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VIRTUAL EXPERTS KNOWLEDGE SHARE

ESMO 2025: GASTRIC AND GASTROESOPHAGEAL CANCER INSIGHTS FOR CLINICAL PRACTICE

Dr Lizzy Smyth (UK)
Prof. Markus Moehler (Germany)
Prof. Aziz Zaanan (France)

19TH NOVEMBER, 2025

DEVELOPED BY GI CONNECT

This programme is developed by GI CONNECT, an international group of experts in the field of gastrointestinal oncology.

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- **Dr Lizzy Smyth** has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies:
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EXPERTS KNOWLEDGE SHARE EDUCATIONAL OBJECTIVES

ESMO 2025: Gastric and Gastroesophageal Cancer Insights for Clinical Practice

- Critically evaluate the latest **clinical trial data presented at ESMO 2025 in gastric and gastroesophageal cancer**, with a focus on translating emerging evidence into optimised patient management strategies
- Explore the role of **biomarker-driven approaches in gastric and gastroesophageal cancer** and their impact on emerging therapeutic strategies in precision oncology

CLINICAL TAKEAWAYS

- **Perioperative FLOT** remains the cornerstone treatment for locally advanced, resectable gastric and GEJ cancers. Adding durvalumab (D) significantly improves survival and pathological response, **establishing D-FLOT as a new therapeutic standard with recent FDA approval**

- **Platinum-doublet chemotherapy plus anti–PD-1** therapy remains the first-line standard for PD-L1–positive metastatic GEA and ESCC, supported by multiple positive randomised trials

- **First-line FGFR2b-targeted therapy added to SOC** has produced only marginal survival benefit and increased ocular toxicity, preventing its establishment as a new first-line option for advanced GEA

- **Anti-angiogenic TKIs** have underperformed in combination with immunotherapy and chemotherapy in both first- and third-line settings for metastatic GEA/ESCC, offering limited overall survival benefit. **VEGF-targeting antibodies** are now under evaluation and may offer improved synergy with PD-1 blockade

INTRODUCING THE SCIENTIFIC COMMITTEE

Dr Lizzy Smyth

Oxford University Hospitals
NHS Foundation Trust
UK

Prof. Markus Moehler

Mainz University Clinic
Germany

Prof. Aziz Zaanan

European Georges
Pompidou Hospital
France

EXPERTS KNOWLEDGE SHARE AGENDA

ESMO 2025: GASTRIC AND GE CANCER INSIGHTS FOR CLINICAL PRACTICE
WEDNESDAY NOVEMBER 19TH, 17:00 TO 18:15 CET / 11:00 TO 12:15 EST

Topic	Facilitator	Timing
Welcome and introductions	COR2ED	5 mins
Where are we going with targeted therapy and immunotherapy?	Dr Lizzy Smyth (UK)	15 mins
What's happening in the peri-operative space?	Prof. Markus Moehler (Germany)	15 mins
What's new for ESCC?	Prof. Aziz Zaanan (France)	15 mins
Panel discussion, patient case scenario discussion and Q&A	All (Dr Lizzy Smyth to facilitate)	20 mins
Summary and close	Dr Lizzy Smyth and COR2ED	5 mins

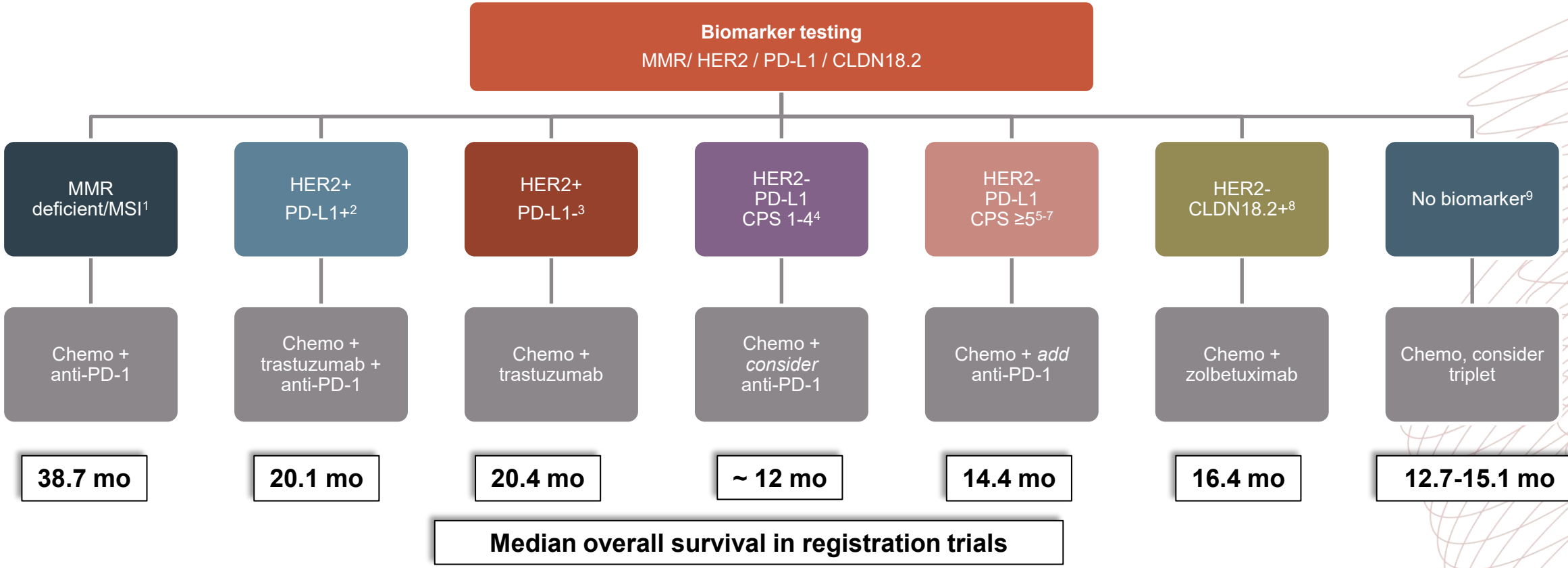
GE, gastroesophageal; ESCC, esophageal squamous cell carcinoma

WHERE ARE WE GOING WITH TARGETED THERAPY AND IMMUNOTHERAPY?

Dr Lizzy Smyth
Oxford University Hospitals
NHS Foundation Trust
UK

WHERE ARE WE WITH TARGETED THERAPY IN GEA?

RECOMMENDED TESTS AND TREATMENTS

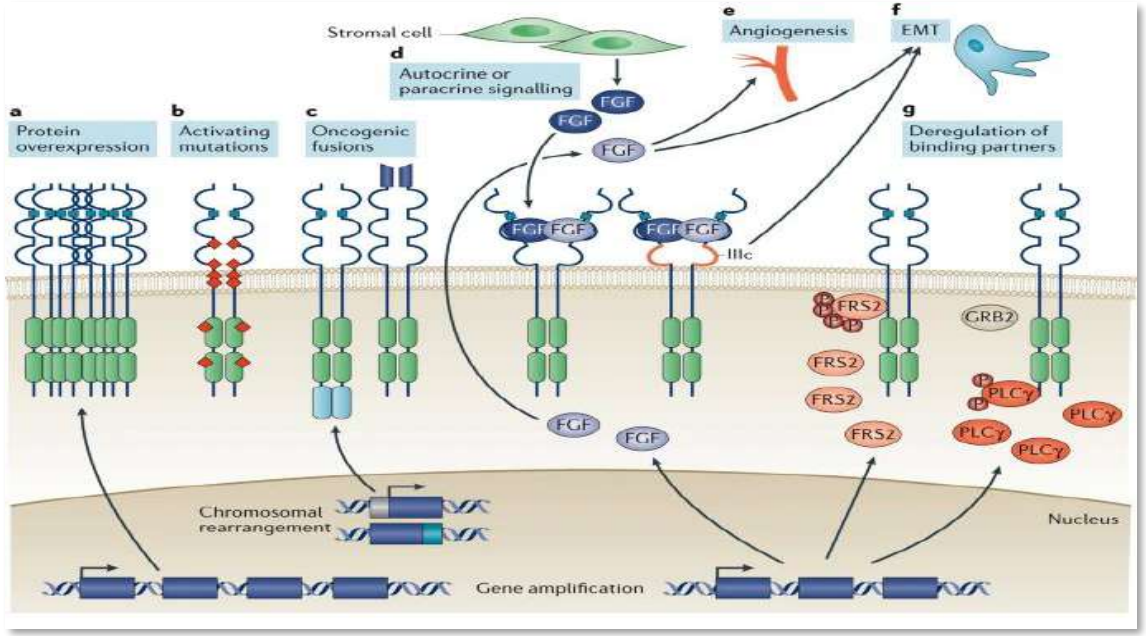


CLDN 18.2, claudin 18 isoform 2; chemo, chemotherapy; CPS, combined positive score; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; MMR, mismatch repair; mo, months; MSI, microsatellite instability; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1

1. Janjigian Y, et al. J Clin Oncol 2024; 42: 2012-2020; 2. Janjigian Y, et al. N Engl J Med. 2024;391:1360-2; 3. Janjigian Y, et al. Abstract 1400O, ESMO 2024 (oral presentation by Lonardi, S); 4. Zhao J, et al. J Clin Oncol. 2022;40:392-402; 5. Janjigian YY, et al. Lancet. 2021. 398:27-40; 6. Janjigian Y, et al. J Clin Oncol. 2025;43:398-8; 7. Shitara K, et al. Nature. 2022;603:942-8; 8. Shitara K, et al. N Engl J Med. 2024;391:1159-62; 9. Zaanan A, et al. Lancet Oncol. 2025; 26:732-44;

FGFR2 AMPLIFICATION IN GASTROESOPHAGEAL CANCER

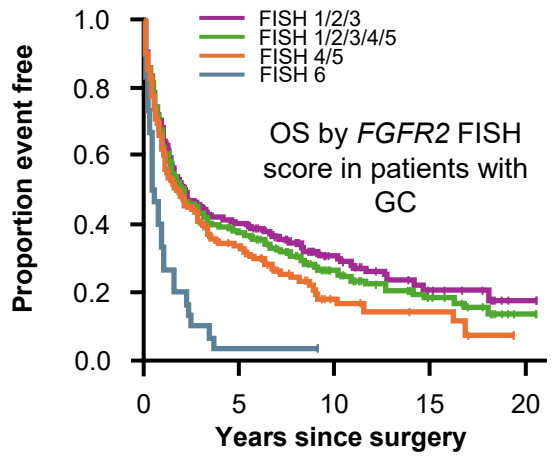
Mechanisms of oncogenic FGFR signalling[1]



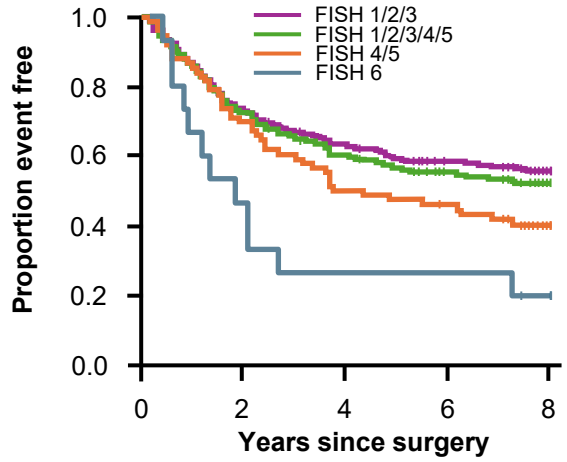
FGFR2 amplification is relatively rare in gastroesophageal cancer (2-9%)[4]

Trials targeting *FGFR2* amplification have not been successful

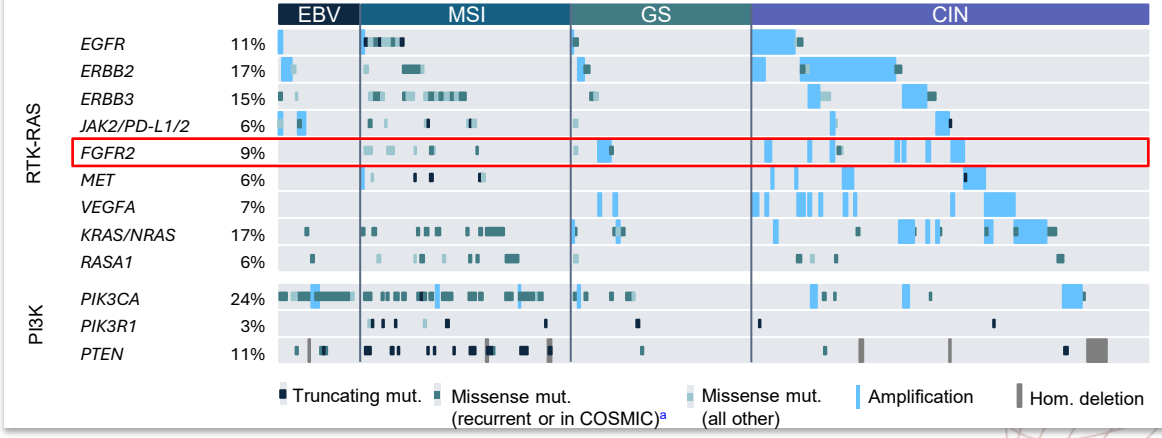
Caucasian cohort (n=394)[2]



South Korean cohort (n=354)[2]



Mutations, copy-number changes and translocations in GC[3]



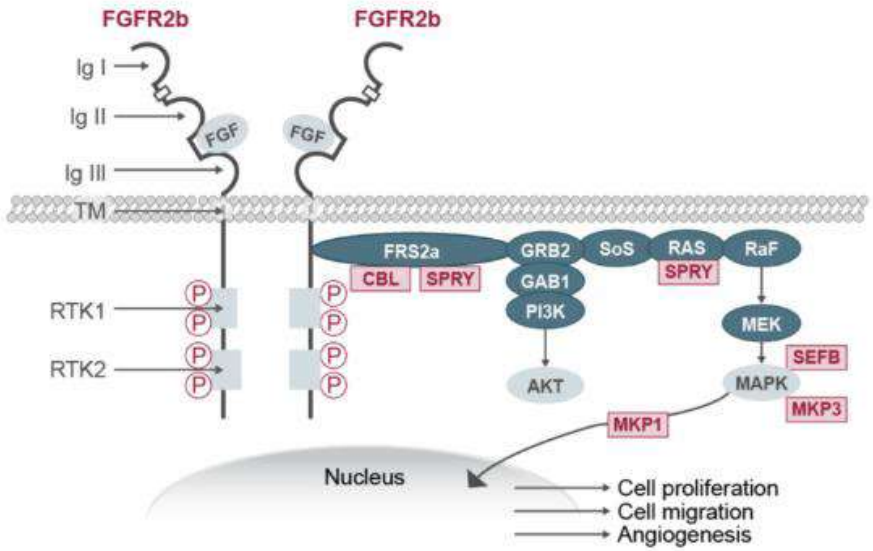
[a] Recurrent in this dataset or in the COSMIC repository

CIN, chromosomal instability; EBV, Epstein-Barr virus; FISH, fluorescence in-situ hybridisation; GC, gastric cancer; GS, genomically stable; MSI, microsatellite instability; OS, overall survival

1. Babina I and Turner NC. Nature Rev Cancer. 2017;17:318-332; 2. Su X, et al. Br J Cancer. 2014;18:967-75; 3. Cancer Genome Atlas Research Network. Nature. 2014;513:202-9; 4. Gordon A, et al. Onco Targets Ther. 2022; 15: 1183-1196

FGFR2b OVEREXPRESSION IN GASTROESOPHAGEAL CANCER

FGFR drives multiple cellular functions[1-3]



FGFR2b, a receptor tyrosine kinase, is a specific IIIb (2b) splice isoform localised to the cell surface of epithelial cells[4-6]

FGF binding causes FGFR2b receptor dimerisation, which activates downstream pathways involved in cell proliferation, migration, and angiogenesis[1]

Detection of FGFR2b protein expression by IHC[1]

FGFR2b protein overexpression can be defined as the presence of moderate (2+) to strong (3+) membranous staining of tumour cells via IHC[1]

Cut-off in FORTITUDE studies is 10% cells to be positive[7,8]

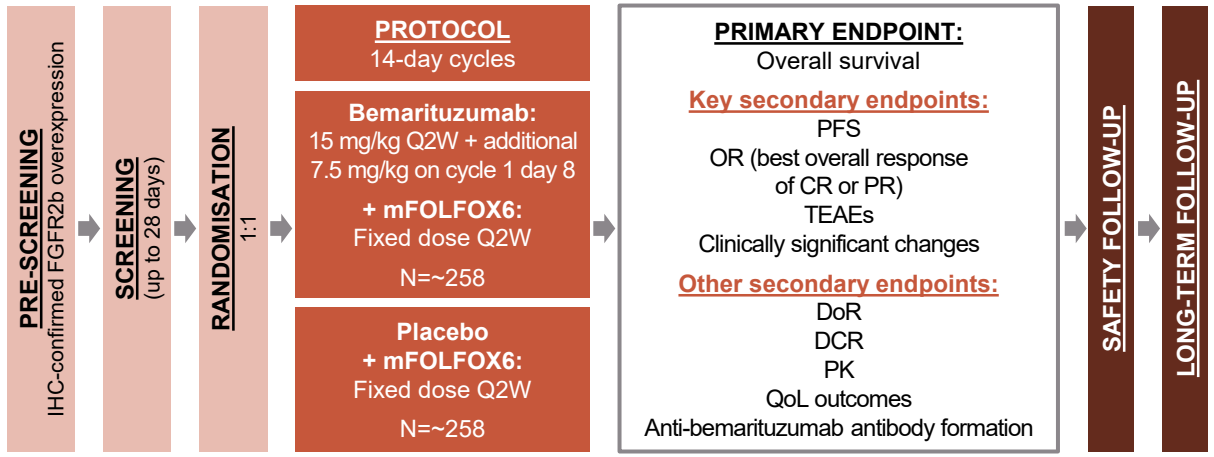
FGF, fibroblast growth factor; IHC, immunohistochemistry; P, phosphate

1. Amgen. FGFR2b: An Emerging Protein Biomarker in Advanced G/GEJ Cancer. Available here (accessed November 2025); 2. Turner N, et al. Nat Rev Cancer. 2010;10:116-29; 3. Khosravi F, et al. Front Cell Dev Biol. 2021;9:672935; 4. Smyth EC, et al. Cancer Treat Rev. 2025;139:102971; 5. Ishiwata T. Front Biosci (Landmark Ed). 2018;23:626-639; 6. Sato Y, et al. J Clin Med. 2023;12:4646; 7. Rha SY, et al. JCO Precis Oncol .2025;9:e2400710; 8. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05111626

FGFR2b IN ADVANCED GASTROESOPHAGEAL CANCER

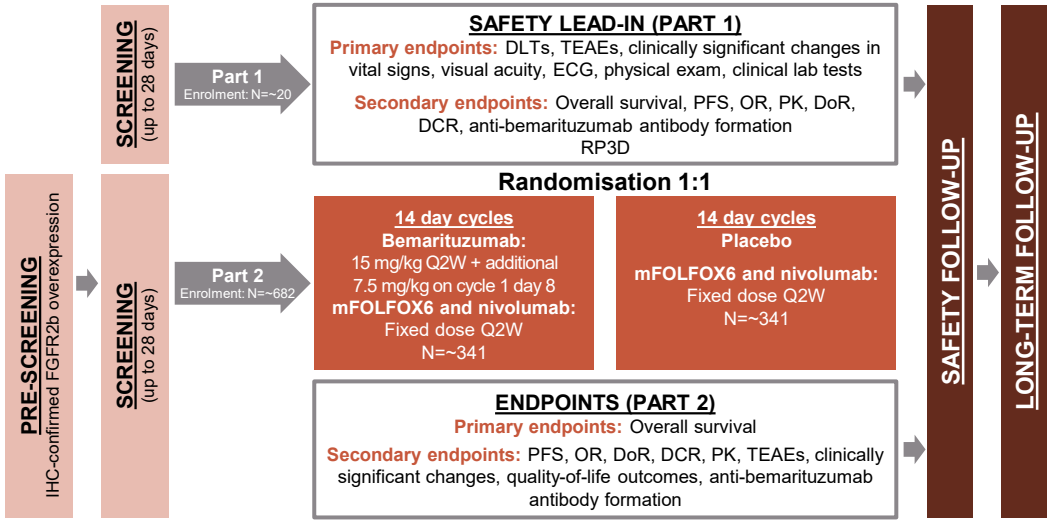
FORTITUDE SERIES

FORTITUDE 101
FOLFOX +/- bemarituzumab[1,2]



Additional value

FORTITUDE 102
FOLFOX-nivo +/- bemarituzumab[3,4]



Synergy

CR, complete response; DCR, disease control rate; DoR, duration of response; DLT, dose limiting toxicity; ECG, electrocardiogram; IHC, immunohistochemistry; mFOLFOX6, modified oxaliplatin, leucovorin, 5-fluorouracil; nivo, nivolumab; OR, objective response; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; Q2W, every 2 weeks; QoL, quality of life; RP3D, recommended phase 3 dose; TEAE, treatment emergent adverse event

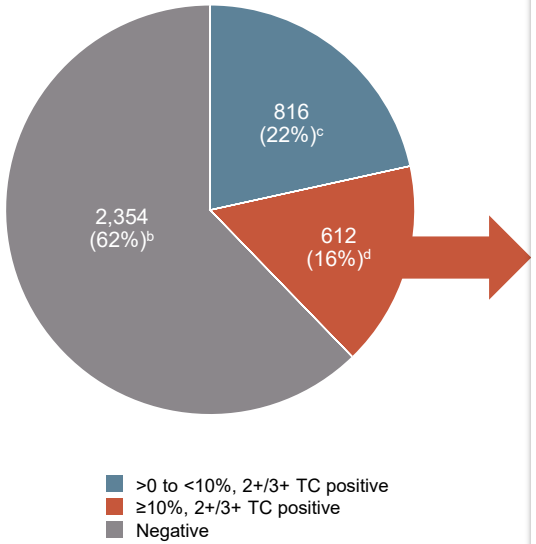
1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05052801; 2. Smyth E, et al. J Clin Oncol. 2022;40:TPS4164-TPS4164; 3. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05111626; 4. Wainberg Z, et al. J Clin Oncol. 2022;40:TPS4165-TPS4165

FORTITUDE-101 SCREENING RESULTS

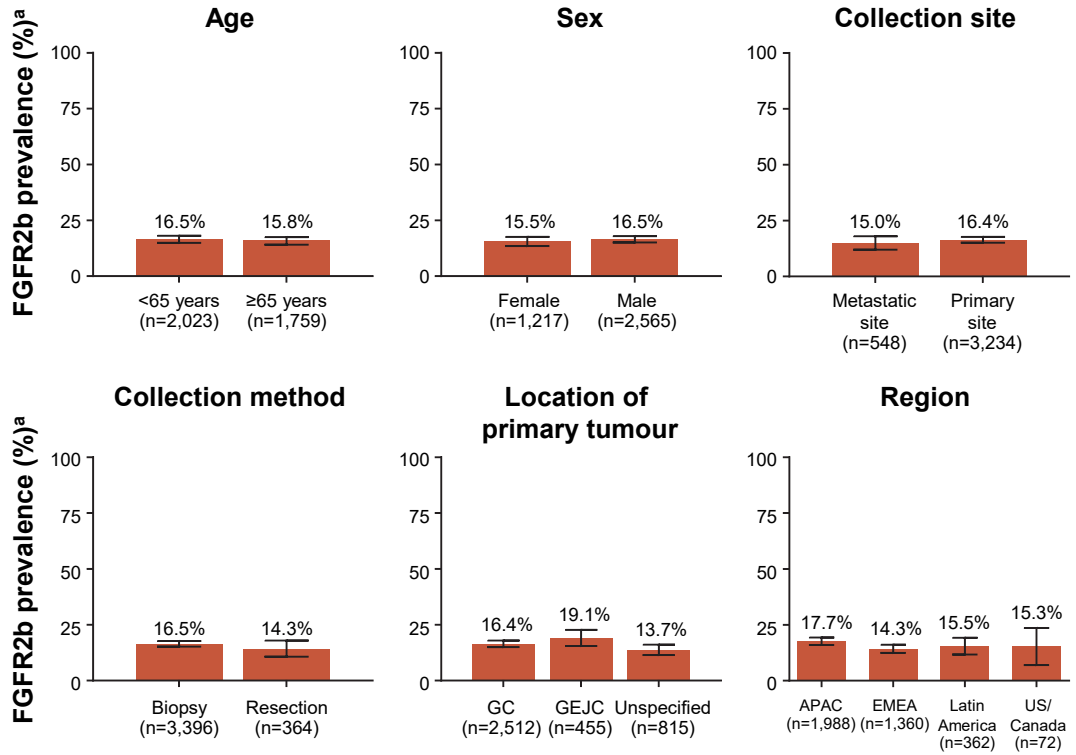
Patient/sample characteristics

Characteristics, n (%)	Patients (N=3,782)
Sex	
Female	1,217 (32)
Male	2,565 (68)
Region	
APAC	1,988 (53)
EMEA	1,360 (36)
Latin America	362 (10)
United States/Canada	72 (2)
Age, years	
<65	2,023 (53)
≥65	1,759 (47)
Tissue collection site	
Metastatic site	548 (14)
Primary site	3,234 (86)
Tissue collection method	
Biopsy	3,396 (90)
Resection	364 (10)
Unknown	22 (1)
Location of primary tumour	
GC	2,512 (66)
GEJC	455 (12)
Unspecified	815 (22)

Prevalence of FGFR2b protein overexpression



Prevalence of FGFR2b protein overexpression by patient/sample characteristics



16% FGFR2 IHC3+ or IHC2+ in >10% tumour cells

Consistent results across age, site of disease, region, biopsy and resection specimens

[a] At ≥10 %, 2+/3+ TC positive; [b]95% CI, 60.7 to 63.8; [c]95% CI, 20.3 to 22.9; [d]95% CI, 15.0 to 17.4

APAC, Asia-Pacific; EMEA, Europe, Middle East and Africa; GC, gastric cancer; GEJC, gastroesophageal junction cancer; IHC, immunohistochemistry; TC, tumour cell; US, United States

Rha SY, et al. JCO Precis Oncol. 2025;9:e2400710

FGFR2b IN ADVANCED GASTROESOPHAGEAL CANCER

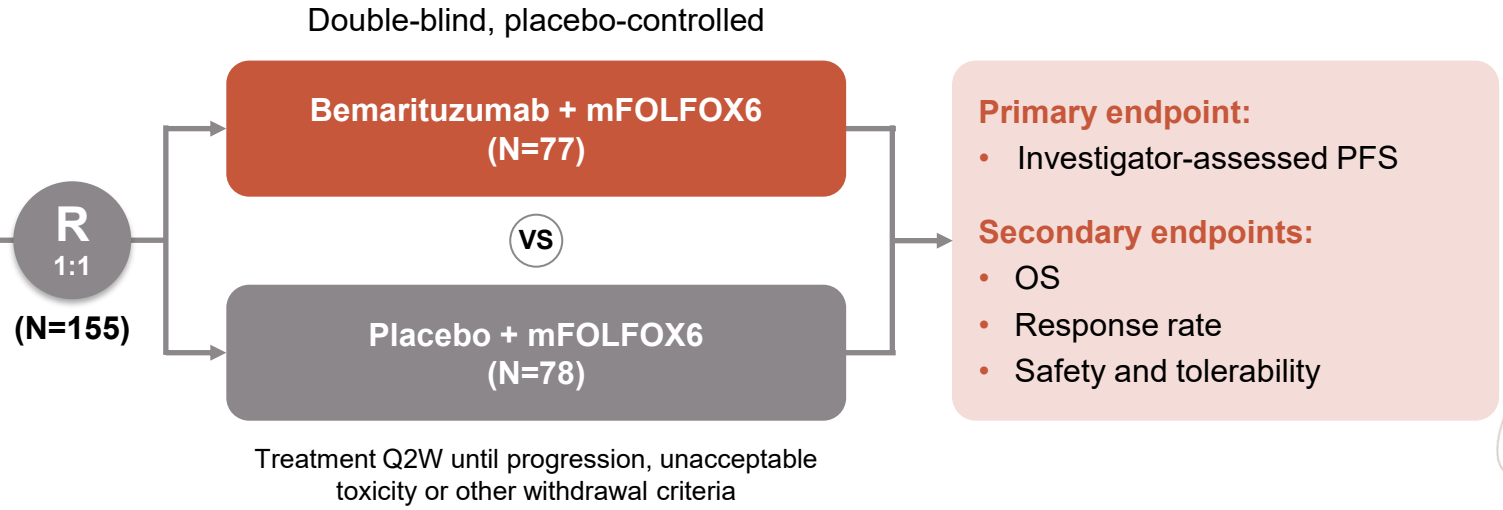
PHASE 2 RANDOMISED FIGHT TRIAL

Key eligibility criteria:

- No prior therapy for locally advanced or metastatic G/GEJC
- RECIST v1.1 evaluable disease
- FGFR2b overexpression by IHC and/or *FGFR2* gene amplification by ctDNA (central testing)
- ECOG PS 0/1
- Not known to be HER2 positive
- May have received 1 dose of mFOLFOX6

Stratification factors:

- Geographic region
- Single dose of mFOLFOX6 during screening
- Prior adjuvant or neoadjuvant chemotherapy



Primary endpoint:

- Investigator-assessed PFS

Secondary endpoints:

- OS
- Response rate
- Safety and tolerability

- Central testing for FGFR2b overexpression: IHC staining (Ventana), cut-off at any 2+/3+ staining intensity
- Central testing for *FGFR2* gene amplification: ctDNA (PGDx), cut-off at 1.5×

ctDNA, circulating tumour DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; G/GEJC, gastric/gastroesophageal junction cancer; IHC, immunohistochemistry; mFOLFOX6, modified oxaliplatin, leucovorin, 5-fluorouracil; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours

Wainberg Z, et al. Lancet Oncol. 2022; 23: 1430-1440; Wainberg Z, et al. Gastric Cancer. 2024;27:558-70; ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03694522

