



Updates in Gastro- Esophageal Cancer

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create a powerpoint presentation of advances in gastric and esophageal cancer



I'm sorry, but as an AI language model, I don't have the capability to create a PowerPoint presentation with graphics and slides. However, I can provide you with some information that you can use to create your own presentation on advances in gastric and esophageal cancer. Here are some key points:

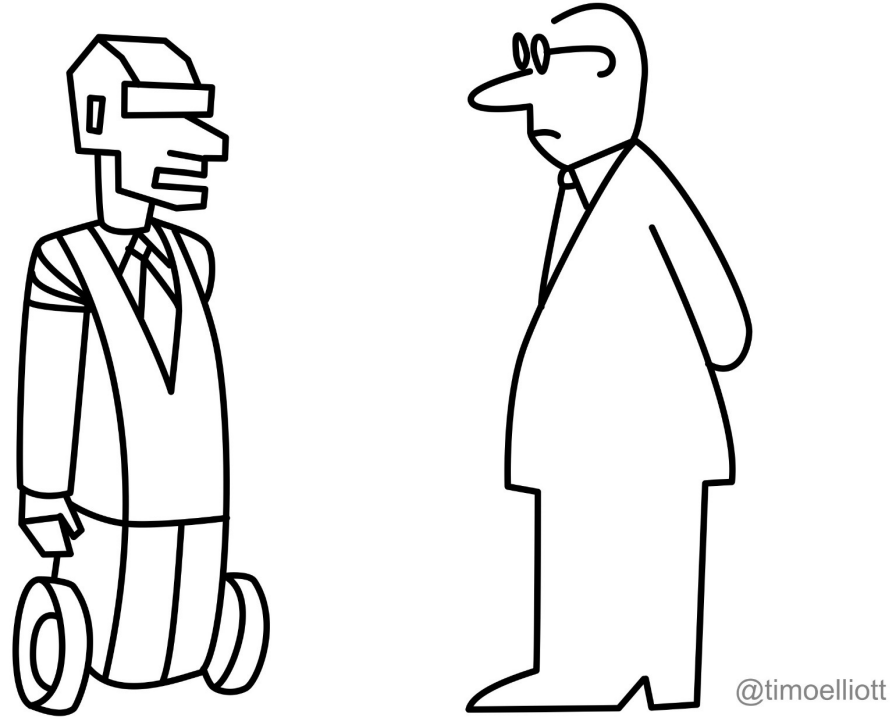


Advances in Gastric Cancer:

- Increased understanding of the molecular biology of gastric cancer has led to the development of targeted therapies. HER2-positive gastric cancer can be treated with trastuzumab, a monoclonal antibody that inhibits HER2.
- Immunotherapy, specifically checkpoint inhibitors, have shown promise in treating advanced gastric cancer. Pembrolizumab, a PD-1 inhibitor, was approved by the FDA in 2017 for the treatment of advanced gastric cancer.
- Laparoscopic and robotic-assisted surgical techniques have improved outcomes and reduced the morbidity associated with traditional open surgery. These techniques have also allowed for more precise lymph node dissection and better staging of the cancer.

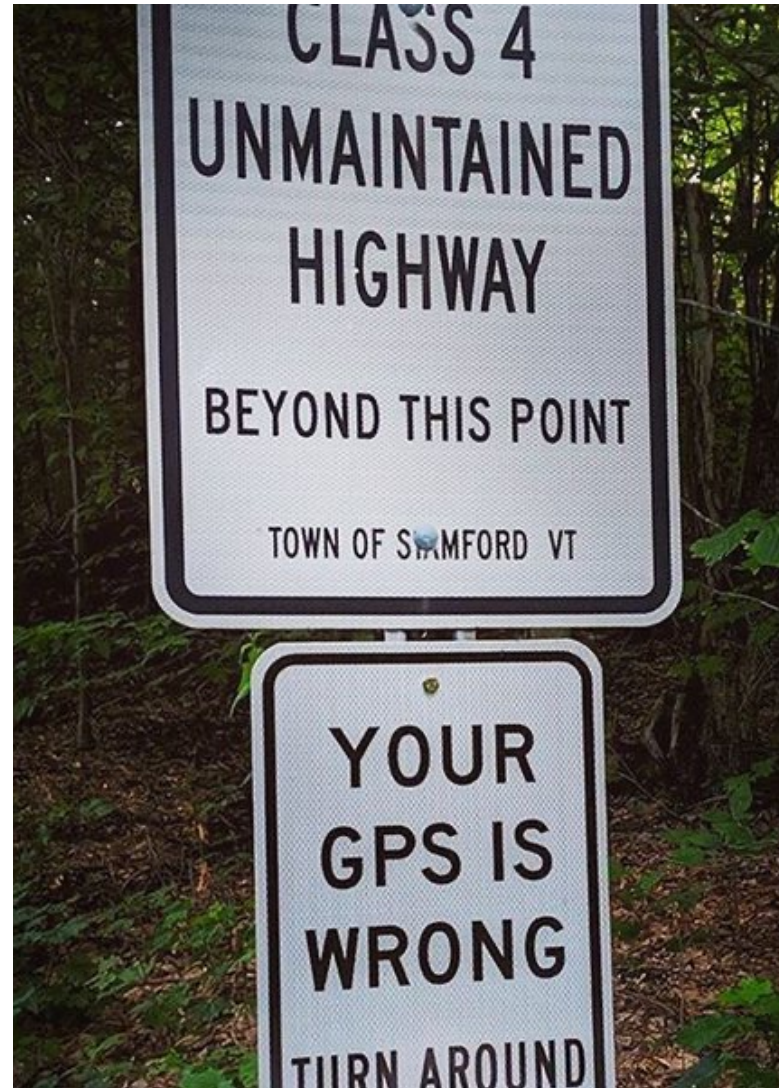
Advances in Esophageal Cancer:

- Advances in endoscopic technology, specifically endoscopic ultrasound (EUS), have allowed for better staging of esophageal cancer. EUS can accurately determine the depth of invasion of the tumor and the involvement of nearby lymph nodes.
- Neoadjuvant therapy, which involves administering chemotherapy and/or radiation prior to surgery, has improved outcomes for patients with locally advanced esophageal cancer. Neoadjuvant therapy can shrink the tumor and make it easier to remove surgically.
- Minimally invasive surgical techniques, such as laparoscopic and robotic-assisted surgery,



*“The good news is I have discovered inefficiencies.
The bad news is that you’re one of them.”*

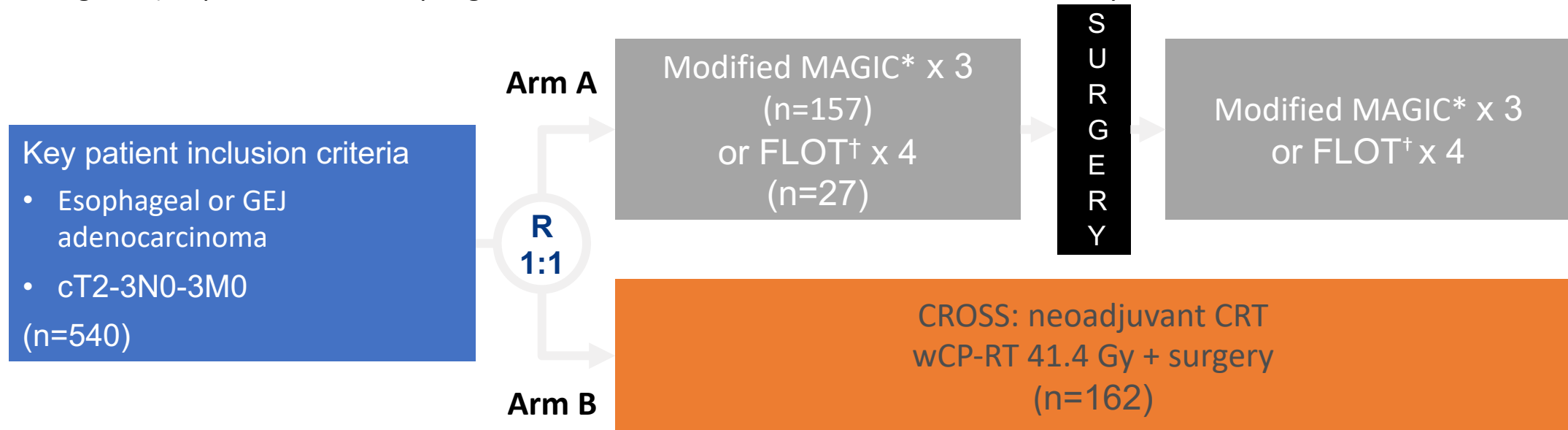
Early Stages



4004: Neo-AEGIS (Neoadjuvant trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): Preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (Modified MAGIC or FLOT protocol) – Reynolds JV, et al

Study objective

- To evaluate the efficacy and safety of the CROSS regimen vs. perioperative chemotherapy (either modified MAGIC or FLOT regimen) in patients with esophageal or GEJ adenocarcinoma in the Neo-AEGIS study



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- DFS, TTF, TRG, R0 rate, postoperative complications, HR-QoL, safety

*ECF/ECX/EOF/EOX; †5FU 2600 mg/m² iv 24 h infusion D1 + leucovorin 200 mg/m² iv D1 + oxaliplatin 85 mg/m² iv D1 + docetaxel 50 mg/m² iv D1 q2w

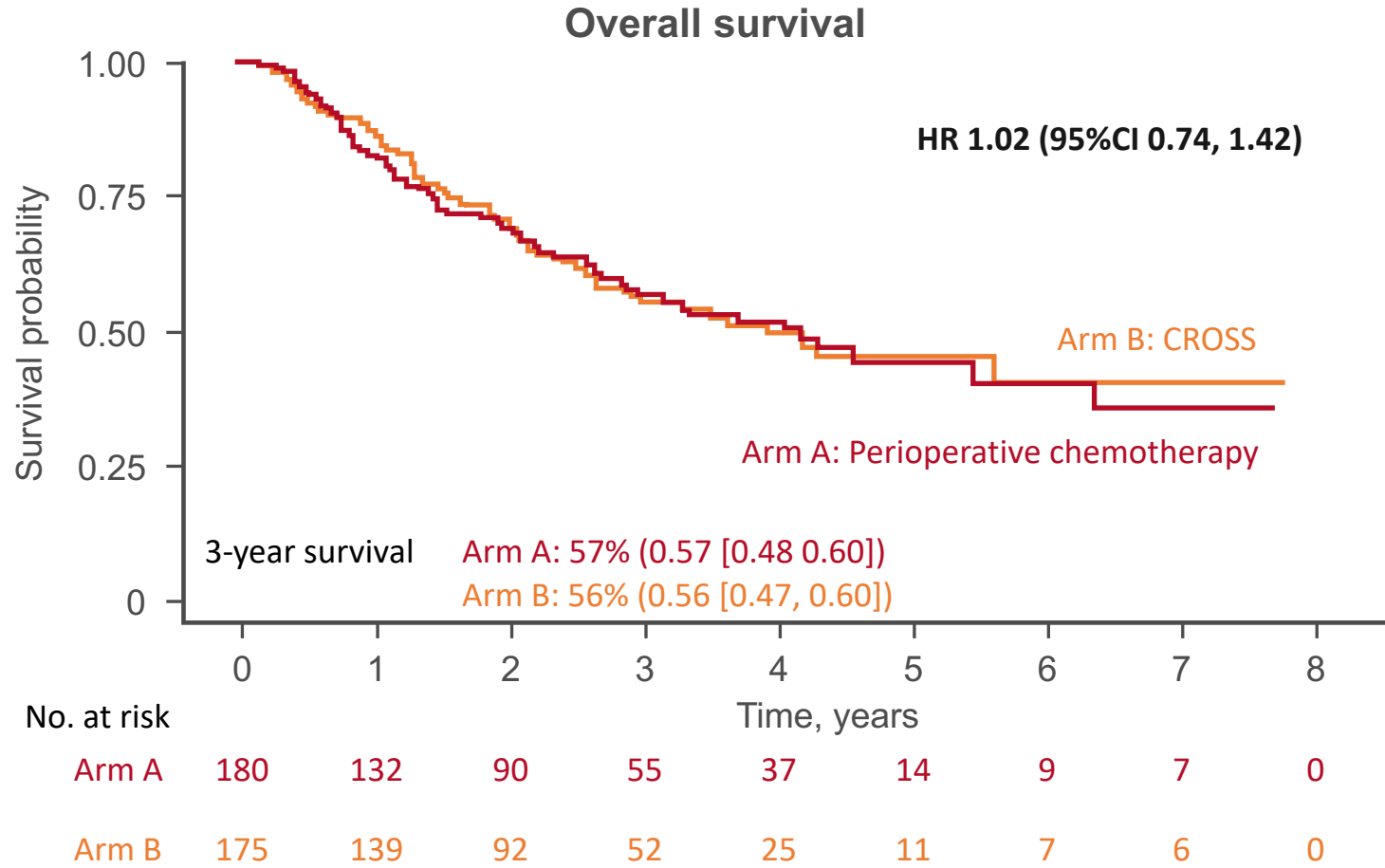
Results: Path, PCR, TRG and R status

	ARM A (Chemo)	ARM B (CROSS)
ypN0	43.8%	60%
ypT3	59.6%	52%
R0	82%	95%
pCR	5.1%	17.3%
TRG1	5.1%	17.3%
TRG 2	7.0%	24.7%
Major Path Response	12.1%	42%
TRG 3	23.4%	32.1%
TRG 4	41.6%	22.4%
TRG 5	22.8%	3.8%

ypN0 (p=0.004)
pCR (p=0.001)
R0 (p< 0.001)
TRG (p< 0.001)

4004: Neo-AEGIS (Neoadjuvant trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): Preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (Modified MAGIC or FLOT protocol) – Reynolds JV, et al

Key results



4004: Neo-AEGIS (Neoadjuvant trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): Preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (Modified MAGIC or FLOT protocol) – Reynolds JV, et al

Key results (cont.)

Postoperative complications, %	Arm A: Chemo (n=157)	Arm B: CROSS (n=162)	p-value
Mortality	1.9	3.0	0.723
Anastomotic leaks	12.0	12.0	
Respiratory			
Pneumonia	19.7	16.0	
ARDS	0.6	4.3	0.067
Respiratory failure	7.6	8.0	
VTE	3.8	3.0	
Cardiac			
Atrial fibrillation	12.7	14.2	
Sepsis	5.0	5.0	

Grade 3–4 AEs, %	Arm A: Chemo	Arm B: CROSS	p-value
Death	1.6	3.0	0.497
Neutropenia	14.1	2.8	<0.001
Diarrhea	10.9	0	<0.001
Neutropenic sepsis	2.7	0.6	0.215
Vomiting	7.6	2.8	0.035
Pulmonary embolism	5.4	5.1	0.872

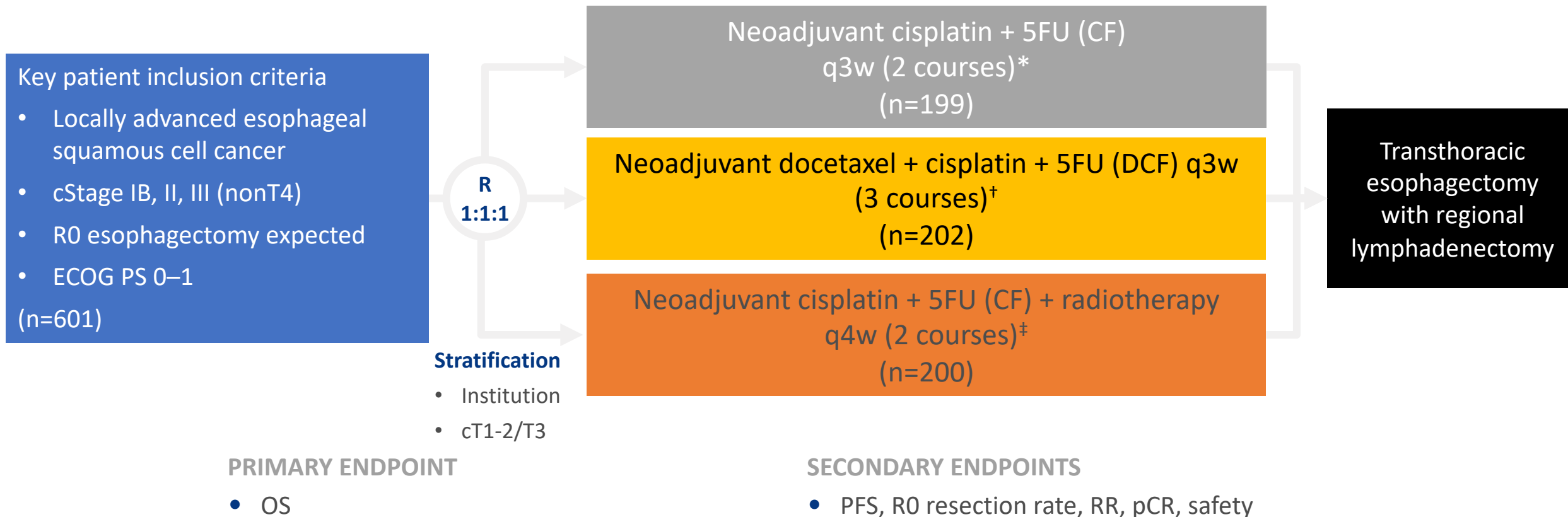
Conclusions

- In patients with esophageal or GEJ adenocarcinoma, perioperative chemotherapy was non-inferior to the CROSS regimen with no differences in postoperative complications
- Patterns of failure might help identify why better responses did not translate on better survival

238: A randomized controlled phase III trial comparing two chemotherapy regimen and chemoradiotherapy regimen as neoadjuvant treatment for locally advanced esophageal cancer, JCOG1109 NExT study – Kato K, et al

Study objective

- To evaluate the efficacy and safety of neoadjuvant chemotherapy or chemoradiotherapy regimens in patients with locally advanced esophageal squamous cell carcinoma in Japanese centers in the JCOG1109 NExT study



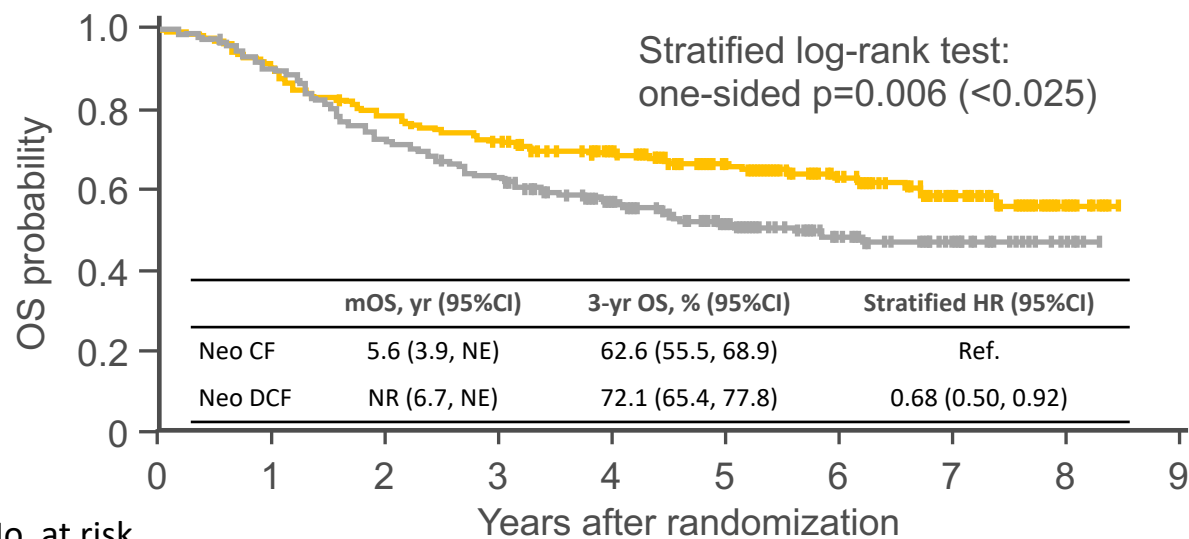
*Cisplatin 80 mg/m² D1 + 5FU 800 mg/m² D1–5; †docetaxel 70 mg/m² D1 + cisplatin 70 mg/m² D1 + 5FU 750 mg/m² D1–5; ‡cisplatin 75 mg/m² D1 + 5FU 1000 mg/m² D1–4 + radiotherapy 41.4 Gy

238: A randomized controlled phase III trial comparing two chemotherapy regimen and chemoradiotherapy regimen as neoadjuvant treatment for locally advanced esophageal cancer, JCOG1109 NExT study – Kato K, et al

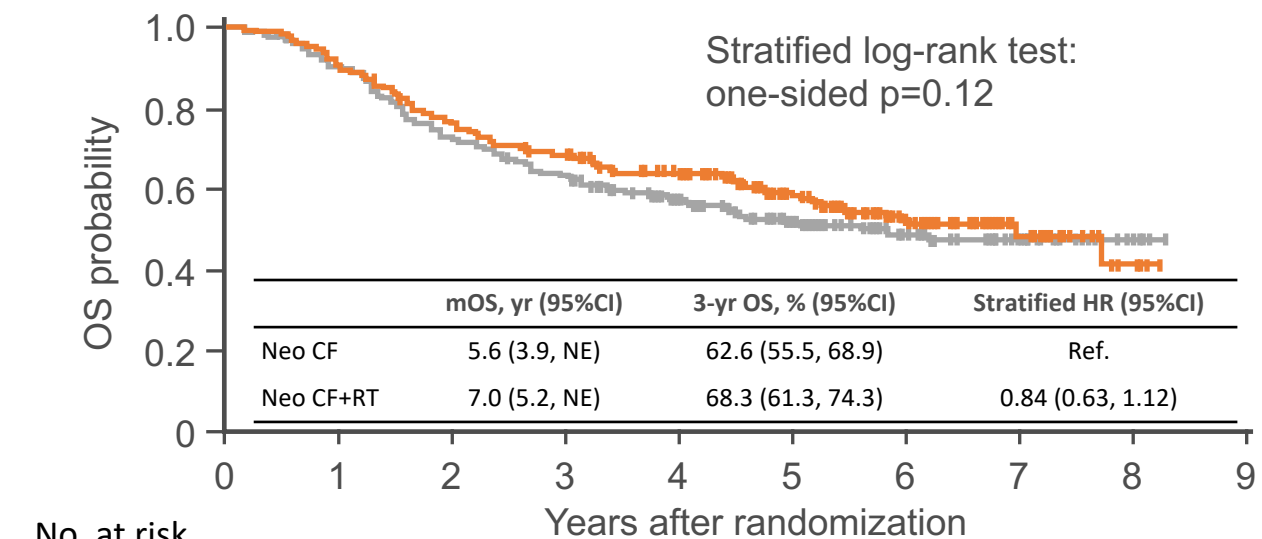
Key results

Overall survival

Neoadjuvant CF vs. neoadjuvant DCF



Neoadjuvant CF vs. neoadjuvant CF + radiotherapy



No. at risk

	0	1	2	3	4	5	6	7	8	9
Neo CF	199	178	143	123	98	66	38	19	4	0
Neo DCF	202	182	156	143	113	82	56	26	8	0

No. at risk

	0	1	2	3	4	5	6	7	8	9
Neo CF	199	178	143	123	98	66	38	19	4	0
Neo CF+RT	200	182	151	133	111	79	47	19	4	0

238: A randomized controlled phase III trial comparing two chemotherapy regimen and chemoradiotherapy regimen as neoadjuvant treatment for locally advanced esophageal cancer, JCOG1109 NExT study – Kato K, et al

Key results (cont.)

