MAYO CLINIC

Advancements in the Treatment of Early Stage Gastroesophageal Adenocarcinoma

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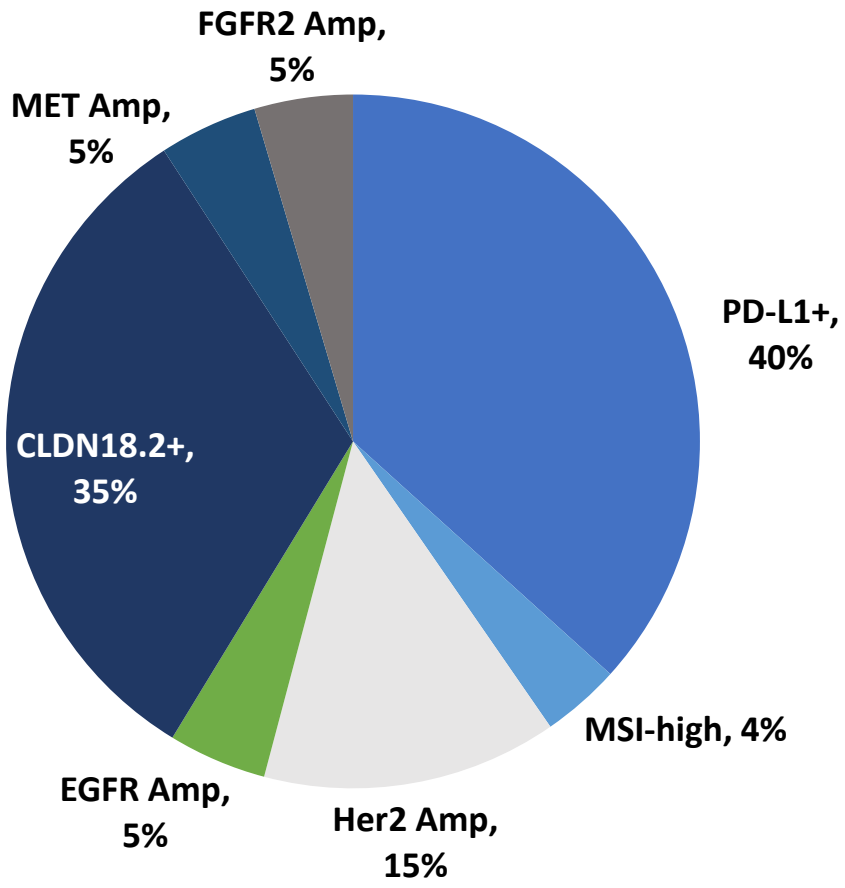
Key Biomarkers in GI Cancers

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

Key Biomarkers for Treatment in Gastroesophageal Cancer



Key markers in advanced disease

- **HER2** positive - 15%-20% of patients, improved survival with non-chemo antibody trastuzumab
- **MSI** high - 3%-5% of patients, high response rates to immunotherapies
- **PD-L1** positive - 30%-50% of patients, identifies those more likely to benefit from immune therapies, likely gradation within PD-L1 +
- **CLDN18.2** high - 30%-35% of patients, response predictor for zolbetuximab

Investigational Biomarkers

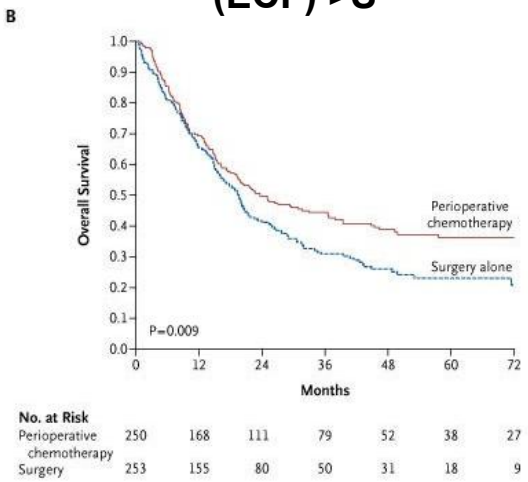
- **FGFR2** amp - 5%-10% of patients, multiple trials of inhibitors
- **FGFR2** high - May be up to 30% of HER2 negative
- **EGFR** amp - 5%-7%, may predict response to EGFR drugs like cetuximab

Shah, M et al. ASCO GI 2024

Evolution of GE treatment over last two decades

MAGIC

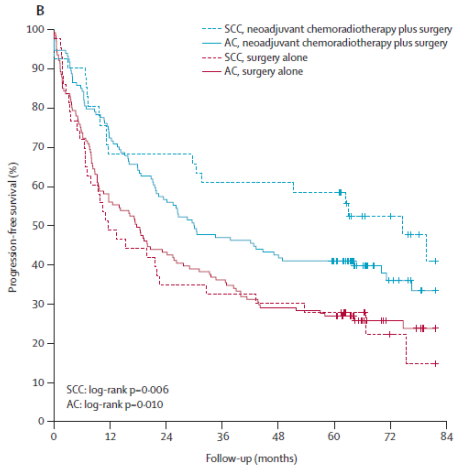
Perioperative chemo (ECF) >S



Gastric, GEJ + esophageal adeno

CROSS

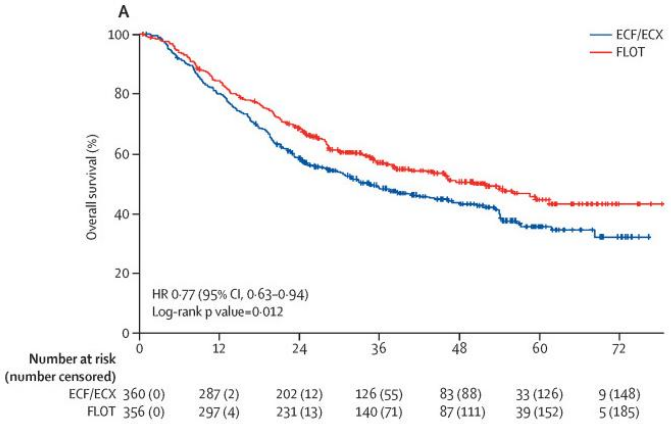
CRT+S> S



GEJ (S1,S2) +esophageal

FLOT-4

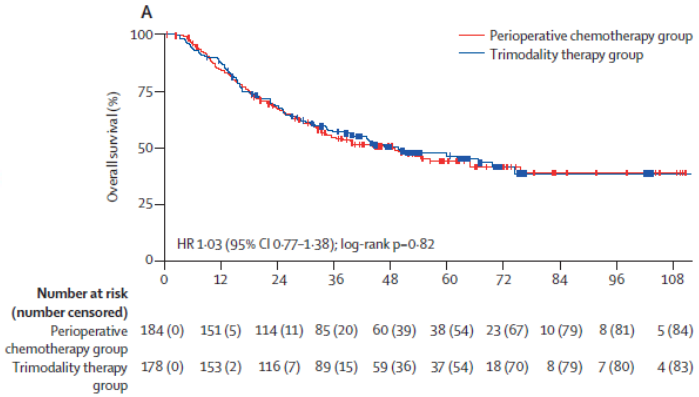
Perioperative FLOT> Periop ECF



Gastric, GEJ (S1,2,3)

Neo-AEGIS

CRT NOT better than ECF



GEJ (S1,2, 3) +esophageal adeno

Cunningham et al. 2006. NEJM
Van Hagen et al. 2012 NEJM
Al-Batran et al. 2009 Lancet
Reynolds et al 2023 Lancet

Current standard

Locally advanced, resectable Gastroesophageal Adenocarcinoma: Modern Treatment Landscape

Esophagus

GEJ

Stomach

CROSS

ESOPEC

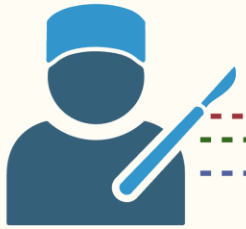
FLOT4-AIO

Neoadjuvant Chemoradiation

-weekly chemotherapy
-carboplatin
-paclitaxel
-daily radiation Mon through Fri
-28 radiation treatments total
~5.5 weeks
-Radiation dose: 41.4-50.4 Gy

FLOT -Durvalumab chemotherapy

Fluorouracil
Leucovorin
Oxaliplatin
Docetaxel



Surgery

path incomplete response?

path complete response? (~23%)

FLOT-Durvalumab chemotherapy

CM577

12 months adjuvant Nivolumab

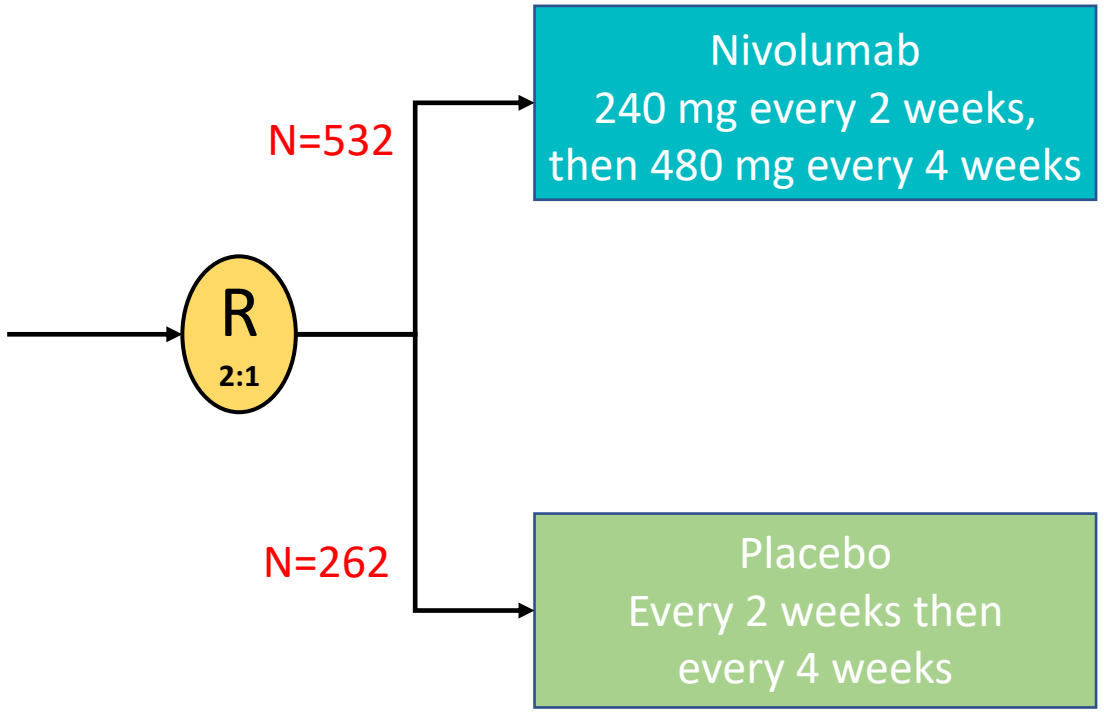
Surveillance

MATTERHORN (encouraging EFS benefit)

Strickland MR and Klempner SK. The IASGO Textbook of Multi-Disciplinary Management to Upper Gastrointestinal Diseases. Chapter 34. In press. Created with BioRender.com.

