Debate: FLOT Versus CROSS for Esophageal Cancer

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Opinion 1: Perioperative Chemotherapy

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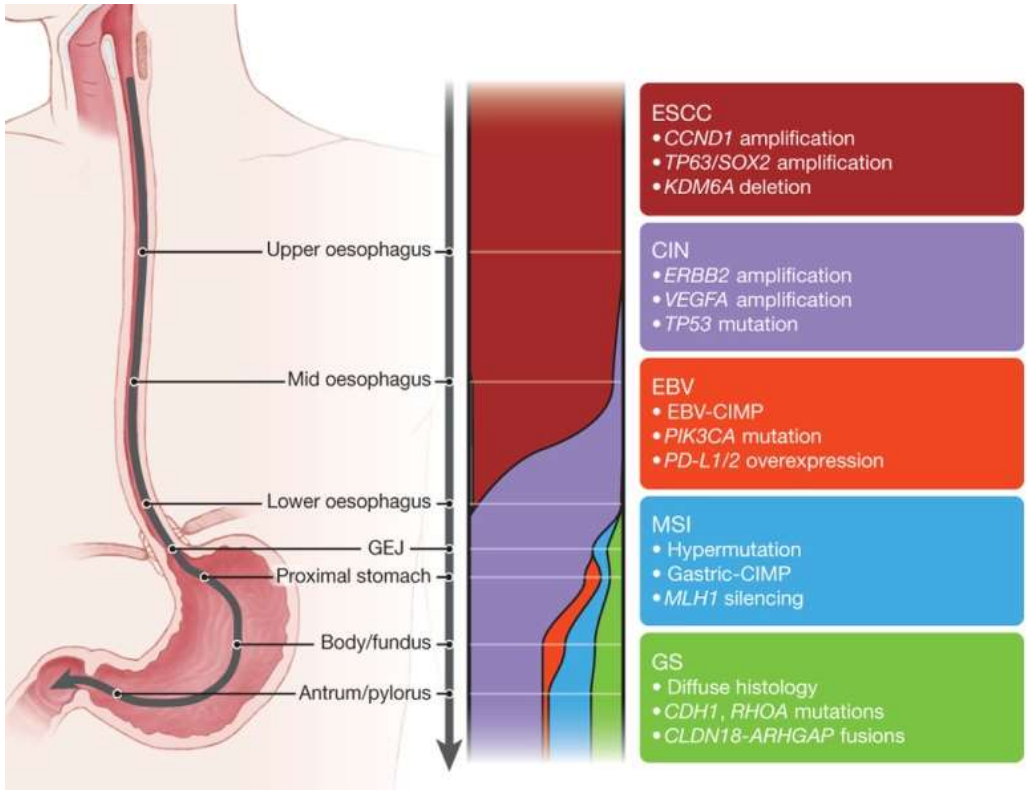
Opinion 1: For perioperative chemo

- Locoregional versus systemic control

- The landmark **CROSS trial** established neoadjuvant CRT as SOC[1]
  - Improved R0 resection rate (92 v 69%)
  - Improved overall survival (48 v 24.4 mos)
  - Compared to surgery alone
  - 75% adenocarcinoma

- Esophageal adeno (EA) is distinct from ESCC
  - Genetically, EA more resembles gastric cancer; ESCC more similar to head and neck cancer[2]
  - ESCC is more radiation sensitive and higher locoregional recurrence rates[3,4]

