ESMO Gastric Cancer Update: The Impact of the Matterhorn Clinical Trial on the Management of Gastric Cancer

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Translating novel therapies for GC / GEJC into clinical practice

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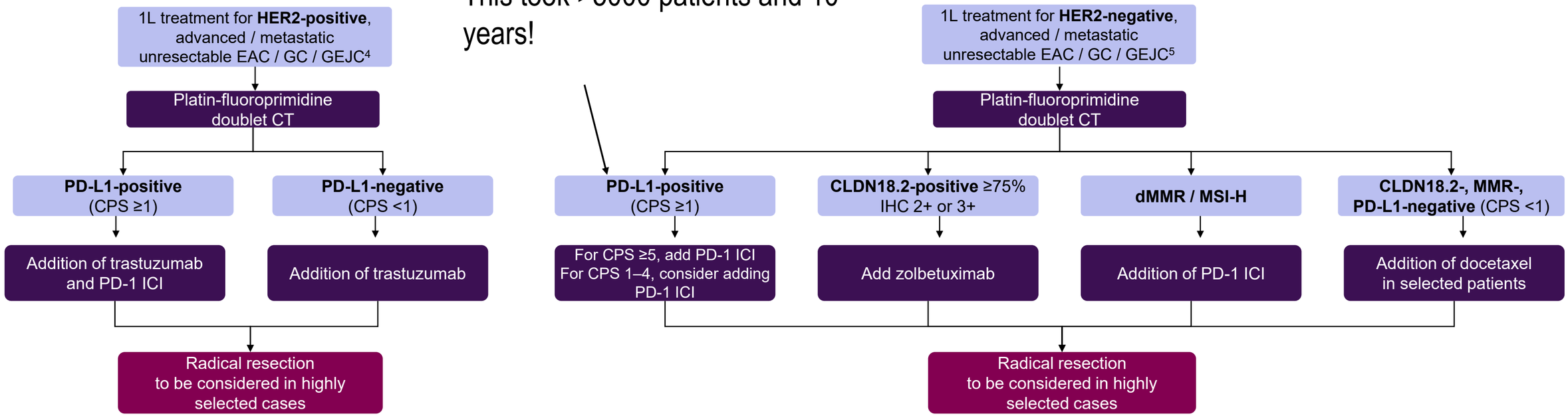
Disclosures

- Dr. Wainberg has served as a consultant or advisor to Alligator, Amgen, Arcus, AstraZeneca, Bayer, Bristol Myers Squibb, Ipsen, Jannsen, Lilly, Merck, Merck KGaA, Novartis, and Pfizer; has received institutional research funding from Merck, Novartis, and Plexxikon; and has been reimbursed for travel, accommodations, or other expenses by Amgen, Lilly, and Merck.

Biomarker expression guides treatment decision-making for advanced unresectable GC / GEJC

- **Gastroesophageal cancers**, such as GC and GEJC, are often detected at an advanced stage of disease, with high mortality rates[1–3]
- The treatment of locally advanced, unresectable or metastatic GC / GEJC depends on the biomarker profile of the patient[4–8]

This took >5000 patients and 10 years!



Adapted from the ESMO Living Guidelines

1L, first-line; CLDN 18.2, Claudin 18.2; CPS, combined positive score; CT, chemotherapy; dMMR, deficient mismatch repair; EAC, oesophageal adenocarcinoma; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HER2, human epidermal growth factor receptor; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; MMR, mismatch repair; MSI-H, microsatellite instability high; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1.

1. Xiao H, et al. *BMC Cancer* 2023;23:186. 2. NIH. Cancer Stat Facts: Stomach Cancer. https://seer.cancer.gov/statfacts/html/stomach.html. Accessed 7 April, 2025. 3. NIH. Cancer Stat Facts: Esophageal Cancer. https://seer.cancer.gov/statfacts/html/esoph.html. Accessed 7 April, 2025. 4. ESMO Gastric Cancer Living Guideline. First-line HER2-positive. v1.4 - September 2024. https://www.esmo.org/guidelines/living-guidelines/esmo-living-guideline-gastric-cancer/metastatic-disease/first-line-for-her2-positive. Accessed 14 August 2025. 5. ESMO Gastric Cancer Living Guideline. First-line HER2-negative. v1.4 - September 2024. https://www.esmo.org/guidelines/living-guidelines/esmo-living-guideline-gastric-cancer/metastatic-disease/first-line-for-her2-negative. Accessed 14 August 2025. 6. Shitara K, et al. *ESMO Open* 2024;9:102226. 7. NCCN Guidelines. Gastric Cancer. v2.2025. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed 16 April 2025. 8. NCCN Guidelines. Esophageal and Esophagogastric Junction Cancers. v2.2025. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed 16 April 2025.

Global guidelines recommend molecular testing to guide treatment decisions in advanced GC / GEJC

Guideline recommendations: molecular testing practices[1–7]

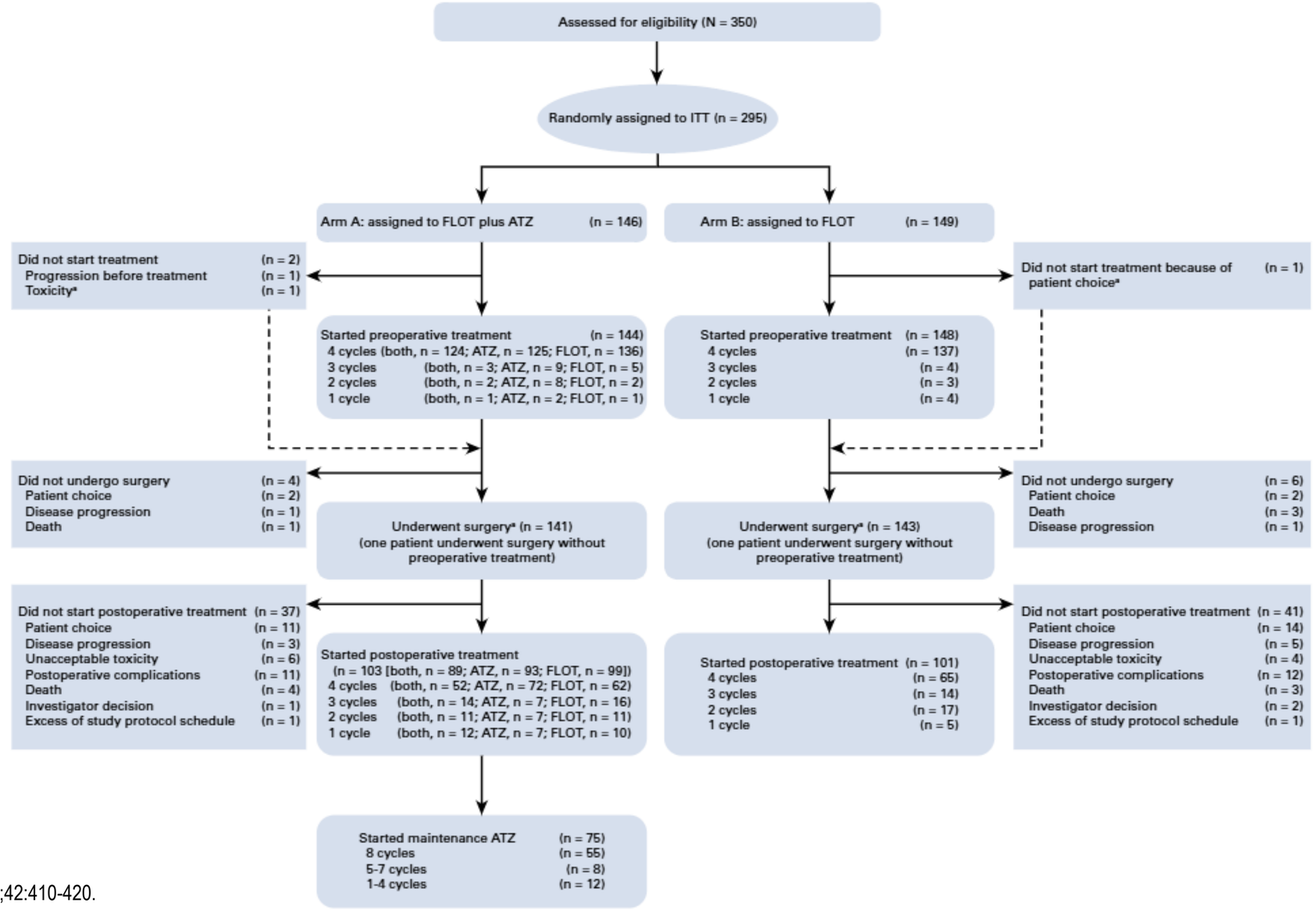
Biomarker		HER2				PD-L1			MSI / MMR			CLDN18.2		
Guidelines		NCCN	ESMO	Pan-Asian	ASCO	NCCN	ESMO	Pan-Asian	NCCN	ESMO	Pan-Asian	NCCN	ESMO	Pan-Asian
Who	All newly diagnosed								✓	✓	✓			
	Locally advanced, recurrent or metastatic	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	†
When	At diagnosis	✓				✓			✓	✓	✓		✓	
	Before 1L		✓	✓	✓		✓	✓						†
	Before 2L / intent to treat	*												†
How		NCCN: IHC / ISH / PCR is preferred initially, followed by NGS if appropriate[1,2]				NCCN: IHC of a minimum 100 tumour cells			PCR / NGS (MSI) and IHC (MMR)			IHC		

*Repeat biomarker testing may be considered at clinical or radiologic progression of advanced or metastatic disease. †Recommended if available.