Checkmate 577 study design

- **Stage II/III esophageal or gastroesophageal junction adenocarcinoma or squamous cell carcinoma**
- **Residual disease after chemoradiotherapy & resection**
- **ECOG 0-1**



***Up to 12 months or until progressive disease or unacceptable toxicity**

Primary endpoint: DFS

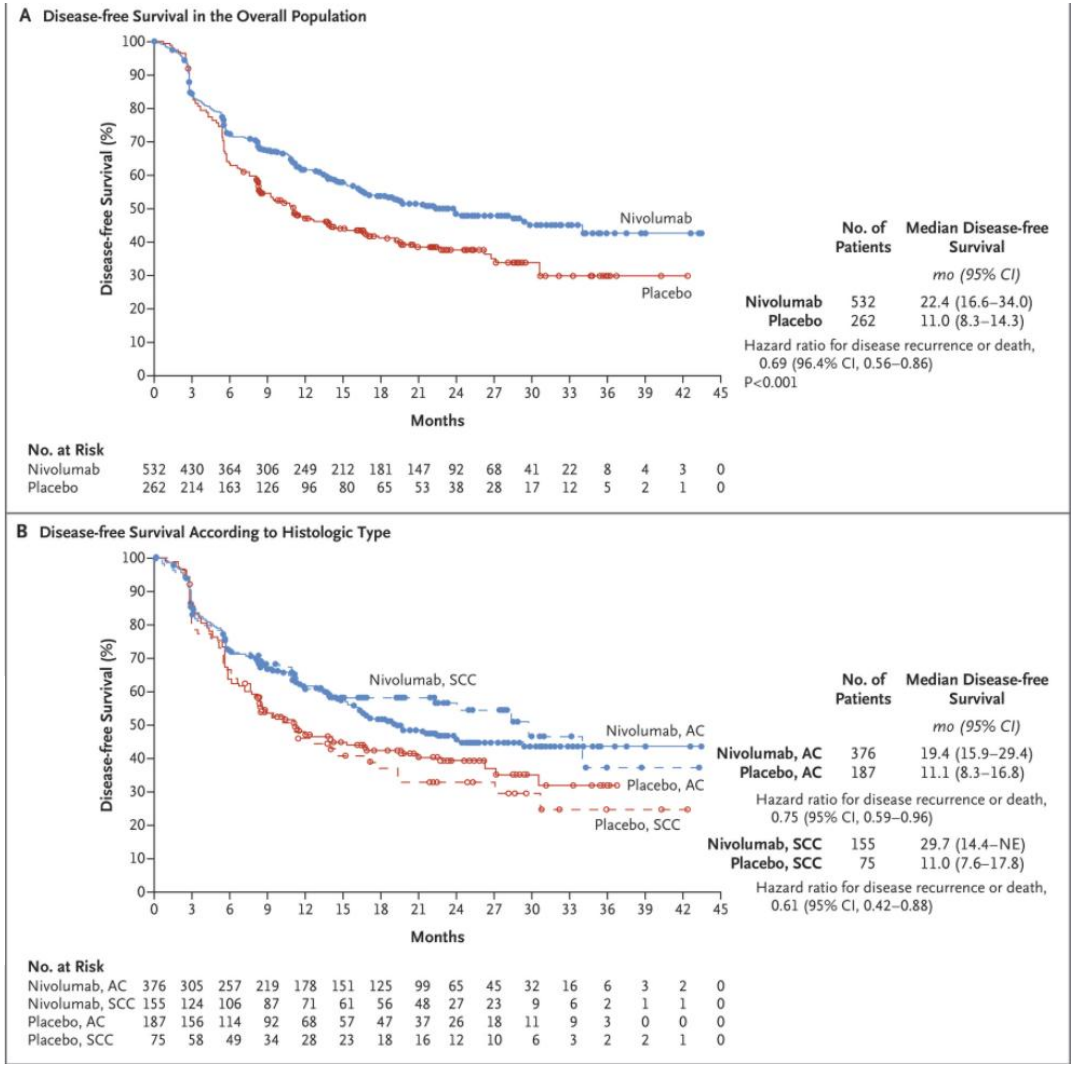
Secondary endpoints: OS, OS at 1, 2 and 3 years

Adapted from Kelly RJ et al. *N Engl J Med.* 2021;384(13):1191-1203.

Checkate 577

- Adjuvant nivolumab after trimodality therapy has DFS benefit

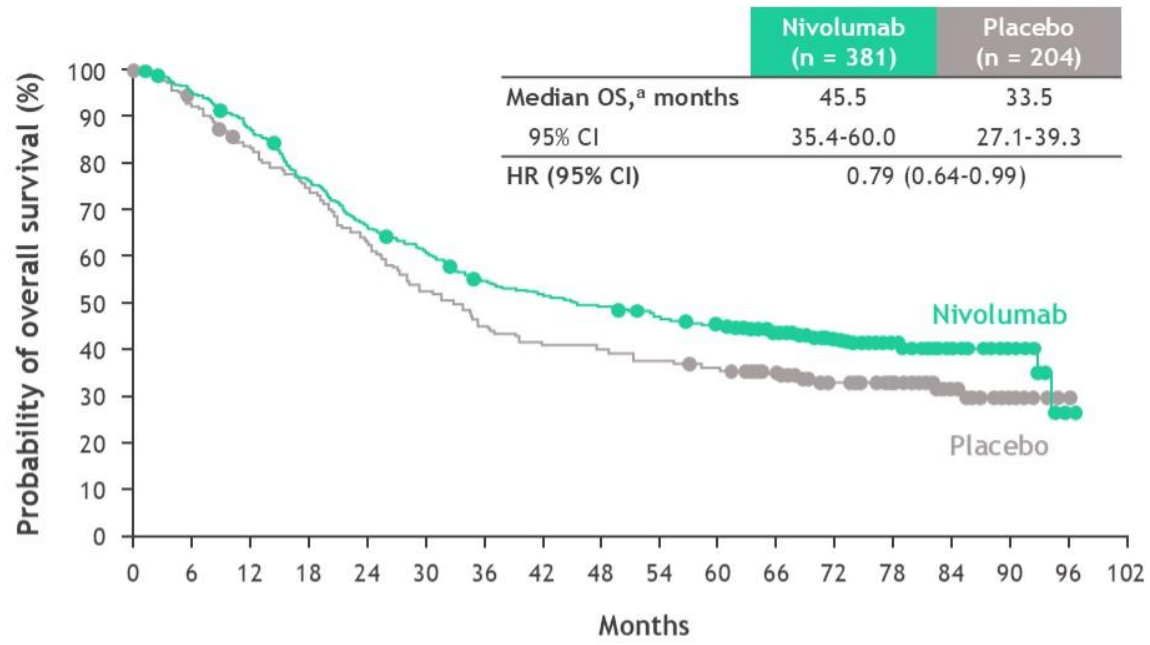
Subgroup	Median Disease-free Survival, months		Unstratified Hazard Ratio (95% CI)
	Nivolumab	Placebo	
PD-L1 CPS expression			
≥5 (n = 371)	29.4	10.2	0.62 (0.46–0.83)
<5 (n = 295)	16.3	11.1	0.89 (0.65–1.22)



Kelly et al. 2021 NEJM

Overall survival by PD-L1 CPS

PD-L1 CPS ≥ 1

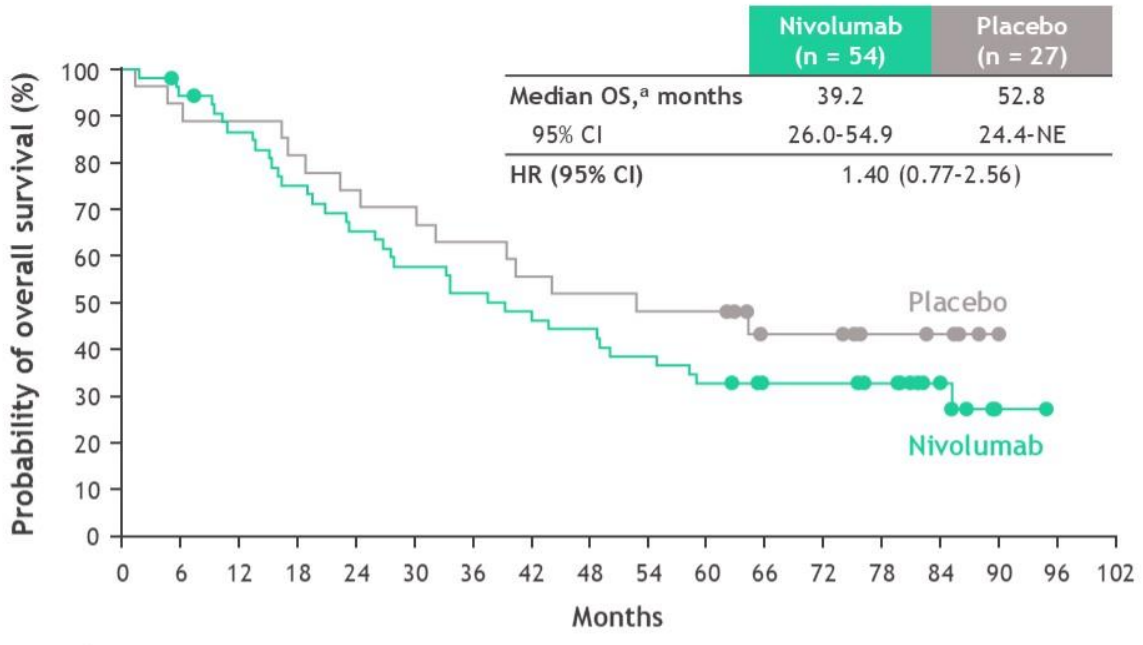


	Nivolumab (n = 381)	Placebo (n = 204)
Median OS,[a] months	45.5	33.5
95% CI	35.4-60.0	27.1-39.3
HR (95% CI)	0.79 (0.64-0.99)	

No. at risk

Nivolumab	381	360	330	287	250	229	203	193	183	172	163	134	106	76	41	18	1	0
Placebo	204	186	167	149	126	106	90	83	80	75	71	60	47	36	19	8	1	0

PD-L1 CPS < 1



	Nivolumab (n = 54)	Placebo (n = 27)
Median OS,[a] months	39.2	52.8
95% CI	26.0-54.9	24.4-NE
HR (95% CI)	1.40 (0.77-2.56)	

No. at risk

Nivolumab	54	50	45	39	34	30	27	25	23	20	17	14	14	12	7	1	0	0
Placebo	27	25	24	22	20	19	17	15	14	13	13	8	8	5	4	0	0	0

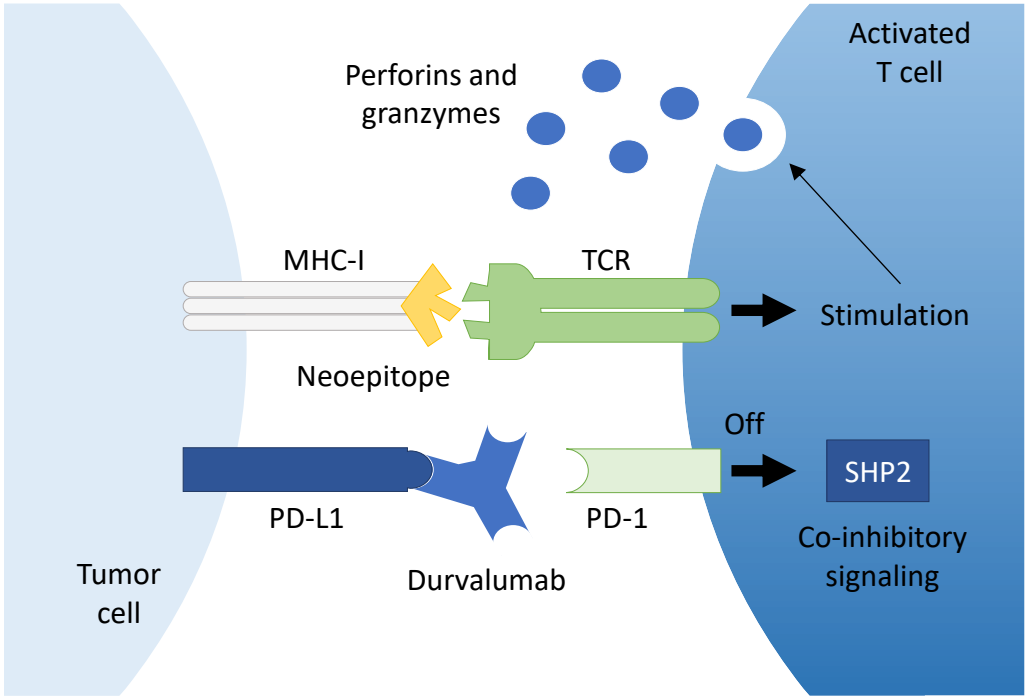
- Improvement in OS with nivolumab vs placebo was enriched in patients with PD-L1 CPS ≥ 1

[a]Median (range) follow-up, 78.3 (60.1-96.6) months.

Kelly et al ASCO 2025

Addition of IO to FLOT

- **FLOT chemotherapy**—fluorouracil, leucovorin, oxaliplatin, and docetaxel—improves survival when combined with surgery for localized gastric and GEJ adenocarcinoma (GEA)
- Adding **anti–PD-1 therapy to chemotherapy** improves survival in metastatic GEA; its role in the perioperative setting, however, remains uncertain



Janjigian, Y, et al. NEJM 2025., Powles, T, et al. NEJM 2024.

