Upper GI Cancer: Esophageal and Gastric-New Developments

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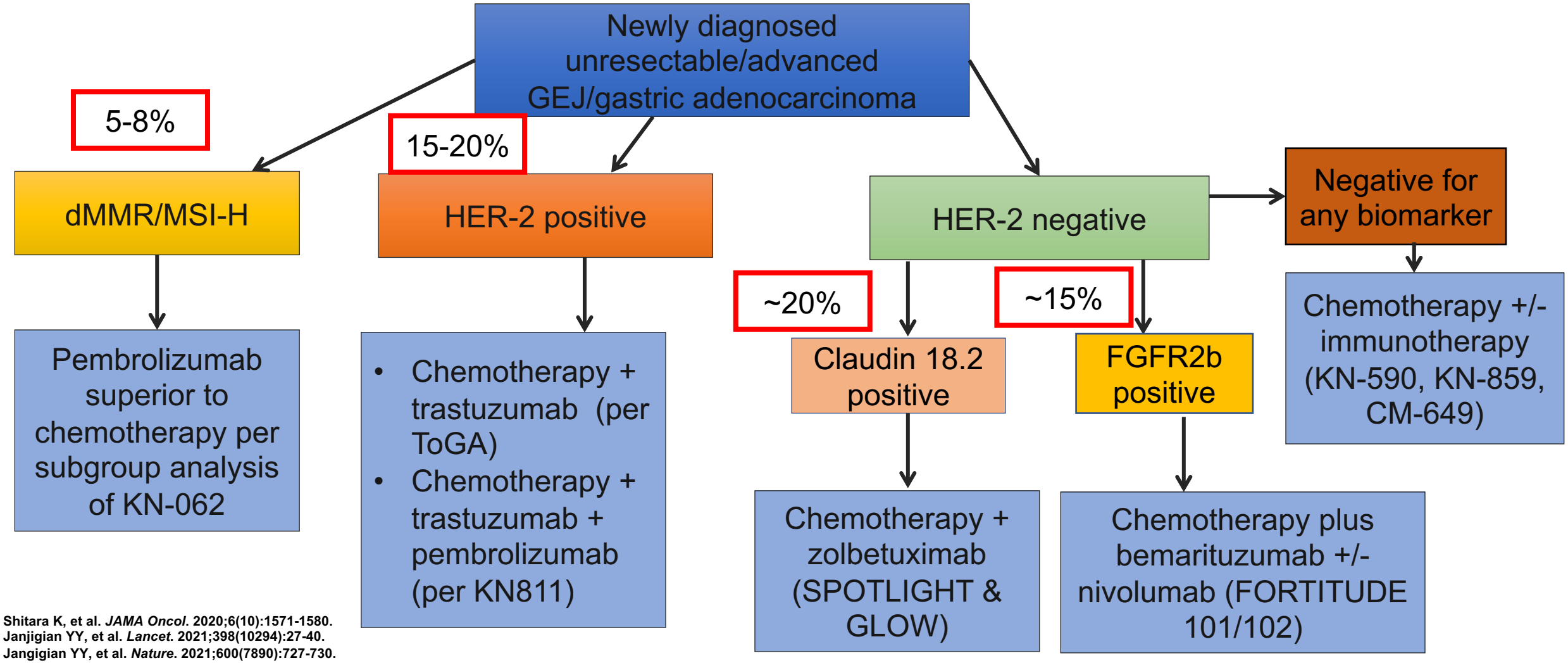
Agenda

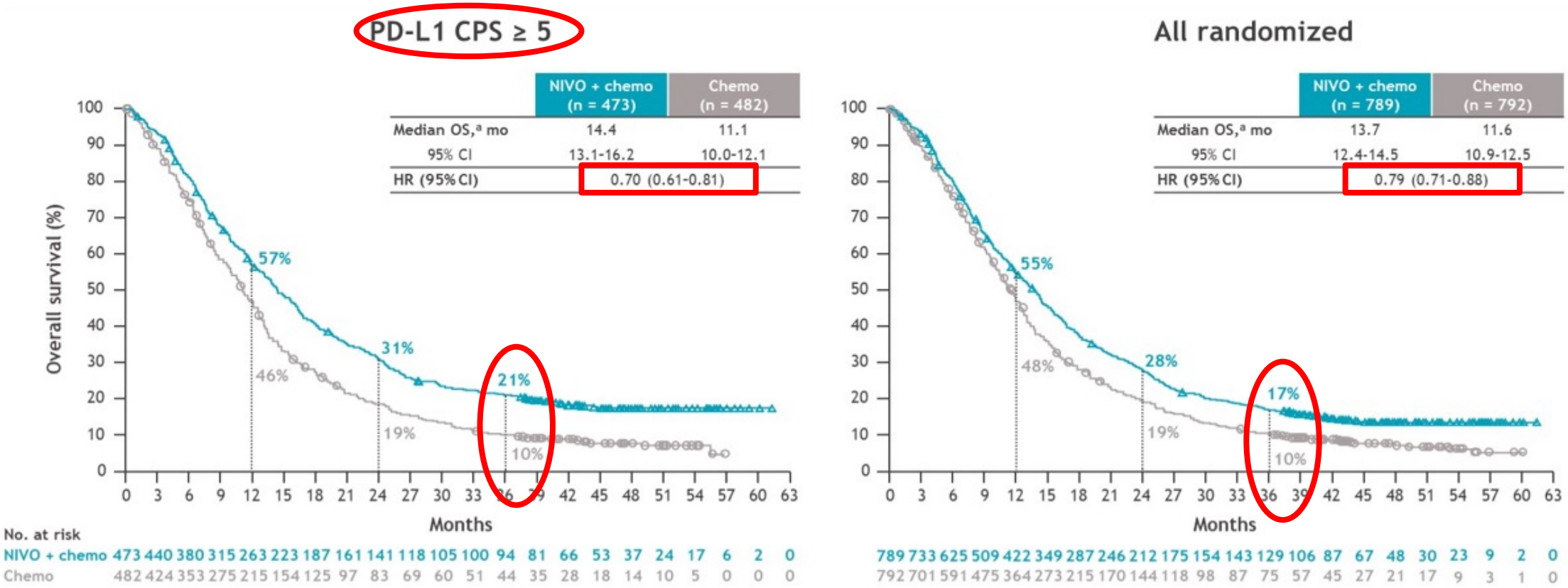
- Current state of art of 1st line treatment of gastroesophageal cancers – Old and New developments
- Update from ASCO 2024 (ESOPEC study)

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

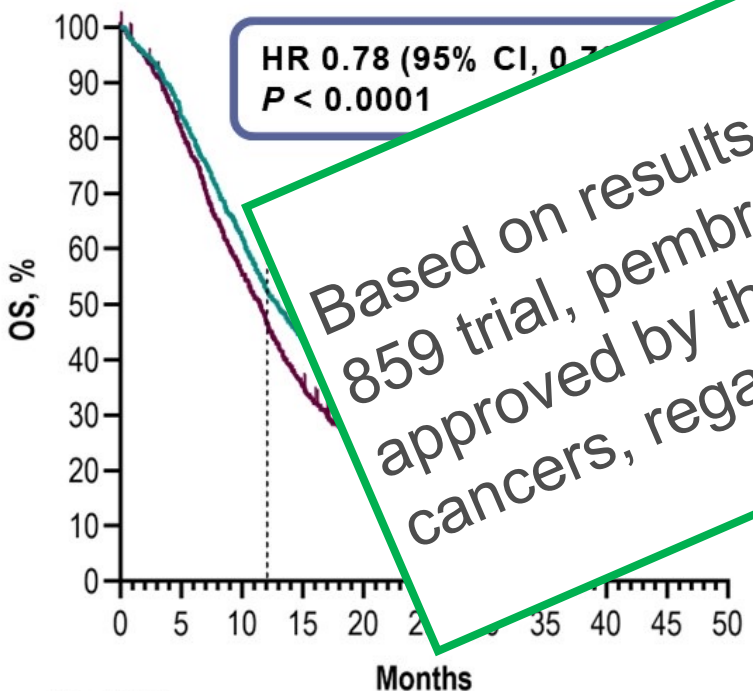
[a]Minimum follow-up, 36.2 months.