1L, first-line; 2L, second-line; AE, adverse event; CLDN18.2, Claudin 18.2; ESMO, European Society for Medical Oncology; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridisation; MMR, mismatch repair; MSI, microsatellite instability; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; PCR, polymerase chain reaction; PD-L1, programmed cell death ligand-1.

1. NCCN Guidelines. Gastric Cancer. v2.2025. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed 16 April 2025. 2. NCCN Guidelines. Esophageal and Esophagogastric Junction Cancers. v2.2025. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed 16 April 2025. 3. Lordick F, et al. Ann Oncol 2022;33:1005–1020. 4. Obermannová R, et al. Ann Oncol 2025;10:104134. 5. Shitara K, et al. ESMO Open 2024;9:102226. 6. Shah MA, et al. J Clin Oncol 2023;41:1470–1491. 7. Bartley AN, et al. J Clin Oncol 2017;35:446-464.

Phase II/III DANTE/IKF-s633 Trial: Perioperative Atezolizumab Plus Fluorouracil, Leucovorin, Oxaliplatin, and Docetaxel for Resectable Esophagogastric Cancer



- Lorenzen S, et al. J Clin Oncol. 2024;42:410-420.

DANTE
Results

- Surgical morbidity (A, 45%; B, 42%) and 60-day mortality (A, 3%; B, 2%) were comparable between arms. Downstaging favored arm A versus arm B (ypT0, 23% *v* 15% [one-sided *P* = .044]; ypT0-T2, 61% *v* 48% [one-sided *P* = .015]; ypN0, 68% *v* 54% [one-sided *P* = .012]).

- Histopathologic complete regression rates (pathologic complete response or TRG1a) were higher after FLOT plus ATZ (A, 24%; B, 15%; one-sided *P* = .032), and the difference was more pronounced in the PD-L1 CPS ≥10 (A, 33%; B, 12%) and MSI (A, 63%; B, 27%) subpopulations. Complete margin-free (R0) resection rates were relatively high in both arms (A, 96%; B, 95%).

- The incidence and severity of adverse events were similar in both groups.

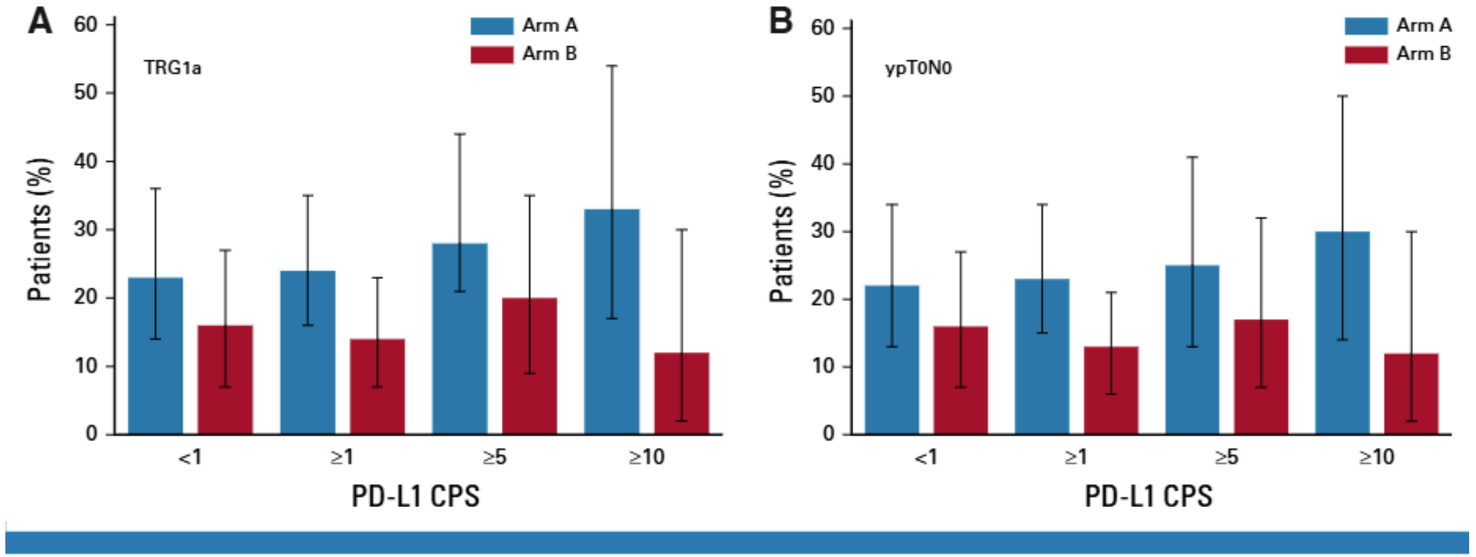


FIG 2. Outcomes by PD-L1 CPS. (A) Complete pathologic regression (TRG1a) and (B) ypT0N0 stage rates with 95% CI on the basis of PD-L1 CPS are shown for arm A and arm B. CPS, combined positive score.

Lorenzen S, et al. J Clin Oncol. 2024;42:410-420.

BERLIN 2025 ESMO congress

Final overall survival and the association of pathological outcomes with event-free survival in MATTERHORN: a randomised, Phase 3 study of durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin and docetaxel in resectable gastric/gastroesophageal junction adenocarcinoma

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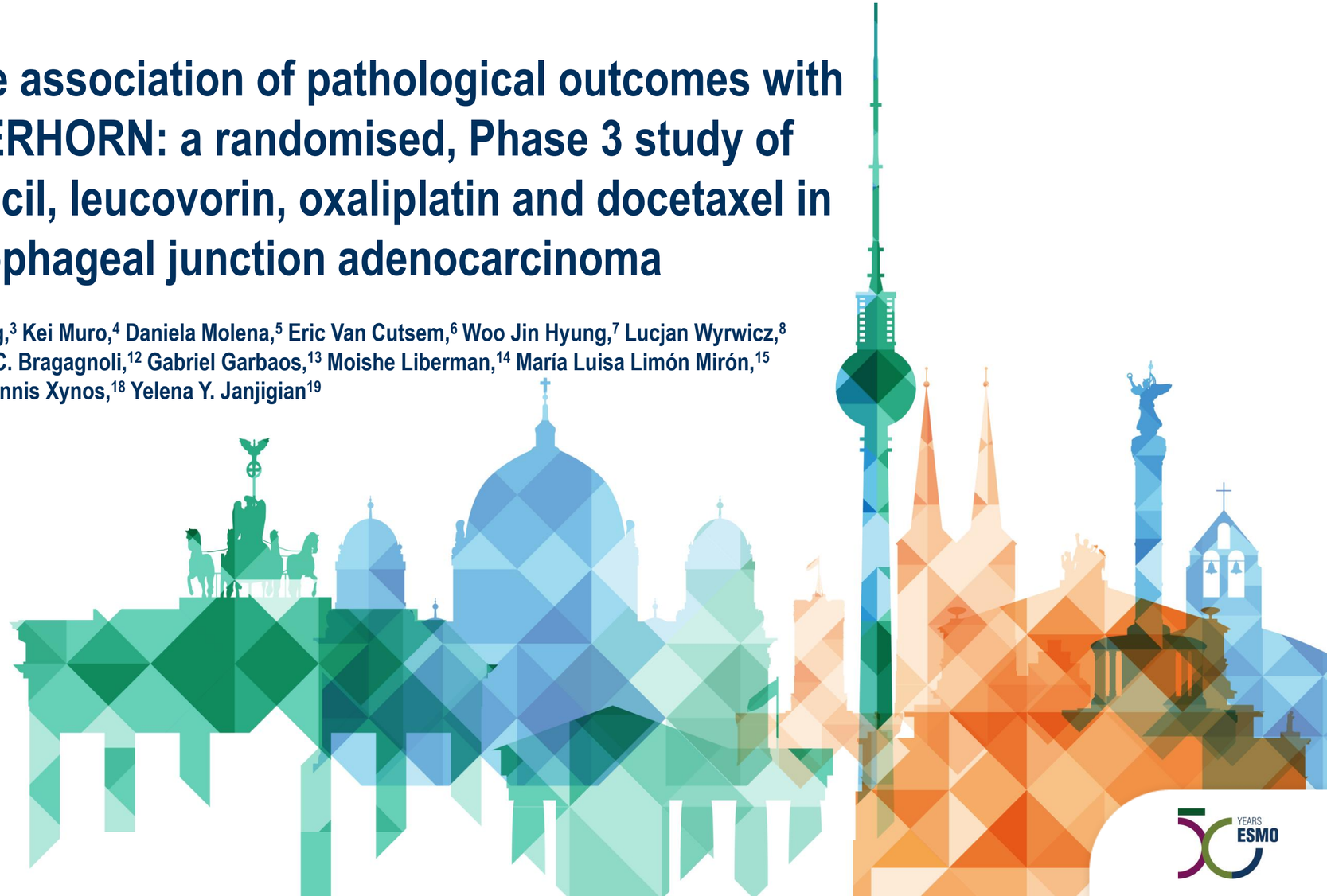


