Finally, Something Practice Changing in Esophageal Carcinoma
PRIMO 2025

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2-6-2025

ACS 2024: Esophageal Cancer

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2024 Estimates

Estimated New Cases

Male			Female		
Prostate	299,010	29%	Breast	310,720	32%
Lung & bronchus	116,310	11%	Lung & bronchus	118,270	12%
Colon & rectum	81,540	8%	Colon & rectum	71,270	7%
Urinary bladder	63,070	6%	Uterine corpus	67,880	7%
Melanoma of the skin	59,170	6%	Melanoma of the skin	41,470	4%
Kidney & renal pelvis	52,380	5%	Non-Hodgkin lymphoma	36,030	4%
Non-Hodgkin lymphoma	44,590	4%	Pancreas	31,910	3%
Oral cavity & pharynx	41,510	4%	Thyroid	31,520	3%
Leukemia	36,450	4%	Kidney & renal pelvis	29,230	3%
Pancreas	34,530	3%	Leukemia	26,320	3%
All sites	**1,029,080**		**All sites**	**972,060**	

Estimated Deaths

Male			Female		
Lung & bronchus	65,790	20%	Lung & bronchus	59,280	21%
Prostate	35,250	11%	Breast	42,250	15%
Colon & rectum	28,700	9%	Pancreas	24,480	8%
Pancreas	27,270	8%	Colon & rectum	24,310	8%
Liver & intrahepatic bile duct	19,120	6%	Uterine corpus	13,250	5%
Leukemia	13,640	4%	Ovary	12,740	4%
Esophagus	12,880	4%	Liver & intrahepatic bile duct	10,720	4%
Urinary bladder	12,290	4%	Leukemia	10,030	3%
Non-Hodgkin lymphoma	11,780	4%	Non-Hodgkin lymphoma	8,360	3%
Brain & other nervous system	10,690	3%	Brain & other nervous system	8,070	3%
All sites	**322,800**		**All sites**	**288,920**	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

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- American Cancer Society. *Cancer Facts & Figures 2024*. Atlanta: American Cancer Society; 2024; Journal of the National Comprehensive Cancer Network 20, 10;10.6004/jnccn.2022.7056

Learning Objectives

- Metastatic Esophageal carcinoma
  - Squamous cell carcinoma: CM-648, KN-590
  - Adenocarcinoma
    - Biomarkers: PDL1, HER2, CLDN18.2, MMR
    - CM-649, Rationale-305

- Adjuvant Esophageal carcinoma
  - CheckMate - 577

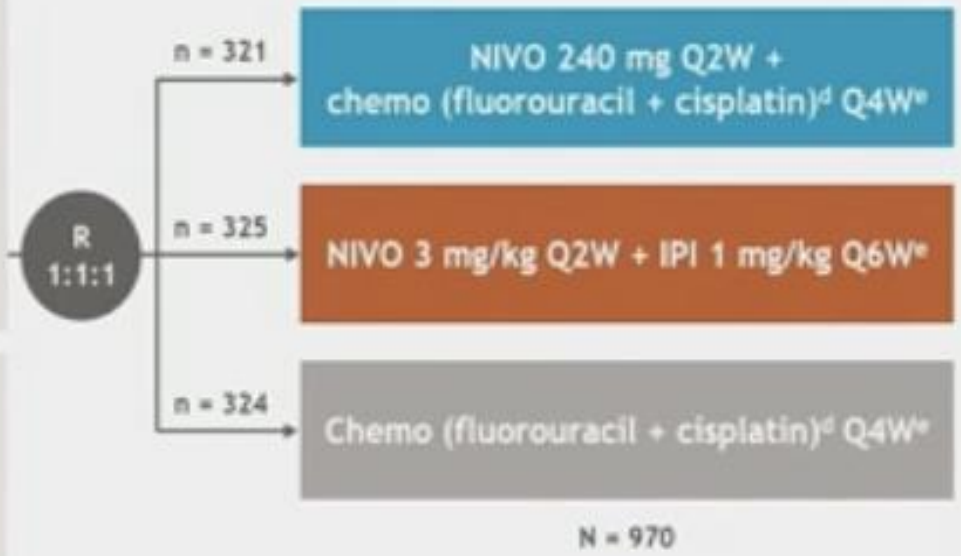
- Neoadjuvant Esophageal carcinoma
  - Esopec, Topgear, Matterhorn, Neonipiga

CheckMate 648 study design

- CheckMate 648 is a global, randomized, open-label phase 3 study[a]

Key eligibility criteria
- Unresectable advanced, recurrent, or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (East Asia[c] vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases (≤ 1 vs ≥ 2)



Primary endpoints:
- OS and PFS[f] (tumor cell PD-L1 ≥ 1%)

Secondary endpoints:
- OS and PFS[f] (all randomized)
- ORR[f] (tumor cell PD-L1 ≥ 1% and all randomized)

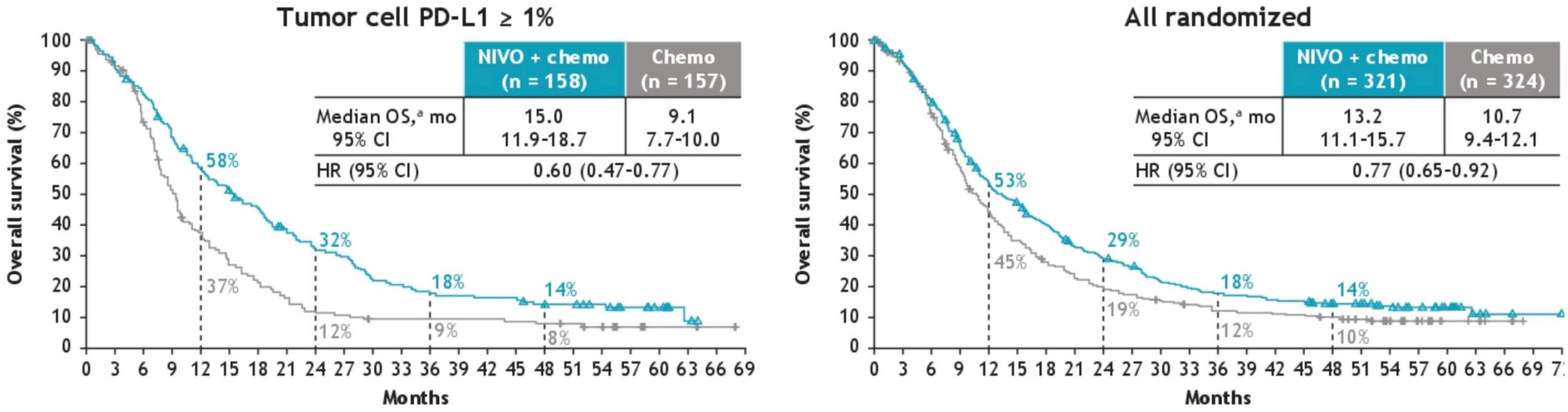
Exploratory endpoint:
- Biomarkers

- At data cutoff (May 17, 2022), the minimum follow-up[g] was 29 months
- Biomarker methods:
  - Gene expression signatures (GES) were assessed by RNA sequencing of baseline tumor tissue[h]
  - TMB and select gene alterations were assessed by whole exome sequencing (WES) of baseline tumor tissue and matching blood samples[i]

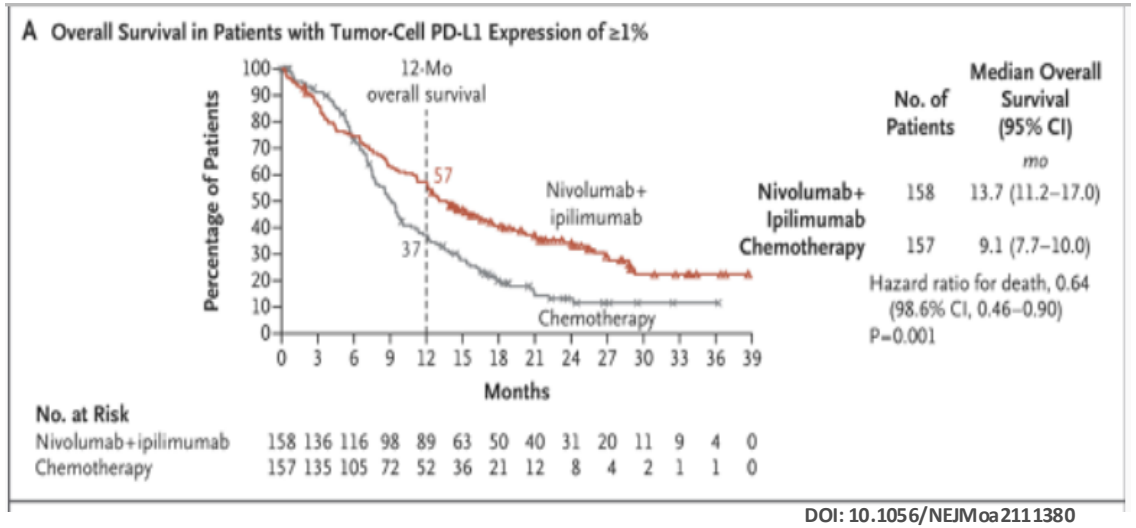
Li, N., Sohal, D. Current state of the art: immunotherapy in esophageal cancer and gastroesophageal junction cancer. *Cancer Immunol Immunother* **72**, 3939–3952 (2023). https://doi.org/10.1007/s00262-023-03566-5

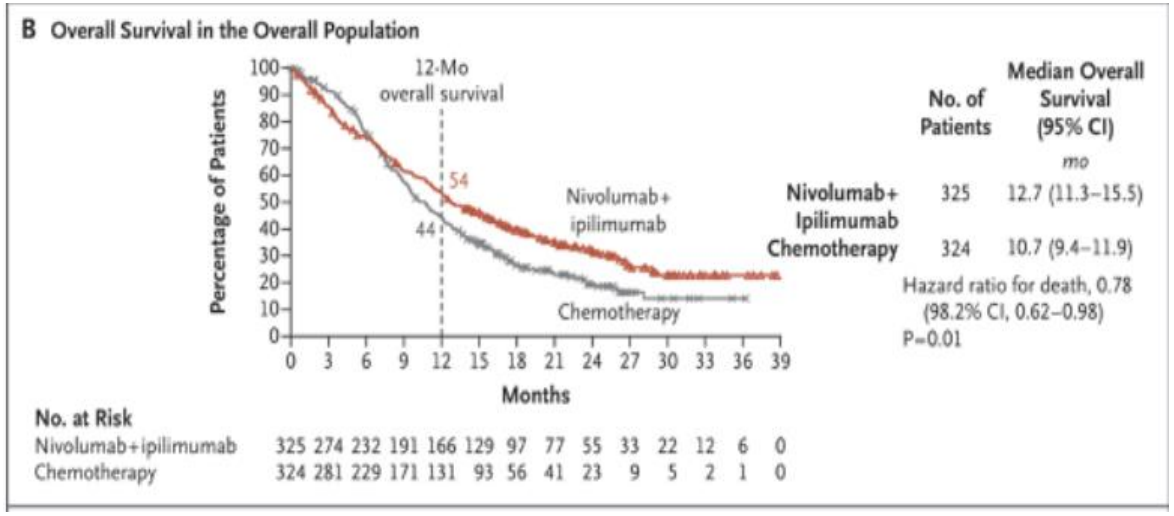
Doki Y et al (2022) Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. N Engl J Med 386(5):449–462

OS: Nivolumab + Chemo vs Chemo



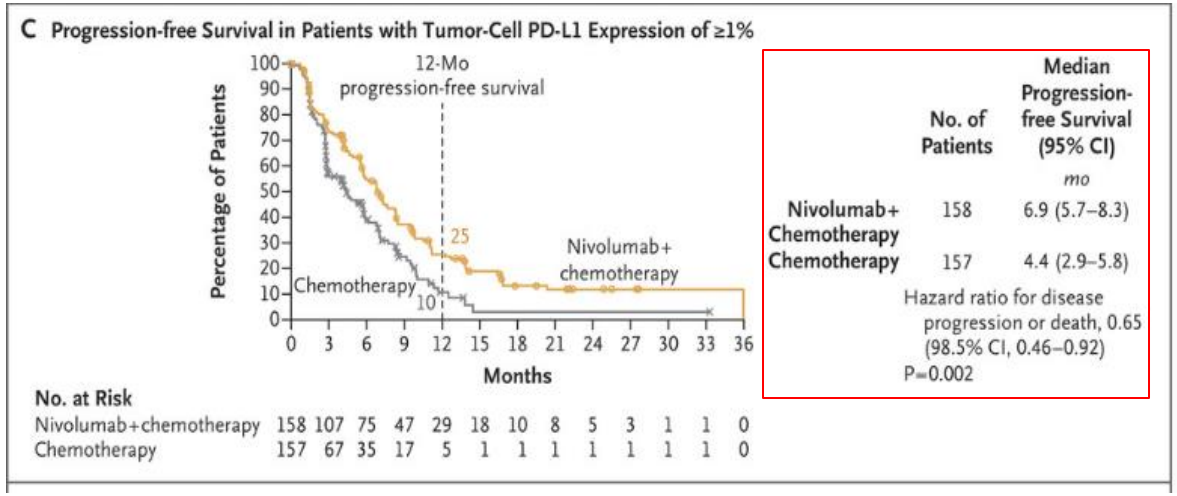
OS: Nivolumab + Ipilimumab vs Chemo

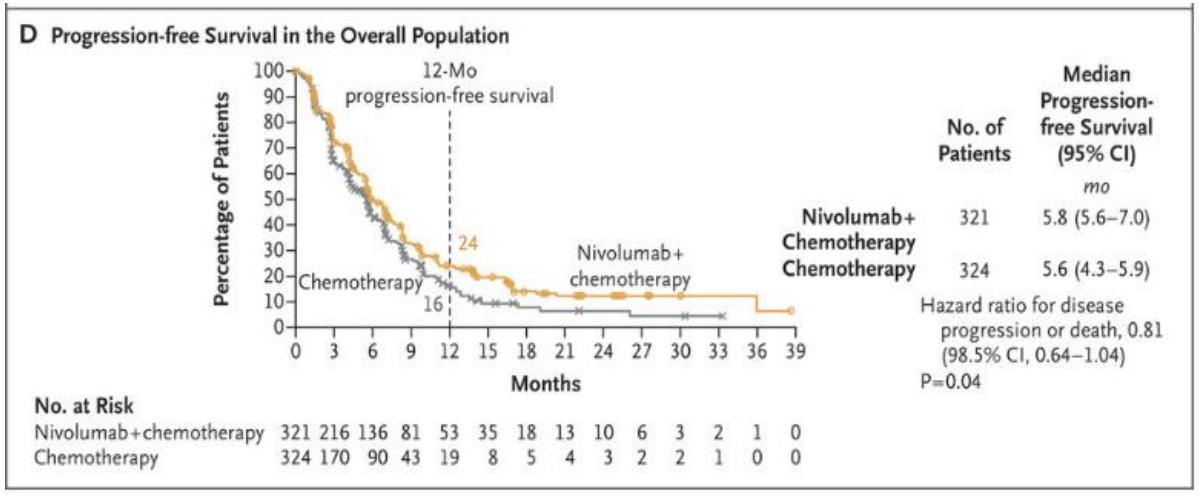




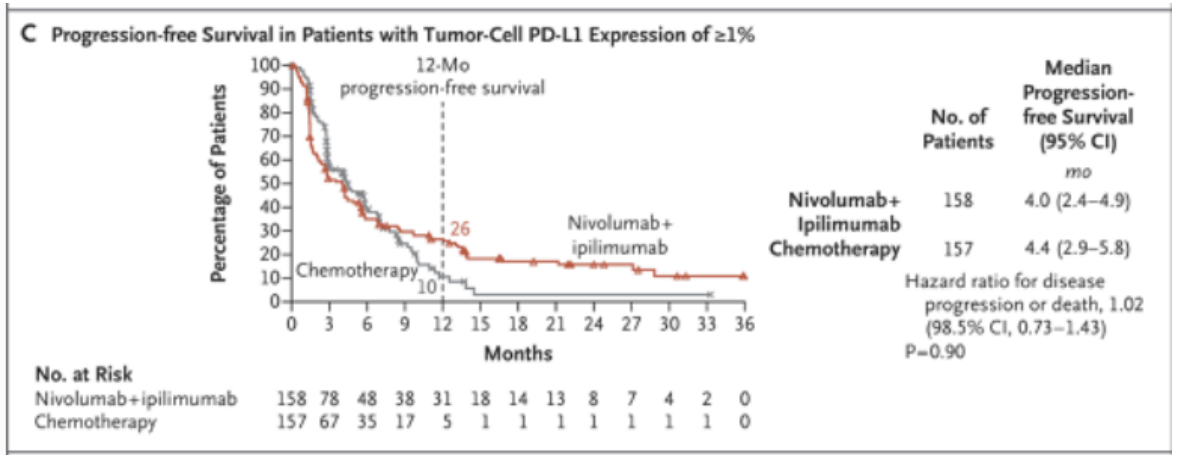
DOI: 10.1056/NEJMoa2111380

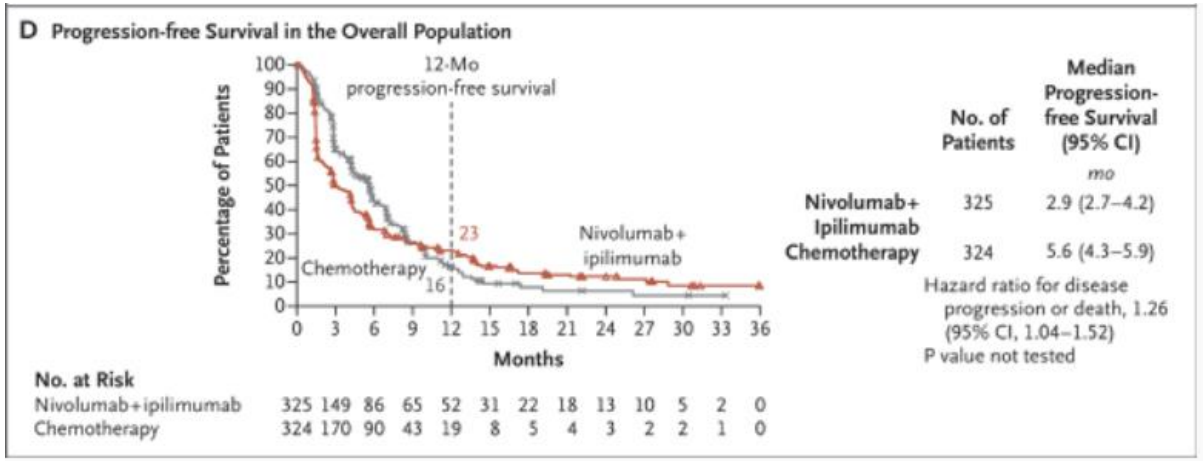
PFS: Nivolumab + Chemo vs Chemo





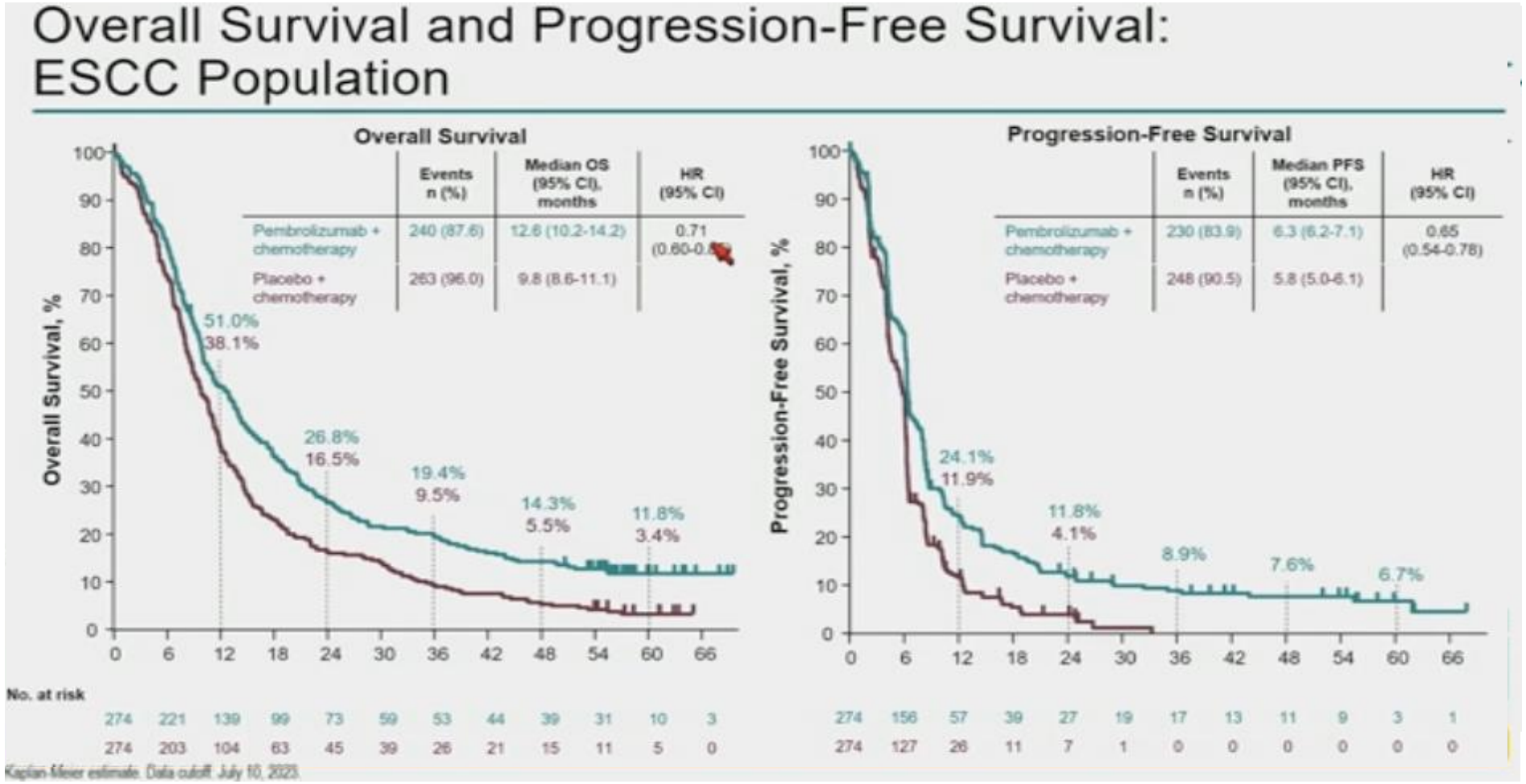
PFS: Nivolumab + Ipilimumab vs Chemo





DOI: 10.1056/NEJMoa2111380

ESCC: KN-590 5-Year Survival Outcomes



Sun JM et al (2021) Pembrolizumab plus chemotherapy vs chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet 398(10302):759–771

NCCN 5.2024

SQUAMOUS CELL CARCINOMA

First-Line Therapy
- Oxaliplatin is preferred over cisplatin due to lower toxicity.

