20as Jornadas HITOS ONCOLÓGICOS: LO MEJOR DE 2025
MADRID 19 - 20 NOVIEMBRE 2025
20 ANIVERSARIO

Tratamiento perioperatorio en cáncer esofagogástrico localizado

Aitana Calvo
Hospital General Universitario Gregorio Marañón, Madrid

DOI Speaking, Advisory, Travel or Grant support: AZ, MSD, Astellas, Novartis, BMS, Merck, BMS, Amgen, Ipsen, Servier, Boehringer-Ilgenheim, Roche, Pfizer, Almiranz, Lilly,

- Ocupación principal
  - Responsable de tumores GE Oncología Médica HGUGM
  - Unidad de Fase I

Actividades regulatorias (decisiones no vinculantes):

- Presidenta del CMH AEMPS
- Vocal del SAG Oncology EMA
- Vocal Ceim HGUGM

International Agency for Research on Cancer
World Health Organization
GLOBAL CANCER OBSERVATORY
CANCER TODAY
GLOBOCAN 2022

STOMACH

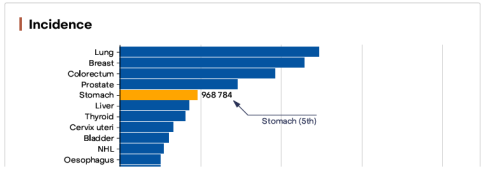
Incidence

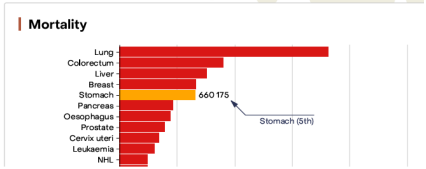
Rank	Cases	ASR (World)
5	968 784	9.2

Mortality

Rank	Deaths	ASR (Wor
5	660 175	6.1

Cancer site ranking





OESOPHAGUS

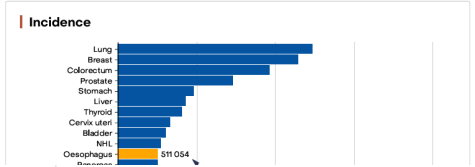
Incidence

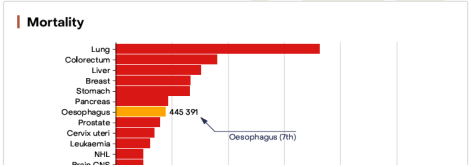
Rank	Cases	ASR (World)
11	511 054	5.0

Mortality

Rank	Deaths	ASR (World)
7	445 391	4.3

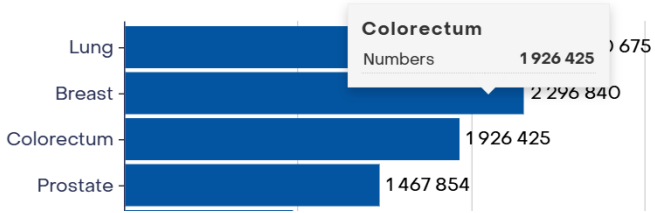
Cancer site ranking





Mortalidad GE: 1.105.566

Incidencia GE: 1.479.838

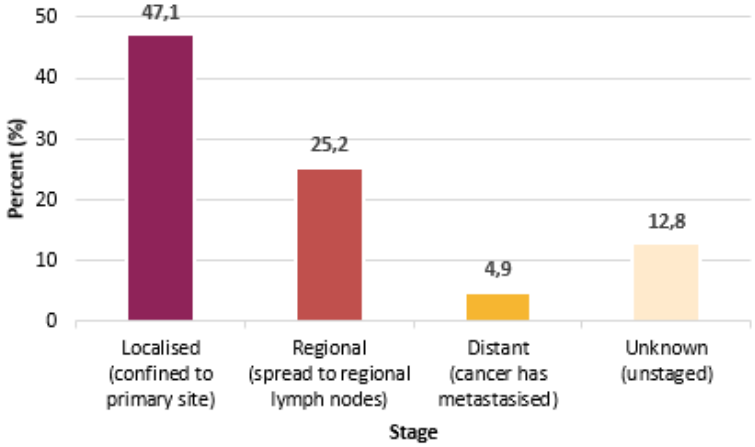


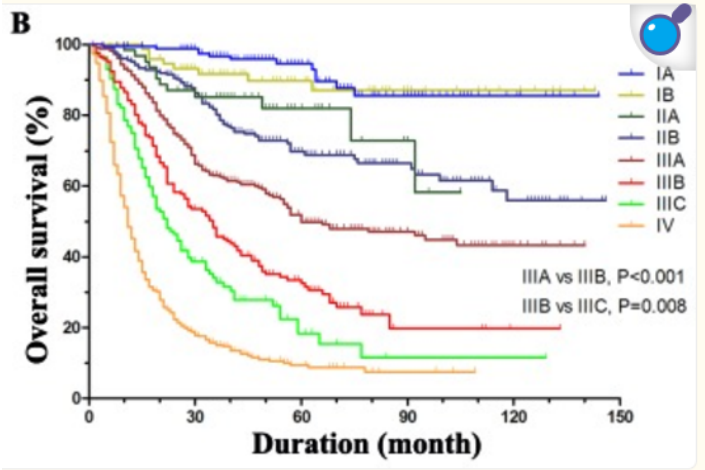
https://gco.iarc.fr/today/en/fact-sheets-cancers

Survival of gastric-oesophageal cancer is strongly related to the stage of the disease at diagnosis

In addition, the type and grade of cancer can affect survival and impact patient management, including treatment selection and eligibility

5-year relative survival by stage at diagnosis





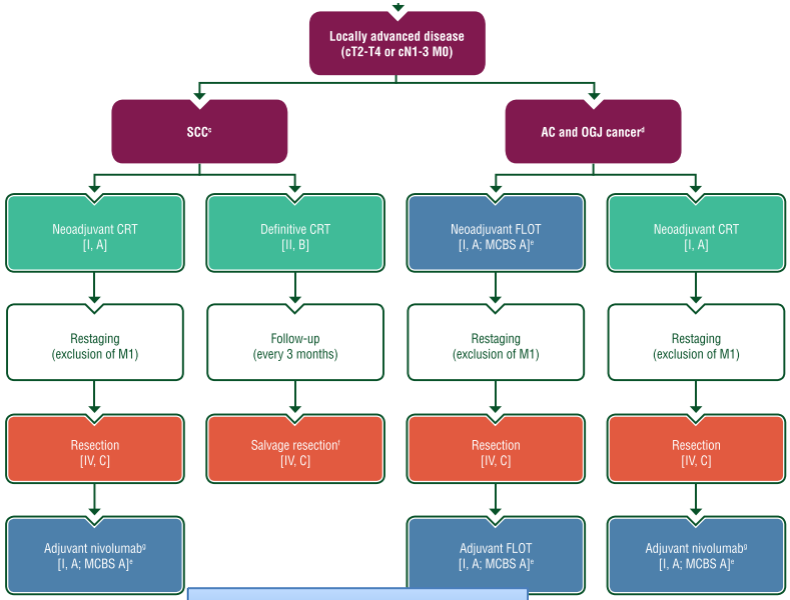
SEER. Cancer Stat Facts: Esophageal

Mol Clin Oncol. 2018 Jul 26;9(4):423–431. doi: 10.3892/mco.2018.1683

Estrategias a principios de 2024

Esófago y UGE

Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up ☆

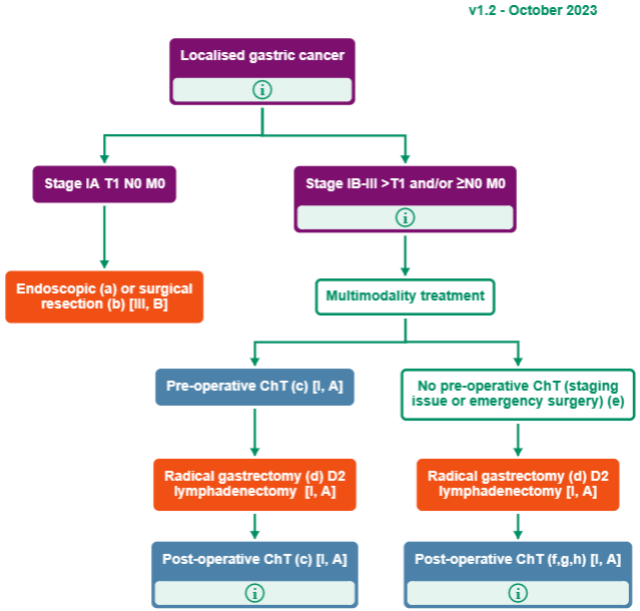


Cross 2012

Checkmate 577

Magic 2006
FLOT4 2019

Gástrico



CROSS

T1N1M0
or
T2–3N0–1M0
Adenocarcinoma
Squamous Cell Carcinoma
n= 363

RANDOM

- Neoadjuvant chemoRT
  Carboplatin AUC 2
  plus paclitaxel 50mg/m2 weekly
  plus 41.4 Gy followed by surgery
  (n=178)
- Surgery
  (n=188)