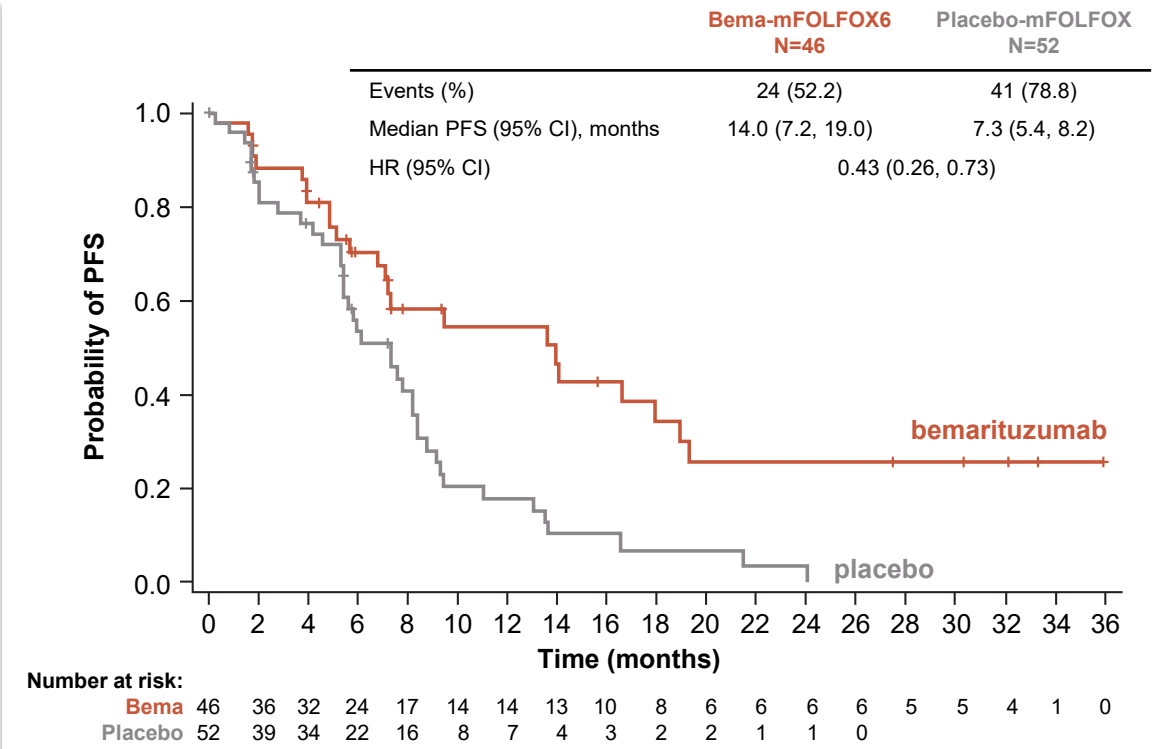
FGFR2b IN ADVANCED GASTROESOPHAGEAL CANCER

FIGHT: PATIENTS WITH 2+/3+ FGFR2b IHC STAINING IN ≥ 10% OF TUMOUR CELLS (N=98)

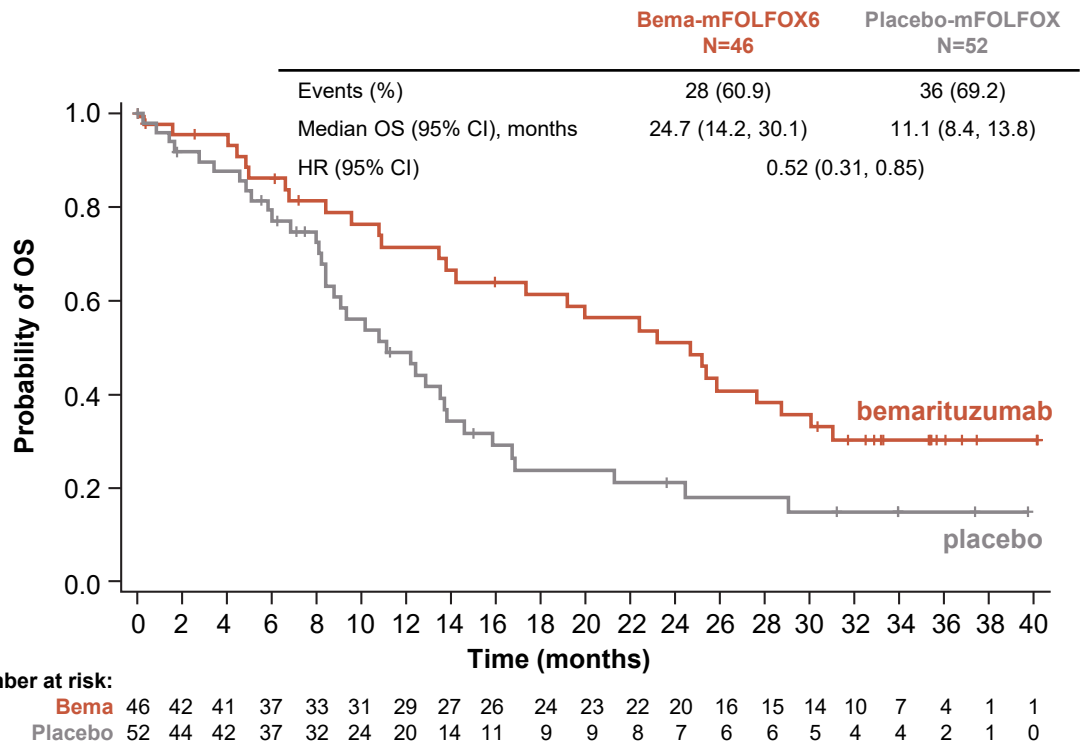
Outcomes in FGFR2b 10% subgroup:

	Bema + mFOLFOX6	Placebo-mFOLFOX6
ORR, %	56.5	36.5

PROGRESSION-FREE SURVIVAL



OVERALL SURVIVAL



bema, bemarituzumab; CI, confidence interval; HR, hazard ratio; IHC, immunohistochemistry; mFOLFOX6, modified oxaliplatin, leucovorin, 5-fluorouracil; ORR, objective response rate; OS, survival; PFS, progression-free survival

Wainberg Z, et al. Gastric Cancer. 2024;27:558-70

FORTITUDE-101: BASELINE CHARACTERISTICS

Characteristic	Efficacy analysis set FGFR2b overexpression (≥ 10% of TC)		Safety analysis set	
	Bemarituzumab (N=159)	Placebo (N=165)	Bemarituzumab (N=275)	Placebo (N=267)
Age, median (range), years	62 (25-82)	62 (27-83)	62 (21-86)	62 (26-88)
Male, %	68	67	71	66
Region, %				
Asia	57	53	40	40
Non-Asia	43	47	60	60
ECOG PS 1, %	61	58	54	56
Primary stie, %				
Gastric	80	81	78	84
GEJ	20	19	22	16
Metastatic disease, %	96	95	98	96
Liver metastases, %	36	37	38	35
Lauren classification diffuse, %	22	22	27	29
PD-L1[a] CPS ≥ 5, %	37	38	34	32
Prior dose of mFOLFOX6, %	47	42	46	43

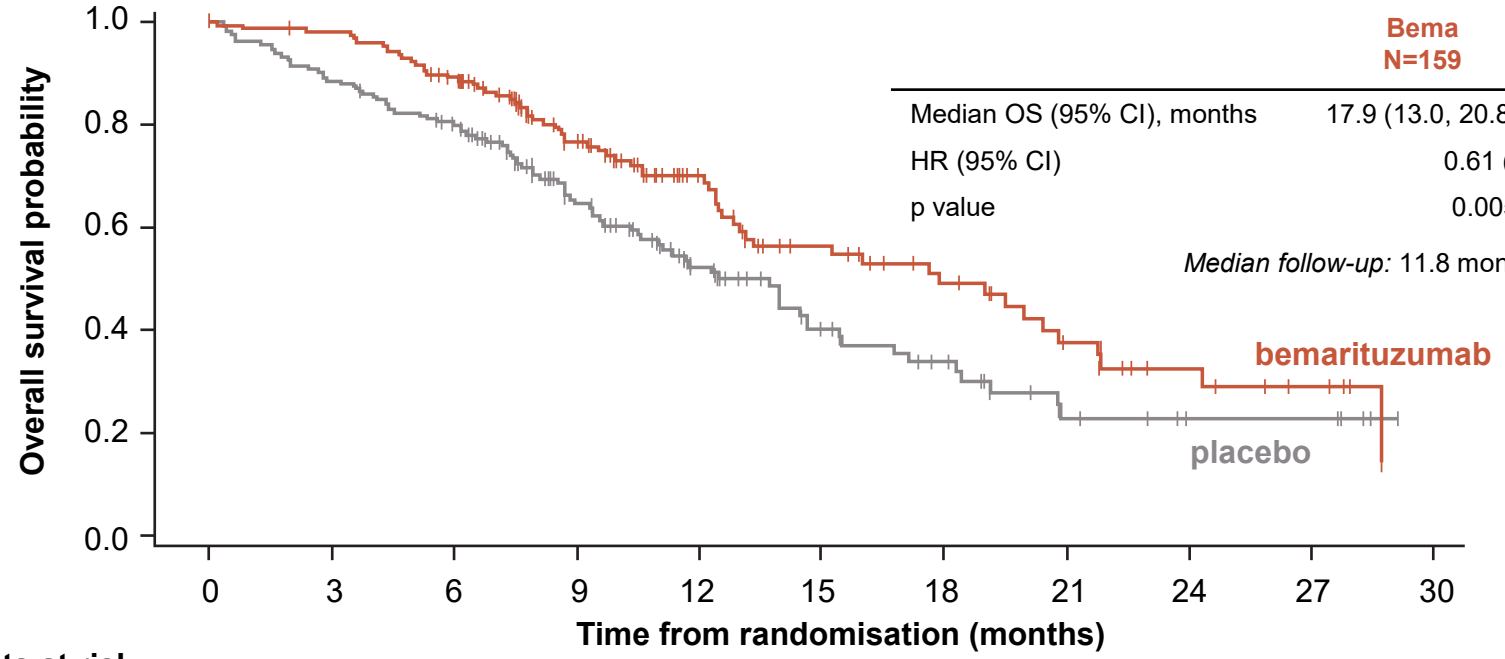
[a] PD-L1 tested by central IHC, PD-L1 (clone 28-8)

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; IHC, immunohistochemistry; mFOLFOX6, modified oxaliplatin, leucovorin, 5-fluorouracil; TC, tumour cell

Rha SY, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965 (Abstract LBA10, ESMO 2025)

FORTITUDE-101: OVERALL SURVIVAL (PRIMARY ANALYSIS)

PATIENTS WITH FGFR2b OVEREXPRESSION IN ≥10% OF TUMOUR CELLS



	Bema N=159	Placebo N=165
Median OS (95% CI), months	17.9 (13.0, 20.8)	12.5 (10.5, 14.7)
HR (95% CI)	0.61 (0.43, 0.86)	
p value	0.005 (2-sided)	

Median follow-up: 11.8 months

No. of patients at risk:

Bemarituzumab	159	154	137	89	53	35	25	15	9	5	0
Placebo	165	146	127	79	45	27	19	9	5	5	0

The OS primary objective was met at the prespecified interim analysis favouring bemarituzumab[a]

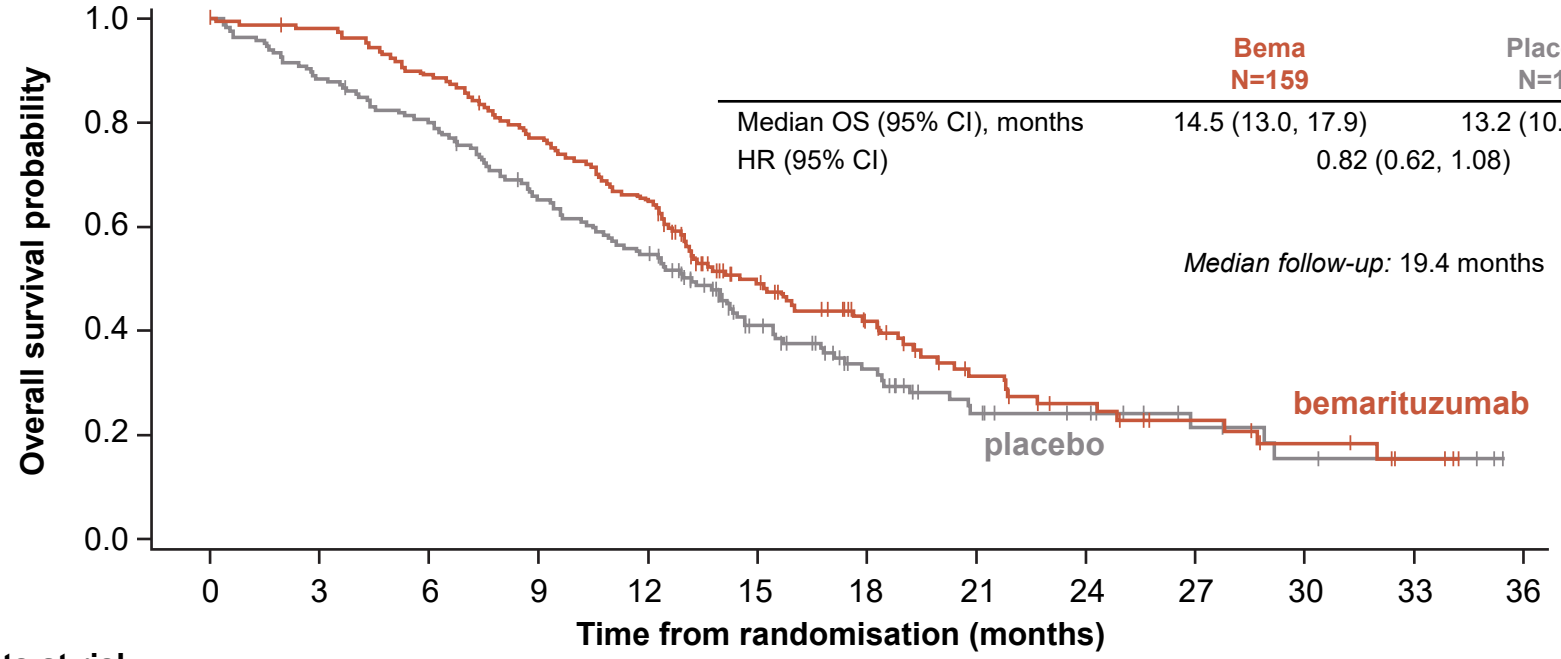
Data cut-off: 9 December 2024; [a]The interim analysis is therefore considered as the primary analysis

bema, bemarituzumab; CI, confidence interval; HR, hazard ratio; OS, overall survival

Rha SY, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965 (Abstract LBA10, ESMO 2025)

FORTITUDE-101: OVERALL SURVIVAL (DESCRIPTIVE FOLLOW-UP ANALYSIS)

PATIENTS WITH FGFR2b OVEREXPRESSION IN ≥10% OF TUMOUR CELLS



	Bema N=159	Placebo N=165
Median OS (95% CI), months	14.5 (13.0, 17.9)	13.2 (10.9, 14.7)
HR (95% CI)	0.82 (0.62, 1.08)	

Median follow-up: 19.4 months

No. of patients at risk:

Bema	159	154	140	120	101	61	39	24	16	11	7	3	0
Placebo	165	146	131	105	88	49	30	18	14	8	5	4	0

Attenuation of the treatment effect was observed at a descriptive analysis after longer follow-up

bema, bemarituzumab; CI, confidence interval; HR, hazard ratio; OS, overall survival

Rha SY, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965 (Abstract LBA10, ESMO 2025)

FORTITUDE-101: SAFETY ANALYSIS

GRADE ≥3 TREATMENT-EMERGENT ADVERSE EVENTS

Grade ≥3 TEAE in >5% patients, %	Bemarituzumab (N=275)	Placebo (N=267)
Visual acuity reduced	33	0
Corneal events		
Punctate keratitis	26	<1
Corneal epithelium defect	14	0
Limbal stem cell deficiency	14	<1
Ulcerative keratitis	8	0
Non-corneal events		
Neutropenia	31	30
Neutrophil count decreased	9	9
Anaemia	9	11
Stomatitis	7	1
Fatigue	5	3

The most common grade ≥3 treatment-emergent adverse events with bemarituzumab were corneal adverse events resulting in visual acuity reduction

Data cut-off: 20 June 2025

TEAE, treatment-emergent adverse events

Rha SY, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965 (Abstract LBA10, ESMO 2025)

INTEGRATE IIb: REGORAFENIB PLUS NIVOLUMAB IN GASTRIC/GASTROESOPHAGEAL CANCER

TRIAL DESIGN

Key eligibility criteria:

- Unresectable locally advanced, metastatic or recurrent GOJ or gastric adenocarcinoma
- ECOG PS score 0 or 1
- Progressed on/intolerant to ≥2 lines of prior therapy including ≥1 platinum agent and one fluoropyrimidine analogue
- HER2-positive participants had to have received trastuzumab

Stratification factors:

- Geographic region (Asia or the rest of the world)
- Prior use of VEGF inhibitors (yes or no)
- Prior use of immunotherapy (yes or no)

R 2:1

Regorafenib
90 mg PO QD on day 1 to day 21 of a 28-day cycle
+
Nivolumab
240 mg IV on day 1 of a 14-day cycle, then following two months of treatment 480 mg IV on day 1 of a 28-day cycle
until disease progression or unacceptable toxicity

Investigator's choice of chemotherapy
a taxane (either paclitaxel or docetaxel), irinotecan, or oral trifluridine/tipiracil
until disease progression or unacceptable toxicity

Primary objective:

- Overall survival (OS)

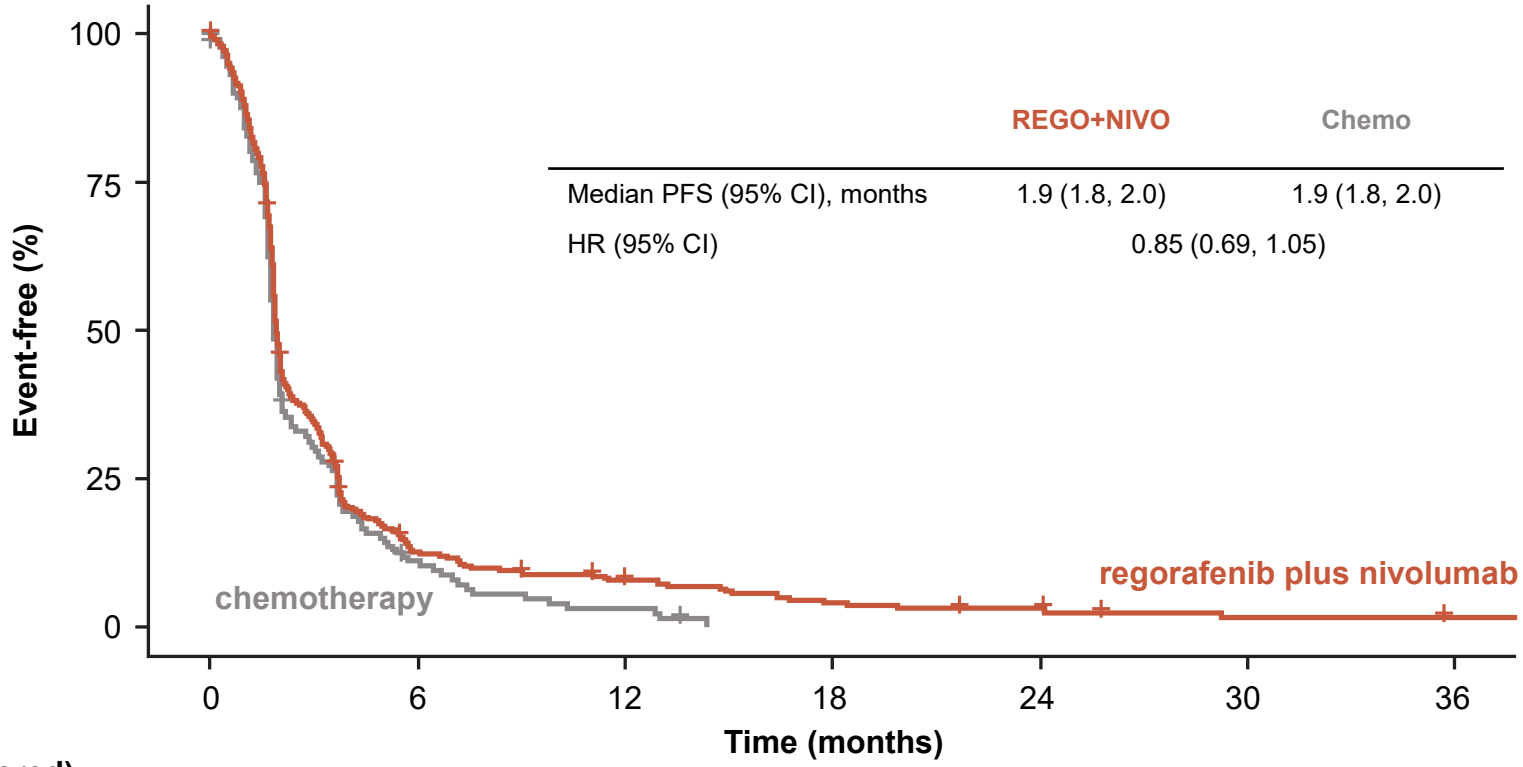
Secondary objectives:

- Progression-free survival (PFS)
- Objective response rate (ORR)
- Duration of response (DoR)
- Disease control rate (DCR)
- Quality of life (QoL)
- Safety

ECOG PS, European Cooperative Oncology Group performance status; GOJ, gastro-oesophageal junction; IV, intravenous; PO, orally; QD, once daily; R, randomisation; VEGF, vascular endothelial growth factor

Goldstein D, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965 (Abstract LBA80, ESMO 2025)

INTEGRATE IIb: PROGRESSION-FREE SURVIVAL



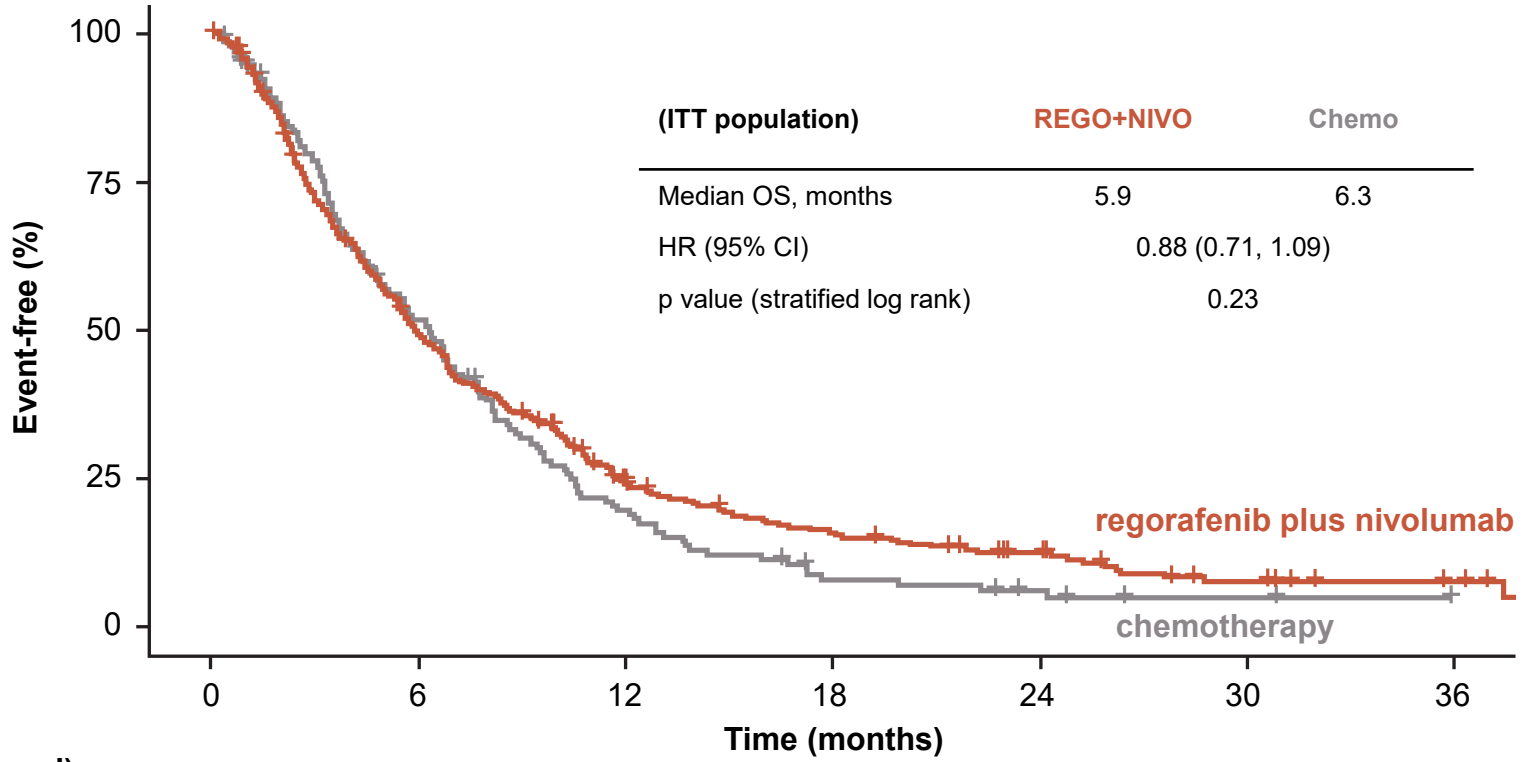
	REGO+NIVO	Chemo
Median PFS (95% CI), months	1.9 (1.8, 2.0)	1.9 (1.8, 2.0)
HR (95% CI)	0.85 (0.69, 1.05)	

No. at risk (no. censored):							
Chemotherapy	153 (0)	14 (19)	4 (19)	0 (20)	0 (20)	0 (20)	0 (20)
Regorafenib plus nivolumab	309 (0)	36 (11)	20 (14)	10 (14)	6 (16)	6 (18)	1 (19)

chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; REGO, regorafenib

Goldstein D, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965 (Abstract LBA80, ESMO 2025)

INTEGRATE IIb: OVERALL SURVIVAL



(ITT population)	REGO+NIVO	Chemo
Median OS, months	5.9	6.3
HR (95% CI)	0.88 (0.71, 1.09)	
p value (stratified log rank)	0.23	

No. at risk (no. censored):								
Chemotherapy	153 (0)	71 (15)	26 (17)	9 (19)	5 (21)	2 (23)	0 (25)	Median f/u 24.7 mo
Regorafenib plus nivolumab	309 (0)	45 (12)	63 (24)	39 (26)	24 (33)	10 (39)	5 (44)	Median f/u 27.8 mo

chemo, chemotherapy; CI, confidence interval; f/u, follow up; HR, hazard ratio; ITT, intention-to-treat; mo, months; OS, overall survival; REGO, regorafenib

Goldstein D, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965 (Abstract LBA80, ESMO 2025)

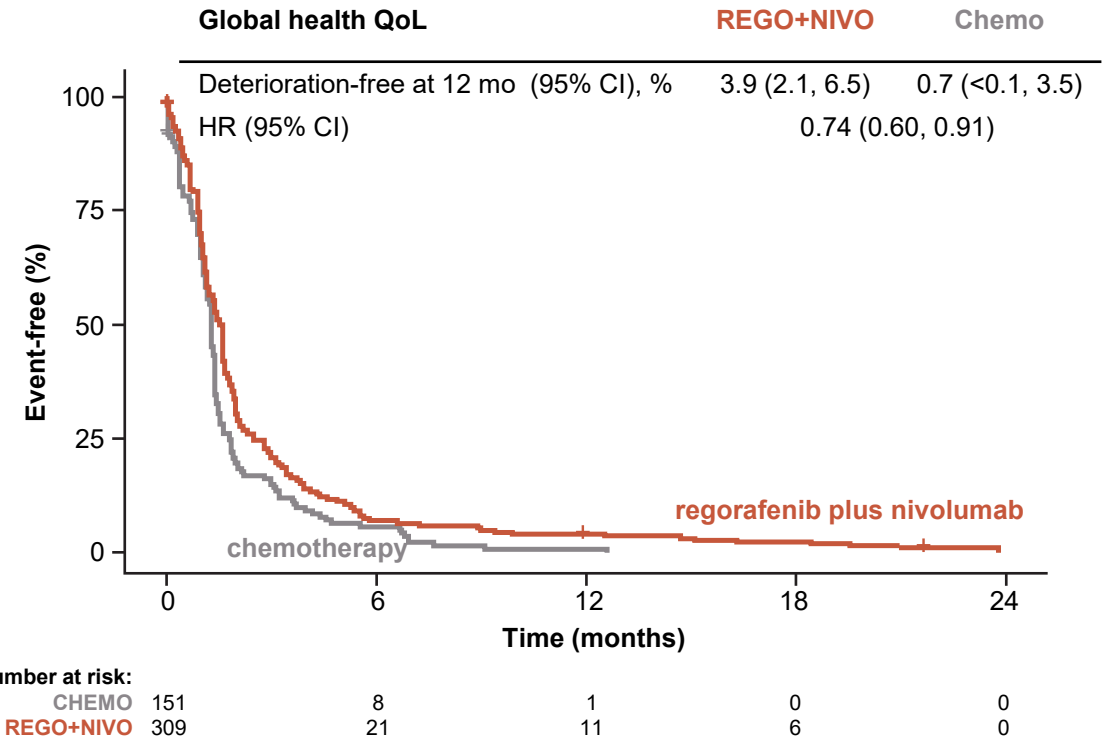
INTEGRATE IIb: SAFETY AND TOLERABILITY

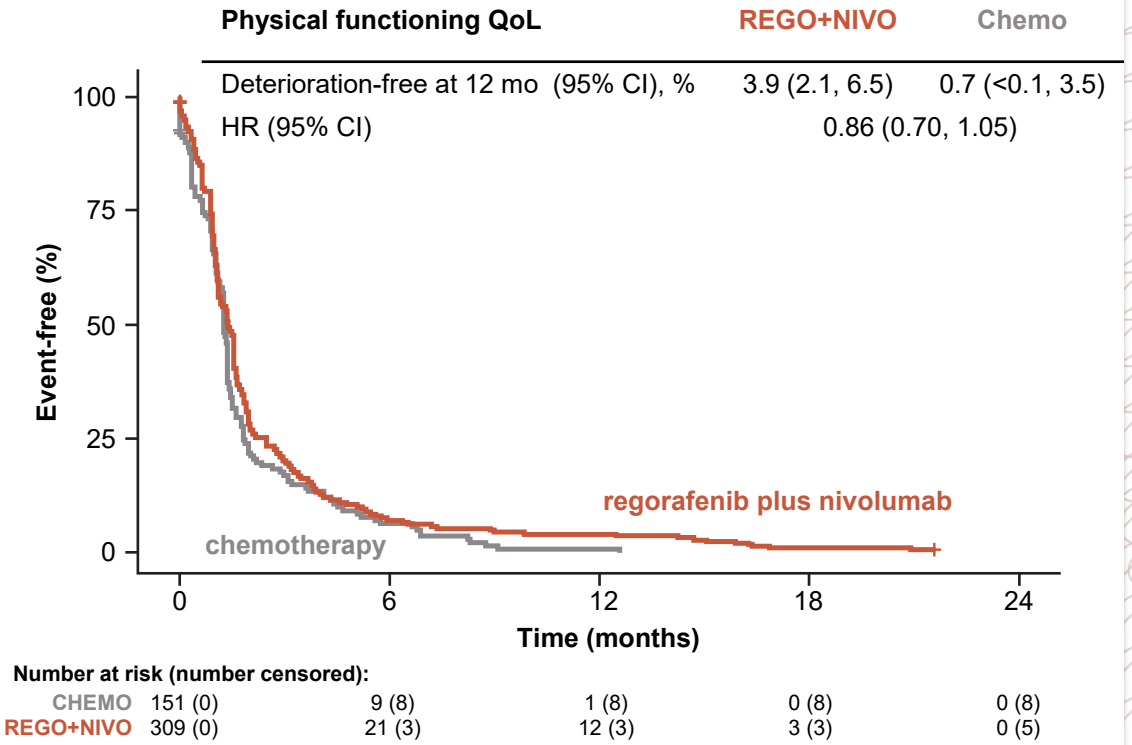
	Regorafenib plus nivolumab (n=300)	Chemotherapy (n=138)
Any AE, n (%)		
G1-5	293 (98)	127 (92)
G3	174 (58)	53 (38)
G4	23 (8)	14 (10)
G5	13 (4)	1 (1)
Any SAE,[a] n (%)		
G1-5	122 (41)	34 (25)
G3	76 (25)	26 (19)
G4	12 (4)	5 (4)
G5	12 (4)	1 (1)
G3-5 AE incidence ≥5%, n (%)		
Anaemia	18 (6)	13 (9)
Nausea	3 (1)	9 (7)
Fatigue	18 (6)	5 (4)
Aspartate aminotransferase increased	15 (5)	4 (3)
Neutrophil count decreased	8 (3)	25 (18)
Platelet count decreased	19 (6)	3 (2)
Rash maculo-papular	15 (5)	–
Hypertension	16 (5)	–