17–21 October 2025

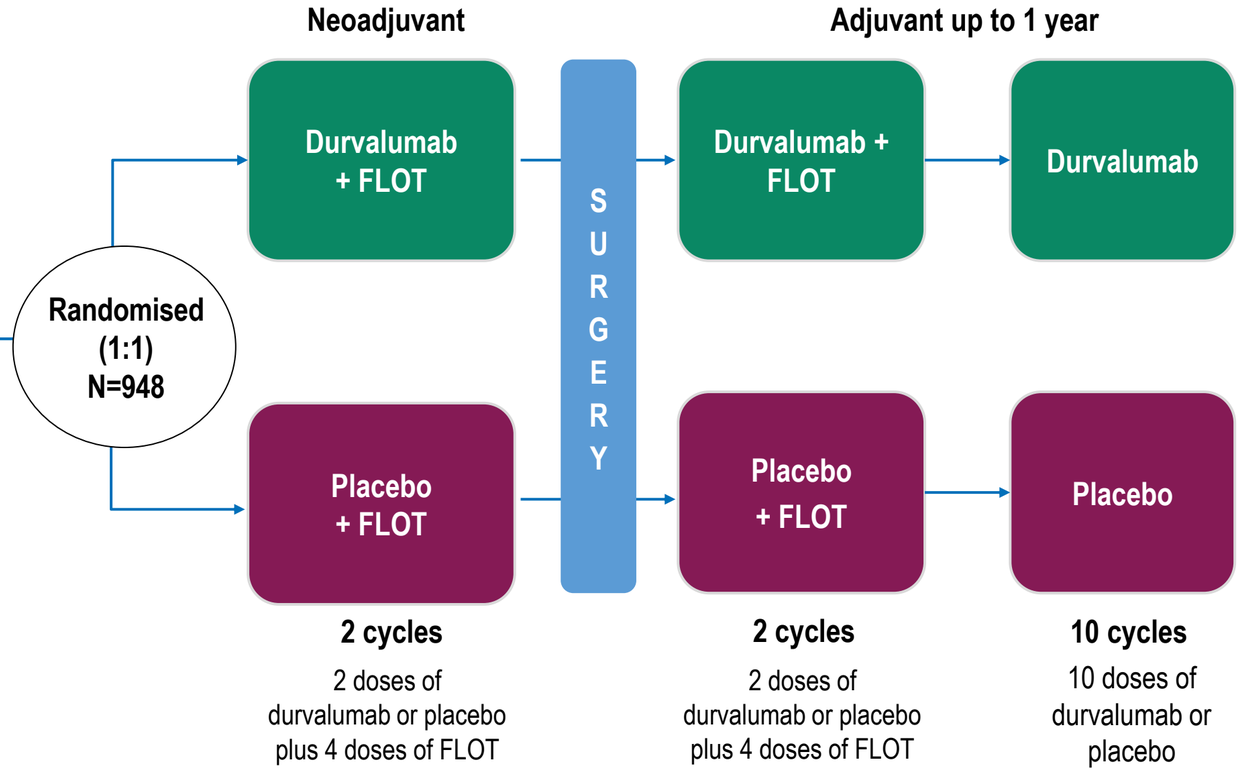
50 YEARS ESMO

MATTERHORN study design[1,2]

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

Study population
- G / GEJ adenocarcinoma
- Stage II–IVA per American Joint Committee on Cancer 8th edition
- No evidence of metastasis
- No prior therapy
- ECOG PS 0 or 1
- Global enrolment from Asia, Europe, North America and South America

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



Primary endpoint:
- EFS

Key secondary endpoints:
- OS
- pCR (central review by modified Ryan criteria)

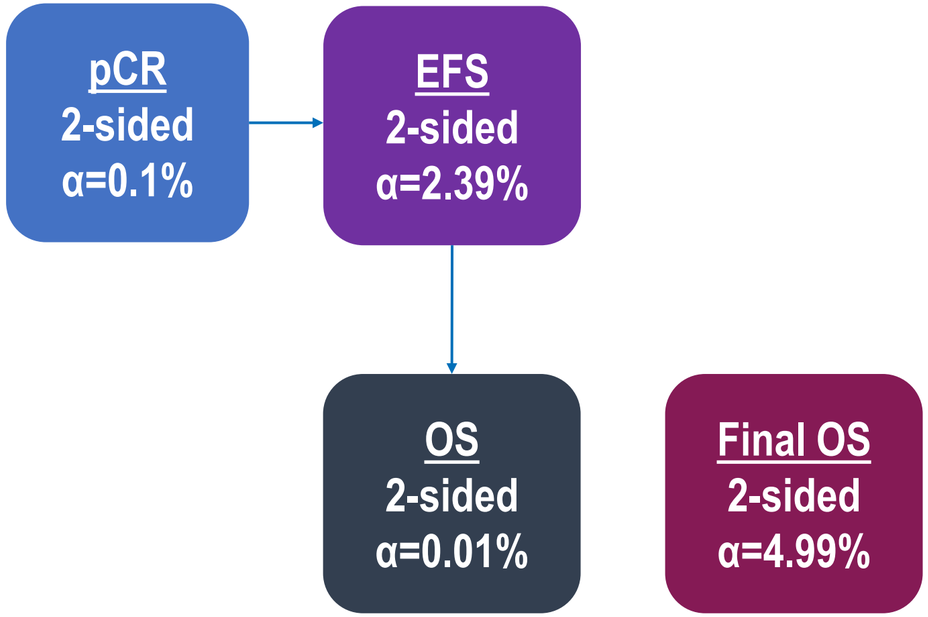
*Measured by immunohistochemistry using VENTANA PD-L1 (SP263) Companion Diagnostic Assay (Roche Diagnostics; investigational use only) and recorded at randomisation on the Interactive Response Technology System, Randomisation and Trial Supply Management, Electronic Case Report Form or from external vendor data from samples collected on or before randomisation.
FLOT: 5-fluorouracil 2600 mg/m^2, leucovorin 200 mg/m^2, oxaliplatin 85 mg/m^2, docetaxel 50 mg/m^2, on Days 1 and 15 Q4W, 4 doses (2 cycles) pre- and post-operative; durvalumab: 1500 mg on Day 1 Q4W, 2 doses (2 cycles) of durvalumab or placebo pre- and post-operative, followed by 10 doses of post-operative durvalumab or placebo monotherapy. Participants underwent surgery 4–8 weeks after last dose of neoadjuvant therapy. Adjuvant therapy began 4–12 weeks post-surgery. Durvalumab or placebo monotherapy may be continued if post-operative FLOT is discontinued due to toxicity.
ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; G / GEJ, gastric / gastroesophageal junction; OS, overall survival; pCR, pathological complete response; PD-L1, programmed cell death ligand-1; PS, performance status; Q4W, every 4 weeks; TAP, tumour area positivity.
1. Janjigian YY, et al. *N Engl J Med* 2025;393:217–230. 2. Janjigian YY, et al. Presented at: ASCO Congress; 30 May–3 June 2025; Chicago, IL. Oral presentation LBA5.

