XXXIII SIMPOSIO INTERNACIONAL INTERNATIONAL SYMPOSIUM
11 - 12 DE DICIEMBRE DE 2025
OVIEDO

# Personalización del tratamiento perioperatorio en adenocarcinoma de esófago M0: claves clínicopatológicas

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# Disclosure information

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- Personal financial interests (consultancy or advisory roles) Amgen, AstraZeneca, BeOne Medicines, Bristol Myers Squibb, Daiichi Sankyo, Jazz Pharmaceuticals, LEO Pharma, Merck Sharp & Dohme, Novartis.

- Grant/research funding Instituto de Salud Carlos III, Gobierno de Navarra, Merck KGaA, Sociedad Española de Oncología Médica.

- Other honoraria (speaking) Astellas, AstraZeneca, BeOne Medicines, Bristol Myers Squibb, Jazz Pharmaceuticals and Merck Sharp & Dohme.



# Outline

- Epidemiology and biology
- Perioperative treatment of the oesophageal adenocarcinoma
- Molecular peculiarities
- Conclusions



# EPIDEMIOLOGY AND BIOLOGY

# Epidemiology

- Esophageal cancer represents the 11th more frequent tumour worldwide, 7th cause of cancer-death
- In Spain, it ranks the 22th in incidence, the 20th in mortality
- In high incoming countries, like in Spain, oesophageal cancer is mainly adenocarcinoma

| TIPO TUMORAL | N |
|---|---|
| Cavidad Oral y Faringe | 7.446 |
| Esófago | 2.300 |
| Estómago | 7.136 |
| Colon | 30.311 |
| Recto | 14.262 |
| Hígado | 6.800 |
| Vesícula biliar | 2.359 |
| Páncreas | 10.338 |
| Laringe | 3.190 |
| Pulmón | 34.506 |
| Melanoma de piel | 9.408 |
| Mama | 37.682 |
| Cérvix Uterino | 2.307 |
| Cuerpo Uterino | 7.428 |
| Ovario | 3.748 |
| Próstata | 32.188 |
| Testículo | 1.677 |
| Riñón (sin pelvis) | 9.774 |
| Vejiga urinaria | 22.435 |
| Encéfalo y sistema nervioso | 4.630 |
| Tiroides | 6.495 |
| Linfoma de Hodgkin | 1.732 |
| Linfomas no hodgkinianos | 10.383 |
| Mieloma | 3.731 |
| Leucemias | 6.264 |
| Otros | 17.573 |
| Todos excepto piel no melanoma | 296.103 |

Fuente: Red Española de Registros de Cáncer (REDECAN).

**Tabla 2.** Estimación del número de nuevos casos de cáncer en España para el año 2025 según tipo tumoral (excluidos los tumores cutáneos no melanoma) (ambos sexos).

Globocan 2024; Informe SEOM: Las cifras del Cáncer en España 2025

# Molecular biology



- **Esophageal cancer** should first be divided depending on the histology:
  - Esophageal **squamous cell carcinoma** (ESCC)
  - Esophageal **adenocarcinoma** (Gastroesophageal adenocarcinoma; GEA)

- **GEA** should be analysed as the same disease, regardless of tumour location, but recognizing a high **intrinsic heterogeneity**:
  - Incidence of middle/distal esophageal adenocarcinoma is increasing (Barret's disease)
  - Gastric cancer incidence is decreasing (H. Pylori eradication, type of food conserves)
  - Young-onset GEA is increasing (environmental and behaviour risk factors)



Arnold Gastroenterology 2020; Ben Aharon Cancer Discov 2023



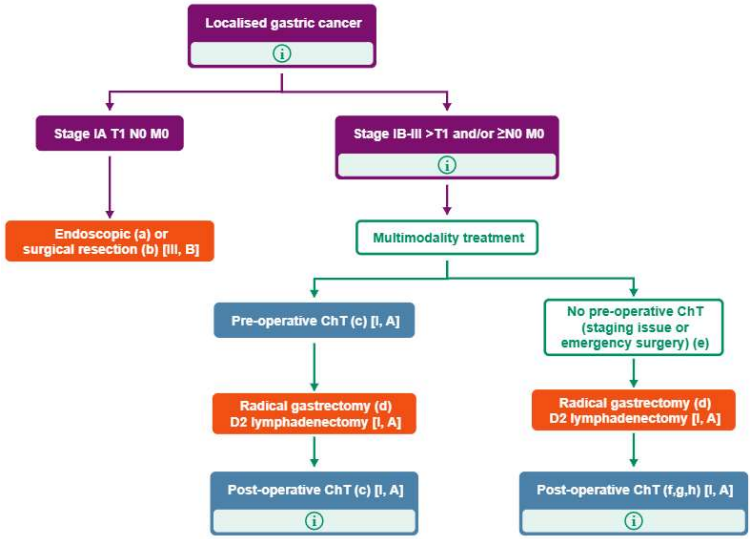
# PERIOPERATIVE TREATMENT OF THE ESOPHAGEAL ADENOCARCINOMA

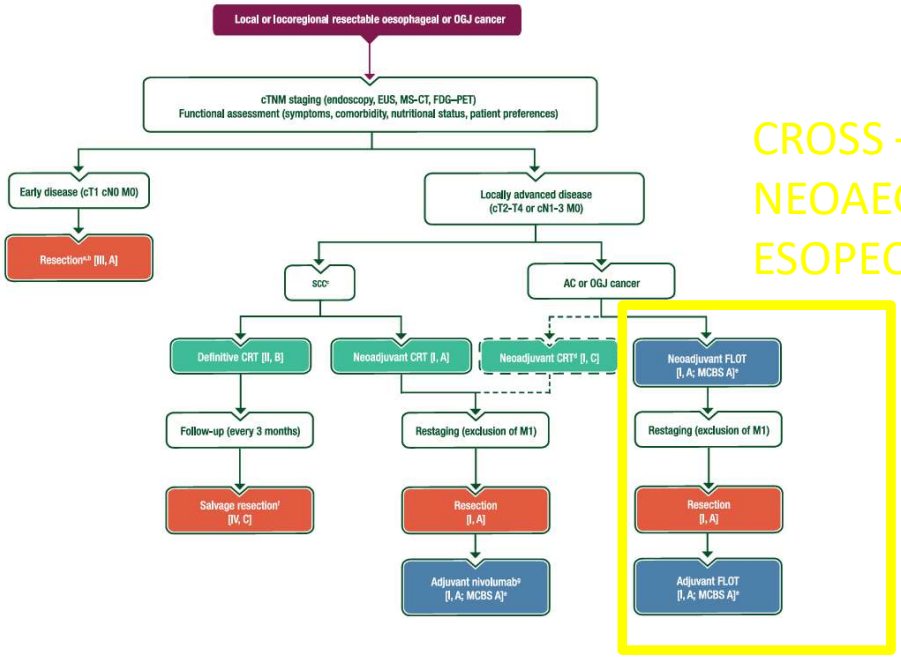
# Perioperative treatment

- Multidisciplinary Tumor Board
  - Diagnosis
  - Treatment approach
    - Surgery (+ prehabilitation)
    - Systemic treatment
    - Nutritional assessment
    - Psychologic support

# Clinical Guidelines

- **FLOT is the SoC for all GEA** (FLOT4 & ESOPEC)




CROSS – CM577
NEOAEGIS
ESOPEC

F. Lordick et al; Ann Oncol 2022; e-update v1.4 September 2024
R. L. Obermannová & T. Leong; ESMO Open 2025
Al Batran; Lancet 2019; Hoeppner NEJM 2025

# The CROSS Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

P. van Hagen, M.C.C.M. Hulshof, J.J.B. van Lanschot, E.W. Steyerberg, M.I. van Berge Henegouwen, B.P.L. Wijnhoven, D.J. Richel, G.A.P. Nieuwenhuijzen, G.A.P. Hospers, J.J. Bonenkamp, M.A. Cuesta, R.J.B. Blaisse, O.R.C. Busch, F.J.W. ten Kate, G.-J. Creemers, C.J.A. Punt, J.T.M. Plukker, H.M.W. Verheul, E.J. Spillenaar Bilgen, H. van Dekken, M.J.C. van der Sangen, T. Rozema, K. Biermann, J.C. Beukema, A.H.M. Piet, C.M. van Rij, J.G. Reinders, H.W. Tilanus, and A. van der Gaast, for the CROSS Group*

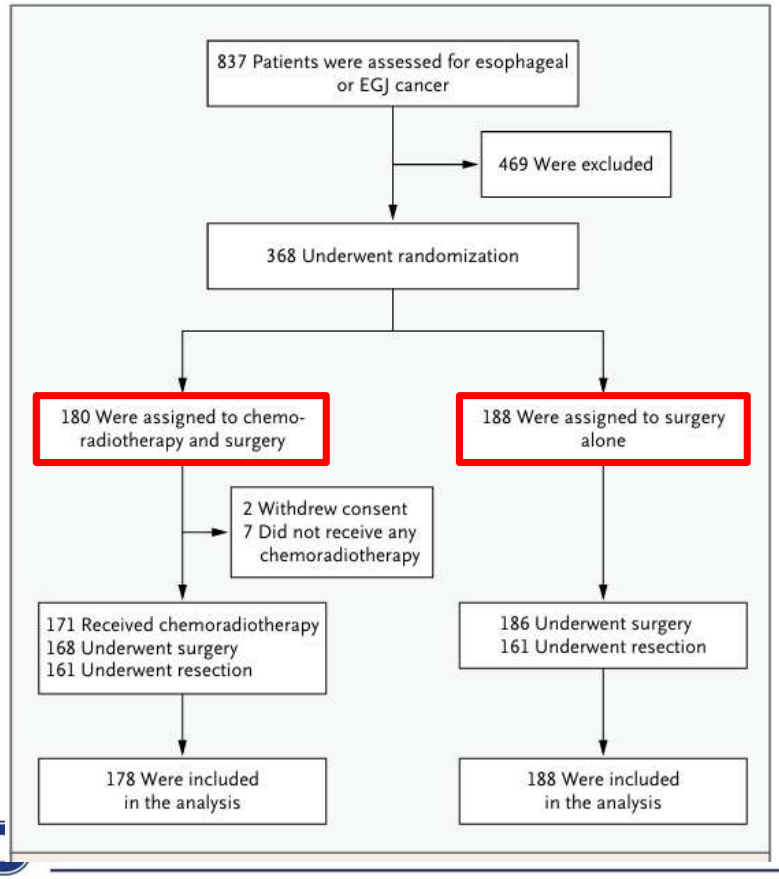
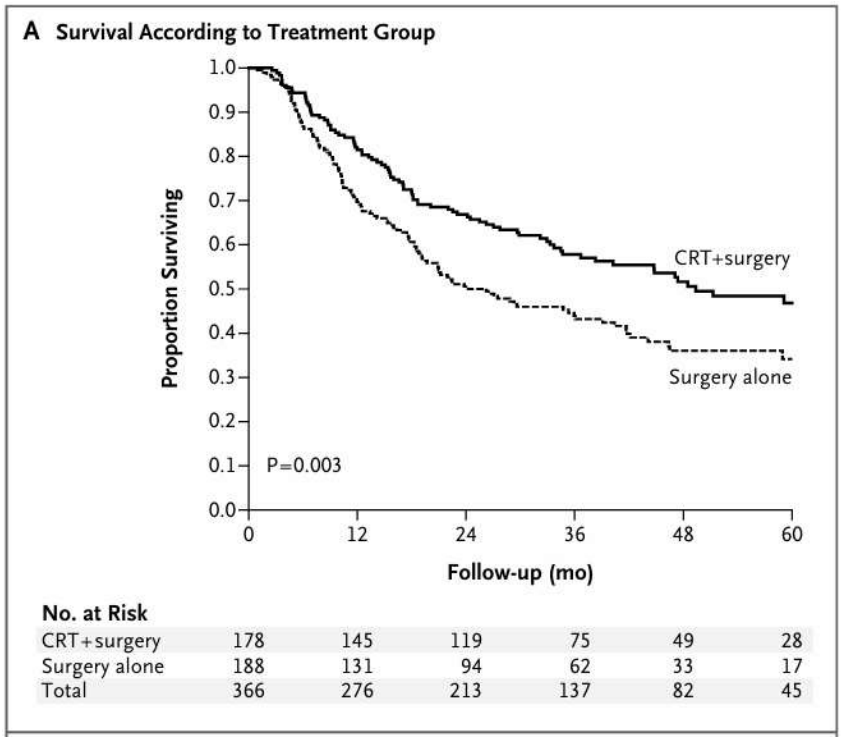
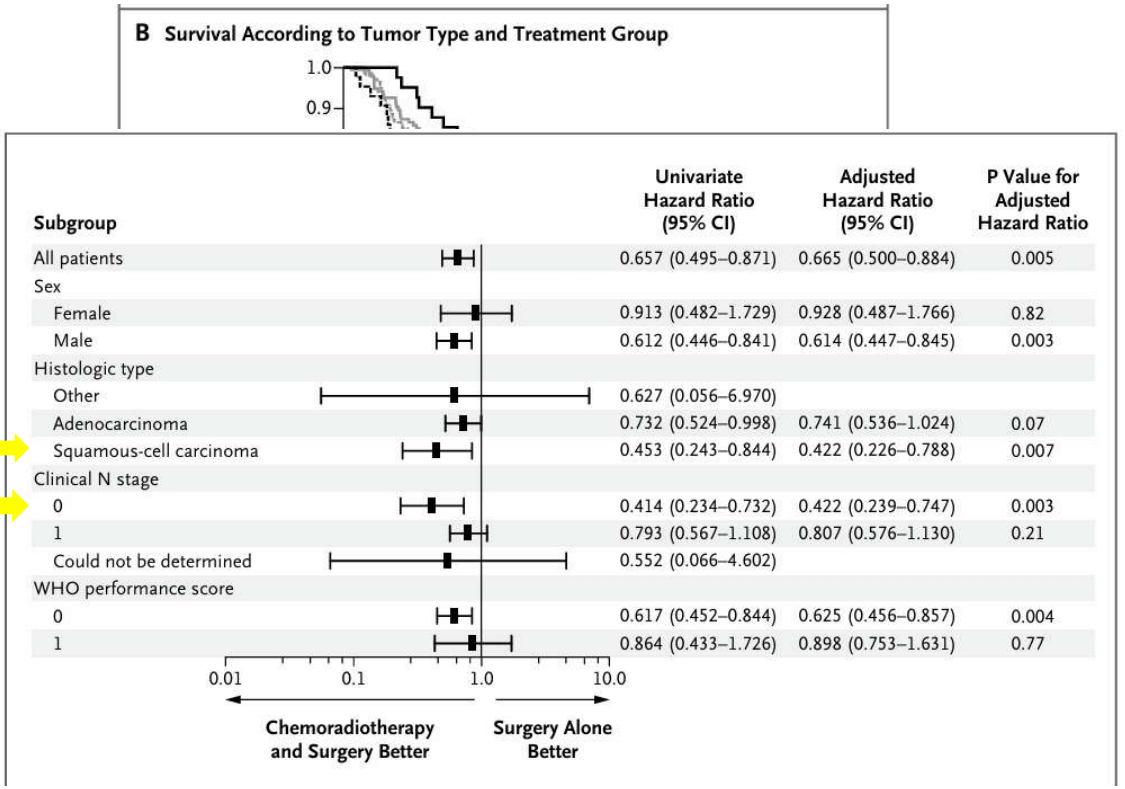