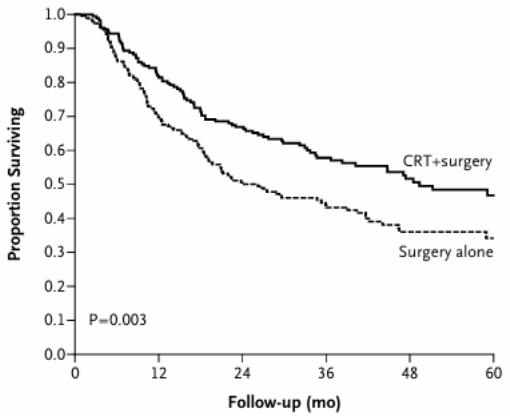
Primary Endpoint: OS

No T4, no >5cm transverse or 8cm length
ECOG 0-1

Squamous **Adenocarcinoma**	43 (23%) **141(75%)**	41 (23%) **141 (75%)**
Site of disease Oesophagus OGJ	 135 (74%) 49 (26%)	 133(74%) 39 (22%)

N Engl J Med 2012;366:2074-84

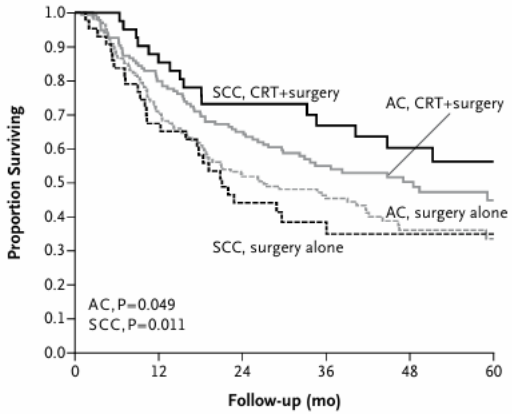
A Survival According to Treatment Group



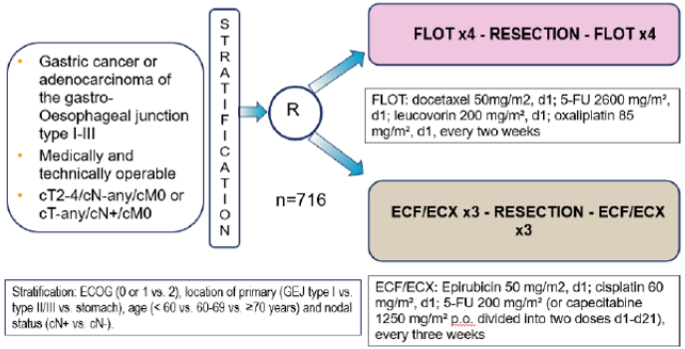
No. at Risk

CRT+surgery	178	145	119	75	49	28
Surgery alone	188	131	94	62	33	17
Total	366	276	213	137	82	45

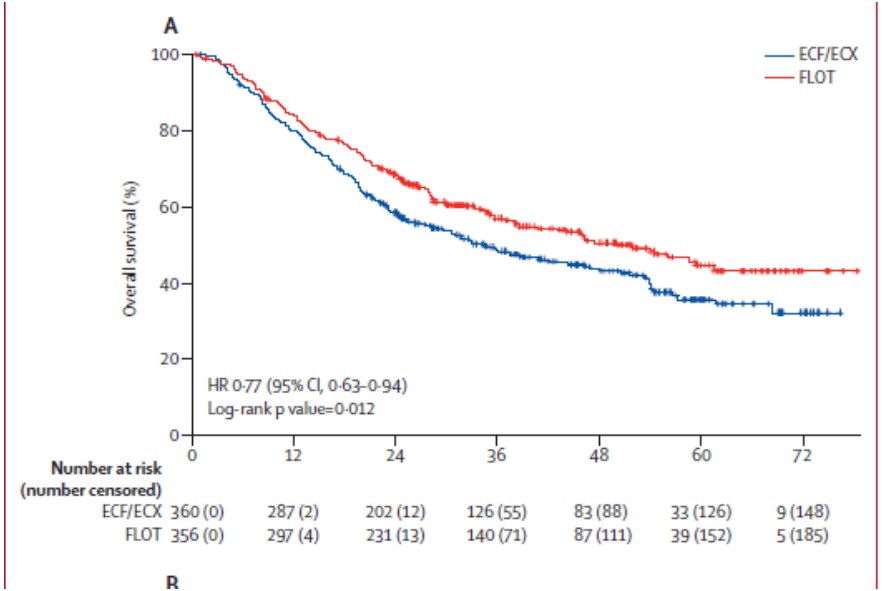
B Survival According to Tumor Type and Treatment Group



FLOT4 AIO



Location		
GEJ Siewert type 1*	85 (24%)	80 (23%)
GEJ Siewert type 2 or 3	115 (32%)	118 (33%)
Stomach	160 (44%)	158 (44%)
cT-stage†		
T1	2 (1%%)	3 (1%)
T2	59 (16%)	49 (14%)
T3	253 (70%)	267 (75%)
T4	33 (9%)	28 (8%)
unclear	13 (4%)	9 (3%)
cN-stage†		
N–	70 (19%)	77 (22%)
N+	290 (81%)	279 (78%)



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

Lancet **2019; 393: 1948–57**

The NEW ENGLAND JOURNAL of MEDICINE

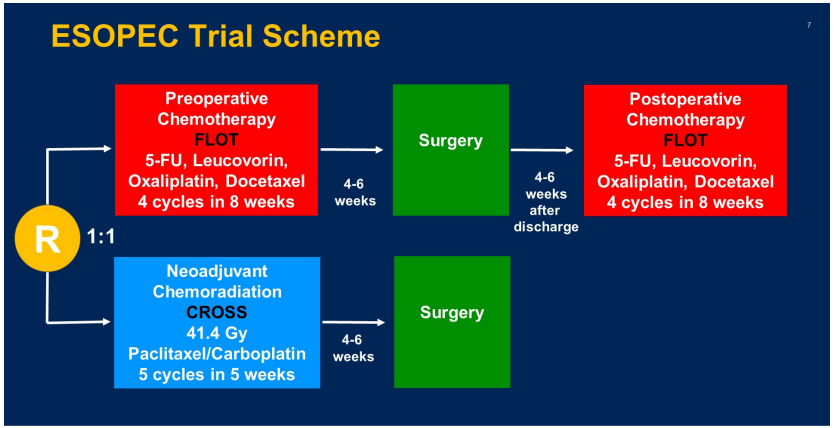
ORIGINAL ARTICLE

Perioperative Chemotherapy or Preoperative Chemoradiotherapy in Esophageal Cancer

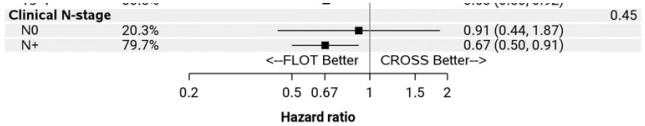
Authors: Jens Hoeppner, M.D., Thomas Brunner, M.D., Claudia Schmoor, Ph.D., Peter Bronsert, M.D., Birte Kulemann, M.D., Rainer Claus, M.D., Stefan Utzolino, M.D., +24, and Florian Lordick, M.D. Author Info & Affiliations

Published January 22, 2025 | N Engl J Med 2025;392:323-335 | DOI: 10.1056/NEJMoa2409408