Josep Tabernero

Statistical considerations[1–3]

- pCR (data cut-off: 01 February 2023)*: assessed after all patients were randomised and either underwent surgery or were deemed ineligible; results were final[3]
- EFS (data cut-off: 20 December 2024)*: triggered at 41% maturity (n=385 events), results were final; OS†: tested at EFS analysis with a minimal α-spend of 0.01% (34% maturity)
- Final OS (data cut-off: 01 September 2025): tested using the remaining α of 4.99%; results shown here

Multiple testing procedure



*An overall 5% α (2-sided) was initially split between the pCR analysis (0.1%) and EFS analysis (4.9%); given the pCR analysis was positive, the α of 0.1% for pCR was recycled to the EFS analysis. At the EFS analysis, an α of 0.01% was allocated to OS.
†Only tested if EFS was statistically significant.
EFS, event-free survival; OS, overall survival; pCR, pathological complete response.
1. Janjigian YY, et al. *N Engl J Med* 2025;393:217–230. 2. Janjigian YY, et al. Presented at: ASCO Congress; 30 May–3 June 2025; Chicago, IL. Oral presentation LBA5. 3. Janjigian YY, et al. *Ann Oncol* 2023;34:S1315–S1316. Abs LBA73.

Baseline characteristics

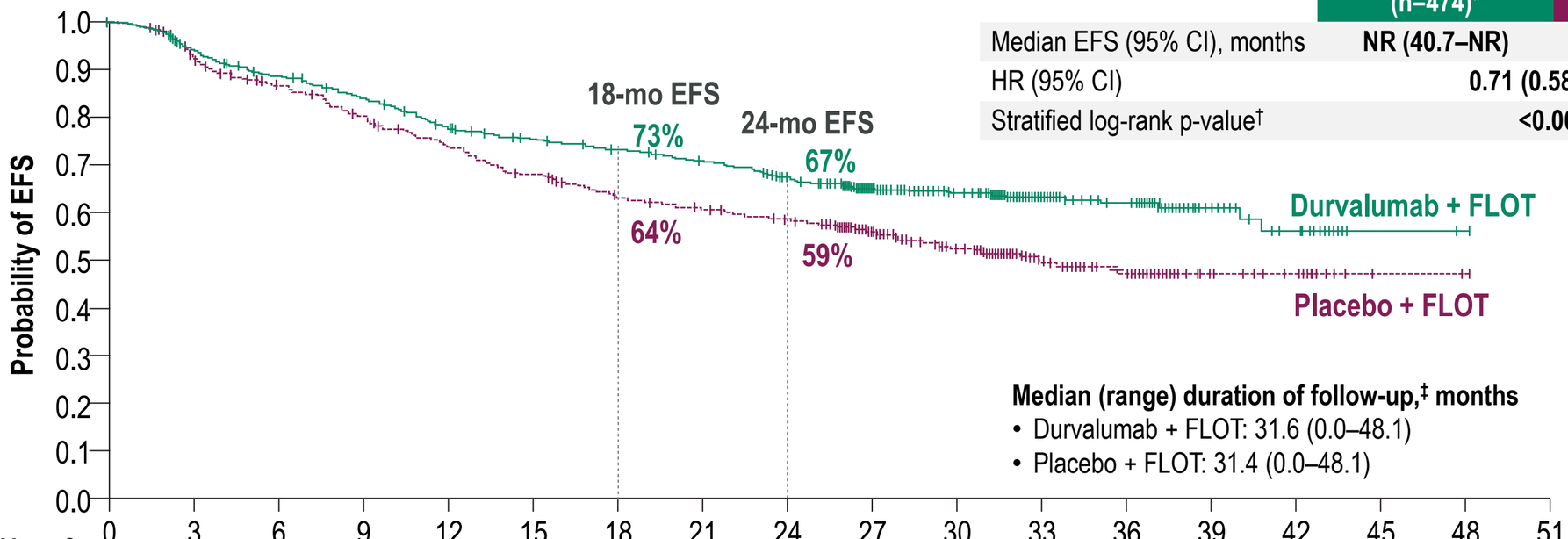
		Central pathology analysis set*		ypN evaluable analysis set†	
		Durvalumab + FLOT (n=385)	Placebo + FLOT (n=372)	Durvalumab + FLOT (n=411)	Placebo + FLOT (n=400)
Median age, years (range)		61.0 (27–84)	63.0 (29–81)	61.0 (27–84)	62.0 (29–81)
Sex, n (%)	Male	264 (68.6)	286 (76.9)	286 (69.6)	304 (76.0)
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	



Median (range) duration of follow-up,‡ months

- Durvalumab + FLOT: 31.6 (0.0–48.1)
- Placebo + FLOT: 31.4 (0.0–48.1)

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.

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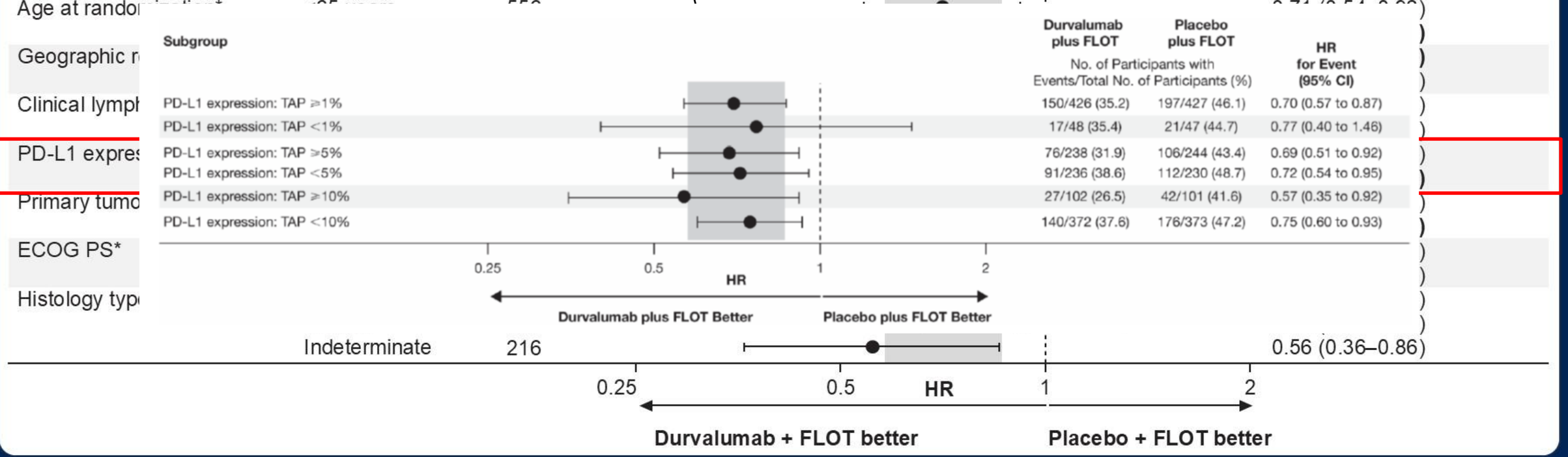
EFS in Key Subgroups: Consistent Benefit Observed

Should This Matter in such a small subset (n=95)?

Subgroup	Category	N	HR for event (95% CI)
All participants		948	0.71 (0.58–0.86)
Sex*	Male	682	0.65 (0.51–0.83)
	Female	266	0.84 (0.58–1.24)
Age at randomization*			
Geographic region			
Clinical lymph node involvement			
PD-L1 expression			
Primary tumor location			
ECOG PS*			
Histology type			
	Indeterminate	216	0.56 (0.36–0.86)

Subgroup	Durvalumab plus FLOT (No. of Participants with Events/Total No. of Participants (%))	Placebo plus FLOT (No. of Participants with Events/Total No. of Participants (%))	HR for Event (95% CI)
PD-L1 expression: TAP ≥1%	150/426 (35.2)	197/427 (46.1)	0.70 (0.57 to 0.87)
PD-L1 expression: TAP <1%	17/48 (35.4)	21/47 (44.7)	0.77 (0.40 to 1.46)
PD-L1 expression: TAP ≥5%	76/238 (31.9)	106/244 (43.4)	0.69 (0.51 to 0.92)
PD-L1 expression: TAP <5%	91/236 (38.6)	112/230 (48.7)	0.72 (0.54 to 0.95)
PD-L1 expression: TAP ≥10%	27/102 (26.5)	42/101 (41.6)	0.57 (0.35 to 0.92)
PD-L1 expression: TAP <10%	140/372 (37.6)	176/373 (47.2)	0.75 (0.60 to 0.93)



Gray band represents the 95% CI for the all-participants HR. The analysis was performed using a Cox proportional hazards model with treatment as the only covariate. The CI was calculated using a profile likelihood approach. Events were defined as the earliest of RECIST v1.1 events, non-RECIST v1.1 events, or deaths of any cause. Analysis was based on BICR assessment and / or locally by pathology testing if clinically required.*Pre-specified per protocol. †Assessed post hoc per local laboratory.
BICR, blinded independent central review; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GEJ, gastroesophageal junction; HR, hazard ratio; PD-L1, programmed cell death ligand-1; PS, performance status; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; TAP, Tumor Area Positivity.