	Neo CF (n=199)	Neo DCF (n=202)	Neo CF + RT (n=200)	Grade 3–4 AEs during neoadjuvant treatment occurring in ≥10%, %	Neo CF (n=193)	Neo DCF (n=196)	Neo CF + RT (n=191)
mPFS, yr (95%CI)	2.7 (1.8, 4.8)	NR (5.2, NE)	5.3 (3.4, NE)				
HR (95%CI)	Ref	0.67 (0.51, 0.88)	0.77 (0.59, 1.01)				
Surgical outcomes, n	188	185	178				
R0, n (%)	168 (90.3)	173 (94.5)	175 (98.9)				
Underwent surgery, n	186	183	177				
pCR, n (%)	4 (2.2)	34 (18.6)	65 (36.7)				
No residual tumor, n (%)	4 (2.2)	40 (21.9)	77 (43.5)				
				Leukocytopenia	6.7	63.8	53.9
				Neutropenia	23.4	85.2	44.5
				Hyponatremia	6.2	26.0	11.0
				Febrile neutropenia	1.0	16.3	4.7
				Appetite loss	8.3	21.4	14.7

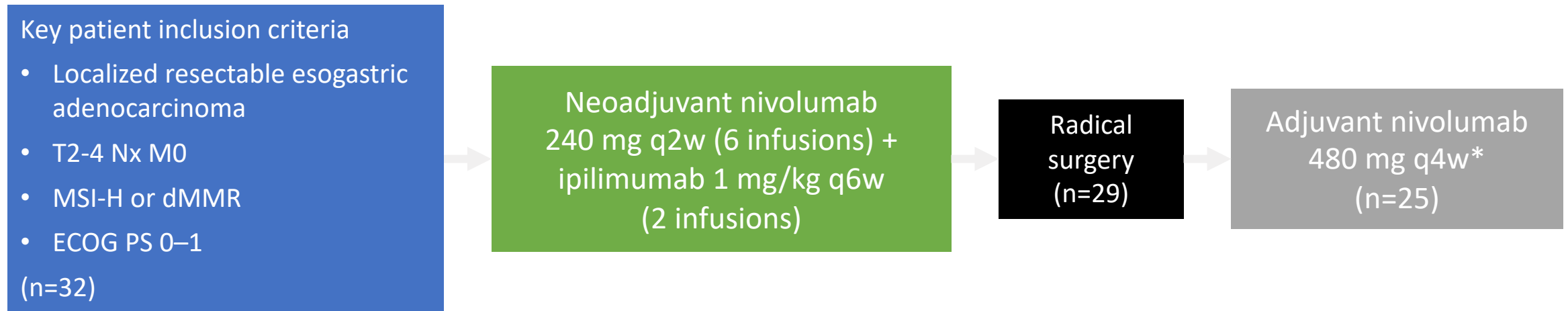
Conclusions

- In patients with locally advanced esophageal squamous cell carcinoma, neoadjuvant DCF, but not neoadjuvant CF + radiotherapy, significantly improved OS compared with neoadjuvant CF and had a manageable safety profile

244: Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in patients (pts) with localized microsatellite instability-high (MSI)/mismatch repair deficient (dMMR) oeso-gastric adenocarcinoma (OGA): The GERCOR NEONIPIGA phase II study – André T, et al

Study objective

- To evaluate the efficacy and safety of neoadjuvant nivolumab + ipilimumab and adjuvant nivolumab in patients with localized MSI-H or dMMR esogastric adenocarcinoma in French centers in the phase 2 GERCOR NEONIPIGA study



PRIMARY ENDPOINT

- pCR

SECONDARY ENDPOINTS

- EFS, OS, safety

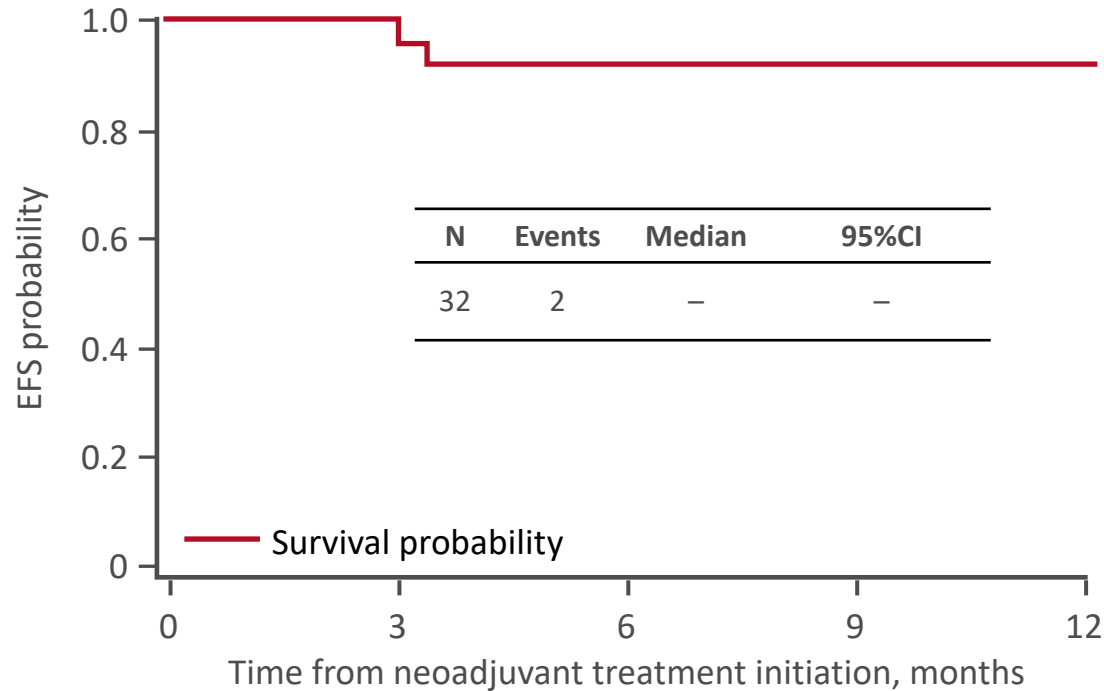
*Only patients with Becker tumor regression grade <3 received adjuvant nivolumab

244: Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in patients (pts) with localized microsatellite instability-high (MSI)/mismatch repair deficient (dMMR) oeso-gastric adenocarcinoma (OGA): The GERCOR NEONIPIGA phase II study – André T, et al

Key results

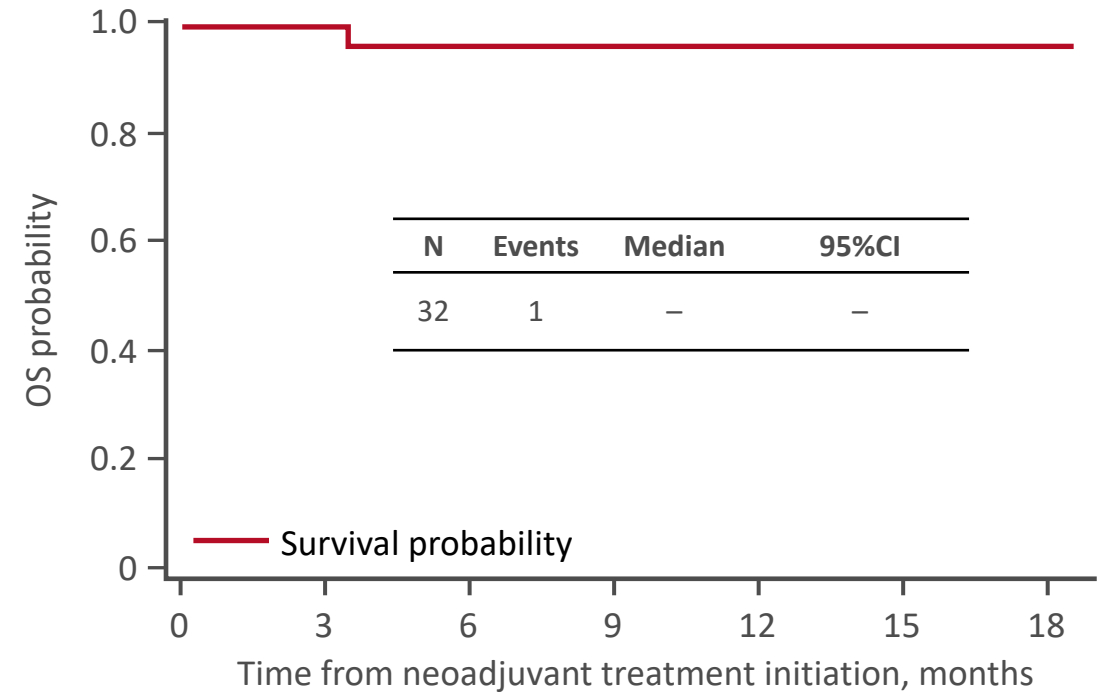
- pCR was achieved by 17 of 29 (58.6%) patients

Event-free survival



No. at risk 32 24 18 12 7

Overall survival



No. at risk 32 32 24 20 15 8 6

Trial Design

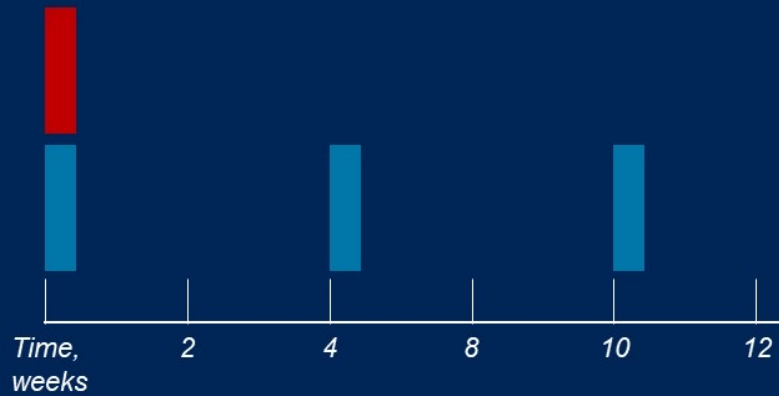
Rsectable Gastric or GEJ cancer

Centrally confirmed MSI-H & dMMR, EBV-
cT \geq 2, any N, M0

Tremelimumab
300 mg on day 1

Durvalumab
1500 mg on day 1, 29 and 57

*** Intensive follow-up**
Every 12 weeks for 2 years: chest-abdomen-pelvis CT scan, EUS with multiple biopsies/nodal FNA, liquid biopsy MRD



Restaging:
CT & PET scan
EUS with multiple biopsies/
nodal FNA,
Liquid biopsy MRD

Cohort 1

Surgery

Standard follow up

14 16 18

IDMC APPROVAL

Cohort 2

Incomplete response

Surgery

Standard follow up

14

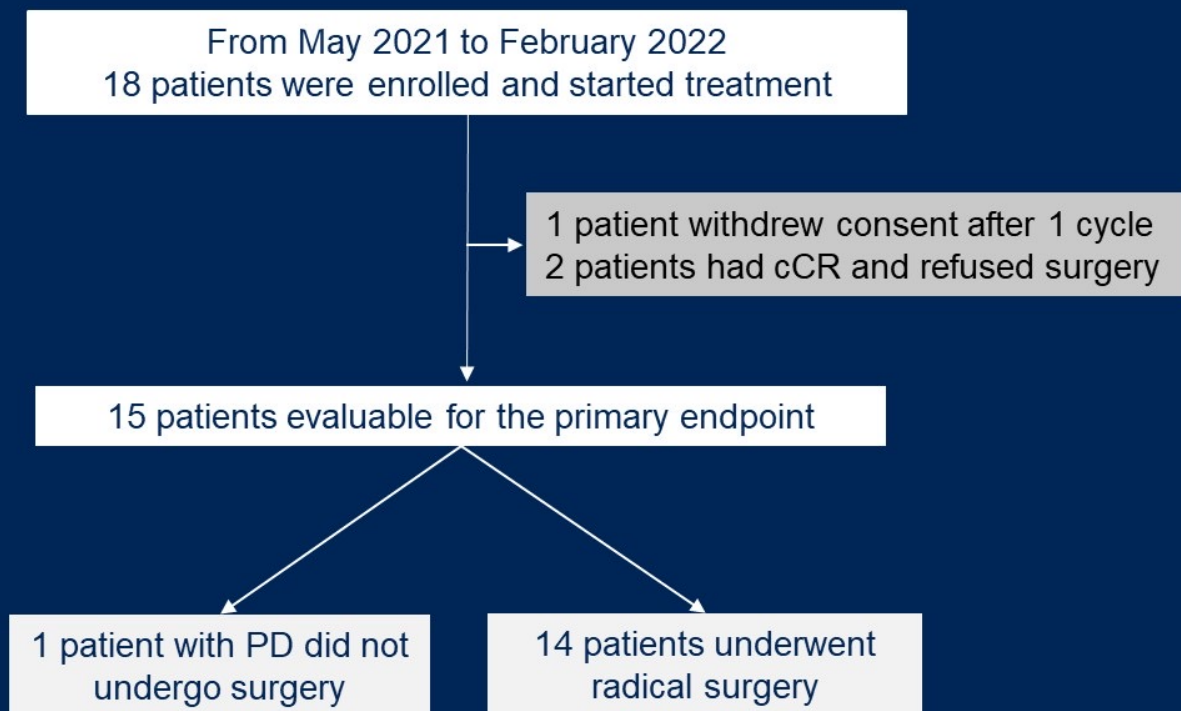
Evidence of Disease/ tumor regrowth

Complete response

Non-operative Management

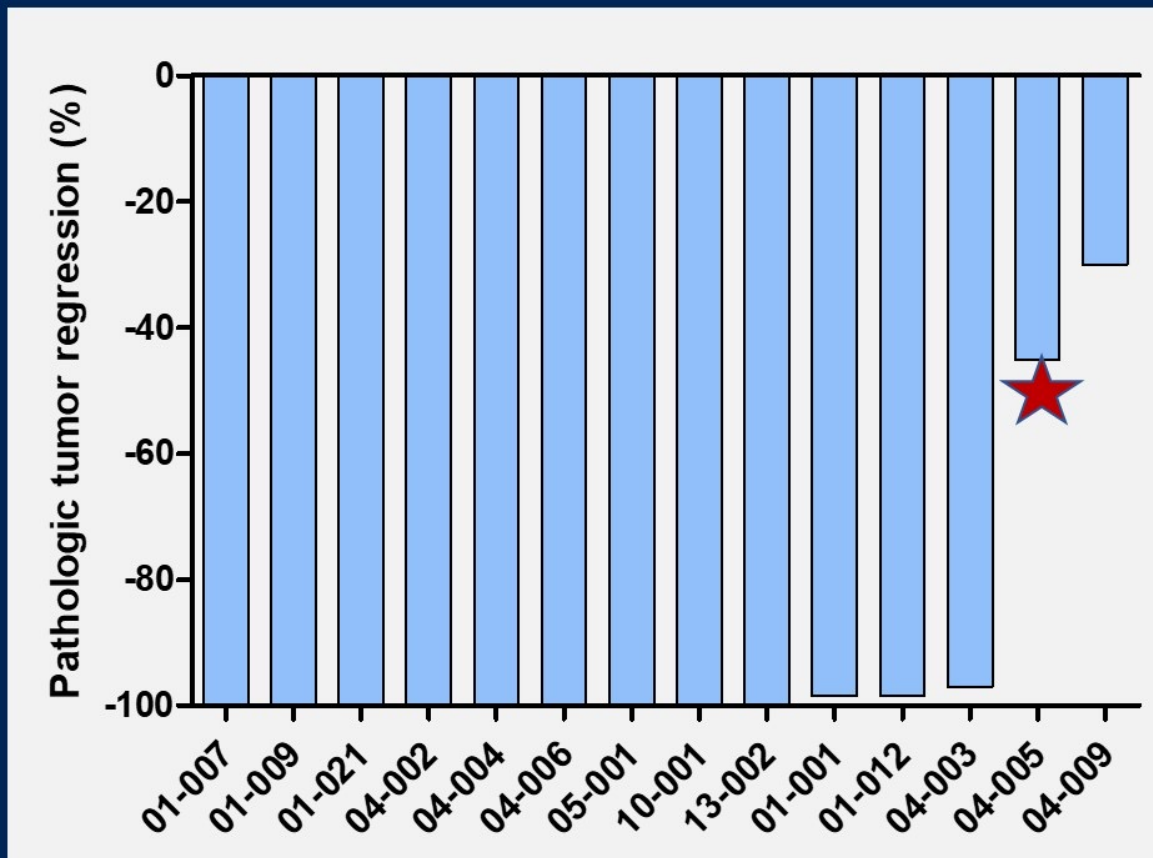
Intensive follow up*

Patients' flow and baseline characteristics



Characteristics	N=18 (%)
Age, years: median (IQR)	71.5 (65-80)
Sex	
Male	12 (67)
Female	6 (33)
ECOG PS	
0	12 (67)
1	6 (33)
Primary site	
Gastric	14 (78)
Gastroesophageal junction	4 (22)
T stage	
T2	1 (5)
T3	10 (56)
T4	7 (39)
N stage	
N0	3 (17)
N1	6 (33)
N2	9 (50)
N bulky	
yes	4 (22)
no	14 (78)

Primary endpoint



TRG Becker	N = 15	%
1a	9	60%
1b	3	20%
3	2	13%

1 patient did not undergo surgery for PD

Among evaluable patients, rate of pCR was 60% and rate of major to complete pathological response (<10% viable cells) was 80%.

 Heterogeneous pMMR/dMMR status at surgery

Survival endpoints

	PFS event	OS event
01-020	Yes	No
04-005	Yes	Yes
13-002	No	Yes
01-009	No	Yes
05-001	No	Yes

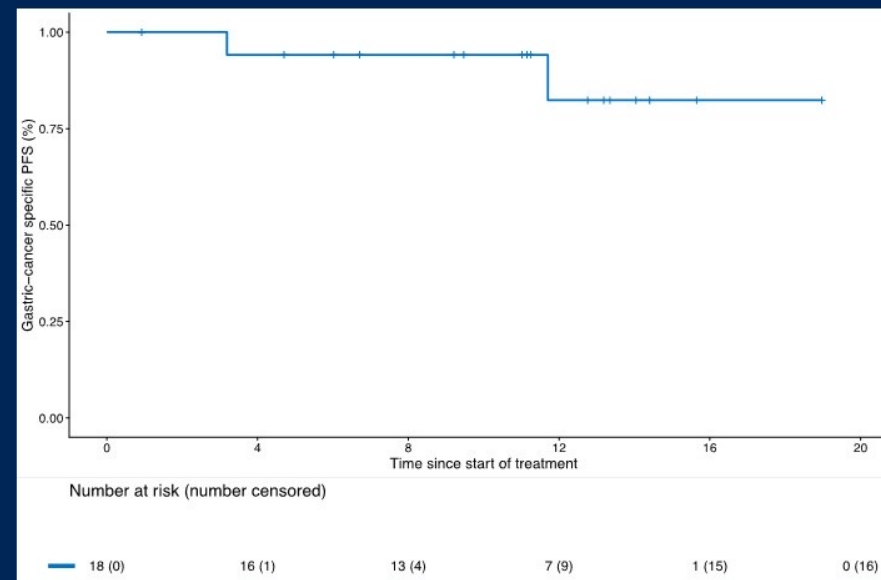
CR to CAPOX

Heterogeneous pMMR/dMMR status

Late postoperative complications

Second primary brain cancer

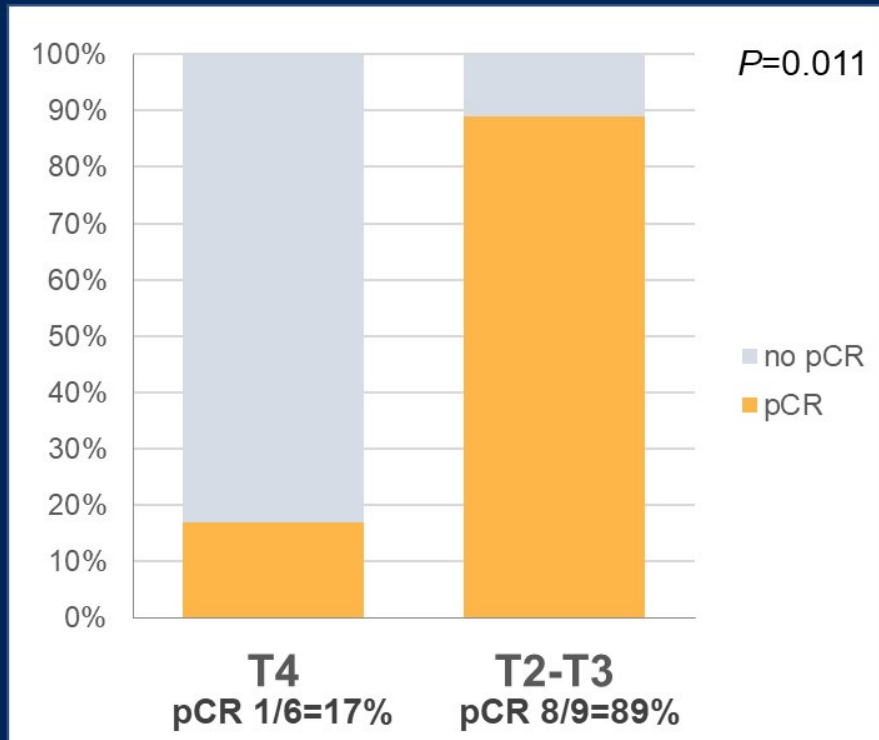
Gastric cancer-specific PFS



Data cutoff date: 16th December 2022, with a median follow up of 13.4 (IQR 9.7-14.2) months

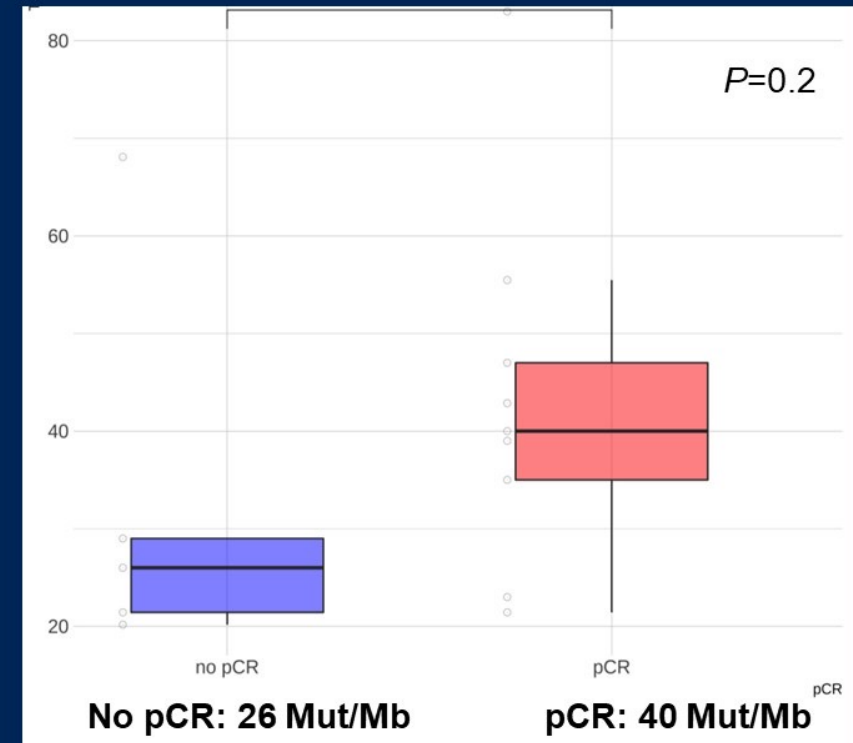
Exploratory analyses

Baseline clinical staging (EUS, CT +/- laparoscopy)



Significant correlation with pCR was found for baseline **cT stage**, but not for **cN stage**.

Baseline Tumor Mutational Burden

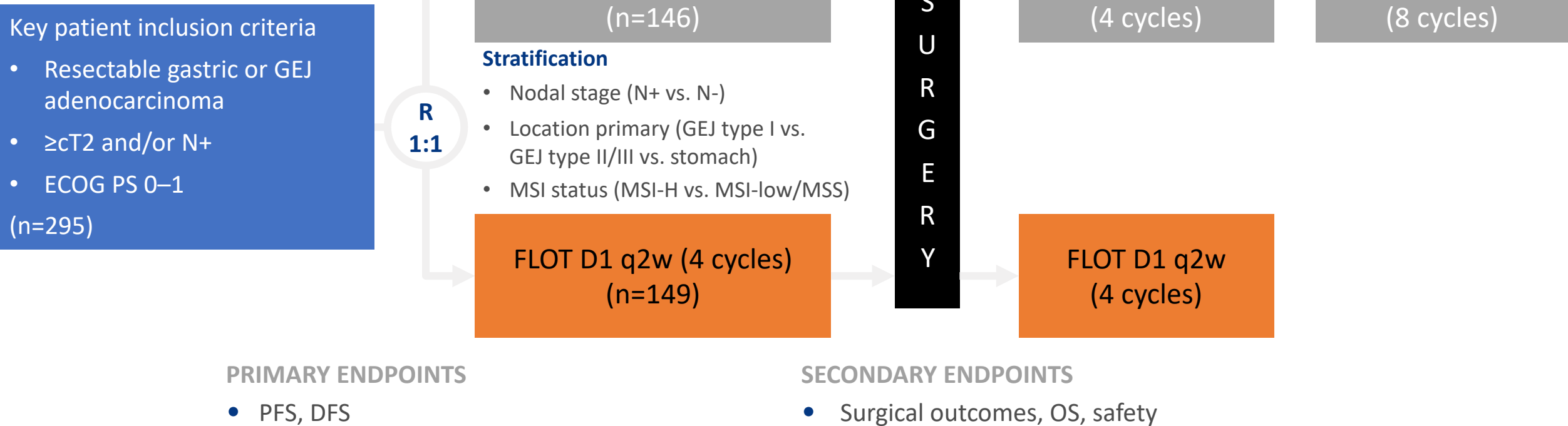


Numerical correlation with pCR was found for baseline **TMB**, but not for **PD-L1 CPS**.

