Where Science Becomes Hope

CHOICE OF SYSTEMIC THERAPY AFTER DURVALUMAB + FLOT FOR GASTROESOPHAGEAL CANCER

Position: VEGF + Chemotherapy

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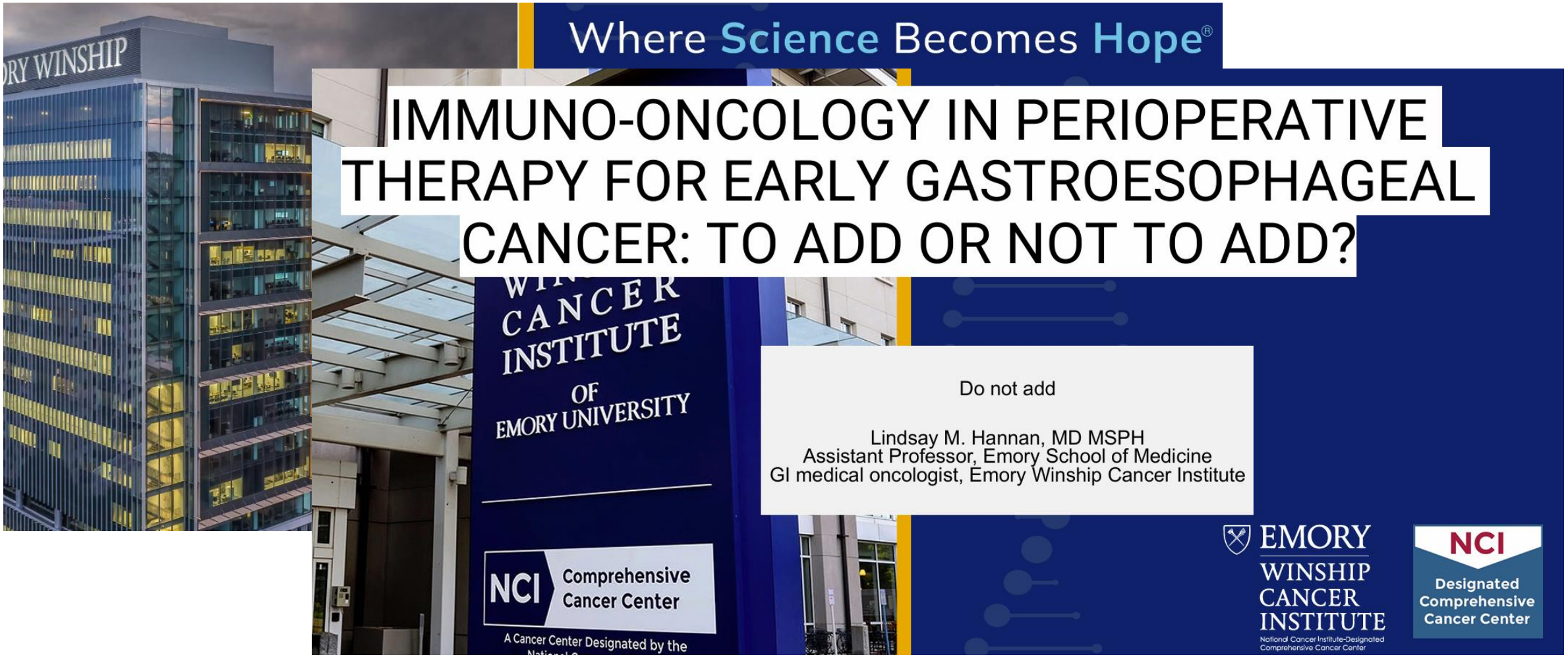
2024 DDHO


Where Science Becomes Hope®
IMMUNO-ONCOLOGY IN PERIOPERATIVE THERAPY FOR EARLY GASTROESOPHAGEAL CANCER: TO ADD OR NOT TO ADD?
Do not add
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Setting the stage
MATTERHORN: FLOT + durvalumab

