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SYSTEMIC THERAPY AFTER DURVA FLOT IN UPPER GI ADENOCARCINOMA: THERE IS STILL A ROLE FOR IO

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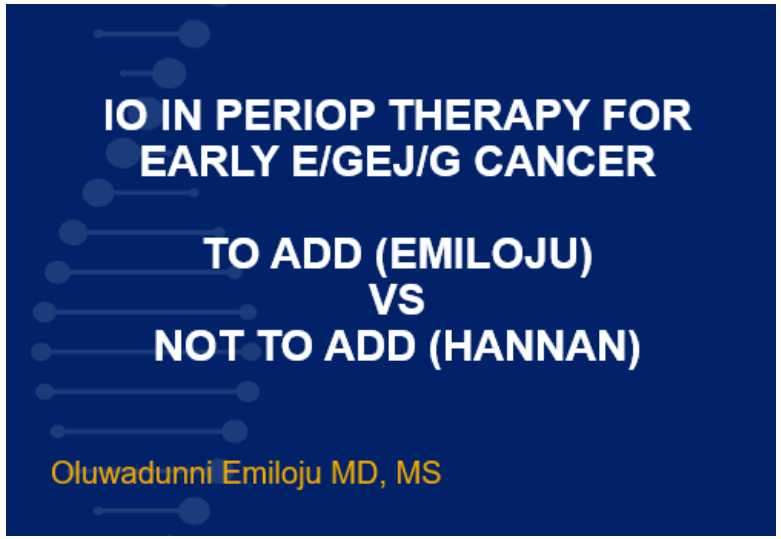
DISCLOSURES

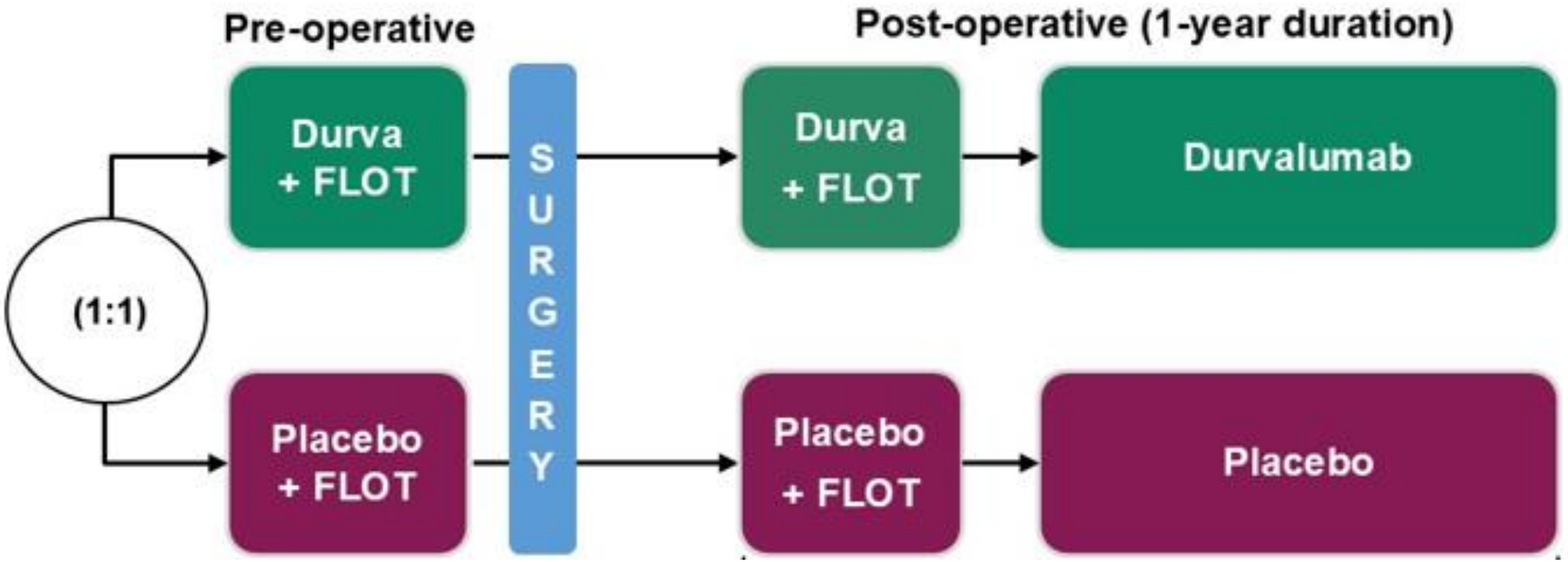
- Coherus Oncology (Research support, institution)
- Genentech (Research support, institution)
- Telix (Stock Ownership)
- Bristol Meyers Squibb (Advisory Board/Consulting)
- Revolution Medicines (Speaker Bureau)

THROWBACK TO DDHO 2024



FAST FORWARD TO 2025

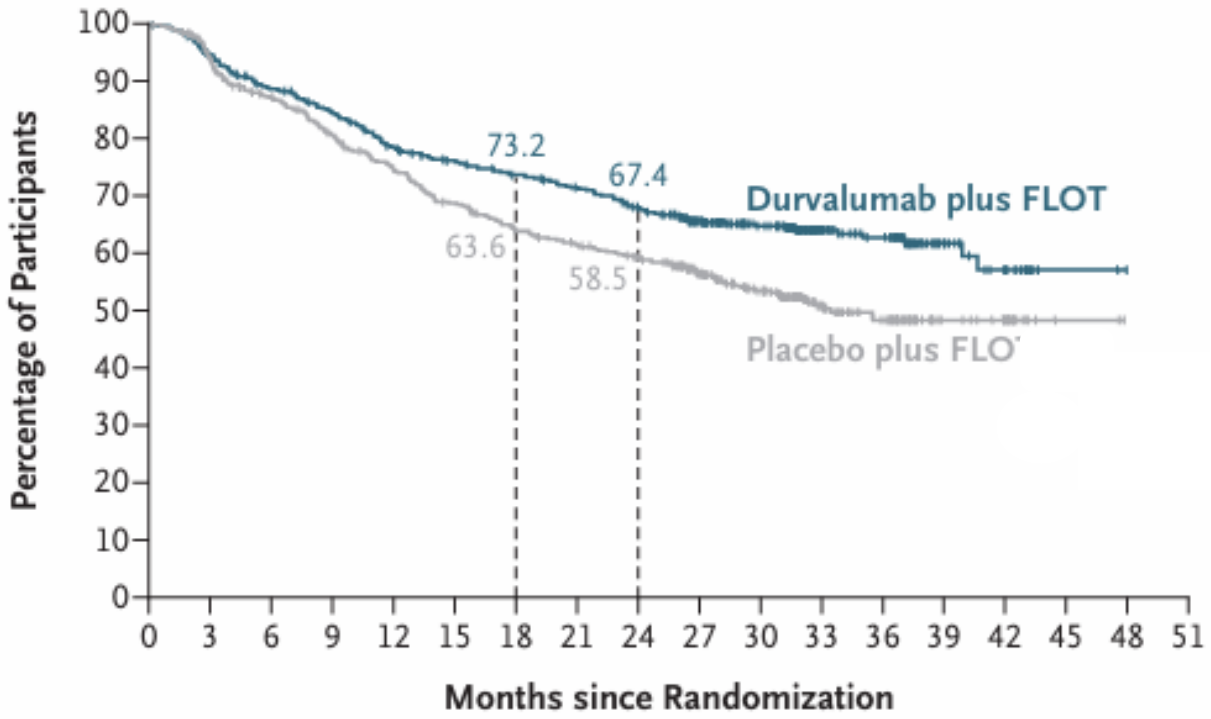
MATTERHORN: DURVA + FLOT FOR RESECTABLE GEJ/G ADENOCARCINOMA