**Table 1. Characteristics of Patients with Resectable Esophageal or Esophagogastric-Junction Cancer, According to Treatment Group.***

| Characteristic | Chemoradiotherapy and Surgery (N=178) | Surgery Alone (N=188) |
|---|---|---|
| Age — yr | | |
| Median | 60 | 60 |
| Range | 36–79 | 36–73 |
| Male sex — no. (%) | 134 (75) | 152 (81) |
| Tumor type — no. (%) | | |
| Adenocarcinoma | 134 (75) | 141 (75) |
| Squamous-cell carcinoma | 41 (23) | 43 (23) |
| Other | 3 (2) | 4 (2) |
| Tumor length — cm† | | |
| Median | 4 | 4 |
| Interquartile range | 3–6 | 3–6 |
| Tumor location — no. (%)† | | |
| Esophagus | | |
| Proximal third | 4 (2) | 4 (2) |
| Middle third | 25 (14) | 24 (13) |
| Distal third | 104 (58) | 107 (57) |
| Esophagogastric junction | 39 (22) | 49 (26) |
| Missing data | 6 (3) | 4 (2) |

# The CROSS Trial

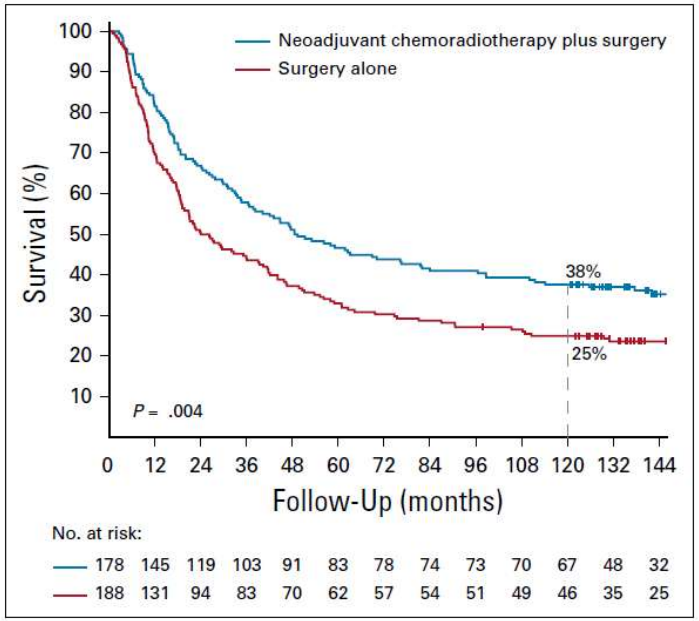


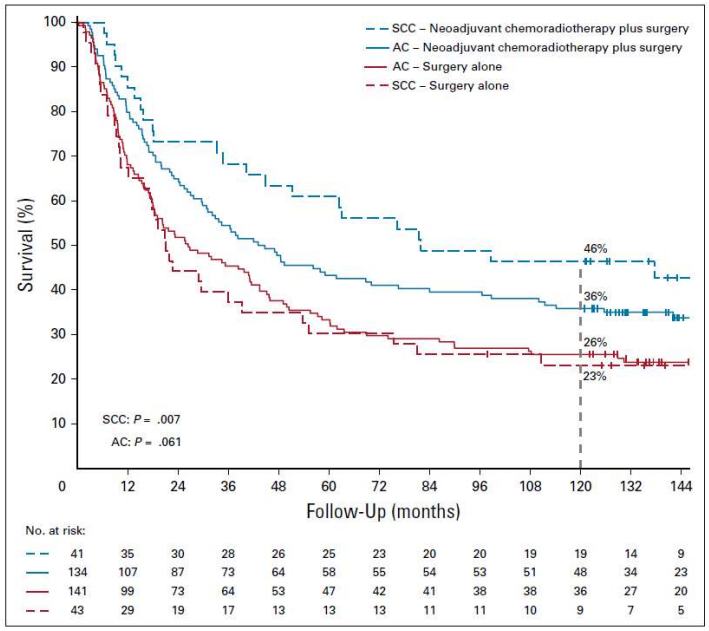




Van Hagen NEJM 2012

# The CROSS Trial (10 year FUP)

Absolute **10-year OS benefit of 13%**; HR = 0.60 (95% CI 0.46-0.80




Shapiro Lancet Oncol 2015 (5y FUP); Eyck J Clin Oncol 2021 (10y FUP)

# The CROSS Trial (10 year FUP)

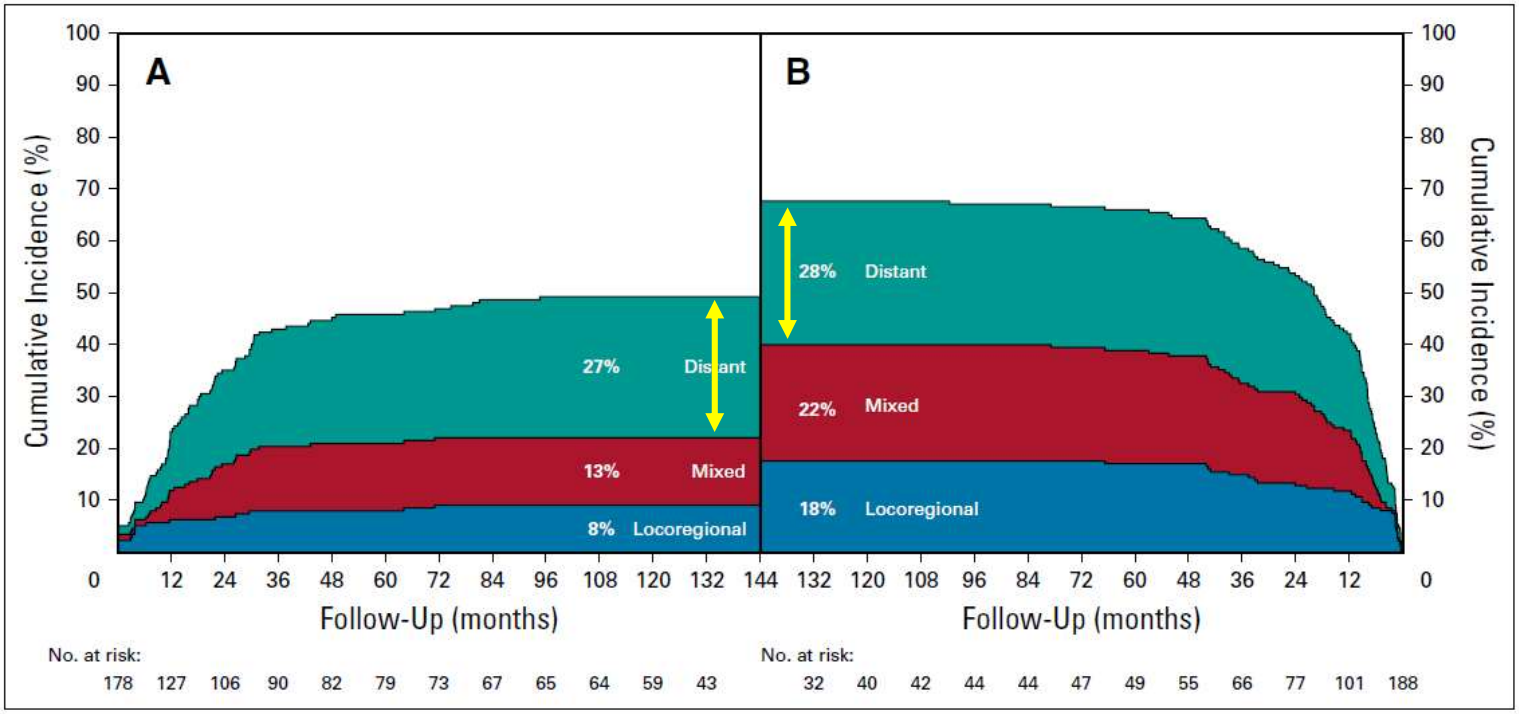



**FIG 6.** Stacked cumulative incidence of relapse location within the (A) neoadjuvant chemoradiotherapy and (B) surgery alone group. The cumulative incidences are stacked. The sum of the three relapse locations represents the total relapse rate.

Shapiro Lancet Oncol 2015 (5y FUP); Eyck J Clin Oncol 2021 (10y FUP)

# Checkmate-577

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## CheckMate 577 study design

- 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])

N = 794 → R 2:1

- n = 532: **Nivolumab** 240 mg Q2W × 16 weeks then 480 mg Q4W
- n = 262: **Placebo** Q2W × 16 weeks then Q4W

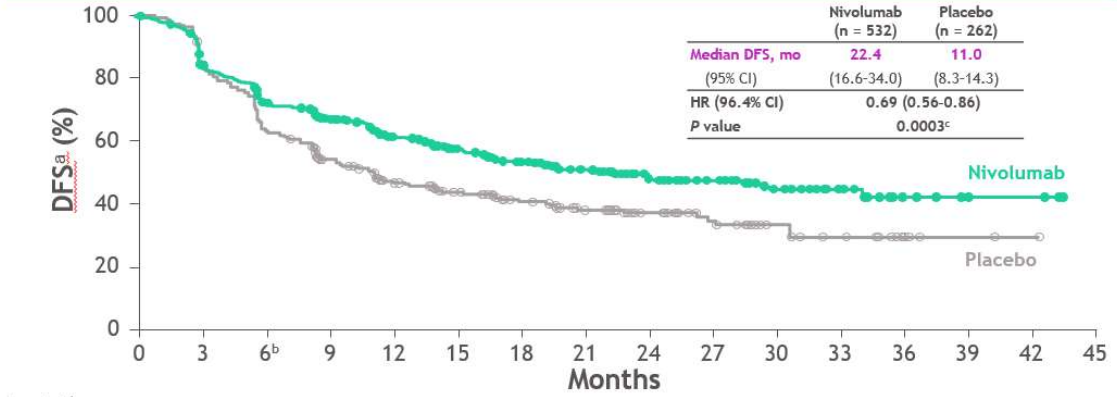
Total treatment duration of up to 1 year[d]

