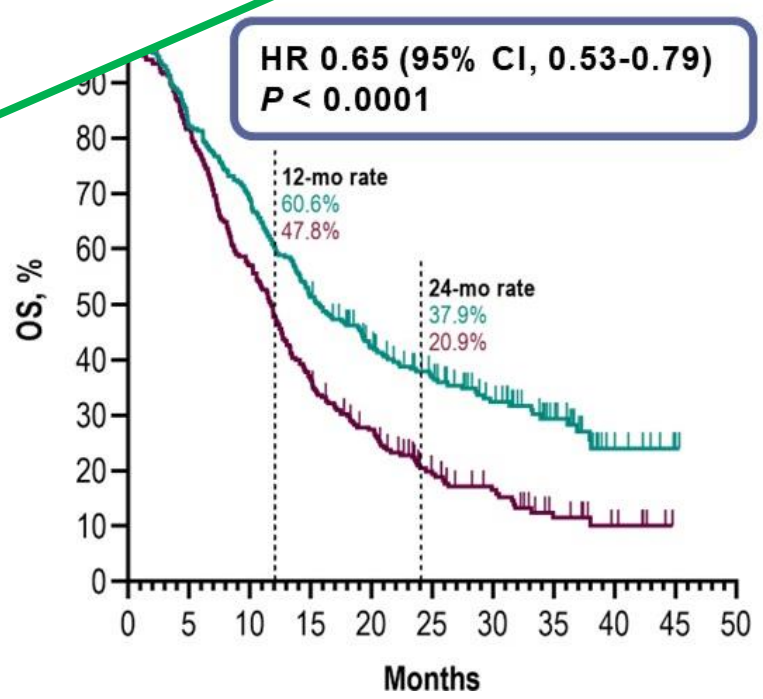
	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	76.3%	12.9 (11.9-14.0)
Placebo + chemo	84.4%	11.5 (10.6-12.1)



PD-L1 CPS ≥10

	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	4%	15.7 (13.8-19.3)
Placebo + chemo	%	11.8 (10.3-12.7)





Based on results from the CheckMate-649 and KEYNOTE-859 trial, pembrolizumab / nivolumab with chemotherapy was approved by the FDA for metastatic HER2-negative G/GEJ cancers, regardless of tumor PD-L1 expression

Pembro, pembrolizumab.

Rha ST, et al. *Ann Oncol*. 2023;34:319-20; Rha SY, et al. ASCO 2023. Abstract 4014.

FDA ODAC Finds Limited Benefit for Checkpoint Inhibitors in Low PD-L1 Gastric Cancer (09/26/24)

In a 2 to 10 vote, the FDA's Oncologic Drug Advisory Committee (ODAC) voted that the risk-benefit assessment is not favorable for the use of checkpoint inhibitors (CPIs) in first-line advanced HER2-negative gastric and gastroesophageal junction (GEJ) adenocarcinoma in patients with PD-L1 expression less than 1

RATIONALE-305: Study Design

Randomized, double-blind, global phase 3 study investigating Tislelizumab (anti-PD-1 mAb)

Key eligibility criteria:

- Histologically confirmed GC/GEJC
- Exclude patients with HER2-positive tumors
- No previous therapy for unresectable, locally advanced or metastatic GC/GEJC

R 1:1

Initial up to 6 treatment cycles[a]

TIS 200 mg IV Q3W + chemo (XELOX or FP)

Maintenance treatment until unacceptable toxicity or disease progression

Placebo IV Q3W + chemo (XELOX or FP)

Primary endpoints

OS in PD-L1+ (PD-L1 TAP score ≥5%) and ITT analysis set

Secondary endpoints[c]

PFS, ORR, DoR, Safety

Stratification

- Region of enrollment
- Peritoneal metastasis
- PD-L1 expression (PD-L1 ≥5% vs <5%)
- Investigator's choice of chemo

Correa MC, et al. ESMO 2024

PD-L1 as a Biomarker in Gastric/GEJ Cancers

- The PD-L1 **Tumor Area Positivity (TAP)** score is a newly developed scoring system evaluating both immune and tumour cells. The TAP score has been analytically developed and validated for advanced GC/GEJC in the RATIONALE-305 study

Scoring methods comparison between TAP Score and CPS

- PD-L1 expression was assessed prospectively by central laboratory using the TAP score, stained by the VENTANA PD-L1 (SP263) assay
- For exploratory purposes, pathologists in the central laboratory scored the same stained samples according to CPS[a]

	TAP Score (%)	CPS
Score Formula	$\frac{\text{Area occupied by PD-L1 staining tumour cells and immune cells}}{\text{Tumour area}} \times 100\%$	$\frac{\text{\# PD-L1 staining tumour cells and immune cells}}{\text{Total \# viable tumour cells}} \times 100\%$
Cell Types Included in PD-L1 Score	• Tumour cells • Immune cells (including lymphocytes, macrophages, histiocytes, reticular dendritic cells, plasma cells, and neutrophils)	• Tumour cells • Immune cells (including lymphocytes and macrophages)
Scoring Method	• Visual-based estimation on tumour area	• Cell count (time consuming)

Moehler, M et al. ESMO GI 2024

RATIONALE-305: Efficacy Outcomes at 3-year Follow-up

Dec 27 2024 The FDA has approved tislelizumab-jsgr in combination with platinum- and fluoropyrimidine-based chemotherapy for the first-line treatment of patients with unresectable or metastatic, HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (≥1)

Table 1. Efficacy Ou

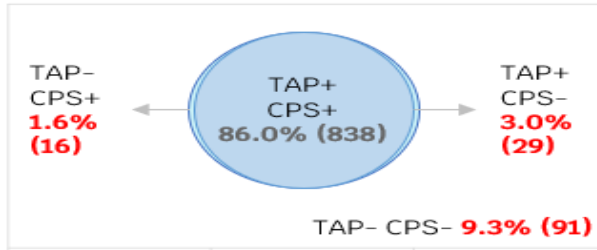
Median OS, m		
HR		
		13.4 (10.5, 16.6)
	, 7.2)	6.2 (5.6, 6.9)
	0.79 (0.68, 0.91)	
	15.0 (11.6, 18.8)	7.5 (5.1, 10.5)
	47.3 (42.9, 51.8)	40.5 (36.2, 45.0)
sponders), mo (95% CI)	8.6 (7.9, 11.1)	7.2 (6.0, 8.5)
esponse at 36 mo, % (95% CI)	24.5 (18.8, 30.6)	14.4 (9.3, 20.5)

Correa MC, et al. ESMO 2024

Substantial Concordance for TAP Score and CPS in Advanced GC/GEJC

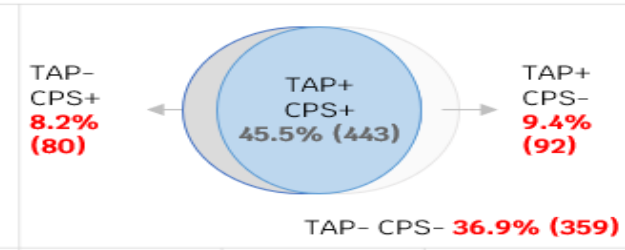
- Good correlation was observed between TAP score and CPS based on interclass correlation coefficient (ICC=0.81 [0.79, 0.83])
- TAP score and CPS showed substantial concordance in terms of overall percent agreement (OPA) and Cohen's Kappa at matched thresholds for each score (OPA [95% CI]: 95% [94, 97] 82% [80,85], and 85% [83,87] at 1%, 5%, and 10% thresholds of each score, respectively)

TAP score 1% vs CPS 1



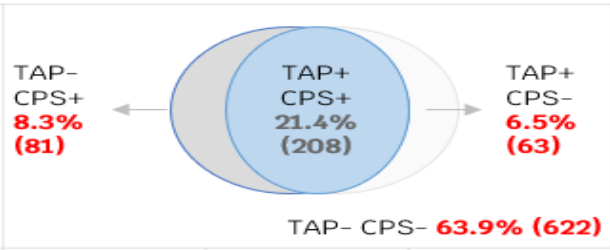
	n/N	Agreement
PPA, % (95% CI)	838/854	98 (97, 99)
NPA, % (95% CI)	91/120	76 (68, 83)
OPA, % (95% CI)	929/974	**95 (94, 97)**
Cohen's Kappa (95% CI)	0.78 (0.71, 0.84)	

TAP score 5% vs CPS 5



	n/N	Agreement
PPA, % (95% CI)	443/523	85 (81, 88)
NPA, % (95% CI)	359/451	80 (76, 83)
OPA, % (95% CI)	802/974	**82 (80, 85)**
Cohen's Kappa (95% CI)	0.64 (0.60, 0.69)	

TAP score 10% vs CPS 10



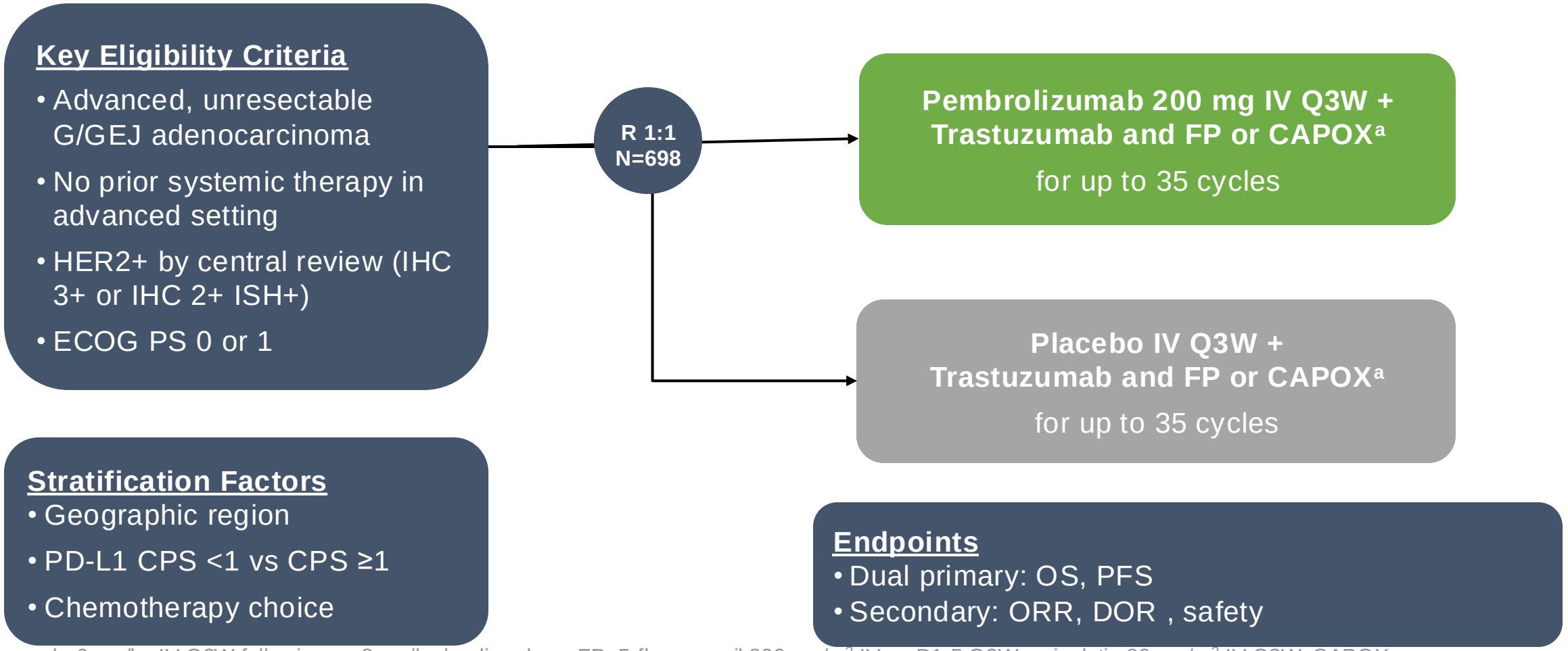
	n/N	Agreement
PPA, % (95% CI)	208/289	72 (66, 77)
NPA, % (95% CI)	622/685	91 (89, 93)
OPA, % (95% CI)	830/974	**85 (83, 87)**
Cohen's Kappa (95% CI)	0.64 (0.59 , 0.69)	