Preferred Regimens
- Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (category 1)[e,g,55]
- Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (category 2A for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[e,g,27]
- Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[31-33]
- Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and nivolumab (category 1)[e,g,55]
- Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[e,g,27]
- Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[31,34-36]
- Nivolumab and ipilimumab[e,g,55]
- MSI-H/dMMR tumors (independent of PD-L1 status)[d]
  - Pembrolizumab[e,g,37-39]
  - Dostarlimab-gxly[e,g,40]
  - Nivolumab and ipilimumab[e,g,26]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab[e,g,26]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab[e,g,27]

Other Recommended Regimens
- Fluorouracil[b,h] and irinotecan[41]
- Paclitaxel with or without carboplatin or cisplatin[42-46]
- Docetaxel with or without cisplatin[47-50]
- Fluoropyrimidine[35,51,52] (fluorouracil[b] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b,53,54]

SQUAMOUS CELL CARCINOMA

Second-Line or Subsequent Therapy
- Dependent on prior therapy and PS

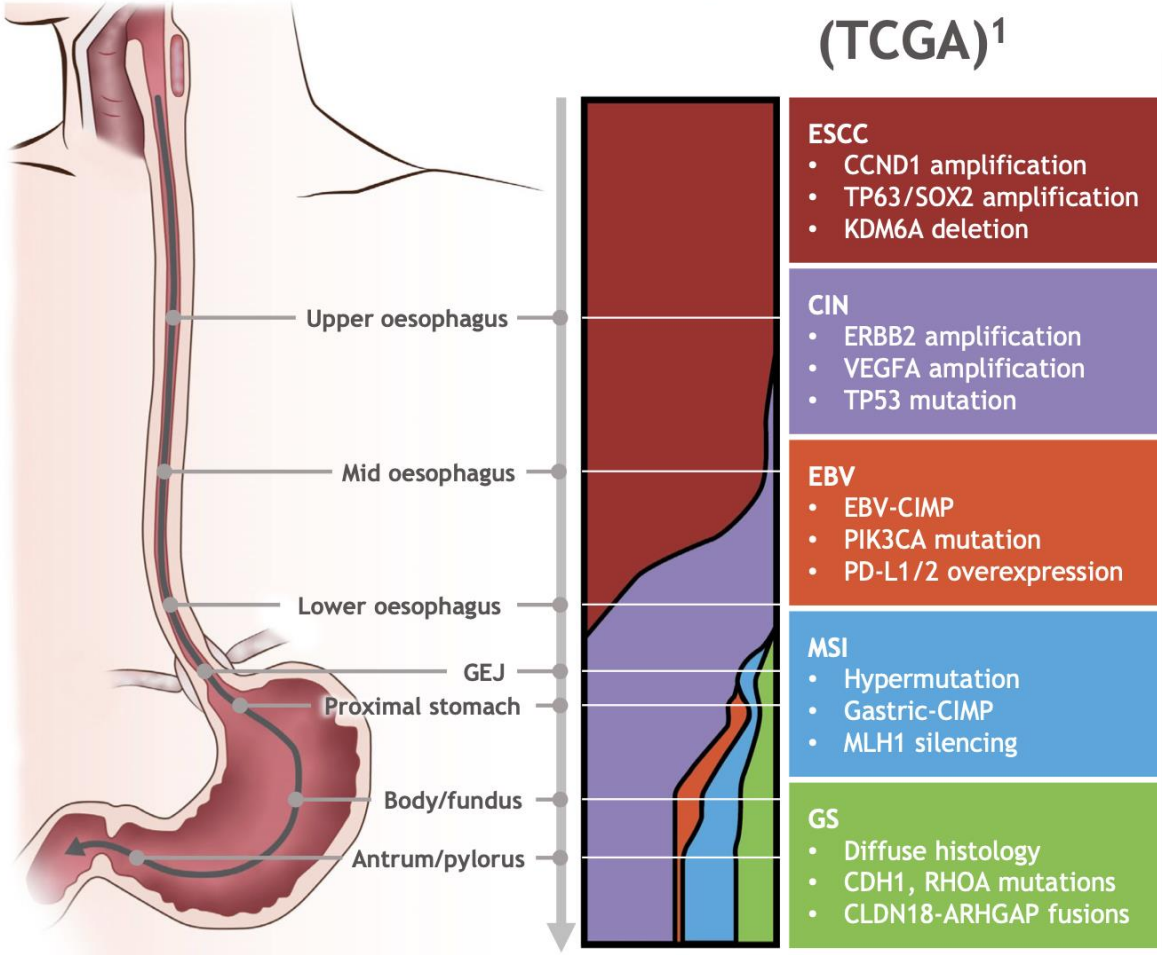
Preferred Regimens
- Nivolumab (category 1)[e,g,76]
- Pembrolizumab[e,g] for tumors with PD-L1 expression levels by CPS of ≥10 (category 1)[77]
- Docetaxel (category 1)[49,50]
- Paclitaxel (category 1)[45,46,58]
- Irinotecan (category 1)[58-61]
- Tislelizumab-jsgr (category 1)[e,l,78,79]
- Fluorouracil[b,h] and irinotecan[59,62,63]

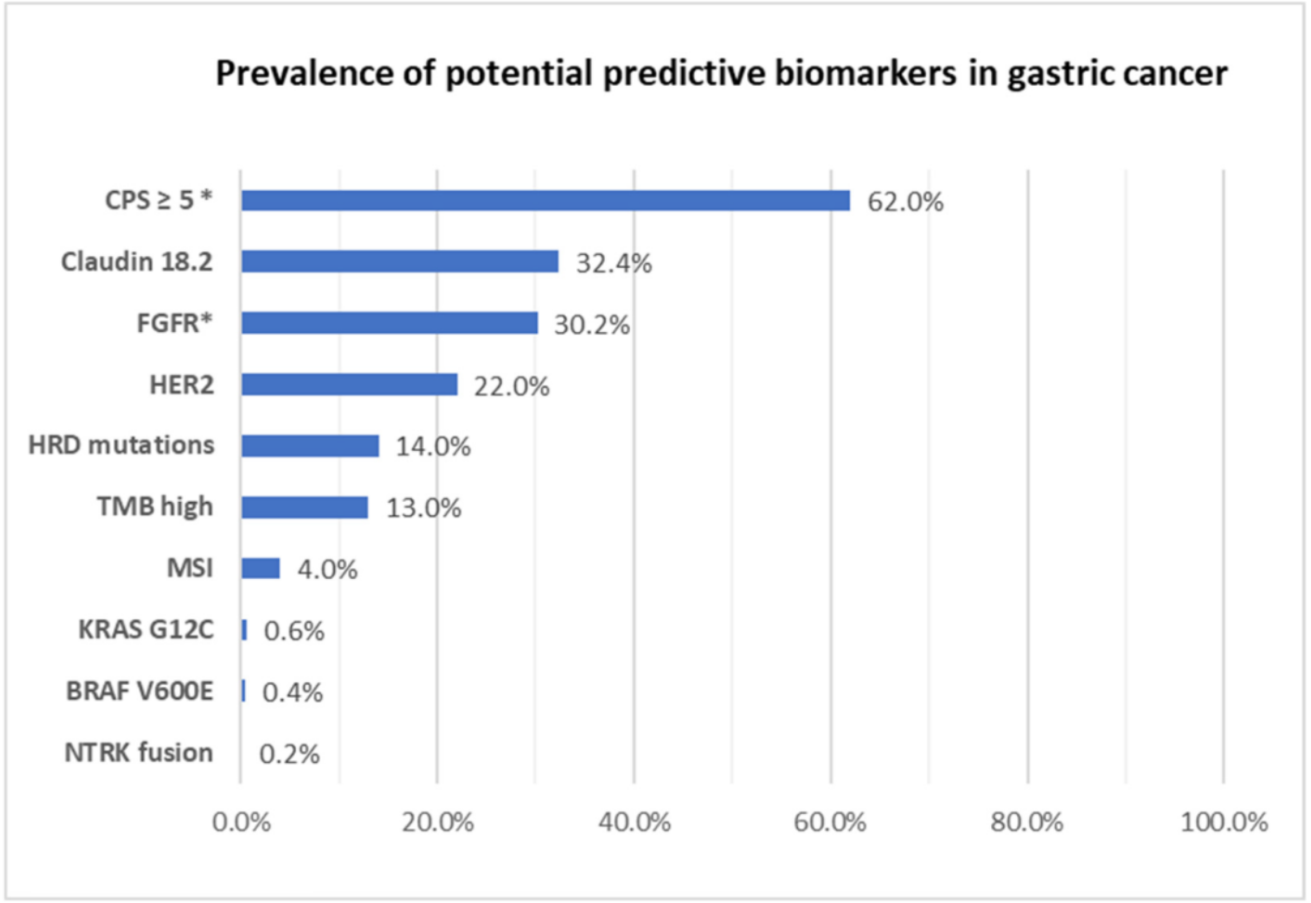
Other Recommended Regimens
- Irinotecan and cisplatin[32,66]
- Docetaxel and irinotecan (category 2B)[69]

Useful in Certain Circumstances[d]
- Entrectinib, larotrectinib, or repotrectinib[j] for *NTRK* gene fusion-positive tumors[70-72]
- Pembrolizumab[e,g] for MSI-H/dMMR tumors[37-39]
- Nivolumab and ipilimumab[e,g] for MSI-H/dMMR tumors[26]
- Pembrolizumab[e,g] for TMB high (≥10 mutations/megabase) tumors[73]
- Dostarlimab-gxly[e,g,k] for MSI-H/dMMR tumors[40]
- Dabrafenib and trametinib for *BRAF* V600E mutated tumors[74]
- Selpercatinib for *RET* gene fusion-positive tumors[75]

Biomarkers in Upper GI Cancers

The Cancer Genomic Atlas (TCGA)[1]





Cancer Genomic Atlas Research Network, Analysis Working Group, et al. *Nature*. 2017;541(7636):169–175.

Malla M, Fuqua J, et al. Optimal First-Line Therapy for Metastatic Adenocarcinoma of the Esophagus. Curr Treat Options Oncol. 2022 Dec;23(12):1748-1760.

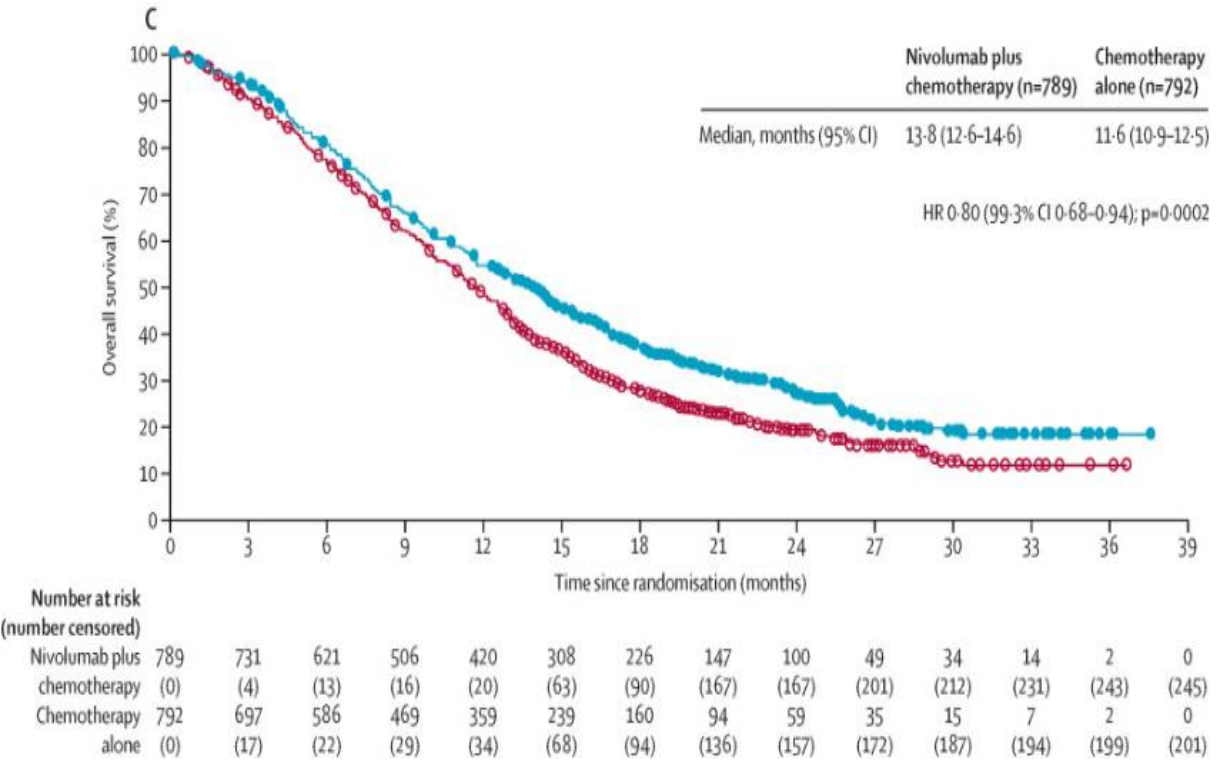
Pihlak R, et al. *Cancers* (Basel). 2023;15(12):3248

Malla M, et al. Curr Treat Options Oncol. 2022 Dec;23(12):1748-1760.

Frontline Chemo-IO Studies

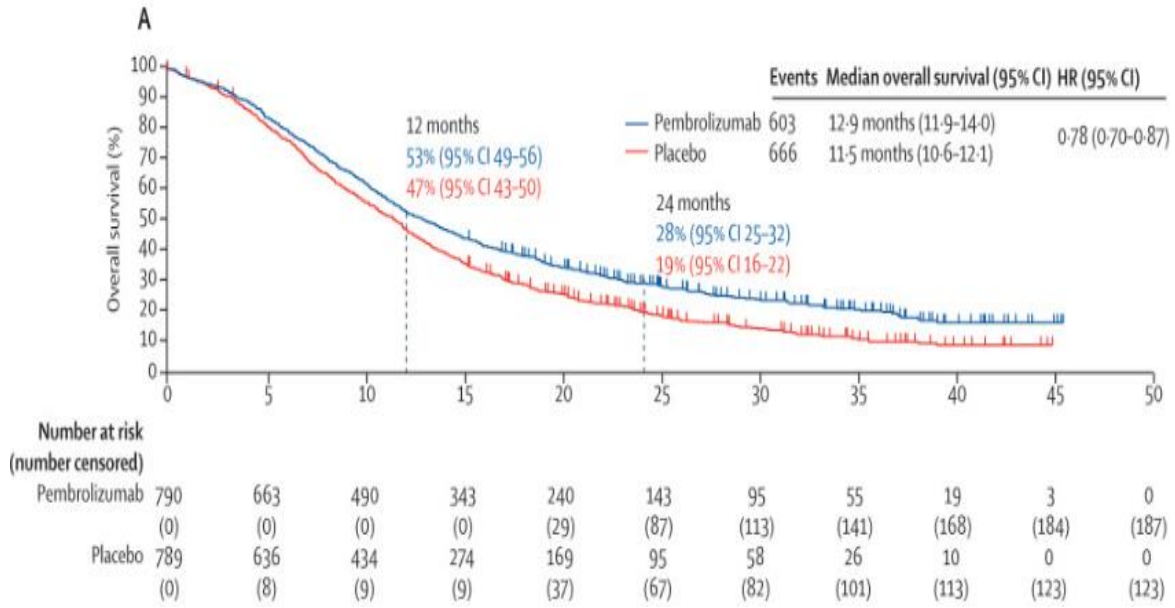
Study	CM-649	ATTRACTION 4	ORIENT 16	KN-859	KN-590	RATIONALE-305
ICI Agent	Nivolumab	Nivolumab	Sintilimab	Pembrolizumab	Pembrolizumab	Tislelizumab
Location	G/GEJ	G/GEJ	G/GEJ	G/GEJ	Esophageal	G/GEJ
Chemotherapy	CAPOX/FOLFOX	CAPOX/SOX	CAPOX	CAPOX/CF	CF	CAPOX/CF
PDL-1 Test	28-8 Dako	28-8 Dako	NA	22C3	22C3	SP263 (TAP score)
CPS	>=5: 60%	>=1: 16%	>=5: 61%	>=10: 35%	>=10: 50%	>=5: 55%
Primary endpoint	OS, PFS	OS, PFS	OS	OS,PFS	OS,PFS	OS
Median OS (M)	13.7 vs 11.6 *14.4 vs 11.1 (CPS >=5)*	17.5 vs 17.1	15.2 vs 12.3	12.9 vs 11.5	11.6 vs 9.9	15 vs 12.9 17.2 vs 12.6 (TAP>=5)

CHECKMATE -649



Janjigian, Yelena Y et al. The Lancet, Volume 398, Issue 10294, 27 - 40

KN-859



Rha, Sun YoungMendez, Guillermo et al. The Lancet Oncology, Volume 24, Issue 11, 1181 - 1195

RATIONALE -305

Baseline Characteristics in the PD-L1+ Analysis Set

		TIS + Chemo (n=274)	Placebo + Chemo (n=272)
Median age, years (range)		61.0 (23.0-83.0)	62.0 (30.0-84.0)
Male sex, % (n)		70.4 (193)	73.9 (201)
Region, % (n)	East Asia[a]	73.7 (202)	73.9 (201)
	Rest of world[b]	26.3 (72)	26.1 (71)
ECOG PS, % (n)	0	35.8 (98)	31.6 (86)
	1	64.2 (176)	68.4 (186)
Primary location, % (n)	Stomach	81.4 (223)	78.7 (214)
	GEJC	18.6 (51)	21.3 (58)
Investigator-chosen chemo, % (n)	XELOX	92.7 (254)	93.4 (254)
	FP	7.3 (20)	6.6 (18)
Metastatic diseases, % (n)		98.5 (270)	98.5 (268)
Peritoneal metastasis, % (n)		41.2 (113)	40.1 (109)
Prior adjuvant/neoadjuvant treatment, % (n)		13.5 (37)	14.0 (38)

Data cutoff: October 08, 2021. Median follow up was 15.9 months in the TIS + chemo arm and 16.8 months in the placebo + chemo arm.
In the ITT population, 54.7% of patients in the TIS + chemo arm and 54.8% of patients in the placebo + chemo arm had a PD-L1 score of ≥5% and were included in the PD-L1+ analysis set.
[a]East Asia includes China (including Taiwan), Japan, and South Korea; [b]Rest of world includes US and EU.

