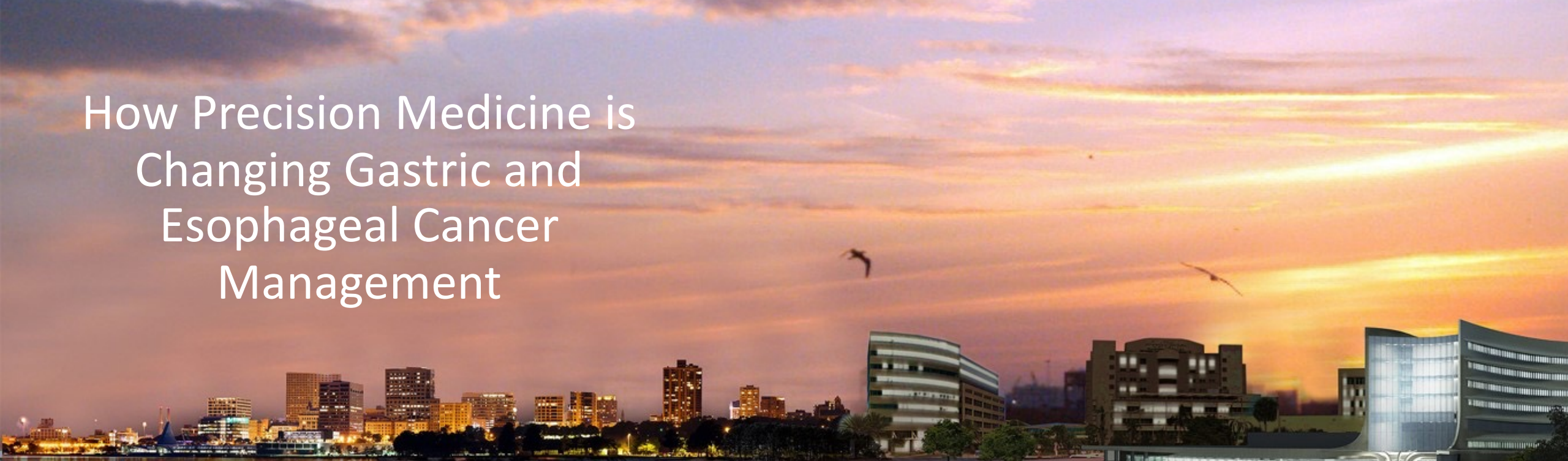
How Precision Medicine is Changing Gastric and Esophageal Cancer Management



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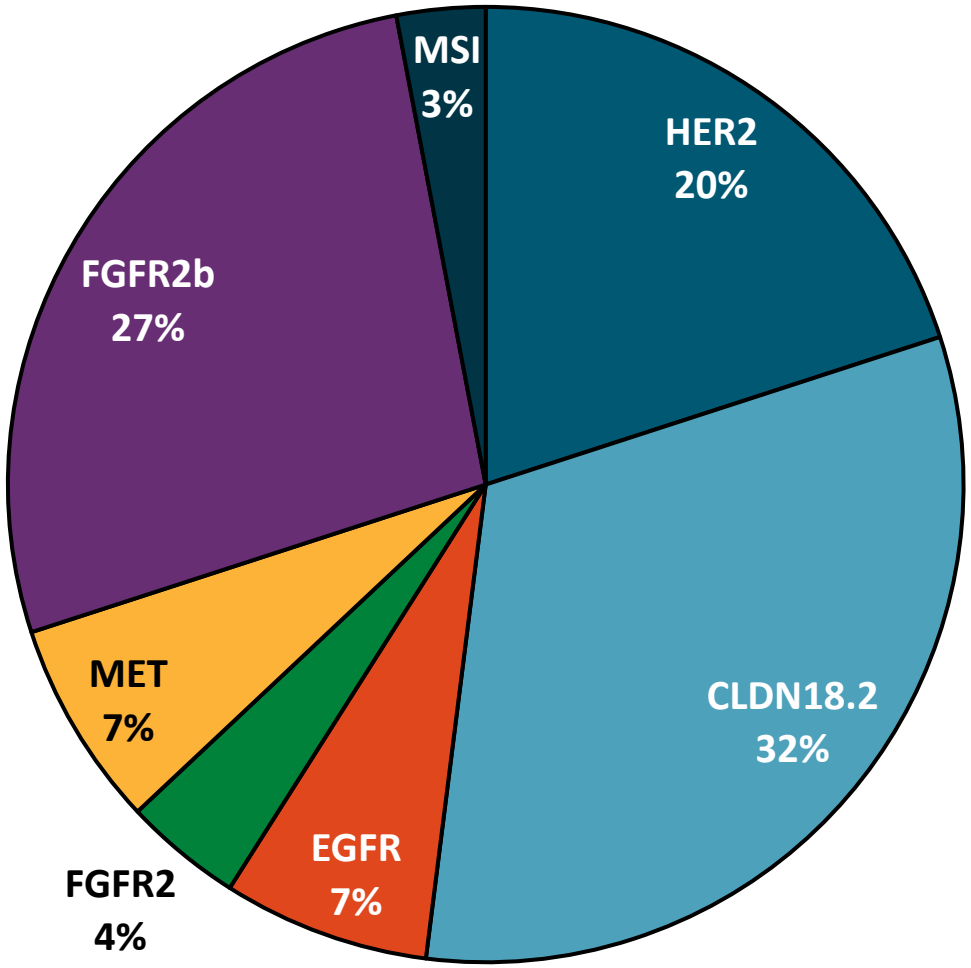
Miami Beach, Florida

Mount Sinai
MEDICAL CENTER

NGS—the Right Tool for the Job



- HER2 status: NGS, FISH, IHC
- MSI status: NGS, PCR, IHC
- PD-L1 score: IHC

- NTRK status: NGS, IHC, FISH
- TMB level: NGS
- CLDN18.2 expression: IHC
- FGFR2 status: NGS, FISH, IHC
- $EGFR_{amp}$ status: NGS, FISH
- MET_{amp} status: NGS, FISH

Lee. J Pathol Transl Med. 2017;51:103. Schoemig-Markieffka. Gastric Cancer. 2021;24:1115.
Cai. J Transl Med. 2019;17:189. Baek. Anticancer Res. 2019;39:6973. Ahn. Mod Pathol. 2016;29:1095.

Slide credit: clinicaloptions.com

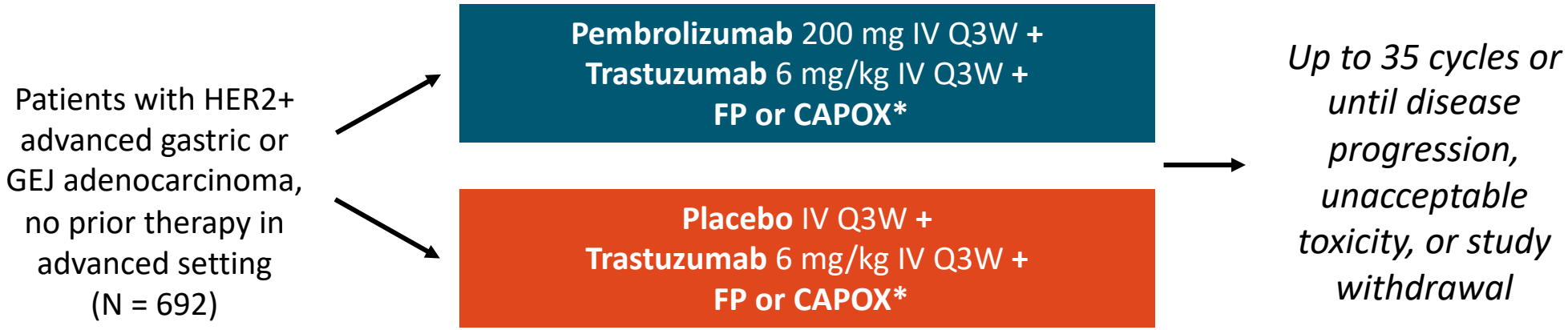
Gastroesophageal Adenocarcinoma Algorithm for HER2 Testing by IHC

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

Bartley. JCO. 2017;35:446. Wolff. Arch Pathol Lab Med. 2018;142:1364.
NCCN. Clinical practice guidelines in oncology: gastric cancer. v.2.2022. nccn.org.

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

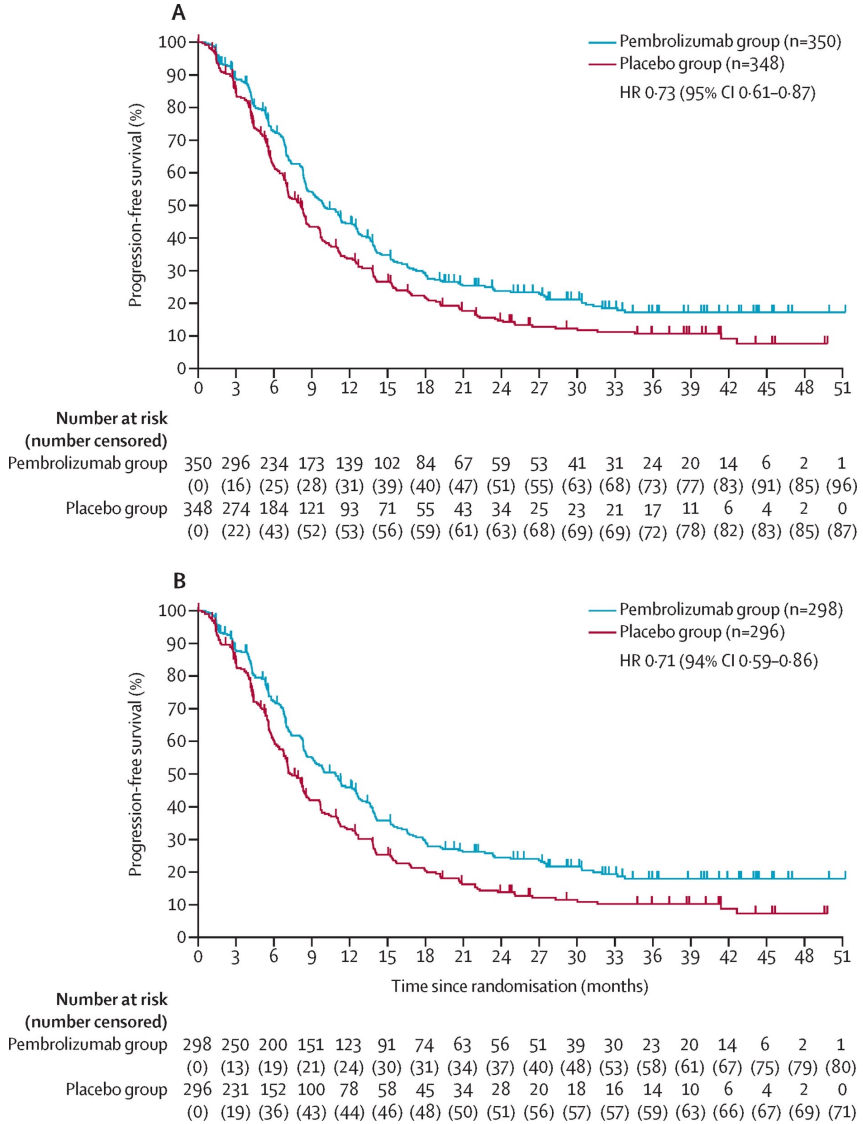
- Randomized, double-blind, placebo-controlled phase III study



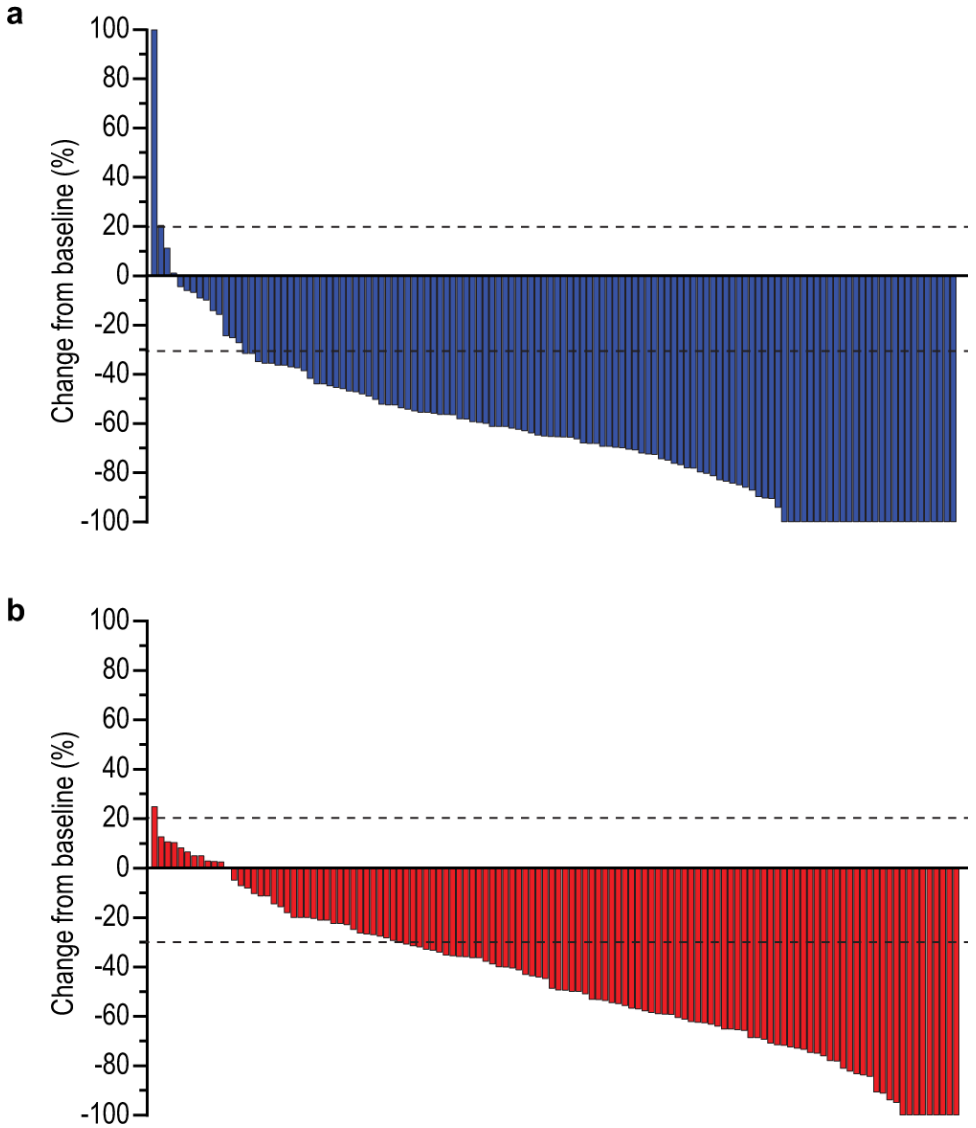
*Trastuzumab 8 mg/kg loading dose.
FP: 5-fluorouracil 800 mg/m^2 IV Days 1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W
CAPOX: capecitabine 1000 mg/m^2 BID Days 1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W

- 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

Janjigian. Nature. 2021;600:727.