Pathological and nodal assessments

- Pathological response was assessed centrally in participants who completed surgery with samples that were evaluable for modified Ryan scoring by central assessment (N=757)
  - **pCR**: modified Ryan score 0 (125 participants [**16.5%**])
  - **Non-pCR**: modified Ryan score 1, 2 and 3 (632 participants [**83.5%**])
  - **MPR**: modified Ryan score 0 and 1 (195 participants [**25.8%**])
  - **Any pathological response**: modified Ryan score 0, 1 and 2 (659 participants [**87.1%**])
- Nodal staging status was assessed locally in participants who completed surgery with samples that were evaluable for nodal involvement by investigator assessment (N=811)
  - **ypN-**: no nodal involvement (418 participants [**51.5%**])
  - **ypN+**: nodal involvement (393 participants [**48.5%**])

Modified Ryan score[1]	Response	Description
0	Complete response	No viable cancer cells
1	Near complete response	Single cells or rare small groups of cancer cells
2	Partial response	Residual cancer with evident tumour regression, but more than single cells or rare small groups of cancer cells
3	Poor or no response	Extensive residual cancer with no evident tumour regression

Data cut-off: 20 December 2024.
MPR, major pathological response; pCR, pathological complete response; ypN, pathological nodal status.
1. College of American Pathologists. Protocol for the examination of specimens from patients with carcinoma of the stomach. https://documents .cap.org/protocols/cp-giupper-stomach-20-4100.pdf. Accessed 11 September 2025.

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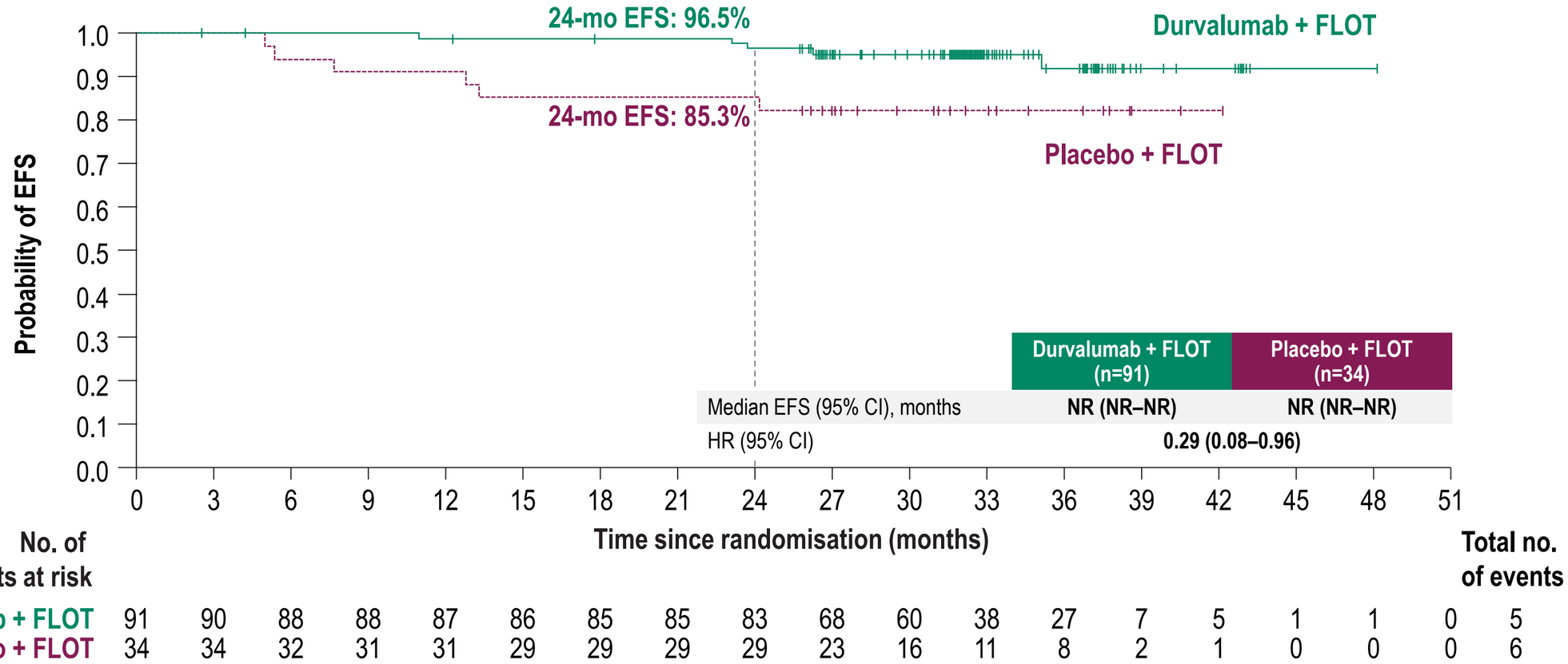
Pathological response and EFS: pCR

EFS was improved with durvalumab + FLOT versus placebo + FLOT among participants who achieved 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

Data cut-off: 20 December 2024. pCR is defined as modified Ryan score of 0. 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.

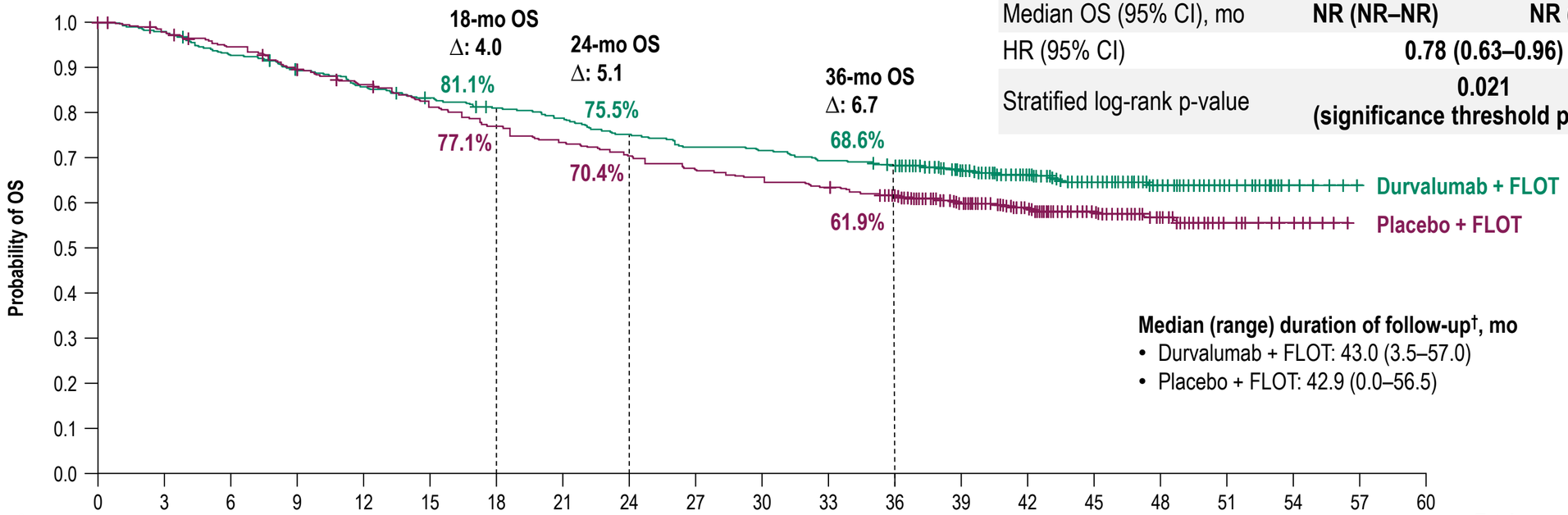
BICR, blinded independent central review; CI, confidence interval; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; HR, hazard ratio; mo, month; NR, not reached; pCR, pathological complete response; RECIST v1.1, Response Evaluation Criteria for Solid Tumors version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

Josep Tabernero

Final OS

A statistically significant and clinically meaningful improvement in OS was observed with durvalumab + FLOT 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 (3.5–57.0)
- 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