4003: Surgical and pathological outcome, and pathological regression, in patients receiving perioperative atezolizumab in combination with FLOT chemotherapy versus FLOT alone for resectable esophagogastric adenocarcinoma: Interim results from DANTE, a randomized, multicenter, phase IIb trial of the FLOT-AIO German Gastric Cancer Group and Swiss SAKK – Al-Batran S-E, et al

Study objective

- To evaluate the efficacy and safety of atezolizumab + FLOT in patients with resectable esophagogastric adenocarcinoma in German and Swiss centers in the phase 2b DANTE study (interim analysis)



FLOT, docetaxel 50 mg/m² + oxaliplatin 85 mg/m² + leucovorin 200 mg/m² + 5FU 2600 mg/m² D1 IV

4003: Surgical and pathological outcome, and pathological regression, in patients receiving perioperative atezolizumab in combination with FLOT chemotherapy versus FLOT alone for resectable esophagogastric adenocarcinoma: Interim results from DANTE, a randomized, multicenter, phase IIb trial of the FLOT-AIO German Gastric Cancer Group and Swiss SAKK – Al-Batran S-E, et al

Key results

AEs, n (%)	Atezolizumab + FLOT (n=144)	FLOT (n=148)
Any grade 3–4	130 (90)	125 (85)
Any grade 5	7 (5)	8 (5)
SAE	99 (69)	98 (66)
Treatment-related SAE	60 (42)	46 (31)
Treatment-related grade 3–4	51 (35)	31 (21)
Treatment-related led to death	1 (<1)	2 (1)

Surgical and margin-free resection, n (%)	Atezolizumab + FLOT (n=146)	FLOT (n=149)
Resectional tumor surgery	141 (97)	143 (96)
Margin-free (R0) resection		
Among those having surgery	135 (96)	136 (95)
ITT	135 (93)	136 (91)
Lymph nodes removed, median (25%, 75% quartile)	30 (5–139)	29 (11–81)

Surgical morbidity/ mortality, n (%)	Atezolizumab + FLOT (n=141)	FLOT (n=143)
Median hospitalization, days	16	15
Complications	64 (45)	60 (42)
Surgical	25 (18)	26 (18)
Medical	35 (25)	27 (19)
Both	4 (3)	7 (5)
Re-operation	14 (10)	16 (11)
Death in hospital	4 (3)	3 (2)
Death 60 days	4 (3)	3 (2)

4003: Surgical and pathological outcome, and pathological regression, in patients receiving perioperative atezolizumab in combination with FLOT chemotherapy versus FLOT alone for resectable esophagogastric adenocarcinoma: Interim results from DANTE, a randomized, multicenter, phase IIb trial of the FLOT-AIO German Gastric Cancer Group and Swiss SAKK – Al-Batran S-E, et al

Key results

Pathological regression*, n (%)	Local assessment				Central assessment			
	TRG1a		TRG1a/b		TRG1a		TRG1a/b	
	Atezo + FLOT	FLOT	Atezo + FLOT	FLOT	Atezo + FLOT	FLOT	Atezo + FLOT	FLOT
All patients (n=295; 146/149)	35 (24)	23 (15)	71 (49)	58 (39)	37 (25)	36 (24)	72 (49)	66 (44)
PD-L1 CPS ≥1 (n=170; 82/88)	20 (24)	13 (15)	42 (51)	40 (46)	21 (26)	20 (23)	43 (52)	41 (47)
PD-L1 CPS ≥5 (n=81; 40/41)	11 (28)	8 (20)	22 (55)	18 (44)	13 (33)	9 (22)	21 (53)	19 (46)
PD-L1 CPS ≥10 (n=53; 27/26)	9 (33)	3 (12)	18 (67)	10 (39)	11 (41)	5 (19)	19 (70)	13 (50)
MSI-H (n=23; 8/15)	5 (63)	4 (27)	6 (75)	7 (47)	5 (63)	4 (27)	6 (75)	7 (47)

Conclusions

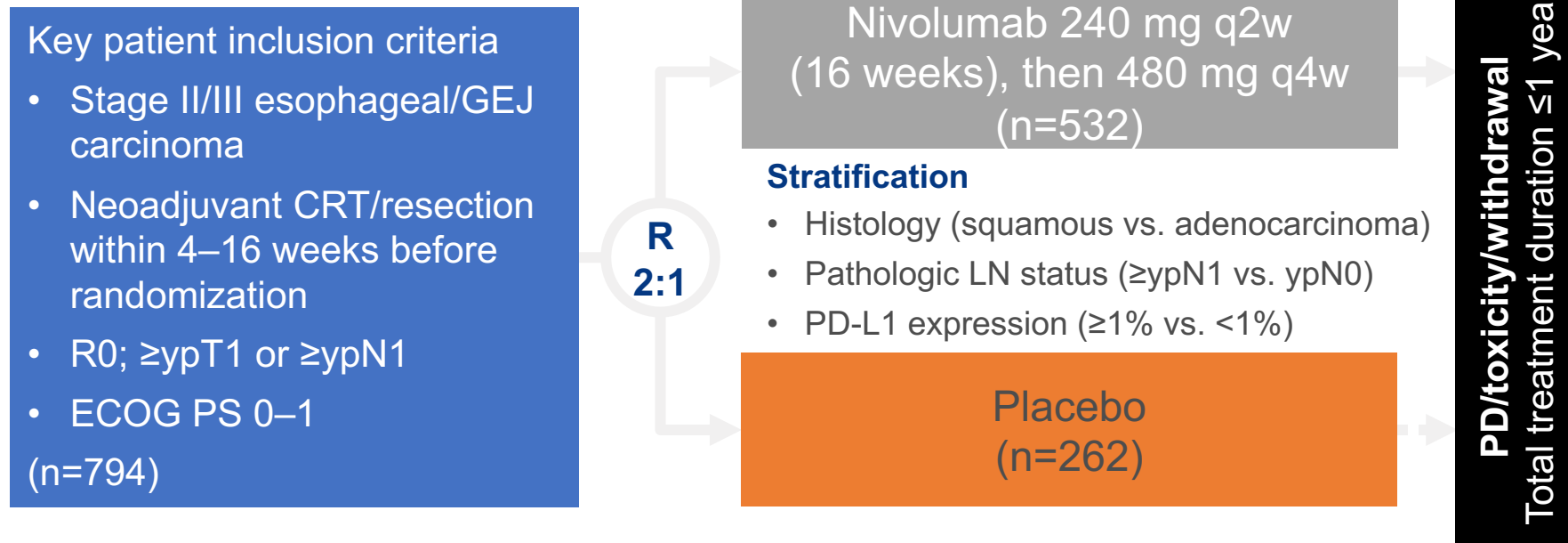
- **In patients with resectable esophagogastric adenocarcinoma, perioperative atezolizumab + FLOT improved downstaging and pathological regression, particularly in those with higher PD-L1 expression or MSI-H tumors and was generally well-tolerated**

*Pathological complete and subtotal regression according to Becker criteria

167: CheckMate 577: Health-related quality of life (HRQoL) in a randomized, double-blind phase III study of nivolumab (NIVO) versus placebo (PBO) as adjuvant treatment in patients (pts) with resected esophageal or gastroesophageal junction cancer (EC/GEJC) – Van Cutsem E, et al

Study objective

- To evaluate the HRQoL of adjuvant nivolumab in patients with esophageal/GEJ cancer and residual disease after CRT and surgery in the CheckMate 577 study



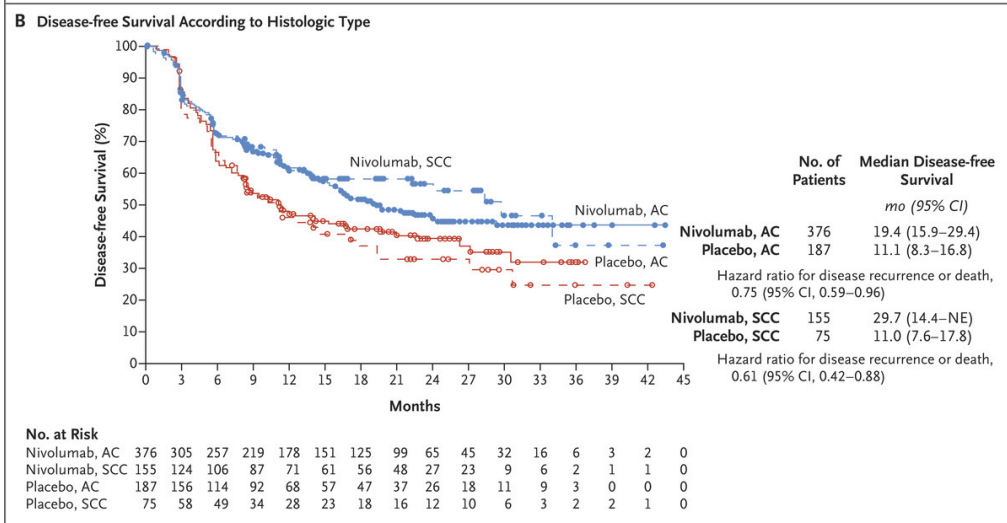
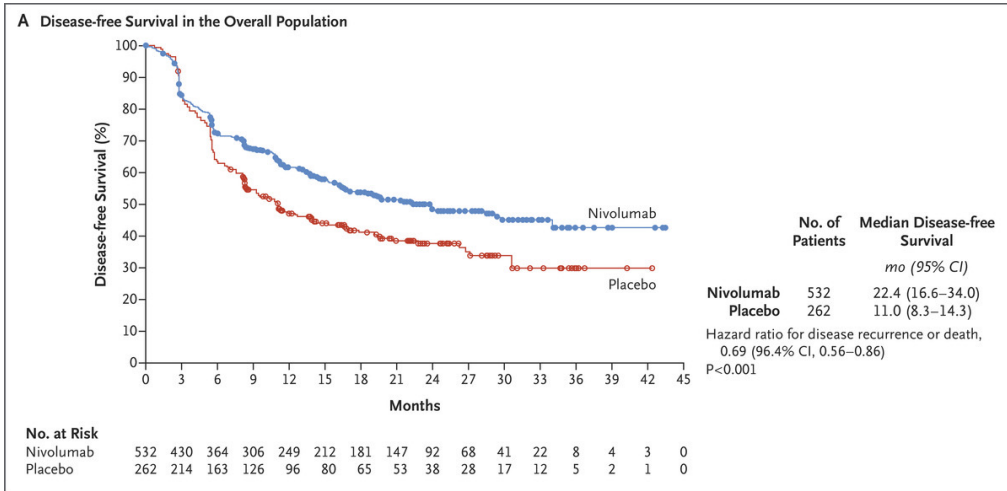
PRIMARY ENDPOINT

- DFS

EXPLORATORY ENDPOINTS

- HRQoL: FACT-E, EQ-5D-3L, ECS, FACT-G7

Disease-free Survival in the Intention-to-Treat Population.

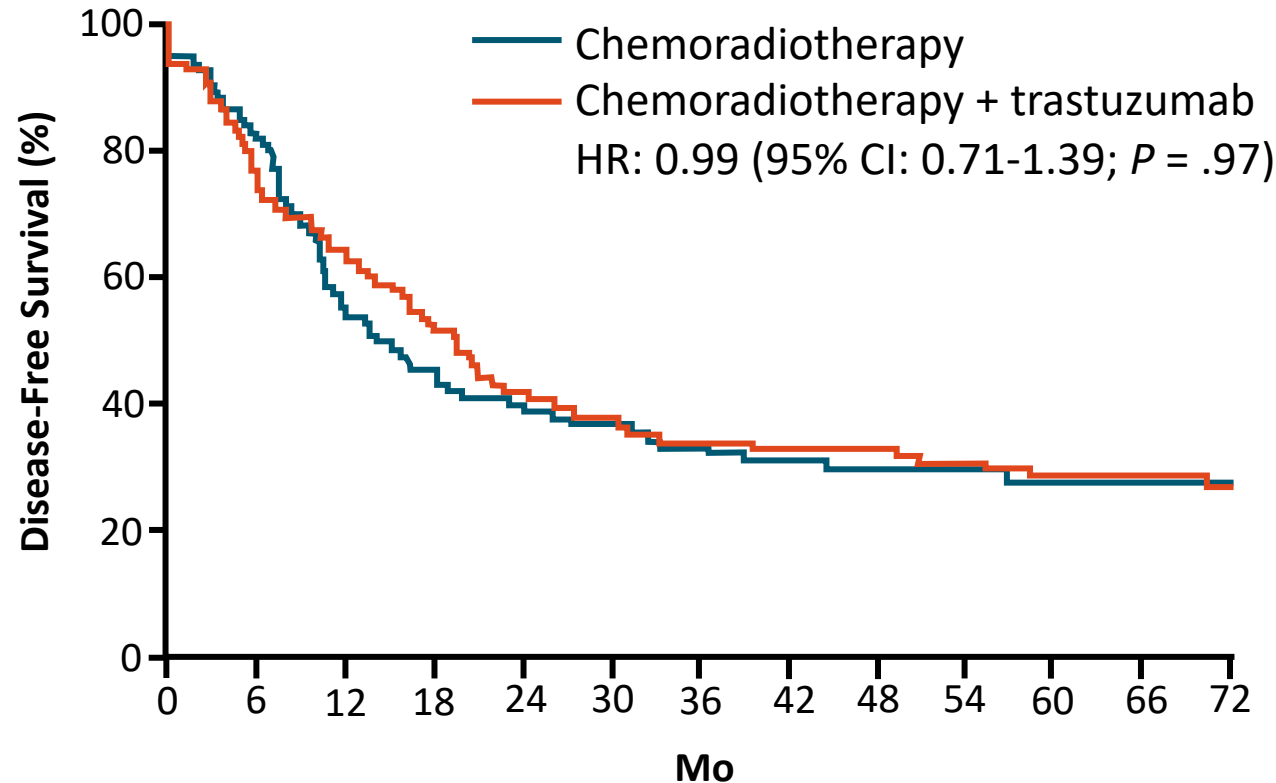


Subgroup	No. of Patients	Median Disease-free Survival (mo)		Unstratified Hazard Ratio (95% CI)	
		Nivolumab	Placebo		
Overall	794	22.4	11.0	0.70	(0.58–0.86)
Age					
<65 yr	507	24.4	10.8	0.65	(0.51–0.84)
≥65 yr	287	17.0	13.9	0.80	(0.57–1.12)
Sex					
Male	671	21.4	11.1	0.73	(0.59–0.91)
Female	123	Not reached	11.0	0.59	(0.35–1.00)
Race					
White	648	21.3	10.9	0.71	(0.57–0.88)
Asian	117	24.0	10.2	0.70	(0.41–1.22)
Black	9	14.4	8.3	0.43	(0.06–3.06)
Other	20	Not reached	14.1	0.48	(0.11–2.02)
Region					
Asia	106	24.0	14.3	0.78	(0.43–1.41)
Other	688	21.4	11.0	0.69	(0.56–0.86)
ECOG performance-status score					
0	464	29.4	11.1	0.73	(0.56–0.96)
1	330	17.0	10.9	0.66	(0.48–0.89)
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 trial entry					
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)

0.00 0.25 0.50 1.00 2.00 4.00
Nivolumab Better Placebo Better

RTOG 1010: Trastuzumab + Trimodality Treatment in Resectable HER2-Positive Esophageal Adenocarcinoma

- Randomized phase III trial of **trimodality therapy (chemoradiation followed by surgery) ± trastuzumab** for patients with newly diagnosed, **HER2+**, stage T1N1-2, T2-3N0-2 esophageal adenocarcinoma involving mid (≤ 25 cm), distal, or esophagogastric junction and up to 5 cm of stomach; **candidate for curative resection** (N = 203)



Advanced Disease

MI

how many more pd-l1 inhibitors will be approved in the future



As an AI language model, I don't have access to information about future drug approvals. Predicting the number of PD-L1 inhibitors that will be approved in the future is beyond the scope of my training and knowledge.



However, it's worth noting that the development of new drugs is a complex and lengthy process that involves preclinical studies, clinical trials, and regulatory approval. It can take several years or even decades for a new drug to be developed and approved, and many drugs do not make it past the initial stages of development.

In addition, the approval of new drugs depends on various factors such as their safety, efficacy, and potential benefits compared to existing treatments. The decision to approve a new drug is made by regulatory agencies such as the FDA in the United States, based on the data from clinical trials and other evidence provided by the drug's manufacturer.

So, while it's possible that new PD-L1 inhibitors may be approved in the future, it's difficult to predict how many will be approved and when they will become available. It's best to **consult with a healthcare provider** or stay up-to-date with the latest research in this area.

MI

do we need more pd-l1 inhibitors in oncology



The development of PD-L1 inhibitors has been a significant advance in the field of oncology, as they have shown promising results in the treatment of various cancers. However, the question of whether we need more PD-L1 inhibitors in oncology is a complex one and depends on several factors.



On the one hand, there is still a significant unmet need for effective cancer treatments, particularly for cancers that are difficult to treat with existing therapies. Therefore, the development of new PD-L1 inhibitors or other immunotherapies may offer a valuable treatment option for patients with these types of cancers.

On the other hand, the development of new PD-L1 inhibitors may also lead to increased **competition in the market and may not necessarily lead to better outcomes for patients.**

Additionally, the development of new drugs is a resource-intensive process, and resources may be better directed towards developing other types of treatments, such as combination therapies that can enhance the effectiveness of existing immunotherapies.

Ultimately, the decision to develop new PD-L1 inhibitors or other cancer treatments depends on several factors, including the unmet medical need, the safety and efficacy of existing therapies, and the availability of resources. It's important to continue to advance research in the field of oncology to develop more effective treatments and improve outcomes for patients with cancer.



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FDA-Approved Indications for Nivolumab and Pembrolizumab in Advanced Gastroesophageal Cancers

Indication	Pembrolizumab	Nivolumab
Gastric	<ul style="list-style-type: none"> ▪ HER2-positive locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma (with trastuzumab and fluoropyrimidine- and platinum-containing CT) as first-line therapy 	<ul style="list-style-type: none"> ▪ Advanced or metastatic gastric or GEJ cancer and esophageal adenocarcinoma with fluoropyrimidine- and platinum-containing CT
Esophageal	<ul style="list-style-type: none"> ▪ Locally advanced or metastatic esophageal or GEJ carcinoma: <ul style="list-style-type: none"> – With platinum- and fluoropyrimidine-based CT, or – For PD-L1 CPS ≥ 10 <i>squamous</i> carcinoma after ≥ 1 line(s) of systemic therapy 	<ul style="list-style-type: none"> ▪ Unresectable advanced or metastatic esophageal <i>squamous</i> cell carcinoma as first-line therapy with fluoropyrimidine- and platinum-based CT OR ipilimumab ▪ See above
Tumor agnostic	<ul style="list-style-type: none"> ▪ MSI-H or MMR deficient or TMB-H (≥ 10 mut/Mb) unresectable or metastatic solid tumors with PD after previous treatment with no satisfactory alternative treatment options 	

Simplified First-line Treatment Algorithm for Advanced Gastroesophageal Adenocarcinomas

	No Biomarkers or HER2-	HER2+
Gastric	Fluoropyrimidine + platinum ± nivolumab (<i>CPS</i> ≥5; CheckMate 649)	Fluoropyrimidine + platinum + trastuzumab ± pembrolizumab (KEYNOTE-811)
Esophageal/ GEJ	Fluoropyrimidine + platinum ± nivolumab (<i>CPS</i> ≥5; CheckMate 649) Fluoropyrimidine + platinum ± pembrolizumab (<i>CPS</i> ≥10; KEYNOTE-590)	Fluoropyrimidine + platinum + trastuzumab ± pembrolizumab (KEYNOTE-811)

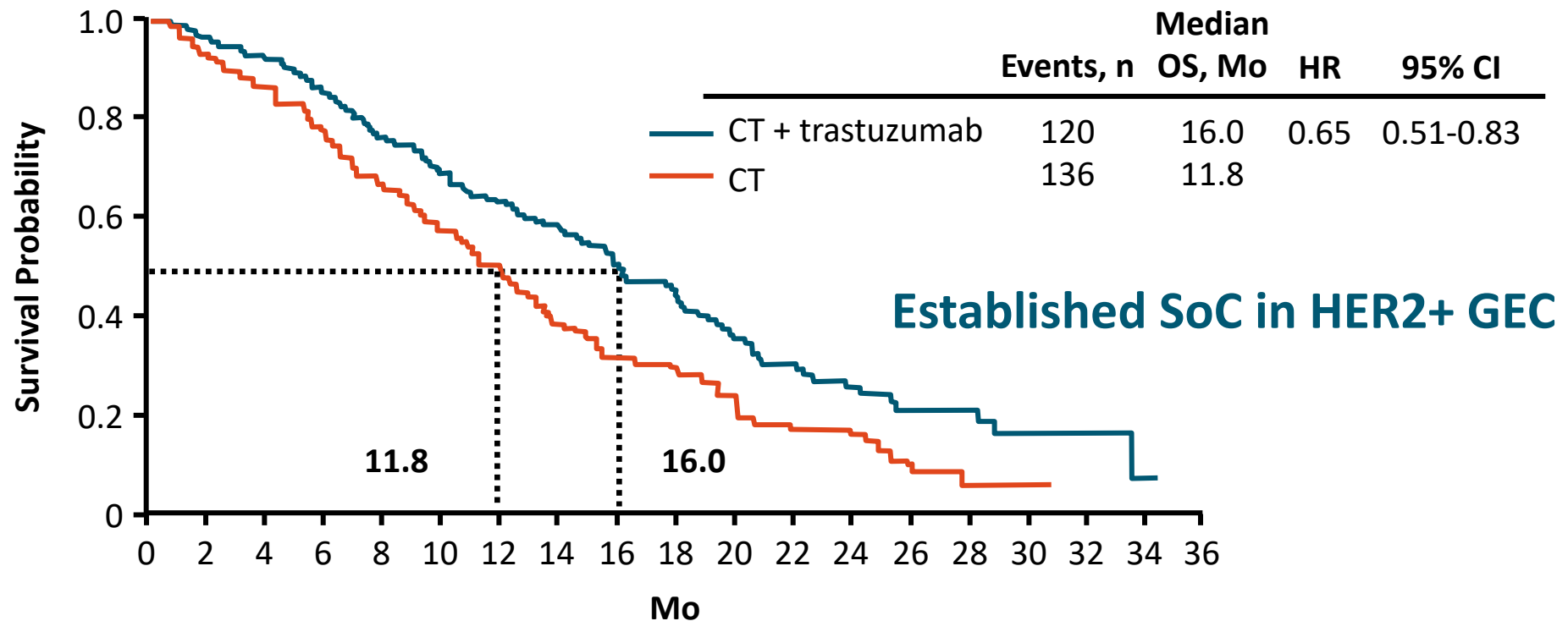
Gastroesophageal Adenocarcinoma Algorithm for HER2 Testing by IHC

HER2 Level Assessment		Gastric		Breast Biopsy
Score	Overexpression	Surgical Specimen	Biopsy Specimen	
0	Negative	No reactivity or membranous reactivity in <10% of TC	No reactivity in any TC	No staining observed or membrane staining incomplete and faint/barely perceptible and in ≤10% of TCs
1+	Negative	Faint/barely perceptible membranous reactivity in ≥10% of TCs; cells reactive only in part of membrane	TC cluster with faint/barely perceptible membranous reactivity regardless of % of TCs stained	Incomplete membrane staining that is faint/barely perceptible and in >10% of TCs
2+	Equivocal	Weak to moderate complete, basolateral, or lateral membranous reactivity in ≥10% of TCs	TC cluster with weak to moderate complete, basolateral, or lateral membranous activity regardless of % of TCs stained	Weak to moderate complete membrane staining in >10% of TCs
3+	Positive	Strong complete, basolateral, or lateral membranous reactivity in ≥10% of TCs	TC cluster with strong complete, basolateral, or lateral membranous activity regardless of % of TCs stained	Circumferential membrane staining that is complete, intense, and in >10% of TCs

ToGA: First-line Trastuzumab + Chemotherapy in Advanced HER2+ Gastric Cancer

- Randomized phase III trial of 5-FU or capecitabine + cisplatin ± trastuzumab for patients with advanced gastric cancer (N = 584)

OS in Patients With IHC 3+ or FISH+ and IHC 2+ (Exploratory Analysis) (N = 446)



History of HER2-Directed Therapy in Advanced Gastric Cancer

First-line Trials

JACOB: chemotherapy*/trastuzumab ± pertuzumab (N = 780)¹

- Median OS: 17.5 vs 14.2 mo (HR: 0.84; *P* = .056)

HELOISE: capecitabine/cisplatin + 2 dose levels of trastuzumab (N = 248)²

LOGiC: capecitabine/oxaliplatin + lapatinib or placebo (N = 545)³

- No difference in median OS (12.2 vs 10.5 mo; HR: 0.91; *P* = .3492)

Second-line Trials

TyTAN: paclitaxel ± lapatinib (N = 261)⁴

GATSBY: taxane[†] vs T-DM1 (N = 412)⁵

T-ACT: paclitaxel ± trastuzumab beyond PD (N = 91)⁶

*Capecitabine/cisplatin or 5-FU. [†]Docetaxel or paclitaxel.