Janjigian. THE LANCET, VOLUME 402, ISSUE 10418,

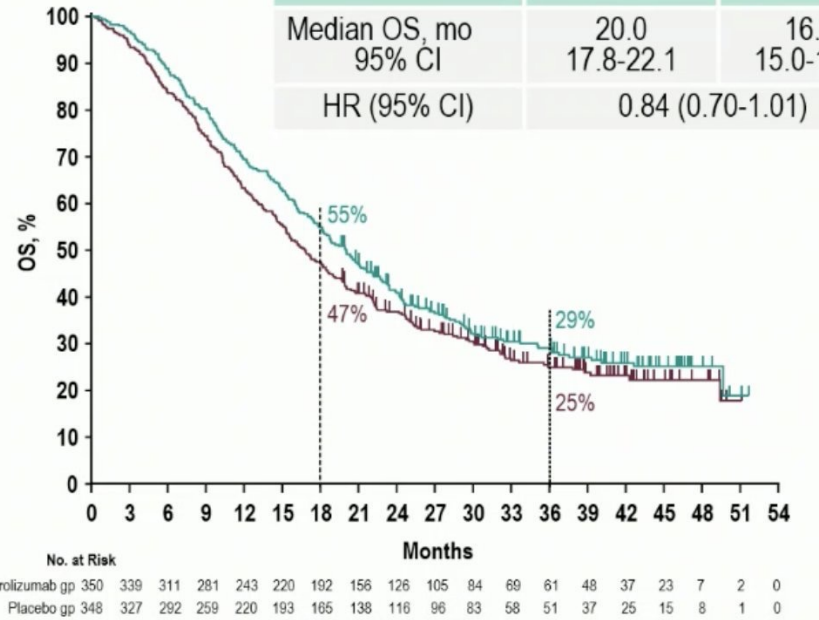


Janjigian. Nature. 2021;600:727.

Overall Survival at IA3

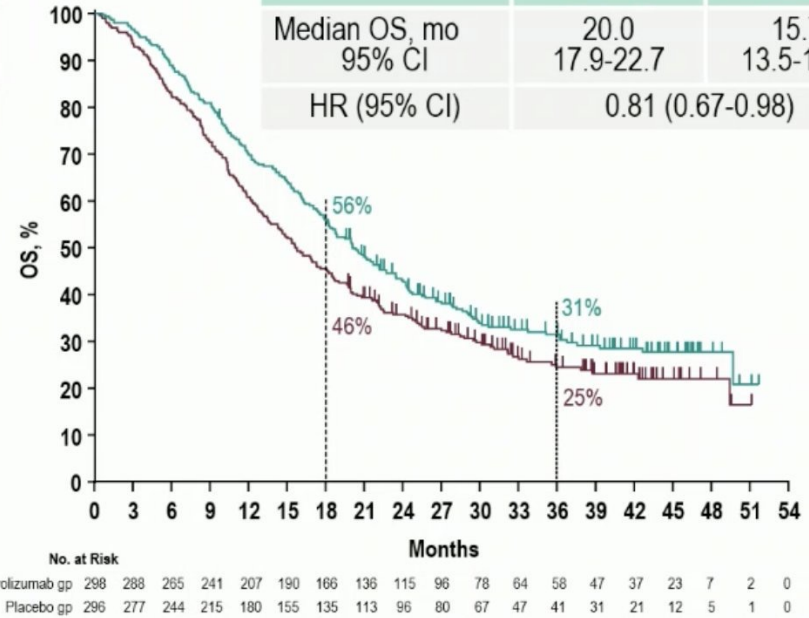
All patients

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



PD-L1 CPS ≥1[a]

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



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

Findings

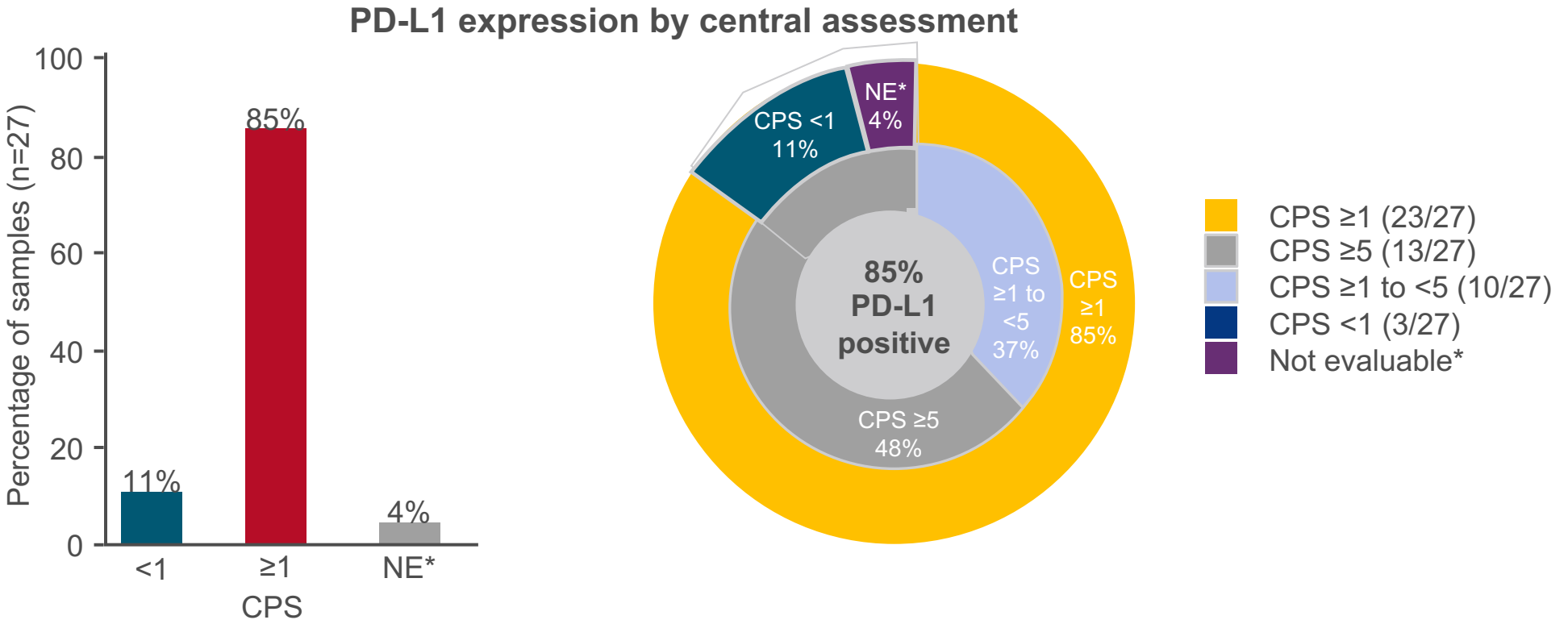
Between Oct 5, 2018, and Aug 6, 2021, 698 patients were assigned to pembrolizumab (n=350) or placebo (n=348). 564 (81%) were male and 134 (19%) were female. At the third interim analysis, 286 (82%) of 350 patients in the pembrolizumab group and 304 (88%) of 346 in the placebo group who received treatment had discontinued treatment, mostly due to disease progression. At the second interim analysis (median follow-up 28·3 months [IQR 19·4–34·3] in the pembrolizumab group and 28·5 months [20·1–34·3] in the placebo group), median progression-free survival was 10·0 months (95% CI 8·6–11·7) in the pembrolizumab group versus 8·1 months (7·0–8·5) in the placebo group (hazard ratio [HR] 0·72, 95% CI 0·60–0·87; p=0·0002). Median overall survival was 20·0 months (17·8–23·2) versus 16·9 months (15·0–19·8; HR 0·87 [0·72–1·06]; p=0·084). At the third interim analysis (median follow-up 38·4 months [IQR 29·5–44·4] in the pembrolizumab group and 38·6 months [30·2–44·4] in the placebo group), median progression-free survival was 10·0 months (8·6–12·2) versus 8·1 months (7·1–8·6; HR 0·73 [0·61–0·87]), and median overall survival was 20·0 months (17·8–22·1) versus 16·8 months (15·0–18·7; HR 0·84 [0·70–1·01]), but did not meet prespecified criteria for significance and will continue to final analysis. Grade 3 or worse treatment-related adverse events occurred in 204 (58%) of 350 patients in the pembrolizumab group versus 176 (51%) of 346 patients in the placebo group. Treatment-related adverse events that led to death occurred in four (1%) patients in the pembrolizumab group and three (1%) in the placebo group. The most common treatment-related adverse events of any grade were diarrhoea (165 [47%] in the pembrolizumab group *vs* 145 [42%] in the placebo group), nausea (154 [44%] *vs* 152 [44%]), and anaemia (109 [31%] *vs* 113 [33%]).

Janjigian. THE LANCET, VOLUME 402, ISSUE 10418,

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**

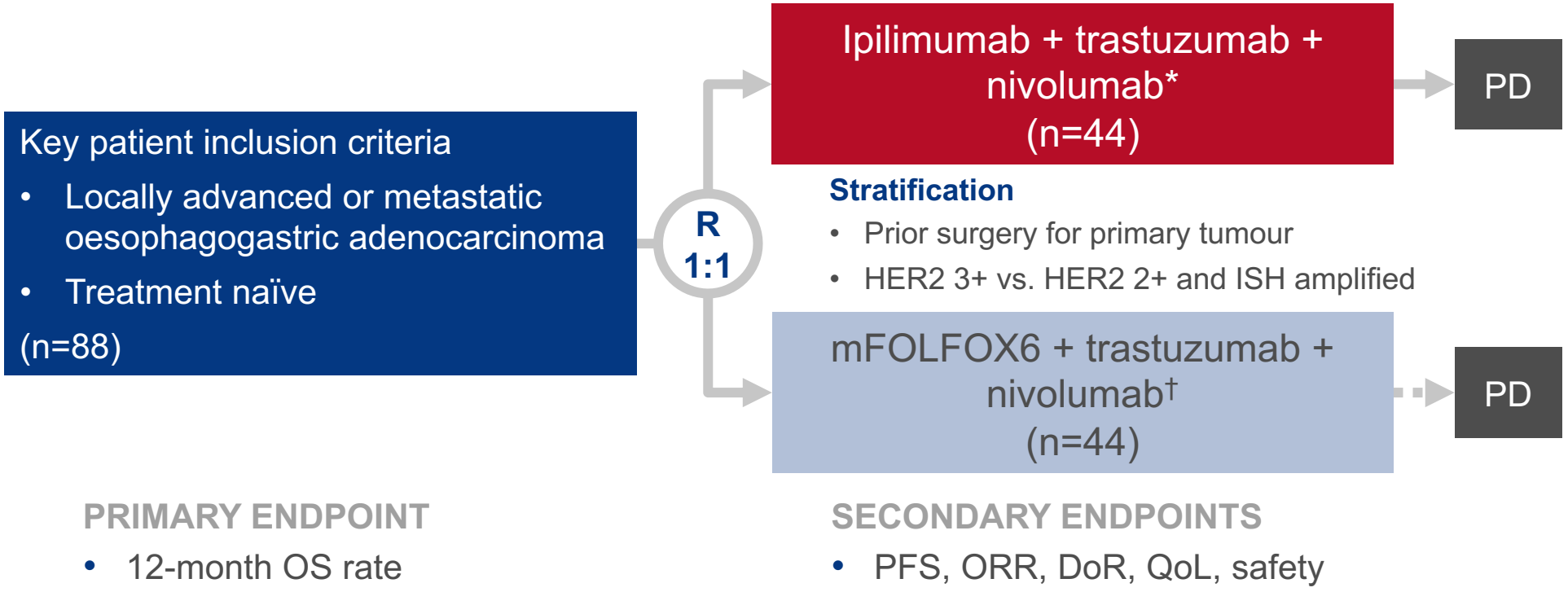
*Not evaluable, there was insufficient number of viable tumour cells (<100) present for PD-L1 testing

Janjigian Y, et al. Ann Oncol 2022;33(suppl):abstr SO-7

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



PRIMARY ENDPOINT

- 12-month OS rate

SECONDARY ENDPOINTS

- PFS, ORR, DoR, QoL, safety

*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/m^2 + 5FU 400 mg/m^2 iv bolus + folinic acid 400 mg/m^2 + 5FU 2400 mg/m^2 46 h iv + trastuzumab 4 mg/kg (loading dose 6 mg/kg) + nivolumab 240 mg q2w

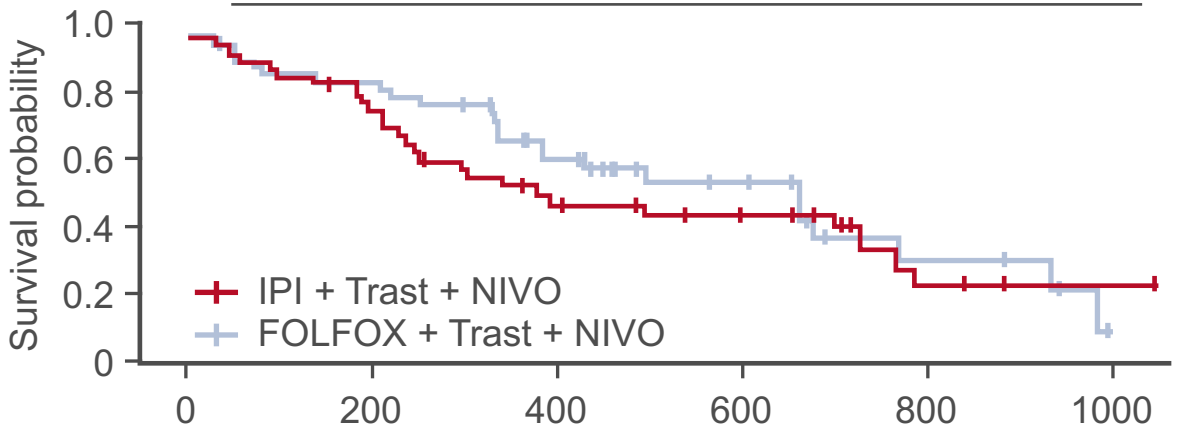
Stein A, et al. Ann Oncol 2021;32(suppl):abstr LBA54

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

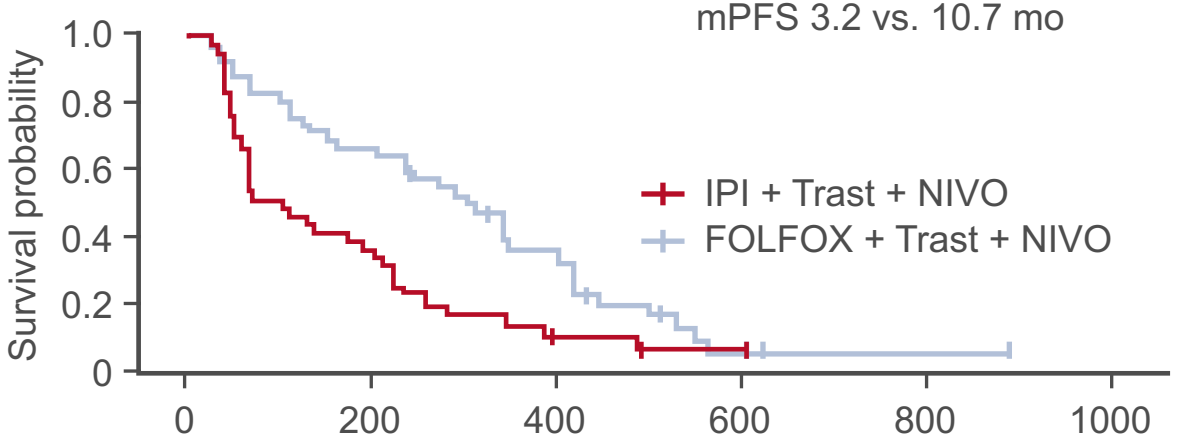
Overall survival

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



No. at risk						
IPI + Trast + NIVO	44	33	19	14	5	1
FOLFOX + Trast + NIVO	44	38	24	13	6	1