Methods

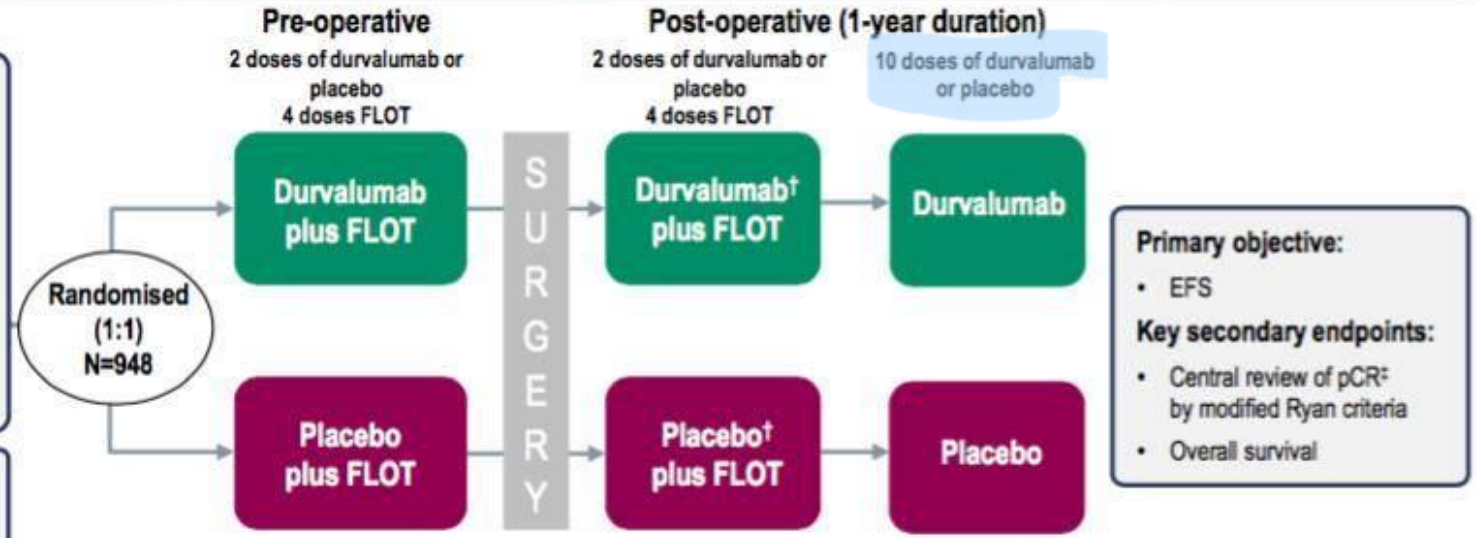
MATTERHORN is a global, Phase 3, randomised, double-blind, placebo-controlled study

Study population

- Gastric and GEJ adenocarcinoma
- Stage II, III and IVA (>T2 N0-3 M0 or T0-4 N+ M0)
- No evidence of metastasis
- No prior therapy
- ECOG PS 0 or 1
- Global enrolment from Asia, Europe, North America and South America

Stratification factors

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



Primary objective:

- EFS

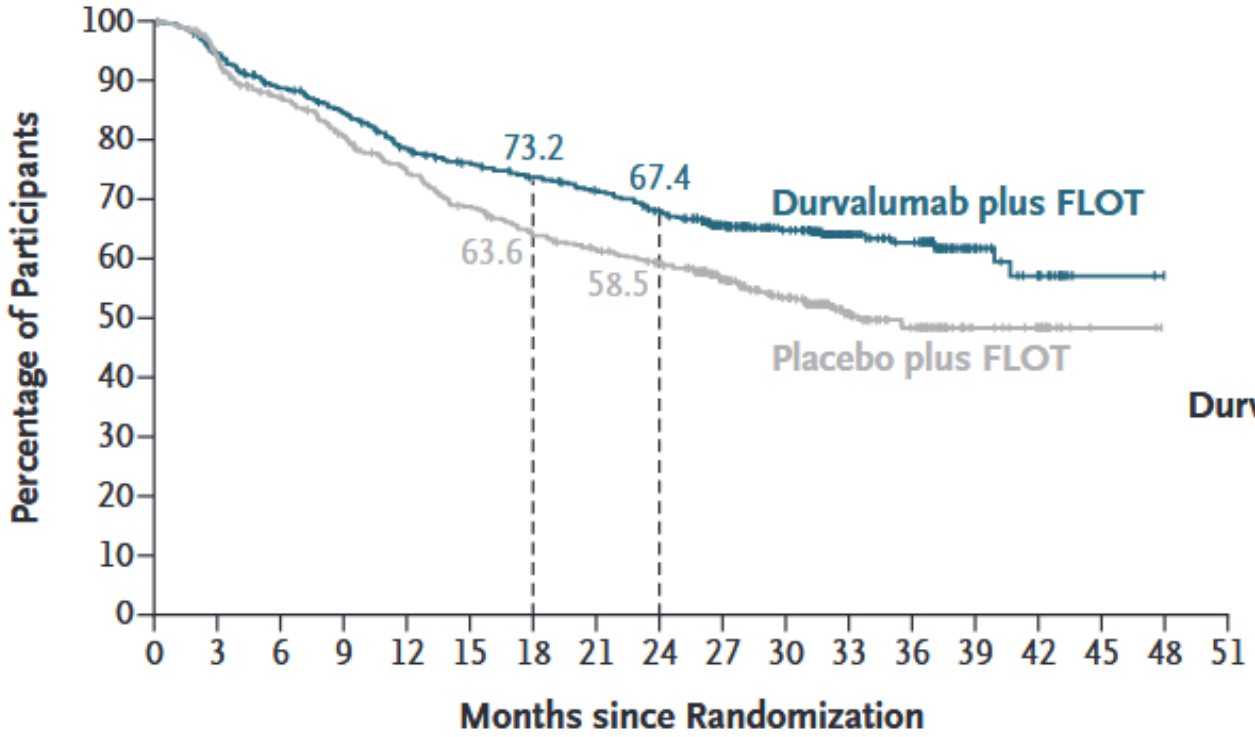
Key secondary endpoints:

- Central review of pCR‡ by modified Ryan criteria
- Overall survival

Durvalumab 1500 mg or placebo Q4W (Day 1) plus FLOT Q2W (Days 1 and 15) for 4 cycles (2 doses of durvalumab or placebo plus 4 doses of FLOT pre- and post-operative) followed by durvalumab or placebo Q4W (Day 1) for 10 further cycles

*Measured by VENTANA PD-L1 (SP263) assay. †Durvalumab or placebo monotherapy may be continued if post-operative FLOT is discontinued due to toxicity. ‡pCR was scored using modified Ryan criteria by central review.
FLOT: 5-fluorouracil 2600 mg/m², oxaliplatin 85 mg/m², docetaxel 50 mg/m², leucovorin 200 mg/m² on Days 1 and 15 Q4W, 2 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.
ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; GEJ, gastro-oesophageal junction; PD-L1, programmed cell death-ligand 1; PS, performance status; pCR, pathological complete response; PD-L1, programmed cell death ligand-1; Q2W, every 2 weeks; Q4W, every 4 weeks; TAP, tumour area positivity.

FLOT + durvalumab : gold standard (G, GEJ)



	No. of Participants with Event/ Total No. of Participants (%)	Median Event-free Survival (95% CI)
		mo
Durvalumab plus FLOT	167/474 (35.2)	NR (40.74–NR)
Placebo plus FLOT	218/474 (46.0)	32.8 (27.86–NR)