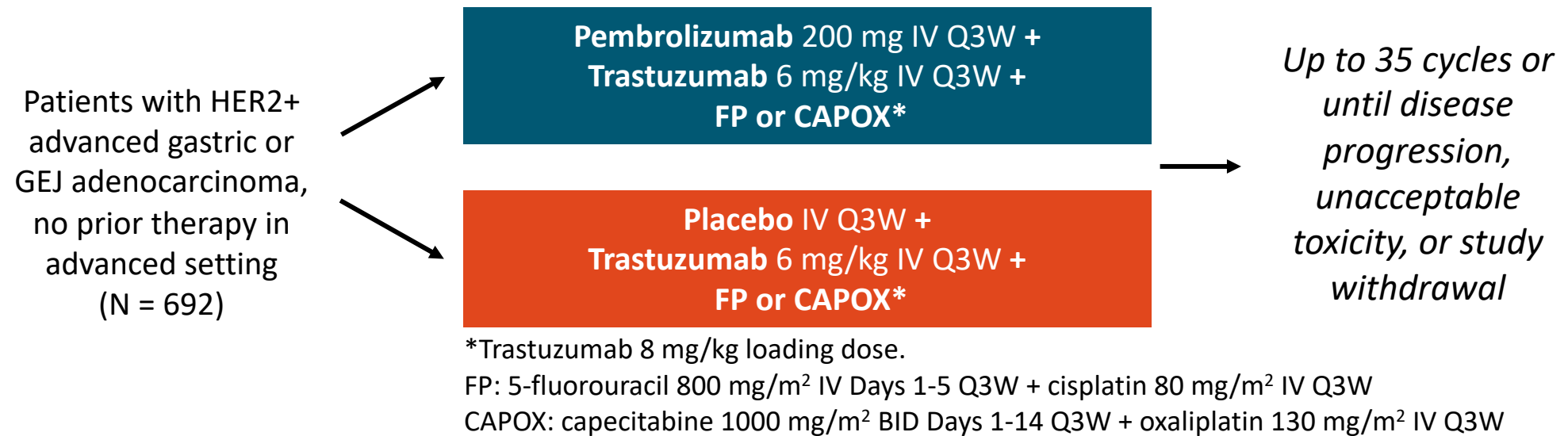
No improvement in outcome in any of these trials

1. Taberero. Lancet Oncol. 2018;19:1372. 2. Shah. JCO. 2017;35:2558. 3. Hecht. JCO. 2016;34:443.

4. Satoh. JCO. 2014;32:2039. 5. Thuss-Patience. Lancet Oncol. 2017;18:640. 6. Makiyama. JCO. 2020;38:1919.

KEYNOTE-811: 1L Pembrolizumab + Trastuzumab + Chemotherapy in HER2+ Metastatic Gastric/GEJ Cancer

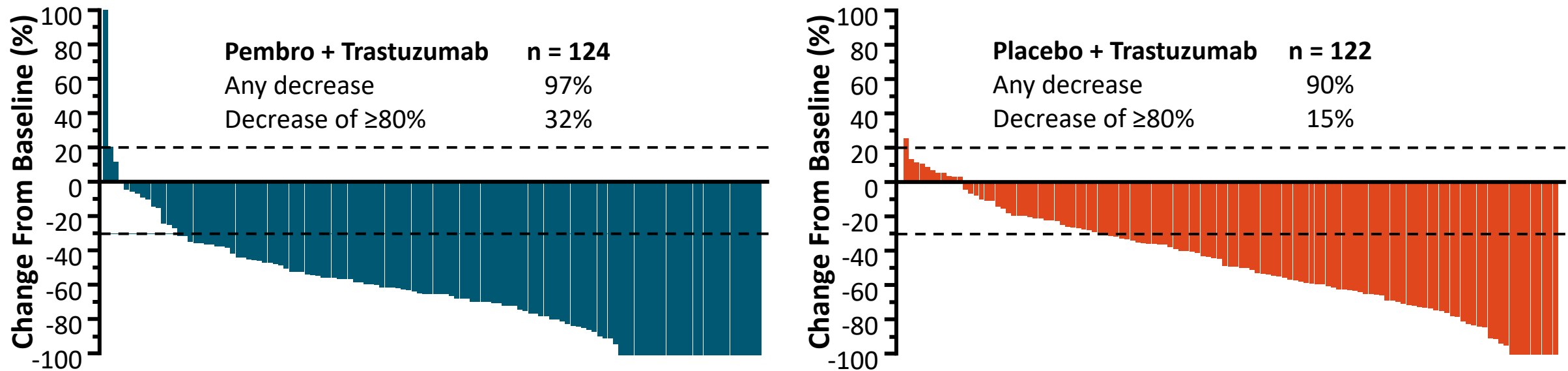
- Randomized, double-blind, placebo-controlled phase III study



- Efficacy analysis: first 264 patients enrolled; safety analysis: 433 patients who received ≥ 1 dose of study medication
- Primary endpoints: OS, PFS per RECIST v1.1 by BICR; secondary endpoints: ORR and DoR per RECIST v1.1 by BICR, safety

KEYNOTE-811: 1L Pembrolizumab + Trastuzumab + Chemotherapy in HER2+ Metastatic Gastric/GEJ Cancer

- Randomized phase III study of trastuzumab + FP or CAPOX ± pembrolizumab for patients with HER2+ advanced gastric or GEJ adenocarcinoma, no prior therapy in advanced setting



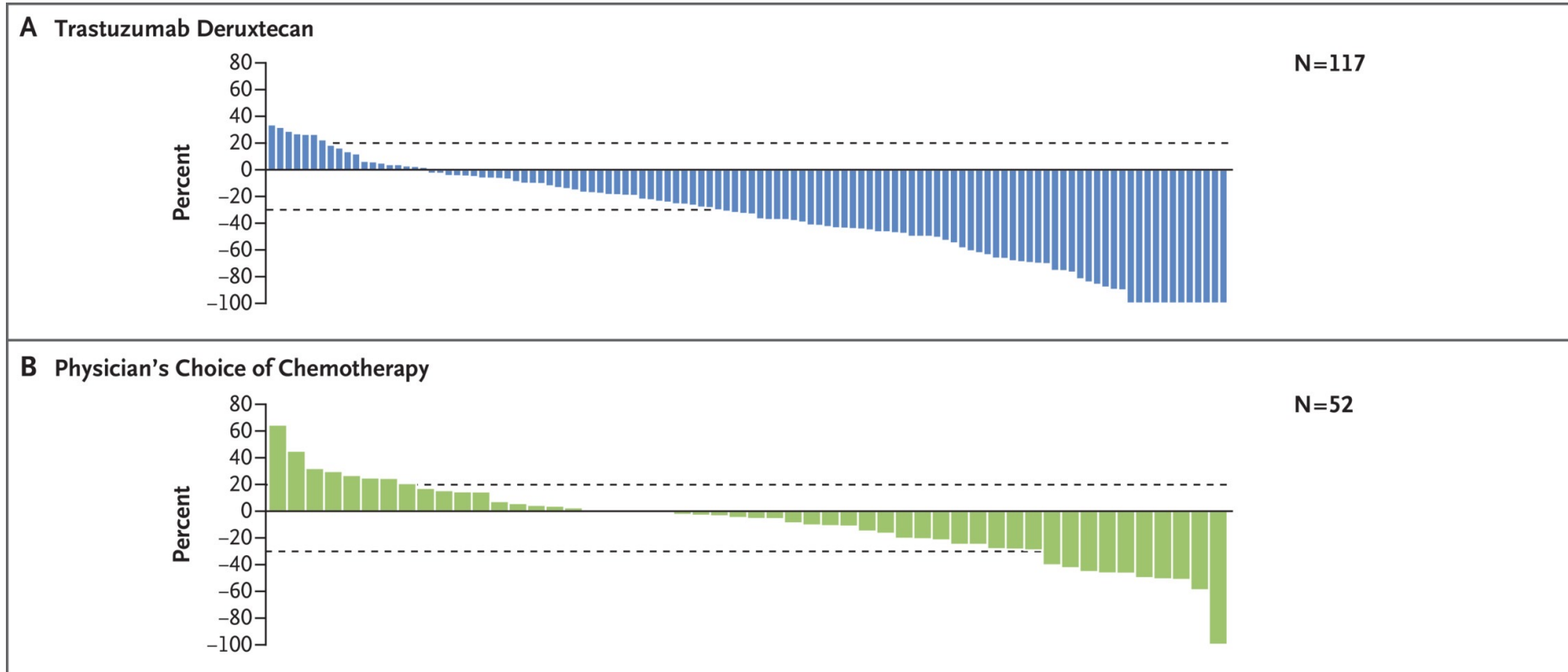
Outcome	Pembrolizumab (n = 133)	Placebo (n = 131)
ORR, % (95% CI)	74.4 (66.2-81.6)	51.9 (43.0-60.7)
ORR difference*	22.7 (11.2-33.7; P = .00006)	

KEYNOTE-811 Interim Analysis: Efficacy

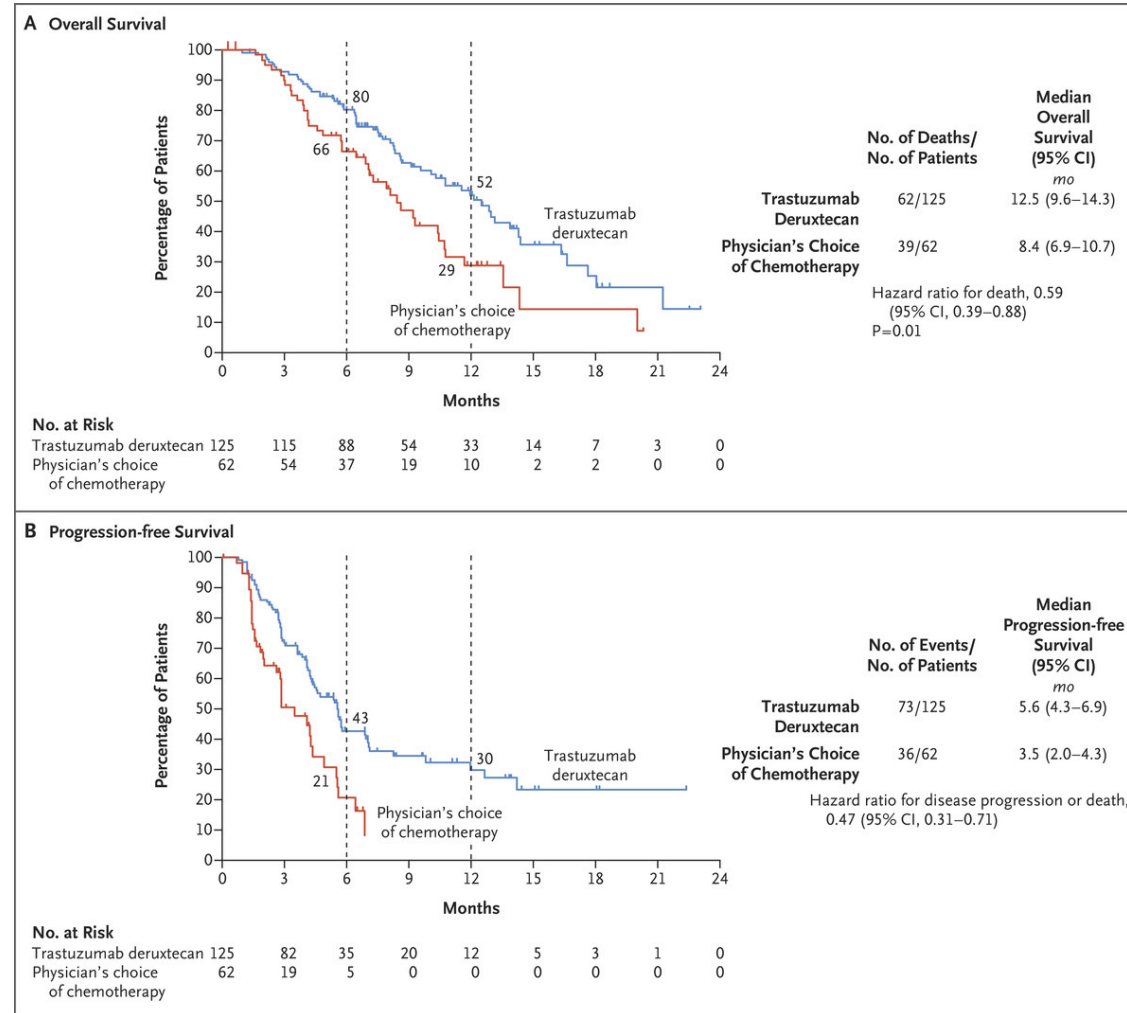
Outcome	Pembrolizumab (n = 133)	Placebo (n = 131)
ORR, % (95% CI)	74.4 (66.2-81.6)	51.9 (43.0-60.7)
ORR difference*	22.7 (11.2-33.7); P = .00006	
DCR, % (95% CI)	96.2 (91.4-98.8)	89.3 (82.7-94.0)
Best response, n (%)		
▪ CR	15 (11)	4 (3)
▪ PR	84 (63)	64 (49)
▪ SD	29 (22)	49 (37)
▪ PD	5 (4)	7 (5)
▪ Not evaluable	0	2 (2)
▪ Not assessed	0	5 (4)
Duration of response [†]	(n = 99)	(n = 68)
▪ Median, mo (range)	10.6 (1.1+ to 16.5+)	9.5 (1.4+ to 15.4+)
▪ ≥6 mo duration, %	70.3	61.4
▪ ≥9 mo duration, %	58.4	51.1
Size reduction from baseline, n (%)	(n = 124)	(n = 122)
▪ Any decrease	97	90
▪ ≥80% decrease	32	15

Original Article

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer



Overall Survival and Progression-free Survival.



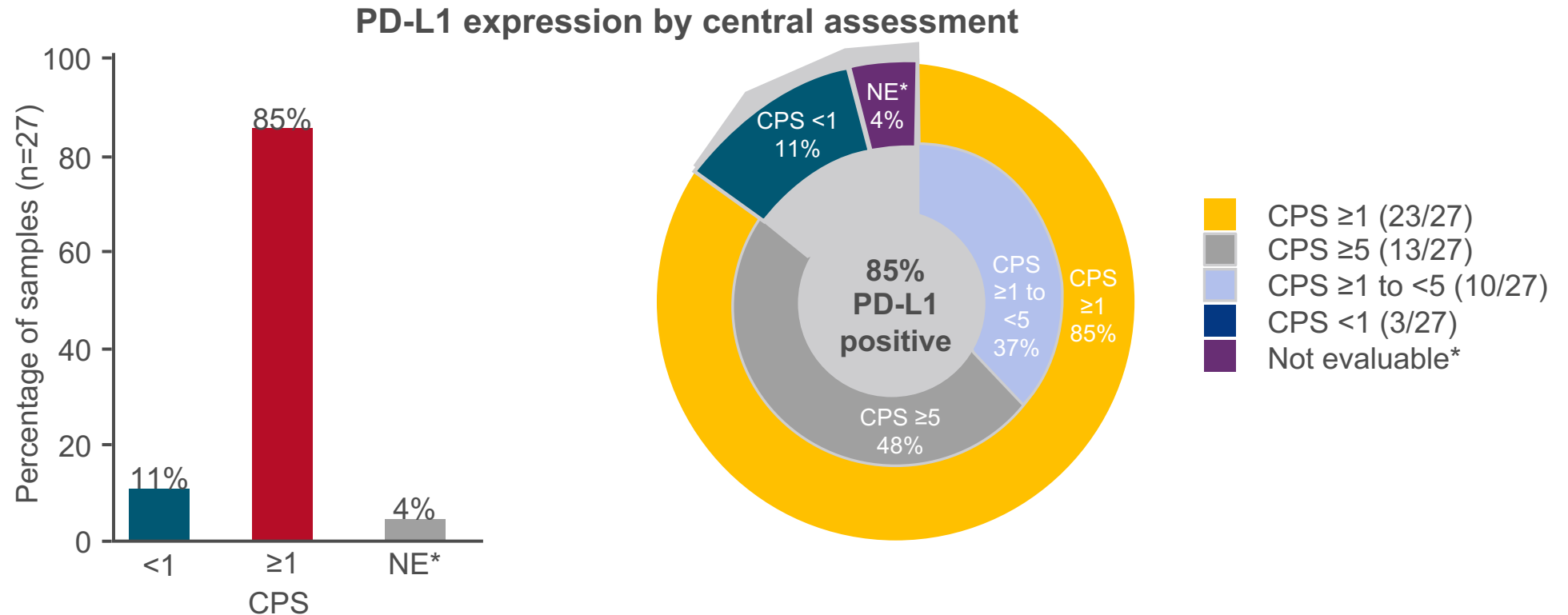
Selected Trials of Combination Therapy for Advanced HER2+ Gastric Cancer

Trial	Regimen	Phase
DESTINY-Gastric04 (NCT04704934)	Trastuzumab deruxtecan vs ramucirumab + paclitaxel	III
MOUNTAINEER-02 (NCT04499924)	Tucatinib + trastuzumab + ramucirumab + paclitaxel vs tucatinib + ramucirumab + paclitaxel vs ramucirumab + paclitaxel	II/III
MAHOGANY (NCT04082364)	Margetuximab ± PD-1 inhibitor ± chemotherapy ± dual checkpoint inhibitor	II/III
INTEGA (NCT03409848)	Ipilimumab or FOLFOX + nivolumab + trastuzumab	II
DESTINY-Gastric03 (NCT04379596)	Trastuzumab deruxtecan ± chemotherapy ± durvalumab	Ib/II
NCT04276493	Zanidatamab + chemotherapy ± tislelizumab	I/II

SO-7: Co-occurring HER2 and PD-L1 expression in patients with HER2-positive trastuzumab-refractory gastric cancer (GC)/gastroesophageal junction adenocarcinoma (GEJA): biomarker analysis from the trastuzumab deruxtecan (T-DXd) DESTINY-Gastric03 trial – Janjigian Y, et al

Key results

- There was 80% concordance between local and central testing for HER2 status



Conclusions

- In patients with HER2+ trastuzumab-refractory gastric or GEJ adenocarcinoma, there was a substantial overlap between HER2 and PD-L1 positivity, which supports the use of dual therapy with an anti-HER2 and anti-PD-L1 agents**

*Not evaluable, there was insufficient number of viable tumour cells (<100) present for PD-L1 testing

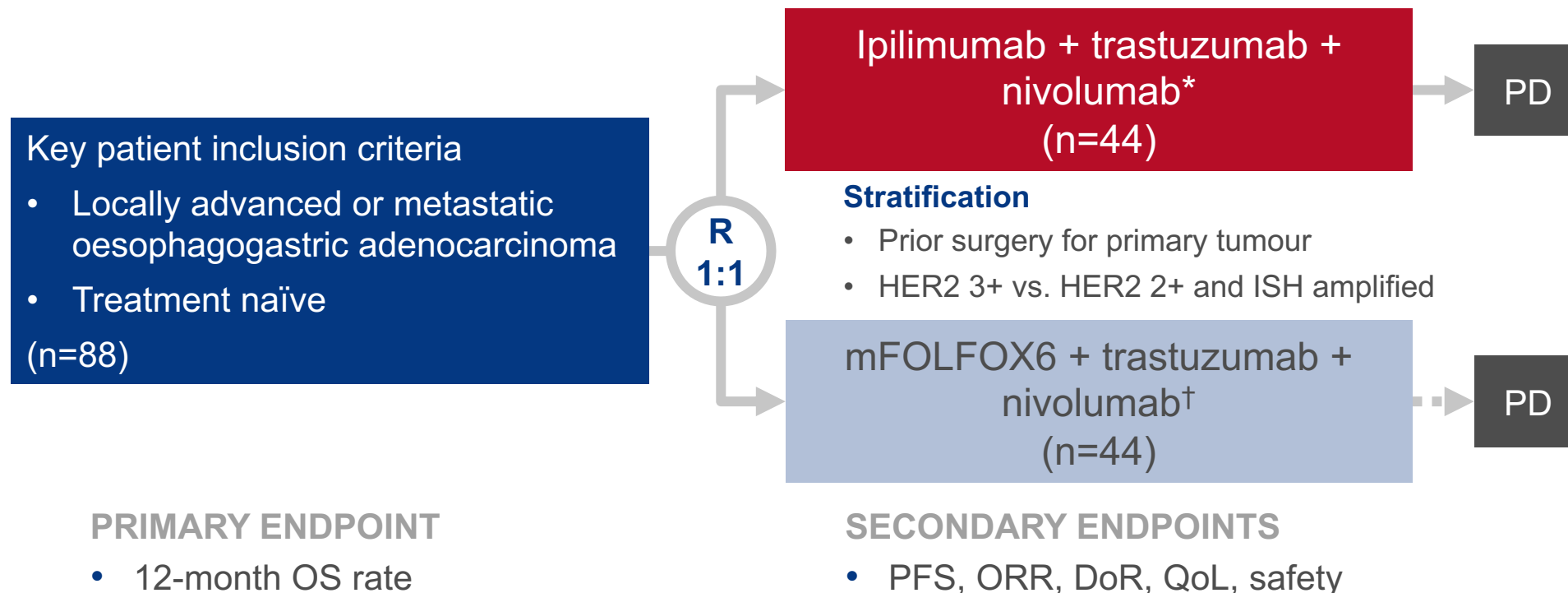
Selected Trials of Combination Therapy for Advanced HER2+ Gastric Cancer

Trial	Regimen	Phase
DESTINY-Gastric04 (NCT04704934)	Trastuzumab deruxtecan vs ramucirumab + paclitaxel	III
MOUNTAINEER-02 (NCT04499924)	Tucatinib + trastuzumab or placebo + ramucirumab + paclitaxel	II/III
MAHOGANY (NCT04082364)	Margetuximab ± PD-1 inhibitor ± chemotherapy ± dual checkpoint inhibitor	II/III
INTEGA (NCT03409848)	Ipilimumab or FOLFOX + nivolumab + trastuzumab	II
DESTINY-Gastric03 (NCT04379596)	Trastuzumab deruxtecan ± chemotherapy ± durvalumab	Ib/II
NCT04276493	Zanidatamab + chemotherapy ± tislelizumab	I/II

LBA54: Ipilimumab or FOLFOX in combination with nivolumab and trastuzumab in previously untreated HER2 positive locally advanced or metastatic esophagogastric adenocarcinoma (EGA) – results of the randomized phase 2 INTEGA trial (AIO STO 0217) – Stein A, et al

Study objective

- To evaluate the efficacy and safety of 1L ipilimumab or mFOLFOX6 combined with trastuzumab + nivolumab in patients with HER2+ locally advanced or metastatic oesophagogastric adenocarcinoma in the INTEGA study



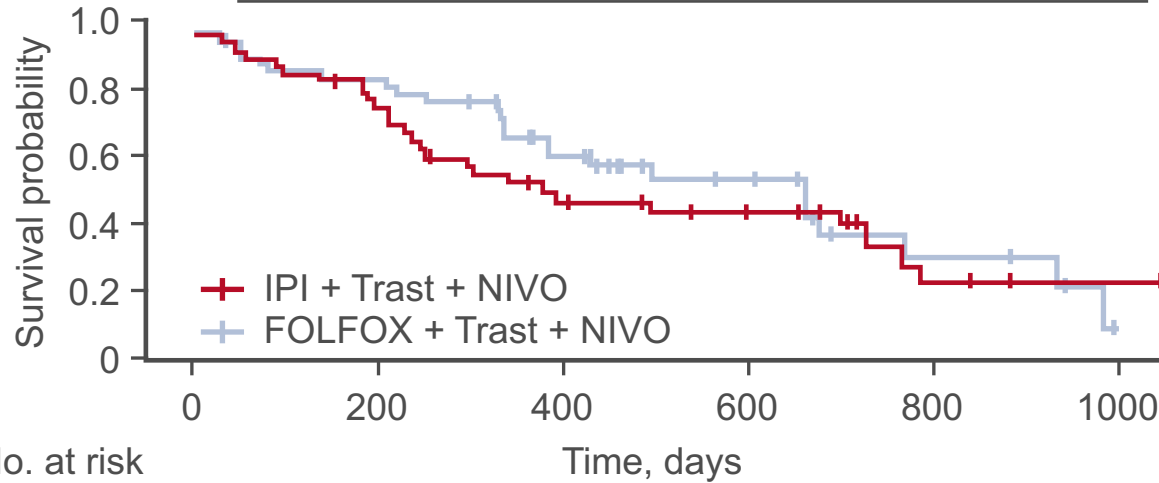
*Ipilimumab 3 mg/kg + trastuzumab 6 mg/kg (loading dose 8 mg/kg) + nivolumab 1 mg/kg q3w (weeks 1–12) then trastuzumab 4 mg/kg + nivolumab 240 mg q2w; †oxaliplatin 85 mg/m² + 5FU 400 mg/m² iv bolus + folinic acid 400 mg/m² + 5FU 2400 mg/m² 46 h iv + trastuzumab 4 mg/kg (loading dose 6 mg/kg) + nivolumab 240 mg q2w

LBA54: Ipilimumab or FOLFOX in combination with nivolumab and trastuzumab in previously untreated HER2 positive locally advanced or metastatic esophagogastric adenocarcinoma (EGA) – results of the randomized phase 2 INTEGA trial (AIO STO 0217) – Stein A, et al

Key results

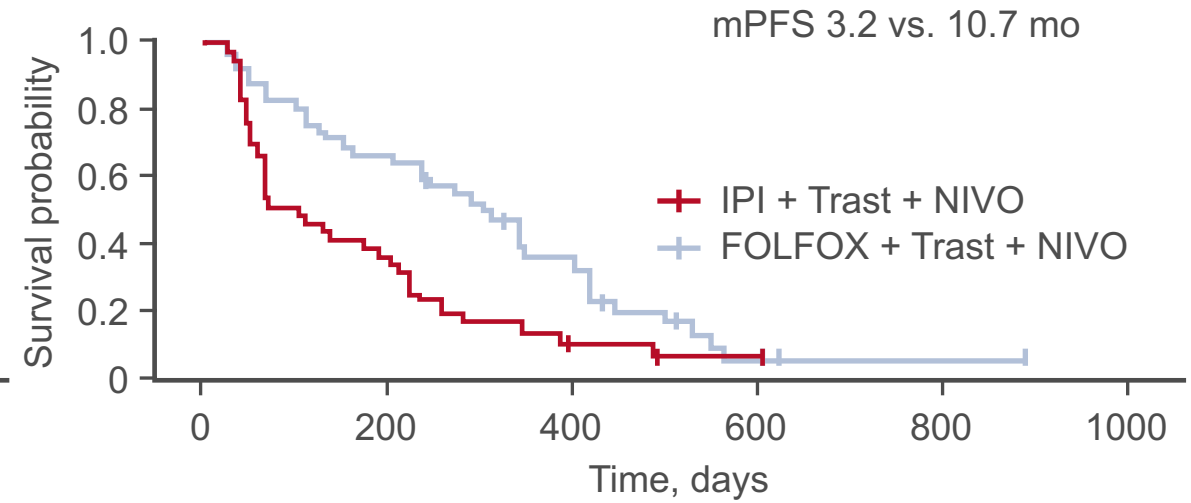
Overall survival

	12-mo OS rate, %	mO, mo
IPI + Trast + NIVO	57%	16.4
FOLFOX + Trast + NIVO	70%	21.8



No. at risk	0	200	400	600	800	1000
IPI + Trast + NIVO	44	33	19	14	5	1
FOLFOX + Trast + NIVO	44	38	24	13	6	1

Progression free survival



No. at risk	0	200	400	600	800	1000
IPI + Trast + NIVO	42	13	3	1	0	
FOLFOX + Trast + NIVO	43	29	12	2	1	0

LBA54: Ipilimumab or FOLFOX in combination with nivolumab and trastuzumab in previously untreated HER2 positive locally advanced or metastatic esophagogastric adenocarcinoma (EGA) – results of the randomized phase 2 INTEGA trial (AIO STO 0217) – Stein A, et al

Key results (cont.)