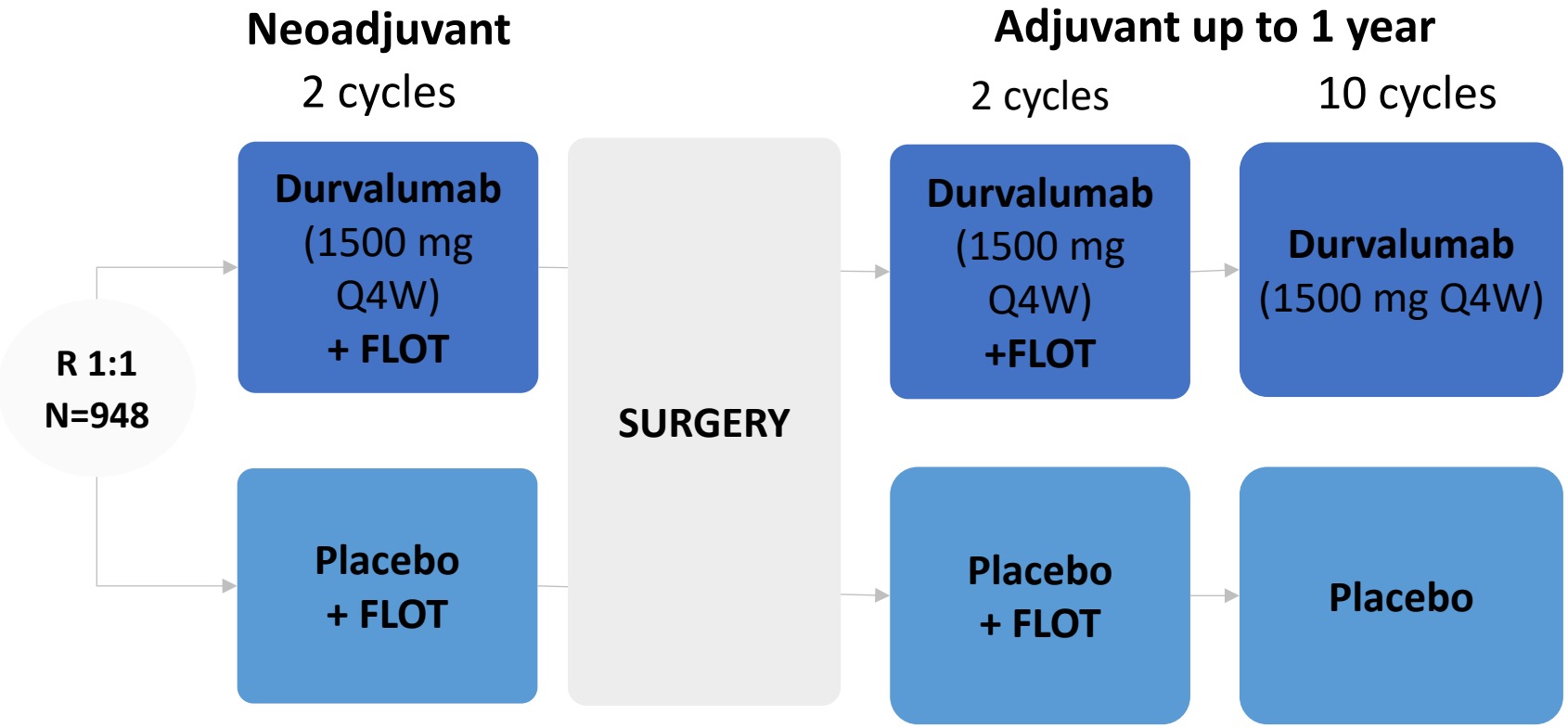
MATTERHORN: Study Design

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

Study population

- **Gastric and GEJ adenocarcinoma**
- Stage II to IVa
- No evidence of metastasis
- No prior therapy
- ECOG PS 0 or 1
- Global enrollment in Asia, Europe, North & South America

Primary endpoint: EFS
Secondary: OS, pCR



Janjigian, Y, *et al.* NEJM 2025.

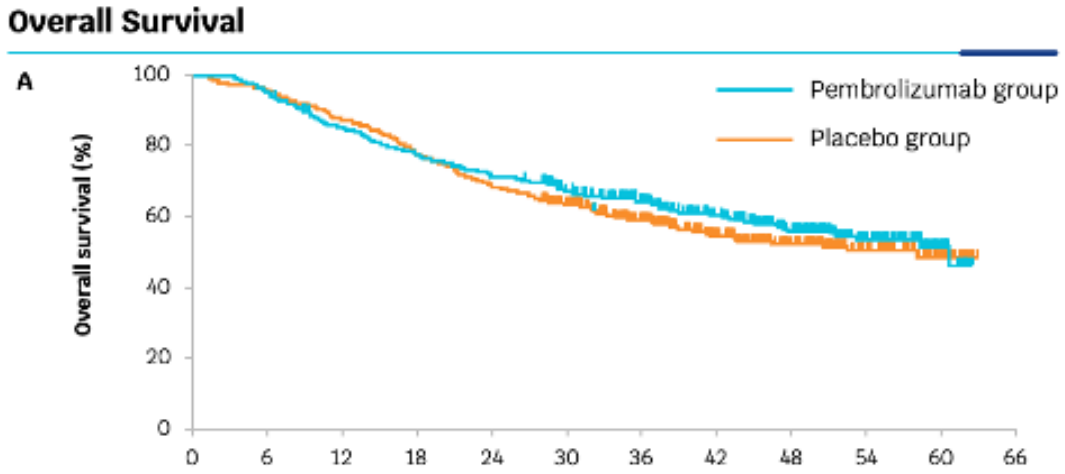
KEYNOTE 585

Perioperative and Adjuvant Settings

Keynote 585

Pembrolizumab 200 mg IV Q3W for up to 3 cycles + FLOT Q2W for up to 4 cycles	Surgery	Pembrolizumab + FLOT	Pembrolizumab IV Q3W for up to 11 cycles
Placebo IV Q3W for up to 3 cycles + FLOT Q2W for up to 4 cycles		Placebo + FLOT	Placebo IV Q3W for up to 11 cycles

HR 0.90 (95% CI 0.73–1.12)



Baseline characteristics

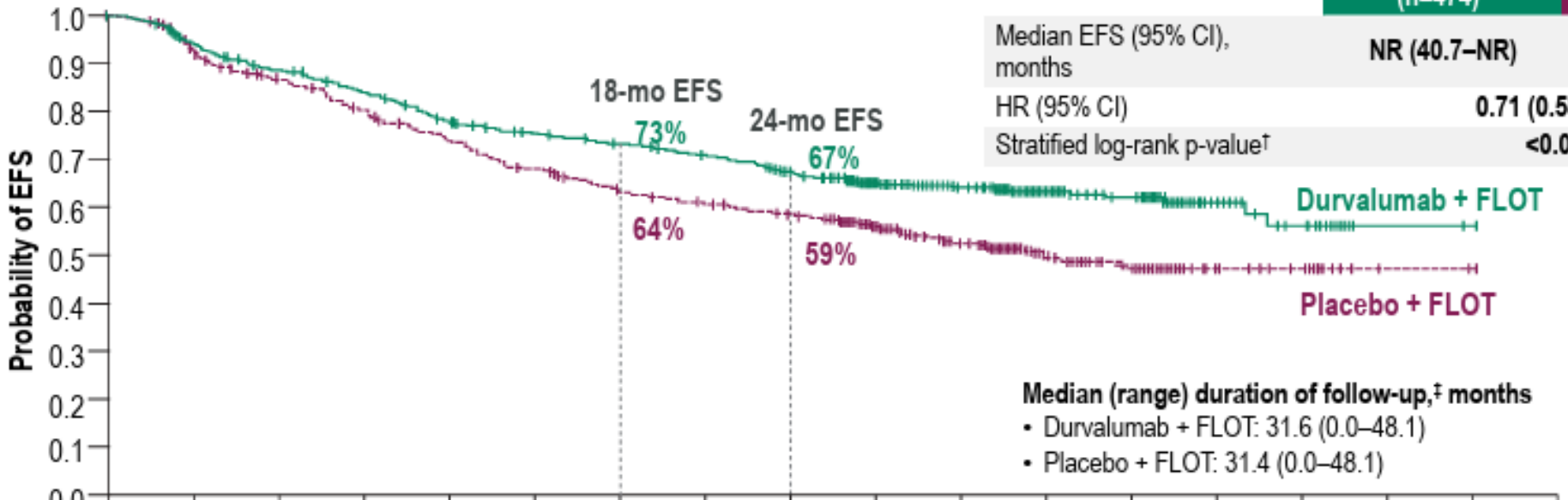
		Central pathology analysis set*		ypN evaluable analysis set†	
		Durvalumab + FLOT (n=385)	Placebo + FLOT (n=372)	Durvalumab + FLOT (n=411)	Placebo + FLOT (n=400)
Median age, years (range)		61.0 (27–84)	63.0 (29–81)	61.0 (27–84)	62.0 (29–81)
Sex, n (%)	Male	264 (68.6)	286 (76.9)	286 (69.6)	304 (76.0)
Geographical region, n (%)	Non-Asia	310 (80.5)	293 (78.8)	336 (81.8)	319 (79.8)
	Asia	75 (19.5)	79 (21.2)	75 (18.2)	81 (20.3)
ECOG PS, n (%)	0 (normal activity)	275 (71.4)	291 (78.2)	292 (71.0)	313 (78.3)
	1 (restricted activity)	110 (28.6)	81 (21.8)	119 (29.0)	87 (21.8)
Site of tumour, n (%)	Gastric	255 (66.2)	244 (65.6)	275 (66.9)	265 (66.3)
	GEJ	130 (33.8)	128 (34.4)	136 (33.1)	135 (33.8)
Primary tumour stage, n (%)	T4	93 (24.2)	91 (24.5)	95 (23.1)	97 (24.3)
	Non-T4	292 (75.8)	281 (75.5)	316 (76.9)	303 (75.8)
Clinical lymph node status, n (%)	N+	264 (68.6)	260 (69.9)	284 (69.1)	280 (70.0)
PD-L1 expression by TAP, n (%)	<1%	38 (9.9)	36 (9.7)	40 (9.7)	39 (9.8)
	≥1%	347 (90.1)	336 (90.3)	371 (90.3)	361 (90.3)
Histology type (investigator assessed), n (%)	Intestinal	195 (50.6)	193 (51.9)	212 (51.6)	207 (51.8)
	Diffuse	102 (26.5)	91 (24.5)	107 (26.0)	100 (25.0)
	Unspecified adenocarcinoma or mixed / other	88 (22.9)	88 (23.7)	92 (22.4)	93 (23.3)
MSI status, n (%)	MSI-high	18 (4.7)	21 (5.6)	17 (4.1)	21 (5.3)
	Not-MSI-high	251 (65.2)	253 (68.0)	270 (65.7)	272 (68.0)
	Not evaluable / missing	116 (30.1)	98 (26.3)	124 (30.2)	107 (26.8)

*Participants who completed surgery with samples that were evaluable for modified Ryan scoring by central assessment. †Participants who completed surgery with samples that were evaluable for nodal involvement by investigator assessment.
Data cut-off: 20 December 2024
ECOG, Eastern Cooperative Oncology Group; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; GEJ, gastroesophageal junction; MSI, microsatellite instability; PD-L1, programmed cell death ligand-1; PS, performance status; TAP, tumour area positivity; TTD, time to deterioration; ypN, pathological nodal status.