**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%)

## Disease-free survival




| | Nivolumab (n = 532) | Placebo (n = 262) |
|---|---|---|
| Median DFS, mo | 22.4 | 11.0 |
| (95% CI) | (16.6-34.0) | (8.3-14.3) |
| HR (96.4% CI) | 0.69 (0.56-0.86) | |
| *P* value | 0.0003[c] | |

| No. at risk | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 532 | 430 | 364 | 306 | 249 | 212 | 181 | 147 | 92 | 68 | 41 | 22 | 8 | 4 | 3 | 0 |
| Placebo | 262 | 214 | 163 | 126 | 96 | 80 | 65 | 53 | 38 | 28 | 17 | 12 | 5 | 2 | 1 | 0 |

- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

Kelly ESMO 2020; Kelly NEJM 2021

# Checkmate-577

| Subgroup | | Median DFS, months | | |
|---|---|---|---|---|
| | | Nivolumab | Placebo | |
| Overall (N = 794) | | 22.4 | 11.0 | |
| Age, years | < 65 (n = 507) | 24.4 | 10.8 | |
| | ≥ 65 (n = 287) | 17.0 | 13.9 | |
| Sex | Male (n = 671) | 21.4 | 11.1 | |
| | Female (n = 123) | Not reached | 11.0 | |
| Race | White (n = 648) | 21.3 | 10.9 | |
| | Asian (n = 117) | 24.0 | 10.2 | |
| ECOG PS | 0 (n = 464) | 29.4 | 11.1 | |
| | 1 (n = 330) | 17.0 | 10.9 | |
| Disease stage at initial diagnosis | II (n = 278) | 34.0 | 13.9 | |
| | III (n = 514) | 19.4 | 8.5 | 0.68 |
| Tumor location | EC (n = 462) | 24.0 | 8.3 | 0.61 |
| | GEJC (n = 332) | 22.1 | 20.6 | 0.87 |
| Histology | Adenocarcinoma (n = 563) | 19.4 | 11.1 | 0.75 |
| | Squamous cell carcinoma (n = 230) | 29.7 | 11.0 | 0.61 |
| Pathologic lymph node status | ypN0 (n = 336) | | 27.0 | 0.74 |
| | ≥ ypN1 (n = 457) | 14.8 | 7.6 | 0.67 |
| Tumor cell PD-L1 expression | ≥ 1% (n = 129) | 19.7 | 14.1 | 0.75 |
| | < 1% (n = 570) | 21.3 | 11.1 | 0.73 |
| | Indeterminate/nonevaluable (n = 95) | | 9.5 | 0.54 |

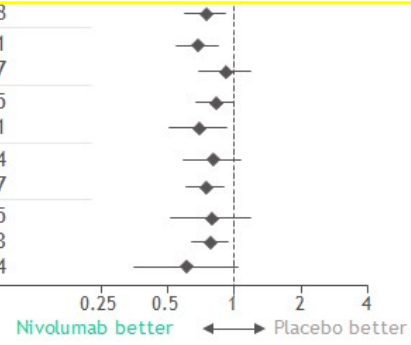
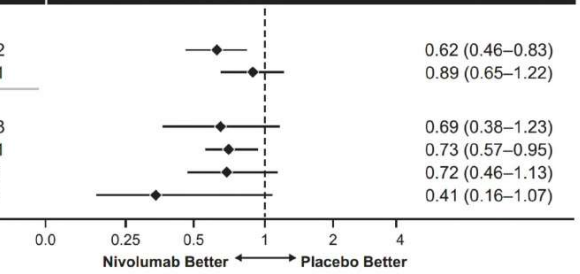



**Figure S2. Post Hoc Assessment of Disease-free Survival by Subgroups.**

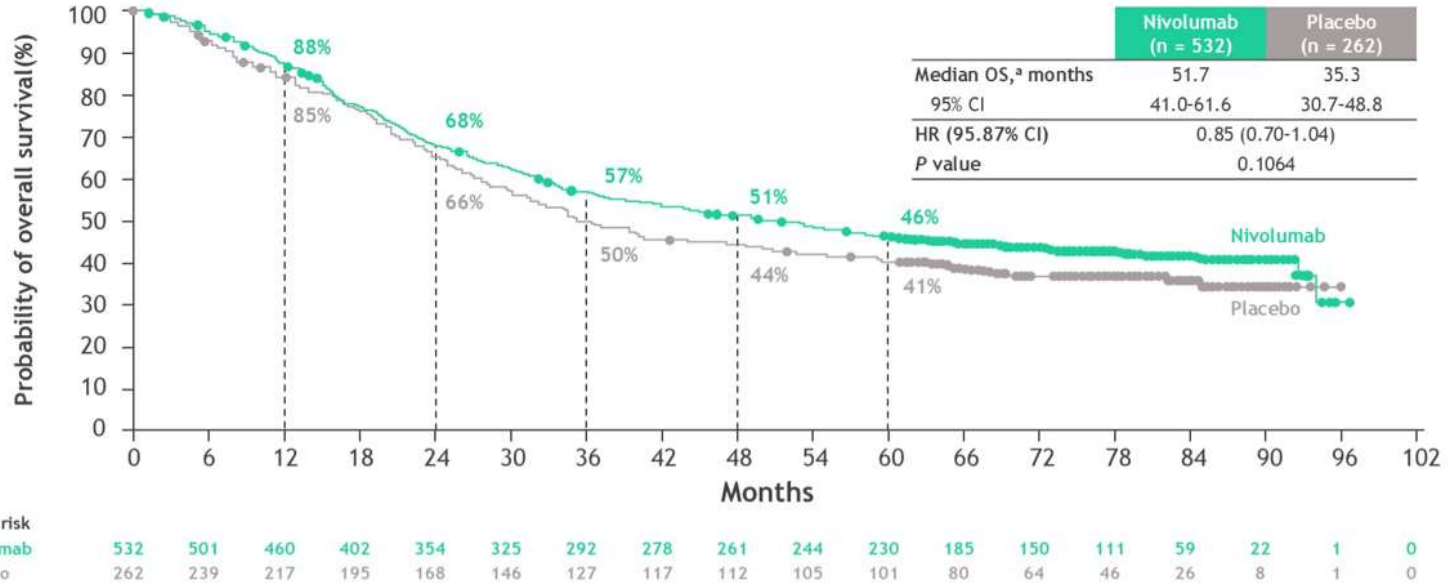
| Subgroup | Median Disease-free Survival, months | | Unstratified Hazard Ratio (95% CI) |
|---|---|---|---|
| | Nivolumab | Placebo | |
| **PD-L1 CPS expression** | | | |
| ≥5 (n = 371) | 29.4 | 10.2 | 0.62 (0.46–0.83) |
| <5 (n = 295) | 16.3 | 11.1 | 0.89 (0.65–1.22) |
| **Radiotherapy dosage** | | | |
| <41.4 Gray (n = 92*) | 19.7 | 13.8 | 0.69 (0.38–1.23) |
| 41.4–50.4 Gray (n = 504) | 24.0 | 11.1 | 0.73 (0.57–0.95) |
| >50.4 Gray (n = 152) | 21.4 | 8.3 | 0.72 (0.46–1.13) |
| Not reported (n = 41) | 14.4 | 6.1 | 0.41 (0.16–1.07) |




Kelly ESMO 2020; Kelly NEJM 2021; Kelly NEJM-supp 2021

# CM577 Final results of OS

## Overall survival




| | Nivolumab (n = 532) | Placebo (n = 262) |
|---|---|---|
| Median OS,[a] months | 51.7 | 35.3 |
| 95% CI | 41.0-61.6 | 30.7-48.8 |
| HR (95.87% CI) | 0.85 (0.70-1.04) | |
| *P* value | 0.1064 | |

| No. at risk | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 532 | 501 | 460 | 402 | 354 | 325 | 292 | 278 | 261 | 244 | 230 | 185 | 150 | 111 | 59 | 22 | 1 | 0 |
| Placebo | 262 | 239 | 217 | 195 | 168 | 146 | 127 | 117 | 112 | 105 | 101 | 80 | 64 | 46 | 26 | 8 | 1 | 0 |

- 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.

# CM577 Final results of OS

CheckMate 577

## Overall survival subgroup analysis

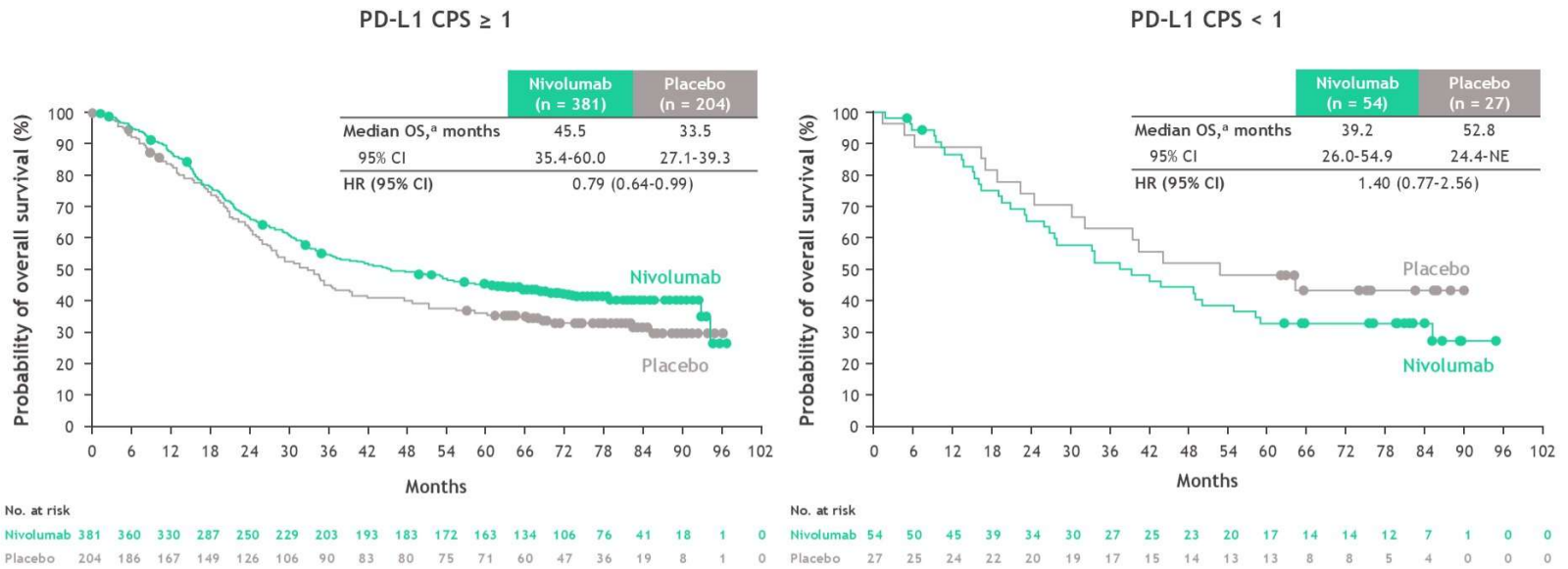
| Category | Subgroup | Median OS, mo | | Unstratified HR (95% CI) |
|---|---|---|---|---|
| | | Nivolumab | Placebo | |
| Overall | N = 794 | 51.7 | 35.3 | 0.85 (0.70-1.03) |
| Age, years | < 65 (n = 507) | 56.4 | 36.6 | 0.83 (0.65-1.06) |
| | ≥ 65 (n = 287) | 39.3 | 35.2 | 0.87 (0.64-1.19) |
| Sex | 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) |


[a]Other/not reported: nivolumab, n = 17; placebo, n = 12. [b]Not reported: nivolumab, n = 2. [c]Other, n = 1. [d]Per case report form. [e]Indeterminate/not evaluable/not reported: nivolumab, n = 68; placebo, n = 27. [f]Indeterminate/not evaluable/not reported: nivolumab, n = 97; placebo, n = 31. [g]Unknown, n = 2.

# CM577 Final results of OS

CheckMate 577

## Overall survival by PD-L1 CPS




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

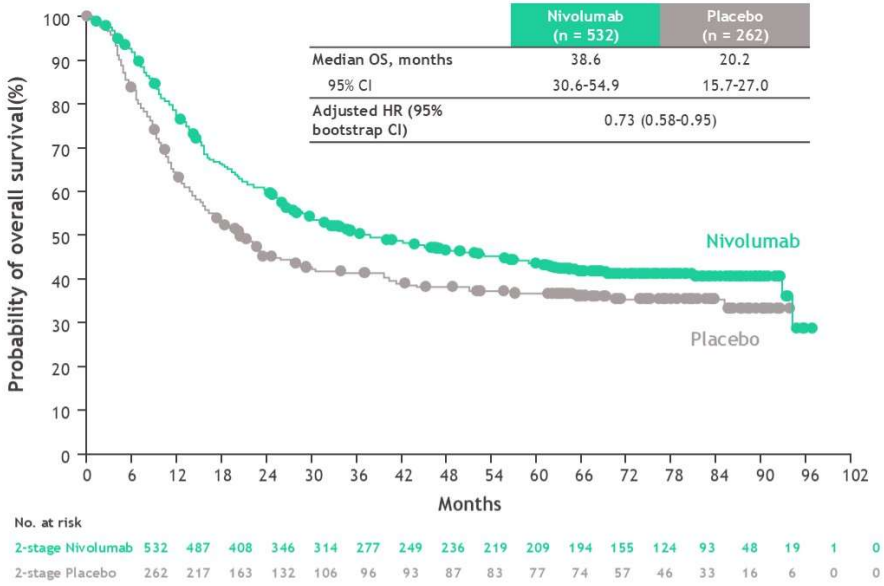
[a]Median (range) follow-up, 78.3 (60.1-96.6) months.