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PDL1 –Positive GC/GEJC

Overall Survival (OS)

Figure 1. OS in Patients Without Peritoneal Metastasis

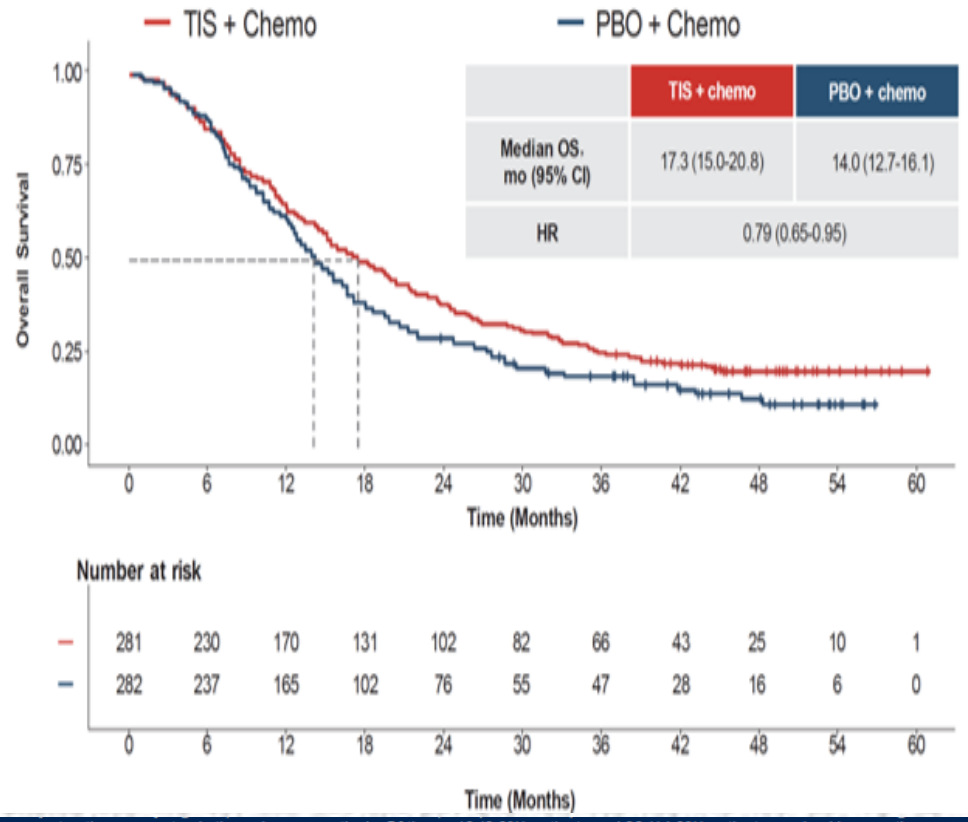
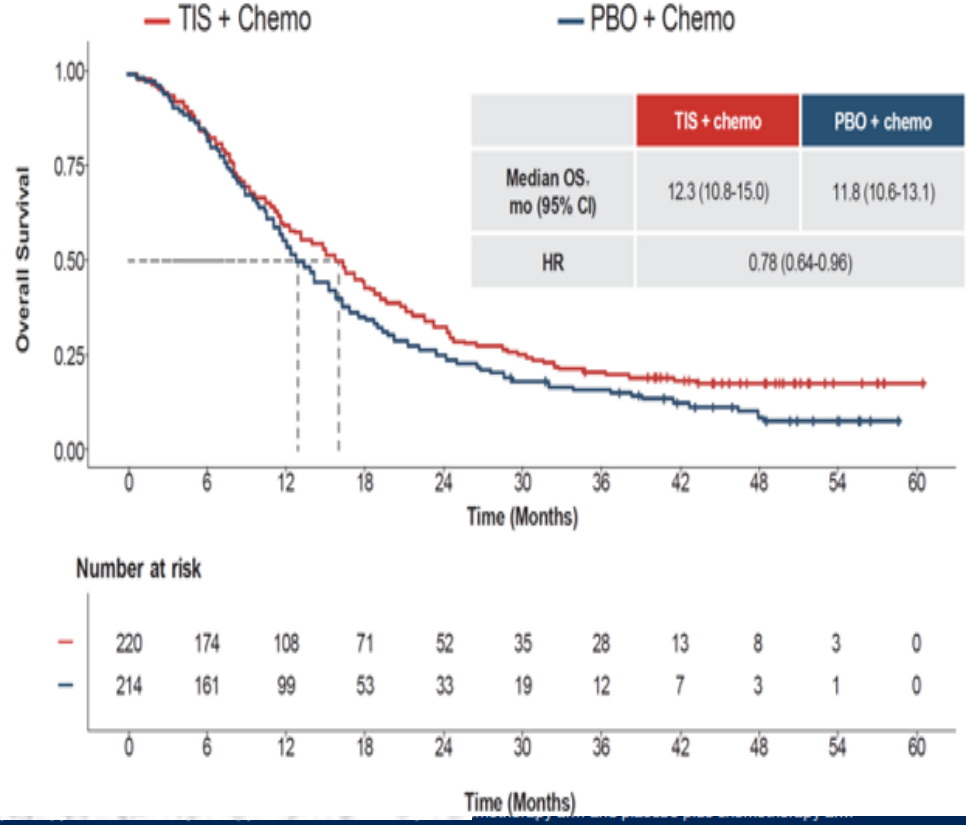


Figure 2. OS in Patients With Peritoneal Metastasis



received subsequent anticancer systemic therapies, respectively. Of those, 19 (6.9%) patients and 38 (14.0%) patients received immunotherapy.

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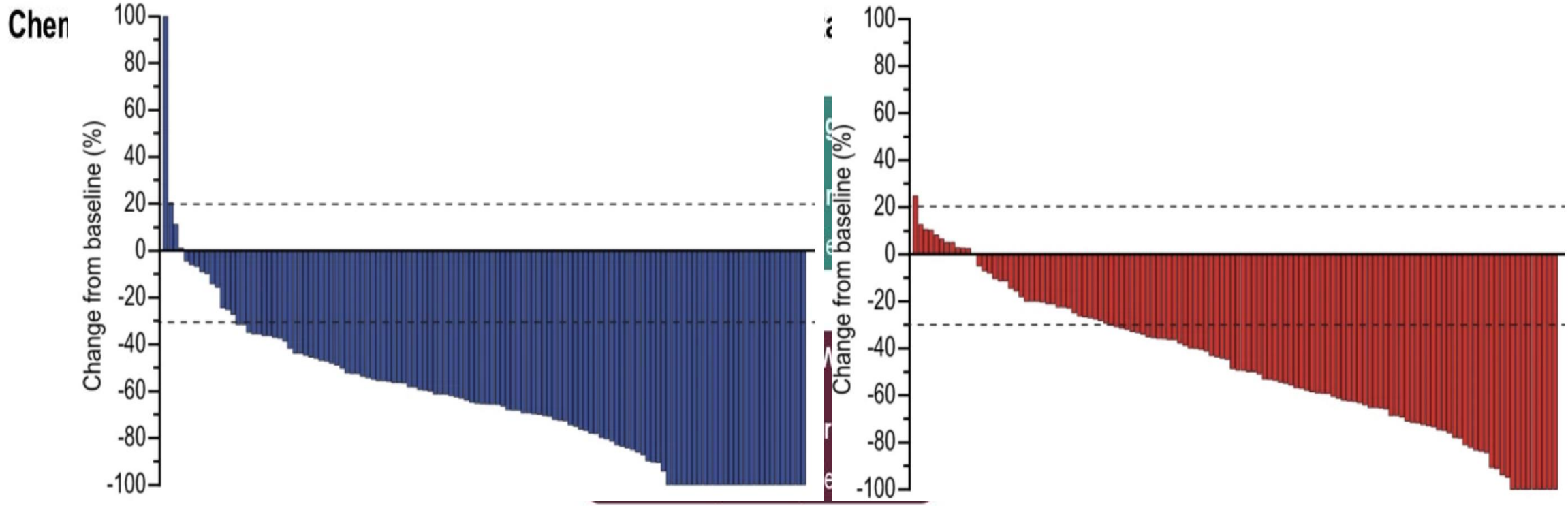
https://doi.org/10.1200/JCO.2023.41.4_suppl.286; Qiu M et al. Poster Presentation at ASCO-GI 2025; 414.

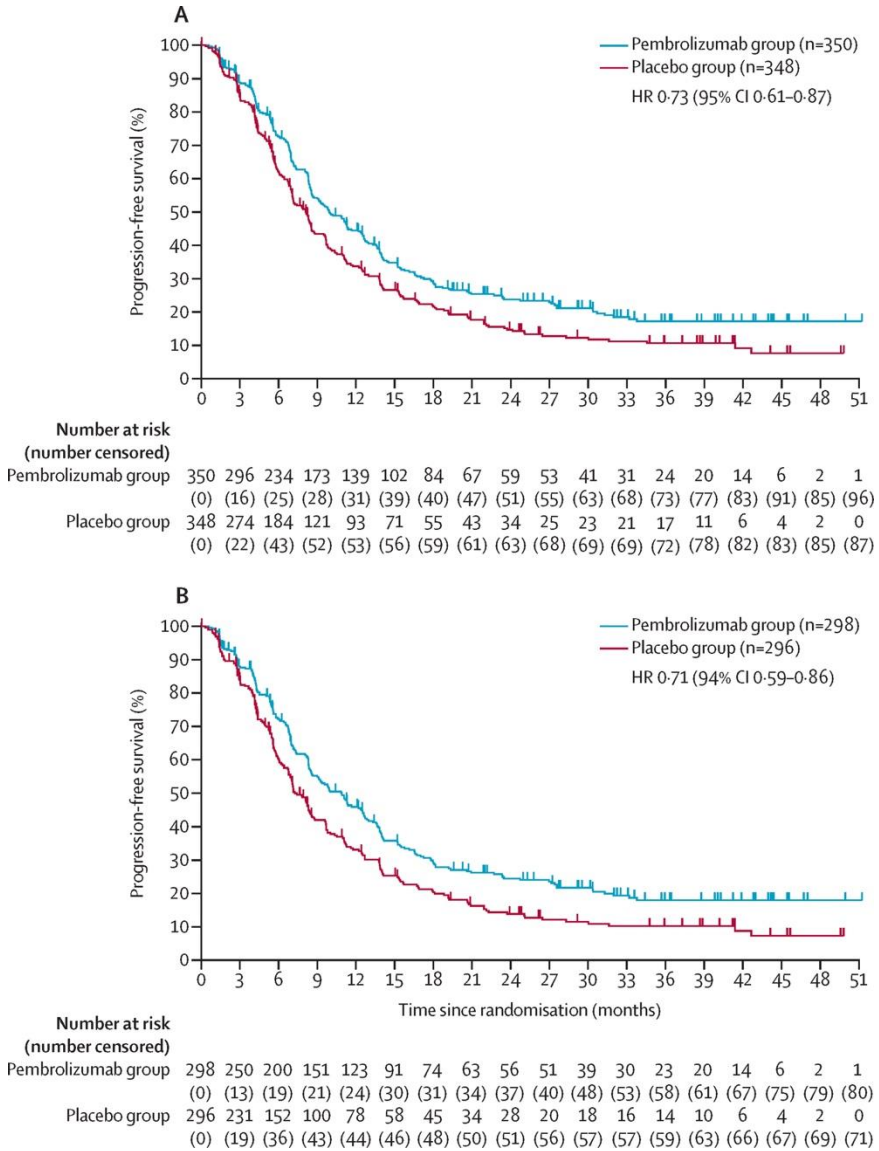
HER-2 GEJ/Gastric Cancers

	Experimental arm (N-124)	Placebo arm (N-122)
ORR	74%	52%



[a]Trastuzumab dose: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP dose: 5-fluorouracil 800 mg/m² IV on D1-5 Q3W + cisplatin 80 mg/m² IV Q3W. CAPOX dose: capecitabine 1000 mg/m² BID on D1-14 Q3W + oxaliplatin 130 mg/m² IV Q3W.
BICR, blinded independent central review; CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100).

anjigan Nature, 2021



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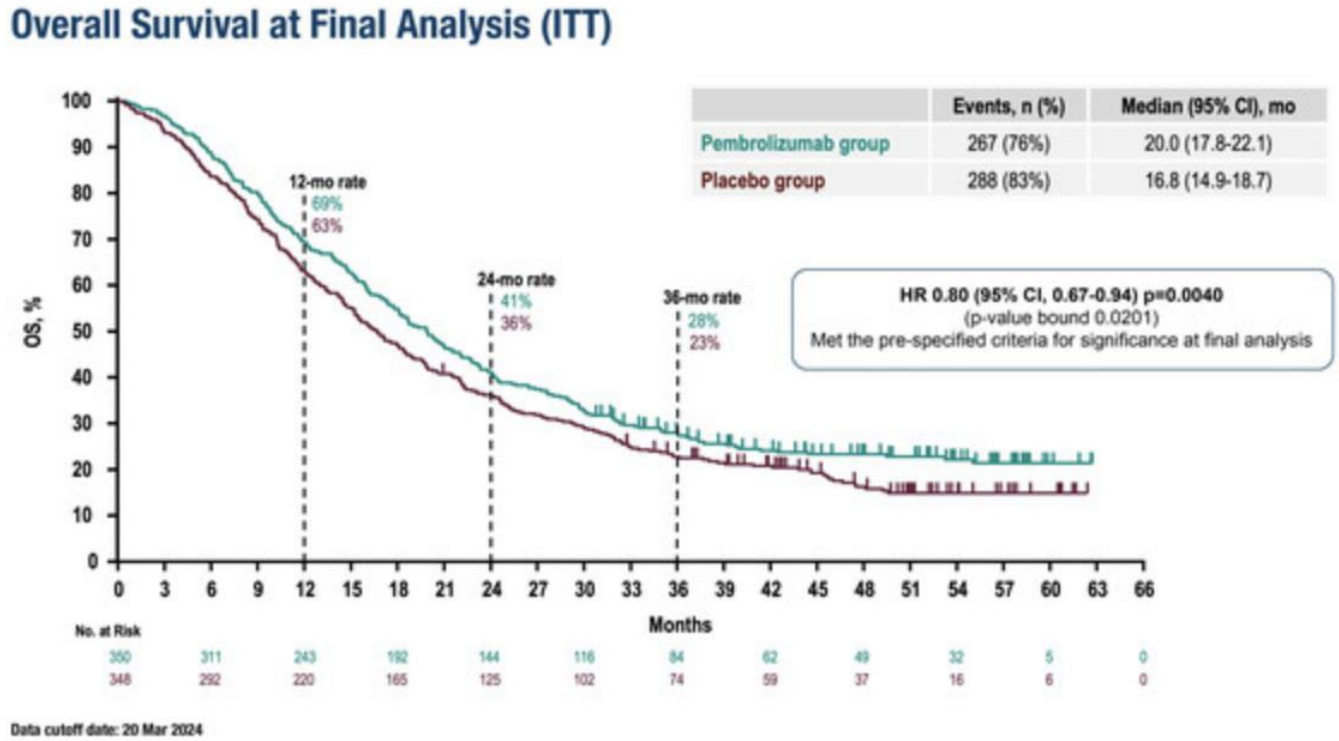


TABLE 1: Survival Status by PD-L1 CPS Level From KEYNOTE-811

	PD-L1 CPS ≥ 1		PD-L1 CPS < 1	
	Pembro Group (n = 298)	Placebo Group (n = 296)	Pembro Group (n = 52)	Placebo Group (n = 52)
Median PFS	10.9 months	7.3 months	9.5 months	9.5 months
Hazard ratio	0.72		0.99	
Median OS	20.1 months	15.7 months	18.2 months	20.4 months
Hazard ratio	0.79		1.10	

CPS = combined positive score; OS = overall survival; Pembro = pembrolizumab; PFS = progression-free survival.

https://ascopost.com/issues/october-25-2024/keynote-811-pembrolizumab-combination-in-first-line-setting-improves-overall-survival-in-gastric-cancer

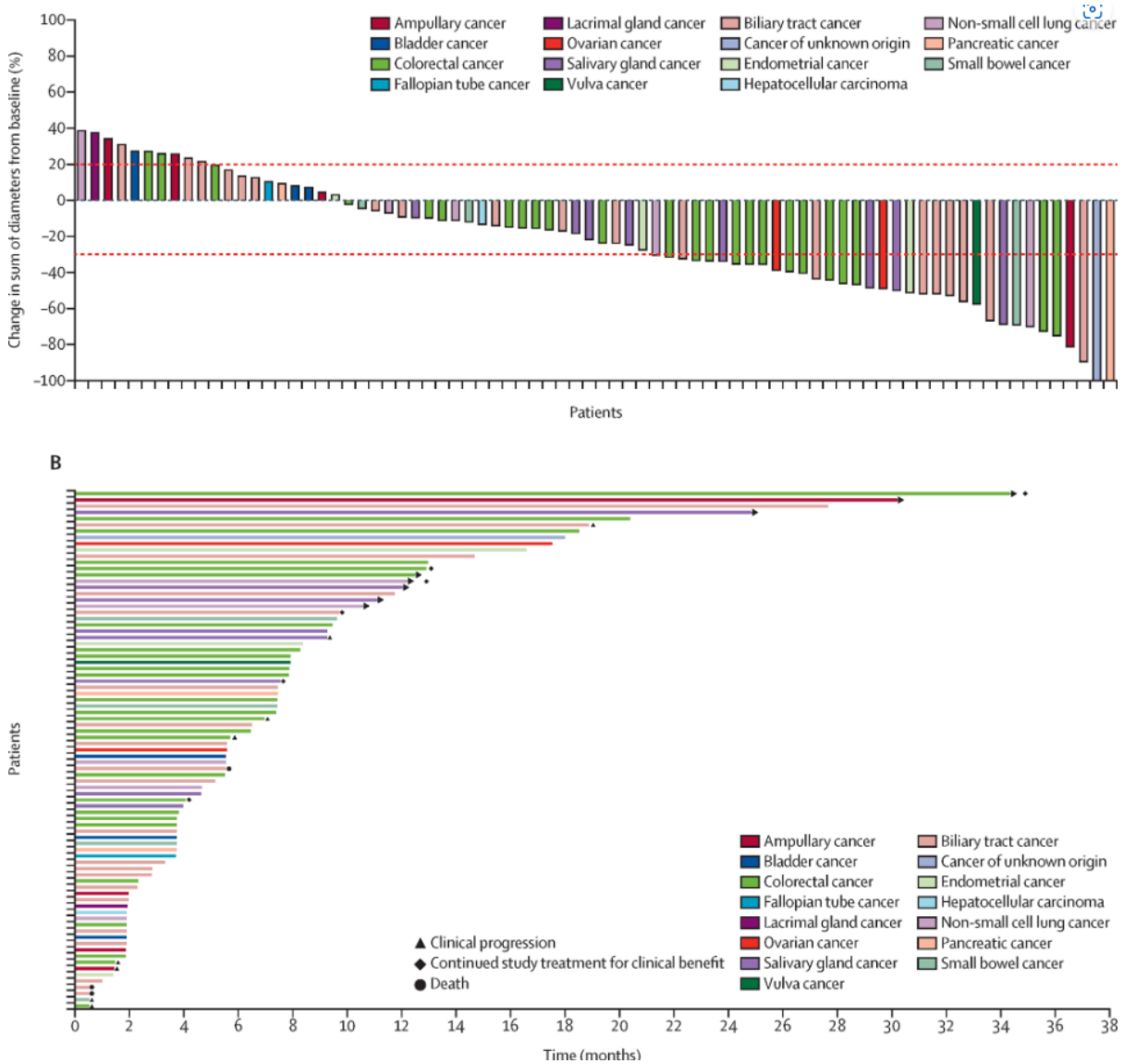
Zanidatamab

Simultaneously binds two HER2 epitopes:
- ECD4 - trastuzumab binding domain
- ECD2 - pertuzumab binding domain

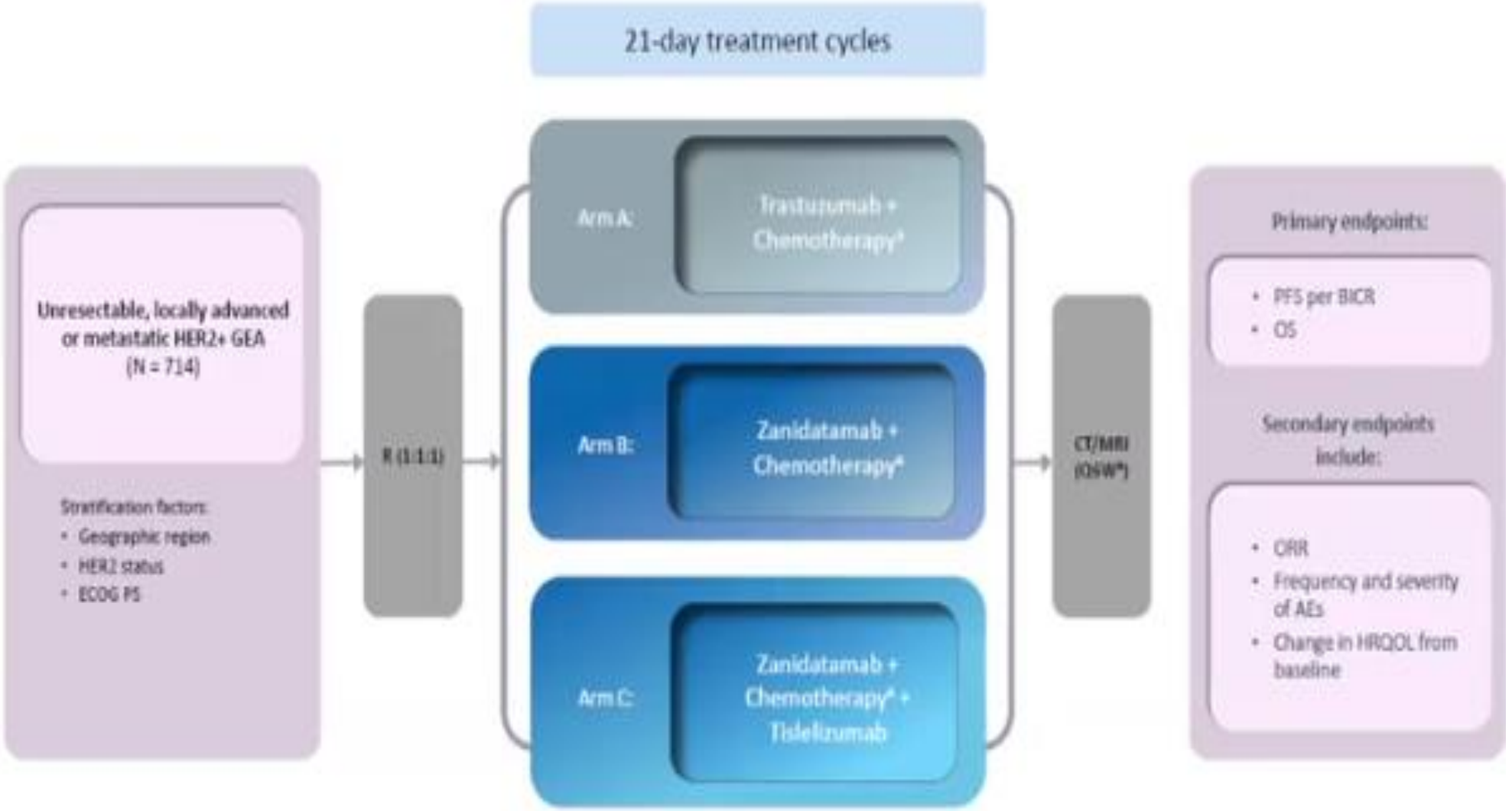
Multiple mechanisms of action:
- improved binding, clustering & receptor internalization
- Inhibition of ligand-dependend & independent proliferation
- Potent activation of ADCC

Meric-Bernstam F, et al. *Lancet Oncol.* 2022;23(12):1558-1570.