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

KEYNOTE-859 Primary Endpoint: Overall Survival

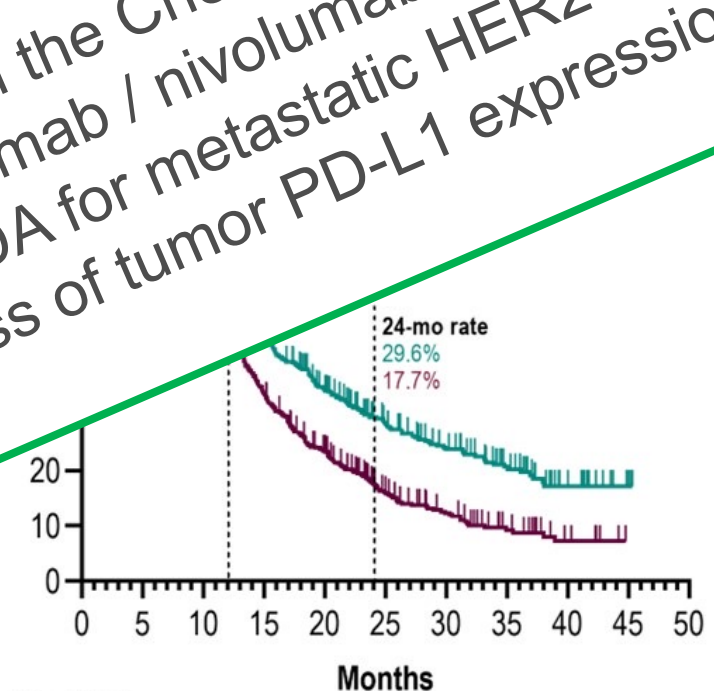
Overall

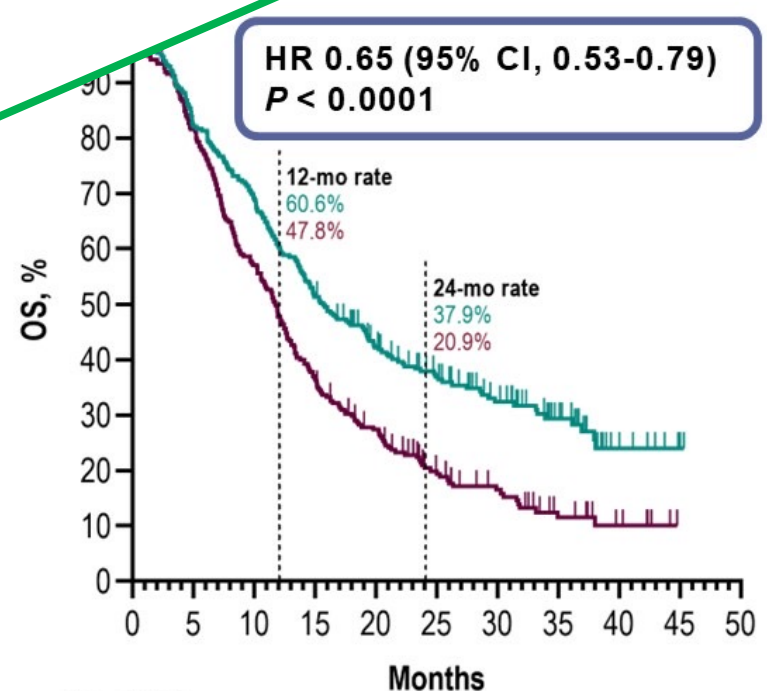
	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	76.3%	12.9 (11.9-14.0)
Placebo + chemo	84.4%	11.5 (10.6-12.1)



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.

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

Key Eligibility Criteria

- Advanced, unresectable G/GEJ adenocarcinoma
- No prior systemic therapy in advanced setting
- HER2+ by central review (IHC 3+ or IHC 2+ ISH+)
- ECOG PS 0 or 1

R 1:1
N=698

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

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

Stratification Factors

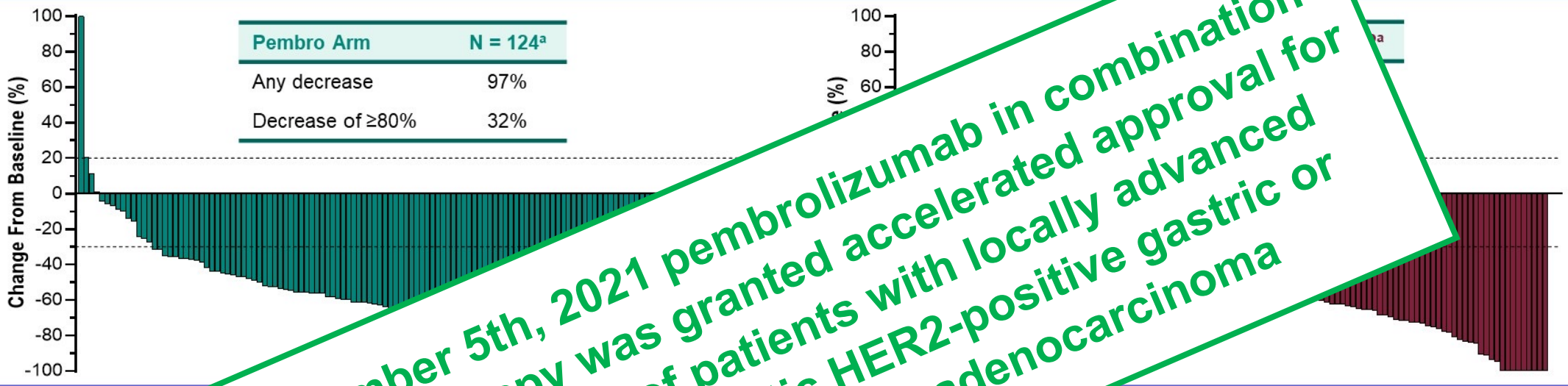
- Geographic region
- PD-L1 CPS <1 vs CPS ≥1
- Chemotherapy choice

Endpoints

- Dual primary: OS, PFS
- Secondary: ORR, DOR , safety

[a]Trastuzumab: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/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)		
ORR		
ORR difference[b]		
DCR	[illegible]% (91.4-98.8)	89.3% (82.7-94.0)

	Pembro Arm (N = 133)	Placebo Arm (N = 131)
ORR	**15 (11%)**	**4 (3%)**
DCR	**84 (63%)**	**64 (49%)**
SD	29 (22%)	49 (37%)
PD	5 (4%)	7 (5%)
Not evaluable	0	2 (2%)
Not assessed	0	5 (4%)

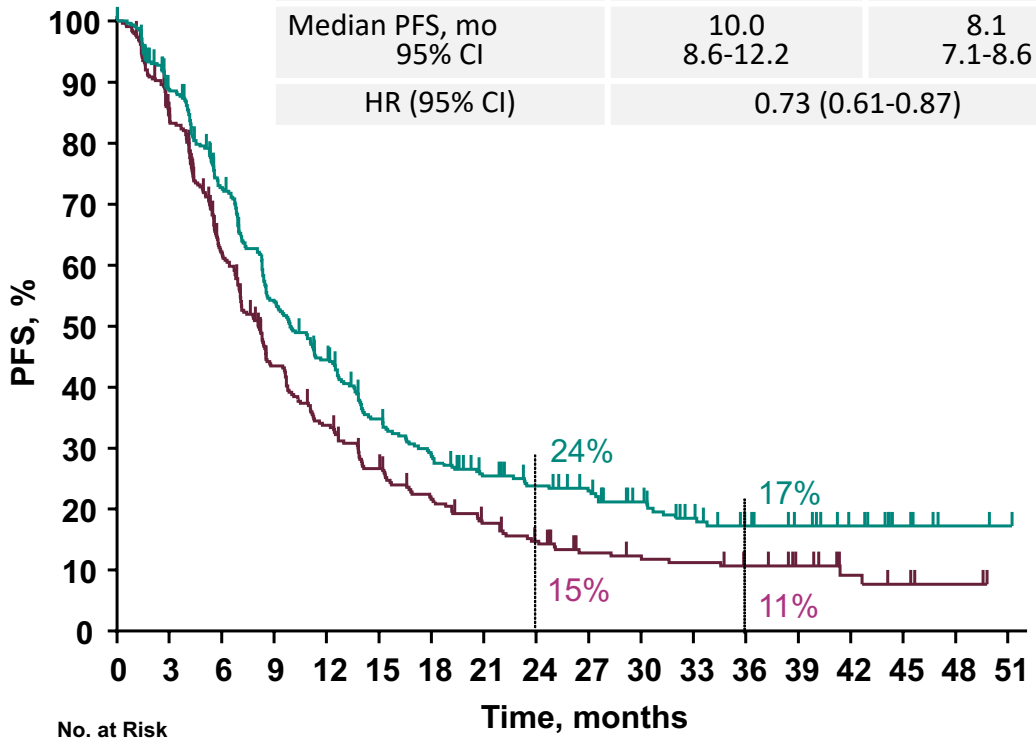
Duration of Response[c]	Pembro Arm (N = 99)	Placebo Arm (N = 68)
Median[d]	10.6 mo	9.5 mo
Range	1.1+ to 16.5+	1.4+ to 15.4+
≥6-mo duration[d]	70.3%	61.4%
≥9-mo duration[d]	58.4%	51.1%

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)	

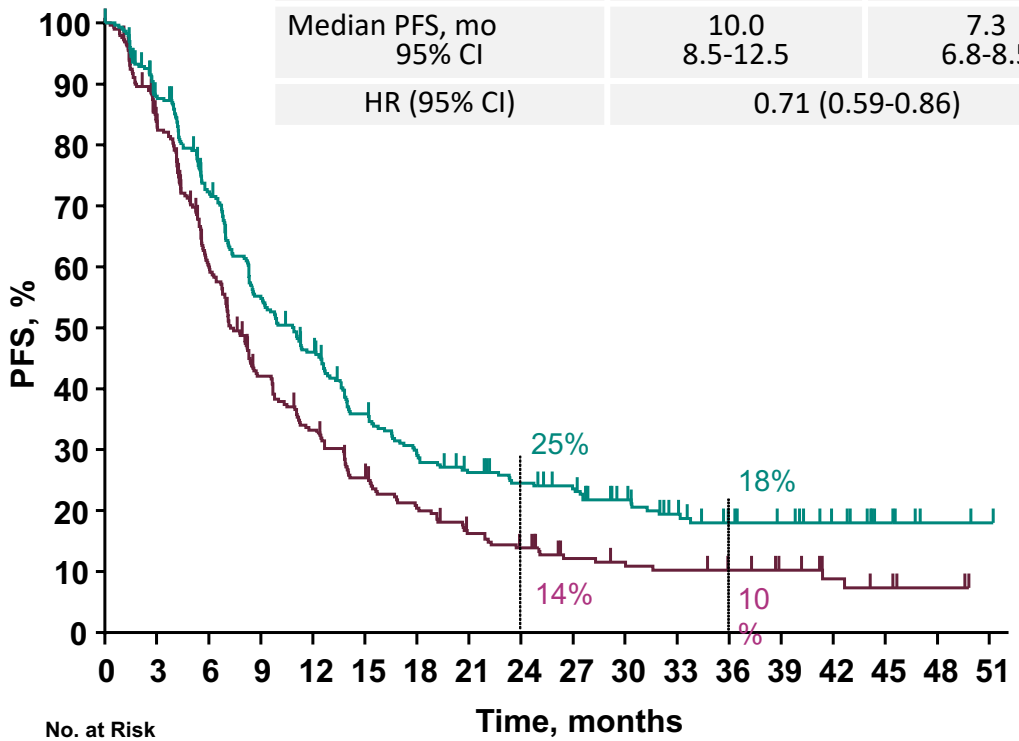


No. at Risk

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.