	ITT		CPS ≥1		CPS ≥5		HER2+ central	
	IPI (n=44)	FOLFOX (n=44)	IPI (n=31)	FOLFOX (n=28)	IPI (n=24)	FOLFOX (n=22)	IPI (n=40)	FOLFOX (n=36)
ORR, %	32	56	36	63	33	67	35	63
mPFS, mo	3.2	10.7	2.2	10.7	2.2	11.0	3.4	10.7
12-mo PFS rate, %	15	37	14	33	7	38	17	36
mDoR, mo	5.8	9.2	-	-	-	-	-	-
mOS, mo	16.4	21.8	16.4	21.6	12.5	21.6	16.4	22.4
12-mo OS rate, %	57	70	54	71	53	72	58	74

Grade ≥3 TRAEs occurring in ≥10%, n (%)	Ipilimumab + Trast + NIVO (n=44)	FOLFOX + Trast + NIVO (n=43)
Any	20 (46)	29 (67)
Diarrhoea	6 (14)	2 (5)
Anaemia	5 (11)	3 (7)
Infection	5 (11)	7 (16)
Fatigue	3 (7)	6 (14)
Leukopenia	2 (5)	10 (23)
Neuropathy	0	5 (11)

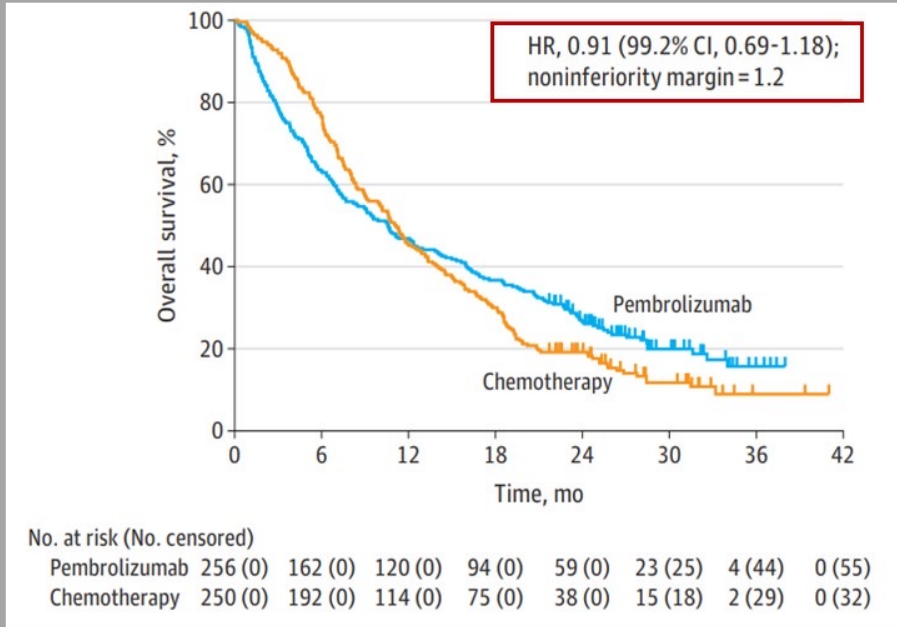
Conclusions

- In patients with HER2+ locally advanced or metastatic oesophagogastric adenocarcinoma, both 1L ipilimumab or FOLFOX combined with trastuzumab + nivolumab were feasible, although the FOLFOX arm demonstrated a higher 12-month OS rate than the ipilimumab arm

PD-L1 Expression – 1st Line Upper GI

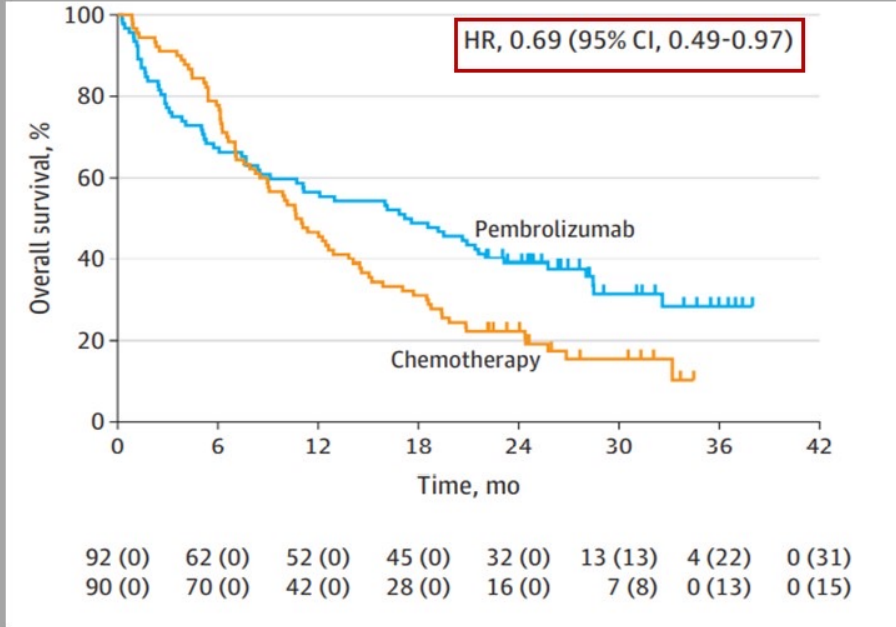
KEYNOTE 062 (G/GEJ Adenocarcinoma)

CPS ≥ 1



PFS (CPS ≥ 1)	HR: 1.66 (1.37-2.01)
ORR (CPS ≥ 1)	Pembro: 15% CT: 37%

CPS ≥ 10

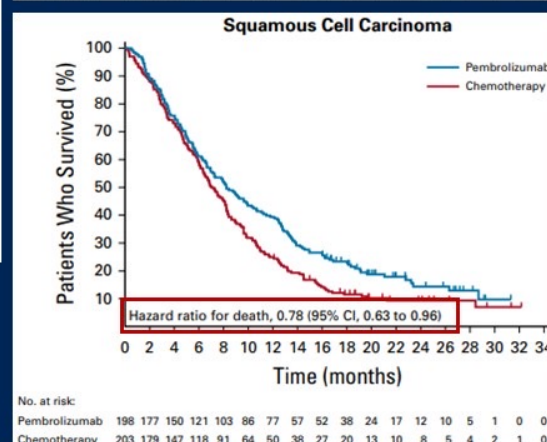
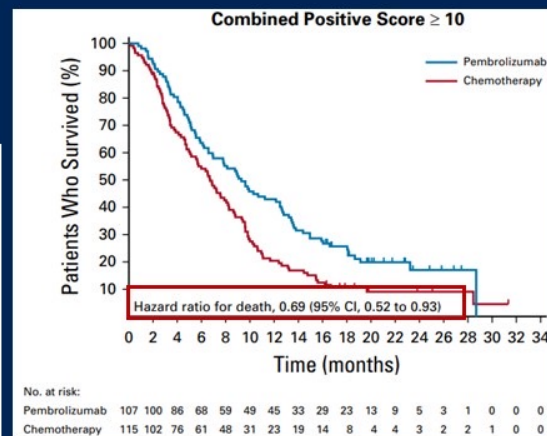
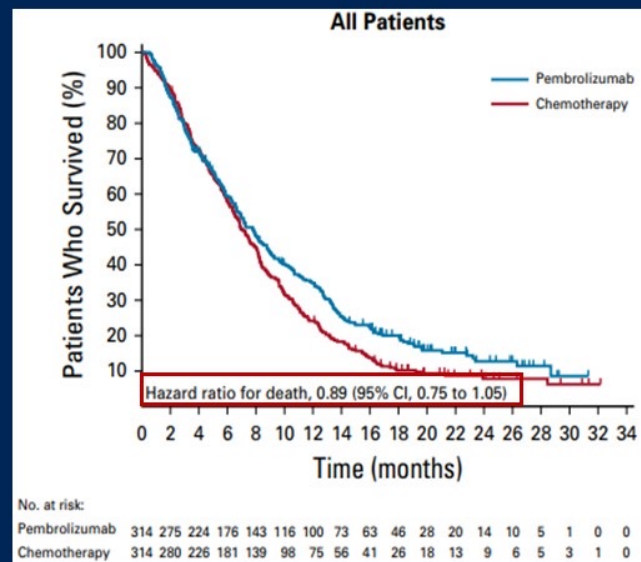


PFS (CPS ≥ 10)	HR: 1.10 (0.79-1.51)
ORR (CPS ≥ 10)	Pembro: 25% CT: 38%

Shitara K, et al. JAMA Oncol. 2020

PD-L1 Expression – 2nd Line Upper GI

KEYNOTE-181 (E/GEJ Adenocarcinoma ~ 36% + Squamous Cell Carcinoma ~ 64%)



OS All Patients

Subgroup	No. of deaths out of No. of patients	Hazard ratio (95% CI)
PD-L1 CPS ≥ 10	191 of 222	0.70 (0.52 to 0.94)
PD-L1 CPS < 10	355 of 397	1.00 (0.81 to 1.24)

Squamous Cell Carcinoma

Subgroup	No. of deaths out of No. of patients	Hazard ratio (95% CI)
PD-L1 CPS ≥ 10	140 of 167	0.64 (0.46 to 0.90)
PD-L1 CPS < 10	202 of 228	0.88 (0.66 to 1.16)

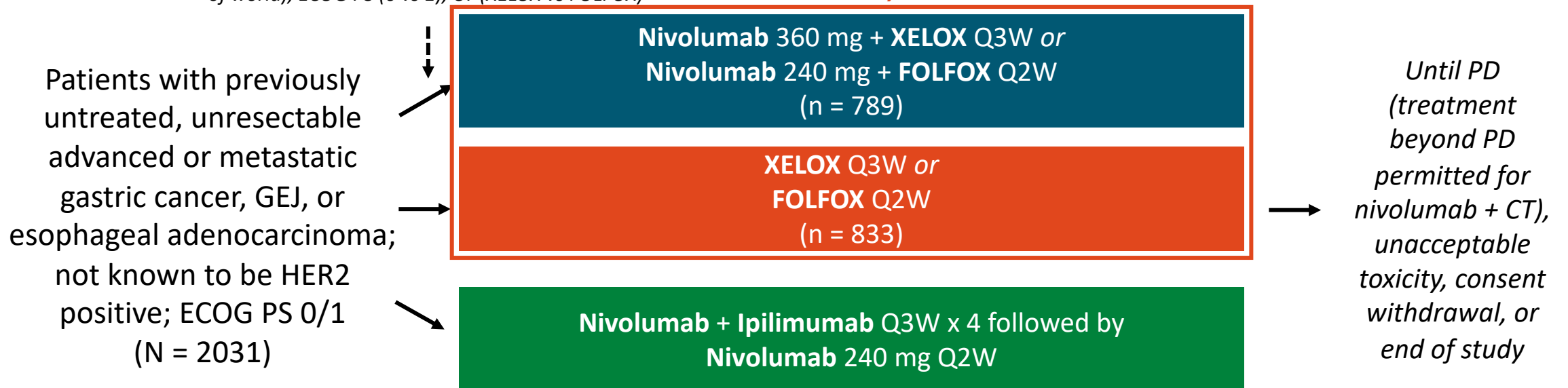
Kojima T, et al. J Clin Oncol. 2020

Updated Results From 1L Nivolumab + CT vs CT for Advanced GEJ Cancers (CheckMate 649): Study Design

- International, randomized, open-label phase III trial

Stratified by PD-L1 ($\geq 1\%$ vs $< 1\%$), region (Asia vs US/Canada vs rest of world), ECOG PS (0 vs 1), CT (XELOX vs FOLFOX)

This Analysis



- Coprimary endpoints:** OS and PFS in patients with PD-L1 CPS ≥ 5

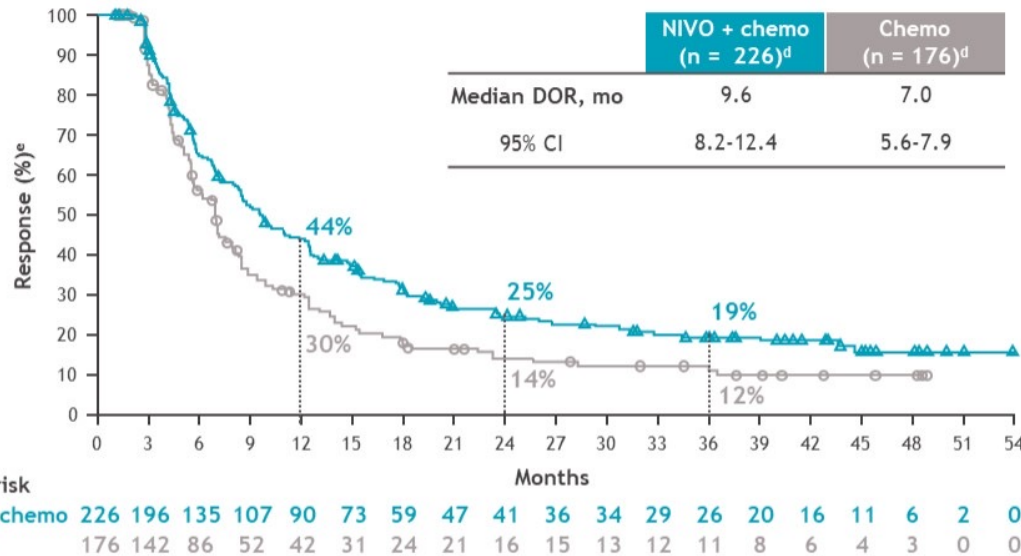
Median follow-up: 24.0 mo in nivolumab + CT arm

- Secondary endpoints:** OS and PFS in all randomized patients and patients with PD-L1 CPS ≥ 10 and ≥ 1 , BICR-assessed ORR

Response and duration of response: 36-month follow-up

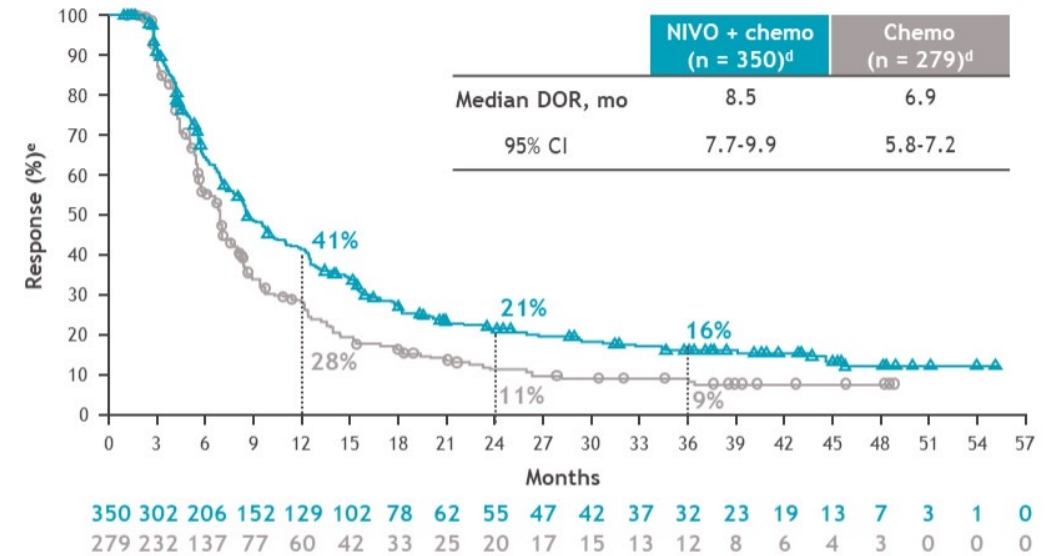
PD-L1 CPS ≥ 5

Response per BICR	NIVO + chemo (n = 378) ^a	Chemo (n = 390) ^a
ORR, ^b % (95% CI)	60 (55-65)	45 (40-50)
CR	13	7
PR	47	38
SD	28	34
PD	7	11



All randomized

Response per BICR	NIVO + chemo (n = 602) ^a	Chemo (n = 607) ^a
ORR, ^c % (95% CI)	58 (54-62)	46 (42-50)
CR	11	7
PR	47	39
SD	28	33
PD	7	10

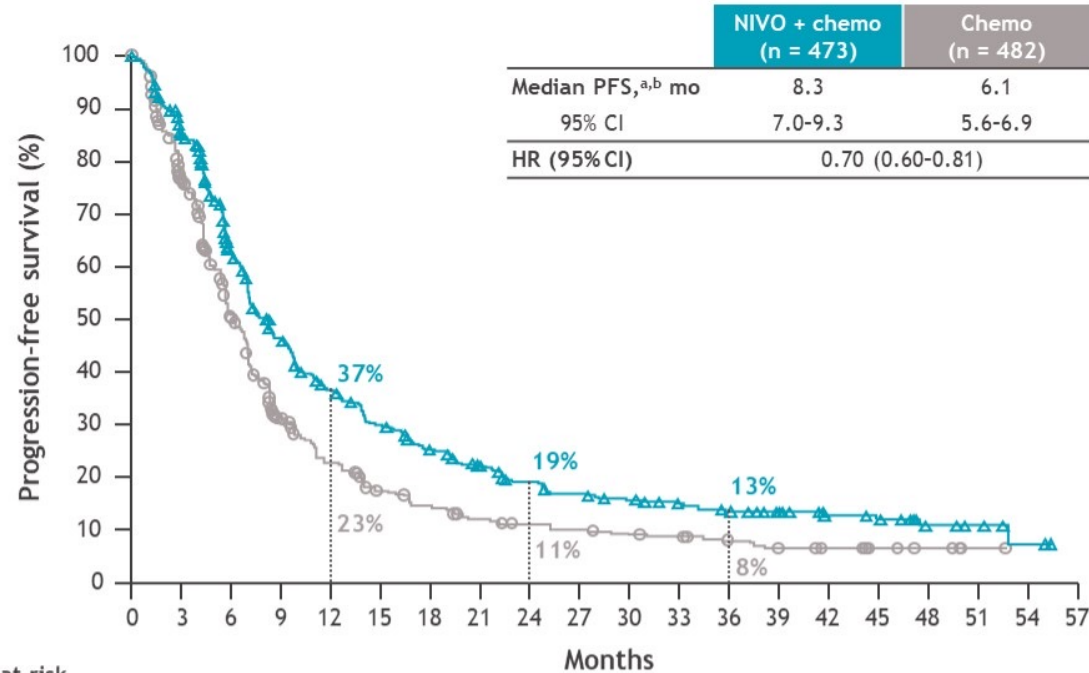


- Higher ORR was maintained, and responses remained more durable with NIVO + chemo vs chemo with longer follow-up

^aRandomized patients who had target lesion measurements at baseline per BICR assessment; ^bUnable to determine: NIVO + chemo, n = 21; chemo, n = 40; ^cUnable to determine: NIVO + chemo, n = 40; chemo, n = 66; ^dNumber of responders; ^ePer BICR assessment.

Progression-free survival: 36-month follow-up

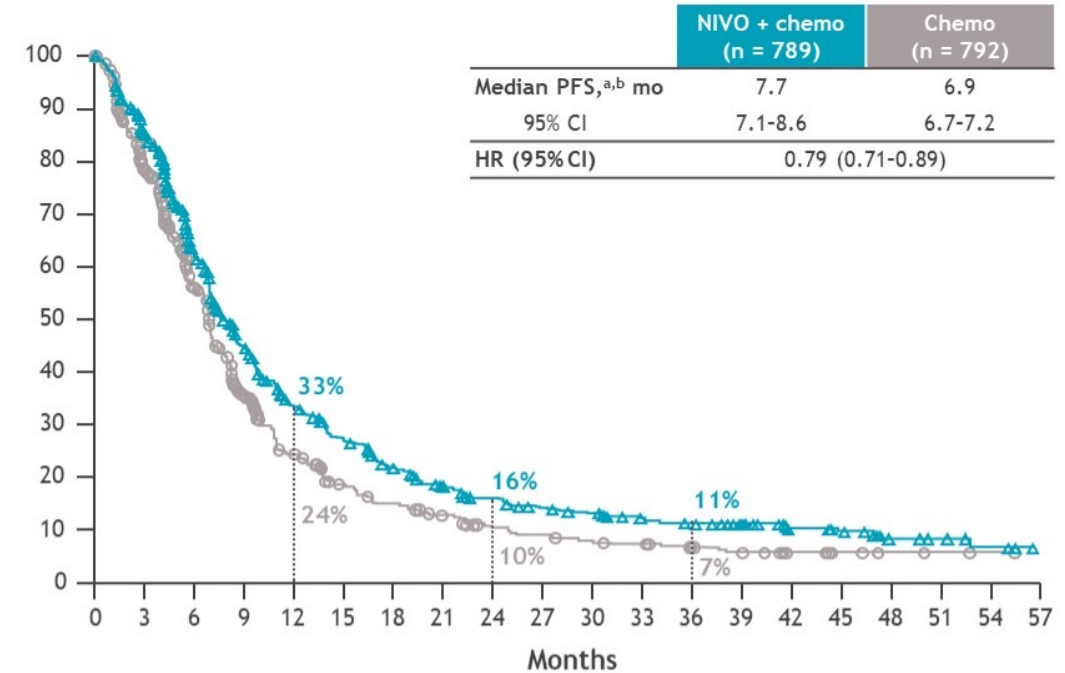
PD-L1 CPS ≥ 5



No. at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
NIVO + chemo	473	386	261	188	143	115	93	75	62	53	47	40	35	26	19	15	8	5	2	0
Chemo	482	331	204	115	81	58	48	37	32	29	25	23	17	13	11	7	5	1	0	0

All randomized



	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
NIVO + chemo	789	641	432	297	210	167	127	98	82	68	61	50	44	34	23	18	10	7	4	0
Chemo	792	552	359	212	134	95	74	59	44	38	31	29	22	16	12	8	6	2	1	0

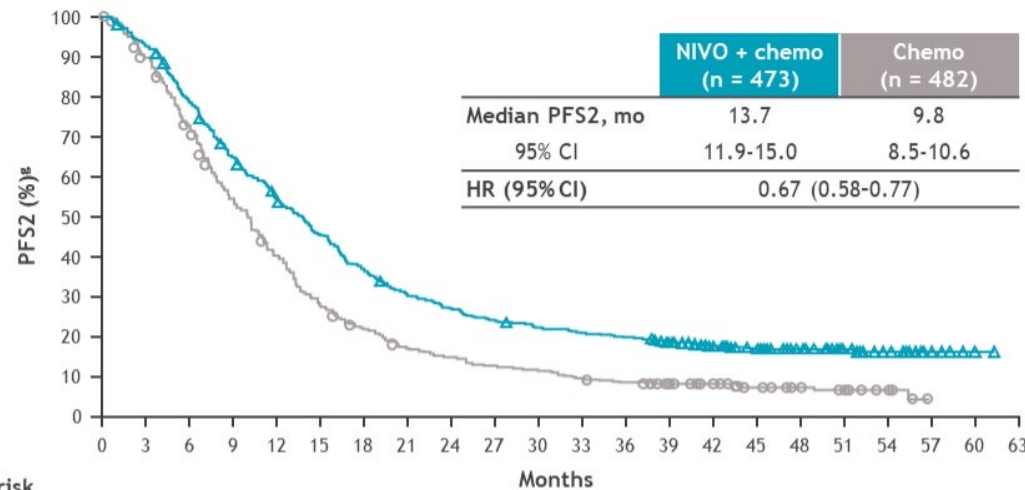
- PFS benefit with NIVO + chemo vs chemo was maintained with longer follow-up in PD-L1 CPS ≥ 5 and all randomized populations

^aPer BICR assessment; ^bMinimum follow-up, 36.2 months.