Strength of Agreement (Kappa)

Sight (0.01 – 0.20)	Fair (0.21 – 0.40)	Moderate (0.41 – 0.60)	Substantial (0.61 – 0.80)	Almost perfect (0.81 – 1.0)

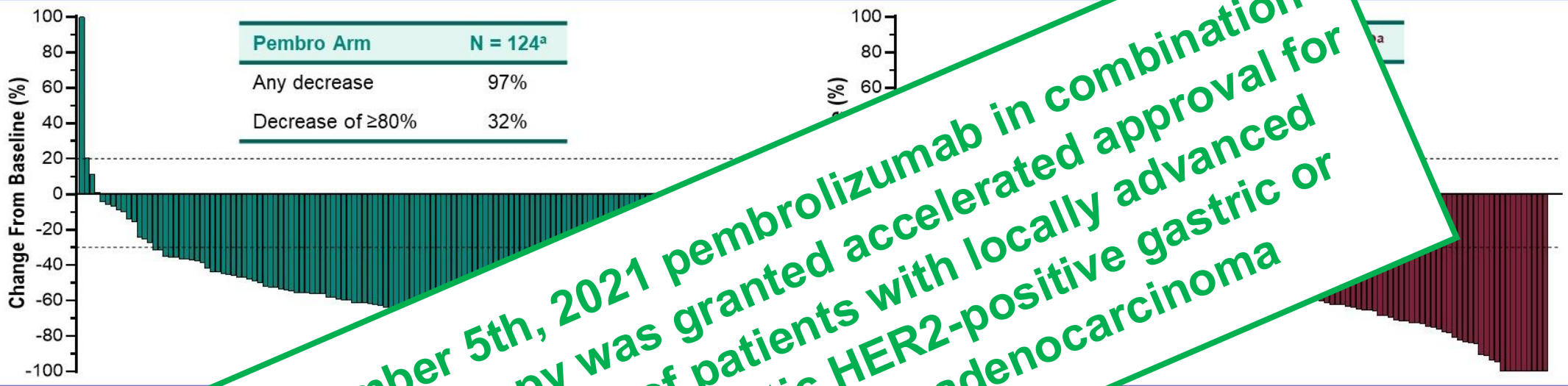
Moehler, M et al. ESMO GI 2024

KEYNOTE-811 Study Design (NCT03615326)
Phase 3 Randomized, Placebo-Controlled



[a]Trastuzumab: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m2 IV Q3W. PFS, ORR, DOR per RECIST by BICR.
BICR, blinded independent central review; CPS, combined positive score; PD-L1, programmed death ligand 1.
Janjigian YY, et al. ESMO 2023. Abstract 15110.

KEYNOTE 811: Interim Analysis Results



On November 5th, 2021 pembrolizumab in combination with chemotherapy was granted accelerated approval for first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma

ORR and DC % (95% CI)		Placebo Arm (N = 131)
ORR	**15 (11%)**	**4 (3%)**
	84 (63%)	**64 (49%)**
ORR difference[b]		
SD	29 (22%)	49 (37%)
PD	5 (4%)	7 (5%)
DCR	89.3% (91.4-98.8)	89.3% (82.7-94.0)
Not evaluable	0	2 (2%)
Not assessed	0	5 (4%)

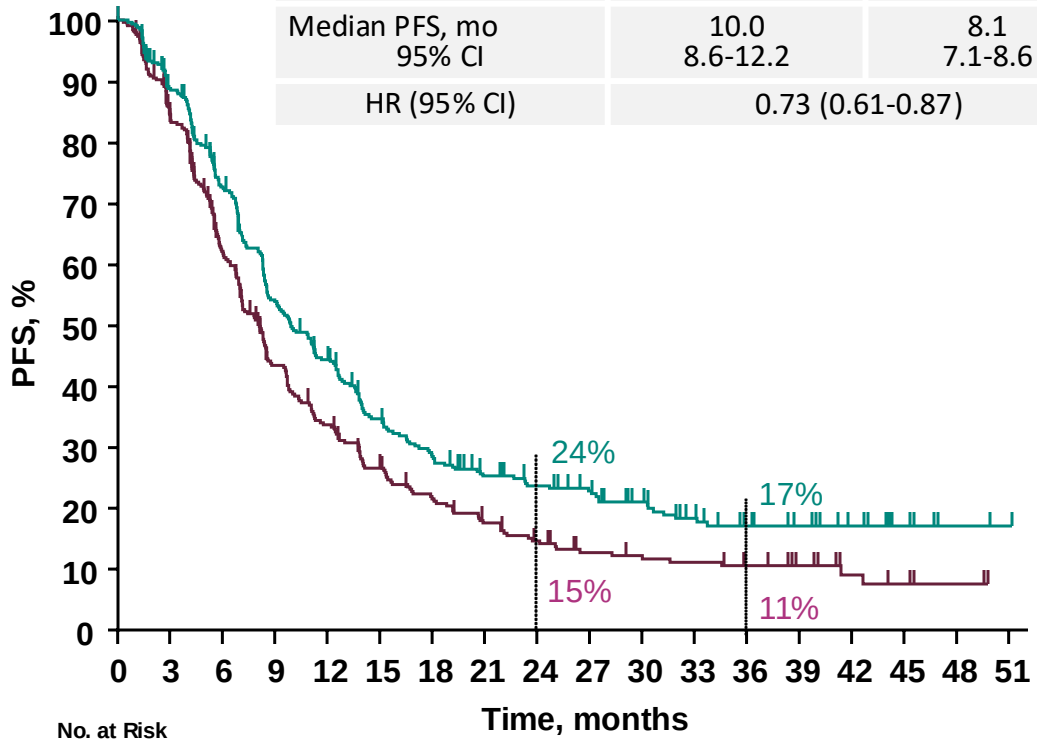
Duration of Response[c]	Pembro Arm (N = 99)	Placebo Arm (N = 68)
Median[d]	10.6 mo	9.5 mo
Range	1.1+ to 16.5+	1.4+ to 15.4+
≥6-mo duration[d]	70.3%	61.4%
≥9-mo duration[d]	58.4%	51.1%

Jangigian YY, et al. *J Clin Oncol*. 2021;39(15_suppl.):4013. Jangigian YY, et al. *Nature*. 2021;600(7890):727-730.

Progression-Free Survival at 38.5 Months of Follow-Up[a] RECIST V1.1, BICR

All patients

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

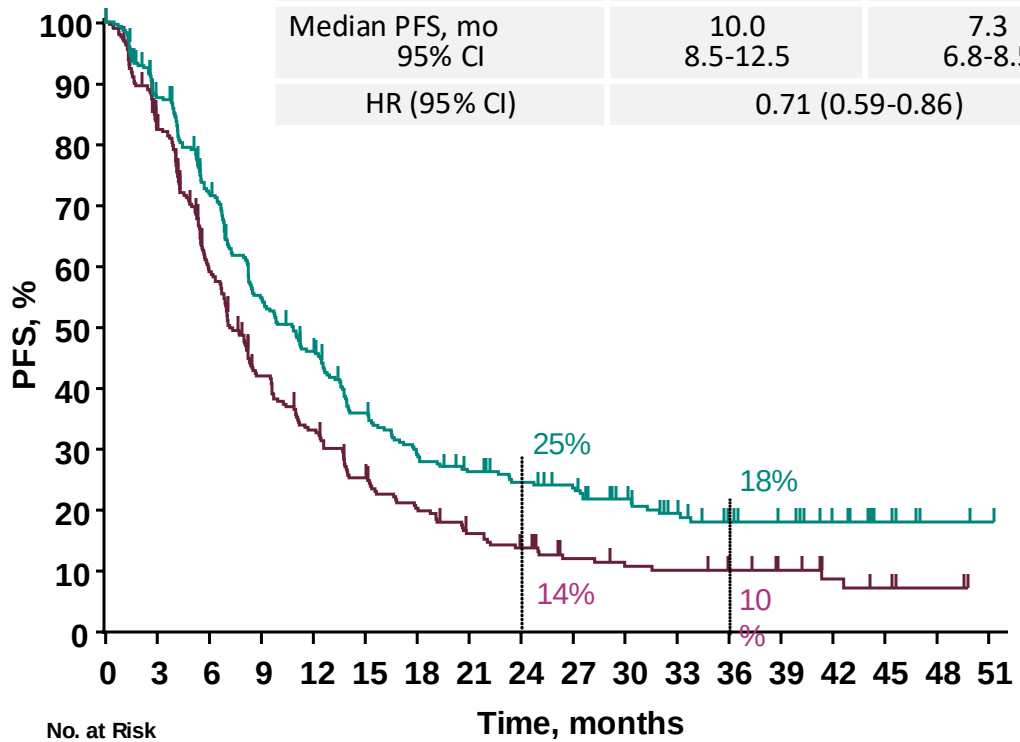


No. at Risk

Pembrolizumab gp	350	296	234	173	139	102	84	67	59	53	41	31	24	20	14	6	2	1
Placebo gp	348	274	184	121	93	71	55	43	34	25	23	21	17	11	6	4	2	0

PD-L1 CPS ≥1[b]

	Pembrolizuab	Placebo
Median PFS, mo 95% CI	10.0 8.5-12.5	7.3 6.8-8.5
HR (95% CI)	0.71 (0.59-0.86)	



No. at Risk

Pembrolizumab gp	298	250	200	151	123	91	74	63	56	51	39	30	23	20	14	6	2	1
Placebo gp	296	231	152	100	78	58	45	34	28	20	18	16	14	10	6	4	2	0

Data cut-off: March 29, 2023.

aMedian follow-up; bNot a prespecified endpoint.