- Two randomized studies of neoadjuvant CRT vs periop chemo in EA



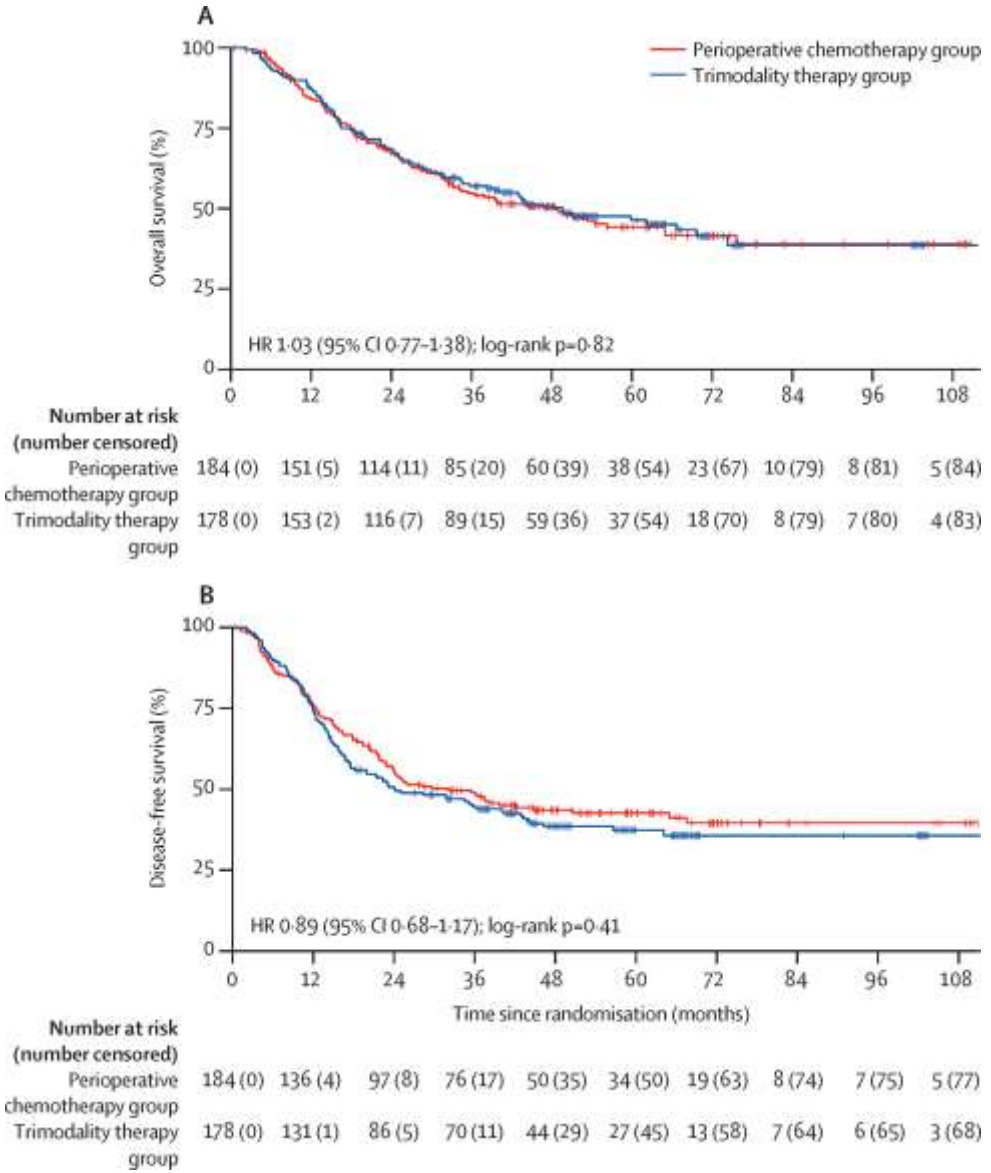
J Kim *et al. Nature* 1–9 (2017) doi:10.1038/nature20805

[1]Van Hagen P et al. N Engl J Med 2012
[2]Kim J et al, Nature 2017
[3]Barbetta A et al, J Thoracic and Cardiovasc Surgery 2019
[4]Xi M et al, Ann of Surgery 2019