Progression free survival



IPI + Trast + NIVO	42	13	3	1	0	
FOLFOX + Trast + NIVO	43	29	12	2	1	0

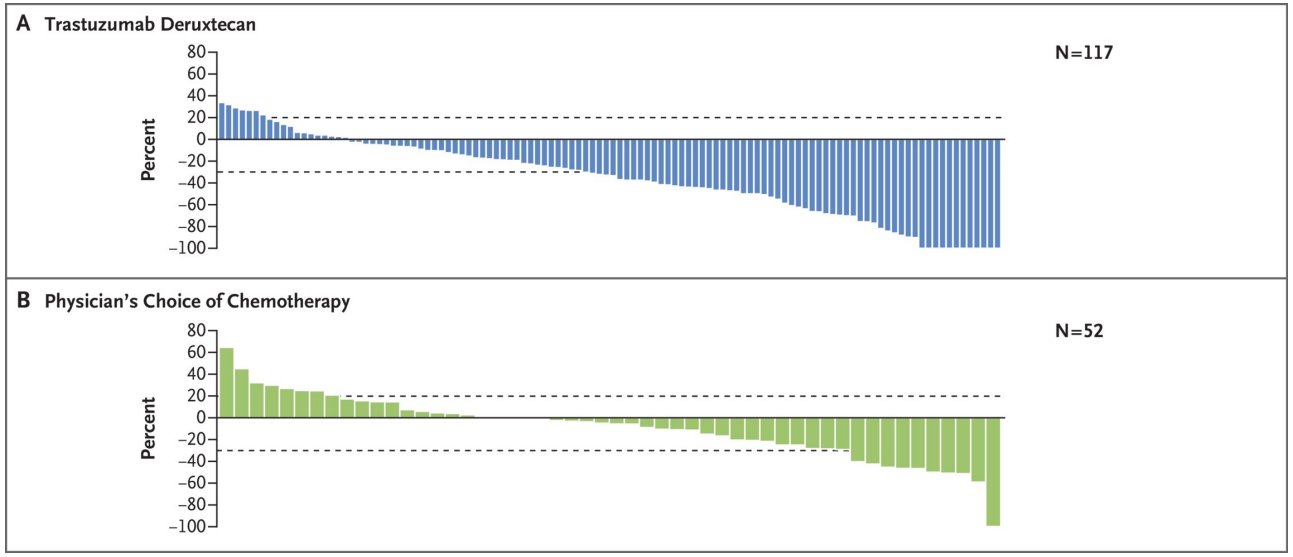
Stein A, et al. Ann Oncol 2021;32(suppl):abstr LBA54

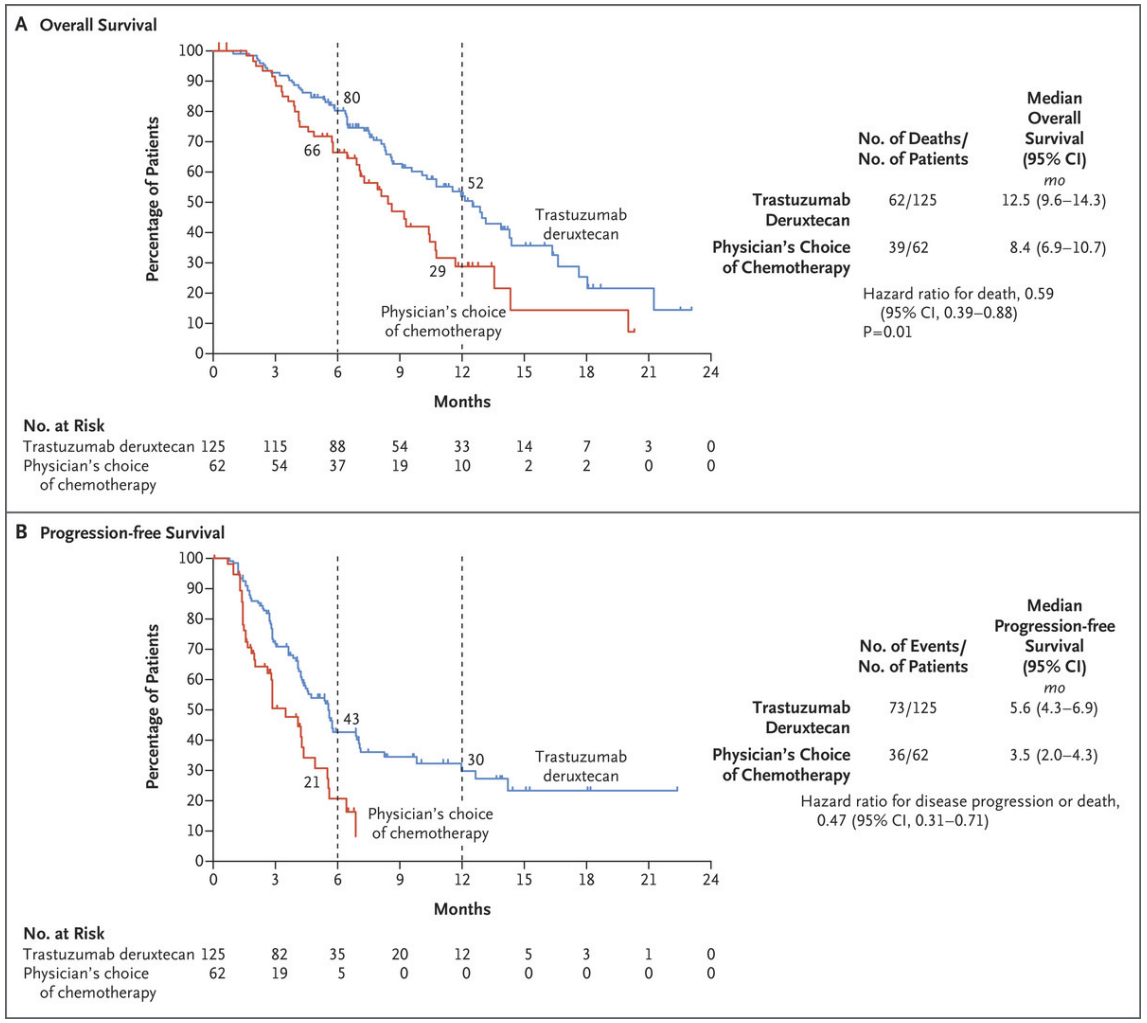
Simplified First-line Treatment Algorithm for Advanced Gastroesophageal Adenocarcinomas

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

Janjigian. Nature. 2021;600:727. Janjigian. Lancet. 2021;398:27. Sun. Lancet. 2021;398:759.

Overall Survival and Progression-free Survival.



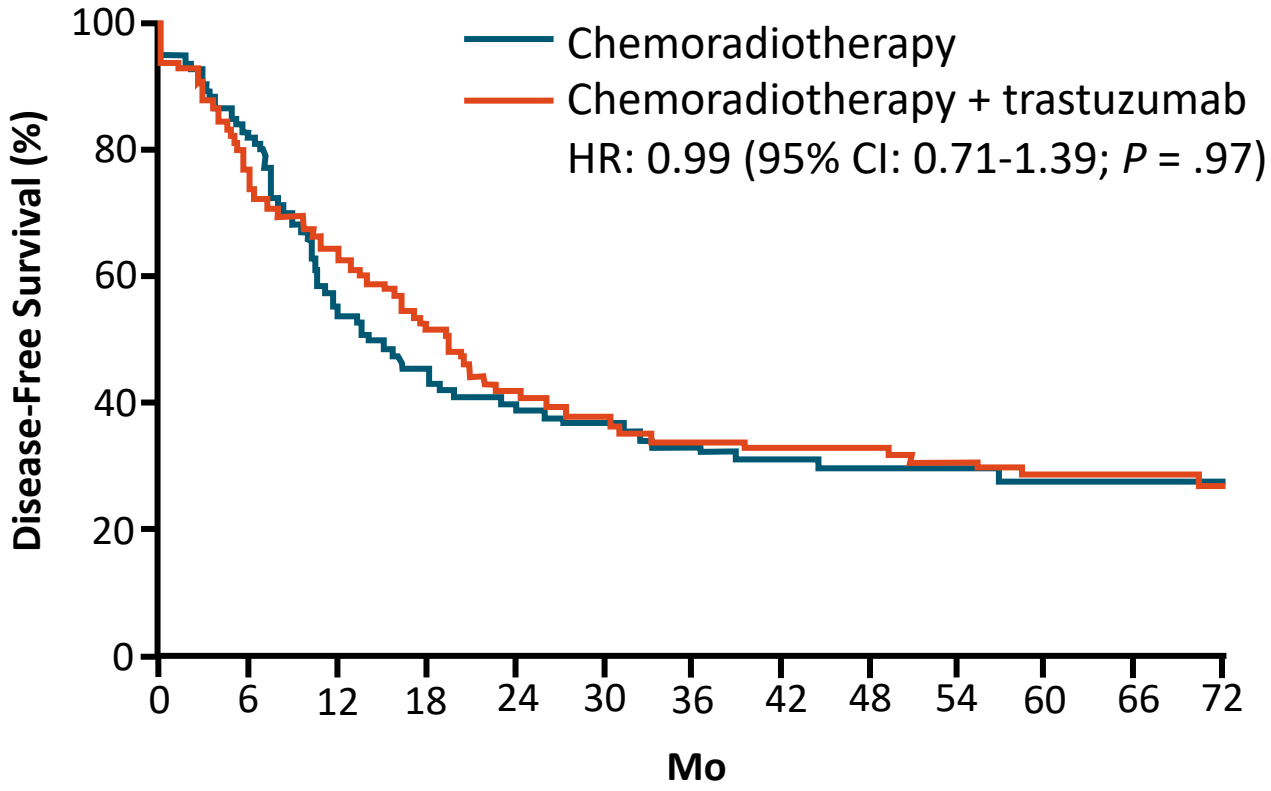


K Shitara et al. N Engl J Med 2020;382:2419-2430.

The NEW ENGLAND JOURNAL of MEDICINE

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)



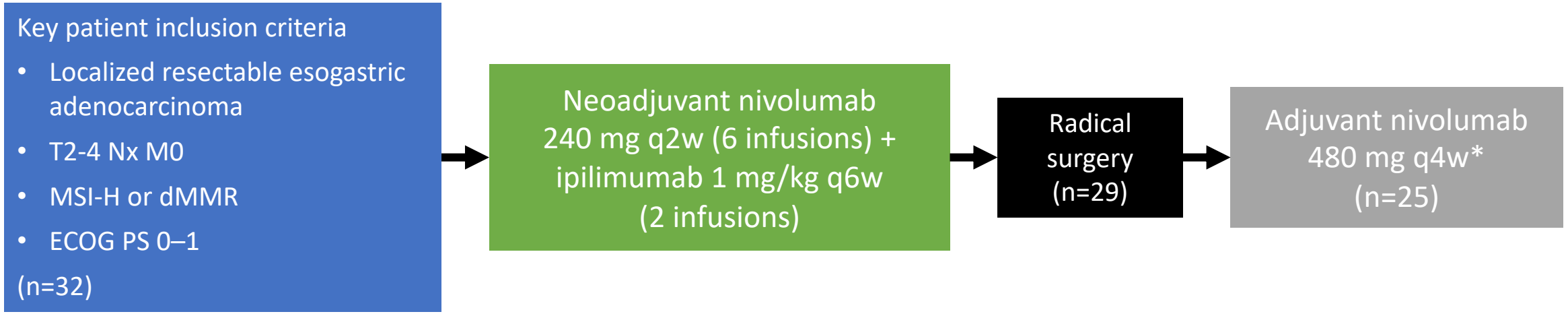
Safran. Lancet Oncol. 2022;23:259.

Slide credit: clinicaloptions.com

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

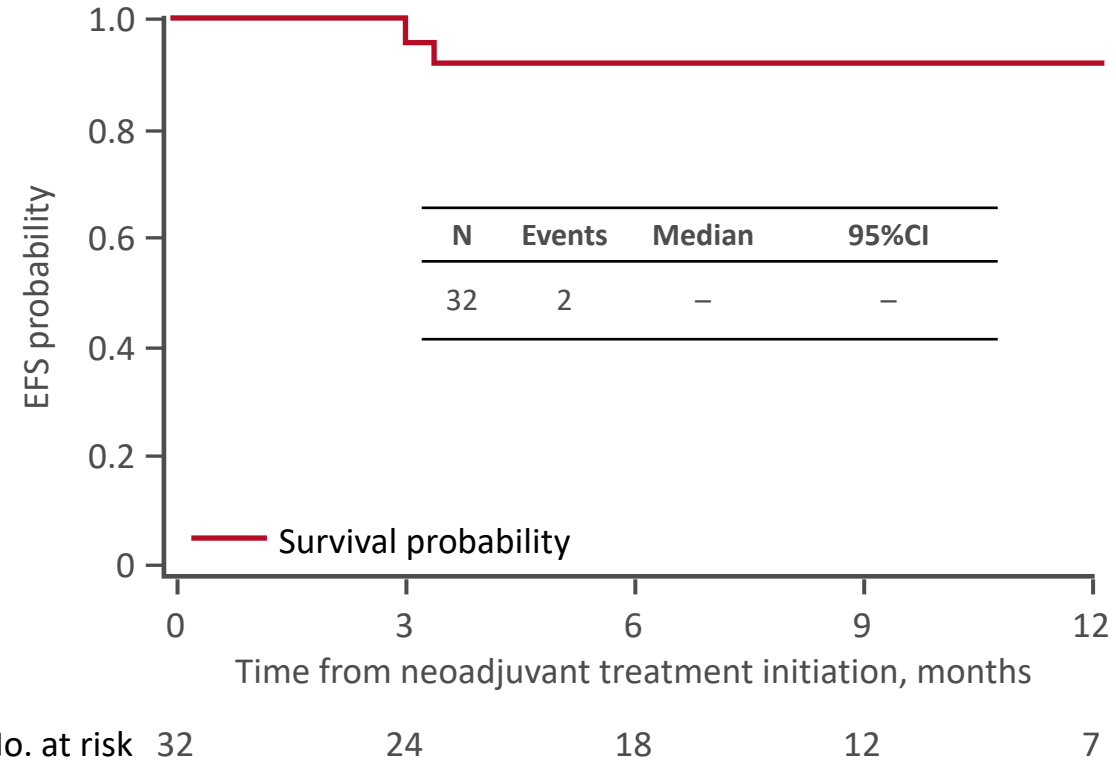
André T, et al. J Clin Oncol 2022;40(suppl):abstr 244