[a] Unlike the experimental arm, expedited reporting of SAEs was not required for the chemotherapy arm if known to be related/expected, so a reporting imbalance was anticipated
Table reflects all randomised participants who received ≥1 dose of study treatments. Participants featured once per row with worst grade (according to NCI-CTCAE v5.0) counted
AE, adverse event; G, grade; NCI-CTCAE, National Cancer Institute - Common Terminology Criteria for Adverse Events; SAE, serious adverse event
Goldstein D, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965 (Abstract LBA80, ESMO 2025)

INTEGRATE IIb: QUALITY OF LIFE

12-MONTH TIME TO DETERIORATION





chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; mo, months; QoL, quality of life; REGO+NIVO, regorafenib + nivolumab

Goldstein D, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965 (Abstract LBA80, ESMO 2025)

CAN WE MAKE A COLD TUMOUR HOT? 1ST LINE LEAP-015

LEAP-015
Chemo vs chemo + pembrolizumab + lenvatinib

Key eligibility criteria:
- ≥ 18 years of age
- Histologically and/or cytologically confirmed locally advanced, unresectable or metastatic G/GEJ or gastroesophageal adenocarcinoma
- HER 2 negative
- No prior treatment
- ECOG PS 0-1
- Measurable disease per RECIST v1.1

Part 1: Open-label safety run-in

N=15 → **INDUCTION**: Lenvatinib 8 mg PO QD + Pembrolizumab 400 mg IV Q6W (×2) + chemotherapy CAPOX Q3W [×4]) or mFOLFOX6 Q2W [×6])

CONSOLIDATION: Lenvatinib 20 mg PO QD + Pembrolizumab 400 mg IV Q6W

Part 2: Randomised open-label

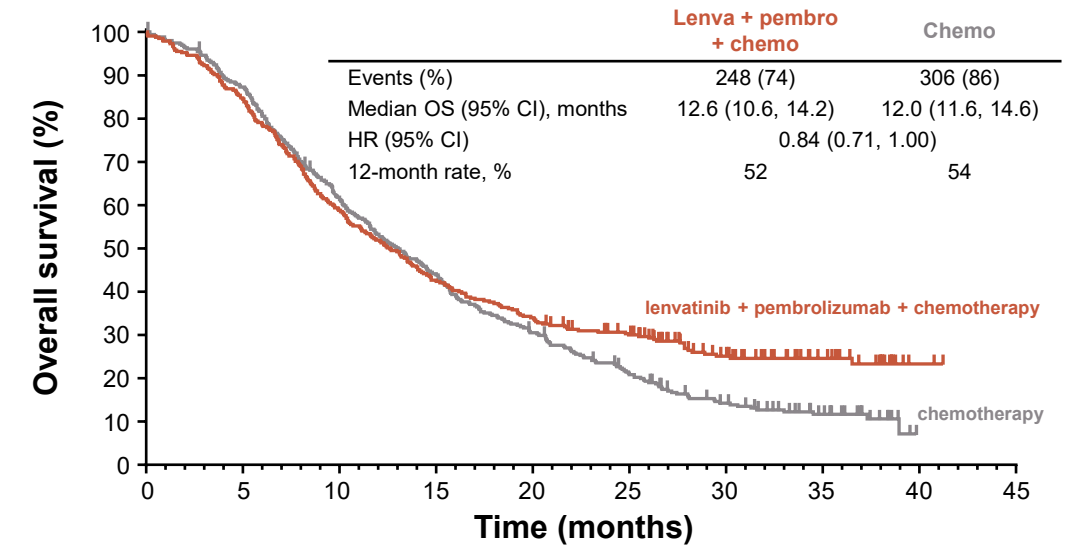
R 1:1 N=880

INDUCTION: Lenvatinib 8 mg PO QD + Pembrolizumab 400 mg IV Q6W (×2) + chemotherapy (CAPOX Q3W [×4]) or mFOLFOX6 Q2W [×6])

CONSOLIDATION: Lenvatinib 20 mg PO QD + Pembrolizumab 400 mg IV Q6W

Chemotherapy
CAPOX Q3W or mFOLFOX6 Q2W
(maximum cycles per local standards)

OS at final analysis in participants with PD-L1 CPS ≥1



3 mo induction chemo + lenva + pembro
↓
Switch to lenva + pembro maintenance

No ↑ OS chemo/lenva/pembro vs chemo alone

OS in combination arm inferior to chemo/pembro in KEYNOTE-859
Higher rate of AE/SAE in lenvatinib-treated patients (G5: 5%[a])

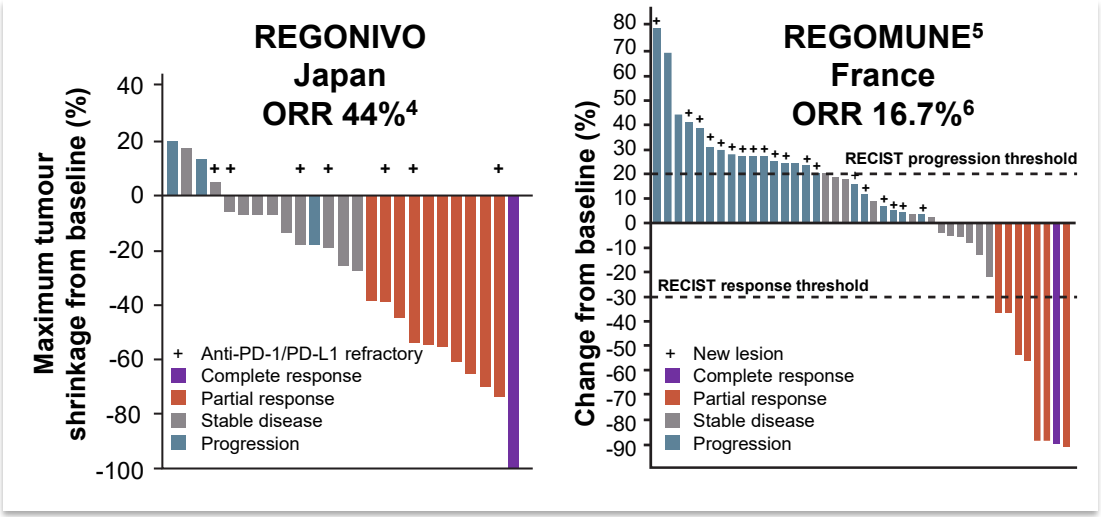
[a] Versus <1% G5 events in chemotherapy group

AE, adverse event; CAPOX, oxaliplatin and capecitabine; chemo, chemotherapy; CI, confidence interval; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; G, grade; G/GEJ, gastric/gastroesophageal junction; HR, hazard ratio; IV, intravenous; lenva, lenvatinib; mFOLFOX6, modified oxaliplatin, leucovorin, 5-fluorouracil; mo, months; OS, overall survival; pembro, pembrolizumab; PO, orally; QD, once a day; QxW, every 'x' weeks; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, serious adverse event

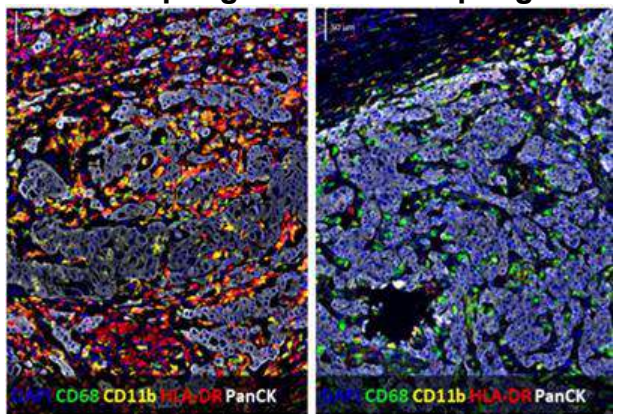
Shitara K, et al. J Clin Oncol. 2025;43:2502-14

ANTI-ANGIOGENICS ARE MODESTLY EFFECTIVE IN ≥ 2ND LINE GEA

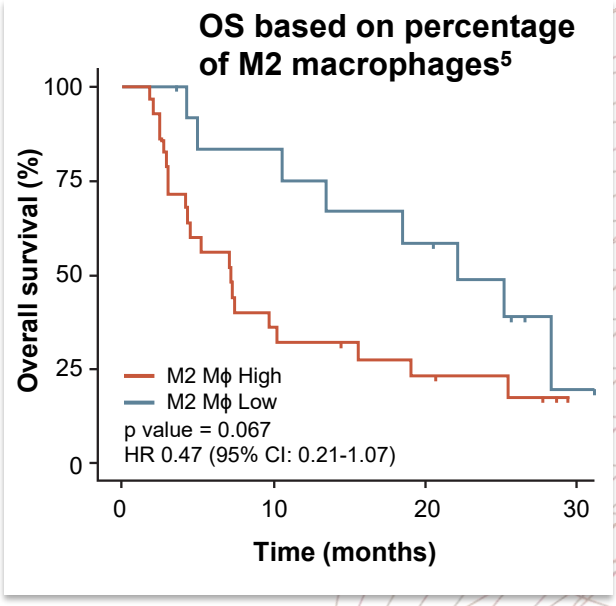
- Monotherapy – regorafenib ORR 2.4%, ramucirumab ORR 3.4%
- Ramucirumab + paclitaxel ~ doubles ORR and ↑ OS



Study	Median PFS (months)	Median OS (months)
REGONIVO (EPOC1603)[4]	**5.6** (95 % CI 2.7-10.4)	**12.3** (95 % CI 5.3-NR)
REGOMUNE[5]	**1.9** (95 % CI 1.8-3.2)	**7.5** (95 % CI 4.5-15.7)



REGOMUNE: M2 macrophage abundance strongly correlates with outcome[5]



INTEGRATE IIb @ESMO 2025 NIVO-REGO failed to show an OS benefit in a global randomised trial[7]

Future trials should focus on:[7]

- Minimal TKI dose needed to inhibit CSF1R/repolarise macrophages
- Biomarker groups most likely to benefit

CI, confidence interval; GEA, gastroesophageal adenocarcinoma; HR, hazard ratio; Mϕ, macrophage; NIVO, nivolumab; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; REGO, regorafenib; TKI, tyrosine kinase inhibitor

1. Pavlakis N, et al. J Clin Oncol. 2024; 43: 453-463; 2. Fuchs CS, et al. Lancet 2014; 383: 31-39; 3. Wilke H, et al. Lancet Oncol 2014; doi.org/10.1016/S1470-2045(14)70420-6; 4. Fukuoka S, et al. J Clin Oncol. 2020;38:2053-61; 5. Cousin S, et al. Mol Can. 2024;23:197; 6. Nakayama I, et al. J. Clin Med. 2023; 12: 3226; 7. Goldstein D, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965 (Abstract LBA80, ESMO 2025)

TARGETING THE TUMOUR MICROENVIRONMENT IN GEA

COULD mAbs SUCCEED WHERE TKIs FAILED?

Anti-angiogenic mAbs demonstrated potential synergy with anti-PD-1 in PD-L1+ve tumours[1,2]

Regimen	Line	N	ORR, %	Median PFS (mo)	Median OS (mo)
Nivolumab + paclitaxel + ramucirumab[1]	2nd	43	37.2	5.1	13.1 13.8 CPS ≥1; 8.0 if <1
Ramucirumab + pembrolizumab[2]	1st	28	25	5.6 8.6 CPS ≥1	14.6 17.3 if CPS ≥1)

Monoclonal antibodies vs TKIs as partner for ICIs

✓Cleaner biology/less off-target effects

✓ Predictable PK

✓ Tolerability & chemo compatibility

Pumitamig (BNT327/BMS986545), due to enter late-stage trials


VOLUME 29 · NUMBER 30 · OCTOBER 20 2011

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

***AVAGAST study*[3]**

Bevacizumab in Combination With Chemotherapy As First-Line Therapy in Advanced Gastric Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase III Study

Atsushi Ohtsu, Manish A. Shah, Eric Van Cutsem, Sun Young Rha, Akira Sawaki, Sook Ryun Park, Ho Yeong Lim, Yasuhide Yamada, Jian Wu, Bernd Langer, Michal Starnawski, and Yoon-Koo Kang

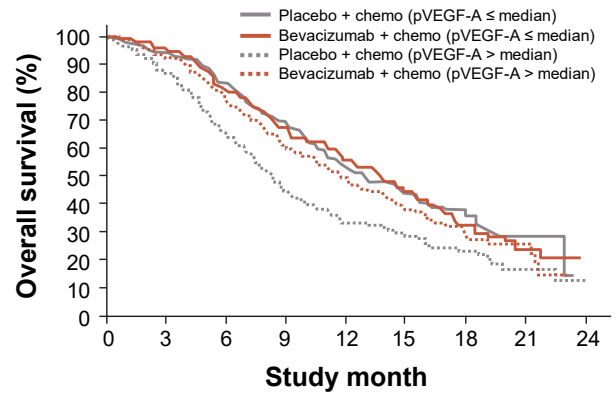
Asian patients ↓ benefit from bevacizumab[4,5]

Smaller tumours, ↓ liver mets and ↑ PS

↑ 2nd line therapy attenuated OS benefit in Asia[6]

↑ Plasma VEGF-A predictive outside Asia[4]

OS by baseline plasma VEGF-A levels[4]



chemo, chemotherapy; CPS, combined positive score; GEA, gastroesophageal adenocarcinoma; ICI, immune checkpoint inhibitor; mAb, monoclonal antibody; mets, metastases; mo, months; ORR, overall/objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PS, performance status; (p)VEGF, (plasma) vascular endothelial growth factor; TKI, tyrosine kinase inhibitor

1. Nakajima TE, et al. Clin Cancer Res. 2021;27:1029-36; 2. Chau I, et al. Cancers. 2020;12:2985; 3. Ohtsu A, et al. J Clin Oncol. 2011;29:3986-76; 4. Van Cutsem E, et al. J Clin Oncol. 2012;30; 5. Shah M, et al. J Clin Oncol. 2012;30 (4_Suppl). Presented at ASCO 2012 Gastrointestinal Cancer Symposium. Abstract 5' 6. Sawaki A, et al. Gastric Cancer 2018; 21:429-438

CONCLUSIONS

- **FGFR2b** remains an actionable target in GEA, the challenge lies in *biomarker refinement*, not target absence
- The **TKI era has under-delivered** — limited selectivity, poor tolerability, have blunted efficacy despite strong pre-clinical rationale
- **Anti-angiogenic TKIs** (regorafenib, lenvatinib) have shown transient activity but failed to improve OS in randomised studies (e.g. INTEGRATE IIb)
- **Monoclonal antibodies targeting VEGF** may restore immune permissiveness, offering cleaner PK/PD and better synergy with PD-1 blockade

GEA, gastroesophageal adenocarcinoma; OS, overall survival; PK/PD, pharmacokinetics/pharmacodynamics; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor

POLLING QUESTION 1

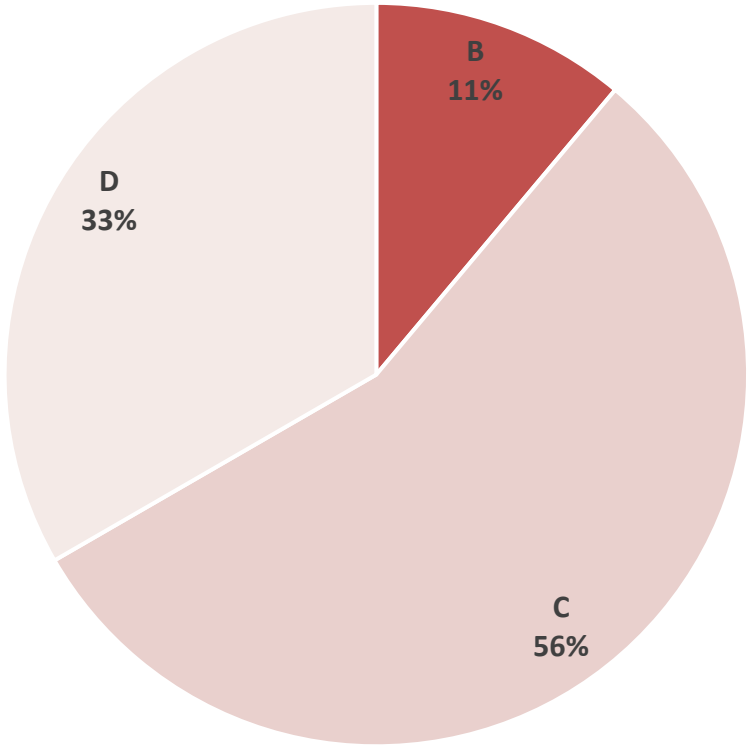
WHICH ARE THE CORRECT BIOMARKERS OF CLINICAL RELEVANCE TO TEST IN ADVANCED UPPER GI CANCER?

A. HER2, EGFR, MMR

B. HER2, MMR, PD-L1

C. HER2, MMR, PD-L1, CLDN18.2

D. HER2, MMR, PD-L1, FGFR2b



GI, gastrointestinal

POLLING QUESTION 2

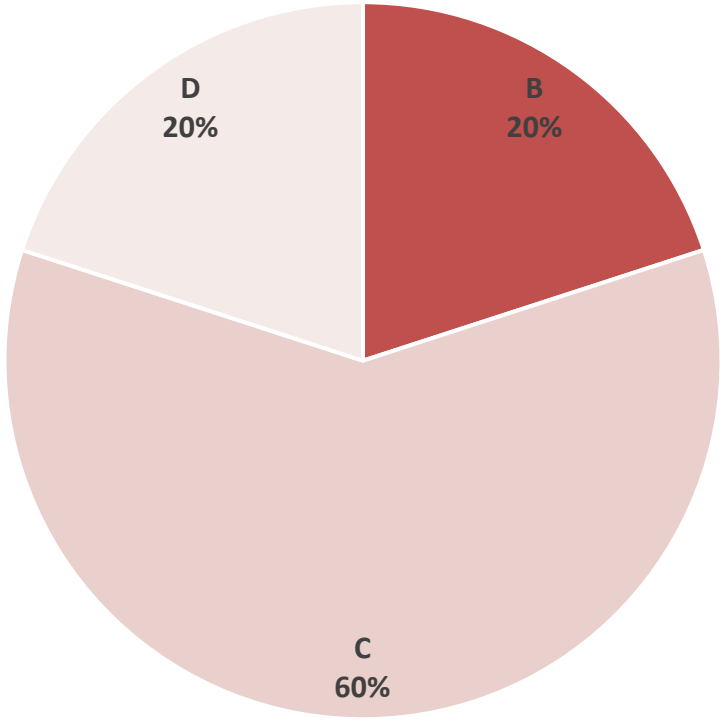
ANTIANGIOGENIC THERAPY IS A RECOMMENDED STANDARD OF CARE IN WHICH LINE OF UPPER GI TREATMENT?

A. Perioperative

B. 1st line

C. 2nd line

D. 3rd line



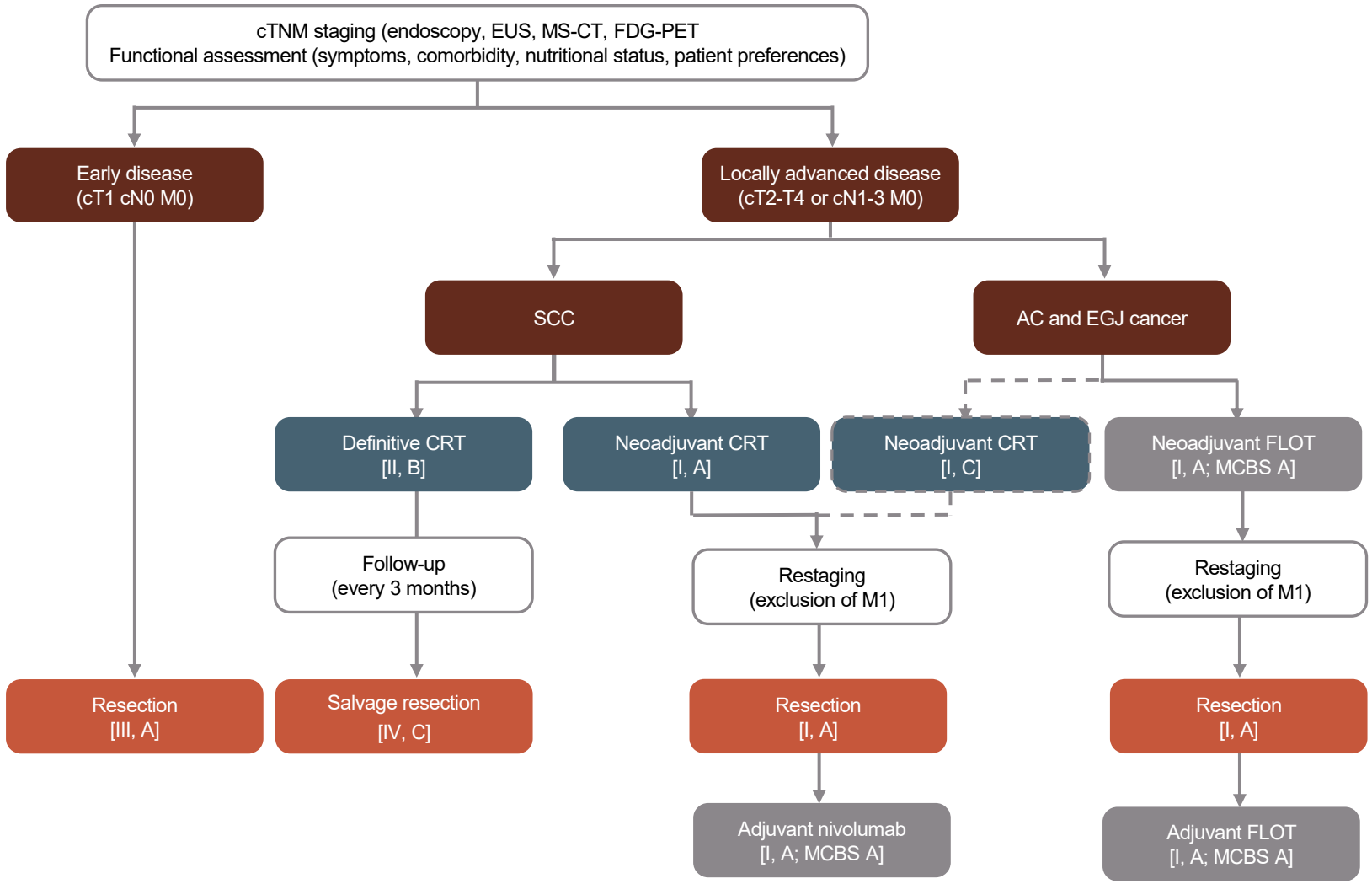
GI, gastrointestinal

WHAT'S HAPPENING IN THE PERI-OPERATIVE SPACE?

FAILURES, PROMISES AND STANDARD TREATMENT

Prof Markus Moehler
Mainz University Clinic
Germany

ESMO GUIDELINES FOR RESECTABLE ESOPHAGEAL CANCER

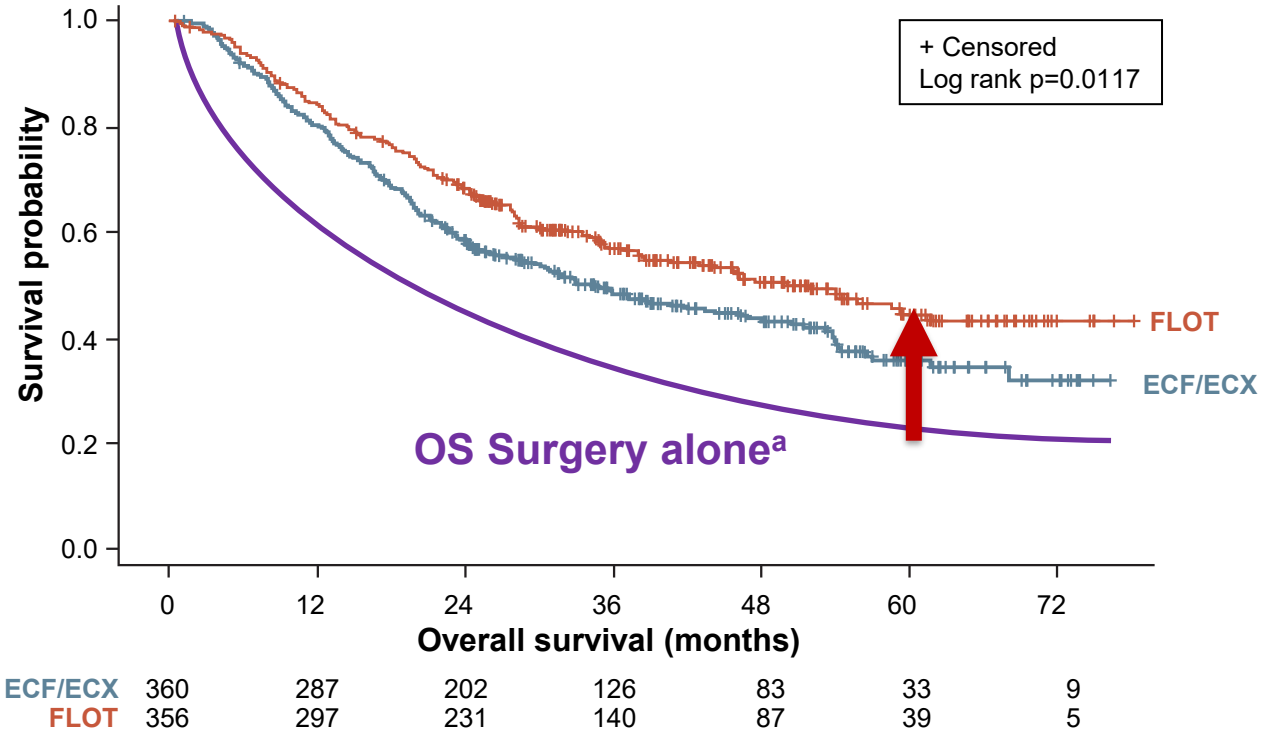


AC, adenocarcinoma; APC, antigen-presenting cells; CRT, chemoradiotherapy; CT, computed tomography; cTNM, clinical Tumour Node Metastasis; dCRT, definitive CRT; EC, esophageal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EGJ, esophagogastric junction; ESCC, esophageal squamous cell carcinoma; EUS, endoscopic ultrasound; FDG-PET, [18F]2-fluoro-2-deoxy-D-glucose-positron emission tomography; FLOT, 5-fluorouracil-leucovorin-oxaliplatin-docetaxel; MCBS, Magnitude of Clinical Benefit Score; MDT, multidisciplinary team; MS-CT, multi-slice-computed tomography; NK cell, natural killer cell; SCC, squamous cell carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand-1; PVR, poliovirus receptor (CD155); SoC, standard of care; TIGIT, T cell immunoreceptor with Ig and ITIM domains

Obermannová R, et al. ESMO Open. 2025;10:104134

FLOT4: PERI-OPERATIVE FLOT

OVERALL SURVIVAL



OS	ECF/ECX	FLOT
mOS, months (95% CI)	35 (27-46)	50 (38-NA)
HR (95% CI)	0.77 (0.63-0.94) p=0.012 (log rank)	

OS, %	ECF/ECX	FLOT
2-year	59	68
3-year	**48**	**57**
5-year	36	45

Median FU: 43 months in both arms

FLOT: estimated OS at 5 Years of 45%

[a] Hypothetical estimate based on historical data

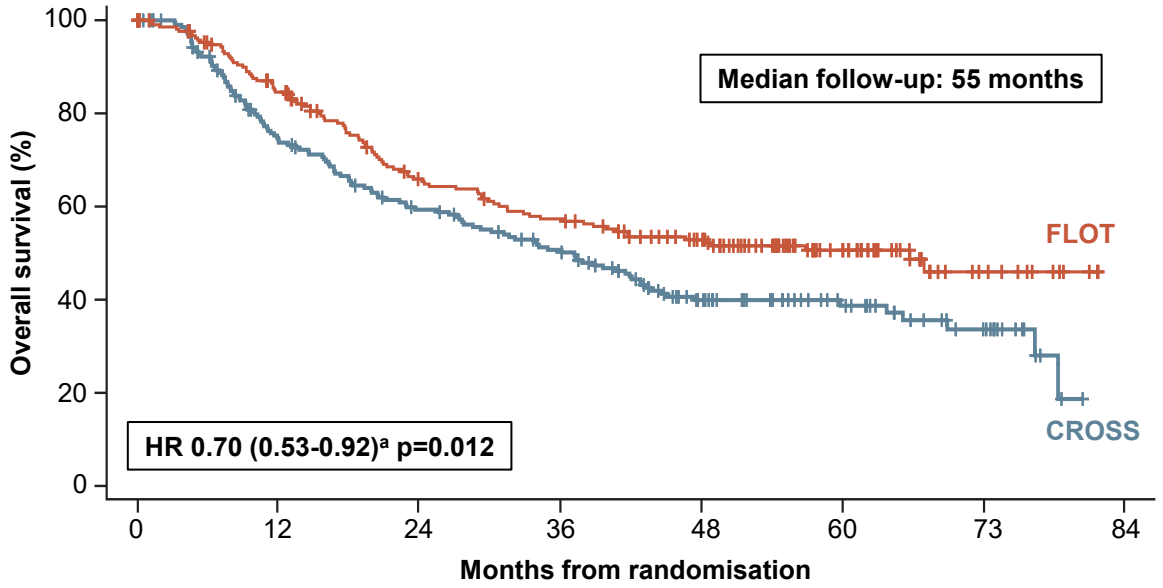
CI, confidence interval; ECF/ECX, epirubicin+cisplatin+5-FU/capecitabine; FLOT, fluorouracil plus leucovorin, oxaliplatin and docetaxel; FU, follow-up; HR, hazard ratio; mOS, (median) overall survival; NA, not applicable