Primary endpoint of EFS[1]

A statistically significant improvement in EFS was observed with durvalumab + FLOT versus placebo + FLOT

	Durvalumab + FLOT (n=474)*	Placebo + FLOT (n=474)*
Median EFS (95% CI), months	NR (40.7–NR)	32.8 (27.9–NR)
HR (95% CI)	0.71 (0.58–0.86)	
Stratified log-rank p-value†	<0.001	

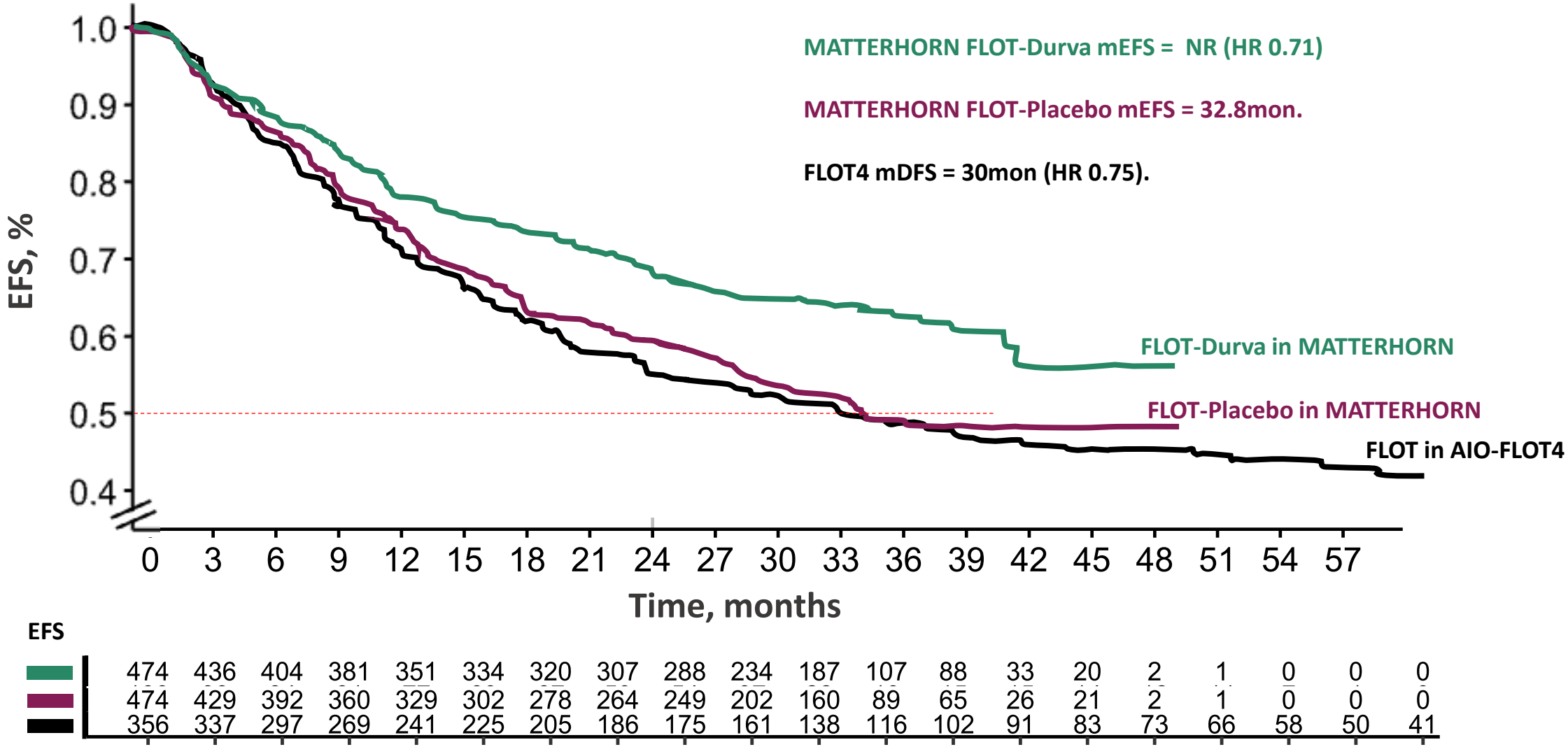


No. of participants at risk																			Total no. of events
Durvalumab + FLOT	474	436	404	381	351	334	320	307	288	234	187	107	88	33	20	2	1	0	167
Placebo + FLOT	474	429	392	360	329	302	278	264	249	202	160	89	65	26	21	2	1	0	218

*Full analysis set (all randomised participants, regardless of treatment received). †The threshold of significance for this analysis was 0.0239. ‡In censored participants.
Events were defined as the earliest of RECIST v1.1 events, non-RECIST v1.1 events or deaths due to any cause. Analysis was based on BICR assessments and / or locally by pathology testing if clinically required. The HR and its CI were estimated from a Cox proportional hazards model, adjusted for geographical region, clinical lymph node status and PD-L1 expression. The CI for the HR was calculated using a profile likelihood approach. The 2-sided p-value was calculated using a stratified log-rank test adjusted for geographical region, clinical lymph node status and PD-L1 expression.
BICR, blinded independent central review; CI, confidence interval; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; HR, hazard ratio; mo, month; NR, not reached; PD-L1, programmed cell death ligand-1; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

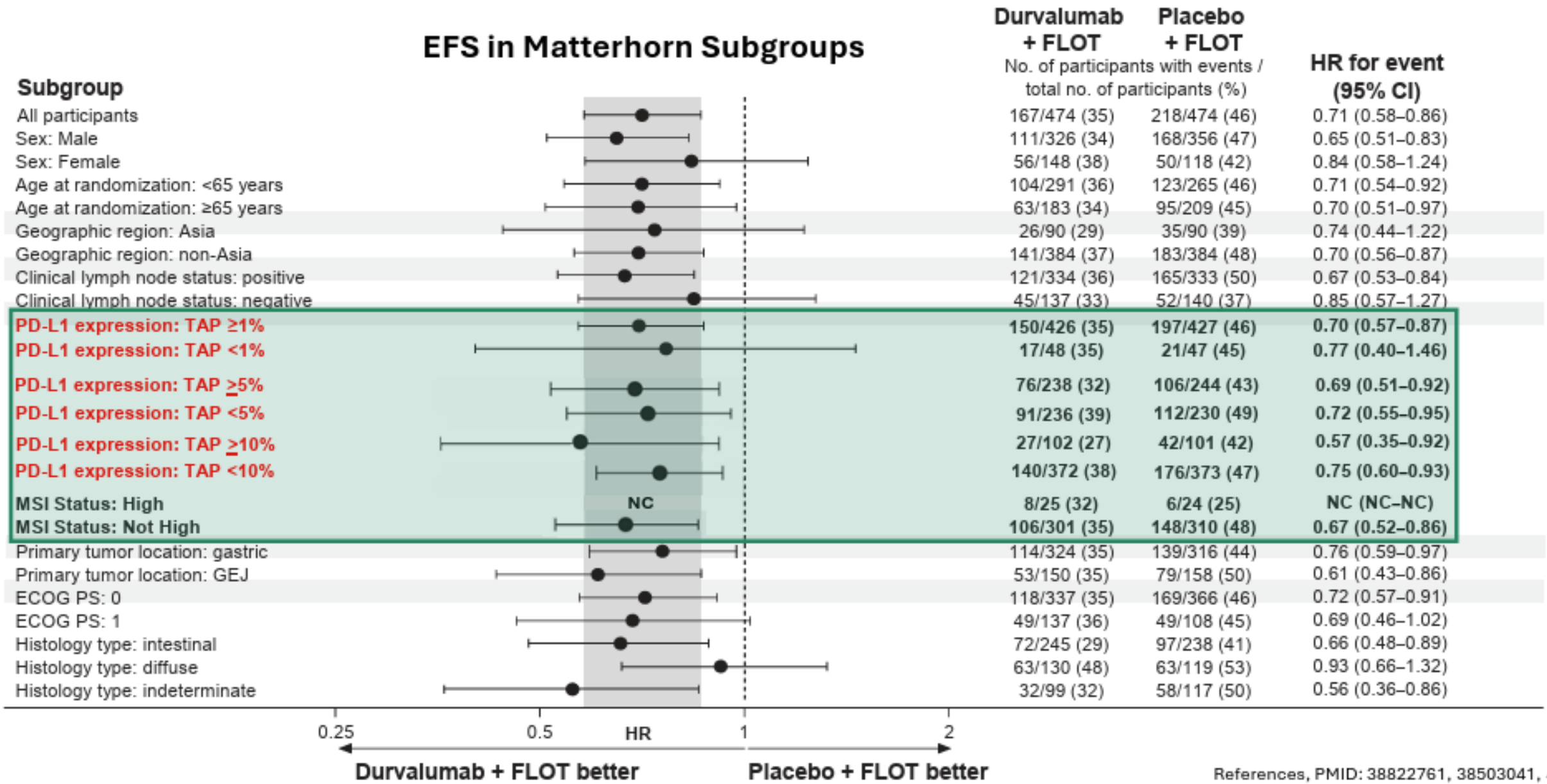
1. Janjigian YY, et al. *N Engl J Med* 2025;393:217–230.

FLOT is a Stable and Modern Control Arm



Unpublished, assisted by Dr. Joseph Zhao

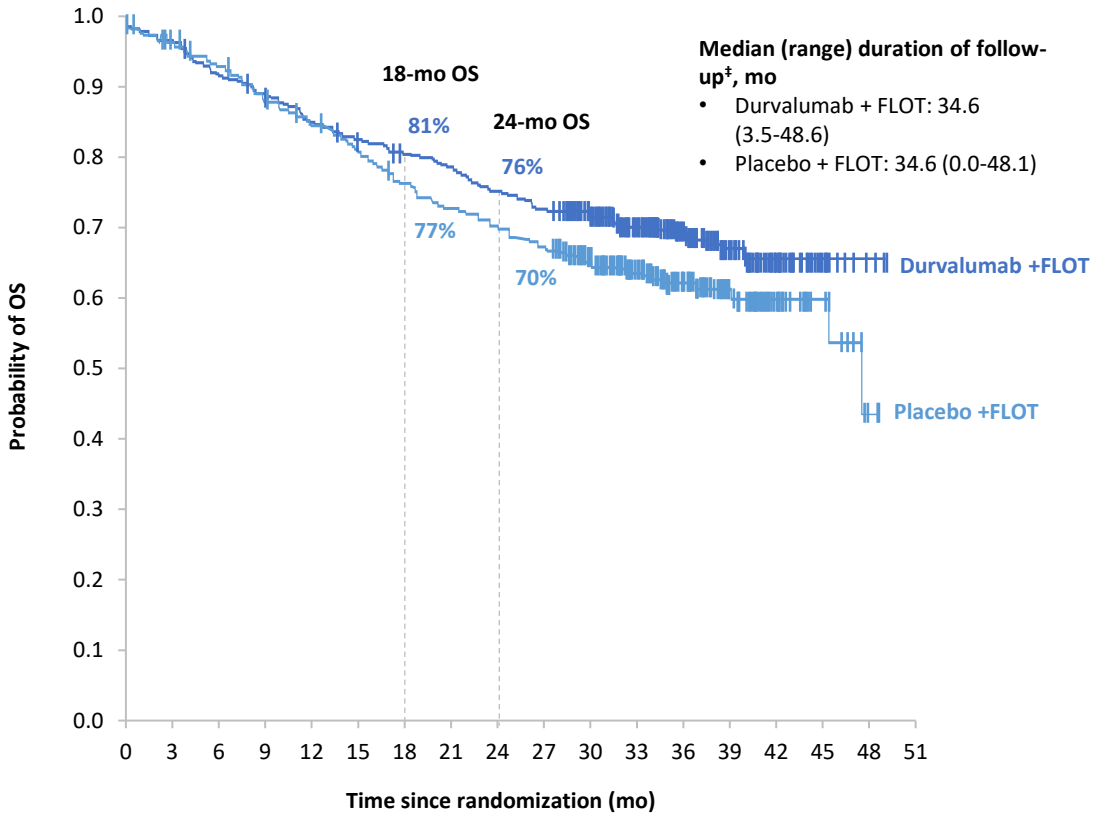
Patient Subgroups



References, PMID: 38822761, 38503041, 403

MATTERHORN: Secondary Endpoints OS and DFS

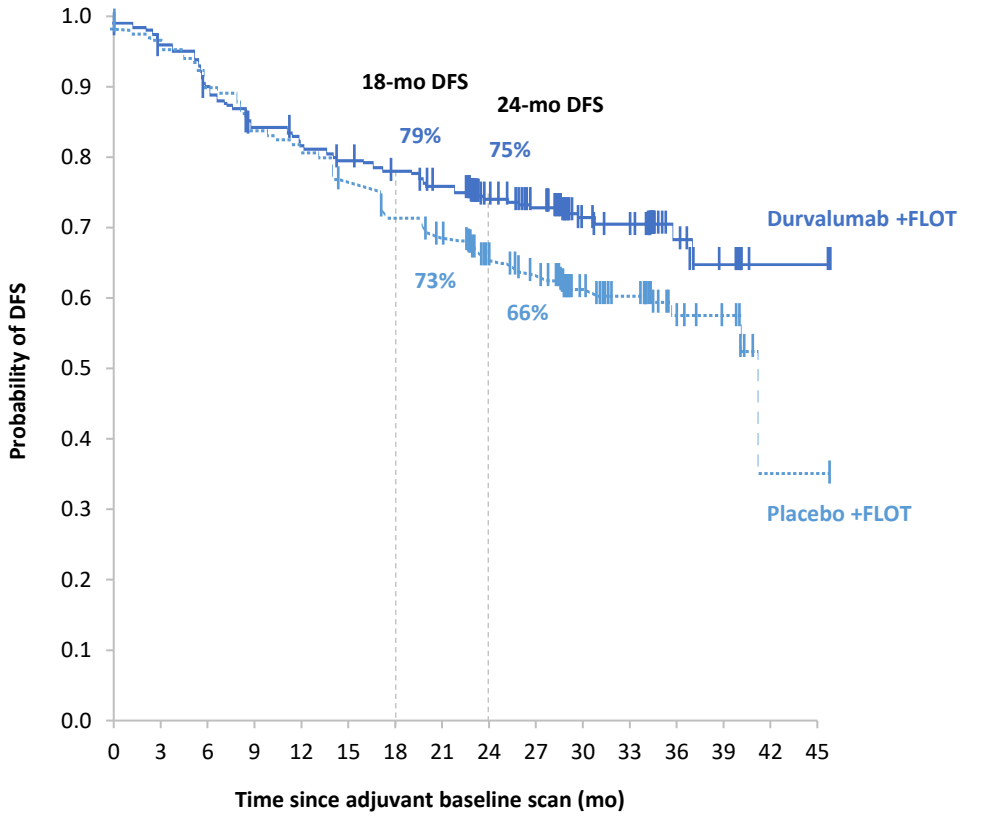
Secondary Endpoint of Overall Survival (OS)