# CM577 Final results of OS

CheckMate 577

## Overall survival adjusted for subsequent therapy

| Subsequent cancer therapy,[a] n (%) | Nivolumab (n = 532) | Placebo (n = 262) |
|---|---|---|
| **Any subsequent therapy** | 245 (46) | 156 (60) |
| **Radiotherapy** | 83 (16) | 68 (26) |
| **Surgery** | 61 (11) | 37 (14) |
| **Systemic anticancer therapy** | 199 (37) | 132 (50) |
| Chemotherapy | 197 (37) | 127 (48) |
| Targeted therapy | 30 (6) | 23 (9) |
| Immunotherapy | 29 (5) | 39 (15) |
| Anti-PD-1 | 27 (5) | 36 (14) |
| Anti-PD-L1 | 1 (<1) | 3 (1) |
| Anti-CTLA4 | 2 (<1) | 1 (<1) |
| BCG vaccine | 1 (<1) | 0 |




- Higher percentage of patients received subsequent systemic therapy in the placebo vs nivolumab group
- Ad hoc analyses using 2-stage method suggest OS benefit with nivolumab vs placebo when adjusting for the confounding effects of subsequent treatments

[a]Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if patient never treated). Patients may have received more than one type of subsequent therapy.

# Neo-AEGIS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

P. van Hagen, M.C.C.M. Hulshof, J.J.B. van Lanschot, E.W. Steyerberg, M.I. van Berge Henegouwen, B.P.L. Wijnhoven, D.J. Richel, G.A.P. Nieuwenhuijzen, G.A.P. Hospers, J.J. Bonenkamp, M.A. Cuesta, R.J.B. Blaisse, O.R.C. Busch, F.J.W. ten Kate, G.-J. Creemers, C.J.A. Punt, J.T.M. Plukker, H.M.W. Verheul, E.J. Spillenaar Bilgen, H. van Dekken, M.J.C. van der Sangen, T. Rozema, K. Biermann, J.C. Beukema, A.H.M. Piet, C.M. van Rij, J.G. Reinders, H.W. Tilanus, and A. van der Gaast, for the CROSS Group*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 6, 2006 VOL. 355 NO. 1

## Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer

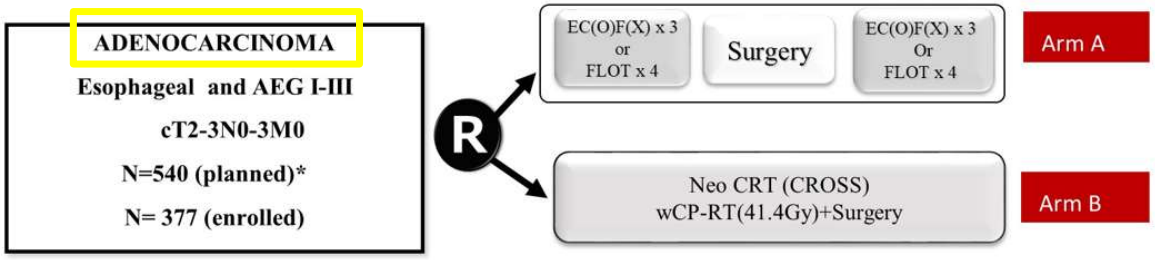
David Cunningham, M.D., William H. Allum, M.D., Sally P. Stenning, M.Sc., Jeremy N. Thompson, M.Chir., Cornelis J.H. Van de Velde, M.D., Ph.D., Marianne Nicolson, M.D., J. Howard Scarffe, M.D., Fiona J. Lofts, Ph.D., Stephen J. Falk, M.D., Timothy J. Iveson, M.D., David B. Smith, M.D., Ruth E. Langley, M.D., Ph.D., Monica Verma, M.Sc., Simon Weeden, M.Sc., and Yu Jo Chua, M.B., B.S., for the MAGIC Trial Participants*

1ary end point: CROSS > MAGIC? (OS)

After FLOT became an option, it was changed to a non-inferiority design

Lowery ASCO GI 2022; Reynolds Lancet Gastroenterol Hepatol 2023

# Neo-AEGIS




*non-inferiority : powered as per first futility analysis (n=71 deaths)

Primary endpoint: Overall survival

Secondary end points: Disease free survival,
Time to treatment failure
Toxicity
Tumor Regression Grade (TRG)
R0 resection
Postoperative complications (ECCG defined, Clavien-Dindo)
Quality of life

**Arm A**: MAGIC (2013-2018) → FLOT or MAGIC (2018-2020)

| | ARM A (Chemo) N = 184 | ARM B (CROSS) N = 178 |
|---|---|---|
| Median (range) age | 64 (35-83) | 64 (45-81) |
| Male | 91.8% | 88.8% |
| MAGIC/FLOT | 157 (85%)/27 (15%) | - |
| cT3 | 84% | 84% |
| cN 1-3 | 60.3% | 56 % |
| *Radical en bloc* Transthoracic Esophagectomy | 75% | 80 % |
| Transhiatal | 1.2% | 4.3% |

Lowery ASCO GI 2022; Reynolds Lancet Gastroenterol Hepatol 2023

# Neo-AEGIS



## Results: Toxicity / AEs Grade 3&4 / Tolerance

| | ARM A (Chemo) | ARM B (CROSS) p | P value |
|---|---|---|---|
| Toxic deaths | 1.6% | 3% | 0.497 |
| Neutropenia | 14.1% | 2.8% | < 0.001 |
| Diarrhea | 10.9% | 0% | < 0.001 |
| Neutropenic Sepsis | 2.2% | 0.6% | 0.215 |
| Vomiting | 7.6% | 2.8% | 0.035 |
| Pulmonary embolism | 5.4% | 5.1% | 0.872 |

## Operative Complications and Severity: No significant differences between treatment arms

| | ARM A (Chemo) N = 162 | ARM B (CROSS) N = 167 |
|---|---|---|
| In hospital mortality | 1.6% | 2.8% p =0.723 |
| Anastomotic Leaks | 11.1% | 11.4% |
| Pneumonia | 19.8% | 15.6% |
| ARDS | 0.6% | 4.2% |
| Respiratory Failure | 7.6% | 8% |
| Venous Thromboembolism | 3.8% | 3% |
| Atrial Fibrillation | 11.1% | 11.4% |
| Clavien-Dindo ≥3<V severity | 23.5% | 22.8% |

Lowery ASCO GI 2022; Reynolds Lancet Gastroenterol Hepatol 2023

# Neo-AEGIS

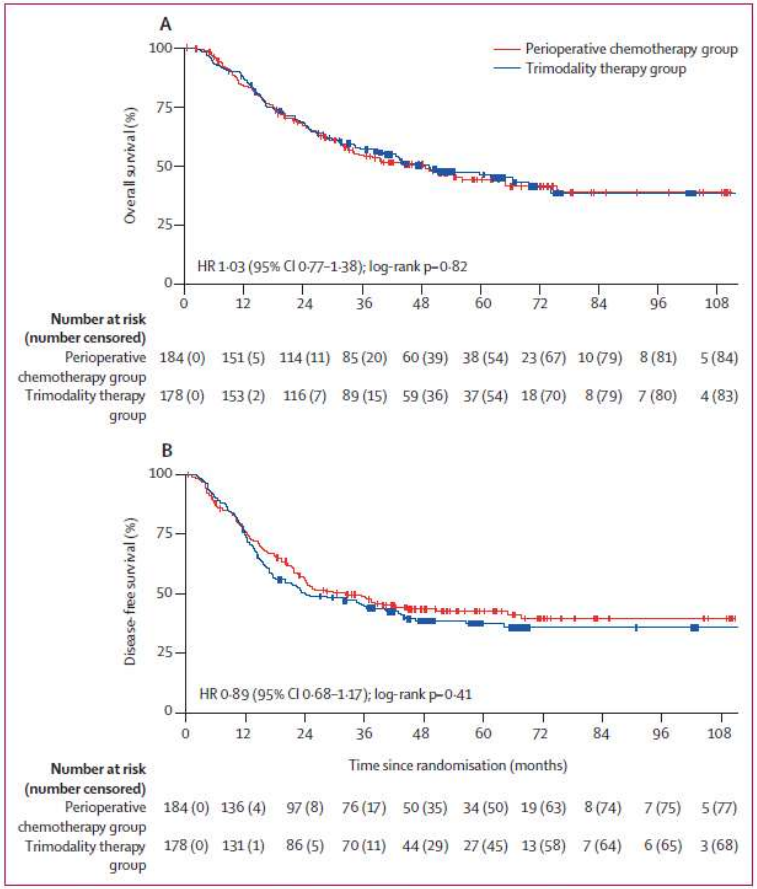


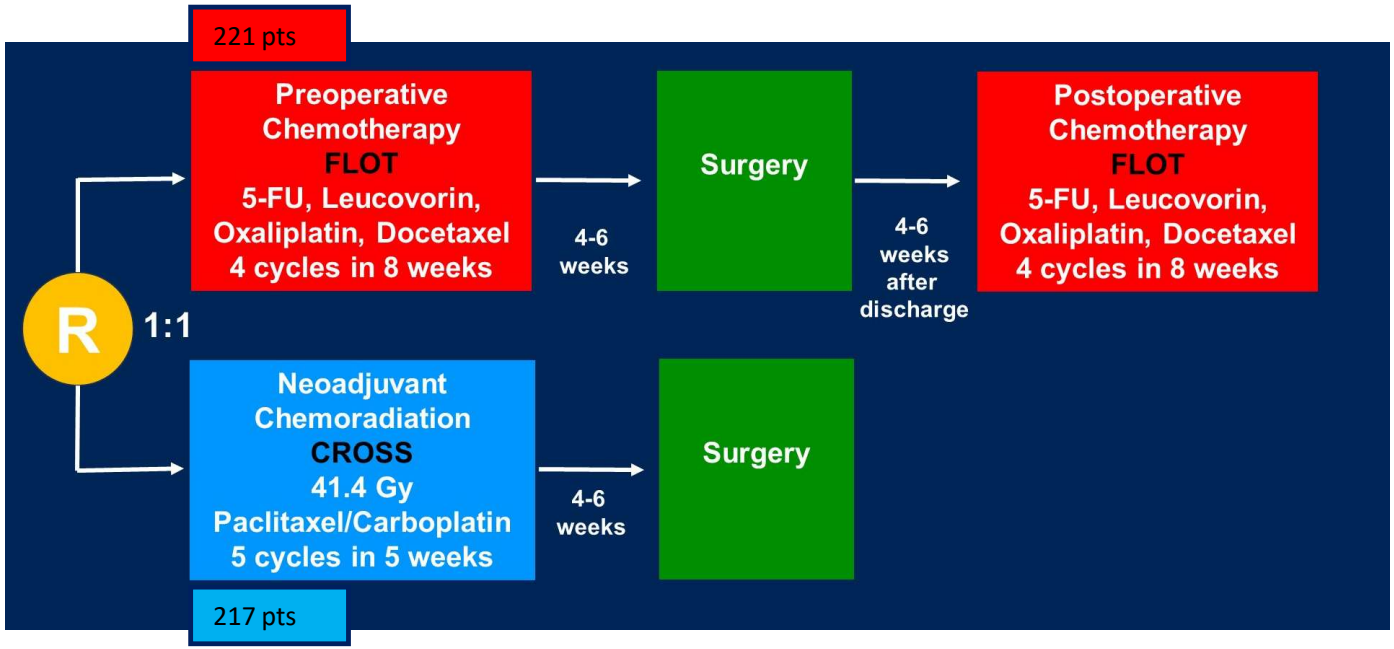

***Figure 2*: Kaplan-Meier estimates of overall survival and disease-free survival in the intention-to-treat population**
(A) Overall survival. (B) Disease-free survival. HR=hazard ratio.