Al-Batran SE, et al. Lancet. 2019;393:1948-57

ESOPEC: EFFICACY (ITT POPULATION)

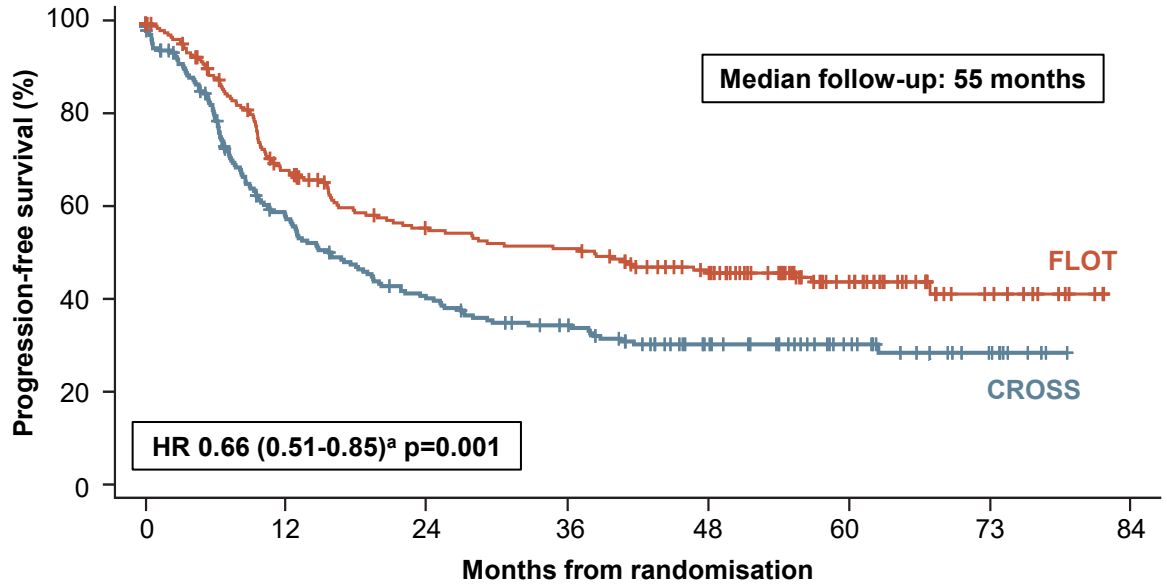
- Peri-operative chemotherapy (FLOT) plus surgery improves overall survival compared to neoadjuvant chemoradiation (CROSS) plus surgery for patients with cT1cN+ and cT2-4a,cN-/+ resectable esophageal adenocarcinoma[1]

OVERALL SURVIVAL (ITT)[2]



FLOT	221	172	124	107	84	44	11	0
CROSS	217	146	113	92	54	32	15	0

PROGRESSION-FREE SURVIVAL (ITT)[2]



FLOT	221	135	101	93	73	39	11	0
CROSS	217	113	78	62	39	22	9	0

[a] Two-sided 95% confidence interval; Cox regression adjusted for N stage and age, stratified for trial site

CROSS, preoperative radiotherapy plus carboplatin and paclitaxel (as used in CROSS study); (c)N, (clinical) Node stage; cT, clinical Tumour stage; FLOT, fluorouracil plus leucovorin, oxaliplatin and docetaxel; HR, hazard ratio; ITT, intention-to-treat

1. Hoeppner J, et al. J Clin Oncol 2024;42(No. 17_Suppl). Abstract LBA1; 2. Hoeppner J, et al. N Engl J Med 2025;392:323-35

ESOPEC TRIAL: SURGERY POPULATION

PATHOLOGY RESULTS

Characteristic	FLOT (N=193)	Pre-operative CRT (N=181)
Median time (range) from end of pre-operative treatment to surgery, days	37 (18-71)	41 (9-79)
Resection status, n (%)		
No tumour resection	1 (0.5)	2 (1.1)
R0: no tumour cells in margins	182 (94.3)	172 (95.0)
R1: tumour cells visible in margins on microscopy	10 (5.2)	7 (3.9)
Pathological lymph-node stage after surgery, n/N (%)		
ypN0 (absence of cancer spreading to lymph nodes)	97/192 (50.5)	98/179 (57.4)
ypN+ (presence of cancer spreading to lymph nodes)	95/192 (49.5)	81/179 (45.3)
Pathological complete response, n/N (%)	32/192 (16.7)	18/179 (10.1)
Pathological tumour regression grade, n/N (%)		
Grade 1a: 0% residual tumour	36/189 (19.0)	24/179 (13.4)
Grade 1b: >0 to <10% residual tumour	47/189 (24.9)	71/179 (39.7)
Grade 2: 10 to 50% residual tumour	46/189 (24.3)	50/179 (27.9)
Grade 3: >50% residual tumour	60/189 (31.7)	34/179 (19.0)

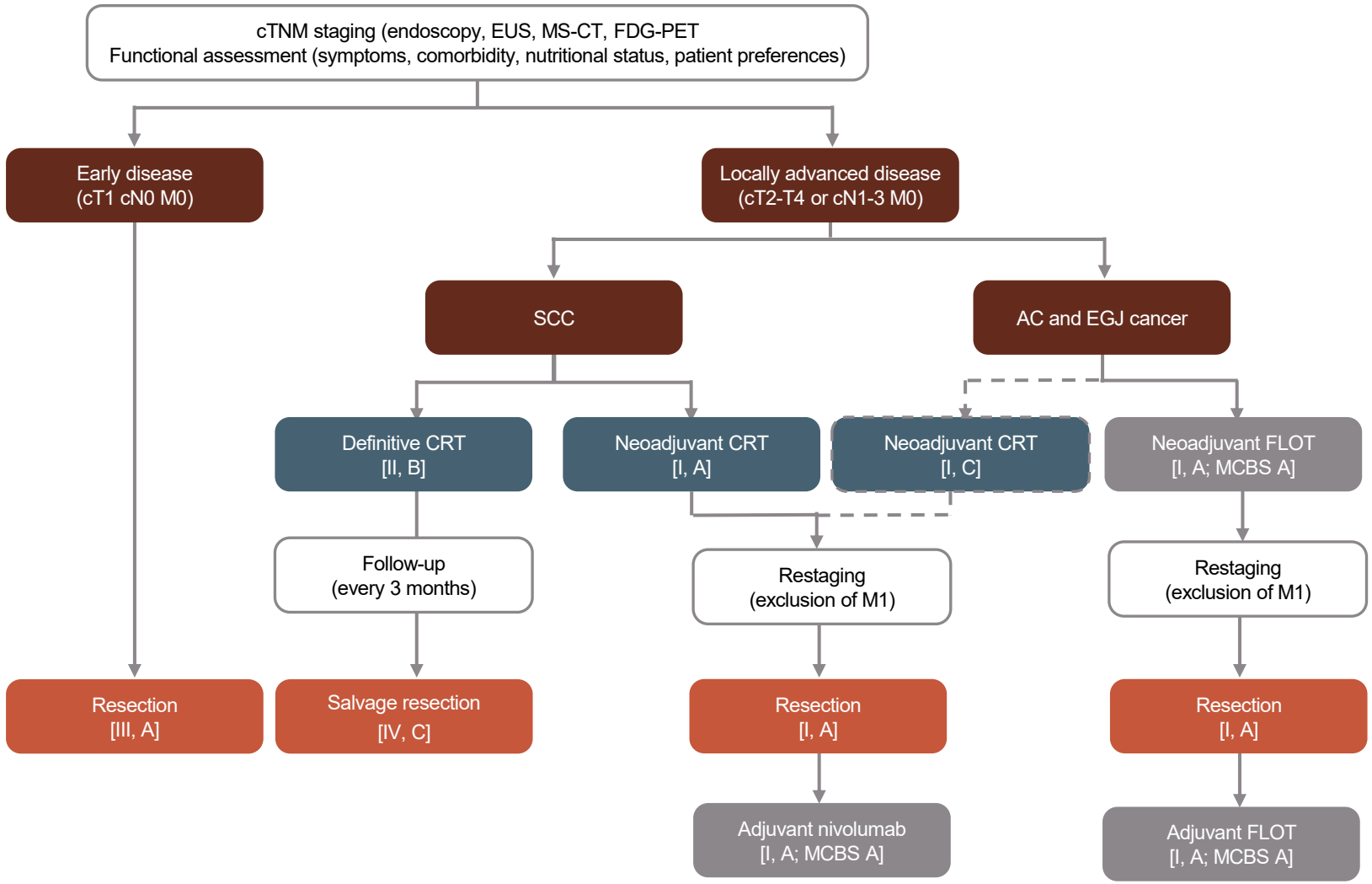
POSTOPERATIVE COMPLICATIONS

Variable	FLOT (N=193)	Pre-operative CRT (N=181)
Clavien–Dindo classification		
Grade 0	65 (33.7)	62 (34.3)
Grade I	40 (20.7)	36 (19.9)
Grade II	27 (14.0)	27 (14.9)
Grade III	45 (23.3)	43 (23.8)
Grade IV	13 (6.7)	8 (4.4)
Grade V	3 (1.6)	5 (2.8)
Death after surgery		
At 30 days	2 (1.0)	3 (1.7)
At 90 days	6 (3.1)	10 (5.6)

CRT, chemoradiotherapy; FLOT, fluorouracil plus leucovorin, oxaliplatin and docetaxel; ypN/T, pathological Nodal/Tumour stage

Hoeppner J, et al. N Engl J Med. 2025;392:323-35

ESMO GUIDELINES FOR RESECTABLE ESOPHAGEAL CANCER



AC, adenocarcinoma; APC, antigen-presenting cells; CRT, chemoradiotherapy; CT, computed tomography; cTNM, clinical Tumour Node Metastasis; dCRT, definitive CRT; EC, esophageal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EGJ, esophagogastric junction; ESCC, esophageal squamous cell carcinoma; EUS, endoscopic ultrasound; FDG-PET, [18F]2-fluoro-2-deoxy-D-glucose-positron emission tomography; FLOT, 5-fluorouracil-leucovorin-oxaliplatin-docetaxel; MCBS, Magnitude of Clinical Benefit Score; MDT, multidisciplinary team; MS-CT, multi-slice-computed tomography; NK cell, natural killer cell; SCC, squamous cell carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand-1; PVR, poliovirus receptor (CD155); SoC, standard of care; TIGIT, T cell immunoreceptor with Ig and ITIM domains

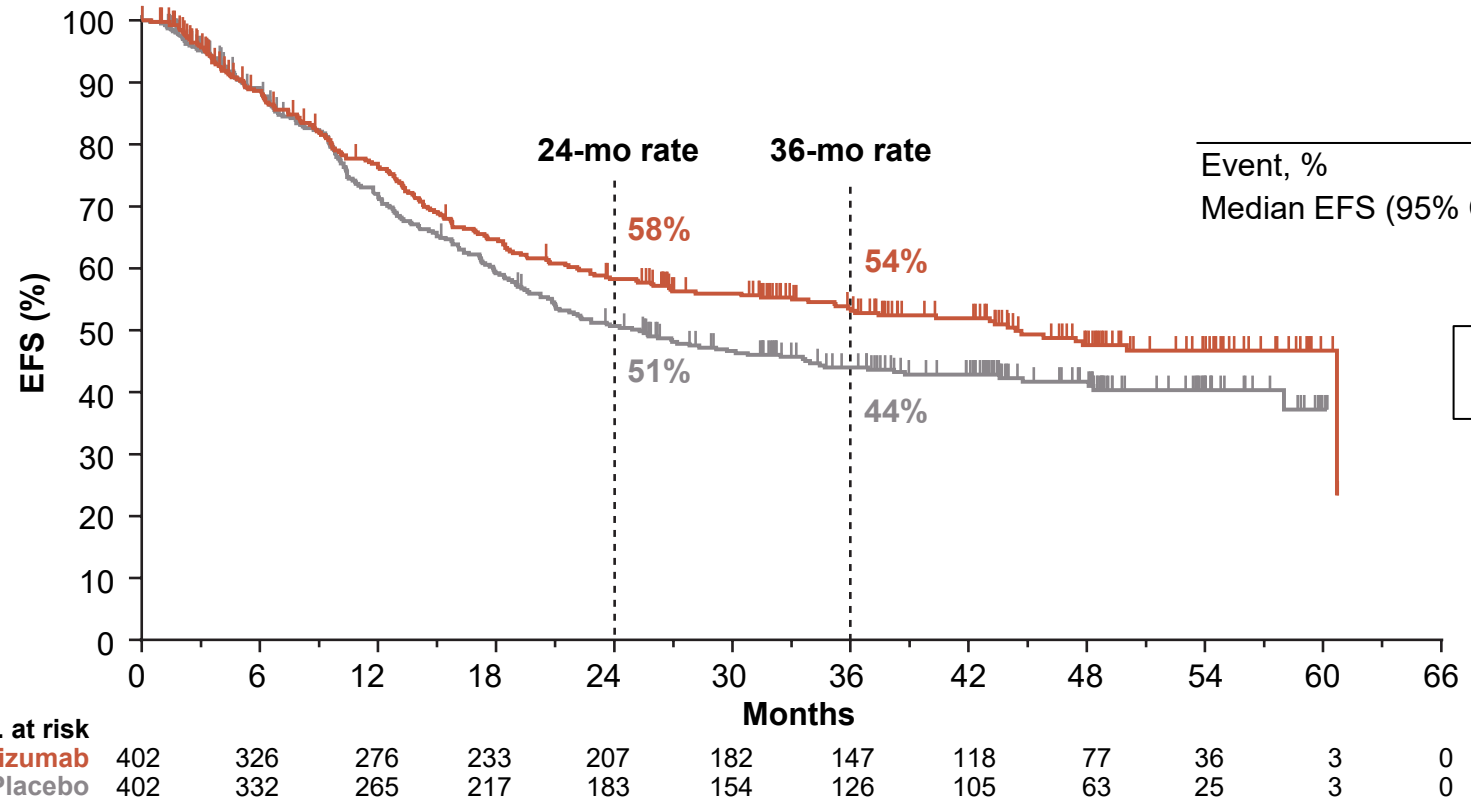
Obermannová R, et al. ESMO Open. 2025;10:104134

ADDITION OF IMMUNOTHERAPY TO FLOT

FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel

PERI-OPERATIVE CHEMOTHERAPY/FLOT ± PEMBROLIZUMAB

EVENT-FREE SURVIVAL: MAIN COHORT



	Pembro	Placebo
Event, %	46	53
Median EFS (95% CI), mo	44.4 (33.0-NR)	25.3 (20.6-33.9)

HR 0.81 (95% CI: 0.67-0.99)
p=0.0198[a]

KEYNOTE-585
positive in trend

[a] Threshold for significance was one-sided p=0.0178
Data cut-off date: 9 Feb 2023.

EFS defined as time from randomisation to first occurrence of radiographic disease progression per RECIST v1.1, local or distant recurrence assessed by CT scan or biopsy if indicated, clinical progression, or death due to any cause per investigator assessment

CI, confidence interval; CT, computed tomography; EFS, event-free survival; FLOT, fluorouracil plus leucovorin, oxaliplatin and docetaxel; HR, hazard ratio; mo, months; NR, not reached; pembro, pembrolizumab; RECIST, Response Evaluation Criteria in Solid Tumours

Shitara K, et al. Ann Oncol. 2023;34(suppl_2):S1316. Abstract LBA74

DANTE: RANDOMISED PHASE 2/3 PERI-OPERATIVE CHEMOTHERAPY +/- ATEZOLIZUMAB

Pathological Regression by CPS Threshold and MSI-H Status

n (%)	Central review[a]			
	TRG1a		TRG1a/b	
	FLOT+atezo	FLOT	**FLOT+atezo**	FLOT
All Patients (N=295)	35 (24) [N=146]	22 (15) [N=149]	71 (49) [N=146]	57 (38) [N=149]
PD-L1 CPS ≥1 (N=170)	20 (24) [N=82]	12 (14) [N=88]	42 (51) [N=82]	39 (44) [N=88]
PD-L1 CPS ≥ 5 (N=81)	11 (**28**) [N=40]	8 (20) [N=41]	22 (**55**) [N=40]	18 (44) [N=41]
PD-L1 CPS ≥ 10 (N=53)	9 (**33**) [N=27]	3 (12) [N=26]	18 (**67**) [N=27]	10 (39) [N=26]
MSI-H (N=23)	5 (63) [N=8]	4 (27) [N=15]	6 (75) [N=8]	7 (47) [N=15]

[a]In 48 cases, central assessment was not possible and local results were consideredAtezo, atezolizumab; CPS, combined positive score; FLOT, fluorouracil plus leucovorin, oxaliplatin and docetaxel; MSI-H, microsatellite instability-high; TRG, tumour regression grade

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

MATTERHORN: STUDY DESIGN[1,2]

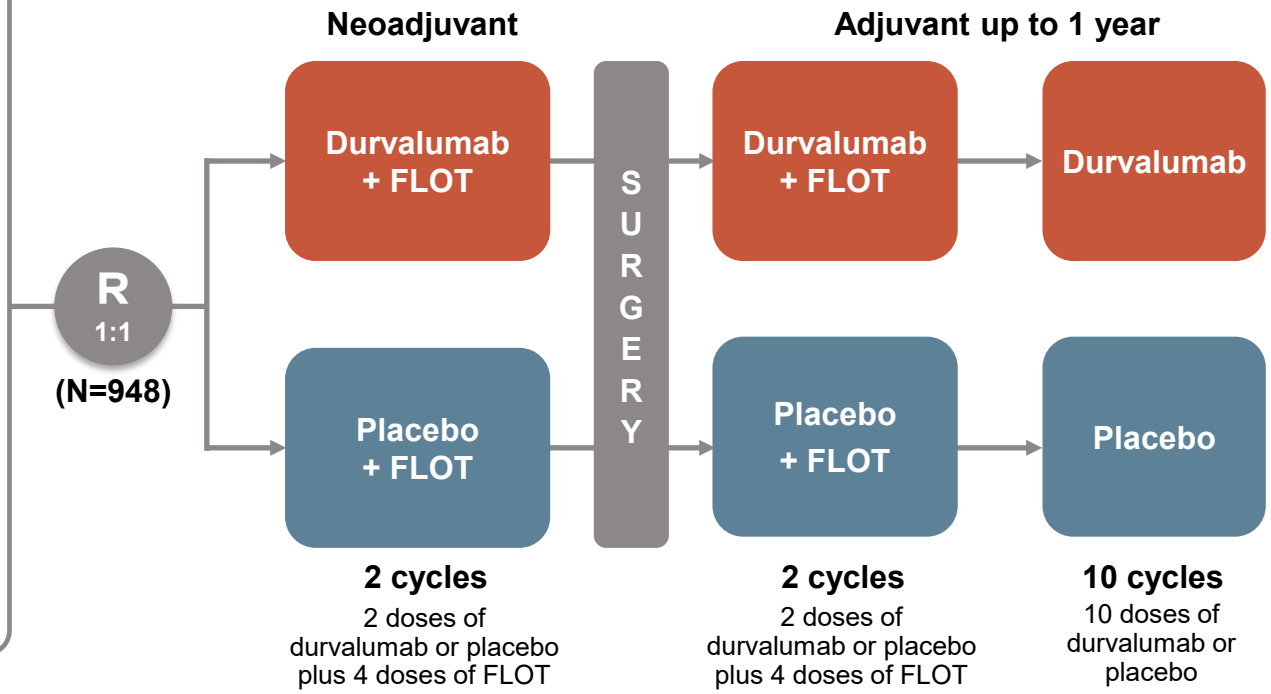
MATTERHORN IS A GLOBAL, PHASE 3, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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%[a]



Primary endpoint:

- EFS

Secondary endpoints:

- OS
- pCR (central review by modified Ryan criteria)

[a] 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

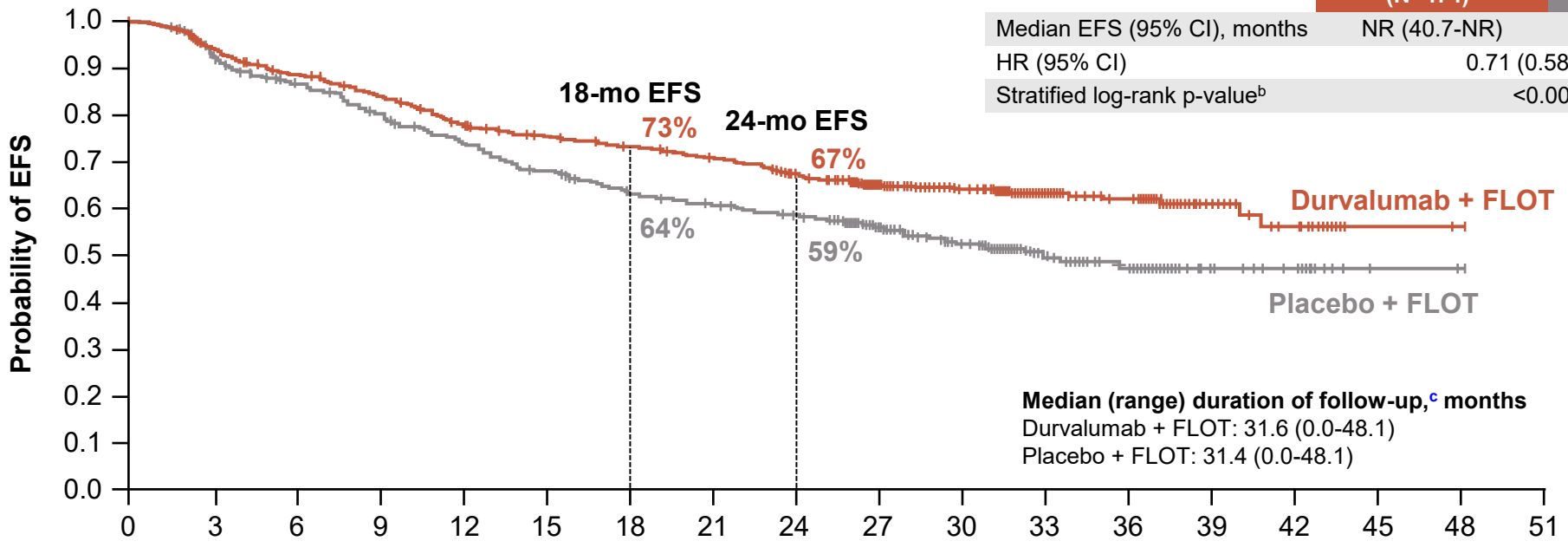
ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; G/GEJ, gastric/gastroesophageal junction; OS, overall survival; pCR, pathological complete response; Q4W, every 4 weeks; R, randomisation; TAP, tumour area positivity

1. Janjigian YY, et al. N Engl J Med. 2025;393:217-30. 2. Janjigian YY, et al. J Clin Oncol. 2025;43(suppl 17). Abstract LBA5. Presented at: ASCO Congress (2025)

MATTERHORN: PRIMARY ENDPOINT OF EFS[1]

A STATISTICALLY SIGNIFICANT IMPROVEMENT IN EFS WAS OBSERVED WITH DURVALUMAB + FLOT VERSUS PLACEBO + FLOT

	Durvalumab + FLOT (N=474)[a]	Placebo + FLOT (N=474)[a]
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[b]	<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

[a] Full analysis set (all randomised participants, regardless of treatment received); [b] The threshold of significance for this analysis was 0.0239; [c] 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

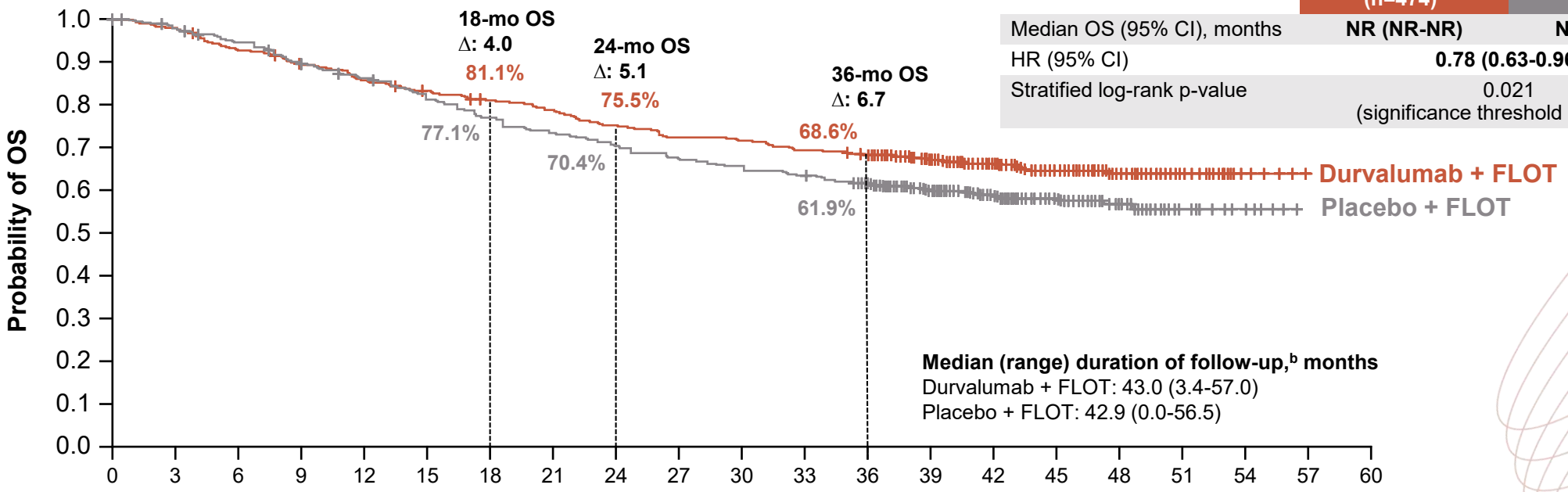
BICR, blinded independent central review; CI, confidence interval; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; HR, hazard ratio; mo, month; NR, not reached; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1

1. Janjigian YY, et al. N Engl J Med. 2025;393:217-30; 2. Janjigian YY, et al. J Clin Oncol. 2025;43(suppl 17). Abstract LBA5. Presented at: ASCO Congress (2025)

MATTERHORN: 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)[a]	Placebo + FLOT (n=474)[a]
Median OS (95% CI), months	**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)	



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

[a] Intention-to-treat analysis set (all randomised participants, regardless of treatment received). [b] 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.