No. of participants at risk																		Total events
Durvalumab + FLOT	474	464	438	422	403	389	376	367	351	338	293	205	143	80	38	8	2	0	145
Placebo + FLOT	474	457	439	414	395	374	354	337	323	309	262	197	128	72	33	11	20	0	176

Secondary Endpoint of Disease-Free Survival (DFS)

DFS improved with durvalumab with FLOT vs Placebo with FLOT in those with R0 resection



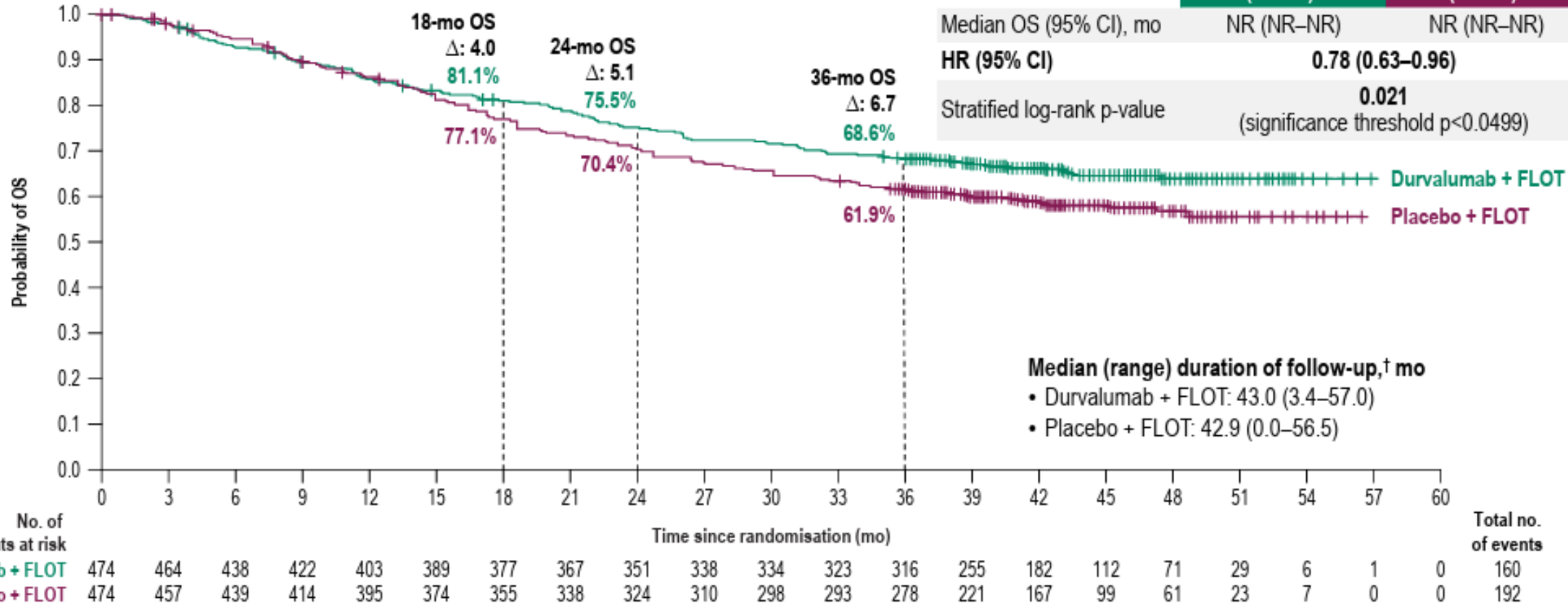
No. of participants at risk																		Total events
Durvalumab + FLOT	339	327	305	283	272	265	258	244	184	168	81	74	19	3	2	0		90
Placebo + FLOT	323	315	293	275	262	245	230	217	157	142	72	56	23	4	2	0		119

Janjigian, Y, *et al.* (2025). Perioperative durvalumab in gastric and gastroesophageal junction cancer. *The New England Journal of Medicine, 390*(22)

Final OS

Durvalumab + FLOT demonstrated a statistically significant and clinically meaningful improvement in OS versus placebo + FLOT in the intention to treat population

	Durvalumab + FLOT (n=474)*	Placebo + FLOT (n=474)*
Median OS (95% CI), mo	NR (NR–NR)	NR (NR–NR)
HR (95% CI)	**0.78 (0.63–0.96)**	
Stratified log-rank p-value	**0.021** (significance threshold p<0.0499)	



Median (range) duration of follow-up,† mo

- Durvalumab + FLOT: 43.0 (3.4–57.0)
- Placebo + FLOT: 42.9 (0.0–56.5)

No. of participants at risk																					Total no. of events
Durvalumab + FLOT	474	464	438	422	403	389	377	367	351	338	334	323	316	255	182	112	71	29	6	1	0	160
Placebo + FLOT	474	457	439	414	395	374	355	338	324	310	298	293	278	221	167	99	61	23	7	0	0	192

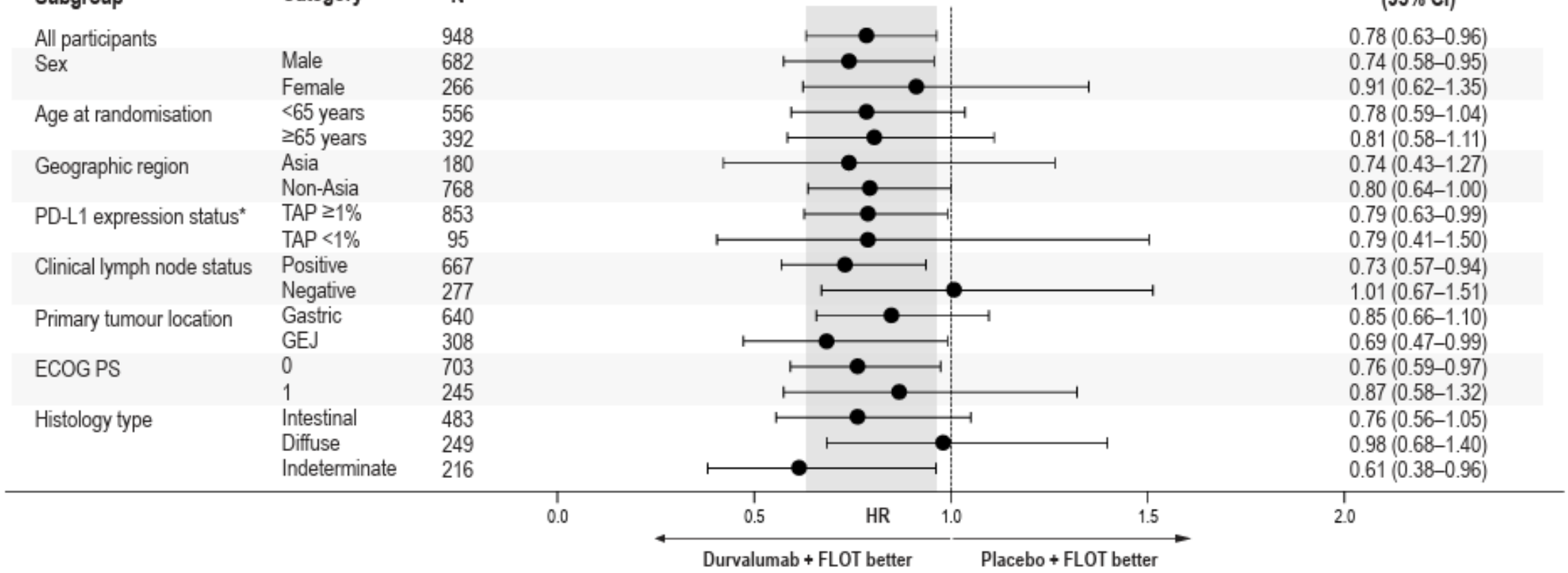
*Intention to treat analysis set (all randomised participants, regardless of treatment received). †In censored participants.
Data cut-off: 01 September 2025. OS maturity: 37.1%. Events were defined as time from randomisation until the date of death due to any cause. The HR and its CI were estimated from a Cox proportional hazards model, adjusted for geographic region, clinical lymph node status, and PD-L1 expression status. The CI for the HR was calculated using a profile likelihood approach. An HR <1 favours durvalumab + FLOT. The two-sided p-value was calculated using a stratified log-rank test adjusting for geographic region, clinical lymph node status, and PD-L1 expression status.
CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; HR, hazard ratio; mo, month; NR, not reached; OS, overall survival; PD-L1, programmed cell death ligand-1.

Josep Tabernero

OS in key subgroups

A consistent benefit in OS was observed with durvalumab + FLOT versus placebo + FLOT in most key subgroups

Subgroup	Category	N	OS HR (95% CI)
All participants		948	0.78 (0.63–0.96)
Sex	Male	682	0.74 (0.58–0.95)
	Female	266	0.91 (0.62–1.35)
Age at randomisation	<65 years	556	0.78 (0.59–1.04)
	≥65 years	392	0.81 (0.58–1.11)
Geographic region	Asia	180	0.74 (0.43–1.27)
	Non-Asia	768	0.80 (0.64–1.00)
PD-L1 expression status*	TAP ≥1%	853	0.79 (0.63–0.99)
	TAP <1%	95	0.79 (0.41–1.50)
Clinical lymph node status	Positive	667	0.73 (0.57–0.94)
	Negative	277	1.01 (0.67–1.51)
Primary tumour location	Gastric	640	0.85 (0.66–1.10)
	GEJ	308	0.69 (0.47–0.99)
ECOG PS	0	703	0.76 (0.59–0.97)
	1	245	0.87 (0.58–1.32)
Histology type	Intestinal	483	0.76 (0.56–1.05)
	Diffuse	249	0.98 (0.68–1.40)
	Indeterminate	216	0.61 (0.38–0.96)



*Measured by immunohistochemistry using VENTANA PD-L1 (SP263) Companion Diagnostic Assay (Roche Diagnostics; investigational use only) and recorded at randomisation on the Interactive Response Technology System, Randomisation and Trial Supply Management, Electronic Case Report Form or from external vendor data from samples collected on or before randomisation. Participants provided a tumour tissue sample at screening to determine PD-L1 status using the TAP scoring method.
Data cut-off: 01 September 2025. The analysis was performed using a Cox proportional hazards model with treatment as the only covariate. An HR <1 favours durvalumab + FLOT. The CI was calculated using a profile likelihood approach. The grey band represents the 95% CI for the intention to treat HR.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; GEJ, gastroesophageal junction; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death ligand-1; TAP, Tumour Area Positivity.