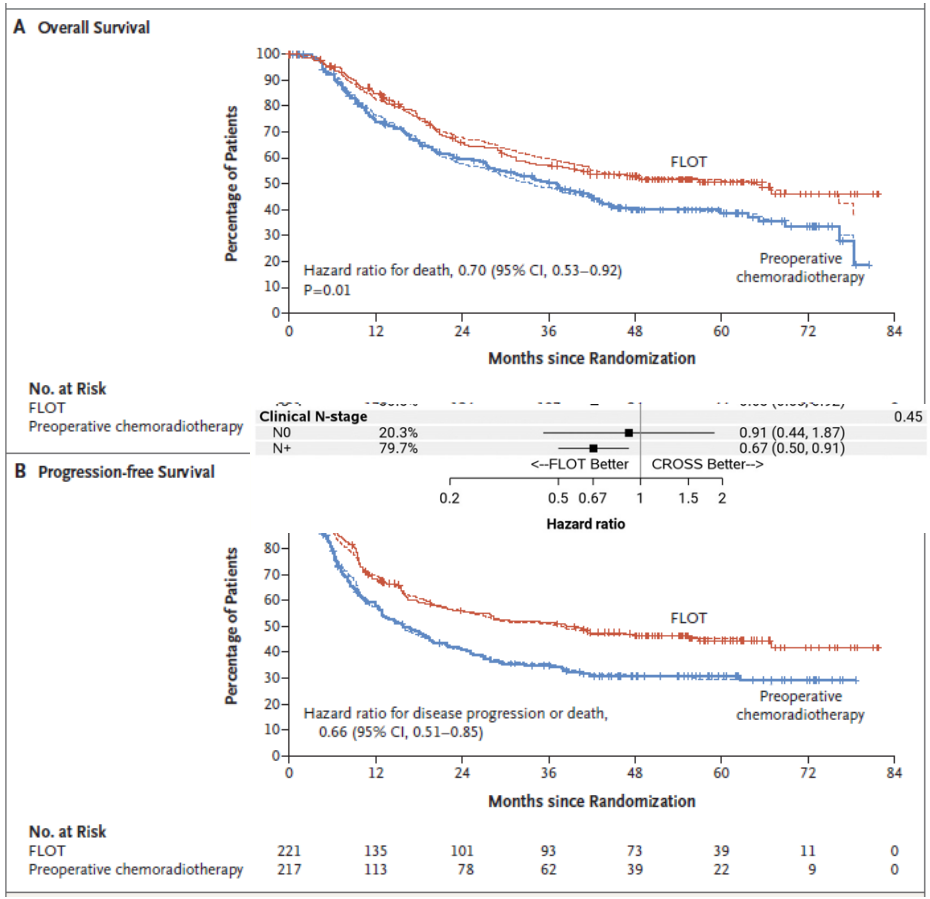
VOL. 392 NO. 4 | Copyright © 2025



Characteristic	FLOT (N = 193)	Preoperative Chemoradiotherapy (N = 181)
Tumor location before therapy — no./total no. (%)¶		
Esophagus, Siewert type I, or both	98/215 (45.6)	97/212 (45.8)
Siewert type II	70/215 (32.6)	62/212 (29.2)
Siewert type III	5/215 (2.3)	5/212 (2.4)
Not classifiable	42/215 (19.5)	48/212 (22.6)
Pathological tumor regression grade — no./total no. (%)**		
Grade 1a: 0% residual tumor††	36/189 (19.0)	24/179 (13.4)
Grade 1b: >0 to <10% residual tumor	47/189 (24.9)	71/179 (39.7)
Grade 2: 10 to 50% residual tumor	46/189 (24.3)	50/179 (27.9)
Grade 3: >50% residual tumor	60/189 (31.7)	34/179 (19.0)

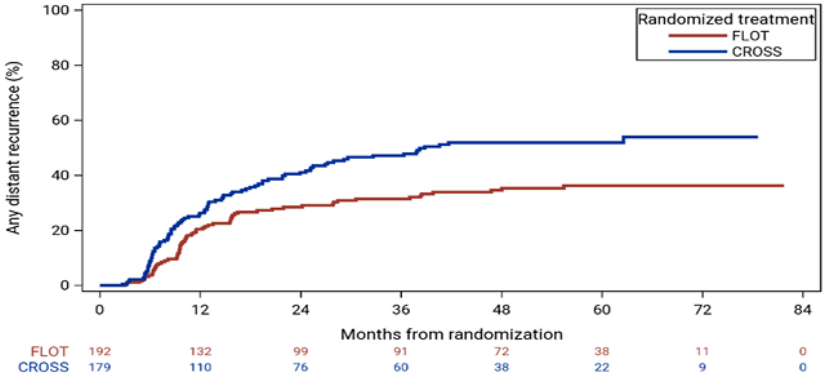


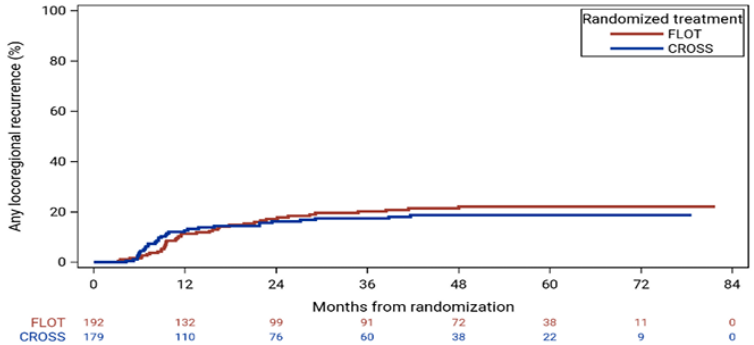
ESOPEC



N Engl J Med. 2025;392(4):323-335

Recurrence patterns in the prospective, randomized, controlled, multicenter phase III ESOPEC trial comparing perioperative chemotherapy with preoperative chemoradiotherapy in patients with esophageal adenocarcinoma.





Hoeppner Abstract #: 4014 2025 ASCO

MATTERHORN Study Design

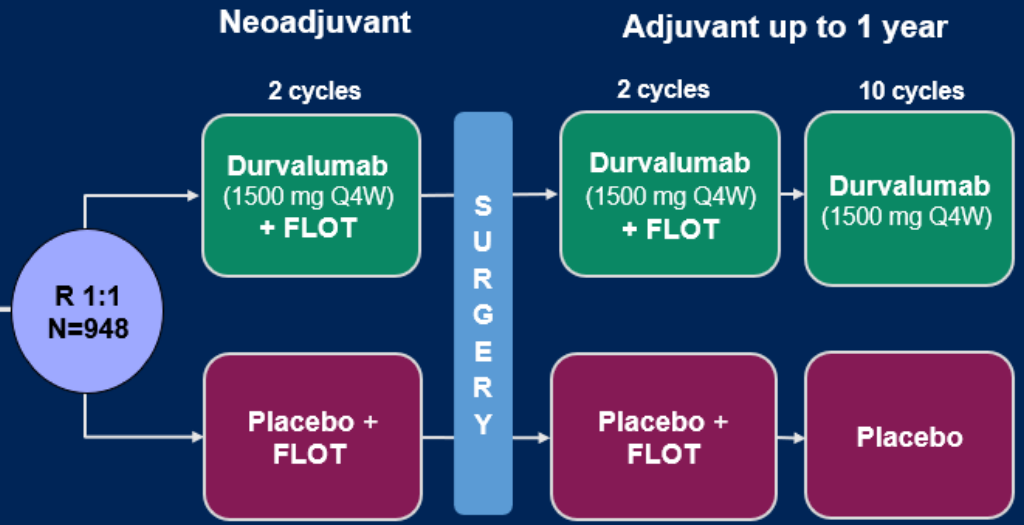
A global, Phase 3, randomized, double-blind, placebo-controlled study

Study population

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

Stratification factors

- Asia vs non-Asia
- Clinical N+ vs N-
- PD-L1: TAP <1% vs TAP ≥1%*



Primary endpoint:

- EFS

Secondary:

- OS
- pCR

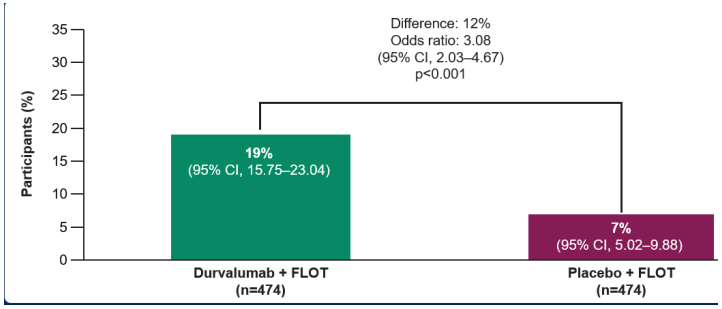
FLOT: 5-fluorouracil 2600 mg/m², leucovorin 200 mg/m², oxaliplatin 85 mg/m², docetaxel 50 mg/m², on Days 1 and 15 Q4W, 4 doses (two cycles) pre- and post-operative; durvalumab: 1500 mg on Day 1 Q4W, 2 doses (two cycles) of durvalumab or placebo pre- and post-operative, followed by 10 doses of post-operative 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 / placebo monotherapy may be continued if FLOT is discontinued due to toxicity. *Measured by IHC using VENTANA PD-L1 (SP263) CDx Assay (Roche Diagnostics; IUO).
ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GEJ, gastroesophageal junction; IHC, immunohistochemistry; IUO, investigational use only; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed cell death ligand-1; PS, performance status; Q4W, every 4 weeks; R, randomized; TAP, Tumor Area Positivity.

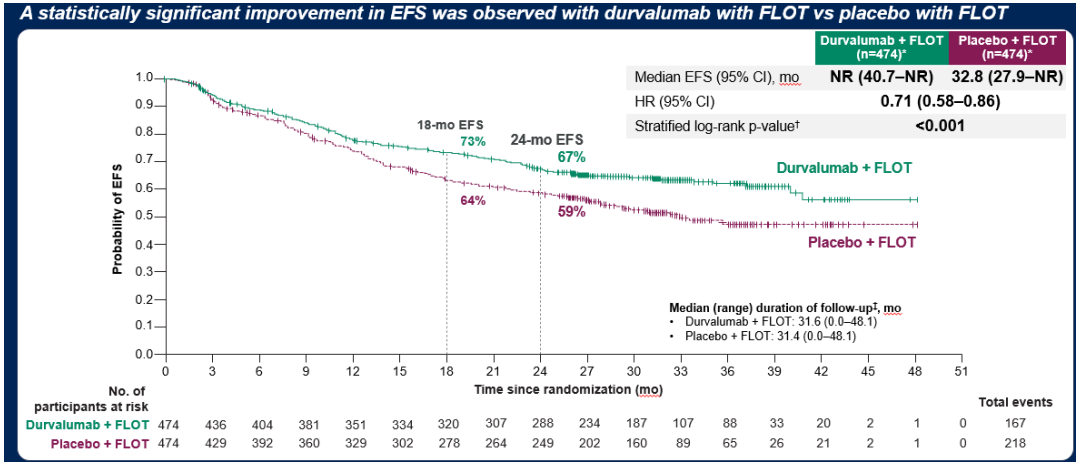
Baseline Characteristics

Balanced in both arms

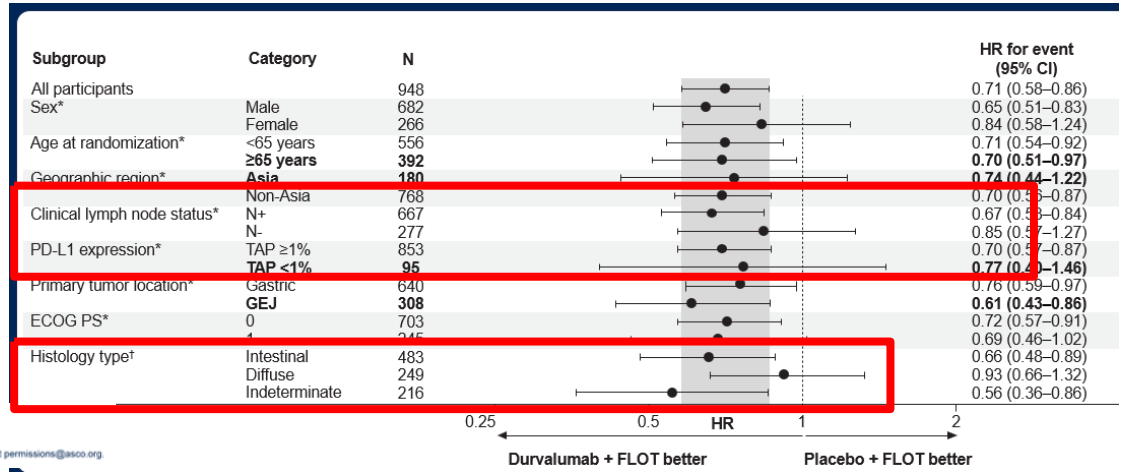
		Durvalumab + FLOT (n=474)*	Placebo + FLOT (n=474)*
Age, years	Median (range)	62 (26–84)	63 (28–83)
Sex, %	Male	69	75
Geographic region, %	Non-Asia	81	81
	Asia	**19**	**19**
ECOG PS, %	0 (normal activity)	71	77
	1 (restricted activity)	29	23
Site of tumor, %	Gastric	68	67
	GEJ	**32**	**33**
Primary tumor stage, %	**T4**	**25**	**25**
	Non-T4	75	75
Clinical lymph node status, %†	**N+**	**69**	**70**
PD-L1 expression by TAP, %‡	<1%	10	10
	≥1%	90	90
Histology type (investigator assessed), %	Intestinal	52	50
	Diffuse	27	25
	Unspecified adenocarcinoma or mixed / other	21	25
MSI status, %§	**MSI-high**	**5**	**5**

	Durvalumab + FLOT (n=474)	Placebo + FLOT (n=474)
Received any neoadjuvant treatment, %	**100**	**99**
Completed durvalumab or placebo	97	95
Completed any FLOT	96	95
Attempted surgery, %	91	90
Completed surgery, %	87	84
R0 resection in those who completed surgery	**92**	**92**
Received any adjuvant treatment, %	77	74
Completed durvalumab or placebo	**52**	**52**
Completed any FLOT	61	64
Active follow-up at data cut-off, %*	**68**	**59**