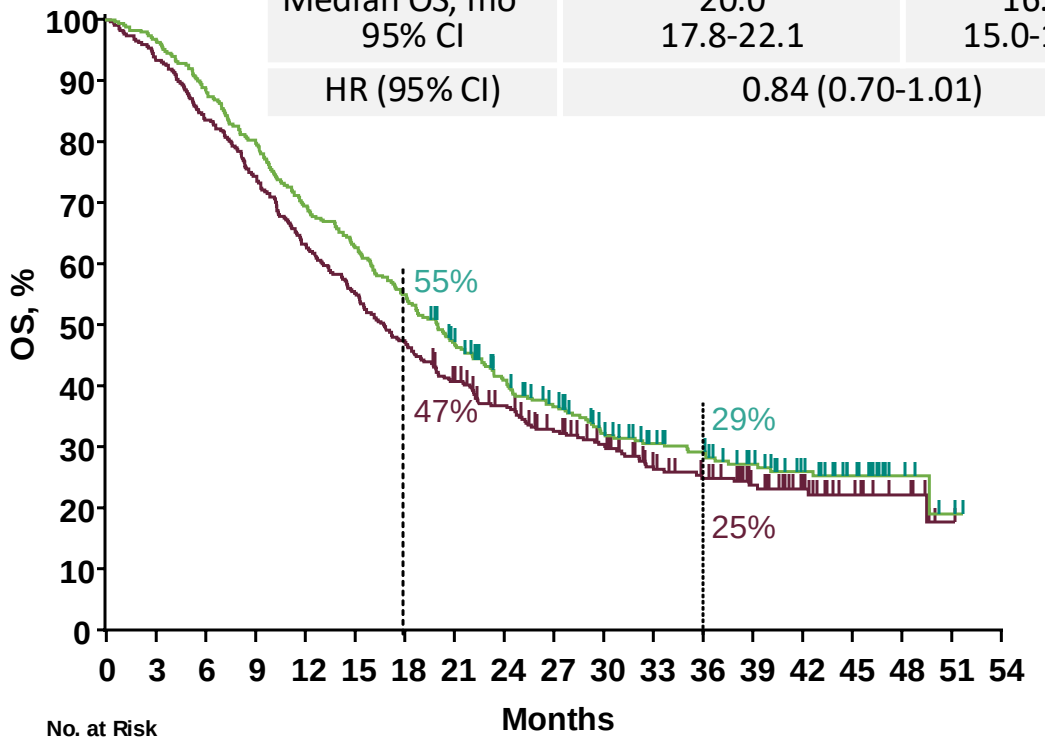
BICR, blinded independent central review; CI, confidence interval; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumors.

Janjigian YY, et al. ESMO 2023. Abstract 15110.

Overall Survival at the Third Interim Analysis

All patients

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

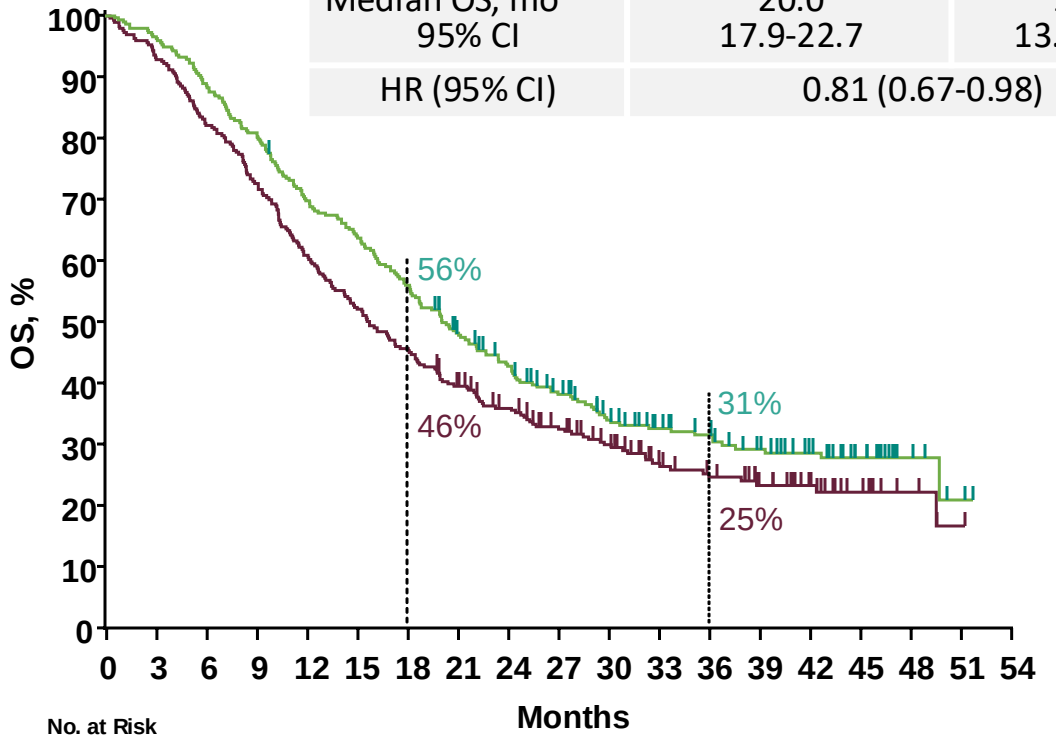


No. at Risk

Pembrolizumab gp	350	339	311	281	243	220	192	156	126	105	84	69	61	48	37	23	7	2	0
Placebo gp	348	327	292	259	220	193	165	138	116	96	83	58	51	37	25	15	8	1	0

PD-L1 CPS ≥1[a]

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



No. at Risk

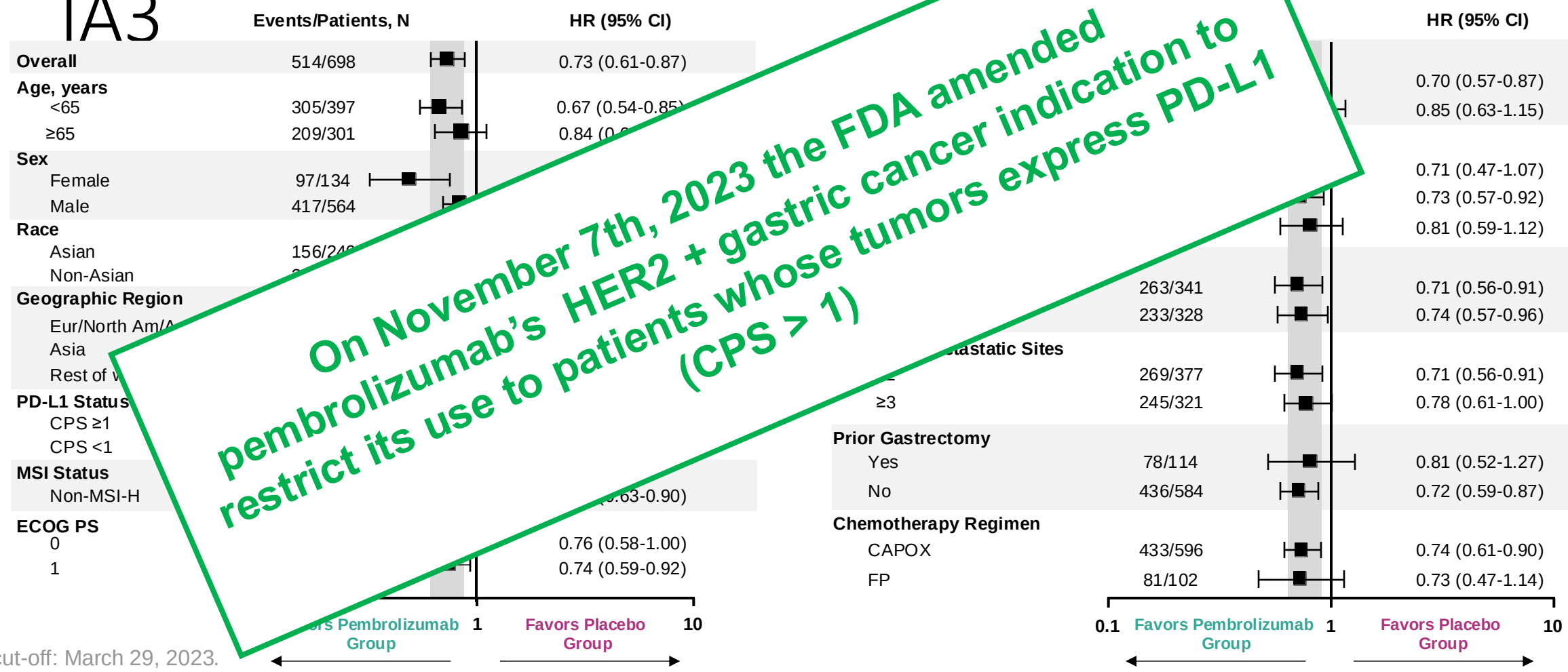
Pembrolizumab gp	298	288	265	241	207	190	166	136	115	96	78	64	58	47	37	23	7	2	0
Placebo gp	296	277	244	215	180	155	135	113	96	80	67	47	41	31	21	12	5	1	0

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

[a]Not a prespecified endpoint.

Janjigian YY, et al. ESMO 2023. Abstract 15110.