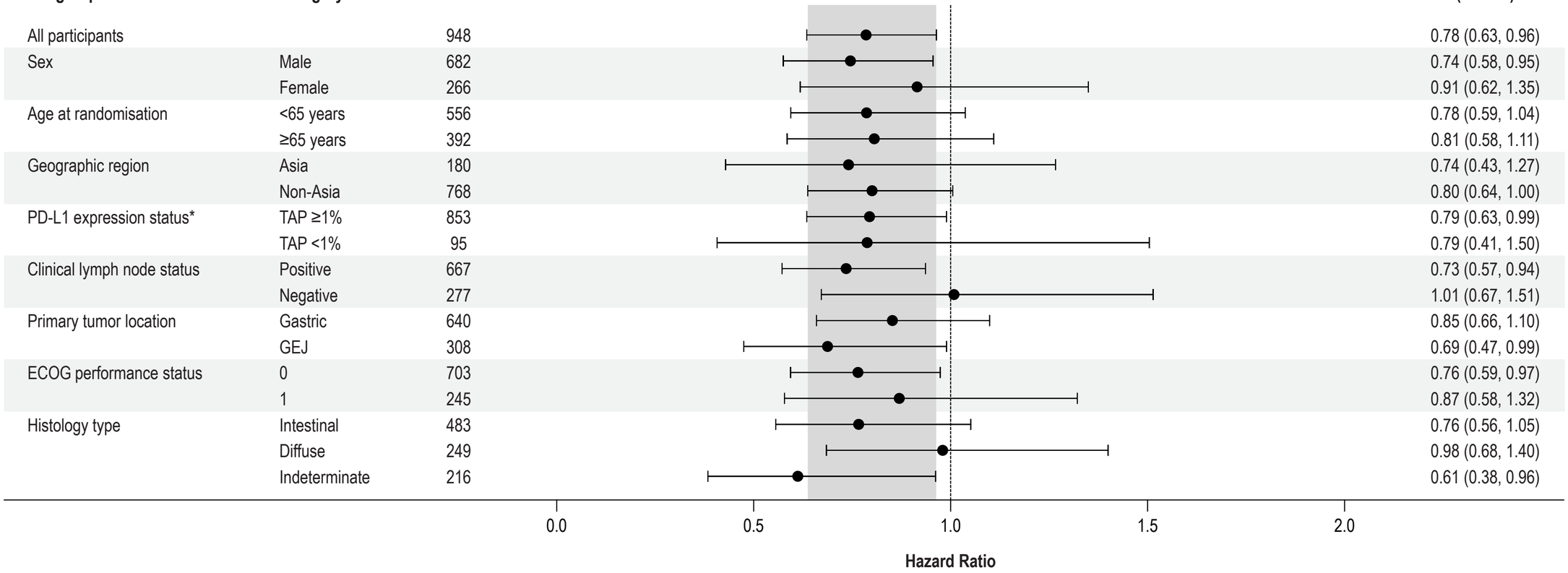
*Intention to treat analysis set (all randomised participants, regardless of treatment received). †In censored participants.
Data cut-off: 01 September 2025. OS maturity: 37.1%. Events were defined as time from randomization until the date of death due to any cause. The HR and its CI were estimated from 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. A 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 tumor location	Gastric	640	0.85 (0.66, 1.10)
	GEJ	308	0.69 (0.47, 0.99)
ECOG performance status	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. A 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, Eastern Cooperative Oncology Group; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death-ligand-1; TAP, Tumour Area Positivity.

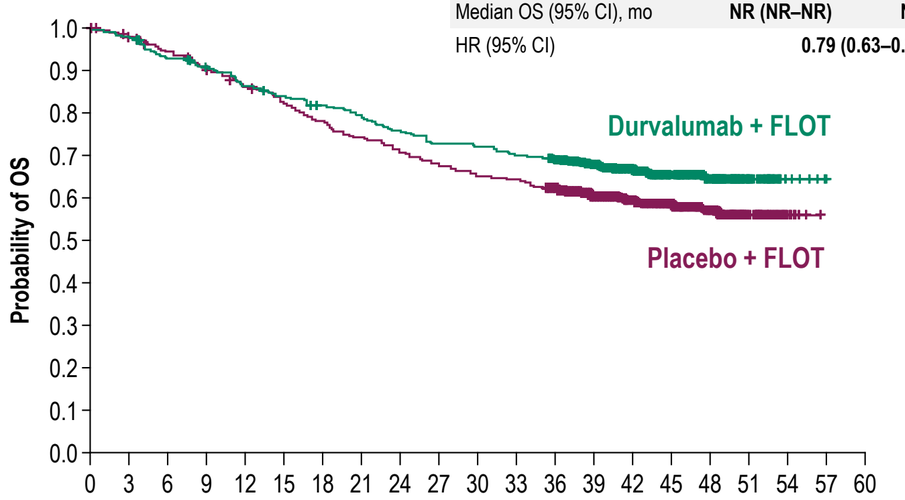
Josep Tabernero

OS by PD-L1 status

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

PD-L1 TAP ≥1%*

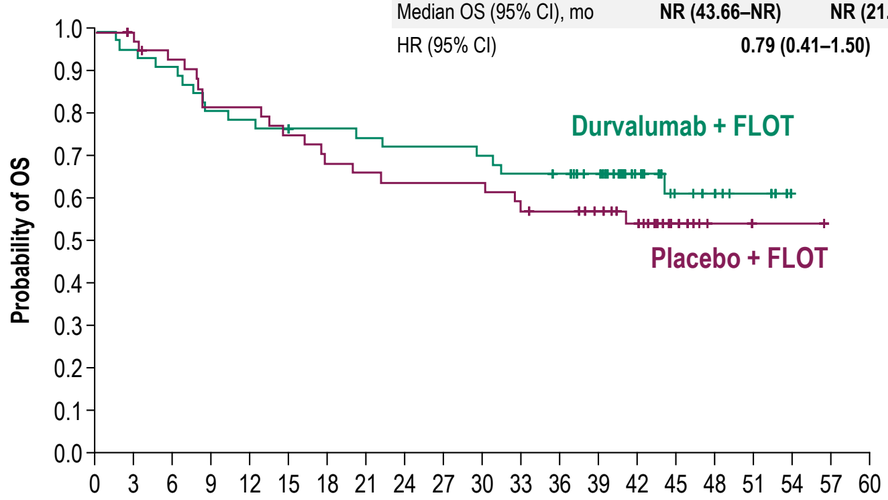
	Durvalumab + FLOT (n=426)	Placebo + FLOT (n=427)
Median OS (95% CI), mo	NR (NR–NR)	NR (NR–NR)
HR (95% CI)	0.79 (0.63–0.99)	



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 no. of events
Durvalumab + FLOT	48	46	44	39	38	36	36	35	34	34	33	31	30	26	17	11	7	4	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	20

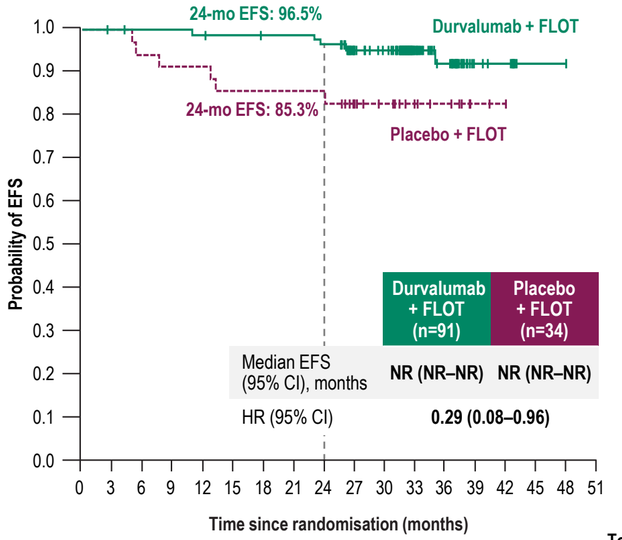
*Measured by immunohistochemistry using VENTANA PD-L1 (SP263) Companion Diagnostic Assay (Roche Diagnostics; investigational use only) and recorded at randomisation on the Interactive Response Technology System, Randomisation and Trial Supply Management, Electronic Case Report Form or from external vendor 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; OS, overall survival; PD-L1, programmed cell death-ligand-1; TAP, Tumour Area Positivity.