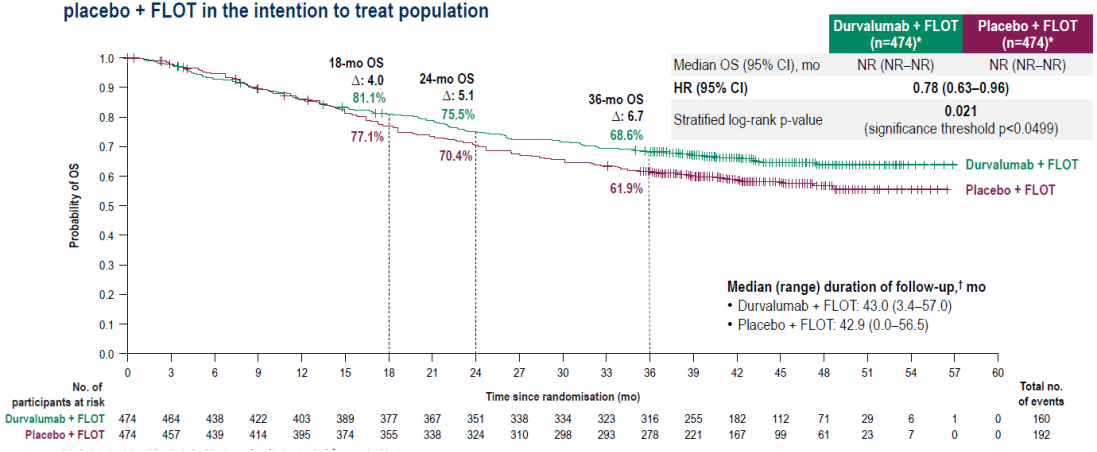


Janjigian YY, et al. *Annal Oncol* 2023;34(suppl 2). Abs LBA73; ESMO 2023



Final OS

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

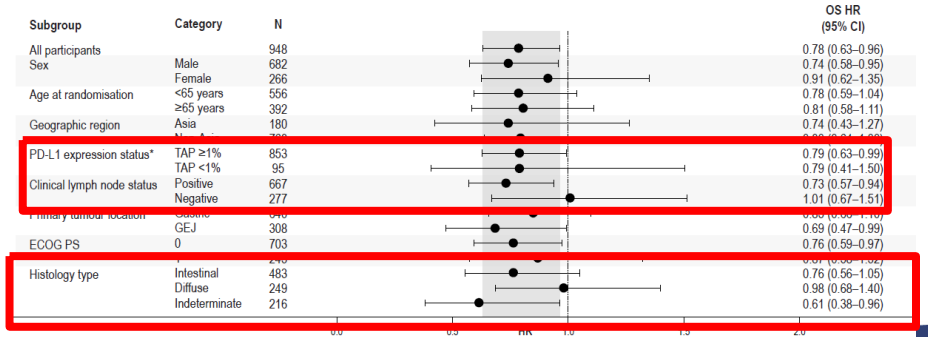


	Durvalumab + FLOT (n=474)*	Placebo + FLOT (n=474)*
Median OS (95% CI), mo	NR (NR–NR)	NR (NR–NR)
HR (95% CI)	0.78 (0.63–0.96)	
Stratified log-rank p-value	0.021 (significance threshold p<0.0499)	

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

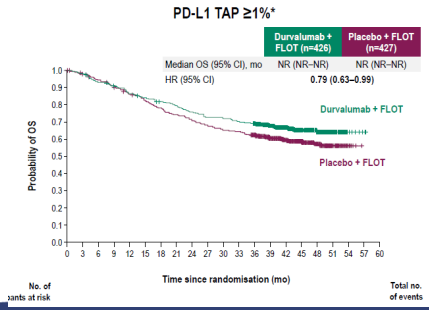
OS in key subgroups

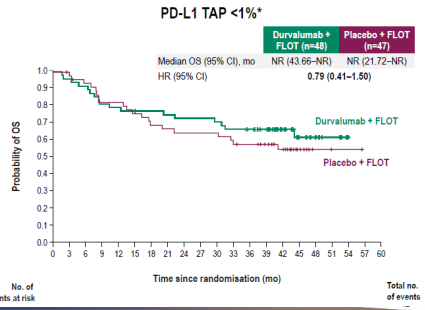
A consistent benefit in OS was observed with durvalumab + FLOT versus placebo + FLOT in most key subgroups



OS by PD-L1 status

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





INTERROGANTES MATTERHORN

1. ¿Qué hacer en u-cN-?

   Cohortes clínicas con tasas de N+ ocultas en cT2N0 del **39 al 45%** (1,2)

1. ¿Qué hacer en cáncer esófago?

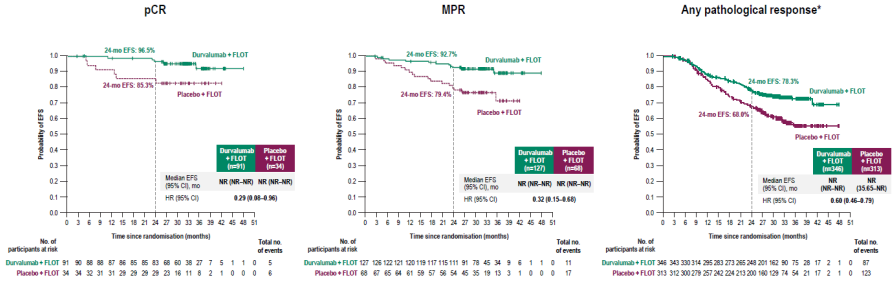
   Datos de la enfermedad avanzada

1. ¿Qué hacer en pCR? ¿en ausencia de respuesta?

2. ¿Qué hacer TAP <1%?

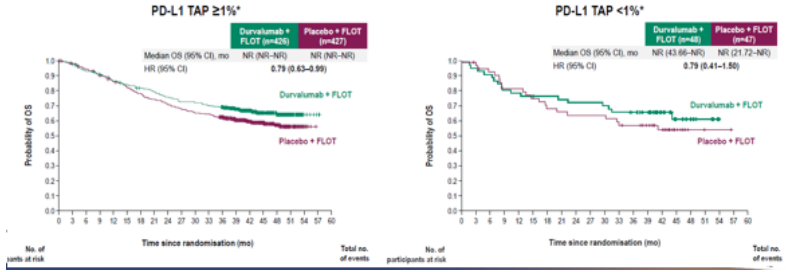
Pathological response and EFS

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



OS by PD-L1 status

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



1. Ann Thorac Surg 96:382–390, 2013 2. J Thorac Cardiovasc Surg 157:1264–1272.e6, 2019

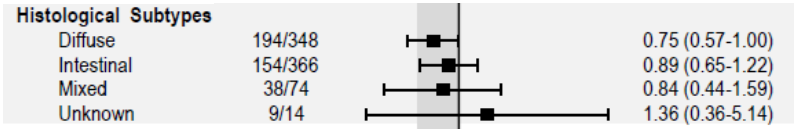
INTERROGANTES MATTERHORN

1. ¿Qué hacer en cáncer gástrico difuso?

QT

FLOT AIO Lancet 2019; 393: 1948–57

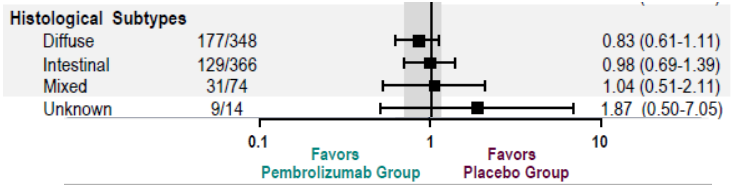
Event-Free Survival



KEYNOTE-585 Study

Shitata. ESMO 2023

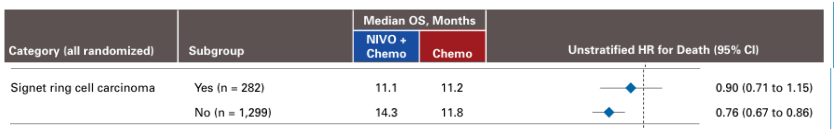
Overall Survival

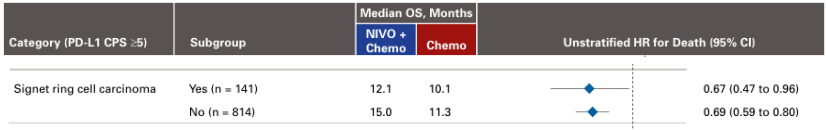


Enfermedad avanzada

Rationale 305?.

Keynote 859. 2023 Nov;24(11):1181-1195.



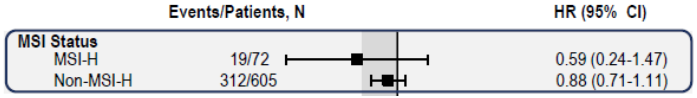


Checkmate 649 J Clin Oncol 2024 42:2012-2020

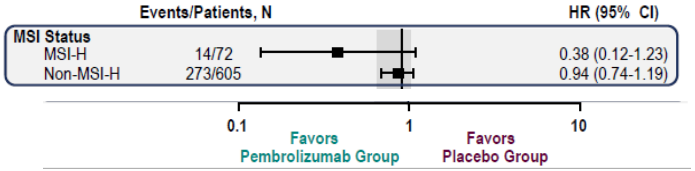
¿Qué hacemos con los pacientes MSI-H?