Progression-Free Survival in Key S roups at IA3

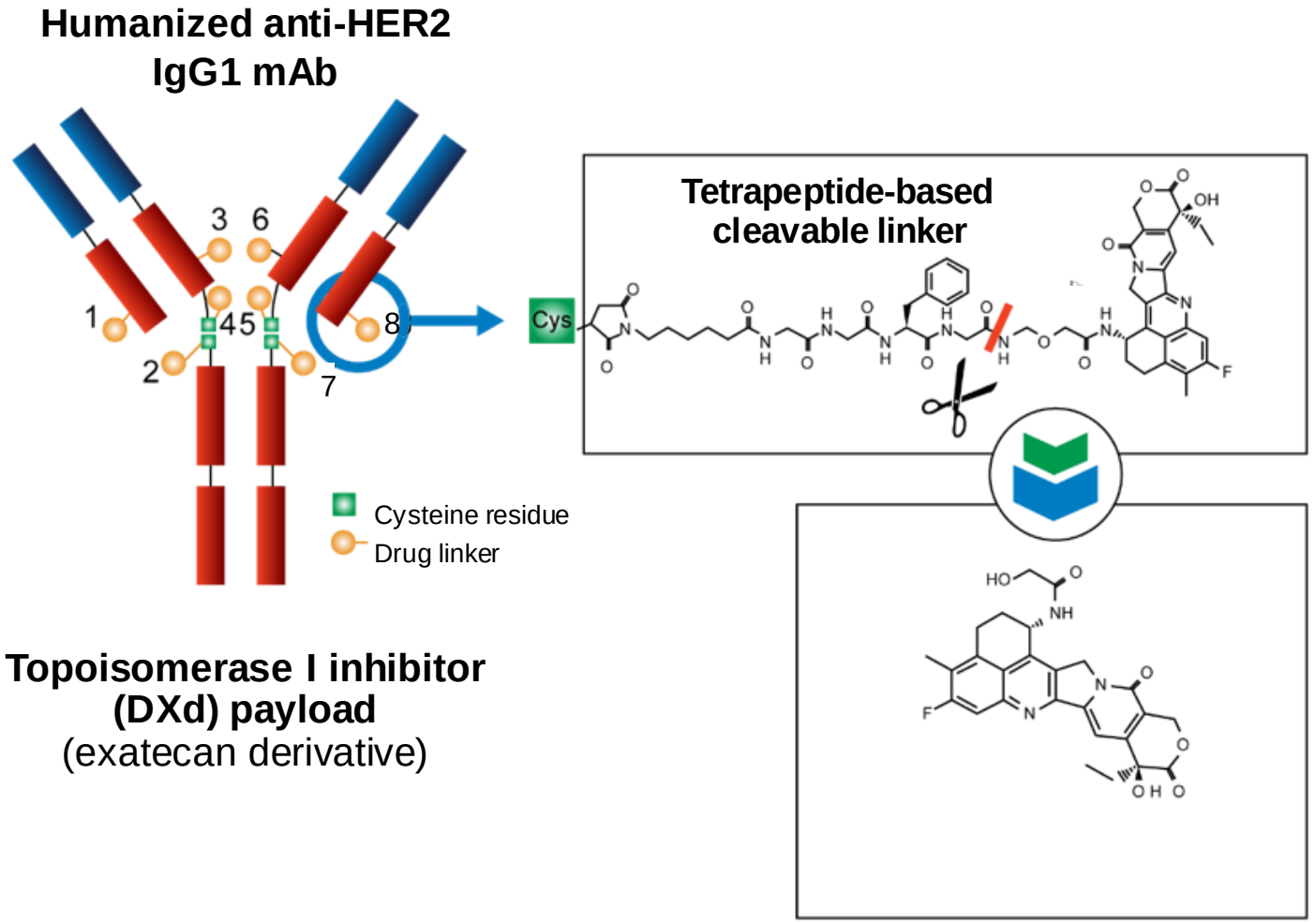


On November 7th, 2023 the FDA amended pembrolizumab's HER2 + gastric cancer indication to restrict its use to patients whose tumors express PD-L1 (CPS > 1)

Data cut-off: March 29, 2023.
CAPOX, oxaliplatin + capecitabine; ECOG, Eastern Cooperative Oncology Group; FP, 5-fluorouracil + cisplatin; MSI, microsatellite instability; PS, performance status.
Janjigian YY, et al. ESMO 2023. Abstract 15110.

Trastuzumab deruxtecan Is a Novel ADC Designed to Deliver an Antitumor Effect[1-3]

- Antibody–drug conjugate of trastuzumab with a topoisomerase inhibitor
- Potential advantages
  - High potency payload
  - High ratio of trastuzumab to payload molecules
  - "Bystander" effect

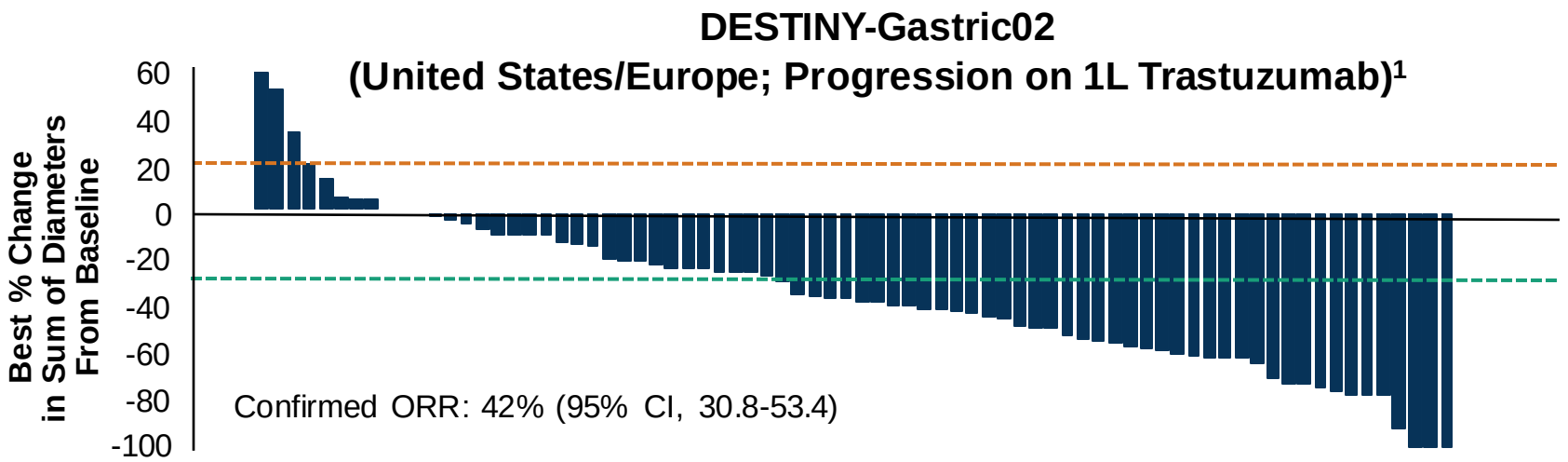


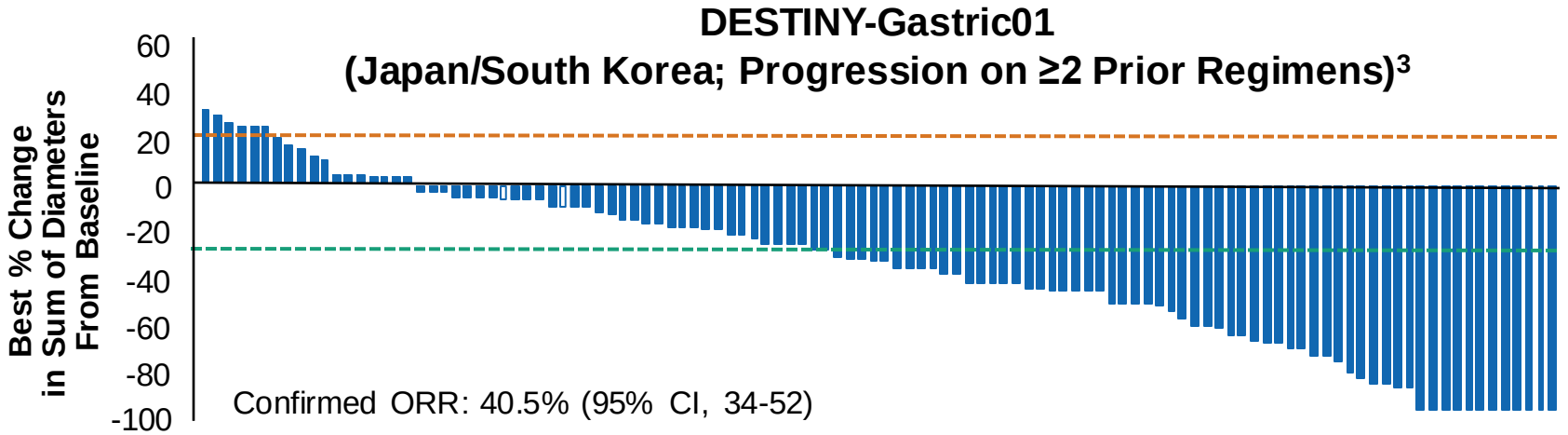
1. Nakada T et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-185. 2. Trail P et al. *Pharmacol Ther.* 2018;181:126-142.
3. Ogitani O et al. *Cancer Sci*. 2016;107:1039-1046.

DESTINY-Gastric01 and 02

Efficacy[1, 2]	T-DXd (N = 79)
ORR, % (95% CI)	42 (30.8-53.4)
Median DOR, mo	8.1
Median PFS, mo (95% CI)	5.6 (4.2-8.3)
Median OS, mo (95% CI)	12.1 (9.4-15.4)

Survival, mo (95% CI)[4]	T-DXd (n = 125)	Chemo (n = 62)
Median OS	12.5 (9.6-14.3)	8.4 (6.9-10.7)
HR for death = 0.59; *P* = .01		
Median PFS	5.6 (4.3-6.9)	3.5 (2.0-4.3)
HR for PD or death = 0.47		





1. Van Cutsem E et al. *Lancet*. 2023;24:744-756. 2. Ku G et al. *Annals of Oncol*. 2022;33(suppl 7):1100. 3. Shitara K et al. *N Engl J Med*. 2020;382:2419.
4. Yamaguchi et al. *J Clin Oncol*. 2022;40(suppl 4):242.