Josep Tabernero

Pathological response and EFS

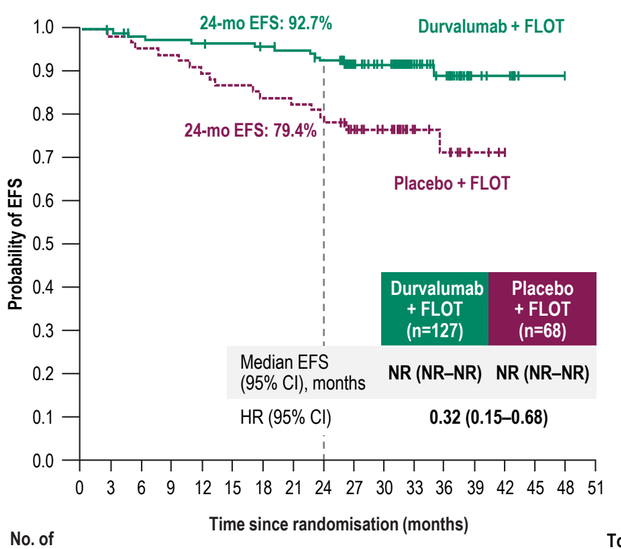
EFS was improved with durvalumab + FLOT versus placebo + FLOT among participants with any degree of pathological response

pCR



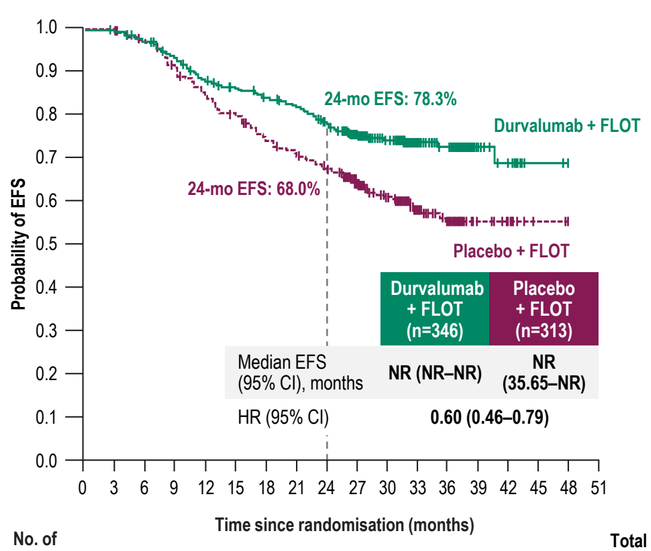
No. of participants at risk																		Total no. of events
Durvalumab + FLOT	91	90	88	88	87	86	85	85	83	68	60	38	27	7	5	1	1	0	5
Placebo + FLOT	34	34	32	31	31	29	29	29	29	23	16	11	8	2	1	0	0	0	6

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; non-pCR is defined as modified Ryan score 1, 2 and 3. 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.

Josep Tabernero

MATTERHORN Study

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)	172 (41.8)	221 (55.3)

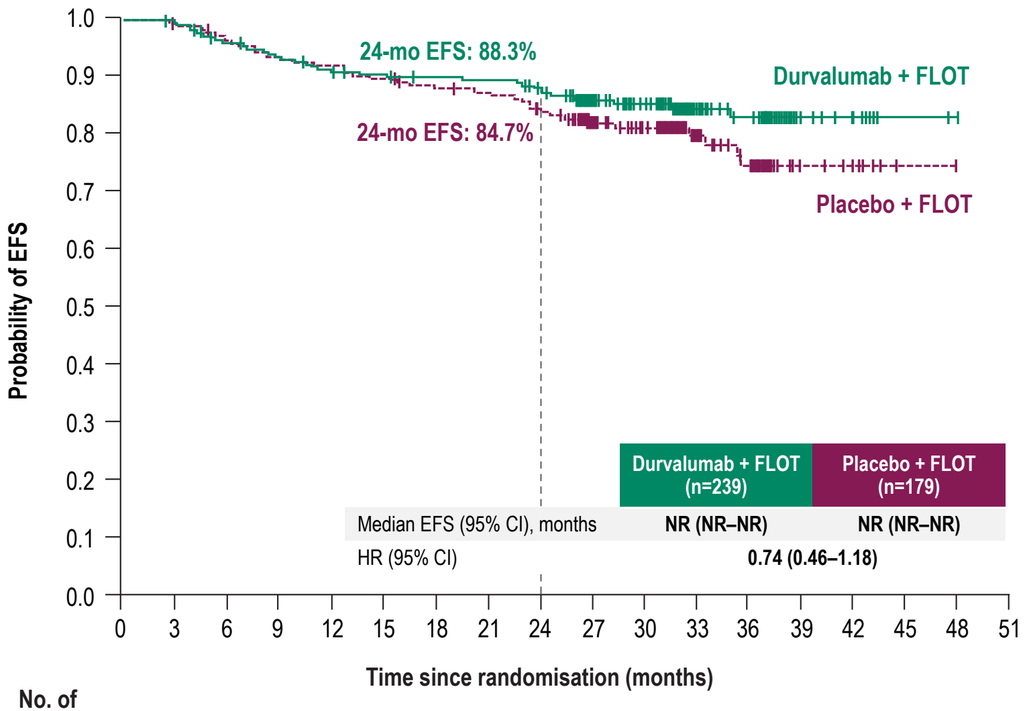
*Participants who completed surgery with samples that were evaluable for nodal involvement by investigator assessment.
Data cut-off: 20 December 2024.
FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; ypN, pathological nodal status.

Josep Tabernero

Nodal staging and EFS

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

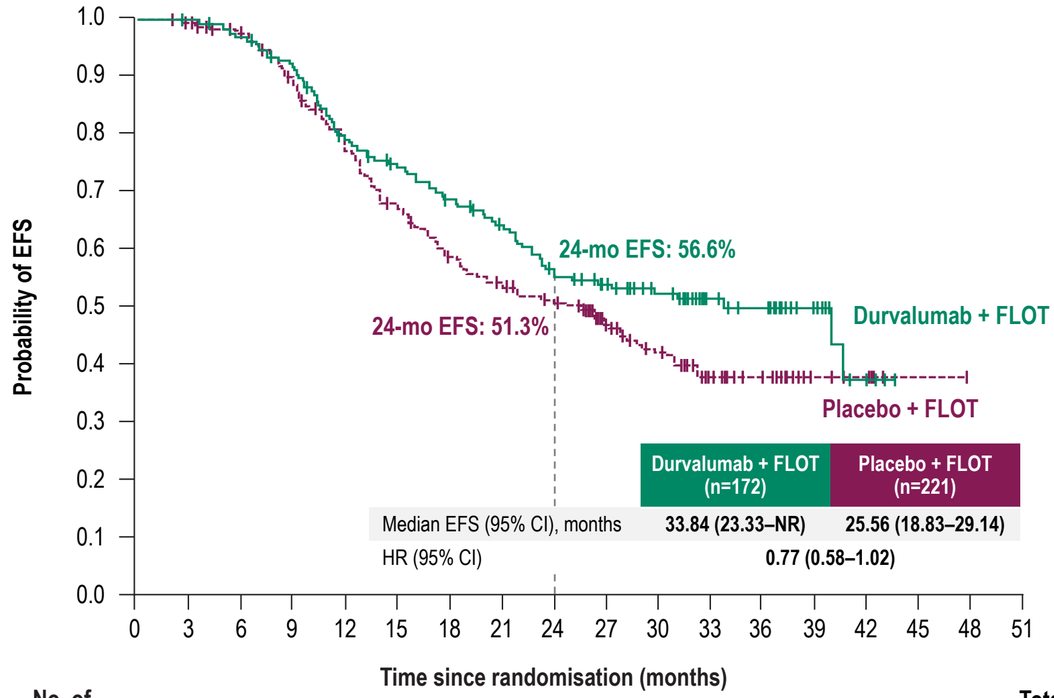
ypN-



	Durvalumab + FLOT (n=239)	Placebo + FLOT (n=179)
Median EFS (95% CI), months	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), months	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 events
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

Conclusions

- Durvalumab + FLOT demonstrated a statistically significant and clinically meaningful improvement in OS versus FLOT alone in the intention to treat population
  - HR, 0.78; 95% CI, 0.63–0.96; p=0.021
- OS improved with durvalumab + FLOT vs placebo + FLOT regardless of PD-L1 status
- Any degree of pathological response was associated with improved EFS for durvalumab + FLOT versus placebo + FLOT
- EFS was also improved regardless of pathological nodal status

A copy of these slides, a plain language summary and supplementary material can be accessed via the QR code above. Copies are for personal use only and may not be reproduced without written permission of the authors.