Activity Across Tumor Types

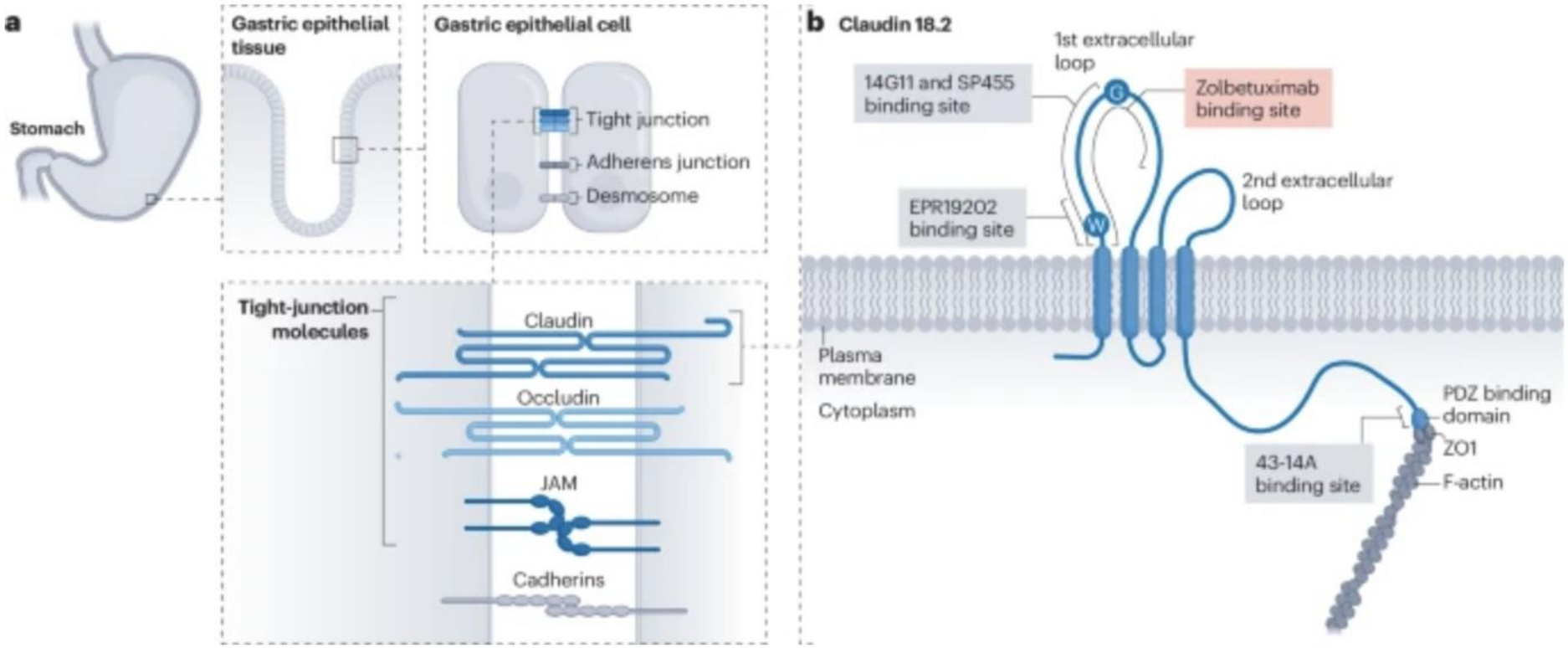


HERIZON-GEA-01: Phase III



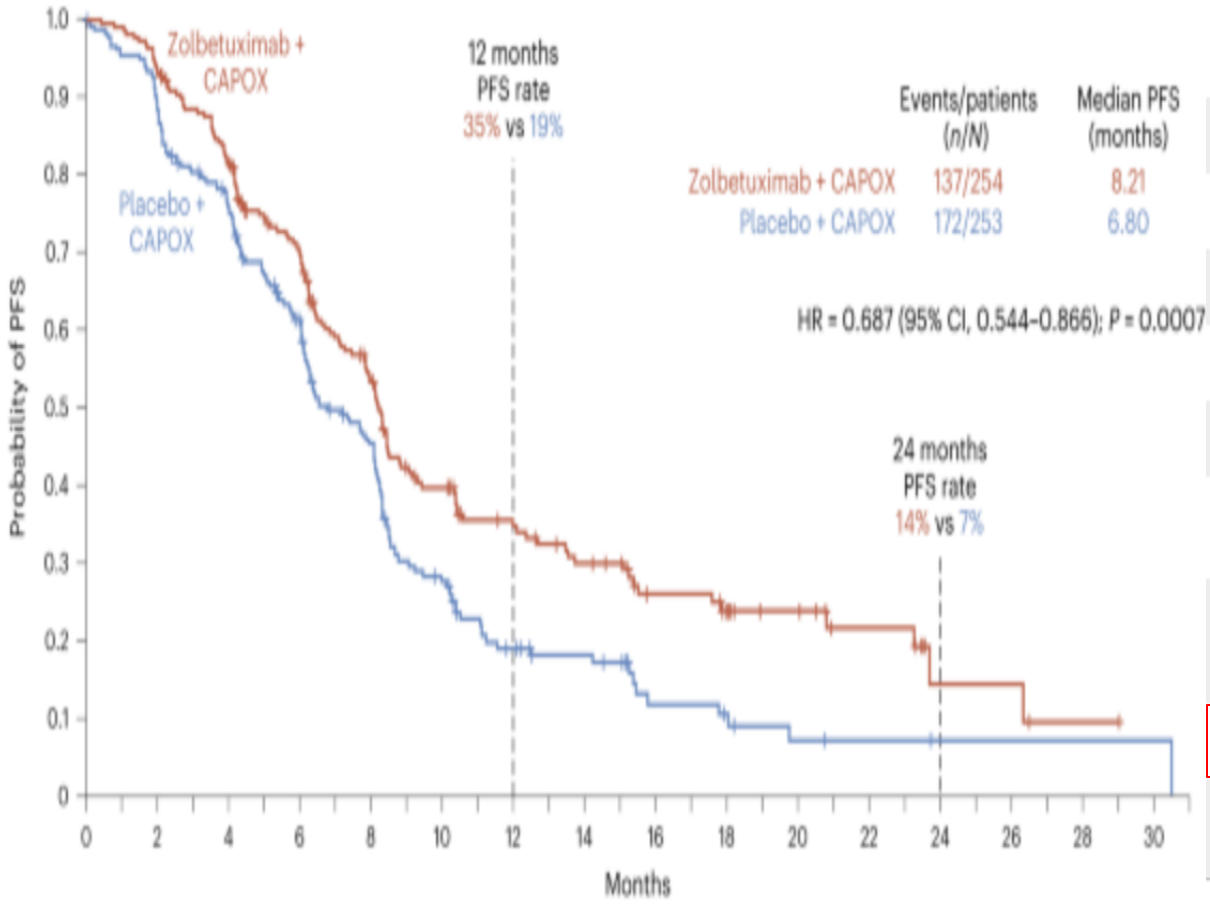
Adapted from: Tabernero J, et al. Presented at: ESMO GI;2022. NCT05152147.

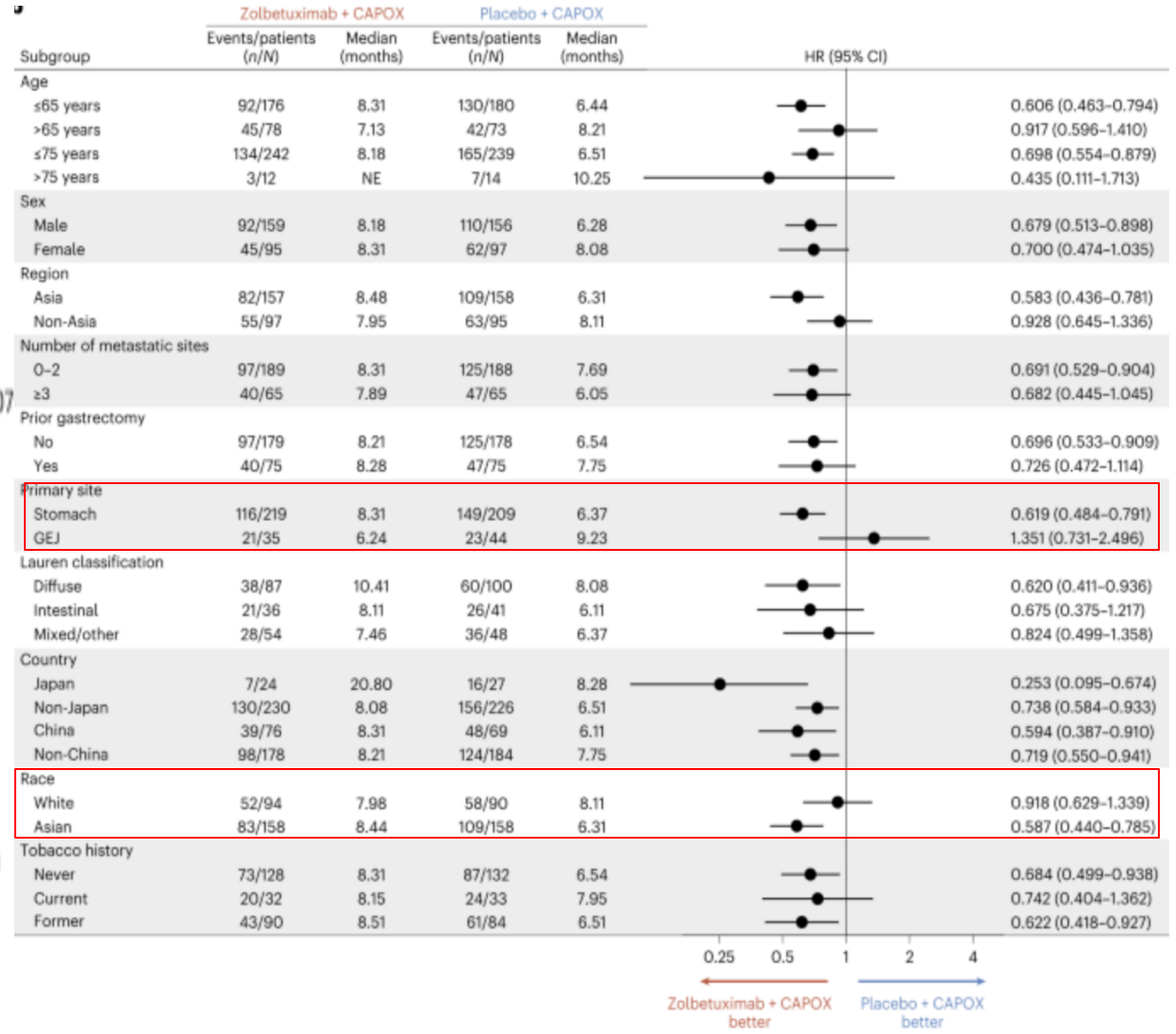
CLDN 18.2



Nakayama, I., Qi, C., Chen, Y. *et al.* Claudin 18.2 as a novel therapeutic target. *Nat Rev Clin Oncol* **21**, 354–369 (2024)

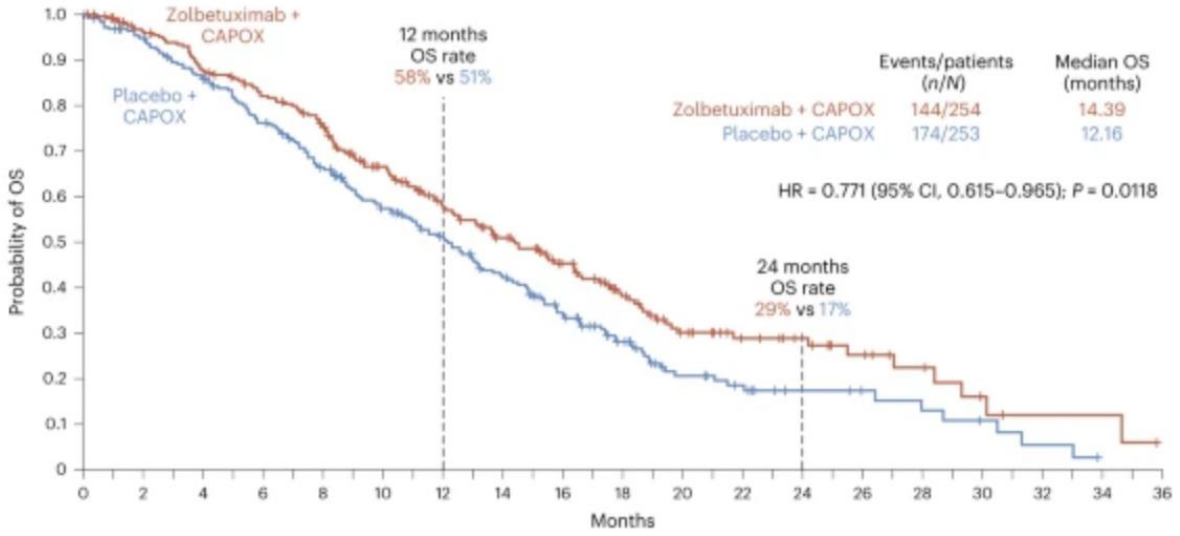
GLOW: CLDN 18.2

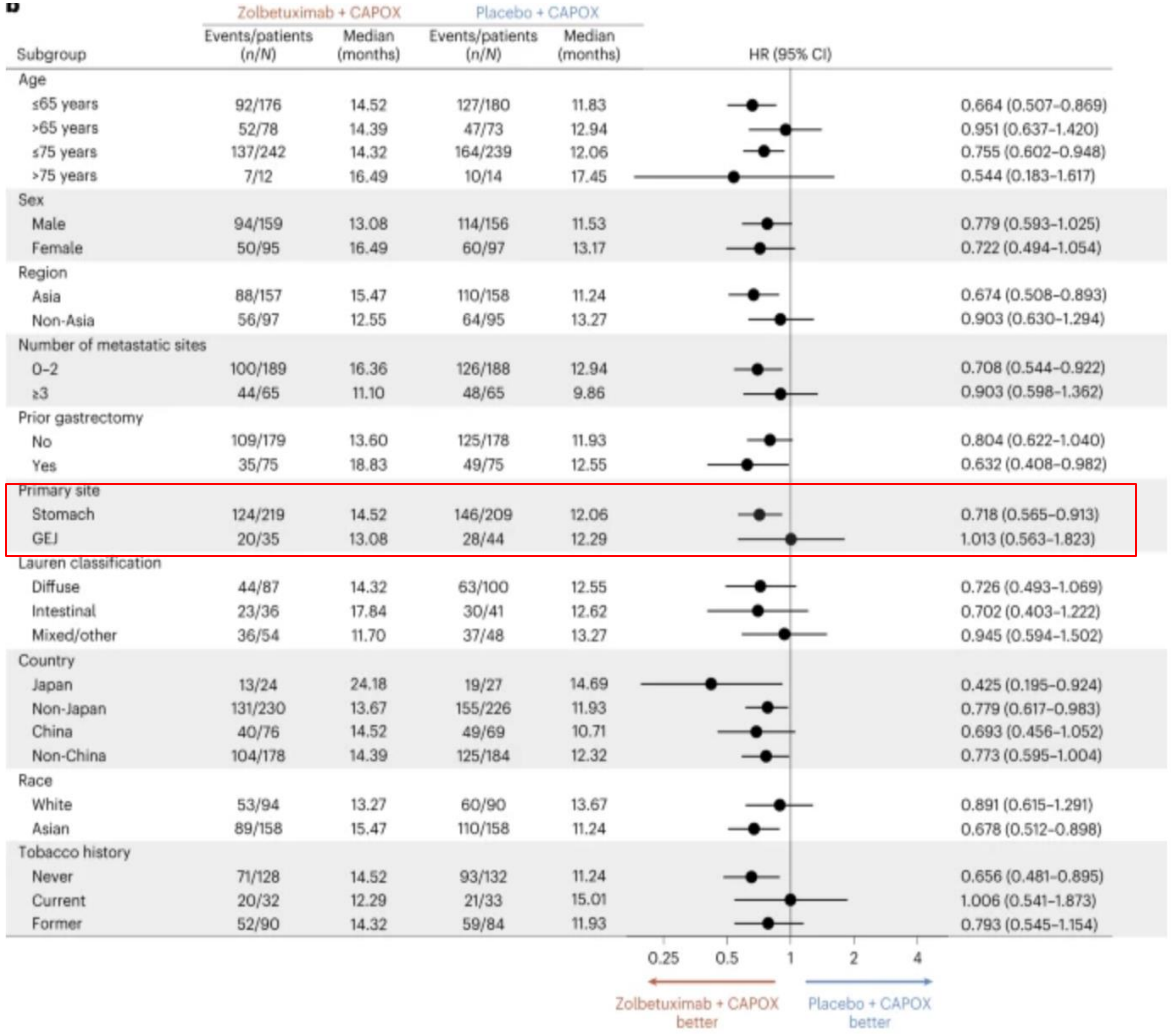




Shah, M. A., Shitara, K., Ajani, J. A., Bang, Y. J., Enzinger, P., Ilson, D., ... & Xu, R. H. (2023). Zolbetuximab plus CAPOX in CLDN18. 2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. *Nature medicine*, *29*(8), 2133-2141.