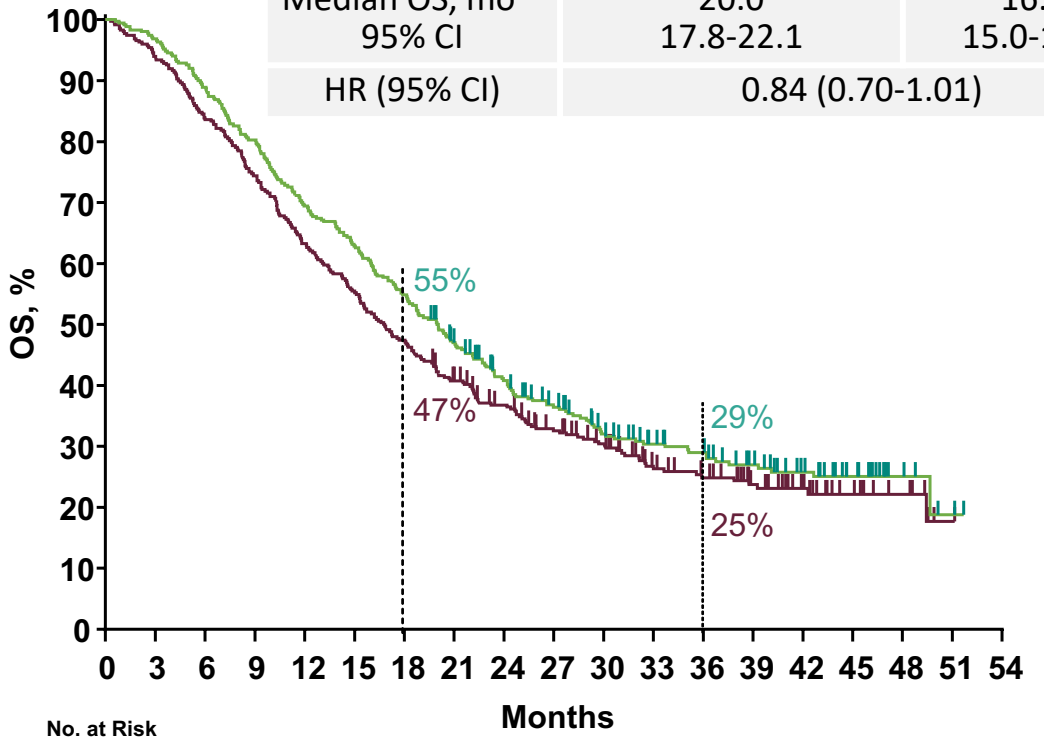
BICR, blinded independent central review; CI, confidence interval; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumors.

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)	

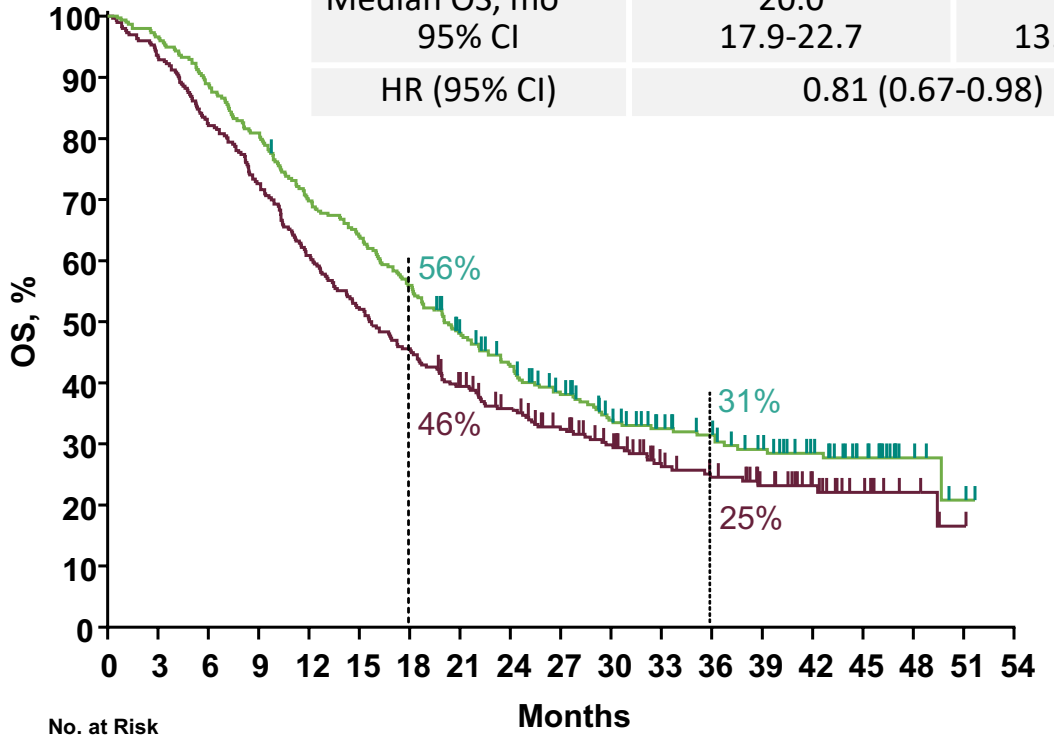


No. at Risk

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

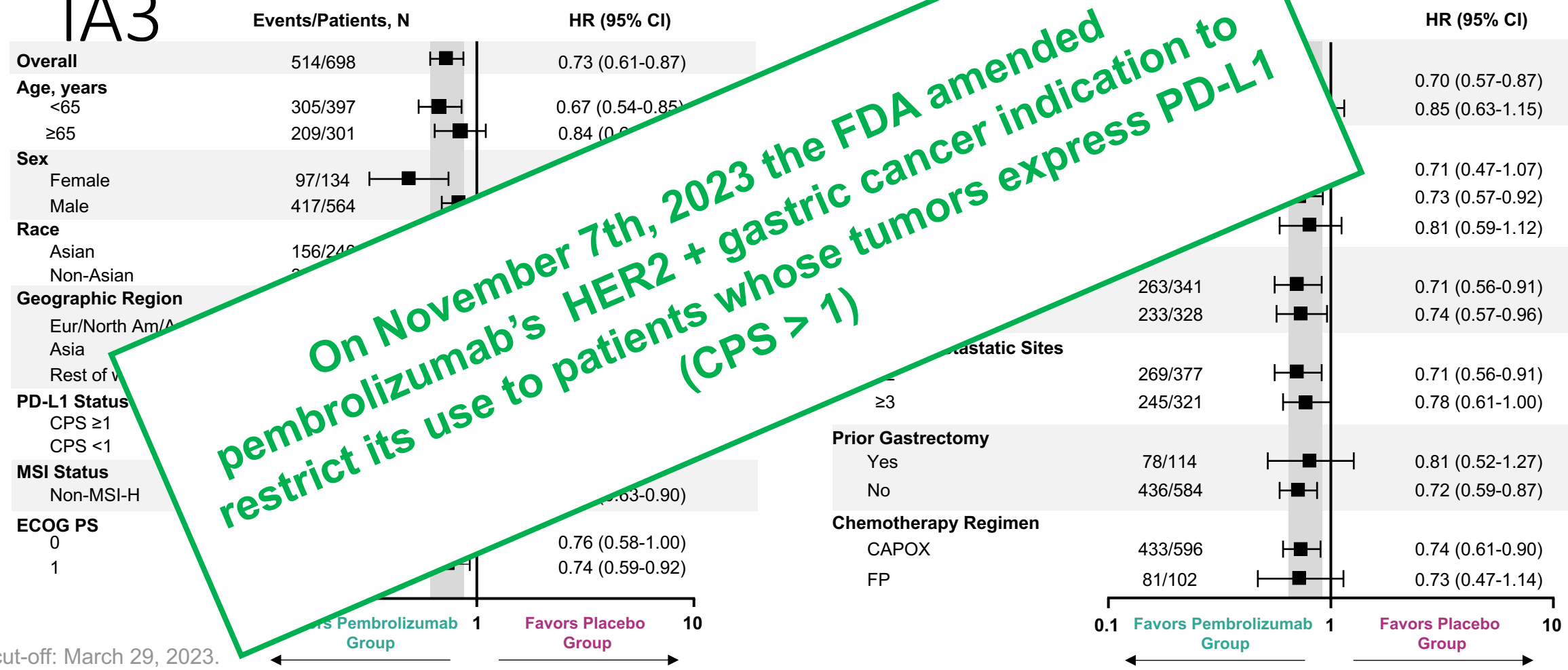
Pembrolizumab gp	298	288	265	241	207	190	166	136	115	96	78	64	58	47	37	23	7	2	0
Placebo gp	296	277	244	215	180	155	135	113	96	80	67	47	41	31	21	12	5	1	0