- Timing of disease recurrence relative to FLOT + Durva will be important

Janjigian et al, NEJM 2025, Klempner, ASCO 2025

MATTERHORN: DURVA + FLOT FOR RESECTABLE GEJ/G ADENOCARCINOMA



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

- 52% completed all the assigned adjuvant durvalumab or placebo
- Reason for Durva discontinuation was not always PD/death
- 15% of patients received IO Post D+FLOT
- Local vs distant recurrence data awaited

248 completed all adjuvant durvalumab treatment
112 discontinued adjuvant durvalumab
- **16 participant decision**
- **27 adverse event**
- **39 condition under investigation worsened**
- **9 subjective disease progression**
- **6 investigator decision**
- **7 death**
- **8 other**

Janjigian et al, NEJM 2025

METASTATIC UPPER GI ADENOCARCINOMA: PREDICTIVE BIOMARKERS

- HER2
- Claudin 18.2
- PD-L1 CPS
- MSI-H or dMMR

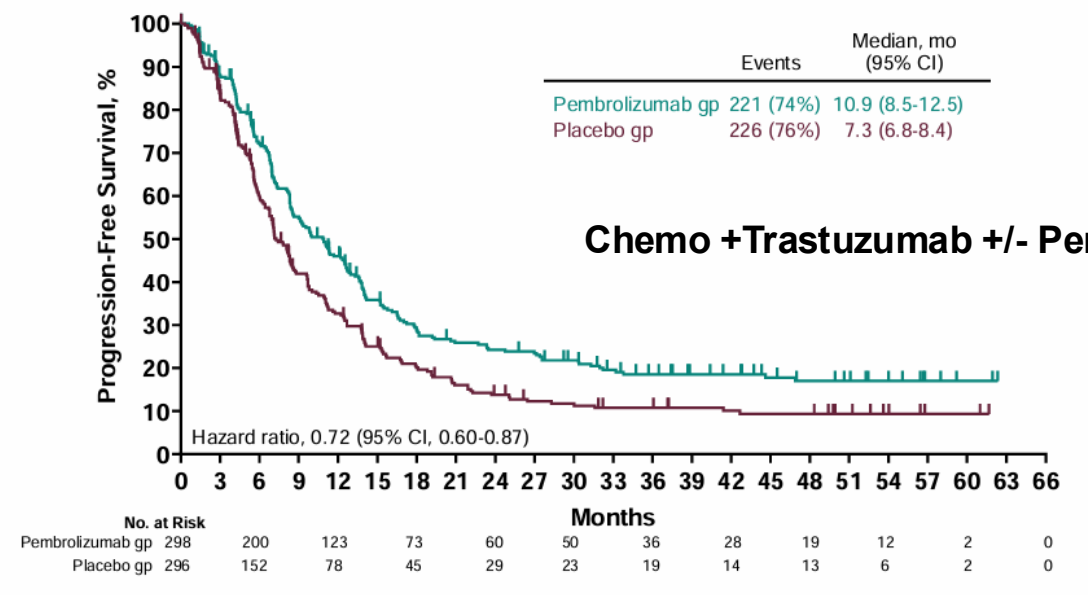
Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

ADENOCARCINOMA
First-Line Therapy • Oxaliplatin is preferred over cisplatin due to lower toxicity.
Preferred • HER2-positive[c] ▸ Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and trastuzumab[31] ▸ Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, trastuzumab, and pembrolizumab for PD-L1 CPS ≥1 (category 1)[b,f,32,33] ▸ Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, and trastuzumab (category 1)[34] ▸ Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, trastuzumab and pembrolizumab for PD-L1 CPS ≥1 (category 1)[b,f,32,33] • HER2-negative[c] ▸ Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)[b,f,35] ▸ Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and pembrolizumab for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)[b,f,36,37] ▸ Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and tislelizumab-jsgr for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)[b,f,38] ▸ Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and zolbetuximab-clzb for CLDN18.2 positive[c] (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[39,40] ▸ Fluoropyrimidine (fluorouracil[a] or capecitabine) and oxaliplatin[41-43] ▸ Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, and pembrolizumab for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)[b,f,36,37] ▸ Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, and tislelizumab-jsgr for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)[b,f,38] ▸ Fluoropyrimidine (fluorouracil[a] or capecitabine) and cisplatin[41,44-46] • MSI-H/dMMR tumors (independent of PD-L1 status) ▸ Pembrolizumab[b,f,47-50] ▸ Dostarlimab-gxly[b,f,51] ▸ Nivolumab and ipilimumab[b,f,35] ▸ Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab[b,f,35] ▸ Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and pembrolizumab[b,f,36]