GLOW: Overall Survival

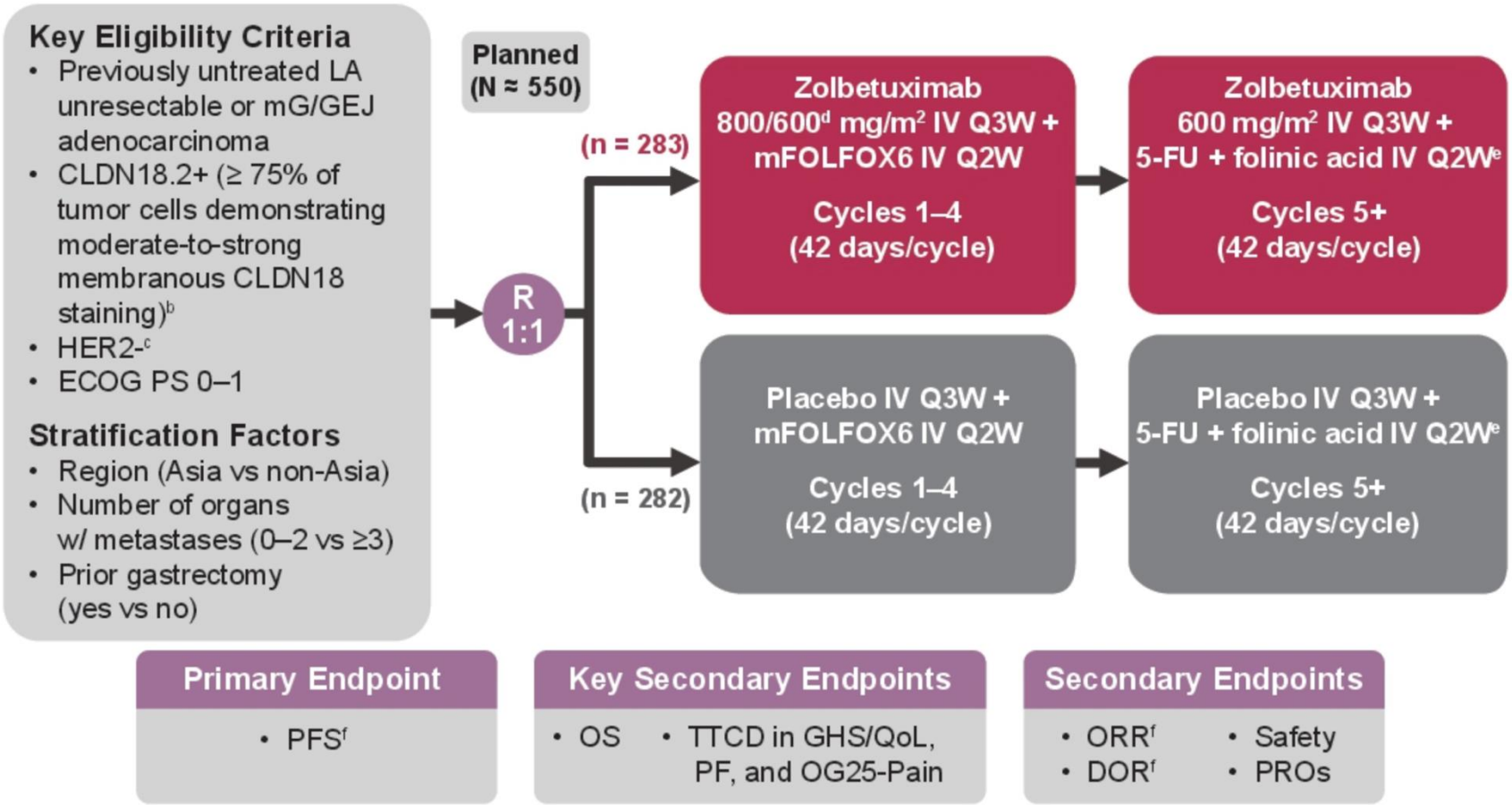




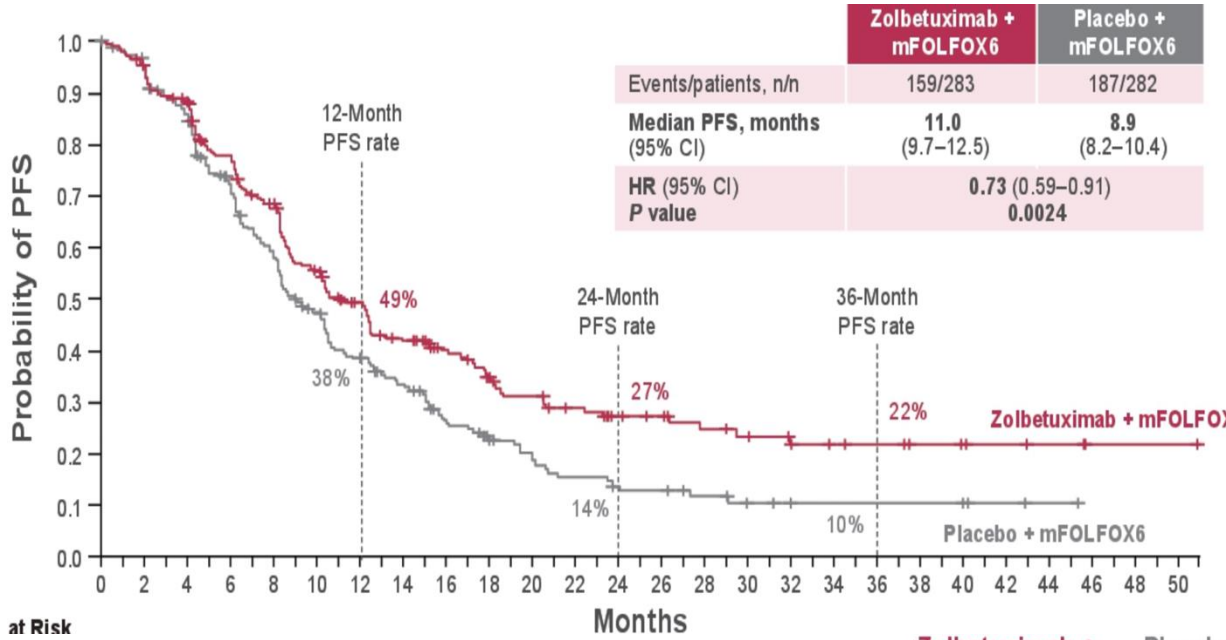
Subgroup	Zolbetuximab + CAPOX Events/patients (n/N)	Zolbetuximab + CAPOX Median (months)	Placebo + CAPOX Events/patients (n/N)	Placebo + CAPOX Median (months)	HR (95% CI)
Age					
≤65 years	92/176	14.52	127/180	11.83	0.664 (0.507–0.869)
>65 years	52/78	14.39	47/73	12.94	0.951 (0.637–1.420)
≤75 years	137/242	14.32	164/239	12.06	0.755 (0.602–0.948)
>75 years	7/12	16.49	10/14	17.45	0.544 (0.183–1.617)
Sex					
Male	94/159	13.08	114/156	11.53	0.779 (0.593–1.025)
Female	50/95	16.49	60/97	13.17	0.722 (0.494–1.054)
Region					
Asia	88/157	15.47	110/158	11.24	0.674 (0.508–0.893)
Non-Asia	56/97	12.55	64/95	13.27	0.903 (0.630–1.294)
Number of metastatic sites					
0–2	100/189	16.36	126/188	12.94	0.708 (0.544–0.922)
≥3	44/65	11.10	48/65	9.86	0.903 (0.598–1.362)
Prior gastrectomy					
No	109/179	13.60	125/178	11.93	0.804 (0.622–1.040)
Yes	35/75	18.83	49/75	12.55	0.632 (0.408–0.982)
Primary site					
Stomach	124/219	14.52	146/209	12.06	0.718 (0.565–0.913)
GEJ	20/35	13.08	28/44	12.29	1.013 (0.563–1.823)
Lauren classification					
Diffuse	44/87	14.32	63/100	12.55	0.726 (0.493–1.069)
Intestinal	23/36	17.84	30/41	12.62	0.702 (0.403–1.222)
Mixed/other	36/54	11.70	37/48	13.27	0.945 (0.594–1.502)
Country					
Japan	13/24	24.18	19/27	14.69	0.425 (0.195–0.924)
Non-Japan	131/230	13.67	155/226	11.93	0.779 (0.617–0.983)
China	40/76	14.52	49/69	10.71	0.693 (0.456–1.052)
Non-China	104/178	14.39	125/184	12.32	0.773 (0.595–1.004)
Race					
White	53/94	13.27	60/90	13.67	0.891 (0.615–1.291)
Asian	89/158	15.47	110/158	11.24	0.678 (0.512–0.898)
Tobacco history					
Never	71/128	14.52	93/132	11.24	0.656 (0.481–0.895)
Current	20/32	12.29	21/33	15.01	1.006 (0.541–1.873)
Former	52/90	14.32	59/84	11.93	0.793 (0.545–1.154)

Shah, M. A., Shitara, K., Ajani, J. A., Bang, Y. J., Enzinger, P., Ilson, D., ... & Xu, R. H. (2023). Zolbetuximab plus CAPOX in CLDN18. 2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. *Nature medicine*, *29*(8), 2133-2141.

SPOTLIGHT

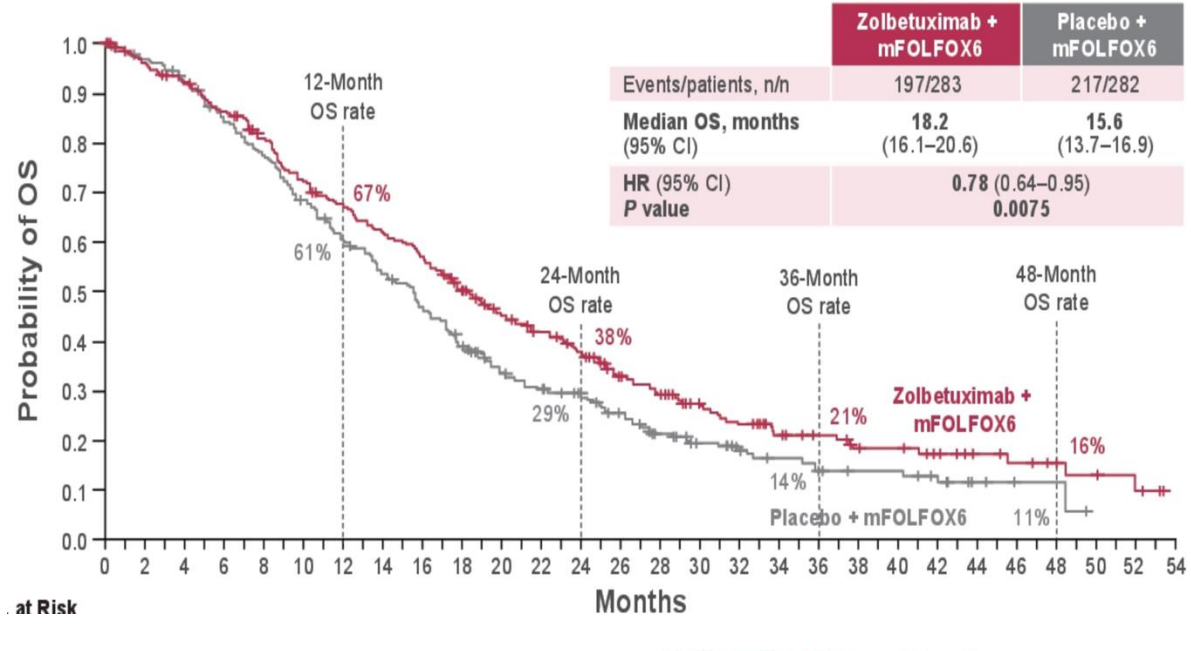


Shitara K, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. Lancet. 2023 May 20;401(10389):1655-1668. doi: 10.1016/S0140-6736(23)00620-7.



	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
Events/patients, n/n	159/283	187/282
Median PFS, months (95% CI)	**11.0** (9.7–12.5)	**8.9** (8.2–10.4)
HR (95% CI)	**0.73** (0.59–0.91)	
***P* value**	**0.0024**	

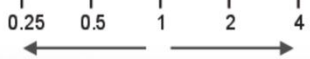
at Risk



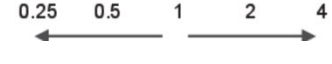
	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
Events/patients, n/n	197/283	217/282
Median OS, months (95% CI)	**18.2** (16.1–20.6)	**15.6** (13.7–16.9)
HR (95% CI)	**0.78** (0.64–0.95)	
***P* value**	**0.0075**	

at Risk

Subgroup	HR (95% CI)	Zolbetuximab + mFOLFOX6 Events/patients (n/n)	Placebo + mFOLFOX6 Events/patients (n/n)
Age, years			
≤ 65	0.76 (0.59–1.00)	102/181	118/181
> 65	0.68 (0.48–0.97)	57/102	69/101
Sex			
Male	0.71 (0.55–0.93)	103/176	123/175
Female	0.77 (0.54–1.11)	56/107	64/107
Region			
Asia	0.55 (0.37–0.83)	45/88	49/89
Non-Asia	0.81 (0.64–1.04)	114/195	138/193
Number of metastatic sites			
0–2	0.71 (0.56–0.91)	119/219	140/219
≥ 3	0.80 (0.53–1.23)	40/64	47/63
Prior gastrectomy			
No	0.82 (0.64–1.05)	116/199	129/200
Yes	0.57 (0.38–0.84)	43/84	58/82
Primary site			
Stomach	0.66 (0.52–0.85)	118/219	138/210
GEJ	1.05 (0.69–1.59)	41/64	49/72
Lauren classification			
Diffuse	0.79 (0.54–1.16)	45/82	68/117
Intestinal	0.60 (0.40–0.91)	44/70	49/66
Mixed/other[c]	0.85 (0.56–1.28)	51/81	42/55

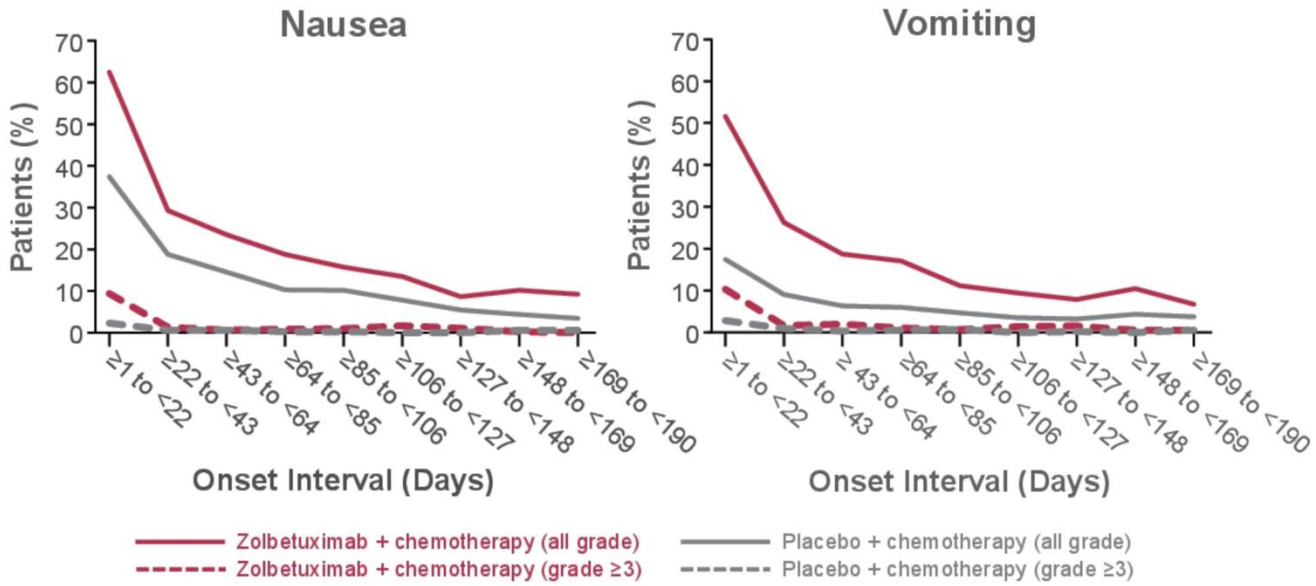


HR (95% CI)	Zolbetuximab + mFOLFOX6 Events/patients (n/n)	Placebo + mFOLFOX6 Events/patients (n/n)
0.82 (0.64–1.05)	126/181	135/181
0.73 (0.53–1.00)	71/102	82/101
0.77 (0.61–0.99)	124/176	139/175
0.82 (0.59–1.12)	73/107	78/107
0.70 (0.49–1.00)	55/88	66/89
0.83 (0.66–1.05)	142/195	151/193
0.81 (0.65–1.02)	145/219	159/219
0.68 (0.47–1.00)	52/64	58/63
0.92 (0.73–1.15)	147/199	154/200
0.57 (0.39–0.83)	50/84	63/82
0.73 (0.58–0.91)	148/219	161/210
1.02 (0.69–1.51)	49/64	56/72
0.91 (0.66–1.27)	63/82	86/117
0.57 (0.38–0.84)	48/70	57/66
0.89 (0.60–1.32)	57/81	44/55



Shitara K, et al.

Figure 1. All occurrences of nausea or vomiting in SPOTLIGHT and GLOW



Zolbetuximab or placebo was administered every 3 weeks. Each onset interval represents a zolbetuximab or placebo infusion, where day 1 of the interval is the day of zolbetuximab or placebo administration. Nausea or vomiting may have occurred during infusion or on any subsequent day during the onset interval.

ES

mab + chemotherapy treatment in CLDN18.2+,
roesophageal junction adenocarcinoma:

Pranob Bhattacharya, DrPH[2], Radhika Ranganath, MD[2]

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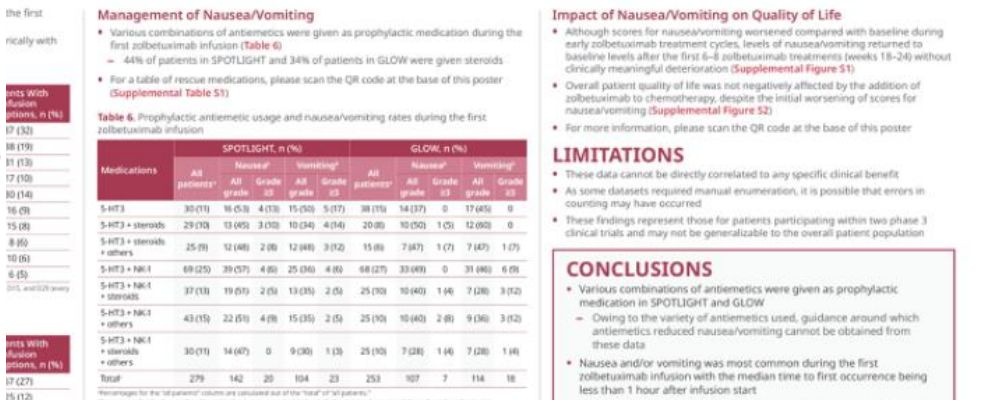

Management of Nausea/Vomiting

- Various combinations of antiemetics were given as prophylactic medication during the first zolbetuximab infusion (Table 6)
  - 44% of patients in SPOTLIGHT and 34% of patients in GLOW were given steroids
- For a table of rescue medications, please scan the QR code at the base of this poster (Supplemental Table S1)

Table 6. Prophylactic antiemetic usage and nausea/vomiting rates during the first zolbetuximab infusion

Medications	SPOTLIGHT, n (%)					GLOW, n (%)				
	All patients[a]	Nausea[a]		Vomiting[a]		All patients[a]	Nausea[a]		Vomiting[a]	
		All grade	Grade ≥3	All grade	Grade ≥3		All grade	Grade ≥3	All grade	Grade ≥3
5-HT3	30 (11)	16 (5.3)	4 (1.3)	15 (5.0)	5 (1.7)	38 (15)	14 (5.7)	0	17 (6.5)	0
5-HT3 + steroids	29 (10)	13 (4.5)	3 (1.0)	10 (3.4)	4 (1.4)	20 (8)	10 (5.0)	1 (.5)	12 (6.0)	0
5-HT3 + steroids + others	25 (9)	12 (4.8)	2 (.8)	12 (4.8)	3 (1.2)	15 (6)	7 (4.7)	1 (.7)	7 (4.7)	1 (.7)
5-HT3 + NK-1	69 (25)	39 (5.7)	4 (.6)	25 (3.6)	4 (.6)	68 (27)	33 (4.9)	0	31 (4.6)	6 (.9)
5-HT3 + NK-1 + steroids	37 (13)	19 (5.1)	2 (.5)	13 (3.5)	2 (.5)	25 (10)	10 (4.0)	1 (.4)	7 (2.8)	3 (1.2)
5-HT3 + NK-1 + others	43 (15)	22 (5.1)	4 (.9)	15 (3.5)	2 (.5)	25 (10)	10 (4.0)	2 (.8)	9 (3.6)	3 (1.2)
5-HT3 + NK-1 + steroids + others	30 (11)	14 (4.7)	0	9 (3.0)	1 (.3)	25 (10)	7 (2.8)	1 (.4)	7 (2.8)	1 (.4)
Total	279	142	20	104	23	253	107	7	114	18

Impact of Nausea/Vomiting on Quality of Life

- Although scores for nausea/vomiting worsened compared with baseline during early zolbetuximab treatment cycles, levels of nausea/vomiting returned to baseline levels after the first 6–8 zolbetuximab treatments (weeks 18–24) without clinically meaningful deterioration (Supplemental Figure S1)
- Overall patient quality of life was not negatively affected by the addition of zolbetuximab to chemotherapy, despite the initial worsening of scores for nausea/vomiting (Supplemental Figure S2)
- For more information, please scan the QR code at the base of this poster

LIMITATIONS

- These data cannot be directly correlated to any specific clinical benefit
- As some datasets required manual enumeration, it is possible that errors in counting may have occurred
- These findings represent those for patients participating within two phase 3 clinical trials and may not be generalizable to the overall patient population

CONCLUSIONS

- Various combinations of antiemetics were given as prophylactic medication in SPOTLIGHT and GLOW
  - Owing to the variety of antiemetics used, guidance around which antiemetics reduced nausea/vomiting cannot be obtained from these data
- Nausea and/or vomiting was most common during the first zolbetuximab infusion with the median time to first occurrence being less than 1 hour after infusion start

- Zolbetuximab or placebo was administered by infusion every 3 weeks
- In SPOTLIGHT and GLOW, the use of neurokinin-1 (NK-1) and serotonin (5-HT3) receptor blockers and other prophylactic antiemetics was recommended per institutional care and guidelines
- Antiemetic prophylaxis was suggested before each treatment; antiemetics could be used in combination
- It was recommended to avoid or minimize the use of corticosteroids, particularly for the first zolbetuximab/placebo treatment; however, use was not prohibited
- Infusion guidelines were amended after SPOTLIGHT initiation to reduce the initial infusion rate of the first zolbetuximab/placebo treatment

RESULTS

Incidence of Nausea or Vomiting

- Zolbetuximab + chemotherapy was administered to 279 patients in SPOTLIGHT and 253 patients in GLOW
- The occurrences of nausea or vomiting were most common during the first zolbetuximab infusion and decreased thereafter (Figure 1)
  - 62% (333/533) of patients experienced nausea and 52% (275/533) of patients experienced vomiting during the first zolbetuximab infusion
  - 29% (156/533) of patients experienced nausea and 26% (140/533) of patients experienced vomiting during the second zolbetuximab infusion

Time in minutes to first occurrence of vomiting, median (min–max); n[a]	38 (0–371); 32	59 (0–264); 36	51 (0–371); 68
Time in minutes to first occurrence of nausea/vomiting, median (min–max); n[a]	48 (0–371); 53	57 (0–264); 44	50 (0–371); 97

[a]Patients with available data.

Infusion Rate and Nausea/Vomiting

- The initial infusion rate (prior to infusion modification due to adverse events [AEs]) was numerically higher in patients who underwent infusion modifications due to AEs than in patients without infusion modifications during the first zolbetuximab infusion (Table 2)
  - In SPOTLIGHT, 85% of patients who underwent infusion modifications experienced nausea/vomiting
  - In GLOW, 79% of patients who underwent infusion modifications experienced nausea/vomiting

Table 2. Infusion modifications required due to any AE (IRR or non-IRR) during the first zolbetuximab infusion

	SPOTLIGHT (n = 279)		GLOW (n = 253)	
Infusion modification needed due to any AE	Yes (n = 96)	No (n = 183)	Yes (n = 52)	No (n = 202)
Initial infusion rate[a], mean / median, mL/h; n[b]	221 / 176; 64	167 / 100; 178	194 / 147; 43	126 / 90; 198
Patients who experienced nausea/vomiting as an IRR or non-IRR, n/n (%)	82/96 (85)	90/183 (49)	41/52 (79)	116/202 (57)

[a]Infusion rate prior to infusion modification due to AEs.
[b]Patients with available infusion rate data.
AE, adverse event; IRR, infusion-related reaction.