Current Status and Next Steps With T-DXd

- The results of **DESTINY-Gastric01 and 02** led to regulatory approvals for T-DXd

  Deruxtecan-nxki has been approved in the US for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

  On April 5, 2024, the Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

- **DESTINY-Gastric04**: phase 3 study of second-line T-DXd versus ramucirumab + paclitaxel (NCT04704934)
- **DESTINY-Gastric03**: phase 1b/2 study of T-DXd + chemotherapy and/or immune checkpoint inhibitors in first and second line (NCT04379596)

Other New and Emerging Anti-HER2 Therapies

Zanidatamab

- Bispecific antibody
- Randomized phase 3 HERIZON-GEA-01 study of zanidatamab + chemo ± tislelizumab as 1L therapy (NCT05152147)

Evorpacept

- Anti-CD47 antibody
- Randomized phase 2/3 ASPEN-06 study of trastuzumab/ramucirumab/ paclitaxel ± evorpacept (NCT05002127)

PRS-343 (cinrebafusp alfa; HER2/4-1BB bispecific)

Newer HER2 ADCs

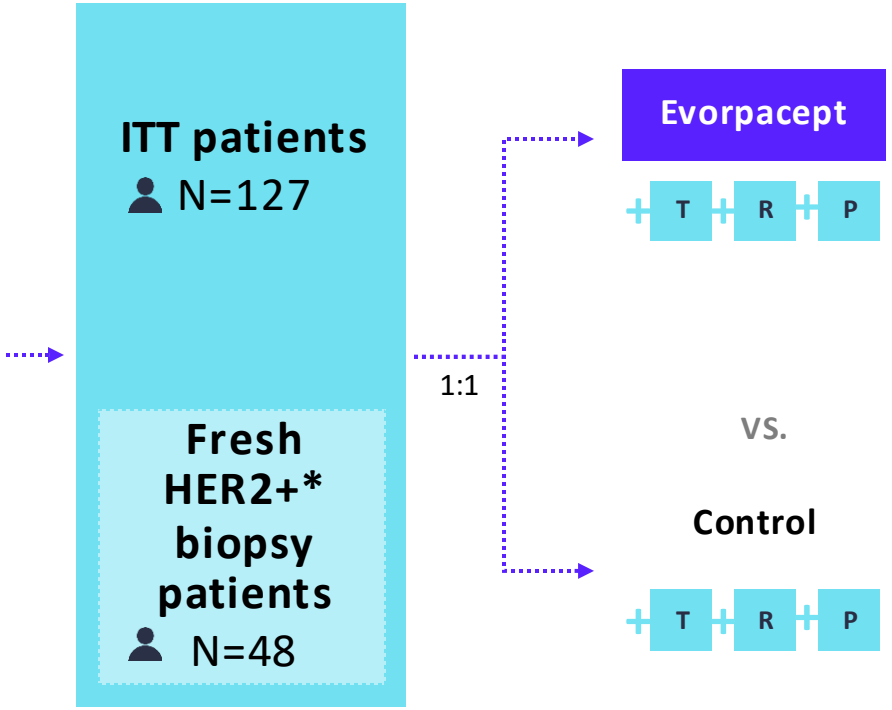
HER2/CD3 bispecific antibodies

HER2 cellular therapy

ASPEN-06 Phase 2: Evorpacept Plus TRP in HER2+ Advanced/Metastatic GC/GEJ Adenocarcinoma

Key eligibility criteria

- HER2+ GC or GEJ that has progressed on or after prior HER2-directed therapy
- 2L or 3L
- Prior trastuzumab deruxtecan and/or checkpoint inhibitors allowed
- Prior CD47-agent, anti-SIRPα, or ramucirumab excluded



Primary endpoints in both ITT and fresh biopsy populations:

- Improvement in ORR* vs assumed historical control of 30% (Wilke et al, Lancet October 2014)
- Improvement in ORR* over internal control (Difference ≥ 10%)

Secondary endpoints

- DOR, PFS, OS

All patients enrolled received a prior HER2-targeted therapy (e.g., trastuzumab) and were enrolled with either a HER2+ fresh or archival biopsy

Evo Evorpacept (30 mg/kg IV Q2W) T Trastuzumab (6 mg/kg > 4 mg/kg Q2W) R Ramucirumab (8 mg/kg Q2W) P Paclitaxel (80 mg/m^2 on day 1, 8, 15 of 28-day cycle)

*FRESH HER2- positive is defined as biopsies that were HER2-positive after receiving prior trastuzumab treatment and were within one month of starting on study
GC- gastric cancer, GEJ- gastroesophageal junction, TRP- trastuzumab, ramucirumab, paclitaxel
Minimization factors: Primary tumor place (i.e., Gastric vs GEJ); Time of biopsy (i.e., fresh vs archival); Region (Asia vs other); Treatment line (i.e., 2nd vs 3rd line); HER2 status (3+ vs 2+/ISH+); Prior T-DXd
*Based on investigator assessment

Shitara K, *et al. GI ASCO 2025*

Evorpacept Added Substantial Activity to the TRP Backbone in ITT

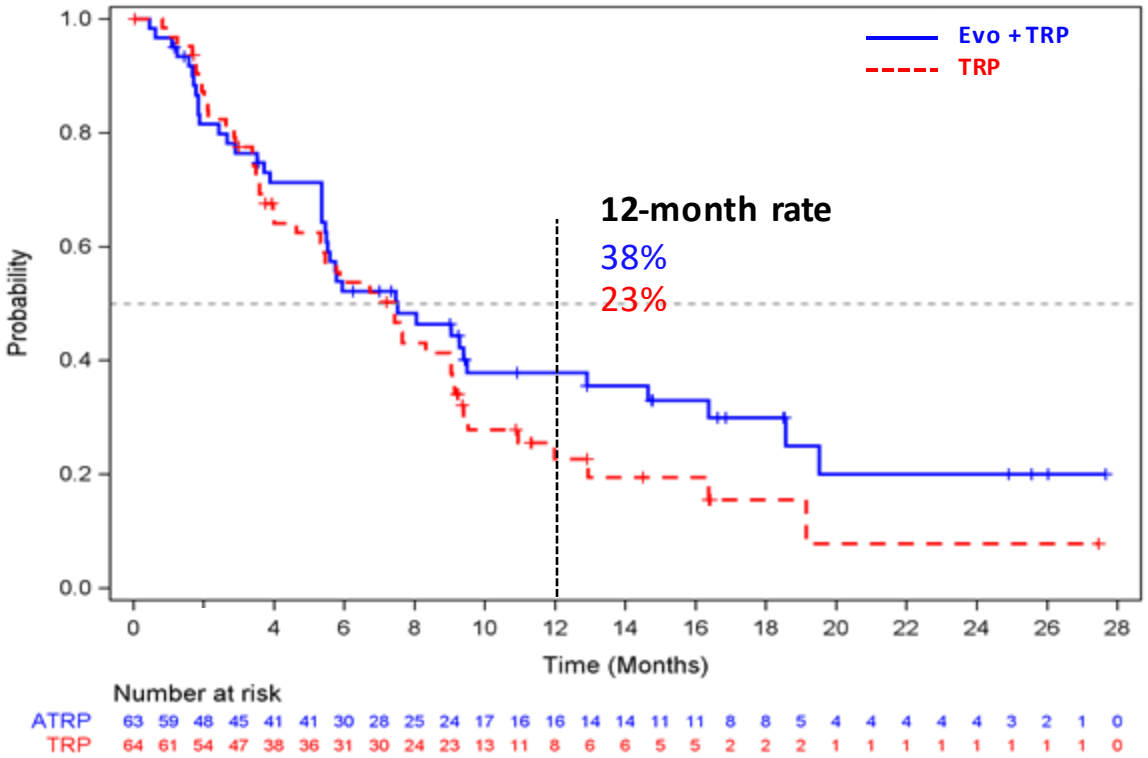
Confirmed ORR and DOR in the ITT population

	Evo + T + R + P N=63	Control: T + R + P N=64
Confirmed ORR, n (%) [95% CI]	**26 (41.3%) [29.0%; 54.4%]**	**17 (26.6%) [16.3%; 39.1%]**
CR (Complete Response)	1 (1.6%)	1 (1.6%)
PR (Partial Response)	25 (39.7%)	16 (25.0%)
SD (Stable Disease)	21 (33.3%)	35 (54.7%)
PD (Progressive Disease)	9 (14.3%)	7 (10.9%)
NE (Not Evaluable)	2 (3.2%)	1 (1.6%)
No Post baseline assessment	5 (7.9%)	4 (6.3%)
Median DOR (months) [95% CI]	**15.7 [7.7; NR]**	**9.1 [5.3; NR]**
Number of events	12 (46.2%)	9 (52.9%)
Median follow up (months)	17.5	16.8

Evo Evorpacept T Trastuzumab R Ramucirumab P Paditaxel

Data Cutoff as of 02 Dec 2024

PFS in the ITT population



	Number of patients with events	Number of patients censored	mPFS [95% CI]
Evo + TRP	40 (63.5%)	23 (36.5%)	7.5 [5.5-12.9]
TRP	47 (73.4%)	17 (26.6%)	7.4 [4.6-9.0]

PFS Hazard Ratio: 0.77 [0.49; 1.20]

Shitara K, *et al. GI ASCO 2025*

Evorpacept Greatly Improved the Response Rate in Patients with Confirmed HER2-Positivity

	HER2+ confirmed with fresh biopsies		HER2+ confirmed with fresh biopsy OR ctDNA+	
	Evo + T + R + P	T + R + P	Evo + T + R + P	T + R + P
N	22	26	47	49
Confirmed ORR, n (%) [95% CI]	**13 (59.1%) [36.4%; 79.3%]**	**6 (23.1%) [9.0%; 43.6%]**	**23 (48.9%) [34.1%; 63.9%]**	**12 (24.5%) [13.3%; 38.9%]**
CR (Complete Response)	0	0	1 (2.1%)	1 (2.0%)
PR (Partial Response)	13 (59.1%)	6 (23.1%)	22 (46.8%)	11 (22.4%)
SD (Stable Disease)	6 (27.3%)	13 (50.0%)	15 (31.9%)	27 (55.1%)
PD (Progressive Disease)	0	5 (19.2%)	4 (8.5%)	6 (12.2%)
NE (Not Evaluable)	0	1 (3.8%)	2 (4.3%)	1 (2.0%)
No Post baseline assessment	3 (13.6%)	1 (3.8%)	3 (6.4%)	3 (6.1%)
Median DOR (months) [95% CI]	**15.7 [4.0; NR]**	**14.5 [7.4; NR]**	**15.7 [7.7; NR]**	**9.1 [3.5; NR]**
Number of events	6 (46.2%)	3 (50.0%)	11 (47.8%)	7 (58.3%)

Evo Evorpacept T Trastuzumab R Ramucirumab P Paditaxel

Shitara K, *et al. GI ASCO 2025*

Data Cutoff as of 02 Dec 2024; NR = not reached; 1 Wilke et al, Lancet October 2014