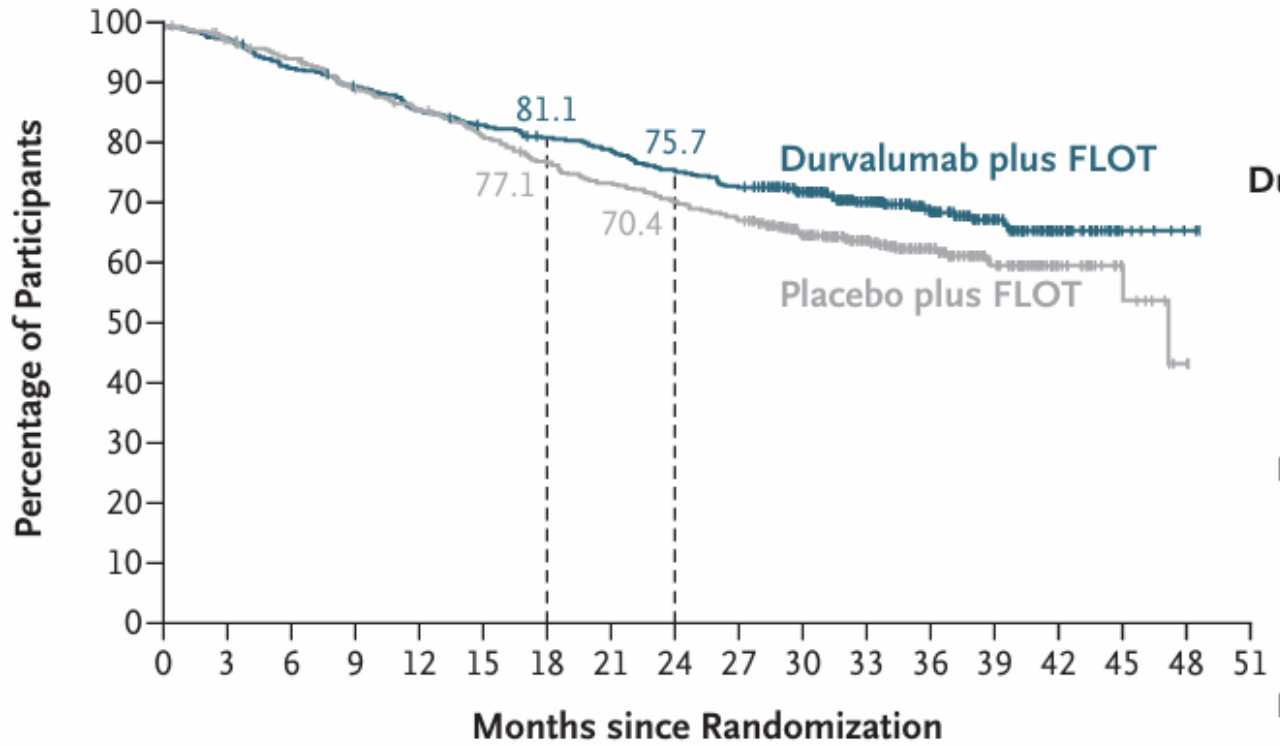
Stratified hazard ratio for event or death, 0.71 (95% CI, 0.58–0.86)
P<0.001 by stratified log-rank test

No. at Risk

Durvalumab plus FLOT	474	436	404	381	351	334	320	307	288	234	187	107	88	33	20	2	1	0
Placebo plus FLOT	474	429	392	360	329	302	278	264	249	202	160	89	65	26	21	2	1	0

FLOT + durvalumab : gold standard (G, GEJ)

A Overall Survival



	No. of Deaths/Total No. of Participants (%)	Median Overall Survival (95% CI)
		mo
Durvalumab plus FLOT	145/474 (30.6)	NR (NR–NR)
Placebo plus FLOT	176/474 (37.1)	47.2 (45.1–NR)
	P=0.03 by stratified log-rank test (exceeding significance threshold of P<0.0001)	
0 to 12 Months		
Durvalumab plus FLOT	67/474 (14.1)	NR (NR–NR)
Placebo plus FLOT	67/474 (14.1)	NR (NR–NR)
	Hazard ratio for death, 0.99 (95% CI, 0.70 to 1.39)	
≥12 Months		
Durvalumab plus FLOT	78/403 (19.4)	NR (NR–NR)
Placebo plus FLOT	109/395 (27.6)	NR (45.1–NR)
	Hazard ratio for death, 0.67 (95% CI, 0.50 to 0.90)	