Progression-free survival 2 (PFS2): 36-month follow-up

PD-L1 CPS ≥ 5

First subsequent therapy, ^{a,b} n (%)	NIVO + chemo (n = 473)	Chemo (n = 482)
Any subsequent therapy	203 (43)	210 (44)
Systemic anticancer therapy ^c	182 (38)	199 (41)
Chemotherapy	177 (37)	190 (39)
Targeted therapy	71 (15)	75 (16)
Immunotherapy ^d	13 (3)	47 (10)

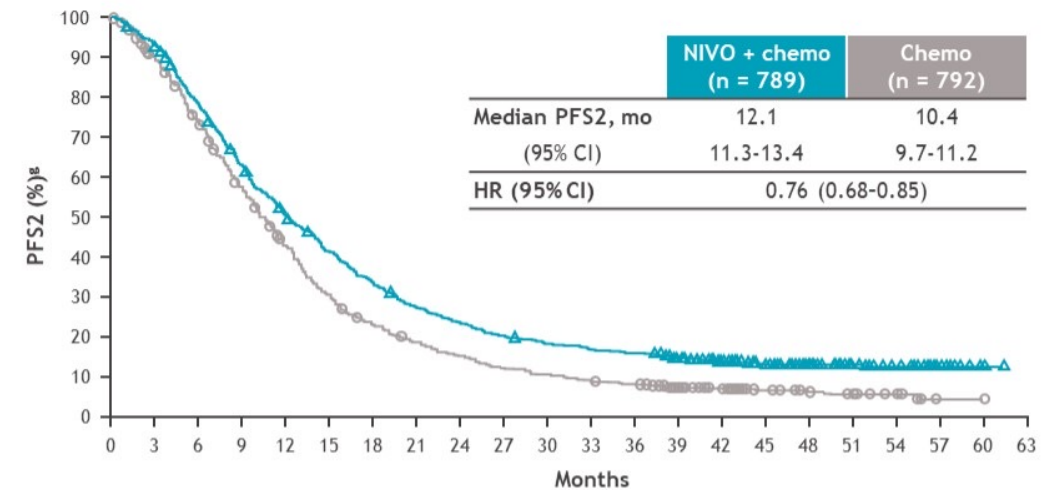


No. at risk

NIVO + chemo	473	438	369	302	251	209	170	139	123	110	99	93	88	78	66	53	37	24	16	6	2	0
Chemo	482	423	336	246	182	127	99	75	66	56	51	42	37	30	25	16	12	9	5	0	0	0

All randomized

First subsequent therapy, ^{a,e} n (%)	NIVO + chemo (n = 789)	Chemo (n = 792)
Any subsequent therapy	337 (43)	351 (44)
Systemic anticancer therapy ^c	303 (38)	332 (42)
Chemotherapy	294 (37)	310 (39)
Targeted therapy	127 (16)	129 (16)
Immunotherapy ^f	20 (3)	78 (10)



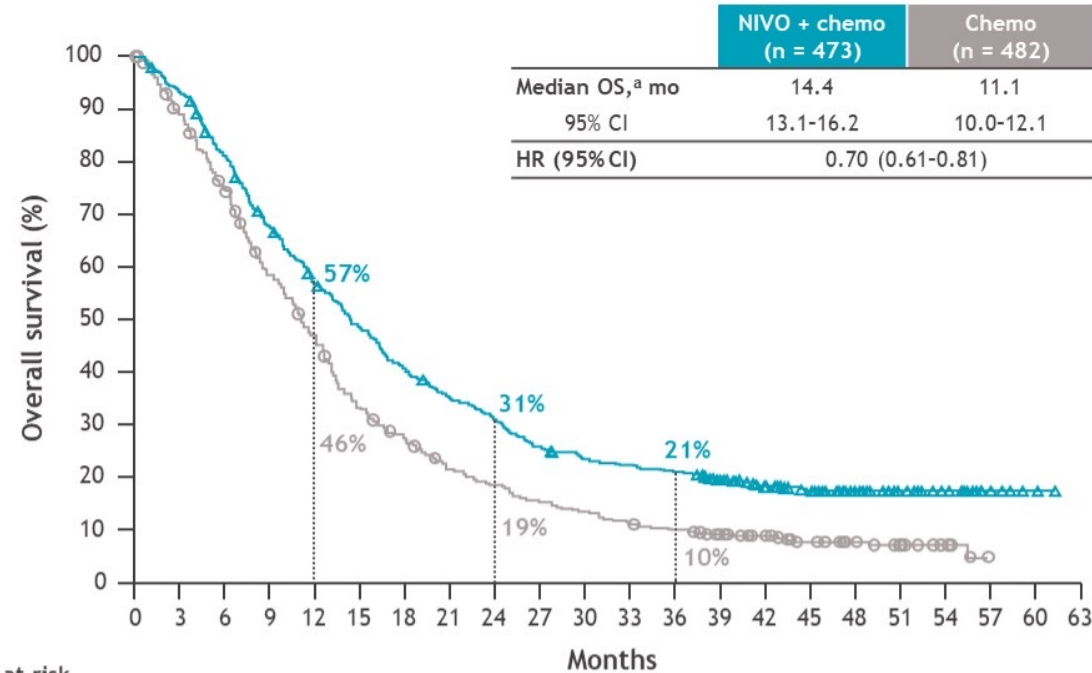
NIVO + chemo	789	731	610	489	389	316	256	209	180	155	138	127	120	100	85	66	47	30	22	9	2	0
Chemo	792	699	570	435	323	230	172	137	113	91	77	66	59	44	35	19	14	11	7	1	1	0

- PFS2 continued to favor NIVO + chemo vs chemo in patients with PD-L1 CPS ≥ 5 and all randomized patients with longer follow-up

^aPatients may have received more than 1 type of subsequent therapy; ^bSubsequent radiotherapy: NIVO + chemo, n = 27; chemo, n = 32. Subsequent surgery: NIVO + chemo, n = 13; chemo, n = 10; ^cPatients may receive multiple subsequent systemic therapies, out of which the first subsequent systemic therapies patients received are summarized in this table regardless of their timing relative to the subsequent radiotherapy and surgery; ^dImmunotherapy includes: atezolizumab, nivolumab, pembrolizumab, toripalimab, and other immunotherapy; ^eSubsequent radiotherapy: NIVO + chemo, n = 46; chemo, n = 52. Subsequent surgery: NIVO + chemo, n = 21; chemo, n = 29; ^fImmunotherapy includes: ipilimumab, nivolumab, pembrolizumab, toripalimab, and other immunotherapy; ^gPFS2, progression-free survival on subsequent therapy (time from randomization to progression after subsequent systemic therapy, initiation of second subsequent systemic therapy, or death, whichever was earlier).

Overall survival: 36-month follow-up

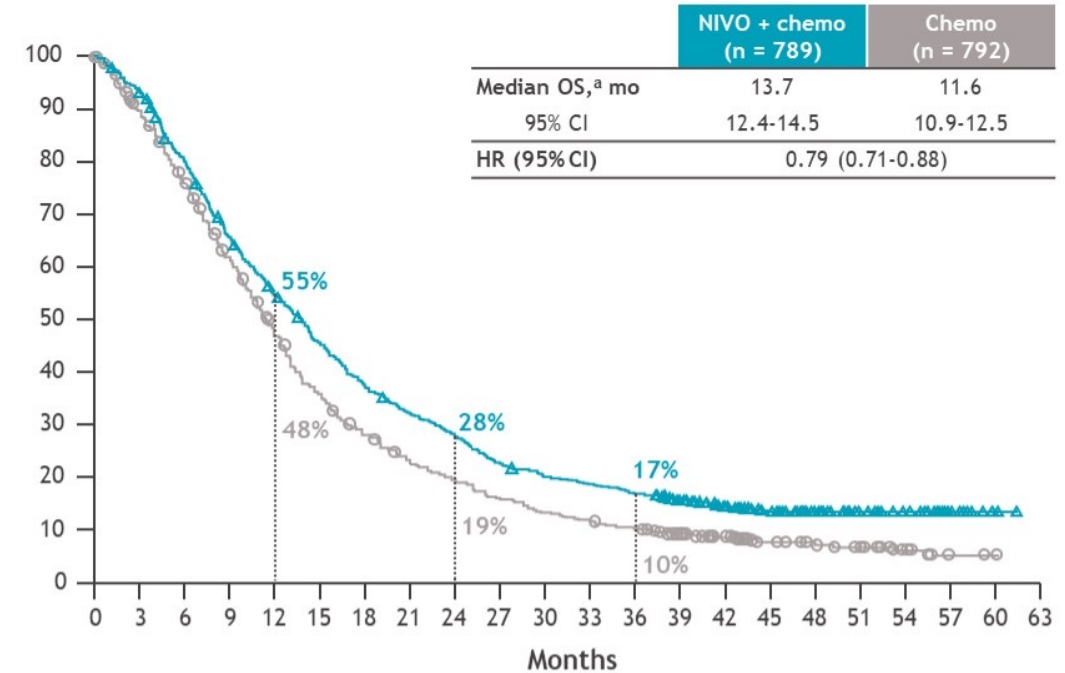
PD-L1 CPS ≥ 5



No. at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63
NIVO + chemo	473	440	380	315	263	223	187	161	141	118	105	100	94	81	66	53	37	24	17	6	2	0
Chemo	482	424	353	275	215	154	125	97	83	69	60	51	44	35	28	18	14	10	5	0	0	0

All randomized



	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63
NIVO + chemo	789	733	625	509	422	349	287	246	212	175	154	143	129	106	87	67	48	30	23	9	2	0
Chemo	792	701	591	475	364	273	215	170	144	118	98	87	75	57	45	27	21	17	9	3	1	0

- 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

^aMinimum follow-up, 36.2 months.

CheckMate 649 Update: Efficacy by PD-L1 CPS Level

Overall Survival

PD-L1 CPS*	n	Median OS, Mo		Unstratified HR [†]
		Nivo + CT	CT	
All Patients	1581	13.8	11.6	0.78
<1	265	13.1	12.5	0.95
≥1	1297	13.8	11.3	0.74
<5	607	12.4	12.3	0.94
≥5	955	14.4	11.1	0.69
<10	795	12.4	12.5	0.91
≥10	767	15.0	10.9	0.66

- OS improved with Nivo + CT at higher PD-L1 CPS cutoffs

Objective Response Rate

PD-L1 CPS [‡]	n	ORR, %		Unweighted ORR Difference, [§] %
		Nivo + CT	CT	
All Patients	1210	58	46	12
<1	179	51	41	10
≥1	1017	59	46	13
<5	428	55	46	9
≥5	768	60	45	15
<10	579	58	47	10
≥10	617	59	44	15

- ORR improved with Nivo + CT across all PD-L1 CPS subgroups

*PD-L1 CPS expression unavailable, n = 19. [†]Unstratified OS HR for death. [‡]Randomized patients with target lesion measurements at baseline per BICR, PD-L1 CPS unavailable, n = 14. [§]Differences may not be exact due to rounding.

Overall survival subgroup analysis: all randomized

Category	Subgroup	Median OS, months ^a		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 1581)		13.7	11.6	0.78	
Age, years	< 65 (n = 961)	12.9	11.8	0.81	
	≥ 65 (n = 620)	14.4	11.3	0.75	
Sex	Male (n = 1100)	14.0	11.3	0.76	
	Female (n = 481)	12.6	12.1	0.83	
Region	Asia (n = 356)	16.3	12.8	0.76	
	US/Canada (n = 263)	15.3	12.1	0.65	
	ROW (n = 962)	12.1	10.9	0.83	
ECOG PS ^b	0 (n = 664)	16.8	14.2	0.83	
	1 (n = 913)	11.5	9.8	0.74	
Primary tumor location	GC (n = 1110)	14.2	11.3	0.75	
	GEJC (n = 260)	12.6	12.8	0.89	
	EAC (n = 211)	12.3	11.6	0.84	
Signet ring cell carcinoma	Yes (n = 282)	11.1	11.2	0.90	
	No (n = 1299)	14.3	11.8	0.76	
Liver metastases ^c	Yes (n = 614)	12.5	10.6	0.72	
	No (n = 918)	14.2	12.3	0.84	
Tumor cell PD-L1 expression ^d	< 1% (n = 1324)	13.1	12.0	0.84	
	≥ 1% (n = 253)	16.1	9.8	0.55	
MSI status ^e	MSS (n = 1378)	13.8	11.5	0.79	
	MSI-H (n = 44)	38.7	12.3	0.34	
Chemotherapy regimen	FOLFOX (n = 828)	13.7	11.8	0.77	
	XELOX (n = 721)	13.8	11.7	0.80	

- OS consistently favored NIVO + chemo vs chemo with longer follow-up across multiple prespecified subgroups in all randomized patients

^aMinimum follow-up, 36.2 months; ^bECOG PS 2, n = 4; ^cNot reported, n = 49; ^dIndeterminate, nonevaluable, or not reported, n = 4; ^eInvalid/not available, n = 159.

Overall survival subgroup analysis: PD-L1 CPS ≥ 5

Category	Subgroup	Median OS, months ^a		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 955)		14.4	11.1	0.69	
Age, years	< 65 (n = 552)	14.4	11.1	0.69	
	≥ 65 (n = 403)	14.3	11.2	0.69	
Sex	Male (n = 680)	14.4	10.8	0.66	
	Female (n = 275)	14.3	12.1	0.77	
Region	Asia (n = 228)	16.1	11.8	0.61	
	US/Canada (n = 137)	18.2	12.6	0.65	
	ROW (n = 590)	13.1	10.4	0.74	
ECOG PS	0 (n = 397)	17.8	13.8	0.74	
	1 (n = 558)	12.6	8.5	0.64	
Primary tumor location	GC (n = 667)	15.0	10.5	0.64	
	GEJC (n = 170)	13.4	13.1	0.81	
	EAC (n = 118)	11.2	11.3	0.80	
Signet ring cell carcinoma	Yes (n = 141)	12.1	10.1	0.67	
	No (n = 814)	15.0	11.3	0.69	
Liver metastases ^b	Yes (n = 407)	13.1	9.8	0.64	
	No (n = 519)	15.5	11.6	0.73	
Tumor cell PD-L1 expression ^c	< 1% (n = 724)	14.2	11.6	0.75	
	$\geq 1\%$ (n = 230)	16.2	8.8	0.54	
MSI status ^d	MSS (n = 847)	14.3	11.1	0.71	
	MSI-H (n = 34)	44.8	8.8	0.29	
Chemotherapy regimen	FOLFOX (n = 479)	14.3	11.3	0.68	
	XELOX (n = 454)	15.0	11.0	0.69	

- OS consistently favored NIVO + chemo vs chemo with longer follow-up across multiple prespecified subgroups in patients with PD-L1 CPS ≥ 5

^aMinimum follow-up, 36.2 months; ^bNot reported, n = 29; ^cIndeterminate, nonevaluable, or not reported, n = 1; ^dInvalid/not available, n = 74.

Efficacy subgroup analysis by PD-L1 CPS: 36-month follow-up

Overall survival

PD-L1 CPS ^a	Number of patients	Median OS, months		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 1581)		13.7	11.6	0.78	
< 1	265	13.1	12.5	0.95	
≥ 1	1297	13.8	11.3	0.75	
< 5	607	12.4	12.3	0.95	
≥ 5	955	14.4	11.1	0.69	
< 10	794	12.4	12.5	0.91	
≥ 10	768	15.0	10.9	0.66	

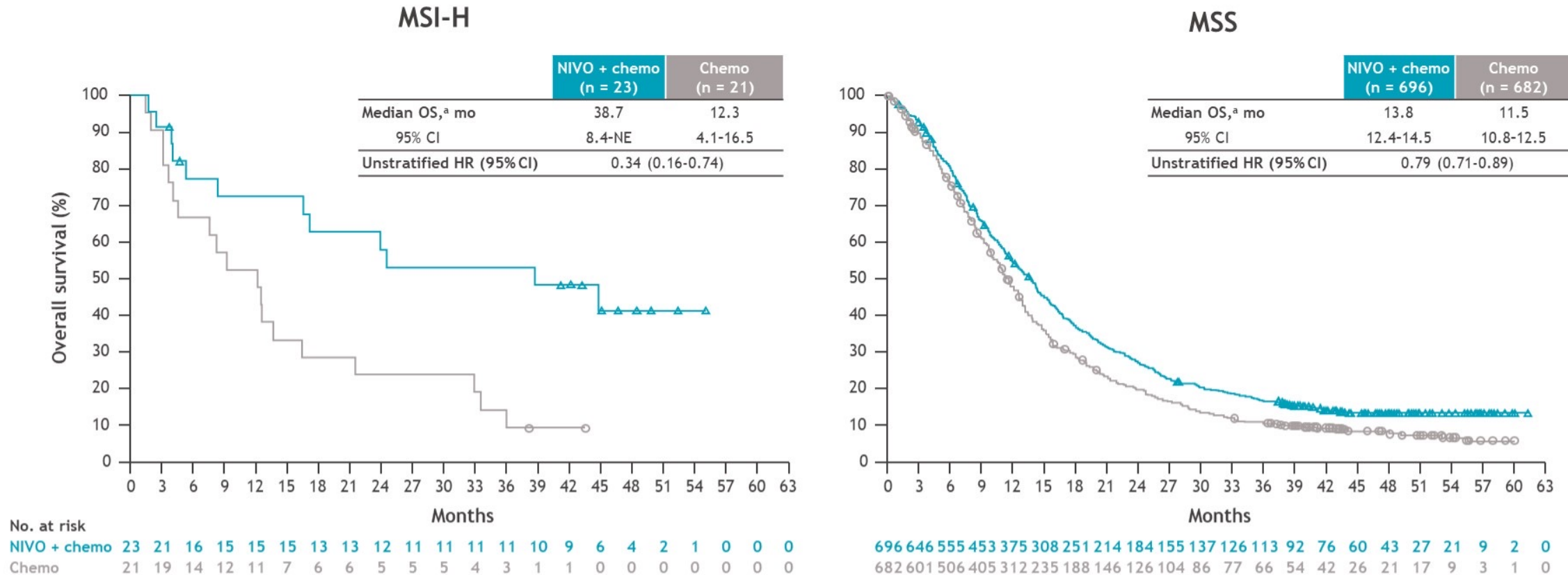
Objective response rate

PD-L1 CPS ^b	Number of patients	Objective response rate, %		Unweighted ORR difference, ^c %	Unweighted ORR difference, ^c % (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 1209)		58	46	12	
< 1	179	51	41	10	
≥ 1	1016	60	46	13	
< 5	427	56	46	9	
≥ 5	768	60	45	15	
< 10	577	58	47	11	
≥ 10	618	59	44	14	

- OS benefit with NIVO + chemo was enriched at higher PD-L1 CPS cutoffs
- ORR was higher vs chemo across all PD-L1 CPS subgroups

^aPD-L1 CPS expression indeterminate/nonevaluable/not reported, n = 19; ^bRandomized patients who had target lesion measurements at baseline, per BICR. PD-L1 CPS expression indeterminate/nonevaluable/not reported, n = 14; ^cPercentages may not reflect an exact difference due to rounding.

Overall survival by MSI status: 36-month follow-up

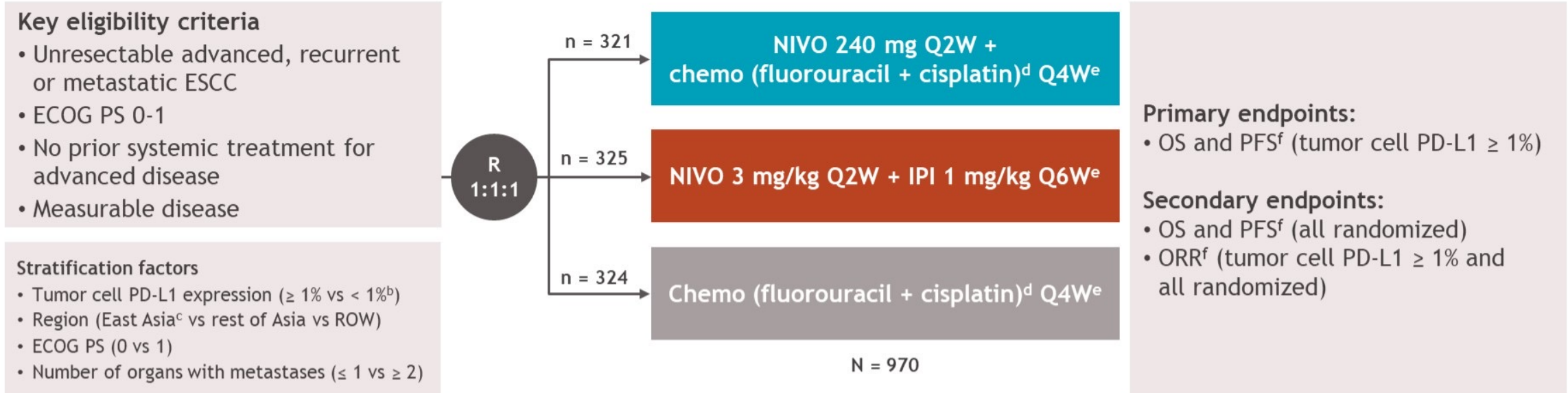


- Longer median OS was observed in all randomized patients with MSI-H and MSS tumors treated with NIVO + chemo vs chemo
 - The magnitude of benefit was greater in patients with MSI-H tumors
 - Patients with MSS tumors had results similar to the all randomized population

^aMinimum follow-up, 36.2 months.

CheckMate 648 study design

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

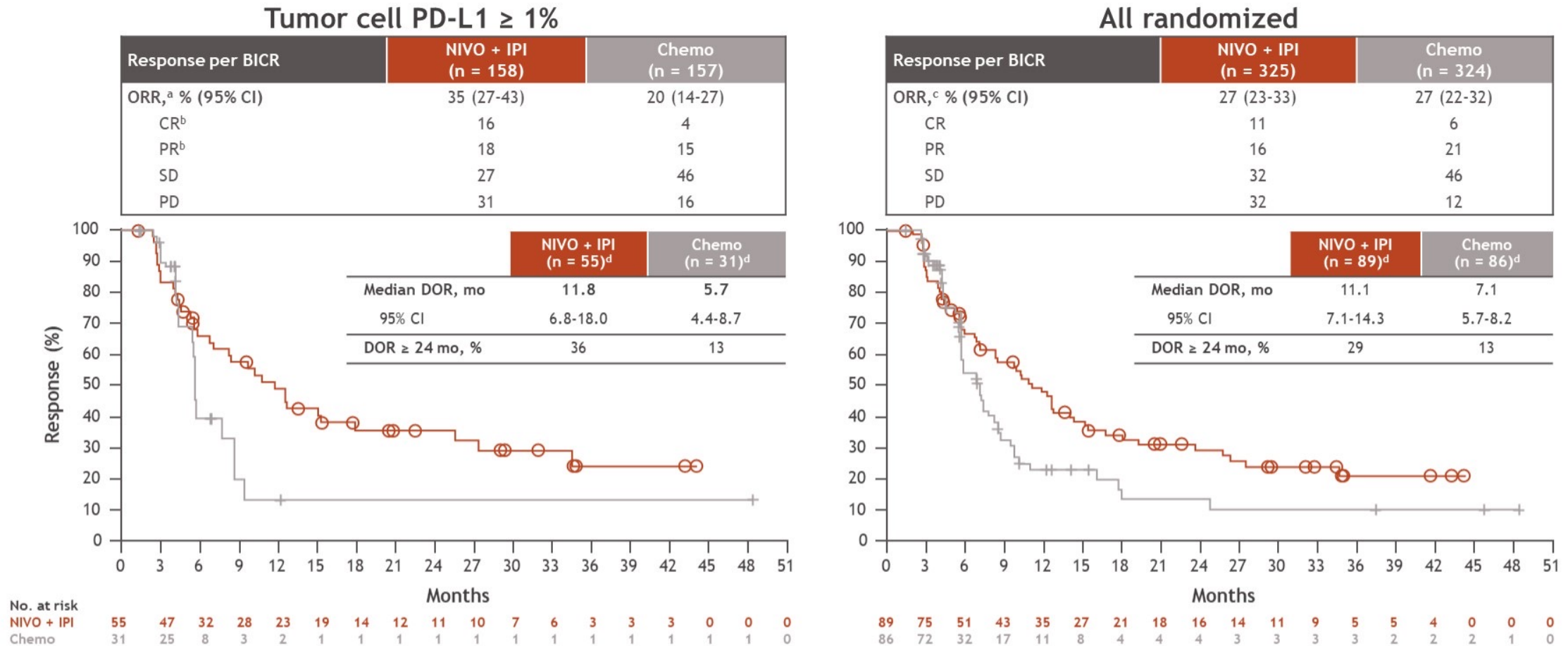


- At data cutoff (May 17, 2022), the minimum follow-up^g was 28.8 months

^aClinicalTrials.gov. NCT03143153; ^b $< 1\%$ includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); ^cEast Asia includes patients from Japan, Korea, and Taiwan;

^dFluorouracil 800 mg/m² IV daily (days 1-5) and cisplatin 80 mg/m² IV (day 1); ^eUntil documented disease progression (unless consented to treatment beyond progression for NIVO + IPI or NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given alone or in combination with IPI for a maximum of 2 years; ^fPer BICR; ^gTime from last patient randomized to clinical data cutoff.