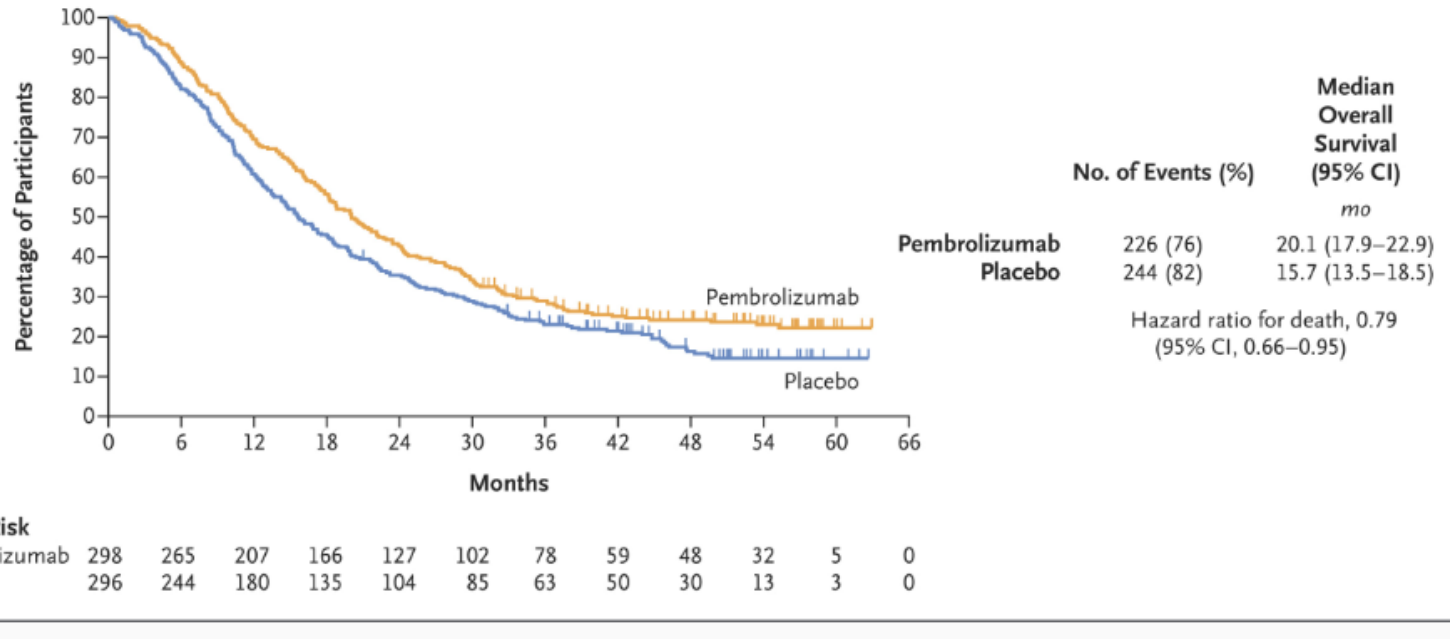
National Comprehensive Cancer Network (NCCN) 2026

HER2+ Stage IV

HER2+ STAGE IV : KEYNOTE 811



Chemo +Trastuzumab +/- Pembrolizumab



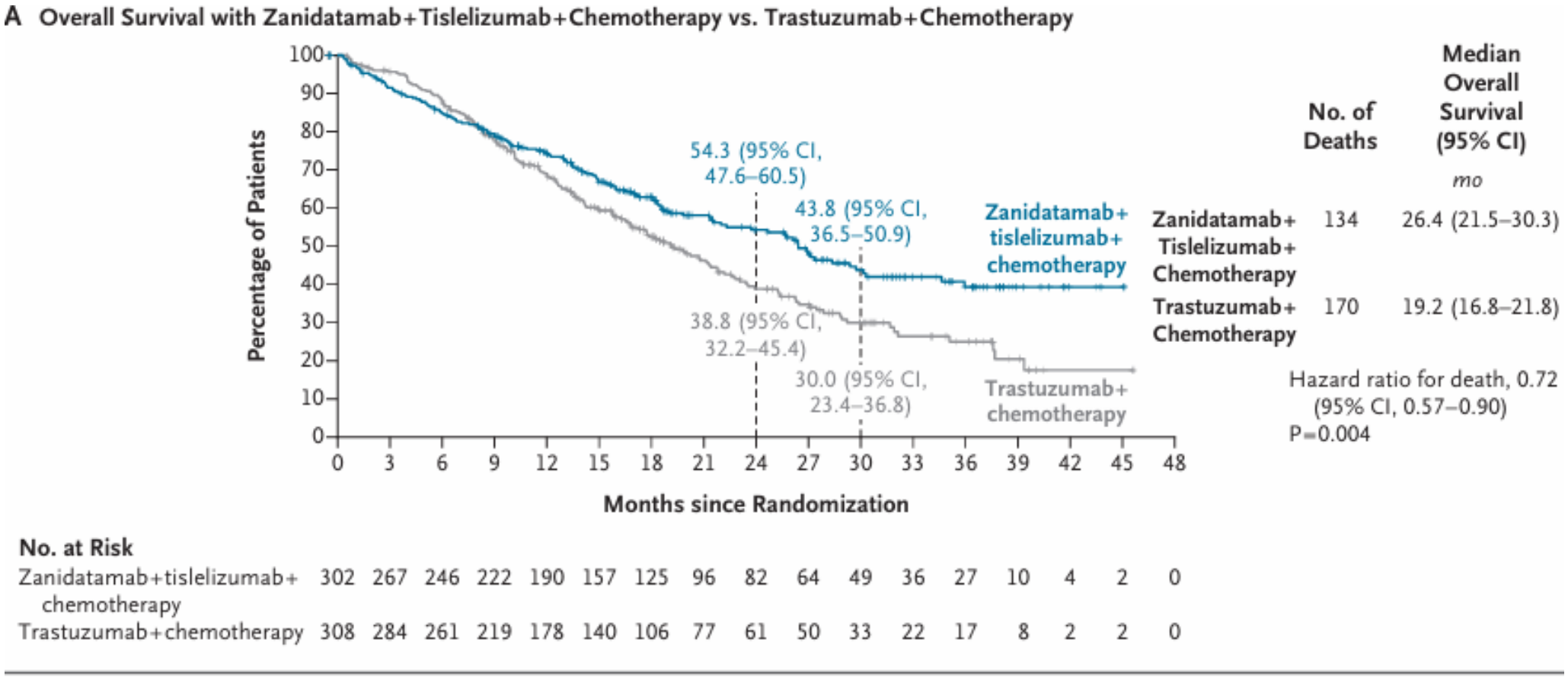
	No. of Events (%)	Median Overall Survival (95% CI)
		mo
Pembrolizumab	226 (76)	20.1 (17.9–22.9)
Placebo	244 (82)	15.7 (13.5–18.5)

Hazard ratio for death, 0.79 (95% CI, 0.66–0.95)

- HER2+, PDL1 + disease requires IO +anti-HER2+ chemo
- There is preclinical rationale for combining HER2 blockade with IO
- Trastuzumab increases HER2 internalization and cross-presentation by APCs and increases HER2-directed T cell response
- Trastuzumab also upregulates checkpoint expression