Neo-AEGIS Trial

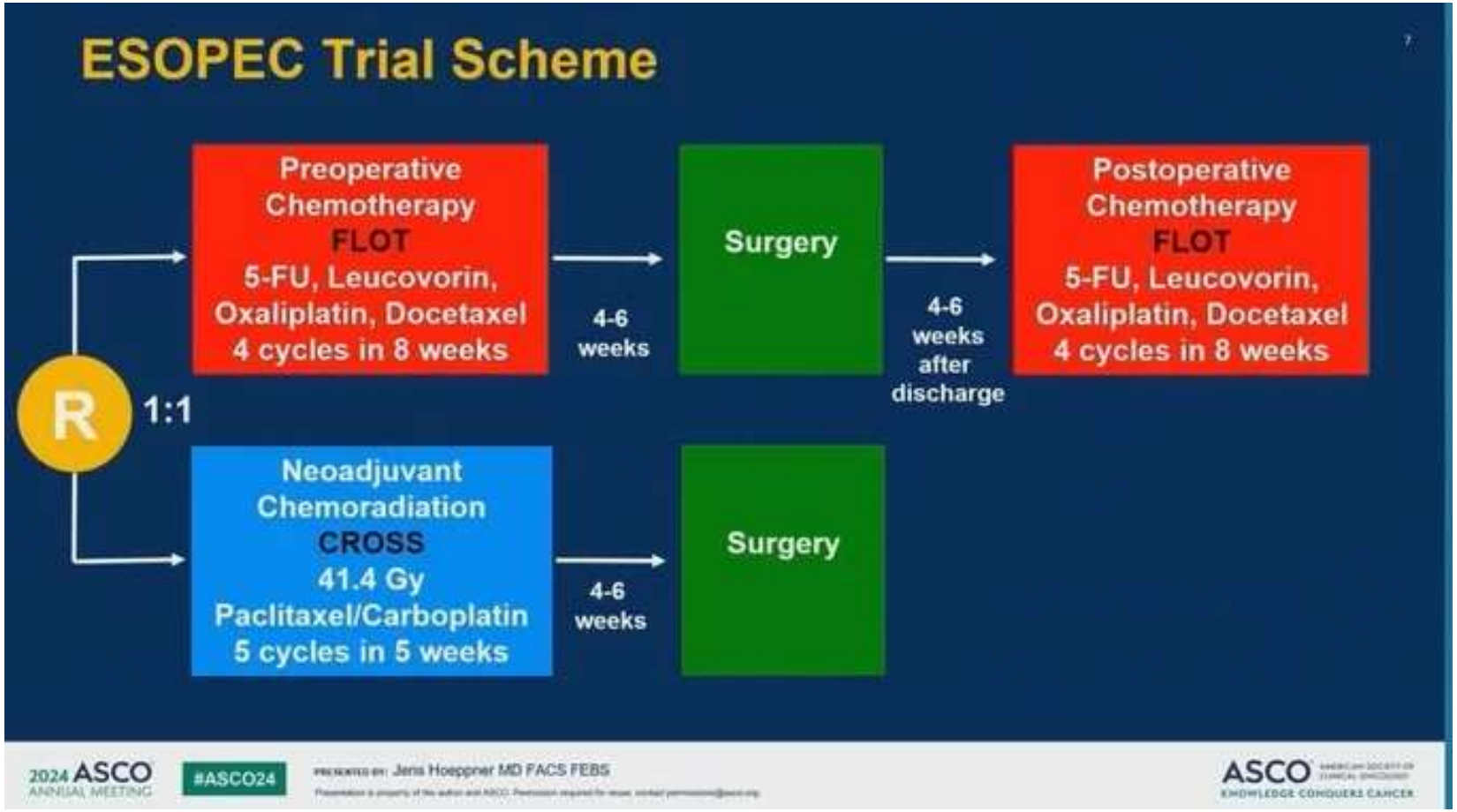
- Randomized open label phase 3 trial
- EC or GEJ, staged T2 or T3 and N0-N3, M0
- Randomized to perioperative chemotherapy (ECF/ECX or FLOT) vs pre-op chemoradiation (CROSS regimen)
- Only 15% in chemo gp received FLOT
- Prematurely terminated after second interim futility analysis