Response and DOR with NIVO + IPI vs chemo: 29-month follow-up

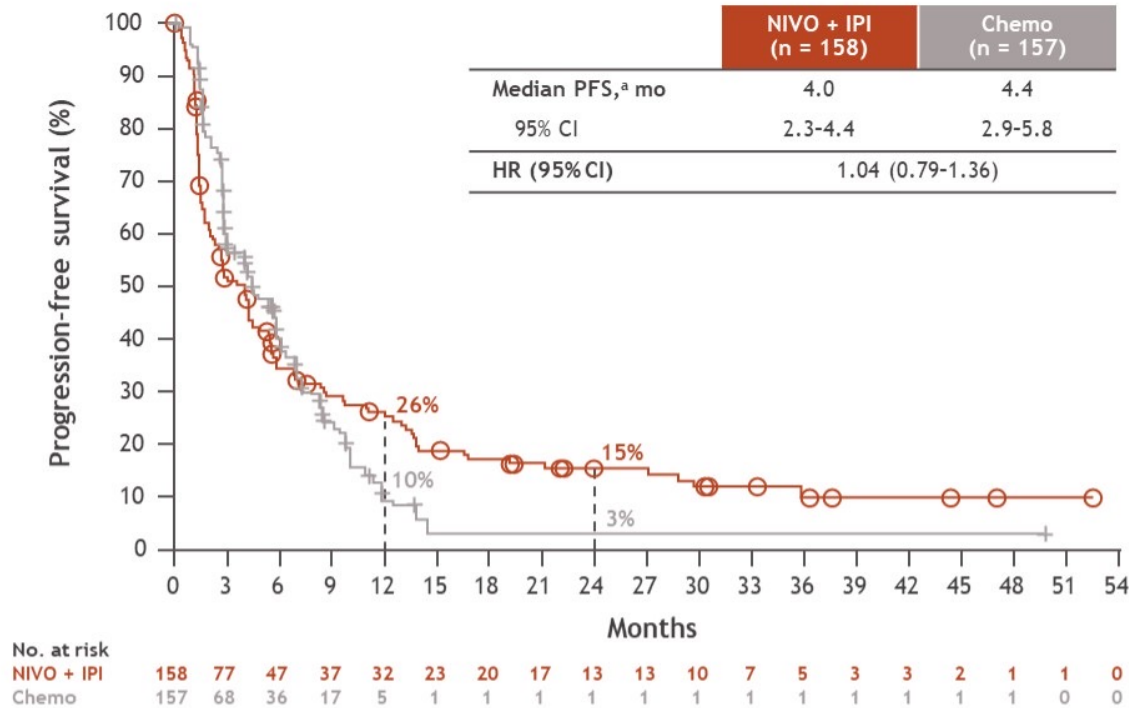


- ORR remained higher in patients with tumor cell PD-L1 ≥ 1%, and responses remained more durable in patients with tumor cell PD-L1 ≥ 1% and all randomized patients with NIVO + IPI vs chemo with longer follow-up

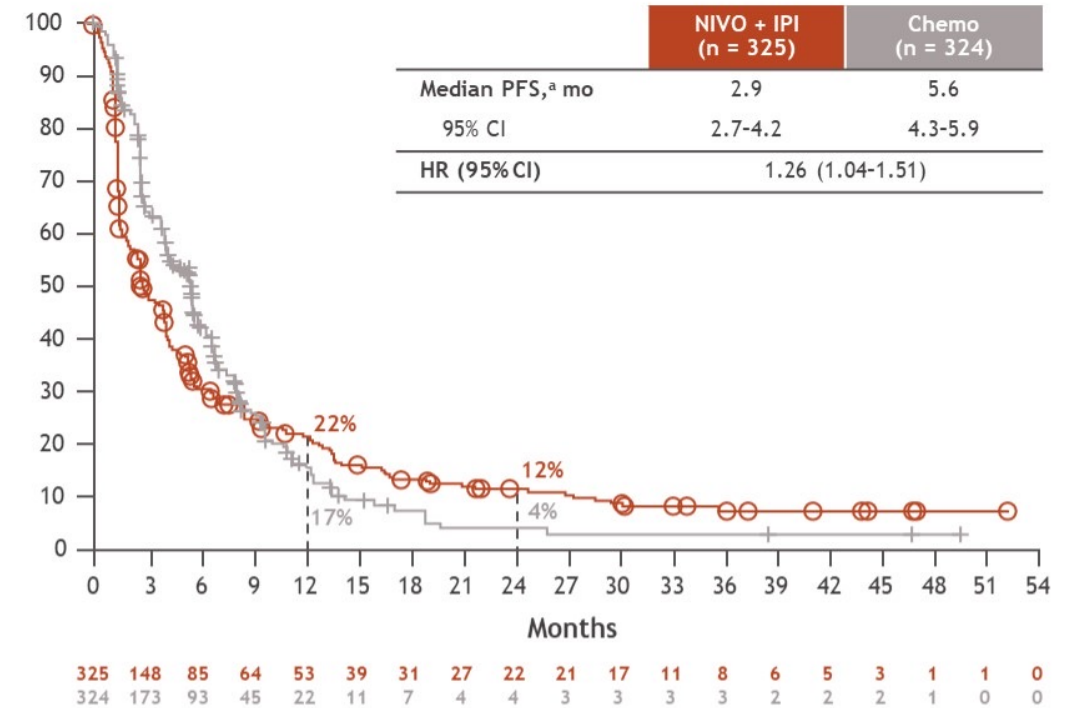
^aUnable to determine best overall response in patients with tumor cell PD-L1 ≥ 1%: NIVO + IPI, n = 11; chemo, n = 29; ^bPercentages may not add up to ORR due to rounding; ^cUnable to determine best overall response in all randomized patients: NIVO + IPI, n = 29; chemo, n = 50; ^dNumber of responders.

PFS with NIVO + IPI vs chemo: 29-month follow-up

Tumor cell PD-L1 $\geq 1\%$ (per BICR)



All randomized (per BICR)

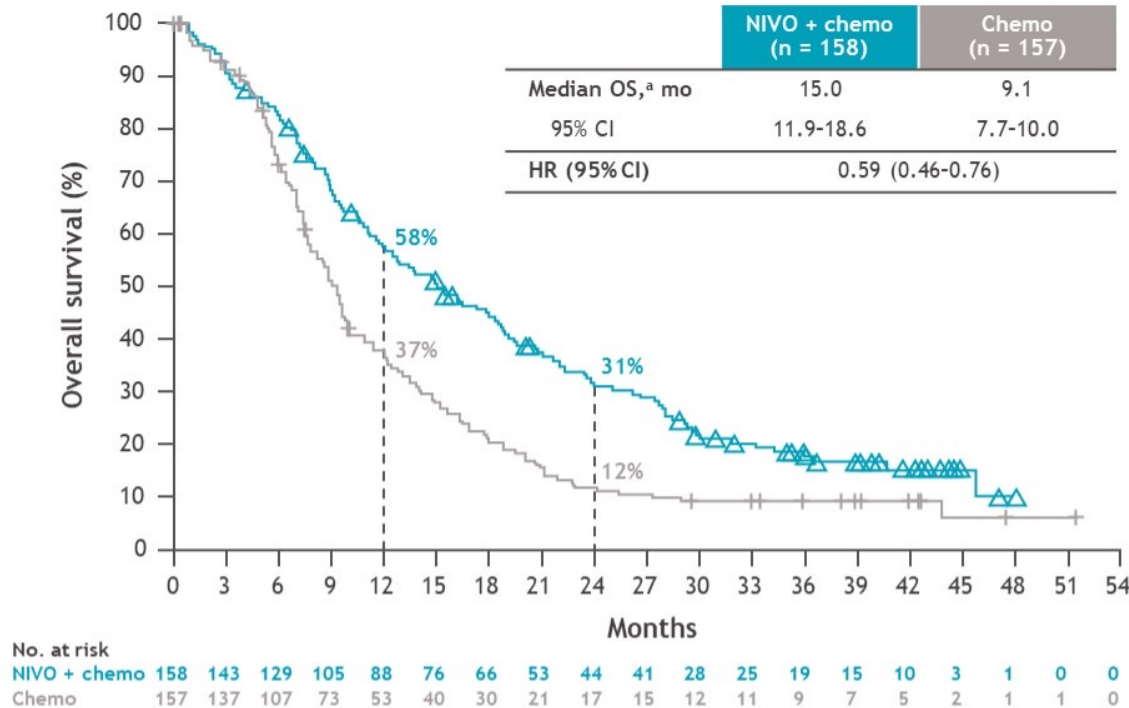


- No PFS benefit was observed with NIVO + IPI vs chemo in either the tumor cell PD-L1 $\geq 1\%$ or all randomized populations with longer follow-up, consistent with previously reported results¹

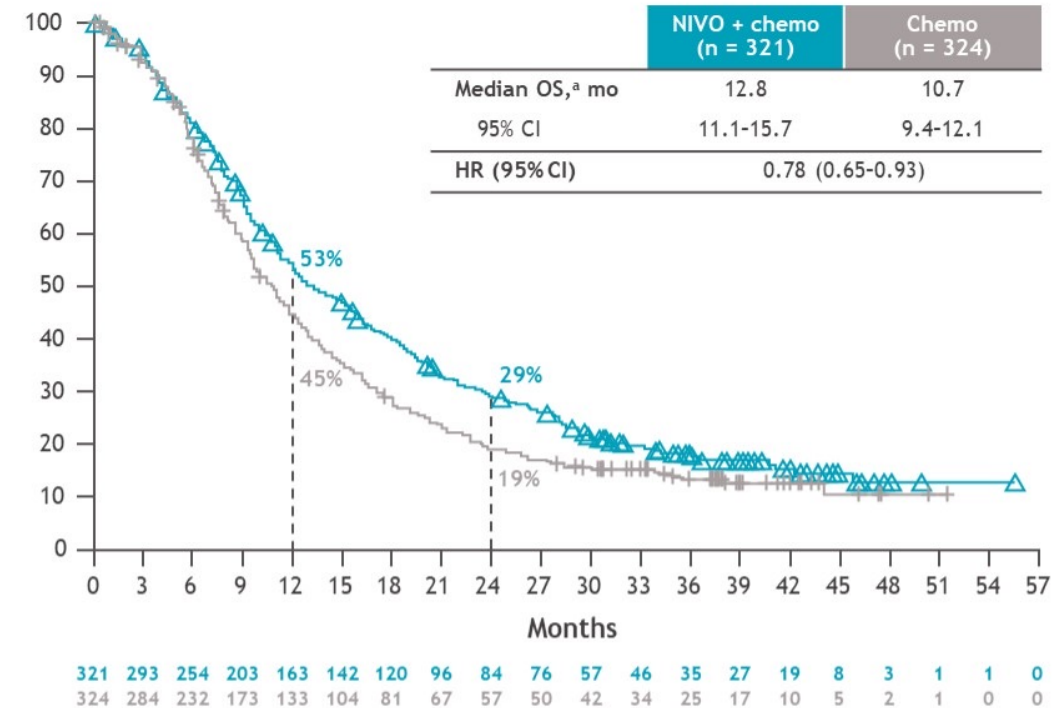
^aMinimum follow-up, 28.8 months. 1. Doki Y, et al. *N Engl J Med* 2022;386:449-462.

OS with NIVO + chemo vs chemo: 29-month follow-up

Tumor cell PD-L1 $\geq 1\%$



All randomized



- Clinically meaningful improvement in OS with NIVO + chemo vs chemo in the tumor cell PD-L1 $\geq 1\%$ and all randomized populations was maintained with longer follow-up
 - Tumor cell PD-L1 $\geq 1\%$: 41% reduction in the risk of death and a 5.9-month improvement in median OS
 - All randomized: 22% reduction in the risk of death and a 2.1-month improvement in median OS

^aMinimum follow-up, 28.8 months.

KEYNOTE-590: First-line Pembrolizumab + Chemotherapy vs Chemotherapy for Esophageal/GEJ Cancer

- Randomized phase III trial of **pembrolizumab + chemo*** vs **chemo*** for previously untreated patients with locally advanced unresectable or metastatic EAC, ESCC, or GEJA (N = 749)

Outcome	All Patients			All Patients PD-L1 CPS ≥10			ESCC			ESCC PD-L1 CPS ≥10		
	Pembro + CT (n = 373)	CT (n = 376)	HR/ P Val	Pembro + CT (n = 186)	CT (n = 197)	HR/ P Val	Pembro + CT (n = 274)	CT (n = 274)	HR/ P Val	Pembro + CT (n = 143)	CT (n = 143)	HR/ P Val
Median OS, [†] mo	12.4	9.8	0.73/ <.0001	13.5	9.4	0.62/ <.0001	12.6	9.8	0.72/ .0006	13.9	8.8	0.57/ <.0001
Median PFS, [†] mo	6.3	5.8	0.65/ <.0001	7.5	5.5	0.51/ <.0001	6.3	5.8	0.65/ <.0001	--	--	--

	CPS ≥10 (n = 383)	All Randomized	CPS <10 (n = 347)
HR for OS	0.62	0.73	0.86

*5-FU + cisplatin. [†]Primary endpoint.

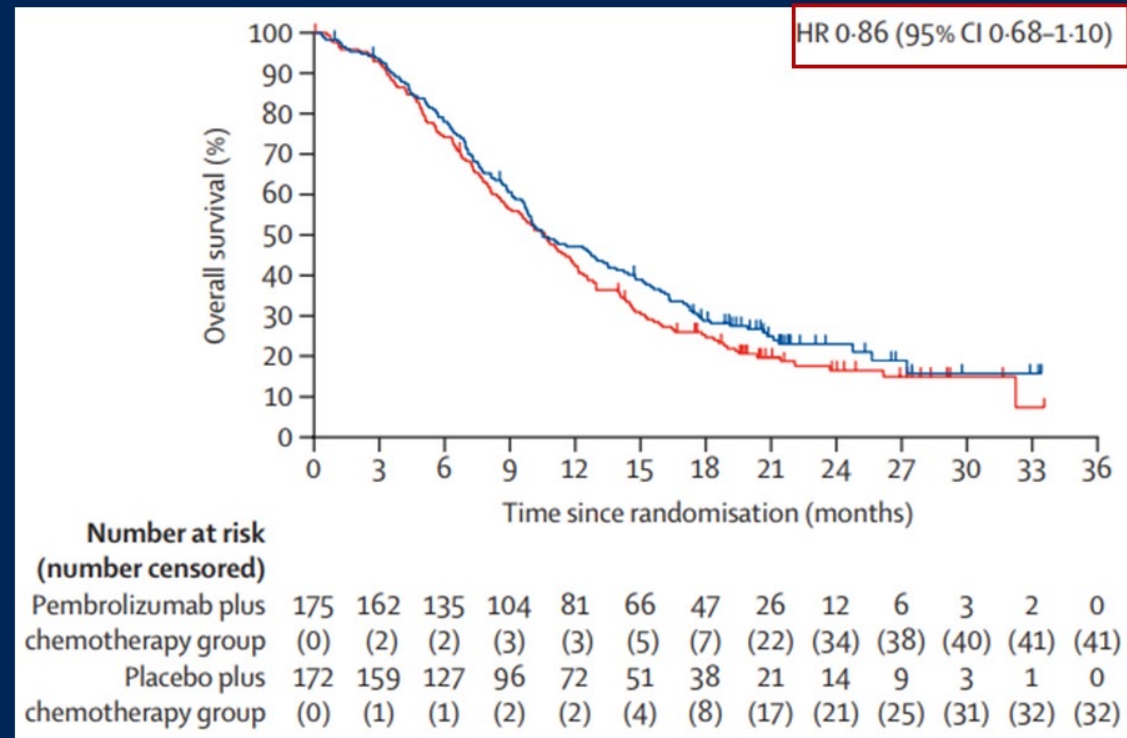
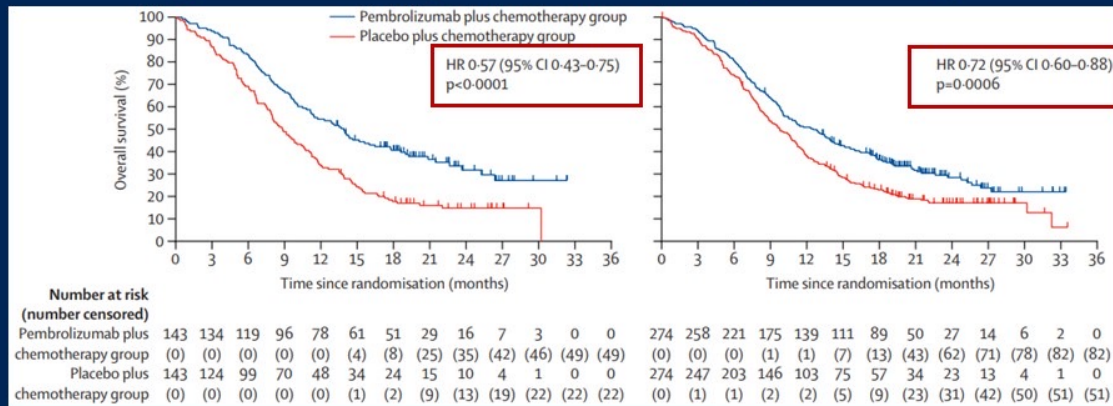
PD-L1 Expression – 1st Line Upper GI

KEYNOTE 590 (E/GEJ Adenocarcinoma ~27% + Squamous Cell Carcinoma ~ 73%)

ESCC CPS ≥ 10

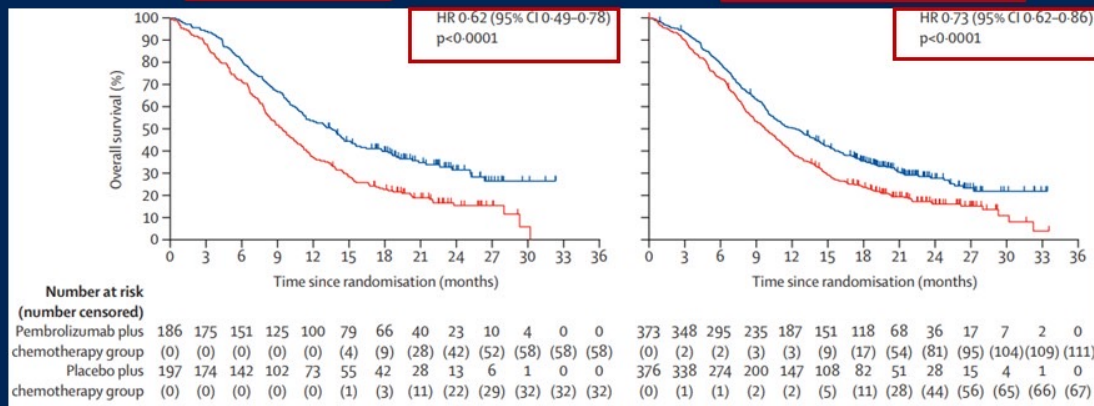
ESCC

CPS < 10



CPS ≥ 10

All Randomised pts

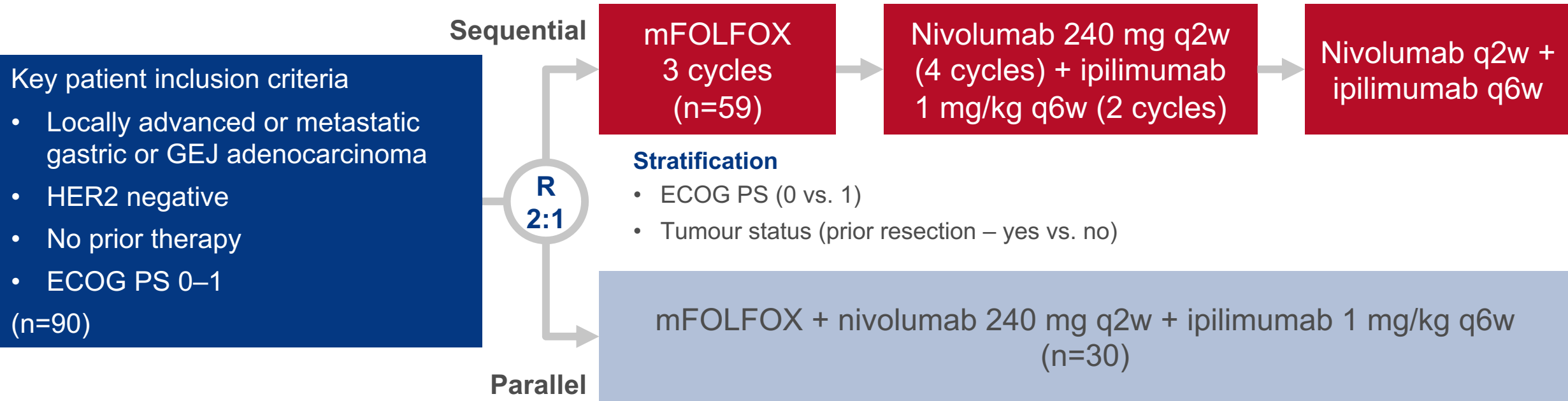


Sun J, et al. Lancet 2021

1203O: FOLFOX plus nivolumab and ipilimumab versus FOLFOX induction followed by nivolumab and ipilimumab in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction – results from the randomized phase 2 Moonlight trial of the AIO – Lorenzen S, et al

Study objective

- To evaluate the efficacy and safety of mFOLFOX induction therapy followed by nivolumab + ipilimumab in previously untreated patients with advanced or metastatic gastric or GEJ adenocarcinoma in the Moonlight study



PRIMARY ENDPOINT

- 6-mo PFS rate

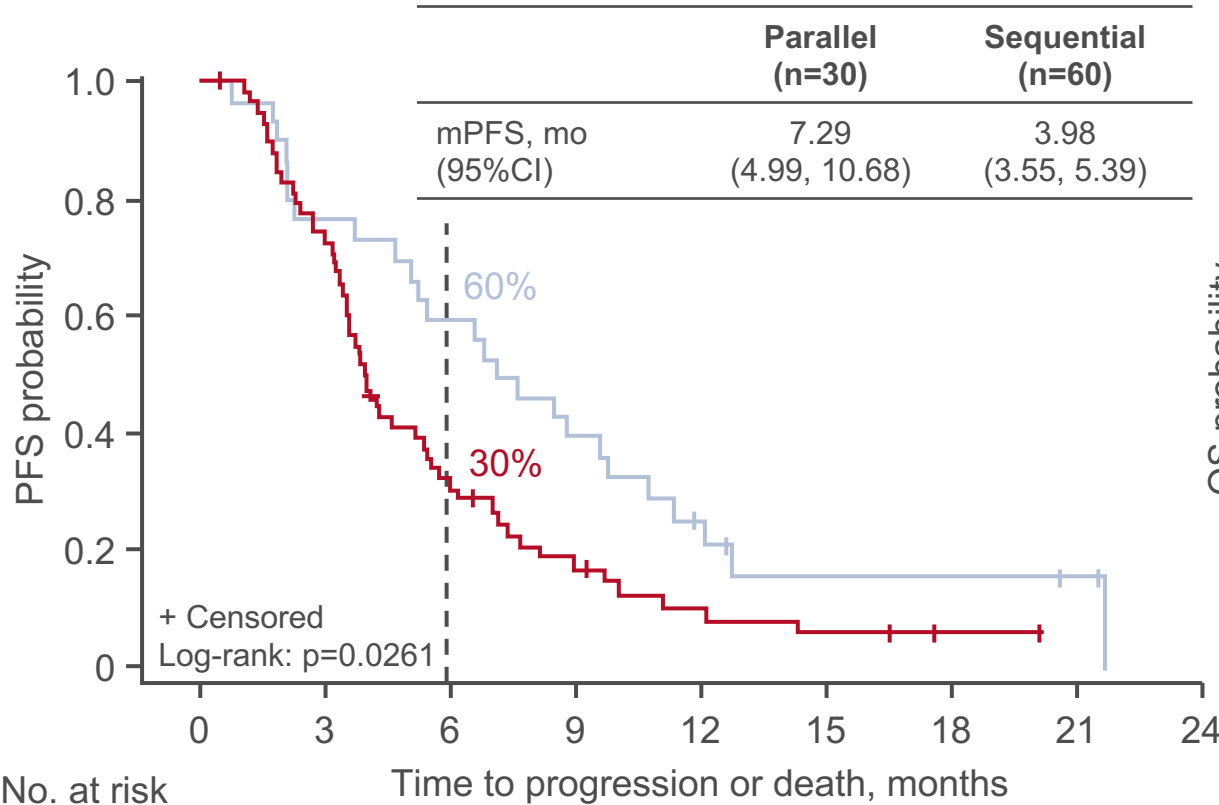
SECONDARY ENDPOINTS

- OS, ORR, safety

1203O: FOLFOX plus nivolumab and ipilimumab versus FOLFOX induction followed by nivolumab and ipilimumab in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction – results from the randomized phase 2 Moonlight trial of the AIO – Lorenzen S, et al

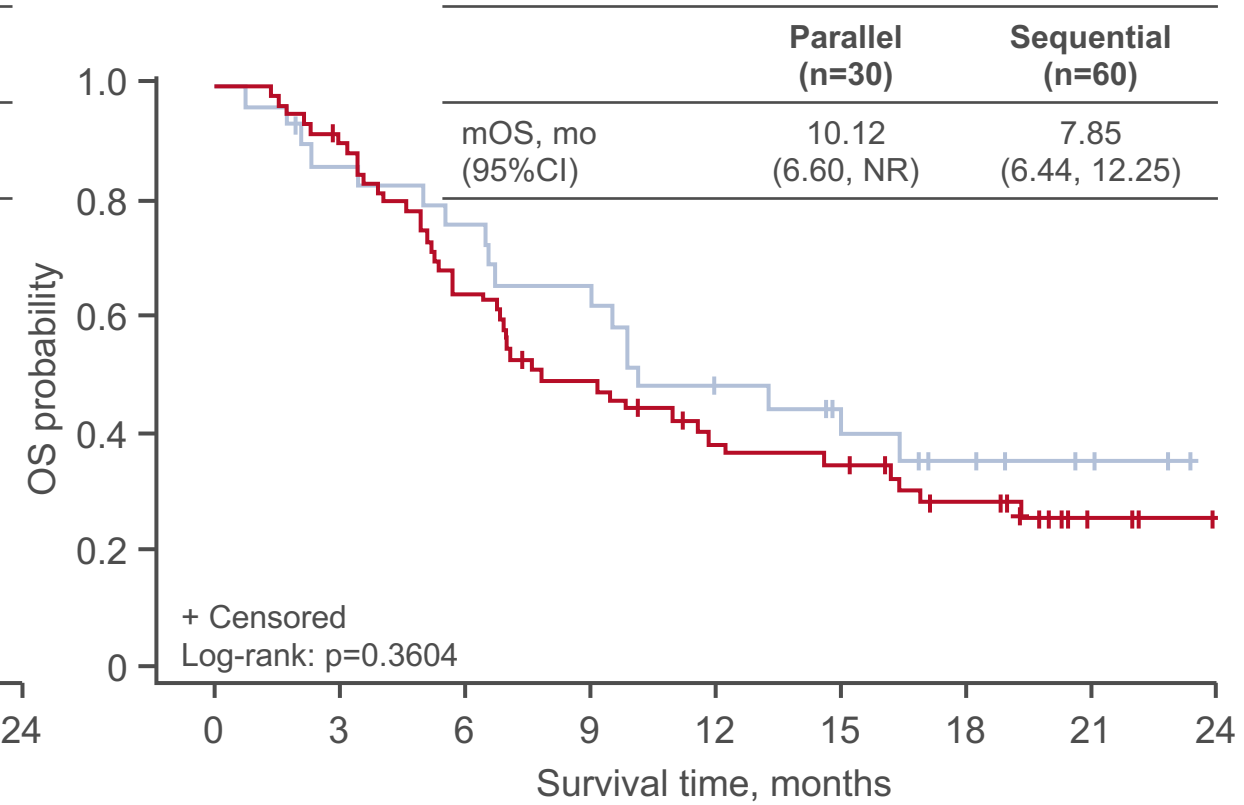
Key results

Progression-free survival



No. at risk	0	3	6	9	12	15	18	21	24
Parallel 30	30	23	18	12	5	3	3	2	0
Sequential 60	60	43	18	10	5	3	1	0	0