No. at Risk

Durvalumab plus FLOT	474	464	438	422	403	389	376	367	351	338	293	205	143	80	38	8	2	0
Placebo plus FLOT	474	457	439	414	395	374	354	337	323	309	262	197	128	72	33	11	2	0

Some assumptions are needed

- **Initial diagnosis**: localized gastroesophageal adenocarcinoma.
- **Treatment:** FLOT + durvalumab administered more or less per protocol.
- There is a metastatic recurrence at some point
- When did the recurrence occur? “early” or “late”
  - Janjigian et al. NEJM 2025;393:217-30 was published 7/17/25.
  - FDA approved durvalumab in combination with FLOT 11/25/2025
  - Assumption is that the patient experienced metastatic recurrence on the **earlier** side (e.g. within 6 months of treatment start and that this would have been during receipt of durvalumab monotherapy).

Other things that might change next line of therapy

- Depends on:
  - HER2/neu
  - MSI/MMR status
  - CLDN18.2
  - NGS for actionable alterations (e.g., FGFR2 amplification, NTRK fusion, BRAF V600E, etc.)
  - Any trial options
  - Performance status

Chemo + VEGF

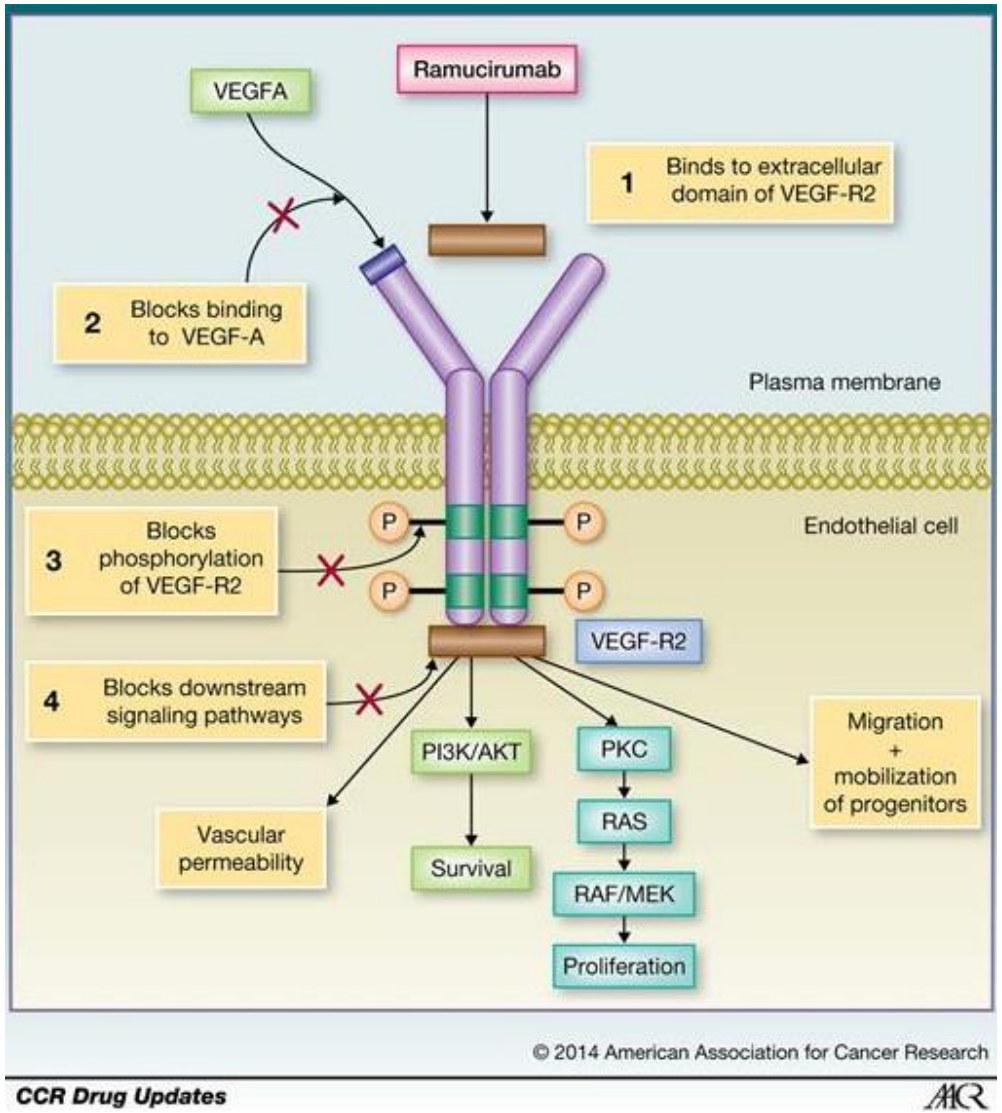
PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy • Dependent on prior therapy and PS