C3D1	190	172 (119–355)
C4D1	174	164 (96–353)
C5D1	164	158 (111–343)
C6D1	151	155 (85–301)
C7D1	116	150 (70–330)
C8D1	111	150 (100–332)
C9D1	104	150 (80–312)
C10D1	84	150 (114–380)

In GLOW, zolbetuximab was administered on D1 every 3 week(s) of treatment cycle.
C, cycle; D, day; min–max, minimum–maximum.

Treatment Discontinuations Due

- Among patients who discontinued treat
  - Discontinuations due to nausea were SPOTLIGHT and 11% (6/54) of patient
  - Discontinuations due to vomiting we SPOTLIGHT and 7% (4/54) of patients

Table 5. Early discontinuations[a] due to nau

Patients who discontinued treatment early, n
Reason for discontinuation, n (%[b])
TEAE[c]
Nausea[d]
Vomiting[d]

[a]Discontinuations within 9 weeks of randomization were considere
[b]Calculated as percentage of patients who discontinued due to rea
[c]Any TEAEs, including nausea, vomiting, and other TEAEs that led
[d]Individual patients may have discontinued due to nausea and/or v
TEAE, treatment-emergent adverse event.

Presented at the American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium 2024; January 18–20, 2024; Moscone West, San Francisco, CA, USA

Table 1. Time to first occurrence of nausea/vomiting reported as an infusion-related reaction during the first zolbetuximab infusion

	SPOTLIGHT (n = 279)	GLOW (n = 253)	Combined (N = 532)
Time in minutes to first occurrence of nausea, median (min–max); n[a]	50 (0–371); 46	55 (0–100); 23	50 (0–371); 69
Time in minutes to first occurrence of vomiting, median (min–max); n[a]	38 (0–371); 32	59 (0–264); 36	51 (0–371); 68
Time in minutes to first occurrence of nausea/vomiting, median (min–max); n[a]	48 (0–371); 53	57 (0–264); 44	50 (0–371); 97

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

ADENOCARCINOMA

First-Line Therapy
- Oxaliplatin is preferred over cisplatin due to lower toxicity.

Preferred Regimens
- HER2 overexpression positive[d]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and trastuzumab[a]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, trastuzumab[a] and pembrolizumab for PD-L1 CPS ≥1 (category 1)[e,g,23,24]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and trastuzumab (category 1)[a,25]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, trastuzumab[a] and pembrolizumab for PD-L1 CPS ≥1 (category 1)[e,g,23,24]
- HER2 overexpression negative[d]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (category 1 for PD-L1 CPS ≥ 5; category 2B for PD-L1 CPS <5)[e,g,26]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab for PD-L1 CPS ≥ 1 (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS 1 to <10)[e,g,27,28]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin and zolbetuximab-clzb for CLDN18.2 positive[d] (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[29,30]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[31-33]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab for PD-L1 CPS ≥ 1 (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS 1 to <10)[e,g,27,28]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[31,34-36]
- MSI-H/dMMR tumors (independent of PD-L1 status)[d]
  - Pembrolizumab[e,g,37-39]
  - Dostarlimab-gxly[e,g,40]
  - Nivolumab and ipilimumab[e,g,26]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab[e,g,26]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab[e,g,27]

Other Recommended Regimens
- Fluorouracil[b,h] and irinotecan[i,41]
- Paclitaxel with or without carboplatin or cisplatin [i,42-46]
- Docetaxel with or without cisplatin[i,47-50]
- Fluoropyrimidine[i,35,51,52] (fluorouracil[b] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b,i,53,54]

[a] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[d] Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[e] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[g] If no prior tumor progression while on therapy with a checkpoint inhibitor.
[h] Capecitabine cannot be used interchangeably with fluorouracil in regimens containing irinotecan.
[i] Trastuzumab should be added to first-line chemotherapy for HER2 overexpression positive adenocarcinoma. An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

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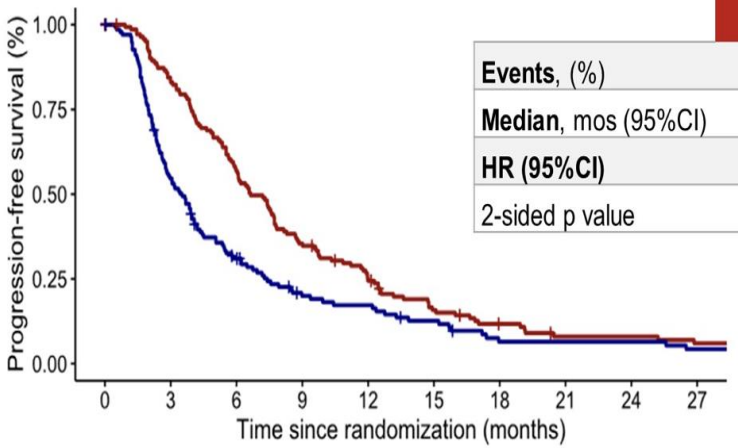
Biomarker Negative

- Her 2 Negative
- PDL1 Negative
- CLDN 18.2 Negative

- Frontline: Chemotherapy alone
- Median OS: <12 months
- % of patients receiving II-line therapy: 40%
- Ramucirumab + Paclitaxel: II-line SOC

SWITCH MAINTENANCE: ARMANI

Primary endpoint: PFS



Number at risk

Arm A (PTX-RAM) n=144	144	117	80	50	33	20	13	8	8	6
Arm B (FOLFOX/CAPOX) n=136	136	73	39	22	19	13	6	6	6	4

	Arm A (PTX-RAM) n=144	Arm B (FOLFOX/CAPOX) n=136
Events, (%)	91%	90%
Median, mos (95%CI)	**6.6** (6.0-7.8)	**3.5** (2.8-4.2)
HR (95%CI)	**0.64 (0.49-0.81)**	
2-sided p value	**P<0.001**	

24-month RMST analysis showed a 2.4-mos average increment in PFS, which was statistically significant (p=0.002).

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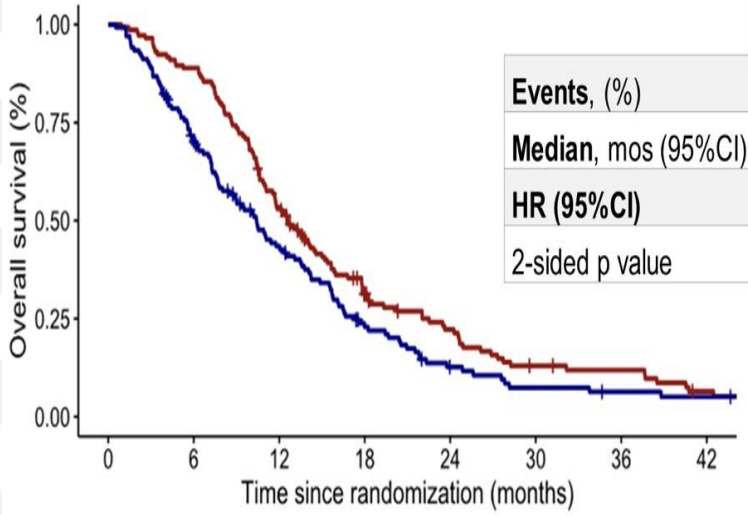
Key secondary endpoint: OS



Number at risk

Arm A (PTX-RAM) n=144	144	128	76	37	24	13	11	5
Arm B (FOLFOX/CAPOX) n=136	136	91	52	25	12	7	5	4

	Arm A (PTX-RAM) n=144	Arm B (FOLFOX/CAPOX) n=136
Events, (%)	86%	85%
Median, mos (95%CI)	**12.6** (11.5-15.0)	**10.4** (8.0-13.1)
HR (95%CI)	**0.75 (0.58-0.97)**	
2-sided p value	**P=0.028**	

The reported numbers are % in the ITT

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SWITCH MAINTENANCE: ARMANI

Safety analysis

Adverse Events	Arm A (PTX-RAM) N= 141		Arm B (FOLFOX/CAPOX) N = 135	
	Any Grade (%)	Grade ≥ 3 (%)	Any Grade (%)	Grade ≥ 3 (%)
Stomatitis/Oral mucositis	14.2	1.4	14.0	1.5
Nausea	12.8	0	18.5	0
Vomiting	6.4	0	6.7	0
Diarrhea	16.3	0	8.9	0
Hand-foot syndrome	1.4	0	11.8	0
Peripheral Neuropathy	61.7	5.7	45.2	6.7
Neutropenia	55.3	26.2	23.0	9.6
Febrile neutropenia	1.4	1.4	0	0
Anemia	27.7	2.1	13.3	3.0
Thrombocytopenia	14.2	0	28.1	0
Hypertension	23.4	6.4	0.7	0
Venous thromboembolism	5.7	2.8	2.2	0

Grade 3 or higher treatment-related adverse events were observed in **40.4%** of patients in the PTX-RAM arm versus **20.7%** of patients in the FOLFOX/CAPOX arm

ORR

DCR

CR

PR

SD

PD

NE[b]

a. Inclu
b. inclu

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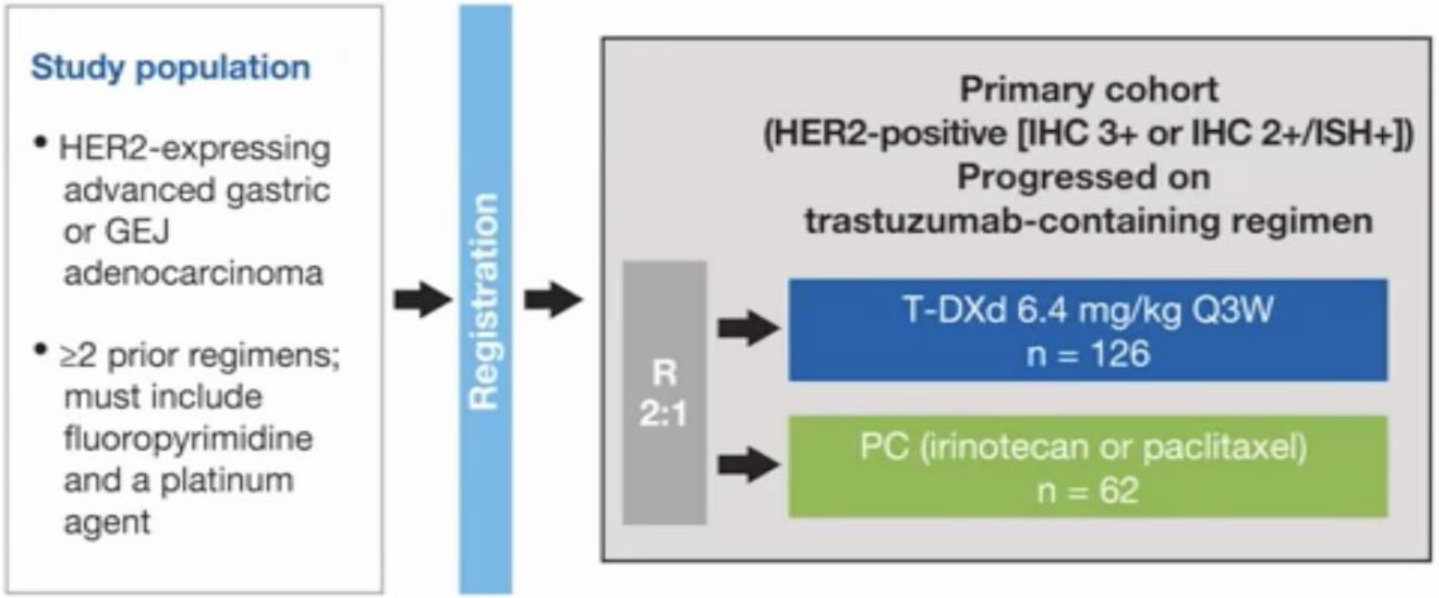
Graph is cut for values exceeding increase in SLD > 100%

DESTINY-GASTRIC 01: Japan, S.Korea

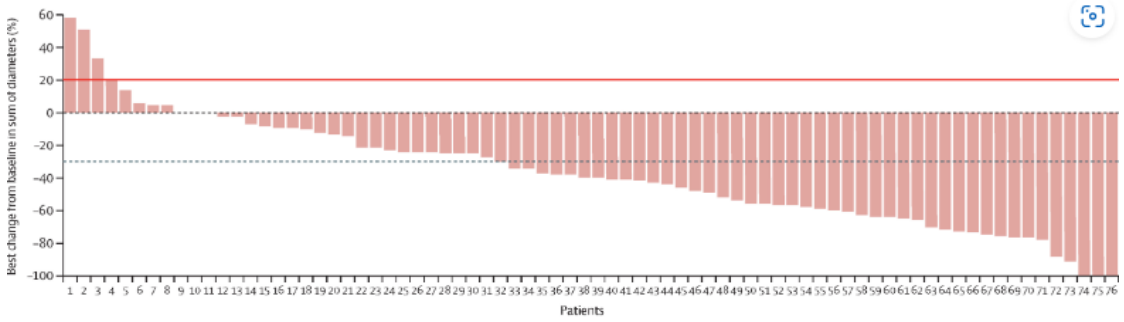


Primary results[a]	T-DXd n = 119	PC chemotherapy n = 56
ORR by ICR, % (95% CI)	51 (42-61)[b]	14 (6-26)
Confirmed ORR by ICR, % (95% CI)	43 (34-52)	12 (5-24)
OS, mo, median (95% CI)	12.5 (9.6-14.3)	8.4 (6.9-10.7)
	HR, 0.59 (95% CI, 0.39-0.88)[c]	
PFS, mo, median (95% CI)	5.6 (4.3-6.9)	3.5 (2.0-4.3)
	HR, 0.47 (95% CI, 0.31-0.71)	

Demographic Variable	T-DXd n = 125	PC Overall n = 62
Median age (range),[a] years	65.0 (34.0-82.0)	66.0 (28.0-82.0)
Female, %	24.0	24.2
Region, %		
Japan/Korea	79.2/20.8	80.6/19.4

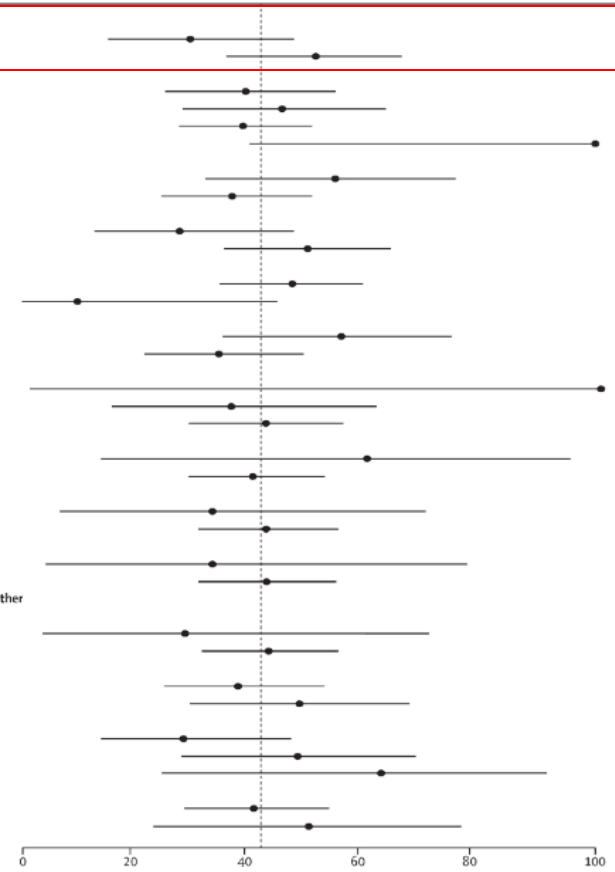
10.1200/JCO.2022.40.4_suppl.322

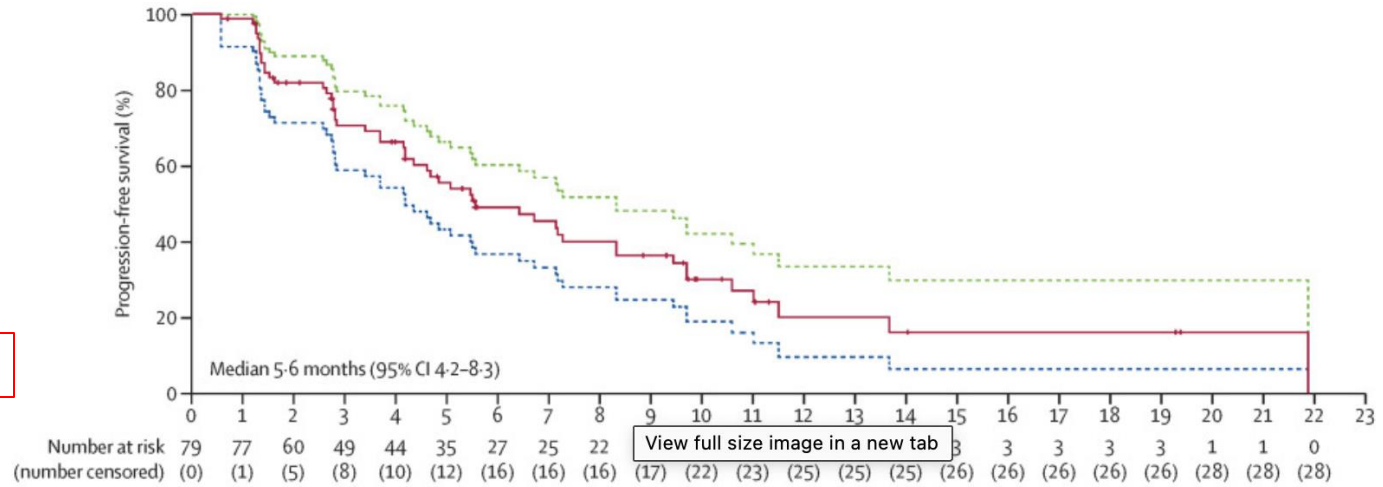
DESTINY-GASTRIC 02: USA, Europe



B

	Patients, n	Complete responses and partial responses, n	Objective response rate (95% CI)
Region			
North America	34	10	29·4 (15·1–47·5)
Europe	45	23	51·1 (35·8–66·3)
Age			
<65 years	46	18	39·1 (25·1–54·6)
≥65 years	33	15	45·5 (28·1–63·6)
<75 years	75	29	38·7 (27·6–50·6)
≥75 years	4	4	100·0 (39·8–100·0)
Sex			
Female	22	12	54·5 (32·2–75·6)
Male	57	21	36·8 (24·4–50·7)
Eastern Cooperative Oncology Group performance status			
0	29	8	27·6 (12·7–47·2)
1	50	25	50·0 (35·5–64·5)
HER2 status			
IHC3+	68	32	47·1 (34·8–59·6)
IHC2+/ISH+	10	1	10·0 (0·3–44·5)
Primary tumour location			
Gastric	27	15	55·6 (35·3–74·5)
GEJ	52	18	34·6 (22·0–49·1)
Histological subtype			
Diffuse	1	1	100·0 (2·5–100·0)
Intestinal	19	7	36·8 (16·3–61·6)
Other	59	25	42·4 (29·6–55·9)
Number of metastatic sites			
<2	5	3	60·0 (14·7–94·7)
≥2	74	30	40·5 (29·3–52·6)
Previous adjuvant or neoadjuvant therapy			
Yes	9	3	33·3 (7·5–70·1)
No	70	30	42·9 (31·1–55·3)
Previous nivolumab or pembrolizumab treatment			
Yes	6	2	33·3 (4·3–77·7)
No	73	31	42·5 (31·0–54·6)
Previous treatment with immune-checkpoint inhibitor or other immuno-oncology therapy			
Yes	7	2	28·6 (3·7–71·0)
No	72	31	43·1 (31·4–55·3)
Liver metastases at baseline			
Yes	50	19	38·0 (24·7–52·8)
No	29	14	48·3 (29·4–67·5)
Renal impairment at baseline			
Normal	32	9	28·1 (13·7–46·7)
Mild	25	12	48·0 (27·8–68·7)
Moderate	8	5	62·5 (24·5–91·5)
Hepatic impairment at baseline			
Normal	64	26	40·6 (28·5–53·6)
Mild	14	7	50·0 (23·0–77·0)