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

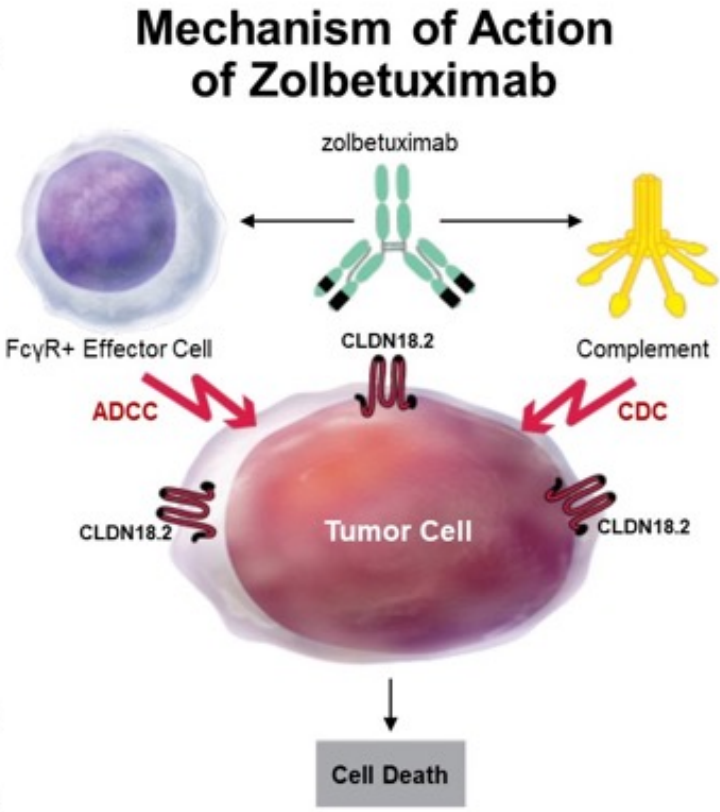


On November 7th, 2023 the FDA amended pembrolizumab's HER2 + gastric cancer indication to restrict its use to patients whose tumors express PD-L1 (CPS > 1)

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.

What is Zolbetuximab?

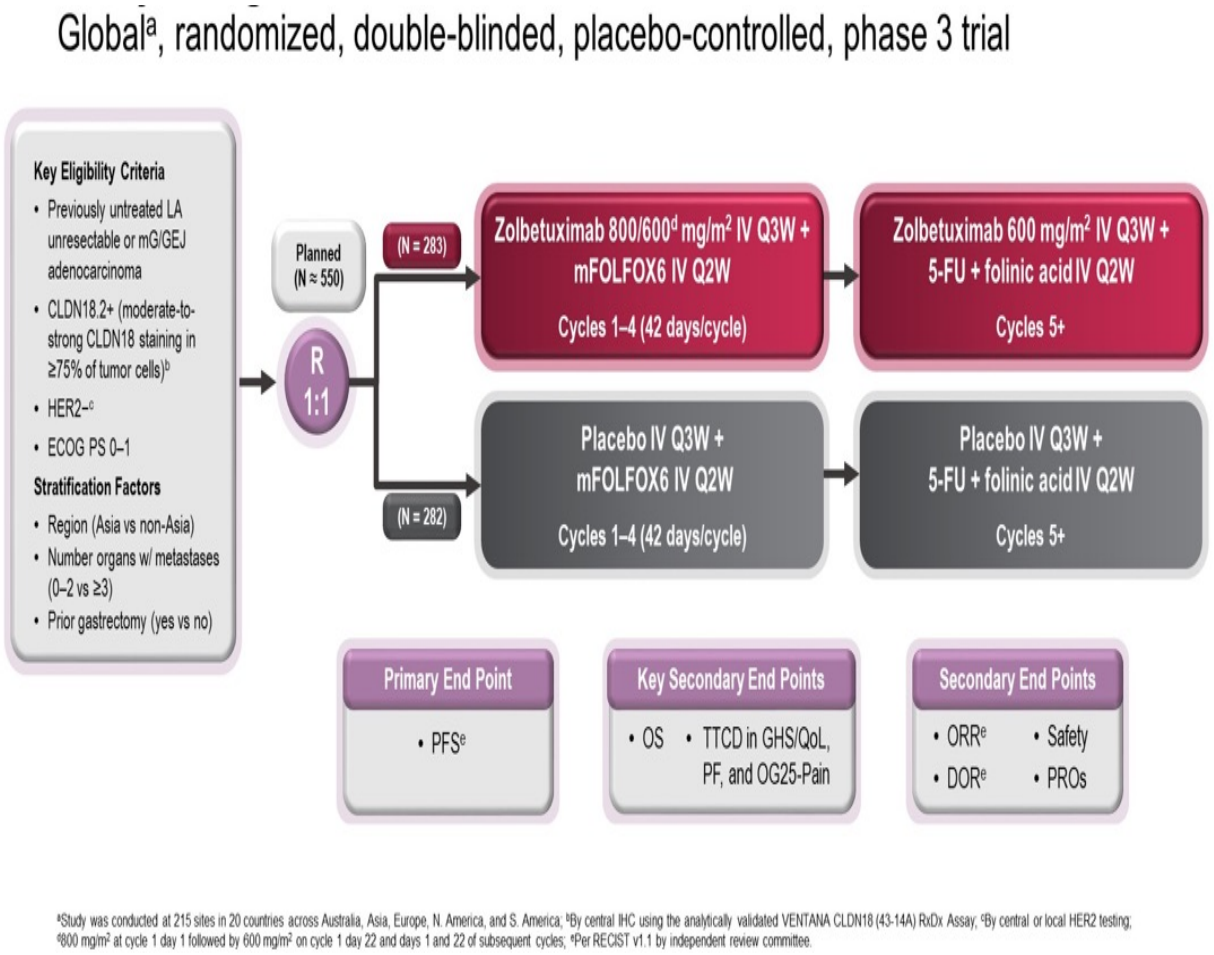
- CLDN18.2 is a tight junction protein normally expressed in gastric mucosa cells and retained in G/GEJ adenocarcinoma[1–8]
- CLDN18.2 may become exposed on the surface of G/GEJ adenocarcinoma cells, making it a promising target[2–8]
- Zolbetuximab is a first-in-class chimeric IgG1 monoclonal antibody 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

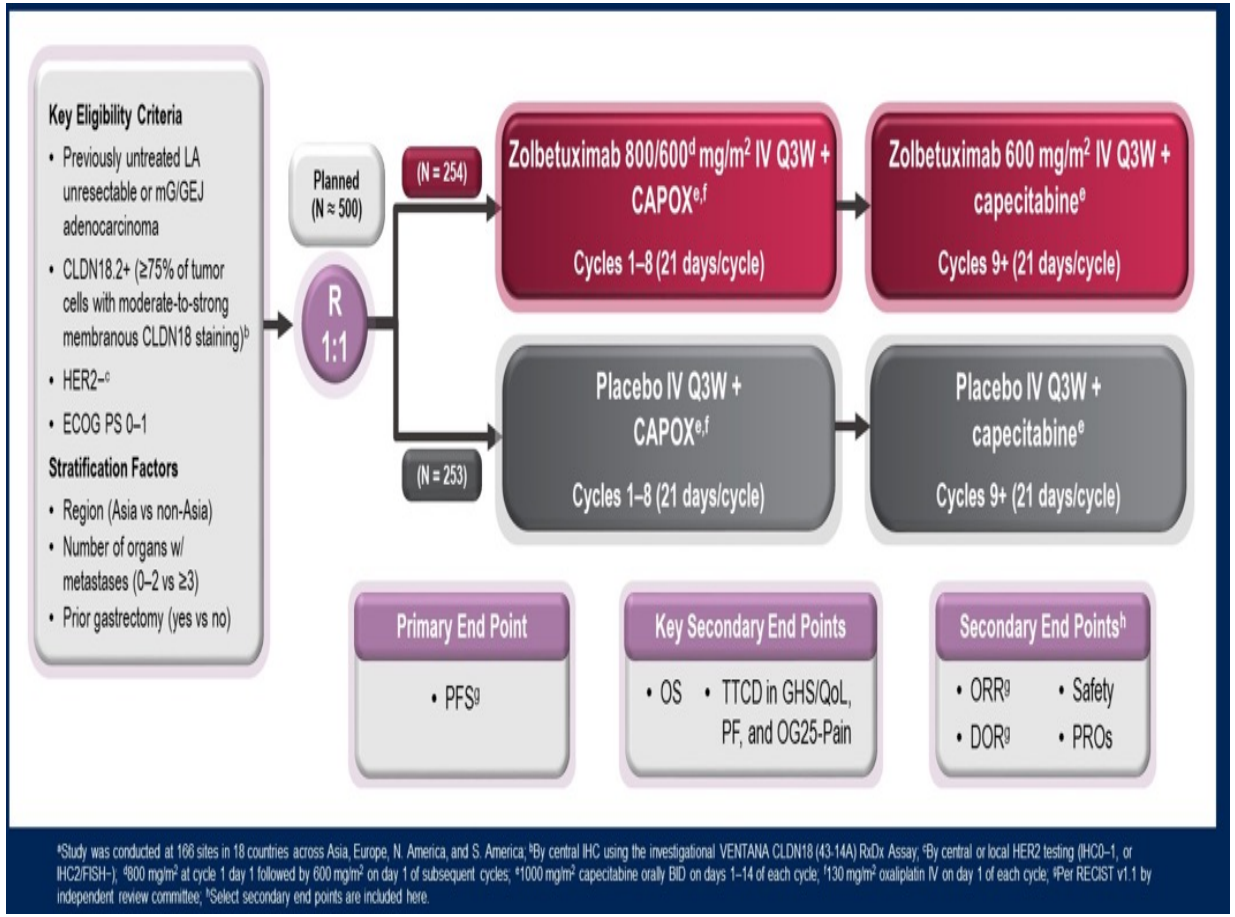


1. Niimi T et al. *Mol Cell Biol.* 2001;21:7380–90; 2. Sahin U et al. *Clin Cancer Res.* 2008;14:7624–34; 3. Moran D et al. *Ann Oncol.* 2018;29:viii14-viii57; 4. Sahin U et al. *Eur J Cancer.* 2018;100:17–26; 5. Rhode C et al. *Jpn J Clin Oncol.* 2019;49:870–6; 6. Türeci Ö et al. *Ann Oncol.* 2019;30:1487-95.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