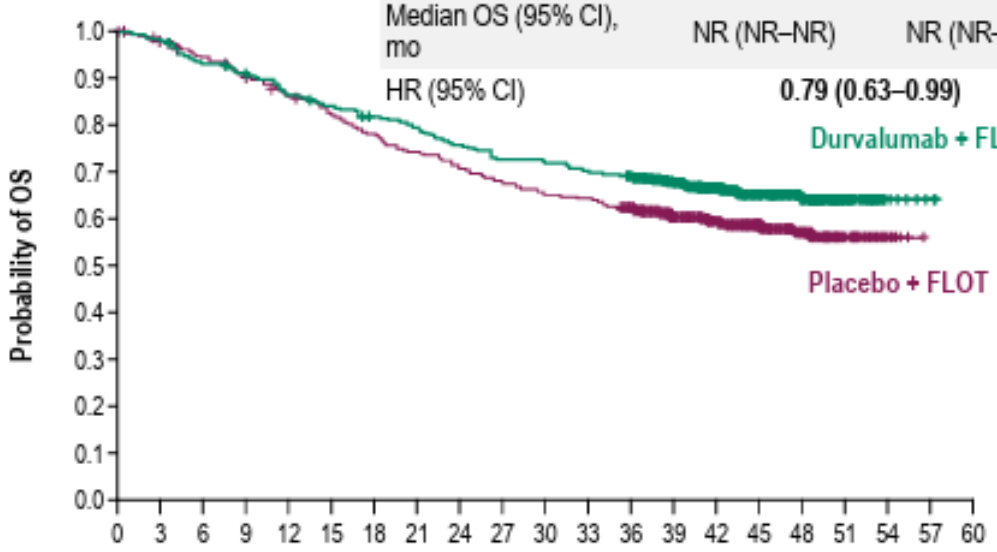
Josep Tabernero

OS by PD-L1 status

OS was improved with durvalumab + FLOT versus placebo + FLOT regardless of PD-L1 status

PD-L1 TAP ≥1%*

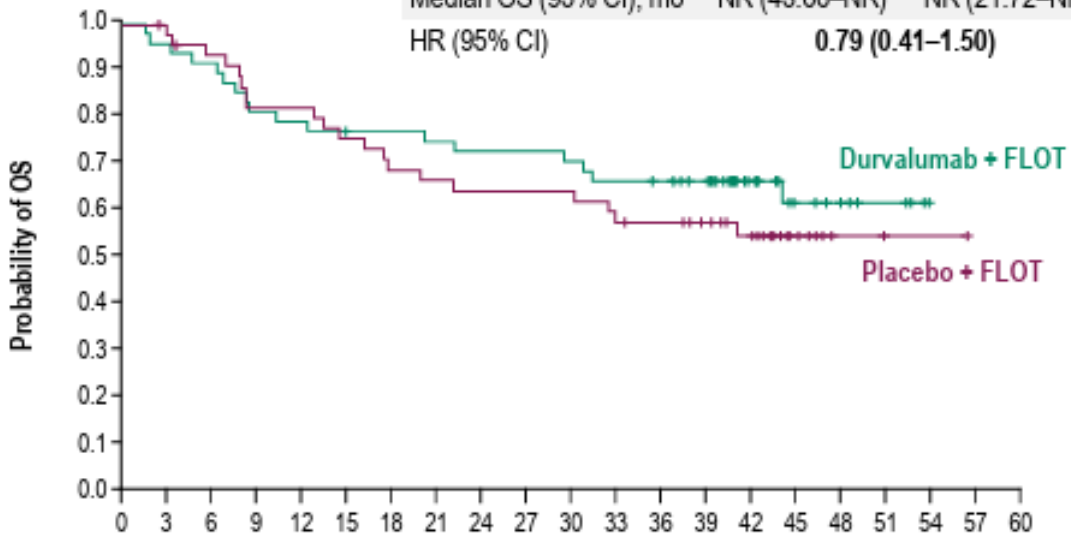
	Durvalumab + FLOT (n=426)	Placebo + FLOT (n=427)
Median OS (95% CI), mo	NR (NR–NR)	NR (NR–NR)
HR (95% CI)	0.79 (0.63–0.99)	



No. of participants at risk																						Total no. of events
Durvalumab + FLOT	426	418	394	383	365	353	341	332	317	304	301	292	286	229	165	101	64	25	6	1	0	143
Placebo + FLOT	427	412	397	377	358	340	324	308	295	281	270	267	253	200	152	91	59	22	6	0	0	172

PD-L1 TAP <1%*

	Durvalumab + FLOT (n=48)	Placebo + FLOT (n=47)
Median OS (95% CI), mo	NR (43.66–NR)	NR (21.72–NR)
HR (95% CI)	0.79 (0.41–1.50)	



No. of participants at risk																						Total of eve
Durvalumab + FLOT	48	46	44	39	38	36	36	35	34	34	33	31	30	26	17	11	7	4	0	0	0	17
Placebo + FLOT	47	45	42	37	37	34	31	30	29	29	28	26	25	21	15	8	2	1	1	0	0	2

*Measured by immunohistochemistry using VENTANA PD-L1 (SP263) Companion Diagnostic Assay (Roche Diagnostics; investigational use only) and recorded at randomisation on the Interactive Response Technology System, Randomisation and Trial Supply Management, Electronic Case Report Form or from external vendor data from samples collected on or before randomisation. Participants provided a tumour tissue sample at screening to determine PD-L1 status using the TAP scoring method.

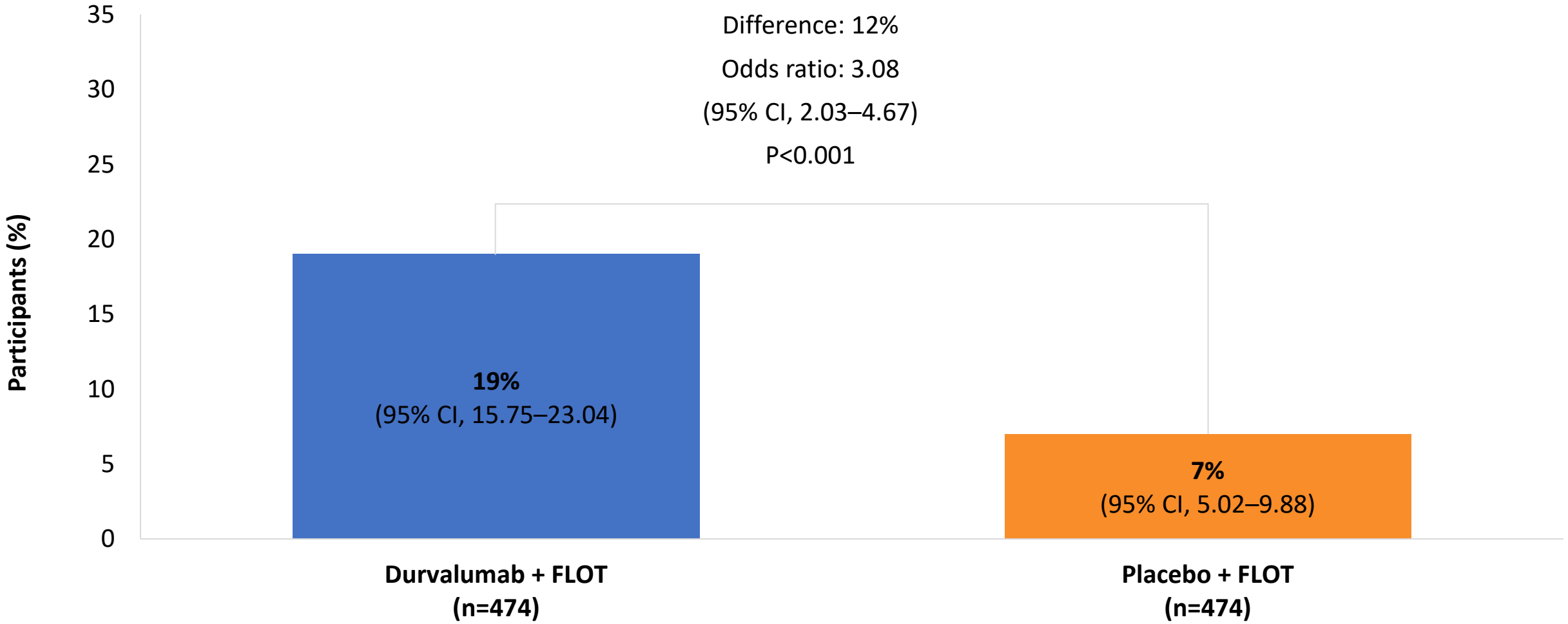
Data cut-off: 01 September 2025. The HR and its CI were estimated from a Cox proportional hazards model. The CI for the HR was calculated using a profile likelihood approach.

CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; HR, hazard ratio; NR, not reached; OS, overall survival; PD-L1, programmed cell death ligand-1; TAP, Tumour Area Positivity.

Josep Tabernero

MATTERHORN: pCR Assesment

pCR: A Statistically Significant Improvement With the Addition of Durvalumab to FLOT

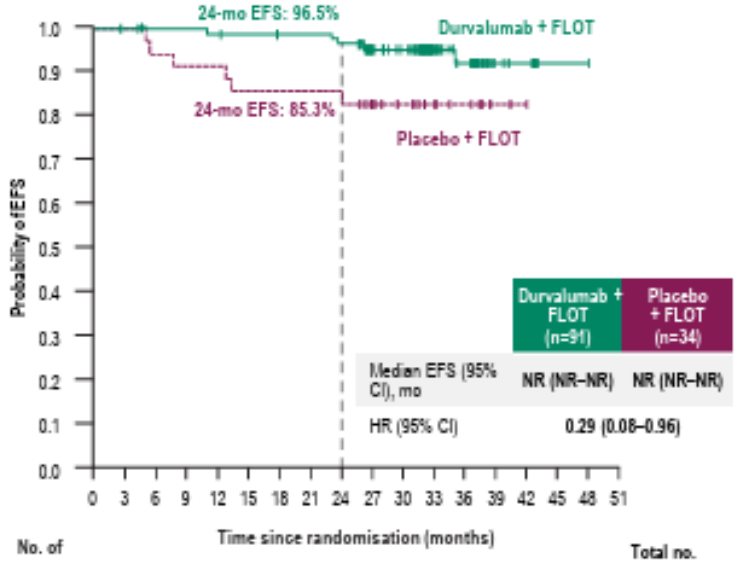


Janjigian, Y, *et al.* (2025). Perioperative durvalumab in gastric and gastroesophageal junction cancer. *The New England Journal of Medicine, 390*(22)

Pathological response and EFS

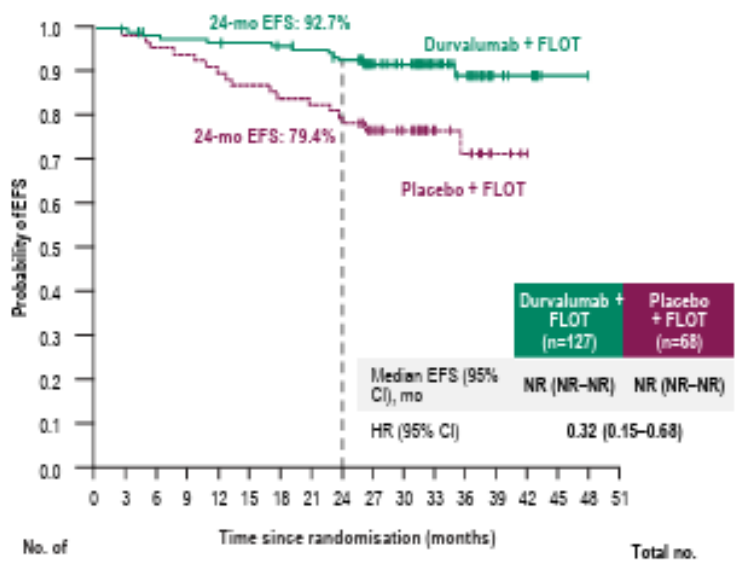
EFS was improved with durvalumab + FLOT versus placebo + FLOT among participants with any degree of pathological response

pCR



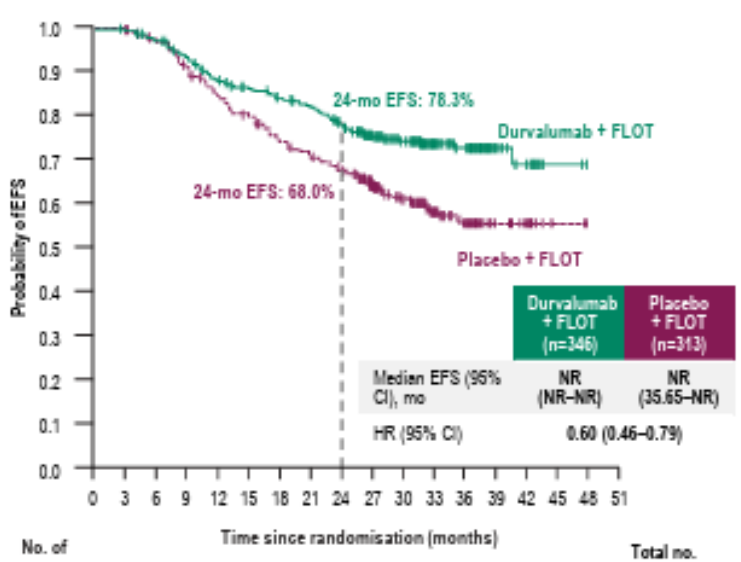
No. of participants at risk																			Total no. of events
Durvalumab + FLOT	91	90	88	88	87	86	85	85	83	68	60	38	27	7	5	1	1	0	5
Placebo + FLOT	34	34	32	31	31	29	29	29	29	23	16	11	8	2	1	0	0	0	6

MPR



No. of participants at risk																			Total no. of events
Durvalumab + FLOT	127	126	122	121	120	119	117	115	111	91	78	45	34	9	6	1	1	0	11
Placebo + FLOT	68	67	65	64	61	59	57	56	54	45	35	19	13	3	1	0	0	0	17

Any pathological response*



No. of participants at risk																			Total no. of events
Durvalumab + FLOT	346	343	330	314	295	283	273	265	248	201	162	90	75	28	17	2	1	0	87
Placebo + FLOT	313	312	300	279	257	242	224	213	200	160	129	74	54	21	17	2	1	0	123

*Among participants who completed surgery with samples that were evaluable for modified Ryan scoring by central assessment, the rate of participants who achieved any pathological response was 89.9% in the durvalumab + FLOT arm and 84.1% in the placebo + FLOT arm.
Data cut-off: 20 December 2024. pCR is defined as modified Ryan score of 0; MPR is defined as modified Ryan score of 0 and 1; any pathological response is defined as modified Ryan score 0, 1, and 2. Events were defined as the earliest of RECIST v1.1 events, non-RECIST v1.1 events or deaths due to any cause. Analysis was based on BICR assessments and / or locally by pathology testing if clinically required. The HR and its CI were estimated from a Cox proportional hazards model. The CI for the HR was calculated using a profile likelihood approach.
BICR, blinded independent central review; CI, confidence interval; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; HR, hazard ratio; mo, month; MPR, major pathological response; NR, not reached; pCR, pathological complete response; RECIST v1.1, Response Evaluation Criteria for Solid Tumors version 1.1.