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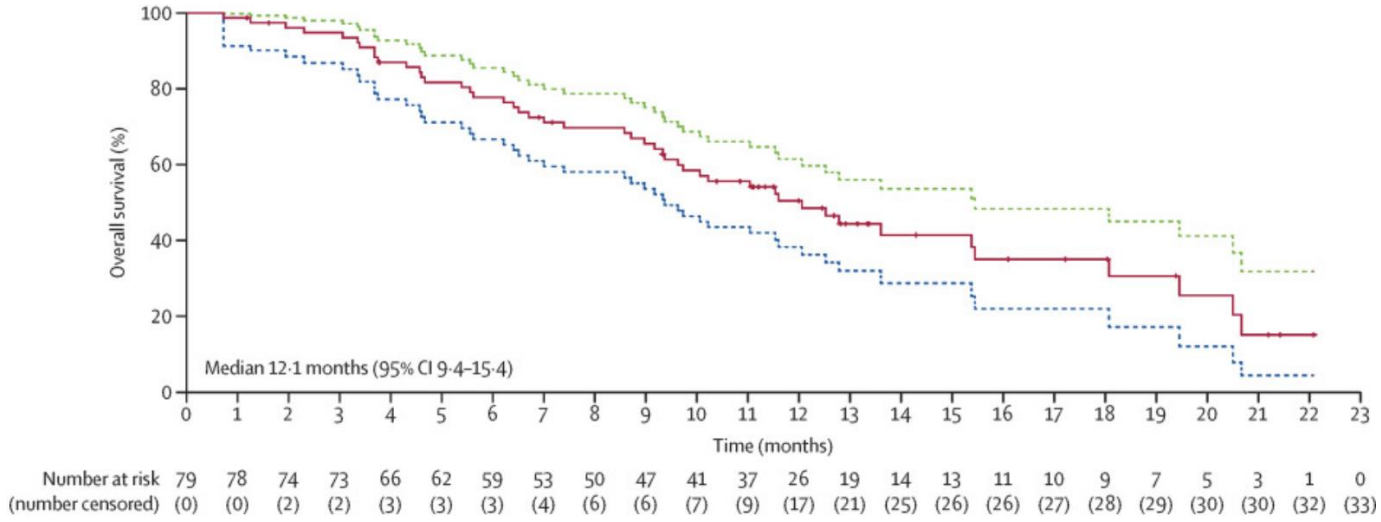
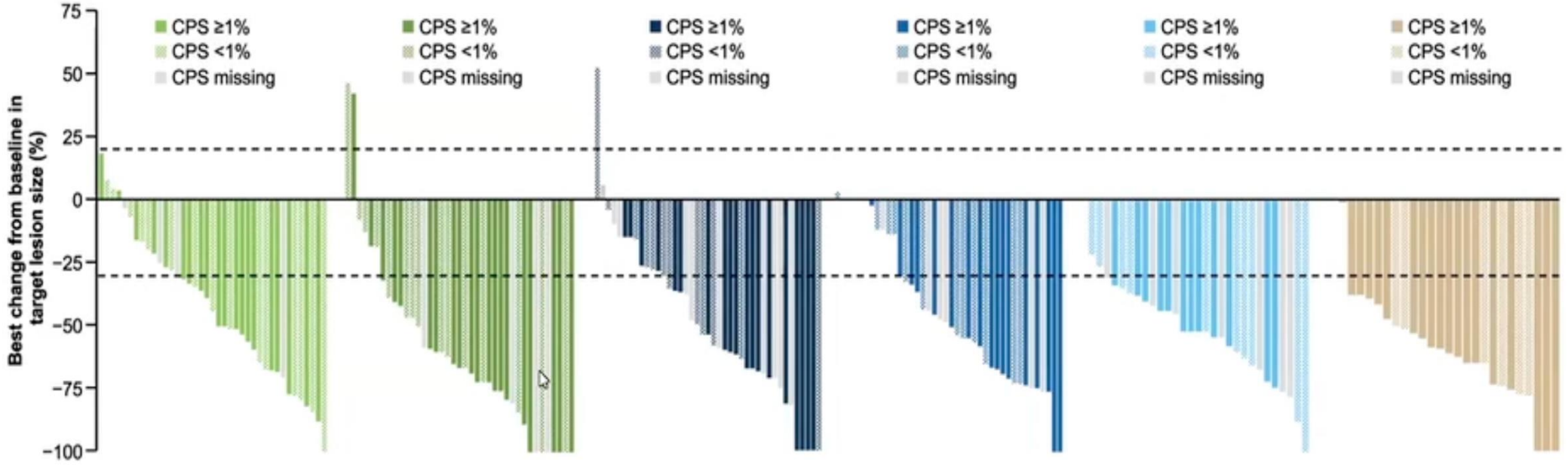


Van Cutsem, Eric et al. The Lancet Oncology, Volume 24, Issue 7, 744 - 756

DESTINY-Gastric03

	T-DXd 6.4 mg/kg n=43	T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² n=41	T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² + pembro n=43	T-DXd 6.4 mg/kg + pembro n=41	T-DXd 5.4 mg/kg + 5-FU/cape 750 mg/m² + pembro n=32	SOC - trastuzumab + 5-FU/cape + cisplatin/oxaliplatin n=29
mFollow up, months	17	21	17	15	5	18
mDOR, months (95% CI)	18 (6, 30)	20 (12, 28)	17 (8, NE)	18 (5, 21)	NE (2, NE)	14 (5, 20)
Confirmed ORR, % (95% CI)	49 (33, 65)	78 (62, 90)	58 (42, 73)	63 (46, 78)	59 (40, 77)	76 (56, 90)
CPS ≥1%	57	77	70	78	62	85
CPS <1%	53	73	39	44	46	71



Assessments were by Investigator using RECIST 1.1. Best percentage change is the maximum reduction or minimum increase from baseline in the target lesion size; the dashed lines at −30% and 20% change in target lesion size indicate the thresholds for partial response and progressive disease, respectively.

	T-DXd 6.4 mg/kg n=42*	T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² n=42	T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² + pembro n=43	T-DXd 6.4 mg/kg + pembro n=41	T-DXd 5.4 mg/kg + 5-FU/cape 750 mg/m² + pembro n=32
Median follow up, months	17	21	17	15	5
All-causality AEs, n (%)	42 (100)	42 (100)	43 (100)	41 (100)	27 (84)
Grade ≥3 AEs	27 (64)	**32 (76)**	**39 (91)**	33 (80)	**11 (34)**
Most common all-causality Grade ≥3 AEs (≥10% in any arm), n (%)					
Anemia	11 (26)	3 (7)	11 (26)	8 (20)	2 (6)
Diarrhea	1 (2)	2 (5)	7 (16)	4 (10)	0
Fatigue†	2 (5)	3 (7)	1 (2)	8 (20)	0
Febrile neutropenia	1 (2)	0	5 (12)	1 (2)	0
Hypokalemia	0	3 (7)	8 (19)	0	0
Leukopenia†	1 (2)	0	5 (12)	0	0
Lipase increased	0	2 (5)	2 (5)	3 (7)	0
Nausea	1 (2)	1 (2)	8 (19)	3 (7)	1 (3)
Neutropenia†	11 (26)	18 (43)	11 (26)	8 (20)	5 (16)
Thrombocytopenia†	2 (5)	3 (7)	5 (12)	1 (2)	1 (3)
Treatment-related SAEs,‡ n (%)	8 (19)	7 (17)	**22 (51)**	**14 (34)**	1 (3)
Treatment-related deaths,‡ n (%)	0	1 (2)	4 (9)	4 (10)	0
Adverse events of special interest, n (%)					
Adjudicated drug-related ILD/pneumonitis§	4 (10)	5 (12)	8 (19)	5 (12)	0
Grade ≥3 drug-related ILD/pneumonitis	0	0	3 (7)	1 (2)	0
Death due to drug-related ILD/pneumonitis	0	0	2 (5)	1 (2)	0
Left ventricular dysfunction	1 (2)	2 (5)	3 (7)	2 (5)	1 (3)

Safety analysis set. Neutropenic sepsis; T-DXd 6.4 mg/kg + 5-FU/cape + pembro: n=1. *One patient allocated to T-DXd 6.4 mg/kg received 5-FU/cape in error and is included in T-DXd 6.4 mg/kg + 5-F
†grouped terms; ‡assessed by the investigator as possibly related to any of the investigational products; §includes ILD/pneumonitis with an onset date / worsening on or after the date of first dose

Adjuvant

CheckMate 577 study design

Baseline characteristics

	Nivolumab (n = 532)	Placebo (n = 262)
Median age (range), years	62 (26-82)	61 (26-86)
Male, %	84	85
Race,[a] %		
White	81	82
Asian	16	13
ECOG PS, %		
0	58	60
1	42	40
Disease stage at initial diagnosis,[b] %		
II	34	38
III	66	62
Tumor location, %		
EC	60	59
GEJC	40	41
Histology,[c] %		
Squamous cell carcinoma	29	29
Adenocarcinoma	71	71
Pathologic lymph node status ≥ ypN1, %	57	58
Tumor-cell PD-L1 expression,[d,e] %		
≥ 1%	17	15
< 1%	70	75
Time from complete resection to randomization, %		
< 10 weeks	34	28
≥ 10 weeks	66	72

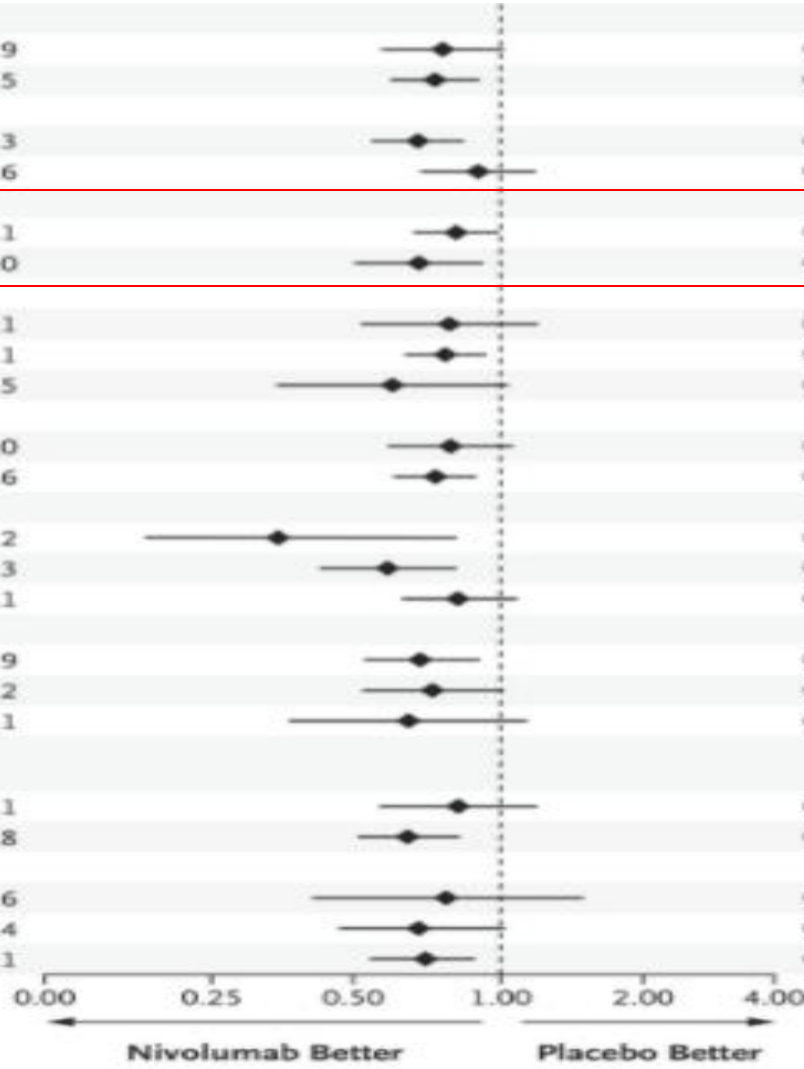
- In a post hoc analysis, a baseline PD-L1 CPS of 5 or higher was observed in 246 of 435 patients (57%) in the nivolumab arm and in 125 of 231 patients (54%) in the placebo arm

[a]Other races not shown; [b]< 1% not reported in the nivolumab arm; [c]< 1% had other histology in the nivolumab arm; [d]PD-L1 expression determined from tumor tissue specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako), which for most patients, was obtained after completion of chemoradiotherapy; [e]13% and 10% of patients had PD-L1 indeterminate or nonevaluable in the nivolumab and placebo arms, respectively.

Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203.

CheckMate 577

Subgroup	No. of Patients	Median Disease-free Survival (Nivolumab)	Median Disease-free Survival (Placebo)	Unstratified Hazard Ratio (95% CI)
Disease stage at initial diagnosis				
II	278	34.0	13.9	0.72 (0.51–1.02)
III	514	19.4	8.5	0.68 (0.53–0.88)
Tumor location at initial diagnosis				
Esophagus	462	24.0	8.3	0.61 (0.47–0.78)
Gastroesophageal junction	332	22.4	20.6	0.87 (0.63–1.21)
Histologic type				
Adenocarcinoma	563	19.4	11.1	0.75 (0.59–0.96)
Squamous-cell carcinoma	230	29.7	11.0	0.61 (0.42–0.88)
Tumor-cell PD-L1 expression				
≥1%	129	19.7	14.1	0.75 (0.45–1.24)
<1%	570	21.3	11.1	0.73 (0.57–0.92)
Indeterminate or could not be evaluated	95	Not reached	9.5	0.54 (0.27–1.05)
Pathological lymph-node status				
ypN0	336	Not reached	27.0	0.74 (0.51–1.06)
≥ypN1	457	14.8	7.6	0.67 (0.53–0.86)
Pathological tumor status				
ypT0	47	34.0	5.2	0.35 (0.15–0.82)
ypT1 or ypT2	308	28.3	9.3	0.60 (0.44–0.83)
ypT3 or ypT4	436	18.9	14.1	0.84 (0.64–1.11)
Histologic grade				
1 or 2	438	29.4	13.9	0.68 (0.51–0.91)
3 or 4	253	14.1	9.2	0.73 (0.52–1.02)
Not assessed	101	Not reached	11.1	0.65 (0.37–1.16)
Time from complete resection to randomization				
<10 wk	256	24.0	14.1	0.84 (0.57–1.22)
≥10 wk	538	21.4	10.8	0.66 (0.52–0.84)
HER2 status				
Positive	63	19.6	7.6	0.78 (0.40–1.55)
Negative	207	21.4	9.4	0.69 (0.46–1.03)
Not reported	522	24.0	11.1	0.70 (0.55–0.90)

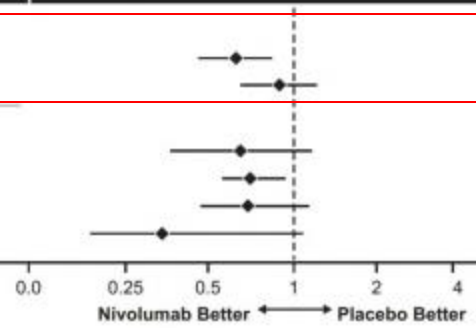


Kelly RJ, et al. N Engl J Med 2021;384:1191-1203.

CheckMate-577

Figure S2. Post Hoc Assessment of Disease-free Survival by Subgroups.

Subgroup	Median Disease-free Survival, months		Unstratified Hazard Ratio (95% CI)
	Nivolumab	Placebo	
PD-L1 CPS expression			
≥5 (n = 371)	29.4	10.2	0.62 (0.46–0.83)
<5 (n = 295)	16.3	11.1	0.89 (0.65–1.22)
Radiotherapy dosage			
<41.4 Gray (n = 92*)	19.7	13.8	0.69 (0.38–1.23)
41.4–50.4 Gray (n = 504)	24.0	11.1	0.73 (0.57–0.95)
>50.4 Gray (n = 152)	21.4	8.3	0.72 (0.46–1.13)
Not reported (n = 41)	14.4	6.1	0.41 (0.16–1.07)



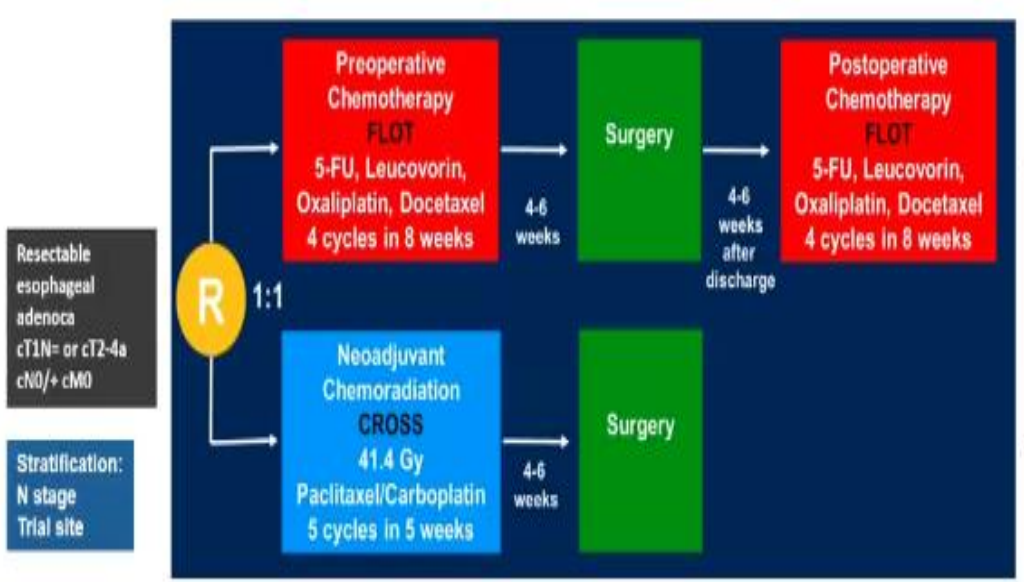
CI denotes confidence interval; CPS, combined positive score; PD-L1, programmed death ligand 1.

* 10 patients (seven in the nivolumab group and three in the placebo group) received total exposure less than 40 Gray (following database lock, investigators amended the total dose of radiotherapy for seven of these patients to 41.4–50.4 Gray).

TRAEs with potential immunologic etiology

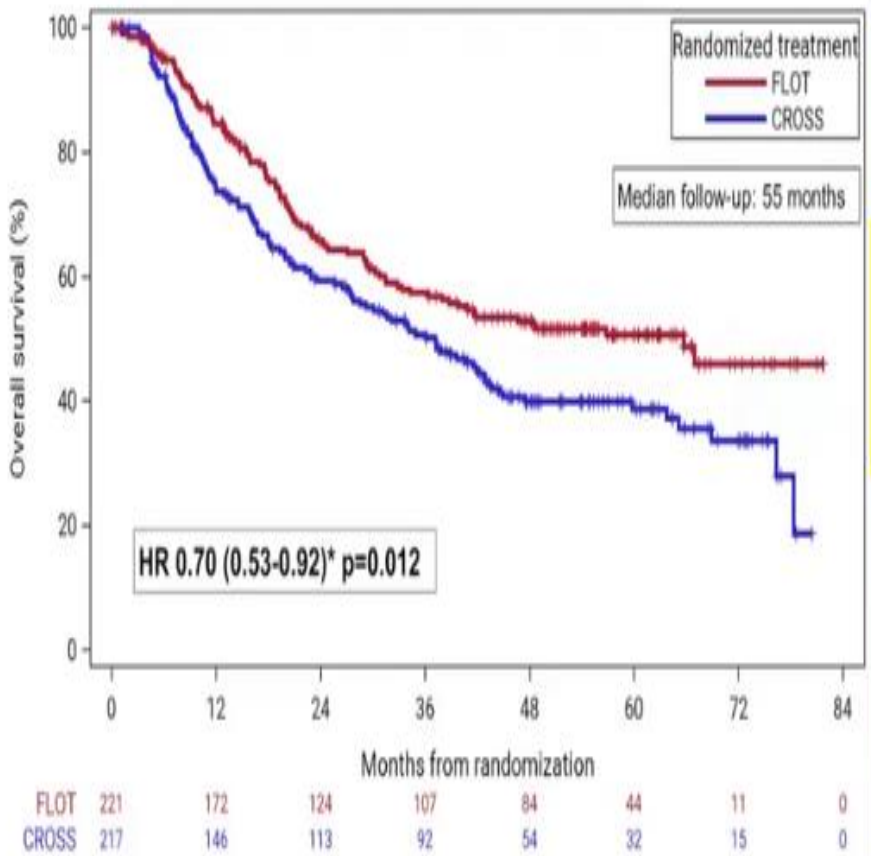
Select TRAEs,[a,b] n (%)	Nivolumab (n = 532)[c]	
	Any grade	Grade 3-4
Endocrine	93 (17)	5 (<1)
Gastrointestinal	91 (17)	4 (<1)
Hepatic	49 (9)	6 (1)
Pulmonary	23 (4)	6 (1)
Renal	7 (1)	1 (<1)
Skin	130 (24)	7 (1)

Neoadjuvant : ESOPEC Study Design



Primary Endpoint: OS

Secondary Endpoints: PFS, pathological stage, post-op complications

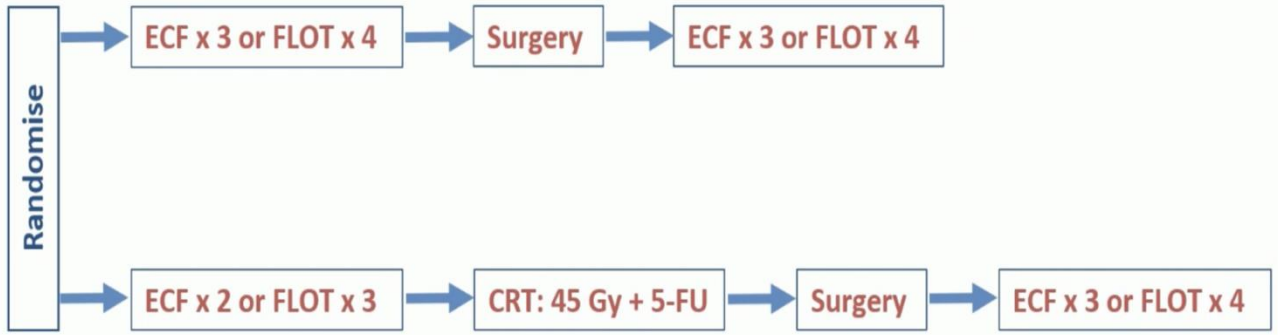


	FLOT	CROSS
Events	97	121
Median OS time (months)	66 95% CI 36 – n.e	37 95% CI 28 – 43
3-year OS rate	57.4%	50.7%
5-year OS rate	50.6%	38.7%

Hoeppner et al, ASCO 2024 Annual Meeting

TOPGEAR
Does CRT Offer Additional Benefit to Peri-op Chemo?