- Path CR rate 4 vs 12%

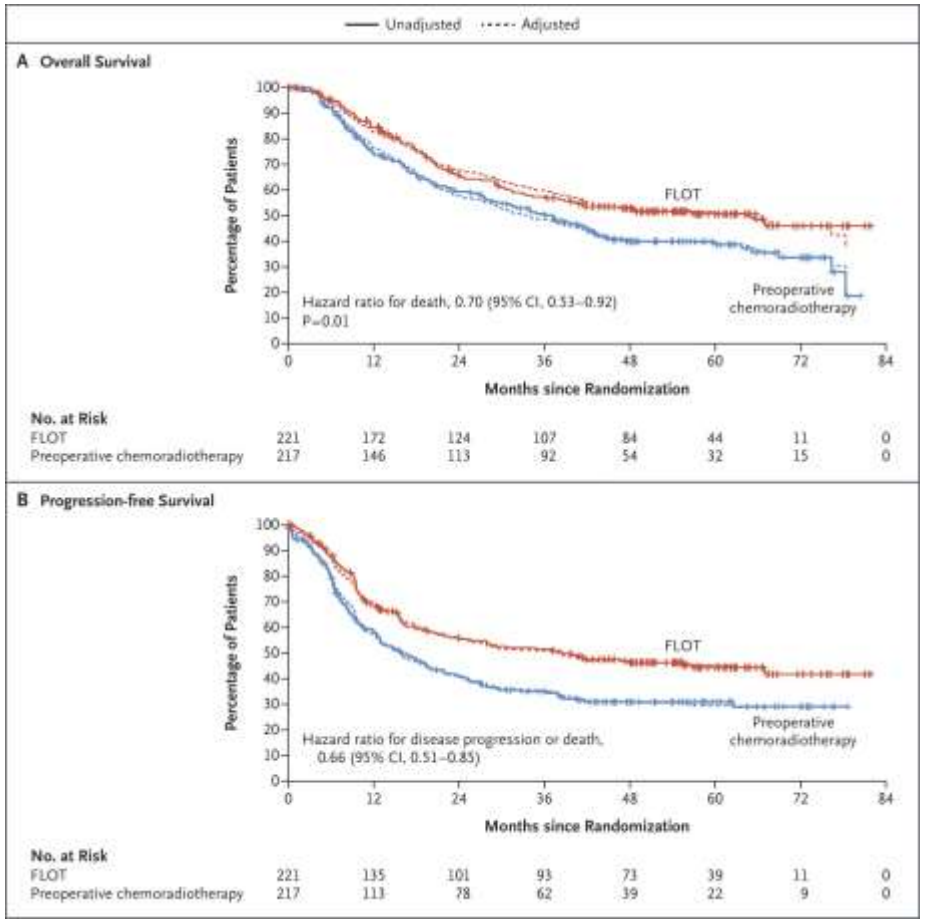


Reynolds JV et al. Lancet Gastro & Hepatol 2023; P1015-1027

ESOPEC trial: CROSS vs FLOT in resectable esophageal adeno



ESOPEC results



Median OS: 66 vs 37 mos

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)

Hoeppner J et al. N Engl J Med2025;392:323-335

What about tolerability?

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

* Shown are serious adverse events and grade 3 or higher adverse events that occurred in at least 2% of the patients in either group. The safety population comprised all the patients who started their assigned treatment before surgery. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 27.0, and are reported according to MedDRA preferred term. Adverse events are reported according to MedDRA system organ class in Tables S4 and S5.

Hoeppner J et al. N Engl J Med2025;392:323-335

What about IO?

- Adjuvant nivolumab approved for patients with residual disease after neoadjuvant chemoradiation for esophageal adeno or SCC based on DFS benefit (22.4 vs 11 months (HR 0.69, p=0.0003))[1]
  - Relative benefit lower in adenocarcinoma
  - OS benefit not yet known
- IO not currently approved with perioperative chemotherapy
  - Keynote-585 (chemo +/- pembro) – No OS benefit[2]
  - MATTERHORN (FLOT +/- durvalumab) – OS data awaited

[1]Kelly RJ et al. N Engl J Med 2021; 384:1191-1203
[2]Shitara K et al. Lancet Onc 2024; P212-224.