| | Perioperative chemotherapy group (n=162) | Trimodality therapy group (n=167) | p value |
|---|---|---|---|
| Tumour pathology | .. | .. | 0·020 |
| ypT0 | 7 (4%) | 23 (14%) | .. |
| ypT1a | 6 (4%) | 8 (5%) | .. |
| ypT1b | 19 (12%) | 26 (16%) | .. |
| ypT2 | 24 (15%) | 22 (13%) | .. |
| ypT3 | 97 (60%) | 84 (50%) | .. |
| ypT4 | 9 (6%) | 4 (2%) | .. |
| Nodal pathology | .. | .. | 0·0035 |
| ypN0 | 71 (44%) | 100 (60%) | .. |
| ypN1 | 50 (31%) | 35 (21%) | .. |
| ypN2 | 16 (10%) | 21 (13%) | .. |
| ypN3 | 25 (15%) | 11 (7%) | .. |
| Tumour regression grade | .. | .. | <0·0001 |
| 1 | 8 (5%) | 23 (14%) | .. |
| 2 | 11 (7%) | 41 (25%) | .. |
| 3 | 38 (23%) | 53 (32%) | .. |
| 4 | 65 (40%) | 39 (23%) | .. |
| 5 | 35 (22%) | 7 (4%) | .. |
| Not evaluable | 5 (3%) | 4 (2%) | .. |
| Pathological complete response | 7 (4%) | 20 (12%) | 0·012 |
| Circumferential margin R0 | 119/145 (82%) | 131/137 (96%) | 0·0003 |
| Number of nodes analysed | 27 (22–37) | 22 (16–31) | 0·0002 |
| Number of nodes involved | 1 (0–3) | 0 (0–2) | 0·0025 |
| Response to therapy by endoscopy | .. | .. | 0·020 |
| Complete response | 23/130 (18%) | 28/138 (20%) | .. |
| Partial response | 62/130 (48%) | 83/138 (60%) | .. |
| No response | 45/130 (35%) | 27/138 (20%) | .. |
| Site of treatment failure (multiple sites possible per patient) | | | |

Differences in pCR did not correlate with survival

Lowery ASCO GI 2022; Reynolds Lancet Gastroenterol Hepatol 2023

# ESOPEC


221 pts
Preoperative Chemotherapy FLOT 5-FU, Leucovorin, Oxaliplatin, Docetaxel 4 cycles in 8 weeks
4-6 weeks
Surgery
4-6 weeks after discharge
Postoperative Chemotherapy FLOT 5-FU, Leucovorin, Oxaliplatin, Docetaxel 4 cycles in 8 weeks
R
1:1
Neoadjuvant Chemoradiation CROSS 41.4 Gy Paclitaxel/Carboplatin 5 cycles in 5 weeks
4-6 weeks
Surgery
217 pts

# ESOPEC

## Main Eligibility Criteria

8

**Inclusion Criteria**

- Histology: Adenocarcinoma
- Esophageal cancer according UICC (TNM7)[1,*]
- Clinical stage cT1N+ or cT2-4a, cN0/+, cM0

**Exclusion Criteria**

- Squamous or other non-adenocarcinoma histology
- Gastric cancer
- Clinical Stage cT1cN0 and cT4b
- Metastatic disease

*Tumors of the esophagus and tumors of which the epicenter is within 5 cm of the esophagogastric junction and also extend into the esophagus.

## Key Trial Endpoints

9

**Primary Endpoint**

- Overall survival (OS)

**Secondary Endpoints**

- Progression free survival (PFS)
- Postoperative pathological stage
- Postoperative complications
- Adverse events
- Recurrence free survival
- Site of tumor recurrence
- Quality of life

# ESOPEC

Table 1. **Baseline Demographic and Clinical Characteristics in the Intention-to-Treat Population.***

| Characteristic | FLOT (N=221) | Preoperative Chemoradiotherapy (N=217) |
|---|---|---|
| Median age (range) — yr | 63 (37–86) | 63 (30–80) |
| Sex — no. (%) | | |
| Male | 197 (89.1) | 194 (89.4) |
| Female | 24 (10.9) | 23 (10.6) |
| ECOG performance-status score — no. (%)† | | |
| 0 | 162 (73.3) | 156 (71.9) |
| 1 | 54 (24.3) | 59 (27.2) |
| 2 | 5 (2.3) | 2 (0.9) |
| Clinical tumor stage — no./total no. (%)‡ | | |
| cT1 | 3/220 (1.4) | 4/216 (1.9) |
| cT2 | 40/220 (18.2) | 33/216 (15.3) |
| cT3 | 155/220 (70.5) | 167/216 (77.3) |
| cT4 | 19/220 (8.6) | 10/216 (4.6) |
| cTx | 3/220 (1.4) | 2/216 (0.9) |
| Clinical lymph-node stage — no. (%)§ | | |
| cN0 | 49 (22.2) | 40 (18.4) |
| cN+ | 172 (77.8) | 177 (81.6) |
| 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) |

# ESOPEC

## Treatment Exposure



| | FLOT Group | CROSS Group |
|---|---|---|
| N | 221 | 217 |
| **Started neoadjuvant treatment** (PP population*) | 93.7 % | 90.3 % |
| Completed neoadjuvant treatment | 87.3 % | 67.7 % |
| Received neoadjuvant treatment plus surgery | 86.0 % | 82.9 % |
| Received adjuvant treatment | 63.3 % | |
| Completed adjuvant treatment | 52.5 % | |

*Per protocol population according to Clinical Trial Protocol and Statistical Analysis Plan

# ESOPEC

XXXIII SIMPOSIO INTERNACIONAL INTERNATIONAL SYMPOSIUM
11 - 12 DE DICIEMBRE DE 2025
OVIEDO

**Table 3. Adverse Events in the Safety Population.***

| Adverse Event | FLOT (N=207) | | Preoperative Chemoradiotherapy (N=196) | |
|---|---|---|---|---|
| | Serious | Grade ≥3 | Serious | Grade ≥3 |
| | *number of patients (percent)* | | | |
| Any event | 98 (47.3) | 120 (58.0) | 82 (41.8) | 98 (50.0) |
| Pneumonia | 11 (5.3) | 12 (5.8) | 17 (8.7) | 18 (9.2) |
| Neutropenia | 1 (0.5) | 41 (19.8) | 0 | 4 (2.0) |
| Leukopenia | 0 | 13 (6.3) | 2 (1.0) | 19 (9.7) |
| Diarrhea | 9 (4.3) | 14 (6.8) | 1 (0.5) | 0 |
| Vomiting | 10 (4.8) | 7 (3.4) | 2 (1.0) | 1 (0.5) |
| Anemia | 2 (1.0) | 9 (4.3) | 2 (1.0) | 5 (2.6) |
| Pleural effusion | 1 (0.5) | 4 (1.9) | 6 (3.1) | 6 (3.1) |
| Pulmonary embolism | 5 (2.4) | 8 (3.9) | 2 (1.0) | 2 (1.0) |
| Infection | 9 (4.3) | 5 (2.4) | 1 (0.5) | 2 (1.0) |
| Atrial fibrillation | 1 (0.5) | 4 (1.9) | 4 (2.0) | 5 (2.6) |
| Dysphagia | 2 (1.0) | 2 (1.0) | 5 (2.6) | 4 (2.0) |
| Sepsis | 2 (1.0) | 2 (1.0) | 4 (2.0) | 5 (2.6) |
| Device-related infection | 5 (2.4) | 3 (1.4) | 3 (1.5) | 2 (1.0) |
| Dehydration | 6 (2.9) | 5 (2.4) | 1 (0.5) | 1 (0.5) |
| Nausea | 4 (1.9) | 8 (3.9) | 1 (0.5) | 0 |
| Acute kidney injury | 6 (2.9) | 3 (1.4) | 2 (1.0) | 0 |
| Impaired gastric emptying | 5 (2.4) | 3 (1.4) | 0 | 1 (0.5) |
| Thrombocytopenia | 0 | 2 (1.0) | 1 (0.5) | 5 (2.6) |
| Chest pain | 0 | 0 | 5 (2.6) | 2 (1.0) |
| Hypotension | 1 (0.5) | 1 (0.5) | 1 (0.5) | 4 (2.0) |
| Polyneuropathy | 0 | 6 (2.9) | 0 | 0 |

**Table 4. Safety in the Surgery Population.**

| Variable | FLOT (N=193) | Preoperative Chemoradiotherapy (N=181) |
|---|---|---|
| | *no. of patients (%)* | |
| 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) |
| Surgical-site complication after surgery | | |
| Anastomotic leakage | 22 (11.4) | 25 (13.8) |
| Intrathoracic fluid collection or abscess resulting in invasive treatment | 28 (14.5) | 26 (14.4) |
| Intraabdominal fluid collection or abscess resulting in invasive treatment | 2 (1.0) | 7 (3.9) |
| Surgical-site infection | 9 (4.7) | 6 (3.3) |
| Superficial incisional infection | 3 (1.6) | 2 (1.1) |
| Deep incisional infection | 3 (1.6) | 2 (1.1) |
| Organ or organ-space infection | 4 (2.1) | 4 (2.2) |
| Non–surgical-site complication after surgery | | |
| Pneumonia | 37 (19.2) | 29 (16.0) |
| Respiratory failure resulting in invasive mechanical ventilation | 8 (4.1) | 9 (5.0) |
| Pulmonary embolism | 6 (3.1) | 3 (1.7) |
| Acute respiratory distress syndrome | 6 (3.1) | 1 (0.6) |
| Major bronchial sputum obstruction with atelectasis | 1 (0.5) | 3 (1.7) |
| Deep venous thrombosis | 0 | 1 (0.6) |
| Death after surgery† | | |
| At 30 days | 2 (1.0) | 3 (1.7) |
| At 90 days | 6 (3.1) | 10 (5.6) |

**AEs G≥3**
58,0% (FLOT) vs. 50,0% (CROSS)

**SAES**
47,3% (FLOT) vs. 41,8% (CROSS)

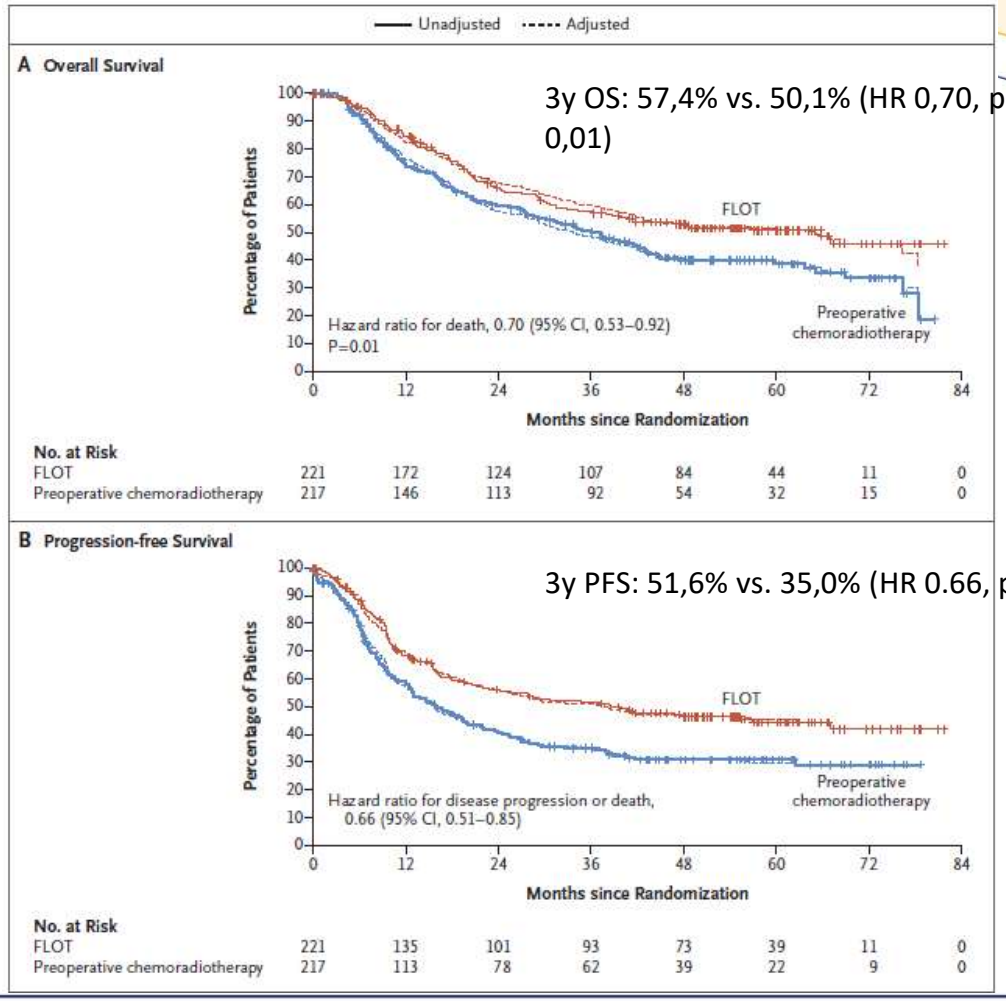
**Mortality at 90d after Surgery**
3,1% (FLOT) vs. 5,6% (CROSS)