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

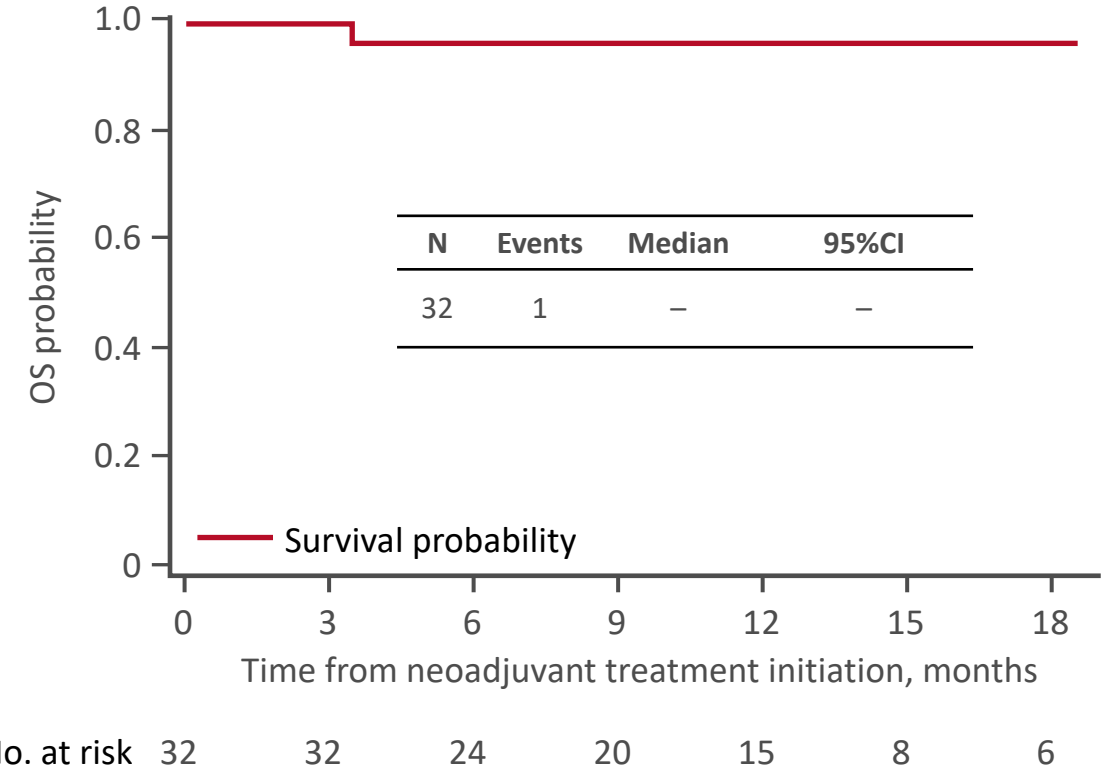
Key results

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

Event-free survival

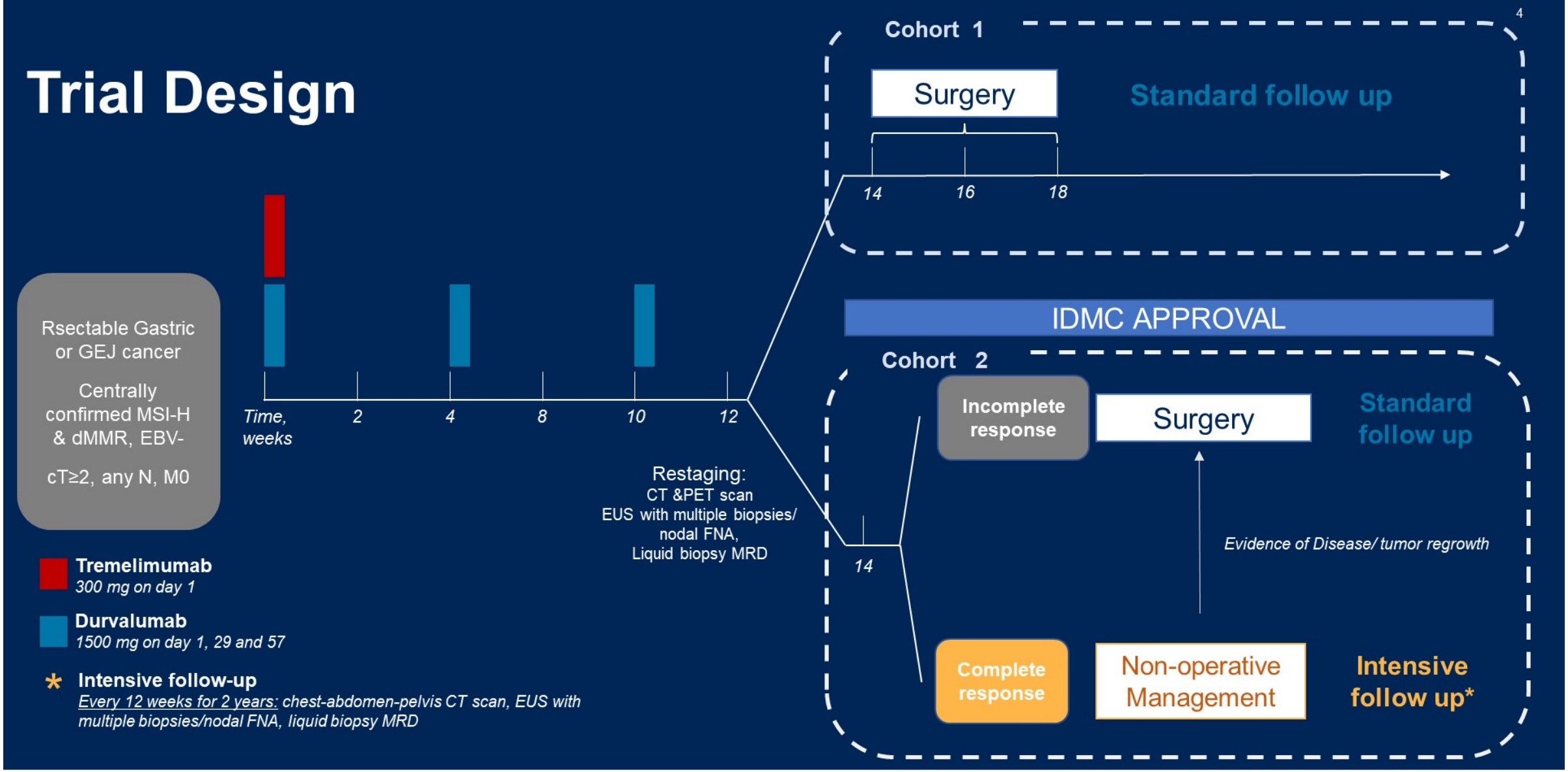


Overall survival



André T, et al. J Clin Oncol 2022;40(suppl):abstr 244

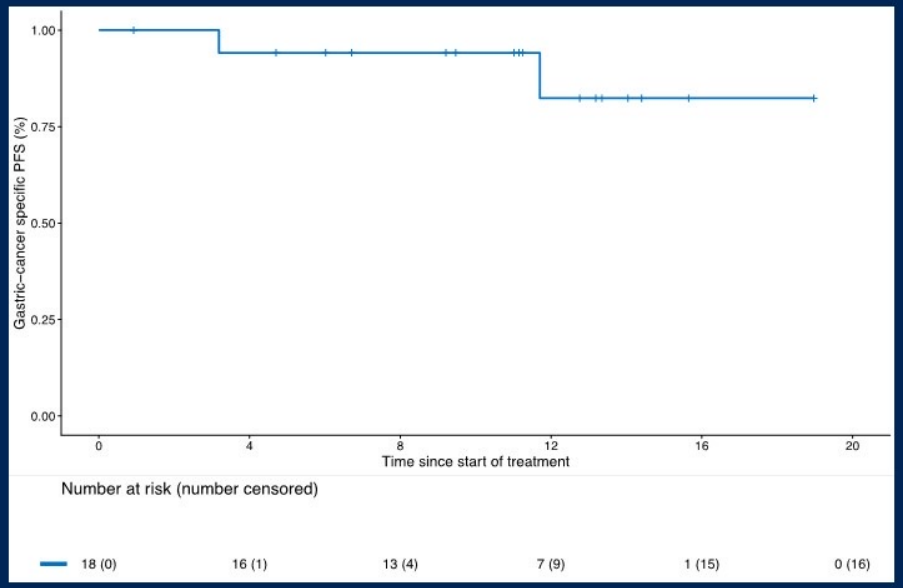
Trial Design



Survival endpoints

	PFS event	OS event	
01-020	Yes	No	CR to CAPOX
04-005	Yes	Yes	Heterogeneous pMMR/dMMR status
13-002	No	Yes	Late postoperative complications
01-009	No	Yes	Late postoperative complications
05-001	No	Yes	Second primary brain cancer

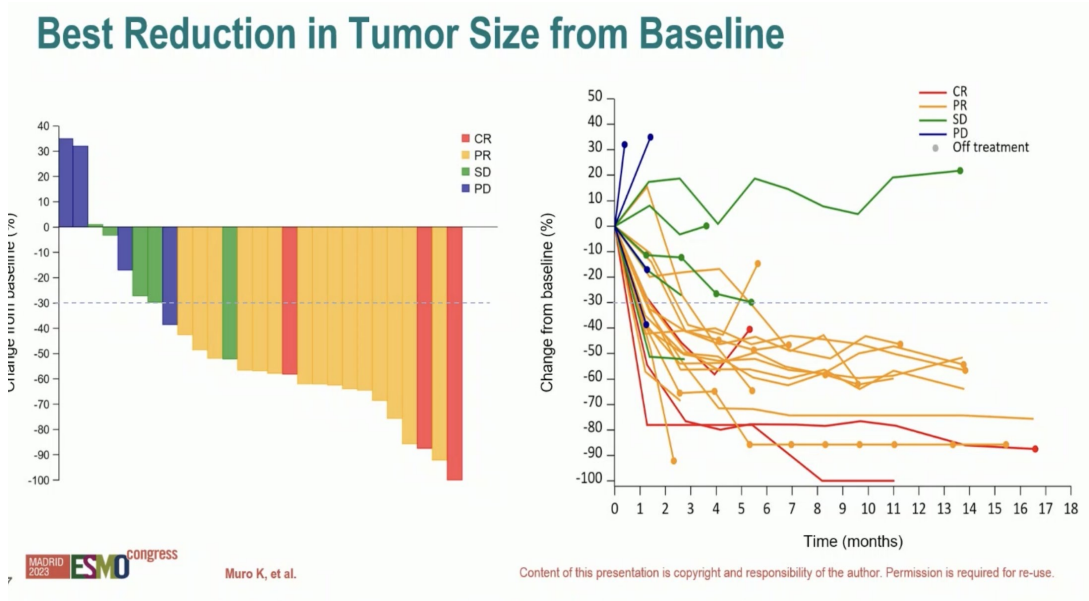
Gastric cancer-specific PFS



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

NO LIMIT

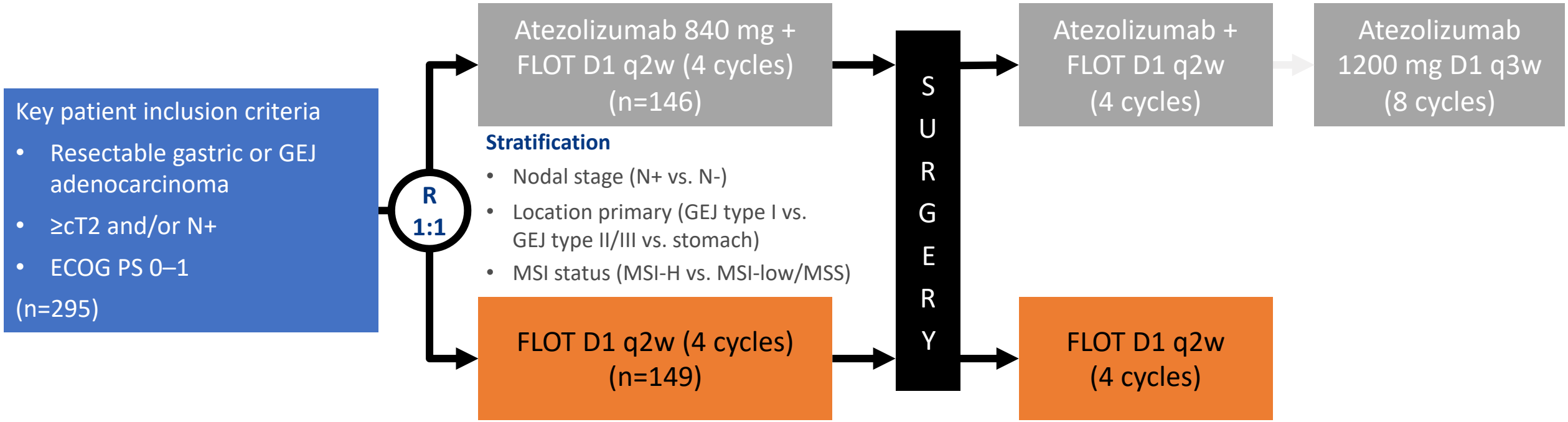
- Nivolumab + low dose ipilimumab as first-line therapy in G/GEJ MSI-H tumor #ESMO23
- ✅1st results of the NO LIMIT phs-II
- 👉935 pts screened, 28 pts included, m age 75yrs
- 👉ORR 62.1%, DCR 79.3%
- 👉mPFS 13.8, mDOR & OS n.r.
- 🧐convincing efficacy, no new safety signal



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)



PRIMARY ENDPOINTS

- PFS, DFS

SECONDARY ENDPOINTS

- Surgical outcomes, OS, safety

FLOT, docetaxel 50 mg/m^2 + oxaliplatin 85 mg/m^2 + leucovorin 200 mg/m^2 + 5FU 2600 mg/m^2 D1 IV

Al-Batran S-E, et al. J Clin Oncol 2022;40(suppl):abstr 4003

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

Al-Batran S-E, et al. J Clin Oncol 2022;40(suppl):abstr 4003

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

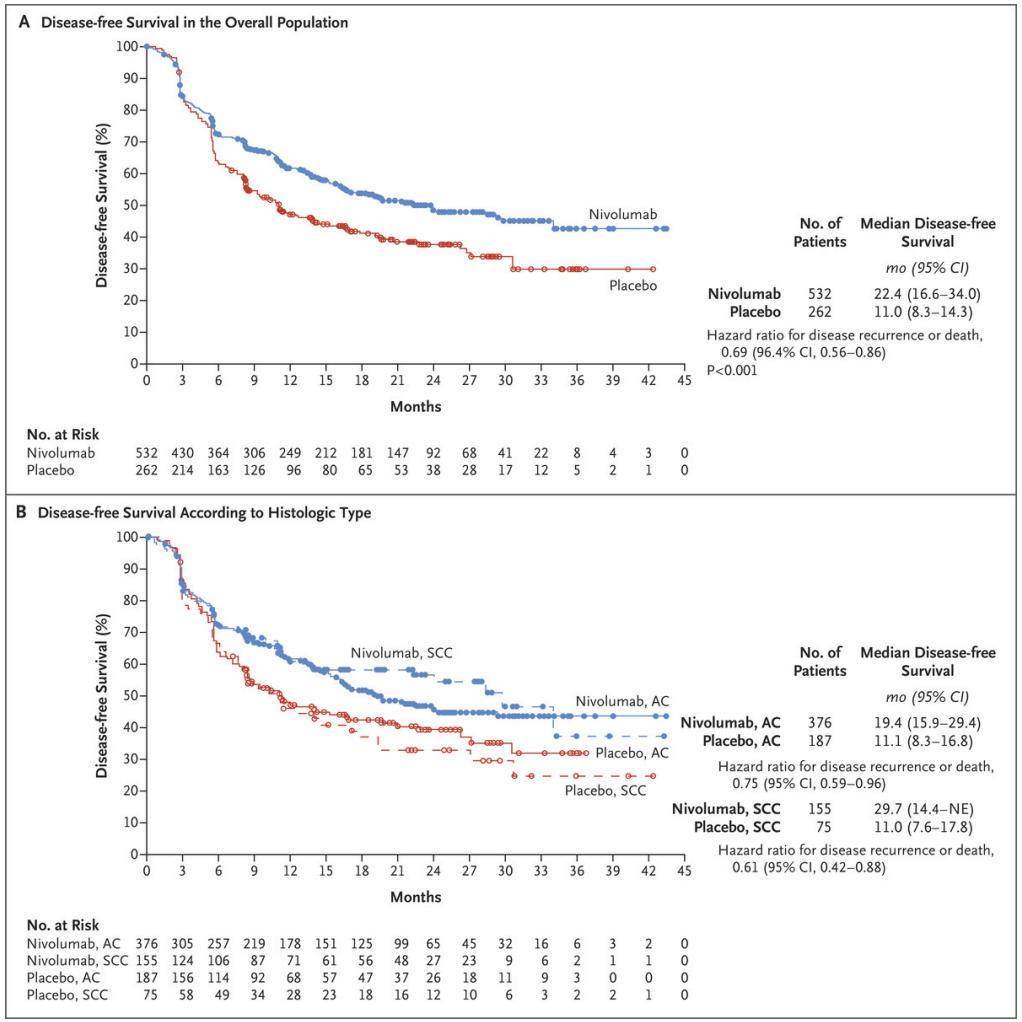


Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Nivolumab (N = 532)	Placebo (N = 262)
Median age (range) — yr	62 (26–82)	61 (26–86)
Male sex — no. (%)	449 (84)	222 (85)
Race — no. (%)†		
White	432 (81)	216 (82)
Asian	83 (16)	34 (13)
Black	7 (1)	2 (<1)
Other	10 (2)	9 (3)
Not reported	0	1 (<1)
Geographic region — no. (%)		
Europe	202 (38)	101 (39)
United States or Canada	167 (31)	88 (34)
Asia	77 (14)	29 (11)
Rest of the world‡	86 (16)	44 (17)
ECOG performance-status score — no. (%)§		
0	308 (58)	156 (60)
1	224 (42)	106 (40)
Disease stage at initial diagnosis — no. (%)		
II	179 (34)	99 (38)
III	351 (66)	163 (62)
Not reported	2 (<1)	0
Tumor location at trial entry — no. (%)		
Esophagus	311 (58)	151 (58)
Gastroesophageal junction	221 (42)	111 (42)
Histologic type — no. (%)¶		
Adenocarcinoma	376 (71)	187 (71)
Squamous-cell carcinoma	155 (29)	75 (29)
Other	1 (<1)	0
Tumor-cell PD-L1 expression at trial entry — no. (%)‖		
<1%	374 (70)	196 (75)
≥1%	89 (17)	40 (15)
Indeterminate or could not be evaluated	69 (13)	26 (10)
Pathological lymph-node status at trial entry — no. (%)**		
≥ypN1	305 (57)	152 (58)
ypN0	227 (43)	109 (42)
Not known	0	1 (<1)
Pathological tumor status at trial entry — no. (%)**		
ypT0	31 (6)	16 (6)
ypT1 or ypT2	202 (38)	106 (40)
ypT3 or ypT4	296 (56)	140 (53)
Not known	3 (<1)	0