KEYNOTE-585 Study

Event-Free Survival



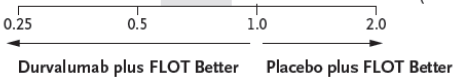
Overall Survival



Shitara ESMO 2023

Event-free Survival

Subgroup	Durvalumab plus FLOT	Placebo plus FLOT	Hazard Ratio for Event (95% CI)
Microsatellite instability status			
High	8/25 (32.0)	6/24 (25.0)	NC (NC–NC)
Not high	106/301 (35.2)	148/310 (47.7)	0.67 (0.52–0.86)
Not evaluable or missing	53/148 (35.8)	64/140 (45.7)	0.72 (0.50–1.04)



NEJM 2025 Jul 17;393(3):217-230

ESTRATEGIA PERIOPERATORIA EN MSI-H

Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability As a Biomarker in Gastric Cancer

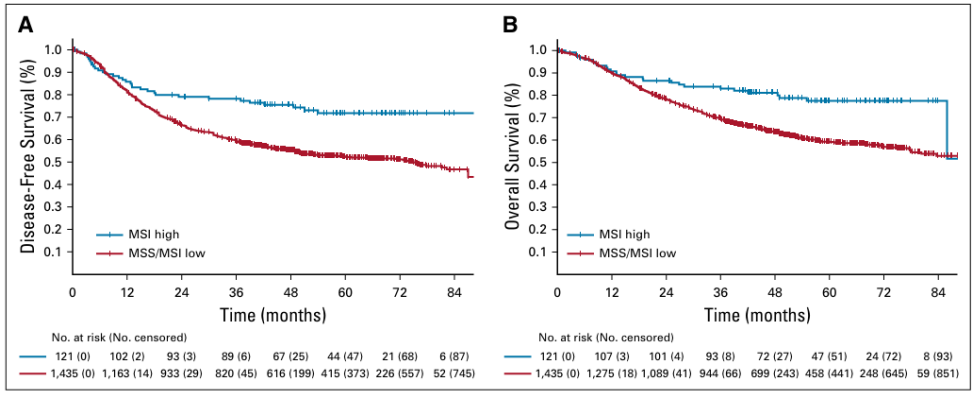


FIG 2. Kaplan-Meier curves of (A) disease-free survival and (B) overall survival according to microsatellite-instability (MSI) status (microsatellite stable [MSS]/MSI-low *v* MSI-high).

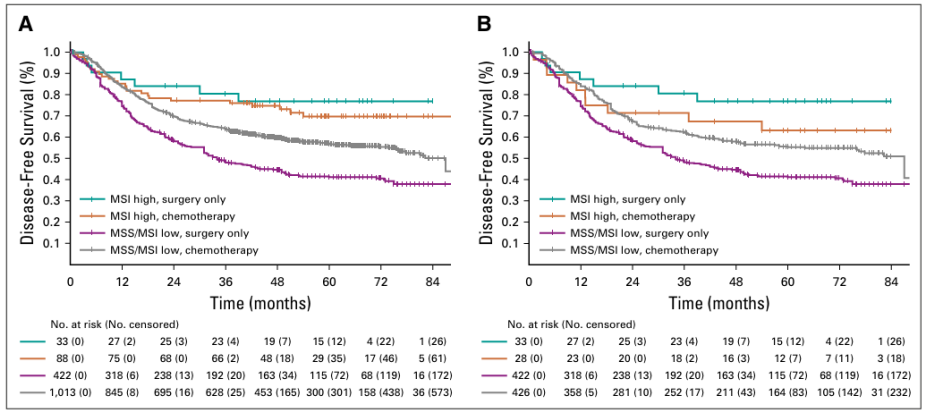


FIG 3. Kaplan-Meier curves of disease-free survival according to treatment (surgery plus chemotherapy *v* surgery only) and microsatellite-instability (MSI) status (MSI-high *v* microsatellite stable [MSS]/MSI-low) in (A) whole trial population and (B) MAGIC and CLASSIC trials only.

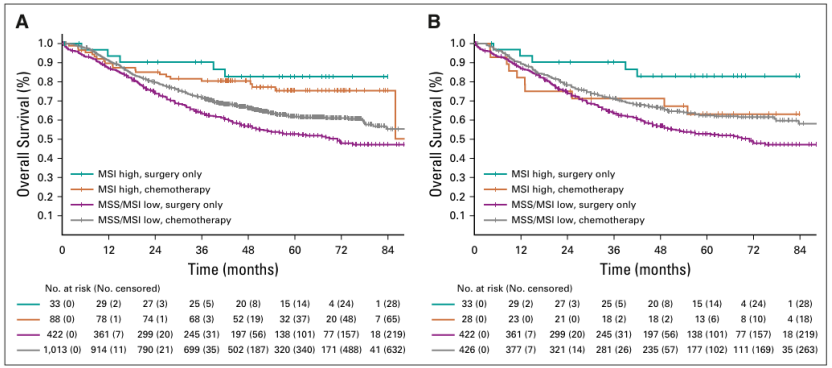


FIG 4. Kaplan-Meier curves of overall survival according to treatment (surgery plus chemotherapy *v* surgery only) and microsatellite-instability (MSI) status (MSI-high *v* microsatellite stable [MSS]/MSI-low) in (A) whole trial population and (B) MAGIC and CLASSIC trials only.

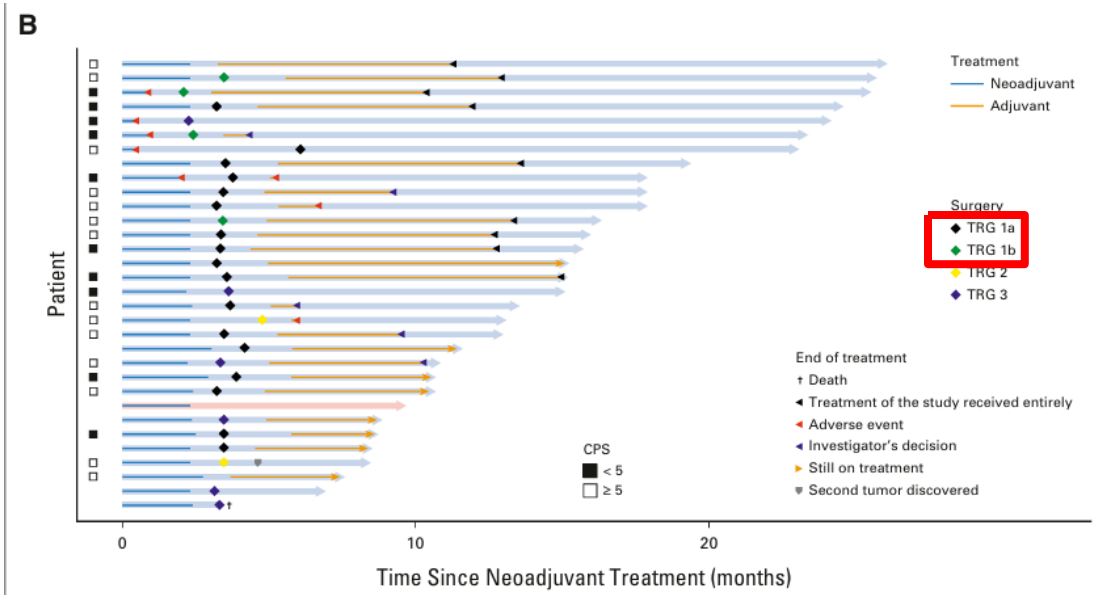
Neoadjuvant Nivolumab Plus Ipilimumab and Adjuvant Nivolumab in Localized Deficient Mismatch Repair/Microsatellite Instability–High Gastric or Esophagogastric Junction Adenocarcinoma: The GERCOR NEONIPIGA Phase II Study

J Clin Oncol **41**, 255-265(2023)

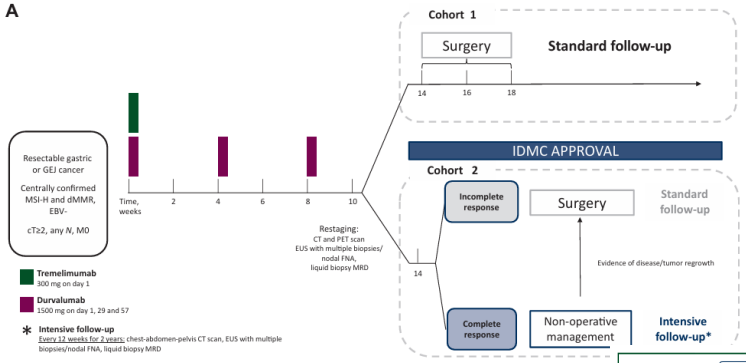
Neoadjuvant nivolumab 240 mg once every two weeks and ipilimumab 1 mg/kg once every six weeks, followed by surgery and adjuvant nivolumab 480 mg once every four weeks