Hoeppner ASCO 2024; Hoeppner NEJM 2025

# ESOPEC

**Table 2. Surgical and Pathological Findings in the Surgery Population.***

| Characteristic | FLOT (N=193) | Preoperative Chemoradiotherapy (N=181) |
|---|---|---|
| Median time from end of preoperative treatment to surgery (range) — days† | 37 (18–71) | 41 (9–79) |
| Resection status — no. (%) | | |
| No tumor resection | 1 (0.5) | 2 (1.1) |
| R0: no tumor cells in margins | 182 (94.3) | 172 (95.0) |
| R1: tumor cells visible in margins on microscopy | 10 (5.2) | 7 (3.9) |
| Resection type — no./total no. (%)‡ | | |
| Transthoracic esophagectomy | 153/192 (79.7) | 153/179 (85.5) |
| Extended gastrectomy | 33/192 (17.2) | 20/179 (11.2) |
| Esophagogastrectomy | 6/192 (3.1) | 6/179 (3.4) |
| Regional lymphadenectomy — no./total no. (%)‡ | | |
| Yes | 191/192 (99.5) | 179/179 (100) |
| No | 1/192 (0.5) | 0 |
| Pathological tumor stage after surgery — no./total no. (%)§ | | |
| ypT0 | 35/192 (18.2) | 23/179 (12.8) |
| ypTis | 1/192 (0.5) | 1/179 (0.6) |
| ypT1 | 28/192 (14.6) | 29/179 (16.2) |
| ypT2 | 30/192 (15.6) | 32/179 (17.9) |
| ypT3 | 93/192 (48.4) | 91/179 (50.8) |
| ypT4 | 5/192 (2.6) | 2/179 (1.1) |
| ypTx | 0 | 1/179 (0.6) |
| Pathological lymph-node stage after surgery — no./total no. (%)¶ | | |
| ypN0 | 97/192 (50.5) | 98/179 (54.7) |
| ypN+ | 95/192 (49.5) | 81/179 (45.3) |
| Pathological complete response — no./total no. (%)‖ | 32/192 (16.7) | 18/179 (10.1) |
| 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) |



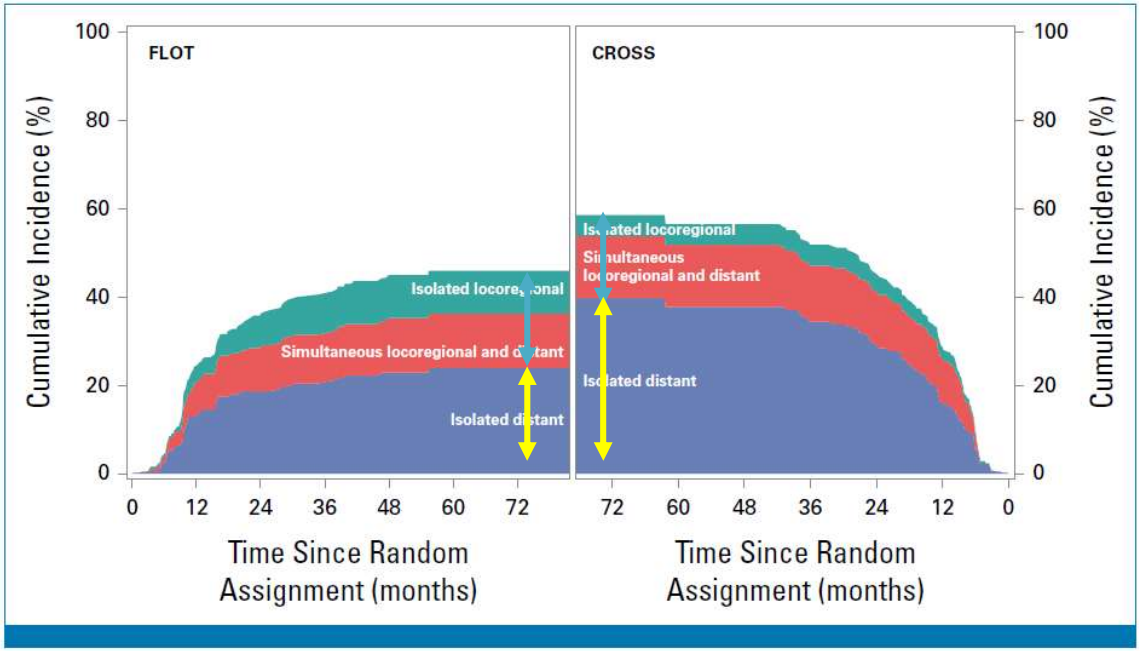

3y OS: 57,4% vs. 50,1% (HR 0,70, p 0,01)

3y PFS: 51,6% vs. 35,0% (HR 0.66, p 0.01)

Hoeppner ASCO 2024; Hoeppner NEJM 2025

# ESOPEC: Recurrence Patterns

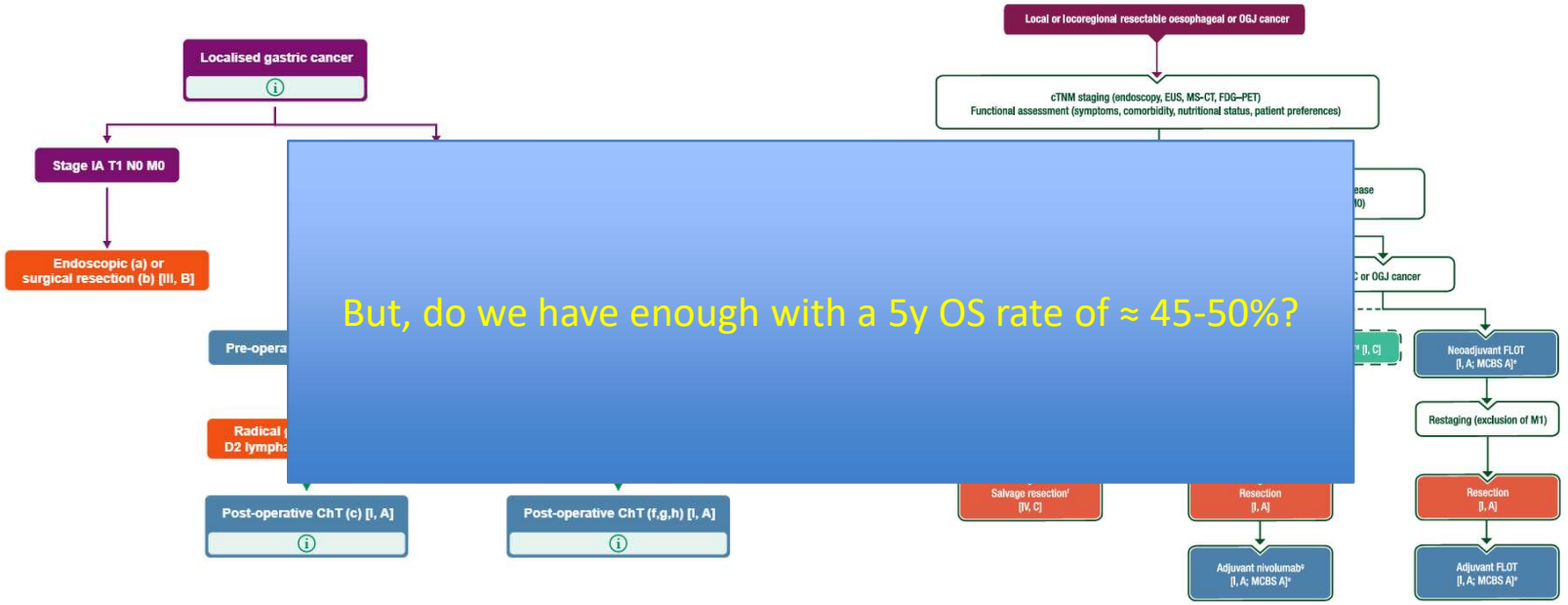
- FLOT improved survival through better systemic tumor control:
  - Reduction in distant tumor recurrences
  - Similar locoregional efficacy




Hoeppner J Clin Oncol 2025

# Clinical Guidelines

- **FLOT is the SoC for all GEA** (FLOT4 & ESOPEC)

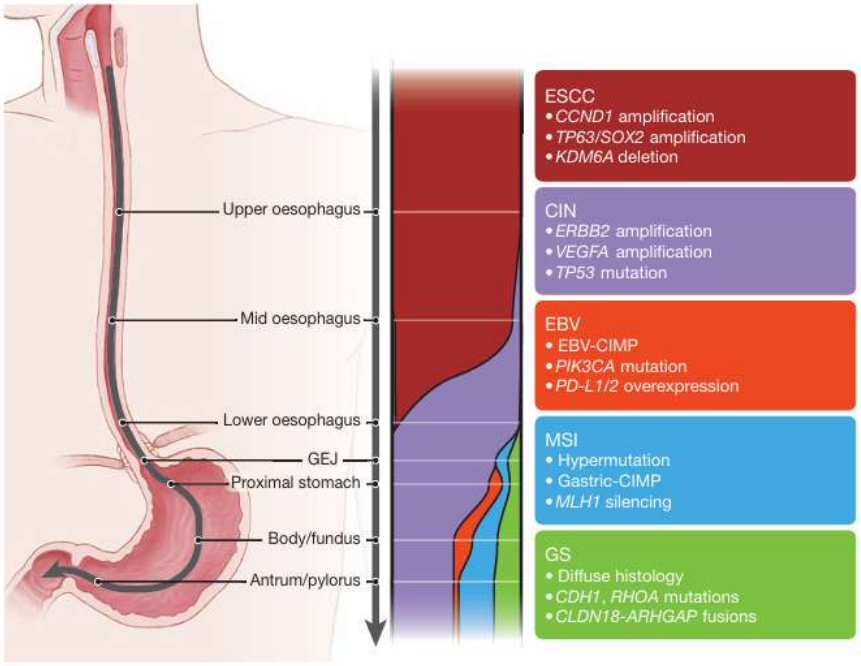


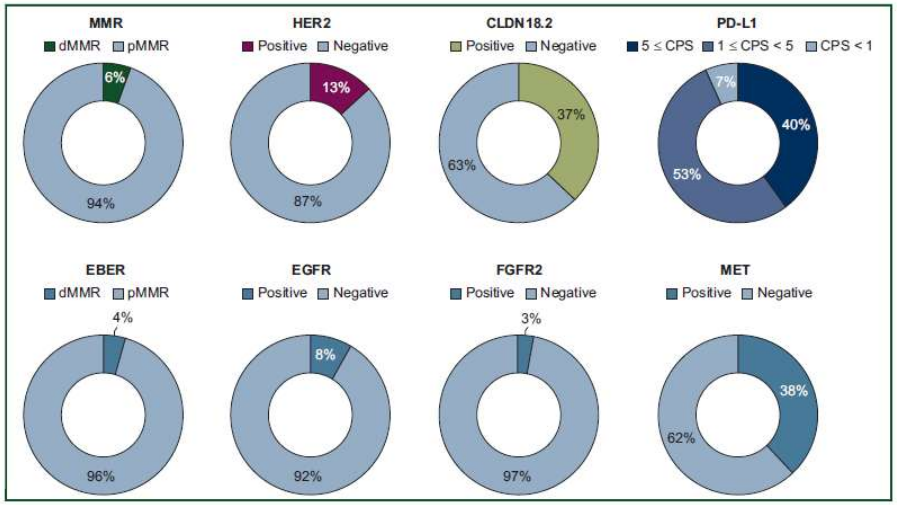

F. Lordick et al; Ann Oncol 2022; e-update v1.4 September 2024
R. L. Obermannová & T. Leong; ESMO Open 2025



# MOLECULAR PECULIARITIES

# Molecular peculiarities



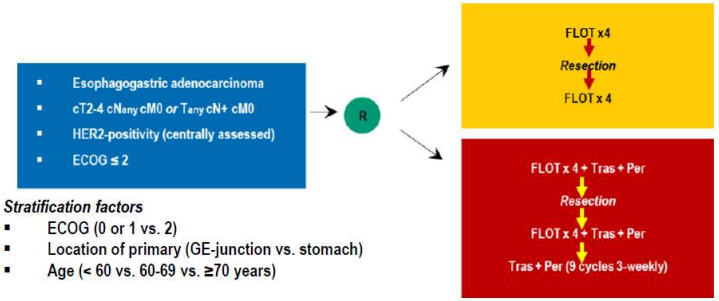




TCGA Nature 2017; Okazaki, ESMO GI Oncol 2024

# HER2-blockade

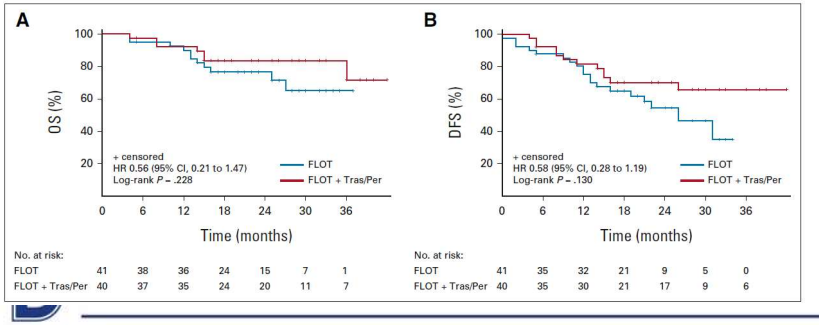
## PETRARCA Trial

Randomized, multicenter, investigator-initiated, phase II/III trial




- Primary endpoint phase II portion: pCR, n=100 pts with exploratory statistics (standard arm 0.120 and experimental arm 0.250)
- Primary endpoint phase III portion: DFS, n=404
- Trial closed during phase II after results from JACOB trial became available

pCR: 12% (FLOT) vs. **35% (FLOT+T+P)**

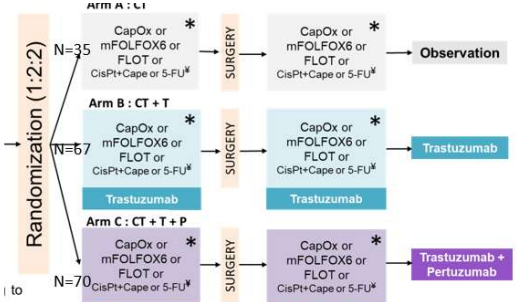



## INNOVATION Trial

Randomized, multicenter, ph3 trial

**KEY EGIBILITY CRITERIA**

- HER-2 positive[a] gastric cancer and esophagogastric junction cancer
- Amenable to gastrectomy/oesophagectomy with curative intent as confirmed by a multidisciplinary team discussion
- UICC (Edition 7th) tumor stage Ib to III, as defined by CT scan and/or MRI
- WHO PS 0 – 1