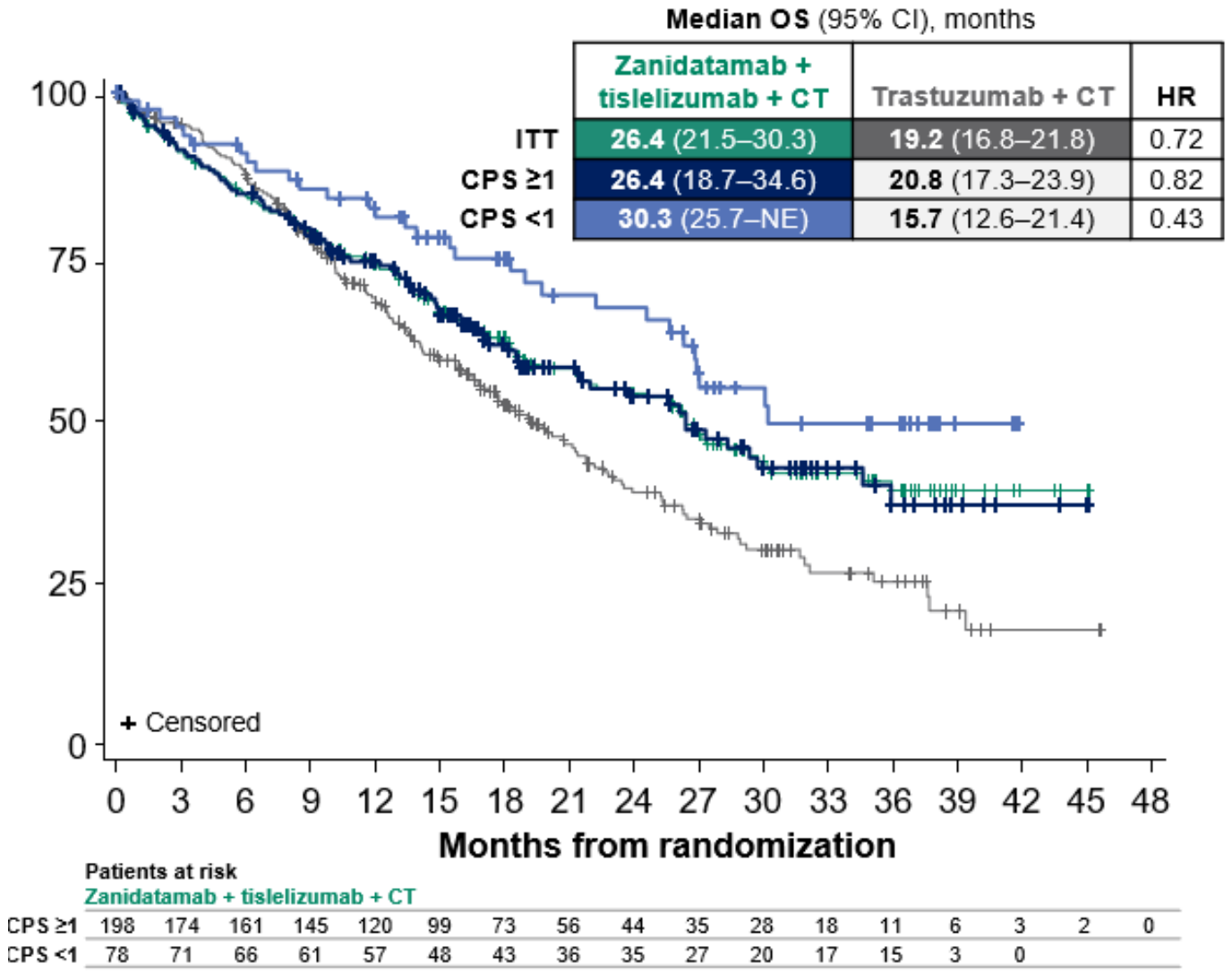
Janjigian et al, Nature 2021, Janjigian et al, NEJM 2024

HER2+ STAGE IV : HERIZON GEA



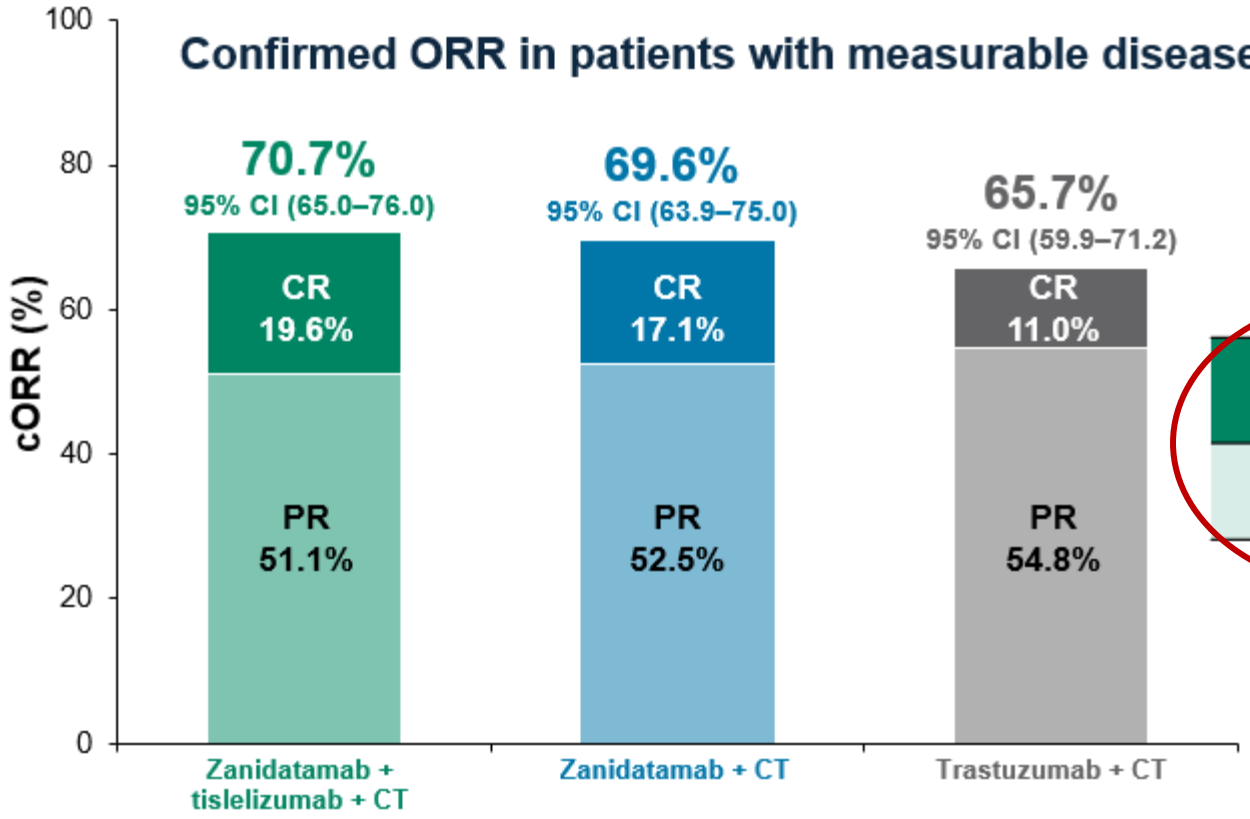
Shitara et al, NEJM 2026

HER2+ STAGE IV : HERIZON GEA



Shitara et al, NEJM 2026, Rha et al ASCO Annual Meeting 2026

HER2+ STAGE IV: HERIZON GEA



Median DOR (95% CI), mo

Zanidatamab + tislelizumab + CT (n = 195)	Zanidatamab + CT (n = 186)	Trastuzumab + CT (n = 198)
20.7 (12.6–37.7)	14.3 (11.5–21.9)	8.3 (6.7–9.8)