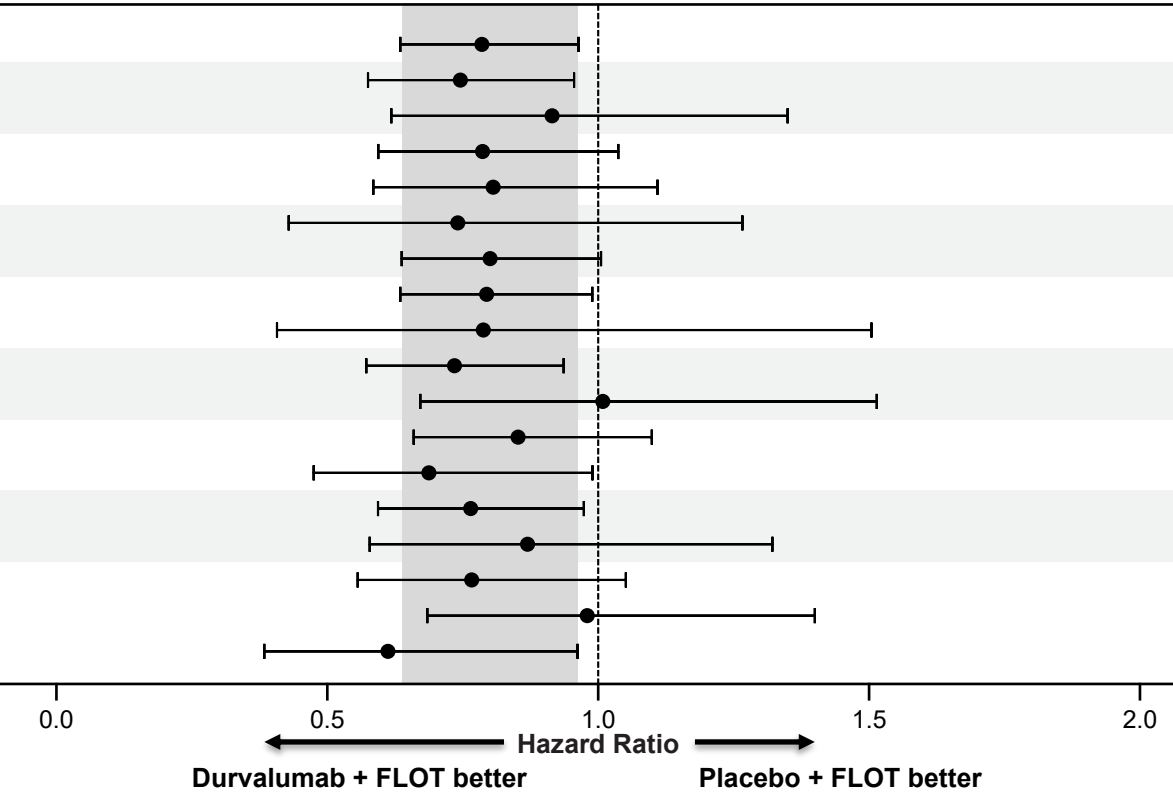
CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; HR, hazard ratio; mo, month; NR, not reached; OS, overall survival

Tabernero J, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965. Presented at ESMO 2025 (Abstract LBA81)

MATTERHORN: 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[a]	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)



[a] 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

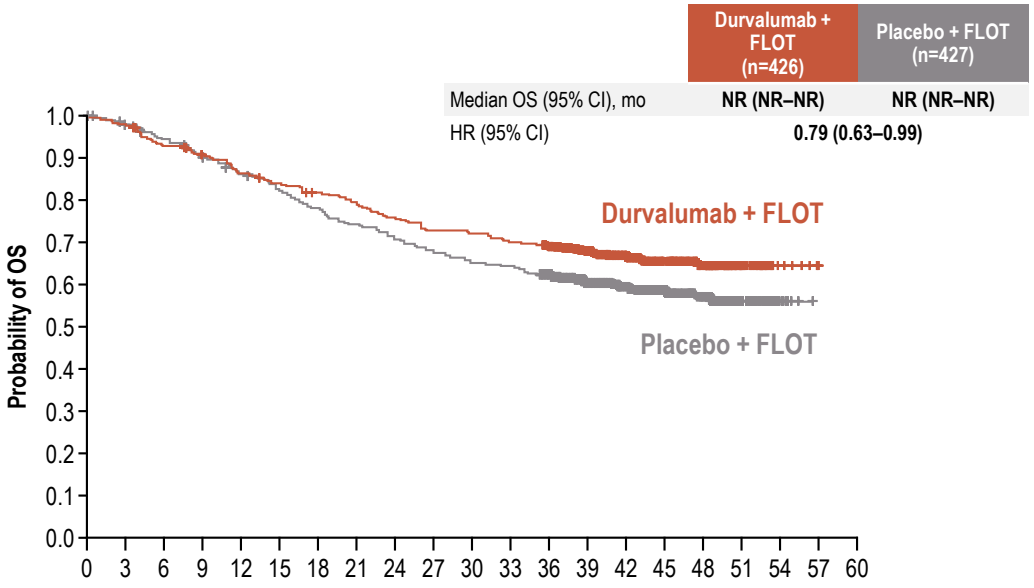
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; GEJ, gastroesophageal junction; HR, hazard ratio; OS, overall survival; TAP, Tumour Area Positivity

Tabernero J, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965. Presented at ESMO 2025 (Abstract LBA81)

MATTERHORN: OS BY PD-L1 STATUS

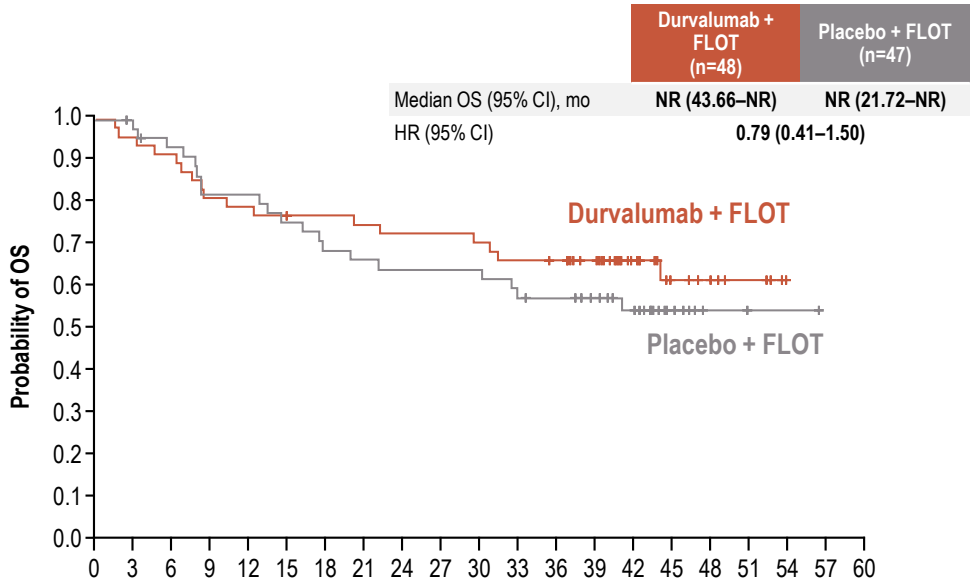
OS WAS IMPROVED WITH DURVALUMAB + FLOT VERSUS PLACEBO + FLOT REGARDLESS OF PD-L1 STATUS

PD-L1 TAP ≥1%[a]



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%[a]



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	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	20

[a] 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

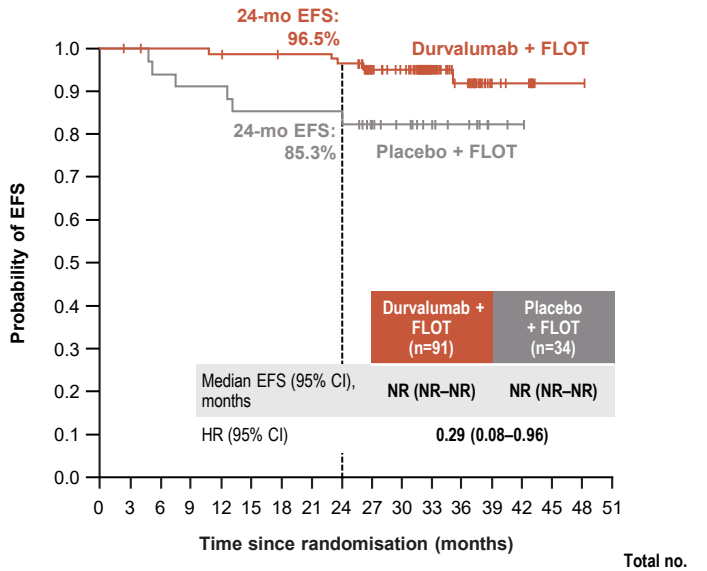
CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; HR, hazard ratio; NR, not reached; OS, overall survival; TAP, Tumour Area Positivity

Tabernero J, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965. Presented at ESMO 2025 (Abstract LBA81)

MATTERHORN: PATHOLOGICAL RESPONSE AND EFS

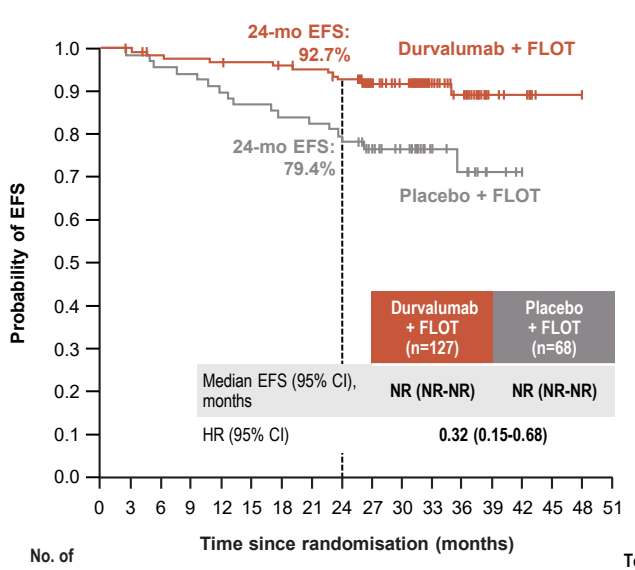
EFS WAS IMPROVED WITH DURVALUMAB + FLOT VERSUS PLACEBO + FLOT AMONG PARTICIPANTS WITH ANY DEGREE OF PATHOLOGICAL RESPONSE

pCR



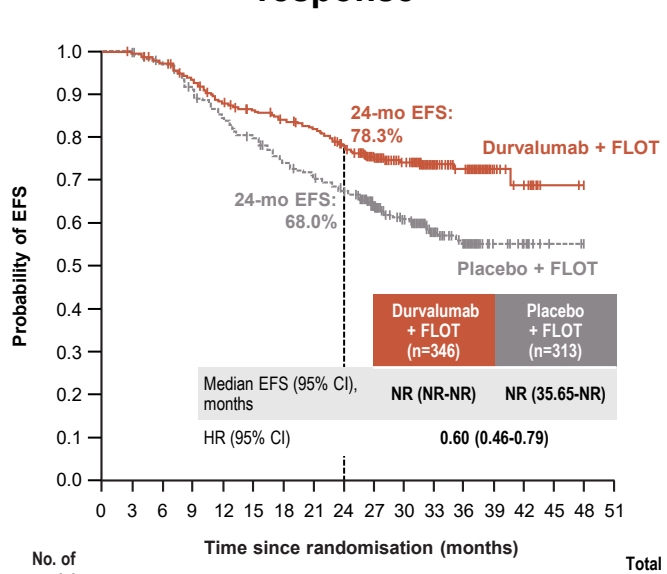
No. of participants at risk																			Total no. of events
Durvalumab + FLOT	91	90	88	88	87	86	85	85	83	68	60	38	27	7	5	1	1	0	5
Placebo + FLOT	34	34	32	31	31	29	29	29	29	23	16	11	8	2	1	0	0	0	6

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[a]



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

[a] 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

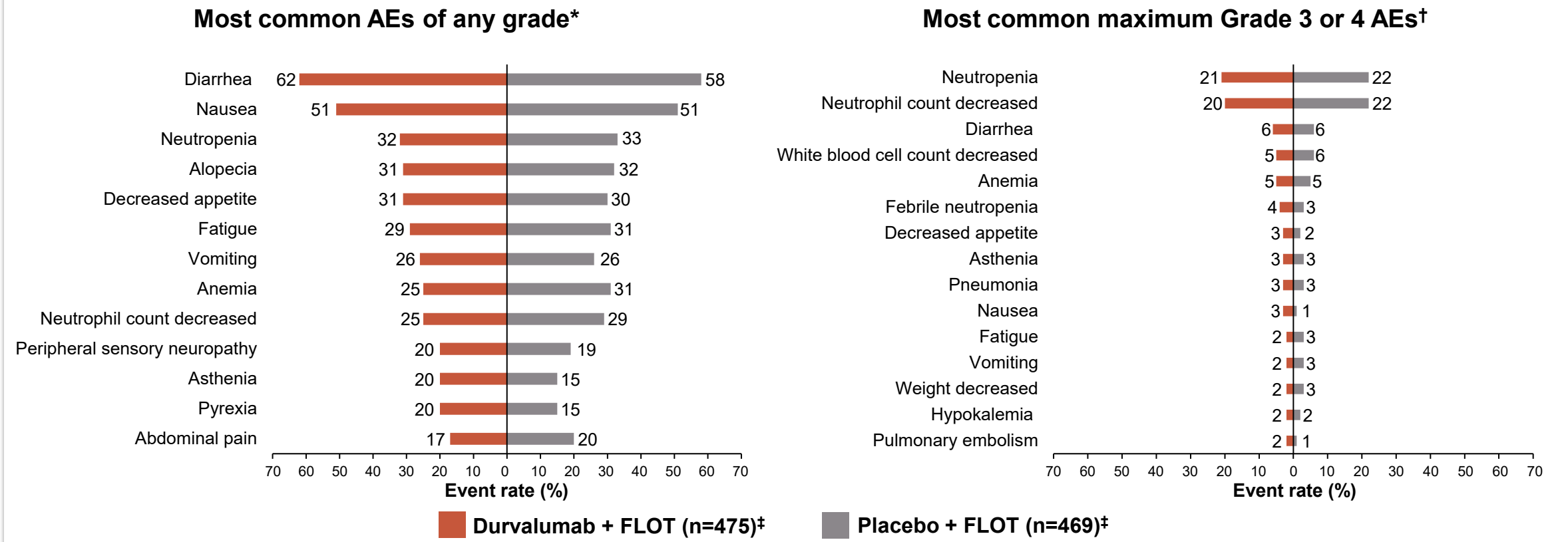
Data cut-off: 20 December 2024. pCR is defined as modified Ryan score of 0; MPR is defined as modified Ryan score of 0 and 1; any pathological response is defined as modified Ryan score 0, 1, and 2 . Events were defined as the earliest of RECIST v1.1 events, non-RECIST v1.1 events or deaths due to any 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 Tumours version 1.1

Tabernero J, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965. Presented at ESMO 2025 (Abstract LBA81)

COMMON AEs: ALIGNED WITH KNOWN PROFILES OF DURVALUMAB AND FLOT

MATTERHORN STUDY



* AEs occurring in ≥20% of participants in any treatment group; † AEs occurring in ≥2% of participants in any treatment group; ‡ Safety analysis set (participants who received at least one dose of study treatment); one participant in the placebo + FLOT group received a single dose of durvalumab and is, therefore, included in the durvalumab + FLOT group for the safety analysis

AE, adverse event; FLOT, 5-flouraoracil, leucovorin, oxaliplatin and docetaxel

Janjigian J, et al. J Clin Oncol 2025; 43: LBA5-LBA5; DOI:10.1200/JCO.2025.43.17_suppl.LBA5 (ASCO 2025, oral presentation)

MATTERHORN: 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

MATTERHORN OS results strongly support peri-operative 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; G/GEJ, gastric/gastroesophageal junction; HR, hazard ratio; OS, overall survival

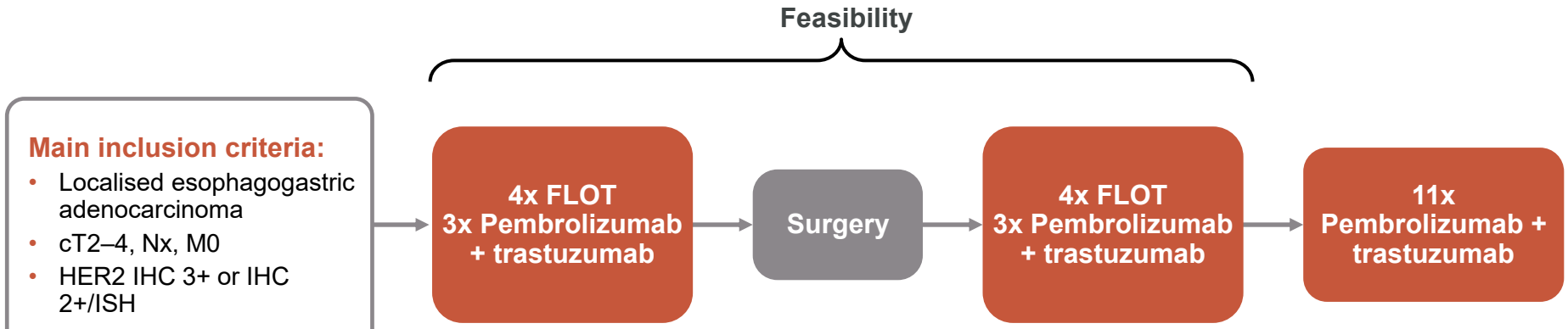
Tabernero J, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965. Presented at ESMO 2025 (Abstract LBA81)

IMMUNOTHERAPY + FLOT
HER2-POSITIVE PATIENTS

FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel

PHERFLOT/IKF053: STUDY DESIGN[1]

PHERFLOT is an open, single-arm, multicentre, exploratory Phase 2 study[1,2]



Main inclusion criteria:

- Localised esophagogastric adenocarcinoma
- cT2–4, Nx, M0
- HER2 IHC 3+ or IHC 2+/ISH

Main exclusion criteria:

- Previous immunotherapy
- Immunodeficiency
- LVEF <55%

Primary endpoint:

- pCR and DFS at 2 years

Secondary endpoints:

- Feasibility
- Safety
- R0 resection
- OS
- DFS

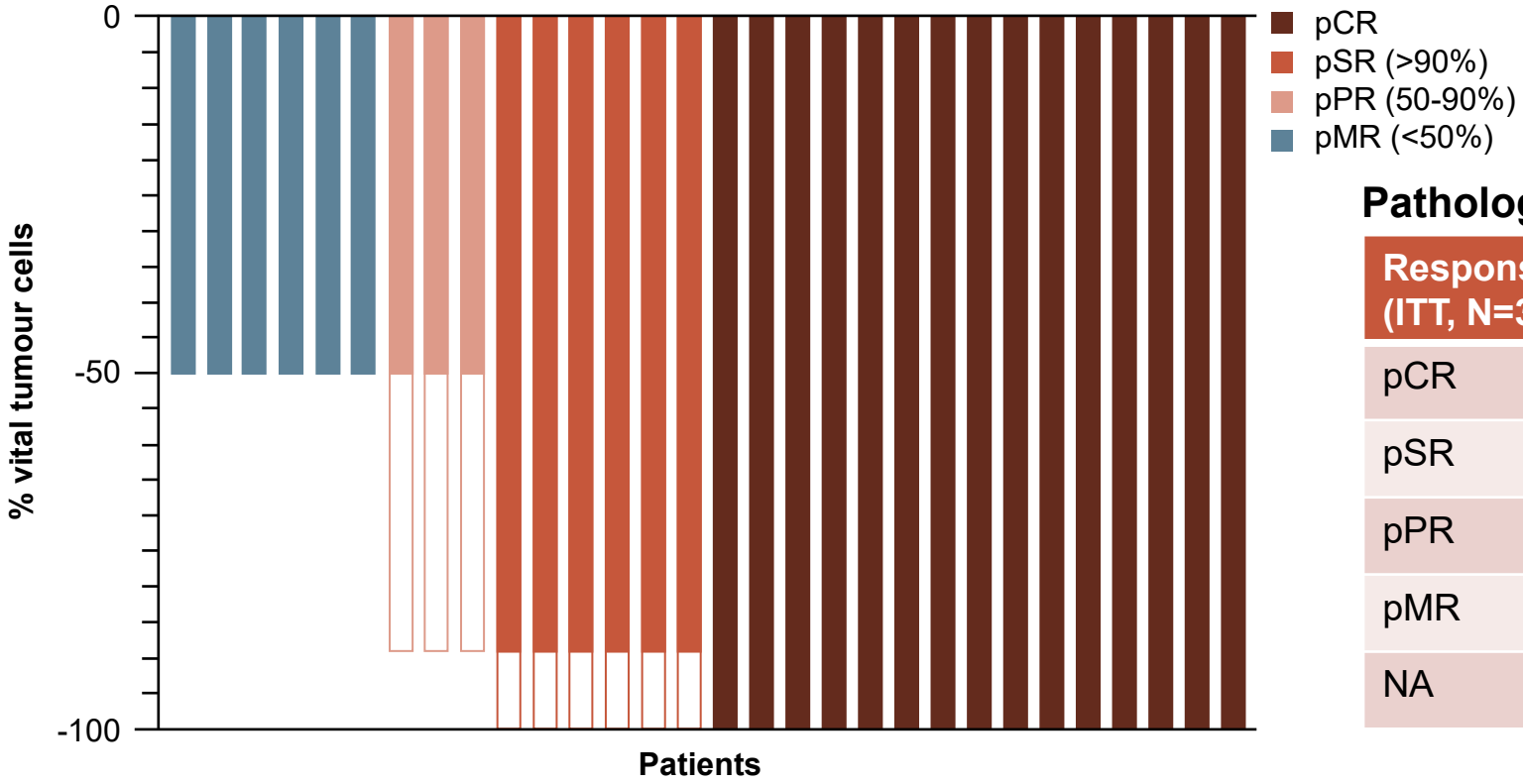
cTNM, clinical Tumour, Nodal, Metastasis stage; DFS, disease-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; IHC, immunohistochemistry; ISH, in-situ hybridisation; LVEF, left ventricular ejection fraction; OS, overall survival; pCR, pathological complete response; R0, microscopically margin-negative resection

1. Tintelnot J et al. Ann Oncol. 2025;36(suppl_2):S1194-S1232. 10.1016/annonc/annonc1931. Presented at ESMO 2025 (Abstract 2095MO); 2. Tintelnot J, et al. Front Oncol. 2023;13:1272175

PHERFLOT/IKF053: PATHOLOGICAL RESPONSE

All patients who consented to surgery underwent R0 resection (N=30)

PATHOLOGICAL TUMOUR REGRESSION



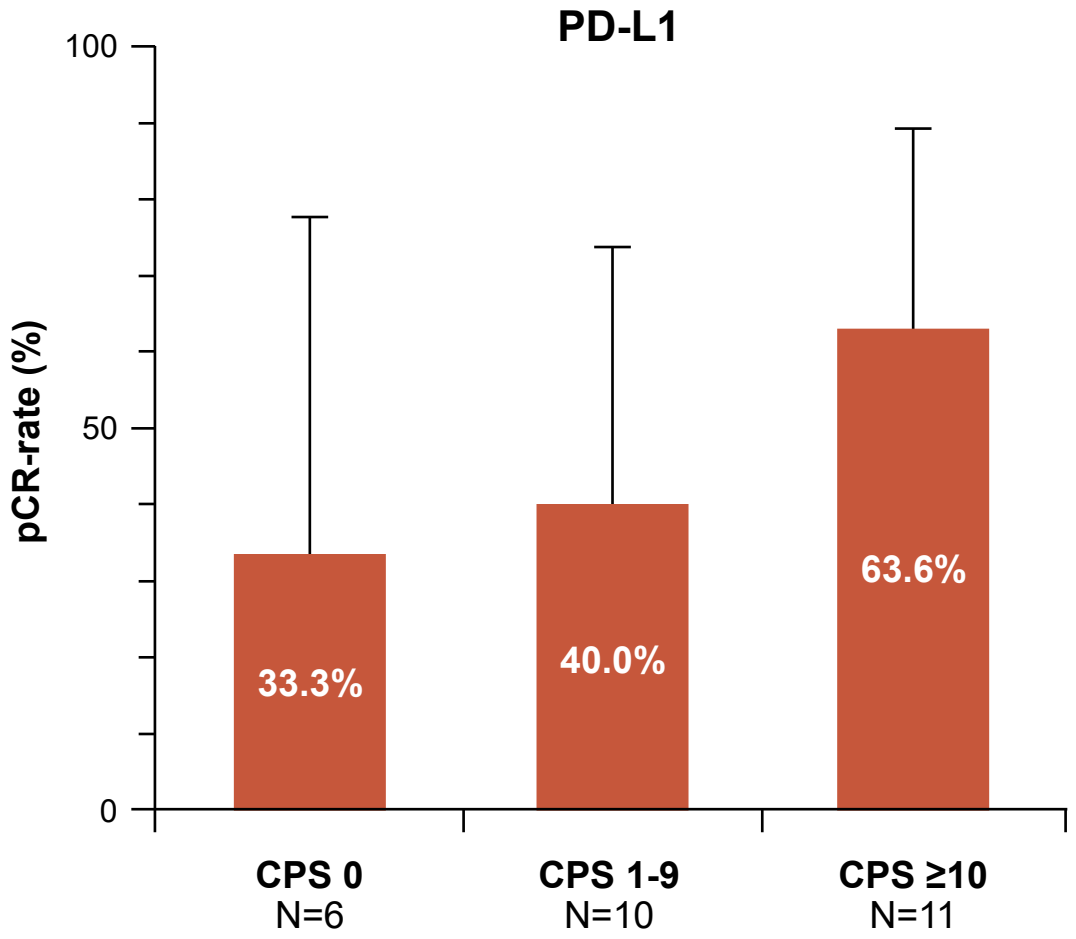
Pathological response outcomes

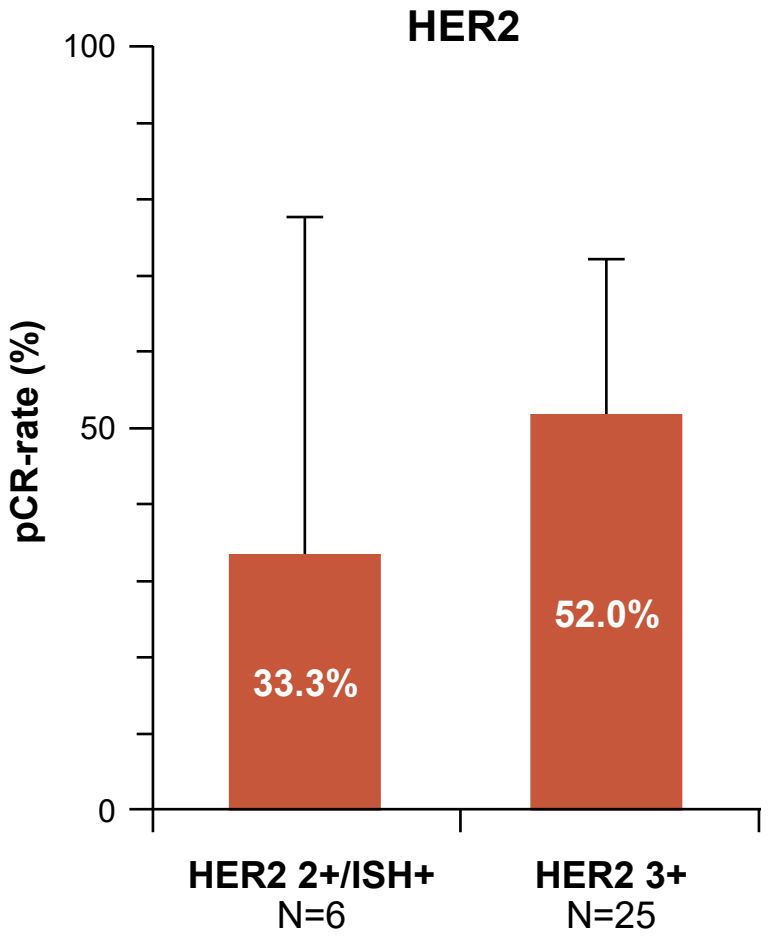
Response category (ITT, N=31)	n (%)	95% CI
pCR	15 (48.4)	30.2-66.
pSR	6 (19.4)	7.5-37.5
pPR	3 (9.7)	2.0-25.8
pMR	5 (19.4)	7.5-37.5
NA	1 (3.2)	-

ITT, intent-to-treat; NA, not applicable; pCR, pathological complete response; pMR, pathological minor response; pPR, pathological partial response; pSR, pathological subtotal response; R0 resection, microscopically margin-negative resection

Tintelnot J et al. Ann Oncol. 2025;36(suppl_2):S1194-S1232. 10.1016/annonc/annonc1931. Presented at ESMO 2025 (Abstract 2095MO); Stein A, et al. Nat Med. 2025: https://doi.org/10.1038/s41591-025-03979-y

PHERFLOT/IKF053: PATHOLOGICAL RESPONSE SUBGROUPS





CPS, combined positive score; ISH, in-situ hybridisation; pCR, pathological complete response

Tintelnot J et al. Ann Oncol. 2025;36(suppl_2):S1194-S1232. 10.1016/annonc/annonc1931. Presented at ESMO 2025 (Abstract 2095MO)

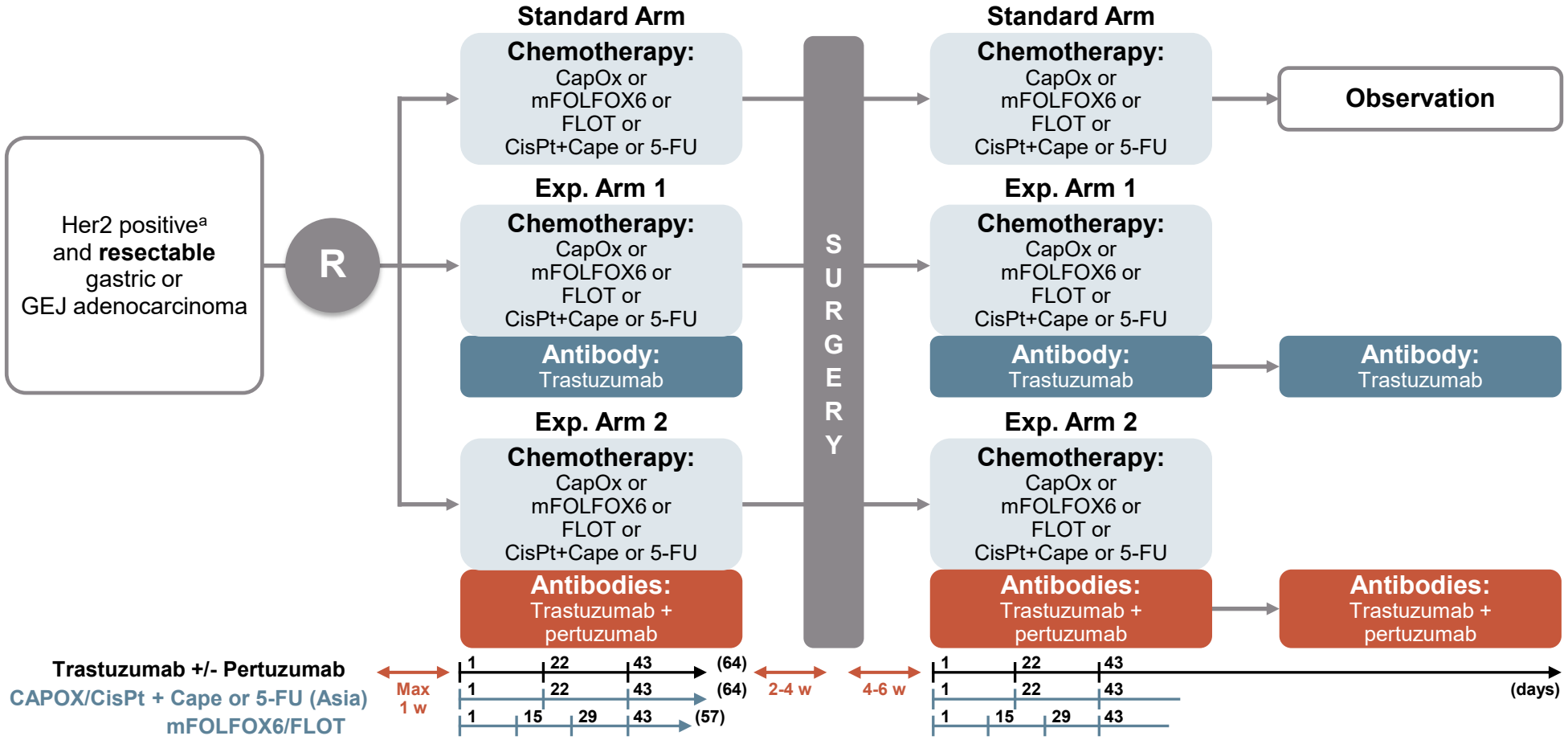
PHERFLOT/IKF053: SUMMARY

- FLOT + pembrolizumab + trastuzumab is feasible
- Safety profile is as expected, except for an increased incidence of grade 3 diarrhoea and higher re-operations
- pCR of ~ 50% and pSR ~ 20% = around a 70% major pathological response (in the ITT)
- Higher response in CPS ≥10 and HER2-3+ patients

CPS, combined positive score; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; ITT, intention-to-treat; pCR, pathological complete response; pSR, pathological subtotal response

Tintelnot J et al. Ann Oncol. 2025;36(suppl_2):S1194-S1232. 10.1016/annonc/annonc1931. Presented at ESMO 2025 (Abstract 2095MO)

INNOVATION TRIAL: TRASTUZUMAB, WITH OR WITHOUT PERTUZUMAB, INTO PERI-OPERATIVE CHEMOTHERAPY OF HER2 POSITIVE STOMACH CANCER