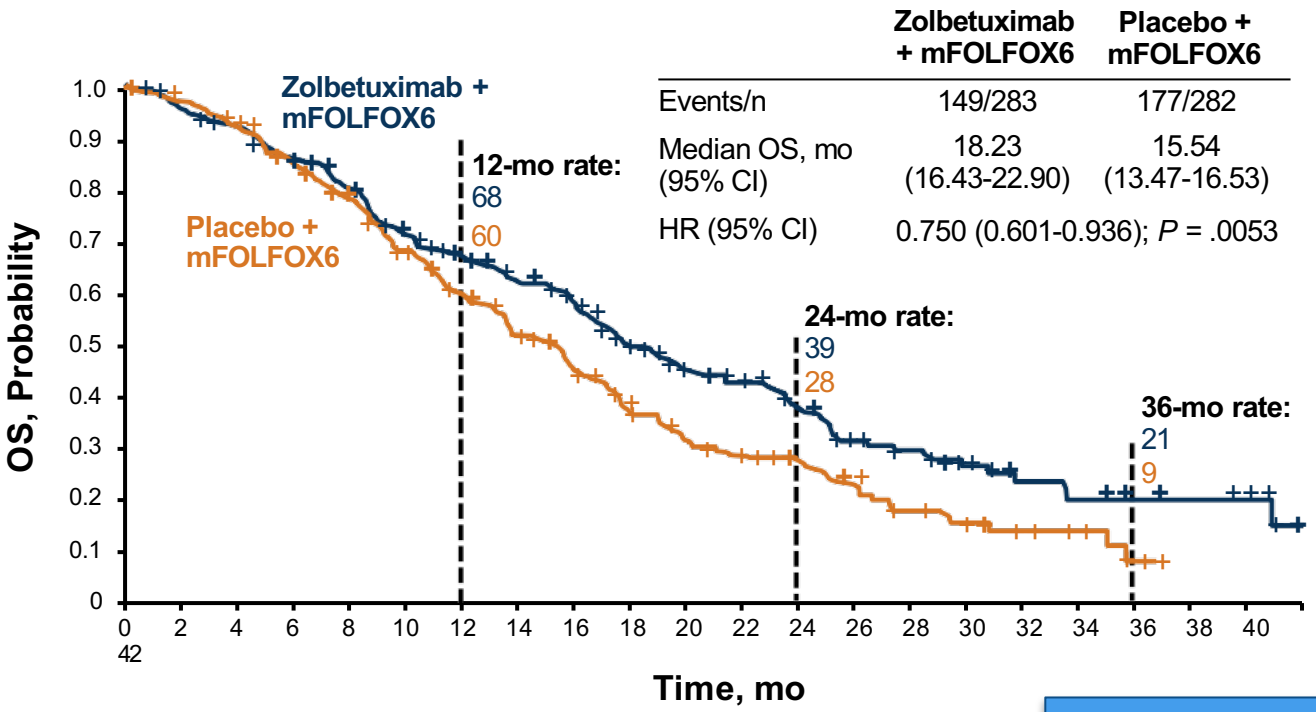




Shah et al. *Lancet*. 2023. (*GLOW*); Shitara et al. *Lancet*. 2023. (*SPOTLIGHT*);

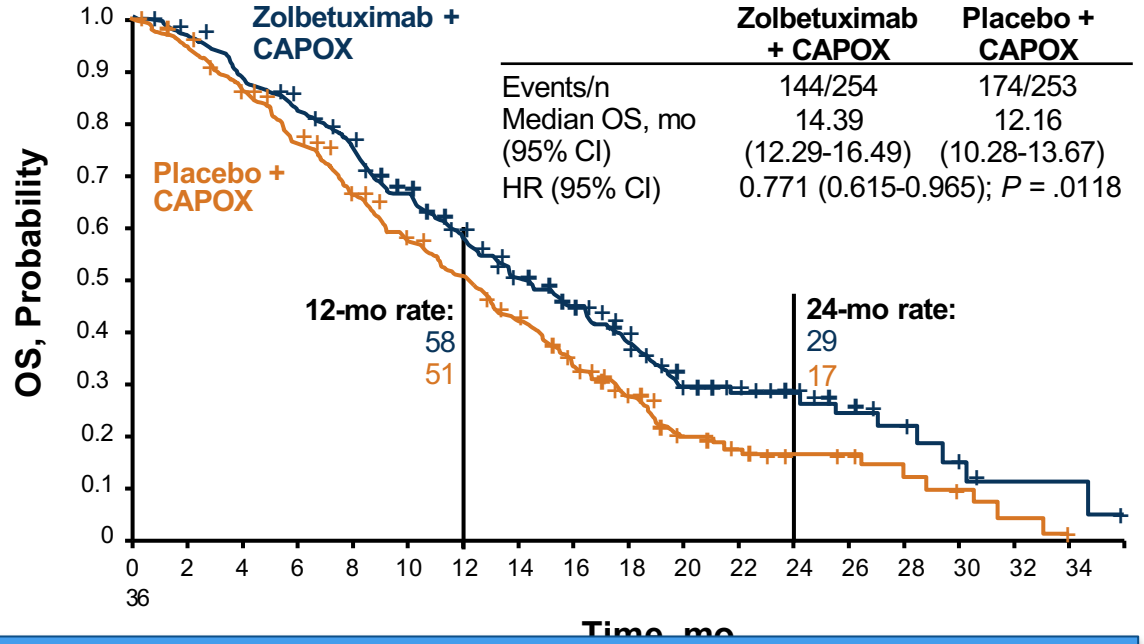
Phase 3 Trials of Zolbetuximab + Chemotherapy[1,2]

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.

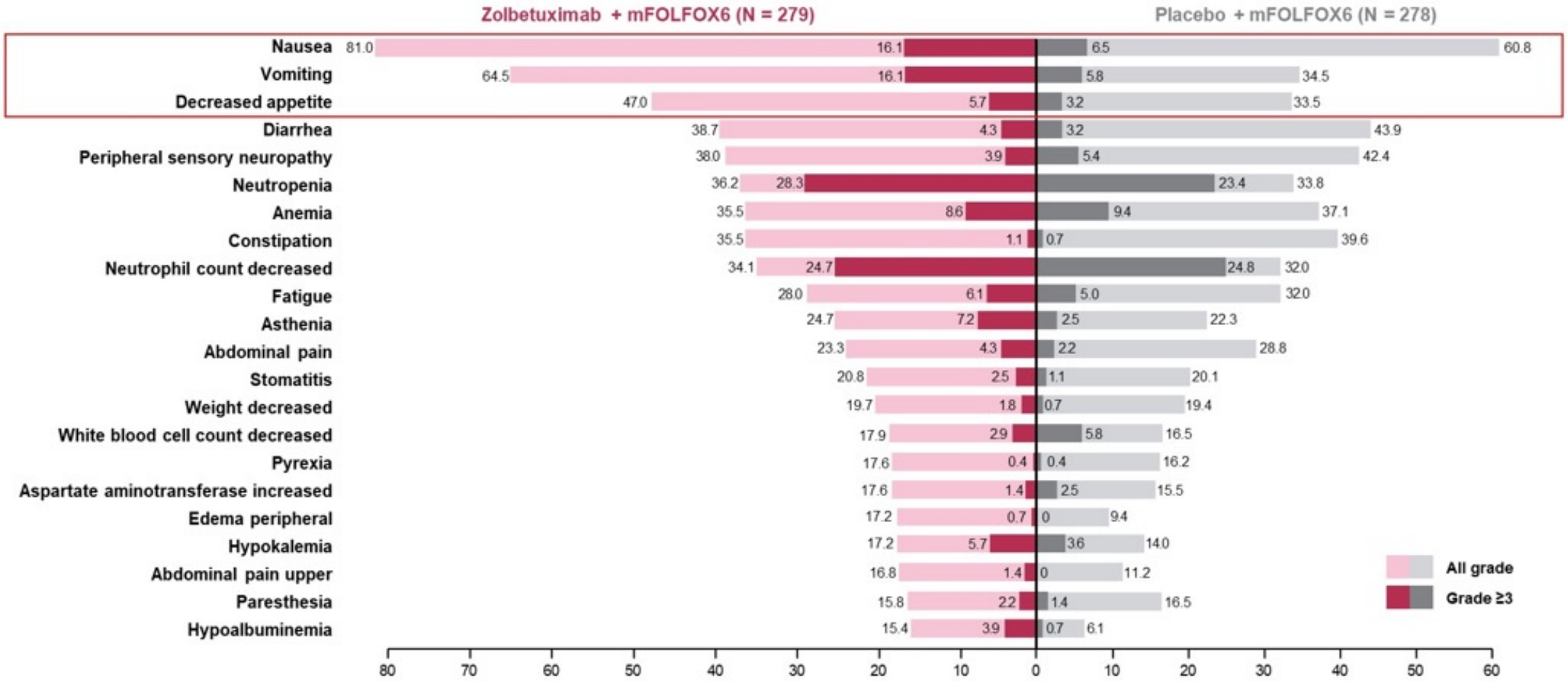
GLOW and SPOTLIGHT – Efficacy Comparison