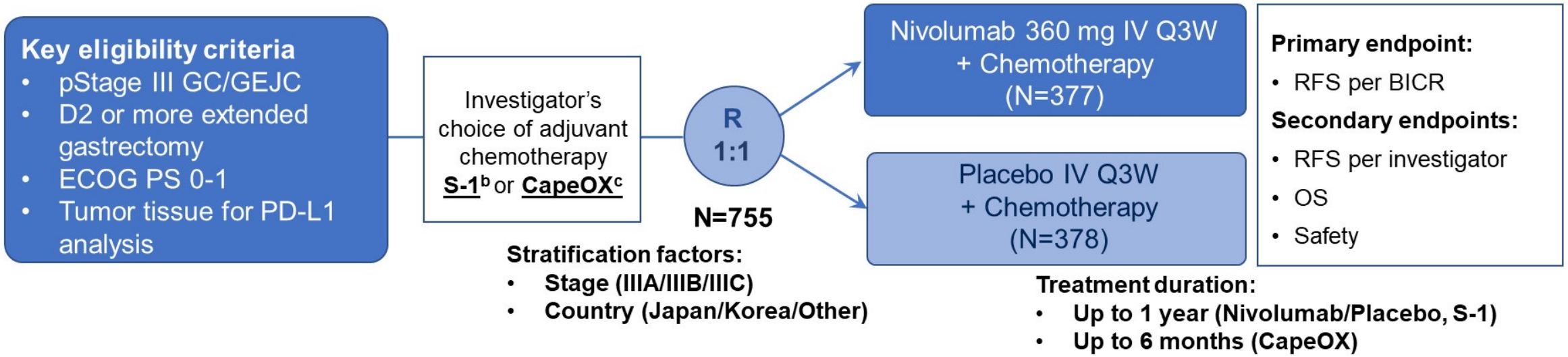
* Percentages may not total 100 because of rounding. ECOG denotes Eastern Cooperative Oncology Group, and PD-L1 programmed death ligand 1.
† Race was reported by the patients.
‡ The "rest of the world" category comprised Argentina, Australia, Brazil, Israel, Mexico, and Turkey.
§ ECOG performance-status scores range from 0 to 5, with higher scores indicating greater disability.
¶ One patient in the nivolumab group had a histologic type of "other" (protocol deviation).
‖ In most patients, tumor-cell PD-L1 expression was determined with the use of the PD-L1 IHC 28-8 pharmDX assay (Dako, Agilent Technologies) from a tumor tissue specimen obtained from the patient after completion of chemoradiotherapy. However, tumor tissue from 40 patients was quantifiable only before chemoradiotherapy.
** Pathological lymph-node status and tumor status are classified according to the criteria of the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer.

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

The NEW ENGLAND JOURNAL of MEDICINE

Study design

- Phase 3, double-blind, placebo-controlled study of Asian patients (Japan, Korea, Taiwan, China)[a]

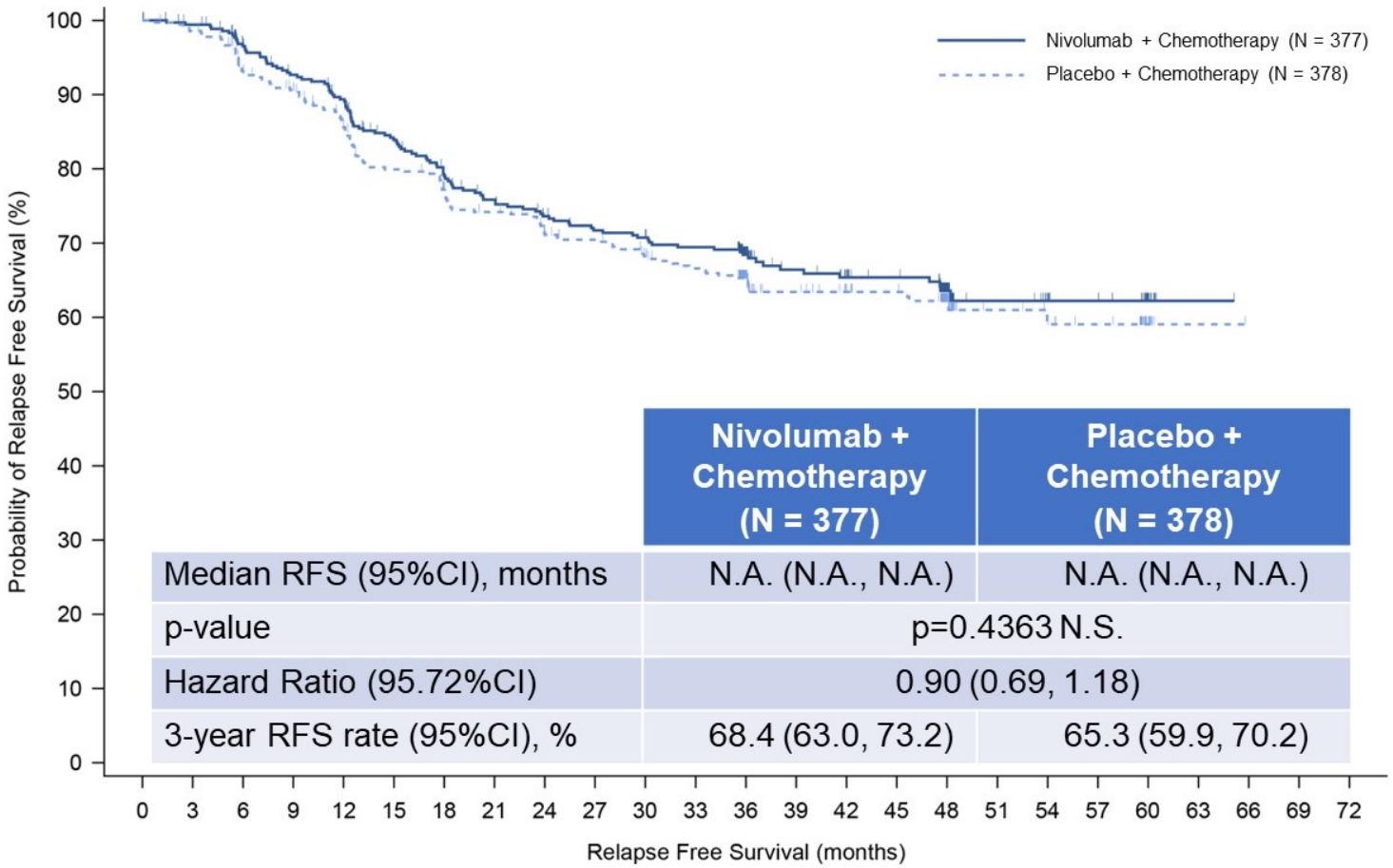


- Planned sample size: 700 patients (assuming HR=0.67; 3-year RFS, 71% vs 60%)
- Patients were randomized from February 2017 to August 2019
- All data are based on a clinical data cutoff of August 2022, at which point the minimum follow-up after the last patient randomized was 36 months

[a]ClinicalTrials.gov number, NCT03006705; [b]**S-1 therapy:** S-1 40 mg/m^2/dose orally twice daily (day1-28) , Q6W; [c]**CapeOX therapy:** Oxaliplatin 130 mg/m^2 IV once daily (day1), and Capecitabine 1000 mg/m^2/dose orally twice daily (day1-14), Q3W.

Abbreviations: BICR, blinded independent central review; CapeOX, capecitabine/oxaliplatin; GC, gastric cancer; GEJC, gastroesophageal junction cancer; IV, intravenous; OS, overall survival; pStage III, pathological stage III; Q3W, every 3 weeks; Q6W, every 6 weeks; RFS, relapse-free survival; S-1, tegafur/gimeracil/oteracil.

Primary endpoint: RFS per BICR



	Nivolumab + Chemotherapy (N = 377)	Placebo + Chemotherapy (N = 378)
Median RFS (95%CI), months	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)
p-value	p=0.4363 N.S.	
Hazard Ratio (95.72%CI)	0.90 (0.69, 1.18)	
3-year RFS rate (95%CI), %	68.4 (63.0, 73.2)	65.3 (59.9, 70.2)

At Risk

Nivolumab + Chemotherapy	377	349	326	310	297	273	255	241	231	223	219	214	162	127	120	114	58	33	28	24	9	1	0	0	0
Placebo + Chemotherapy	378	353	324	311	288	267	254	242	228	223	212	204	148	118	110	107	57	33	30	26	10	1	0	0	0

Methods

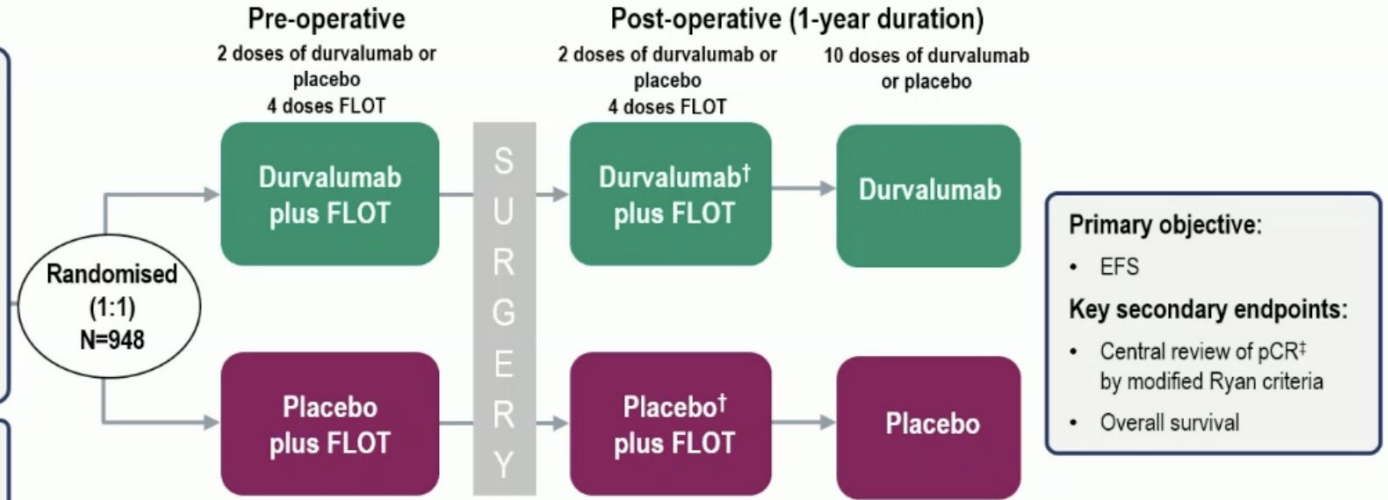
MATTERHORN is a global, Phase 3, randomised, double-blind, placebo-controlled study

Study population

- Gastric and GEJ adenocarcinoma
- Stage II, III and IVA (>T2 N0-3 M0 or T0-4 N+ M0)
- No evidence of metastasis
- No prior therapy
- ECOG PS 0 or 1
- Global enrolment from Asia, Europe, North America and South America

Stratification factors

- Geographic region: Asia versus non-Asia
- Clinical lymph node status: positive versus negative
- PD-L1 status: TAP <1% versus TAP ≥1%*



Primary objective:

- EFS

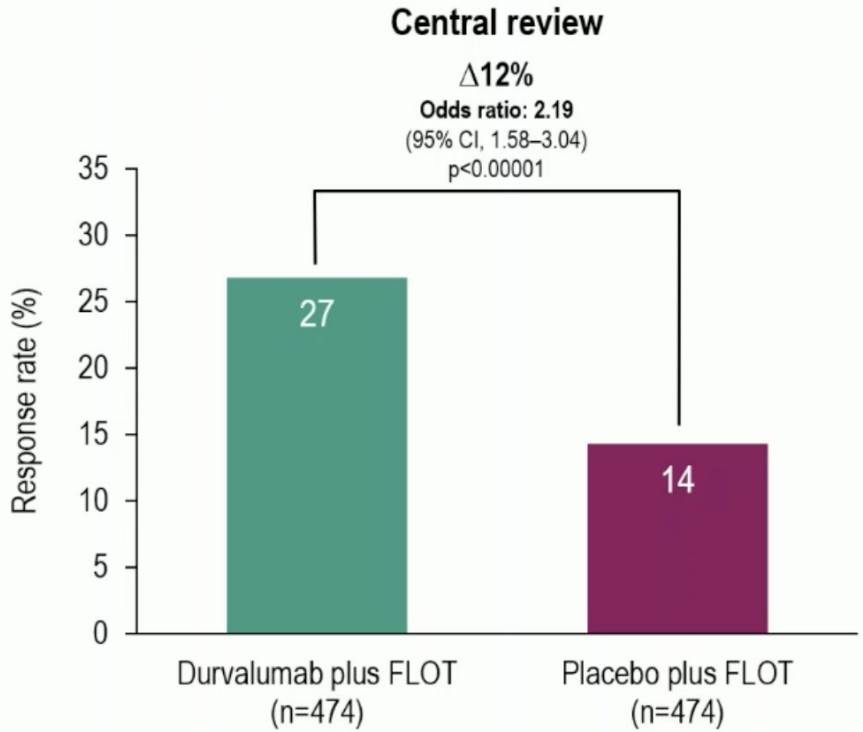
Key secondary endpoints:

- Central review of pCR‡ by modified Ryan criteria
- Overall survival

Durvalumab 1500 mg or placebo Q4W (Day 1) plus FLOT Q2W (Days 1 and 15) for 4 cycles (2 doses of durvalumab or placebo plus 4 doses of FLOT pre- and post-operative) followed by durvalumab or placebo Q4W (Day 1) for 10 further cycles

*Measured by VENTANA PD-L1 (SP263) assay. †Durvalumab or placebo monotherapy may be continued if post-operative FLOT is discontinued due to toxicity. ‡pCR was scored using modified Ryan criteria by central review.
FLOT: 5-fluorouracil 2600 mg/m^2, oxaliplatin 85 mg/m^2, docetaxel 50 mg/m^2, leucovorin 200 mg/m^2 on Days 1 and 15 Q4W, 2 doses (two cycles) pre- and post-operative; durvalumab: 1500 mg on Day 1 Q4W, 2 doses (two cycles) of durvalumab or placebo pre- and post-operative.
ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; GEJ, gastro-oesophageal junction; PD-L1, programmed cell death-ligand 1; PS, performance status; pCR, pathological complete response; PD-L1, programmed cell death ligand-1; Q2W, every 2 weeks; Q4W, every 4 weeks; TAP, tumour area positivity.