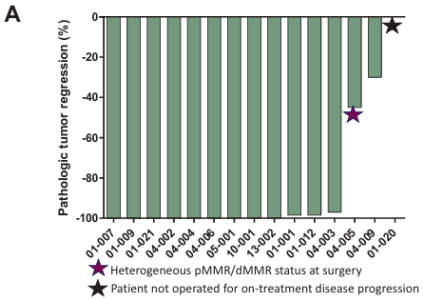
TABLE 4. Pathologic Characteristics of Patients Who Underwent Surgery (the mITT population)

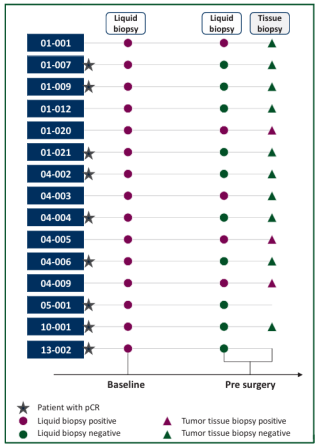
Characteristic	Patients (n = 29), No. (%)
ypT stage	
ypT0	19 (65)[a]
ypT1a	1 (3)
ypT1b	2 (7)
ypT2	2 (7)
ypT3	5 (17)
ypN stage	
ypN0	23 (79)
ypN1	6 (21)

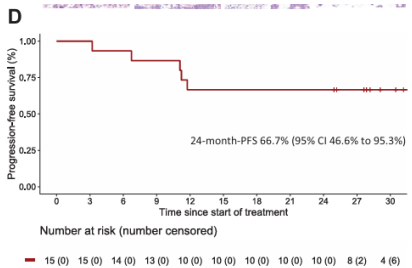


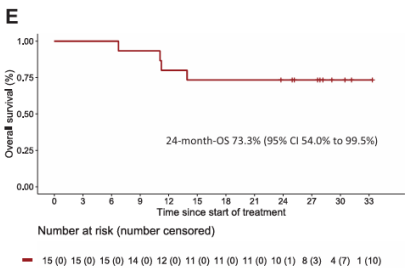
Tremelimumab and durvalumab as neoadjuvant or non-operative management strategy of patients with microsatellite instability-high resectable gastric or gastroesophageal junction adenocarcinoma: the INFINITY study by GONO

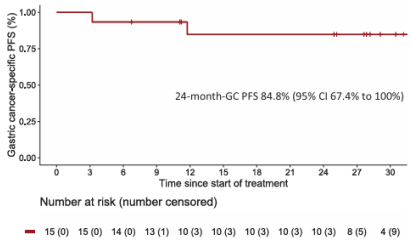


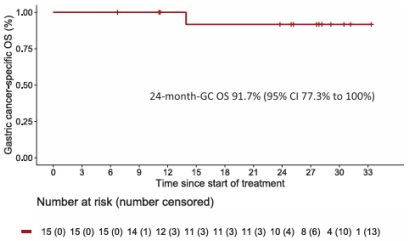






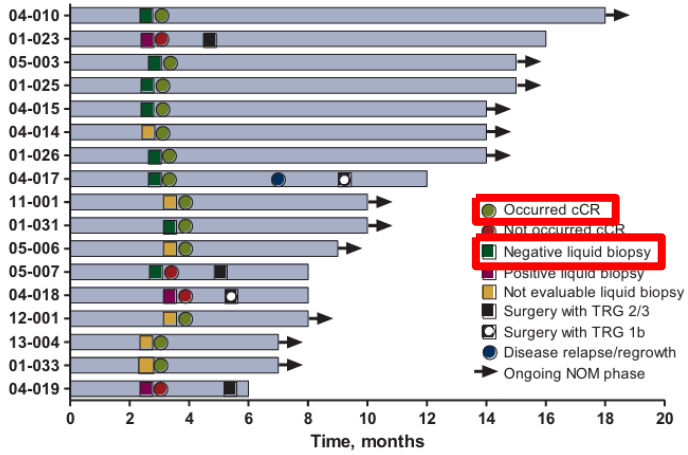


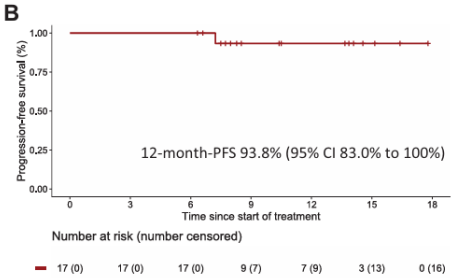


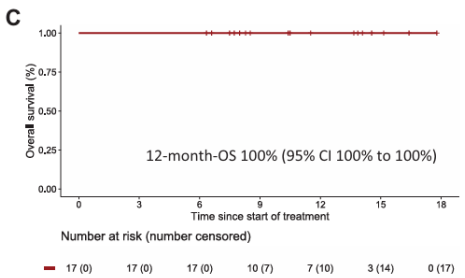


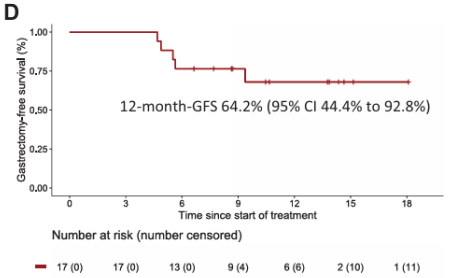
Ann Oncol 2025 Mar;36(3):285-296

Tremelimumab and durvalumab as neoadjuvant or non-operative management strategy of patients with microsatellite instability-high resectable gastric or gastroesophageal junction adenocarcinoma: the INFINITY study by GONO









C epidermoide de esófago

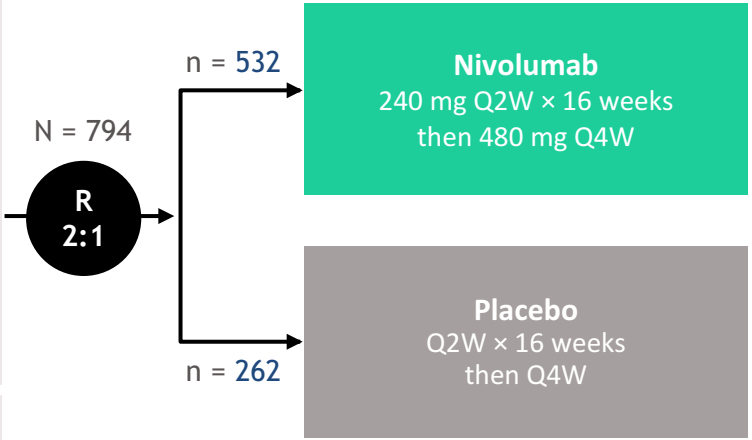
- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

Key eligibility criteria

- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0–1

Stratification factors

- Histology (squamous vs adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 vs ypN0)
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[c])



Total treatment duration of up to 1 year[d]

Primary endpoint:

- DFS[e]

Secondary endpoints:

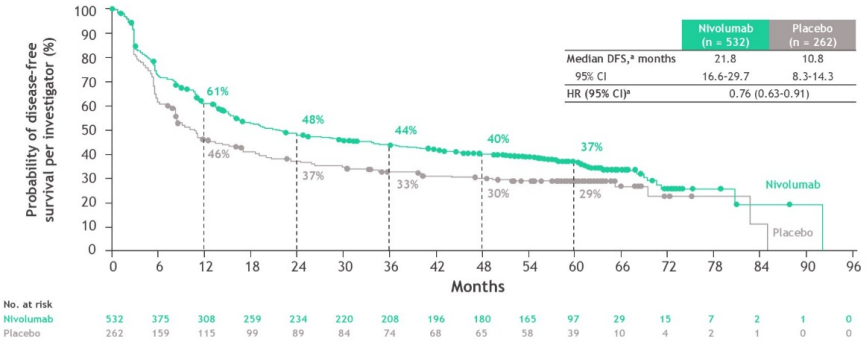
- OS[f]
- OS rate at 1, 2, and 3 years

- Median follow-up was 24.4 months (range, 6.2–44.9)[g]
- Geographical regions: Europe (38%), US and Canada (32%), Asia (13%), rest of the world (16%)

[a]ClinicalTrials.gov number, NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a pre-specified interim analysis; [f]The study will continue as planned to allow for future analysis of OS; [g]Time from randomization date to clinical data cutoff (May 12, 2020).