Overall survival



No. at risk	0	3	6	9	12	15	18	21	24
Parallel 30	30	25	22	19	13	10	7	4	0
Sequential 60	60	54	38	28	20	18	12	3	0

1203O: FOLFOX plus nivolumab and ipilimumab versus FOLFOX induction followed by nivolumab and ipilimumab in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction – results from the randomized phase 2 Moonlight trial of the AIO – Lorenzen S, et al

Key results

	Parallel (n=30)	Sequential (n=60)
ORR, % (95%CI)	46.7 (28, 66)	30.0 (19, 43)
BOR, %		
CR	10.0	6.7
PR	36.7	23.3
SD	33.3	43.3
PD	10.0	15.0
mDoR, mo (95%CI)	8.36 (2.99, 18.76)	4.30 (1.91, 8.74)
PD-L1 CPS ≥1, n	13	24
mOS, mo (95%CI)	16.46 (2.07, NR)	6.87 (5.13, 7.59)
mPFS, mo (95%CI)	5.22 (2.07, NR)	3.75 (3.06, 5.55)
PD-L1 CPS <1, n	14	17
mPFS, mo (95%CI)	6.87 (2.07, 9.53)	3.98 (2.23, 6.21)

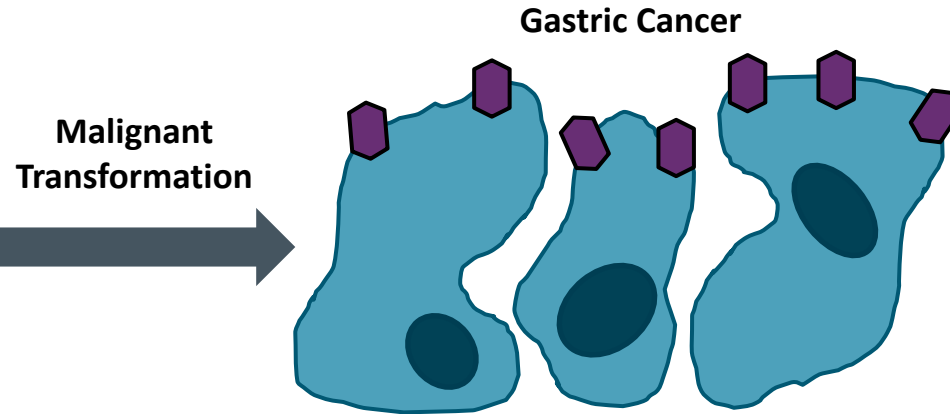
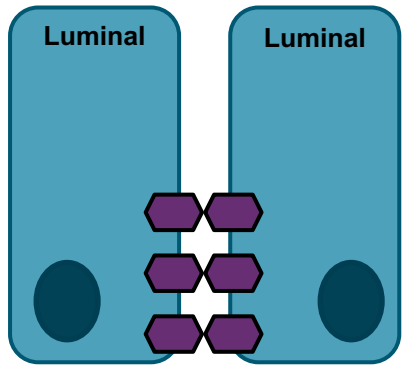
Grade ≥3 TRAEs, n (%)	Parallel (n=30)	Sequential (n=60)
Any	21 (70.0)	26 (43.3)
Serious	10 (33.3)	10 (16.7)
Led to death	1 (3.3)	1 (1.7)

Conclusions

- In patients with advanced or metastatic gastric or GEJ adenocarcinoma, 1L FOLFOX + nivolumab + ipilimumab given in parallel demonstrated greater benefits than sequential treatment, although this should be interpreted with caution as the patient numbers were small and PD-L1 expression was low

Claudin18.2—Leveraging Biology

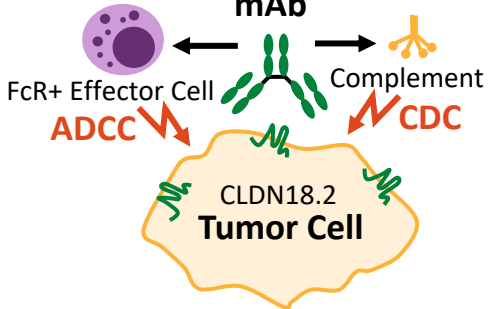
Normal Gastric Epithelia



Malignant Transformation

CLDN18.2

mAb



IMAB362-Coated Tumor Cell Debris
Proinflammatory, Chemoattractant Environment

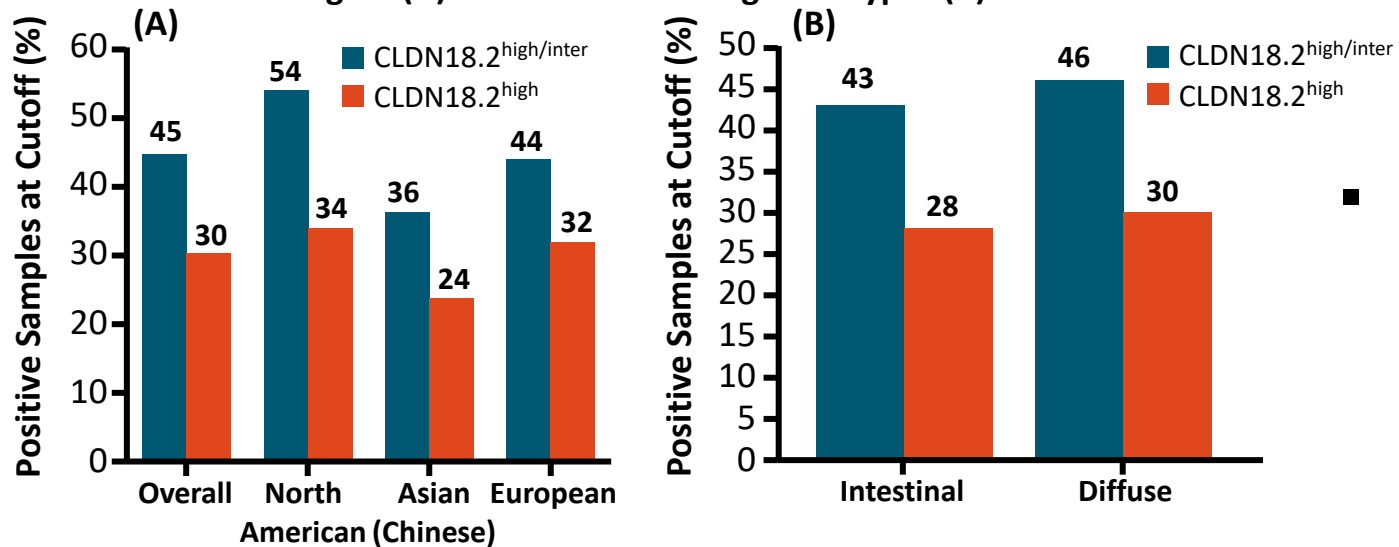
Crosspresentation by APCs

T-Cell Infiltration

Induction of Adaptive T-Cell immunity

Baek. Anticancer Res. 2019;39:6973.

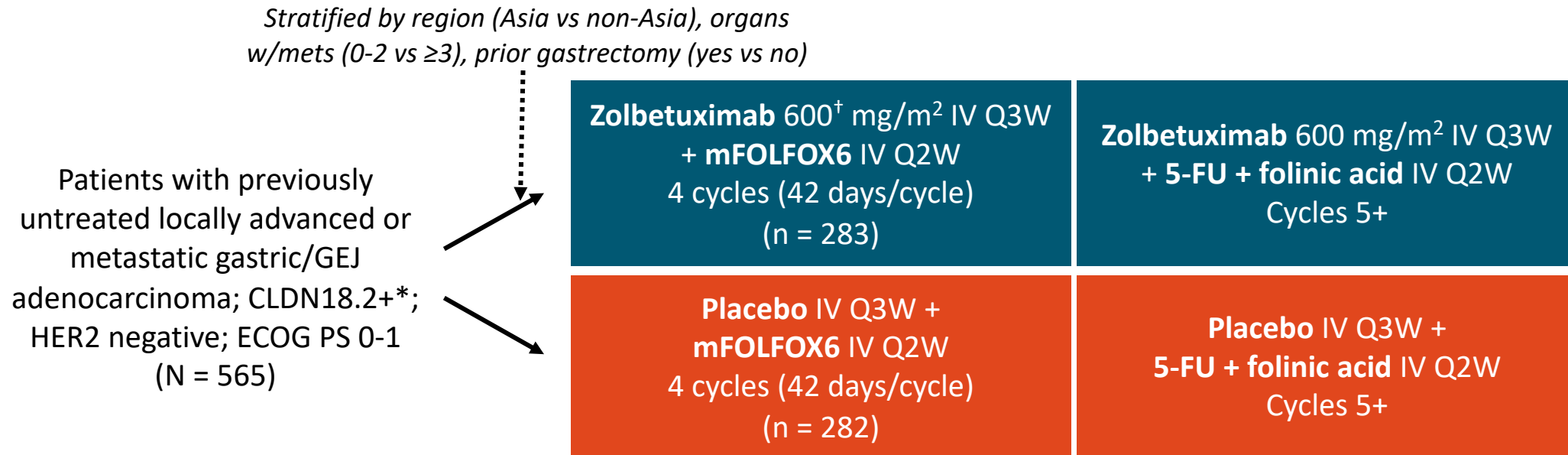
CLDN18.2 Prevalence Based on IHC Staining at 2 Cutoffs Overall and by Region (A) and Across Histologic Subtypes (B)



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

SPOTLIGHT: Study Design

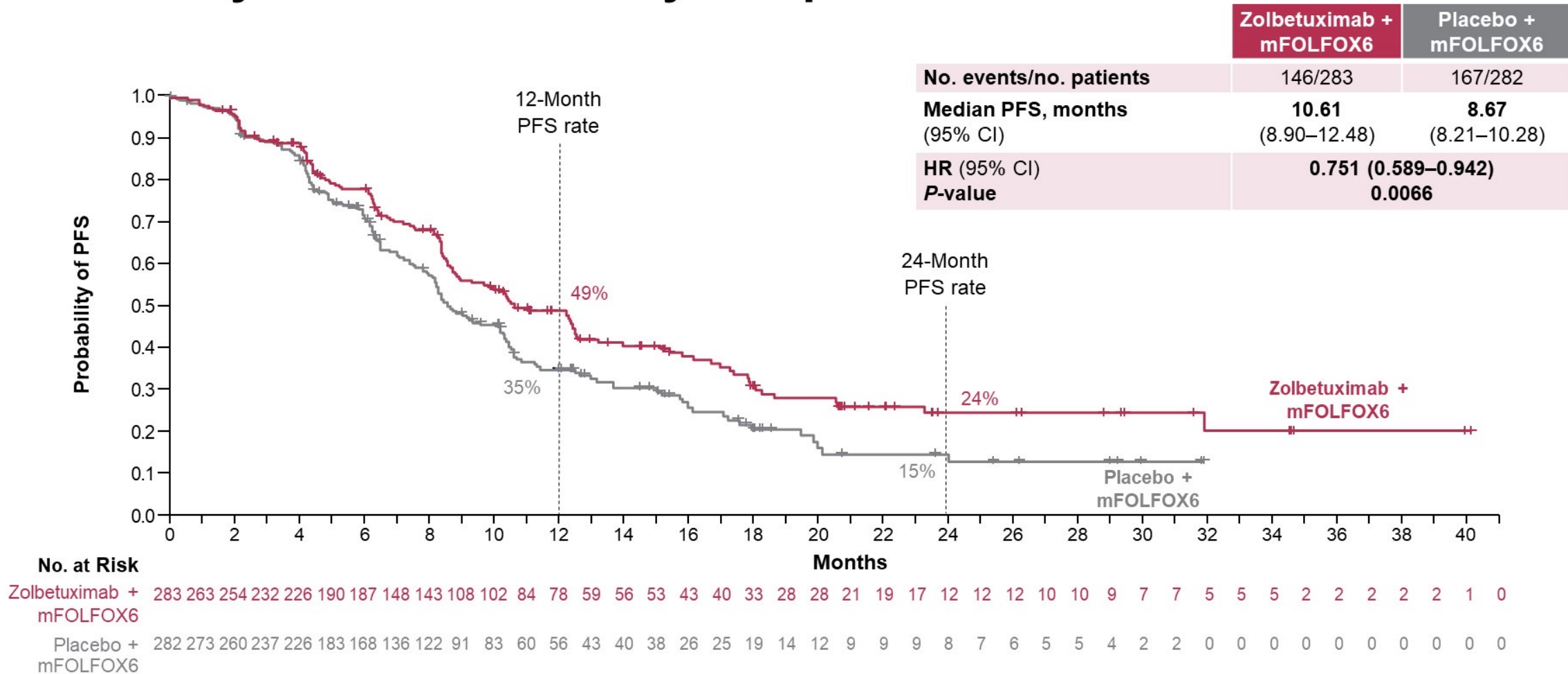
- Global, randomized, double-blind phase III trial



*Moderate-to-strong CLDN18 staining in $\geq 75\%$ of tumor cells. [†]First dose only: 800 mg/m².

- Primary endpoint:** PFS
- Secondary endpoints:** OS, TTCD (GHS/QoL, PF, and QLQ-OG25-Pain score)
- Additional endpoints:** ORR, DoR, safety, PROs

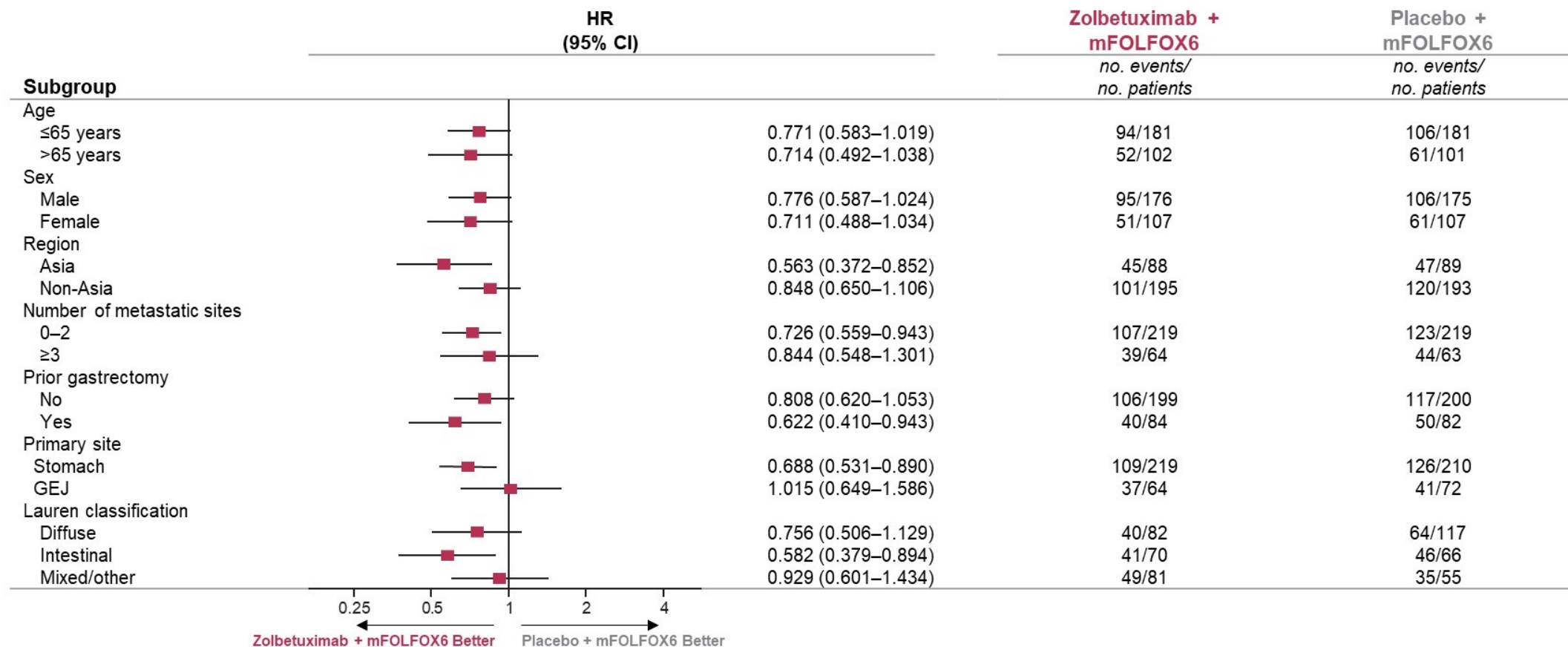
Primary End Point: PFS by Independent Review Committee^a



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

Data cutoff: September 9, 2022; Median follow-up = 12.94 months (zolbetuximab + mFOLFOX6) vs 12.65 months (placebo + mFOLFOX6).
^aPer RECIST version 1.1.

Primary End Point: PFS^a Subgroup Analysis

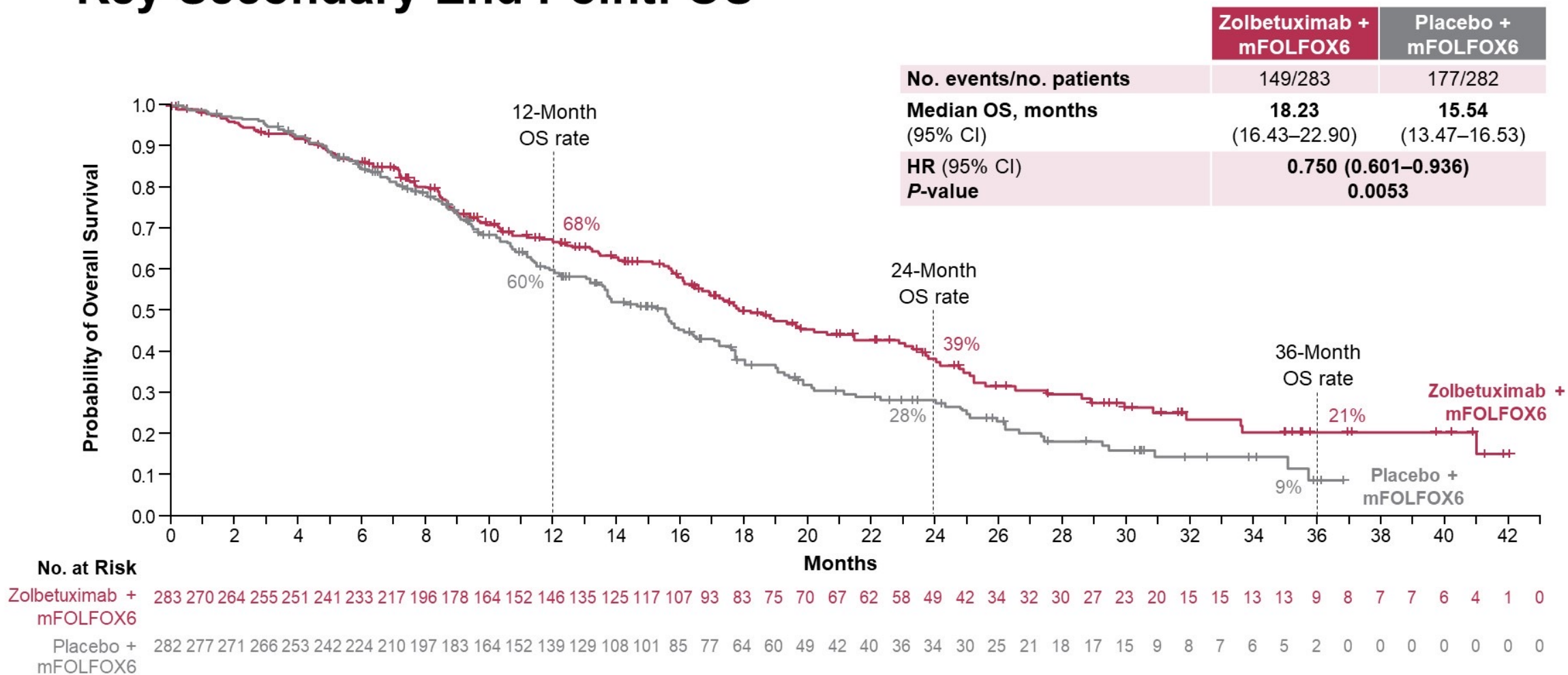


- PFS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 across most subgroups

Data cutoff: September 9, 2022.

^aPer RECIST version 1.1 by independent review committee.

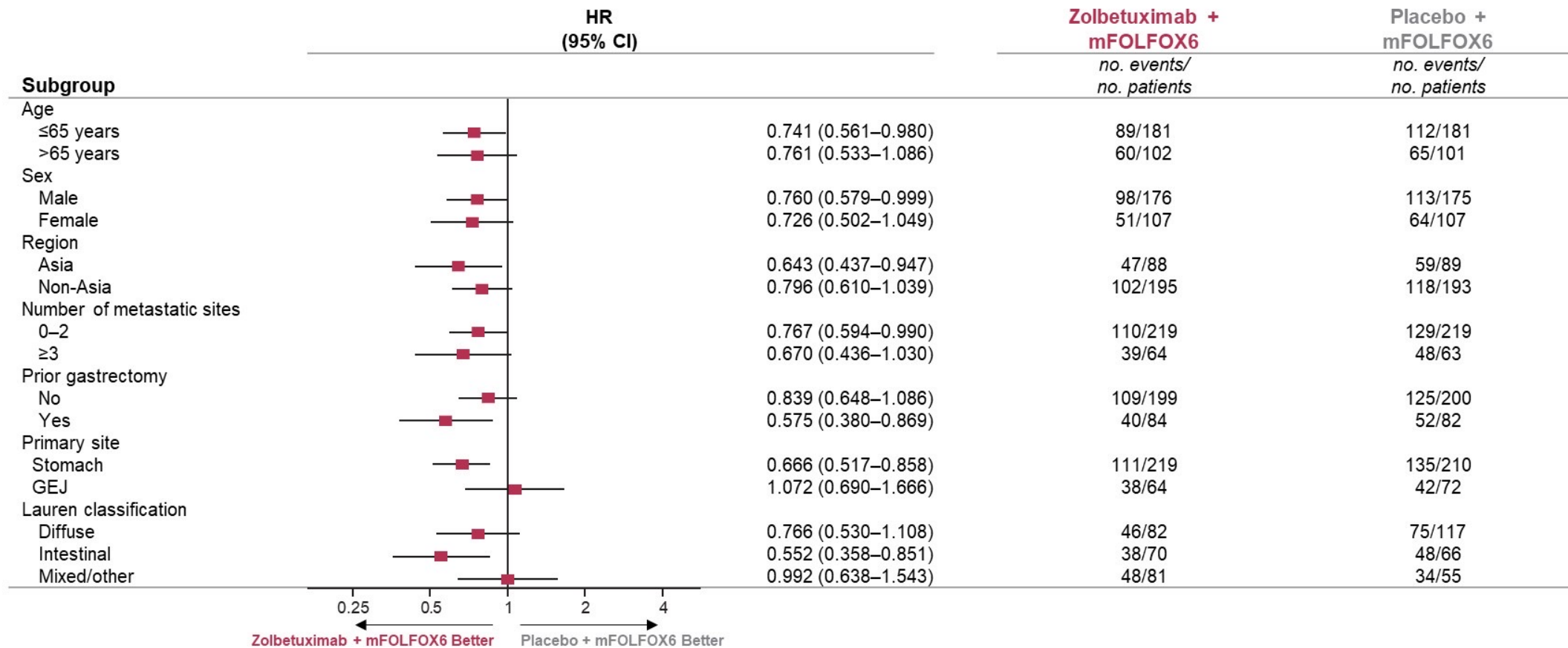
Key Secondary End Point: OS



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

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

Key Secondary End Point: OS Subgroup Analysis



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

Data cutoff: September 9, 2022.

SPOTLIGHT: TEAEs in $\geq 20\%$ of Patients

Adverse Event, %	Zolbetuximab + mFOLFOX6 (n = 279)		Placebo + mFOLFOX6 (n = 278)	
	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3
Nausea	81.0	16.1	60.8	6.5
Vomiting	64.5	16.1	34.5	5.8
Decreased appetite	47.0	5.7	33.5	3.2
Diarrhea	38.7	4.3	43.9	3.2
Peripheral sensory neuropathy	38.0	3.9	42.4	5.4
Neutropenia	36.2	28.3	33.8	23.4
Anemia	35.5	8.6	37.1	9.4
Constipation	35.5	1.1	37.1	9.4
Neutrophil count decreased	34.1	24.7	32.0	24.8
Fatigue	28.0	6.1	32.0	5.0
Asthenia	24.7	7.2	22.3	2.5
Abdominal pain	23.3	4.3	28.8	2.2
Stomatitis	20.8	2.5	20.1	1.1



make a joke about ai and oncology



Sure, here's a joke about AI and oncology:



Why did the oncologist consult with an AI language model?

To get a second opinion and a byte-sized perspective on the tumor!



make a joke about ai and oncology



Sure, here's an AI and oncology joke:



Why did the AI refuse to diagnose cancer in the oncology clinic?

Because it didn't want to be labeled as a malignant algorithm!

My computer beat me at chess



It was no match for my kickboxing skills