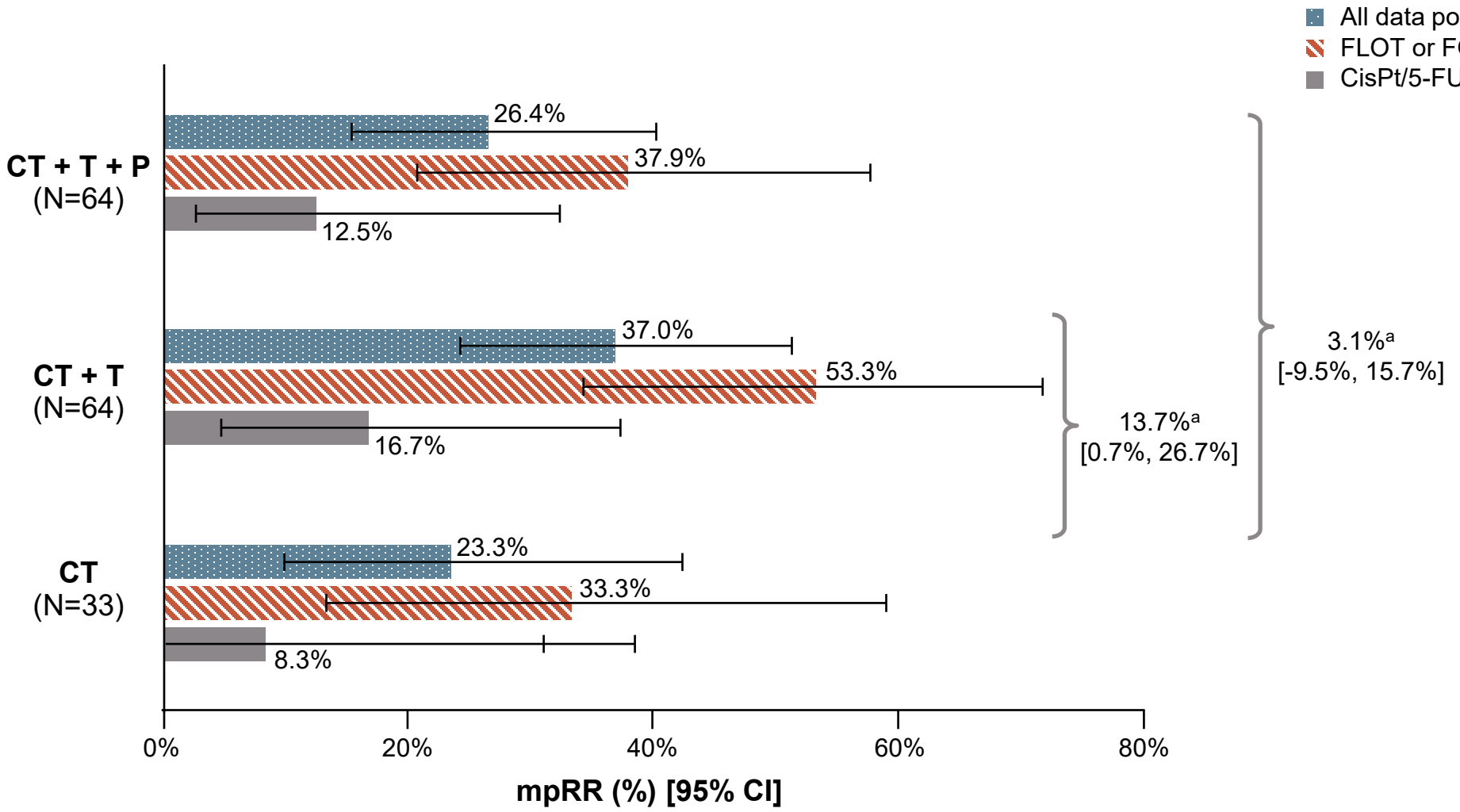


[a] Confirmed by central screening

5-FU, 5-fluorouracil; cape, capecitabine; CapOx, capecitabine, oxaliplatin; CisPt, cisplatin; FLOT, 5-FU, leucovorin, oxaliplatin and docetaxel; GEJ, gastroesophageal junction; mFOLFOX6, modified FOLFOX6 regimen (FOLFOX: oxaliplatin+5-FU+leucovorin); w, weeks

Wagner A, et al. BMC Cancer. 2019;19:494

INNOVATION: PRIMARY ENDPOINT – mpRR – IMPACT OF CT BACKBONE



- Primary endpoint not met for the pre-specified criteria of efficacy for the combination of CT+T+P
- CT+T showed interesting response rates

[a] Difference in mpRR between each experimental arm and CT arm (80% CI)

5-FU, 5-fluorouracil; CapOx, capecitabine, oxaliplatin; CI, confidence interval; CisPt, cisplatin; CT, chemotherapy; FLOT, 5-FU, leucovorin, oxaliplatin and docetaxel; mpRR, major pathological response rate; P, pertuzumab; T, trastuzumab

Wagner A, et al. Ann Oncol. 2023;34:S182. Presented at ESMO GI 2023 (Abstract O-5, oral presentation)

SUMMARY: WHAT DOES THIS PERI-OPERATIVE DATA MEAN FOR ESOPHAGOGASTRIC JUNCTION CANCER PATIENTS?

- Peri-operative chemotherapy provides a significant survival benefit for patients with locally advanced gastric cancer
- Peri-operative FLOT combined with targeted therapy or immunotherapy shows promising signs of enhancing pathological regression
- Adding immunotherapy (durvalumab) to FLOT improved pathologic downstaging and disease-free and overall survival (MATTERHORN); benefit for pembrolizumab + FLOT remains uncertain (KEYNOTE-585)
- It is an important standard of care to pre-operatively discuss gastric cancer patients in interdisciplinary tumour boards, with gastroenterologists, surgeons, radiation- and medical- oncologists to optimise treatment and improve cure rates

FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; OS, overall survival

POLLING QUESTION 1

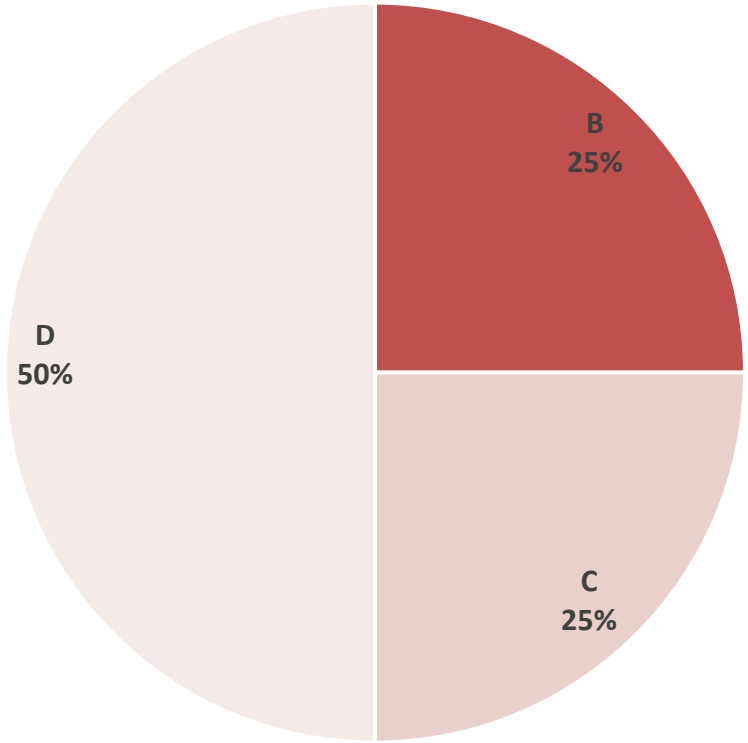
WHICH OF THE FOLLOWING IS NOT A MAIN GOAL OF PERI-OPERATIVE CHEMOTHERAPY COMBINED WITH IMMUNOTHERAPY FOR ESOPHAGOGASTRIC JUNCTION CANCER IN PATIENTS WITH GOOD OVERALL HEALTH?

A. To improve pathological regression and quality of life

B. To prolong disease-free and overall survival

C. For squamous cell carcinoma, to use neoadjuvant radiochemotherapy (CROSS) and adjuvant nivolumab if no complete pathological response is achieved after curative resection

D. To give only adjuvant therapy instead of neoadjuvant therapy in all T3 N+ patients



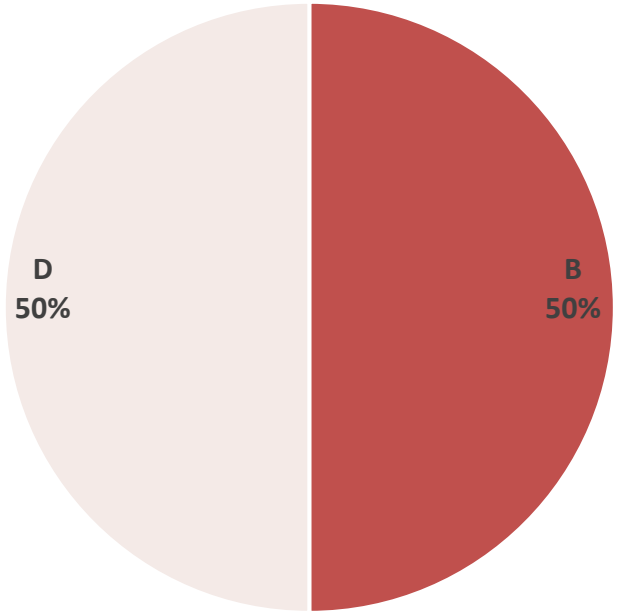
CROSS, preoperative radiotherapy plus carboplatin and paclitaxel (as used in CROSS study); N, Nodal (staging); T, Tumour (staging)

POLLING QUESTION 2

WHICH OF THE FOLLOWING STATEMENTS ABOUT PERI-OPERATIVE CHEMOTHERAPY FOR GASTRIC CANCER ARE CORRECT?

1. Peri-operative chemotherapy provides a significant survival benefit for patients with locally advanced gastric cancer
2. Adding immunotherapy to FLOT further improved tumour downstaging and disease-free survival
3. In the MATTERHORN trial, FLOT combined with durvalumab showed a significant improvement in overall survival compared with FLOT alone in locally advanced gastric cancer
4. It is an important standard of care to pre-operatively discuss gastric cancer patients in interdisciplinary tumour boards, with gastroenterologists, surgeons, radiation- and medical- oncologists to optimise treatment
and improve cure rates

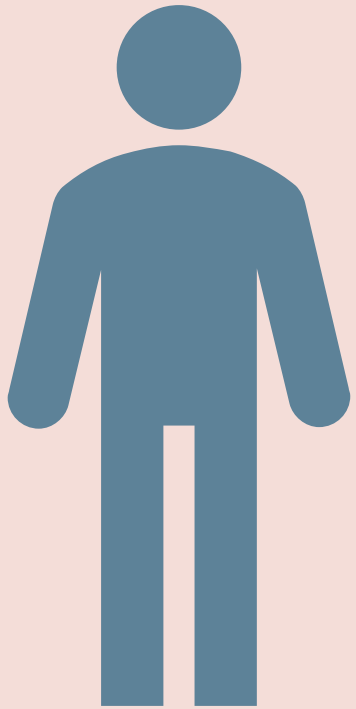
A. Only statement 4 is correct
B. All statements are correct
C. Only statements 1 and 2 are correct
D. Only statements 1, 2 and 3 are correct
E. None of the statements are correct



WHAT'S NEW FOR ESOPHAGEAL SQUAMOUS CELL CARCINOMA?

Prof. Aziz Zaanan
European Georges Pompidou Hospital, France

PATIENT CASE 1



Patient

- 75 years old, male, ECOG PS 2
- He has been consuming alcohol and tobacco for over 40 years
- Main comorbidities : severe chronic obstructive bronchopneumopathy
- Dysphagia for past 6 weeks, weight loss (-3 kg/2 months)
- Gastroscopy and biopsies showed a squamous cell carcinoma in the middle third of the esophagus
- CT scan / EUS / FDG-PET: **cT4bN+M0**

MDT : unresectable esophageal squamous cell carcinoma
→ Definitive chemoradiotherapy (dCRT)

CT, computed tomography; dCRT, definitive CRT; ECOG PS, Eastern Cooperative Oncology Group performance status; cTNM, clinical Tumour Node Metastasis; EUS, endoscopic ultrasound; FDG-PET, [18F]2-fluoro-2-deoxy-D-glucose-positron emission tomography; MDT, multidisciplinary team

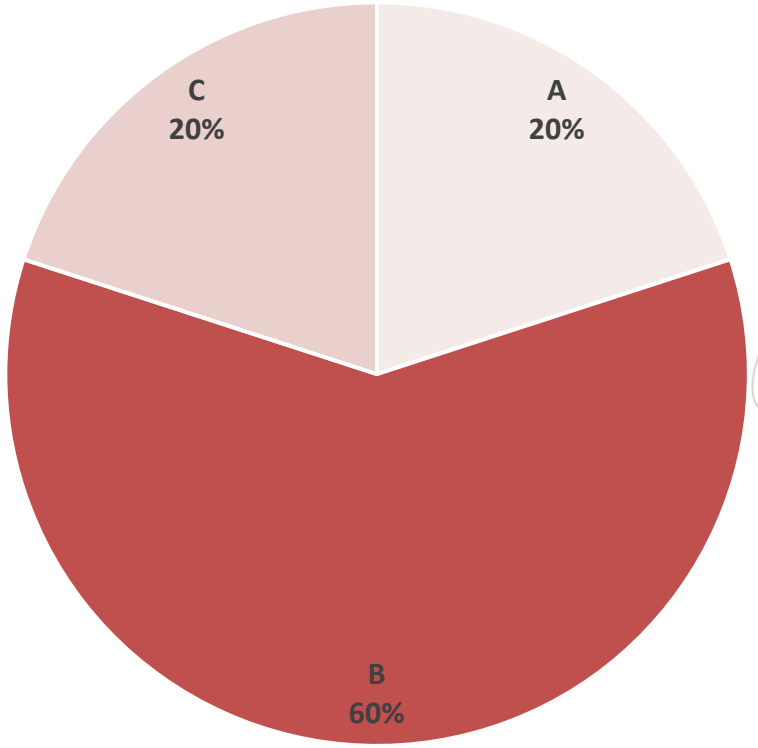
POLLING QUESTION 1

WHICH OF THE FOLLOWING REGIMENS REPRESENTS THE TRADITIONAL STANDARD APPROACH FOR DEFINITIVE CHEMORADIOTHERAPY (CRT)?

A. CROSS regimen (paclitaxel + carboplatin and 41,4 Gy)

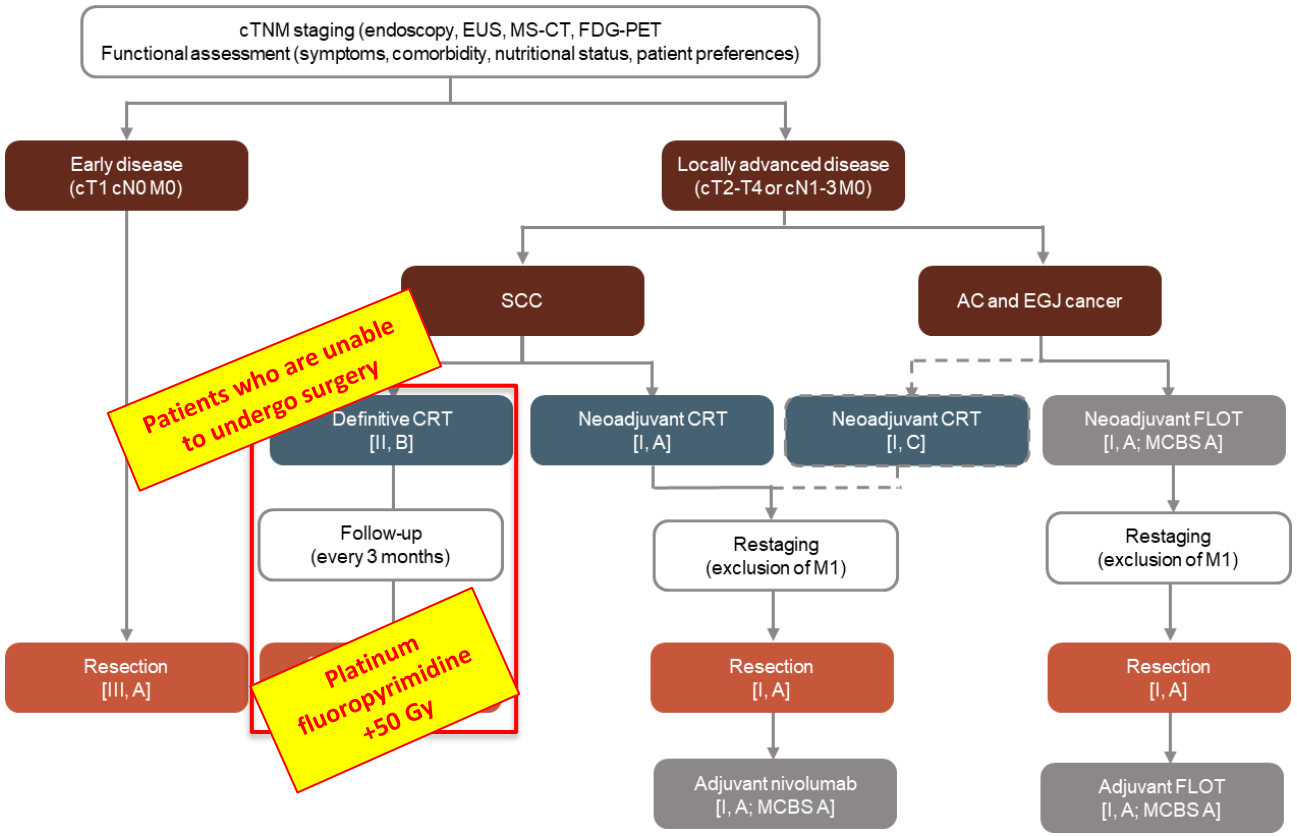
B. Platinum + fluoropyrimidine chemotherapy, and 50 Gy

C. Platinum + fluoropyrimidine chemotherapy, and 60 Gy

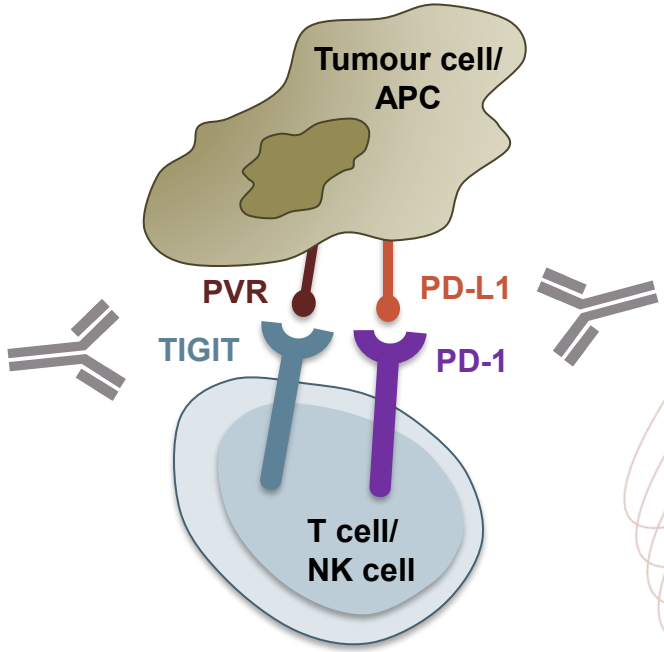


ESMO-GUIDELINES ESOPHAGEAL CANCER

Treatment algorithm for local/locoregional resectable EC/EGJ cancer[1]



Consolidation immunotherapy can improve clinical outcomes ?



The **SoC for unresectable locally advanced ESCC is dCRT**
→ However, **40–60% of patients experience recurrence** after dCRT and 5-year survival rate is approximately 10–30%[2]

SKYSCRAPER-07 trial

AC, adenocarcinoma; APC, antigen-presenting cells; CRT, chemoradiotherapy; CT, computed tomography; cTNM, clinical Tumour Node Metastasis; dCRT, definitive CRT; EC, esophageal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EGJ, esophagogastric junction; ESCC, esophageal squamous cell carcinoma; EUS, endoscopic ultrasound; FDG-PET, [18F]2-fluoro-2-deoxy-D-glucose-positron emission tomography; FLOT, 5-fluorouracil-leucovorin-oxaliplatin-docetaxel; MCBS, Magnitude of Clinical Benefit Score; MDT, multidisciplinary team; MS-CT, multi-slice-computed tomography; NK cell, natural killer cell; SCC, squamous cell carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand-1; PVR, poliovirus receptor (CD155); SoC, standard of care; TIGIT, T cell immunoreceptor with Ig and ITIM domains

1. Obermannová R, et al. ESMO Open. 2025;10:104134; 2. Xie R, et al. Front Oncol. 2024;14:1303068

SKYSCRAPER-07: A PHASE 3, RANDOMISED STUDY OF ATEZOLIZUMAB WITH OR WITHOUT TIRAGOLUMAB IN PATIENTS WITH UNRESECTABLE ESCC THAT HAS NOT PROGRESSED FOLLOWING DEFINITIVE CONCURRENT CHEMORADIOTHERAPY

Chau I, et al. Abstract 2094O, ESMO 2025

ESCC, esophageal squamous cell carcinoma

SKYSCRAPER-07: A GLOBAL, PHASE 3, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

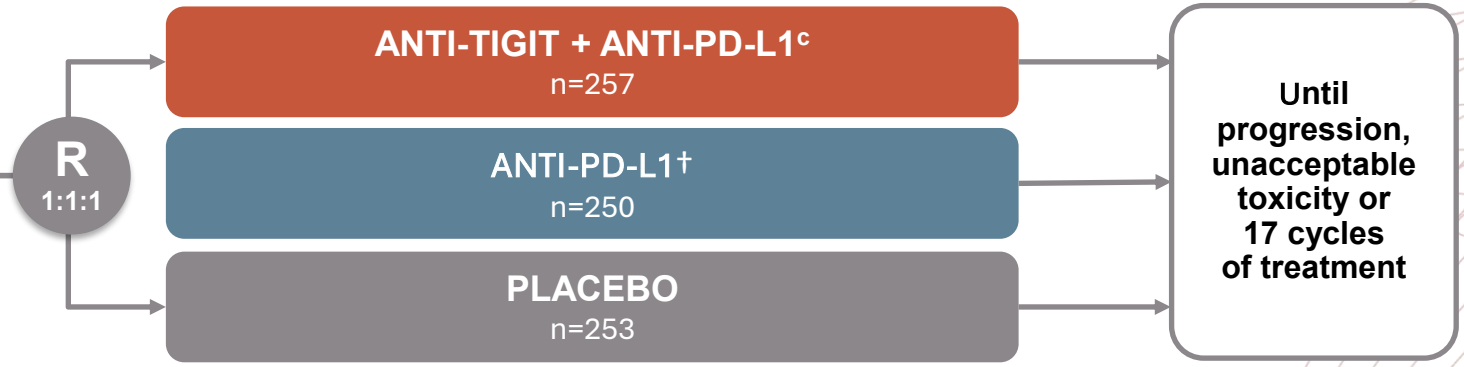
SKYSCRAPER-07 (NCT04543617) aimed to determine the efficacy and safety of atezo with or without tira in patients with unresectable ESCC following dCRT

Key eligibility criteria:

- Stage II–IVA or IVB with SCLN metastases only[a] ESCC
- Tissue available for PD-L1 testing
- No PD after receiving concurrent dCRT
- ECOG PS 0 or 1

Stratification factors:

- **Geographic region** (Asia vs Rest of world)
- **ESCC stage prior to dCRT** (II vs III vs IV)
- **PD-L1 status**[b] (TAP score <10% vs ≥10%)



[c]*Tira 600 mg IV Q3W + atezo 1200 mg IV Q3W*
[d]*Atezo 1200 mg IV Q3W + pbo IV Q3W*

Patients were recruited between 28 September 2020 and 31 August 2023 at 166 centres in 28 countries or regions

[a] Patients who were diagnosed with Stage IVB cervical or upper thoracic ESCC with SCLN metastases only and deemed suitable for dCRT were eligible
[b] Assessed by a central laboratory through use of the investigational VENTANA PD-L1 (Ab clone SP263) CDx assay

Ab, antibody; atezo, atezolizumab; CDx, companion diagnostic assay; dCRT, definitive chemoradiotherapy; ECOG PS, Eastern Cooperative Oncology Group performance score; ESCC, esophageal squamous cell carcinoma; IV, intravenous; PD, progressive disease; Q3W, every 3 weeks; R, randomisation; SCLN, supraclavicular lymph node; TAP, tumour area positivity; tira, tiragolumab; TIGIT, T cell immunoreceptor with Ig and ITIM domains

Chau I, et al. Ann Oncol. 2025;36(suppl_2):S1181-S1182. (Abstract 2094O, ESMO 2025)

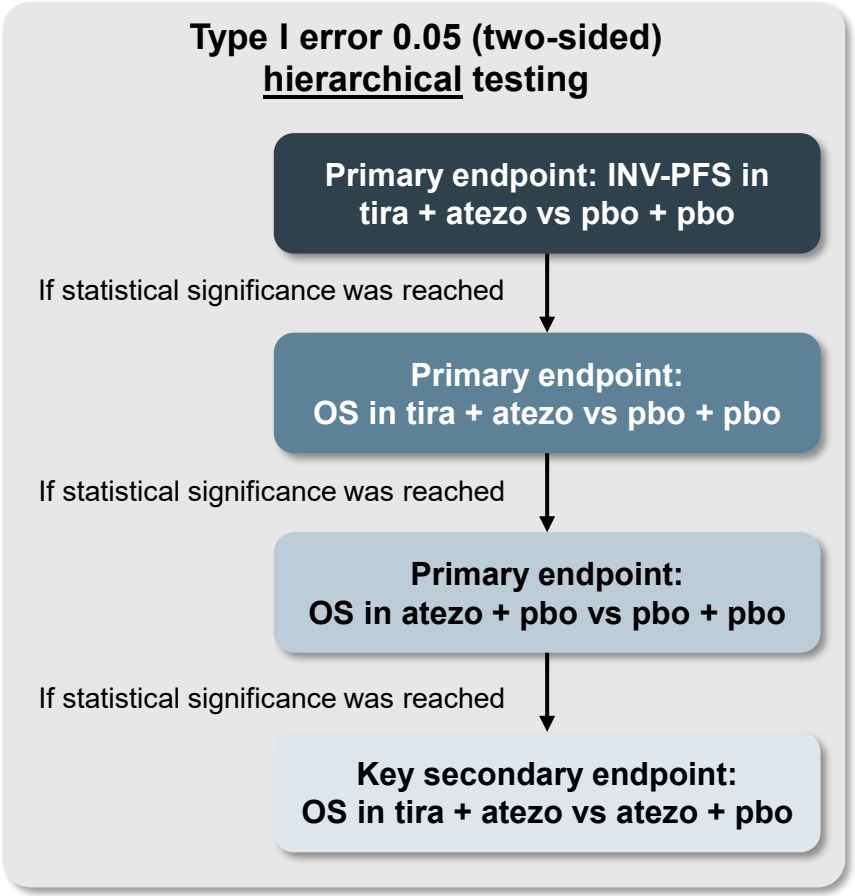
SKYSCRAPER-07: STATISTICAL ANALYSIS PLAN AND TREATMENT DISPOSITION

Primary endpoints

- **Tiragolumab + atezolizumab vs placebo :** INV-PFS; OS
- **Atezolizumab vs placebo :** OS

Secondary endpoints

- **Tiragolumab + atezolizumab vs placebo:** IRF-PFS
- **Atezolizumab vs placebo :** INV-PFS, IRF-PFS
- **Tira + atezo vs atezo :** INV-PFS, IRF-PFS, OS
- Safety



atezo, atezolizumab; INV, investigator assessed; IRF, independent review facility; OS, overall survival; pbo, placebo; PFS, progression-free survival; tira, tiragolumab

Chau I, et al. Ann Oncol. 2025;36(suppl_2):S1181-S1182. (Abstract 2094O, ESMO 2025)

SKYSCRAPER-07: BASELINE CHARACTERISTICS

	Tira + atezo (N=257)	Atezo + pbo (N=250)	Pbo + pbo (N=253)
Median age, years	66.0	66.0	66.0
≥65 years, n (%)	147 (57.2)	138 (55.2)	144 (56.9)
Male, n (%)	183 (71.2)	190 (76.0)	191 (75.5)
Geographic region, n (%): Asia / rest of world	159 (61.9) / 98 (38.1)	157 (62.8) / 93 (37.2)	158 (62.5) / 95 (37.5)
Race, n (%): Asian / White / Black or Africa American	160 (62.3) / 94 (36.6) / 3 (1.2)	158 (63.2) / 90 (36.0) / 2 (0.8)	159 (62.8) / 91 (36.0) / 3 (1.2)
Baseline ECOG PS, n (%): 0 / 1	103 (40.1) / 154 (59.9)	79 (31.6) / 171 (68.4)	97 (38.3) / 156 (61.7)
PD-L1 (Ab clone SP263), n (%):			
TAP <10% / ≥10%	163 (63.4) / 94 (36.6)	160 (64.0) / 90 (36.0)	162 (64.0) / 91 (36.0)
TAP <1% / ≥1%	34 (13.2) / 223 (86.8)	37 (14.8) / 213 (85.2)	35 (13.8) / 218 (86.2)
Disease stage prior to dCRT, n (%): II / III / IVA / IVB	58 (22.6) / 131 (51.0) / 55 (21.4) / 13 (5.1)	56 (22.4) / 125 (50.0) / 55 (22.0) / 14 (5.6)	54 (21.3) / 128 (50.6) / 53 (20.9) / 18 (7.1)
Location of primary EC, n (%): Upper third / middle third / lower third	127 (49.4) / 98 (38.1) / 32 (12.5)	114 (45.6) / 98 (39.2) / 38 (15.2)	127 (50.2) / 89 (35.2) / 37 (14.6)
Type of prior concurrent chemotherapy, n (%): Taxane / non-taxane[a]	115 (44.7) / 142 (55.3)	106 (42.4) / 144 (57.6)	118 (46.6) / 135 (53.4)
Best response to dCRT, n (%):			
CR / PR / SD / Non-CR or non-PD	37 (14.4) / 135 (52.5) / 63 (24.5) / 22 (8.6)	34 (13.6) / 125 (50.0) / 71 (28.4) / 20 (8.0)	37 (14.6) / 121 (47.8) / 72 (28.5) / 21 (8.3)
PD / not estimable	0 / 0	0 / 0	1 (0.4) / 1 (0.4)