Conclusions

- Perioperative FLOT chemotherapy improves PFS and OS compared to neoadjuvant chemoradiation in resectable adenocarcinoma of the esophagus, GEJ
- FLOT toxicity is manageable, and symptomatic relief can be rapid
- An overall survival benefit to perioperative IO for GE adenocarcinoma has not yet been established

Thank You!

FLOT Versus CROSS for Esophageal Cancer

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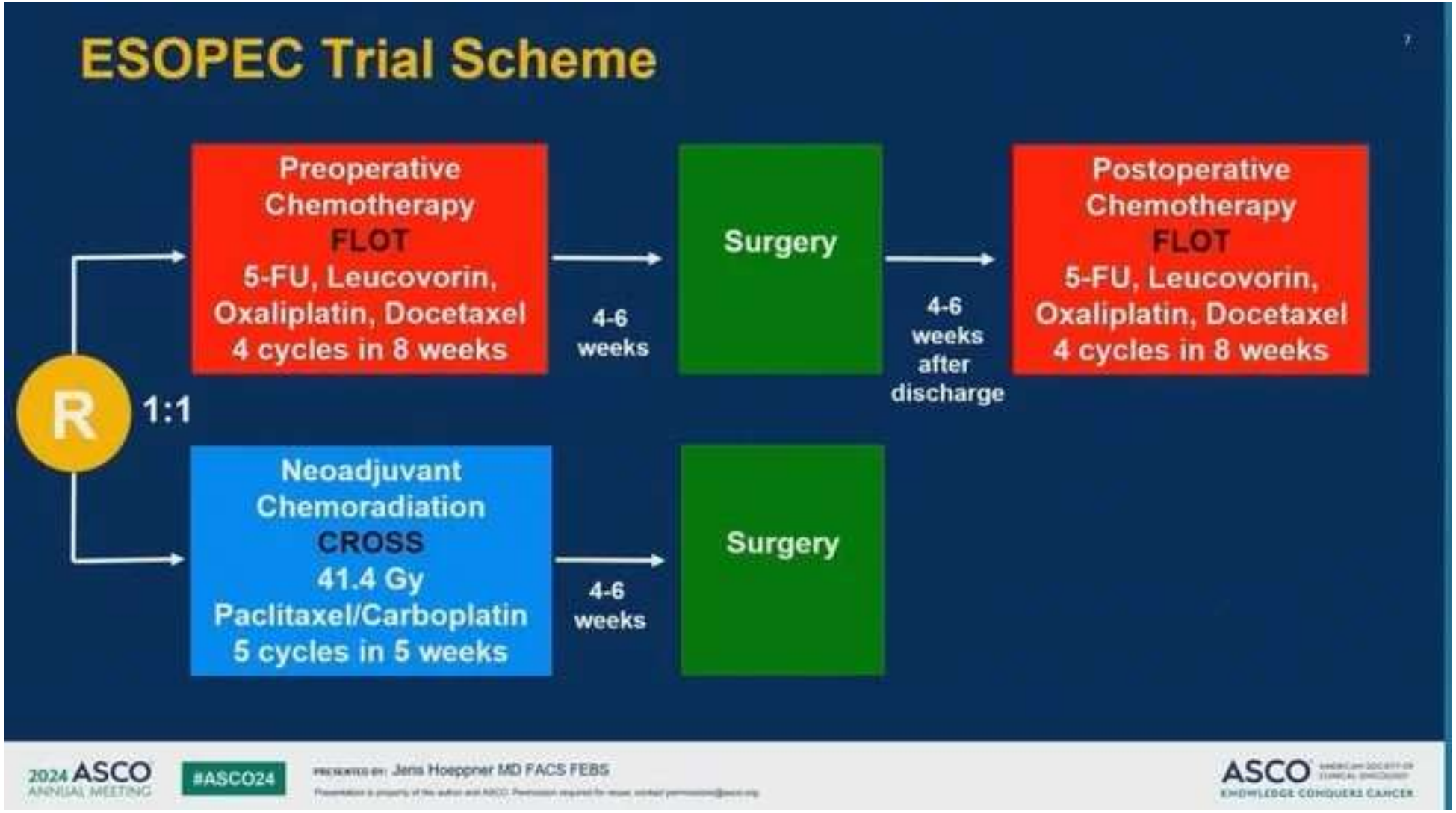
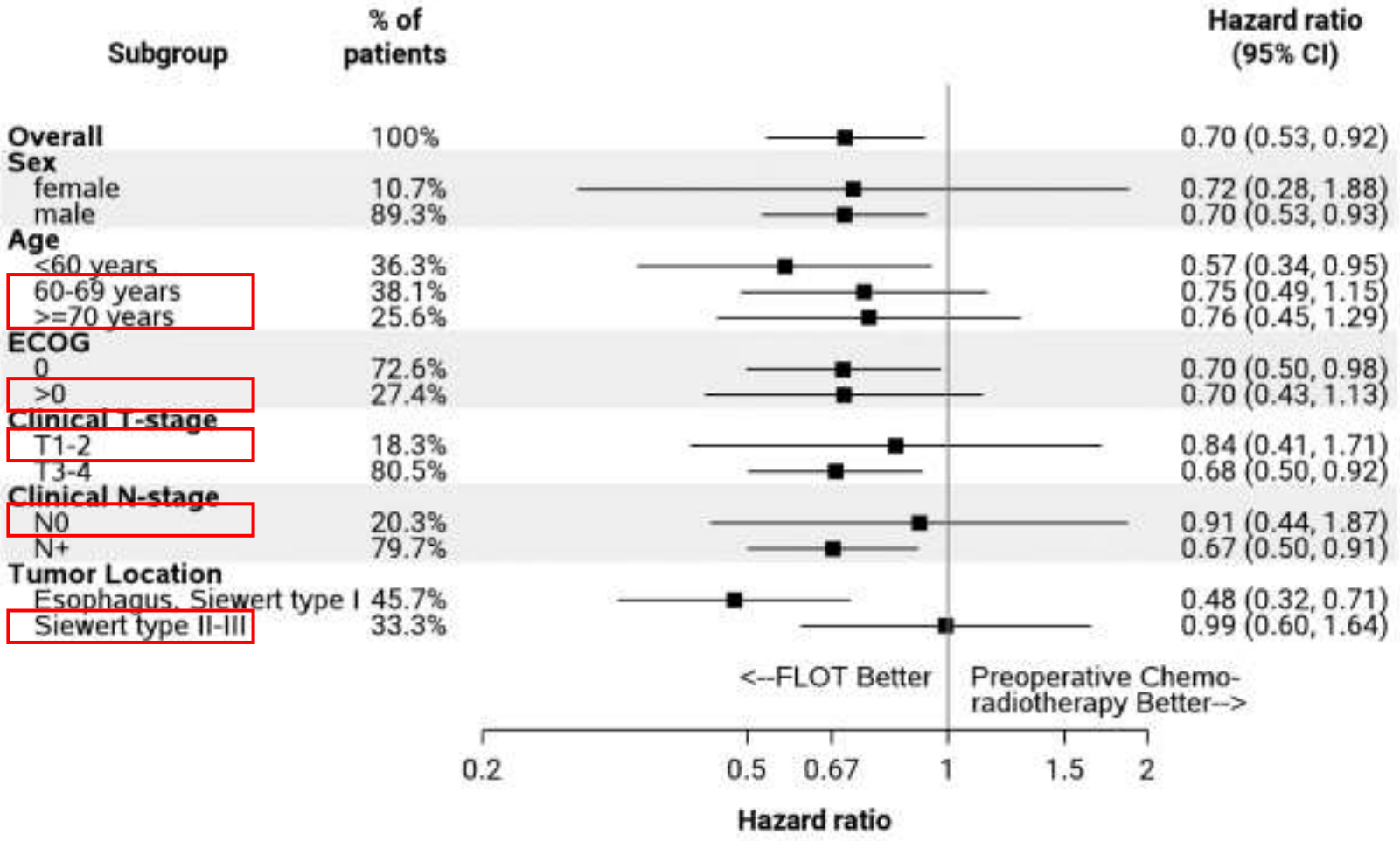
ESOPEC trial