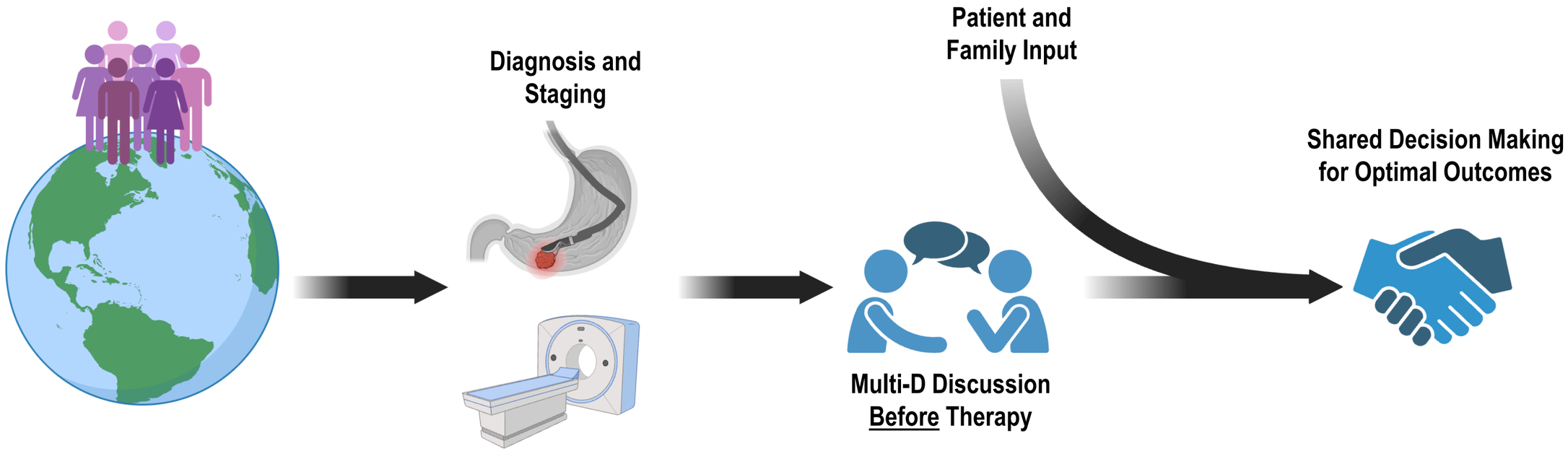
MATTERHORN OS results strongly support perioperative durvalumab + FLOT as a new global standard of care for patients with localised G / GEJ adenocarcinoma

CI, confidence interval; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; HR, hazard ratio; G / GEJ, gastric / gastroesophageal junction; OS, overall survival; PD-L1, programmed cell death-ligand-1.

Josep Tabernero

Hiking Together Is Better For Everyone

Question	MATTERHORN Answer	My Comments
Can we do it globally?	YES	• Multi-D is important to ensure pre-op consideration • Global phase III support periop strategy



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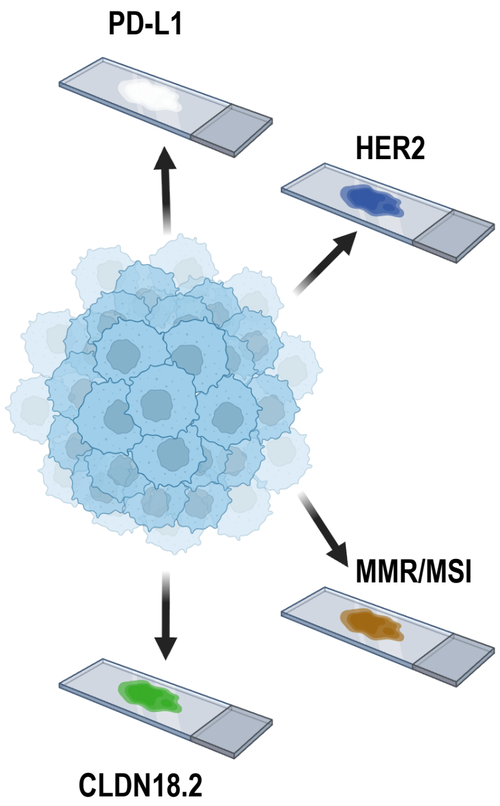
Harnessing Every Handhold to Climb Faster

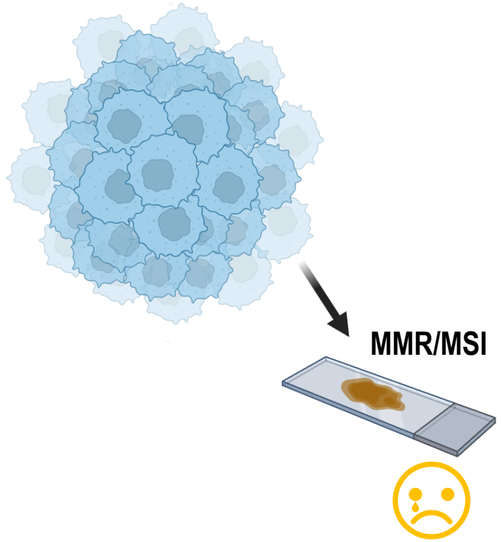
2025 Stage IV GC/GEJ



Biomarker-directed Tx

- Trastuzumab (HER2+)
- T-DXd (HER2+)
- Zolbetuximab (CLDN18.2+)
- Multiple PD-1/L1 (PD-L1+)

2025 Stage II-III GC/GEJ



Durvalumab + FLOT
(D-FLOT)

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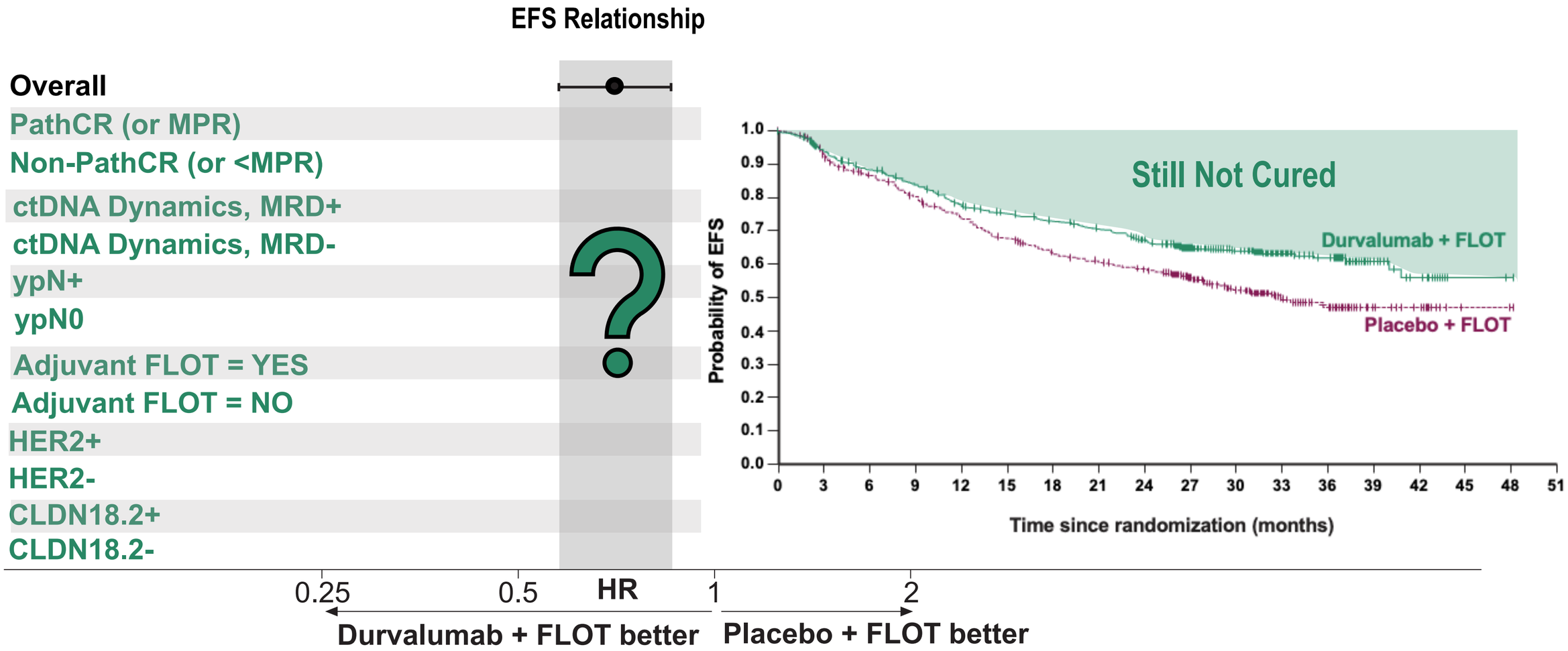
MATTERHORN Will Teach Us More



- MATTERHORN is a global well conducted randomized phase 3 trial
  - Positive based on EFS endpoint
  - OS positive, new standard of care
- What more can we learn?
  - Moving forward, EFS could be considered the standard
  - Identifying the subgroups who truly benefit (or not) is critical in the setting of curative therapy: risk-benefit analysis is highly important


THANK YOU
HOLLYWOOD
UCLA