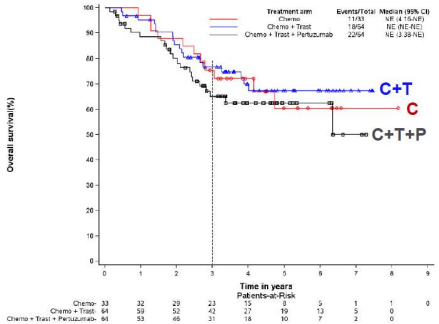



pCR: 12% (CT) vs. **37% (CT + T)** vs. 26.4% (CT + T + P)

## OS – Results in the Overall Population

| Arm (N) | Observed Events | Median (95% CI) (Years) | % at 3 Year(s) (95% CI) | Hazard Ratio (95% CI) |
|---|---|---|---|---|
| CT (N=33) | 11 | Not reached | 75.6 (57.1, 87.0) | 1.00 |
| CT+T (N=64) | 18 | Not reached | 76.9 (64.1, 85.6) | 0.89 (0.42, 1.88) |
| CT+T+P (N=64) | 22 | Not reached | 65.2 (51.3, 76.1) | 1.29 (0.62, 2.66) |

| Cause of death | CT (N=11) | CT+T (N=18) | CT+T+P (N=22) | Total (N=51) |
|---|---|---|---|---|
| Progression of disease (PD) | 8 (72.7) | 13 (72.2) | 17 (77.3) | 38 (74.5) |
| Toxicity | 0 (0.0) | 2 (11.1) | 2 (9.1) | 4 (7.8) |
| Cardiovascular disease (not due to tox. or PD) | 1 (9.1) | 0 (0.0) | 0 (0.0) | 1 (2.0) |
| Other | 1 (9.1) | 3 (16.7) | 2 (9.1) | 6 (11.8) |
| Missing | 1 (9.1) | 0 (0.0) | 1 (4.5) | 2 (3.9) |



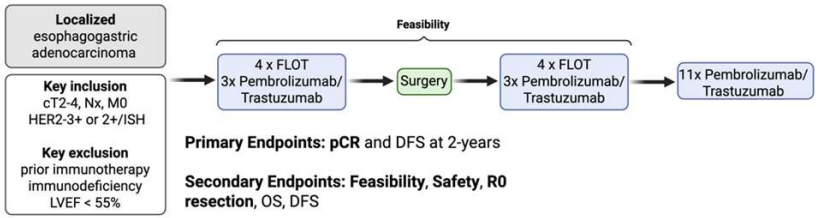



Hofheinz et al; J Clin Oncol 2022
Wagner et al; ASCO GI 2025

# HER2-blockade

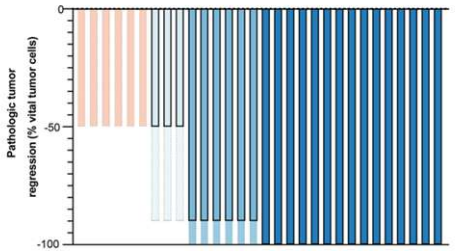
## PHERFLOT/IKF-053 (AIO STO 0321)

### Trial overview




### Pathological response

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




| | 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% |

### Safety

**Grade ≥3 AEs in >10% of patients**

| NCI CTC Term | Grade1 | Grade2 | Grade3 | Grade4 | Grade5 | Total |
|---|---|---|---|---|---|---|
| Diarrhea | 5 (16.1%) | 9 (29.0%) | 12 (38.7%) | | | 26 (83.9%) |
| Weight loss | 3 (9.7%) | 10 (32.3%) | 5 (16.1%) | | | 18 (58.1%) |
| White blood cell decreased | 5 (16.1%) | 6 (19.4%) | 4 (12.9%) | | | 15 (48.4%) |
| Neutrophil count decreased | 1 (3.2%) | 3 (9.7%) | 5 (16.1%) | 3 (9.7%) | | 12 (38.7%) |
| Anemia | 2 (6.5%) | 3 (9.7%) | 4 (12.9%) | | | 9 (29.0%) |
| Sepsis | | | 4 (12.9%) | 1 (3.2%) | 1 (3.2%) | 6 (19.4%) |

| Surgical Morbidity | PHERFLOT | FLOT4 |
|---|---|---|
| Re-operation | **8 (26.7%)** | **34 (10%)** |
| Time in hospital (median) | 14 days | 15 days |
| 30-day postoperative mortality | 0 | 2% |

Tintelnot ESMO 2025; Stein Nat Med 2025

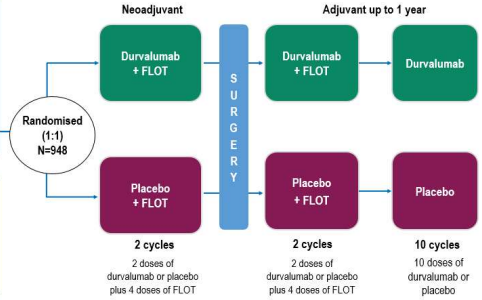
# Immunotherapy

## MATTERHORN study design[1,2]

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

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

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



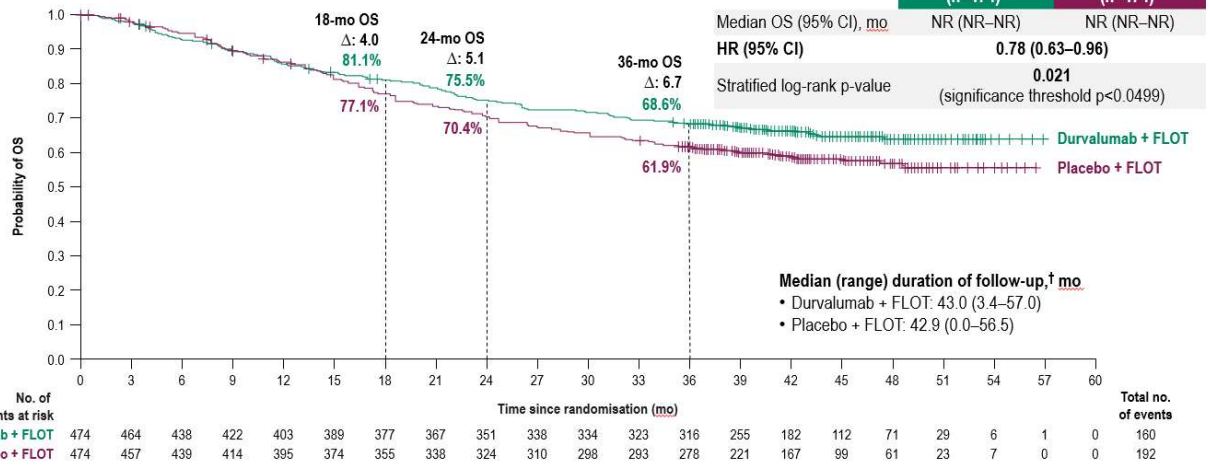

**Primary endpoint:**
- EFS

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

## 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 |

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

Tabernero ESMO 2025; Janjijian NEJM 2025

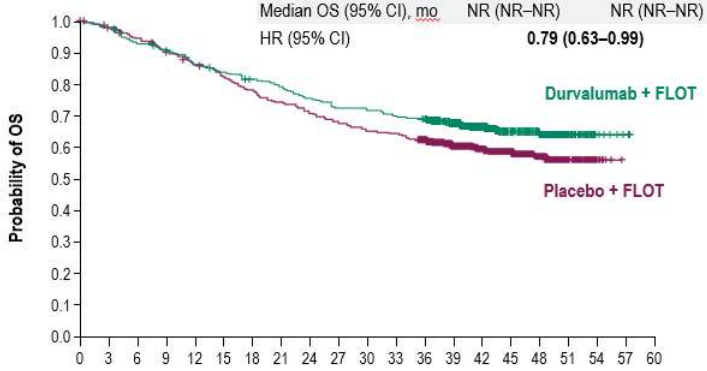
# Immunotherapy

## OS by PD-L1 status

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

**PD-L1 TAP ≥1%***

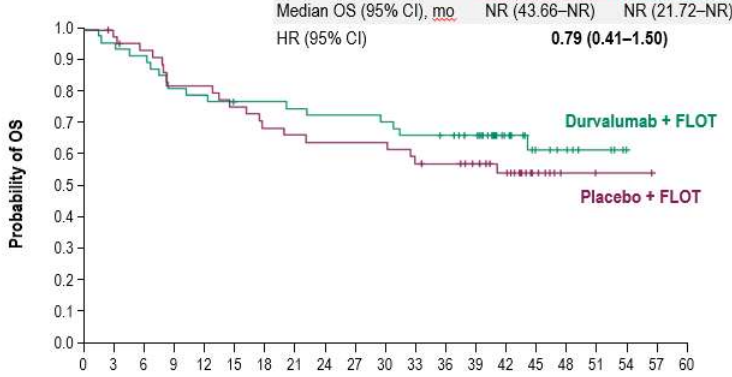
| | Durvalumab + FLOT (n=426) | Placebo + FLOT (n=427) |
|---|---|---|
| Median OS (95% CI), mo | NR (NR–NR) | NR (NR–NR) |
| HR (95% CI) | 0.79 (0.63–0.99) | |




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

**PD-L1 TAP <1%***

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




| No. of participants at risk | | | | | | | | | | | | | | | | | | | | | | Total no. of events |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Durvalumab + FLOT | 48 | 46 | 44 | 39 | 38 | 36 | 36 | 35 | 34 | 34 | 33 | 31 | 30 | 26 | 17 | 11 | 7 | 4 | 0 | 0 | 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 |

*Measured by immunohistochemistry using VENTANA PD-L1 (SP263) Companion Diagnostic Assay (Roche Diagnostics; investigational use only) and recorded at randomisation on the Interactive Response Technology System, Randomisation and Trial Supply Management, Electronic Case Report Form or from external vendor data from samples collected on or before randomisation. Participants provided a tumour tissue sample at screening to determine PD-L1 status using the TAP scoring method.
Data cut-off: 01 September 2025. The HR and its CI were estimated from a Cox proportional hazards model. The CI for the HR was calculated using a profile likelihood approach.
CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; HR, hazard ratio; NR, not reached; OS, overall survival; PD-L1, programmed cell death ligand-1; TAP, Tumour Area Positivity.