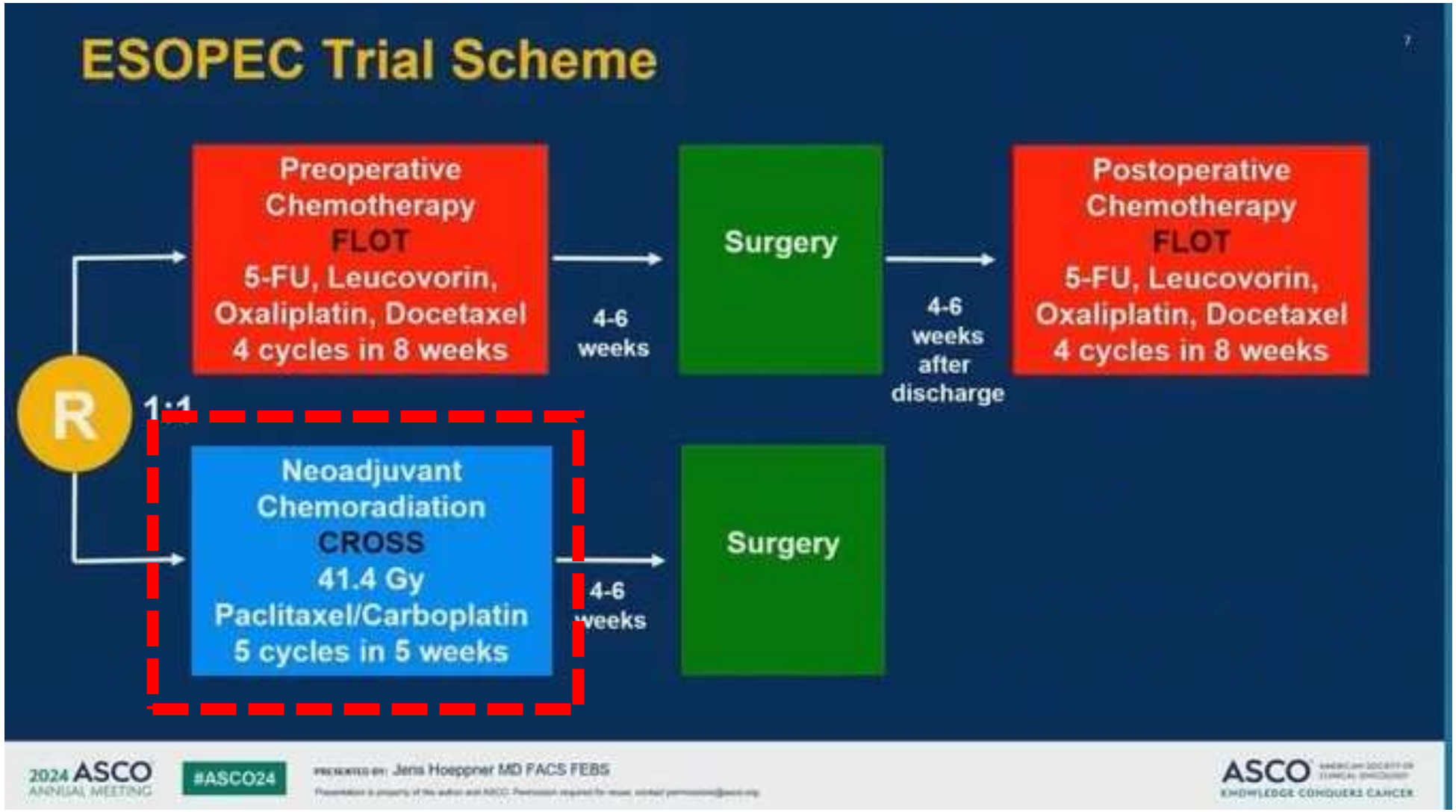


ESOPEC subgroup analysis of OS



[1]Hoeppner et al NEJM 2025

ESOPEC trial

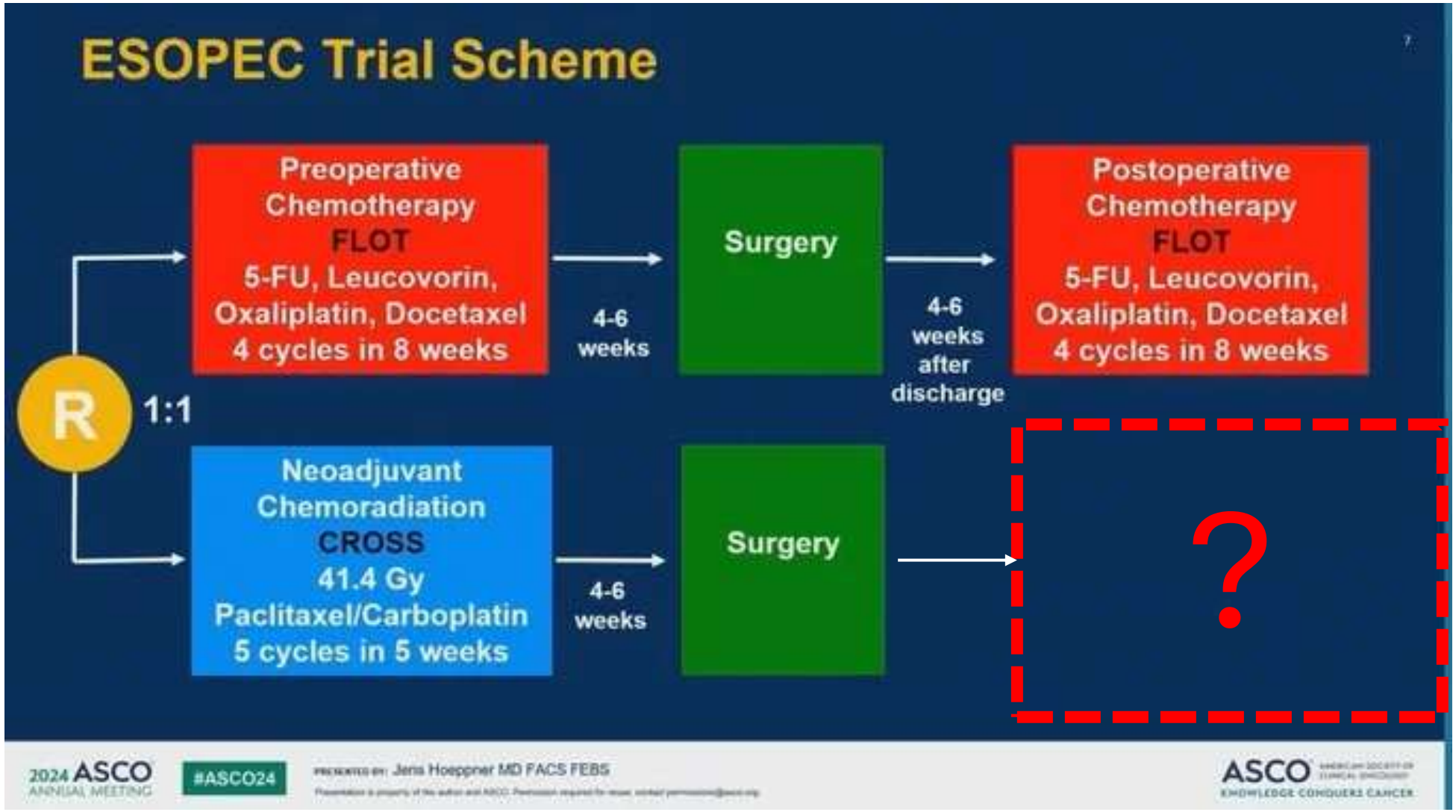


CROSS arm caveats

- Radiation dose used in CROSS (41.4 Gy) is lower than the typical standard in the U.S.[1,2]
  - Higher radiation dose up to 50.4 Gy associated with higher pCR.[2]
- CROSS arm allowed 3D conformal technique (how many received 3DCRT)?
- Neoadjuvant Chemo:
  - Only 67.7% completed 5 weeks in CROSS arm (but over 80% completed 4+ weeks) (87.3% completed neoadjuvant FLOT)
  - **10% did not receive chemo in CROSS arm (ITT)**