Combined complete and near-complete pathological response



Near-complete pathological response = single or rare small groups of cancer cells at time of resection per modified Ryan criteria

Participants achieve pCR if there is no residual viable tumour cells found at primary tumour and resected lymph nodes at the time of resection, meaning a pathological regression of -100%, based on central (or local) assessment. Central review of pCR was scored using modified Ryan criteria.
CI, confidence interval; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; pCR, pathological complete response.

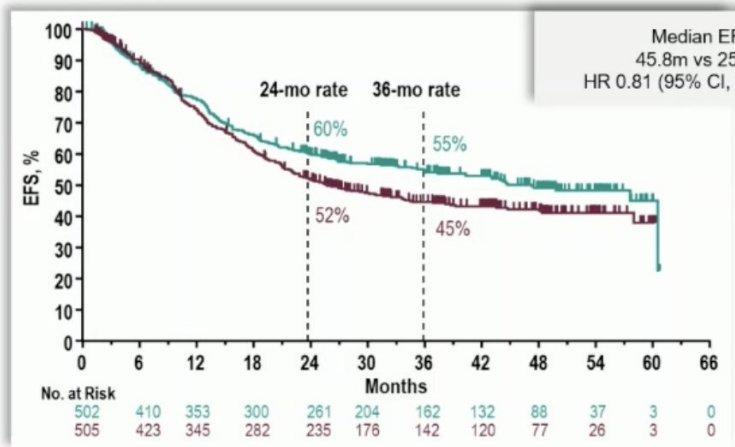
Pathological response subgroup analysis (central review)

	Durvalumab plus FLOT, N	Placebo plus FLOT, N	Pathological complete response Odds ratio (95% CI)	Combined complete and near-complete pathological response Odds ratio (95% CI)
All participants	474	474	3.08 (2.03–4.67)	2.19 (1.58–3.04)
Sex				
Male	326	356	3.35 (2.07–5.41)	2.22 (1.54–3.22)
Female	148	118	2.53 (1.09–5.89)	2.47 (1.18–5.18)
Age group				
<65 years	291	265	2.71 (1.53–4.79)	2.16 (1.39–3.37)
≥65 years	183	209	3.70 (2.01–6.84)	2.29 (1.41–3.73)
Location at screening				
GC	324	316	2.56 (1.50–4.38)	1.69 (1.12–2.55)
GEJC	150	158	4.20 (2.14–8.21)	3.50 (2.01–6.07)
TNM classification				
T4	117	117	2.81 (1.18–6.67)	2.14 (1.07–4.26)
Non-T4	357	357	3.16 (1.96–5.09)	2.20 (1.52–3.19)
Clinical lymph node status				
Positive	334	333	3.23 (1.97–5.30)	2.14 (1.45–3.18)
Negative	137	140	2.62 (1.20–5.74)	2.26 (1.25–4.08)
PD-L1 expression at baseline				
<1%	48	47	0.98 (0.19–5.11)	1.94 (0.60–6.29)
≥1%	426	427	3.33 (2.15–5.13)	2.21 (1.57–3.11)
<5%	236	230	2.25 (1.11–4.57)	2.30 (1.35–3.92)
≥5%	238	244	3.79 (2.25–6.39)	2.20 (1.44–3.35)
Region				
Asia	90	90	3.96 (1.39–11.26)	2.41 (1.14–5.06)
Non-Asia	384	384	2.92 (1.85–4.61)	2.13 (1.48–3.07)
Country				
Germany	47	70	2.88 (1.13–7.35)	2.72 (1.21–6.12)
Non-Germany	427	404	3.34 (2.08–5.36)	2.21 (1.54–3.18)

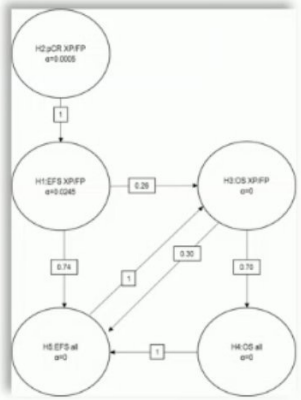
Participants achieve pCR if there is no residual viable tumour cells found at primary tumour and resected lymph nodes at the time of resection, meaning a pathological regression of -100%, based on central (or local) assessment. Central review of pCR was scored using modified Ryan criteria.
CI, confidence interval; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; pCR, pathological complete response; PD-L1, programmed cell death ligand-1.

KEYNOTE 585 event free survival

Improved pCR fails to translate into better EFS for most patients



Median EFS
45.8m vs 25.7m
HR 0.81 (95% CI, 0.68-0.97)

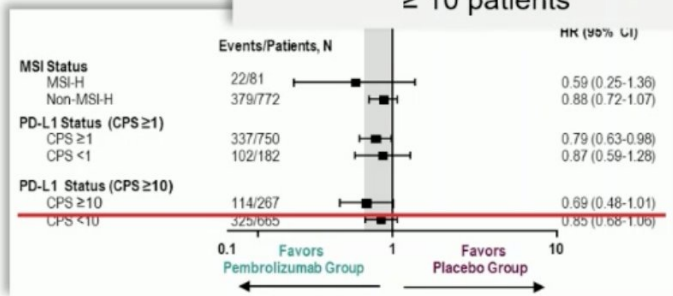


Statistical failure
α loss & multiplicity

20 month ↑ in EFS could be clinically meaningful
But….

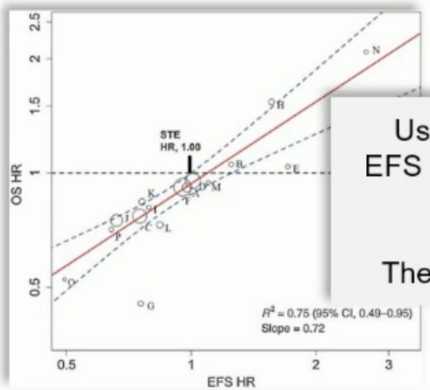
1) Comparing to inferior baseline than standard of care
2) Driven by PD-L1 positive/high subgroup
3) Has a "head-start" because of 9 months extra adjuvant treatment

Chemo+PD-1 ↑↑EFS in PD-L1 CPS ≥ 10 patients



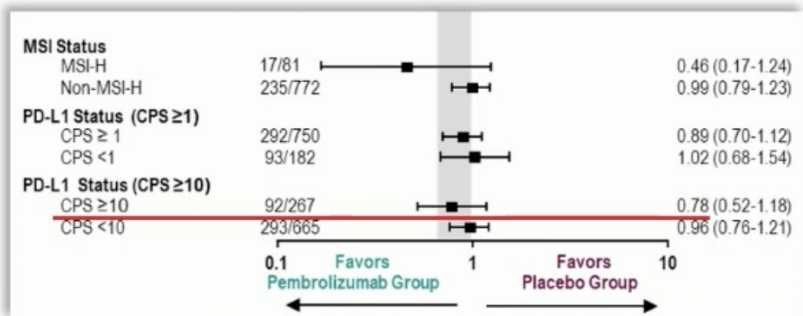
KEYNOTE 585 overall survival

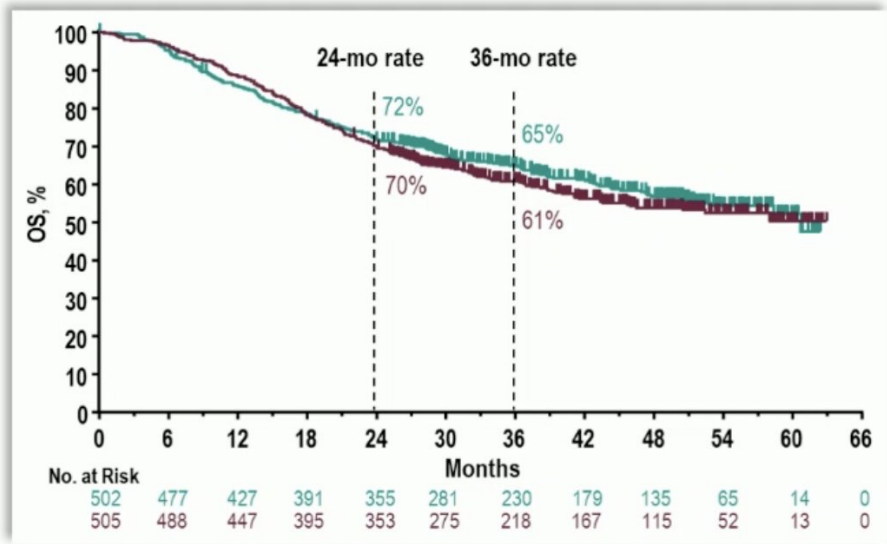
No overall survival benefit for adding pembrolizumab to perioperative chemotherapy



Usually, fair agreement
EFS vs OS in 16 UGI RCTs
r^2=0.76

These were **chemo** trials





Unlikely any benefit in MSS, CPS <10

No increase in cure for most patients

MADRID 2023 ESMO congress

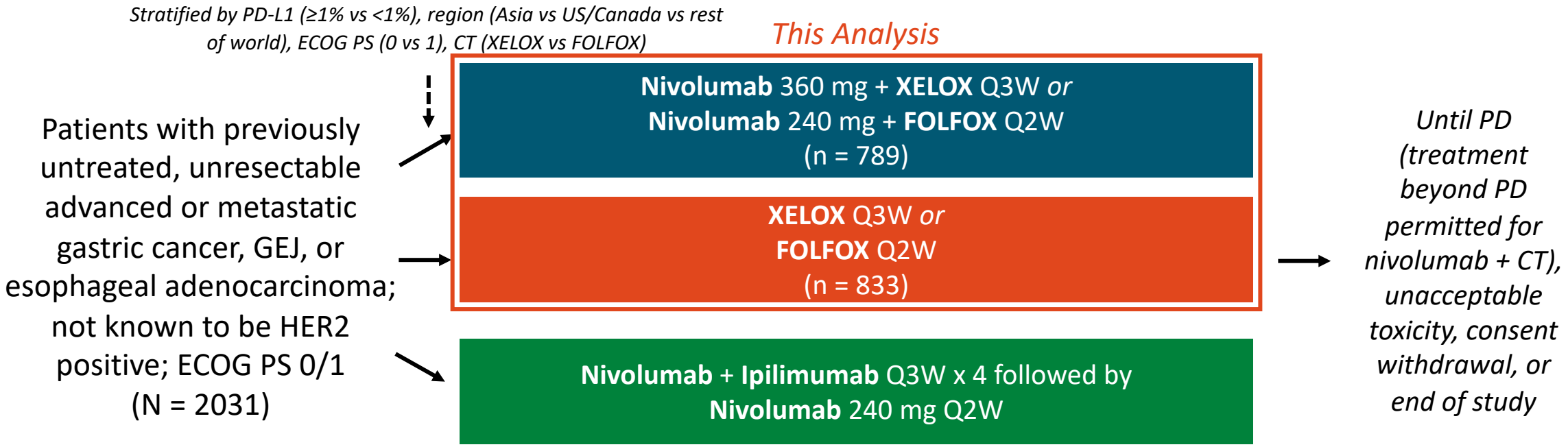
Elizabeth Smyth MD

Wainberg et al, *CCR*, 2023

- Triplet Vs. Doublet
- Duration of the therapy
- Population (Asian vs Global)
- Antibody

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

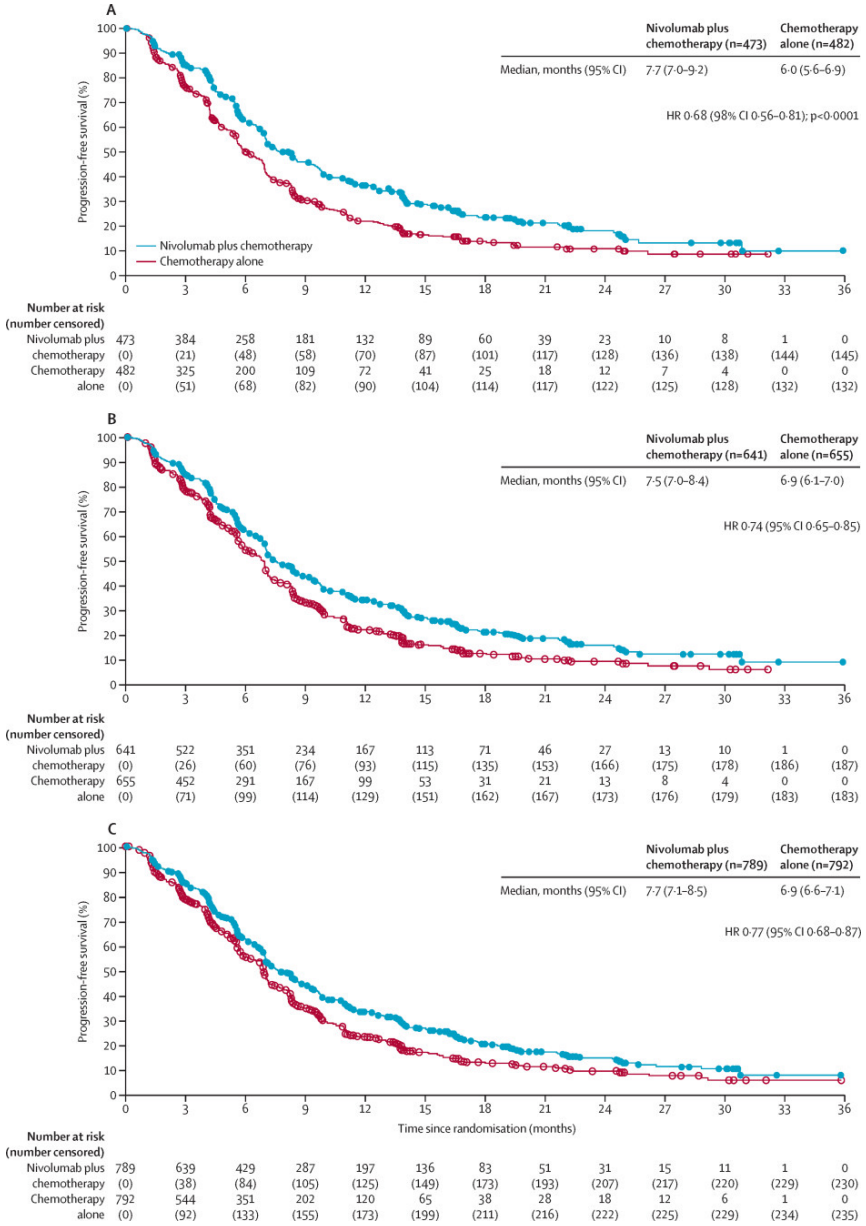
- International, randomized, open-label phase III trial