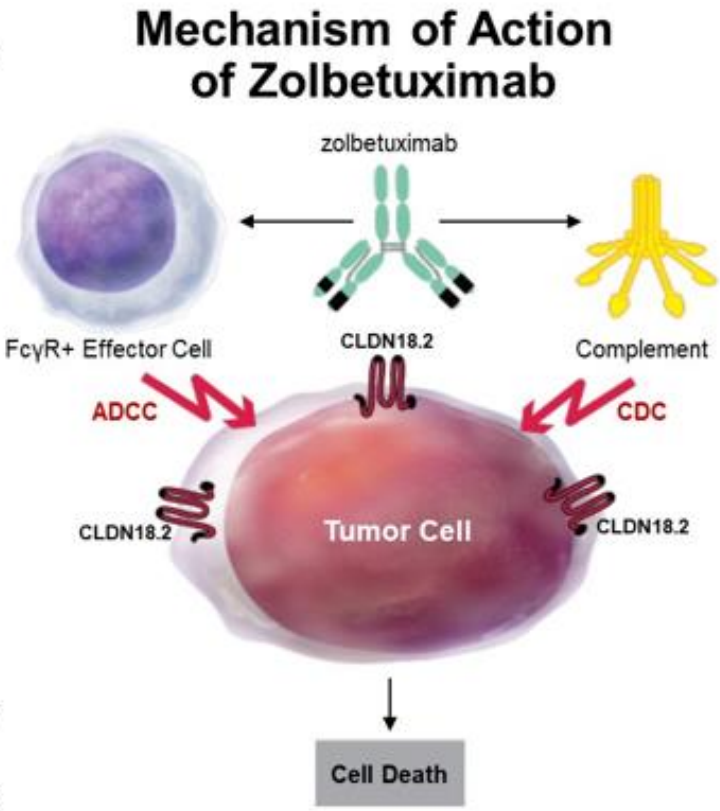
Summary of second line treatment

Trial	Treatment	N	ORR (%)	DOR (m) [95% CI]	PFS (m) [95% CI]
≥2L ASPEN-06 Fresh Biopsy or ctDNA+	**Evo + T + R + P**	**47**	**48.9%**	**15.7** [7.7 – NR]	**7.5** [5.5-14.7]
	T + R + P	49	24.5%	9.1 [3.5 – NR]	**6.7** [4.0-9.0]
≥2L RAINBOW[1]	Ramucirumab/paclitaxel	330	28% [23; 33]	4.4 [2.8 – 7.5]	4.4 [4.2 - 5.3]
	paclitaxel	335	16% [13; 20]	2.8 [1.4 - 4.4]	2.9 [2.8 - 3.0]
≥3L DESTINY Gastric01 Ph2 Study[2]	trastuzumab-deruxtecan	126	41% [31.8; 49.6]	11.3 [5.6-NE]	5.6 [4.3-6.9]
	physicians' choice	62	11% [4.7; 21.9]	3.9 [3.0-4.9]	3.5 [2.0-4.3]
≥2L ASPEN-06 – Fresh Biopsy	**Evo + T + R + P**	**22**	**59.1%**	**15.7** [4.0 - NE]	**9.5** [5.4 – 19.5]
	T + R + P	26	23.1%	14.5 [7.4 - NE]	7.1 [2.9 – 9.1]
2L EU/US Destiny Gastric02 Phase 2[3]	trastuzumab-deruxtecan (fresh biopsy required)	79	42% [30.8-53.4]	8.1 [5.9-NR]	5.6 [4.2-8.3]

1 Wilke et al, Lancet October 2014; 2 Enhertu US product insert, and Shitara et al, NEJM June 18, 2020; NE could not be estimated; 3 Van Cutsem, et al, Lancet Oncology, 2023
Data Cutoff as of 02 Dec 2024

What is Zolbetuximab?

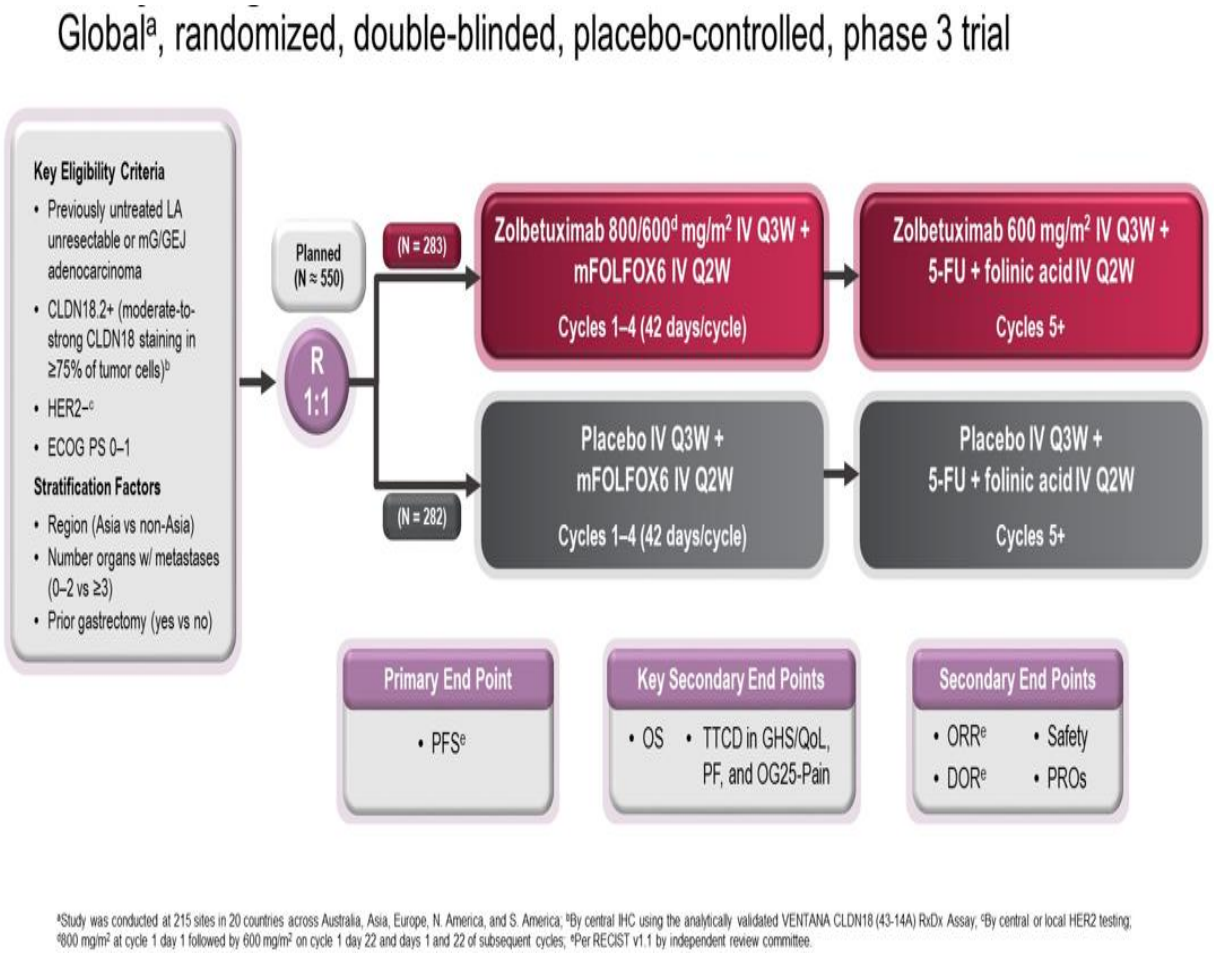
- CLDN18.2 is a tight junction protein normally expressed in gastric mucosa cells and retained in G/GEJ adenocarcinoma[1–8]
- CLDN18.2 may become exposed on the surface of G/GEJ adenocarcinoma cells, making it a promising target[2–8]
- Zolbetuximab is a first-in-class chimeric IgG1 monoclonal antibody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

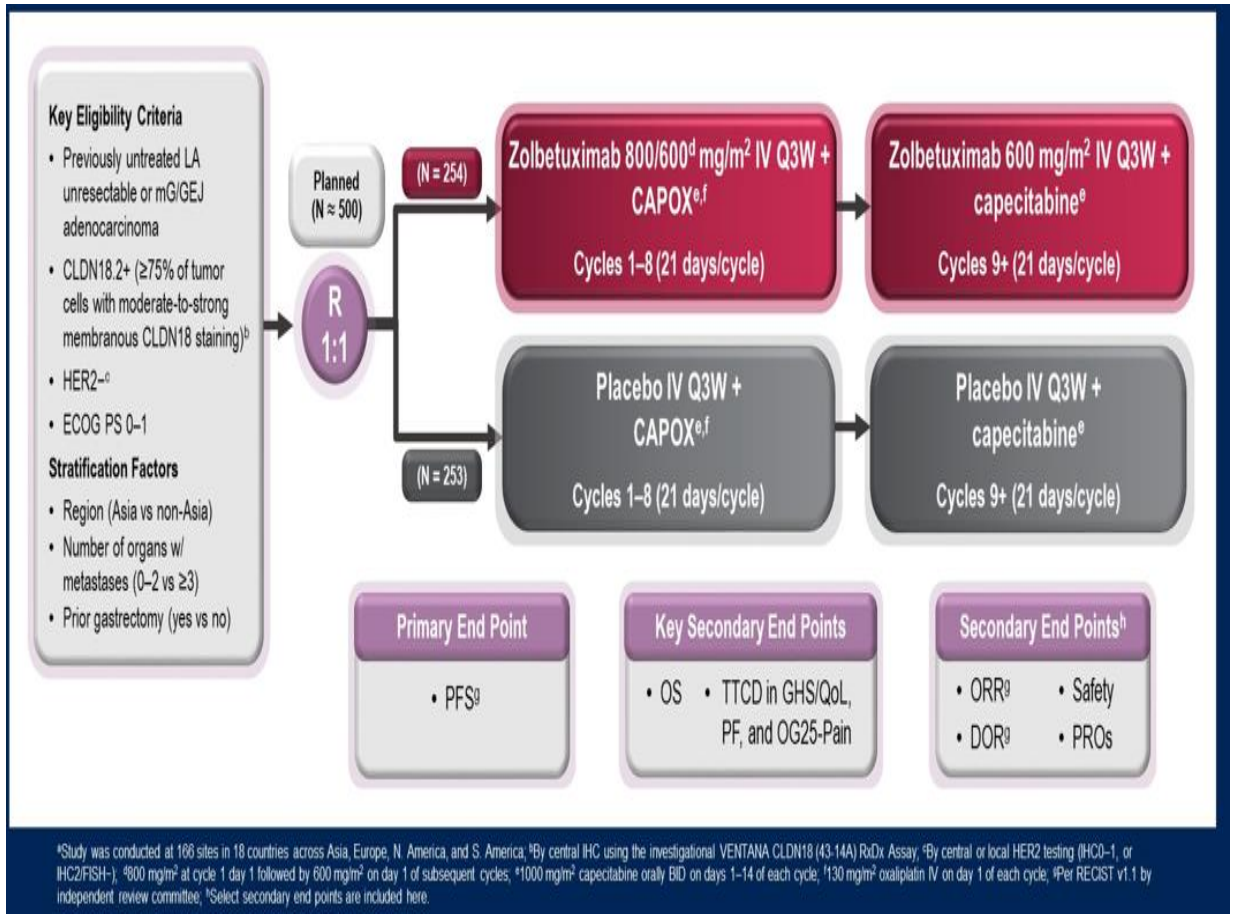


1. Niimi T et al. *Mol Cell Biol.* 2001;21:7380–90; 2. Sahin U et al. *Clin Cancer Res.* 2008;14:7624–34; 3. Moran D et al. *Ann Oncol.* 2018;29:viii14-viii57; 4. Sahin U et al. *Eur J Cancer.* 2018;100:17–26; 5. Rhode C et al. *Jpn J Clin Oncol.* 2019;49:870–6; 6. Türeci Ö et al. *Ann Oncol.* 2019;30:1487-95.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