Data cut-off: 18 February 2025. [a]Flouropyrimidine

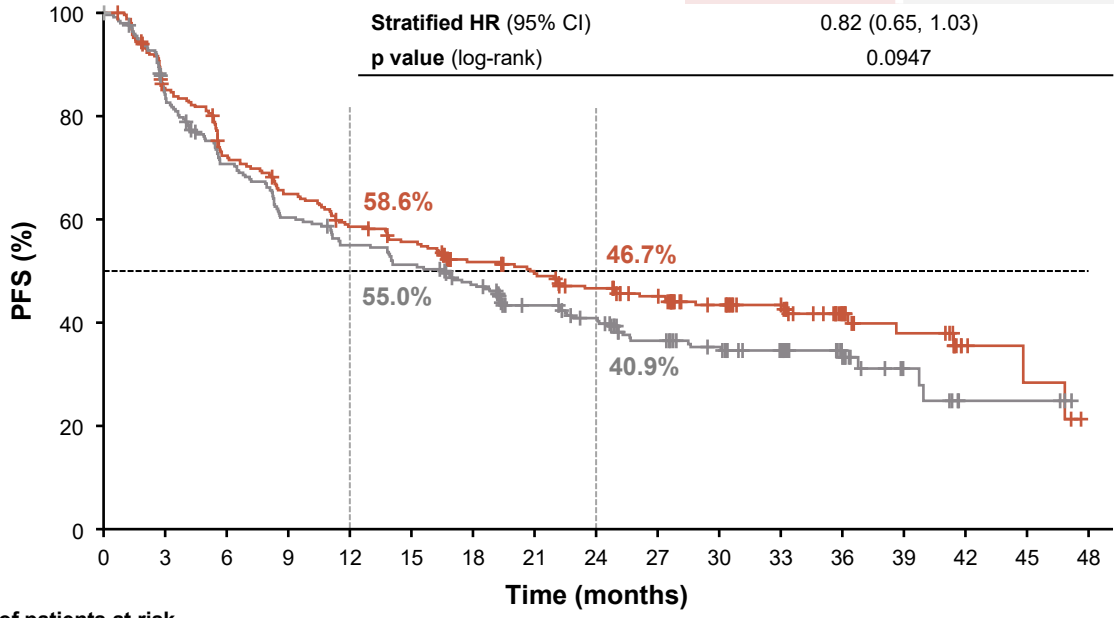
Ab, antibody; atezo, atezolizumab; CR, complete response; dCRT, definitive chemoradiotherapy; EC, esophageal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; pbo, placebo; PD, progressive disease; PR, partial response; SD, stable disease; TAP, tumour area positivity; tira, tiragolumab

Chau I, et al. Ann Oncol. 2025;36(suppl_2):S1181-S1182. (Abstract 2094O, ESMO 2025)

SKYSCRAPER-07: PFS AND OS IN THE DOUBLET VS PLACEBO ARMS

Primary endpoint: INV-PFS

	Tira + atezo (N=257)	Pbo + pbo (N=253)
Patients with events, n (%)	141 (54.9)	157 (62.1)
Median PFS (95% CI), months	20.8 (13.9, 28.8)	16.6 (11.2, 19.4)
Stratified HR (95% CI)	0.82 (0.65, 1.03)	
p value (log-rank)	0.0947	

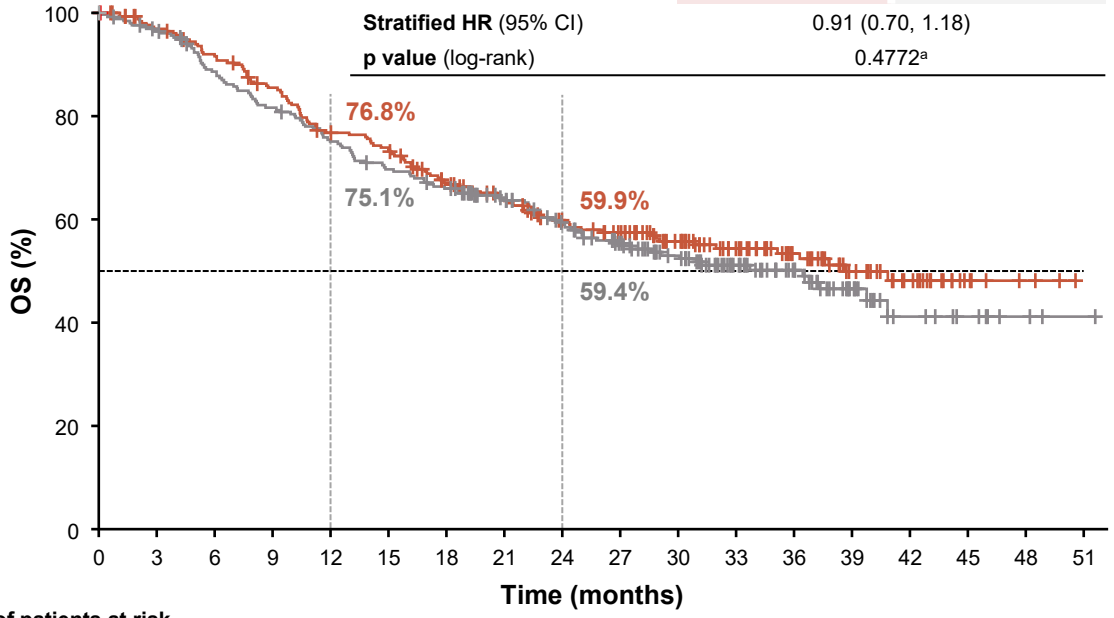


No. of patients at risk

Tira + atezo	257	209	175	156	140	131	115	107	96	86	67	54	30	19	6	4	NE
Pbo + pbo	253	207	171	146	132	123	109	89	80	64	56	42	26	10	3	3	NE

Primary endpoint: OS

	Tira + atezo (N=257)	Pbo + pbo (N=253)
Patients with events, n (%)	111 (43.2)	118 (46.6)
Median OS (95% CI), months	38.6 (28.8, NE)	36.4 (25.8, NE)
Stratified HR (95% CI)	0.91 (0.70, 1.18)	
p value (log-rank)	0.4772[a]	



No. of patients at risk

Tira + atezo	257	241	227	208	186	178	155	140	124	113	90	70	52	35	23	7	3	NE
Pbo + pbo	253	239	216	199	182	167	157	139	121	102	84	62	46	25	11	7	3	1

→ This means that all other subsequent analyses become exploratory

[a] Descriptive only

Data cut-off: 18 February 2025. Median survival follow-up: 25.0 months.

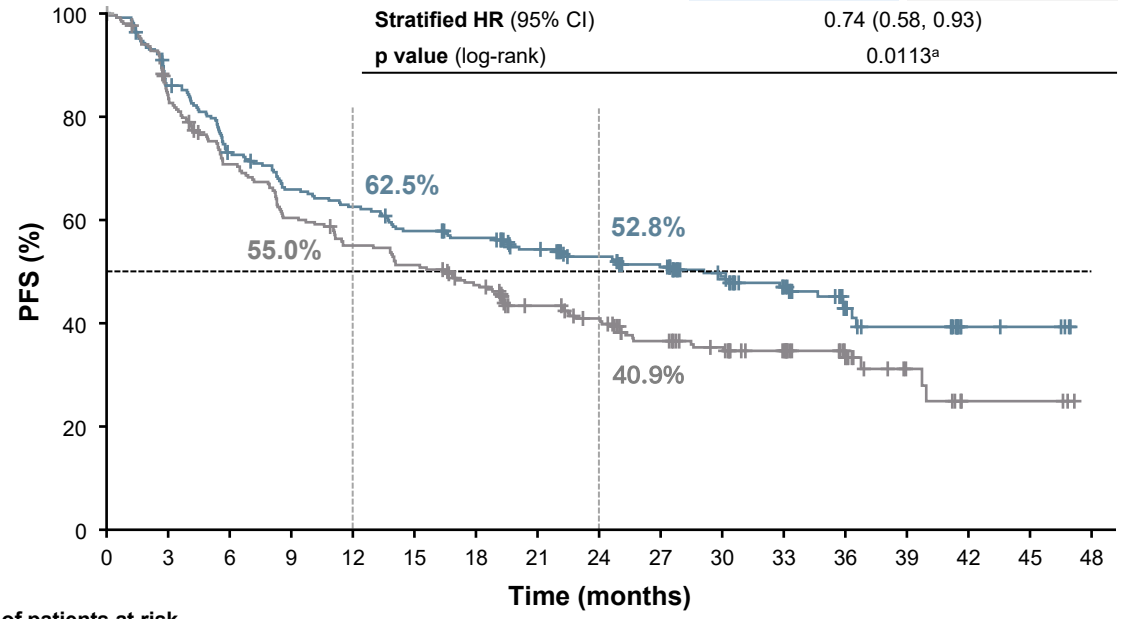
atezo, atezolizumab; CI, confidence interval; HR, hazard ratio; INV, investigator assessed; NE, not evaluable; OS, overall survival; pbo, placebo; PFS, progression-free survival; tira, tiragolumab

Chau I, et al. Ann Oncol. 2025;36(suppl_2):S1181-S1182. (Abstract 2094O, ESMO 2025)

SKYSCRAPER-07: PFS AND OS IN THE ATEZO VS PLACEBO ARMS

Secondary endpoint: INV-PFS

	Atezo + pbo (N=250)	Pbo + pbo (N=253)
Patients with events, n (%)	128 (51.2)	157 (62.1)
Median PFS (95% CI), months	29.1 (19.0, 36.3)	16.6 (11.2, 19.4)
Stratified HR (95% CI)	0.74 (0.58, 0.93)	
p value (log-rank)	0.0113[a]	

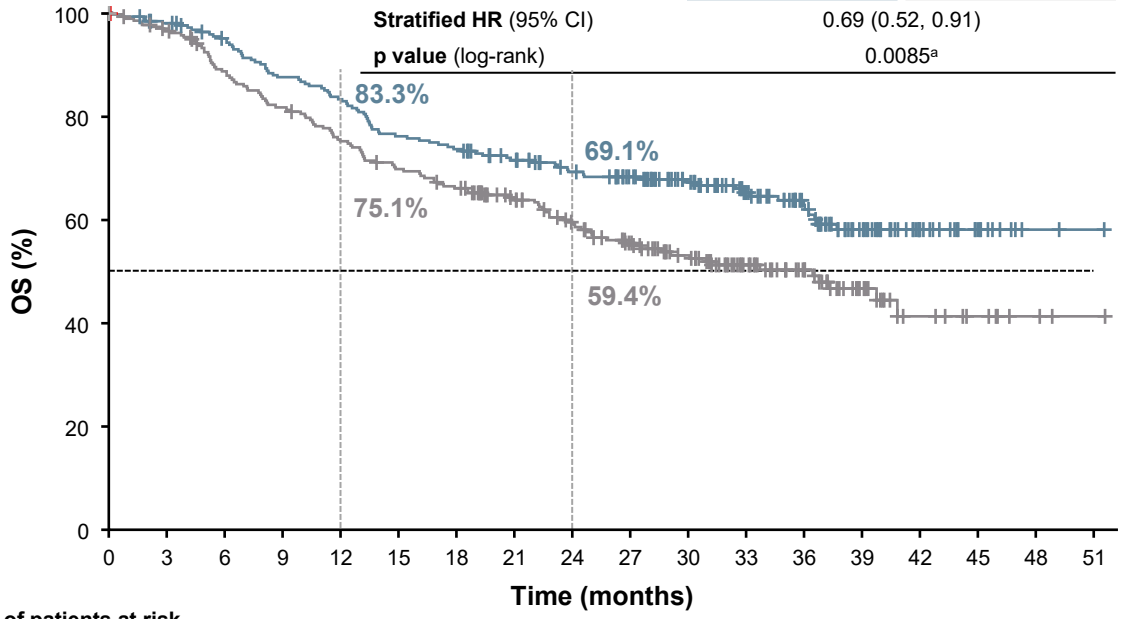


No. of patients at risk

Atezo + pbo	250	207	174	156	148	136	130	118	108	99	77	56	30	20	7	6	NE
Pbo + pbo	253	207	171	146	132	123	109	89	80	64	56	42	26	10	3	3	NE

Primary endpoint: OS

	Atezo + pbo (N=250)	Pbo + pbo (N=253)
Patients with events, n (%)	88 (35.2)	118 (46.6)
Median OS (95% CI), months	NE	36.4 (25.8, NE)
Stratified HR (95% CI)	0.69 (0.52, 0.91)	
p value (log-rank)	0.0085[a]	



No. of patients at risk

Atezo + pbo	250	238	226	208	198	181	175	163	149	138	115	92	69	45	23	12	2	1
Pbo + pbo	253	239	216	199	182	167	157	139	121	102	84	62	46	25	11	7	3	1

[a] Descriptive only

Data cut-off: 18 February 2025. Median survival follow-up: 25.0 months

atezo, atezolizumab; CI, confidence interval; HR, hazard ratio; INV, investigator assessed; NE, not evaluable; OS, overall survival; pbo, placebo; PFS, progression-free survival

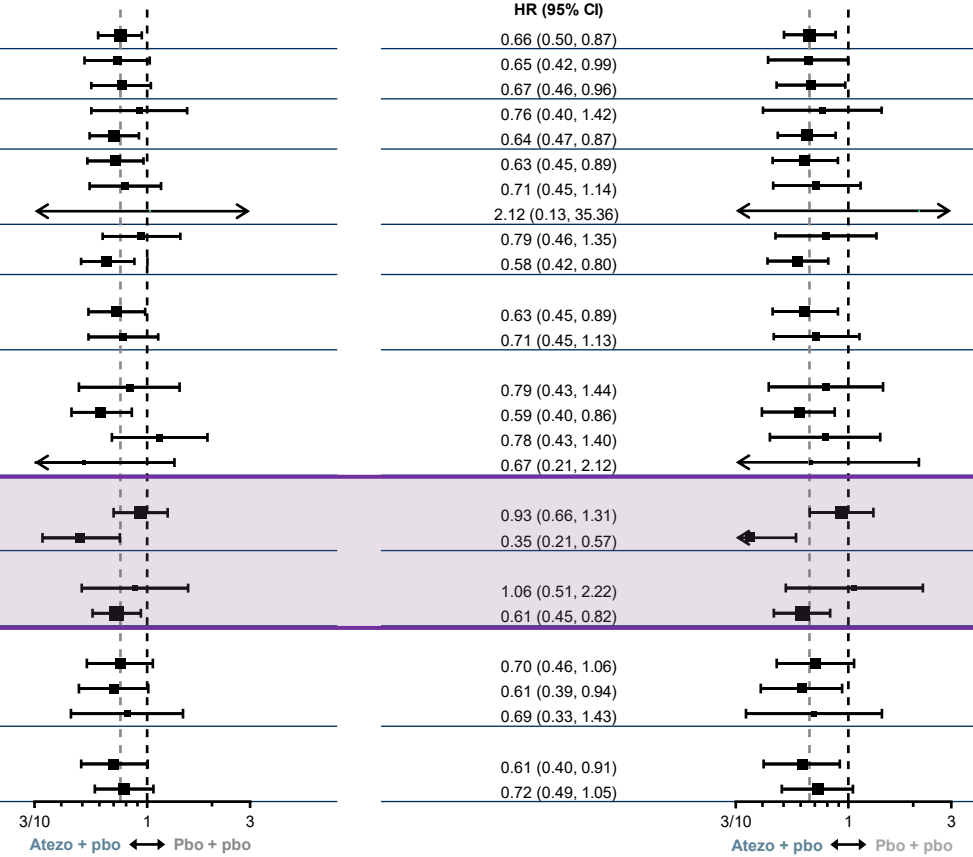
Chau I, et al. Ann Oncol. 2025;36(suppl_2):S1181-S1182. (Abstract 2094O, ESMO 2025)

SKYSCRAPER-07: PFS AND OS SUBGROUP ANALYSIS IN THE ATEZO VS PLACEBO ARMS

TAP≥10% HR 0.49 (% pts BSL: ~36%)

TAP≥1% HR 0.72 (% pts BSL: ~86%)

		INV-PFS No. of patients			OS	
		Atezo + pbo	Pbo + pbo	HR (95% CI)		HR (95% CI)
All patients		250	253	0.75 (0.59, 0.94)		0.66 (0.50, 0.87)
Age	<65 years	112	109	0.73 (0.51, 1.03)		0.65 (0.42, 0.99)
	≥65 years	138	144	0.76 (0.55, 1.04)		0.67 (0.46, 0.96)
Sex	Female	60	62	0.92 (0.55, 1.53)		0.76 (0.40, 1.42)
	Male	190	191	0.70 (0.54, 0.92)		0.64 (0.47, 0.87)
Race	Asian	158	159	0.71 (0.53, 0.96)		0.63 (0.45, 0.89)
	White	90	91	0.79 (0.54, 1.16)		0.71 (0.45, 1.14)
	Black or African American	2	3	1.03 (0.09, 11.55)		2.12 (0.13, 35.36)
Baseline ECOG PS	0	79	97	0.94 (0.62, 1.43)		0.79 (0.46, 1.35)
	1	171	156	0.65 (0.49, 0.87)		0.58 (0.42, 0.80)
Geographic region						
	Asia	157	158	0.72 (0.53, 0.98)		0.63 (0.45, 0.89)
	Rest of World	93	95	0.77 (0.53, 1.13)		0.71 (0.45, 1.13)
Disease stage prior to dCRT						
	Stage II	56	54	0.83 (0.48, 1.41)		0.79 (0.43, 1.44)
	Stage III	125	128	0.61 (0.44, 0.85)		0.59 (0.40, 0.86)
	Stage IVA	55	53	1.14 (0.68, 1.90)		0.78 (0.43, 1.40)
	Stage IVB	14	18	0.51 (0.20, 1.33)		0.67 (0.21, 2.12)
PD-L1 TAP score by SP263[a] (cut-off: 10%)						
	<10%	160	162	0.93 (0.70, 1.24)		0.93 (0.66, 1.31)
	≥10%	90	91	0.49 (0.33, 0.75)		0.35 (0.21, 0.57)
PD-L1 TAP score by SP263[a] (cut-off: 1%)						
	<1%	37	35	0.88 (0.50, 1.55)		1.06 (0.51, 2.22)
	≥1%	213	218	0.72 (0.56, 0.93)		0.61 (0.45, 0.82)
Location of primary ESCC						
	Upper	114	127	0.75 (0.53, 1.06)		0.70 (0.46, 1.06)
	Middle	98	89	0.70 (0.48, 1.01)		0.61 (0.39, 0.94)
	Lower	38	37	0.81 (0.44, 1.47)		0.69 (0.33, 1.43)
Type of prior concurrent chemotherapy						
	Taxane	106	118	0.70 (0.49, 1.00)		0.61 (0.40, 0.91)
	Non-taxane	144	135	0.78 (0.57, 1.07)		0.72 (0.49, 1.05)



[a] SP263: PD-L1 antibody clone for IHC

Data cut-off: 18 February 2025. Median survival follow-up: 25.0 months

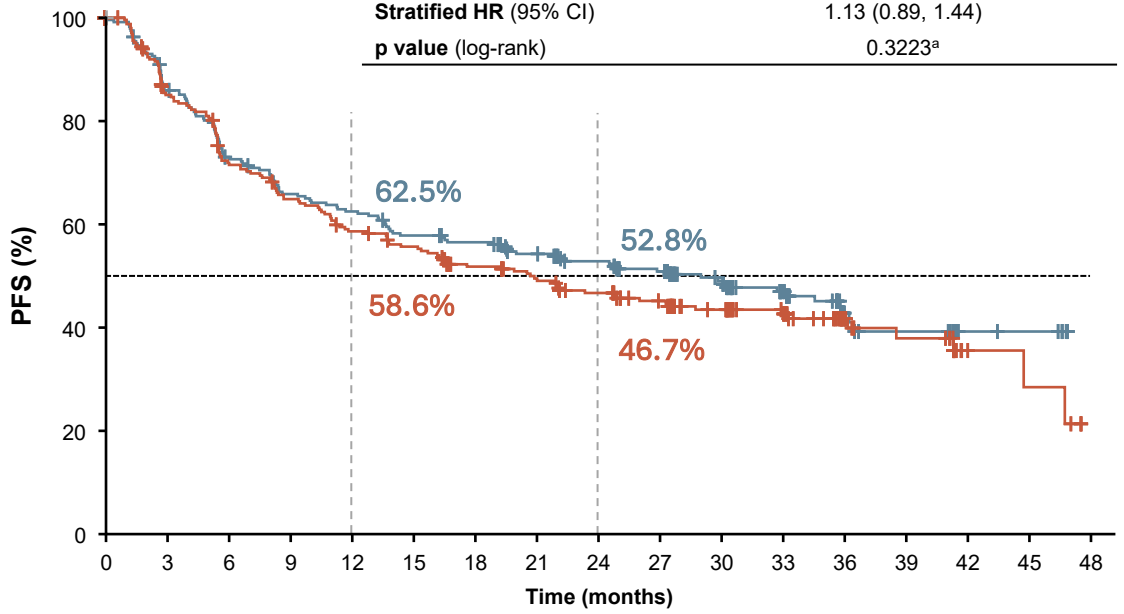
atezo, atezolizumab; CI, confidence interval; dCRT, definitive chemoradiotherapy; ECOG PS, Eastern Cooperative Oncology Group performance score; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; INV, investigator; OS, overall survival; pbo, placebo; PFS, progression-free survival; TAP, tumour area positivity

Chau I, et al. Ann Oncol. 2025;36(suppl_2):S1181-S1182. (Abstract 2094O, ESMO 2025)

SKYSCRAPER-07: PFS AND OS IN THE DOUBLET VS ATEZO ARMS

Secondary endpoint: INV-PFS

	Tira + atezo (N=257)	Atezo + pbo (N=250)
Patients with events, n (%)	141 (54.9)	128 (51.2)
Median PFS (95% CI), months	20.8 (13.9, 28.8)	29.1 (19.0, 36.3)
Stratified HR (95% CI)	1.13 (0.89, 1.44)	
p value (log-rank)	0.3223[a]	

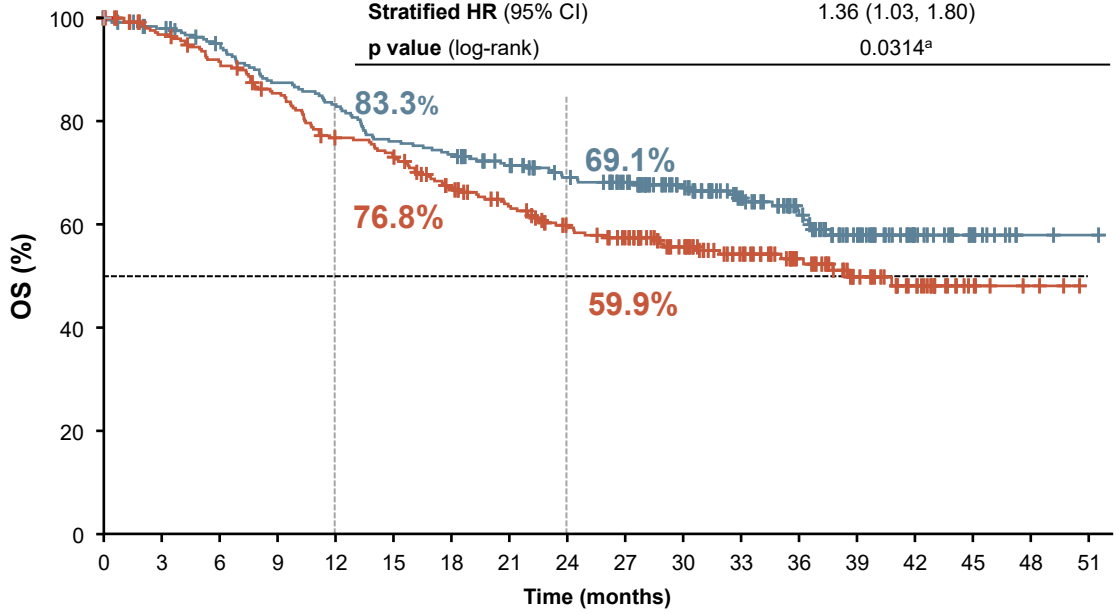


No. of patients at risk

Tira + atezo	257	209	175	156	140	131	115	107	96	86	67	54	30	19	6	4	NE
Atezo + pbo	250	207	174	156	148	136	130	118	108	99	77	56	30	20	7	6	NE

Secondary endpoint: OS

	Tira + atezo (N=257)	Atezo + pbo (N=250)
Patients with events, n (%)	111 (43.2)	88 (35.2)
Median OS (95% CI), months	38.6 (28.8, NE)	NE
Stratified HR (95% CI)	1.36 (1.03, 1.80)	
p value (log-rank)	0.0314[a]	



No. of patients at risk

Tira + atezo	257	241	227	208	186	178	155	140	124	113	90	70	52	35	23	7	3	NE
Atezo + pbo	250	238	226	208	198	181	175	163	149	138	115	92	69	45	23	12	2	1

[a] Descriptive only

Data cut-off: 18 February 2025. Median survival follow-up: 25.0 months

atezo, atezolizumab; CI, confidence interval; HR, hazard ratio; INV, investigator assessed; NE, not evaluable; OS, overall survival; pbo, placebo; PFS, progression-free survival; tira, tiragolumab

Chau I, et al. Ann Oncol. 2025;36(suppl_2):S1181-S1182. (Abstract 2094O, ESMO 2025)

SKYSCRAPER-07: SAFETY SUMMARY[a]

	Tira + atezo (N=254)	Atezo + pbo (N=250)	Pbo + pbo (N=251)
Median number of doses received	Tira: 12; atezo: 12	Atezo: 17; pbo: 17	Pbo (tira): 16; pbo (atezo): 17
Median treatment duration, months	8.9[b]	11.0[b]	11.0[b]
All-grade AEs any cause, n (%)	246 (96.9)	235 (94.0)	226 (90.0)
Treatment-related	**190 (74.8)**	**163 (65.2)**	**139 (55.4)**
Grade 3/4 AEs, n (%)	86 (33.9)	69 (27.6)	58 (23.1)
Treatment-related	**41 (16.1)**	**24 (9.6)**	**24 (9.6)**
Grade 5 AEs, n (%)	12 (4.7)	15 (6.0)	15 (6.0)
Treatment-related	**3 (1.2)**	**2 (0.8)**	**4 (1.6)**
Serious AEs, n (%)	75 (29.5)	64 (25.6)	58 (23.1)
Treatment-related	**24 (9.4)**	**16 (6.4)**	**13 (5.2)**
AEs leading to, n (%):			
Dose interruption	**111 (43.7)**	**85 (34.0)**	**81 (32.3)**
Treatment discontinuation	**23 (9.1)**	**17 (6.8)**	**10 (4.0)**
All-grade AESIs, n (%)	162 (63.8)	141 (56.4)	102 (40.6)
Grade 3/4	12 (4.7)	13 (5.2)	8 (3.2)
Grade 5	2 (0.8)	1 (0.4)	0
Requiring systemic corticosteroids	44 (17.3)	23 (9.2)	18 (7.2)
Requiring systemic immunosuppressants	4 (1.6)	1 (0.4)	2 (0.8)

-5 cycles atezo in the doublet arm

+9.6% TRAEs

+7.4% AESIs

TIRA adds toxicity and impairs ATEZO delivery ?