Preferred • Ramucirumab and paclitaxel (category 1)[59] • Fam-trastuzumab deruxtecan-nxki for HER2-positive[b] adenocarcinoma (category 1)[60,61] • Docetaxel (category 1)[52,53] • Paclitaxel (category 1)[48,49,62] • Irinotecan (category 1)[62-65] • Fluorouracil[a,g] and irinotecan[63,66,67] • Trifluridine and tipiracil for third-line or subsequent therapy (category 1)[68]
Other Recommended • Ramucirumab (category 1)[69] • Irinotecan and cisplatin[34,70] • Fluorouracil and irinotecan + ramucirumab[a,g,71,72] • Irinotecan and ramucirumab[73] • Docetaxel and irinotecan (category 2B)[74]
Useful in Certain Circumstances[b] • Entrectinib, larotrectinib, or repotrectinib[i] for *NTRK 1/2/3* gene fusion-positive tumors[75-77] • Pembrolizumab[c,f] for MSI-H/dMMR tumors[42,78-80] • Nivolumab and ipilimumab[c,f] for MSI-H/dMMR tumors[28] • Pembrolizumab[c,f] for TMB-high (TMB-H) (≥10 mutations/megabase) tumors[42,81] • Dostarlimab-gxly[c,f,j] for MSI-H/dMMR tumors[43] • Dabrafenib and trametinib for *BRAF* V600E-mutated tumors[82] • Selpercatinib for *RET* gene fusion-positive tumors[83]

Ramucirumab

- Monoclonal antibody (IgG1) vs VEGFR2
- VEGF and VEGFR-2-mediated signalling and angiogenesis contribute to the pathogenesis of gastric cancer
- Reduces tumor growth and vascularity