- **CROSS arm: 11 patients had metastatic disease on PET but still included in study analysis**

[1]Ising et al. J Gastrointestinal Surgery 2019
[2]Semenkovic et al. Ann Thoracic Surg 2020

CROSS arm did not include adjuvant IO

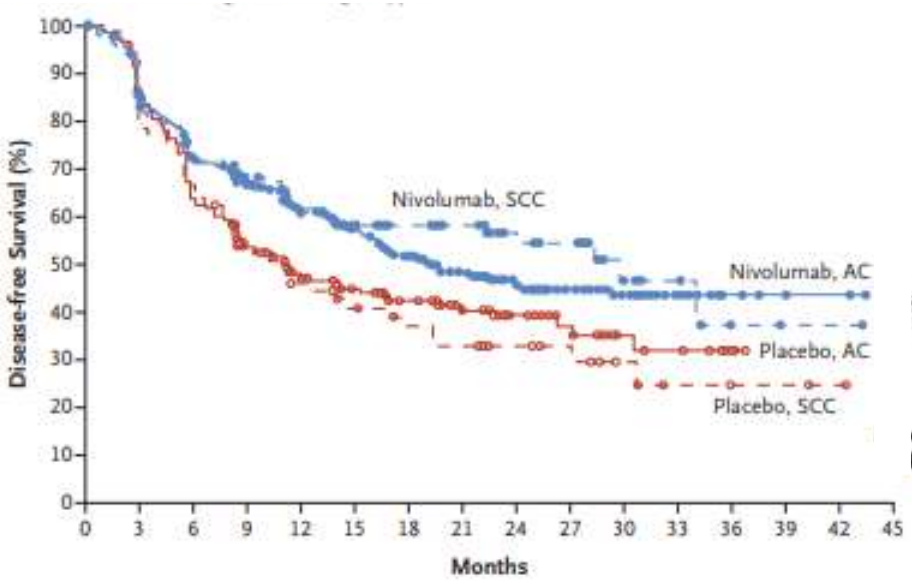


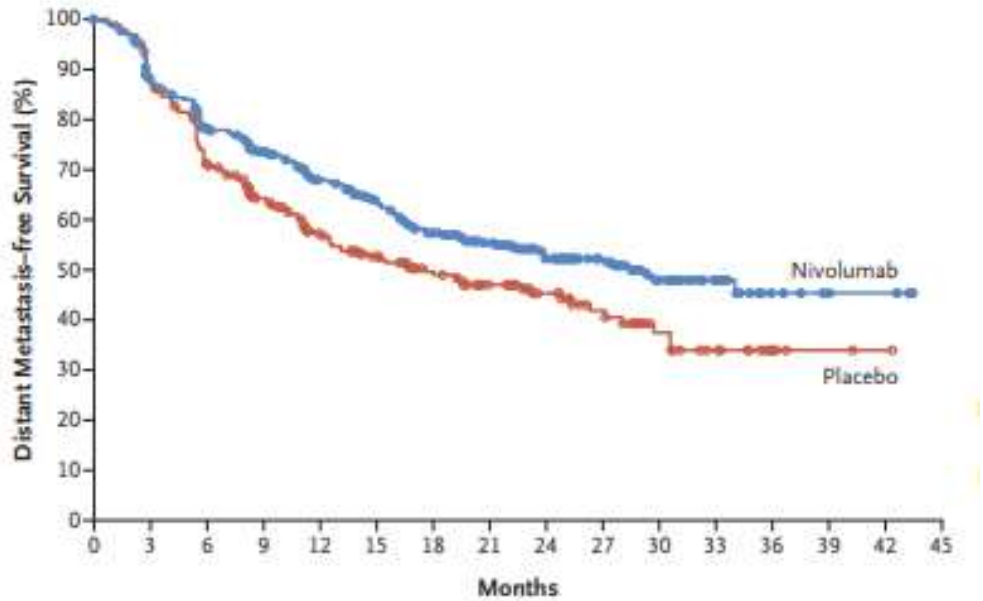
CROSS arm did not include adjuvant IO

Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

- CheckMate 577[1] showed disease-free and distant metastasis-free survival benefit with the addition of nivolumab

*secondary endpoint OS pending





[1]Ronan et al. NEJM 2021

Real World: Will the patient go to surgery or not?