	GLOW CAPOX + zolbetuximab vs CAPOX + placebo Patients (N = 254 vs 253)	SPOTLIGHT mFOLFOX6 + zolbetuximab vs mFOLFOX 6 vs placebo Patients (N = 283 vs 282)
Median P… free Survi…		…)
Median Overall Survival	**14.32 vs 12.16 months** **HR 0.771** **(95% CI 0.624-0.952; P = 0.0079)**	**18.2 vs 15.6 months** **HR 0.778** **(95% CI 0.637 - 0.949; P = 0.0067)**
Objective Response Rate (CR + PR)	**54.1% vs 48.5%**	**61.1% vs 62.4%**

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

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

TEAEs Occurring in ≥ 15% of Patients



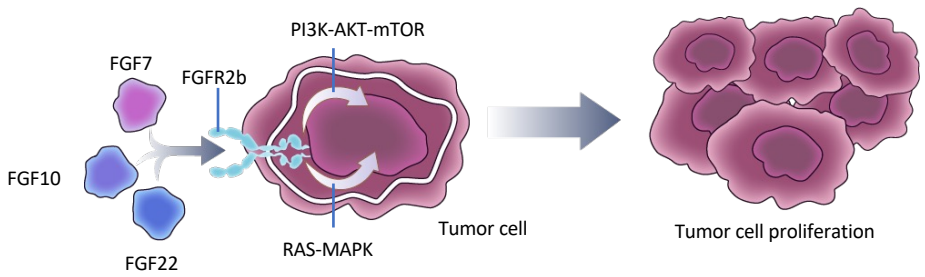
- The most common TEAEs with zolbetuximab + mFOLFOX6 were nausea and vomiting as on-target effects

FGFR2b in Cancer

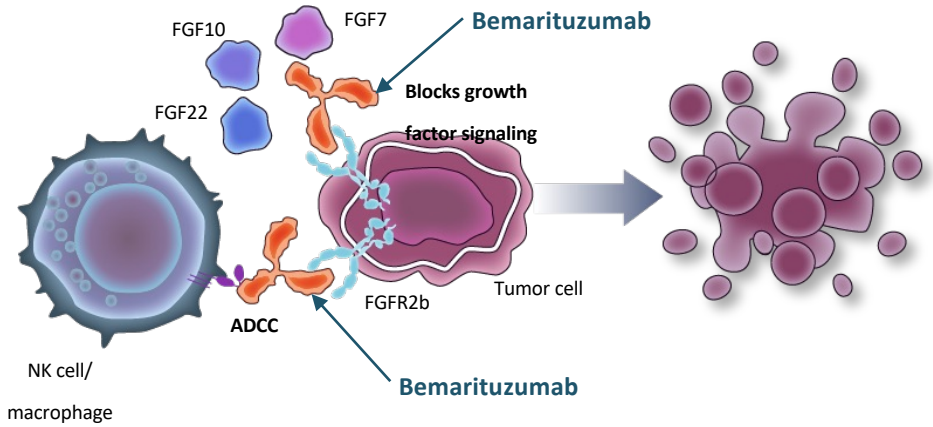
FGFR2b is a member of the FGFR family (FGFR1-4) and is a splice form of FGFR2

FGFR2b overexpression: 3%-61% of gastric cancer depending on tumor stage and assay

FGFR tyrosine kinase inhibitors have shown clinical benefit in cancers with FGFR mutations, fusions, or translocations



- Bemarituzumab is an IgG1 antibody specific to the FGFR2b receptor



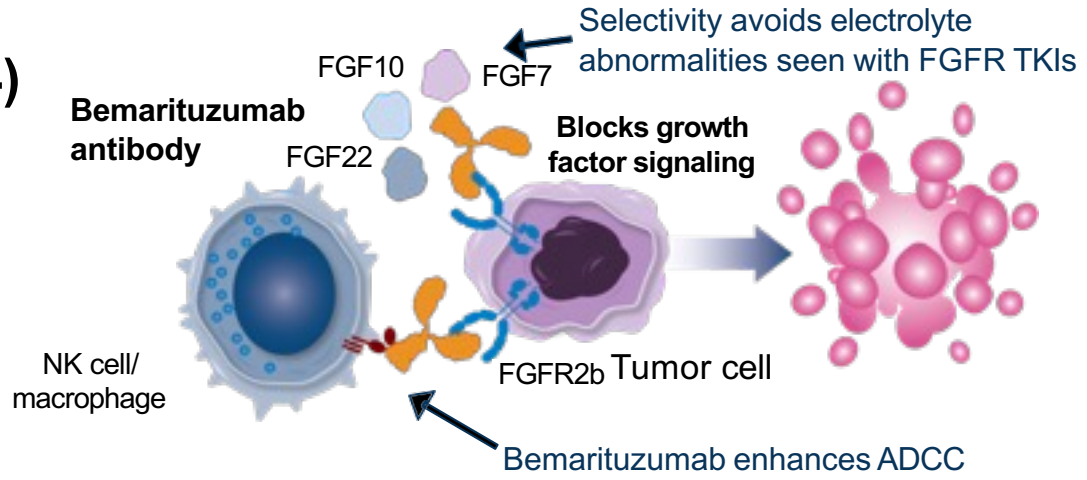
NK = natural killer; mTOR = mammalian target of rapamycin; MAPK = mitogen-activated protein kinase

Han N et al. *Pathobiology*. 2015;82(6):269-79. Nagatsuma AK et al. *Gastric Cancer*. 2015;18(2):227-38. Loriot Y et al. *N Engl J Med*. 2019;381(4):338-48. Catenacci DVT et al. *J Clin Oncol*. 2020;38(21):2418-26. Adapted from Catenacci DVT et al. *Future Oncol*. 2019;15(18):2073-82.

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

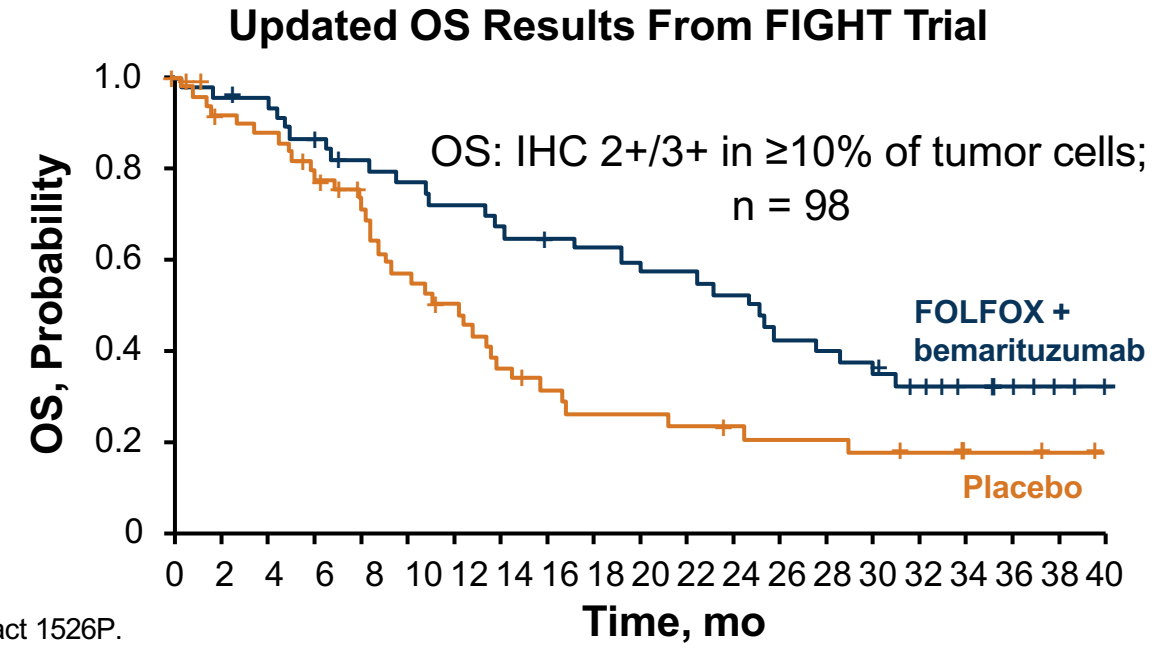
Bemarituzumab (anti-FGFR2b mAb, AMG522, FPA144)

- 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.
- However as of Jan 12, 2024 FDA has not approved zolbetuximab due to unresolved deficiencies following its pre-license inspection of a third-party manufacturing facility.