- Shitara, *et al. GI ASCO (*2023). LBA292

Two Studies
SPOTLIGHT and GLOW

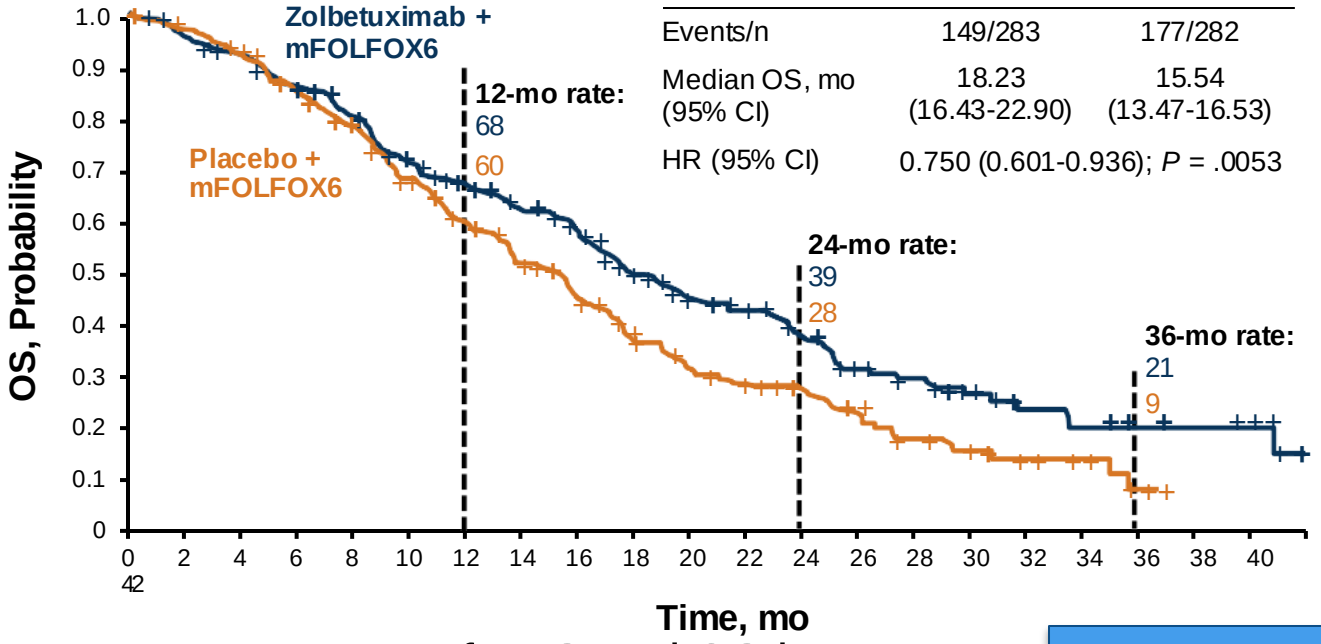




Shah et al. *Lancet*. 2023. (*GLOW*); Shitara et al. *Lancet*. 2023. (*SPOTLIGHT*);

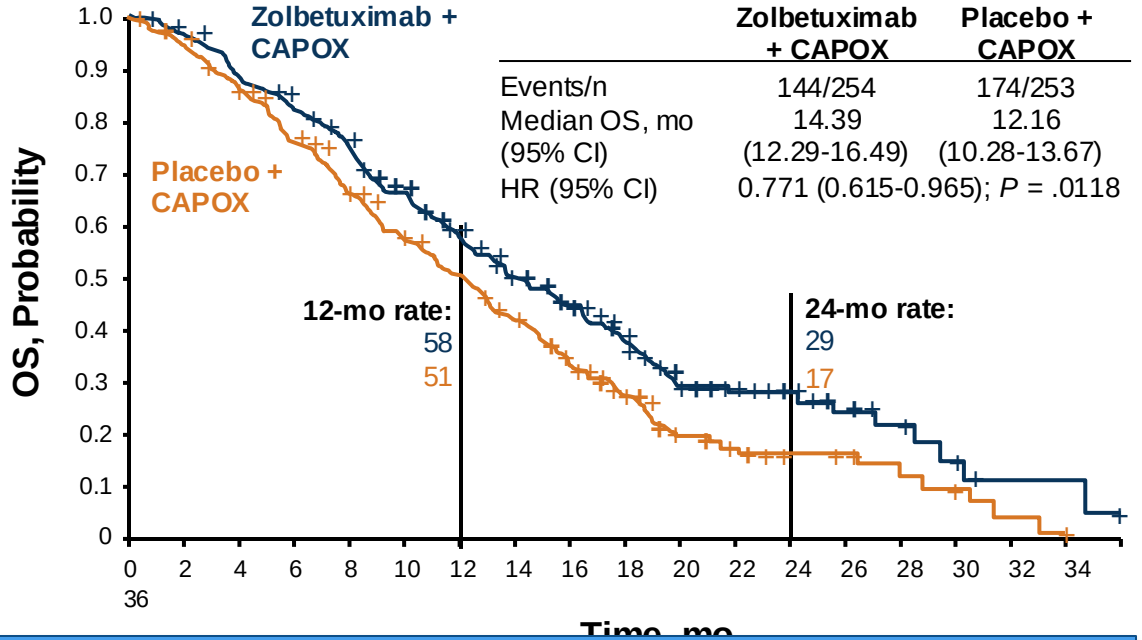
Phase 3 Trials of Zolbetuximab + Chemotherapy[1,2]

SPOTLIGHT
Zolbetuximab + FOLFOX



	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
Events/n	149/283	177/282
Median OS, mo (95% CI)	18.23 (16.43-22.90)	15.54 (13.47-16.53)
HR (95% CI)	0.750 (0.601-0.936); *P* = .0053	

GLOW
Zolbetuximab + CAPOX



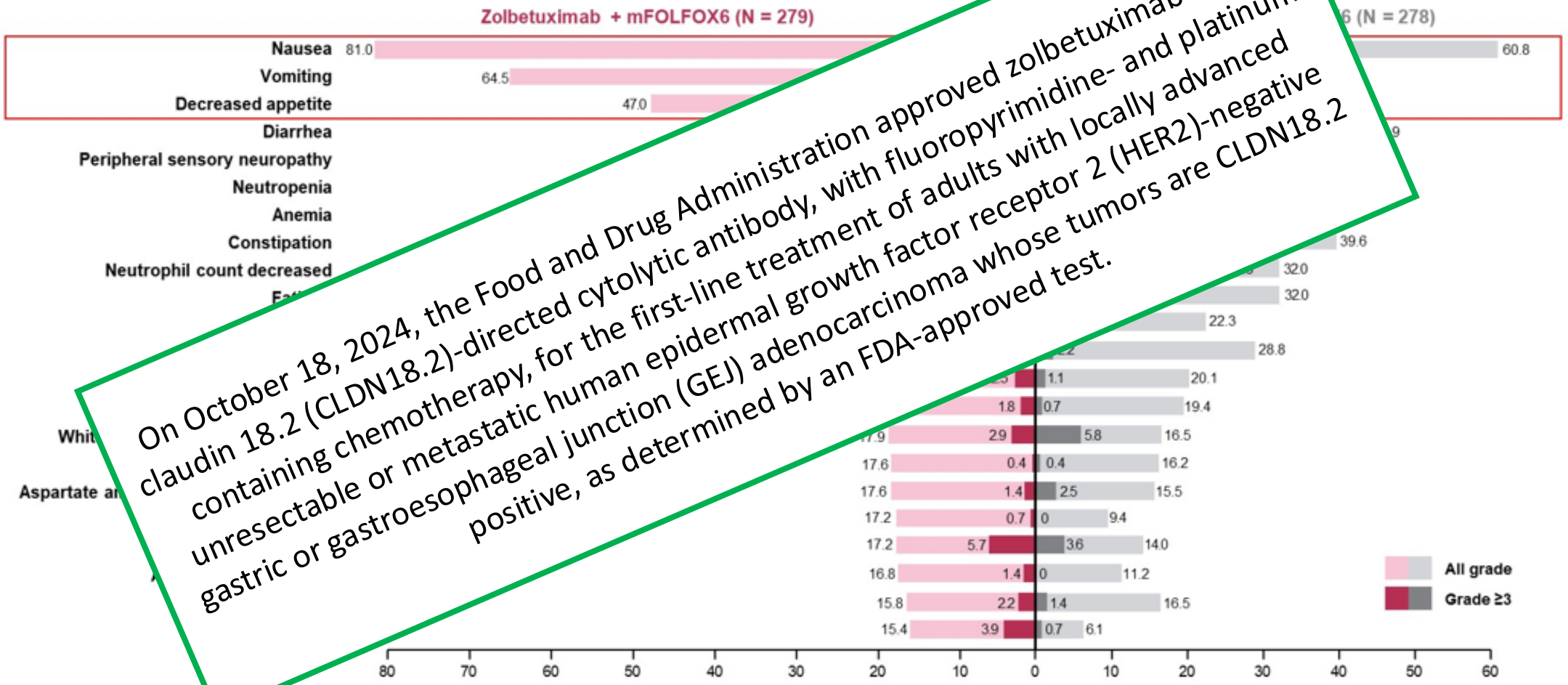
	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/n	144/254	174/253
Median OS, mo (95% CI)	14.39 (12.29-16.49)	12.16 (10.28-13.67)
HR (95% CI)	0.771 (0.615-0.965); *P* = .0118	

- Improvement of PFS and OS in two studies
- Notable toxicities: nausea and vomiting at first infusion

ASCO 2024
Final overall survival results from the phase 3 SPOTLIGHT trial[3]
mOS (ITT): 18.23 vs 15.57
mOS (PPS): 21.49 vs 16.39

1. Shitara K et al. *Lancet.* 2023;401:1655-1668. 2. Shah M et al. *Nat Med.* 2023;29:2133-2141. 3. Shitara K et al. ASCO 2024. Abstract 4036.

TEAEs Occurring in ≥ 15% of P nts



On October 18, 2024, the Food and Drug Administration approved zolbetuximab-clzb, a claudin 18.2 (CLDN18.2)-directed cytolytic antibody, with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are CLDN18.2 positive, as determined by an FDA-approved test.