Shitara et al, NEJM 2026

Claudin 18.2+, HER2- Stage IV

CLAUDIN 18.2+, HER2- STAGE IV GEJ/GASTRIC: ILLUSTRO

- Zolbetuximab is a CLDN18.2 mAb
- Zolbe + Chemo vs Chemo in Phase 3 trials
  - median PFS 9.2 vs 8.2 months (HR 0.71, 95% CI: 0.61–0.83)
  - median OS 16.4 vs 13.7 months (HR 0.77, 95% CI: 0.67–0.89)

- In the chemo +IO vs chemo studies median PFS ≈ 7mos

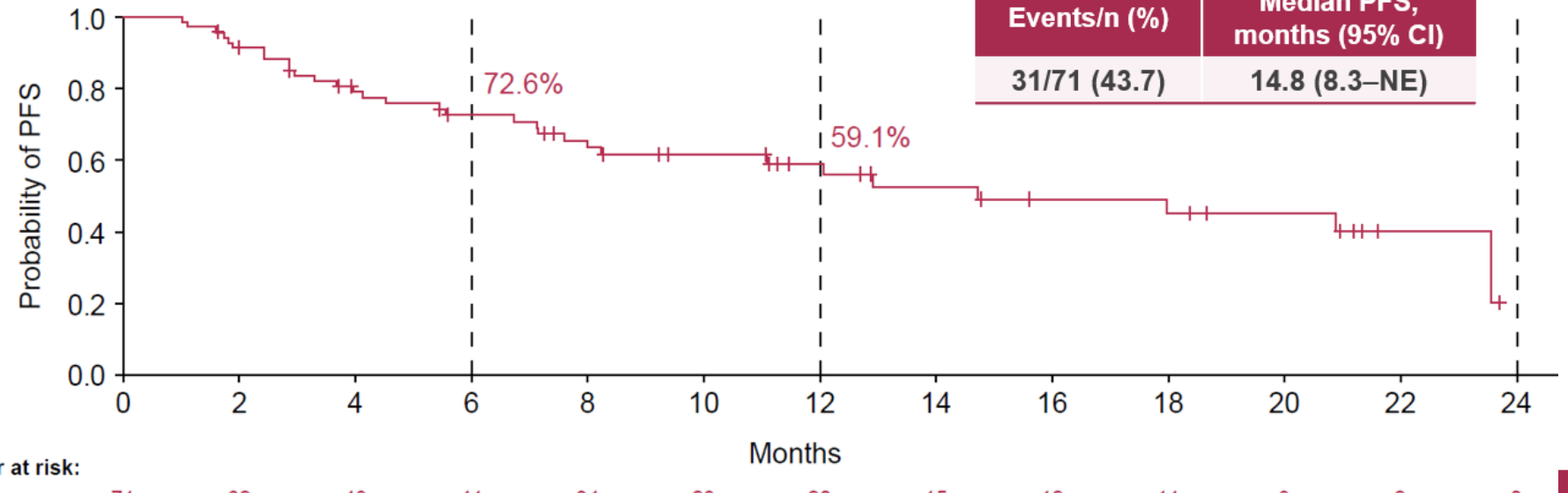
- Preclinical rationale for combining Zolbe with IO and chemo
  - Zolbe increases antigen release and APC priming
  - co-targeting the PD-1 pathway can amplify tumor-specific T cell response

- Illustro is a phase II study of Zolbe + Nivolumab + FOLFOX (N=71)
  - *Median PFS was 14.8 months with zolbetuximab + mFOLFOX6 + nivolumab*

Shitara et al, Nature Med 2026. Shitara et al, ASCO GI 2026

CLAUDIN 18.2+ STAGE IV GEJ/GASTRIC: ILLUSTRO

Events/n (%)	Median PFS, months (95% CI)
31/71 (43.7)	14.8 (8.3–NE)

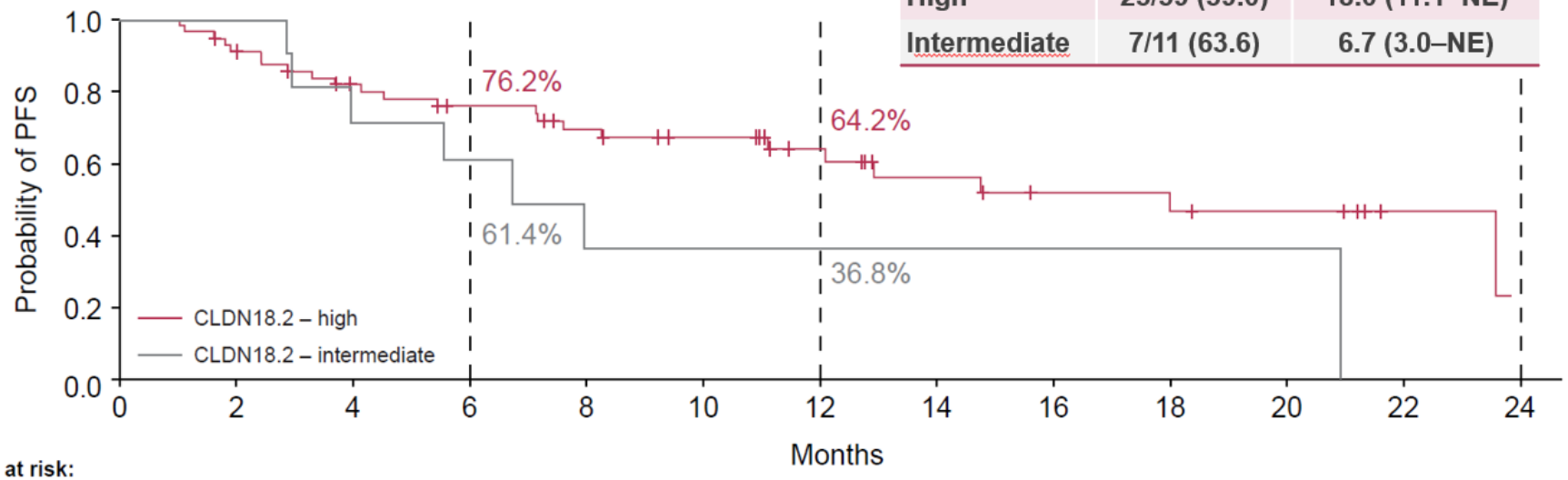


Chemo + Zolbetuximab + Nivolumab

r at risk:

71	62	49	41	34	29	20	15	12	11	9	2	0

CLDN18.2	Events/n (%)	Median PFS, months (95% CI)
High	23/59 (39.0)	18.0 (11.1–NE)
Intermediate	7/11 (63.6)	6.7 (3.0–NE)



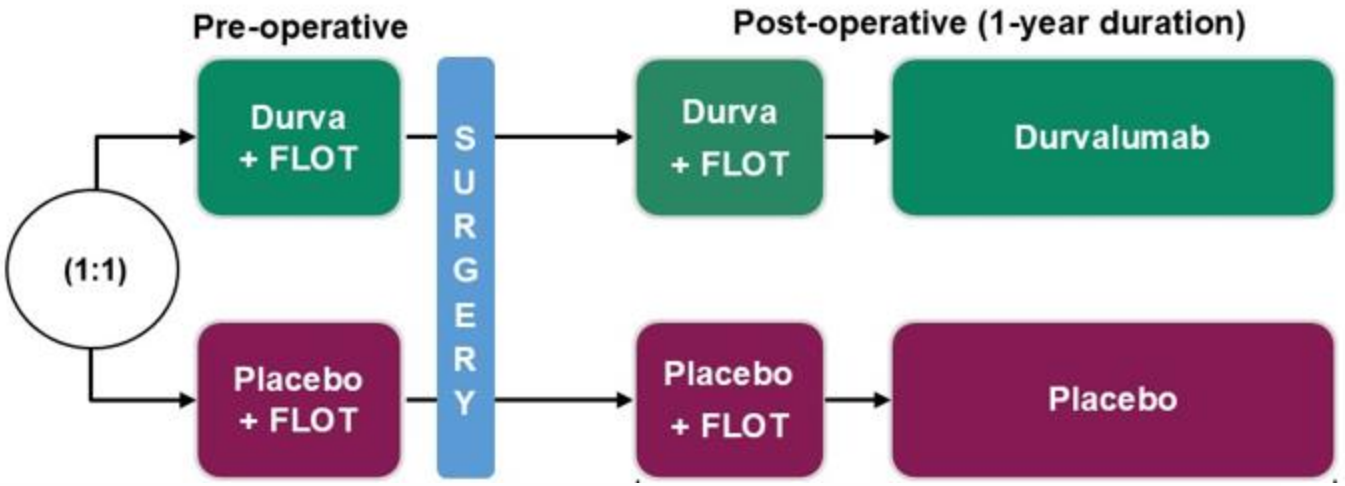
Number at risk:

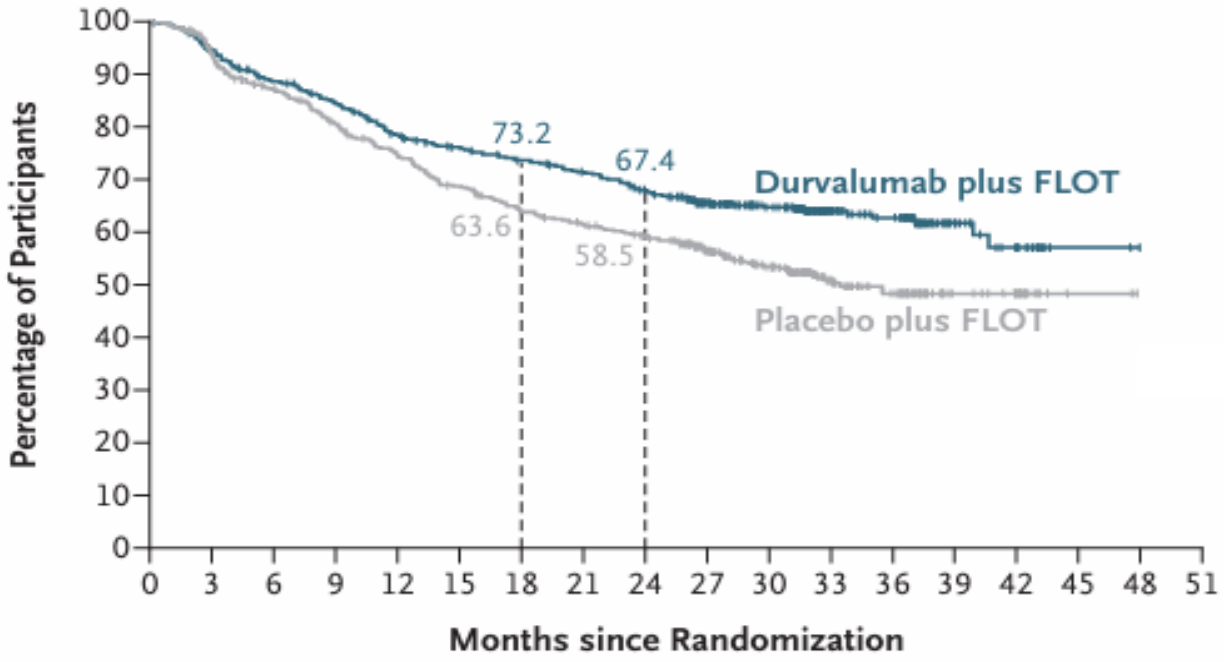
CLDN18.2 – high	59	51	42	36	31	26	18	13	10	9	8	2	0
CLDN18.2 – intermediate	11	11	7	5	3	3	2	2	2	2	1	0	0