Nodal staging assessment by investigator

The rate of participants who achieved ypN- was higher in those receiving durvalumab + FLOT versus placebo + FLOT

	Durvalumab + FLOT (n=411)*	Placebo + FLOT (n=400)*
ypN staging at surgery, n (%)	411 (100.0)	400 (100.0)
Total N-	239 (58.2)	179 (44.8)
Downstaged to N-	148 (36.0)	112 (28.0)
Persistent N-	89 (21.7)	67 (16.8)
Total N+ (persistent or upstaged)	171 (41.6)	220 (55.0)

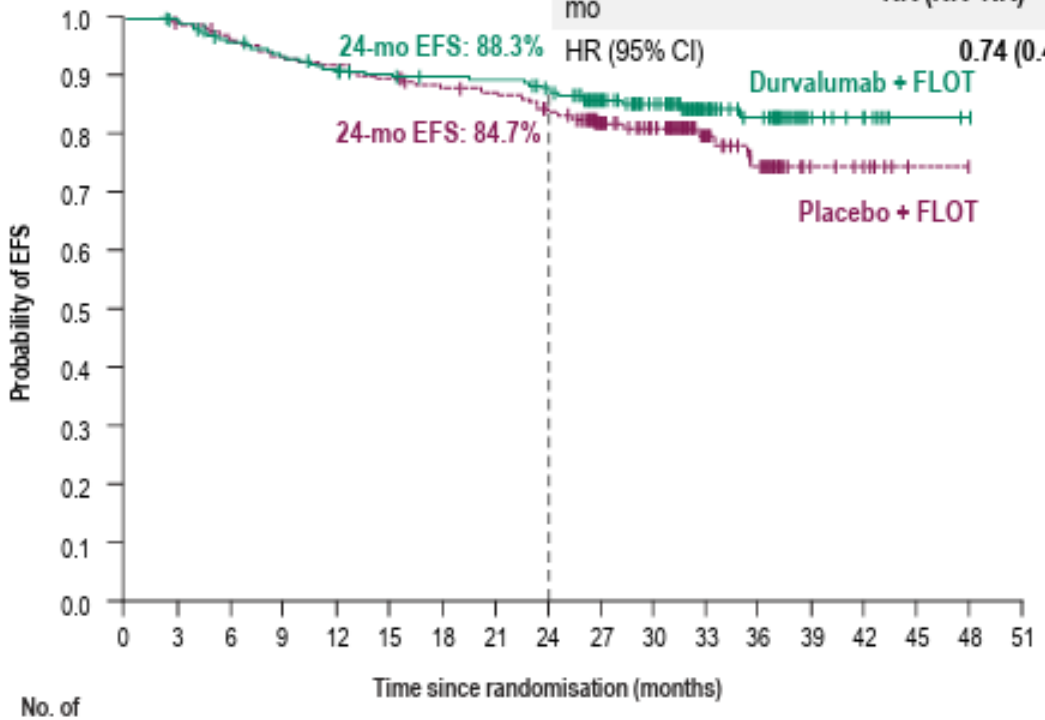
*Participants who completed surgery with samples that were evaluable for nodal involvement by investigator assessment.
Data cut-off: 20 December 2024.
FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; ypN, pathological nodal status.

Nodal staging and EFS

EFS was improved with durvalumab + FLOT versus placebo + FLOT, regardless of ypN status

ypN-

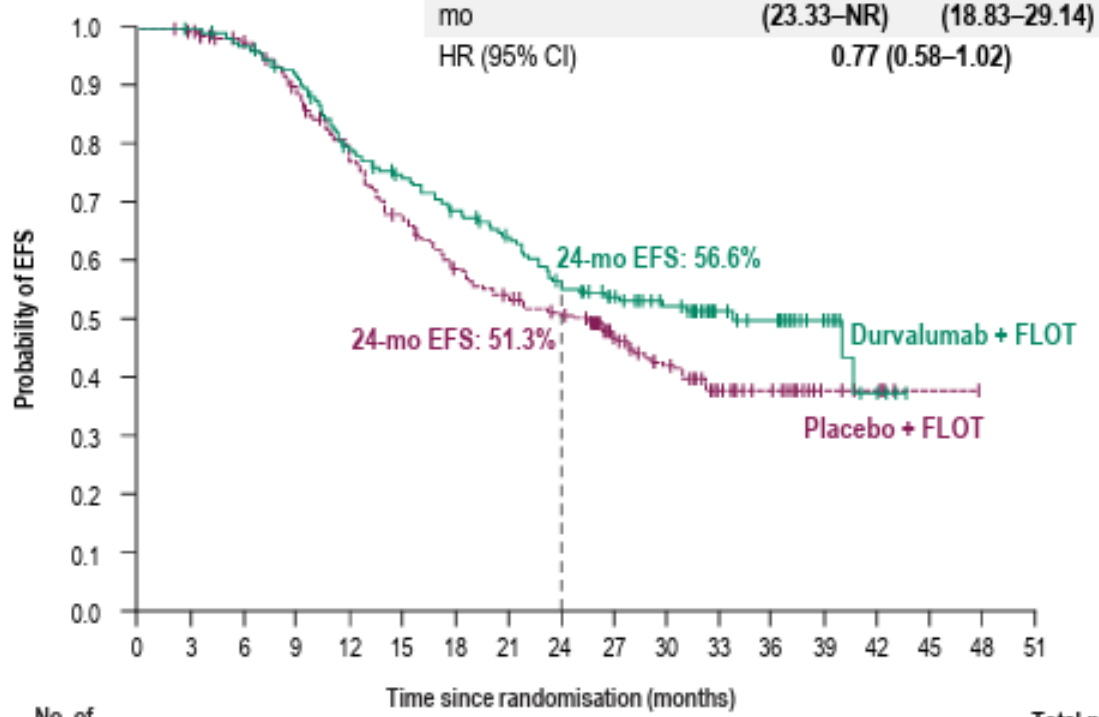
	Durvalumab + FLOT (n=239)	Placebo + FLOT (n=179)
Median EFS (95% CI), mo	NR (NR–NR)	NR (NR–NR)
HR (95% CI)	0.74 (0.46–1.18)	



No. of participants at risk																			Total no. of events
Durvalumab + FLOT	239	237	224	217	211	206	203	202	196	158	123	71	57	19	15	2	1	0	35
Placebo + FLOT	179	178	172	166	163	159	155	152	145	123	99	57	40	16	13	1	1	0	36

ypN+

	Durvalumab + FLOT (n=172)	Placebo + FLOT (n=221)
Median EFS (95% CI), mo	33.84 (23.33–NR)	25.56 (18.83–29.14)
HR (95% CI)	0.77 (0.58–1.02)	



No. of participants at risk																			Total no. of event
Durvalumab + FLOT	172	171	165	154	132	121	110	100	87	72	60	32	28	13	5	0	0		81
Placebo + FLOT	221	218	207	187	161	139	119	108	100	75	59	31	25	10	8	1	0		121

Data cut-off: 20 December 2024. Events were defined as the earliest of RECIST v1.1 events, non-RECIST v1.1 events or deaths due to any cause. Analysis was based on BICR assessments and / or locally by pathology testing if clinically required. The HR and its CI were estimated from a Cox proportional hazards model. The CI for the HR was calculated using a profile likelihood approach.

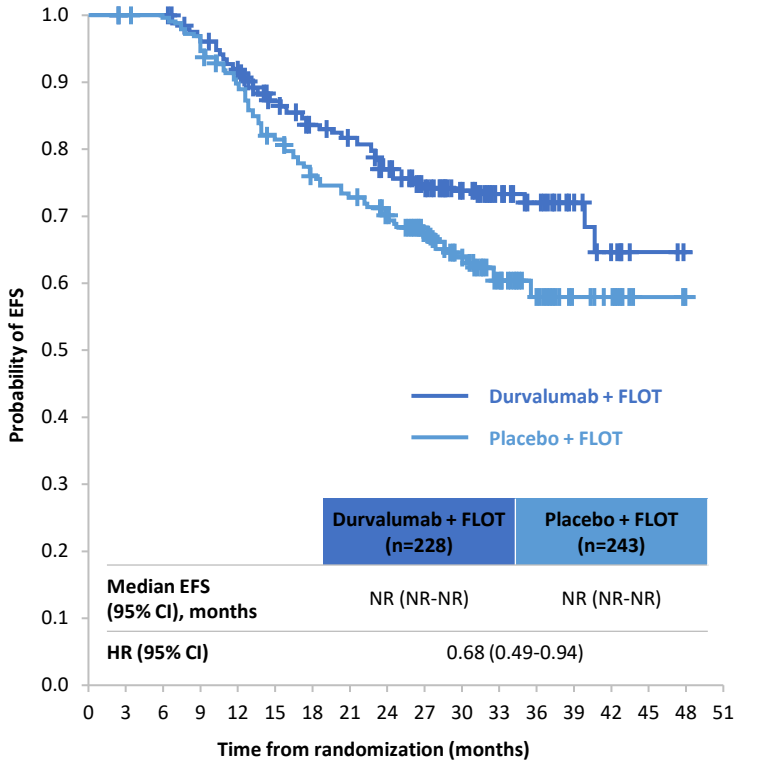
BICR, blinded independent central review; CI, confidence interval; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; HR, hazard ratio; mo, month; NR, not reached; RECIST v1.1, Response Evaluation Criteria for Solid Tumors version 1.1; ypN, pathological nodal status.