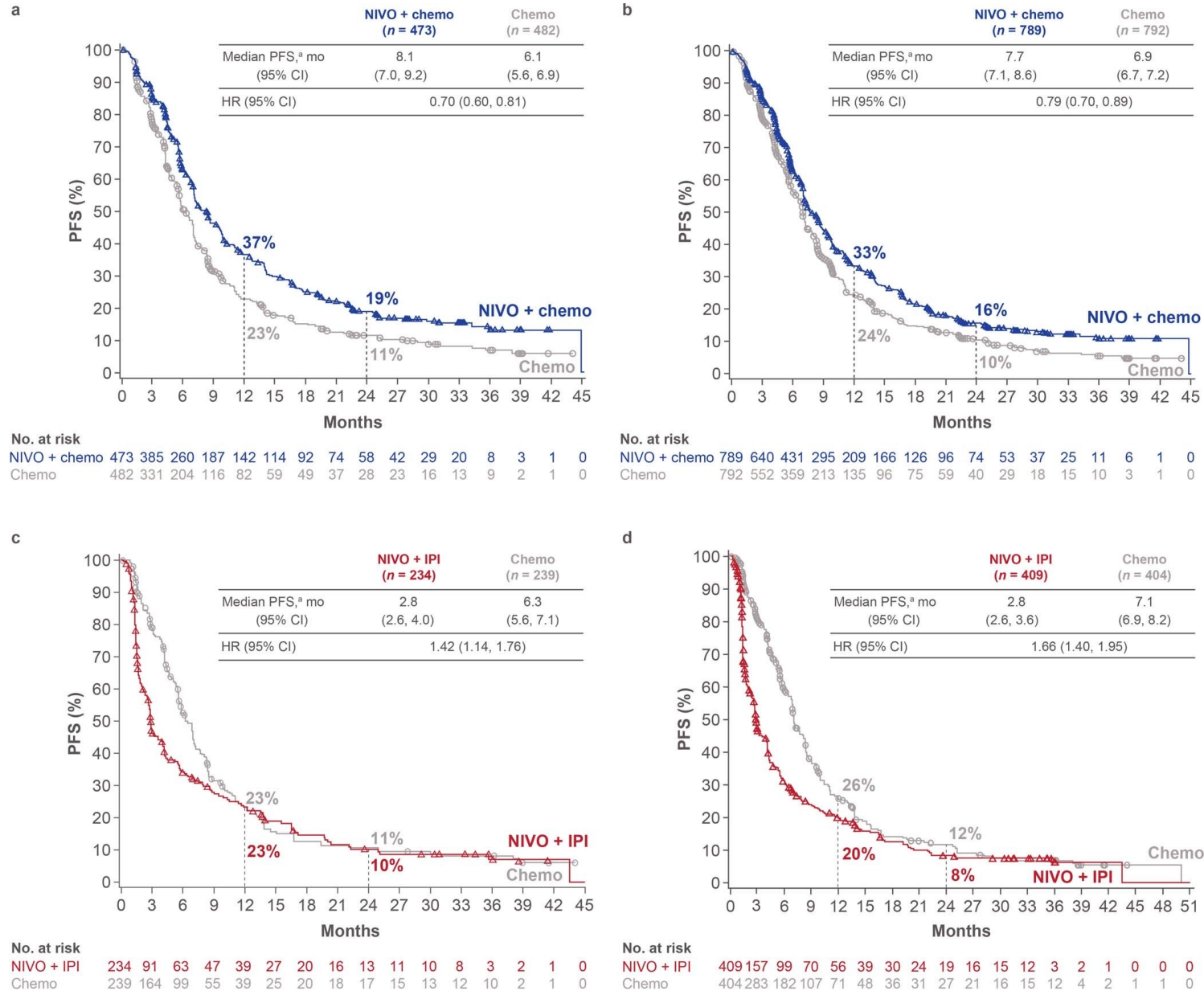
- **Coprimary endpoints:** OS and PFS in patients with PD-L1 CPS ≥5
- **Secondary endpoints:** OS and PFS in all randomized patients and patients with PD-L1 CPS ≥10 and ≥1, BICR-assessed ORR

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

Janjigian. Lancet. 2021;398:27. Shitara. ASCO GI 2022. Abstr 240.

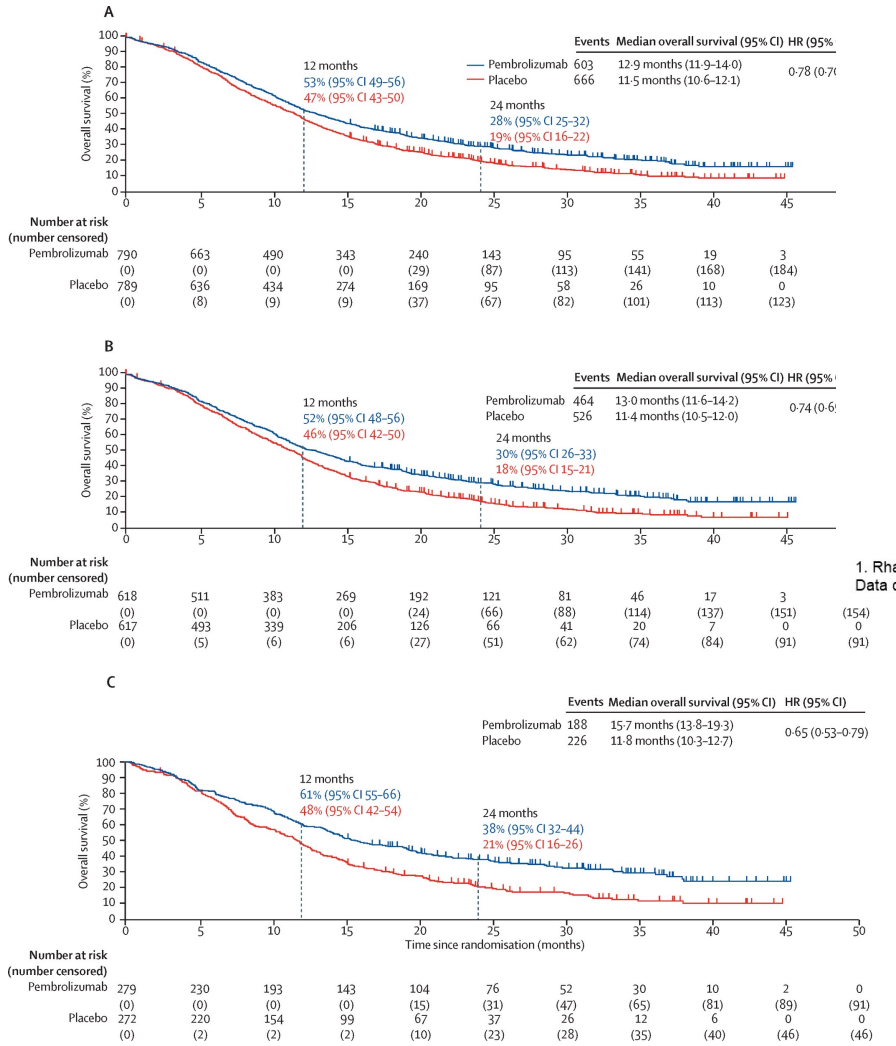


Janjigian. Lancet. 2021;398:27



Janjigian. *Nature* **volume 603**, pages942–948 (2022)

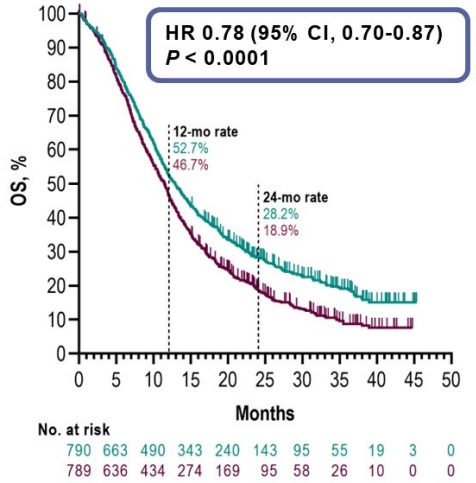
Keynote 859



Primary Endpoint: OS

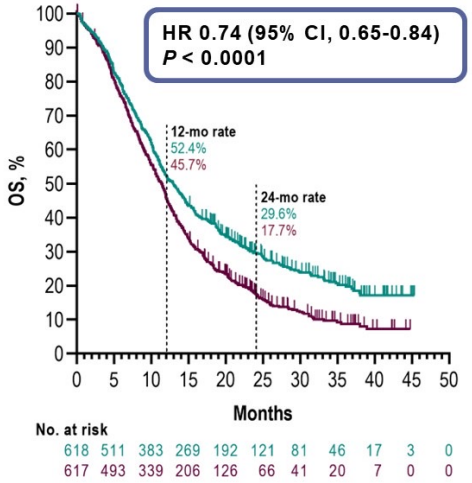
Overall[1]

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



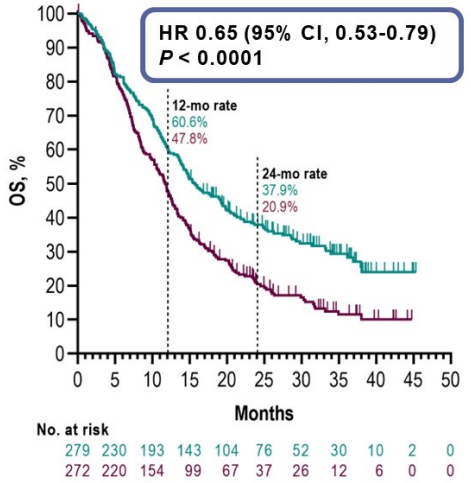
PD-L1 CPS ≥1

	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	75.1%	13.0 (11.6-14.2)
Placebo + chemo	85.3%	11.4 (10.5-12.0)



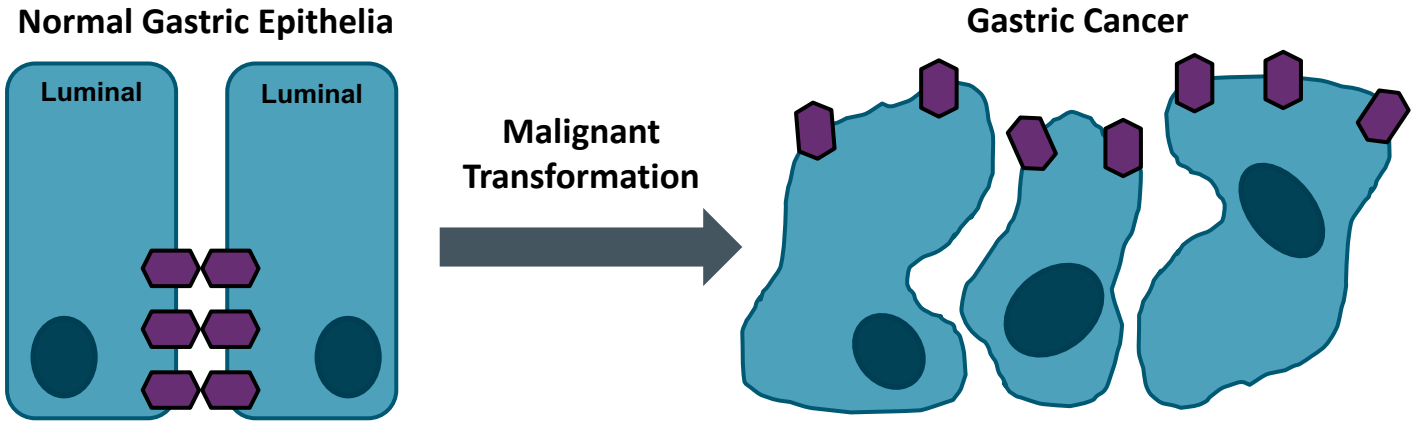
PD-L1 CPS ≥10

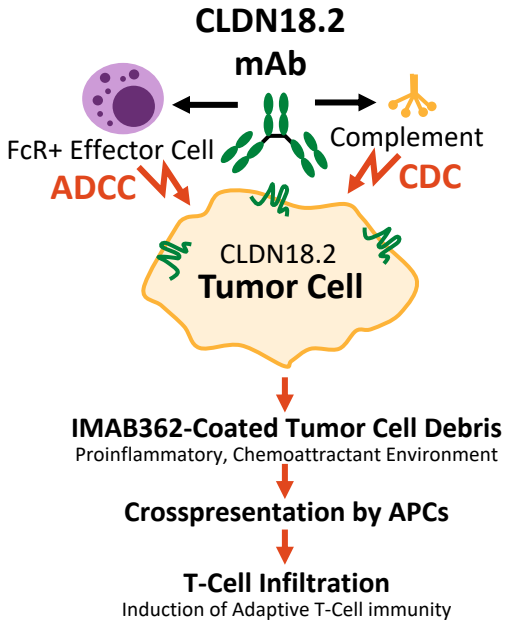
	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	67.4%	15.7 (13.8-19.3)
Placebo + chemo	83.1%	11.8 (10.3-12.7)