Shitara et al, Nature Med 2026. Shitara et al, ASCO GI 2026

HER2-, PDL1+ Stage IV

HER2-, PDL1+ STAGE IV





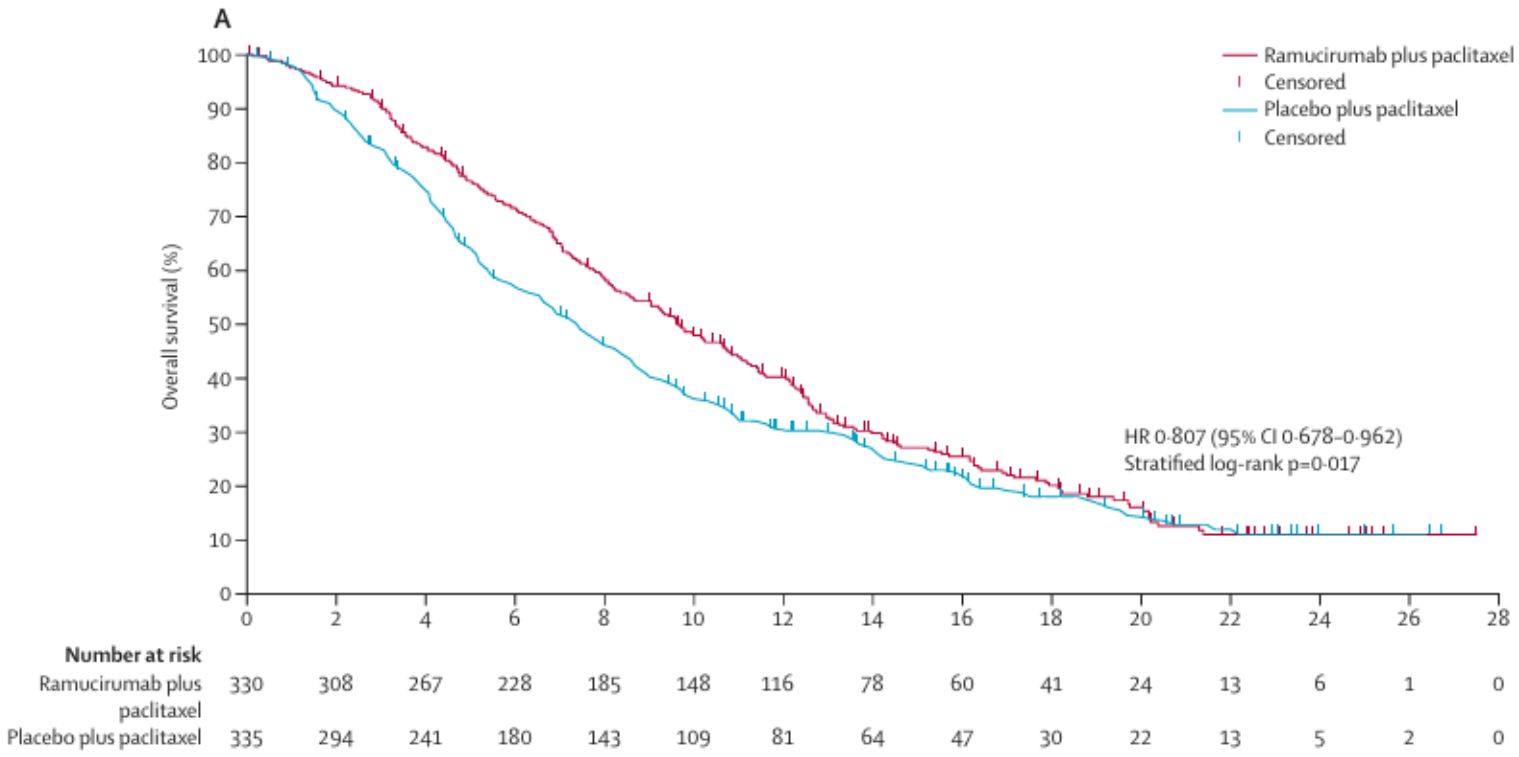
No. at Risk

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

- Timing of disease recurrence relative to FLOT + Durva is important
- Progression during FLOT + Durva requires novel treatments

Janjigian et al, NEJM 2025, Klempner, ASCO 2025

HER2-, PDL1+ STAGE IV- RAINBOW 2014

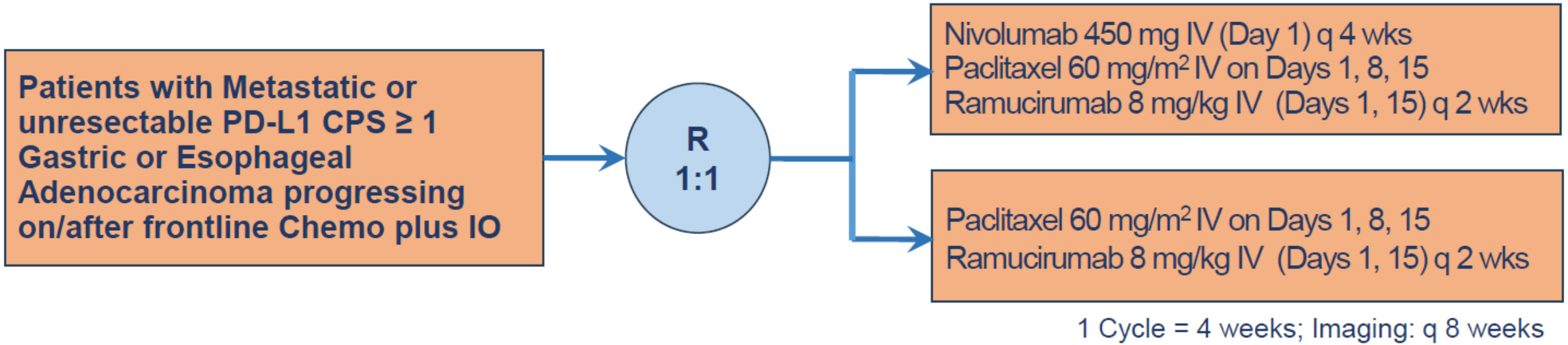


- Current standard 2nd line:
  - Paclitaxel +/- Ramucirumab
  - mPFS 4.4 vs 2.9 mos (HR 0·635; p<0.0001)
  - mOS 9.6 vs 7.4 mos (HR 0·807; p=0·017).