Josep Tabernero

EFS by FLOT completion status

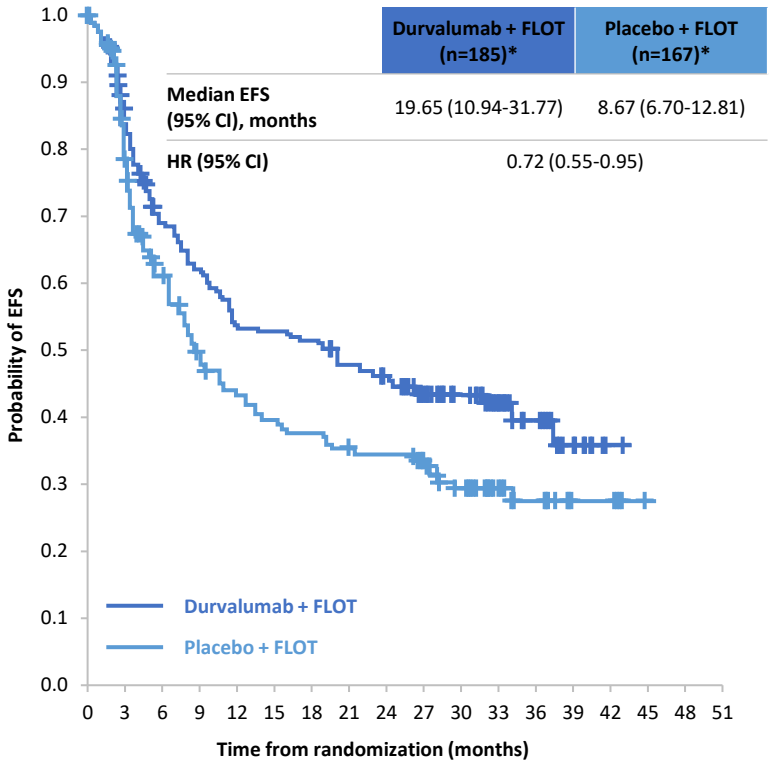
- EFS was improved with durvalumab + FLOT versus placebo + FLOT regardless of FLOT completion status

Participants who completed all cycles of FLOT



No. of participants at risk																		Total no. of events
Durvalumab + FLOT	228	227	227	217	204	189	177	172	160	132	112	66	57	25	16	2	1	0	59
Placebo + FLOT	243	243	242	233	215	196	180	173	162	132	104	59	46	20	16	2	1	0	89

Participants who discontinued all FLOT



No. of participants at risk																		Total no. of events
Durvalumab + FLOT	183	146	114	102	89	87	85	78	74	58	41	22	14	4	1	0		98
Placebo + FLOT	167	124	88	69	60	55	52	48	47	39	30	17	11	4	4	0		104

FLOT discontinuation and EFS

	Durvalumab + FLOT (n=474)	Placebo + FLOT (n=470)	EFS HR (95% CI)
Discontinued any FLOT components, n (%)	246 (51.9)	227 (48.3)	0.68 (0.53-0.88)
Discontinued 1 FLOT components, n (%)	47 (9.9)	45 (9.6)	
Discontinued 2 FLOT components, n (%)	15 (3.2)	15 (3.2)	0.35 (0.16-0.71)†
Discontinued 3 FLOT components, n (%)	1 (0.2)	0	
Discontinued all FLOT, n (%)*	183 (38.6)	167 (35.5)	0.72 (0.55-0.95)

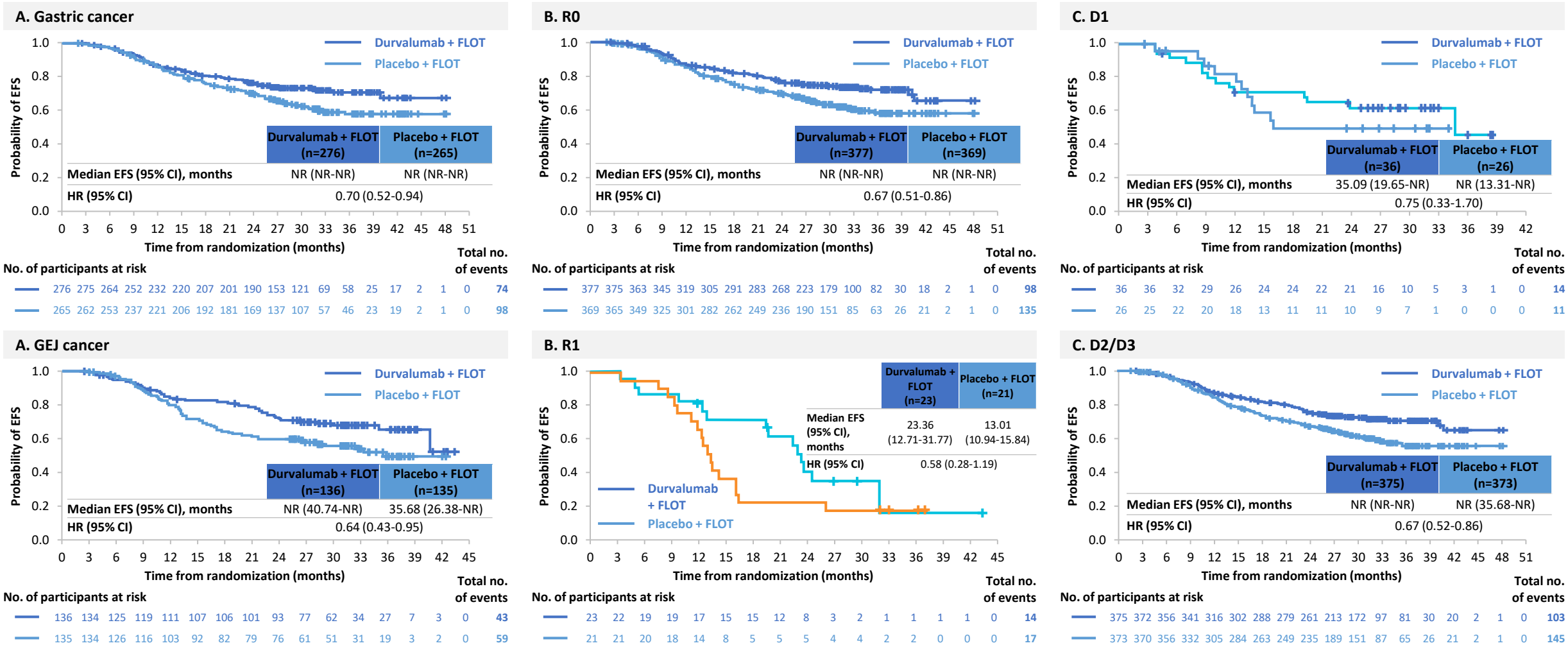
Analyses performed in the intention-to-treat analysis set (all randomized participants, regardless of treatment received). HRs show durvalumab + FLOT versus placebo + FLOT, with an HR <1 favoring durvalumab + FLOT.
*Includes 62 participants in the durvalumab + FLOT arm and 70 participants in the placebo + FLOT arm who did not complete surgery. †In participants who discontinued 1, 2, or 3 of the 4 FLOT components.
CI, confidence interval; HR, hazard ratio; NR, not reached.

EFS benefit with durvalumab + FLOT : Surgical Journey

EFS

- EFS improved with durvalumab + FLOT versus placebo + FLOT regardless of tumor location (**Figure 2A**), resection margin (**Figure 2B**), and lymphadenectomy type (**Figure 2C**)

Figure 2. EFS by (A) tumor location, (B) resection margin, and (C) lymphadenectomy type



Molena, D et al. ASCO GI 2026

MATTERHORN: Safety

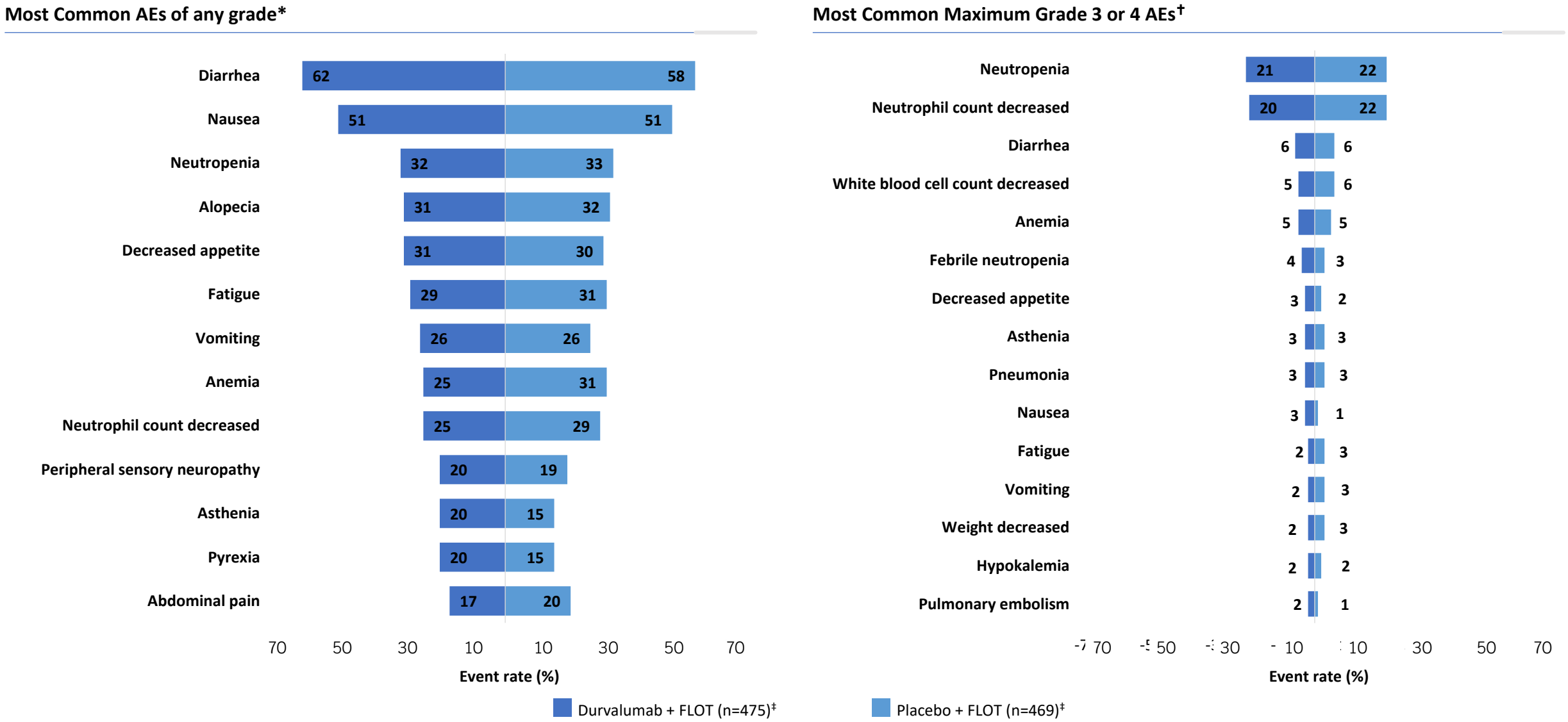
Safety: AEs Aligned With Known Profiles

No new concerns identified with durvalumab and FLOT

	Durvalumab + FLOT (n=475)*	Placebo + FLOT (n=469)*
Any Grade AE, %	**99**	**99**
Possibly related to any study treatment	95	95
Grade 3 or 4 AE, %	**72**	**71**
Possibly related to any study treatment	60	59
Serious AE, %	**48**	**44**
AE leading to discontinuation of any study treatment, %	**30**	**23**
Durvalumab or placebo	10	6
Any FLOT	25	20
AE with outcome of death, %	**5**	**4**
Possibly related to durvalumab or placebo	1	<1
Possibly related to FLOT	1	<1
imAE (any grade), %†	**23**	**7**
Grade 3 or 4 imAE	7	4
Any AE leading to surgery not being performed, %	**1**	**<1**
Any AE leading to a delay in surgery, %‡	**2**	**3**

Janjigian, Y, *et al.* (2025). Perioperative durvalumab in gastric and gastroesophageal junction cancer. *The New England Journal of Medicine, 390*(22)

MATTERHORN: Adverse Effects



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NCCN Guidelines: Esophageal and Esophagogastric Junction Cancers V1.2026

Principles of systemic therapy

Perioperative Systemic Therapy	Definitive Chemoradiation (Infusional fluorouracil can be replaced with capecitabine)
Preferred • Fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT)(category 1) • FLOT[a] + durvalumab for PD-L1 CPS ≥1 or TAP ≥1% (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)	**Preferred** • Paclitaxel and carboplatin[5] • Fluorouracil[a] and oxaliplatin (category 1)
Other Recommended • Fluorouracil and cisplatin (category 1) • Fluoropyrimidine and oxaliplatin	**Other Recommended** • Fluorouracil and cisplatin (category 1) • Cisplatin with docetaxel or paclitaxel • Irinotecan and cisplatin (category 2B) • Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)
Preoperative Chemoradiation **(Infusion fluorouracil[a] can be replaced with capecitabine)**	**Postoperative Systemic Therapy**
Preferred • Paclitaxel and carboplatin (category 1) • Fluorouracil[a] and oxaliplatin (category 1)	**Preferred** • Nivolumab only after preoperative chemoradiation with R0 resection and residual disease (category 1)
Other Recommended • Fluorouracil and cisplatin (category 1) • Irinotecan and cisplatin (category 2B) • Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)	**Other Recommended** • Capecitabine and oxaliplatin • Fluorouracil[a] and oxaliplatin • Fluoropyrimidine (infusional fluorouracil[a] or capecitabine) before and after fluoropyrimidine-based chemoradiation
Neoadjuvant or Perioperative Immunotherapy	
Useful in certain circumstances • MSI-H/dMMR tumors – Dostarlimab-gxly for neoadjuvant therapy only – Nivolumab and ipilimumab followed by nivoluma – Pembrolizumab – Tremelimumab and durvalumab for neoadjuvant therapy only	

THANK YOU