[a] Five patients (two each in the tira + atezo and pbo + pbo arms, and one in the atezo + pbo arm) did not receive any study treatment and therefore were excluded from the safety-evaluable set; one patient assigned to tira + atezo arm received atezo only and was included in the atezo + pbo safety population

[b] Treatment duration was the same in both treatment arms

Data cut-off: 18 February 2025

AE(SI), adverse event (of special interest); atezo, atezolizumab; pbo, placebo; tira, tiragolumab; TRAE, treatment-related adverse event

Chau I, et al. Ann Oncol. 2025;36(suppl_2):S1181-S1182. (Abstract 2094O, ESMO 2025)

SKYSCRAPER-07: SUMMARY

- **SKYCRAPER-07 did not meet the primary PFS/OS endpoint** for tiragolumab + atezolizumab vs placebo + placebo in patients with unresectable locally advanced ESCC following dCRT[1]
- **Atezolizumab monotherapy demonstrated clinically meaningful improvements in PFS and OS** vs placebo + placebo, and the benefit was generally observed across key clinically relevant subgroups[1]
  - Per the hierarchical testing plan, formal statistical testing comparing the atezolizumab + placebo vs placebo + placebo arms was not done, after the primary PFS endpoint was not met for tiragolumab + atezolizumab vs placebo + placebo

- Does timing matter? Concurrent with radiochemotherapy vs consolidation afterwards? Phase 3 Trials ongoing

PD-1/PD-L1 trials in locally advanced ESCC

Trial / NCT ID	Agent(s)	Regimen	Population	Primary endpoint(s)	Sponsor
KEYNOTE-975 (NCT04210115)[2,3]	Pembrolizumab vs placebo (anti–PD-1)	Concurrent with dCRT → Maintenance / placebo	Locally advanced, unresectable esophageal carcinoma (SCC & adenocarcinoma)	OS; EFS	Merck (MSD)
KUNLUN (NCT04550260)[4]	Durvalumab vs placebo (anti–PD-L1)	Concurrent with dCRT → Maintenance / placebo	Locally advanced, unresectable ESCC (Stage II–IVA)	PFS (BICR); key secondary: OS	AstraZeneca
RATIONALE-311 (NCT03957590)[5,6]	Tislelizumab vs placebo (anti–PD-1)	Concurrent with dCRT	Inoperable / localised ESCC (Stage II–IV)	PFS (BICR); key secondary: OS	BeiGene
ESCORT-CRT (NCT04426955)[7]	Camrelizumab vs placebo (anti–PD-1)	Concurrent with dCRT	Locally advanced, ESCC	PFS (IRC) Key secondary: PFS (INV), OS	Jiangsu HengRui

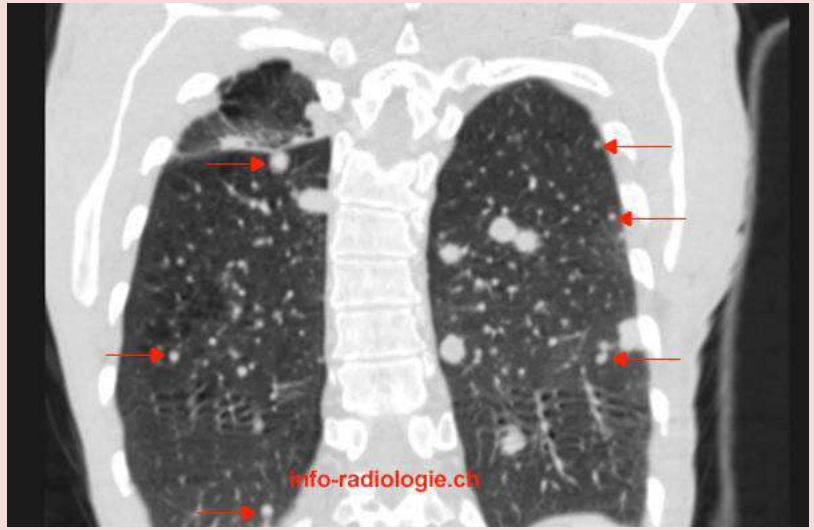
BICR, blinded independent central review; dCRT, definitive chemoradiotherapy; EFS, event-free survival; (E)SCC, (esophageal) squamous cell carcinoma; INV, investigator; IRC, independent review committee; OS, overall survival; PFS, progression-free survival

1. Chau I, et al. Ann Oncol. 2025;36(suppl_2):S1181-S1182. (Abstract 2094O, ESMO 2025); 2. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04210115; 3. Shah MA, et al. Future Oncol. 2021;17:1143-1153; 4. https://clinicaltrials.gov/study/NCT04550260; 5. https://clinicaltrials.gov/study/NCT03957590; 6. Yu R, et al Future Oncol. 2021;17:4081-4089; 7. https://clinicaltrials.gov/study/NCT04426955

PATIENT CASE 2

Patient

- 67 years old, male, ECOG PS 1
- No major comorbidities
- Dysphagia for past 6 weeks; weight loss (-3Kg/2 months)
- Gastroscopy and biopsies showed a **squamous cell carcinoma in the middle third of the esophagus**
- CT scan: **cTxN+M1**



CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; cTNM, clinical Tumour Node Metastasis

POLLING QUESTION 2

- In patients with **metastatic esophageal squamous cell carcinoma**, the standard treatment consists of a **platinum-based doublet chemotherapy** combined with (select all that apply):

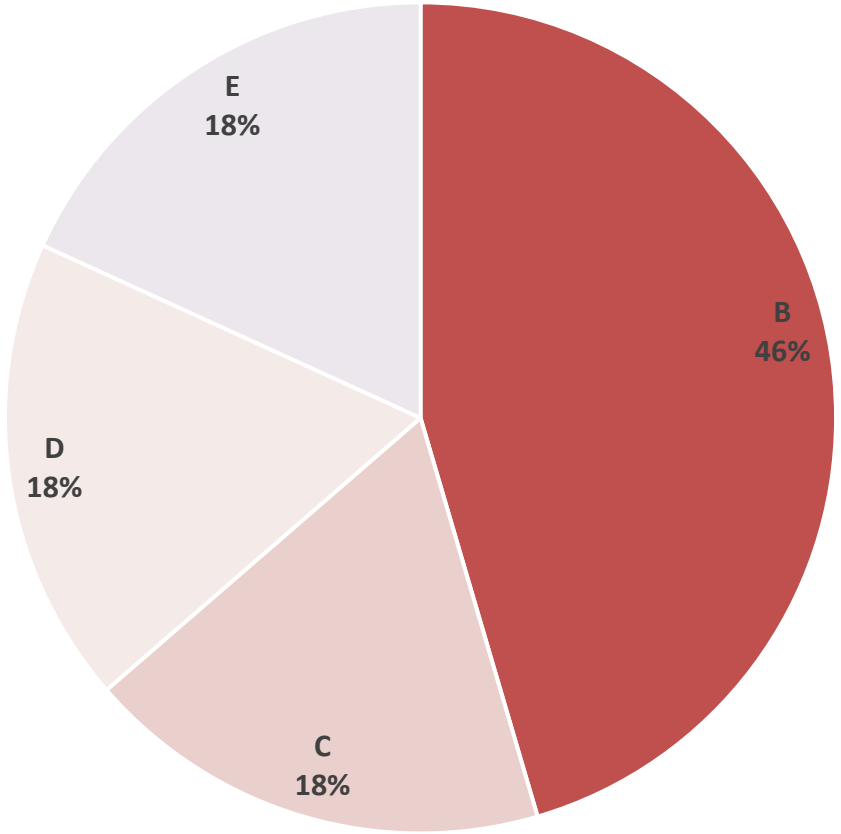
A. Pembrolizumab if CPS ≥1

B. Pembrolizumab if CPS ≥10

C. Nivolumab if TPS ≥1%

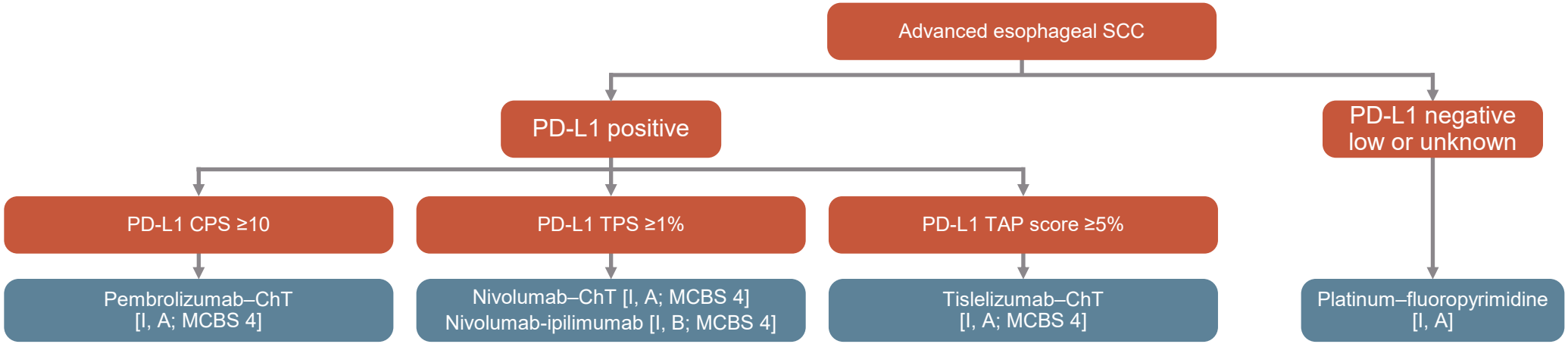
D. Nivolumab if TPS ≥10%

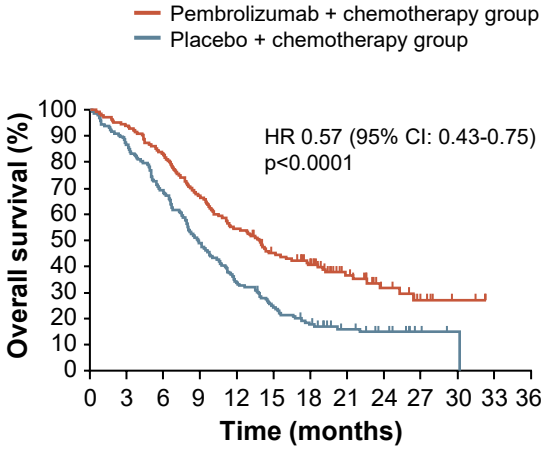
E. Tislelizumab if TAP ≥5



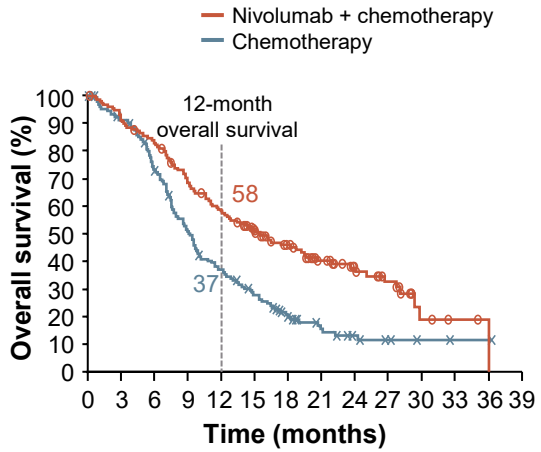
CPS, combined positive score; TAP, tumour area positivity; TPS, tumour proportion score

ESMO-GUIDELINES ESOPHAGEAL CANCER[1,a]

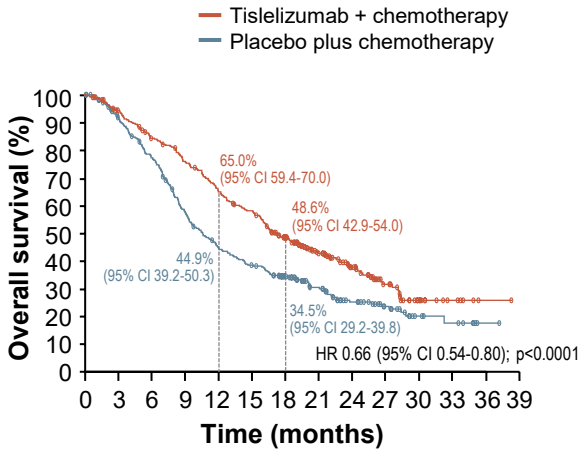




KEYNOTE-590[2]



CHECKMATE 648[3]



RATIONALE-306[4]

?

Targeting anti-angiogenesis pathway can improve clinical outcomes

LEAP-014 trial

LENVATINIB

tyrosine kinase inhibitor targeting the VEGF-R

[a] First-line treatment options presented

ChT, chemotherapy; CI, confidence interval; CPS, combined positive score; HR, hazard ratio; MCBS, Magnitude of Clinical Benefit Score; SCC, squamous cell carcinoma; TPS, tumour proportion score

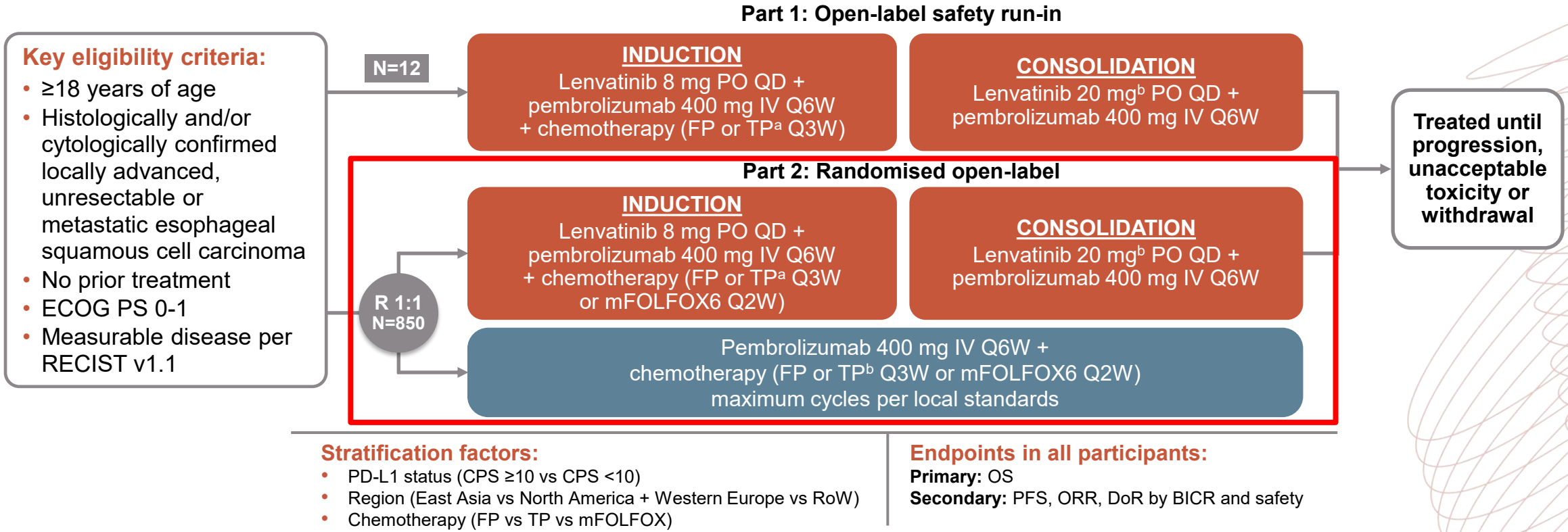
1. Obermannová R, et al. ESMO Open. 2025;10:104134; 2. Sun J-M, et al. Lancet. 2021;398:759-71; 3. Doki y, et al. N Engl J Med. 2022;386:449-62; 4. Xu J, et al. Lancet Oncol. 20923;24:483-95

LENVATINIB PLUS PEMBROLIZUMAB AND CHEMOTHERAPY VS PEMBROLIZUMAB AND CHEMOTHERAPY IN UNTREATED METASTATIC ESOPHAGEAL SQUAMOUS CELL CARCINOMA: THE RANDOMISED PHASE 3 LEAP-014 STUDY

Sun J-M, et al. Abstract LBA79, ESMO 2025

LEAP-014: PHASE 3, RANDOMISED TRIAL IN UNTREATED METASTATIC ESCC

NCT04949256



[a] Only in participants from China, Republic of Korea, Hong Kong and Taiwan (could make up no more than 10% of population [Part 2 only])
[b] Dose titrated up to 20 mg only in participants who tolerated lenvatinib 8 mg in the induction phase

BICR, blinded independent central review; CPS, combined positive score; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; FP, cisplatin plus 5-FU; IV, intravenous; mFOLFOX, oxaliplatin plus 5-FU plus leucovorin; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, orally; QD, once a day; Q'x'W, every 'x' weeks; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; RoW, rest of world; TP, paclitaxel plus cisplatin

Sun J-M, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965 (Abstract LBA79, ESMO 2025)

LEAP-014: BASELINE CHARACTERISTICS

Characteristic, n (%)[a]	Lenvatinib + pembrolizumab + chemotherapy N=423	Pembrolizumab + chemotherapy N=427
Median age (range), years	64 (27-86)	66 (40-84)
≥65 years	209 (49)	240 (56)
Male	331 (78)	334 (78)
Race		
Asian	279 (66)	285 (67)
White	131 (31)	130 (30)
Other/missing[b]	13 (3)	12 (3)
Geographic region		
East Asia	278 (66)	281 (66)
North America/Western Eur	69 (16)	66 (15)
Rest of world	76 (18)	80 (19)
ECOG PS		
0	147 (35)	168 (39)
1	273 (64)	257 (60)

Characteristic, n (%)	Lenvatinib + pembrolizumab + chemotherapy N=423	Pembrolizumab + chemotherapy N=427
PD-L1 CPS		
≥1	396 (94)	399 (93)
<1	27 (6)	28 (7)
≥10	277 (66)	277 (65)
<10	146 (34)	150 (35)
Brain metastases		
Yes	2 (<1)	1 (<1)
No	421 (99)	426 (100)
Current disease stage		
IVA	3 (1)	2 (<1)
IVB	420 (99)	426 (100)
Chemotherapy choice		
FP	102 (24)	100 (23)
TP	42 (10)	43 (10)
mFOLFOX6	277 (65)	283 (66)

[a] Except for the first row, which presents median (range)

[b] Other includes American Indian or Alaska Native, Black or African American, and participants with multiple races indicated

Data cut-off: 8 May 2025

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; Eur, Europe; FP, cisplatin plus 5-FU; mFOLFOX, oxaliplatin plus 5-FU plus leucovorin; TP, paclitaxel plus cisplatin

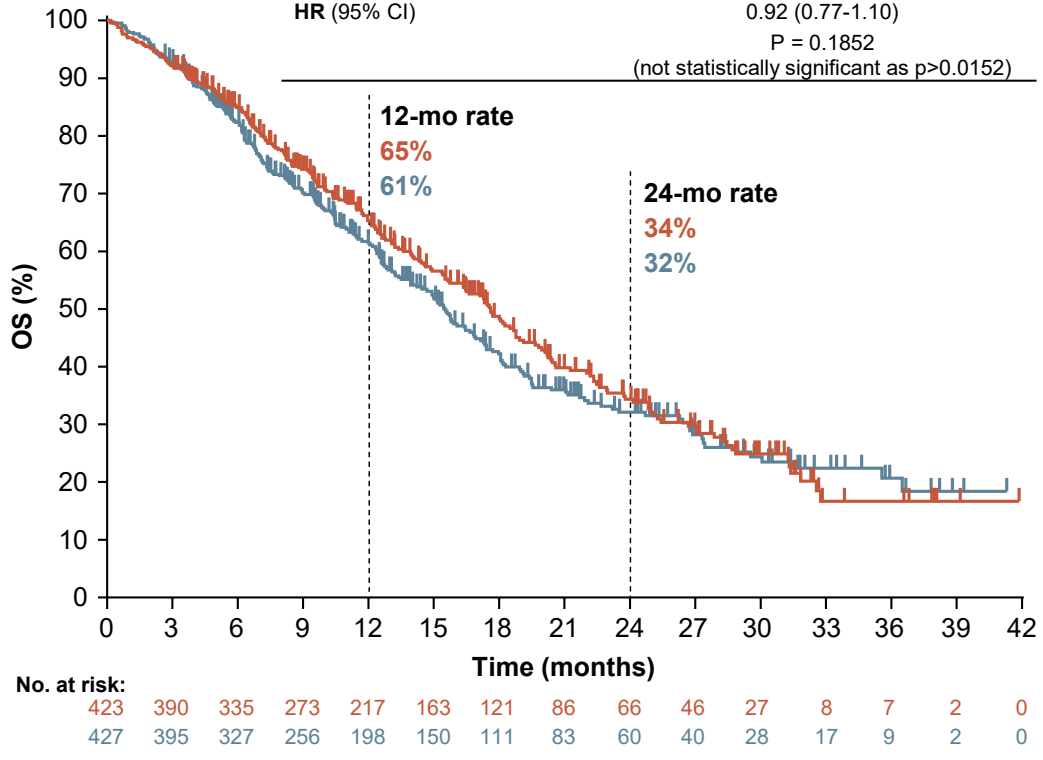
Sun J-M, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965 (Abstract LBA79, ESMO 2025)

LEAP-014: OVERALL SURVIVAL

ALL PARTICIPANTS AND PD-L1 CPS ≥10

All randomised participants

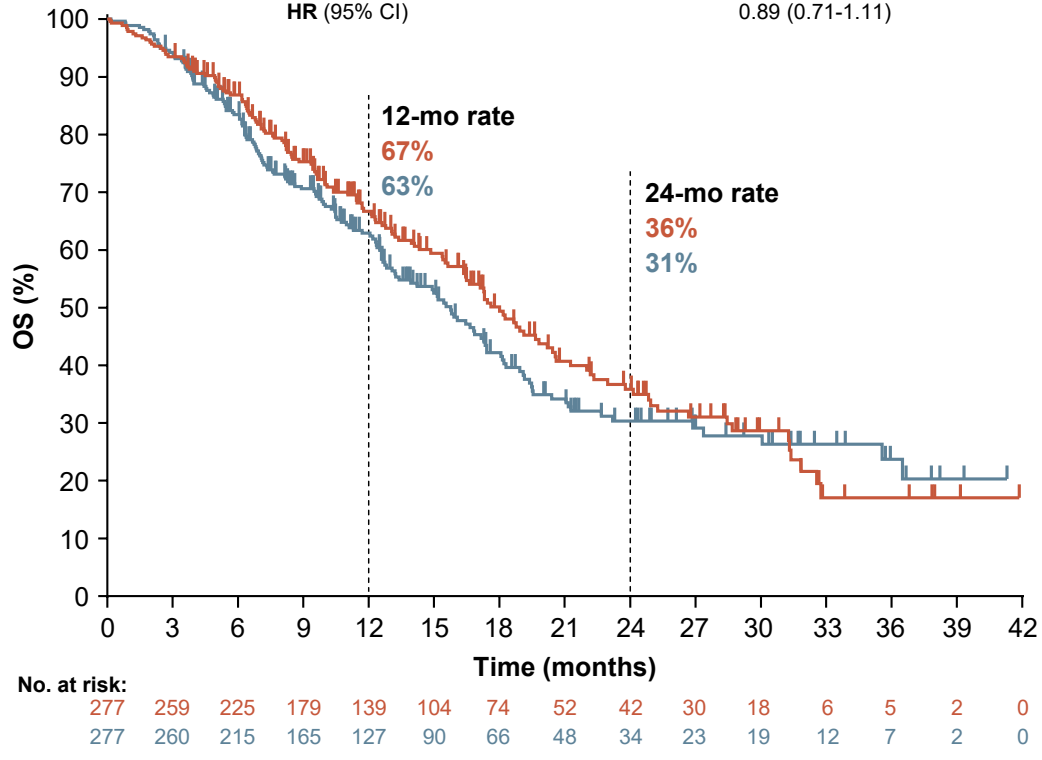
	Len + pembro + chemo	Pembro + chemo
Patients with events, n (%)	236 (56)	246 (58)
Median OS (95% CI), months	17.6 (15.5-19.1)	15.5 (13.5-17.2)
HR (95% CI)	0.92 (0.77-1.10)	
	P = 0.1852	
	(not statistically significant as p>0.0152)	



No. at risk:														
423	390	335	273	217	163	121	86	66	46	27	8	7	2	0
427	395	327	256	198	150	111	83	60	40	28	17	9	2	0

PD-L1 CPS ≥10

	Len + pembro + chemo	Pembro + chemo
Patients with events, n (%)	145 (52)	152 (55)
Median OS (95% CI), months	18.0 (16.4-20.4)	15.8 (13.1-17.4)
HR (95% CI)	0.89 (0.71-1.11)	



No. at risk:														
277	259	225	179	139	104	74	52	42	30	18	6	5	2	0
277	260	215	165	127	90	66	48	34	23	19	12	7	2	0

Data cut-off: 8 May 2025

chemo, chemotherapy; CI, confidence interval; CPS, combined positive score; HR, hazard ratio; len, lenvatinib; mo, month; OS, overall survival; pembro, pembrolizumab

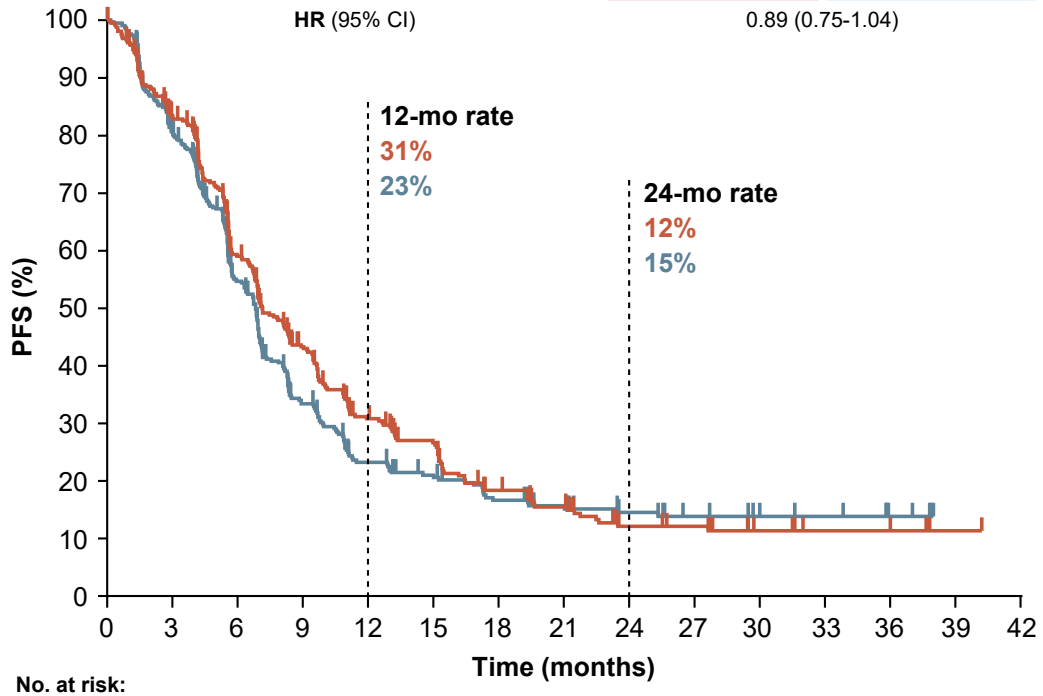
Sun J-M, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965 (Abstract LBA79, ESMO 2025)

LEAP-014: PROGRESSION-FREE SURVIVAL

ALL PARTICIPANTS AND PD-L1 CPS ≥10 (RECIST V1.1, BICR)

All randomised participants

	Len + pembro + chemo	Pembro + chemo
Patients with events, n (%)	291 (69)	298 (70)
Median PFS (95% CI), months	7.2 (6.8-8.4)	6.9 (5.8-7.0)
HR (95% CI)	0.89 (0.75-1.04)	

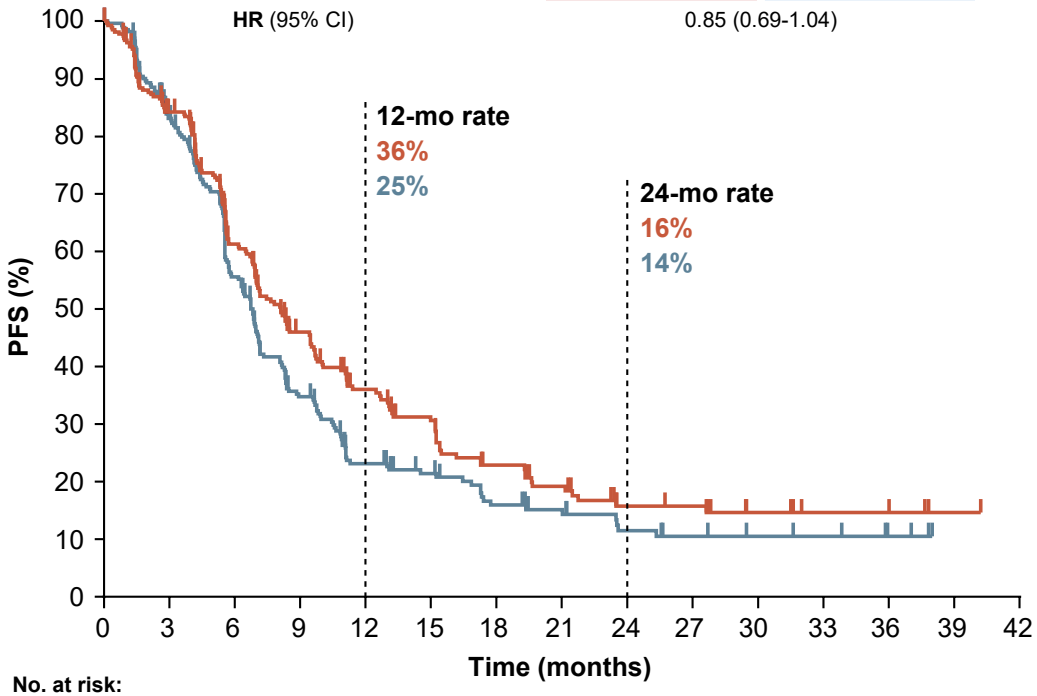


No. at risk:

423	325	207	135	86	66	40	31	18	16	9	5	5	1	0
427	314	193	104	65	51	38	29	21	16	11	10	4	0	0

PD-L1 CPS ≥10

	Len + pembro + chemo	Pembro + chemo
Patients with events, n (%)	180 (65)	190 (69)
Median PFS (95% CI), months	8.1 (6.9-9.5)	6.9 (6.3-7.2)
HR (95% CI)	0.85 (0.69-1.04)	



No. at risk:

277	215	139	90	62	48	32	25	15	14	8	4	4	1	0
277	207	131	74	44	34	23	18	12	9	7	6	3	0	0

Data cut-off: 8 May 2025

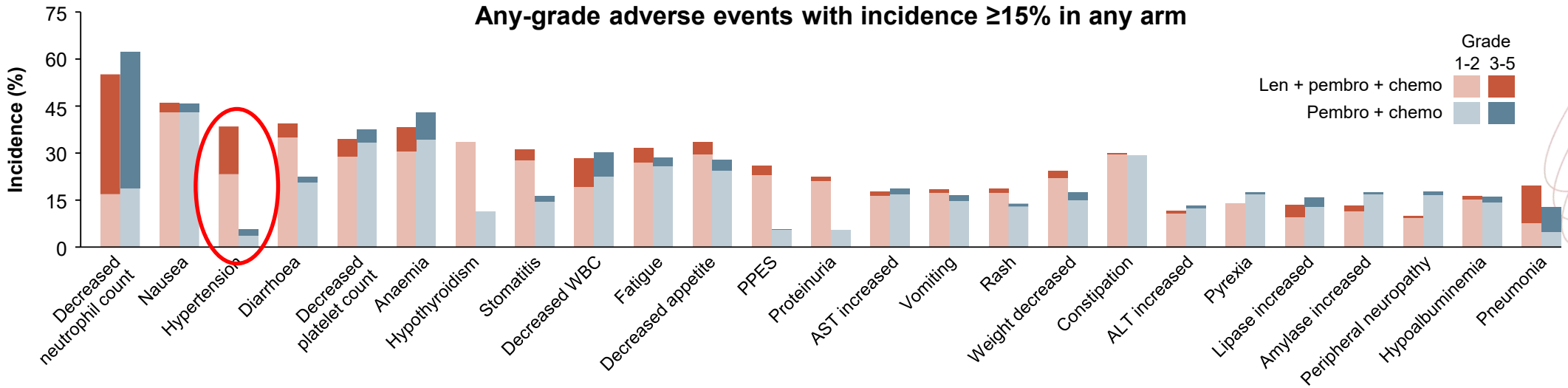
BICR, blinded independent central review; chemo, chemotherapy; CI, confidence interval; CPS, combined positive score; HR, hazard ratio; len, lenvatinib; mo, month; pembro, pembrolizumab; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours

Sun J-M, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965 (Abstract LBA79, ESMO 2025)

LEAP-014: SAFETY

SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS

	Len + pembro + chemo N=421	Pembro + chemo N=426
Median (range) duration of treatment, months	7.1 (0.03-41.9)	5.6 (0.03-28.8)
Any grade AEs, n (%)	419 (99.5)	423 (99.3)
Grade ≥3	342 (81.2)	337 (79.1)
Grade 5	41 (9.7)	49 (11.5)
Led to discontinuation of any drug	140 (33.3)	166 (39.0)
Treatment-related, n (%)	409 (97.1)	411 (96.5)



Data cut-off: 8 May 2025

AE, adverse event; ALT, alanine aminotransferasel AST, aspartate aminotransferase; chemo, chemotherapy; len, lenvatinib; pembro, pembrolizumab; PPES, plantar-palmar erythrodysesthesia syndrome; WBC, white blood count

Sun J-M, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965 (Abstract LBA79, ESMO 2025)

LEAP-014: SUMMARY

- Lenvatinib plus pembrolizumab and chemotherapy did not significantly improve OS as first-line treatment for metastatic ESCC vs pembrolizumab plus chemotherapy
  - OS HR 0.92 (95% CI: 0.77-1.10) p=0.1852 (p>0.0152 not statistically significant)
  - PFS and ORR were not tested for statistical significance, as the OS hypothesis was not positive
- Safety profiles were generally consistent with the known safety profiles of lenvatinib in combination with pembrolizumab and chemotherapy or the pembrolizumab plus chemotherapy regimen
- No new safety signals were observed for lenvatinib or pembrolizumab

→ platinum-based doublet chemotherapy + anti-PD1 monoclonal antibody remains the SOC in 1st line for PD-L1 positive metastatic ESCC

CI, confidence interval; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SOC, standard of care

Sun J-M, et al. Ann Oncol. 2025;36(suppl_2):S1-S60. 10.1016/annonc/annonc1965 (Abstract LBA79, ESMO 2025)

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