Hansjochen Wilke et al, Lancet Oncol 2014

HER2- STAGE IV: ONGOING CLINICAL TRIALS

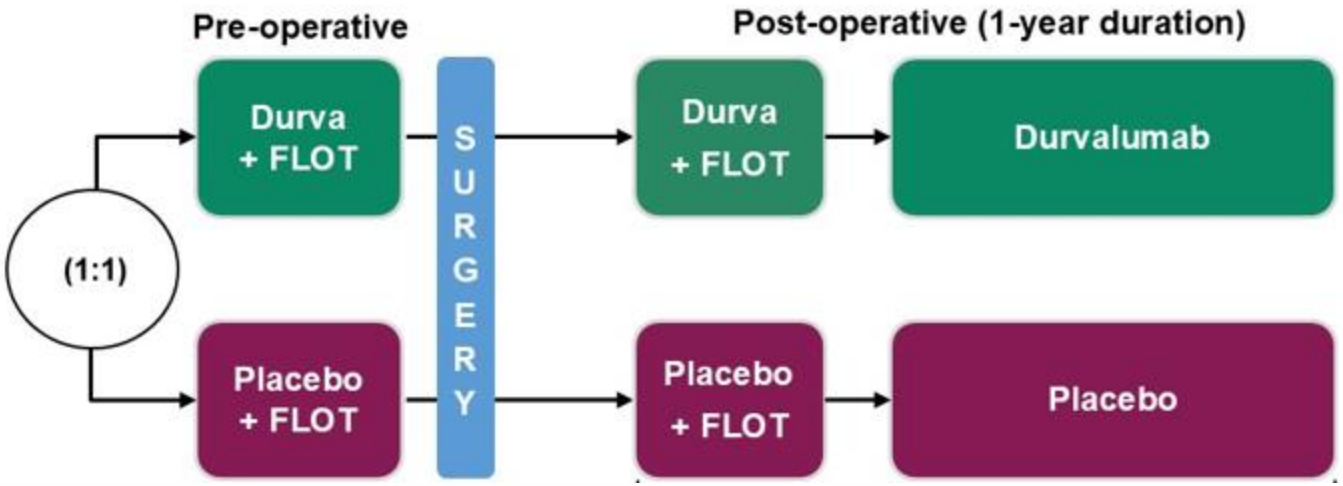
- Progression during FLOT + Durva requires novel treatments
  - S2303 (PARAMUNE, NCT06203600)
  - Strong rationale: synergy between anti-VEGF and IO

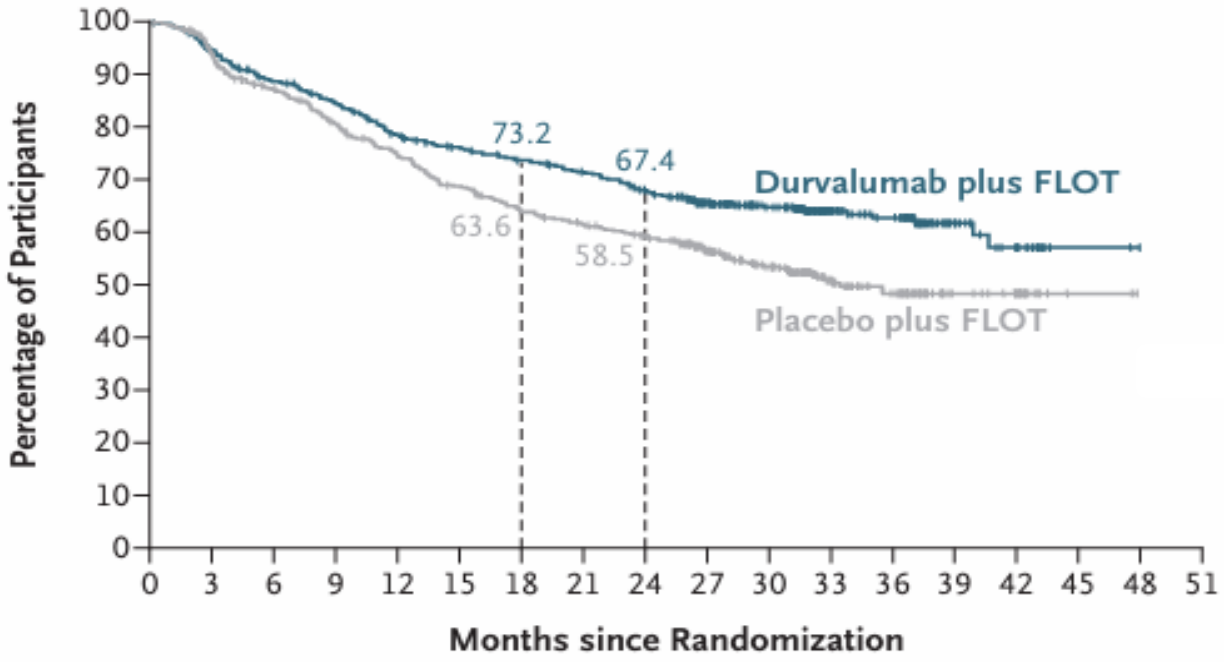


HER2- STAGE IV: ONGOING CLINICAL TRIALS

- Progression during FLOT + Durva requires novel treatments
  - Novel IO agents
    - Tagmokitug (anti-CCR8) + Toripalimab (anti-PD1) (NCT06657144)
  - Novel IO agents
    - T Cell engagers
    - ADCs +/- ICI
    - Cellular therapies including CAR-T therapy

HER2-, PDL1+ STAGE IV





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- Timing of disease recurrence relative to FLOT + Durva is important
- Progression during IO only may be amenable to re-intensification with chemo in PDL1+ tumors
- Progression after 1 yr of adjuvant treatment may be amenable to chemo + IO re-challenge in PDL1+ tumors

Janjigian et al, NEJM 2025, Klempner, ASCO 2025

HER2- PDL1+ STAGE IV GEJ/GASTRIC

CHECKMATE 649

Population	Median OS (Nivo+Chemo vs Chemo)	Median PFS (Nivo+Chemo vs Chemo)	OS HR
CPS ≥5	14.4 vs 11.1 mo	8.3 vs 6.1 mo	0.71
CPS ≥1	13.8 vs 11.4 mo		0.75

KEYNOTE-859

Population	Median OS (Pembro+Chemo vs Placebo+Chemo)	Median PFS	OS HR	PFS HR
CPS ≥1	13.0 vs 11.4 mo	6.9 vs 5.6 mo	0.74	0.72
CPS ≥10	15.7 vs 11.8 mo	8.1 vs 5.6 mo	0.65	0.62

RATIONALE-305

Population	Median OS	Median PFS	OS HR	PFS HR
TAP ≥5%	17.2 vs 12.6 mo	4.2 vs 5.9 mo	0.74	0.67

Janjigian, et al. Lancet. 2021, Janjigian, et al ESMO Open 2026, Rha et al Lancel Oncol 2023, Qui et al, BMJ 2024

CONCLUSION

- HER2+ PDL1+ Benefits from IO (+ anti-HER2 + Chemo)
- Claudin 18.2+, PDL1+ Benefits from IO + antiCLDN + Chemo
- HER2- PDL1+ progressing on FLOT + Durva offer novel IO clinical trial options
- HER2- PDL1+ may benefit from SOC IO + chemo depending on timing of recurrence
- The IO component improves efficacy, confers durability, is usually well tolerated

Benjamin A. Weinberg et al., Am Soc Clin Oncol Educ Book 44, e432034(2024)

THANK YOU