Moving on to ASCO 2024

MOFFITT CANCER CENTER

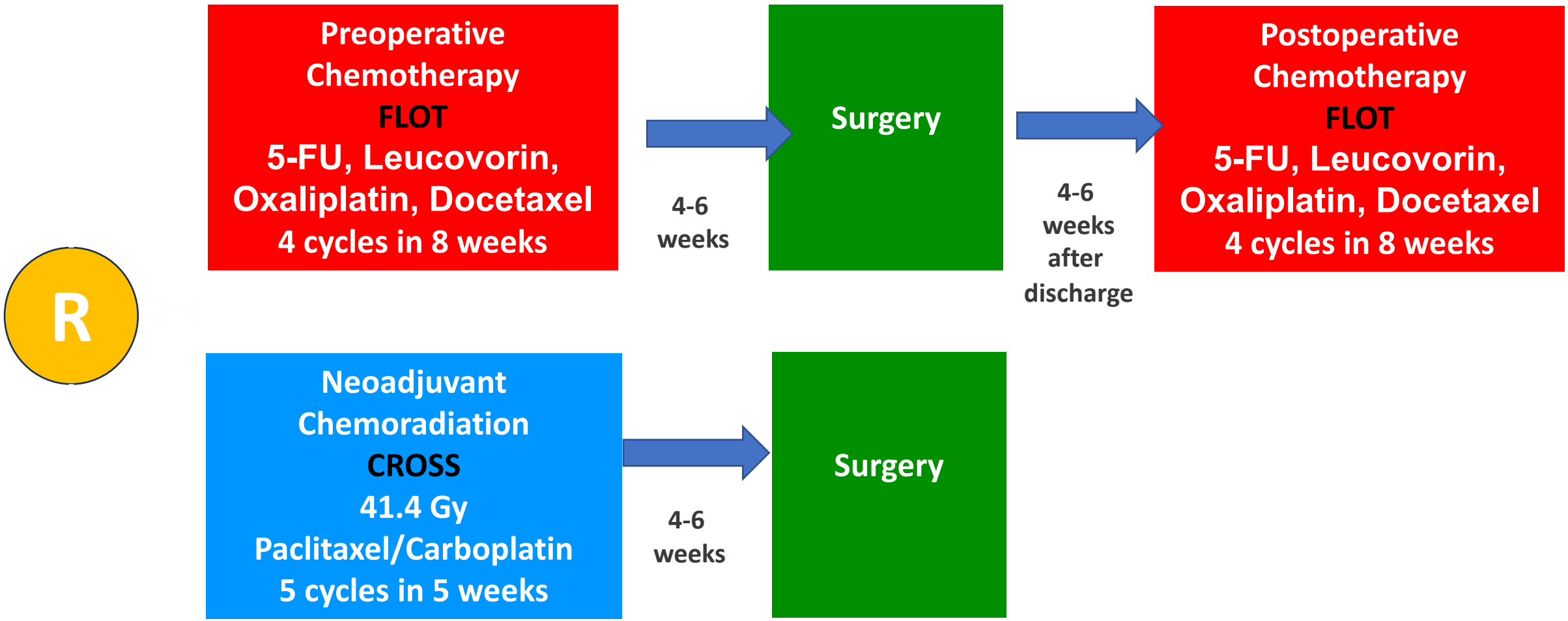
2024 ASCO® ANNUAL MEETING

Perioperative Chemotherapy (FLOT) versus Neoadjuvant Chemoradiotherapy (CROSS) for Resectable Esophageal Adenocarcinoma

The ESOPEC Trial (NCT02509286)

J Hoeppner, F Lordick, T Brunner, C Schmoor, B Kulemann, UP Neumann, G Folprecht, T Keck, F Benedix, M Schmeding, E Reitsamer, CJ Bruns, JF Lock, B Reichert, M Ghadimi, K Wille, I Gockel, JR Izbicki, S Utzolino, P Grimminger

ESOPEC Trial Scheme



Jens Hoeppner et al LBA 1 ASCO 2024

Main Eligibility Criteria

Inclusion Criteria

- **Histology: Adenocarcinoma**
- **Esophageal cancer according UICC (TNM7)[1,*]**
- **Clinical stage cT1N+ or cT2-4a, cN0/+, cM0**

Exclusion Criteria

- **Squamous or other non-adenocarcinoma histology**
- **Gastric cancer**
- **Clinical Stage cT1cN0 and cT4b**
- **Metastatic disease**

Tumors of the esophagus and tumors of which the epicenter is within 5 cm of the esophagogastric junction and also extend into the esophagus.

1. Sobin LH UICC TNM 7th edition 2009

Key Trial Endpoints

Primary Endpoint

Overall survival (OS)

Progression free survival (PFS)

Postoperative pathological stage

Postoperative complications

Adverse events

Recurrence free survival

Site of tumor recurrence

Quality of life

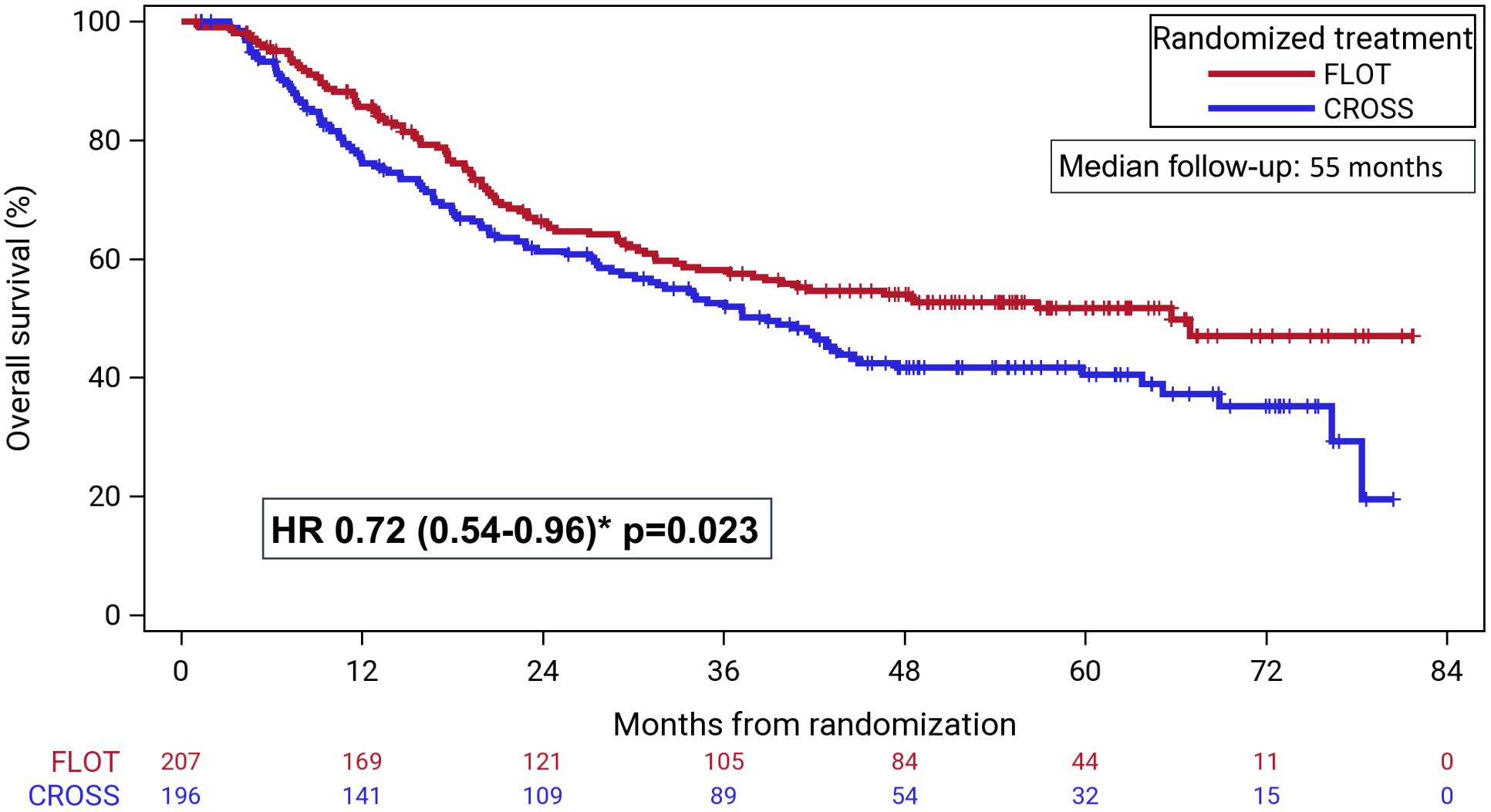
Jens Hoeppner et al LBA 1 ASCO 2024

Characteristics of ESOPEC Trial Patients

	FLOT Group	CROSS Group
N	221	217
Age mean (SD) in years	63.1 (8.6)	62.6 (9.8)
Sex male	89.1 %	89.4 %
ECOG		
> 0	26.7%	28.1%
Clinical T-stage		
cT1-2	19.5%	17.1%
cT3-4	79.1%	81.9%
Clinical N-stage		
cN0	22.2%	18.4%
cN+	77.8%	81.6%

1. Missing: 2 patients
2. Siewert BJS 1998
3. Tx:5 patients; Missing 2 patients

Overall Survival – PP Population



	FLOT	CROSS
Events	**92**	**110**
Median OS time (months)	**66** 95% CI 38 – n.e	**39** 95% CI 29 – 45
3-year OS rate	**58.1%**	**52.6%**
5-year OS rate	**51.8%**	**40.5%**