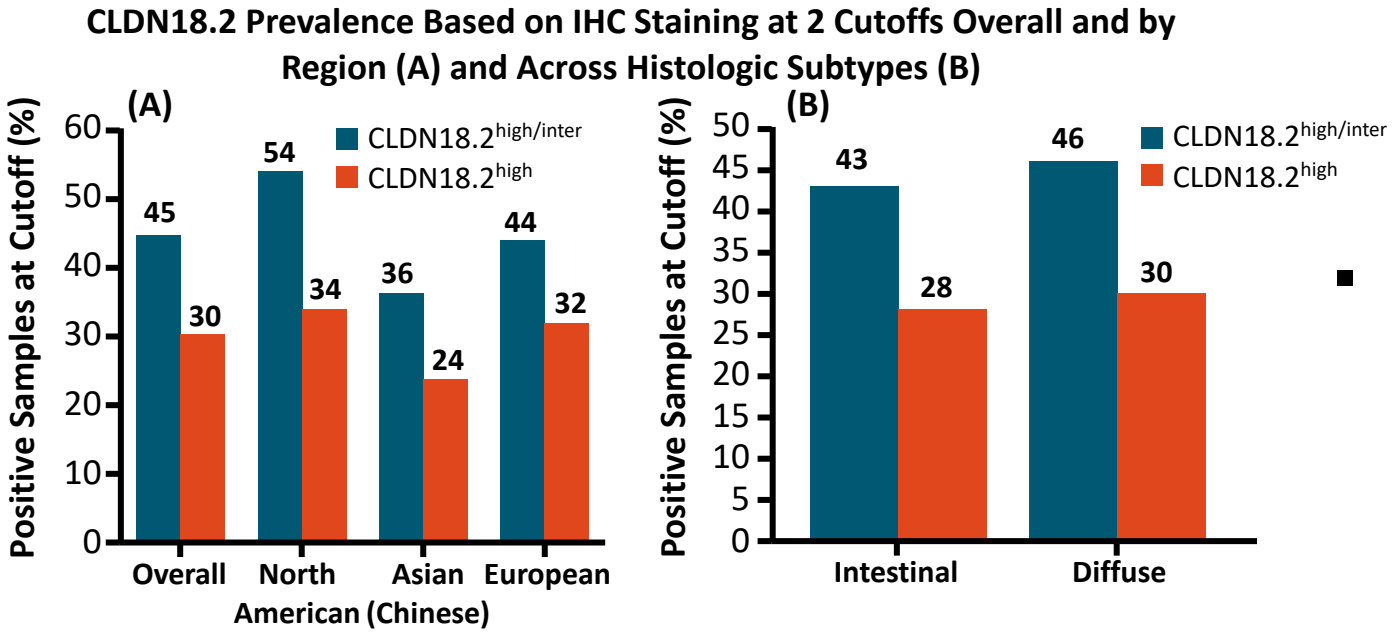


1. Rha SY et al. *Ann Oncol* 2023;34:319-320.
Data cutoff date: October 3, 2022.

Claudin18.2—Leveraging Biology







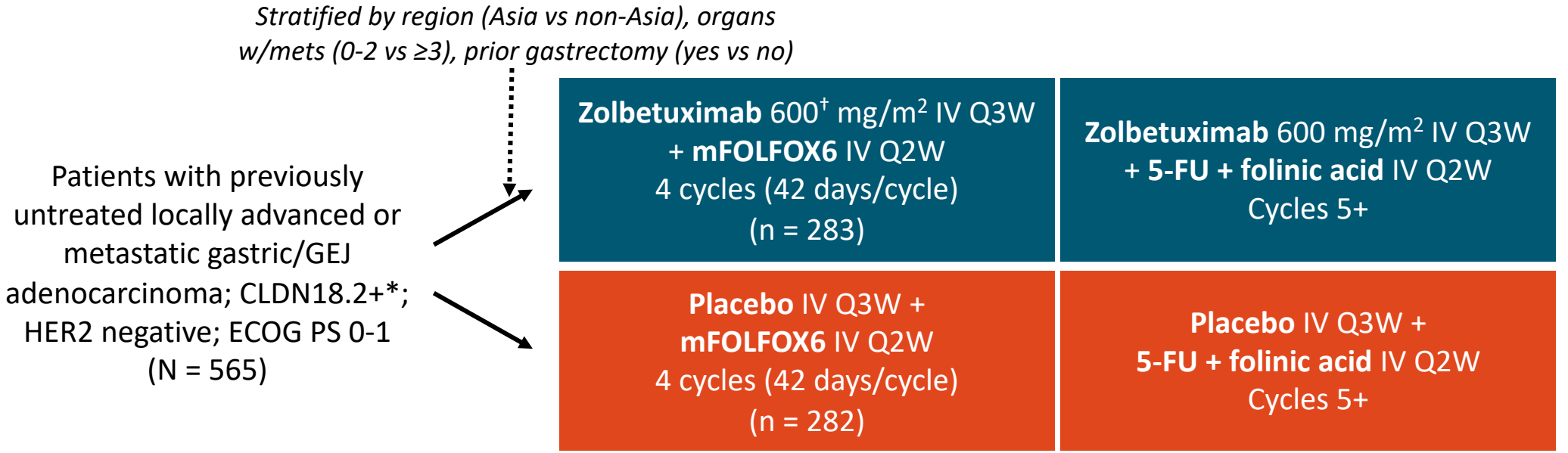
- Claudin18.2 is a major structural component of intercellular tight junctions
- Not routinely expressed in any normal tissue outside gastric mucosa (cancer-restricted antigen)
- Broadly expressed in several tumor types including gastric, GEJ, biliary, and pancreatic

Baek. Anticancer Res. 2019;39:6973.

Slide credit: clinicaloptions.com

SPOTLIGHT: Study Design

- Global, randomized, double-blind phase III trial



*Moderate-to-strong CLDN18 staining in ≥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

Shitara. ASCO GI 2023. Abstr LBA292.

Slide credit: clinicaloptions.com

SPOTLIGHT: Baseline Characteristics

Characteristic	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = 282)
Median age, yr (range)	62.0 (27-83)	60.0 (20-86)
Male, n (%)	176 (62.2)	175 (62.1)
Region: Asia/Non-Asia, n (%)	88 (31.1)/ 195 (68.9)	89 (31.6)/ 193 (68.4)
0-2 organs with metastases, n (%) ▪ ≥3	219 (77.4) 64 (22.6)	219 (77.7) 63 (22.3)
Prior gastrectomy, n (%) ▪ Yes ▪ No	84 (29.7) 199 (70.3)	82 (29.1) 200 (70.9)
Primary site, n (%) ▪ Stomach ▪ GEJ	219 (77.4) 64 (22.6)	210 (74.5) 72 (25.5)

Characteristic	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = 282)
Lauren classification, n (%) ▪ Diffuse ▪ Intestinal ▪ Mixed/others	 82 (29.1) 70 (24.8) 130 (45.9)	 117 (42.1) 66 (23.7) 95 (33.7)
ECOG PS 0/1, n (%)	125 (44.8)/ 153 (54.8)	115 (41.4)/ 163 (58.6)
Subsequent anticancer therapy, %	48	53

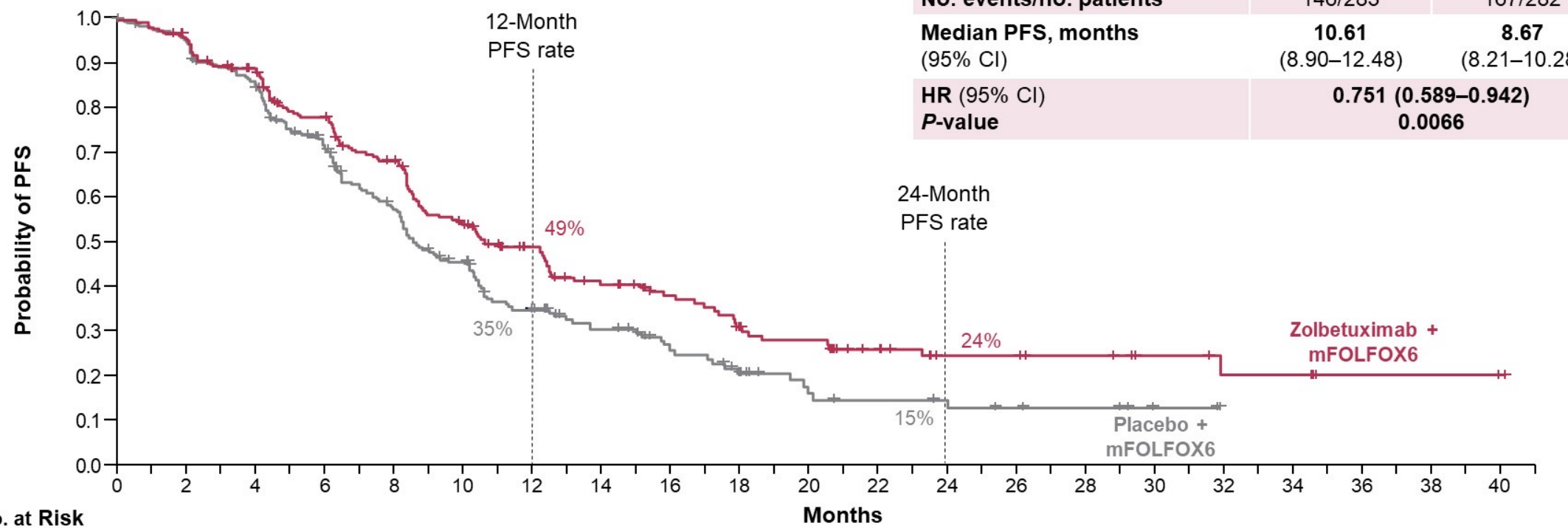
- PD-L1 CPS ≥5: 41/311 (13.2%) (ad hoc analysis using 28-8 pharmDx IHC assay)

Shitara. ASCO GI 2023. Abstr LBA292.

Slide credit: clinicaloptions.com

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

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



No. at Risk

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

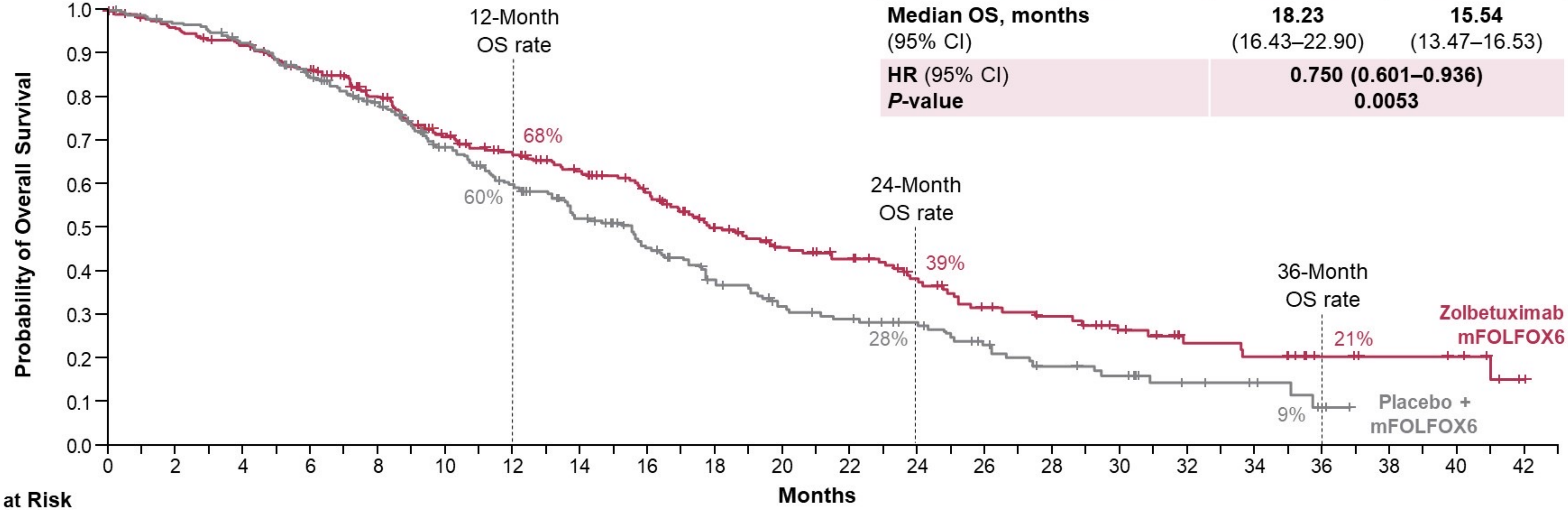
- PFS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

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

[a]Per RECIST version 1.1.

Key Secondary End Point: OS

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



No. at Risk

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

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

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

SPOTLIGHT: TEAEs in ≥20% of Patients

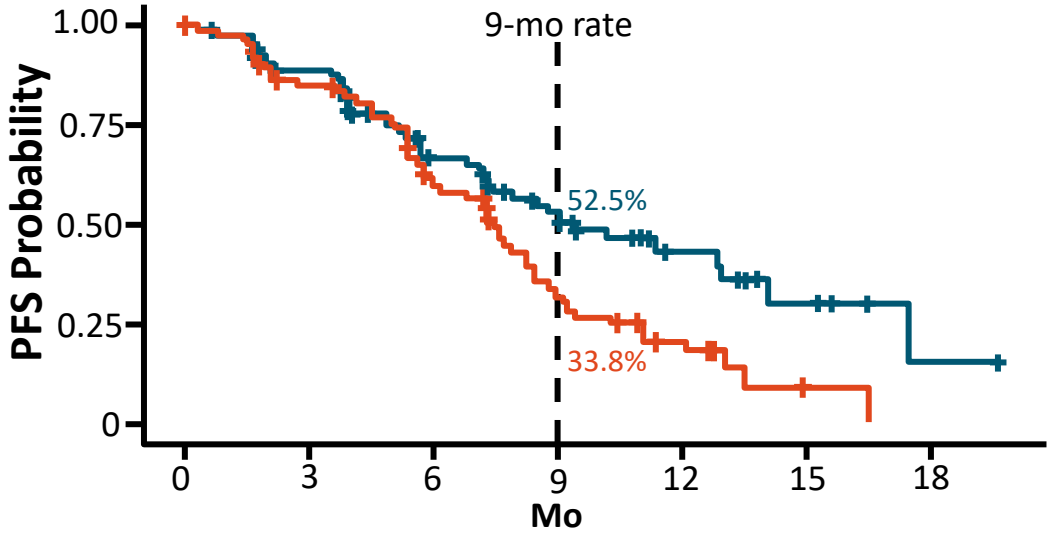
Adverse Event, %	Zolbetuximab + mFOLFOX6 (n = 279)		Placebo + mFOLFOX6 (n = 278)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Nausea	81.0	16.1	60.8	6.5
Vomiting	64.5	16.1	34.5	5.8
Decreased appetite	47.0	5.7	33.5	3.2
Diarrhea	38.7	4.3	43.9	3.2
Peripheral sensory neuropathy	38.0	3.9	42.4	5.4
Neutropenia	36.2	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

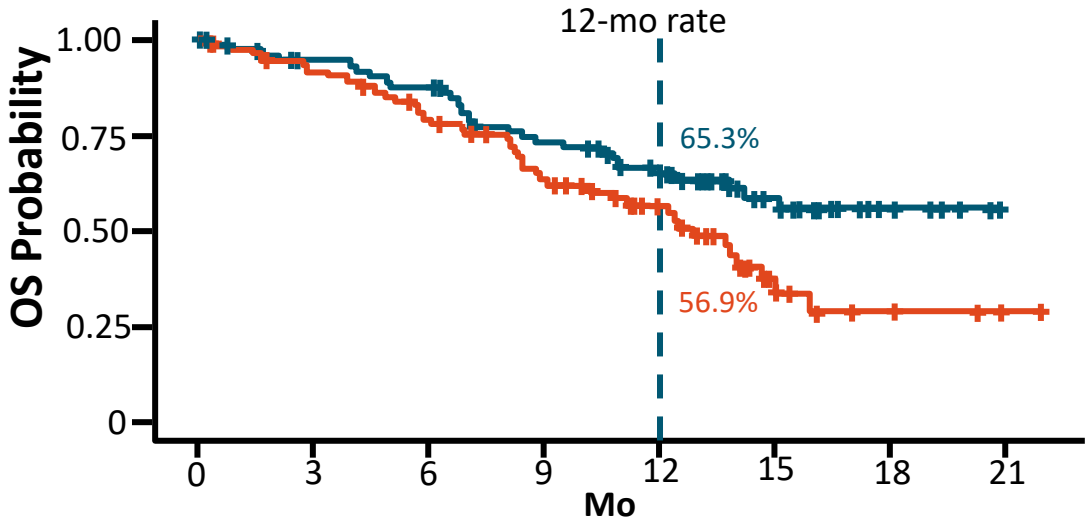
Shitara. ASCO GI 2023. Abstr LBA292.

Slide credit: clinicaloptions.com

FIGHT: First-line Bemarituzumab + mFOLFOX6 vs Placebo + mFOLFOX6 in Advanced Gastric/GEJ Cancer

- Randomized phase II trial of bemarituzumab (anti-FGFR2b antibody) or placebo + (both + mFOLFOX6) for patients with no prior therapy and unresectable locally advanced or metastatic gastric/GEJ adenocarcinoma with *FGFR2b* overexpression/amplification (N = 155)





	Bema + mFOLFOX6 (n = 77)	Placebo + mFOLFOX6 (n = 78)	
Median PFS, mo	9.5	7.4	HR 0.68; *P* = .0727)
Median OS, mo	Not reached	12.9	HR 0.58; *P* = .0268)

- Ongoing phase III: FORTITUDE-101 (bemarituzumab + mFOLFOX6, NCT05052801)

Wainberg. ASCO GI 2021. Abstr LBA160.

Slide credit: clinicaloptions.com

FDA

The FDA has issued a complete response letter (CRL) regarding the biologics license application (BLA) seeking the approval of zolbetuximab for the treatment of patients with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are Claudin18.2 (CLDN18.2) positive.[1]

The FDA stated that the agency cannot approve the BLA by the Prescription Drug User Fee Act action date on January 12, 2024, because of unresolved deficiencies following its pre-license inspection of a third-party manufacturing facility for zolbetuximab. The FDA did not cite any concerns related to the clinical data for zolbetuximab and is not requesting additional clinical trials.