Key eligibility criteria: resectable adenocarcinoma of stomach or GOJ (Siewert type II ≤ 2cm oesophageal involvement, and Siewert type III); stage IB–IIIC, ie.T3–T4 and/or N-positive



ECF = epirubicin, cisplatin, 5-FU
FLOT = 5-FU, leucovorin, oxaliplatin, docetaxel

Surgical and pathological outcomes

	Preop CRT N=286	Periop CT N=288	P-value
D1+ or D2 lymphadenectomy	188 (83.6%)	192 (81.0%)	
RO resection	208 (92.4%)	206 (87.7%)	0.09
R1 resection	15 (6.7%)	29 (12.3%)	
ypTNM stage:	(N=231)	(N=247)	
ypT0, ypTis	38 (16.5%)	18 (7.3%)	<0.001
ypT1/2	73 (31.6%)	62 (25.2%)	
ypT3/4	120 (51.9%)	166 (67.5%)	
ypN negative	125 (54.1%)	104 (42.3%)‡	<0.01
ypN positive	106 (45.9%)	142 (57.7%)	
Pathological Response:			
Grade 1a: 0% residual tumour (pCR)	36 (16.8%)	18 (8.0%)	<0.0001
Grade 1b: <10% residual tumour	70 (32.7%)	48 (21.3%)	
Grade 2: 10-50% residual tumour	61 (28.5%)	69 (30.7%)	
Grade 3: >50% residual tumour	47 (22.0%)	90 (40.0%)	

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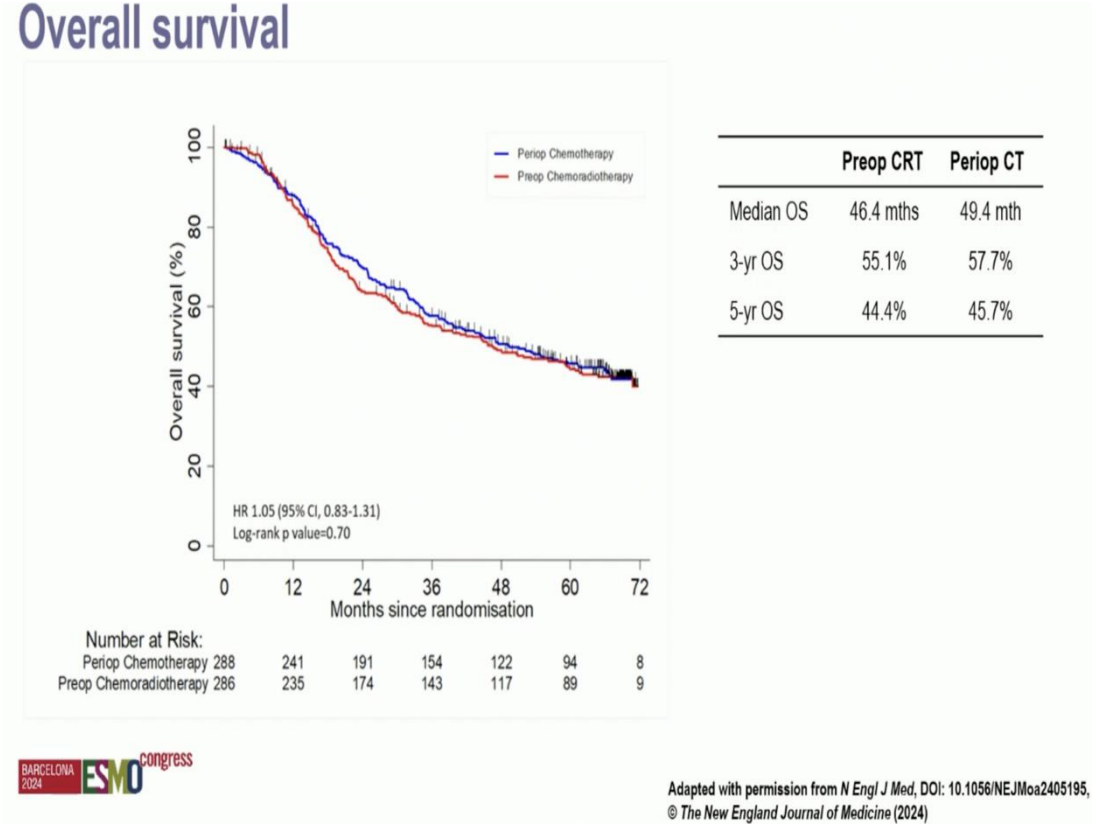
TOPGEAR



	Preop CRT	Periop CT
Median OS	46.4 mths	49.4 mth
3-yr OS	55.1%	57.7%
5-yr OS	44.4%	45.7%

BARCELONA 2024 ESMO congress

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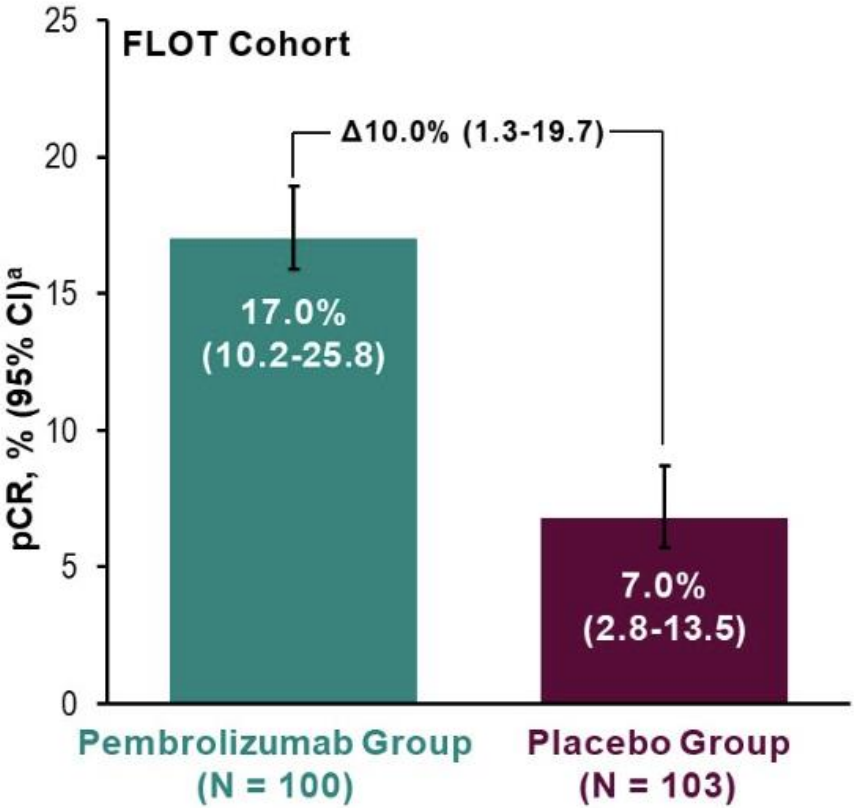
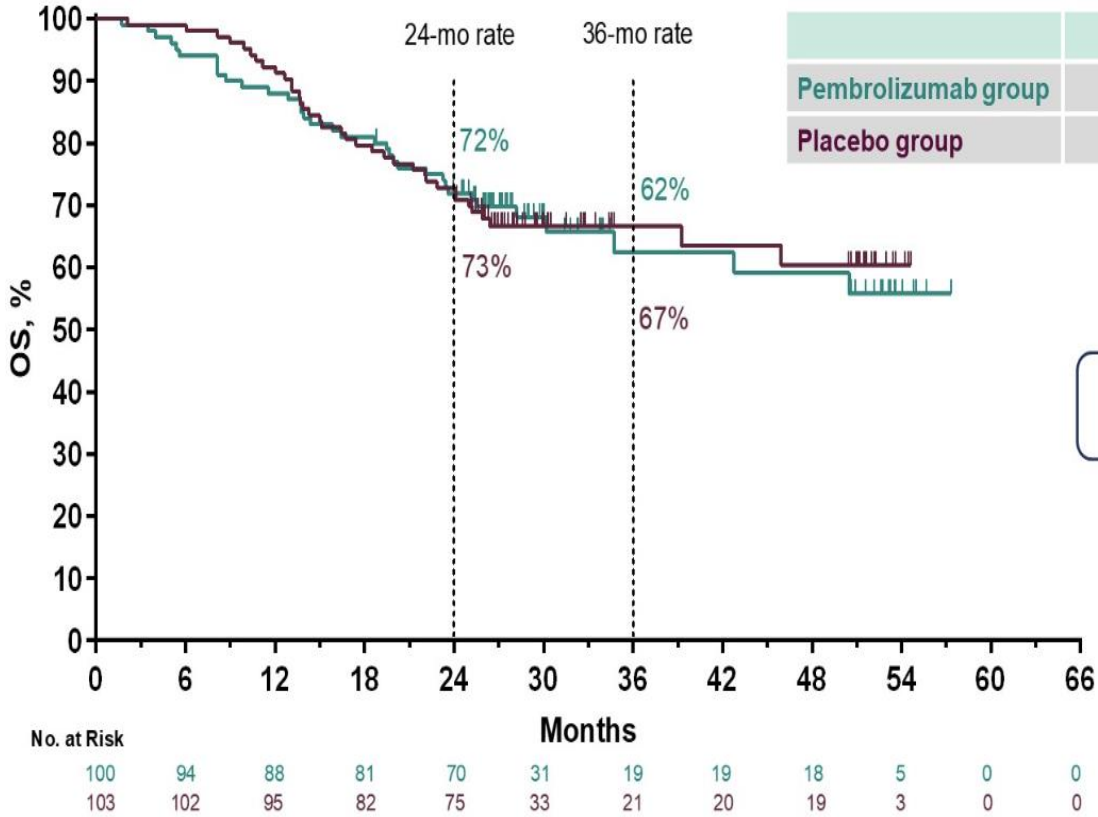
- No Additional benefit with CRT to peri-operative Chemo
- Increased pCR with XRT didn't lead to improved OS

- Peri-operative chemo: SOC for Es/GJ/G Adenocarcinoma

KEYNOTE-585 Study Design





	Events	Median (95% CI), mo
Pembrolizumab group	35%	NR (34.7-NR)
Placebo group	35%	NR (45.9-NR)

HR 1.04 (95% CI, 0.66-1.66)

Stratification factors
- Geographic region (Asia versus non-Asia)
- Tumor staging (II vs III vs IVa)
- Chemotherapy backbone (XP/FP vs FLOT)

Endpoints:
- Primary: safety
- Key secondary: pathCR rate per BICR, EFS per investigator, OS

J Clin Oncol 42, 2024 (suppl 3; abstr 247)

MATTERHORN

Baseline characteristics

		Durvalumab plus FLOT (n=474)	Placebo plus FLOT (n=474)
Age (years), median (range)		62 (26–84)	63 (28–83)
Male, n (%)		326 (69)	356 (75)
ECOG PS, n (%)	0	337 (71)	366 (77)
Primary tumor location, n (%)	Gastric	324 (68)	316 (67)
	GEJ	150 (32)	158 (33)
Siewert status, n (%)	Type 1	44 (9)	55 (12)
	Type 2	72 (15)	68 (14)
	Type 3	34 (7)	35 (7)
Primary tumor stage, n (%)	T0–T2	50 (11)	36 (8)
	T3	307 (65)	321 (68)
	T4	117 (25)	117 (25)
Clinical lymph node status,* n (%)	Positive	329 (69)	330 (70)
PD-L1 expression status by TAP,† n (%)	<1%*	48 (10)	47 (10)
	≥1%*	426 (90)	427 (90)
	<5%	236 (50)	230 (49)
	≥5%	238 (50)	244 (51)
	<10%	372 (78)	373 (79)
	≥10%	102 (22)	101 (21)
MSI status,‡ n / N (%)	MSI-high	25 / 326 (8)	24 / 334 (7)
	Non-MSI-high	301 / 326 (92)	310 / 334 (93)
Histology type, n (%)	Intestinal	174 (37)	168 (35)
	Diffuse	104 (22)	85 (18)
	Unspecified adenocarcinoma or other	196 (41)	221 (47)

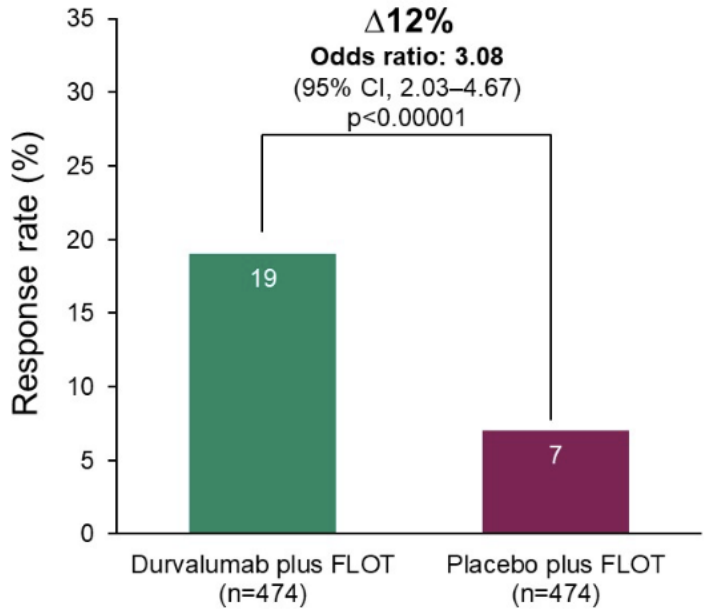
MATTERHORN

Pathological staging of participants who underwent surgery

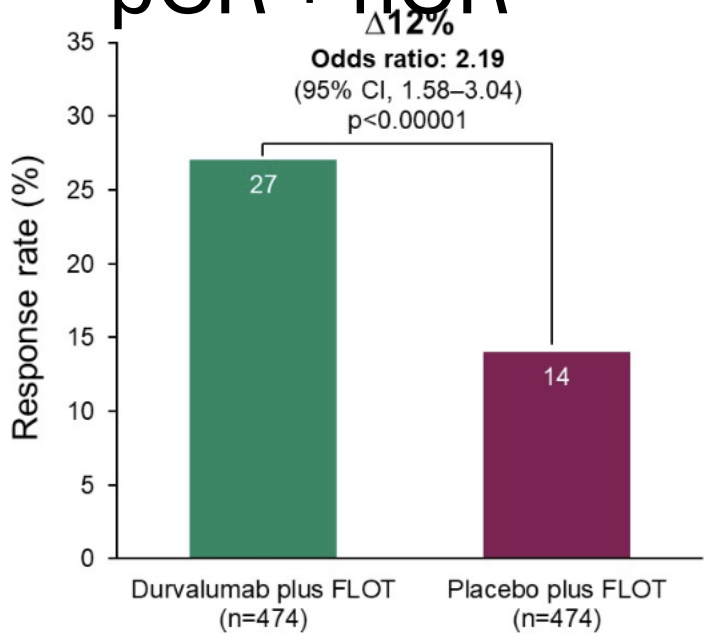
A higher percentage of participants achieved T0 and N0 with durvalumab plus FLOT versus placebo plus FLOT

Stage	Durvalumab plus FLOT (n=430)	Placebo plus FLOT (n=422)
T0, n (%)	98 (23)	45 (11)
N0, n (%)	223 (52)	154 (36)
T stage, n (%)		
≤T1	153 (36)	98 (23)
T2	54 (13)	46 (11)
T3	131 (30)	165 (39)
T4	48 (11)	65 (15)
M1, n (%)	4 (1)	7 (2)
Missing, n (%)	40 (9)	47 (11)

Path CR



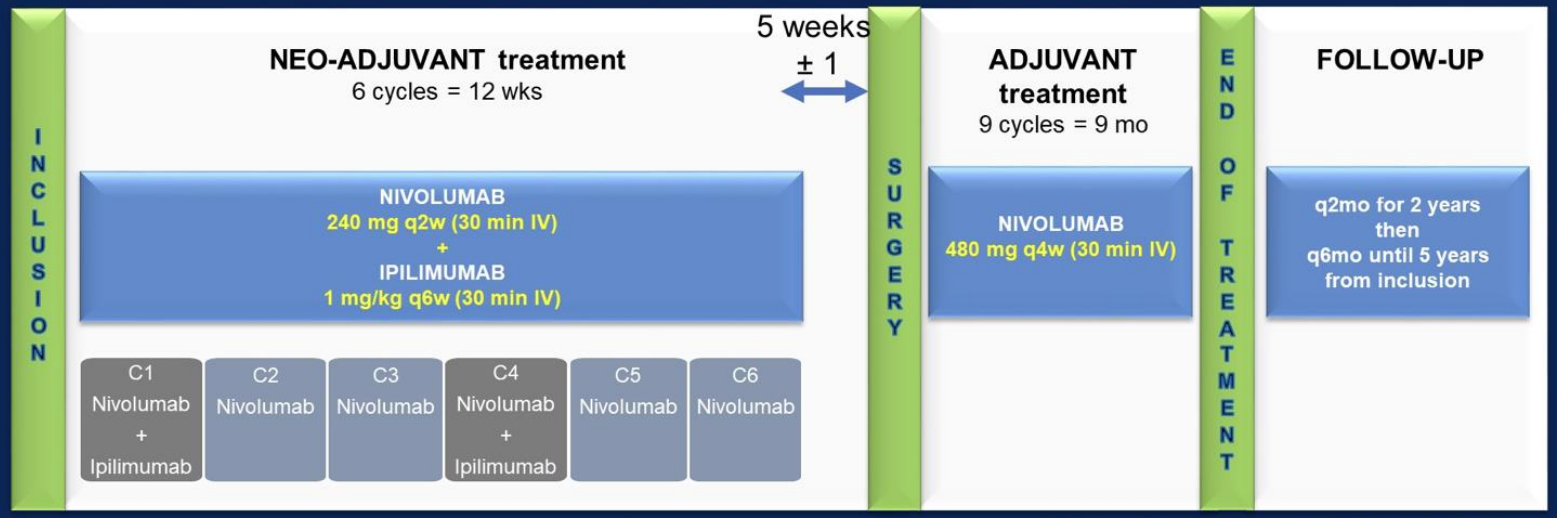
pCR + nCR



MSI-H

NEONIPIGA: Study design/metods

- Phase II study evaluating efficacy of neo-adjuvant nivolumab and ipilimumab followed by adjuvant nivolumab in pts with resectable OGA MSI/dMMR, T2-T4 NxM0
- The primary objective was pathological complete response rate (pCRR).



ClinicalTrials.gov: NCT04006262

ASCO Gastrointestinal Cancers Symposium #GI22

PRESENTED BY: Thierry André, MD

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Abstract 244

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Overall Population (n=32)		
	n	%
Male/Female	23/9	72/28
Age, median (min-max) Yrs	65	40-84
Tumor localisation		
Gastric/ Gastro-esophageal Junction	16/16	50/50
Histological type		
Intestinal	24	75
Diffuse	6	19
Missing	2	6
Echo-Endoscopy		
uT2/uT3/not done	4/22/6	12/69/19
dMMR (Immunochemistry)	32/32	100
loss of MLH1 and/or PMS2	26	81.25
loss of MSH2 and/or MSH6	6	18.75
MSI (PCR)	9/9	100
Lynch syndrome		
Yes/No (germline)/ongoing or unknown	6/21/5	19/68/13
ECOG PS at baseline		
0/1	19/13	59/41

- Pathologic Complete Response rate: 59%
- ~94% patients: DFS @ 12months
- 25%: >=Gr ¾ AE

Conclusions

- Esophageal, GEJ, Gastric Cancers: Heterogenous
  - Biomarkers: Personalized management (PDL1, CLDN 18.2, HER2, MMR)
- PDL1 Positive (CPS >=1):
  - PDL1 + SCC: Chemo + ICI, Doublet ICI, Chemo alone
  - PDL1 + Adeno: Chemo + ICI, Chemo alone
- CLDN 18.2 Positive:
  - GEJ/Gastric: Chemo + Zolbetuximab
    - GI-toxicities
- HER2 Positive: Chemo + Trastuzumab + ICI
- Biomarker negative:
  - Chemotherapy alone
    - Switch maintenance

Conclusions Contd.

- Neoadjuvant:
  - ESOPEC: Peri-op Chemo (FLOT) is superior to CRT in EC/GEJ adenocarcinoma
  - TOPGEAR: No benefit of additional CRT to peri-op CRT
  - Non-surgical candidates: CRT
  - FLOT + ICI: Improved pCR, Pending mature OS results
  - MSI-H: Nivolumab + Ipilimumab

- Adjuvant
  - Nivolumab: EC, GEJ adenocarcinoma
  - Neoadjuvant CRT with CROSS
  - CRT → Surgery → Nivo: Option for patients who can't tolerate peri-op FLOT

Thank you

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