Rainbow trial (2014) - PFS

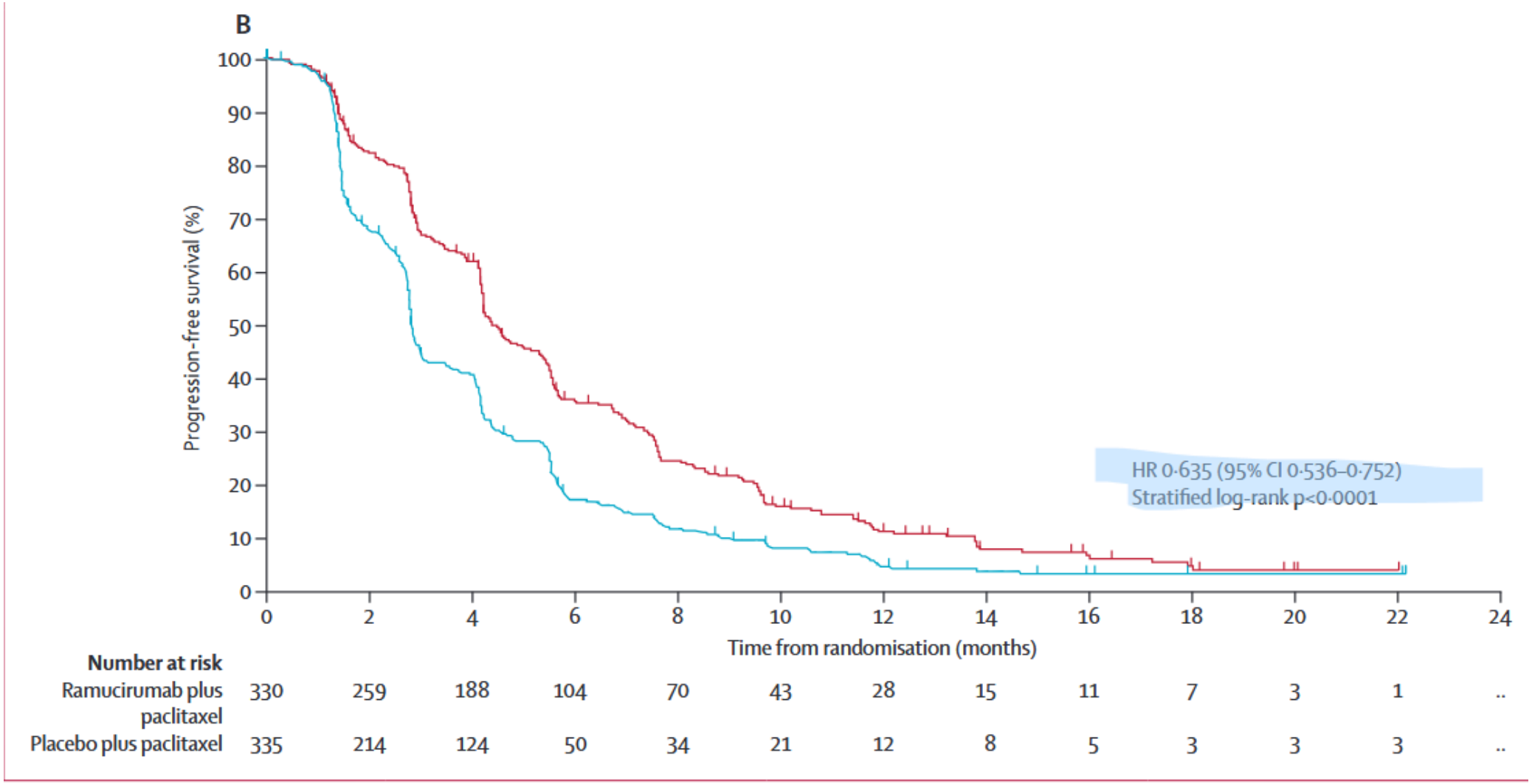
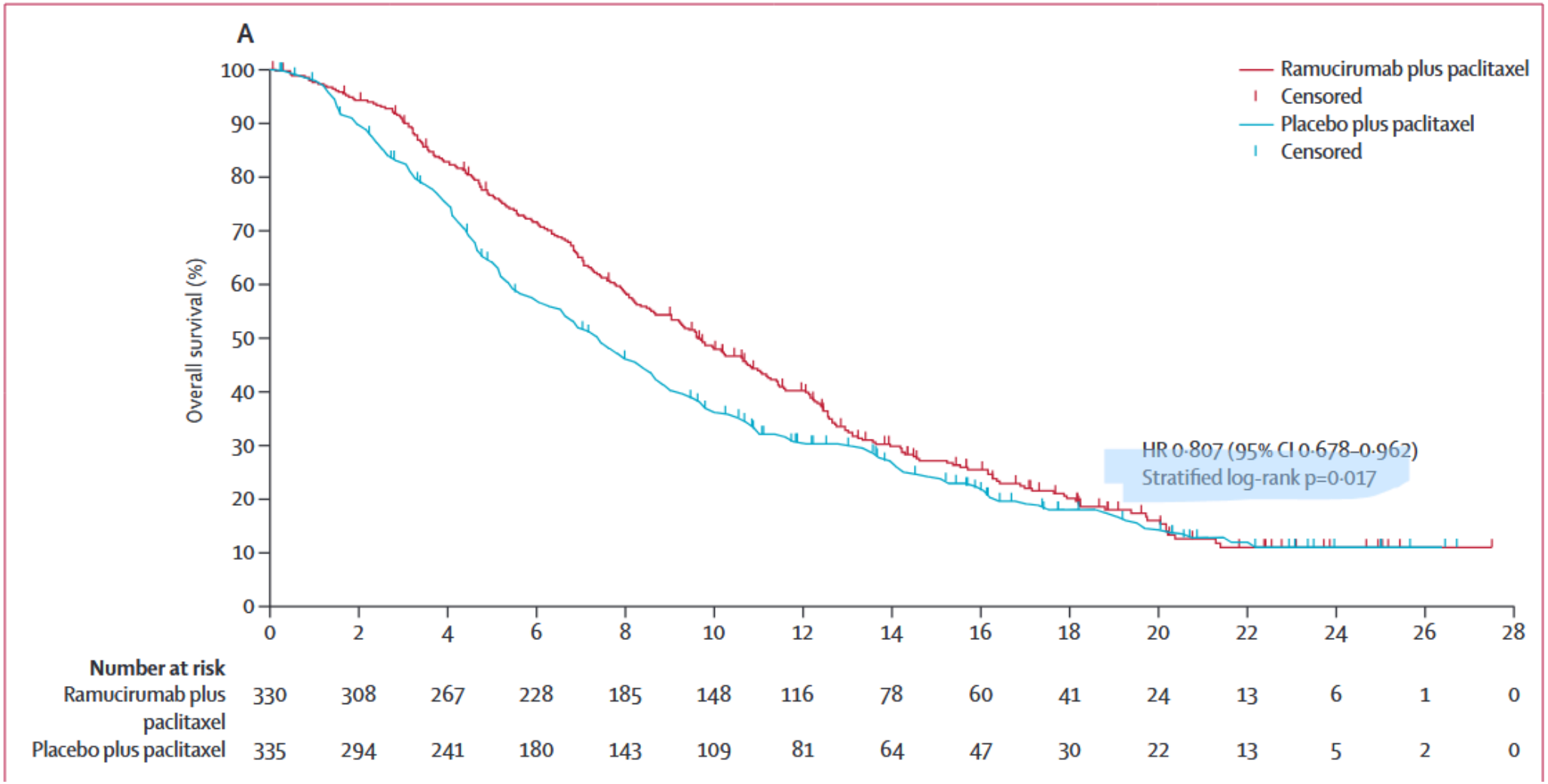


Figure 2: **Kaplan-Meier curves of overall survival (A) and progression-free survival (B)**
HR=hazard ratio.

Rainbow trial (2014) - OS



What about continuing the ICI?

- Some support from retrospective analyses:
  - Front Immunol 2025. Dec 10; 16:1697712. n=83, Qingdao University Affiliated Yantai Yuhuangding Hospital
  - Hum Vaccin Immunother. 2024 Nov 4;20 (1):2423479. n=85 Jiangsu Cancer Hospital
  - Clinical Oncol 2026 Jul 55; 104180. n=96. Nanjing Drum Tower Hospital of Nanjing University Medical School

Ongoing trial – PARAMUNE (SWOG S2303)

- NCT06203600
- Adding Nivolumab to Usual Treatment for People With Advanced Stomach or Esophageal Cancer, PARAMUNE Trial
- Phase III nivolumab + paclitaxel + ramucirumab versus randomized to paclitaxel + ramucirumab.
- Site PI: Dr. Oluwadunni Emiloju MD

Should another checkpoint inhibitor be given/continued?

- No evidence
- No evidence
- No evidence
- Why give up VEGF therapy?
- $$$$$

- Need additional data

Thank you!