Histology[c]	Adenocarcinoma	376 (71)	187 (71)
	Squamous cell carcinoma	155 (29)	75 (29)

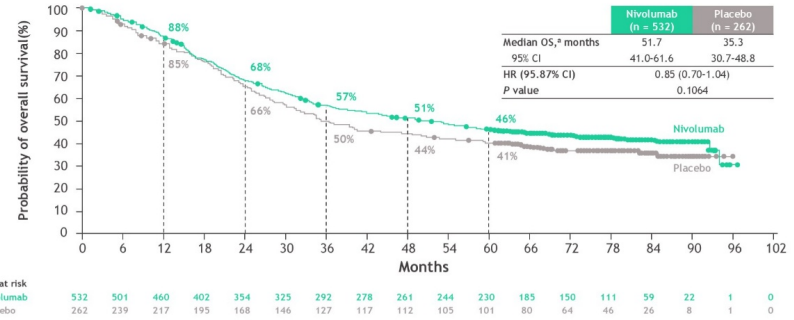
Disease-free survival



- Clinically meaningful improvement in DFS with nivolumab vs placebo was maintained with longer follow-up

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

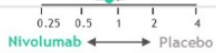
Overall survival



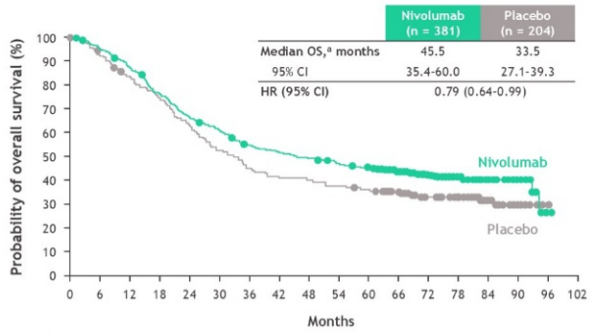
- Median OS was 16.4 months longer and the 5-year OS rate was higher with nivolumab vs placebo, suggesting clinically meaningful improvement in OS, although statistical significance was not met

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

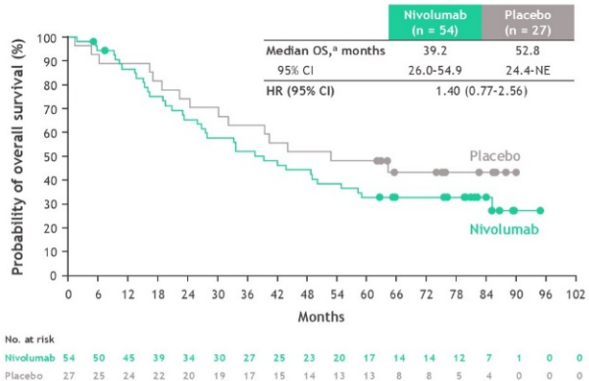
Category	Subgroup	Median OS, mo		Unstratified HR (95% CI)
		Nivolumab	Placebo	
Overall	N = 794	51.7	35.3	0.85 (0.70-1.03)
Age, years	< 65 (n = 507)	56.4	36.6	0.83 (0.65-1.06)
	≥ 65 (n = 287)	39.3	35.2	0.87 (0.64-1.19)
Sex	Male (n = 671)	45.5	34.7	0.88 (0.72-1.08)
	Female (n = 123)	NR	48.0	0.70 (0.41-1.19)
Race[a]	White (n = 648)	49.5	34.8	0.84 (0.68-1.03)
	Asian (n = 117)	61.5	NR	1.10 (0.63-1.93)
ECOG PS	0 (n = 464)	60.5	40.3	0.85 (0.66-1.10)
	1 (n = 330)	37.2	32.1	0.84 (0.63-1.12)
Disease stage at initial diagnosis[b]	II (n = 278)	58.2	44.1	0.86 (0.62-1.19)
	III (n = 516)	49.3	32.8	0.84 (0.66-1.06)
Tumor location at trial entry	Esophagus (n = 467)	49.5	31.4	0.69 (0.54-0.88)
	Gastroesophageal junction (n = 327)	54.9	64.2	1.14 (0.83-1.56)
Histologic type[c,d]	Adenocarcinoma (n = 563)	51.7	40.2	0.92 (0.73-1.15)
	Squamous cell carcinoma (n = 230)	50.7	31.4	0.72 (0.51-1.03)
Tumor cell PD-L1 expression[e]	≥ 1% (n = 128)	60.0	51.2	0.88 (0.54-1.43)
	< 1% (n = 571)	47.7	34.6	0.82 (0.66-1.02)
PD-L1 CPS[f]	≥ 1 (n = 585)	45.5	33.5	0.79 (0.64-0.99)
	< 1 (n = 81)	39.2	52.8	1.40 (0.77-2.56)
Pathologic lymph node status[d,g]	ypN0 (n = 333)	92.8	68.5	0.81 (0.58-1.14)
	≥ ypN1 (n = 459)	33.6	28.0	0.86 (0.68-1.10)



PD-L1 CPS ≥ 1



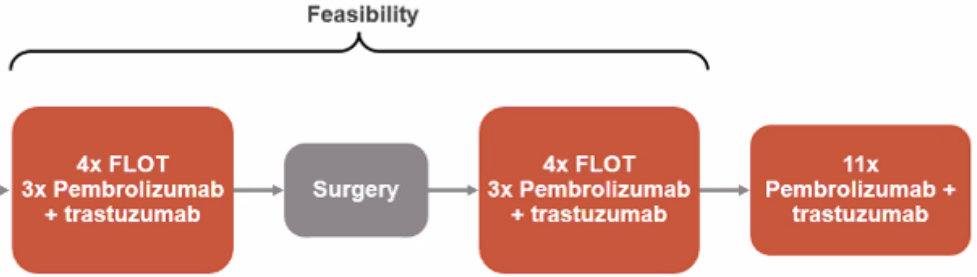
PD-L1 CPS < 1



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

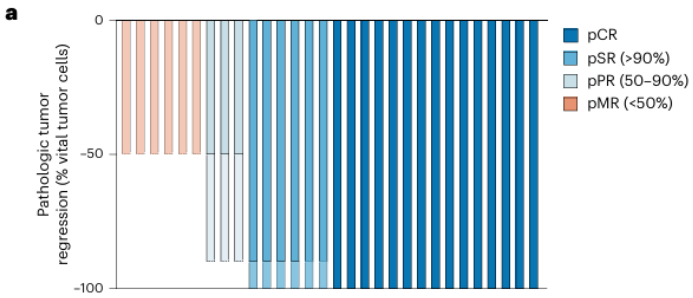
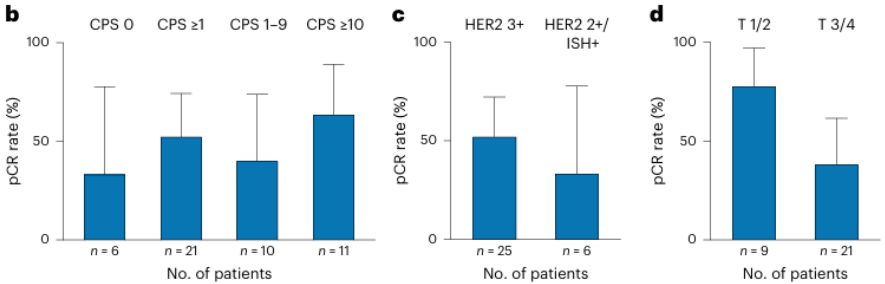


Table 2 | Pathological response in the ITT population

	pCR	pSR	pPR	pMR	NA
ITT, *n*=31	*n*=15, 48.4% (30.2–66.9)	*n*=6, 19.4% (7.5–37.5)	*n*=3, 9.7% (2.0–25.8)	*n*=6, 19.4% (7.5–37.5)	*n*=1, 3.2%

n, number of patients; 95% CIs are shown in parentheses.



Nat Med (2025). https://doi.org/10.1038/s41591-025-03979-y

CONCLUSIONES

1. En el carcinoma epidermoide la QRT seguida de nivolumab continúa siendo el estándar de tratamiento (¿CPS<1?)
2. Quimioterapia perioperatoria + durvalumab es el nuevo estándar de tratamiento en adenocarcinoma gástrico y UGE
3. Búsqueda de biomarcadores predictivos de respuesta
4. En MSI-H replantear el papel de la QT