Tabernero ESMO 2025; Janjijian NEJM 2025

# Immunotherapy in MSI-H

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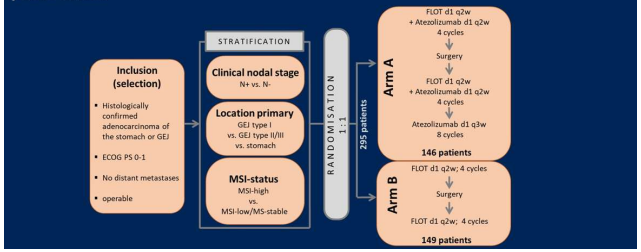
## DANTE (Ph 2)

**DANTE is an investigator-initiated phase-II trial with the potential to transition into a phase-III trial**




**Pathological response (local vs. central assessment)**

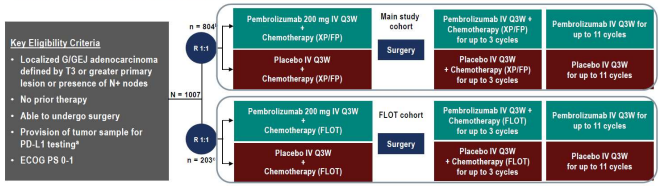
| Pathological Regression FLOT + Atezolizumab (arm A) vs. FLOT (arm B) | Local assessment TRG1a[2] A | Local assessment TRG1a[2] B | Local assessment TRG1a/b[3] A | Local assessment TRG1a/b[3] B | Central assessment[1] TRG1a[2] A | Central assessment[1] TRG1a[2] B | Central assessment[1] TRG1a/b[3] A | Central assessment[1] TRG1a/b[3] B |
|---|---|---|---|---|---|---|---|---|
| All patients (N= 295; 146\|149) | 35 (24%) | 23 (15%) | 71 (49%) | 58 (39%) | 37 (25%) | 36 (24%) | 72 (49%) | 66 (44%) |
| PD-L1 CPS ≥1 (N=170; 82\|88) | 20 (24%) | 13 (15%) | 42 (51%) | 40 (46%) | 21 (26%) | 20 (23%) | 43 (52%) | 41 (47%) |
| PD-L1 CPS ≥5 (N=81; 40\|41) | 11 (28%) | 8 (20%) | 22 (55%) | 18 (44%) | 13 (33%) | 9 (22%) | 21 (53%) | 19 (46%) |
| PD-L1 CPS ≥10 (N=53; 27\|26) | 9 (33%) | 3 (12%) | 18 (67%) | 10 (39%) | 11 (41%) | 5 (19%) | 19 (70%) | 13 (50%) |
| MSI high (N=23; 8\|15) | 5 (63%) | 4 (27%) | 6 (75%) | 7 (47%) | 5 (63%) | 4 (27%) | 6 (75%) | 7 (47%) |

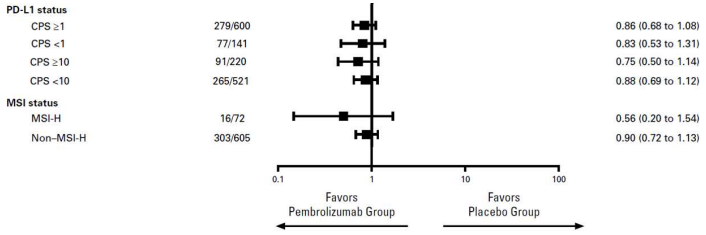
[1]central assessment by one pathologist based on a representative tumor sample
[2]pathological complete regression acc. to Becker
[3]pathological subtotal regression acc. to Becker

## KEYNOTE-585 (Ph 3)

**KEYNOTE-585 STUDY DESIGN**

Randomized, Double-Blind, Phase 3 Trial of Neoadjuvant and Adjuvant Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy in G/GEJ Adenocarcinoma

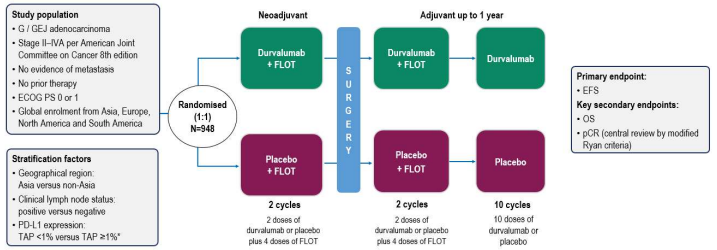


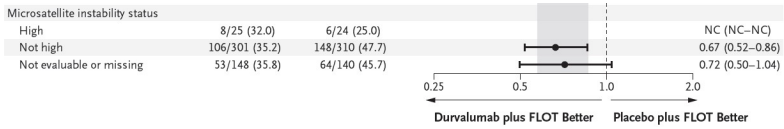




## MATTERHORN (Ph 3)

**MATTERHORN study design[1,2]**

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




Al Batran ASCO 2022, Lorenzen JCO 2023
Shitara ESMO 2023; Shitara Lancet Oncol 2023; Shitara ESMO GI 2024; Shitara NEJM 2024
Tabernero ESMO 2025; Janjijian NEJM 2025

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**GERCOR NEONIPIGA**

- 32 pts
- Neoadjuvant NIVO 240 q2w x6 & IPI 1mg/kg q6w x2 → Surgery → NIVO 480 q4w x9
- 29 pts underwent surgery
  - pCR: 17 (58.6%)
- 3 did not have surgery
  - Endoscopic complete response

**INFINITY**

- 15 pts
- Neoadjuvant TREME 300mg & DURVA 1500mg q4w x3 → Surgery → NIVO 480 q4w x9
- Among evaluable patients, 60% of pCR
- One of the non-responders had an heterogeneous pMMR/dMMR status at surgery



André J Clin Oncol 2022; Pietrantonio ASCO GI 2023

# Immunotherapy in MSI-H

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Original Reports | Gastrointestinal Cancer

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## Neoadjuvant CTLA-4/PD-(L)1 Blockade Versus Surgery +/− Chemotherapy in Deficient Mismatch Repair/Microsatellite Instability–High Resectable Gastroesophageal Adenocarcinoma: Individual Patient Data Pooled Analysis

Alessandra Raimondi, MD[1]; Gabriele Tinè, PhD[2]; Alexej Ballhausen, MD[3]; Sara Lonardi, MD[4]; David Tougeron, MD[5]; Gianmarco Ricagno, MD[4,6]; Floriana Nappo, MD[4]; Ferdinando De Vita, MD[7]; Matthew Nankivell, MD[8]; David Cunningham, MD[9]; Jeeyun Lee, MD[10]; Won Ki Kang, MD[10]; Jae-Ho Cheong, MD[11]; Yoon Young Choi, MD[12]; Giovanni Randon, MD[1]; Michele Prisciandaro, MD[1]; Chiara C. Pircher, MD[1]; Paolo Manca, MD[1]; Margherita Ambrosini, MD[1]; Roberta Fazio, MD[1]; Francesca Bergamo, MD[4]; Guillaume Piessen, MD[13]; Elizabeth C. Smyth, MD[14]; Dominik Paul Modest, MD[3]; Rosalba Miceli, PhD[2]; Thierry André, MD[15]; and Filippo Pietrantonio, MD[1]

DOI https://doi.org/10.1200/JCO-25-00447

Original Reports | Precision Medicine

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## Immune Checkpoint Inhibitors for Mismatch Repair–Deficient Gastroesophageal Adenocarcinoma: Outcomes and Feasibility of Nonoperative Management at Mayo Clinic

Oudai Sahwan, MBBS[1]; Fares Jamal, MD[1]; Rish Pai, MD[2]; Cody Eslinger, MD[1]; Shaylene McCue, MS[3]; Mitesh Borad, MD[1]; Mojun Zhu, MD[4]; Priya Pai, MBBS[5]; Hao Xie, MD, PhD[4]; Robert McWilliams, MD[4]; Nguyen Tran, MD[4]; Travis E. Grotz, MD[6]; Fang-Shu Ou, PhD[3]; Nabil Wasif, MD[7]; Jason Starr, DO[8]; Tanios Bekaii-Saab, MD[1]; Christina Wu, MD[1]; Harry Yoon, MD[4]; Daniel Ahn, DO[1]; and Mohamad Bassam Sonbol, MD[1]

Multiple data supporting ICIs in the neoadjuvant setting of MSI-H GEA tumors, with potential organ-preservation strategies

Raimondi J Clin Oncol 2025; Sahwan JCO Prec Oncol 2025



# CONCLUSIONS



# Conclusions

- Esophageal adenocarcinoma (EAC) should be considered a same entity together with G/GEJ adenocarcinoma → GEA
  - Albeit recognizing molecular heterogeneity
- FLOT4 is the current SoC for GEA, with two specific studies supporting this statement in EAC (NEO-AEGIS and ESOPEC)
- But still, the estimated 5y OS remains poor (≈ 45-50%), with stresses a need for innovative strategies including biomarkers, risk stratification tools and adaptive treatment designs



# Conclusions

- Biomarkers: HER2+ve and MSI-H tumors would be better approached with targeted agents
- Better assessment procedures: Potential value of the ctDNA and PET/CT FAPI imaging
- Adaptive treatment designs: needed in those cases with worse pathological response/regression grade

ARTICLE OPEN

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Clinical Studies

# Does perioperative FLOT increase cure rates in resectable esophageal adenocarcinoma? A mixture cure model analysis

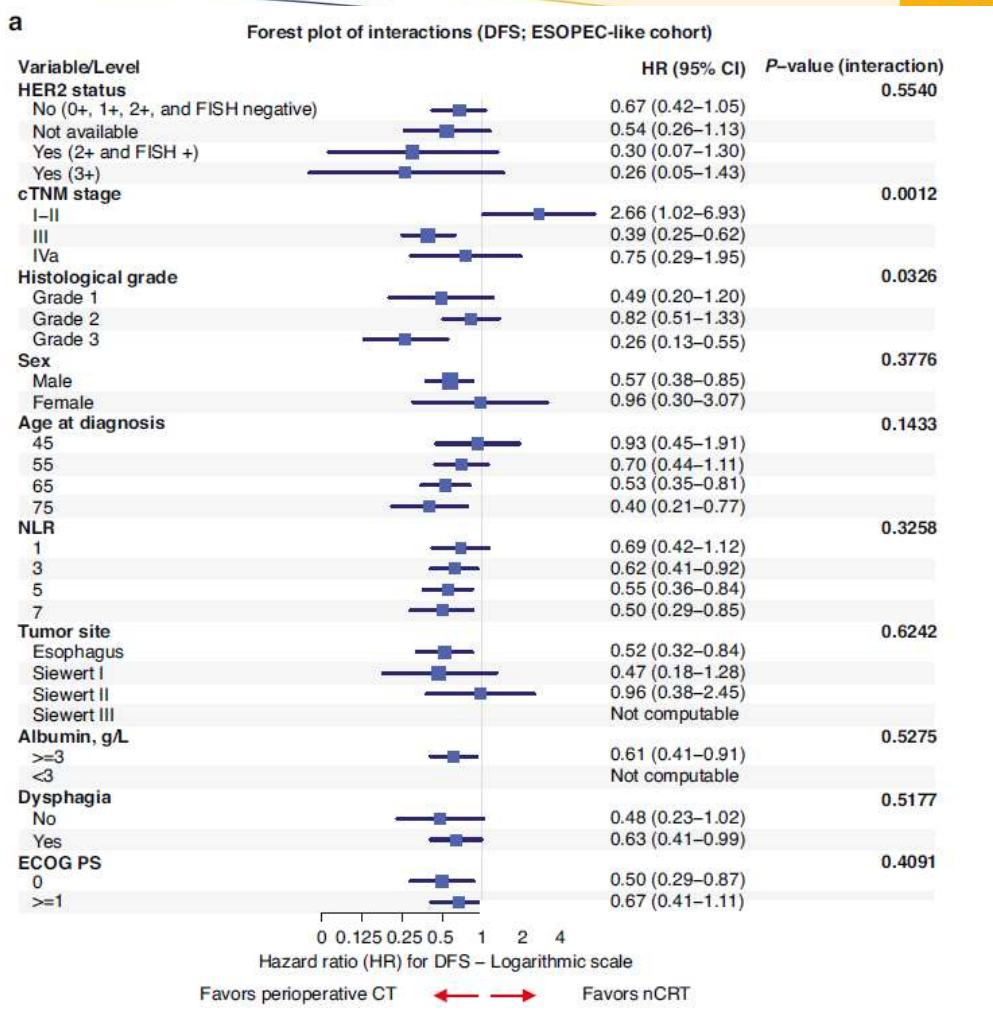
Lucía Mateos[1,29], Paula Jiménez-Fonseca[1,29], Javier Gallego[3], Arturo Lecumberri[4], Ana Custodio[5], Eva Martínez de Castro[6], Raquel Hernández San Gil[7], Ana Fernández Montes[8], María Luisa Limón[9], Rosario Vidal-Tocino[10], Juana María Cano[11], Javier López Robles[12], Mireia Gil[13], Daniel Acosta Eyzaguirre[14], Gema Marín Zafra[15], Antonio José Mérida-García[16], Alejandro Francisco Fernández[17], Paula Ribera Fernández[18], Cinta Hierro[19], María Carmen Riesco[20], Montse García Araque[21], Maribel Ruiz Martín[22], Paola Pimentel[23], Laura Visa[24], Paula Cerdá[25], Mónica Granja[26], Ana Belén Rupérez Blanco[27], Lourdes Gutiérrez[28] and Alberto Carmona-Bayonas[12]✉



## AGAMENON-SEOM registry

- Patients treated with FLOT associate with higher cure rates than those treated with CROSS, mostly in selected high-risk subgroups

cT2 “infradiagnosticado” en ≈ 45% de pacientes



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