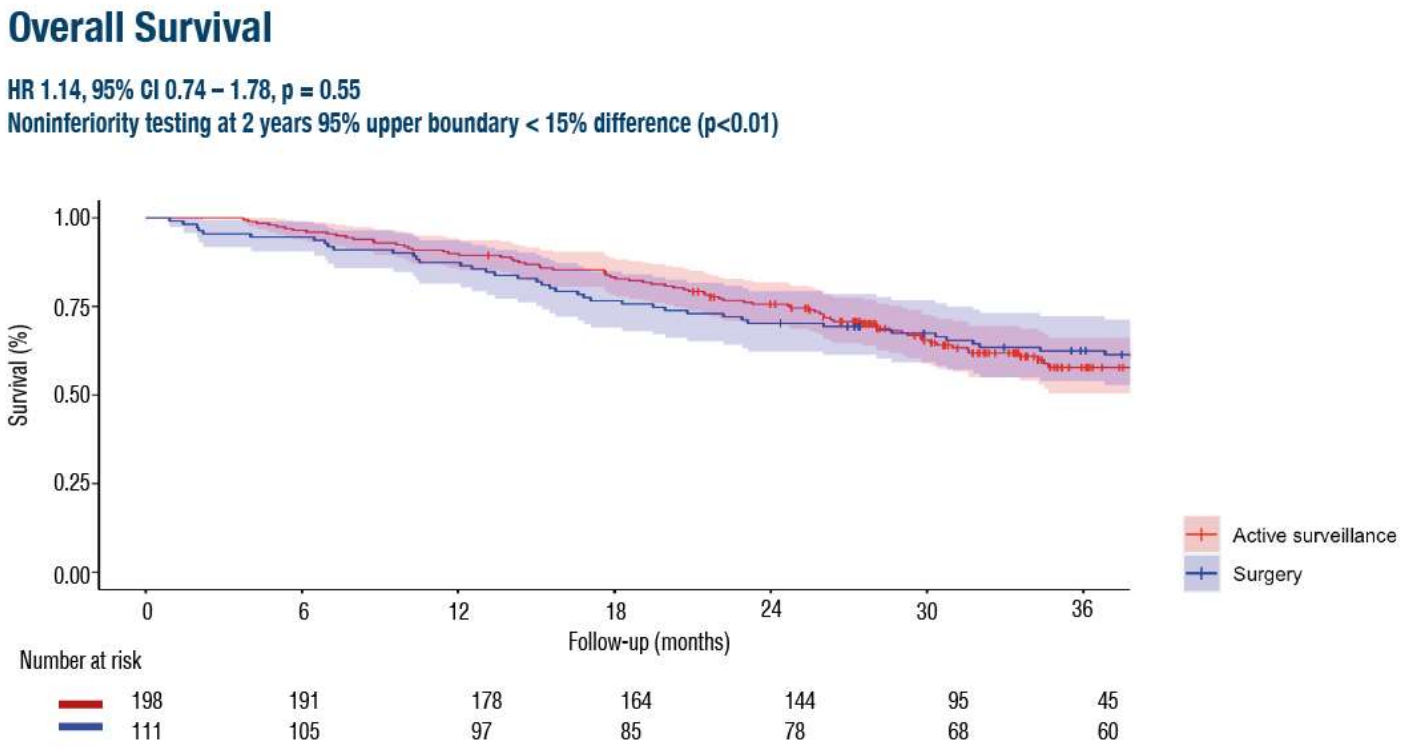
- ESOPEC FLOT arm patients were fit (median age 63 years, 73% ECOG 0)
  - Yet, 7.2% of patients who started FLOT did not receive surgery in this favorable cohort

- Some patients receiving FLOT will not go on to surgery[1,2] :
  - 26.3% (≥ 80 years), 13.9% (75–79 years), 10.2% (70–74 years)

[1]Keywani et al. Gastric Cancer 2023
[2]Skjoldbirk et al. Geriatric Oncology 2024

Real World: Will the patient go to surgery or not?

- High rate of complications inherent with esophagectomy[1]
- Increasing data for watchful waiting after clinical complete response (CCR)[2,3,4]



- Some patients just don't want esophagectomy

[1]Mariette et al. NEJM 2019
[2]van der Wilk et al. Ann Surg 2021
[3]Bondzi-Simpson et al. J Thorac Cardiovasc Surg 2024
[4]Noordman BJ BMC Cancer 2018

Conclusions

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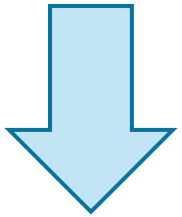
Perioperative Chemotherapy or Preoperative Chemoradiotherapy in Esophageal Cancer



Perioperative Chemotherapy or Preoperative **Low-Dose Chemoradiotherapy (followed by esophagectomy in those who are willing and able) without Adjuvant Immunotherapy** for Esophageal **Adenocarcinoma**

Conclusions

1. ESOPEC: practice-shifting results show peri-op FLOT > CROSS for resectable adenocarcinomas with some caveats:

2. Caveats:
    1. Older patients/lower burden of disease showed no difference on subset analysis
    2. CROSS radiation dose is low
    3. Some in CROSS arm received less than full chemo, or already had metastatic disease
    4. No adjuvant nivolumab in CROSS arm (CheckMate 577)
    5. Some patients don’t want, can’t get, or may not need surgery

Thank you!