Two-sided 95% confidence interval; Cox regression adjusted for N stage and age, stratified for trial site

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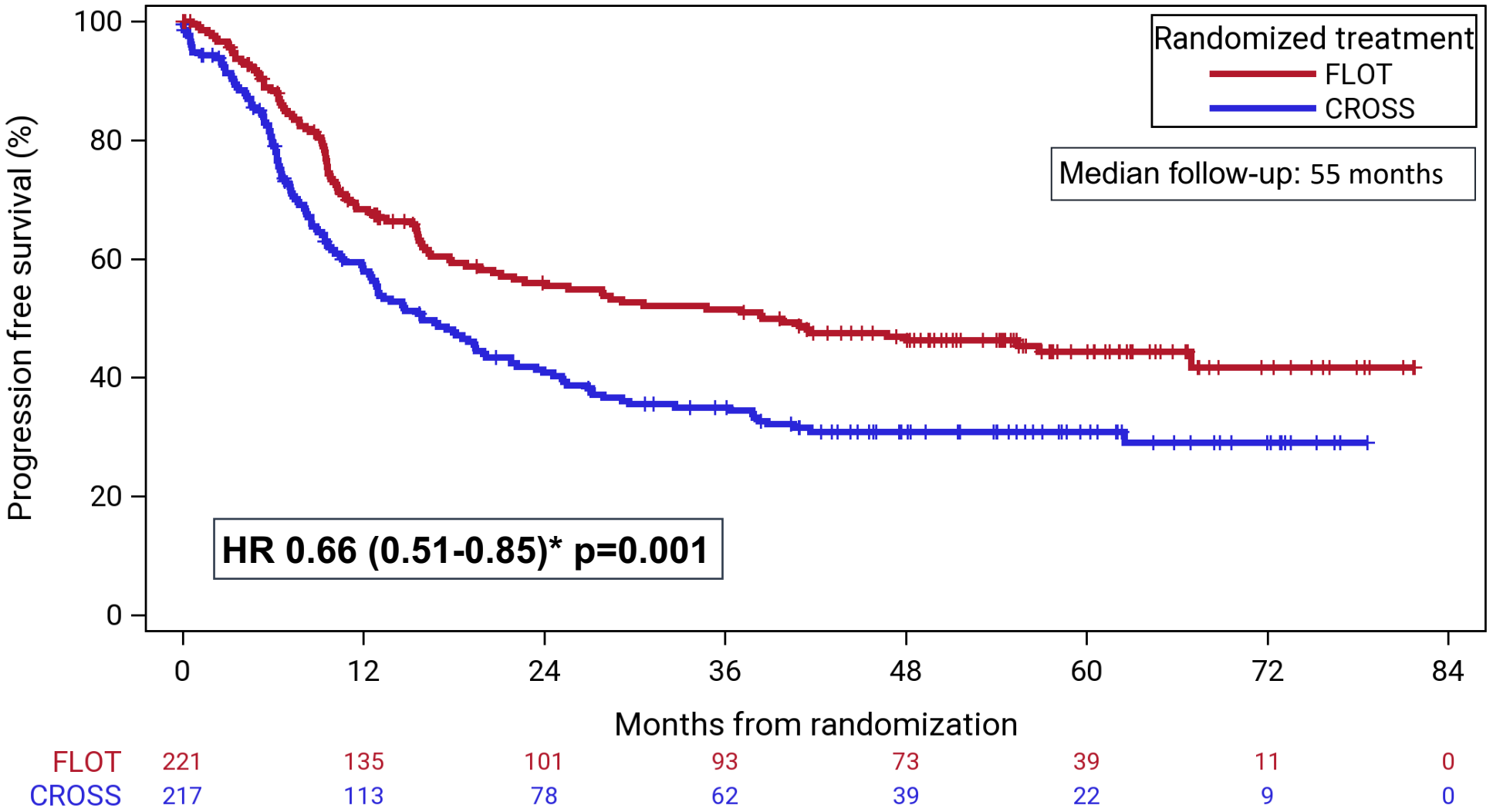
Progression Free Survival – ITT Population



	FLOT	CROSS
Events	107	137
Median PFS time (months)	38 95% CI 21 – n.e.	16 95% CI 12 – 22
3-year PFS rate	51.6%	35.0%
5-year PFS rate	44.4%	30.9%

*Two-sided 95% confidence interval; Cox regression adjusted for N stage and age, stratified for trial site

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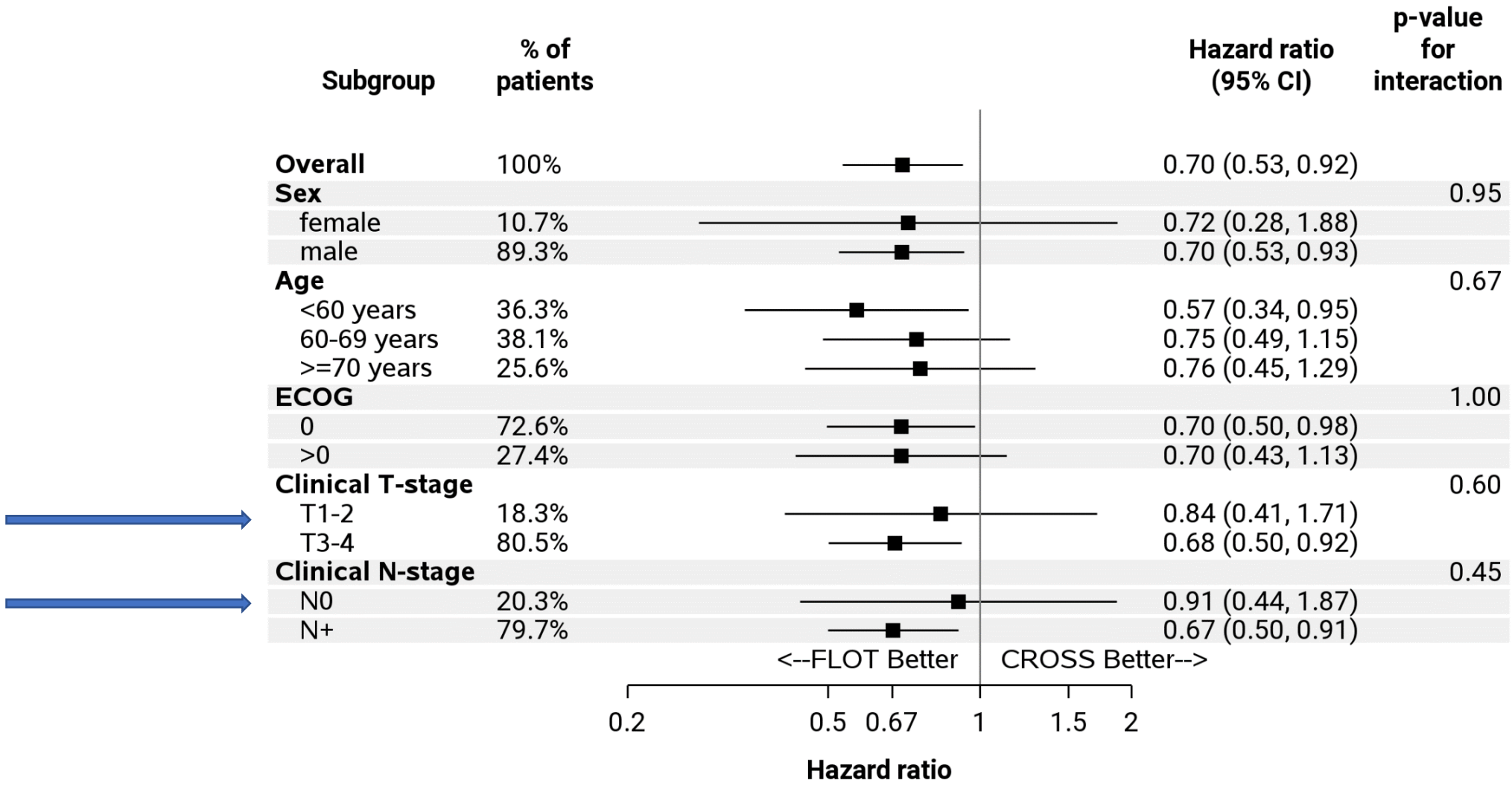
Overall Survival in Exploratory Subgroups



Treatment Exposure

	FLOT Group	CROSS Group
N	**221**	**217**
Started neoadjuvant treatment (PP population*)	**93.7 %**	**90.3 %**
Completed neoadjuvant treatment	**87.3 %**	**67.7 %#**
Received neoadjuvant treatment plus surgery	**86.0 %**	**82.9 %**
Received adjuvant treatment	**63.3 %**	
Completed adjuvant treatment	**52.5 %**	

protocol population according to Clinical Trial Protocol and Statistical Analysis Plan

#Completion rate (41.4Gy) of radiotherapy **98%**

Conclusions

- Perioperative FLOT improved median overall survival (OS) by 29 months when compared with neoadjuvant CROSS.
- Surgical complications and postoperative mortality were similar in the FLOT and CROSS arms
- FLOT will likely be adopted as a more standard approach in the United States for esophageal and GEJ adenocarcinomas
- However we cannot conclude that perioperative FLOT is better than preoperative CROSS and adjuvant nivolumab.

Thank You for Your Attention

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