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

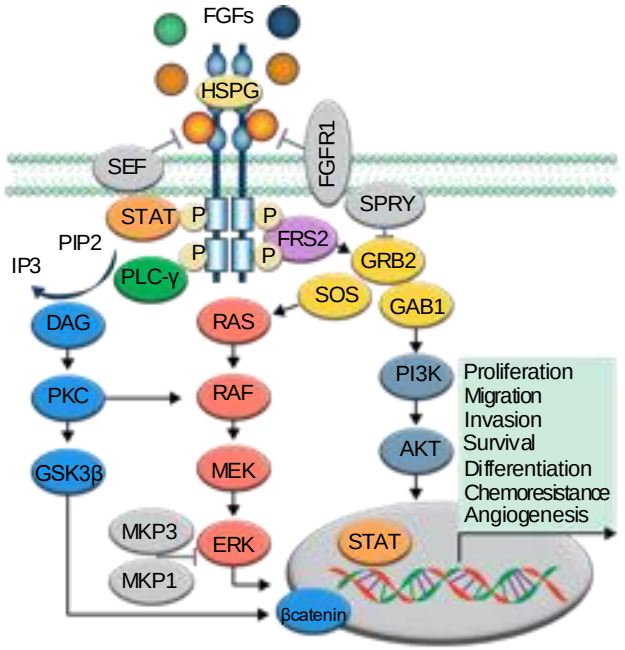
FGFR2 in GC and FGFR-TKI[1-7]

FGFR2 in gastric cancer

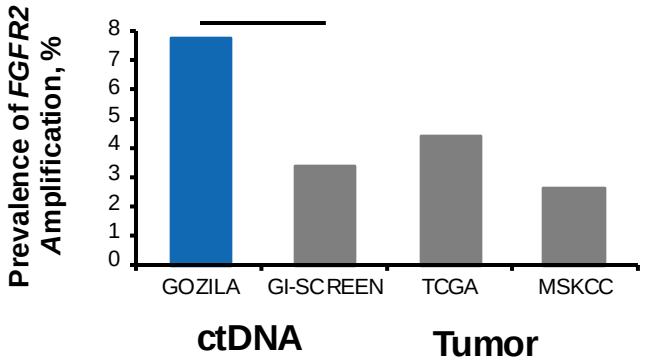
- *FGFR2* amp in 3%-5% in GC
- *FGFR2b* expression in ~30% in GC
  - FIGHT: 29% IHC+ and 4% for ctDNA+
  - 62% of enrolled pts had >10% tumors cells staining

Anti-FGFR2 TKIs

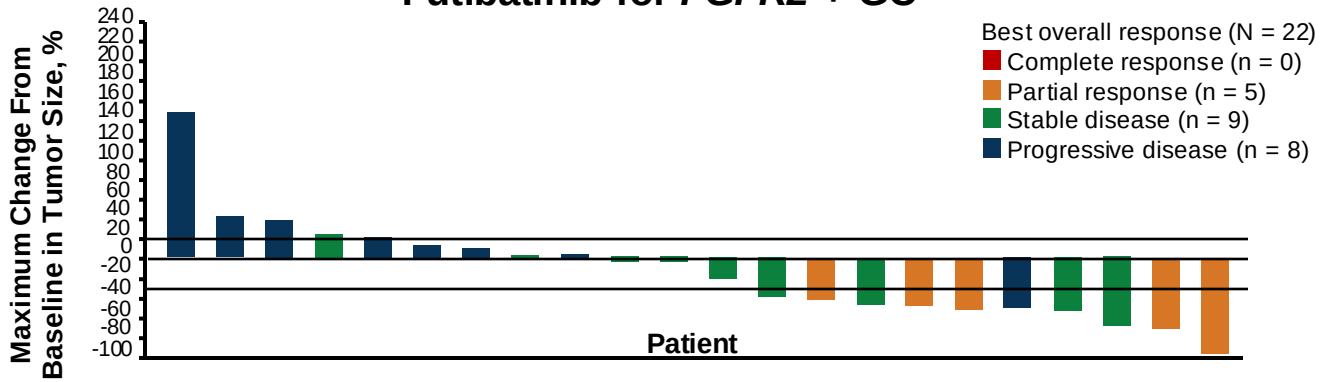
- AZD4547 in Shine study: no response, no improvement in OS vs PTX
- Futibatinib (TAS120): ORR 18% with *FGFR2* amp (CN >10)
- Infigratinib: ORR 25% with *FGFR2* amp+
  - Response duration is short with emerging *MET* or other gene alterations at resistance (need combination)



Frequency of *FGFR2* Amp



Futibatinib for *FGFR2* + GC

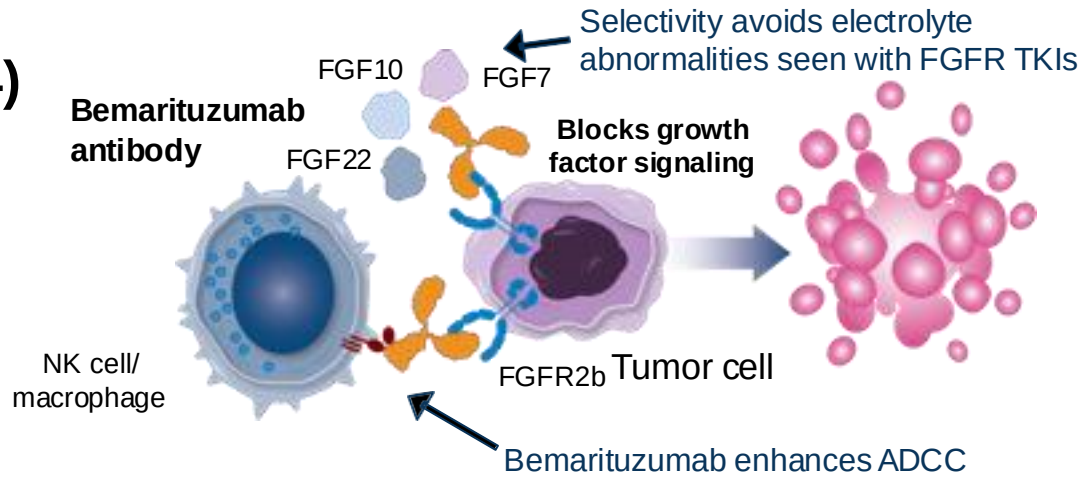


1. Jogo T et al. *Clin Cancer Res*. 2021; 27(20):5619-5627. 2. Catenacci DVT et al. ASCO 2021. Abstract 4010. 3. Ooki A, Yamaguchi K. *Gastric Cancer*. 2021;24:1169-1183. 4. Van Cutsem E et al. *Ann Oncol*. 2017;28:1316-1324. 5. Doi T et al. *Cancer Sci*. 2023;114:574-585. 6. Satoh T et al. ESMO-GI 2023. Abstract SO-10. 7. Syed Y. *Drugs*. 2022;82:1737-1743.

Anti-FGFR2b Monoclonal Antibody: Bemarituzumab[1,2]

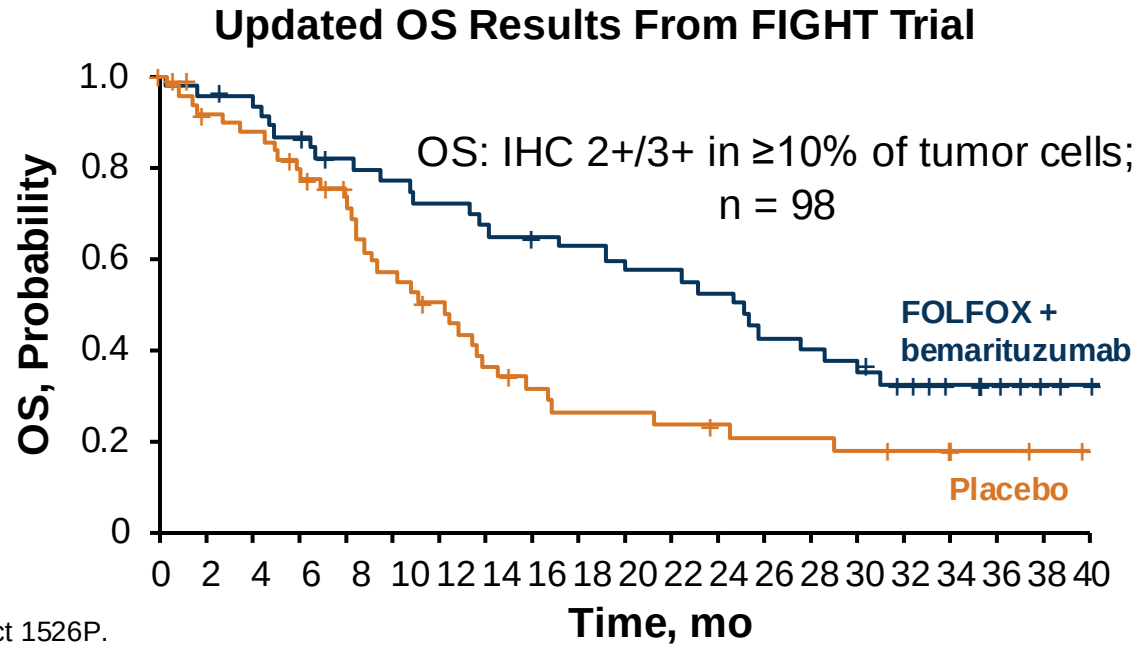
Bemarituzumab (anti-FGFR2b mAb, AMG522, FPA144)

- ORR as single agent 18%
- Less electrolyte abnormalities than TKI
- Reversible corneal toxicities are common



FIGHT trial (rP2 of FOLFOX + bema vs + placebo)

- mPFS 9.5 vs 7.4 (HR 0.72) in ITT / HR 0.43 in ≥10%
- mOS 19.2 vs 13.5 (HR 0.77) in ITT/ HR 0.52 in ≥10%
- 27.6% d/c bema by corneal events
- Two P3 are ongoing
  - FORTITUDE-101 (chemo + bema, NCT05052801)
  - FORTITUDE-102 (chemo + nivo + bema, NCT05111626)



1. Catenacci DVT et al. *J Clin Oncol*. 2020:38:2418-2426. 2. Wainberg ZA et al. ESMO-GI 2023. Abstract 1526P.

Summary

- In HER2 negative patients, there is now FDA approval of chemotherapy plus immunotherapy. The magnitude of benefit of adding immunotherapy increases with selection of high PD-L1 cases.
- The addition of pembrolizumab in the KEYNOTE-811 trial improved PFS and ORR, particularly in dual HER2 and PD-L1 overexpressed tumors (CPS > 1)
- Claudin 18.2 is a new biomarker and zolbetuximab is a monoclonal antibody targeting this. Two studies- SPOTLIGHT and GLOW have shown PFS and OS benefit with the addition of zolbetuximab to chemotherapy in the first line setting.
- T-DXd can provide benefit in second-line or later settings, regardless of prior ICI exposure

Thank You for Your Attention

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